SYNTHESIS AND GOLD-CATALYZED TRANSFORMATIONS OF ALLENIC COMPOUNDS

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Abstract

This thesis is concerned with the synthesis of allenic compounds and their gold-catalyzed isomerization reactions. Its general aim is the development of new reaction methodologies within these topics and the work has been published in two separate articles. After an introductory chapter (covering relevant literature upto 2010) three separate projects are discussed:

1. Development of tandem enzyme/gold-catalyzed reaction where lipase-catalyzed kinetic resolution of α-allenic acetates [$R^1{}_2CCCH(CHR^2OAc)$] (R^1,R^2 = alkyl) leads to the formation of α-hydroxyallenes with 86-99% *ee* and this transformation is followed by the cycloisomerization of the α-hydroxyallenes to the corresponding 2,5-dihydrofurans in a one-pot reaction. It is found that the two transformations work well in one pot except in the case where R^2 is branched, which are not hydrolysed.

2. A new approach is developed for the synthesis of allenyl acetates [$Ar(R^1)CCCH(O_2CR^2)$] (R^1 = alkyl, R^2 = Me, Ph, *t*-Bu) using cuprate-mediated S_N2' nucleophilic substitution to propargylic dicarboxylates. The reaction was successfull with a range of substrates (11 examples). Investigation on a catalytic variant for the synthesis of the above allenyl acetates. Nickel-catalyzed S_N2' nucleophilic substitution to propargylic dicarboxylates gives the highest selectivity of the desired allenic products but the transformation is not very high-yielding. Attempts towards an asymmetric reaction are thwarted by low enantioselectivities (<22% *ee*).

3. Comparing the reactivity of propargylic acetates and allenyl acetates (prepared in Sections 2-3) in the gold-catalyzed synthesis of indenes. It was discovered that the allenyl acetates prepared earlier yield indenes with up to quantitative yields and high chemoselectivity, whereas propargylic acetates with terminal a alkyne group only yielded a mixture of cyclization and elimination products.

Acknowledgements

First of all I should like to thank both of my supervisors, Prof. Simon Woodward and Prof. Norbert Krause. I should like to thank them both for the support and ideas they gave me during these years. Also, I should like to thank them for the supportive and optimistic atmosphere where I was always encouraged to pursue and test my own ideas. Finally, special thanks to Prof. Woodward for the group meetings and the missions which taught me a lot.

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Abbreviations

Acc	Acceptor
AK Amano	Lipase from *Pseudomonas fluorecens* from Amano Enzymes
BINOL	1,1'-Bi-2-naphthol
CAN	Cerium (IV) ammonium nitrate
COD	1,5-Cyclooctadiene
dba	Dibenzylideneacetone
DHP	Dihydropyran
DIBAH / DIBAL	diisobutylaluminium hydride
diglyme	*Bis*(2-methoxyethyl) ether
DIOP	(-)-2,2-Dimethyl-4,5-((diphenylphosphino)dimethyl)dioxolane)
DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
dppb	1,2-*Bis(*diphenylphosphino*)*benzene
dppe	1,2-*Bis*(diphenylphosphino)ethane
dppf	1,1'-*Bis*(diphenylphosphino)ferrocene
dppm	1,1-*Bis*(diphenylphosphino)methane
dppp	1,3-*Bis*(diphenylphosphino)propane
DPS	*tert*-butyldiphenylsilyl (TBDPS)
IPr	*N,N´-bis*(2,6-diisopropylphenyl)imidazol-2-ylidene
MIC	Minimum inhibitory concentration
MTBE	Methyl *tert*-butyl ether
mTHF	2-methyl tetrahydrofuran
NIS	*N*-iodosuccinimide
NOBIN	2-amino-2'-hydroxy-1,1'-binaphthyl
Piv	Pivalate ester
PPL	Porcine Pancreatic lipase

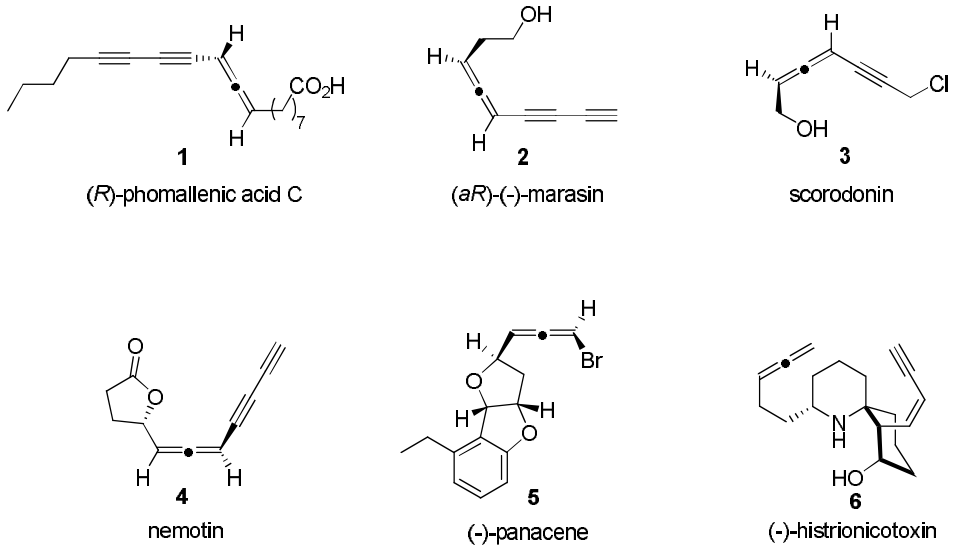
PS Amano SD	Lipase from *Burcholderia cepacia* from Amano Enzymes
Pybox	2,6-*Bis*[(4R)-4-phenyl-2-oxazolinyl]pyridine
TBS	*tert*-butyldimethylsilyl

1 Introduction to allene chemistry and gold-catalyzed organic transformations

This thesis focuses on the synthesis of allenic compounds and on gold-catalyzed transformations of allenic and propargylic compounds. This introductory chapter gives an overview on the two topics (literature upto 2010) without going into extensive detail. Allene synthesis, and the versatility of allenes as building blocks in organic synthesis, is discussed and illustrated with examples from natural products and their synthesis. Gold catalysis is then discussed with some recent examples. The background for the topic of each following chapter (Chapters 2-5) will be introduced in detail in the beginning of each chapter.

1.1 Allenes in organic chemistry

The cumulative double-bond structure of allenes is often present in nature. There are over 150 reported natural products with allene structure [1], many of which have interesting biological properties. Some examples of allenic natural products that have recently been synthesized are given in Scheme 1.



Scheme 1

In 2006, Ondeyka *et al.* isolated phomallenic acids A-C from the fermentation broth of *Phoma* sp [2]. From the phomallenic acid family, phomallenic acid C **1** has shown the highest activity as type FASII inhibitor (MICs in the range of 0.77-3.9 μg/ml against *Staphylococcus aureus* (MRSA) and *Haemophilus influenzae*) [3] and might be a selective agent against infection

diseases. Total synthesis of phomallenic acid C was first reported by Wu and co-workers in 2007 [4]. This was followed by synthetic approaches from two other groups: Watanabe in 2008 [5] and 2009 [6] and Shishido 2008 [7].

Marasins are a group of natural products having considerable bioactivity against numerous bacteria including Mycobacterium turberculosis. (*aR*)-(-)-Marasin **2** was isolated from *Marasimus ramealis* in 1959 and *Cortillenus berceleyanus* in 1966 [8] and its first total synthesis was accomplished in 1988 by Graaf and co-workers who also tested the bioactivity of marasin against *Staphylococcus aureus* [9]. Graaf obtained the product (*aR*)-(-)-marasin with very low, 0.5% *ee*. There are recent examples of the synthesis of (*aR*)-(-)-marasin *via* biosynthetic route by Hodge 2005 [10] as well as a very recent example from Wu 2010 [11] which allows the synthesis of the natural product with 75% *ee*.

Scorodonin **3** was isolated from *Marasmius scorodonius* and it has inhibiting effects on the growth of bacteria, yeasts and filamentous fungi [12]. Its first total synthesis with 63% *ee* for the final product was accomplished by Wu and co-workers in 2010 [13]. The first enantioselective synthesis of nemotin was also reported in 2010 by Wu and co-workers [14]. Nemotin **4** was isolated in 1950 by Robbins [15] and the structure completely determined by Leeming in 1955 [16].

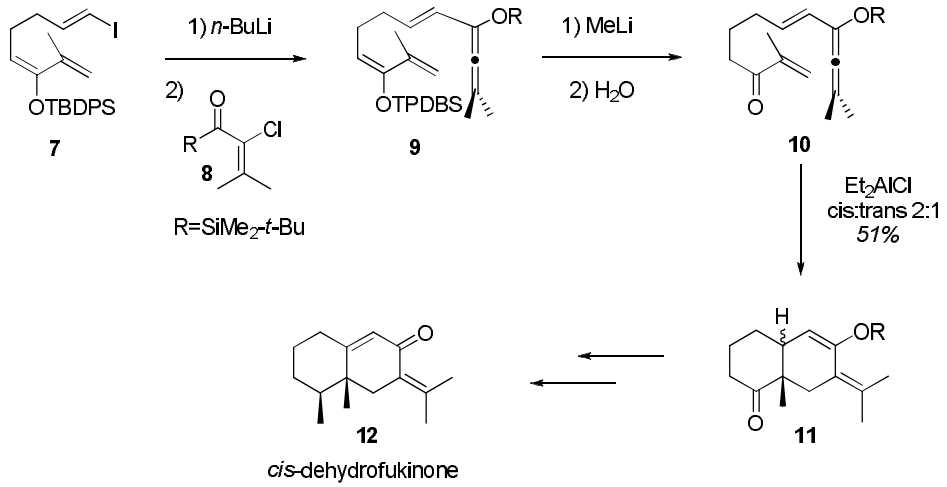
Panacene **5** was isolated in 1977 from a sea hare [17]. Racemic panacene was first synthesized by Feldman in 1982 [18] and in 2006 Boukouvalas and Snieckus reported the first enantioselective total synthesis [19].

Poison arrow frogs of South America have toxic allenic products in their skin for defence. In 1970 Witkop and co-workers collected a series of skin extracts from Colombian frogs of family Dendrobates histrionicus and reported the structures of new spiroalcaloids containing acetylenic and allenic substitutents [20]. These compounds can be highly toxic, but some of them also show inhibiting activity to the nicotinic acetylcholine receptor with (-)-histrionicotoxin **6** being the most potent inhibitor within the histrionicotoxins family [21]. The first total synthesis of (-)-histrionicotoxin was reported by Holmes in 2008 [22].

The several recent syntheses of allenic natural products prove that these compounds are of great interest to the modern organic chemist. Allenic compounds are interesting not only for the synthetic challenges that they present but also for their potential biological activities.

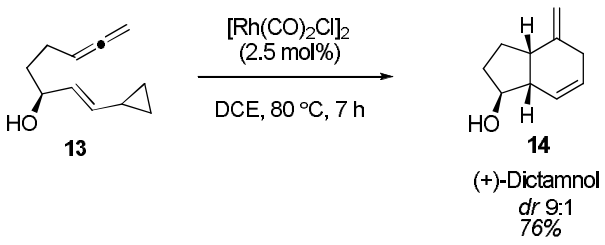
Allenic compounds are present in nature but allenes are also valuable building blocks and in organic synthesis. The importance of allenes in organic synthesis is based on the unique reactive properties of cumulative double bonds. Allenes can undergo various cycloaddition reactions both intra- and intermolecularly. Allenic compounds also perform well in various cycloisomerizations, as well as coupling reactions. Allenes also possess the property of axial chirality that can be transferred to a new chiral center in many reactions of allenic compounds [1a].

Reich and co-workers have studied the synthesis and reactivity of siloxyvinylallenes **9**. They reported a total synthesis of *cis*-dehydydrofukinone **12** in 1986 [23]. The key step in this synthesis was a Diels-Alder cyclization of enone-allene **10** in the presence of a Lewis acid to give cycloadduct **11** which can be further modified to the natural product **12** (Scheme 2).



Scheme 2

Another example of an allenic moiety as an intermediate in total synthesis is from Wender and co-workers from 1999 [24]. They carried out the total synthesis of (+)-dictamnol **14** by using a rhodium-catalyzed [5+2]-cycloaddition reaction of allenylvinylcyclopropane **13** to yield the product **14** in high diastereoselectivity (Scheme 3).



Scheme 3

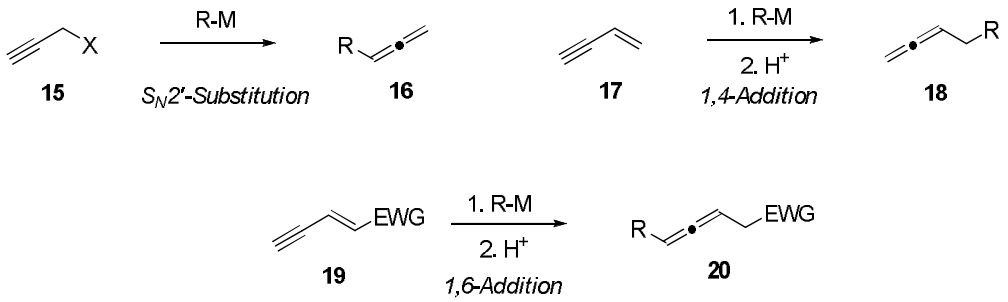
In the following discussion on allene synthesis, as well as in Chapter 2, additional examples of allenes as starting materials in the synthesis of complex structures are presented.

1.1.1 Synthetic methods towards allenic compounds

In the thousands of publications on allene synthesis, there are a plethora of synthetic methods to access these compounds [25]. Two methods are discussed in detail here, which are also used in this thesis. These are the use of stoichiometric organometallic reagents, focusing on reactions with cuprates and aluminium hydrides; secondly the use of transition metal catalysis in allene synthesis will be discussed.

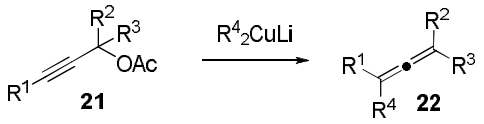
1.1.1.1 Use of stoichiometric organometallic reagents in synthesis of allenes

Metal-mediated allene synthesis can be summarized in to three fundamental methodologies; S_N2' nucleophilic substitution to propargylic electrophiles **15**, 1,4-addition to enynes **17** and 1,6-addition to acceptor-substituted enynes **19** (Scheme 4). Often in these reactions the organometallic reagent used is an organocopper reagent as many combinations of organocopper reagents and leaving groups result in clean conversions to the allene product.



Scheme 4

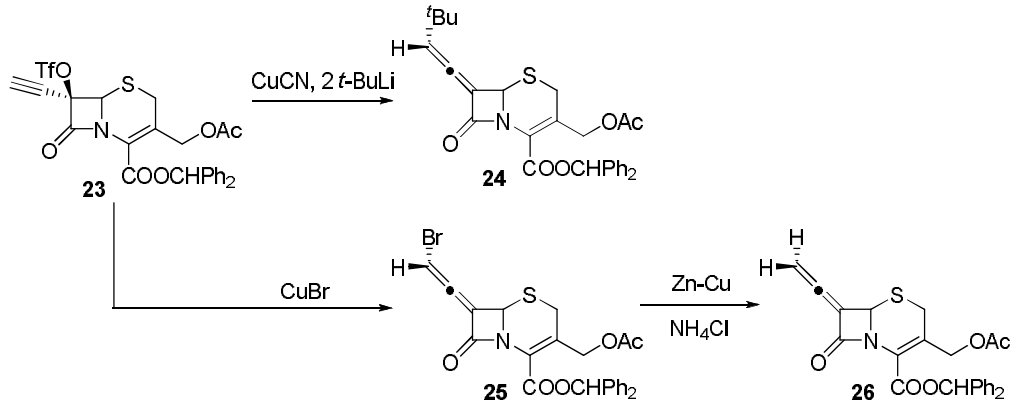
The first example of organocopper-mediated allene synthesis was reported by Rona and Crabbé in 1968 [26]. They used a lithium dialkylcuprate in the synthesis of allenes **22** from propargylic acetates **21** (Scheme 5).



Scheme 5

Since the pioneering work of Rona and Crabbé several methods have been developed including changes both in the propargylic electrophile and the cuprate reagent. The propargylic system often carries a carboxylate [26], an epoxide [27], an ether or acetal [28] or a halide [29] as a leaving group but the substrate can also be a propargylic tosylate [30] or even aziridine [31]. The organocopper reagents have also evolved to various functionalized cuprates derived from organolithium [32], Grignard [33] and organozinc [34] reagents.

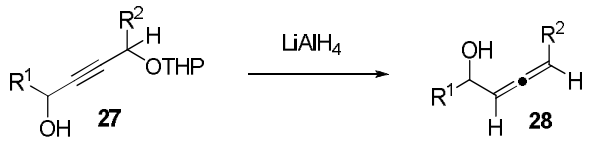
Organocopper-mediated allene synthesis has found its applications in total synthesis of natural or bioactive products. 7-Vinylidenecephem sulphones **24** and **25** were prepared by organocopper-mediated S_N2' nucleophilic substitution of propargylic triflates [35]. Two types of copper reagents were employed; copper(I) bromide and the cyanocuprate $(t\text{-Bu})_2CuCNLi_2$, both yielded the corresponding allenic products with 100% stereospecificity *via* an *anti* S_N2' displacement of the leaving group (Scheme 6). Bromoallene **25** can be reduced with zinc-copper couple to the terminally unsubstituted allene **26**.



Scheme 6

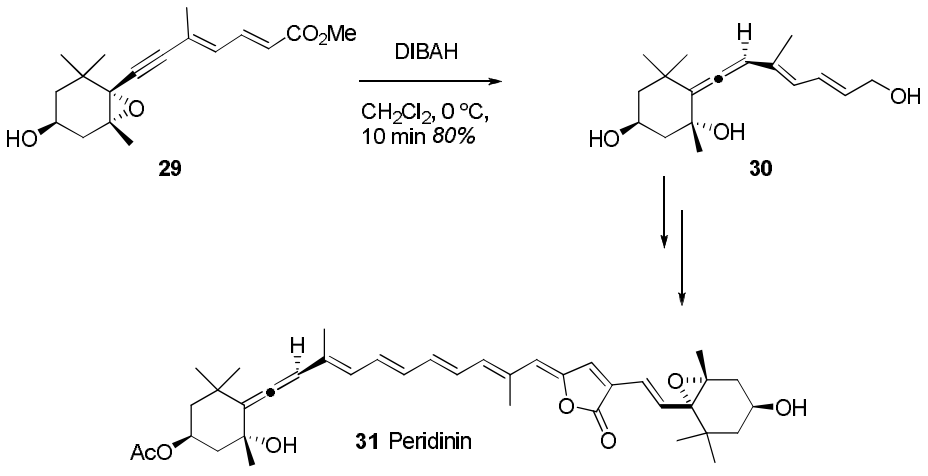
Although there are many other methods for metal-mediated allene synthesis [1a] we will concentrate here on methods using aluminium hydrides as this method has been used in this thesis.

Aluminium hydrides, such as lithium aluminium hydride and diisobutylaluminium hydride (DIBAH) can transform various propargylic electrophiles to the corresponding allenes. The use of aluminium hydrides has proved particularly useful in the synthesis of α-hydroxyallenes [36]. The reductive substitution of lithium aluminium hydride to mono-THP ether of bispropargylic alcohols **27** yields α-hydroxyallenes **28** with high selectivity and yield (Scheme 7).



Scheme 7

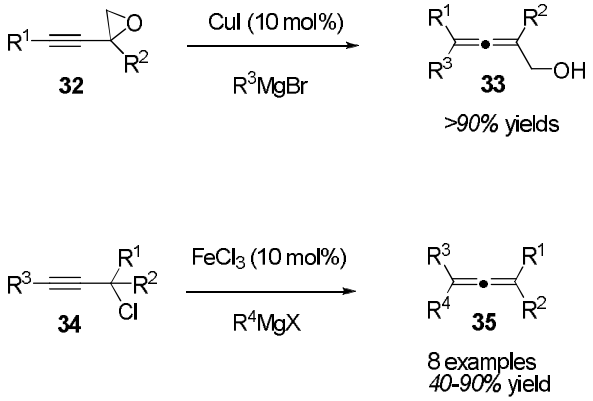
The aluminium hydride mediated allene synthesis has also found applications in total synthesis as in the synthesis of peridinin **31**, a carotenoid isolated from planctonic algae dinoflagellates [37]. In the total synthesis, the allenic building block of the natural product is synthesized by reacting a propargylic epoxide **29** with diisobutylaluminium hydride to give α-hydroxyallene **30** (Scheme 8).



Scheme 8

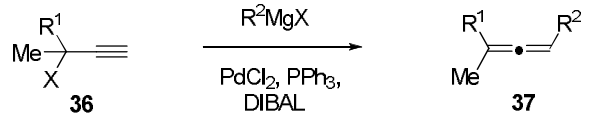
1.1.1.2 Transition metal -catalyzed synthesis of allenes

There are also reports of using catalytic amounts of transition metals in the synthesis of allenes. In this approach the starting material is also often a propargylic electrophile dating from the seminal work of Vermeer from 1974 who synthesized α-hydroxyallenes **33** from propargylic epoxides **32** with Grignard reagents in presence of 10 mol% of copper(I) iodide (Scheme 9) [27]. In 1976 Pasto successfully synthesized allenes **35** from propargylic chlorides **34** with Grignard reagent and iron(III) chloride as catalyst (Scheme 9) [38].



Scheme 9

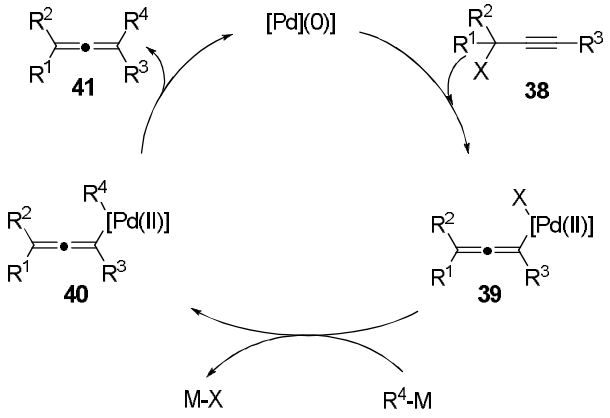
After the first reports on iron- and copper-catalyzed allene formations other transition metals have also been found efficient in allene synthesis. Probably the most frequently used transition metal catalysts in this approach are palladium catalysts. In 1980 Jeffery-Luong and Linstrumelle applied palladium(II) chloride with phosphine ligands to an S_N2' nucleophilic substitution of a Grignard reagent to propargylic electrophile **36** (Scheme 10) [39]. Since then various palladium catalysts as well as different organometallic reagents have been successfully used [25].



Scheme 10

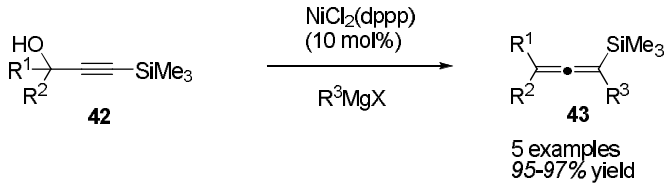
The mechanism of the palladium-catalyzed S_N2' nucleophilic substitution is shown in Scheme 11 [40]. A (σ-allenyl)palladium(II) species **39** forms in an oxidative addition with the

propargylic substrate **38**. This complex can then react with a carbon nucleophile, such as organomagnesium, -zinc or –boron reagents *via* transmetallation. Reductive elimination yields the allenic product **41** and the [Pd(0)] catalyst. The mechanism resembles that of a cross-coupling reaction, except that the propargylic substrates rearrange to allenyls in the oxidative addition step (Scheme 11).



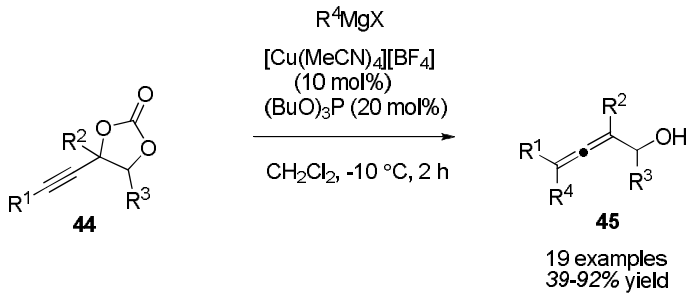
Scheme 11

Copper and nickel catalysts have also been used to catalyze the synthesis of allenes. The first examples of nickel-catalyzed allene synthesis are from 1985 [41] when Michelotti studied the reactions of propargylic alcohols **42** with Grignard reagents in the presence of nickel catalysts (Scheme 12).



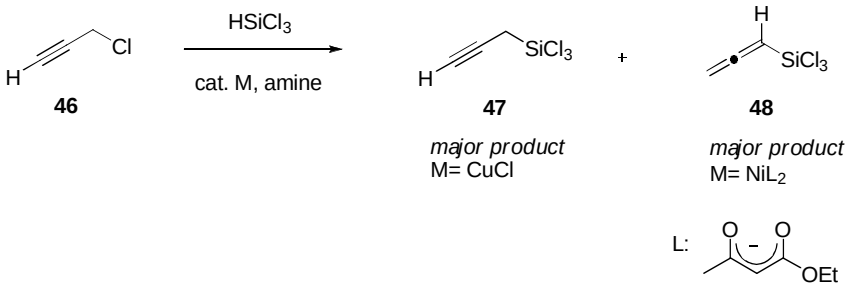
Scheme 12

Copper catalysis was one of the first methods used in allene synthesis (Scheme 9) but is of current interest as well. Woodward and Krause reported a new synthesis for α-hydroxyallenes in 2009. The copper-catalyzed S_N2' reaction was used to form the allenic products **45** from propargylic dioxolanones **44** [42]. The reaction yields α-hydroxyallenes with high regioselectivity (Scheme 13).



Scheme 13

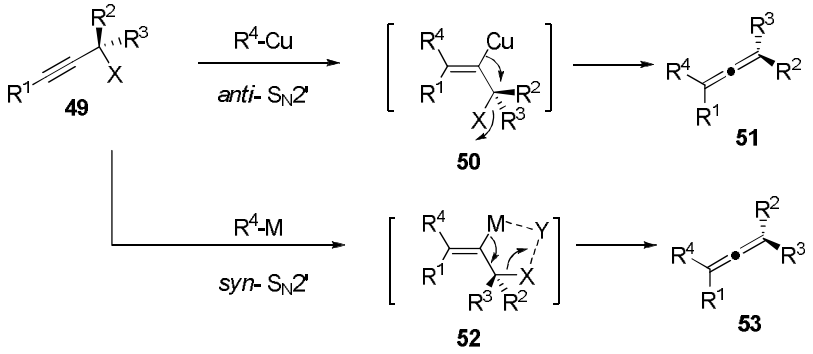
In some cases the regioselectivity in the S_N2' *vs* S_N2 reaction is dependent on the transition metal used. A good example of this is Kobayashi's report from 1995 (Scheme 14) [43]. In the S_N2' reaction of silanes with propargylic halides **46** the desired regioselectivity towards S_N2' nucleophilic substitution (product **48**) is obtained with a nickel catalyst while copper catalysts tested yielded mostly S_N2-product **47**.



Scheme 14

1.1.2 Asymmetric synthesis of allenic compounds

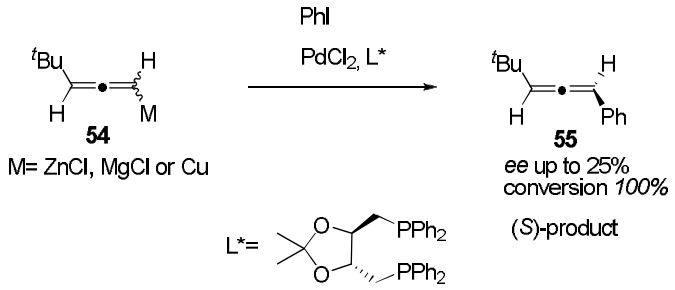
Enantioselective synthesis of allenes is a topic that is of current interest to many research groups. There are several methods to obtain enantiomerically enriched allenes and the most common are listed here. Probably the most used method is to use center-to-axis chirality transfer starting from enantiomerically enriched propargylic alcohols. This approach is popular due to the easily available starting materials. The S_N2' reaction can proceed via *anti*- or *syn*-selectivity. With organocopper reagents *anti*-S_N2' reaction is often favored [44]. There are also examples of using a catalytic amount of a copper salt with a Grignard reagent to obtain *syn*-selectivity [45] (Scheme 15).



Scheme 15

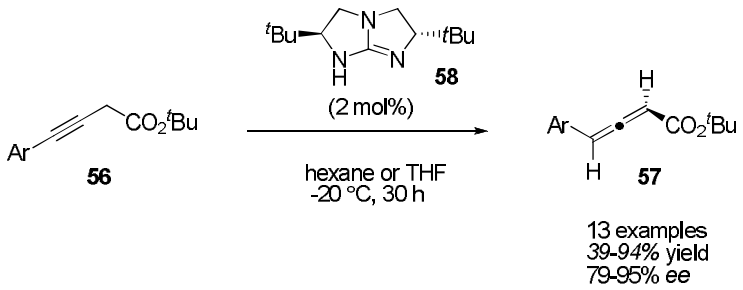
Besides the use of different copper reagents, several other methods have been reported that use the center-to-axis chirality transfer from propargylic alcohol derivatives to allenes. These include intramolecular rearrangements [46], palladium-catalyzed reactions [47], reductions of propargylic alcohol derivatives with lithium hydrides to the corresponding allenes [48] and many others.

Enantiomerically enriched or pure allenes can also be prepared *via* direct asymmetric synthesis. First success in catalytic direct asymmetric allene synthesis was achieved by Elsevier and co-workers in 1989 [49]. They reported a coupling reaction of a racemic allenyl-metal compound **54** with iodobenzene in the presence of a palladium catalyst and a chiral ligand (Scheme 16). The best *ee* obtained for allenes **55** with this method was 25%.



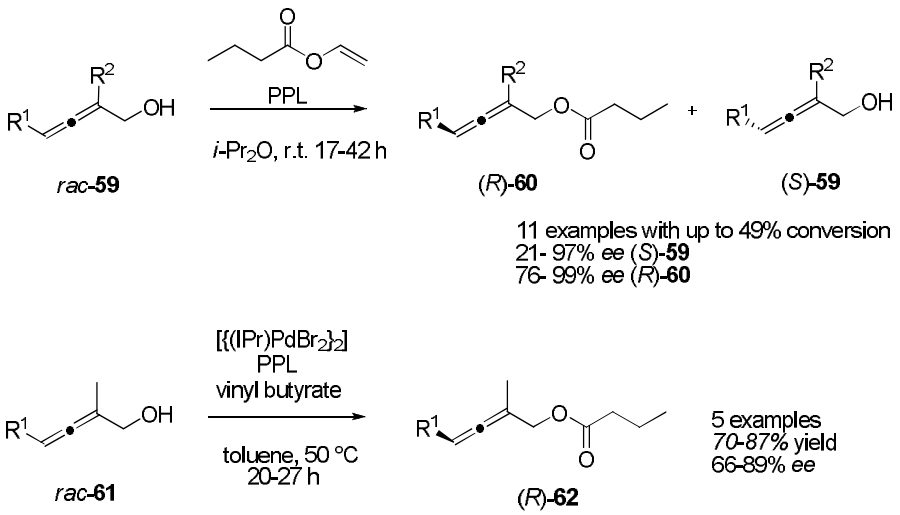
Scheme 16

Recently (2009) guanidine-catalyzed isomerization of alkynoates **56** to the corresponding allenoates **57** was reported by Huang and Tan [50]. The reaction takes place *via* a base catalyzed 1,3-proton shift. The resulting allenoates **57** are obtained with high yields and in most cases with over 90% *ee* (Scheme 17).



Scheme 17

Classical kinetic resolution has been applied to the preparation of enantiomerically enriched allenes by several research groups very recently. In two reports from Bäckvall in 2009-2010 Porcine pancreatic lipase (PPL) -catalyzed kinetic resolution [51], and lipase/palladium-catalyzed dynamic kinetic resolution were used to prepare compounds (*R*)-**60** and (*R*)-**62** [52] (Scheme 18). By kinetic resolution is meant a process, where a racemic material reacts with a chiral catalyst and the two enantiomers having unequal rates of the reaction results to resolution of the enantiomers. Dynamic kinetic resolution can be achieved by adding a second catalyst, which is able to racemize the starting material.



Scheme 18

Bäckvall has also reported some examples of cinchonidine mediated kinetic resolution of axially chiral allenic acids in 2008 [53]. Additionally, in 2010 Gong reported the use of biphosphoric acid in the kinetic resolution of axially chiral allenic acids [54]. There is also a

report on the optimization of the enantioselectivity of a lipase from *Pseudomonas aeruginosa* towards allenic compounds [55].

1.2 Gold catalysis in organic synthesis

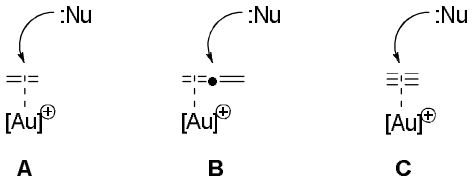
The use of gold catalysts in organic synthesis has seen a tremendous rise in the 21st century. Gold catalysts are generally considered as safe and simple to use and the resultant reactions are normally easy to perform. Often gold-catalyzed reactions can be performed under very mild reaction conditions with reasonably short reaction times. Gold catalysts often show excellent chemoselectivity towards unsaturated C-C π systems, leaving other functional groups untouched.

Most gold catalysts exist in two oxidation states: Au(I) and Au(III). Gold catalysts, as platinum catalysts, do not undergo traditional redox catalytic cycles of oxidative addition and reductive elimination like many other transition metal catalysts. Instead, gold catalysts tend to stay in one oxidation state through the reaction. The first gold catalysts were simple halide salts such as $AuCl_3$. The catalyst activity can be enhanced by creating cationic gold-species, which can be stabilized with phosphine or *N*-heterocyclic carbene ligands [56]. Often a silver co-catalyst is used to create the cationic gold-complex *in situ* [57].

Many gold-catalyzed reactions have to be performed in organic solvents. Some gold salts, however, also perform well also in aqueous solutions. The gold acid $HAuCl_4$ and $NaAuCl_4$ [58] are active in water under air. Ionic liquids have also been used as solvents with the gold catalysts $Bu_4N[AuCl_4]$ [59] and $AuBr_3$ [60].

1.2.1 Gold-catalyzed organic transformations

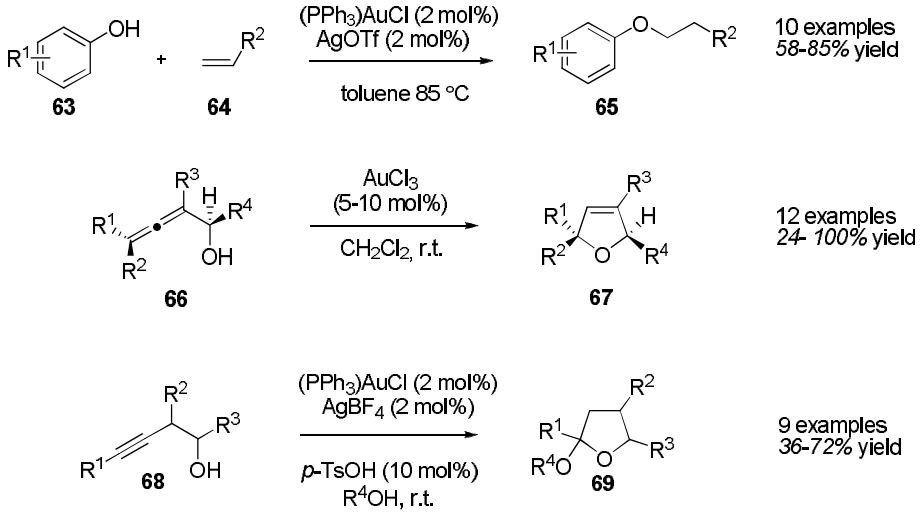
The π-electrophilicity of gold catalysts is their most important property when used as catalysts in organic chemistry. Gold catalysts have even been named as π-acids [57] due to their affinity to bind to C-C multiple bonds. The activation of a π-ligand (alkene **A**, allene **B** or alkyne **C**) renders the π system electrophilic and thus activates the π system towards a nucleophilic attack (Scheme 19).



Scheme 19: Activation of unsaturated C-C π-systems with cationic gold-complexes.

The nucleophile in the reaction can be delivered in an intramolecular or intermolecular manner. Both carbon and heteroatom nucleophiles have been extensively used [61]. The reaction mechanisms of such reactions have been reviewed recently [62].

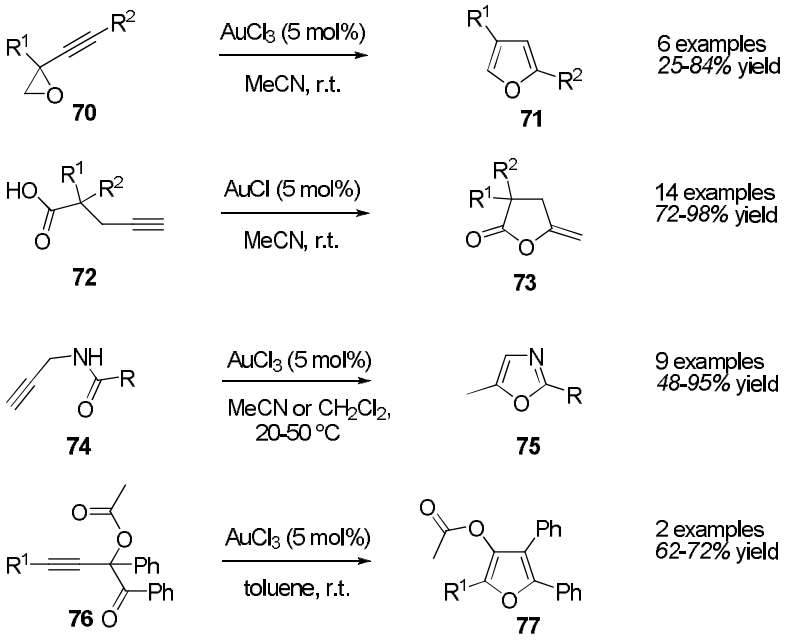
Alkenes, allenes and alkynes have all been used as substrates for gold-activated nucleophilic attack (Scheme 20). Gold catalysts can activate substitution of phenols **63** to unactivated alkenes **64** [63], catalyze the cycloisomerization of α-hydroxyallenes **66** to 2,3-dihydrofurans **67** [64] and promote the cyclosomerization of homopropargylic alcohols **68** to tetrahydrofuranol ethers **69** [65]. Allenes and alkynes are more reactive substrates due to their sp-hybrid carbon atoms which render them more electrophilic than similarly substituted alkenes allowing the reactions to be performed at room temperature.



Scheme 20

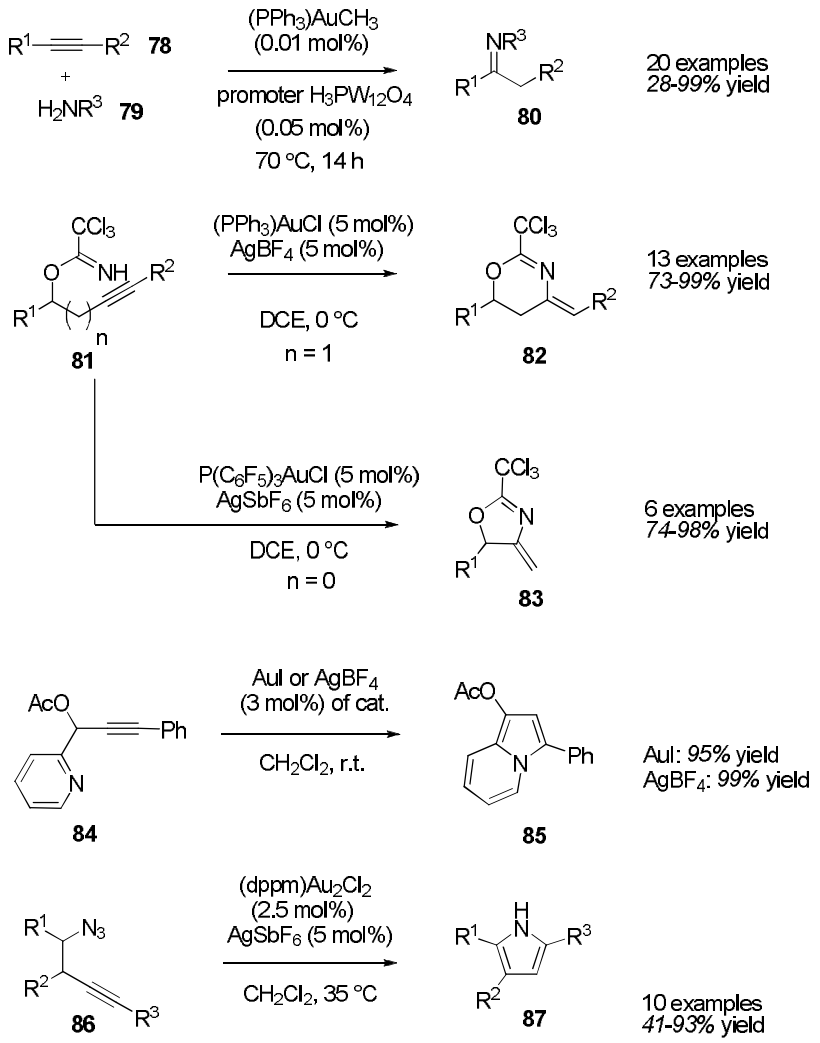
In Chapters 2 and 5 gold-catalyzed reactions of allenes will be discussed in detail. Reactions of gold catalysts with some alkynes are discussed in Chapter 5. In this Chapter are presented representative examples of alkyne π-systems as substrates in gold catalysis.

Besides alcohols, other oxygen nucleophiles have been used in gold-activated reactions. Alkynes can be activated towards intramolecular nucleophilic attack of epoxides **70** [66], carboxylic acids **72** [67], amides **74** [68] and ketones **76** [69] forming substituted furans **71** and **77**, lactones **73** and oxazoles **75** (Scheme 21). With different oxygen nucleophiles the reactions are often performed at room temperature.



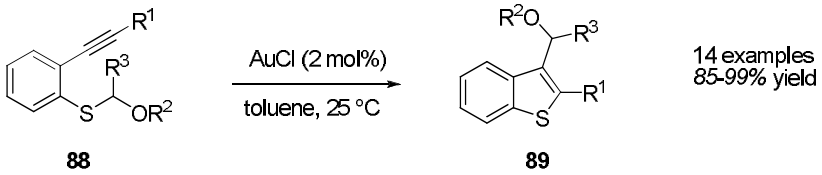
Scheme 21

Nitrogen-based nucleophiles can also be used, recent examples using alkyne substrates are presented in Scheme 22. Gold-catalyzed hydroamination has been known since 1987 [70]. Scheme 22 presents a recent intermolecular version of this reaction which yields imines **80** from alkynes **78** and amines **79** [71]. Imidates **81** can also be used in hydroamination [72] to form 4,5-dihydrooxazoles **83** and 5,6-dihydro-1,3-oxazines **82** under very mild reaction conditions. Even pyridine compounds **84** work well as nucleophiles forming *N*-fused heterocycles **85** [73] under gold- and silver-catalysis. Azides **86** display a gold-catalyzed Schmidt reaction giving pyrroles **87** with elimination of N_2 [74].



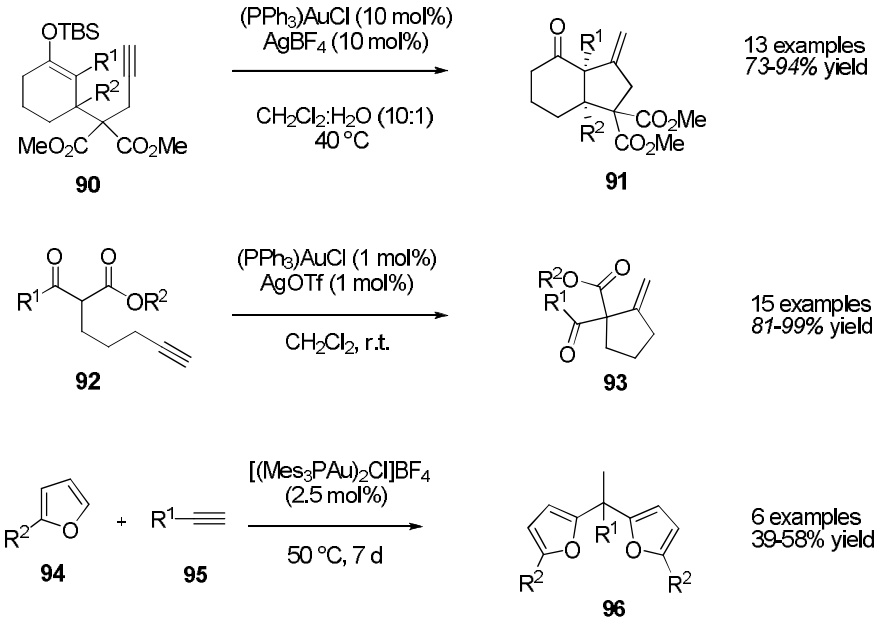
Scheme 22

Among sulphur-nucleophiles, acetylenic thioethers **88** react cleanly forming 2,3-substituted benzothiophnes **89** with excellent yields [75] (Scheme 23). Other thiols have been used in the hydrothiolation of conjugated olefins [76] as well as in the cycloisomerization of α-thioallenes [77] which will be discussed further in Chapter 2.



Scheme 23

Besides heteroatom nucleophiles, there are a plethora of examples of different carbon nucleophiles which react with gold-activated alkynes (Scheme 24). Enol ethers **90** react with alkynes to form bicyclic compounds **91** [78]. Different β-ketoester–nucleophiles **92** also work well in similar reactions [79]. Gold catalysts also perform well in Friedel-Crafs–type chemistry where different aromatic species, such as substituted furans **94**, react with gold-activated alkynes **95** or other π-systems [80], although this reaction can have problems of selectivity as in some cases double-addition occur (as in Scheme 24).

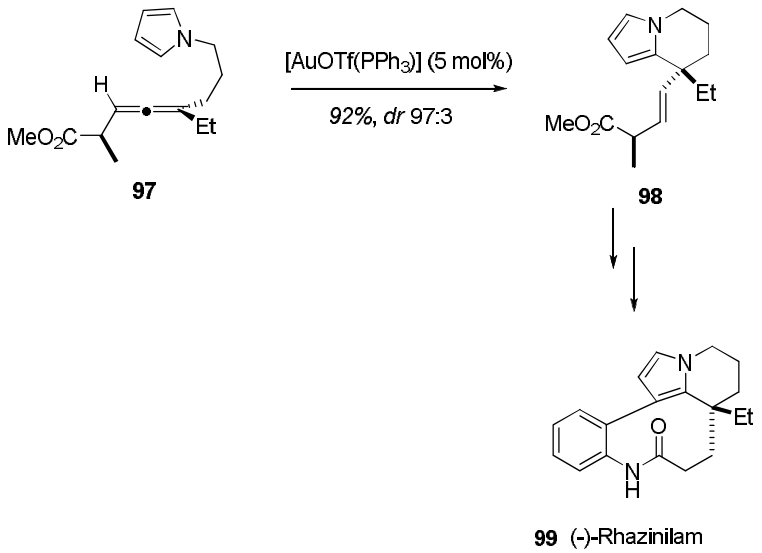


Scheme 24

The examples above are only representative examples from the recent literature and simple reactions were deliberately selected. There are also many tandem reactions that often have several nucleophiles present in the reaction mixture [61]. The development of asymmetric gold-catalyzed reactions has thrived in recent years and new chiral gold-ligand -complexes are being developed and tested in catalysis more and more [81]. This area of gold catalysis has been intentionally excluded from this introduction as there are no examples of reactions of this type in this thesis.

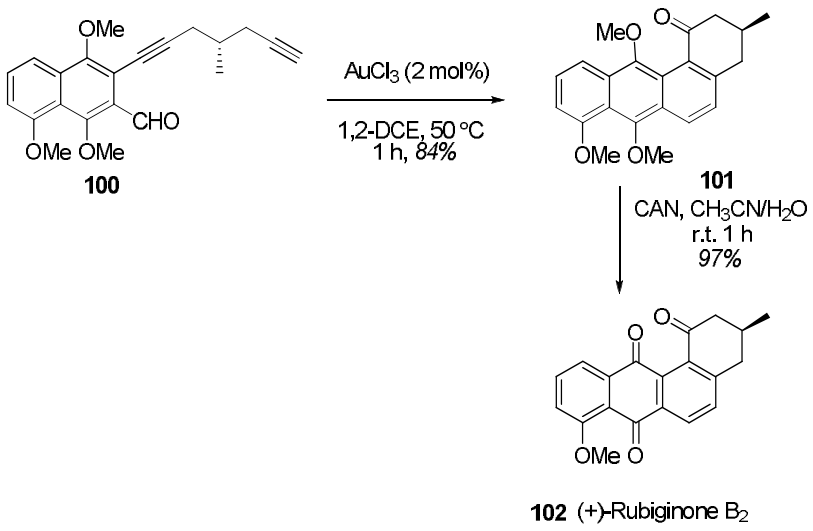
Gold-catalyzed reactions allow simple starting materials to be turned into complex products under mild conditions and thence have found their applications also in natural product synthesis. The synthesis of (-)-rhazinilam **99** was reported by Nelson in 2006 [82]. One of the

key steps in the total synthesis was a gold-catalyzed intramolecular hydroarylation of allene **97** with the pyrrole ring (Scheme 25).



Scheme 25

Another example of the use of gold catalysts in the total synthesis of bioactive natural products is the synthesis of (+)-Rubiginone B_2 **102**, which belongs to the family of angucyclinone antibiotics [83]. The key step in the total synthesis of (+)-Rubiginone B_2 was a gold-catalyzed [4+2] benzannulation forming two rings of the product in one step (Scheme 26).



Scheme 26

1.3 Aims of the thesis

As described in the introduction, allenic compounds are of interest to organic chemist due to the challenges presented by their synthesis but also for their ability to act as versatile building blocks in organic synthesis. The aim of this thesis was to study both the synthesis and usability of some allenic compounds with following projects:

1. Development of gold/enzyme –catalyzed transformations of α-allenic acetates.

Before this thesis work there has been no examples in the literature of gold catalysis working in one-pot manner with a lipase. The possibility for this kind of reactivity is tested to prove that such reaction can exist. There would be several applications for a synthetic method where gold catalysis can be combined with chiral induction from a lipase.

2. Development of new methodologies towards the synthesis of allenyl carboxylates.

Allenyl acetates are a group of compounds not widely present in the chemical literature and there are limited ways to access these compounds. New methods to access allenyl acetates will be studied as there are a number of compounds that cannot be accessed by the literature methods. Allenyl acetates are highly reactive compounds and can prove to have interesting properties as substrates in cyclization –or transition metal-catalyzed reactions.

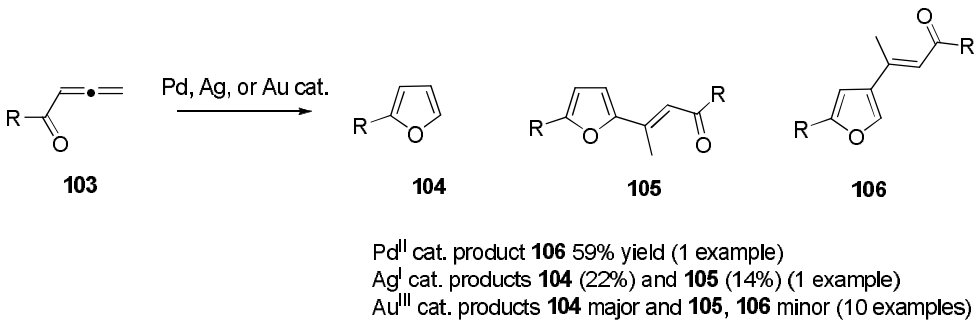
3. The reactivity of allenyl acetates will be tested in the presence of gold catalysts.

Allenyl acetates are studied as starting materials for the synthesis of indenes. The reactivity of allenyl acetates synthesized in this thesis work will be compared to that of propargylic acetates.

2 Tandem enzyme/gold –catalysis; from racemic α-allenic acetates to enantiomerically enriched 2,5-dihydrofurans in one pot

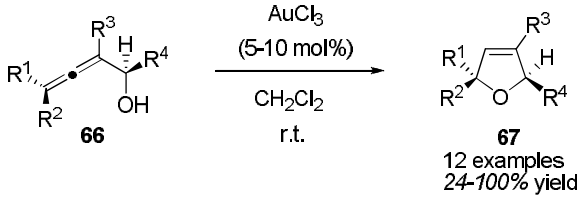
2.1 Background and introduction

Allenes carrying a heteroatom in the α- or β-position are likely to undergo cyclization to heterocycles in the presence of a gold catalyst. This type of reaction has been studied extensively over the past decade. The first examples of this type of reactivity were reported by Marshall in 1992 using a silver catalyst and in 2000 Hashmi tested gold catalysts in a similar reaction [84]. They accomplished the cycloisomerization of α-allenyl ketone **103** to substituted furans **104** (Scheme 27). This reaction also yielded two different dimeric products **105** and **106** but subsequently the reaction was optimized by Che to yield only furans **104** [85]. Other groups have also contributed to the expanding scope of this reaction [86].



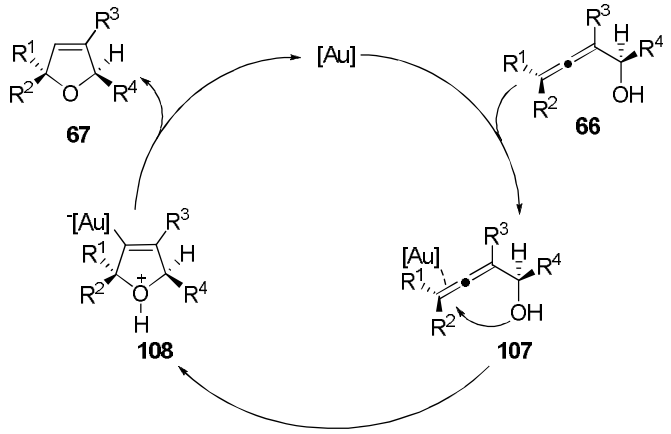
Scheme 27: Cycloisomerization of α-allenyl ketone by Hashmi [84].

The synthesis of furans has a drawback in that the product is achiral. This reduces the potential applications of the reaction in natural product synthesis. In 2001 Krause reported a synthesis of 2,5-dihydrofurans **67** starting from α-hydroxyallenes **66** [64][87]. Earlier similar reactions had been catalyzed by HCl gas in chloroform [88], by Amberlyst resins [89] or silver catalysts [90]. The acid-catalyzed methods have limitations in their scope as some substrates are acid-labile and undergo elimination reactions. Gold catalysts are mild electrophiles which removes the possibility of elimination reactions and allows these reactions to be performed at room temperature. The cycloisomerization of α-hydroxyallenes **66** (Scheme 28) in presence of a $AuCl_3$ furnishes tri-and tetrasubstituted dihydrofurans **67** with complete axis-to-center chirality transfer (the chirality is transferred from the axis of the allene to a new chiral center in the product) in case of alkyl- and alkenyl-substituted α-hydroxyallenes.



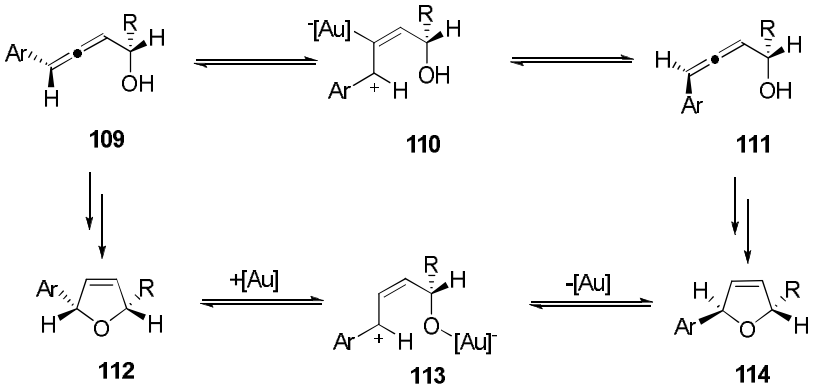
Scheme 28

Coordination of the carbophilic gold catalyst to the allenic double bond affords π-complex **107**, which undergoes 5-*endo*-cyclization to the zwitterionic σ-gold species. Protodeauration leads to the dihydrofurans **67** and regenerates the gold catalyst. As the gold catalyst does not epimerize the allenic bond the reaction normally proceeds with full stereocontrol (Scheme 29).



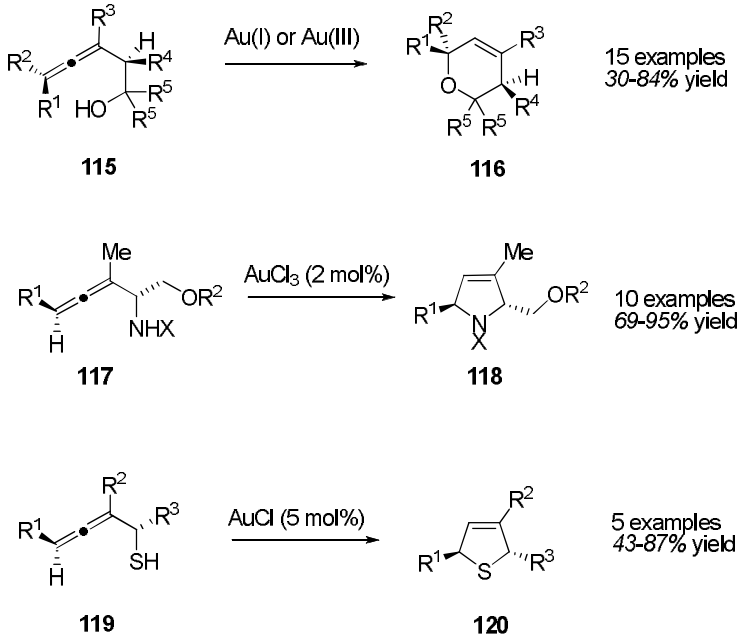
Scheme 29

However, when the allene carries a phenyl or electron-rich aromatic substituent, the allene **109** or product 2,5-dihydrofuran **112** can epimerize in the course of the reaction (Scheme 30) [91]. The epimerization probably proceeds via a benzylic cation intermediate **110** or **113**. This can be prevented by using additives in the reaction or using a coordinating solvent such as THF, or lowering the reaction temperature to –30 °C. The cycloisomerization of α-hydroxyallenes has been optimized further so that only 0.05 mol% of the catalyst is actually necessary for full conversions [92].



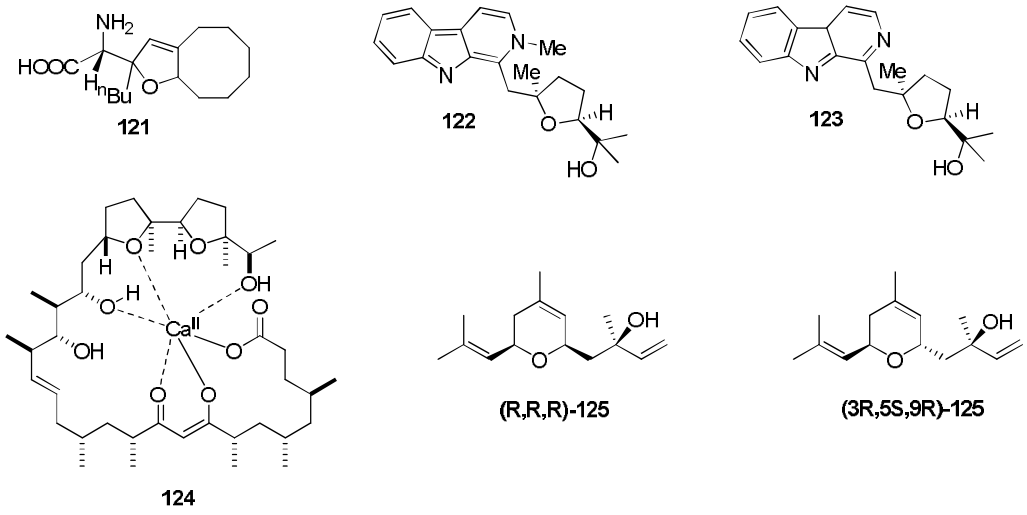
Scheme 30

Similar methodology has been developed for various allenic moieties carrying a heteroatom at the α- or β-position (Scheme 31). β-Hydroxyallenes **115** undergo *6-endo*-cyclization under gold-catalyzed conditions giving dihydropyrans **116** as products [93]. This reaction is slow without additives but in the presence of NIS the reaction speeds up tremendously [94]. This effect is probably caused by a very rapid iododeauration of a σ-gold intermediate by NIS. Aminoallenes **117** give pyrrolines **118** under similar reaction conditions [95]. Even thioallenes **119** give 2,5-dihydrothiophenes **120** in the presence of a gold catalyst [77][96] although sulfides are known to coordinate strongly to gold this does not apparently inhibit the reaction [97].



Scheme 31

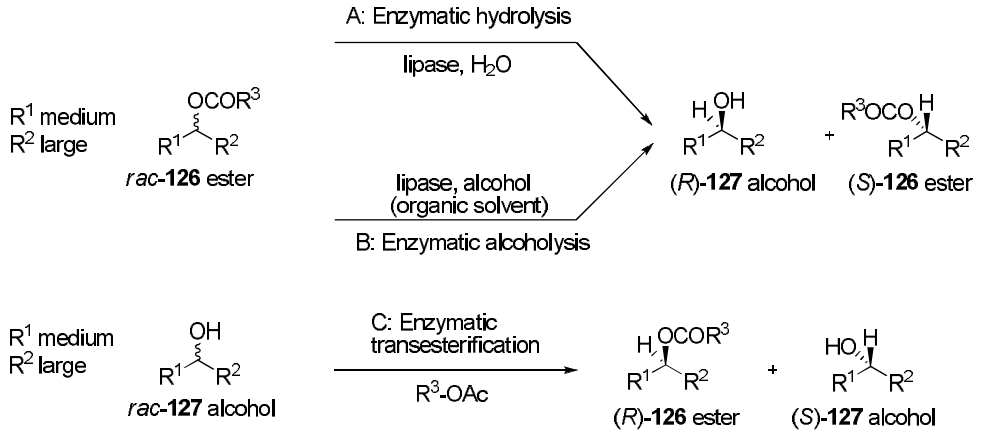
The tendency of allenes with heteroatoms in the α- or β-position to undergo cycloisomerizations with axis-to-center chirality transfer in the presence of gold catalysts has been extensively used in the synthesis of natural products (Scheme 32). The cycloisomerization of α-hydroxyallenes has been used in the synthesis of furanomycin derivatives **121** [98], in the total synthesis of (-)-isocyclocapitelline **123** and (-)-isochrysotricine **122** [92] as well as in the synthesis of ionomycin calcium complex **124** [99]. Cycloisomerization of β-hydroxyallenes to dihydropyrans has been exploited in the synthesis of (*R*,*R*,*R*)- and (*3R*,*5S*,*9R*)-bejarols **125** [100].



Scheme 32

2.1.1 Lipase-catalyzed kinetic resolution

Lipase-catalyzed kinetic resolution is an efficient tool to access chiral secondary esters and alcohols. When a secondary ester **126** has two substituents R^1 and R^2, of which R^1 is medium sized or small and R^2 is large, an appropriate lipase can hydrolyze only the (*R*) -enantiomer of this ester (Route A, Scheme 33). The same happens in the esterification of a secondary alcohol: the (*R*) -enantiomer of the alcohol reacts whilst the (*S*) -enantiomer remains unchanged (Route C, Scheme 33) [101].



Scheme 33

The selectivity of a certain lipase towards the reactive enantiomer of the substrate is described by the selectivity factor. When a racemic starting material (enantiomers *R* and *S*) reacts with chiral catalyst *B** the products *R'* and *S'* form with reaction rates k_R and k_S (Equation 1).

Equation 1

$$R \overset{B*}{\rightarrow} R'$$

$$S \overset{B*}{\rightarrow} S'$$

The selectivity factor *S* can be derived from the ratio of the two reaction rates k_R and k_S. When the reaction rates are presented as functions of *ee* and conversion (*C*), the selectivity factor can be derived as in Equation 2, which is relatively easy to calculate as the *ee* and conversion can be obtained from experimental data (such as GC or HPLC data). The calculation of the selectivity factor was proposed by Kagan and Fiaud in 1988 [102].

Equation 2

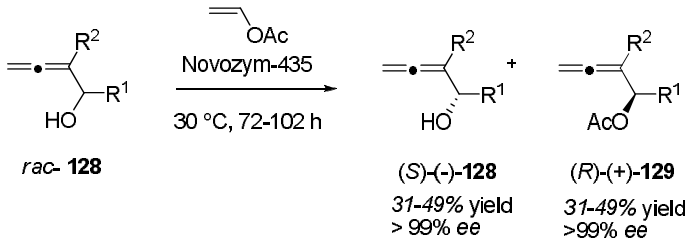
$$S = \frac{kR}{kS} = \frac{\ln[1 - C(1 + ee')]}{\ln[1 - C(1 - ee')]}$$

In Equation 2, *ee'* is the enantiomeric excess of the product and this is calculated by Equation 3.

Equation 3

$$ee' = \frac{([R'] - [S'])}{([R'] + [S'])}$$

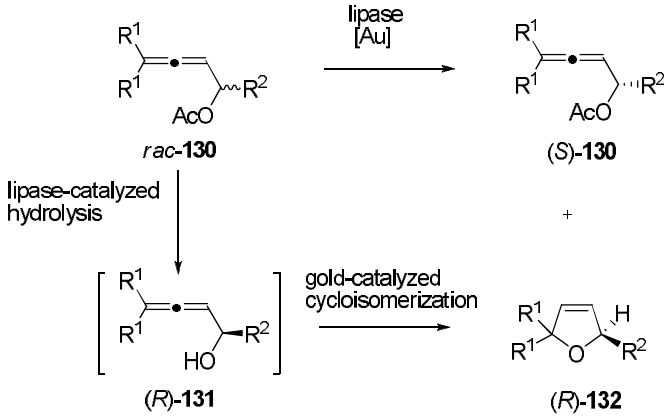
α-Hydroxyallenes are desirable starting materials in organic synthesis. This group of organic compounds is also special for the reason that they can have axial chirality, as well as a chiral center next to the allenic moiety. Ma reported the kinetic resolution of α-hydroxyallenes **128** with Lipase B from *Candida Antarctica* (Novozym-435) [103]. They presented twelve examples of this reaction with very high yields and *ee* values (Scheme 34).



Scheme 34

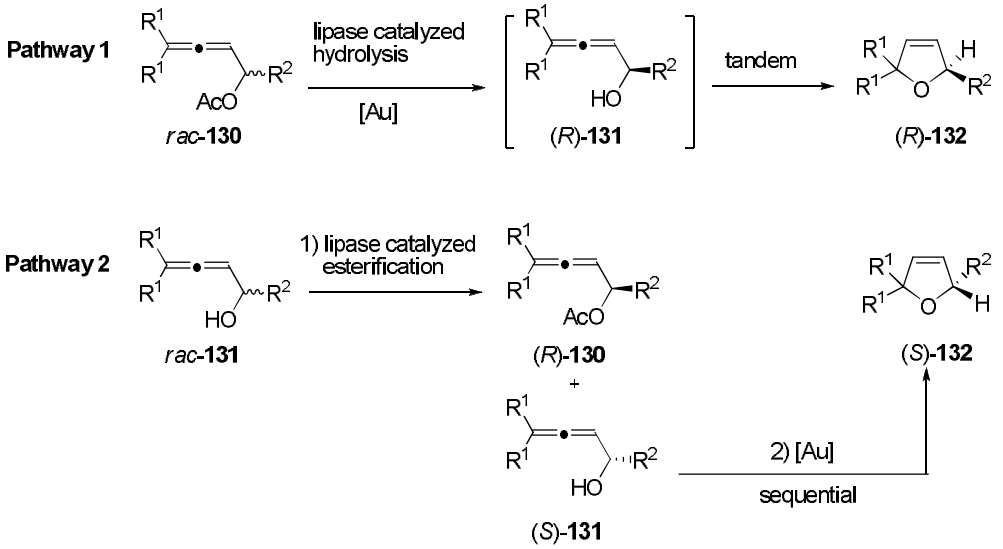
2.2 Enzyme/gold-catalyzed tandem reactions

The objective of this project was to develop a reaction that combines enzymatic kinetic resolution and gold-catalyzed cycloisomerization in one pot (Scheme 35). In the ideal case, racemic α-allenic acetate **130** can be resolved with a lipase to form α-hydroxyallene (*R*)-**131** with high enantiomeric excess. The forming α-hydroxyallene (*R*)-**131** could be cyclized in the same reaction pot in the presence of a gold catalyst to form 2,5-dihydrofuran (*R*)-**132**. The methodology would permit the transformation of racemic α-allenic acetate **130** to enantiomerically enriched 2,5-dihydrofuran (*R*)-**132** in one pot.



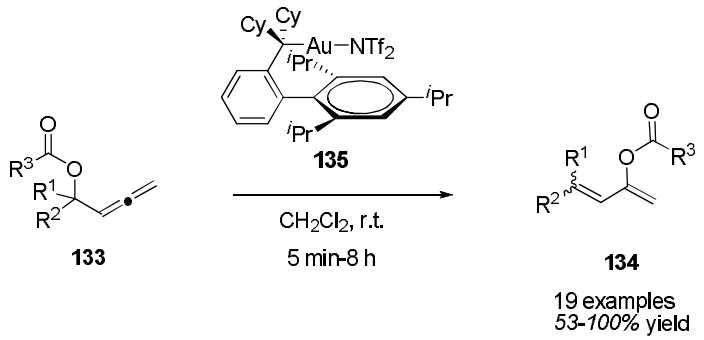
Scheme 35

There are two approaches to this methodology: (i) a method with simultaneous addition of the enzyme and gold precatalyst; both are added to the reaction mixture in the beginning of the reaction (Scheme 36, pathway 1). For this method to work the reaction must be started with the allenic acetate *rac*-**130** which is hydrolyzed in the course of the reaction to yield enantioenriched alcohol (*R*)-**131** which will directly react to the corresponding 2,5-dihydrofuran (*R*)-**132**. (ii) A 'first lipase then gold catalyst' sequence where the gold catalyst is added only when half of the starting material has reacted (Scheme 36, pathway 2). If this method is used, the reaction can also start with racemic α-hydroxyallene *rac*-**131**.



Scheme 36

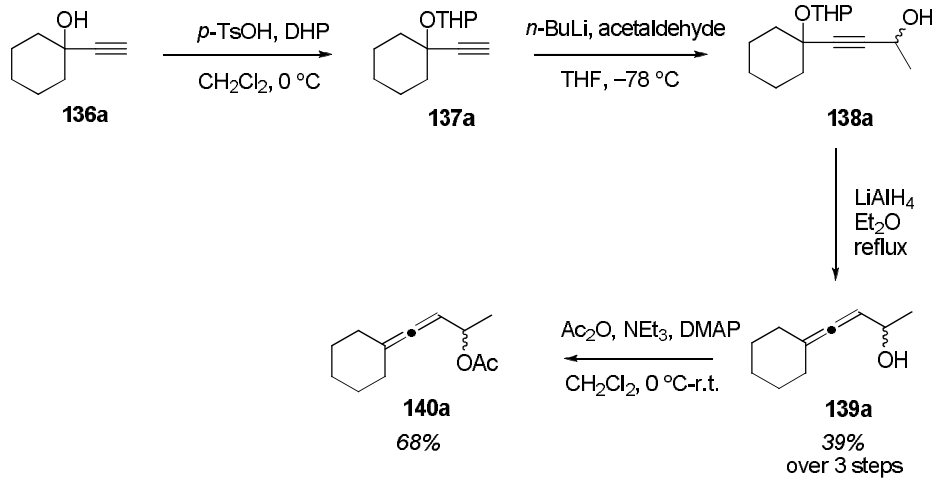
There is an additional competing reaction with α-allenic esters in the presence of a gold catalyst (Scheme 37). Gagosz and co-workers reported in 2007 an isomerization reaction of α-allenic esters **133** to 1,3-butadien-2-ol esters **134** [104]. With selected gold catalyst **135** the reaction proceeds to completion within five minutes with substrates **133** with unsaturated R^1 and R^2 substituents. A similar rearrangement has also been reported for allylic acetates [105].



Scheme 37

2.2.1 Synthesis of racemic α-allenic acetates

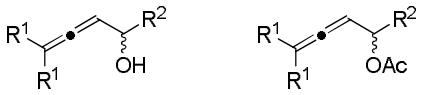
The practical work was started by synthesizing several racemic α-allenic acetates. The synthesis of racemic α-allenic acetate **140a** was started from propargylic alcohol **136a** (Scheme 38). The alcohol was first protected as the tetrahydropyranyl ether to give **137a**. Deprotonation of the terminal alkyne followed by the addition of acetaldehyde gave propargylic alcohol **138a**. Compound **138a** was then subjected to $LiAlH_4$ reduction giving the S_N2' nucleophilic substitution product **139a**. This three-step reaction route gives racemic α-hydroxyallenes **139** in moderate to high yields (30-76%). This route is convenient as intermediates **137** and **138** do not need to be purified. Alcohol **139a** is then esterified to α-allenic ester **140a**.



Scheme 38

Nine different α-allenic acetates were prepared by varying the size of R^1 and R^2 groups. All these substrates carry a chiral center α to the acetate group and have no axial chirality (Table 1).

Table 1.



rac-**139 a-i** *rac*-**140 a-i**

139/140	R^1	R^2	Yield (%)[a] **139** (over 3 steps)	Yield (%)[a] **140**
a	$(CH_2)_5$	Me	39	68
b	$(CH_2)_5$	*n*-Pr	50	80
c	Me	Me	60	68
d	Me	*n*-Pr	38	50
e	Me	*n*-Oct	76	92
f	Me	*c*-Hex	61	85
g	$(CH_2)_5$	*c*-Hex	58	86
h	$(CH_2)_4$	*n*-Pr	60	81
i	$(CH_2)_5$	$(CH_2)_2Ph$	50	83

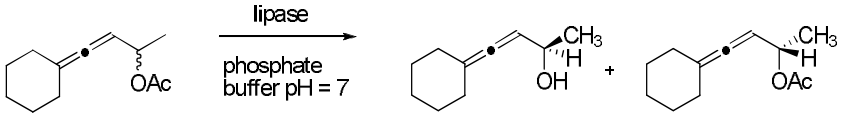
a) Isolated yield.

2.2.2 Optimization of lipase-catalyzed kinetic resolution

Screening of lipases for the kinetic resolution was undertaken by hydrolyzing ester **140a** in phosphate buffer. The nine lipases in Table 2 are from a lipase basic kit from Sigma Aldrich and were used as received. Conversion and *ee* of the hydrolysis was followed with gas

chromatography using a chiral column FS-Lipodex-G *octakis*(2,3-di-*O*-pentyl-6-*O*-methyl)-γ-cyclodextrin which separates the product alcohol **139a** to its two enantiomers. Unfortunately, ester **140a** is not separated with this gas chromatography column. All of the lipases in Table 2 were selective toward the same enantiomer of the product alcohol. As no internal standard was used in these reactions, the GC yield given might have an error or some percentage. This can be seen in entry d as the yield is too high for the high enantiomeric excess.

Table 2. Lipase screening for **140a**



rac-**140a** (*R*)-**139a** (*S*)-**140a**

Entry	Lipase	Reaction time (h)	GC yield (%)[a] **139a**	*ee* (%) (*R*)-**139a**
a	Lipase from *Aspergillus*	16	9	18
b	Lipase from *Candida antarctica*	16	54	40
c	Lipase from *Candida cylindracea*	16	99	-
d	Lipase from *Mucor miehei*	16	38	95
		23	57	94
e	Lipase from *Pseudomonas cepacia*	16	31	94
		23	35	94
f	Lipase from *Pseudomonas fluorecens*	16	27	99
		23	34	93
g	Lipase from *Rhizopus arrhizus*	16	6	-
h	Lipase from *Rhizopus niveus*	16	-	-
i	Lipase from *Hog pancreas*	16	15	50

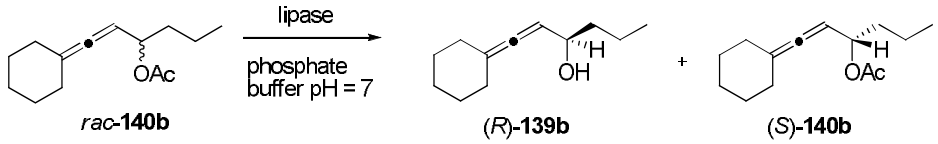
a) GC yield. *Reaction conditions*: Acetate **140a** (5 mg) was stirred vigorously in phosphate buffer (1 ml) and enzyme (5 mg) was added. Aliquots of the reaction mixtures were extracted with Et_2O and the organic layer was used in gas chromatography analysis.

With acetate **140a** three lipases gave >90% enantioselectivities and usable conversions to alcohol **139a** (entries d, e and f). Next the three most promising lipases: lipases from *Mucor miehei*, *Pseudomonas cepacia* and *Pseudomonas fluorecens* were studied further with other substrates.

With **140b**, the lipase from *Mucor miehei*, that had been the most active catalyst with **140a** was now completely inactive (Table 3, entry a). The seemingly small two-carbon change in the R^2 sidechain was enough to inactivate the enzyme. With lipases from *Pseudomonas cepacia* and

Pseudomonas fluorecens the hydrolysis was considerably slower as compared to **140a**; 40 hour reaction time was needed for 8-11% conversion (entries b and c).

Table 3. Lipase screening for **41b**



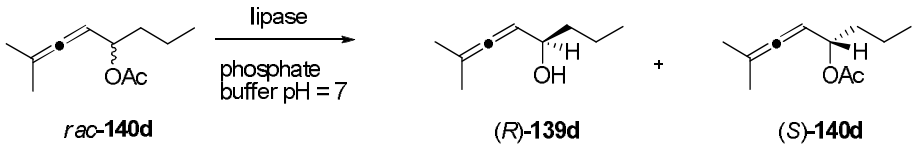
rac-**140b** (*R*)-**139b** (*S*)-**140b**

Entry	Lipase	Reaction time (h)	GC yield (%)[a] (*R*)-**139b**	*ee* (%) (*R*)-**139b**
a	Lipase from *Mucor miehei*	40	-	-
b	Lipase from *Pseudomonas cepacia*	40	11	86
c	Lipase from *Pseudomonas fluorecens*	40	8	92

a) GC yield. *Reaction conditions*: Acetate **140b** (5 mg) was stirred vigorously in phosphate buffer (1 ml) and enzyme (5 mg) was added.

One more substrate, **140d**, was screened with the three lipases to see how the size of R^1 affects the activity of the enzyme. As expected with similar propyl-chain as with **140b**, the lipase from *Mucor miehei* gave again very low conversion (Table 4 entry a). The lipase from *Pseudomonas fluorecens* only gave 8% conversion for the alcohol **139d**. However, with 40 hour reaction time the lipase from *Pseudomonas cepacia* gave 40% conversion with very high *ee* (97%) to the alcohol **139d** (Table 4 entry b).

Table 4. Lipase screening for **140d**



rac-**140d** (*R*)-**139d** (*S*)-**140d**

Entry	Lipase	Reaction time (h)	GC yield (%)[a] (*R*)-**139d**	*ee* (%) (*R*)-**139d**
a	Lipase from *Mucor miehei*	40	3	-
b	Lipase from *Pseudomonas cepacia*	40	40	97
c	Lipase from *Pseudomonas fluorecens*	40	8	92

a) GC yield. *Reaction conditions*: Acetate **140d** (5 mg) was stirred vigorously in phosphate buffer (1 ml) and enzyme (5 mg) was added.

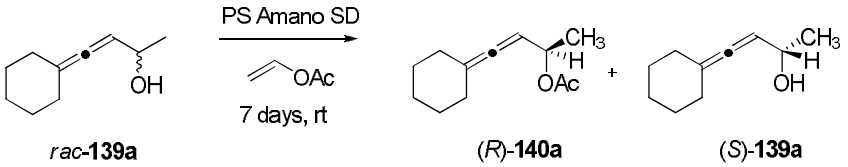
From the initial screening (Tables 2-4) two lipases, *Pseudomonas cepacia* and *Pseudomonas fluorecens* were chosen for further study. Although the initial screening was carried out with lipases from Sigma Aldrich the following reactions were carried out with lipases produced by Amano Enzymes [106]. Lipases used will be named according to their Amano product names: AK Amano (lipase from *Pseudomonas fluorecens*) and PS Amano SD (lipase from *Burcholderia cepacia*). Although the lipases from *Burcholderia cepacia* and *Pseudomonas cepacia* are named differently, they stem from the same biological source and thus have similar selectivities [107].

2.2.2.1 Attempts on alcoholysis and esterification

The alcoholysis of **140a** with lipases AK Amano and PS Amano SD was tried. However, although the reaction works well in water it did not work when alcohol was used as a solvent. Several different alcohol-organic solvent mixtures were tested as well as alcohol/water-ionic liquid mixtures, but the conversions maximized at 7% of alcohol **139a** after one week reaction time [108].

The esterification of alcohol **139a** was attempted with lipase PS Amano SD. Esterification with vinyl acetate as solvent gave the desired (*R*)-acetate **140a** as product but the reaction was very slow. The enantioselectivity was not as good as with the hydrolysis. When 57% of the alcohol has reacted to the corresponding acetate **140a**, the *ee* of the remaining alcohol **139a** was only 85%. This reaction pathway was not studied further.

Table 5. Esterification of **139a** with PS Amano SD and vinyl acetate



rac-**139a** (*R*)-**140a** (*S*)-**139a**

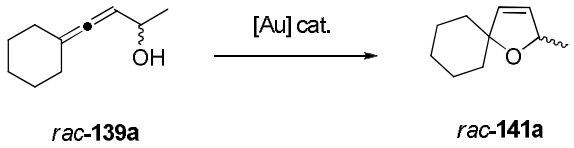
Sample	Time	GC yield (%)[a] (*R*)-**140a**	*ee* (%) (*S*)-**139a**
a	1 h	4	-
b	4 h	6	-
c	23 h	24	-
d	2 days	35	37
e	7 days	57	85

a) GC yield. To *rac*-**139** (5 mg) in 0.25 ml of vinyl acetate was added lipase PS Amano SD with vigorous stirring. Samples for GC analysis were diluted with Et_2O and filtrated through Celite.

2.2.3 Synthesis of racemic 2,5-dihydrofurans

To be able follow the tandem-reactions with gas chromatography a racemic sample of each cycloisomerization product was needed as a reference. The synthesis of racemic 2,5-dihydrofurans **141** was optimized with α-hydroxyallene **139a** (Table 6).

Table 6.



rac-**139a** *rac*-**141a**

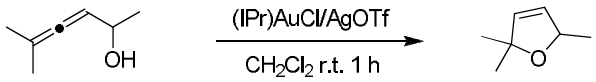
Entry	Catalyst	Cat. (mol%)	Solvent	Time	Yield (%)[a] **141a**
a	$HAuCl_4$	5	H_2O:THF (100:1)	1 h	46
b	$NaAuCl_4$	5	H_2O:THF (100:1)	45 min	54
c	$AuCl_3$	3	CH_2Cl_2	28 h	63
d	$AuBr_3$	3	CH_2Cl_2	17 h	54
e	$AuBr_3$	2	[bmim][PF_6]	48 h	39
f	(IPr)AuCl/AgOTf	5	CH_2Cl_2	1 h	95
g	(PPh_3)AuCl/AgOTf	5	CH_2Cl_2	24 h	60

a) Isolated yield.

The reactions in Table 6 were run until the starting material had disappeared. However, the reaction did not yield the desired product selectively in every case. The most efficient catalyst for the cycloisomerization was a gold(I)-carbene complex Au(IPr)Cl with silver(I)-triflate as

co-catalyst. Within one hour reaction time this catalyst system yielded 2,5-dihydrofuran **141a** with a 95% isolated yield (Table 6, entry f). Reference compounds **141a-j** (Table 7) were all prepared with this methodology. The starting material for **141j** had been prepared by another group member [109]. Compound **141c** was too volatile to be fully analyzed but on TLC the reaction went to full conversion.

Table 7.



139 **141**

141	R^1	R^2	Yield (%)[a] **141**
a	$(CH_2)_5$	Me	95
b	$(CH_2)_5$	*n*-Pr	47
c	Me	Me	100[b]
d	Me	*n*-Pr	100[b]
e	Me	*n*-Oct	98
f	Me	*c*-Hex	96
g	$(CH_2)_5$	*c*-Hex	98
h	$(CH_2)_4$	*n*-Pr	90
i	$(CH_2)_5$	$(CH_2)_2Ph$	67
j	$(CH_2)_5$	*i*-Bu	87

a) Isolated yield, b) Full conversion on TLC but the product was too volatile to isolate with reproducible yields.

2.2.4 Optimization of the tandem reaction

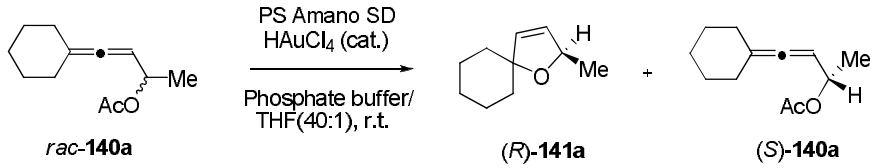
As the lipase catalyzed kinetic resolution gave promising results in aqueous solutions (Tables 2-4) and some reactivity towards the 2,5-dihydrofuran product was obtained with water-soluble gold catalysts (Table 6, entries a and b), it was decided at this point that some initial tests with the tandem catalysis should be carried out. It was decided that the simultaneous addition of gold- and lipase catalysts was most interesting to try first.

Optimization of the tandem reaction was carried out with substrates **140a** and **140b**. Initially, the two lipases PS Amano SD and AK Amano were used in the optimization but PS Amano SD showed higher selectivity towards the substrates **140a** and **140b**. In Table 6 there are two gold catalysts that are water soluble. These are the chloroauric derivatives $HAuCl_4$ and $NaAuCl_4$. In Table 6 these catalysts did not give very high yields of the cycloisomerization

product. However, they could be used in aqueous solution and it was easy to prepare stock solutions of these water-soluble catalysts. From the two catalysts chloroauric acid $HAuCl_4$ gave slightly higher conversions to **141a** in the first tandem reaction attempts so this catalyst was chosen for further optimization. Tetrahydrofuran was used as co-solvent as it improves the solubility of the substrate to the aqueous reaction mixture.

In the presence of 10 mg of the lipase (with 10 mg of starting material **140a**) and 1 mol% $HAuCl_4$, substrate **140a** afforded 2,5-dihydrofuran **141a** with high enantiomeric excess (>90%) but only <30% conversion after 48 hours at room temperature (Table 8, entry a). Increasing the temperature to +50 °C gave a similar result after 24 hours but some unidentified byproducts also formed in the reaction mixture (entry b). When the amount of lipase was increased to 100 mg, conversion to **141a** reached 50% but the stereoselectivity suffered (entry c). No reaction at all took place when 10 mol% of gold catalyst was used (entry d) which means that the ratio of enzyme to gold precatalyst strongly affects the conversion of the acetate **140a** to alcohol **139a**.

Table 8. Effect of the amount of gold catalyst and temperature for conversion to **141a**



rac-**140a** (*R*)-**141a** (*S*)-**140a**

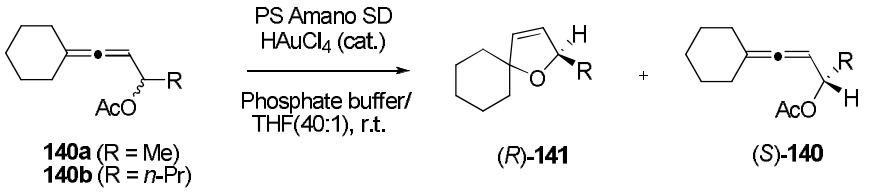
Entry	Lipase (mg)	$HAuCl_4$ (mol%)	t (h)	GC yield (%)[a] (*R*)-**141a**	*ee* (%) (*R*)-**141a**
a	10	1	48	25-30	90-95
b	10	1	24 [b]	25-30	90-95
c	100	1	24	45-50	55-60
d	10	10	24	0	-

a) GC yield b) Reaction temperature: +50 °C. Reaction conditions: **140a** (10 mg) in 2 mL of phosphate buffer (pH 7) and 50 μL of THF was treated with PS Amano SD (30000 U) and aqueous $HAuCl_4$ solution at room temperature.

As the reactions in Table 8 were tested several times, the reaction did not always yield exactly the same GC yield and *ee* for the product **141a**. This is the reason for the percentage unit difference given in Table 8 for the results (for example entry a GC yield 25-30%). For the next reactions the amount of gold precatalyst was decreased to 0.5 mol% and these reaction conditions were tested with different amounts of the enzyme. With 10 mg of lipase (Table 9, entry a) a high *ee* of 96% was obtained for **141a** but only at 27% conversion. Larger amounts

of the lipase (entries b and c) resulted to higher conversions but lower *ee* values of **141a**. However, this was not observed for the slightly bulkier propyl-substituted **140b** which gave high conversion 45% with 94% *ee* to the 2,5-dihydrofuran **141b** (entry d).

Table 9. Optimizing the amount of lipase for **140a** and **140b**



140a (R = Me)
140b (R = *n*-Pr)

(*R*)-**141**

(*S*)-**140**

Entry	**140**	Lipase (mg)	$HAuCl_4$ (mol%)	Time (h)	GC yield (%)[a] (*R*)-**141**	*ee* (%) (*R*)-**141**
a	**140a**	10	0.5	24	27	96
b	**140a**	50	0.5	48	35	87
c	**140a**	100	0.5	48	46	63
d	**140b**	100	0.5	48	45	94

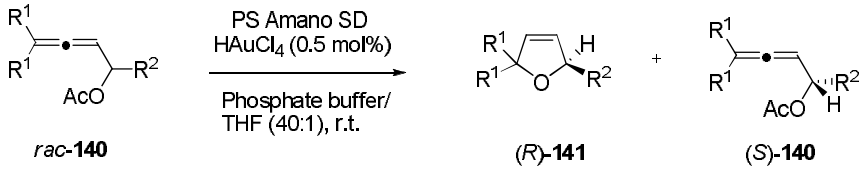
a) GC yield. Reaction conditions: **140** (10 mg) in 2 mL of phosphate buffer (pH 7) and 50 µL of THF was treated with PS Amano SD (30000 U) and aqueous $HAuCl_4$ solution at room temperature.

2.2.5 Scope and limitations of the tandem reaction

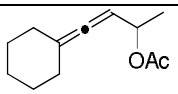
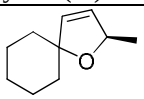
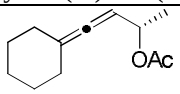
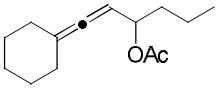
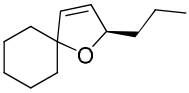
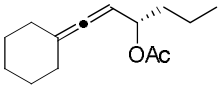
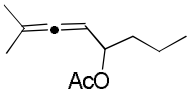
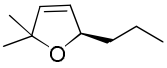
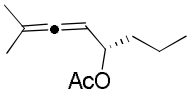
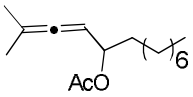
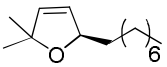
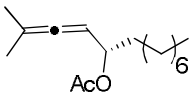
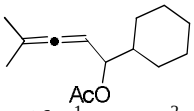
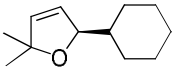
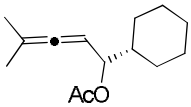
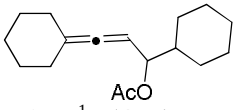
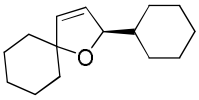
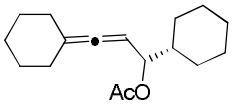
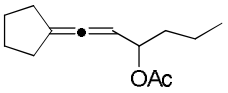
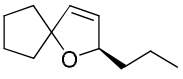
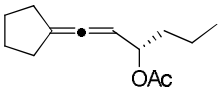
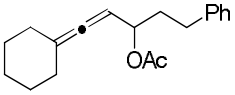
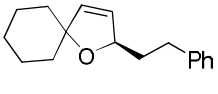
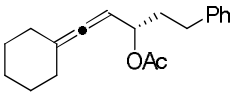
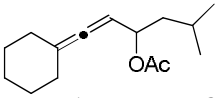
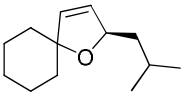
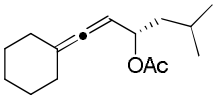
Having discovered that the enzyme and gold precatalyst do not compromise each other as long as the amount of gold catalyst is kept low, the tandem reaction was tested with α-allenic acetates **140a-j** (Table 10). The reaction works well with substrates that have straight alkyl chains as R^2 (entries 1, 2, 3, 4 and 7). However when R^2 is branched either at the α or β carbon, the reaction gives very low, or no conversion at all. A phenyl substituent further away from the ester (entry 8) gives low, 4% conversion of **141i**. If the branching is closer to the acetate, such as a cyclohexyl group (entries 5 and 6) or an *i*-butyl (entry 9), no reaction occurs. The lipase is very sensitive to any steric hindrance in R^2.

The reaction is more tolerant towards R^1 substituents, both five- and six-membered rings are well tolerated as in **140a**, **140b** and **140h** which all give good *ee* values, 88-95%, and yields to **141** (entries 1, 2 and 7). Acyclic R^1 groups are also well tolerated as seen with **140d** and **140e** and these substrates give the highest enantioselectivities, up to 99%, for **141** (entries 3 and 4).

Table 10.

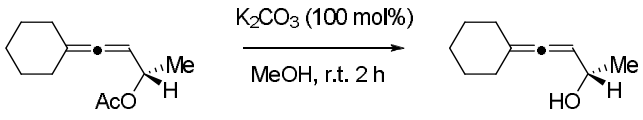


rac-**140** (*R*)-**141** (*S*)-**140**

Entry	*rac*-**140**	(*R*)-**141** yield (%) / *ee* (%)	(*S*)-**140** yield (%) / *ee* (%)
1			
	140a R^1= $(CH_2)_5$, R^2= Me	**141a** yield 28%[a] *ee* 86%	**140a** yield 31%[a] *ee* 93%
2			
	140b R^1= $(CH_2)_5$, R^2= *n*Pr	**141b** yield 45%[a] *ee* 95%	**140b** yield 40%[a] *ee* >95%
3			
	140d R^1= Me, R^2= *n*-Pr	**141d** yield 46%[b] *ee* 99%	**140d** yield - *ee* -
4			
	140e R^1= Me, R^2= *n*-Oct	**141e** yield 50%[a] *ee* 98%	**140e** yield 36%[a] *ee* 95%
5			
	140f R^1= Me, R^2= *c*-Hex	*no reaction*	*no reaction*
6			
	140g R^1= $(CH_2)_5$, R^2= *c*-Hex	*no reaction*	*no reaction*
7			
	140h R^1= $(CH_2)_4$, R^2= *n*-Pr	**141h** yield 38%[a] *ee* 88%	**140h** yield 33%[a] *ee* >95%
8			
	140i R^1= $(CH_2)_5$ R^2= $(CH_2)_2$Ph	**141i** yield 4%[b] ee -	**140i** yield - ee -
9			
	140j R^1= $(CH_2)_5$, R^2= *i*-Bu	*no reaction*	*no reaction*

a) isolated yield b) GC conversion
Reaction conditions for test reaction: **140** (10 mg) in 2 mL of phosphate buffer (pH 7) and 50 µL of THF was treated with PS Amano SD (30000 U) and aqueous $HAuCl_4$ solution (0.5 mol%) at room temperature for 24-48h.
Reaction conditions for isolated yield: **140** (0.5 mmol) in 15 mL of phosphate buffer (pH 7) and 0.1 mL of THF was treated with PS Amano SD (30000 U) and aqueous $HAuCl_4$ solution (0.5 mol%) at room temperature for 48 h.

The *ee* of the remaining acetate (*S*)-**140** was determined in each case by hydrolyzing the acetate **140** in methanol with potassium carbonate and analyzing the product (*S*)-alcohol **139** with gas chromatography (Scheme 39).



(*S*)-**140a** (*S*)-**139a**

Scheme 39

Some of the spirocyclic products **141** had interesting odour-properties as many of them had distinctive and strong sweetish smells. This behavior is known for spirocyclic ethers which are used in perfume industry and the property is likely to stem from the osmophoric oxygen atom in the 2,5-dihydrofuran ring [110].

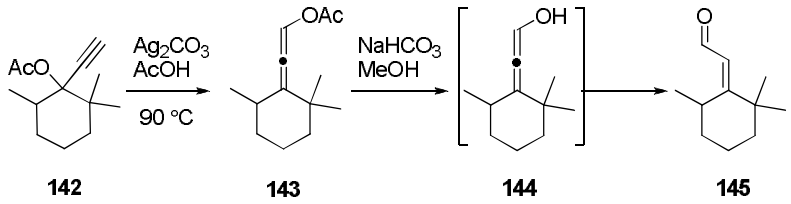
2.2.6 Summary

This project was the first example of an enzyme/gold-catalyzed tandem reaction. Some of this work was published in 2009 [111]. It was shown that the two catalysts tolerate each other well. The reaction works well for a set of racemic α-allenic esters yielding the enantiomerically enriched (*R*)-2,5-dihydofurans **141** with 28-50% yield and 86-99% *ee* and the remaining enantiomerically enriched (*S*)-acetates **140** with 31-40% yield and 93-95% *ee*. However, the drawback is that the lipase used, PS Amano SD, is highly sensitive to any steric hindrance on the racemic acetate and this sets limitations to the scope of the reaction.

3 S_N2' approach to the synthesis of allenyl acetates

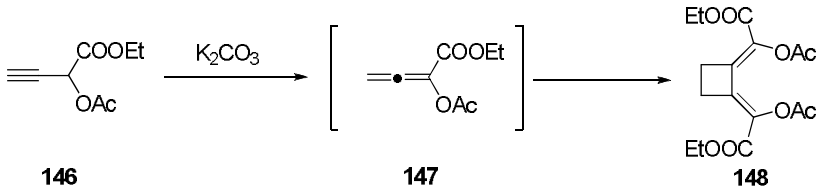
3.1 Introduction to the synthesis of allenyl acetates

The first report in the literature of allenyl acetates is from 1959 [112]. Saucy and co-workers prepared aldehyde **145** from the propargylic acetate **142**, by rearranging it to the corresponding allenyl acetate **143** and then hydrolyzing the acetate to enol **144** that spontaneously enolizes to the corresponding aldehyde **145** (Scheme 40). Quite harsh conditions were used for the acetate rearrangement: the reaction mixture was heated to 90 °C for 1.5 h with acetic acid as solvent.



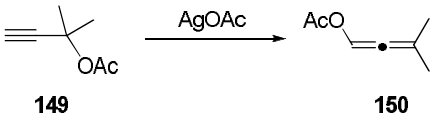
Scheme 40

Verny and Vessière studied propargylic transpositions and reported two allenyl acetates in 1969 [113]. They discovered two different methods that led them to the allenyl acetate moiety. Firstly ethyl 2-acetoxybut-3-ynoate **146** rearranges to the corresponding allene **147** in aqueous potassium carbonate solution. This then undergoes a [2+2] cylization spontaneously at room temperature to give the dimer of the allene with a cyclobutane structure **148** (Scheme 41).



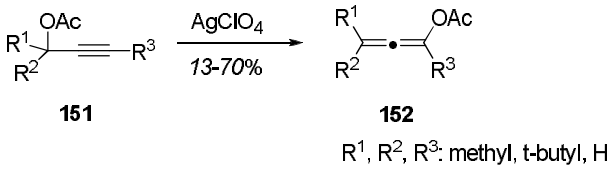
Scheme 41

Verny and Vessière also tried an silver(I)acetate-catalyzed rearrangement of propargylic acetates **149**. This silver-promoted rearrangement gave allenyl acetate **150** as product. This method later became the most frequently used reaction route to allenyl acetates (Scheme 42).



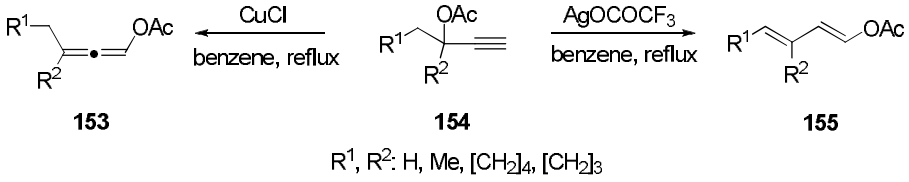
Scheme 42

The silver-catalyzed rearrangement of propargylic acetates has been widely used in the synthesis of allenyl acetates. In 1973 [114] Cookson used silver perchlorate in the synthesis of one allenyl acetate, and the same year Schmid [115] undertook an extensive investigation on the mechanism and kinetics of the reaction. These studies were followed by a reaction scope study by Schiavelli [116] in 1977. In this report six allenyl acetates were made but Schiavelli mentions that *a phenyl group as a substituent in the R^1 or R^2 position is not tolerated* (Scheme 43).



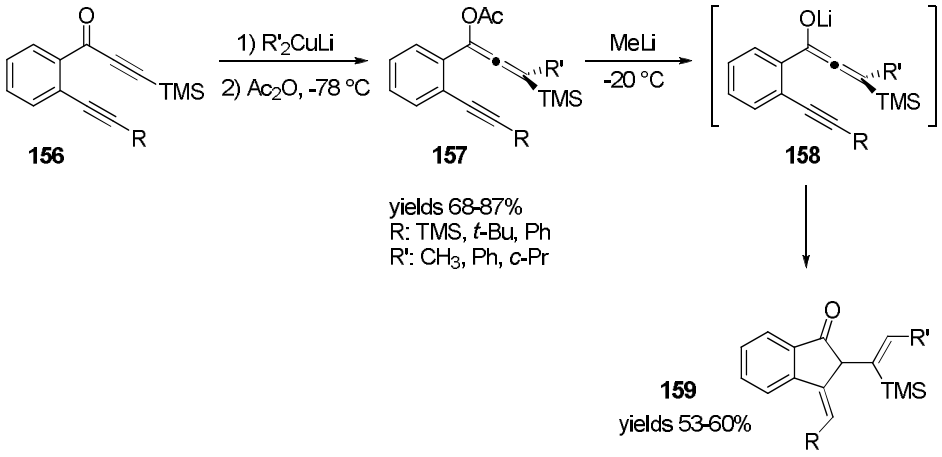
Scheme 43

There is one report of a copper-catalyzed rearrangement of propargylic acetates by Parsons in 1980 [117] (Scheme 44). This is a chemoselective diene/allene synthesis from propargylic acetates **154** controlled by catalyst choise. In Parson's work there are only fully saturated substituents at the R^1 and R^2 positions.



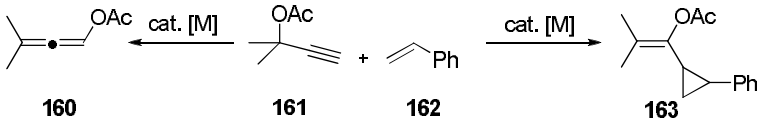
Scheme 44

In 2000 Lipton and co-workers [118] reported a novel synthesis of allenyl acetates **157** (Scheme 45). They performed the allenyl acetate synthesis by treating acetylenic ketones **156** with cuprate reagents and trapping the resultant enolates with acetic anhydride. The enyne-allene core underwent a cyclization after lithiation to give substituted indanones **159**.



Scheme 45

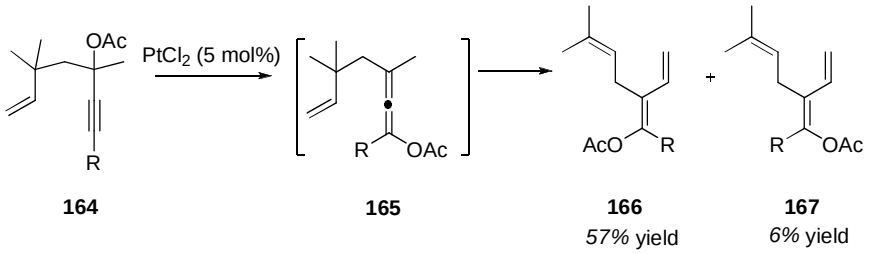
Uemura and co-workers (2003) reacted propargylic carboxylates **161** under ruthenium-catalyzed conditions with alkenes **162** with the object of making cyclopropanes **163**. Whilst testing different transition metals as catalysts they made some allenyl acetates **160** as well [119]. Surprisingly, the rhodium catalyst promoted allene formation was very efficient (Scheme 46).



cat. M	cyclopropane:	allene
$[RuCl_2(CO)_3]_2$	90	0
$[Rh(OCOCF_3)_2]_2$	trace	99
$IrCl_3$	45	53
$AuCl_3$	63	26
$PtCl_2$	93	7

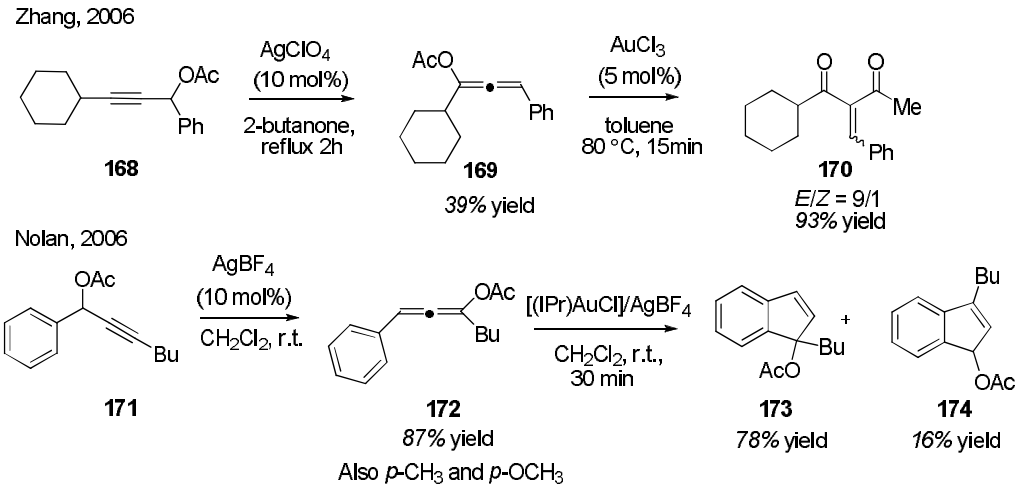
Scheme 46

Although in Uemura's report platinum catalysis did not provide any allenyl acetate under the reaction conditions, Malacria indicated in 2004 [120] that a $PtCl_2$-catalyzed tandem [3,3]-rearrangement of enyne acetate **164** could lead to the formation of intermediate allenyl acetate **165** (Scheme 47).



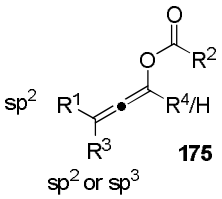
Scheme 47

There are limited examples of $AgBF_4$- and $AgClO_4$-catalyzed rearrangements of propargylic acetates bearing an aromatic substituent. One example of such a rearrangement from Zhang [121] and three compounds from Nolan [122] are known, both from 2006 (Scheme 48). Zhang and co-workers were investigating the gold-catalyzed rearrangement of propargylic acetate **168** to α-alkylidene or benzylidene-β-diketones **170** while Nolan and co-workers studied gold-catalyzed intramolecular hydroarylation that gives mixtures of indenes **173** and **174** from allenes **172**.



Scheme 48

The objective of our own project was to study the synthesis of allenyl acetates. Structure **175** in Scheme 49 is an allenyl acetate where R^4 is a proton and either R^1 or R^3 is an unsaturated substituent. These were of particular interest as such compounds are completely absent in the chemical literature. There are examples of R^1 as an sp^2 substituent, but in these cases R^4 is always a saturated alkyl group. On the other hand there are also examples of R^4 being a proton but again there is no unsaturation in R^1 or R^2.

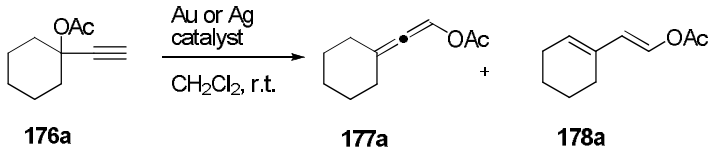


Scheme 49

3.2 Testing literature methods in the synthesis of allenyl acetates

As summarized in the introduction, allenyl acetates are often obtained as rearrangement products from propargylic acetates. The viability of the literature rearrangements was first tested with all-saturated 1-ethynylcyclohexyl acetate **176a** (Table 11). Often a mixture of allene **177a** and diene **178a** was obtained from this reaction (Entries a-d and f). Diene product **178a** can arise from the allene **177a** *via* a 1,3-proton shift. The two products **177a** and **178a** could not be separated by flash column chromatography so their ratio was determined by ^{1}H NMR spectroscopy. Only $AgBF_4$ gave allene **177a** as the sole product (entry g). Another silver(I) catalyst, AgOTf, gave a good selectivity to the corresponding diene **178a** (entry d); the reactivity of AgOTf might also be due to the presence of free acid in the reagent bottle as the condition of the catalyst was not studied. Gold catalysts always yielded mixtures of the two products, though the favored product with gold catalysts was allene **177** (entries a-c).

Table 11

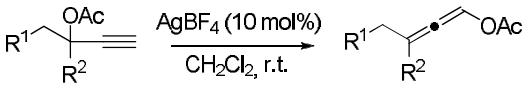


Entry	Catalyst	Cat. (mol%)	Time	Yield (%)[a]	**177a:178a**
a	$AuCl_3$	(5)	15 min	60	92:8
b	$Au(PPh_3)Cl$: $AgBF_4$	(5:5)	10 min	77	95:5
c	Au(IPr)Cl: $AgBF_4$	(5:5)	10 min	64	92:8
d	AgOTf	(10)	3 h	73	11:89
e	AgOAc	(10)	24 h	-	-
f	$AgNO_3$	(10)	24 h	47	49:51
g	$AgBF_4$	(10)	4 h	94	100:0

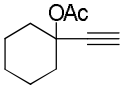
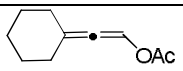
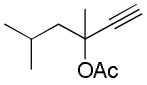
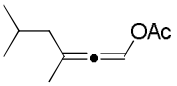
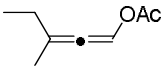
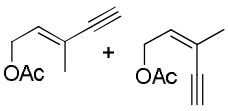
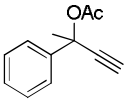
a) Isolated yield. Screening conditions: To **176a** (1 mmol, 0.16 g, 100 mol%) in 5 ml of freshly distilled CH_2Cl_2 was added catalyst at room temperature. Reaction was quenched after time indicated by filtration through celite and product was purified with flash column chromatography.

The limitations and scope of the silver-catalyzed rearrangement were studied with $AgBF_4$ as catalyst (table 12). The rearrangement of **176** to allenyl acetate **177** works well only for substrates with fully saturated sidechains R^1 and R^2 (entries a-c). With an alkene α to the acetate, the acetate group prefers to undergo a [3,3]-rearrangement to the alkene (entry d) forming enyne products (*E*/*Z*) **-179**. When an aromatic substituent is placed as R^2 (entry e) no products can be isolated at all but a very complex reaction mixture forms in short reaction time.

Table 12



176 **177**

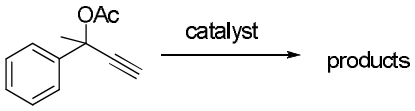
	Substrate **176 a-e**	Time	Yield and product (%)[a]
a		4 h	 94% **177a**
b		1 h	 71% **177b**
c		1 h	 64% **177c**
d		2 h	 68% 1:1 mixture enynes *E*/*Z* **-179**
e		5 min	starting material consumed, no isolable products

a) Isolated yield. Experimental procedure: To acetylene **176** (1 mmol, 100 mol%) in 5 ml of freshly distilled CH_2Cl_2 was added $AgBF_4$ (10 mol%) at room temperature. Reactions were quenched after time indicated by filtration through Celite and the product was purified with flash column chromatography.

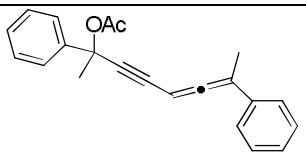
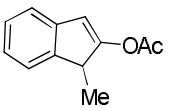
As the rearrangement with $AgBF_4$ failed with aromatic substrate **176e** it was tested with other literature methods (Table 13). Allenyl acetates have been prepared with gold- and copper catalysts [117,119]. However, with **176e** these methods did not yield the desired allenic products but copper(I)-chloride gave an addition product **180** as only isolable product (entry a)

and the gold catalyst Au(IPr)Cl gave indene **181** as the only isolable product (entry b). The reaction of entry a is known, this was first reported in 1975 [123].

Table 13

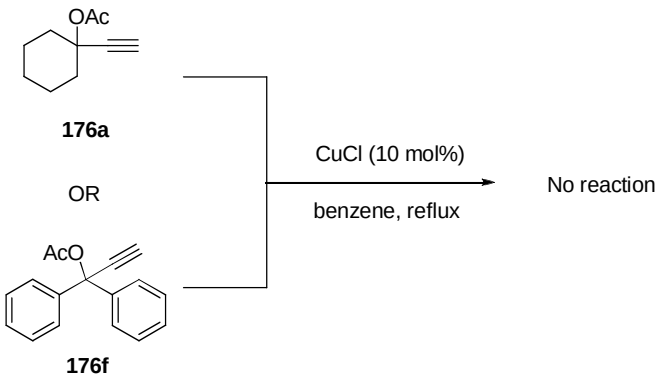


176e

Entry	Catalyst and reaction conditions	Yield and product (%)[a]
a	CuCl (10 mol%) benzene, reflux, 30 min	 30% **180**
b	Au(IPr)Cl (5 mol%) CH_2Cl_2, r.t. 5 min	 38% **181**

a) Isolated yield. Experimental procedure is described in detail in the Experimental Section.

Out of curiosity the CuCl-catalyzed reaction (entry a Table 13) was also tried with two other propargylic acetates **176a** and **176f**, but no addition product similar to **180** could be isolated. In fact only starting material was isolated after a 30 min-2 hour reflux in both cases (Scheme 50).



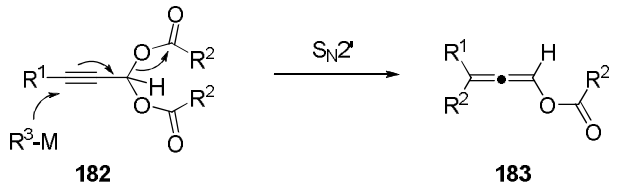
Scheme 50

As a conclusion literature methods were tested in the synthesis of allenyl acetates (Scheme 49) but they failed to deliver the desired reactivity for the allenyl acetate **175** when R^1 or R^2 is an

sp^2 unit. It was concluded that it would be necessary to develop new methodology for the synthesis of allenyl acetates.

3.3 Allenyl acetates from propargylic diacetates

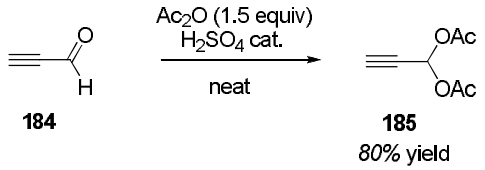
A new method was envisioned for the preparation of allenyl acetates. S_N2' nucleophilic substitution of propargylic electrophiles is a common way to obtain allenes and the substrate can be a propargylic acetate where the acetate acts as a leaving group [26]. The only change that should be made to this reaction would be to use a propargylic diacetate **182** instead of a monoacetate (Scheme 51). S_N2' nucleophilic substitution of diacetate **182** should give allenyl acetate **183** as product.



Scheme 51

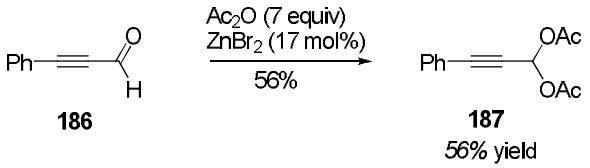
3.3.1 Synthesis of propargylic diacetates

At the inception of this project there were only two examples in the literature of propargylic diacetates. One example from 1978 [124] by Wille and Schwab is **185** (Scheme 52). They started from propargylic aldehyde **184** and added acetic anhydride in the presence of a catalytic amount of sulphuric acid. No solvent was used in this reaction.



Scheme 52

The second example was from 1999 [125] when Havelková and co-workers, while making trialdehydes, obtained one propargylic gem-diacetate **187** as byproduct (Scheme 53). In this case the diacetate was also made starting from a propargylic aldehyde **186** but this time $ZnBr_2$ was used to catalyze the reaction. Havelková also mentions in the report that the diacetate **187** was a remarkably stable compound.

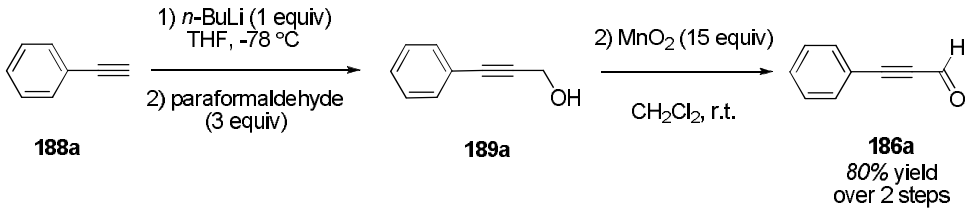


Scheme 53

In each publication only one propargylic diacetate was reported. However, there are a number of examples of other diacetates in the literature. These are always made from the corresponding aldehydes with Lewis or Brønstedt acid catalysis [126].

3.3.1.1 Synthesis of propargylic aldehydes

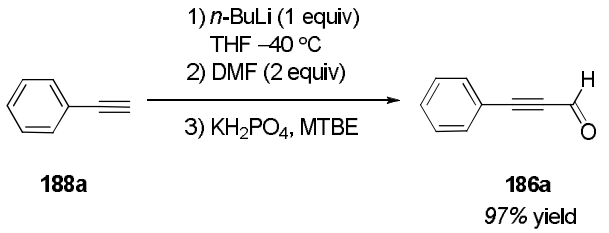
Propargylic aldehydes **186** were prepared as starting materials for the synthesis of propargylic diacetates. There are several ways to make these compounds. In the beginning of this project a two-step, one-purification synthetic route was used (Scheme 54). First, a terminal acetylene **188a** was deprotonated with *n*-BuLi followed by addition of paraformaldehyde, which gave propargylic alcohol **189a** as product. The crude product alcohol could be oxidized to the corresponding aldehyde **186a** with manganese dioxide. A large excess of manganese oxide (15 equivalents) was needed for complete conversion but the reagent could be used several times after drying it in the oven (80 °C) overnight. The same manganese oxide was used up to 5 times without loss of activity.



Scheme 54

There is, however, an easier route from Larsen and co-workers to make propargylic aldehydes that takes only one reaction step from terminal acetylene and often gives very high conversion to the product (Scheme 55) [127]. In this reaction route the deprotonation of terminal acetylene **188a** is followed by addition of dimethylformamide which is then hydrolysed with KH_2PO_4 to give directly the propargylic aldehyde **186a**. According to the authors it is important to do the hydrolysis in inverse order. The reaction mixture has to be added to a solution of aqueous

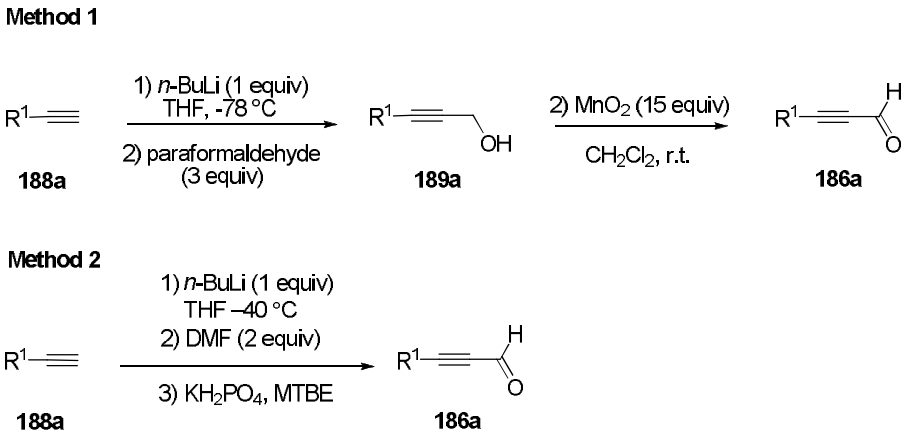
KH_2PO_4 and not *vice versa*, so that the leaving group (lithiated dimethylamine $LiNMe_2$, proposed by the authors) does not react with the desired product.



Scheme 55

Using these two methods eight propargylic aldehydes **186** with different unsaturated R^1 substituents were synthesized (Table 14).

Table 14



189/**186**	R^1	**189** Yield (%)[a]	**186** Yield (%)[a] *via* method 1	**186** Yield (%)[a] *via* method 2
a	Ph	90	95	97
b	4-MeC_6H_4	71	82	-
c	3-MeC_6H_4	99	70	-
d	4-$MeOC_6H_4$	71	79	-
e	1-cyclohexene	66	56	-
f	$(CH_2)_2Ph$	63	77	-
g	phenanthrenyl	64	66	-
h	4-*t*-BuC_6H_4	-	-	95

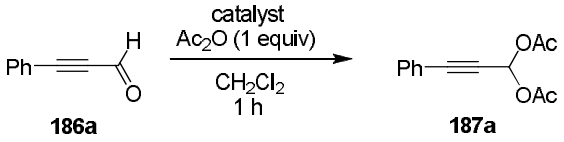
a) Isolated yield.

3.3.1.2 Optimization of diacetate synthesis

Literature methods for the preparation of diacetates from aldehydes often use Lewis acids or Brønstedt acids as catalysts. Quite early on it was discovered that if an excess of acetic

anhydride was used in the reaction it co-eluted with the product diacetate during column chromatography so a goal was set of using only one equivalent of the anhydride. After testing six different catalysts (Table 15) iron(III)-chloride gave the best yield for the diesterification. With 10 mol% of $FeCl_3$ an isolated yield of 83% of the diacetate product **187a** was obtained (entry d). In Table 15 also smaller amounts of iron(III)-chloride could be used successfully (entries g and h) but typically on larger scale (>1 g) the reaction needs 10 mol% of the catalyst to give high conversion to the product. Heating up the reaction mixture (entry i) had no remarkable effect on the conversion.

Table 15



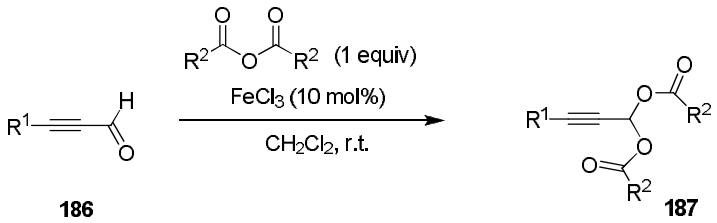
Entry	Catalyst	GC yield of **187a** (%) (isolated)
a	$AlBr_3$ (10 mol%)	0
b	$AlCl_3$ (10 mol%)	46
c	$Al(O^iPr)_3$ (10 mol%)	0
d	$FeCl_3$ (10 mol%)	85 (83)
e	$SnCl_2$ (10 mol%)	0
f	H_2SO_4 (10 mol%)	3
g	$FeCl_3$ (2 mol%)	56
h	$FeCl_3$ (5 mol%)	91
i	$FeCl_3$ (10 mol%) reflux	88

Screening conditions: Catalyst (2-10 mol%) was dissolved in CH_2Cl_2 (2 ml) at room temperature and aldehyde **186a** (50 mg, 0.38 mmol, 100 mol%) was added in 0.25 ml of CH_2Cl_2 followed by acetic anhydride (36 µl, 0.38 mmol, 100 mol%). After 1 h the reaction was quenched with saturated aqueous $NaHCO_3$ and an aliquot of dried organic phase was used for GC analysis.

3.3.1.3 Scope of diacetate synthesis

The scope and limitations of the diacetate synthesis were studied (Table 16). In total, ten different diacetates **187** were synthesized. Among different R^1 substituents only the *p*-methoxyphenyl group gave a clearly lower yield in the reaction. The reason for this might be due to electronic deactivation arising from the electron-donating methoxy group in the *para*-position (entry d). Anhydrides of pivalic and benzoic acids were tested in the reaction as well (entries i and j); they both gave the desired dicarboxylate, only in lower yield than when acetic anhydride was used.

Table 16



186 187

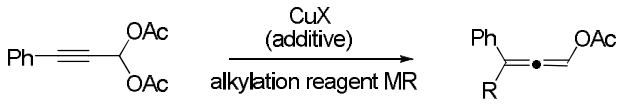
Entry	R^1	R^2	Time (h)	Yield **187a-j** (%)[a]	(brsm) (%)[b]
a	Ph	Me	1	83	(97)
b	4-MeC_6H_4	Me	2	63	(89)
c	3-MeC_6H_4	Me	3	72	
d	4-$MeOC_6H_4$	Me	24	26	(54)
e	1-cyclohexene	Me	24	49	(70)
f	$(CH_2)_2Ph$	Me	5	62	(79)
g	phenanthrenyl	Me	18	51	(77)
h	4-*t*-BuC_6H_4	Me	20	60	(76)
i	Ph	^{t}Bu	0.5	46	
j	Ph	Ph	6	20	

a) Isolated yield. b) Isolated yield based on recovered starting material.

3.3.2 S_N2' nucleophilic substitution of propargylic diacetates with a cuprate

S_N2' nucleophilic substitution was first tested with propargylic diacetate **187a**. Initial reactions were tried with a Gilman cuprate [128] as an alkylation reagent. The reagent was prepared from both copper(I)-iodide and copper(I)-cyanide (Table 17, entries a and b) but both gave only traces of the desired allene **190a**. Next magnesium cuprates were screened with LiBr included as an additive. With methyl Grignard the results were not very promising as the yields were around 30% (entries c and d). However, when the Grignard reagent was changed to ethylmagnesium bromide (entry f), 52% of allene **190b** was obtained. The solvent had a big role with the ethyl Grignard reaction, as in Et_2O the yield was only 35% of **190b** (entry e). The best results were obtained when the amount of cuprate used was reduced by half to 2.5 equivalents and this was applied to the LiBr additive as well (entries g and h). Smaller amounts of the cuprate led to low conversions. Reducing the temperature to –10 °C gave 88% yield of the desired allene **190b** (entry h).

Table 17



187a

190a R = Me
190b R = Et

Entry	Alkylation reagent (equiv)	CuX (equiv)	Additive (equiv)	Solvent	T (°C)	yield (%)[a] **190 a** or **b**
a	MeLi (3.2)	CuI (1.6)	-	Et_2O	–78[b]	traces
b	MeLi (5.3)	CuCN (5.4)	-	Et_2O	–78[b]	traces
c	MeMgBr (2.4)	CuI (2.5)	LiBr (2.5)	THF	0	30
d	MeMgBr (2.4)	CuCN (2.5)	LiBr (5.0)	THF	0	24
e	EtMgBr (4.8)	CuI (5.0)	LiBr (5.0)	Et_2O	0	35
f	EtMgBr (4.9)	CuI (5.0)	LiBr (5.0)	THF	0	52
g	EtMgBr (2.4)	CuI (2.5)	LiBr (2.5)	THF	0	72
h	EtMgBr (2.4)[c]	CuI (2.5)	LiBr (2.5)	THF	–10	88

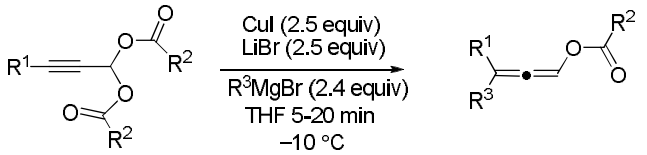
a) Isolated yield. b) Reaction started at 0 °C and cooled down to –78 ºC before addition of starting material. c) Grignard reagent as 1 M solution MTBE instead of 3 M solution in Et_2O as in the other attempts with EtMgBr.

As a control experiment the S_N2' reaction was tested once without the copper reagent. When ethylmagnesium bromide was reacted with propargylic diacetate **187a**, no allenyl acetate **190b** formed but a mixture of other products was obtained.

3.3.2.1 Scope of S_N2' reaction

The scope and limitations of the cuprate-mediated S_N2' reaction were studied. Firstly, different Grignard reagents were tested (Table 18, entries a-c and l-n). The reaction works well with unbranched saturated alkyl Grignards (entries a-c) although methyl Grignard gives lower yield (30%, entry a). Unfortunately, branched (entry l) or unsaturated (entries m and n) Grignard reagents do not give any of allene **190**. The reason for this behaviour could lie in the steric hindrance caused by branched Grignard reagents containing isopropyl or phenyl group. Even when the reaction mixture was warmed to ambient temperature only starting material was recovered. Seven different R^1 substituents were tested with ethylmagnesium bromide and they all gave moderate to good yields (entries b and f-k). Pivalate and benzoate carboxylates were also well tolerated (entries d and e).

Table 18



187 **190**

Entry	R^1	R^2	Grignard (R^3)	Yield **190a-n** (%) [a]
a	Ph	Me	MeMgBr	30
b	Ph	Me	EtMgBr	88
c	Ph	Me	*n*-BuMgCl	65
d	Ph	^{t}Bu	EtMgBr	78
e	Ph	Ph	EtMgBr	74
f	4-MeC_6H_4	Me	EtMgBr	81
g	3-MeC_6H_4	Me	EtMgBr	46
h	1-cyclohexene	Me	EtMgBr	67
i	$(CH_2)_2$Ph	Me	EtMgBr	51
j	phenanthrenyl	Me	EtMgBr	51
k	4-*t*-BuC_6H_4	Me	EtMgBr	53
l	Ph	Me	*i*-PrMgCl	-
m	Ph	Me	PhMgCl	-
n	Ph	Me	H_2C=CHMgCl	-

a) Isolated yield.

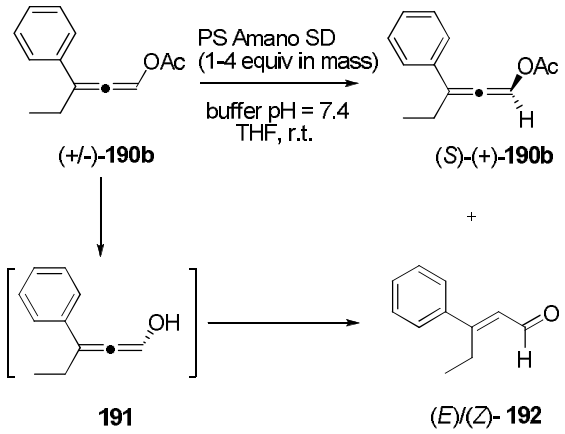
The reactions in Table 18 were mostly carried out on a 200-500 mg scale. The best yields for the S_N2' reactions were obtained when the reaction was scaled up to 1-1.5 grams. Scale-up of the reactions was somewhat compromised by the instability of the compounds **190 a-k**. Even when the allenyl acetates were prepared to be used in further reactions it made no sense to prepare them in large amounts. At room temperature the allenyl acetates **190** started to decompose in matter of hours and even in the freezer in a couple of days. The allenyl acetates **190** did not decompose to one identifiable compound but gave a very complex decomposition mixture.

3.3.3 Lipase-catalyzed kinetic resolution of allenyl acetates

The synthesis and kinetic resolution of axially chiral allenes was discussed in Chapter 1. There are methods to enzymatically resolve allenic acids with Porcine pancreatic lipase [51,52]. Lipases from *Pseudomonas fluorecens* and *Burcholderia cepacia* were tested initially with substrate **190b**. The lipase from *Burcholderia cepacia* (will be from now on referred to as PS Amano SD) gave high *ee* values already in the initial tests. In Table 19 is described the short optimization of the reaction. The reaction was first tried with 100 mg of enzyme *vs* 100 mg of starting material *rac*-**190b** (entry 1 in table 19) but only 70% *ee* was obtained with 31% yield

of allenyl acetate (*S*)-**190b**. With a larger amount of the enzyme (400 mg *vs* 100 mg allenic acetate) an *ee* of 85% was obtained in 1.5 hours and an *ee* of 88% in 2 hours reaction time for the allenyl acetate (*S*)-**190b** (entries b and c). A small amount of THF was used in the reactions to facilitate the substrate to dissolve. The hydrolysis product, alcohol **191**, tautomerizes to the corresponding aldehyde **192**.

Table 19

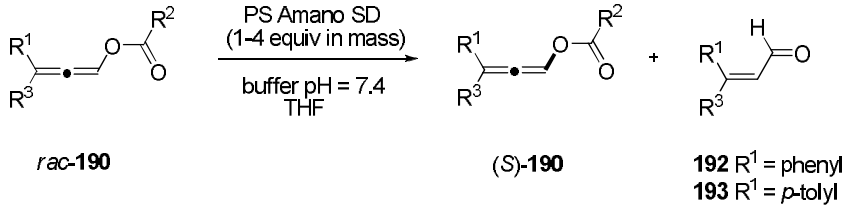


Entry	Time	PS[b]	*ee* (%) (*S*)-(+)-**190b**	Yield (%)[a] (*S*)-(+)-**190b**	Yield (%)[a] *E*/*Z*-**192**
a	3 h 15 min	100 mg	70	31	35
b	1 h 30 min	400 mg	85	45	54
c	2 h	400 mg	88	32	65

a) isolated yield. b) Lipase PS Amano SD, amout of lipase per 100 mg of substrate *rac*-**190b**.

The kinetic resolution with PS Amano SD was tested altogether with four different allenyl acetates (Table 20). Changing the acetate group on allene **190** to pivalate or benzoate stops the reaction completely (entries c and d), as the active site of the enzyme is too small for such large carboxylates. What was surprising, however, is that changing the R^1 group of the allenyl acetate **190** from phenyl to *p*-tolyl caused a dramatic descent in the *ee* of the allenyl acetate (*S*)-**190** (entry b). This reaction seems to be very sensitive to substitution on R^1 of **190**.

Table 20



Entry	R^1	R^2	Yield **190** (%)[a]	*ee* **190** (%)	Aldehyde (%)[a]
a	Ph	Me	32 ((*S*)-**190b**)	88 (**190b**)	65 (**192**)
b	*p*-tolyl	Me	25 ((*S*)-**190f**)	45 (**190f**)	56 (**193**)
c	Ph	^{t}Bu	-	-	-
d	Ph	Ph	-	-	-

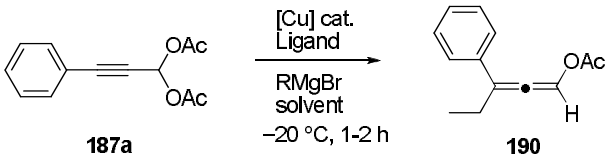
a) isolated yield.

3.4 Towards a catalytic method for the synthesis of allenyl acetates

It was proved that allenyl acetates can be synthesized from propargylic diacetates using a cuprate reagent derived from copper(I)-iodide and Grignard reagents. For good conversions the reaction needed 2.5 equivalents of the cuprate. It was appealing to attempt to develop the reaction further towards a catalytic variant. Using a catalytic amount of a transition metal catalyst would be first of all more economical, but also it would have the advantage that asymmetric ligands could be tested in the reaction to induce chirality to the product allene.

3.5 Attempts with copper-catalyzed S_N2' reaction

The search for a catalytic S_N2' reaction was started with copper catalysts as there are several examples of this type of tranformation in the literature [42,45]. Different catalysts, solvents, and ligands were tested. Additionally different alkylation reagents (AlR_3, ZnR_2 and RMgBr) were tested in the copper-catalyzed reaction, but only Grignard reagents gave the desired product **190** (Scheme 56).



Scheme 56

From the beginning it was clear that the biggest problem in this reaction was its chemoselectivity. The reactions were followed with gas chromatography and many byproducts

were visible in the GC data of the crude reaction mixtures. To get a better insight into the reaction some of these, when using ethyl-Grignard reagent, were isolated and analyzed giving the identities described in Figure 1. There is no complete set of analytical data for any of the byproducts as they could not be isolated cleanly, but these are the structures deduced from NMR data.

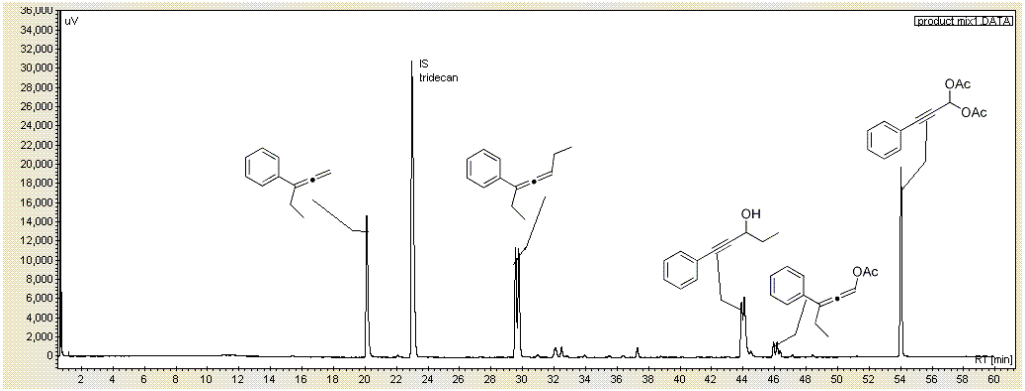
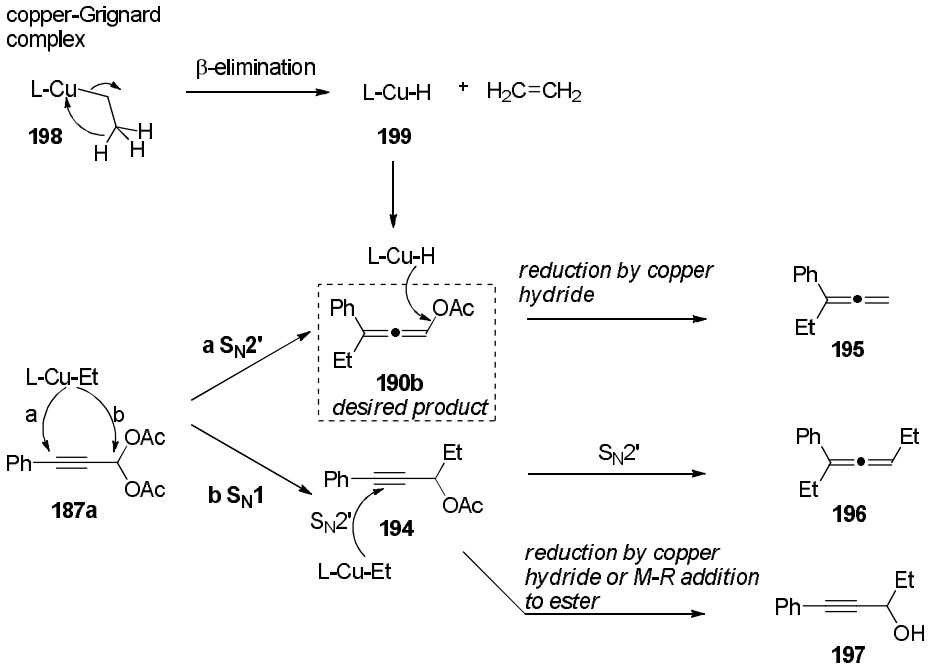


Figure 1

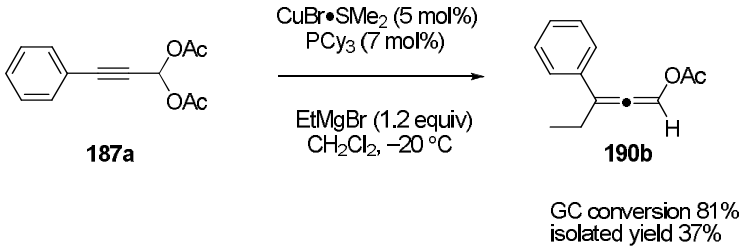
The reaction of diacetate **187** can proceed *via* S_N1 or S_N2' nucleophilic substitution giving compounds **194** or **190**. The reactive complex **198** formed from the copper catalyst and ethyl-Grignard reagent can react to form a copper hydride **199** *via* β-elimination. The copper hydride could further reduce both **190b** and **194** yielding terminally unsubstituted allene **195** and alcohol **197**. Propargylic acetate **194** could also react again with cuprate **198** to form disubstituted allene **196** (Scheme 57).



Scheme 57

The organocuprate-mediated S_N2' reaction in Chapter 3 to form allenyl acetates **190** from diacetates **187** was tested once without the copper reagent. In the presence of Grignard reagents it only gave a complex product mixture and no allenyl acetate **190**. This might be the problem in the catalytic reaction as well, as there will be 'free' Grignard reagent in the reaction mixture which can react directly with diacetate **187**.

Different pre-catalysts were tested incuding: CuBr•SMe_2, $Cu(OAc)_2$, Cu(TC), CuI, CuCl, CuBr, $CuBr_2$, $CuCl_2$, $[Cu(MeCH)_4][BF_4]$ and $Cu(OAc)_2$•H_2O. From these catalysts CuBr•SMe_2 showed better selectivity towards allene **190** than the rest, although the selectivity was highly dependent on solvent, temperature and ligand. The best ligand donors regarding conversion and selectivity to allene **190** seemed to be phosphines, and PCy_3 was mostly used as the ligand in this screening. The solvent dependency gave no clear trend, but generally the best conversions were observed with CH_2Cl_2. The screening of different reaction conditions was followed with gas chromatography, and up to 81% GC conversions were recorded with the 'optimized' conditions. When this reaction was scaled up from 50 mg to 100 mg of substrate **187**, only up to 37% isolated yields were obtained (Scheme 58). The product was isolated after quenching the reaction with saturated aqueous NH_4Cl solution and purified with flash column chromatography.



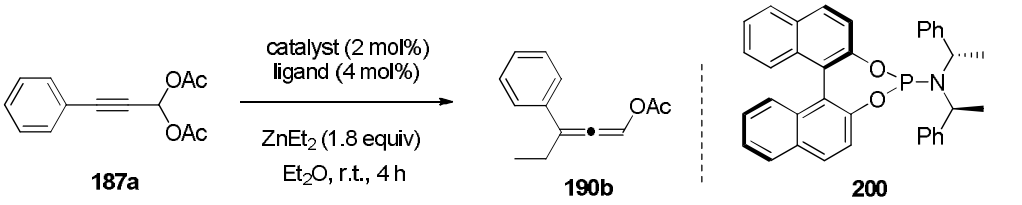
Scheme 58

As the reaction seemed too sensitive to be scaled up to useful quantities, this approach was abandoned and different transition metals were tested instead. The copper-catalyzed reaction was tested some 250 times varying the ligand, catalyst, solvent and temperature as carousel and automated GC techniques allowed fast screening of reaction conditions. Additionally, 30 chiral ligands were tested with this reaction but the allenic acetates **190** obtained were always racemic.

3.6 Nickel-catalyzed S_N2' reaction

As the copper-catalyzed approach gave no desired results, additional transition metal pre-catalysts were tested in the synthesis of allenyl acetates **190**. Six different transition metals including iron-, ruthenium-, rhodium-, iridium-, nickel- and palladium-catalysts were tried (Table 21). All of these catalysts were tested first both with $AlMe_3$ and $ZnEt_2$. Only the reactions with $ZnEt_2$ are presented in Table 21 as $AlMe_3$ did not give any conversion to the desired product **190**. All of the catalysts were tested both with and without a ligand, and Feringa's phosphoramidite ligand **200** [129] was chosen for the screening because a large number of successful asymmetric syntheses has been developed with it [130]. From these test reactions nickel catalyst $Ni(acac)_2$ gave the highest conversions to the desired product **190** both with and without a ligand (entries e and k). No *ee* was obtained with the phosphoramidite ligand **200** in any case.

Table 21



L*: (R_a,S_c,S_c)-phosphoramidite ligand

Entry	Catalyst (2 mol%)	Ligand (4 mol%)	GC yield (%) **190b**
a	$FeCl_3$	-	-
b	$Ru(MeCN)_2COD$	-	-
c	$[RhCl(COD)]_2$	-	4
d	$[IrCl(COD)]_2$	-	-
e	$Ni(acac)_2$	-	27
f	$Pd_2(dba)_3$	-	3
g	$FeCl_3$	L*	-
h	$Ru(MeCN)_2COD$	L*	-
i	$[RhCl(COD)]_2$	L*	2
j	$[IrCl(COD)]_2$	L*	-
k	$Ni(acac)_2$	L*	16
l	$Pd_2(dba)_3$	L*	-

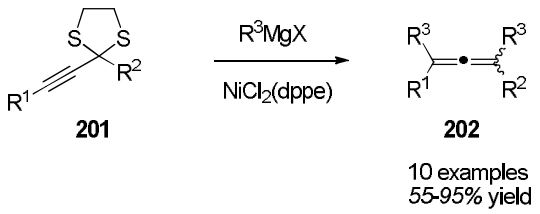
Screening conditions: At room temperature catalyst (0.04 mmol, 2 mol%) and ligand (4.0 mg, 0.08 mmol, 4 mol%) were charged in carousel tube under argon and 5 ml of Et_2O was added. After 10 min diacetate **187a** (50 mg, 0.21 mmol, 100 mol%) was added in 1 ml of Et_2O followed by dropwise addition of $ZnEt_2$ (1M in hexanes, 0.38 ml, 0.38 mmol, 1.8 equiv). The reaction was quenched with saturated aqueous NH_4Cl and the organic phase was dried over $MgSO_4$ and used for GC analysis.

The nickel catalyst $Ni(acac)_2$ clearly showed highest conversions, up to 27% (entry e) in the first screening. Optimization was continued with this nickel-catalyzed system.

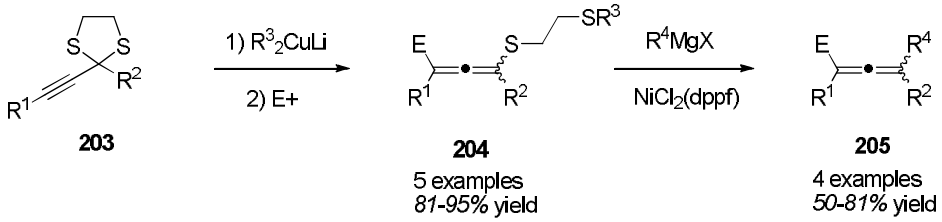
3.6.1 Background on nickel-catalyzed synthesis of allenes

There are reports of both Grignard reagents and zinc reagents being used with nickel catalysts in allene synthesis. It is also known that the chemoselectivity of S_N2 *vs* S_N2' can depend on the transition metal used in case of copper and nickel catalysts [43].

Luh reported in 1996 [131] and 1997 [132] a synthesis of allenes from propargylic dithioacetals **201** with nickel catalyst and Grignard reagent. In this reaction the Grignard is coupled twice (Scheme 59). Different R groups could be substituted on the allene moiety when the first substitution was done with a cuprate and the reaction quenched with an electrophile. The second substitution was done on the C-S bond with a nickel reagent yielding allenes **205** (Scheme 60).

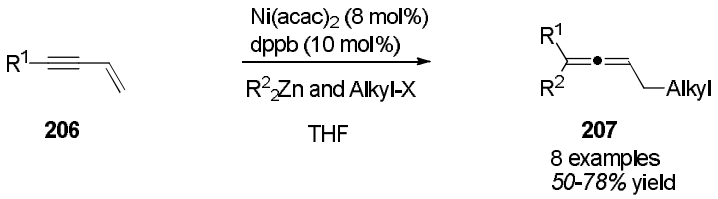


Scheme 59



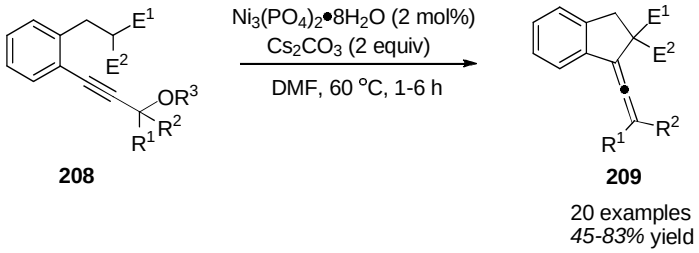
Scheme 60

Kambe reported the three-component coupling of enynes **206** with alkyl halides and zinc reagents under nickel-catalyzed conditions (Scheme 61) [133]. The authors propose a formation of an alkyl-radical from alkyl halides by single electron transfer from the nickelate complex. The resulting alkyl radical reacts with the enyne **206** yielding a vinyl radical intermediate, which can react with Ni-R^2 to give the allenic product **207** after a reductive elimination.



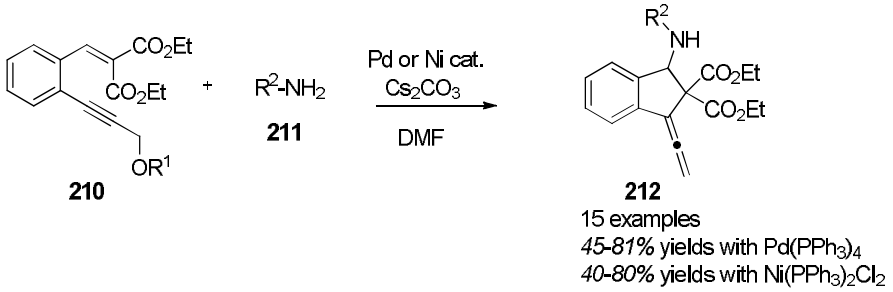
Scheme 61

There are also some examples of intramolecular couplings to form allenes under nickel catalysis. Liang reported the synthesis of allenyl-indenes **209** in 2008 by Michael-addition type intramolecular nucleophilic substitution to a nickel-activated alkyne. Following elimination of an ether group yields the allenyl-indene product **209** with moderate to good yields (Scheme 62) [134].



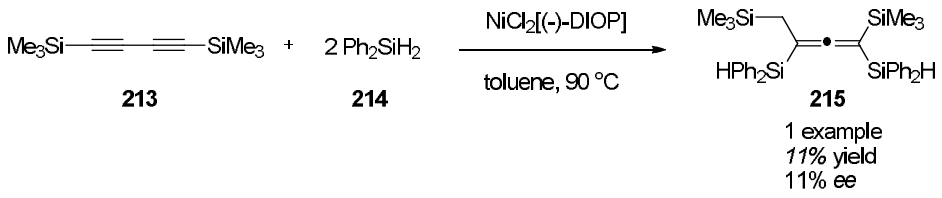
Scheme 62

Liang expanded his allenyl-indene synthesis to three-component couplings by adding a nitrogen nucleophile **211** to the reaction (Scheme 63) [135]. This reaction works with both palladium catalysts and with nickel catalysts. Nickel-catalyzed reactions were performed under air, whereas the palladium-catalyzed reactions needed argon atmosphere. This tandem reaction gives allenyl-indenes **212** with high degree of substitution. The proposed reaction mechanism involves a Michael addition of the amine to the Michael acceptor and following attack of the malonate-type carbon nucleophile to the transition metal activated alkyne.



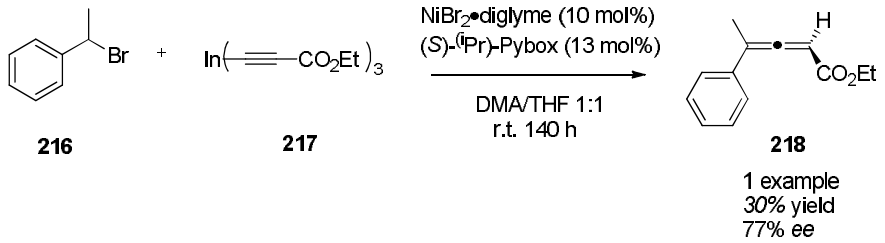
Scheme 63

There are also some examples of the synthesis of chiral allenic compounds using nickel catalysis. In 2000 Tillack and co-workers reported a hydrosilylation of butadiynes **213** to chiral allenes **215** with rhodium and nickel catalysts in the presence of chiral phosphine ligands. The drawback of this reaction is a low enantioselectivity. With a rhodium catalyst the allene product was obtained with up to 27% *ee* while a nickel catalyst gave only 11% *ee* (Scheme 64) [136].



Scheme 64

In 2008 Sarandeses and co-workers published an enantioselective synthesis of benzyl-substituted alkynes *via* nickel-catalyzed cross-coupling reactions of trialkynylindium reagents with racemic secondary benzyl bromides. When studying the scope of this reaction, trialkynylindium derivative of ethyl propiolate **217** surprisingly afforded an allene product **218** with 30% yield and 77% *ee* (Scheme 65) [137]. This was the only example of allene synthesis in the report.

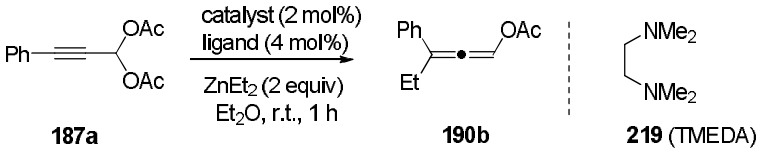


Scheme 65

3.6.2 Optimization of nickel-catalyzed S_N2' reaction

The optimization of nickel-catalyzed S_N2' reaction was started by testing different nickel catalysts without ligands (Table 22, entries a-h) and $Ni(acac)_2$ showed the highest activity in the reaction. Some simple ligands were tested with this catalyst (Table 22, entries i-l). Phosphine and phosphate ligands lowered the activity of the catalyst whereas the diamine ligand TMEDA **219** improved the conversion from 37% (without a ligand) to 46% (entries a and l). The presence of an amine ligand seemed to accelerate the reaction.

Table 22



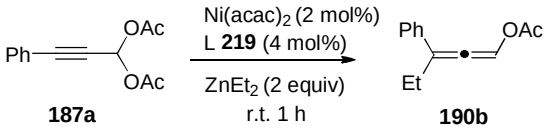
187a **190b** **219** (TMEDA)

Entry	Catalyst (5 mol%)	Ligand (7 mol%)	GC yield **190b** (%) (isolated)
a	$Ni(acac)_2$		37 (38 in 4 h)
b	$Ni(acac)_2 \cdot 2H_2O$		35
c	$NiCl_2 \cdot 6H_2O$		-
d	$Ni(acac)F_6 \cdot H_2O$		26
e	$Ni(PPh_3)_2Cl_2$		-
f	$NiCl_2$ anhydr		11
g	$Ni(SO_3) \cdot 6H_2O$		-
h	$Ni(PPh_3)_2Br_2$		1
i	$Ni(acac)_2$	PCy_3	2
j	$Ni(acac)_2$	PPh_3	3
k	$Ni(acac)_2$	$P(OBu)_3$	2
l	$Ni(acac)_2$	**219** (TMEDA)	46

Screening conditions: At room temperature the nickel catalyst (5 mol%) and ligand (7 mol%) were charged in a Schlenck tube with 5 ml of Et_2O. After 10 min diacetate **187a** (50 mg, 0.21 mmol, 100 mol%) was added in 1 ml of Et_2O followed by addition of $ZnEt_2$ (1M in hexanes, 0.42 ml, 0.42 mmol, 200 mol%). After 1h the reaction was quenched with saturated aqueous NH_4Cl solution and an aliquot of dried organic phase was used in GC analysis.

Five solvents were compared with $Ni(acac)_2$ and ligand **219**. From the five, the reaction in diethyl ether gave the best conversion to the allene **190b** (Table 23, entry a).

Table 23



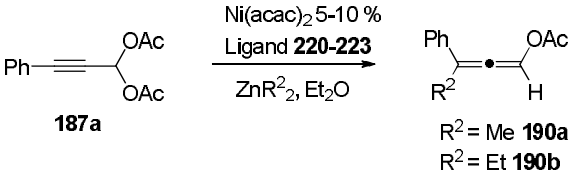
187a **190b**

Entry	$Ni(acac)_2$ (mol%)	L **219** (mol%)	Solvent	GC yield **190b** (%)
a	5	7	Et_2O	46
b	5	7	THF	14
c	5	7	2-Me-THF	26
d	5	7	CH_2Cl_2	-
e	5	7	toluene	25

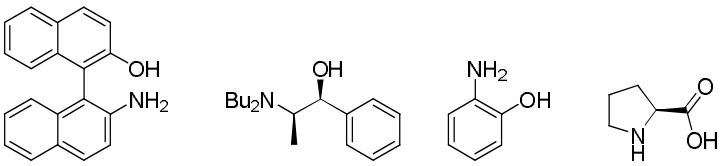
Screening conditions: At room temperature the nickel catalyst (3.1 mg, 0.01 mmol, 5 mol%) and ligand (2.2 ul, 0.014 mmol, 7 mol%) were charged in carousel tube and 5 ml of solvent was added. After 5-10 min diacetate **187a** (50 mg, 0.21 mmol, 100 mol%) was added in 1 ml of solvent followed by dropwise addition of $ZnEt_2$ (1M in hexanes 0.42 ml, 0.42 mmol, 200 mol%). The reaction was quenched with saturated aqueous NH_4Cl and organic phase was dried with $MgSO_4$ and used in GC analysis.

After the discovery of ligand-acceleration with nitrogen donor ligands some more ligands were tested. Several reaction conditions were tested with ligands **220**-**223**. When 5-7 equivalents of ZnR_2 were used higher yields of **190a-b** were attained.

Table 24



Ligands



(+/-)-**220** **221** **222** **223**

Entry	$Ni(acac)_2$ (mol%)	Ligand (mol%)	T (°C)	Time (h)	ZnR_2 (equiv)	Yield **190a/b** (%)[a]
a	5	**220** (7)	+4 °C	3 h	$ZnEt_2$ (7)	64
b	5	**220** (7)	+4 °C	4 h	$ZnEt_2$ (5)	62
c	5	**220** (7)	+4 °C	22 h	$ZnMe_2$ (5)	10
d	5	**221** (7)	+4 °C	2 h	$ZnEt_2$ (7)	54
e	10	**221** (15)	+4 °C	0.5 h	$ZnEt_2$ (7)	60
f	5	**221** (7)	–5 °C	2.5 h	$ZnEt_2$ (7)	48
g	5	**222** (7)	+4 °C	22 h	$ZnEt_2$ (5)	58
h	5	**223** (7)	+4 °C	1 h	$ZnEt_2$ (5)	47

a) Isolated yield. General conditions: $Ni(acac)_2$ (5-10 mol%) and ligand (7-15 mol%) were charged in Schlenk tube and 10 ml of Et_2O was added. The reaction was cooled to the temperature required. After 5 min substrate **187a** and ZnR_2 were added.

With racemic NOBIN **220** the reaction yielded allenyl acetate **190b** with over 60% isolated yields. Some different addition methods were tested with **220**. Diacetate **187a** was added first to the reaction mixture followed by rapid addition of 5 equiv. of zinc reagent and 2 equiv. of zinc reagent was added after 1 hour reaction time (entry a). Zinc reagent was added before diacetate, which was added slowly over 1 hour (entry b). Both addition methods give very

similar isolated yields, 64% and 62% respectively. $ZnMe_2$ gives very low yields of the allene product (entry c).

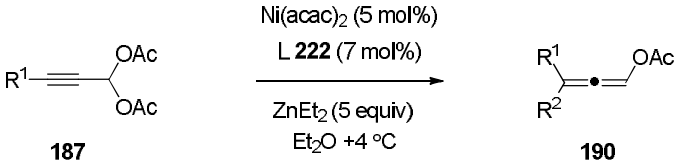
With ligand **221** were tested different methods for adding the zinc reagent. In both entries d and e, $ZnEt_2$ was added only after the diacetate. Adding $ZnEt_2$ portion-wise over 1 hour had little effect (entry d) compared to adding it all at once (entry e). With fast addition of diethylzinc the yield of the allene product is somewhat higher (60% *vs* 54%) after 30 minutes reaction time. When the reaction is cooled down to –5 °C the yield drops to 48% (entry f).

From the tests in entries a-e was it concluded that it is best to add all the zinc reagent in the beginning and then slowly add the diacetate substrate. With simple 2-aminophenol as ligand (**222**) the yield 58% (entry g) is quite close to the 64% yield obtained with ligand **220** (entry a). Reaction with proline **223** gives the allenyl acetate **190b** with 47% isolated yield (entry h).

3.6.3 Testing different substrates on nickel-catalyzed S_N2' reaction

The nickel-catalyzed S_N2' reaction was tested with four other substrates (Table 25). As in Table 24 there was not one ligand dramatically better than the others, 2-aminophenol **222** was used as ligand with a selection of substrates. With *p*-tolyl-substitutent (entry a) reaction with ligand **222** gave a yield of 53% and the reaction with $(CH_2)_2Ph$ substituent reached 50% isolated yield (entry d). However when *m*-tolyl or 1-cyclohexene substituents were tested the yields clearly dropped (entries b and c). The reaction times in entries c and d are shorter than those in entries a and b. It was discovered that the allene product is formed in the beginning of the reaction but soon there starts to form other products as well (particularly in case of entry c). If the reaction is left on for longer times in the end none of the allenyl acetate can be isolated but it seems that the product starts to react further and only a complex product-mixture is obtained.

Table 25



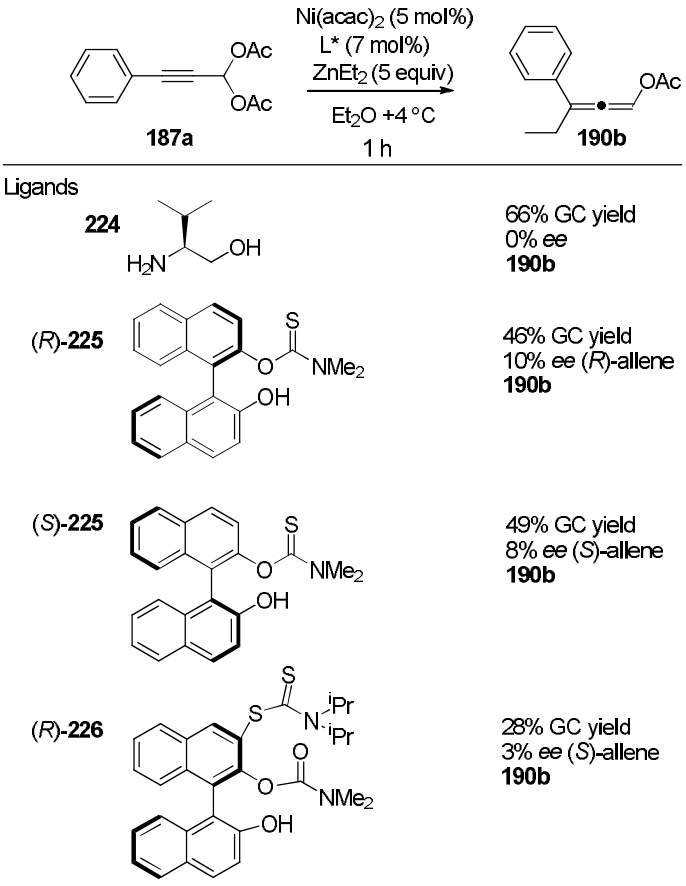
187 190

Entry	R^1	Time	Yield **190** (%)[a]	(brsm %)[b]
a	*p*-tolyl	3 h	53 (**190f**)	(93)
b	*m*-tolyl	3 h	27 (**190g**)	(79)
c	1-cyclohexene	1.5 h	38 (**190h**)	(82)
d	$(CH_2)_2Ph$	1 h	50 (**190i**)	(99)

a) Isolated yield. b) Isolated yield based on recovered starting material.

3.6.4 Attempts towards catalytic asymmetric S_N2' reaction

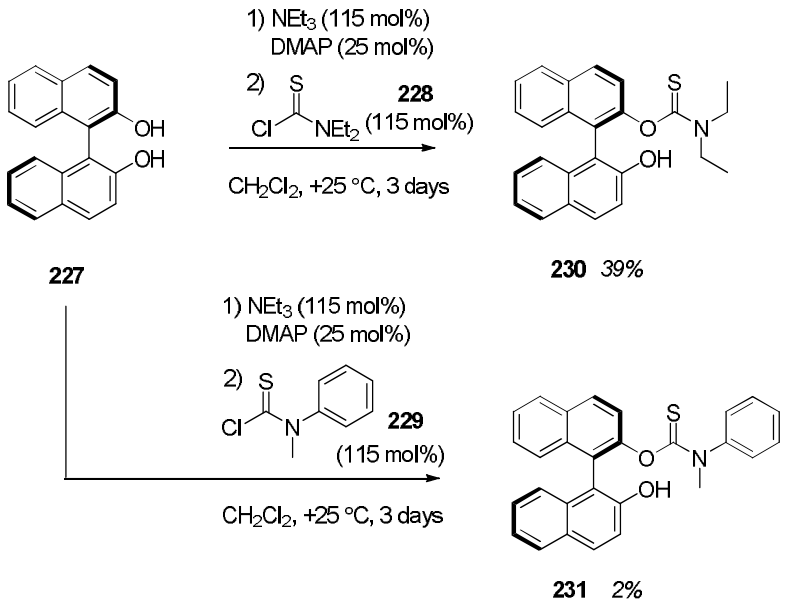
Some chiral ligands were tested in the S_N2' reaction. Amino-alcohol ligands were of particular interest as they seemed to accelerate the reaction most. Unfortunately enantiopure NOBIN (**220**) was not available at the time as it is an expensive ligand to buy. Chiral ligands in Table 24 did not yield any *ee* to the product allene **190b** so few others were tested (Scheme 66). The ligands in Scheme 74 are commercially available or made by previous group members.



Scheme 66

Thiocarbamate ligand (*R*)-**225** gave 10% *ee* of enantiomer (*R*)-**190b**. With the corresponding (*S*)-ligand (*S*)-**225** 8% *ee* to enantiomer (*S*)-**190b** was observed. Here the assignment of the allenyl acetate **190b** enantiomers is based on the assignment made with kinetic resolution results in Chapter 3. The (*R*)-ligand gives the opposite enantiomer of **190b** and (*S*)-ligand gives the same enantiomer of **190b** as in the kinetic resolution with lipase from *Burcholderia cepacia.*

Thiocarbamate ligands are not commercially available, but they are also not difficult to make [138]. Thiocarbamate ligands can be accessed from BINOL **227** and thiocarbamoyl chlorides in the presence of a base. The choice in commercially available thiocarbamoyl chlorides is limited, but two different chlorides **229** and **229** are available (Scheme 67). The synthesis of two new ligands **230** and **231** is described in Scheme 67. The one-pot synthesis yielded ligand **230** with 39% yield and ligand **231** with very low, 2% yield.

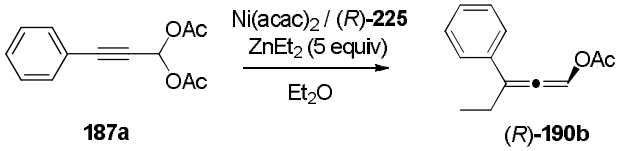


Scheme 67

Unfortunately, the newly made ligands **230** and **231** showed no stereoselectivity at all in the nickel-catalyzed S_N2' reaction. The ligands with the only enantioselectivity remain (*R*)- and (*S*)-**225**.

In an attempt to improve the *ee* values the reaction temperature was lowered to –10 °C but this gave similar *ee* (8%) and conversion (49%) to the allenyl acetate **190b** as earlier at +4 °C (entry a, Table 26). When the reaction temperature was lowered to –70 °C a higher *ee* of 22% was observed for the allenyl acetate but conversion dropped to 31% (entry b). In entries c and d the catalyst/ligand mixture was left stirring at room temperature before cooling the reaction down for the addition of diacetate **187a** and the zinc reagent. This modified reaction was tested with 5 mol% and with 10 mol% of catalyst (entries d and c respectively) but in both cases the *ee* and conversion of allene product **190b** was lower than without the pre-stirring.

Table 26



187a (*R*)-**190b**

Entry	$Ni(acac)_2$ (mol%)	(*R*)-**225** (mol%)	Temperature (°C)	Time (h)	GC yield (%) **190b**	*ee* **190b** (%)
a	5	7	–10	4	49	8
b	5	7	–70	4	31	22
c	10	14	–70[a]	4	6	7
d	5	7	–70[a]	4	14	7

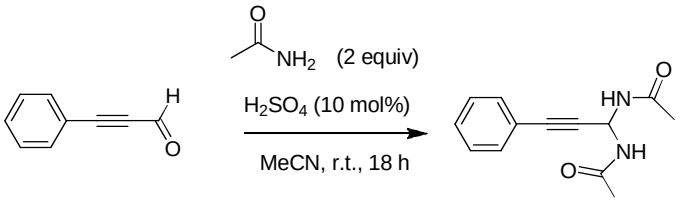
General conditions: $Ni(acac)_2$ (5-10 mol%) and ligand (7-15 mol%) were charged in Schlenk tube and 10 ml of Et_2O was added. The reaction was cooled to the temperature required. After 5 min substrate **187a** and ZnR_2 were added. a)The ligand and catalyst were stirred at room temperature for 30 min before the reaction was cooled down to the temperature indicated in the table.

Other alkylation reagents were also tested. Aluminium reagents $AlMe_3$ and $AlEt_3$ as well as Grignard reagent EtMgBr were tested in this reaction but none of them gave any conversion to the desired product. As a control experiment the reaction was also tested with ligand (*R*)-**225** without the nickel catalyst, but no reaction occurred.

3.7 Other reactions with the substrates and methodology developed this chapter

3.7.1 Propargylic diacetamide and propargylic *bis*-methoxyether in S_N2' nucleophilic substitution

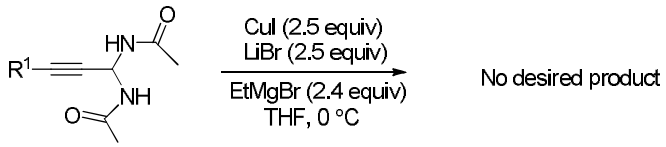
Inspired by the easy synthesis of propargylic diacetates diacetamide **232** was also prepared. There are plenty of examples in the literature for this type of diacetamides (although none of them propargylic) and the synthesis is often started from the corresponding aldehyde [139]. This reaction was attempted a couple of times with different reaction times, temperatures and catalysts but the best result, 57% yield of **232**, was obtained simply with sulphuric acid as catalyst and reaction time of 18 h (Scheme 68).



186a **232**
57% yield

Scheme 68

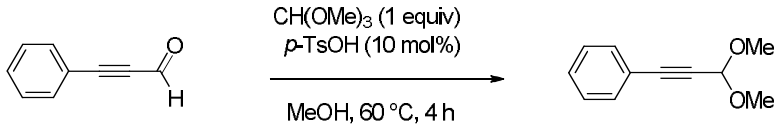
Diacetamide **232** was subjected to the cuprate-mediated S_N2' reaction to see whether an amido-allene could be made. The reaction was carried out under the optimized conditions for a propargylic diacetate (Scheme 69). However, none of the desired product formed.



232

Scheme 69

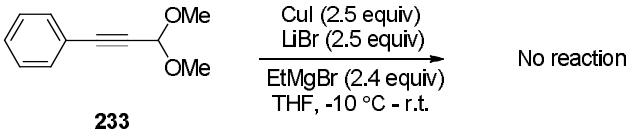
Propargylic acetal **233** was prepared to be tested in the cuprate-mediated S_N2' reaction. *Bis*-methoxyether **233** was synthesized from propargylic aldehyde **186a** using one equivalent of trimethoxymethane and a catalytic amount of *p*-toluenesulphonic acid [140]. Heating the reaction mixture at 60 °C for 4 hours gave propargylic acetal **233** in 50% yield after purification by distillation (Scheme 70).



186a **233**
50% yield

Scheme 70

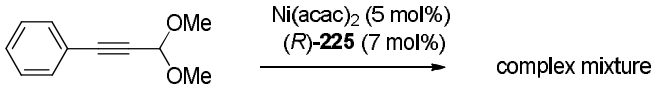
Cuprate mediated S_N2' reaction with acetal **233** was attempted. However, only the starting material was recovered and no allene was formed (Scheme 71).



233

Scheme 71

The nickel-catalyzed S_N2' reaction was tested also with a propargylic acetal **233**. However, attempts to react this substrate with $ZnEt_2$ in presence of a nickel catalyst resulted in a complex mixture from which no desired product could be isolated (Scheme 72).

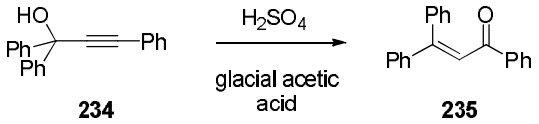


233

Scheme 72

3.7.2 Propargylic diacetates in Meyer-Schuster rearrangement

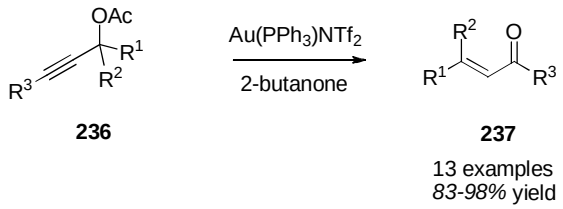
Some reactions were also carried out with the propargylic diacetates **187**. The the most succesful was a Meyer-Schuster rearrangement [141]. In 1922 Meyer and Schuster reported an acid-catalyzed rearrangement of propargylic alcohol **234** to enone **235** (Scheme 73).



234 **235**

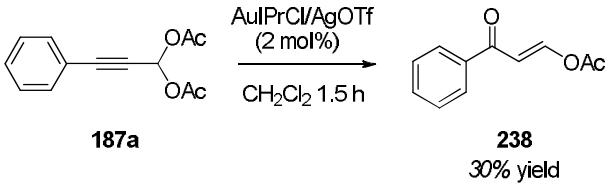
Scheme 73

A gold-catalyzed Meyer-Schuster rearrangement was developed in 2007 by both Nolan [142] and Zhang [143]. The two groups have studied the reaction quite thoroughly including computational studies and extensive studies on the scope of the reaction. Both groups started the synthesis of enones **237** from propargylic acetates **236** (Scheme 74).



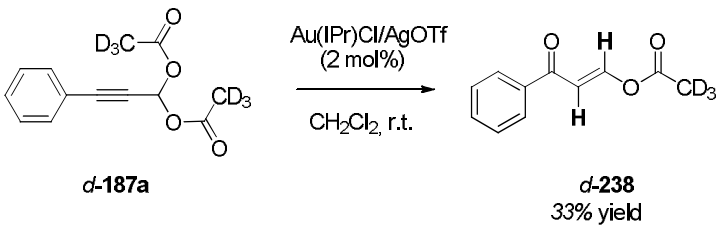
Scheme 74

The reactivity of propargylic diacetate **187a** was tested under gold-catalyzed conditions with Au(IPr)Cl/AgOTf as catalyst system and enone **238** was obtained with high selectivity but only moderate 30% isolated yield (Scheme 75). This reaction was carried out in non-distilled CH_2Cl_2 which is not an optimal solvent as the reaction needs some water. Nolan [142] debated that the reaction proceeds *via* an addition of water to the gold-activated alkyne, and as the acetate acts as leaving group the resulting hydroxyallene tautomerizes to the product enone. The reaction could be optimized by using wet solvents that would probably enhance the reaction rate and conversion.



Scheme 75

The reaction was tested once with a deuterated diacetate *d*-**187a** to see if any of the deuterium would be integrated into the final product. This was not the case and product *d*-**238** only contains protons on the alkene moiety (Scheme 76).



Scheme 76

The Meyer-Schuster reaction for propargylic *gem*-diacetates has not been previously reported in the literature. This short study extends the scope in the literature. However, this reaction was not considered to be interesting enough on its own, and no further optimization or scope study was carried out.

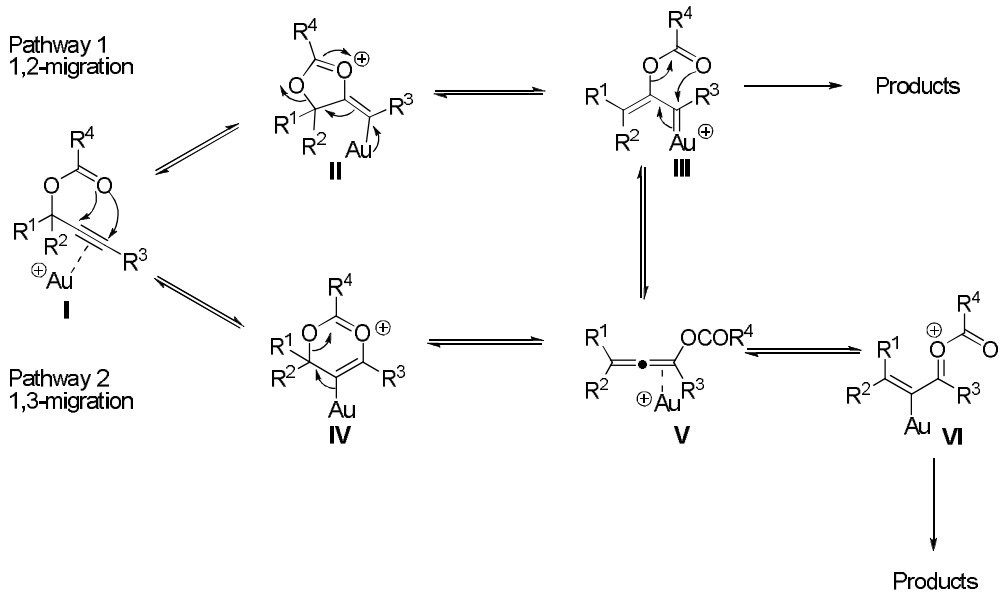
3.7.3 Summary

Two new methods were developed for the synthesis of allenyl acetates. The first method developed uses a cuprate-mediated S_N2' nucleophilic substitution. The new methodology permits the synthesis of allenyl acetates with an aromatic substituent at *C3* of the allenic compound and could be successfully applied to a family of substrates. The organocuprate-mediated reaction was reliable, several commercially available Grignard reagents could be used, and it was also easy to scale up to gram quantities without any loss in the yield. Secondly, advances were made towards a catalytic S_N2' reaction. An advantage of a catalytic version of this reaction could be the atom-economy of the transformation or asymmetric synthesis of the allenic products. However, in this case the nickel-catalyzed reaction proved unreliable and atom-economy cannot be claimed as 5-7 equivalents of zinc-reagent were needed for moderate yields. The synthesis of enantiomerically enriched allenic products did not work very well with this catalytic reaction as only up to 22% *ee* values were observed. Some of the work in Chapter 3 was published in 2010 [144].

4 Gold-catalyzed synthesis of indenes from allenyl acetates and propargylic acetates

4.1 Introduction to gold-catalyzed reactions of propargylic carboxylates

Propargylic carboxylates are highly versatile starting materials in gold-catalyzed reactions and their reactivity in the presence of a gold catalysts has been studied extensively [145]. A plethora of different rearrangement- and cyclization products can be obtained from propargylic carboxylates because of the ability of the carboxylate group to migrate on the gold-activated alkyne. The mechanistic explanation of the reactions often starts with 1,2- or 1,3 migration of the carboxylate (pathways 1 and 2 in Scheme 77), which leads to the formation of highly reactive intermediates; allenyl carboxylates **(V)** and gold carbenoids **(III)**.

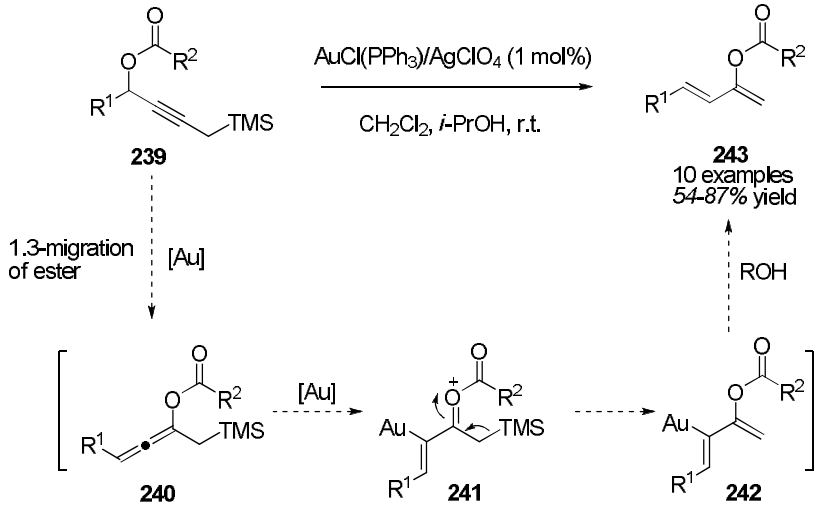


Scheme 77 Activation of propargylic carboxylate with a cationic gold-complex.

As the gold carbenoid **(III)** and allenyl carboxylate **(V)** can also transform into each other, the cycle forms a 'golden carousel' [146]. DFT calculations of the energy barriers show that the transformation of propargylic carboxylate **(I)** *via* two consecutive 1,2-shifts to **(V)** would be more preferential than one 1,3-shift. The highest energy transition state on the pathway from **(I)** *via* two consecutive 1,2-shifts to **(V)** is lower in energy than the highest energy transition state from **(I)** to **(V)** via direct 1,3-shift. However, in the computational study the differences in

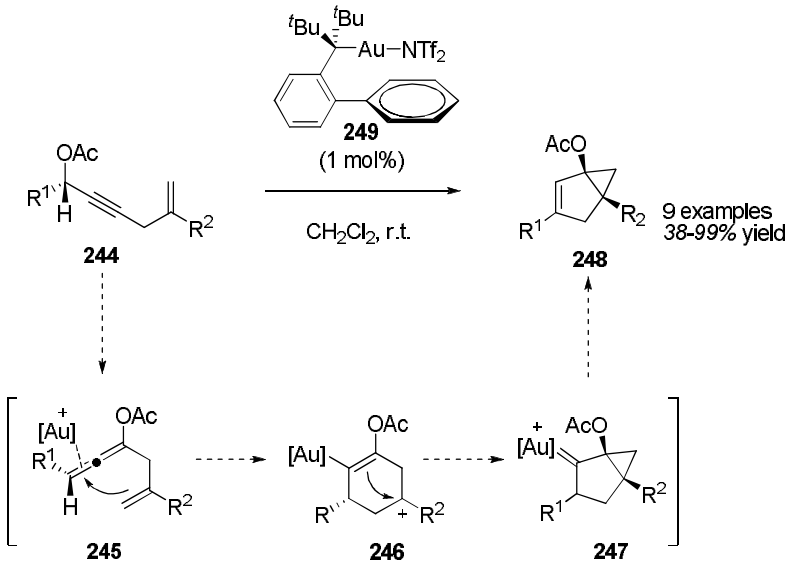
the energy barriers were so small that using different substrates or catalysts could affect the favored reaction route and thus the two reaction pathways are competitive.

There are some clear cases in the literature where the reactivity of a propargylic carboxylate can be explained by a preference toward 1,2- or 1,3-shifts. These two migrations present *5-exo-* and *6-endo-dig* modes of the nucleophilic attack of the carbonyl group to the activated alkyne. Internal alkynes often favor the *6-endo-dig* cyclization as in the synthesis of alkenyl enol acetates **243** from trimethylsilylmethyl-substituted propargylic carboxylates **239** (Scheme 78) where the reaction mechanism can be explained *via* the formation of allenyl carboxylate intermediate **240** [147].



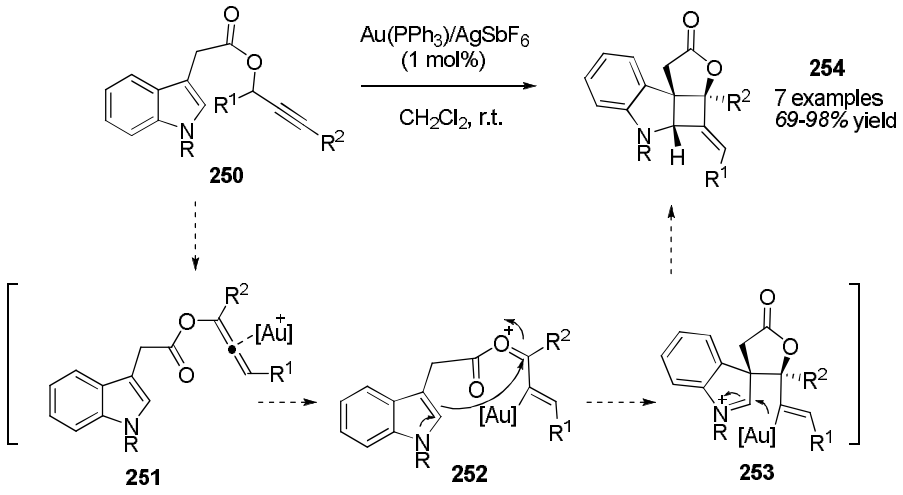
Scheme 78

Another example of favored *6-endo-dig* cyclization is the synthesis of bicyclo[3.1.0]hexanes **248** from 5-en-2-yn-1-yl acetates **244** (Scheme 79) [148]. The mechanism for this reaction can also be explained with the formation of allenic intermediate **245** followed by the attack of the intramolecular alkene on the gold-activated allene and consecutive cyclization of the cationic intrermediate **246**.



Scheme 79

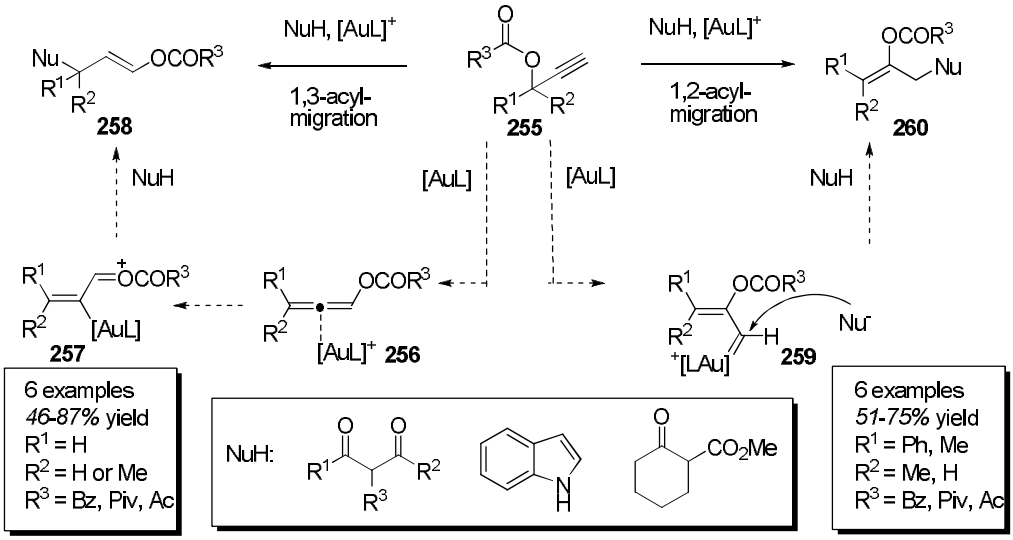
More complex structures can be accessed when an internal nucleophile is added to the substrate structure. For example, the nucleophile can be an indole as in Scheme 80 [149]. As before, propargylic carboxylate **250** transforms to an allenic intermediate **251**, which in turn is activated by the gold catalyst and this results in oxonium species **252**. The oxonium species can cyclize to the 3-position of the indole group and when this is followed by intramolecular trapping of the resulting iminium species **253** the cyclobutane ring **254** is formed.



Scheme 80

In some cases the favored reaction route goes via 1,2-migration of the carboxylate group. Echavarren and co-workers studied a nucleophilic substitution of carbon nucleophiles with

different propargylic carboxylates **255** with a terminal alkyne [150]. They discovered that the substitution can go *via* the allenic intermediate **256** or *via* gold carbenoid intermediate **259** depending on the substitution pattern of substrate **255** (Scheme 81). The conclusion was that terminal propargylic carboxylates with less hindered carboxylate groups (small R^1 and R^2) are more likely to undergo 1,3-migration and the propargylic carboxylates with large R^1 and R^2 groups would be more likely to choose 1,2- migration pathway. The authors also admitted that the factors that influence the regioselectivity in this reaction are not yet completely understood.

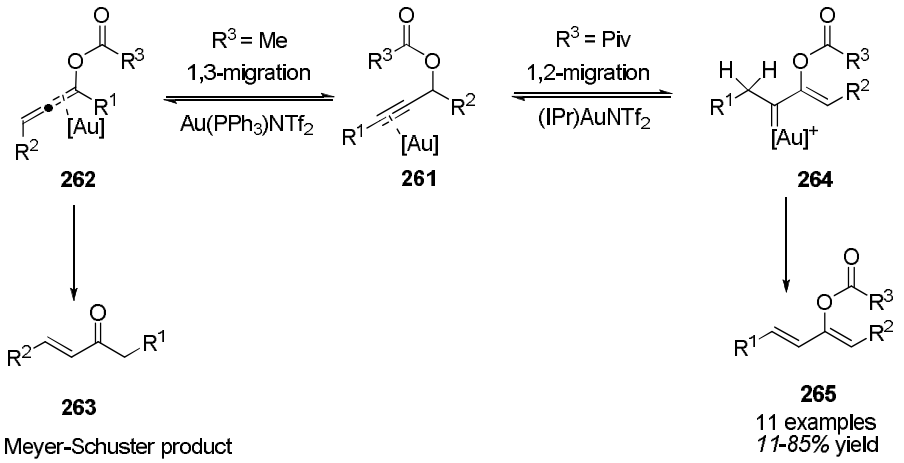


Scheme 81

To conclude (Schemes 78-81) there are some empirical rules for the preference of propargylic carboxylates to undergo 1,2- or 1,3 migrations. Internal alkynes often favor the 1,3-route which leads to allenyl acetate-type reactivity whereas terminal or electron-poor alkynes favor the 1,2-route that leads to gold carbenoid-type reactivity [145a]. There are exceptions to these rules and the reactivity of the propargylic carboxylate can be reversed by tuning the substitution and catalyst used.

Zhang and co-workers reported a synthesis of (1*Z*,3*E*)-2-pivaloxy-1,2-dienes **265** from propargylic pivalates **261** (R^3 = *t*-Bu) where the regioselectivity is completely the reverse of the general rules (Scheme 82) [151]. The propargylic pivalates **261** used in the synthesis had electronically unbiased internal alkynes and in earlier work of Zhang very similar substrates had been used in Meyer-Schuster type rearrangements with $Au(PPh_3)NTf_2$ as catalyst and

propargylic acetate as substrate (1.3-migration, Scheme 82) [141, 142, 143]. The preference to *5-exo-dig* cyclization was attained by using $IPrAuNTf_2$ as catalyst and a bulky pivalate as starting material.



Scheme 82

As a conclusion the reactivity of propargylic carboxylates in the presence of gold catalysts often involves allenic intermediates. Propargylic and allenic carboxylates are even often considered as 'equivalent' in gold-catalyzed conditions because often both will give similar final products.

4.2 Introduction to the synthesis of indenes

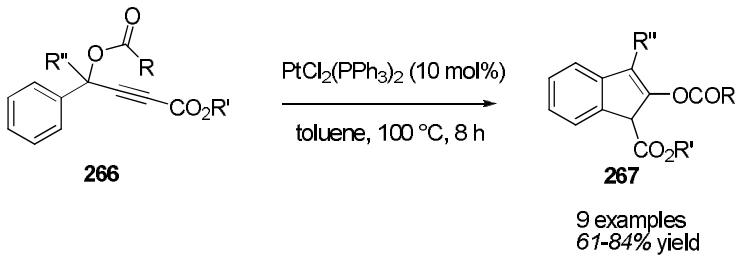
Indenes are widely used building blocks in organic chemistry. Indenes are used in the search for new pharmaceuticals, for example new anti-inflammatory agents [152] antidepressives [153] and compounds with psychological activity [154]. Indenes also find their place in materials science as starting materials for new conducting polymers [155] and liquid crystals [156]. Indene-containing structures are often used as ligands in transition metal chemistry. Examples of ruthenium [157], rhodium [158] and zirconium [159] complexes with indenyl ligands are commonly encountered.

4.2.1.1 General methods in indene synthesis

There are various ways to synthesize indenes and some of these are briefly reviewed below. These examples do not cover all the methodology available but will provide a small insight to the literature methods.

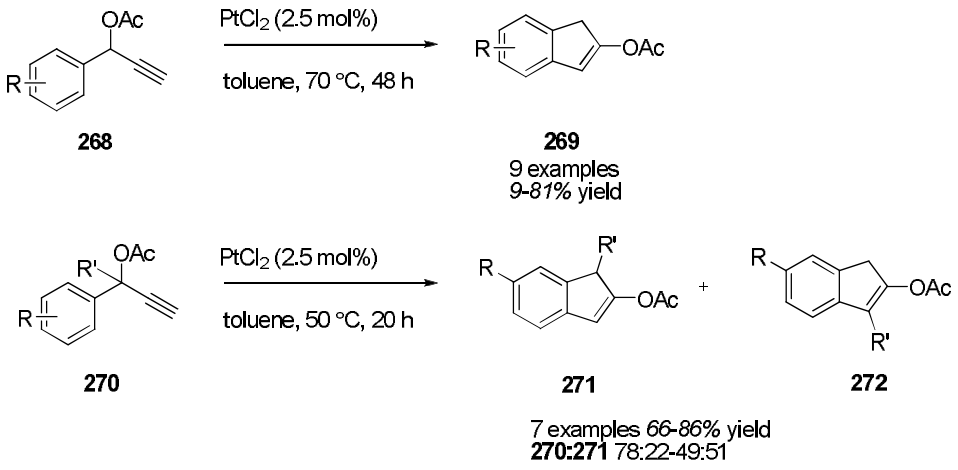
4.2.1.2 Platinum-catalyzed indene synthesis

Platinum catalysis has been used to prepare various indenes [160]. Both *t*-propargyl carboxylates and *sec*-propargyl carboxylates have been successfully used as starting materials. Sarpong and co-workers [160a] carried out a synthesis of indenes **267** starting from tertiary propargylic carboxylates **266** carrying a carboxylate function at *C1* position. They obtained only one isomer of the product indene **267** (Scheme 83). The reaction conditions are quite harsh as high temperatures and long reaction times are required.



Scheme 83

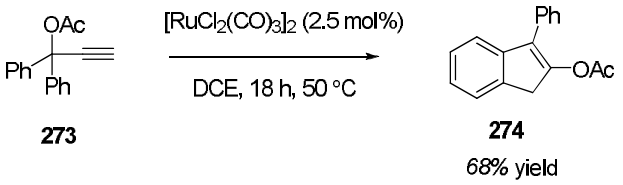
Ohe and co-workers published a similar synthesis of indenes starting from secondary and tertiary acetates **268** and **270** carrying terminal alkynes [160b]. Ohe also used $PtCl_2$ as catalyst. The reaction was selective with secondary acetates towards indenes **269** with mostly moderate yields. However, when tertiary acetates were used, the product indene was always obtained as a mixture of two isomers **271** and **272** (Scheme 84). In Ohe's methodology long reaction times are also required to obtain the indene product.



Scheme 84

4.2.1.3 Ruthenium-catalyzed indene synthesis

Ruthenium catalysts can yield indenes from propargylic acetates [119]. Only one example of this reaction is published. Using the ruthenium catalyst there were no byproducts from **273** reported and only indene **274** is formed selectively (Scheme 85).



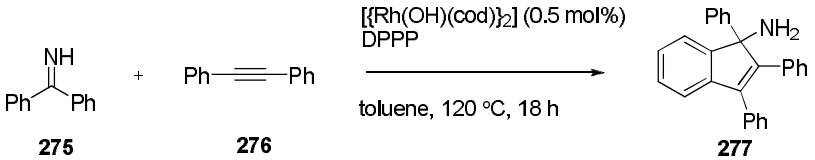
273 **274**

68% yield

Scheme 85

4.2.1.4 Rhodium-catalyzed indene synthesis

Rhodium catalysts have also been applied to indene synthesis [161]. For example, coupling between ketimine **275** and internal alkyne **276** led to [3+2] annulations giving amino-substituted indene **277** with high yield and selectivity (Scheme 86).



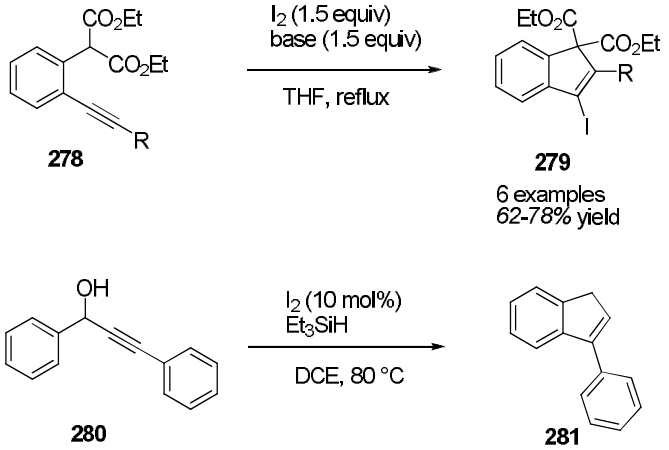
275 **276** **277**

94% yield

Scheme 86

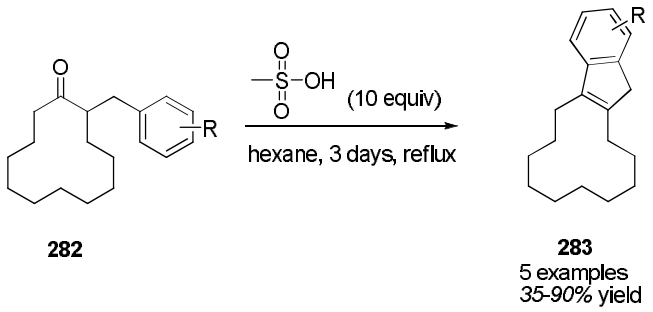
4.2.1.5 Non-transition metal-catalyzed synthesis of indenes

An electrophilic cyclization of 2-substituted ethynylmalonates **278** to indenes **279** has been reported in the presence of stoichiometric iodine and base [162] (Scheme 87). Diaryl propargyl alcohols **280** have been cyclized to indenes **281** with Et_3SiH and catalytic iodine [163] (Scheme 87).



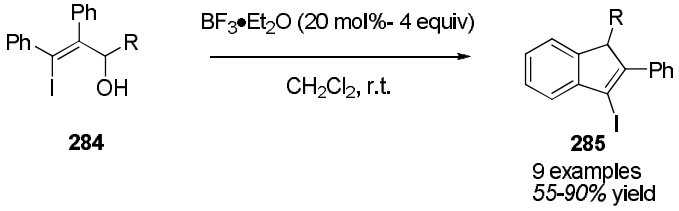
Scheme 87

Indenes have also been synthesized in the presence of Brønstedt acids [164]. Using tenfold amount of methanesulphonic acid yielded cyclododecano[b]indenes **283** with moderate to high yields from α-benzylcyclododecanones **282** (Scheme 88).



Scheme 88

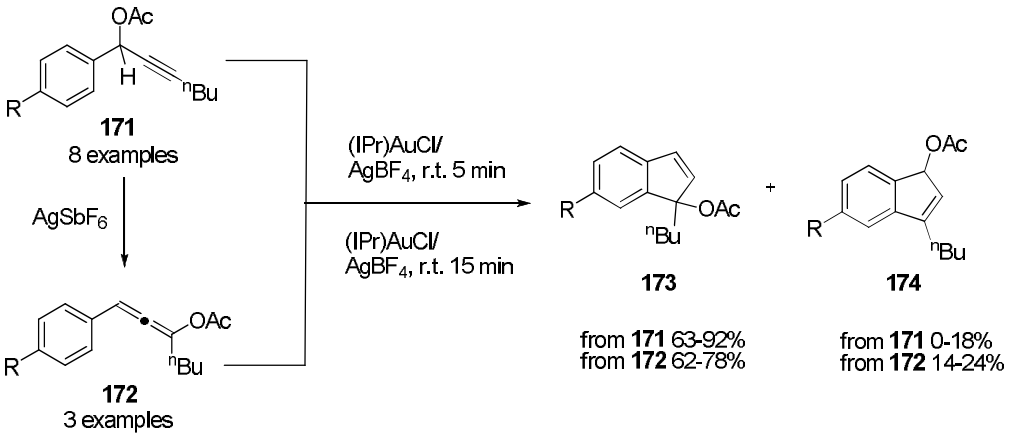
A Lewis acid-catalyzed Friedel-Crafts reaction has also been used in indene synthesis [165]. An example of this method is the synthesis of 3-iodoindenes **285** from iodinated allylic alcohols **284** with BF_3•Et_2O as catalyst or reagent (Scheme 89). There are also other examples where Lewis acids have been used in indene synthesis [166].



Scheme 89

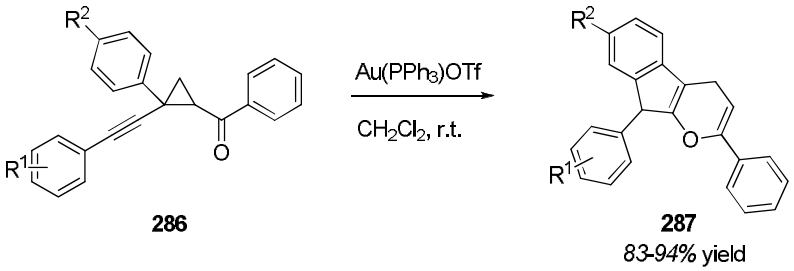
4.2.1.6 Gold-catalyzed indene synthesis

Gold catalysis has also found its place in indene synthesis. Nolan and co-workers reported in 2006 a cycloisomerisation of propargylic acetates **171** and allenyl acetates **172** to the corresponding indenes **173** and **174** (Scheme 90) [122][167]. They often obtained high yields and chemoselectivity to indene **173** but indene **174** was formed as minor product in some cases. With allenes **172** every example gave a mixture of products. The allenyl acetates **172** were prepared by silver-catalyzed rearrangement and they gave very similar product pattern as propargylic acetate **171**. In this approach the allenyl acetate and the propargylic acetate could be called 'equivalent' in the reaction conditions as both give similar products and yields in the gold-catalyzed reaction. The reaction conditions are very mild as the tranformation proceeds at room temperature and with short reaction times.



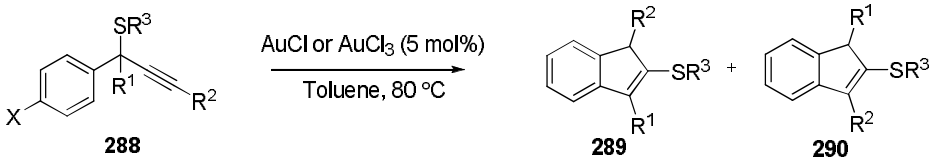
Scheme 90

Zhang and co-workers have also developed a gold-catalyzed indene synthesis. They published a synthesis of indenes **287** with 3 fused rings [168] (Scheme 91). A propargylic cyclopropane **286** rearranges to give indene structure **287** as product.



Scheme 91

Reaction of propargylic sulphides **288** with gold catalysts has also been reported [169] (Scheme 92). In this case indenes **289** and **290** are always prepared as a mixture. Instead of the oxygen of an carboxylate group it is the lone pair on sulfur that attacks the gold-activated alkyne forming a three-membered ring intermediate, which then opens to a gold carbenoid species. The authors made a large study and the product preference depends on the substituents R^1, R^2 and R^3.

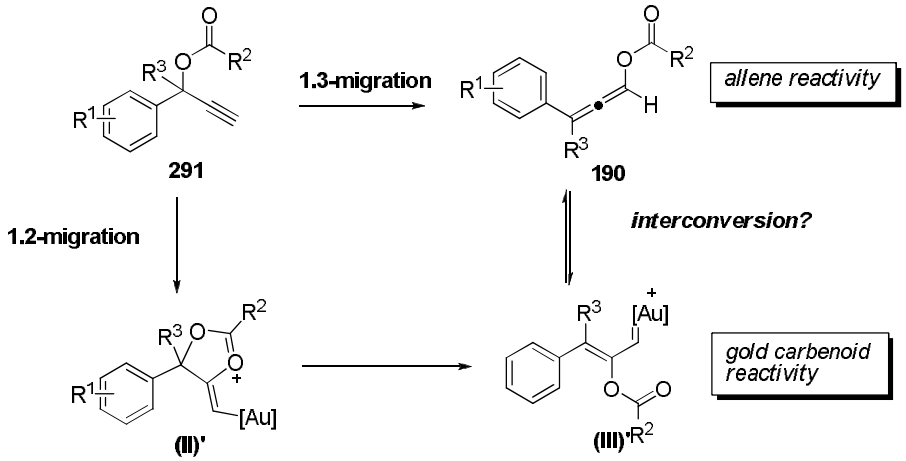


Scheme 92

In conclusion indenes can be synthesized from various starting materials and by several catalytic methods. In many cases the prefered starting material for these indene synthesis is a propargylic carboxylate or a propargylic alcohol. When comparing the different methods it can also be concluded that the gold-catalyzed indene synthesis often represents the mildest and fastest methodology, as elevated temperatures are rarely needed. The negative side in gold-catalyzed indene synthesis is that it often yields product mixtures and there are clearly some problems with chemoselectivity. The same issues apply to platinum catalysis. The mechanistic proposals in the publications related above often explain the problems in the chemoselectivity as due to competing 1,2- and 1,3- migrations of the propargylic carboxylates, as there is not always one clear preference which one of the two mechanisms is favored in the reaction. It would be desirable to develop a mild gold-catalyzed synthesis of indenes that is selective towards one indene product.

4.3 Allenyl acetates and propargylic acetates in gold-catalyzed indene synthesis

In Chapter was described the synthesis of allenyl acetates **190**. If these allenyl acetates are compared with their 'equivalent' propargylic acetates the conclusion would be that under gold-catalyzed conditions the allenyl acetate **190** can arise from propargylic acetate **291** (Scheme 93). Propargylic acetates with a terminal alkyne can also react *via* 1,2-acyloxy migration to give gold carbenoids **(III)'** but, according to Nolan's 'golden carousel,' [146] also this could be in equilibrium with the allenyl acetate **190**.



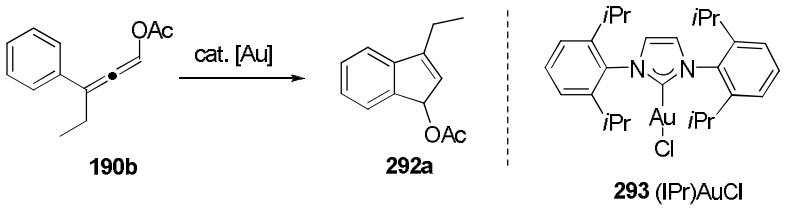
Scheme 93

The reactivity of allenyl acetates **190** under gold-catalyzed conditions is discussed in this chapter and their reactivity compared to that of propargylic acetates **291**. The reaction mechanism for both substrates is discussed in detail.

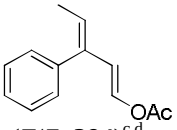
4.3.1 Indene synthesis with allenyl acetates: optimization and scope

The reactivity of allenyl acetate **190a** towards gold catalysts was tested with the expectation of obtaining a mixture of indene products. Initial attempts with $AuCl_3$ and $AuCl(PPh_3)$ were thwarted by the formation of complex reaction mixtures but gold-carbene complex Au(IPr)Cl (**293**) with a AgOTf co-catalyst immediately gave a very high yield of 3-ethyl-1*H*-inden-1-yl acetate **292a** (Table 27). Silver catalyst alone yielded a diene **294** as only isolable product (entry d).

Table 27



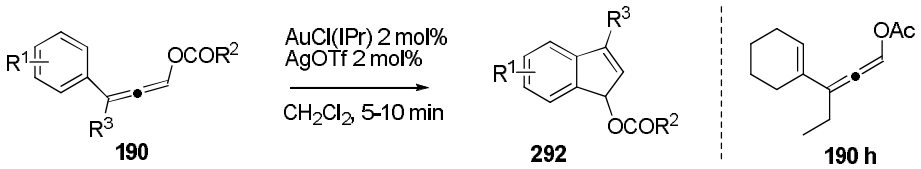
190b **292a** **293** (IPr)AuCl

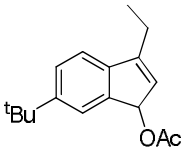
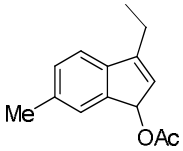
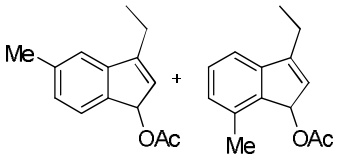
Entry	Catalyst	Time (min)	Solvent[a]	Yield (%) **292a**
a	$AuCl_3$ (2 mol%)	20	CH_2Cl_2	12[b]
b	(PPh_3)AuCl/AgOTf (2/2 mol%)	20	CH_2Cl_2	50[b]
c	(IPr)AuCl/AgOTf (2/2 mol%)	10	CH_2Cl_2	99[c]
d	AgOTf (5 mol%)	30	CH_2Cl_2	 37% (*E*/*Z*- **294**)[c,d]
e	(IPr)AuCl (2 mol%)	45	CH_2Cl_2	starting material recovered

a) Reactions preformed in CH_2Cl_2 as 0.1 mmol/ml solution of allene **190b**. b) NMR yield. c) Isolated yield. d) Only isolable product.

A small study of the scope of the gold-catalyzed reaction was carried out. As no byproducts form with the Au(IPr)Cl/AgOTf catalyst system up to quantitative yields of indenes **292** are attained. Pivalate and benzoate esters are tolerated providing high yields (Table 28 entries d and e). When the reaction was scaled up (> 0.5 gram scale), only 1 mol% of the catalyst was enough to provide up to quantitative isolated yields of **292**. The cycloisomerization was tested with one non-aromatic allene **190h** (entry i) but this gave no desired product.

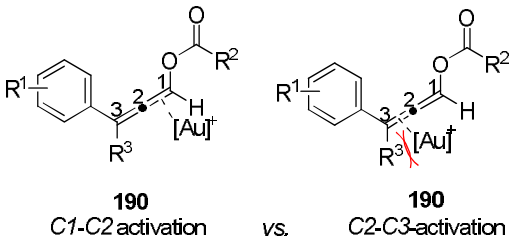
Table 28



Entry	R^1	R^2	R^3	Yield (%)[a] **292a-h**
a	H	Me	Et	99[b]
b	H	Me	Me	69
c	H	Me	*n*-Bu	92
d	H	Ph	Et	82
e	H	*t*-Bu	Et	96
f	4-*t*-Bu	Me	Et	 97
g	4-Me	Me	Et	 70
h	3-Me	Me	Et	 92% combined yield
i	1-cyclohexene	Me	Et	-

a) Isolated yield. b) 1 mol% of catalyst used (>0.5 g scale).

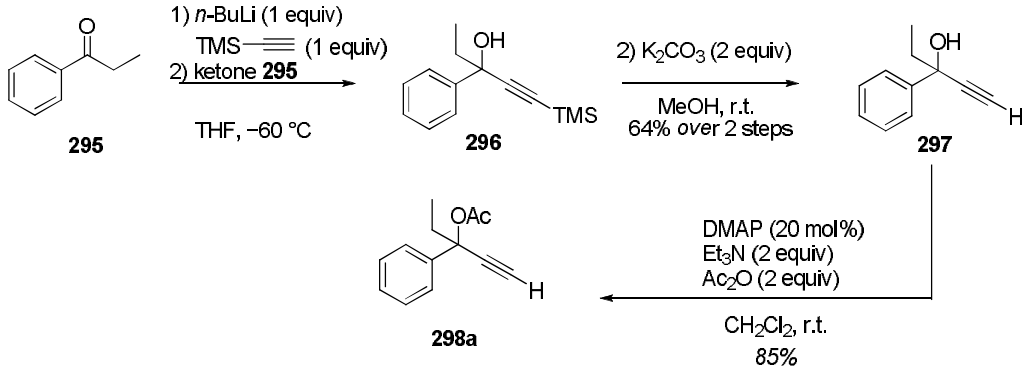
The reaction of allenyl acetates **190** with Au(IPr)Cl catalyst is very selective as only one indene product forms in the reaction. The reaction is also very fast and often over in 1-2 minutes and only due to the slowness of TLC-reaction monitoring the reaction times are assigned over 5 minutes. The selectivity of the reaction is likely due to the unhindered *C1-H* α to the acetate group. As the gold catalyst favors this unhindered *C1-C2* bond there is no competition between the two allenic bonds to be activated towards the carbocyclization (Scheme 94). The mechanism of this cyclization is discussed in detail later in the chapter.



Scheme 94

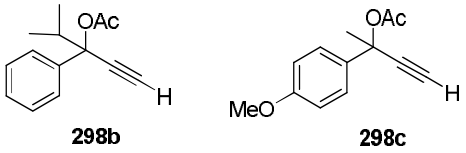
4.3.2 Constitutional isomers of two propargylic acetates

To study the reactivity of propargylic acetates some of these compounds were prepared. The ethyl-substituted propargylic acetate **298a** was synthesized starting from propiophenone **295**. The addition of lithiated trimethylsilylacetylene resulted in TMS-substituted propargylic alcohol **296** which was desilylated to give 3-phenylpent-1-yn-3-ol **297** with 64% yield over two steps. Alcohol **297** could be transformed to the corresponding acetate **298a** (Scheme 95).



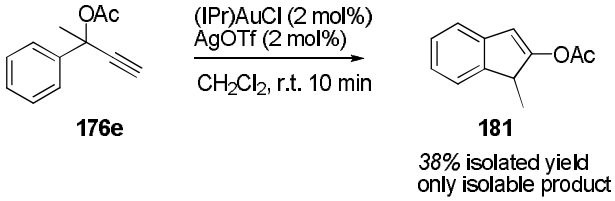
Scheme 95

Attempts were made to prepare *i*-Pr substituted and Ar-OMe substituted acetates **298b** and **298c**. However, the last step on the synthetic route (Scheme 95) proved problematic with these substrates, so the two compounds were never obtained in good yield or purity (Scheme 96).



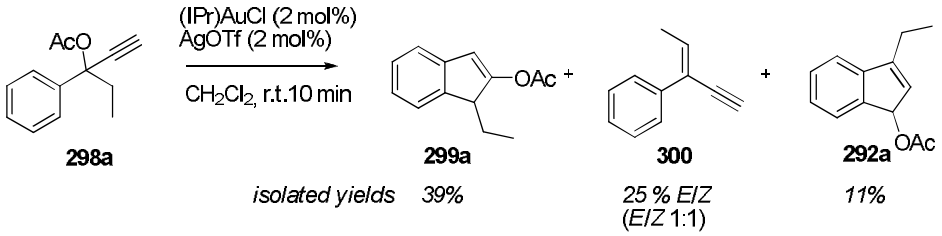
Scheme 96

The gold-catalyzed reaction of propargylic acetate **176e** has been described already in Chapter 3 (Table 13), where attempts were made to synthesize allenyl acetates with literature methods (Scheme 97). This reaction gave 1-methyl-1*H*-inden-2-yl acetate **181** with 38% yield. Despite the low yield **181** was the only product that could be isolated from the complex reaction mixture.



Scheme 97

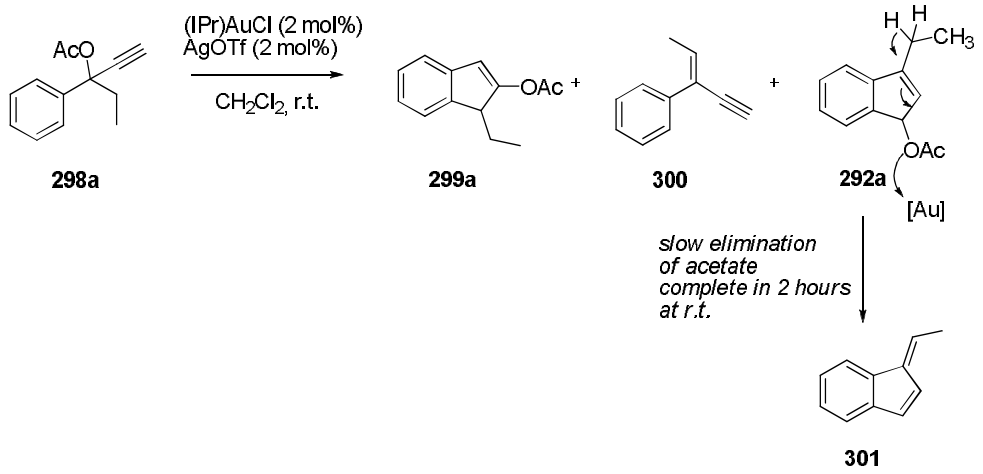
A similar test reaction was carried out with the ethyl-substituted propargylic acetate **298a** (Scheme 98). This substrate also gives 1-*Et*-1-*H*-inden-2-yl acetate **299a** as the major product (39%) but also some of the 3-*Et*-1-*H*-inden-1-yl acetate **292a** (11%), which is the only product obtained from allenyl acetate **190b**. A considerable amount, 25% of the substrate, is consumed to enyne product **300** arising from elimination of the acetate, which shows that the gold catalyst has also some oxophilic Lewis acid character.



Scheme 98

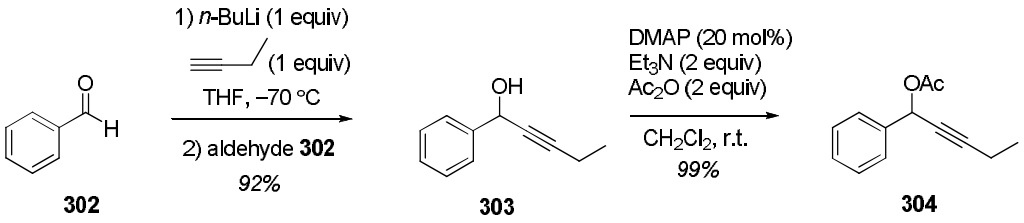
It was difficult to reproduce the isolated yields from the reaction in Scheme 98. The major products, indene **299a** and enyne **300**, were always isolable with approximately the same ratio. However, it seemed that the indene **292a** was somehow consumed if the reaction was left running for longer times. This problem was studied further and observed that the indene **292a** forms an elimination product **301** in the reaction mixture (Scheme 99). This behavior was never seen with the indene synthesis starting from allenyl acetates **190**, probably because of short reaction times. If the reaction was left running at room temperature, after 2 hours none of

indene **292a** was present in the reaction. The elimination could be followed with NMR experiments the results of which are described in detail in the experimental section.



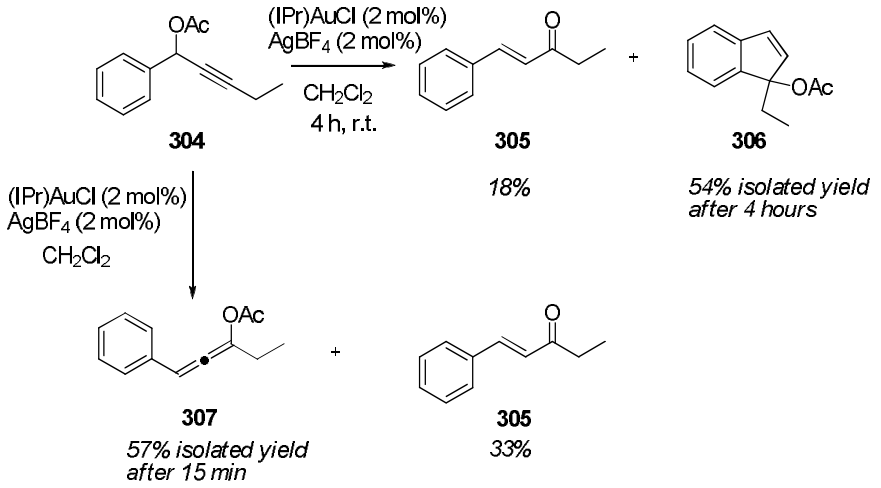
Scheme 99

Propargylic acetate **304** is a constitutional isomer of **298a** (Scheme 100). The acetate **304** was synthesized so that the reactivity of the two propargylic acetates in the presence of gold catalysts could be compared. The synthesis was started from benzaldehyde **302** and 1-butyne. Gaseous 1-butyne had to be first condensed in a Schlenck tube at –78 °C before deprotonation with *n*-BuLi and following addition of benzaldehyde **302**. This reaction route yielded propargylic alcohol **303** with 92% yield and following transformation to acetate **304** was nearly quantitative.



Scheme 100

When the propargylic acetate **304** was reacted with Au(IPr)Cl, allenyl acetate **307** was the major product (57% yield) after 15 min reaction time (Scheme 101). At longer reaction times (4 hours), indene **306** was isolated with 54% yield. With propargylic acetate **304** the reaction clearly proceeds *via* allenic acetate **307**. A considerable amount of Meyer-Schuster enone **305** also forms in both cases [141, 142, 143].



Scheme 101

4.3.3 Reaction mechanisms for the formation of indenes

4.3.3.1 Reaction mechanism for the cycloisomerization of allenyl acetate 190b

Chapter 3 described the synthesis of enantiomerically enriched allenenyl acetate (*S*)-(+)-**190b** by lipase-catalyzed kinetic resolution and this was now used to access enantiomerically enriched samples of the allene. Gold-catalyzed cycloisomerization of **190b** is a fast reaction at room temperature but when the reaction mixture is cooled down to 0 °C the reaction slows down enough that it can be followed by gas chromatography. Samples were taken from the reaction mixture and filtered through Celite to remove the catalyst and the samples were used for gas chromatography analysis. Chiral gas chromatography column *octakis*(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin separates both **190b** and **292a** to their enantiomers.

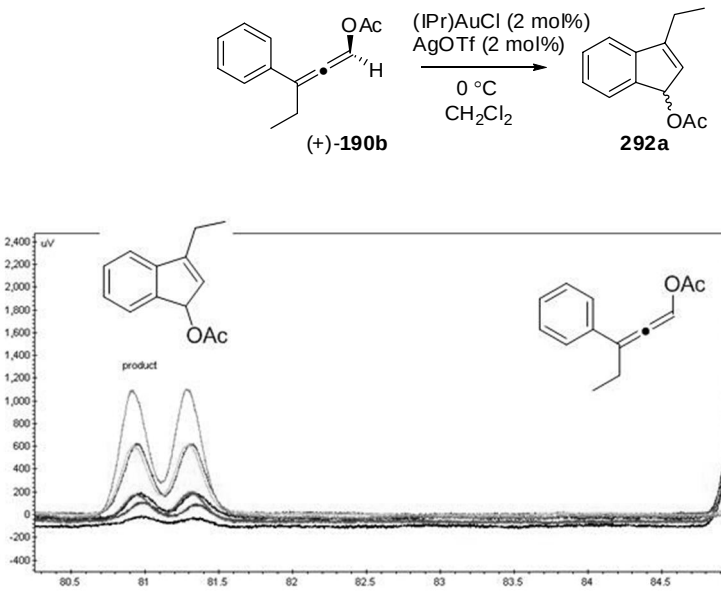


Figure 2

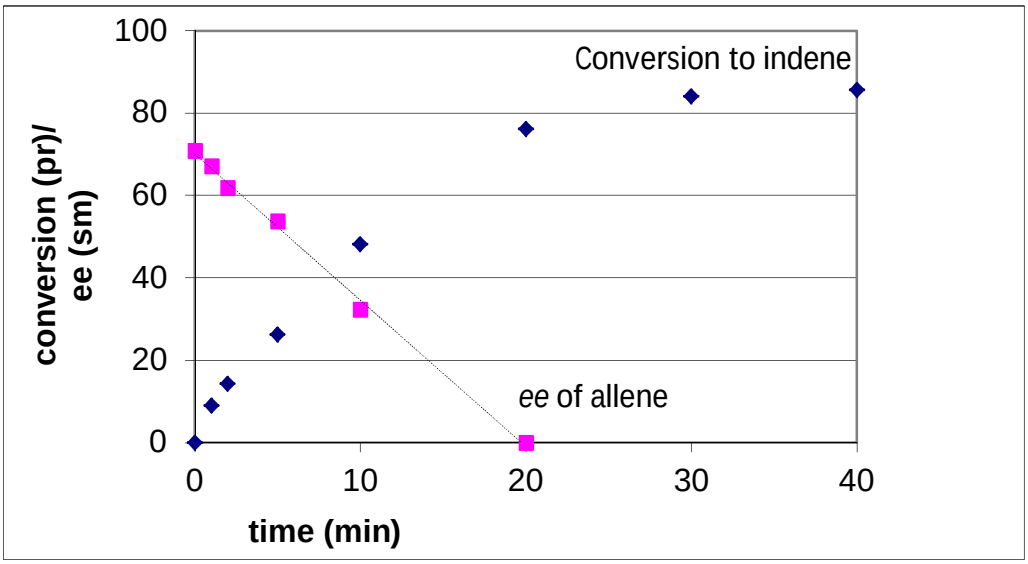
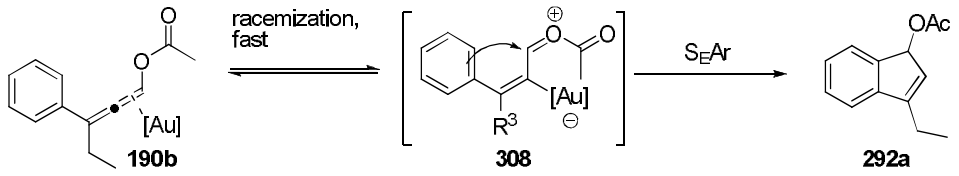


Figure 3

The gas chromatography data (Figures 2 and 3) show that the allene (+)-**190b** is racemized in the course of the reaction. After 20 minutes reaction time only racemic allene **190b** is left. There must be a planar intermediate **308** in equilibrium with the allene **190b**. Intermediate **308** can cyclize *via* electrophilic aromatic substitution (S_EAr); racemic indene **292a** is obtained as product (Scheme 102).



Scheme 102

At first the objective was only to follow the chirality transfer in the cycloisomerization of allenyl acetate **190b** but these results were encouraging as a clear insight was obtained to how the gold-catalyzed reaction proceeds. At this point a gas chromatography program was optimized, which separated 1-*H*-allenic acetate **190b**, 1-*H*-propargylic acetate **298a** and indenes **292a** and **299a** to their enantiomers.

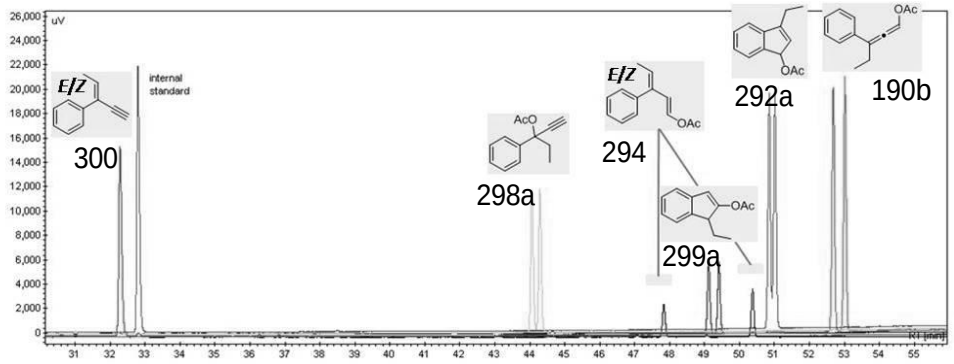


Figure 4: GC retention times of **292a** (t_r ~ 50.86/51.01 min), **190b** (t_r ~ 52.68/53.02 min), **298a** (t_r ~ 44.06/44.29 min), **299a** (t_r ~ 49.12/49.41 min), **300** (t_r ~ 32.28 min) and **294** (t_r ~ 47.84/50.38 min) on GC column *octakis*(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin. Compounds **304** (t_r ~46.75/47.13 min), **307** (t_r ~ 49.29/49.83 min) and **306** (t_r ~ 43.80 min) can be separated from the rest. All chiral compounds except for **306** are separated to their enantiomers.

The reaction with **190b** was run again on this program, this time the reaction temperature was set to -10 °C. The results are similar to those obtained earlier (Figure 2). The reaction proceeds cleanly without the formation of any of the propargylic acetate **198a**. None of the compounds in Figure 4, except for **190a** and **292a**, are seen in the course of the reaction.

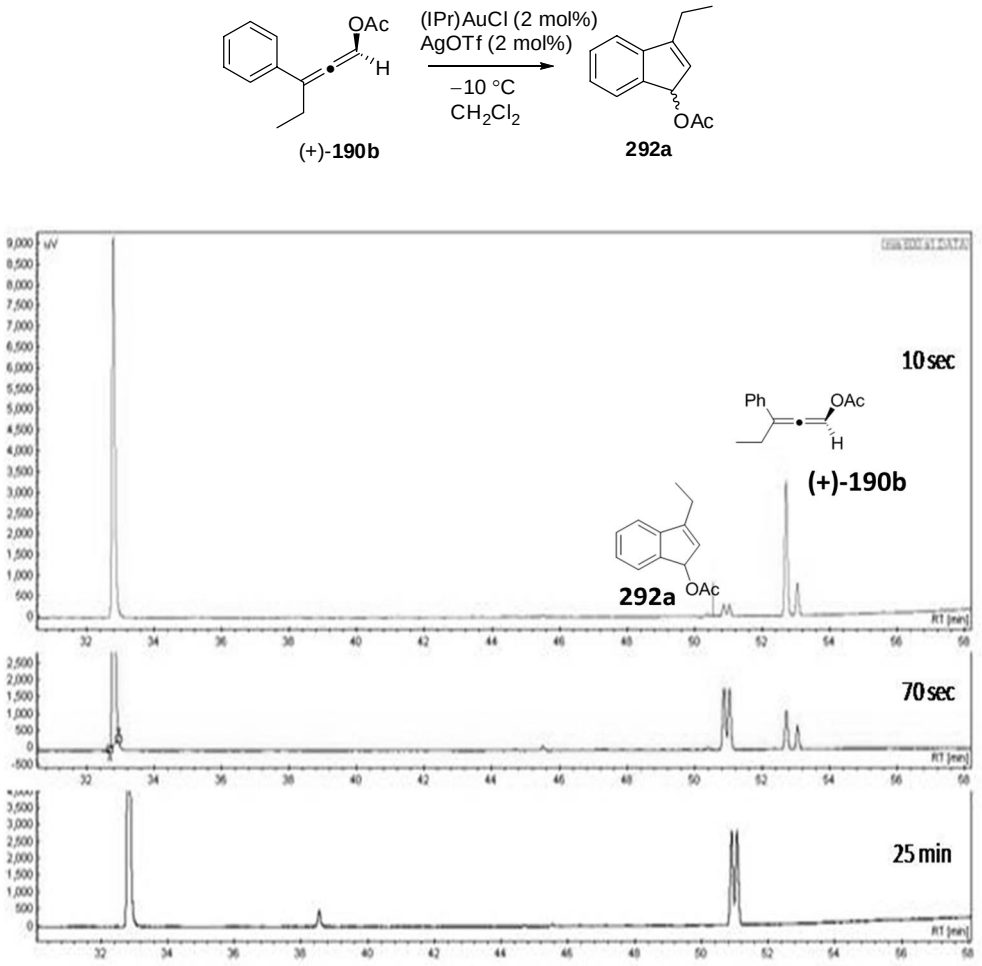
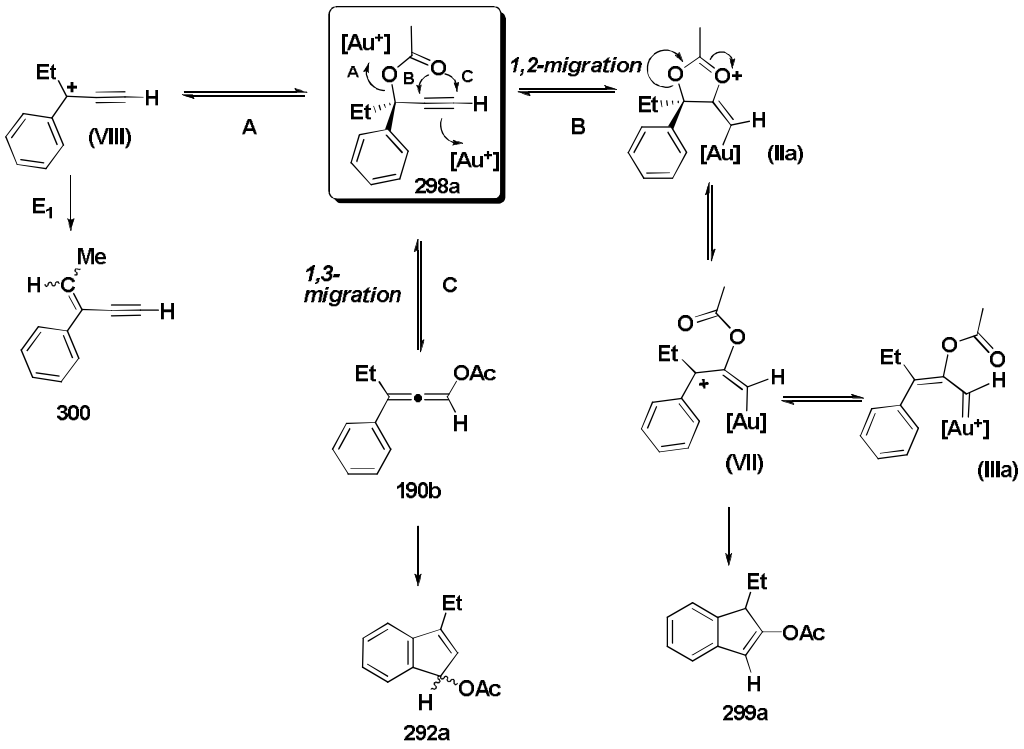


Figure 5

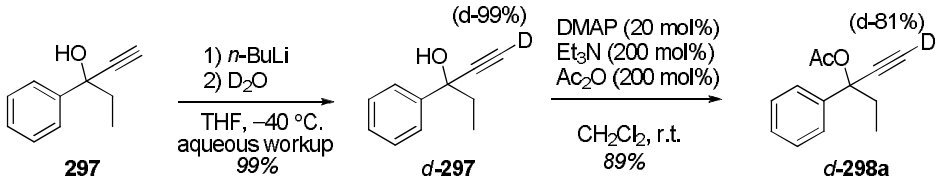
4.3.3.2 Reaction mechanism for the cycloisomerization of propargylic acetate 298a

The mechanism of gold-catalyzed cycloisomerization of propargylic acetate **298a** is proposed in Scheme 103. The reaction can take three courses. The first option is the 1,2-migration of the acetate group (route B) which leads to the major product **299a** *via* gold carbenoid complex **(IIIa)**. Secondly, the gold catalyst can act as oxophilic Lewis acid (Route A) which leads to the elimination of the acetate group and to product **300**. Thirdly, the propargylic acetate **299a** can rearrange to the allenic acetate **190b** which will quickly cyclize to minor indene product **292a** (Route C).



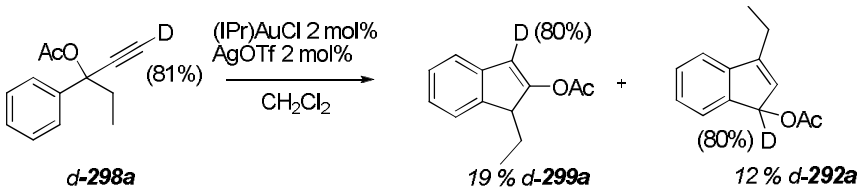
Scheme 103

To further confirm the reaction mechanism in Scheme 103 deuterium-labelled propargylic acetate *d*-**298a** was prepared (Scheme 104). 3-Phenylpent-1-yn-3-ol **297** was deprotonated with *n*-BuLi and the reaction was quenched with deuterium oxide to give *d*-**297** with 99% yield after aqueous workup (*d*-purity 99%). Propargylic acetate *d*-**298a** was obtained with 89% yield and 81% *d*-purity.



Scheme 104

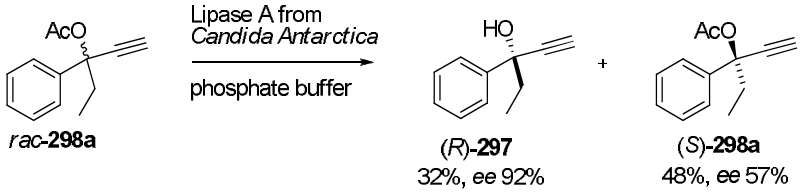
The *d*-labeled propargylic acetate *d*-**298a** was subjected to gold catalysis and it gave indene products *d*-**299a** and *d*-**292a** as expected (Scheme 105). Deuterium-label test supports the proposed reaction mechanism as it maps to the expected *H*-atom positions in Scheme 103.



Scheme 105

4.3.3.3 Some unclear mechanistic results with propargylic acetate 298a

Enantiomerically enriched acetate **298a** can be accessed by kinetic resolution with Lipase A from *Candida Antarctica* (Scheme 106). Acetate (*S*)-**298a** is obtained with 48% yield and 57% *ee* and alcohol (*R*)-**297a** with 32% yield and 92% *ee*.



Scheme 106

When the gold-catalyzed cycloisomerization reaction of (*S*)-**298a** was cooled to –10 °C it could be monitored with the same method as the cycloisomerization of alleneacetate **190b** (Figure 6).

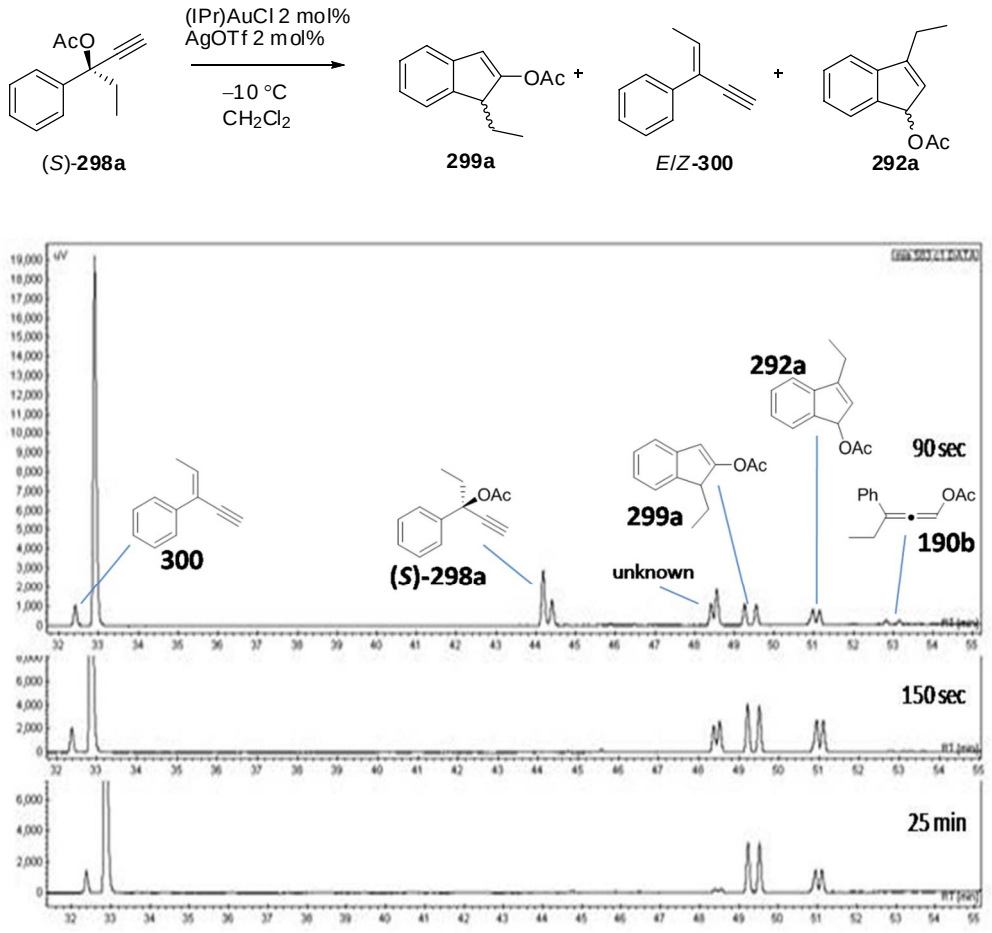
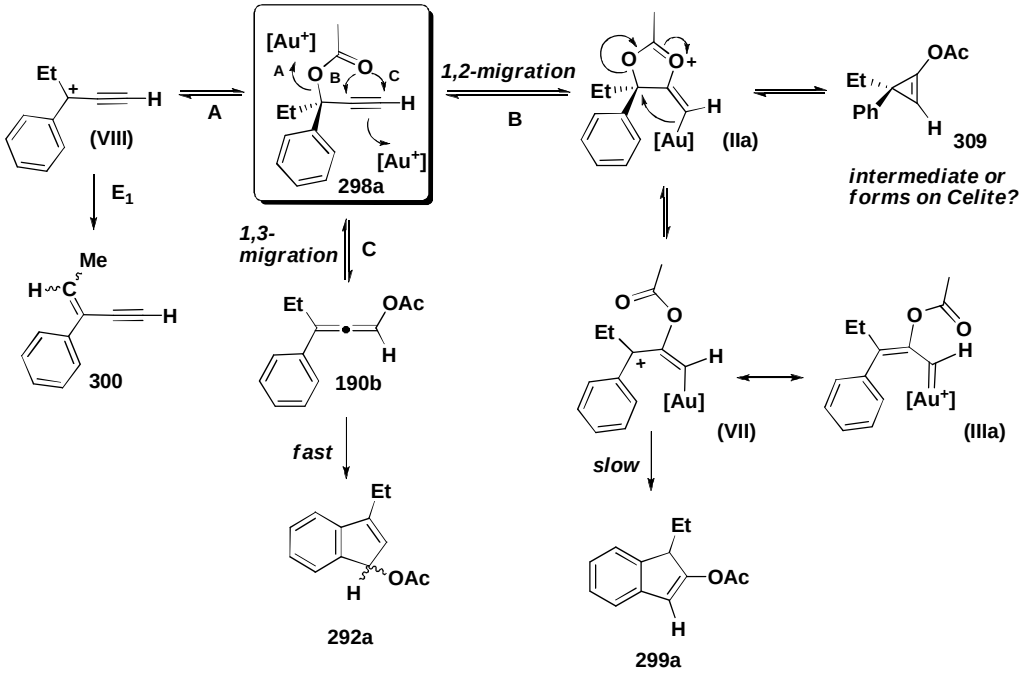


Figure 6

The following conclusions can be drawn from Figure 6. The elimination product **300** forms right in the beginning of the reaction along with some **190b**. Any allene **190b** formed rapidly cyclizes to indene **292a**. There is also an unknown chiral compound visible in the reaction mixture. The unknown compound elutes as two peaks with retention time (t_r ~ 48.41/ 48.56 min). It is formed with partial transfer of chirality (best seen at 90 sec, Figure 6). As the unknown compound vanishes towards the end of the reaction it was at first assigned as an intermediate in the reaction pathway. As significant quantities (>10 mol-%) of this compound can be detected by both NMR and gas chromatography, it cannot be a gold-bound species such as **(IIa)** or **(VII)** (Scheme 107) as normally presented as intermediates of 1,2-acyloxy migration (route B, Scheme 107). Additionally, such intermediates are very unlikely to survive GC analysis. The unknown compound was too reactive to be isolated, so only partial ^{1}H and ^{13}C NMR data could be obtained on the reaction mixture. These data are tentatively assigned to

the cyclopropene acetate **309** (Scheme 107). The cyclopropene acetate **309** is expected to arise from **298a** with transfer of chirality.

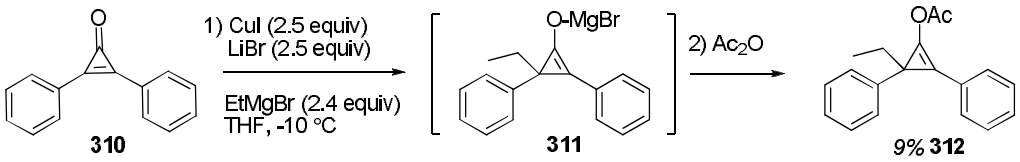


Scheme 107

The unknown compound (assigned as **309**) could not be isolated to allow a full set of analytical data to be attained. Some information of the structure could be gathered from NMR data of crude reaction mixtures. As the compound could not be isolated and purified, it is not certain whether the compound forms in the reaction mixture or on Celite as the reaction must be quenched before GC analysis. It must also be mentioned that this compound is decomposed if it gets in touch with silica gel. The gold-catalyzed reaction is so fast that the GC samples could not be run without quenching the reaction first. Attempts were made to subject the intermediate to the gold-catalyzed reaction conditions, but it did not clearly react to any of the known isolable products. It could be that this unknown compound forms on Celite from one of the reactive intermediates and this is the reason it is no more visible in the end of the reaction.

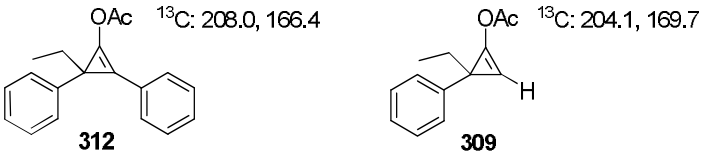
Due to the rarity of cyclopropene acetates in the primary literature we attempted the preparation of an analogue of the proposed structure **309**. Commercially available 2,3-diphenylcycloprop-2-enone **310** was treated first with an ethyl cuprate and the resulting enolate

311 reacted with Ac_2O (Scheme 108). 3-Ethyl-2,3-diphenylcycloprop-1-enyl acetate **312** was attained in low (9%) isolated yield.



Scheme 108

The ^{13}C NMR data of **312** was compared to those of **309** (Scheme 109). There are some similarities to these two compounds. However, as the complete analytic data of **309** could not be obtained this structure remains tentative.



Scheme 109

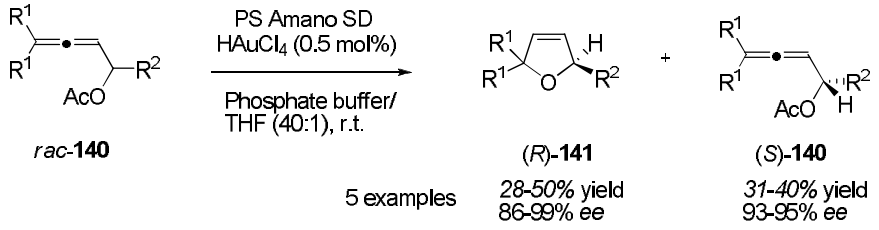
4.3.4 Summary

A thorough study of the reactivity of allenyl acetates **190** and propargylic acetates **298** in the presence of gold catalyst has been presented. It was discovered that allenyl acetates **190** are excellent substrates for the synthesis of indenes **292** as the reaction with Au(IPr)Cl/AgOTf proceeds with complete chemoselectivity. It was also discovered that although often allenyl acetates and propargylic acetates having the same substitution pattern are 'equivalent' in gold-catalyzed reactions, this is not the case with allenes **190** as they yield different products than their 'equivalent' propargylic acetates **298**.

5 Conclusion and future work

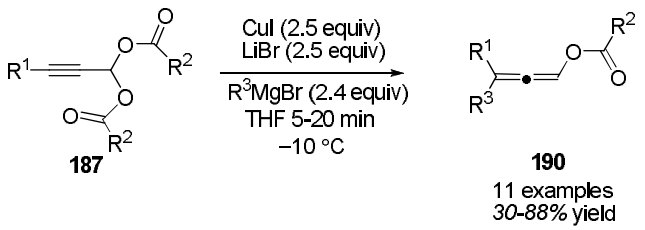
Although this thesis was composed of three separate projects, the common aim was to develop new synthetically useful reaction methodologies towards the preparation and transformations of allenic compounds. The most important findings of this work can be summarized as follows:

- Some α-allenic acetates are excellent substrates for lipase-catalyzed kinetic resolution yielding α-hydroxyallenes in high enantioselectivities. The α-hydroxyallenes can be transformed into 2,5-dihydrofurans with a gold catalyst in the same reaction pot. This tandem transformation worked well with five substrates yielding 2,5-dihydrofurans with 28-50% yield and 86-99% *ee* and the remaining α-allenic acetates with 31-40% yield and 93-95% *ee* (Scheme 110). It was also discovered that bulky substituents next to the acetate group is detrimental to this transformation as the active site on the lipase (lipase from *Burcholderia cepacia*) is too small.



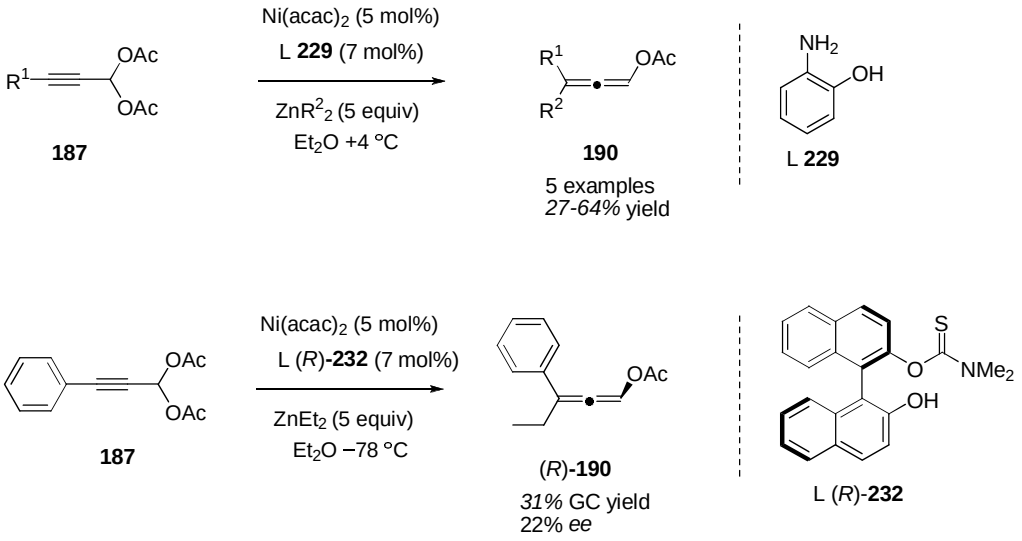
Scheme 110

- Allenyl acetates can be synthesized *via* a cuprate-mediated S_N2' substitution reaction. This method gives access to allenyl acetates with substitution pattern that cannot be accessed with literature methods. Altogether eleven allenyl acetates were synthesized with this method with 30-88% yields (Scheme 111).



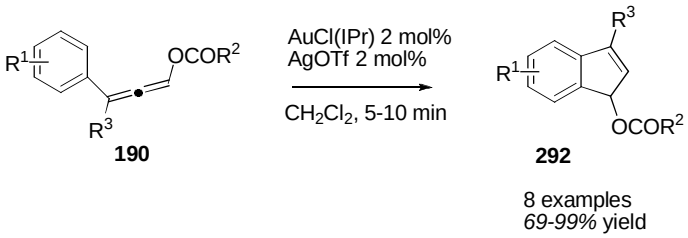
Scheme 111

- In attempts to develop a catalytic variant of the S_N2' nucleophilic substitution it was discovered that a nickel-catalyzed S_N2' reaction with amino-alcohol ligand and zinc alkylation reagent gives the highest chemoselectivity of the desired allenyl acetate product. However, the reaction yields allenyl acetates with only up to 64% yields. By using chiral ligands up to an 22% *ee* was obtained for the allenic product (Scheme 112).



Scheme 112

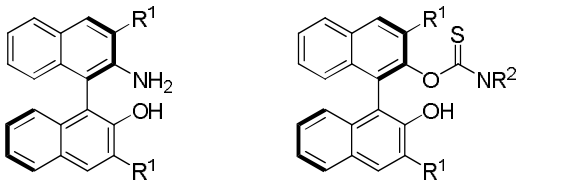
- Allenyl acetates under gold-catalyzed reaction conditions can yield indenes with up to quantitative yields and excellent chemoselectivity. Altogether eight indenes were prepared with 69-99% yield (Scheme 113). Propargylic acetates with terminal alkyne did not undergo selective cycloisomerization but yielded only product mixtures.



Scheme 113

Particularly the third point has potential for further study as the nickel-catalyzed S_N2' substitution reaction has potential for an asymmetric transformation. A full library of BINAM-

based or thiocarbamate ligands with bulky substituents (Scheme 114) should be synthesized and tested in this reaction. Although this work was beyond the scope of this thesis, the groundwork has been presented here.

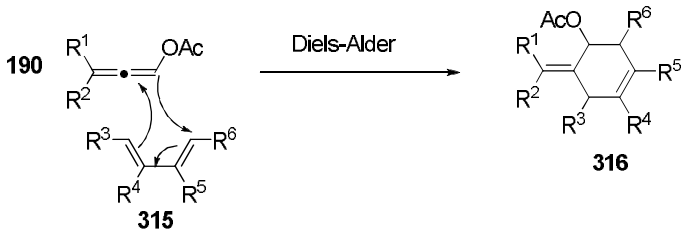


313
NOBIN-type ligands

314
thiocarbamate-type ligands

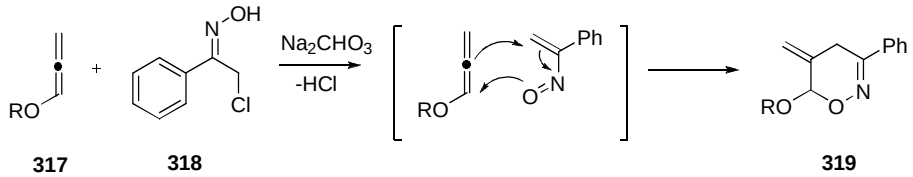
Scheme 114

Further reactions could also be developed with the allenyl acetates. The allenyl acetates synthesized in this work might have interesting applications for instance in Diels-Alder type cyclization reactions (Scheme 115).



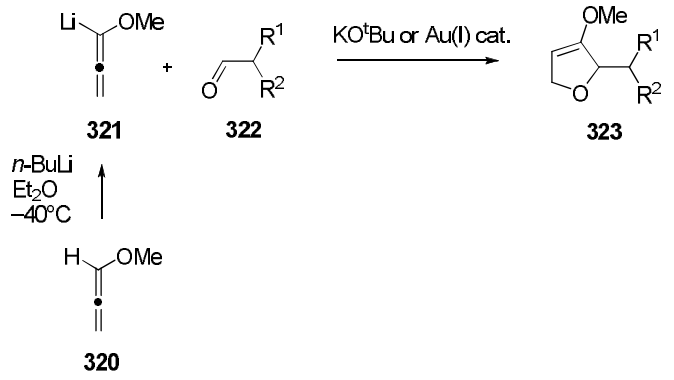
Scheme 115

Reissig reported Diels-Alder-type cyclizations of allenic ethers **317** in 2002 [170] with oximes **318** resulting to interesting heterocycles **319** (Scheme 116).



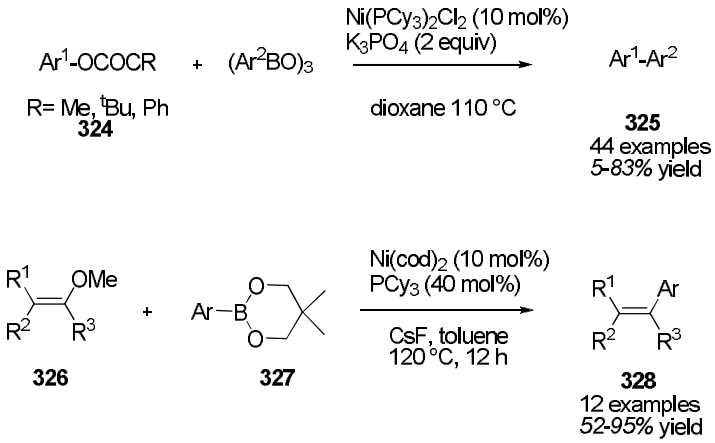
Scheme 116

There are also known [3+2] cyclizations performed with allenic ethers **320** and aldehydes **322** [171] (Scheme 117). This type of transformation might also be interesting to try with allenic acetates prepared within this thesis work.



Scheme 117

What might be also interesting to try are couplings of the allenic acetate. There are plenty of examples of couplings of aromatic or allylic esters **324** and **326** with boronic acids under nickel-catalyzed conditions [172] (Scheme 118). This type of reaction has, however, not been reported for an allenic carboxylate.



Scheme 118

In conclusion, the projects presented in this thesis work towards efficient methods to synthesize allenic compounds, and their use in gold-catalyzed transformations, and resulted in the development of several new reaction methodologies. The work also gave access to several new compounds. The work presented in this thesis will act as a base for new inspiring ideas and several research projects could arise from the work started in this thesis.

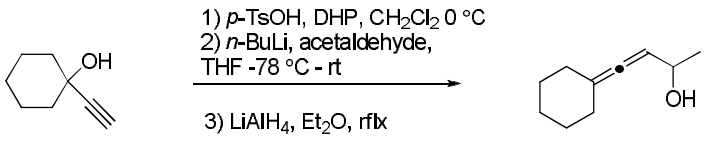
6 Experimental data

6.1 General remarks

All reactions involving air sensitive materials were carried out under argon atmosphere using standard Schlenk techniques. Reagents and catalysts were purchased reagent grade and used without further purification. Aldehydes were distilled prior to use. Diethyl ether and tetrahydrofuran were distilled under argon from Na-benzophenone and dichloromethane was distilled from CaH_2. All other chemicals were purchased from commercial sources and used as received. Column chromatography was carried out with Acros silica gel 60 and petroleum ether used in column chromatography had boiling range 40 °C-60 °C. ^{1}H and ^{13}C NMR spectra were recorded with Bruker DRX 400, DRX 500, DPX400 or AV400 spectrometers at room temperature with $CDCl_3$ as solvent, and signals are assigned as singlet (s), doublet (d), triplet (t), quartet (q), quintet, sextet and septet. Chemical shifts were determined relative to the residual solvent peaks ($CDCl_3$: δ=7.26 for protons, δ=77.1 for carbon atoms). *J* values are given in Hertz. Infrared spectra were recorded using Bruker Tensor 27 spectrometer. Specific rotations were measured using Perkin Elmer 341 or ADP440 polarimeter BS at ambient conditions and are given in 10^{-1} deg cm^2 g^{-1}; *c* is in g per 100 cm^3 of solvent. Mass spectra were obtained on Bruker Daltonics micro TOF (ESI), Bruker Daltonics APEX 4 ECR FTMS (EI) and VG Autospec (EI). Elemental analyses were performed using a Fisons Instruments EA 1108 CHN elemental analyser. Gas Chromatographers used were Varian 420 or CE Instruments GC 8000 and columns used was *octakis*(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin and *octakis*(2,3-di-*O*-pentyl-6-*O*-methyl)-γ-cyclodextrin.

6.2 Tandem Enzyme/Gold –catalyzed reactions

4-Cyclohexylidenebut-3-en-2-ol: general procedure for α-hydroxyallenes 139 (139a)



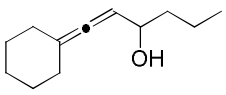
39% over 3 steps

A solution of 1-ethynylcyclohexanol (2.5 g, 20 mmol, 100 mol%) and DHP (2.75 ml, 30 mmol, 150 mol%) in dry CH_2Cl_2 (10 ml) was cooled to 0 ºC and *p*-TsOH (0.038 g, 0.2 mmol, 1

mol%) was added. The reaction was quickly warmed to rt and then cooled to –78 ºC. To the reaction mixture was first added THF (10 ml) followed by dropwise addition of *n*-BuLi (2.5 M, 8 ml, 20 mmol, 100 mol%). After 30 min stirring (typically the reaction mixture warmed to about –40 ºC during this time) acetaldehyde (1.3 ml, 22 mmol, 110 mol%) was added and reaction allowed to warm slowly to rt. The reaction was quenched with saturated NH_4Cl solution and the aqueous phase was extracted three times with Et_2O. The combined organics were washed with saturated aqueous NaCl solution and dried with Na_2SO_4 and concentrated *in vacuo* to provide the intermediate for the next step.

To a slurry of $LiAlH_4$ (1.5 g, 40 mmol, 200 mol%) in Et_2O (50 ml) was added dropwise a solution of previous crude product dissolved in Et_2O (20 ml). The reaction mixture was refluxed for 2 h and then the reaction was quenched with water at 0 ºC. The reaction mixture was filtered through a pad of Celite which was washed with Et_2O (3 x 30 ml). The reaction solvents were evaporated and the residue purified by flash column chromatography (30:1-10:1 cyclohexane:EtOAc) to give the product as a clear oil (1.18 g, 7.74 mmol, 39% over 3 steps). $\mathbf{R_f}$ = 0.36 (4:1 cyclohexane: EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.16-5.14 (m, 1H), 4.30-4.26 (m, 1H), 2.15-2.11 (m, 4H), 1.64 (s, 1H, *OH*), 1.60-1.50 (m, 6H), 1.27 (d, 3H, *J* = 6.5 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 196.0, 106.5, 95.1, 66.4, 31.8, 27.6, 26.2, 23.6; **IR** (cm $^{-1}$) ν_{max} 3595 (alcohol), 3302, 3053, 2980, 2934, 2855, 1447, 1423, 1265, 1075, 739, 705; **MS** m/z (EI), for $C_{10}H_{16}O$ [M+] calc. 152.1196, found 152.1189, error 4.45 ppm; **GC separation**: the temperature program 70 ºC 5min, 70 ºC-115 ºC 2 ºC/min gave retention times for enantiomers of (23.79/24.31 min).

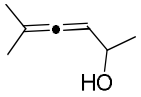
1-Cyclohexylidenehex-1-en-3-ol (139b)



1-Ethynylcyclohexanol (2.5 g, 20 mmol, 100 mol%) and butanal (1.9 ml, 22 mmol, 110 mol%) gave the title compound as a clear oil (2.8 g, 10 mmol, 50%); $\mathbf{R_f}$ = 0.42 (4:1 cyclohexane: EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.10-5.08 (m, 1H), 4.10-4.08 (m, 1H), 2.15-2.11 (m, 4H), 1.63-1.37 (m, 10 H), 0.93 (t, 3H, *J* = 7.2 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 196.2, 106.0, 93.6, 69.9, 39.6, 31.5 (2*C* diastereotopic), 27.4 (2*C* diastereotopic), 26.0, 18.6, 13.9; **IR**

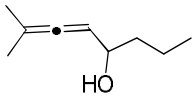
(cm $^{-1}$) ν_{max} 3598, 3054, 2985, 2958, 2933, 2873, 2855; **MS** m/z (EI), for $C_{12}H_{20}O$ [M+] calc. 180.15109, found 180.1511, error 1.42 ppm; **GC separation**: the temperature program 100 ºC 5 min, 100-130 ºC 2 ºC/min gave retention times for enantiomers of (19.24/19.44 min).

5-Methylhexa-3,4-dien-2-ol (139c)



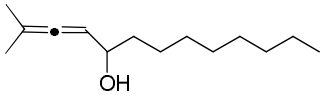
2-Methylbut-3-yn-2-ol (2.0 ml, 20 mmol, 100 mol%) and acetaldehyde (1.3 ml, 22 mmol, 110 mol%) gave the title compound as a slightly yellow oil (1.4 g, 12 mmol, 60%); $\mathbf{R_f}$ = 0.22 (4:1 cyclohexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.16-5.06 (m, 1H), 4.29-4.23 (m, 1H), 1.80 (bs, 1H), 1.7 (m, 6H, 2 x *CH*$_3$ diastereotopic), 1.25 (d, 3H, *J* = 6.5 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 199.4, 99.0, 95.2, 66.3, 27.0, 23.6, 20.8 (2*C* diastereotopic); **IR** (cm $^{-1}$) ν_{max} 3597, 3054, 2983, 2930, 2911, 2872, 2854, 1266, 738, 705; **MS** m/z (EI), for $C_7H_{12}O$ [M+] calc. 112.0888, found 112.0883, error 4.37 ppm; **GC separation**: the temperature program 40 ºC 5 min, 40 ºC-80 ºC 2 ºC/min gave retention times for enantiomers of (17.96/19.42 min). The NMR data in literature corresponds to this experimental data [173].

7-Methylocta-5,6-dien-4-ol (139d)



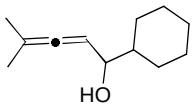
2-Methylbut-3-yn-2-ol (2.0 ml, 20 mmol, 100 mol%) and butanal (2.0 ml, 22 mmol, 110 mol%) gave the title compound as a clear oil (1.1 g, 7.7 mmol, 38%); $\mathbf{R_f}$ = 0.39 (4:1 cyclohexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.05-5.08 (m, 1H), 4.11-4.06 (m, 1H), 1.71 (2 x d, app. t, 6H, *J* = 3.01 Hz, 2 x *CH*$_3$ diastereotopic), 1.57-1.35 (m, 5H) 0.93 (t, 3H, *J* = 7.2 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 199.8, 98.8, 93.9, 70.2, 39.8, 20.8 (2*C* diastereotopic), 18.8, 14.2; **IR** (cm $^{-1}$) ν_{max} 3427, 3055, 2963, 2936, 2874, 1729, 1382, 1266, 739, 705; **MS** m/z (EI), for $C_9H_{16}O$ [M+] calc. 140.1196, found 140.1199, error 2.21 ppm; **GC separation**: the temperature program 40 ºC 5min, 40 ºC-90 ºC 0.5 ºC/min gave retention times for the enantiomers of (59.71/60.57 min).

2-Methyltrideca-2,3-dien-5-ol (139e)



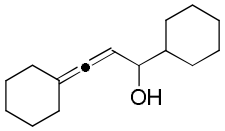
2-Methylbut-3-yn-2-ol (2.0 ml, 20 mmol, 100 mol%) and nonanal (3.1 g, 22 mmol, 110 mol-%) gave the title compound as a clear oil (3.2 g, 15 mmol, 76%); $\mathbf{R_f}$ = 0.45 (4:1 cyclohexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.09-5.04 (m, 1H), 4.13-4.06 (m, 1H), 1.71 (2 x d, app. t, 6H, *J* = 2.6 Hz, 2 x *CH*$_3$ diasterotopic), 1.61 (1H, *OH*), 1.54-1.23 (m, 14H), 0.87 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 200.0, 98.7, 93.9, 70.4, 37.7, 32.0, 29.8 (2*C*), 29.4, 25.6, 22.8, 20.8 (2*C*), 14.3; **IR** (cm $^{-1}$) ν_{max} 3366, 2926, 2855, 2359, 1970; **MS** m/z (EI), for $C_{14}H_{26}O$ [M+] calc. 210.1978, found 210.1983, error 2.49 ppm; **GC separation**: the temperature program 40 ºC 5 min, 40 ºC-100 ºC 0.5 ºC/min gave retention times for the enantiomers of (97.5/98.4 min).

1-Cyclohexyl-4-methylpenta-2,3-dien-1-ol (139f)



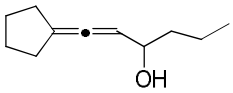
2-Methylbut-3-yn-2-ol (2.0 ml, 20 mmol, 100 mol%) and cyclohexanecarbaldehyde (2.7 ml, 22 mmol, 110 mol%) gave the title compound as a clear oil (2.2 g, 12 mmol, 61%); $\mathbf{R_f}$ = 0.41 (4:1 cyclohexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.06-5.03 (m, 1H), 3.86-3.82 (m, 1H), 1.86-1.74 (m, 2H), 1.71 (2 x d, app. t, 6H, *J* = 3.3 Hz, 2 x *CH*$_3$ diasterotopic), 1.67-1.54 (m, 2H), 1.42-1.36 (m, 1H), 1.27-0.98 (m, 6H), *OH* not observed; **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 200.1, 98.7, 92.3, 74.5, 44.2, 28.8, 28.4, 26.7, 26.3, 20.8; **IR** (cm $^{-1}$) ν_{max} 3600, 3054, 2985, 2929, 2854, 2305, 1450, 1421, 1265, 895, 746, 705; **MS** m/z (EI), for $C_{12}H_{20}O$ [M+] calc. 180.1509, found 180.1509, error 0.23 ppm; **GC separation**: the temperature program 80 ºC 5 min, 80 ºC-220 ºC 5 ºC/min a single retention time of (17.32 min).

1-Cyclohexyl-3-cyclohexylideneprop-2-en-1-ol (139g)



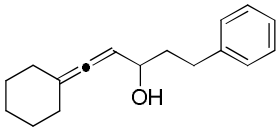
1-Ethynylcyclohexanol (2.6 g, 20 mmol, 100 mol%) and cyclohexanecarbaldehyde (2.7 ml, 22 mmol, 110 mol%) gave the title compound as a very viscose clear oil (2.6 g, 12 mmol, 58%); $\mathbf{R_f}$ = 0.45 (4:1 cyclohexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.08-5.06 (m, 1H), 3.86-3.82 (m, 1H), 2.15-2.11 (m, 4H), 1.86-1.53 (m, 11H), 1.42-1.39 (m, 1H), 1.26-0.99 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 196.6, 106.2, 92.2, 74.5, 44.1, 31.7, 28.9, 28.4, 27.6, 26.7, 26.2; **IR** (cm $^{-1}$) ν_{max} 3598, 3054, 2986, 2930, 2854, 1448, 142, 1265, 895, 746, 705; **MS** m/z (EI), for $C_{15}H_{24}O$ [M+] calc. 220.1822, found 220.1812, error 4.31 ppm; **GC separation**: the temperature program 90 ºC 5 min, 90 ºC-220 ºC 2 ºC/min gave a single retention time of (42.53 min).

1-Cyclopentylidenehex-1-en-3-ol (139h)



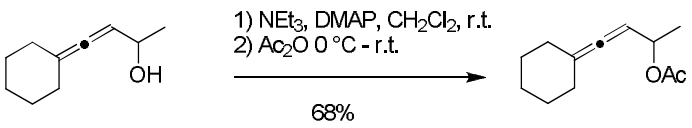
1-Ethynylcyclopentanol (2.2 g, 20 mmol, 100 mol%) and butanal (1.9 g, 22 mmol, 110 mol%) gave the title compound as a light yellow oil (1.0 g, 12 mmol, 60%); $\mathbf{R_f}$ = 0.36 (4:1 cyclohexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.18-5.15 (m, 1H), 4.14-4.07 (m, 1H), 2.38-2.35 (m, 5H), 1.71-1.34 (m, 8H), 0.92 (t, 3H, *J* = 7.3 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 195.1, 107.3, 96.4, 70.2, 39.8, 31.6 (2*C*), 27.2, 18.8, 14.2; **IR** (cm $^{-1}$) ν_{max} 3398, 2958, 2871, 2252, 1436, 1383, 1015, 909, 734, 650; **MS** m/z (EI), for $C_{11}H_{18}O$ [M+] calc. 166.1352, found 166.1347, error 2.99 ppm; **GC separation**: the temperature program 40 ºC 5 min, 40 ºC - 220 ºC 10 ºC/min gave retention times for the enantiomers of (42.07/43.08 min).

1-Cyclohexylidene-5-phenylpent-1-en-3-ol (139i)



1-Ethynylcyclohexanol (2.6 g, 20 mmol, 100 mol%) and hydrocinnamaldehyde (3.2 ml, 24 mmol, 120 mol-%) gave the title compound as a clear oil (2.5 g, 10 mmol, 50%); $\mathbf{R}_f$ = 0.47 (4:1 cyclohexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.31-7.28 (m, 2H), 7.23-7.18 (m, 3H), 5.16-5.14 (m, 1H), 4.16-4.11 (m, 1H), 2.81-2.68 (m, 2H), 2.18-2.15 (m, 4H), 1.91-1.86 (m, 2H), 1.67-1.51 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 196.6, 142.2, 128.6, 128.4, 125.8, 106.3, 93.6, 69.6, 39.2, 31.8 (2*C*), 27.5, 26.1; **IR** (cm $^{-1}$) ν_{max} 3362, 3062, 3026, 2930, 2853, 2252, 1965, 1460, 1446, 1031, 971, 909, 742, 700, 650 ; **MS** m/z (EI), for $C_{17}H_{22}O$ [M+] calc. 242.1665, found: 242.1675, error 4.01 ppm; **GC separation**: the temperature program 40 ºC 5 min, 40 ºC - 220 ºC 10 ºC/min gave a single retention time of (25.41 min).

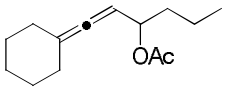
4-Cyclohexylidenebut-3-en-2-yl Acetate: general procedure to α-allenic acetates 140 (140a)



To a solution of 4-cyclohexylidenebut-3-en-2-ol (**139a**, 2.8 g, 18.4 mmol, 100 mol%) in dry CH_2Cl_2 (450 ml) at r.t. was added DMAP (0.45 g, 3.7 mmol, 20 mol%) and NEt_3 (5.1 ml, 36.8 mmol, 200 mol%). The reaction mixture was cooled to 0 ºC and Ac_2O (3.5 ml, 36.8 mmol, 200 mol%) was added. The mixture was left to stir at r.t. overnight. The reaction mixture was concentrated in a rotary evaporator and the residue was purified by flash column chromatography (10:1 cyclohexane: EtOAc) to give the title compound as a clear oil (2.4 g, 12.4 mmol, 68%)**;** $\mathbf{R}_f$ = 0.65 (4:1 cyclohexane: EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.35-5.29 (m, 1H), 5.11-5.09 (m, 1H), 2.15-2.09 (m, 4H), 2.04 (s, 3H), 1.62-1.52 (m, 6H), 1.31 (d, 3H, *J* = 6.5 Hz, CH_3 terminal); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 198.3, 170.6, 105.7, 90.6, 69.4, 31.4, 27.5, 26.2, 21.6, 19.9; **IR** (cm $^{-1}$) ν_{max} 3055, 2983, 2933, 2892, 2855, 1732, 1447, 1371, 1265, 1246, 1039, 739; **MS** m/z (EI), for $C_{12}H_{18}O_2$ [M+] calc. 194.1301, found

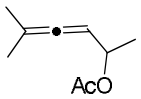
194.1295, error 3.01 ppm; **GC separation**: the temperature program 70 ºC 5min, 70 ºC-115 ºC 2 ºC/min gave a single retention time of (26.14 min).

1-Cyclohexylidenehex-1-en-3-yl Acetate (140b)



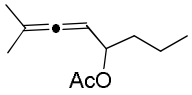
1-Cyclohexylidenehex-1-en-3-ol (**139b**, 2.0 g, 11 mmol, 100 mol%) gave the title compound as a clear oil (2.0 g, 8.8 mmol, 80%); $\mathbf{R_f}$ = 0.66 (4:1 cyclohexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.21-5.16 (m, 1H), 5.02-5.00 (m, 1H), 2.14-2.11 (m, 4H), 2.04 (s, 3H), 1.65-1.33 (m, 10H), 0.92 (t, 3H, *J* = 6.8 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 198.6, 170.5, 105.0, 89.3, 73.0, 36.3, 31.4, 27.5, 26.2, 21.6, 18.8; **IR** (cm $^{-1}$) ν_{max} 2958, 2932, 2855, 1968, 1733, 1371, 1240, 1018, 739; **MS** m/z (EI), for $C_{14}H_{22}O_2$ [M+] calc. 222.1614, found 222.1612, error 1.17 ppm; **GC separation**: the temperature program 100 ºC 5 min, 100-130 ºC 2 ºC/min gave a single retention time of (20.96 min).

5-Methylhexa-3,4-dien-2-yl Acetate (140c)



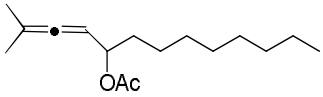
5-Methylhexa-3,4-dien-2-ol (**139c**, 0.56 g, 5 mmol, 100 mol%) gave the title compound as a clear oil (0.53 g, 3.4 mmol, 68%); $\mathbf{R_f}$ = 0.52 (4:1 cyclohexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.31-5.29 (m, 1H), 5.08-5.06 (m, 1H), 2.03 (s, 3H), 1.69 (app. d, 6H, *J* = 3.0 Hz, 2 x *CH*$_3$ diastereotopic), 1.29 (d, 3H, *J* = 6.5 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 201.7, 170.6, 98.4, 90.7, 69.4, 21.5, 20.4 (2*C* diastereotopic, 2 x CH_3), 19.9; **IR** (cm $^{-1}$) ν_{max} 3054, 2986, 2931, 1727, 1371, 1265, 1046, 739, 705; **MS** m/z (EI), for $C_9H_{14}O_2$ [M+] calc. 154.0988, found 154.0987, error 0.63 ppm; **GC separation**: the temperature program 40 ºC 5 min, 40 ºC-80 ºC 2 ºC/min gave retention times for the enantiomers of (18.19/18.53 min).

7-Methylocta-5,6-dien-4-yl Acetate (140d)



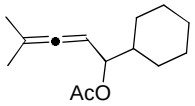
7-Methylocta-5,6-dien-4-ol (**139d**, 0.68 g, 5 mmol, 100 mol%) gave the title compound as a clear oil (0.45 g, 2.5 mmol, 50%); $\mathbf{R_f}$ = 0.63 (4:1 cyclohexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.18-5.16 (m, 1H), 5.00-4-97 (m, 1H), 2.03 (s, 3H), 1.70-1.68 (m, 6H, 2 x *CH*$_3$ diastereotopic), 1.64-1.53 (m, 2H), 1.42-1.30 (m, 2H), 0.91 (t, 3H, *J* = 7.5 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 202.0, 170.6, 97.8, 89.4, 72.9, 36.4, 21.5, 20.4 (2*C* diastereotopic), 18.8, 14.0; **IR** (cm $^{-1}$) ν_{max} 3054, 2962, 2913, 2874, 1728, 1371, 1265, 1249, 739, 705; **MS** m/z (EI), for $C_{11}H_{18}O_2$ [M+] calc. 182.1301, found 182.1294, error 4.20 ppm; **GC separation**: the temperature program 40 ºC 5min, 40 ºC-90 ºC 0.5 ºC/min gave retention times for the enantiomers of (55.23/56.13 min).

2-Methyltrideca-2,3-dien-5-yl Acetate (140e)



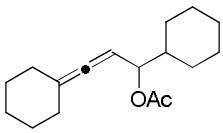
2-Methyltrideca-2,3-dien-5-ol (**139e**, 1.1 g, 5 mmol, 100 mol%) gave the title compound as a clear oil (1.2 g, 4.6 mmol, 92%); $\mathbf{R_f}$ = 0.54 (4:1 cyclohexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.17-5.15 (m, 1H), 5.00-4.97 (m, 1H), 2.04 (s, 3H), 1.70-1.68 (m, 6H, 2 x *CH*$_3$ diastereotopic), 1.64-1.50 (m, 2H), 1.33-1.26 (m, 12H), 0.88 (t, 3H, *J* = 7.2 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 202.0, 170.6, 97.8, 89.5, 73.2, 34.3, 32.0, 29.7, 29.5 (2*C*), 25.5, 22.8, 21.5, 20.4 (2*C*), 14.3; **IR** (cm $^{-1}$) ν_{max} 3155, 2928, 2857, 2254, 1972, 1726, 1251, 912, 735, 651; **MS** m/z (EI), for $C_{16}H_{28}O_2$ [M+] calc. 252.2084, found 252.2096, error 4.95 ppm; **GC separation**: the temperature program 40 ºC 5 min, 40 ºC-220 ºC 10 ºC/min gave a single retention time of (18.83 min).

1-Cyclohexyl-4-methylpenta-2,3-dienyl Acetate (140f)



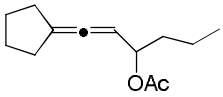
1-Cyclohexyl-4-methylpenta-2,3-dien-1-ol (**139f**, 0.90 g, 5 mmol, 100 mol%) gave the title compound as a clear oil (0.95 g, 4.3 mmol, 85%); $\mathbf{R_f}$ = 0.57 (4:1 cyclohexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 4.98-4.89 (m, 2H), 2.04 (s, 3H), 1.78-1.73 (m, 4H), 1.69 (d, 3H, *J* = 2.8 Hz, *CH*$_3$ diastereotopic), 1.67 (d, 3H, *J* = 2.8 Hz, *CH*$_3$ diastereotopic), 1.54-1.50 (m, 1H), 1.26-0.98 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 202.4, 170.6, 97.2, 87.8, 77.2, 41.8, 28.7 (2*C*), 26.1 (2*C*), 21.4, 20.4; **IR** (cm $^{-1}$) ν_{max} 3155, 2983, 2931, 2855, 2253, 1753, 1724, 1250, 908, 732, 651; **MS** m/z (EI), for $C_{14}H_{22}O_2$ [M+] calc. 222.1614, found 222.1613, error 0.49 ppm; **GC separation**: the temperature program 80 ºC 5 min, 80 ºC-220 ºC 5 ºC/min gave a single retention time of (17.56 min).

1-Cyclohexyl-3-cyclohexylideneallyl Acetate (140g)



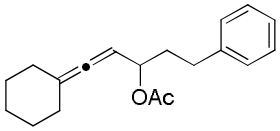
1-Cyclohexyl-3-cyclohexylideneprop-2-en-1-ol (**139g**, 1.1 g, 5 mmol, 100 mol%) gave the title compound as a viscose clear oil (1.1 g, 4.3 mmol, 86%); $\mathbf{R_f}$ = 0.57 (4:1 cyclohexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.00-4.92 (m, 2H), 2.14-2.08 (m, 4H), 2.05 (s, 3H), 1.78-1.72 (m, 4H), 1.64-1.49 (m, 8H), 1.26-0.99 (m, 5H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 199.0, 170.6, 104.5, 87.6, 41.8, 31.4, 31.3, 28.9, 28.6, 27.4, 26.6, 26.2, 26.1 (2*C*); **IR** (cm $^{-1}$) ν_{max} 2931, 2855, 2253, 1725, 1249, 910, 734; **MS** m/z (EI), for $C_{17}H_{26}O_2$ [M+] calc. 262.1927, found 262.1920, error 2.84 ppm; **GC separation**: the temperature program 90 ºC 5 min, 90 ºC-220 ºC 2 ºC/min, gave a single retention time of (43.69 min).

1-Cyclopentylidenehex-1-en-3-yl Acetate (140h)



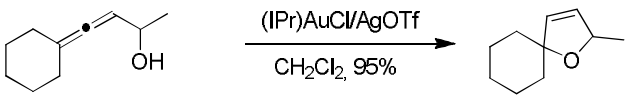
1-Cyclopentylidenehex-1-en-3-ol (**139h**, 0.83 g, 5 mmol, 100 mol%) gave the title compound as a clear oil (0.84 g, 4.0 mmol, 81%); $\mathbf{R_f}$ = 0.58 (4:1 cyclohexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.20-5.18 (m, 1H), 5.10-5.05 (m, 1H), 2.38-2.31 (m, 4H), 2.03 (s, 3H), 1.70-1.64 (m, 4H), 1.62-1.51 (m, 2H), 1.38-1.29 (m, 2H), 0.90 (t, 3H, *J* = 7.5 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 197.4, 170.6, 106.3, 91.8, 73.0, 36.3, 31.3, 27.2 (2*C*), 21.5, 18.8, 14.0; **IR** (cm $^{-1}$) ν_{max} 2961, 2253, 1727, 1372, 1248, 912, 742, 651; **MS** m/z (EI), for $C_{13}H_{20}O_2$ [M+] calc. 208.1458, found 208.1461, error 1.56 ppm; **GC separation**: the temperature program 40 ºC 5 min, 40 ºC - 220 ºC 10 ºC/min gave a single retention time of (16.81 min).

1-Cyclohexylidene-5-phenylpent-1-en-3-yl Acetate (140i)



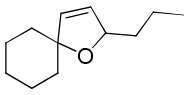
1-Cyclohexylidene-5-phenylpent-1-en-3-ol (**139i**, 1.2 g, 5 mmol, 100 mol%) gave the title compound as a clear oil (1.2 g, 4.1 mmol, 83%); $\mathbf{R_f}$ = 0.59 (4:1 cyclohexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.31-7.27 (m, 2H), 7.21-7.18 (m, 3H), 5.23 (m, 1H), 5.09-5.07 (m, 1H), 2.73-2.65 (m, 2H), 2.21-2.10 (m, 4H), 2.06 (s, 3H), 1.68-1.49 (m, 8H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 198.7, 170.5, 141.6, 128.5 (2*C*), 126.0, 105.3, 89.1, 72.5, 35.8, 31.8, 31.4, 27.4, 27.0, 26.1, 21.4; **IR** (cm $^{-1}$) ν_{max} 3028, 2929, 2853, 2253, 1968, 1735, 1449, 1372, 1245, 1021, 911, 738, 651; **MS** m/z (EI) for $C_{19}H_{24}O_2$ [M+] calc. 284.1771, found 284.1772, error 0.36 ppm; **GC separation**: the temperature program 40 ºC 5 min, 40 ºC - 220 ºC 10 ºC/min, gave a single retention time of (24.8 min).

2-Methyl-1-oxaspiro[4.5]dec-3-ene: general procedure to racemic 2,5-dihydrofurans (141a)



To a solution of 4-cyclohexylidenebut-3-en-2-ol (**139a**, 76 mg, 0.5 mmol, 100 mol%) in CH_2Cl_2 (10 ml) at r.t.was added (IPr)AuCl (15 mg, 0.025 mmol, 5 mol%) and AgOTf (7 mg, 0.025 mmol, 5 mol%). After 1h the reaction mixture was filtered through a pad of Celite, which was washed with Et_2O (3 x 30 ml). The combined organics were concentrated *in vacuo* and purified by flash column chromatography (30:1 pentane:Et_2O) to give the product as a clear oil (72 mg, 0.47 mmol, 95%); $\mathbf{R_f}$ = 0.74 (4:1 cyclohexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.87 (dd, 1H, *J* = 6.0, 2.0 Hz), 5.70 (dd, 1H, *J* = 6.0, 1.2 Hz), 4.91-4.90 (m, 1H), 1.63-1.73 (m, 2H), 1.53-1.61 (m, 4H), 1.37-1.50 (m, 4H), 1.25 (d, 3H, *J* = 6.5 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 133.4, 130.4, 89.6, 80.5, 39.6, 39.1, 37.6, 25.6, 23.5 (2*C*); **IR** (cm $^{-1}$) ν_{max} 2973, 2934, 2858, 2253, 1088 (cyclic ether), 908, 734, 650; **MS** m/z (EI), for $C_{10}H_{16}O$ [M+] calc. 152.1196, found: 152.1190, error 3.44 ppm; **GC separation**: the temperature program 70 ºC 5min, 70 ºC-115 ºC 2 ºC/min gave retention times for the enantiomers of (7.75/8.48 min).

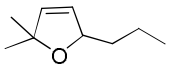
2-Propyl-1-oxaspiro[4.5]dec-3-ene (141b)



1-Cyclohexylidenehex-1-en-3-ol (**139b**, 86 mg, 0.5 mmol, 100 mol%) was suspended in distilled water (10 ml) and THF (0.1 ml) was added. The starting material does not dissolve entirely but forms small droplets in the reaction mixture. Solution of $HAuCl_4$ (0.15 M in H_2O, 0.17 ml, 0.025 mmol, 5 mol%) was added to the reaction mixture which was left to stir at r.t. for 1 h. The reaction mixture was extracted with Et_2O (2 x 10 ml) and the combined organics were dried over Na_2SO_4. Purification by flash column chromatography (30:1 pentane:Et_2O) gave the title compound as a light yellow oil (42 mg, 0.23 mmol, 47%); $\mathbf{R_f}$ = 0.67 (4:1 cyclohexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.90 (dd, 1H, *J* = 6.0, 2.0), 5.72 (dd,

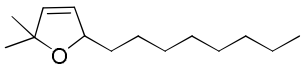
1H, *J* = 6.0, 0.80 Hz), 4.81-4.78 (m, 1H), 1.76-1.64 (m, 4H), 1.60-1.49 (m, 9H), 1.48-1.37 (m, 1H), 0.93 (t, 3H, *J* = 7.3 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 133.60, 129.0, 89.2, 84.5, 39.6, 39.1, 37.7, 25.7 (*2C*), 23.8, 18.8, 14.4; **IR** (cm $^{-1}$) ν_{max} 3053, 2934, 1448, 1265, 1110, 705; **MS** m/z (EI), for $C_{12}H_{20}O$ [M+] calc. 180.1509, found: 180.1513, error 2.40 ppm; **GC separation**: the temperature program 100 ºC 5 min, 100-130 ºC 2 ºC/min gave retention times for the enantiomers of (8.32/8.77 min).

2,2-Dimethyl-5-propyl-2,5-dihydrofuran (141d)



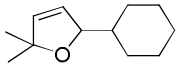
7-Methylocta-5,6-dien-4-ol (**139d**, 70 mg, 0.5 mmol, 100 mol%) gave the product as a clear oil. Full conversion based on TLC, but the product was so volatile that no isolated yield could be recorded; $\mathbf{R_f}$ = 0.59 (4:1 cyclohexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.68 (dd, 1H, *J* = 6.0, 2.0 Hz), 5.64 (dd, 1H, *J* = 6.0, 1.0 Hz), 4.82-4.79 (m, 1H), 1.49 (bs, 6H), in between in solvents 4H multiplet, 0.92 (t, 3H, *J* = 7.6 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 135.4, 128.4, 87.1, 85.0, 39.4, 28.0, 27.1, 26.0, 18.8; **IR** (cm $^{-1}$) ν_{max} 2977, 2873, 2253, 1111, 907, 732, 651; **MS** m/z (EI), for $C_9H_{16}O$ [M+] calc. 140.1196, found 140.1195, error 0.20 ppm; **GC separation**: the temperature program 40 ºC 5min, 40 ºC-90 ºC 0.5 ºC/min gave retention times for enantiomers of (9.74/10.42 min).

2,2-Dimethyl-5-octyl-2,5-dihydrofuran (141e)



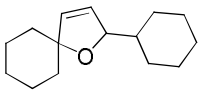
2-Methyltrideca-2,3-dien-5-ol (**139e**, 0.11 g, 0.5 mmol, 100 mol%) gave the title compound as a yellow oil (0.10 g, 0.49 mmol, 98%); $\mathbf{R_f}$ = 0.62 (4:1 cyclohexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.70 (dd, 1H, *J* = 6.0, 2.5 Hz), 5.65 (dd, 1H, *J* = 6.0, 1.5 Hz), 4.81-4.78 (m, 1H), 1.55-1.49 (m, 2H), 1.32 (s, 6H), 1.29-1.25 (m, 12H), 0.87 (t, 3H, *J* = 6.8 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 135.4, 128.4, 87.1, 85.2, 37.1, 32.0, 30.0, 29.7, 29.4, 28.1, 25.5, 22.8, 14.3; **IR** (cm $^{-1}$) ν_{max} 2928, 2856, 2253, 1098, 911, 735; **MS** m/z (EI), for $C_{14}H_{26}O$ [M+] calc. 210.1978, found 210.1988, error 4.59 ppm; **GC separation**: the temperature program 40 ºC 5 min, 40 ºC-100 ºC 0.5 ºC/min gave retention times for the enantiomers of (93.07/94.07 min).

5-Cyclohexyl-2,2-dimethyl-2,5-dihydrofuran (141f)



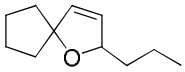
1-Cyclohexyl-4-methylpenta-2,3-dien-1-ol (**139f**, 90 mg, 0.5 mmol, 100 mol%) gave the title compound as a clear oil (86 mg, 0.48 mmol, 96%); $\mathbf{R_f}$ = 0.62 (4:1 cyclohexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.72 (dd, 1H, *J* = 6.0, 2.5 Hz), 5.66 (dd, 1H, *J* = 6.0, 1.0 Hz), 4.61-4.59 (m, 1H), 1.80-1.64 (m, 7H), 1.42-1.40 (m, 1H), 1.31 (s, 3H), 1.28 (s, 3H), 1.01-0.96 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 135.8, 126.7, 89.8, 86.9, 43.5, 29.2, 28.9, 26.8, 26.4, 26.3; **IR** (cm $^{-1}$) ν_{max} 2976, 2928, 2854, 2253, 907, 732, 651; **MS** m/z (EI), for $C_{12}H_{20}O$ [M+] calc. 180.1509, found 180.1509, error 0.43 ppm; **GC separation**: the temperature program 80 ºC 5 min, 80 ºC-220 ºC 5 ºC/min gave retention times for the enantiomers of (9.35/9.60 min).

2-Cyclohexyl-1-oxaspiro[4.5]dec-3-ene (141g)



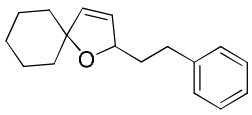
1-Cyclohexyl-3-cyclohexylideneprop-2-en-1-ol (**139g**, 110 mg, 0.5 mmol, 100 mol%) gave the title compound as a clear oil (107 mg, 0.49 mmol, 98%); $\mathbf{R_f}$ = 0.70 (4:1 cyclohexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.90 (dd, 1H, *J* = 6.0, 2.5 Hz), 5.72 (dd, 1H, *J* = 6.0, 1.0 Hz), 4.57 (m, 1H), 1.82-1.62 (m, 9H), 1.59-1.39 (m, 6H), 1.26-1.10 (m, 4H), 1.02-0.93 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 134.0, 127.3, 89.2, 88.9, 43.8, 38.5, 37.8, 29.4, 28.8, 26.8, 25.7, 23.9, 23.7; **IR** (cm $^{-1}$) ν_{max} 2931, 2854, 2253, 1450, 1064, 907, 734, 651; **MS** m/z (EI), for $C_{15}H_{24}O$ [M+] calc. 220.1822, found 220.1815, error 2.89 ppm; **GC separation**: the temperature program 90 ºC 5 min, 90 ºC-220 ºC 2 ºC/min gave retention times for the enantiomers of (27.25/27.61 min).

2-Propyl-1-oxaspiro[4.4]non-3-ene (141h)



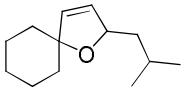
1-Cyclopentylidenehex-1-en-3-ol (**139h**, 83 mg, 0.5 mmol, 100 mol%) gave the title compound as a clear oil (75 g, 0.45 mmol, 90%); $\mathbf{R_f}$ = 0.60 (4:1 cyclohexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.70 (s, 2H), 4.77 (t, 1H, *J* = 5.8 Hz), 1.80-1.70 (m, 4H), 1.62-1.59 (m, 4H), 1.52-1.49 (m, 2H), 1.41-1.33 (m, 2H), 0.92 (t, 3H, *J* = 7.3 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 133.4, 128.8, 97.4, 84.8, 40.2, 39.2, 38.8, 27.1, 24.8 (2*C*), 18.6, 14.5; **IR** (cm $^{-1}$) ν_{max} 2960, 2253, 1466, 1384, 913, 743, 651; **MS** m/z (EI), for $C_{11}H_{18}O$ [M+] calc. 166.1352, found: 166.1354, error 1.10 ppm; **GC separation**: the temperature program 40 ºC 5 min, 40 ºC - 220 ºC 10 ºC/min gave retention times for the enantiomers of (12.22/12.40 min).

2-Phenethyl-1-oxaspiro[4.5]dec-3-ene (141i)



1-Cyclohexylidene-5-phenylpent-1-en-3-ol (**139i**, 120 mg, 0.5 mmol, 100 mol%) gave the title compound as a clear oil (81 mg, 33 mmol, 67%); $\mathbf{R_f}$ = 0.68 (4:1 cyclohexane:EtOAc) ; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.31-7.25 (m, 2H), 7.23-7.17 (m, 3H), 5.93 (dd, 1H, *J* = 6.0, 2.3 Hz), 5.73 (dd, 1H, *J* = 6.0, 1.0 Hz), 4.87-4.84 (m, 1H), 2.73-2.69 (m, 2H), 1.89-1.83 (m, 2H), 1.75-1.69 (m, 2H), 1.64-1.57 (m, 4H), 1.51-1.45 (m, 4H) ; **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 142.6, 134.2, 128.7, 128.6, 128.4, 125.8, 89.4, 84.0, 39.1 (2*C*), 37.7, 31.9, 27.1, 25.7, 23.8 (2*C*); **IR** (cm $^{-1}$) ν_{max} 2934, 2253, 1384, 912, 743, 651; **MS** m/z, for $C_{16}H_{20}O$ [M+] calc. 242.1671, GC-MS (EI) found peak 242, ESI found peak 241.7; **GC separation**: the temperature program 40 ºC 5 min, 40 ºC - 220 ºC 10 ºC/min gave a single retention time of (21.98 min).

2-Isobutyl-1-oxaspiro[4.5]dec-3-ene (141j)



1-Cyclohexylidene-5-methylhex-1-en-3-ol (97 mg, 0.5 mmol, 100 mol%) gave the title compound as a clear oil (85 mg, 0.44 mmol, 87%); $\mathbf{R_f}$ = 0.73 (4:1 cyclohexane:EtOAc) ; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 5.88 (dd, 1H, *J* = 6.0, 2.5 Hz), 5.74 (dd, 1H, *J* = 6.0, 1.5 Hz), 4.85-4.81 (m, 1H), 1.81-1.67 (m, 3H), 1.59-1.54 (m, 4H), 1.49-1.31 (m, 6H), 0.93 (dd, 6H, *J* = 6.5, 2.5 Hz) ; **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C 133.4, 129.5, 89.1, 83.2, 47.2, 39.5, 37.7, 27.1, 25.7 (2*C*), 23.8 (2*C*), 23.3 (2*C*); **IR** (cm $^{-1}$) ν_{max} 2934, 2253, 1384, 908, 735, 651; **MS** m/z (EI), for $C_{13}H_{22}O$ [M+] calc. 194.1665, found 194.1663, error 1.23 ppm; **GC separation**: the temperature program 40 ºC 5 min, 40 ºC-220 ºC 10 ºC/min gave retention times for the enantiomers of (9.09/9.13 min).

Preparation of phosphate buffer (pH = 7)

Disodium hydrogenphosphate (Na_2HPO_3) (1.42 g, 10.0 mmol) was dissolved in 100 ml water. Sodium dihydrogenphosphate (NaH_2PO_4) (1.58 g, 13.1 mmol) was dissolved in 100 ml water in a separate flask. Disodium hydrogenphosphate solution (100 ml) and sodium dihydrogenphosphate solution (43.3 ml) were combined. For this solution pH paper shows pH 7.

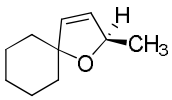
General procedure for tandem gold/enzyme-catalyzed reaction on test scales

The racemic allenic acetoxy compound (10 mg) was dissolved in 2 ml of phosphate buffer (pH = 7) and THF (50 µl). Lipase from *Burkholderia cepacia* (PS Amano SD) was added (amount 10-100 mg) followed by an addition of $HAuCl_4$ solution (0.012 M in water, 20 µl, 0.5 mol%) and the reaction was stirred at room temperature for a given time while being monitored by GC analysis. GC samples were taken from the reaction mixture with a Pasteur pipette (0.1 ml) and extracted with Et_2O (0.1 ml). The organic layer was used directly for GC analysis.

General procedure for tandem gold/enzyme-catalyzed reaction on preparative scales

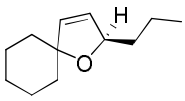
General reaction conditions: The allenic acetoxy compound (0.5 mmol) was suspended in a mixture of phosphate buffer (15 ml, pH = 7) and THF (0.1 ml). The starting material does not dissolve entirely but forms little droplets in the reaction mixture. Lipase from *Burkholdia cepacia* (PS Amano SD) was added (160-800 mg) followed by an addition of $HAuCl_4$ solution (0.012 M in water, 0.2 ml, 0.5 mol%). The reaction was stirred at r.t. until the desired conversion was reached by GC analysis. GC samples were taken from the reaction mixture with a Pasteur pipette (0.1 ml) and extracted with Et_2O (0.1 ml). The organic fraction was used for GC analysis. The reaction mixture was extracted 5 times with Et_2O and the combined organics were washed with saturated NaCl solution and dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (eluent 30:1 pentane: Et_2O) to give the desired products.

(*R*)-2-methyl-1-oxaspiro[4.5]dec-3-ene (*R*)-(141a)



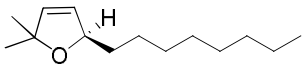
Racemic 4-cyclohexylidenebut-3-en-2-yl acetate (**140a**, 80 mg, 0.5 mmol, 100 mol%) was dissolved in phosphate buffer solution (15 ml) and THF (0.1 ml) was added. Lipase PS Amano SD (160 mg) was added with vigorous stirring and when an aggregate-free suspension was formed, $HAuCl_4$ solution (0.012 M in water, 0.2 ml, 0.0025 mmol, 0.5 mol%) was added and reaction stirred vigorously at room temperature for 48 h. After workup and purification the following products were obtained: (*R*)-**141a** (21 mg, 28%); *ee* 86 %; $[\alpha]_D = -45.2$ (*c* = 0.38, CH_2Cl_2); (*S*)-**140a** (30 mg, 31%); *ee* 93 %; $[\alpha]_D = -58.7$ (*c* = 0.45, CH_2Cl_2).

(*R*)-2-propyl-1-oxaspiro[4.5]dec-3-ene (*R*)-(141b)



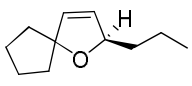
Racemic 1-cyclohexylidenehex-1-en-3-yl acetate (**140b**, 110 mg, 0.5 mmol, 100 mol%) was dissolved in phosphate buffer solution (15 ml) and THF (0.1 ml) was added. Lipase PS Amano SD (700 mg) was added with vigorous stirring and when an aggregate-free suspension was formed, $HAuCl_4$ solution (0.012 M in water, 0.2 ml, 0.0025 mmol, 0.5 mol%) was added and reaction stirred vigorously at room temperature for 48 h. After workup and purification following products were obtained: (*R*)-**141b** (41 mg, 45%); *ee* 95 %; $[\alpha]_D$ = –50.3 (*c* = 0.74, CH_2Cl_2); (*S*)-**140b** (44 mg, 40%); *ee* > 95 %; $[\alpha]_D$ = –49.8 (*c* = 1.4, CH_2Cl_2).

(*R*)-2,2-dimethyl-5-octyl-2,5-dihydrofuran (*R*)-(141e)



Racemic 2-methyltrideca-2,3-dien-5-yl acetate (**140e**, 126 mg, 0.5 mmol, 100 mol%) was dissolved in phosphate buffer solution (15 ml) and THF (0.1 ml) was added. Lipase PS Amano SD (600 mg) was added with vigorous stirring and when an aggregate-free suspension was formed, $HAuCl_4$ solution (0.012 M in water, 0.2 ml, 0.0025 mmol, 0.5 mol%) was added and reaction stirred vigorously at room temperature for 48 h. After workup and purification the following products were obtained: (*R*)-**141e** (53 mg, 50%); *ee* 98 %; $[\alpha]_D$ = –39.1 (*c* = 1.4, CH_2Cl_2); (*S*)-**140e** (45 mg, 36%); *ee* = 95 %; $[\alpha]_D$ = –38.0 (*c* = 0.65, CH_2Cl_2).

(*R*)-2-propyl-1-oxaspiro[4.4]non-3-ene (*R*)-(141h)



Racemic 1-cyclopentylidenehex-1-en-3-yl acetate (**140h**, 105 mg, 0.5 mmol, 100 mol%) was dissolved in phosphate buffer solution (15 ml) and THF (0.1 ml) was added. Lipase PS Amano SD (800 mg) was added with vigorous stirring and when an aggregate-free suspension was formed, $HAuCl_4$ solution (0.012 M in water, 0.2 ml, 0.0025 mmol, 0.5 mol%) was added and

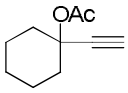
reaction stirred vigorously at room temperature for 48 h. After workup and purification the following products were obtained: (*R*)-**141h** (32 mg, 38%); *ee* 88 %; $[\alpha]_D = -47.2$ (*c* = 0.64, CH_2Cl_2); (*S*)-**140h** (35 mg, 33%); *ee* > 95 %; $[\alpha]_D = -56.6$ (*c* = 0.70, CH_2Cl_2).

General procedure for determining the *ee* of acetates (*S*)-140

Acetate (S)-**140** (0.1 mmol, 100 mol%) was dissolved in methanol (1.5 ml) at r.t. and K_2CO_3 (14 mg, 0.1 mmol, 100 mol%) was added. After 2 hours water (1 ml) was added to the the reaction mixture and the reaction mixture was extracted with Et_2O (0.5 ml). The organic fraction was dried with Na_2SO_4 and used directly for gas chromatography analysis.

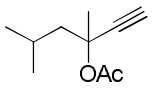
6.3 S_N2' approach to the synthesis of allenyl acetates

1-Ethynylcyclohexyl Acetate: general procedure towards propargylic acetates (176a)



To 1-ethynylcyclohexanol (1.24 g, 10 mmol, 100 mol%) in CH_2Cl_2 (175 ml) at r.t. was added dimethylaminopyridine (0.24 g, 2 mmol, 20 mol%) and triethylamine (2.8 ml, 20 mmol, 200 mol%). The reaction was cooled to 0 °C and acetic anhydride (2.0 ml, 20 mmol, 200 mol%) was added slowly. The mixture was stirred at room temperature overnight and then concentrated in a rotary evaporator. Purification of the crude product by flash column chromatography (10:1 petroleum ether:Et_2O) gave **176a** as a clear oil with quantitative yield (1.71 g, 10 mmol, 100%). $\mathbf{R_f}$ = 0.45 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.60 (s,1H), 2.16-2.10 (m, 2H), 2.05 (s, 3H), 1.88-1.82 (m, 2H), 1.65-1.59 (m, 4H), 1.55-1.49 (m, 1H), 1.36-1.30 (m, 1H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 169.3, 83.6, 75.1, 74.2, 36.9 (2 x *CH_2*), 25.1, 22.5 (2 x *CH_2*), 21.9; **IR** (cm $^{-1}$) ν_{max} 3306, 2941, 1735, 1369, 1240, 1025; **MS** m/z (EI) for $C_8H_{12}O$ (M-C_2H_2O) calc. 124.0883, found 124.0883, error 0.1 ppm. NMR data in the literature corresponds to the experimental data [174].

3,5-Dimethylhex-1-yn-3-yl Acetate (176b)



The starting material 3,5-dimethyl-1-hexyn-3-ol (1.47 ml, 10 mmol, 100 mol%) gave the title compound as a clear oil (1.52 g, 9.03 mmol, 90%). $\mathbf{R_f}$ = 0.64 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.55 (s, 1H), 2.02 (s, 3H), 2.01-1.94 (m, 1H), 1.89-1.84 (m, 1H), 1.77-1.71 (m, 1H), 1.69 (s, 3H), 0.99 (2 x d, app. t, 6H, *J* = 6.8 Hz, 2 x *CH*$_3$ diastereotopic); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 169.3, 84.2, 75.0, 73.3, 49.4, 27.1, 24.8, 24.1, 23.7, 22.1; **IR** (cm $^{-1}$) ν_{max} 3306, 2961, 1735, 1370, 1248; **MS** m/z (EI) only fragments of product found; for $C_9H_{13}O_2$ [M-CH_4] calc. 153.0910, found 153. 0910, error 0.20 ppm.

3-Methylpent-1-yn-3-yl Acetate (176c)

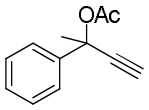
The starting material 3-methyl-1-pentyn-3-ol (1.12 ml, 10 mmol, 100 mol%) gave the title compound as a clear oil (1.15 g, 8.17 mmol, 82%). $\mathbf{R_f}$ = 0.47 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.54 (s, 1H), 2.03 (s, 3H), 2.00-1.82 (m, 2H), 1.66 (s, 3H), 1.02 (t, 3H, *J* = 7.6 Hz); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 169.4, 83.7, 75.3, 73.1, 34.3, 25.9, 21.9, 8.4; **IR** (cm $^{-1}$) ν_{max} 3306, 3010, 1736, 1370, 1250; **MS** m/z (EI) found [M-Me]+ $C_7H_9O_2$ calc. 125.0597, found 125.0597, error 0.20 ppm. The NMR data in the literature corresponds to the experimental data [175].

3-Methylpent-1-en-4-yn-3-yl Acetate (176d)

The starting material 3-methyl-1-penten-4-yn-3-ol (0.96 g, 10 mmol, 100 mol%) gave the title compound as a clear oil (1.07 g, 7.77 mmol, 78%). $\mathbf{R_f}$ = 0.44 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.98 (dd, 1H, *J* = 17.2, 10.4 Hz), 5.58 (dd, 1H, *J* = 17.2, 0.4 Hz), 5.25 (dd, 1H, *J* = 10.4, 0.4 Hz), 2.67 (s, 1H), 2.04 (s, 3H), 1.71 (s, 3H); **^{13}C NMR** (67.9 MHz,

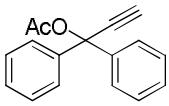
$CDCl_3$) δ_C 168.9, 138.4, 115.7, 82.1, 74.8, 74.0, 28.4, 21.8; **IR** (cm $^{-1}$) ν_{max} 3306, 3009, 1741, 1370, 1249, 1066; **MS** m/z (EI) found [M-Me]+ $C_7H_7O_2$ calc. 123.0441, found 123.0441, error 0.10 ppm. The NMR data in the literature corresponds to the experimental data [176].

2-Phenylbut-3-yn-2-yl Acetate (176e)



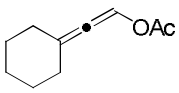
The starting material 2-phenyl-3-butyn-2-ol (2.9 g, 20 mmol, 100 mol%) gave the title compound as a clear oil (4.0 g, 20 mmol, 100%). $\mathbf{R_f}$ = 0.62 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.60-7.58 (m, 2H), 7.39-7.35 (m, 2H), 7.32-7.28 (m, 1H), 2.82 (s, 1H), 2.09 (s, 3H), 1.90 (s, 3H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 168.6, 142.1, 128.3, 127.9, 124.7, 82.9, 75.5, 75.3, 32.0, 21.7; **IR** (cm $^{-1}$) ν_{max} 3306, 3009, 1744, 1369, 1241, 1063; **MS** m/z (ESI) for $C_{12}H_{12}NaO_2$ [M+Na] calc. 211.0730, found 211.0743, error 6.40 ppm. The NMR data in the literature corresponds to the experimental data [160b].

1,1-Diphenylprop-2-ynyl Acetate (176f)



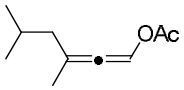
The starting material 1,1-diphenyl-2-propyn-1-ol (2.08 g, 10 mmol, 100 mol%) gave the title compound as a colourless solid (1.77 g, 7.1 mmol, 71%). $\mathbf{R_f}$ = 0.25 (20:1 petroleum ether:EtOAc), **M.p.** 77-78 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.56-7.53 (m, 4H), 7.37-7.27 (m, 6H), 3.01 (s, 1H), 2.19 (s, 3H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 168.1, 142.0, 128.3, 128.0, 126.1, 82.3, 79.0, 78.0, 21.8; **IR** (cm $^{-1}$) ν_{max} 3305, 3009, 1752, 1493, 1450, 1369, 1240; **MS** m/z (ESI) for $C_{17}H_{14}NaO_2$ [M+Na] calc. 273.0886, found 273.0876, error 3.80 ppm. The NMR in the literature corresponds to the experimental data [177].

2-Cyclohexylidenevinyl Acetate: general procedure for the silver catalyzed rearrangement of propargylic acetates (177a)



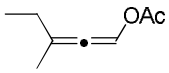
To 1-ethynylcyclohexyl acetate (0.16 g, 1.0 mmol, 100 mol%) in CH_2Cl_2 (5 ml) at r.t. was added $AgBF_4$ (19 mg, 0.1 mmol, 10 mol%). After 4 hours reaction was quenched by filtration through a pad of Celite and the product was concentrated on a rotary evaporator. The residue was purified by flash column chromatography (30:1 pentane:Et_2O), which gave the title compound as a clear oil (0.15 g, 0.94 mmol, 94%). $\mathbf{R_f}$ = 0.75 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.21 (quintet, 1H, *J* = 1.2 Hz), 2.24-2.20 (m, 4H), 2.12 (s, 3H), 1.70-1.52 (m, 6H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 186.4, 168.9, 118.6, 107.8, 32.6, 27.2, 25.8, 21.0; **IR** (cm $^{-1}$) ν_{max} 2936, 1973, 1739, 1447, 1241, 1037; **MS** m/z (EI) for $C_{10}H_{14}O_2$ calc. 166.0988, found 166.0988, error 0.40 ppm. The NMR in literature corresponds to experimental data [178].

3,5-Dimethylhexa-1,2-dienyl Acetate (177b)



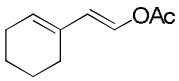
The starting material 3,5-dimethylhex-1-yn-3-yl acetate (0.17 g, 1.0 mmol, 100 mol%) gave the title compound as a clear oil (0.12 g, 0.71 mmol, 71%). $\mathbf{R_f}$ = 0.82 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.27 (m, app. sextet, 1H, *J* = 2.0 Hz), 2.13 (s, 3H), 1.97-1.94 (m, 2H), 1.81-1.80 (m, 4H), 0.91 (2 x d, 6H, *J* = 6.8 Hz, 2 x *CH_3* diastereotopic); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 190.0, 168.9, 114.8, 109.1, 44.6, 30.9, 26.3, 22.5, 22.3, 20.9, 20.6; **IR** (cm $^{-1}$) ν_{max} 2959, 1977, 1741, 1370, 1240, 1042; **MS** m/z (EI) only fragments of product found; for $C_7H_{10}O_2$ [M-C_3H_6] calc. 126.0675, found 126.0675, error 0.1 ppm.

3-Methylpenta-1,2-dienyl Acetate (177c)



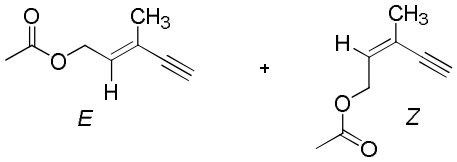
The starting material 3-methylpent-1-yn-3-yl acetate (0.14 g, 1.0 mmol, 100 mol%) gave the title compound as a clear oil (0.93 g, 0.64 mmol, 64%). $\mathbf{R_f}$ = 0.74 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.31 (m, app. sextet, 1H, *J* = 2.1 Hz), 2.13 (s, 3H), 2.15-1.99 (m, 2H), 1.84-1.83 (m, 3H), 1.03 (t, 3H, *J* = 7.2 Hz); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 188.9, 168.8, 117.9, 110.2, 28.2, 21.0, 20.4, 11.9; **IR** (cm $^{-1}$) ν_{max} 2973, 1982, 1741, 1455, 1370, 1255, 1038; **MS** m/z (EI) for $C_8H_{12}O_2$ calc. 140.0832, found 140.0832, error 0.1 ppm. The NMR in literature corresponds to experimental data [178].

(*E*)-2-Cyclohexenylvinyl Acetate (as earlier with AgOTf as catalyst) (178a)



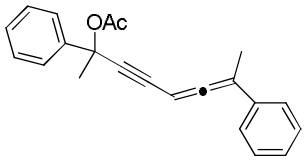
Starting material 1-ethynycyclohexyl acetate (0.16 g, 1.0 mmol, 100 mol%) with AgOTf (25 mg, 0.1 mmol, 10 mol%) as catalyst gave a mixture of the title compound and 2-cyclohexylidenevinyl acetate (allenic product) with a 1:0.12 ratio (0.12 g, 0.73 mmol, 73%) as a yellow oil. These two compounds could not be separated by flash column chromatography. $\mathbf{R_f}$ = 0.75 (9:1 petroleum ether:Et_2O) for product mixture; Data for **178a**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.28-7.25 (m, 1H), 6.03 (d, 1H, *J* = 13.2 Hz), 5.71-5.69 (m, 1H), 2.13 (s, 3H), 2.12-2.09 (m, 4H), 1.69-1.57 (m, 4H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 168.2, 133.6, 132.0, 129.0, 119.0, 25.8, 24.6, 22.3, 22.2, 20.8; **IR** (cm $^{-1}$) ν_{max} 2931, 1743, 1372, 1240, **MS** m/z (EI) for $C_{10}H_{14}O_2$ calc. 166.0988, found 166.0991, error 1.5 ppm.

(*E*)-and (*Z*)- 3-Methylpent-2-en-4-ynyl Acetate (*E*/*Z*-179)



The starting material 3-methylpent-1-en-4-yn-3-yl acetate (0.14 g, 1.0 mmol, 100 mol%) gave a mixture of the title compounds as a yellow oil (0.07 g, 0.5 mmol, 50%). The (*E*)- and (*Z*)-isomers could not be separated with flash column chromatography and their absolute configuration could not be identified by NMR spectroscopy so they were named isomer A and isomer B, ratio of A:B = 0.18:1 (A being the minor isomer) and this naming is used for ^{1}H NMR. $\mathbf{R_f}$ = 0.50 (10:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.02-5.98 (m, 1H)A, 5.89-5.85 (m, 1H)B, 4.78-4.76 (m, 2H)B, 4.65-4.63 (m, 2H)A, 3.20 (s, 1H)B, 2.87 (s, 1H)A, 2.06 (s, 3+3H)A+B, 1.92-1.91 (m, 3H)B, 1.88-1.87 (m, 3H)A; **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 170.9, 132.0, 131.9, 122.4, 82.9, 81.2, 76.0, 62.9, 60.4, 23.0, 20.9, 17.5; **IR** (cm $^{-1}$) ν_{max} 3305, 3011, 1737, 1240; **MS** m/z (EI) for $C_8H_{10}O_2$ calc. 138.0675, found 138.0674, error 0.9 ppm.

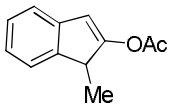
2,7-Diphenylocta-5,6-dien-3-yn-2-yl Acetate (180)



The starting material 2-phenylbut-3-yn-2-yl acetate (0.37 g, 2 mmol, 100 mol%) was dissolved in benzene (30 ml) at r.t. and CuCl (10 mg, 0.1 mmol, 5 mol%) was added. The reaction was refluxed for 30 min, cooled to r.t. and filtrated through a pad of Celite and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (20:1-10:1 pentane:Et_2O) and the title compound was obtained as a yellow oil (0.92 g, 0.29 mmol, 30%). $\mathbf{R_f}$ = 0.32 (20:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.58-7.56 (m, 2H), 7.43-7.24 (m, 8H), 5.85 (q, 1H, *J* = 2.8 Hz), 2.17 (dd, 3H, *J* = 2.8, 1.2 Hz), 2.08 (s, 3H), 1.90 (s, 3H); **^{13}C NMR** (67.9 Mz, $CDCl_3$) δ_C 213.7, 168.6, 142.7, 135.4, 128.5, 128.3, 127.7, 127.4, 126.2, 124.9, 103.1, 88.8, 80.0, 77.2, 76.2, 32.1, 21.8, 16.6, **IR** (cm $^{-1}$) ν_{max} 3156, 3011, 2253,

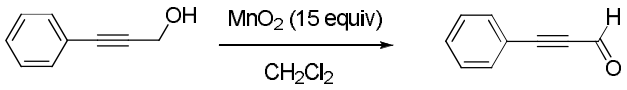
1743, 910; **MS** m/z (ESI) for $C_{22}H_{20}NaO_2$ [M+Na] calc. 339.1356, found 339.1357, error 0.60 ppm. The NMR in literature corresponds to experimental data [124].

1-Methyl-1*H*-inden-2-yl Acetate (181)



To 2-phenylbut-3-yn-2-yl acetate (94 mg, 0.5 mmol, 100 mol%) in CH_2Cl_2 (10 ml) at r.t. was added Au(IPr)Cl (15 mg, 0.025 mmol, 5 mol%) and AgOTf (6.4 mg, 0.025 mmol, 5 mol%). After 50 min the reaction mixture was filtrated through a pad of Celite and product was concentrated on a rotary evaporator. The residue was purified by flash column chromatography (30:1 pentane:Et_2O) and the title compound was obtained as a clear oil (36 mg, 0.19 mmol, 38%). $\mathbf{R_f}$ = 0.75 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.31-7.14 (m, 4H), 6.62 (d, 1H, *J* = 1.2 Hz), 3.59 (m, 1H), 2.28 (s, 3H), 1.34 (d, 3H, *J* = 7.6 Hz); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 168.0, 159.9, 141.7, 142.8, 126.8, 124.5, 122.3, 121.0, 113.1, 43.2, 21.3, 14.8; **IR** (cm $^{-1}$) ν_{max} 2971, 1764, 1600, 1463, 1370, 1199; **MS** m/z (ESI) for $C_{12}H_{12}NaO_2$ [M+Na] calc. 211.0730, found 211.0742, error 5.80 ppm. The title compound is identified in the literature, but no NMR data of this single isomer is available [160b].

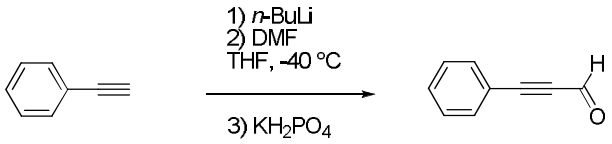
3-Phenylpropiolaldehyde: general procedure for the synthesis of propargylic aldehydes 186 starting from alcohols 189 (186a)



To 3-phenylprop-2-yn-1-ol (**189a**, 1.32g, 10 mmol, 100 mol%) in CH_2Cl_2 (200 ml, used as received) was added activated MnO_2* (13.0 g, 150 mmol, 15 equiv) and the reaction was stirred vigorously overnight at room temperature. The reaction was quenched by filtration through Celite and the solvents were evaporated on a rotary evaporator. If necessary, the residue was purified by flash column chromatography (9:1 petroleum ether:Et_2O) but often the crude product was used in the next reaction step without further purification (1.24 g, 9.5 mmol, 95%).

*The manganese oxide used in this reaction can be activated by drying it overnight in an 80 °C oven. The same manganese oxide could be used at least up to five times without loss of activity.

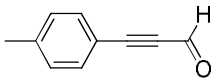
3-Phenylpropiolaldehyde: general procedure starting from phenylacetylene



To phenylacetylene (5.5 ml, 50 mmol, 100 mol%) in THF (125 ml) at -40 °C was added slowly *n*-BuLi (1.6 M, 31.3 ml, 50 mmol, 100 mol%) followed by anhydrous DMF (dried over molecular sieves: 7.75 ml, 100 mmol, 200 mol%). The reaction mixture was then poured into a vigorously stirred biphasic solution prepared from 10% aqueous solution of KH_2PO_4 (27 g of KH_2PO_4 in 270 ml H_2O, 200 mmol, 400 mol%) and MTBE (250 ml) cooled to 5 °C. The layers were separated and the organic layer was washed with water (2 x 200 ml). The combined aqueous layers were then extracted with MTBE (150 ml) and all the combined organic fractions were dried over $MgSO_4$, filtered and concentrated on a rotary evaporator to give 3-phenylpropiolaldehyde as a clear oil (6.35 g, 49 mmol, 97%). The crude product was often used in the next reaction step without further purification but the aldehyde can be purified by flash column chromatography (9:1 petroleum ether:Et_2O).

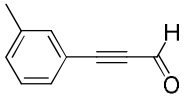
R_f = 0.67 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.43 (s, 1H), 7.62-7.60 (m, 2H), 7.49-7.48 (m, 1H), 7.43-7.39 (m, 2H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 176.9, 133.4, 131.4, 128.8, 119.5, 95.2, 88.5; **IR** (cm $^{-1}$) ν_{max} 3011, 2976, 2191, 1659, 1248, 1046, 980, 877; **MS** m/z (EI) for $C_9H_6O_1$ calc. 130.0419, found 130.0417, error 1.5 ppm. The NMR data in the literature correspond to the experimental data [179].

3-*p*-Tolylpropiolaldehyde (186b)



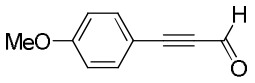
The starting material 3-*p*-tolylprop-2-yn-1-ol (**189b**, 1.4 g, 9.7 mmol, 100 mol%) gave the title compound as a yellow oil (1.2 g, 8.0 mmol, 82%) and recovered starting material (0.17 g, 1.2 mmol, 12%). $\mathbf{R_f}$ = 0.83 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.41 (s, 1H), 7.51-7.49 (m, 2H), 7.21-7.20 (m, 2H), 2.39 (s, 3H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 176.8, 142.2, 133.3, 129.5, 116.3, 95.9, 88.4, 21.8; **IR** (cm $^{-1}$) ν_{max} 2187, 1656, 1606, 1509, 985, 820; **MS** m/z (EI) for $C_{10}H_8O$ calc. 144.0575, found 144.0570, error 1.62 ppm The NMR data in the literature correspond to the experimental data [180].

3-*m*-Tolylpropiolaldehyde (186c)



The starting material 3-*m*-tolylprop-2-yn-1-ol (**189c**, 1.1 g, 7.4 mmol, 100 mol%) gave the title compound as a yellow oil (0.75 g, 5.2 mmol, 70%). $\mathbf{R_f}$ = 0.75 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.42 (s, 1H), 7.43-7.42 (m, 2H), 7.30-7.29 (m, 2H), 2.37 (s, 3H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 176.8, 138.6, 133.7, 132.2, 130.4, 128.6, 119.2, 95.2, 88.2, 21.1; **IR** (cm $^{-1}$) ν_{max} 2253, 2187, 1659, 1467, 1382, 1097, 909, 651; **MS** m/z (EI) for $C_{10}H_8O$ calc. 144.0570, found 144.0570, error 0.10 ppm.

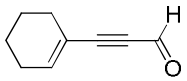
3-(4-Methoxyphenyl)propiolaldehyde (186d)



The starting material 3-(4-methoxyphenyl)prop-2-yn-1-ol (**189d**, 0.83 g, 5.1 mmol, 100 mol%) gave the title compound as a yellow solid (0.64 g, 4.0 mmol, 79%). $\mathbf{R_f}$ = 0.66 (4:1 petroleum ether:EtOAc); **M.p.** 44-45 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.39 (s, 1H), 7.58-7.55 (m, 2H), 6.93-6.90 (m, 2H), 3.85 (s, 3H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 176.7, 162.2, 135.4, 116.5, 114.5, 96.6, 55.5, one quaternary carbon could not be seen; **IR** (cm $^{-1}$) ν_{max} 2183, 1653, 1602,

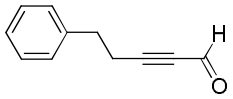
1510, 1256, 982, 835; **MS** m/z (EI) for $C_{11}H_{12}O_3Na$ [M+MeOH+Na] calc. 215.0684, found 215.0679, error 2.32 ppm. The NMR data in the literature correspond to the experimental data [180].

3-Cyclohexenylpropiolaldehyde (186e)



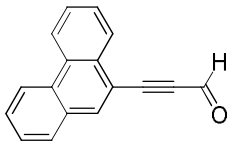
The stating material 3-cyclohexenylprop-2-yn-1-ol (**189e**, 1.4 g, 10 mmol, 100 mol%) gave the title compound as a yellow oil (0.76 g, 5.6 mmol, 56%) and recovered starting material (0.41 g, 3.0 mmol, 26%). $\mathbf{R_f}$ = 0.70 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.30 (s, 1H), 6.55-6.53 (m, 1H), 2.21-2.16 (m, 4H), 1.70-1.60 (m, 4H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 177.0, 144.1, 119.3, 97.8, 87.1, 28.1, 26.3, 21.9, 21.0; **IR** (cm $^{-1}$) ν_{max} 2254, 2179, 1655, 1467, 1383, 908, 651; **MS** m/z (EI), for $C_9H_{10}O$ calc. 134.0726, found 134.0726, error 0.10 ppm. The NMR data in the literature correspond to the experimental data [181].

5-Phenylpent-2-ynal (186f)



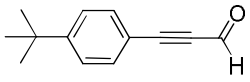
The starting material 5-phenylpent-2-yn-1-ol (**189f**, 0.62 g, 3.9 mmol, 100 mol%) gave the title compound as a clear oil (0.47 g, 3.0 mmol, 77%). $\mathbf{R_f}$ = 0.80 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.16 (s, 1H), 7.34-7.31 (m, 2H), 7.27-7.22 (m, 3H), 2.92 (t, 2H, *J* = 7.2 Hz), 2.72 (t, 2H, *J* = 7.2 Hz) ; **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 177.1, 139.4, 128.6, 128.3, 126.7, 97.9, 82.1, 33.7, 21.2; **IR** (cm $^{-1}$) ν_{max} 2202, 1663, 1137; **MS** m/z (EI), for $C_{11}H_{10}O_1Na$ [M+Na] calc. 181.0629, found 181.0624, error 2.76 ppm.

3-(Phenanthren-9-yl)propiolaldehyde (186g)



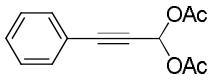
The starting material 3-(phenanthren-9-yl)prop-2-yn-1-ol (**189g**, 0.48 g, 2.1 mmol, 100 mol%) gave the title compound as a yellow solid (0.32 g, 1.4 mmol, 66%). $\mathbf{R_f}$ = 0.71 (4:1 petroleum ether:EtOAc); **M.p.** 94-95 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.59 (s, 1H), 8.68-8.63 (m, 2H), 8.39-8.37 (m, 1H), 8.19 (s, 1H), 7.88-7.86 (m, 1H), 7.74-7.69 (m, 3H), 7.63-7.61 (m, 1H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 176.5, 136.3, 131.5, 130.4 (2*C*), 129.9, 129.2, 129.1, 127.6 (2*C*), 127.3, 126.4, 122.9, 122.7, 115.8, 93.6, 92.6; **IR** (cm $^{-1}$) ν_{max} 3156, 2988, 2856, 2253, 2184, 1656; **MS** m/z (ESI) for $C_{17}H_{10}O_1Na$ [M+Na] calc. 253.0624, found 253.0626, error 0.80 ppm.

3-(4-*t*-Butylphenyl)propiolaldehyde (186h)



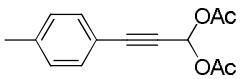
The starting material 1-*t*-butyl-4-ethynylbenzene (4.0 g, 25 mmol, 100 mol%) gave the title compound as a yellow oil (4.5 g, 24 mmol, 95%). $\mathbf{R_f}$ = 0.59 (9:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.42 (s, 1H), 7.56-7.53 (m, 2H), 7.44-7.42 (m, 2H), 1.33 (s, 9H); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 177.0, 155.3, 133.4, 126.0, 116.5, 96.1, 88.6, 35.3, 31.2; **IR** (cm $^{-1}$) ν_{max} 3011, 2189, 1656, 1604, 986, 839; **MS** m/z (ESI), for $C_{13}H_{14}NaO$ [M+Na] calc. 209.0937, found 209.0936, error 0.20 ppm.

3-Phenylprop-2-yne-1,1-diyl Diacetate: general procedure towards propargylic diacetates (187a)



Solid $FeCl_3$ (0.24 g, 1.5 mmol, 10 mol%) was dissolved in CH_2Cl_2 (150 ml) at r.t. and left to stir for 15 min before addition of 3-phenylpropiolaldehyde (**186a**, 2.1 g, 15 mmol, 100 mol%) in 10 ml of CH_2Cl_2 followed by the addition of Ac_2O (1.4 ml, 15 mmol, 100 mol%). After 3 hours the reaction was quenched with saturated aqueous $NaHCO_3$ solution. The mixture was washed three times with saturated aqueous $NaHCO_3$ solution, and the combined aqueous layers were re-extracted once with CH_2Cl_2. The combined organic fractions were washed once more with saturated aqueous $NaHCO_3$ solution, then with saturated aqueous NaCl solution and dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (30:1-10:1 petroleum ether:EtOAc) to give the title compound as a yellow oil (2.9 g, 12.4 mmol, 83%). Some remaining aldehyde could be recovered (0.27 g, 2.1 mmol, 14%). $\mathbf{R_f}$ = 0.61 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.51-7.48 (m, 3H), 7.38-7.31 (m, 3H), 2.15 (s, 6H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 168.1, 132.1, 129.5, 128.3 (2*C*), 86.8, 81.4, 80.0, 20.7; **IR** (cm $^{-1}$) ν_{max} 3010, 2976, 2895, 2240, 1826, 1767, 1372, 1245, 1126, 1046, 956, 877; **MS** m/z (ESI) for $C_{13}H_{12}O_4Na$ [M+Na] calc. 255.0628, found 255.0624, error 1.30 ppm. The NMR data in the literature correspond to the experimental data [125].

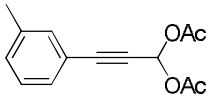
3-*p*-Tolylprop-2-yne-1,1-diyl Diacetate (187b)



The starting material 3-*p*-tolylpropiolaldehyde (**186b**, 0.33 g, 2.3 mmol, 100 mol%) gave the title compound as a yellow solid (0.35 g, 1.4 mmol, 63%) and recovered starting material (0.080g, 0.55 mmol, 26%). $\mathbf{R_f}$ = 0.43 (4:1 petroleum ether:EtOAc); **M.p.** 64-65 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.48 (s, 1H), 7.39-7.37 (m, 2H), 7.14-7.12 (m, 2H), 2.35 (s, 3H), 2.15 (s, 6H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 168.2, 139.8, 132.0, 129.1, 117.7, 87.0, 80.8, 80.0, 21.6,

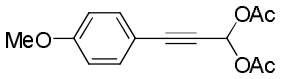
20.7; **IR** (cm $^{-1}$) ν_{max} 3156, 2253, 1766, 1466, 1375, 910; **MS** m/z (ESI) for $C_{14}H_{14}O_4Na$ [M+Na] calc. 269.0784, found 269.0785, error 0.40 ppm.

3-*m*-Tolylprop-2-yne-1,1-diyl Diacetate (187c)



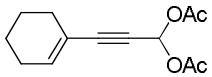
The starting material 3-*m*-tolylpropiolaldehyde (**186c**, 0.58 g, 4.1 mmol, 100 mol%) gave the title compound as a yellow oil (0.73 g, 2.9 mmol, 72%). $\mathbf{R_f}$ = 0.61 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.48 (s, 1H), 7.33-7.29 (m, 2H), 7.24-7.19 (m, 2H), 2.33 (s, 3H), 2.15 (s, 6H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 168.2, 138.2, 132.7, 130.4, 129.2, 128.3, 120.6, 87.0, 81.1, 80.1, 21.2, 20.8; **IR** (cm $^{-1}$) ν_{max} 2254, 1768, 1467, 1378, 1097, 907, 651; **MS** m/z (ESI) for $C_{14}H_{14}O_4Na$ [M+Na] calc. 269.0784, found 269.0790, error 1.90 ppm.

3-(4-Methoxyphenyl)prop-2-yne-1,1-diyl Diacetate (187d)



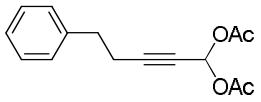
The starting material 3-(4-methoxyphenyl)propiolaldehyde (**186d**, 0.59 g, 3.7 mmol, 100 mol%) gave the title compound as a yellow oil (0.25 g, 0.95 mmol, 26%) and recovered starting material (0.15 g, 1.1 mmol, 27%). $\mathbf{R_f}$ = 0.33 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.47 (s, 1H), 7.45-7.41 (m, 2H), 6.86-6.83 (m, 2H), 3.81 (s, 3H), 2.15 (s, 6H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 168.2, 160.5, 133.7, 114.0, 112.7, 86.9, 80.4, 80.1, 55.3, 20.7; **IR** (cm $^{-1}$) ν_{max} 3156, 2253, 1767, 1606, 1511, 1466, 1376, 1096, 906; **MS** m/z (ESI) for $C_{14}H_{14}O_5Na$ [M+Na] calc. 285.0733, found 285.0734, error 0.20 ppm.

3-Cyclohexenylprop-2-yne-1,1-diyl Diacetate (187e)



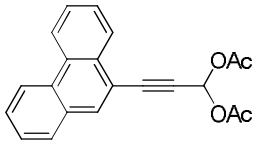
The starting material 3-cyclohexenylpropiolaldehyde (**186e**, 0.60 g, 4.5 mmol, 100 mol%) gave the title compound as a colourless solid (0.52 g, 2.2 mmol, 49%) and recovered starting material (0.13 g, 0.93 mmol, 21%). $\mathbf{R}_f$ = 0.59 (4:1 petroleum ether:EtOAc); **M.p.** 58-69 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.36 (s, 1H), 6.27-6.25 (m, 1H), 2.12 (s, 6H), 2.17-2.09 (m, 2H), 1.63-1.55 (m, 6H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 168.2, 138.4, 118.9, 88.7, 80.1, 78.8, 28.5, 25.7, 22.0, 21.2, 20.7; **IR** (cm $^{-1}$) ν_{max} 2254, 1765, 1467, 1380, 1097, 907, 651; **MS** m/z (ESI) for $C_{13}H_{16}O_4Na$ [M+Na] calc. 259.0941, found 259.0946, error 2.20 ppm.

5-Phenylpent-2-yne-1,1-diyl Diacetate (187f)



The starting material 5-phenylpent-2-ynal (**186f**, 0.85 g, 5.4 mmol, 100 mol%) gave the title compound as a yellow oil (0.87 g, 3.3 mmol, 62%) and recovered stating material (0.14 g, 0.91 mmol, 17%). $\mathbf{R}_f$ = 0.46 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.31-7.28 (m, 2H), 7.24-7.19 (m, 4H), 2.85 (t, 2H, *J* = 7.9 Hz), 2.56-2.52 (m, 2H), 2.11 (s, 6H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 168.2, 140.0, 128.4 (2*C*), 126.5, 87.7, 79.8, 73.9, 34.3, 20.8, 20.7; **IR** (cm $^{-1}$) ν_{max} 3156, 2989, 2253, 1765, 1467, 1375, 1246, 1163, 1096, 903; **MS** m/z (ESI) for $C_{15}H_{16}O_4Na$ [M+Na] calc. 283.0941, found 283.0944, error 1.10 ppm.

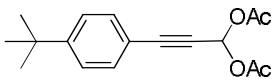
3-(Phenanthren-9-yl)prop-2-yne-1,1-diyl Diacetate (187g)



The starting material 3-(phenanthren-9-yl)propiolaldehyde (**186g**, 71 mg, 0.31 mmol, 100 mol%) gave the title compound as a yellow thick oil (52 mg, 0.15 mmol, 51%) and recovered starting material (18 mg, 0.08 mmol, 26%). $\mathbf{R}_f$ = 0.53 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.69-8.65 (m, 2H), 8.39-8.37 (m, 1H), 8.09 (s, 1H), 7.87-7.85 (m, 1H),

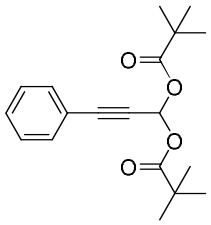
7.72-7.68 (m, 3H), 7.68 (s, 1H), 7.66-7.60 (m, 1H), 2.22 (s, 6H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 168.3, 133.5, 130.7 (3*C*), 130.0, 128.8, 128.1, 127.3 (2*C*), 127.1, 126.6, 122.8, 122.6, 117.2, 85.7, 85.2, 80.2, 20.8; **IR** (cm $^{-1}$) ν_{max} 3156, 2988, 2253, 1766, 1375, 901; **MS** m/z (ESI) for $C_{21}H_{16}O_4Na$ [M+Na] calc. 355.0941, found 355.0927, error 3.80 ppm.

3-(4-*t*-Butylphenyl)prop-2-yne-1,1-diyl Diacetate (187 h)



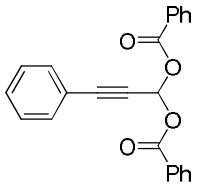
The starting material 3-(4-*t*-butylphenyl)propiolaldehyde (**186h**, 4.5 g, 24 mmol, 100 mol%) gave the title compound as a dark oil (1.1 g, 3.7 mmol, 16%) and starting material (2.7 g, 14 mmol, 60%). $\mathbf{R_f}$ = 0.17 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.48 (s, 1H), 7.43-7.42 (m, 2H), 7.35-7.33 (m, 2H), 2.15 (s, 6H), 1.31 (s, 9H) ; **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 168.2, 152.9, 131.9, 125.4, 117.7, 87.0, 80.8, 80.1, 34.9, 31.1, 20.7; **IR** (cm $^{-1}$) ν_{max} 2968, 2240, 1766, 1242; **MS** m/z (ESI), for $C_{17}H_{24}NO_4$ [M+NH_4] calc. 306.1700, found 306.1692, error 2.70 ppm.

3-Phenylprop-2-yne-1,1-diyl *bis*(2,2-Dimethylpropanoate) (187i)



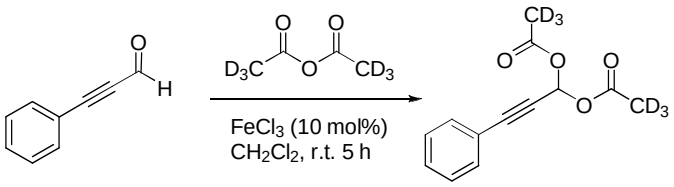
The starting material 3-phenylpropiolaldehyde (**186a**, 2.0 g, 15 mmol, 100 mol%) and pivalic anhydride (2.8 g, 15 mmol, 100 mol%) gave the title compound as a thick yellow oil (2.2 g, 7.0 mmol, 46%). $\mathbf{R_f}$ = 0.83 (9:1 petrol ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.52-7.49 (m, 2H), 7.48 (s, 1H), 7.40-4.31 (m, 3H), 1.24 (s, 18H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 175.7, 132.1, 129.3, 128.3, 121.1, 86.3, 81.9, 80.3, 38.8, 26.8; **IR** (cm $^{-1}$) ν_{max} 3011, 2241, 1751, 1492; **MS** m/z (ESI) for $C_{19}H_{24}NaO_4$ [M+Na] calc. 339.1567, found 339.1565, error 0.60 ppm.

3-Phenylprop-2-yne-1,1-diyl Dibenzoate (187j)



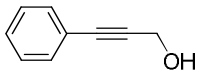
The starting material 3-phenylpropiolaldehyde (**186a**, 2.0 g, 15 mmol, 100 mol%) and benzoic anhydride (3.4 g, 15 mmol, 100 mol%) gave the title compound as a colourless solid (1.0 g, 2.9 mmol, 20%). Purification by crystallization from EtOAc/petroleum ether. $\mathbf{R_f}$ = 0.60 (9:1 petroleum ether:Et_2O); **M.p.** 111-112 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.16-8.13 (m, 4H), 8.04 (s, 1H), 7.63-7.54 (m, 4H), 7.49-7.45 (m, 4H), 7.39-7.32 (m, 3H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 163.9, 133.8, 132.2, 130.2, 129.5, 128.6, 128.5, 128.4, 120.9, 87.1, 81.7, 81.1; **IR** (cm $^{-1}$) ν_{max} 3066, 2244, 1744, 1272, **MS** m/z (ESI) for $C_{23}H_{16}NaO_4$ [M+Na] calc. 379.0941, found 379.0942, error 0.30 ppm.

3-Phenylprop-2-yne-1,1-diyl *d*-diacetate (*d*-187a)



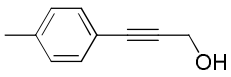
The starting material 3-phenylpropiolaldehyde (**186a**, 1 g, 7.7 mmol, 100 mol%) and *d*-acetic anhydride (0.72 ml, 7.7 mmol, 100 mol%) gave the title compound as yellow oil (1.0 g, 4.2 mmol, 55%). $\mathbf{R_f}$ = 0.23 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.52-7.49 (m, 2H), 7.49 (s, 1H), 7.40-7.31 (m, 3H), 2.13 (quintet, 0.03H, *J* = 2.0 Hz, *CD_3*); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 169.2, 132.1, 129.5, 128.4, 120.8, 86.7, 81.5, 79.9, 20.0 (t, CD_3, *J* = 20.1 Hz); **IR** (cm $^{-1}$) ν_{max} 3045, 2241, 1763, 1493, 1249; **MS** m/z (ESI), for $C_{13}H_6D_6NaO_4$ [M+Na] calc. 261.1004, found 261.0997, error 2.70 ppm.

3-Phenylprop-2-yn-1-ol: general procedure towards propargylic alcohols (189a)



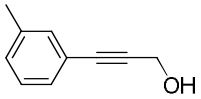
To phenylacetylene (6.6 ml, 60 mmol, 100 mol%) in THF (30 ml) at -78 °C was added slowly *n*-BuLi (2M, 30 ml, 60 mmol, 100 mol%). After 30 min (temperature usually around -50 °C) paraformaldehyde (5.4 g, 180 mmol, 300 mol%) was added in three portions and the reaction was left to warm up to room temperature overnight. The mixture was diluted with Et_2O and quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted three times with Et_2O and the combined organic layers were washed with brine, then dried with $MgSO_4$ and concentrated *in vacuo*. Further purification was not always needed for the next reaction step but the product can be purified by flash column chromatography (10:1 petrol ether:Et_2O). The product was obtained as a yellow oil (7.1 g, 54 mmol, 90%). $\mathbf{R_f}$ = 0.31 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.45-7.43 (m, 2H), 7.33-7.31 (m, 3H), 4.50 (s, 2H), 1.80 (bs, 1H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 131.8, 131.7, 128.5, 128.3, 87.2, 85.7, 51.6; **IR** (cm $^{-1}$) ν_{max} 3606, 3403, 1490, 3006, 2872, 1443, 1383, 1031, 1021; **MS** m/z (EI) for C_9H_8O calc. 132.0575, found 132.0570, error 0.65 ppm. The NMR in the literature corresponds to the experimental data [182].

3-*p*-Tolylprop-2-yn-1-ol (189b)



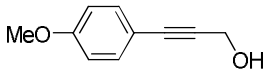
The starting material 4-ethynyltoluene (1.0 g, 8.6 mmol, 100 mol%) gave the title compound as a clear oil (0.89 g, 6.1 mmol, 71%). $\mathbf{R_f}$ = 0.44 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.34-7.32 (m, 2H), 7.12-7.10 (m, 2H), 4.49 (s, 2H), 2.34 (s, 3H), 1.88 (bs, 1H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 138.6, 131.5, 129.0, 119.4, 86.0, 85.8, 51.6, 21.4; **IR** (cm $^{-1}$) ν_{max} 3607, 3407, 3004, 2924, 2871, 2237, 1731, 1510, 1382, 1025, 820; **MS** m/z (EI) for $C_{10}H_{10}O_1Na$ [M+Na] calc. for 169.0629, found 169.0624, error 2.71 ppm. The NMR data in literature corresponds to experimental data [183].

3-*m*-Tolylprop-2-yn-1-ol (189c)



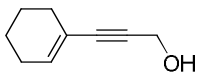
The starting material *m*-tolylacetylene (1.0 g, 8.6 mmol, 100 mol%) gave the title compound as a yellow oil (1.2 g, 8.5 mmol, 99%). $\mathbf{R_f}$ = 0.21 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.27-7.13 (m, 4H), 4.49 (s, 2H), 2.32 (s, 3H), 1.70 (bs, 1H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 138.0, 132.3, 129.4, 128.7, 128.2, 122.3, 86.8, 85.9, 51.7, 21.2; **IR** (cm $^{-1}$) ν_{max} 3601, 2254, 1381, 909, 651; **MS** m/z (EI) calc. for $C_{10}H_{10}O$ 146.0726, found 146.0726, error 0.10 ppm.

3-(4-Methoxyphenyl)prop-2-yn -1-ol (189d)



The starting material 4-ethynylanisole (1.0 g, 7.6 mmol, 100 mol%) gave the title compound as a yellow solid (0.88 g, 5.4 mmol, 71%) and recovered starting material (0.25 g, 1.9 mmol, 25%). $\mathbf{R_f}$ = 0.30 (4:1 petroleum ether:EtOAc); **M.p.** 61-62 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.38-7.36 (m, 2H), 6.84-6.83 (m, 2H), 4.48 (s, 2H), 3.81 (s, 2H), 2.17 (bs, 1H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 159.7, 133.2, 114.6, 113.9, 85.8, 85.6, 55.3, 51.7; **IR** (cm $^{-1}$) ν_{max} 3688, 3605, 3002, 2937, 2840, 2234, 1607, 1509, 1248, 1034, 833; **MS** m/z (EI), for $C_{10}H_{10}O_2Na$ [M+Na] calc. 185.0578, found 185.1. The Mp [184] and NMR [185] data in the literature correspond to the experimental data.

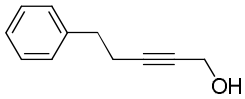
3-Cyclohexenylprop-2-yn-1-ol (189e)



The starting material 1-ethynylcyclohexene (2.0 g, 19 mmol, 100 mol%) gave the title compound as a clear oil (1.7 g, 12 mmol, 66%). $\mathbf{R_f}$ = 0.25 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H δ 6.13-6.11 (m, 1H), 4.37 (d, 2H, *J* = 4.81 Hz), 2.13-2.07 (m, 4H), 1.66-1.54 (m, 5H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 135.5, 120.1, 87.6, 84.5, 51.7, 29.1, 25.6, 22.2, 21.4; **IR** (cm $^{-1}$) ν_{max} 3600, 3156, 2254, 1467, 1381, 910, 651; **MS** m/z (EI), for $C_9H_{12}O$

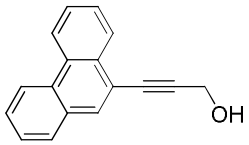
calc. 136.0883, found 136.0883, error 0.10 ppm. The NMR data in the literature corresponds to the experimental data [186].

5-Phenylpent-2-yn-1-ol (189f)



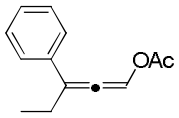
The starting material 4-phenyl-1-butyne (1.0 g, 7.7 mmol, 100 mol%) gave the title compound as a clear oil (0.77 g, 4.8 mmol, 63%) and recovered starting material (0.38 g, 2.9 mmol, 37%). $\mathbf{R_f}$ = 0.39 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.32-7.28 (m, 2H), 7.24-7.20 (m, 3H), 4.23 (t, 2H, *J* = 2.4 Hz), 2.84 (t, 2H, *J* = 7.6 Hz), 2.52 (tt, 2H, *J* = 2.4, 7.6 Hz), 1.72 (bs, 1H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 140.5, 128.4 (2*C*), 126.3, 87.9, 85.7, 51.3, 34.9, 20.9; **IR** (cm $^{-1}$) ν_{max} 3611, 3387, 3065, 3007, 2931, 2868, 2223, 1496, 1453, 1384, 1007; **MS** m/z (EI) for $C_{11}H_{12}O_1Na$ [M+Na] calc. 183.0786, found 183.0780, error 1.32 ppm. The NMR data in literature correspond to experimental data [187].

3-(Phenanthren-9-yl)prop-2-yn-1-ol (189g)



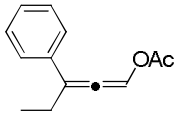
The starting material 9-ethynylphenanthrene (0.88 g, 4.3 mmol, 100 mol%) gave the title compound as a yellow solid (0.65 g, 2.8 mmol, 64%) and recovered starting material (0.29 g, 1.4 mmol, 34%). $\mathbf{R_f}$ = 0.27 (4:1 petroleum ether:EtOAc); **M.p.** 126-127 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.69-8.63 (m, 2H), 8.44-8.42 (m, 1H), 7.99 (s, 1H), 7.84-7.81 (m, 1H), 7.69-7.64 (m, 3H), 7.61-7.59 (m, 1H), 4.69 (s,2H), 2.07 (bs, 1H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 132.2, 131.0, 130.9, 130.3, 130.0, 128.5, 127.5, 127.1, 127.0, 126.9, 126.8, 122.7, 122.5, 118.9, 91.7, 83.9, 51.8; **IR** (cm $^{-1}$) ν_{max} 3029, 3017, 2253, 1230, 1224, 1207, 802; **MS** m/z (ESI) for $C_{17}H_{12}O_1Na$ [M+Na] calc. 255.0780, found 255.0784, error 1.40 ppm.

3-Phenylpenta-1,2-dienyl Acetate: Method 1 to the synthesis of allenyl acetates *via* cuprate mediated S_N2' nucleophilic substitution (190b)



CuI (0.62 g, 3.3 mmol, 250 mol%) and LiBr (0.28 g, 3.3 mmol, 250 mol%) were dried briefly in a Schlenck tube under vacuum with a heat gun. The mixture was cooled to room temperature and flushed with argon, cooled to –10 ºC and THF (25 ml) was added. EtMgBr (1 M in MTBE, 3.2 ml, 3.2 mmol, 240 mol%) was added slowly and after 10 min 3-phenylprop-2-yne-1,1-diyl diacetate (**187a**, 0.3 g, 1.3 mmol, 100 mol%) was added in THF (5 ml). After 30 min the reaction was quenched with a saturated aqueous NH_4Cl/NH_3 solution (prepared by adding 10 ml of NH_3 to 500 ml of saturated aqueous NH_4Cl solution) and left to stir 2-3 min at –10 °C. The mixture was diluted with Et_2O (150 ml) and the organic fraction was extracted and washed with NH_4Cl/NH_3 solution 3-4 times or until the aqueous phase was not blue. The organic phase was then washed with saturated aqueous NaCl solution, dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (30:1 pentane:Et_2O) and product was obtained as a yellow oil (0.23 g, 1.1 mmol, 88%). Compound data as described in method 2.

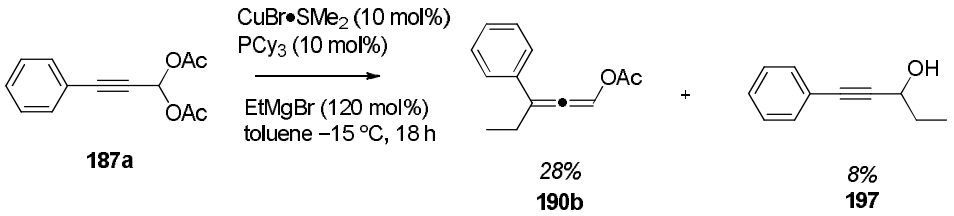
3-Phenylpenta-1,2-dienyl Acetate: Method 2 to the synthesis of allenyl acetates *via* nickel catalyzed S_N2' nucleophilic substitution (190b)



Solid $Ni(acac)_2$ (TOXIC!) (6.4 mg, 0.025 mmol, 5 mol%) and (±)-NOBIN (10 mg, 0.035 mmol, 7 mol%) were charged in a Schlenck tube and Et_2O (5 ml) added. The reaction mixture was cooled to +4 °C and after 10 min $ZnEt_2$ (1 M in hexanes, 2.5 ml, 2.5 mmol, 500 mol%) was added. After another 10 min **187a** (0.116 g, 0.5 mmol, 100 mol%) was added in Et_2O (5 ml) over 1 h *via* a syringe pump. After 3 h the reaction was quenched with saturated aqueous NH_4Cl solution and the aqueous layer was extracted three times with Et_2O. The combined organics were washed with saturated aqueous NaCl solution, dried over $MgSO_4$ and

concentated *in vacuo*. The residue was purified by flash column chromatography (30:1 pentane:Et_2O) and the title compound was obtained as a yellow oil (0.063 g, 0.31 mmol, 62%). $\mathbf{R_f}$ = 0.78 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.73 (t, 1H, *J* = 2.6 Hz), 7.48-7.45 (m, 2H), 7.37-7.27 (m, 3H), 2.65-2.51 (m, 2H), 2.17 (s, 3H), 1.18 (t, 3H, *J* = 7.8 Hz); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 192.5, 168.7, 135.7, 128.4, 128.0, 126.6, 121.8, 113.4, 24.3, 20.9, 12.2; **IR** (cm $^{-1}$) ν_{max} 3010, 1750, 1372, 1240; **MS** m/z (ESI) for $C_{13}H_{14}O_2Na$ [M+Na] calc. 225.0886, found 225.0893, error 2.90 ppm.

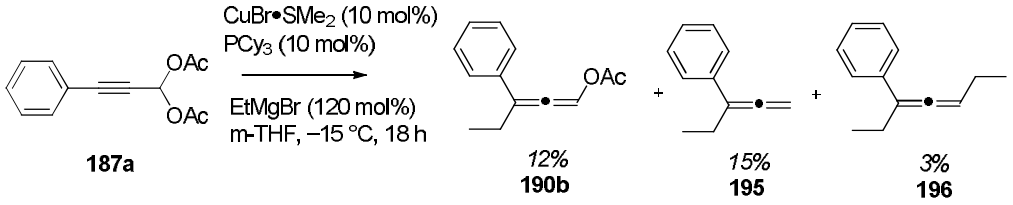
Copper-catalyzed synthesis of allenyl acetate 190b in toluene



$CuBr•SMe_2$ (8.8 mg, 0.043 mmol, 10 mol%) and PCy_3 (12.1 mg, 0.043 mmol, 10 mol%) were charged in a Schlenk tube and toluene (5 ml) was added at r.t and the mixture was cooled down to –20 °C. Diacetate (187a, 100 mg, 0.43 mmol, 100 mol%) was added in CH_2Cl_2 (1 ml) followed by addition of EtMgBr (2 M, 0.26 ml, 0.52 mmol, 120 mol%) over 30 minutes. The reaction was let to stir at –20 °C for 2 hours before quenching the reaction by addition of saturated aqueous NH_4Cl solution. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were concentrated on a rotary evaporator to give 3-phenylpenta-1,2-dienyl acetate (**190b**, 24 mg, 0.12 mmol, 28%) and 1-Phenylpent-1-yn-3-ol (**197**, 5.5 mg, 0.03 mmol, 8%).

1-Phenylpent-1-yn-3-ol (**197**); $\mathbf{R_f}$ = 0.80 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.45-7.42 (m, 2H), 7.31-7.28 (m, 3H), 4.55 (t, 1H, *J* = 7.2 Hz), 2.30 (bs, 1H, *OH*), 1.87-1.79 (m, 2H), 1.08 (t, 3H, *J* = 7.6 Hz); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 131.6, 128.3, 128.2, 122.6, 90.0, 84.8, 64.1, 30.9, 9.5; **IR** compound was not pure enough for analysis; **MS** m/z (EI) for $C_{11}H_{12}O$ calc. 160.0888, found 160.0891, error 1.7 ppm. The NMR data in the literature correspond to the experimental data [188].

Copper-catalyzed synthesis of allenyl acetate 190b in toluene

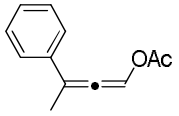


Same procedure as above with mTHF as solvent gave 3-phenylpenta-1,2-dienyl acetate (**190b**, 10.3 mg, 0.05 mmol, 12%), penta-1,2-dien-3-ylbenzene (**195**, 9.3 mg, 0.06 mmol, 15%) and hepta-3,4-dien-3-ylbenzene (**196**, 2.2 mg, 0.01 mmol, 3%).

Penta-1,2-dien-3-ylbenzene (195); Yellow oil, $\mathbf{R_f}$ = 0.95 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.40-7.15 (m, 5H), 5.07 (t, 2H, *J* = 3.6 Hz), 2.44-2.37 (m, 2H), 1.13 (m, 3H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 208.4, 136.5, 128.3, 126.5, 128.9, (106.7), 78.7 (CH_2), 22.4, 12.5 sample contained impurities in the NMR spectra; **IR** compound was not pure enough for analysis; **MS** m/z (EI) for $C_{11}H_{12}$ calc. 144.0939, found 144.0925, error 9.8 ppm. The NMR data in the literature correspond to the experimental data [189].

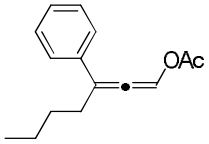
Hepta-3,4-dien-3-ylbenzene (196); Yellow oil, $\mathbf{R_f}$ = 0.95 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.44-7.17 (m, 5H), 5.64-5.60 (m, 1H), 2.46-2.42 (m, 2H), 2.19-2.11 (m, 2H), 1.15 (t, 3H, *J* = 6.8 Hz), 1.08 (t, 3H, *J* = 6.8 Hz); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 203.1, (128.2, 126.3, 125.7, 96.8, 22.8, 22.3, 13.5, 12.6) sample contained impurities in the NMR spectra; **IR** compound was not pure enough for analysis; **MS** m/z (EI) for $C_{13}H_{16}$ calc. 172.1252, found 172. 1259, error 4.3 ppm.

3-Phenylbuta-1,2-dienyl Acetate (190a)



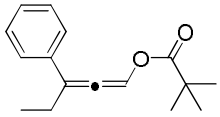
Using method 1, the starting material 3-phenylprop-2-yne-1,1-diyl diacetate (**187a**, 0.23 g, 1.0 mmol, 100 mol%) and MeMgBr (0.8 ml, 3 M, 2.4 mmol, 240 mol%) gave the title compound as a yellow oil (0.056 g, 0.30 mmol, 30%). $\mathbf{R_f}$ = 0.84 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.63 (q, 1H, *J* = 2.0 Hz), 7.50-7.47 (m, 2H), 7.38-7.26 (m, 3H), 2.25 (d, 3H, *J* = 2.0 Hz), 2.17 (s, 3H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 193.1, 168.7, 135.7, 128.4, 128.1, 126.4, 114.7, 111.2, 20.9, 18.4; **IR** (cm $^{-1}$) ν_{max} 3156, 2253, 1748, 1466, 1373, 1098, 906; **MS** m/z (ESI) for $C_{12}H_{12}O_2Na$ [M+Na] calc. 211.0730, found 211.0737, error 3.50 ppm.

3-Phenylhepta-1,2-dienyl Acetate (190c)



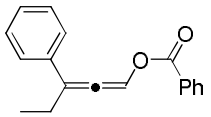
Using method 1, the starting material 3-phenylprop-2-yne-1,1-diyl diacetate (**187a**, 0.23 g, 1.0 mmol, 100 mol%) with *n*-BuMgCl (1.2 ml, 2 M, 2.4 mmol, 240 mol%) gave the title compound as a yellow oil (0.15 g, 0.65 mmol, 65%). $\mathbf{R_f}$ = 0.84 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.69 (t, 1H, *J* = 1.8 Hz), 7.48-7.45 (m, 2H), 7.36-7.27 (m, 3H), 2.63-2.49 (m, 2H), 2.17 (s, 3H), 1.60-1.53 (m, 2H), 1.47-1.38 (m, 2H), 0.94 (t, 3H, *J* = 7.6 Hz); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 192.8, 168.8, 135.7, 128.5, 128.0, 126.7, 120.1, 112.7, 31.0, 29.9, 22.4, 21.0, 13.9; **IR** (cm $^{-1}$) ν_{max} 3156, 2254, 1747, 1467, 1381, 1097, 907; **MS** m/z (ESI) for $C_{15}H_{18}O_2Na$ [M+Na] calc. 253.1199, found 253.1199, error 0.10 ppm.

3-Phenylpenta-1,2-dienyl Pivalate (190d)



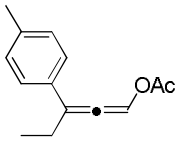
Using method 1, the starting material 3-phenylprop-2-yne-1,1-diyl *bis*(2,2-dimethylpropanoate) (**187i**, 0.63 g, 2.0 mmol, 100 mol%) gave the title compound as a yellow oil (0.38 g, 1.6 mmol, 78%). $\mathbf{R_f}$ = 0.85 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.71 (t, 1H, *J* = 1.8 Hz), 7.49-7.46 (m, 2H), 7.36-7.25 (m, 3H), 2.67-2.49 (m, 2H), 1.26 (s, 9H), 1.17 (t, 3H, *J* = 6.3 Hz); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 192.8, 176.4, 135.9, 128.4, 127.9, 126.6, 121.3, 113.7, 39.1, 27.1, 24.3, 12.3; **IR** (cm $^{-1}$) ν_{max} 2974, 1964, 1736, 1277, 1134, **MS** m/z (ESI) for $C_{16}H_{20}NaO_2$ [M+Na] calc. 267.1356, found 267.1342, error 5.00 ppm.

3-Phenylpenta-1,2-dienyl Benzoate (190e)



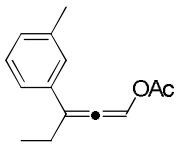
Using method 1, the starting material 3-phenylprop-2-yne-1,1-diyl dibenzoate (**187j**, 0.71 g, 2.0 mmol, 100 mol%) gave the title compound as a yellow oil (0.39 g, 1.5 mmol, 74%). $\mathbf{R_f}$ = 0.75 (9:1 petroleum ether: Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.13-8.11 (m, 2H), 7.99 (t, 1H, *J* = 2.2 Hz), 7.61-7.44 (m, 6H), 7.38-7.27 (m, 2H), 2.72-2.54 (m, 2H), 1.22 (t, 3H, *J* = 7.0 Hz), **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 193.1, 164.4, 135.7, 133.4, 130.0, 129.4, 128.5 (2*C*), 128.1, 126.7, 121.9, 113.8, 30.9, 24.3, 12.3; **IR** (cm $^{-1}$) ν_{max} 3065, 2973, 2935, 1966, 1725, 1266; **MS** m/z (ESI) for $C_{18}H_{16}NaO_2$ [M+Na] calc. 287.1043, found 287.1037, error 1.90 ppm.

3-*p*-Tolylpenta-1,2-dienyl Acetate (190f)



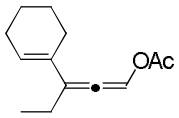
Using method 1, the starting material 3-*p*-tolylprop-2-yne-1,1-diyl diacetate (**187b**, 0.49 g, 2.0 mmol, 100 mol%) gave the title compound as a yellow oil (0.35 g, 1.6 mmol, 81%). $\mathbf{R_f}$ = 0.51 (20:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.71 (t, 3H, *J* = 1.9 Hz), 7.38-7.35 (m, 2H), 7.16-7.14 (m, 2H), 2.63-2.49 (m, 2H), 2.35 (s, 3H), 2.17 (s, 3H), 1.17 (t, 3H, *J* = 6.1 Hz); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 191.9, 168.8, 138.0, 132.7, 129.2, 126.5, 121.7, 113.2, 24.3, 21.2, 21.0, 12.3; **IR** (cm $^{-1}$) ν_{max} 2253, 1746, 1466, 1380, 1097, 906, 651; **MS** m/z (ESI) for $C_{14}H_{16}O_2Na$ [M+Na] calc. 239.1043, found 239.1041, error 0.60 ppm.

3-*m*-Tolylpenta-1,2-dienyl Acetate (190g)



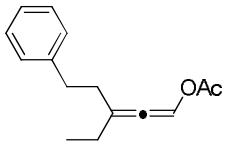
Using method 1, the starting material 3-*m*-tolylprop-2-yne-1,1-diyl diacetate (**187c**, 0.1 g, 0.41 mmol, 100 mol%) gave the title compound as a yellow oil (46 mg, 0.21 mmol, 46%). $\mathbf{R_f}$ = 0.5 (20:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.73-7.72 (m, 1H), 7.28-7.23 (m, 3H), 7.10-7.08 (m, 1H), 2.64-2.54 (m, 2H), 2.36 (s, 3H), 2.18 (s, 3H), 1.17 (t, 3H, *J* = 7.2 Hz); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 192.3, 168.7, 138.0, 135.6, 128.8, 128.3, 127.3, 123.6, 121.9, 113.2, 24.4, 21.4, 21.0, 12.3; **IR** (cm $^{-1}$) ν_{max} 2969, 1957, 1755, 1603, 1368, 1208; **MS** m/z (ESI) for $C_{14}H_{16}O_2Na$ [M+Na] calc. 239.1043, found 239.1048, error 2.30 ppm.

3-Cyclohexenylpenta-1,2-dienyl Acetate (190h)



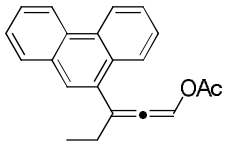
Using method 1, the starting material 3-cyclohexenylprop-2-yne-1,1-diyl diacetate (**187e**, 0.16 g, 0.7 mmol, 100 mol%) gave the title compound as a yellow oil (0.10 g, 0.47 mmol, 67%). $\mathbf{R_f}$ = 0.66 (20:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.55-7.54 (m, 1H), 5.98-5.96 (m, 1H), 2.36-2.28 (m, 2H), 2.16-2.09 (m, 4H), 2.14 (s, 3H), 1.66-1.57 (m, 4H), 1.06 (t, 3H, *J* = 7.2 Hz); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 191.5, 168.8, 132.5, 125.9, 123.6, 113.1, 27.2, 26.0, 22.7 (2*C*), 22.2, 21.0, 12.3; **IR** (cm $^{-1}$) ν_{max} 2931, 1952, 1754, 1368; **MS** m/z (ESI) for $C_{13}H_{18}O_2Na$ [M+Na] calc. 229.1199, found 229.1202, error 1.30 ppm; **Anal. calc**. for $C_{13}H_{18}O_2$ C, 76.0; H, 8.8, found C, 76.2; H, 8.9%.

3-Ethyl-5-phenylpenta-1,2-dienyl Acetate (190i)

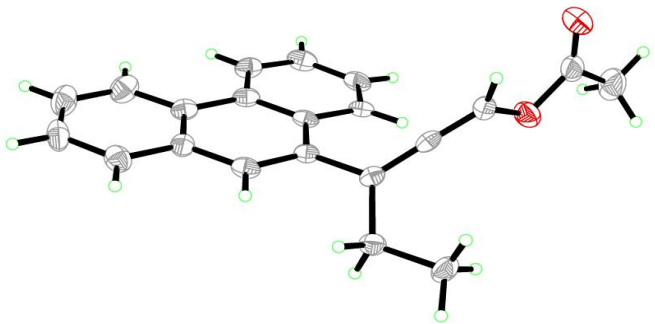


Using method 1, the starting material 5-phenylpent-2-yne-1,1-diyl diacetate (**187f**, 0.20 g, 0.77 mmol, 100 mol%) gave the title compound as a clear oil (83 mg, 0.36 mmol, 51%). $\mathbf{R_f}$ = 0.37 (20:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.43 (m, app. q, 1H, *J* = 2.0 Hz), 7.30-7.27 (m, 2H), 7.20-7.17 (m, 3H), 2.79-2.75 (m, 2H), 2.47-2.30 (m, 2H), 2.14 (s, 3H), 2.13-2.04 (m, 2H), 1.04 (t, 3H, *J* = 7.9 Hz); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 188.7, 168.8, 141.7, 128.4, 128.3, 125.9, 122.2, 112.3, 35.5, 33.7, 27.2, 21.0, 11.9; **IR** (cm $^{-1}$) ν_{max} 2254, 1741, 1466, 1380, 912, 651; **MS** m/z (ESI) for $C_{15}H_{19}O_2$ [M+H] calc. 231.1380, found 231.1375, error 2.00 ppm.

3-(Phenanthren-9-yl)penta-1,2-dienyl Acetate (190j)



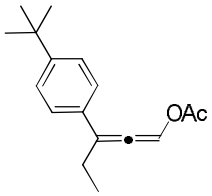
Using method 1, the starting material 3-(phenanthren-9-yl)prop-2-yne-1,1-diyl diacetate (**187g**, 0.14 g, 0.41 mol, 100 mol%) with EtMgBr (0.33 ml, 3 M, 0.98 mmol, 240 mol%) gave the title compound as a colourless solid (0.064 g, 0.21 mmol, 51%) which can be recrystallized from isopropyl alcohol to give colourless needles. $\mathbf{R_f}$ = 0.81 (4:1 petroleum ether:EtOAc); **M.p.** 79-80 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.75-8.67 (m, 2H), 8.17-8.15 (m, 1H), 7.89-7.87 (m, 1H), 7.70-7.60 (m, 6H), 2.68-2.63 (m, 2H), 2.17 (s, 3H), 1.22 (t, 3H, *J* = 7.6 Hz); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 192.5, 168.5, 134.6, 131.3, 130.7, 129.9, 128.6, 126.8 (2*C*), 126.6 (2*C*), 126.0, 125.9, 123.0, 122.5, 120.6, 111.6, 29.1, 21.0, 12.3; **IR** (cm $^{-1}$) ν_{max} 3072, 3004, 2975, 2935, 2360, 1974, 1743, 1370, 1240, 1067, 1045; **MS** m/z (ESI) for $C_{21}H_{22}NO_2$ [M+NH_4] calc. 320.1645, found 320.1638, error 2.30 ppm.



Crystal data for **190j**. $C_{21}H_{18}O_2$, *M* = 302.35, monoclinic, *a* = 8.380(2), *b* = 7.611(2), *c* = 24.952(7) Å, β = 94.366(5)º, *U* = 1586.8(7) Å^3, *T* = 150(2) K, space group $P2_1/c$ (No. 14), *Z* = 4, μ(Mo-*K*α) = 0.080 mm^{-1}, 2789 unique reflections measured, corrected for absorption (R_{int} 0.070) and used in all calculations. The H atoms in the methyl group centred on C7 are disordered by rotation about the C6—C7 bond: this was modelled by two orientations, the

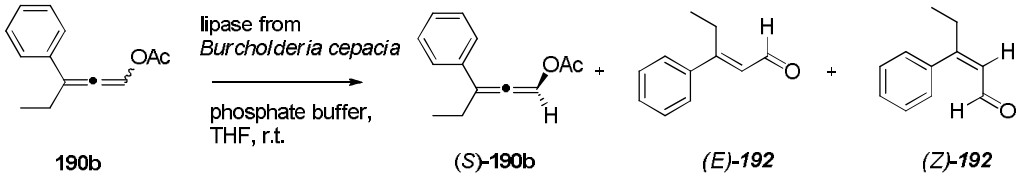
occupancies of which refined to 0.52(4) and 0.48(4). Final R_1 [2139 $F \geq 4\sigma(F)$] = 0.0670 and *wR*(all F^2) was 0.158.

3-(4-*t*-Butylphenyl)penta-1,2-dienyl Acetate (190k)



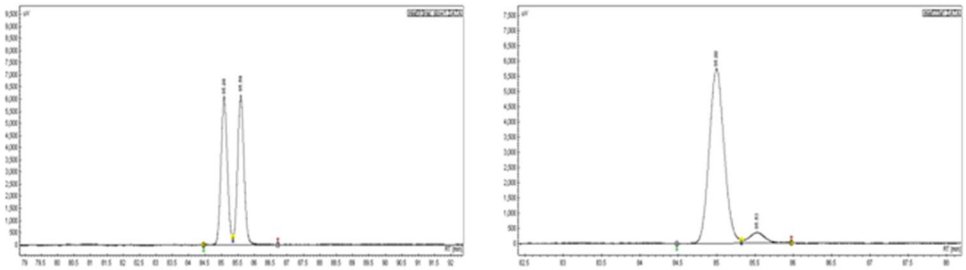
Using method 1, the starting material 3-(4-tert-butylphenyl)prop-2-yne-1,1-diyl diacetate (**187h**, 0.5 g, 1.7 mmol, 100 mol%) gave the title compound as a clear oil (0.24 g, 0.92 mmol, 53%). $\mathbf{R_f}$ = 0.82 (4:1 petroleum ether: Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.71-7.70 (m, 1H), 7.42-7.36 (m, 4H), 2.65-2.53 (m, 2H), 2.16 (s, 3H), 1.32 (s, 9H), 1.18 (t, 3H, *J* = 8 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 192.2, 168.8, 151.2, 132.8, 126.2, 125.4, 121.6, 113.2, 34.6, 31.2, 24.2, 21.0, 12.3; **IR** (cm $^{-1}$) ν_{max} 2968, 2254, 1745, 1369, 1048; **MS** m/z (ESI), for $C_{17}H_{22}NaO_2$ [M+Na] calc. 281.1512, found 281.1504, error 2.90 ppm.

General procedure for the kinetic resolution of allenyl acetates: (*S*)-3-Phenylpenta-1,2-dienyl Acetate and (*E*)- And (*Z*)-3-phenylpent-2-enal (*E*/*Z*)-(192)



To *rac*-3-phenylpenta-1,2-dienyl acetate [(±)-**190b** (105 mg, 0.52 mmol, 100 mol%)] was added THF (0.2 ml) and phosphate buffer (15 ml, pH = 7.4) at r.t. with vigorous stirring. Lipase from *Burcholderia cepacia* (PS Amano SD) (400 mg) was added with vigorous stirring in small portions. After 2 hours the reaction mixture was extracted five times with Et_2O and the combined organics were concentrated on a rotary evaporator. The residue was purified by flash column chromatography (30:1 pentane:Et_2O) which gave the title compound (*S*)-**190b** (32 mg, 0.16 mmol, 31%, *ee* 88%) with $[\alpha]_D$ = +83.9 (*c* = 0.65 in $CHCl_3$, d = 0.25) and a 1:1 mixture of (*E*)- and (*Z*)- 3-phenylpent-2-enals **192** (55 mg, 0.34 mmol, 65%).

The two enantiomers of (*S*)-**190b** can be separated with GC column *octakis*(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin program 40 °C–150 °C 1 °C/min, which gave the two enantiomers with retention times of (85.08/85.59 min).

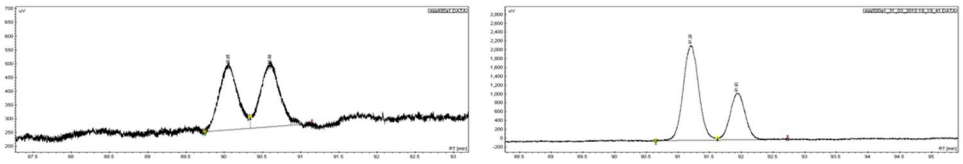


Byproducts of the kinetic resolution of **190b** were obtained as 1:1 mixture of isomers. (*E*)- And (*Z*)- aldehydes could not be separated with flash column chromatography. $\mathbf{R_f}$ = 0.50 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 10.20 (d, 1H, *J* = 8.0 Hz)*E*, 9.49 (d, 1H, *J* = 8.0 Hz)*Z*, 7.55-7.28 (m, 5+5H), 6.29 (d, 1H, *J* = 8.0 Hz)*E*, 6.14 (dt, 1H, *J* = 8.0, 2.0 Hz)*Z*, 3.10 (q, 2H, *J* = 7.6 Hz)*E*, 2.64 (qd, 2H, *J* = 7.6, 2.0 Hz)*Z*, 1.22 (t, 3H, *J* = 7.6 Hz)*E*, 1.14 (t, 3H, *J* = 7.6 Hz)*Z*; **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 193.8, 191.0, 167.9, 164.6, 129.9, 128.9, 128.8, 128.5, 128.4, 128.2, 128.0, 127.5, 127.4, 127.0, 126.8, 126.6, 32.7, 23.3, 15.0, 12.0; **IR** (cm $^{-1}$) ν_{max} 1752, 1663, **MS** m/z (EI) for $C_{11}H_{12}NaO$ [M+Na] calc. 183.0780, found 183.0788, error 4.4 ppm. ^{1}H NMR of the *Z*-isomer in the literature corresponds to the experimental data and was used for the assignment of the isomers [190].

(*S*)-3-*p*-Tolylpenta-1,2-dienyl acetate (*S*)-(190f) and (*E*)- and (*Z*)-3-*p*-tolylpent-2-enal (*E*/*Z*)-(193)

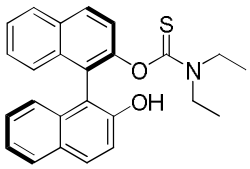
The *rac*-3-*p*-tolylpenta-1,2-dienyl acetate [(±)-**190f** (0.13 g, 0.61 mmol, 100 mol%)] and PS Amano SD (0.53 g) gave after 1 hour the title compound (*S*)-**190f** (33 mg, 0.15 mmol, 25%, *ee* 45%) with $[\alpha]_D$ = +43.2 (*c* = 0.61 in CH_3Cl, d = 0.25) and a 1:1 mixture of (*E*)- and (*Z*)-3-*p*-tolylpent-2-enals **193** (59 mg, 0.34 mmol, 56%).

The two enantiomers of (*S*)-3-*p*-tolylpenta-1,2-dienyl acetate were separated with GC column *octakis*(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin, program 40 °C-150 °C 0.5 °C/min which gave the two enantiomers with retention times of (91.20/91.93 min).



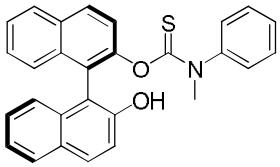
Byproducts of the kinetic resolution of 3-*p*-tolylpenta-1,2-dienyl acetate **190f**. (*E*)- And (*Z*)-aldehydes could not be separated with flash column chromatography and they were assigned according to aldehydes (*E*/*Z*)-**(192)**. $\mathbf{R_f}$ = 0.50 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 10.15 (d, 1H, *J* = 7.8 Hz)*E*, 9.47 (d, 1H, *J* = 8.0 Hz)*Z*, 7.43-7.04 (m, 5+5H), 6.26 (d, 1H, *J* = 7.8 Hz)*E*, 6.09 (dt, 1H, *J* =8.0, 1.4 Hz)*Z*, 3.05 (q, 2H, *J* = 7.6 Hz)*E*, 2.59 (qd, 2H, *J* = 7.2, 1.4 Hz)*Z*, 2.39 (s, 3+3H), 1.18 (t, 3H, *J* = 7.6 Hz)*E*, 1.09 (t, 3H, *J* = 7.2 Hz)*Z*; **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 194.0, 191.0, 140.0, 139.0, 134.9, 129.5, 129.0, 128.5, 127.2, 126.6, 126.2, 32.6, 23.1, 21.2, 15.1, 12.1; **IR** (cm $^{-1}$) ν_{max} 1751, 1661, **MS** m/z (EI) for $C_{12}H_{14}NaO$ [M+Na] calc. 197.0937, found 197.0947, error 4.9 ppm.

(*R*)-*O*-2'-Hydroxy-1,1'-binaphthyl-2-yl Diethylcarbamothioate (230): General procedure to the synthesis of catbamothioate ligands



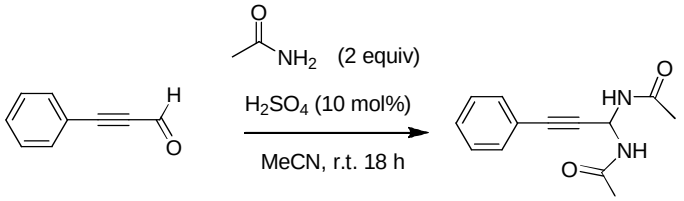
To (*R*)-BINOL (0.63 g, 2.2 mmol, 100 mol%) in a Schlenk tube at r.t. was added CH_2Cl_2 (25 ml). Triethylamine (0.35 ml, 2.53 mmol, 115 mol%) and DMAP (67 mg, 0.55 mmol, 25 mol%) were added followed by the addition of diethylthiocarbamoyl chloride (0.38 g, 2.53 mmol, 115 mol%). The reaction was stirred at +25 °C waterbath for 3 days. The mixture was quenched with saturated aqueous NH_4Cl solution and washed 3 times with 1 M HCl and once with saturated aqueous NaCl solution. The organic fractions were dried over Na_2SO_4 and concentrated *in vacuo* to provide a yellow foam. This was purified by flash column chromatography (CH_2Cl_2 with 2% EtOH) which gave a yellow thick oil. The oil was stirred with petroleum ether overnight and the colourless solid that formed was filtrated. The title compound was obtained as a colourless solid (0.34 g, 0.85 mmol, 39%). **M.p.** 123-124°C (literature 142-143°C); $\mathbf{R}_f$ = 0.37 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.09 (d, 1H, *J* = 8.8 Hz), 7.99 (d, 1H, *J* = 8.4 Hz), 7.89 (d, 1H, *J* = 9.2 Hz), 7.86-7.84 (m, 1H), 7.54-7.50 (m, 1H), 7.46 (d, 1H, *J* = 8.8 Hz), 7.38-7.24 (m, 5H), 7.14-7.12 (m, 1H), 5.96 (s, 1H, *OH*), 3.74-3.59 (m, 2H), 3.21 (sextet, 1H, *J* = 6.8 Hz), 2.90 (sextet, 1H, *J* = 7.2 Hz), 1.09 (t, 3H, *J* = 6.8 Hz), 0.50 (t, 3H, *J* = 7.2 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 186.3, 152.2, 151.2, 133.8, 133.6, 132.1, 130.0, 129.9, 129.1, 128.2, 127.9, 127.2, 126.5, 126.2, 125.8, 124.6, 124.1, 123.4, 123.0, 119.4, 115.0, 48.0, 43.6, 12.1, 11.5; **IR** (cm $^{-1}$) ν_{max} 3355, 3063, 2985, 2938, 1621, 1598, 1520 (S=C strong), 1433, 1286, 1241, 1162; **MS** m/z (ESI Positive), for $C_{25}H_{23}NNaO_2S$ [M+Na] calc. 424.1342, found 424.1346, error 1.10 ppm; $[\alpha]_D$ = +332.0 (*c* = 0.97 in $CHCl_3$). The NMR data in the literature corresponds to the experimental data [191].

(*R*)-*O*-2'-Hydroxy-1,1'-binaphthyl-2-yl Methyl(phenyl)carbamothioate (231)



(*R*)-BINOL (0.63 g, 2.2 mmol, 100 mol%) and *N*-methyl-*N*-phenylthiocarbamoyl chloride (0.47 g, 2.53 mmol, 115 mol%) gave the title compound as a grey powder (20 mg, 0.046 mmol, 2%), which contained minor impurities even after purification. **M.p.** 82-83 °C; $\mathbf{R}_f$ = 0.37 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.03-7.93 (m, 5H), 7.52-7.32 (m, 4H), 7.07-6.98 (m, 3H), 6.80-6.76 (m, 3H), 6.22-6.20 (m, 2H), 5.71 (s, 1H), 3.52 (s, 3H); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 187.3, 151.9, 151.2, 142.1, 134.0, 133.5, 132.1, 130.2, 130.0, 129.9, 129.0, 128.7, 128.2, 127.8, 127.3, 127.1, 126.6, 126.3, 125.7, 124.81, 124.77, 123.7, 123.6, 123.0, 119.2, 114.9, 44.6; **IR** (cm $^{-1}$) ν_{max} 3692, 2928, 2855, 2338, 1600, 1494, 1386, 1181; **MS** m/z (ESI Positive), for $C_{28}H_{21}NNaO_2S$ [M+Na] calc. 458.1185, found 458.1189, error 0.80 ppm; $[\alpha]_D$ = +136.9 (*c* = 0.43 in $CHCl_3$).

***N*,*N*'-(3-Phenylprop-2-yne-1,1-diyl)diacetamide (232)**



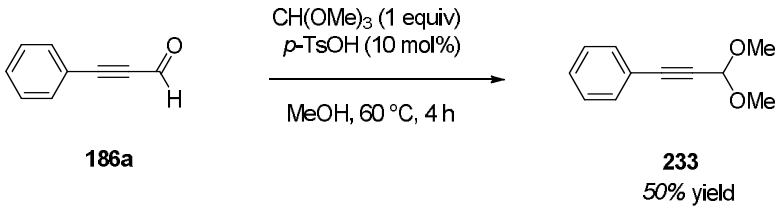
186a **232**

57% yield

3-Phenylpropiolaldehyde (**186a**, 0.65 g, 5 mmol, 100 mol%) was dissolved in MeCN (11 ml) at r.t. and the flask was flushed with argon. Acetamide (0.59 g, 10 mmol, 200 mol%) and H_2SO_4 (0.05 g, 0.5 mmol, 10 mol%) were added and the reaction was stirred vigorously for 2 days. Solids formed in the reaction and these were collected by filtration, washed well with MeCN and dried *in vacuo*. Product **232** was obtained as a colourless solid (0.66 g, 2.9 mmol, 57%). **M.p.** 230-232 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ_H 7.46-7.43 (m, 2H), 7.37-7.32 (m, 3H), 6.50 (s, 1H), 1.96 (s, 6H), *NH* was not visible in ^{1}H spectrum; **^{13}C NMR** (67.9 MHz, CD_3OD) δ_C 172.0, 132.8, 129.9, 129.5, 123.4, 86.0, 83.6, 47.1, 22.4; **IR** (cm $^{-1}$) ν_{max} 3687,

3444, 3291, 3012, 1671, 1646, 1443, 1240, **MS** m/z (ESI) for $C_{13}H_{14}N_2NaO_2$ calc. 253.0947, found 253.0955, error 3.10 ppm.

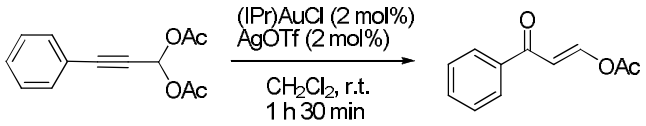
(3,3)-Dimethoxyprop-1-ynyl)benzene (233)



186a **233**
50% yield

To 3-phenylpropiolaldehyde (**186a**, 2.0 g, 15.4 mmol, 100 mol%) in MeOH (15.5 ml) at r.t. were added trimethoxymethane (1.7 ml, 15.4 mmol, 100 mol%) and *p*-TsOH (0.29 g, 1.54 mmol, 10 mol%) and the reaction mixture was heated up to +60 °C for 3 hours. The mixture was cooled to r.t. and the solvents were evaporated. The residue was distilled to give the title compound as a clear oil (1.3 g, 7.6 mmol, 50%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.50-7.47 (m, 2H), 7.34-7.32 (m, 3H), 5.38 (s, 1H), 3.40 (s, 6H); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 132.0, 129.0, 128.4, 121.7, 93.6, 85.9, 83.5, 52.7; **IR** (cm $^{-1}$) ν_{max} 3621, 3464, 3010, 2976, 2833, 2227, 1490, 1445, 1360, 1250, 1107, 1052; **MS** m/z (EI), for $C_{11}H_{12}NaO_2$ [M+Na] calc. 199.0730, found 199.0731, error 0.80 ppm.

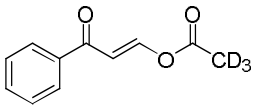
(*E*)-3-oxo-3-Phenylprop-1-enyl Acetate (238): General procedure for the Meyer-Schuster reaction of diacetates 187



To 3-phenylprop-2-yne-1,1-diyl diacetate (**187a**, 50 mg, 0.22 mmol, 100 mol%) in CH_2Cl_2 (20 ml) at r.t. were added Au(IPr)Cl (2.3 mg, 0.004 mmol, 2 mol%) and AgOTf (1.0 mg, 0.004 mmol, 2 mol%). After 1 h 30 min the reaction mixture was filtered through a pad of Celite with a CH_2Cl_2 wash and concentrated *in vacuo*. The residue was purified by flash column chromatography (4:1 petroleum ether:Et_2O), which gave the title compound as a white solid (12 mg, 0.062 mmol, 28%). **M.p.** 57-58°C; $\mathbf{R_f}$ = 0.29 (4:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.40 (d, 1H, *J* = 12.4 Hz), 7.92-7.89 (m, 2H), 7.59-7.46 (m, 3H), 6.79 (d,

1H, *J* = 12.4 Hz), 2.26 (s, 3H); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 190.4, 166.9, 150.2, 137.8, 133.0, 128.6, 128.3, 109.9, 20.6; **IR** (cm $^{-1}$) ν_{max} 3011, 2360, 1776, 1674, 1615, 1191, 1135; **MS** m/z (EI), for $C_{11}H_{10}NaO_3$ [M+Na] calc. 213.0522, found 213.0521, error 0.6 ppm.

(*E*)-3-oxo-3-Phenylprop-1-enyl d_3-acetate (*d*-238)



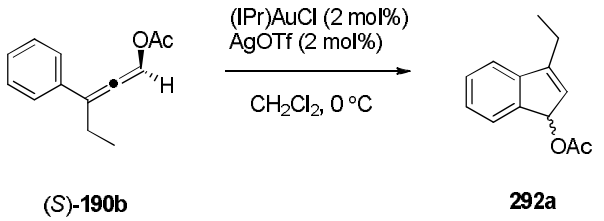
The starting material 3-phenylprop-2-yne-1,1-diyl *d*-diacetate (*d*-**187a**, 50 mg, 0.21 mmol, 100 mol%) with 2 h reaction time gave the title compound as a white solid (12 mg, 0.063 mmol, 33%). $\mathbf{R_f}$ = 0.29 (4:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.40 (d, 1H, *J* = 12.4 Hz), 7.92-7.89 (m, 2H), 7.60-7.46 (m, 3H), 6.79 (d, 1H, *J* = 12.4 Hz), 2.23 (quintet, 0.04H, *CD_3*, *J* = 2.4 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 190.4, 166.9, 150.2, 137.8, 133.0, 128.6, 128.3, 109.9, 20.0 (t, *CD_3*, *J* = 20.1 Hz); **IR** (cm $^{-1}$) ν_{max} 3156, 2902, 2254, 1770, 1675, 910; **MS** m/z (EI), for $C_{11}H_7D_3NaO_3$ [M+Na] calc. 216.0710, found 216.0705, error 2.4 ppm.

6.4 Gold-catalyzed synthesis of indenes

3-Ethyl-1*H*-inden-1-yl Acetate: general procedure for the gold-catalyzed cyclization of allenic acetates (292a)

To 3-phenylpenta-1,2-dienyl acetate (**190b**, 140 mg, 0.64 mmol, 100 mol%) in CH_2Cl_2 (10 ml) at r.t. were added Au(IPr)Cl (9.2 mg, 0.013 mmol, 2.0 mol%) and AgOTf (2.8 mg, 0.013 mmol, 2.0 mol%) under air. After 10 min the reaction mixture was filtrated through a pad of silica gel with a CH_2Cl_2 wash and product, 3-ethyl-1*H*-inden-1-yl acetate **292a**, was obtained as yellow oil (140 mg mg, 0.64 mmol, 99%). The product did not need to be purified but it could be subjected to flash column chromatography (30:1 pentane:Et_2O). $\mathbf{R_f}$ = 0.64 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.44-7.43 (m, 1H, *Ar-H*), 7.34-7.30 (m, 1H, *Ar-H*), 7.25-7.19 (m, 2H, *Ar-H*), 6.20-6.18 (m, 1H, *C1-H*), 6.06-6.05 (m, 1H, *C2-H*), 2.54-2.47 (m, 2H, *C12-H*), 2.15 (s, 3H, *C11-H*), 1.27 (t, 3H, *J* = 7.6 Hz, *C13-H*); **^{13}C NMR** (67.9 MHz, $CDCl_3$) δ_C 171.6 (*C10*), 149.8 (*C3*), 144.0 (*C8*), 142.7 (*C9*), 128.7, 126.3 (*C2*), 125.8, 124.1, 119.3, 77.2 (*C1*), 21.2 (*C11*), 20.7 (*C12*), 11.6 (*C13*); **IR** (cm $^{-1}$) ν_{max} 2973, 1732, 1372, 1241, **MS** m/z (ESI) for $C_{13}H_{14}NaO_2$ [M+Na] calc. 225.0886, found 225.0884, error 1.10 ppm. The GC trace of the title compound with column *octakis*(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin and temperature gradient program 60 °C-150 °C 2 °C/min gave retention times for the enantiomers of (50.86/51.01 min).

Following the cyclization of 190b by gas chromatography



(*S*)-**190b** **292a**

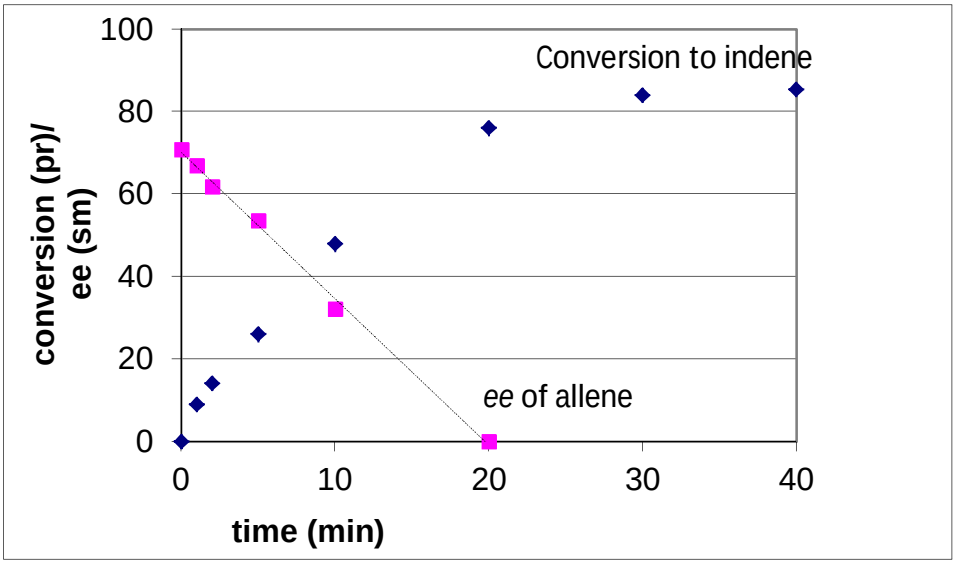
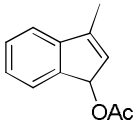


Table 29

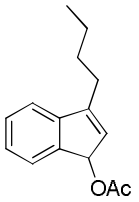
Time (min)	GC yield **292a** (%)	*Ee* of **190b** (%)
0	0	70.8
1	9.0	67.0
2	14.2	61.8
5	26.1	53.7
10	48.1	32.2
20	76.1	0
30	84.0	0
40	85.5	0
50	85.5	0
60	85.5	0

3-Methyl-1*H*-inden-1-yl Acetate (292b)



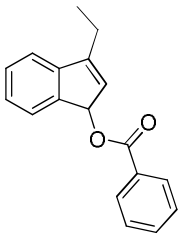
The starting material 3-phenylbuta-1,2-dienyl acetate (**190a**, 80 mg, 0.42 mmol, 100 mol%) gave the title compound as a yellow oil (51 mg, 0.27 mmol, 64%). $\mathbf{R_f}$ = 0.69 (9:1 petroleum ether:Et_2O);**^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.43-7.41 (m, 1H), 7.33-7.31 (m, 1H), 7.24-7.22 (m, 2H), 6.19-6.18 (m, 1H), 6.07-6.05 (m, 1H), 2.14 (s, 3H), 2.12 (d, 3H, *J* = 1.6 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 171.5, 133.5, 143.8, 142.5, 128.8, 127.9, 126.2, 124.0, 119.3, 76.7, 21.2, 13.0; **IR** (cm $^{-1}$) ν_{max} 3011, 1732, 1626, 1372, 1244; **MS** m/z (EI) for $C_{12}H_{12}NaO_2$ [M+Na] calc. 211.0730, found 211.0723, error 3.10 ppm. The NMR data in the literature correspond to the experimental data [192].

3-Butyl-1*H*-inden-1-yl Acetate (292c)



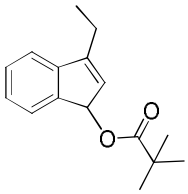
The starting material 3-phenylhepta-1,2-dienyl acetate (**190c**, 0.36 g, 1.6 mmol, 100%) gave the title compound as a clear oil (0.33 g, 1.4 mmol, 92%). $\mathbf{R_f}$ = 0.68 (4:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.44-7.19 (m, 4H), 6.18-6.17 (m, 1H), 6.05-6.04 (m, 1H), 2.50-2.46 (m, 2H), 2.14 (s, 3H), 1.69-1.62 (m, 2H), 1.46-1.61 (m, 2H), 0.96 (t, 3H, *J* = 7.2 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 171.6, 148.3, 144.1, 142.7, 128.7, 126.6, 126.2, 124.1, 119.4, 76.7, 29.5, 27.2, 22.6, 21.2, 13.9; **IR** (cm $^{-1}$) ν_{max} 3012, 2960, 2361, 1732, 1372, 1243; **MS** m/z (ESI), for $C_{15}H_{18}NaO_2$ [M+Na] calc. 253.1199, found 253.1198, error 0.50 ppm. The NMR data in the literature correspond to the experimental data [167].

3-Ethyl-1*H*-inden-1-yl Benzoate (292d)



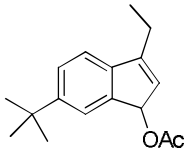
The starting material 3-phenylpenta-1,2-dienyl benzoate (**190e**, 92 mg, 0.35 mmol, 100 mol%) gave the title compound as a yellow oil (68.7 mg, 0.26 mmol, 82%). $\mathbf{R_f}$ = 0.68 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.09-8.07 (m, 2H), 7.58-7.50 (m, 2H), 7.45-7.41 (m, 1H), 7.37-3.21 (m, 4H), 6.44-6.42 (m, 1H), 6.19-6.17 (m, 1H), 2.58-2.51 (m, 2H), 1.30 (t, 3H, *J* = 7.4 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 167.1, 149.8, 144.1, 142.9, 133.0, 130.1, 129.8, 128.7, 128.3, 126.2, 126.1, 124.2, 119.3, 77.1, 20.7, 11.7; **IR** (cm $^{-1}$) ν_{max} 2973, 1713, 1452, 1268; **MS** m/z (ESI) for $C_{18}H_{16}NaO_2$ [M+Na] calc. 287.1043, found 287.1038, error 1.50 ppm.

3-Ethyl-1*H*-inden-1-yl Pivalate (292e)



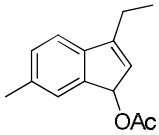
The starting material 3-phenylpenta-1,2-dienyl pivalate (**190d**, 0.15 g, 0.61 mmol, 100%) gave the title compound as a clear oil (0.14 g, 0.59 mmol, 96%). $\mathbf{R_f}$ = 0.87 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.38-7.18 (m, 4H), 6.19-6.17 (m, 1H), 6.04-6.03 (m, 1H), 2.54-2.50 (m, 2H), 1.28 (t, 3H, *J* = 7.2 Hz), 1.24 (s, 9H); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 179.1, 149.4, 144.0, 143.2, 128.5, 126.3 (2*C*), 123.8, 119.3, 76.5, 39.0, 27.2, 20.7, 11.7; **IR** (cm $^{-1}$) ν_{max} 2973, 2934, 2254, 1719, 1159; **MS** m/z (ESI), for $C_{16}H_{20}NaO_2$ [M+Na] calc. 267.1356, found 267.1344, error 4.20 ppm.

6-*t*-Butyl-3-ethyl-1*H*-inden-1-yl Acetate (292f)



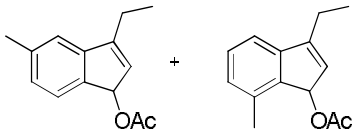
The starting material 3-(4-*t*-butylphenyl)penta-1,2-dienyl acetate (**190k**, 0.18 g, 0.68 mmol, 100 %) gave the title compound as a clear oil (0.17 g, 0.65 mmol, 97%). $\mathbf{R_f}$ = 0.77 (4:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.48-7.47 (m, 1H), 7.37-7.34 (m, 1H), 7.18-7.16 (m, 1H), 6.19-6.18 (m, 1H), 6.02-6.00 (m, 1H), 2.52-2.46 (m, 2H), 2.16 (s, 3H), 1.33 (s, 9H), 1.26 (t, 3H, *J* = 7.6 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 171.6, 149.7, 142.6, 141.4, 125.5 (2*C*), 125.3, 121.4, 118.8, 76.7, 34.8, 31.5, 21.3, 20.7, 11.7; **IR** (cm $^{-1}$) ν_{max} 3011, 2970, 1731, 1602, 1243; **MS** m/z (ESI), for $C_{17}H_{22}NaO_2$ [M+Na] calc. 281.1512, found 281.1501, error 4.00 ppm.

3-Ethyl-6-methyl-1*H*-inden-1-yl Acetate (292g)



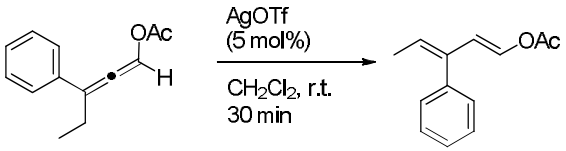
The starting material 3-*p*-tolylpenta-1,2-dienyl acetate (**190f**, 0.17 g, 0.79 mmol, 100 mol%) gave the title compound as clear oil (0.12 g, 0.55 mmol, 70%). $\mathbf{R_f}$ = 0.49 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.26-7.25 (m, 1H), 7.13-7.12 (m, 2H), 6.17-6.16 (m, 1H), 6.00-5.97 (m, 1H), 2.50-2.47 (m, 2H), 2.36 (s, 3H), 2.14 (s, 3H), 1.26 (t, 3H, *J* = 7.2 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 171.6, 149.8, 143.0, 141.3, 136.2, 129.2, 125.2, 124.9, 119.1, 76.7, 21.4, 21.2, 20.7, 11.7; **IR** (cm $^{-1}$) ν_{max} 3011, 2972, 1732, 1372, 1243; **MS** m/z (ESI), for $C_{14}H_{16}NaO_2$ [M+Na] calc. 239.1043, found 239.1042, error 0.30 ppm.

3-Ethyl-5-methyl-1*H*-inden-1-yl Acetate and 3-ethyl-7-methyl-1*H*-inden-1-yl Acetate (292h mixture of isomers)



The starting material 3-*m*-tolylpenta-1,2-dienyl acetate (**190g**, 0.24 g, 1.1 mmol, 100 mol%) gave the title compounds as a clear oil and inseparable mixture of isomers (0.22 g, 1.0 mmol, 92%). $\mathbf{R}_f$ = 0.50 (9:1 petroleum ether:Et_2O); The isomers could not be identified so they are named as A and B (A:B 2:1) **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.31 (d, 1H, *J* = 7.6 Hz)A, 7.23 (d, 1H, *J* = 8.0 Hz)B, 7.09-7.01 (m, 2+2H)A/B, 6.25-6.23 (m, 1H)B, 6.16-6.15 (m, 1H)A, 6.08-6.06 (m, 1H)B, 6.04-6.03 (m, 1H)A, 2.52-2.46 (m, 2+2H)A/B, 2.38 (s, 3H)A, 2.31 (s, 3H)B, 2.14 (s, 3H)B, 2.13 (s, 3H)A, 1.27 (t, 3H, *J* = 7.2 Hz)A, 1.25 (t, 3H, *J* = 7.6 Hz)B; **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 171.6 (A), 171.3 (B), 149.8, 144.2, 144.1, 140.0, 139.8, 138.7, 134.2, 129.0, 128.1, 126.8, 126.1, 125.6, 123.9, 120.3, 117.1, 76.5 (A), 76.3 (B), 21.6, 21.2, 21.0, 20.7, 20.6, 17.9, 11.7 (2*C*) ; **IR** (cm $^{-1}$) ν_{max} 3011, 2972, 1732, 1372, 1243; **MS** m/z (ESI), for $C_{14}H_{16}NaO_2$ [M+Na] calc. 239.1043, found 239.1042, error 0.10 ppm.

3-Phenylpenta-1,3-dienyl Acetate (1*E*/*Z*, 3*E*/*Z*) (294)



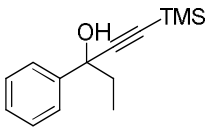
190b 2 isomers **294**

A mixture of two isomers was obtained as product. As the compound is not known in the literature, it could not be distigued whether the final products were isomers of *C1 E*/*Z* or *C3 E*/*Z*.

3-Phenylpenta-1,2-dienyl acetate (**190b**, 0.1 g, 0.49 mmol, 100 mol%) was dissolved in CH_2Cl_2 (5 ml) at r.t. and AgOTf (6.3 mg, 0.024 mmol, 5 mol%) was added. The reaction was stirred 30 minutes at room temperature, then filtered through a pad of silica with a CH_2Cl_2 wash and concentrated *in vacuo*. The crude product was purified by flash column chromatography (9:1

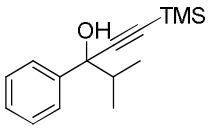
petroleum ether: Et_2O) to give the product as a mixture of two isomers as a yellow oil (37 mg, 0.18 mmol, 37%). $\mathbf{R_f}$ = 0.54 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.38-7.17 (m, 10 H)A/B, 7.13 (d, 1H, *J* = 12.4 Hz)A, 6.82 (d, 1H, *J* = 12.8 Hz)B, 6.52 (d, 1H, *J* = 12.4)A, 6.25 (d, 1H, *J* = 12.8 Hz)B, 5.75 (q, 1H, *J* = 6.8 Hz)B, 5.58 (q, 1H, *J* = 6.8 Hz)A, 2.13 (s, 3H)A, 2.08 (s, 3H)B, 1.86 (d, 3H, *J* = 6.8 Hz)A, 1.56 (d, 3H, *J* = 6.8 Hz)B; **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 167.9, 167.8, 141.5, 139.2, 137.7, 137.4, 137.0, 136.3, 129.2, 128.8, 128.5, 128.4, 128.2, 128.0, 127.3, 127.1, 127.0, 126.6, 120.2, 112.6, 30.9, 20.7, 14.8, 14.1; **IR** (cm $^{-1}$) ν_{max} 3156, 2903, 2254, 1794, 1752, 1466 1373, 1103, 919; **MS** m/z (ESI), for $C_{13}H_{14}NaO_2$ [M+Na] calc. 225.0886, found 225.0884, error 0.80 ppm. The GC trace of the title compound with the column *octakis*(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin and temperature gradient program 60 °C-150 °C 2 °C/min gave retention times for the isomers of (47.84/50.38 min).

3-Phenyl-1-(trimethylsilyl)pent-1-yn-3-ol (296)



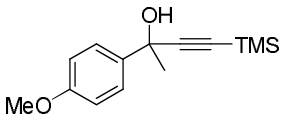
Trimethylsilylacetylene (8.3 ml, 60 mmol, 100 mol%) was dissolved in THF (200 ml) and cooled to -60 °C. A solution of *n*-BuLi (1.6 M, 37.5 ml, 60 mmol, 100 mol%) was added slowly. After 30 min propiophenone (8 g, 60 mmol, 100 mol%) was added to the reaction mixture and the reaction was left to warm to room temperature overnight. The reaction was quenched with the addition of a saturated aqueous NH_4Cl solution. After separating the phases, the aqueous phase was re-extracted with Et_2O. The combined organic fractions were washed with saturated aqueous NaCl solution, dried with $MgSO_4$ and concentrated *in vacuo*. This procedure gave the title compound as a 3:1 inseparable mixture of product and starting material as a yellow oil (12.3 g). This mixture was used directly in the next step. $\mathbf{R_f}$ = 0.76 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.53-7.50 (m, 2H), 7.28-7.16 (m, 3H), 2.27 (s, 1H), 1.94-1.76 (m, 2H), 0.85 (t, 3H, *J* = 7.60 Hz), 0.13 (s, 9H); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 144.3, 128.1, 127.6, 125.5, 107.6, 90.7, 74.2, 38.3, 9.1, -0.1; **IR** (cm $^{-1}$) ν_{max} 3589, 2971, 2254; **MS** m/z (ESI), for $C_{14}H_{20}NaOSi$ [M+Na] calc. 255.1176, found 255.1169, error 2.60 ppm. The NMR data in the literature correspond to the experimental data [193].

4-Methyl-3-phenyl-1-(trimethylsilyl)pent-1-yn-3-ol (296b)



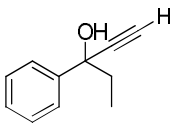
The starting material 2-methyl-1-phenylpropan-1-one (1.0 g, 6.7 mmol, 100 mol%) gave the title compound as a clear oil (1.3 g, 5.2 mmol, 78%). $\mathbf{R_f}$ = 0.86 (4:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.62-7.59 (m, 2H), 7.37-7.26 (m, 3H), 2.30 (s, 1H), 2.08 (septet, 1H, *J* = 6.4 Hz), 1.07 (d, 3H, *J* = 6.4 Hz), 0.80 (d, 3H, *J* = 6.4 Hz), 0.23 (s, 9H); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 143.6, 127.8, 127.6, 126.1, 106.6, 91.5, 77.4, 40.3, 18.0, 17.4, 0.0; **IR** (cm $^{-1}$) ν_{max} 3593, 2167, 1251; **MS** m/z (ESI), for $C_{15}H_{22}NaOSi$ [M+Na] calc. 269.1332, found 269.1332, error 0.10 ppm.

2-(4-Methoxyphenyl)-4-(trimethylsilyl)but-3-yn-2-ol (296c)



The starting material 4'-methoxyacetophenone (1.0 g, 6.7 mmol, 100 mol%) gave the title compound as a colourless solid (1.0 g, 4.1 mmol, 61%). **M.p.** 62-63 °C; $\mathbf{R_f}$ = 0.70 (4:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.59-7.57 (m, 2H), 6.90-6.88 (m, 2H), 3.82 (s, 3H), 2.17 (s, 1H), 1.74 (s, 3H), 0.21 (s, 9H); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 159.1, 137.6, 126.3, 113.5, 109.0, 89.1, 69.8, 55.3, 33.2, 0.1; **IR** (cm $^{-1}$) ν_{max} 3588, 2168, 1611, 1510, 1251, 846; **MS** m/z (EI), for $C_{14}H_{20}NaO_2Si$ [M+Na] calc. 271.1125, found 271.1122, error 1.00 ppm.

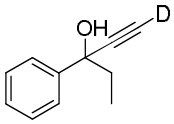
3-Phenylpent-1-yn-3-ol (297)



Crude 3-phenyl-1-(trimethylsilyl)pent-1-yn-3-ol **296** (as 3:1 mixture of starting material and propiophenone) (12.2 g, 53 mmol [calc. for MW of **296**], 100 mol%) was dissolved in MeOH (100 ml) and freshly ground K_2CO_3 (14.5 g, 105 mmol, 200 mol%) was added. The reaction

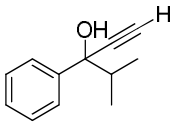
was stirred at room temperature overnight and then quenched by addition of 100 ml water, followed by extraction to CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography gave the title compound as a clear oil (6.1 g, 38 mmol, 64% over 2 steps). $\mathbf{R_f}$ = 0.65 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.64-7.62 (m, 2H), 7.39-7.26 (m, 3H), 2.69 (s, 1H), 2.37 (s, 1H), 2.04-1.90 (m, 2H), 0.97 (t, 3H, *J* = 7.2 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 143.9, 128.2, 127.8, 125.4, 86.0, 74.1, 73.8, 38.2, 8.9; **IR** (cm $^{-1}$) ν_{max} 3590, 3306, 2976, 1449, 1327; **MS** m/z (EI), for $C_{11}H_{12}O$ [M] calc. 160.0888, found 160.1885, error 1.90 ppm. The GC trace of the title compound with column *octakis*(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin and the temperature gradient program 60 °C-150 °C 2 °C/min gave retention times for the enantiomers of (45.86/46.49 min).

1-*d*-3-Phenylpent-1-yn-3-ol (*d*-297)



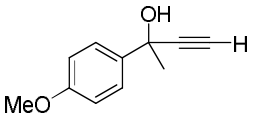
The starting material 3-phenylpent-1-yn-3-ol (**297**, 1.0 g, 6.24 mmol 100 mol%) was dissolved in dry THF (50 ml) and *n*-BuLi (1.6 M in hexanes, 8.0 ml, 12.8 mmol, 205 mol%) was added slowly at -60 °C. After 30 min the reaction was taken out of the cold bath and D_2O (1 ml) was added while the reaction was kept under argon atmosphere. The reaction mixture was diluted with Et_2O and washed once with brine. The organic layer was dried on Mg_2SO_4 and concentrated *in vacuo*. The product (1.0 g, 6.16 mmol, 99%) was obtained as a clear oil and did not need further purification. The product was >98% isotopically pure based on ^{1}H NMR spectroscopy. $\mathbf{R_f}$ = 0.65 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.64-7.61 (m, 2H), 7.39-7.28 (m, 3H), 2.69 (s, 0.01 H), 2.36 (s, 1H), 2.06-1.83 (m, 2H), 0.97 (t, 3H, *J* = 7.2 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 143.9, 128.2, 127.8, 125.4, 85.6, 73.8, 38.2, 8.9, *CD* could not be seen; **IR** (cm $^{-1}$) ν_{max} 3590, 3011, 2595, 1978, 1492, 1449, 1327; **MS** m/z (EI), for $C_{11}H_{11}DO$ [M] calc. 161.0951, found 161.0955, error 2.50 ppm.

4-Methyl-3-phenylpent-1-yn-3-ol (297b)



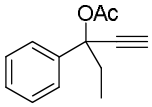
The starting material 4-methyl-3-phenyl-1-(trimethylsilyl)pent-1-yn-3-ol (**296b**, 1.2 g, 4.9 mmol, 100 mol%) gave the title compound as a clear oil (0.7 g, 4.0 mmol, 82%). $\mathbf{R_f}$ = 0.76 (4:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.63-7.60 (m, 2H), 7.38-7.26 (m, 3H), 2.69 (s, 1H), 2.36 (s, 1H), 2.12 (septet, 1H, *J* = 6.8 Hz), 1.08 (d, 3H, *J* = 6.8 Hz), 0.84 (d, 3H, *J* = 6.8 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 143.3, 127.9, 127.7, 126.0, 84.9, 74.9, 40.1, 17.8, 17.3, one quaternary carbon was not visible in ^{13}C spectrum; **IR** (cm $^{-1}$) ν_{max} 3593, 3306, 2970, 1682, 1448, 1014; **MS** m/z (EI), for $C_{12}H_{14}O$ [M] calc. 174.1045, found 174.1040, error 2.90 ppm. The NMR data in literature correspond to this experimental data [194].

2-(4-Methoxyphenyl)but-3-yn-2-ol (297c)



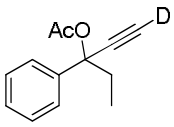
The starting material 2-(4-methoxyphenyl)-4-(trimethylsilyl)but-3-yn-2-ol (**296c**, 1.0 g, 4.0 mmol, 100 mol%) gave the title compound as a clear oil (0.59 g, 3.3 mmol, 83%). $\mathbf{R_f}$ = 0.39 (4:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.60-7.57 (m, 2H), 6.91-6.87 (m, 2H), 3.81 (s, 3H), 2.67 (s, 1H), 2.38 (s, 1H), 1.78 (s, 3H); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 159.2, 137.2, 126.2, 113.6, 87.4, 72.9, 69.5, 55.3, 33.0; **IR** (cm $^{-1}$) ν_{max} 3589, 3306, 3011, 2840, 2555, 1610, 1510, 1253; **MS** m/z (EI), for $C_{11}H_{12}O_2$ [M] calc. 176.0837, found 176.0833, error 2.30 ppm. The NMR data in literature correspond to this experimental data [195].

3-Phenylpent-1-yn-3-yl Acetate (298a)



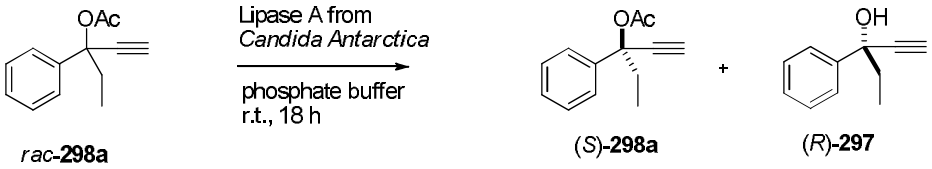
The starting material 3-phenylpent-1-yn-3-ol (**297**, 6.1 g, 38 mmol, 100 mol%) was dissolved in CH_2Cl_2 (300 ml) at r.t. and dimethylaminopyridine (2.3 g, 19 mmol, 50 mol%) and triethylamine (10.6 ml, 76 mmol, 200 mol%) were added. Acetic anhydride (7.2 ml, 76 mmol, 200 mol%) was added slowly and the reaction left to stir overnight. The mixture was concentrated *in vacuo* to an oil. Purification of the residue by flash column chromatography (9:1 petroleum ether:Et_2O) gave the title compound as a clear oil (6.6 g, 32 mmol, 85%). $\mathbf{R_f}$ = 0.72 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.53-7.51 (m, 2H), 7.36-7.26 (m, 3H), 2.82 (s, 1H), 2.23-2.16 (m,1H), 2.08 (s, 3H), 2.01-1.95 (m, 1H), 0.94 (t, 3H, *J* = 7.6 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 168.6, 140.9, 128.2, 127.8, 125.2, 81.7, 79.3, 76.4, 37.4, 21.7, 8.5; **IR** (cm $^{-1}$) ν_{max} 3306, 2980, 2117, 1743, 1242; **MS** m/z (ESI), for $C_{13}H_{14}NaO_2$ [M+Na] calc. 225.0886, found 225.0876, error 4.30 ppm. The GC trace of the title compound with column *octakis*(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin and the temperature gradient program 60 °C-150 °C 2 °C/min gave retention times for the enantiomers of (44.06/44.29 min).

1-*d*-3-Phenylpent-1-yn-3-yl Acetate (*d*-298)



The starting material 1-*d*-3-phenylpent-1-yn-3-ol *d*-**297** (0.9 g, 5.6 mmol, 100 mol%) gave the title compound as a clear oil (1.0 g, 4.9 mmol, 89%) with 81% isotopic purity. $\mathbf{R_f}$ = 0.72 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.53-7.51 (m, 2H), 7.37-7.28 (m, 3H), 2.82 (s, 0.19H), 2.21-2.14 (m, 1H), 2.08 (s, 3H), 2.02-1.95 (m, 1H), 0.94 (t, 3H, *J* = 7.2 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 168.6, 140.9, 128.2, 127.8, 125.2, 79.3, 76.4, 37.4, 21.7, 8.5, *CD* could not be seen; **IR** (cm $^{-1}$) ν_{max} 3306, 3010, 2596, 1984, 1743, 1493, 1369, 1242; **MS** m/z (ESI), for $C_{13}H_{13}DNaO_2$ [M+Na] calc. 226.0949, found 226.0942, error 3.00 ppm.

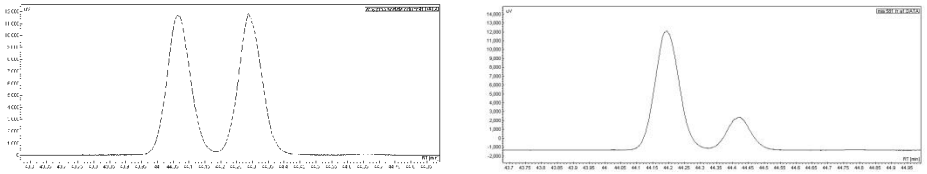
Kinetic resolution of 3-Phenylpent-1-yn-3-yl Acetate (298a)



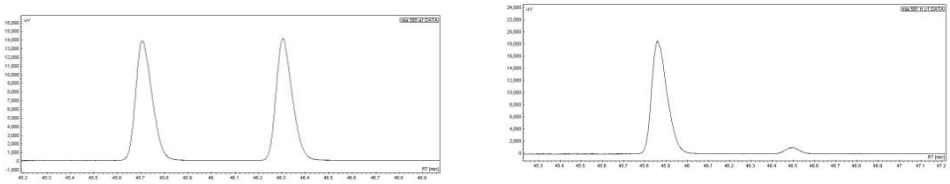
rac-**298a** (*S*)-**298a** (*R*)-**297**

To 3-phenylpent-1-yn-3-yl acetate **298a** (0.50 g, 2.5 mmol, 100 %) in phosphate buffer solution (20 ml) was added lipase A from *Candida Antarctica* (1.0 g on solid support) with vigorous stirring at r. t. After 18 hours the products were extracted with Et_2O (5 x 20 ml) and the combined organics concentrated *in vacuo.* Purification by flash column chromatography gave (*R*)-alcohol and (*S*)- acetate as products: (*S*)-**298a** (0.25 g, 1.2 mmol, 48%); *ee* 57 %; $[\alpha]_D$ = -33.9 (*c* = 0.86, $CHCl_3$), and (*R*)-297 (0.13 g, 0.81 mmol, 32%); *ee* 90 %; $[\alpha]_D$ = -0.93 (*c* = 0.60, $CHCl_3$).

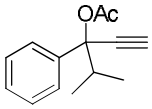
3-phenylpent-1-yn-3-yl acetate (**298a**)



3-phenylpent-1-yn-3-ol (**297**)

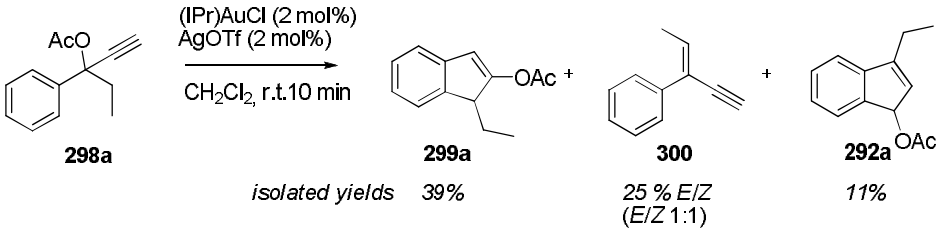


4-Methyl-3-phenylpent-1-yn-3-yl Acetate (298b)



The starting material 4-methyl-3-phenylpent-1-yn-3-ol **297b** (0.59 g, 3.4 mmol, 100 mol%) gave the title compound as a yellow solid containing a mixture of starting material and product (20% starting material remaining) (0.54 g, 2.5 mmol, 74%). $\mathbf{R_f}$ = 0.76 (4:1 petroleum ether: Et_2O); **M.p.** 39-40 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.52-7.49 (m, 2H), 7.35-7.25 (m, 3H), 2.80 (s, 1H), 2.27-2.21 (septet, 1H, *J* = 6.4 Hz), 2.06 (s, 3H), 1.18 (d, 3H, *J* = 6.4 Hz), 0.72 (d, 3H, *J* = 6.4 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 168.5, 140.4, 128.0, 127.7, 125.6, 85.5, 79.9, 76.3, 53.4, 40.0, 21.7, 17.8, 16.9; **IR** (cm $^{-1}$) ν_{max} 3306, 3011, 2338, 1743, 1242; **MS** m/z (ESI), for $C_{14}H_{16}NaO_2$ [M+Na] calc. 239.1043, found 239.1038, error 2.10 ppm. NOTE: In this reaction the R_f values of starting material and product are identical.

Products from gold-catalyzed transformation of 3-phenylpent-1-yn-3-yl acetate 298a:



To 3-phenylpent-1-yn-3-yl acetate (**298b**, 130 mg, 0.65 mmol, 100 mol%) in CH_2Cl_2 (10 ml) at r.t. were added Au(IPr)Cl (9.2 mg, 0.013 mmol, 2.0 mol%) and AgOTf (2.8 mg, 0.013 mmol, 2.0 mol%). After 10 min the reaction mixture was filtrated through a pad of silica gel with a CH_2Cl_2 wash and the solvents were evaporated on a rotary evaporator. Purification of the residue by column chromatography (30:1 pentane:Et_2O) gave 1-ethyl-1*H*-inden-2-yl acetate (**299a**, 51 mg, 0.25 mmol, 39%), 3-Ethyl-1*H*-inden-1-yl acetate (**292a**, 14 mg, 0.07 mmol, 11%) and *Z*-or *E*-pent-3-en-1-yn-3-ylbenzene (**300**, 23 mg, 0.16 mmol, 25%).

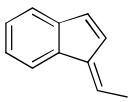
1-Ethyl-1*H*-inden-2-yl acetate (299a)

Clear oil, $\mathbf{R}_f$ = 0.28 (30:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.31-7.22 (m, 3H), 7.16-7.12 (m, 1H), 6.65-6.64 (m, 1H), 3.62-3.59 (m, 1H), 2.27 (s, 3H), 1.96-1.83 (m, 2H), 0.76 (t, 3H, *J* = 7.2 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 168.1, 158.0, 142.5, 141.0, 126.7, 124.3, 122.6, 121.0, 114.3, 49.0, 22.4, 21.3, 9.3; **IR** (cm $^{-1}$) ν_{max} 2969, 1761, 1601, 1463, 1192; **MS** m/z (ESI), for $C_{13}H_{14}NaO_2$ [M+Na] calc. 225.0886, found 225.0890, error 1.70 ppm. The GC trace of the title compound with column *octakis*(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin and the temperature gradient program 60 °C-150 °C 2 °C/min gave retention times for the enantiomers of (49.12/49.41 min).

(*Z*)- Or (*E*)-pent-3-en-1-yn-3-ylbenzene (300)

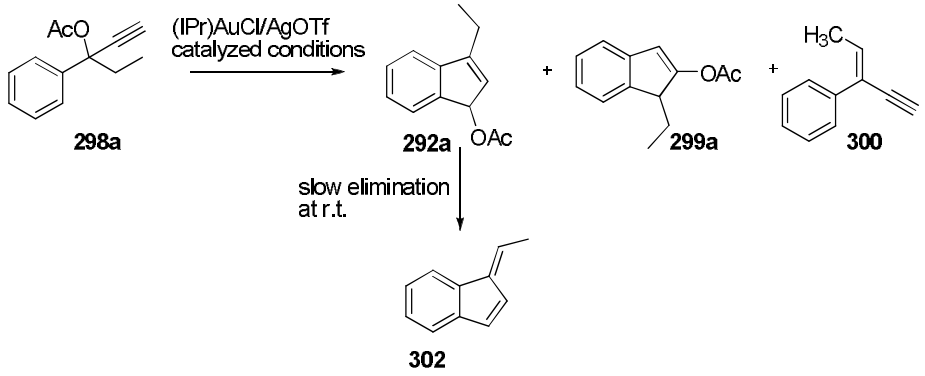
Yellow oil, $\mathbf{R}_f$ = 0.75 (20:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.61-7.58 (m, 2H), 7.36-7.24 (m, 3H), 6.56 (qd, 1H, *J* = 6.8, 0.8 Hz), 3.37 (s, 1H), 2.10 (d, 3H, *J* = 6.8 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 137.8, 134.8, 128.3, 127.5, 125.8, 123.6, 83.3, 80.8, 16.9; **IR** (cm $^{-1}$) ν_{max} 3306, 3009, 2914, 1711, 1598, 1495, 1440, 1363; **MS** m/z (EI), for $C_{11}H_{10}$ [M] calc. 142.0783, found 142.0777, error 4.20 ppm. The GC trace of the title compound with column *octakis*(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin and the temperature gradient program 60 °C-150 °C 2 °C/min gave a single retention time of (32.28 min).

(*E*)-1-Ethylidene-1H-indene (302)



Full data for the elimination product could not be obtained as it co-elutes in column chromatography with pent-3-en-1-yn-3-ylbenzene **300** and both have the same mass so the structure is tentatively assigned as **302**. $\mathbf{R}_f$ = 0.75 (20:1 petroleum ether: Et_2O); ***partial* ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.91-6.89 (m, 1H), 6.83-6.82 (m, 1H), 6.73-6.67 (m, 1H), 2.20 (d, 3H, *J* = 7.2 Hz); The GC trace of the title compound with column *octakis*(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin and the temperature gradient program 60 °C-150 °C 2 °C/min gave a single retention time of (32.28 min). The NMR data in literature is in accord with the experimental data [196].

The following NMR data in Figures 7-10 are taken from the gold catalyzed reaction of 3-phenylpent-1-yn-3-yl acetate **298a** after 1min, 8min, 30min and 2 hours and it can be seen how 3-ethyl-1*H*-inden-1-yl acetate **292a** disappears slowly and is replaced by another compound tentatively assigned as **302** based on its NMR data.



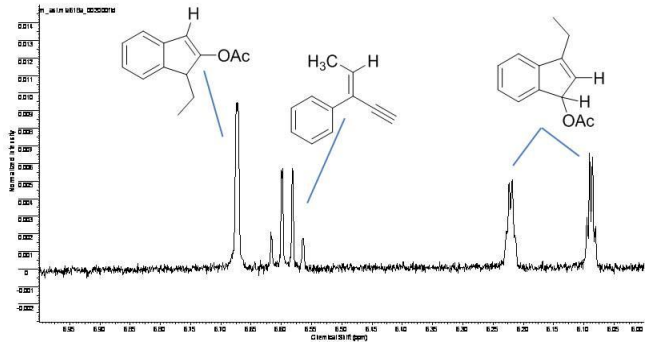


Figure 7: 2 min reaction time

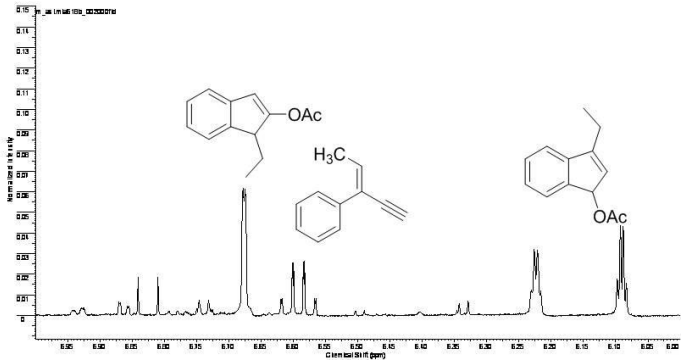


Figure 8: 8 min reaction time

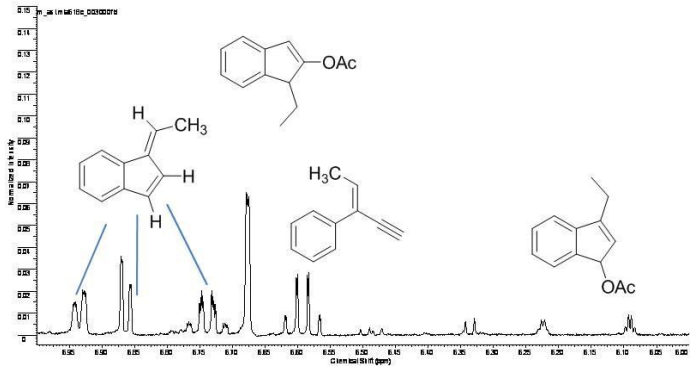


Figure 9: 30 min reaction time

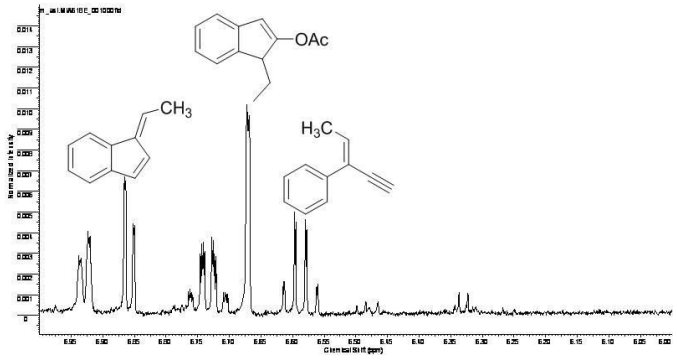
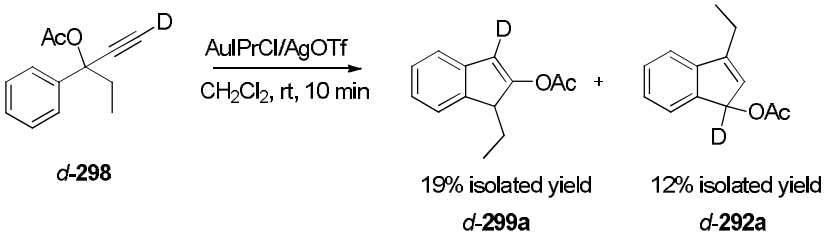


Figure 10: 2 h reaction time

Gold-catalyzed cycloisomerization of deuterium labeled 1-*d*-3-phenylpent-1-yn-3-yl acetate *d*-298

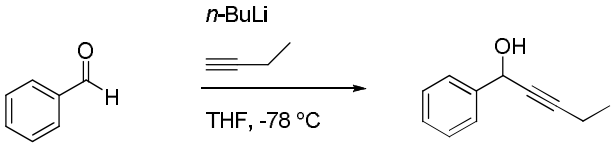


Using the same procedure as with the synthesis of indenes **292a-h** the gold-catalyzed cycloisomerization of 1-*d*-3-phenylpent-1-yn-3-yl acetate (*d*-**298**, 0.5 g, 2.5 mmol, 100 mol%) gave 3-*d*-1-Ethyl-1*H*-inden-2-yl acetate (*d*-**299a**, clear oil, 96 mg, 0.47 mmol, 19%) with 80% isotopic purity and 3-Ethyl-1-*d*-inden-1-yl acetate (*d*-**292a**, clear oil, 62 mg, 0.31 mmol, 12%) with 80% isotopic purity.

3-*d*-1-Ethyl-1*H*-inden-2-yl acetate *d*-299a; $\mathbf{R_f}$ = 0.28 (30:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.32-7.21 (m, 3H), 7.17-7.13 (m, 1H), 6.65-6.64 (m, 0.2H), 3.62-3.59 (m, 1H), 2.27 (s, 3H), 2.00-1.82 (m, 2H), 0.76 (t, 3H, *J* = 7.6 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 168.0, 157.9, 142.5, 141.0, 128.4, 126.7, 124.3, 122.6, 120.9, 48.9, 22.4, 21.3, 9.3; **IR** (cm $^{-1}$) ν_{max} 2969, 1762, 1599, 1567, 1461, 1371, 1192; **MS** m/z (ESI), for $C_{13}H_{13}DNaO_2$ [M+Na] calc. 226.0949, found 226.0944, error 2.00 ppm.

3-Ethyl-1-*d*-inden-1-yl acetate (*d*-292a); $\mathbf{R_f}$ = 0.64 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.44-7.15 (m, 4H), 6.20-6.19 (m, 0.2H), 6.06-6.05 (m, 1H), 2.54-2.48 (m, 2H), 2.15 (s, 3H), 1.28 (t, 3H, *J* = 7.6 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 171.6, 149.9, 144.1, 142.7, 128.8, 126.3, 126.2, 125.8, 119.3, 77.2, 12.2, 20.7, 11.6; **IR** (cm $^{-1}$) ν_{max} 3011, 2972, 1731, 1431, 1371, 1242; **MS** m/z (ESI), for $C_{13}H_{13}DNaO_2$ [M+Na] calc. 226.0949, found 226.0945, error 1.70 ppm.

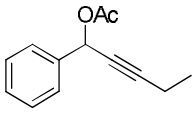
1-Phenylpent-2-yn-1-ol (303)



1-Butyne (~1.2 ml, 18.9 mmol, 100 mol%) was condensed in a Schlenk tube under argon at -78 °C. Freshly distilled THF (20 ml) was cooled to -78 °C and added slowly to the butyne. A cold solution of *n*-BuLi (11.8 ml, 1 M in hexanes, 18.9 mmol, 100 mol%) was added dropwise and after 30 min benzaldehyde (1.9 ml, 18.9 mmol, 100 mol%) was added and the reaction was left to warm to room temperature overnight. The mixture was quenched with saturated aqueous NH_4Cl and the aqueous layer was re-extracted twice with Et_2O. The combined organic layers were washed with saturated aqueous NaCl solution and dried over Mg_2SO_4. The crude product was concentrated *in vacuo* and purified by flash column chromatography (9:1 petroleum ether:Et_2O). The title compound was obtained as a clear oil (2.79 g, 17.4 mmol, 92%). $\mathbf{R_f}$ = 0.69 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.56-7.53 (m, 2H), 7.40-7.30 (m, 3H), 5.45 (dt, 1H, *J* = 6.0, 2.0 Hz), 2.29 (qd, 2H, *J* = 7.6, 2.0 Hz), 2.10 (d, 2H, *J* = 6.0 Hz, *OH*), 1.18 (t, 3H, *J* = 7.6 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 141.2, 128.5, 128.2, 126.6, 89.0, 79.3, 64.8, 13.7, 12.5; **IR** (cm $^{-1}$) ν_{max} 3593, 3066, 3011, 2981, 2230, 1603, 1494,

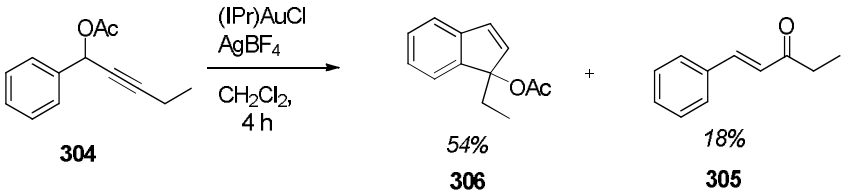
1374, 991; **MS** m/z (EI), for $C_{11}H_{12}NaO$ [M+Na] calc. 183.0780, found 183.0783, error 1.6 ppm. The NMR data in the literature correspond to the experimental data [197].

1-Phenylpent-2-ynyl acetate (304)



The same procedure was used as with tertiary propargylic acetate **298a**. The starting material 1-phenylpent-2-yn-1-ol **303** (2.0 g, 12.5 mmol, 100 mol%) gave the title compound as a clear oil (2.5g, 12.5 mmol, 99%). $\mathbf{R_f}$ = 0.87 (4:1 petroleum ether:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.53-7.50 (m, 2H), 7.40-7.32 (m, 3H), 6.46 (t, 1H, *J* = 2.0 Hz), 2.29 (qd, 2H, *J* = 7.6, 2.0 Hz), 2.10 (s, 3H), 1.17 (t, 3H, *J* = 7.6 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 169.9, 137.7, 128.7, 128.5, 127.7, 89.6, 76.0, 66.0, 21.2, 13.5, 12.5; **IR** (cm $^{-1}$) ν_{max} 3011, 2982, 2941, 2238, 1734, 1371, 1242; **MS** m/z (ESI positive), for $C_{13}H_{14}NaO_2$ [M+Na] calc. 225.0886, found 225.0879, error 3.00 ppm. The GC trace of the title compound with column *octakis*(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin and the temperature gradient program 60 °C-150 °C 2 °C/min gave retention times for the enantiomers of (46.75/47.13 min).

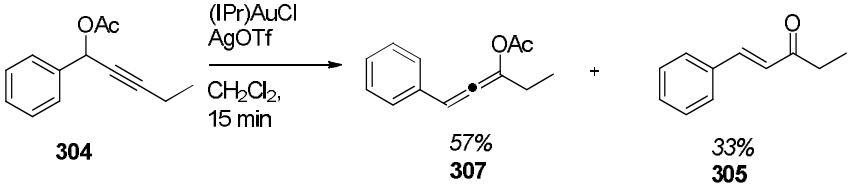
Gold-catalyzed isomerization of 1-phenylpent-2-ynyl acetate 304 with long reaction time and $AgBF_4$ as cocatalyst



The starting material 1-phenylpent-2-ynyl acetate (**304**, 0.2 g, 0.99 mmol, 100 mol%) was dissolved in CH_2Cl_2 (10ml) at r.t. and Au(IPr)Cl (12 mg, 0.02 mmol, 2 mol%) and $AgBF_4$ (5.1 mg, 0.02 mmol, 2 mol%) were added. After 15 min the reaction was quenched by filtration through a pad of silica to give a product mixture of 1-ethyl-1*H*-inden-1-yl acetate (**306**, 0.11 g, 0.57 mmol, 54%) and (*E*)-1-phenylpent-1-en-3-one **305** 18%.

1-Ethyl-1*H*-inden-1-yl acetate (306); $\mathbf{R_f}$ = 0.50 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.35-7.33 (m, 1H), 7.27-7.16 (m, 3H), 6.73 (dd, 1H, *J* = 6.0, 0.8 Hz), 6.54 (d, 1H, *J* = 6.0 Hz), 2.30-2.21 (m, 1H), 2.04-1.95 (m, 1H), 2.01 (s, 3H), 0.79 (t, 3H, *J* = 7.2 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 169.9, 145.3, 142.3, 137.3, 132.4, 128.5, 126.1, 122.0, 121.6, 91.2, 28.7, 21.8, 8.4; **IR** (cm $^{-1}$) ν_{max} 2977, 2254, 1735, 1464, 1251, 909; **MS** m/z (ESI Positive), for $C_{13}H_{14}NaO_2$ [M+Na] calc. 225.0886, found 225.0884, error 1.10 ppm. The GC trace of the title compound with column *octakis*(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin and the temperature gradient program 60 °C-150 °C 2 °C/min gave a single retention time of (43.80 min).

Gold-catalyzed isomerization of 1-phenylpent-2-ynyl acetate with short reaction time and AgOTf as cocatalyst

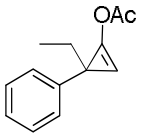


The starting material 1-Phenylpent-2-ynyl acetate (**304**, 0.2 g, 0.99 mmol, 100 mol%) was dissolved in CH_2Cl_2 (10ml) at r.t. and Au(IPr)Cl (12 mg, 0.02 mmol, 2 mol%) and AgOTf (5.1 mg, 0.02 mmol, 2 mol%) were added. After 15 min the reaction was quenched by elution through a pad of silica to give product mixture of 1-phenylpenta-1,2-dien-3-yl acetate (**307**, clear oil, 0.11 g, 0.56 mmol, 57%) and (*E*)-1-phenylpent-1-en-3-one (**305**, 52 mg, 0.33 mmol, 33%).

1-Phenylpenta-1,2-dien-3-yl acetate (307); $\mathbf{R_f}$ = 0.58 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.44-7.42 (m, 2H), 7.35-7.31 (m, 2H), 7.27-7.23 (m, 1H), 6.62 (t, 1H, *J* = 3.2 Hz), 2.40-2.33 (m, 2H), 2.15 (s, 3H), 1.07 (t, 3H, *J* = 7.6 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 196.3, 168.7, 133.9, 128.6, 128.4, 128.0, 127.8, 105.1, 25.0, 21.0, 10.7; **IR** (cm $^{-1}$) ν_{max} 3011, 2977, 2939, 2880, 2337, 1963, 1747, 1331, 1241; **MS** m/z (EI), for $C_{13}H_{14}NaO_2$ [M+Na] calc. 225.0886, found 225.0887, error 0.50 ppm. The GC trace of the title compound with column *octakis*(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin and the temperature gradient program 60 °C-150 °C 2 °C/min gave retention times for the enantiomers of (49.29/49.83 min).

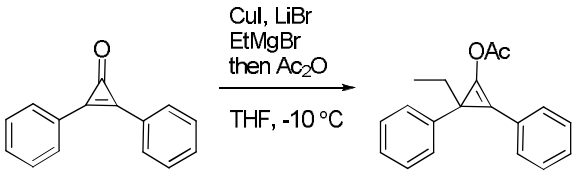
(*E*)-1-Phenylpent-1-en-3-one (305); $\mathbf{R_f}$ = 0.39 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.56 (d, 1H, *J* = 16.8 Hz), 7.56-7.54 (m, 2H), 7.41-7.39 (m, 3H), 6.75 (d, 1H, *J* = 16.8 Hz), 2.71 (q, 2H, *J* = 7.2 Hz), 1.18 (t, 3H, *J* = 7.2 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 200.9, 142.2, 134.6, 130.3, 128.9, 128.2, 126.0, 34.0, 8.2; **IR** (cm $^{-1}$) ν_{max} 3011, 2982, 2941, 1749, 1688, 1662, 1610, 1578, 1191; **MS** m/z (ESI Positive), for $C_{11}H_{12}NaO$ [M+Na] calc. 183.0780, found 183.0777, error 2.00 ppm. The NMR data in the literature correspond to this experimental data [198].

3-Ethyl-3-phenylcycloprop-1-enyl Acetate (309)



Tentatively assumed as the intermediate in the gold-catalyzed cycloisomerization of **298a**. As this compound could not be isolated, only NMR from the reaction mixture could be obtained and the compounds in the reaction mixture overlap with some of the NMR signals of putative **309**. Following NMR data could be assigned for the intermediate: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.44-7.42 (m, 1H), 2.58-2.53 and 2.35-2.30 (2 x m, 2H, *CH_2 α to asym. center*), 1.92 (s, 3H), 0.61 (t, 3H, *J* = 7.6 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 204.1, 169.8, 76.7, 26.8, 7.0.

3-Ethyl-2,3-diphenylcycloprop-1-enyl Acetate (312)

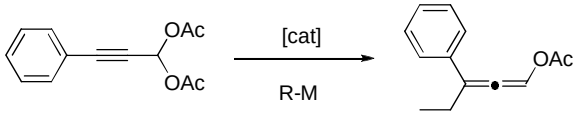


CuI (0.92 g, 4.9 mmol, 250 mol%) and LiBr (0.42 g, 4.9 mmol, 250 mol%) were dried briefly under vacuum with a heat gun. The reaction flask was flushed with argon and THF (40 ml) was added. The reaction was cooled to -10 °C and EtMgBr (1 M in MTBE, 4.7 ml, 4.7 mmol, 240 mol%) was added followed by the addition of 2,3-diphenylcycloprop-2-enone (0.4 g, 1.9 mmol, 100 mol) in three portions. After 1 h 30 min Ac_2O (0.4 ml, 4.2 mmol, 218 mol%) was added and the reaction was warmed to r.t. for 30 min. The reaction was quenched with saturated aqueous NH_4Cl/NH_3 solution (prepared by adding 10 ml of 35% NH_3 to 500 ml of

saturated NH_4Cl solution) and the organic layer was washed 3-4 times with the quench solution until the aqueous layer was no longer blue. The combined aqueous layers were re-extracted once with Et_2O and then the combined organic layers were washed with saturated aqueous NaCl solution and dried over Mg_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (30:1-20:1 petroleum ether:Et_2O) gave the title compound as a yellow oil (47 mg, 0.17 mmol, 9%). $\mathbf{R_f}$ = 0.35 (9:1 petroleum ether:Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.59-7.56 (m, 2H), 7.41-7.24 (m, 8H), 2.37-2.31 (m, 2H, *CH_2 α to asym. center*), 2.31 (s, 3H), 0.91 (t, 3H, *J* = 7.6 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 207.9, 166.3, 145.4, 129.3, 128.5, 128.1, 127.8, 126.7, 125.8, 92.5, 40.6, 26.7, 20.8, 11.6; **IR** (cm $^{-1}$) ν_{max} 3062, 3011, 2967, 2932, 2875, 1863, 1774, 1685, 1598, 1184; **MS** m/z (ESI Positive), for $C_{19}H_{18}NaO_2$ [M+Na] calc. 301.1199, found 301.1209, error 3.20 ppm.

6.4.1 Example of GC calibration for screening reaction conditions

Many of the reactions where several catalytic conditions were screened were followed on gas chromatography. Here is given one example of how the GC was calibrated in the case of the S_N2' reaction of propargylic diacetates.



Calibration plot was made for starting material (SM) and for the product (PR). First two standard solutions were prepared:

Solution 1 (SM): 0.26 g (1.13 mmol) of 3-phenylprop-2-yne-1,1-diyl diacetate **187a** in 10 ml of 2-Me-THF

Solution 2 (PR): 0.26 g (1.31 mmol) of 3-phenylpenta-1,2-dienyl acetate **190b** in 10 ml of 2-Me-THF

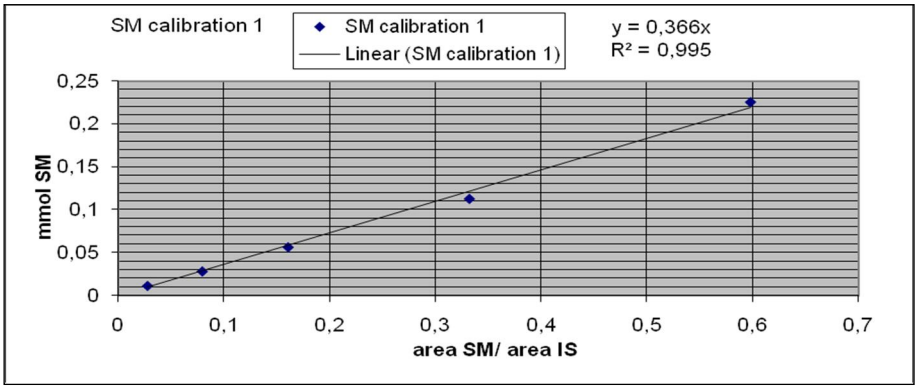
Five samples were made containing both solutions (Table 30).

Table 30

sample	V(sol 1)	n (SM)	V(sol 2)	n (PR)
1	2 ml	0.225 mmol	0.1 ml	0.013 mmol
2	1 ml	0.113 mmol	0.25 ml	0.033 mmol
3	0.5 ml	0.056 mmol	0.5 ml	0.065 mmol
4	0.25 ml	0.028 mmol	1 ml	0.131 mmol
5	0.1 ml	0.013 mmol	2 ml	0.262 mmol

Samples were prepared according to the following procedure: To 5 ml of 2-Me-THF was added the volumes of solutions 1 and 2 and this mixture was 'quenched' with saturated aqueous NH_4Cl containing 2% of ammonia. To the organic layer was added 50 µl of tridecane and organic layer was dried over $MgSO_4$ and used in GC analysis.

These concentrations were chosen because the carousel test reactions were run with 50 mg (0.22 mmol) 3-phenylprop-2-yne-1,1-diyl diacetate as starting material. This means that the amount of product and starting material in the reaction mixture always falls to the calibration curve and no extrapolation is needed. Also the same amount (50 µl) of tridecane is always used in each test reaction. When the amount of a reaction component (in mmol) is plotted against the ration of the reaction component and internal standard, the calibration gave the following linear plots (Figure 11):



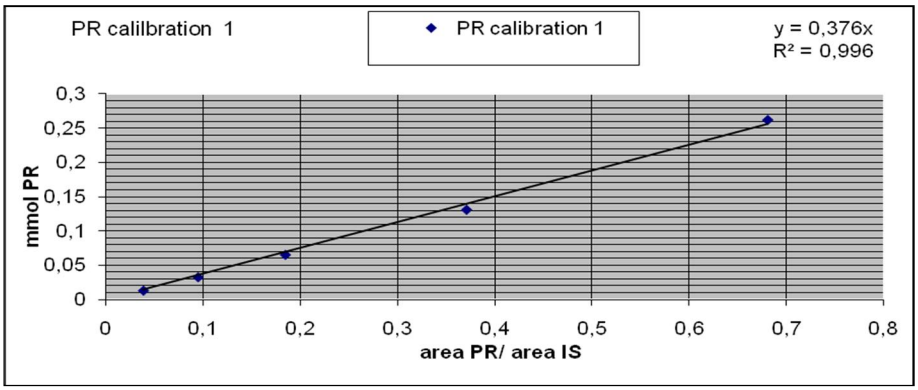


Figure 11

From this plot the amount (in mmol) of the reaction component can be calculated in an unknown sample according to following equation:

Equation 4

$$n(SM)unk = k(calibrationcurve)_{SM}\, x \frac{area(SM)unk}{area(IS)unk}$$

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