New preparations of diazo compounds and studies of their metal catalysed diverted insertion reactions

Vol. 1 - Results and Discussion

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Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy

Submitted: December 2015

Abstract:

This Thesis reports some advances in the preparation and metal catalysed reactions of diazo compounds. After an introduction presenting the synthesis routes and the main transformations of this class of compound (**Chapter I**), the focus is placed on the dehydrogenation of unsubstituted hydrazones as a route to diazo compounds. A review of the reagents previously used for this transformation is followed by the description of the development of the use of potassium *N*-iodo *p*-toluenesulfonamide (iodamine-T) as a new reagent for this reaction and its application to a number of hydrazones (**Chapter II**). After presenting the advantages offered by the handling of diazo compounds in a flow environment, the preparation of a *N*-iodosulfonamide functionalised resin and its application to the generation of diazocarbonyl compounds in flow are described (**Chapter III**). A number of examples for the further reaction of diazo compounds generated by this protocol in various in-line reactions (O-H and N-H insertion, cyclopropanation and C-H insertion) are described. In particular, the synthesis of spiro-β-lactones by C-H insertion and their further conversion to oxetanes are presented.

Moving away from the preparation of diazocarbonyl compounds towards their metal catalysed insertion reactions, the recently described concept of diverted insertion reaction of metallocarbenes into X-H bonds (X = O, N) is first presented and the features of this process are reviewed in light of recent examples (**Chapter IV**). Following its fortuitous

discovery, the diverted insertion reaction of metallocarbenes derived from diazocarbonyl compounds into β-hydroxyketones to give highly functionalised and stereodefined tetrahydrofurans is described (**Chapter V**). Based on this process, efforts towards the synthesis of naturally occurring hyperlactone C and related compounds are discussed in the same Section. Finally, the application of a diverted insertion strategy to the preparation of functionalised and stereodefined pyrrolidines products from diazocarbonyl compounds and various β-aminoketone derivatives is described (**Chapter VI**).

The following articles were published during the course of this Thesis:

Potassium N-Iodo p-Toluenesulfonamide (TsNIK, Iodamine-T): A New Reagent for the Oxidation of Hydrazones to Diazo Compounds. S. M. Nicolle, C. J. Moody, *Chem. Eur. J.* **2014**, *20*, 4420-4425

Alkyl halide-free heteroatom alkylation and epoxidation facilitated by a recyclable polymer-supported oxidant for the in-flow preparation of diazo compounds. S. M. Nicolle, C. J. Hayes, C. J. Moody, *Chem. Eur. J.* **2015**, *21*, 4576-4579

Stereoselective synthesis of highly substituted tetrahydrofurans by diverted carbene O–H insertion reaction. S. M. Nicolle, W. Lewis, C. J. Hayes, C. J. Moody, *Angew. Chem. Int. Ed.* **2015**, *43*, 8485-8489

Acknowledgements:

First, I would like to thank my supervisors, Prof. Chris Moody and Prof. Chris Hayes, for giving me the opportunity to work on this topic and for their help and support along the way. The past three years have certainly been quite exciting and entertaining, in great part thanks to the C13 lab troops, whom I would also like to acknowledge here for the many enriching interactions and for their role in keeping an enjoyable atmosphere in the lab and a more than decent biscuits and cakes selection on a day to day basis. So thank you to all, in order of desk distance: Sophie, Hiroki san, Maxime, Hannah, Eve, Adam, Chris, Lorna, everyone called Alex who at some point settled in C13, and all the others. My thanks especially go to those who helped in the correction of this manuscript: the irreplaceable Dr Martyn "Daddy" Inman, Dr Alex Murray, Dr Andy "Dr. No" Nortcliff and of course Dr Russ "Kitty" Kitson and his sharp eyes. I would also like to thank the people from the chemistry department analytical services which, through their technical ability and helpful disposition, have greatly contributed to the realisation of the work presented here. My gratitude also goes to Dane Toplis and Tom Clayton for their help in their role as organic research technicians, to Prof. Derek Irvine and Dr Kevin Adlington for their help with the thermal stability studies and to Dr William Lewis for the crystal structure determinations. To finish, I would like to thank Pippa for the support she dispensed me with on a daily basis during the last three years and during the redaction of this manuscript.

Abbreviations:

BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BPR	back pressure regulator
Bz	benzoyl
Cbz	benzyloxycarbonyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DOSP	*N*-(*p*-dodecylphenylsulfonyl)proline
EDA	ethyl diazoacetate
ESI-MS	Electrospray Ionisation Mass Spectrometry
esp	α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid
EWG	electron withdrawing group
FG	functional group
hfacac	hexafluoroacetate
HIV	Human Immunodeficiency Virus
LPS	lipopolysaccharide
mCPBA	*meta*-chloroperbenzoic acid
MEPY	methyl 2-pyrrolidone-5(*S*)-carboxylate
MPPIM	methyl 2-oxo-3-(3-phenylpropanoyl)imidazolidine-4-carboxylate
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
PMP	*para*-methoxyphenyl
PTAD	(1-adamantyl)-(*N*-phthalimido)acetate
S-MEOX	methyl 2-oxazolidone-4(*S*)-carboxylate
TBS	*tert*-butyldimethylsilyl
*t*Bu	*tert*-butyl
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl, triflyl
THF	tetrahydrofuran
TMS	trimethylsilyl
Tol	toluene
TPP	tetraphenylporphyrin
Ts	tosyl
UV	ultra-violet

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Chapter I - Introduction to the chemistry of diazo compounds

"*Tout avantage a ses inconvénients et réciproquement.*"

[every advantage has its drawback, and vice versa]

Shadok proverb (written by Jacques Rouxel)

I. Diazo compounds

I.1. Generalities

Aliphatic diazo compounds (**Figure I-1**, structure **1**) are versatile intermediates in organic synthesis and their chemistry has been extensively studied since the first example of this class of compound, ethyl diazoacetate **2**, was originally synthesised by Curtius in 1883.[1] In the century following this milestone synthesis, this class of compound has continued to attract chemists' interest, and diazo chemistry remains to this day a widely studied field,[2] with a particular focus on the chemistry of diazocarbonyl substrates (**1** with $R^1 = C(O)R$).[3]

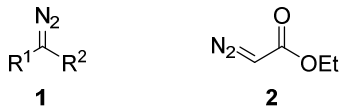


Figure I-1: general structure of diazo compounds

The main transformations of diazo compounds are presented in **Figure I-2**. Most of the attention dedicated to this class of substrates focuses on their role as carbene precursors (generated thermally or photochemically by loss of molecular nitrogen) and as metallocarbene precursors. These generally short-lived metal-bound carbenes are commonly generated by transition metal catalysed loss of molecular nitrogen. This last area of research, initially restrained to copper(I) or copper(II) catalysed processes, underwent an important development with the introduction of rhodium(II) dimer complexes in the 1970s.[3] The use of rhodium(II) catalysis in the decomposition of diazo compounds has

allowed for tremendous improvements in terms of selectivity,[4] as for instance reflected by the development of cascade reaction processes.[5] Reaction of metallocarbenes derived from diazo compounds include cyclopropanation, C-H insertion,[6] sulfur, nitrogen, oxonium[7] and carbonyl ylide formation[8] and X-H insertion (X = O, N, S, P...).[9]

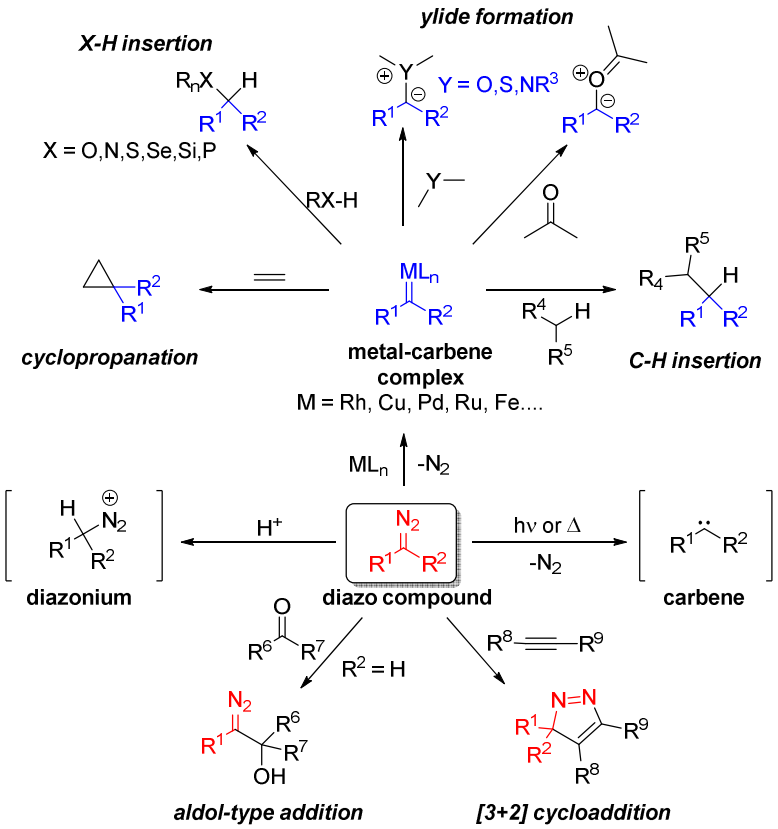


Figure I-2: main transformations of diazo compounds

Beside the generation of reactive carbene species, acids can also mediate the decomposition of diazo compounds via protonation of the diazo carbon to give a variety of products (carbocation, rearrangement product, formal O-H insertion product...) *via* an unstable aliphatic diazonium species. Some transformations of diazo compounds also involve the conservation of the carbon – nitrogen bond. Examples of such reactions

are given by the "aldol-type" condensation of monosubsituted diazo compounds with carbonyl compounds, and by [3+2] cycloadditions reactions, in which diazo compounds act as 1,3-dipoles (**Figure I-2**).[3b,c]

I.2. Stability of diazo compounds

A typical feature of diazo compounds is their inherent labile nature. These substrates are indeed generally sensitive to acids, light, metals but also thermally labile. The stability of a given diazo compound is nevertheless heavily dependent on the electronic nature of its substituents. As a rule, diazo compounds are stabilised through substitution with functional groups capable of delocalising the partial negative charge borne by the diazo carbon. For instance, substitution with a carbonyl group leads to significant stabilisation through the mesomeric form **3c** as shown in **Figure I-3** This effect is also observed with silylated diazoalkanes **4** that display a surprising stability due to the ability of the silicon group to stabilise a negative charge in the α-position.[10]

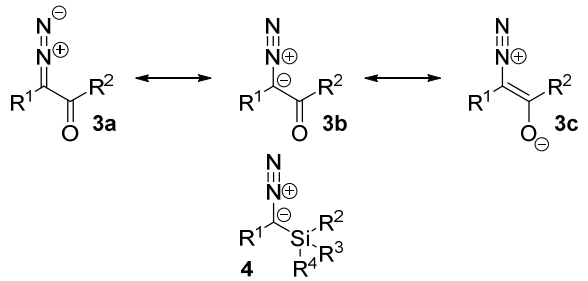


Figure I-3: stabilisation of diazo compounds

A general trend in the stability of diazo compounds is presented in **Figure I-4**. Strong variations are observed between the bench-stable diazo compounds bearing two electron withdrawing groups and

unstabilised small diazoalkanes. The latter are commonly both highly toxic and prone to violent decomposition, as demonstrated by the simplest and perhaps most hazardous of this subclass of compound: the gaseous diazomethane (thermally and photochemically labile, highly acid sensitive, decomposes explosively in contact with sharp surface or metal, skin irritant, high acute toxicity, powerful carcinogen).[11]

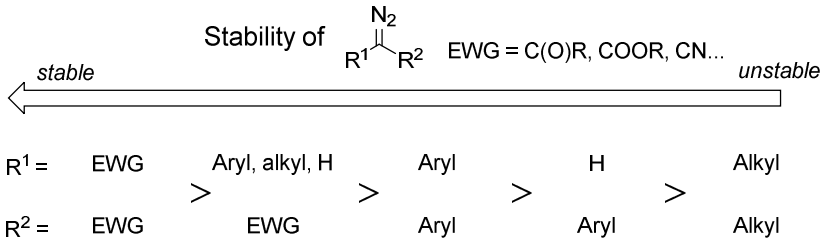


Figure I-4: trends in the stability of diazo compounds

Notwithstanding the relative stability of some diazo compounds, their limited use in industrial processes and their scarce commercial availability are certainly consequences of their lability and potential for fast and exothermic nitrogen release and the resulting hazard associated with their handling. Efforts described in the recent literature have been concentrated on reducing the risks associated with diazo compounds with the development of *in situ* generation methods, or the use of microreactors and continuous flow systems to ensure the confinement of hazardous intermediates (discussed in **Chapter III**).[12]

I.3. Synthesis of diazo compounds

While the occurrence of a diazo moiety in molecules found in Nature is rare,[13] a wide range of such compounds can be prepared in the

laboratory. The literature dealing with the preparation of diazo compounds spans more than a century of research and is therefore abundant.[10] Strikingly, and despite the long standing interest in this class of substrates, the inventory of strategies for their preparation is continually supplemented by new methods and by variations of existing protocols.[14] Following the organisation proposed by Regitz,[10] the existing routes can be classified according to the following features (**Figure I-5**).

- From a compound possessing a functional group bearing one nitrogen atom, the diazo moiety is constructed by condensation with a nitrogen-containing reaction partner. This category includes the diazotisation of amines (route **A**, historically the first method, employed by Curtius for the synthesis of ethyl diazoacetate from glycine)[1] and the Forster reaction (route **B**, condensation of oximes with ammonia in the presence of sodium hypochlorite).[15]
- From a suitable acceptor substrate: the two nitrogen atoms of the diazo group are transferred from a donor reagent by a condensation–fragmentation pathway. This includes the most popular diazo transfer route (route **C**) which allows the conversion of active methylene compounds (bearing one or two electron withdrawing substituents) to a diazo compounds. Arenesulfonyl azides are commonly used as diazo transfer reagents.[16]
- From a compound bearing two nitrogen atoms, functional group modifications give the CN_2 moiety. This class includes the

dehydrogenation of simple hydrazones (route **F**), the base mediated decomposition of tosylhydrazones (the Bamford–Stevens reaction, route **E**),[17] the alkaline cleavage of *N*-alkyl *N*-nitroso derivatives (route **D**, where R^3 group is a base labile group: carbamate, ureas, carboxamide, arylsulfonamide and guanidine have been used).

- From a triazene precursor (generally obtained from coupling of diazonium salts and amines) by fragmentation (route **G**). This includes the relatively recent phosphine mediated conversion of azides to diazo compounds which proceed *via* triazene intermediates.[18]
- From a compound already bearing the diazo moiety by substitution at the diazo carbon atom or functional group modification (route **H**). This includes the recently reported palladium catalysed coupling of diazoacetates and α-diazocarbonyl compounds with aryl and vinyl iodides.[19]

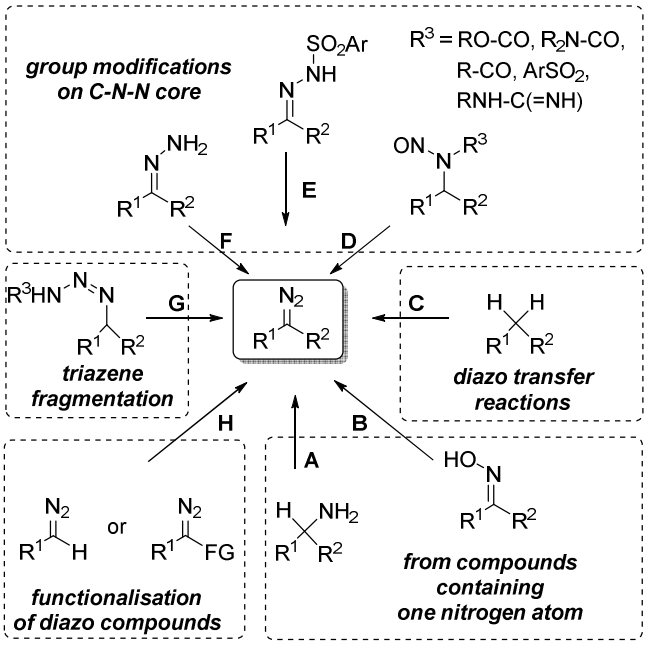


Figure I-5: main routes for the preparation of diazo compounds

It is noteworthy that these routes are often complementary and that none of them has been proven to give universal access to the important structural and electronic diversity of diazo compounds. **Figure I-6** presents the relationship between the different subclasses of diazo compounds and the synthesis methods preferred from their preparation.

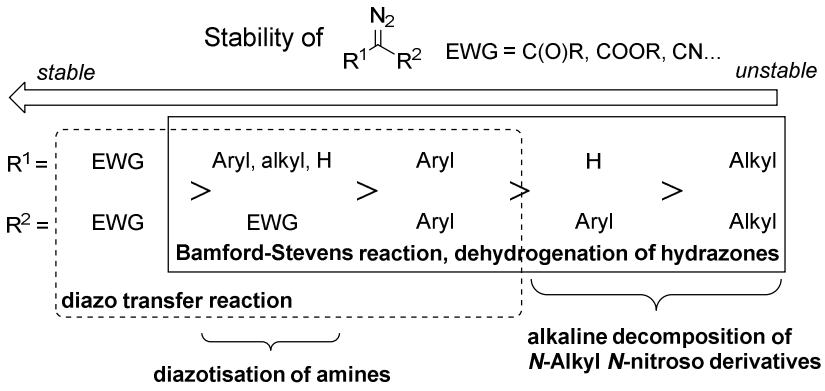


Figure I-6: preferred routes to different subclasses of diazo compounds

The diazo transfer reaction using sulfonyl azides is probably the most popular method for the preparation of diazocarbonyl compounds because of its efficiency and wide applicability.[14] Although this method classically requires a substrate bearing at least one strong acceptor substituent, several variants have been developed for less activated substrates such as simple ketones or esters.[20] It is nevertheless not applicable for substrate that lack activation. The less stable aliphatic diazoalkanes are preferably synthesised by oxidation of hydrazones or alkaline cleavage of *N*-methyl-*N*-nitroso derivatives. Of all methods, the dehydrogenation of hydrazones and the Bamford-Stevens reaction have proved applicable to the broadest range of diazo compounds. A review of the methods available for the dehydrogenation of hydrazones is given in **Chapter II**.

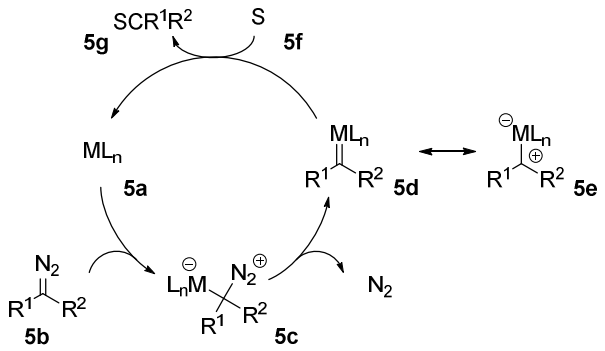
II. Metal catalysed reactions of diazo compounds

General features of the main transformations of metallocarbenes generated from diazo compounds are treated in this Section. Most examples considered here involve diazocarbonyl compounds, as this class of substrates have received a wider coverage than their less stable counterparts.[3,21]

II.1. Metallocarbene reactivity

The metal catalysed decomposition of diazo compounds results in loss of nitrogen and the generation of highly reactive metallocarbenes (**Scheme I-1**), that commonly undergo transformations with a selectivity much superior to that of free carbenes, and therefore have found wide application in organic synthesis. A number of metals have been established to promote this process, including: Cu, Rh, Ru, Pd, Ir, Os, Fe, Pt, Ni, Mo, and W.[3b] The accepted mechanism for the catalytic decomposition of diazo compounds is presented in **Scheme I-1** and involves the attack of the nucleophilic diazo carbon onto the Lewis acidic metal catalyst **5a** to generate diazonium species **5c**. Irreversible loss of nitrogen generates the metal-bond intermediate **5d-e**. This species can be depicted as a metal bound carbene **5d** possessing a σ-metal-carbon bond and a π-bond formed by backbonding of metal center d-orbitals to the carbon empty p-orbital. The electrophilic nature of this intermediate is also well represented by the canonical form **5e.** The nature of the metal and the electronic nature of the ligands can influence the balance between

these resonance structures **5d** and **5e** and therefore the reactivity of metallocarbene intermediates. Reaction with a substrate **5f** then releases the product **5g** and the active catalyst **5a**.



Scheme I-1: metal catalysed decomposition of diazo compounds

The use of copper(I) and copper(II) catalysts dates back to the early days of the field, although they often have been supplanted by rhodium(II) dimer catalysts and their superior catalytic performances. New developments in copper-catalysed reaction of diazo compounds have nevertheless triggered a renewal of the field.[22] The use of palladium(II) catalysts has also recently undergone a significant expansion.[23] Rhodium catalysis remains nonetheless the most widely used since the introduction of the rhodium(II) acetate dimer ($Rh_2(OAc)_4$).[24] This complex presents a "paddlewheel" type of geometry **6a** that is common to all other carboxylate (as **6b-e**), carboxamidate (as **7a-c**) and phosphonate rhodium dimer complexes (**Figure I-7**).[4,25] A large number of rhodium dimer complexes have been prepared and their catalytic activities accessed, with ligand variations commonly leading to dramatic change in reactivity and selectivity.[26] Importantly, the introduction of chiral ligands can lead to homochiral complexes such as Davies' Rh_2(*S*-DOSP)$_4$

6e[27] and Doyle's Rh_2(*S*-MEPY)$_4$ **7c**[28] that can promote enantioselective transformations.

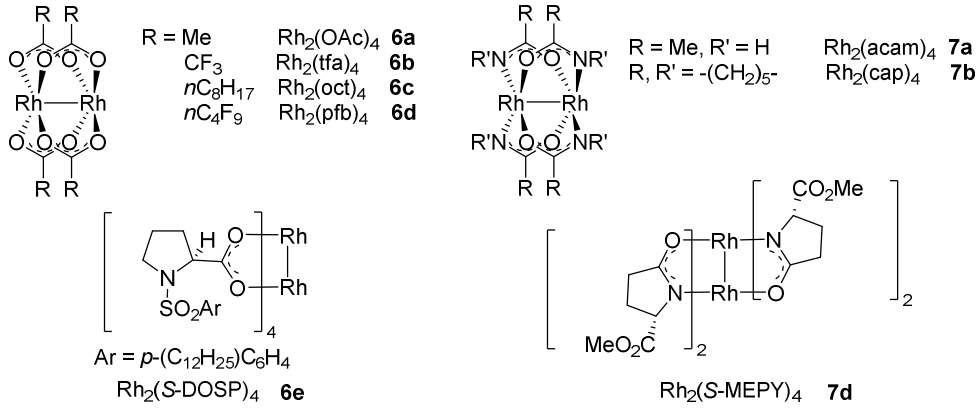


Figure I-7: common rhodium(II) dimer catalysts

Besides the nature of the metal and of the ligands, the reactivity of metallocarbenes also hinges on the substitution of the carbene center. In parallel to the diazo compound stability trend (**Figure I-4**), the reactivity of commonly used metallocarbenes has also been classified by Davies according to the substitution on the metallocarbene carbon (**Figure I-8**).[6,29]

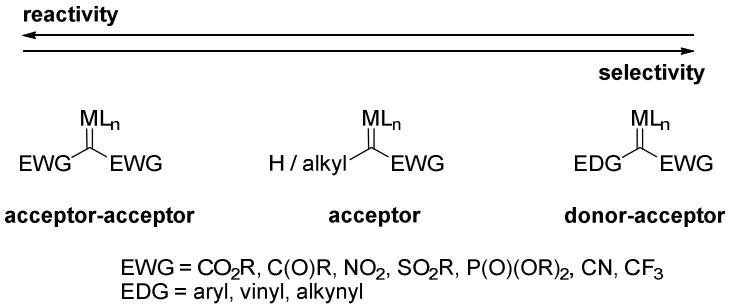


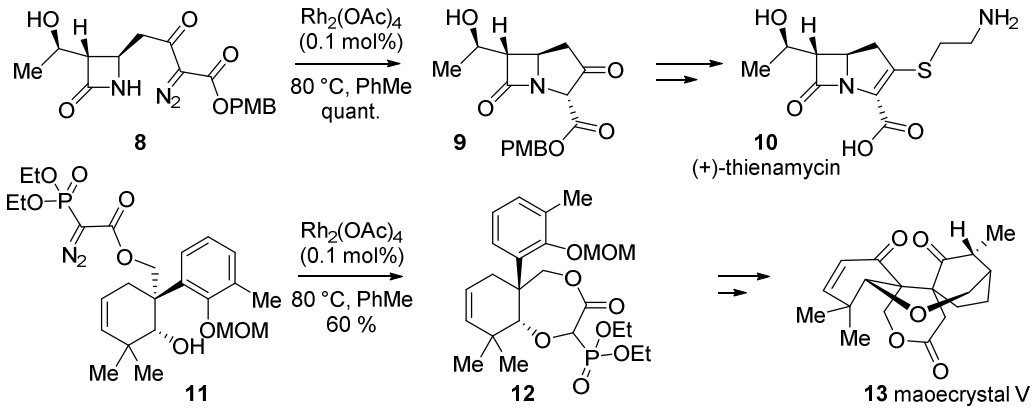
Figure I-8: Davies' classification of metallocarbenes

Acceptor-acceptor metallocarbenes are the most electrophilic and their reactions are often characterised by low selectivity. Acceptor metallocarbene, such as these derived from alkyl substituted diazoesters

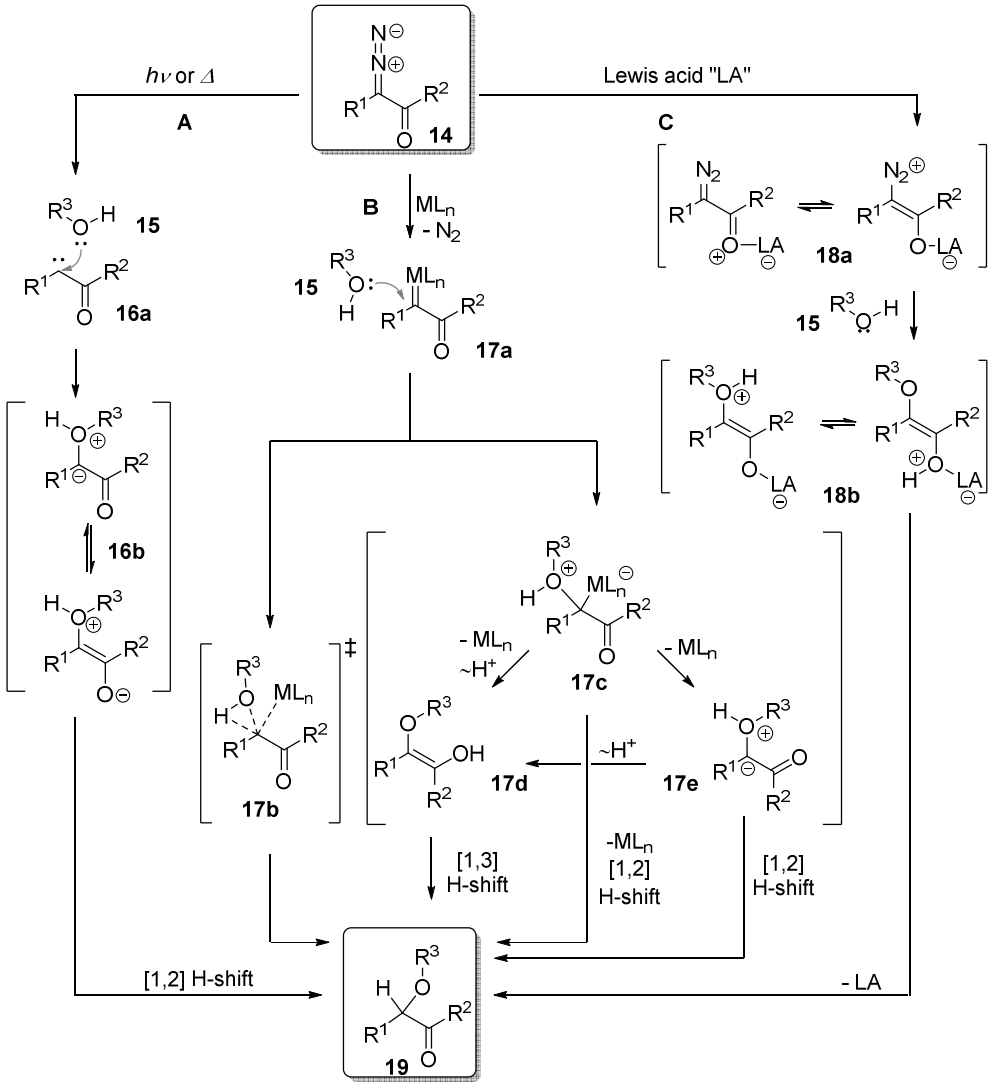
are often encountered in intramolecular reactions and are known to easily undergo hydride shift to yield alkenes.[30] Acceptor metallocarbenes bearing a hydrogen atom, such as the one derived from EDA **2**, are often unselective in intermolecular reactions and possess a tendency to form alkenes by carbene dimerisation. Donor-acceptor metallocarbenes on the other hand offer the highest selectivity, particularly in intermolecular reactions and generally have a lower tendency to dimerise.[31]

II.2. X-H insertion reactions (X = N, O, S)

Insertion of carbenes or metallocarbenes derived from diazo compounds into polar X-H bonds is a powerful method for the formation of C-X bonds (where X = N, O, S...) and this field has been extensively studied since early studies on diazo compounds.[3b,9] The utility of this transformation in organic synthesis is illustrated by its application in total synthesis of natural products such as the synthesis of (+)-thienamycin **10** [32] by Merck scientists or the synthesis of maoecrystal V **13** by Yang and co-workers (**Scheme I-2**).[33]



Scheme I-2: examples of N-H and O-H insertion reactions



Scheme I-3: O-H insertion reaction mechanism

Brønsted acids, such as sulfonic or carboxylic acids, can react with diazo compounds under purely thermal conditions and lead to the O-H insertion product via a protonation/dinitrogen displacement mechanism. Less acidic compounds such as alcohols, thiols and amines can undergo insertion reaction but necessitate the addition of a catalyst (metal catalyst or other Lewis acid), high temperatures or UV/visible light irradiation. Other mechanisms must therefore be considered: the alternatives for the O-H insertion reaction are presented on **Scheme I-3** (N-H and S-H

insertion reactions are considered analogous).[3b] Under photochemical or thermal conditions (**Scheme I-3**, route **A**), the decomposition of the diazo compound **14** can generate a highly reactive free carbene **16a**. By reaction of the intermediate **16a** with an alcohol **15**, an intermediate oxonium **16b** is formed which then rearranges to the final product **19** by a formal [1,2]-H shift. Due to the lack of selectivity of free carbenes that lead to a number of secondary processes, the thermal/photochemical route is often the least efficient for this transformation.

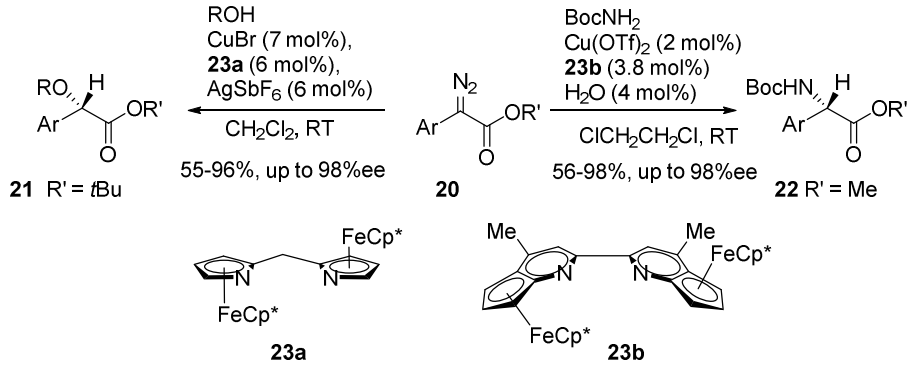
The metal catalysed alternative has been extensively studied, most commonly with rhodium or copper complexes, but iron, ruthenium and iridium complexes have also been used (**Scheme I-3**, route **B**).[9] This transformation is generally considered to involve the first formation of a metallocarbene **17a** from diazo compound **14**, although studies on iron(III) porphyrin catalysed N-H insertion reactions have suggested otherwise.[34] Reaction of the electrophilic metallocarbene **17a** with alcohol **15**, though it has been suggested to proceed *via* a concerted mechanism (transition state **17b**),[35] is more widely considered to proceed via *the* formation of oxonium ylide **17c**. The observed possibility of trapping transient ylides (such as **17c**) with various electrophiles represents a strong argument in favour of a stepwise pathway (this particular reactivity is discussed in **Chapter IV**). From **17c**, the formation of the product **19** necessitates an additional H-shift. The exact pathway followed by the reaction is critical for processes involving the transfer of chirality from the metal catalyst. Cleavage of the carbon-metal bond can

lead to the metal free ylide **17e** while an additional intramolecular proton transfer gives the (*Z*)-enol **17d**. Recent computational studies have shown that the reaction pathway, and in particular the nature of the intermediate, are metal-dependent. While rhodium(II) carboxylate catalysts proceed *via* a metal free intermediate as **17d-e**, copper catalysts are suggested to proceed *via* metal bound ylide such as **17c**.[36] Additionally, enol **17d** has been proposed as an intermediate in rhodium catalysed O-H[37] and N-H insertion.[38] Finally, calculations have suggested that the intramolecular [1,2]-H shift from ylide **17e** to product **19** possesses a relatively high activation energy. [36-38]

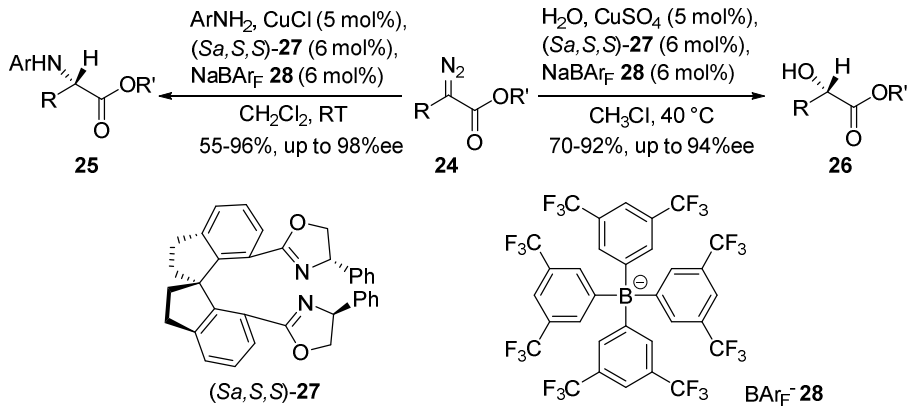
The mechanism of the Lewis acid catalysed decomposition of diazo compounds (**Scheme I-3**, route **C**) has not been fully investigated and is generally considered not to involve a carbene intermediate. Coordination of the acid ("LA") to the carbonyl can activate the substrate for nucleophilic attack by alcohol **15** to give intermediate **18b**, from which a proton shift and the elimination of the Lewis acid lead to the final ether **19**.

For for some time, a method allowing the efficient transfer of chirality in X-H insertion reactions (X = O, N) remained elusive when chiral rhodium catalysts were used. However, a return to copper catalysis led to significant developments in this area.[39] The first breakthrough was reported by Fu and co-workers in 2006, with the asymmetric O-H insertion of metallocarbene derived from aryldiazoacetate esters **20** using copper/bisazaferrocene catalyst **23a**.[40] An N-H insertion reaction of

aryldiazoacetates **20** into *t*-butyl carbamate was later described using a similar catalytic system based on asymmetric ligand **23b** (**Scheme I-4**).[41]



Scheme I-4: asymmetric N-H and O-H insertion reactions described by Fu and co-workers

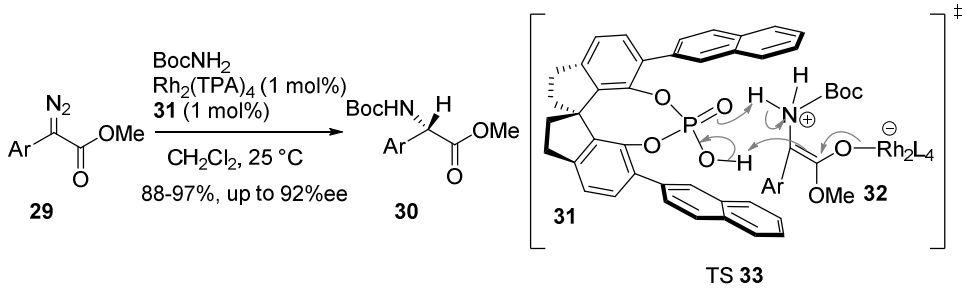


Scheme I-5: asymmetric N-H and O-H insertion reactions described by Zhou and co-workers

Zhou and co-workers have also reported a catalytic system based on copper(I) salts and bisoxazoline ligand **27** that was applied to O-H insertion,[42] N-H insertion (**Scheme I-5**),[43] S-H insertion,[44] but also insertion into less polar Si-H bonds.[45] Interestingly, the same group also reported a system based on asymmetric iron(II) catalysed O-H insertion

using similar types of ligands.[46] The use of other copper catalysts have since been reported in asymmetric O-H and N-H insertion processes.[47]

Another development originating from the Zhou group was reported in 2011 and is based on the use of *non-chiral* rhodium catalyst (i.e. rhodium triphenylacetate dimer $Rh_2(TPA)_4$) in conjunction with chiral phosphoric acid **31** (**Scheme I-6**). In this reaction, the chiral phosphoric acid **31** is proposed to be involved in the final proton transfer step occurring on ylide **32**, that leads to the formation of the stereocenter (as depicted on the proposed transition state **33**).[48] Extensions of this work to S-H insertion[49] and to N-H insertion reactions of diazoketones were also reported later.[50]

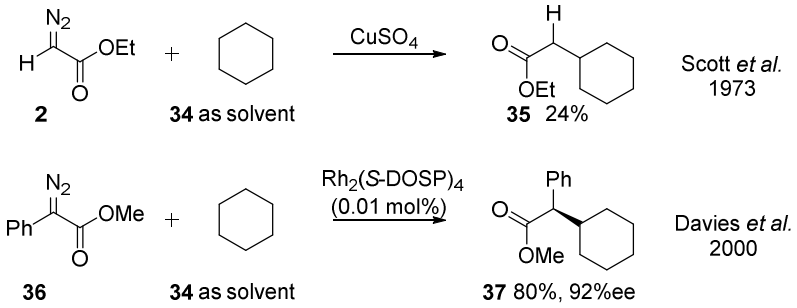


Scheme I-6: asymmetric N-H insertion reaction using chiral phosphoric acids

II.3. C-H insertion reactions

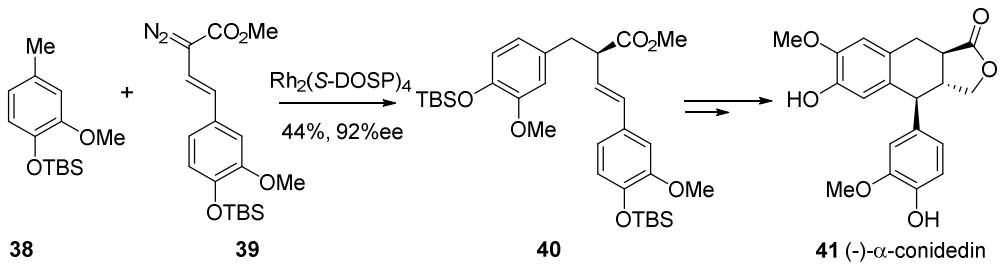
Metallocarbene insertion reactions also occur into bonds of low polarity such as C-H and Si-H bonds. C-H insertion in particular is a highly attractive process that allows the formation of a C-C bond across an inactivated C-H bond and is indisputably one of the most useful transformations of metallocarbenes. High levels of chemo- and enantioselectivity can be attained through the use of rhodium carboxylate

and carboxamidate catalysts, which now dominate this field.[6,26] The tremendous advances made in the field of C-H insertion become apparent when one considers the early report of copper(I) catalysed C-H insertion reaction of EDA **2** into cyclohexane[51] **34** compared with the similar reaction of methyl phenyldiazoacetate **36** catalysed by Rh_2(*S*-DOSP)$_4$ **6e** (**Scheme I-7**).[52]



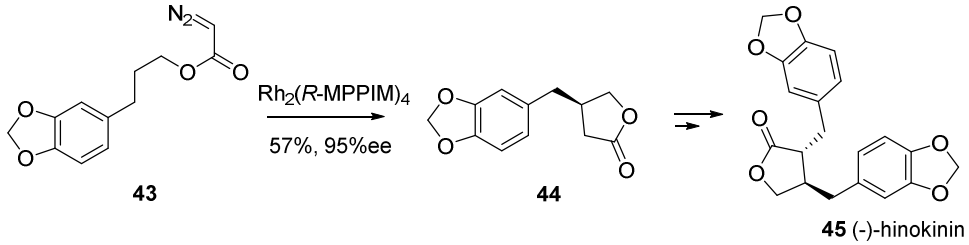
Scheme I-7: evolutions in intermolecular C-H insertion reactions

This last example also illustrates the use of donor-acceptor metallocarbene in stereoselective C-H insertion reactions pioneered and largely developed by the group of Davies.[53] Such transformations were applied to the preparation of several natural products, as for example the synthesis of (-)-α-conidendrin **41** that features an enantioselective benzylic C-H insertion (**Scheme I-8**).[54]



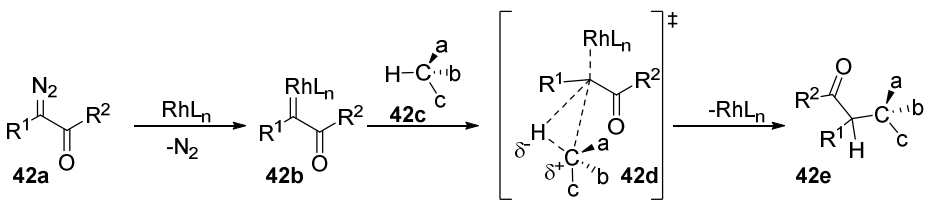
Scheme I-8: synthesis of (-)-α-conidendrin by Davies and co-workers

C-H insertion reactions of metallocarbenes nevertheless find a wider application in intramolecular processes. The group of Doyle has for instance investigated the use of homochiral rhodium carboxamidate complexes in intramolecular C-H insertion of diazoacetate derivatives[55] and applied this method to the construction of a series of lignan lactones, as illustrated by the synthesis of (-)-hinokinin **45** (**Scheme I-9**).[56]



Scheme I-9: synthesis of (-)-hinokinin by Doyle and co-workers

The mechanistic understanding of the metallocarbene C-H insertion reaction is not complete, but it is generally considered to take place in a single step (**Scheme I-10**).[6] A cohort of computational and mechanistic studies have led to the conclusion that the insertion event takes place over a three-centred transition state **42d** through a concerted but asynchronous mechanism characterised by a build up of positive charge on the alkane carbon during the formation of the new C-C bond. Importantly, the C-H insertion proceeds via a complete retention of configuration on the alkane **42c**.

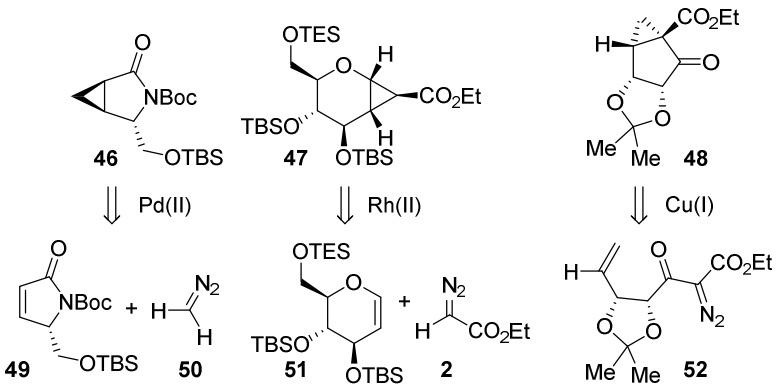


Scheme I-10: proposed mechanism for C-H insertion reactions

The thorough investigation of C-H insertion processes has allowed for the definition of clear trends in selectivity that helps predict the outcome of these processes with new substrates.[6,26,29,57] In general, the formation of 5-membered rings (usually *trans*) is preferred in the absence of other controlling factors, due to entropic factors. This preference can be overridden by the presence of a heteroatom (i.e. O or N) that activates its geminal C-H bonds towards insertion. Similarly, benzylic positions are activated for C-H insertion, while C-H bonds substituted with an electron-withdrawing group are particularly unreactive. The selectivity for substituted C-H bonds follows the reactivity trend 3° > 2° >>1° C-H bond, although the insertion on tertiary carbons might be inhibited by steric repulsion. These observations are in line with the proposed mechanism in which the alkane carbon bears a partial positive charge (as in **42d**, **Scheme I-10**).

II.4. Cyclopropanation

The catalytic cyclopropanation of alkenes using diazo compounds is one of the major routes to this class of 3-membered rings, and has been extensively studied.[3b,c,58] This transformation is known for a wide variety of diazo compounds, as illustrated by the examples presented in **Scheme I-11** featuring cyclopropanation reactions using diazomethane **50**,[59] ethyl diazoacetate **2**[60] and a diazodicarbonyl substrate **52**.[61]

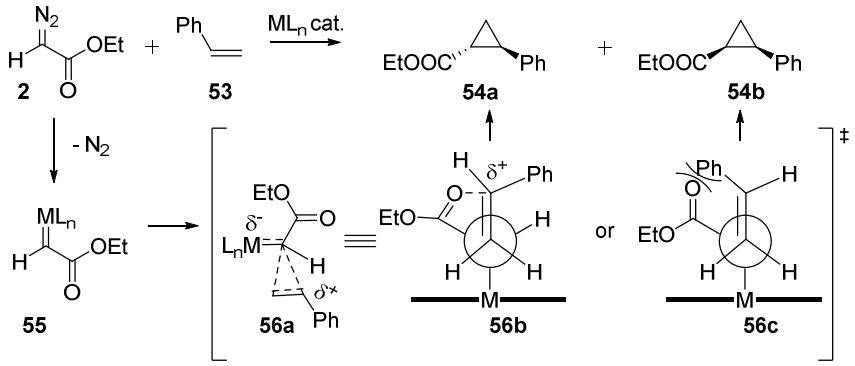


Scheme I-11: examples of cyclopropanation reactions

As with other transformations involving metallocarbenes, the use of diazocarbonyl compounds in cyclopropanation reaction is the most documented. Copper and rhodium are generally the catalysts of choice for these substrates, although numerous other metals have been used.[3b,62] This reaction also occurs under thermal or photochemical conditions *via* the free carbene, but metal catalysed processes allow for more efficient and selective reactions. Additionally, the use of homochiral metal complexes has led to the discovery of an abundant collection of catalysts for asymmetric cyclopropanation reactions.[58]

Typically, the product distribution in this reaction (such as the ratio of *cis*/*trans* cyclopropanes) varies with all parameters: the nature of the diazo compound, of the olefin, of the metal used and whether the process is intra- or intermolecular.[3b] A global tendency to favour the more thermodynamically stable *trans* isomer is nevertheless generally observed.[63] For instance, the benchmark reaction of ethyl diazoacetate **3** with styrene **53** predominantly gives the *trans*-cyclopropane **54a**, (*cis*/*trans* = 1:1.6 with rhodium acetate as the catalyst).[64] The proposed

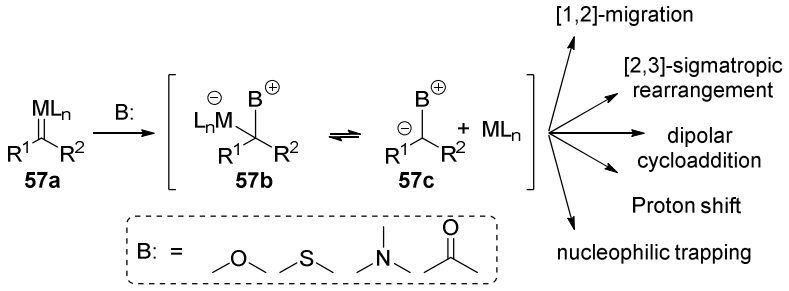
mechanisms for metallocarbene cyclopropanation reactions usually involve an asynchronous, concerted carbene transfer to the olefin substrate featuring a build-up of positive charge on one olefinic carbon.[65] The mechanism proposed by Doyle for the rhodium catalysed reaction of EDA **2** with styrene **53** is a representative example.[64] It features the approach of the electrophilic metallocarbene **55** onto the olefin **53**, that orientates the bulkier phenyl group away from the "wall" formed by the metal ligand (see the structure of $Rh_2(OAc)_4$ **6a** in **Figure I-7**) to give two transition states **56b** and **56c** (**Scheme I-12**). Steric interactions between the ester carbonyl and the phenyl group additionally favour the transition state **56b**, that also features stabilisation of the partial positive charge on **53** by the ester carbonyl.



Scheme I-12: rhodium(II) catalysed cyclopropanation using EDA and styrene

II.5. Ylide formation

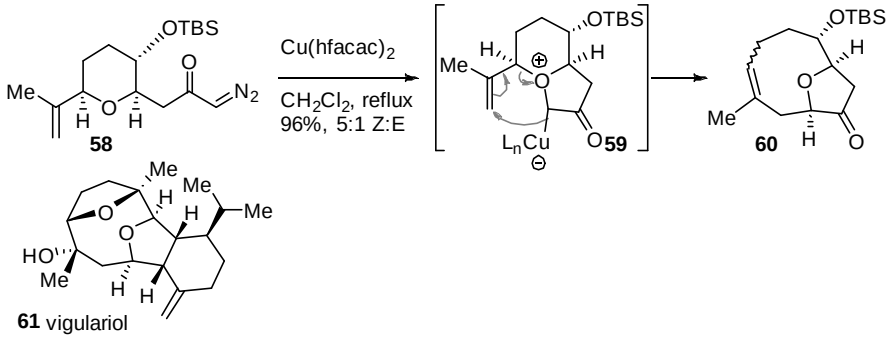
Metallocarbenes generated from diazocarbonyl compounds generally possess a strong electrophilic character that allow them to react readily with various Lewis bases (chiefly ethers,[7] thioethers, tertiary amines and carbonyl compounds[66], **Scheme I-13**) to generate ylide species.[3b,c,8]



Scheme I-13: ylide formation from metallocarbenes

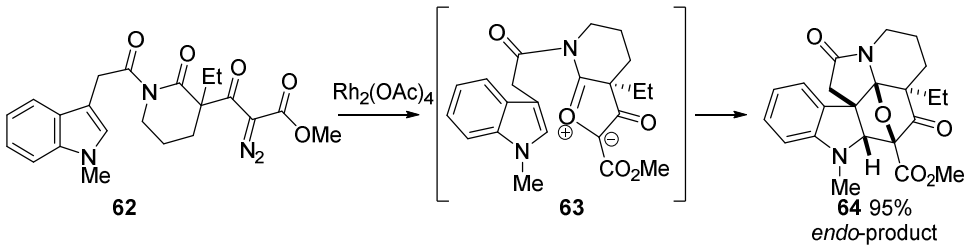
With the exception of some sulfur ylides that can be isolated, these zwitterionic species are generally very reactive and undergo further intra- or intermolecular transformations. These processes include [2,3]-sigmatropic rearrangements (from allyl-substituted oxonium, sulfur and nitrogen ylides), [1,2]-shifts (typically with oxonium, sulfur and nitrogen ylides, also referred to as Stevens rearrangements), proton shifts and dipolar cycloadditions (typically from carbonyl ylides). Ylides formed from metallocarbenes can react as metal-bound ylide **57b** or as metal-free ylide **57c** *via* an initial metal-carbon bond cleavage. This last possibility can critically limit the efficiency of asymmetric induction using homochiral metal complexes.[67]

Several applications of metallocarbene-derived ylide reactions to the synthesis of complexes products have been reported. This reactivity indeed allows the rapid elaboration of complex structures through multiple C-C bonds formation and skeletal rearrangement. Clark and co-workers for instance developed an ylide-based approach to the macrocylic core of vigulariol **61** (**Scheme I-14**). Treatment of diazoketone **58** with $Cu(hfacac)_2$ led to the formation of ylide **59** that underwent a ring extension to **60** by a [2,3]-sigmatropic rearrangement.[68]



Scheme I-14: ylide-based approach to vigulariol

The group of Padwa has contributed greatly to the development of cascade processes initiated by metallocarbene reactions, in particular processes involving initial formation of carbonyl ylides.[5] One breathtaking example is certainly the approach to the Aspidosperma alkaloids pentacyclic core (as in **64**, **Scheme I-15**) developed by Padwa and co-workers. Product **64** is formed by treatment of diazo compound **62** with rhodium(II) acetate dimer that initiates a metallocarbene formation/carbonyl ylide formation/intramolecular [3+2]-cycloaddition sequence setting 4 carbon centres in the process.[69]



Scheme I-15: cascade processes for the construction of aspidosperma alkaloids' pentacyclic core

III. Conclusion

This Chapter presents the main aspects of the chemistry associated with diazo compounds, from their synthesis to their metal catalysed transformations involving metallocarbene intermediates. This introduction provides an overview of the diversity of processes associated with these versatile substrates, which widespread use is still hampered by their limited availability and the risks associated with their preparation and handling. The development of new protocols for the preparation of diazo compounds to address some of these limitations is described in **Chapters II** and **III**. In the remaining **Chapters IV-VI**, the development of methodologies based on metal catalysed insertion reactions of diazo compounds involving reactive metallocarbenes intermediates, introduced in this Chapter, will be discussed.

Chapter II - A new reagent for the oxidation of hydrazones to diazo compounds

"*Un optimiste est un homme qui plante deux glands et qui part s'acheter un hamac*." [an optimist is a man who plants two acorns and goes buy himself a hammock] **Pierre Dac**

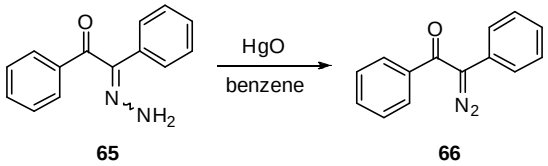
I. Introduction

At the outset of this project, the objective was to develop a method for the preparation of diazo compounds that was to obey the following specifications: atom economy, user-friendliness (limitation in the use of hazardous reagents), ease of application and transferability to a flow environment. Amongst the established routes to diazo compounds presented in **Chapter I**, the dehydrogenation of unsubstituted hydrazones route clearly presents the highest potential for atom economy, the mass difference between the product and the starting material being only 2 ua. Moreover, the hydrazone itself can be generated from the corresponding ketone through condensation with hydrazine, a process that produces water as the single by-product. The oxidation of hydrazones was therefore chosen as the field of study for the present research endeavour.

This Chapter starts with a review of the pre-existing methods for the oxidation of hydrazones to diazo compounds. A progression towards the discovery of a new reagent for this transformation follows. Finally, the synthesis of various hydrazone precursors and their oxidation under the set of conditions previously discovered are discussed.

II. The oxidation of hydrazones to diazo compounds

The preparation of a diazo compound by the dehydrogenation of the corresponding hydrazone is a transformation now more than 125 years old, and has featured amongst the early routes for the preparation of diazo compounds.[10] In 1889, Theodor Curtius reported the preparation of azibenzil **66** by the oxidation of benzil monohydrazone **65** with mercury(II) oxide (**Scheme II-1**).[70] The following Section gives an overview of the wealth of procedures described for this reaction, organised according to the nature of the oxidant.

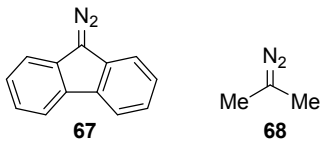


65 **66**

Scheme II-1: preparation of azibenzil by Curtius

II.1.1. Metal-based oxidants

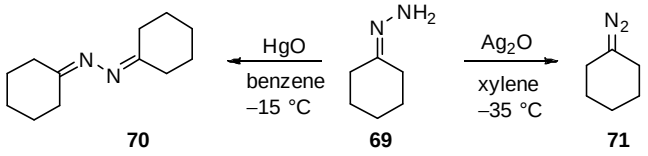
Mercury(II) oxide was used almost exclusively until the second half of the twentieth century before being replaced by silver(I) oxide and manganese(IV) oxide. The use of mercury(II) oxide nevertheless allows the preparation of a diversity of diazo compounds, ranging from 9-diazofluorene[71] **67** to the reactive diazopropane **68** (**Figure II-1**).[72]



67 **68**

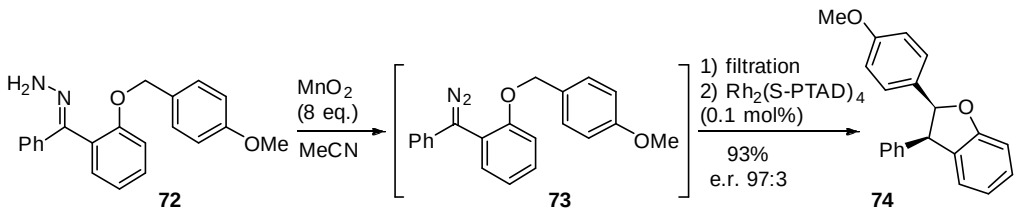
Figure II-1: diazo compounds obtained by oxidation using mercury(II) oxide

The use of silver(I) oxide leads to increased reaction rates in comparison with mercury oxide, an advantage that can be decisive in the synthesis of unstable diazo compounds such as diazocyclohexane **71** (**Scheme II-2**). Reaction of cyclohexanone hydrazone **69** with mercury(II) oxide was found to give azine **70**, a known decomposition product of diazocyclohexane **71**.[73]



Scheme II-2: oxidation of cyclohexanone hydrazone

Manganese(IV) oxide has been more broadly used than mercury(II) and silver(I) oxide after its reactivity for the oxidation of hydrazones was established.[74] It remains today the reagent of choice for this transformation, as illustrated by several recent applications,[75] such as the preparation of benzodihydrofurans (as **74**) by an oxidation/enantioselective C-H insertion reported by Shaw and co-workers (**Scheme II-3**).[76]



Scheme II-3: preparation of benzodihydrofurans by an oxidation/enantioselective C-H insertion sequence

Manganese(IV) oxide is best used freshly prepared as its active form (from potassium permanganate and a manganese(II) salt) and a large excess of reagent is commonly required. Alumina supported potassium

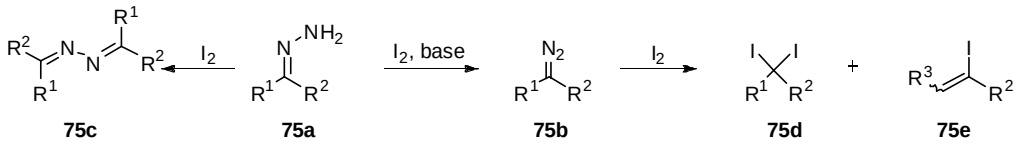
permanganate has also been described for the oxidation of a small number of hydrazones.[77]

Lead(IV) acetate,[10] nickel(II) peroxide[78] and chromium(IV) oxide (Magtrieve™)[79] have also been used in isolated cases but do not present any clear advantages over the aforementioned methods.

Methods based on copper(I),[80] copper(II)[81] and cobalt(II)[82] catalysts, using oxygen as the final oxidant, have been sparingly reported for the oxidation of hydrazones to diazo compounds. These catalytic systems are nevertheless limited by the fact that copper(I), copper(II) and cobalt(II) are also known to catalyse the decomposition of diazo compounds (**Chapter I**).

II.1.2. Iodine based oxidants

Molecular iodine is known to be active in the oxidation of hydrazones, as noted by Barton and co-workers,[83] but usually leads to various products by degradation of the diazo compound.[84] For instance, diphenyl diazomethane (**75b**, R^1 = R^2 = Ph) can be obtained from the corresponding hydrazone **75a** when a base (i.e. triethylamine) is used; whereas the corresponding azine **75c** is obtained without the use of a base. However, a number of hydrazones **75a** were found to yield vinyl iodide **75e** (from ketone hydrazone) or gem-diiodide **75d** (from aldehyde hydrazone, R^1 = H) under the triethylamine/iodine conditions (**Scheme II-4**).

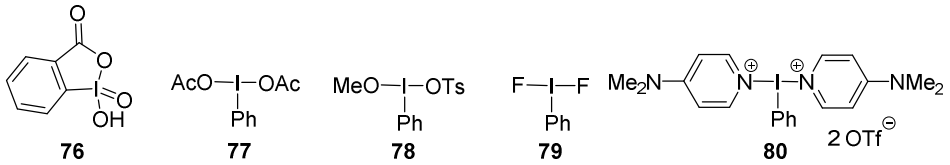


75c **75a** **75b** **75d** **75e**

Scheme II-4: iodine mediated oxidation of hydrazones

A method for the synthesis of aryldiazomethane derivatives from their corresponding hydrazones has also been described, using iodine as catalyst, tetramethylguanidine, and a peracid as the final oxidant.[85]

Hypervalent iodine compounds in the oxidation state I(V) and I(III) have been used in the oxidation of hydrazone. Periodinane *o*-iodoxybenzoic acid (IBX) **76** (**Figure II-2**) is for instance reported to convert hydrazones to their corresponding azines, except in the case of benzil monohydrazone **65**, that was converted to azibenzil **66** in quantitative yield.[86] Various iodine(III) species have been reported to react with hydrazones and the outcome is strongly dependent on the conditions used and the nature of the substituents of the trivalent iodine. For instance, [methoxy(tosyloxy)iodo]benzene (MTIB) **78** and (diacetoxyiodo)benzene (DAIB) **77** give tosylates and acetates, presumably *via* the acid promoted decomposition of the corresponding diazo compound.[87] On the other hand, when DAIB **77** is used in presence of a base such as cyclohexylamine,[88] or when bis(pyridinium)iodobenzene ditriflate **80** is used, the isolation of the diazo compound is possible.[89] Myers and co-workers also reported an esterification protocol based on the use of (difluoroiodo)benzene **79** with *N*-TBS protected hydrazones;[90] a protocol that was later modified to allow the isolation of reactive diazo compounds.[91]

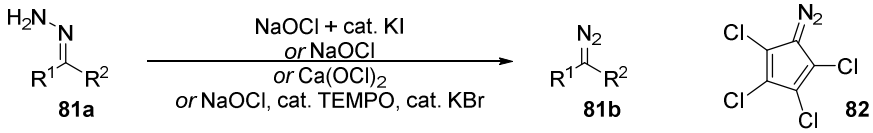


76 **77** **78** **79** **80**

Figure II-2: hypervalent iodine reagents applied to the oxidation of hydrazones

II.1.3. Other methods

A small collection of methods based on hypochloride salts as stoichiometric oxidants has been described (**Scheme II-5**). The biphasic oxidation of benzophenone hydrazones derivatives with sodium hypochlorite, in the presence of an iodide salt, is the object of a patent.[92] Similarly, tetrachlorocyclopentadienone hydrazone was oxidised to the corresponding diazo compound **82** using a sodium hypochlorite solution, this time without the addition of an iodide salt.[93] Calcium hypochlorite in methanol has also been used effectively by Danishefsky and co-workers in the oxidation of a limited number of hydrazones.[74] More recently, a method involving sodium hypochlorite, sub-stoichiometric amounts of TEMPO and of bromide salts has also been reported.[94]



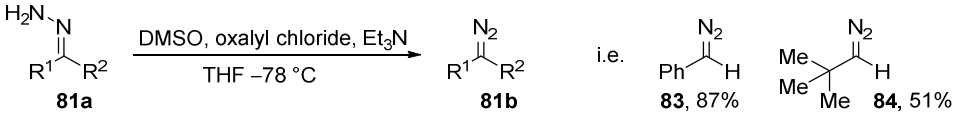
81a **81b** **82**

Scheme II-5: hypochloride mediated hydrazone oxidations

Other methods not corresponding to any of the categories above are also known. Some of these are anecdotal, such as the use of triphenylbismuth carbonate,[95] *N,N*-bis(trifluoromethyl)amine oxyl[96] or the electrolytic oxidation of hydrazone in methanol in the presence of potassium iodide (used for the preparation of azibenzil **2**).[97] The oxidation of hydrazones

directly under a atmosphere of oxygen can be achieved by prior deprotonation to the hydrazone anions with a strong base such as methyl lithium,[98] sodium[99] and sodium ethoxide (used for diazofluorene **67**).[100]

An interesting and relatively recent development is the application of Swern conditions to the oxidation of hydrazone, that allows the preparation of reactive diazo compounds such as phenyldiazomethane **83** or *t*-butyldiazomethane **84** (**Scheme II-6**).[91,101]



81a **81b** **83**, 87% **84**, 51%

Scheme II-6: hydrazones oxidation under Swern conditions

III. Development of a new reagent for the oxidation of hydrazones to diazo compounds

III.1. Screening of oxidation conditions.

With in mind the objectives expressed previously in **Section I** of this Chapter, a screening of oxidation conditions was carried out using hydrazones **65**, **85** and **86** (**Table II-1**). In particular, the acid and thermal sensitivity of diphenyldiazomethane **87** are more pronounced than that of diazocarbonyl compounds such as azibenzil **66** or of diazoketone **36**; it was therefore predicted that an oxidation method successfully applied to hydrazone **85** would be applicable to **65** or **86**. The screening results are summarised in **Table II-1**.

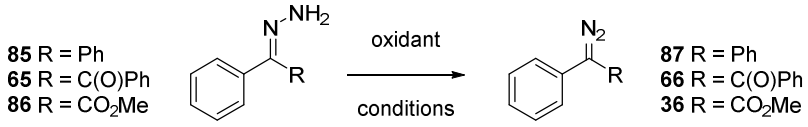


Table II-1: screening of oxidation conditions

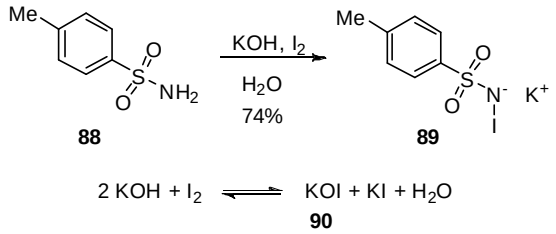
entry	R =	oxidant	conditions	yield %
1	Ph, **85**	DDQ (1.1 eq)	THF, 0 °C	30[a] **87**
2	C(O)Ph, **65**	DDQ (1.1 eq)	THF, 0 °C	93 **66**
3	C(O)Ph, **65**	mCPBA (1.05eq)	I_2 (0.02 mol%), TMG (1.1 eq),[b] CH_2Cl_2, 0 °C	62 **66**
4	CO_2Me, **86**	mCPBA (1.05eq)	I_2 (0.02 mol%),TMG (1.1 eq),[b] CH_2Cl_2, 0 °C	72 **36**
5	Ph, **85**	mCPBA (1.05eq)	I_2 (0.02 mol%),TMG (1.1 eq),[b] CH_2Cl_2, 0 °C	(78)[c] 53 **87**
6	Ph, **85**	mCPBA (1.3 eq)	I_2 (0.02 mol%),TMG (2 eq),[b] CH_2Cl_2, –40 °C	(90)[c] **87**
7	Ph, **85**	CH_3CO_3H (1.3 eq)	I_2 (0.02 mol%),TMG (5 eq),[b] CH_2Cl_2, 0 °C	56 **87**
8	CO_2Me, **86**	CH_3CO_3H (1.3 eq)	I_2 (0.02 mol%),TMG (5 eq),[b] CH_2Cl_2, 0 °C	89 **36**
9	Ph, **85**	DAIB (1.1 eq)	TMG (2.3 eq),[b] CH_2Cl_2, 0 °C	60[d] **87**
10	Ph, **85**	PIFA (1.1 eq)	TMG (2.3 eq),[b] CH_2Cl_2, 0 °C	80[d] **87**
11	Ph, **85**	PS-DAIB[e] (1.1 eq)	TMG (2.3 eq),[b] CH_2Cl_2, 0 °C to reflux	0[f] **87**
12	Ph, **85**	NIS (1.1 eq)	TMG (1.1 eq),[b] CH_2Cl_2, –78 °C	(71)[c,g] **87**
13	Ph, **85**	NIS (1.1 eq)	Et_3N (1.1 eq), CH_2Cl_2, –78 °C	(81)[c,g] **87**

[a] contaminated with DDQ-by-products; [b] TMG = 1,1,3,3-tetramethylguanidine; [c] yield in brackets based on ^1H NMR analysis of the crude mixture; [d] contaminated by iodobenzene; [e] PS-DAIB = polystryrene supported (diacetoxyiodo)benzyl; [f] no reaction observed; [g] the corresponding azine was obtained in mixture, accounting for the remaining mass balance.

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was first investigated. This reagent is a versatile oxidant and is typically used in stoichiometric amount, although some catalytic DDQ-oxidation methods have been recently reported.[102] Application of this reagent gave an excellent yield of diazo compound **66**, but failed to give clean conversion of hydrazone **85** to diphenyldiazomethane **87** (entries 1-2). The method developed by Wilson and co-workers advocates the use of peracid (such as mCPBA) in the presence of catalytic iodine and an excess of base, preferably guanidine base TMG.[85] An interesting feature of this protocol

is the extremely low iodine loading, as low as 0.02 mol%, which is nevertheless essential for the process. This method gave moderate to good conversions of hydrazones **85**, **65**, and **86** to the corresponding diazo compounds (**87**, **66** and **36**) under the reported conditions (entries 3-5). The lowering of the temperature to –40 °C and the use of an increased excess of base allowed some improvement in the conversion of **85** to **87** (entry 6). The replacement of mCPBA by peracetic acid nevertheless led to a decrease in the isolated yield of diazo compound **87** (entry 7), while methyl phenyldiazoacetate **36** was obtained in good yield (entry 8). Hypervalent iodine compounds DAIB **77** and its trifluorinated analogue [bis(trifluoroacetoxy)iodo]benzene (PIFA), in presence of a base, gave good conversion of hydrazone **85** to diazo compound **87** (entries 9-10). Unfortunately, the production of iodobenzene as a by-product severely complicated the isolation of **87**. To circumvent this issue, the commercially available polymer-supported DAIB (PS-DAIB) was used (entry 11). Disappointingly, no reaction occurred when this reagent was used under the previously applied conditions. Interestingly, a classical iodination reagent such as *N*-iodosuccinimide (NIS), in association with an equivalent of base, was found to promote the reaction (entries 12-13). The best results were obtained by lowering the reaction temperature to −78 °C and by using triethylamine as a base, giving full conversion of hydrazone **85** to a mixture of diazo compound **87** and the corresponding azine.

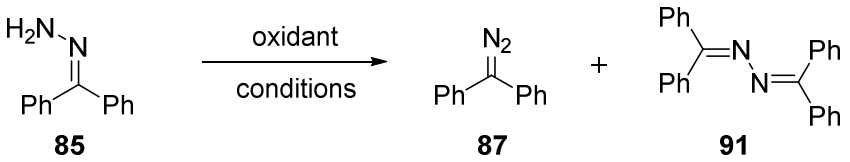
Based on the last results obtained with iodine-based reagents, the use of the relatively exotic *p*-toluene *N*-iodosulfonamide potassium salt **89** (iodamine-T, TsNIK) was investigated (**Scheme II-7**).



Scheme II-7: preparation of iodamine-T

The potassium salt **89** was first reported[103] in 1923 and has since scarcely been used as a reagent in organic synthesis,[104] while it has found some use as a oxidometric titrant.[105] Following the original procedure, the preparation of **89** from the inexpensive *p*-toluenesulfonamide **88** was carried out on multigram scale (**Scheme II-7**). Although the mechanism of this transformation has not been investigated, it likely involves potassium hypoiodite **90**, product of the disproportionation of iodine in alkaline media. In fact, iodamine-T **89** can be regarded as a stable organic equivalent to hypoiodite **90**, that readily decomposes in solution.[106] Potassium salt **89** is air stable and can be stored in a sealed vessel at room temperature for several months without appreciable decomposition. Although it slowly decomposes in neutral solution with production of iodine and precipitation of the sulfonamide **88**, its stability increases in alkaline solutions. The formation of hydrates of **89** was not observed, and it was additionally found to be stable at temperatures up to 220 °C, the temperature at which sudden decomposition with iodine release was observed.

The results obtained in the oxidation of benzophenone hydrazone **85** using iodamine-T **89** are summarised in **Table II-2**.



85 **87** **91**

Table II-2: oxidation conditions using iodamine-T

entry	conditions	results %[a]		
		87	**91**	**85**
1	TsNIK **89** (1.1 eq), MeOH/H_2O (49:1)	27		53
2	TsNIK **89** (1.1 eq), THF/H_2O (23:2)	84	3	nd[b]
3	TsNIK **89** (1.1 eq), THF/KOH (1M) (4:1)	**94**	**nd**	**4**
4	TsNIK **89** (1.05 eq), dry THF, 18-crown-6 (0.1 eq)	90	2	6
5	TsNIK **89** (1.1 eq), dry DMF	88	nd	11
6	Aqueous "KOI"[c] H_2O/Et_2O	79	nd	20
7	TsNClNa (1.1 eq), dry THF, 18-crown-6 (0.1 eq)	25	38	35
8	TsNClNa (1.1 eq), dry DMF	21	4	74
9	TsNClK (1.1 eq), dry DMF	<2	nd	>98

[a] yields based on ^1H NMR analysis of the product mixture; [b] nd = not detected; [c] freshly made by the addition of iodine to a solution of potassium hydroxide (20 eq KOI).

While the use of aqueous methanol as solvent gave a sluggish reaction, likely due to reaction of **89** with methanol (entry 1), the use of a mixture of THF and water led to efficient conversion of **85** to diphenyldiazomethane **87** (entry 2). The use of a mixture of THF and aqueous potassium hydroxide (1M) was found to be optimal and gave the desired product **87** in good purity (entry 3). The reaction was also successful under dry conditions in DMF or in THF (entries 4-5). The addition of 18-crown-6 to promote dissolution of **89** was necessary in the latter case. Interestingly, treatment of an ethereal solution of benzophenone hydrazone **85** with a large excess of freshly prepared aqueous potassium hypoiodite **90** solution gave a 20% conversion to

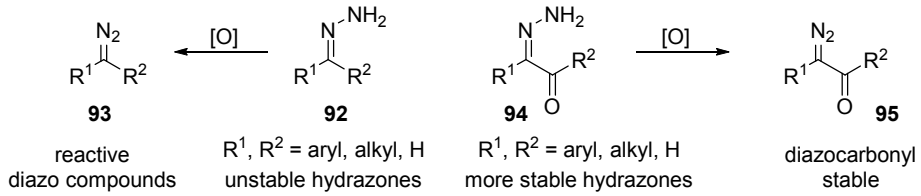
diphenyldiazomethane **87** (entry 6). This result shows that potassium hypoiodite, despite its marked instability, is an active species in this oxidation. In comparison with iodamine-T **89**, chloramine-T (TsNClNa, used in its trihydrate form), gave sluggish reaction characterised by low conversion of **85** to diazo compound **87** (entries 7-8). Similar results were obtained when the potassium salt of chloramine-T (TsNClK)[107] was used (entry 9). An interesting feature of this protocol is the facile isolation of the final product. Indeed, potassium iodide and sulfonamide **88** are the sole by-products in this process and are readily removed by washing with aqueous potassium hydroxide (1M). Interestingly, the sulfonamide **88** can be extracted from the aqueous phase after reaction by an acidification/extraction sequence and can therefore, in principle, be recycled.

Encouraged by the results obtained using iodamine-T **89**, a series of hydrazones were prepared to investigate the scope of the oxidation of hydrazones to diazo compounds using this reagent.

III.2. Synthesis of hydrazones as precursors to diazo compounds

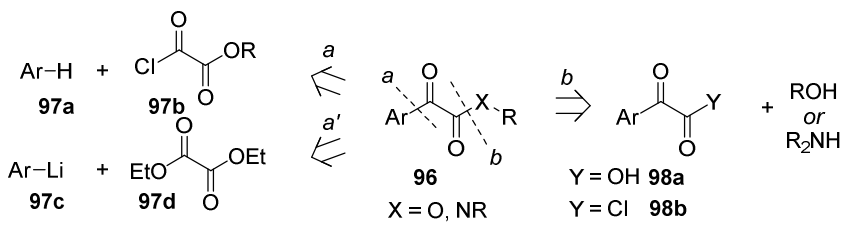
Unsubstituted hydrazones are classically prepared from the corresponding carbonyl compound (ketone or aldehyde) by condensation with hydrazine, hydrazine hydrate or a hydrazine salt. The stability of the corresponding hydrazone is nevertheless dependent on the nature of the carbonyl compound (**Scheme II-8**). Hydrazones **92** derived from simple ketones and aldehydes can be notoriously challenging to prepare and are

often unstable, readily decomposing to give the corresponding azine, amongst other products.[108] On the other hand, hydrazones **94** derived from α-ketocarbonyl compounds have been found to possess an improved stability profile.[109] Additionally, hydrazones derived from α-ketocarbonyl compounds would give access to diazocarbonyl compounds **95** by oxidation, a much studied class of diazo compounds (**Chapter I**). The hydrazones prepared in this study are therefore mostly derived from α-ketocarbonyl compounds.



Scheme II-8: stability profiles of diazo compounds and their corresponding hydrazones

α-Ketoesters and α-ketoamides that were not commercially available were prepared by one of the routes presented in **Scheme II-9**. Friedel–Crafts acylation of substituted aromatics **97a** with ethyl chlorooxoacetate **97b** (**Scheme II-9**, route **a**) or acylation of a lithiated derivative **97c** with diethyl oxalate **97d** (route **a'**) give arylglyoxylate derivatives **96**. Various ester and amide derivatives were obtained by coupling reaction using the corresponding ketoacid **98a** or *via* the acyl chloride **98b**.



Scheme II-9: preparation of ketoeters and α-ketoamides

A short study of the condensation of some α-ketoester derivatives with hydrazine hydrate revealed that the addition of a stoichiometric amount of weak Brønsted acid is crucial to minimise azine and hydrazide formation, in line with the few previously reported syntheses of this type of hydrazones.[109-110] The conditions described by Ciganek (method **A**, hydrazine hydrate in acetic acid, water and methanol)[109] or the use of hydrazine hydrate and benzoic acid in THF (method **B**) were applied to a series of α-ketoesters and α-ketoamides **99a-ae** (**Table II-3**).

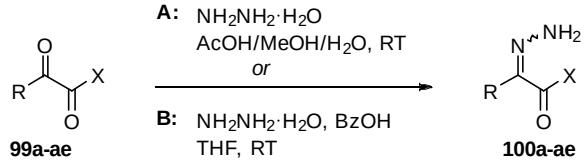
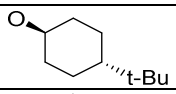
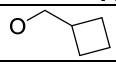
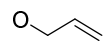
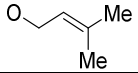
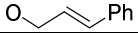
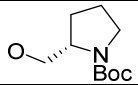
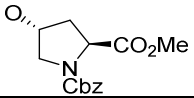
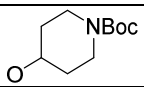
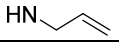
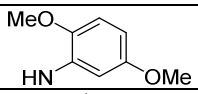
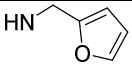
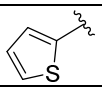
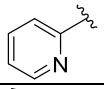
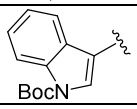
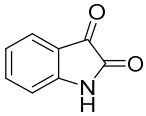
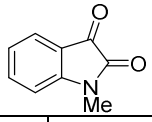
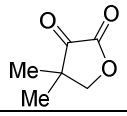


Table II-3: preparation of hydrazones

entry	R	X	N°	yield % (method)	*E/Z* ratio	N°
1	Ph	OEt	**99a**	99 (**A**) 97 (**B**)[a]	23/77 26/74	**100a**
2	Ph	O*i*-Pr	**99b**	99 (**B**)	33/67	**100b**
3	Ph	OC_4H_7	**99c**	98 (**B**)	69/31	**100c**
4	Ph	OC_5H_9	**99d**	92 (**B**)	34/62	**100d**
5	Ph	OC_6H_{11}	**99e**	98 (**A**) 99 (**B**)[a]	18/82 30/70	**100e**
6	Ph		**99f**	84 (**B**)	28:78	**100f**
7	Ph		**99g**	99 (**B**)	66/70	**100g**
8	Ph		**99h**	91 (**A**) 90 (**B**)[a]	24/76 28/72	**100h**
9	Ph		**99i**	74 (**B**)	37/63	**100i**
10	Ph		**99j**	87 (**B**)	27/73	**100j**
11	Ph		**99k**	94 (**B**)	32/68	**100k**
12	Ph		**99l**	87 (**A**)	17/83	**100l**
13	4-OMe-C_6H_4	OEt	**99m**	77 (**A**) 92 (**B**)[a]	22/78 23/77	**100m**
14	2-OMe-C_6H_4	OEt	**99n**	94 (**A**)	35/65	**100n**
15	4-Br-C_6H_4	OEt	**99o**	96 (**B**)	37/63	**100o**
16	4-Br-C_6H_4		**99p**	89 (**A**)	22/78	**100p**

entry	R	X	N°	yield % (method)	*E/Z* ratio	N°
17	Ph		**99q**	99 (**B**)	16/84	**100q**
18	Ph		**99r**	98 (**B**)	8/92	**100r**
19	Ph		**99s**	98 (**B**)	12/88	**100s**
20	Ph	NHC_6H_{11}	**99t**	91 (**B**)	12/88	**100t**
21	Ph	$N(i\text{-}Pr)_2$	**99u**	70 (**B**)[d]	E only	**100u**
22		OEt	**99v**	37 (**A**)	34/66	**100v**
23		OEt	**99w**	51 (**B**)[a]	9/91	**100w**
24		OMe	**99x**	54 (**B**)	48/52	**100x**
25			**99y**	65 (**B**)[a]	89/11	**100y**
26			**99z**	98 (**B**)[a]	85/15	**100z**
27	H	OEt	**99aa**	91 (**B**)	E only	**100aa**
28	CH_3	OEt	**99ab**	91 (**A**) 48 (**B**)[a]	100/0 93/7	**100ab**
29	iPr	OEt	**99ac**	92 (**A**) 92 (**B**)[a] 99 (**B**)[a,b]	34/62 37/63 89/11	**100ac**
30	CH_2CH_2Ph	OEt	**99ad**	99 (**A**) 98 (**B**)[a]	87/13 6/94	**100ad**
31			**99ae**	96 (**B**)[b]	88/12	**100ae**

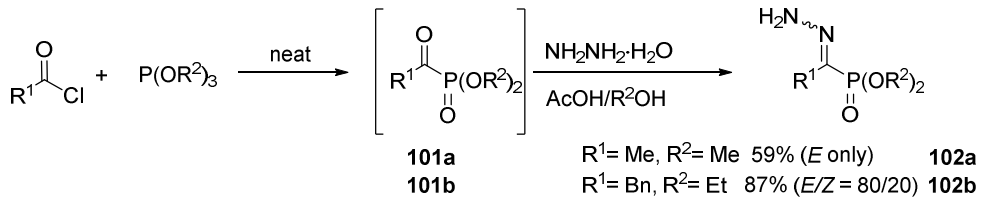
[a] hydrazone isomers were not separated; [b] hydrazine acetate was used instead of hydrazine hydrate and benzoic acid; [c] acetic acid used instead of benzoic acid; [d] reaction in THF at reflux using 1.5 eq of hydrazine hydrate

Hydrazones derived from phenylglyoxylates (**Table II-3**, entries 1-16) were obtained in high yields using either method **A** or **B**, with good tolerance for carbamate functional groups (entries 11, 12 and 16) and aryl group functionalisation (entries 13-16). For substrates containing a 2-pyridyl, a 2-thienyl or a 3-indolyl substituent (entries 22-24), the reduced reactivity of the ketone carbonyl led to the formation of hydrazone products **100v-x** in moderate yields, while the production of hydrazide through displacement of the ester alkoxy residue was

identified as a major pathway. Hydrazones **100q-t** derived from secondary ketoamides **99q-t** (entries 17 - 20) were obtained in good yields following the same method applied to the related ketoesters. On the other hand, tertiary ketoamide **99u** required high temperature and a slight excess of hydrazine hydrate to give full conversion to hydrazone **100u** (entry 21). Isatin **99y** and *N*-methyl isatin **99z** both gave the corresponding hydrazones **100y-z** in good yield using method **B** (entries 21-22). A number of hydrazones derived from alkyl ketoesters **99ab-ae** were obtained in good yield using the sets of conditions **A** or **B** (entries 28-31) as for ethyl glyoxylate **99aa**, which gave the monosubstituted hydrazone **100aa** in 91% yield (entry 27).

Most hydrazones were found as a mixture of (*E*)- and (*Z*)- isomers, in line with previous reports.[110] On the other hand, the stability of the resulting hydrazones **100a-ae** was found to be variable. Although all examples presented in **Table II-3** were stable enough to be isolated and characterised, a number of hydrazones were found to undergo slow decomposition upon storage at room temperature. For instance, while monosubstituted **100aa** showed signs of decomposition only a day after isolation, phenyl substituted hydrazone (*E*)-**100a** was stable under the same conditions over several months. All hydrazones were stable over a prolonged period of time, when stored sealed in the dark at –5 °C. Partial isomerisation between the (*E*)- and (*Z*)-isomer was observed in some cases upon storage or in solution in deuterated chloroform.

α-Ketophosphonate hydrazones **102a-b** were prepared in a similar manner (**Scheme II-10**). A Michaelis-Arbuzov reaction was used to form the corresponding α-ketophosphonates **101a-b** which were directly condensed with hydrazine hydrate in presence of acetic acid.[111]



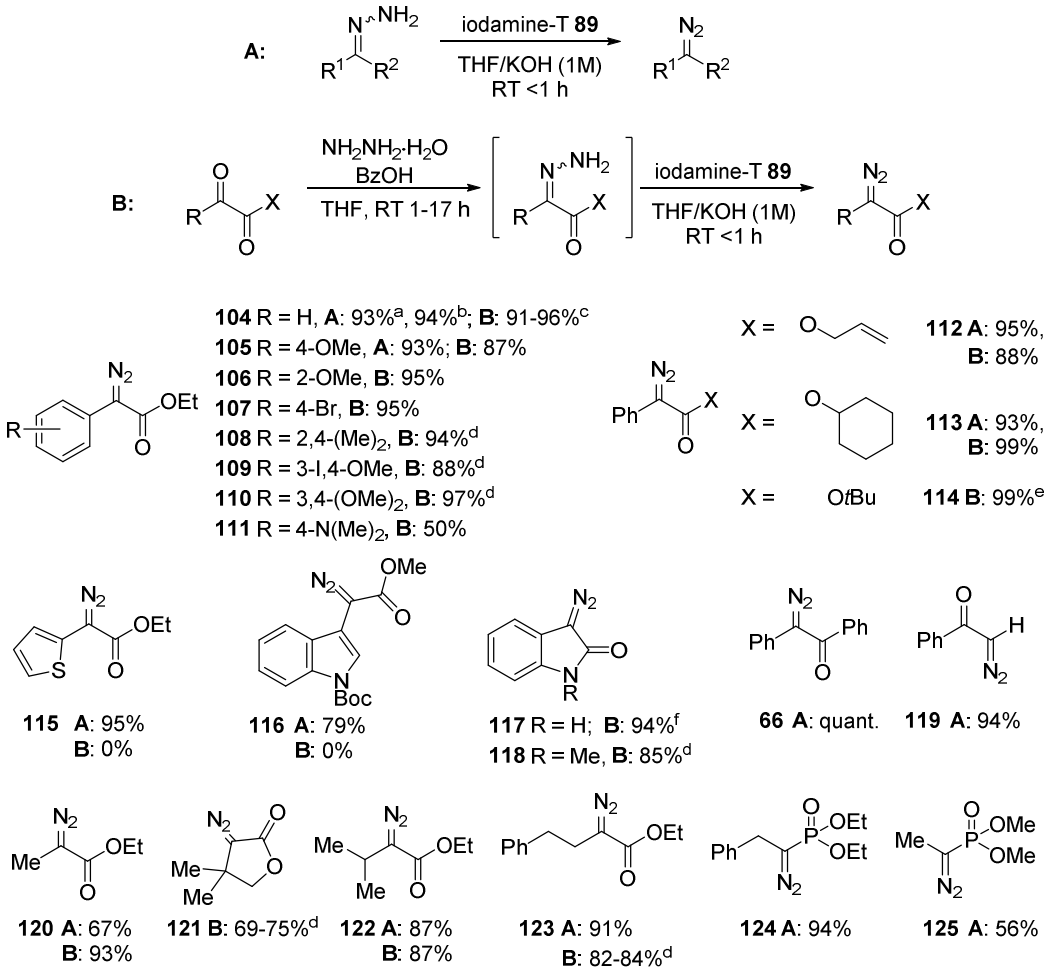
Scheme II-10: preparation of α-ketophosphonate hydrazones

Other hydrazones used were obtained following previously described methods (detail given in the **Experimental Section**). The hydrazones thus prepared were used in oxidation processes described in **Section III.3** of this Chapter or in **Chapter III.**

III.3. Hydrazone oxidations using iodamine-T

Some of the previously prepared hydrazones (**Section III.2**) were found to be readily oxidised by iodamine-T **89** using the procedure described in **Section III.1** (**Scheme II-11**, method **A**). The corresponding diazo compounds (diazoester **104-116** and **120-123**; diazoketones **66** and **119**; diazophosphonates **124-125**) were obtained through complete and fast conversion of the corresponding hydrazones. As previously noted, a simple aqueous work-up gave the diazo compounds in satisfactory purity and no further purification was required. In the case of hydrazone **100a**, it was established that both the (*E*)- or (*Z*)-isomer were oxidised to give diazo compound **104** in near quantitative yield. This observation, along with the variable stability of the hydrazone previously prepared,

motivated the development of a one-pot protocol combining hydrazone formation and iodamine-T oxidation. This was realised by carring out the reaction in THF and by adding a stoichiometric amount of aqueous potassium hydroxide after hydrazone formation to neutralise the equivalent of benzoic acid before addition of iodamine-T. This process was applied and found to be highly effective, leading to the isolation of targeted diazo compounds in good to excellent yields, while final purification by chromatography was still avoided in most cases (**Scheme II-11**, method **B**).

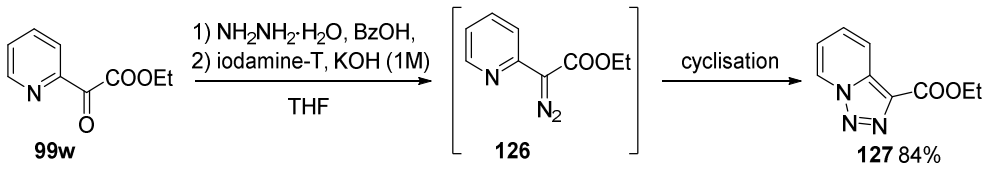


All reactions were carried out on 1 mmol scale, unless otherwise indicated; [a] from (*Z*)-hydrazone; [b] from (*E*)-hydrazone; [c] series of 6 reactions on a 10-20 mmol scale; [d] 5 mmol scale; [e] 10 mmol scale; [f] yield after purification by column chromatography.

Scheme II-11: oxidation of hydrazones using iodamine-T and one-pot process from the corresponding ketone

The one-pot protocol (**Scheme II-11**, method **B**) was found to be easily amendable to scale-up and a number of diazo compounds were prepared on a gram-scale and in high yields. This one-pot procedure was nonetheless only applicable to the ketone precursors that can be cleanly converted to the corresponding hydrazones by the method previously developed (**Table II-3**, method **B**). Thus thienylketone **99v** and indolylketone **99x**, which are converted in the corresponding hydrazone in moderate yields, gave mixtures of products containing small quantities of the desired diazo compounds, that could not be isolated.

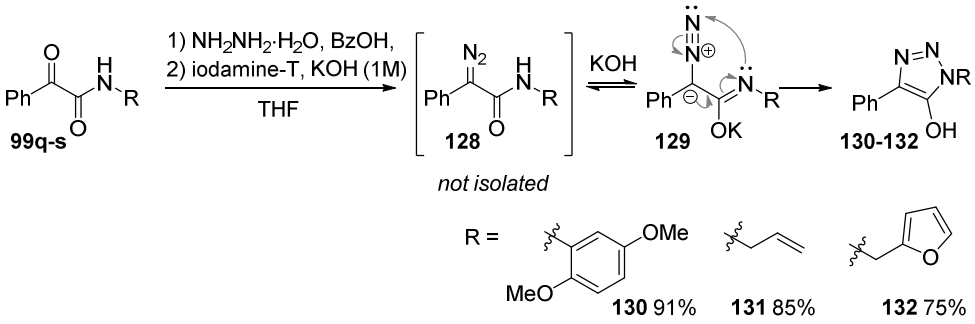
Pyridyldiazoacetate **126** could not be isolated and was found to undergo a complete cyclisation to the [1,2,3]triazolo[1,5-*a*]pyridine **127** (**Scheme II-12**). Such 1,5-cyclisations of pyridyldiazomethane derivatives have previously been described with diazo compounds obtained by the diazo transfer route.[112] In fact, it is well established that diazo compounds bearing a C=N or C=S in the α-position can readily undergo cyclisation to give 1,2,3-triazoles and 1,2,3-thiadiazoles, respectively.[10,113]



Scheme II-12: cyclisation of pyridyldiazoacetate 126

A similar cyclisation event was found to take place with the diazoamides derived from α-ketoamides **99q-s** by one-pot hydazone formation/oxidation process previously described (**Scheme II-13**). In each of these three cases, the corresponding diazoamide **128** was found to undergo a rapid cyclisation under the basic reaction conditions to give

the corresponding 1,2,3-triazol-5-ol (such as products **130-132**), presumably *via* an amidate intermediate **129**. The structure of triazole **131** was unequivocally assigned by X-ray crystallography (observed in its zwitterionic form **131b**, **Figure II-3**).



Scheme II-13: cyclisation of diazoamides to 1,2,3-triazoles

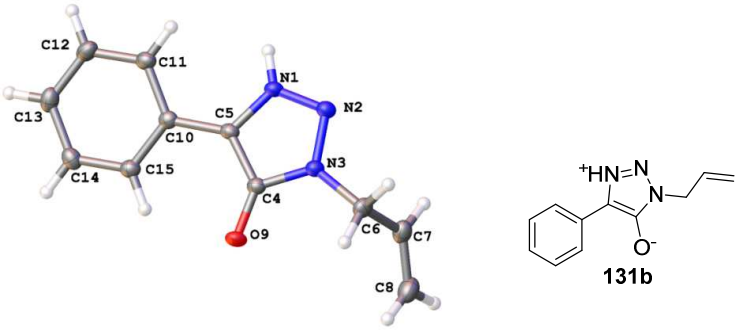
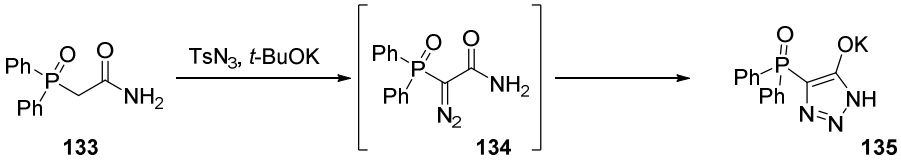


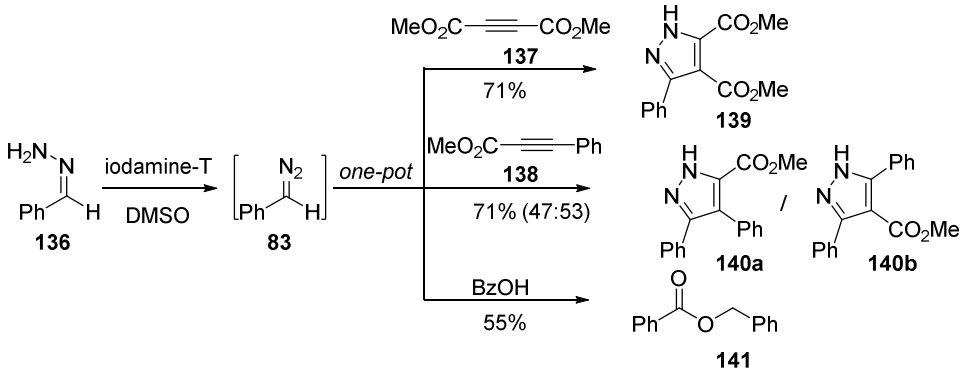
Figure II-3: Crystal structure of triazole 131b

Such diazoamide cyclisation processes have previously been observed, as illustrated by the synthesis of triazole **135** from phosphorylacetamide **133** by a diazo transfer route, reported in 1969 by Regitz and co-workers (**Scheme II-14**).[113b]



Scheme II-14: example of a diazoamide cyclisation

The preparation of unstabilised diazo compounds by iodamine-T oxidation of the corresponding hydrazones was not fully investigated. Still, promising results have been obtained with benzaldehyde hydrazone **136** (**Scheme II-15**). The corresponding diazo compound **83** was not isolated but trapped *in situ* by addition of benzoic acid to give ester **141** (in 55% yield). Alternatively, the addition of a dipolarophile such as dimethyl acetylenedicarboxylate **137** or methyl phenylpropiolate **138**, led to the isolation of pyrazoles **139** and **140a**-**b**, that both derived from a [3+2] cyloaddition/ tautomerisation sequence.



Scheme II-15: reactions of phenyldiazomethane 83

Chapter III - Generation of diazo compounds in flow

"I suppose it is tempting, if the only tool you have is a hammer, to treat everything as if it were a nail." **Abraham H. Maslow** in The Psychology of Science (1966).

I. Introduction

I.1. Chemistry in a flow environment

While the research in academic organic synthesis laboratories has classically been associated with the use of small to medium-sized batch reactors since the early days of this field, the use of continuous flow reactors has been a long time feature in the bulk chemical industry. Recent technological developments, along with the emergence of combinatorial chemistry, the incentive for process intensification and for the development of "green" processes, have all led to the development of bench-scale continuous flow apparatus and to their popularisation in the past two decades (an example of a commercial bench-scale flow unit example is depicted in **Figure III-1**).[114]

Figure III-1: bench-scale flow kit (Vapourtec™ E-series)[115]

These systems offer clear advantages in terms of their potential for automation, but they also allow a better control of the reaction parameters (such as the temperature, mixing and the stoichiometric

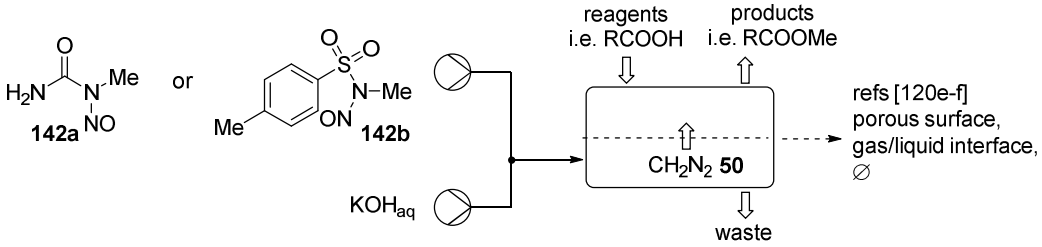
ratios), a better process reproducibility and facilitated scale-up. Through the use of bench-scale continuous flow devices, the safety aspects of a process are usually improved in comparison with a batch alternative when dealing with hazardous reagents/intermediates, highly exothermic reactions or extreme pressure/temperature conditions.[116] The past 15 years have witnessed a tremendous development in techniques and technologies for the synthesis of organic compounds in a flow environment.[117] A particularly interesting development is the application of this technology to access otherwise inaccessible reactivities, thus making the use of flow chemistry a valuable tool for the discovery of new processes.[75a,118]

I.2. Preparation of diazo compounds in flow

Given the hazards associated with their use (explosivity, toxicity), diazo compounds are particularly suitable substrates for use in continuous flow techniques. Based on these considerations, and taking into account the rich chemistry of this class of compounds (**Chapter I**), it is not surprising that the development of processes involving diazo compounds in a flow environment has accompanied the development of flow chemistry and attracted the attention of several research groups.[12]

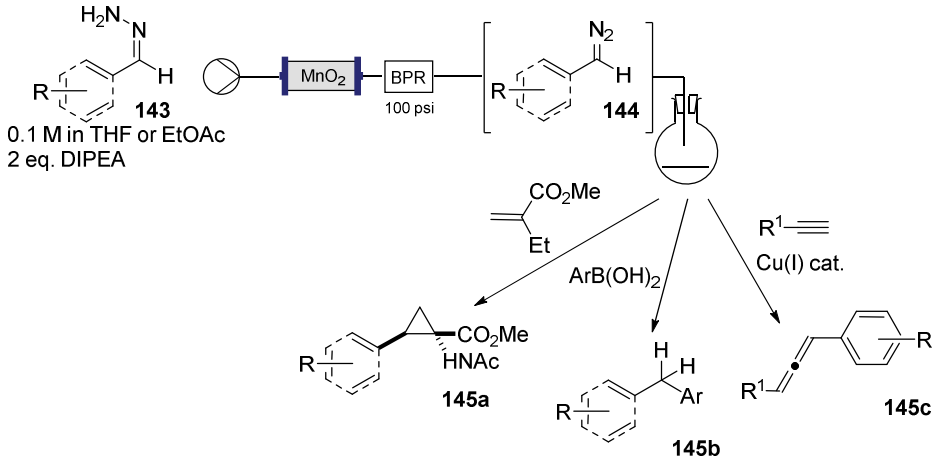
Particular efforts have been applied for the development of continuous flow processes involving diazomethane **50**, a synthetically valuable yet highly hazardous compound due its volatility, acute toxicity and explosive nature.[119] Translating the preferred route to diazomethane, the alkaline decomposition of *N*-nitroso derivatives (such as *N*-methyl-*N*-nitrosourea

142a or Diazald® **142b**), from batch conditions to a flow environment has represented the main strategy for the production of **2** in flow.[120] Amongst the protocols reported for this transformation, the use of an hydrophobic membrane[120e] and of a "tube-in-tube" strategy[120f] represent ingenious strategies to extract the gaseous diazomethane **50** from the aqueous phase in a continuous manner (**Scheme III-1**).



Scheme III-1: strategies for the generation of diazomethane in flow

Several protocols have been described for the generation of higher diazoalkanes in continuous flow. Kirschning and co-workers developed a strategy based on the decomposition of tosylhydrazones (Bamford-Stevens reaction) and applied this strategy to the metal free coupling of aryldiazo compounds with boronic acids to generate biarylmethane derivatives.[121] Simple aldehyde hydrazones **143**, inherently less stable than their tosyl-substituted counterparts, have been recently used by Ley and co-workers to generate reactive unsubstituted diazo compounds **144** by oxidation using manganese(IV) oxide (**Scheme III-2**).[75,122] A number of protocols were designed to use the diazo compounds produced this way, such as the sp^2-sp^3 coupling with arylboronic acids,[75a] cyclopropanation reactions[75b] or the preparation of allenes **145c** (**Scheme III-2**).[122]

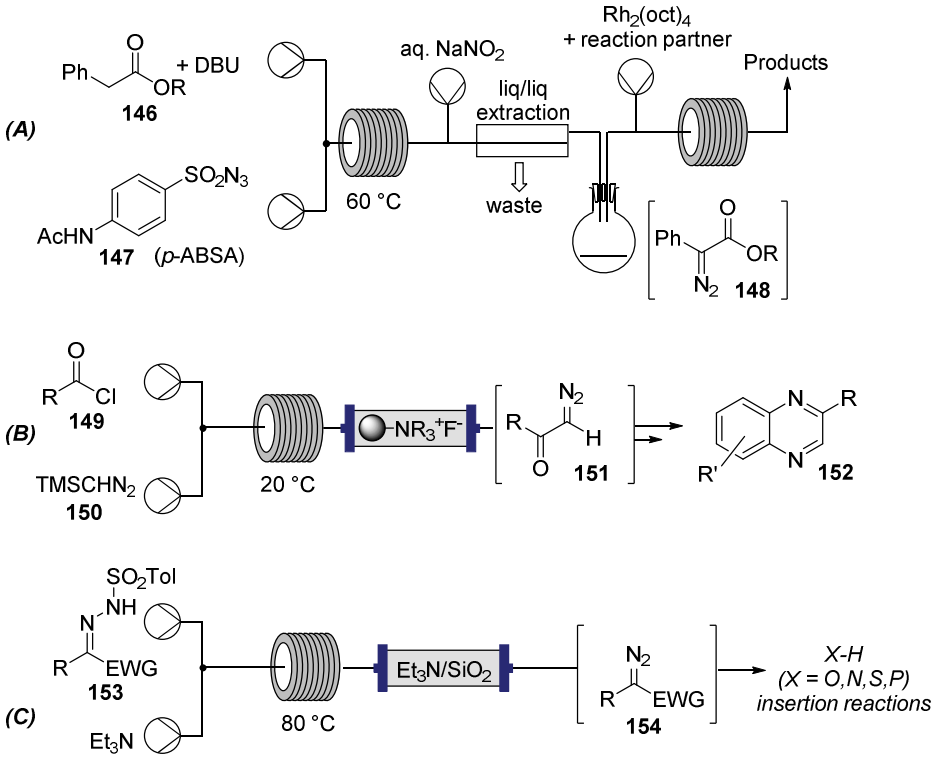


Scheme III-2: Ley's protocol for the oxidation of hydrazone in flow

Diazocarbonyl compounds, being more stable than their alkyl counterparts, are often less problematic to prepare, although still prone to exothermic decomposition.[12a] A number of protocols capitalising on the favourable safety aspects of flow chemistry for the use of diazocarbonyl compounds have been described. These transformations include enantioselective cyclopropanations,[123] ketoester synthesis,[124] fluorination,[125] alkyne synthesis[126] and photochemical benzannulation.[127]

An additional element of risk is introduced by the reagents used for the preparation of diazocarbonyl compounds. Typically, these substrates are prepared by the diazo transfer route using organic azides as the diazo transfer reagents. These can indeed present serious issues for their use on scale due to their potential toxicity and explosive behaviours.[128] Wheeler and co-worker were first to describe a flow-based diazo transfer protocol using a combination of DABCO and trisyl azide.[129] The diazo transfer approach was recently further exploited by Wirth and co-workers with the development of a flow protocol for the synthesis and in-line reaction

of phenyl diazoacetates **148** using the safer diazo transfer reaction *p*-acetamidobenzenesulfonyl azide (*p*-ABSA **147**)[130] (**Scheme III-3**, **A**).[131]



Scheme III-3: methods for the generation of diazocarbonyl compounds in flow

Other approaches for the synthesis of diazocarbonyls have been described, such as the generation of ethyl diazoacetate **2** in flow through the classical diazotisation route.[132] A report from the Ley group described the preparation of diazoketones **151** in flow from the reaction of the commercially available trimethylsilyldiazomethane **150** with acyl chlorides **9** (**Scheme III-3**, **B**).[133] In this protocol, the output containing the diazoketone **151** is directly used for further continuous flow transformations that ultimately lead to quinoxalines **152**. A method based on the thermal decomposition of tosyl hydrazone **153** (the Bamford-Stevens reaction) has also been disclosed by our group (**Scheme III-3**, **C**).

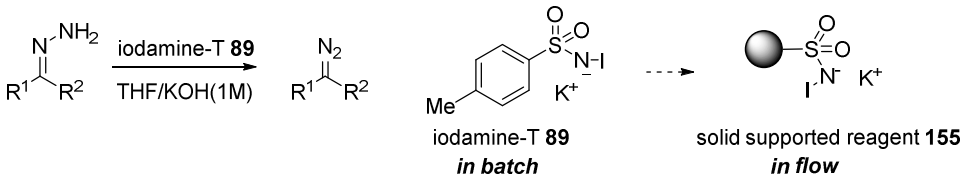
This procedure allowed the preparation of various diazoesters **154** that can be isolated or directly consumed in an in-line rhodium catalysed X-H insertion step (X = O, N, P, S).[134]

At the onset of this work, no example had been reported for the application of the oxidation of hydrazones as a route for the preparation of diazo compounds in flow. Investigations towards the development of such a protocol were therefore started.

II. Preparation of a polymer supported reagent for the oxidation of hydrazones

II.1. Introduction

Following on the development of iodamine-T **89** as a reagent for the oxidation of hydrazones to diazo compounds (**Chapter I**), the translation of the conditions previously used in batch to a flow environment was investigated. A straightforward approach would consist of preparation of a solid phase reagent **155** that could then be used to convert a solution of hydrazone flowing through it (**Scheme III-4**).

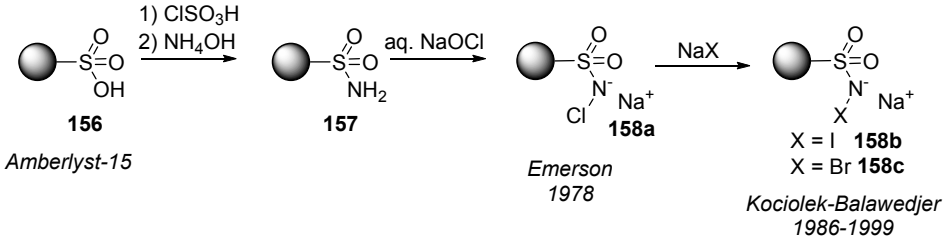


Scheme III-4: oxidation of hydrazone, from batch to flow

II.2. Preparation of a solid phase reagent

A review of the literature revealed that polymers bearing *N*-halosulfonamide moieties have previously been reported by several

groups. In 1978, Emerson and co-workers prepared the resin **158a** bearing the *N*-chlorosulfonamide functionality and applied it to water disinfection.[135] Their procedure started with commercially available Amberlyst-15® **156** (cross polymer of styrene and divinylbenzene bearing sulfonic acid groups) that was first converted to the sulfonamide-functionalised resin **157** in two steps and finally chlorinated using sodium hypochlorite (**Scheme III-5**). The resin **158a** obtained by this process possessed oxidising properties that were attributed to the presence of *N*-chlorosulfonamide functionalities. Interestingly, reduction of the *N*-chlorosulfonamide groups in resin **158a** gave the sulfonamide resin **157** back, which was then recycled.

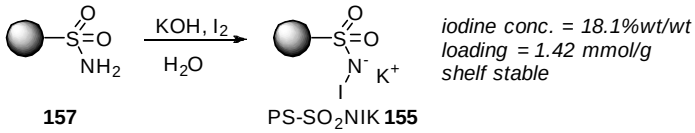


Scheme III-5: reported preparation of various *N*-halosulfonamide functionalised resins

Kociolek-Balawejder and co-workers later reported the preparation of *N*-iodo and *N*-bromosulfonamide functionalised polymers **158b**[136] and **158c**,[137] both obtained by halogen exchange reactions from Emerson's *N*-chlorosulfonamide resin **158a** (**Scheme III-5**). The use of **158b** was investigated for the oxidation of residual cyanide in aqueous solutions.[136]

Using the conditions developed by Emerson, the sulfonamide functionalised polystyrene **157** was successfully prepared from readily

available Amberlyst-15® **156**. Treatment of **157** with iodine in aqueous potassium hydroxide solution gave a material that showed oxidising properties measurable by iodometric titration (1.30-1.60 mmol/g over several samples). Elemental analysis of a sample of this resin (**155**) gave an iodine content of 19.4% that was correlated to the content calculated from the loading determined by titration (iodometric titration: 1.42 mmol/g that corresponds to a calculated 18.1% active iodine). The small difference found between these values was attributed to the presence of residual potassium iodide on the resin. The functional group modifications between resins **157** and **155** was also followed by infra-red spectroscopy through the disappearance of the strong $S(=O)_2$ stretching bands, at 1155 and 1322 cm^{-1}, present in **157** but absent in the iodinated material **155**. On the basis of these observations the resin obtained was assumed to bear *N*-iodosulfonamide residues (as depicted in **155**, **Scheme III-6**).



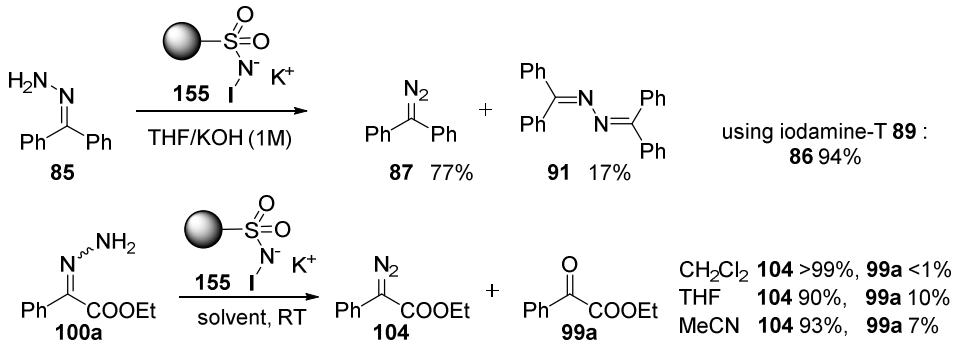
Scheme III-6: preparation of *N*-iodosulfonamide resin 155

The use of different alkali metal hydroxides in the preparation of **155** was found to give the following trend for the loading of the final resin (in mmol/g): potassium (1.42) > sodium (0.91) > lithium (0.69). The iodinated resin used for all the work in this Thesis was prepared using potassium hydroxide, as illustrated in **Scheme III-6.**

Resin **155** was found to be stable at room temperature in a sealed vessel. Storage in air led to the appearance of an orange to red colouration of the resin and to the release of small quantities of iodine in solution, which can be associated with aerobic oxidation of the residual iodide present on the resin. Contact with acid led to leaching of iodine and loss of oxidising properties.

II.3. The use of resin PS-SO_2NIK in the oxidation of hydrazones

The use of the functionalised resin **155** for the oxidation of hydrazones was investigated. Using the same conditions as the analogous iodamine-T **89** (described in **Chapter II**), the resin **155** gave results inferior to those obtained with **89** in the oxidation of benzophenone hydrazone **85**, with a more pronounced tendency for the formation of the decomposition product **91** (**Scheme III-7**). The use of other solvents led to the production of azine **91** as the major product. On the other hand, oxidation of hydrazone **100a** proceeded in high yield. A screen of alternative solvents revealed that dichloromethane gave the best results for this transformation, giving diazo compound **104** in quantitative yield after a simple filtration of the resin.



Scheme III-7: use of resin PS-SO_2NIK for the oxidation of hydrazones

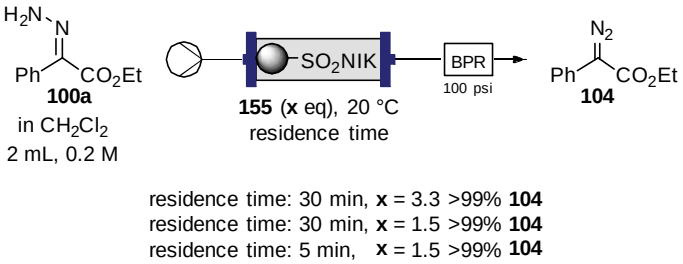
When the reaction was carried out in THF or acetonitrile, iodine leaching was observed, which is likely due to oxidation of iodide by the resin itself. The formation of ketone **99a** as by-product accompanied the production of iodine in these cases. This product was suspected to arise from the decomposition of diazo compound **104** by iodine followed by hydrolysis with residual water.[138]

III. Diazo compound generation in flow

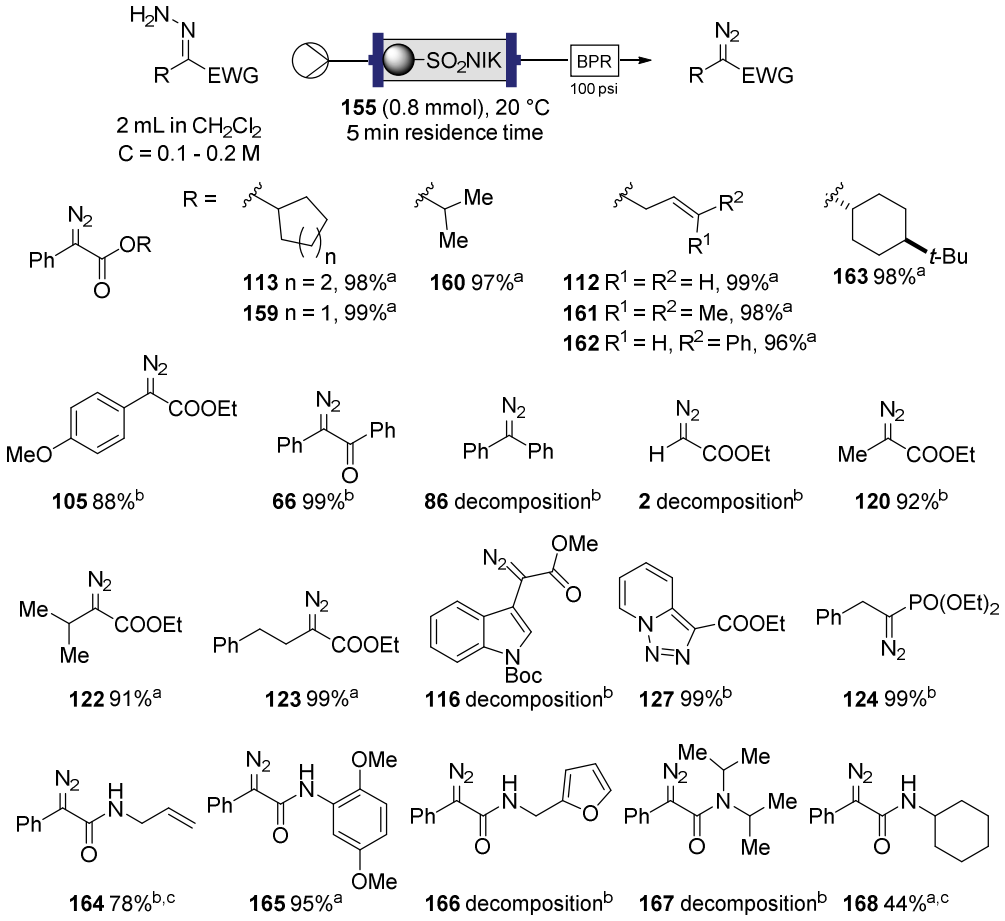
III.1. Substrate scope in the oxidation of hydrazones using the resin PS-SO_2NIK

Reactions in flow were carried out using the resin **155** packed in a reagent column that was connected to an R4/R2+ Vapourtec™ flow system (**Scheme III-8**). The hydrazone was introduced into the system as a 0.2 M solution in dichloromethane, pumped through the resin using dichloromethane as the eluent and the output solution was analysed. Reaction of hydrazone **100a** on resin **155** under these conditions was found to be relatively fast and a residence time of 5 minutes was enough to give complete conversion of hydrazone **100a** using a slight excess of resin **155** (1.5 eq, based on titration) and with no retention of material on

the resin. Importantly, the output solution contained only diazo compound **104** with no organic by-products. The potassium iodide produced during the reduction of resin **155** is retained on the solid phase.



Scheme III-8: oxidation of hydrazone 100a in flow



Yield determined by ^{1}H MNR analysis of the final product; [a] hydrazone solution C = 0.2 M; [b] hydrazone solution C = 0.1 M; [c] obtained in limited purity after attempted purification on column chromatography.

Scheme III-9: hydrazone oxidations in flow using resin PS-SO_2NIK

A number of hydrazones were used to probe the scope of this oxidation process (**Scheme III-9**). The preparation of the hydrazones used in this Section is described in **Chapter II**. The use of resin **155** in flow turned out to be ideal for the preparation of aryldiazoesters (**105**, **112**, **113** and **159**-**163**), that were obtained in near quantitative yields. Some aliphatic diazoesters (**120**-**123**), diazoketone **66** and diazophosphonate **124** were also obtained in high yields. Typically, complete conversion of the starting hydrazone was observed after a residence time of 5 minutes. The corresponding ketoester (as **99a**, **Scheme III-8**) were identified as side-products and minor components of the output solutions in a number of cases. On the other hand, a number of diazo compounds were not obtained by this method, namely ethyl diazoacetate **2**, diphenyldiazomethane **87** and indolyldiazoacetate **116**. The 1,2,3-triazolo[1,5-*a*]pyridine **127** was obtained as product of quantitative cyclisation of the corresponding diazo compound, as previously observed (**Chapter II**). The diazo compounds **164**-**168**, derived from ketoamides hydrazones **100q**-**u**, led to variable results that appeared to be highly dependent on the amide nitrogen substitution. Diazoamides **166**-**167** were not obtained by this process, while compounds **164** and **168** were obtained in limited purity after column chromatography and appeared to be relatively unstable during purification. On the other hand, electron-rich diazoamide **165** was obtained in 95% yield. Compounds **164**-**165** and **168** represent three relatively rare examples of isolation of secondary diazoamides. In fact, the preparation of this type of compound by other routes is normally hindered by the cyclisation of the diazoamide

to the corresponding 5-hydroxy 1,2,3-triazole under basic conditions (as discussed in **Chapter II**, **Section III.3**). No triazole was identified in the output solution in the preparation of **164**-**168**.

The results were not affected when the hydrazones substrate used was the (*E*)-, (*Z*)-isomer or a mixture thereof. In cases where the hydrazone formation gave near-quantitative yields of hydrazone as a mixture of isomers (**Chapter II**, **Section III.2**), the mixture of hydrazones obtained after a single aqueous work-up was used for oxidation in flow, thus avoiding one purification step. Due to the fact that the resin **155** can be used in excess without affecting the efficiency of the transformation, three oxidations were carried out in sequence on several different hydrazones using the same cartridge load of resin **155** (the initial loading was in this case tripled).

III.2. Thermal stability studies

The present process allows the preparation of notoriously reactive diazo compounds from their corresponding hydrazones (**Section III.2**). To assess the safety benefit of this method, the comparative thermal stability data of the diazo compound **104** and the corresponding hydrazone precursor **100a** have been obtained. The thermogravimetric analysis (TGA) of diazo compound **104** displays a mass loss peaking at 123 °C (**Figure III-2**) that correspond to an exothermic process, as determined by differential scanning calorimetry (DSC, **Figure III-3**). On the other hand, both hydrazones (*Z*)-**100a** and (*E*)-**100a** showed a mass loss peaking at 194 and 203 °C, respectively, which corresponded in both

cases to an endothermic process. These data unsurprisingly confirm the better safety profile of precursor hydrazones **100a** in comparison with diazo compound **104**.

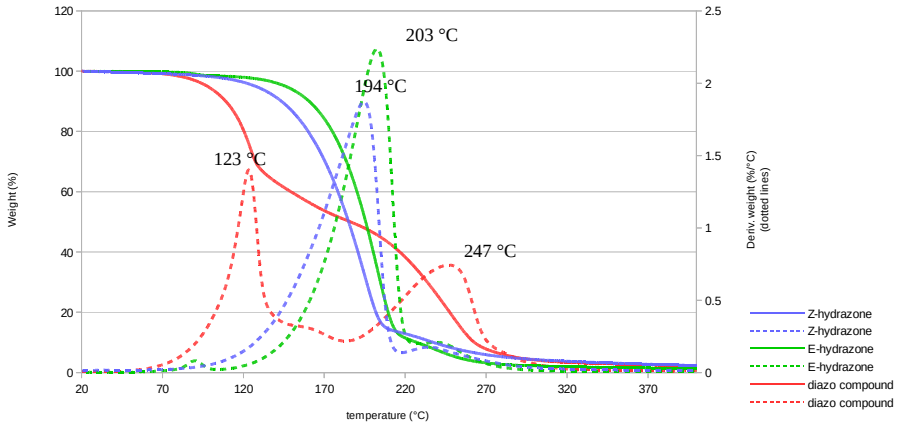


Figure III-2: TGA analysis of diazo compound 104 and hydrazones (*E*)-100a and (*Z*)-100a

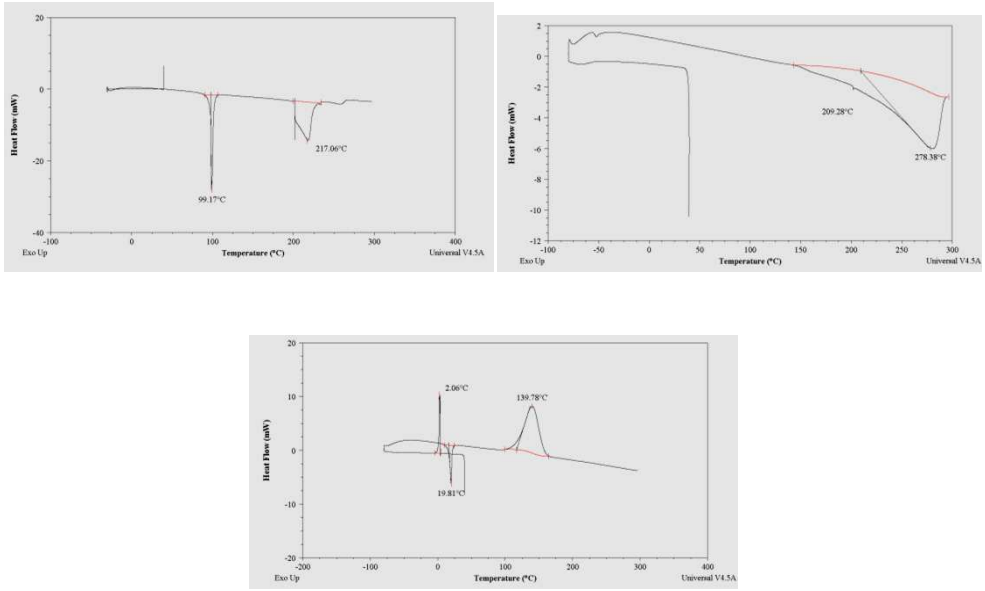
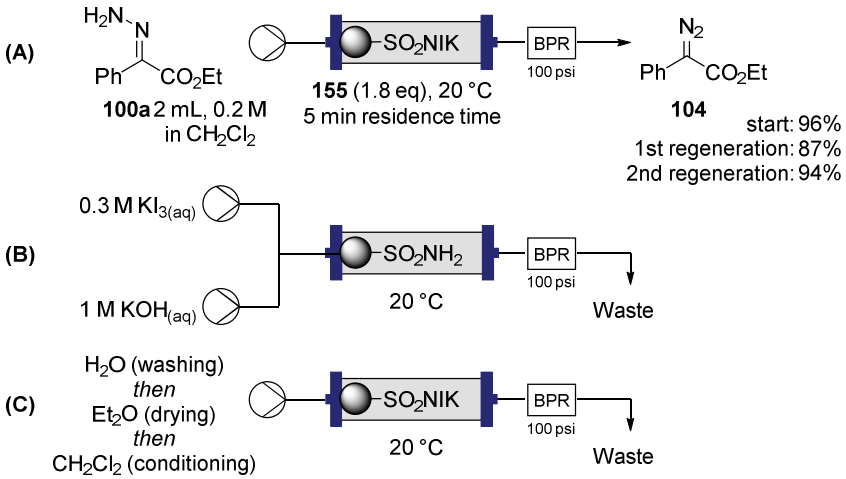


Figure III-3: DSC analysis of hydrazones (*E*)-100a (top left), hydrazone (*Z*)-100a (top right), and diazo compound 104 (bottom)

III.3. Regeneration of the resin PS-SO_2NIK

Upon reaction with a hydrazone, the functionalised resin **155** is converted back into its precursor sulfonamide functionalised resin **157**, which can therefore be recycled. This was first carried out in a batch fashion on up to 20 g of material, giving a regenerated resin **155** with only a small loss of oxidative properties. Following the loading of the resin obtained after each recycling cycle, the following values were obtained (mmol/g): 1.45 (initial loading), 1.54, 1.57, 1.33, 1.30. The small decrease in loading observed might be due to partial hydrolysis of the sulfonamide groups upon repeated regeneration.

Regeneration of the resin was also carried out in flow using a single cartridge full of resin **155** (**Scheme III-10**). The oxidation of hydrazone **100a** was first carried out giving diazo compound **104** (step **A**, 96% yield). The regeneration of the resin was then achieved by injecting an aqueous solution of potassium triiodide and an aqueous solution of potassium hydroxide, first combined in a T-piece, through the resin (step **B**). After regeneration, the resin was washed with water, dried with ether and conditioned with dichloromethane (step **C**) before being applied to the oxidation of hydrazone **100a** again. Diazo compound **104** was then obtained in 87% (after a first regeneration) and 94% (after a second regeneration). Variable yields were likely due to the presence of residual water on the resin, following incomplete drying of the resin with ether (step **C**). Other drying methods were not investigated.



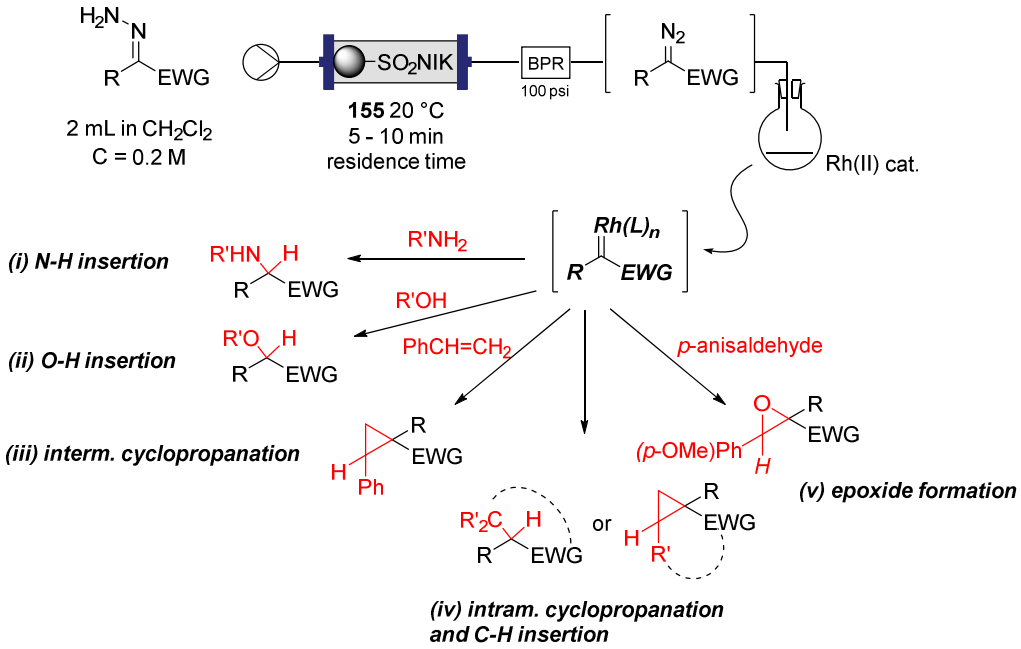
Scheme III-10: regeneration of resin 155 in flow

Transformations in continuous flow involving stoichiometric amounts of immobilised reagents are intrinsically less readily scalable than homogeneous systems.[139] The demonstrated possibility of recycling the resin under continuous flow conditions opens the possibility of a complete automation of the process, although this was not further investigated.

III.4. In-line processes using diazo compounds generated in flow

As pointed out in **Chapter I**, diazo compounds are versatile intermediates in organic synthesis. To illustrate the advantage of the hydrazone oxidation process described in **Section III.1** of this Chapter, a series of processes involving rhodium catalysed decomposition of diazo compounds were selected. These reactions were carried out by directly adding the resin output solution to an additional vessel containing a rhodium(II) dimer catalyst and the corresponding reaction partner (**Scheme III-11**). Processes involving metal catalysed decomposition of

diazo compounds classically require the slow addition of the diazo component in order to minimise the amount of carbene dimerisation products formed. In the present protocol, slow addition is an in-built feature and the addition rate is easily tuned by modifying the flow rate (and hence the residence time) of the oxidation step. The various intramolecular (C-H insertion, cyclopropanation), and intermolecular processes carried out (O-H, N-H insertion, cyclopropanation, epoxide formation) are detailed in the following Section.



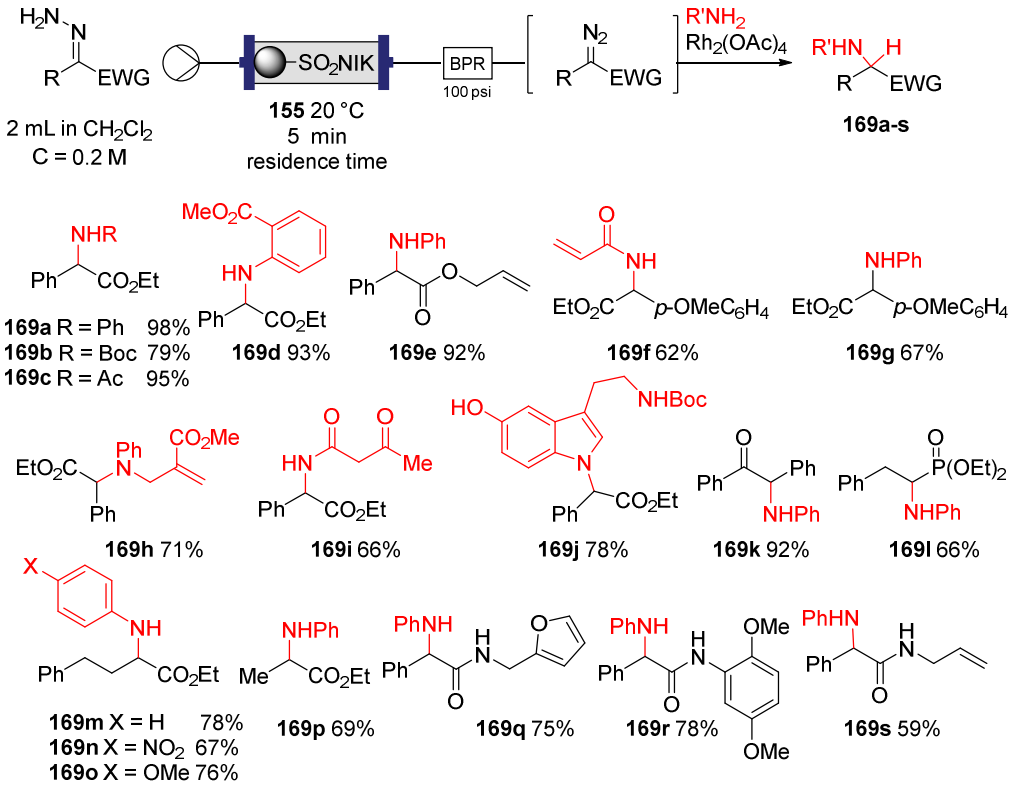
Conditions: CH_2Cl_2 as solvent (i) $Rh_2(OAc)_4$ (1 mol%), NH reagent (1.2 eq), (ii) $Rh_2(oct)_4$ (1 mol%), OH reagent (1.2 eq), (iii) $Rh_2(oct)_4$ (1 mol%), styrene (1.2 eq), (iv) $Rh_2(oct)_4$ (1 mol%,) (v) $Rh_2(oct)_4$ (1 mol%), aldehyde (1.2 eq).

Scheme III-11: in-line transformations using diazo compounds generated in flow

III.4.1. N-H Insertion reactions

N-H Insertion reactions of rhodium carbenoids with aniline, amide and carbamate derivatives are well established processes.[9] Unsurprisingly, rhodium carbenoids derived from aryldiazoacetates **104**, **112** and **105** generally gave good to excellent yields of insertion product using anilines

(**169a,d,e,g**), *t*-butyl carbamate (**169b**) and amides (**169c,f,i**) (**Scheme III-12**). A N-H insertion reaction using a functionalised secondary aniline gave **169h** in 71% yield while the use of *N*-Boc serotonin gave insertion into the indole N-H bond in 78% yield (product **169j**).



Yields based on starting hydrazone; conditions: $Rh_2(OAc)_4$ (1 mol%), NH reagent (1.2 eq) in CH_2Cl_2

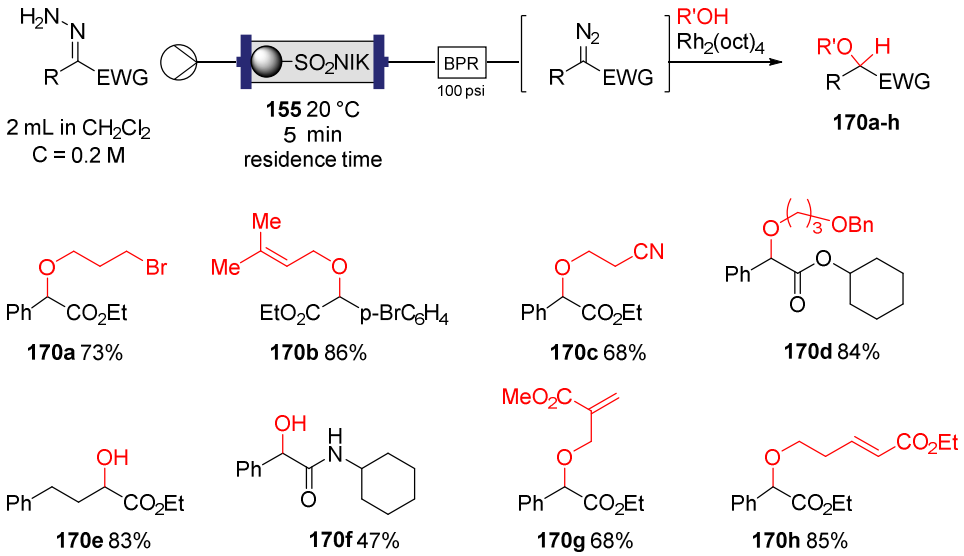
Scheme III-12: N-H insertion products

Insertion products derived from diazoketone **66** and diazophosphonate **124** with aniline were also obtained in good yields (**169k,l**). Alkyl substituted diazoacetates **120** and **123** were successfully generated in flow and used in N-H insertion reactions using various aniline derivatives to give products **169m-p**. Although diazoamides produced by oxidation of their corresponding hydrazone precursors **100q-t** proved hard to isolate in a few cases (**Section III.1** of this Chapter), their direct use in N-H

insertion reactions using aniline led to good yields of products **169q-s**. This set of results also shows the predominance of aniline N-H insertion processes over other metallocarbene transformations such as intramolecular cyclopropanation, as illustrated by products **169i** and **169s**, or such as hydride shift, as proved by the isolation of products **169m-p** in good yields.

III.4.2. O-H Insertion reactions

When the resin output solution was directed to a vessel containing rhodium(II) octanoate dimer and an alcohol, O-H insertion products were obtained (**Scheme III-13**).



Yields based on starting hydrazone; conditions: $Rh_2(oct)_4$ (1 mol%), OH reagent (1.2 eq) in CH_2Cl_2 at reflux; for **170e** and **170f**, an excess of "wet ether" was used.

Scheme III-13: O-H insertion products

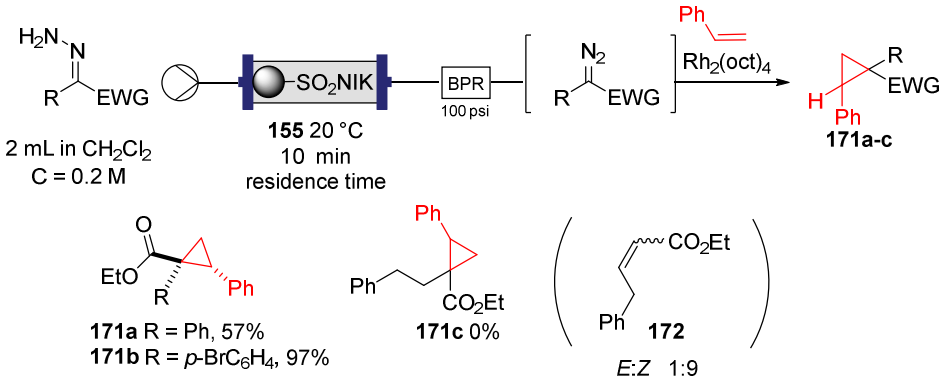
Various functionalised primary alcohols were used such as 3-bromopropanol (in **170a**), prenyl alcohol (in **170b**), 3-hydroxypropionitrile (in **170c**) and benzyloxypropanol (in **170d**). Insertion into the O-H bond of water was also successful using an excess

of "wet" ether and gave α-hydroxyester **170e** and α-hydroxyamide **170f**. As previously noted, O-H insertion occurred predominantly over cyclopropanation when alkene-tethered alcohols were used, as illustrated by the isolation of products **170b** and **170g-h** in good yields.[140]

Heteroatom alkylation reactions represent the single most important class of transformations in modern drug development programmes.[141] These transformations are classically carried out using alkyl halides as alkylating agents, which present toxicity issues and the risk of residual presence in the drug active principal ingredient. It is worth noting that N-H and O-H insertion processes using metallocarbenes represent an interesting alternative to the use of alkyl halides, as these highly reactive species do not persist in the reaction media and can be generated from diazo compounds under mild conditions.

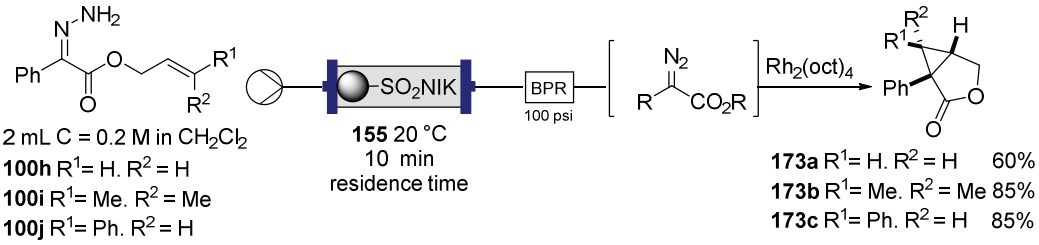
III.4.3. Cyclopropanation reactions

The reaction of rhodium-bound carbenes derived from aryldiazoacetates with olefins leads to the formation of cyclopropanes with commonly high diastereoselectivity.[65a,142] Indeed, using diazo compounds generated in flow, cyclopropanes **171a** (57% yield) and **171b** (97% yield) were both obtained as single diastereoisomers using styrene in presence of rhodium(II) octanoate (**Scheme III-14**). With alkyl diazoacetate **123** the competitive metallocarbene hydride shift process was much faster than the intermolecular cyclopropanation and the predominantly (*E*)-alkene **172** was obtained as the major product.



Yields based on starting hydrazone; conditions: $Rh_2(oct)_4$ (1 mol%), styrene (1.2 eq) in CH_2Cl_2 at reflux

Scheme III-14: styrene cyclopropanation products



Yields based on starting hydrazone; conditions: $Rh_2(oct)_4$ (1 mol%) in CH_2Cl_2 at reflux

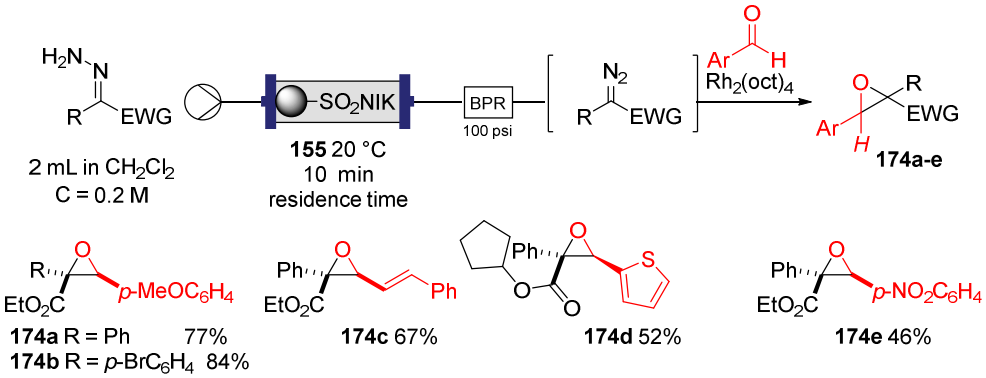
Scheme III-15: intramolecular cyclopropanation products

With suitable hydrazones bearing allylic ester moieties such as **100h-j**, intramolecular cyclopropanation of the corresponding diazo compounds by treatment with rhodium octanoate gave the bicylic compounds **173a-c** (**Scheme III-15**). Fused cyclopropanes **173a-c** were obtained in each case as a single diastereoisomer, in line with previously reported results.[143]

III.4.4. Epoxide formation

The stereoselective epoxide formation of aromatic aldehydes and donor-acceptor metallocarbenes was reported in 2001 by both the group of Doyle and the group of Davies.[144] This transformation is proposed to proceed *via* cyclisation of a carbonyl ylide. Using aryldiazoacetate generated in flow, various epoxides were prepared using *p*-anisaldehyde

(**174a-b**), cinnamaldehyde (**174c**), 2-thiophenecarboxaldehyde (**174d**), and *p*-nitrobenzaldehyde (**Scheme III-16**).



Yields based on starting hydrazone; conditions: $Rh_2(oct)_4$ (1 mol%) in CH_2Cl_2 at reflux

Scheme III-16: epoxide products

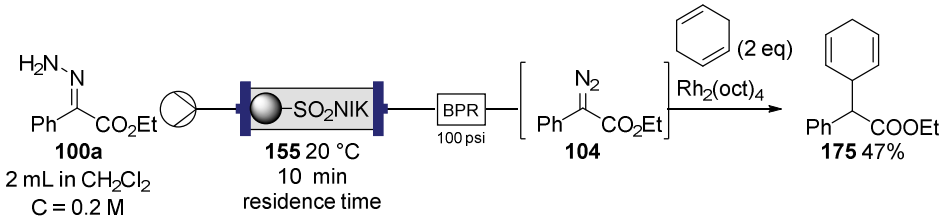
The epoxides obtained were found to be invariably *cis*, as noted in the initial reports.[144] Interestingly, this is the opposite diastereoisomer from that obtained in the equivalent Darzens reaction from an α-haloester and an aldehyde.[145] This route to epoxides also represents an alternative to the classical peroxide-mediated oxidation of alkenes.

III.4.5. C-H Insertion reactions

The insertion reaction of metallocarbenes into C-H bonds undeniably represents one of their most synthetically useful transformations (**Chapter I**). A series of C-H insertion processes were investigated using the diazo compounds generated in flow from their corresponding hydrazones.

Intermolecular C-H insertion can be particularly challenging. Based on a report from Müller and co-workers,[146] the C-H insertion product **175**

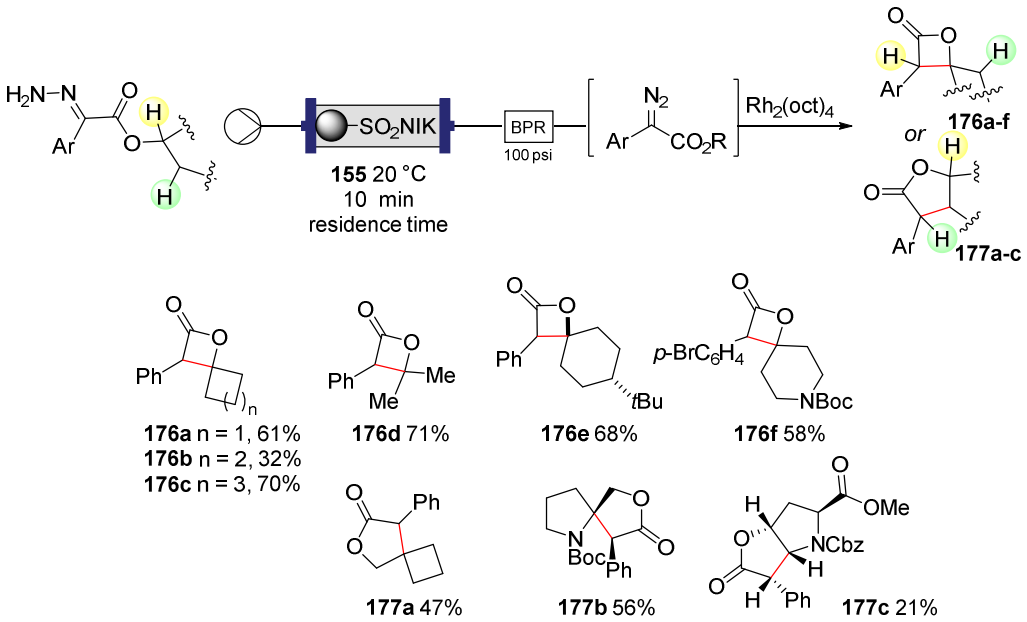
from ethyl phenyldiazoacetate **104** and cyclohexa-1,4-diene was nevertheless obtained in a modest 47% yield (**Scheme III-17**).



Scheme III-17: C-H insertion reaction using cyclohexa-1,4-diene

C-H Insertion processes can attain high level of selectivity when carefully selected substrates and conditions are used. Some factors influencing the selectivity of these processes are presented in **Chapter I** (**Section III.2**). The presence of an heteroatom, for instance, is known to activate vicinal C-H bonds. This effect can lead to the formation of β-lactones by intramolecular C-H insertion from diazoester derivatives.[147] Using diazo compounds generated in flow from selected hydrazones precursors, a series of β-lactones were obtained (**176a-f**, **Scheme III-18**). In particular, the use of hydroxycycloalkyl esters gave spiro-lactones **176a-c** and **176e-f** in variable yields. The β-lactone **176e** derived from *trans*-4-*tert*-butylcyclohexanol was obtained in 68% yields and X-ray crystallography confirmed that insertion into the tertiary C-H bond had occurred with retention of configuration (**Figure III-4**). γ-Lactones were obtained as major products when insertion into a secondary C-H bond was superseded by insertion into a tertiary C-H bond and bicyclic compounds **177a-b** were obtained. Prolinol derived lactone **177b** (isolated as a single diastereoisomer) and spiro-bicycle **177a** were obtained in moderate

yields with no traces of β-lactone formation, while 4-hydroxyproline derivative **177c** was obtained in low yield (21%) as major product from a mixture. Product **177c** originates from a C-H insertion into the secondary C-H bond into the α-position to the nitrogen atom and its stereochemistry was deduced from a NOESY experiment which allowed the observation of correlation between vicinal protons (represented in **Scheme III-18**). The absolute configuration of product **177b** was determined by X-ray crystallography (**Figure III-5**).



Yields based on starting hydrazone; conditions: $Rh_2(oct)_4$ (1 mol%), in CH_2Cl_2 at reflux

Scheme III-18: intramolecular C-H insertion products

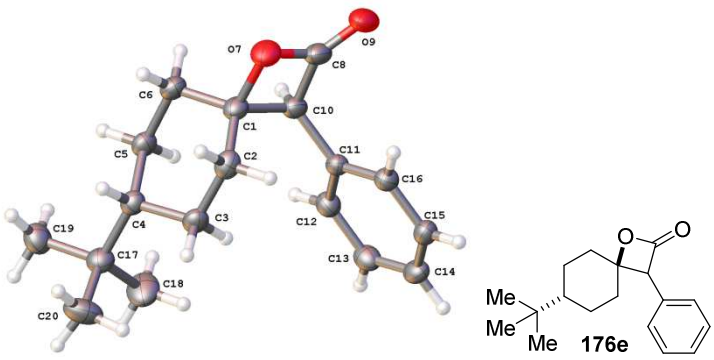


Figure III-4: crystal structure of lactone 176e

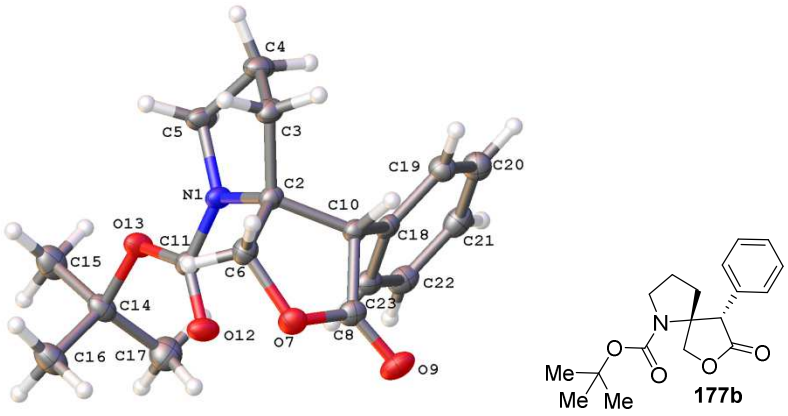
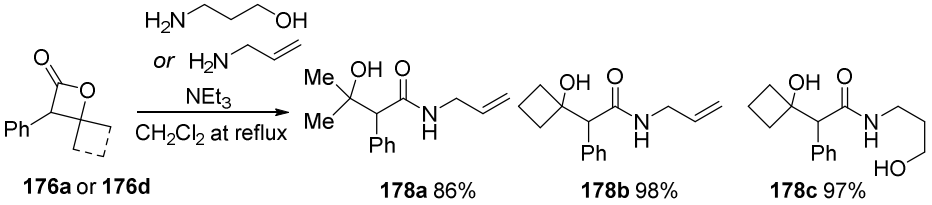


Figure III-5: crystal structure of lactone 177b

III.4.6. β-Lactone derivatisation reactions

β-Lactones are strained heterocycles that represent a class of reactive intermediates in organic synthesis.[148] The intramolecular metallocarbene C-H insertion using diazo compounds generated in flow, described in the previous Section, represents an interesting strategy for the preparation of these substrates. The diversification of the β-lactones obtained by this strategy was further investigated.

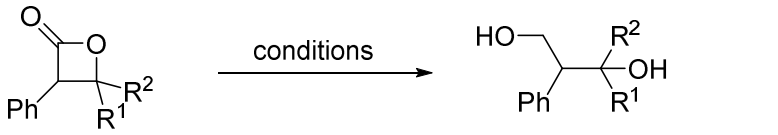
Opening of the strained spiro-lactone ring of product **176a** and **176d** with primary amines gave a straightforward access to β-hydroxyamides **178a-c** in high yield (**Scheme III-19**).



Scheme III-19: β-lactone ring opening products

Oxetanes containing spiro-cycles have emerged as compounds of interest in the search of new drug scaffolds due to their dense and well-defined stereostructure.[149] The conversion of β-lactones to the corresponding

oxetanes in one step is not a known process, although a number of protocols are available for the direct reduction of higher lactones to the corresponding cyclic ether in one step.[150] When applied to β-lactone **176d**, these protocol failed to give any oxetane products. A two-step reduction/cyclisation procedure was then investigated. The optimisation of the reduction step is presented in **Table III-1**.



176a R^1,R^2 = cyclobutane
176c R^1,R^2 = cyclohexane
176d R^1 = R^2 = Me

179a R^1,R^2 = cyclobutane
179c R^1,R^2 = cyclohexane
179d R^1 = R^2 = Me

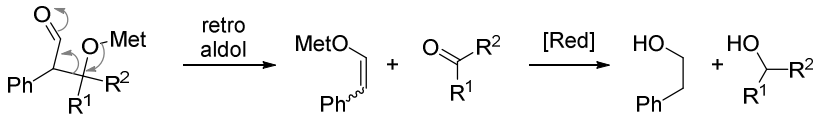
Table III-1: β-lactone reduction conditions screening

entry	R^1, R^2		conditions	diol yield %	
1	R^1 = R^2 = Me	**176d**	$NaBH_4$, MeOH/THF, 0 °C to RT	Traces[a]	**179d**
2	R^1 = R^2 = Me	**176d**	$LiAlH_4$, THF, 0 °C	50	**179d**
3	R^1 = R^2 = Me	**176d**	DiBAl-H, THF, 0 °C	51	**179d**
4	cyclobutane	**176a**	$LiAlH_4$, THF, 0 °C	54	**179a**
5	cyclohexane	**176c**	1) NaOH THF/H_2O, 0°C to RT 2) BH_3, THF, 0°C to RT	0[a,b]	**179c**
6	cyclohexane	**176c**	$LiEt_3BH$,[c] THF 0°C	traces[a]	**179c**
7	cyclohexane	**176c**	$LiAlH_4$,[c] THF, RT	48	**179c**
8	cyclohexane	**176c**	$LiAlH_4$,[c] THF, 0 °C	59	**179c**
9	cyclohexane	**176c**	$LiAlH_4$,[c] PhMe 0 °C	46	**179c**
10	cyclohexane	**176c**	DiBAl-H,[c] THF, 0 °C	66	**179c**
11	cyclohexane	**176c**	DiBAl-H,[c] PhMe, 0 °C	61	**179c**
12	cyclohexane	**176c**	DiBAl-H,[c] CH_2Cl_2, 0 °C	68	**179c**

[a] fragmentation by retro-aldol reaction was the major reaction pathway; [b] hydrolysis to the corresponding hydroxyacid was quantitative; [c] a solution of β-lactone was added to a solution of the reductant

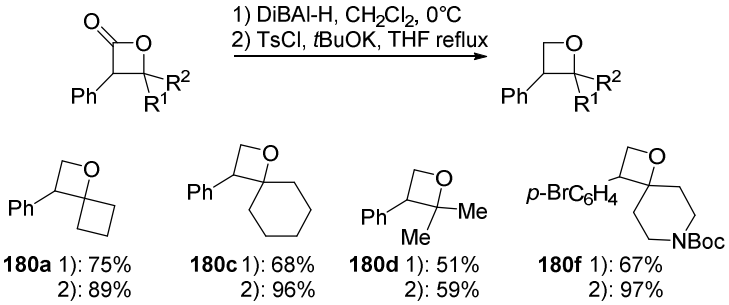
Reduction of β-lactones (**176a** and **176c-d**) to the corresponding diols (**179a** and **179c-d**) proved more difficult than expected and common reduction conditions led to decomposition of the substrates, mainly *via* a retro-aldol fragmentation (**Scheme III-20**). Sodium borohydride reduction of lactone **176d** (entry 1) and lithium triethylborohydride reductions of lactone **176c** (entry 6) led to fragmentation products.

Decomposition by retro-aldol fragmentation was the sole process observed in the borane reduction of the carboxylic acid derived from **176c** by hydrolysis (entry 5). Lithium aluminium hydride and diisobutylaluminium hydride (DiBAl-H) were found to give the best results in the reduction of lactones **176a** and **176c-d** (entries 2-4 and 7-12). Optimisation of the reaction conditions using β-lactone **176c** (entries 7-12) led to diol **179c** in 68% yield when DiBAl-H was used in dichloromethane (entry 12).



Scheme III-20: fragmentation by retro-aldol reaction

Cyclisation of the diol to the oxetane was found to occur readily using tosyl chloride and potassium *tert*-butoxide in THF at reflux (**Scheme III-21**).



Scheme III-21: conversion of β-lactones to oxetanes

Although the mechanism of this transformation was not examined in detail, it was considered to involve an initial sulfonylation of the primary alcohol, followed by the alkylation of the tertiary alcohol by deprotonation and displacement of the tethered *p*-benzenesulfonate *via* a

S_N2-type mechanism. The oxetanes **180a**, **180c-d** and **180f** were obtained *via* this two-steps procedure from the corresponding β-lactones. The structure of oxetane **180f** was confirmed by X-ray crystallography (**Figure III-6**).

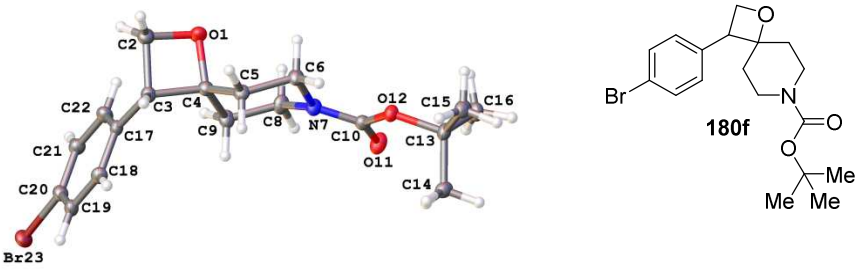


Figure III-6: crystal structure of oxetane 180f

IV. Conclusions and perspectives on the use of the resin PS-SO_2NIK

The translation of the method for the oxidation of hydrazones to diazo compounds presented in **Chapter II** from batch conditions to flow conditions resulted in the preparation and use of functionalised resin **155**. In a number of cases, the use of this recyclable material for the oxidation of hydrazones in flow provided clean solutions of diazo compounds, which were directly used in a variety of in-line transformations without isolation or purification. Using this protocol, a number of metallocarbene derived products were obtained, thereby accessing small libraries of structurally diverse compounds (amino acid derivatives, α-alkoxyesters, cyclopropanes, epoxides, β- or γ-lactones). Using the resulting β-lactones, a series of derivatisation products were obtained. In particular, the preparation of a series of oxetane-containing

spiro-cycles derived from β-lactones demonstrates the viability of a C-H insertion route for the synthesis these compounds.

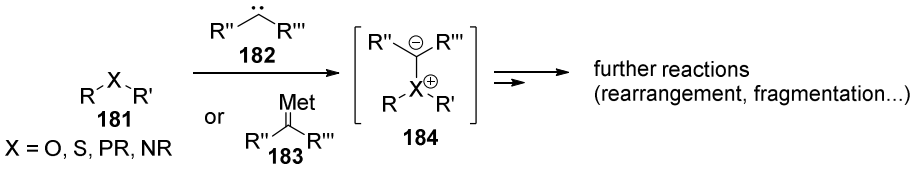
Chapter IV - The diverted insertion reaction of metallocarbenes

"I am at work on the second vol. of the Cirripedia, of which creatures I am wonderfully tired: I hate a barnacle as no man ever did before" ***C. R. Darwin*** *(Letter to W. D. Fox, 24.10.1852)*

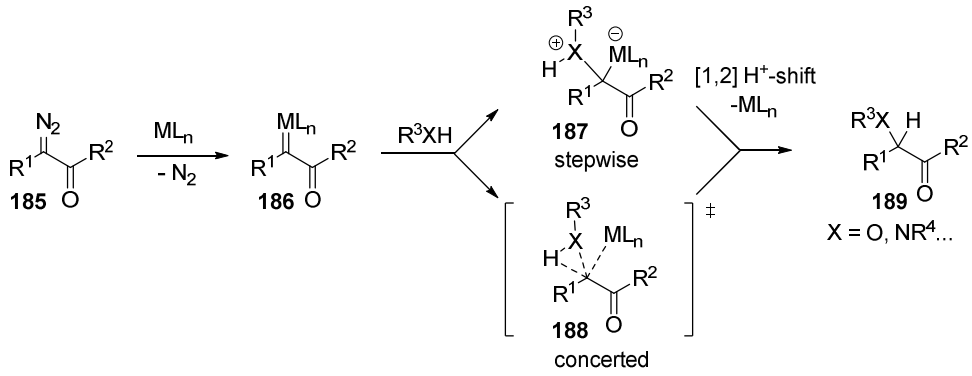
I. Introduction: metallocarbenes, insertion processes and onium ylides

Following the description of the main reactivities of metallocarbenes derived from diazo compounds in **Chapter I**, the present Chapter focuses on the discovery and development of new reactions based on processes initiated by O-H and N-H insertion reactions of metallocarbenes.

The generation of onium ylides **184** of nitrogen, oxygen, sulfur or phosphorus by reactions involving carbenes **182** (or metallocarbenes **183**) is one of the most important methods to access the reactivity of these high-energy intermediates (**Scheme IV-1**).[5,7-8] The involvement of onium (oxonium or ammonium) ylides **187** in X-H insertion processes (X = O, N), as opposed to a concerted insertion pathway (via transition state **188**) similar to that generally accepted in C-H insertion processes, has been debated (**Scheme IV-2** and **Chapter I**).[3b,35]

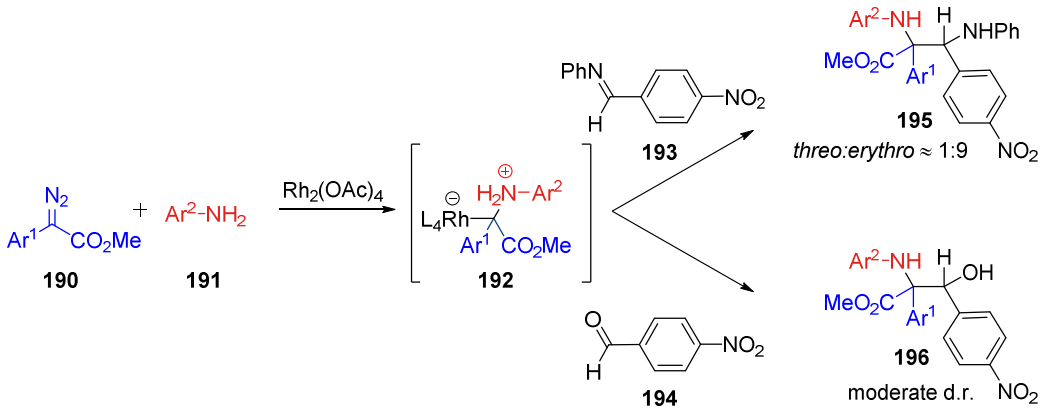


Scheme IV-1: ylide formation from metallocarbene



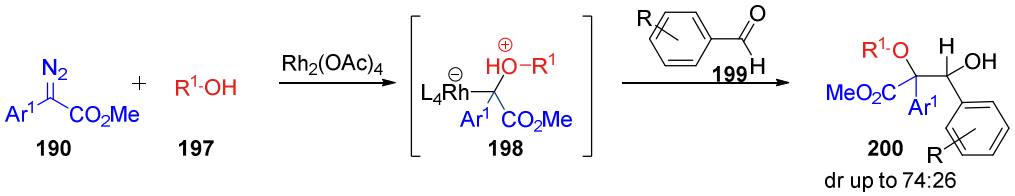
Scheme IV-2: concerted and stepwise mechanisms of an X-H insertion reaction

Strong evidence in favour of a stepwise mechanism in the case of the N-H insertion reaction has been presented by the group of Hu in 2003 with the serendipitous discovery of the rhodium catalysed reaction of aryldiazoacetates **190**, anilines **191** and imines **193** to give diamine derivatives **195** (**Scheme IV-3**).[151] In this example, Hu and co-workers realised that the final diamine product **195** was derived from a reactive intermediate which they identified as ammonium ylide **192**. This species is proposed to be generated by the attack of aniline **191** onto the rhodium bound carbene derived from **190**, and is then trapped by the electrophilic imine derivative **193**. The whole process gave moderate yields of the *erythro*-diamine preferably over its *threo*-isomer of **195**, demonstrating the potential of this new reactivity. Shortly thereafter, arylaldehydes (in particularly electron-deficient arylaldehydes such as **194**) were also shown to promote successful trapping of the proposed ylide intermediate **192** in overall moderate dr (**Scheme IV-3**).[152]



Scheme IV-3: early examples of diverted insertion reactions

Analogous results were rapidly reported in the related O-H insertion process, such as the possibility of trapping putative oxonium ylide intermediate **198** using aromatic aldehyde **199** (**Scheme IV-4**).[153]



Scheme IV-4: trapping of oxonium ylides by aromatic aldehydes described by Hu[153]

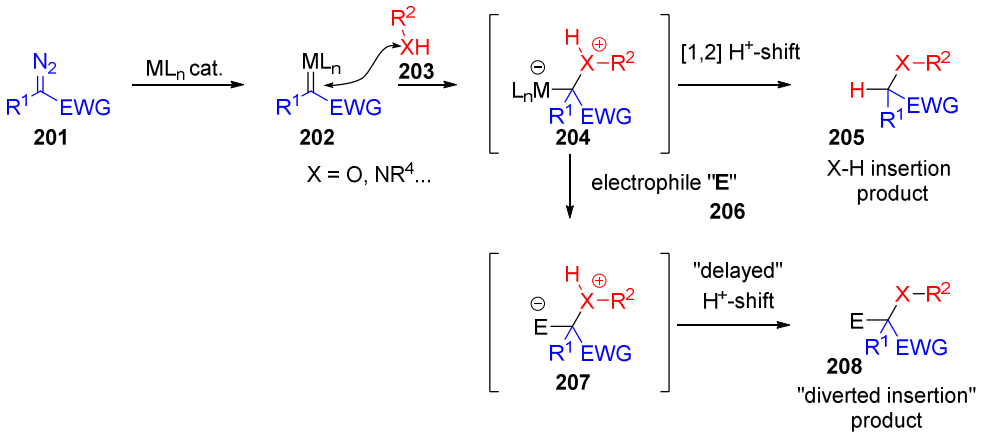
Importantly, these modest initial results illustrated a new kind of reactivity derived from the existence of transient intermediates in X-H insertion reactions pathways and the possibility to trap them, giving rise to functionalised products. In the decade following the first report of this reactivity, a wealth of examples has been reported and significant advances have been made in this expanding field. The general features of this process and the most significant progress are summarised in this Chapter. In particular, the application of transient ylide trapping to the synthesis of functionalised heterocycles as well as some mechanistic aspects of this transformation will be discussed. For full coverage up to 2012, a published review article can be consulted.[154]

II. Advances in the trapping of transient ylides derived from metallocarbenes (diverted insertion reaction)

II.1. Definitions and general features

The interception of the reactive intermediate in O-H and N-H insertion reaction pathways by means of trapping with an electrophile has overwhelmingly been referred to in the existing literature as “onium ylide trapping”. [154] In this Chapter, this process will instead be referred to as “diverted insertion reaction”, a term we coined in order to conveys the

concept that the reaction is initiated as an insertion reaction but is rerouted by the trapping of an transient intermediate (such as **204**) with an electrophile **206**, ultimately giving the more functionalised "diverted" insertion product **208** (**Scheme IV-5**).



Scheme IV-5: diversion of an X-H insertion process

Some examples of products obtained by diverted insertion reaction are shown in **Figure IV-1**. Typical procedures for the class of transformation involve several components:

1) A diazo compound as metallocarbene precursor. In the majority of cases, electron-rich to neutral aryldiazoacetates or diazooxindoles (precursor to donor-acceptor metallocarbenes) are used.[153,155] Ethyl diazoacetate[156] or diazoacetophenone[156c,157] have also been used successfully. Alkyl diazoacetates have been sporadically used and usually give inferior results to their aromatic counterpart.[156e,158] Although they are rarely used successfully in these processes, diverted insertion reactions using diazophosphonates[159] and diazomalonates[160] have been reported.

2) A metal complex to generate a metallocarbene from the diazo precursor. Rhodium(II) acetate dimer[154] or other rhodium(II) dimer catalysts[159,161] have been used predominantly, although copper(I),[162] copper(II)[155d,155s] and iron(III)[156b] catalysts (in conjunction with ethyl diazoacetate and aliphatic amines) give better results in some cases. In one isolated example, a transition metal-free procedure involving the use of indium tribromide has been reported. Although the corresponding mechanism is undetermined, it is postulated not to involve a carbene intermediate.[163]
3) An alcohol[153,155f-i,157a,162,164] including water[155b,155o,156d,e,165] or an amine derivative (mostly aniline[152,155c,155j,155r,156f,159,166] derivatives, although carbamates[167] and aliphatic amines[156b] have been used). Only one example involving a thiol has been reported so far.[155p]
4) An electrophile. *N*-Aryl imines of aromatic aldehydes have been largely used, despite the limited functionalisation possibilities of the resulting *N*-aryl amine.[155f,g,155i,155l,m,155t,156d,e,157a,164a,165b,168] A more synthetically useful alternative is the use of sulfinyl imines, which in addition can also act as chiral auxiliaries.[155i] Electron-deficient aryl aldehydes have been used, although they are usually associated with moderate stereoselectivity.[155d,155h,161-162] Alkynals[165a] and formalin[169] (aqueous formaldehyde solution) have also been used. Several studies found that non-symmetrical activated ketones such as isatin derivatives,[155d,155n,163,164b]

α-ketoesters,[155n,162-163] azetidinedione derivatives[156a] and ethyl glyoxylates[155r] give good products diastereomeric ratios. A number of examples using Michael acceptors have been reported, such as enones,[155a-c,155j,155s,156b,156f,157b,164d,170] β,γ-unsaturated *N*-sulfonylimines, [171] *p*-benzoquinones,[160b] benzylidene Meldrum's acid or 4-oxo-enoates.[172] When enones are used, a well defined chemoselectivity for 1,2- or 1,4-addition is observed, depending on the reaction conditions (i.e. the diazo compound and the Lewis acid additives employed).[156f,160b,164d] Trapping of the transient ylide by a Michael acceptor through a 1,4-addition occurs less readily than the corresponding 1,2-addition and requires additional activation of the substrate by Lewis acid catalysis, as illustrated in by a number of examples[155b,155s] or Brønsted acid catalysis.[155b,170] Azodicarboxylates have also been used as electrophiles, giving either aminals,[156c] *N*,*S*-ketals[155p] or imines (by in situ aminal fragmentation).[155o,155q]

5) An additive or co-catalyst. Brønsted acids such as BINOL-derived phosphoric acids;[155f,g,155m,155r,156d,157a,165b,167,170] Lewis acids based on zirconium,[155h,155t] zinc,[155b] indium,[164d] silver[164a,164d] salts or titanium alkoxide [160b,161] have been employed. Their use is discussed in the next Section.

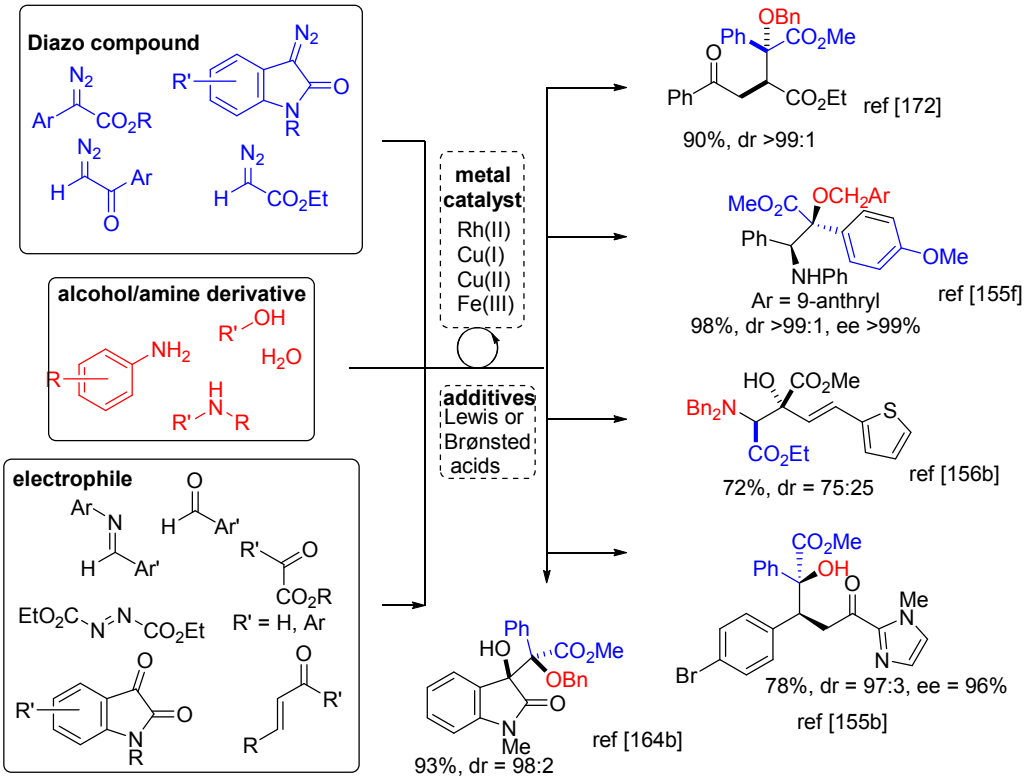
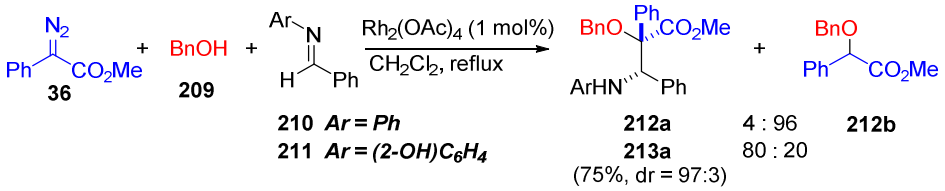


Figure IV-1: examples of diverted insertion reactions

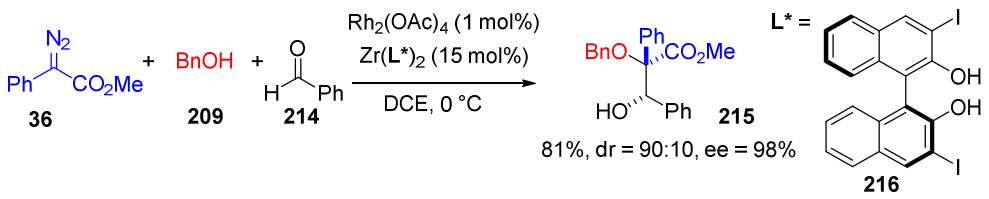
II.2. Recent developments in diverted insertion processes

In diverted insertion processes involving an intermolecular reaction between a reactive ylide-derived intermediate and an electrophile (such as that presented in **Scheme IV-6**), fine tuning of the reaction components are required to attain process efficiency and stereoselectivity control. For example, Hu and co-workers found that when benzyl alcohol **209** is used in conjunction with imine **210**, the diverted insertion product **212a** is obtained in trace amounts while the "classical" insertion product **212b** dominates. On the other hand, the use of hydrogen bonding activated imine **211** leads to dramatic changes in the reaction outcome and the diverted insertion product **213a** is obtained in high yield and diastereomeric ratio (**Scheme IV-6**).[155i]

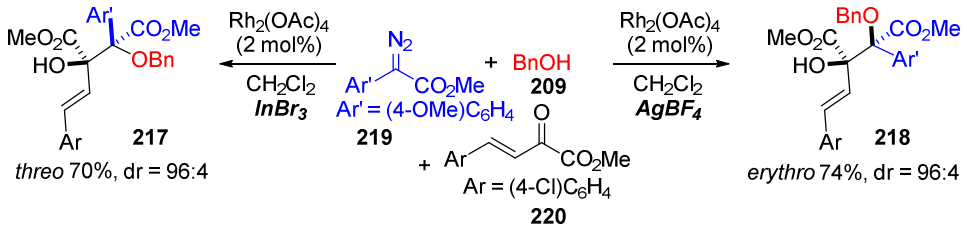


Scheme IV-6: selectivity in the trapping of oxonium ylides by imines

Beyond the tuning of the electronic nature of the reaction components, the use of Lewis acid co-catalysts can also favour the three-component reaction over the "classical" insertion reaction. Thus, the use of titanium alkoxides, in conjunction with aldehydes and alcohols, was reported to suppress simple O-H insertion.[161] Additionally, the introduction of a chiral co-catalyst provides a handle for chirality transfer during the reaction. A zirconium/BINOL **216** complex [155h,155t] (**Scheme IV-7**) or a zinc triflate/bis-oxazoline ligand system[155b] have been employed for this purpose. The use of Lewis acid is thought to activate the electrophilic substrate (particularly aldehydes and activated ketones) to promote the "aldol-like" addition step. In one case, a change in Lewis acid co-catalyst from silver tetrafluoroborate to indium tribromide has been shown to result in a switch of diastereoselectivity giving either the *erythro*-product **218** or the *threo*-product **217** (**Scheme IV-8**).[164d]

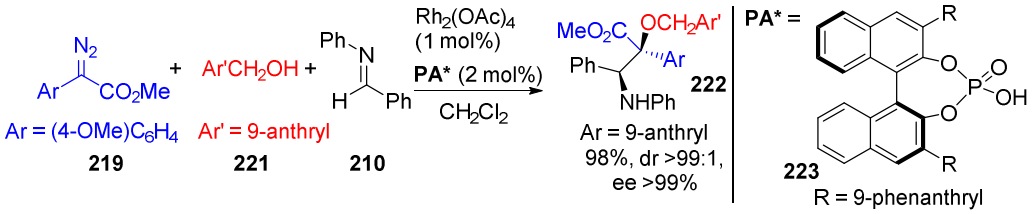


Scheme IV-7: asymmetric synthesis of diols by diverted insertion using a zirconium/BINOL complexe[155h,155t]

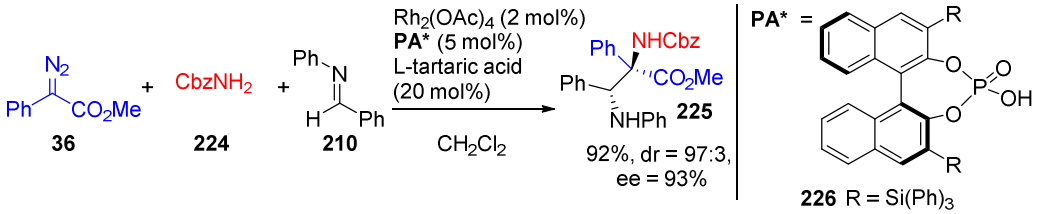


Scheme IV-8: selectivity in rhodium acetate/Lewis acid co-catalysed trapping of oxonium ylides [164d]

Following the observation that Brønsted acids accelerate the three-component diverted insertion reaction, Hu and co-workers reported that the use of enantiopure BINOL-derivated phosphoric acids result in diverted insertion products being obtained with high enantioselectivity (**Scheme IV-9** and **IV-10** for examples). This strategy has been applied to the three-component reactions involving imines as the electrophile in conjunction with alcohols,[155f,g,157a] water,[156d,165b] anilines[155r] and carbamates.[167] The phosphoric acid has been proposed to act as a "proton shuttle" promoting the intermolecular aldol-like reaction as illustrated by the proposed transition state **227a** (**Figure IV-2**).[155f] On the other hand, to rationalise the formation of the *anti*-aminoalcohol **222** as the major product in the three-component reaction of diazo compound **36**, carbamate **225** and imine **210** (**Scheme IV-10**), Hu and co-workers proposed a transition state featuring a simple acidic activation of the imine **210** by sterically hindered phosphoric acid **226** (represented in **227b**, **Figure IV-2**).[167] In both examples featured in **Scheme IV-9** and **IV-10**, no detailed mechanism for the induction of chirality has been proposed so far.



Scheme IV-9: asymmetric diverted O-H insertion reaction involving a chiral phosphoric acid



Scheme IV-10: asymmetric diverted N-H insertion reaction involving a chiral phosphoric acid

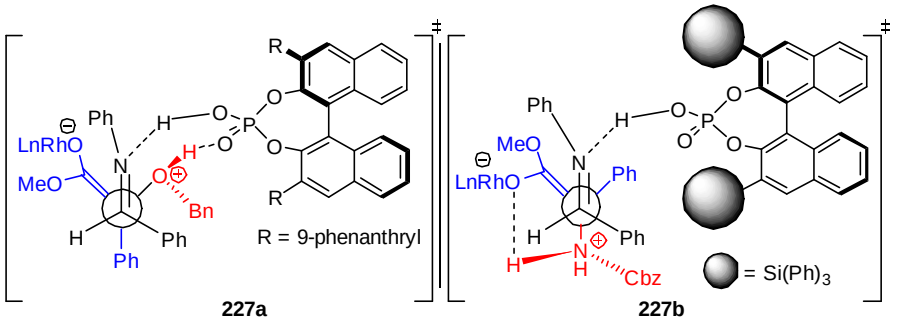
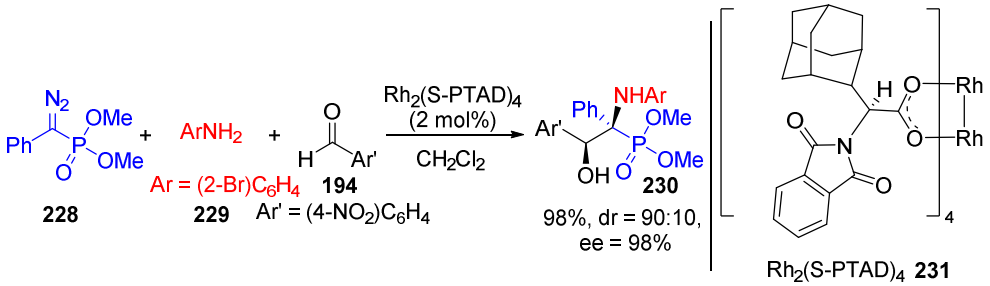


Figure IV-2: proposed transition states

It is noteworthy that examples of chiral induction using chiral rhodium or copper complexes are extremely rare in diverted insertion processes reported in the literature. In an early study, Hu and co-workers noted that several chiral rhodium complexes led to racemic products in the three-component reaction between diazo compounds, alcohol and imines.[161] The only example of successful chiral rhodium catalysed enantioselective diverted insertion reactions comes from the group of Che who showed that a diazophosphonate such as **228**, aniline **229** and electron-deficient aldehyde **194** gave rise to functionalised aminophosphonate **230** in high

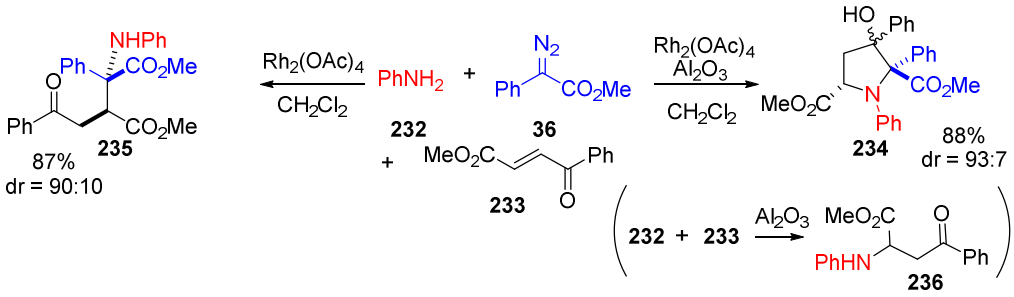
yield and enantioselectivity when the homochiral complex Rh_2(*S*-PTAD)$_4$ **231** was used (**Scheme IV-11**).[159]



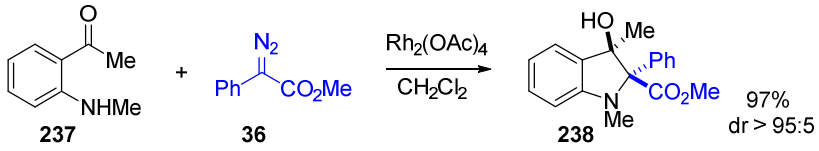
Scheme IV-11: asymmetric diverted N-H insertion using a chiral rhodium dimer complex

II.3. Application to the synthesis of heterocycles

The use of bifunctional reagents in diverted insertion processes can lead in one step to functionalised heterocycles. This concept is illustrated by the synthesis of functionalised 3-hydroxypyrrolidines by Hu and co-workers.[155c] They found that the rhodium catalysed reaction of a diazo compound such as **36**, aniline **232** and 4-oxo-enoate **233** gives 3-hydroxypyrrolidines **234** (**Scheme IV-12**). This process first requires the aniline **232** and the Michael acceptor **233** to react together in the presence of alumina to give β-aminoketone **236**. The remarkable feature of this process is the high stereoselectivity of the intramolecular aldol-like cyclisation, as only two diastereoisomeres of **234** were observed in a ratio of ca. 1:10. Interestingly, amino ketone **235** was the major product when the addition order of the various components did not allow for the formation of **236**. Similarly to β-aminoketones **236**, 2-aminophenyl ketones **237** undergo cyclisation to give only the *cis*-3-hydroxylindoline **238** (**Scheme IV-13**).[158]

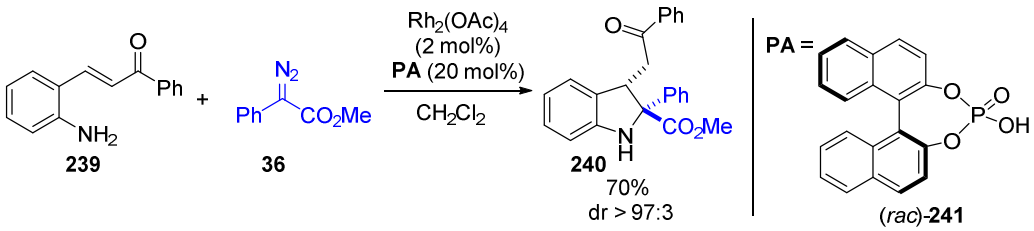


Scheme IV-12: multicomponent reactions of diazo compounds, anilines and oxoenoates[155c]



Scheme IV-13: indoline synthesis by intramolecular ammonium ylide trapping[158]

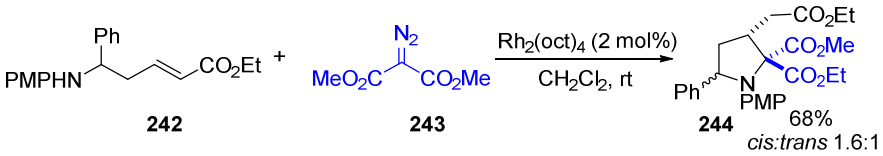
Hu and co-workers have also reported intramolecular ylide intermediate trapping using an aniline tethered enone such as **239** to give indoline derivatives **240** in moderate yields but with full selectivity for the *cis*-isomer (**Scheme IV-14**).[170] In this protocol, activation of the enone **239** using racemic phosphoric acid **241** was indispensable, while chiral induction using asymmetric phosphoric acids gave moderate results.



Scheme IV-14: acid assisted synthesis of indolines by intramolecular ammonium ylide trapping[170]

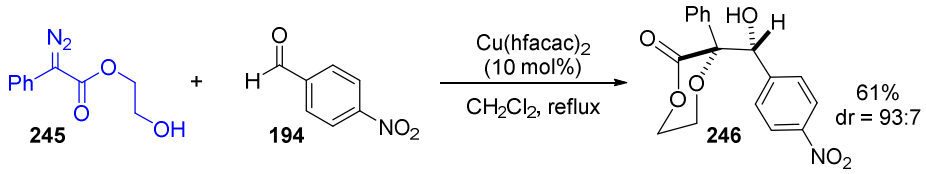
Diazodicarbonyl compounds are rarely successfully used in diverted insertion reactions. Nevertheless, one example of a diverted insertion reaction using diazomalonate **243** has recently been reported by Nikolaev and co-workers.[160a] In this process, unsaturated *N*-aryl aminoester **242**

and dimethyl diazomalonate **243** give rise to pyrrolidines **244** in modest yield as a mixture of *cis*- and *trans*-isomers using only rhodium octanoate dimer as the catalyst under typical reaction conditions (**Scheme IV-15**). Interestingly, no simple N-H insertion product was detected during their studies.



Scheme IV-15: pyrrolidine synthesis described by Nikolaev[160a]

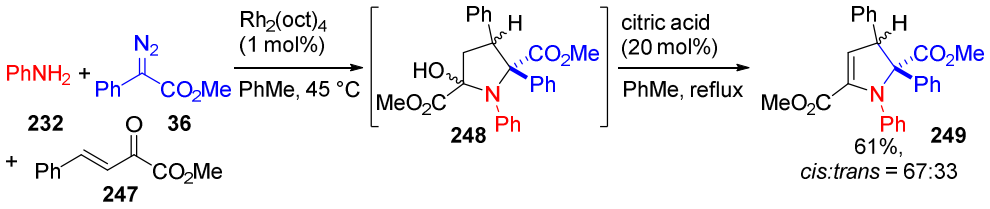
A different approach, using bifunctional diazo compound **245**, has been reported by Hu and co-workers in 2014 (**Scheme IV-16**).[155d] In this system, the O-H insertion process is initiated in an intramolecular fashion and trapping of the reactive intermediate occurs intermolecularly using an electron-deficient aldehyde such as **194** to give functionalised dioxane **246**.



Scheme IV-16: synthesis of functionalised dioxanes by Hu[155d]

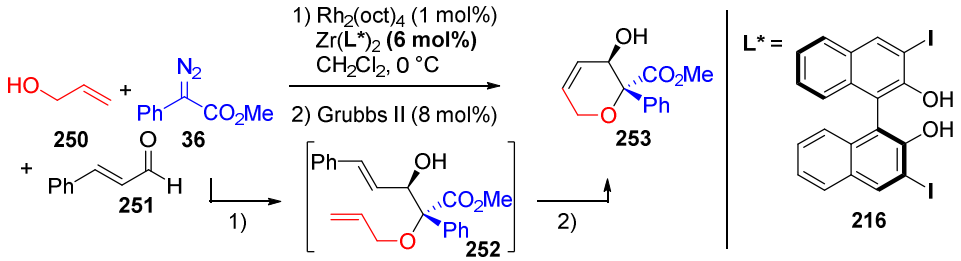
Another strategy employed by Hu and co-workers for the synthesis of heterocycles by diverted insertion relies on a tandem diverted insertion/cyclisation step carried out in a one pot fashion. This strategy is illustrated by the synthesis of dihydropyrroles such as **249** from 2-oxo-enoate **247**, diazo compound **36** and aniline **232** (**Scheme IV-17**). The diverted insertion process gives the 1,4-addition/intramolecular addition

product aminal **248** as a mixture of diastereoisomers, which can be dehydrated in a one-pot fashion to give **71**.[155j]



Scheme IV-17: dihydropyrroles synthesis by Hu[155j]

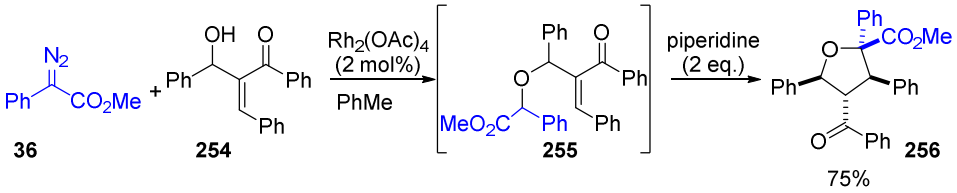
A diversity oriented approach recently reported by Hu and co-workers is based on the application of their precedent findings related to diverted O-H and N-H insertion reactions to produce functionalised aminoalcohol or diol derivatives which can be cyclised in a one-pot fashion.[155t] For example, asymmetric diol derivative **252** is obtained by the rhodium acetate/zirconium alkoxide co-catalysed three-component reaction[155h] of diazo compound **36**, allylic alcohol **250** and styryl aldehyde **251**. Without isolation of **252**, addition of Grubbs catalyst leads to *2H*-pyran **253** by ring closing metathesis (**Scheme IV-18**).



Scheme IV-18: heterocycles synthesis by rhodium acetate/zirconium alkoxide co-catalysed three-component reaction[155t]

Another related example is the preparation of substituted tetrahydrofurans **256** from aryldiazoacetate **36** and allylic alcohol **254** (**Scheme IV-19**).[173] While the rhodium catalysed O-H insertion conditions failed to give the expected cyclic diverted insertion product,

addition of piperidine to the reaction mixture led to the intramolecular cyclisation of linear product **255** to give a single isomer of tetrahydrofuran **256**.



Scheme IV-19: one-pot synthesis of tetrahydrofurans by Hu[173]

II.4. Mechanism of the diverted insertion reaction

The exact mechanism of the diverted insertion reaction is not known in detail. While the generation of a metallocarbene **258** from the diazo component **257** most likely initiates the process, the exact nature of the reactive species derived from the metallocarbene which undergoes reaction with the electrophilic component ("**E**") has not been investigated (**Figure IV-3**). On the other hand, several computational studies have been carried out considering the related metal catalysed O-H[36-37] or N-H[38,174] insertion of aryldiazoacetates. These studies suggest that the rhodium catalysed X-H (X = O, N...) insertion of aryldiazoacetates (**257** with R^1 = Ar and R^2 = OR) proceeds via a metal-free intermediate (such as **259c-e**), [36-37] while the analogous copper catalysed process occurs via a metal-bound intermediate (such as **259a-b**).[36] These finding are in good agreement with experimental results obtained in the field.[36] The groups of Sunoj and Fang both found an insertion reaction pathway involving an intermediate (*Z*)-enol (such as **259e**),[37-38,174] originating from an intramolecular [1,4]-proton shift on the corresponding ylide **259d**.

Although the terminating event differs between the insertion process (proton shift) and the diverted insertion process (electrophilic trapping), understanding of the nature of the intermediate in the former process might help gain insight into the latter.

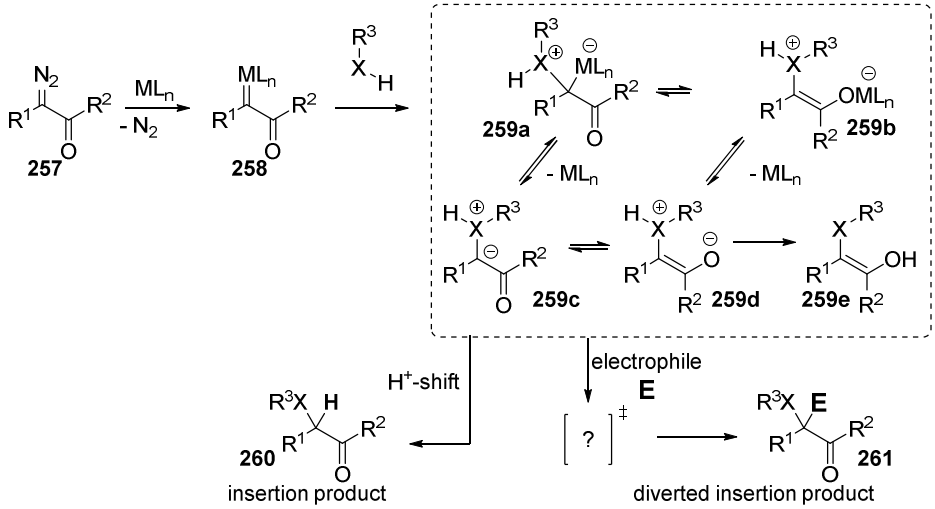
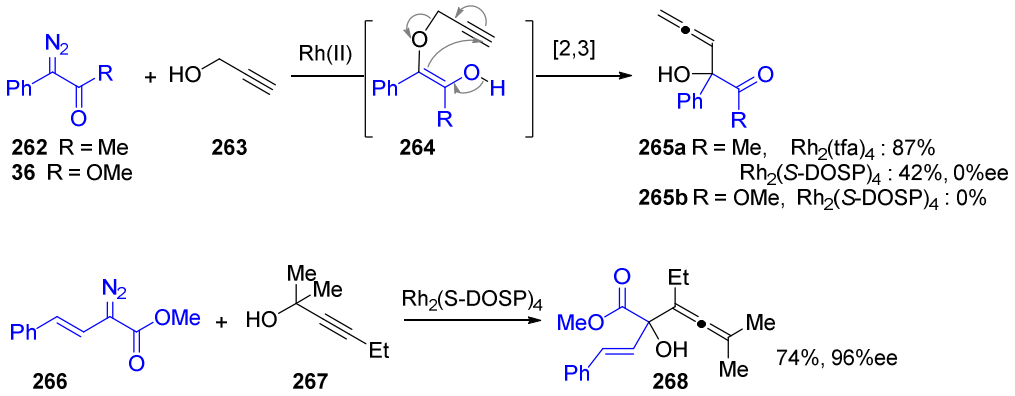


Figure IV-3: possible intermediates in X-H diverted insertion processes

Along with the unknown nature of the reactive intermediate and the variation of behaviour between different metal catalysts, the situation becomes more confused when the influences of the diazo compound and of the alcohol/amine components are considered. As noted by Hu and co-workers, the absence of chiral induction in the three-component reaction of an aryldiazoester, an alcohol, and an imines catalysed by a chiral rhodium catalyst suggests a metal-free intermediate.[161] On the other hand, Che and co-workers found that diazophosphonates, anilines and aldehydes give diverted insertion products with high enantioselectivity under chiral rhodium complex catalysis, hinting strongly at a metal-bond intermediate (**Scheme IV-11**).[159] In earlier studies on the rhodium catalysed O-H insertion/[2,3]-sigmatropic rearrangement cascade of

diazo compounds with propargyl alcohols (**Scheme IV-20**), Wood and co-workers found that the use of diazoketone **262** led to α-hydroxyallene **265a** via (*Z*)-enol **264** (similar to intermediate **259e** in **Figure IV-3**).[175] The existence of an intermediate enol **264** was further illustrated by Davies and co-workers who showed that the product **265a** was obtained as a racemic mixture when the homochiral rhodium complexe Rh_2(*S*-DOSP)$_4$ was used. On the other hand, the analogous diazoester **36** gave only the O-H insertion product with no traces of allene **265b**. The same authors observed that styryl diazoester **266** gave a good yield of the insertion/rearrangement product **268**. They additionally established that chiral induction using Rh_2(*S*-DOSP)$_4$ was highly effective. Computational studies of this process confirmed the existence of a rhodium-bond intermediate which undergoes the rearrangement.[176]



Scheme IV-20: O-H insertion/sigmatropic rearrangement cascades

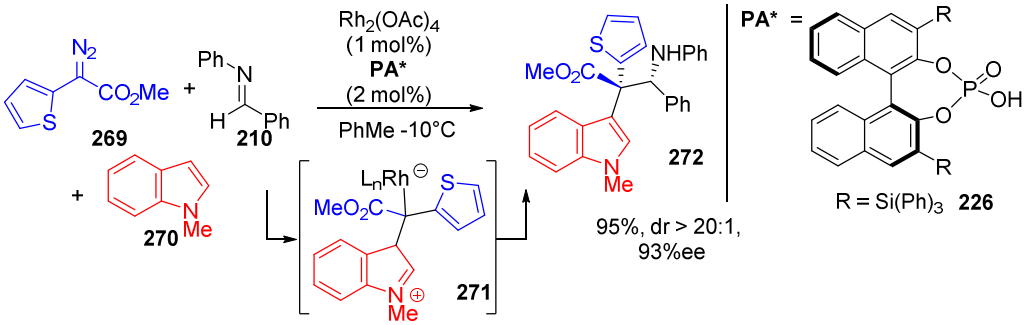
It is hard to draw any general conclusion regarding the mechanism of diverted insertion processes. Experimental results show disparate results accompanying change in each of the various components involved in the process: the nature of the metal catalyst, the diazo compound used, the alcohol/amine and the electrophile. Based on the existing reported

results, it is nevertheless likely that diverted insertion reactions of diazoesters involve a metal-free intermediate when rhodium carboxylate dimers are used as catalysts, which represents the majority of reported examples.

II.5. Extensions of the diverted insertion reaction

Interestingly, the concept behind the diverted insertion reaction, namely the electrophilic trapping of reactive intermediate generated by the reaction of metallocarbenes with nucleophilic substrates, can be extended to some C-H insertion processes.[177]

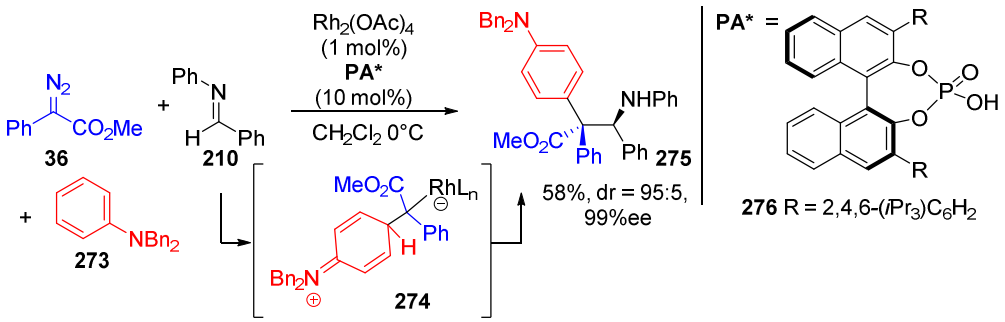
In 2012, Hu and co-workers reported the trapping of zwitterionic intermediates such as **271**, generated by C-3 alkylation of indole **270**, to give C-3 substituted indole **272**.[177b] Chiral induction using the previously established homochiral phosphoric acid strategy gave the product **272** with high enantioselectivity (**Scheme IV-21**).



Scheme IV-21: asymmetric trapping of zwitterionic intermediates generated by C-3 alkylation of indoles

The group of Hu also recently reported an extension of this strategy with the diverted C-H insertion of electron-rich arenes with diazoester and imines (**Scheme IV-21**).[177a] In this strategy, the reactive ylide-like

intermediate **274** (obtained by the attack of electron-rich arene **273** onto the electrophilic metallocarbene derived from **36**) is trapped by imine **210**, giving the functionalised arene **275** with high enantioselectivity. Once again, the process is rendered enantioselective by using chiral phosphoric acid derivative **276**. The acid is proposed to promote the trapping event by simultaneously activating the imine **210** and to act as a proton shuttle during the ylide trapping event.



Scheme IV-22: asymmetric trapping of zwitterionic intermediates generated by *para*-alkylation of anilines

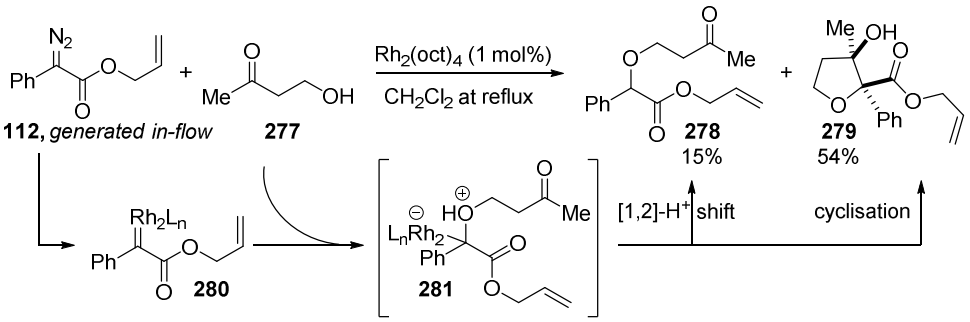
Chapter V - Synthesis of substituted tetrahydrofurans by diverted insertion reactions

"Am I jumping the gun, Baldrick, or are the words 'I have a cunning plan' marching with ill-deserved confidence in the direction of this conversation?" **Captain Blackadder** in Blackadder Goes Forth (written by R. Curtis and B. Elton)

I. Diverted insertion reactions of diazo compounds and β-hydroxyketones

I.1.Serendipitous discovery of the title process

Studies of insertion reactions of metallocarbenes derived from diazo compounds generated in flow (**Chapter III**) led to the serendipitous discovery of the diverted O-H insertion reaction of aldol compounds (β-hydroxyketones) to tetrahydrofurans. The reaction of diazo compound **112** with 4-hydroxybutan-2-one **277** led to the isolation of a mixture containing the expected O-H insertion product **278** along with an additional isomeric product which was identified as 3-hydroxytetrahydrofuran **279** (**Scheme V-1**). Interestingly, this cyclic compound was obtained as a single isomer which was identified as the *cis*-isomer **279**. In view of the previously described methodologies based on the trapping of transient ylides in O-H insertion processes (**Chapter IV**), compound **279** is hypothesised to arise from the diversion of a classical O-H insertion process via trapping of an intermediate ylide **281**. This species can accordingly be generated by the attack of alcohol **277** onto the electrophilic rhodium-bond carbene **280** produced from diazo compound **112**.



Scheme V-1: serendipitous discovery of the title process

The tetrahydrofuran ring is a commonly found motif in naturally occurring and bioactive compounds belonging to various structural classes such as lignans,[178] acetogenins,[179] ionophores,[180] and macrolides.[181] The possibility to access substituted tetrahydrofurans through a convergent approach using easily available β-hydroxyketones and diazo compounds, as demonstrated in **Scheme V-1**, represents an attractive perspective. The results of further investigations of this process are presented in this Chapter.

I.2. Reaction optimisation and scope of the process

The reaction of ethyl phenyldiazoacetate **104** and hydroxyketone **277** was studied as a model system to seek reaction conditions favouring the production of cyclic compound **283** over linear product **282**. A variety of copper(I), copper(II) and rhodium(II) dimer complexes were found to promote the formation of tetrahydrofuran **283** (**Table V-1**). Copper(II) triflate was first found to give a reasonable yield of cyclic product **283** (65%, entry 1). Using this catalyst, a number of reaction parameters were modified such as a lower temperature (entry 2), a higher catalyst loading (entry 3), the addition of a Lewis acid (entry 4-5) and the addition of a Brønsted acid (entry 6). All these changes were found to be detrimental to the overall yield of the insertion process. Amongst other copper catalysts screened (entries 8-14), copper(I) triflate toluene complex gave the best results (**283** obtained in 82% yield, entry 14). Lowering of the catalyst loading to 1 mol% led to a minor drop of the yield of product **283** down to

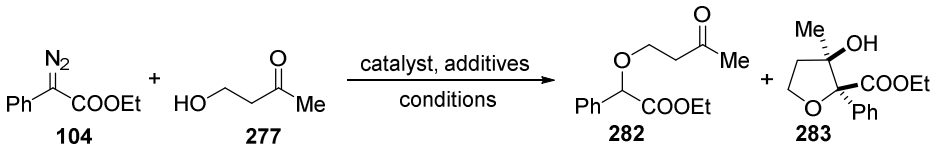


Table V-1: condition optimisation for the synthesis of 283

entry	catalyst	mol %	conditions/additives [a]	ratio **104**:**277**	products yield %	
					282	**283**
1	$Cu(OTf)_2$	5	CH_2Cl_2 at reflux, 1h	1.1 : 1	18	65
2	$Cu(OTf)_2$	5	CH_2Cl_2 RT, 1h	1.1 : 1	10	34
3	$Cu(OTf)_2$	20	CH_2Cl_2 at reflux, 1h	1.1 : 1	25	37
4	$Cu(OTf)_2$	5	$Zn(OTf)_2$ (0.1 eq), CH_2Cl_2 at reflux, 1h	1.1 : 1	11	58
5	$Cu(OTf)_2$	5	$InBr_3$ (0.1 eq), CH_2Cl_2 at reflux, 1h	1.1 : 1	15	52
6	$Cu(OTf)_2$	5	TsOH (0.1 eq), CH_2Cl_2 at reflux, 1h	1.1 : 1	9	29
7	$Cu(OTf)_2$	5	CH_2Cl_2 at reflux, 1h	1.3 : 1	15	72
8	CuI	5	CH_2Cl_2 at reflux, 24h	1.1 : 1	/[b]	
9	$Cu(OAc)_2$	5	CH_2Cl_2 at reflux, 24h	1.1 : 1	/[b]	
10	CuOAc	5	CH_2Cl_2 at reflux, 4h	1.3 : 1	22	68
11	$Cu(MeCN)_4BF_4$	5	CH_2Cl_2 at reflux, 1h	1.3 : 1	36	54
12	$Cu(TFA)_2$	5	CH_2Cl_2 at reflux, 1h	1.3 : 1	8	74
13	$Cu(Acac)_2$	5	CH_2Cl_2 at reflux, 1h	1.3 : 1	11	63
14	$(CuOTf)_2$·PhMe	5	CH_2Cl_2 at reflux, 1h	1.3 : 1	9	82
15	$(CuOTf)_2$·PhMe	1	CH_2Cl_2 at reflux, 1h	1.3 : 1	5	77
16	$Rh_2(oct)_4$	1	CH_2Cl_2 at reflux, 1h	1.3 : 1	25	70
17	$Rh_2(oct)_4$	1	NEt_3 (100 mol%), CH_2Cl_2 at reflux, 1h	1.3 : 1	78	0
18	$Rh_2(TFA)_4$	1	CH_2Cl_2 at reflux, 1h	1.3 : 1	19	39
19	$Rh_2(piv)_4$	1	CH_2Cl_2 at reflux, 1h	1.3 : 1	3	78
20	$Rh_2(pfbm)_4$	1	CH_2Cl_2 at reflux, 1h	1.3 : 1	< 2	75
21	Rh_2(*S*-DOSP)$_4$	1	CH_2Cl_2 at reflux, 1h	1.3 : 1	< 2	85
22	Rh_2(*S*-PTAD)$_4$	1	CH_2Cl_2 at reflux, 1h	1.3 : 1	2	77
23	Rh_2(*S*-MEPY)$_4$	1	CH_2Cl_2 at reflux, 3h	1.3 : 1	< 2	89
24	[Ru(*p*-cymene)Cl_2]$_2$	2	CH_2Cl_2 RT, 24h	1 : 1.2	8	8
25	BF_3·OEt_2	20	CH_2Cl_2 at reflux, 30 min	1.1 : 1	53	0
26	$HClO_4$ (4 eq), CH_2Cl_2, RT, 15 min			1 : 2	17(65)[c]	0
27	DCE at reflux, 20h			1 : 2	0	13
28	Visible light,[d] TFT, 4h			1 : 2	0	Traces

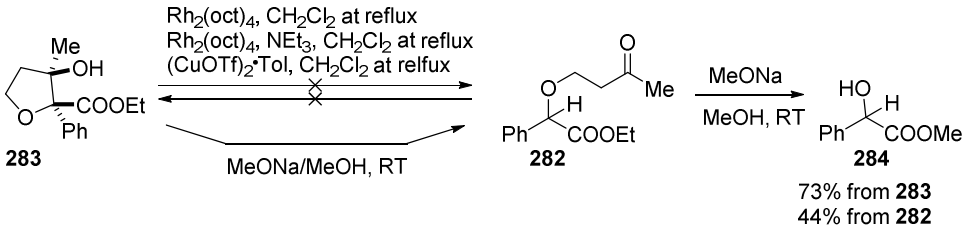
[a] using slow addition of **104** to the reaction mixture; [b] very slow decomposition of diazo compound **104**; [c] yield in bracket refers to isolated ethyl mandelate; [d] the visible light source was a 400 W HQI-T metal halide lamp;[182] **abbreviations:** oct = octanoate; TFA = trifluoroacetate; piv = pivaloate; pfbm = perfluorobutyramide;[183] Rh_2(*S*-DOSP)$_4$ = tetrakis[(*S*)-(-)-*N*-(*p*-dodecylphenylsulfonyl)prolinato] dirhodium(II);[27] Rh_2(*S*-PTAD)$_4$ = Tetrakis[(*R*)-(-)-(1-adamantyl)-(*N*-phthalimido)acetato] dirhodium(II);[184] Rh_2(*S*-MEPY)$_4$ = dirhodium(II)tetrakis[methyl 2-pyrrolidone-5(*S*)-carboxylate];[28] DCE = 1,2-dichloroethane, TFT = trifluorotoluene.

77% (entries 15-16). Amongst the rhodium dimer complexes investigated (entries 16-23), high yields of cyclic product **283** were achieved with Doyle's rhodium carboxamide dimer Rh_2(*S*-MEPY)$_4$[28] (89%, entry 23) and Davies' rhodium carboxylate dimer Rh_2(*S*-DOSP)$_4$[27] (85%, entry 21). In both cases, the linear product **282** was not observed. On the other hand, rhodium octanoate dimer gave a reasonable yield of cyclic product **283** along with 25% yield of insertion product **282** (entry 16). Intriguingly, the linear product **282** was obtained exclusively when the reaction was carried out using rhodium octanoate in the presence of stoichiometric amounts of triethylamine (entry 17). The use of ruthenium catalyst [Ru(*p*-cymene)Cl_2]$_2$ led to low overall yields (entry 24), while the use of boron trifluoride or perchloric acid led solely to the isolation of linear product **282** (entry 25-26). Interestingly, purely thermal conditions led to the isolation of the cyclic product **283** in low yield, showing that the cyclisation event can occur under metal-free conditions (entry 27).

Whilst not giving optimum results with the particular set of substrates **104** and **277**, rhodium octanoate dimer was identified, along with copper(I) triflate, as a suitable catalyst to explore the scope of the diverted insertion process. In comparison with other efficient rhodium complexes identified in the screening presented above, rhodium octanoate indeed presents the advantage of being available at a lesser cost.

Control experiments revealed that no retro-aldol pathway is operating under the reaction conditions to convert **283** to **282**, including in the

presence of triethylamine (**Scheme V-2**). Accordingly, no cyclisation of linear alkoxyester **282** was observed under the reaction conditions, excluding it as intermediate on the pathway to tetrahydrofuran **283**. On the other hand, the application of harsher conditions, such as the use of sodium methoxide, did promote retro-aldol ring opening of tetrahydrofuran **283** to give **282**. Further reaction of **282** under these conditions led to methyl mandelate **284** as single isolated product. **284** is presumably obtained from **282** via an elimination/transesterification sequence.



Scheme V-2: control reactions

Having determined two sets of conditions maximising the production of 3-hydroxytetrahydrofuran **283** by a diverted insertion process, the scope of the reaction was studied with respect to the diazo component used (**Figure V-1, Scheme V-3**). Strikingly, in all the following examples, only the C-2/C-3 *cis*-tetrahydrofuran isomer was produced during the cyclisation event. While copper(I) triflate toluene complex (conditions A) was found to give the best results for the formation of tetrahydrofuran **283**, it rapidly became apparent that rhodium octanoate (conditions B) is a more efficient catalyst when electron-rich aryldiazocarbonyl compounds (such as **105**, **285**, **287** and **118**) were used. On the other hand, when 4-bromophenyl diazo compound **107** was used, both catalytic

systems (conditions A or B, **Scheme V-3**) gave similar results. Moving to *p*-nitrophenyl derivative **286**, the tetrahydrofuran product **289d** was obtained in appreciable yield only under copper catalysis. For this particular example, no cyclopropanation product was observed in significant amounts under either set of conditions.

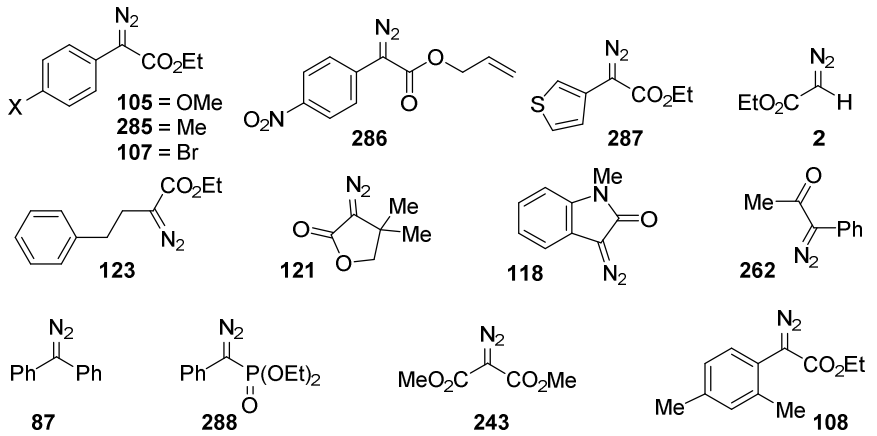
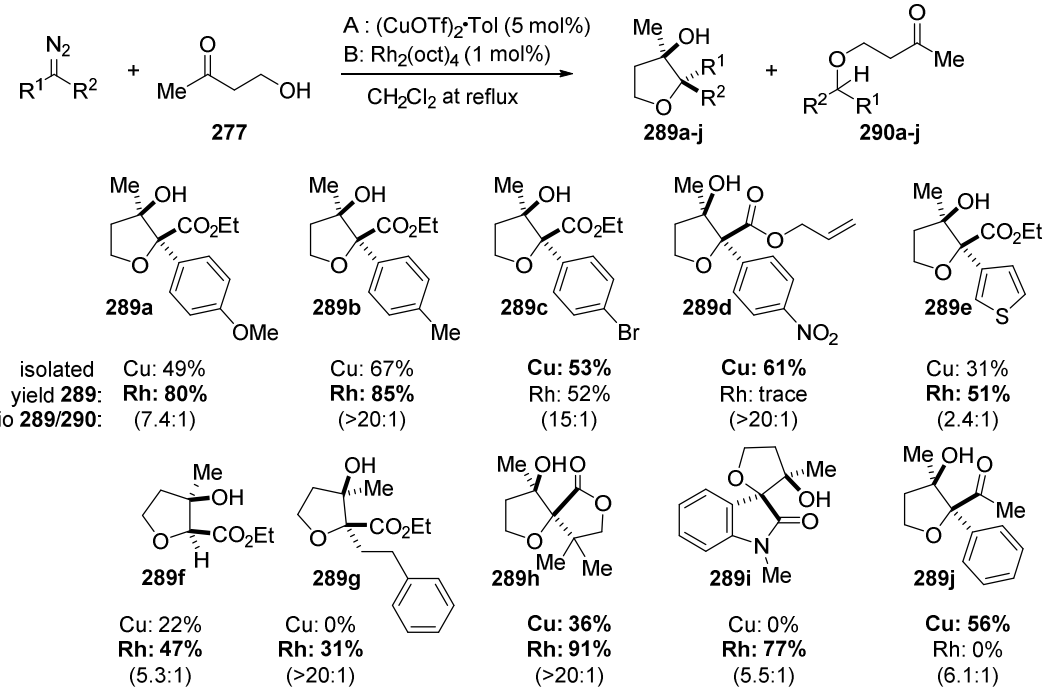


Figure V-1: diazo compounds used in this study



Scheme V-3: tetrahydrofurans products

Ethyl diazoacetate **2** was found to give tetrahydrofuran product **289f**, albeit using a large excess of **2**, because of the presence of a competing

carbene dimerisation product leading to diethyl fumarate and diethyl maleate. When the transient metallocarbene possesses an α-hydrogen, a hydride shift is possible and this process was found to compete with the insertion pathway. Thus tetrahydrofuran **289g** was obtained in moderate yield from diazo compound **123**. On the other hand, when no α-hydrogen is present, such as in the metallocarbene derived from diazo compound **121**, the insertion/cyclisation event can proceed to give high yield of product **289h**. A change to diazoketone **262** led to a dramatic change in the reaction outcome when rhodium octanoate was used as only the O-H insertion product **290j** was isolated. On the other hand, tetrahydrofuran product **289j** was obtained under copper(I) triflate catalysis. It is noteworthy that in all the latter successful examples, the linear products **290** were commonly identified as secondary products in variable quantities. Other diazo compounds such as diphenyldiazomethane **87** or diazophosphonate **288** gave complex mixtures of products with no clear evidence for the occurrence of O-H insertion, whereas diazomalonate **243** gave solely the linear O-H insertion product using both set of conditions A or B. Additionally, *ortho*-substituted diazo ester **108** gave only traces of cyclic product with significant quantities of linear insertion product. This last result suggests that ortho-substitution of the aryldiazoacetate component favours the simple insertion process.

The attention was then turned towards possible variations of the β-hydroxyketone component of the reaction (**Figure V-2, Scheme V-4**).

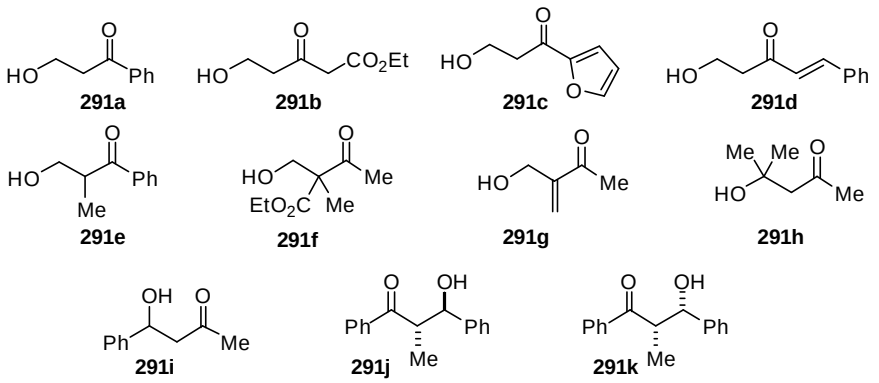
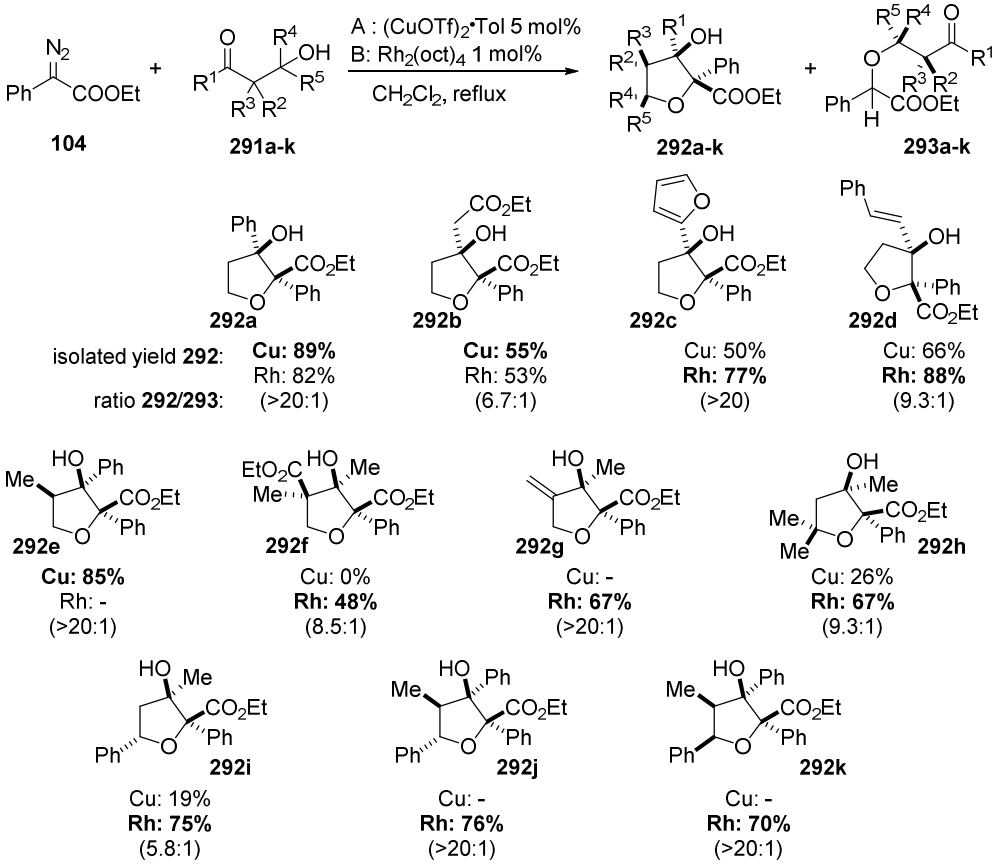


Figure V-2: β-hydroxyketones used in this study



Scheme V-4: tetrahydrofurans products

Using diazo compound **104**, various hydroxyketones **291a-k** were probed to explore the possibility of preparing functionalised tetrahydrofurans and the level of stereocontrol featured in the cyclisation process. Gratifyingly, a number of hydroxyketones were found to give good to excellent yields of tetrahydrofuran products including phenyl ketone

291a (to give **292a**), ketoester **291b** (to give **292b**), furyl ketone **291c** (to give **292c**), enones **291d** and **291g** (to give **292d** and **292g**). The structure of tetrahydrofuran **292d** was confirmed by X-ray crystallography (**Figure V-3**). Aldol compound **291e** possessing a methyl group in the α-position gave the *cis,cis*-tetrahydrofuran **292e** under copper catalysis, thus demonstrating a high level of stereocontrol over the C-4 position of the final product. Using disubstituted aldol product **291f**, a single isomer of tetrahydrofuran **292f** was isolated. Di-and tri-substituted hydroxyketones **291h-k** gave tetrahydrofurans **292h-k** in good yields. In these cases, rhodium octanoate dimer was found to be superior to copper(I) triflate.

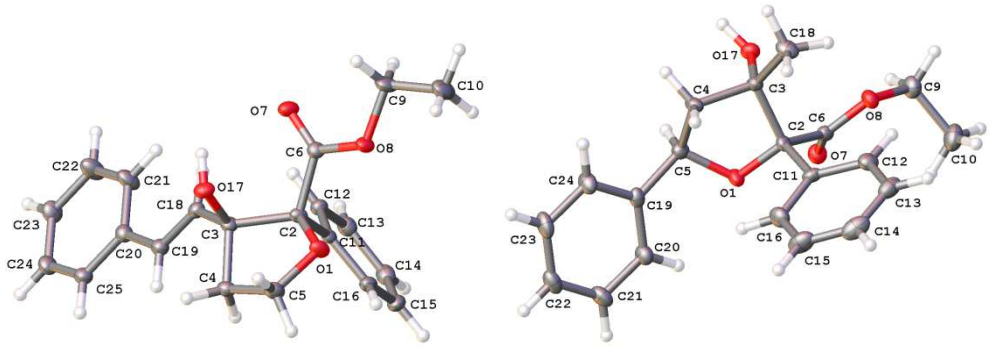


Figure V-3: crystal structures of compounds 292d and 292i

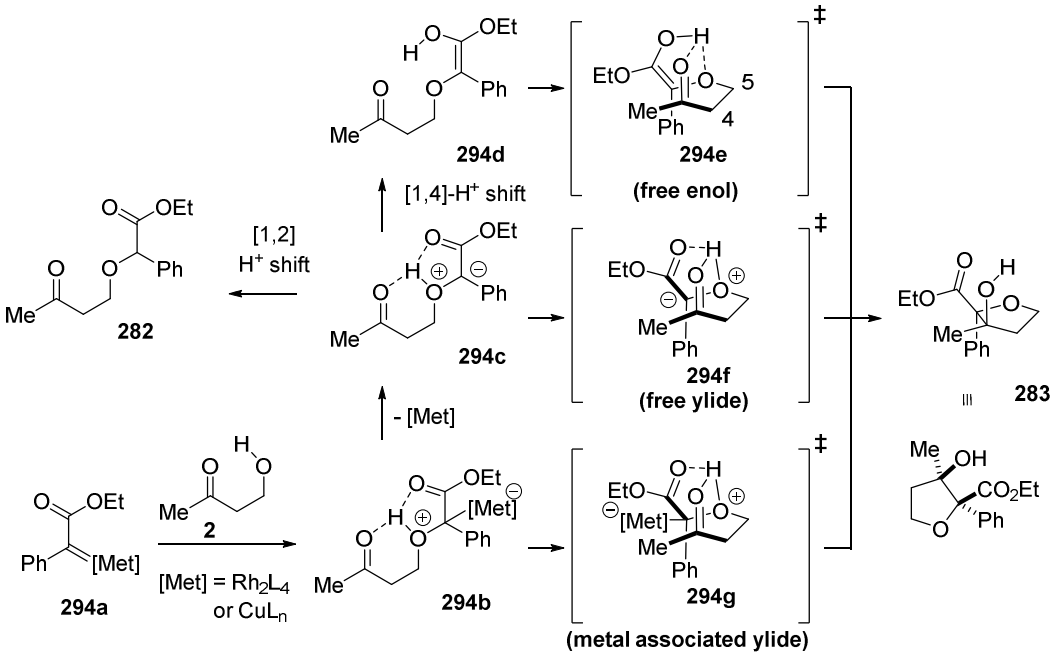
Strikingly, stereocontrol can be extended to the C-5 position of the final cyclic product, as illustrated by the use of β-substituted hydroxyketone **291i** which gave tetrahydrofuran product **292i** in 75% yield as a single isomer **(Scheme V-4**). Unsurprisingly, the use of enantio-enriched β-hydroxyketone **291i** (77% ee) gave tetrahydrofuran product **292i** with no erosion of chirality (**292i** obtained with 85% ee). The absolute configuration of product **292i** was determined unambiguously by X-ray

crystallography (**Figure V-3**). Finally, highly substituted tetrahydrofurans **292j** and **292k** were obtained in good yield from the corresponding aldol products **291j** and **291k**, respectively. The substituents' configurations in these products were identified on the basis of various 2D-NMR experiments. It is noteworthy that the preparation of products **292j** and **292k** illustrate the fact that the stereocontrol exerted by the C-4 substituent of the final product in favour of the *cis*-isomer overrides the control by the C-5 substituent of the cyclic product.

I.3.Discussions of possible mechanism

The control experiments presented above (**Scheme V-2**) support the assumption initially made that both linear product **282** and cyclic product **283** are not directly related but rather derive from competing pathways. Based on the wealth of examples reported in the literature during the past decades (**Chapter IV**), the existence of a transient ylide intermediate (**294b**, **Scheme V-5**) that results from the attack of the alcohol **277** onto the electrophilic metallocarbene **294a**, is assumed. The exclusive formation of the *cis*-isomer of tetrahydrofuran **283** can be rationalised by considering a concomitant aldol-type cyclisation / proton transfer event proceeding *via* a highly ordered transition state (such as **294f-g**), featuring some degree of hydrogen bonding between the ester and ketone carbonyl accompanying the hydrogen transfer process. In this scenario, both metal associated ylide **294b** or metal-free ylide **294c** can be considered. Additionally, several computational studies investigating metallocarbene N-H and O-H insertion processes have suggested an

intermediate free (*E*)-enol **294d** (generated by intramolecular [1,4]-H shift) as a favoured pathway (as discussed in **Chapter IV Section II.4**).[37-38,176] In the present process, such an intermediate furnishes a straightforward explanation to the observed diastereoselectivity of the cyclisation process which then equates to an aldol addition (*via* transition state **294e**).



Scheme V-5: proposed mechanism for the formation of tetrahydrofuran 283

To probe the nature of the cyclisation intermediate, the possibility of inducing chirality on the newly formed stereocentres was studied using diazoacetate **104** and hydroxyketones **291a** in conjunction with various chiral catalysts (**Table V.2, Figure V-4**). Chiral rhodium catalysts (Rh_2(*S*-DOSP)$_4$ **6e**,[27] Rh_2(*S*-MEPY)$_4$ **7d**,[28] Rh_2(*S*-TFPTTL)$_4$ **295**,[185] gave tetrahydrofuran product **292a** in excellent yield, but as a racemic mixture (entries 1-4), while the use of Rh_2(*S*-PTAD)$_4$ **231**[184] gave the desired product in only 7% ee. These observations strongly suggest a metal-free

cyclisation under rhodium catalysis. On the other hand, the use of *i*Pr-Box ligand **296** in conjunction with copper(I) triflate as the metal source gave the same product **292a** (72% yield) in moderate enantiomeric excess of 31%, suggesting a metal-bound cyclising intermediate. These results are in agreement with computational studies comparing rhodium and copper catalysed O-H insertion process (**Chapter IV Section II-4**).[36]

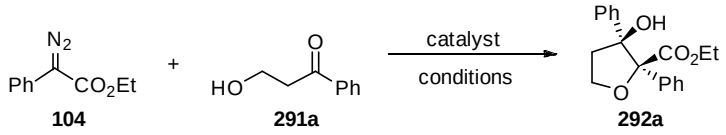


Table V.2: use of chiral metal complexes for the synthesis of 292a

entry	catalyst, conditions	yield %	ee %
1	Rh_2(*S*-DOSP)$_4$ **6e** (1 mol%), CH_2Cl_2 at reflux, 1h	89	< 2
2	Rh_2(*S*-DOSP)$_4$ **6e** (1 mol%), pentane 0 °C, 1h	34	< 2
3	Rh_2(*S*-MEPY)$_4$ **7d** (1 mol%), CH_2Cl_2 at reflux, 1h	91	< 2
4	Rh_2(*S*-TFPTTL)$_4$ **295** (1 mol%), CH_2Cl_2 at reflux, 1h	95	< 2
5	Rh_2(*S*-PTAD)$_4$ **231** (1 mol%), CH_2Cl_2 at reflux, 1h	85	7
6	*i*PrBox-ligand **296** (7 mol%), $(CuOTf)_2$·PhMe (2.5mol %) CH_2Cl_2 at reflux, 2h	72	31

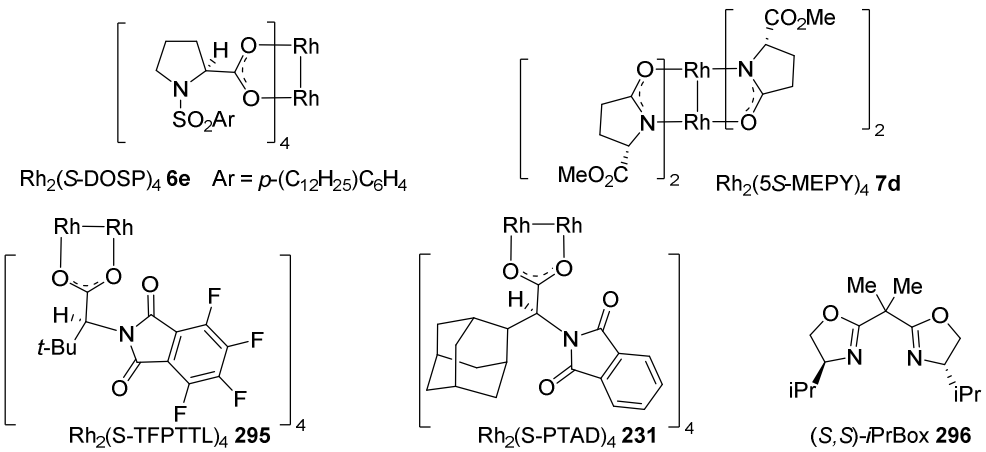


Figure V-4: chiral rhodium catalysts used in this study

With the proposed transition states presented in **Scheme V-5**, the diastereoselectivity of the process can be now discussed (**Figure V-5**, only the cyclisation of the free ylide is considered for clarity). The formation of

the (C-4)-*cis*-isomer of hydroxytetrahydrofuran **292e** can be explained on the basis of steric repulsions during the cyclisation event, as represented in transition states **297a-b**. The same rationale can be applied to tetrahydrofurans **292f** and **292j-k** (**Scheme V-4**). On the other hand, the pronounced preference for the (C-5)-*trans*-isomer of product **292i** is less evident to justify. On the hypothesis that the cyclisation transition state assumes a conformation such as that illustrated by **298a-b**, the phenyl group might be preferentially positioned a in pseudo-equatorial position (as in **298b**) to avoid unfavourable 1,3-diaxal interactions (as in **298a**).

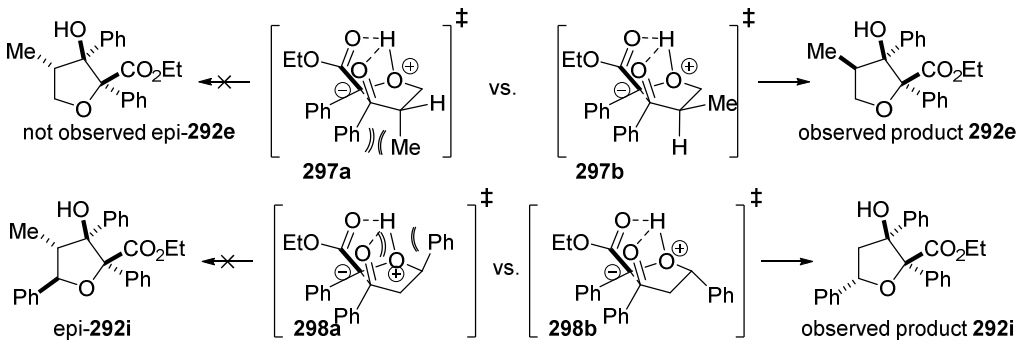
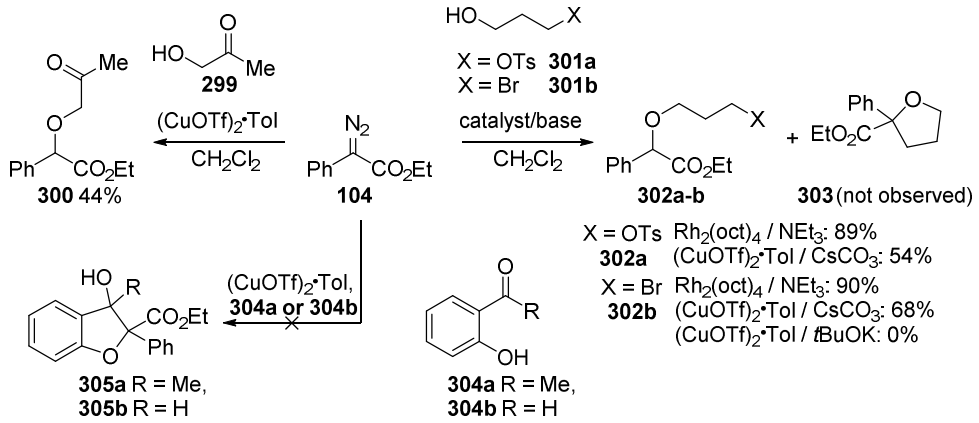


Figure V-5: rationale for the observed stereoselectivity in the formation of products 292e and 292i

II. Insertion reactions of other electrophile-tethered ketones

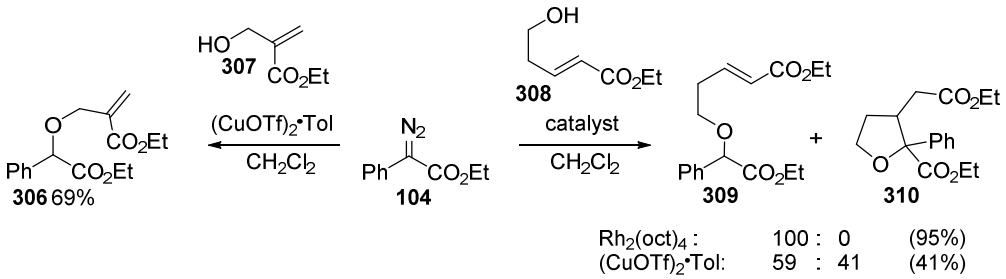
Following the results obtained with β-hydroxyketones, the behaviour of other electrophile-tethered alcohols under O-H insertion conditions was investigated. Unsurprisingly, hydroxyacetone **299** and diazo compound **104** did not give the corresponding cyclised product under previously established conditions (**Section I.2**). On the other hand, 2'-hydroxyacetophenone **304a** and salicylaldehyde **304b** failed to yield any appreciable amount of the corresponding cyclic products **305a-b**

under copper catalysis. Tosyloxypropanol **301a** and bromopropanol **301b** gave good yields of O-H insertion products **302a-b** using either rhodium(II) octanoate or copper(I) triflate catalyst, along with stoichiometric amounts of base, whilst no observable amount of tetrahydrofuran **303** was produced (**Scheme V-6**).



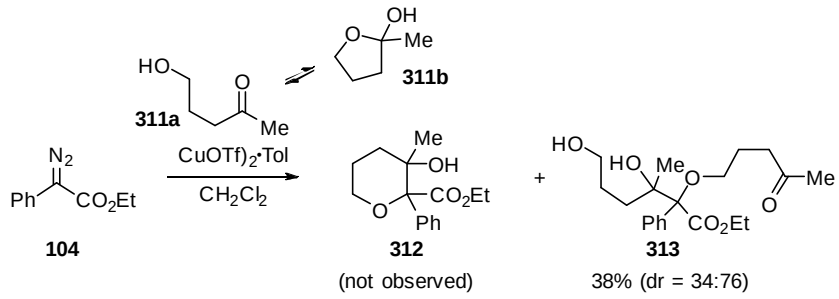
Scheme V-6: insertion reaction of diazo compound 104 with various electrophile tethered alcohols

The diverted insertion of alcohols tethered with a Michael acceptor moiety was also briefly explored (**Scheme V-7**). The use of acrylate derivative **307** and diazo compound **104** under copper catalysis led only to the O-H insertion product **306** with no detectable trace of the corresponding cyclic product. This result is in line with previously reported results from Hu and co-workers.[173] 5-Hydroxypentenoate **308** also yielded the linear product **309** as single product under rhodium catalysis. On the other hand, the use of copper(I) triflate as the catalyst led to a inseparable mixture of **309** with an additional product which was identified as tetrahydrofuran **310**. This promising result was not further investigated and the configuration of the ring substituents in **310** was not established.



Scheme V-7: insertion reaction of diazo compound 104 with acrylate derivatives

The use of δ-hydroxyketones in the diverted insertion reaction might lead to the synthesis of tetrahydropyrans. To examine this prospect, hydroxypentanone **311a** was used along with diazo compound **104** under copper catalysis (**Scheme V-8**). It is worth noting that **311a** is found in solution in equilibrium with its hemiacetal form **311b** (ratio 67:43 at room temperature in deuterated chloroform in favour of **311a**), which might undermine the efficiency of the insertion process. The reaction leads to a mixture of products from which none of the desired tetrahydropyran **312** was observed. On the other hand, a rather intriguing set of compounds identified as both diastereoisomers of **313** were obtained in low yield from this mixture (38%, based on **311a**). These products are likely to result from an *inter*molecular ylide trapping event as opposed to the *intra*molecular process expected.



Scheme V-8: attempted synthesis of tetrahydropyran 312

III. Approach to the synthesis of hyperolactone C

III.1. Introduction and retrosynthesis

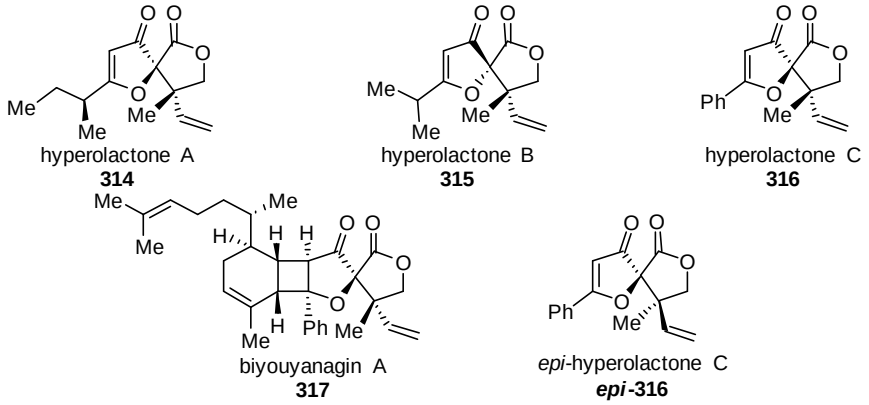


Figure V-6: hyperolactones A-C and related compounds

The isolation of secondary metabolites from plants used in traditional medicine has often led to the discovery and characterization of compounds possessing both biological activities of particular interest and unusual structural features. The extraction and characterisation from *Hypericum chinense L.*, a plant of the Guttiferae family, of a series of unique spiro-lactones **314** - **316** (named hyperolactone A, B and C, respectively) provides a good example of such an instance (**Figure V-6**).[186] In particular, hyperolactone C **316** has been found to be part of a more complex naturally occurring product, biyouyanagin A **317**, a potent anti-HIV agent which was isolated from a closely related plant.[186] Further studies revealed that the bioactivity exhibited by **317** is likely due to its hyperolactone C structural element.[187] Related structure-activity relationship studies also revealed that the isomer *epi*-hyperolactone C **318** possesses anti-inflammatory properties (LPS-

induced cytokine production inhibitory properties).[188] Syntheses for all compounds hyperolactones A **314** ,[189] B **315**,[190] C **316**[190a,191] and biyouyanagin **317**[187,191b] have been reported.

Hyperolactone C **316** was identified as an attractive target to apply the diverted insertion reaction described in **Section II** of this Chapter. Following the retrosynthetic analysis outlined in **Figure V-7**, an access to the core spiro-structure **318** was to be obtained by the diverted insertion reaction of a diazolactone **322** and a β-hydroxycarbonyl compound such as compounds **319-321**. The spiro-dihydrofuranone **318** could either be built from a β-hydroxyaldehyde **319** by diverted insertion/oxidation sequence, from an activated ester **320** by direct diverted insertion, or from an α-hydroxyketone **321** *via* a diverted insertion reaction/oxidative cleavage sequence. The level of control exerted by the chiral center of **322** during the insertion/cyclisation process is at this stage one major unknown. It is worth mentioning that a late stage oxidation of ketone **318**, as shown on **Figure V-7**, has previously featured in syntheses of **316**.[191c,d]

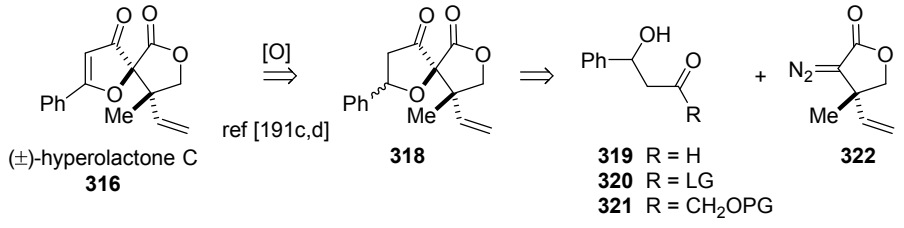
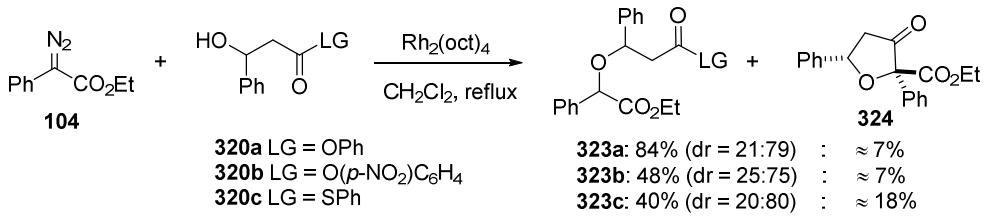


Figure V-7: retrosynthetic analysis.

III.2. Dihydrofuran-3(*2H*)-ones synthesis by a diverted insertion strategy

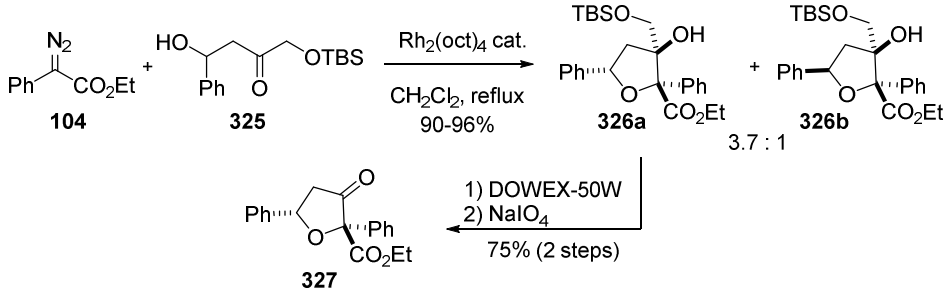
In order to determine conditions which could directly lead to the formation of dihydrofuran-3(*2H*)-ones by diverted insertion reaction, several hydroxyester derivatives **320a-b** possessing a potential leaving group (LG) were investigated (**Scheme V-9**). Using diazo compound **104** and rhodium octanoate as the catalyst, the linear O-H insertion products **323a-c** were obtained in all cases as the major product and as a mixture of diastereoisomers. The use of copper(I) triflate catalyst with **320a** only led to low overall insertion yield and complex mixture of compounds. Using **320a-c**, the desired compound **324** was nevertheless identified in small amounts in mixtures, which rendered its isolation and characterisation difficult. Despite the proof that this approach can lead directly to dihydrofuranone **324**, it was not further investigated.



Scheme V-9: synthesis of dihydrofuranone 324 from hydroxyesters 320a-c

A more succesful approach to dihydrofuranone **324** was based on the use of dihydroxyketone derivative **325** (**Scheme V-10**). Using diazo compound **104**, the diverted insertion reaction of **325** gave high yields of the corresponding tetrahydrofuran which was obtained as two diastereoisomeric products **326a** and **326b**. As previously observed

(**Section I.2**), the (C-5)-*cis*-isomer **326a** was obtained preferentially. Its conversion to **327** was carried out in two steps and good overall yield.



Scheme V-10: synthesis of dihydrofuranone 327

Having developed a strategy for the construction of the dihydrofuranone core by diverted insertion reaction, diazolactone **121** was used as a model substrate for the construction of the spiro-core of hyperolactone C **316** (**Table V-3**). Unfortunately, the use of rhodium octanoate as the catalyst only gave a low yield of the desired diverted insertion product **328** obtained as an inseparable mixture of the two expected isomers **328a** and **328b** (entry 1). The main product of this reaction was found to be the butenolide **330**, which is likely to derive from metallocarbene **329** by [1,2]-methyl group migration. [1,2]-Shifts of carbenes and metallocarbene are indeed well documented processes[192] and examples of methyl group migration are known.[193] Lowering the reaction temperature to 0 °C led to a marginally better result (entry 2), while the reaction was inhibited at –40 °C (entry 3). A series of other rhodium complexes failed to improve the selectivity for the insertion products **328a-b** (entries 4-9), while copper catalysts gave more promising results (entries 10-12). A real breakthrough was achieved when copper(I) acetate was used as the catalyst (entry 14), although this procedure was found to require an

initiation period with the addition of diazo compound at 0 °C to give reproducible results (entries 14-15).

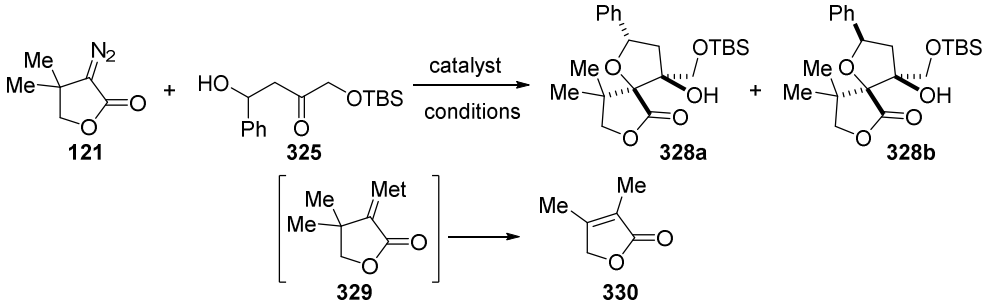
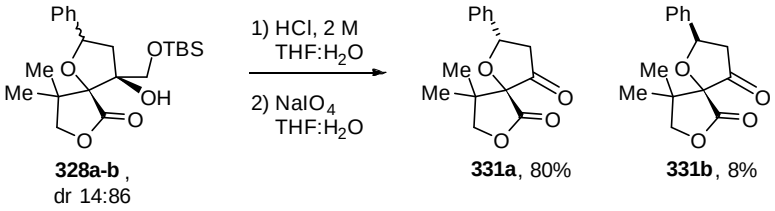


Table V-3: conditions screening for the preparation of spiro-compounds 328a-b

entry	Conditions	yield **328a-b** %	dr	**325** recovered
1	$Rh_2(oct)_4$ (1 mol%) CH_2Cl_2 at reflux	7[a]	1:9	92
2	$Rh_2(oct)_4$ (1 mol%) CH_2Cl_2 0 °C	21[b]	1:9	76
3	$Rh_2(oct)_4$ (1 mol%) CH_2Cl_2 –40 °C	no reaction	/	/
4	$Rh_2(pfmb)_4$ (1 mol%) CH_2Cl_2 0 °C	traces [b,c]	/	/
5	Rh_2(*S*-MEOX)$_4$ (1 mol%) CH_2Cl_2 0 °C to 80°C	not observed [b,c]	/	/
6	$Rh_2(esp)_2$ (1 mol%) CH_2Cl_2 0 °C	traces [b,c]	/	/
7	$Rh_2(TFA)_4$ (1 mol%) CH_2Cl_2 0 °C	not observed [b,c]	/	/
8	Rh_2(*S*-DOSP)$_4$ (1 mol%) CH_2Cl_2 0 °C	traces [b,c]	/	/
9	Rh_2(*S*-TFPTTL)$_4$ (1 mol%) CH_2Cl_2 0 °C	traces [b,c]	/	/
10	$(CuOTf)_2$·PhMe (5 mol%) CH_2Cl_2 0 °C	18-22[b]	8:92	66
11	$(CuOTf)_2$·PhMe (5 mol%) THF 0 °C	13[b]	7:93	68
12	$Cu(hfacac)_2$ (5 mol%) CH_2Cl_2 0 °C to RT	33[b]	9:91	59
13	no catalyst, CH_2Cl_2 at reflux	7[b,c]	/	/
14	CuOAc (5 mol%) CH_2Cl_2 0 °C to reflux	65-72	14:86	22-34
15	CuOAc (5 mol%) CH_2Cl_2 RT to reflux	12-42[b]	11:89	41-54

[a] all reactions carried out with a **121**:**325** ratio of 1.3:1; [b] **330** was found to be the major compound in mixture; [c] based on ^{1}H NMR analysis of the crude product

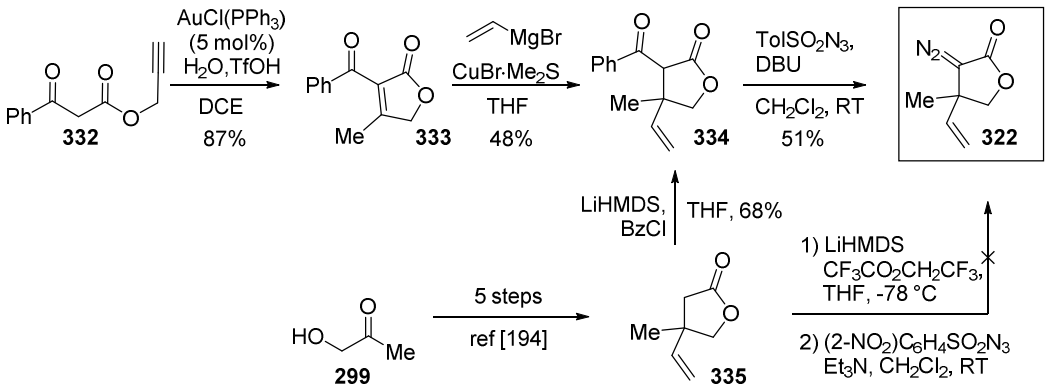
The isomeric mixture of compounds **328a-b** was then converted to the desired dihydrofuranone structure in a straightforward manner to give the two diastereoisomeric compounds **331a** and **331b** in good overall yield (**Scheme V-11**), one oxidation step away from giving the full spiro-structure found in hyperolactone C **316**.



Scheme V-11: preparation of spiro-lactones 331a-b

III.3. Construction of the lactone ring

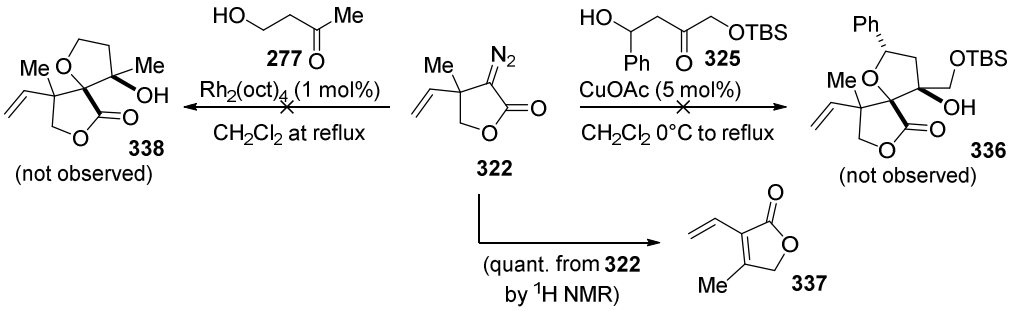
With a strategy for the construction of the spiro-structure of **316** in hand, the attention was then turned towards the preparation of racemic diazo compound **322**. Lactone **335** (available in five steps from hydroxyacetone **299**)[194] was first identified as a suitable precursor for **322** but failed to undergo the trifluoroacetylation/diazo transfer sequence[20a] known for γ-lactones substrates.[195] On the other hand, benzoylation product **334** was found to undergo debenzoylative diazo transfer[20b] to give **322** in a satisfactory yield. Ketoester **334** was also obtained by a more direct route from propargyl ester **332** through a gold-catalysed annulation[196]/cuprate conjugate addition sequence (**Scheme V-289**).



Scheme V-12: preparation of diazo compound 322

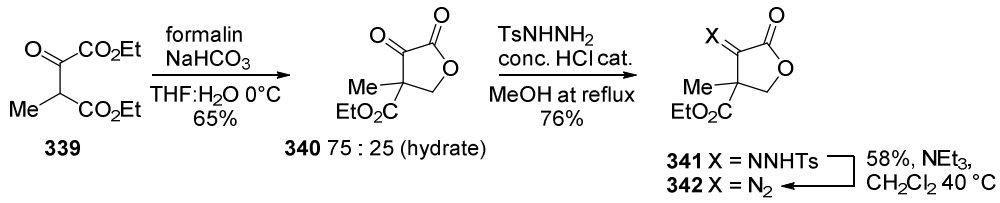
However, diazo compound **322** failed to give any appreciable amounts of spiro-compound **336** when treated under the diverted insertion

conditions previously determined with hydroxyketone **325** (**Scheme V-13**). Instead of the desired insertion product, diazo compound **322** was cleanly converted to a butenolide which was identified as vinyl-migration product **337**. The same outcome was observed using primary ketoalcohol **277**, which should undergo O-H insertion more readily than secondary alcohol **325**. This is not surprising when considering the known enhanced migratory aptitude of the vinyl group[197] (as in **322**) compared with the methyl group (as in **121**) in [1,2] shift reactions known to occur in carbenes and metallocarbenes.[198] Alternatives to the use of **322** were therefore sought.



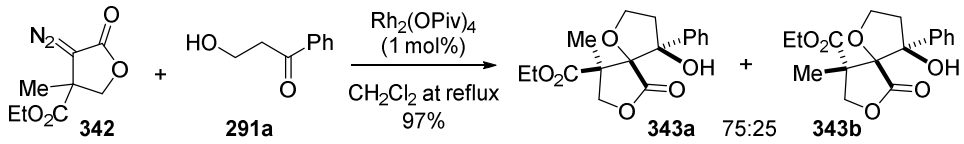
Scheme V-13: preparation of spiro-lactone 336

Racemic diazo compound **342** was selected for further studies on the basis that the replacement of the vinyl group of **322** by an ester group might reduce issues previously encountered with fast [1,2]-migration at the corresponding metallocarbene. Diazo compound **342** was obtained in a straightforward manner in three steps from ketoester **339** via tosylhydrazone **341** (**Scheme V-14**).



Scheme V-14: preparation of diazo compound 342

To evaluate the diastereoselectivity of the diverted insertion reaction using diazo compound **342**, this substrate was reacted with hydroxyketone **291a** in the presence of rhodium pivalate as the catalyst (**Scheme V-15**). A high yield of a partially separable mixture of two diastereoisomers was obtained, which after careful investigation revealed to be spiro-compounds **343a** and **343b** in a 75:25 ratio. The structure of the major isomer **343a** was determined on the basis of a NOESY experiment. This result illustrates the existence of a moderate differentiation between the two faces of lactone **342** during the insertion/cyclisation event. The preferential formation of **343a** can be explained on the basis of stronger steric repulsions between the phenyl group of **291a** and the larger ethyl ester group of **342**.



Scheme V-15: diverted insertion reaction of diazo compound 342 and hydroxyketone 291a

When diazo compound **342** was used in conjunction with hydroxyketone **325**, inseparable mixtures containing four diastereoisomers were obtained (**Table V-4**), which were identified as spiro-lactones **344a-b** on the basis of their spectral data and of results obtained previously. In particular, the structures **344a** and **344b** were attributed to the major

isomers in mixture on the basis of further transformations. The use of copper(I) acetate as the catalyst gave a poor selectivity (entry 1) whereas a series of rhodium catalysts gave a moderate selectivity for **344a** and **344b** over **344c** and **344d** (entries 2-5). The best results were obtained using rhodium octanoate as the catalyst (entry 2). Interestingly, the apparent metal complex dependence of the product isomeric distribution challenges the metal-free cyclisation step proposed in **Section I.3**.

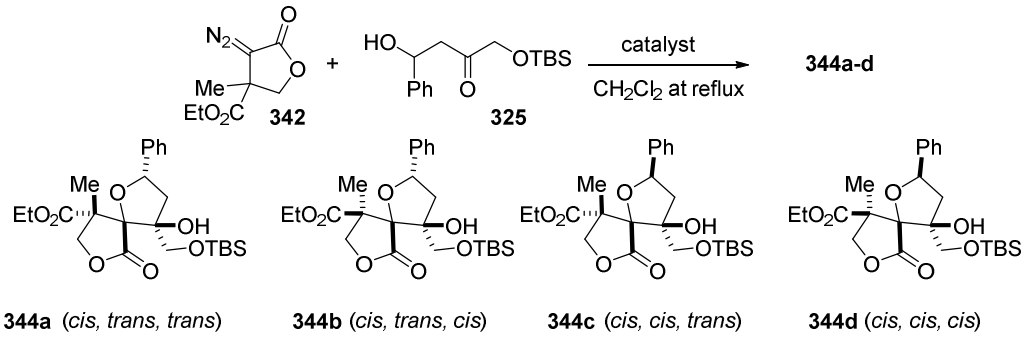


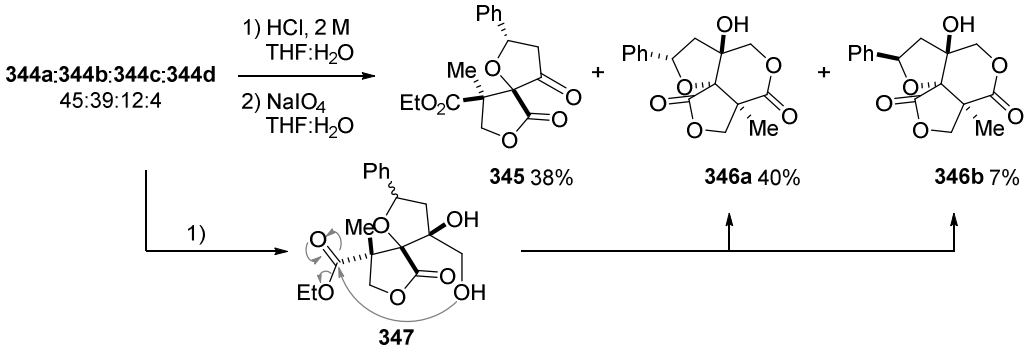
Table V-4: diverted insertion reaction of diazo compound 342 and hydroxyketone 325

entry	catalyst	yield %	ratio **344a** : **344b** : **344c** : **344d**
1	CuOAc (5 mol%)	67	33 : 33 : 14 : 20
2	$Rh_2(OAc)_4$ (1 mol%)	75	60 : 27 : 9 : 4
3	$Rh_2(OPiv)_4$ (1 mol%)	58	48 : 38 : 12 : 1
4	$Rh_2(esp)_2$ (1 mol%)	30	48 : 34 : 14 : 4
5	Rh_2(*S*-DOSP)$_4$ (1 mol%)	48	45 : 39 : 12 : 4

Overall yields for the diverted insertion process were found to be moderate to good, proving the reduced tendency of diazo compound **342** to give carbene rearrangement products when compared to diazolactones **322** or **121**. The isomer distribution of **344a-d** underlines the poor facial selectivity exerted by the C-4 subsituents of diazolactone **342** (**344a/344c** : **344b/344d** = 69 : 31, entry 2), giving in small excess the isomers **344a** and **344c** which exhibit the same geometry as

hyperolactone C **316**. On the other hand, the preference for the tetrahydrofuran (C-5) *trans*-isomer (**344a**/**344b** : **344c**/**344d** = 87:13) reflects previous results obtained with diazo compound **121**.

As isomers **344a-d** could not be separated, they were carried through the deprotection/oxidative cleavage steps as a mixture (**Scheme V-16**). This sequence resulted in the isolation of the expected spiro-lactone **345** along with two tricyclic products **346a-b**. The latter compounds are likely derived from an intramolecular transesterification of intermediate diol **347** occurring under the acidic deprotection conditions. No other deprotection conditions were investigated.



Scheme V-16: further reactions of spiro-lactones 344a-d

IV. Conclusion

The metal catalysed diverted insertion reaction of diazo compounds and β-hydroxyketones has been discovered and developed to allow the construction of densely functionalised 3-hydroxytetrahydrofurans using a variety of substrates and with a high degree of stereoselectivity. Although an asymmetric version of this reaction was not fully investigated, some encouraging results were obtained using a chiral copper catalyst. The use of chiral Lewis acids or chiral Brønsted acid, as discussed in **Chapter IV**,

were not investigated in the present case, but might offer another opportunity to render this process asymmetric.

In an attempt to apply this methodology to the synthesis of hyperolactone C **316**, several major obstacles were encountered. Although the key spiro-structure containing a dihydrofuranone ring was successfully constructed (i.e. **331a-b** and **345**), the introduction of key functionalities via a substituted diazolactone were hampered by [1,2]-migration events on the metallocarbene (using diazo compounds **121** and **322**) and by poor diastereoselectivity (using **342**). Careful selection of the diazo component of the reaction and investigation of further catalyst systems for the insertion/cyclisation step should allow for better control over both these parameters and offer an access to hyperolactone C and related compounds.

Chapter VI - Synthesis of substituted pyrrolidines by diverted insertion reactions

„Alles hat ein Ende nur die Wurst hat zwei“ [everything has an end except the sausage, which has two] **S. Remmler, 1986**

I. Aminoketones in diverted insertion reactions

I.1. Introduction

Functionalised pyrrolidines feature in a number of bioactive compounds occurring in Nature and generated by modern drug development programmes. In particular, the 3-hydroxypyrrolidine motif is represented amongst natural products such as the mycotoxin paraherquamide **348**,[199] the potent proteasome inhibitor salinosporamide A[200] **349** and the apoptosis inducing peptides polyoxypeptin A and B **350a-b** (**Figure VI-1**).[201]

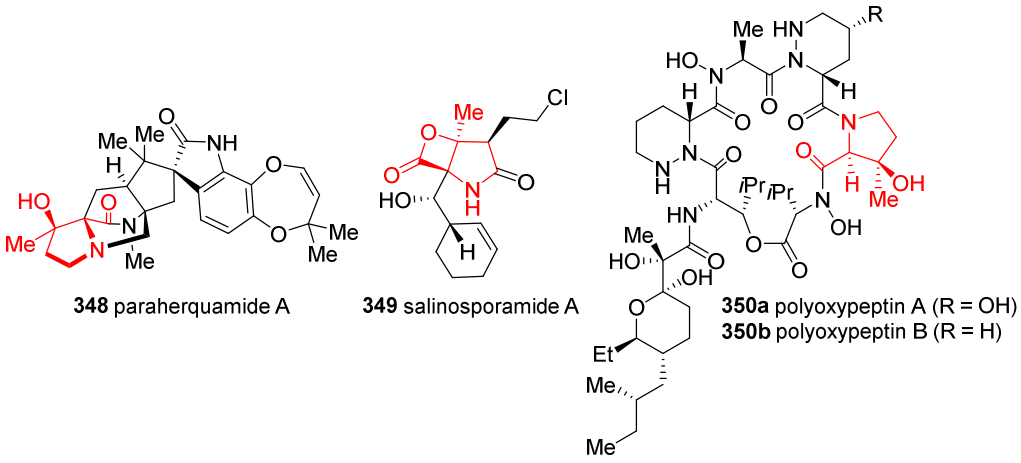
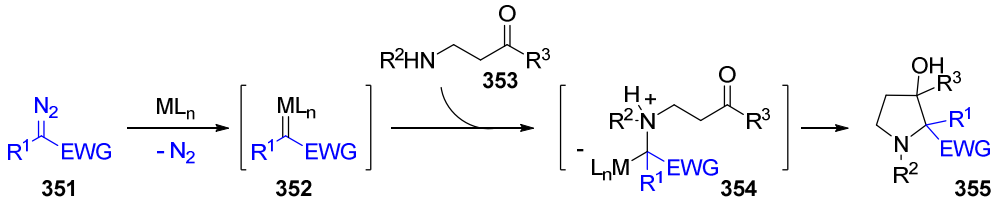


Figure VI-1: naturally occurring compounds possessing a 3-hydroxypyrrolidine motif

Following on from the development of a diverted insertion approach to tetrahydrofurans from the metal catalysed reaction of diazo compounds with β-hydroxyketones (described in **Chapter V**), an adaptation of this method to the synthesis of 3-hydroxypyrrolidines was investigated. Based on the same principle as the analogous O-H insertion, the generation of a transient ammonium ylide intermediate **354** from the attack of amine

353 onto metallocarbene **352** is expected to lead to cyclisation onto the neighbouring ketone to give pyrrolidine **355** (**Scheme VI-1**).



Scheme VI-1: synthesis of 3-hydroxypyrrolidines by diverted insertion reaction

In fact, similar reports by the group of Hu have highlighted the viability of this route (discussion in **Chapter IV**, **Section II.3**). In particular, it was shown that aminoketones generated *in situ* by conjugate addition of aniline derivatives **356** onto 4-oxo-enoates **358**, give 3-hydroxypyrrolidines **359** by a diverted insertion reaction with aryldiazoacetates **357** (**Figure VI-2**).[155c] Under the same conditions, aminophenylketone **361** gives clean conversion to the corresponding *cis*-3-hydroxyindolines **360**.[158]

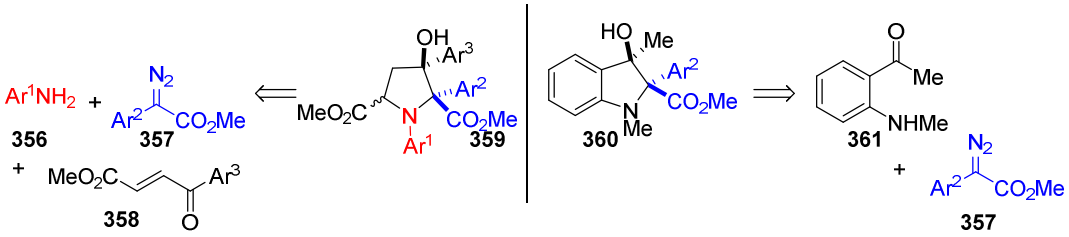


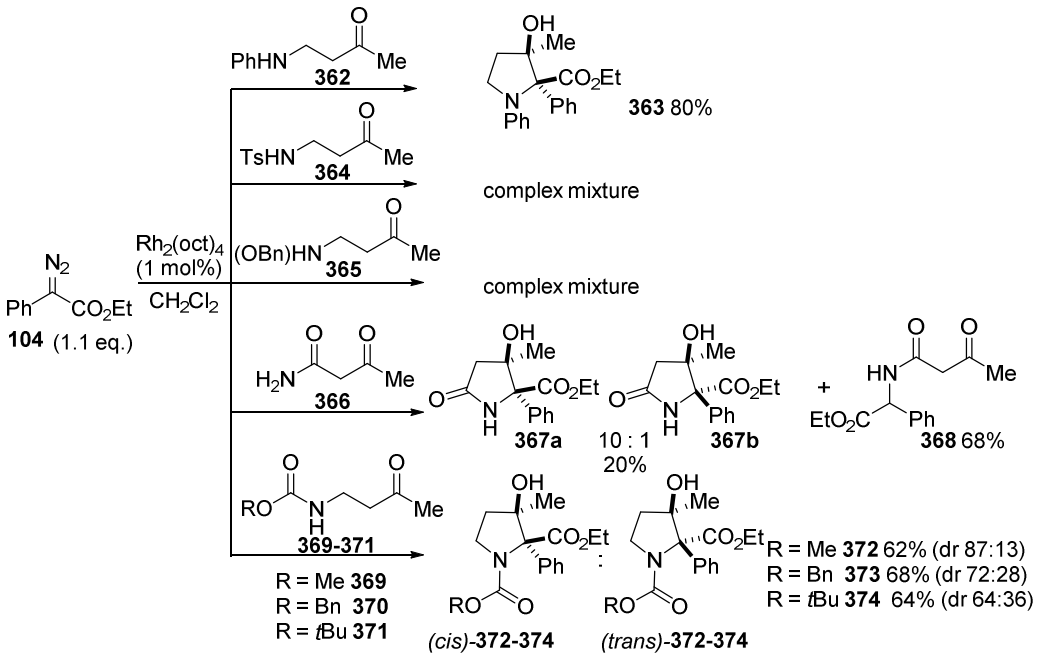
Figure VI-2: previously reported examples of the title process

These examples illustrate the possibility of inducing cyclisation by intramolecular ylide trapping with high stereoselectivity when aniline derivatives are used. In fact, a number of other amine derivatives are known to undergo N-H insertion under metal complex catalysis (carbamates, amides, as discussed in **Chapter I**), but their use for the

construction of pyrrolidines by the diverted insertion reaction has not been documented. In particular, the use of removable *N*-functional groups could enhance the synthetic utility of this process. Investigations on the use of various aminoketone derivatives in diverted insertion reactions are presented in this Chapter.

I.2. Screening of various aminoketones

The rhodium octanoate catalysed reactions of series of aminoketones derivatives **362**, **364-366**, and **369-371** with phenyldiazoacetate **104** was investigated (**Scheme VI-2**). This initial screening revealed that, as suggested by Hu's previous report,[155c] *N*-aryl aminoketone **362** led to the corresponding pyrrolidine as a single diastereoisomer (identified as the *cis*-isomer **363**) with no traces of simple N-H insertion product. On the other hand, sulfonamide **364** and *N*-benzyloxy amine **365** gave complex mixtures of products. Interestingly, the use of acetoacetamide **366** led to the isolation of the *cis*-pyrrolidinone **367a** in low yield and in mixture with an isomeric product which was identified as the *trans*-isomer **367b**. In this case, the N-H insertion product **368** was obtained as the main product. A series of ketocarbamates **369-371** were found to give moderate yields of diverted insertion products **372-374** which were isolated in all cases as inseparable mixtures of *cis*- and *trans*-isomers. Identification of the major isomer in the mixtures was rendered difficult by the pronounced rotameric behaviour of **372-374** in solution in deuterated solvents at room temperature.



Scheme VI-2: screening of aminoketone derivatives

Further investigations were carried out for the three classes of aminoketone derivatives identified in the screening as potential reaction partners in the diverted insertion reaction. The results are presented in the following Sections.

II. Use of acetoacetamides for the synthesis of pyrrolidinones

The use of acetoacetamides in diverted insertion reactions to give 3-hydroxypyrrolidinones (such as **367a-b**, **Scheme VI-2**) is of particular interest due to the existence of a number of natural products based on this structure. Nonpeptidic proteasome inhibitors lactacystin **375**, omuralide **376** (isolated from a *Streptomyces* strain),[202] salinosporamides A **349** and B **377** (isolated from bacterium *Salinospora tropica* found in marine sediments)[200,203] are all found to display strong proteasome inhibition activity and have for this reason attracted a great

deal of attention from both academia and industry as a potent candidate for cancer therapy (**Figure VI-3**).[204]

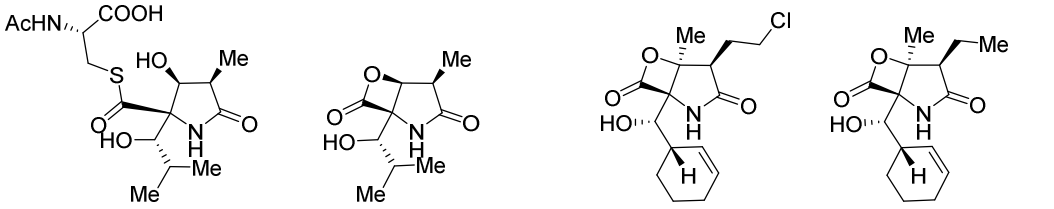


Figure VI-3: salinosporamide A and structurally related compounds

As already presented (**Scheme VI-2**), the rhodium octanoate catalysed reaction of diazo compound **104** and acetoacetamide **366** yields a mixture of N-H insertion product **368** and cyclic products **367a-b**. A variety of conditions was screened to investigate the possibility of favouring the formation of pyrrolidinones **367a-b** over that of linear product **368** (**Table VI-1**). Amongst the various metal catalysts used (entries 1-8), only rhodium dimer catalysts were found to promote the formation of **367a-b**, albeit in low yield. Using rhodium octanoate, several variations of the reaction conditions such as the concentration (entries 8-10), the reaction temperature (entry 11) and solvent used (entries 12-14) did not lead to significant changes in the **367**:**368** ratio. The use of various additives such as Lewis acids (entries 15-17), Brønsted acids (entries 18-19) or triethylamine (entry 20) did not influence the final products ratio, while solely showing detrimental effects on the overall yield of the reaction. Using diazo compound **104** in a larger excess under rhodium pivalate catalysis gave the cyclic products **367a-b** in a 34% yield (ratio **367a**:**367b** 8:2). In all cases, an unseparable mixture of pyrrolidinones **367a-b** (**367a**:**367b** ratios varied from 10:1 to 8:2) was

obtained. The relative configuration of pyrrolidinone **367a** was determined on the basis of a NOESY experiment.

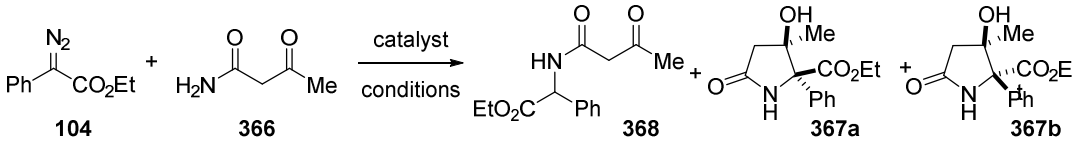


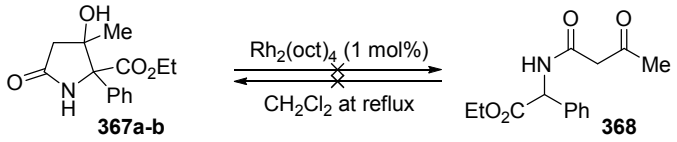
Table VI-1: conditions screening in the preparation of cyclic products 367a-b

entry	catalyst	additive	conditions	yield **368** %	yield **367a-b** %[a]	ratio **368**:**367a-b**
1	$Rh_2(tfa)_4$ (1 mol%)	none	CH_2Cl_2 reflux, 1.1 eq **104** 30min	27[b]	5[b]	84:16
2	$Rh_2(pfmb)_4$ (1 mol%)	none	CH_2Cl_2 reflux, 1.1 eq **104** 16h	40[b]	11[b]	78:12
3	CuOTf (5 mol%)	none	CH_2Cl_2 reflux, 1.1 eq **104**	traces	n.d.	/
4	$Cu(acac)_2$ (5 mol%)	none	CH_2Cl_2 reflux, 1.1 eq **104**	no reaction		/
5	$Cu(hfacac)_2$ (5 mol%)	none	CH_2Cl_2 reflux, 1.1 eq **104**	no reaction		/
6	$[Ru(p\text{-}Cy)Cl_2]_2$ (2 mol%)	none	CH_2Cl_2 reflux, 1.1 eq **104**	70[b]	n.d	100:0
7	Fe(III)ClTPP (1 mol%)	none	CH_2Cl_2 reflux, 1.1 eq **104**	no reaction		/
8	$Rh_2(oct)_4$ (1 mol%)	none	CH_2Cl_2 reflux, 1.1 eq **104** C = 0.1 M	68	20	77:23
9	$Rh_2(oct)_4$ (1 mol%)	none	CH_2Cl_2 reflux, 1.1 eq **104** C = 0.05 M	76[b]	22[b]	77:23
10	$Rh_2(oct)_4$ (1 mol%)	none	CH_2Cl_2 reflux, 1.1 eq **104** C = 0.2 M	75[b]	21[b]	78:22
11	$Rh_2(oct)_4$ (1 mol%)	none	CH_2Cl_2 –5 °C to RT, 1.1 eq **104**	42	25	63:37
12	$Rh_2(oct)_4$ (1 mol%)	none	PhMe reflux, 1.1 eq **104**	62	24	72:28
13	$Rh_2(oct)_4$ (1 mol%)	none	MeCN RT, 1.1 eq **104**	48[b](49)[c]	23[b](17)[c]	68:32
14	$Rh_2(oct)_4$ (1 mol%)	none	THF RT, 1.1 eq **104**	45[b](44)[c]	17[b](6)[c]	73:27
15	$Rh_2(oct)_4$ (1 mol%)	$Zn(OTf)_2$ (10 mol%)	CH_2Cl_2 reflux, 1.1 eq **104**	59	18	77:23
16	$Rh_2(oct)_4$ (1 mol%)	$TiCl_4$ (15 mol%)	CH_2Cl_2 reflux, 1.1 eq **104**	37[b]	n.d	100:0
17	$Rh_2(oct)_4$ (1 mol%)	$Ti(i\text{PrO})_4$ (15 mol%)	CH_2Cl_2 reflux, 1.1 eq **104**	76[b]	10[b]	88:12
18	$Rh_2(oct)_4$ (1 mol%)	BzOH (100 mol%)	CH_2Cl_2 reflux, 1.1 eq **104**	55	15	79:21

entry	catalyst	additive	conditions	yield **368** %	yield **367a-b** %[a]	ratio **368**:**367a-b**
19	$Rh_2(oct)_4$ (1 mol%)	PA[d] (20 mol%)	CH_2Cl_2 reflux, 1.1 eq **104**	44[b]	22[b]	67:33
20	$Rh_2(oct)_4$ (1 mol%)	NEt_3 (100 mol%)	CH_2Cl_2 reflux, 1.1 eq **104**	63	17	79:21
21	$Rh_2(piv)_4$ (1 mol%)	none	CH_2Cl_2 reflux, 1.3 eq **104**	53	34	61:39

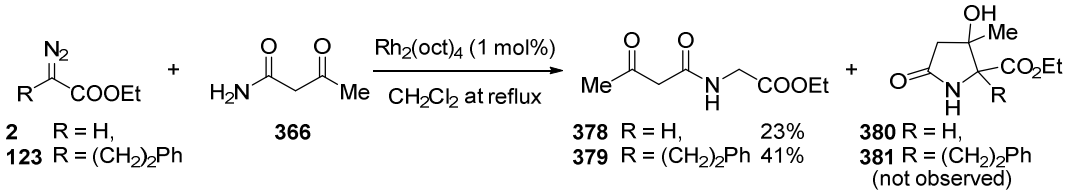
[a] products **367a-b** were obtained in a ratio varying from 4:1 to 10:1; [b] LC-MS yields (based on calibration); [c] yield in brackets is isolated yield; [d] PA refers to (*rac*)-BINOL derived phosphoric acid.

Control experiments revealed that the linear product **368** is not converted into pyrrolidinones **367a-b** under the reaction conditions determined above. Similarly, cyclic products **367a-b** do not undergo retro-aldol reaction to give **368** under the same conditions (**Scheme VI-3**).



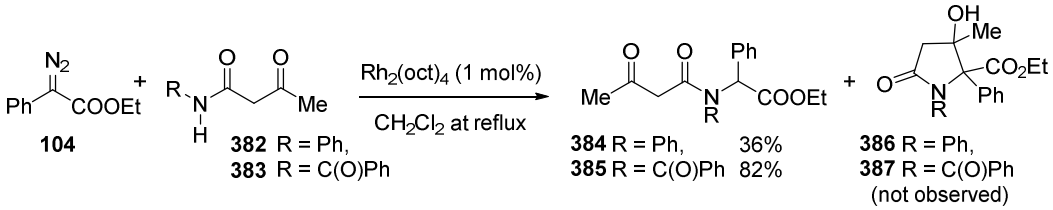
Scheme VI-3: control experiments

The influence of the diazo compound structure was briefly studied with the application of the standard reaction conditions to ethyl diazoacetate **2** and alkyl diazoacetate **123**. In both cases, only the linear product was isolated in typically low yields due to major competitive reaction pathways, namely carbene dimerisation for **2** and metallocarbene α-hydride shift in the case of **123** (see **Scheme VI-4**).

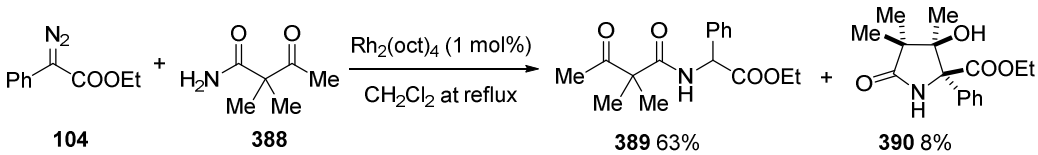


Scheme VI-4: diverted insertion reaction using acetoacetamide 366

Some structural modifications to the acetamide component were also implemented. *N*-Phenyl acetoacetamide **382** and imide **383** gave only the corresponding linear N-H insertion products **384-385** and the corresponding cyclic products **386-387** were not observed (**Scheme VI-5**). The use of dimethylacetamide **388** was expected to promote cyclisation by suppressing the keto-enol equilibrium and thus enhancing the ketone reactivity and by making use of the known gem-dialkyl effect (also called the Thorpe-Ingold effect).[205] The effect observed was opposite, as the products **389** and **390** were obtained in a combined 71% in a 9:1 ratio in favour of the open chain product (**Scheme VI-6**), In comparison, a ratio of 77:23 was obtained without the gem-dimethyl groups (**Table VI-1**, entry 8). Cyclic product **390** was obtained as one isomer which was identified as the *cis*-pyrrolidinone on the basis of the trend previously observed.



Scheme VI-5: diverted insertion reaction using acetoacetamides 382-383



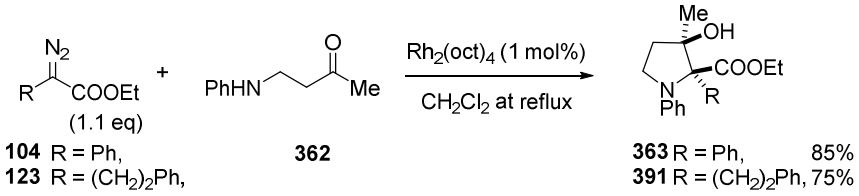
Scheme VI-6: diverted insertion reaction using acetoacetamide 388

To conclude, the use of acetoacetamide in diverted insertion has been shown to lead to 3-hydroxypyrrolidinones in a limited number of examples. In all cases, the N-H insertion product was obtained as the main

product. While variations of a number of reaction parameters was found to have no influence on the reaction output, the investigation of the substrate steric and electronic requirements in further studies might allow for improvements in the product selectivity of this reaction.

III. Use of *N*-aryl aminoketones for the synthesis of pyrrolidines

As established during the initial screening (**Section I.2**), the diverted insertion reaction of aryldiazo compound **104** with *N*-phenyl aminoketone **362** gives a good yield of pyrrolidine **363** as the *cis*-isomer exclusively. Similarly, the use of diazo compound **123** gave the corresponding *cis*-pyrrolidine **391** in 75% yield, thus showing that the insertion process is in this case favoured over the metallocarbene [1,2]-H migration which is commonly encountered with this type of substrate (**Scheme VI-7**).



104 R = Ph,
123 R = $(CH_2)_2$Ph,

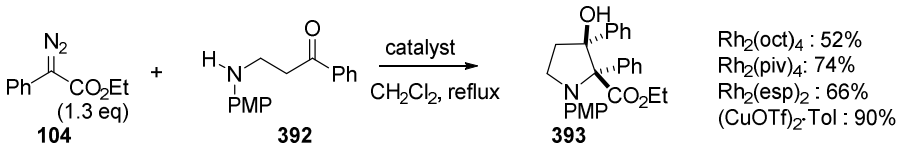
362

363 R = Ph, 85%
391 R = $(CH_2)_2$Ph, 75%

Scheme VI-7: synthesis of *N*-phenyl pyrrolidines 363 and 391

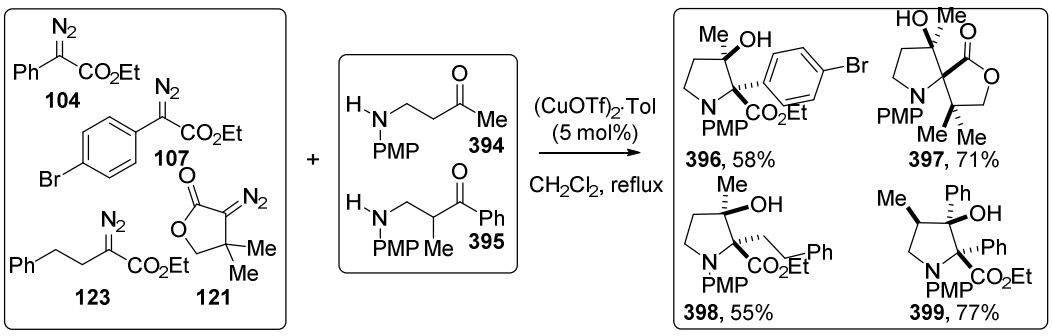
Despite the good results obtained using aminoketone **362**, the difficulty of removing the *N*-phenyl group for further functionalisation of the corresponding pyrrolidine prompted the investigation of an alternative substrate. *N*-*para*-Methoxyphenyl (PMP) aminoketone **392** was chosen as *N*-PMP-groups can be cleaved under oxidative conditions.[206] A simple change in the electronic nature of the *N*-aryl group from phenyl in **362** to

PMP in **392** led to a consequent drop in the yield of the corresponding pyrrolidine **393** under rhodium octanoate dimer catalysis. A short catalyst screening revealed copper(I) triflate as a superior catalyst and pyrrolidine **393** was obtained in 90% as a single isomer (**Scheme VI-8).**



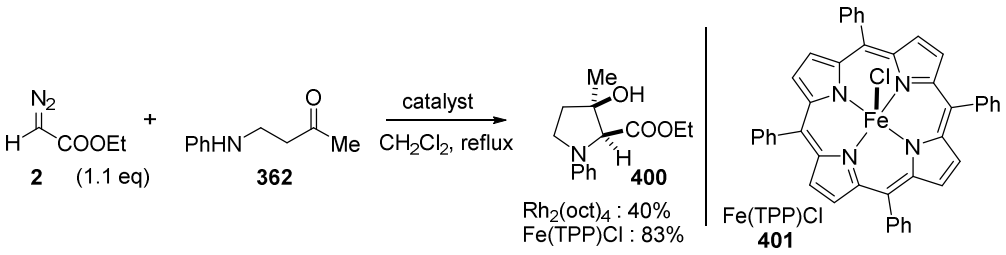
Scheme VI-8: synthesis of *N*-PMP pyrrolidine 393

Using the conditions established above, a small set of diazo compounds and *N*-PMP aminoketones were converted to the corresponding *N*-PMP pyrrolidines to investigate some of the possibilities offered by this process (**Scheme VI-9**). Doing so, it was confirmed that alkyl diazoesters such as **123** and **121** as well as *p*-bromophenyl diazoacetate **107** are competent substrates for this reaction. Additionally, the use of α-substituted aminoketone **395** led to the isolation of C-4 substituted *cis,cis*-pyrrolidine **399** as a single diastereoisomer, therefore illustrating a high level of diastereoselectivity of the cyclisation process (analogous to that previously found in the tetrahydrofuran derivatives presented in **Chapter V**).



Scheme VI-9: preparation of various *N*-PMP pyrrolidines

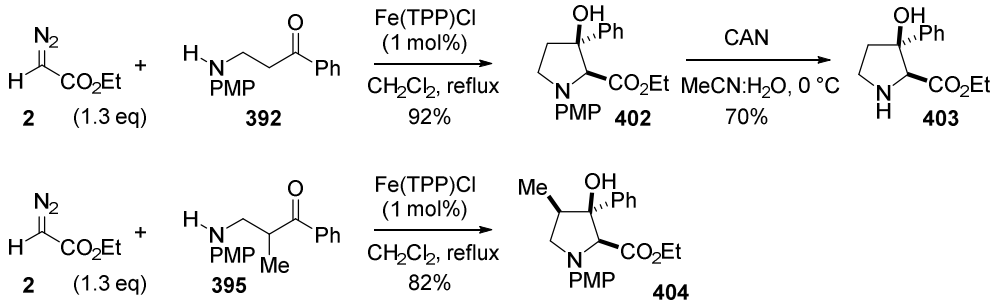
When ethyl diazoacetate (EDA) **2** was used in conjunction with aminoketone **362** under rhodium catalysis, the corresponding 3-hydroxyproline derivative **400** was obtained in moderate yield along with diethyl maleate and fumarate as evidence for a carbene dimerisation pathway operating under these conditions (**Scheme VI-9**). Iron(III) tetraphenylporphyrin chloride **401** (Fe(TPP)Cl) has previously been reported as a competent catalyst for the N-H insertion of anilines with EDA.[34,207] Using Fe(TPP)Cl as the catalyst for the reaction of aminoketone **362** and EDA **2** resulted in the clean formation of cyclic product **400** as a single diastereoisomer in 83% yield.



Scheme VI-10: preparation of pyrrolidine 400 by iron catalysed diverted insertion reaction

The result obtained with *N*-phenyl aminoketone **362** translated very well to *N*-PMP aminoketone **392** and the corresponding *N*-PMP pyrrolidine **402** was obtained in a 92% yield using Fe(TPP)Cl as the catalyst (**Scheme VI-11**). More interestingly, the PMP-group of substrate **402** was successfully cleaved using cerium(IV) ammonium nitrate (CAN) to give proline derivative **403**. The structure of pyrrolidine **403** was confirmed by X-ray crystallography (**Figure VI-4**). Additionally, the use of α-substituted aminoketone **395** gave the corresponding (C-4)-substituted

PMP-pyrrolidine as a single product which was identified as the *cis,cis*-isomer **404** on the basis of NOESY-experiments.



Scheme VI-11: iron catalysed pyrrolidines synthesis

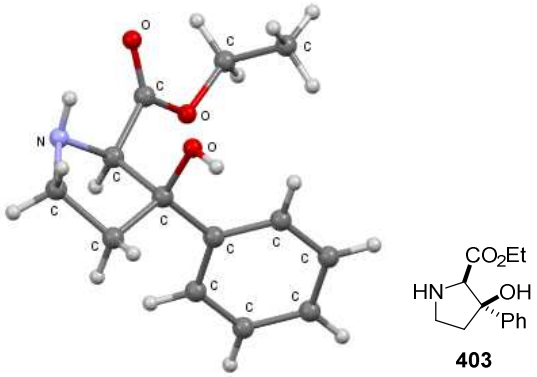


Figure IV-4: crystal structure of pyrrolidine 403

In conclusion, some interesting perspectives have been opened in the use of *N*-aryl aminoketones in diverted insertion reactions. In particular, the use of an iron(III) porphyrin in conjunction with ethyl diazoacetate deserves further investigation into its substrate scope and into the mechanism at work in this transformation. The use of *N*-PMP aminoketones and the possibility of cleaving this group to reveal the free amine clearly expand the applicability of this process.

IV. Ketocarbamates for the synthesis of pyrrolidines

The use of carbamates in N-H insertion reaction presents the clear advantage of facilitating *N*-group cleavage to allow for further functionalisation of the products. Nevertheless, the decreased nucleophilicity of the carbamate nitrogen, compared to aniline derivatives, make N-H insertion processes using carbamates a more challenging transformation. In fact, the carbamate N-H insertion process has been proposed to follow a concerted mechanism,[208] in analogy with C-H insertion processes, although evidences for a stepwise mechanism have later been reported by Hu and co-workers.[167]

IV.1. Reaction optimisation

An initial screening of reaction conditions using phenyl diazoacetate **104** and ketocarbamates **369**-**371** revealed that rhodium octanoate promotes the N-H insertion/cyclisation process to give pyrrolidines **372**-**374** in moderate yields and as inseparable mixture of isomers (**Table VI-2**, entries 1-3). Identification of the isomers **372**-**374** was made difficult due to their isolation as mixtures and their rotameric behaviour in solution at room temperature. The major component in the mixture was later identified as the *cis*-isomer (shown in *cis*-**372**-**374**). The overall yield was increased using a larger excess of diazo compound **104** (entry 4). Under these conditions, the use of rhodium pivalate dimer gave pyrrolidine **372** as a single diastereoisomer which was identified as the *cis*-isomer (entry 5). While rhodium catalyst performed better than copper catalyst

with substrates **369** and **371** (entries 6-7), a series of rhodium carboxylate dimer catalysts were screened revealing rhodium pivalate as the superior catalyst with substrate **371** (entries 8-13). In a number of cases, unidentified products from intramolecular processes on the metallocarbene derived from **104** were detected, while a large amount of unreacted aminoketone **371** was recovered. This observation shows that the success of the intermolecular carbamate N-H insertion might easily be superseded by competing intramolecular metallocarbene pathways. Remarkably, only the *cis*-isomer of pyrrolidine **374** was identified during this screening, and the structure of this compound was confirmed by X-ray crystallography (**Figure VI-8**). Variation of some reaction parameters such as temperature and solvent (entries 14-18) had only a detrimental effect on the insertion yield. In particular, when THF was used as the solvent (entry 15), C-H insertion involving solvent molecules, a previously documented process,[52] was found to be the main reaction. An increased excess of diazo compound allowed full conversion of aminoketone **371** (entry 20) and a further yield improvement was brought about by the use of Dubois' catalyst, rhodium carboxylate $Rh_2(esp)_2$ **405**[209] (entry 20, **Figure VI-5**). Using complex **405**, the catalyst loading was decreased down to 0.25 mol% without significant decrease in the isolated yield of **374** (entry 21). Interestingly, and contrary to the analogous tetrahydrofuran synthesis (**Chapter V**), the addition of triethylamine to the reaction mixture totally inhibited the insertion process giving a complex mixture of products (entry 22).

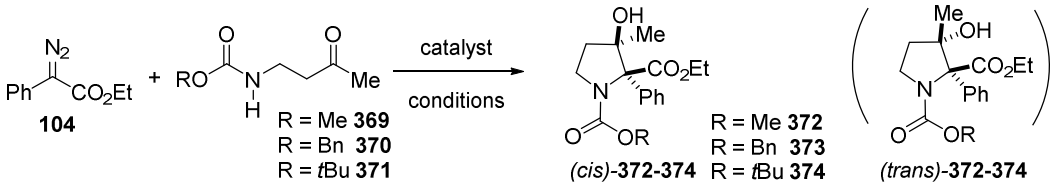


Table VI-2: conditions screening in the preparation of pyrrolidines 372-374 from ketocarbamate derivatives 369-371

entry	R =	Catalyst	conditions	yield **372-374** % (dr)	**369-371** recovered %
1	Boc	$Rh_2(oct)_4$ (1mol%)	DCM reflux[a] **104:371** = 1.1:1	46 (36:64)	n.d[c]
2	Cbz	$Rh_2(oct)_4$ (1mol%)	DCM reflux[a] **104:370** = 1.1:1	68 (28:72)	n.d
3	Me	$Rh_2(oct)_4$ (1mol%)	DCM reflux[a] **104:369** = 1.1:1	62 (13:87)	n.d
4	Me	$Rh_2(oct)_4$ (1mol%)	DCM reflux[a] **104:369** = 1.3:1	87 (17:83)	11
5	Me	$Rh_2(piv)_4$ (1mol%)	DCM reflux[a] **104:369** = 1.3:1	78 (> 20:1)	20
6	Me	$Cu(hfacac)_2$ (5mol%)	DCM reflux[a] **104:369** = 1.3:1	32 (> 20:1)	n.d
7	Boc	$(CuOTf)_2$·Tol (5mol%)	DCM reflux[b] **104:371** = 1.3:1	Traces	80
8	Boc	$Rh_2(oct)_4$ (1mol%)	DCM reflux[b] **104:371** = 1.3:1	67 (> 20:1)	8[d]
9	Boc	$Rh_2(pfbm)_4$ (1mol%)	DCM reflux[b] **104:371** = 1.3:1	11 (> 20:1)	53[d]
10	Boc	$Rh_2(TPA)_4$ (1mol%)	DCM reflux[b] **104:371** = 1.3:1	16 (> 20:1)	72[d]
11	Boc	$Rh_2(S\text{-}DOSP)_4$ (1mol%)	DCM reflux[b] **104:371** = 1.3:1	33 (> 20:1)	40[d]
12	Boc	$Rh_2(S\text{-}PTAD)_4$ (1mol%)	DCM reflux[b] **104:371** = 1.3:1	27 (> 20:1)	48[d]
13	Boc	$Rh_2(piv)_4$ (1mol%)	DCM reflux[a] **104:371** = 1.3:1	77 (> 20:1)	9[d]
14	Boc	$Rh_2(piv)_4$ (1mol%)	DCM 0 °C[b] **104:371** = 1.3:1	30 (> 20:1)	59[d]
15	Boc	$Rh_2(piv)_4$ (1mol%)	THF reflux[b] **104:371** = 1.3:1	Traces[e]	n.d
16	Boc	$Rh_2(piv)_4$ (1mol%)	Toluene reflux[b] **104:371** = 1.3:1	60 (> 20:1)	35[d]
17	Boc	$Rh_2(piv)_4$ (1mol%)	$CHCl_3$ reflux[b] **104:371** = 1.3:1	65 (> 20:1)	25[d]
18	Boc	$Rh_2(piv)_4$ (1mol%)	DCE reflux[b] **104:371** = 1.3:1	35 (> 20:1)	64[d]
19	Boc	$Rh_2(piv)_4$ (1mol%)	DCM reflux[b] **104:371** = 1.5:1	79 (> 20:1)	< 2
20	Boc	$Rh_2(esp)_2$ (1mol%)	DCM reflux[b] **104:371** = 1.5:1	86 (> 20:1)	< 2
21	**Boc**	**$Rh_2(esp)_2$ (0.25mol%)**	**DCM reflux[b] 104:371 = 1.5:1**	**83 (> 20:1)**	**< 2**
22	Boc	$Rh_2(esp)_2$ (1mol%)	DCM reflux[b] +NEt_3 (100 mol%) **104:371** = 1.5:1	0	n.d.

[a] addition time of **104** was 30 min; [b] addition time of **104** was 60 min; [c] n.d. = not determined; [d] isolated as a mixture with cyclic product **374**; [e] C-H insertion into solvent molecules was the main process.

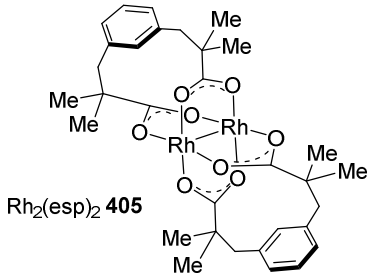
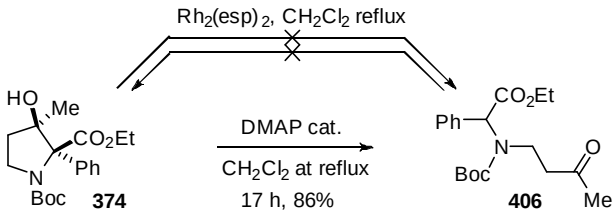


Figure VI-5: structure of $Rh_2(esp)_2$ 405

Importantly, the product **406** resulting from a simple N-H insertion reaction was not observed during the screening of conditions. (**Table VI-2**). This compound was nevertheless produced from pyrrolidine **374** by reaction with a base such as DMAP through a retro-aldol ring opening (**Scheme VI-12**). Neither retro-aldol of **374** to **406**, nor cyclisation of product **406** to **374**, were observed under the neutral N-H insertion reaction conditions. This result confirms the hypothesis that **406** is not a precursor of pyrrolidine **374** under the reaction conditions, in agreement with the mechanism outlined in **Scheme VI-1**.



Scheme VI-12: control reactions

IV.2. Scope of the process

With the optimised reaction conditions, the scope of the process was first investigated using the set of diazo compounds presented in **Figure VI-6** to give the corresponding pyrrolidines, presented in **Scheme VI-13**. It rapidly transpired from this study that the N-H insertion process is highly

sensitive to the electronic nature of the diazo compound employed and clear trends were identified.

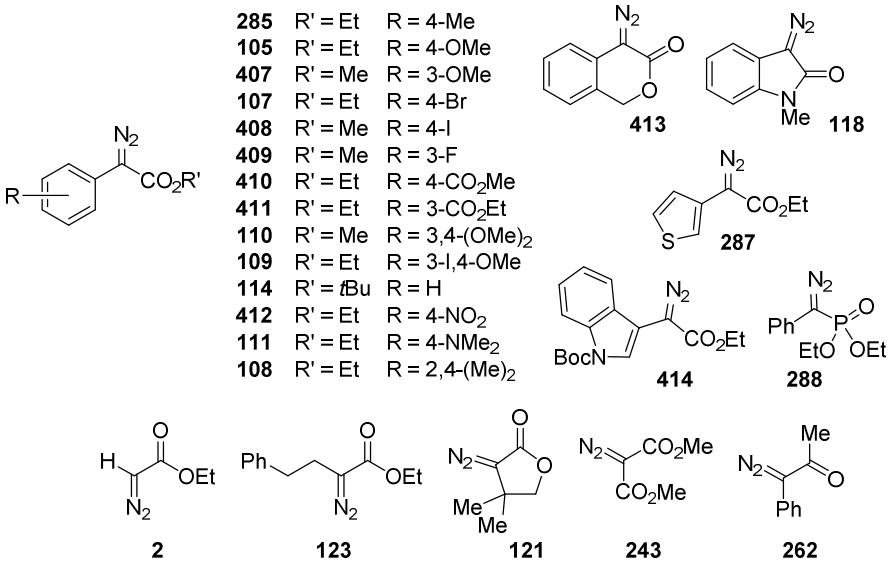
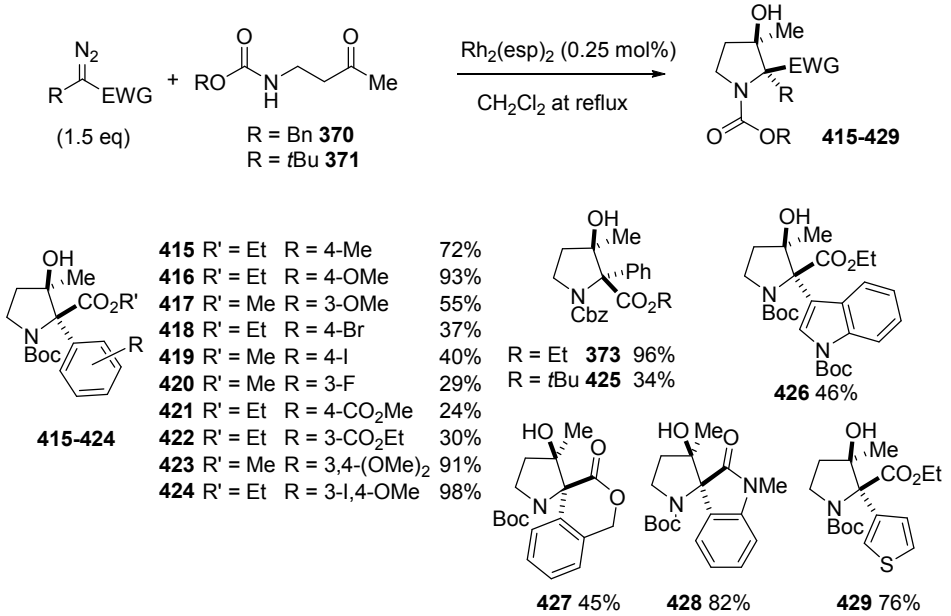


Figure VI-6: diazo compounds used in this study



Scheme VI-13: *N*-Boc pyrrolidines products

When electron-rich aryldiazo compounds such as **285**, **105**, **407**, **110**, **109**, **118**, and **287** were used, the corresponding pyrrolidines **415-417**, **423-424** and **428-429** were obtained in high yield (with the exception of

4-dimethylamino **111** which led to a complex mixture of products). On the other hand, the presence of a single halogen substituent on the aromatic ring (as in 4-bromo **107**, 4-iodo **408** and 3-fluoro **409**) was sufficient to cause a considerable decrease in the efficiency of the process and the corresponding *N*-Boc pyrrolidines **418**-**420** were only obtained in moderate yields. This effect was even more marked when the aromatic ring was substituted with an electron-withdrawing group in the 4- or even 3-position, such as in diazo compounds **410** and **411** (products **421** and **422** were obtained in 24% and 30% yield, respectively). The insertion process was inhibited by the use of strongly electron-withdrawing groups; in particular, no pyrrolidine formation was observed using 4-nitrophenyldiazo compound **412**.

In these low yielding examples, the production of a complex mixture of products was observed, amongst which compounds **430**-**432** were commonly identified on the basis of NMR and ESI-MS data (**Figure VI-7**). The possibility of an *O*-attack of the carbamate on the transient metallocarbene followed by *tert*-butyl group cleavage explains the formation of product **430**,[210] while the presence of water can lead to O-H insertion to give **432**. The formation of products of type **431**, on the other hand, is less easily explained and might be initiated by formation of an alkoxyketene by Wolff-rearrangement of the metallocarbene (similar metal-catalysed processes are known, for example with silylated diazoester[211] or in the thermal and photochemical reactions of cyclic diazoesters).[212]

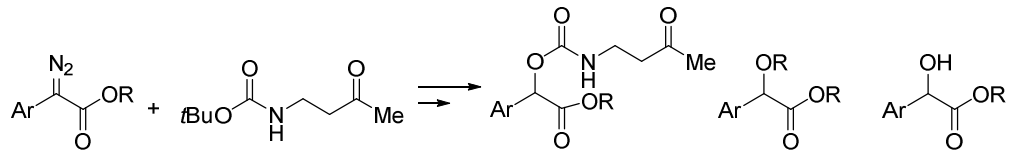


Figure VI-7: by-products observed

The pyrrolidine synthesis presented in **Scheme VI-13** was also found to be sensitive to steric factors such as *ortho*-substitution of the aryl group on the diazo component. 2,4-Dimethylphenyl diazo compound **108** (**Figure VI-6**) gave a complex mixture of products in which traces of the corresponding pyrrolidine were identified. Additionally, *tert*-butyl phenyldiazoacetate **114** gave pyrrolidine **425** in only 34% yield, while ethyl phenyldiazoacetate **104** gave *N*-Cbz pyrrolidine **373** in 96% yield. A number of diazo compounds were unsuitable for this reaction: ethyl diazoacetate **2** gave carbene dimerisation products exclusively; alkyl diazo compounds **123** and **121** gave metallocarbene [1,2]-migration products; diazophosphonate **288** failed to react under the given conditions; diazoketone **262** gave a complex mixture of products and diazomalonate **243** predominantly gave the linear N-H insertion product.

When pyrrolidines were successfully prepared under the optimised conditions (products **415-429**, **Scheme VI-13**), they were invariably found as the *cis*-isomer exclusively and in no case was the *trans*-isomer detected. All products **415-429** showed rotameric equilibrium at room temperature in deuterated solvent and variable temperature ^{1}H NMR experiments did not show clear signal coalescence at up to 90 °C. On the other hand, the structure of product **428** was confirmed by X-ray

crystallography, clearly showing the *cis*-arrangement of the hydroxyl- and ester carbonyl functionalities (**Figure VI-8**).

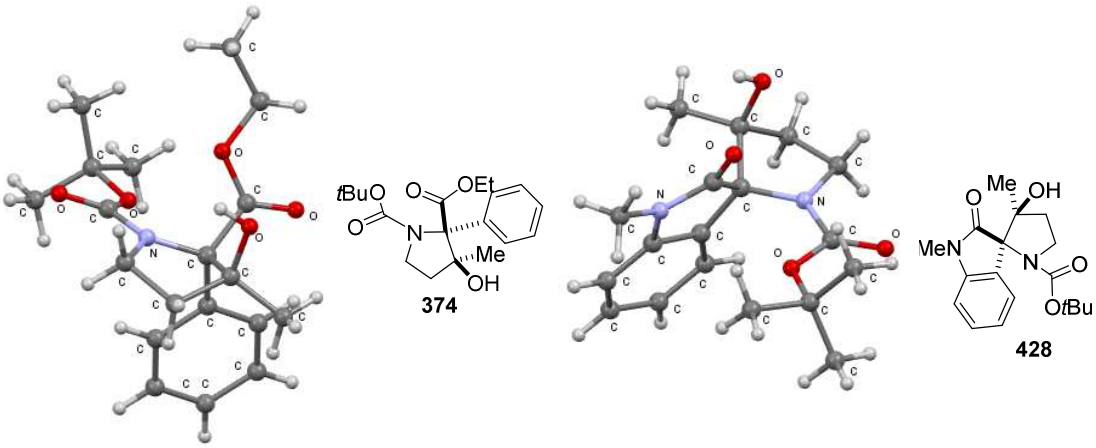


Figure VI-8: crystal structurea of products 374 and 428

Next, the reactions of a series of ketocarbamates with diazo compound **104** under the previously determined optimal conditions were investigated, and the N-H insertion/cyclisation was found to take place with a variety of substrates (**Figure VI-9**, **Scheme VI-14**). Vinylketone **433** gave pyrrolidine **444** in good yield, while ketoester **437** led to functionalised pyrrolidine **448**. The series of aryl ketone **434-436** illustrates the detrimental effect of electron-donating substitution on the aromatic ring (such as in **435**) on the yield of cyclised product. Indeed, *p*-methoxyphenyl pyrroldine **446** was obtained in 38% yield, a result that can be compared with phenyl pyrrolidine **445**, obtained in 81% yield. With α-substituted ketones **439-440**, pyrrolidines **450** and **451** were obtained in high yields and in both cases as the *cis,cis*-isomer, as determined on the basis of NOESY-experiments. This last result is in line with all previous observations (see **Chapter V** and **Section III** of this Chapter). On the other hand, β-substitution of the aminoketone (as in

substrates **441**-**443**) completely inhibited N-H insertion and the corresponding pyrrolidines were not observed.

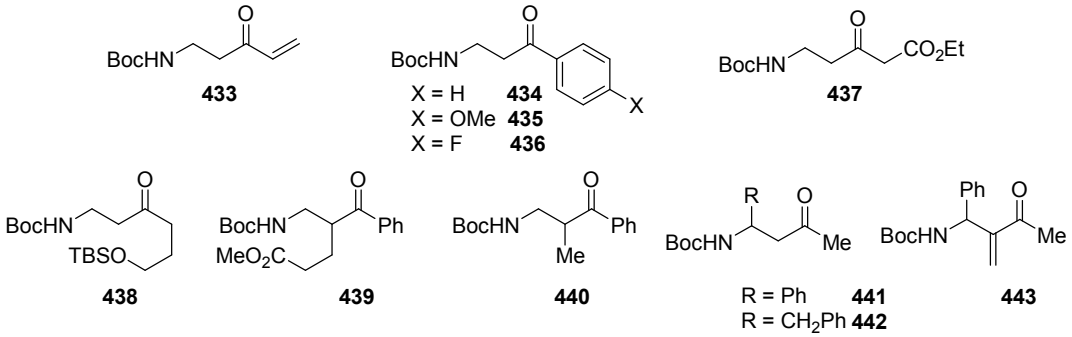
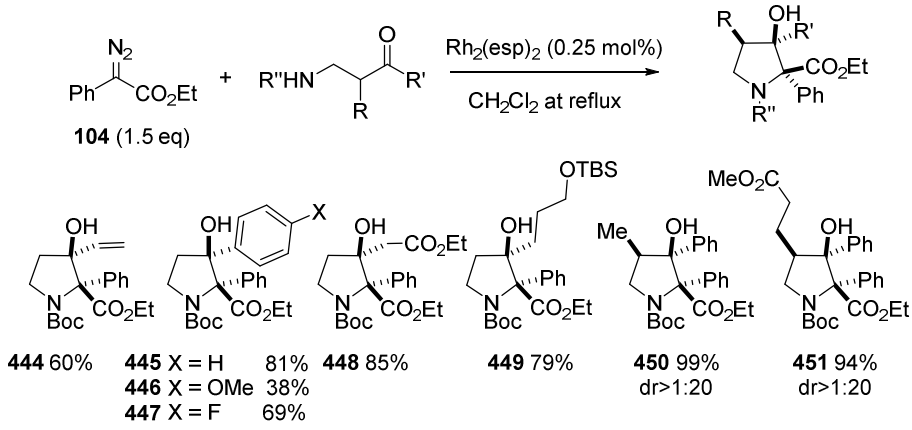


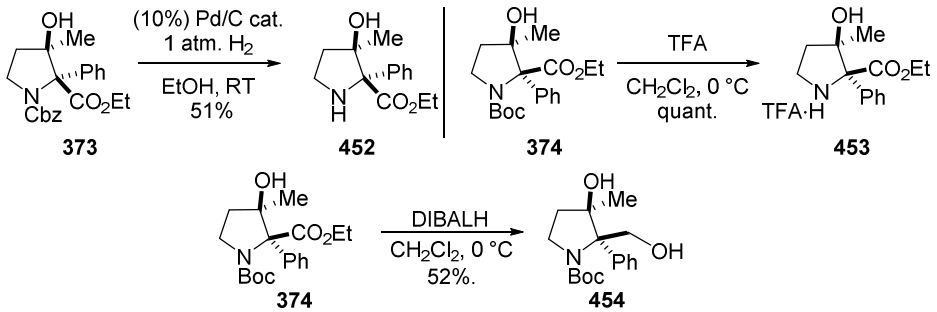
Figure VI-9: ketocarbamates used in this study



Scheme VI-14: *N*-Boc pyrrolidines products

In all the previous examples (**Scheme VI-13** and **VI-14**), the non-detection of the "classical" N-H insertion product suggests that the intramolecular ammonium ylide trapping process is extremely efficient when ketocarbamates (**369-371** and **433-440**) are used, leading exclusively to pyrrolidines when the N-H insertion process can be initiated. On the other hand, the limited scope of the reaction seems to be due to the sensitivity of the N-H insertion process to the electronic nature of the diazo compound and the steric profile of both diazo and ketocarbamate components.

Additionaly, *N*-group cleavage to give the corresponding *N*-*H* pyrrolidines was showed to be possible (**Scheme VI-15**). Thus, *N*-Boc pyrrolidine **374** was converted into trifluoroacetate salt **453** in quantitative yield. Alternatively, Cbz-protected pyrrolidine **373** was converted to the free amine **452** in an unoptimised 51% yield, with the retro-aldol ring opening product accounting for the rest of the mass balance. Reduction of the ester moiety of **374** was also possible and carried out using di*iso*butylaluminium hydride to give diol **454** in 52% yield.



Scheme VI-15: further transformations of pyrrolidines 373 and 374

V. Conclusion

Various β-aminoketone derivatives have been shown to undergo the diverted insertion reaction to give pyrrolidine derivatives. The features of this transformation were found to present some analogies with the methodology based on β-hydroxyketones presented in **Chapter V**, namely a pronounced selectivity for *cis*-pyrrolidines. Although showing promising results, the application of this process to acetoacetamides requires further investigation. The use of *N*-aryl aminoketones, on the other hand, in particular the use of *N*-PMP aminoketones, allows for an efficient synthesis of pyrrolidines under copper(I) or iron(III) catalysis. The diverted insertion reaction of ketocarbamates was finally established as a

synthetically useful, yet more challenging process. An extensive survey of this transformation nevertheless led to a definition of its scope and pointed out the requirements for a successful reaction. Further work on these processes should be aimed at documenting the mechanisms at work depending on the various aminoketone derivatives used. In particular, the role of the metal catalyst during cyclisation needs to be clarified in order to evaluate the possibility of chiral induction from the metal centre to render this process asymmetric.

Conclusion

The research presented in this Thesis spans over various aspects of the chemistry of diazo compounds introduced in **Chapter I**, ranging from the preparation of these versatile intermediates, to the discovery of new processes involving metallocarbene derived from their metal catalysed decomposition.

The initial aim of this work was to develop a user friendly, simple and metal-free procedure for the preparation of diazo compounds from their corresponding unsubstituted hydrazones. This objective was attained through the use of easily available Iodamine-T (potassium *N*-iodo *p*-toluenesulfonamide) described in **Chapter II**. This strategy was subsequently adapted to the generation of diazocarbonyl compounds in flow, through the use of a recyclable *N*-iodosulfonamide functionalised resin. Diazo compounds generated in this fashion were directly used in further rhodium catalysed transformations, without isolation of potential hazardous and unstable diazo intermediates. Using this protocol, small libraries of carbene derived products, such as O-H, N-H insertion products, epoxides, cyclopropanes, and C-H insertion products were obtained (**Chapter III**). In particular, intramolecular C-H insertion gave a series of β-lactones which were converted to the corresponding oxetanes and spiro-oxetane in two steps, thus illustrating a new route to these valuable products.

During the screening of various O-H insertion reactions using diazocarbonyl compounds, an insertion/cyclisation process leading to the stereoselective synthesis of tetrahydrofurans from β-hydroxyketones was discovered (described in **Chapter V**). This reactivity was rationalised by the intramolecular trapping of a transient ylide generated in the course of the metallocarbene insertion process. The literature describing this type of process, which can be referred to as "diverted insertion" reactions, is presented in **Chapter IV**. The investigation into the stereoselective synthesis of functionalised tetrahydrofurans by a diverted insertion reaction route is presented in **Chapter V**, along with the application of this methodology to an approach towards the naturally occurring product hyperolactone C. Similarly to β-hydroxyketones giving tetrahydrofurans, β-aminoketone derivatives were found to give pyrrolidines through the metal catalysed diverted insertion reaction using diazocarbonyl compounds (**Chapter VI**). The stereoselective preparation of functionalised heterocyclic products generated by diverted insertion reactions of diazocarbonyl compounds with bifunctional reagents (i.e. hydroxyketones or aminoketones, **Chapters V-VI**) represents a convergent strategy for the preparation of these important classes of compounds and might find applications in natural product synthesis or in the design of bioactive small molecules.

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New preparations of diazo compounds and studies of their metal catalysed diverted insertion reactions

Vol. 2 - Experimental Section

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Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy

Submitted: December 2015

Table of contents

I. General information

Commercially available reagents were used throughout, without purification unless otherwise stated. Anhydrous tetrahydrofuran and dichloromethane were freshly distilled according to standard procedures; tetrahydrofuran was distilled from sodium benzophenone ketyl radical and dichloromethane from calcium hydride. Anhydrous toluene and anhydrous ether were obtained from anhydrous solvent dispenser by filtration over activated alumina. Other anhydrous solvents used were obtained commercially. When anhydrous solvents were used, reactions were carried out in flame-dried vessels under an argon atmosphere. Light petroleum refers to the fraction with bp 40 - 60 °C. Ether refers to diethyl ether. All aqueous solutions were prepared using deionised water. Saturated brine refers to aqueous saturated solution of sodium chloride.

Analytical thin layer chromatography was carried out on aluminium backed plates coated with Merck Kieselgel 60 GF_{254} and visualised under UV light at 254 and/or 360 nm. Chemical staining was also routinely used with either ethanolic vanillin or aqueous basic potassium permanganate. Flash chromatography was carried out using Davisil silica 60 Å at medium pressure, with the eluent specified.

Infrared spectra were recorded in solution using a PerkinElmer 1600 series FT-IR spectrometer, using NaCl cells over the range 4000 - 600 cm^{-1}. For solid samples, infrared spectra were recorded using Nicolet Avatar 320 FTR-IR spectrometer equipped with an OMNI-Sampler™

Smart Accessory for HATR (Germanium crystal, DTGS detector) over the range 4000 - 600 cm^{-1}.

NMR spectra were recorded at 298 K using Bruker AV500 instrument (500 MHz ^{1}H frequency, 125 MHz ^{13}C frequency), AV400, DPX400 (400 MHz ^{1}H frequency, 100 MHz ^{13}C frequency, ^{31}P frequency 162 MHz) or DPX300 (300 MHz ^{1}H frequency, 75 MHz ^{13}C frequency) instruments. Chemical shifts are quoted in parts per million (ppm), referenced to chloroform (7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR), dimethylsulfoxide (2.50 ppm for ^{1}H NMR, 39.51 ppm for ^{13}C NMR), acetone (2.05 ppm for ^{1}H NMR, 29.84 ppm for ^{13}C NMR) or methanol (3.31 ppm for ^{1}H NMR, 49.00 ppm for ^{13}C NMR) as internal standards and coupling constants, *J*, are quoted in Hz. Multiplicity of each signal is designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sxt, sextet; spt, septet; m, multiplet; app, apparent; br, broad or combinations thereof. In the ^{13}C NMR spectra, signals corresponding to C, CH, CH_2 and CH_3 were assigned from DEPT experiments. Triphenylphosphine was used as a secondary standard for the calibration in ^{31}PNMR experiments (primary standard: phosphoric acid). Trichlorofluoromethane was used as standard for the calibration of ^{19}FNMR experiments.

Mass spectra were routinely recorded on a Bruker MicroTOF 61 mass spectrometer using electrospray ionisation source (referred as ESI-HRMS) and (when indicated) by gas chromatography-coupled Mass spectrometry on a JEOL AccuToF GCv4G using a electron ionisation source (referred as GC-HRMS).

Melting points were measured on a Riechert-Kofler hot stage apparatus and are uncorrected. Elemental analyses were carried out using an Exeter Analytical CE-440 Elemental Analyser on dry homogeneous sample of material.

Reactions in flow were carried out on a Vapourtec system composed of a R4 heating unit and a R2+ pumping unit equipped with two 2 mL PTFE sample loop. The functionalised resin was packed in an adapted column (Omnifit® 100 x 6.6 mm). Reactions were programmed and monitored using the Vapourtec software Flowcommander. Back pressure regulators (100 psi) were obtained from IDEX®.

The compound nomenclature was generated using the software package ChemBiodraw® which uses the CambridgeSoft Name=Struct algorithm (based on IUPAC official rules and recommendations).[1] When available, trivial names were used for simple compounds. The atom numbering system used in the description of ^{1}H NMR spectra aims at giving a clear description of peak assignments and does not always reflect the systematic numbering given in the compound name. In the description of relative stereochemistry (**sections IV and V**), the use of the descriptors *cis*- and *trans*- refers to the substitution of the ring system of interest (i.e. tetrahydrofuran and pyrrolidine ring).

II. Chapter II Experimental

II.1. Preparation of ketone precursors

The α-ketoester and α-ketoamides used in this study were either obtained commercially or prepared by the following method:

Ethyl 2-(4-methoxyphenyl)-2-oxoacetate **99m**, ethyl 2-(2-methoxy-phenyl)-2-oxoacetate **99n**, ethyl 2-(4-bromophenyl)-2-oxoacetate **99o**, ethyl 2-oxo-2-(2-thienyl)acetate **99v,** ethyl 2-(2,4-dimethylphenyl)-2-oxoacetate, ethyl 2-(3,4-dimethoxyphenyl)-2-oxoacetate, ethyl 2-(3-iodo-4-methoxyphenyl)-2-oxoacetate, ethyl 2-(4-(dimethylamino)-phenyl)-2-oxoacetate were prepared by Friedel-Crafts acylation from the corresponding aromatic compound with ethyl oxalyl chloride, following a previously described protocol.[2] *tert*-Butyl 3-(2-methoxy-2-oxoacetyl)indole-1-carboxylate **99x** was prepared by acylation of 1-H indole,[3] followed by Boc-protection.[4] Allyl 2-oxo-2-phenylacetate[5] **99h**, cyclohexyl 2-oxo-2-phenylacetate[5] **99e** and *tert*-butyl 2-oxo-2-phenylacetate[6] were prepared according to previously described procedures. Cbz-protected methyl (*2S,4R*)-4-hydroxypyrrolidine-2-carboxylate **99k** was amiably given by Prof. C. J. Hayes.

The other α-ketoesters and α-ketoamides used in this study were obtained by one of the following protocols:

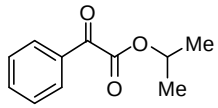
General procedure A: Dicyclohexyl carbodiimide (1.2 eq) was added to a solution of phenylglyoxylic acid (1.2 eq), 4-dimethylaminopyridine (0.2 eq) and the given alcohol (1.0 eq) in anhydrous dichloromethane

(4 mL/mmol) at 0 °C under argon. The resulting mixture was stirred for 5 min at this temperature, then warmed up to room temperature and stirred for 16 h. The reaction was quenched by addition of saturated aqueous ammonium chloride solution (10 mL). The urea by-product was filtered and washed with dichloromethane (1 mL/mmol). Water (0.8 mL/mmol) was added to the filtrate and the organic phase was separated and dried over $MgSO_4$. The volatiles were evaporated under reduced pressure and the residue was purified by column chromatography using the indicated solvent system.

General procedure B: A solution of 2-oxo-2-phenylacetyl chloride (or 2-oxo-2-(4-bromophenyl)acetyl chloride) was prepared by slow addition of oxalyl chloride (1.05 eq) to a solution of phenylglyoxylic acid (resp. 4-bromophenylglyoxylic acid, 1.05 eq) and dimethylformamide (3 drops for 5 mL of solvent) in dichloromethane (1.25 mL/mmol) at 0 °C under argon. The resulting mixture was then stirred at room temperature until no gas evolution was observed (generally after 3 h at room temperature). The yellow acyl chloride solution was transferred to a syringe and slowly added to a mixture of the given alcohol (1.0 eq) and imidazole (2.1 eq) in dichloromethane (1.25 mL/mmol alcohol) at 0 °C under argon. The resulting mixture was stirred at 0 °C for 5 min then warmed to room temperature and stirred until completion of the reaction as judged by TLC analysis. The reaction mixture was then poured into aqueous ammonium chloride solution (15%, 2.5 mL/mmol) and extracted with ethyl acetate (15 mL/mmol). The organic phase was washed with

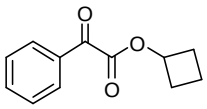
water (5.0 mL/mmol), brine (5.0 mL/mmol) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a residue that was purified by column chromatography using the indicated solvent system.

Isopropyl 2-oxo-2-phenylacetate 99b



Obtained by **general procedure A** from isopropanol (1.15 mL, 15.0 mmol). Purified by column chromatography using the elution gradient ethyl acetate in light petroleum 5 to 10% to give the *title compound* as a yellow oil (1.42 g, 84%). (Found: M+Na$^+$, 215.0679. $C_{11}H_{12}NaO_3$ requires 215.0679); ν_{max} ($CHCl_3$)/cm^{-1} 2987, 1739, 1692; δ_H (400 MHz; $CDCl_3$) 7.99 (2 H, d, *J* 7.5, ArH), 7.61 - 7.72 (1 H, m, ArH), 7.51 (2 H, t, *J* 7.5, ArH), 5.33 (1 H, sept, *J*6.2, CH), 1.42 (6 H, d, *J* 6.2, CH_3); δ_C (100 MHz; $CDCl_3$) 186.9 (C), 163.8 (C), 134.9 (CH), 132.7 (C), 130.1 (CH), 129.0 (CH), 70.8 (CH), 21.9 (CH_3). The data obtained match those previously reported.[7]

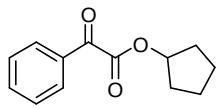
Cyclobutyl 2-oxo-2-phenylacetate 99c



Obtained by **general procedure B** from from cyclobutanol (157 µL, 2.00 mmol). Purified by column chromatography using 5% ethyl acetate in light petroleum to give the *title compound* as a colourless liquid (379 mg, 93%); (Found: M+Na$^+$, 227.0673. $C_{12}H_{12}NaO_3$ requires 227.0679); ν_{max} ($CHCl_3$)/cm^{-1} 1731, 1690, 1177, 980; δ_H (400 MHz; $CDCl_3$) 7.95 - 8.06 (2 H, m, ArH) 7.66 (1 H, tt, *J* 7.5, 1.5, ArH) 7.48 - 7.54 (2 H, m, ArH) 5.28 (1 H, quin.d, *J* 7.5, 1.0, CH) 2.44 - 2.53 (2 H, m, CH_2) 2.20 - 2.33 (2 H, m, CH_2) 1.90 (1 H, qtd, *J* 10.3, 2.8, 1.0, CH_2) 1.65 - 1.78 (1 H, dtt, *J* 11.0, 10.3, 8.2, CH_2); δ_C (100 MHz; $CDCl_3$)

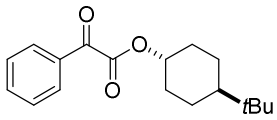
186.5 (C), 163.3 (C), 135.0 (CH), 132.7 (C), 130.2 (CH), 129.0 (CH), 70.9 (CH), 30.4 (CH_2), 13.8 (CH_2).

Cyclopentyl 2-oxo-2-phenylacetate 99d



Obtained by **general procedure A** from cyclopentanol (1.36 mL, 15.0 mmol). Purified by column chromatography using the elution gradient ethyl acetate in light petroleum 3 to 5% to give the *title compound* as a colourless oil (2.96 g, 90%). (Found: M+Na^+, 241.0832. $C_{13}H_{14}NaO_3$ requires 241.0835); ν_{max} ($CHCl_3$)/cm^{-1} 2971, 1729, 1691; δ_H (400 MHz; $CDCl_3$) 7.96 - 8.01 (2 H, m, ArH), 7.65 (1 H, tt, *J* 7.5, 1.3, ArH), 7.51 (2 H, t, *J* 7.5, ArH), 5.48 (1 H, tt, *J* 6.0, 2.9, CH), 1.94 - 2.07 (2 H, m, CH_2), 1.56 - 1.93 (6 H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 186.9 (C), 164.1 (C), 134.9 (CH), 132.7 (C), 130.1 (CH), 129.0 (CH), 79.8 (CH), 32.8 (CH_2), 23.8 (CH_2).

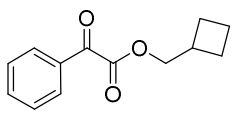
***trans*-4-*tert*-Butylcyclohexyl 2-oxo-2-phenylacetate 99f**



Obtained by **general procedure A** from *trans*-4-*tert*-butylcyclohexan-1-ol[8] (940 mg, 6.01 mmol). Purified by column chromatography using 5% ethyl acetate in light petroleum to give the *title compound* as a colourless solid (1.39 g, 80%). mp 55 - 57 °C; (Found: M+Na^+, 311.1605. $C_{18}H_{24}NaO_3$ requires 311.1618); ν_{max} ($CHCl_3$)/cm^{-1} 2958, 1729, 1690; δ_H (400 MHz; $CDCl_3$) 7.94 - 8.05 (2 H, m, ArH), 7.61 - 7.72 (1 H, m, ArH), 7.51 (2 H, t, *J* 7.8, ArH), 4.96 (1 H, tt, *J* 11.3, 4.5, CH), 2.08 - 2.33 (2 H, m, CH_2), 1.80 - 1.96 (2 H, m, CH_2), 1.40 - 1.58 (2 H, m, CH_2), 1.10 - 1.26 (2 H, m, CH_2), 1.04 (1 H, tt, *J* 11.8, 2.8, CH), 0.87 (9 H, s, *t*Bu); δ_C (100 MHz; $CDCl_3$) 186.9 (C), 163.8 (C), 134.9 (CH),

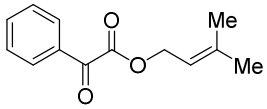
132.7 (C), 130.1 (CH), 129.0 (CH), 76.6 (CH), 47.0 (CH), 32.5 (C), 32.0 (CH_2), 27.7 (CH_3), 25.6 (CH_2). The data match those previously reported.[9]

Cyclobutylmethyl 2-oxo-2-phenylacetate 99g



Obtained by **general procedure B** from cyclobutanemethanol (943 μL, 10.0 mmol). Purified by column chromatography using 3% ethyl acetate in light petroleum to give the *title compound* as a colourless oil (2.14 g, 98%). (Found: M+Na^+, 241.0847. $C_{13}H_{14}NaO_3$ requires 241.0835); ν_{max} ($CHCl_3$)/cm^{-1} 1733, 1690; δ_H (400 MHz; $CDCl_3$) 7.92 - 8.06 (2 H, m, ArH), 7.60 - 7.71 (1 H, m, ArH), 7.45 - 7.56 (2 H, m, ArH), 4.37 (2H, d, *J* 6.7, OCH_2), 2.76 (1 H, spt, *J* 7.5, CH), 2.06 - 2.17 (2 H, m, cyclobutane CH_2), 1.77 - 2.02 (4 H, m, cyclobutane CH_2); δ_C (100 MHz; $CDCl_3$) 186.7 (C), 164.3 (C), 135.0 (CH), 132.6 (C), 130.1 (CH), 129.0 (CH), 70.0 (CH_2), 34.0 (CH), 24.9 (CH_2), 18.5 (CH_2).

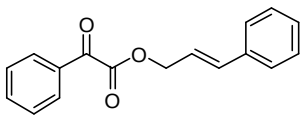
3-Methylbut-2-enyl 2-oxo-2-phenylacetate 99i



Obtained by **general procedure A** from 3-methyl-2-buten-1-ol (2.03 mL, 20.0 mmol). Purified by column chromatography using the elution gradient ethyl acetate in light petroleum 8 to 10% to give the *title compound* as a yellow oil (3.46 g, 79%). (Found: M+Na^+, 241.0827. $C_{13}H_{14}NaO_3$ requires 241.0835); ν_{max} ($CHCl_3$)/cm^{-1} 1733, 1690, 1192, 1176; δ_H (400 MHz; $CDCl_3$) 7.97 - 8.02 (2 H, m, ArH), 7.65 (1 H, t, *J* 7.5, ArH), 7.47 - 7.54 (2 H, m, ArH), 5.43 - 5.50 (1 H, m, =CH), 4.88 (2 H, d, *J* 7.4, CH_2), 1.79 (3 H, s, CH_3), 1.78 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 186.6 (C), 164.0 (C), 141.3 (C), 135.0 (CH),

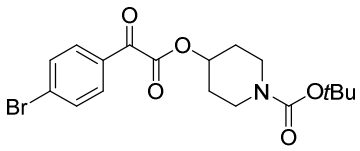
132.7 (C), 130.2 (CH), 129.0 (CH), 117.5 (CH), 63.1 (CH_2), 25.9 (CH_3), 18.3 (CH_3). The data obtained match those previously reported.[10]

Cinnamyl 2-oxo-2-phenylacetate 99j



Obtained by **general procedure A** from cinnamyl alcohol (2.67 g, 20.0 mmol). Purified by column chromatography using the elution gradient ethyl acetate in light petroleum 8 to 10% to give the *title compound as* a yellow oil (4.35 g, 82%). (Found: M+Na^+, 289.0822. $C_{17}H_{14}NaO_3$ requires 289.0835); ν_{max} ($CHCl_3$)/cm^{-1} 1737, 1690, 1192, 1175; δ_H (400 MHz; $CDCl_3$) 7.99 - 8.12 (2 H, m, ArH), 7.70 (1 H, tt, *J* 7.5, 1.4, ArH), 7.55 (2 H, t, *J* 8.0, ArH), 7.42 - 7.48 (2 H, m, ArH), 7.30 - 7.41 (3 H, m, ArH), 6.82 (1 H, d, *J* 15.8, =CH), 6.42 (1H, dt, *J* 15.8, 6.7, =CH), 5.08 (2 H, dd, *J* 6.7, 1.1, CH_2); δ_C (100 MHz; $CDCl_3$) 186.2 (C), 163.7 (C), 136.1 (CH), 136.0 (C), 135.1 (CH), 132.6 (C), 130.2 (CH), 129.1 (CH), 128.8 (CH), 128.6 (CH), 126.9 (CH), 121.7 (CH), 66.8 (CH_2). The data obtained match those previously reported.[11]

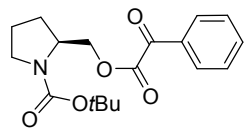
***tert*-Butyl 4-(2-(4-bromophenyl)-2-oxoacetoxy)piperidine-1-carboxylate 99p**



Obtained by **general procedure B** from *N*-Boc 4-hydroxypiperidine (404 mg, 2.00 mmol). Purified by column chromatography using 20% ethyl acetate in light petroleum. Viscous yellow oil (812 mg, 96%); (Found: M+Na^+, 434.0574. $C_{18}H_{22}{}^{79}BrNNaO_5$ requires 434.0579); ν_{max} ($CHCl_3$)/cm^{-1} 1738, 1688, 1400, 1192; δ_H (400 MHz; $CDCl_3$) 7.80 - 7.88 (2 H, m, ArH), 7.60 - 7.68 (2 H, m, ArH), 5.22 (1 H, tt, *J* 8.0, 3.9, CH), 3.66 - 3.81 (2 H, m, CH_2), 3.28 (2 H, ddd, *J* 13.6,

8.5, 3.7, CH_2), 1.98 (2 H, m, CH_2), 1.76 (2 H, dtd, *J* 12.9, 8.5, 3.9, CH_2), 1.45 (9 H, s, *t*Bu); δ_C (100 MHz; $CDCl_3$) 185.0 (C), 162.8 (C), 154.7 (C), 132.5 (CH), 131.4 (CH), 131.3 (C), 130.7 (C), 80.0 (C), 72.8 (CH), 40.9 (CH_2), 30.5 (CH_2), 28.5 (CH_3).

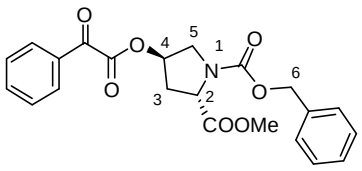
(*S*)-*tert*-Butyl 2-(2-oxo-2-phenylacetoxy)methylpyrrolidine-1-carboxylate 99k



Obtained by **general procedure B** from *N*-Boc prolinol (797 mg, 4.00 mmol), following the general procedure described above. Purified by column chromatography using 20% ethyl acetate in light petroleum. Pale yellow oil (1.11 g, 83%); $[\alpha]_D^{24}$ −29.0 (*c* 1.50, $CHCl_3$); (Found: M+Na^+, 356.1455. $C_{18}H_{23}NNaO_5$ requires 356.1468); ν_{max} ($CHCl_3$)/cm^{-1} 1738, 1688; signal broadening was observed in deuterated chloroform at room temperature due to rotamer interconversion. Resolution of the signals was observed in deuterated DMSO above 65 °C. δ_H (400 MHz; $CDCl_3$) 7.98 (2 H, d, *J* 6.6, ArH), 7.65 (1 H, t, *J* 7.4, ArH), 7.50 (2 H, m, ArH), 4.36 - 4.59 (2 H, m, CH_2O), 3.97 - 4.27 (1 H, m CH), 3.22 - 3.46 (2 H, m, CH_2), 1.75 - 2.11 (4 H, m, CH_2), 1.42-1.50 (9 H, two overlapping s, *t*Bu); δ_H (270 MHz, DMSO-d_6, 90 °C) 7.92 - 8.07 (2 H, m, ArH), 7.73 - 7.87 (1 H, m, ArH), 7.54 - 7.69 (2 H, m, ArH), 4.51 (1 H, dd, *J* 10.7, 6.1, OCH_2), 4.42 (1 H, dd, *J* 10.7, 4.0, OCH_2), 3.97 - 4.14 (1 H, m, CH), 3.15 - 3.42 (2 H, m, CH_2), 1.67 - 2.15 (4 H, m, CH_2), 1.42 (9 H, s, *t*Bu); δ_C (100 MHz; $CDCl_3$) 186.3 (C), 163.7 (C), 154.7 (C), 135.1 (CH), 132.5 (C), 130.1 (CH), 129.0 (CH), 80.1 (C), 79.7 (C), 66.2 (CH_2), 55.6 (CH), 47.0 (CH_2), 46.7 (CH_2), 29.1 (CH_2), 28.6 (CH_3), 28.1 (CH_2),

23.9 (CH_2), 23.1 (CH_2), doubling of some signals is due to the presence of rotameric mixtures.

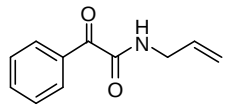
(*2S,4R*)-1-Benzyl 2-methyl 4-(2-oxo-2-phenylacetoxy)pyrrolidine-1,2-dicarboxylate 99l



Obtained by **general procedure B** from Cbz-protected methyl (*2S,4R*)-4-hydroxypyrrolidine-2-carboxylate (444 mg, 1.59 mmol). Purified by column chromatography using 50% ethyl acetate in light petroleum to give the *title compound* as a viscous yellow oil (602 mg, 92%); $[\alpha]_D^{24}$−12.8 (c 1.90, $CHCl_3$); (Found: M+Na$^+$, 434.1227. $C_{22}H_{21}NNaO_7$ requires 434.1210); ν_{max} ($CHCl_3$)/cm^{-1} 1745, 1705, 1175; two rotameric forms coexist in deuterated chloroform at room temperature (ratio 1:1), coalescence was observed in deuterated DMSO at 90 °C, δ_H (400 MHz; $CDCl_3$) 7.89 - 8.03 (2 H, m, ArH both rotamers), 7.62 - 7.70 (1 H, m, ArH, both rotamers), 7.44 - 7.55 (2 H, m, ArH, both rotamers), 7.26 - 7.36 (5 H, m, ArH, both rotamers), 5.53 - 5.64 (1 H, m, H4, both rotamers), 5.21 (1 H, d, *J* 12.4, H6 one rotamer), 5.17 (1 H, d, *J* 12.5, H6 one rotamer), 5.13 (1 H, d, *J* 12.5, H6 one rotamer), 5.02 (1 H, d, *J* 12.4, H6 one rotamer), 4.53 (1 H, dt, *J* 14.2, 8.0, H2 both rotamers), 3.81 - 3.99 (2 H, m, H5 both rotamers), 3.77 (3 H, s, OMe one rotamer), 3.55 (3 H, s, OMe one rotamer), 2.51 - 2.66 (1 H, m, H3 both rotamers), 2.37 (1 H, ddd, *J* 13.9, 8.0, 5.3, H3 both rotamers); δ_H (270MHz, DMSO-d_6, 90 °C) 7.92 - 8.03 (2 H, m, ArH), 7.72 - 7.83 (1 H, m, ArH), 7.55 - 7.65 (2 H, m, ArH), 7.24 - 7.41 (5 H, m, ArH), 5.58 - 5.68 (1 H, m, H4), 5.13 (1 H, d, *J* 12.7, H6), 5.07 (1 H, d, *J* 12.7, H6), 4.47 (1 H, t, *J* 8.0, H2), 3.85 (1 H, dd, *J* 12.4, 4.4,

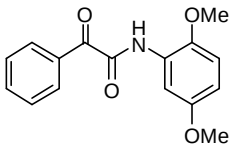
H5), 3.79 (1H, ddd, *J* 12.4, 2.3, 1.2, H5), 3.65 (3 H, s, CH_3), 2.62 (1 H, dddd, *J* 14.3, 8.0, 3.0, 1.2, H3), 2.41 (1 H, ddd, *J* 14.3, 8.0, 5.4, H3); δ_C (100 MHz; $CDCl_3$) 185.43 (C), 185.39 (C), 172.5 (C), 172.4 (C), 163.1 (C), 154.6 (C), 154.1 (C), 136.2 (C), 136.1 (C), 135.3 (CH), 132.2 (C), 130.04 (CH), 129.98 (CH), 129.1 (CH), 128.6 (CH), 128.5 (CH), 128.22 (CH), 128.17 (CH), 128.00 (CH), 127.96 (CH), 74.7 (CH), 74.0 (CH), 67.6 (CH_2), 67.5 (CH_2), 57.8 (CH), 57.5 (CH), 52.6 (CH_3), 52.4 (CH_2), 52.4 (CH_3), 51.9 (CH_2), 36.5 (CH_2), 35.5 (CH_2), two quaternary carbon and two CH signals were not observed, doubling of some signals is due to the presence of rotameric mixtures.

_N_-Allyl-2-oxo-2-phenylacetamide 99q



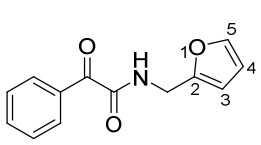
Obtained by **general procedure B** from allylamine (0.75 mL, 10.0 mmol). Purified by column chromatography using 10% ethyl acetate in light petroleum to give the *title compound* as a colourless solid (1.47 g, 78%); mp 59 - 60 °C (lit.[12] mp 56 - 58 °C (from chloroform)); (Found: M+Na^+, 212.0693. $C_{11}H_{11}NNaO_2$ requires 212.0687); ν_{max} ($CHCl_3$)/cm^{-1}; 3415, 1671, 1598, 1519, 1449, 1179;δ_H (400 MHz; $CDCl_3$) 8.32 - 8.38 (2 H, m, ArH), 7.59 - 7.66 (1 H, m, ArH), 7.44 - 7.52 (2 H, m, ArH), 7.18 (1 H, br s, NH), 5.90 (1 H, ddt, *J* 17.1, 10.2, 5.7, vinylic CH), 5.28 (1 H, dq, *J* 17.1, 1.5, vinylic CH), 5.22 (1 H, dq, *J* 10.2, 1.5, vinylic CH), 4.02 (2 H, tt, *J* 5.7, 1.5, CH_2); δ_C (100 MHz; $CDCl_3$) 187.7 (C), 161.7 (C), 134.6 (CH), 133.4 (C), 133.1 (CH), 131.4 (CH), 128.6 (CH), 117.4 (CH_2), 41.9 (CH_2).

***N*-(2,5-Dimethoxyphenyl)-2-oxo-2-phenylacetamide 99r**



Obtained by **general procedure B** from 2,5-dimethoxyaniline (1.53 g, 10.0 mmol). Purified by column chromatography using 10% ethyl acetate in light petroleum to give the *title compound* as a orange solid (2.56 g, 90%); mp 76 - 77 °C; (Found: C, 67.23; H, 5.29; N, 4.87. $C_{16}H_{15}NO_4$ requires C, 67.36; H, 5.30; N, 4.91%); (Found: M+Na$^+$, 308.0893. $C_{16}H_{15}NNaO_4$ requires 308.0893); ν_{max} ($CHCl_3$)/cm^{-1} 3374, 1674, 1532, 1486; δ_H (400 MHz; $CDCl_3$) 9.55 (1 H, br s, NH), 8.36 - 8.45 (2 H, m, ArH), 8.22 (1 H, d, *J* 3.1, ArH), 7.65 (1 H, t, *J* 7.7, ArH), 7.51 (2 H, t, *J* 7.7, ArH), 6.85 (1 H, d, *J* 8.9, ArH), 6.67 (1 H, dd, *J* 8.9, 3.1, ArH), 3.89 (3 H, s, OMe), 3.82 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 187.5 (C), 159.1 (C), 153.9 (C), 143.2 (C), 134.6 (CH), 133.4 (C), 131.5 (CH), 128.7 (CH), 127.1 (C), 111.1 (CH), 110.1 (CH), 106.1 (CH), 56.4 (CH_3), 56.0 (CH_3).

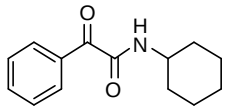
***N*-(2-Furylmethyl)-2-oxo-2-phenylacetamide 99s**



Obtained by **general procedure B** from furfurylamine (884 µL, 10.0 mmol). Purified by column chromatography using 10% ethyl acetate in light petroleum to give the *title compound* as a colourless solid (1.74 g, 76%); mp 83 - 84 °C (from ethanol); (Found: C, 67.97; H, 4.83; N, 6.09. $C_{13}H_{11}NO_3$ requires C, 68.11; H, 4.84; N, 6.11%); (Found: M+Na$^+$, 252.0628. $C_{13}H_{11}NNaO_3$ requires 252.0631); ν_{max} ($CHCl_3$)/cm^{-1} 3415, 1671, 1516; δ_H (400 MHz; $CDCl_3$) 8.30 - 8.38 (2 H, m, ArH), 7.61 (1 H, tt, *J* 7.5, 1.3, ArH), 7.40 - 7.53 (3 H, m, ArH and NH), 7.37 (1 H, dd, *J* 1.8, 0.8, H4), 6.25 - 6.39 (2 H, m, H3 and H5), 4.56 (2 H, d, *J* 5.8, CH_2); δ_C (100 MHz; $CDCl_3$) 187.4 (C), 161.5 (C),

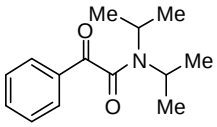
150.2 (C), 142.7 (CH), 134.6 (CH), 133.4 (C), 131.3 (CH), 128.6 (CH), 110.6 (CH), 108.2 (CH), 36.4 (CH_2).

_N_-Cyclohexyl-2-oxo-2-phenylacetamide 99t



Obtained by **general procedure B** from cyclohexylamine (1.65 mL, 14.4 mmol). Purified by column chromatography using ethyl acetate 10% in light petroleum to give the *title compound* as a colourless solid (2.76 g, 83%). (Found: M+Na^+, 254.1145. $C_{14}H_{17}NNaO_2$ requires 254.1151); mp 130 - 133 °C; ν_{max} ($CHCl_3$)/cm^{-1} 1667, 1518; δ_H (400 MHz; $CDCl_3$) 8.28 - 8.33 (2 H, m, ArH), 7.53 - 7.62 (1 H, m, ArH), 7.45 (2 H, t, *J* 7.7, ArH), 7.00 (1 H, br s, NH), 3.76 - 3.93 (1 H, m, CH), 1.90 - 2.05 (2 H, m, CH_2), 1.75 (2 H, dt, *J* 13.4, 3.7, CH_2), 1.63 (1 H, dt, *J* 12.9, 3.7, CH_2), 1.13 - 1.50 (5 H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 188.2 (C), 161.0 (C), 134.4 (CH), 133.5 (C), 131.3 (CH), 128.5 (CH), 48.6 (CH), 32.8 (CH_2), 25.5 (CH_2), 24.8 (CH_2). The data match those previously reported.[13]

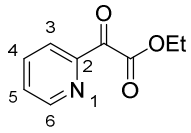
_N,N_-Diisopropyl-2-oxo-2-phenylacetamide 99u



Obtained by **general procedure B** from di-isopropylamine (2.10 mL, 14.3 mmol). Purified by column chromatography using the elution gradient 5 to 20% ethyl acetate in light petroleum to give the *title compound* as a colourless solid (2.89 g, 82%). (Found: M+Na^+, 256.1307. $C_{14}H_{19}NNaO_2$ requires 256.1308); mp 124 - 125 °C (mp lit.[14] 125 °C); ν_{max} ($CHCl_3$)/cm^{-1} 1682, 1640; δ_H (400 MHz; $CDCl_3$) 7.87 - 7.96 (2 H, m, ArH), 7.61 (1 H, tt, *J* 7.7, 1.3, ArH), 7.49 (2 H, t, *J* 7.7, ArH), 3.68 (1 H, sept, *J* 6.6, CH), 3.58 (1 H, sept, *J* 6.9, CH),

1.57 (6 H, d, *J* 6.9, CH_3), 1.16 (6 H, d, *J* 6.6, CH_3); δ_C (100 MHz; $CDCl_3$) 191.1 (C), 167.0 (C), 134.5 (CH), 133.5 (C), 129.6 (CH), 129.1 (CH), 50.3 (CH), 46.2 (CH), 20.6 (CH_3), 20.4 (CH_3). The data obtained match previously reported data.[14-15]

Ethyl 2-oxo-2-(pyridin-2-yl)acetate 99w



Following a procedure described in a patent,[16] a solution of 2-bromopyridine (2.0 mL, 21 mmol) in anhydrous ether (50 mL) was prepared under anhydrous conditions and stirred at −78 °C under an argon atmosphere. Butyllithium (1.5 M; 14 mL, 21 mmol) was added over 5 min, upon which the solution showed an intense red colour. The mixture was stirred at this temperature for 30 min and subsequently transferred *via* a cannula to a solution of diethyl oxalate (10.0 mL, 73.6 mmol) in anhydrous ether (100 mL) at 0 °C. The addition was completed after approximately 5 min, and the mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched by slow addition of a saturated aqueous sodium hydrogen carbonate solution (60 mL) and the resulting mixture was extracted with ethyl acetate (2×50 mL). The combined organic phases were separated, washed with water (40 mL), saturated brine (20 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a liquid, principally constituted of excess diethyl oxalate. Purification by column chromatography (elution gradient ethyl acetate in light petroleum, 20% to 50%) gave the *title compound* as a red oil (781 mg, 21%); (Found: M+Na^+, 202.0480. $C_9H_9NNaO_3$ requires

202.0480); ν_{max} ($CHCl_3$)/cm^{-1} 2987, 1742, 1710, 1324, 1257, 1020; δ_H (400 MHz; $CDCl_3$) 8.72 - 8.78 (1 H, ddd, *J* 4.8, 1.5, 1.1, H6), 8.10 (1 H, dt, *J* 7.8, 1.1, H3), 7.90 (1 H, td, *J* 7.8, 1.5, H4), 7.54 (1 H, ddd, *J* 7.8, 4.8, 1.1, H5), 4.49 (2 H, q, *J* 7.3, C$\underline{H}_2$$CH_3$), 1.42 (3 H, t, *J* 7.3, CH_2C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 187.8 (C), 165.4 (C), 150.5 (C), 150.0 (CH), 137.3 (CH), 128.4 (CH), 123.5 (CH), 62.3 (CH_2), 14.2 (CH_3). The data are consistent with the literature.[16-17]

II.2. Hydrazone synthesis

The preparation of the hydrazones used in this study is described below, with exception of 2-hydrazono-1-phenylethanone, which was prepared following the procedure described by Hauptmann,[18] and benzil monohydrazone **65**, which was prepared following a known procedure.[19]

The stereochemistry of the C=N double bond in the hydrazones **100a-ae** was determined on the basis of their ^{1}H NMR chemical shifts and IR spectra. The data obtained for the pair of isomers were rationalised as followed: (a) the possibility of an intramolecular hydrogen bond in the (*Z*)-ketoester hydrazones (and also ketoamide and ketophosphonate) leads to a shift in the IR carbonyl resonance towards lower frequencies (in the range of 7-39 cm^{-1} lower than the (*E*)-isomer); (b) the same effect was responsible for the deshielding of the NH_2 proton in the ^{1}H NMR spectrum of the (*Z*)-isomers (measured in $CDCl_3$; 1.25-2.40 ppm downfield compared to the (*E*)-isomer); (c) a decreased capacity to form intermolecular hydrogen bond, which often results in (*Z*)-hydrazones

being isolated as oils whilst (*E*)-hydrazones were obtained as crystalline solids. Similar observations were made for the ketophosphonate hydrazones **102a-b** and their stereochemistry was determined on this basis.

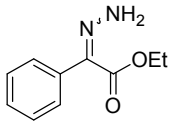
Hydrazones described in **Vol. 1 Chapter II Table II-3** were obtained by one of the following procedures:

General procedure C.[20] Hydrazine hydrate (1 eq) was slowly added to a mixture of glacial acetic acid (80 mL/mmol) and water (80 mL/mmol) cooled in an ice bath. The α-ketoester or -amide (1 eq) was added to the mixture at room temperature. A volume of methanol was then added in order to obtain a homogeneous solution (when necessary). The reaction mixture was stirred at room temperature until completion of the reaction as judged by TLC. The volatiles were removed under reduced pressure. Water (1.6 mL/mmol) was added to the residue and the mixture was extracted with ethyl acetate (3.0 mL/mmol). The combined organic phases were washed with saturated aqueous sodium hydrogen carbonate (1.0 mL/mmol), saturated brine (0.5 mL/mmol) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a residue that was purified by column chromatography (when indicated).

General procedure D. Hydrazine hydrate (1 eq) was added to a solution of benzoic acid (1 eq) and α-ketoester or -amide (1 eq) in THF (3 mL/mmol), upon which the hydrazine benzoate precipitated from the solution. The mixture was stirred at room temperature during which the visible precipitate disappeared completely. The solution was poured into

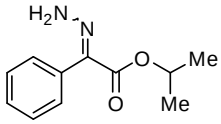
saturated aqueous sodium hydrogen carbonate solution (2.0 mL/mmol) and extracted with ethyl acetate (6.0 mL/mmol). The combined organic phases were washed with saturated brine (0.5 mL/mmol) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave a residue that was purified by column chromatography (when indicated).

(*E*)- and (*Z*)- Ethyl 2-hydrazono-2-phenylacetate 100a



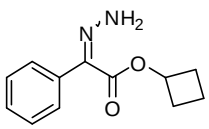
Obtained by **general procedure C** from ethyl 2-oxo-2-phenylacetate **99a** (4.00 mL, 25.2 mmol) with a reaction time of 24 h. Purified by column chromatography using the elution gradient 12 to 50 % ethyl acetate in light petroleum. **(*Z*)-Ethyl 2-hydrazono-2-phenylacetate**: yellow oil (3.68 g, 76%); (Found: $M+H^+$, 193.0984. $C_{10}H_{13}N_2O_2$ requires 193.0977); ν_{max} ($CHCl_3$)/cm^{-1} 3486, 3291, 3010, 1687, 1564, 1266, 1149, 1021; δ_H (400 MHz; $CDCl_3$) 8.40 (2 H, br s, NH_2), 7.54 - 7.49 (2 H, m, ArH), 7.38 - 7.26 (3 H, m, ArH), 4.31 (2 H, q, *J* 7.2, $C\underline{H}_2CH_3$), 1.33 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 163.0 (C), 136.8 (C), 131.3 (C), 128.3 (CH), 128.0 (CH), 127.6 (CH), 60.8 (CH_2), 14.3 (CH_3). **(*E*)-Ethyl 2-hydrazono-2-phenylacetate**: yellow solid (1.11 g, 23%); mp 96 - 97 °C (lit.[21]no mp reported); (Found: $M+Na^+$, 215.0793. $C_{10}H_{12}N_2NaO_2$ requires 215.0796); ν_{max} ($CHCl_3$)/cm^{-1} 3474, 3317, 3011, 1710, 1573, 1330, 1137, 1047; δ_H (400 MHz; $CDCl_3$) 7.48 - 7.52 (2 H, m, ArH), 7.41 (1 H, t, *J* 7.2, ArH), 7.29 (2 H, d, *J* 7.2, ArH), 6.21 (2 H, br s, NH_2), 4.30 (2 H, q, *J* 7.2, $C\underline{H}_2CH_3$), 1.33 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 164.5 (C), 137.7 (C), 129.7 (C), 129.5 (CH), 129.3 (CH), 128.9 (CH), 61.4 (CH_2), 14.5 (CH_3). Data recorded are consistent with the literature.[21]

(*E*)- and (*Z*)-Isopropyl 2-hydrazono-2-phenylacetate 100b



Obtained by **general procedure D** from isopropyl 2-oxo-2-phenylacetate **99b** (765 mg, 3.98 mmol) with a reaction time of 17 h. Purified by column chromatography using the elution gradient 7 then 50% ethyl acetate in light petroleum. **(*Z*)-Isopropyl 2-hydrazono-2-phenylacetate**: yellow oil that solidified upon standing (551 mg, 67%); mp 45 - 46 °C; (Found: M+Na^+, 229.0938. $C_{11}H_{14}N_2NaO_2$ requires 229.0947); ν_{max} ($CHCl_3$)/cm^{-1} 3485, 1684, 1562, 1269, 1161, 1104; δ_H (400 MHz; $CDCl_3$) 8.34 (2 H, br s, NH_2), 7.49 - 7.56 (2 H, m, ArH), 7.26 - 7.38 (3 H, m, ArH), 5.22 (1 H, sept, *J* 6.3, CH), 1.32 (6 H, d, *J* 6.3, CH_3); δ_C (100 MHz; $CDCl_3$) 162.6 (C), 136.9 (C), 131.9 (C), 128.2 (CH), 127.9 (CH), 127.5 (CH), 68.7 (CH), 21.9 (CH_3). **(*E*)-Isopropyl 2-hydrazono-2-phenylacetate**: colourless solid (267 mg, 32%); mp 49 - 50 °C; (Found: M+Na^+, 229.0947. $C_{11}H_{14}N_2NaO_2$ requires 229.0947); ν_{max} ($CHCl_3$)/cm^{-1} 3473, 1703, 1106 ,1017; δ_H (400 MHz; $CDCl_3$) 7.42 - 7.49 (2 H, m, ArH), 7.35 - 7.42 (1 H, m, ArH), 7.21 - 7.32 (2 H, m, ArH), 6.25 (2 H, br s, NH_2), 5.14 (1 H, sept, *J* 6.3, CH), 1.29 (6 H, d, *J* 6.3, CH_3); δ_C (100 MHz; $CDCl_3$) 164.1 (C), 137.7 (C), 129.8 (C), 129.2 (CH), 129.1 (CH), 128.9 (CH), 68.7 (CH), 21.9 (CH_3).

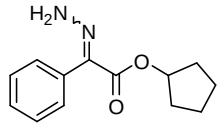
(*Z*) and (*E*)-Cyclobutyl 2-hydrazono-2-phenylacetate 100c



Obtained by **general procedure D** from cyclobutyl 2-oxo-2-phenylacetate **99c** (360 mg, 1.76 mmol) with a reaction time of 16 h. Purified by column chromatography using the elution gradient 30 to 50% ethyl acetate in light petroleum. **(*Z*)-Cyclobutyl 2-hydrazono-2-phenylacetate**: colourless oil that

solidified on standing (116 mg, 30%); mp 33 - 34 °C; (Found: M+H$^+$, 219.1124. $C_{12}H_{15}N_2O_2$ requires 219.1128); ν_{max} ($CHCl_3$)/cm^{-1} 3485, 3011, 1684, 1564, 1265, 1152; δ_H (400 MHz; $CDCl_3$) 8.44 (2 H, br s, NH_2), 7.49 - 7.60 (2 H, m, ArH), 7.28 - 7.40 (3 H, m, ArH), 5.17 (1 H, quin.d, *J* 7.5, 1.0, CH), 2.36 - 2.47 (2 H, m, CH_2), 2.09 - 2.21 (2 H, m, CH_2), 1.84 (1 H, qtd, *J* 10.0, 2.8, 1.0, CH_2), 1.68 (1 H, dtt, *J* 11.0, 10.0, 8.3, CH_2); δ_C (100 MHz; $CDCl_3$) 162.4 (C), 136.8 (C), 131.0 (C), 128.3 (CH), 127.9 (CH), 127.5 (CH), 69.3 (CH), 30.4 (CH_2), 13.8 (CH_2). **(*E*)-Cyclobutyl 2-hydrazono-2-phenylacetate**: yellow oil that solidified on standing (260 mg, 68%); mp 62 - 63 °C; (Found: M+H$^+$, 219.1121. $C_{12}H_{15}N_2O_2$ requires 219.1128); ν_{max} ($CHCl_3$)/cm^{-1} 3474, 3010, 1706; δ_H (400 MHz; $CDCl_3$) 7.43 - 7.50 (2 H, m, ArH), 7.37 - 7.43 (1 H, m, ArH), 7.23 - 7.31 (2 H, m, ArH), 6.24 (2 H, br s, NH_2), 5.10 (1 H, quin.d, *J* 7.5, 1.0, CH), 2.30 - 2.43 (2 H, m, CH_2), 2.10 - 2.23 (2 H, m, CH_2), 1.79 (1 H, qtd, *J* 10.5, 2.6, 1.0, CH_2), 1.55 - 1.68 (1 H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 164.0 (C), 137.5 (C), 129.6 (C), 129.4 (CH), 129.2 (CH), 128.9 (CH), 69.7 (CH), 30.5 (CH_2), 13.6 (CH_2).

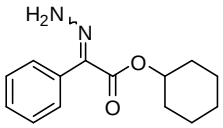
(*E*)- and (*Z*)-Cyclopentyl 2-hydrazono-2-phenylacetate 100d



Obtained by **general procedure D** from cyclopentyl 2-oxo-2-phenylacetate **99d** (977 mg, 4.48 mmol) with a reaction time of 17 h. Purified by column chromatography using the elution gradient 7 then 50% ethyl acetate in light petroleum. **(*Z*)-Cyclopentyl 2-hydrazono-2-phenylacetate**: yellow oil that solidified upon standing (671 mg, 64%); mp 41 - 42 °C; (Found: M+Na$^+$, 255.1108. $C_{13}H_{16}N_2NaO_2$ requires 255.1104); ν_{max} ($CHCl_3$)/cm^{-1}

3485, 1682, 1562, 1268, 1152; δ_H (400 MHz; $CDCl_3$) 8.38 (2 H, br s, NH_2), 7.47 - 7.56 (2 H, m, ArH), 7.25 - 7.37 (3 H, m, ArH), 5.37 (1 H, tt, *J* 5.9, 2.8, CH), 1.85 - 1.98 (2 H, m, CH_2), 1.55 - 1.83 (6 H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 162.9 (C), 136.9 (C), 131.7 (C), 128.2 (CH), 127.8 (CH), 127.5 (CH), 77.9 (CH), 32.8 (CH_2), 23.7 (CH_2). **(*E*)-Cyclopentyl 2-hydrazono-2-phenylacetate**: colourless solid (336 mg, 32%); mp 92 - 93 °C; (Found: M+Na^+, 255.1108. $C_{13}H_{16}N_2NaO_2$ requires 255.1104); ν_{max} ($CHCl_3$)/cm^{-1} 3473, 1703, 1334, 1137; δ_H (400 MHz; $CDCl_3$) 7.42 - 7.48 (2 H, m, ArH), 7.35 - 7.41 (1 H, m, ArH), 7.22 - 7.29 (2 H, m, ArH), 6.22 (2 H, s, NH_2), 5.26 (1 H, tt, *J* 6.4, 3.3, CH), 1.81 - 1.95 (2 H, m, CH_2), 1.46 - 1.79 (6 H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 164.4 (C), 137.9 (C), 129.9 (C), 129.3 (CH), 129.1 (CH), 128.9 (CH), 78.0 (CH), 32.7 (CH_2), 23.8 (CH_2).

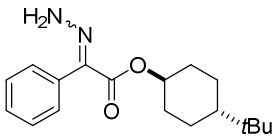
(*E*)- and (*Z*)-cyclohexyl 2-hydrazono-2-phenylacetate 100e



Obtained by **general procedure C** from cyclohexyl 2-oxo-2-phenylacetate **99e** (508 mg, 2.19 mmol) with a reaction time of 5 h. Purified by column chromatography using the elution gradient 5 then 50% ethyl acetate in light petroleum. **(*Z*)-Cyclohexyl 2-hydrazono-2-phenylacetate**: colourless solid (436 mg, 80%); mp 57 - 58 °C; (Found: M+Na^+, 269.1256. $C_{14}H_{18}N_2NaO_2$ requires 269.1266); ν_{max} ($CHCl_3$)/cm^{-1} 3485, 3288, 3009, 2941, 2862, 1681, 1562, 1293, 1263, 1162, 1150, 1121; δ_H (400 MHz; $CDCl_3$) 8.34 (2 H, br s, NH_2), 7.50 - 7.56 (2 H, m, ArH), 7.26 - 7.38 (3 H, m, ArH), 4.96 - 5.04 (1 H, m, OCH), 1.83 - 1.94 (2 H, m, CH_2), 1.63 - 1.75 (2 H, m, CH_2), 1.22 - 1.59 (6 H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 162.5 (C), 136.9

(C), 132.0 (C), 128.3 (CH), 127.9 (CH), 127.5 (CH), 73.4 (CH), 31.6 (CH_2), 25.4 (CH_2), 23.7 (CH_2). **(*E*)-Cyclohexyl 2-hydrazono-2-phenylacetate**: colourless solid (96 mg, 18%); mp 117 - 118 °C; (Found: M+Na^+, 269.1251. $C_{14}H_{18}N_2NaO_2$ requires 269.1266); ν_{max} ($CHCl_3$)/cm^{-1} 3473, 3316, 3008, 2940, 2862, 1703, 2573, 1338, 1304, 1240, 1138, 1042, 1018; δ_H (400 MHz; $CDCl_3$) 7.44 - 7.49 (2 H, m, ArH), 7.37 - 7.44 (1 H, m, ArH), 7.30 (2 H, dd, *J* 8.3, 1.3, ArH), 6.19 (2 H, br s, NH_2), 4.84 - 4.96 (1 H, m, OCH), 1.84 -1.95 (2 H, m, CH_2), 1.63 - 1.74 (2 H, m, CH_2), 1.14 - 1.58 (6 H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 164.0 (C), 138.3 (C), 130.0 (C), 129.3 (CH), 129.2 (CH), 128.9 (CH), 73.8 (CH), 31.7 (CH_2), 25.5 (CH_2), 24.0 (CH_2).

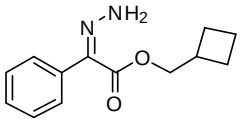
(*E*) and (*Z*)-*trans*-4-*tert*-Butylcyclohexyl 2-hydrazono-2-phenylacetate 100f



Obtained by **general procedure D** from *trans*-4-*tert*-butylcyclohexyl 2-oxo-2-phenylacetate **99f** (576 mg, 2.00 mmol) with a reaction time of 15 h. Purified by column chromatography using the elution gradient 10 to 40% ethyl acetate in light petroleum. **(*Z*)-*trans*-4-*tert*-Butylcyclohexyl 2-hydrazono-2-phenylacetate**: colourless solid (366 mg, 60%); mp 94 - 95 °C; (Found: M+H^+, 303.2054. $C_{18}H_{27}N_2O_2$ requires 303.2067); ν_{max} ($CHCl_3$)/cm^{-1} 3485, 2957, 1683, 1562, 1268, 1159; δ_H (400 MHz; $CDCl_3$) 8.31 (2 H, br s, NH_2), 7.47 - 7.57 (2 H, m, ArH), 7.26 - 7.37 (3 H, m, ArH), 4.85 (1 H, tt, *J* 11.3, 4.5, CH), 2.05 - 2.16 (2 H, m, CH_2), 1.77 - 1.91 (2 H, m, CH_2), 1.32 - 1.46 (2 H, m, CH_2), 1.08 - 1.21 (2 H, m, CH_2), 1.01 (1 H, tt, *J* 11.8, 3.1, CH), 0.86 (9 H, s, *t*Bu); δ_C (100 MHz; $CDCl_3$) 162.6 (C), 136.9 (C), 131.9 (C), 128.2 (CH), 127.9 (CH), 127.5 (CH), 74.6 (CH), 47.1 (CH),

32.4 (C), 32.1 (CH_2), 27.7 (CH_3), 25.6 (CH_2). **(*E*)-*trans*-4-*tert*-Butylcyclohexyl 2-hydrazono-2-phenylacetate**: colourless solid (147 mg, 24%); mp 138 - 139 °C; (Found: M+H^+, 303.2064. $C_{18}H_{27}N_2O_2$ requires 303.2067); $\nu_{max}(CHCl_3)/cm^{-1}$ 3473, 2956, 1703, 1019; δ_H (400 MHz; $CDCl_3$) 7.45 - 7.52 (2 H, m, ArH), 7.38 - 7.44 (1 H, m, ArH), 7.27 - 7.33 (2 H, m, ArH), 6.18 (2 H, s, NH_2), 4.80 (1 H, tt, *J* 11.3, 4.5, CH), 2.02 - 2.16 (2 H, m, CH_2), 1.75 - 1.87 (2 H, m, CH_2), 1.34 - 1.49 (2 H, m, CH_2), 1.05 - 1.19 (2 H, m, CH_2), 0.99 (1 H, tt, *J* 11.8, 2.9, CH), 0.84 (9 H, s, *t*Bu); δ_C (100 MHz; $CDCl_3$) 164.1 (C), 138.2 (C), 129.9 (C), 129.4 (CH), 129.2 (CH), 129.0 (CH), 74.9 (CH), 47.2 (CH), 32.4 (C), 32.1 (CH_2), 27.7 (CH_3), 25.6 (CH_2).

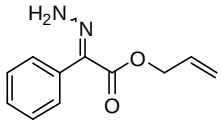
(*E*) and (*Z*)-Cyclobutylmethyl-2-hydrazono-2-phenylacetate 100g



Obtained by **general procedure D** from cyclobutylmethyl 2-oxo-2-phenylacetate **99g** (873 mg, 4.00 mmol) with a reaction time of 21 h. Purified by column chromatography using the elution gradient 10 then 50% ethyl acetate in light petroleum. **(*Z*)-Cyclobutylmethyl-2-hydrazono-2-phenylacetate**: colourless oil (607 mg, 65%); (Found: M+H^+, 233.1294. $C_{13}H_{17}N_2O_2$ requires 233.1285); ν_{max} $(CHCl_3)/cm^{-1}$ 3485, 1686, 1565; δ_H (400 MHz; $CDCl_3$) 8.41 (2 H, br s, NH_2), 7.49 - 7.56 (2 H, m, ArH), 7.27 - 7.37 (3 H, m, ArH), 4.22 (2 H, d, *J* 7.3, CH_2), 2.68 (1 H, spt, *J* 7.3, CH), 2.00 - 2.12 (2 H, m, CH_2), 1.74 - 1.99 (4 H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 163.1 (C), 136.8 (C), 131.3 (C), 128.3 (CH), 127.9 (CH), 127.6 (CH), 68.5 (CH_2), 34.0 (CH), 24.9 (CH_2), 18.4 (CH_2). **(*E*)-Cyclobutylmethyl-2-hydrazono-2-**

phenylacetate: colourless solid (315 mg, 34%); mp 65 - 66 °C; (Found: M+Na$^+$, 255.1113. $C_{13}H_{16}N_2NaO_2$ requires 255.1104); ν_{max} ($CHCl_3$)/cm^{-1} 3474, 1709; δ_H (400 MHz; $CDCl_3$) 7.42 - 7.50 (2 H, m, ArH), 7.35 - 7.42 (1 H, m, ArH), 7.24 - 7.31 (2 H, m, ArH), 6.30 (2 H, br s, NH_2), 4.18 (2 H, d, *J* 7.3, CH_2), 2.65 (1 H, spt, *J* 7.3, CH), 1.95 - 2.09 (2 H, m, CH_2), 1.66 - 1.92 (4 H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 164.6 (C), 137.3 (C), 129.8 (C), 129.3 (CH), 129.1 (CH), 128.8 (CH), 69.0 (CH_2), 34.2 (CH), 24.8 (CH_2), 18.4 (CH_2).

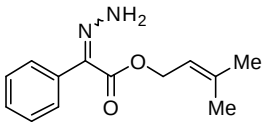
(*E*)- and (*Z*)-Allyl 2-hydrazono-2-phenylacetate 100h



Obtained by **general procedure C** from allyl 2-hydrazono-2-phenylacetate **99h** (304 mg, 1.60 mmol) with a reaction time of 5 h. Purified by column chromatography using the elution gradient 5 then 50% ethyl acetate in light petroleum. **(*Z*)-Allyl 2-hydrazono-2-phenylacetate**: yellow oil (256 mg, 69%); (Found: M+Na$^+$, 227.0793. $C_{11}H_{12}N_2NaO_2$ requires 227.0796); ν_{max} ($CHCl_3$)/cm^{-1} 3486, 3292, 3012, 1688, 1566, 1295, 1265, 1149, 1006, 937; δ_H (400 MHz; $CDCl_3$) 8.45 (2 H, br s, NH_2), 7.49-7.55 (2 H, m, ArH), 7.27-7.38 (3 H, m, ArH), 5.98 (1 H, ddt, *J* 17.2, 10.6, 5.8, vinylic CH), 5.32 (1 H, dd, *J* 17.2, 1.3, vinylic CH), 5.25 (1 H, dd, *J* 10.6, 1.3, vinylic CH), 4.75 (2 H, dt, *J* 5.8, 1.3, CH_2); δ_C (100 MHz; $CDCl_3$) 162.6 (C), 136.7 (C), 131.7 (CH), 130.8 (C), 128.4 (CH), 128.0 (CH), 127.7 (CH), 118.8 (CH_2), 65.3 (CH_2). **(*E*)-Allyl 2-hydrazono-2-phenylacetate**: yellow oil (73 mg, 22%); (Found: M+Na$^+$, 227.0795. $C_{11}H_{12}N_2NaO_2$ requires 227.0796); ν_{max} ($CHCl_3$)/cm^{-1} 3475, 3009, 1712, 1572, 1325, 1310; δ_H (400 MHz; $CDCl_3$) 7.46-7.53 (2 H, m, ArH), 7.42 (1 H, t, *J* 7.3, ArH), 7.28-7.33 (2 H, m,

ArH), 6.27 (2 H, br s, NH_2), 5.91-6.04 (1 H, ddt, *J* 17.2, 10.3, 5.8, vinylic CH), 5.31 (1 H, dq, *J* 17.2, 1.4, vinylic CH), 5.23 (1 H, dq, *J* 10.3, 1.4, vinylic CH), 4.74 (2 H, dt, *J* 5.8, 1.4, CH_2); δ_C (100 MHz; $CDCl_3$) 164.2 (C), 137.4 (C), 132.2 (CH), 129.6 (C) 129.5 (CH), 129.3 (CH), 129.0 (CH), 118.8 (CH_2), 66.0 (CH_2).

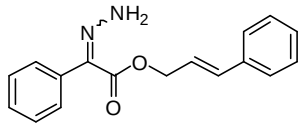
(*E*)- and (*Z*)-3-Methylbut-2-enyl 2-hydrazono-2-phenylacetate 100i



Obtained by **general procedure D** from 3-methylbut-2-enyl 2-oxo-2-phenylacetate **99i** (655 mg, 3.00 mmol) with a reaction time of 15 h. Purified by column chromatography using the elution gradient 10 to 40% ethyl acetate in light petroleum. **(*Z*)-3-Methylbut-2-enyl 2-hydrazono-2-phenylacetate**: colourless oil that solidified upon standing (452 mg, 47%); mp 24 - 25 °C; (Found: M+Na^+, 255.1098. $C_{13}H_{16}N_2NaO_2$ requires 255.1104); ν_{max} ($CHCl_3$)/cm^{-1} 3485, 1687, 1564, 1264, 1147; δ_H (400 MHz; $CDCl_3$) 8.39 (2 H, br s, NH_2), 7.49 - 7.57 (2 H, m, ArH), 7.26 - 7.38 (3 H, m, ArH), 5.40 (1 H, t.sept, *J* 7.2, 1.3, =CH), 4.76 (2 H, d, *J* 7.2, CH_2), 1.77 (3 H, s, CH_3), 1.74 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 163.0 (C), 139.6 (C), 136.8 (C), 131.3 (C), 128.3 (CH), 127.9 (CH), 127.6 (CH), 118.3 (CH), 61.6 (CH_2), 25.8 (CH_3), 18.2 (CH_3). **(*E*)-3-Methylbut-2-enyl 2-hydrazono-2-phenylacetate**: colourless solid (190 mg, 27%); mp 74 - 75 °C; (Found: M+Na^+, 255.1096. $C_{13}H_{16}N_2NaO_2$ requires 255.1104); ν_{max} ($CHCl_3$)/cm^{-1} 3474, 3009, 1706; δ_H (400 MHz; $CDCl_3$) 7.44 - 7.51 (2 H, m, ArH), 7.37 - 7.43 (1 H, m, ArH), 7.27 - 7.31 (2 H, m, ArH), 6.21 (2 H, br s, NH_2), 5.41 (1 H, tsept, *J* 7.2, 1.4, =CH), 4.74 (2 H, d, *J* 7.2, CH_2), 1.73 (3 H, s, CH_3), 1.71

(3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 164.6 (C), 139.1 (C), 137.6 (C), 129.7 (C), 129.4 (CH), 129.2 (CH), 128.9 (CH), 118.7 (CH), 62.4 (CH_2), 25.9 (CH_3), 18.2 (CH_3).

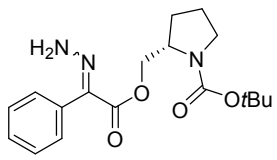
(*E*)- and (*Z*)-Cinnamyl 2-hydrazono-2-phenylacetate 100j



Obtained by **general procedure D** from cinnamyl 2-oxo-2-phenylacetate **99j** (794 mg, 3.00 mmol) with a reaction time of 14 h. Purified by column chromatography using the elution gradient ethyl acetate in light petroleum, 10 to 40%. **(*Z*)-Cinnamyl 2-hydrazono-2-phenylacetate**: colourless gum (531 mg, 63%); (Found: M+Na^+, 303.1095. $C_{17}H_{16}N_2NaO_2$ requires 303.1106); ν_{max} ($CHCl_3$)/cm^{-1} 3486, 3008, 1689, 1566, 1261, 1147; δ_H (400 MHz; $CDCl_3$) 8.48 (2 H, br s, NH_2), 7.52 - 7.59 (2 H, m, ArH), 7.25 - 7.42 (8 H, m, ArH), 6.68 (1 H, d, *J* 15.8, =CH), 6.32 (1 H, dt, *J* 15.8, 6.3, =CH), 4.91 (2 H, dd, *J* 6.3, 1.3, CH_2); δ_C (100 MHz; $CDCl_3$) 162.7 (C), 136.7 (C), 136.2 (C), 134.7 (CH), 130.9 (C), 128.8 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 127.7 (CH), 126.8 (CH), 122.6 (CH), 65.3 (CH_2). **(*E*)-Cinnamyl 2-hydrazono-2-phenylacetate**: yellow solid (107 mg, 24%); mp 132 - 133 °C; (Found: M+H^+, 303.1096. $C_{17}H_{16}N_2NaO_2$ requires 303.1195); ν_{max} ($CHCl_3$)/cm^{-1} 3475, 1709, 1138; δ_H (400 MHz; $CDCl_3$) 7.47 - 7.53 (2 H, m, ArH), 7.41 - 7.46 (1 H, m, ArH), 7.21 - 7.40 (7 H, m, ArH), 6.66 (1 H, d, *J* 15.8, =CH), 6.36 (1 H, dt, *J* 15.8, 6.5, =CH), 6.24 (2 H, br s, NH_2), 4.90 (2 H, dd, *J* 6.5, 1.3, CH_2); δ_C (100 MHz; $CDCl_3$) 164.3 (C), 137.5 (C), 136.4 (C), 134.8 (CH), 129.6 (CH), 129.4 (CH), 129.0 (CH), 128.7 (CH), 128.4 (C), 128.2 (CH), 126.8 (CH), 123.2 (CH),

66.0 (CH_2). Isomerization to the (*Z*)-isomer in solution in $CDCl_3$ was observed.

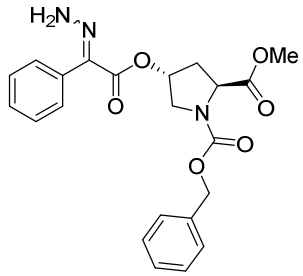
(S)-*tert*-Butyl 2-((2-hydrazono-2-phenylacetoxy)methyl)pyrrolidine-1-carboxylate 100k



Obtained by **general procedure D** from (*S*)-*tert*-butyl 2-(2-oxo-2-phenylacetoxy)methyl-pyrrolidine-1-carboxylate **99k** (502 mg, 1.51 mmol) with a reaction time of 16 h. Purified by column chromatography using the elution gradient 30 to 70% ethyl acetate in light petroleum. **(*S*)-*tert*-Butyl 2-(2-(*Z*)-hydrazono-2-phenylacetoxy)methylpyrrolidine-1-carboxylate**: colourless oil (333 mg, 64%); (Found: M+Na$^+$, 370.1730. $C_{18}H_{25}N_3NaO_4$ requires 370.1737); ν_{max} ($CHCl_3$)/cm^{-1} 3486, 1686; signal broadening was observed in deuterated chloroform at room temperature due to rotamer interconversion. δ_H (400 MHz; $CDCl_3$) 8.47 (2 H, br s, NH_2), 7.46 (2 H, d, *J* 6.3, ArH), 7.26 - 7.38 (3 H, m, ArH), 4.15 - 4.41 (2 H, m, CH_2O), 3.88 - 4.14 (1 H, m, CH), 3.08 - 3.47 (2 H, m, CH_2), 1.57 - 2.08 (4 H, m, CH_2), 1.46 (9 H, s, *t*Bu); δ_C (100 MHz; $CDCl_3$) 162.8 (C), 154.4 (C), 136.8 (C), 130.7 (C), 128.3 (CH), 127.9 (CH), 127.6 (CH), 79.9 (C), 79.6 (C), 65.2 (CH_2), 64.9 (CH_2), 55.5 (CH), 46.9 (CH_2), 46.6 (CH_2), 29.1 (CH_2), 28.6 (CH_3), 28.3 (CH_2), 23.7 (CH_2), 22.9 (CH_2), one quaternary carbon signal was not observed, doubling of some signals is due to the presence of rotameric mixtures. **(*S*)-*tert*-Butyl 2-(2-(*E*)-hydrazono-2-phenylacetoxy)methyl-pyrrolidine-1-carboxylate**: colourless oil (157 mg, 30%); (Found: M+Na$^+$, 370.1736. $C_{18}H_{25}N_3NaO_4$ requires 370.1737); ν_{max} ($CHCl_3$)/cm^{-1}

3476, 3011, 1713, 1686; signal broadening was observed in deuterated chloroform at room temperature due to rotamer interconversion. δ_H (400 MHz; $CDCl_3$) 7.36 - 7.52 (3 H, m, ArH), 7.24 - 7.29 (2 H, m, ArH), 6.27 (2 H, br s, NH_2), 3.87 - 4.33 (3 H, m, CH and CH_2O), 3.06 - 3.35 (2 H, m, CH_2), 1.60 - 1.97 (4 H, m, CH_2), 1.44 (9 H, s, *t*Bu); δ_C (100 MHz; $CDCl_3$) 164.3 (C), 137.2 (C), 129.8 (C), 129.4 (CH), 129.3 (CH), 128.9 (CH), 79.8 (C), 65.7 (CH_2), 65.4 (CH_2), 55.6 (CH), 46.5 (CH_2), 28.9 (CH_2), 28.6 (CH_3), 22.8 (CH_2), one quaternary carbon signal was not observed, doubling of some signals is due to the presence of rotameric mixtures.

(*2S,4R*)-1-Benzyl 2-methyl 4-(2-hydrazono-2-phenylacetoxy)pyrrolidine-1,2-dicarboxylate 100l

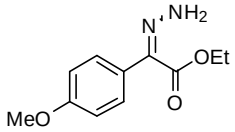


Obtained by **general procedure C** from (*2S,4R*)-1-benzyl 2-methyl 4-(2-oxo-2-phenylacetoxy)-pyrrolidine-1,2-dicarboxylate **99l** (529 mg, 1.29 mmol) with a reaction time of 4 h. Purified by column chromatography using the elution gradient 40% then 70% ethyl acetate in light petroleum. **(*2S,4R*)-1-Benzyl 2-methyl 4-(2-(*Z*)-hydrazono-2-phenylacetoxy)pyrrolidine-1,2-dicarboxylate**: yellow oil (395 mg, 72%); (Found: $M+H^+$, 426.1647. $C_{22}H_{24}N_3O_6$ requires 426.1660); ν_{max} ($CHCl_3$)/cm^{-1} 3684, 3487, 3011, 1748, 1705, 1421; two rotameric forms coexist in deuterated chloroform at room temperature (ratio 1:1); δ_H (400 MHz; $CDCl_3$) 8.56 (2 H, br s, NH_2 both rotamers), 7.26 - 7.44 (10 H, m, ArH both rotamers), 5.45 (1 H, m, CH both rotamers), 5.01 - 5.25 (2 H, m, CH_2O both rotamers), 4.45 (1 H, t, *J* 7.8, CH one rotamer), 4.37 (1 H, t, *J* 7.9, CH one rotamer), 3.76 (3 H, s, OMe

one rotamer), 3.67 - 3.93 (2 H, m, both rotamers), 3.56 (3 H, s, OMe one rotamer), 2.39 - 2.51 (1 H, m, CH_2 both rotamers), 2.27 (1 H, ddd, *J* 13.8, 7.8, 5.0, CH_2 both rotamers); δ_C (100 MHz; $CDCl_3$) 172.6 (C), 172.5 (C), 162.05 (C), 162.00 (C), 154.2 (C), 136.38 (C), 136.32 (C), 136.28 (C), 136.27 (C), 129.7 (C), 128.6 (CH), 128.5 (CH), 128.22 (CH), 128.19 (CH), 128.13 (CH), 128.11 (CH), 128.03 (CH), 128.01 (CH), 127.97 (CH), 127.95 (CH), 127.7 (CH), 127.6 (CH), 72.9 (CH), 72.2 (CH), 67.5 (CH_2), 67.5 (CH_2), 57.9 (CH_3), 57.7 (CH_3), 52.63 (CH_2), 52.61 (CH), 52.4 (CH), 52.1 (CH_2), 36.4 (CH_2), 35.4 (CH_2), two quaternary carbon signals were not observed. **(*2S,4R*)-1-Benzyl 2-methyl 4-(2-(*E*)-hydrazono-2-phenylacetoxy)-pyrrolidine-1,2-dicarboxylate**: Colourless oil (86 mg, 15%); (Found: $M+H^+$, 426.1638. $C_{22}H_{24}N_3O_6$ requires 426.1660); ν_{max} ($CHCl_3$)/cm^{-1} 3477, 3011, 1747, 1704, 1422; two rotameric forms coexist in deuterated chloroform at room temperature (ratio 1:1); δ_H (400 MHz; $CDCl_3$) 7.18 - 7.52 (10 H, m, ArH both rotamers), 6.38 (2 H, br s, NH_2 both rotamers), 5.41 (1 H, m, CH both rotamers), 5.19 (1 H, d, *J* 12.4, CH_2O one rotamer), 5.15 (1 H, d, *J* 12.5, CH_2O one rotamer), 5.10 (1 H, d, *J* 12.5, CH_2O one rotamer), 5.01 (1 H, d, *J* 12.4, CH_2O one rotamer), 4.45 (1 H, t, *J* 7.6, CH one rotamer), 4.41 (1 H, t, *J* 7.7, CH one rotamer), 3.74 (3 H, s, OMe one rotamer), 3.63 - 3.89 (2 H, m, CH_2 both rotamers), 3.53 (3 H, s, OMe one rotamer), 2.40 - 2.53 (1 H, m, CH_2 both rotamers), 2.21 - 2.31 (1 H, m, CH_2 both rotamers); δ_C (100 MHz; $CDCl_3$) 172.8 (C), 172.6 (C), 164.0 (C), 163.9 (C), 154.8 (C), 154.2 (C), 136.7 (C), 136.6 (C), 136.45 (C), 136.40 (C), 129.7 (CH), 129.6 (CH), 129.41 (CH), 129.39 (CH), 128.9 (CH), 128.8 (CH), 128.62 (CH), 128.57 (CH), 128.20 (CH), 128.15 (CH), 128.1 (CH), 128.0

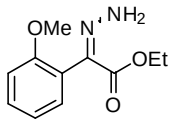
(CH), 73.4 (CH), 72.6 (CH), 67.6 (CH_2), 67.44 (CH_2), 58.1 (CH_3), 57.9 (CH_3), 52.7 (CH_2), 52.6 (CH), 52.4 (CH), 52.2 (CH_2), 36.6 (CH_2), 35.6 (CH_2), two quaternary carbon signals were not observed.

(*E*)- and (*Z*)-Ethyl 2-hydrazono-2-(4-methoxyphenyl)acetate 100m



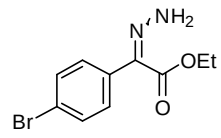
Obtained by **general procedure C** from ethyl 2-(4-methoxyphenyl)-2-oxoacetate **99m** (2.00 g, 9.62 mmol) with a reaction time of 3 h. Purified by column chromatography using the elution gradient 5 then 50% ethyl acetate in light petroleum. **(*Z*)-Ethyl 2-hydrazono-2-(4-methoxyphenyl)acetate**: yellow oil (1.28 g, 60%); (Found: M+Na^+, 245.0903. $C_{11}H_{14}N_2NaO_3$ requires 245.0902);ν_{max} ($CHCl_3$)/cm^{-1} 3485, 3293, 3008, 1688, 1609, 1565, 1513, 1300, 1268, 1250, 1177, 1147, 991, 835; δ_H (400 MHz; $CDCl_3$) 8.25 (2 H, br s, NH_2), 7.45 (2 H, d, *J* 8.8, ArH), 6.88 (2 H, d, *J* 8.8, ArH), 4.31 (2 H, q, *J* 7.2, C$\underline{H}_2$$CH_3$), 3.82 (3 H, s, OMe), 1.33 (3 H, t, *J* 7.2, CH_2C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 163.1 (C), 159.3 (C), 131.5 (C), 129.5 (CH), 129.4 (C), 113.5 (CH), 60.8 (CH_2), 55.4 (CH_3), 14.3 (CH_3). **(*E*)-Ethyl 2-hydrazono-2-(4-methoxyphenyl)acetate**: pale yellow solid (368 mg, 17%); mp 91 - 92 °C; (Found: M+Na^+, 245.0899. $C_{11}H_{14}N_2NaO_3$ requires 245.0902); ν_{max} ($CHCl_3$)/cm^{-1}; 3472, 3314, 3008, 1709, 1610, 1575, 1511, 1328, 1292, 1250, 1177, 1047, 1030; δ_H (400 MHz; $CDCl_3$) 7.25 (2 H, d, *J* 8.8, ArH), 7.00 (2 H, d, *J* 8.8, ArH), 6.18 (2 H, br s, NH_2), 4.31 (2 H, q, *J* 7.2, C$\underline{H}_2$$CH_3$), 3.84 (3 H, s, OMe), 1.34 (3 H, t, *J* 7.2, CH_2C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 164.7 (C), 137.5 (C), 130.4 (CH), 130.2 (C), 121.5 (C), 114.7 (CH), 61.4 (CH_2), 55.4 (CH_3), 14.4 (CH_3).

(*E*)- and (*Z*)-Ethyl 2-hydrazono-2-(2-methoxyphenyl)acetate 100n



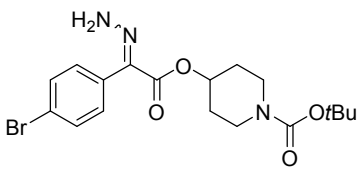
Obtained by **general procedure C** from ethyl 2-(2-methoxyphenyl)-2-oxoacetate **99n** (536 mg, 2.57 mmol) with a reaction time of 3 h. Purified by column chromatography using the elution gradient 5 to 50% ethyl acetate in light petroleum. **(*Z*)-Ethyl 2-hydrazono-2-(2-methoxyphenyl)acetate**: yellow oil (350 mg, 61%); (Found: M+Na$^+$, 245.0896. $C_{11}H_{14}N_2NaO_3$ requires 245.0902); ν_{max} ($CHCl_3$)/cm^{-1} 3484, 3299, 3007, 1693, 1570, 1493, 1465, 1269, 1243, 1147, 1113, 1029; δ_H (400 MHz; $CDCl_3$) 8.16 (2 H, br s, NH_2), 7.28-7.34 (2 H, m, ArH), 6.98 (1 H, td, *J* 7.4, 1.0, ArH), 6.87 (1 H, dd, *J* 8.7, 1.0, ArH), 4.22 (2 H, q, *J* 7.2, C$\underline{H}_2$CH$_3$), 3.78 (3 H, s, OMe), 1.19 - 1.25 (3 H, q, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 163.1 (C), 157.8 (C), 130.7 (C), 130.1 (CH), 129.6 (CH), 126.6 (C), 120.8 (CH), 110.6 (CH), 60.4 (CH_2), 55.4 (CH_3), 14.3 (CH_3). **(*E*)-Ethyl 2-hydrazono-2-(4-methoxyphenyl)acetate**: yellow solid (190 mg, 33%); mp 69 - 70 °C; (Found: M+Na$^+$, 245.0891. $C_{11}H_{14}N_2NaO_3$ requires 245.0902); ν_{max} ($CHCl_3$)/cm^{-1}: 3473, 3316, 3008, 1711, 1603, 1578, 1491, 1464, 1330, 1270, 1247, 1112, 1036; δ_H (400 MHz; $CDCl_3$) 7.37-7.44 (1 H, ddd, *J* 8.3, 7.5, 1.7, ArH), 7.17 (1 H, dd, *J* 7.5, 1.7, ArH), 7.05 (1 H, td, *J* 7.5, 0.9, ArH), 6.99 (1 H, d, *J* 8.3, ArH), 6.14 (2 H, br s, NH_2), 4.29 (2 H, q, *J* 7.2, C$\underline{H}_2$CH$_3$), 3.79 (3 H, s, OMe), 1.32 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 164.6 (C), 157.1 (C), 136.0 (C), 131.2 (CH), 130.3 (CH), 121.2 (CH), 118.7 (C), 111.7 (CH), 61.2 (CH_2), 55.8 (CH_3), 14.4 (CH_3).

(*E*) and (*Z*)-Ethyl 2-(4-bromophenyl)-2-hydrazonoacetate 100o



Obtained by **general procedure D** from ethyl 2-(4-bromophenyl)-2-oxoacetate **99o** (767 mg, 2.98 mmol) with a reaction time of 14 h. Purified by column chromatography using the elution gradient 10 to 50% ethyl acetate in light petroleum. **(*Z*)-Ethyl 2-(4-bromophenyl)-2-hydrazonoacetate**: off-yellow solid (453 mg, 60%); mp 51 - 52 °C; (Found: M+Na$^+$, 292.9891. $C_{10}H_{11}{}^{79}BrN_2NaO_2$ requires 292.9896); ν_{max} ($CHCl_3$)/cm^{-1} 3487, 3289, 1688, 1565, 1261, 1152; δ_H (400 MHz; $CDCl_3$) 8.52 (2 H, br s, NH_2), 7.46 (2 H, dt, *J* 8.8, 2.1, ArH), 7.40 (2 H, dt, *J* 8.8, 2.1, ArH), 4.30 (2 H, q, *J* 7.2, C$\underline{H}_2$CH$_3$), 1.32 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 162.7 (C), 135.8 (C), 131.0 (CH), 129.9 (CH), 129.7 (C), 121.6 (C), 60.9 (CH_2), 14.3 (CH_3). **(*E*)-Ethyl 2-(4-bromophenyl)-2-hydrazonoacetate**: colourless solid (290 mg, 36%); mp 106 - 107 °C; (Found: M+Na$^+$, 292.9893. $C_{10}H_{11}{}^{79}BrN_2NaO_2$ requires 292.9896); ν_{max} ($CHCl_3$)/cm^{-1} 3474, 3318, 3011, 1710; δ_H (400 MHz; DMSO-d_6) 7.74 (2 H, br s, NH_2), 7.62 - 7.67 (2 H, m, ArH), 7.13 - 7.20 (2 H, m, ArH), 4.11 (2 H, q, *J* 7.1, C$\underline{H}_2$CH$_3$), 1.19 (3 H, t, *J* 7.1, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; DMSO-d_6) 164.3 (C), 131.7 (CH), 131.4 (CH), 130.7 (C), 130.2 (C), 121.7 (C), 59.8 (CH_2), 14.2 (CH_3). The (*E*)-hydrazone was found to undergo isomerization to the (*Z*)-hydrazone at room temperature in $CDCl_3$.

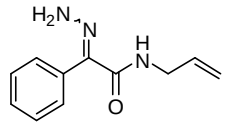
***tert*-Butyl 4-(2-(4-bromophenyl)-2-hydrazonoacetoxy)piperidine-1-carboxylate 100p**



Obtained by **general procedure C** from *tert*-butyl 4-(2-(4-bromophenyl)-2-oxoacetoxy)-

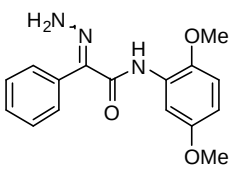
piperidine-1-carboxylate **99p** (965 mg, 2.34 mmol) with a reaction time of 8 h. Purified by column chromatography using the elution gradient 10 to 50% ethyl acetate in light petroleum. **(*Z*)-*tert*-Butyl 4-(2-(4-bromophenyl)-2-hydrazonoacetoxy)piperidine-1-carboxylate**: colourless solid (691 mg, 69%); mp 127 - 128 °C; (Found: M+Na$^+$, 448.0840. $C_{18}H_{24}{}^{79}BrN_3NaO_4$requires 448.0842); ν_{max} ($CHCl_3$)/cm^{-1} 3487, 1685; δ_H (400 MHz; $CDCl_3$) 8.59 (2 H, br s, NH_2), 7.43 - 7.47 (2 H, m, ArH), 7.34 - 7.39 (2 H, m, ArH), 5.14 (1 H, tt, *J* 7.4, 3.6, CH), 3.49 - 3.59 (2 H, m, CH_2), 3.34 (2 H, ddd, *J* 13.5, 7.9, 3.8, CH_2), 1.83 - 1.94 (2 H, m, CH_2), 1.62 - 1.73 (2 H, m, CH_2), 1.45 (9 H, s, *t*Bu); δ_C (100 MHz; $CDCl_3$) 161.9 (C), 154.7 (C), 135.7 (C), 131.1 (CH), 129.9 (CH), 129.4 (C), 121.7 (C), 79.9 (C), 70.5 (CH), 40.9 (CH_2), 30.6 (CH_2), 28.5 (CH_3). **(*E*)-*tert*-Butyl 4-(2-(4-bromophenyl)-2-hydrazonoacetoxy)piperidine-1-carboxylate**: colourless solid (195 mg, 20%); mp 142 - 143 °C; (Found: M+Na$^+$, 448.0842. $C_{18}H_{24}{}^{79}BrN_3NaO_4$ requires 448.0842); ν_{max} ($CHCl_3$)/cm^{-1} 3476, 1685; δ_H (400 MHz; $CDCl_3$) 7.57 - 7.64 (2 H, m, ArH), 7.14 - 7.19 (2 H, m, ArH), 6.23 (2 H, br s, NH_2), 5.05 (1 H, tt, *J* 8.3, 3.8, CH), 3.57 - 3.69 (2 H, m, CH_2), 3.17 (2 H, ddd, *J* 13.4, 8.3, 3.8, CH_2), 1.86 (2 H, ddt, *J* 12.9, 6.3, 3.8, CH_2), 1.63 (2 H, tdd, *J* 12.9, 8.3, 3.8, CH_2), 1.43 (9 H, s, *t*Bu); δ_C (100 MHz; $CDCl_3$) 163.4 (C), 154.8 (C), 136.0 (C), 132.6 (CH), 130.6 (CH), 128.5 (C), 123.8 (C), 79.8 (C), 71.0 (CH), 41.1 (CH_2), 30.7 (CH_2), 28.5 (CH_3).

(*E*)- and (*Z*)-*N*-Allyl-2-hydrazono-2-phenylacetamide 100q



Obtained by **general procedure D** from *N*-allyl-2-oxo-2-phenylacetamide **99q** (285 mg, 1.50 mmol) with a reaction time of 20 h. Purified by column chromatography using 30% ethyl acetate in light petroleum. **(*Z*)-*N*-Allyl-2-hydrazono-2-phenylacetamide**: pale yellow solid (257 mg, 84%); mp 45 - 46 °C; (Found: M+Na$^+$, 226.0949. $C_{11}H_{13}N_3NaO$ requires 226.0951); ν_{max} ($CHCl_3$)/cm^{-1} 3431, 3003, 1656, 1556, 1511, 1168; δ_H (400 MHz; $CDCl_3$) 8.05 (2 H, br s, NH_2), 7.42 - 7.49 (2 H, m, ArH), 7.29 - 7.41 (3 H, m, ArH), 5.87 (1 H, br s, NH), 5.80 (1 H, ddt, *J* 17.1, 10.3, 5.7, vinylic CH), 5.09 - 5.19 (2 H, m, vinylic CH_2), 3.91 (2 H, tt, *J* 5.7, 1.5, CH_2); δ_C (100 MHz; $CDCl_3$) 163.7 (C), 136.6 (C), 135.3 (C), 133.6 (CH), 128.9 (CH), 128.5 (CH), 128.1 (CH), 116.8 (CH_2), 41.4 (CH_2). **(*E*)-*N*-Allyl-2-hydrazono-2-phenylacetamide**: yellow oil (46 mg, 15%); (Found: M+Na$^+$, 226.0950. $C_{11}H_{13}N_3NaO$ requires 226.0951); ν_{max} ($CHCl_3$)/cm^{-1} 3419, 3006, 1663, 1516; δ_H (400 MHz; $CDCl_3$) 7.42 - 7.49 (2 H, m, ArH), 7.35 - 7.41 (1 H, m, ArH), 7.28 - 7.33 (2 H, m, ArH), 7.08 (1 H, br s, NH), 5.86 - 5.95 (3 H, m, vinylic CH and NH_2), 5.23 (1 H, dq, *J* 17.1, 1.6, vinylic CH), 5.14 (1 H, dq, *J* 10.2, 1.4, vinylic CH), 3.96 (2 H, tt, *J* 5.8, 1.6, CH_2); δ_C (100 MHz; $CDCl_3$) 164.2 (C), 140.8 (C), 134.7 (CH), 129.3 (CH), 129.1 (CH), 129.0 (CH), 116.2 (CH_2), 41.8 (CH_2), one quaternary carbon signal was not observed.

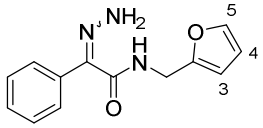
(*E*)- and (*Z*)-*N*-(2,5-Dimethoxyphenyl)-2-hydrazono-2-phenylacetamide 100r



Obtained by **general procedure D** from *N*-(2,5-dimethoxyphenyl)-2-oxo-2-phenylacetamide

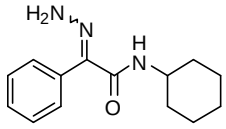
99r (855 mg, 3.00 mmol) with a reaction time of 20 h. Purified by column chromatography using 25% ethyl acetate in light petroleum. **(*Z*)-*N*-(2,5-Dimethoxyphenyl)-2-hydrazono-2-phenyl-acetamide**: yellow solid (806 mg, 90%); mp 114 - 115 °C; (Found: M+Na$^+$, 322.1158. $C_{16}H_{17}N_3NaO_3$ requires 322.1162); ν_{max} ($CHCl_3$)/cm^{-1} 3481, 3389, 1660, 1601, 1530, 1482; δ_H (400 MHz; $CDCl_3$) 8.36 (2 H, br s, NH_2), 8.16 (1 H, br s, NH), 8.14 (1 H, d, *J* 2.9, ArH), 7.55 (2 H, dd, *J* 8.0, 1.3, ArH), 7.35 - 7.48 (3 H, m, ArH), 6.73 (1 H, d, *J* 8.9, ArH), 6.59 (1 H, dd, *J* 8.9, 2.9, ArH), 3.81 (3 H, s, OMe), 3.63 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 161.8 (C), 153.9 (C), 142.7 (C), 136.5 (C), 134.9 (C), 128.9 (CH), 128.6 (CH), 128.5 (CH), 127.7 (C), 111.1 (CH), 109.2 (CH), 106.3 (CH), 56.4 (CH_3), 55.9 (CH_3). **(*E*)-*N*-(2,5-Dimethoxyphenyl)-2-hydrazono-2-phenyl-acetamide**: off-yellow solid (70 mg, 8%); mp 115 - 116 °C; (Found: M+Na$^+$, 322.1155. $C_{16}H_{17}N_3NaO_3$ requires 322.1162); ν_{max} ($CHCl_3$)/cm^{-1} 3467, 3374, 1671, 1601, 1531, 1486; δ_H (400 MHz; $CDCl_3$) 9.61 (1 H, br s, NH), 8.22 (1 H, d, *J* 3.0, ArH), 7.48 - 7.54 (2 H, m, ArH), 7.40 - 7.46 (1 H, m, ArH), 7.33 - 7.38 (2 H, m, ArH), 6.82 (1 H, d, *J* 8.9, ArH), 6.57 (1 H, dd, *J* 8.9, 3.0, ArH), 5.98 (2 H, br s, NH_2), 3.89 (3 H, s, OMe), 3.75 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 162.2 (C), 154.0 (C), 142.6 (C), 141.2 (C), 129.5 (CH), 129.2 (CH), 129.1 (CH), 128.9 (C), 128.7 (C), 111.1 (CH), 108.8 (CH), 105.0 (CH), 56.5 (CH_3), 55.9 (CH_3).

(*E*)- and (*Z*)-*N*-(2-Furylmethyl)-2-hydrazono-2-phenylacetamide 100s



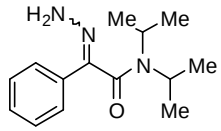
Obtained by **general procedure D** from *N*-(2-furylmethyl)-2-oxo-2-phenylacetamide **99s** (688 mg, 3.00 mmol) with a reaction time of 20 h. Purified by column chromatography using 40% ethyl acetate in light petroleum. **(*Z*)-*N*-(2-Furylmethyl)-2-hydrazono-2-phenylacetamide**: yellow oil (628 mg, 86%); (Found: M+Na$^+$, 266.0894. $C_{13}H_{13}N_3NaO_2$ requires 266.0900); ν_{max} ($CHCl_3$)/cm^{-1} 3480, 3431, 3011, 1656, 1514; δ_H (400 MHz; $CDCl_3$) 8.02 (2 H, br s, NH_2), 7.39 - 7.47 (2 H, m, ArH), 7.28 - 7.39 (4 H, m, ArH and H3), 6.29 (1 H, dd, *J* 3.1, 1.9, H4), 6.20 (1 H, d, *J* 3.1, H5), 6.16 (1 H, br s, NH), 4.45 (2 H, d, *J* 5.8, CH_2); δ_C (100 MHz; $CDCl_3$) 163.6 (C), 150.7 (C), 142.3 (CH), 136.4 (C), 135.1 (C), 128.8 (CH), 128.4 (CH), 128.0 (CH), 110.5 (CH), 107.6 (CH), 35.9 (CH_2). **(*E*)-*N*-(2-Furylmethyl)-2-hydrazono-2-phenylacetamide**: pale yellow solid (88 mg, 12%); mp 92 - 93 °C (Found: M+Na$^+$, 266.0888. $C_{13}H_{13}N_3NaO_2$ requires 266.0900); ν_{max} ($CHCl_3$)/cm^{-1} 3420, 3011, 1663, 1514; δ_H (400 MHz; $CDCl_3$) 7.42 - 7.50 (2 H, m, ArH), 7.27 - 7.42 (5 H, m, ArH and NH), 6.33 (1 H, dd, *J* 3.1, 1.9, ArH), 6.26 (1 H, dd, *J* 3.1, 0.6, ArH), 5.85 (2 H, br s, NH_2), 4.52 (2 H, d, *J* 5.8, CH_2); δ_C (100 MHz; $CDCl_3$) 164.2 (C), 151.8 (C), 142.2 (CH), 140.8 (C), 129.4 (CH), 129.2 (CH), 129.03 (CH), 128.99 (C), 110.5 (CH), 107.4 (CH), 36.5 (CH_2).

(*E*) and (*Z*)-*N*-Cyclohexyl-2-hydrazono-2-phenylacetamide 100t



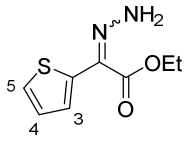
Obtained by **general procedure D** from *N*-cyclohexyl-2-oxo-2-phenylacetamide **99t** (927 mg, 4.00 mmol) with a reaction time of 24 h. Purified by column chromatography using the elution gradient 20 to 40% ethyl acetate in light petroleum. **(*Z*)-*N*-Cyclohexyl-2-hydrazono-2-phenylacetamide**: colourless solid (790 mg, 80%); mp 116 - 117 °C; (Found: $M+H^+$, 246.1597. $C_{14}H_{20}N_3O$ requires 246.1601); ν_{max} ($CHCl_3$)/cm^{-1} 3419, 1651, 1513; δ_H (400 MHz; $CDCl_3$) 7.92 (2 H, br s, NH_2), 7.43 - 7.50 (2 H, m, ArH), 7.30 - 7.41 (3 H, m, ArH), 5.61 (1 H, d, *J* 6.1, NH), 3.79 - 3.99 (1 H, m, CH), 1.87 - 1.97 (2 H, m, CH_2), 1.55 - 1.73 (3 H, m, CH_2), 1.31 - 1.46 (2 H, m, CH_2), 1.04 - 1.20 (3 H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 163.0 (C), 136.7 (C), 136.5 (C), 128.9 (CH), 128.5 (CH), 128.0 (CH), 48.1 (CH), 33.0 (CH_2), 25.5 (CH_2), 24.9 (CH_2). **(*E*)-*N*-Cyclohexyl-2-hydrazono-2-phenylacetamide**: colourless oil that solidified upon standing (107 mg, 11%); mp 108 - 110 °C; (Found: $M+H^+$, 246.1593. $C_{14}H_{20}N_3O$ requires 246.1601); ν_{max} ($CHCl_3$)/cm^{-1} 2935, 1656, 1515; δ_H (400 MHz; $CDCl_3$) 7.43 - 7.49 (2 H, m, ArH), 7.35 - 7.41 (1 H, m, ArH), 7.28 - 7.33 (2 H, m, ArH), 6.90 (1 H, d, *J* 7.6, NH), 5.78 (2 H, s, NH_2), 3.75 - 3.87 (1 H, m, CH), 1.89 - 2.01 (2 H, m, CH_2), 1.67 - 1.78 (2 H, m, CH_2), 1.61 (1 H, dt, *J* 12.6, 3.8, CH_2), 1.31 - 1.45 (2 H, m, CH_2), 1.16 - 1.29 (3 H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 163.3 (C), 141.6 (C), 129.3 (CH), 129.1 (CH), 128.9 (CH), 48.1 (CH), 33.3 (CH_2), 25.7 (CH_2), 25.0 (CH_2), one quaternary carbon was not observed.

(*E*)-2-Hydrazono-*N*,*N*-diisopropyl-2-phenylacetamide 100u



Obtained by a modification of **general procedure D** from *N*,*N*-diisopropyl-2-oxo-2-phenylacetamide **99u** (933 mg, 4.00 mmol) by the action of hydrazine hydrate (244 μL, 4.62 mmol) and benzoic acid (569 mg, 4.66 mmol) in refluxing tetrahydrofuran (16 mL) with a reaction time of 3 h. Purified by column chromatography using the elution gradient 10 to 40% ethyl acetate in light petroleum. Colourless solid (692 mg, 70%); mp 126 - 128 °C; (Found: M+Na$^+$, 268.1411. $C_{14}H_{19}N_3NaO$ requires 268.1420); ν_{max} ($CHCl_3$)/cm^{-1} 2981, 1616; δ_H (400 MHz; $CDCl_3$); 7.52 - 7.62 (2 H, m, ArH), 7.27 - 7.39 (3 H, m, ArH), 5.65 (2 H, s, NH_2), 3.78 (1 H, spt, *J* 6.7, CH), 3.51 (1 H, spt, *J* 6.9, CH), 1.60 (6 H, d, *J* 6.9, CH_3), 1.07 (6 H, d, *J* 6.7, CH_3); δ_C (100 MHz; $CDCl_3$) 165.5 (C), 147.2 (C), 134.2 (C), 128.9 (CH), 128.7 (CH), 125.3 (CH), 50.9 (CH), 46.2 (CH), 21.2 (CH_3), 20.6 (CH_3).

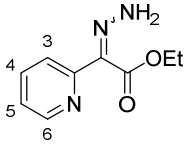
(*E*)- and (*Z*)-Ethyl 2-hydrazono-2-(thienyl)acetate 100v



Obtained by **general procedure C** from ethyl 2-oxo-2-(2-thenyl)acetate **99v** (322 mg, 1.75 mmol) with a reaction time of 39 h. Purified by column chromatography using the elution gradient 10 to 40% ethyl acetate in light petroleum .**(*Z*)-Ethyl 2-hydrazono-2-(thienyl)acetate**: yellow solid (83 mg, 24%); mp 45 - 46 °C; (Found: M+Na$^+$, 221.0352. $C_8H_{10}N_2NaO_2S$ requires 221.0355); ν_{max} ($CHCl_3$)/cm^{-1} 3485, 3011, 1688, 1287, 1155; δ_H (400 MHz; $CDCl_3$) 8.48 (2 H, br s, NH_2), 7.40 (1 H, dd, *J* 3.7, 1.0, H5), 7.17 (1 H, dd, *J* 5.1, 1.0, H3), 6.98 (1 H, dd, *J* 5.1, 3.7, H4), 4.37 (2 H, q, *J* 7.2, $C\underline{H}_2CH_3$), 1.42 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 162.0 (C), 140.9 (C), 127.2 (CH), 126.2

(C), 125.2 (CH), 124.7 (CH), 61.1 (CH_2), 14.3 (CH_3). **(*E*)-Ethyl 2-hydrazono-2-(thienyl)acetate**: yellow solid (45 mg, 13%); mp 63 - 64 °C; (Found: M+Na^+, 221.0352. $C_8H_{10}N_2NaO_2S$ requires 221.0355); ν_{max} ($CHCl_3$)/cm^{-1} 1711, 1239; δ_H (400 MHz; $CDCl_3$) 7.53 (1 H, dd, *J* 5.1, 1.1, H3), 7.32 (1 H, dd, *J* 3.6, 1.1, H5), 7.15 (1 H, dd, *J* 5.1, 3.6, H4), 6.75 (2 H, br s, NH_2), 4.33 (2 H, q, *J* 7.2, C$\underline{H}_2$$CH_3$), 1.36 (3 H, t, *J* 7.2, CH_2C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 164.3 (C), 130.5 (C), 129.2 (CH), 128.7 (C), 128.6 (CH), 127.0 (CH), 61.7 (CH_2), 14.4 (CH_3).

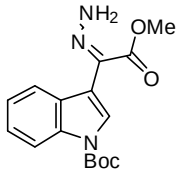
(*E*)- and (*Z*)-Ethyl 2-hydrazono-2-(pyridin-2-yl)acetate 100w



Obtained by **general procedure D** from ethyl 2-oxo-2-(pyridin-2-yl)acetate **99w** (128 mg, 714 μmol) with a reaction time of 12 h. Obtained as a mixture of (*E*) and (*Z*)-isomers after the described aqueous work-up (ratio *E*/*Z*: 9/91). Yellow solid (70 mg, 51%); (Found: M+Na^+, 216.0745. $C_9H_{11}N_3NaO_2$ requires 216.0743); ν_{max} ($CHCl_3$)/cm^{-1} 3470, 3006, 1703, 1571, 1267; **(*Z*)-isomer**: δ_H (400 MHz; $CDCl_3$) 9.51 (2 H, s, NH_2) 8.55 (1 H, ddd, *J* 4.9, 1.9, 1.0, H6), 8.02 (1 H, dt, *J* 8.3, 1.0, H3), 7.77 (1 H, ddd, *J* 8.3, 7.6, 1.9, H4), 7.21 (1 H, ddd, *J* 7.6, 4.9, 1.0, H5), 4.35 (2 H, q, *J* 7.2, C$\underline{H}_2$$CH_3$), 1.38 (3 H, t, *J* 7.2, CH_2C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 165.4 (C), 152.5 (C), 146.8 (CH), 136.7 (CH), 127.9 (C), 124.4 (CH), 122.4 (CH), 61.1 (CH_2), 14.5 (CH_3); **(*E*)-isomer**: δ_H (400 MHz; $CDCl_3$) 8.57 - 8.60 (1 H, m, H6), 8.46 (2 H, s, NH_2), 7.66 (1 H, dt, *J* 7.9, 1.4, H3), 7.55 (1 H, ddd, *J* 7.9, 7.5, 1.1, H4), 7.17 (1 H, ddd, *J* 7.5, 4.9, 1.4, H5), 4.32 (2 H, d, *J* 7.2, C$\underline{H}_2$$CH_3$), 1.29 (3 H, t, *J* 7.2, CH_2C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$)162.9 (C), 149.0 (CH), 136.1 (CH), 124.2 (C),

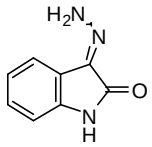
123.0 (CH), 122.3 (CH), 60.9 (CH_2), 14.2 (CH_3), one quaternary carbon was not detected.

(*E*)- and (*Z*)-*tert*-Butyl 3-(1-hydrazono-2-methoxy-2-oxoethyl)-indole-1-carboxylate 100x



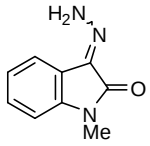
Obtained by **general procedure D** from *tert*-butyl 3-(2-methoxy-2-oxoacetyl)-*1H*-indole-1-carboxylate **99x** (455 mg, 1.50 mmol) with a reaction time of 20 h. Purified by column chromatography using 25% ethyl acetate in light petroleum. **(*Z*)-*tert*-Butyl 3-(1-hydrazono-2-methoxy-2-oxoethyl)indole-1-carboxylate**: yellow oil (135 mg, 28%); (Found: M+Na^+, 340.1265. $C_{16}H_{19}N_3NaO_4$ requires 340.1268); ν_{max} ($CHCl_3$)/cm^{-1} 1729, 1699, 1452, 1381, 1251, 1157, 1102; δ_H (400 MHz; $CDCl_3$) 8.54 (2 H, br s, NH_2), 8.14 (1 H, d, *J* 8.0, ArH), 8.08 (1 H, d, *J* 8.0, ArH), 7.92 (1 H, s, ArH), 7.29 - 7.36 (1 H, m, ArH), 7.21 - 7.29 (1 H, m, ArH), 3.89 (3 H, s, OMe), 1.69 (9 H, s, *t*Bu); δ_C (100 MHz; $CDCl_3$) 163.2 (C), 149.9 (C), 135.3 (C), 129.1 (C), 125.6 (C), 125.4 (CH), 124.6 (CH), 123.0 (CH), 122.2 (CH), 116.4 (C), 115.0 (CH), 83.9 (C), 51.7 (CH_3), 28.3 (CH_3). **(*E*)-*tert*-Butyl 3-(1-hydrazono-2-methoxy-2-oxoethyl)indole-1-carboxylate**: yellow solid (123 mg, 26%); mp 132 - 134 °C; (Found: M+Na^+, 340.1272. $C_{16}H_{19}N_3NaO_4$ requires 340.1268); ν_{max} ($CHCl_3$)/cm^{-1} 1734, 1374, 1154, 1102; δ_H (400 MHz; $CDCl_3$) 8.21 (1 H, d, *J* 8.3, ArH), 7.76 (1 H, s, ArH), 7.32 - 7.39 (2 H, m, ArH), 7.22 - 7.28 (1 H, m, ArH), 6.41 (2 H, s, NH_2), 3.86 (3 H, s, OMe), 1.68 (9 H, s, *t*Bu); δ_C (100 MHz; $CDCl_3$) 165.2 (C), 149.3 (C), 135.4 (C), 130.7 (C), 127.4 (C), 127.1 (CH), 125.2 (CH), 123.2 (CH), 120.8 (CH), 115.8 (CH), 108.8 (C), 84.7 (C), 52.6 (CH_3), 28.3 (CH_3).

(*E*) and (*Z*)-3-Hydrazonoindolin-2-one 100y



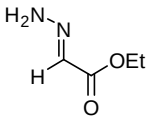
Obtained by **general procedure D** from isatin **99y** (120 mg, 815 μmol) with a reaction time of 3 h. Obtained as a mixture of (*E*) and (*Z*)-isomers after an aqueous work-up (ratio *E*/*Z*: 89/11, isomerises upon standing in favour of the (*Z*)-isomer). Orange solid (84 mg, 64%); (Found: M+Na$^+$, 184.0480. $C_8H_7N_3NaO$ requires 184.0487); ν_{max} (ATR)/cm^{-1} 1686, 1587, 1555, 1463, 1204; **(*E*)-isomer**: δ_H (400 MHz; DMSO-d_6) 10.35 (1 H, s, NH), 8.76 (2 H, br s, NH_2), 7.90 (1 H, d, *J* 7.5, ArH), 7.20 (1 H, td, *J* 7.8, 1.0, ArH), 6.96 (1 H, td, *J* 7.5, 1.0, ArH), 6.83 (1 H, d, *J* 7.8, ArH); δ_C (100 MHz; DMSO-d_6) 162.8 (C), 138.7 (C), 127.1 (CH), 126.2 (C), 122.3 (C), 121.4 (CH), 117.5 (CH), 110.0 (CH); **(*Z*)-isomer**: δ_H (400 MHz; DMSO-d_6) 10.68 (1 H, s, NH), 10.53 (1 H, d, *J* 14.0, NH_2), 9.54 (1 H, d, *J* 14.0, NH_2), 7.35 (1 H, d, *J* 7.5, ArH), 7.15 (1 H, td, *J* 7.8, 1.0, ArH), 6.97 (1 H, dt, *J* 7.5, 1.0, ArH), 6.83 - 6.87 (1 H, m, ArH); δ_C (100 MHz; DMSO-d_6) 165.8 (C), 140.5 (C), 128.7 (CH), 128.5 (C), 122.7 (CH), 121.0 (CH), 116.9 (C), 109.6 (CH). Following a previously described procedure,[22] the **(*Z*)-isomer** was obtained as a yellow solid; mp 210 °C (decomp) (lit.[22] mp 226 °C); (Found: M+Na$^+$, 184.0481. $C_8H_7N_3NaO$ requires 184.0487); ν_{max} (ATR)/cm^{-1} 3134, 1683, 1656, 1586, 1548, 1465, 1191, 978, 746, 678; δ_H (300 MHz; DMSO-d_6) 10.68 (1 H, s, NH), 10.54 (1 H, d, *J* 14.0, NH_2), 9.54 (1 H, d, *J* 14.0, NH_2), 7.35 (1 H, d, *J* 7.5, ArH), 7.15 (1 H, dt, *J* 7.8, 1.0, ArH), 6.97 (1 H, dt, *J* 7.5, 1.0, ArH), 6.86 (1 H, dt, *J* 7.8, 1.0, ArH); δ_C (75 MHz; DMSO-d_6) 162.8 (C), 138.6 (C), 127.0 (CH), 126.2 (C), 122.2 (C), 121.3 (CH), 117.4 (CH), 110.0 (CH). The data are consistent with the literature.[22]

(*E*)- and (*Z*)-3-Hydrazono-1-methylindolin-2-one 100z



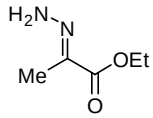
Obtained by **general procedure D** from *N*-methylisatin **99z** (161 mg, 1.00 mmol) with a reaction time of 1 h. Obtained as a mixture of (*E*) and (*Z*)-isomers after an aqueous work-up (ratio *E*/*Z* : 85/15). Red solid (172 mg, 98%); (Found: M+Na$^+$, 198.0644. $C_9H_9N_3NaO$ requires 198.0638); ν_{max} (ATR)/cm^{-1} 1691, 1675, 1607, 1588, 1489, 1468; **(*E*)-isomer**: δ_H (400 MHz; DMSO-d_6) 8.87 (2 H, br s, NH_2), 7.95 (1 H, d, *J* 7.6, ArH), 7.29 (1 H, t, *J* 7.6, ArH), 7.04 (1 H, d, *J* 7.6, ArH), 7.01 (1 H, t, *J* 7.6, ArH), 3.15 (3 H, s, CH_3); δ_C (100 MHz; DMSO-d_6) 164.4 (C), 141.6 (C), 128.6 (CH), 127.6 (C), 122.3 (CH), 121.5 (CH), 116.1 (C), 108.2 (CH), 25.6 (CH_3); **(*Z*)-isomer**: δ_H (400 MHz; DMSO-d_6) 10.51 (1 H, d, *J* 14.3, NH_2), 9.62 (1 H, d, *J* 14.3, NH_2), 7.40 (1 H, d, *J* 7.7, ArH), 7.24 (1 H, t, *J* 7.5, ArH), 6.94 - 7.10 (2 H, m, ArH) 3.35 (3 H, s, CH_3); δ_C (100 MHz; DMSO-d_6) 160.8 (C), 140.0 (C), 127.0 (CH), 125.4 (C), 121.9 (CH), 121.3 (C), 117.2 (CH), 108.6 (CH), 25.1 (CH_3). The data are consistent with the literature.[23]

(*E*)-Ethyl 2-hydrazonoacetate 100aa



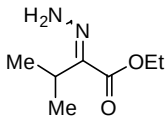
Obtained by **general procedure D** from ethyl glyoxylate **99aa** (50% w toluene solution; 0.99 mL, 5.00 mmol) with a reaction time of 1 h. Purified by column chromatography using 50% ethyl acetate in light petroleum. Colourless oil (530 mg, 91%); ν_{max} ($CHCl_3$)/cm^{-1} 3491, 3009, 2941, 1696, 1576, 1283, 1192, 1118; δ_H (400 MHz; $CDCl_3$) 7.03 (1 H, s, CH), 6.44 (2 H, br s, NH_2), 4.26 (2 H, q, *J* 7.2, C$\underline{H}_2$CH$_3$), 1.31 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 164.2 (C), 129.4 (CH), 61.0 (CH_2), 14.4 (CH_3). The data are consistent with the literature.[24]

(*E*)-Ethyl pyruvate hydrazone 100ab



Obtained by **general procedure C** from ethyl pyruvate **99ab** (2.00 mL, 18.1 mmol) with a reaction time of 17 h. Purified by column chromatography using the elution gradient 50% ethyl acetate in light petroleum to 100% ethyl acetate. Colourless solid (2.15 g, 91%); mp 49 - 50 °C; (Found: M+Na$^+$, 153.0634. $C_5H_{10}N_2NaO_2$ requires 153.0640); ν_{max} ($CHCl_3$)/cm^{-1} 3467, 3335, 3010, 1707, 1596, 1370, 1327, 1261, 1135, 1025; δ_H (400 MHz; $CDCl_3$) 5.95 (2 H, br s, NH_2), 4.26 (2 H, q, *J* 7.2, C$\underline{H}_2$CH$_3$), 1.94 (3 H, s, CH_3), 1.32 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 165.1 (C), 137.1 (C), 61.4 (CH_2), 14.4 (CH_3), 9.6 (CH_3).

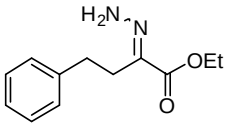
***(E*)- and (*Z*)-Ethyl 3-methyl-2-oxobutanoate hydrazone 100ac**



Obtained by **general procedure C** from 3-methyl 2-oxobutyrate **99ac** (1.00 g, 6.95 mmol) with a reaction time of 23 h. Purified by column chromatography using the elution gradient 13 to 50% ethyl acetate in light petroleum. **(*Z*)-Ethyl 3-methyl-2-oxobutanoate hydrazone**: yellow oil (635 mg, 58%); (Found: M+Na$^+$, 181.0956. $C_7H_{14}N_2NaO_2$ requires 181.0953); ν_{max} ($CHCl_3$)/cm^{-1} 3480, 3298, 2972, 2937, 1688, 1570, 1469, 1369, 1270, 1159, 1084, 1026; δ_H (400 MHz; $CDCl_3$) 7.93 (2 H, br s, NH_2), 4.24 (2 H, q, *J* 7.1, C$\underline{H}_2$CH$_3$), 2.90 (1 H, spt, *J* 6.8, C$\underline{H}$(CH$_3$)$_2$), 1.33 (3 H, t, *J* 7.1, CH$_2$C$\underline{H}_3$), 1.08 (6 H, d, *J* 6.8, CH(C$\underline{H}_3$)$_2$); δ_C (100 MHz; $CDCl_3$) 163.0 (C), 136.4 (C), 60.2 (CH_2), 31.0 (CH), 21.1 (CH_3), 14.3 (CH_3). **(*E*)-Ethyl 3-methyl-2-oxobutanoate hydrazone**: colourless solid (379 mg, 34%); mp 80 - 81 °C (lit.[25] mp 89 - 91°C); (Found: M+Na$^+$, 181.0969. $C_7H_{14}N_2NaO_2$ requires 181.0953); ν_{max} ($CHCl_3$)/cm^{-1} 3462, 3003, 2939, 1710, 1591, 1373, 1323, 1186, 1148,

1038; δ_H (400 MHz; $CDCl_3$) 5.97 (2 H, br s, NH_2), 4.25 (2 H, q, *J* 7.1, $C\underline{H}_2CH_3$), 2.97 (1 H, spt, *J* 7.0, $C\underline{H}(CH_3)_2$), 1.33 (3 H, t, *J* 7.1, $CH_2C\underline{H}_3$), 1.25 (6 H, d, *J* 7.0, $CH(C\underline{H}_3)_2$); δ_C (100 MHz; $CDCl_3$) 164.4 (C), 144.6(C), 60.9 (CH_2), 24.6 (CH), 18.4 (CH_3), 14.4 (CH_3).

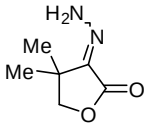
(*E*)- and (*Z*)-Ethyl 2-oxo-4-phenylbutanoate hydrazone 100ad



Obtained by **general procedure C** from ethyl 2-oxo-4-phenylbutanoate **99ad** (2.00 mL, 10.6 mmol) with a reaction time of 1 h. Purified by column chromatography using the elution gradient 13 to 50% ethyl acetate in light petroleum. **(*Z*)-Ethyl 2-oxo-4-phenylbutanoate hydrazone**: yellow oil (279 mg, 12%); (Found: M+Na^+, 243.1094. $C_{12}H_{16}N_2NaO_2$ requires 243.1109); ν_{max} ($CHCl_3$)/cm^{-1} 3483, 3298, 2986, 2937, 1690, 1570, 1303, 1179, 1120; δ_H (400 MHz; $CDCl_3$) 8.09 (2 H, br s, NH_2), 7.32-7.26 (2 H, m, ArH), 7.24-7.16 (3 H, m, ArH), 4.22 (2 H, q, *J* 7.2, $C\underline{H}_2CH_3$), 2.87-2.79 (2 H, m, CH_2), 2.73-2.66 (2 H, m, CH_2), 1.32 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 163.0 (C), 142.1 (C), 130.8 (C), 128.6 (CH), 128.5 (CH), 126.0 (CH), 60.4 (CH_2), 35.3 (CH_2), 34.4 (CH_2), 14.3 (CH_3). **(*E*)-Ethyl 2-oxo-4-phenylbutanoate hydrazone**: yellow oil (2.15 g, 87%); (Found: C, 65.32; H, 7.35; N, 12.42. $C_{12}H_{16}N_2NaO_2$ requires C, 65.43; H, 7.32; N, 12.72%); (Found: M+Na^+, 243.1082. $C_{12}H_{16}N_2NaO_2$ requires 243.1109); ν_{max} ($CHCl_3$)/cm^{-1} 3463, 3328, 3010, 1705, 1596, 1376, 1327, 1257, 1176, 1097, 1068; δ_H (400 MHz; $CDCl_3$) 7.36-7.29 (2 H, m, ArH), 7.28-7.21 (3 H, m, ArH), 5.79 (2 H, br s, NH_2), 4.31 (2 H, q, *J* 7.2, $C\underline{H}_2CH_3$), 2.88-2.75 (4 H, m, CH_2), 1.37 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$); δ_C (100

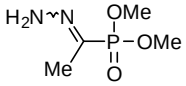
MHz; $CDCl_3$) 164.9 (C), 141.0 (C), 139.8 (C) 128.9 (CH), 128.4 (CH), 126.6 (CH), 61.3 (CH_2), 31.4 (CH_2), 26.4 (CH_2), 14.4 (CH_3).

(*Z*)- and (*E*)-3-Hydrazono-4,4-dimethyldihydrofuran-2(*3H*)-one 100ae



Obtained by **general procedure D** from 4,4-dimethyldihydrofuran-2,3-dione **99ae** (192 mg, 1.50 mmol) with a reaction time of 20 h. Purified by column chromatography using the elution gradient 50 to 90% ethyl acetate in light petroleum. **(*Z*)-3-Hydrazono-4,4-dimethyldihydrofuran-2(*3H*)-one**: yellow oil (24 mg, 11%); (Found: M+Na^+, 165.0637. $C_6H_{10}N_2NaO_2$ requires 165.0634); ν_{max} ($CHCl_3$)/cm^{-1} 3485, 1732, 1593, 1124, 1010; δ_H (400 MHz; $CDCl_3$) 7.98 (2 H, br s, NH_2), 4.14 (2 H, s, CH_2), 1.25 (6 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 165.0 (C), 134.7 (C), 79.5 (CH_2), 37.9 (C), 26.2 (CH_3). **(*E*)-3-Hydrazono-4,4-dimethyldihydrofuran-2(*3H*)-one**: colourless solid (181 mg, 85%); mp 159 - 160 °C; (Found: M+Na^+, 165.0637. $C_6H_{10}N_2NaO_2$ requires 165.0634); ν_{max} ($CHCl_3$)/cm^{-1} 3476, 3356, 1771, 1610; δ_H (400 MHz; DMSO-d_6) 7.97 (2 H, s, NH_2), 3.94 (2 H, s, CH_2), 1.32 (6 H, s, CH_3); δ_C (100 MHz; DMSO-d_6) 167.5 (C), 132.9 (C), 77.3 (CH_2), 36.4 (C), 21.3 (CH_3).

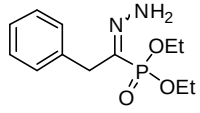
(*E*)-Dimethyl 1-hydrazonoethylphosphonate 102a



Trimethylphosphite (3.9 mL, 33.4 mmol) was slowly added to acetyl chloride (2.4 mL, 33.4 mmol) over 30 min under an atmosphere of argon at 0 °C and the mixture was heated at 65 °C for 1 h. After cooling, methanol (40 ml) was added to the mixture and a solution of hydrazine hydrate (3.2 mL, 65.9 mmol) in methanol (60 mL)

and glacial acetic acid (6 mL) were added over 20 min. The mixture was stirred for 14 h at room temperature and the solvent was removed under reduced pressure to give a residue that was subjected to column chromatography (8% methanol in ethyl acetate) to give *the title compound* as a colourless solid (3.31 g, 59%); mp 68 - 69 °C; (Found: M+Na$^+$, 189.0407. $C_4H_{11}N_2NaO_3P$ requires 189.0405); ν_{max} ($CHCl_3$)/cm^{-1} 3463, 3006, 2956, 1250, 1037, 837; δ_H (400 MHz; $CDCl_3$) 6.02 (2 H, br s, NH_2), 3.75 (6 H, dt, J_{HP} 10.8, OMe), 1.88 (3 H, dt, J_{HP} 11.0, CH_3); δ_C (100 MHz; $CDCl_3$) 137.7 (d, J_{CP} 238, C), 53.0 (d, J_{CP} 5.8, CH_3), 11.4 (d, J_{CP} 22, CH_3); δ_P (162 MHz; $CDCl_3$) 14.8 (m).

(*E*)- and (*Z*)-Diethyl 1-hydrazono-2-phenylethylphosphonate 102b



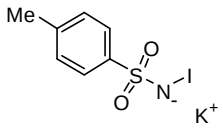
Triethylphosphite (1.71 mL, 10 mmol) was added to 2-phenylacetyl chloride (1.33 mL, 10 mmol) over 5 min at 0 °C under an argon atmosphere. The mixture was subsequently stirred at room temperature for 2 h, upon which absolute ethanol (10 mL) was added. The solution obtained was added to a solution of hydrazine hydrate (0.49 mL, 10 mmol) in a mixture of ethanol and acetic acid (10:1, 11 mL) at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 20 h. The solution was then poured into water (20 mL) and extracted with dichloromethane (3 × 50 mL). The organic phases were combined, washed with saturated brine (15 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave an oil which was purified by column chromatography (elution gradient ethyl acetate in light petroleum 50% to 100%) to give the *title compounds*. **(*Z*)-**

Diethyl 1-hydrazono-2-phenylethylphosphonate: yellow liquid (472 mg, 17%); (Found: M+Na$^+$, 293.1012. $C_{12}H_{19}N_2NaO_3P$ requires 293.1026); ν_{max} ($CHCl_3$)/cm^{-1} 2999, 1240, 1046, 1022, 975; δ_H (400 MHz; $CDCl_3$) 7.45 (2 H, br s, NH_2), 7.15 - 7.33 (5 H, m, ArH), 3.92 - 4.04 (2 H, m, C$\underline{H}_2$CH$_3$), 3.73 - 3.85 (2 H, m, C$\underline{H}_2$CH$_3$), 3.62 (2 H, d, J_{HP} 10.7, CH_2), 1.18 (6 H, t, J 7.0, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 138.4 (C), 129.2 (CH), 128.4 (CH), 126.6 (CH), 62.2 (d, J_{CP} 5.1, CH_2), 41.0 (d, J_{CP} 26.0, CH_2), 16.2 (d, J_{CP} 6.6, CH_3), one quaternary carbon signal was not observed; δ_P (162 MHz; $CDCl_3$) 8.2 (m).

(*E*)-Diethyl 1-hydrazono-2-phenylethylphosphonate: yellow solid (1.893 g, 70%); mp 42 - 43 °C; (Found: M+Na$^+$, 293.1012. $C_{12}H_{19}N_2NaO_3P$ requires 293.1026); ν_{max} ($CHCl_3$)/cm^{-1} 2998, 1246, 1049, 1027, 972; δ_H (400 MHz; $CDCl_3$) 7.16 - 7.32 (5 H, m, ArH), 6.19 (2 H, br s, NH_2), 4.01 - 4.18 (4 H, m, C$\underline{H}_2$CH$_3$), 3.73 (2 H, d, J_{HP} 12.0, CH_2), 1.27 (6 H, t, J 7.0, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 134.7 (d, J_{CP} 3.7, C), 129.2 (CH), 128.4 (CH), 127.2 (CH), 62.6 (d, J_{CP} 5.9, CH_2), 32.8 (d, J_{CP} 22.7, CH_2), 16.5 (d, J_{CP} 5.9, CH_3), one quaternary carbon signal was not observed; δ_P (162 MHz; $CDCl_3$) 12.2 (m).

II.3. Hydrazones oxidation

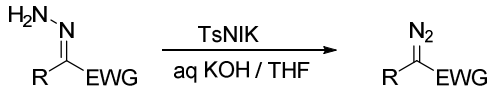
Potassium *N*-iodo *p*-toluenesulfonamide (TsNIK) 89



Prepared by a modification of a procedure previously described.[26] A solution of *p*-toluenesulfonamide **88** (4.55 g, 26.6 mmol) in aqueous potassium hydroxide (10%; 11.5 mL) was added to a solution of potassium iodide (18.0 g, 108 mmol) and iodine (9.00 g, 35.5 mmol) in water (20 mL). Aqueous potassium hydroxide (50%; 6 mL) was added, upon which loss of the colouration due to iodine occurred and a yellow precipitate appeared. The yellow solid was filtered, dried under suction and washed with ether (20 mL) to give the *title compound* as a yellow solid (6.57 g, 74%); mp 220 °C (decomp.) (lit.[26] no mp reported); (Found: C, 24.89; H, 2.01; N, 3.95. $C_7H_7INO_2S$ requires C, 25.08; H, 2.10; N, 4.18%); ν_{max} (ATR)/cm^{-1} 1191, 1065, 959, 664, 625; δ_H (400 MHz; DMSO-d_6) 7.50 (2 H, d, *J* 8.0, ArH), 7.15 (2 H, d, *J* 8.0, ArH), 2.31 (3 H, s, CH_3); δ_C (100 MHz; DMSO-d_6) 144.0 (C), 138.1 (C), 128.0 (CH), 126.6 (CH), 20.8 (CH_3). The product showed no signs of decomposition when stored in the dark at room temperature over several weeks but decomposed violently with iodine release when heated above 220 °C.

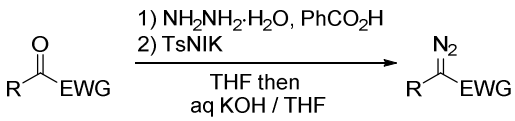
Diazo compounds were obtained by oxidation using TsNIK **89** from the corresponding hydrazone precursor (**general procedure E**) or over a one-pot procedure from the corresponding ketone precursors (**general procedure F**).

General procedure E:



A suspension of potassium *N*-iodo *p*-toluenesulfonamide **89** (369 mg, 1.1 mmol) in a solution of hydrazone (1.00 mmol) in THF (4 mL) was prepared. For the hydrazones that were solid at room temperature, THF was added to a mixture of the hydrazone and potassium *N*-iodo *p*-toluenesulfonamide **89**. Aqueous potassium hydroxide (1 M) was slowly added to the THF suspension (to obtain a final volume ratio KOH(1 M):THF of 1:4). This caused dissolution of the potassium salt in the mixture and the appearance of a yellow to red colouration. In all cases the reaction was complete after stirring for 1 h at room temperature. The mixture was poured into aqueous potassium hydroxide (1 M; 5 mL) and extracted with ether (30 mL). The ethereal phase was washed with aqueous potassium hydroxide (1 M; 5 mL), saturated brine (5 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave diazo compounds which were >95% pure as judged by ^1H NMR spectroscopy.

General procedure F:

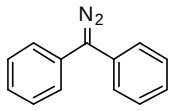


The starting α-ketoester (1.00 mmol) and benzoic acid (123 mg, 1.00 mmol) were dissolved in THF (4 mL) and hydrazine hydrate (49 µL, 1.00 mmol) was added. The mixture was stirred at room temperature for

16 h or until disappearance of the colourless hydrazine salt precipitate and completion of the reaction as judged by TLC analysis. Aqueous potassium hydroxide (1 M; 1 mL) was then added at room temperature, followed by slow addition of potassium *N*-iodo *p*-toluenesulfonamide (402 mg, 1.2 mmol). The reaction progress was monitored by TLC. When required, additional quantities of TsNIK were added to the mixture (in 0.1 mmol portion). After completion, the reaction mixture was poured into aqueous potassium hydroxide (1 M; 5 mL) and extracted with ether (30 mL). The ethereal phase was washed with aqueous potassium hydroxide (1 M; 5 mL), saturated brine (5 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave diazo compounds that were >95% pure as judged by ^{1}H NMR spectroscopy.

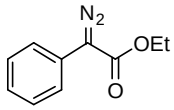
The following diazo compounds were prepared:

Diphenyldiazomethane 87



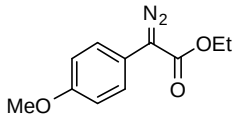
Obtained from benzophenone hydrazone **85** (196 mg, 1.00 mmol) by **general procedure E** (193 mg, 94%, purity 95% as judged by ^{1}H NMR). Purple solid; mp 29 - 30 °C (lit.[27] mp 30 °C); the compound did not ionise under the ESI-HRMS conditions used; ν_{max} ($CHCl_3$)/cm^{-1} 3063, 3011, 2045 (CN_2), 1595, 1496, 651; δ_H (400 MHz; $CDCl_3$) 7.40 (2 H, m, ArH), 7.31 (2 H, d, *J* 7.5, ArH), 7.19 (1 H, t, *J* 7.5, ArH); δ_C (100 MHz; CD_3OD) 130.7 (C), 130.3 (CH), 126.8 (CH), 126.2 (CH), the signal due to $\underline{C}N_2$ was not observed. The data are consistent with the literature.[27-28]

Ethyl 2-diazo-2-phenylacetate 104



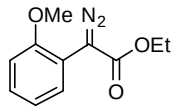
Obtained from ethyl 2-hydrazono-2-phenylacetate **100a** (97 mg, 0.5 mmol) by **general procedure E** (92 mg, 95%) or from ethyl 2-oxo-2-phenylacetate **99a** (100μL, 0.62 mmol) by **general procedure F** (116 mg, 97%). Orange oil; the compound did not ionise under the ESI-HRMS conditions used; ν_{max} ($CHCl_3$)/cm^{-1} 2985, 2090 (CN_2), 1698, 1248, 1174; δ_H (400 MHz; $CDCl_3$) 7.49 (2 H, d, *J* 7.3, ArH), 7.41-7.35 (2 H, m, ArH), 7.18 (1 H, td, *J* 1.3, 7.4, ArH), 4.34 (2 H, q, *J* 7.2, $C\underline{H}_2CH_3$), 1.34 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 165.4 (C), 129.1 (CH), 125.9 (CH), 125.8 (C), 124.1 (CH), 61.1 (CH_2), 14.6 (CH_3), the signal due to $\underline{C}N_2$ was not observed. The data are consistent with the literature.[29]

Ethyl 2-diazo-2-(4-methoxyphenyl)acetate 105



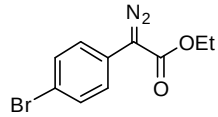
Obtained from ethyl 2-hydrazono-2-(4-methoxyphenyl)acetate **100m** (105 mg, 0.47 mmol) by **general procedure E** (97 mg, 93%) and from ethyl 2-(4-methoxyphenyl)-2-oxoacetate **99m** (103 mg, 0.50 mmol) by **general procedure F** (95 mg, 87%). Red solid; mp 43 °C (lit.[30]no mp reported); the compound did not ionise under the ESI-HRMS conditions used; ν_{max} ($CHCl_3$)/cm^{-1} 3009, 2985, 2087 (CN_2), 1695, 1514, 1257, 1173; δ_H (400 MHz; $CDCl_3$) 7.97 (2 H, d, *J* 9.0, ArH), 6.95 (2 H, d, *J* 9.0, ArH), 4.41 (2 H, q, *J* 7.2, $C\underline{H}_2CH_3$), 3.86 (3 H, s, OMe), 1.39 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 165.9 (C), 158.2 (C), 126.1 (CH), 117.2 (C), 114.7 (CH), 61.1 (CH_2), 55.5 (CH_3), 14.7 (CH_3), signal due to $\underline{C}N_2$ not observed. The data are consistent with the literature.[30]

Ethyl 2-diazo-2-(2-methoxyphenyl)acetate 106



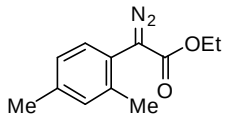
Obtained from 2-hydrazono-2-(2-methoxyphenyl)acetate **100n** (140 mg, 0.63 mmol) by **general procedure E** (123 mg, 89%). Yellow oil; the compound did not ionise under the ESI-HRMS conditions used; ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2984, 2102 (CN_2), 1689, 1498, 1255, 1028; δ_H (400 MHz; $CDCl_3$) 7.56 (1 H, dd, *J* 7.8, 1.5, ArH), 7.23 - 7.28 (1 H, m, ArH), 7.02 (1 H, td, *J* 7.8, 1.0, ArH), 6.90 (1 H, dd, *J* 8.3, 1.0, ArH), 4.30 (2 H, q, *J* 7.2, $C\underline{H}_2CH_3$), 3.86 (3 H, s, OMe), 1.32 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 166.4 (C), 155.6 (C), 130.3 (CH), 128.7 (CH), 121.3 (CH), 114.0 (C), 111.0 (CH), 60.8 (CH_2), 55.7 (CH_3), 14.7 (CH_3), the signal due to $\underline{C}N_2$ was not observed.

Ethyl 2-(4-bromophenyl)-2-diazoacetate 107



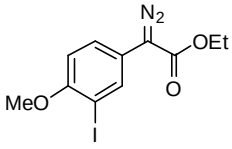
Obtained from ethyl 2-(4-bromophenyl)-2-oxoacetate **99o** (257 mg, 1.00 mmol) by **general procedure F** (255 mg, 95%). Orange solid; mp 48 - 49 °C (lit.[31]mp 54 °C); the compound did not ionise under the ESI-HRMS conditions used; ν_{max} ($CHCl_3$)/cm^{-1} 2091 (CN_2), 1699; δ_H (400 MHz; $CDCl_3$) 7.46 - 7.52 (2 H, m, ArH), 7.33 - 7.39 (2 H, m, ArH), 4.33 (2 H, q, *J* 7.1, $C\underline{H}_2CH_3$), 1.34 (3 H, t, *J* 7.1, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 165.0 (C), 132.1 (CH), 125.5 (CH), 125.0 (C), 119.4 (C), 61.3 (CH_2), 14.6 (CH_3). The signal for $\underline{C}N_2$ was not observed. The data are consistent with the literature.[31]

Ethyl 2-diazo-2-(2,4-dimethylphenyl)acetate 108



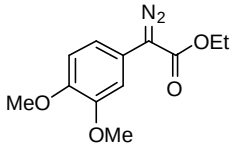
Obtained from ethyl 2-(2,4-dimethylphenyl)-2-oxoacetate (1.03 g, 5.00 mmol) by **general procedure F** (1.02 g, 94%). Orange oil; the compound did not ionise under the ESI-HRMS conditions used; ν_{max} ($CHCl_3$)/cm^{-1} 2090 (CN_2), 1692; δ_H (400 MHz; $CDCl_3$) 7.25 - 7.31 (1 H, m, ArH), 7.04 - 7.10 (2 H, m, ArH), 4.29 (2 H, q, *J* 7.1, $C\underline{H}_2CH_3$), 2.33 (3 H, s, CH_3), 2.27 (3 H, s, CH_3), 1.31 (3 H, t, *J* 7.1, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 139.0 (C), 137.8 (C), 131.6 (CH), 130.9 (CH), 127.3 (CH), 121.3 (C), 61.2 (CH_2), 21.3 (CH_3), 20.0 (CH_3), 14.7 (CH_3), two quaternary carbon signals were not observed.

Ethyl 2-diazo-2-(3-iodo-4-methoxyphenyl)acetate 109



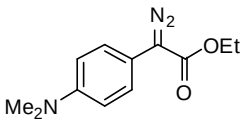
Obtained from ethyl 2-(3-iodo-4-methoxyphenyl)-2-oxoacetate (869 mg, 2.60 mmol) by **general procedure F** (790 mg, 88%). Orange solid; mp 85 °C (decomposition); (Found: $M+Na^+$, 368.9710. $C_{11}H_{11}IN_2NaO_3$ requires 368.9707); ν_{max} ($CHCl_3$)/cm^{-1} 3008, 2984, 2088 (CN_2), 1695, 1494; δ_H (400 MHz; $CDCl_3$) 7.85 (1 H, d, *J* 2.3, ArH), 7.43 (1 H, dd, *J* 8.8, 2.3, ArH), 6.83 (1 H, d, *J* 8.8, ArH), 4.31 (2 H, q, *J* 7.1, CH_2CH_3), 3.87 (3 H, s, CH_3), 1.33 (3 H, t, *J* 7.1, CH_2CH_3); δ_C (100 MHz; $CDCl_3$) 165.4 (C), 156.6 (C), 135.2 (CH), 125.9 (CH), 119.4 (C), 111.3 (CH), 86.7 (C), 61.2 (CH_2), 56.6 (CH_3), 14.6 (CH_3), the signal for $\underline{C}N_2$ was not observed.

Ethyl 2-diazo-2-(3,4-dimethoxyphenyl)acetate 110



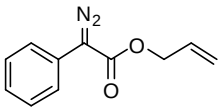
Obtained from ethyl 2-(3,4-dimethoxyphenyl)-2-oxoacetate (765 mg, 3.21 mmol) by **general procedure F** (781 mg, 97%). Red solid; mp 66 - 67 °C (lit.[32] 81 °C); (Found: M+Na$^+$, 273.0841. $C_{12}H_{14}N_2NaO_4$ requires 273.0846); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2984, 2085(CN_2), 1693, 1517, 1255; δ_H (400 MHz; $CDCl_3$) 7.19 (1 H, d, *J* 1.8, ArH), 6.81 - 6.93 (2 H, m, ArH), 4.31 (2 H, q, *J* 7.2, C<u>H</u>$_2$CH$_3$), 3.89 (3 H, s, CH_3), 3.87 (3 H, s, CH_3), 1.33 (3 H, t, *J* 7.2, CH$_2$C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 165.8 (C), 149.6 (C), 148.0 (C), 117.7 (C), 116.5 (CH), 111.8 (CH), 108.5 (CH), 61.1 (CH_2), 56.1 (CH_3), 56.0 (CH_3), 14.6 (CH_3), the signal for <u>C</u>N$_2$ was not observed. The data are consistent with the literature.[32]

Ethyl 2-diazo-2-(4-(dimethylamino)phenyl)acetate 111



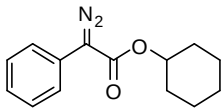
Obtained from ethyl 2-(4-(dimethylamino)phenyl)-2-oxoacetate (187 mg, 845 μmol) by **general procedure F** (116 mg, 50%). Red oil; (Found: M+H$^+$, 234.1239. $C_{12}H_{16}N_3O_2$ requires 234.1237); ν_{max} ($CHCl_3$)/cm^{-1} 3008, 2985, 2083(CN_2), 1693, 1522; δ_H (400 MHz; $CDCl_3$) 7.27 - 7.39 (2 H, m, ArH), 6.73 - 6.84 (2 H, m, ArH), 4.32 (2 H, q, *J* 7.2, C<u>H</u>$_2$CH$_3$), 2.95 (6 H, s, CH_3), 1.33 (3 H, q, *J* 7.2, CH$_2$C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 166.4 (C), 149.2 (C), 126.2 (CH), 133.2 (CH), 111.8 (C), 60.9 (CH_2), 40.6 (CH_3), 14.6 (CH_3), the signal for <u>C</u>N$_2$ was not observed.

Allyl 2-diazo-2-phenylacetate 112



Obtained from allyl 2-hydrazono-2-phenylacetate **100h** (101 mg, 0.5 mmol) by **general procedure E** (95 mg, 95%) and from allyl 2-oxo-2-phenylacetate **99h** (96 mg, 0.50 mmol) by **general procedure F** (91 mg, 88%). Orange oil; the compound did not ionise under the ESI-HRMS conditions used; ν_{max} ($CHCl_3$)/cm^{-1}; 2951, 2091 (CN_2), 1699, 1247, 1156; δ_H (400 MHz; $CDCl_3$) 7.46 - 7.53 (2 H, m, ArH), 7.35 - 7.43 (2 H, m, ArH), 7.19 (1 H, tt, *J* 7.3, 1.3, ArH), 5.99 (1 H, ddt, *J* 17.2, 10.5, 5.6, vinylic CH), 5.37 (1 H, dq, *J* 17.2, 1.4, vinylic CH_2), 5.28 (1 H, dq, *J* 10.5, 1.4, vinylic CH_2), 4.78 (2 H, dt, *J* 5.6, 1.4, CH_2); δ_C (100 MHz; $CDCl_3$) 164.9 (C), 132.2 (CH), 129.1 (CH), 126.0 (CH), 125.6 (C), 124.1 (CH), 118.5 (CH_2), 65.6 (CH_2), the signal due to $\underline{C}N_2$ was not observed. The data are consistent with the literature.[5]

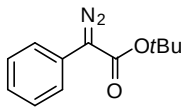
Cyclohexyl 2-diazo-2-phenylacetate 113



Obtained from cyclohexyl 2-hydrazono-2-phenylacetate **100e** (113 mg, 0.46 mmol) by **general procedure E** (105 mg, 93%) and from cyclohexyl 2-oxo-2-phenylacetate **99e** (116 mg, 0.50 mmol) by **general procedure F** (121 mg, 99%). Orange oil; (Found: M+Na^+, 267.1104. $C_{14}H_{16}N_2NaO_2$ requires 267.1104); ν_{max} ($CHCl_3$)/cm^{-1} 2941, 2090 (CN_2), 1693, 1246, 1169; δ_H (400 MHz; $CDCl_3$) 7.47 - 7.52 (2 H, m, ArH), 7.35 - 7.41 (2H, m, ArH), 7.17 (1 H, t, *J* 7.3, ArH), 4.94 - 5.03 (1 H, m, OCH), 1.86 - 1.97 (2 H, m, CH_2), 1.74 (2 H, m, CH_2), 1.24 - 1.61 (6 H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 164.8 (C), 128.9 (CH), 125.9 (C), 125.7 (CH), 124.0 (CH), 73.3 (CH), 31.8 (CH_2), 25.4 (CH_2), 23.6

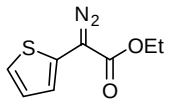
(CH_2), the signal due to $\underline{C}N_2$ was not observed. The data are consistent with the literature.[5]

tert-Butyl 2-diazo-2-phenylacetate 114



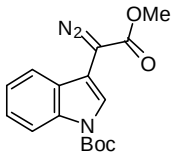
Obtained from *tert*-butyl 2-oxo-2-phenylacetate (574 mg, 2.78 mmol) by **general procedure F** (605 g, 99%). Orange oil; the compound did not ionise under the ESI-HRMS conditions used; ν_{max} ($CHCl_3$)/cm^{-1} 3008, 2088(CN_2), 1693, 1147; δ_H (400 MHz; $CDCl_3$) 7.42 - 7.50 (2 H, m, ArH), 7.34 - 7.40 (2 H, m, ArH), 7.07 - 7.24 (1 H, m, ArH), 1.56 (9 H, s, *t*Bu); δ_C (100 MHz; $CDCl_3$) 164.7 (C), 129.0 (C), 126.2 (CH), 125.7 (CH), 124.1 (CH), 82.1 (C), 28.5 (CH_3), the signal due to $\underline{C}N_2$ was not observed. The data are consistent with the literature.[33]

Ethyl 2-diazo-2-(2-thienyl)acetate 115



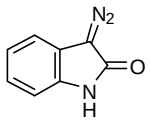
Obtained from ethyl 2-hydrazono-2-(2-thienyl)acetate **100v** (100 mg, 0.50 mmol) by **general procedure E** (93 mg, 95%). Deep red oil; (Found: M+Na^+, 219.0202. $C_8H_8N_2NaO_2S$ requires 219.0199); ν_{max} ($CHCl_3$)/cm^{-1} 2087 (CN_2), 1695, 1289; δ_H (400 MHz; $CDCl_3$) 7.31 (1 H, dd, *J* 5.1, 1.2, ArH), 7.03 (1 H, dd, *J* 5.1, 3.7, ArH), 6.82 (1 H, dd, *J* 3.7, 1.2, ArH), 4.35 (2 H, q, *J* 7.2, $C\underline{H}_2CH_3$), 1.34 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 165.2 (C), 127.0 (CH), 126.0 (C), 125.7 (CH), 121.1 (CH), 61.7 (CH_2), 14.6 (CH_3), the signal due to $\underline{C}N_2$ was not observed.

tert-Butyl 3-(1-diazo-2-methoxy-2-oxoethyl)indole-1-carboxylate 116



Obtained from *tert*-butyl 3-(1-hydrazono-2-methoxy-2-oxoethyl)indole-1-carboxylate **100x** (158 mg, 0.5 mmol) by **general procedure E** (130 mg, 79%). Orange solid; mp 85 °C (decomp) (lit.[34] mp 86 - 87 °C); (Found: M+Na$^+$, 338.1110. $C_{16}H_{17}N_3NaO_4$ requires 338.1111); ν_{max} ($CDCl_3$)/cm^{-1} 2089 (CN_2), 1732, 1703, 1372, 1246, 1155; δ_H (400 MHz; $CDCl_3$) 8.22 (1 H, d, *J* 8.2, ArH), 7.87 (1 H, s, ArH), 7.49 (1 H, d, *J* 7.9, ArH), 7.32 - 7.41 (1 H, m, ArH), 7.22 - 7.30 (1 H, m, ArH), 3.89 (3 H, s, OMe), 1.68 (9 H, s, *t*Bu); δ_C (100 MHz; $CDCl_3$) 149.4 (C), 135.4 (C), 127.6 (C), 125.1 (CH), 124.0 (CH), 123.1 (CH), 118.5 (CH), 115.8 (CH), 103.1 (C), 84.3 (C), 52.4 (CH_3), 28.3 (CH_3), the signals due to $\underline{C}N_2$ and one other quaternary carbon were not observed. The data are consistent with the literature.[34]

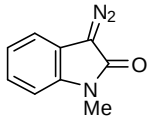
3-Diazoindolin-2-one 117



Obtained from isatin **99y** (119 mg, 0.8 mmol) by **general procedure F** (120 mg, 94%) with modified work-up conditions: ethyl acetate was used instead of ether for the extraction step. The product was purified by column chromatography (30 % ethyl acetate in light petroleum). Red solid; mp 161 °C (decomp) (lit.[35] mp 168 °C (decomp)); (Found: M+Na$^+$, 182.0331. $C_8H_5N_3NaO$ requires 182.0330); ν_{max} ($CHCl_3$)/cm^{-1} 3449, 2118, 2099(CN_2), 1693, 1468, 1402, 1191; δ_H (400 MHz; CD_3OD) 7.27-7.30 (1 H, m, ArH), 7.13 (1 H, td, *J* 7.6, 1.2, ArH), 7.06 (1 H, dd, *J* 7.6, 1.0, ArH), 6.95 - 6.98 (1 H, m, ArH); δ_C (100 MHz; CD_3OD) 169.4 (C), 132.3 (C), 125.1 (CH), 121.7 (CH), 118.3 (CH), 117.2

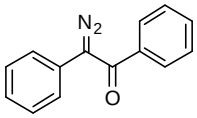
(C), 110.1 (CH). The signal due to $\underline{C}N_2$ was not observed. The data are consistent with the literature.[35]

3-Diazo-1-methylindolin-2-one 118



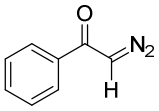
Obtained from *N*-methylisatin **99z** (161 mg, 1.0 mmol) by **general procedure F** (154 mg, 89%). Red solid; mp 84 - 85°C (lit.[36] mp 87 - 89 °C); (Found: M+Na$^+$, 196.0486. $C_9H_7N_3NaO$ requires 196.0481); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2105 (CN_2), 2095 (CN_2), 1678; δ_H (400 MHz; $CDCl_3$) 7.16 - 7.23 (2 H, m, ArH), 7.04 - 7.12 (1 H, m, ArH), 6.91 (1 H, d, *J* 7.6, ArH), 3.32 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 166.9 (C), 134.6 (C), 125.6 (CH), 122.2 (CH), 118.3 (CH), 116.8 (C), 108.7 (CH), 26.9 (Me). The signal for $\underline{C}N_2$ was not observed.

2-Diazo-1,2-diphenylethanone 66



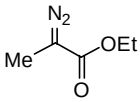
Obtained from benzyl monohydrazone **65** (224 mg, 1.0 mmol) by **general procedure E** (222 mg, 100%). Yellow solid; mp 73 - 74 °C (lit.[28b] mp 79 °C; lit.[37] mp 66 - 67 °C); the compound did not ionise under the ESI-HRMS conditions used; ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2078 (CN_2), 1622, 1352, 1283, 850, 646; δ_H (400 MHz; $CDCl_3$) 7.59 - 7.65 (2 H, m, ArH), 7.36 - 7.53 (7 H, m, ArH), 7.26 (1 H, t, *J* 7.7, ArH); δ_C (100 MHz; acetone-d_6) 188.5 (C), 139.3 (C), 132.4 (CH), 129.7 (CH), 129.4 (CH), 128.4 (CH), 127.5 (CH), 126.6 (CH), the signals due to $\underline{C}N_2$ and one other quaternary carbon were not observed. The data are consistent with the literature.[28b,37]

2-Diazo-1-phenylethanone 119



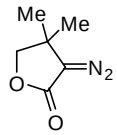
Obtained from 2-hydrazono-1-phenylethan-1-one (119 mg, 0.8 mmol) by **general procedure E** (110 mg, 94%). Orange solid; mp 43 - 44 °C (lit.[18] mp 49°C); (Found: 2M+Na^+, 315.0849. $C_{16}H_{12}N_4NaO_2$ requires 315.0852); ν_{max} ($CHCl_3$)/cm^{-1} 2111 (CN_2), 1624, 1364; δ_H (400 MHz; $CDCl_3$) 7.72 - 7.79 (2 H, m, ArH), 7.50 - 7.56 (1 H, m, ArH), 7.39 - 7.47 (2 H, m, ArH), 5.91 (1 H, s, CH); δ_C (100 MHz; $CDCl_3$) 186.4 (C), 136.7 (C), 132.8 (CH), 128.7 (CH), 126.8 (CH), 54.3 (CH). The data are consistent with the literature.[18]

Ethyl 2-diazopropanoate 120



Obtained from ethyl 2-hydrazonopropanoate **100ab** (80 mg, 0.6 mmol) by **general procedure E** (53 mg, 67%) and from ethyl pyruvate **99ab** (96 μL, 0.8 mmol) by **general procedure F** (106 mg, 96%). Yellow liquid (lit.[38] bp 50 °C/20 mmHg); the compound did not ionise under the ESI-HRMS conditions used; ν_{max} ($CHCl_3$)/cm^{-1} 2985, 2086 (CN_2), 1682, 1328, 1310, 1140; δ_H (400 MHz; $CDCl_3$) 4.22 (2 H, q, *J* 7.2, C<u>H</u>$_2$CH$_3$), 1.96 (3 H, s, Me), 1.27 (3 H, t, *J* 7.2, CH$_2$C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 60.9 (CH_2), 14.7 (CH_3), 8.6 (CH_3), the signals due to <u>C</u>O and <u>C</u>N_2 were not observed. The data are consistent with the literature.[39]

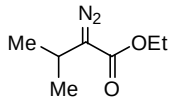
3-Diazo-4,4-dimethyldihydrofuran-2(*3H*)-one 121



Obtained from 4,4-dimethyldihydrofuran-2,3-dione **99ae** (103 mg, 0.8 mmol) by **general procedure F** (76 mg, 68%). Yellow oil; the compound did not ionise under the ESI-HRMS conditions used; ν_{max} ($CHCl_3$)/cm^{-1} 2970, 2099 (CN_2), 1732, 1377, 1146, 1058, 1015;

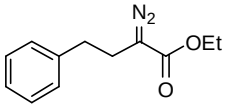
δ_H (300 MHz; $CDCl_3$) 4.05 (2 H, s, CH_2), 1.41 (6 H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 169.3 (C), 78.7 (CH_2), 39.0 (C), 26.0 (CH_3), the signal due to $\underline{C}N_2$ was not observed. The data are consistent with the literature.[40]

Ethyl 2-diazo-3-methylbutanoate 122



Obtained from ethyl 2-hydrazono-3-methylbutanoate **100ac** (144 mg, 0.91 mmol) by **general procedure E** (124 mg, 87%) and from ethyl 3-methyl-2-oxobutanoate **99ac** (113 mg, 0.8 mmol) by **general procedure F** (107 mg, 87%). Yellow oil; the compound did not ionise under the ESI-HRMS conditions used; ν_{max} ($CHCl_3$)/cm^{-1} 2979, 2084 (CN_2), 1683, 1390, 1270, 1092; δ_H (400 MHz; $CDCl_3$) 4.21 (2 H, q, *J* 7.2, $C\underline{H}_2CH_3$), 2.75 (1 H, spt, *J* 6.9, CH), 1.27 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$), 1.14 (6 H, d, *J* 6.9, CH_3); δ_C (100 MHz; $CDCl_3$) 60.7 (CH_2), 23.3 (CH), 20.7 (CH_3), 14.7 (CH_3), the signals due to $\underline{C}O$ and $\underline{C}N_2$ were not observed. The data are consistent with the literature.[5]

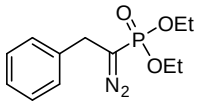
Ethyl 2-diazo-4-phenylbutanoate 123



Obtained from ethyl 2-hydrazono-4-phenylbutanoate **100ad** (112 mg, 0.5 mmol) by **general procedure E** (101 mg, 91%) and from ethyl 2-oxo-4-phenylbutanoate **99ad** (95 μL, 0.5 mmol) by **general procedure F** (92 mg, 84%). Yellow oil; the compound did not ionise under the ESI-HRMS conditions used; ν_{max} ($CHCl_3$)/cm^{-1} 3008, 2985, 2087 (CN_2), 1682, 1373, 1315, 1173, 1115; δ_H (400 MHz; $CDCl_3$) 7.27 - 7.34 (2 H, m, ArH), 7.17 - 7.25 (3 H, m, ArH), 4.22 (2 H, q, *J* 7.2, $C\underline{H}_2CH_3$), 2.84 (2 H, t, *J* 7.8, CH_2), 2.61 (2 H, t, *J* 7.8, CH_2), 1.27 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 140.2 (C), 128.6 (CH), 128.5

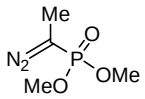
(CH), 126.4 (CH), 60.9 (CH_2), 34.0 (CH_2), 25.4 (CH_2), 14.5 (CH_3), the signals due to $\underline{C}O$ and $\underline{C}N_2$ were not observed. The data are consistent with the literature.[5]

Diethyl 1-diazo-2-phenylethylphosphonate 124



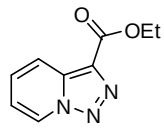
Obtained from diethyl (1-hydrazono-2-phenylethyl)phosphonate **102b** (135 mg, 0.5 mmol) by **general procedure E** (127 mg, 94%). Yellow liquid; the compound did not ionise under the ESI-HRMS conditions used; ν_{max} ($CHCl_3$)/cm^{-1} 3001, 2082 (CN_2), 1248, 1025, 1050, 972; δ_H (400 MHz; $CDCl_3$) 7.30 - 7.36 (2 H, m, ArH), 7.22 - 7.29 (3 H, m, ArH), 3.96 - 4.17 (4 H, m, $C\underline{H}_2CH_3$), 3.44 (2 H, d, J_{HP} 9.8, CH_2), 1.30 (6 H, td, J 7.0, J_{HP} 0.3, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 137.5 (d, J_{CP} 2.9, C), 128.9 (CH), 128.5 (CH), 127.3 (CH), 62.6 (d, J_{CP} 5.9, CH_2), 30.3 (d, J_{CP} 8.8, CH_2), 16.3 (d, J_{CP} 6.6, CH_3), the signal due to $\underline{C}N_2$ was not observed; δ_P (162 MHz; $CDCl_3$) 21.0 (m).

Dimethyl 1-diazoethylphosphonate 125



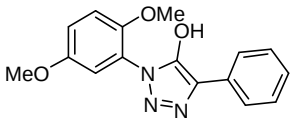
Obtained from dimethyl (1-hydrazonoethyl)phosphonate **102a** (104 mg, 1.0 mmol) by **general procedure E** (57 mg, 56%). Yellow liquid; the compound did not ionise under the ESI-HRMS conditions used; ν_{max} ($CHCl_3$)/cm^{-1} 3009, 2954, 2852, 2087 (CN_2), 1459, 1253, 1030, 832; δ_H (400 MHz; CD_3OD) 3.76 (6 H, d, J_{PH} 11.5, OMe), 1.85 (3 H, d, J_{PH} 9.8, CH_3); δ_C (100 MHz; CD_3OD) 53.6 (d, J_{CP} 5.4, CH_3), 8.6 (d, J_{CP} 7.7, CH_3), the signal due to CN_2 was not observed; δ_P (162 MHz; CD_3OD) 26.6 (m). The data are consistent with the literature.[41]

Ethyl [1,2,3]triazolo[1,5-*a*]pyridine-3-carboxylate 127



Obtained from ethyl 2-hydrazono-2-(pyridin-2-yl)acetate **99w** (89 mg, 0.5 mmol) by **general procedure F** with modified work-up conditions: ethyl acetate was used instead of ether for the extraction step. The product was purified by column chromatography using 40% ethyl acetate in light petroleum. Colourless solid (80 mg, 84%); mp 105 - 106 °C; (Found: M+Na$^+$, 214.0589. $C_9H_9N_3NaO_2$ requires 214.0592); ν_{max} ($CHCl_3$)/cm^{-1} 1724, 1707, 1545, 1270, 1069; δ_H (400 MHz; $CDCl_3$) 8.79 - 8.86 (1 H, m, ArH), 8.28 (1 H, dd, *J* 8.8, 1.1, ArH), 7.54 (1 H, ddd, *J* 8.8, 6.8, 0.9, ArH), 7.15 (1 H, td, *J* 6.8, 1.1, ArH), 4.52 (2 H, q, *J* 7.2, C$\underline{H}_2$CH$_3$), 1.48 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 161.5 (C), 135.2 (C), 129.7 (C), 129.2 (CH), 126.0 (CH), 119.5 (CH), 116.5 (CH), 60.5 (CH_2), 14.6 (CH_3). The data are consistent with the literature.[42]

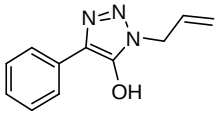
1-(2,5-Dimethoxyphenyl)-4-phenyl-*1H*-1,2,3-triazol-5-ol 130



Obtained from *N*-(2-furylmethyl)-2-oxo-2-phenylacetamide **99r** (286 mg, 1.0 mmol) by **general procedure F** using the following work-up conditions: after completion of the reaction, the mixture was poured into aqueous potassium hydroxide (1 M; 5 mL) and agitated vigorously. An aqueous solution of aqueous acetic acid (10%) was then slowly added until pH = 5, followed by addition of a saturated solution of sodium thiosulfate (2 mL). The precipitate formed was filtrated, washed with dichloromethane (20 mL) and dried to give the *title compound* as an off-white solid (271 mg, 91%); mp 173 - 174°C (decomp); (Found: M+Na$^+$, 320.1009. $C_{16}H_{15}N_3NaO_3$ requires 320.1006); ν_{max} (ATR)/cm^{-1} 1605,

1507, 1227, 774, 649; δ_H (400 MHz; $CDCl_3$) 11.65 (1 H, br s, OH), 7.90 (2 H, d, *J* 7.5, ArH), 7.44 (2 H, t, *J* 7.5, ArH), 7.27 (1 H, t, *J* 7.5, ArH), 7.22 (1 H, d, *J* 9.1, ArH), 7.15 (1 H, dd, *J* 9.1, 2.8, ArH), 7.07 (1 H, d, *J* 2.8, ArH), 3.77 (3 H, s, OMe), 3.74 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 152.9 (C), 148.5 (C), 131.1 (C), 128.6 (CH), 126.5 (CH), 124.3 (CH), 123.6 (C), 116.7 (CH), 114.2 (CH), 113.8 (CH), 56.3 (CH_3), 55.8 (CH_3), two quaternary carbon signals were not observed.

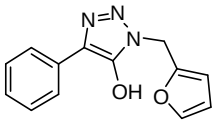
1-Allyl-4-phenyl-*1H*-1,2,3-triazol-5-ol 131



Obtained from *N*-allyl-2-oxo-2-phenylacetamide **99q** (95 mg, 0.5 mmol) by **general procedure F** using the following work-up conditions: after completion of the reaction, the mixture was poured into aqueous potassium hydroxide (1 M; 5 mL) and agitated vigorously. An aqueous solution of acetic acid (10%) was then slowly added until pH = 5 and the mixture was extracted with ethyl acetate (4 × 20 mL). The combined organic phases were washed with saturated brine (15 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a solid residue that was purified by column chromatography (elution gradient methanol in dichloromethane, 5% to 10%) to give *the title compound* as a colourless solid (85 mg, 85%); mp 162 - 164 °C (decomp); (Found: M+Na^+, 224.0772. $C_{11}H_{11}N_3NaO$ requires 224.0794); ν_{max} (ATR)/cm^{-1} 1613, 1568, 814, 767; δ_H (400 MHz; DMSO-d_6) 7.88 (2 H, d, *J* 7.6, ArH), 7.40 (2 H, t, *J* 7.6, ArH), 7.23 (1 H, t, *J* 7.6, ArH), 6.00 (1 H, ddt, *J* 17.0, 10.5, 5.6, vinylic CH_2), 5.22 (1 H, dd, *J* 10.5, 1.5, vinylic CH), 5.10 (1 H, dd, *J* 17.0, 1.5, vinylic CH_2), 4.80 (2 H, d, *J* 5.6, CH_2);

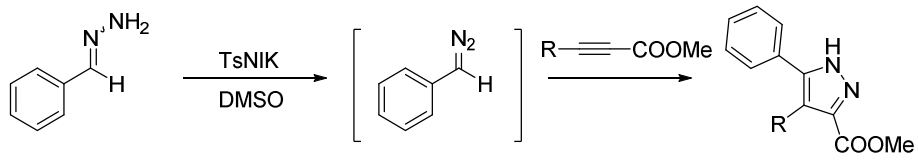
δ_C (100 MHz; DMSO-d_6) 133.1 (CH), 131.6 (C), 129.0 (CH), 126.0 (CH), 124.5 (CH), 118.0 (CH_2), 47.7 (CH_2), two quaternary carbon signals were not observed.

1-(2-Furylmethyl)-4-phenyl-*1H*-1,2,3-triazol-5-ol 132



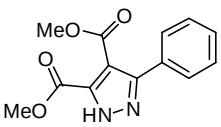
Obtained from *N*-(2,5-dimethoxyphenyl)-2-oxo-2-phenylacetamide **99s** (229 mg, 1.0 mmol) by **general procedure F** using the following work-up conditions: after completion of the reaction, the mixture was poured into aqueous potassium hydroxide (1 M; 5 mL) and agitated vigorously. An aqueous solution of aqueous acetic acid (10%) was then slowly added until pH = 5, followed by addition of a saturated solution of sodium thiosulfate (2 mL). The precipitate formed was filtrated and washed with ether (20 mL). The resulting solid was further purified by column chromatography using the elution gradient: methanol in dichloromethane, 5% to 10% to give the *title compound* as a colourless solid (181 mg, 75%); mp 194 - 195 °C (decomp); (Found: M+Na$^+$, 264.0740. $C_{13}H_{11}N_3NaO_2$ requires 264.0743); ν_{max} (ATR)/cm^{-1} 1604, 1575, 762, 649; δ_H (400 MHz; DMSO-d_6) 11.78 (1 H, br s, OH), 7.85 (2 H, d, *J* 7.4, ArH), 7.64 (1 H, dd, *J* 1.8, 0.8, ArH), 7.42 (2 H, t, *J* 7.4, ArH), 7.25 (1 H, t, *J* 7.4, ArH), 6.47 (1 H, br d, *J* 3.1, ArH), 6.45 (1 H, dd, *J* 3.1, 1.8, ArH), 5.40 (2 H, s, CH_2); δ_C (100 MHz; DMSO-d_6) 148.7 (C), 143.3 (CH), 128.6 (CH), 126.6 (CH), 124.2 (CH), 110.8 (CH), 109.2 (CH), 41.7 (CH_2), three quaternary carbon signals were not observed.

Pyrazoles derived from phenyldiazomethane 83



General procedure G: Benzaldehyde hydrazone **136** (1.0 eq) was dissolved in DMSO (concentration: 0.3 M) and TsNIK (1.05 eq) was slowly added under vigorous stirring at room temperature. After stirring for 5 min, the alkyne (1.2 eq) was added to the solution of phenyldiazomethane **83** and the resulting mixture was stirred at room temperature for the time indicated. The reaction mixture was then poured into water (10 mL/mmol) and extracted with ethyl acetate (30 mL/mmol). The organic phase was washed with potassium hydroxide solution (1 M; 10 mL/mmol), brine (5 mL/mmol) and dried over $MgSO_4$. The volatiles were evaporated under reduced pressure and the resulting residue was purified by column chromatography.

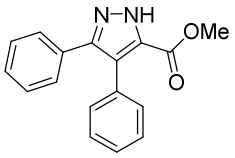
Dimethyl 3-phenyl-*1H*-pyrazole-4,5-dicarboxylate 139



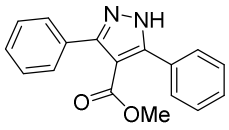
Obtained by **general procedure G** using benzaldehyde hydrazone **136** (100 mg, 0.83 mmol) and dimethyl acetylene dicarboxylate **137** (120 µL, 0.98 mmol). Reaction time: 1 h. purification by column chromatography using 40% ethyl acetate in light petroleum. The *title compound* was obtained as a yellow solid (153 mg, 71%); mp 59 - 60 °C; (Found: M+Na$^+$, 283.0681. $C_{13}H_{12}N_2NaO_4$ requires 283.0689); ν_{max} ($CHCl_3$)/cm^{-1} 3429, 3011, 1728; δ_H (400 MHz; $CDCl_3$) 7.58 (2 H, m, ArH), 7.34 - 7.49 (3 H, m, ArH), 3.83 (3 H, s, CH_3), 3.81 (3 H, s, CH_3), the signal due to NH was not observed; δ_C (100 MHz; $CDCl_3$) 164.4

(C), 161.3 (C), 146.4 (C), 129.7 (CH), 128.8 (CH), 128.3 (C), 128.1 (CH), 113.2 (C), 52.5 (CH_3), 52.4 (CH_3), one quaternary carbon signal was not observed.

Methyl 3,4-diphenyl-*1H*-pyrazole-5-carboxylate 140a and methyl 3,5-diphenyl-*1H*-pyrazole-4-carboxylate 140b



140a



140b

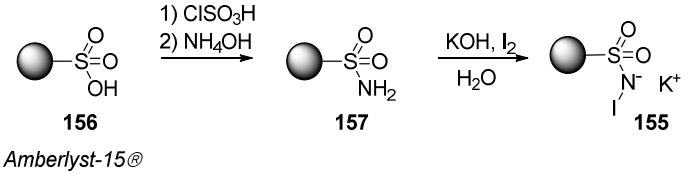
Obtained by **general procedure G** using benzaldehyde hydrazone **136** (330 mg, 2.74 mmol) and methyl phenylpropiolate **138** (485 µL, 3.29 mmol). Reaction time: 4 h. Purification by column chromatography using the elution gradient 20% to 50% ethyl acetate in light petroleum. **Methyl 3,5-diphenyl-*1H*-pyrazole-4-carboxylate 140b**: colourless solid (253 mg, 33%); mp 171 - 172 °C (lit.[43] mp 180 °C); (Found: M+Na^+, 301.0931. $C_{17}H_{14}N_2NaO_2$ requires 301.0947); ν_{max} (ATR)/cm^{-1} 3150 (br), 1711; δ_H (400 MHz; $CDCl_3$) 7.47 - 7.57 (4 H, m, ArH), 7.32 - 7.44 (6 H, m, ArH), 3.62 (3 H, s, CH_3), the signal due to NH was not obseved; δ_C (100 MHz; $CDCl_3$) 164.6 (C), 150.8 (C), 130.8 (C), 129.0 (CH), 128.3 (CH), 108.8 (C), 51.3 (CH_3), the signals for the remaining CH was not observed. **Methyl 3,4-diphenyl-*1H*-pyrazole-5-carboxylate 140a**: colourless solid (292 mg, 38%); mp 214 - 215 °C; (lit.[43] mp 215 °C); (Found: M+Na^+, 301.0936. $C_{17}H_{14}N_2NaO_2$ requires 301.0947); ν_{max} (ATR)/cm^{-1} 3280 (br), 1732; δ_H (400 MHz; DMSO-d_6) 7.12 - 7.44 (10 H, m, ArH), 3.68 (3 H, s, CH_3), the signal due to NH was not obseved; δ_C (100 MHz; DMSO-d_6) 132.3 (C), 130.3 (CH), 128.4 (CH), 127.9 (CH), 127.5 (CH), 127.2 (CH), 51.4 (CH_3), the signals for the remaining CH

and the 5 remaining quaternary carbons were not observed. The data obtained are consistent with the literature.[43]

III. Chapter III Experimental

III.1. Preparation of resin 155

***N*-iodosulfonamide functionalised resin (PS-TsNIK) 155**



The two first steps of this procedure were previously described in the synthesis of chlorinated tosylamide functionalised polystyrene.[44]

Preparation of the sulfonamide functionalised resin 157: Commercial Amberlyst® 15 resin **156** (10.7 g, finely ground and dried *in vacuo*, loading indicated by manufacturer: 4.7 mmol/g) were placed under argon. Chlorosulfonic acid (20 mL, 0.30 mol) was added and the resulting slurry was heated at 70 °C for 1 h. Once cooled to room temperature, dichloromethane (50 mL) was added and the resin was filtered, washed with several portions of dichloromethane (3×50 mL) and carefully with a mixture of THF : dichloromethane (1 : 9, 2×50 mL). The black resin thus obtained was carefully added in portions to aqueous ammonium hydroxide solution (35%; 120 mL) and the suspension was stirred for 20 h at room temperature. The resin was then filtered, washed with water (60 mL) and ether (20 mL). The sulfonamide-functionalised resin **157** was obtained as an off-white powder after drying under reduced pressure.

Preparation of PS-TsNIK resin 155 (procedure also used for the regeneration of used resin): The sulfonamide-functionalised resin was suspended in a mixture of water (5 mL/g resin) and concentrated aqueous potassium hydroxide solution (50%; 2.4 mL/g resin). Iodine (2.0 g/g resin) was added at room temperature in 4 equal portions with 5 min stirring between each addition. Upon addition, the solution takes up a pale yellow colouration and the suspension was stirred for 5 min, at which point the iodine was entirely dissolved. The resin was filtered, washed with aqueous potassium hydroxide solution (10%; 1.4 mL/g resin), water (3×5 mL/g resin) and ether (2×10 mL/g resin). The yellow resin was dried in air under aspiration for 1 h and under high vaccum for 48 h (NOTE: alternatively, the resin can be dried in a desiccator over dry potassium hydroxide, the use of phosphorus pentoxide as dessicant was found to degrade the functionalised resin). The oxidative properties of the material obtained by this method were determined by the titration method described below. The loadings obtained by this method were found in the 1.30-1.60 mmol/g range. **Titration procedure:** The resin **155** (100 mg) and potassium iodide (200 mg) were suspended in dilute hydrochloric acid (1 M; 2.5 mL) and stirred for 10 min. The suspension was titrated by a sodium thiosulfate solution (0.10 M) in presence of a few drops of starch indicator (1% in water) until a stable discolouration was obtained.

IR spectra were obtained for the sulfonamide-functionalised resin and the final resin (**Figure E1**) : ν_{max} (ATR)/cm^{-1}: PS-$TsNH_2$: 1156 (ν_s S=O), 1322 (ν_{as} S=O); PS-TsNIK: 1080.

Iodine elemental analysis was performed by Warwick Analytical Services and gave an average iodine content of 19.4%wt/wt on a sample of resin **155** (iodometric titration: 1.42 mmol/g, correspond to a calculated 18.1%wt/wt iodine).

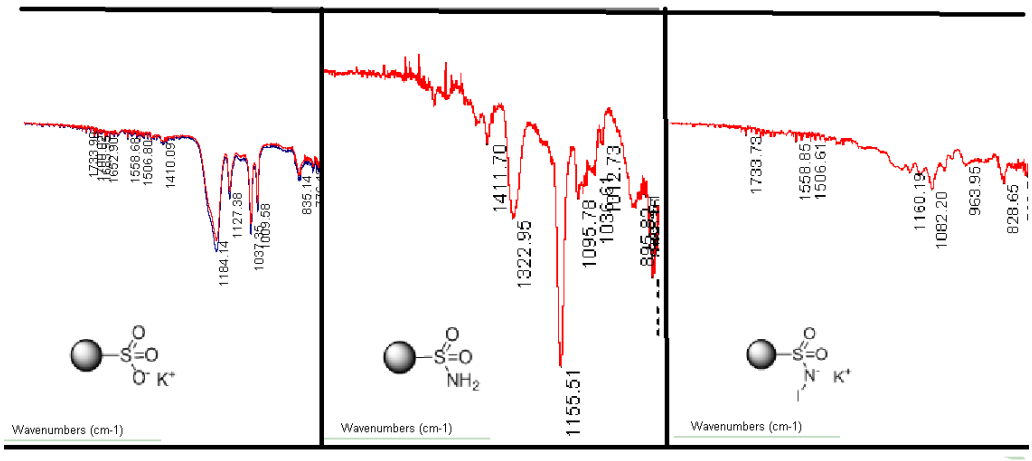


Figure E1: IR comparison of some functionalised resins.

In flow recycling procedure (Figure E2): The functionalised resin (530 mg) was packed in an adapted column (Omnifit®100 x 6.6 mm), which was fitted to one of the reactor slots of the R4 unit. A backpressure regulator (100 psi) was placed between collection and column. A solution of hydrazone **100a** (2 mL, 0.2 M in dichloromethane) was injected into one of the injection loops on the R2+ unit and pumped through the system using dichloromethane as eluent. The residence time in the column was set to 5 min. Using the dispersion model, the output solution (3.8 mL)

containing the diazo compound was collected in a single vessel. The solvent was then switched to water. A solution of potassium iodide/iodine (0.3 M/0.2 M) in water (flow rate: 0.5 mL/min) and a solution of potassium hydroxide (0.1 M) in water (flow rate 0.5 mL/min) contained in separate reagent bottles were mixed in a T-piece placed before the cartridge and pumped through the resin for 40 min (total volume of each solution: 20 mL). The solvent was then switched to anhydrous ether which was then pumped through the resin (flow rate 1 mL/min for 30 min, total volume 30 mL). The solvent was then switched back to dichloromethane and the procedure was repeated. Analysis of the final mixture gave the following conversions over two recycling: 96% (initial oxidation), 87% (after first recycling), 94% (after second recycling). No starting hydrazone was obtained in the final product, with the only impurity observed being the corresponding ketone.

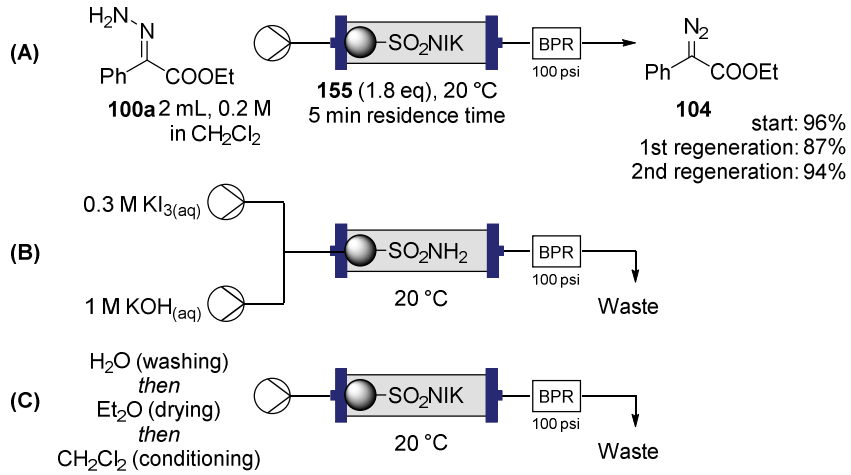


Figure E2: regeneration of resin 155 in flow

III.2. Hydrazones oxidation in flow

General procedure H: the functionalised resin **155** (0.8 mmol of active iodine, calculated using the loading determined by titration) was packed in an adapted column (Omnifit® 100 x 6.6 mm) which was fitted to one of the reactor slots of the R4 unit. Solutions of hydrazone (in the range 0.1 - 0.2 M in dichloromethane) were injected into one of the injection loops on the R2+ unit and pumped through the system using dichloromethane as eluent. A backpressure regulator (100 psi) was placed between collection and the column (**Figure E3**). The reactions were programmed and monitored using the software Vapourtec Flowcommander. For simple oxidation, the residence time in the column was set to 5 min. Using the dispersion model, the output solution (3.8 mL) containing the diazo compound was collected in a single vessel. Evaporation of the solvent gave the diazo compound either pure or as a mixture with the corresponding ketone (yields were determined by integration using ^{1}H NMR analysis of the final product). (NOTE: up to three successive oxidation runs were carried out using the same cartridge load of resin **155**. In this case, the quantity of resin used was multiplied by three, the residence time kept to 5 min and the collection volume adapted to the output according to the dispersion model).

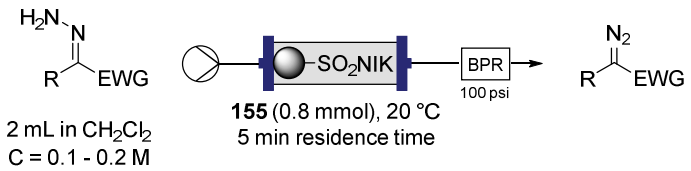
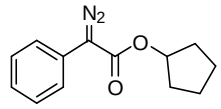


Figure E3: oxidation of hydrazones in flow using resin 155

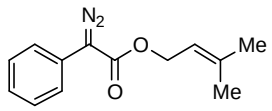
The following diazo compounds were obtained (NOTE: for diazo compounds already discussed in **Vol. 1 Chapter II**, refer to the corresponding experimental). Yields indicated for simple oxidation refer to conversions determined by ^{1}H NMR of the final product (unless otherwise indicated).

Cyclopentyl 2-diazo-2-phenylacetate 159



Obtained by **general procedure H** from hydrazone **100d** (c = 0.2 M, 2 mL). Orange oil (99%); (Found: M+Na$^+$, 253.0944. $C_{13}H_{14}N_2NaO_2$ requires 253.0947); ν_{max} ($CHCl_3$)/cm^{-1} 2089(CN_2), 1694, 1248, 1158; δ_H (400 MHz; $CDCl_3$) 7.45 - 7.50 (2 H, m, ArH), 7.34 - 7.41 (2 H, m, ArH), 7.17 (1 H, tt, *J* 7.5, 1.2, ArH), 5.37 (1 H, tt, *J* 5.9, 2.9, CH), 1.85 - 2.00 (2 H, m, CH_2), 1.59 - 1.85 (6 H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 165.2 (C), 129.0 (CH), 125.9 (C), 125.8 (CH), 124.1 (CH), 78.1 (CH), 33.0 (CH_2), 23.8 (CH_2), the signal due to $\underline{C}N_2$ was not observed.

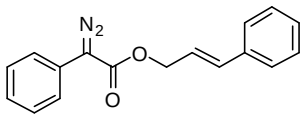
3-Methylbut-2-enyl 2-diazo-2-phenylacetate 161



Obtained by **general procedure H** from hydrazone **100i** (c = 0.2 M, 2 mL). Orange oil (98%); (Found: M+Na$^+$, 253.0945. $C_{13}H_{14}N_2NaO_2$ requires 253.0947); ν_{max} ($CHCl_3$)/cm^{-1} 2090, 1695, 1246; δ_H (400 MHz; $CDCl_3$) 7.46 - 7.51 (2 H, m, ArH), 7.35 - 7.41 (2 H, m, ArH), 7.18 (1 H, tt, *J* 7.3, 1.3, ArH), 5.40 (1 H, tsept, *J* 7.2, 1.4, =CH), 4.77 (2 H, d, *J* 7.2, CH_2), 1.78 (3 H, br s, CH_3), 1.75 (3 H, br s, CH_3); δ_C (100 MHz; $CDCl_3$) 165.4 (C), 139.5 (C), 129.1 (CH), 125.9 (CH), 124.1 (CH), 118.8 (CH), 62.0 (CH_2), 25.9 (CH_3), 18.3 (CH_3), two quaternary carbon

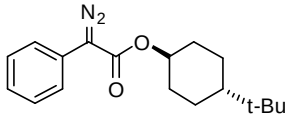
signals were not observed. The data obtained match those previously reported.[45]

Cinnamyl 2-diazo-2-phenylacetate 162



Obtained by **general procedure H** from hydrazone **100j** (c = 0.2 M, 2 mL). Yellow solid (96%); mp 53 - 54 °C (mp lit.[46] not reported); (Found: M+Na$^+$, 301.0937. $C_{17}H_{14}N_2NaO_2$ requires 301.0947); ν_{max} ($CHCl_3$)/cm^{-1} 2091(CN_2), 1698, 1245, 1154; δ_H (400 MHz; $CDCl_3$) 7.48 - 7.53 (2 H, m, ArH), 7.25 - 7.44 (7 H, m, ArH), 7.20 (1 H, tt, *J* 7.4, 1.2, ArH), 6.71 (1 H, br d, *J* 15.8, =CH), 6.35 (1 H, dt, *J* 15.8, 6.4, =CH), 4.94 (2 H, dd, *J* 6.4, 1.3, CH_2); δ_C (100 MHz; $CDCl_3$) 165.1 (C), 136.3 (C), 134.7 (CH), 129.1 (CH), 128.8 (CH), 128.3 (CH), 126.8 (CH), 126.0 (CH), 125.6 (C), 124.2 (CH), 123.2 (CH), 65.6 (CH_2) the signal due to $\underline{C}N_2$ was not observed. The data obtained match those previously reported.[46]

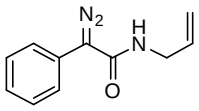
***trans*-4-*tert*-Butylcyclohexyl 2-diazo-2-phenylacetate 163**



Obtained by **general procedure H** from hydrazone **100f** (c = 0.2 M, 2 mL). Orange solid (98%); mp 72 - 73 °C; (Found: M+Na$^+$, 323.1727. $C_{18}H_{24}N_2NaO_2$ requires 323.1730); ν_{max} ($CHCl_3$)/cm^{-1} 2957, 2089 (CN_2), 1692, 1244; δ_H (400 MHz; $CDCl_3$) 7.45 - 7.51 (2 H, m, ArH), 7.34 - 7.42 (2 H, m, ArH), 7.13 - 7.22 (1 H, m, ArH), 4.83 (1 H, tt, *J* 11.3, 4.5, CH), 2.06 - 2.18 (2 H, m, CH_2), 1.77 - 1.91 (2 H, m, CH_2), 1.31 - 1.48 (2 H, m, CH_2), 1.15 (2 H, dtd, *J* 13.3, 12.1, 3.4, CH_2), 1.02 (1 H, tt, *J* 12.1, 2.8, C$\underline{H}$), 0.87 (9 H, s, *t*Bu); δ_C (100 MHz; $CDCl_3$) 165.0 (C), 129.0 (CH), 126.0 (C), 125.8 (CH), 124.1 (CH), 74.7 (CH), 47.2

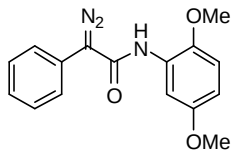
(CH), 32.49 (CH_2), 32.46 (C), 27.7 (CH_3), 25.6 (CH_2), the signal due to $\underline{C}N_2$ was not observed.

_N_-Allyl-2-diazo-2-phenylacetamide 164



Obtained by **general procedure H** from hydrazone **100q** (c = 0.1 M, 2 mL). Obtained in limited purity after an additional column chromatography using 20% ethyl acetate in light petroleum. Orange solid (32 mg, 78%); (Found: M+Na^+, 224.0786. $C_{11}H_{11}N_3NaO$ requires 224.0794); mp 62-63 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3437, 2089 (CN_2), 2059, 1632, 1510; δ_H (400 MHz; $CDCl_3$) 7.41 - 7.47 (2 H, m, ArH), 7.34 - 7.39 (2 H, m, ArH), 7.28 - 7.33 (1 H, m, ArH), 5.80 - 5.91 (1 H, m, vinylic CH), 5.50 (1 H, br s, NH), 5.11 - 5.21 (2 H, m, vinylic CH_2), 3.99 (2 H, tt, *J* 5.7, 1.6, CH_2); δ_C (100 MHz; $CDCl_3$) 164.7 (C), 134.4 (CH), 129.9 (CH), 127.8 (CH), 127.7 (CH), 126.5 (C), 116.6 (CH_2), 42.68 (CH_2), the signal due to $\underline{C}N_2$ was not observed.

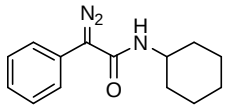
2-Diazo-_N_-(2,5-dimethoxyphenyl)-2-phenylacetamide 165



Obtained by **general procedure H** from hydrazone **100r** (c = 0.2 M, 2 mL). Orange solid (95%); mp 86-87 °C; (Found: M+Na^+, 320.0998. $C_{16}H_{15}N_3NaO_3$ requires 320.1006); ν_{max} ($CHCl_3$)/cm^{-1} 3399, 2088 (CN_2), 2059, 1532, 1245; δ_H (400 MHz; $CDCl_3$) 8.15 (1 H, d, *J* 3.0, ArH), 7.99 (1 H, br s, NH), 7.43 - 7.53 (4 H, m, ArH), 7.33 - 7.38 (1 H, m, ArH), 6.75 (1 H, d, *J* 8.8, ArH), 6.55 (1 H, dd, *J* 8.8, 3.0, ArH), 3.80 (3 H, s, OMe), 3.71 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 162.5 (C), 154.1 (C), 142.2 (C), 129.9 (CH), 128.9 (C), 128.1 (CH),

127.8 (CH), 126.2 (C), 111.0 (CH), 108.7 (CH), 105.5 (CH), 56.5 (CH_3), 55.9 (CH_3), the signal due to $\underline{C}N_2$ was not observed.

***N*-Cyclohexyl-2-diazo-2-phenylacetamide 168**



Obtained in limited purity by **general procedure H** from hydrazone **100t** (c = 0.2 M, 2 mL) after purification by column chromatography using 10% ethyl acetate in light petroleum on silica neutralised by 5% triethylamine in 10% ethyl acetate in light petroleum. Orange solid (43 mg, 44%); the compound did not ionise under the ESI-HRMS conditions used; mp 96 - 97 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3425, 2087, 2057, 1226, 1510; δ_H (400 MHz; $CDCl_3$) 7.40 - 7.46 (2 H, m, ArH), 7.31 - 7.37 (2 H, m, ArH), 7.26 - 7.31 (1 H, m, ArH), 5.30 (1 H, d, *J* 6.9, NH), 3.90 (1 H, tdt, *J* 11.5, 6.9, 3.4, C$\underline{H}$N), 1.90 - 1.99 (2 H, m, cyclohexane CH_2), 1.55 - 1.72 (3 H, m, cyclohexane CH), 1.31 - 1.45 (2 H, m, cyclohexane CH), 1.06 - 1.20 (3 H, m, cyclohexane CH); δ_C (100 MHz; $CDCl_3$) 163.7 (C), 129.8 (CH), 127.5 (CH), 127.3 (CH), 126.9 (C), 49.1 (CH), 33.5 (CH_2), 25.6 (CH_2), 25.0 (CH_2), the signal due to $\underline{C}N_2$ was not observed.

III.3. Tandem oxidation in flow / metallocarbene reaction

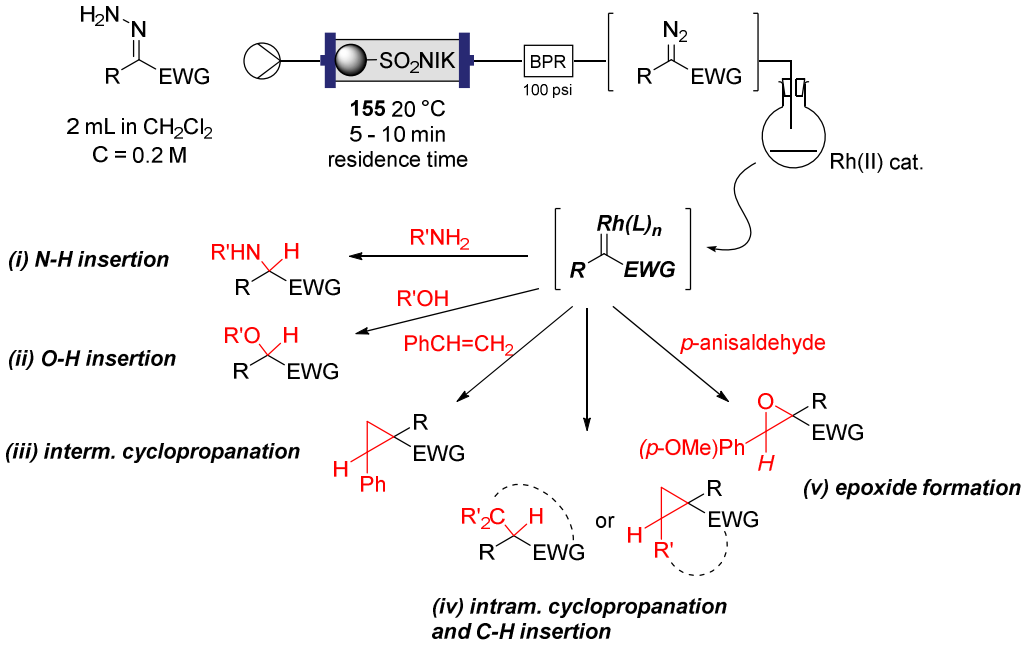
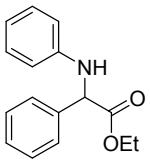


Figure E4: in-line processes involving diazo compounds generated in flow

III.3.1. Tandem oxidation in flow / N–H Insertion

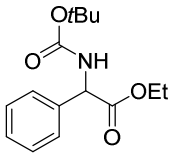
General procedure I: The solution of diazo compound in dichloromethane (from hydrazone solutions, 2 mL of 0.1-0.2 M solution) was prepared following the **general procedure H** for the oxidation of hydrazone solution in flow and using the following parameters: residence time: 5 min, collected volume: 4.5 mL, packed reactor volume: 1 mL. The output solution was added to a solution of rhodium(II) acetate dimer (1 mol%) and the corresponding amide/aniline/carbamate compound (1.2 eq) in dichloromethane (1 mL) at room temperature. After addition, the resulting mixture was stirred for 16 h and the solvent was removed under reduced pressure to give a residue that was purified by column chromatography.

Ethyl 2-phenyl-2-(phenylamino)acetate 169a



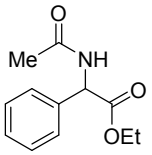
Obtained by **general procedure I** from hydrazone **100a** (c = 0.2 M, 2 mL) using aniline (44 μL, 0.48 mmol), purified by column chromatography using 2% ethyl acetate in light petroleum. Colourless solid (101 mg, 98%); mp 84 - 85 °C (lit.[29] mp 86 °C); (Found: M+H$^+$, 256.1328. $C_{16}H_{18}NO_2$ requires 256.1332); ν_{max} ($CHCl_3$)/cm^{-1} 3420, 1733, 1603, 1506, 1314; δ_H (400 MHz; $CDCl_3$) 7.49 - 7.56 (2 H, m, ArH), 7.28 - 7.41 (3 H, m, ArH), 7.10 - 7.18 (2 H, m, ArH), 6.67 - 6.74 (1 H, m, ArH), 6.58 (2 H, dd, *J* 8.6 1.0, ArH), 5.08 (1 H, s, CH), 5.00 (1 H, br s, NH), 4.10 - 4.30 (2 H, m, C$\underline{H}_2$CH$_3$), 1.23 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 171.9 (C), 146.1 (C), 137.8 (C), 129.3 (CH), 128.9 (CH), 128.3 (CH), 127.3 (CH), 118.2 (CH), 113.5 (CH), 61.9 (CH$_2$), 60.9 (CH), 14.2 (CH$_3$). The data match those previously reported.[29]

Ethyl 2-(*tert*-butoxycarbonylamino)-2-phenylacetate 169b



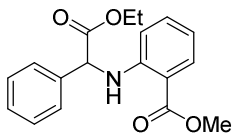
Obtained by **general procedure I** from hydrazone **100a** (c = 0.2 M, 2 mL) using *t*-butyl carbamate (56 mg, 0.48 mmol), purified by column chromatography using elution gradient 5% to 10% ethyl acetate in light petroleum. Colourless oil (88.4 mg, 79%); (Found: M+Na$^+$, 302.1355. $C_{15}H_{21}NNaO_4$ requires 302.1363); ν_{max} ($CHCl_3$)/cm^{-1}; 3438, 1730, 1711, 1496, 1165; δ_H (400 MHz; $CDCl_3$) 7.27 - 7.40 (5 H, m, ArH), 5.56 (1 H, br s, NH), 5.30 (1 H, d, *J* 7.3, CH), 4.07 - 4.27 (2 H, m, C$\underline{H}_2$CH$_3$), 1.43 (9 H, s, *t*Bu), 1.20 (3 H, t, *J* 7.5, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 171.2 (C), 154.9 (C), 137.2 (C), 128.9 (CH), 128.4 (CH), 127.2 (CH), 80.1 (C), 61.8 (CH$_2$), 57.7 (CH), 28.4 (CH$_3$), 14.1 (CH$_3$). The data match those previously reported.[47]

Ethyl 2-acetamido-2-phenylacetate 169c



Obtained by **general procedure I** from hydrazone **100a** (c = 0.2 M, 2 mL) using acetamide (28 mg, 0.48 mmol), purified by column chromatography using 50% ethyl acetate in light petroleum. Colourless oil (84 mg, 95%); (Found: M+Na$^+$, 244.0942. $C_{12}H_{15}NNaO_3$ requires 244.0944); ν_{max} ($CHCl_3$)/cm^{-1} 3431, 3011, 1736, 1677, 1599; δ_H (400 MHz; $CDCl_3$) 7.27 - 7.39 (5 H, m, ArH), 6.63 (1 H, d, *J* 6.8, NH), 5.57 (1 H, d, *J* 6.8, CH), 4.08 - 4.27 (2 H, m, C$\underline{H}_2$CH$_3$), 2.01 (3 H, s, CH_3), 1.20 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 171.1 (C), 169.5 (C), 136.8 (C), 129.0 (CH), 128.5 (CH), 127.3 (CH), 62.0 (CH_2), 56.5 (CH), 23.1 (CH_3), 14.1 (CH_3). The data match those previously reported.[48]

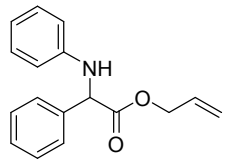
Methyl 2-((2-ethoxy-2-oxo-1-phenylethyl)amino)benzoate 169d



Obtained by **general procedure I** from hydrazone **100a** (c = 0.2 M, 2 mL) using methyl anthranilate (62 µL, 0.48 mmol), purified by column chromatography using 30% to 50% dichloromethane in light petroleum. Colourless solid (116 mg, 93%); mp 86 - 87 °C; (Found: M+Na$^+$, 336.1204. $C_{18}H_{19}NNaO_4$ requires 336.1206); ν_{max} ($CHCl_3$)/cm^{-1} 3341, 1738, 1687; δ_H (400 MHz; $CDCl_3$) 8.94 (1 H, d, *J* 5.8, NH), 7.94 (1 H, dd, *J* 8.1, 1.5, ArH), 7.48 - 7.56 (2 H, m, ArH), 7.27 - 7.39 (3 H, m, ArH), 7.22 (1 H, td, *J* 7.8, 1.5, ArH), 6.61 (1 H, m, ArH), 6.41 (1 H, d, *J* 8.1, ArH), 5.16 (1 H, d, *J* 5.8, CH), 4.25 (1 H, dq, *J* 10.7, 7.2, C$\underline{H}_2$CH$_3$), 4.17 (1 H, dq, *J* 10.7, 7.2, C$\underline{H}_2$CH$_3$), 3.91 (3 H, s, CH_3), 1.22 (3 H, t, *J* 7.1, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 171.2 (C), 168.9 (C), 149.0 (C), 137.5

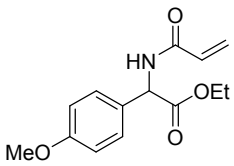
(C), 134.6 (CH), 131.9 (CH), 129.0 (CH), 128.4 (CH), 127.3 (CH), 115.7 (CH), 112.2 (CH), 111.3 (C), 62.0 (CH_2), 60.5 (CH), 51.8 (CH_3), 14.2 (CH_3).

Allyl 2-phenyl-2-(phenylamino)acetate 169e



Obtained by **general procedure I** from hydrazone **100h** (c = 0.2 M, 2 mL) using aniline (44 µL, 0.48 mmol), purified by column chromatography using 3% ethyl acetate in light petroleum. Yellow oil (99 mg, 92%); (Found: M+H$^+$, 268.1316. $C_{17}H_{18}NO_2$ requires 268.1332); ν_{max} ($CHCl_3$)/cm^{-1} 1737, 1603, 1506, 1313, 1253; δ_H (400 MHz; $CDCl_3$) 7.49 - 7.57 (2 H, d, *J* 7.1, ArH), 7.29 - 7.41 (3 H, m, ArH), 7.08 - 7.20 (2 H, m, ArH), 6.72 (1 H, t, *J* 7.3, ArH), 6.59 (2 H, d, *J* 7.7, ArH), 5.84 (1 H, ddt, *J* 17.0, 10.5, 5.6, vinylic CH), 5.19 (1 H, dq, *J* 10.5, 1.3, vinylic CH_2), 5.18 (1 H, dq, *J* 17.0, 1.4, vinylic CH_2), 5.13 (1 H, s, CH), 4.67 (1 H, ddt, *J* 13.3, 5.6, 1.3, CH_2), 4.62 (1 H, ddt, *J* 13.3, 5.6, 1.3, CH_2); δ_C (100 MHz; $CDCl_3$) 171.6 (C), 146.0 (C), 137.7 (C), 131.5 (CH), 129.4 (CH), 129.0 (CH), 128.4 (CH), 127.4 (CH), 118.6 (CH_2), 118.2 (CH), 113.6 (CH), 66.2 (CH_2), 60.9 (CH).

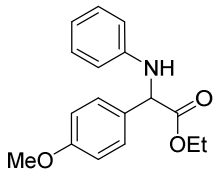
Ethyl 2-acrylamido-2-(4-methoxyphenyl)acetate 169f



Obtained by a modification of **general procedure I** from hydrazone **100m** (c = 0.2 M, 2 mL) using acrylamide (34 mg, 0.48 mmol). The diazo compound solution in anhydrous dichloromethane (generated following the procedure for the oxidation of hydrazone solution in flow) was added to a solution of rhodium acetate dimer (2 mg, 1 mol%) in anhydrous dichloromethane at reflux. After addition the reaction mixture was stirred

for 30 min at reflux and cooled to room temperature. Removal of the solvent under reduced pressure gave a residue that was purified by column chromatography using 30% ethyl acetate in light petroleum to give the *title compound*. Colourless solid (65 mg, 62%); mp 130 - 131 °C; (Found: M+Na$^+$, 286.1050. $C_{14}H_{17}NNaO_4$ requires 286.1050); ν_{max} ($CHCl_3$)/cm^{-1} 3423, 1734, 1675, 1512; δ_H (400 MHz; $CDCl_3$) 7.26 - 7.33 (2 H, m, ArH), 6.79 - 6.93 (2 H, m, ArH), 6.57 (1 H, d, *J* 7.0, NH), 6.31 (1 H, dd, *J* 16.9, 1.5, vinylic CH_2), 6.15 (1 H, dd, *J* 16.9, 10.1, vinylic CH), 5.67 (1 H, dd, *J* 10.1, 1.5, vinylic CH_2), 5.58 (1 H, d, *J* 7.0, CH), 4.24 (1 H, dq, *J* 10.7, 7.2, C$\underline{H}_2$CH$_3$), 4.15 (1 H, dq, *J* 10.7, 7.2, C$\underline{H}_2$CH$_3$), 3.79 (3 H, s, OCH_3), 1.22 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 171.2 (C), 164.7 (C), 159.8 (C), 130.3 (CH), 128.8 (C), 128.7 (CH), 127.5 (CH_2), 114.5 (CH), 62.1 (CH_2), 56.0 (CH), 55.4 (CH_3), 14.1 (CH_3).

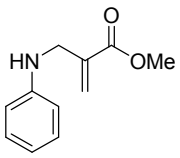
Ethyl 2-(4-methoxyphenyl)-2-(phenylamino)acetate 169g



Obtained by **general procedure I** from hydrazone **100m** (c = 0.2 M, 2 mL) using aniline (44 µL, 0.48 mmol), purified by column chromatography using 5% ethyl acetate in light petroleum. Yellow oil (76 mg, 67%); (Found: M+H$^+$, 286.1437. $C_{17}H_{20}NO_3$ requires 286.1438); ν_{max} ($CHCl_3$)/cm^{-1} 3421, 3010, 1732, 1604, 1509; δ_H (400 MHz; $CDCl_3$) 7.42 - 7.48 (2 H, m, ArH), 7.12 - 7.19 (2 H, m, ArH), 6.88 - 6.93 (2 H, m, ArH), 6.72 (1 H, tt, *J* 7.5, 0.9, ArH), 6.57 - 6.62 (2 H, m, ArH), 5.05 (1 H, s, CH), 4.95 (1 H, br s, NH), 4.15 - 4.26 (2 H, two overlapping dq, *J* 10.8, 7.0, C$\underline{H}_2$CH$_3$), 3.80 (3 H, s, OMe), 1.24 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 172.1 (C), 159.6 (C), 146.1 (C),

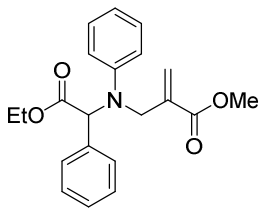
129.7 (C), 129.3 (CH), 128.4 (CH), 118.0 (CH), 114.3 (CH), 113.5 (CH), 61.8 (CH_2), 60.2 (CH), 55.3 (CH_3), 14.1 (CH_3).

Methyl 2-((phenylamino)methyl)acrylate



Tetrakis(triphenylphosphine)palladium(0) (55 mg, 47.6 μmol) was added to a mixture of aniline (326 μL, 3.59 mmol) and methyl 2-(acetoxymethyl)acrylate[49] (380 mg, 2.39 mmol) in anhydrous tetrahydrofuran (10 mL) at room temperature and the resulting mixture was stirred under argon for 5 days. The solvent was removed under reduced pressure to give a residue that was purified by column chromatography using 10% ethyl acetate in light petroleum to give the *title compound* as yellow oil (420 mg, 92%); (Found: $M+H^+$, 192.1023. $C_{11}H_{14}NO_4$ requires 192.1019); ν_{max} ($CHCl_3$)/cm^{-1} 3449, 1715, 1603; δ_H (400 MHz; $CDCl_3$) 7.14 - 7.21 (2 H, m, ArH), 6.72 (1 H, tt, *J* 7.3, 1.0, ArH), 6.57 - 6.63 (2 H, m, ArH), 6.28 (1 H, q, *J* 1.2, vinylic CH_2), 5.80 (1 H, q, *J* 1.2, vinylic CH_2), 4.09 (1 H, br s, NH), 4.04 (2 H, t, *J* 1.2, CH_2), 3.79 (3 H, s, OCH_3); δ_C (100 MHz; $CDCl_3$) 167.0 (C), 147.6 (C), 137.4 (C), 129.4 (CH), 126.0 (CH_2), 117.9 (CH), 113.2 (CH), 52.0 (CH_3), 44.9 (CH_2). The data match those previously reported.[50]

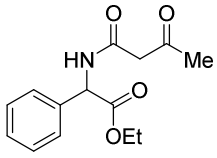
Methyl 2-((2-ethoxy-2-oxo-1-phenylethyl)(phenyl)amino)methyl-acrylate 169h



Obtained by **general procedure I** from hydrazone **100a** (c = 0.2 M, 2 mL) using methyl 2-((phenylamino)methyl)acrylate (92 mg, 0.48 mmol), purified by column chromatography using 30% dichloromethane in light petroleum. Colourless oil (100 mg, 71%);

(Found: M+H$^+$, 354.1700. $C_{21}H_{24}NO_4$ requires 354.1700); ν_{max} ($CHCl_3$)/cm^{-1} 1737, 1717, 1599, 1504; δ_H (400 MHz; $CDCl_3$) 7.30 - 7.39 (5 H, m, ArH), 7.22 - 7.29 (2 H, m, ArH), 6.82 - 6.87 (1 H, m, ArH), 6.76 - 6.82 (2 H, m, ArH), 6.16 (1 H, q, *J* 1.7, vinylic CH_2), 5.74 (1 H, q, *J* 1.7, vinylic CH_2), 5.70 (1 H, s, CHN), 4.21 - 4.32 (4 H, m, CH_2 and C$\underline{H}_2$CH$_3$), 3.72 (3 H, s, CH_3), 1.27 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 171.9 (C), 166.7 (C), 148.7 (C), 136.2 (C), 135.2 (C), 129.3 (CH), 129.1 (CH), 128.7 (CH), 128.5 (CH), 125.9 (CH_2), 118.6 (CH), 113.9 (CH), 65.9 (CH), 61.4 (CH_2), 51.8 (CH_3), 49.3 (CH_2), 14.3 (CH_3).

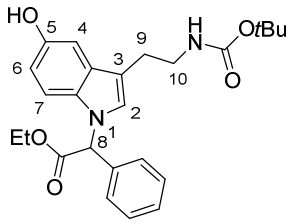
Ethyl 2-(3-oxobutanamido)-2-phenylacetate 169i



Obtained by a modification of **general procedure I** from hydrazone **100a** (c = 0.2 M, 2 mL) using acetoacetamide (49 mg, 0.48 mmol) and rhodium octanoate dimer (3 mg, 1 mol%) as the catalyst, purified by column chromatography using 50% ethyl acetate in light petroleum. Off-white solid (69 mg, 66%); mp 70-71 °C; (Found: M+Na$^+$, 286.1043. $C_{14}H_{17}NNaO_4$ requires 286.1050); ν_{max} ($CHCl_3$)/cm^{-1} 3420, 3339, 1737, 1716, 1673; observed in equilibrium with its enol form (ratio 6:94 in favour of the ketoamide form) in deuterated chloroform at room temperature. Only the signals for the ketoamide form are reported, δ_H (400 MHz; $CDCl_3$) 7.90 (1 H, d, *J* 7.0, NH), 7.27 - 7.42 (5 H, m, ArH), 5.54 (1 H, d, *J* 7.0, CH), 4.21 (1 H, dq, *J* 10.8, 7.2, C$\underline{H}_2$CH$_3$), 4.12 (1 H, dq, *J* 10.8, 7.2, C$\underline{H}_2$CH$_3$), 3.46 (1 H, d, *J* 17.1, CH_2), 3.39 (1 H, d, *J* 17.1, CH_2), 2.23 (3 H, s, CH_3), 1.20 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 204.0 (C), 170.6 (C), 165.2 (C), 136.4 (C),

129.0 (CH), 128.6 (CH), 127.3 (CH), 62.0 (CH_2), 56.8 (CH), 49.6 (CH_2), 31.0 (CH_3), 14.1 (CH_3).

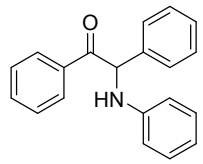
Ethyl 2-(3-(2-(*tert*-butoxycarbonyl)amino)ethyl-5-hydroxy-*1H*-indol-1-yl)-2-phenylacetate 169j



Obtained by a modification of **general procedure I** from hydrazone **100a** (c = 0.2 M, 2 mL) using *N*-Boc serotonin (132 mg, 0.48 mmol). The diazo compound solution in anhydrous dichloromethane (generated following the procedure for the oxidation of hydrazone solution in flow) was added to a solution of rhodium acetate (2 mg, 1 mol%) in anhydrous dichloromethane at reflux. After addition, the reaction mixture was stirred for 30 min at reflux and cooled to room temperature. Removal of the solvent under reduced pressure gave a residue that was purified by column chromatography using 20% ethyl acetate in light petroleum to give the *title compound*. Yellow oil (133 mg, 78%); (Found: M+Na^+, 461.2055. $C_{25}H_{30}N_2NaO_5$ requires 461.2052); ν_{max} ($CHCl_3$)/cm^{-1} 3604, 3452, 1744, 1707, 1170; δ_H (400 MHz; $CDCl_3$) 7.35 - 7.42 (3 H, m, ArH), 7.30 - 7.34 (2 H, m, ArH), 7.15 (1 H, d, *J* 8.8, H7), 7.01 (1 H, d, *J* 2.2, H4), 6.88 (1 H, s, H2), 6.80 (1 H, dd, *J* 8.8, 2.2, H6), 6.10 (1 H, s, H8), 5.37 (1 H, br s, OH), 4.66 (1 H, br s, NH), 4.18 - 4.33 (2 H, m, C$\underline{H}_2CH_3$), 3.36 (2 H, q, *J* 6.9, H10), 2.80 (2 H, t, *J* 6.9, H9), 1.42 (9 H, s, *t*Bu), 1.26 (3 H, t, *J* 7.1, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 169.8 (C), 156.1 (C), 150.1 (C), 134.8 (C), 132.3 (C), 129.03 (CH), 129.00 (C), 128.9 (CH), 128.0 (CH), 125.5 (CH), 112.1 (C), 111.9 (CH), 109.9 (CH), 103.9 (CH), 62.2 (CH), 62.0 (CH_2), 60.5 (C), 40.6 (CH_3), 28.4 (CH_2), 25.9

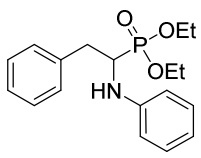
(CH_2), 14.1 (CH_3). The structure was assigned on the basis of various 2D-NMR experiments.

1,2-Diphenyl-2-(phenylamino)ethanone 169k



Obtained by **general procedure I** from hydrazone **65** (c = 0.15 M, 2 mL) using aniline (44 µL, 0.48 mmol), purified by column chromatography using 5% ethyl acetate in light petroleum. Yellow solid (79 mg, 92%); mp 94 - 95 °C (lit.[51] mp 97 - 98 °C); (Found: M+H$^+$, 288.1374. $C_{20}H_{18}NO$ requires 288.1383); ν_{max} ($CHCl_3$)/cm^{-1} 3413, 3011, 1685, 1602, 1505; δ_H (400 MHz; $CDCl_3$) 7.98 - 8.05 (2 H, m, ArH), 7.55 (1 H, tt, *J* 7.3, 1.2, ArH), 7.41 - 7.50 (4 H, m, ArH), 7.30 (2 H, t, *J* 7.7, ArH), 7.19 - 7.24 (1 H, m, ArH), 7.12 - 7.19 (2 H, m, ArH), 6.67 - 6.75 (3 H, m, ArH), 6.06 (1 H, s, CH), 5.46 (1 H, br s, NH); δ_C (100 MHz; $CDCl_3$) 197.2 (C), 146.2 (C), 137.8 (C), 135.2 (C), 133.6 (CH), 129.4 (CH), 129.2 (CH), 129.0 (CH), 128.8 (CH), 128.2 (CH), 128.2 (CH), 118.0 (CH), 113.6 (CH), 62.8 (CH). The data match those previously reported.[51]

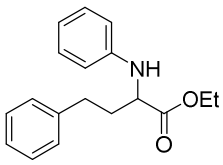
Diethyl 2-phenyl-1-(phenylamino)ethylphosphonate 169l



Obtained by **general procedure I** from hydrazone **102b** (c = 0.2 M, 2 mL) using aniline (44 µL, 0.48 mmol), purified by column chromatography using 50% ethyl acetate in light petroleum. Light brown solid (88 mg, 66%); mp 74 - 75 °C; (Found: C, 64.65; H, 7.23; N, 4.06. $C_{18}H_{24}NO_3P$ requires C, 64.85; H, 7.26; N, 4.20%); (Found: M+Na$^+$, 356.1401. $C_{18}H_{24}NNaO_3P$ requires 356.1391); ν_{max} ($CHCl_3$)/cm^{-1} 3419, 2997, 1601, 1506, 1053, 1028; δ_H (400 MHz;

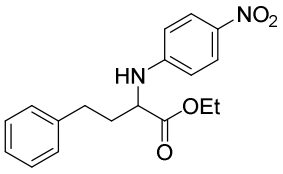
$CDCl_3$) 7.15 - 7.25 (5 H, m, ArH), 7.10 (2 H, tt, *J* 7.4, 2.1, ArH), 6.68 (1 H, t, *J* 7.3, ArH), 6.55 (2 H, d, *J* 7.8, ArH), 4.00 - 4.15 (4 H, m, $C\underline{H}_2CH_3$), 3.89 - 4.00 (1 H, m, CH), 3.81 (1 H, br s, NH), 3.27 (1 H, ddd, *J* 14.3, 12.3, 4.8, CH_2), 2.98 (1 H, ddd, *J* 14.3, 10.6, 8.8, CH_2) 1.25 (3 H, t, *J* 7.1, $CH_2C\underline{H}_3$), 1.15 (3 H, t, *J* 7.1, $CH_2C\underline{H}_3$) ; δ_C (100 MHz; $CDCl_3$) 146.9 (d, J_{CP} 5.4, C), 137.5 (d, J_{CP} 12.3, C), 129.5 (CH), 129.3 (CH), 128.5 (CH), 126.7 (CH), 118.3 (CH), 113.8 (CH), 63.0 (d, J_{CP} 6.9, CH_2), 62.2 (d, J_{CP} 7.7, CH_2), 52.6 (d, J_{CP} 156.4, CH), 36.6 (d, J_{CP} 3.8, CH_2), 16.50 (d, J_{CP} 5.4, CH_3), 16.45 (d, J_{CP} 4.6, CH_3).

Ethyl 4-phenyl-2-(phenylamino)butanoate 169m



Obtained by **general procedure I** from hydrazone **100ad** (c = 0.2 M, 2 mL) using aniline (44 µL, 0.48 mmol), purified by column chromatography using 5% ethyl acetate in light petroleum. Yellow oil (89 mg, 78%); (Found: $M+H^+$, 284.1648. $C_{18}H_{22}NO_2$ requires 284.1645); ν_{max} ($CHCl_3$)/cm^{-1} 3418, 1732, 1603, 1507; δ_H (400 MHz; $CDCl_3$) 7.34 - 7.42 (2 H, m, ArH), 7.21 - 7.33 (5 H, m, ArH), 6.78 - 6.87 (1 H, m, ArH), 6.65 - 6.73 (2 H, d, *J* 7.8, ArH), 4.21 - 4.35 (3 H, m, NH and CH_2), 4.13 - 4.21 (1 H, m, CH), 2.86 (2 H, q, *J* 7.2, $C\underline{H}_2CH_3$), 2.27 (1 H, ddd, *J* 13.8, 7.7, 5.8, CH_2), 2.09 - 2.21 (1 H, m, CH_2), 1.30 - 1.37 (3 H, m, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 174.1 (C), 146.9 (C), 141.0 (C), 129.4 (CH), 128.6 (CH), 128.6 (CH), 126.2 (CH), 118.4 (CH), 113.7 (CH), 61.2 (CH_2), 56.2 (CH), 34.7 (CH_2), 31.9 (CH_2), 14.3 (CH_3).

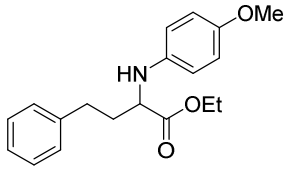
Ethyl 2-((4-nitrophenyl)amino)-4-phenylbutanoate 169n



Obtained by **general procedure I** from hydrazone **100ad** (c = 0.2 M, 2 mL) using *p*-nitroaniline

(66 mg, 0.48 mmol), purified by column chromatography using 10% ethyl acetate in light petroleum. Yellow oil (88 mg, 67%); (Found: M+Na$^+$, 351.1297. $C_{18}H_{20}N_2NaO_4$ requires 351.1315); ν_{max} ($CHCl_3$)/cm^{-1} 3411, 1734, 1601, 1327; δ_H (400 MHz; $CDCl_3$) 8.02 - 8.09 (2 H, m, ArH), 7.27 - 7.34 (2 H, m, ArH), 7.20 - 7.25 (1 H, m, ArH), 7.14 - 7.20 (2 H, m, ArH), 6.43 - 6.52 (2 H, m, ArH), 5.02 (1 H, br d, *J* 6.7, NH), 4.23 (2 H, q, *J* 7.1, C$\underline{H}_2$CH$_3$), 4.16 (1 H, q, *J* 6.7, CH), 2.75 - 2.82 (2 H, two overlapping dt, *J* 14.1, 7.4, CH_2), 2.25 (1 H, dtd, *J* 13.5, 7.4, 6.7, CH_2), 2.13 (1 H, ddd, *J* 13.5, 7.4, 6.7, CH_2), 1.30 (3 H, t, *J* 7.1, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 172.6 (C), 151.9 (C), 140.3 (C), 138.9 (C), 128.8 (CH), 128.6 (CH), 126.6 (CH), 126.4 (CH), 111.9 (CH), 61.9 (CH_2), 55.2 (CH), 34.1 (CH_2), 31.6 (CH_2), 14.4 (CH_3).

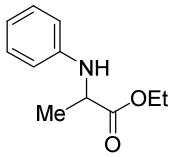
Ethyl 2-((4-methoxyphenyl)amino)-4-phenylbutanoate 169o



Obtained **general procedure I** from hydrazone **100ad** (c = 0.2 M, 2 mL) using *p*-anisidine (59 mg, 0.48 mmol), purified by column chromatography using 10% ethyl acetate in light petroleum. Yellow oil (96 mg, 76%); (Found: M+H$^+$, 314.1742. $C_{19}H_{24}NO_3$ requires 314.1751); ν_{max} ($CHCl_3$)/cm^{-1} 3410, 1731, 1513; δ_H (400 MHz; $CDCl_3$) 7.27 - 7.33 (2 H, m, ArH), 7.17 - 7.24 (3 H, m, ArH), 6.72 - 6.79 (2 H, m, ArH), 6.54 - 6.61 (2 H, m, ArH), 4.16 (2 H, q, *J* 7.1, C$\underline{H}_2$CH$_3$), 3.98 (1 H, dd, *J* 7.2, 5.9, CH), 3.94 (1 H, br s, NH), 3.74 (3 H, s, OCH_3), 2.78 (2 H, t, *J* 7.8, CH_2), 2.15 (1 H, dtd, *J* 13.7, 7.8, 5.9, C), 2.04 (1 H, dtd, *J* 13.7, 7.8, 7.2, CH_2), 1.24 (3 H, t, *J* 7.1, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 174.4 (C), 152.9 (C), 141.14 (C), 141.09 (C), 128.7 (CH), 128.6 (CH), 126.3 (CH), 115.4 (CH), 115.0 (CH), 61.2 (CH_2),

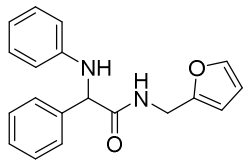
57.5 (CH), 55.8 (CH_3), 34.9 (CH_2), 32.0 (CH_2), 14.4 (CH_3). The data match those previously reported.[52]

Ethyl 2-(phenylamino)propanoate 169p



Obtained **general procedure I** from hydrazone **100ab** (c = 0.1 M, 2 mL) using aniline (44 µL, 0.48 mmol), purified by column chromatography using 5% ethyl acetate in light petroleum. Yellow oil (27 mg, 69%); (Found: M+Na^+, 216.1000. $C_{11}H_{15}NNaO_2$ requires 216.0995); ν_{max} ($CHCl_3$)/cm^{-1} 3416, 1733, 1603, 1506; δ_H (400 MHz; $CDCl_3$) 7.15 - 7.22 (2 H, m, ArH), 6.74 (1 H, tt, *J* 7.3, 1.0, ArH), 6.62 (2 H, dd, *J* 8.6, 1.0, ArH), 4.20 (1 H, br s, NH), 4.19 (2 H, q, *J* 7.2, C<u>H</u>$_2$$CH_3$), 4.13 (1 H, q, *J* 6.9, CH), 1.48 (3 H, d, *J* 6.9, CH_3), 1.26 (3 H, t, *J* 7.2, CH_2C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 174.7 (C), 146.7 (C), 129.4 (CH), 118.4 (CH), 113.6 (CH), 61.2 (CH_2), 52.2 (CH), 19.0 (CH_3), 14.3 (CH_3). The data match those previously reported.[29]

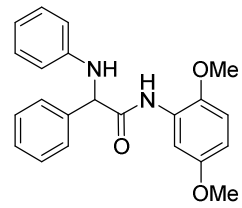
***N*-(2-Furylmethyl)-2-phenyl-2-(phenylamino)acetamide 169q**



Obtained by **general procedure I** from hydrazone **100s** (c = 0.2 M, 2 mL) using aniline (44 µL, 0.48 mmol), purified by column chromatography using the elution gradient ethyl acetate in light petroleum, 10 to 20%. Colourless solid (92 mg, 75%); mp 104 - 106 °C; (Found: M+H^+, 307.1434. $C_{19}H_{19}N_2O_2$ requires 307.1441); ν_{max} ($CHCl_3$)/cm^{-1}; 3397, 3009, 1676, 1603, 1501; δ_H (400 MHz; $CDCl_3$) 7.29 - 7.49 (6 H, m, ArH), 7.15 - 7.24 (2 H, m, ArH), 7.10 (1 H, t, *J* 5.5, N<u>H</u>), 6.81 (1 H, t, *J* 7.4, ArH), 6.63 (2 H, d, *J* 7.6, ArH), 6.28 (1 H, dd, *J* 3.1, 1.9, ArH), 6.11 (1 H, dd, *J* 3.1, 0.6, ArH), 4.79

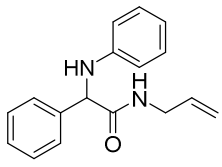
(1 H, s, C<u>H</u>), 4.55 (1 H, dd, *J* 15.6, 5.5, C<u>H</u>$_2$), 4.50 (1 H, br s, NH), 4.37 (1 H, dd, *J* 15.6, 5.5, C<u>H</u>$_2$); δ_C (100 MHz; $CDCl_3$) 171.3 (C), 151.1 (C), 146.7 (C), 142.2 (CH), 138.8 (C), 129.4 (CH), 129.3 (CH), 128.7 (CH), 127.5 (CH), 119.3 (CH), 114.0 (CH), 110.5 (CH), 107.4 (CH), 64.3 (CH), 36.6 (CH_2).

_N_-(2,5-Dimethoxyphenyl)-2-phenyl-2-(phenylamino)acetamide 169r



Obtained by **general procedure I** for N-H insertion from hydrazone **100r** (c = 0.2 M, 2 mL) using aniline (44 µL, 0.48 mmol), purified by column chromatography using 20% ethyl acetate in light petroleum. Brown solid (113 mg, 78%); mp 144 - 145 °C; (Found: C, 72.54; H, 6.16; N, 7.71. $C_{22}H_{22}N_2O_3$ requires C, 72.91; H, 6.12; N, 7.73%); (Found: M+H$^+$, 363.1709. $C_{22}H_{23}N_2O_3$ requires 363.1703); ν_{max} ($CHCl_3$)/cm^{-1}; 1684, 1602, 1531, 1501; δ_H (400 MHz; $CDCl_3$) 9.16 (1 H, s, NH), 8.11 (1 H, d, *J* 3.0, ArH), 7.50 - 7.57 (2 H, m, ArH), 7.33 - 7.45 (3 H, m, ArH), 7.17 - 7.24 (2 H, m, ArH), 6.79 - 6.85 (1 H, m, ArH), 6.76 (1 H, d, *J* 8.9, ArH), 6.72 (2 H, dd, *J* 8.5, 0.9, ArH), 6.57 (1 H, dd, *J* 8.9, 3.0, ArH), 4.89 (1 H, s, CH), 4.66 (1 H, br s, NH), 3.77 (3 H, s, OMe), 3.65 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 169.4 (C), 154.1 (C), 146.7 (C), 142.8 (C), 138.8 (C), 129.5 (CH), 128.9 (CH), 128.1 (C), 127.6 (CH), 119.5 (CH), 114.2 (CH), 111.8 (CH), 109.4 (CH), 105.9 (CH), 65.3 (CH), 56.8 (CH_3), 55.9 (CH_3), one CH signal was not observed.

_N_-Allyl-2-phenyl-2-(phenylamino)acetamide 169s



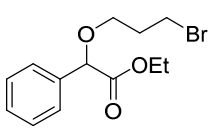
Obtained by **general procedure I** from hydrazone **100q** (c = 0.2 M, 2 mL), purified by column

chromatography using 15% ethyl acetate in light petroleum. Brown solid (113 mg, 78%); (Found: M+H$^+$, 267.1490. $C_{17}H_{19}N_2O$ requires 267.1492); mp 104-105 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3397, 1673, 1603, 1501; δ_H (400 MHz; $CDCl_3$) 7.44 - 7.49 (2 H, m, ArH), 7.32 - 7.43 (3 H, m, ArH), 7.20 (2 H, t, *J* 7.9, ArH), 6.82 (1 H, br s, N<u>H</u>), 6.81 (1 H, t, *J* 7.5, ArH), 6.65 (2 H, d, *J* 7.7, ArH), 5.71 - 5.84 (1 H, ddt, *J* 15.9, 10.7, 5.4, vinylic CH), 5.00 - 5.11 (2 H, m, vinylic CH_2), 4.78 (1 H, s, C<u>H</u>), 4.61 (1 H, br s, N<u>H</u>), 3.82 - 3.99 (2 H, m, C<u>H</u>$_2$); δ_C (100 MHz; $CDCl_3$) 171.2 (C), 146.7 (C), 139.0 (C), 133.9 (CH), 129.4 (CH), 129.3 (CH), 128.7 (CH), 127.4 (CH), 119.2 (CH), 116.4 (CH_2), 114.0 (CH), 64.2 (CH), 41.8 (CH_2).

III.3.2. Tandem oxidation in flow / O–H Insertion

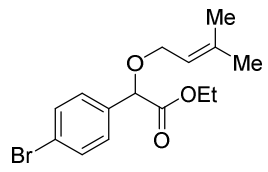
General procedure J: The solution of diazo compound in anhydrous dichloromethane (from 2 mL of 0.2 M hydrazone solution) was prepared following the **general procedure H** for the oxidation of hydrazone solution in flow and using the following parameters: residence time: 10 min, collected volume: 4.5 mL, packed reactor volume: 1 mL. The output solution was added to a solution of rhodium(II) octanoate dimer (3 mg, 4 μmol, 1 mol%) and the corresponding alcohol (1.2 eq) in anhydrous dichloromethane (1 mL) at reflux under argon. After addition, the resulting mixture was cooled to room temperature, the solvent removed under reduced pressure and the residue was purified by column chromatography.

Ethyl 2-(2-bromopropoxy)-2-phenylacetate 170a



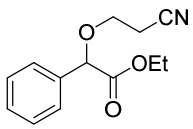
Obtained by the **general procedure J** hydrazone **100a** using 3-bromopropanol (43 μL, 0.48 mmol). Purified by column chromatography using 10% ethyl acetate in light petroleum. Colourless oil (97 mg, 73%); (Found: M+Na$^+$, 323.0233. $C_{13}H_{17}Na^{79}BrO_3$ requires 323.0259); ν_{max} ($CHCl_3$)/cm^{-1} 1746; δ_H (400 MHz; $CDCl_3$) 7.42 - 7.47 (2 H, m, ArH), 7.30 - 7.39 (3 H, m, ArH), 4.86 (1 H, s, CH), 4.21 (1 H, dq, *J* 10.4, 7.2, C<u>H</u>$_2$CH$_3$), 4.15 (1 H, dq, *J* 10.4, 7.2, C<u>H</u>$_2$CH$_3$), 3.69 (1 H, ddd, *J* 9.4, 6.1, 5.1, CH_2), 3.51 - 3.62 (3 H, m, CH_2), 2.13 - 2.23 (2 H, m, CH_2), 1.22 (3 H, t, *J* 7.2, CH_2C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 170.9 (C), 136.6 (C), 128.8 (CH), 128.7 (CH), 127.2 (CH), 81.5 (CH), 67.4 (CH_2), 61.4 (CH_2), 33.0 (CH_2), 30.6 (CH_2), 14.2 (CH_3).

Ethyl 2-(4-bromophenyl)-2-(3-methylbut-2-enyloxy)acetate 170b



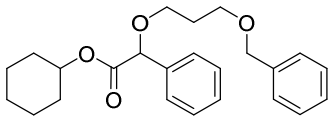
Obtained by **general procedure J** from hydrazone **100o** using 3-methyl-2-buten-1-ol (49 μL, 0.48 mmol). Purified by column chromatography using 5% ethyl acetate in light petroleum. Colourless oil (112 mg, 86%); (Found: M+Na$^+$, 349.0404. $C_{15}H_{19}{}^{79}BrNaO_3$ requires 349.0410); ν_{max} ($CHCl_3$)/cm^{-1} 1744; δ_H (400 MHz; $CDCl_3$) 7.45 - 7.51 (2 H, m, ArH), 7.31 - 7.37 (2 H, m, ArH), 5.37 (1 H, tqq, *J* 7.1, 2.8, 1.3, =CH), 4.85 (1 H, s, OC<u>H</u>), 4.10 - 4.24 (2 H, m, C<u>H</u>$_2$CH$_3$), 3.98 - 4.09 (2 H, m, CH_2), 1.75 (3 H, br s, CH_3), 1.62 (3 H, br s, CH_3), 1.18 - 1.24 (3 H, m, CH_2C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 170.8 (C), 138.7 (C), 136.0 (C), 131.8 (CH), 129.1 (CH), 122.7 (C), 120.2 (CH), 79.1 (CH), 66.1 (CH_2), 61.5 (CH_2), 26.0 (CH_3), 18.2 (CH_3), 14.2 (CH_3).

Ethyl 2-(2-cyanoethoxy)-2-phenylacetate 170c



Obtained by **general procedure J** from hydrazone **100a** using 3-hydroxypropionitrile (33 μL, 0.48 mmol). Purified by column chromatography using the elution gradient 20% to 40% ethyl acetate in light petroleum. Colourless oil (63 mg, 68%); (Found: M+Na$^+$, 256.0941. $C_{13}H_{15}NNaO_3$ requires 256.0944); ν_{max} ($CHCl_3$)/cm^{-1} 2257, 1751; δ_H (400 MHz; $CDCl_3$) 7.41 - 7.47 (2 H, m, ArH), 7.31 - 7.41 (3 H, m, ArH), 4.92 (1 H, s, CH), 4.21 (1 H, dq, *J* 10.8, 7.2, C$\underline{H}_2$CH$_3$), 4.15 (1 H, dq, *J* 10.8, 7.2, C$\underline{H}_2$CH$_3$), 3.78 (1 H, dt, *J* 9.2, 6.6, CH_2), 3.67 (1 H, dt, *J* 9.2, 6.6, CH_2), 2.68 (2 H, t, *J* 6.6, CH_2), 1.21 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 170.1 (C), 135.6 (C), 129.1 (CH), 128.8 (CH), 127.3 (CH), 117.5 (C), 81.4 (CH), 64.2 (CH_2), 61.6 (CH_2), 18.9 (CH_2), 14.1 (CH_3).

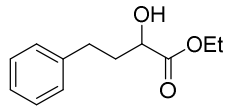
Cyclohexyl 2-(3-(benzyloxy)propoxy)-2-phenylacetate 170d



Obtained by **general procedure J** from hydrazone **100e** using 3-benzyloxy-1-propanol (76 μL, 0.48 mmol). Purified by column chromatography using 10% ethyl acetate in light petroleum. Yellow oil (128 mg, 84%); (Found: M+Na$^+$, 405.2033. $C_{24}H_{30}NaO_4$ requires 405.2036); ν_{max} ($CHCl_3$)/cm^{-1} 3010, 2940, 2863, 1740; δ_H (400 MHz; $CDCl_3$) 7.41 - 7.48 (2 H, m, ArH), 7.24 - 7.38 (8 H, m, ArH), 4.84 (1 H, s, CH), 4.81 (1 H, spt, *J* 3.8, cyclohexane CH), 4.44 - 4.55 (2 H, m, PhC$\underline{H}_2$O), 3.63 (2 H, t, *J* 6.3, CH_2), 3.55 - 3.73 (2 H, m, CH_2), 1.98 (2 H, quin, *J* 6.3, CH_2), 1.77 - 1.87 (1 H, m, cyclohexane CH_2), 1.63 - 1.74 (2 H, m, cyclohexane CH_2), 1.20 - 1.59 (7 H, m, cyclohexane CH_2); δ_C (100 MHz; $CDCl_3$) 170.6 (C), 138.7 (C), 137.1 (C),

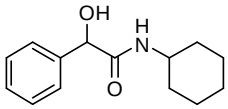
128.55 (CH), 128.50 (CH), 128.45 (CH), 127.7 (CH), 127.6 (CH), 127.2 (CH), 81.4 (CH), 73.4 (CH), 73.1 (CH_2), 67.3 (CH_2), 67.0 (CH_2), 31.6 (CH_2), 31.2 (CH_2), 30.2 (CH_2), 25.4 (CH_2), 23.6 (CH_2), 23.5 (CH_2).

Ethyl 2-hydroxy-4-phenylbutanoate 170e



Obtained by a modification of **general procedure J** from hydrazone **100ad** using water saturated ether (2 mL) at reflux instead of dichloromethane for the catalyst solution. Purified by column chromatography using 10% ethyl acetate in light petroleum. Colourless oil (66 mg, 83%); (Found: M+Na^+, 231.0991. $C_{12}H_{16}NaO_3$ requires 231.0992); ν_{max} ($CHCl_3$)/cm^{-1} 3537, 1728; δ_H (400 MHz; $CDCl_3$) 7.26 - 7.32 (2 H, m, ArH), 7.17 - 7.24 (3 H, m, ArH), 4.16 - 4.24 (1 H, m, CH), 4.22 (2 H, q, *J* 7.2, C<u>H</u>$_2$$CH_3$), 2.94 (1 H, br s, OH), 2.70 - 2.85 (2 H, m, CH_2), 2.13 (1 H, dddd, *J* 13.8, 9.6, 7.2, 4.0, CH_2), 1.96 (1 H, dddd, *J* 13.8, 9.1, 7.7, 6.0, CH_2), 1.29 (3 H, t, *J* 7.2, CH_2C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 175.4 (C), 141.3 (C), 128.7 (CH), 128.5 (CH), 126.1 (CH), 69.8 (CH), 61.9 (CH_2), 36.1 (CH_2), 31.2 (CH_2), 14.3 (CH_3). The data match those previously reported.[53]

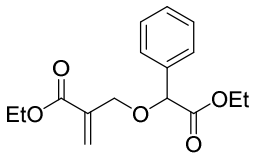
***N*-Cyclohexyl-2-hydroxy-2-phenylacetamide 170f**



Obtained by a modification of **general procedure J** from hydrazone **100t** using water saturated ether (2 mL) at reflux instead of dichloromethane for the catalyst solution. Purified by column chromatography using the elution gradient 20% to 50% ethyl acetate in light petroleum. Colourless solid (44 mg, 47%); mp 91-92 °C (lit.[54] no mp reported); (Found: C, 71.87; H, 8.32; N, 5.91.

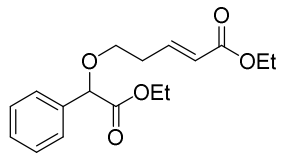
$C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00%); (Found: M+H$^+$, 234.1479. $C_{14}H_{20}NO_2$ requires 234.1489); ν_{max} ($CHCl_3$)/cm^{-1} 3694, 3609, 1669, 1523; δ_H (400 MHz; $CDCl_3$) 7.26 - 7.37 (5 H, m, ArH), 6.30 (1 H, d, *J* 8.0, NH), 4.89 (1 H, s, CH), 4.16 (1 H, br s, OH), 3.69 (1 H, dtt, *J* 8.0, 6.7, 3.8, C<u>H</u>N), 1.73 - 1.89 (2 H, m, cyclohexane CH_2), 1.50 - 1.73 (3 H, m, cyclohexane CH_2), 1.24 - 1.37 (2 H, m, cyclohexane CH_2), 1.00 - 1.20 (3 H, m, cyclohexane CH_2); δ_C (100 MHz; $CDCl_3$) 171.5 (C), 139.9 (C), 128.8 (CH), 128.5 (CH), 126.9 (CH), 74.1 (CH), 48.3 (CH), 32.94 (CH_2), 32.86 (CH_2), 25.5 (CH_2), 24.79 (CH_2), 24.77 (CH_2). The data match those previously reported.[54]

Ethyl 2-((2-ethoxy-2-oxo-1-phenylethoxy)methyl)acrylate 170g



Obtained by **general procedure J** from hydrazone **100a** using ethyl 2-(hydroxymethyl)acrylate (59 μL, 0.48 mmol). Purified by column chromatography using 5% ethyl acetate in light petroleum. Colourless oil (80 mg, 68%); (Found: M+Na$^+$, 315.1203. $C_{16}H_{20}NaO_5$ requires 315.1203); ν_{max} ($CHCl_3$)/cm^{-1} 1744, 1712; δ_H (400 MHz; $CDCl_3$) 7.44 - 7.50 (2 H, m, ArH), 7.30 - 7.40 (3 H, m, ArH), 6.34 (1 H, q, *J* 1.4, vinylic CH_2), 5.98 (1 H, q, *J* 1.4, vinylic CH_2), 4.96 (1 H, s, CH), 4.32 (1 H, dt, *J* 14.0, 1.4, CH_2) 4.10 - 4.27 (5 H, m, CH_2 and C<u>H</u>$_2$CH$_3$), 1.28 (3 H, t, *J* 7.0, CH$_2$C<u>H</u>$_3$), 1.22 (3 H, t, *J* 7.1, CH$_2$C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 170.8 (C), 165.8 (C), 136.8 (C), 136.5 (C), 128.8 (CH), 128.7 (CH), 127.3 (CH), 126.4 (CH_2), 81.0 (CH), 67.8 (CH_2), 61.4 (CH_2), 60.9 (CH_2), 14.3 (CH_3), 14.2 (CH_3).

Ethyl (*E*)-5-(2-ethoxy-2-oxo-1-phenylethoxy)pent-2-enoate 170h



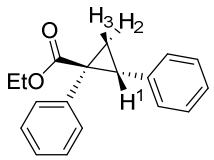
Obtained by **general procedure J** from hydrazone **100a** using ethyl (*E*)-5-hydroxypent-2-enoate[55] (69 mg, 0.48 mmol). Purified by column chromatography using 10% ethyl acetate in light petroleum. Colourless oil (104 mg, 85%); (Found: M+Na$^+$, 329.1359. $C_{17}H_{22}NNaO_5$ requires 329.1371); ν_{max} ($CHCl_3$)/cm^{-1} 3514, 1741, 1736; δ_H (400 MHz; $CDCl_3$) 7.40 - 7.47 (2 H, m, ArH), 7.28 - 7.39 (3 H, m, ArH), 6.96 (1 H, dt, *J* 15.6, 6.8, CH), 5.90 (1 H, dt, *J* 15.6, 1.4, CH), 4.85 (1 H, s, OCH), 4.08 - 4.27 (4 H, m, C$\underline{H}_2$CH$_3$), 3.67 (1 H, dt, *J* 9.1, 6.8, OCH$_2$), 3.55 (1 H, dt, *J* 9.1, 6.8, OCH$_2$), 2.56 (2 H, qd, *J* 6.8, 1.4, CH$_2$), 1.27 (3 H, t, *J* 7.1, CH$_2$C$\underline{H}_3$), 1.21 (3 H, t, *J* 7.1, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 170.8 (C), 166.5 (C), 145.1 (CH), 136.5 (C), 128.8 (CH), 128.7 (CH), 127.3 (CH), 123.3 (CH), 81.4 (CH), 67.9 (CH$_2$), 61.4 (CH$_2$), 60.4 (CH$_2$), 32.6 (CH$_2$), 14.4 (CH$_3$), 14.2 (CH$_3$).

III.3.3. Tandem oxidation in flow / cyclopropanation

General procedure K: the solution of diazo compound in anhydrous dichloromethane (from 2 mL of 0.2 M hydrazone solution) was prepared following the **general procedure H** for the oxidation of hydrazone solution in flow and using the following parameters: residence time: 10 min, collected volume: 4.5 mL, packed reactor volume: 1 mL. The output solution was added to a solution of styrene (55 µL, 0.48 mmol) and rhodium(II) octanoate dimer (3 mg, 4 µmol, 1 mol%) in anhydrous dichloromethane (1 mL) at reflux under argon. After addition, the resulting mixture was cooled down to room temperature, the solvent

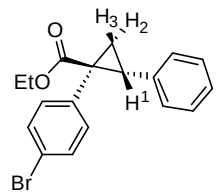
removed under reduced pressure and the residue purified by column chromatography.

Ethyl *trans*-1,2-diphenylcyclopropanecarboxylate 171a



Obtained by **general procedure K** from hydrazone **100a**. Purified by column chromatography using 2% ethyl acetate in light petroleum. Colourless oil (61 mg, 57%); (Found: M+Na$^+$, 289.1196. $C_{18}H_{18}NaO_2$ requires 289.1199); ν_{max} ($CHCl_3$)/cm^{-1} 3009, 1707, 1260; δ_H (400 MHz; $CDCl_3$) 7.10 - 7.16 (3 H, m, ArH), 7.00 - 7.10 (5 H, m, ArH), 6.74 - 6.83 (2 H, m, ArH), 4.06 - 4.24 (2 H, m, C$\underline{H}_2$CH$_3$), 3.12 (1 H, dd, *J* 9.3, 7.3, H1), 2.15 (1 H, dd, *J* 9.3, 4.9, H3), 1.89 (1 H, dd, *J* 7.3, 4.9, H2), 1.19 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 173.8 (C), 136.6 (C), 135.0 (C), 132.0 (CH), 128.1 (CH), 127.8 (CH), 127.7 (CH), 127.0 (CH), 126.3 (CH), 61.4 (CH_2), 37.7 (C), 33.0 (CH), 20.2 (CH_2), 14.3 (CH_3). The data obtained match those previously reported.[56]

Ethyl *trans*-1-(4-bromophenyl)-2-phenylcyclopropanecarboxylate 171b

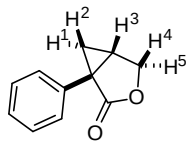


Obtained by **general procedure K** from hydrazone **100o**. Purified by column chromatography using 2% ethyl acetate in light petroleum. Yellow oil that solidified upon standing (134 mg, 97%); mp 85 - 87 °C; (Found: M+Na$^+$, 367.0307. $C_{18}H_{17}{}^{79}BrNaO_2$ requires 367.0304); ν_{max} ($CHCl_3$)/cm^{-1} 1710, 1258; δ_H (400 MHz; $CDCl_3$) 7.22 - 7.28 (2 H, m, ArH), 7.05 - 7.13 (3 H, m, ArH), 6.87 - 6.93 (2 H, m, ArH), 6.75 - 6.82 (2 H, m, ArH), 4.05 - 4.22 (2 H, m, C$\underline{H}_2$CH$_3$), 3.11 (1 H, dd, *J* 9.3, 7.4, H1), 2.14 (1 H, dd, *J* 9.3, 5.0, H3), 1.84 (1 H, dd, *J* 7.4, 5.0, H2), 1.19 (3 H, t, *J* 7.1, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$)

173.3 (C), 136.1 (C), 134.2 (C), 133.7 (CH), 130.9 (CH), 128.1 (CH), 128.0 (CH), 126.6 (CH), 121.2 (C), 61.5 (CH_2), 37.1 (C), 33.1 (CH), 20.1 (CH_2), 14.3 (CH_3).

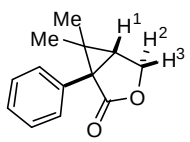
General procedure L: the solution of diazo compound in anhydrous dichloromethane (from 2 mL of 0.2 M hydrazone solution) was prepared following the **general procedure H** for the oxidation of hydrazone solution in flow and using the following parameters: residence time: 10 min, collected volume: 4.5 mL, packed reactor volume: 1 mL. The output solution was added to a solution of rhodium(II) octanoate dimer (3 mg, 4 μmol, 1 mol%) in anhydrous dichloromethane (1 mL) at reflux under argon. After addition, the resulting mixture was cooled to room temperature, the solvent removed under reduced pressure and the residue purified by column chromatography.

***cis*-1-Phenyl-3-oxabicyclo[3.1.0]hexan-2-one 173a**



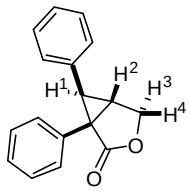
Obtained by **general procedure L** from hydrazone **100h**. Purified by column chromatography using 20 % ethyl acetate in light petroleum to give the *title compound* as a colourless oil (42 mg, 60%); (Found: M+H$^+$, 175.0755. $C_{11}H_{11}O_2$ requires 175.0754); ν_{max} ($CHCl_3$)/cm^{-1} 1767; δ_H (400 MHz; $CDCl_3$) 7.43 (2 H, d, *J* 7.3, ArH), 7.35 (2 H, t, *J* 7.3, ArH), 7.27 - 7.32 (1 H, m, ArH), 4.46 (1 H, dd, *J* 9.3, 4.7, H4), 4.29 (1 H, d, *J* 9.3, H5), 2.56 (1 H, dt, *J* 7.8, 4.7, H3), 1.65 (1 H, dd, *J* 7.8, 4.7, H1), 1.36 (1 H, t, *J* 4.7, H2); δ_C (100 MHz; $CDCl_3$) 176.2 (C), 134.2 (C), 128.7 (CH), 128.4 (CH), 127.8 (CH), 68.2 (CH_2), 31.8 (C), 25.2 (CH), 20.3 (CH_2). The data obtained match those previously reported.[46]

cis-6,6-Dimethyl-1-phenyl-3-oxabicyclo[3.1.0]hexan-2-one 173b



Obtained by **general procedure L** from hydrazone **100i**. Purified by column chromatography using 15 % ethyl acetate in light petroleum to give the *title compound* as a colourless solid (69 mg, 85%); mp 51 - 52 °C (mp lit.[45-46] not reported); (Found: M+Na$^+$, 225.0874. $C_{13}H_{14}NaO_2$ requires 225.0886); ν_{max} ($CHCl_3$)/cm^{-1} 1761, 1177; δ_H (400 MHz; $CDCl_3$) 7.27 - 7.42 (5 H, m, ArH), 4.52 (1 H, dd, *J* 9.8, 5.4, H3), 4.25 (1 H, dd, *J* 9.8, 0.7, H2), 2.39 (1 H, dd, *J* 5.4, 0.7, H1), 1.32 (3 H, s, CH_3), 0.87 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 175.1 (C), 132.9 (C), 129.8 (CH), 128.5 (CH), 127.8 (CH), 65.5 (CH_2), 42.2 (C), 33.2 (CH), 27.7 (C), 22.8 (CH_3), 15.8 (CH_3). The data obtained match those previously reported.[45-46]

cis,cis-1,6-Diphenyl-3-oxabicyclo[3.1.0]hexan-2-one 173c

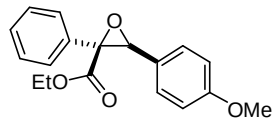


Obtained by **general procedure L** from hydrazone **100j** Purified by column chromatography using 15 % ethyl acetate in light petroleum to give the *title compound* as a colourless solid (85 mg, 85%); mp 112 - 113 °C (mp lit.[46] not reported); (Found: M+Na$^+$, 273.0877. $C_{17}H_{14}NaO_2$ requires 273.0886); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 1769; δ_H (400 MHz; $CDCl_3$) 7.15 - 7.25 (5 H, m, ArH), 7.06 - 7.14 (3 H, m, ArH), 6.79 - 6.90 (2 H, m, ArH), 4.63 (1 H, dd, *J* 9.3, 4.5, H4), 4.50 (1 H, d, *J* 9.3, H3), 3.10 (1 H, t, *J* 4.5, H2), 2.72 (1 H, d, *J* 4.5, H1); δ_C (100 MHz; $CDCl_3$) 175.5 (C), 133.8 (C), 130.7 (CH), 129.9 (C), 128.3 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.1 (CH), 68.5 (CH_2), 40.1 (C), 35.5 (CH), 27.5 (CH). The data obtained match those previously reported.[46]

III.3.4. Tandem oxidation in flow/ epoxide formation

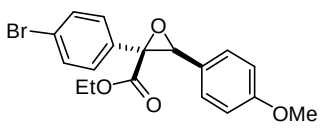
General procedure M: the solution of diazo compound in anhydrous dichloromethane (from 2 mL of 0.2 M hydrazone solution) was prepared following the **general procedure H** for the oxidation of hydrazone solution in flow and using the following parameters: residence time: 10 min, collected volume: 4.5 mL, packed reactor volume: 1 mL. The output solution was added to a solution of aldehyde (0.48 mmol) and rhodium(II) octanoate dimer (3 mg, 4 μmol, 1 mol%) in anhydrous dichloromethane (1 mL) at reflux under argon. After addition, the resulting mixture was cooled to room temperature, the solvent removed under reduced pressure and the residue purified by column chromatography.

Ethyl *cis*-3-(4-methoxyphenyl)-2-phenyloxirane-2-carboxylate 174a



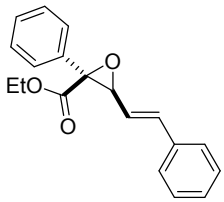
Obtained by **general procedure M** from hydrazone **100a** and *p*-anisaldehyde (58 μL, 0.48 mmol). Purified by column chromatography using 5% to 10% ethyl acetate in light petroleum. Colourless oil (92 mg, 77%); (Found: M+Na$^+$, 321.1088. $C_{18}H_{18}NaO_4$ requires 321.1097); ν_{max} ($CHCl_3$)/cm^{-1} 1737, 1516, 1250; δ_H (400 MHz; $CDCl_3$) 7.61 - 7.68 (2 H, m, ArH), 7.30 - 7.45 (5 H, m, ArH), 6.90 (2 H, d, *J* 8.7, ArH), 4.10 (1 H, s, CH), 4.00 - 4.09 (2 H, m, C$\underline{H}_2$CH$_3$), 3.81 (3 H, s, CH$_3$), 1.05 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 166.8 (C), 160.0 (C), 135.0 (C), 128.8 (CH), 128.6 (CH), 127.5 (CH), 126.3 (CH), 126.0 (C), 113.9 (CH), 67.0 (C), 65.8 (CH), 61.5 (CH$_2$), 55.4 (CH$_3$), 14.0 (CH$_3$).

Ethyl *cis*-2-(4-bromophenyl)-3-(4-methoxyphenyl)oxirane-2-carboxylate 174b



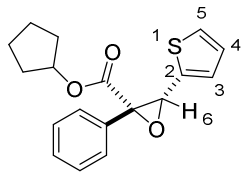
Obtained by **general procedure M** from hydrazone **100o** and *p*-anisaldehyde (58 μL, 0.48 mmol). Purified by column chromatography using 5% to 10% ethyl acetate in light petroleum. Colourless solid (126 mg, 84%); mp 50 - 51 °C; (Found: M+Na$^+$, 399.0197. $C_{18}H_{17}{}^{79}BrNaO_4$ requires 399.0202); ν_{max} ($CHCl_3$)/cm^{-1} 1738, 1614, 1516, 1251; δ_H (400 MHz; $CDCl_3$) 7.53 (4 H, s, ArH), 7.31 (2 H, d, *J* 8.6, ArH), 6.88 (2 H, d, *J* 8.6, ArH), 3.97 - 4.11 (3 H, m, C$\underline{H}_2$CH$_3$ and CH), 3.81 (3 H, s, CH_3), 1.05 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 166.5 (C), 160.1 (C), 134.1 (C), 131.8 (CH), 128.0 (CH), 127.6 (CH), 125.6 (C), 123.0 (C), 113.9 (CH), 66.5 (C), 66.0 (CH), 61.7 (CH_2), 55.4 (CH_3), 14.0 (CH_3).

Ethyl *cis*-2-phenyl-3-((*E*)-styryl)oxirane-2-carboxylate 174c



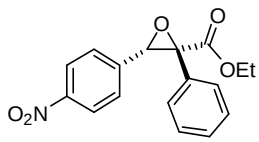
Obtained by **general procedure M** from hydrazone **100a** and cinnamaldehyde (60 μL, 0.48 mmol). Purified by column chromatography using 2% ethyl acetate in light petroleum. Pale yellow oil (76 mg, 67%); (Found: M+Na$^+$, 317.1155. $C_{19}H_{18}NaO_3$ requires 317.1148); ν_{max} ($CHCl_3$)/cm^{-1} 1736, 1602, 1193; δ_H (400 MHz; $CDCl_3$) 7.57 - 7.67 (2 H, m, ArH), 7.27 - 7.45 (8 H, m, ArH), 6.90 (1 H, br d, *J* 15.9, CH), 6.12 (1 H, dd, *J* 15.9, 7.7, CH), 4.30 (2 H, q, *J* 7.2, C$\underline{H}_2$CH$_3$), 3.73 (1 H, dd, *J* 7.7, 0.6, CH), 1.30 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 167.8 (C), 137.1 (CH), 135.9 (C), 135.0 (C), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 126.8 (CH), 126.6 (CH), 122.1 (CH), 65.8 (CH), 65.6 (C), 62.0 (CH_2), 14.4 (CH_3).

Cyclopentyl *cis*-2-phenyl-3-(2-thienyl)oxirane-2-carboxylate 174d



Obtained by **general procedure M** from hydrazone **100d** and 2-thiophenecarboxaldehyde (45 μL, 0.48 mmol). Purified by column chromatography using 3% ethyl acetate in light petroleum. Colourless oil (66 mg, 52%); (Found: M+Na$^+$, 337.0864. $C_{18}H_{18}NaO_3S$ requires 337.0869); ν_{max} ($CHCl_3$)/cm^{-1} 1737; δ_H (400 MHz; $CDCl_3$) 7.59 - 7.65 (2 H, m, ArH), 7.33 - 7.44 (3 H, m, ArH), 7.29 (1 H, dd, *J* 5.0, 1.3, H5), 7.14 (1 H, ddd, *J* 3.5, 1.3, 0.8, H3), 7.01 (1 H, dd, *J* 5.0, 3.5, H4), 5.15 (1 H, tt, *J* 6.0, 2.8, cyclopentane CH), 4.27 (1 H, d, *J* 0.8, H6), 1.27 - 1.86 (8 H, m, cyclopentane CH_2); δ_C (100 MHz; $CDCl_3$) 166.3 (C), 137.1 (C), 134.5 (C), 128.9 (CH), 128.7 (CH), 127.1 (CH), 126.3 (CH), 126.2 (CH), 125.9 (CH), 79.0 (CH), 67.6 (C), 62.7 (CH), 32.6 (CH_2), 32.4 (CH_2), 23.8 (CH_2), 23.6 (CH_2).

Ethyl *cis*-3-(4-nitrophenyl)-2-phenyloxirane-2-carboxylate 174e

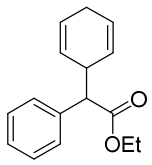


Obtained by **general procedure M** from hydrazone **100a** and *p*-nitrobenzaldehyde (73 mg, 0.48 mmol). Purified by column chromatography using 5% ethyl acetate in light petroleum. Colourless solid (58 mg, 46%); mp 95 - 96 °C (Found: M+Na$^+$, 336.0842. $C_{17}H_{15}NNaO_5$ requires 336.0842); ν_{max} ($CHCl_3$)/cm^{-1} 1744, 1526, 1349; δ_H (400 MHz; $CDCl_3$) 8.20 - 8.28 (2 H, m, ArH), 7.56 - 7.68 (4 H, m, ArH), 7.38 - 7.50 (3 H, m, ArH), 4.23 (1 H, s, CH), 3.96 - 4.09 (2 H, m, C$\underline{H}_2$CH$_3$), 1.02 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 166.0 (C), 148.2 (C), 141.1 (C), 134.0 (C), 129.3 (CH), 128.9 (CH), 127.3 (CH), 126.3 (CH), 123.7 (CH), 67.3 (C), 64.7 (CH), 61.9 (CH_2), 14.1 (CH_3).

III.3.5. Tandem oxidation in flow / C–H insertion

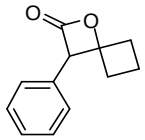
General procedure N: the solution of diazo compound in anhydrous dichloromethane (from 2 mL of 0.2 M hydrazone solution) was prepared following the **general procedure H** for the oxidation of hydrazone solution in flow and using the following parameters: residence time: 10 min, collected volume: 4.5 mL, packed reactor volume: 1 mL. The output solution was added to a solution of rhodium(II) octanoate dimer (3 mg, 4 μmol, 1 mol%) in anhydrous dichloromethane (1 mL) at reflux under argon. For intermolecular C-H insertion, the solution also contained the corresponding insertion reaction partner. After addition, the resulting mixture was cooled to room temperature, the solvent removed under reduced pressure and the residue purified by column chromatography.

Ethyl 2-(cyclohexa-2,5-dienyl)-2-phenylacetate 175



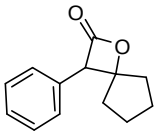
Obtained by **general procedure N** from hydrazone **100a** using cyclohexa-1,4-diene (76 μL, 0.8 mmol), purified by column chromatography using 3% ethyl acetate in light petroleum. Colourless liquid (46 mg, 47%); (Found: M+Na$^+$, 265.1194. $C_{16}H_{18}NaO_2$ requires 265.1204); ν_{max} ($CHCl_3$)/cm^{-1}; 3011, 2984, 1725, 1273, 1160; δ_H (400 MHz; $CDCl_3$), 7.22 - 7.41 (5 H, m, ArH), 5.64 - 5.86 (3 H, m, CH), 5.23 - 5.30 (1 H, m, CH), 4.05 - 4.24 (2 H, m, C$\underline{H}_2$CH$_3$), 3.43 - 3.55 (1 H, m, CH), 3.40 (1 H, d, *J* 10.4, CH), 2.57 - 2.65 (2 H, m, CH_2), 1.22 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 173.1 (C), 137.0 (C), 128.8 (CH), 128.6 (CH), 127.4 (CH), 126.8 (CH), 126.3 (CH), 126.1 (CH), 125.9 (CH), 60.9 (CH_2), 58.6 (CH), 38.7 (CH), 26.5 (CH_2), 14.3 (CH_3). The data obtained match those previously reported.[57]

3-Phenyl-1-oxaspiro[3.3]heptan-2-one 176a



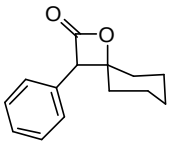
Obtained by **general procedure N** from hydrazone **100c**. Purified by column chromatography using 20% ethyl acetate in light petroleum. Colourless oil (46 mg, 61%); (Found: M+Na$^+$, 211.0732. $C_{12}H_{12}NaO_2$ requires 211.0730); ν_{max} ($CHCl_3$)/cm^{-1} 3044, 2942, 1819, 1066; δ_H (400 MHz; $CDCl_3$) 7.31 - 7.45 (3 H, m, ArH), 7.15 - 7.23 (2 H, m, ArH), 4.67 (1 H, s, CH), 2.68 - 2.79 (1 H, m, CH_2), 2.50 (1 H, ddtd, *J* 12.8, 8.5, 4.3, 1.0, CH_2), 2.30 - 2.41 (1 H, m, CH_2), 1.82 - 1.96 (2 H, m, CH_2), 1.50 (1 H, ddq, *J* 11.3, 9.5, 8.5, CH_2); δ_C (100 MHz; $CDCl_3$) 169.0 (C), 131.9 (C), 129.2 (CH), 128.4 (CH), 128.2 (CH), 83.9 (C), 63.7 (CH), 34.4 (CH_2), 29.5 (CH_2), 12.1 (CH_2).

3-Phenyl-1-oxaspiro[3.4]octan-2-one 176b



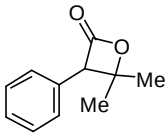
Obtained by **general procedure N** from hydrazone **100d**. Purified by column chromatography using 2% ethyl acetate in light petroleum. Colourless oil (26 mg, 32%); (Found: M+H$^+$, 203.1073. $C_{13}H_{15}O_2$ requires 203.1067); ν_{max} ($CHCl_3$)/cm^{-1} 2967, 1812, 1498, 1453, 1338, 1129; δ_H (400 MHz; $CDCl_3$) 7.28 - 7.43 (3 H, m, ArH), 7.17 - 7.23 (2 H, m, ArH), 4.78 (1 H, s, CH), 2.23 - 2.36 (1 H, m, CH_2), 2.09 (1 H, dt, *J* 14.4, 8.2, CH_2), 1.37 - 1.94 (6 H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 169.9 (C), 132.2 (C), 129.2 (CH), 128.3 (CH), 92.6 (C), 61.6 (CH), 38.1 (CH_2), 33.2 (CH_2), 23.9 (CH_2), 23.5 (CH_2), one aromatic CH signal was not observed.

3-Phenyl-1-oxaspiro[3.5]nonan-2-one 176c



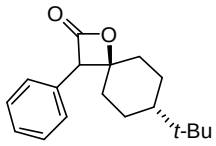
Obtained by **general procedure N** from hydrazone **100e**. Purified by column chromatography using 2% ethyl acetate in light petroleum. Colourless oil (60 mg, 70%); (Found: M+Na$^+$, 239.1032. $C_{14}H_{16}NaO_2$ requires 239.1043); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2941, 1810, 1498, 1450, 1192, 1149, 1122, 879; δ_H (400 MHz; $CDCl_3$) 7.28 - 7.40 (3 H, m, ArH), 7.19 - 7.24 (2 H, m, ArH), 4.49 (1 H, s, CH), 2.01 - 2.11 (1 H, m, CH_2), 1.89 - 1.99 (1 H, m, CH_2), 1.43 - 1.82 (6 H, m, CH_2), 1.21 - 1.40 (2 H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 170.0 (C), 131.0 (C), 128.8 (CH), 128.2 (CH), 83.8 (C), 64.0 (CH), 37.7 (CH_2), 32.3 (CH_2), 24.7 (CH_2), 23.3 (CH_2), 22.1 (CH_2), one aromatic CH signal was not observed. The data obtained match those previously reported.[58]

4,4-Dimethyl-3-phenyloxetan-2-one 176d



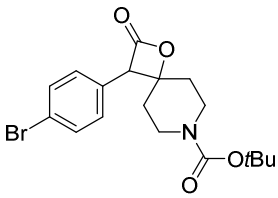
Obtained by **general procedure N** from hydrazone **100b**. Purified by column chromatography using 2% ethyl acetate in light petroleum. Colourless oil (50 mg, 71%); (Found: M+Na$^+$, 199.0731. $C_{11}H_{12}NaO_2$ requires 199.0730); ν_{max} ($CHCl_3$)/cm^{-1} 2981, 1811, 1268, 1244, 1071; δ_H (400 MHz; $CDCl_3$) 7.30 - 7.41 (3 H, m, ArH), 7.18 - 7.24 (2 H, m, ArH), 4.63 (1 H, s, CH), 1.77 (3 H, s, CH_3), 1.21 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 169.2 (C), 131.7 (C), 129.1 (CH), 128.2 (CH), 128.1 (CH), 81.8 (C), 64.0 (CH), 28.0 (CH_3), 23.3 (CH_3). The data obtained match those previously reported.[59]

trans-7-_tert_-Butyl-3-phenyl-1-oxaspiro[3.5]nonan-2-one 176e



Obtained by **general procedure N** from hydrazone **100f**. Purified by column chromatography using 2% ethyl acetate in light petroleum. yellow oil that solidifies upon standing (73 mg, 68%); mp 83 - 85 °C; (Found: M+H$^+$, 273.1835. $C_{18}H_{25}O_2$ requires 273.1849); ν_{max} ($CHCl_3$)/cm^{-1} 2959, 2864, 1814, 1368, 1033; δ_H (400 MHz; $CDCl_3$) 7.32 - 7.43 (3 H, m, ArH), 7.21 - 7.29 (2 H, m, ArH), 4.51 (1 H, s, CH), 2.13 (1 H, dq, *J* 12.2, 3.4, CH_2), 1.87 - 2.07 (3 H, m, CH_2), 1.71 (1 H, td, *J* 13.5, 4.6, CH_2), 1.32 - 1.41 (1 H, m, CH_2), 1.17 - 1.31 (1 H, m, CH_2), 1.03 (1 H, tt, *J* 12.2, 3.4, CH), 0.78 (9 H, s, *t*Bu), 0.39 (1 H, qd, *J* 13.5, 4.0, CH_2); δ_C (100 MHz; $CDCl_3$) 169.9 (C), 131.0 (C), 129.7 (CH), 128.8 (CH), 128.5 (CH), 83.7 (C), 64.1 (CH), 46.1 (CH), 38.3 (CH_2), 32.4 (C), 31.7 (CH_2), 27.5 (CH_3), 24.9 (CH_2), 23.5 (CH_2). The *cis*-isomer of this compound has previously been reported.[60]

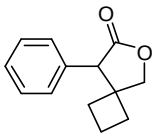
tert-Butyl 3-(4-bromophenyl)-2-oxo-1-oxa-7-azaspiro[3.5]nonane-7-carboxylate 176f



Obtained by **general procedure N** from hydrazone **100p**. Purified by column chromatography using 20% ethyl acetate in light petroleum. Colourless solid (92 mg, 58%); mp 130 - 132 °C; (Found: M+Na$^+$, 418.0609. $C_{18}H_{22}{}^{79}BrNNaO_4$ requires 418.0624); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2981, 1818, 1687, 1427, 1161; a rotameric mixture was obtained in deuterated chloroform at room temperature, giving broad or overlapping signals in ^{1}H and ^{13}C NMR experiments; δ_H (400 MHz; $CDCl_3$) 7.52 (2 H, d, *J* 8.4, ArH), 7.08 (2 H, d, *J* 8.4, ArH), 4.54 (1 H, s, CH), 3.90 - 4.05 (1 H, m, CH_2),

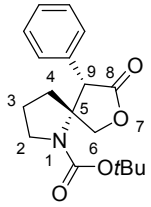
3.63 - 3.85 (1 H, m, CH_2), 3.16 - 3.29 (1 H, m, CH_2), 2.94 - 3.14 (1 H, m, CH_2), 1.99 - 2.12 (2 H, m, CH_2), 1.43 (9 H, s, *t*Bu), 1.32 - 1.66 (2 H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 168.2 (C), 154.5 (C), 132.4 (CH), 130.2 (CH), 129.1 (C), 122.7 (C), 81.4 (C), 80.2 (C), 63.3 (CH), 36.6 (CH_2), 32.2 (CH_2), 28.5 (CH_3).

8-Phenyl-6-oxaspiro[3.4]octan-7-one 177a



Obtained by **general procedure N** from hydrazone **100g**. Purified by column chromatography using 10% ethyl acetate in light petroleum. Colourless solid (38 mg, 47%); mp 101 - 102 °C; (Found: M+Na$^+$, 225.0895. $C_{13}H_{14}NaO_2$ requires 225.0886); ν_{max} ($CHCl_3$)/cm^{-1} 3067, 2986, 1770, 1366, 1126, 1014; δ_H (400 MHz; $CDCl_3$) 7.29 - 7.43 (3 H, m, ArH), 7.12 - 7.19 (2 H, m, ArH), 4.48 (1 H, d, *J* 8.9, OCH_2), 4.29 (1 H, d, *J* 8.9, OCH_2), 3.61 (1 H, s, CH), 2.00 - 2.22 (2 H, m, cyclobutane CH_2), 1.66 - 1.91 (3 H, m, cyclobutane CH_2), 1.47 - 1.60 (1 H, m, cyclobutane CH_2); δ_C (100 MHz; $CDCl_3$) 177.0 (C), 133.9 (C), 129.6 (CH), 128.8 (CH), 127.8 (CH), 77.5 (CH_2), 55.7 (CH), 47.9 (C), 30.1 (CH_2), 27.5 (CH_2), 15.9 (CH_2).

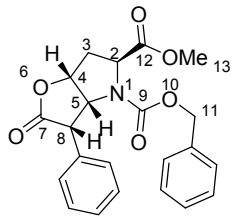
***tert*-Butyl (*5R,9S*)-8-oxo-9-phenyl-7-oxa-1-azaspiro[4.4]nonane-1-carboxylate 177b**



Obtained by **general procedure N** from hydrazone **100k**. Purified by column chromatography using 20% ethyl acetate in light petroleum. Colourless solid (71 mg, 56%); mp 174 - 175 °C; $[\alpha]_D^{24}$ +229.7 (*c* 1.50, $CHCl_3$), (Found: M+Na$^+$, 340.1493. $C_{18}H_{23}NNaO_4$ requires 340.1525); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2928, 1771, 1688, 1394, 1151; Two rotamers were observed in deuterated

chloroform at room temperature (ratio 70:30), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**). H NMR in DMSO-d_6 showed coalescence above 70 °C, δ_H (400 MHz; $CDCl_3$) 7.25 - 7.39 (5 H, m, ArH **majR**; 5 H, m, ArH **minR**), 4.65 (1 H, d, *J* 9.9, H6 **majR**), 4.58 (1 H, d, *J* 10.2, H6 **minR**), 4.42 (1 H, d, *J* 10.2, H6 **minR**), 4.37 (1 H, d, *J* 9.9, H6 **majR**), 3.77 (1 H, s, H9 **majR**), 3.74 (1 H, s, H9 **minR**), 3.35 (1 H, q, *J* 9.0, H2 **minR**), 3.25 (1 H, dt, *J* 10.5, 7.9, H2 **majR**), 2.67 - 2.81 (1 H, m, H2 **majR**; 1 H, m, H2 **minR**), 2.29 - 2.40 (1 H, m, H4 **majR**; 1 H, m, H4 **minR**), 2.10 - 2.29 (1 H, m, H4 **majR**; 1 H, m, H4 **minR**), 1.59 - 1.69 (2 H, m, H3 **majR**; 2 H, m, H3 **minR**), 1.58 (9 H, s, *t*Bu **minR**), 1.43 (9 H, s, *t*Bu **majR**); δ_H (270 MHz; DMSO-d_6, 90 °C) 7.26 - 7.35 (5 H, m, ArH), 4.48 (1 H, d, *J* 10.1, H6), 4.39 (1 H, d, *J* 10.1, H6), 4.14 (1 H, s, H9), 3.23 (1 H, dt, *J* 10.5, 7.7, H2), 2.59 (1 H, ddd, *J* 10.5, 8.2, 4.3, H2), 2.42 (1 H, ddd, *J* 13.0, 6.9, 4.3, H4), 2.18 (1 H, ddd, *J* 13.0, 9.9, 7.4, H4), 1.44 - 1.69 (2 H, m, H3), 1.42 (9 H, s, *t*Bu); δ_C (100 MHz; $CDCl_3$) 176.0 (C **minR**), 175.7 (C **majR**), 154.2 (C **majR**), 153.4 (C **minR**), 132.8 (C **majR**), 132.5 (C **minR**), 130.7 (CH **majR**), 130.2 (CH **minR**), 128.7 (CH **minR**), 128.4 (CH **majR**), 128.3 (CH **minR**), 128.0 (CH **majR**), 82.8 (C **minR**), 80.2 (C **majR**), 75.2 (CH_2 **majR**), 75.0 (CH_2 **minR**), 68.5 (C **majR**), 68.2 (C **minR**), 56.9 (CH **minR**), 56.0 (CH **majR**), 48.8 (CH_2 **minR**), 48.2 (CH_2 **majR**), 42.2 (CH_2 **minR**), 40.4 (CH_2 **majR**), 28.5 (CH_3 **majR** and **minR**), 22.1 (CH_2 **majR**), 21.2 (CH_2 **minR**).

4-Benzyl 5-methyl (*2S,4R,5R,8R*)-2-oxo-3-phenylhexahydro-*4H*-furo[3,2-b]pyrrole-4,5-dicarboxylate 177c

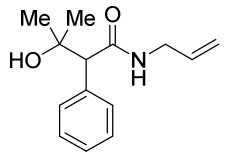


Obtained by **general procedure N** from hydrazone **100l**. Purified by column chromatography using the elution gradient 30% to 50% ethyl acetate in light petroleum. Yellow gum (33 mg, 21%); $[\alpha]_D^{24}$ −72.6 (c 1.50, $CHCl_3$); (Found: M+Na$^+$, 418.1266. $C_{22}H_{21}NNaO_6$ requires 418.1261); ν_{max} ($CHCl_3$)/cm^{-1} 2928, 1785, 1749, 1709, 1412, 1354, 1150; a mixture of two rotamers was obtained in deuterated chloroform at room temperature (ratio 56:44), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**). H NMR in DMSO d-6 showed coalescence at 90 °C; δ_H (400 MHz; $CDCl_3$) 7.24 - 7.40 (6 H, m, ArH **majR**; 6 H, m, ArH **minR**), 7.12 - 7.19 (2 H, m, ArH **majR**; 2 H, m, ArH **minR**), 7.06 - 7.11 (2 H, m, ArH **minR**), 7.01 (2 H, dd, *J* 6.4, 2.9, ArH **majR**), 5.21 - 5.32 (1 H, m, H4 **majR**; 1 H, m, H4 **minR**), 5.17 (1 H, dd, *J* 8.8, 7.7, H5 **minR**), 5.08 (1 H, dd, *J* 8.1, 6.9, H5 **majR**), 4.90 (1 H, d, *J* 12.1, H11 **majR**), 4.84 (1 H, d, *J* 12.3, H11 minor **minR**), 4.75 (1 H, d, *J* 12.3, H11 **minR**), 4.38 (1 H, t, *J* 7.3, H2 **majR**), 4.23 (1 H, d, *J* 8.8, H8 **minR**), 4.21 (1 H, dd, *J* 7.3, 5.7, H2 **minR**), 4.06 (1 H, d, *J* 8.1, H8 **majR**), 3.97 (1 H, d, *J* 12.1, H11 **majR**), 3.75 (3 H, s, H13 **majR**), 3.46 (3 H, s, H13 **minR**), 2.59 (1 H, ddd, *J* 14.2, 7.3, 3.5, H3 **majR**), 2.38 - 2.52 (1 H, m, H3 **majR**; 2 H, m, H3 **minR**); δ_C (100 MHz; $CDCl_3$) 176.4 (C **minR**), 175.9 (C **majR**), 172.0 (C **minR**), 171.6 (C **majR**), 153.8 (C **minR**), 153.6 (C **majR**), 135.7 (C **minR**), 135.6 (C **majR**), 133.31 (C **minR**), 133.27 (C **majR**), 129.9 (CH **majR**), 129.8 (CH **minR**), 128.8 (CH **majR**), 128.53 (CH **majR**), 128.51 (CH **minR**), 128.48

(CH **majR**), 128.3 (CH **majR**), 128.21 (CH **majR**), 128.18 (CH **minR**), 128.1 (CH **minR**), 127.9 (CH **minR**), 80.3 (CH **majR**), 78.7 (CH **minR**), 67.5 (CH_2 **minR**), 67.3 (CH_2 **majR**), 61.9 (CH **minR**), 61.8 (CH **majR**), 59.3 (CH **majR**), 59.2 (CH **minR**), 52.8 (CH_3 **majR**), 52.5 (CH_3 **minR**), 51.9 (CH **majR**), 51.3 (CH **minR**), 37.1 (CH_2 **minR**), 36.3 (CH_2 **majR**), one aromatic CH signal was not observed. The stereoconfiguration of the bicycle was determined on the basis of various 2D-NMR experiments.

III.3.6. Products derived from β-lactones

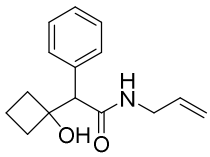
_N_-Allyl-3-hydroxy-3-methyl-2-phenylbutanamide 178a



To a mixture of lactone **176d** (96 mg, 0.54 mmol) and triethylamine (76 μL, 0.55 mmol) in dichloromethane (1 mL) was added allylamine (187 μL, 2.5 mmol). The resulting mixture was heated at 40 °C for 24 h, cooled down to room temperature and poured onto an aqueous ammonium chloride solution (10%w, 20 mL). The resulting mixture was extracted with ethyl acetate (40 mL). The organic phase was washed with water (10 mL), brine (10 mL) and dried over $MgSO_4$. Solvent removal under reduced pressure gave a residue that was purified by column chromatography using 30% ethyl acetate in light petroleum to give the *title compound* as a colourless solid (108 mg, 86%); mp 66 - 67 °C; (Found: $M+Na^+$, 256.1314. $C_{14}H_{19}NNaO_2$ requires 256.1308); ν_{max} ($CHCl_3$)/cm^{-1} 3443, 3005, 2933, 1657, 1519; δ_H (400 MHz; $CDCl_3$) 7.26 - 7.40 (5 H, m, ArH), 6.23 (1 H, br s, NH), 5.73 (1 H, ddt, *J* 17.1, 10.5, 5.6, vinylic CH), 5.10 (1 H, s, OH), 5.05 (1 H, dq, *J* 10.5, 1.6, vinylic CH_2), 5.03 (1 H, dq, *J* 17.1, 1.6, vinylic CH_2), 3.84

(1 H, dtt, *J* 15.9, 5.6, 1.6, CH_2), 3.76 (2 H, dtt, *J* 15.9, 5.6, 1.6, CH_2), 3.32 (1 H, s, CH), 1.33 (3 H, s, CH_3), 1.01 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 174.3 (C), 136.7 (C), 133.7 (CH), 129.6 (CH), 128.5 (CH), 127.6 (CH), 116.4 (CH_2), 72.3 (C), 61.1 (CH), 41.7 (CH_2), 30.1 (CH_3), 27.1 (CH_3).

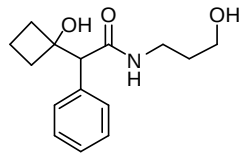
_N_-Allyl-2-(1-hydroxycyclobutyl)-2-phenylacetamide 178b



To a mixture of lactone **176a** (94 mg, 0.5 mmol) and triethylamine (76 μL, 0.55 mmol) in dichloromethane (1 mL) was added allylamine (187 μL, 2.5 mmol). The resulting mixture was heated at 40 °C for 20 h, cooled down to room temperature and poured onto an aqueous ammonium chloride solution (10%w, 20 mL). The resulting mixture was extracted with ethyl acetate (40 mL). The organic phase was washed with water (10 mL), brine (10 mL) and dried over $MgSO_4$. Solvent removal under reduced pressure gave a residue that was purified by column chromatography using 40% ethyl acetate in light petroleum to give the *title compound* as a colourless solid (120 mg, 98%); mp 97 - 98 °C; (Found: M+Na^+, 268.1319. $C_{15}H_{19}NNaO_2$ requires 268.1308); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3441, 1659, 1602, 1520; δ_H (400 MHz; $CDCl_3$) 7.27 - 7.41 (5 H, m, ArH), 6.30 (1 H, br s, NH), 5.74 (1 H, ddt, *J* 16.5, 10.9, 5.4, vinylic CH), 5.01 - 5.09 (2 H, overlapping dq, *J* 10.9, 1.5 and dq , *J* 16.5, 1.5, vinylic CH_2), 4.81 (1 H, s, OH), 3.74 - 3.88 (2 H, m, CH_2N), 3.62 (1 H, s, CH), 2.19 - 2.30 (1 H, m, cyclobutane CH_2), 2.09 - 2.18 (1 H, m, cyclobutane CH_2), 1.91 - 2.03 (1 H, m, cyclobutane CH_2), 1.77 - 1.89 (2 H, m, cyclobutane CH_2), 1.51 - 1.64 (1 H, m, cyclobutane CH_2); δ_C (100 MHz; $CDCl_3$) 173.5 (C), 136.0 (C), 133.8

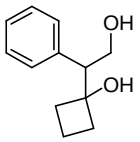
(CH), 129.5 (CH), 128.5 (CH), 127.6 (CH), 116.4 (CH_2), 76.3 (C), 58.5 (CH), 41.8 (CH_2), 36.4 (CH_2), 32.8 (CH_2), 12.6 (CH_2).

2-(1-Hydroxycyclobutyl)-*N*-(2-hydroxypropyl)-2-phenylacetamide 178c



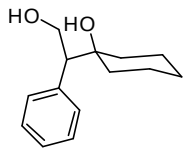
To a mixture of lactone **176a** (96 mg, 0.51 mmol) and triethylamine (76 μL, 0.55 mmol) in dichloromethane (1 mL) was added 3-aminopropanol (190 μL, 2.5 mmol). The resulting mixture was heated at 40 °C for 20 h, cooled down to room temperature and poured into aqueous ammonium chloride solution (10%w, 20 mL). The resulting mixture was extracted with ethyl acetate (40 mL). The organic phase was washed with water (10 mL), brine (10 mL) and dried over $MgSO_4$. Solvent removal under reduced pressure gave a residue that was purified by column chromatography using 50% ethyl acetate in light petroleum to give the *title compound* as a colourless oil (131 mg, 97%); (Found: M+Na^+, 286.1408. $C_{15}H_{21}NNaO_3$ requires 286.1414); ν_{max} ($CHCl_3$)/cm^{-1} 3440, 3007, 2947, 1648, 1526; δ_H (400 MHz; $CDCl_3$) 7.22 - 7.38 (5 H, m, ArH), 6.87 (1 H, t, *J* 5.8, NH), 4.92 (1 H, s, OH), 3.59 (1 H, s, CH), 3.49 (2 H, t, *J* 5.8, CH_2O), 3.40 (1 H, br s, OH), 3.30 (2 H, qd, *J* 5.8, 2.0, CH_2N), 2.05 - 2.32 (2 H, m, cyclobutane CH_2), 1.91 - 2.01 (1 H, m, cyclobutane CH_2), 1.75 - 1.87 (2 H, m, cyclobutane CH_2), 1.50 - 1.64 (3 H, m, cyclobutane CH_2 and CH_2); δ_C (100 MHz; $CDCl_3$) 174.8 (C), 135.9 (C), 129.3 (CH), 128.5 (CH), 127.6 (CH), 76.1 (C), 59.3 (CH_2), 58.3 (CH), 36.4 (CH_2), 36.2 (CH_2), 32.8 (CH_2), 32.0 (CH_2), 12.5 (CH_2).

1-(2-Hydroxy-1-phenylethyl)cyclobutan-1-ol 179a



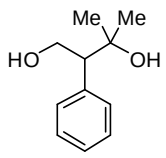
A solution of 3-phenyl-1-oxaspiro[3.3]heptan-2-one **176a** (67.0 mg, 356 μmol) in anhydrous dichloromethane (1.5 mL) was added dropwise to a solution of diisobutylaluminium hydride (1 M in dichloromethane, 1.07 mL, 1.07 mmol) in anhydrous dichloromethane (1.0 mL) at 0 °C under argon. The resulting mixture was stirred for 60 min, before saturated aqueous Rochelle salt solution (3 mL) was added and the resulting mixture was stirred at room temperature for 60 min. Water (5 mL) was added and the resulting mixture was extracted with dichloromethane (3×20 mL). The organic phases were washed with brine (10 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using 35% ethyl acetate in light petroleum to give the *title compound* as a colourless oil (51.5 mg, 75%); (Found: M+Na$^+$, 215.1052. $C_{12}H_{16}NaO_2$ requires 215.1043); ν_{max} ($CHCl_3$)/cm^{-1} 3609, 3500, 3007, 2989; δ_H (400 MHz; $CDCl_3$) 7.23 - 7.42 (5 H, m, ArH), 4.11 (1 H, dd, *J* 11.1, 5.4, OCH_2), 4.01 (1 H, dd, *J* 11.1, 5.4, OCH_2), 3.06 (1 H, br s, OH), 2.96 (1 H, t, *J* 5.4, CH), 2.52 (1 H, br s, OH), 2.24 - 2.34 (1 H, m, cyclobutane CH_2), 2.04 - 2.14 (2 H, m, cyclobutane CH_2), 1.74 - 1.88 (2 H, m, cyclobutane CH_2), 1.41 - 1.51 (1 H, m, cyclobutane CH_2); δ_C (100 MHz; $CDCl_3$) 139.2 (C), 129.5 (CH), 128.5 (CH), 127.1 (CH), 78.3 (C), 63.7 (CH_2), 54.0 (CH), 36.2 (CH_2), 34.9 (CH_2), 12.7 (CH_2).

1-(2-Hydroxy-1-phenylethyl)cyclohexan-1-ol 179c



A solution of 3-phenyl-1-oxaspiro[3.5]nonan-2-one **176c** (52.0 mg, 240 μmol) in anhydrous dichloromethane (1.5 mL) was added dropwise to a solution of diisobutylaluminium hydride (1 M in dichloromethane, 0.72 mL, 0.72 mmol) in anhydrous dichloromethane (1.0 mL) at 0 °C under argon. The resulting mixture was stirred for 60 min, before saturated aqueous Rochelle salt solution (3 mL) was added and the resulting mixture was stirred at room temperature for 60 min. Water (5 mL) was added and the resulting mixture was extracted with ethyl acetate (2×30 mL). The organic phases were washed with brine (10 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using 30% ethyl acetate in light petroleum to give the *title compound* as a colourless solid (36 mg, 68%); mp 95 - 96 °C; (Found: M+Na^+, 234.1354. $C_{14}H_{20}NaO_2$ requires 234.1356); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3605, 3007, 2937, 2859; δ_H (400 MHz; $CDCl_3$) 6.84 - 7.62 (5 H, m, ArH), 4.17 (1 H, dd, *J* 10.8, 6.5, OCH_2), 4.06 (1 H, dd, *J* 10.8, 6.5, OCH_2), 2.87 (1 H, t, *J* 6.5, CH), 2.69 (1 H, br s, OH), 2.40 (1 H, br s, OH), 1.01 - 1.85 (10 H, m, CH_2 cyclohexane); δ_C (100 MHz; $CDCl_3$) 139.7 (C), 129.8 (CH), 128.4 (CH), 127.1 (CH), 74.2 (C), 63.4 (CH_2), 57.1 (CH), 36.8 (CH_2), 34.7 (CH_2), 25.7 (CH_2), 21.8 (CH_2), 21.7 (CH_2).

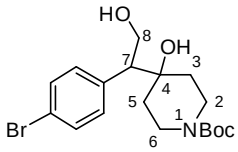
3-Methyl-2-phenylbutane-1,3-diol 179d



Lithium aluminium hydride (57 mg, 1.5 mmol) was added to a solution of 4,4-dimethyl-3-phenyloxetan-2-one **176d**

(88 mg, 0.5 mmol) in anhydrous THF (5 mL) at 0 °C under argon. The resulting mixture was stirred for 2 h and carefully quenched by addition of aqueous saturated Rochelle salt solution (7 mL) and stirred for 90 min. The black aluminium solid residue was filtered off, washed with ethyl acetate (20 mL) and the resulting biphasic filtrate was separated. The organic phase was washed with brine (10 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using 50% ethyl acetate in light petroleum to give the *title compound* as a colourless solid (45 mg, 50%); mp 73 - 74 °C; (Found: M+Na^+, 203.1030. $C_{11}H_{16}NaO_2$ requires 203.1043); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3607, 3004, 2976, 1602; δ_H (400 MHz; $CDCl_3$) 7.21 - 7.36 (5 H, m, ArH), 4.24 (1 H, dd, *J* 11.0, 7.6, OCH_2), 4.00 (1 H, dd, *J* 11.0, 6.0, OCH_2), 3.17 (1 H, br s, OH), 3.10 (1 H, br s, OH), 2.94 (1 H, dd, *J* 7.6, 6.0, CH), 1.25 (3 H, s, CH_3), 1.20 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 139.8 (C), 129.4 (CH), 128.5 (CH), 127.2 (CH), 74.0 (C), 64.1 (CH_2), 57.5 (CH), 29.9 (CH_3), 26.4 (CH_3).

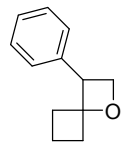
tert-Butyl 4-(1-(4-bromophenyl)-2-hydroxyethyl)-4-hydroxy-piperidine-1-carboxylate 179f



A solution of *tert*-butyl 3-(4-bromophenyl)-2-oxo-1-oxa-7-azaspiro[3.5]nonane-7-carboxylate **176f** (50 mg, 0.126 mmol) in anhydrous dichloromethane (1 mL) was added dropwise to a solution of diisopropylaluminium hydride (1 M in dichloromethane, 378 μL, 0.378 mmol) in anhydrous dichloromethane (1 mL) at 0 °C under argon. The resulting mixture was stirred for 1 h. Saturated Rochelle salt solution (3 mL) and water (3 mL)

were slowly added to the mixture which was subsequently warmed to room temperature and stirred for 30 min. The resulting solution was extracted with ethyl acetate (2×20 mL) and the organic phases were combined, washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a residue that was purified by column chromatography using the elution gradient 50 to 70% ethyl acetate in light petroleum to give the *title compound* as a colourless oil (36 mg, 71%); (Found: M+Na$^+$, 422.0939. $C_{18}H_{26}{}^{79}BrNNaO_4$ requires 422.0937); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3606, 3006, 2927, 2855, 1681, 1601, 1429, 1247, 1150; δ_H (400 MHz; $CDCl_3$) 7.42 (2 H, d, *J* 8.4, ArH), 7.15 (2 H, d, *J* 8.4, ArH), 4.02 - 4.16 (2 H, m, H8), 3.61 - 3.99 (2 H, m, H2/6), 2.91 - 3.24 (2 H, m, H2/6), 2.75 (1 H, t, *J* 5.5, H7), 2.71 (1 H, s, OH), 2.14 (1 H, t, *J* 4.3, OH), 1.62 - 1.83 (1 H, m, H3/5), 1.33 - 1.55 (3 H, m, H3/5), 1.40 (9 H, s, *t*Bu); δ_C (100 MHz; $CDCl_3$) 154.8 (C), 138.2 (C), 131.6 (CH), 131.2 (CH), 121.2 (C), 79.6 (C), 72.1 (C), 63.3 (CH_2), 55.9 (CH), 39.6 (CH_2 br s), 36.3 (CH_2), 34.5 (CH_2 br s), 28.4 (CH_3), one CH_2 signal was not observed, signal broadening due to the existence of a rotameric equilibrium was observed.

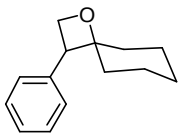
3-Phenyl-1-oxaspiro[3.3]heptane 180a



To a solution of 1-(2-hydroxy-1-phenylethyl)cyclobutan-1-ol **179a** (47.0 mg, 244 μmol) in anhydrous THF (8 mL) at 0 °C under argon was added potassium *tert*-butoxide (33 mg, 0.29 mmol) and *p*-toluenesulfonyl chloride (56 mg, 0.29 mmol). The resulting mixture was warmed to room temperature and stirred for 2 h. Potassium *tert*-butoxide (52 mg, 0.46 mmol) was added and the resulting mixture was heated at reflux for 4 h. Upon cooling, saturated ammonium

chloride solution (3 mL) and water (10 mL) were added and the resulting mixture was extracted with ethyl acetate (2×20 mL). The organic phase was washed with brine (10 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using 5% ethyl acetate in light petroleum to give the *title compound* as a colourless oil (38 mg, 89%); (GC-HRMS: Found: M^+, 174.1045. $C_{12}H_{14}O$ requires 174.1045); ν_{max} ($CHCl_3$)/cm^{-1} 3005, 2989, 1272, 973; δ_H (400 MHz; $CDCl_3$) 7.32 - 7.42 (4 H, m, ArH), 7.26 - 7.32 (1 H, m, ArH), 4.84 (1 H, dd, *J* 8.0, 6.3, CH_2O), 4.61 (1 H, t, *J* 6.3, CH_2O), 3.98 (1 H, dd, *J* 8.0, 6.3, CH), 2.34 - 2.50 (2 H, m, cyclobutane CH_2), 1.84 - 2.06 (2 H, m, cyclobutane CH_2), 1.53 - 1.65 (1 H, m, cyclobutane CH_2), 1.12 - 1.28 (1 H, m, cyclobutane CH_2); δ_C (100 MHz; $CDCl_3$) 139.1 (C), 128.7 (CH), 127.9 (CH), 127.2 (CH), 91.4 (C), 71.3 (CH_2), 50.2 (CH), 39.0 (CH_2), 33.1 (CH_2), 11.3 (CH_2).

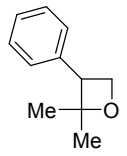
3-Phenyl-1-oxaspiro[3.5]nonane 180c



To a solution of 1-(2-hydroxy-1-phenylethyl)cyclohexan-1-ol **179c** (50 mg, 227 μmol) in anhydrous THF (7 mL) at 0 °C under argon was added potassium *tert*-butoxide (33 mg, 0.29 mmol) and *p*-toluenesulfonyl chloride (48 mg, 0.25 mmol). The resulting mixture was warmed to room temperature and stirred for 1 h. Potassium *tert*-butoxide (41 mg, 0.36 mmol) was added and the resulting mixture was heated at reflux for 16 h. Upon cooling, saturated ammonium chloride solution (5 mL) and water (10 mL) were added and the resulting mixture was extracted with ethyl acetate (3×20 mL). The organic phase was

washed with brine (20 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using 10% ethyl acetate in light petroleum to give the *title compound* as a colourless oil (44 mg, 96%); (Found: M+Na^+, 225.1246. $C_{14}H_{18}NaO_4$ requires 225.1250); ν_{max} ($CHCl_3$)/cm^{-1} 3003, 2936, 2887, 2857, 1483, 977; δ_H (400 MHz; $CDCl_3$) 7.20 - 7.40 (5 H, m, ArH), 4.70 - 4.83 (2 H, m, OCH_2), 3.84 (1 H, dd, *J* 8.3, 6.9, CH), 1.84 - 2.06 (2 H, m, CH_2), 1.61 - 1.75 (1 H, m, CH_2), 1.44 - 1.60 (2 H, m, CH_2), 1.15 - 1.43 (4 H, m, CH_2), 0.94 - 1.10 (1 H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 137.8 (C), 128.5 (CH), 128.4 (CH), 126.9 (CH), 89.0 (C), 69.0 (CH_2), 49.8 (CH), 40.4 (CH_2), 33.7 (CH_2), 25.2 (CH_2), 22.5 (CH_2), 21.6 (CH_2).

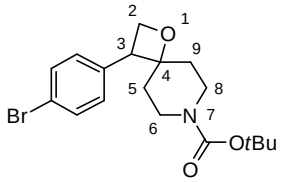
2,2-Dimethyl-3-phenyloxetane 180d



To a solution of 3-methyl-2-phenylbutane-1,3-diol **179d** (37.5 mg, 208 μmol) in anhydrous THF (7 mL) at 0 °C under argon was added potassium *tert*-butoxide (28 mg, 0.25 mmol) and *p*-toluenesulfonyl chloride (49 mg, 0.26 mmol). The resulting mixture was warmed to room temperature and stirred for 2 h. Additional potassium *tert*-butoxide (45 mg, 0.40 mmol) was added and the resulting mixture was heated at reflux for 18 h. Upon cooling, saturated ammonium chloride solution (3 mL) and water (10 mL) were added and the resulting mixture was extracted with ethyl acetate (50 mL). The organic phase was washed with brine (10 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using 10% ethyl acetate in light petroleum to give the

title compound as a colourless oil (20 mg, 59%); (GC-HRMS: Found: M^+, 162.1044. $C_{11}H_{14}O$ requires 162.1045); ν_{max} ($CHCl_3$)/cm^{-1} 3001, 2972, 1603, 967; δ_H (400 MHz; $CDCl_3$) 7.33 - 7.39 (2 H, m, ArH), 7.20 - 7.29 (3 H, m, ArH), 4.83 (1 H, dd, *J* 8.1, 6.5, OCH_2), 4.75 (1 H, dd, *J* 8.1, 6.5, OCH_2), 3.99 (1 H, app t, *J* 8.1, CH), 1.60 (3 H, s, CH_3), 1.05 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 138.3 (C), 128.5 (CH), 127.9 (CH), 127.0 (CH), 88.0 (C), 68.0 (CH_2), 49.8 (CH), 31.0 (CH_3), 24.6 (CH_3).

tert-Butyl 3-(4-bromophenyl)-1-oxa-7-azaspiro[3.5]nonane-7-carboxylate 180f



To a solution of *tert*-butyl 4-(1-(4-bromophenyl)-2-hydroxyethyl)-4-hydroxypiperidine-1-carboxylate **179f** (34 mg, 85 μmol) in THF (anhydrous, 2.6 mL) cooled to 0 °C was added tosyl chloride (19 mg, 0.10 mmol) and potassium *tert*-butoxide (26 mg, 0.23 mmol) under argon. The resulting mixture was warmed up to room temperature, stirred for 80 min, heated at reflux and stirred for 90 min. The reaction mixture was cooled to room temperature and quenched by the addition of saturated ammonium chloride solution (5 mL) and water (10 mL). The resulting mixture was extracted with ethyl acetate (2×20 mL). The organic phases were combined, washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give the *title compound* as a colourless solid (32 mg, 97%) without further purification; mp 99 - 100 °C; (Found: M+Na^+, 404.0832. $C_{18}H_{24}{}^{79}BrNNaO_3$ requires 404.0832); ν_{max} ($CHCl_3$)/cm^{-1} 3006, 2928, 1682, 1429, 1239, 1137; δ_H (400 MHz; $CDCl_3$) 7.42 - 7.52 (2 H, m, ArH), 7.14 (2 H, d, *J* 8.3, ArH), 4.82 (1 H, dd,

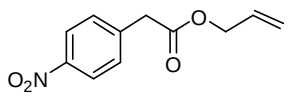
J 8.3, 7.0, H2), 4.74 (1 H, t, *J* 7.0, H2), 3.84 (1 H, dd, *J* 8.3, 7.0, H3), 3.58 - 3.79 (1 H, m, H6/8), 3.33 - 3.44 (1 H, m, H6/8), 3.26 (1 H, ddd, *J* 13.3, 10.5, 3.2, H6/8), 3.05 (1 H, ddd, *J* 13.3, 10.8, 3.2, H6/8), 2.09 (1 H, d, *J* 13.3, H5/9), 1.87 (1 H, ddd, *J* 13.3, 11.0, 4.4, H5/9), 1.60 (1 H, d, *J* 13.7, H5/9), 1.43 (9 H, m, *t*Bu), 1.12 - 1.31 (1 H, m, H5/9); δ_C (100 MHz; $CDCl_3$) 154.8 (C), 135.9 (C), 131.8 (CH), 129.9 (CH), 121.2 (C), 86.6 (C), 79.7 (C), 68.9 (CH_2), 48.7 (CH), 39.1 (CH_2), 33.3 (CH_2), 29.8 (CH_2), 28.5 (CH_3), one CH_2 signal was not observed, signal broadening due to the existence of a rotameric equilibrium was observed.

IV. Chapter V Experimental

IV.1. Preparation of diazo compounds

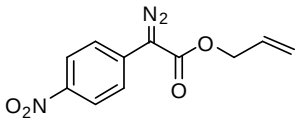
1-Diazo-1-phenylpropan-2-one **262** was prepared according to a previously described procedure. [61] The following diazo compounds were prepared by oxidation of the corresponding hydrazone using iodamine-T **89** according to the procedure described in **section II** of this experimental section: ethyl 2-diazo-2-phenylacetate **104**, ethyl 2-(4-methoxyphenyl)-2-diazoacetate **105**, ethyl 2-(4-methylphenyl)-2-diazoacetate **285**, ethyl 2-(4-bromophenyl)-2-diazoacetate **107**, ethyl 2-diazo-4-phenylbutanoate **123**, 3-diazo-4,4-dimethyldihydrofuran-2(*3H*)-one **121**, 3-diazo-1-methylindolin-2-one **118**.

Allyl 2-(4-nitrophenyl)acetate



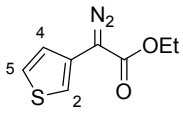
N,*N*'-Dicyclohexylcarbodiimide (3.40 g, 16.5 mmol) was added to a solution of 4-nitrophenylacetic acid (2.72 g, 15 mmol), 4-dimethylaminopyridine (366 mg, 3.0 mmol) and allyl alcohol (1.12 mL, 16.5 mmol) in anhydrous dichloromethane (60 mL) stirred under argon and cooled in an ice bath. The resulting solution was stirred for 10 min, warmed up to room temperature and stirred for 15 h. Saturated aqueous ammonium chloride solution (10 mL) was added to the solution and the urea by-product was removed by filtration and washed with dichloromethane (20 mL). The resulting biphasic mixture was separated and the aqueous phase was extracted with dichloromethane (20 mL). The combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a residue that was purified by column chromatography using 10% ethyl acetate in light petroleum to give the *title compound* as a yellow oil (3.26 g, 98%); (Found: M+Na^+, 244.0587. $C_{11}H_{11}NNaO_4$ requires 244.0580); ν_{max} ($CHCl_3$)/cm^{-1} 1736, 1523, 1349; δ_H (400 MHz; $CDCl_3$) 8.11 - 8.24 (2 H, m, ArH), 7.40 - 7.51 (2 H, m, ArH), 5.88 (1 H, ddt, *J* 17.2, 10.5, 5.8, vinylic CH), 5.27 (1 H, dq, *J* 17.2, 1.2, vinylic CH), 5.23 (1 H, dq, *J* 10.5, 1.2, vinylic CH), 4.60 (2 H, dt, *J* 5.8, 1.2, CH_2), 3.76 (2 H, s, CH_2); δ_C (100 MHz; $CDCl_3$) 169.9 (C), 147.3 (C), 141.3 (C), 131.7 (CH), 130.4 (CH), 123.8 (CH), 118.9 (CH_2), 66.0 (CH_2), 41.0 (CH_2). The data matched those previously reported.[62]

Allyl 2-diazo-2-(4-nitrophenyl)acetate 286



1,8-Diazabicycloundec-7-ene (1.12 mL, 7.5 mmol) was slowly added to a stirred solution of allyl 2-(4-nitrophenyl)acetate (1.11 g, 5.0 mmol) and 4-acetamidobenzenesulfonyl azide (1.20 g, 5.0 mmol) in acetonitrile (15 mL) cooled in an ice bath. The resulting solution was stirred for 10 min, warmed to room temperature and stirred for 16 h. The solvent was removed under reduced pressure and ether (50 mL) and saturated aqueous ammonium chloride solution (15 mL) were added to the residue. The biphasic mixture was separated and the aqueous phase was extracted with ether (50 mL). The combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave a residue that was purified by column chromatography using 20% ethyl acetate in light petroleum to give the *title compound* as a orange solid (730 mg, 59%), mp 74 - 75 °C; the compound did not ionise under the ESI-HRMS conditions used; ν_{max} ($CHCl_3$)/cm^{-1} 2098 (CN_2), 1706, 1596, 1517, 1333; δ_H (400 MHz; $CDCl_3$) 8.16 - 8.26 (2 H, m, ArH), 7.62 - 7.70 (2 H, m, ArH), 5.98 (1 H, ddt, *J* 17.2, 10.4, 5.7, vinylic CH), 5.38 (1 H, dq, *J* 17.2, 1.4, vinylic CH_2), 5.30 (1 H, dq, *J* 10.4, 1.4, vinylic CH_2), 4.79 (2 H, dt, *J* 5.7, 1.4, CH_2); δ_C (100 MHz; $CDCl_3$) 163.5 (C), 145.2 (C), 133.9 (C), 131.7 (CH), 124.4 (CH), 123.3 (CH), 119.2 (CH_2), 66.1 (CH_2), the signal due to CN_2 was not observed.

Ethyl 2-diazo-2-(3-thienyl)acetate 287



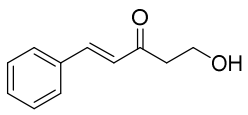
1,8-Diazabicycloundec-7-ene (1.20 mL, 8.0 mmol) was slowly added to a stirred solution of ethyl 3-thienylacetate (0.60 mL, 4.0 mmol) and 4-acetamidobenzenesulfonyl azide (1.44 g, 6.0 mmol) in acetonitrile (15 mL) cooled in an ice bath. The resulting solution was stirred for 10 min, warmed to room temperature and stirred for 18 h. The solvent was removed under reduced pressure and ether (50 mL) and saturated aqueous ammonium chloride solution (30 mL) were added to the residue. The biphasic mixture was separated and the aqueous phase was extracted with ether (50 mL). The combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave a residue that was purified by column chromatography using 3% ethyl acetate in light petroleum to give the *title compound* as a red oil (555 mg, 71%); the compound did not ionise under the ESI-HRMS conditions used; ν_{max} ($CHCl_3$)/cm^{-1} 2985, 2088 (CN_2), 1732, 1697, 1311, 1266; δ_H (400 MHz; $CDCl_3$) 7.41 (1 H, dd, *J* 3.0, 1.3, H2), 7.38 (1 H, dd, *J* 5.0, 3.0, H5), 7.04 (1 H, dd, *J* 5.0, 1.3, H4), 4.33 (2 H, q, *J* 7.1, $C\underline{H}_2CH_3$), 1.34 (3 H, t, *J* 7.1, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 165.6 (C), 126.5 (CH), 124.1 (C), 123.8 (CH), 117.9 (CH), 61.3 (CH_2), 14.6 (CH_3), the signal due to CN_2 was not observed.

IV.2. Preparation of β-hydroxyketones

The following β-hydroxyketones were prepared following previously described procedures: 3-hydroxy-1-phenylpropan-1-one **291a**,[63] ethyl

5-hydroxy-3-oxopentanoate **291b**,[64] ethyl 2-(hydroxymethyl)-2-methyl-3-oxobutanoate **291f**,[65] 3-(hydroxymethyl)but-3-en-2-one **291g**,[66] 4-hydroxy-4-phenylbutan-2-one **291i**,[67] enantioenriched 4-hydroxy-4-phenylbutan-2-one **291i** was prepared by *L*-proline catalysed aldol reaction following a previously reported procedure,[68] *anti*- and *syn*-3-hydroxy-2-methyl-1,3-diphenylpropan-1-one **291j** and **291k**.[69]

(*E*)-5-Hydroxy-1-phenylpent-1-en-3-one 291d

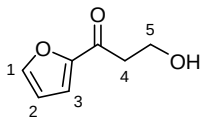


Benzylideneacetone (731 mg, 5.0 mmol) dissolved in anhydrous THF (2 mL) was added to a solution of freshly prepared lithium diisopropylamide[70] (5.25 mmol) in anhydrous THF (12 mL) at −78 °C under argon and the resulting mixture was stirred at this temperature for 1 h. Trimethylsilyl chloride (0.79 mL, 6.22 mmol) was added dropwise at −78 °C and the mixture was warmed up to room temperature and stirred for 3 h. Saturated aqueous sodium hydrogen carbonate solution (7 mL) and water (3 mL) were added and the resulting mixture was extracted with ethyl acetate (70 mL). The organic phase was washed with saturated aqueous sodium hydrogen carbonate solution (10 mL), brine (15 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the TMS-enol ether which was used in the next step without further purification.

To a solution containing scandium triflate (246 mg, 0.5 mmol) in THF (18 mL) was added aqueous formaldehyde solution (37%; 1.86 mL, 25.0 mmol), the previously prepared TMS-enol ether and water (2 mL). The resulting solution was stirred for 16 h at room temperature. The

volatiles were evaporated under reduced pressure to give a residue to which was added ethyl acetate (60 mL) and water (10 mL). The organic phase was separated and washed with hydrochloric acid (1 M; 10 mL), water (10 mL), brine (15 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a residue that was purified on column chromatography using 50 % ethyl acetate in light petroleum to give *the title compound* as a yellow oil (199 mg, 22%); (Found: $M+Na^+$, 199.0735. $C_{11}H_{12}NaO_2$ requires 199.0730); ν_{max} ($CHCl_3$)/cm^{-1} 3603, 3011, 1683, 1655, 1607; δ_H (400 MHz; $CDCl_3$) 7.50 - 7.64 (3 H, m, ArH), 7.56 (1 H, d, *J* 16.1, CH), 7.35 - 7.43 (2 H, m, ArH), 6.74 (1 H, d, *J* 16.1, CH), 3.96 (2 H, t, *J* 5.3, CH_2O), 2.94 (2 H, t, *J* 5.3, CH_2), 2.79 (1 H, br s, OH); δ_C (100 MHz; $CDCl_3$) 200.6 (C), 143.7 (CH), 134.3 (C), 130.9 (CH), 129.1 (CH), 128.5 (CH), 126.3 (CH), 58.2 (CH_2), 42.3 (CH_2). The data matched those previously reported.[71]

1-(2-Furyl)-3-hydroxypropan-1-one 291c

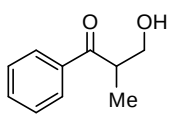


Furyl methyl ketone (0.50 mL, 5.0 mmol) was added to a solution of freshly prepared lithium diisopropylamide[70] (5.24 mmol) in anhydrous THF (12 mL) at −78 °C under argon and the resulting mixture was stirred at this temperature for 1 h. Trimethylsilyl chloride (0.79 mL, 6.22 mmol) was added dropwise at −78 °C and the mixture was warmed up to room temperature and stirred for 3 h. Saturated aqueous sodium hydrogen carbonate solution (7 mL) and water (3 mL) were added and the resulting mixture was extracted with ethyl acetate (70 mL). The organic phase was washed with saturated

aqueous sodium hydrogen carbonate solution (10 mL), brine (15 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the TMS-enol ether which was used in the next step without further purification.

To a solution containing scandium triflate (246 mg, 0.5 mmol) in THF (18 mL) was added aqueous formaldehyde solution (37%; 1.86 mL, 25.0 mmol), the previously prepared TMS-enol ether and water (2 mL). The resulting solution was stirred for 16 h at room temperature. The volatiles were evaporated under reduced pressure to give a residue to which was added ethyl acetate (60 mL) and water (10 mL). The organic phase was separated and washed with water (10 mL), brine (15 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a residue that was purified on column chromatography using 50 % ethyl acetate in light petroleum to give *the title compound* as a red oil (94 mg, 13%); (Found: M+Na^+, 163.0371. $C_7H_8NaO_3$ requires 163.0366); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3606, 3011, 1669, 1571, 1469, 1397, 1062; δ_H (400 MHz; $CDCl_3$) 7.58 - 7.62 (1 H, m, H1), 7.22 (1 H, d, *J* 3.6, H3), 6.55 (1 H, dd, *J* 3.6, 1.6, H2), 4.00 (2 H, q, *J* 5.7, H5), 3.09 (2 H, t, *J* 5.7, H4), 2.57 (1 H, t, *J* 5.7, OH); δ_C (100 MHz; $CDCl_3$) 189.2 (C), 152.6 (C), 146.9 (CH), 117.8 (CH), 112.5 (CH), 58.0 (CH_2), 40.5 (CH_2).

3-Hydroxy-2-methyl-1-phenylpropan-1-one 291e



Propiophenone (665 µL, 5.0 mmol) was added to a solution of freshly prepared lithium diisopropylamide[70] (5.25 mmol) in anhydrous THF (12 mL) at −78 °C under argon and the

resulting mixture was stirred at this temperature for 1 h. Trimethylsilyl chloride (0.79 mL, 6.22 mmol) was added dropwise at −78 °C and the mixture was warmed up to room temperature and stirred for 3 h. Saturated aqueous sodium hydrogen carbonate solution (7 mL) and water (3 mL) were added and the resulting mixture was extracted with ethyl acetate (70 mL). The organic phase was washed with saturated aqueous sodium hydrogen carbonate solution (10 mL), brine (15 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the TMS-enol ether which was used in the next step without further purification.

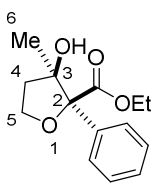
To a solution containing scandium triflate (246 mg, 0.5 mmol) in THF (18 mL) was added aqueous formaldehyde solution (37%; 1.86 mL, 25.0 mmol), the previously prepared TMS-enol ether and water (2 mL). The resulting solution was stirred for 18 h at room temperature. The volatiles were evaporated under reduced pressure to give a residue to which was added ethyl acetate (60 mL) and water (10 mL). The organic phase was separated and washed with aqueous hydrochloric acid (1 M, 10 mL), water (10 mL), brine (15 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a residue that was purified on column chromatography using 50 % ethyl acetate in light petroleum to give *the title compound* as a colourless oil (690 mg, 84%); (Found: $M+Na^+$, 187.0735. $C_{10}H_{12}NaO_2$ requires 187.0730); ν_{max} ($CHCl_3$)/cm^{-1} 3609, 3008, 2977, 2938, 2881, 1674, 1597, 1448, 1239, 976; δ_H (400 MHz; $CDCl_3$) 7.90 - 7.99 (2 H, m, ArH), 7.51 - 7.60 (1 H, m, ArH), 7.41 - 7.50 (2 H, m, ArH),

3.92 (1 H, dd, *J* 10.6, 7.1, CH_2O), 3.77 (1 H, dd, *J* 10.6, 4.0, CH_2O), 3.66 (1 H, quin.d, *J* 7.1, 4.0, CH), 2.64 (1 H, br s, OH), 1.21 (3 H, d, *J* 7.1, CH_3); δ_C (100 MHz; $CDCl_3$) 204.5 (C), 136.2 (C), 133.4 (CH), 128.8 (CH), 128.5 (CH), 64.6 (CH_2), 43.0 (CH), 14.6 (CH_3). The data matched those previously reported.[72]

IV.3. Synthesis of 3-hydroxytetrahydrofurans

General procedure O: to a solution containing the metal catalyst [rhodium(II) acetate dimer (4.0 mg, 5.0 μmol) or copper(I) triflate toluene complex (13 mg, 25 μmol)] and the β-hydroxyketone (0.5 mmol) in anhydrous dichloromethane (3 mL) at reflux under argon was added a solution of diazo compound (0.65 mmol in 2 mL anhydrous dichloromethane) over 30 min. The resulting solution was stirred for 30 min at reflux and subsequently cooled to room temperature. Removal of the solvent under reduced pressure gave a residue that was purified by column chromatography using the solvent system indicated to give the desired tetrahydrofuran compound.

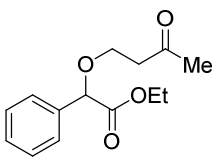
Ethyl *cis*-3-hydroxy-3-methyl-2-phenyltetrahydrofuran-2-carboxylate 283



Obtained by **general procedure O** using copper(I) triflate toluene complex (13 mg, 0.025 mmol), ethyl 2-diazo-2-phenylacetate **104** (123 mg, 0.65 mmol) and 4-hydroxybutan-2-one **277** (43 μL, 0.5 mmol); purified using 20 % ethyl acetate in light petroleum. The *title compound* was obtained as a colourless oil (102 mg, 82%); (Found: $M+Na^+$, 273.1086. $C_{14}H_{18}NaO_4$

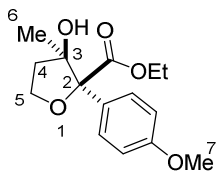
requires 273.1097); ν_{max} ($CHCl_3$)/cm^{-1} 3472, 2985, 2899, 1709, 1448, 1370, 1271, 1069, 1042; δ_H (400 MHz; $CDCl_3$) 7.52 - 7.57 (2 H, m, ArH), 7.26 - 7.37 (3 H, m, ArH), 4.16 - 4.29 (4 H, m, overlapping C<u>H</u>$_2$CH$_3$ and H5), 3.88 (1 H, br s, OH), 1.96 - 2.13 (2 H, m, H4), 1.23 (3 H, t, *J* 7.1, CH$_2$C<u>H</u>$_3$), 1.13 (3 H, s, H6); δ_C (100 MHz; $CDCl_3$) 173.7 (C), 138.0 (C), 128.2 (CH), 128.1 (CH), 125.5 (CH), 89.2 (C), 81.8 (C), 66.2 (CH_2), 62.0 (CH_2), 38.9 (CH_2), 24.2 (CH_3), 14.1 (CH_3).

Ethyl 2-(3-oxobutoxy)-2-phenylacetate 282



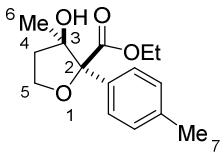
Following a modification of **general procedure O**, ethyl 2-diazo-2-phenylacetate **104** (123 mg, 0.65 mmol) in solution in anhydrous dichloromethane (2 mL) was added over 30 min to a solution containing rhodium octanoate dimer (4 mg, 0.005 mmol), triethylamine (70 µL, 0.5 mmol) and 4-hydroxybutan-2-one **277** (43 µL, 0.5 mmol) in anhydrous dichloromethane (2 mL); purified using 20 % ethyl acetate in light petroleum. The *title compound* was obtained as a colourless oil (98 mg, 78%); (Found: M+Na$^+$, 273.1085. $C_{14}H_{18}NaO_4$ requires 273.1097); ν_{max} ($CHCl_3$)/cm^{-1} 3008, 2985, 1742, 1716, 1263, 1121; δ_H (400 MHz; $CDCl_3$) 7.39 - 7.44 (2 H, m, ArH), 7.28 - 7.37 (3 H, m, ArH), 4.87 (1 H, s, CH), 4.19 (1 H, dq, *J* 10.7, 7.2, C<u>H</u>$_2$CH$_3$), 4.12 (1 H, dq, *J* 10.7, 7.2, C<u>H</u>$_2$CH$_3$), 3.80 (1 H, dt, *J* 9.4, 6.4, CH_2), 3.71 (1 H, dt, *J* 9.4, 6.4, CH_2), 2.77 (2 H, t, *J* 6.4, CH_2), 2.18 (3 H, s, CH_3), 1.20 (3 H, t, *J* 7.2, CH$_2$C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 207.0 (C), 170.8 (C), 136.5 (C), 128.8 (CH), 128.7 (CH), 127.3 (CH), 81.6 (CH), 64.9 (CH_2), 61.3 (CH_2), 43.7 (CH_2), 30.6 (CH_3), 14.2 (CH_3).

Ethyl *cis*-3-hydroxy-2-(4-methoxyphenyl)-3-methyltetrahydro-furan-2-carboxylate 289a



Obtained by **general procedure O** using rhodium octanoate dimer (4 mg, 0.005 mmol), ethyl 2-(4-methoxyphenyl)-2-diazoacetate **105** (143 mg, 0.65 mmol) and 4-hydroxybutan-2-one **277** (43 μL, 0.5 mmol); purified using 30% ethyl acetate in light petroleum. The *title compound* was obtained as a colourless oil (112 mg, 80%); (Found: M+Na$^+$, 303.1218. $C_{15}H_{20}NaO_5$ requires 303.1203); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3572, 1709, 1511, 1251; δ_H (400 MHz; $CDCl_3$) 7.46 (2 H, d, *J* 8.9, ArH), 6.85 (2 H, d, *J* 8.9, ArH), 4.11 - 4.31 (4 H, m, C$\underline{H}_2$CH$_3$ and H5), 3.81 (1 H, s, OH), 3.79 (3 H, s, H7), 1.92 - 2.13 (2 H, m, H4), 1.23 (3 H, t, *J* 7.1, CH$_2$C$\underline{H}_3$), 1.14 (3 H, s, H6); δ_C (100 MHz; $CDCl_3$) 173.8 (C), 159.4 (C), 130.1 (C), 126.8 (CH), 113.6 (CH), 89.1 (C), 81.9 (C), 66.1 (CH_2), 62.0 (CH_2), 55.3 (CH_3), 38.9 (CH_2), 24.1 (CH_3), 14.2 (CH_3).

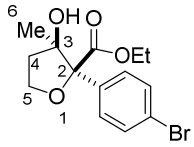
Ethyl *cis*-3-hydroxy-3-methyl-2-(*p*-tolyl)tetrahydrofuran-2-carboxylate 289b



Obtained by **general procedure O** using rhodium octanoate dimer (4 mg, 0.005 mmol), ethyl 2-(4-methylphenyl)-2-diazoacetate **285** (133 mg, 0.65 mmol) and 4-hydroxybutan-2-one **277** (43 μL, 0.5 mmol); purified using 25% ethyl acetate in light petroleum. The *title compound* was obtained as a yellow oil (114 mg, 85%); (Found: M+Na$^+$, 287.1254. $C_{15}H_{20}NaO_4$ requires 287.1254); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3007, 2985, 1709, 1291, 1269, 1077, 1042; δ_H (400 MHz; $CDCl_3$) 7.39 - 7.45 (2 H, m,

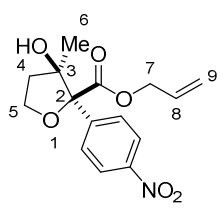
ArH), 7.10 - 7.19 (2 H, m, ArH), 4.15 - 4.31 (4 H, m, H5 and C<u>H</u>$_2$CH$_3$), 3.82 (1 H, s, OH), 2.33 (3 H, s, H7), 1.96 - 2.12 (2 H, m, H4), 1.24 (3 H, t, *J* 7.1, CH$_2$C<u>H</u>$_3$), 1.14 (3 H, s, H6); δ_C (100 MHz; $CDCl_3$) 173.7 (C), 137.8 (C), 135.1 (C), 128.9 (CH), 125.4 (CH), 89.3 (C), 81.8 (C), 66.2 (CH_2), 62.0 (CH_2), 38.9 (CH_2), 24.2 (CH_3), 21.2 (CH_3), 14.1 (CH_3).

Ethyl *cis*-2-(4-bromophenyl)-3-hydroxy-3-methyltetrahydrofuran-2-carboxylate 289c



Obtained by **general procedure O** using copper(I) triflate toluene complex (13 mg, 0.025 mmol), ethyl 2-(4-bromophenyl)-2-diazoacetate **107** (175 mg, 0.65 mmol) and 4-hydroxybutan-2-one **277** (43 μL, 0.5 mmol); purified using the elution gradient 20 % to 30% ethyl acetate in light petroleum. The *title compound* was obtained as a colourless oil (87 mg, 53%); (Found: M+Na$^+$, 351.0205. $C_{14}H_{17}{}^{79}BrNaO_4$ requires 351.0202); ν_{max} ($CHCl_3$)/cm^{-1} 3470, 2985, 2900, 1709, 1486, 1264, 1076, 1010; δ_H (400 MHz; $CDCl_3$) 7.40 - 7.49 (4 H, m, ArH), 4.13 - 4.28 (4 H, m, H5 and C<u>H</u>$_2$CH$_3$), 3.83 (1 H, s, OH), 2.09 (1 H, ddd, *J* 12.7, 7.8, 5.4, H4), 1.99 (1 H, dt, *J* 12.7, 7.8, H4), 1.23 (3 H, t, *J* 7.2, CH$_2$C<u>H</u>$_3$), 1.11 (3 H, s, H6); δ_C (100 MHz; $CDCl_3$) 173.3 (C), 137.0 (C), 131.3 (CH), 127.4 (CH), 122.3 (C), 88.6 (C), 81.8 (C), 66.2 (CH_2), 62.2 (CH_2), 39.0 (CH_2), 24.1 (CH_3), 14.1 (CH_3).

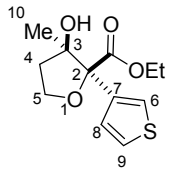
Allyl *cis*-3-hydroxy-3-methyl-2-(4-nitrophenyl)tetrahydrofuran-2-carboxylate 289d



Obtained by **general procedure O** using copper(I) triflate toluene complex (13 mg, 0.025 mmol), allyl

2-diazo-2-(4-nitrophenyl)acetate **286** (160 mg, 0.65 mmol) and 4-hydroxybutan-2-one **277** (43 μL, 0.5 mmol); purified using 2% methanol in dichloromethane. The *title compound* was obtained as a colourless oil (94 mg, 61%); (Found: M+Na$^+$, 330.0958. $C_{15}H_{17}NNaO_6$ requires 330.0954); ν_{max} ($CHCl_3$)/cm^{-1} 3493, 2988, 1715, 1604, 1352, 1272, 1079; δ_H (400 MHz; $CDCl_3$) 8.16 - 8.25 (2 H, m, ArH), 7.74 - 7.82 (2 H, m, ArH), 5.83 (1 H, ddt, *J* 17.1, 10.1, 5.9, H8), 5.24 (1 H, dq, *J* 17.1, 1.2, H9), 5.21 (1 H, dq, *J* 10.1, 1.2, H9), 4.60 - 4.74 (2 H, two overlapping ddt, *J* 13.1, 5.9, 1.2, H7), 4.27 (1 H, td, *J* 8.4, 6.5, H5), 4.20 (1 H, td, *J* 8.4, 6.5, H5), 3.82 (1 H, s, OH), 2.20 (1 H, ddd, *J* 12.5, 8.4, 6.5, H4), 2.05 (1 H, ddd, *J* 12.5, 8.4, 6.5, H4), 1.08 (3 H, s, H6); δ_C (100 MHz; $CDCl_3$) 172.6 (C), 147.9 (C), 144.8 (C), 131.0 (CH), 126.8 (CH), 123.4 (CH), 119.6 (CH_2), 88.4 (C), 82.0 (C), 66.7 (CH_2), 66.4 (CH_2), 39.3 (CH_2), 24.2 (CH_3).

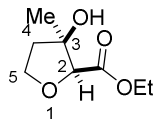
Ethyl *cis*-3-hydroxy-3-methyl-2-(3-thienyl)tetrahydrofuran-2-carboxylate 289e



Obtained by **general procedure O** using rhodium octanoate dimer (4 mg, 0.005 mmol), ethyl 2-diazo-2-(3-thienyl)acetate **287** (127 mg, 0.65 mmol) and 4-hydroxybutan-2-one **277** (43 μL, 0.5 mmol); purified using the elution gradient 20% to 40% ethyl acetate in light petroleum. The *title compound* was obtained as a yellow oil (66 mg, 51%); (Found: M+Na$^+$, 279.0660. $C_{12}H_{16}NaO_4S$ requires 279.0662); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3606, 1744, 1711, 1602, 1280, 1079; δ_H (400 MHz; $CDCl_3$) 7.37 (1 H, dd, *J* 3.1, 1.3, H6), 7.26 (1 H, dd, *J* 5.0, 3.1, H9), 7.19 (1 H, dd, *J* 5.0, 1.3, H8), 4.18 - 4.31 (4 H, m, H5 and C$\underline{H}_2$CH$_3$), 3.08 (1 H, s, OH), 2.03 (2 H, dd, *J* 7.9, 6.1, H4), 1.28

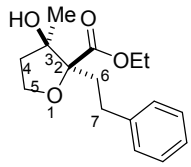
(3 H, s, H10), 1.29 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 172.4 (C), 140.0 (C), 126.3 (CH), 125.6 (CH), 122.4 (CH), 90.2 (C), 82.4 (C), 66.6 (CH_2), 62.0 (CH_2), 38.9 (CH_2), 24.0 (CH_3), 14.2 (CH_3).

Ethyl *cis*-3-hydroxy-3-methyltetrahydrofuran-2-carboxylate 289f



Obtained by a modification of **general procedure O** using rhodium octanoate dimer (4 mg, 0.005 mmol), ethyl diazoacetate **2** (137 mg, 1.3 mmol) and 4-hydroxybutan-2-one **277** (43 μL, 0.5 mmol); purified using the elution gradient 50% to 70% ethyl acetate in light petroleum. The *title compound* was obtained as a colourless oil (41 mg, 47%); (Found: M+Na$^+$, 197.0786. $C_8H_{14}NaO_4$ requires 197.0784); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3605, 2985, 1746, 1602, 1111, 1084; δ_H (400 MHz; $CDCl_3$) 4.24 (2 H, two overlapping dq, *J* 7.2, 5.7, $C\underline{H}_2CH_3$), 4.16 (1 H, td, *J* 8.7, 6.9, H5), 4.12 (1 H, s, H2), 3.94 (1 H, td, *J* 8.7, 3.9, H5), 2.44 (1 H, br s, OH), 2.09 (1 H, ddd, *J* 12.7, 6.9, 3.9, H4), 2.00 (1 H, dt, *J* 12.7, 8.7, H4), 1.53 (3 H, s, CH_3), 1.29 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 170.3 (C), 85.2 (CH), 79.9 (C), 67.6 (CH_2), 61.3 (CH_2), 41.3 (CH_2), 25.1 (CH_3), 14.3 (CH_3).

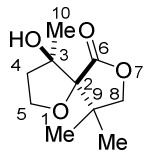
Ethyl *cis*-3-hydroxy-3-methyl-2-phenethyltetrahydrofuran-2-carboxylate 289g



Obtained by **general procedure O** using rhodium octanoate dimer (4 mg, 0.005 mmol), ethyl 2-diazo-4-phenylbutanoate **123** (142 mg, 0.65 mmol) and 4-hydroxybutan-2-one **277** (43 μL, 0.5 mmol); purified using 50% ethyl acetate in light petroleum. The *title compound* was obtained as a colourless oil (43 mg, 31%); (Found: M+Na$^+$, 301.1397. $C_{16}H_{22}NaO_4$

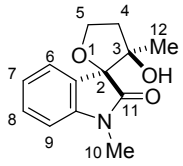
requires 301.1416); ν_{max} ($CHCl_3$)/cm^{-1} 3579, 3008, 2985, 1741, 1454, 1259, 1175, 1092, 1062; δ_H (400 MHz; $CDCl_3$) 7.25 - 7.31 (2 H, m, ArH), 7.15 - 7.21 (3 H, m, ArH), 4.25 (2 H, q, *J* 7.1, C<u>H</u>$_2$CH$_3$), 4.16 (1 H, q, *J* 8.4, H5), 3.95 - 4.05 (1 H, m, H5), 2.83 (1 H, ddd, *J* 13.3, 12.1, 4.7, H7), 2.37 - 2.46 (2 H, overlapping ddd and br s, *J* 13.3, 12.1, 4.7, H7 and OH), 2.25 (1 H, ddd, *J* 13.3, 12.1, 4.7, H6), 2.02 - 2.10 (2 H, m, H4), 1.62 (1 H, ddd, *J* 13.3, 12.1, 4.7, H6), 1.46 (3 H, s, CH_3), 1.33 (3 H, t, *J* 7.1, CH_2C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 172.1 (C), 141.7 (C), 128.5 (CH), 126.1 (CH), 91.3 (C), 81.8 (C), 65.4 (CH_2), 61.3 (CH_2), 40.1 (CH_2), 37.4 (CH_2), 30.6 (CH_2), 22.1 (CH_3), 14.5 (CH_3), one aromatic CH signal was not observed.

cis-4-Hydroxy-4,9,9-trimethyl-1,7-dioxaspiro[4.4]nonan-6-one 289h



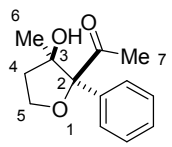
Obtained by **general procedure O** using rhodium octanoate dimer (4 mg, 0.005 mmol), 3-diazo-4,4-dimethyldihydrofuran-2(*3H*)-one **121** (91 mg, 0.65 mmol) and 4-hydroxybutan-2-one **277** (43 µL, 0.5 mmol); purified using 20 % ethyl acetate in light petroleum . The *title compound* was obtained as a colourless oil (91 mg, 91%); (Found: M+Na$^+$, 223.1960. $C_{10}H_{16}NaO_4$ requires 223.1946); ν_{max} ($CHCl_3$)/cm^{-1} 3553, 2986, 1754, 1365, 1081, 1013; δ_H (400 MHz; $CDCl_3$) 4.08 (1 H, d, *J* 7.9, H8), 3.97 (1 H, ddd, *J* 10.4, 8.4, 3.0, H5), 3.89 (1 H, td, *J* 8.4, 7.8, H5), 3.73 (1 H, d, *J* 7.9, H8), 2.92 (1 H, s, OH), 2.73 (1 H, ddd, *J* 12.2, 9.7, 8.4, H4), 2.03 (1 H, ddd, *J* 12.2, 7.8, 3.0, H4), 1.41 (3 H, s, H10), 1.24 (3 H, s, CH_3), 1.12 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 176.9 (C), 85.9 (C), 79.1 (CH_2), 78.1 (C), 64.9 (CH_2), 41.6 (CH_2), 41.1 (C), 23.3 (CH_3), 21.0 (CH_3), 17.7 (CH_3).

cis-3-Hydroxy-1',3-dimethyl-4,5-dihydro-(_3H_)-spiro[furan-2,3'-indolin]-2'-one 289i



Obtained by **general procedure O** using rhodium octanoate dimer (4 mg, 0.005 mmol), 3-diazo-1-methylindolin-2-one **118** (112 mg, 0.65 mmol) and 4-hydroxybutan-2-one **277** (43 μL, 0.5 mmol); purified using 1% methanol in dichloromethane. The *title compound* was obtained as a colourless oil (90 mg, 77%); (Found: M+Na$^+$, 256.0950. $C_{13}H_{15}NNaO_3$ requires 256.0944); ν_{max} ($CHCl_3$)/cm^{-1} 3435, 3011, 2900, 1707, 1614, 1471, 1099; δ_H (400 MHz; $CDCl_3$) 7.33 (1 H, td, *J* 7.8, 1.0, H7), 7.23 (1 H, dd, *J* 7.8, 1.0, H6), 7.09 (1 H, td, *J* 7.8, 1.0, H8), 6.86 (1 H, br d, *J* 7.8, H9), 4.45 (1 H, ddd, *J* 8.8, 8.0, 7.2, H5), 4.27 (1 H, s, OH), 4.26 (1 H, ddd, *J* 8.8, 8.0, 3.7, H5), 3.21 (3 H, s, H10), 2.51 (1 H, ddd, *J* 12.5, 7.2, 3.7, H4), 2.34 (1 H, dt, *J* 12.5, 8.8, H4), 1.13 (3 H, s, H12); δ_C (100 MHz; $CDCl_3$) 176.6 (C), 143.7 (C), 129.9 (CH), 128.8 (C), 124.8 (CH), 123.3 (CH), 108.9 (CH), 87.1 (C), 81.7 (C), 67.9 (CH_2), 40.1 (CH_2), 26.5 (CH_3), 23.2 (CH_3).

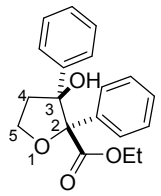
1-(_cis_-3-Hydroxy-3-methyl-2-phenyltetrahydrofuran-2-yl)ethan-1-one 289j



Obtained by **general procedure O** using copper(I) triflate toluene complex (13 mg, 0.025 mmol), 1-diazo-1-phenylpropan-2-one **262** (104 mg, 0.65 mmol) and 4-hydroxybutan-2-one **277** (43 μL, 0.5 mmol); purified using the elution gradient 5% to 10% ethyl acetate in light petroleum. The *title compound* was obtained as a colourless solid (62 mg, 56%); mp 39 - 40 °C; (Found: M+Na$^+$, 243.0992. $C_{13}H_{16}NaO_3$ requires 243.0992); ν_{max} ($CHCl_3$)/cm^{-1}

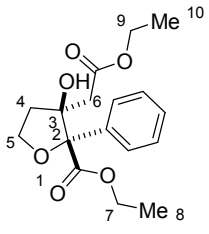
3576, 3465, 3006, 2987, 1699, 1352, 1063; δ_H (400 MHz; $CDCl_3$) 7.45 - 7.53 (2 H, m, ArH), 7.28 - 7.39 (3 H, m, ArH), 4.20 (2 H, t, *J* 7.3, H5), 4.11 (1 H, s, OH), 2.13 (3 H, s, H7), 1.95 - 2.11 (2 H, m, H4), 1.07 (3 H, s, H6); δ_C (100 MHz; $CDCl_3$) 214.3 (C), 137.3 (C), 128.4 (CH), 128.1 (CH), 125.6 (CH), 91.4 (C), 81.8 (C), 66.0 (CH_2), 39.4 (CH_2), 27.1 (CH_3), 24.9 (CH_3).

Ethyl *cis*-3-hydroxy-2,3-diphenyltetrahydrofuran-2-carboxylate 292a



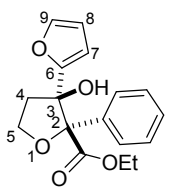
Obtained by **general procedure O** using copper(I) triflate toluene complex (13 mg, 0.025 mmol), ethyl 2-diazo-2-phenylacetate **104** (123 mg, 0.65 mmol) and 3-hydroxy-1-phenylpropan-1-one **291a** (83 mg, 0.5 mmol); purified using 20% ethyl acetate in light petroleum. The *title compound* was obtained as a colourless oil (145 mg, 89%); (Found: $M+Na^+$, 335.1246. $C_{19}H_{20}NaO_4$ requires 335.1254); ν_{max} ($CHCl_3$)/cm-1 3447, 3011, 2985, 1734, 1705, 1448, 1265, 1132, 1096, 1067, 1030; δ_H (400 MHz; $CDCl_3$) 7.02 - 7.20 (10 H, m, ArH), 4.66 (1 H, br s, OH), 4.47 (2 H, dd, *J* 8.9, 5.5, H5), 4.17 - 4.30 (2 H, two overlapping dt, *J* 10.6, 7.1, $C\underline{H}_2CH_3$), 2.68 (1 H, dt, *J* 13.0, 8.9, H4), 2.28 (1 H, dt, *J* 13.0, 5.5, H4), 1.24 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 173.2 (C), 140.7 (C), 137.3 (C), 127.7 (CH), 127.5 (CH), 127.29 (CH), 127.25 (CH), 126.8 (CH), 126.0 (CH), 90.8 (C), 85.9 (C), 66.8 (CH_2), 62.2 (CH_2), 39.6 (CH_2), 14.1 (CH_3).

Ethyl *cis*-3-(2-ethoxy-2-oxoethyl)-3-hydroxy-2-phenyltetrahydrofuran-2-carboxylate 292b



Obtained by **general procedure O** using copper(I) triflate toluene complex (13 mg, 0.025 mmol), ethyl 2-diazo-2-phenylacetate **104** (123 mg, 0.65 mmol) and ethyl 5-hydroxy-3-oxopentanoate **292b** (81 mg, 0.5 mmol); purified using 20% ethyl acetate in light petroleum. The *title compound* was obtained as a colourless oil (89 mg, 55%); (Found: M+Na$^+$, 345.1303. $C_{17}H_{22}NaO_6$ requires 345.1309); ν_{max} ($CHCl_3$)/cm^{-1} 3533, 3011, 2985, 1722, 1371, 1272, 1098, 1070, 1027; δ_H (400 MHz; $CDCl_3$) 7.54 - 7.63 (2 H, m, ArH), 7.27 - 7.38 (3 H, m, ArH), 4.24 - 4.42 (4 H, m, H5 and H7), 4.23 (1 H, s, OH), 4.11 (2 H, q, *J* 7.2, H9), 2.89 (1 H, d, *J* 15.3, H6), 2.23 (1 H, ddd, *J* 12.9, 7.0, 3.8, H4), 2.12 - 2.19 (1 H, m, H4), 2.08 (1 H, d, *J* 15.3, H6), 1.26 (3 H, t, *J* 7.2, H10), 1.22 (3 H, t, *J* 7.2, H8); δ_C (100 MHz; $CDCl_3$) 172.0 (C), 171.8 (C), 137.6 (C), 128.4 (CH), 128.3 (CH), 126.2 (CH), 90.7 (C), 82.3 (C), 67.2 (CH_2), 62.0 (CH_2), 61.0 (CH_2), 41.0 (CH_2), 36.5 (CH_2), 14.2 (CH_3), 14.1 (CH_3).

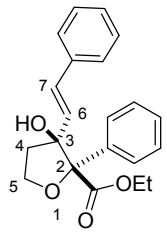
Ethyl *cis*-3-(2-furyl)-3-hydroxy-2-phenyltetrahydrofuran-2-carboxylate 292c



Obtained by **general procedure O** using rhodium octanoate dimer (4 mg, 0.005 mmol), ethyl 2-diazo-2-phenylacetate **104** (123 mg, 0.65 mmol) and 1-(2-furyl)-3-hydroxypropan-1-one **291c** (71 mg, 0.5 mmol); purified using 15% ethyl acetate in light petroleum. The *title compound* was obtained as a slowly crystallising yellow solid (116 mg, 77%); mp 52 - 53 °C; (Found:

M+Na⁺, 325.1060. $C_{17}H_{18}NaO_5$ requires 325.1046); ν_{max} ($CHCl_3$)/cm^{-1} 3532, 2985, 2929, 2901, 1718, 1391, 1269, 1096, 1069, 1017; δ_H (400 MHz; $CDCl_3$) 7.20 (1 H, dd, *J* 1.8, 0.8, H9), 7.14 - 7.19 (5 H, m, ArH), 6.18 (1 H, dd, *J* 3.3, 1.8, H8), 6.02 (1 H, dd, *J* 3.3, 0.8, H7), 4.51 (1 H, br s, OH), 4.41 - 4.49 (2 H, m, H5), 4.26 (2 H, q, *J* 7.1, C<u>H</u>$_2$CH$_3$), 2.60 (1 H, dtd, *J* 12.8, 9.5, 1.6, H4), 2.21 (1 H, ddd, *J* 12.8, 6.0, 3.3, H4), 1.25 (3 H, t, *J* 7.1, CH$_2$C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 172.3 (C), 153.0 (C), 141.7 (CH), 137.8 (C), 127.9 (CH), 127.7 (CH), 125.3 (CH), 110.4 (CH), 108.1 (CH), 91.8 (C), 83.2 (C), 67.1 (CH_2), 62.2 (CH_2), 36.7 (CH_2), 14.1 (CH_3).

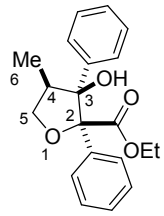
Ethyl *cis*-3-hydroxy-2-phenyl-3-((*E*)-styryl)tetrahydrofuran-2-carboxylate 292d



Obtained by **general procedure O** using rhodium octanoate dimer (4 mg, 0.005 mmol), ethyl 2-diazo-2-phenylacetate **104** (123 mg, 0.65 mmol) and (*E*)-5-hydroxy-1-phenylpent-1-en-3-one **291d** (88 mg, 0.5 mmol); purified using 30% ethyl acetate in light petroleum. The *title compound* was obtained as a colourless solid (149 mg, 88%); mp 151 - 152 °C; (Found: M+Na⁺, 361.1424. $C_{21}H_{22}NaO_4$ requires 361.1410); ν_{max} ($CHCl_3$)/cm^{-1} 3542, 3011, 2985, 1712, 1448, 1294, 1268, 1099, 1073, 1025; δ_H (400 MHz; $CDCl_3$) 7.50 - 7.56 (2 H, m, ArH), 7.16 - 7.38 (8 H, m, ArH), 6.65 (1 H, d, *J* 16.1, H7), 5.94 (1 H, d, *J* 16.1, H6), 4.35 - 4.49 (2 H, m, H5), 4.26 (2 H, q, *J* 7.2, C<u>H</u>$_2$CH$_3$), 3.91 (1 H, d, *J* 1.5, OH), 2.18 - 2.28 (1 H, m, H4), 2.10 (1 H, ddd, *J* 12.9, 6.3, 3.2, H4), 1.25 (3 H, t, *J* 7.2, CH$_2$C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 172.5 (C), 138.0 (C), 136.8 (C), 130.3 (CH), 129.4

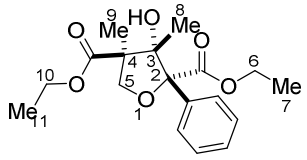
(CH), 128.6 (CH), 128.3 (CH), 128.1 (CH), 127.7 (CH), 126.6 (CH), 126.0 (CH), 91.7 (C), 84.1 (C), 67.5 (CH_2), 62.2 (CH_2), 38.2 (CH_2), 14.1 (CH_3).

Ethyl *cis,cis*-3-hydroxy-4-methyl-2,3-diphenyltetrahydrofuran-2-carboxylate 292e



Obtained by **general procedure O** using copper(I) triflate toluene complex (13 mg, 0.025 mmol), ethyl 2-diazo-2-phenylacetate **104** (123 mg, 0.65 mmol) and 3-hydroxy-2-methyl-1-phenylpropan-1-one **291e** (82 mg, 0.5 mmol); purified using 20% ethyl acetate in light petroleum. The *title compound* was obtained as a slowly crystallising colourless solid (139 mg, 85%); mp 70 - 71 °C; (Found: M+Na^+, 349.1416. $C_{20}H_{22}NaO_4$ requires 349.1410); ν_{max} ($CHCl_3$)/cm^{-1} 3599, 3009, 2983, 2888, 1732, 1446, 1267, 1092, 1074, 1057, 998; δ_H (400 MHz; $CDCl_3$) 7.12 - 7.23 (4 H, m, ArH), 6.95 - 7.11 (6 H, m, ArH), 4.52 (1 H, t, *J* 7.9, H5), 4.19 - 4.28 (2 H, m, C<u>H</u>$_2$CH$_3$), 4.14 (1 H, dd, *J* 10.7, 7.9, H5), 3.75 (1 H, d, *J* 0.6, OH), 2.81 (1 H, ddq, *J* 10.7, 7.9, 6.8, H4),1.23 (3 H, t, *J* 7.2, CH$_2$C<u>H</u>$_3$), 0.85 (3 H, d, *J* 6.8, H6); δ_C (100 MHz; $CDCl_3$) 171.8 (C), 138.5 (C), 138.0 (C), 127.8 (CH), 127.49 (CH), 127.47 (CH), 127.32 (CH), 127.31 (CH), 126.7 (CH), 93.6 (C), 86.8 (C), 73.3 (CH_2), 61.9 (CH_2), 40.6 (CH), 14.1 (CH_3), 8.3 (CH_3).

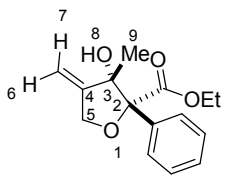
Diethyl *cis*, *trans*-3-hydroxy-3,4-dimethyl-2-phenyltetrahydro-furan-2,4-dicarboxylate 292f



Obtained by **general procedure O** using rhodium octanoate dimer (4 mg, 0.005 mmol), ethyl 2-diazo-2-phenylacetate **104** (123 mg, 0.65 mmol) and ethyl 2-(hydroxymethyl)-2-methyl-3-oxobutanoate **291f**

(88 mg, 0.5 mmol); purified using 10% ethyl acetate in light petroleum. The *title compound* was obtained as a colourless oil (81 mg, 48%); (Found: M+Na$^+$, 359.1482. $C_{18}H_{24}NaO_6$ requires 359.1465); ν_{max} ($CHCl_3$)/cm^{-1} 3557, 2984, 2904, 1724, 1447, 1369, 1279, 1104, 1066, 1034; δ_H (400 MHz; $CDCl_3$) 7.75 - 7.84 (2 H, m, ArH), 7.30 - 7.39 (3 H, m, ArH), 4.84 (1 H, d, *J* 8.8, H5), 4.12 - 4.28 (4 H, m, H6 and H10), 4.03 (1 H, d, *J* 8.8, H5), 3.73 (1 H, s, OH), 1.40 (3 H, s, H8), 1.25 - 1.34 (6 H, two overlapping t, *J* 6.4 and *J* 6.8, H7 and H11), 1.15 (3 H, s, H9); δ_C (100 MHz; $CDCl_3$) 173.4 (C), 172.5 (C), 137.9 (C), 128.1 (CH), 128.0 (CH), 126.6 (CH), 91.7 (C), 85.1 (C), 74.7 (CH_2), 62.0 (CH_2), 61.2 (CH_2), 56.4 (C), 21.5 (CH_3), 20.2 (CH_3), 14.2 (CH_3), 14.1 (CH_3).

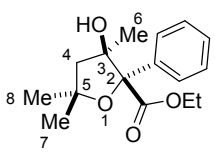
Ethyl *cis*-3-hydroxy-3-methyl-4-methylene-2-phenyltetrahydro-furan-2-carboxylate 292g



Obtained by **general procedure O** using rhodium octanoate dimer (4 mg, 0.005 mmol), ethyl 2-diazo-2-phenylacetate **104** (123 mg, 0.65 mmol) and 3-(hydroxymethyl)but-3-en-2-one **291g** (88 mg, 0.5 mmol); purified using 10% ethyl acetate in light petroleum. The *title compound* was obtained as a colourless oil (88 mg, 67%); (Found: M+Na$^+$, 285.1102. $C_{15}H_{18}NaO_4$ requires 285.1097); ν_{max} ($CHCl_3$)/cm^{-1} 3474, 2986, 2936, 2873, 1704, 1368, 1259, 1092, 1059, 1032; δ_H (400 MHz; $CDCl_3$) 7.55 - 7.67 (2 H, m, ArH), 7.28 - 7.41 (3 H, m, ArH), 5.33 (1 H, t, *J* 2.3 H7), 4.99 (1 H, t, *J* 2.3, H6), 4.71 (1 H, dt, *J* 13.5, 2.3, H5), 4.68 (1 H, q, *J* 1.2, OH), 4.57 (1 H, dt, *J* 13.5, 2.3, H5), 4.24 (1 H, dq, *J* 10.8, 7.2, C$\underline{H}_2$CH$_3$), 4.13 (1 H, dq, *J* 10.8, 7.2, C$\underline{H}_2$CH$_3$), 1.19 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$), 0.94 (3 H, d, *J* 1.2, H9); δ_C (100 MHz;

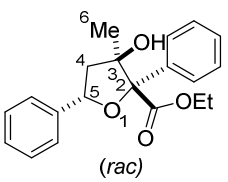
$CDCl_3$) 174.4 (C), 152.6 (C), 135.8 (C), 128.3 (CH), 128.2 (CH), 125.3 (CH), 105.0 (CH_2), 86.0 (C), 81.3 (C), 68.5 (CH_2), 62.1 (CH_2), 24.1 (CH_3), 14.1 (CH_3).

Ethyl *cis*-3-hydroxy-3,5,5-trimethyl-2-phenyltetrahydrofuran-2-carboxylate 292h

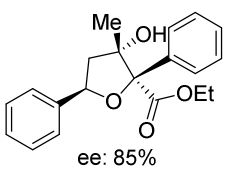


Obtained by **general procedure O** using rhodium octanoate dimer (4 mg, 0.005 mmol), ethyl 2-diazo-2-phenylacetate **104** (123 mg, 0.65 mmol) and 4-hydroxy-4-methylpentan-2-one **291h** (63 μL, 0.5 mmol); purified using 5% ethyl acetate in light petroleum. The *title compound* was obtained as a colourless oil (93 mg, 67%); (Found: M+Na^+, 301.1420. $C_{16}H_{22}NaO_4$ requires 301.1410); ν_{max} ($CHCl_3$)/cm^{-1} 3469, 3009, 2983, 1702, 1448, 1386, 1300, 1258, 1088, 1059, 1033; δ_H (400 MHz; $CDCl_3$) 7.46 - 7.55 (2 H, m, ArH), 7.26 - 7.36 (3 H, m, ArH), 5.01 (1 H, br s, OH), 4.11 - 4.27 (2 H, m, C$\underline{H}_2$$CH_3$), 2.28 (1 H, d, *J* 12.9, H4), 2.11 (1 H, d, *J* 12.9, H4), 1.46 (3 H, s, H8), 1.40 (3 H, s, H7), 1.19 (3 H, t, *J* 7.2, CH_2C$\underline{H}_3$), 0.94 (3 H, s, H6); δ_C (100 MHz; $CDCl_3$) 176.3 (C), 137.8 (C), 128.2 (CH), 127.8 (CH), 124.9 (CH), 87.4 (C), 82.2 (C), 80.0 (C), 61.9 (CH_2), 52.7 (CH_2), 30.3 (CH_3), 29.9 (CH_3), 26.3 (CH_3), 13.9 (CH_3).

Ethyl *cis*, *trans*-3-hydroxy-3-methyl-2,5-diphenyltetrahydrofuran-2-carboxylate and ethyl (*2S,3R,5S*)-3-hydroxy-3-methyl-2,5-diphenyltetrahydrofuran-2-carboxylate 292i



(*rac*)



ee: 85%

(a) The racemic product was obtained by **general procedure O** using rhodium octanoate dimer

(4 mg, 0.005 mmol), ethyl 2-diazo-2-phenylacetate **104** (123 mg, 0.65 mmol) and racemic 4-hydroxy-4-phenylbutan-2-one **291i** (82 mg, 0.5 mmol); purified using the elution gradient 5% to 10% ethyl acetate in light petroleum. The racemic product was obtained as a colourless oil (103 mg, 63%); (Found: M+Na$^+$, 349.1421. $C_{20}H_{22}NaO_4$ requires 349.1410); ν_{max} ($CHCl_3$)/cm^{-1} 3496, 3011, 2938, 1730, 1449, 1268, 1239, 1063, 1029; δ_H (400 MHz; $CDCl_3$) 7.64 - 7.71 (2 H, m, ArH), 7.48 - 7.57 (2 H, m, ArH), 7.28 - 7.45 (6 H, m, ArH), 5.46 (1 H, t, *J* 8.0, H5), 4.22 - 4.39 (2 H, m, C$\underline{H}_2$CH$_3$), 4.14 (1 H, s, OH), 2.54 (1 H, dd, *J* 12.6, 8.0, H4), 2.13 (1 H, dd, *J* 12.6, 8.0, H4), 1.26 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$), 1.09 (3 H, s, H6); δ_C (100 MHz; $CDCl_3$) 173.9 (C), 141.4 (C), 138.0 (C), 128.6 (CH), 128.3 (CH), 128.1 (CH), 127.6 (CH), 126.1 (CH), 125.7 (CH), 90.5 (C), 82.3 (C), 78.1 (CH), 62.1 (CH_2), 46.9 (CH_2), 26.0 (CH_3), 14.2 (CH_3).

(b) The chiral product was obtained by **general procedure O** using rhodium octanoate dimer (4 mg, 0.005 mmol), ethyl 2-diazo-2-phenylacetate **104** (123 mg, 0.65 mmol) and enantioenriched 4-hydroxy-4-phenylbutan-2-one **291i** (82 mg, 0.5 mmol, enantiomeric excess 77%, determined by HPLC : Daicel Chiralcel OD-R, i-PrOH/hexane 5:95, UV 215 nm, flow rate 1.0 mL/min. *R*-isomer, t_R 25.6 min and *S*-isomer, t_R 24.4 min); purified using the elution gradient 5% to 10% ethyl acetate in light petroleum. The enantio-enriched product **292i** (enantiomeric excess 85%, determined by HPLC : Daicel Chiralcel AD, i-PrOH/hexane 5:95, UV 215 nm, flow rate 1.0 mL/min. (*2S,3R,5S*)-isomer, t_R 8.9 min and (*2R,3S,5R*)-isomer, t_R 13.5 min) was obtained as a colourless solid (121

mg, 75%); crystallisation from cyclohexane gave the pure (*2S,3R,5S*)-isomer (as determined by Xray crystallography; mp 86 - 87 °C; $[\alpha]_D^{24}$ +68.1 (*c* 0.1, $CHCl_3$); other data as below.

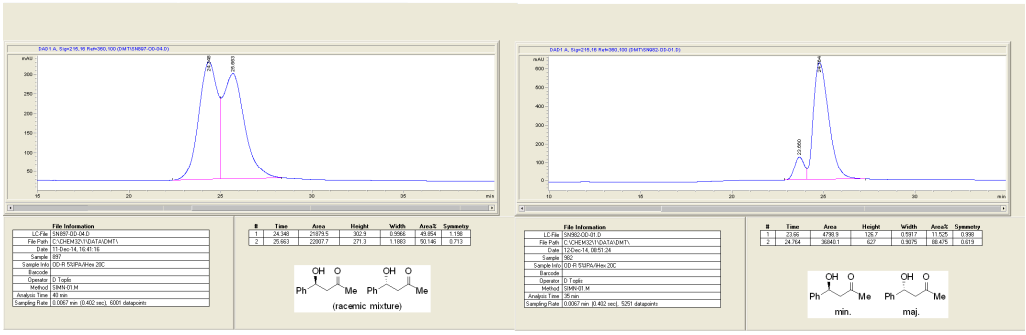


Figure E5: HPLC report for racemic hydroxyketone 291i (left) and enantioenriched 291i (right)

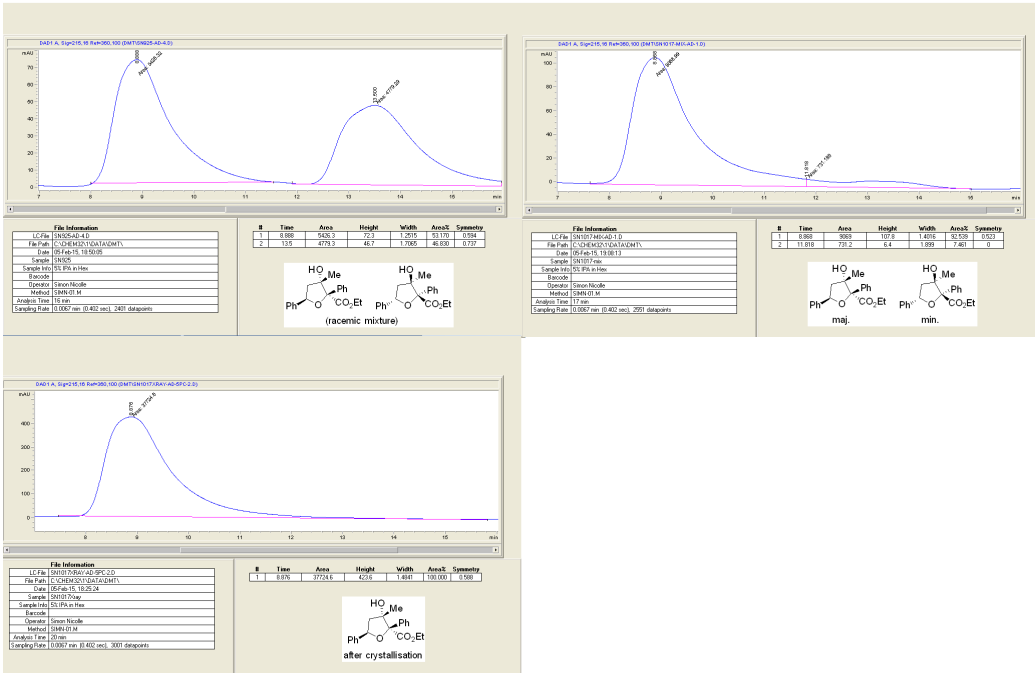
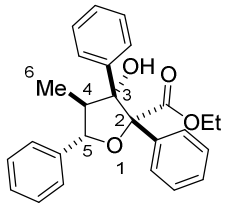


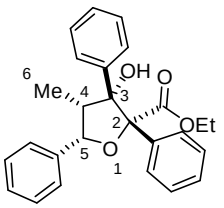
Figure E6: HPLC report for racemic tetrahydrofuran 292i (top left), tetrahydrofuran 292i obtained from chiral alcohol 291i before crystallisation (top right) and after crystallisation (bottom).

Ethyl *cis*,*trans*,*trans*- 3-hydroxy-4-methyl-2,3,5-triphenyltetra-hydrofuran-2-carboxylate 292j



Obtained by **general procedure O** using rhodium octanoate dimer (4 mg, 0.005 mmol), ethyl 2-diazo-2-phenylacetate **104** (123 mg, 0.65 mmol) and *anti*-3-hydroxy-2-methyl-1,3-diphenylpropan-1-one **291j** (120 mg, 0.5 mmol); purified using 1% methanol in dichloromethane. The *title compound* was obtained as a colourless oil (154 mg, 76%); (Found: M+Na$^+$, 425.1729. $C_{26}H_{26}NaO_4$ requires 425.1723); ν_{max} ($CHCl_3$)/cm^{-1} 3596, 3008, 2984, 2936, 1737, 1701, 1447, 1063, 1032, 997; δ_H (400 MHz; $CDCl_3$) 7.63 - 7.71 (2 H, m, ArH), 7.44 - 7.52 (2 H, m, ArH), 7.37 - 7.43 (1 H, m, ArH), 7.24 - 7.30 (2 H, m, ArH), 7.02 - 7.17 (8 H, m, ArH), 5.25 (1 H, d, *J* 10.5, H5), 4.27 (2 H, q, *J* 7.2, C$\underline{H}_2$CH$_3$), 4.14 (1 H, s, OH), 2.73 (1 H, dq, *J* 10.5, 6.7, H4), 1.24 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$), 0.82 (3 H, d, *J* 6.7, H6); δ_C (100 MHz; $CDCl_3$) 173.0 (C), 140.0 (C), 138.9 (C), 138.2 (C), 128.7 (CH), 128.5 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 127.33 (CH), 127.28 (CH), 126.94 (CH), 126.88 (CH), 93.3 (C), 88.0 (C), 85.6 (CH), 62.0 (CH_2), 49.3 (CH), 14.1 (CH_3), 8.2 (CH_3).

Ethyl *cis*,*cis*,*cis*-3-hydroxy-4-methyl-2,3,5-triphenyltetrahydro-furan-2-carboxylate 292k



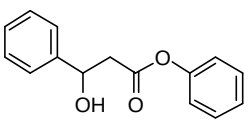
Obtained by **general procedure O** using rhodium octanoate dimer (4 mg, 0.005 mmol), ethyl 2-diazo-2-phenylacetate **104** (123 mg, 0.65 mmol) and *syn*-3-hydroxy-2-methyl-1,3-diphenylpropan-1-one **291k** (120 mg, 0.5 mmol); purified using dichloromethane. The *title compound* was obtained as a

colourless solid (141 mg, 70%); mp 62 - 64 °C; (Found: M+Na$^+$, 425.1730. $C_{26}H_{26}NaO_4$ requires 425.1723); ν_{max} ($CHCl_3$)/cm^{-1} 3567, 3007, 2983, 2938, 1734, 1446, 1369, 1262, 1095, 1072; δ_H (400 MHz; $CDCl_3$) 7.64 (2 H, d, *J* 7.4, ArH), 7.39 (2 H, t, *J* 7.4, ArH), 7.29 (1 H, t, *J* 7.4, ArH), 7.11 - 7.27 (8 H, m, ArH), 7.06 (2 H, d, *J* 7.4, ArH), 5.83 (1 H, d, *J* 9.4, H5), 4.39 (1 H, dq, *J* 10.8, 7.2, C$\underline{H}_2$CH$_3$), 4.29 (1 H, dq, *J* 10.8, 7.2, C$\underline{H}_2$CH$_3$), 3.16 (1 H, dq, *J* 9.4, 7.2, H4), 2.95 (1 H, s, OH), 1.35 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$), 0.62 (3 H, d, *J* 7.2, H6); δ_C (100 MHz; $CDCl_3$) 170.7 (C), 140.7 (C), 138.3 (C), 137.4 (C), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.7 (CH), 127.50 (CH), 127.47 (CH), 127.4 (CH), 127.2 (CH), 126.9 (CH), 94.3 (C), 88.3 (C), 83.4 (CH), 61.8 (CH_2), 43.8 (CH), 14.3 (CH_3), 9.3 (CH_3).

IV.4. Studies towards the preparation of the hyperolactone spirocyclic core

S-Phenyl 3-hydroxy-3-phenylpropanethioate **320c** was prepared according to a previously described method. [73]

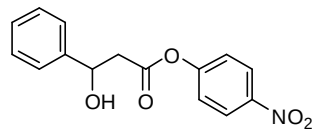
Phenyl 3-hydroxy-3-phenylpropanoate 320a



Magnesium bromide ethyl etherate (361 mg, 1.40 mmol) was added at room temperature to a solution containing benzaldehyde (112 µL, 1.10 mmol) and phenyl acetate (127 µL, 1.00 mmol) in dichloromethane (5 mL), followed by *N*,*N*-diisopropylethylamine (350 µL, 2.00 mmol). The resulting mixture was stirred for 40 min at room temperature and quenched by the addition of aqueous hydrochloric acid (1 M, 10 mL). Dichloromethane (20 mL) was added, the phases were separated and the aqueous phase was extracted

with additional dichloromethane (10 mL). The combined organic phases were dried over $MgSO_4$ and the volatiles were removed under reduced pressure. The *title compound* was obtained by column chromatography using 20% ethyl acetate in light petroleum as a colourless solid (178 mg, 73%); mp 68 °C (lit:[74] no mp reported); (Found: M+Na$^+$, 265.0828. $C_{15}H_{14}NaO_3$ requires 265.0835); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3606, 2927, 1745, 1601, 1192; δ_H (400 MHz; $CDCl_3$) 7.30 - 7.48 (7 H, m, ArH), 7.20 - 7.28 (1 H, m, ArH), 7.01 - 7.10 (2 H, m, ArH), 5.26 (1 H, dt, *J* 8.8, 3.9, CH), 3.04 (1 H, d, *J* 3.9, OH), 3.01 - 3.10 (1 H, dd, *J* 16.3, 8.8, CH_2), 2.97 (1 H, dd, *J* 16.3, 3.9,CH_2); δ_C (100 MHz; $CDCl_3$) 170.8 (C), 150.5 (C), 142.4 (C), 129.6 (CH), 128.8 (CH), 128.1 (CH), 126.2 (CH), 125.9 (CH), 121.6 (CH), 70.5 (CH), 43.7 (CH_2). The data obtained match these previously reported.[74]

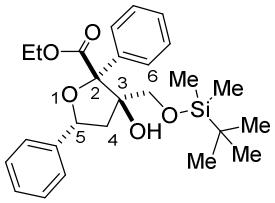
4-Nitrophenyl 3-hydroxy-3-phenylpropanoate 320b



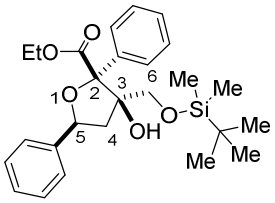
Magnesium bromide ethyl etherate (1.81 g, 7.00 mmol) was added at room temperature to a solution containing benzaldehyde (560 μL, 5.50 mmol) and *p*-nitrophenyl acetate (905 mg, 5.00 mmol) in dichloromethane (35 mL), followed by *N*,*N*-diisopropylethylamine (1.74 mL, 10.0 mmol). The resulting mixture was stirred for 25 min at room temperature and quenched by the addition of a mixture of aqueous hydrochloric acid (2 M, 40 mL) and crushed ice (50 g). The phases were separated and the aqueous phase was extracted with additional dichloromethane (20 mL). The combined organic phases were dried over $MgSO_4$ and the volatiles were removed under reduced pressure. The *title compound* was obtained

by column chromatography using 30% ethyl acetate in light petroleum as a colourless oil (868 mg, 60%); (Found: M+Na$^+$, 310.0688. $C_{15}H_{13}NNaO_5$ requires 310.0686); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3605, 2927, 1759, 1527, 1348; δ_H (400 MHz; $CDCl_3$) 8.18 - 8.35 (2 H, m, ArH), 7.37 - 7.47 (4 H, m, ArH), 7.31 - 7.37 (1 H, m, ArH), 7.18 - 7.29 (2 H, m, ArH), 5.28 (1 H, dt, *J* 8.8, 4.0, CH), 3.10 (1 H, dd, *J* 16.3, 8.8, CH_2), 3.00 (1 H, dd, *J* 16.3, 4.0, CH_2), 2.76 (1 H, d, *J* 4.0, OH); δ_C (100 MHz; $CDCl_3$) 169.6 (C), 155.2 (C), 145.6 (C), 142.2 (C), 128.9 (CH), 128.4 (CH), 125.8 (CH), 125.4 (CH), 122.6 (CH), 70.6 (CH), 43.8 (CH_2).

Ethyl *cis,cis* and *cis,trans*-3-(((*tert*-butyldimethylsilyl)-oxy)methyl)-3-hydroxy-2,5-diphenyltetrahydrofuran-2-carboxylate 326a-b



(*cis*,*trans*)-**326a**



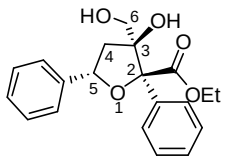
(*cis*,*cis*)-**326b**

Obtained by **the general procedure** using rhodium octanoate dimer (4 mg, 0.005 mmol), ethyl 2-diazo-2-phenylacetate **104** (123 mg, 0.65 mmol) and 1-((*tert*-butyldimethyl-silyl)oxy)-4-hydroxy-4-phenylbutan-2-one[75] **325** (147 mg, 0.5 mmol); purified using the elution gradient 5 to 10% ethyl acetate in light petroleum. **Ethyl *cis,cis*-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-hydroxy-2,5-diphenyltetra-hydrofuran-2-carboxylate 326b**:

colourless oil (52 mg, 23%); (Found: M+Na$^+$, 479.2227. $C_{26}H_3NaO_5Si$ requires 479.2232); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3008, 2956, 2930, 2857, 2930, 1731, 1709, 1601, 1463, 1448, 1257, 1096, 1029, 839; δ_H (400 MHz; $CDCl_3$) 7.61 - 7.69 (2 H, m, ArH), 7.48 - 7.55 (2 H, m, ArH), 7.27 - 7.40 (6 H, m, ArH), 5.42 (1 H, dd, *J* 8.4, 7.4, H5), 4.39 (1 H, s, OH), 4.25 (1 H, dq, *J* 10.8,

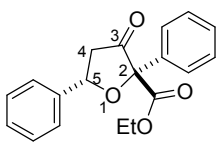
7.2, C<u>H</u>$_2$CH$_3$), 4.16 (1 H, dq, *J* 10.8, 7.2, C<u>H</u>$_2$CH$_3$), 3.41 (1 H, d, *J* 10.4, H6), 3.32 (1 H, d, *J* 10.4, H6), 2.82 (1 H, dd, *J* 12.7, 7.4, H4), 2.32 (1 H, dd, *J* 12.7, 8.4, H4), 1.20 (3 H, t, *J* 7.2, CH$_2$C<u>H</u>$_3$), 0.86 (9 H, s, *t*Bu), −0.02 (3 H, s, CH$_3$), −0.05 (3 H, s, CH$_3$); δ_C (100 MHz; CDCl$_3$) 173.5 (C), 142.7 (C), 136.8 (C), 128.4 (CH), 128.11 (CH), 128.06 (CH), 127.5 (CH), 126.0 (CH), 125.8 (CH), 88.0 (C), 84.4 (C), 79.5 (CH), 66.4 (CH$_2$), 61.9 (CH$_2$), 43.4 (CH$_2$), 26.0 (CH$_3$), 18.4 (C), 14.0 (CH$_3$), −5.3 (CH$_3$), −5.5 (CH$_3$). **Ethyl *cis,trans*-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-hydroxy-2,5-diphenyltetrahydro-furan-2-carboxylate 326a**: colourless oil (167 mg, 73%); (Found: M+Na$^+$, 479.2229. $C_{26}H_3NaO_5Si$ requires 479.2232); ν_{max} (CHCl$_3$)/cm^{-1} 3691, 3010, 2956, 2929, 2856, 1711, 1602, 1363, 1256, 1093, 1060, 1031, 839; δ_H (400 MHz; CDCl$_3$) 7.82 (2 H, dd, *J* 8.0, 1.6, ArH), 7.55 (2 H, d, *J* 7.4, ArH), 7.41 (2 H, t, *J* 7.4, ArH), 7.27 - 7.37 (4 H, m, ArH), 5.55 (1 H, dd, *J* 10.0, 5.6, H5), 4.33 (1 H, dq, *J* 10.9, 7.2, C<u>H</u>$_2$CH$_3$), 4.27 (1 H, dq, *J* 10.9, 7.2, C<u>H</u>$_2$CH$_3$), 3.96 (1 H, d, *J* 0.6, OH), 3.45 (1 H, d, *J* 10.2, H6), 3.18 (1 H, d, *J* 10.2, H6), 2.38 (1 H, dd, *J* 12.4, 5.6, H4), 2.14 (1 H, ddd, *J* 12.4, 10.0, 0.6, H4), 1.30 (3 H, t, *J* 7.2, CH$_2$C<u>H</u>$_3$), 0.85 (9 H, s, *t*Bu), −0.08 (3 H, s, CH$_3$) −0.10 (3 H, s, CH$_3$); δ_C (100 MHz; CDCl$_3$) 171.9 (C), 140.8 (C), 137.5 (C), 128.6 (CH), 128.1 (CH), 128.0 (CH), 127.8 (CH), 126.7 (CH), 126.4 (CH), 91.4 (C), 84.7 (C), 79.0 (CH), 66.5 (CH$_2$), 61.7 (CH$_2$), 43.8 (CH$_2$), 25.9 (CH$_3$), 18.3 (C), 14.3 (CH$_3$), −5.5 (CH$_3$), −5.6 (CH$_3$).

Ethyl *cis,trans*-3-hydroxy-3-(hydroxymethyl)-2,5-diphenyltetrahydrofuran-2-carboxylate



The DOWEX® 50WX4-200 resin (120 mg) was added to a solution of ethyl *cis,trans*-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-hydroxy-2,5-diphenyltetrahydrofuran-2-carboxylate **326a** (62 mg, 0.135 mmol) in ethanol (2 mL) at room temperature and the resulting mixture was stirred for 18 h. The resin was removed by filtration, washed with ethanol (2×2 mL) and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using 50% ethyl acetate in light petroleum to give the *title compound* as a colourless solid (36 mg, 78%); mp 95 °C; (Found: M+Na$^+$, 365.1357. $C_{20}H_{22}NaO_5$ requires 365.1359); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3605, 2927, 1709, 1602, 1299, 1271, 1239, 1061, 1030; δ_H (400 MHz; $CDCl_3$) 7.58 - 7.73 (2 H, m, ArH), 7.52 (2 H, d, *J* 7.5, ArH), 7.42 (2 H, t, *J* 7.5, ArH), 7.27 - 7.39 (4 H, m, ArH), 5.52 (1 H, dd, *J* 9.5, 6.4, H5), 4.22 - 4.43 (3 H, m, OH and C$\underline{H}_2$CH$_3$), 3.42 (1 H, d, *J* 11.5, H6), 3.16 (1 H, dd, *J* 11.5, 9.2, H6), 2.42 (1 H, dd, *J* 12.8, 6.4, H4), 2.23 - 2.37 (1 H, dd, *J* 12.8, 9.5, H4), 2.34 (1 H, br s, OH), 1.28 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 173.5 (C), 140.5 (C), 136.9 (C), 128.7 (CH), 128.61 (CH), 128.58 (CH), 127.9 (CH), 126.2 (CH), 125.7 (CH), 90.8 (C), 84.5 (C), 78.9 (CH), 66.3 (CH_2), 62.5 (CH_2), 42.2 (CH_2), 14.1 (CH_3).

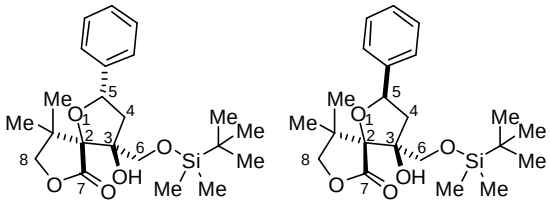
Ethyl *trans*-3-oxo-2,5-diphenyltetrahydrofuran-2-carboxylate 327



Sodium periodiate (65 mg, 0.33 mmol) was added in one portion to a solution of ethyl *cis, trans*-3-hydroxy-

3-(hydroxymethyl)-2,5-diphenyltetrahydro-furan-2-carboxylate (49 mg, 0.143 mmol) in THF (0.8 mL) and water (0.8 mL) at room temperature and the reaction mixture was stirred for 4 h. Water (10 mL) was added and the resulting mixture was extracted with ether (10 mL). The organic phase was washed with brine (5 mL) and dried over $MgSO_4$. Removal of the volatiles under reduced pressure gave a residue that was purified by column chromatography to give the *title compound* as a colourless solid (43 mg, 97%); mp 54 °C; (Found: M+Na$^+$, 333.1095. $C_{19}H_{18}NaO_4$ requires 333.1097); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3606, 2927, 2855, 1771, 1740, 1602, 1240, 1136, 1030; δ_H (400 MHz; $CDCl_3$) 7.82 (2 H, dd, *J* 8.2, 1.3, ArH), 7.50 - 7.55 (2 H, m, ArH), 7.33 - 7.49 (6 H, m, ArH), 5.58 (1 H, dd, *J* 10.8, 5.9, H5), 4.29 (2 H, q, *J* 7.2, C$\underline{H}_2$CH$_3$), 3.04 (1 H, dd, *J* 18.1, 5.9, H4), 2.64 (1 H, dd, *J* 18.1, 10.8, H4), 1.31 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 206.7 (C), 167.7 (C), 139.7 (C), 134.8 (C), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.3 (CH), 126.4 (CH), 125.8 (CH), 87.4 (C), 77.6 (CH), 62.7 (CH_2), 44.2 (CH_2), 14.2 (CH_3).

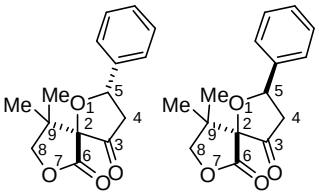
cis, trans and *cis, cis*-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-hydroxy-9,9-dimethyl-2-phenyl-1,7-dioxaspiro[4.4]nonan-6-one 328a-b



A solution containing 3-diazo-4,4-dimethyldihydrofuran-2(*3H*)-one **121** (36.5 mg, 0.26 mmol) in anhydrous dichloromethane (2 mL) was added over 30 min to a solution of 1-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-4-phenylbutan-2-one[75] **325** (59 mg, 0.2 mmol) and copper(I) acetate (1.2 mg, 0.01 mmol)

in anhydrous dichloromethane (1 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h, warmed up at room temperature and stirred for 2 h. Finally, the reaction was heated at reflux for 16 h. The mixture was cooled to room temperature and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using 13% ethyl acetate in light petroleum to give the *title compound* as an inseparable mixture of isomers (ratio 86:14). Colourless solid (59 mg, 72%); mp 83 - 84 °C; (Found: M+Na$^+$, 429.2068. $C_{22}H_{34}NaO_5Si$ requires 429.2068); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3606, 2928, 1758, 1602, 1464, 1239, 838; only the signals observed for the major isomer are reported here. δ_H (400 MHz; $CDCl_3$) 7.22 - 7.39 (5 H, m, ArH), 5.24 (1 H, dd, *J* 9.9, 5.4, H5), 4.18 (1 H, dd, *J* 8.0, 0.7, H8), 3.90 (1 H, dd, *J* 10.1, 1.5, H6), 3.81 (1 H, d, *J* 8.0, H8), 3.57 (1 H, d, *J* 10.1, H6), 3.09 (1 H, s, CH_3), 2.89 (1 H, ddd, *J* 13.0, 9.9, 1.5, H4), 2.53 (1 H, dd, *J* 13.0, 5.4, H4), 1.33 (3H, s, CH_3), 1.24 (3H, s, CH_3), 0.84 (9 H, s, *t*Bu), −0.01 (3 H, s, CH_3); −0.05 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 174.9 (C), 142.3 (C), 128.6 (CH), 127.6 (CH), 125.5 (CH), 87.6 (C), 81.2 (C), 78.9 (CH_2), 76.6 (CH), 65.4 (CH_2), 43.1 (CH_2), 41.4 (C), 26.0 (CH_3), 21.7 (CH_3), 18.5 (C), 18.3 (CH_3), −5.3 (CH_3), −5.5 (CH_3).

cis and *trans*-9,9-Dimethyl-2-phenyl-1,7-dioxaspiro[4.4]nonane-4,6-dione 331a-b

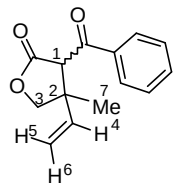


To a solution of 4-(((*tert*-butyldimethylsilyl)-oxy)methyl)-4-hydroxy-9,9-dimethyl-2-phenyl-1,7-dioxaspiro[4.4]nonan-6-one **328a-b** (ratio **328a**:**328b**, 86:14; 49 mg, 0.12 mmol) in THF (1.0 mL) was added aqueous hydrochloric acid (2 M, 0.5 mL) and the resulting solution was

stirred for 19 h at room temperature. Water was added (10 mL) and the reaction mixture was extracted with ethyl acetate (10 mL). The organic phase was washed with brine (5 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give the crude diol which was used in the next step without further purification. The diol was dissolved in a mixture of THF (0.6 mL) and water (0.6 mL), sodium periodinate (55 mg, 0.276 mmol) was added and the resulting mixture was stirred at room temperature for 18 h. Water (10 mL) was added and the resulting mixture was extracted with ether (20 mL), the organic phase was washed with brine (10 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure. The *title compounds* were obtained by column chromatography using 20% ethyl acetate in light petroleum. ***trans*-9,9-Dimethyl-2-phenyl-1,7-dioxaspiro[4.4]nonane-4,6-dione 331a**; colourless oil (25 mg, 80%); (Found: M+Na$^+$, 283.0942. $C_{15}H_{16}NaO_4$ requires 283.0941); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3011, 2927, 1788, 1753, 1602, 1114, 1009; δ_H (400 MHz; $CDCl_3$) 7.31 - 7.49 (5 H, m, ArH), 5.75 (1 H, dd, *J* 11.0, 5.8, H5), 4.49 (1 H, d, *J* 8.4, H8), 4.02 (1 H, d, *J* 8.4, H8), 2.99 (1 H, dd, *J* 17.8, 5.8, H4), 2.54 (1 H, dd, *J* 17.8, 11.0, H4), 1.27 (3 H, s, CH_3), 1.14 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 209.7 (C), 172.8 (C), 139.5 (C), 128.9 (CH), 128.7 (CH), 126.0 (CH), 89.8 (C), 77.2 (CH), 76.3 (CH_2), 45.6 (CH_2), 42.9 (C), 22.8 (CH_3), 18.1 (CH_3). ***cis*-9,9-Dimethyl-2-phenyl-1,7-dioxaspiro[4.4]nonane-4,6-dione 331b**; colourless oil (2.5 mg, 8%); (Found: M+Na$^+$, 283.0937. $C_{15}H_{16}NaO_4$ requires 283.0941); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3606, 2927, 1788, 1753, 1602, 1116, 1008; δ_H (400 MHz; $CDCl_3$) 7.54 - 7.62 (2 H, m, ArH), 7.32 - 7.46 (3 H, m, ArH),

5.39 (1 H, dd, *J* 10.0, 6.5, H5), 4.42 (1 H, d, *J* 8.5, H8), 4.00 (1 H, d, *J* 8.5, H8), 2.99 (1 H, dd, *J* 18.6, 6.5, H4), 2.75 (1 H, dd, *J* 18.6, 10.0, H4), 1.25 (3 H, s, CH_3), 1.23 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 209.1 (C), 171.6 (C), 140.1 (C), 129.0 (CH), 128.9 (CH), 126.4 (CH), 90.0 (C), 78.9 (CH), 75.7 (CH_2), 45.6 (CH_2), 43.3 (C), 22.9 (CH_3), 19.6 (CH_3).

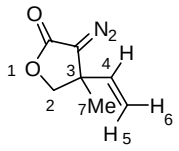
3-Benzoyl-4-methyl-4-vinyldihydrofuran-2(*3H*)-one (mixture of diastereoisomers) 334



To a suspension of copper(I) bromide dimethyl sulfide complex (108 mg, 0.52 mmol) in anhydrous THF (3 mL) at −40 °C under argon was added a solution of vinyl magnesium bromide (1.0 M in THF, 1.05 mL, 1.05 mmol). The resulting mixture was stirred for 25 min, cooled to −78 °C and 3-benzoyl-4-methylfuran-2(*5H*)-one[76] **333** (101 mg, 0.50 mmol) dissolved in anhydrous THF (2 mL) was added dropwise. The resulting mixture was stirred for 1 h at −78 °C, quenched by the addition of saturated aqueous ammonium chloride solution (3 mL), warmed to room temperature and extracted with ethyl acetate (60 mL). The organic phase was washed with water (20 mL), brine (20 mL) and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using 25% ethyl acetate in light petroleum. The *title compound* was obtained as a mixture of diastereoisomers (ratio 1:1); colourless oil (55 mg, 48%); (Found: M+Na^+, 253.0843. $C_{14}H_{14}NaO_3$ requires 253.0835); ν_{max} ($CHCl_3$)/cm^{-1} 2973, 1779, 1673, 1326, 1302, 1030; δ_H (400 MHz; $CDCl_3$) 7.82 - 7.95 (2 H, m, ArH **both isomers**), 7.57 - 7.68 (1 H, m, ArH **both isomers**), 7.41 - 7.55 (2 H, m, ArH **both isomers**),

6.02 (1H, dd, *J* 17.3, 10.7, H4 **one isomer**), 5.72 (1 H, dd, *J* 17.4, 10.8, H4 **one isomer**), 5.24 (1 H, d, *J* 10.7, H6 **one isomer**), 5.22 (1 H, d, *J* 17.3, H5 **one isomer**), 5.14 (1 H, d, *J* 17.4, H5 **one isomer**), 5.06 (1 H, d, *J* 10.8, H6 **one isomer**), 4.56 (1 H, d, *J* 8.7, H3 **one isomer),** 4.48 (1 H, s, H1 **one isomer**), 4.32 (1 H, s, H1 **one isomer**), 4.26 (2 H, s, H3 **one isomer**), 4.06 (1 H, d, *J* 8.7, H3 **one isomer**), 1.48 (3 H, s, H7 **one isomer**), 1.12 (3 H, s, H7 **one isomer**); δ_C (100 MHz; $CDCl_3$) 194.6 (C), 194.4 (C), 173.6 (C), 173.5 (C), 141.1 (CH), 136.8 (CH), 136.7 (C), 136.6 (C), 134.3 (CH), 134.2 (CH), 129.1 (CH), 129.03 (CH), 128.95 (CH), 117.2 (CH_2), 115.0 (CH_2), 76.7 (CH_2), 76.6 (CH_2), 60.1 (CH), 57.1 (CH), 47.1 (C), 46.7 (C), 24.4 (CH_3), 18.9 (CH_3), one CH signal was not observed.

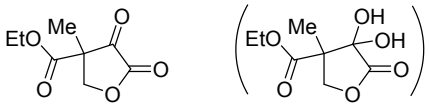
3-Diazo-4-methyl-4-vinyldihydrofuran-2(*3H*)-one 322



1,8-Diazabicycloundec-7-ene (300 µL, 2.00 mmol) was added to a mixture of *p*-toluenesulfonylazide (2.5 mL of 11% solution in toluene, 1.25 mmol) and 3-benzoyl-4-methyl-4-vinyldihydrofuran-2(*3H*)-one (230 mg, 1.00 mmol) at room temperature in dichloromethane (10 mL). The resulting mixture was heated to reflux, stirred for 16 h, cooled down to ambient temperature and poured into water (25 mL). The resulting biphasic mixture was extracted with ether (50 mL). The organic phase was washed with water (15 mL), brine (15 mL) and dried over $MgSO_4$. The ether was removed under reduced pressure to give a yellow liquid residue that was purified by column chromatography on aluminium oxide (activated, Brockmann grade I) using the elution gradient 50 to 100% ether in light petroleum to

give the *title compound* as a clear yellow oil (78 mg, 51%); the product was found to be stable over several months in isolated form or in solution in anhydrous dichloromethane when kept in the dark at −5°C. The compound did not ionised under the MS/ESI conditions used; ν_{max} ($CHCl_3$)/cm^{-1} 2102 (CN_2), 1734, 1385, 1371, 1265; δ_H (400 MHz; $CDCl_3$) 5.96 (1 H, dd, *J* 17.4, 10.6, H4), 5.27 (1 H, d, *J* 10.6, H6), 5.23 (1 H, d, *J* 17.4, H5), 4.14 (1 H, d, *J* 8.7, H2), 4.06 (1 H, d, *J* 8.7, H2), 1.51 (3 H, s, H7); δ_C (100 MHz; $CDCl_3$) 168.5 (C), 138.6 (CH), 115.6 (CH_2), 77.2 (CH_2), 44.0 (C), 22.2 (CH_3), the signal due to $\underline{C}N_2$ was not observed.

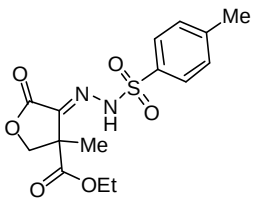
Ethyl 3-methyl-4,5-dioxotetrahydrofuran-3-carboxylate 340 (in mixture with its hydrate)



To a vigorously stirred solution of diethyl 2-methyl-3-oxosuccinate **339** (1.88 mL, 10.0 mmol) in THF (40 mL) cooled in an ice bath was added sodium hydrogencarbonate (2.52 g, 30.0 mmol), followed by aqueous formaldehyde (3.15 mL, 35% solution). Water (20 mL) was added and the resulting clear solution was stirred for 20 min. The reaction mixture was then poured into water (80 mL) and extracted with ether (3×60 mL). The combined organic phases were then washed with brine (40 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using 50% ether in light petroleum. The *title compound* was obtained in mixture with the corresponding hydrate (ratio 75:25). Colourless oil (1.216 g, 65%); (Found: M+MeOH+Na^+, 241.0688. $C_9H_{14}NaO_6$ requires 241.0689); ν_{max} ($CHCl_3$)/cm^{-1} 2986, 1799, 1747, 1268, 1249, 1002; **ketoester form**:

δ_H (400 MHz; $CDCl_3$) 5.05 (1 H, d, *J* 9.9, CH_2), 4.44 (1 H, d, *J* 9.9, CH_2), 4.21 (2 H, q, *J* 7.2, $C\underline{H}_2CH_3$), 1.54 (3 H, s, CH_3), 1.24 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 190.7 (C), 167.5 (C), 158.7 (C), 73.7 (CH_2), 63.4 (CH_2), 51.8 (C), 17.8 (CH_3), 13.9 (CH_3); **Hydrate form**: δ_H (400 MHz; $CDCl_3$) 4.45 (1 H, d, *J* 9.5, CH_2), 4.29 (2 H, br s, OH), 4.13 - 4.28 (2 H, m, $C\underline{H}_2CH_3$), 4.06 (1 H, d, *J* 9.5, CH_2), 1.35 (3 H, s, CH_3), 1.25 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 173.9 (C), 171.3 (C), 94.4 (C), 72.8 (CH_2), 62.0 (CH_2), 52.7 (C), 16.6 (CH_3), 14.0 (CH_3).

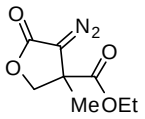
Ethyl 3-methyl-5-oxo-4-(2-tosylhydrazono)tetrahydrofuran-3-carboxylate 341



p-Toluenesulfonyl hydrazide (1.369 g, 7.35 mmol) was added to a solution of ethyl 3-methyl-4,5-dioxotetrahydrofuran-3-carboxylate **340** (1.50 g, 7.35 mmol) in methanol (35 mL) and the resulting mixture was heated at reflux for 2 h. Concentrated hydrochloric acid (4 drops) was then added and the reaction mixture was heated at reflux for an additional 3 h. The resulting solution was cooled down in an ice bath and the volatiles were removed under reduced pressure to give a solid residue that was purified by column chromatography using the elution gradient 20% to 40% ethyl acetate in light petroleum. The *title compound* was obtained as a colourless solid (1.98 g, 76%); mp 115 - 116 °C; (Found: $M+Na^+$, 377.0776. $C_{15}H_{18}N_2NaO_6S$ requires 377.0778); ν_{max} ($CHCl_3$)/cm^{-1} 3234, 3042, 2985, 1744, 1599, 1386, 1372, 1357, 1291, 1266, 1171, 1085, 981; δ_H (400 MHz; $CDCl_3$) 11.47 (1 H, s, NH), 7.76 - 7.87 (2 H, m, ArH), 7.32 (2 H, d, *J* 8.0, ArH), 4.86 (1 H, d, *J* 9.4, CH_2), 4.19 (1 H, d, *J* 9.4, CH_2), 4.10

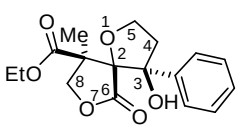
(2 H, q, *J* 7.2, C<u>H</u>$_2$CH$_3$), 2.43 (3 H, s, CH$_3$), 1.52 (3 H, s, CH$_3$), 1.11 (3 H, t, *J* 7.2, CH$_2$C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 170.6 (C), 163.0 (C), 144.8 (C), 137.2 (C), 135.2 (C), 129.8 (CH), 128.0 (CH), 76.0 (CH_2), 62.6 (CH_2), 48.3 (C), 21.7 (CH_3), 20.7 (CH_3), 13.9 (CH_3).

Ethyl 4-diazo-3-methyl-5-oxotetrahydrofuran-3-carboxylate 342



A solution of ethyl 3-methyl-5-oxo-4-(2-tosylhydrazono)-tetrahydrofuran-3-carboxylate **341** (470 mg, 1.36 mmol) and triethylamine (280 μL, 2.01 mmol) in dichloromethane (4 mL) was heated at reflux for 90 min. Once cooled to room temperature, the mixture was filtered through a silica plug neutralised using 5% triethylamine in dichloromethane and eluted using dichloromethane. The *title compound* was obtained as a yellow oil (152 mg, 58%); (Found: M+Na$^+$, 221.0546. $C_8H_{10}N_2NaO_4$ requires 221.0533); ν_{max} ($CHCl_3$)/cm^{-1} 2938, 2113 (CN_2), 1737, 1389, 1375, 1253, 1109, 1014; δ_H (400 MHz; $CDCl_3$) 4.79 (1 H, d, *J* 9.3, CH_2), 4.18 - 4.33 (2H, two overlapping dq, *J* 10.8, 7.1, C<u>H</u>$_2$CH$_3$), 4.04 (1 H, d, *J* 9.3, CH_2), 1.66 (3 H, s, CH_3), 1.31 (3 H, t, *J* 7.1, CH$_2$C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 172.3 (C), 168.1 (C), 73.6 (CH_2), 62.8 (CH_2), 47.3 (C), 22.9 (CH_3), 14.2 (CH_3), the signal due to <u>C</u>N_2 was not observed.

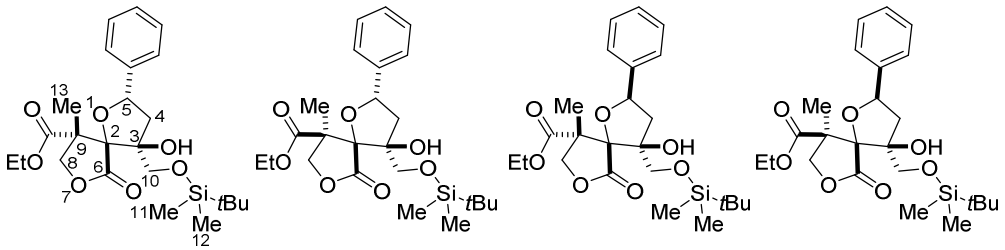
Ethyl *cis,cis*-4-hydroxy-9-methyl-6-oxo-4-phenyl-1,7-dioxaspiro-[4.4]nonane-9-carboxylate 343a



A solution of ethyl 4-diazo-3-methyl-5-oxotetrahydrofuran-3-carboxylate **342** (51.5 mg, 0.26 mmol) in anhydrous dichloromethane (2 mL) was added over 30 min to a solution of 3-hydroxy-1-phenylpropan-1-one **291a** (30 mg, 0.20 mmol) and rhodium pivalate dimer (1.2 mg, 2.0 μmol) at reflux

under argon. The reaction mixture was stirred for 30 min after addition, cooled to room temperature and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using 30% ethyl acetate in light petroleum to give the *title compound* as a colourless solid (30 mg, 47%) and another fraction containing the *title compound* and an isomeric product identified as the *cis*,*trans*-isomer (ratio 1:1, 32 mg, 50%). The configuration shown above is based on various 2D-NMR experiments; mp 108 - 109 °C; (Found: M+Na$^+$, 343.1148. $C_{17}H_{20}NaO_6$ requires 343.1152); ν_{max} ($CHCl_3$)/cm^{-1} 3552, 2989, 2904, 1768, 1738, 1292, 1239, 1151, 1079, 1051, 1020; δ_H (400 MHz; $CDCl_3$) 7.27 - 7.41 (5 H, m, ArH), 4.25 - 4.42 (2 H, m, H5), 4.16 (1 H, s, OH), 4.00 (1 H, d, *J* 9.1, H8), 3.95 - 4.09 (2 H, m, C<u>H</u>$_2$CH$_3$), 3.92 (1 H, d, *J* 9.1, H8), 2.68 - 2.89 (2 H, m, H4), 1.18 (3 H, t, *J* 7.2, CH$_2$C<u>H</u>$_3$), 0.74 (3 H, s, CH$_3$); δ_C (100 MHz; $CDCl_3$) 174.5 (C), 171.7 (C), 141.1 (C), 128.3 (CH), 128.0 (CH), 126.5 (CH), 87.6 (C), 81.8 (C), 73.8 (CH_2), 66.6 (CH_2), 61.8 (CH_2), 51.1 (C), 42.0 (CH_2), 15.2 (CH_3), 13.8 (CH_3).

Ethyl 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-hydroxy-9-methyl-6-oxo-2-phenyl-1,7-dioxaspiro[4.4]nonane-9-carboxylate 344a-d (mixture of isomers)

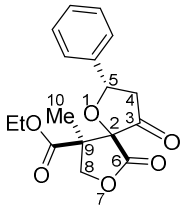


A solution of ethyl 4-diazo-3-methyl-5-oxotetrahydrofuran-3-carboxylate **342** (178 mg, 0.90 mmol) in anhydrous dichloromethane (2 mL) was

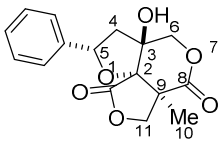
added over 30 min to a solution of 1-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-4-phenylbutan-2-one[75] **325** (204 mg, 692 μmol) and Rh_2(*S*-DOSP)$_4$ (6.6 mg, 3.5 μmol, added as 0.66 mL of a 10 mg/mL solution in dichloromethane) at reflux under argon. The reaction mixture was stirred for 30 min after addition, cooled to room temperature and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using the elution gradient 10 to 20% ethyl acetate in light petroleum to give the *title compound* as a colourless oil (201 mg, 48%). The product was obtained as a mixture containing four isomeric products in the ratio 45:38:12:4. The stereochemistry of these four products was inferred from various 2D-NMR experiments and from subsequent transformations. (Found: M+Na$^+$, 487.2131. $C_{24}H_{36}NaO_7Si$ requires 487.2123); only the signal for the two major isomers **344a** (**A**) and **344b** (**B**) are reported herein: δ_H (400 MHz; $CDCl_3$) 7.16 - 7.44 (5 H, m, ArH **344a**; 5 H, m, ArH **B**), 5.45 (1 H, dd, *J* 8.2, 7.5, H5 **A**), 5.35 (1 H, dd, *J* 9.1, 6.0, H5 **B**), 4.85 (1 H, d, *J* 8.6, H8 **B**), 4.50 (1 H, d, *J* 9.1, H8 **A**), 4.15 (1 H, d, *J* 10.7, H10 **B**), 4.12 (1 H, d, *J* 9.1, H8 **A**), 4.07 - 4.34 (2 H, m, C$\underline{H}_2$CH$_3$ **A**; 2 H, m, C$\underline{H}_2$CH$_3$ **B**), 4.04 (1 H, d, *J* 8.6, H8 **B**), 3.78 (1 H, d, *J* 10.4, H10 **A**), 3.73 (1 H, br s, OH **A**), 3.65 (1 H, br s, OH **B**), 3.63 (1 H, d, *J* 10.7, H10 **B**), 3.55 (1 H, d, *J* 10.4, H10 **A**), 2.86 (1 H, ddd, *J* 12.6, 9.1, 1.5, H4 **B**), 2.73 (1 H, dd, *J* 13.0, 8.2, H4 **A**), 2.51 (1 H, dd, *J* 12.6, 6.0, H4 **B**), 2.25 (1 H, dd, *J* 13.0, 7.5, H4 **A**), 1.59 (3 H, s, H13 **B**), 1.54 (3 H, s, H13 **A**), 1.29 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$ **A**), 1.26 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$ **B**), 0.86 (9 H, s, *t*Bu **A**), 0.83 (9 H, s, *t*Bu **B**), 0.03 (3 H, s, H11/12 **A**), 0.00 (3 H, s, H11/12 **A**), −0.02 (3 H, s, H11/12 **B**), −0.09 (3 H, s, H11/12 **B**); δ_C (100 MHz; $CDCl_3$) 173.5 (C **A**),

172.8 (C **B**), 172.6 (C **A**), 170.3 (C **B**), 141.9 (C **B**), 141.4 (C **A**), 128.6 (CH **A**), 128.5 (CH **B**), 127.8 (CH **A**), 127.5 (CH **B**), 125.9 (CH **A**), 125.3 (CH **B**), 87.9 (C **B**), 87.7 (C **A**), 82.0 (C **B**), 81.8 (C **A**), 78.11 (CH **A**), 78.06 (CH **B**), 74.3 (CH_2 **B**), 72.9 (CH_2 **A**), 66.1 (CH_2 **B**), 65.8 (CH_2 **A**), 62.0 (CH_2 **A**), 61.9 (CH_2 **B**), 52.2 (C **B**), 51.4 (C **A**), 44.4 (CH_2 **A**), 42.7 (CH_2 **B**), 26.0 (CH_3 **A**), 25.9 (CH_3 **B**), 18.59 (C **A**), 18.57 (CH_3 **B**), 18.4 (C **B**), 17.4 (CH_3 **A**), 14.1 (CH_3 **B**), 13.9 (CH_3 **A**), −5.3 (CH_3 **A**), −5.4 (CH_3 **A** and **B**), −5.5 (CH_3 **B**).

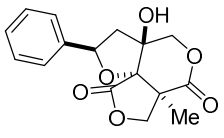
Ethyl *trans,cis*-9-methyl-4,6-dioxo-2-phenyl-1,7-dioxaspiro[4.4]-nonane-9-carboxylate 345, *cis,trans,trans*- and *cis,cis,trans*-3a-hydroxy-6a-methyl-2-phenylhexahydro-*6H*,*9H*-difuro[3,2-c:3,4-d]pyran-6,9-dione 346a-b



(*trans,cis*)-**345**



(*cis,trans,trans*)-**346a**



(*cis,cis,trans*)-**346b**

To a solution of 3-hydroxytetrahydrofuran **344a-d** (ratio **344a**:**344b**:**344c**:**344d**, 45:36:12:4; 200 mg, 0.43 mmol) in THF (3.6 mL) was added aqueous hydrochloric acid (2 M, 1.8 mL) and the resulting solution was stirred for 17 h at room temperature. Water was added (10 mL) and the reaction mixture was extracted with ethyl acetate (50 mL). The organic phase was washed with brine (10 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give the crude diol which was used in the next step without further purification. The diol was dissolved in a mixture of THF (2.0 mL) and water (2.0 mL), sodium periodinate (255 mg, 1.29 mmol) was added and the resulting mixture was stirred at room temperature for 20 h. Water

(10 mL) was added and the mixture was extracted with ether (40 mL), the organic phase was washed with brine (10 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure. The *title compounds* were obtained by column chromatography using the elution gradient 25 to 50% ethyl acetate in light petroleum. **Ethyl *trans,cis*-9-methyl-4,6-dioxo-2-phenyl-1,7-dioxaspiro[4.4]nonane-9-carboxylate 345**; colourless oil (52.5 mg, 38%); (Found: M+Na$^+$, 341.1000. $C_{17}H_{18}NaO_6$ requires 341.0996); ν_{max} ($CHCl_3$)/cm^{-1} 2985, 2927, 1789, 1757, 1730, 1290, 1155, 1113, 1010; δ_H (400 MHz; $CDCl_3$) 7.28 - 7.43 (5 H, m, ArH), 5.64 (1 H, dd, *J* 11.0, 5.9, H5), 4.65 (1 H, d, *J* 9.3, H8), 4.27 (1 H, d, *J* 9.3, H8), 4.11 - 4.36 (2 H, two overlapping dq, *J* 10.7, 7.2, C$\underline{H}_2$CH$_3$), 3.03 (1 H, dd, *J* 17.8, 5.9, H4), 2.65 (1 H, dd, *J* 17.8, 11.0, H4), 1.45 (3 H, s, H10), 1.23 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 207.7 (C), 171.0 (C), 170.3 (C), 139.0 (C), 128.9 (CH), 128.8 (CH), 125.9 (CH), 86.3 (C), 77.9 (CH), 73.0 (CH_2), 62.3 (CH_2), 52.6 (C), 45.8 (CH_2), 15.6 (CH_3), 14.1 (CH_3). ***cis,trans,trans*-3a-Hydroxy-6a-methyl-2-phenylhexahydro-*6H*,*9H*-difuro[3,2-c:3,4-d]pyran-6,9-dione 346a**; colourless solid (52.5 mg, 40%); mp 141 - 142 °C; (Found: M+Na$^+$, 327.0640. $C_{16}H_{16}NaO_6$ requires 327.0845); ν_{max} ($CHCl_3$)/cm^{-1} 3042, 1756, 1371, 1261, 1142, 1090, 1044,; δ_H (400 MHz; $CDCl_3$) 7.26 - 7.41 (5 H, m, ArH), 5.81 (1 H, t, *J* 7.9, H5), 4.91 (1 H, d, *J* 9.5, H11), 4.27 - 4.44 (2 H, m, H6), 4.15 (1 H, d, *J* 9.5, H11), 3.84 (1 H, br s, OH), 2.84 (1 H, dd, *J* 13.6, 7.9, H4), 2.09 (1 H, dd, *J* 13.6, 7.9, H4), 1.59 (3 H, s, H10); δ_C (100 MHz; $CDCl_3$) 174.2 (C), 171.5 (C), 140.0 (C), 128.9 (CH), 128.4 (CH), 125.5 (CH), 85.9 (C), 79.9 (CH), 77.2 (C), 74.0 (CH_2), 71.3 (CH_2), 46.8 (C), 43.9 (CH_2), 18.4 (CH_3). ***cis,cis,trans*-3a-Hydroxy-6a-**

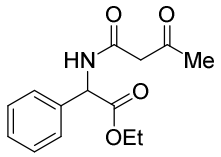
methyl-2-phenylhexahydro-*6H*,*9H*-difuro[3,2-c:3,4-d]pyran-6,9-dione 346b; colourless solid (9 mg, 7%); mp 165 - 167 °C; (Found: M+Na$^+$, 327.0638. $C_{16}H_{16}NaO_6$ requires 327.0845); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 2927, 2854, 1757, 2602, 1406, 1239; δ_H (400 MHz; $CDCl_3$) 7.31 - 7.52 (5 H, m, ArH), 5.16 (1 H, dd, *J* 11.1, 5.5, H5), 5.10 (1 H, d, *J* 9.5, H11), 4.57 (1 H, d, *J* 12.3, H6), 4.50 (1 H, d, *J* 12.3, H6), 4.06 (1 H, d, *J* 9.5, H11), 3.16 (1 H, s, OH), 2.70 (1 H, dd, *J* 13.2, 11.1, H4), 2.52 (1 H, dd, *J* 13.2, 5.5, H4), 1.53 (3 H, s, H10); δ_C (100 MHz; $CDCl_3$) 174.5 (C), 171.2 (C), 139.1 (C), 129.04 (CH), 128.97 (CH), 126.6 (CH), 85.1 (C), 82.9 (CH), 78.2 (C), 74.3 (CH_2), 70.4 (CH_2), 46.9 (C), 45.0 (CH_2), 17.6 (CH_3).

V. Chapter VI Experimental

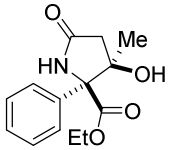
V.1. Synthesis of pyrrolidinones from acetoacetamides

Ethyl 2-diazo-2-phenylacetate **104** was prepared as described in **Section II** of this experimental.

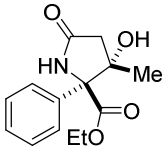
Ethyl 2-(3-oxobutanamido)-2-phenylacetate 368, *cis*- and *trans*-ethyl 3-hydroxy-3-methyl-5-oxo-2-phenylpyrrolidine-2-carboxylate 367a-b



368



367a



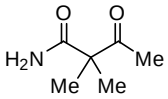
367b

A solution of ethyl 2-diazo-2-phenylacetate **104** (123 mg, 0.65 mmol) in anhydrous dichloromethane (2 mL) was added over 30 min to a solution of acetoacetamide **366** (51 mg, 0.50 mmol) and rhodium pivalate dimer (3.0 mg, 5.0 μmol) in anhydrous dichloromethane (3 mL) at reflux under

argon. After addition, the mixture was stirred at reflux for 30 min, cooled to room temperature and the solvent was removed under reduced presure to give a residue that was purified by column chromatography using the elution gradient 50% to 75% ethyl acetate in light petroleum to give the *title compounds*. **Ethyl 2-(3-oxobutanamido)-2-phenylacetate 368**: Off-white solid (70 mg, 53%); mp 70 - 71 °C; (Found: M+Na$^+$, 286.1043. $C_{14}H_{17}NNaO_4$ requires 286.1050); ν_{max} ($CHCl_3$)/cm^{-1} 3420, 3339, 1737, 1716, 1673; observed in equilibrium with its enol form (ratio 6:94 in favour of the ketoamide form) in deuterated chloroform at room temperature. Only the signals for the ketoamide form are reported, δ_H (400 MHz; $CDCl_3$) 7.90 (1 H, d, *J* 7.0, NH), 7.27 - 7.42 (5 H, m, ArH), 5.54 (1 H, d, *J* 7.0, CH), 4.21 (1 H, dq, *J* 10.8, 7.2, C$\underline{H}_2$CH$_3$), 4.12 (1 H, dq, *J* 10.8, 7.2, C$\underline{H}_2$CH$_3$), 3.46 (1 H, d, *J* 17.1, CH_2), 3.39 (1 H, d, *J* 17.1, CH_2), 2.23 (3 H, s, Me), 1.20 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 204.0 (C), 170.6 (C), 165.2 (C), 136.4 (C), 129.0 (CH), 128.6 (CH), 127.3 (CH), 62.0 (CH_2), 56.8 (CH), 49.6 (CH_2), 31.0 (CH_3), 14.1 (CH_3). ***cis*- and *trans*- Ethyl 3-hydroxy-3-methyl-5-oxo-2-phenylpyrrolidine-2-carboxylate 367a and 367b**: Yellow oil (45 mg, 34%); (Found: M+Na$^+$, 286.1041. $C_{14}H_{17}NNaO_4$ requires 286.1050); ν_{max} ($CHCl_3$)/cm^{-1} 3432, 3011, 2936, 1711, 1258, 909; obtained as an inseparable mixture (ratio 81:19). Only the signal of the major *cis*-isomer are reported, δ_H (400 MHz; $CDCl_3$) 7.48 - 7.55 (2 H, m, ArH), 7.33 - 7.45 (3 H, m, ArH), 6.92 (1 H, s, NH), 4.32 (1 H, dq, *J* 10.6, 7.2, C$\underline{H}_2$CH$_3$), 4.26 (1 H, dq, *J* 10.6, 7.2, C$\underline{H}_2$CH$_3$), 4.00 (1 H, br s, OH), 2.48 (1 H, d, *J* 16.7, CH_2), 2.42 (1 H, d, *J* 16.7, CH_2), 1.28 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$), 1.20 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 175.3 (C), 170.7 (C),

136.5 (C), 129.0 (CH), 128.9 (CH), 125.7 (CH), 79.7 (C), 75.8 (C), 62.6 (CH_2), 44.3 (CH_2), 24.4 (CH_3), 14.0 (CH_3).

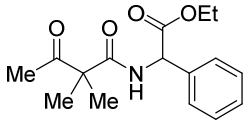
2,2-Dimethyl-3-oxobutanamide 388



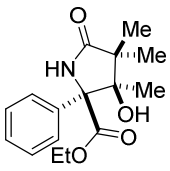
Acetoacetamide **366** (2.02 g, 20.0 mmol) was dissolved in anhydrous dimethylformamide (60 mL) at 0 °C under argon and sodium hydride (60% in mineral oil, 880 mg, 22.0 mmol) was added to the mixture. The mixture was stirred for 10 min at 0 °C until no gas evolution was observed and methyl iodide (1.37 mL, 22.0 mmol) was added. The resulting mixture was warmed up to room temperature, stirred for 1 h then cooled to 0 °C. After the addition of additional sodium hydride (60% in mineral oil, 880 mg, 22.0 mmol), the resulting mixture was stirred for 20 min and methyl iodide (1.37 mL, 22.0 mmol) was added. The reaction mixture was warmed up to room temperature and stirred for 18 h. Saturated ammonium chloride solution (10 mL) and water (10 mL) were added and the resulting mixture was concentrated under reduced pressure. Water (20 mL) was then added and the mixture was extracted with dichloromethane (3×40 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give a solid residue that was recrytallised from ethanol (5 mL). The *title compound* was obtained as a colourless solid (1.62 g, 67%); mp 119 °C (lit.[77] mp 121-122 °C); (Found: M+Na^+, 152.0675. $C_6H_{11}NNaO_2$ requires 152.0682); ν_{max} ($CHCl_3$)/cm^{-1} 3518, 3408, 3006, 1688; δ_H (400 MHz; DMSO-d6) 7.25 (1 H, br s, NH_2), 7.14 (1 H, br s, NH_2), 2.07 (3 H, s, CH_3), 1.21 (6 H, s, CH_3); δ_C (100 MHz; DMSO-d6) 207.4

(C), 175.0 (C), 55.3 (C), 25.7 (CH_3), 21.9 (CH_3). The data are consistent with the literature.[77]

Ethyl 2-(2,2-dimethyl-3-oxobutanamido)-2-phenylacetate 389 and *cis*-ethyl 3-hydroxy-3,4,4-trimethyl-5-oxo-2-phenylpyrrolidine-2-carboxylate 390



389



390

A solution of ethyl 2-diazo-2-phenylacetate **104** (104 mg, 0.55 mmol) in anhydrous dichloromethane (2 mL) was added over 30 min to a solution of 2,2-dimethyl-3-oxobutanamide **388** (61 mg, 0.5 mmol) and rhodium octanoate dimer (3.9 mg, 5.0 μmol) in anhydrous dichloromethane (3 mL) at reflux under argon. After addition, the mixture was stirred at reflux for 30 min, cooled to room temperature and the solvent was removed under reduced presure to give a residue that was purified by column chromatography using the elution gradient 30% to 70% ethyl acetate in light petroleum to give the *title compounds.* **Ethyl 2-(2,2-dimethyl-3-oxobutanamido)-2-phenylacetate 389**; colourless oil (89 mg, 63 %); (Found: M+Na^+, 314.1346. $C_{16}H_{21}NNaO_4$ requires 314.1363); ν_{max} ($CHCl_3$)/cm^{-1} 3430, 2985, 1736, 1678, 1497, 1468, 1182; Present as a mixture of rotamers in a ratio 83:17 in solution in deuterated chloroform at room temperature, only the signals associated with the major rotamer are reported here: δ_H (400 MHz; $CDCl_3$) 7.29 - 7.39 (5 H, m, ArH), 6.76 (1 H, d, *J* 6.1, NH), 5.47 (1 H, d, *J* 6.7, C<u>H</u>N), 4.12 - 4.21 (2 H, two overlapping dq, *J* 10.8, 7.2, C<u>H</u>$_2$$CH_3$), 2.14 (3 H, s, CH_3), 1.41 (3 H, s, CH_3), 1.38 (3 H, s, CH_3), 1.20 (3 H, t, *J* 7.2, CH_2C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 208.6 (C), 171.7 (C), 170.6 (C), 136.3

(C), 129.1 (CH), 128.7 (CH), 127.3 (CH), 62.1 (CH_2), 57.0 (CH), 56.0 (C), 26.2 (CH_3), 22.42 (CH_3), 22.38 (CH_3), 14.1 (CH_3). ***cis*-Ethyl 3-hydroxy-3,4,4-trimethyl-5-oxo-2-phenylpyrrolidine-2-carboxylate 390**: colourless solid (11 mg, 8 %); mp 181-182 °C; (Found: M+Na^+, 314.1346. $C_{16}H_{21}NNaO_4$ requires 314.1363); ν_{max} ($CHCl_3$)/cm^{-1} 3693, 3427, 1707, 1602, 1253, 1034; δ_H (400 MHz; $CDCl_3$) 7.69 - 7.75 (2 H, m, ArH), 7.34 - 7.45 (3 H, m, ArH), 7.16 (1 H, br s, NH), 4.24 - 4.29 (2 H, two overlapping dq, *J* 10.9, 7.2, C<u>H</u>$_2$$CH_3$), 4.20 (1 H, s, OH), 1.19 - 1.38 (6 H, overlapping t, *J* 7.2, CH_2C<u>H</u>$_3$; and s, CH_3), 1.17 (3 H, s, CH_3), 0.86 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 180.7 (C), 171.9 (C), 137.1 (C), 128.7 (CH), 128.6 (CH), 126.8 (CH), 83.2 (C), 74.1 (C), 62.7 (CH_2), 48.3 (C), 22.6 (CH_3), 20.5 (CH_3), 18.9 (CH_3), 14.0 (CH_3).

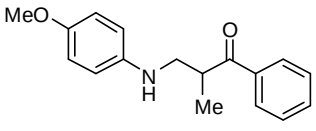
V.2. Synthesis of *N*-aryl 3-hydroxypyrrolidines

Diazo compounds used in this study were prepared as described in **section II** of this experimental.

V.2.1. Preparation of *N*-aryl aminoketones

The following *N*-aryl aminoketones used in this study were prepared according to previously described procedures: 4-(phenylamino)butan-2-one **362**,[78] 4-((4-methoxyphenyl)amino)butan-2-one **394**[79] and 3-((4-methoxyphenyl)amino)-1-phenylpropan-1-one **392**.[79]

3-(4-Methoxyphenyl)amino-2-methyl-1-phenylpropan-1-one 395



Paraformaldehyde (450 mg, 15.0 mmol) and dimethylamine hydrochloride (1.22 g, 15.0

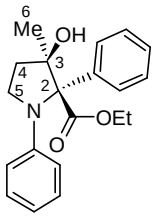
mmol) were added to a solution of propiophenone (1.34 g, 10.0 mmol) in ethanol (5 mL) and the resulting mixture was heated at reflux for 24 h. The reaction mixture was cooled to room temperature and *p*-anisidine (1.23 g, 10.0 mmol) and water (4 mL) were added. The resulting solution was heated at reflux for 15 h. Upon cooling down to room temperature, water (4 mL) was added and the mixture was extracted with ether (100 mL). The organic phase was washed with saturated aqueous ammonium chloride solution (20 mL), brine (20 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using 20% ethyl acetate in light petroleum to give the *title compound* as an orange oil (1.20 g, 45%); (Found: $M+H^+$, 270.1493. $C_{17}H_{20}NO_2$ requires 270.1489); ν_{max} ($CHCl_3$)/cm^{-1} 3441, 3009, 1678, 1506, 1250; δ_H (400 MHz; $CDCl_3$) 7.87 - 7.98 (2 H, m, ArH), 7.52 - 7.61 (1 H, m, ArH), 7.41 - 7.50 (2 H, m, ArH), 6.73 - 6.81 (2 H, m, ArH), 6.53 - 6.61 (2 H, m, ArH), 3.84 (1 H, quin.d, *J* 7.3, 5.3, CH), 3.74 (3 H, s, OCH_3), 3.56 (1 H, dd, *J* 13.1, 7.3, CH_2), 3.26 (1 H, dd, *J* 13.1, 5.3, CH_2), 1.26 (3 H, d, *J* 7.3, CH_3), the signal due to NH was not observed; δ_C (100 MHz; $CDCl_3$) 203.7 (C), 152.3 (C), 142.1 (C), 136.5 (C), 133.3 (CH), 128.8 (CH), 128.4 (CH), 115.0 (CH), 114.4 (CH), 55.9 (CH_3), 47.8 (CH_2), 40.4 (CH), 16.1 (CH_3).

5.2.2. Synthesis of *N*-aryl 3-hydroxypyrrolidines

General procedure Q: a solution containing the diazo compound in anhydrous dichloromethane (2 mL) was added over 30 min to a solution containing the aminoketone (0.3 mmol or 0.5 mmol) and the

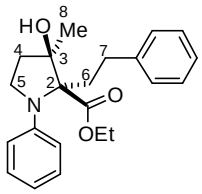
corresponding catalyst in anhydrous dichloromethane (1 mL or 2 mL) at reflux under argon. After addition, the resulting mixture was stirred at reflux for an additional 30 min, cooled down and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography on silica gel using the elution system indicated.

Ethyl *cis*-3-hydroxy-3-methyl-1,2-diphenylpyrrolidine-2-carboxylate 363



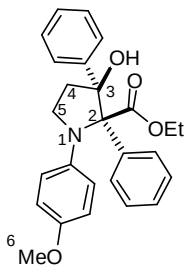
Following the **general procedure Q** using ethyl 2-diazo-2-phenylacetate **104** (2 mL, 0.275 M solution, 0.55 mmol), 4-(phenylamino)butan-2-one **362** (82 mg, 0.5 mmol) and rhodium octanoate dimer (4.0 mg, 5.1 μmol). The *title compound* was obtained by column chromatography using 20% ethyl acetate in light petroleum. Orange oil (153 mg, 85%); (Found: M+H$^+$, 326.1747. $C_{20}H_{24}NO_3$ requires 326.1751); ν_{max} ($CHCl_3$)/cm^{-1} 3005, 2983, 1729, 1600, 1505, 1491, 1335, 1297, 1248, 1153, 1026; δ_H (400 MHz; $CDCl_3$) 7.49 - 7.80 (2 H, m, ArH), 7.22 - 7.36 (3 H, m, ArH), 7.07 (2 H, t, *J* 8.1, ArH), 6.66 (1 H, t, *J* 7.3, ArH), 6.40 (2 H, d, *J* 8.1, ArH), 4.20 (1 H, dq, *J* 10.7, 7.2, C$\underline{H}_2$CH$_3$), 4.14 (1 H, dq, *J* 10.7, 7.2, C$\underline{H}_2$CH$_3$), 3.85 (1 H, q, *J* 8.0, H5), 3.78 (1 H, td, *J* 8.0, 5.1, H5), 2.65 (1 H, br s, OH), 2.30 (1 H, ddd, *J* 12.5, 8.0, 5.1, H4), 2.07 (1 H, dt, *J* 12.5, 8.0, H4), 1.08 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$), 1.01 (3 H, s, H6); δ_C (100 MHz; $CDCl_3$) 172.0 (C), 146.6 (C), 137.2 (C), 128.5 (CH), 128.3 (CH), 127.9 (CH), 127.5 (CH), 116.9 (CH), 114.7 (CH), 84.4 (C), 78.9 (C), 61.5 (CH$_2$), 48.2 (CH$_2$), 36.7 (CH$_2$), 25.2 (CH$_3$), 14.0 (CH$_3$).

Ethyl *cis*-3-hydroxy-3-methyl-2-phenethyl-1-phenylpyrrolidine-2-carboxylate 391



Following the **general procedure Q** using ethyl 2-diazo-4-phenylbutanoate **123** (2 mL, 0.275 M solution, 0.55 mmol), 4-(phenylamino)butan-2-one **362** (82 mg, 0.5 mmol) and rhodium octanoate dimer (4.0 mg, 5.1 μmol). The *title compound* was isolated by column chromatography using the elution gradient 10 to 25% ethyl acetate in light petroleum. Colourless oil (132 mg, 75%); (Found: M+H$^+$, 354.2056. $C_{22}H_{28}NO_3$ requires 354.2064); ν_{max} ($CHCl_3$)/cm^{-1} 3693, 3605, 3003, 1727, 1600, 1504, 1356; δ_H (400 MHz; $CDCl_3$) 7.19 - 7.26 (4 H, m, ArH), 7.13 - 7.18 (1 H, m, ArH), 7.00 - 7.06 (2 H, m, ArH), 6.71 - 6.79 (1 H, m, ArH), 6.61 (2 H, dd, *J* 8.8, 0.8, ArH), 4.12 - 4.20 (2 H, two overlapping dq, *J* 10.8, 7.2, C$\underline{H}_2$CH$_3$), 3.71 (1 H, td, *J* 9.4, 7.7, H5), 3.63 (1 H, ddd, *J* 9.4, 8.2, 3.5 H5), 2.57 - 2.78 (2 H, m, H6 and OH), 2.32 - 2.56 (3 H, m, H6 and H7), 2.12 - 2.26 (2 H, m, H4), 1.56 (3 H, s, CH$_3$), 1.17 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 172.4 (C), 146.2 (C), 141.8 (C), 128.9 (CH), 128.5 (CH), 128.4 (CH), 126.1 (CH), 117.0 (CH), 113.5 (CH), 83.1 (C), 76.3 (C), 61.5 (CH$_2$), 47.4 (CH$_2$), 38.7 (CH$_2$), 34.9 (CH$_2$), 31.2 (CH$_2$), 22.7 (CH$_3$), 14.2 (CH$_3$).

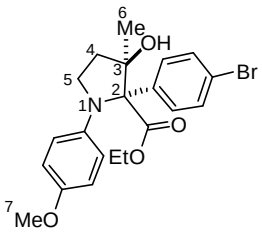
Ethyl *cis*-3-hydroxy-1-(4-methoxyphenyl)-2,3-diphenylpyrroli-dine-2-carboxylate 393



Following the **general procedure Q** using ethyl 2-diazo-2-phenylacetate **104** (2 mL, 0.195 M solution, 0.39 mmol), 3-((4-methoxyphenyl)amino)-1-phenylpropan-1-one **392** (76.5 mg, 0.30 mmol) and

copper(I) triflate toluene complex (8.0 mg, 15.0 μmol). The *title compound* was isolated by column chromatography using the elution gradient 15 to 20% ethyl acetate in light petroleum. Pale brown solid (113 mg, 90%); 91 - 92 °C; (Found: M+H$^+$, 418.2029. $C_{26}H_{28}NO_4$ requires 418.2013); ν_{max} ($CHCl_3$)/cm^{-1} 3605, 3064, 3009, 1732, 1513, 1245; δ_H (400 MHz; $CDCl_3$) 7.18 - 7.24 (1 H, m, ArH), 7.05 - 7.17 (3 H, m, ArH), 6.94 - 7.04 (6 H, m, ArH), 6.67 - 6.75 (2 H, m, ArH), 6.32 - 6.41 (2 H, m, ArH), 4.16 - 4.30 (2 H, m, C$\underline{H}_2$CH$_3$), 4.11 (1 H, td, *J* 9.2, 6.8, H5), 3.98 (1 H, s, OH), 3.92 (1 H, td, *J* 9.2, 1.4, H5), 3.71 (3 H, s, H6), 2.72 (1 H, dt, *J* 12.5, 9.2, H4), 2.17 (1 H, ddd, *J* 12.5, 6.8, 1.4, H4), 1.13 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 171.6 (C), 151.6 (C), 140.5 (C), 139.7 (C), 136.2 (C), 129.7 (CH), 127.9 (CH), 127.4 (CH), 127.2 (CH), 127.1 (CH), 126.9 (CH), 115.0 (CH), 114.3 (CH), 87.9 (C), 80.6 (C), 62.1 (CH_2), 55.8 (CH_3), 48.1 (CH_2), 35.2 (CH_2), 14.1 (CH_3).

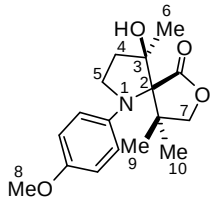
Ethyl *cis*-2-(4-bromophenyl)-3-hydroxy-1-(4-methoxyphenyl)-3-methylpyrrolidine-2-carboxylate 396



Following the **general procedure Q** using ethyl 2-diazo-2-(4-bromophenyl)acetate **107** (2 mL, 0.195 M solution, 0.39 mmol), 4-((4-methoxyphenyl)amino)butan-2-one **394** (58 mg, 0.3 mmol) and copper(I) triflate toluene complex (8.0 mg, 15 μmol). The *title compound* was isolated by column chromatography using the elution gradient 20 to 40% ethyl acetate in light petroleum. Viscous colourless oil (76 mg, 58%); (Found: M+H$^+$, 434.0959. $C_{21}H_{25}{}^{79}BrNO_4$ requires 434.0961); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3605, 3073, 1727, 1601, 1513, 1245;

δ_H (400 MHz; $CDCl_3$) 7.39 (1 H, d, *J* 8.7, ArH), 7.31 - 7.65 (3 H, m, ArH), 6.64 - 6.70 (2 H, m, ArH), 6.21 - 6.36 (2 H, m, ArH), 4.07 - 4.21 (2 H, two overlapping dq, *J* 10.8, 7.0, $C\underline{H}_2CH_3$), 3.75 (2 H, t, *J* 7.0, H5), 3.69 (3 H, s, H6), 2.71 (1 H, br s, OH), 2.36 (1 H, dt, *J* 12.3, 7.0, H4), 2.03 (1 H, dt, *J* 12.3, 7.0, H4), 1.07 (3 H, t, *J* 7.0, $CH_2C\underline{H}_3$), 0.96 (3 H, s, H6); δ_C (100 MHz; $CDCl_3$) 172.1 (C), 151.5 (C), 140.8 (C), 136.6 (C), 130.8 (CH), 130.6 (CH), 121.7 (C), 115.1 (CH), 114.1 (CH), 84.1 (C), 78.6 (C), 61.6 (CH_2), 55.7 (CH_3), 48.6 (CH_2), 37.0 (CH_2), 25.6 (CH_3), 14.1 (CH_3).

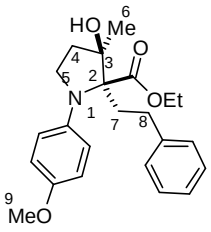
cis-4-Hydroxy-1-(4-methoxyphenyl)-4,9,9-trimethyl-7-oxa-1-azaspiro[4.4]nonan-6-one 397



Following the **general procedure Q** using 3-diazo-4,4-dimethyldihydrofuran-2(*3H*)-one **121** (2 mL, 0.195 M solution, 0.39 mmol), 4-((4-methoxyphenyl)amino)butan-2-one **394** (58 mg, 0.3 mmol) and copper(I) triflate toluene complex (8.0 mg, 15 μmol). The *title compound* was isolated by column chromatography using the elution gradient 20 to 30% ethyl acetate in light petroleum. Colourless solid (65 mg, 71%); mp 120 - 121 °C; (Found: M+H$^+$, 306.1709. $C_{17}H_{24}NO_4$ requires 306.1709); ν_{max} ($CHCl_3$)/cm^{-1} 3565, 3009, 2979, 1741, 1508, 1246; δ_H (400 MHz; $CDCl_3$) 6.97 - 7.43 (2 H, m, ArH), 6.59 - 6.94 (2 H, m, ArH), 3.77 (3 H, s, H8), 3.40 (1 H, d, *J* 8.5, H7), 3.36 (1 H, ddd, *J* 9.8, 8.6, 7.9, H5), 3.13 (1 H, ddd, *J* 10.9, 9.8, 3.1, H5), 3.06 (1 H, d, *J* 8.5, H7), 2.71 (1 H, s, OH), 2.74 (1 H, ddd, *J* 12.0, 10.9, 7.9, H4), 1.94 (1 H, ddd, *J* 12.0, 8.6, 3.1, H4), 1.54 (3 H, s, H10), 1.29 (3 H, s, H6), 1.20 (3 H, s, H9); δ_C (100 MHz; $CDCl_3$) 179.3 (C), 158.1 (C), 141.6 (C), 129.8 (CH), 114.6 (CH), 80.1 (C), 78.4 (C), 76.3 (CH_2),

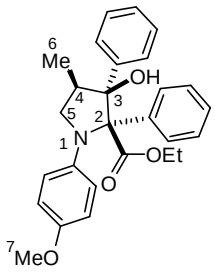
55.5 (CH_3), 54.0 (CH_2), 41.2 (C), 40.1 (CH_2), 25.2 (CH_3), 24.5 (CH_3), 18.6 (CH_3).

Ethyl *cis*-3-hydroxy-1-(4-methoxyphenyl)-3-methyl-2-phenethyl-pyrrolidine-2-carboxylate 398



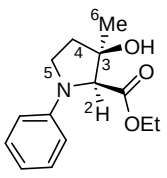
Following the **general procedure Q** using ethyl 2-diazo-4-phenylbutanoate **123** (2 mL, 0.195 M solution, 0.39 mmol), 4-((4-methoxyphenyl)amino)-butan-2-one **394** (58 mg, 0.3 mmol) and copper(I) triflate toluene complex (8.0 mg, 15 μmol). The *title compound* was isolated by column chromatography using the elution gradient 30 to 50% ethyl acetate in light petroleum. Yellow oil (63 mg, 55%); (Found: $M+H^+$, 384.2193. $C_{23}H_{30}NO_4$ requires 384.2169); ν_{max} ($CHCl_3$)/cm^{-1} 3007, 2980, 1727, 1602, 1513, 1246; δ_H (400 MHz; $CDCl_3$) 7.19 - 7.26 (2 H, m, ArH), 7.11 - 7.19 (1 H, m, ArH), 7.04 (2 H, d, *J* 7.0, ArH), 6.73 - 6.91 (2 H, m, ArH), 6.51 - 6.69 (2 H, m, ArH), 4.07 - 4.26 (2 H, two overlapping dq, *J* 11.0, 7.2, C$\underline{H}_2$CH$_3$), 3.77 (3 H, s, H9), 3.66 (1 H, q, *J* 8.8, H5), 3.56 (1 H, td, *J* 8.8, 3.1, H5), 2.79 (1H, br s, OH), 2.31 - 2.61 (4 H, m, H4 and H8), 2.10 - 2.26 (2 H, m, H7), 1.55 (3 H, s, H6), 1.18 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 172.7 (C), 151.8 (C), 142.0 (C), 140.6 (C), 128.5 (CH), 128.4 (CH), 126.1 (CH), 115.0 (CH), 114.5 (CH), 82.9 (C), 76.2 (C), 61.4 (CH_2), 55.8 (CH_3), 47.7 (CH_2), 38.8 (CH_2), 35.0 (CH_2), 31.2 (CH_2), 22.9 (CH_3), 14.3 (CH_3).

Ethyl *cis,cis*-3-hydroxy-1-(4-methoxyphenyl)-4-methyl-2,3-diphenylpyrrolidine-2-carboxylate 399



Following the **general procedure Q** using ethyl 2-diazo-2-phenylacetate **104** (2 mL, 0.195 M solution, 0.39 mmol), 3-((4-methoxyphenyl)amino)-2-methyl-1-phenylpropan-1-one **395** (81 mg, 0.30 mmol) and copper(I) triflate toluene complex (8.0 mg, 15 μmol). The *title compound* was isolated by column chromatography using 20% ethyl acetate in light petroleum. Yellow oil (99.5 mg, 77%); (Found: $M+H^+$, 432.2159. $C_{27}H_{30}NO_4$ requires 432.2169); ν_{max} ($CHCl_3$)/cm^{-1} 3287, 3009, 2937, 1732, 1513, 1345, 1243; δ_H (400 MHz; $CDCl_3$) 6.77 - 7.32 (10 H, m, ArH), 6.63 - 6.74 (2 H, m, ArH), 6.21 - 6.43 (2 H, m, ArH), 4.14 - 4.27 (2 H, m, C<u>H</u>$_2$CH$_3$), 3.87 (1 H, dd, *J* 8.9, 6.9, H5), 3.75 (1 H, dd, *J* 10.3, 8.9, H5), 3.71 (3 H, s, H7), 3.63 (1 H, s, OH), 2.93 (1 H, dquin, *J* 10.3, 6.9, H4), 1.12 (3 H, t, *J* 7.1, CH$_2$C<u>H</u>$_3$), 0.98 (3 H, d, *J* 6.9, H6); δ_C (100 MHz; $CDCl_3$) 171.3 (C), 151.4 (C), 140.3 (C), 137.5 (C), 135.9 (C), 127.9 (CH), 127.5 (CH), 127.3 (CH), 126.9 (CH), 114.6 (CH), 114.3 (CH), 88.9 (C), 81.8 (C), 62.1 (CH_2), 55.8 (CH_3), 54.2 (CH_2), 36.8 (CH), 14.0 (CH_3), 9.8 (CH_3), two (CH) peaks were not observed.

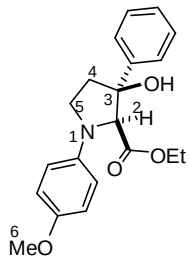
Ethyl *trans*-3-hydroxy-3-methyl-1-phenylpyrrolidine-2-carboxylate 400



Following the **general procedure Q** using ethyl diazoacetate **2** (2 mL, 0.275 M solution, 0.55 mmol), 4-(phenylamino)butan-2-one **362** (82 mg, 0.5 mmol) and meso-tetraphenylporphyrin iron(III) chloride complex (3.5 mg, 5.0 μmol).

The *title compound* was isolated by column chromatography using the elution gradient 10 to 20% ethyl acetate in light petroleum. Yellow oil (103 mg, 83%); (Found: M+H$^+$, 250.1431. $C_{14}H_{20}NO_3$ requires 250.1438); ν_{max} ($CHCl_3$)/cm^{-1}3690, 3600, 3011, 2982, 1737, 1575, 1506, 1376, 1184; δ_H (400 MHz; $CDCl_3$) 7.20 - 7.29 (2 H, m, ArH), 6.70 - 6.79 (1 H, m, ArH), 6.54 (2 H, dd, *J* 8.7, 0.9, ArH), 4.17 - 4.33 (2 H, two overlapping dq, *J* 10.8, 7.2, C$\underline{H}_2$CH$_3$), 4.02 (1 H, s, H2), 3.69 (1 H, td, *J* 8.9, 3.8, H5), 3.32 - 3.43 (1 H, m, H5), 2.63 (1 H, br s, OH), 2.40 (1 H, dt, *J* 12.1, 8.9, H4), 2.04 (1 H, ddd, *J* 12.1, 7.5, 3.8, H4), 1.51 (3 H, s, H6), 1.28 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 172.5 (C), 146.7 (C), 129.3 (CH), 117.1 (CH), 111.8 (CH), 78.6 (C), 70.7 (CH), 61.3 (CH_2), 46.5 (CH_2), 37.9 (CH_2), 27.7 (CH_3), 14.4 (CH_3).

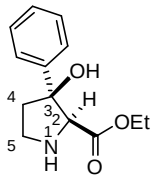
Ethyl *cis*-3-hydroxy-1-(4-methoxyphenyl)-3-phenylpyrrolidine-2-carboxylate 402



Following the **general procedure Q** using ethyl diazoacetate **2** (2 mL, 0.325 M solution, 0.65 mmol), 3-((4-methoxyphenyl)amino)-1-phenylpropan-1-one **392** (128 mg, 0.50 mmol) and meso-tetraphenylporphyrin iron(III) chloride complex (3.5 mg, 5.0 μmol). The *title compound* was isolated by column chromatography using 30% ethyl acetate in light petroleum. Grey solid (157 mg, 92%); mp 121 - 122 °C; (Found: M+H$^+$, 342.1700. $C_{20}H_{24}NO_4$ requires 342.1700); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3009, 2928, 1721, 1510, 1243; δ_H (400 MHz; $CDCl_3$) 7.39 - 7.44 (2 H, m, ArH), 7.32 - 7.37 (2 H, m, ArH), 7.27 - 7.31 (1 H, m, ArH), 6.84 - 6.89 (2 H, m, ArH), 6.50 - 6.56 (2 H, m, ArH), 4.44 (1 H, s,

H2), 4.17 - 4.31 (2 H, two overlapping dq, *J* 11.0, 7.1, C<u>H</u>$_2$CH$_3$), 3.76 (3 H, s, H6), 3.74 (1 H, td, *J* 8.3, 3.6, H5), 3.33 (1 H, td, *J* 8.3, 7.3, H5), 2.76 (1 H, s, OH), 2.65 (1 H, dt, *J* 12.3, 8.3, H4), 2.33 (1 H, ddd, *J* 12.3, 7.3, 3.6, H4), 1.23 (3 H, t, *J* 7.1, CH$_2$C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 172.4 (C), 152.0 (C), 145.1 (C), 140.7 (C), 128.8 (CH), 127.9 (CH), 124.7 (CH), 115.2 (CH), 112.8 (CH), 81.5 (C), 71.1 (CH), 61.4 (CH_2), 56.0 (CH_3), 46.7 (CH_2), 39.4 (CH_2), 14.4 (CH_3).

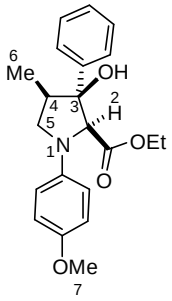
Ethyl *cis*-3-hydroxy-3-phenylpyrrolidine-2-carboxylate 403



A solution of cerium(IV) ammonium nitrate (241 mg, 0.44 mmol) in water (0.5 mL) was added to a solution of ethyl *cis*-3-hydroxy-1-(4-methoxyphenyl)-3-methyl-pyrrolidine-2-carboxylate **402** (50 mg, 0.146 mmol) in acetonitrile (1.5 mL) cooled in an ice bath. The resulting solution was stirred for 30 min, water (5 mL) was added and the mixture was extracted with dichloromethane (3×15 mL). Aqueous potassium hydroxide (1 M) was added slowly to the aqueous phase until pH ~ 9 and the mixture was extracted with dichloromethane (3×15 mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give the *title compound* as a colourless solid (24 mg, 70%) without further purification; mp 115 - 116 °C; (Found: M+H$^+$, 236.1292. $C_{13}H_{18}NO_3$ requires 236.1281); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3605, 3065, 1729, 1602, 1239; δ_H (400 MHz; $CDCl_3$) 7.45 - 7.54 (2 H, m, ArH), 7.32 - 7.39 (2 H, m, ArH), 7.24 - 7.31 (1 H, m, ArH), 4.14 (1 H, dq, *J* 10.7, 7.2, C<u>H</u>$_2$CH$_3$), 4.04 (1 H, dq, *J* 10.7, 7.2,

C<u>H</u>$_2$CH$_3$), 3.93 (1 H, s, H2), 3.42 (1 H, ddd, *J* 10.4, 8.8, 7.4, H5), 3.18 (1 H, ddd, *J* 10.4, 8.8, 3.5, H5), 2.76 (2 H, br s, OH and NH), 2.35 (1 H, dt, *J* 13.5, 8.8, H4), 2.15 (1 H, ddd, *J* 13.5, 7.4, 3.5, H4), 1.09 (3 H, t, *J* 7.2, CH$_2$C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 171.7 (C), 143.3 (C), 128.3 (CH), 127.3 (CH), 125.1 (CH), 83.4 (C), 71.4 (CH), 61.2 (CH_2), 45.4 (CH_2), 43.9 (CH_2), 14.1 (CH_3).

Ethyl *cis,cis*-3-hydroxy-1-(4-methoxyphenyl)-3,4-dimethyl-pyrrolidine-2-carboxylate 404



Following the **general procedure Q** using ethyl diazoacetate **2** (2 mL, 0.325 M solution, 0.65 mmol), 3-((4-methoxyphenyl)amino)-2-methyl-1-phenylpropan-1-one **395** (135 mg, 0.50 mmol) and meso-tetraphenylporphyrin iron(III) chloride complex (3.5 mg, 5.0 μmol). The *title compound* was isolated by column chromatography using 20% ethyl acetate in light petroleum. Yellow oil (146 mg, 82%); (Found: M+H$^+$, 356.1875. $C_{21}H_{26}NO_4$ requires 356.1856); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3008, 1732, 1602, 1514, 1243; δ_H (400 MHz; $CDCl_3$) 7.47 - 7.56 (2 H, m, ArH), 7.35 - 7.42 (2 H, m, ArH), 7.28 - 7.34 (1 H, m, ArH), 6.79 - 6.88 (2 H, m, ArH), 6.46 - 6.55 (2 H, m, ArH), 4.49 (1 H, s, H2), 4.15 (1 H, dq, *J* 10.8, 7.2, C<u>H</u>$_2$CH$_3$), 4.07 (1 H, dq, *J* 10.8, 7.2, C<u>H</u>$_2$CH$_3$), 3.75 (3 H, s, H7), 3.65 (1 H, t, *J* 8.9, H5), 3.62 (1 H, dd, *J* 9.5, 8.9, H5), 3.05 (1 H, s, OH), 2.71 (1 H, ddq, *J* 9.5, 8.9, 6.8, H4), 1.04 (3 H, t, *J* 7.2, CH$_2$C<u>H</u>$_3$), 0.95 (3 H, d, *J* 6.8, H6); δ_C (100 MHz; $CDCl_3$) 171.6 (C), 152.1 (C), 141.8 (C), 140.7 (C), 128.4 (CH), 127.6 (CH), 125.6 (CH), 115.0 (CH), 113.6 (CH), 83.5 (C), 73.2 (CH), 61.4 (CH_2), 56.3 (CH_2), 56.0 (CH_3), 44.4 (CH), 14.2 (CH_3), 9.7 (CH_3).

V.3. Pyrrolidines from ketocarbamate precursors

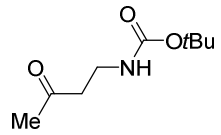
V.3.1. Preparation of diazo compounds

The diazo compounds used in this study were prepared by the following route: **a)** by the oxidation of the corresponding hydrazone as described in **Section II** of this experimental**:** for ethyl 2-diazo-2-phenylacetate **104**, ethyl 2-diazo-2-(4-methoxyphenyl)acetate **105**, ethyl 2-(4-bromophenyl)-2-diazoacetate **107**, ethyl 2-diazo-2-(3,4-dimethoxyphenyl)acetate **110**, ethyl 2-diazo-2-(3-iodo-4-methoxyphenyl)acetate **109**, 3-diazo-1-methylindolin-2-one **118**, *tert*-butyl 2-diazo-2-phenylacetate **114**, ethyl 2-diazo-4-phenylbutanoate **123**, 3-diazo-4,4-dimethyldihydrofuran-2(*3H*)-one **121**, ethyl 2-diazo-2-(4-(dimethylamino)phenyl)acetate **111**, ethyl 2-diazo-2-(2,4-dimethylphenyl)acetate **108**, diethyl (diazo(phenyl)-methyl)phosphonate **262**; **b)** by diazo transfer reaction as previously described for methyl 2-diazo-2-(3-methoxyphenyl)acetate **407**,[80] *tert*-butyl 3-(1-diazo-2-ethoxy-2-oxoethyl)-*1H*-indole-1-carboxylate **414**, ethyl 2-diazo-2-(3-thienyl)acetate **287**,[80] methyl 2-diazo-2-(4-iodophenyl)acetate **408**,[81] 4-diazoisochroman-3-one **413**,[82] ethyl 2-diazo-2-(4-nitrophenyl)acetate **412**,[83] diethyl 2-diazomalonate **243**,[84] 1-diazo-1-phenylpropan-2-one **262**;[85] **c)** by cross-coupling using ethyl diazoacetate **2** and the corresponding iodide, following the previously described method,[86] for ethyl 2-diazo-2-(3-fluorophenyl)acetate **409**, methyl 4-(1-diazo-2-ethoxy-2-oxoethyl)benzoate **410** and ethyl 3-(1-diazo-2-ethoxy-2-oxoethyl)benzoate **411**.

V.3.2. Preparation of ketocarbamates

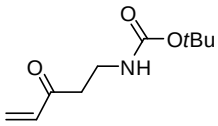
The preparation of the ketocarbamates used in this study is reported below, with exeption of benzyl (3-oxobutyl)carbamate[87] **370** and ethyl 5-((*tert*-butoxycarbonyl)amino)-3-oxopentanoate[88] **437** which were obtained by previously described routes.

tert-Butyl (3-oxobutyl)carbamate 371



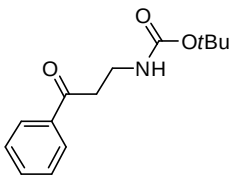
To a solution of *tert*-butyl (3-(methoxy(methyl)amino)-3-oxopropyl)carbamate[89] (1.64 g, 7.06 mmol) in anhydrous THF (50 mL) cooled to −78 °C under argon was added a solution of methylmagnesium bromide (3.0 M in THF, 5.88 mL, 17.6 mmol) dropwise. The resulting mixture was warmed to 0 °C and stirred at this temperature for 90 min, after which saturated aqueous ammonium chloride solution (20 mL) and water (20 mL) were slowly added. The mixture was then warmed to room temperature and extracted with ethyl acetate (100 mL). The organic phase was washed with brine (20 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using 40% ethyl acetate in light petroleum to give the *title compound* as a colourless oil (1.15 g, 87%); (Found: M+Na^+, 210.1111. $C_9H_{17}NaO_3$ requires 210.1101); ν_{max} ($CHCl_3$)/cm^{-1} 3458, 3008, 2981, 1712, 1505, 1397, 1240, 1167; δ_H (400 MHz; $CDCl_3$) 4.99 (1 H, br s, NH), 3.34 (2 H, q, *J* 6.0, CH_2), 2.66 (2 H, t, *J* 6.0, CH_2), 2.15 (3 H, s, CH_3), 1.42 (9 H, s, *t*Bu); δ_C (100 MHz; $CDCl_3$) 208.3 (C), 156.0 (C), 79.4 (C), 43.6 (CH_2), 35.3 (CH_2), 30.3 (CH_3), 28.5 (CH_3).

tert-Butyl (3-oxopent-4-en-1-yl)carbamate 433



To a solution of *tert*-butyl (3-(methoxy(methyl)amino)-3-oxopropyl)carbamate[89] (697 mg, 3.0 mmol) in anhydrous THF (20 mL) cooled to −78 °C under argon was added a solution of vinylmagnesium bromide (1.00 M in THF, 6.60 mL, 6.60 mmol) dropwise. The resulting mixture was warmed to 0 °C and stirred at this temperature for 90 min, after which saturated aqueous ammonium chloride solution (10 mL) and water (10 mL) were slowly added. The mixture was then warmed to room temperature and extracted with ethyl acetate (80 mL). The organic phase was washed with brine (20 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using 20% ethyl acetate in light petroleum to give the *title compound* as a colourless solid (366 mg, 47%); mp 88 - 89 °C; (Found: M+Na$^+$, 222.1103. $C_{10}H_{17}NNaO_3$ requires 222.1101); ν_{max} ($CHCl_3$)/cm^{-1} 3458, 3049, 3008, 1707, 1602, 1506, 1368, 1168; δ_H (400 MHz; $CDCl_3$) 6.33 (1 H, dd, *J* 17.7, 10.4, vinylic CH), 6.22 (1 H, dd, *J* 17.7, 1.3, vinylic CH), 5.88 (1 H, dd, *J* 10.4, 1.3, vinylic CH), 5.03 (1 H, br s, NH), 3.41 (2 H, q, *J* 5.8, CH_2), 2.82 (2H, t, *J* 5.8, CH_2), 1.41 (9 H, s, *t*Bu); δ_C (100 MHz; $CDCl_3$) 200.1 (C), 156.0 (C), 136.7 (CH), 129.1 (CH_2), 79.4 (C), 39.4 (CH_2), 35.3 (CH_2), 28.5 (CH_3). The data obtained are consistent with the literature.[89]

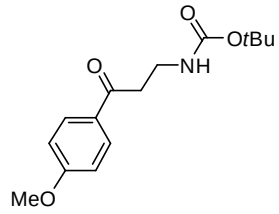
tert-Butyl (3-oxo-3-phenylpropyl)carbamate 434



To a solution of *tert*-butyl (3-(methoxy-(methyl)amino)-3-oxopropyl)carbamate[89] (697 mg,

3.00 mmol) in anhydrous THF (20 mL) cooled to −78 °C under argon was added a solution of phenylmagnesium bromide (0.755 M in THF, 8.14 mL, 6.14 mmol) dropwise. The resulting mixture was warmed to 0 °C and stirred at this temperature for 90 min, after which saturated aqueous ammonium chloride solution (10 mL) and water (10 mL) were slowly added. The mixture was then warmed to room temperature and extracted with ethyl acetate (60 mL). The organic phase was washed with brine (20 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using 20% ethyl acetate in light petroleum to give the *title compound* as a slowly crystallising colourless solid (610 mg, 81%); mp 59 - 60 °C; (Found: M+Na^+, 272.1260. $C_{14}H_{19}NNaO_3$ requires 272.1257); ν_{max} ($CHCl_3$)/cm^{-1} 3458, 3009, 1706, 1686, 1497, 1240, 1183; δ_H (400 MHz; $CDCl_3$) 7.92 - 8.02 (2 H, m, ArH), 7.55 - 7.63 (1 H, m, ArH), 7.44 - 7.52 (2 H, m, ArH), 5.18 (1 H, br s, NH), 3.56 (2 H, q, *J* 5.8, CH_2), 3.22 (2 H, t, *J* 5.8, CH_2), 1.44 (9 H, s, *t*Bu); δ_C (100 MHz; $CDCl_3$) 199.5 (C), 156.1 (C), 136.7 (C), 133.5 (CH), 128.8 (CH), 128.1 (CH), 79.3 (C), 38.8 (CH_2), 35.6 (CH_2), 28.5 (CH_3).

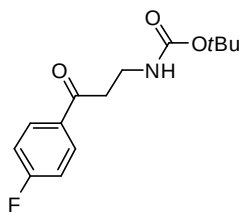
tert-Butyl (3-(4-methoxyphenyl)-3-oxopropyl)carbamate 435



To a solution of *tert*-butyl (3-(methoxy(methyl)-amino)-3-oxopropyl)carbamate[89] (186 mg, 0.80 mmol) in anhydrous THF (5 mL) cooled to −78 °C under argon was added a solution of 4-methoxyphenylmagnesium bromide (0.43 M in THF, 4.09 mL, 1.76 mmol)

dropwise. The resulting mixture was stirred for 35 min, warmed to 0 °C and stirred at this temperature for 75 min, after which saturated aqueous ammonium chloride solution (5 mL) and water (5 mL) were slowly added. The mixture was then warmed to room temperature and extracted with ethyl acetate (40 mL). The organic phase was washed with brine (10 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using the elution gradient 10 to 30% ethyl acetate in light petroleum to give the *title compound* as a yellow oil (106 mg, 47%); (Found: M+Na$^+$, 302.1370. $C_{15}H_{21}NNaO_4$ requires 302.1363); ν_{max} ($CHCl_3$)/cm^{-1} 3457, 3008, 2980, 1705, 1673, 1575, 1366, 1261, 1240, 1172; δ_H (400 MHz; $CDCl_3$) 7.93 (2 H, d, *J* 8.8, ArH), 6.93 (2 H, d, *J* 8.8, ArH), 5.16 (1 H, br s, NH), 3.87 (3 H, s, CH_3), 3.52 (2 H, q, *J* 5.7, CH_2), 3.14 (2 H, t, *J* 5.7, CH_2), 1.42 (9 H, s, *t*Bu); δ_C (100 MHz; $CDCl_3$) 198.0 (C), 163.8 (C), 156.1 (C), 130.5 (CH), 129.9 (C), 113.9 (CH), 79.3 (C), 55.6 (CH_3), 38.4 (CH_2), 35.7 (CH_2), 28.5 (CH_3).

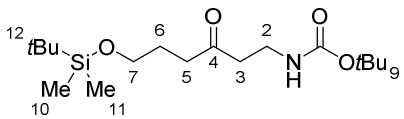
tert-Butyl (3-(4-fluorophenyl)-3-oxopropyl)carbamate 436



To a solution of *tert*-butyl (3-(methoxy-(methyl)amino)-3-oxopropyl)carbamate[89] (186 mg, 0.80 mmol) in anhydrous THF (5 mL) cooled to −78 °C under argon was added a solution of 4-fluorophenylmagnesium bromide (0.69 M in THF, 2.43 mL, 1.67 mmol) dropwise. The resulting mixture was stirred for 35 min, warmed to 0 °C and stirred at this temperature for 75 min, after which saturated aqueous ammonium

chloride solution (5 mL) and water (5 mL) were slowly added. The mixture was then warmed to room temperature and extracted with ethyl acetate (40 mL). The organic phase was washed with brine (10 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using the elution gradient 10 to 30% ethyl acetate in light petroleum to give the *title compound* as a pale yellow solid (98.5 mg, 46%); mp 62 - 63 °C; (Found: M+Na$^+$, 290.1167. $C_{14}H_{18}FNNaO_3$ requires 290.1163); ν_{max} ($CHCl_3$)/cm^{-1} 3459, 3011, 2981, 1708, 1600, 1506, 1366, 1238, 1156; δ_H (400 MHz; $CDCl_3$) 7.87 - 8.12 (2 H, m, ArH), 7.04 - 7.12 (2 H, m, ArH), 5.18 (1 H, br s, NH), 3.50 (2 H, q, *J* 5.8, CH_2), 3.14 (2 H, t, *J* 5.8, CH_2), 1.38 (9 H, s, *t*Bu); δ_C (100 MHz; $CDCl_3$) 197.8 (C), 165.9 (C, d, J_{CF} 256), 156.0 (C), 133.2 (C, d, J_{CF} 3), 130.8 (CH, d, J_{CF} 9), 115.8 (CH, d, J_{CF} 17), 79.3 (C), 38.7 (CH_2), 35.5 (CH_2), 28.5 (CH_3).

tert-Butyl (6-((*tert*-butyldimethylsilyl)oxy)-3-oxohexyl)carbamate 438

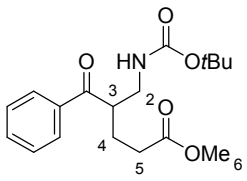


To a solution of 3-chloro-1-propanol (1.00 mL, 12.0 mmol) in THF (15 mL) at −20 °C under argon was added a solution of isopropylmagnesiumbromide lithium chloride complex (1.25 M in THF, 9.6 mL, 12.0 mmol) and the resulting mixture was stirred at −20 °C for 10 min. Magnesium turnings (350 mg, 14.4 mmol) were added, followed by a drop of 1,2-dibromoethane. The mixture was allowed to warm up to room temperature over 20 min and was then heated at reflux for 2 h, before being cooled to room temperature and added over 10 min through a

cannula to a solution of (3-(methoxy(methyl)amino)-3-oxopropyl)carbamate[89] (926 mg, 4.00 mmol) in anhydrous THF (10 mL) under argon and cooled in an ice bath. The resulting mixture was stirred at 0 °C for 75 min and quenched by the addition of saturated aqueous ammonium chloride solution (15 mL) and water (10 mL). The mixture was extracted twice with ethyl acetate (80 mL then 20 mL), the organic phases were washed with brine (20 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using 25% light petroleum in ethyl acetate to give the *title compound* as a colourless oil (771 mg, 83%); the free alcohol readily decomposed and was therefore directly used for the subsequent step. The free alcohol (411 mg, 1.78 mmol) was dissolved in anhydrous dichloromethane (4 mL). 4-(Dimethylamino)pyridine (43 mg, 0.35 mmol), triethylamine (285 µL, 2.12 mol) and *tert*-butyldimethylsilyl chloride (285 mg, 1.96 mmol) were added at room temperature and the resulting mixture was stirred for 24 h. Saturated aqueous ammonium chloride solution (5 mL) and water (2 mL) were added and the resulting mixture was extracted with ethyl acetate (40 mL). The organic phase was washed with water (5 mL), brine (10 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using 20% ethyl acetate in light petroleum to give the *title compound* as a viscous colourless oil (200 mg, 33%). (Found: M+Na^+, 368.2230. $C_{17}H_{35}NNaO_4Si$ requires 368.2228); ν_{max} ($CHCl_3$)/cm^{-1} 3457, 3008, 2956, 1709, 1505, 1255, 1169, 1098, 836; δ_H (400 MHz; $CDCl_3$) 5.01 (1 H, br s, NH), 3.60 (2 H, t, *J* 6.4, H7), 3.34 (2 H,

q, *J* 5.7, H2), 2.64 (2 H, t, *J* 5.7, H3), 2.48 (2 H, t, *J* 7.0, H5), 1.77 (2 H, tt, *J* 7.0, 6.4, H6), 1.42 (9 H, s, H9), 0.87 (9 H, s, H12), 0.02 (6 H, s, H10/11); δ_C (100 MHz; $CDCl_3$) 210.5 (C), 156.0 (C), 79.3 (C), 62.2 (CH_2), 42.7 (CH_2), 39.5 (CH_2), 35.3 (CH_2), 28.5 (CH_3), 26.8 (CH_2), 26.0 (CH_3), 18.4 (C), −5.2 (CH_3).

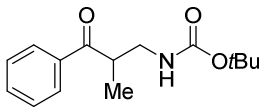
Methyl 4-(((*tert*-butoxycarbonyl)amino)methyl)-5-oxo-5-phenyl-pentanoate 439



To a mixture of *tert*-butyl (3-oxo-3-phenylpropyl)carbamate **434** (187 mg, 0.75 mmol) and methyl acrylate (71 µL, 0.79 mmol) in anhydrous THF (4 mL) cooled in an ice bath at 0 °C was added potassium *tert*-butoxide (42 mg, 0.37 mmol) and the reaction mixture was stirred for 2 h. Saturated aqueous ammonium chloride solution (10 mL) and water (5 mL) were added and the resulting mixture was extracted with ethyl acetate (40 mL). The organic phase was washed with brine (15 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using the elution gradient 15 to 40% ethyl acetate in light petroleum to give the *title compound* as a colourless oil (131 mg, 52%). (Found: $M+Na^+$, 358.1629. $C_{18}H_{25}NNaO_5$ requires 358.1625); ν_{max} ($CHCl_3$)/cm^{-1} 3458, 2981, 1730, 1707, 1677, 1505, 1239, 1168; δ_H (400 MHz; $CDCl_3$) 7.87 - 8.02 (2 H, m, ArH), 7.53 - 7.61 (1 H, m, ArH), 7.43 - 7.51 (2 H, m, ArH), 4.94 (1 H, br s, NH), 3.79 - 3.89 (1 H, m, H3), 3.62 (3 H, s, H6), 3.44 (1 H, dt, *J* 13.7, 6.8, H2), 3.35 (1 H, dt, *J* 13.7, 5.1, H2), 2.24 - 2.52 (2 H, m, H5), 2.07 (1 H, ddt, *J* 14.0, 8.3, 6.8, H4), 1.82 (1 H, ddt, *J* 14.0, 8.5, 6.8, H4), 1.38 (9 H,

s, *t*Bu); δ_C (100 MHz; $CDCl_3$) 203.1 (C), 173.5 (C), 156.1 (C), 136.7 (C), 133.6 (CH), 128.9 (CH), 128.6 (CH), 79.5 (C), 51.7 (CH_3), 45.2 (CH), 41.5 (CH_2), 31.2 (CH_2), 28.4 (CH_3), 25.0 (CH_2).

tert-Butyl (2-methyl-3-oxo-3-phenylpropyl)carbamate 440

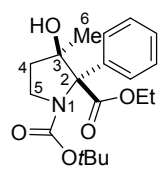


Sodium hydride (60% dispersion in mineral oil, 66 mg, 1.65 mmol) was added to a solution of *tert*-butyl (3-oxo-3-phenylpropyl)carbamate **434** (373 mg, 1.50 mmol) in anhydrous THF (5 mL) at 0 °C under argon and the reaction was stirred for 25 min. Iodomethane (103 μL, 1.65 mmol) was then added dropwise, the mixture was allowed to warm up to room temperature and stirred for 14 h. Saturated aqueous ammonium chloride solution (5 mL) and water (5 mL) were added and the resulting mixture was extracted with ethyl acetate (30 mL). The organic phase was washed with brine (10 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using 15% ethyl acetate in light petroleum to give the *title compound* as a colourless oil (315 mg, 80%); (Found: M+Na^+, 286.1423. $C_{15}H_{21}NNaO_3$ requires 286.1414); ν_{max} ($CHCl_3$)/cm^{-1} 3459, 2981, 1707, 1680, 1507, 1240, 1168; δ_H (400 MHz; $CDCl_3$) 7.93 - 7.99 (2 H, m, ArH), 7.52 - 7.60 (1 H, m, ArH), 7.43 - 7.50 (2 H, m, ArH), 4.97 (1 H, br s, NH), 3.78 (1 H, sxt, *J* 6.8, CH), 3.39 (2 H, t, *J* 6.8, CH_2), 1.40 (9 H, s, *t*Bu), 1.19 (3 H, d, *J* 6.8, CH_3); δ_C (100 MHz; $CDCl_3$) 203.7 (C), 156.2 (C), 136.3 (C), 133.4 (CH), 128.9 (CH), 128.6 (CH), 79.4 (C), 43.0 (CH_2), 41.4 (CH), 28.5 (CH_3), 15.8 (CH_3).

V.3.3. 3-Hydroxypyrrolidine synthesis

General procedure P: a solution containing the diazo compound (0.45 mmol) in anhydrous dichloromethane (2 mL) was added over 1 h to a solution containing the aminoketone (0.3 mmol), rhodium bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] ($Rh_2(esp)_2$, 0.6 mg, 0.75 μmol, added as a 2.0 g/L solution in anhydrous dichloromethane) in anhydrous dichloromethane (2 mL) at reflux under argon. After addition, the resulting mixture was stirred at reflux for an additional 30 min, cooled down and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography on silica gel using the elution system indicated.

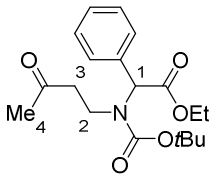
1-(*tert*-Butyl) 2-ethyl-*cis*-3-hydroxy-3-methyl-2-phenylpyrroli-dine-1,2-dicarboxylate 374



Following the **general procedure P** and using diazo compound **104** and amino ketone **371**, the *title compound* was obtained by column chromatography using 35% ethyl acetate in light petroleum. Colourless solid (87.5 mg, 83%); mp 122 - 123 °C; (Found: M+Na$^+$, 372.1777. $C_{19}H_{27}NNaO_5$ requires 372.1781); ν_{max} ($CHCl_3$)/cm^{-1} 3061, 3009, 1742, 1690, 1394, 1367, 1257, 1138; Two rotamers were observed in deuterated chloroform at room temperature (ratio 70:30). Partial coalescence was observed above 80 °C in DMSO-*d*$_6$. The signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**). δ_H (400 MHz; $CDCl_3$) 7.52 - 7.68 (2 H, d, *J* 7.3, ArH **majR**; 2 H, d, *J* 7.3, ArH **minR**), 7.17 - 7.35 (3 H, m, **majR**; 3 H, m, ArH **minR**), 4.14 - 4.40 (2 H, m, C$\underline{H_2}$CH$_3$ **majR**; 2 H, m, C$\underline{H_2}$CH$_3$ **minR**), 3.76 -

3.91 (2 H, m, H5 **majR**; 1 H, m, H5 **minR**), 3.63 - 3.75 (1 H, m, H5 **minR**), 2.66 (1 H, br s, OH **minR**), 2.35 (1 H, br s, OH **majR**), 1.82 - 2.14 (2 H, m, H4 **majR**; 2 H, m, H4 **minR**), 1.56 (3 H, s, H6 **minR**), 1.46 (3 H, s, H6 **majR**), 1.24 - 1.39 (3 H, m, $CH_2C\underline{H}_3$ **majR**; 3 H, m, $CH_2C\underline{H}_3$ **minR**), 1.11 (9 H, s, *t*Bu **majR**), 0.98 (9 H, s, *t*Bu **minR**); δ_C (100 MHz; $CDCl_3$) 170.7 (C **majR**), 170.6 (C **minR**), 154.4 (C **majR**), 154.0 (C **minR**), 139.0 (C **majR**), 137.4 (C **minR**), 127.6 (CH **minR**), 127.5 (CH **majR**), 127.3 (CH **minR**), 127.1 (CH **majR**), 127.0 (CH **majR**), 84.7 (C **majR**), 83.5 (C **minR**), 80.1 (C **majR**), 80.0 (C **minR**), 78.1 (C **majR**), 61.7 (CH_2 **minR**), 61.5 (CH_2 **majR**), 45.7 (CH_2 **minR**), 45.2 (CH_2 **majR**), 37.3 (CH_2 **minR**), 36.7 (CH_2 **majR**), 28.5 (CH_3 **minR**), 28.0 (CH_3 **majR**), 25.3 (CH_3 **majR**), 25.0 (CH_3 **minR**), 14.3 (CH_3 **majR**), 14.2 (CH_3 **minR**), a (C) and a (CH) peak attributed to the minor rotamer were not observed.

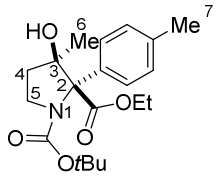
Ethyl 2-((*tert*-butoxycarbonyl)(3-oxobutyl)amino)-2-phenylacetate 406



1-(*tert*-Butyl) 2-ethyl-*cis*-3-hydroxy-3-methyl-2-phenylpyrrolidine-1,2-dicarboxylate **374** (40 mg, 114 µmol) and 4-(dimethylamino)pyridine (5 mg, 41 µmol) were dissolved in dichloromethane (1.0 mL) and stirred at reflux for 14 h. The reaction mixture was cooled down and the solvent was removed under reduced pressure to give a residue that was purified by column chromatography using 20% ethyl acetate in light petroleum to give the *title compound* as a colourless oil (34.3 mg, 86%); (Found: M+Na^+, 372.1789. $C_{19}H_{27}NNaO_5$ requires 372.1781); ν_{max} ($CHCl_3$)/cm^{-1} 3008, 2982, 1739, 1710, 1689, 1602, 1409, 1368, 1160; Two rotamers were

observed in deuterated chloroform at room temperature (ratio 56:44), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**). δ_H (400 MHz; $CDCl_3$) 7.29 - 7.39 (3 H, m, ArH **majR**; 3 H, m, ArH **minR**), 7.21 - 7.28 (2 H, m, ArH, **majR**; 2 H, m, ArH **minR**), 5.89 (1 H, br s, H1 **majR**), 5.59 (1 H, br s, H1 **minR**), 4.23 (2 H, q, *J* 7.2, $C\underline{H}_2CH_3$ **majR**; 2 H, q, *J* 7.2, $C\underline{H}_2CH_3$ **minR**), 3.12 - 3.60 (2 H, m, H2 **majR**; 2 H, m, H2 **minR**), 2.59 - 2.75 (1 H, m, H3 **majR**; 1 H, m, H3 **minR**), 2.45 (1 H, br s, H3 **minR**), 2.08 - 2.32 (1 H, m, H3 **majR**), 1.98 (3 H, s, H4 **majR**; 3 H, s, H4 **minR**), 1.46 (9 H, s, *t*Bu **majR**; 9 H, s, *t*Bu **minR**), 1.18 - 1.30 (3 H, m, $CH_2C\underline{H}_3$ **majR**; 3 H, m, $CH_2C\underline{H}_3$ **minR**); δ_C (100 MHz; $CDCl_3$) 207.6 (C **majR**), 171.1 (C **majR**), 155.9 (C **majR**), 155.0 (C **minR**), 138.2 (C **minR**), 135.2 (C **majR**), 129.1 (CH **majR**), 128.9 (CH **majR**), 128.6 (CH **majR**), 80.9 (C **majR**), 63.9 (CH **minR**), 62.5 (CH **majR**), 61.4 (CH_2 **majR**), 43.6 (CH_2 **majR**), 42.9 (CH_2 **minR**), 40.7 (CH_2 **minR**), 40.2 (CH_2 **majR**), 30.2 (CH_3 **majR**), 28.5 (CH_3 **majR**), 14.3 (CH_3 **majR**), three (C), three (CH) and one (CH_2) peaks attributed to the minor rotamer were not observed.

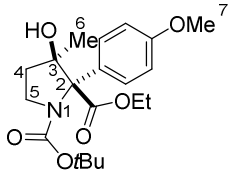
1-(*tert*-Butyl) 2-ethyl *cis*-3-hydroxy-3-methyl-2-(p-tolyl)pyrrolidine-1,2-dicarboxylate 415



Following **general procedure P** and using diazo compound **285** and amino ketone **371**, the *title compound* was obtained by column chromatography using the elution gradient 20 to 35% ethyl acetate in light petroleum. Colourless solid (78.5 mg, 72%); mp 116 - 117 °C; (Found: $M+Na^+$, 386.1935. $C_{20}H_{29}NNaO_5$ requires 386.1938); ν_{max} ($CHCl_3$)/cm^{-1} 3691,

3006, 2981, 1741, 1690, 1602, 1393, 1367, 1256, 1240, 1162; Two rotamers were observed in deuterated chloroform at room temperature (ratio 74:26), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 7.36 - 7.54 (2 H, m, ArH **majR**; 2 H, m, ArH **minR**), 7.09 (2 H, d, *J* 8.2, ArH **majR**; 2 H, d, *J* 8.2, ArH **minR**), 4.08 - 4.41 (2 H, m, C$\underline{H}_2$CH$_3$ **majR**; 2 H, m, C$\underline{H}_2$CH$_3$ **minR**), 3.59 - 3.91 (2 H, m, H5 **majR**; 2 H, m, H5 **minR**), 2.74 (1 H, br s, OH **minR**), 2.45 (1 H, br s, OH **majR**), 2.33 (3 H, s, H7 **majR**), 2.30 (3 H, s, H7 **minR**), 1.81 - 2.13 (2 H, m, H4 **majR**; 2 H, m, H4 **minR**), 1.45 (9 H, s, *t*Bu **minR**), 1.25 - 1.37 (3 H, m, CH$_2$C$\underline{H}_3$ **majR**; 3 H, m, CH$_2$C$\underline{H}_3$ **minR**), 1.11 (9 H, s, *t*Bu **majR**), 1.01 (3 H, s, H6 **minR**), 0.97 (3 H, s, H6 **majR**); δ_C (100 MHz; $CDCl_3$) 170.8 (C **majR**), 154.5 (C **majR**), 136.7 (C **majR**), 135.9 (C **majR**), 128.4 (CH **minR**), 128.2 (CH **majR**), 127.2 (CH **minR**), 127.0 (CH **majR**), 84.8 (C **majR**), 83.4 (C **minR**), 80.1 (C **majR**), 79.9 (C **minR**), 78.0 (C **majR**), 61.7 (CH$_2$ **minR**), 61.5 (CH$_2$ **majR**), 45.7 (CH$_2$ **minR**), 45.2 (CH$_2$ **majR**), 37.3 (CH$_2$ **minR**), 36.7 (CH$_2$ **majR**), 28.5 (CH$_3$ **minR**), 28.0 (CH$_3$ **majR**), 25.2 (CH$_3$ **majR**), 24.9 (CH$_3$ **minR**), 21.0 (CH$_3$ **majR** and **minR**), 14.4 (CH$_3$ **majR**), 14.2 (CH$_3$ **minR**), five (C) peaks attributed to the minor rotamer were not observed.

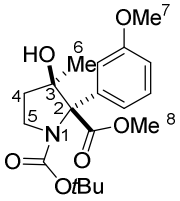
1-(*tert*-Butyl) 2-ethyl *cis*-3-hydroxy-2-(4-methoxyphenyl)-3-methylpyrrolidine-1,2-dicarboxylate 416



Following **general procedure P** and using diazo compound **105** and amino ketone **371**, the *title compound* was obtained by column chromatography using the elution gradient 20 to 35 % ethyl acetate in light petroleum.

Colourless solid (106 mg, 93%); mp 93 - 94 °C; (Found: M+Na$^+$, 402.1892. $C_{20}H_{29}NNaO_6$ requires 402.1887); ν_{max} ($CHCl_3$)/cm^{-1} 3009, 2981, 1740, 1690, 1475, 1393, 1367, 1253, 1184, 1162, 1033; Two rotamers were observed in deuterated chloroform at room temperature (ratio 74:26), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 7.38 - 7.58 (2 H, m, ArH **majR**; 2 H, m, ArH **minR**), 6.80 (2 H, d, *J* 8.9, ArH **majR**; 2 H, d, *J* 8.9, ArH **minR**), 4.07 - 4.43 (2 H, m, C$\underline{H}_2$CH$_3$ **majR**; 2 H, m, C$\underline{H}_2$CH$_3$ **minR**), 3.53 - 3.92 (2 H, m, H5 **majR**; 2 H, m, H5 **minR**), 3.78 (3 H, s, H7 **majR**), 3.75 (3 H, s, H7 **minR**), 2.85 (1 H, br s, OH **minR**), 2.64 (1 H, br s, OH **majR**), 1.73 - 2.14 (2 H, m, H4 **majR**; 2 H, m, H4 **minR**), 1.43 (9 H, s, *t*Bu **minR**), 1.20 - 1.36 (3 H, m, CH$_2$C$\underline{H}_3$ **majR**; 3 H, m, CH$_2$C$\underline{H}_3$ **minR**), 1.10 (9 H, s, *t*Bu **majR**), 0.98 (3 H, s, H6 **minR**), 0.95 (3 H, s, H6 **majR**);δ_C (100 MHz; $CDCl_3$) 170.8 (C **majR**), 170.7 (C **minR**), 158.7 (C **minR**), 158.6 (C **majR**), 154.4 (C **majR**), 153.9 (C **minR**), 131.1 (C **majR**), 129.6 (C **minR**), 128.5 (CH **minR**), 128.3 (CH **majR**), 113.0 (CH **minR**), 112.7 (CH **majR**), 84.7 (C **majR**), 83.4 (C **minR**), 80.0 (C **majR**), 79.9 (C **minR**), 77.6 (C **majR**), 61.6 (CH$_2$ **minR**), 61.4 (CH$_2$ **majR**), 55.3 (CH$_3$ **majR**), 45.6 (CH$_2$ **minR**), 45.1 (CH$_2$ **majR**), 37.2 (CH$_2$ **minR**), 36.6 (CH$_2$ **majR**), 28.5 (CH$_3$ **minR**), 28.0 (CH$_3$ **majR**), 25.2 (CH$_3$ **majR**), 24.8 (CH$_3$ **minR**), 14.3 (CH$_3$ **majR**), 14.2 (CH$_3$ **minR**), one (C) and one (CH$_3$) peak attributed to the minor rotamer were not observed.

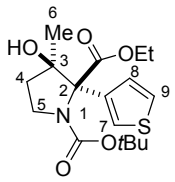
1-(*tert*-Butyl) 2-ethyl *cis*-3-hydroxy-2-(3-methoxyphenyl)-3-methylpyrrolidine-1,2-dicarboxylate 417



Following **general procedure P** and using diazo compound **407** and amino ketone **371**, the *title compound* was obtained by column chromatography using the elution gradient 20 to 50% ethyl acetate in light petroleum. Colourless solid (60 mg, 55%); mp 116 - 118 °C; (Found: M+Na$^+$, 388.1733. $C_{19}H_{27}NNaO_6$ requires 388.1731); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3605, 3010, 2980, 1746, 1691, 1601, 1394, 1246, 1160; Two rotamers were observed in deuterated chloroform at room temperature (ratio 76:24), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 7.07 - 7.31 (3 H, m, ArH **majR**; 3 H, m, ArH **minR**), 6.79 (1 H, d, *J* 6.7, ArH **majR**; 1 H, d, *J* 6.7, ArH **minR**), 3.60 - 3.90 (8 H, m, H5 and H7 and H8 **majR**; 8 H, m, H5 and H7 and H8 **minR**), 2.74 (1 H, br s, OH **minR**), 2.53 (1 H, br s, OH **majR**), 1.74 - 2.15 (2 H, m, H4 **majR**; 2 H, m, H4 **minR**), 1.44 (9 H, br s, *t*Bu **minR**), 1.10 (9 H, s, *t*Bu **majR**), 1.00 (3 H, s, H6 **majR**; 3 H, s, H6 **minR**); δ_C (100 MHz; $CDCl_3$) 171.2 (C **majR**), 159.1 (C **majR**), 154.3 (C **majR**), 154.1 (C **minR**), 140.8 (C **majR**), 139.2 (C **minR**), 128.5 (CH **minR**), 128.4 (CH **majR**), 119.8 (C **minR**), 119.5 (CH **majR**), 113.8 (CH **minR**), 113.5 (CH **majR**), 112.5 (CH **minR**), 112.3 (CH **majR**), 84.8 (C **majR**), 83.6 (C **minR**), 80.1 (C **minR**), 80.0 (C **majR**), 78.4 (C **majR**), 77.9 (C **minR**), 55.3 (CH_3 **majR**), 52.5 (CH_3 **minR**), 52.2 (CH_3 **majR**), 45.7 (CH_2 **minR**), 45.2 (CH_2 **majR**), 37.3 (CH_2 **minR**), 36.7 (CH_2 **majR**), 28.5 (CH_3 **minR**), 28.0 (CH_3 **majR**),

25.1 (CH_3 **majR**), 24.9 (CH_3 **minR**), one (C), one (CH) and one (CH_3) peak attributed due to the minor rotamer were not observed.

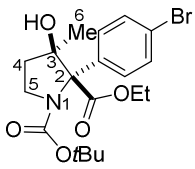
1-(*tert*-Butyl) 2-ethyl *cis*-3-hydroxy-3-methyl-2-(3-thienyl)pyrrolidine-1,2-dicarboxylate 429



Following the **general procedure P** and using diazo compound **287** and amino ketone **371**, the *title compound* was obtained by column chromatography using the elution gradient 20 to 40% ethyl acetate in light petroleum. Yellow solid (81 mg, 76%); mp 112 - 113 °C; (Found: M+Na^+, 378.1346. $C_{17}H_{25}NNaO_5S$ requires 378.1346); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3603, 3008, 2981, 1737, 1692, 1392, 1264, 1160, 1138; Two rotamers were observed in deuterated chloroform at room temperature (ratio 80:20), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 7.48 (1 H, dd, *J* 3.0, 1.2, H7 **majR**), 7.40 (1 H, d, *J* 1.8, H7 **minR**), 7.14 - 7.21 (1 H, m, H9 **majR**; 1 H, m, H9 **minR**), 7.05 - 7.13 (1 H, m, H8 **majR**; 1 H, m, H8 **minR**), 4.12 - 4.40 (2 H, m, C$\underline{H}_2$$CH_3$ **majR**; 2 H, m, C$\underline{H}_2$$CH_3$ **minR**), 3.65 - 3.88 (2 H, m, H5 **majR**; 2 H, m, H5 **minR**), 2.71 (1 H, s, OH **minR**), 2.55 (1 H, s, OH **majR**), 1.85 - 2.05 (2 H, m, H4 **majR**; 2 H, m, H4 **minR**), 1.43 (9 H, s, *t*Bu **minR**), 1.25 - 1.36 (3 H, m, CH_2C$\underline{H}_3$ **majR**; 3 H, m, CH_2C$\underline{H}_3$ **minR**), 1.12 (9 H, s, *t*Bu **majR**), 1.03 (3 H, s, H6 **majR**; 3 H, s, H6 **minR**); δ_C (100 MHz; $CDCl_3$) 170.4 (C **majR**), 170.0 (C **minR**), 154.3 (C **majR**), 153.8 (C **minR**), 140.7 (C **majR**), 139.4 (C **minR**), 127.9 (CH **minR**), 127.7 (CH **majR**), 124.1 (CH **minR**), 124.0 (CH **majR**), 122.6 (CH **minR**), 122.1 (CH **majR**), 84.5 (C **majR**), 83.3 (C **minR**), 80.0 (C **majR**), 76.8 (C **majR**), 76.5 (C **minR**), 61.7 (CH_2 **minR**),

61.5 (CH_2 **majR**), 45.5 (CH_2 **minR**), 45.0 (CH_2 **majR**), 37.2 (CH_2 **minR**), 36.6 (CH_2 **majR**), 28.5 (CH_3 **minR**), 28.0 (CH_3 **majR**), 24.5 (CH_3 **majR**), 24.1 (CH_3 **minR**), 14.4 (CH_3 **majR**), 14.2 (CH_3 **minR**), one (C) peak attributed to the minor isomer was not observed.

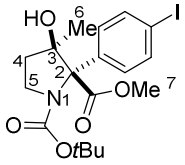
1-(*tert*-Butyl) 2-ethyl *cis*-2-(4-bromophenyl)-3-hydroxy-3-methylpyrrolidine-1,2-dicarboxylate 418



Following the **general procedure P** and using diazo compound **107** and amino ketone **371**, the *title compound* was obtained by column chromatography using the elution gradient 20 to 40% ethyl acetate in light petroleum. Colourless solid (48 mg, 37%); mp 128 - 129 °C (Found: M+Na^+, 450.0893. $C_{19}H_{26}{}^{79}BrNNaO_5$ requires 450.0887); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3605, 3009, 2982, 1742, 1694, 1602, 1393, 1275, 1161; Two rotamers were observed in deuterated chloroform at room temperature (ratio 70:30), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 7.33 - 7.65 (4 H, m, ArH **majR**; 4 H, m, ArH **minR**), 4.11 - 4.37 (2 H, m, C$\underline{H}_2$$CH_3$ **majR**; 2 H, m, C$\underline{H}_2$$CH_3$ **minR**), 3.56 - 3.93 (2 H, m, H5 **majR**; 2 H, m, H5 **minR**), 2.62 (1 H, br s, OH **minR**), 2.44 (1 H, br s, OH **majR**), 2.03 - 2.19 (1 H, m, H4 **majR**; 1 H, m, H4 **minR**), 1.79 - 1.99 (1 H, m, H4 **majR**; 1 H, m, H4 **minR**), 1.45 (9 H, s, *t*Bu **minR**), 1.22 - 1.38 (3 H, m, CH_2C$\underline{H}_3$ **majR**; 3 H, m, CH_2C$\underline{H}_3$ **minR**), 1.13 (9 H, s, *t*Bu **majR**), 0.96 (3 H, br s, H6 **minR**), 0.94 (3 H, s, H6 **majR**); δ_C (100 MHz; $CDCl_3$) 170.5 (C **majR**), 170.3 (C **minR**), 154.2 (C **majR**), 154.1 (C **minR**), 138.1 (C **majR**), 136.7 (C **minR**), 130.7 (CH **minR**), 130.5 (CH **majR**), 129.2 (CH **majR**), 129.0 (CH **minR**), 121.6

(C **minR**), 121.3 (C **majR**), 84.6 (C **majR**), 83.3 (C **minR**), 80.5 (C **majR**), 80.3 (C **minR**), 77.6 (C **majR**), 77.4 (C **minR**), 61.9 (CH_2 **minR**), 61.7 (CH_2 **majR**), 45.7 (CH_2 **minR**), 45.2 (CH_2 **majR**), 37.5 (CH_2 **minR**), 36.9 (CH_2 **majR**), 28.5 (CH_3 **minR**), 28.0 (CH_3 **majR**), 25.5 (CH_3 **majR**), 25.2 (CH_3 **minR**), 14.3 (CH_3 **majR**), 14.2 (CH_3 **minR**).

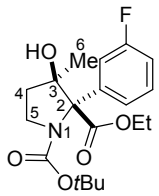
1-(*tert*-Butyl) 2-ethyl *cis*-2-(4-iodophenyl)-3-hydroxy-3-methylpyrrolidine-1,2-dicarboxylate 419



Following the **general procedure P** and using diazo compound **408** and amino ketone **371**, the *title compound* was obtained by column chromatography using the elution gradient 20 to 40% ethyl acetate in light petroleum. Colourless solid (55.5 mg, 40%); mp 111 - 112 °C; (Found: M+Na^+, 484.0611. $C_{18}H_{24}INNaO_5$ requires 484.0591); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3605, 3005, 2981, 1746, 1709, 1695, 1393, 1367, 1239, 1161; Two rotamers were observed in deuterated chloroform at room temperature (ratio 76:24), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 7.56 - 7.67 (2 H, m, ArH **majR**; 2 H, m, ArH **minR**), 7.28 - 7.45 (2 H, m, ArH **majR**; 2 H, m, ArH **minR**), 3.58 - 3.98 (5 H, m, H5 and H7, **majR**; 5 H, m, H5 and H7, **minR**), 2.66 (1 H, br s, OH **minR**), 2.49 (1 H, br s, OH **majR**), 2.03 - 2.16 (2 H, m, H4 **majR**; 2 H, m, H4 **minR**), 1.82 - 1.95 (2 H, m, H4 **majR**; 2 H, m, H4 **minR**), 1.44 (9 H, br s, *t*Bu **minR**), 1.12 (9 H, br s, *t*Bu **majR**), 0.95 (3 H, s, H6 **majR**; 3 H, s, H6 **minR**); δ_C (100 MHz; $CDCl_3$) 171.0 (C **majR**), 154.1 (C **majR**), 138.8 (C **majR**), 136.7 (CH **minR**), 136.6 (CH **majR**), 129.4 (CH **minR**), 129.3 (CH **majR**), 93.5 (C **minR**), 93.1 (C **majR**), 84.6

(C **majR**), 83.4 (C **minR**), 80.4 (C **majR**), 77.9 (C **majR**), 52.7 (CH_3 **minR**), 52.4 (CH_3 **majR**), 45.7 (CH_2 **minR**), 45.2 (CH_2 **majR**), 37.5 (CH_2 **minR**), 36.8 (CH_2 **majR**), 28.5 (CH_3 **minR**), 28.0 (CH_3 **majR**), 25.4 (CH_3 **majR**), 25.2 (CH_3 **minR**), five (C) peaks attributed the minor rotamer were not observed.

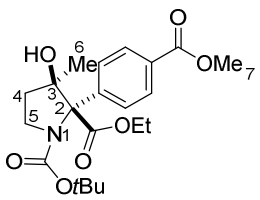
1-(*tert*-Butyl) 2-ethyl *cis*-2-(3-fluorophenyl)-3-hydroxy-3-methylpyrrolidine-1,2-dicarboxylate 420



Following the **general procedure P** and using diazo compound **409** and amino ketone **371**, the *title compound* was obtained by column chromatography using the elution gradient 20 to 30% ethyl acetate in light petroleum. Colourless solid (285 mg, 29%); mp 120 - 121 °C; (Found: M+Na^+, 390.1692. $C_{19}H_{26}FNNaO_5$ requires 390.1687); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3604, 3008, 2981, 1742, 1694, 1393, 1367, 1240, 1161, 1137; Two rotamers were observed in deuterated chloroform at room temperature (ratio 74:26), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 7.32 - 7.52 (2 H, m, ArH **majR**; 2 H, m, ArH **minR**), 7.20 - 7.30 (1 H, m, ArH **majR**; 1 H, m, ArH **minR**), 6.88 - 7.04 (1 H, m, ArH **majR**; 1 H, m, ArH **minR**), 4.12 - 4.42 (2 H, m, C$\underline{H}_2$$CH_3$ **majR**; 2 H, m, C$\underline{H}_2$$CH_3$ **majR**), 3.59 - 3.93 (2 H, m, H5 **majR**; 2 H, m, H5 **minR**), 2.56 (1 H, br s, OH **minR**), 2.37 (1 H, s, OH **majR**), 2.06 - 2.17 (1 H, m, H4 **majR**; 1 H, m, H4 **minR**), 1.81 - 2.02 (1 H, m, H4 **majR**; 1 H, m, H4 **minR**), 1.46 (9 H, s, *t*Bu **minR**), 1.24 - 1.38 (3 H, m, CH_2C$\underline{H}_3$ **majR**; 3 H, m, CH_2C$\underline{H}_3$ **majR**), 1.12 (9 H, s, *t*Bu **majR**), 0.98 (3 H, s, H6 **majR**; 3 H, s, H6 **minR**); δ_F (376 MHz; $CDCl_3$) −113.7 (m, **majR**), −113.8

(m, **minR**); δ_C (100 MHz; $CDCl_3$) 170.4 (C **majR**), 162.4 (C, d, J_{CF} 243, **majR**), 154.2 (C **majR**), 141.9 (C, J_{CF} 8, **majR**), 140.4 (C, J_{CF} 8, **minR**), 129.0 (CH, J_{CF} 9, **minR**), 128.8 (CH, J_{CF} 8, **majR**), 123.0 (CH, J_{CF} 2, **minR**), 122.7 (CH, J_{CF} 2, **majR**), 114.7 (CH, J_{CF} 25, **majR**), 114.0 (CH, J_{CF} 21, **majR**), 84.8 (C **majR**), 83.5 (C **minR**), 80.4 (C **majR**), 80.3 (C **minR**), 77.8 (C **majR**), 61.9 (CH_2 **minR**), 61.7 (CH_2 **majR**), 45.7 (CH_2 **minR**), 45.2 (CH_2 **majR**), 37.4 (CH_2 **minR**), 36.8 (CH_2 **majR**), 28.5 (CH_3 **majR**), 28.0 (CH_3 **minR**), 25.4 (CH_3 **majR**), 25.1 (CH_3 **minR**), 14.3 (CH_3 **majR**), 14.2 (CH_3 **minR**), four (C) and two (CH) peaks attributed to the minor rotamer were not observed.

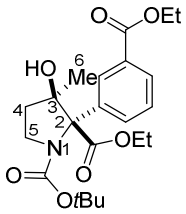
1-(*tert*-Butyl) 2-ethyl *cis*-3-hydroxy-2-(4-(methoxycarbonyl)-phenyl)-3-methylpyrrolidine-1,2-dicarboxylate 421



Following the **general procedure P** and using diazo compound **410** and amino ketone **371**, the *title compound* was obtained by column chromatography using the elution gradient 20 to 50% ethyl acetate in light petroleum. Colourless solid (30 mg, 24%); mp 122 - 124 °C; (Found: $M+Na^+$, 430.1841. $C_{21}H_{29}NNaO_7$ requires 430.1836); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3605, 3009, 2982, 1716, 1692, 1602, 1393, 1367, 1284, 1161, 1116; Two rotamers were observed in deuterated chloroform at room temperature (ratio 73:27), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 7.88 - 8.02 (2 H, m, ArH **majR**; 2 H, m, ArH **minR**), 7.72 (2 H, d, *J* 7.5, ArH **majR**), 7.67 (2 H, d, *J* 7.9, ArH **minR**), 4.12 - 4.42 (2 H, m, C$\underline{H}_2$$CH_3$ **majR**; 2 H, m, C$\underline{H}_2$$CH_3$ **minR**), 3.91 (3 H, s, H7 **majR**), 3.89 (3 H, s, H7 **minR**), 3.58 - 3.99 (2 H, m,

H5 **majR**; 2 H, m, H5 **minR**), 2.64 (1 H, br s, OH **minR**), 2.46 (1 H, br s, OH **majR**), 2.10 - 2.23 (1 H, m, H4 **majR**; 1 H, m, H4 **minR**), 1.84 - 2.01 (1 H, m, H4 **majR**; 1 H, m, H4 **minR**), 1.45 (9 H, s, *t*Bu **minR**), 1.24 - 1.37 (3 H, m, $CH_2C\underline{H}_3$ **majR**; 3 H, m, $CH_2C\underline{H}_3$ **minR**), 1.10 (9 H, s, *t*Bu **majR**), 0.92 (3 H, s, H6 **majR**; 3 H, s, H6 **minR**); δ_C (100 MHz; $CDCl_3$) 170.4 (C **majR**), 167.1 (C **majR**), 154.2 (C **majR**), 144.2 (C **majR**), 129.0 (C **majR**), 128.9 (CH **minR**), 128.8 (CH **majR**), 127.4 (CH **minR**), 127.3 (CH **majR**), 84.8 (C **majR**), 83.5 (C **minR**), 80.5 (C **majR**), 78.0 (C **majR**), 61.9 (CH_2 **minR**), 61.8 (CH_2 **majR**), 52.2 (CH_3 **majR**), 45.7 (CH_2 **minR**), 45.2 (CH_2 **majR**), 37.6 (CH_2 **minR**), 37.0 (CH_2 **majR**), 28.5 (CH_3 **minR**), 28.0 (CH_3 **majR**), 25.6 (CH_3 **majR**), 25.3 (CH_3 **minR**), 14.3 (CH_3 **majR**), 14.2 (CH_3 **minR**), seven (C) and one (CH_3) peaks attributed to the minor rotamer were not observed.

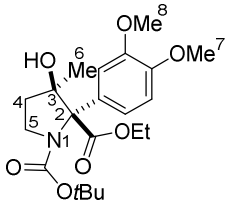
1-(*tert*-Butyl) 2-ethyl *cis*-2-(3-(ethoxycarbonyl)phenyl)-3-hydroxy-3-methylpyrrolidine-1,2-dicarboxylate 422



Following the **general procedure P** and using diazo compound **411** and amino ketone **371**, the *title compound* was obtained by column chromatography using the elution gradient 20 to 40% ethyl acetate in light petroleum. Colourless solid (38 mg, 30%); mp 94 - 95 °C; (Found: M+Na^+, 444.2007. $C_{22}H_{31}NNaO_7$ requires 444.1993); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3605, 2982, 1741, 1698, 1602, 1393, 1368, 1280, 1239, 1161; Two rotamers were observed in deuterated chloroform at room temperature (ratio 70:30), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 8.22 (1 H, br s, ArH **majR**), 8.13 (1 H, br s,

ArH **minR**), 7.84 - 8.00 (2 H, m, ArH **majR**; 2 H, m, ArH **minR**), 7.38 (1 H, t, *J* 7.8, ArH **majR**; 1 H, t, *J* 7.8, ArH **minR**), 4.09 - 4.46 (4 H, m, C$\underline{H}_2$CH$_3$ **majR**; 4 H, m, C$\underline{H}_2$CH$_3$ **minR**), 3.59 - 3.97 (2 H, m, H5 **majR**; 2 H, m, H5 **minR**), 2.78 (1 H, br s, OH **minR**), 2.60 (1 H, br s, OH **majR**), 2.10 - 2.30 (1 H, m, H4 **majR**; 1 H, m, H4 **minR**), 1.74 - 2.00 (1 H, m, H4 **majR**; 1 H, m, H4 **minR**), 1.46 (9 H, s, *t*Bu **minR**), 1.24 - 1.41 (6 H, m, CH$_2$C$\underline{H}_3$ **majR**; 6 H, m, CH$_2$C$\underline{H}_3$ **minR**), 1.10 (9 H, s, *t*Bu **majR**), 0.95 (3 H, s, H6 **minR**), 0.92 (3 H, s, H6 **majR**); δ_C (100 MHz; $CDCl_3$) 170.6 (C **majR**), 170.4 (C **minR**), 166.8 (C **majR**), 154.3 (C **majR**), 139.2 (C **majR**), 137.9 (C **minR**), 132.5 (CH **minR**), 132.1 (CH **majR**), 129.9 (C **minR**), 129.8 (C **majR**), 128.6 (CH **minR**), 128.4 (CH **majR**), 128.3 (CH **majR**), 127.6 (CH **minR**), 127.5 (CH **majR**), 84.5 (C **majR**), 83.4 (C **minR**), 80.5 (C **majR**), 80.3 (C **minR**), 77.7 (C **majR**), 61.9 (CH$_2$ **minR**), 61.8 (CH$_2$ **majR**), 61.1 (CH$_2$ **majR**), 61.0 (CH$_2$ **minR**), 45.7 (CH$_2$ **minR**), 45.2 (CH$_2$ **majR**), 37.6 (CH$_2$ **minR**), 37.1 (CH$_2$ **majR**), 28.5 (CH$_3$ **minR**), 28.0 (CH$_3$ **majR**), 25.8 (CH$_3$ **majR**), 25.3 (CH$_3$ **minR**), 14.5 (CH$_3$ **majR**), 14.3 (CH$_3$ **majR**), 14.2 (CH$_3$ **minR**), three (C), one (CH) and one (CH$_3$) peaks attributed to the minor rotamer were not observed.

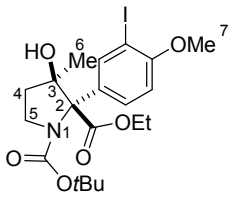
1-(*tert*-Butyl) 2-ethyl *cis*-2-(3,4-dimethoxyphenyl)-3-hydroxy-3-methylpyrrolidine-1,2-dicarboxylate 423



Following the **general procedure P** and using diazo compound **110** and amino ketone **371**, the *title compound* was obtained by column chromatography using the elution gradient 25 to 60% ethyl acetate in light petroleum. Colourless oil (112 mg, 91%); (Found: M+Na$^+$, 432.1996. $C_{21}H_{31}NNaO_7$

requires 432.1993); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3605, 3010, 2981, 1739, 1689, 1518, 1393, 1257, 1142, 999; Two rotamers were observed in deuterated chloroform at room temperature (ratio 70:30), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**). δ_H (400 MHz; $CDCl_3$) 7.19 - 7.36 (1 H, m, ArH **majR**; 1 H, m, ArH **minR**), 7.06 (1 H, d, *J* 7.5, ArH **majR**), 7.00 (1 H, d, *J* 8.3, ArH **minR**), 6.72 - 6.78 (1 H, m, ArH **majR**; 1 H, m, ArH **minR**), 4.06 - 4.35 (2 H, m, $C\underline{H}_2CH_3$ **majR**; 2 H, m, $C\underline{H}_2CH_3$ **minR**), 3.57 - 3.91 (8 H, m, H5, H7 and H8 **majR**; 8 H, m, H5, H7 and H8 **minR**), 2.73 (1 H, br s, OH **majR**), 2.57 (1 H, br s, OH **minR**), 1.77 - 2.09 (2 H, m, H4 **majR**; 2 H, m, H4 **minR**), 1.42 (9 H, s, *t*Bu **minR**), 1.19 - 1.34 (3 H, m, $CH_2C\underline{H}_3$ **majR**; 3 H, m, $CH_2C\underline{H}_3$ **minR**), 1.10 (9 H, s, *t*Bu **majR**), 0.96 (3 H, s, H6 **majR**; 3 H, s, H6 **minR**); δ_C (100 MHz; $CDCl_3$) 170.8 (C **majR**), 170.6 (C **minR**), 154.4 (C **majR**), 153.9 (C **minR**), 148.2 (C **minR**), 148.0 (C **majR**), 147.9 (C **minR**), 147.8 (C **majR**), 131.7 (C **majR**), 130.1 (C **minR**), 119.5 (CH **minR**), 119.4 (CH **majR**), 111.7 (CH **minR**), 111.0 (CH **majR**), 110.4 (CH **minR**), 109.9 (CH **majR**), 84.8 (C **majR**), 83.5 (C **minR**), 80.0 (C **majR**), 79.9 (C **minR**), 77.7 (C **majR**), 61.6 (CH_2 **minR**), 61.4 (CH_2 **majR**), 55.9 (CH_3 **majR**), 55.8 (CH_3 **majR**), 45.6 (CH_2 **minR**), 45.2 (CH_2 **majR**), 37.2 (CH_2 **minR**), 36.6 (CH_2 **majR**), 28.4 (CH_3 **minR**), 28.0 (CH_3 **majR**), 25.1 (CH_3 **majR**), 24.8 (CH_3 **minR**), 14.3 (CH_3 **majR**), 14.1 (CH_3 **minR**), one (C) and two (CH_3) peaks attributed to the minor rotamer were not observed.

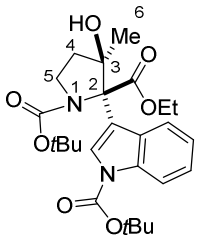
1-(*tert*-Butyl) 2-ethyl *cis*-3-hydroxy-2-(3-iodo-4-methoxyphenyl)-3-methylpyrrolidine-1,2-dicarboxylate 424



Following the **general procedure P** and using diazo compound **109** and amino ketone **371**, the *title compound* was obtained by column chromatography using the elution gradient 25 to 50% ethyl acetate in light petroleum. Colourless solid (148 mg, 98%); mp 72 - 74 °C; (Found: C, 47.57; H, 5.65; N, 2.62. $C_{20}H_{28}INO_6$ requires C, 47.54; H, 5.59; N, 2.77%); (Found: M+Na$^+$, 528.0858. $C_{20}H_{28}INNaO_6$ requires 528.0854); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3603, 3008, 2981, 1741, 1693, 1492, 1393, 1256, 1163; Two rotamers were observed in deuterated chloroform at room temperature (ratio 73:27), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 7.90 (1 H, br s, ArH **majR**; 1 H, br s, ArH **minR**), 7.66 (1 H, d, *J* 8.0, ArH **majR**), 7.56 (1 H, d, *J* 9.2, ArH **minR**), 6.74 (1 H, d, *J* 8.8, ArH **majR**; 1 H, d, *J* 8.8, ArH **minR**), 4.09 - 4.39 (2 H, m, C$\underline{H}_2$CH$_3$ **majR**; 2 H, m, C$\underline{H}_2$CH$_3$ **minR**), 3.57 - 3.95 (5 H, m, H5 and H7 **majR**; 5 H, m, H5 and H7 **minR**), 2.66 (1 H, br s, OH **minR**), 2.46 (1 H, br s, OH **majR**), 2.01 - 2.19 (1 H, m, H4 **majR**; 1 H, m, H4 **minR**), 1.80 - 1.93 (1 H, m, H4 **majR**; 1 H, m, H4 **minR**), 1.46 (9 H, s, *t*Bu **minR**), 1.22 - 1.35 (3 H, m, CH$_2$C$\underline{H}_3$ **majR**; 3 H, m, CH$_2$C$\underline{H}_3$ **minR**), 1.14 (9 H, s, *t*Bu **majR**), 1.00 (3 H, s, H6 **minR**), 0.97 (3 H, s, H6 **majR**); δ_C (100 MHz; $CDCl_3$) 170.6 (C **majR**), 157.2 (C **majR**), 154.3 (C **majR**), 154.0 (C **minR**), 138.4 (CH **minR**), 138.1 (CH **majR**), 132.9 (C **majR**), 131.5 (C **minR**), 128.8 (CH **majR**), 109.9 (CH **minR**), 109.5 (CH **majR**), 85.3 (C **minR**), 84.6 (C **majR**), 84.6 (C **majR**), 83.4 (C **minR**), 80.4 (C **majR**), 80.3 (C **minR**),

61.8 (CH_2 **minR**), 61.7 (CH_2 **majR**), 56.4 (CH_3 **majR**), 45.6 (CH_2 **minR**), 45.2 (CH_2 **majR**), 37.4 (CH_2 **minR**), 36.8 (CH_2 **majR**), 28.5 (CH_3 **minR**), 28.1 (CH_3 **majR**), 25.5 (CH_3 **majR**), 25.1 (CH_3 **minR**), 14.3 (CH_3 **majR**), 14.2 (CH_3 **minR**), three (C), one (CH) and one (CH_3) peaks attributed the minor rotamer were not observed. One (C) peak attributed to the major isomer was not observed.

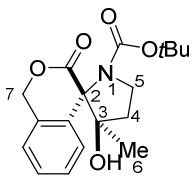
1-(*tert*-Butyl) 2-ethyl *cis*-2-(1-(*tert*-butoxycarbonyl)-*1H*-indol-3-yl)-3-hydroxy-3-methylpyrrolidine-1,2-dicarboxylate 426



Following the **general procedure P** and using diazo compound **414** and amino ketone **371**, the *title compound* was obtained by column chromatography using the elution gradient 30 to 50% ethyl acetate in light petroleum. Colourless oil (68 mg, 46%); (Found: $M+Na^+$, 511.2419. $C_{26}H_{36}N_2NaO_7$ requires 511.2415); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3605, 3007, 2982, 1729, 1710, 1370, 1258, 1242, 1158; Two rotamers were observed in deuterated chloroform at room temperature (ratio 66:34), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 8.19 (1 H, d, *J* 8.0, ArH **majR**; 1 H, d, *J* 8.0, ArH **majR**), 8.10 (1 H, br s, ArH **majR**), 8.03 (1 H, br s, ArH **minR**), 7.43 - 7.52 (1 H, m, ArH **majR**; 1 H, m, ArH **minR**), 7.08 - 7.31 (2 H, m, ArH **majR**; 2 H, m, ArH **minR**), 4.14 - 4.46 (2 H, m, $C\underline{H}_2CH_3$ **majR**; 2 H, m, $C\underline{H}_2CH_3$ **minR**), 3.72 - 4.00 (2 H, m, H5 **majR**; 2 H, m, H5 **minR**), 2.49 (1 H, br s, OH **minR**), 2.34 (1 H, br s, OH **majR**), 2.16 - 2.27 (2 H, m, H4 **majR**), 1.96 - 2.09 (2 H, m, H4 **minR**), 1.68 (9 H, s, *t*Bu **majR**), 1.65 (9 H, s, *t*Bu **minR**), 1.40 (9 H, s, *t*Bu **minR**), 1.27 - 1.45 (3 H, m, $CH_2C\underline{H}_3$ **majR**; 3 H, m,

$CH_2C\underline{H}_3$ **minR**), 1.12 (3 H, s, H6 **majR**; 3 H, s, H6 **minR**), 0.94 (9 H, s, *t*Bu **majR**); δ_C (100 MHz; $CDCl_3$) 171.1 (C **majR**), 154.4 (C **majR**), 153.8 (C **minR**), 149.9 (C **majR**), 135.3 (C **majR**), 129.6 (C **majR**), 125.3 (CH **minR**), 124.9 (CH **majR**), 124.1 (CH **majR**), 124.0 (CH **minR**), 122.9 (CH **majR**), 122.4 (CH **minR**), 120.7 (CH **majR**), 118.6 (C **majR**), 117.7 (C **minR**), 115.4 (CH **minR**), 115.2 (CH **majR**), 84.7 (C **majR**), 83.9 (C **majR**), 83.7 (C **minR**), 80.1 (C **minR**), 75.4 (C **majR**), 75.3 (C **minR**), 61.8 (CH_2 **minR**), 61.6 (CH_2 **majR**), 45.8 (CH_2 **minR**), 45.2 (CH_2 **majR**), 38.4 (CH_2 **minR**), 37.7 (CH_2 **majR**), 28.5 (CH_3 **minR**), 28.3 (CH_3 **majR**), 27.8 (CH_3 **majR**), 25.9 (CH_3 **majR**), 25.5 (CH_3 **minR**), 14.4 (CH_3 **majR**), 14.2 (CH_3 **minR**), four (C), one (CH) and one (CH_3) peaks attributed to the minor rotamer were not observed.

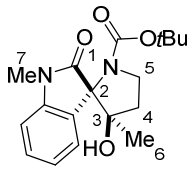
tert-Butyl *cis*-3'-hydroxy-3'-methyl-3-oxospiro[isochromane-4,2'-pyrrolidine]-1'-carboxylate 427



Following the **general procedure P** and using diazo compound **413** and amino ketone **371**, the *title compound* was obtained by column chromatography using the elution gradient 30 to 50% ethyl acetate in light petroleum. Yellow solid (45 mg, 45%); mp 178 - 179 °C; (Found: M+Na^+, 356.1474. $C_{18}H_{23}NNaO_5$ requires 356.1474); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3606, 3005, 1739, 1697, 1602, 1382, 1243, 1177; Two rotamers were observed in deuterated chloroform at room temperature (ratio 75:25), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 7.08 - 7.42 (4 H, m, ArH **majR**; 4 H, m, ArH **minR**), 5.75 (1 H, d, *J* 14.1, H7 **majR**), 5.74 (1 H, d, *J* 14.1, H7 **minR**), 5.18 (1 H, d,

J 14.1, H7 **minR**), 5.13 (1 H, d, *J* 14.1, H7 **majR**), 3.93 - 4.09 (1 H, m, H5 **majR**; 1 H, m, H5 **minR**), 3.54 (1 H, td, *J* 10.4, 6.8, H5 **majR**; 1 H, td, *J* 10.4, 6.8, H5 **minR**), 2.89 (1 H, br s, OH **majR**), 2.83 (1 H, br s, OH **minR**), 2.41 - 2.59 (1 H, m, H4 **majR**; 1 H, m, H4 **minR**), 1.95 - 2.03 (1 H, m, H4 **majR**; 1 H, m, H4 **minR**), 1.40 (9 H, s, *t*Bu **minR**), 1.01 (9 H, s, *t*Bu **majR**), 0.99 (3 H, s, H6 **majR**), 0.95 (3 H, s, H6 **minR**); δ_C (100 MHz; $CDCl_3$) 172.4 (C **majR**), 154.0 (C **minR**), 153.9 (C **majR**), 135.1 (C **majR**), 133.7 (C **minR**), 130.5 (C **minR**), 130.4 (C **majR**), 127.8 (CH **minR**), 127.7 (CH **majR**), 127.6 (CH **minR**), 127.5 (CH **majR**), 126.2 (CH **majR**), 125.6 (CH **minR**), 124.5 (CH **minR**), 124.2 (CH **majR**), 85.3 (C **majR**), 84.5 (C **minR**), 80.58 (C **majR**), 73.3 (C **majR**), 70.3 (CH_2 **minR**), 70.2 (CH_2 **majR**), 45.9 (CH_2 **minR**), 45.4 (CH_2 **majR**), 38.4 (CH_2 **minR**), 38.0 (CH_2 **majR**), 28.5 (CH_3 **minR**), 27.7 (CH_3 **majR**), 25.6 (CH_3 **majR**), 25.3 (CH_3 **minR**), three (C) peaks attributed to the minor rotamer were not observed.

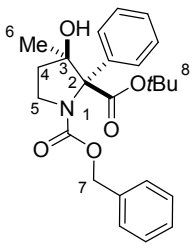
tert-Butyl _cis_-3'-hydroxy-1,3'-dimethyl-2-oxospiro[indoline-3,2'-pyrrolidine]-1'-carboxylate 428



Following the **general procedure P** and using diazo compound **118** and amino ketone **371**, the *title compound* was obtained by column chromatography using the elution gradient 30 to 50% ethyl acetate in light petroleum. Pale yellow solid (82 mg, 82%); mp 99 - 100 °C; (Found: M+Na^+, 355.1625. $C_{18}H_{24}N_2NaO_4$ requires 355.1628); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3010, 2979, 1700, 1614, 1393, 1368, 1131; Two rotamers were observed in deuterated chloroform at room temperature (ratio 80:20), the signals observed are reported for the major rotamer (**majR**) and minor rotamer

(**minR**); δ_H (400 MHz; $CDCl_3$) 7.23 - 7.35 (1 H, m, ArH **majR**; 1 H, m, ArH **minR**), 6.99 - 7.13 (2 H, m, ArH **majR**; 2 H, m, ArH **minR**), 6.80 - 6.92 (1 H, m, ArH **majR**; 1 H, m, ArH **minR**), 4.98 (1 H, s, OH **minR**), 4.72 (1 H, s, OH **majR**), 3.74 - 3.87 (2 H, m, H5 **majR**; 1 H, m, H5 **minR**), 3.67 - 3.75 (1 H, m, H5 **minR**), 3.28 (3 H, s, H7 **minR**), 3.22 (3 H, s, H7 **majR**), 2.09 - 2.23 (2 H, m, H4 **majR**; 2 H, m, H4 **minR**), 1.32 (9 H, s, *t*Bu **minR**), 1.01 (9 H, s, *t*Bu **majR**), 0.87 (3 H, s, H6 **majR**), 0.83 (3 H, s, H6 **minR**); δ_C (100 MHz; $CDCl_3$) 176.2 (C **majR**), 175.7 (C **minR**), 153.3 (C **majR**), 153.1 (C **minR**), 143.4 (C **minR**), 143.2 (C **majR**), 130.1 (C **majR**), 129.4 (C **minR**), 129.2 (CH **majR**), 129.1 (CH **minR**), 123.2 (CH **majR**), 123.1 (CH **minR**), 123.0 (CH **majR**), 122.8 (CH **minR**), 108.8 (CH **minR**), 108.3 (CH **majR**), 82.3 (C **majR**), 81.2 (C **minR**), 80.22 (C **minR**), 80.19 (C **majR**), 72.3 (C **majR**), 71.9 (C **minR**), 45.7 (CH_2 **minR**), 45.3 (CH_2 **majR**), 37.8 (CH_2 **minR**), 37.0 (CH_2 **majR**), 28.4 (CH_3 **minR**), 27.8 (CH_3 **majR**), 26.8 (CH_3 **minR**), 26.6 (CH_3 **majR**), 22.6 (CH_3 **majR**), 22.2 (CH_3 **minR**).

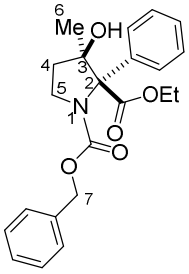
1-Benzyl 2-(*tert*-butyl) *cis*-3-hydroxy-3-methyl-2-phenylpyrrolidine-1,2-dicarboxylate 425



Following the **general procedure P** and using diazo compound **114** and amino ketone **370**, the *title compound* was obtained by column chromatography using the elution gradient 20 to 40% ethyl acetate in light petroleum. Colourless solid (42.5 mg, 34%); mp 135 - 136 °C; (Found: M+Na$^+$, 434.1951. $C_{24}H_{29}NNaO_5$ requires 434.1938); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3603, 3009, 1740. 1698, 1411, 1350, 1151; Two rotamers were observed in deuterated chloroform at room temperature (ratio 68:32),

the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 7.50 - 7.67 (2 H, m, ArH **majR**; 2 H, m, ArH **minR**), 7.21 - 7.46 (5 H, m, ArH **majR**; 4 H, m, ArH **minR**), 7.03 - 7.17 (2 H, m, ArH **majR**; 2 H, m, ArH **minR**), 6.64 - 6.73 (1 H, m, ArH **majR**; 2 H, m, ArH **minR**), 5.18 (1 H, d, *J* 12.5, H7 **minR**), 5.11 (1 H, d, *J* 12.5, H7 **minR**), 5.05 (1 H, d, *J* 12.7, H7 **majR**), 4.81 (1 H, d, *J* 12.7, H7 **majR**), 3.64 - 4.02 (2 H, m, H5 **majR**; 2 H, m, H5 **minR**), 2.88 (1 H, s, OH **minR**), 2.61 (1 H, s, OH **majR**), 1.81 - 2.17 (2 H, m, H4 **majR**; 2 H, m, H4 **minR**), 1.44 (9 H, s, H8 **minR**), 1.36 (9 H, s, H8 **majR**), 0.98 (3 H, s, H6 **majR**; 3 H, s, H6 **minR**); δ_C (100 MHz; $CDCl_3$) 169.2 (C **majR**), 169.0 (C **minR**), 155.4 (C **majR**), 154.6 (C **minR**), 138.6 (C **majR**), 137.2 (C **minR**), 137.1 (C **minR**), 136.0 (C **majR**), 128.5 (CH **minR**), 128.3 (CH **minR**), 128.1 (CH **majR**), 127.8 (CH **majR**), 127.6 (CH **minR**), 127.5 (CH **majR**), 127.39 (CH **minR**), 127.36 (CH **minR**), 127.29 (CH **majR**), 127.26 (CH **majR**), 127.1 (CH **majR**), 84.7 (C **majR**), 83.4 (C **minR**), 82.9 (C **minR**), 82.7 (C **majR**), 78.4 (C **majR**), 78.2 (C **minR**), 67.0 (CH_2 **minR**), 66.9 (CH_2 **majR**), 45.9 (CH_2 **majR**), 45.6 (CH_2 **minR**), 37.4 (CH_2 **minR**), 36.6 (CH_2 **majR**), 28.0 (CH_3 **minR**), 27.9 (CH_3 **majR**), 25.5 (CH_3 **majR**), 25.2 (CH_3 **minR**), one (CH) peak attributed to the minor rotamer was not observed.

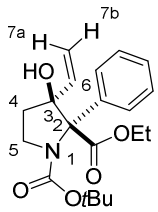
1-Benzyl 2-ethyl *cis*-3-hydroxy-3-methyl-2-phenylpyrrolidine-1,2-dicarboxylate 373



Following the **general procedure P** and using diazo compound **104** and amino ketone **370**, the *title compound* was obtained by column chromatography

using the elution gradient 20 to 40% ethyl acetate in light petroleum. Colourless oil (110 mg, 96%); (Found: M+Na$^+$, 406.1626. $C_{22}H_{25}NNaO_5$ requires 406.1625); ν_{max} ($CHCl_3$)/cm^{-1} 3009, 2985, 1742, 1699, 1410, 1350, 1258, 1160, 1134, 1029; Two rotamers were observed in deuterated chloroform at room temperature (ratio 68:32), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 7.52 - 7.69 (2 H, m, ArH **majR**; 2 H, m, ArH **minR**), 7.22 - 7.45 (5 H, m, ArH **majR**; 4 H, m, ArH **minR**), 7.05 - 7.21 (2 H, m, ArH **majR**; 2 H, m, ArH **minR**), 6.72 - 6.80 (1 H, m, ArH **majR**; 2 H, m, ArH **minR**), 5.19 (1 H, d, *J* 12.4, H7 **minR**), 5.10 (1 H, d, *J* 12.4, H7 **minR**), 4.95 (1 H, d, *J* 12.8, H7 **majR**), 4.89 (1 H, d, *J* 12.8, H7 **majR**), 3.73 - 4.36 (4 H, m, C$\underline{H}_2$CH$_3$ and H5 **majR**; 4 H, m, C$\underline{H}_2$CH$_3$ and H5 **minR**), 2.92 (1 H, s, OH **minR**), 2.74 (1 H, s, OH **majR**), 1.82 - 2.14 (2 H, m, H4 **majR**; 2 H, m, H4 **minR**), 1.21 (3 H, t, *J* 7.1, CH$_2$C$\underline{H}_3$ **minR**), 1.10 (3 H, t, *J* 7.1, CH$_2$C$\underline{H}_3$ **majR**), 1.00 (3 H, s, H6 **majR**; 3 H, s, H6 **minR**); δ_C (100 MHz; $CDCl_3$) 170.2 (C **majR**), 170.1 (C **minR**), 155.3 (C **majR**), 154.6 (C **minR**), 138.5 (C **majR**), 137.1 (C **minR**), 137.0 (C **minR**), 136.1 (C **majR**), 128.5 (CH **minR**), 128.1 (CH **majR**), 128.0 (CH **minR**), 127.84 (CH **majR**), 127.75 (CH **minR**), 127.5 (CH **majR**), 127.43 (CH **minR**), 127.38 (CH **majR**), 127.3 (CH **majR**), 127.1 (CH **minR**), 126.9 (CH **majR**), 84.8 (C **majR**), 83.5 (C **minR**), 78.4 (C **majR**), 67.0 (CH$_2$ **minR**), 66.8 (CH$_2$ **majR**), 61.8 (CH$_2$ **minR**), 61.5 (CH$_2$ **majR**), 46.0 (CH$_2$ **majR**), 45.6 (CH$_2$ **minR**), 37.2 (CH$_2$ **minR**), 36.4 (CH$_2$ **majR**), 25.1 (CH$_3$ **majR**), 24.9 (CH$_3$ **minR**), 14.0 (CH$_3$ **majR**), one (C), one (CH) and one (CH$_3$) peaks attributed to the minor rotamer were not observed.

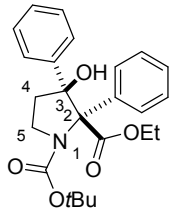
1-(*tert*-Butyl) 2-ethyl *cis*-3-hydroxy-2-phenyl-3-vinylpyrrolidine-1,2-dicarboxylate 444



Following the **general procedure P** and using diazo compound **104** and amino ketone **433**, the *title compound* was obtained by column chromatography using the elution gradient 20 to 50% ethyl acetate in light petroleum. Colourless solid (65 mg, 60%); mp 96 - 97 °C; (Found: M+Na$^+$, 384.1786. $C_{20}H_{27}NNaO_5$ requires 384.1781); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3605, 3011, 2982, 1743, 1692, 1391, 1367, 1239, 1162; Two rotamers were observed in deuterated chloroform at room temperature (ratio 73:27), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 7.53 (2 H, d, *J* 7.0, ArH **majR**), 7.46 (2 H, d, *J* 7.4, ArH **minR**), 7.21 - 7.31 (3 H, m, ArH **majR**; 3 H, m, ArH **minR**), 5.43 - 5.57 (1 H, m, H6 **minR**), 5.46 (1 H, dd, *J* 17.0, 10.7, H6 **majR**), 5.26 (1 H, d, *J* 17.2, H7a **minR**), 5.18 (1 H, d, *J* 17.0, H7a **majR**), 5.03 (1 H, d, *J* 10.7, H7b **minR**), 4.97 (1 H, d, *J* 10.7, H7b **majR**), 4.11 - 4.43 (2 H, m, C$\underline{H}_2$CH$_3$ **majR**; 2 H, m, C$\underline{H}_2$CH$_3$ **minR**), 3.90 (2 H, dd, *J* 8.5, 5.3, H5 **majR**; 1 H, m, H5 **minR**), 3.68 - 3.81 (1 H, m, H5 **minR**), 3.50 (1 H, s, OH **minR**), 2.83 (1 H, s, OH **majR**), 1.91 - 2.17 (2 H, m, H4 **majR**; 2 H, m, H4 **minR**), 1.47 (9 H, s, *t*Bu **minR**), 1.34 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$ **majR**), 1.29 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$ **minR**), 1.12 (9 H, s, *t*Bu **majR**); δ_C (100 MHz; $CDCl_3$) 170.2 (C **majR**), 154.3 (C **majR**), 138.3 (CH **majR**), 138.1 (C **majR**), 128.1 (CH **minR**), 127.7 (CH **majR**), 127.43 (CH **minR**), 127.39 (CH **majR**), 127.3 (CH **majR**), 115.0 (CH$_2$ **minR**), 114.6 (CH$_2$ **majR**), 86.0 (C **majR**), 84.6 (C **minR**), 80.3 (C **majR**), 80.2 (C **minR**), 78.4 (C **majR**), 77.8 (C **minR**),

62.1 (CH_2 **minR**), 61.7 (CH_2 **majR**), 45.8 (CH_2 **minR**), 45.5 (CH_2 **majR**), 36.1 (CH_2 **minR**), 35.4 (CH_2 **majR**), 28.5 (CH_3 **minR**), 28.0 (CH_3 **majR**), 14.3 (CH_3 **majR**), 14.2 (CH_3 **minR**), three (C) and two (CH) peaks attributed to the minor rotamer were not observed.

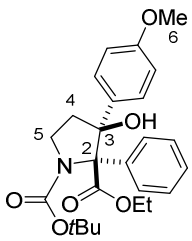
1-(*tert*-Butyl) 2-ethyl *cis*-3-hydroxy-2,3-diphenylpyrrolidine-1,2-dicarboxylate 445



Following the **general procedure P** and using diazo compound **104** and amino ketone **434**, the *title compound* was obtained by column chromatography using the elution gradient 15 to 30% ethyl acetate in light petroleum. Colourless solid (100 mg, 81%); mp 142 - 143 °C; (Found: M+Na^+, 434.1942. $C_{24}H_{29}NNaO_5$ requires 434.1943); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3604, 3008, 2982, 1746, 1693, 1392, 1368, 1255, 1173, 1145; Two rotamers were observed in deuterated chloroform at room temperature (ratio 65:35), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 6.87 - 7.28 (10 H, m, ArH **majR**; 8 H, m, ArH **minR**), 6.73 (2 H, d, *J* 7.8, ArH **minR**), 5.12 (1 H, s, OH **minR**), 4.16 - 4.56 (2 H, m, C$\underline{H}_2$$CH_3$ **majR**; 2 H, m, C$\underline{H}_2$$CH_3$ **minR**), 3.80 - 4.13 (3 H, m, OH and H5 **majR**; 2 H, m, H5 **minR**), 2.37 - 2.71 (1 H, m, H4 **majR**; 1 H, m, H4 **minR**), 1.94 (1 H, dd, *J* 12.6, 6.1, H4 **majR**; 1 H, dd, *J* 12.6, 6.1, H4 **minR**), 1.51 (9 H, s, *t*Bu **minR**), 1.37 (3 H, t, *J* 7.2, CH_2C$\underline{H}_3$ **majR**), 1.30 (3 H, t, *J* 7.2, CH_2C$\underline{H}_3$ **minR**), 1.16 (9 H, s, *t*Bu **majR**); δ_C (100 MHz; $CDCl_3$) 170.8 (C **minR**), 170.4 (C **majR**), 154.2 (C **majR**), 154.0 (C **minR**), 139.6 (C **minR**), 139.2 (C **majR**), 137.2 (C **majR**), 135.5 (C **minR**), 128.7 (CH **minR**), 128.3 (CH **majR**), 128.15 (CH **minR**), 128.09 (CH **majR**), 127.7

(CH **minR**), 127.5 (CH **majR**), 127.3 (CH **minR**), 127.2 (CH **minR**), 127.1 (CH **majR**), 127.0 (CH **majR**), 126.7 (CH **minR**), 126.6 (CH **majR**), 87.8 (C **majR**), 86.3 (C **minR**), 80.6 (C **majR**), 80.5 (C **minR**), 78.6 (C **majR**), 77.7 (C **minR**), 62.6 (CH_2 **minR**), 62.1 (CH_2 **majR**), 45.4 (CH_2 **minR**), 45.1 (CH_2 **majR**), 34.4 (CH_2 **minR**), 34.1 (CH_2 **majR**), 28.6 (CH_3 **minR**), 28.1 (CH_3 **majR**), 14.3 (CH_3 **majR**), 14.1 (CH_3 **minR**).

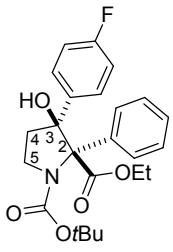
1-(*tert*-Butyl) 2-ethyl *cis*-3-hydroxy-3-(4-methoxyphenyl)-2-phenylpyrrolidine-1,2-dicarboxylate 446



Following the **general procedure P** and using diazo compound **104** and amino ketone **435**, the *title compound* was obtained by column chromatography using the elution gradient 30 to 40% ethyl acetate in light petroleum. Colourless oil (50 mg, 38%); (Found: M+Na^+, 464.2055. $C_{25}H_{31}NNaO_6$ requires 464.2049); ν_{max} ($CHCl_3$)/cm^{-1} 3006, 2981, 1745, 1693, 1393, 1368, 1242, 1145; Two rotamers were observed in deuterated chloroform at room temperature (ratio 67:33), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 7.06 - 7.14 (1 H, m, ArH **majR**; 1 H, m, ArH **minR**), 7.02 (2 H, t, *J* 7.6, ArH **majR**; 2 H, t, *J* 7.6, ArH **minR**), 6.89 - 6.96 (1 H, m, ArH **majR**; 2 H, m, ArH **minR**), 6.87 (2 H, d, *J* 8.8, ArH **majR**; 2 H, d, *J* 8.8, ArH **minR**), 6.76 (1 H, d, *J* 7.8, ArH **majR**), 6.61 - 6.71 (2 H, m, ArH **majR**; 2 H, m, ArH **minR**), 4.99 (1 H, s, OH **minR**), 4.30 (2 H, q, *J* 7.2, C<u>H</u>$_2$$CH_3$ **majR**), 4.14 - 4.52 (2 H, m, C<u>H</u>$_2$$CH_3$ **minR**), 3.81 - 4.09 (3 H, m, OH and H5 **majR**; 2 H, m, H5 **minR**), 3.77 (3 H, s, H6 **minR**), 3.76 (3 H, s, H6 **majR**), 2.33 - 2.58 (1 H, m, H4 **majR**; 1 H, m, H4 **minR**), 1.90 (1 H, dd, *J*

12.6, 6.0, H4 **majR**; 1 H, dd, *J* 12.6, 6.0, H4 **minR**), 1.50 (9 H, s, *t*Bu **minR**), 1.36 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$ **majR**), 1.30 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$ **minR**), 1.16 (9 H, s, *t*Bu **majR**); δ_C (100 MHz; $CDCl_3$) 170.7 (C **minR**), 170.4 (C **majR**), 159.45 (C **minR**), 159.38 (C **majR**), 154.3 (C **majR**), 154.0 (C **minR**), 137.3 (C **majR**), 135.7 (C **minR**), 131.7 (C **minR**), 131.4 (C **majR**), 128.7 (CH **minR**), 128.4 (CH **minR**), 128.34 (CH **majR**), 128.28 (CH **majR**), 127.3 (CH **minR**), 127.1 (CH **majR**), 126.7 (CH **minR**), 126.6 (CH **majR**), 112.9 (CH **minR**), 112.8 (CH **majR**), 87.6 (C **majR**), 86.1 (C **minR**), 80.5 (C **majR**), 80.4 (C **minR**), 78.6 (C **majR**), 77.8 (C **minR**), 62.5 (CH_2 **minR**), 62.1 (CH_2 **majR**), 55.3 (CH_3 **majR**), 45.4 (CH_2 **minR**), 45.0 (CH_2 **majR**), 34.6 (CH_2 **minR**), 34.3 (CH_2 **majR**), 28.6 (CH_3 **minR**), 28.1 (CH_3 **majR**), 14.3 (CH_3 **majR**), 14.1 (CH_3 **minR**), one (CH_3) peak attributed to the minor rotamer was not observed.

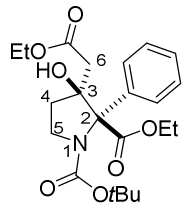
1-(*tert*-Butyl) 2-ethyl *cis*-3-(4-fluorophenyl)-3-hydroxy-2-phenylpyrrolidine-1,2-dicarboxylate 447



Following the **general procedure P** and using diazo compound **104** and amino ketone **436**, the *title compound* was obtained by column chromatography using the elution gradient 30 to 40% ethyl acetate in light petroleum. Colourless solid (89 mg, 69%); mp 95 - 96 °C; (Found: $M+Na^+$, 452.1847. $C_{24}H_{28}FNNaO_5$ requires 452.1844); ν_{max} ($CHCl_3$)/cm^{-1} 3007, 1746, 1692, 1393, 1239, 1145, 1120; Two rotamers were observed in deuterated chloroform at room temperature (ratio 66:34), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 6.70 - 7.15 (9 H, m, ArH **majR**; 9 H, m, ArH

minR), 4.99 (1 H, s, OH **minR**), 4.30 (2 H, q, *J* 7.2, C<u>H</u>$_2$CH$_3$ **majR**), 4.15 - 4.54 (2 H, m, C<u>H</u>$_2$CH$_3$ **minR**), 3.79 - 4.14 (3 H, m, H5 and OH **majR**; 2 H, m, H5 **minR**), 2.33 - 2.60 (1 H, m, H4 **majR**; 1 H, m, H4 **minR**), 1.90 (1 H, dd, *J* 12.7, 6.0, H4 **majR**; 1 H, dd, *J* 12.7, 6.0, H4 **minR**), 1.49 (9 H, s, *t*Bu **majR**), 1.36 (2 H, t, *J* 7.2, CH$_2$C<u>H</u>$_3$ **majR**), 1.29 (2 H, t, *J* 7.1, CH$_2$C<u>H</u>$_3$ **minR**), 1.13 (9 H, s, *t*Bu **majR**); δ_F (376 MHz; $CDCl_3$); −114.34 (m, **minR**), −114.37 (m, **majR**); δ_C (100 MHz; $CDCl_3$) 170.5 (C **minR**), 170.2 (C **majR**), 162.7 (C, J_{CF} 247, **minR**), 162.5 (d, J_{CF} 247, C **majR**), 154.2 (C **majR**), 153.9 (C **minR**), 137.3 (C **majR**), 135.5 (C **minR**), 135.4 (d, J_{CF} 3, C **minR**), 135.1 (d, J_{CF} 3, C **majR**), 129.0 (d, J_{CF} 7, CH **minR**), 128.9 (d, J_{CF} 8, CH **majR**), 128.6 (CH **minR**), 128.1 (CH **majR**), 127.4 (CH **minR**), 127.2 (CH **majR**), 126.82 (CH **minR**), 126.77 (CH **majR**), 114.4 (d, J_{CF} 21, CH **minR**), 114.2 (d, J_{CF} 21, CH **majR**), 87.4 (C **majR**), 85.9 (C **minR**), 80.6 (C **majR**), 80.6 (C **minR**), 78.6 (C **majR**), 77.8 (C **minR**), 62.6 (CH_2 **minR**), 62.1 (CH_2 **majR**), 45.3 (CH_2 **minR**), 45.0 (CH_2 **majR**), 34.7 (CH_2 **minR**), 34.4 (CH_2 **majR**), 28.5 (CH_3 **minR**), 28.0 (CH_3 **majR**), 14.3 (CH_3 **majR**), 14.1 (CH_3 **minR**).

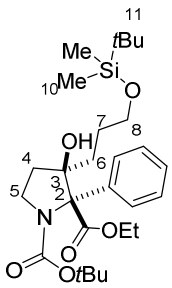
1-(*tert*-Butyl) 2-ethyl *cis*-3-(2-ethoxy-2-oxoethyl)-3-hydroxy-2-phenylpyrrolidine-1,2-dicarboxylate 448



Following the **general procedure P** and using diazo compound **104** and amino ketone **437**, the *title compound* was obtained by column chromatography using the elution gradient 20 to 40% ethyl acetate in light petroleum. Colourless oil (107 mg, 85%); (Found: M+Na$^+$, 444.1993. $C_{22}H_{31}NNaO_7$ requires 444.1993); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3476, 3010,

2982, 1708, 1393, 1368, 1239, 1160; Two rotamers were observed in deuterated chloroform at room temperature (ratio 76:24), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 7.52 - 7.77 (2 H, m, ArH **majR**; 1 H, m, ArH **minR**), 7.19 - 7.31 (3 H, m, ArH **majR**; 4 H, m, ArH **minR**), 4.46 (1 H, s, OH **minR**), 4.42 (1 H, s, OH **majR**), 4.12 - 4.35 (2 H, m, $C\underline{H}_2CH_3$ **majR**; 2 H, m, $C\underline{H}_2CH_3$ **minR**), 3.98 - 4.07 (2 H, m, $C\underline{H}_2CH_3$ **majR**; 2 H, m, $C\underline{H}_2CH_3$ **minR**), 3.75 - 3.95 (2 H, m, H5 **majR**; 1 H, m, H5 **minR**), 3.70 (1 H, ddd, *J* 10.8, 7.8, 4.5, H5 **minR**), 2.47 (1 H, d, *J* 16.7, H6 **minR**), 2.45 (1 H, d, *J* 16.2, H6 **majR**), 2.20 - 2.29 (1 H, m, H4 **majR**; 1 H, m, H4 **minR**), 1.84 - 2.02 (1 H, m, H4 **majR**; 2 H, m, H4 and H6 **minR**), 1.85 (1 H, d, *J* 16.2, H6 **majR**), 1.42 (9 H, s, *t*Bu **minR**), 1.30 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$ **majR**), 1.26 (3 H, t, *J* 7.2, $CH_2C\underline{H}_3$ **minR**), 1.12 - 1.18 (3 H, m, $CH_2C\underline{H}_3$ **majR**; 3 H, m, $CH_2C\underline{H}_3$ **minR**), 1.05 (9 H, s, *t*Bu **majR**); δ_C (100 MHz; $CDCl_3$) 172.6 (C **majR**), 169.9 (C **majR**), 169.7 (C **minR**), 154.1 (C **majR**), 153.8 (C **minR**), 138.3 (C **majR**), 136.9 (C **minR**), 127.9 (CH **minR**), 127.7 (CH **majR**), 127.51 (CH **minR**), 127.45 (CH **minR**), 127.40 (CH **majR**), 127.3 (CH **majR**), 84.3 (C **majR**), 83.1 (C **minR**), 80.0 (C **majR**), 79.9 (C **minR**), 77.7 (C **majR**), 77.4 (C **minR**), 61.5 (CH_2 **minR**), 61.4 (CH_2 **majR**), 61.14 (CH_2 **majR**), 61.08 (CH_2 **minR**), 45.8 (CH_2 **minR**), 45.4 (CH_2 **majR**), 40.9 (CH_2 **majR**), 40.7 (CH_2 **minR**), 35.4 (CH_2 **minR**), 35.0 (CH_2 **majR**), 28.4 (CH_3 **minR**), 27.9 (CH_3 **majR**), 14.3 (CH_3 **majR**), 14.1 (CH_3 **minR**), 14.0 (CH_3 **majR**), one (C) and one (CH_3) peaks attributed to the minor rotamer were not observed.

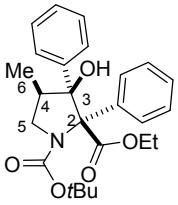
1-(*tert*-Butyl) 2-ethyl *cis*-3-(3-((*tert*-butyldimethylsilyl)oxy)-propyl)-3-hydroxy-2-phenylpyrrolidine-1,2-dicarboxylate 449



Following the **general procedure P** and using diazo compound **104** and amino ketone **438**, the *title compound* was obtained by column chromatography using the elution gradient 20 to 30% ethyl acetate in light petroleum. Colourless solid (121 mg, 79%); mp 98 - 99 °C; (Found: M+Na$^+$, 530.2915. $C_{27}H_{45}NNaO_6Si$ requires 530.2908); ν_{max} ($CHCl_3$)/cm^{-1} 3340, 3004, 2980, 2957, 2931, 1744, 1687, 1392, 1257, 1172, 839; Two rotamers were observed in deuterated chloroform at room temperature (ratio 77:23), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 7.47 - 7.75 (2 H, m, ArH **majR**; 2 H, m, ArH **minR**), 7.12 - 7.30 (3 H, m, ArH **majR**; 3 H, m, ArH **minR**), 4.06 - 4.38 (2 H, m, C$\underline{H}_2$CH$_3$ **majR**; 2 H, m, C$\underline{H}_2$CH$_3$ **minR**), 3.64 - 3.92 (3 H, m, H5 and OH **majR**; 3 H, m, H5 and OH **minR**), 3.36 - 3.59 (2 H, m, H8 **majR**; 2 H, m, H8 **minR**), 1.78 - 2.16 (2 H, m, H4 **majR**; 2 H, m, H4 **minR**), 1.43 (9 H, s, H9 **minR**), 1.38 - 1.65 (3 H, m, H7 and H6 **majR**; 1 H, m, H7 **minR**), 1.23 - 1.33 (3 H, m, CH$_2$C$\underline{H}_3$ **majR**; 3 H, m, CH$_2$C$\underline{H}_3$ **minR**), 0.95 - 1.40 (1 H, m, H7 **majR**; 3 H, m, H6 and H7 **minR**), 1.05 (9 H, s, H9 **majR**), 0.82 (9 H, s, H11 **majR**; 9 H, s, H11 **minR**), −0.03 - 0.01 (6 H, overlapping s, H10 **majR**; 6 H, overlapping s, H10 **minR**); δ_C (100 MHz; $CDCl_3$) 170.6 (C **majR**), 170.4 (C **minR**), 154.3 (C **majR**), 153.9 (C **minR**), 139.5 (C **majR**), 137.9 (C **minR**), 127.6 (CH **minR**), 127.5 (CH **majR**), 127.4 (CH **minR**), 127.15 (CH **majR**), 127.09 (CH **minR**), 126.9 (CH **majR**), 86.5 (C **majR**), 85.2 (C **minR**), 79.7 (C **majR**), 79.6 (C **minR**), 79.0

(C **majR**), 78.6 (C **minR**), 63.5 (CH_2 **majR**), 61.3 (CH_2 **minR**), 61.1 (CH_2 **majR**), 45.8 (CH_2 **minR**), 45.4 (CH_2 **majR**), 34.5 (CH_2 **minR**), 34.3 (CH_2 **majR**), 34.0 (CH_2 **majR**), 33.8 (CH_2 **minR**), 28.5 (CH_3 **minR**), 27.9 (CH_3 **majR**), 26.7 (CH_2 **majR**), 26.0 (CH_3 **majR**), 18.3 (C **majR**), 14.3 (CH_3 **majR**), 14.2 (CH_3 **minR**), −5.40 (CH_3 **minR**), −5.43 (CH_3 **majR**), −5.5 (CH_3 **majR**), one (C), two (CH_2) and two (CH_3) peaks attributed to the minor rotamer were not observed.

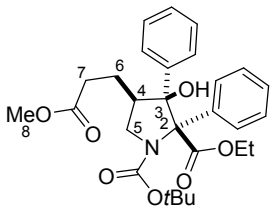
1-(*tert*-Butyl) 2-ethyl *cis,cis*-3-hydroxy-4-methyl-2,3-diphenyl-pyrrolidine-1,2-dicarboxylate 450



Following the **general procedure P** and using diazo compound **104** and amino ketone **440**, the *title compound* was obtained by column chromatography using the elution gradient 25 to 40% ethyl acetate in light petroleum. Colourless oil (126 mg, 99%); (Found: M+Na^+, 448.2099. $C_{25}H_{31}NNaO_5$ requires 448.2094); ν_{max} ($CHCl_3$)/cm^{-1} 3010, 2981, 1746, 1692, 1393, 1240, 1174, 1147; Two rotamers were observed in deuterated chloroform at room temperature (ratio 63:37), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 6.80 - 7.25 (10 H, m, ArH **majR**; 8 H, m, ArH **minR**), 6.72 (2 H, d, *J* 7.7, ArH **minR**), 4.65 (1 H, s, OH **minR**), 4.16 - 4.51 (2 H, m, C$\underline{H}_2$$CH_3$ **majR**; 2 H, m, C$\underline{H}_2$$CH_3$ **minR**), 4.11 (1 H, dd, *J* 10.5, 8.0, H5 **majR**), 3.94 (1 H, dd, *J* 10.0, 8.0, H5 **minR**), 3.65 (1 H, s, OH **majR**), 3.59 (1 H, dd, *J* 10.0, 6.3, H5 **minR**), 3.56 (1 H, dd, *J* 10.5, 6.8, H5 **majR**), 2.56 - 2.85 (1 H, m, H4 **majR**; 1 H, m, H4 **minR**), 1.51 (9 H, s, *t*Bu **minR**), 1.37 (3 H, t, *J* 7.2, CH_2C$\underline{H}_3$ **majR**), 1.30 (3 H, t, *J* 7.1, CH_2C$\underline{H}_3$ **minR**), 1.15 (9 H, s,

*t*Bu **majR**), 0.90 (3 H, d, *J* 6.7, H6 **minR**), 0.89 (3 H, d, *J* 6.7, H6 **majR**); δ_C (100 MHz; $CDCl_3$) 170.5 (C **minR**), 170.2 (C **majR**), 154.0 (C **majR**), 153.7 (C **minR**), 137.9 (C **minR**), 137.5 (C **majR**), 136.9 (C **majR**), 135.3 (C **minR**), 128.8 (CH **minR**), 128.4 (CH **minR**), 127.95 (CH **minR**), 127.92 (CH **minR**), 127.8 (CH **majR**), 127.6 (CH **majR**), 127.5 (CH **majR**), 127.2 (CH **minR**), 127.0 (CH **majR**), 126.5 (CH **majR**), 126.4 (CH **majR**), 88.5 (C **majR**), 87.0 (C **minR**), 80.4 (C **majR**), 80.3 (C **minR**), 79.6 (C **majR**), 78.9 (C **minR**), 62.4 (CH_2 **minR**), 62.0 (CH_2 **majR**), 51.7 (CH_2 **minR**), 51.3 (CH_2 **majR**), 36.9 (CH **minR**), 36.2 (CH **majR**), 28.5 (CH_3 **minR**), 28.0 (CH_3 **majR**), 14.3 (CH_3 **majR**), 14.1 (CH_3 **minR**), 9.5 (CH_3 **minR**), 9.4 (CH_3 **majR**), one (CH) peak attributed to the minor rotamer was not observed.

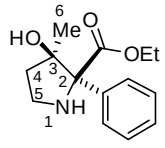
1-(*tert*-Butyl) 2-ethyl *cis,cis*-3-hydroxy-4-(3-methoxy-3-oxo-propyl)-2,3-diphenylpyrrolidine-1,2-dicarboxylate 451



Following the **general procedure P** and using diazo compound **104** and amino ketone **439**, the *title compound* was obtained by column chromatography using the elution gradient 25 to 40% ethyl acetate in light petroleum. Colourless solid (160 mg, 94%); mp 115 - 116 °C; (Found: M+Na^+, 520.2317. $C_{28}H_{35}NNaO_7$ requires 520.2306); ν_{max} ($CHCl_3$)/cm^{-1} 3411, 3007, 2981, 1732, 1693, 1602, 1393, 1368, 1256, 1172, 1148, 909; Two rotamers were observed in deuterated chloroform at room temperature (ratio 65:35), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 6.76 - 7.24 (10 H, m, **majR**; 8 H, m, ArH **minR**), 6.71 (2 H, d, *J* 7.7, ArH **minR**), 4.82 (1 H, s, OH **minR**), 4.30 (2 H, q, *J* 7.2, C<u>H</u>$_2$CH$_3$ **majR**), 4.16 - 4.53 (2 H, m,

C<u>H</u>$_2$CH$_3$ **minR**), 4.17 (1 H, dd, *J* 10.2, 8.0, H5 **majR**), 3.98 (1 H, dd, *J* 9.9, 8.1, H5 **minR**), 3.86 (1 H, s, OH **majR**), 3.59 - 3.66 (1 H, m, H5 **majR**; 1 H, m, H5 **minR**), 3.58 (3 H, s, H8 **minR**), 3.56 (3 H, s, H8 **majR**), 2.60 - 2.82 (1 H, m, H4 **majR**; 1 H, m, H4 **minR**), 2.13 - 2.35 (2 H, m, H7 **majR**; 2 H, m, H7 **minR**), 1.60 - 1.82 (2 H, m, H6 **majR**; 2 H, m, H6 **minR**), 1.50 (9 H, s, *t*Bu **minR**), 1.36 (3 H, t, *J* 7.2, CH$_2$C<u>H</u>$_3$ **majR**), 1.29 (3 H, t, *J* 7.2, CH$_2$C<u>H</u>$_3$ **minR**), 1.14 (9 H, s, *t*Bu **majR**); δ_C (100 MHz; $CDCl_3$) 173.66 (C **majR**), 173.63 (C **minR**), 170.3 (C **minR**), 170.0 (C **majR**), 153.9 (C **majR**), 153.6 (C **minR**), 137.7 (C **minR**), 137.5 (C **majR**), 136.9 (C **majR**), 135.1 (C **minR**), 128.7 (CH **minR**), 128.3 (CH **minR**), 128.0 (CH **minR**), 127.9 (CH **majR**), 127.7 (CH **minR**), 127.5 (CH **majR**), 127.4 (CH **majR**), 127.3 (CH **minR**), 127.1 (CH **minR**), 127.0 (CH **majR**), 126.6 (CH **majR**), 126.5 (CH **majR**), 88.4 (C **majR**), 86.9 (C **minR**), 80.4 (C **majR**), 79.8 (C **majR**), 79.1 (C **minR**), 62.4 (CH_2 **minR**), 61.9 (CH_2 **majR**), 51.6 (CH_3 **majR**), 50.4 (CH_2 **minR**), 50.0 (CH_2 **majR**), 41.8 (CH **minR**), 41.0 (CH **majR**), 32.2 (CH_2 **minR**), 32.0 (CH_2 **majR**), 28.5 (CH_3 **minR**), 28.0 (CH_3 **majR**), 21.5 (CH_2 **minR**), 21.2 (CH_2 **majR**), 14.2 (CH_3 **majR**), 14.0 (CH_3 **minR**), one (C) and one (CH_3) peaks attributed to the minor rotamer were not observed.

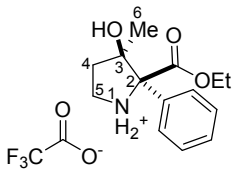
Ethyl *cis*-3-hydroxy-3-methyl-2-phenylpyrrolidine-2-carboxylate 452



A suspension of palladium on carbon (10%, 15 mg, 14 µmol) in a solution of benzyl 2-ethyl *cis*-3-hydroxy-3-methyl-2-phenylpyrrolidine-1,2-dicarboxylate **373** (106 mg, 276 µmol) in ethanol (4 mL) was placed under an atmosphere of hydrogen *via* argon and the resulting mixture was stirred for 16 h at room

temperature. The heterogeneous mixture was filtered through Celite and the resulting solid was washed with dichloromethane (2×20 mL). The volatiles were removed from the filtrate under reduced pressure to give a residue that was purified by column chromatography using 60% ethyl acetate in light petroleum to give the *title compound* as a colourless oil (35 mg, 51%); (Found: M+H$^+$, 250.1445. $C_{14}H_{20}NO_3$ requires 250.1438); ν_{max} ($CHCl_3$)/cm^{-1} 3009, 2928, 1729, 1242, 1178, 1029; δ_H (400 MHz; $CDCl_3$) 7.54 - 7.69 (2 H, m, ArH), 7.15 - 7.46 (3 H, m, ArH), 4.36 (1 H, br s, NH), 4.06 - 4.30 (2 H, two overlapping dq, *J* 10.8, 7.2, C$\underline{H}_2$CH$_3$), 3.15 - 3.35 (2 H, m, H5), 2.43 (1 H, br s, OH), 1.91 - 2.10 (2 H, m, H4), 1.23 (3 H, t, *J* 7.2, CH$_2$C$\underline{H}_3$), 1.05 (3 H, s, H6); δ_C (100 MHz; $CDCl_3$) 176.0 (C), 139.1 (C), 128.1 (CH), 127.6 (CH), 126.2 (CH), 81.4 (C), 74.3 (C), 61.7 (CH_2), 41.4 (CH_2), 38.7 (CH_2), 24.7 (CH_3), 14.1 (CH_3).

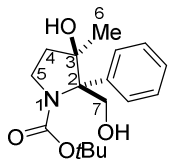
cis-2-(Ethoxycarbonyl)-3-hydroxy-3-methyl-2-phenylpyrrolidin-1-ium 2,2,2-trifluoroacetate 453



Trifluoroacetic acid (0.24 mL) was added to a solution of 1-(*tert*-butyl) 2-ethyl-*cis*-3-hydroxy-3-methyl-2-phenylpyrrolidine-1,2-dicarboxylate **374** in dichloromethane (1.2 mL) cooled in an ice bath. The reaction mixture was warmed to room temperature and stirred for 90 min. The volatiles were removed under reduced pressure to give the *title compound* as a pale brown solid (76 mg, quant.); mp 106 - 108 °C; (Found: M+H$^+$, 250.1438. $C_{14}H_{20}NO_3$ requires 250.1447); ν_{max} ($CHCl_3$)/cm^{-1} 3006 (br), 1739, 1667, 1602, 1267, 1191, 1144; δ_H (400 MHz; $CDCl_3$) 7.49 - 7.61 (2 H, m, ArH), 7.35 - 7.46 (3 H, m, ArH), 4.19 - 4.36 (2 H, m, C$\underline{H}_2$CH$_3$), 3.93 (1 H, td, *J* 10.0,

8.5, H5), 3.75 (1 H, td, *J* 10.0, 2.0, H5), 2.23 (1 H, ddd, *J* 13.2, 8.5, 2.0, H4), 2.07 (1 H, dt, *J* 13.2, 10.0, H4), 1.48 (3 H, s, CH_3), 1.26 (3 H, t, *J* 7.1, $CH_2C\underline{H}_3$); δ_F (376 MHz; $CDCl_3$) −75.5; δ_C (100 MHz; $CDCl_3$) 167.8 (C), 131.2 (C), 129.8 (CH), 129.2 (CH), 126.0 (CH), 82.6 (C), 81.3 (C), 63.8 (CH_2), 42.8 (CH_2), 36.5 (CH_2), 22.1 (CH_3), 13.7 (CH_3), the signals due to the trifluoroacetate, NH_2 and OH were not observed.

tert-Butyl _cis_-3-hydroxy-2-(hydroxymethyl)-3-methyl-2-phenyl-pyrrolidine-1-carboxylate 454



A solution of 1-(*tert*-butyl) 2-ethyl-*cis*-3-hydroxy-3-methyl-2-phenylpyrrolidine-1,2-dicarboxylate **374** (68 mg, 0.195 mmol) in anhydrous dichloromethane (1.5 mL) was added over 5 min to a solution of diisobutylaluminium hydride (1.0 M in dichloromethane, 585 μL, 585 μmol) under argon cooled in an ice bath. The resulting solution was stirred at 0 °C for 60 min, allowed to warm up to room temperature and stirred for 90 min. Diisobutylaluminium hydride (1.0 M in dichloromethane, 390 μL, 390 μmol) was added and the resulting solution was stirred at room temperature for 1 h. Aqueous saturated Rochelle salt solution (3 mL) was added and the mixture was stirred for 1 h. Water (3 mL) was added and the mixture was extracted with ethyl acetate (2×30mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and the volatiles were removed under reduced pressure to give a residue that was purified by column chromatography using 50% ethyl acetate in light petroleum to give the *title compound* as a colourless oil (31 mg, 52%); (Found: M+Na^+, 300.1688. $C_{17}H_{25}NNaO_4$ requires 300.1676);

ν_{max} ($CHCl_3$)/cm^{-1} 3009, 2980, 1678, 1602, 1394, 1368, 1167, 1145; Two rotamers were observed in deuterated chloroform at room temperature (ratio 64:36), the signals observed are reported for the major rotamer (**majR**) and minor rotamer (**minR**); δ_H (400 MHz; $CDCl_3$) 7.19 - 7.36 (3 H, m, ArH **majR**; 3 H, m, ArH **minR**), 7.04 - 7.13 (2 H, m, ArH **majR**; 2 H, m, ArH **minR**), 4.52 (1 H, d, *J* 10.9, H7 **minR**), 4.30 - 4.47 (2 H, m, H7 **majR**), 4.24 (1 H, d, *J* 10.9, H7, **minR**), 4.16 (1 H, br s, OH **majR**), 3.96 (1 H, t, *J* 9.3, H5 **minR**), 3.65 - 3.84 (2 H, m, H5 **majR**; 1 H, m, H5 **majR**), 3.29 (1 H, br s, OH **majR**), 2.88 (1 H, br s, OH **minR**), 1.64 - 1.97 (2 H, m, H4 **majR**; 2 H, m, H4 **minR**), 1.48 (9 H, s, *t*Bu **majR**), 1.17 (9 H, s, *t*Bu **minR**), 1.05 (3 H, s, H6 **majR**), 0.96 (3 H, s, H6 **minR**), one OH peak was not observed; δ_C (100 MHz; $CDCl_3$) 156.0 (C **majR**), 154.7 (C **minR**), 143.2 (C **minR**), 140.5 (C **majR**), 128.1 (CH **majR**), 127.3 (CH **minR**), 127.1 (CH **minR**), 126.9 (CH **majR**), 125.7 (CH **minR**), 84.9 (C **minR**), 83.3 (C **majR**), 80.6 (C **majR**), 80.4 (C **minR**), 74.9 (C **majR**), 73.1 (C **minR**), 66.1 (CH_2 **minR**), 65.0 (CH_2 **majR**), 46.3 (CH_2 **majR**), 46.0 (CH_2 **minR**), 36.0 (CH_2 **minR**), 35.6 (CH_2 **majR**), 28.6 (CH_3 **majR**), 28.2 (CH_3 **minR**), 25.2 (CH_3 **minR**), 23.8 (CH_3 **majR**). One aromatic CH peak due to the major rotamer was not observed.

Annexe - Crystal structures

All measurements were performed on a Agilent SuperNovaII diffractometer using a copper microfocus X-ray source and Oxford Cryosystems low-temperature device. For each crystal, the data collection and refinement parameters are given in **Tables A-1-9**, and views of the molecules are shown in **Figures A-1-9** (Displacement ellipsoids are drawn at the 50% probability level). Data reduction for was performed with CrysAlisPro, Agilent Technologies, Version 1.171.36.28a (release 18-03-2013 CrysAlis171.NET). The absorption correction type is Gaussian and the numerical absorption corrections are based on gaussian integration over a multifaceted crystal model.

I. Crystal structure of 1-allyl-4-phenyl-*1H*-1,2,3-triazol-5-ol 131b

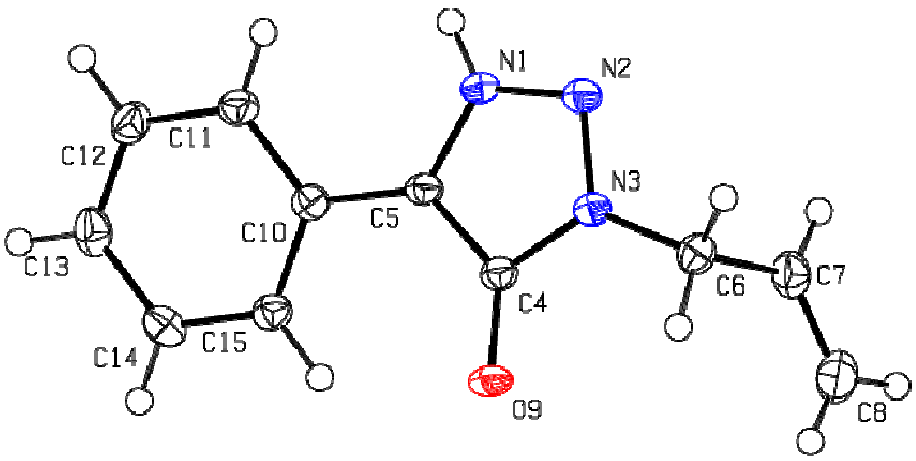


Figure A-1: ORTEP plot of 131b

Table A-1: experimental detail

Crystal data	
Chemical formula	$C_{11}H_{11}N_3O$
molecular weight ($gmol^{-1}$)	201.23
Crystal system, space group	Monoclinic, *C*2/*c*
Temperature (K)	120
a, *b*, *c* (Å)	15.1523 (10), 6.0064 (3), 21.6086 (14)
β (°)	93.286 (6)
V ($Å^3$)	1963.4 (2)
Z	8
F(000)	848
D_x ($Mg\ m^{-3}$)	1.362
Radiation type	Cu K_α
No. of reflections for cell measurement	4411
θ range (°) for cell measurement	5.8–73.5
μ (mm^{-1})	0.74
Crystal shape	plank
Colour	clear colourless
Crystal size (mm)	0.61 × 0.28 × 0.17
Data collection	
Diffractometer	GV1000,Atlas diffractometer
Radiation source	(Cu) X-ray Source

T_{min}, T_{max}	0.861, 1.468
N° of measured, independent and observed [$I > 2s(I)$] reflections	7292, 1972, 1871
R_{int}	0.018
θ values (°)	q_{max} = 74.7, q_{min} = 5.9
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.626
Refinement	
$R[F^2 > 2s(F^2)]$, $wR(F^2)$, S	0.034, 0.086, 1.06
No. of reflections	1972
No. of parameters	136
H-atom treatment	H-atom parameters constrained
Weighting scheme	$w = 1/[s^2(F_o^2) + (0.0388P)^2 + 1.619P]$ where $P = (F_o^2 + 2F_c^2)/3$
$\Delta_{\rho max}$, $\Delta_{\rho min}$ (e Å^{-3})	0.22, -0.21

II. Crystal structure of *trans*-7-*tert*-butyl-3-phenyl-1-oxaspiro[3.5]nonan-2-one 176e

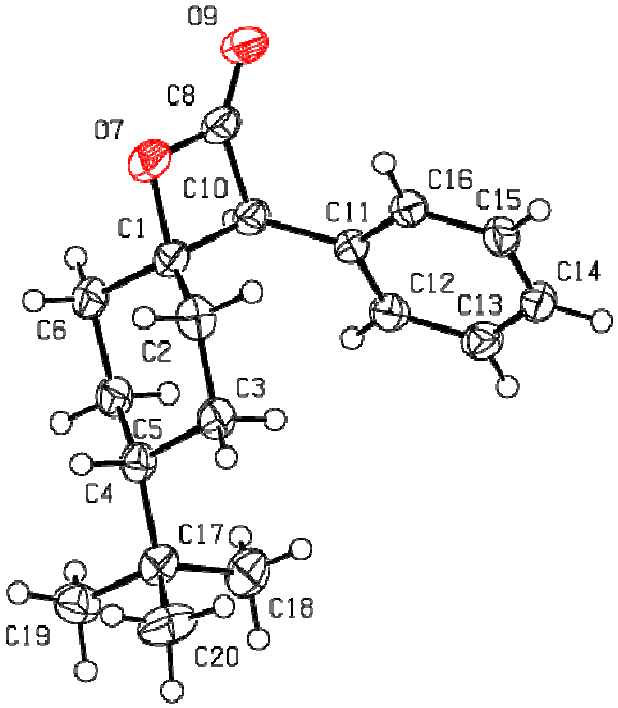


Figure A-2: ORTEP plot of 176e

Table A-2: experimental detail

Crystal data	
Chemical formula	$C_{18}H_{24}O_2$
molecular weight ($gmol^{-1}$)	272.37
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	120
a, b, c (Å)	16.5156 (4), 10.2222 (3), 28.3897 (7)
β (°)	95.489 (3)
V (Å^3)	4770.9 (2)
Z	12
F(000)	1776
D_x ($Mg\ m^{-3}$)	1.138
Radiation type	Cu K_α
No. of reflections for cell measurement	7931

θ range (°) for cell measurement	4.3–74.5
μ (mm^{-1})	0.56
Crystal shape	Plate
Colour	Clear colourless
Crystal size (mm)	0.57 × 0.42 × 0.11
Data collection	
Diffractometer	GV1000,Atlas diffractometer
Radiation source	(Cu) X-ray Source
T_{min}, T_{max}	0.982, 0.995
N° of measured, independent and observed [$I > 2s(I)$] reflections	19143, 9409, 7647
R_{int}	0.030
θ values (°)	θ_{max} = 74.2, θ_{min} = 2.7
$(\sin \theta/\lambda)_{max}$ ($Å^{-1}$)	0.624
Refinement	
$R[F^2 > 2s(F^2)]$, $wR(F^2)$, S	0.083, 0.226, 1.06
No. of reflections	9409
No. of parameters	550
H-atom treatment	H-atom parameters constrained
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.1487P)^2 + 1.132P]$ where $P = (F_o^2 + 2F_c^2)/3$
$\Delta_{\rho max}$, $\Delta_{\rho min}$ (e $Å^{-3}$)	0.80, -0.36

III. Crystal structure of *tert*-butyl (*5R,9S*)-8-oxo-9-phenyl-7-oxa-1-azaspiro[4.4]nonane-1-carboxylate 177c

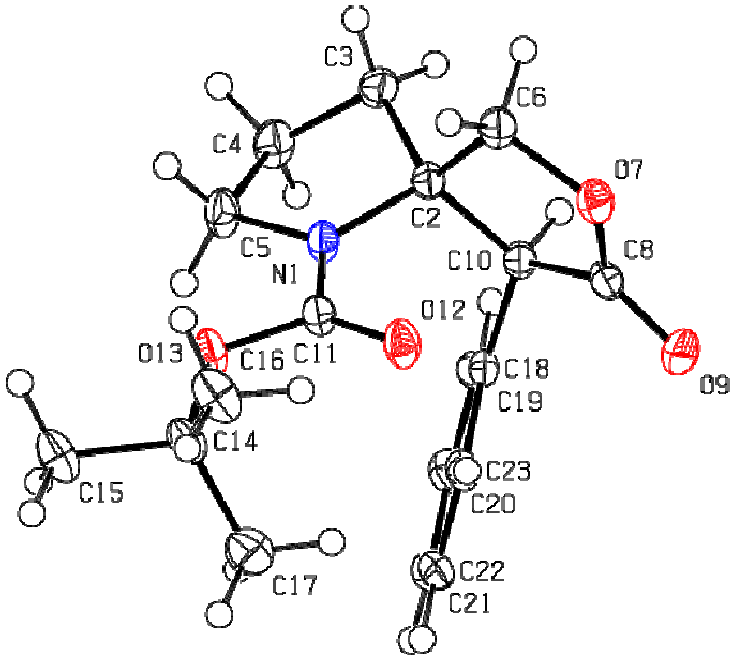


Figure A-3: ORTEP plot of 177c

Table A-3: experimental detail

Crystal data	
Chemical formula	$C_{18}H_{23}NO_4$
molecular weight ($gmol^{-1}$)	317.37
Crystal system, space group	Monoclinic, $P2_1$
Temperature (K)	120
a, *b*, *c* (Å)	10.14180 (16), 8.64981 (11), 19.8188 (3)
β (°)	102.8771 (16)
V ($Å^3$)	1694.87 (5)
Z	4
F(000)	680
D_x ($Mg\ m^{-3}$)	1.244
Radiation type	Cu K_α
No. of reflections for cell measurement	9743
θ range (°) for cell measurement	4.5–74.4
μ (mm^{-1})	0.71

Crystal shape	Needle
Colour	Clear colourless
Crystal size (mm)	1.07 × 0.07 × 0.06

Data collection

Diffractometer	GV1000,Atlas diffractometer
Radiation source	(Cu) X-ray Source
T_{min}, T_{max}	0.732, 0.970
N° of measured, independent and observed [$I > 2s(I)$] reflections	14007, 6714, 6475
R_{int}	0.034
θ values (°)	θ_{max} = 74.4, θ_{min} = 4.5
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.625

Refinement

$R[F^2 > 2s(F^2)]$, $wR(F^2)$, S	0.033, 0.085, 1.02
No. of reflections	6714
No. of parameters	431
H-atom treatment	H-atom parameters constrained
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0487P)^2 + 0.0789P]$ where $P = (F_o^2 + 2F_c^2)/3$
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.16, -0.18

IV. Crystal structure of *tert*-butyl 3-(4-bromophenyl)-1-oxa-7-azaspiro[3.5]nonane-7-carboxylate 180f

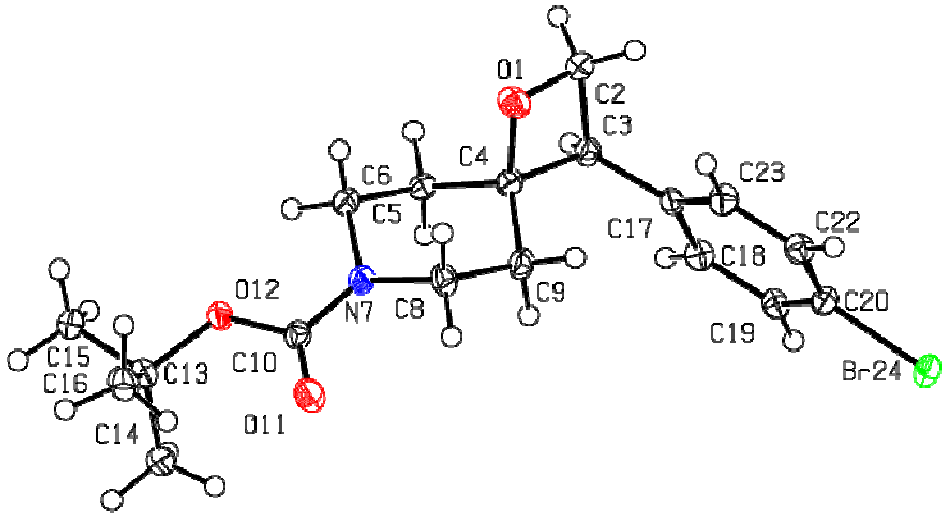


Figure A-4: ORTEP plot of 180f

Table A-4: experimental detail

Crystal data	
Chemical formula	$C_{18}H_{24}BrNO_3$
molecular weight ($gmol^{-1}$)	382.29
Crystal system, space group	Triclinic, $P\bar{1}$
Temperature (K)	120
a, b, c (Å)	8.4489 (14), 10.8155 (14), 10.8203 (17)
α, β, γ (°)	75.877 (12), 68.968 (15), 73.515 (13)
V (Å^3)	873.7 (3)
Z	2
F(000)	396
D_x ($Mg\ m^{-3}$)	1.453
Radiation type	Cu K_α
No. of reflections for cell measurement	3294
θ range (°) for cell measurement	4.3–74.0
μ (mm^{-1})	3.32
Crystal shape	Plate
Colour	Clear colourless
Crystal size (mm)	0.11 × 0.09 × 0.02

Data collection

Diffractometer	GV1000,TitanS2 diffractometer
Radiation source	(Cu) X-ray Source
T_{min}, T_{max}	0.764, 0.941
N° of measured, independent and observed [$I > 2s(I)$] reflections	5916, 3403, 3024
R_{int}	0.052
θ values (°)	θ_{max} = 74.4, θ_{min} = 4.3
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.625

Refinement

$R[F^2 > 2s(F^2)]$, $wR(F^2)$, S	0.043, 0.113, 1.03
No. of reflections	3403
No. of parameters	211
H-atom treatment	H-atom parameters constrained
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0592P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$\Delta_{\rho max}$, $\Delta_{\rho min}$ (e Å^{-3})	0.53, - 0.50

V. Crystal structure of ethyl *cis*-3-hydroxy-2-phenyl-3-((*E*)-styryl)tetrahydrofuran-2-carboxylate 292d

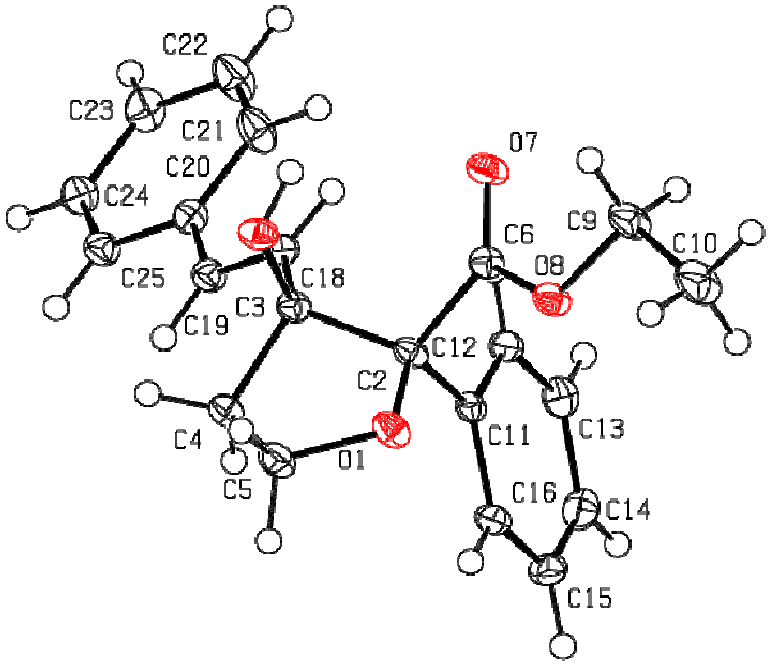


Figure A-5: ORTEP plot of 292d

Table A-5: experimental detail

Crystal data	
Chemical formula	$C_{21}H_{22}O_4$
molecular weight ($gmol^{-1}$)	338.38
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	120
a, b, c (Å)	9.8552 (7), 11.1716 (8), 16.0380 (12)
β (°)	102.887 (8)
V ($Å^3$)	1721.3 (2)
Z	4
F(000)	720
D_x ($Mg\ m^{-3}$)	1.306
Radiation type	Cu K_α
No. of reflections for cell measurement	3382
θ range (°) for cell measurement	4.6–74.3
μ (mm^{-1})	0.73

Crystal shape	Block
Colour	Clear colourless
Crystal size (mm)	0.40 × 0.25 × 0.18
Data collection	
Diffractometer	GV1000,Atlas diffractometer
Radiation source	(Cu) X-ray Source
T_{min}, T_{max}	0.827, 0.902
N° of measured, independent and observed [$I > 2s(I)$] reflections	7179, 3407, 3083
R_{int}	0.027
θ values (°)	θ_{max} = 74.4, θ_{min} = 4.6
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.625
Refinement	
$R[F^2 > 2s(F^2)]$, $wR(F^2)$, S	0.041, 0.108, 1.06
No. of reflections	3407
No. of parameters	230
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.057P)^2 + 0.4846P]$ where $P = (F_o^2 + 2F_c^2)/3$
$\Delta_{\rho max}$, $\Delta_{\rho min}$ (e Å^{-3})	0.25, -0.25

VI. Crystal structure of ethyl (*2S,3R,5S*)-3-hydroxy-3-methyl-2,5-diphenyltetrahydrofuran-2-carboxylate 292i

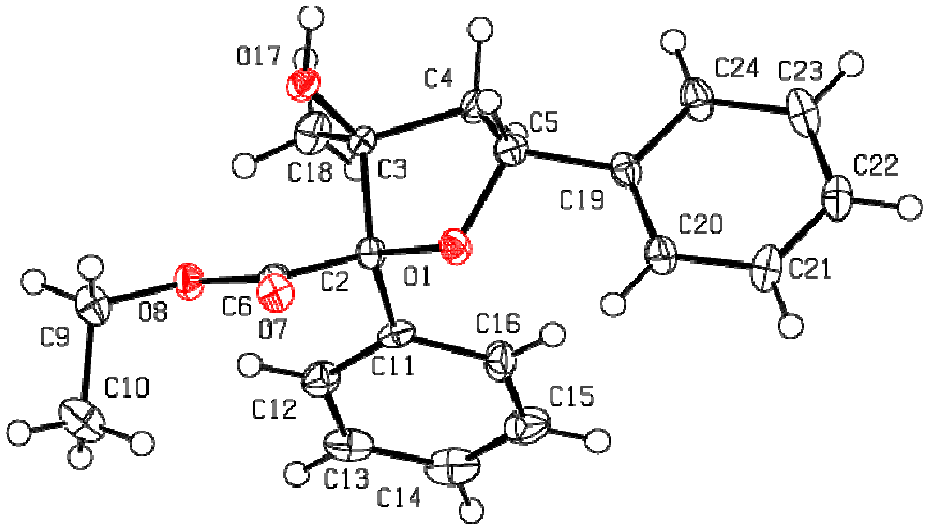


Figure A-6: ORTEP plot of 292i

Table A-6: experimental detail

Crystal data	
Chemical formula	$C_{20}H_{22}O_4$
molecular weight ($gmol^{-1}$)	326.37
Crystal system, space group	Triclinic, *P*1
Temperature (K)	120
a, *b*, *c* (Å)	8.4063 (5), 8.7617 (6), 11.6146 (7)
α, β, γ (°)	90.271 (5), 101.872 (5), 93.175 (6)
V ($Å^3$)	835.75 (10)
Z	2
F(000)	348
D_x ($Mg\ m^{-3}$)	1.297
Radiation type	Cu K_α
No. of reflections for cell measurement	10808
θ range (°) for cell measurement	5.0–76.8
μ (mm^{-1})	0.73
Crystal shape	Block
Colour	Clear colourless

Crystal size (mm)	0.67 × 0.55 × 0.35
Data collection	
Diffractometer	GV1000,Atlas diffractometer
Radiation source	(Cu) X-ray Source
T_{min}, T_{max}	0.719, 0.808
N° of measured, independent and observed [$I > 2s(I)$] reflections	17530, 6559, 6468
R_{int}	0.031
θ values (°)	θ_{max} = 77.1, θ_{min} = 5.1
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.632
Refinement	
$R[F^2 > 2s(F^2)]$, $wR(F^2)$, S	0.064, 0.197, 1.07
No. of reflections	6559
No. of parameters	443
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.1014P)^2 + 1.8011P]$ where $P = (F_o^2 + 2F_c^2)/3$
$\Delta_{\rho max}$, $\Delta_{\rho min}$ (e Å^{-3})	0.56, -0.37

VII. Crystal structure of ethyl *cis*-3-hydroxy-3-methyl-2-phenylpyrrolidine-2-carboxylate 403

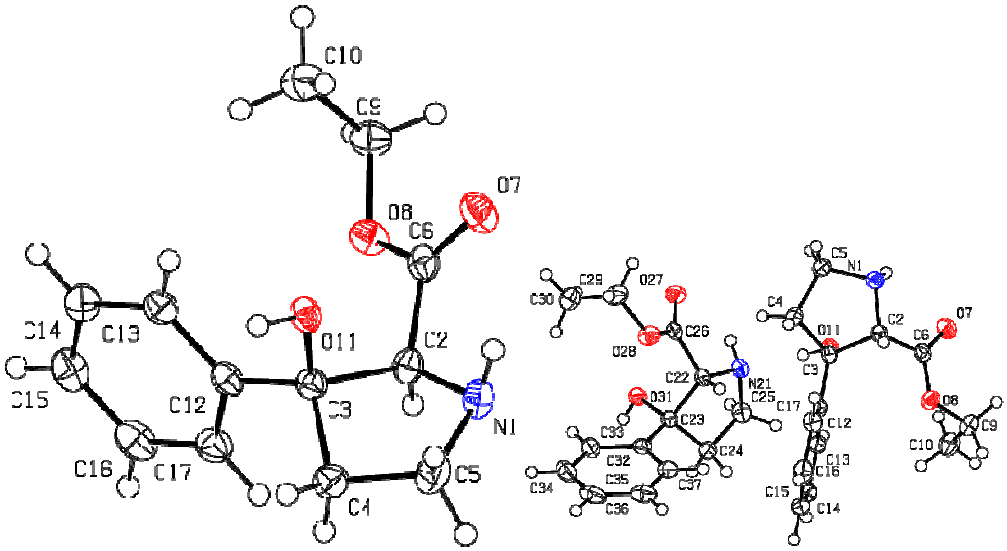


Figure A-9: ORTEP plot of 403

Table A-9: experimental detail

Crystal data	
Chemical formula	$2(C_{13}H_{17}NO_3)$
molecular weight ($gmol^{-1}$)	470.55
Crystal system, space group	Monoclinic, *Pc*
Temperature (K)	120
a, *b*, *c* (Å)	9.53455 (16), 14.3283 (2), 10.02125 (17)
β (°)	114.960 (2)
V ($Å^3$)	1241.18 (4)
Z	2
F(000)	504
D_x ($Mg\ m^{-3}$)	1.259
Radiation type	Cu K_α
No. of reflections for cell measurement	17234
θ range (°) for cell measurement	4.8–74.3
μ (mm^{-1})	0.73
Crystal shape	Plate
Colour	Clear colourless

Crystal size (mm)	0.14 × 0.12 × 0.04
Data collection	
Diffractometer	GV1000,Atlas diffractometer
Radiation source	(Cu) X-ray Source
T_{min}, T_{max}	0.920, 0.976
N° of measured, independent and observed [$I > 2s(I)$] reflections	22586, 4797, 4708
R_{int}	0.038
θ values (°)	θ_{max} = 74.3, θ_{min} = 5.1
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.624
Refinement	
$R[F^2 > 2s(F^2)]$, $wR(F^2)$, S	0.033, 0.088, 1.03
No. of reflections	4797
No. of parameters	321
H-atom treatment	4
Weighting scheme	H atoms treated by a mixture of independent and constrained refinement
$\Delta_{\rho max}$, $\Delta_{\rho min}$ (e Å^{-3})	$w = 1/[\sigma^2(F_o^2) + (0.0612P)^2 + 0.1221P]$ where $P = (F_o^2 + 2F_c^2)/3$

VIII. Crystal structure of 1-(*tert*-butyl) 2-ethyl-*cis*-3-hydroxy-3-methyl-2-phenylpyrrolidine-1,2-dicarboxylate 374

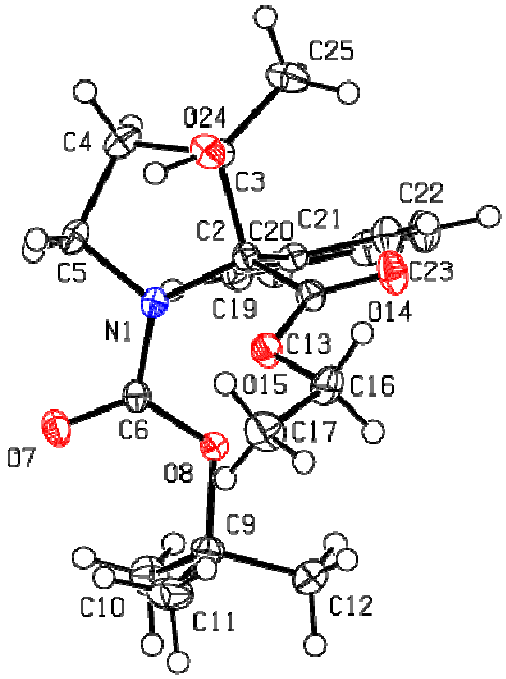


Figure A-7: ORTEP plot of 374

Table A-7: experimental detail

Crystal data	
Chemical formula	$C_{19}H_{27}NO_5$
molecular weight ($gmol^{-1}$)	349.41
Crystal system, space group	Triclinic, $P\bar{1}$
Temperature (K)	120
a, b, c (Å)	9.1288 (8), 9.6594 (10), 11.4907 (10)
α, β, γ (°)	96.820 (8), 96.239 (7), 109.574 (9)
V ($Å^3$)	935.92 (16)
Z	2
F(000)	376
D_x ($Mg\ m^{-3}$)	1.240
Radiation type	Cu K_α
No. of reflections for cell measurement	4308
θ range (°) for cell measurement	4.9–74.1
μ (mm^{-1})	0.73

Crystal shape	Block
Colour	Clear colourless
Crystal size (mm)	0.62 × 0.51 × 0.28
Data collection	
Diffractometer	GV1000,Atlas diffractometer
Radiation source	(Cu) X-ray Source
T_{min}, T_{max}	0.712, 0.833
N° of measured, independent and observed [$I > 2s(I)$] reflections	6411, 3628, 3410
R_{int}	0.025
θ values (°)	θ_{max} = 73.8, θ_{min} = 4.9
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.623
Refinement	
$R[F^2 > 2s(F^2)]$, $wR(F^2)$, S	0.041, 0.110, 1.08
No. of reflections	3628
No. of parameters	234
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0583P)^2 + 0.2752P]$ where $P = (F_o^2 + 2F_c^2)/3$
$\Delta_{\rho max}$, $\Delta_{\rho min}$ (e Å^{-3})	0.30, -0.24

IX. Crystal structure of *tert*-Butyl *cis*-3'-hydroxy-1,3'-dimethyl-2-oxospiro-[indoline-3,2'-pyrrolidine]-1'-carboxylate 428

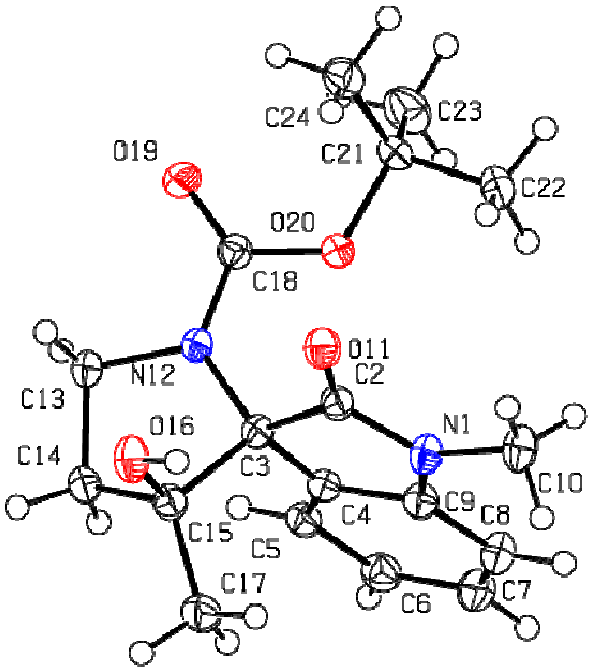


Figure A-8: ORTEP-plot of 428

Table A-8: experimental detail

Crystal data	
Chemical formula	$C_{18}H_{24}N_2O_4$
molecular weight ($gmol^{-1}$)	332.39
Crystal system, space group	Triclinic, $P\bar{1}$
Temperature (K)	120
a, b, c (Å)	8.8457 (9), 9.0850 (11), 12.1886 (12)
α, β, γ (°)	100.760 (9), 92.584 (8), 115.523 (11)
V (Å^3)	859.63 (18)
Z	2
F(000)	356
D_x ($Mg\ m^{-3}$)	1.284
Radiation type	Cu K_α
No. of reflections for cell measurement	4391
θ range (°) for cell measurement	3.7–73.5

μ (mm^{-1})	0.74
Crystal shape	Block
Colour	Clear colourless
Crystal size (mm)	0.70 × 0.64 × 0.25
Data collection	
Diffractometer	SuperNova, Titan S2 diffractometer
Radiation source	(Cu) X-ray Source
T_{min}, T_{max}	0.709, 0.860
N° of measured, independent and observed [$I > 2s(I)$] reflections	5959, 3346, 3087
R_{int}	0.035
θ values (°)	θ_{max} = 74.0, θ_{min} = 3.7
$(\sin \theta/\lambda)_{max}$ ($Å^{-1}$)	0.623
Refinement	
$R[F^2 > 2s(F^2)]$, $wR(F^2)$, S	0.044, 0.117, 1.04
No. of reflections	3346
No. of parameters	225
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0706P)^2 + 0.2258P]$ where $P = (F_o^2 + 2F_c^2)/3$
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e $Å^{-3}$)	0.35, -0.26

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