New Reactive Sites Enabled *via* an Allyl-to-Allyl 1,4-Rh(III) Migration

Thesis Submitted in Accordance with the Requirement of the University of Nottingham for the Degree of Doctor of Philosophy

By

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“Ο επιμένων νικά”

(Who persists, wins)

Greek proverb

Declaration

I hereby declare that, except for where specific reference is made to other sources, the work contained within this thesis is the original work of my own research since the registration of the PhD degree in September 2014, and any collaboration is clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification.

Acknowledgements

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Di, it was always a pleasure of course teaching you pool/snooker, aside from chemistry. Thank you for indirectly reminding me not to pay too much attention to all the ‘‘naysayers’’ also.

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Thank you all very much,

Stamatis

Contents

List of abbreviations

1,4-mig	1,4-migration
β-H elim	*β*-hydride elimination
Δ	heat
σ-CAM	*σ*-complex assisted metathesis
Ac	acetyl
Am	amyl
Ar	aryl
atm	atmosphere
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthalene
BIPHEP	2,2′-bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BQ	benzoquinone
br	broad
Bu	butyl
Bz	benzoyl
cat.	catalyst
CMD	concerted–metallation–deprotonation
cod	cyclooctadiene
Cp	cyclopentadiene
CPME	cyclopentylmethyl ether
Cp*	pentamethylcyclopentadiene
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DFT	density functional theory
DG	directing group
DIBAL-H	diisobutylaluminium hydride
DMA	dimethylacetamide
DMAP	4-(dimethylamino)pyridine

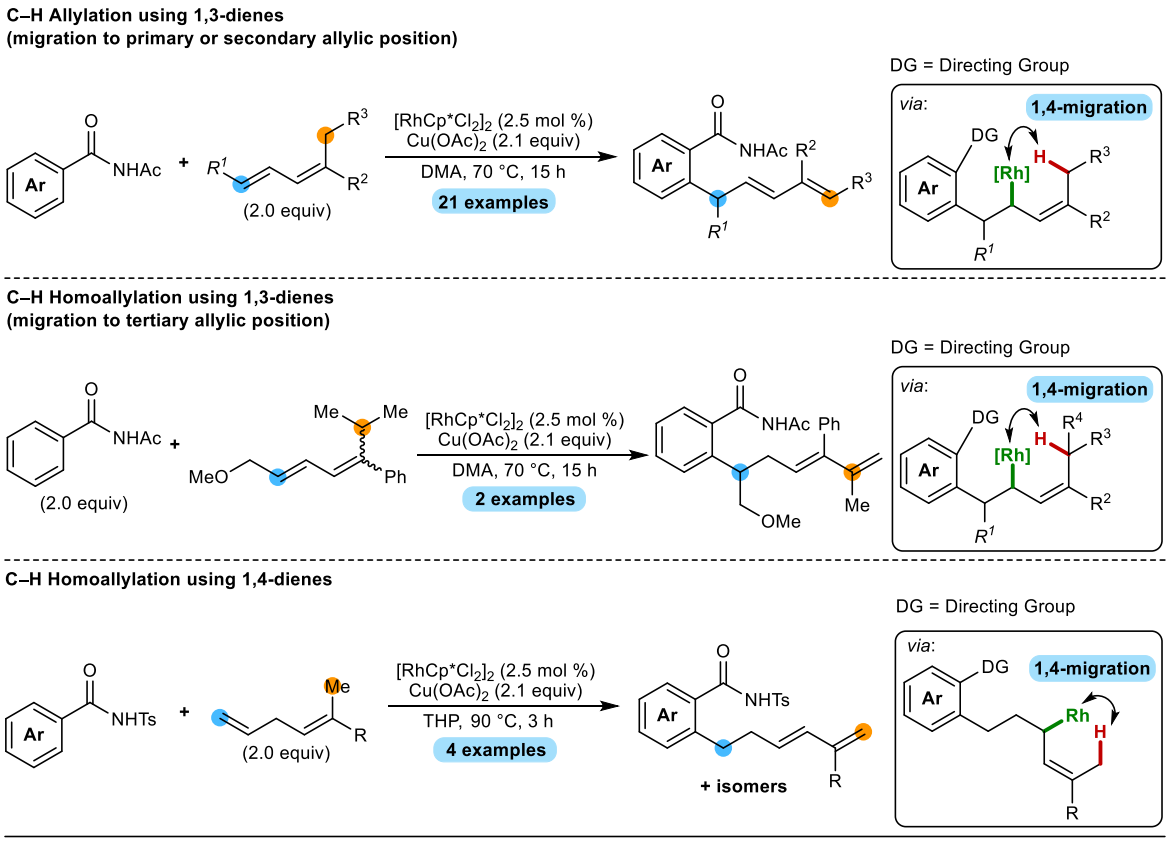
DMC	dimethyl carbonate
DMF	dimethyldformamide
DMSO	dimethylsulfoxide
dppm	bis(diphenylphosphino)-methane
dppp	1,3-bis(diphenylphosphino)propane
EI	electron impact
Et	ethyl
equiv	equivalents
ESI	electrospray ionisation
EWG	electron-withdrawing group
Fur	furyl
hept	heptet
HRMS	high resolution mass spectrometry
i-	*iso*-
IR	infared
KIE	kinetic isotope effect
L	ligand
m	multiplet
M	metal
Me	methyl
MS	molecular sieves
n-	normal-
NBS	*N*-bromosuccinimide
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOESY	nuclear overhauser effect spectroscopy
NR	no reaction
PEPPSI IPr	[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
Ph	phenyl
pin	pinacol
Piv	pivaloyl
Pr	propyl

py	pyridine
q	quartet
quin	quintet
R_f	retention fraction
RT	room temperature
s	singlet
t	triplet
t-	tertiary-
TBDPS	*tert*-butyldiphenylsilane
TBS	*tert*-butyldimethylsilane
TBME	*tert*-butylmethyl ether
temp.	temperature
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TES	triethylsilane
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilane
TLC	thin layer chromatography
TMS	trimethylsilane
TMU	tetramethylurea
Ts	tosyl
UV	ultraviolet

Abstract

Rhodium-Catalysed Oxidative C–H Allylation or Homoallylation of benzamides with 1,3- or 1,4-Dienes by Allyl-to-Allyl 1,4-Rh(III) Migration

The Rh(III)-catalysed oxidative C–H allylation and homoallylation of *N*-acetylbenzamides with 1,3-dienes is described. The presence of allylic hydrogens *cis* to the less substituted alkene of the 1,3-diene is important for the success of these reactions, though not essential. With the assistance of reactions using deuterated 1,3-dienes, a proposed mechanism is provided. The key step is postulated to be the first reported examples of allyl-to-allyl 1,4-Rh(III) migration. Importantly, migration to primary or secondary allylic position results in allylation products, whereas migration to a tertiary position leads to homoallylation. Using 1,4-dienes as the coupling partner, *N*-tosylbenzamides are homoallylated. Preliminary results indicate a mixture of isomer products, with major isomer resulting from an allyl-to-allyl 1,4-Rh(III) migration.

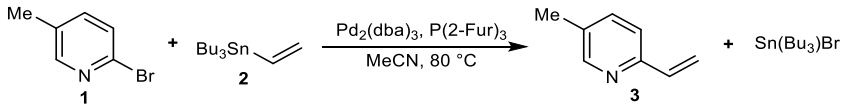


1 Introduction

1.1 C–H bond activation

The demand for environmentally benign and sustainable chemical methodologies has inspired scientists to pursue efficient and economic ways to construct chemical bonds.[1] Moreover, C–C bonds are present in the majority of all synthetically valuable molecules, therefore their straightforward construction warrants continuous exploration. Since C–H bonds are ubiquitous in nature, the ability to transform C–H to C–C bonds is of great importance. Because of the high dissociation energy of C–H bonds (105 kcal mol^{-1} for methane and 110 kcal mol^{-1} for benzene), metal-mediation is frequently required for these to be activated.[2] Though, this has far-reaching practical implications, including but not limited to efficient methodology development for biologically active scaffolds, polymers as well as the replacement of current petrochemical feedstock with less expensive and more readily available hydrocarbons.[1] The realm of metal-mediated C–H activation has intrigued chemists for the past three decades and has been extensively reviewed.[3–10]

Conventional methods, for instance transmetallation using organo-main group reagents or oxidative addition using organic halides, involve the use of pre-functionalised substrates. These are often expensive and often involve generating stoichiometric amounts of waste.[11–16] A number of these incorporate the use of toxic reagents, an example here being the Stille cross-coupling, where aryl bromide **1** is coupled with organostannane **2** in the presence of a palladium catalyst, forming alkene **3** (Scheme 1).[17]



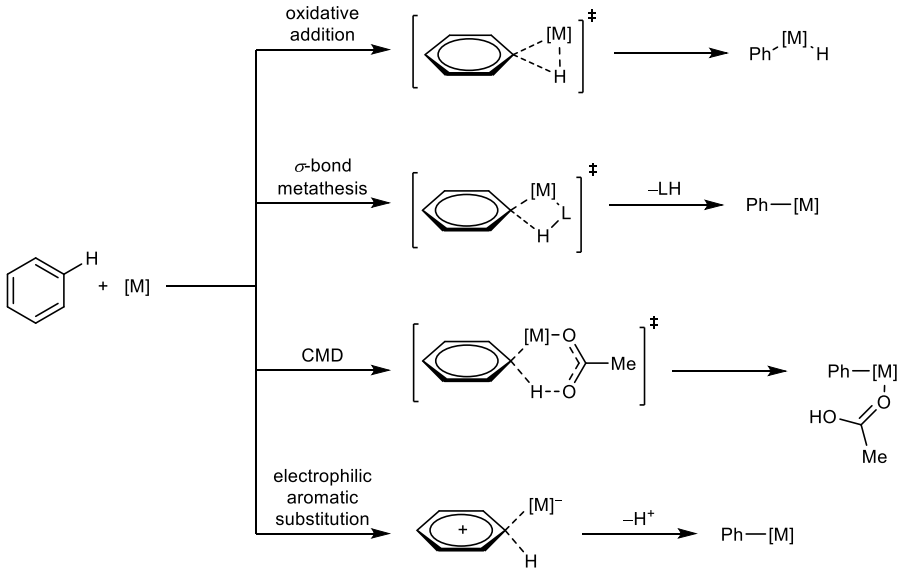
Scheme 1. Stille cross-coupling example

The directing group-assisted metal-catalysed C–H activation approach provides a more eco-friendly and step-economic option to preceding methods as the formation of

reactive organometallic intermediates and prior activation or functionalisation of C–H bonds is not needed.

1.2 Modes of C–H activation

Several modes of C–H activation have been proposed and evaluated for oxidative metal-catalysed C–H activation.[8,13,18,19] In particular, oxidative addition for electron-rich late transition metals, σ-bond metathesis for early transition metals, base-assisted concerted metalation–deprotonation (CMD), and an electrophilic aromatic substitution-type mode for electron-deficient late transition metals (Scheme 2). Herein, unless otherwise stated, the C–H activation step is considered to proceed *via* an acetate-assisted concerted metalation–deprotonation, with respect to the chemistry described regarding Rh(III) oxidative catalysis.



Scheme 2. Modes of C–H activation. [M] = metal complex, L = ligand

1.3 Coordination-directed metallation

Due to the vast number of C–H bonds present in molecules, selectively activating C–H bonds can be problematic, especially if several C–H bonds are susceptible to activation concurrently, leading to low selectivity (regio-, enantio- and chemo-) or even over-functionalisation of the starting reagents. These features can be controlled in two manners, either by natural selectivity or by ligand coordination effects.

Natural selectivity can be achieved based on the electronic or the steric properties of the molecule. In this type of reactions C–H functionalisation is dictated at specific positions without the use of external guidance. For instance, this 'innate' reactivity is encountered in the functionalisation of aromatic systems in which selectivity is achieved due to electron density distribution variations (Figure 1).[2]

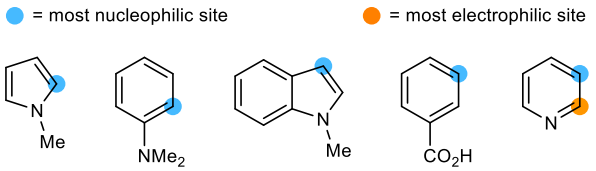


Figure 1. Examples of molecules with natural selectivity at specific positions

Aside from this natural selectivity chemists have employed strategies which in turn are able to direct functionalisation at positions that would not be feasible by natural selectivity. This involves the use of directing groups. A directing group is a moiety containing a heteroatom, generally N, O, P or S, capable of donating its lone pair and weakly binding to the metal centre.[2] Weak binding to the metal centre is necessary to avoid catalyst poisoning.[2] Selected examples of *ortho*- and *meta*-directing groups are presented below (Figure 2).[20–23]

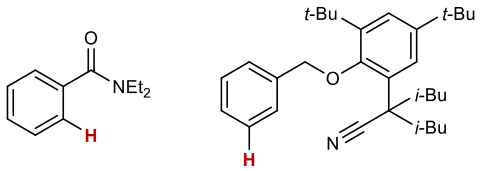
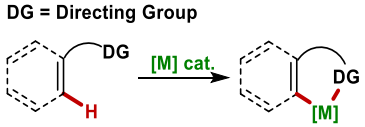


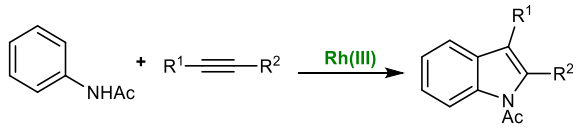
Figure 2. Selected examples of *ortho*- and *meta*-directing groups

Once the metal-directing group intermediate is formed only C–H bonds proximal to the metal are able to be activated, leading to high chemoselectivity. The use of directing groups in this manner is generally referred to as coordination-directed metallation. A representative example is illustrated below wherein the metal complex activates the C–H bond *ortho* to the directing group (Scheme 3).



Scheme 3. Coordination-directed metallation using directing groups

Despite their broad utility in organocatalysis directing groups are retained in the final product, this being their main limitation. However, there have been examples such as oxidative annulations in which they are incorporated into the target molecule, as well as instances where they act as internal oxidants thus nullifying the need for external oxidants (Scheme 4 and Figure 3).[2, 24] Furthermore, in recent literature many directing groups can be removed under certain reaction conditions without being detrimental to other functional groups within the molecule.[25–28]



Scheme 4. Incorporation of the directing group into the target molecule

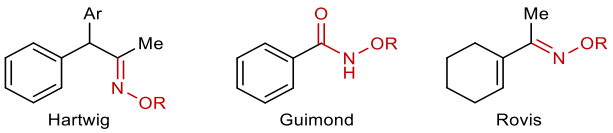
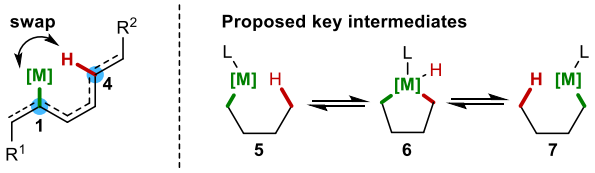


Figure 3. Examples of directing groups that can act as internal oxidants

1.4 Remote C–H activation *via* through-space 1,4-metal migrations

As described in section 1.1, achieving high chemoselectivity whilst catalytically activating C–H bonds is of great synthetic value and appeal. A complementary approach to directing group-assisted C–H activation involves utilising transition metals to perform C–H activation *via* through-space 1,4-metal migrations. This field is developing rapidly and as a result has not been reviewed extensively.[29,30] This type of C–H activation can lead to a net "metal migration" from the carbon atom where the metal is first introduced to a distal carbon, in this case four carbons away, where C–H activation can ensue (Scheme 5). This is an interesting approach as frequently it can be problematic and challenging in introducing the metal moiety at such positions in the molecule. Furthermore, concurrent migration of a hydrogen accompanies the metal's migration, resulting in the hydrogen migrating to the metal's site of origin. Additionally, it should be noted that metal migrations are generally considered to be reversible.[29,30] It is also proposed that the mechanism of the migration itself, for Pd(II)

and Rh(I), involves initial oxidative addition of **5** forming 5-membered metallacycle **6**, followed by reductive elimination generating intermediate **7** (Scheme 5).



Scheme 5. 1,4-Metal migration and proposed key intermediates in Pd(II) and Rh(I) systems

The two most prevalent metals reported to perform this transformation are Pd(II) and Rh(I).[29,30] The field of 1,4-migration is developing rapidly. It is noteworthy to mention that in recent years, additional transition metals capable of undergoing a 1,4-migration have also been reported, including Ru, Ir, Pt, Co and Ni.[31–39] Moreover, in certain systems the metal can undergo consecutive migrations to different sites of the molecule, thus highlighting the superior and complex nature of the 1,4-metal migration.

1.5 Research topics discussed

Herein, the chemistry reviewed is focused on means of activating C–H bonds that until recently were considered to be chemically inert. Specifically, C–H bonds present in alkene and allyl moieties are studied. Two concepts of activating these types of bonds are selected, directed C–H activation, and remote C–H activation *via* 1,4-metal migration.

The functionalisation of aromatic systems with alkenes *via* directed C–H activation has been extensively studied and a series of examples using Ru, Pd, Rh, Ir, Re, Co, Mn, Ni, Fe and Cu transition metals have been reported.[2,10,40] Firstly, the directing group-assisted Rh(III)-catalysed oxidative C–H functionalisation of arenes with alkene moieties as the coupling partners is discussed. A wide range of directing groups can be used in these types of reactions, and therefore the following section has been categorised depending on the directing group that is employed as well as whether an external or internal oxidant is used. Pioneering research using representative directing groups has been selected that is relevant to the chemistry outlined in the results and discussion section.

Secondly, regarding remote C–H activation *via* 1,4-metal migrations, reactions reviewed have been categorised according to the metal of choice as well as the sites at which the metal migrates from and to. Furthermore, examples are also discussed in which the above two C–H activation concepts are utilised collectively in a single methodology.

This review solely focuses on rhodium as the catalyst, this is done to provide an overview of its reactivity and therefore correlate it to the research and discussion section which uses Rh(III) as the catalyst.

1.6 Rh(III) C–H activation catalysts

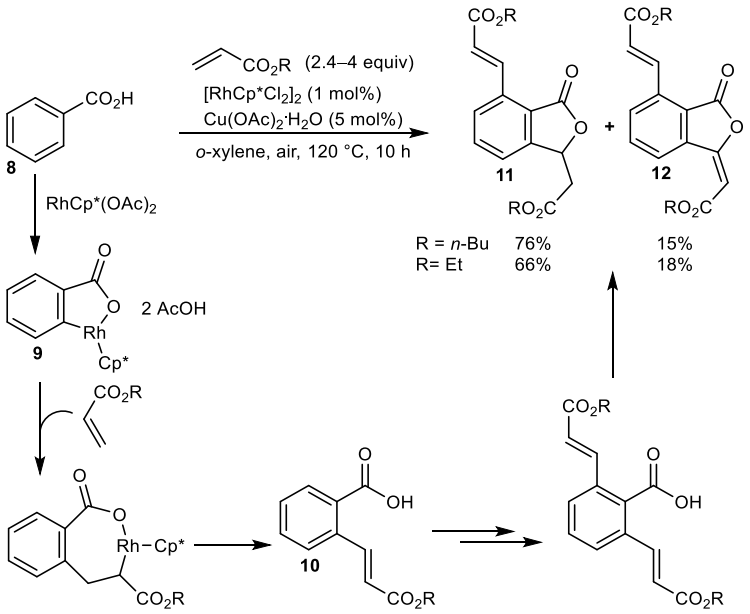
High efficiency, selectivity and functional group tolerance can be achieved with the use of Rh(III) in oxidative coupling reactions of aromatic substrates with alkenes.[9,10,41] Two of the most widely employed Rh(III) complexes are $[RhCp^*Cl_2]_2$ and $[RhCp^*(MeCN)_3]^{2+}$.[41] Recently, Cramer and co-workers developed a series of cyclopentadienyl ligands that demonstrated high reactivity and excellent enantioselectivity.[42] This area is continually being explored and facile construction of C–X (X = C, O, and N) bonds *via* C–H activation should find widespread applications in the preparation of organics, natural products and materials. Despite their increased cost, their use will still be favoured over other transition metals that are unable to undergo similar transformations, provided that high selectivity and efficiency can be achieved.

1.7 Oxidative C–H activation of alkenes using external oxidants

1.7.1 Carboxylic acid as the directing group

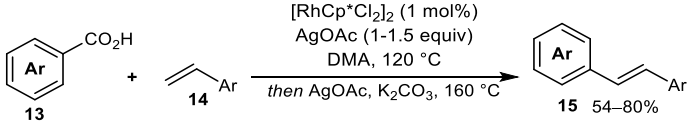
Carboxylic acids are capable of *ortho*-directing cyclorhodation and have thus been extensively documented.[43] Important, pioneering work was established in this area by Satoh and Miura who successfully developed the catalytic coupling of activated alkenes to arenes with the use of carboxylic acids as *ortho*-directing groups.[44,45] Their methodology involved the use of $[RhCp^*Cl_2]_2$ (1 mol%) accompanied by a catalytic

amount of $Cu(OAc)_2$ (5 mol%) under aerobic conditions, generating water as the sole by-product. A simplified catalytic cycle was proposed (Scheme 6) in which Rh(III) coordinated to benzoic acid **8** generating the orthorhodation intermediate **9**. This was then able to facilitate an alkene insertion and successive *β*-hydride elimination would form the monovinylated benzoic acid **10**. Interestingly, a second vinylation occured prior to the nucleophilic cyclisation yielding the observed 7-vinyl phthalide derivatives **11** and **12**. Oxygen accompanied by $Cu(OAc)_2$ could oxidise the Rh(I) species back to the catalytically active Rh(III) species.

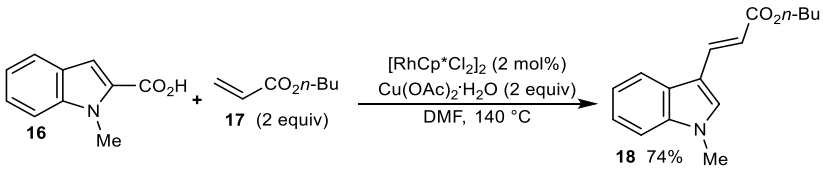


Scheme 6. Coupling of activated alkenes with benzoic acid proposed catalytic cycle

Elaborating on their work in this area Satoh and Miura developed catalytic methodologies wherein the carboxyl group could be cleaved during the coupling of benzoic acids **13** with a broad range of styrenes **14** (Scheme 7).[46,47] The reaction tolerated halogens, as well as both electron-donating and -withdrawing groups about the aromatic ring. The carboxyl group was cleaved under relatively harsh conditions when treated with a mixture of K_2CO_3 and AgOAc affording various stilbenes **15** in good yield. The decarboxylative coupling of benzoic acids **16** with activated alkenes **17** was later applied to heterocyclic aromatic compounds **18** (Scheme 8).[46]



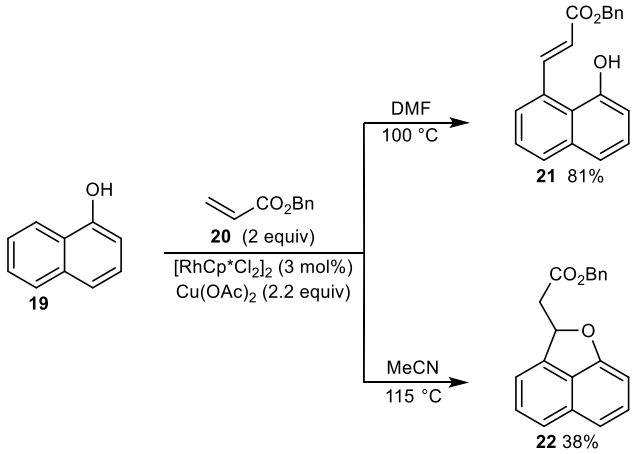
Scheme 7. Decarboxylative coupling of benzoic acids with styrenes



Scheme 8. Example of decarboxylative coupling of an indole derivative with an acrylate

1.7.2 Hydroxyl as the directing group

Hydroxyl is a widely used directing group either in its anionic or neutral form.[48] Nevertheless, Rh(III) oxidative C–H functionalisation reactions with alkenes are quite limited, with only a single reported example so far employing the hydroxyl directing group (Scheme 9).[49] Herein, 1-naphthols **19** are treated with acrylates **20** in the presence of $[RhCp^*Cl_2]_2$ (3 mol%) and $Cu(OAc)_2$ (2.2 equiv). Importantly, in this reaction the solvent dictates whether simple alkenylation occurs to give **21** or whether alkenylation followed by a Michael cyclisation takes place to give **22**.

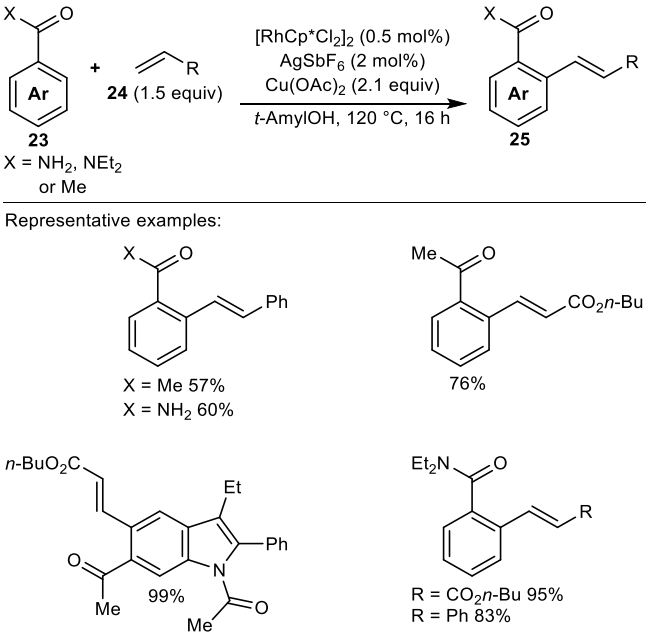


Scheme 9. Hydroxyl-directed coupling of acrylates with 1-naphthols

1.7.3 Carbonyls (ketone, amide, aldehyde, ester, carbamate and acetanilide) as the directing group

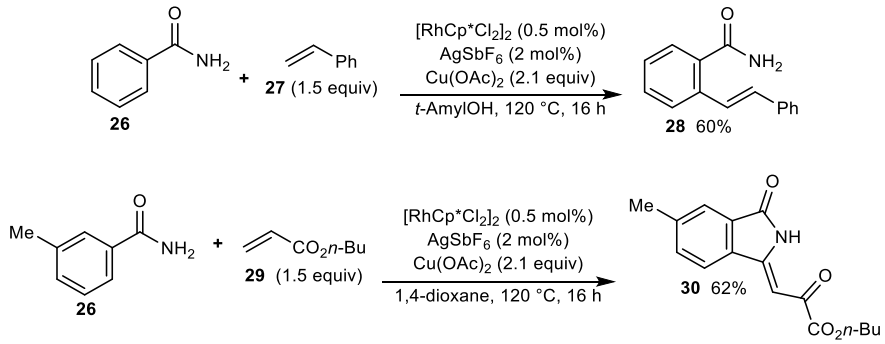
Recently, Glorius and colleagues reported catalytic alkenylation of benzamides and acetophenones **23** in good to excellent yields (Scheme 10).[21] Their methodology utilised $[RhCp^*Cl_2]_2$ (0.5 mol%) as the catalyst and stoichiometric amounts of $Cu(OAc)_2$ (2.1 equiv) as the external oxidant with $AgSbF_6$ (2 mol%) as an additive.

Alkene coupling partners **24** can vary from both electron-withdrawing and -donating aryl rings to acrylates.



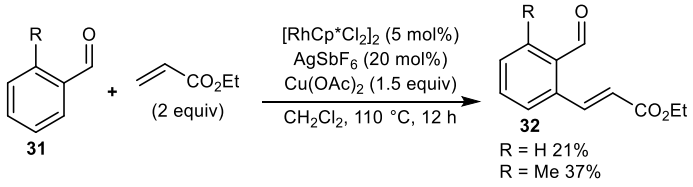
Scheme 10. Alkenylation of acetophenones and benzamides

This methodology was attractive because it utilised low catalyst loadings, readily available, cheap starting materials and afforded the desired products **25** in high yield. However, it should be noted that only activated alkenes were used as coupling partners and any less reactive alkenes, bearing alkyl substituents for instance, were not reported. High temperatures were also used. Furthermore, the electronic and steric properties of the ketone substrates were investigated. With respect to sterics, C–H functionalisation of the less sterically hindered site occurred when multisite functionalisation was possible. Importantly, when electron-withdrawing groups *meta* to the acetyl group were present the reaction did not proceed even at increased catalyst loadings. Interestingly, primary benzamides **26** when coupled with acrylates **29** afforded lactams **30** with an *exo*-cyclic (*Z*)-C=C bond *via* a two-fold oxidation as opposed to when styrenes **27** were used which gave alkenylated products **28** (Scheme 11). When comparing acrylates to styrenes it is possible that the carbonyl present in the acrylate moiety aids in the stabilisation of the rhodacycle which would not be possible with aryl-substituted alkenes.



Scheme 11. Examples of different reactivity in primary benzamides depending on alkenes used

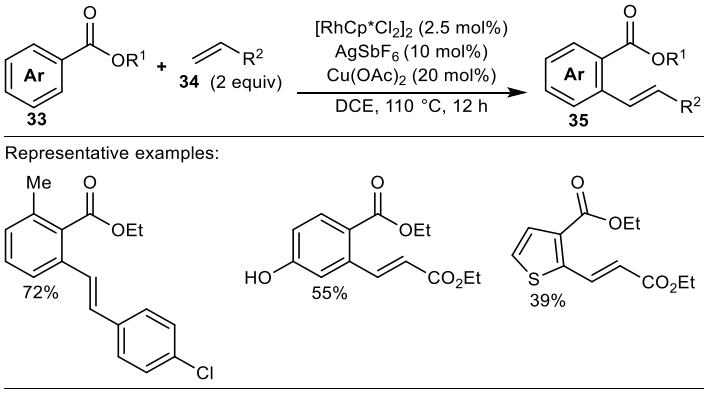
There is a lack of catalytic procedures in which aldehydes function as efficient directing groups.[50,51] This is evident in particular under oxidative conditions, likely due to decarbonylation that can take place as a side reaction and as a result the CO generated often interferes with the reactivity of the catalyst.[41] With respect to alkenylation of arenes under Rh(III)-catalysed oxidative conditions, there has been only one example wherein aldehydes **31** functioned as directing groups (Scheme 12).[52] This methodology reported by Chang requires an increased Rh(III) loading (5 mol%) accompanied by $AgSbF_6$ (20 mol%) as an additive and stoichiometric $Cu(OAc)_2$ (1.5 equiv). Furthermore, the alkenylated product **32** was isolated in relatively low yield due to significant amount of decarbonylation. It is clear that due to the limited application of aldehydes as directing groups further research is required in this area.



Scheme 12. Aldehyde-directed alkenylation of arenes

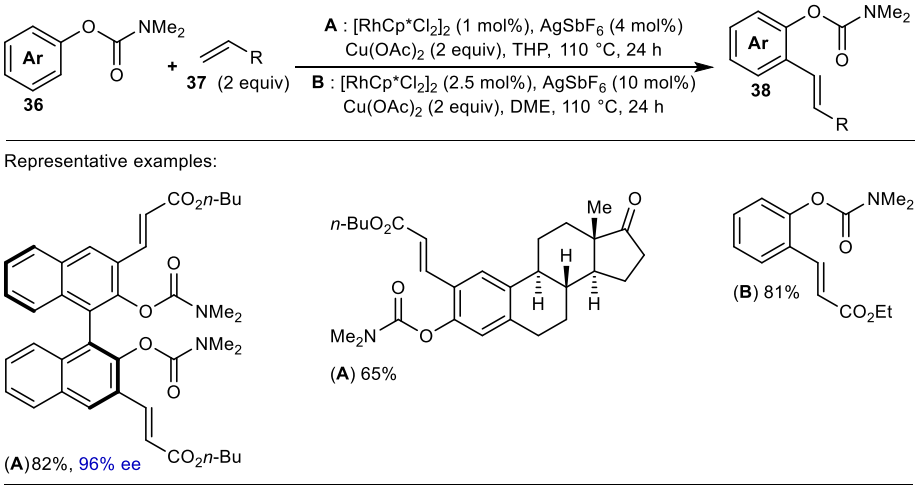
Concurrently to their efforts with aldehydes as directing groups, Chang and co-workers published the alkenylation of benzoate esters **33**, highlighting the directing capability of esters (Scheme 13).[52] Their methodology makes use of $[RhCp^*Cl_2]_2$ (2.5 mol%) as the catalyst in the presence of $AgSbF_6$ (10 mol%) and catalytic amounts of $Cu(OAc)_2$ (20 mol%) affording the alkenylated benzoate esters and esters of heteroaryl carboxylic acids **35** in moderate yield, using acrylates and styrenes **34** as effective coupling partners. Interestingly, hydroxyl substituents on the aryl ring do not affect the directing functionality of the ester even though hydroxyls have demonstrated the

ability to direct *ortho*-alkenylation. Additionally, when oxygen is employed as the sole oxidant no reaction takes place. Through KIE studies on the basis of intramolecular competition give K_H/K_D = 2.3, suggesting that C–H bond cleavage is likely to be involved in the turnover limiting step.



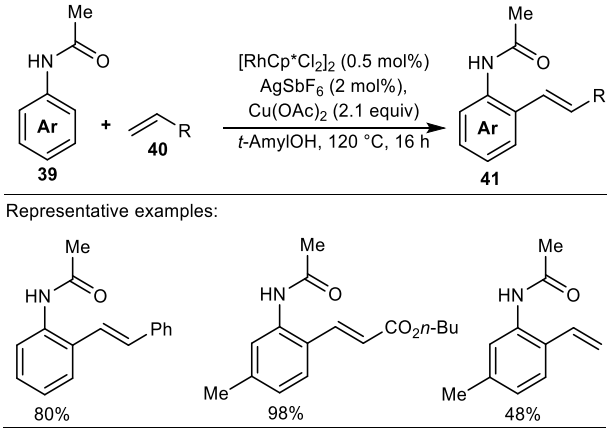
Scheme 13. Rh(III)-catalysed C–H alkenylation of carboxylates

Carbamates **36** have also demonstrated the ability to activate C–H bonds at *ortho*-positions of arenes, an example here being phenol carbamates **36** reported by Liu and Loh respectively.[53,54] Traditional Rh(III) conditions were applied with $AgSbF_6$ as an additive and the use of stoichiometric $Cu(OAc)_2$ as the oxidant (Scheme 14). The carbonyl group of the carbamate acted as an efficient directing group forming a 6-membered rhodacycle intermediate, nevertheless the alkenylation proceeded in a fundamentally similar manner. Regarding the alkene coupling partners **37** the methodology was restricted to styrenes and activated alkenes such as acrylates, though the products **38** were isolated in high yield with similar regioselectivity. Moreover, dialkenylation could be achieved when both *ortho* C–H bonds were present. It is noteworthy to mention that analogous KIE values of 3.1 and 3.5 were calculated for the oxidative alkenylation of phenyl *N*,*N*-dimethylcarbamate, suggesting a correlation in the oxidative alkenylation of carbamates, benzoates, and benzamides.[53,54]



Scheme 14. Rh(III)-catalysed C–H alkenylation of carbamates

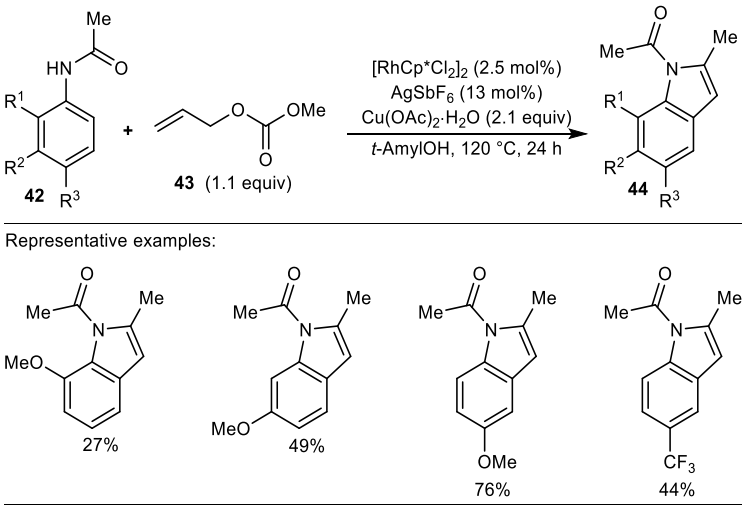
Glorius and co-workers have made significant contributions in this area.[8,55,56] In 2010, they reported a Rh(III)-catalysed alkenylation and vinylation of acetanilides **39**, which are generally considered to be of low reactivity, with alkenes **40** (Scheme 15A).[55] The reaction conditions were identical to previously described examples where benzamides and acetophenones were coupled with alkenes catalytically (Scheme 10).[21] Here the low catalyst loadings as well as the broad range of substituents tolerated about the aryl ring made this an attractive route towards alkenyl-substituted acetanilidines **41** in moderate to high yields.



Scheme 15A. Rh(III)-catalysed alkenylation of acetanilides

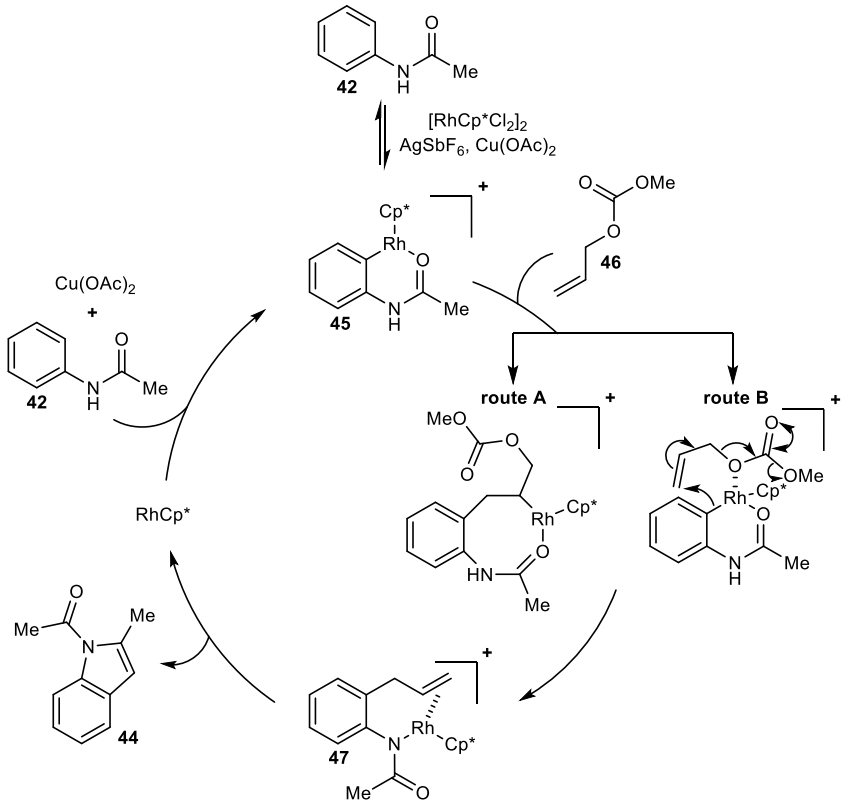
Moreover, anilides **42** were successfully used to prepare a range of indoles **44** *via* a Rh(III)-catalysed tandem C–H allylation followed by an oxidative cyclisation using allyl methyl carbonate **43** as the coupling partner (Scheme 15B).[57] Electron-rich anilides were generally more efficient than electron-poor or -neutral anilides.

Substituents about the aryl ring were tolerated, though *ortho* and *meta* substitution resulted in lower yields. Recently, this chemistry was also performed on enol carbamates.[58]



Scheme 15B. Rh(III)-catalysed tandem C–H allylation and oxidative cyclisation of anilides

It is proposed that key cationic Rh(III) intermediate **45** is formed *in situ via* a Cu and Ag salt synergistic effect (Scheme 16). Next, coordination and migratory insertion of the alkene **46** followed by *β*-oxygen elimination generates intermediate **47** (route A). It is also proposed that intermediate **47** can also be formed *via* initial coordination of Rh(III) to the allyl carbonate at the allyl-bearing oxygen facilitating an S_N2' process (route B). *Syn*-amidorhodation in **47**, followed by *β*-H elimination and isomerisation affords the corresponding indole **44**. Finally, $Cu(OAc)_2$ acts as an oxidant to re-oxidise Rh(I) to Rh(III).

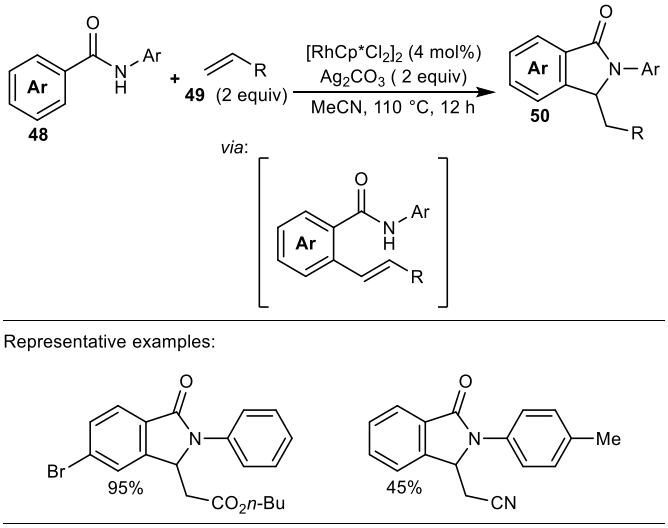


Scheme 16. Proposed catalytic cycle generating indoles from anilidines

1.7.4 N–H protic amides, amidines and trichloroacetimidamides as the directing group

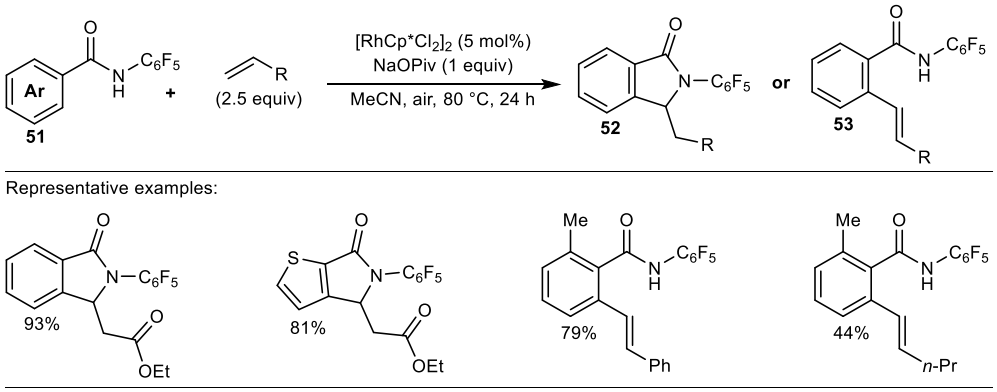
As described previously in Scheme 11, when primary or secondary amides (i.e. protic amides) are involved in C–H activation reactions the nitrogen atom has a direct effect in the outcome of the reaction as it is able to coordinate to Rh(III) and be part of the rhodacycle intermediate that is generated (see section 1.7.3).[8] This subsection provides a discussion of additional examples where protic amides are encountered.

For instance, Li successfully applied *N*-arylbenzamides **48** to the oxidative alkenylation under Rh(III) catalytic conditions with stoichiometric Ag_2CO_3 as the oxidant (Scheme 17).[59] This methodology worked well with activated alkenes **49**, such as acrylates, enones and acrylamides, but not as effectively with styrenes. It was postulated that the target γ-lactam products **50** were formed *via* an alkenylation-1,4-conjugate addition sequence. It is also shown that selectivity of the C–H functionalised bonds is governed by steric as well as electronic effects.



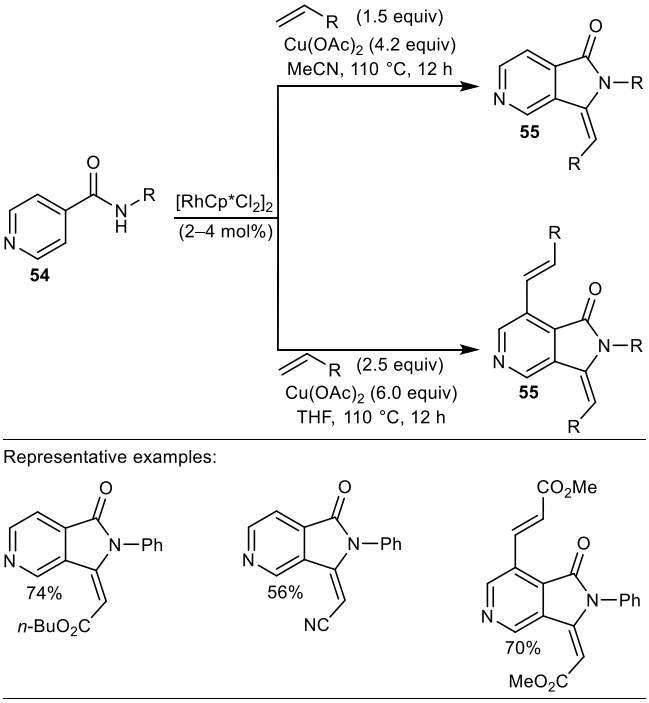
Scheme 17. Catalytic Rh(III) alkenylation of *N*-arylbenzamides.

In 2015, Yu improved the alkenylation of *N*-arylbenzamides **51** using air as the only oxidant hence avoiding the use of any copper or silver salts as co-oxidants.[60] Herein, $[RhCp^*Cl_2]_2$ (5 mol%) was used as the catalyst to provide *γ*-lactams **52** or alkenyl benzamide products **53** in excellent yield (Scheme 18). Moreover, an *N*-pentafluoroaryl benzamide motif was crucial for achieving catalytic turnovers. The *γ*-lactam formed primarily when acrylates were used as coupling partners whereas aryl- and alkyl-substituted alkenes afforded the non-cyclised product. The researchers mentioned that base-mediated 1,4-conjugate addition of the acidic *N*-pentafluoroaryl moiety onto the pendant enoate enabled the formation of the *γ*-lactam product. In addition, an acetate base was also necessary for the reaction to proceed efficiently, the base was likely to play a significant role in the re-oxidation of Rh(I) to Rh(III) during the catalytic cycle. The reaction tolerated both electron-withdrawing and -donating substituents about the benzamide. Reactions with heterocyclic amides proceeded efficiently under these conditions as well. Importantly, it was shown that the acidity of the aryl C–H bonds dictated where alkenylation took place. For instance, benzamides with a fluoride at the *meta* position once reacted afforded *ortho*-alkenylation as the major regioisomer, whereas the presence of a methyl group at the *meta* position produced the *para*-alkenylated lactam. With respect to the alkene scope, both activated and less reactivate alkenes underwent the transformation in good yields, but disubstituted alkenes proved to be unreactive.



Scheme 18. Rh(III)-catalysed C–H alkenylation of benzamides with air as the sole oxidant

This methodology was further extended by Li to include isonicotinamides **54**.[61] Here, catalytic amounts of $[RhCp^*Cl_2]_2$ (2–4 mol%) were required as well as stoichiometric $Cu(OAc)_2$ (4.2–6.0 equiv) to afford the target *γ*-lactones **55** *via* a two-fold oxidation (Scheme 19).[61]

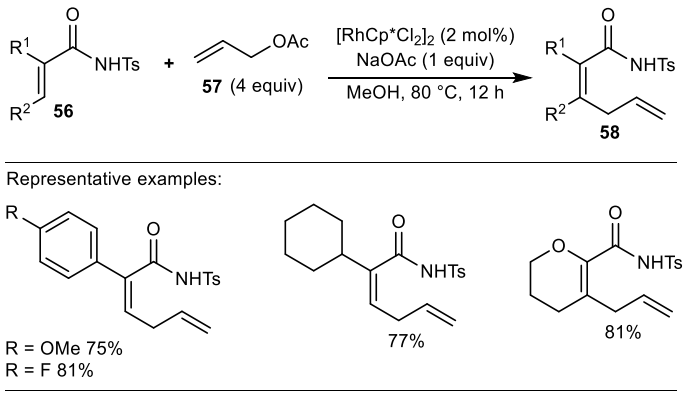


Scheme 19. Examples of Rh(III)-catalysed mono- and dialkenylation of isonicotinamides

It should be noted that this strategy provided *trans-exo*-cyclised products as opposed to earlier reports by Glorius where structurally similar benzamide precursors gave *cis-γ*-lactones (see Scheme 11).[8] Also, different solvents demonstrated a synergistic role in obtaining mono- or disubstituted alkenylation *via* a two- or three-fold oxidation respectively. Notably, the researchers mentioned that monoalkenylation was not a

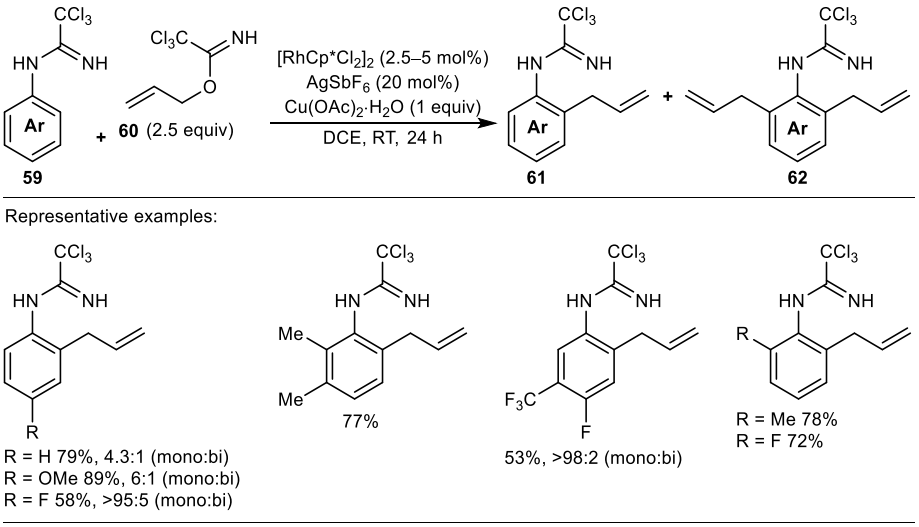
precursor to the dialkenylation product. It can be concluded that electronically different heterocarboxamides have different selectivity which is further enhanced by the appropriate choice of solvent.

Loh and co-workers showed that carboxamides **56** can also undergo Rh(III)-catalysed C–H allylation reactions in the presence of allyl acetate **57** to afford substituted 1,4-dienes **58** (Scheme 20).[62] This methodology tolerated aryl, alkyl and alkoxy substituents at R^1, and substitution at R^2 was also possible. Allyl bromides have also been employed as electrophilic allylating partners.[63]



Scheme 20. Rh(III)-catalysed C–H allylation of carboxamides with allyl acetate

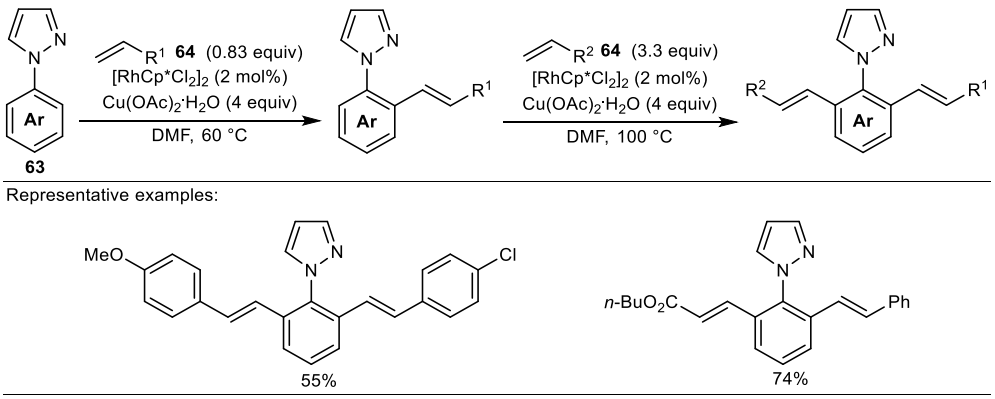
An example using the N–H in trichloroacetimidamides **59** as the directing moiety was demonstrated by Maji, affording allylated products **61** and **62** (Scheme 21).[64] Herein, allyl carbonate or allyl-2,2,2-trichloroacetimidate **60** were used as the coupling partner of the trichloroacetimidamide. Generally, a mixture of bi- and monoallylated products were formed; though this could be controlled by altering the temperature. In addition, electron-rich arenes were more reactive as opposed to electron-poor arenes. Importantly though, electron-poor arenes generally afforded the monoallylated products predominantly, whereas electron-rich lowered the selectivity of the reaction.



Scheme 21. Rh(III)-catalysed C–H allylation of trichloroacetimidamides

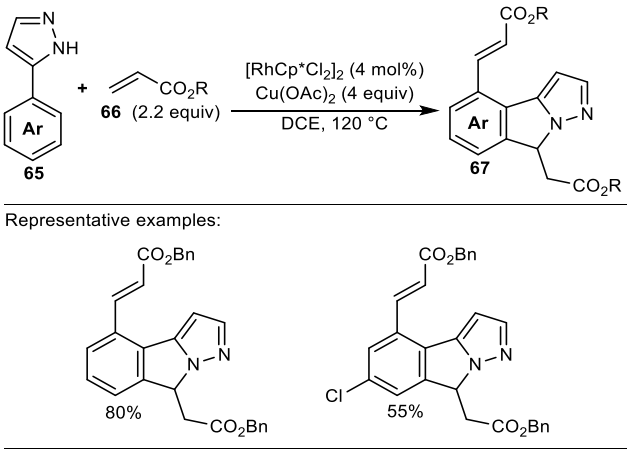
1.7.5 Pyrazoles, pyrimidinyls, pyridines, oximes, oxazoles and thiazoles as the directing group

A considerable breakthrough with respect to unprecedented directing group reactivity was achieved by Satoh and Miura when coupling alkenes **63** with *N*-arylpyrazoles **64** (Scheme 22).[65] Admittedly, the substrate scope of their methodology was limited to styrenes and acrylates. In order for the reaction to be selective towards monoalkenylation, the alkene was used as the limiting reagent. Additionally, the selectivity of mono- *versus* divinylation can be tuned by selecting substrates that can dictate the selectivity through steric interaction of the substituents about the arenes. For example, introducing a 5-methyl group to the pyrazole ring created unfavourable steric interactions between it and the vinyl group therefore rendering the second cyclometallation both thermodynamically and kinetically unfeasible.



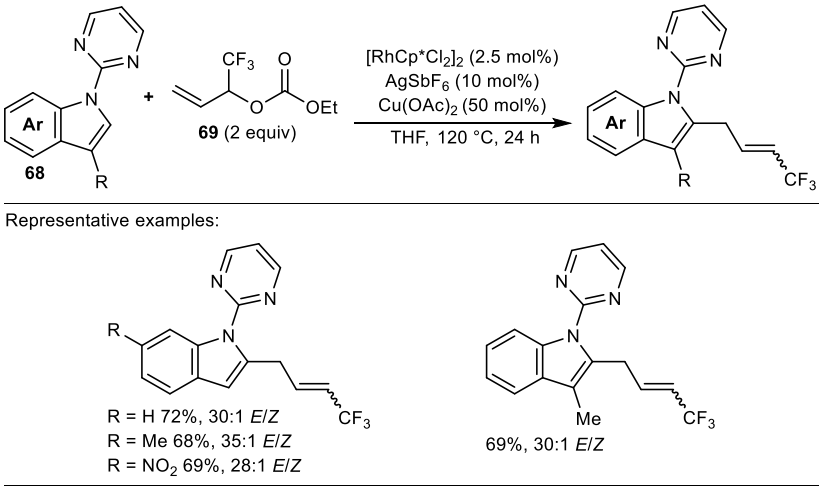
Scheme 22. Selective Rh(III)-catalysed vinylation of *N*-phenylpyrazoles

Similarly, Li reported the coupling of acrylates **66** with N–H 5-phenylpyrazoles **65** in high selectivity.[66] The conditions used were very similar to those reported by Satoh and Miura (Scheme 22).[65] In all cases only the oxidative dialkenylation-aza-1,4-conjugate addition product **67** was obtained (Scheme 23).



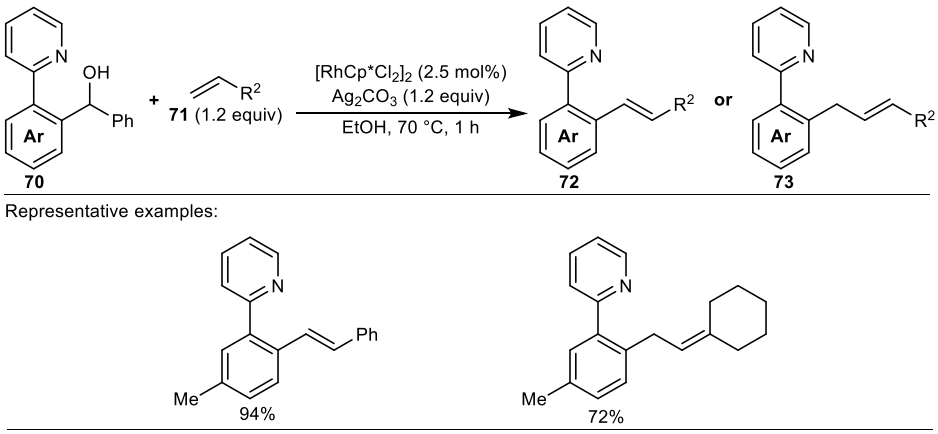
Scheme 23. Rh(III)-catalysed C–H dialkenylation of N–H 5-arylpyrazoles

Importantly, trifluoromethylallylation was achieved using allyl carbonates **68** and compounds **69** containing the pyrimidinyl moiety as the directing group (Scheme 24).[67] Here, both electron-deficient and -rich indoles were successfully trifluoromethylallylated in good yields. Substitution at the 3-position was also possible. Impressively, excellent *E*/*Z* ratios of the vinyl trifluoromethyl moiety were observed. In addition, acryloyl silanes could be coupled to indoles incorporating the pyrimidinyl directing group.[68]



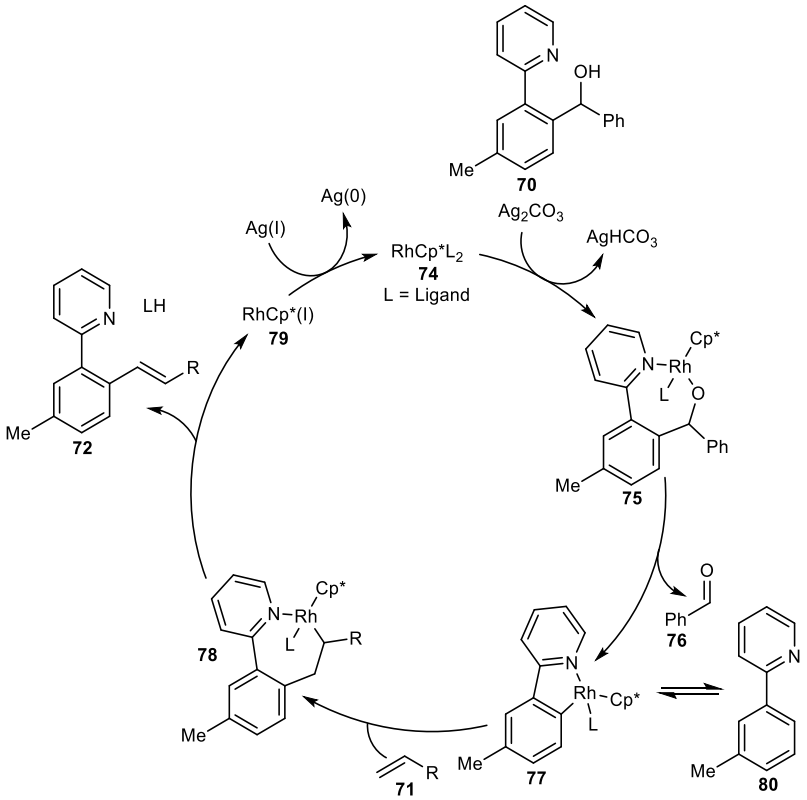
Scheme 24. Rh(III)-catalysed C–H trifluoroallylation of indoles with allyl carbonates

Pyridines have also been encountered in methodologies as *ortho*-directing groups.[69,70] Regarding arene alkenylations, an intriguing and rare study reported by Shi extended the idea of C–H activation to C–C activation in 2-arylpyridines under Rh(III) oxidative conditions (Scheme 25).[70] Here, phenyl(2-(pyridine-2-yl)phenyl)methanols **70** were reacted generally with styrenes **71** under conventional C–H activation conditions affording vinylation products **72**. Two examples using alkyl-substituted terminal alkenes **71** were reported, which gave C=C bond migrated products **73**. Surprisingly, expected *ortho*-C–H functionalisation did not take place, instead C–C functionalisation was preferred. When excess vinyl starting reagent and oxidant were used then subsequent C–H functionalisation was possible. Moreover, this approach was compatible with both secondary and tertiary alcohols, generating aldehydes and ketones as the side-product respectively.



Scheme 25. Rh(III)-catalysed C–C activation and C–H activation

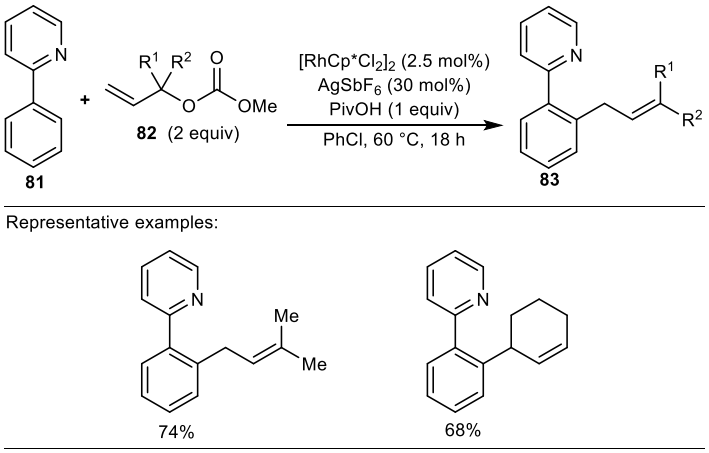
The proposed catalytic cycle involves the initial coordination of the Rh(III) species **74** to the N and O atoms of phenyl(2-(pyridine-2-yl)phenyl)methanol **70** forming a 7-membered cyclic intermediate **75** (Scheme 26). *β*-Hydride elimination is favoured, releasing the aldehyde **76** as a side-product as well as 5-membered rhodacycle **77**. Rhodaycle **77** next undergoes migratory insertion into alkene **71** to form intermediate **78**. This is followed by another *β*-hydride elimination yielding the desired product **72** in addition to Rh(I) **79**, which is then re-oxidised in the presence of Ag(I) to Rh(III) **74**.



Scheme 26. Proposed catalytic cycle involving C–C bond activation

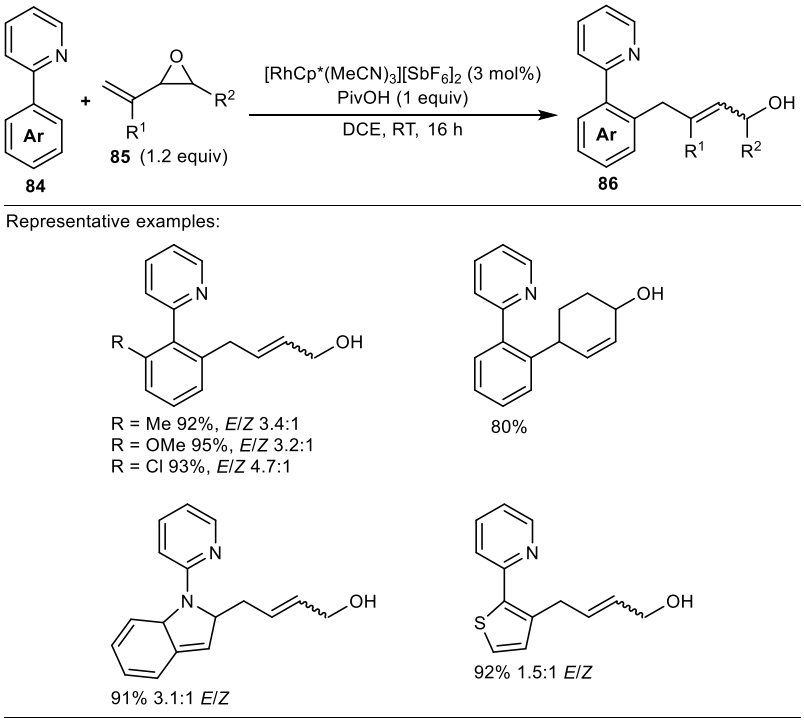
Particularly, it was mentioned that **77** had been isolated thus reinforcing this hypothesis. Interestingly, traces of **80** were also observed which could be generated through sequential protonation of **77**. In theory, **80** could undergo C–H activation and carry on through the cycle, though this was disproved by additional studies conducted by the team. Through a competition experiment it was shown that C–C activation is more facile than C–H activation thus it is most likely to be in effect.

Glorius and co-workers were also able to show that in the presence of allyl carbonates **82**, C–H allylation of 2-phenylpyridines **81** was achieved, forming allylation products **83** (Scheme 27).[71] The catalytic cycle proposed was analogous to that reported by Saá (Scheme 16). As a final point, it was also demonstrated that other substrates bearing a pyrazole and pyrimidinyl directing group, as well as *N*-*i*-Pr$_2$ benzamides were capable of performing the C–H allylation.[71] In addition, Kim and colleagues showed that the amide moiety in indolines is also an effective directing group, displaying similar chemical reactivity with allyl carbonates.[72]



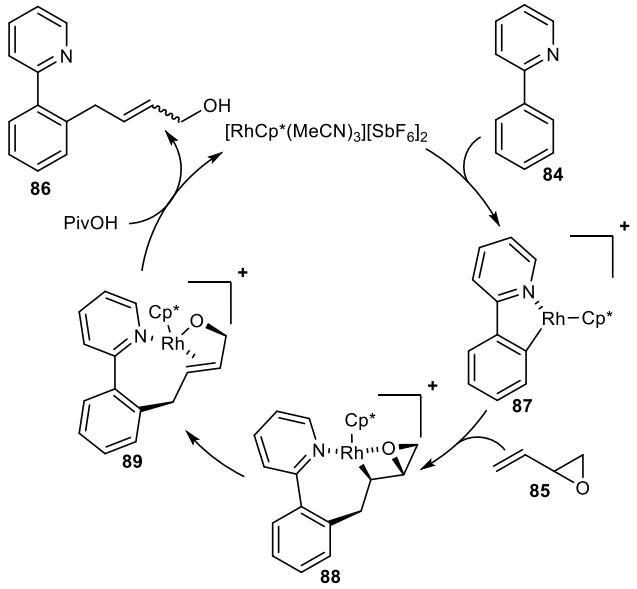
Scheme 27. Rh(III)-catalysed allylation of 2-phenylpyridines

Expanding on this chemistry, Li employed 2-vinyloxiranes **85** as the coupling partner thus generating a range of allylic alcohol products **86** (Scheme 28).[73] To avoid biallylation generally *ortho*- or *meta*-substituents were required. With respect to the arene scope, a range of substituted 2-phenylpyridines **84** were used, both electron-deficient and -rich; other such as indoles and thiophenes were also compatible. Furthermore, directing groups such as pyrazoles, pyrimidinyls and *N*-methoxyimines could be used instead of pyridines.[73] This methodology was further developed by Wang, to include vinyl dioxonalones and vinyl cyclopropanes as complementary coupling partners; this time allylating *N*-methoxybenzamides.[74–76] An additional example using vinyl benzoxazinanones as the electrophilic allylating agent was also developed by Li.[77]



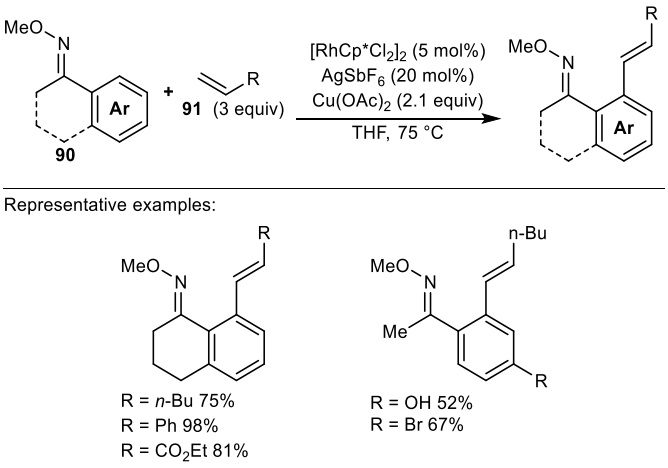
Scheme 28. Rh(III)-catalysed C–H allylation of arenes with 2-vinyloxiranes

A proposed catalytic cycle involves C–H activation of the arene **84** generating a 5-membered rhodacycle **87** (Scheme 29). This in turn undergoes migratory insertion with 2-vinyloxirane **85** giving an alkylrhodium species **88** with the proximal epoxide. Subsequent *β*-oxygen elimination is preferred over *β*-hydride elimination, due to the strain release of the epoxide, generating a rhodiumalkoxide **89**. Finally, protonolysis affords the isolated product **86**.



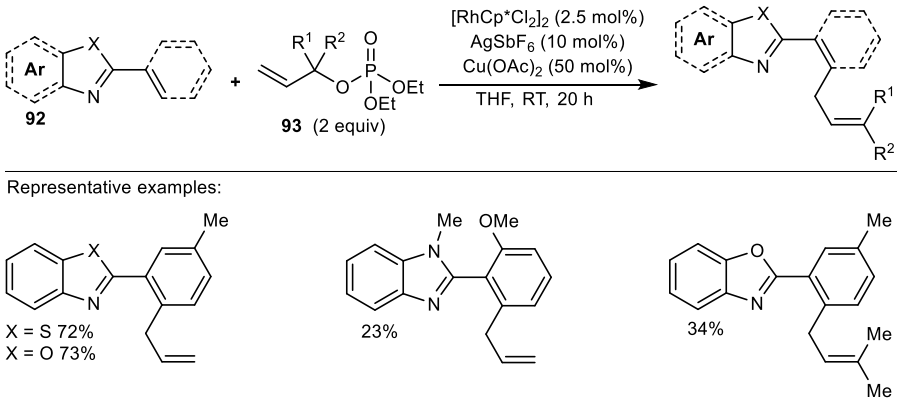
Scheme 29. Postulated catalytic cycle generating allylic alcohols from 2-vinyloxiranes

An elegant and rare methodology where *N*-methoxyarylketoimines **90** were alkenylated catalytically *via* a Rh(III) and $AgSbF_6$ system with $Cu(OAc)_2$ as a stoichiometric oxidant was reported by Ellman and Bergman (Scheme 30).[78] This procedure is interesting because it successfully couples alkenes **91** that are considered to be less reactive, for example alkyl-substituted alkenes, as well as traditionally encountered, more reactive styrenes and acrylates. The number of synthetic strategies that utilise less reactive alkenes are limited, therefore these type of investigations should be encouraged.[55] Furthermore, common functional groups, such as hydroxyl, halogen and nitrile, were able to survive the reactions moderate conditions. The only disadvantages here would be the increased catalyst loading as well as the amount of alkene (3 equiv) required for a synthetically viable yield. Recently, oximes were also used to synthesise isoquinolines *via* oxidative Rh(III) catalysis.[79]



Scheme 30. Rh(III)-catalysed C–H alkenylation of ketoimines

More recently, oxazoles **92**, thiazoles **92** and imidazoles **92** were exploited performing allylation reactions using allyl acetates, -carbonates and –phosphonates **93**, as well as vinyl dioxanones and -oxiranes (Scheme 31).[80] Electron-rich arenes generally afforded higher yields in comparison to electron-poor. Biallylation was generally encountered unless a substituent was placed at the *ortho*- or *meta*-position.



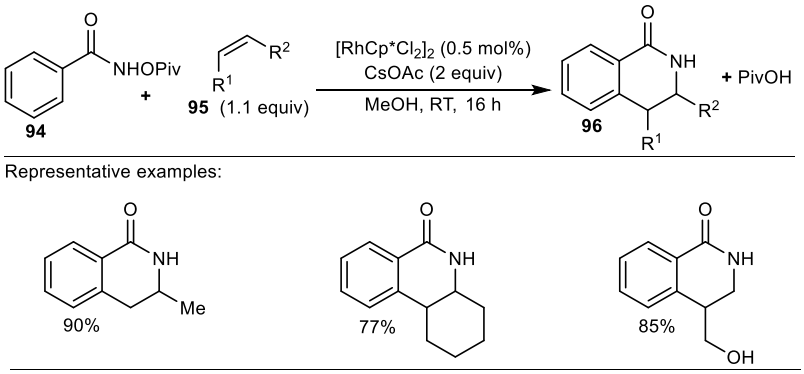
Scheme 31. Oxazoes, thiazoles and imidazoles as directing groups in Rh(III)-catalysed allylations

1.8 Oxidative C–H activation using internal oxidants

Throughout oxidative metal catalysis traditionally an external oxidant is necessary to regenerate the active catalyst. As a result, the reduced product of the oxidant is generated as waste. A more environmentally friendly alternative exploits the ability of certain directing groups to act as internal oxidants thus eliminating the need for stoichiometric oxidants.[81,82]

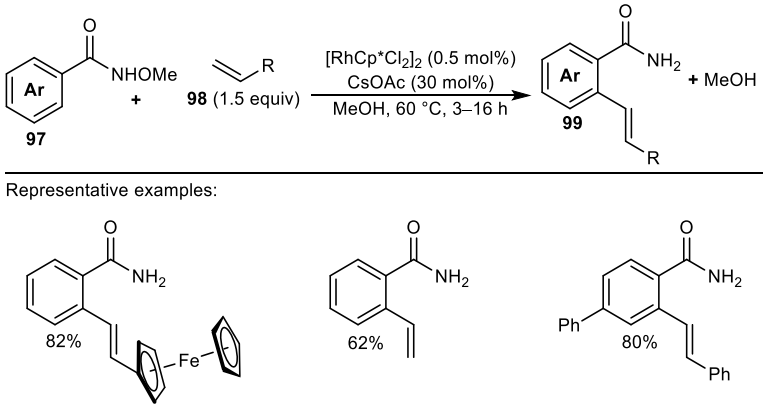
1.8.1 *N*-Alkoxybenzamides and derivatives as the directing group

Innovative work was conducted by Guimond and co-workers whom discovered the first examples of Rh(III)-catalysed, overall redox neutral synthesis of N–H isoquinolones *via* catalytic *ortho*-C–H activation of *N*-methoxybenzamides with alkynes.[83] As part of their studies with alkynes they showed that alkenes **94** could also be coupled to *N*-pivaloylbenzamides **95** (Scheme 32).[84] Impressively, here the *N*-pivaloylamide group functioned both as a directing group as well as an oxidant, and was incorporated into the target molecule **96** at the end of the cycle. This methodology used $[RhCp^*Cl_2]_2$ (0.5 mol%) as the catalyst and CsOAc (2 equiv) as an acetate additive. Importantly, both electron-rich and -poor, internal and terminal alkenes were readily coupled at room temperature with various functional groups being tolerated. Furthermore, heterobicyclic alkenes can also undergo this transformation.[85]



Scheme 32. Rh(III)-catalysed C–H functionalisation of *N*-pivaloxybenzamides and alkenes

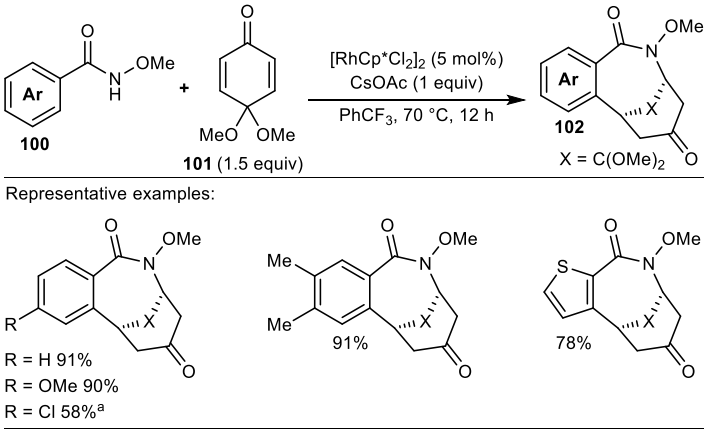
On the other hand, Glorius established that under slightly different conditions Rh(III)-catalysed redox-neutral coupling of *N*-methoxybenzamides **97** with activated alkenes **98** such as styrenes and acrylates afforded *ortho*-alkenylated primary benzamides **99**.[86] In most cases, monoalkenylation was observed (Scheme 33). These results contradicted the original studies carried out by Guimond in which *N*-pivaloxybenzamides afforded dihydroxyquinolones **96** (Scheme 32).[84] This clearly stated that the appropriate choice of directing group determined the selectivity of the reaction with respect to product formation. In addition, Glorius showed that the *ortho*-alkenylated primary benzamides were not possible intermediates under Guimond's conditions yielding the dihydroxyquinolones. Recently, allyl acetates were also coupled to *N*-methoxybenzamides to give either alkenylated or allylated products; this was dictated by the solvent.[87]



Scheme 33. Rh(III)-catalysed C–H alkenylation of *N*-methoxybenzamides

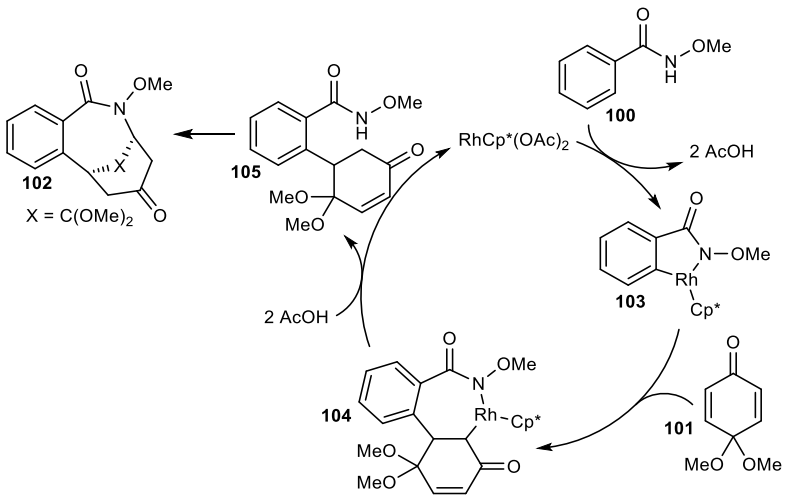
Interestingly, recently an example of Rh(III) catalysis involving C–H activation of *N*-methoxybenzamides **100** was reported in which rhodium exists in the same oxidation

state throughout the entire transformation.[88] Herein, quinone monoacetals **101** are used as the coupling partner, enabling access to bridged 9-membered heterocycles **102** (Scheme 34). Arenes incorporating electron-withdrawing substituents generally required high catalyst loadings to proceed efficiently.



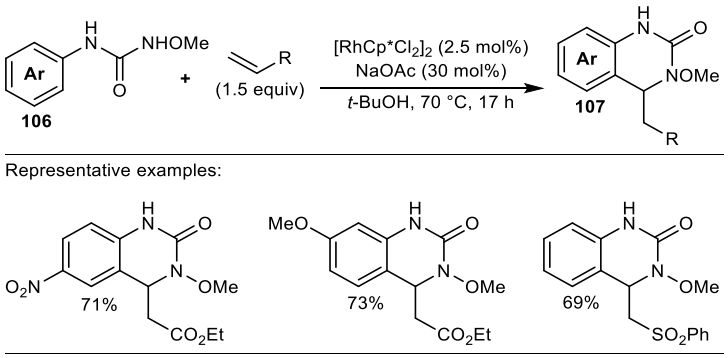
Scheme 34. Rh(III)-catalysed coupling of *N*-methoxybenzamides to quinone monoacetals. [a] Conducted using $[RhCp^*Cl_2]_2$ (10 mol%)

A catalytic cycle was reported in which $Rh(OAc)_2$ reacted with *N*-methoxybenzamide **100** to form rhodacycle **103** and two equivalents of AcOH (Scheme 35). Coordination and migratory insertion of the quinone monoacetal **101** resulted in intermediate **104**. Acetolysis of the rhodium complex **104** afforded intermediate **105**, which was then able to undergo, in the presence of a base, an intramolecular aza-Michael addition furnishing the desired product **102** as well as regenerate the catalytically active Rh(III) species.



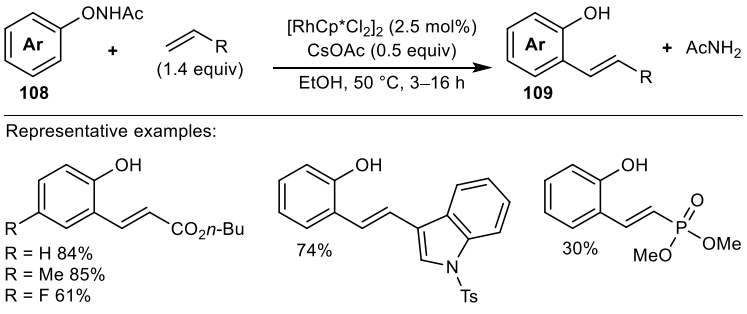
Scheme 35. Proposed catalytic cycle generating 9-membered heterocycles

Glorius expanded upon the applications of *N*-methoxybenzamides with the use of structurally similar *N*-methoxy-*N*'-aryl ureas **106** as both directing groups and internal oxidants (Scheme 36).[89] Interestingly, the use of external oxidants in this transformation were less effective in comparison, thus highlighting the superior nature of the N–O bond of the ureas. In addition, the *N*–OMe bond remained intact in the cyclised products **107**. It was also demonstrated that the hydroamination step could simply be catalysed by NaOAc.



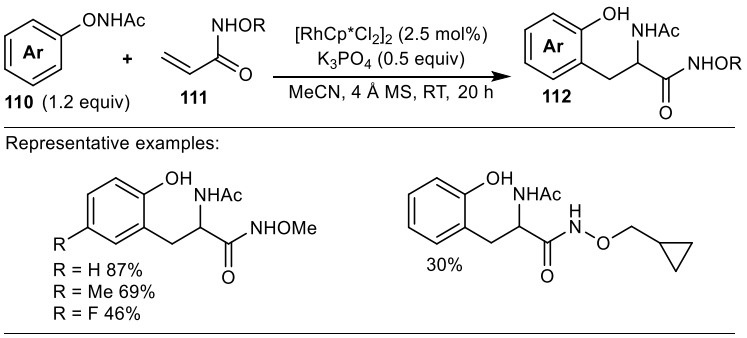
Scheme 36. Rh(III)-catalysed C–H functionalisation of *N*-methoxy-*N*'-aryl ureas and alkenes

An analogous approach by Lu and co-workers utilises the acetamido group as an internal oxidant in *N*-phenoxyacetamides **108** to generate alkenylated phenols **109** as the products and acetamide (Scheme 37).[90] Similar to previous examples, this chemistry relies on the N–O cleavage which re-oxidises the catalyst. The reaction generally uses activated alkenes, such as acrylates, acrylamides, styrenes and cyano- or phosphonoacetate-substituted alkenes. Furthermore, substitution about the aryl ring is tolerated, though electron-deficient systems generally result in lower yields.



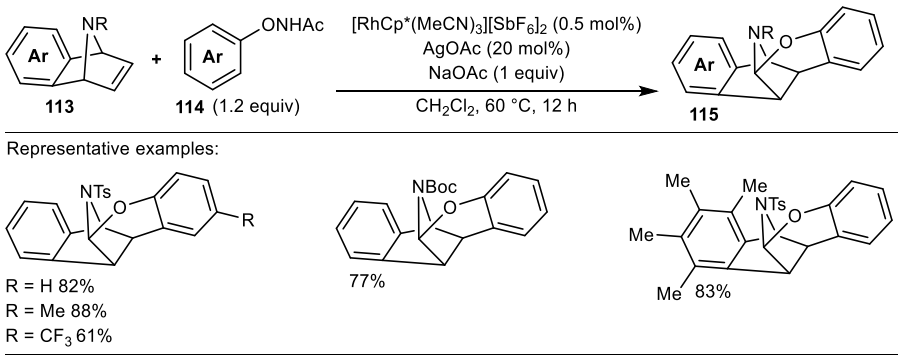
Scheme 37. *N*-phenoxyacetamides as internal oxidants in Rh(III)-catalysed alkenylations

Using *N*-alkoxyacrylamides **111** as the coupling partner for *N*-phenoxyacetamides **110**, Lu was also able to produce acyclic alkene carboamination products **112**, as opposed to alkenylated, under redox-neutral conditions (Scheme 38).[91] The amide group in the *N*-alkoxyacrylamides was necessary for the C–N bond formation step. Regarding the *N*-phenoxyacetamide scope, substituents about the arene were tolerated, similarly electron-withdrawing groups generally lowered the efficacy of the transformation.



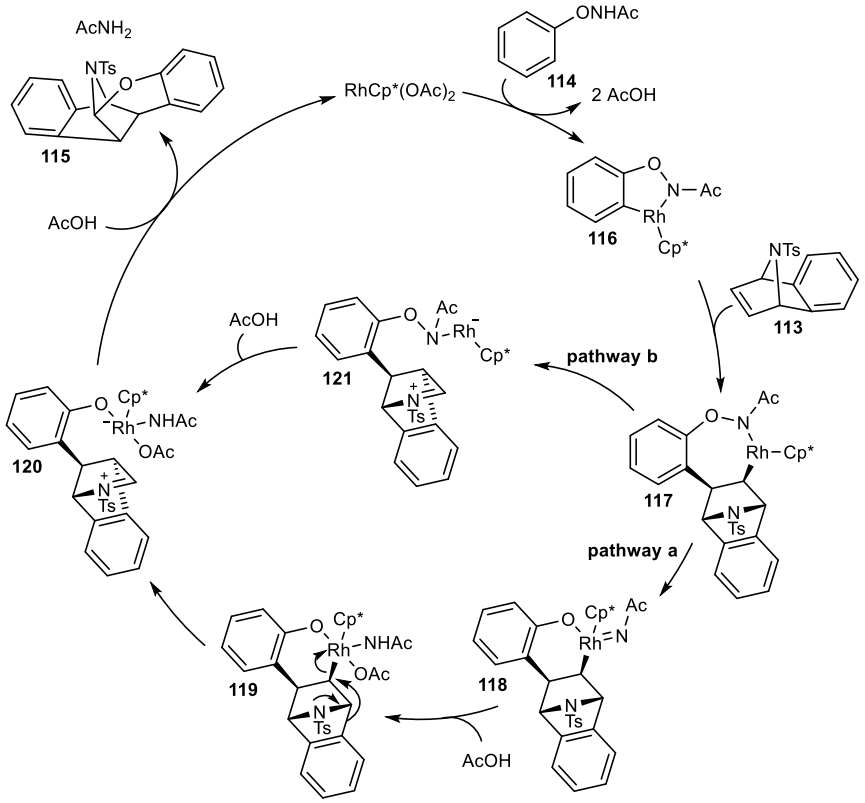
Scheme 38. *N*-phenoxyacetamides as internal oxidants in Rh(III)-catalysed carboaminations

Impressively, using 7-azabenzonorbornadiene **113** and *N*-phenoxyacetamides **114** bridged polycyclic molecules **115** could be synthesised (Scheme 39).[92] This methodology involved combining Rh(III) C–H activation with a Wagner-Meerwein-type rearrangement. The reaction proceeded smoothly in the presence of electron-rich or -neutral substituents about the aryl ring of the *N*-phenoxyacetamide as well as the 7-azabenzonorbonadiene, though electron-deficient aryls hindered the reaction in both cases.



Scheme 39. Rh(III)-catalysed coupling of *N*-phenoxyacetamides and 7-aza-benzonorbornadienes

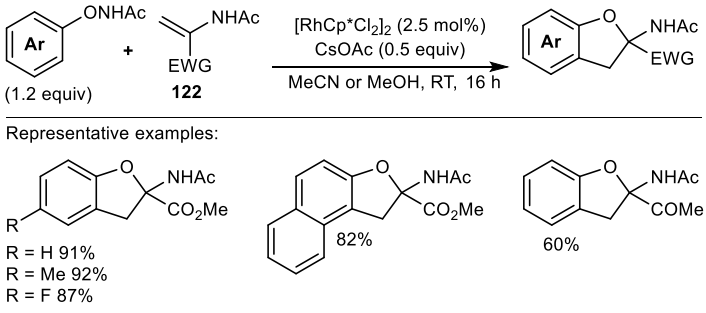
A catalytic cycle is postulated in which the catalytically active species $RhCp^*(OAc)_2$ is formed *in situ* followed by C–H activation of the *N*-phenoxyacetamide **114** generating rhodacycle **116** (Scheme 40). Coordination and migratory insertion of the alkene **113** allows a 7-membered rhodacycle **117** to be formed. Next, cleavage of the N–O bond by Rh(III) generates a Rh(V) nitrene species **118**, which after acetolysis gives **119**. The high in oxidation state Rh(V) complex **119** rearranges to form a Rh(III) intermediate **120**, which upon subsequent intramolecular nucleophilic attack of the phenolate at the iminium yields the product **115**, as well as acetamide and the catalytically active $Rh(OAc)_2$ by ligand exchange. An alternative pathway involves a Wagner-Meerwein-type rearrangement of **117** to **121**, followed by oxidative addition in the presence of AcOH to generate the common intermediate **120**.



Scheme 40. Proposed catalytic cycle of Rh(III)-catalysed coupling of *N*-phenoxyacetamides and 7-aza-benzonorbornadienes

The use of *N*-phenoxyacetamides has also been found in carbooxygenation reactions, this time using 1,1-disubstituted alkenes **122** incorporating the crucial acetamido moiety (Scheme 41).[93] The reaction proceeds well regardless of the electronic and steric nature of the substituents about the aryl ring of the *N*-phenoxyacetamide. A key limitation here being the necessity of an electron-withdrawing substituent at the 1-

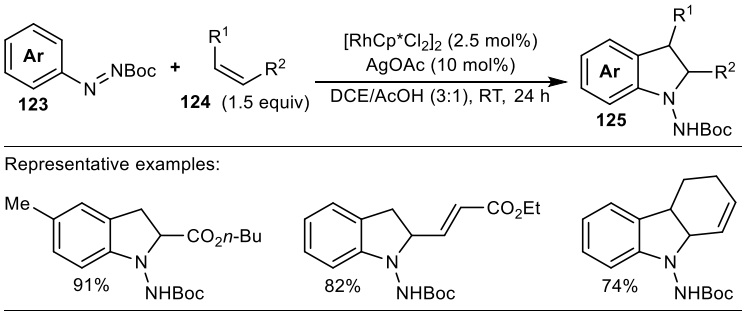
position of the alkene. Additionally, only terminal alkenes expressed any reactivity. Interestingly, using 3,3-disubstituted cyclopropenes as the coupling partner yielded transannulated products.[94]



Scheme 41. Rh(III)-catalysed coupling of *N*-phenoxyacetamides and 1,1-disubstituted alkenes

1.8.2 Diazenecarboxylates as the directing group

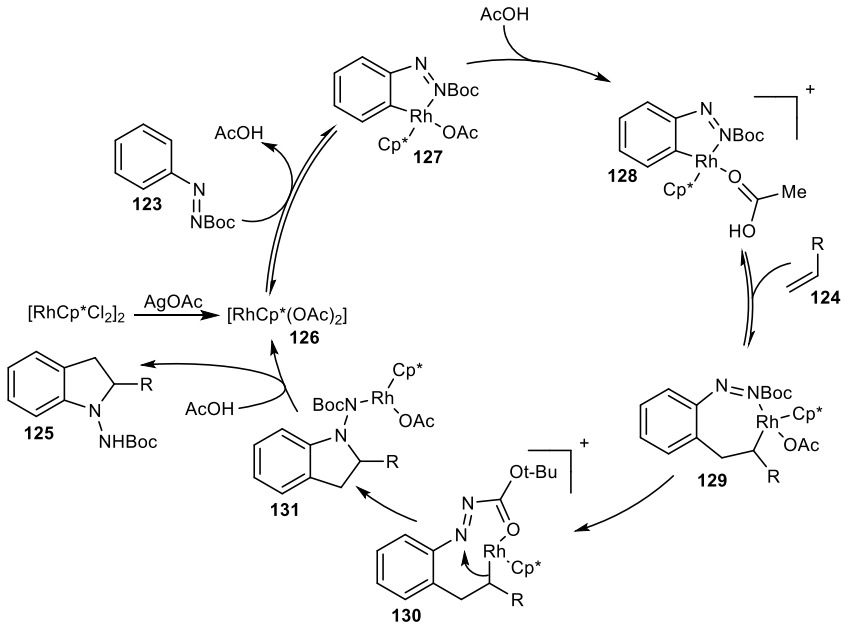
Very recently, Glorius reported the use of diazenecarboxylates **123** as efficient directing groups yielding 1-aminoindoline derivatives **125** at room temperature without the use of external oxidants (Scheme 42).[95] Herein, $[RhCp^*Cl_2]_2$ (2.5 mol%) was used as the catalyst along with AgOAc (10 mol%) which was involved in the halogen exchange of the catalyst. With respect to the aryl ring, a range of functional groups including alkyl, aryl, halogen, ester and ether groups were tolerated. The alkenes **124** used as coupling agents were generally styrenes and acrylates, with two examples of 1,3-dienes.



Scheme 42. Rh(III)-catalysed C–H functionalisation of diazenecarboxylates and alkenes

A catalytic cycle is postulated based on mechanistic studies and literature precedent (Scheme 43).[95] The active Rh(III) species **126** coordinates to diazenecarboxylate **123** forming intermediate **127**. Next, an acetate ligand dissociates with the aid of AcOH

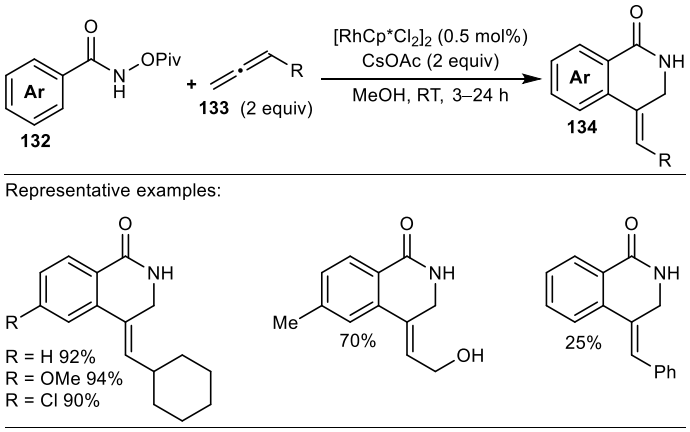
forming a cationic Rh(III) complex **128**.[96] Subsequently, the alkene **124** once coordinated to the metal centre inserts generating a 7-membered rhodacycle intermediate **129**. Presumably, rhodacycle **129** rearranges to a more stable 6-membered coordinatively saturated Rh(III) species **130** by chelation with the Boc group, which prevents the competitive *β*-hydride elimination.[95] Consequently, intermediate **130** may undergo a nucleophilic addition to the N=N forming the cyclised intermediate **131**. Finally, acetolysis by AcOH affords the desired product **125**.



Scheme 43. Postulated catalytic cycle wherein diazenecarboxylates initiate a novel cyclative capture

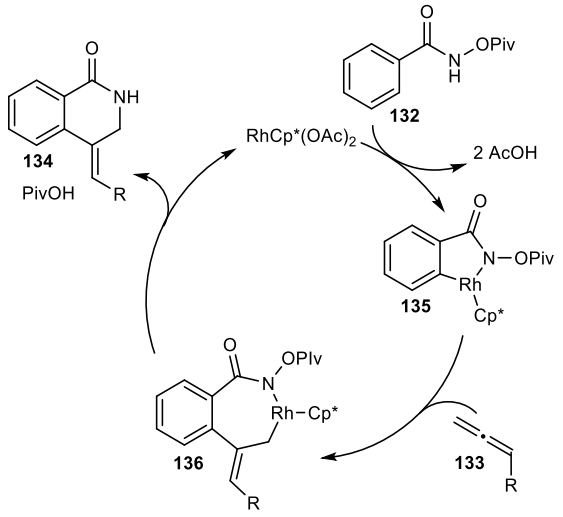
1.9 Miscellaneous oxidative C–H activation catalysis using allenes, 1,3-dienes and ketenes as coupling partners

The 1,3-diene and allene moieties are highly valuable and versatile synthetic intermediates in organic synthesis.[97–99] Despite their critical importance, their use as coupling partners in C–H activation has been rarely exploited, particularly under Rh(III) conditions. The first example utilising allenes **133** *via* Rh(III) catalysis was reported by Glorius in 2012 (Scheme 44).[100] This methodology used *N*-pivaloxybenzamides **132** as the ideal coupling partners due to the ability of the N–O bond to act as the internal oxidant. Here, annulated products **134** are synthesised, incorporating a broad range of electronically different substituents, generally in good to excellent yields.



Scheme 44. Rh(III)-catalysed annulation of *N*-pivaloxybenzamides with allenes

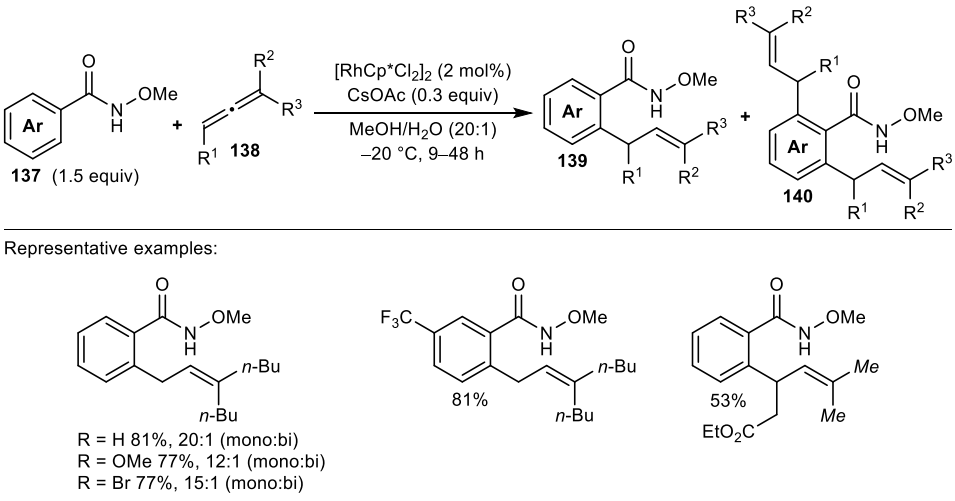
Regarding the catalytic process, $Rh(OAc)_2$ in the presence of the *N*-pivaloxybenzamide **132** undergoes carborhodation to give **135** (Scheme 45). Next, migratory insertion of the allene **133** at the less sterically hindered site generates rhodacycle **136**. As a final point, reductive elimination affords product **134** and PivOH. Concurrently, N–O bond cleavage results in the re-oxidation of Rh(I) to Rh(III).



Scheme 45. Proposed catalytic cycle annulation of *N*-pivaloxybenzamides with allenes

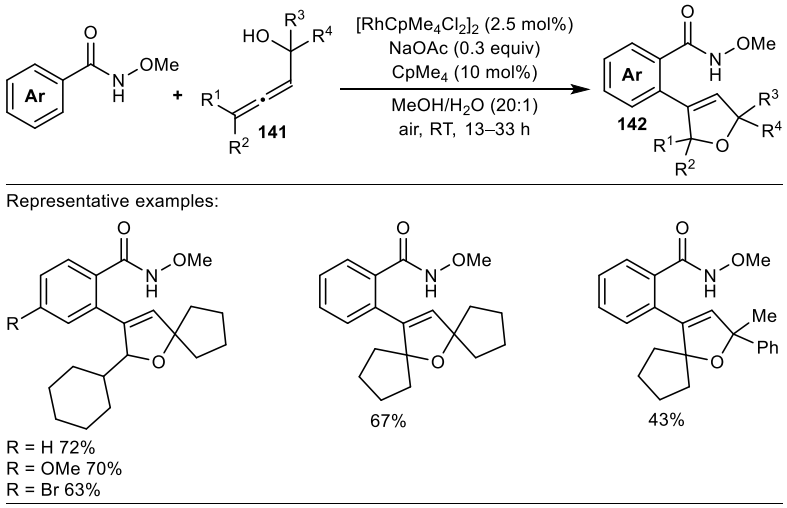
This work was closely followed by Ma's findings in 2012, using *N*-methoxybenzamides **137** and allenes **138** to afford allylated products **139** and **140** (Scheme 46).[101] Interestingly, Glorius reported no reactivity using *N*-methoxybenzamide with his conditions. As a general note, both mono- and biallylation was observed, though the products could be separated. Additionally, biallylation could

be prevented by using of *ortho*- or *meta*-substituents. Also, internal allenes yielded monoallylated products exclusively.



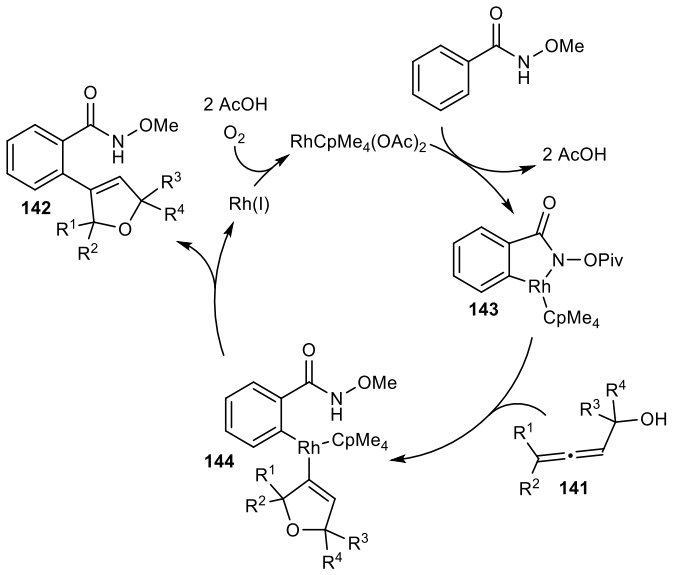
Scheme 46. Rh(III)-catalysed C–H allylation of *N*-methoxybenzamides with allenes

Ma elaborated upon his work by including tertiary allenols **141** to afford 2,5-dihydrofuran derivatives **142** (Scheme 47).[102] Interestingly no bi-C–H functionalisation was observed, unlike the previous chemistry. Both electron-donating and -withdrawing substituents about the benzamide resulted in good yields. Initially, $[RhCp^*Cl_2]_2$ was used as the catalyst, though when the cyclopentadienyl ligand was altered to tetramethylcyclopentadiene ($CpMe_4$) the conversion increased. Moreover, it was shown that when $CpMe_4$ was used as a catalytic additive accompanying $[RhCpMe_4Cl_2]_2$ the conversion increased even further. Based on their preliminary screening, it was postulated that the bulk of the ligand on Rh(III), was important in achieving good yields. Notably, the N–O bond remained intact throughout this transformation suggesting that O_2 was the sole oxidant. Subsequent studies by Liu and Lu showed that primary and secondary allenols afforded γ-lactams as the products.[103]



Scheme 47. Rh(III)-catalysed C–H functionalisation of *N*-methoxybenzamides and allenes generating 2,5-dihydrofurans

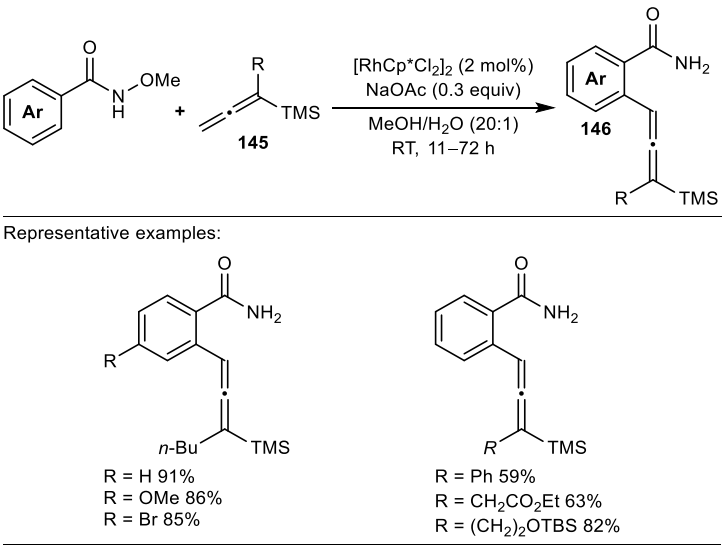
Four potential catalytic pathways were considered, out of which the most likely one was outlined (Scheme 48). The catalytically active species RhCp*($CpMe_4$) underwent carborhodation with the appropriate benzamide generating rhodacycle **143**. Followed by coordination of allene **141** to Rh(III) and cyclic oxyrhodation giving intermediate **144**. Upon reductive elimination the desired product **142** was released as well as Rh(I), which in turn was re-oxidised by O_2.



Scheme 48. Proposed catalytic cycle generating 2,5-dihyfrofurans

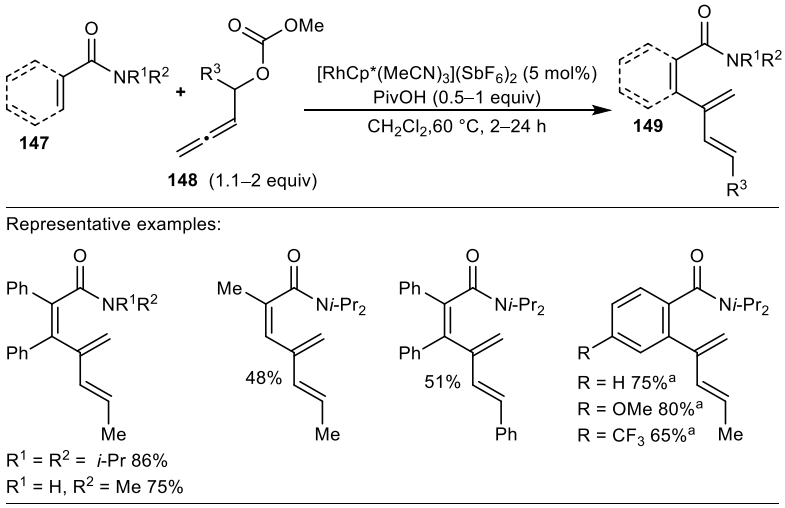
Similarly, Ma and colleagues have also coupled allenylsilanes **145** with *N*-methoxybenzamides affording alkenylated products **146** in good to excellent yields (Scheme 49).[104] The transformation worked efficiently at room temperature,

regardless of the substituents about the benzamide. With respect to the reaction scope using allenes, only terminal allenes were effective, though only TMS-substituted allenes were reported. Interestingly, in these examples the N–O bond was cleaved thus acting as an internal oxidant. This methodology was later modified using allenylsilanes incorporating a homoallyl moiety, furnishing 8-membered lactams as the products.[105]



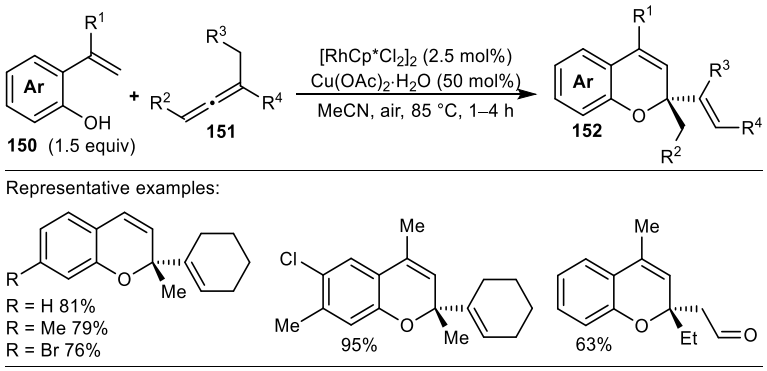
Scheme 49. Rh(III)-catalysed C–H allenylation of *N*-methoxybenzamides with allenes

Furthermore, Glorius successfully coupled allenyl carbinol carbonates **148** with alkenyl amides **147** thus incorporating the 1,3-diene moiety in the target product **149** (Scheme 50).[106] A wide range of products were synthesised using this methodology. In particular, the *N*-moiety in the directing group could be changed and both substituted alkenes and arenes could be used without hindering the efficiency of the reaction. Also, terminal allenes were necessary, though various allenyl carbinol carbonates were tolerated. More recently, allenyl esters were also utilised to give similar conjugated alkenes as the products.[107] An enantioselective approach was also developed by Cramer and co-workers.[42]



Scheme 50. Rh(III)-catalysed C–H functionalisation of *N*-methoxybenzamides and allenes. [a] Conducted using $Cu(OAc)_2$ (15 mol%) as an additive

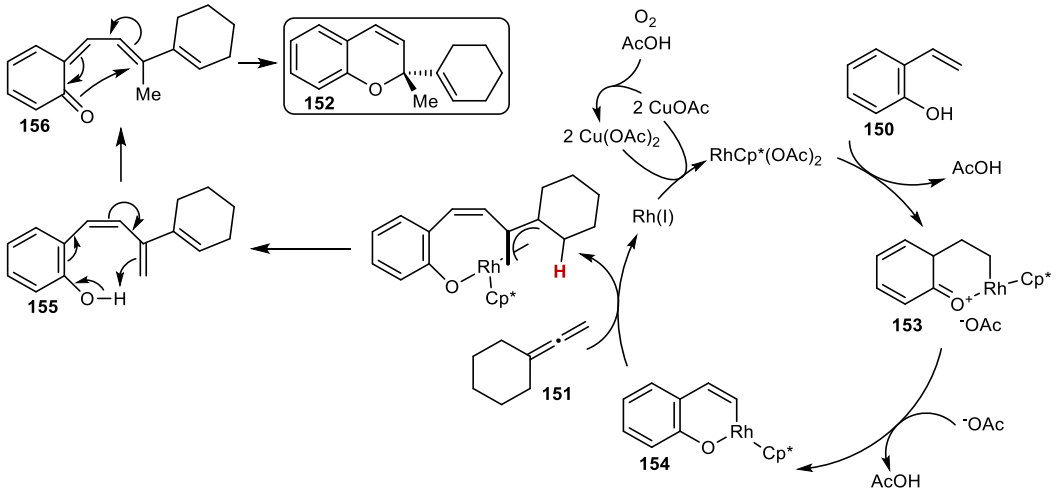
Mascereñas and Gulías have successfully used 2-alkenylphenols **150** as both the directing group and nucleophile affording 2*H*-chromenes **152** when reacted with allenes **151** (Scheme 51).[108] This methodology resembled Ma's, in which allenols were used as the nucleophile when coupled with benzamides (Scheme 47).[102] A range of substituents about the phenols were reported, as well as a good functional group tolerance with respect to the allene moiety. Interestingly, in the case of primary and secondary allenols, the corresponding aldehydes and ketones were afforded respectively.



Scheme 51. Rh(III)-catalysed annulation of 2-alkenylphenols with allenes

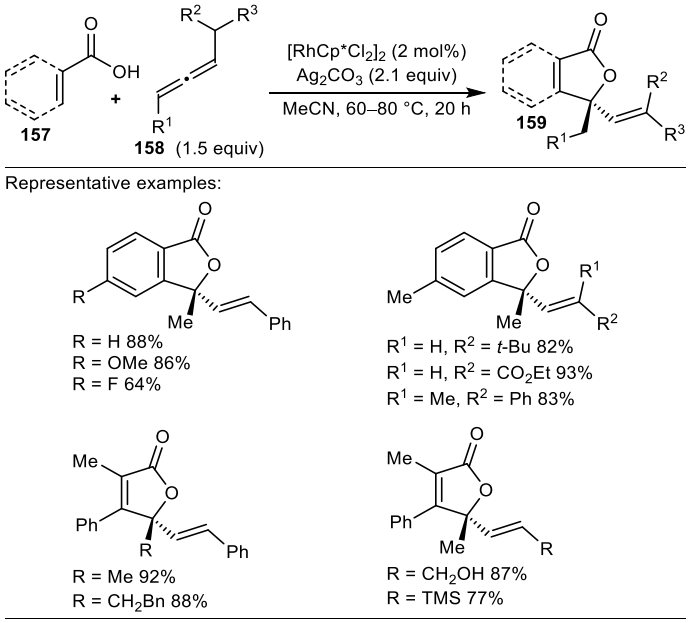
Based on deuterium studies the researchers proposed the following catalytic cycle (Scheme 52). The cycle is likely initiated by coordination of $RhCp^*(OAc)_2$ to the appropriate phenol **150**, with subsequent intramolecular attack of the conjugated alkene on the Rh(III) centre to give intermediate **153**. Next, re-aromatisation results in

intermediate **154** that is then able to coordinate to the relevant allene **151**, forming a π-allylrhodium species **155**. A 1,3-allylic transposition and β-hydride elimination followed by a [1,7]-proton transfer forms enone **156**, which is then able to undergo a 6π-electrocyclic rearrangement furnishing product **152**. The catalytically active Rh(III) species is regenerated by Rh(I) oxidation.



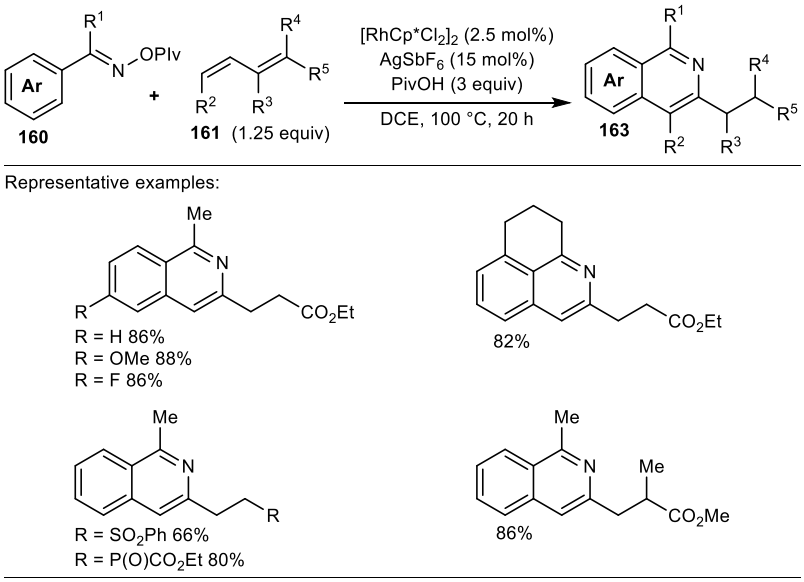
Scheme 52. Proposed catalytic cycle generating 2*H*-chromenes

Aryl and alkenyl carboxylic acids **157** have also demonstrated their utility in Rh(III)-catalysed C–H functionalisation reactions with allenes **158** affording annulated products **159** (Scheme 53).[109] The alkenyl and aryl moiety of the carboxylic acids have a broad functional group tolerance, though electron deficient systems generally provided lower yields. Substitution at both termini of the allene were also tolerated. Importantly, comparing this methodology to those previously reported by Glorius, Ma, and Gulías in which similar allenes are used (Schemes 44, 46 and 51), it is clear that the choice of directing group dictated what type of transformation took place, *i.e.* [4+1], [4+2] annulation, allylation and [5+1] annulation respectively.[100,101,108,109]



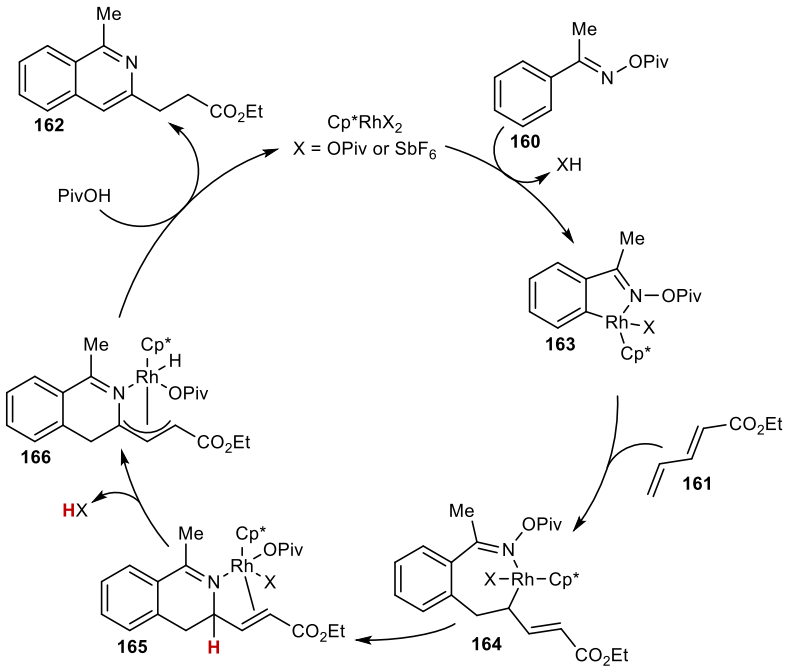
Scheme 53. Rh(III)-catalysed annulation of carboxylic acids with allenes

In 2014, Glorius demonstrated that 1,3-dienes **161** can undergo oxidative annulation reactions with *N*-pivaloxyketimines **160** to generate isoquinolines **162** *via* C–H activation followed by aromatisation (Scheme 54).[97] Both electron-rich and -poor substituents are tolerated about the arene. Polysubstituted dienes consisting of different functionality are employed, though in all examples an electron-withdrawing functional group is necessary. Herein, the N–O bond in the directing group is utilised as the internal oxidant. Certain substrates require the use of stoichiometric AgOAc (2.1 equiv) to achieve reactivity. Thus far, this is the only methodology in the literature in which 1,3-dienes are utilised under oxidative or redox-neutral Rh(III) catalysis.



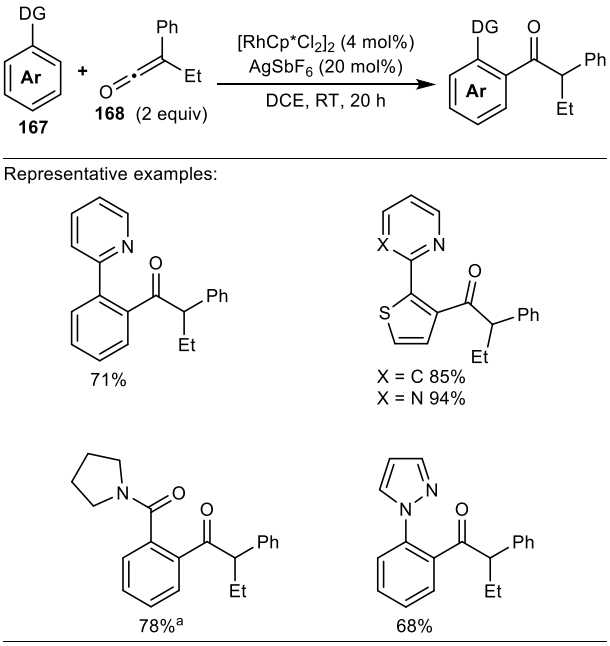
Scheme 54. Rh(III)-catalysed C–H functionalisation of *N*-pivaloxyketimines and 1,3-dienes

The proposed catalytic cycle is initiated by generating a Rh(III) complex by ligand exchange from $[RhCp^*Cl_2]_2$ with $AgSbF_6$ and PivOH, followed by C–H activation of oxime **160** forming rhodacycle **163** (Scheme 55). Next coordination and insertion of diene **161** generates a 7-membered rhodacycle **164**. Rhodacycle **164** could undergo a C–N bond formation and N–O bond cleavage accompanied by a double bond coordination generating complex **165**. Subsequently, β-hydride abstraction allows π-allylrhodium hydride species **166** to form. The desired isoquinoline **162** is then furnished *via* isomerisation and re-aromatisation of the molecule.



Scheme 55. Proposed catalytic cycle generating isoquinolines

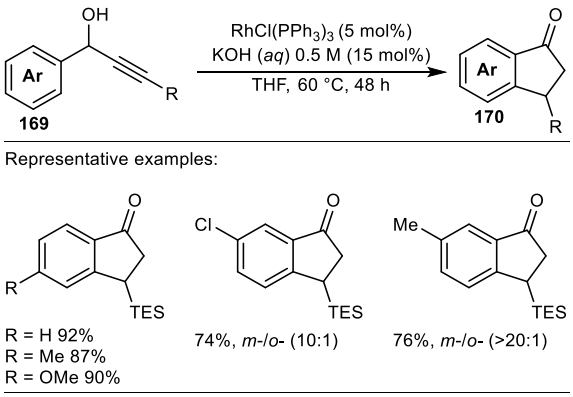
The ketene moiety has also been largely underexplored in Rh(III) catalysis. To date only a single methodology has been reported, in which ketenes **168** are used as acylating agents for arenes **167** bearing *N*-heteroarenes or amides as directing groups, under redox-neutral Rh(III) conditions (Scheme 56).[110] An extensive ketene scope was not reported.



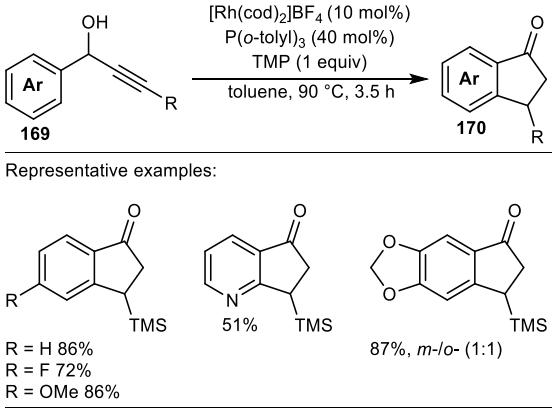
Scheme 56. Rh(III)-catalysed C–H acylation of arenes with ketenes

1.10 1,4-Rhodium migration from C(sp^2) to C(sp^2) centres

Rhodium, in particular Rh(I), is the second most widely documented metal capable of undergoing a 1,4-migration. Out of which, migration from C(sp^2) to C(sp^2) centres is the most reported. The first example demonstrating a vinyl-to-aryl Rh(I) migration was reported independently by Hayashi and Iwasawa, in 2005.[111,112] Herein, silyl substituted alkynes **169** are transformed into indanones **170** *via* Rh(I) catalysis (Scheme 57 and 58). In comparison, both methodologies employ similar conditions, though Hayashi's are less harsh. Furthermore, substrates having *meta*-substitution result in a mixture of regioisomers. Both methodologies can tolerate a range of substituents about the arene moiety of the alkyne and comparable yields are obtained in examples in which similar substrates are used. Additionally, an enantioselective variant of this process has been developed.[113]

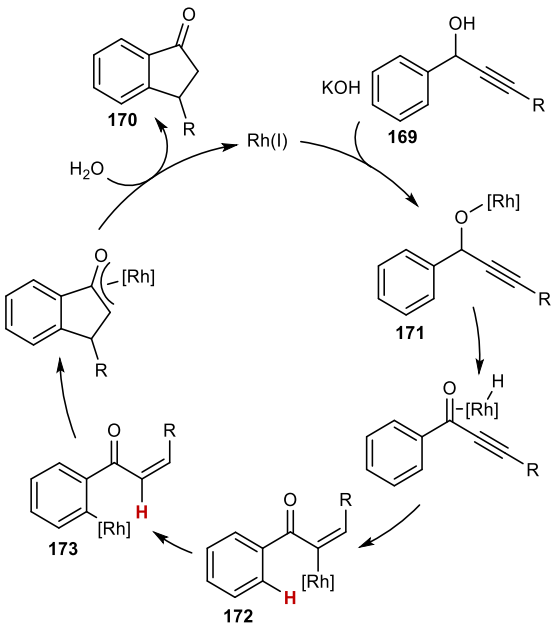


Scheme 57. Vinyl-to-aryl 1,4-rhodium migration (Hayashi's conditions)



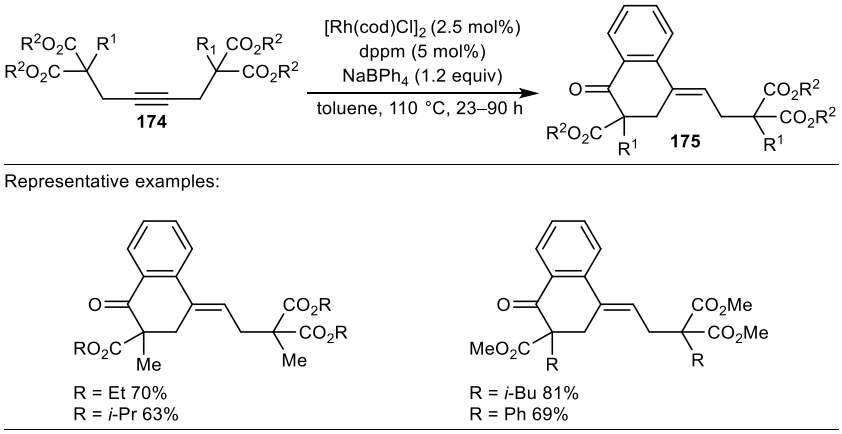
Scheme 58. Vinyl-to-aryl 1,4-rhodium migration (Iwasawa's conditions)

The proposed mechanism for the formation of **170** is shown in Scheme 59. In the presence of a base the alkoxyrhhodium intermediate **171** was formed. Subsequently, *β*-hydride elimination followed by hydrorhodation would generate vinylrhodium species **172**. Next, rhodium could undergo a 1,4-migration forming arylrhodium intermediate **173**. Upon an intramolecular conjugate addition and protonolysis the desired product **170** was furnished, as well as the catalytically active Rh(I) complex.



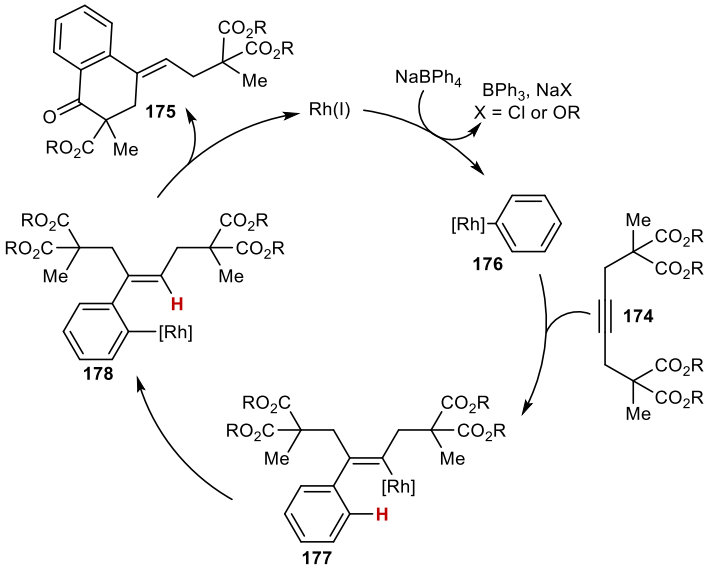
Scheme 59. Proposed catalytic cycle in which vinyl-to-aryl 1,4-rhodium migration occurs

Recently, several methodologies were developed in which boron species were used to introduce various arenes, generally across alkynes *via* transmetallation with the rhodium catalyst. This then enabled rhodium to further functionalise the molecule exploiting its ability to undergo a 1,4-migration. Early studies were performed by Hayashi showing that Rh(I) was able to achieve the aforementioned.[114] This was developed thereafter by Murakami and colleagues.[115,116] Here, alkynes **174** are reacted with $NaBPh_4$ (1.2 equiv), in the presence of $[Rh(cod)Cl]_2$ (2.5 mol%) and dppm (5 mol%), affording ketones **175** (Scheme 60).



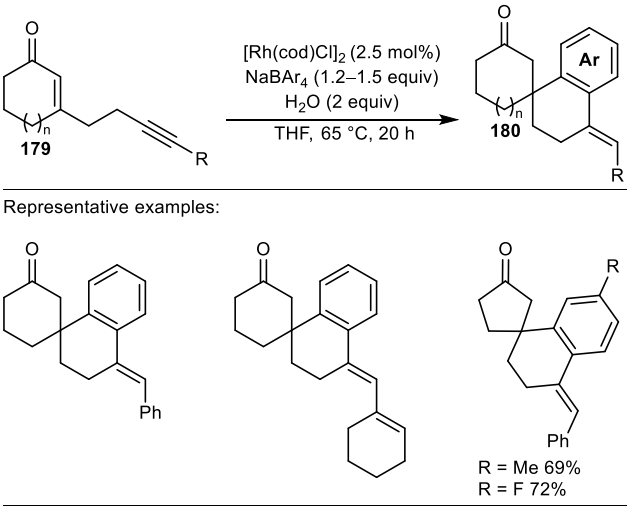
Scheme 60. Vinyl-to-aryl 1,4-rhodium migration followed by cyclisation

A proposed catalytic cycle was reported in which Rh(I) species underwent transmetallation with $NaBPh_4$ forming arylrhodium intermediate **176** (Scheme 61). This was followed by insertion across alkyne **174** generating vinylrhodium(I) species **177**, capable of migrating to the aryl position and forming **178**. Finally, intramolecular cyclisation onto the proximal ester afforded ketone **175**.



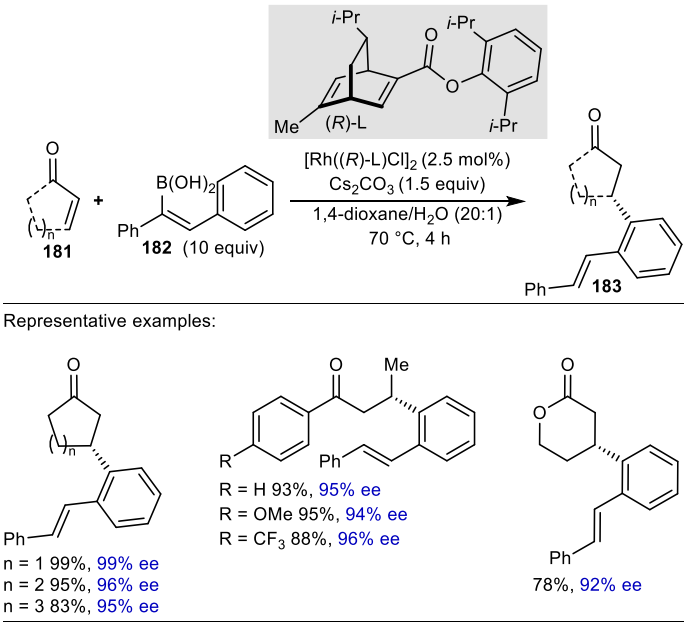
Scheme 61. Proposed catalytic cycle in which vinyl-to-aryl 1,4-rhodium migration occurs

An analogous methodology was developed wherein the product forming step involved a conjugate addition yielding spirocarbocycles **180** (Scheme 62).[117] A range of internal alkynes **179** and sodium tetraarylborates were used successfully. This was also achieved enantioselectively.[117]



Scheme 62. Vinyl-to-aryl 1,4-rhodium migration followed by conjugate addition

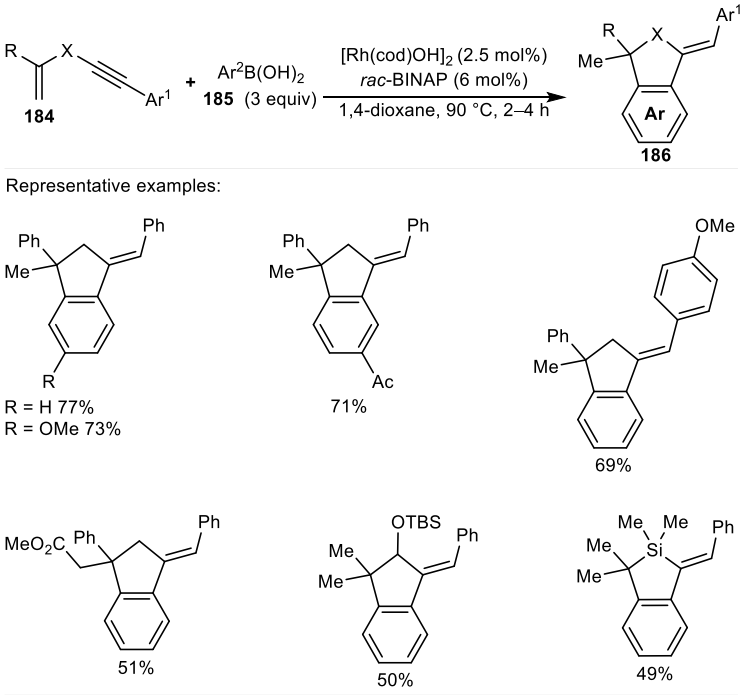
An enantioselective intermolecular variant has also been developed using vinylboronic acid **182** and enones **181** (Scheme 63).[118,119] Here, the 1,4-addition products **183** were synthesised in good to high yields and excellent enantioselectivity. It should be noted that the enantioselectivity was marginally affected by the electronics and size of the enone employed.



Scheme 63. Vinyl-to-aryl 1,4-rhodium migration followed by enantioselective conjugate addition

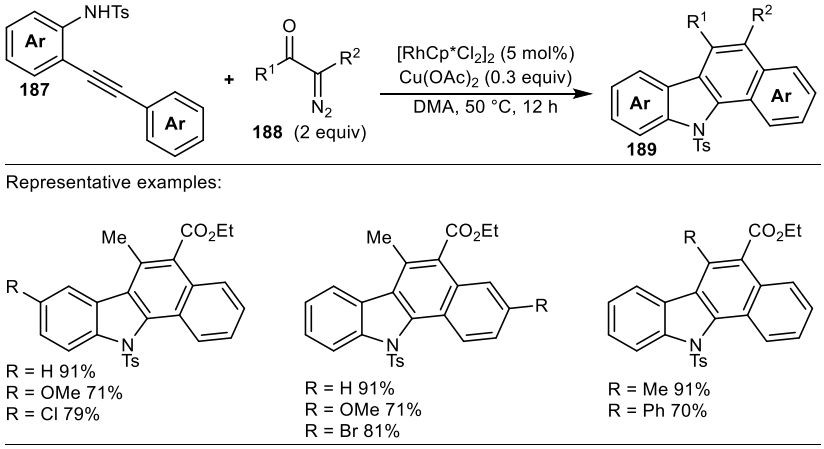
Similarly, 1,4-enynes **184** were annulated with arylboronic acids **185** *via* a vinyl-to-aryl 1,4-rhodium migration followed by an intramolecular addition to the pendant alkene moiety (Scheme 64).[120] Annulated products **186** were obtained in moderate to

good yields. Regarding the scope of the 1,4-enyne, only aryl substituents at the alkyne terminus were reported, whereas both alkyl and aryl groups were successful at the 2-position of the alkene. Interestingly, silicon could be incorporated into the enyne, as opposed to having a methylene linker between the alkene and alkyne moieties. Preliminary enantioselective studies were also conducted.



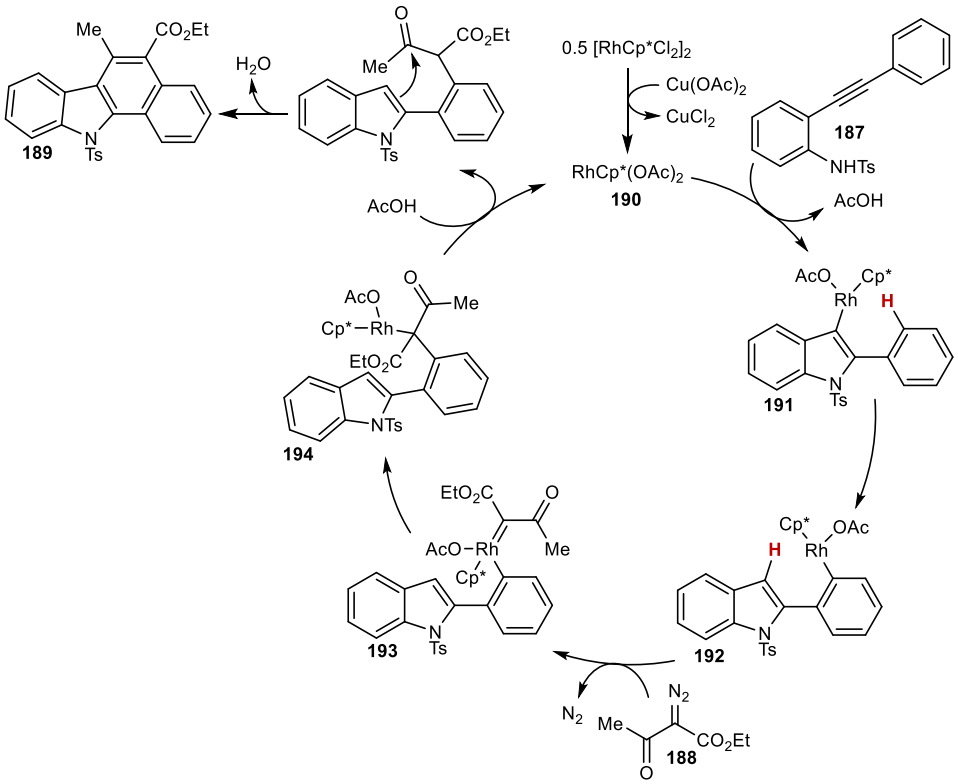
Scheme 64. Vinyl-to-aryl 1,4-rhodium migration followed by cyclisation

Furthermore, Yao reported the first aryl-to-aryl Rh(III) migration wherein benzo[α]carbazoles **189** were synthesised from alkynes **187** and diazo compounds **188** (Scheme 65).[121] The reaction tolerated a wide range of substituents about both aryl rings of **189**, though both electron-rich and -poor generally decreased the yields. This was more aparent in electron-rich systems.



Scheme 65. Synthesis of benzo[α]carbazoles *via* an aryl-to-aryl 1,4-rhodium migration

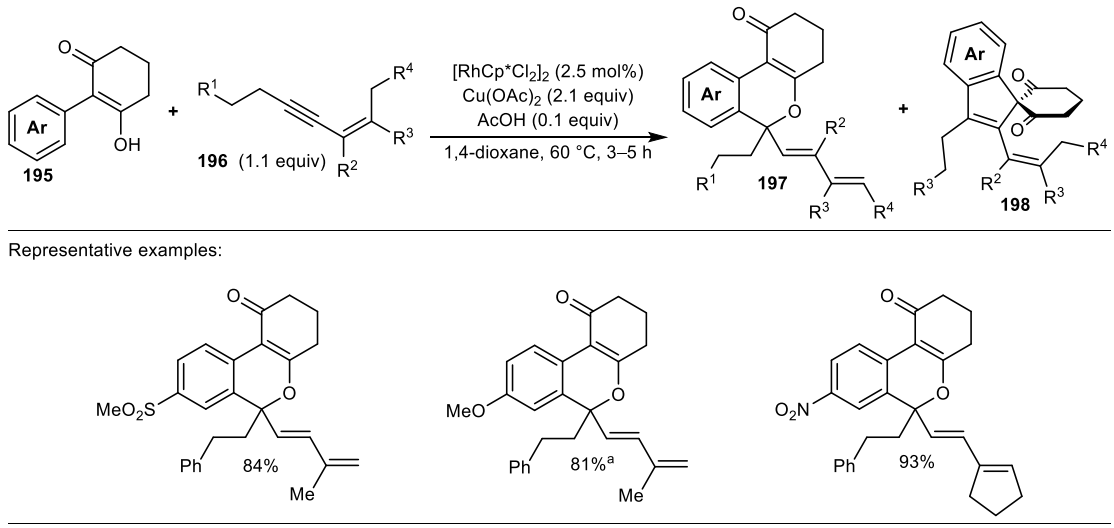
Based on the literature precedent as well as deuterium studies conducted by the researchers, a plausible catalytic cycle was proposed (Scheme 66). Initial coordination of alkyne **187** to Rh(III) species **190** followed by intramolecular attack of the nitrogen allowed the formation of intermediate **191**. An aryl-to-aryl 1,4-Rh(III) migration could take place forming **192**. Diazo compound **188** reacted with **192** generating a rhodium carbenoid complex **193**, with the loss of N_2. Next, migratory insertion of **193** produced intermediate **194**. As a final sequence, protonolysis followed by intramolecular cyclisation turned over product **189** and Rh(III) **190**.



Scheme 66. Proposed catalytic cycle in which aryl-to-aryl 1,4-rhodium migration occurs

1.11 1,4-Rhodium migration from C(sp^2) to C(sp^3) centres

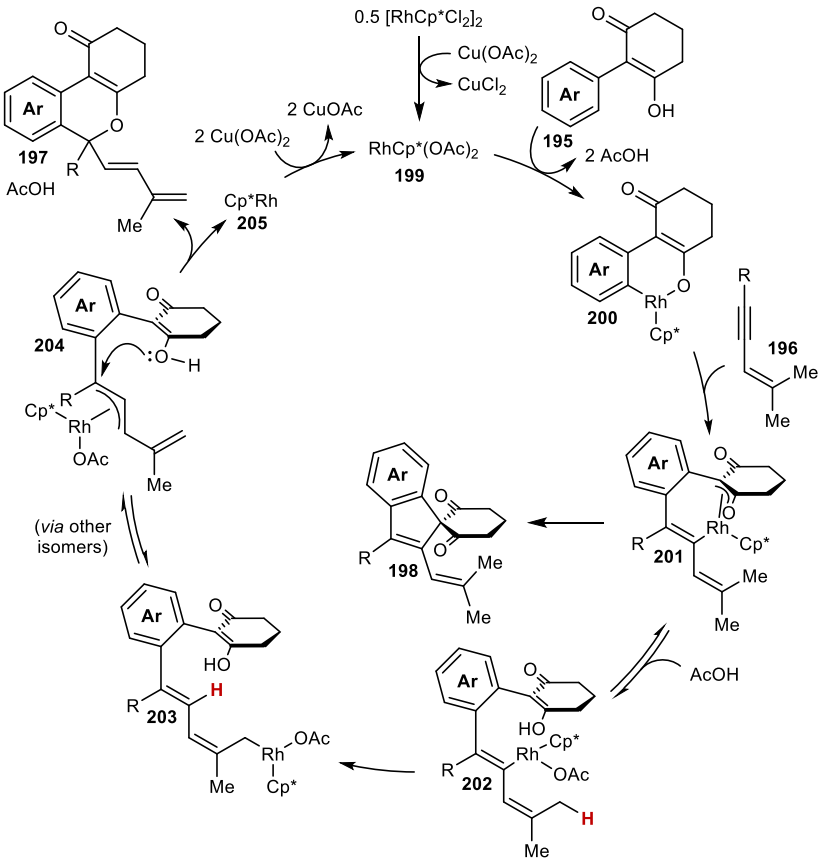
Recently, pioneering work was conducted by Lam and co-workers in the field of C–H activation. Specifically, the use of directing group-assisted C–H activation was merged with through-space C–H activation. This was achieved in a reaction system in which 1,3-enynes **196** were annulated with 2-aryl 1,3-dicabonyls **195**, yielding heterocyclic products **197** and **198** (Scheme 67).[122] The catalyst of choice here was $[RhCp^*Cl_2]_2$ and the key was a novel alkenyl-to-allyl 1,4-Rh(III)-migration. Regarding the one-carbon oxidative annulation's substrate scope, a mixture of spiroindenes **198** and benzopyrans **197** were generally afforded. Though the selectivity for either of the products could be controlled by altering the electronics of the starting 1,3-dicarbonyl reagents. For instance, electron-withdrawing groups at the *para*-position of the 2-aryl ring tended to afford benzopyrans almost exclusively, whereas electron-donating groups gave mixtures with spiroindenes being the major products.



Scheme 67. One-carbon oxidative annulation *via* an alkenyl-to-allyl 1,4-rhodium migration. [a] **197**/**198** (17:64)

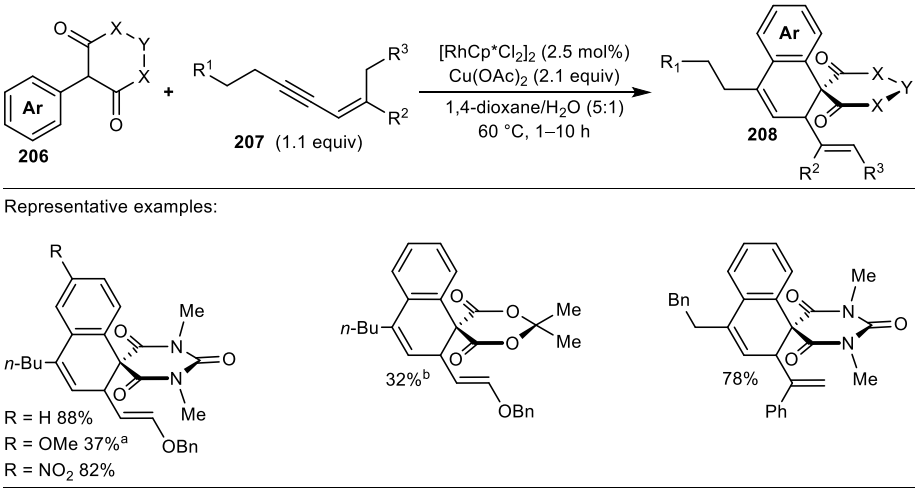
In addition, it was shown that only allylic hydrogens *cis* to the alkyne acted as one-carbon partners, which is likely to be due to the proximity of *cis* hydrogens with the metal complex as opposed to *trans*. Furthermore, mechanistic studies demonstrated that the process involved a 1,4-migration and thus a catalytic cycle was postulated (Scheme 68).

Rhodium diacetate complex **199** is generated *in situ* from $[RhCp^*Cl_2]_2$ and $Cu(OAc)_2$, this is followed by C–H activation of substrate **195** to give rhodacycle **200**. Subsequently, 1,3-enyne **196** coordinates and inserts to **200** forming new rhodacycle intermediate **201**. Reductive elimination of intermediate **201** then affords spiroindene **198**. However, an alternative pathway involves the reversible protonolysis of **201** with AcOH generating the alkenylrhodium species **202**, which is postulated to undergo a 1,4-rhodium migration giving a new allylrhodium species **203**. Presumably, σ-allylrhodium species **203** interconverts with the π-allylrhodium species **204** through isomerisation. Finally, nucleophilic attack of the π-allylrhodium moiety of **204** by the enol oxygen provides the benzopyran **197** as well as Rh(I) species **205**, which in turn is re-oxidised to the active Rh(III) species **199** by $Cu(OAc)_2$.



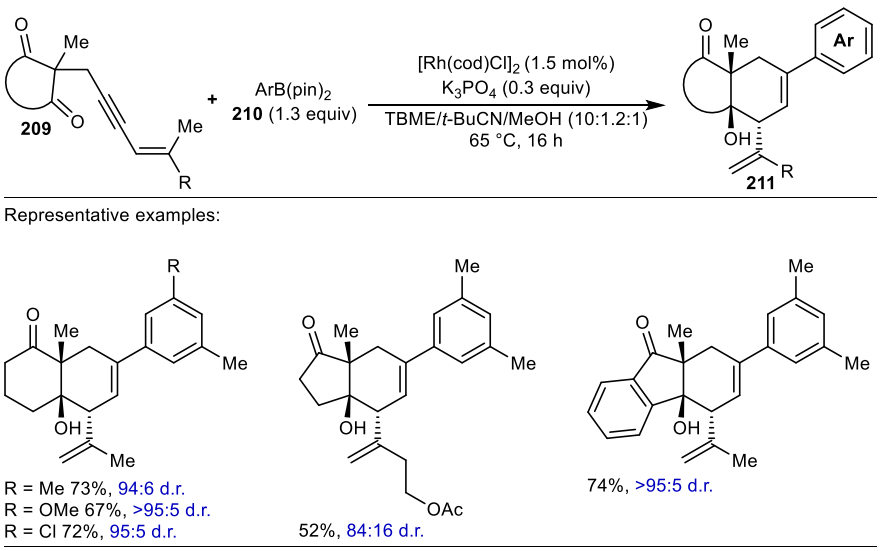
Scheme 68. Proposed catalytic cycle in which vinyl-to-allyl 1,4-rhodium migration occurs

Similar chemistry was performed using 1,3-enynes **207** and 2-aryl cyclic 1,3-dicarbonyls **206** to synthesise spiroindalines **208**, this time *via* an all-carbon [3+3] annulation, utilising the ability of rhodium to migrate from alkenyl to allylic positions (Scheme 69).[123] Interestingly, using this class of diketones did not afford any of the one-carbon annulation products as described above (Scheme 68). An analogous pattern is observed with respect to reactivity; electron-rich arenes are less efficient coupling partners.



Scheme 69. All-carbon oxidative annulation *via* a vinyl-to-allyl 1,4-rhodium migration. [a] Conducted in DMF. [b] Conducted using $[RhCp^*Cl_2]_2$ (5 mol%)

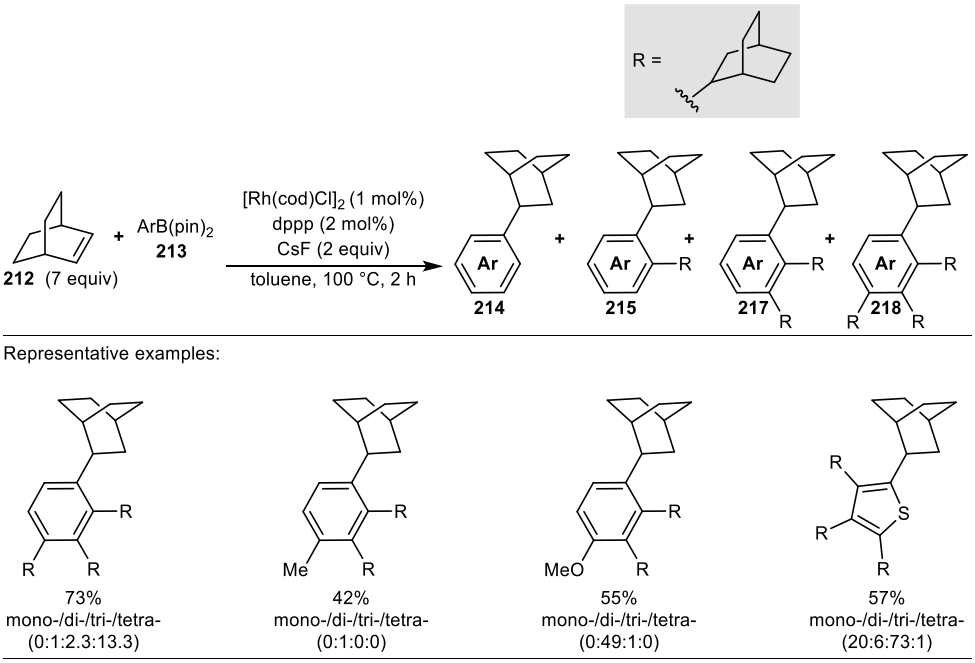
Very recently, an intramolecular alkenyl-to-allyl migration was developed using $[Rh(cod)Cl_2]_2$ (1.5 mol%) as the catalyst enabling the synthesis of bicyclic products **211** from enynes **209** and arylboronic acids **210** (Scheme 70).[124] Moderate to good yields were achieved in high diastereoselectivities. The key limitation here being the necessity of arylboronic acids with substituents at the 3,5- or 2-positions. This was strategically enforced to prevent any competing alkenyl-to-aryl migration. The mechanism proposed was similar to previously described Rh(I) chemistry. Transmetallation with the arylboronic acid and migratory insertion with the alkyne, enabled rhodium to migrate from the alkenyl to the allylic position followed by cyclisation furnishing product **211**.



Scheme 70. Alkenyl-to-allyl 1,4-rhodium migration followed by diastereoselective allylation

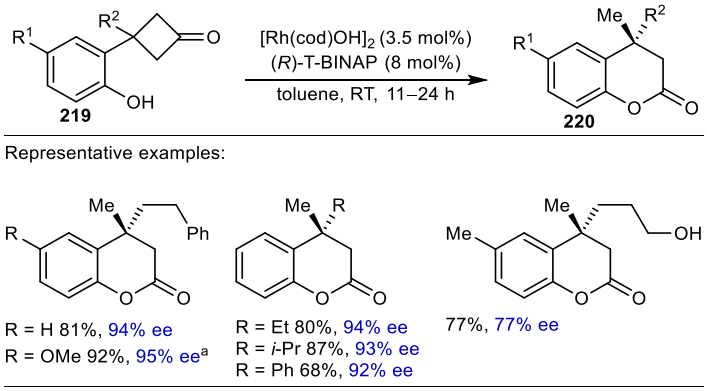
1.12 1,4-Rhodium migration from C(sp^3) to C(sp^2) centres

The first alkyl to aryl 1,4-Rh(I) migration was reported by Miura and colleagues, importantly this was also the first reported migration of Rh(I) from any site about a molecule.[125] Subsequent computational studies have also been performed, investigating the mechanism in detail.[126] In this methodology upon transmetallation with an arylboronic acid **213** and migratory insertion with norbornene **212**, rhodium was able to migrate from the alkyl position to the aryl, yielding alkylated products **214–218** after protonolysis (Scheme 71). Interestingly, having achieved the first alkylation, instead of protonolysis, subsequent alkylations are favoured *via* an alkyl to aryl 1,4-migration.



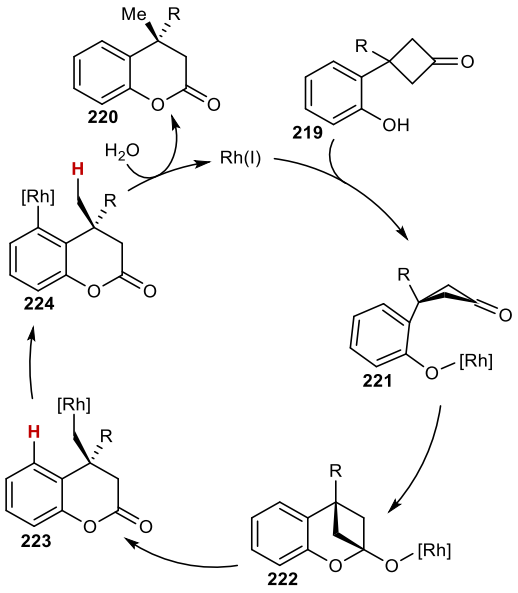
Scheme 71. Alkyl to aryl 1,4-rhodium migration yielding polyalkylated arenes

Furthermore, an intramolecular approach was also developed in which cyclobutanones tethered to phenols **219** undergo cyclisation followed by an alkyl-to-aryl 1,4-Rh(I) migration affording esters **220** in high enantioselectivities (Scheme 72).[127] Regarding the substrate scope, only phenols with *para*-substituents were reported. Additionally, alkyl and aryl groups could be tolerated at the 4-position in cyclobutanone.



Scheme 72. Alkyl-to-aryl 1,4-rhodium migration yielding cyclic esters. [a] Conducted in toluene/THF (4:1)

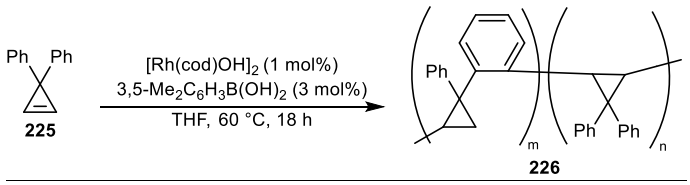
A plausible mechanism consists of initial generation of a rhodium aryloxide species **221**, followed by intramolecular addition to the carbonyl generating a rhodium cyclobutanolate intermediate **222** (Scheme 73). Next, *β*-carbon elimination results in the opening of the cyclobutane skeleton forming **223**. Subsequent migration of rhodium from the alkyl position to the aryl allows for the formation of **224**. Finally, protonolysis furnishes the isolated product **220**. Analogous methodologies have also been developed yielding indanols enantioselectively.[128,129]



Scheme 73. Proposed catalytic cycle in which alkyl to aryl 1,4-rhodium migration occurs

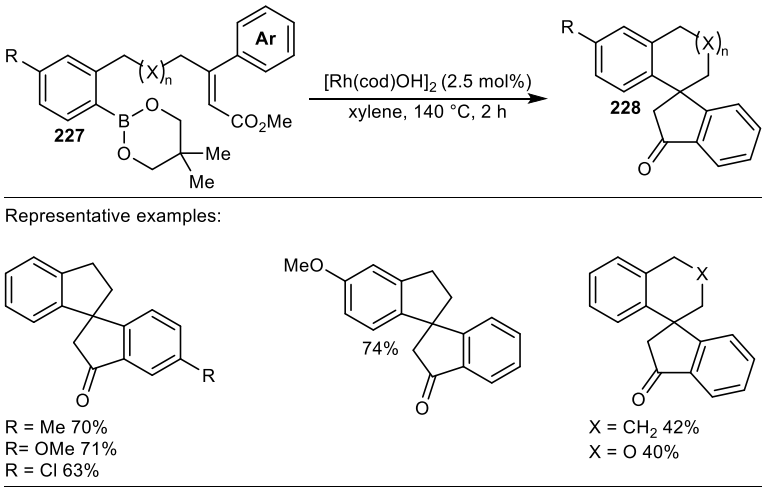
Rh(I) catalysis has also been successful in promoting polymerisations of 3,3-diarylcyclopropnenes **225**, *via* an alkyl-to-aryl 1,4-Rh(I) migration, yielding cyclopropane polymers **226** (Scheme 74).[130] Herein, an arylboronic acid is used as an initiator in catalytic amounts which transmetallates with rhodium and subsequently

inserts into cyclopropene. This enables an alkyl-to-aryl 1,4-Rh(I) migration and the resulting arylrhodium species can insert with another molecule of cyclopropene, propagating the sequence and finally forming the polymer.



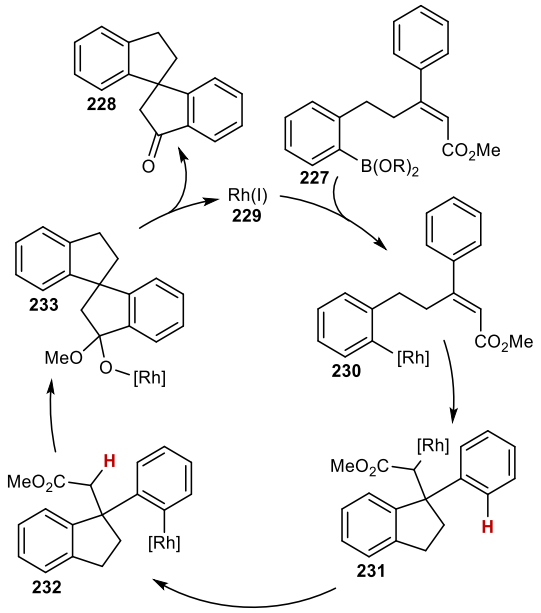
Scheme 74. Alkyl-to-aryl 1,4-rhodium migration yielding cyclopropyl polymers

Recently, Matsuda demonstrated that neopentyl boronic acids **227** in the presence of $[Rh(cod)OH]_2$ (2.5 mol%) can afford spirocyclic 1-indanones **228** (Scheme 75).[131] The key step in this chemistry was postulated to be an alkyl-to-aryl 1,4-Rh(I) migration. The substrate scope was not very broad and could be considered to be contrived. In addition, enantioselective attempts were also performed, though no significant success was reported.



Scheme 75. Alkyl-to-aryl 1,4-rhodium migration yielding spirocyclic 1-indanones

The proposed mechanism involves initial transmetallation of the boronate species **227** with Rh(I) species **229** generating **230** (Scheme 76). Consequently, migratory insertion with the tethered alkene moiety affords an alkylrhodium intermediate **231**, which is able to undergo a 1,4-migration generating the corresponding arylrhodium intermediate **232**. Intramolecular addition at the ester forms an alkoxyrhodium intermediate **233**, which upon protonation yields isolated product **228**.

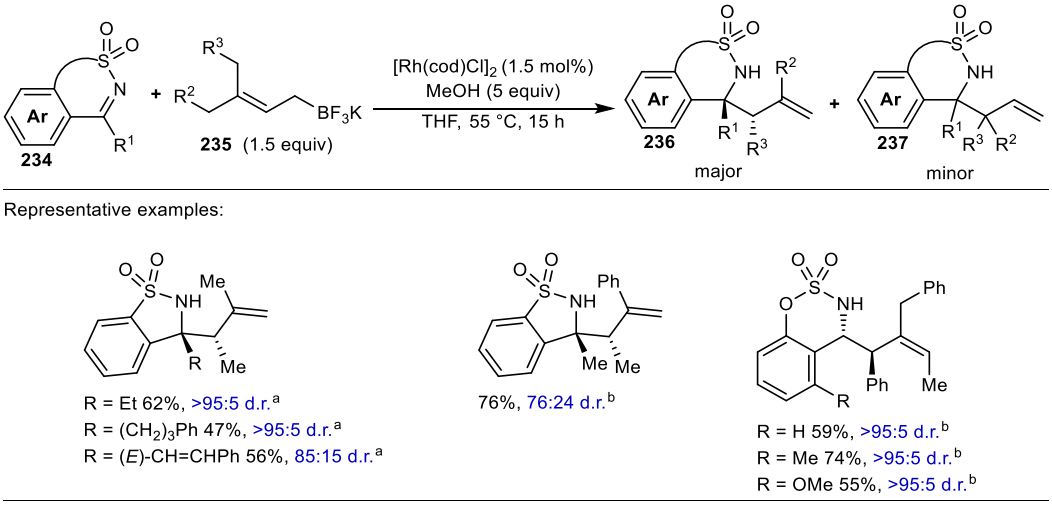


Scheme 76. Proposed catalytic cycle in which alkyl to aryl 1,4-rhodium migration occurs

1.13 1,4-Rhodium migration from C(sp^3) to C(sp^3) centres

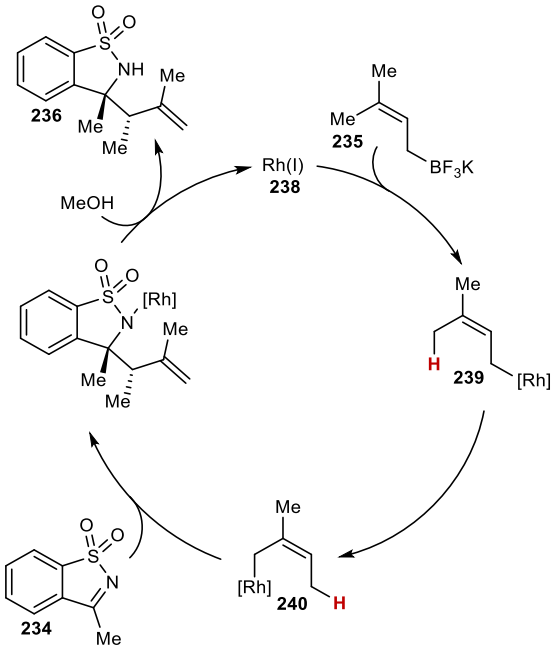
Importantly, migration from C(sp^3) to C(sp^3) is very rare in the literature. To date only two examples have been documented in which rhodium, in particular Rh(I), can perform this class of migration.[132,133]

The first example of Rh(I) migrating from an allylic to another allylic position within a molecule was reported by Lam and co-workers.[132] In this chemistry allyltrifluoroborates **235** are reacted with cyclic imines **234** in the presence of $[Rh(codCl]_2$ (1.5 mol%) yielding allylated products **236** and **237** generally in high diastereoselectivities (Scheme 77). Examples achieving high enantioselectivities were also reported. Though a key limitation here being the use of activated aldimines and ketimines as the only type of electrophile that could successfully undergo this transformation.



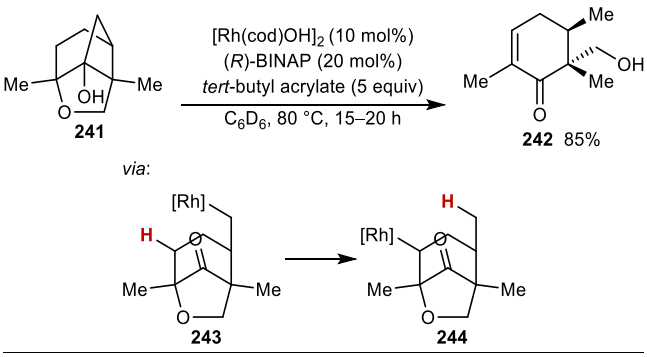
Scheme 77. Allylation of imines *via* an allyl-to-allyl 1,4-rhodium migration (major product). [a] Isolated yields of major product. [b] Minor product not detected

Moreover, the minor product is believed to be generated by direct allylation of the cyclic imine without involving a metal migration. Regarding the major product, a proposed mechanism was reported involving initial transmetallation of allyltrifluoroborate **235** with Rh(I) species **238**, generating an allylrhodium species **239** (Scheme 78). Next, migration to the *cis*-allylic position would form allylrhodium species **240**, capable of allylating imine **234** and upon protonolysis affording isolated product **236**.



Scheme 78. Proposed catalytic cycle in which allyl-to-allyl 1,4-rhodium migration occurs

The second example was discovered whilst investigating the C–H and C–C bond activation/cleavage in pinene derivatives **241** (Scheme 79).[133] Herein, the key step was postulated to be an alkyl-to-alkyl 1,4-Rh(I) migration from intermediate **243** to **244**. Subsequent *β*-alkoxy elimination allowed for the formation of the cyclohexenone analogue **242**. The above was supported by computational as well as experimental studies.

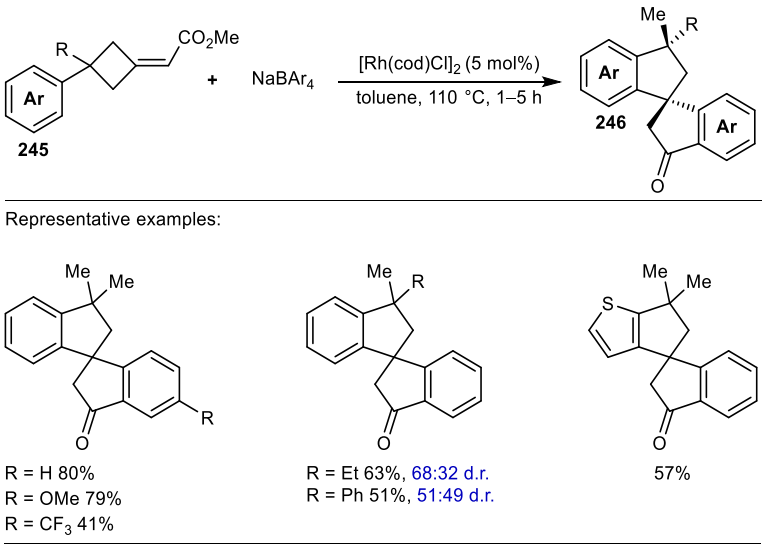


Scheme 79. Alkyl-to-alkyl 1,4-rhodium migration yielding a cyclohexanone analogue

1.14 Consecutive 1,4-rhodium migrations

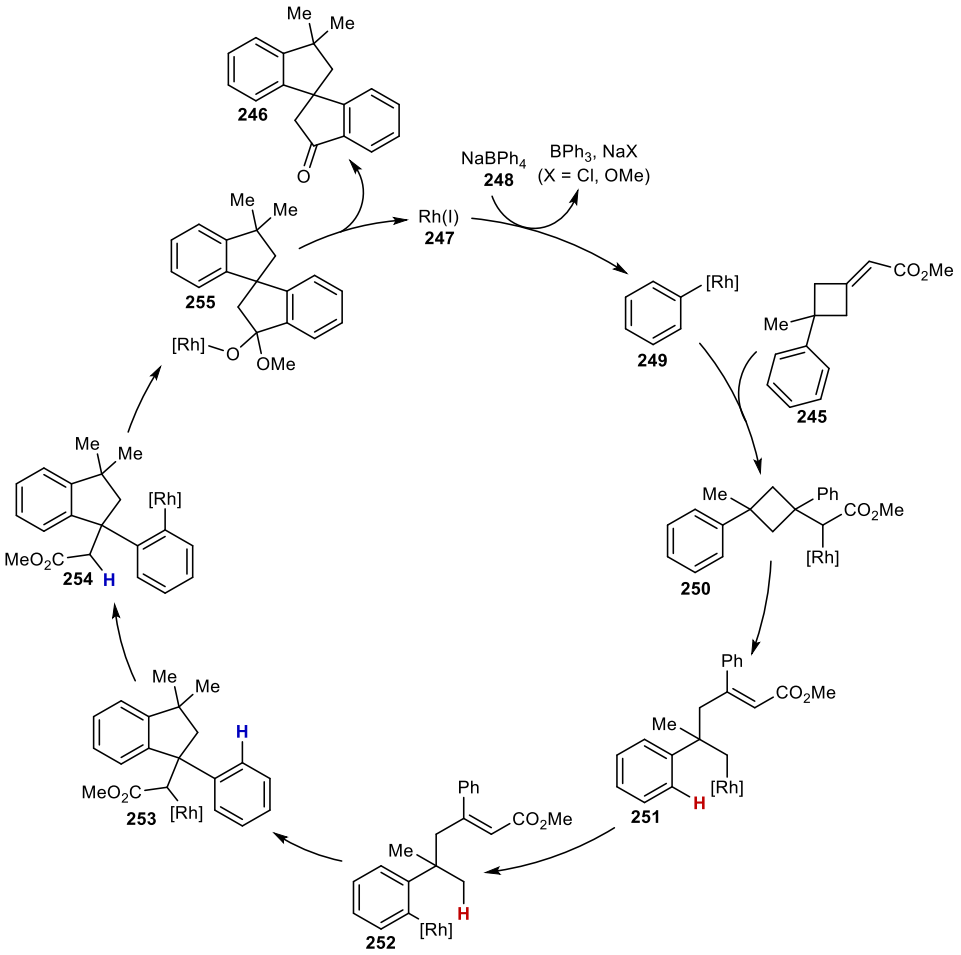
Consecutive 1,4-rhodium migrations have been reported, albeit not extensively. In addition, limited examples exist in the literature using palladium also, in which a mixture of products are generally afforded.[134–137] Importantly though, if this strategy could be developed to achieve high chemoselectivity it would be of great impact to the chemical community.

Related to their previous work in the area of 1,4-Rh(I) migration in spirocyclisations (Scheme 75), Matsuda and colleagues also developed a catalytic spirocyclisation reaction forming 1,1-spirobiindan-3-ones **246** from (3-arylcyclobutylidene)acetates **245** *via* a 1,4-Rh(I) migration cascade (Scheme 80).[138]



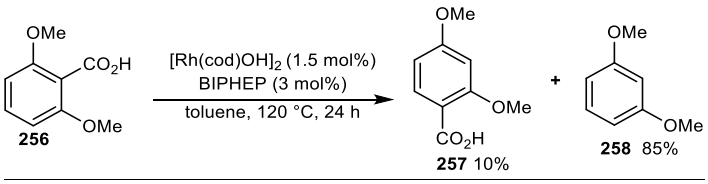
Scheme 80. Spirocyclisation involving two alkyl-to-aryl 1,4-rhodium migrations

The reported catalytic cycle involves initial transmetallation of Rh(I) **247** with boron species **248** forming arylrhodium intermediate **249** (Scheme 81). This is followed by a 1,4-addition to enoate **245**, giving (cyclobutylmethyl)rhodium complex **250**. Next, *β*-carbon elimination occurs, releasing the strain of the 4-membered ring, producing alkylrhodium **251**. Consequently, an alkyl-to-aryl migration affords the arylrhodium species **252**, which upon a second 1,4-addition forms alkylrhodium complex **253**. A second 1,4-migration generates arylrhodium intermediate **254**. Subsequent 1,2-addition forms the spirocyclised alkoxyrhodium intermediate **255**. Finally, *β*-oxygen elimination furnishes the observed product **246**.



Scheme 81. Proposed catalytic cycle in which two alkyl-to-aryl 1,4-rhodium migration occur

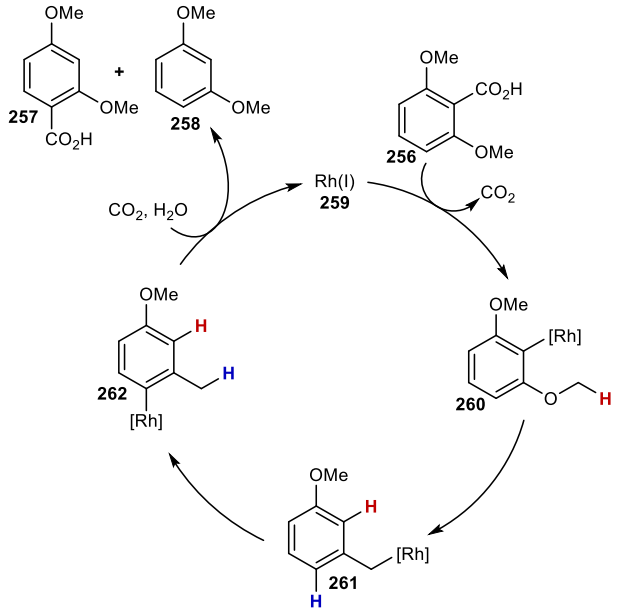
The second and final example of consecutive rhodium 1,4-migrations was reported by Zhao in 2013.[139] This example involved a methoxy-directed net 1,3-migration of rhodium about 2,6-dimethoxybenzoic acid **256** which is proposed to consist of two 1,4-migrations yielding 2,4-dimethoxybenzoic acid **257** and 1,3-dimethoxybenzene **258** (Scheme 82).



Scheme 82. Isomerisation and decarboxylation of 2,6-dimethoxybenzoic acid involving two 1,4-rhodium migrations

Regarding the mechanism, there has been some ambiguity whether it occurs *via* consecutive 1,4-migrations, though thus far this is considered the most probable mechanism (Scheme 83). Initial decarboxylation of **256** is achieved in the presence of

Rh(I) species **259**, giving arylrhodium intermediate **260**. Thereon, rhodium is proposed to migrate to the C(sp^3) centre in the methoxy group generating an alkylrhodium species **261**. A second 1,4-migration to the aryl position *para* to the non-activated methoxy group produces intermediate **262**. As a final point, protonolysis and carboxylation would yield both products **257** and **258** respectively.



Scheme 83. Proposed catalytic cycle in which two 1,4-rhodium migrations occur

1.15 Summary on C–H activation

In conclusion, an overview of Rh(III) oxidative coupling reactions of alkenes, allenes, ketenes and dienes with various aromatic systems in the presence of directing groups was discussed. Both neutral and cationic Rh(III) complexes stabilised by a Cp* ligand and the aid of proximal neutral and anionic heteroatoms have demonstrated to be efficient in activating C–H bonds. These methodologies generally use Cu(II), Ag(I) or O_2 as oxidants, as well as internal oxidants in which the N–O bond of the directing group is exploited. Furthermore, careful choice of directing group more than often results in different types of transformations, including but not limited to alkenylations, allylations and various annulations. In addition, Rh(III) catalysis has proven to have a high tolerance for a range of functional groups as well as unique reactivity and selectivity in comparison to other transition metals. Notably, C–H activation has shown to be an attractive and a more environmentally friendly approach to generating

complex molecules, especially in the synthesis of heterocycles and natural product precursors.

It is evident that while many valuable transformations can be achieved *via* Rh(III) oxidative C–H functionalisation there are some limitations with respect to the coupling partners. In most cases activated alkenes can only be coupled with arenes, whilst examples with less reactive species such as aliphatic or simple disubstituted alkenes are scarce. Moreover, to our knowledge allylation or homoallylation of arenes with 1,3-dienes under Rh(III) oxidative conditions has not been accomplished. Rh(III) catalysis has found a broad use in organic synthesis and we envisage additional valuable synthetic strategies will be developed based on its intrinsic reactivity.

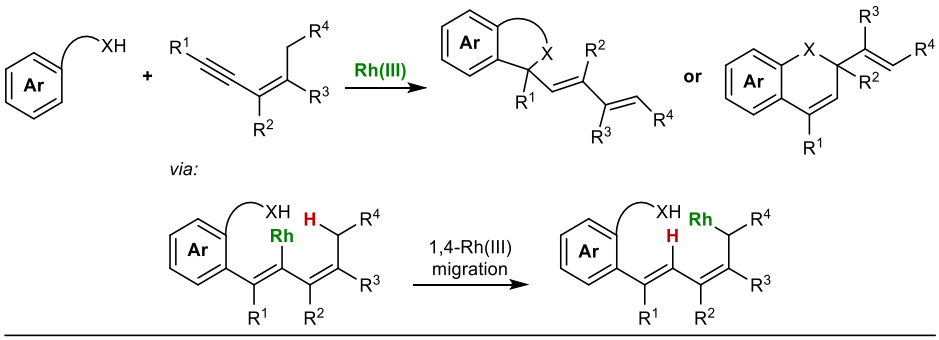
Furthermore, remote C–H activation is a powerful and important tool for synthetic chemists. Rhodium has shown unparalleled reactivity in this area, thus demonstrating its utility. The 1,4-migration, when achieved in high chemoselectivity, is synthetically appealing as it allows chemists to access molecules of high complexity by means that are not always feasible or straightforward *via* other routes. At this point 1,4-metal migrations from C(sp^3) to C(sp^3) centres are very limited for Rh(I). Specifically, for Rh(III), migrations from C(sp^3) to C(sp^3) centres are unknown. Of note, reports of consecutive 1,4-migrations are also limited. Additionally, methodologies combining directing-group assisted C–H activation with remote C–H activation, *via* metal migrations, are also in their infancy. Developing methodologies that can utilise the underexplored types of migration as well as exploiting consecutive migrations will significantly impact the chemical community.

2 Results & Discussion

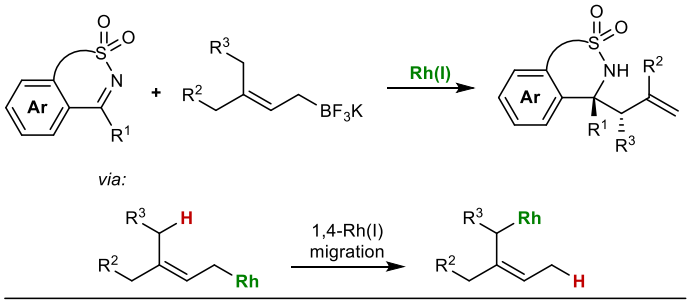
2.1 Aims

Having discussed both directing group-assisted and remote C–H activation, it is evident that there is lack of knowledge concerning metal migrations form C(sp^3) to C(sp^3) centres. Furthermore, the combination of directed and remote C–H activation in a single methodology is scarce in the literature. We aimed to explore migrations at these sites exploiting Rh(III), which is currently unknown. We envisaged that focusing on this area will give the chemical community an insight into the ability of Rh(III) to engage in 1,4-migrations as well as developing its synthetic utility. A secondary objective involved developing a methodology that makes use of less reactive alkene moieties in Rh(III) catalysis. As discussed, a key limitation in Rh(III)-catalysed oxidative alkenylations and allylations is the use of activated alkenes to achieve synthetically viable yields or any reactivity at all. We also aimed to investigate Rh(III)-catalysed C–H homoallylation reactions which are unknown.

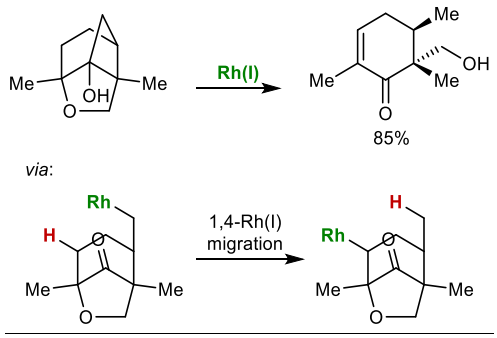
Recently, the Lam research group demonstrated that Rh(III) can function as a catalyst in oxidative annulations of 1,3-enynes with 2-aryl 1,3-dicarbonyl compounds (Scheme 84).[122,123] The key step in this transformation is a novel alkenyl-to-allyl 1,4-migration. Moreover, it was shown that Rh(I) can engage in C(sp^3) to C(sp^3) migrations, the only metal reported thus far able to undergo this type of migration (Scheme 85 and 86).[132,133]



Scheme 84. Examples of alkenyl-to-allyl 1,4-Rh(III) migration

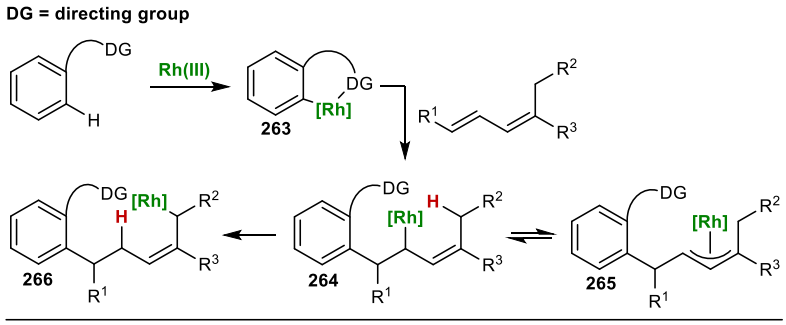


Scheme 85. Example of allyl-to-allyl 1,4-Rh(I) migration



Scheme 86. Example of alkyl-to-alkyl 1,4-Rh(I) migration

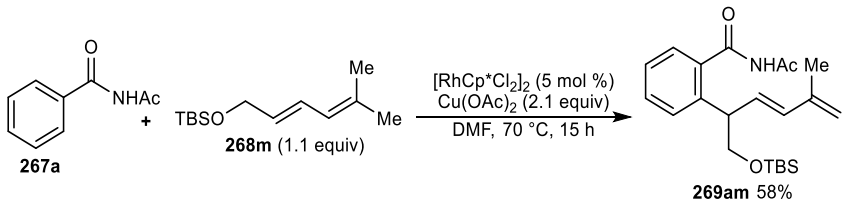
From these reports, we developed an interest whether C(sp^3) to C(sp^3), in particular allyl-to-allyl, 1,4-Rh(III) migrations would be feasible. To test this hypothesis, we proposed a system where a 1,3-diene would react with coupling partner in the presence of Rh(III) (Scheme 87). Upon directed C–H activation, rhodacycle **263** would be formed, which would react with the 1,3-diene to give *σ*-allylrhodium(III) intermediate **264**. This could exist as the *π*-allylrhodium(III) species **265** or undergo a 1,4-Rh(III) migration to the other *cis*-allylic position to generate **266**. Although the final fate of **266** would be unknown, this methodology could serve as a valuable addition to the presently limited examples of catalytic C–H functionalisations involving 1,3-dienes, provided high overall chemo-, regio-, and stereoselectivity was exhibited.



Scheme 87. Proposed experiment to investigate possible allyl-to-allyl 1,4-Rh(III) migration

2.2 Development of Rh(III)-catalysed oxidative C–H allylation of *N*-acetylbenzamides with 1,3-dienes

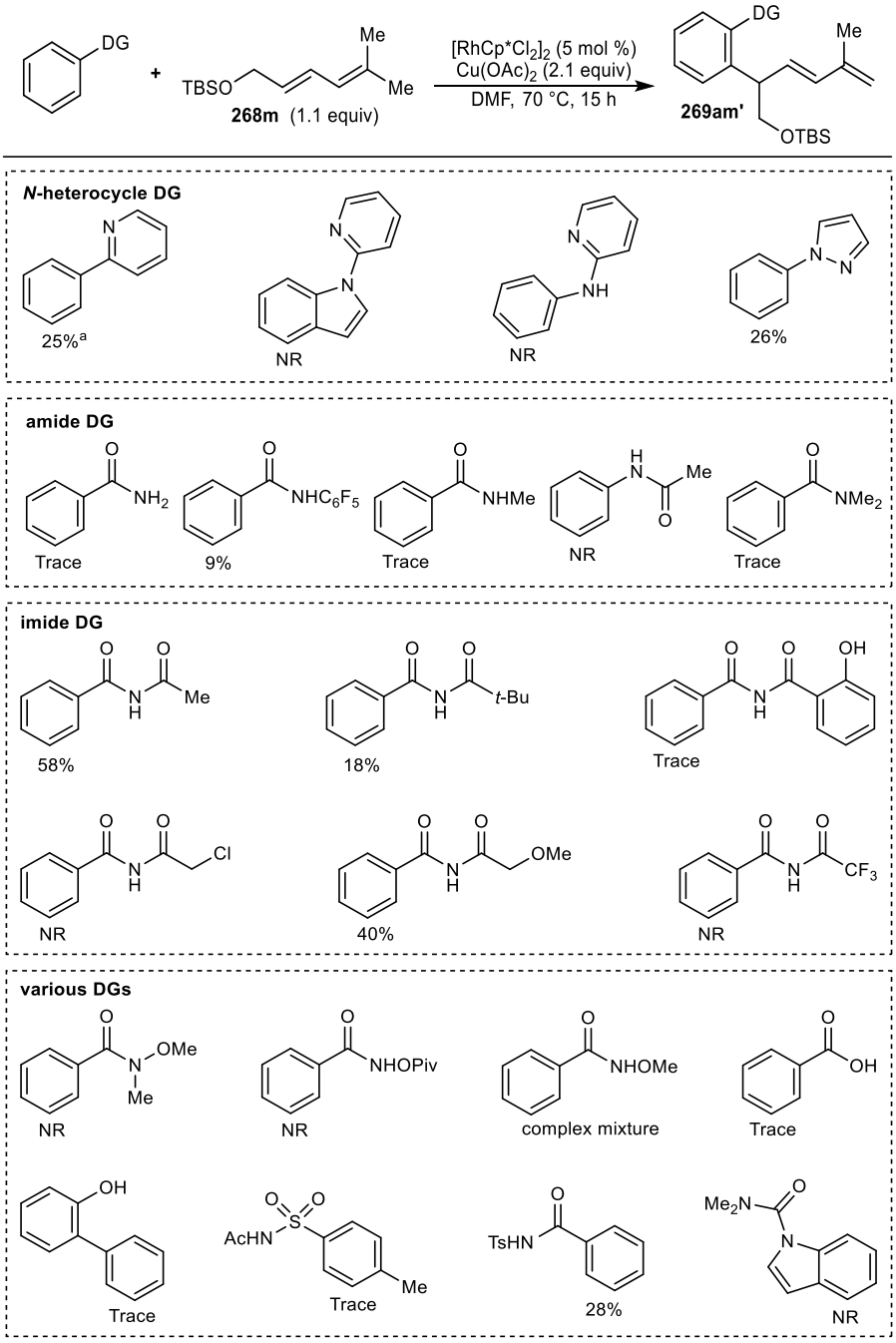
The first experiment we conducted involved the use of *N*-acetylbenzamide **267a** and 1,3-diene **268m** with $[RhCp^*Cl_2]_2$ (5 mol%) as the catalyst and $Cu(OAc)_2$ as the stoichiometric oxidant. This led to the formation of product **269am**, *via* an allyl-to-allyl 1,4-Rh(III) migration, in 58% yield (Scheme 88). The remainder of the mass balance was starting material.



Scheme 88. Initial reaction conditions. Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard

A range of directing groups were screened to determine the most efficient coupling partner (Table 1). Substrates with imides as the directing group generally afforded higher yields of allylation product **269am'**. Furthermore, certain nitrogen-containing heterocycles also afforded the product, though in lower yields.

Table 1. Directing groups examined

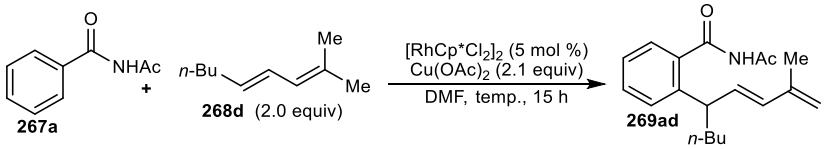


Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [a] Conducted at 120 °C

From the directing group screen, *N*-acetylbenzamide **267a** was selected as the coupling partner. Next, a temperature screen was performed (Table 2). A different 1,3-diene **268d** was chosen due to its ease of preparation. Two equivalents of 1,3-diene **268d** were used due to its volatility. The yield of **269d** at 70 °C was 58% (Table 2, Entry 3). Lowering the temperature decreased the conversion, whereas at temperatures

above 70 °C, degradation of the 1,3-diene was observed by ^{1}H NMR spectroscopy and TLC (Table 2, Entries 1, 2, 4–6).

Table 2. Temperature screening

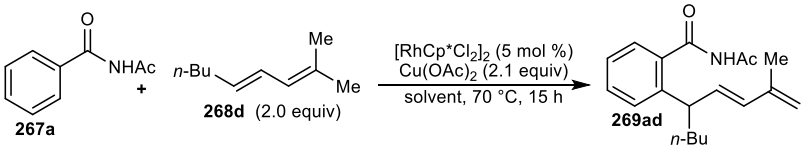


Entry	Temperature (°C)	Yield (%)
1	50	28
2	60	53
3	70	58
4	80	48
5	90	44
6	120	32

Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard

The second parameter that was investigated was the solvent (Table 3). The highest yields were achieved using DMF, DMA and acetone (Table 3, Entries 9, 11, 14). No clear conclusion can be drawn about why these solvents worked the best. Hydrocarbons, ethers, halogenated solvents, alcohols, DMSO, DMC and EtOAc gave a trace amount or no product (Table 3, Entries 1–7, 13, 15 and 17). Importantly, using water as the co-solvent hindered the reaction (Table 3, Entry 10).

Table 3. Solvent screening



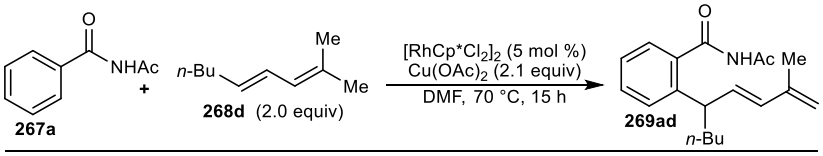
Entry	Solvent (0.1 M)	Yield (%)
1	toluene	NR
2	1,4-dioxane	NR
3	cyclohexane	NR
4	CH_2Cl_2	trace
5	PhCl	trace
6	*t*-BuOH	9
7	*t*-AmOH	6
8	*t*-AmOH/DMF (4:1)	29
9	DMF	58
10	DMF/H_2O (9:1)	24
11	DMA	56
12	TMU	complex
13	DMSO	NR
14	acetone	33
15	DMC	3
16	CH_3CN	14
17	EtOAc	trace

Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard

Additionally, when the reaction was conducted under air or oxygen, product **269ad** was afforded in 38 and 26% yield respectively; whereas under inert atmosphere the yield of product **269ad** was 58%. These experiments suggested that oxygen was harmful to the reaction.

Subsequently, screening of solvent concentration with respect to benzamide **267a**, the limiting reagent, was undertaken. This showed that a concentration of 0.1 M afforded the highest yield (Table 4, Entry 3).

Table 4. Concentration screening

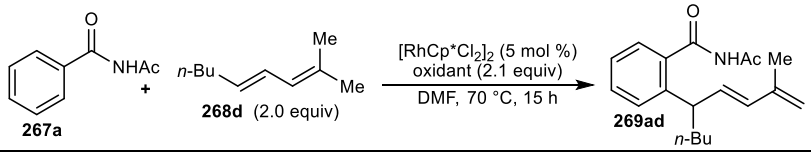


Entry	Concentration of **267a** (M)	Yield (%)
1	0.033	12
2	0.050	33
3	0.10	58
4	0.20	23
5	0.30	25

Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard

A number of oxidants were examined though only Cu(II) and Ag(I) carboxylates were effective in re-oxidising Rh(I) to Rh(III) under these conditions (Table 5). When using oxidants lacking carboxylate ligands, NaOAc (2.1 equiv) was added as a necessary additive to aid in the C–H activation step. The use of $Cu(OAc)_2{\cdot}H_2O$ decreased the yield to 46%, suggesting that even 2.1 equivalents of water were harmful to the reaction.

Table 5. Oxidant screening



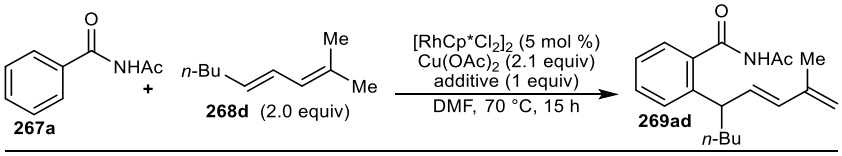
267a 269ad

Inorganic oxidant	Organic oxidant[a]	Other inorganic oxidants[a]
AgOAc (41)	BQ (NR)	$PhI(OAc)_2$ (NR)
$Mn(OAc)_3 \cdot H_2O$ (NR)	TEMPO (NR)	$K_2S_2O_8$ (NR)
$Cu(OAc)_2$ (58)	NMO (NR)	oxone (NR)
$Cu(OAc)_2 \cdot H_2O$ (46)	pyridine *N*-oxide (6)	Ag_2O (NR)
$Cu(OPiv)_2$ (43)	$(BzO)_2$ (Trace)	Ag_2CO_3 (NR)
Cu(2-ethylhexanoate)$_2$ (40)	(*t*-BuO)$_2$ (Trace)	CuO (7)[b]
Cu(2-pyrazinecarboxylate)$_2$ (NR)		$CuCl_2$ (NR)
		$CuSO_4$ (14)[b]
		$Cu(acac)_2$ (Trace)
		KO_2 (Trace)
		MnF_3 (Trace)
		MnO_2 (5)

Yield in parentheses determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [a] NaOAc (2.1 equiv) was used as an additive. [b] Conducted by David J. Burns

Next, from the proposed reaction mechanism the relevant by-products were identified (for detailed mechanism see Scheme 110). According to the proposed mechanism, after reaction completion, AcOH (2 equiv), $CuCl_2$ (10 mol%) and CuOAc (2 equiv) should be generated as by-products. The analogous experiments were conducted to determine whether any of these by-products hindered the reaction (Table 6). The use of AcOH (1 equiv) as an additive gave a yield of 28%, indicating that the AcOH generated *in situ* was likely to harm the reaction (Table 6, Entry 1). Furthermore, when $CuCl_2$ (1 equiv) was used no product formation was observed (Table 6, Entry 2). However, this was generated in substoichiometric quantities, thus its effect may be negligible. In addition, the use of CuOAc (1 equiv) had no effect on the reaction (Table 6, Entry 3). Furthermore, desiccants such as Na_2SO_4 and molecular sieves (MS 3 Å) were used in independent experiments to 'mop-up' adventitious water, though there was no improvement in yield (Table 6, Entries 4 and 5).

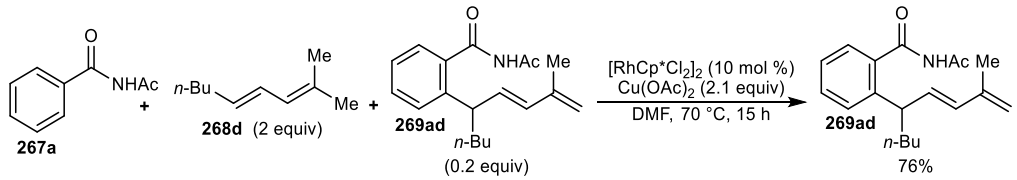
Table 6. Screening of additives



Entry	Additive (1.0 equiv)	Yield (%)
1	AcOH	28
2	$CuCl_2$	Trace
3	CuOAc	54
4	Na_2SO_4	41
5	MS 3 Å	52[a] (58)[b] (55)[c]

Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [a] MS (5 mg) used. [b] MS (10 mg) used. [c] MS (20 mg) used. Reactions conducted on a 0.05 mmol scale, with respect to **267a**

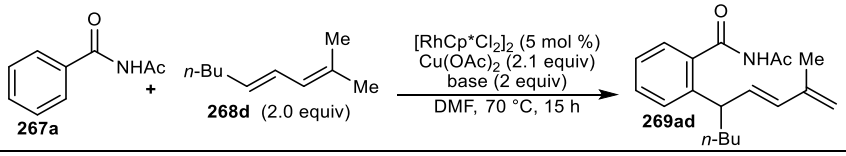
We also considered whether product **269ad** formed could inhibit the reaction. This hypothesis was disproved by conducting the relevant control experiment using **267a** (0.2 equiv) as an additive (Scheme 89). No effect was observed and **269ad** was formed in 76% yield, which was consistent with the expected yield plus the amount of additive used (0.2 equiv).



Scheme 89. Using the product as an additive. Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard

We next focused our efforts on using a base as a buffer which would react with the AcOH generated *in situ* (Table 7). However, the use of a base generally resulted in a lower conversion of **267a** to product **269ad**. Different equivalents of base were also examined though without any improvements. Interestingly, NaOAc and Na_3PO_4 had negligible effect on the conversion of the reaction.

Table 7. Screening of bases

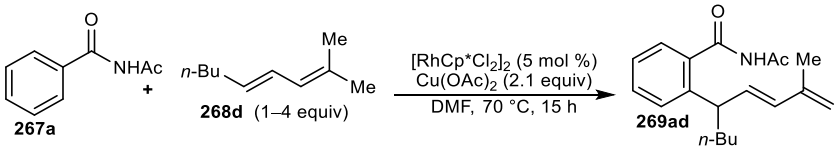


Phosphate	Carbonate	Alkoxide/aryloxide	Carboxylate	Amine
Na_3PO_4 (46)	K_2CO_3 (complex)	NaO*t*-Bu (6)	NaOAc (53)	Et_3N (9)
Na_3PO_4 (52)[a]	K_2CO_3 (15)[a]	NaO*i*-Pr (21)	LiOAc·$2H_2O$ (42)	py (NR)
K_3PO_4 (11)	$NaHCO_3$ (13)	NaOMe (24)	KOAc (12)	py (NR)[c]
K_2HPO_4 (13)	Li_2CO_3 (34)	LiO*t*-Bu (38)	NaOPiv·H_2O (6)	
	Cs_2CO_3 (Trace)	KOPh (21)	NaOPiv·H_2O (38)[a]	
			NaOPiv·H_2O (27)[b]	
			NaOPiv·H_2O (30)[c]	

Yield in parentheses determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [a] base (1.0 equiv) used. [b] base (0.5 equiv) used

Additionally, higher yields were generally achieved when 1,3-diene **268d** was used in excess (Table 8, Entries 2–4). However, no significant increase in yield was observed when greater than two equivalents of 1,3-diene were used (Table 8, Entries 3 and 4).

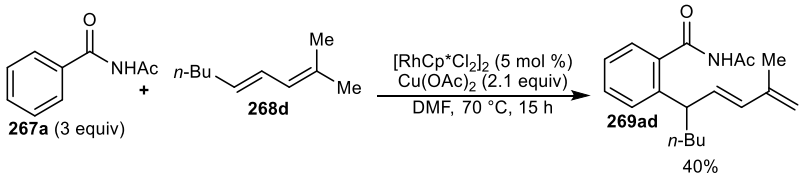
Table 8. Screening of 1,3-diene (**2d**) equivalents



Entry	1,3-Diene (equiv)	Yield (%)
1	1	38
2	2	58
3	3	55
4	4	56

Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard

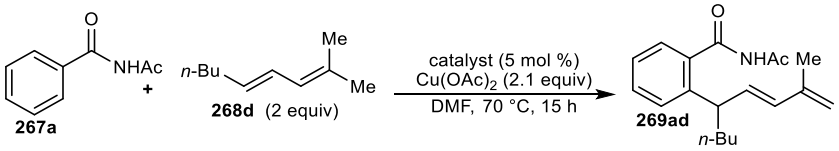
In contrast, when three equivalents of benzamide **267a** were used, a lower yield of 40% was observed (Scheme 90). At this time, it is not clear why higher conversion was achieved when 1,3-diene **268d** was used in excess.



Scheme 90. Using *N*-acetylbenzamide in excess. Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard

Importantly, increasing the catalyst loading to 10 mol% marginally affected the efficacy of the reaction (Table 9, Entry 1). Moreover, the catalyst loading could be lowered to 2.5 mol% without experiencing any drastic loss in conversion (Table 9, Entry 1). Additional metal complexes were also examined, though none were superior to $[RhCp^*Cl_2]_2$ (Table 9, Entries 2–6).

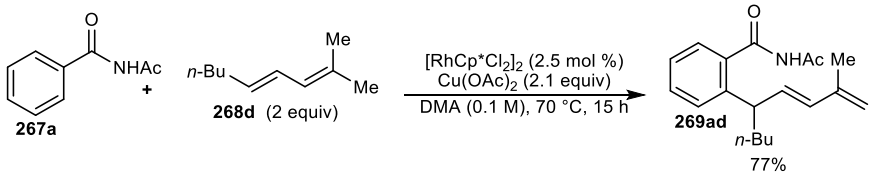
Table 9. Screening of catalyst loading and other metal complexes



Entry	Catalyst	Yield (%)
1	$[RhCp^*Cl_2]_2$	58 (52)[a] (56)[b]
2	$[RhCp^*(MeCN)_3](SbF_6)_2$	35
3[c]	$Rh(3,5\text{-}(t\text{-}Bu)_2Cp)Cl_2$	22
4	$[IrCp^*Cl_2]_2$	Trace
5	$CoCp^*COI_2$	NR
6	PdPEPPSI-IPr	NR

Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [a] $[RhCp^*Cl_2]_2$ (10 mol%) was used. $[RhCp^*Cl_2]_2$ (2.5 mol%) was used. [c] Conducted by David J. Burns

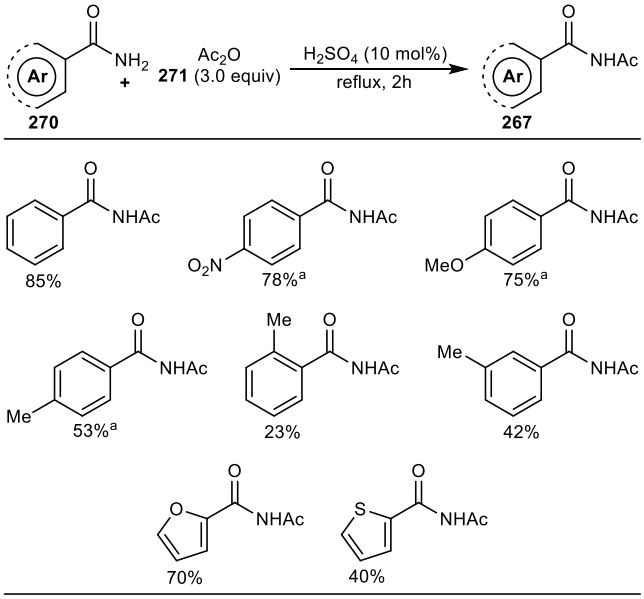
Overall, the two most detrimental components to the transformation were considerd to be water and AcOH. The commercially available $Cu(OAc)_2$ was gently heated under vacuum to evaporate any residual water and AcOH present. Surprisingly, freshly dried $Cu(OAc)_2$ boosted the yield of **269ad** from 58 to 77%. As a result, a final set of conditions were settled upon (Scheme 91).



Scheme 91. Final set of conditions

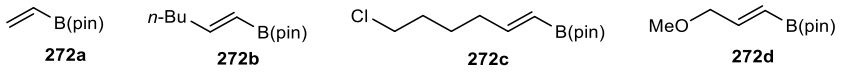
2.3 Substrate syntheses for Rh(III)-catalysed oxidative C–H allylation of *N*-acetylbenzamides with 1,3-dienes

The reaction of benzamide **270** and acetic anhydride **271**, using sulfuric acid as the catalyst, afforded a range of *N*-acetylbenzamides **267** (Scheme 92). The experimental set-up was very straightforward and the products were easily purified by recrystallisation.



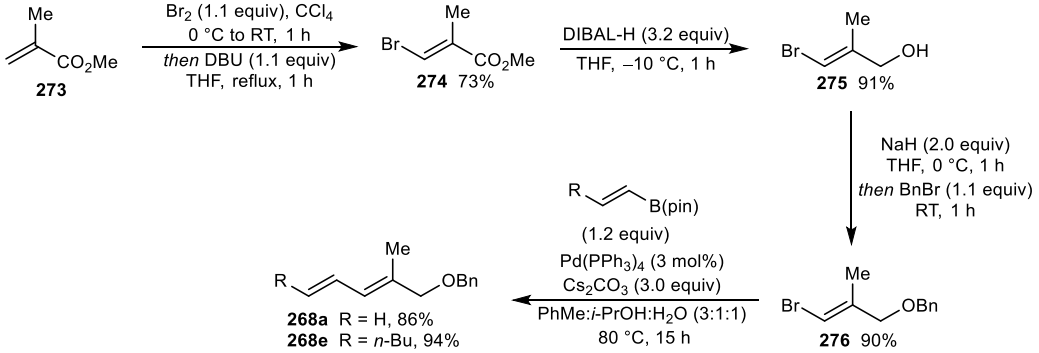
Scheme 92. Synthesis of *N*-acetylbenzamides **267**. [a] Synthesised by David J. Burns

On the other hand, synthesising 1,3-dienes proved to be more challenging and time-consuming. To avoid preparing mixtures of geometric isomers, which are generally encountered in Wittig-type reactions, the Suzuki-Miyaura reaction was used. Alkenyl boronate esters **272a–272d** were purchased, whereas vinyl halides were prepared according to literature procedures, though generally required several number of steps to be prepared (Scheme 93).



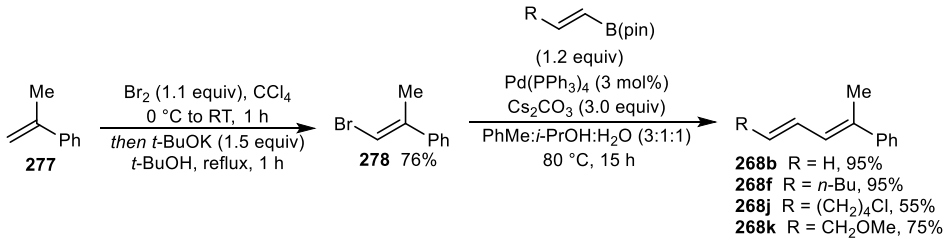
Scheme 93. Commercially available alkenyl boronate esters

For instance, 1,3-diene **268a** and **268e** required a five-step synthesis route (Scheme 94). The commercially available alkene **273** was brominated and upon elimination afforded vinyl bromide **274** in 73% yield. This was then reduced to alcohol **275** with DIBAL-H, in 91% yield. The reaction of alcohol **275** with benzyl bromide and sodium hydride gave ether **276** in 90 % yield, which was used in the Suzuki-Miyaura step to give the final 1,3-dienes **268a** and **268e** in 86 and 94% yield respectively.



Scheme 94. Synthesis route of 1,3-dienes **268a** and **268e**

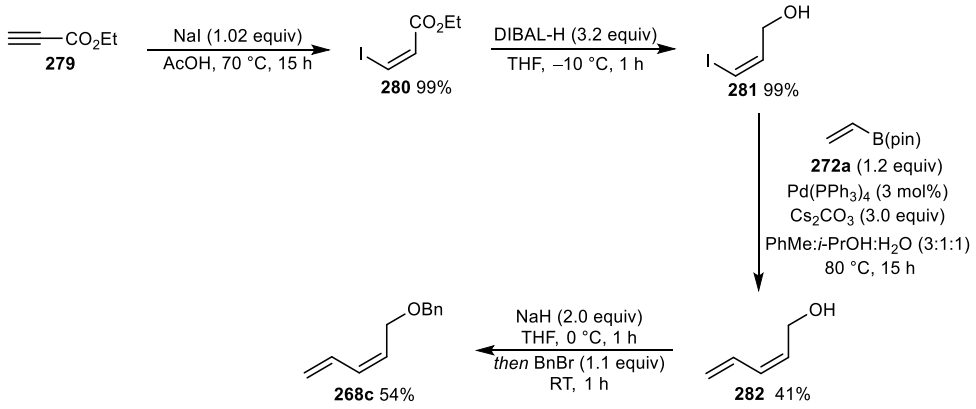
Phenyl-substituted 1,3-dienes **268b**, **268f**, **268j** and **268k** were prepared from vinyl bromide **278** (Scheme 95). Vinyl bromide **278** was prepared from alkene **277**, *via* bromination followed by elimination, in an overall yield of 76%.



Scheme 95. Synthesis route of 1,3-dienes **268b**, **268f**, **268j** and **268k**

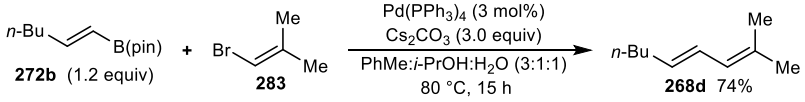
The preparation of a mono-substituted 1,3-diene, such as **268c**, required a different approach, starting from ethyl propiolate **279** (Scheme 96). Initial reaction of ethyl propiolate with sodium iodide in glacial acetic acid afforded vinyl iodide **280** in 99% yield. Next, reduction of ester **280** using DIBAL-H gave corresponding alcohol **281** in 99% yield. A Suzuki-Miyaura reaction was performed using vinyl iodide **281** and

vinyl boronate ester **272a** to give 1,3-diene **282** in 41% yield. Subsequent benzylation of **282** using benzyl bromide and sodium hydride afforded the final 1,3-diene **268c** in 54% yield.



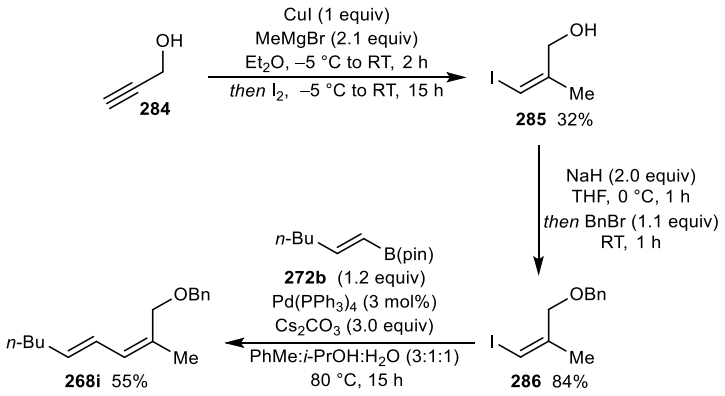
Scheme 96. Synthesis route of 1,3-dienes **282** and **268c**

Using commercially available vinyl bromide **283** and alkenyl boronate ester **272b**, the geminal dimethyl 1,3-diene **268d** was synthesised in 74% yield under Suzuki-Miyaura conditions (Scheme 97).



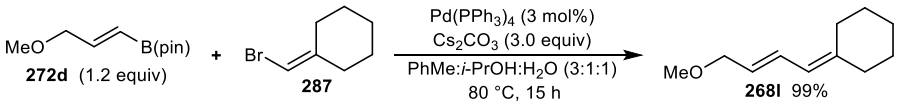
Scheme 97. Synthesis route of 1,3-diene **268d**

1,3-Diene **268i** in the Z-configuration at the trisubstituted alkene was prepared in four steps, starting from alkyne **284** (Scheme 98). Vinyl iodide **285** was synthesised in 32% yield from propargyl alcohol **284** when reacted with MeMgBr, CuI and iodine. Next, benzylation afforded vinyl iodide **286** in 84% yield. Finally, **286** was coupled with alkenyl boronate ester **272b** to give 1,3-diene **268i** in 55% yield.



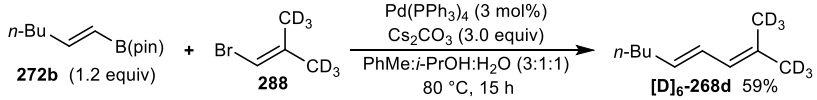
Scheme 98. Synthesis route of 1,3-diene **268i**

1,3-Diene **268l**, containing geminal methylene groups, was prepared in 99% yield, *via* a Suzuki-Miyaura reaction, by coupling commercially available vinyl bromide **287** with alkenyl boronate ester **272d** (Scheme 99).



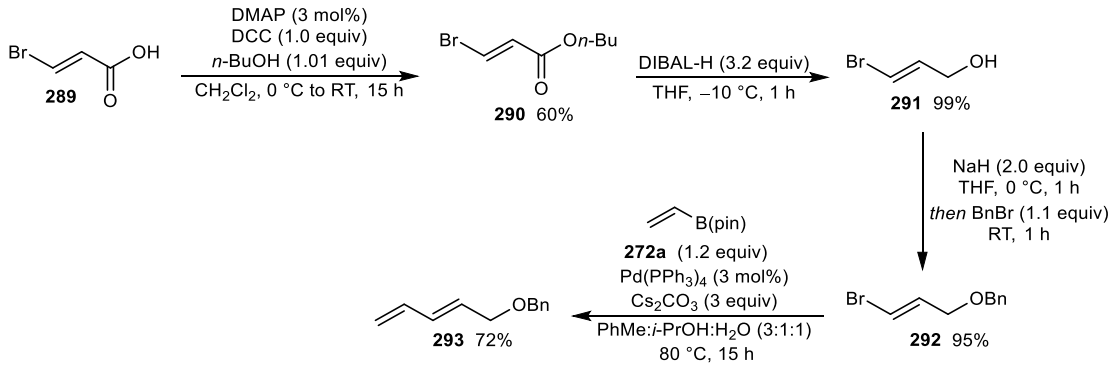
Scheme 99. Synthesis route of 1,3-diene **268l**

Hexadeuterated 1,3-diene $[D]_6$-**268d** was prepared from vinyl bromide **288** and alkenyl boronate ester **272b** *via* a Suzuki-Miyaura coupling, in 59% yield (Scheme 100).



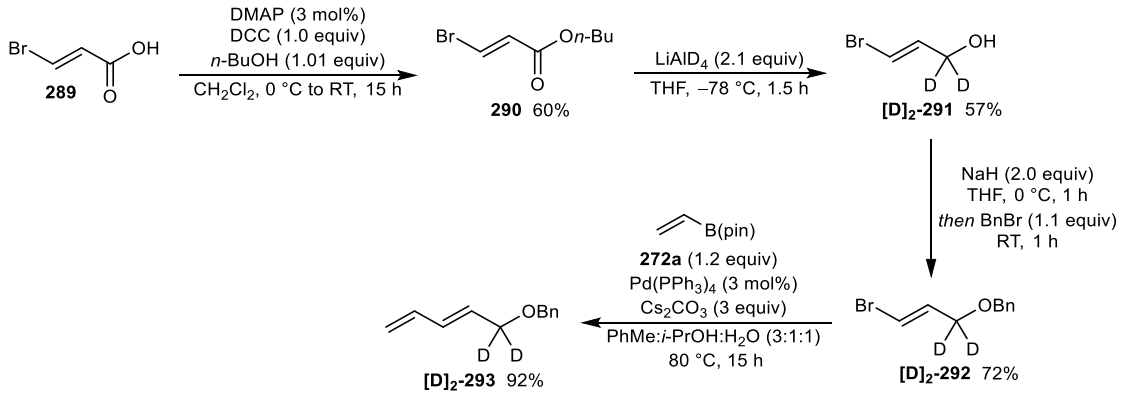
Scheme 100. Synthesis route of $[D]_6$-**268d**

Monosubstituted 1,3-diene **293** was synthesised starting from carboxylic acid **289** (Scheme 101). Carboxylic acid **289** was coupled with *n*-BuOH using DCC and a catalytic amount of DMAP, to give ester **290** in 60% yield. Ester **290** was then reduced by DIBAL-H to the corresponding alcohol **291**, in 99% yield. Next, alcohol **291** was reacted with sodium hydride and benzyl bromide to afford ether **292** in 95% yield, which was used in the Suzuki-Miyaura step giving 1,3-diene **293** in 72% yield.



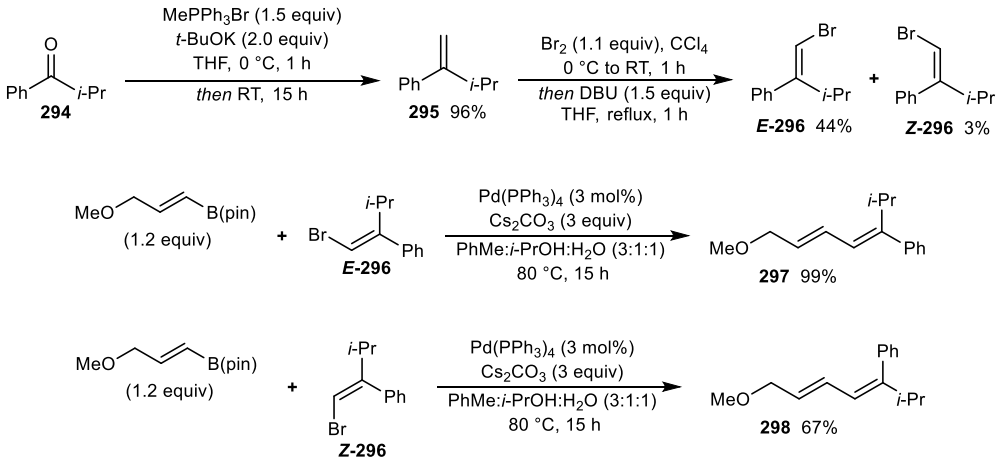
Scheme 101. Synthesis route of 1,3-diene **293**

Dideuterated 1,3-diene $[D]_2$-**293** was also prepared in an analogous manner to 1,3-diene **293**, starting from carboxylic acid **289** (Scheme 102). This was converted to ester **260** in 60% yield, and reduced to alcohol $[D]_2$-**291** using $LiAlD_4$, in 57% yield. Benzylation proceeded smoothly and afforded product $[D]_2$-**292** in 72% yield. Suzuki-Miyuara cross-coupling was then performed to give the dideuterated 1,3-diene $[D]_2$-**293** in 92% yield.



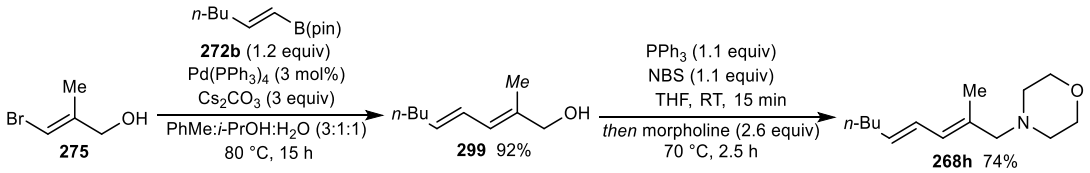
Scheme 102. Synthesis route of 1,3-diene $[D]_2$-**293**

1,3-Dienes **297** and **298**, containing an *i*-Pr group at the trisubstituted alkene, were prepared starting from ketone **294** (Scheme 103). A Wittig reaction of ketone **294** with $MePPh_3Br$ in the presence of *t*-BuOK was performed, yielding alkene **295** in 96% yield. This was brominated and upon elimination afforded both *E*-**296** and *Z*-**296** vinyl bromides in 44 and 3% yield. These were then subjected to Suzuki-Miyaura conditions giving 1,3-diene **297** and **298** in 99 and 67% yield respectively.



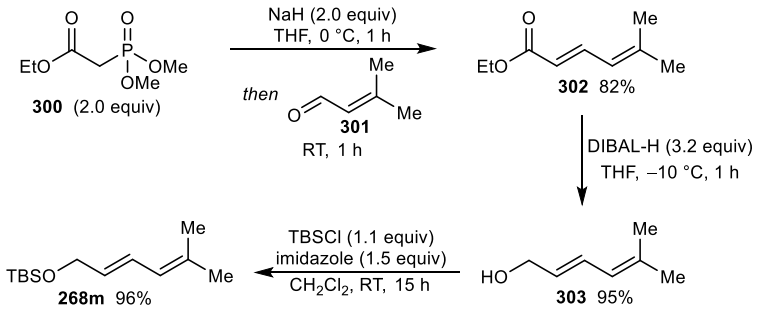
Scheme 103. Synthesis route of 1,3-dienes **297** and **298**

Next, 1,3-diene **299** was prepared in 92% yield by coupling vinyl bromide **275** with alkenyl boronate ester **272b** (Scheme 104). The 1,3-diene formed was reacted with PPh_3 and NBS followed by morpholine giving 1,3-diene **268h** in 74% yield.



Scheme 104. Synthesis of 1,3-dienes **299** and **268h**

1,3-Diene **268m** was prepared *via* an alternative route to the Suzuki-Miyuara cross-coupling (Scheme 105). A Horner-Wadsworth-Emmons reaction using ethyl phosphonoacetate **300**, enal **301** and sodium hydride afforded 1,3-diene **302** in 82% yield. This was reduced to alcohol **303** using DIBAL-H, in 95% yield. Finally, silyl ether **268m** was formed in 96% yield by reacting alcohol **303** with TBSCl in the presence of imidazole.

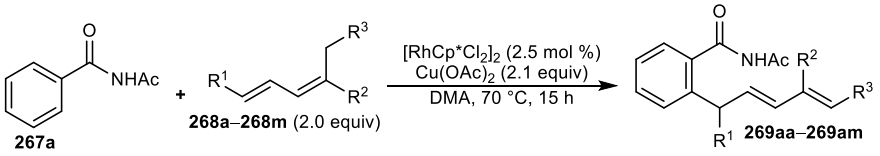


Scheme 105. Synthesis of 1,3-diene **268m**

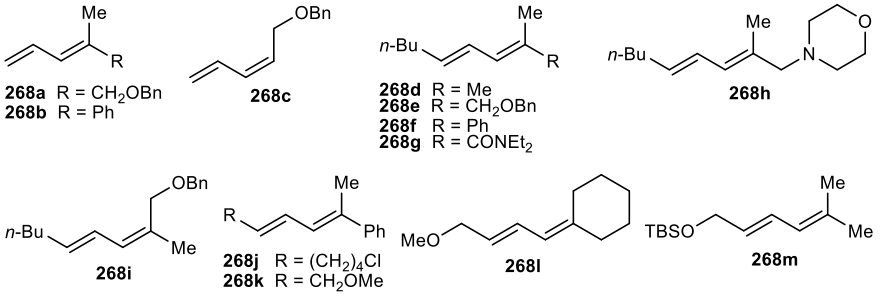
2.4 Substrate scope of Rh(III)-catalysed oxidative C–H allylation of *N*-acetylbenzamides with 1,3-dienes

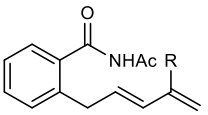
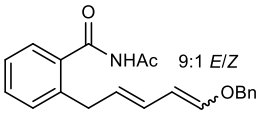
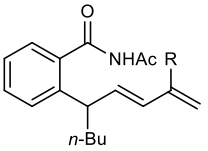
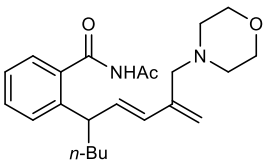
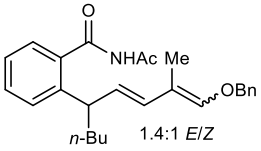
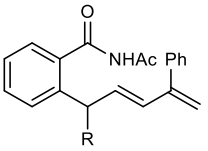
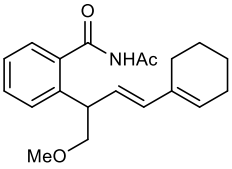
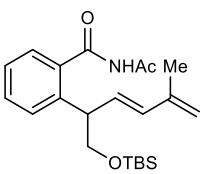
Having finalised the reaction conditions for the allylation of *N*-acetylbenzamides, the substrate scope of the reaction was evaluated. Firstly, the scope of the reaction with respect to 1,3-dienes was examined. Terminal 1,3-dienes were tolerated to give products in moderate to good yields, ranging from 48 to 61% yield (Table 10, Entries 1–3). To avoid significant diallylation, when using terminal 1,3-dienes, benzamide **267a** was used in excess (2 equiv). In addition, R^2 could be either an alkyl or an aryl group, giving the allylated products in good yields, ranging from 63 to 77% yield (Table 10, Entries 4–6). However, when R^2 was an amide group a lower yield of 26% was achieved (Table 10, Entry 7). Furthermore, when using the more reactive aryl-substituted 1,3-dienes **268e**, **268j** and **268k**, two equivalents of benzamide **267a** were used to prevent diallylation. This afforded the corresponding products in 62, 63 and 76% yield (Table 10, Entries 6, 10 and 11). Notably, the morpholine moiety was tolerated giving a yield of 60% (Table 10, Entry 8). Moreover, using 1,3-diene **268i**, which is a geometrical isomer of 1,3-diene **268e**, afforded dienol benzyl ether **269al** in 31% yield. The reaction did not go to completion, though none of **269ae** was detected in this reaction. Importantly, metal migration to a methylene position was also successful, giving product **269al** in 82% yield, thus highlighting the versatility of this transformation (Table 10, Entry 12). Product **269am** containing a silyl ether was also synthesised, however it was isolated in a moderate yield of 36% (Table 10, Entry 13).

Table 10.1,3-Diene scope



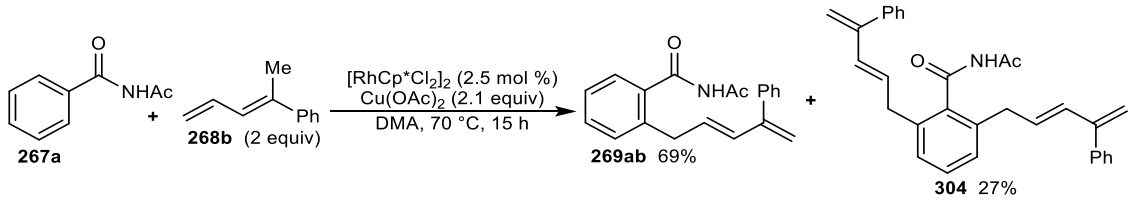
1,3-dienes:



Entry	1,3-Diene	Product		R	Yield (%)
1[a]	**268a**		**269aa**	CH_2OBn	50
2[a]	**268b**		**269ab**	Ph	48
3[a]	**268c**		**269ac**		61
4	**268d**		**269ad**	Me	77
5	**268e**		**269ae**	CH_2OBn	77
6[a]	**268f**		**269af**	Ph	63
7	**268g**		**269ag**	$CONEt_2$	26
8	**268h**		**269ah**		60
9	**268i**		**269ai**		31
10[a]	**268j**		**269aj**	$(CH_2)_4Cl$	62
11[a]	**268k**		**269ak**	CH_2OMe	76
12	**268l**		**269al**		82
13	**268m**		**269am**		36 (58)[b]

[a] Conducted using **267a** (2 equiv). [b] Yield determined by ^{1}H NMR spectroscopy using 1,3,5- trimethoxybenzene as the internal standard

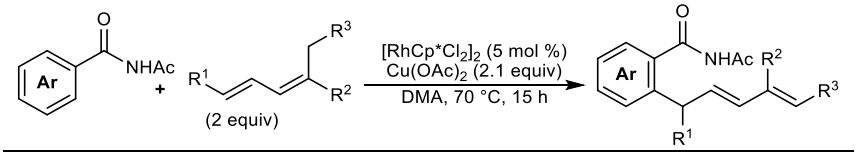
Of note, using terminal 1,3-diene **268b** in excess afforded a significant amount of the diallylation product **304**, a result of both *ortho*-positions of **267a** being functionalised (Scheme 106). However, we demonstrated that the selectivity of mono- *vesrus* diallylation could be controlled by increasing the equivalents of benzamide used, to two (Table 10, Entry 2).

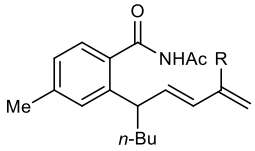
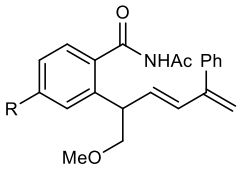
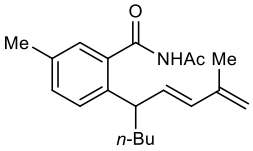
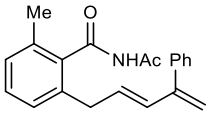
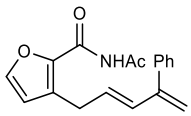
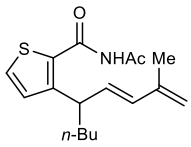


Scheme 106. Diallylation achieved when using terminal 1,3-diene in excess

Next, the scope of the reaction with respect to *N*-acetylbenzamide was examined with representative 1,3-dienes (Table 11). An electron-withdrawing substituent at the *para*-position, such as nitro, had negligible impact on the reaction in comparison to non-substituted benzamides, yielding product **269dk** in 75% yield (Table 11, Entry 4). On the other hand, an electron-donating *para* substituent, such as methoxy, gave product **269ck** in a lower yield of 46% (Table 11, Entry 3). Notably, *meta*- and *ortho*-substituents were also tolerated (Table 11, Entries 5 and 6). When one of the *ortho*-positions is blocked, the reaction can be driven to completion, resulting in 98% yield of product **269fb** (Table 11, Entry 6). Additionally, 5-membered carboxamides **267g** and **267h** could also undergo C–H allylation, though affording products **269gb** and **269hd** in modest yields of 40 and 38% respectively (Table 11, Entries 7 and 8).

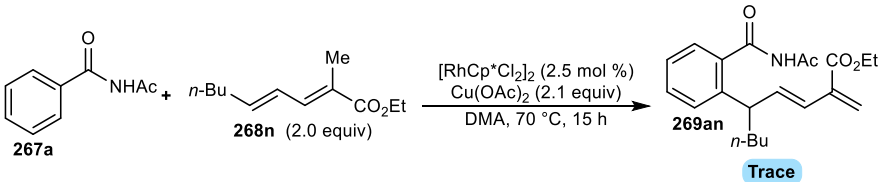
Table 11. *N*-acetylbenzamide scope



Entry	1,3-Diene	Product		R	Yield (%)
1	**268d**		**269bd**	Me	53
2	**268e**		**269be**	CH_2OBn	53
3[a]	**268k**		**269ck**	OMe	46
4[a]	**268k**		**269dk**	NO_2	75
5	**268d**		**269ed**		64
6	**268b**		**269fb**		98
7	**268b**		**269gb**		40
8	**268d**		**269hd**		38

[a] Conducted using *N*-acetylbenzamide **267** (2 equiv)

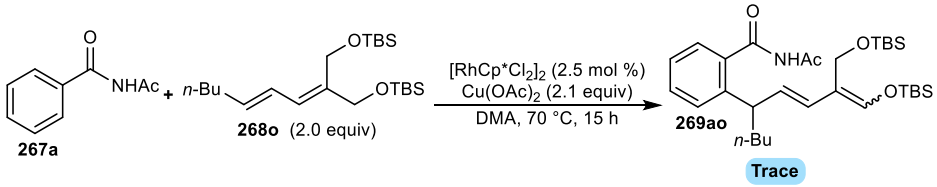
A trace amount of product **269an** was observed when reacting 1,3-diene **268n** containing an ester group, and the starting materials were recovered (Scheme 107). It is not known why this 1,3-diene was not effective.



Scheme 107. Experiment using a 1,3-diene incorporating an ester

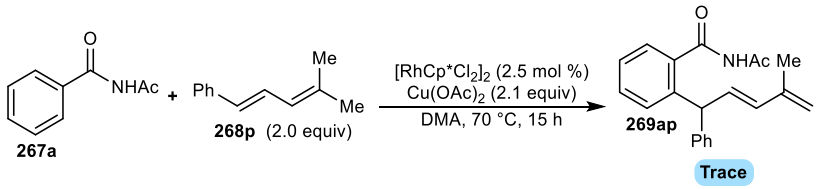
Furthermore, using 1,3-diene **268o** afforded a trace amount of the expected product **269ao**, and the starting reagents were recovered (Scheme 108). It is possible that due

to increased steric congestion caused by the bulky CH_2OTBS moieties, migration to the methylene position was not feasible.



Scheme 108. Experiment using a 1,3-diene incorporating a disilyl ether

Interestingly, 1,3-diene **268p**, incorporating a phenyl group at the mono-substituted terminus of the 1,3-diene, gave a trace amount of expected product **269ap** (Scheme 109). This lack of reactivity is also evident in relevant examples in the literature, where most alkenes used are terminal (see introduction section for examples).[8] Also, when styrenes are used, C–H functionalisation occurs exclusively at the alkenyl methylene. In this case, the terminal ends of the 1,3-diene are relatively sterically hindered, thus making C–H functionalisation challenging. Electronic effects induced by the phenyl could also play a role.

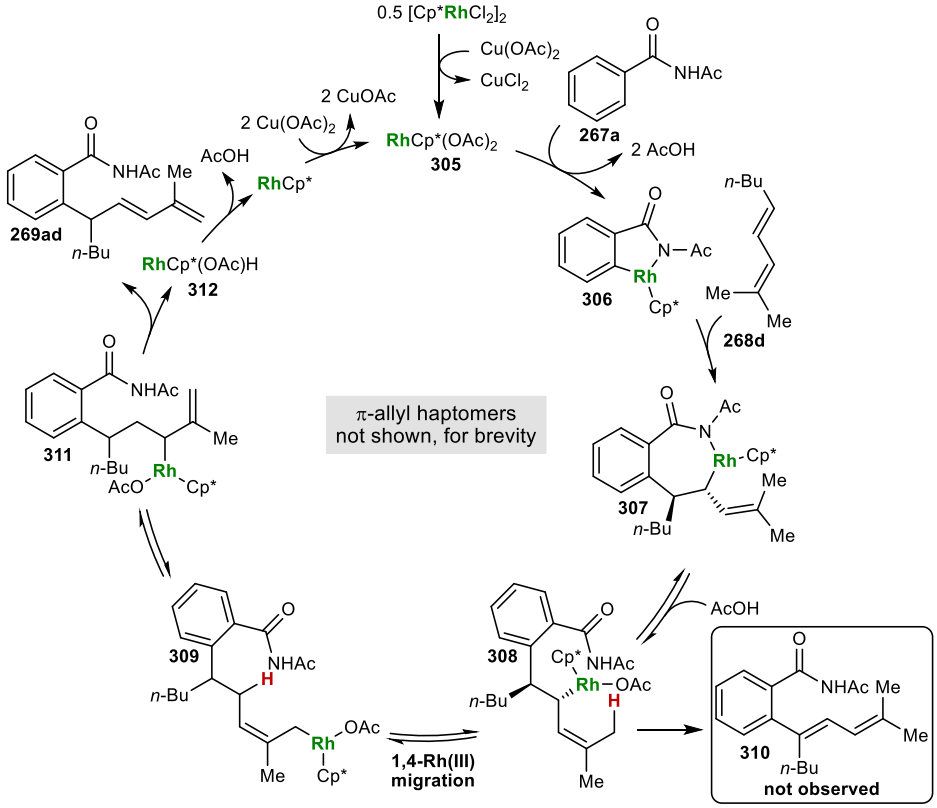


Scheme 109. Experiment using a 1,3-diene incorporating a phenyl

2.5 Mechanistic analysis of Rh(III)-catalysed oxidative C–H allylation of *N*-acetylbenzamides with 1,3-dienes

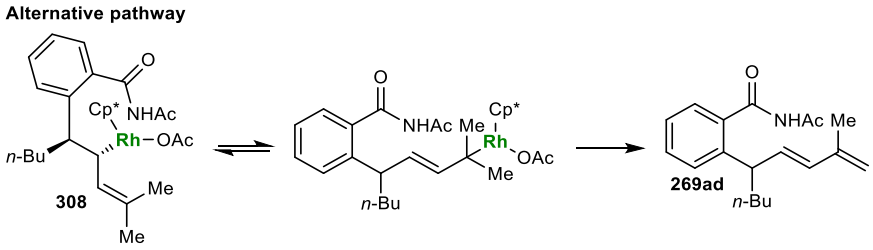
The proposed catalytic cycle begins with generation of the catalytically active $RhCp^*(OAc)_2$ species **305** *in situ*, by ligand exchange with $Cu(OAc)_2$ (Scheme 110). Next, C–H activation of benzamide **267a** affords a 5-membered rhodacycle **306** capable of coordinating to 1,3-diene **268d** at the less-substituted alkene and undergoing a migratory insertion, which forms *σ*-allylrhodium species **307**. Subsequent acetolysis of **307** is possible, resulting in intermediate **308**, which can then undergo a 1,4-migration to the other *cis*-allylic position **309**. Intriguingly, product **310** resulting from direct *β*-hydride elimination of **308** is not observed. However, *β*-

hydride elimination cannot be completely excluded as it may be reversible if in fact it were to occur. Furthermore, it is possible that the aforementioned acetolysis step does not take place, instead rhodium remains bound to the directing group, as coordinatively saturated Rh(III) species **307**, and as a result migration could be favoured over *β*-hydride elimination. There is literature precedent in which competitive *β*-hydride elimination is prevented by chelation with the directing group, allowing for an alternative pathway to take place (Scheme 43).[95] Through a 1,3-allylic transposition **309** is able to form *σ*-allylrhodium species **311**. *β*-Hydride elimination then furnishes the isolated product **269ad** and Rh(III) species **312** which upon reductive elimination and re-oxidation by $Cu(OAc)_2$ the catalytically active species **305** is regenerated.



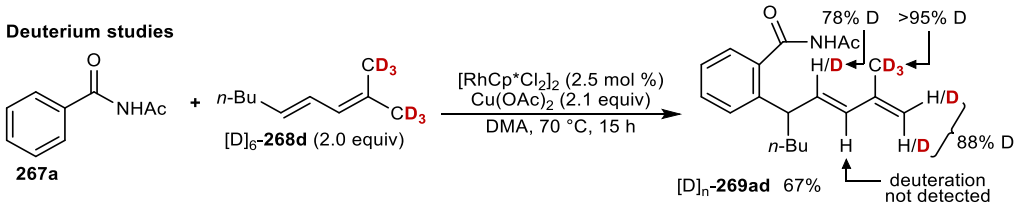
Scheme 110. Proposed catalytic cycle in which an allyl-to-allyl 1,4-Rh(III) migration occurs

The possibility of an alternative pathway was considered. In this pathway intermediate **308** instead of undergoing a 1,4-migration could undergo a 1,3-allylic transposition and subsequent *β*-hydride elimination yielding the same product **269ad** (Scheme 111).



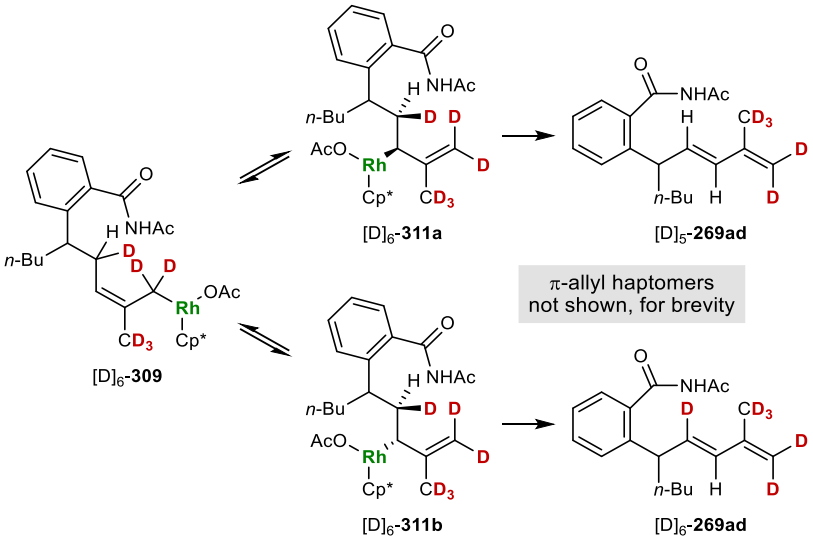
Scheme 111. Alternative pathway

An experiment using hexadeuterated 1,3-diene [D_6]-**268d** was conducted to support the 1,4-migration hypothesis (Scheme 112). This reaction afforded the deuterated product [D]$_n$-**269ad** in 67% yield.



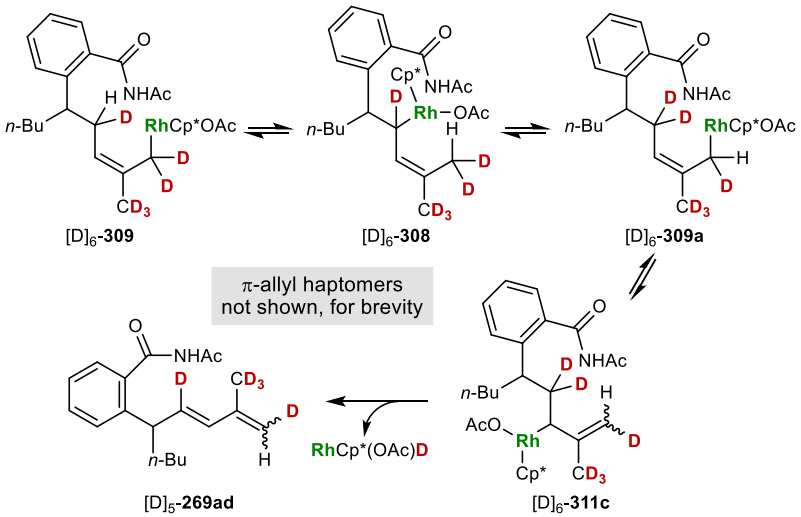
Scheme 112. Experiment using hexadeuterated 1,3-diene [D_6]-**268d**

The first observation of note was the significant, but incomplete, deuterium incorporation (78% D) observed from one of the CD_3 groups to the alkenyl carbon proximal to the benzene ring in product [D]$_n$-**269ad** (Scheme 112). The partial deuteration at this site may be explained by considering that σ-π-σ-isomerisation (1,3-allylic transposition) of [D]$_6$-**309** could afford [D]$_6$-**311a** or [D]$_6$-**311b** (Scheme 113). Next, deuterium depletion could occur by β-deuteride elimination of [D]$_6$-**311a** to give [D]$_5$-**269ad**, while β-hydride elimination of [D]$_6$-3**11b** would give [D]$_6$-**269ad**.



Scheme 113. *β*-Deuteride elimination accounting for partial deuteration (78% D)

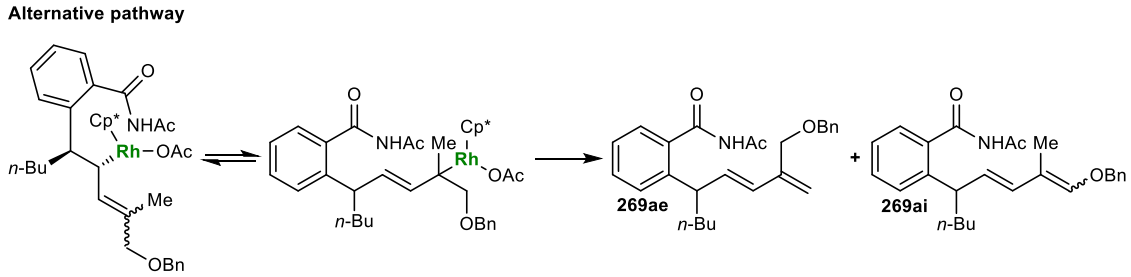
Secondly, partial deuterium incorporation (88% D) is also observed at the alkenyl methylene site of [D]$_n$-**269ad** (Scheme 114). This observation suggests that the metal migration is likely to be reversible between [D]$_6$-**309**, [D]$_6$-**308**, and [D]$_6$-**309a** leading to deuterium–hydrogen exchange between the two *cis*-allylic positions (Scheme 114). Finally, *σ*-*π*-*σ*-isomerisation of **[**D]$_6$-**309a** would provide [D]$_6$-**311c**, from which *β*-deuteride elimination would give [D]$_5$-**269ad**, thus accounting for the deuterium depletion at the alkenyl methylene site.



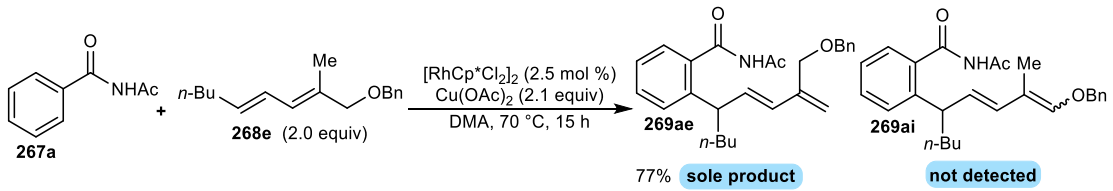
Scheme 114. Reversible allyl-to-allyl 1,4-Rh(III) migration accounting for partial deuteration (88% D)

Additionally, substrates containing non-identical geminal groups, such as **268e** or **268i**, should result in a mixture of products **269ae** and **269ai** if an isomerisation followed by *β*-hydride elimination took place (Scheme 115). Instead only a single

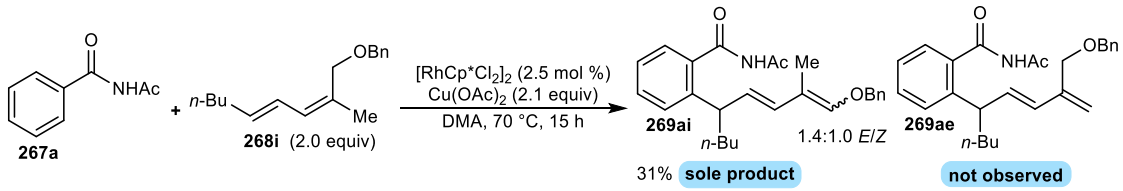
product was detected when using 1,3-diene **268e** and **268i** (Schemes 116 and 117). These experiments also supported that a 1,4-migration pathway was more likely to occur over the alternative pathway consisting of an isomerisation followed by *β*-hydride elimination (Scheme 115).



Scheme 115. Proposed products generated for alternative pathway

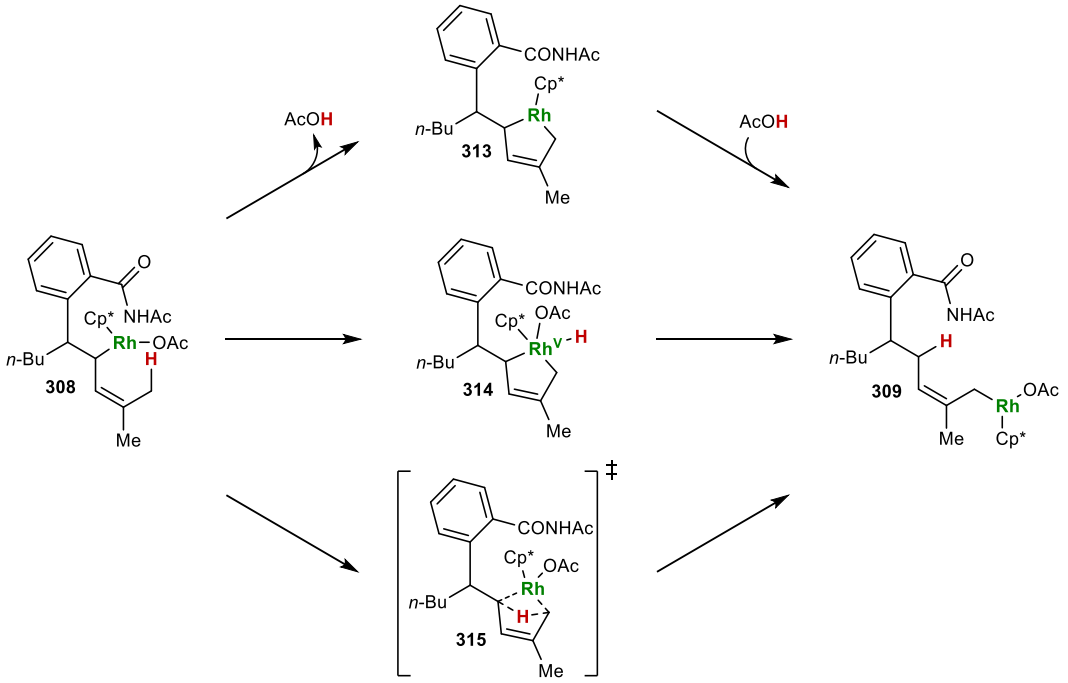


Scheme 116. Experiment using 1,3-diene **268e**



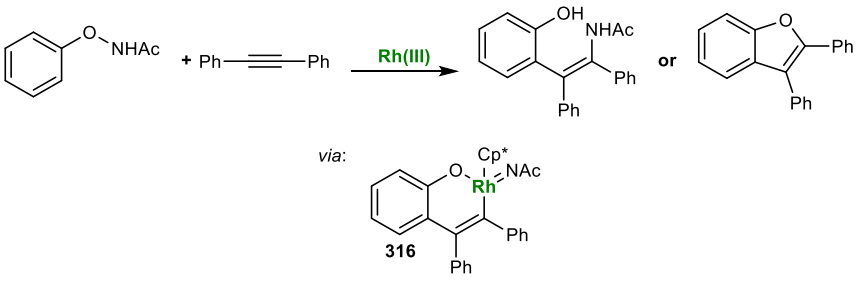
Scheme 117. Experiment using 1,3-diene **268i**

Based on literature precedent we have outlined three possible routes regarding the actual mechanism of the allyl-to-allyl 1,4-Rh(III) migration (Scheme 118). First, a mechanism similar to that proposed for alkenyl-to-allyl 1,4-Rh(III) migration was possible (Schemes 67 and 69).[122,123] This would involve an acetate assisted, concerted–metallation–deprotonation of **308**, which would give rhodacycle **313**, which after acetolysis would form the other key *σ*-allylrhodium intermediate **309**.



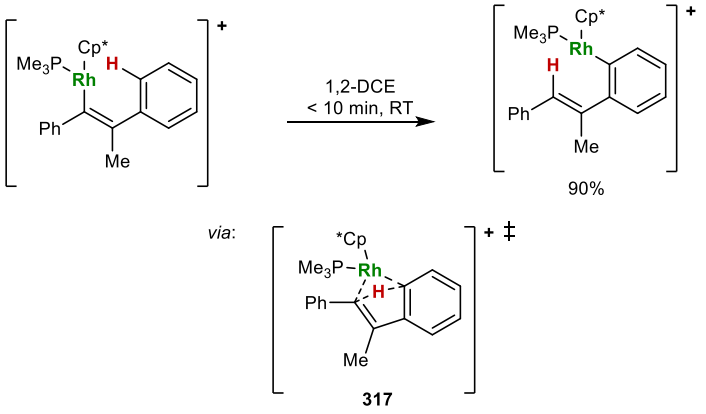
Scheme 118. Possible allyl-to-allyl 1,4-Rh(III) migration mechanisms

Alternatively, **308** could undergo C–H oxidative addition to form a Rh(V) species **314**, which upon C–H reductive elimination would generate **309** (Scheme 118).[92,140,141] Of note, thus far Rh(V) complexes are not known to be intermediates in 1,4-Rh(III) migrations, though they have been postulated as intermediates in various C–H functionalisation methodologies, in the form of Rh(V)-nitrenoids.[92,140,141] An example involving Rh(V)-nitrenoid intermediate **316**, supported by DFT studies, was recently reported by Wu and colleagues (Scheme 119).[141]



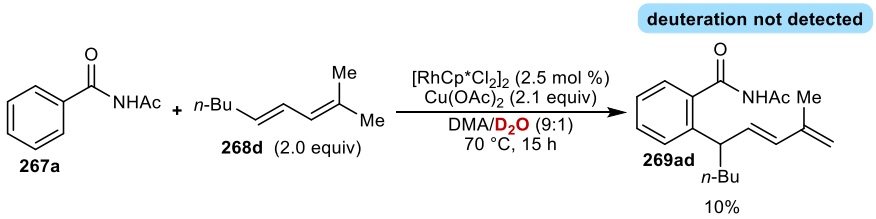
Scheme 119. Proposed Rh(V) intermediate in C–H functionalisation

Finally, the formation of **309** could proceed *via* *σ*-complex-assisted metathesis involving transition state **315** (Scheme 118).[142–144] In comparison, the first example of alkenyl-to-aryl 1,4-Rh(III) migration was studied by Kantchev and co-workers, and was postulated to proceed *via* the formation of *σ*-complex transition state **317**; this was supported by DFT calculations (Scheme 120).[32,142,143]

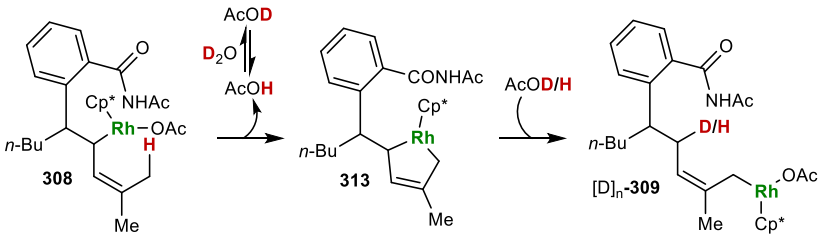


Scheme 120. Proposed σ-CAM for alkenyl-to-aryl 1,4-Rh(III) migration

To investigate the possibility of an acetate-assisted CMD pathway *via* intermediate **313**, the reaction of *N*-acetylbenzamide **267a** with 1,3-diene **268d** was conducted in a 9:1 mixture of DMA/D_2O (Scheme 121). Here, AcOH would be generated during the CMD step, which in the presence of D_2O would produce a mixture of AcOD/H (Scheme 122). As a result, $[D]_n$-**309** would be expected to form due to partial deuteronolysis of **313**, as observed in alkenyl-to-allyl 1,4-Rh(III) migrations.[122,123] In the event, D_2O markedly decreased the efficiency of oxidative C–H allylation. Nevertheless, **269ad** was isolated in 10% yield without any deuterium incorporation. This result may suggest that the intermediacy of **313** is less likely and that C–H oxidative addition–reductive elimination or σ-CAM pathways may be more probable mechanisms for allyl-to-allyl 1,4-Rh(III) migration.

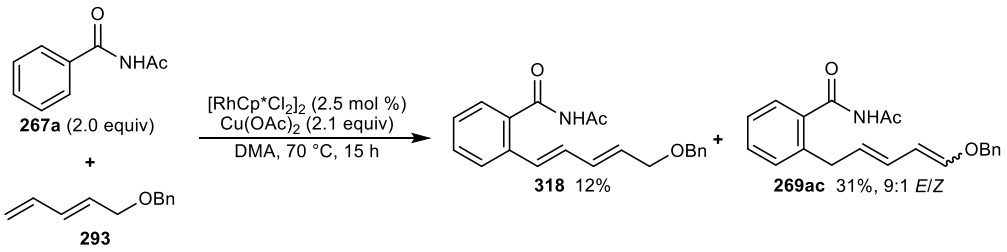


Scheme 121. Rh(III)-catalysed oxidative C–H allylation in the presence of D_2O



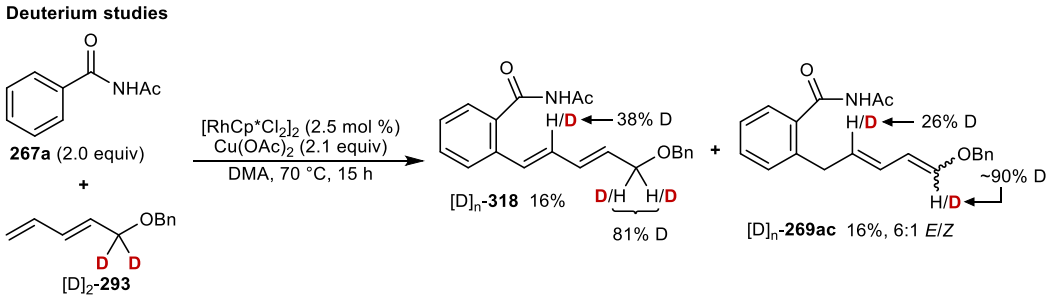
Scheme 122. Proposed intermediates in acetate-assisted CMD mechanism in the presence of D_2O

Thus far, we have only described examples of 1,3-dienes containing *cis*-allylic hydrogens (section 2.4). The reaction of 1,3-diene **293**, lacking *cis*-allylic hydrogens, with *N*-acetylbenzamide **267a** afforded both alkenylation **318** and allylation **269ac** products, in 12 and 31% yield respectively (Scheme 123).



Scheme 123. Rh(III)-catalysed oxidative C–H alkenylation and allylation using 1,3-diene **293**

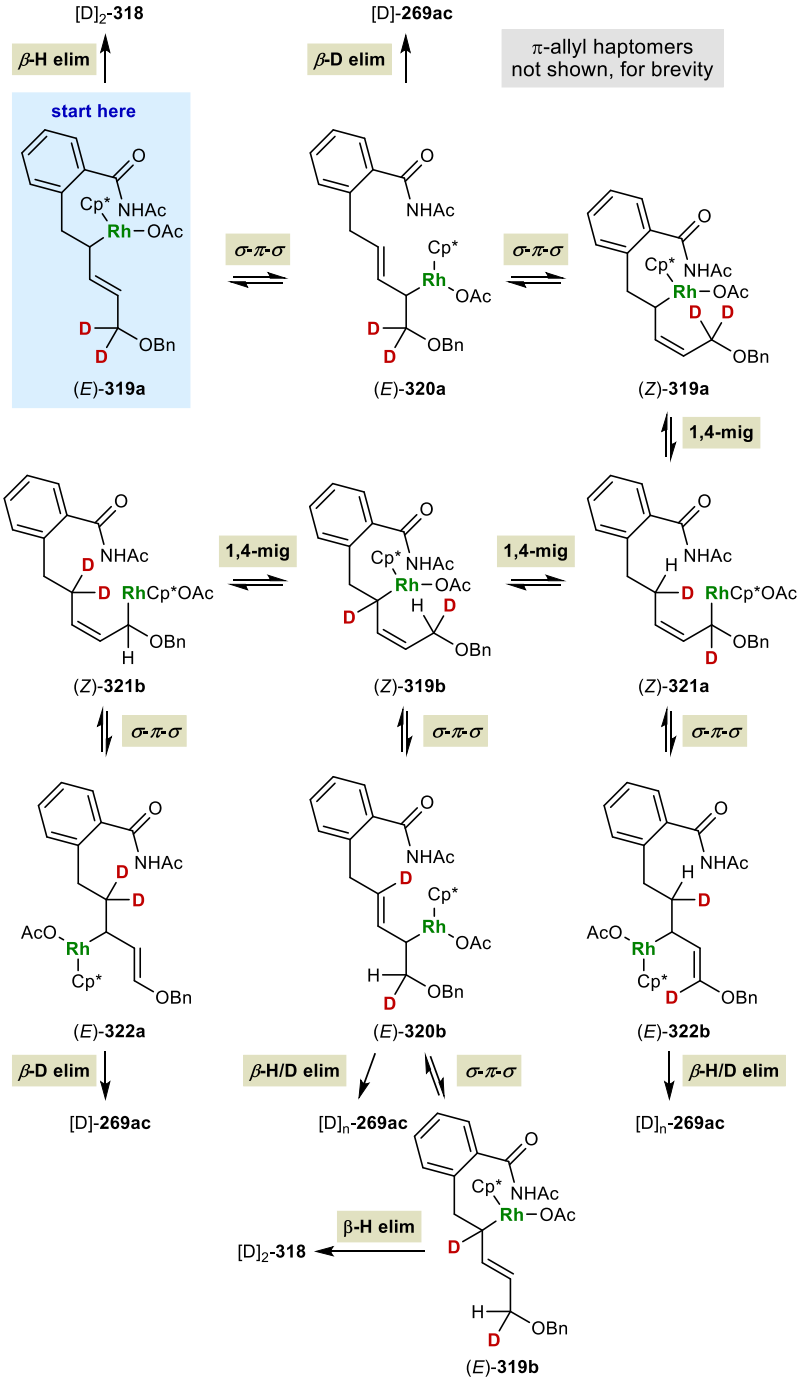
The analogous experiment was conducted using dideuterated 1,3-diene [D]$_2$-**293** to investigate whether 1,4-Rh(III)-migration was a key step in the formation of either of these products (Scheme 124). Indeed, both alkenylation [D]$_n$-**318** and allylation [D]$_n$-**269ac** products displayed considerable deuterium incorporation (38 and 26% D respectively) at the alkenyl position two carbons away from the benzene ring, which is consistent with the allyl-to-allyl 1,4-Rh(III) migration mechanism.



Scheme 124. Rh(III)-catalysed oxidative C–H alkenylation and allylation using 1,3-diene [D]$_2$-**293**

The considerable 1,4-deuterium transfer in both ([D]$_n$-**318**) and [D]$_n$-**269ac** indicated that a complex mechanism was operative, involving the interconversion between numerous allylrhodium moieties by σ-π-σ isomerisation, *E*/*Z* isomerisation, and allyl-to-allyl 1,4-Rh(III) migration pathways (Scheme 125). Foremost, the reaction of **267a** and [D]$_2$-**293** in the presence of [RhCp*Cl$_2$]$_2$, following the initial steps of the catalytic cycle shown in Scheme 110 leads to (*E*)-**319a**, which after β-hydride elimination could afford a dideuterated isomer ([D]$_2$-**318**) of alkenylation product ([D]$_n$-**318**). However, intermediate ((*E*)-**319a**) could also undergo σ-π-σ isomerisation into ((*E*)-**320a**), which

would give a monodeuterated allylation product [D]-**269ac** after *β*-deuteride elimination.



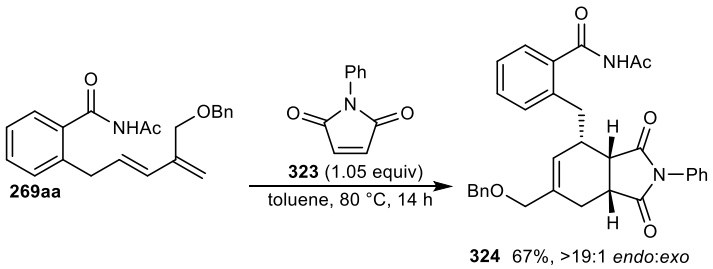
Scheme 125. Possible pathways accounting for 1,4-deuterium transfer

Alternatively, (*E*)-**319a** upon *σ*-*π*-*σ* isomerisation with concomitant *E*/*Z* isomerisation would generate (*Z*)-**319a**, from which a series of reversible allyl-to-allyl 1,4-Rh(III) migrations involving either a 1,4-deuterium or a 1,4-hydrogen shift would result in the formation of new allylrhodium moieties (*Z*)-**321a**, (*Z*)-**319b**, and (*Z*)-**321b**. The

aforementioned three intermediates could provide (*E*)-**322a**, (*E*)-**320b**, and (*E*)-**322b**, respectively, *via* *σ*-*π*-*σ* isomerisation, from which *β*-hydride or *β*-deuteride elimination would furnish mono- and dideuterated isomers of $[D]_n$-**269ac**. As a final point, *σ*-*π*-*σ* isomerisation of (*E*)-**320b** to (*E*)-**319b** and subsequent *β*-hydride elimination would yield a dideuterated isomer $[D]_2$-**293** of $[D]_n$-**318**.

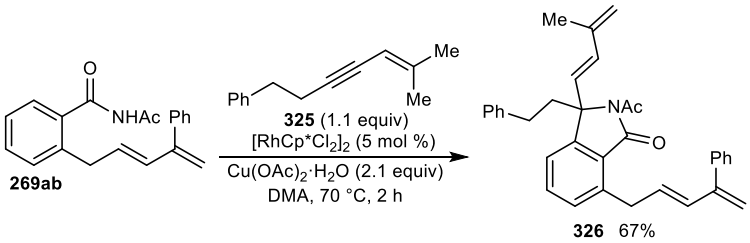
2.6 Product elaborations of Rh(III)-catalysed oxidative C–H allylation of *N*-acetylbenzamides with 1,3-dienes

The synthetic utility of allylation product **269aa** was demonstrated by performing a Diels–Alder reaction with *N*-phenylmaleimide **323**, affording adduct **324** in 67% with >19:1 *endo*:*exo* selectivity (Scheme 126).



Scheme 126. Diels–Alder reaction using **269aa**

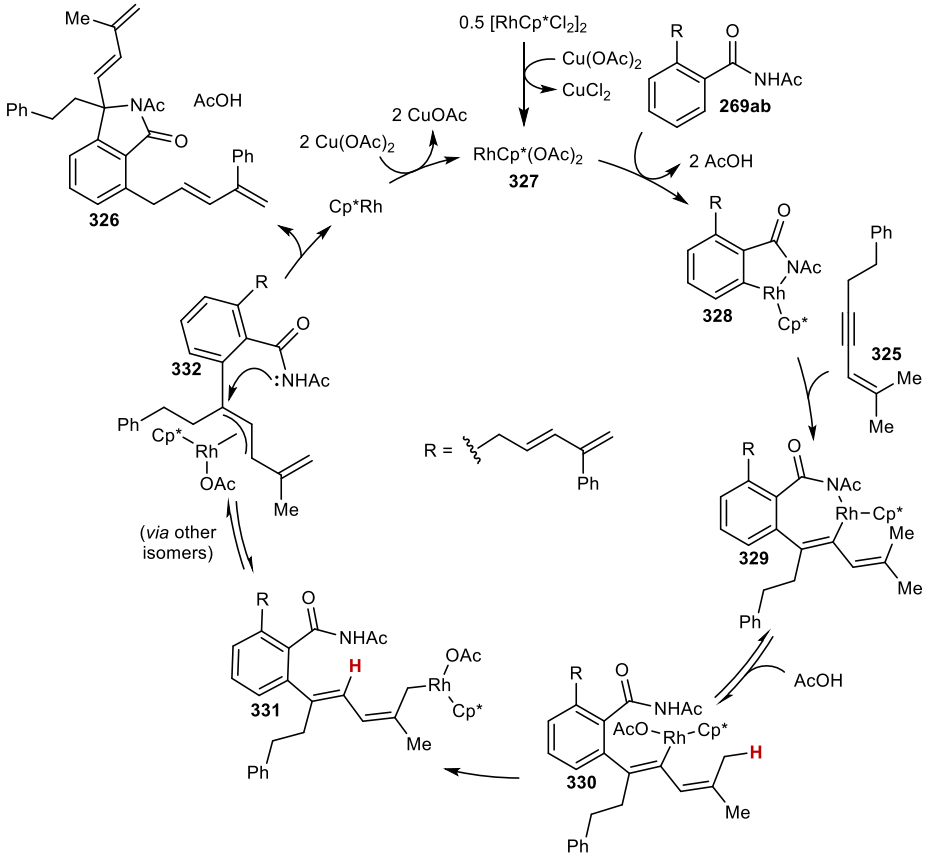
Additionally, a second C–H functionalisation was performed on product **269ab** using 1,3-enyne **325**, furnishing annulation product **326** in 67% yield (Scheme 127). This transformation involves an alkenyl-to-allyl 1,4-Rh(III) migration as the key step.[122]



Scheme 127. C–H functionalisation of **269ab** involving an alkenyl-to-allyl 1,4-Rh(III) migration

The postulated catalytic cycle involves the formation of the catalytically active Rh(III) species **327**, which upon cyclorhodation with **269ab** forms rhodacycle **328** (Scheme 128). Next, migratory insertion of 1,3-enyne **325** forms an alkenylrhodium species

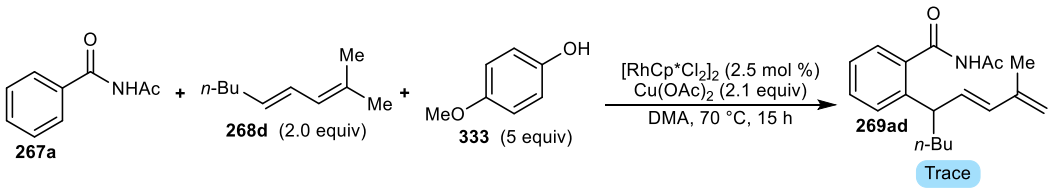
329, that upon acetolysis gives **330**, which then undergoes an alkenyl-to-allyl 1,4-Rh(III) migration generating σ-allylrhodium intermediate **331**. Through a 1,3-allylic transposition, a new allyl rhodium intermediate is formed, which can exist in the form of π-allyl intermediate **332**. Finally, cyclisation of the nitrogen onto π-allylrhodium species **332** furnishes [4+1] annulation product **326**.



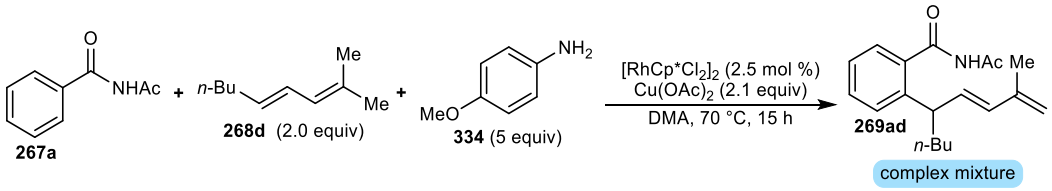
Scheme 128. Mechanism for formation of product **326**

2.7 Attempts at intercepting the allylrhodium(III) species generated in Rh(III)-catalysed oxidative C–H allylation of *N*-acetylbenzamides with 1,3-dienes

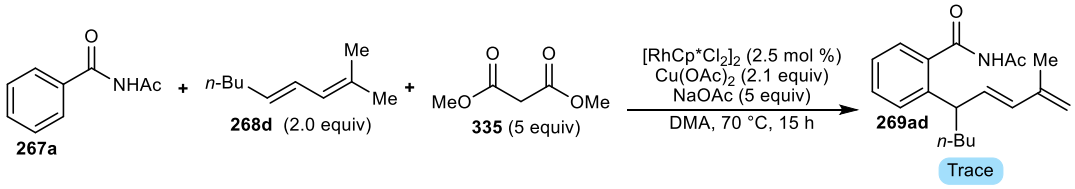
Next, attempts were made to intercept any of the π-allylrhodium(III) species generated *in situ* (Schemes 129–132). Based on relevant literature, allylrhodium(III) species are considered to be electrophilic, and thus a range of external nucleophiles (**333–336**) were included in the allylation reactions.[122,123] In all experiments, no products incorporating the nucleophile were detected; instead, trace amounts of the standard allylation product **269ad** were observed in all cases aside from when using *para*-anisidine (**334**) which gave a complex mixture containing **269ad**.



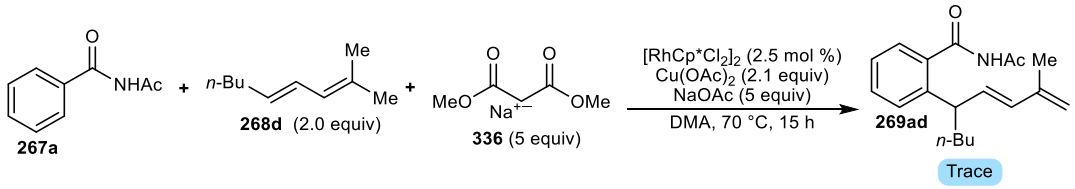
Scheme 129. Experiment using *para*-anisole (**333**) to intercept π-allylrhodium(III) intermediates



Scheme 130. Experiment using *para*-anisidine (**334**) to intercept π-allylrhodium(III) intermediates



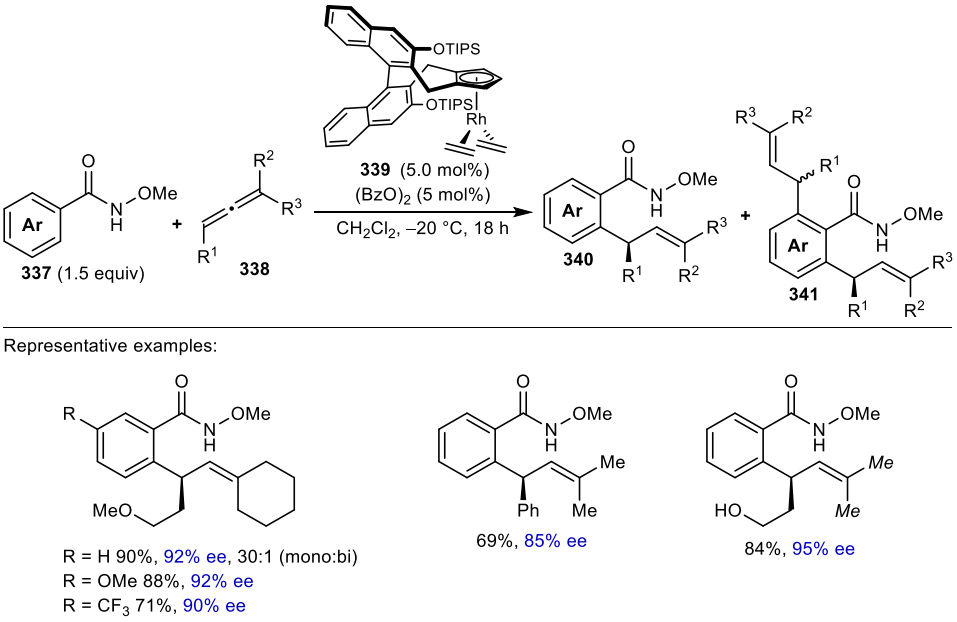
Scheme 131. Experiment using dimethyl malonate (**335**) to intercept π-allylrhodium(III) intermediates



Scheme 132. Experiment using dimethyl malonate sodium salt (**336**) to intercept π-allylrhodium(III) intermediates

2.8 Enantioselective Rh(III)-catalysed oxidative C–H allylation of *N*-acetylbenzamides with 1,3-dienes

Enantioselective methodologies constructing heterocycles or carbocycles with the use of chiral cyclopentadienyl ligands under Rh(III) catalysis have recently been developed by Cramer, You and Lam.[42,145–148] Cramer and co-workers first reported the allylation of *N*-methoxybenzamides **337** with allenes **338**, using rhodium complex **339**, which afforded allylation products in high enantioselectivities and good to excellent yields (Scheme 133).[42] When non-substituted benzamides are used both mono- and biallylation products **340** and **341** are generally yielded.



Scheme 133. Enantioselective allylation of *N*-methoxybenzamides

The high enantioselectivity was achieved by creating a well-defined chiral pocket, due to the chiral ligand. The selectivity and reactivity of the chiral pocket could be controlled by adjusting the substitution at the 2-position of the binaphthyl moiety bound to the cyclopentadienyl ligand (Figure 4). The rhodium complex formed could be described as a pocket consisting of a side and back wall.

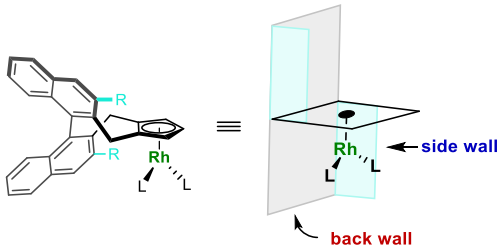
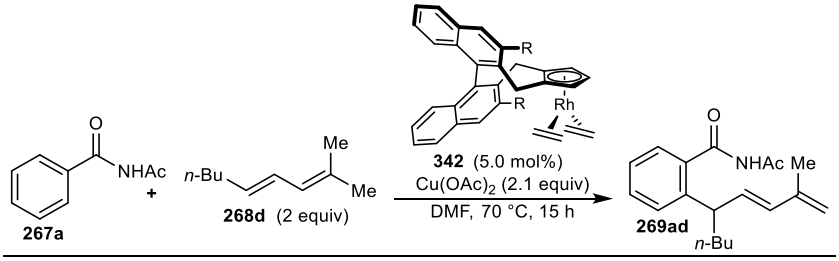


Figure 4. Chiral Cp ligands for enantioselective C–H functionalisations

Having developed a racemic methodology for the allylation of *N*-acetylbanzemides with 1,3-dienes, we became interested in whether an enantioselective variant would be possible. Rhodium complexes **342** bound to chiral cyclopentadienyl ligands were tested in the C–H allylation of *N*-acetylbenzamide **267a** with 1,3-diene **268d** (Table 12). Using the chiral rhodium complexes gave similar yields to the achiral complex, $[RhCp^*Cl_2]_2$, though only low to moderate enantioselectivities were achieved.

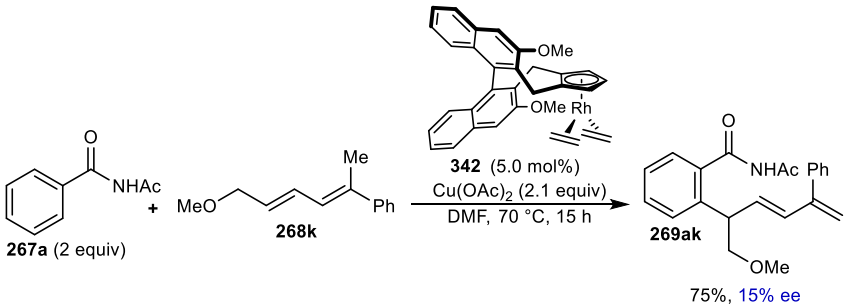
Table 12. Screening of chiral cyclopentadienyl ligands



Entry	Rh complex **342**	Yield (%)	ee (%)
1	R = OMe	61	30 (NR)[a]
2	R = TBDPS	60	31
3	R = TIPS	54	20

Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. Conducted by David J. Burns. [a] NR at RT or 40 °C

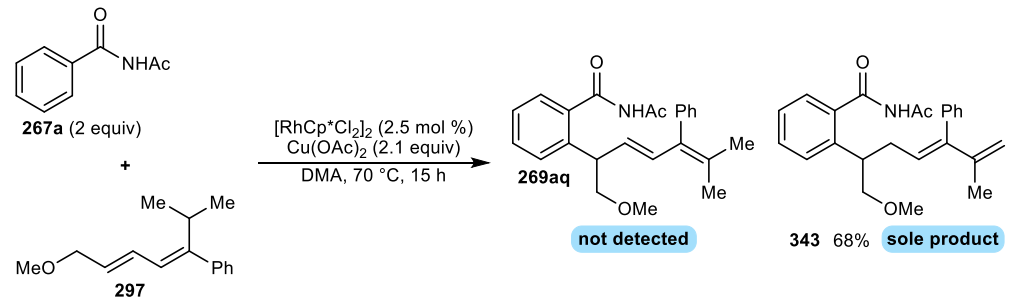
To investigate whether the moderate enantioselectivities were due to substrate **268d** an alternative 1,3-diene, **268k**, was also used in an experiment with *N*-acetylbenzamide **267a** (Scheme 134). However, this gave a lower enantioselectivity of 15%.



Scheme 134. Enantioselectivity using 1,3-diene **268k**. Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. Conducted by David J. Burns

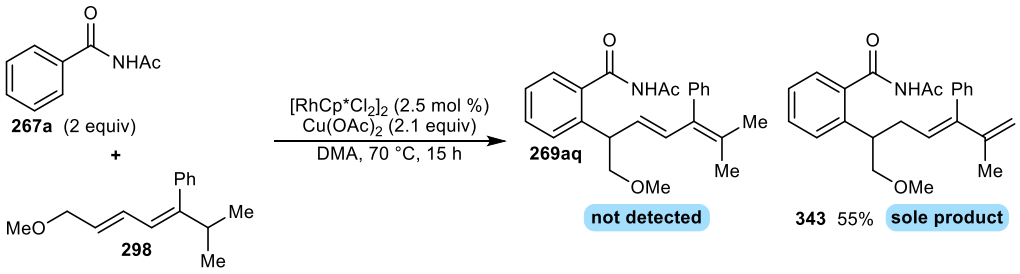
2.9 Rh(III)-catalysed oxidative C–H homoallylation of *N*-acetylbenzamides with 1,3-dienes: migration to a tertiary carbon

As described in section 2.4, the feasibility of the allyl-to-allyl 1,4-Rh(III) migration was established, in which the allylic position to which rhodium migrated to was either a primary or secondary carbon. Following this study, migration to a tertiary allylic carbon was also investigated, using 1,3-diene **297** and *N*-acetylbenzamide **267a** (Scheme 135). Surprisingly, the expected allylation product **269aq** was not formed; instead homoallylation product **343** was isolated as the sole product in 68% yield.



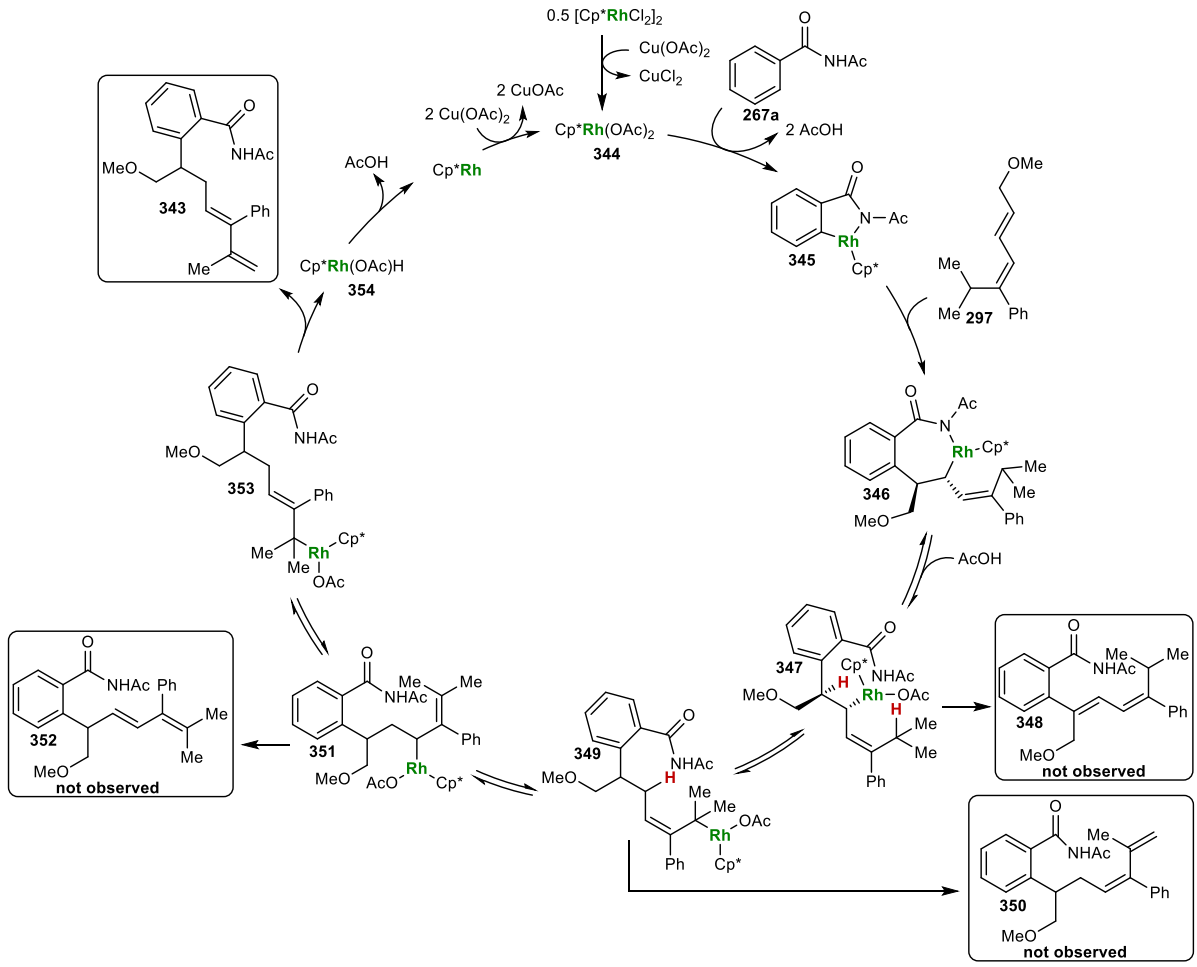
Scheme 135. Rh(III)-catalysed oxidative C–H homoallylation

Intriguingly, using 1,3-diene **298**, which is in the *E*-configuration at the trisubstituted alkene, did not form allylation product **269aq**. Instead the same homoallylation product **343** was isolated in 55% yield (Scheme 136).



Scheme 136. Rh(III)-catalysed oxidative C–H homoallylation

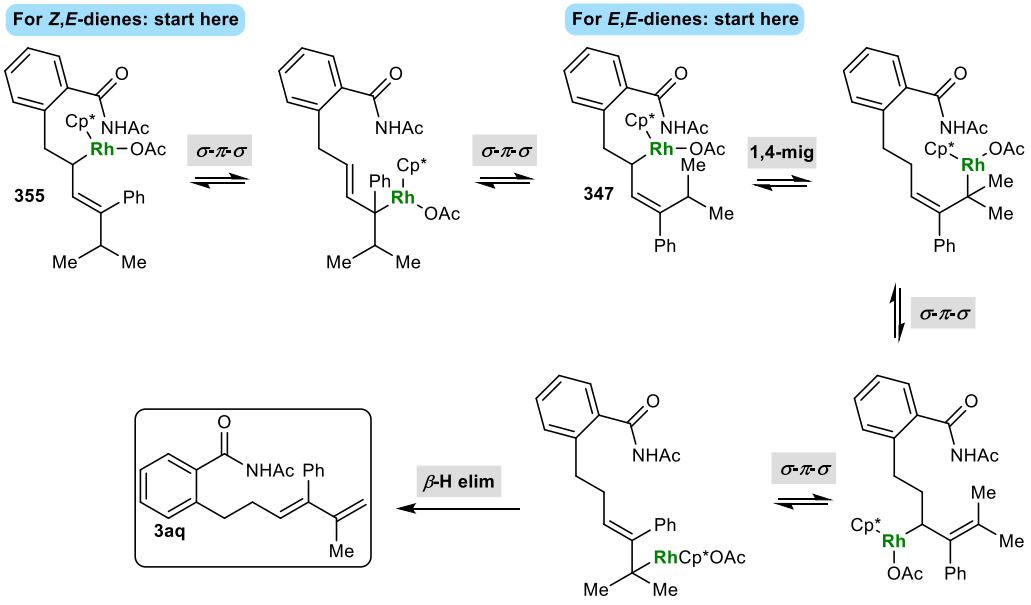
A proposed catalytic cycle demonstrating how product **343** could form is outlined in Scheme 137. Initially, benzamide **267a** undergoes C–H activation in the presence of RhCp*$(OAc)_2$ species **344** to form rhodacycle **345**. Next, migratory insertion of 1,3-diene **297** gives allylrhodium species **346**. Subsequent acetolysis generates intermediate **347**. In this instance, *β*-hydride elimination could occur forming **348**, though none of **348** is observed. Instead, an allyl-to-allyl 1,4-Rh(III) migration takes place generating **349**. From **349**, *β*-hydride elimination is possible, producing **350**; instead, **349** undergoes *σ*-*π*-*σ* isomerisation to form **351**. Here, *β*-hydride elimination is possible, giving product **352**, nevertheless **352** is not detected; instead, *σ*-*π*-*σ* isomerisation occurs which generates **353**. In summary, an *E*/*Z* isomerisation occurs from **349** to **353**. Finally, *β*-hydride elimination furnishes the isolated product **343** as well as RhCp*(OAc)H **354**, which upon reductive elimination and re-oxidation regenerates the catalytically active rhodium complex **344**.



Scheme 137. Proposed catalytic cycle in which an allyl-to-allyl 1,4-Rh(III) migration occurs

It is unclear why product **343** forms exclusively over the other potential products **348**, **350** and **352**. It is possible that allyl-to-allyl 1,4-Rh(III) migration and 1,3-allylic transpositions proceed at rates greater than the rates of *β*-hydride eliminations, and thus **348**, **350** and **352** may undergo alkene re-insertion to reform **347**, **349** and **351** respectively. This would result in the accumulation of intermediate **353**, which may be a more thermodynamically stable intermediate, and over time would generate the sole product, **343**.

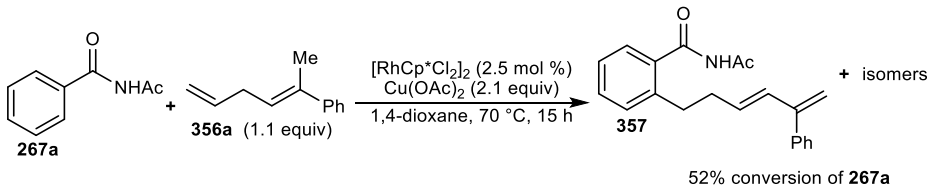
An analogous mechanism can be proposed when using 1,3-diene **298** (Scheme 138). Similarly, after the first few steps in the catalytic cycle shown in Scheme 137, intermediate **355** (as opposed to **347**) can be formed, which upon consecutive *σ*-*π*-*σ* isomerisations would form the common allylrhodium species **347**. Hereon, allyl-to-allyl 1,4-Rh(III) migration and the subsequent steps described in Scheme 137 would afford the product **343**.



Scheme 138. Proposed mechanism for the formation of allylrhodium species **347** using 1,3-diene **298**

2.10 Development of Rh(III)-catalysed oxidative C–H homoallylation of *N*-acetylbenzamides with 1,4-dienes

Having successfully developed the first examples of allyl-to-allyl 1,4-Rh(III) migration in a reaction system involving *N*-acetylbenzamides and 1,3-dienes, we examined the reactivity of 1,4-dienes. Excitingly, the reaction of *N*-acetylbenzamide **267a** with 1,4-diene **356a** resulted in homoallylation product **357** as the major product (Scheme 139). However, homoallylation product **357** was likely to be accompanied by other isomers according to the complex crude ^{1}H NMR spectrum. Product **357** was extremely hard to purify by chromatography and as a result only the characteristic peaks were identified by ^{1}H NMR spectroscopy.

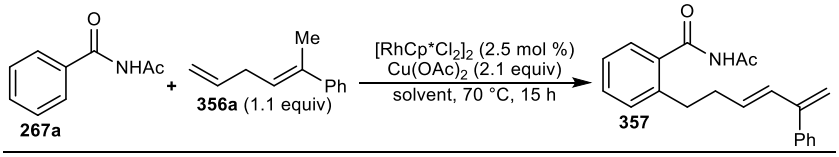


Scheme 139. Initial discovery

Initial solvent screening was performed to examine whether this would increase the conversion of benzamide **267a** to product **357** (Table 13). Surprisingly, DMA gave no reaction, whilst 1,4-dioxane, 2-MeTHF and THP gave similar yields of 52, 53 and

57% respectively (Table 13, Entries 1–5). When using THP as the solvent a crude ^{1}H NMR spectrum with fewer side-products was obtained, thus THP was selected as the reaction solvent. Extensive solvent screening was not conducted.

Table 13. Solvent screening

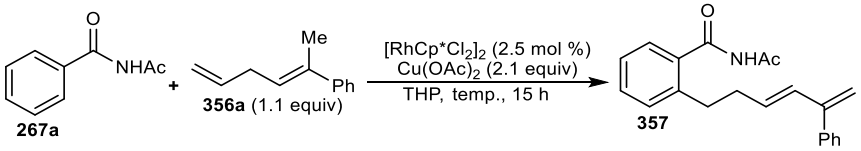


Entry	Solvent	Conversion (%)
1	DMA	NR
2	1,4-dioxane	52
3	THF	30
4	2-MeTHF	53
5	THP	57
6	1,2-dimethoxyethane	14
7	diethylene glycol dimethyl ether	50
8	CPME	50

Conversion determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard

Next, the reaction temperature was examined (Table 14). The optimum temperature ranged from 70–90 °C, lower temperatures resulted in lower conversion of benzamide **267a** to product **357**.

Table 14. Temperature screening

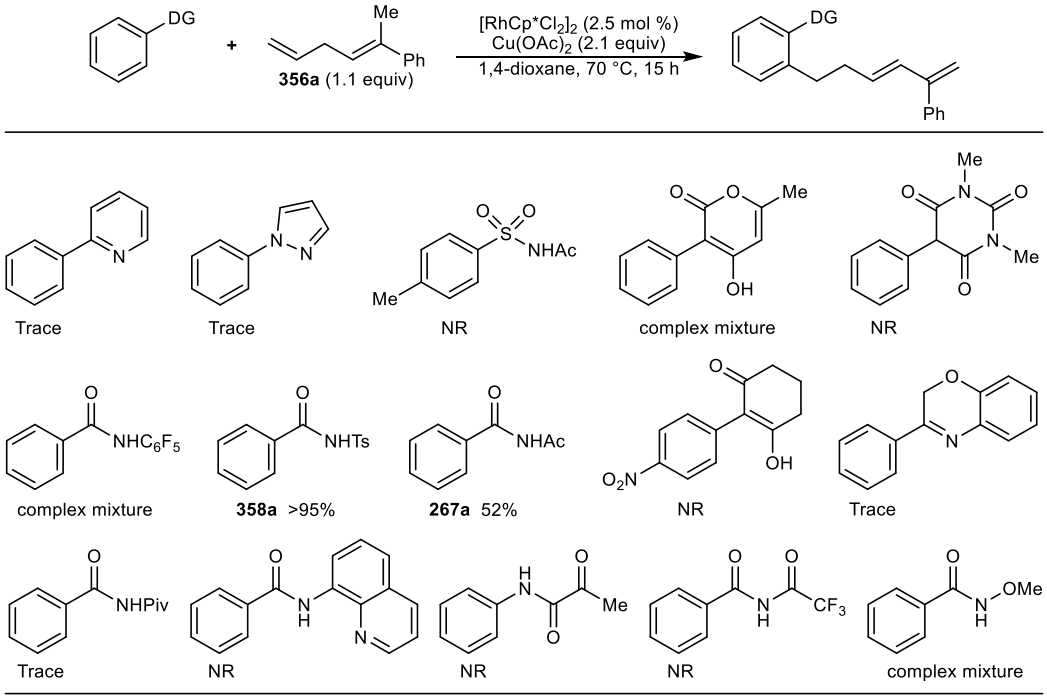


Entry	Temperature (°C)	Conversion (%)
1	50	20
2	60	39
3	70	57
4	90	60

Conversion determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard

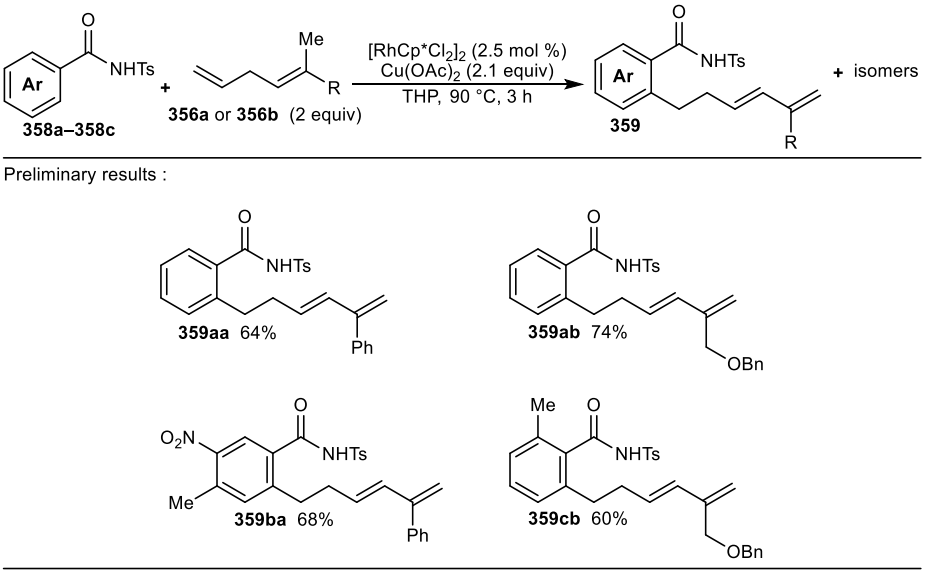
After preliminary solvent and temperature screening, various substrates containing other directing groups were examined (Table 15). The majority of these gave no reaction, though in the case of *N*-tosylbenzamide **358a** full conversion was achieved.

Table 15. Directing groups examined



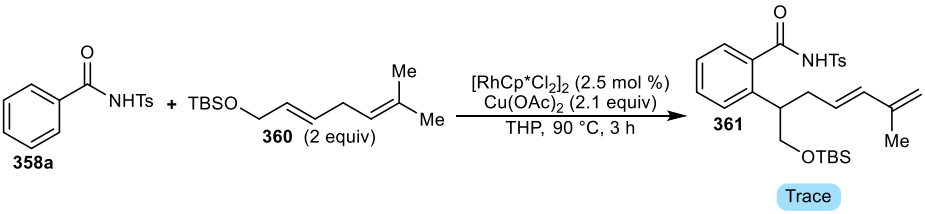
Conversion determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard

Consequently, a final set of conditions were determined, using THP as the solvent at 90 °C for 3 h (Scheme 140). A preliminary substrate scope was also examined. As a general note, all substrates examined led to full conversion of the starting benzamide **358**, though mixtures of isomers were generally encountered. Furthermore, purification of the products was very challenging.



Scheme 140. Preliminary substrate scope. Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. Yield refers to the yield of the homoallylation product

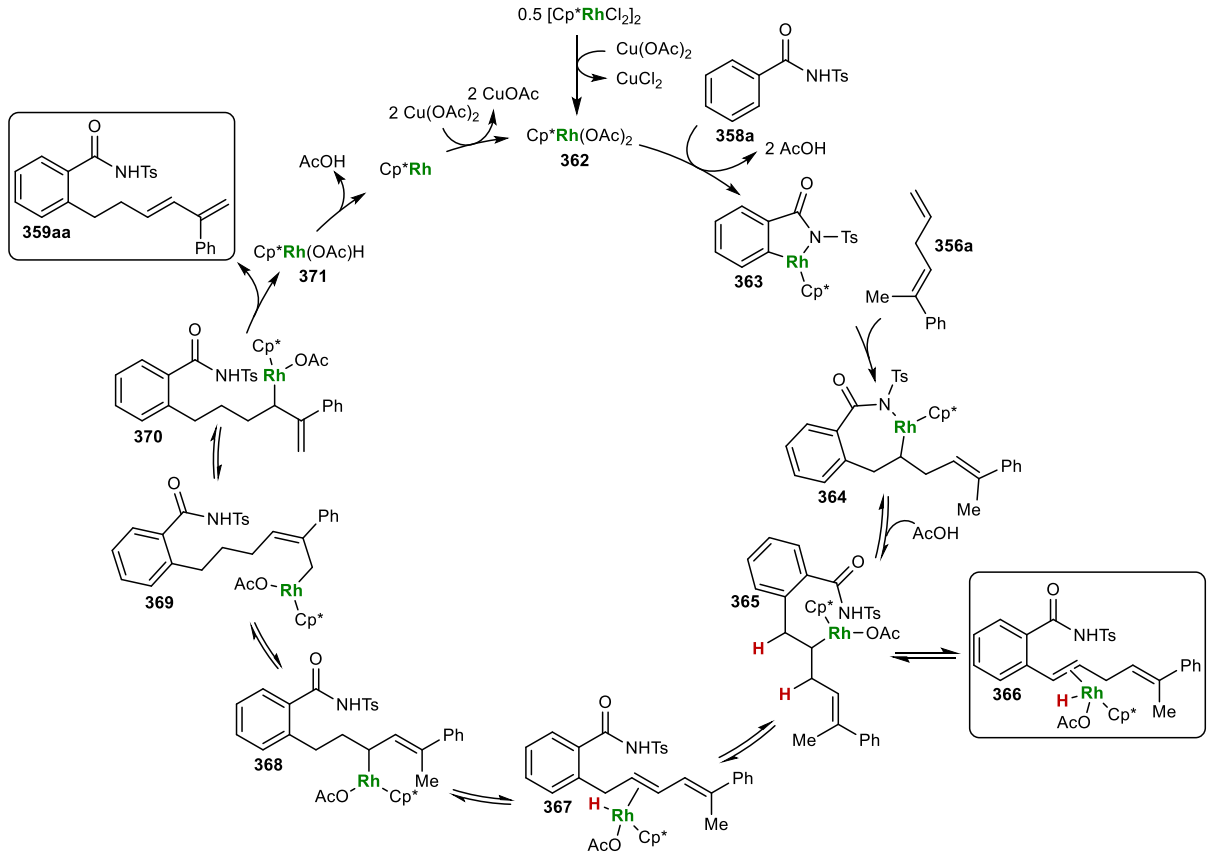
Additionally, an experiment using internal 1,4-diene **360** with benzamide **358a** in the presence of $[RhCp^*Cl_2]_2$ (2.5 mol%) resulted in trace amounts of product **361** (Scheme 141). The starting reagents were recovered. Further investigations need to be undertaken to verify whether this methodology is limited to terminal 1,4-dienes only.



Scheme 141. Reaction using internal 1,4-diene **360**

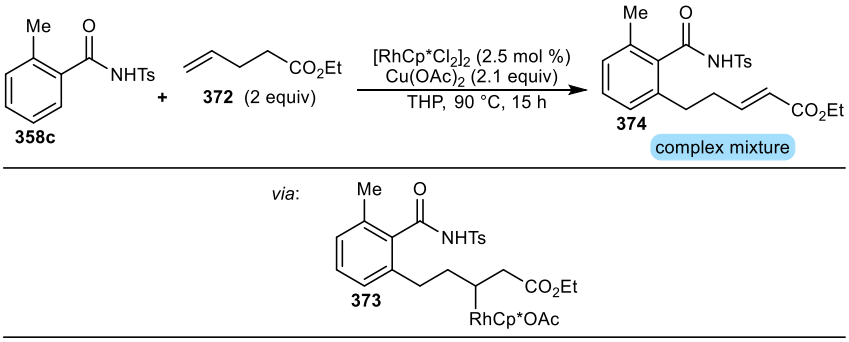
A postulated mechanism is described in which the formation of homoallylation product **359aa** is discussed (Scheme 142). Initial C–H activation of benzamide **358a**, with the use of *in situ* generated $RhCp^*(OAc)_2$ species **362**, is achieved forming rhodacycle **363**. Next, coordination and insertion of 1,4-diene **356a** affords homoallylrhodium species **364**, which can react with AcOH to form intermediate **365**. At this point, rhodium can undergo *β*-hydride elimination with either *β*-hydrogens (highlighted in red). Both are feasible and thus both of **366** and **367** could be formed. However, *via* alkene re-insertion of **366**, intermediate **365** is re-formed allowing for intermediate **367** to predominate. This is likely to be thermodynamically driven due to the conjugated 1,3-diene intermediate **367** that is formed. Subsequently, migratory

insertion of **367** generates an allylrhodium species **368**, which can undergo an allyl-to-allyl 1,4-Rh(III) migration to form **369**. Next, *σ*-*π*-*σ* isomerisation generates **370**, which upon *β*-hydride elimination yields the major isomer **359aa** as well as RhCp*(OAc)H **371**. Finally, reductive elimination of **371** and re-oxidation by $Cu(OAc)_2$ regenerates **362**.



Scheme 142. Proposed catalytic cycle in which an allyl-to-allyl 1,4-Rh(III) migration occurs

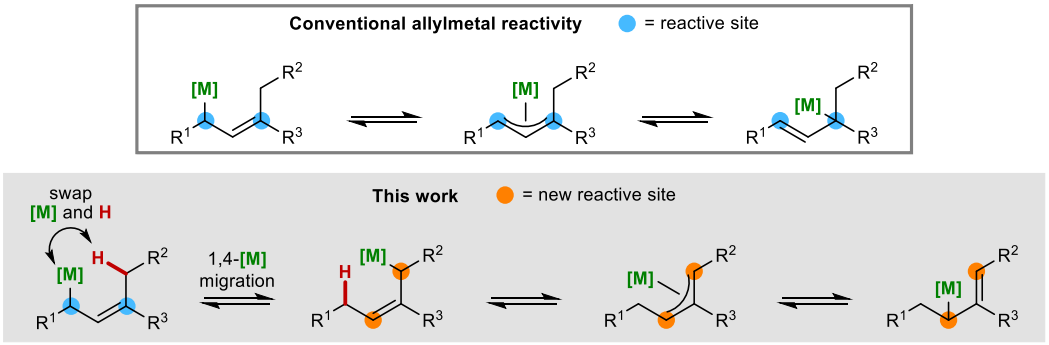
Next, our attention was turned to a reaction system that may minimise the formation of potential minor isomers. Here, substrate **372** was selected as a possible candidate (Scheme 143). Substrates containing ester groups can thermodynamically drive the formation of alkylrhodium species, such as **373**, through a series of reversible migratory insertions, *β*-hydride eliminations and alkene re-insertions.[149] Intermediate **373** could then either be trapped by an external nucleophile, or in this case, lacking a nucleophile, would form acrylate **374** *via* *β*-hydride elimination. However, the reaction of benzamide **358c** with alkene **372** gave a complex mixture and was not investigated further.



Scheme 143. Reaction of alkene **372** with benzamide **358c**

2.11 Summary on allyl-to-allyl 1,4-Rh(III) migration and proposed future work

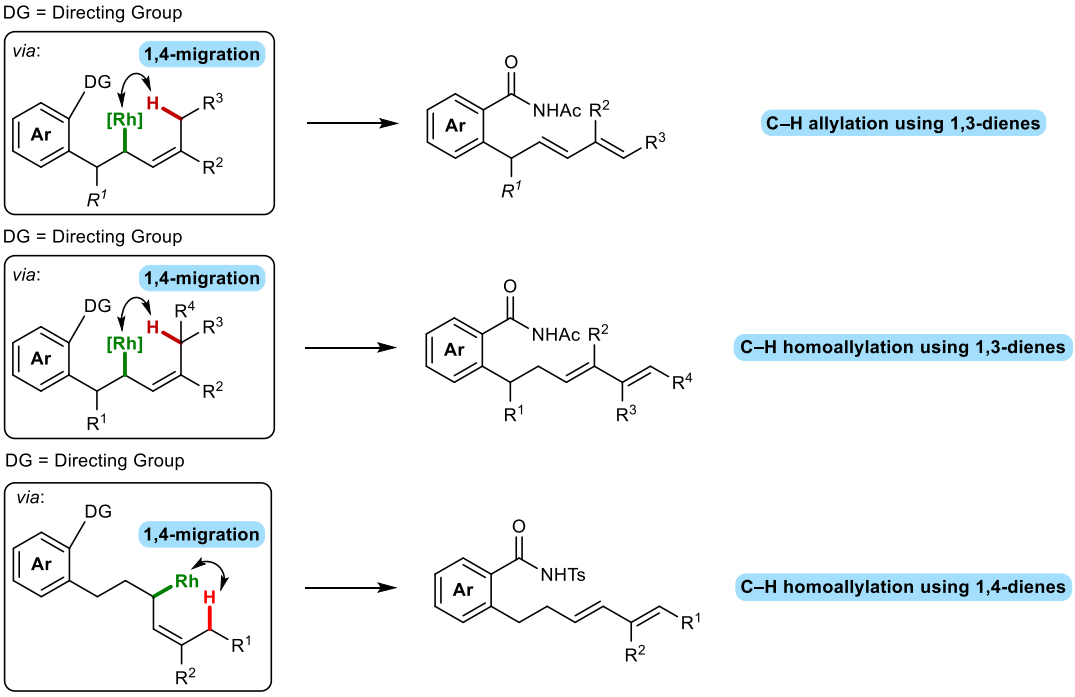
Allyl-to-allyl migrations are of key importance in synthesis when achieved in high regio- and chemoselectivity. Through this novel reactivity new reactive sites are generated which could hold great synthetic potential, as they provide a complementary alternative to conventional 1,3-allylic transpositions (Scheme 144).



Scheme 144. New reactive sites enabled *via* allyl-to-allyl 1,4-Rh(III) migration

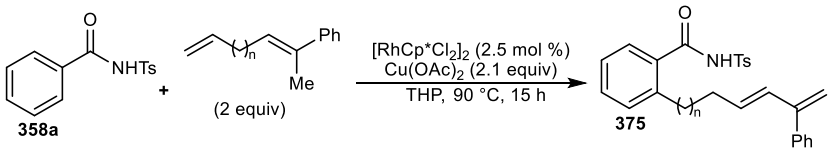
Literature precedent as well as the research discussed in this report attest to the high versatility and utility of rhodium in organic synthesis. Herein, are described the first examples of allyl-to-allyl 1,4-Rh(III) migration that enable the formation of allylation as well as homoallylation products, when benzamides are reacted with 1,3-dienes or 1,4-dienes (Scheme 145). The presence of allylic hydrogens *cis*- to the less-substituted alkene of the diene is important for the success of these reactions in achieving good to excellent yields, though not essential. With the assistance of reactions using deuterated 1,3-dienes, the mechanisms of allylation of *N*-acetylbenzamides have been discussed. These results indicate that reversible interconversion of numerous allylrhodium(III) species by σ-π-σ isomerisation, *E*/*Z* isomerisation, and allyl-to-allyl 1,4-Rh(III)

migration pathways occur on timescales that are rapid compared to product-forming *β*-hydride (or *β*-deuteride) elimination steps. The possibility that these isomerisation processes might occur, should be taken into consideration in any future design of new reactions involving allylrhodium(III) species.



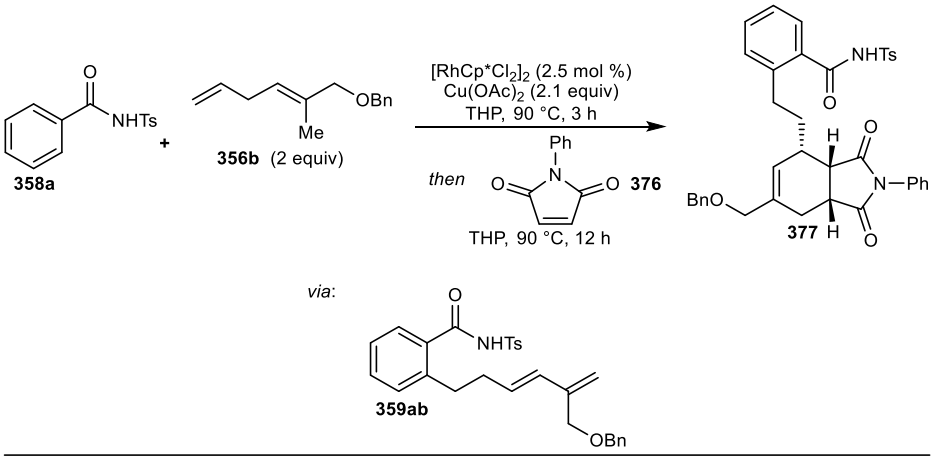
Scheme 145. Summary of C–H functionalisations enabled *via* allyl-to-allyl 1,4-Rh(III) migration

Regarding future research, it is important to study in-depth and understand the mechanism of C–H homoallylation of *N*-tosylbenzamides with 1,4-dienes. This will assist in overcoming challenging issues that are currently present, such as the formation of other isomers. Expanding the substrate scope may provide useful knowledge also. For instance, the linker between the two alkene moieties in the 1,4-diene can be extended, and the reaction outcome monitored to determine whether the reaction could be driven to product **375** in high selectivity (Scheme 146).



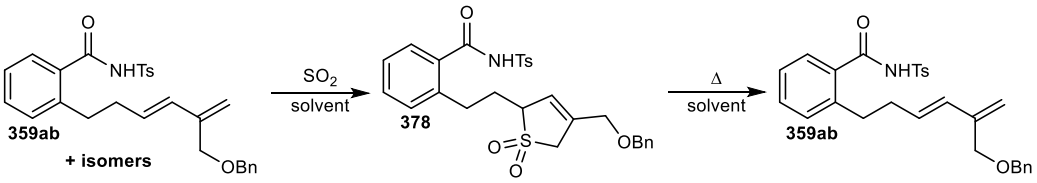
Scheme 146. Extending the linker between the two alkene moieties in (**62**)

Furthermore, a three-component system may also be possible, in which benzamide **358a**, 1,4-diene **356b** and activated alkenes such *N*-phenylmaleimide **376** could react to give product **377** as the major product (Scheme 147). It is proposed that alkene **376** would undergo a Diels-Alder reaction with the major homoallylation isomer, **359ab**, generated *in situ*, without reacting with other isomers that do not contain the 1,3-diene moiety. This would also make purification simpler as the retention factor of Diels-Alder adduct **377** will be different to the previously encountered isomers. The addition of alkene **376** might have to be done having confirmed the consumption of the starting benzamide **358a**, still in a one-pot fashion. This would be done to avoid possible coupling of alkene **376** with benzamide **358a**. Further investigation of the synthetic potential of allyl-to-allyl 1,4-metal migrations is ongoing.



Scheme 147. Three-component coupling

Alternatively, to isolate homoallylation product **359ab** as as a single isomer, the mixture of isomers can be reacted with sulfur dioxide to form sulfolene **378** (Scheme 148). Once sulfolene **378** is isolated and purified it could be heated and converted back to the desired 1,3-diene product **359ab** (Scheme 148).



Scheme 148. Proposal for isolating isomer **359ab**

3 Experimental

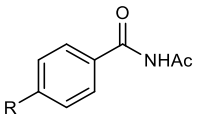
3.1 Rh(III)-catalysed oxidative C–H allylation of *N*-acetylbenzamides with 1,3-dienes

3.1.1 General information

Unless specified otherwise, all reactions were carried out under an atmosphere of argon. Unless specified otherwise, all commercially available reagents and solvents were used as received. THF was dried and purified by passage through activated alumina columns using a solvent purification system. All petroleum ether used was 40–60 °C petroleum ether. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates with a fluorescent indicator. Compounds were visualised by exposure to UV light or by dipping the plates into solutions of potassium permanganate or vanillin followed by heating. Flash column chromatography was carried out using silica gel (Fisher Scientific 60 Å particle size 35–70 micron). Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. The solvent of recrystallisation is reported in parentheses. Infra-red spectra were recorded on a Nicolet Avatar 360 FT instrument on the neat compound using the attenuated total refraction technique. NMR spectra were acquired on Bruker DPX300, AV400, AV(III)400, or DPX400 spectrometers at room temperature. ^{1}H and ^{13}C NMR spectra were referenced to external tetramethylsilane *via* the residual protonated solvent (^{1}H) or the solvent itself (^{13}C). All chemical shifts are reported in parts per million (ppm). For $CDCl_3$, the shifts are referenced to 7.26 ppm for ^{1}H NMR spectroscopy and 77.16 ppm for ^{13}C NMR spectroscopy. High-resolution mass spectra were recorded using electrospray ionisation (ESI) or electron impact ionisation (EI) techniques at the School of Chemistry, University of Nottingham.

3.1.2 Synthesis of substrates

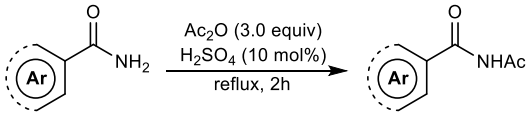
Preparation of *N*-acetylbenzamides



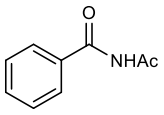
267b R = Me
267c R = OMe
267d R = NO_2

Substrates **267b–267d** were prepared by David J. Burns.

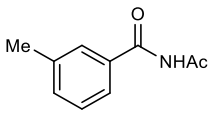
General procedure A: Preparation of *N*-acetylbenzamides



To a solution of the benzamide (1.0 equiv) in acetic anhydride (Ac_2O) (3.0 equiv) was added conc. H_2SO_4 (10 mol%) and the mixture heated to reflux for 2 h. The resulting mixture was cooled, quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (three times). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the crude mixture by recrystallisation from cyclohexane:EtOAc gave the title compound.

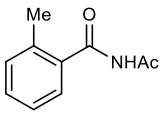


***N*-Acetylbenzamide (267a).** The title compound was prepared according to General procedure A from 3-methylbenzamide (3.21 g, 26.5 mmol), Ac_2O (7.5 mL, 79 mmol) and conc. H_2SO_4 (0.14 mL, 2.6 mmol) to give benzamide **1a** as a white crystalline solid (3.68 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (1H, br s, N**H**), 7.90–7.76 (2H, m, Ar**H**), 7.67–7.57 (1H, m, Ar**H**), 7.56–7.42 (2H, m, Ar**H**), 2.63 (3H, s, C**H**$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.8 (C), 165.9 (C), 133.4 (CH), 132.8 (C), 129.1 (2 × CH), 127.9 (2 × CH), 25.7 (CH_3); Physical and spectral properties were in accordance with the literature.[150]

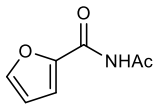


***N*-Acetyl-3-methylbenzamide (267e).** The title compound was prepared according to General procedure A from 3-methylbenzamide (3.58 g, 26.5 mmol), Ac_2O (7.5 mL, 79 mmol) and conc. H_2SO_4 (0.14 mL, 2.6 mmol) to give benzamide **1e** as a white crystalline solid (1.97 g, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (1H, br s, N**H**), 7.67–7.62

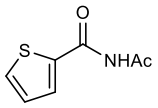
(2H, m, Ar**H**), 7.43–7.36 (2H, m, Ar**H**), 2.61 (3H, s, C**H**$_3$), 2.43 (3H, s, ArC**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.4 (C), 165.9 (C), 139.2 (C), 134.2 (CH), 132.8 (C), 129.1 (CH), 128.4 (CH), 124.7 (CH), 25.6 (CH_3), 21.5 (CH_3); Physical and spectral properties were in accordance with the literature.[151]



***N*-Acetyl-2-methylbenzamide (267f).** The title compound was prepared according to General procedure A from 2-methylbenzamide (3.58 g, 26.5 mmol), Ac_2O (7.5 mL, 79 mmol) and conc. H_2SO_4 (0.14 mL, 2.6 mmol) to give benzamide **1f** as a white solid (1.08 g, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (1H, br s, N**H**), 7.45 (1H, dd, *J* = 7.7, 1.4 Hz, Ar**H**), 7.39 (1H, td, *J* = 7.5, 1.4 Hz, Ar**H**), 7.28–7.23 (2H, m, Ar**H**), 2.57 (3H, s, C**H**$_3$), 2.48 (3H, s, ArC**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.4 (C), 168.1 (C), 137.6 (C), 134.0 (C), 131.8 (CH), 131.6 (CH), 127.1 (CH), 126.1 (CH), 25.6 (CH_3), 20.2 (CH_3); Physical and spectral properties were in accordance with the literature.[152]



***N*-Acetylfuran-2-carboxamide (267g).** The title compound was prepared according to General procedure A from 2-furan carboxamide (881 mg, 8.00 mmol), Ac_2O (1.7 mL, 18 mmol) and conc. H_2SO_4 (43 μL, 0.80 mmol) and was purified by column chromatography (3:2 petroleum ether:EtOAc) instead of recrystallisation to give *aryl-carboxamide* **6** as an off-white powder (857 mg, 70%). R_f 0.18 (3:2 petroleum ether:EtOAc); m.p. 132−134 °C (CH_2Cl_2); IR 3247 (NH), 3127, 1688 (C=O), 1480, 1376, 1278, 1023 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (1H, br s, N**H**), 7.55 (1H, d, *J* = 0.7 Hz, Ar**H**), 7.34 (1H, d, *J* = 3.5 Hz, Ar**H**), 6.60 (1H, dd, *J* = 3.5, 1.7 Hz, Ar**H**), 2.58 (3H, s, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.4 (C), 155.8 (C), 146.3 (C), 145.8 (CH), 118.2 (CH), 113.3 (CH), 25.7 (CH_3); HRMS (ESI) Exact mass calculated for $[C_7H_8NO_3]^+$ $[M+H]^+$: 154.0499, found: 154.0500.

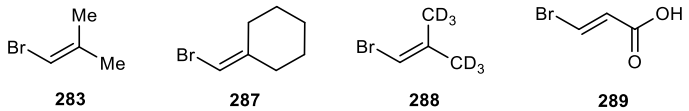


***N*-Acetylthiophene-2-carboxamide (267h)**

The title compound was prepared according to General procedure A from 2-thiophene carboxamide (3.00 g, 23.6 mmol), Ac_2O (4.9 mL, 51.9 mmol) and conc. H_2SO_4 (0.13 mL, 2.4 mmol) at reflux for a reaction time of 2 h and was purified by column chromatography (petroleum ether:EtOAc 5:1) to give *aryl-carboxamide* **267h** as a white powder (1.60 g, 40%). R_f 0.55 (petroleum ether:EtOAc 2:1); m.p.

132−134 °C (CH_2Cl_2); IR 3270 (NH), 3090, 1713 (C=O), 1673 (C=O), 1475, 1294, 1260, 1020, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.30 (1H, s, N**H**), 7.83 (1H, dd, *J* = 3.9, 1.0 Hz, Ar**H**), 7.67 (1H, dd, *J* = 4.9, 1.0 Hz, Ar**H**), 7.16 (1H, dd, *J* = 4.9, 3.9 Hz, Ar**H**), 2.61 (3H, s, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.1 (C), 160.3 (C), 137.8 (C), 133.8 (CH), 130.8 (CH), 128.5 (CH), 25.8 (CH_3). Exact mass calculated for $C_7H_8NO_2S$ $[M+H]^+$: 170.0270, found: 170.0273, exact mass calculated for $C_7H_7NNaO_2S$ $[M+Na]^+$: 190.0090, found 190.0099, exact mass calculated for $C_7H_{11}N_2O_2S$ $[M+NH_4]^+$: 187.0536, found 187.0534.

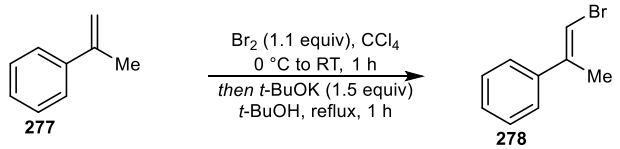
Preparation of alkenyl halides



283 **287** **288** **289**

Alkenyl bromides **283** and **287** were purchased from Sigma-Aldrich. Substrates **288** and **289** were synthesised by David J. Burns.

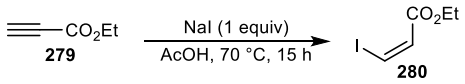
(*E*)-(1-Bromoprop-1-en-2-yl)benzene (278)



277 **278**

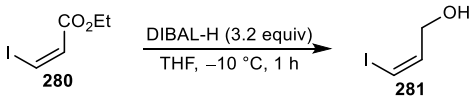
To a solution of alkene **277** (2.60 mL, 20.0 mmol) in CCl_4 (30 mL) was added bromine (1.23 mL, 24.0 mmol) dropwise at 0 °C. The reaction mixture was left for 1 h whilst it gradually reached room temperature. Next, saturated sodium thiosulfate solution was added to remove excessive bromine, separated, extracted with CH_2Cl_2 (20 mL × 3), dried ($MgSO_4$) and concentrated *in vacuo*. The dibrominated intermediate was then dissolved in *t*-BuOH (100 mL) and *t*-BuOK (3.37 g, 30.0 mmol) was added and heated to reflux for 1 h. The reaction was quenched by adding brine (15 mL), separated and extracted with EtOAc (15 mL × 3). The combined organic phases were washed with 1.0 M aqueous HCl (50 mL), followed by brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane) gave alkenyl bromide **278** as a colourless oil (2.98 g, 76%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.33 (5H, m, Ar**H**), 6.47 (1H, q, *J* = 1.4 Hz, **H**CBr), 2.25 (3H, d, *J* = 1.4 Hz, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.6 (C), 141.1 (C), 128.6 (2 × CH), 128.0 (CH), 126.1 (2 × CH), 105.5 (CH), 19.8 (CH_3); Physical and spectral properties were in accordance with the literature.[153]

(*Z*)-3-Iodoprop-2-en-1-ol (280)



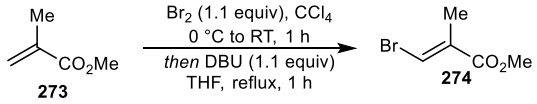
To ethyl propiolate (2.0 mL, 20 mmol) in glacial acetic acid (10 mL) was added NaI (3.00 g, 20.0 mmol) and the mixture was stirred at 70 °C for 15 h. Next, saturated aqueous Na_2SO_3 (10 mL) and 1.0 M aqueous NaOH (10 mL) were added, the layers were separated, and the aqueous layer was further extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash column chromatography (Et_2O) to give the vinyl iodide **280** as a yellow oil (4.43 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (1H, dd, *J* = 8.9, 0.9 Hz, IC**H**), 6.88 (1H, d, *J* = 8.9 Hz, ICH=C**H**), 4.24 (2H, q, *J* = 7.1 Hz, C**H**$_2$), 1.31 (3H, t, *J* = 7.1 Hz, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.7 (C), 130.0 (CH), 94.8 (CH), 60.9 (CH_2), 14.3 (CH_3); Physical and spectral properties were in accordance with the literature.[154]

Ethyl (*Z*)-3-iodoacrylate (281)



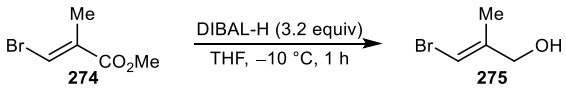
To a stirred solution of ester **280** (6.33 g, 28.0 mmol) in THF (30 mL) was added DIBAL-H (1.0 M in hexane, 90.0 mL, 90.0 mmol) dropwise at –10 °C and the mixture was left to stir for 1 h. The reaction was quenched with EtOAc (20 mL), followed by saturated aqueous potassium sodium tartrate solution (20 mL), and the mixture was stirred vigorously for 15 min. The mixture was decanted to remove the biphasic liquid layer and the sludgy residue was washed with EtOAc (3 × 25 mL). The washings were combined with the biphasic liquid layer, H_2O (50 mL) was added, and the aqueous layer was separated and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was dissolved in Et_2O, filtered through a plug of silica using further Et_2O as eluent, and concentrated *in vacuo* to leave the alcohol **281** as a colourless oil (5.11 g, 99%), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (1H, dt, *J* = 7.7, 5.7 Hz, ICH=C**H**), 6.36 (1H, dt, *J* = 7.7, 1.5 Hz, IC**H**), 4.24 (2H, td, *J* = 5.7, 1.5 Hz, C**H**$_2$), 1.73 (1H, t, *J* = 5.7 Hz, O**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 140.1 (CH), 82.5 (CH), 65.6 (CH_2); Physical and spectral properties were in accordance with the literature.[154]

Methyl (*E*)-3-bromo-2-methylacrylate (274)



To a solution of alkene **273** (53.3 mL, 500 mmol) in CCl_4 (500 mL) was added bromine (28.2 mL, 550 mmol) dropwise at 0 °C. The reaction mixture was left for 1 h whilst it gradually reached room temperature. Next, saturated sodium thiosulfate solution (100 mL) was added to remove excessive bromine, separated, extracted with CH_2Cl_2 (100 mL × 3), dried ($MgSO_4$) and concentrated *in vacuo*. The dibrominated intermediate was then dissolved in THF (500 mL) and 1,8-diazabicyclo[5,4,0]-udec-7-ene (82.0 mL, 550 mmol) was added and heated to reflux for 1 h. The reaction was quenched by adding brine (100 mL), separated and extracted with EtOAc (150 mL × 3). The combined organic phases were washed with 1.0 M aqueous HCl (200 mL), followed by brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by flash column chromatography (4:1 petroleum ether:Et_2O) gave alkenyl bromide **274** as a colourless oil (65.1 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (1H, q, *J* = 1.5 Hz, C**H**), 3.76 (3H, s, OC**H**$_3$), 2.00 (3H, d, *J* = 1.5 Hz, CC**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.7 (C), 134.0 (C), 123.1 (CH), 52.4, (CH_3), 15.8 (CH_3); Physical and spectral properties were in accordance with the literature.[155]

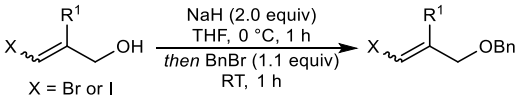
Methyl (*E*)-3-bromo-2-methylprop-2-en-1-ol (275)



To a stirred solution of ester **274** (5.00 g, 28.0 mmol) in THF (30 mL) was added DIBAL-H (1.0 M in hexane, 90.0 mL, 90.0 mmol) dropwise at –10 °C and the mixture was left to stir for 1 h. The reaction was quenched with EtOAc (20 mL), followed by saturated aqueous potassium sodium tartrate solution (20 mL), and the mixture was stirred vigorously for 15 min. The mixture was decanted to remove the biphasic liquid layer and the sludgy residue was washed with EtOAc (3 × 25 mL). The washings were combined with the biphasic liquid layer, H_2O (50 mL) was added, and the aqueous layer was separated and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was dissolved in Et_2O, filtered through a plug of silica using further Et_2O as eluent, and concentrated *in vacuo* to leave the alcohol **275** as a colourless oil (3.82 g, 91%), which was used without further purification. ^{1}H NMR (400 MHz,

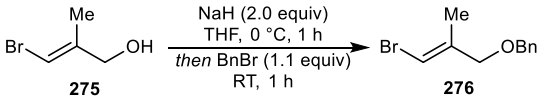
$CDCl_3$) δ 6.23 (1H, q, *J* = 1.4 Hz, C**H**), 4.11–4.09 (2H, m, C**H**$_2$), 2.06 (1H, br, O**H**), 1.83 (3H, d, *J* = 1.4 Hz, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.2 (C), 104.3 (CH), 66.8 (CH_2), 16.8 (CH_3); Physical and spectral properties were in accordance with the literature.[155]

General procedure B: preparation of alkenyl halides *via* benzylation



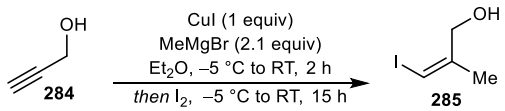
To a stirred solution of the alcohol (1.0 equiv) in THF (2 mL/mmol of alcohol) at 0 °C was added NaH (2.0 equiv) and the mixture was stirred at 0 °C for 1 h. Then, benzyl bromide (1.1 equiv) was added; the reaction was warmed to room temperature and stirred for a further 1 h. Next, 2.0 M aqueous HCl was added, the layers were separated, and the aqueous layer was further extracted with Et_2O (two times). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash column chromatography gave the title compound.

(*E*)-{[(3-Bromo-2-methylallyl)oxy]methyl}benzene (276)



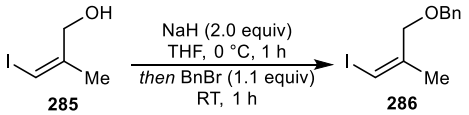
The title compound was prepared according to General procedure B from alcohol **275** (3.02 g, 20.0 mmol), NaH (1.60 g of 60% wt. in mineral oil, 40.0 mmol) and benzyl bromide (2.64 mL, 22.0 mmol) and purified by flash column chromatography (gradient elution; petroleum ether to 20:1 petroleum ether:Et_2O) to give ether **276** (4.34 g, 90%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.30 (5H, m, Ar**H**), 6.25 (1H, m, BrC**H**), 4.49 (2H, s, OC**H**$_2$Ph), 3.97 (2H, d, 1.0 Hz, C**H**$_2$OBn), 1.85 (1H, d, *J* = 1.0 Hz, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.9 (C), 138.0 (C), 128.6 (2 × CH), 127.9 (CH), 127.8 (2 × CH), 105.2 (CH), 73.7 (CH_2), 72.1 (CH_2), 17.1 (CH_3). Physical and spectral properties were in accordance with the literature.[156]

(*Z*)-3-Iodo-2-methylprop-2-en-1-ol (285)



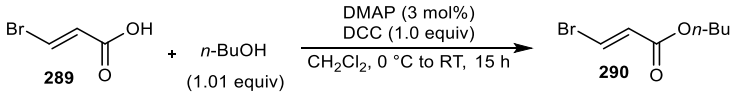
To a suspension of CuI (6.55 g, 34.4 mmol) in Et_2O (100 mL) at –5 °C was added propargyl alcohol 284 (2.0 mL, 34 mmol). Next, MeMgBr (3 M in Et_2O, 24.0 mL, 72.1 mmol) was added dropwise and the solution was stirred for 30 min at –5 °C. A solution of iodine (8.73 g, 34.4 mmol) in Et_2O (20 mL) was added and the reaction vessel was allowed to reach room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl (25 mL). The aqueous layer was separated and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5:1 petroleum ether:EtOAc) gave alcohol **285** as a yellow oil (2.19 g, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96–5.95 (1H, m, C**H**), 4.21 (2H, s, C**H**$_2$), 2.41 (1H, br, O**H**), 1.95 (2H, d, *J* = 1.6 Hz, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 146.1 (CH), 75.0 (CH), 68.1 (CH_2), 21.8 (CH_3); Physical and spectral properties were in accordance with the literature.[157]

(*Z*)-{[(3-Iodo-2-methylallyl)oxy]methyl}benzene (286)



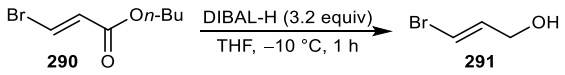
The title compound was prepared according to General procedure B from alcohol **285** (990 mg, 5.00 mmol), NaH (400 mg of 60% wt. in mineral oil, 10.0 mmol) and benzyl bromide (0.66 mL, 5.5 mmol) and purified by flash column chromatography (gradient elution; petroleum ether to 20:1 petroleum ether:Et_2O) to give ether **286** (1.21 g, 84%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.29 (5H, m, Ar**H**), 6.10–6.08 (1H, m, IC**H**), 4.51 (2H, s, OC**H**$_2$Ph), 4.19 (2H, d, 0.9 Hz, C**H**$_2$OBn), 1.99 (1H, d, *J* = 1.5 Hz, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.4 (C), 138.2 (C), 128.5 (2 × CH), 127.9 (2 × CH), 127.8 (CH), 76.2 (CH), 75.0 (CH_2), 72.2 (CH_2), 22.0 (CH_3). Physical and spectral properties were in accordance with the literature.[156]

Butyl (*E*)-3-bromoacrylate (290)



To a solution of the carboxylic acid **289** (7.49 g, 49.5 mmol) and *N*,*N*'-dicyclohexylcarbodiimide (10.29 g, 49.5 mmol) in CH_2Cl_2 (80 mL) at 0 °C was added a solution of DMAP (148 mg, 1.48 mmol) in CH_2Cl_2 (60 mL) *via* cannula over 2 min, followed by 1-butanol (4.6 mL, 50 mmol). The mixture was stirred at 0 °C and left to reach room temperature overnight. The precipitate formed was then removed by filtration and the filtrate was washed with saturated aqueous $NaHCO_3$ solution (150 mL) followed by 2.0 M aqueous HCl solution (150 mL). The filtrate was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10:1 petroleum ether:Et_2O) gave the *ester* **290** as a pale yellow oil (6.20 g, 60%). R_f = 0.38 (10:1 petroleum ether:Et_2O); IR 2959, 1717 (C=O), 1604, 1296, 1260, 1226, 1150, 1003, 939, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (1H, d, *J* = 13.9 Hz, C**H**=CHC=O), 6.51 (1H, d, *J* = 13.9 Hz, C**H**C=O), 4.14 (2H, t, *J* = 6.7 Hz, OC**H**$_2$), 1.67–1.60 (2H, m, OCH$_2$C**H**$_2$), 1.43–1.34 (2H, m, C**H**$_2$CH$_3$) 0.93 (3H, t, *J* = 7.4 Hz, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.0 (C), 129.0 (CH), 126.6 (CH), 65.0 (CH_2), 30.7 (CH_2), 19.2 (CH_2), 13.8 (CH_3); HRMS (EI) Exact mass calculated for $[C_7H_{11}O_2Br]^+$ $[M]^+$: 176.9546, found: 176.9549.

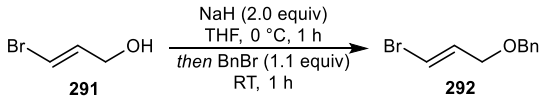
(*E*)-3-Bromoprop-2-en-1-ol (291)



To a stirred solution of ester **290** (2.07 g, 10.0 mmol) in THF (10 mL) was added DIBAL-H (1.0 M in hexane, 32.0 mL, 32.0 mmol) dropwise at –10 °C and the mixture was left to stir for 1 h. The reaction was quenched with EtOAc (20 mL), followed by saturated aqueous potassium sodium tartrate solution (10 mL), and the mixture was stirred vigorously for 15 min. The mixture was decanted to remove the biphasic liquid layer and the sludgy residue was washed with EtOAc (3 × 20 mL). The washings were combined with the biphasic liquid layer, H_2O (50 mL) was added, and the aqueous layer was separated and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was dissolved in Et_2O, filtered through a plug of silica using further

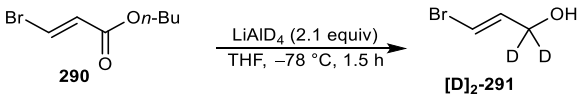
Et_2O as eluent, and concentrated *in vacuo* to leave alcohol **291** as a colourless oil (1.35 g, 99%), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36–6.34 (2H, m, C**H**=C**H**), 4.10–4.09 (2H, m, C**H**$_2$), 2.04 (1H, br, O**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.6 (CH), 107.8 (CH), 63.0 (CH_2); Physical and spectral properties were in accordance with the literature.[158]

(*E*)-{[(3-Bromoallyl)oxy]methyl}benzene (292)



The title compound was prepared according to General procedure B from alcohol **291** (1.37 g, 10.0 mmol), NaH (480 mg of 60% wt. in mineral oil, 20.0 mmol) and benzyl bromide (1.31 mL, 11.0 mmol) and purified by flash column chromatography (gradient elution; petroleum ether to 20:1 petroleum ether:Et_2O) to give ether **292** (2.19 g, 95%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.28 (5H, m, Ar**H**), 6.41–6.30 (2H, m, BrC**H**=C**H**), 4.53 (2H, s, OC**H**$_2$Ph), 3.99 (2H, dd, *J* = 5.3, 0.8 Hz, C**H**$_2$OBn); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.9 (C), 134.3 (CH), 128.6 (2 × CH), 128.0 (CH), 127.9 (2 × CH), 108.7 (CH), 77.4 (CH_2), 69.7 (CH_2); Physical and spectral properties were in accordance with the literature.[159]

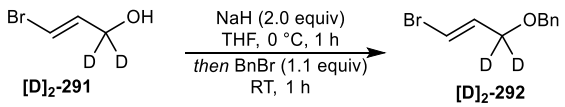
(*E*)-3-Bromoprop-2-en-1,1-d$_2$-1-ol ([D]$_2$-291)



To a suspension of $LiAlD_4$ (199 mg, 4.74 mmol) at –78 °C in THF (2 mL) was added ester **290** (468 mg, 2.26 mmol) in THF (1 mL) dropwise and the mixture was stirred at –78 °C for 1.5 h. The reaction was warmed to 0 °C by replacing the dry ice/acetone bath with an ice bath, quenched carefully with EtOAc (5 mL) followed by *i*-PrOH (2 mL) and saturated aqueous potassium sodium tartrate solution (2 mL), and the mixture was stirred vigorously for 15 min. The mixture was decanted to remove the biphasic liquid layer and the sludgy residue was washed with EtOAc (3 × 5 mL). The washings were combined with the biphasic liquid layer, H_2O (10 mL) was added, and the aqueous layer was separated and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography

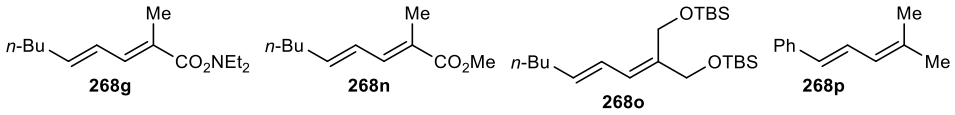
(gradient elution; 9:1 petroleum ether: EtOAc to 5:2 petroleum ether:EtOAc) to give *alcohol* **[D]$_2$-291** as a pale yellow oil (179 mg, 57%). R_f = 0.36 (5:2 petroleum ether:EtOAc); IR 3300 (OH), 2923, 1077, 1032, 960, 924, 715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (2H, s, C**H**=C**H**), 1.66 (1H, br s, O**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.5 (CH), 108.1 (CH), 62.5 (CD_2, p, *J* = 22.0 Hz); HRMS (EI) Exact mass calculated for $[C_3H_3OBrD_2]^+$ $[M]^+$: 137.9644, found: 137.9644.

(*E*)-{[(3-Bromoallyl-1,1-d$_2$)oxy]methyl}benzene ([D]$_2$-292)



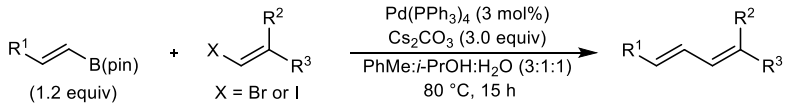
The title compound was prepared according to General procedure B from alcohol **[D]$_2$-291** (179 mg, 1.29 mmol), NaH (103 mg of 60% wt. in mineral oil, 2.58 mmol), and benzyl bromide (0.17 mL, 1.42 mmol) and purified by flash column chromatography (gradient elution; petroleum ether to 20:1 petroleum ether:Et_2O) to give *ether* **[D]$_2$-292** (213 mg, 72%) as a yellow oil. R_f = 0.42 (20:1 petroleum ether:Et_2O); IR 2852, 1453, 1354, 1294, 1094, 735, 716, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.32 (5H, m, Ar**H**), 6.44–6.34 (2H, m, C**H**=C**H**), 4.55 (2H, s, C**H**$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.8 (C), 134.1 (CH), 128.5 (2 × CH), 127.82 (CH), 127.75 (2 × CH), 108.7 (CH), 77.2 (CH_2), 68.9 (CD_2, p, *J* = 21.8 Hz); HRMS (EI) Exact mass calculated for $[C_{10}H_9OBrD_2]^+$ $[M]^+$: 228.0113, found: 228.0101.

Preparation of 1,3-dienes



1,3-Dienes **268g, 268n–268p** were prepared by David J. Burns.

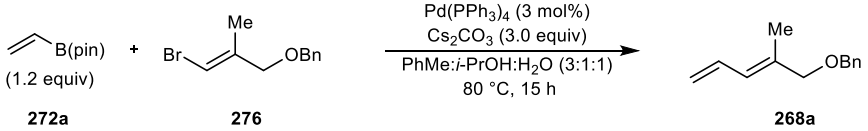
General procedure C: preparation of 1,3-dienes



To suspension of Cs_2CO_3 (3.0 equiv) in PhMe:*i*-PrOH:H_2O (3:1:1, 2 mL/mmol of alkenyl halide), $Pd(PPh_3)_4$ (3 mol%) under Ar, was added alkenyl boronate ester (1.2 equiv) and alkenyl halide (1.0 equiv). The mixture was stirred vigorously at 80 °C for 15 h. Once cooled the reaction mixture was diluted with water, Et_2O and was further

extracted with Et_2O (three times). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by flash column chromatography gave the title compound.

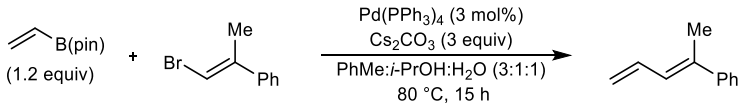
(*E*)-{[(2-Methylpenta-2,4-dien-1-yl)oxy]methyl}benzene (268a)



272a **276** **268a**

The title compound was prepared according to General procedure C from alkenyl bromide **276** (724 mg, 3.00 mmol), alkenyl boronate ester **272a** (0.76 mL, 3.6 mmol), Cs_2CO_3 (2.93 g, 9.00 mmol) and $Pd(PPh_3)_4$ (104 mg, 90.0 µmol) and was purified by flash column chromatography (40:1 petroleum ether:Et_2O) to give a colourless oil (532 mg, 94%). R_f 0.30 (40:1 petroleum ether:Et_2O); IR 2852, 1453, 1352, 1071, 987, 902, 734, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.37 (5H, m, Ar**H**), 6.66 (1H, dt, *J* = 16.9, 10.8 Hz, CH_2=C**H**), 6.14 (1H, dd, *J* = 10.8, 0.4 Hz, CH_2=CHC**H**), 5.26 (1H, dd, *J* = 16.9, 1.3 Hz, C**H**$_2$=), 5.16 (1H, d, *J* = 10.8 Hz, C**H**$_2$=), 4.52 (2H, s, C**H**$_2$Ph), 4.01 (2H, s, C**H**$_2$OBn), 1.85 (3H, s, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.6 (C), 135.5 (CH), 132.7 (C), 128.5 (2 × CH), 127.9 (2 × CH), 127.7 (CH), 127.6 (CH), 117.3 (CH_2), 75.7 (CH_2), 71.9 (CH_2), 14.5 (CH_3); HRMS (EI) Exact mass calculated for $[C_{13}H_{16}O]^+$ [M]$^+$: 188.1196, found: 188.1204.

(*E*)-Penta-2,4-dien-2-ylbenzene (268b)

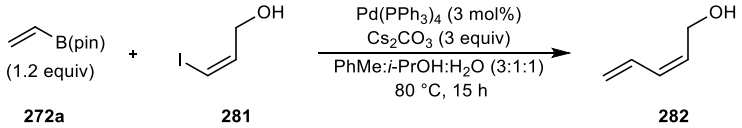


272a **278** **268b**

The title compound was prepared according to General procedure C from alkenyl bromide **278** (450 mg, 2.28 mmol), alkenyl boronate ester **272a** (0.58 mL, 3.3 mmol), Cs_2CO_3 (2.23 g, 6.84 mmol) and $Pd(PPh_3)_4$ (79 mg, 0.068 mmol) and was purified by flash column chromatography (petroleum ether) to give a colourless oil (312 mg, 95%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.49–7.45 (2H, m, Ar**H**), 7.37–7.23 (3H, m, Ar**H**), 6.78 (1H, ddd, *J* = 16.7, 11.0, 10.1 Hz, CH_2=C**H**CH), 6.54 (1H, dd, *J* = 11.0, 1.2 Hz, CH_2=CHC**H**), 5.34 (1H, dd, *J* = 16.7, 1.9 Hz, C**H**$_2$=), 5.21 (1H, dd, *J* = 10.1, 1.9 Hz, C**H**$_2$=), 2.20–2.19 (3H, m, C**H**$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 143.1 (C), 136.9 (C), 133.7 (CH), 128.4 (2 × CH), 127.9 (CH), 127.3 (CH), 125.8 (2 × CH), 117.7

(CH_2), 16.2 (CH_3); Physical and spectral properties were in accordance with the literature.[160]

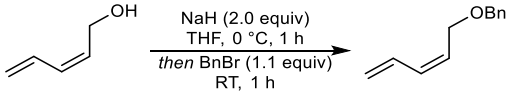
(*Z*)-Penta-2,4-dien-1-ol (282)



272a **281** **282**

The title compound was prepared according to General procedure C from alkenyl iodide **281** (920 mg, 5.00 mmol), alkenyl boronate ester **272a** (1.02 mL, 6.00 mmol), Cs_2CO_3 (4.89 g, 15.0 mmol) and $Pd(PPh_3)_4$ (173 mg, 0.150 mmol) and was purified by flash column chromatography (5:2 petroleum ether:EtOAc) to give a pale yellow oil (172 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (1H, dddd, *J* = 16.8, 11.2, 10.2, 1.1 Hz, CH_2=C**H**), 6.09 (1H, t, *J* = 11.2 Hz, CH_2=CHC**H**), 5.65–5.59 (1H, m, =C**H** CH_2), 5.25 (1H, d, *J* = 16.8 Hz, C**H**$_2$=), 5.18 (1H, d, *J* = 10.2 Hz, C**H**$_2$=), 4.31 (2H, d, C**H**$_2$OH), 1.86 (1H, br s, O**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 131.6 (CH), 131.3 (CH), 130.2 (CH), 119.4 (CH_2), 58.8 (CH_2). Physical and spectral properties were in accordance with the literature.[161]

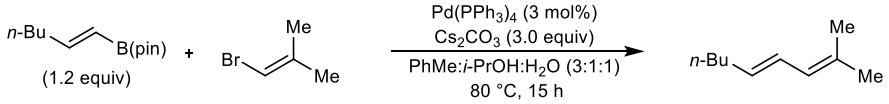
(*Z*)-[(Penta-2,4-dien-1-yloxy)methyl]benzene (268c)



282 **268c**

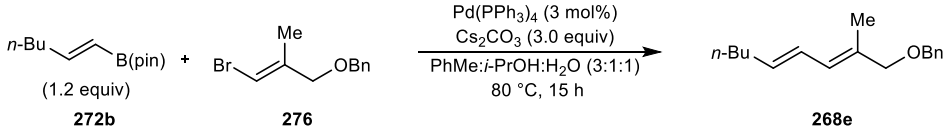
The title compound was prepared according to General procedure B from alcohol **282** (171 mg, 2.00 mmol), NaH (120 mg of 60% wt. in mineral oil, 4.00 mmol) and benzyl bromide (0.26 mL, 22 mmol) and purified by flash column chromatography (gradient elution; petroleum ether to 20:1 petroleum ether:Et_2O) to give ether **2c** (189 mg, 54%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.29 (5H, m, Ar**H**), 6.62 (1H, dddd, *J* = 16.8, 11.2, 10.1, 1.0 Hz, CH_2=C**H**), 6.24 (1H, m, C**H**CH=CH_2), 5.71–5.63 (1H, m, =C**H**CH_2), 5.29 (1H, d, *J* = 16.8, 1.8 Hz, C**H**$_2$=), 5.20 (1H, d, *J* = 10.1 Hz, C**H**$_2$=), 4.55 (2H, s, OC**H**$_2$Ph), 4.23 (2H, dd, *J* = 6.7, 1.4 Hz, C**H**$_2$OBn); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.3 (C), 132.2 (CH), 131.8 (CH), 128.5 (2 × CH), 128.0 (CH), 127.9 (2 × CH), 127.7 (CH), 119.2 (CH_2), 72.3 (CH_2), 65.9 (CH_2). Physical and spectral properties were in accordance with the literature.[162]

(*E*)-2-Methylnona-2,4-diene (268d)



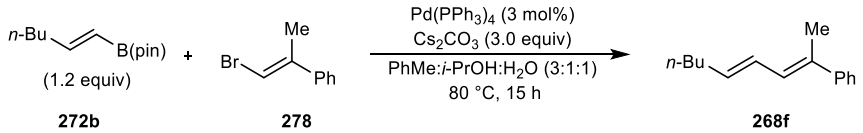
The title compound was prepared according to General procedure C from alkenyl bromide **283** (2.05 mL, 20.0 mmol), alkenyl boronate ester **272b** (5.04 g, 24.0 mmol), Cs_2CO_3 (19.6 g, 60.0 mmol) and $Pd(PPh_3)_4$ (693 mg, 0.600 mmol) and was purified by flash column chromatography (petroleum ether) to give a colourless oil (2.04 g, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 (1H, ddt, *J* = 15.0, 10.8, 1.5 Hz, CH_2=C**H**CH), 5.79 (1H, dd, *J* = 10.8, 1.2 Hz, CH_2=CHC**H**), 5.56 (1H, dt, *J* = 14.6, 7.0 Hz, C**H**$_2$=), 2.23–2.06 (2H, m, C**H**$_2$CH), 1.75 (6H, d, *J* = 4.7 Hz, C**H**$_3$CC**H**$_3$), 1.40–1.29 (4H, m, CH_3(C**H**$_2$)$_2$), 0.93 (3H, t, *J* = 7.1 Hz, C**H**$_3$CH$_2$) ; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 132.8 (C), 132.2 (CH), 126.8 (CH), 125.2 (CH), 32.7 (CH_2), 32.0 (CH_2), 26.0 (CH_3), 22.4 (CH_2), 18.3 (CH_3), 14.1 (CH_3); Physical and spectral properties were in accordance with the literature.[163]

({[(2*E*,4*E*)-2-Methylnona-2,4-dien-1-yl]oxy}methyl)benzene (268e)



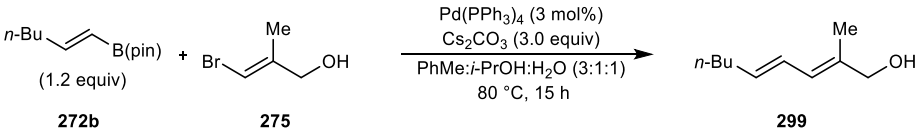
The title compound was prepared according to General procedure C from alkenyl bromide **276** (1.93 g, 8.00 mmol), alkenyl boronate ester **272b** (2.02 g, 9.60 mmol), Cs_2CO_3 (7.82 g, 24.0 mmol) and $Pd(PPh_3)_4$ (277 mg, 0.240 mmol) and was purified by flash column chromatography (gradient elution; petroleum ether to 40:1 petroleum ether:Et_2O) to give a pale yellow oil (1.69 g, 86%). R_f 0.45 (30:1 petroleum ether:Et_2O); IR 2924, 1454, 1070, 967, 733, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.27 (5H, m, Ar**H**), 6.30 (1H, ddt, *J* = 14.9, 10.8, 1.3 Hz, CH=C**H**CH), 6.06 (1H, d, *J* = 10.8 Hz, CH=CHC**H**), 5.76–5.69 (1H, m, C**H**=CHCH), 4.48 (2H, s, C**H**$_2$Ph), 3.97 (2H, s, C**H**$_2$OBn), 2.17–2.12 (2H, m, C**H**$_2$CH), 1.82 (3H, s, =CC**H**$_3$), 1.42–1.35 (4H, m, CH_3(C**H**$_2$)$_2$), 0.93 (3H, t, *J* = 7.1 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.7 (C), 135.4 (CH), 132.1 (C), 128.4 (2 × CH), 127.8 (2 × CH), 127.6 (CH), 127.5 (CH), 126.0 (CH), 76.1 (CH_2), 71.6 (CH_2), 32.8 (CH_2), 31.7 (CH_2), 22.4 (CH_2), 14.4 (CH_3), 14.1 (CH_3); HRMS (EI) Exact mass calculated for $[C_{17}H_{24}O]^+$ $[M]^+$: 244.1822, found: 244.1831.

[(2*E*,4*E*)-Nona-2,4-dien-2-yl]benzene (268f)



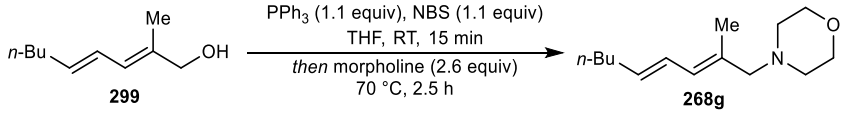
The title compound was prepared according to General procedure C from alkenyl bromide **278** (1.38 g, 7.00 mmol), alkenyl boronate ester **272b** (1.77 g, 8.40 mmol), Cs_2CO_3 (6.84g, 21.0 mmol) and $Pd(PPh_3)_4$ (243 mg, 0.210 mmol) and was purified by flash column chromatography (petroleum ether) to give a colourless oil (1.34 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.47 (2H, m, Ar**H**), 7.38–7.34 (2H, m, Ar**H**), 7.29–7.45 (1H, m, Ar**H**), 6.53–6.45 (2H, m, CH=C**H**C**H**), 5.88 (1H, m, C**H**=CHCH), 2.26–2.20 (2H, m, C**H**$_2$CH), 2.20 (3H, s, =CC**H**$_3$), 1.52–1.35 (4H, m, CH_3(C**H**$_2$)$_2$), 0.98 (3H, t, *J* = 7.1 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.5 (C), 136.2 (CH), 133.7 (C), 128.4 (CH × 2), 127.5 (CH), 127.2 (CH), 126.8 (CH), 125.6 (2 × CH), 33.0 (CH_2), 31.8 (CH_2), 22.5 (CH_2), 16.0 (CH_3), 14.1 (CH_3). Physical and spectral properties were in accordance with the literature.[164]

(2*E*,4*E*)-2-Methylnona-2,4-dien-1-ol (299)



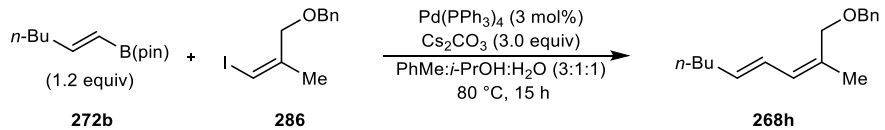
The title compound was prepared according to General procedure C from alkenyl bromide **275** (2.05 g, 13.6 mmol), alkenyl boronate ester **272b** (3.42 g, 16.3 mmol), Cs_2CO_3 (13.3 g, 40.8 mmol) and $Pd(PPh_3)_4$ (474 mg, 0.408 mmol) and was purified by flash column chromatography (5:1 petroleum ether:EtOAc) to give a colourless oil (1.94 g, 92%). R_f 0.28 (5:1 petroleum ether:EtOAc); IR 3311 (OH), 2923, 1455, 1377, 1004, 966 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (1H, dd, *J* = 15.0, 10.8 Hz, CH=C**H**CH), 6.01 (1H, d, *J* = 10.8 Hz, CH=CHC**H**), 5.73–5.66 (1H, m, C**H**=CHCH), 4.04 (2H, s, C**H**$_2$OH), 2.14–2.08 (2H, m, C**H**$_2$CH), 1.77 (3H, s, =CC**H**$_3$), 1.55 (1H, br s, O**H**), 1.34 (4H, m, CH_3(C**H**$_2$)$_2$), 0.89 (3H, t, *J* = 7.1 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 135.4 (CH), 134.8 (C), 125.9 (CH), 125.5 (CH), 68.8 (CH_2), 32.8 (CH_2), 31.7 (CH_2), 22.4 (CH_2), 14.2 (CH_3), 14.1 (CH_3); HRMS (EI) Exact mass calculated for $[C_{10}H_{18}O]^+$ [M]$^+$: 154.1352, found: 154.1359.

4-[(2*E*,4*E*)-2-Methylnona-2,4-dien-1-yl]morpholine (268g)



To a solution of the allylic alcohol **299** (463 mg, 3.00 mmol) in THF (6 mL) was added triphenylphosphine (866 mg, 3.30 mmol) followed by *N*-bromosuccinimide (NBS) (587 mg, 3.30 mmol). After 15 min, morpholine (0.69 mL, 7.9 mmol) was added dropwise and the resulting solution heated to 70 ºC for 2.5 h. Upon cooling to room temperature, the reaction mixture was diluted with Et_2O (10 mL) and filtered through a pad of Celite® (Et_2O). The filtrate was then extracted with 1.0 M aqueous HCl (60 mL). The product-containing aqueous layer was then washed with Et_2O (3 × 40 mL) and made alkaline by the addition of 2.0 M aqueous NaOH (200 mL). The aqueous solution was extracted with Et_2O (3 × 120 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by flash column chromatography (1:1 CH_2Cl_2:EtOAc) gave *allylic amine* **268g** (493 mg, 74%) as a colourless oil. R_f 0.23 (5:1 petroleum ether:EtOAc); IR 2925, 2805, 1453, 1345, 1389, 1289, 1267, 1130, 1005, 908, 864 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.23 (1H, ddt, *J* = 15.0, 10.8, 1.4 Hz, CH=C**H**CH), 5.90 (1H, d, *J* = 10.8 Hz, C**H**=CHCH), 5.66–5.59 (1H, m, CH=CHC**H**), 3.66 (4H, t, *J* = 4.6 Hz, C$\mathbf{H}_2$OC$\mathbf{H}_2$), 2.84 (2H, s, CC$\mathbf{H}_2$N), 2.33–2.31 (4H, t, *J* = 4.6 Hz, C$\mathbf{H}_2$NC$\mathbf{H}_2$), 2.11–2.05 (2H, m, C$\mathbf{H}_2$CH), 1.74 (3H, s, =CC$\mathbf{H}_3$), 1.38–1.27 (4H, m, CH_3(C$\mathbf{H}_2$)$_2$), 0.88 (3H, t, *J* = 7.1 Hz, C$\mathbf{H}_3$$CH_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 134.4 (CH), 132.4 (C), 127.9 (CH), 126.1 (CH), 67.8 (CH_2), 67.2 (2 × CH_2), 53.7 (2 × CH_2), 32.7 (CH_2), 31.7 (CH_2), 22.4 (CH_2), 15.5 (CH_3), 14.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{12}H_{28}NNaO]^+$ $[M+Na]^+$: 225.2063, found: 225.2051.

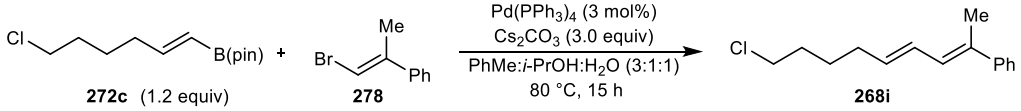
({[(2*Z*,4*E*)-2-Methylnona-2,4-dien-1-yl]oxy}methyl)benzene (268h)



The title compound was prepared according to General procedure C from alkenyl iodide **286** (576 mg, 2.00 mmol), alkenyl boronate ester **272b** (504 mg, 2.40 mmol), Cs_2CO_3 (1.96 g, 6.00 mmol) and $Pd(PPh_3)_4$ (69 mg, 0.060 mmol) and was purified by flash column chromatography (gradient elution; petroleum ether to 40:1 petroleum ether:Et_2O) to give a pale yellow oil (270 mg, 55%). R_f 0.43 (30:1 petroleum

ether:Et_2O); IR 2926, 1453, 1069, 967, 734, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (5H, m, Ar**H**), 6.26–6.19 (1H, m, CH=C**H**CH), 6.00 (1H, d, *J* = 11.0 Hz, CH=CHC**H**), 5.67–5.60 (1H, m, C**H**=CHCH), 4.46 (2H, s, C**H**$_2$Ph), 4.13 (2H, s, C**H**$_2$OBn), 2.10–2.05 (2H, m, C**H**$_2$CH), 1.85 (3H, s, =CC**H**$_3$), 1.38–1.31 (4H, m, CH_3(C**H**$_2$)$_2$), 0.93 (3H, t, *J* = 7.1 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.7 (C), 134.9 (CH), 132.1 (C), 129.7 (CH), 128.5 (2 × CH), 128.0 (2 × CH), 127.7 (CH), 125.6 (CH), 71.7 (CH_2), 68.6 (CH_2), 32.6 (CH_2), 31.7 (CH_2), 22.4 (CH_2), 21.9 (CH_3), 14.1 (CH_3); HRMS (EI) Exact mass calculated for $[C_{17}H_{24}O]^+$ $[M]^+$: 244.1822, found: 244.1831.

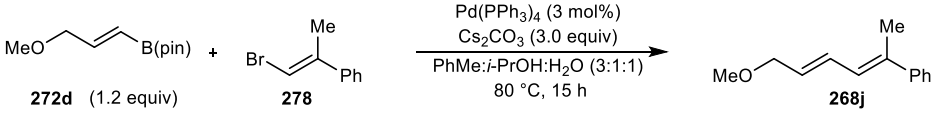
[(2*E*,4*E*)-7-Chlorohepta-2,4-dien-2-yl]benzene (268i)



272c (1.2 equiv) **278** **268i**

The title compound was prepared according to General procedure C from alkenyl bromide **278** (587 mg, 2.00 mmol), alkenyl boronate ester **272c** (0.51 mL, 2.4 mmol), Cs_2CO_3 (1.96 g, 6.00 mmol) and $Pd(PPh_3)_4$ (69 mg, 0.060 mmol) and was purified by flash column chromatography (petroleum ether) to give a colourless oil (256 mg, 55%). R_f 0.75 (petroleum ether); IR 2934, 1493, 1444, 963, 756, 733, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.45 (2H, m, Ar**H**), 7.38–7.32 (2H, m, Ar**H**), 7.27–7.23 (1H, m, Ar**H**), 6.51–6.43 (2H, m, CH=C**H**C**H**), 5.85–5.78 (1H, m, C**H**=CHCH), 3.58 (2H, t, *J* = 6.7 Hz, ClC**H**$_2$), 2.24 (2H, q, *J* = 7.3 Hz, C**H**$_2$CH), 2.18 (3H, s, C**H**$_3$), 1.88–1.81 (2H, m, C**H**$_2$), 1.65–1.58 (2H, m, C**H**$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.4 (C), 134.8 (CH), 134.3 (C), 128.4 (2 × CH), 127.9 (CH), 127.2 (CH), 126.9 (CH), 125.7 (2 × CH), 45.1 (CH_2), 32.4 (CH_2), 32.2 (CH_2), 26.8 (CH_2), 16.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{15}H_{19}Cl]^+$ $[M]^+$: 234.1170, found: 234.1171.

[(2*E*,4*E*)-6-Methoxyhexa-2,4-dien-2-yl]benzene (268j)

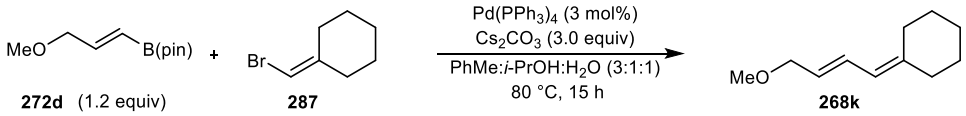


272d (1.2 equiv) **278** **268j**

The title compound was prepared according to General procedure C from alkenyl bromide **278** (394 mg, 2.00 mmol), alkenyl boronate ester **272d** (0.51 mL, 2.4 mmol), Cs_2CO_3 (1.96 g, 6.00 mmol) and $Pd(PPh_3)_4$ (69 mg, 0.060 mmol) and was purified by flash column chromatography (30:1 petroleum ether:Et_2O) to give a yellow oil (281

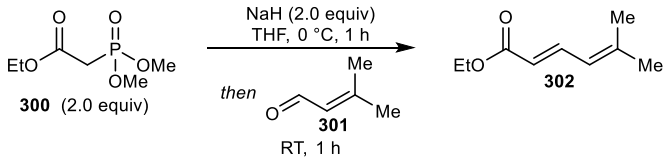
mg, 75%). R_f 0.45 (30:1 petroleum ether:Et_2O); IR 2924, 1446, 1117, 964, 750, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52–7.50 (2H, m, Ar**H**), 7.40–7.37 (2H, m, Ar**H**), 7.32–7.28 (1H, m, Ar**H**), 6.74 (1H, ddt, *J* = 14.9, 11.0, 1.3 Hz, CH=C**H**CH), 6.54 (1H, d, *J* = 11.0 Hz, CH=CHC**H**), 5.94 (1H, dt, *J* = 14.9, 6.1 Hz C**H**=CHCH), 4.10 (2H, d, *J* = 6.1 Hz, OC$\mathbf{H}_2$), 3.43 (3H, s, C$\mathbf{H}_3$O), 2.24 (3H, s, =CC$\mathbf{H}_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.0 (C), 136.7 (C), 130.1 (CH), 129.5 (CH), 128.3 (2 × CH), 127.2 (CH), 126.3 (CH), 125.7 (2 × CH), 73.1 (CH_2), 58.0 (CH_3), 16.1 (CH_3); HRMS (EI) Exact mass calculated for $[C_{13}H_{16}O]^+$ $[M]^+$: 188.1196, found: 188.1197.

(*E*)-(4-Methoxybut-2-en-1-ylidene)cyclohexane (268k)



The title compound was prepared according to General procedure C from alkenyl bromide **287** (0.20 mL, 1.5 mmol), alkenyl boronate ester **272d** (0.36 mL, 1.7 mmol), Cs_2CO_3 (1.47 g, 4.50 mmol) and $Pd(PPh_3)_4$ (52 mg, 0.045 mmol) and was purified by flash column chromatography (40:1 petroleum ether:Et_2O) to give a pale yellow oil (247 mg, 99%). R_f 0.32 (40:1 petroleum ether:Et_2O); IR 2924, 1447, 1117, 964 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.51 (1H, ddt, *J* = 15.1, 11.0, 1.2 Hz, CH=C**H**CH), 5.79 (1H, d, *J* = 11.0 Hz, CH=CHC**H**), 5.65 (1H, dt, *J* = 15.1, 6.3 Hz, C**H**=CHCH), 3.95 (2H, dd, *J* = 6.3, 0.8 Hz, OC$\mathbf{H}_2$), 3.33 (3H, s, C$\mathbf{H}_3$), 2.29–2.27 (2H, m, =CC$\mathbf{H}_2$), 2.13 (2H, br s, =CC$\mathbf{H}_2$), 1.56 (6H, br s, CH_2(C$\mathbf{H}_2$)$_3$$CH_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.5 (C), 129.1 (CH), 126.7 (CH), 121.3 (CH), 73.3 (CH_2), 57.9 (CH_3), 37.4 (CH_2), 29.4 (CH_2), 28.7 (CH_2), 27.9 (CH_2), 26.9 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{11}H_{18}NaO]^+$ $[M+Na]^+$: 189.1250, found: 189.1247.

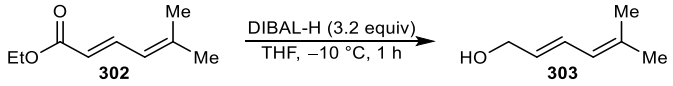
Ethyl (*E*)-5-methylhexa-2,4-dienoate (302)



To a stirred suspension of sodium hydride (600 mg, 15.0 mmol) in THF (10 mL) was added triethyl phosphonoacetate **300** (3.96 mL, 20.0 mmol) at 0 °C and the resulting mixture was stirred for 1 h. Next, 3-methyl-2-butenal **301** (1.17 mL, 10.0 mmol) was added and the solution was left stirring at room temperature for 1 h. The reaction

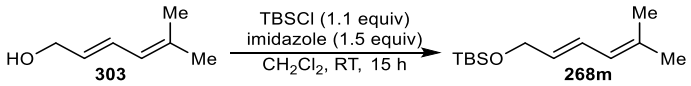
mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (10:1 petroleum ether: Et_2O) gave 1,3-diene **302** (1.25 g, 82%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (1H, dd, *J* = 15.2, 11.5 Hz, C**H**CH=CCH_3), 5.97 (1H, d, *J* = 11.5 Hz, C**H**=CCH_3), 5.75 (1H, d, *J* = 15.2 Hz, O=CC**H**), 4.19 (2H, q, *J* = 7.1 Hz, CH_3C**H**$_2$), 1.87 (6H, d, *J* = 5.6 Hz, C(C**H**$_3$)$_2$), 1.28 (3H, t, *J* = 7.1 Hz, C**H**$_3$CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.8 (C), 146.3 (C), 141.1 (CH), 123.8 (CH), 118.7 (CH), 60.2 (CH_2), 26.7 (CH_3), 19.1 (CH_3), 14.5 (CH_3). Physical and spectral properties were in accordance with the literature.[165]

(*E*)-5-Methylhexa-2,4-dien-1-ol (303)



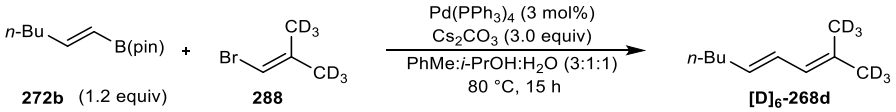
To a stirred solution of ester **302** (970 mg, 6.29 mmol) in THF (7 mL) was added DIBAL-H (1.0 M in toluene, 20.1 mL, 20.1 mmol) dropwise at –10 °C and the mixture was left to stir for 1 h. The reaction was diluted with EtOAc (10 mL), quenched with saturated aqueous potassium sodium tartrate solution (10 mL), and the mixture was stirred vigorously for 15 min. The mixture was decanted to remove the biphasic liquid layer and the sludgy residue was washed with EtOAc (3 × 10 mL). The washings were combined with the biphasic liquid layer, H_2O (25 mL) was added, and the aqueous layer was separated and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was dissolved in Et_2O, filtered through a plug of silica using further Et_2O as eluent, and concentrated *in vacuo* to leave alcohol **303** as a colourless oil (671 mg, 95%), which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (1H, dd, *J* = 15.0, 11.0 Hz, C**H**CH=CCH_3), 5.83 (1H, d, *J* = 11.0 Hz, C**H**=CCH_3), 5.70 (1H, dt, *J* = 15.0, 6.1 Hz, HOCH_2C**H**), 4.17 (2H, t, *J* = 6.1 Hz, C**H**$_2$), 1.77 (6H, d, *J* = 6.1 Hz, C(C**H**$_3$)$_2$), 1.55 (1H, s, **H**O); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 136.4 (C), 129.1 (CH), 128.5 (CH), 124.3 (CH), 63.9 (CH_2), 26.1 (CH_3), 18.4 (CH_3). Physical and spectral properties were in accordance with the literature. [165]

(*E*)-*tert*-Butyldimethyl((5-methylhexa-2,4-dien-1-yl)oxy)silane (268m).



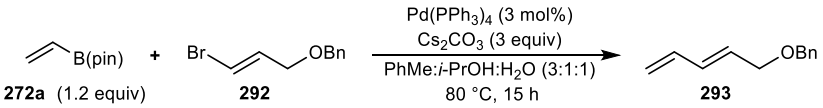
To a stirred solution of alcohol **303** (227 mg, 2.00 mmol) in CH_2Cl_2 (5 mL) was added TBSCl (332 mg, 2.20 mmol) followed by imidazole (204 mg, 3.00 mmol) and stirred at room temperature for 15 h. The reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (MgSO4), filtered, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (10:1 petroleum ether: Et_2O) gave 1,3-diene **268m** (436 mg, 96%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (1H, ddt, *J* = 14.9, 11.0, 1.7 Hz, C**H**CH=CCH$_3$), 5.83 (1H, dd, *J* = 11.0, 1.0 Hz, CHC**H**=CCH$_3$), 5.62 (1H, dt, *J* = 14.9, 5.4 Hz, CH$_2$C**H**), 4.22 (2H, d, *J* = 5.4 Hz, C**H**$_2$), 1.76 (6H, d, *J* = 8.8 Hz, C(C**H**$_3$)$_2$), 0.92 (9H, s, Si(C**H**$_3$)$_3$), 0.07 (6H, s, Si(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 135.2 (C), 129.8 (CH), 126.8 (CH), 124.6 (CH), 64.1 (CH_2), 26.1 (4 × CH_3), 18.6 (C), 18.4 (CH_3), –5.0 (2 × CH_3). Physical and spectral properties were in accordance with the literature.[166]

(*E*)-2-(Methyl-d$_3$)nona-2,4-diene-1,1,1-d$_3$ ([D]$_6$-268d)



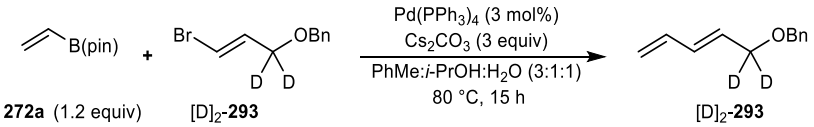
The title compound was prepared according to General procedure C from alkenyl bromide **288** (1.03 g, 7.30 mmol), alkenyl boronate ester **272b** (1.85 g, 8.80 mmol), Cs_2CO_3 (7.17 g, 22.0 mmol) and $Pd(PPh_3)_4$ (254 mg, 0.220 mmol) and was purified by flash column chromatography (petroleum ether) to give a colourless oil (626 mg, 59%). R_f 0.72 (petroleum ether); IR 2957, 1465, 1047, 975, 890, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (1H, ddt, *J* = 15.0, 10.8, 1.4 Hz, CH=C**H**CH), 5.79 (1H, d, *J* = 10.8 Hz, CH=CHC**H**), 5.59–5.52 (1H, m, C**H**=CHCH), 2.11–2.06 (2H, m, C**H**$_2$CH), 1.39–1.26 (4H, m, CH$_3$(C**H**$_2$)$_2$), 0.90 (3H, t, *J* = 7.1 Hz, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 132.5 (C), 132.2 (CH), 130.5 (C), 126.8 (CH), 125.3 (CH), 32.7 (CH_2), 32.0 (CH_2), 22.4 (CH_2), 14.1 (CH_3); HRMS (EI) Exact mass calculated for $[C_{10}H_{12}D_6]^+$ $[M]^+$: 144.1780, found: 144.1781.

(*E*)-[(Penta-2,4-dien-1-yloxy)methyl]benzene (293)



The title compound was prepared according to General procedure C from alkenyl bromide **292** (274 mg, 1.00 mmol), alkenyl boronate ester **272a** (0.20 mL, 1.2 mmol), Cs_2CO_3 (977 mg, 3.00 mmol) and $Pd(PPh_3)_4$ (35 mg, 0.030 mmol) and was purified by flash column chromatography (40:1 petroleum ether:Et_2O) to give a pale yellow oil (126 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.35 (5H, m, Ar**H**), 6.44–6.28 (2H, m, CH_2=C**H**C**H**), 5.85 (1H, dt, *J* = 14.7, 6.0 Hz, C**H**CH_2), 5.27–5.23 (1H, m, C**H**$_2$=), 5.15–5.12 (1H, m, C**H**$_2$=), 4.55 (2H, s, C**H**$_2$Ph), 4.10 (2H, d, *J* = 6.4 Hz, C**H**$_2$OBn); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.4 (C), 136.5 (CH), 133.4 (CH), 130.2 (CH), 128.5 (2 × CH), 127.9 (2 × CH), 127.7 (CH), 117.7 (CH_2), 72.3 (CH_2), 70.3 (CH_2); Physical and spectral properties were in accordance with the literature.[167]

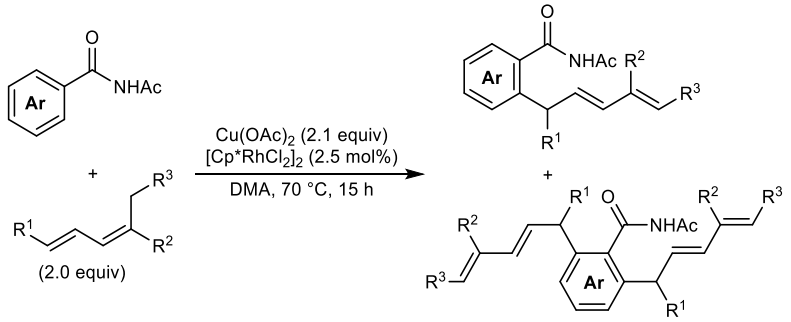
(*E*)-{[(Penta-2,4-dien-1-yl-1,1-d$_2$)oxy]methyl}benzene ([D]$_2$-293)



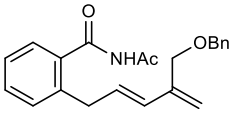
The title compound was prepared according to General procedure C from alkenyl bromide [D]$_2$-**292** (134 mg, 0.59 mmol), alkenyl boronate ester **272a** (0.12 mL, 0.70 mmol), Cs_2CO_3 (580 mg, 1.78 mmol), and $Pd(PPh_3)_4$ (21 mg, 0.018 mmol) and was purified by flash column chromatography (20:1 petroleum ether:Et_2O) to give a pale yellow oil (95 mg, 92%). R_f 0.35 (20:1 petroleum ether:Et_2O); IR 2854, 1105, 1003, 904, 733, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.31 (5H, m, Ar**H**), 6.47–6.31 (2H, m, CH_2=C**H**C**H**), 5.87 (1H, d, *J* = 14.8 Hz, C**H**CD_2), 5.28 (1H, dd, *J* = 17.0, 1.7 Hz, C**H**$_2$=), 5.16 (1H, dd, *J* = 9.4, 1.7 Hz, C**H**$_2$=), 4.57 (2H, s, C**H**$_2$Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.3 (C), 136.4 (CH), 133.4 (CH), 130.0 (CH), 128.4 (2 × CH), 127.8 (2 × CH), 127.6 (CH), 117.6 (CH_2), 72.1 (CH_2), 69.5 (CD_2, quin, *J* = 21.6 Hz); HRMS (EI) Exact mass calculated for $[C_{12}H_{12}OD_2]^+$ $[M]^+$: 176.1165, found: 176.1200.

3.1.3 Oxidative C–H allylation of benzamides with 1,3-dienes

General procedure D: oxidative C–H allylation of benzamides with 1,3-dienes



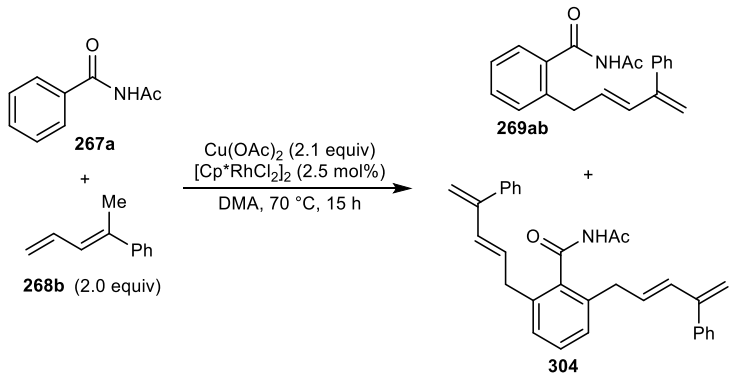
To a microwave vial was added the appropriate *N*-acetyl benzamide (0.30 mmol), $[Cp^*RhCl_2]_2$ (4.6 mg, 7.5 μmol), $Cu(OAc)_2$[**] (114 mg, 0.630 mmol), and the appropriate 1,3-diene (0.60 mmol). The vessel was then sealed, flushed with Ar, and DMA (3 mL) was added. The reaction was then heated at 70 ºC for 15 h. The reaction was cooled to room temperature, filtered through a short pad of silica using Et_2O (20 mL) as eluent, and concentrated *in vacuo*. Purification of the residue by flash column chromatography or preparative thin layer chromatography gave the title compound(s). [**]*Note*: $Cu(OAc)_2$ was purified by heating under vacuum with a heat gun to remove residual AcOH and H_2O. This purification is important to obtain good yields of the products.



(*E*)-*N*-Acetyl-2-{4-[(benzyloxy)methyl]penta-2,4-dien-1-yl}benzamide (269aa). The title compound was prepared according to General procedure D from benzamide **267a** (98 mg, 0.60 mmol) and *1,3-diene* **268a** (57 mg, 0.30 mmol). Purification of the residue by flash column chromatography (15:2 CH_2Cl_2: EtOAc) gave *allylation product* **269aa** (55 mg, 50%) as a yellow oil. R_f 0.47 (15:2 CH_2Cl_2: EtOAc); IR 3262 (NH), 2929, 1719 (C=O), 1259, 1019, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (1H, s, N**H**), 7.42–7.38 (2H, m, Ar**H**), 7.29–7.21 (7H, m, Ar**H**), 6.09 (1H, d, *J* = 16.0 Hz, CH_2CH=C**H**), 5.92 (1H, dt, *J* = 16.0, 6.7 Hz, CH_2C**H**=CH), 5.18 (1H, s, =C**H**$_2$), 5.10 (1H, s, =C**H**$_2$), 4.45 (2H, s, C**H**$_2$Ph), 4.13 (2H, s, C**H**$_2$OBn), 3.61 (2H, d, *J* = 6.6 Hz, C**H**$_2$CH=CH) , 2.50 (3H, s, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.7 (C), 168.0 (C), 142.0 (C), 139.3 (C), 138.4 (C), 134.4 (C), 131.7 (2 × CH), 131.2 (CH), 129.0 (CH), 128.5 (2 × CH), 127.8 (2 × CH), 127.7 (CH), 127.2 (CH), 126.8 (CH), 116.8

(CH_2), 72.0 (CH_2), 70.5 (CH_2), 36.8 (CH_2), 25.5 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{22}H_{23}NNaO_3]^+$ $[M+Na]^+$: 372.1570, found: 372.1577.

(*E*)-*N*-Acetyl-2-(4-phenylpenta-2,4-dien-1-yl)benzamide (269ab) and *N*-acetyl-2,6-bis[(*E*)-4-phenylpenta-2,4-dien-1-yl]benzamide (304)

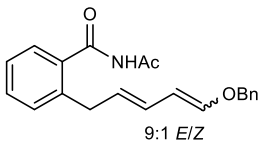


The title compounds were prepared according to General procedure D from benzamide **267a** (49 mg, 0.30 mmol) and 1,3-diene **268b** (86 mg, 0.60 mmol) and were purified by flash column chromatography (2:1 petroleum ether: Et_2O) to give *bisallylated product* **304** as a yellow oil (36 mg, 27%) followed by *monoallylated product* **269ab** as a pale yellow oil which solidified upon standing (93 mg, 69%).

Data for **269ab**: R_f 0.35 (2:1 petroleum ether: Et_2O); IR 3256 (NH), 3020, 1697 (C=O), 1257, 749, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (1H, s, N**H**), 7.45–7.41 (2H, m, Ar**H**), 7.34–7.27 (7H, m, Ar**H**), 6.32 (1H, d, *J* = 15.6 Hz, CH_2CH=C**H**), 5.76 (1H, dd, *J* = 15.6, 6.7 Hz, CH_2C**H**), 5.21 (1H, d, *J* = 1.5 Hz, =C**H**$_2$), 5.11 (1H, d, *J* = 1.5 Hz, =C**H**$_2$), 3.67 (2H, d, *J* = 6.7 Hz, C**H**$_2$CH), 2.55 (3H, s, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.7 (C), 168.0 (C), 147.7 (C), 140.3 (C), 139.2 (C), 134.4 (C), 133.7 (CH), 131.7 (CH), 131.5 (CH), 131.2 (CH), 128.28 (2 × CH), 128.25 (2 × CH), 127.6 (CH), 127.3 (CH), 126.8 (CH), 116.3 (CH_2), 36.6 (CH_2), 25.5 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{20}H_{20}NO_2]^+$ $[M+H]^+$: 306.1489, found: 306.1483.

Data for **304**: R_f 0.48 (2:1 petroleum ether: Et_2O); IR 3383 (NH), 3010, 2964, 1720 (C=O), 1464, 1374, 1262, 1019 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (1H, s, N**H**), 7.36–7.27 (11H, m, Ar**H**), 7.11 (2H, d, *J* = 7.7 Hz, Ar**H**), 6.33 (2H, d, *J* = 15.6 Hz, 2 × CH_2CH=C**H**), 5.73 (2H, dt, *J* = 15.6, 6.7 Hz, 2 × CH_2C**H**), 5.23 (2H, br s, 2 × =C**H**$_2$), 5.15 (2H, d, *J* = 1.5 Hz, 2 × =C**H**$_2$), 3.48 (4H, d, *J* = 6.7 Hz, 2 × C**H**$_2$CH), 2.50 (3H, s, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.7 (C), 168.6 (C), 147.6 (2 × C), 140.2 (2 × C), 136.5 (2 × C), 135.6 (C), 133.8 (2 × CH), 131.0 (2 × CH), 130.2 (CH), 128.29 (4 × CH), 128.26 (4 × CH), 128.2 (2 × CH), 127.6 (2 × CH), 116.5 (2 × CH_2), 36.8 (2

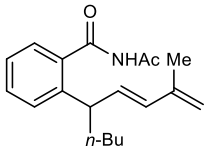
× CH_2), 25.7 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{31}H_{30}NO_2]^+$ $[M+H]^+$: 448.2271, found: 448.2278.



***N*-Acetyl-2-[(2*E*,4*E*)-5-(benzyloxy)penta-2,4-dien-1-yl]benzamide (269ac).** The title compound was prepared according to General procedure D from benzamide **267a** (98 mg, 0.60 mmol) and 1,3-diene **268c** (52 mg, 0.30 mmol) and was purified by flash column chromatography (15:10:2 CH_2Cl_2:pentane:EtOAc) to give an orange oil as a 9:1 inseparable mixture of *E*/*Z*-isomers (61 mg, 61%).

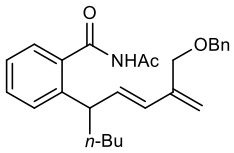
Data for *E*-isomer: R_f 0.35 (15:10:2 CH_2Cl_2:pentane:EtOAc); IR 3276 (NH), 2927, 1692 (C=O), 1372, 1263, 1157, 1018, 973, 733, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (1H, s, N**H**), 7.46–7.41 (2H, m, Ar**H**), 7.37–7.29 (7H, m, Ar**H**), 6.57 (1H, d, *J* = 12.4 Hz, C**H**OBn), 5.92 (1H, dd, *J* = 15.2, 10.6 Hz, CH_2CH=C**H**), 5.66–5.56 (2H, m, CH_2CH=CHC**H** and CH_2C**H**), 4.77 (2H, s, C**H**$_2$Ph), 3.57 (2H, d, *J* = 6.7 Hz, C**H**$_2$CH), 2.55 (3H, s, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.7 (C), 168.0 (C), 149.8 (CH), 139.8 (C), 136.8 (C), 134.3 (C), 131.7 (CH), 131.2 (CH), 128.7 (2 × CH), 128.4 (CH), 128.2 (CH), 127.7 (2 × CH), 127.4 (CH), 126.7 (CH), 126.5 (CH), 107.1 (CH), 71.9 (CH_2), 36.7 (CH_2), 25.6 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{21}H_{21}NNaO_3]^+$ $[M+Na]^+$: 358.1414, found: 358.1420.

Characteristic signals for *Z*-isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 6.53–6.46 (1H, m, CH_2CH=C**H**CH), 6.00 (1H, d, *J* = 6.3 Hz, C**H**OBn), 5.07 (1H, dd, *J* = 10.9, 6.3 Hz, CH_2CH=CHC**H**).

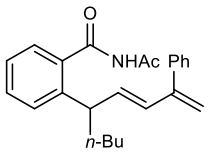


(*E*)-*N*-Acetyl-2-(2-methylnona-1,3-dien-5-yl)benzamide (269ad). The title compound was prepared according to General procedure D from benzamide **267a** (49 mg, 0.30 mmol) and 1,3-diene **268d** (83 mg, 0.60 mmol) and was purified by flash column chromatography (2:1 petroleum ether: Et_2O) to give a pale yellow oil (69 mg, 77%). R_f 0.42 (2:1 petroleum ether:Et_2O); IR 3263 (NH), 2929, 1694 (C=O), 1372, 1260, 1019, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (1H, s, N**H**), 7.48–7.44 (1H, m, Ar**H**), 7.40–7.37 (2H, m, Ar**H**), 7.28–7.24 (1H, m, Ar**H**), 6.13 (1H, d, *J* = 15.7 Hz, CHCH=C**H**), 5.72 (1H, dd, *J* = 15.7, 7.8 Hz, CHC**H**=CH), 4.90 (2H, s, =C**H**$_2$), 3.83–3.77 (1H, m, ArC**H**), 2.57 (3H, s, C**H**$_3$C=O), 1.80 (3H, s, =CC**H**$_3$), 1.78–1.73 (2H, m, C**H**$_2$CH), 1.32–1.13 (4H, m, CH_3(C**H**$_2$)$_2$), 0.86 (3H, t, *J* = 7.1 Hz, C**H**$_3$$CH_2$); ^{13}C NMR (100.6

MHz, $CDCl_3$) δ 172.6 (C), 168.5 (C), 143.6 (C), 141.7 (C), 134.9 (C), 133.4 (2 × CH), 131.5 (CH), 128.2 (CH), 127.0 (CH), 126.3 (CH), 116.1 (CH_2), 44.2 (CH), 35.8 (CH_2), 29.9 (CH_2), 25.6 (CH_3), 22.7 (CH_2), 18.7 (CH_3), 14.1 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{19}H_{25}NNaO_2]^+$ $[M+Na]^+$: 322.1778, found: 322.1780.

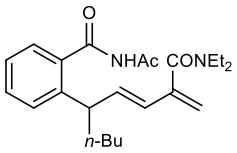


(*E*)-*N*-Acetyl-2-{2-[(benzyloxy)methyl]nona-1,3-dien-5-yl}benzamide (269ae). The title compound was prepared according to General procedure D from benzamide **267a** (49 mg, 0.30 mmol) and *1,3-diene* **268e** (154 mg, 0.600 mmol) and was purified by flash column chromatography (3:2 Et_2O:petroleum ether) to give an orange oil (94 mg, 77%). R_f 0.35 (3:2 Et_2O:petroleum ether); IR 3263 (NH), 2929, 1695 (C=O), 1372, 1259, 1018, 908 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (1H, s, N**H**), 7.42–7.22 (9H, m, Ar**H**), 6.06 (1H, d, *J* = 16.0 Hz, CHCH=C**H**), 5.89 (1H, dd, *J* = 16.0, 7.9 Hz, CHC**H**=CH), 5.17 (1H, s, =C**H**$_2$), 5.11 (1H, s, =C**H**$_2$), 4.47–4.41 (2H, m, C**H**$_2$Ph), 4.15 (2H, s, C**H**$_2$OBn), 3.79–3.73 (1H, m, ArC**H**), 2.54 (3H, s, C**H**$_3$C=O), 1.74–1.69 (2H, m, C**H**$_2$CH), 1.32–1.09 (4H, m, CH_3(C**H**$_2$)$_2$), 0.83 (3H, t, *J* = 7.1 Hz, C**H**$_3$$CH_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.4 (C), 168.3 (C), 143.4 (C), 142.0 (C), 138.4 (C), 134.8 (C), 134.3 (CH), 131.6 (CH), 130.2 (CH), 128.5 (2 × CH), 128.2 (CH), 127.9 (2 × CH), 127.7 (CH), 127.0 (CH), 126.4 (CH), 117.2 (CH_2), 71.9 (CH_2), 70.7 (CH_2), 44.6 (CH), 35.8 (CH_2), 29.9 (CH_2), 25.6 (CH_3), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{26}H_{32}NO_3]^+$ $[M+H]^+$: 406.2377, found: 406.2378.



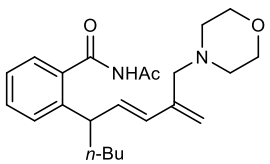
(*E*)-*N*-Acetyl-2-(2-phenylnona-1,3-dien-5-yl)benzamide (269af). The title compound was prepared according to General procedure D from benzamide **267a** (98 mg, 0.60 mmol), and 1,3-diene **268f** (60 mg, 0.30 mmol) and was purified by flash column chromatography (2:1 petroleum ether: Et_2O) to give a yellow oil (68 mg, 63%). R_f 0.33 (2:1 petroleum ether:Et_2O); IR 3266 (NH), 2928, 1693 (C=O), 1372, 1261, 1018, 752, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, s, N**H**), 7.41–7.23 (9H, m, Ar**H**), 6.27 (1H, d, *J* = 15.7 Hz, CHCH=C**H**), 5.72 (1H, dd, *J* = 15.7, 7.9 Hz, CHC**H**=CH), 5.18 (1H, d, *J* = 1.5 Hz, =C**H**$_2$), 5.08 (1H, d, *J* = 1.5 Hz, =C**H**$_2$), 3.85–3.80 (1H, m, ArC**H**), 2.55 (3H, s, C**H**$_3$C=O), 1.74–1.68 (2H, m, C**H**$_2$CH), 1.31–1.12 (4H, m, CH_3(C**H**$_2$)$_2$), 0.84 (3H, t, *J* = 7.1 Hz, C**H**$_3$$CH_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.6 (C), 168.4 (C), 147.7 (C), 143.4 (C), 140.4 (C), 136.7 (CH), 134.8 (C), 132.1 (CH), 131.6 (CH), 128.31 (2

× CH), 128.25 (2 × CH), 128.2 (CH), 127.5 (CH), 127.0 (CH), 126.4 (CH), 116.3 (CH_2), 44.4 (CH), 35.8 (CH_2), 29.9 (CH_2), 25.6 (CH_3), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI) Exact mass calculated for [$C_{24}H_{28}NO_2$] $[M+H]^+$: 362.2115, found: 362.2106.



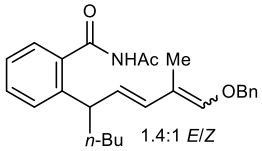
(*E*)-*N*-Acetyl-2-(2-(diethylcarbamoyl)nona-1,3-dien-5-yl)benzamide (269ag)

The title compound was prepared according to General procedure D from benzamide **267a** (64 mg, 0.39 mmol), $[Cp^*RhCl_2]_2$ (4.6 mg, 7.5 μmol), $Cu(OAc)_2$ (114 mg, 0.630 mmol), and 1,3-diene **268g** (67 mg, 0.30 mmol) at 70 °C for a reaction time of 12 h and was purified by flash column chromatography (5:1 Et_2O:petroleum ether) to give a pale yellow oil (30 mg, 26%). R_f 0.23 (5:1 Et_2O:petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (1H, s, N**H**), 7.45–7.37 (2H, m, Ar**H**), 7.32–7.30 (1H, m, Ar**H**), 7.27–7.23 (1H, m, Ar**H**), 6.04 (1H, d, *J* = 15.9 Hz, ArCHCH=C**H**), 5.75 (1H, dd, *J* = 15.9, 7.9 Hz, ArCHC**H**=CH), 5.13 (1H, s, C=CH**H'**), 5.06 (1H, s, C=C**H**H'), 3.83 (1H, m, *J* = 7.5 Hz, ArC**H**), 3.48–3.39 (2H, m, C**H**$_2$CH$_3$), 3.19 (2H, q, *J* = 7.1 Hz, C**H**$_2$CH$_3$), 2.55 (3H, s, C(O)C**H**$_3$), 1.72 (2H, dd, *J* = 14.9, 7.5 Hz, C**H**$_2$(CH$_2$)$_2$CH$_3$), 1.32–1.24 (4H, m, CH$_2$(C**H**$_2$)$_2$CH$_3$), 1.15 (3H, t, 7.1 Hz, CH$_2$C**H**$_3$), 1.02 (3H, t, 7.1 Hz, CH$_2$C**H**$_3$), 0.83 (3H, t, *J* = 7.0 Hz, (CH$_2$)$_3$C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.4 (C), 169.7 (C), 168.3 (C), 144.3 (C), 142.9 (C), 137.1 (CH), 134.8 (C), 131.6 (CH), 128.6 (CH), 128.2 (CH), 127.0 (CH), 126.5 (CH), 115.2 (CH_2), 44.0 (CH), 42.7 (CH_2), 38.5 (CH_2), 35.7 (CH_2), 29.8 (CH_2), 25.6 (CH_3), 22.7 (CH_2), 14.4 (CH_3), 14.1 (CH_3), 12.9 (CH_3). Exact mass calculated for $C_{23}H_{33}N_2O_3$ $[M+H]^+$: 385.2486, found: 385.2500, exact mass calculated for $C_{23}H_{32}N_2NaO_3$ $[M+Na]^+$: 407.2305, found 407.2309, exact mass calculated for $C_{23}H_{36}N_3O_3$ $[M+NH_4]^+$: 402.2751, found 402.2752.



(*E*)-*N*-Acetyl-2-[2-(morpholinomethyl)nona-1,3-dien-5-yl]benzamide (269ag). The title compound was prepared according to General procedure D from benzamide **267a** (49 mg, 0.30 mmol) and *1,3-diene* **268g** (134 mg, 0.60 mmol) and was purified by flash column chromatography (1:1 petroleum ether:EtOAc) to give an orange oil (69 mg, 60%). R_f 0.35 (2:3 petroleum ether:EtOAc); IR 3261 (NH), 2929, 1696 (C=O), 1264, 1114, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (1H, s, N**H**), 7.48–7.44 (1H, m, Ar**H**), 7.40–7.38 (2H, m, Ar**H**), 7.26–7.24 (1H, m, Ar**H**) 6.10–6.00

(2H, m, CHC**H**=C**H**), 5.05 (1H, s, =C**H**$_2$), 5.04 (1H, s, =C**H**$_2$), 3.78–3.73 (1H, m, ArC**H**), 3.62 (4H, t, *J* = 4.4 Hz, C**H**$_2$OC**H**$_2$), 3.11–3.00 (2H, m, CC**H**$_2$N), 2.58 (3H, s, C**H**$_3$C=O), 2.36 (4H, br s, C**H**$_2$NC**H**$_2$), 1.76–1.71 (2H, m, C**H**$_2$CH), 1.35–1.14 (4H, m, CH$_3$(C**H**$_2$)$_2$), 0.86 (3H, t, *J* = 7.0 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.5 (C), 168.5 (C), 143.6 (C), 141.7 (C), 134.9 (C), 134.3 (CH), 131.5 (CH), 131.1 (CH), 128.1 (CH), 127.0 (CH), 126.4 (CH), 117.1 (CH_2), 67.2 (2 × CH_2), 61.4 (CH_2), 53.6 (2 × CH_2), 44.6 (CH), 35.9 (CH_2), 29.9 (CH_2), 25.6 (CH_3), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{23}H_{32}N_2NaO_3]^+$ $[M+Na]^+$: 407.2305, found: 407.2306.



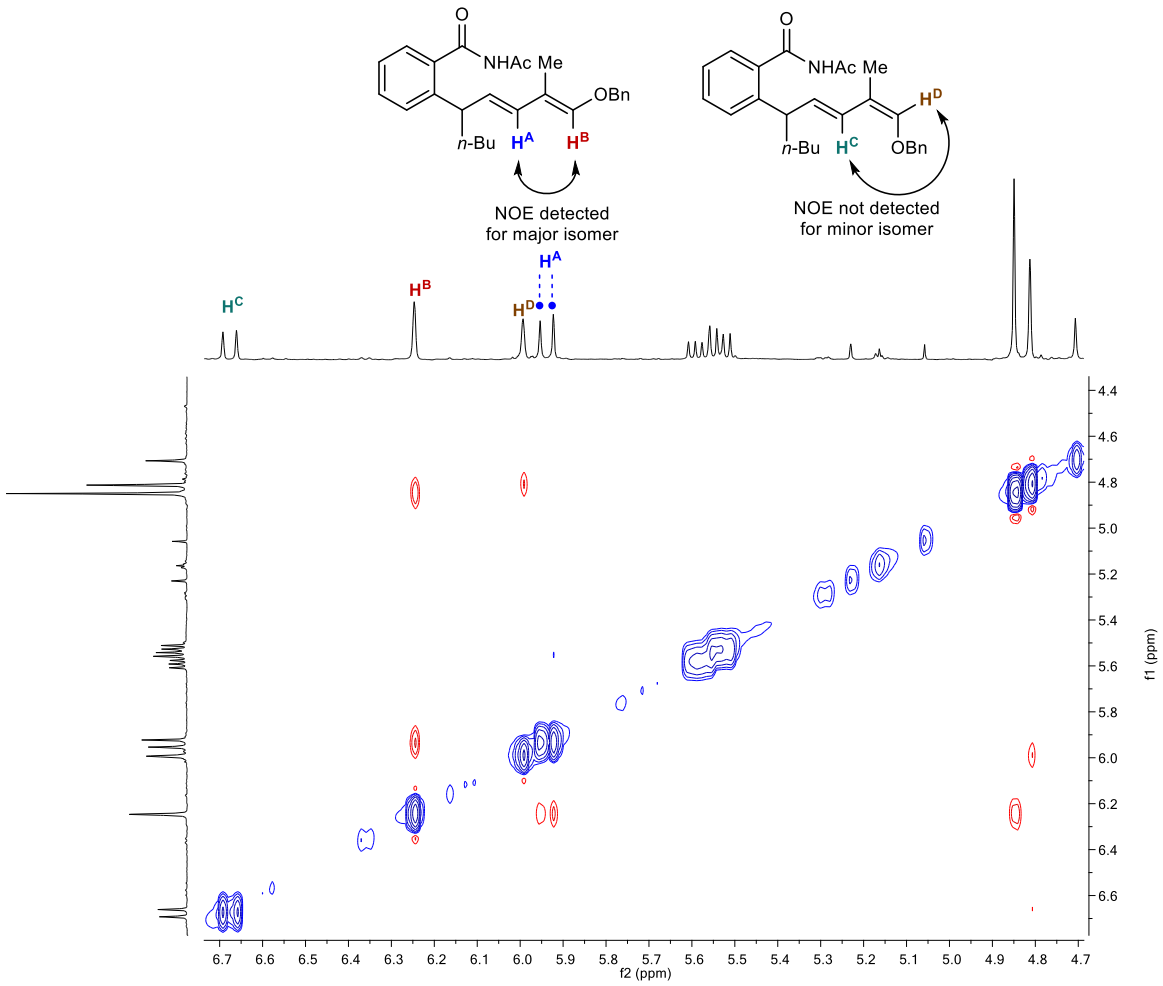
***N*-Acetyl-2-[1-(benzyloxy)-2-methylnona-1,3-dien-5-yl]benzamide (269ah).** The title compound was prepared according to General procedure D from benzamide **267a** (49 mg, 0.30 mmol), $[Cp^*RhCl_2]_2$ (4.6 mg, 7.5 μmol), $Cu(OAc)_2$ (114 mg, 0.630 mmol), and *1,3-diene* **268h** (147 mg, 0.60 mmol) at 70 °C for a reaction time of 15 h and was purified by flash column chromatography (15:15:2 CH_2Cl_2:petroleum ether:EtOAc) to give an orange oil as an 1.4:1 inseparable mixture of *E*/*Z*-isomers (38 mg, 31%). R_f 0.27 (15:15:2 CH_2Cl_2:petroleum ether:EtOAc); IR 3264 (NH), 2929, 1694 (C=O), 1257, 1146, 1072, 973, 752, 697 cm^{-1}; HRMS (ESI) Exact mass calculated for $[C_{26}H_{31}NNaO_3]^+$ $[M+Na]^+$: 428.2196, found: 428.2198.

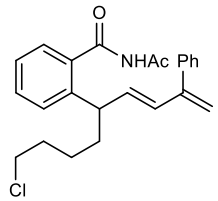
Data for *E*-isomer*:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (1H, br s, N**H**), 7.50–7.25 (9H, m, Ar**H**), 6.25 (1H, s, C**H**OBn), 5.94 (1H, d, *J* = 15.5 Hz, CHCH=C**H**), 5.54 (1H, dd, *J* = 15.5, 7.9 Hz, CHC**H**=CH), 4.85 (2H, s, C**H**$_2$Ph), 3.77–3.71 (1H, m, ArC**H**), 2.58 (3H, s, C**H**$_3$C=O), 1.82–1.72 (2H, m, C**H**$_2$CH), 1.75 (3H, d, *J* = 1.1 Hz, =CC**H**$_3$), 1.35–1.28 (4H, m, CH$_3$(C**H**$_2$)$_2$), 0.91–0.86 (3H, m, C**H**$_3$CH$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.4 (C), 168.5 (C), 147.0 (CH), 144.0 (C), 137.5 (C), 134.8 (C), 131.5 (CH), 130.7 (2 × CH), 128.64 (CH), 128.11 (2 × CH), 128.06 (CH), 127.45 (CH), 127.1 (CH), 126.2 (CH), 114.5 (C), 74.1 (CH_2), 44.75 (CH), 36.3 (CH_2), 29.9 (CH_2), 25.58 (CH_3), 22.76 (CH_2), 14.7 (CH_3), 14.11 (CH_3).

Data for *Z*-isomer*:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (1H, br s, N**H**), 7.50–7.25 (9H, m, Ar**H**), 6.68 (1H, d, *J* = 15.7 Hz, CHCH=C**H**), 5.99 (1H, s, C**H**OBn), 5.59 (1H, dd, *J* = 15.7, 7.9 Hz, CHC**H**=CH), 4.81 (2H, s, C**H**$_2$Ph), 3.89–3.83 (1H, m, ArC**H**), 2.55 (3H, s, C**H**$_3$C=O), 1.82–1.72 (2H, m, C**H**$_2$CH), 1.61 (3H, d, *J* = 1.2 Hz, =CC**H**$_3$), 1.35–1.28 (4H, m, CH$_3$(C**H**$_2$)$_2$), 0.91–0.86 (3H, m, C**H**$_3$CH$_2$); ^{13}C NMR (100.6 MHz,

$CDCl_3$) δ 172.4 (C), 168.5 (C), 143.9 (C), 143.4 (CH), 137.6 (C), 135.1 (C), 131.4 (CH), 131.0 (2 × CH), 128.61 (CH), 128.2 (2 × CH), 128.0 (CH), 127.51 (CH), 126.9 (CH), 125.8 (CH), 112.3 (C), 73.9 (CH_2), 44.77 (CH), 35.8 (CH_2), 29.9 (CH_2), 25.52 (CH_3), 22.82 (CH_2), 14.13 (CH_3), 9.9 (CH_3).

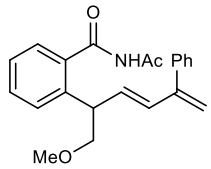
NOESY alkenyl region expansion



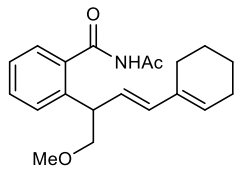


(*E*)-*N*-Acetyl-2-(1-chloro-6-phenylhepta-4,6-dien-3-yl)benzamide (269ai). The title compound was prepared according to General procedure D from benzamide **267a** (98 mg, 0.60 mmol), and *1,3-diene* **268i** (70 mg, 0.30 mmol) and was purified by flash column chromatography (15:5:2 CH_2Cl_2: petroleum ether: EtOAc) to give a pale yellow oil (74 mg, 62%). R_f 0.35 (1:1 petroleum ether:Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (1H, s, N**H**), 7.47–7.39 (2H, m, Ar**H**), 7.36–7.25 (7H, m, Ar**H**), 6.32 (1H, d, *J* = 15.7 Hz, CHCH=C**H**), 5.74 (1H, dd, *J* = 15.7, 8.0 Hz, CHC**H**=CH), 5.21 (1H, d, *J* = 1.6 Hz, =C**H**$_2$), 5.12 (1H, d, *J* = 1.6 Hz, =C**H**$_2$), 3.92–3.86 (1H, m, ArC**H**),

3.50 (2H, t, *J* = 6.7 Hz, ClC**H**$_2$), 2.57 (3H, s, C**H**$_3$), 1.82–1.74 (4H, m, ClCH$_2$(C**H**$_2$)$_2$), 1.55–1.45 (1H, m, C**H**$_2$CH), 1.41–1.30 (1H, m, C**H**$_2$CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.5 (C), 168.3 (C), 147.5 (C), 143.2 (C), 140.3 (C), 136.1 (CH), 134.6 (C), 132.5 (CH), 131.7 (CH), 128.29 (2 × CH), 128.26 (2 × CH), 128.2 (CH), 127.6 (CH), 127.0 (CH), 126.5 (CH), 116.5 (CH_2), 44.9 (CH_2), 44.2 (CH), 35.2 (CH_2), 32.5 (CH_2), 25.6 (CH_3), 25.0 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{24}H_{27}ClNO_2]^+$ $[M+H]^+$: 396.1725, found: 396.1715.

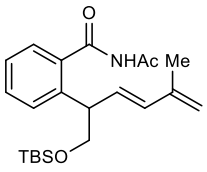


(*E*)-*N*-Acetyl-2-(1-methoxy-5-phenylhexa-3,5-dien-2-yl)benzamide (269aj). The title compound was prepared according to General procedure D from benzamide **267a** (98 mg, 0.60 mmol) and *1,3-diene* **268j** (57 mg, 0.30 mmol) and was purified by flash column chromatography (5:1 CH_2Cl_2: EtOAc) to give a pale yellow oil (80 mg, 76%). R_f 0.30 (1:1 petroleum ether:Et_2O); IR 3251 (NH), 2934, 1691 (C=O), 1571, 1236, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (1H, s, N**H**), 7.53 (1H, dd, *J* = 7.7, 1.1 Hz, Ar**H**), 7.47 (1H, td, *J* = 7.7, 1.6 Hz, Ar**H**), 7.35–7.24 (7H, m, Ar**H**), 6.36 (1H, dd, *J* = 15.9, 0.7 Hz, CHCH=C**H**), 5.71 (1H, dd, *J* = 15.9, 6.7 Hz, CHC**H**=CH), 5.23 (1H, br s, =C**H**$_2$), 5.15 (1H, d, *J* = 1.6 Hz, =C**H**$_2$), 4.18–4.13 (1H, m, ArC**H**), 3.87 (1H, dd, *J* = 8.6, 4.8 Hz, OC**H**$_2$), 3.65 (1H, dd, *J* = 10.3, 8.6 Hz, OC**H**$_2$), 3.35 (3H, s, C**H**$_3$O), 2.55 (3H, s, C**H**$_3$C=O); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.5 (C), 168.7 (C), 147.4 (C), 139.9 (C), 139.5 (C), 136.3 (C), 133.6 (CH), 131.7 (CH), 131.5 (CH), 128.8 (CH), 128.31 (2 × CH), 128.28 (2 × CH), 127.9 (CH), 127.7 (CH), 127.1 (CH), 117.1 (CH_2), 77.4 (CH_2), 59.2 (CH_3), 44.5 (CH), 25.9 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{22}H_{24}NO_3]^+$ $[M+H]^+$: 350.1751, found: 350.1749.

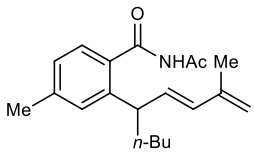


(*E*)-*N*-Acetyl-2-[4-(cyclohex-1-en-1-yl)-1-methoxybut-3-en-2-yl]benzamide (269ak). The title compound was prepared according to General procedure D from benzamide **267a** (49 mg, 0.30 mmol) and *1,3-diene* **268k** (100 mg, 0.600 mmol) and was purified by flash column chromatography (10:5:2 CH_2Cl_2:petroleum ether:EtOAc) to give a pale yellow oil (80 mg, 82%). R_f 0.45 (10:5:2 CH_2Cl_2:petroleum ether:EtOAc); IR 3250 (NH), 2927, 1696 (C=O), 1372, 1270, 1100, 1018, 755, 728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (1H, s, N**H**), 7.53–7.45 (2H, m, Ar**H**), 7.36–7.28 (2H, m, Ar**H**), 6.06 (1H, d, *J* = 15.9 Hz, CHCH=C**H**), 5.69 (1H, br s, =C**H**CH_2), 5.56 (1H, dd,

J = 15.9, 6.7 Hz, CHC**H**=CH), 4.10–4.05 (1H, m, ArC**H**), 3.84 (1H, dd, *J* = 8.6, 4.8 Hz, OC**H**$_2$), 3.65 (1H, dd, *J* = 10.3, 8.6 Hz, OC**H**$_2$), 3.35 (3H, s, C**H**$_3$O), 2.54 (3H, s, C**H**$_3$C=O), 2.10–2.07 (4H, m, C**H**$_2$(CH$_2$)$_2$C**H**$_2$), 1.67–1.54 (4H, m, CH$_2$(C**H**$_2$)$_2$CH$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.6 (C), 168.8 (C), 140.2 (C), 136.3 (C), 135.6 (CH), 135.1 (C), 131.4 (CH), 130.1 (CH), 128.8 (CH), 127.9 (CH), 127.0 (CH), 124.1 (CH), 77.8 (CH$_2$), 59.2 (CH$_3$), 44.5 (CH), 25.94 (CH$_2$), 25.88 (CH$_3$), 24.5 (CH$_2$), 22.6 (CH$_2$), 22.5 (CH$_2$); HRMS (ESI) Exact mass calculated for $[C_{20}H_{26}NO_3]^+$ $[M+H]^+$: 328.1907, found: 328.1908.

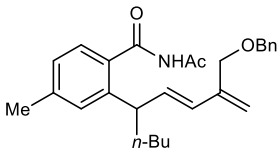


(*E*)-*N*-Acetyl-2-{1-[(*tert*-butyldimethylsilyl)oxy]-5-methylhexa-3,5-dien-2-yl}benzamide (269am). The title compound was prepared according to General procedure D from benzamide **267a** (49 mg, 0.30 mmol) and 1,3-diene **268m** (136 mg, 0.600 mmol) and was purified by flash column chromatography (gradient elution 10:1 petroleum ether:Et_2O to 2:1 petroleum ether:Et_2O) to give a pale yellow oil (42 mg, 36%). R_f 0.45 (2:1 petroleum ether:Et_2O); IR 3248 (NH), 2955, 2858, 1722 (C=O), 1697 (C=O), 1471, 1411, 1260, 1090, 911, 837, 734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59–7.41 (2H, m, Ar**H**), 7.40–7.27 (2H, m, Ar**H**), 6.19 (1H, d, *J* = 15.9 Hz, CHCH=C**H**), 5.71 (1H, dd, *J* = 15.9, 6.1 Hz, CHC**H**=CH), 4.94 (2H, d, *J* = 6.9 Hz, =C**H**$_2$), 4.14 (2H, m, TBSOC**H**$_2$), 3.88–3.75 (1H, m, ArC**H**), 2.53 (3H, s, C**H**$_3$C=O), 1.81 (3H, s, CC**H**$_3$), 0.73 (9H, s, Si(C**H**$_3$)$_3$), –0.07 (6H, d, *J* = 19.2 Hz, Si(C**H**$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.6 (C) 168.8 (C), 141.5 (C), 140.0 (C), 136.5 (C), 135.2 (CH), 131.5 (CH), 128.9 (CH), 128.3 (CH), 127.9 (CH), 127.1 (CH), 116.9 (CH$_2$), 68.8 (CH$_2$), 45.9 (CH), 26.2 (CH$_3$), 25.8 (3 × CH$_3$), 18.6 (CH$_3$), 18.5 (C), –5.5 (CH$_3$), –5.7 (CH$_3$); HRMS (ESI) Exact mass calculated for $C_{22}H_{34}NO_3Si$ $[M+H]^+$: 388.2302, found: 388.2318.

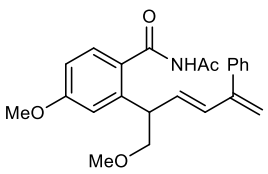


(*E*)-*N*-Acetyl-4-methyl-2-(2-methylnona-1,3-dien-5-yl)benzamide (269bd). The title compound was prepared according to General procedure D from benzamide **267b** (53 mg, 0.30 mmol) and 1,3-diene **268d** (83 mg, 0.60 mmol) and was purified by flash column chromatography (2:1 petroleum ether: Et_2O) to give a pale yellow oil which solidified upon standing (50 mg, 53%). R_f 0.23 (2:1 petroleum ether:Et_2O); m.p. 50−52 °C (Et_2O); IR 3271 (NH), 2929, 1697 (C=O), 1467, 1277, 968 cm^{-1}; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 8.23 (1H, s, N**H**), 7.30 (H, d, *J* = 7.8 Hz, Ar**H**), 7.17 (1H, s, Ar**H**), 7.06 (1H, dd, *J* = 7.8, 0.8 Hz, Ar**H**), 6.14 (1H, d, *J* = 15.7 Hz, CHCH=C**H**), 5.72 (1H, dd, *J* = 15.7, 7.8 Hz, CHC**H**=CH), 4.90 (2H, s, =C**H**$_2$), 3.85–3.79 (1H, m, ArC**H**), 2.56 (3H, s, C**H**$_3$C=O), 2.38 (3H, s, ArC**H**$_3$), 1.81 (3H, s, =CC**H**$_3$), 1.77–1.71 (2H, m, C**H**$_2$CH), 1.33–1.11 (4H, m, CH_3(C**H**$_2$)$_2$), 0.86 (3H, t, *J* = 7.1 Hz, C**H**$_3$$CH_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.7 (C), 168.4 (C), 143.9 (C), 142.0 (C), 141.8 (C), 133.6 (CH), 133.3 (CH), 131.9 (C), 128.8 (CH), 127.2 (CH), 127.1 (CH), 116.0 (CH_2), 44.0 (CH), 35.9 (CH_2), 29.9 (CH_2), 25.5 (CH_3), 22.8 (CH_2), 21.8 (CH_3), 18.8 (CH_3), 14.1 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{20}H_{27}NNaO_2]^+$ $[M+Na]^+$: 336.1934, found: 336.1942.

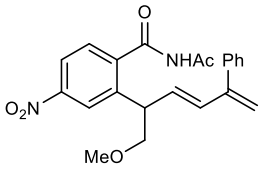


(*E*)-*N*-Acetyl-2-{2-[(benzyloxy)methyl]nona-1,3-dien-5-yl}-4-methylbenzamide (269be). The title compound was prepared according to General procedure D from benzamide **267b** (53 mg, 0.30 mmol) and 1,3-diene **268e** (154 mg, 0.600 mmol) and was purified by flash column chromatography (1:1 Et_2O:petroleum ether) to give an orange oil (67 mg, 53%). R_f 0.52 (3:2 Et_2O:petroleum ether); IR 3263 (NH), 2928, 1680 (C=O), 1262, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (1H, s, N**H**), 7.37–7.27 (6H, m, Ar**H**), 7.15 (1H, s, Ar**H**), 7.07 (1H, d, *J* = 7.8 Hz, Ar**H**), 6.10 (1H, d, *J* = 16.0 Hz, CHCH=C**H**), 5.91 (1H, dd, *J* = 16.0, 8.0 Hz, CHC**H**=CH), 5.20 (1H, s, =C**H**$_2$), 5.14 (1H, s, =C**H**$_2$), 4.51–4.44 (2H, m, C**H**$_2$Ph), 4.22–4.15 (2H, m, C**H**$_2$OBn), 3.83–3.77 (1H, m, ArC**H**), 2.56 (3H, s, C**H**$_3$C=O), 2.36 (3H, s, ArC**H**$_3$), 1.75–1.70 (2H, m, C**H**$_2$CH, 1.33–1.10 (4H, m, CH_3(C**H**$_2$)$_2$), 0.86 (3H, t, *J* = 7.0 Hz, C**H**$_3$$CH_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.6 (C), 168.3 (C), 143.8 (C), 142.05 (C), 142.02 (C), 138.5 (C), 134.4 (CH), 131.9 (C), 130.1 (CH), 128.8 (CH), 128.5 (2 × CH), 127.9 (2 × CH), 127.7 (CH), 127.13 (CH), 127.11 (CH), 117.1 (CH_2), 71.9 (CH_2), 70.7 (CH_2), 44.4 (CH), 35.9 (CH_2), 29.9 (CH_2), 25.5 (CH_3), 22.8 (CH_2), 21.8 (CH_3) 14.1 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{27}H_{33}NNaO_3]^+$ $[M+Na]^+$: 442.2353, found: 442.2356.

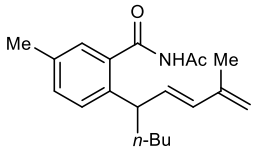


(*E*)-*N*-Acetyl-4-methoxy-2-(1-methoxy-5-phenylhexa-3,5-dien-2-yl)benzamide (269cj). The title compound was prepared according to General procedure D from benzamide **267c** (116 mg, 0.600 mmol) and 1,3-diene **268j** (57 mg, 0.30

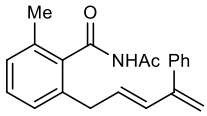
mmol) and was purified by flash column chromatography (10:2:2 CH_2Cl_2: petroleum ether: EtOAc) to give a pale yellow oil (52 mg, 46%). R_f 0.40 (10:2:2 CH_2Cl_2: petroleum ether: EtOAc); IR 3246 (NH), 2931, 1691 (C=O), 1570, 1236, 1108, 1017, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.92 (1H, s, N**H**), 7.56 (1H, d, *J* = 8.6 Hz, Ar**H**), 7.35–7.26 (5H, m, Ar**H**), 6.85 (1H, dd, *J* = 8.6, 2.6 Hz, Ar**H**), 6.80 (1H, d, *J* = 2.6 Hz, Ar**H**), 6.38 (1H, dd, *J* = 15.9, 0.6 Hz, CHCH=C**H**), 5.71 (1H, dd, *J* = 15.9, 6.7 Hz, CHC**H**=CH), 5.26 (1H, br s, =C**H**$_2$), 5.17 (1H, d, *J* = 1.6 Hz, =C**H**$_2$), 4.26–4.19 (1H, m, ArC**H**), 3.88 (1H, dd, *J* = 8.6, 4.9 Hz, OC**H**$_2$), 3.85 (3H, s, ArOC**H**$_3$), 3.68 (1H, dd, *J* = 10.2, 8.6 Hz, OC**H**$_2$), 3.37 (3H, s, C**H**$_3$OCH$_2$), 2.56 (3H, s, C**H**$_3$C=O); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.8 (C), 168.2 (C), 162.2 (C), 147.4 (C), 142.2 (C), 140.0 (C), 133.5 (CH), 131.8 (CH), 131.1 (CH), 128.8 (C), 128.32 (2 × CH), 128.30 (2 × CH), 127.7 (CH), 117.1 (CH_2), 113.9 (CH), 112.0 (CH), 77.3 (CH_2), 59.2 (CH_3), 55.5 (CH_3), 44.3 (CH), 25.9 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{23}H_{25}NNaO_4]^+$ $[M+Na]^+$: 402.1676, found: 402.1676.



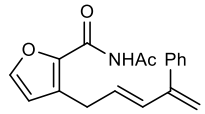
(*E*)-*N*-Acetyl-2-(1-methoxy-5-phenylhexa-3,5-dien-2-yl)-4-nitrobenzamide (269dj). The title compound was prepared according to General procedure D from benzamide **267d** (125 mg, 0.600 mmol) and 1,3-diene **268j** (57 mg, 0.30 mmol) and was purified by flash column chromatography (10:1:2 CH_2Cl_2: petroleum ether: EtOAc) to give a pale yellow solid (89 mg, 75%). R_f 0.65 (5:1 CH_2Cl_2:EtOAc); m.p. 87−88 °C (Et_2O/petroleum ether); IR 3269 (NH), 2931, 1698 (C=O), 1525 (NO_2), 1350 (NO_2), 1262, 1019, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.05 (1H, s, N**H**), 8.15–8.13 (2H, m, Ar**H**), 7.69 (1H, d, *J* = 8.1 Hz, Ar**H**), 7.36–7.30 (3H, m, Ar**H**), 7.25–7.23 (2H, m, Ar**H**), 6.40 (1H, d, *J* = 15.9 Hz, CHCH=C**H**), 5.68 (1H, dd, *J* = 15.9, 6.7 Hz, CHC**H**=CH), 5.27 (1H, br s, =C**H**$_2$), 5.20 (1H, d, *J* = 1.0 Hz, =C**H**$_2$), 4.22–4.16 (1H, m, ArC**H**), 3.92 (1H, dd, *J* = 8.7, 4.7 Hz, OC**H**$_2$), 3.68 (1H, dd, *J* = 10.6, 8.7 Hz, OC**H**$_2$), 3.37 (3H, s, C**H**$_3$O), 2.55 (3H, s, C**H**$_3$C=O); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.0 (C), 166.9 (C), 149.6 (C), 147.0 (C), 141.76 (C), 141.75 (C), 139.5 (C), 134.9 (CH), 130.2 (CH), 129.8 (CH), 128.4 (2 × CH), 128.2 (2 × CH), 127.9 (CH), 123.1 (CH), 122.1 (CH), 118.0 (CH_2), 76.8 (CH_2), 59.3 (CH_3), 44.6 (CH), 25.9 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{22}H_{22}N_2NaO_5]^+$ $[M+Na]^+$: 417.1421, found: 417.1423.



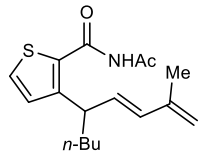
(*E*)-*N*-Acetyl-5-methyl-2-(2-methylnona-1,3-dien-5-yl)benzamide (269d). The title compound was prepared according to General procedure D from benzamide **267e** (53 mg, 0.30 mmol) and 1,3-diene **268d** (83 mg, 0.60 mmol) and was purified by flash column chromatography (2:1 petroleum ether: Et_2O) to give a pale yellow oil (60 mg, 64%). R_f 0.37 (2:1 petroleum ether:Et_2O); IR 3261 (NH), 2928, 1700 (C=O), 1373, 1266, 967, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (1H, s, N**H**), 7.26 (1H, br s, Ar**H**), 7.21 (1H, br s, Ar**H**), 7.28–7.24 (1H, m, Ar**H**), 6.11 (1H, d, *J* = 15.7 Hz, CHCH=C**H**), 5.71 (1H, dd, *J* = 15.7, 7.8 Hz, CHC**H**=CH), 4.89 (2H, s, =C**H**$_2$), 3.78–3.73 (1H, m, ArC**H**), 2.56 (3H, s, C**H**$_3$C=O), 2.34 (3H, s, ArC**H**$_3$), 1.80 (3H, s, =CC**H**$_3$), 1.73 (2H, m, C**H**$_2$CH), 1.43–1.10 (4H, m, CH_3(C**H**$_2$)$_2$), 0.85 (3H, t, *J* = 7.1 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.5 (C), 168.5 (C), 141.7 (C), 140.4 (C), 136.1 (C), 134.7 (C), 133.7 (CH), 133.2 (CH), 132.3 (CH), 128.1 (CH), 127.5 (CH), 115.9 (CH_2), 43.9 (CH), 35.8 (CH_2), 29.9 (CH_2), 25.5 (CH_3), 22.7 (CH_2), 20.9 (CH_3), 18.7 (CH_3), 14.1 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{20}H_{27}NNaO_2]^+$ $[M+Na]^+$: 336.1934, found: 336.1945.



(*E*)-*N*-Acetyl-2-methyl-6-(4-phenylpenta-2,4-dien-1-yl)benzamide (269fb). The title compound was prepared according to General procedure D from benzamide **267f** (53 mg, 0.30 mmol) and 1,3-diene **268b** (87 mg, 0.60 mmol) and was purified by flash column chromatography (3:2 petroleum ether: Et_2O) to give a pale yellow oil which solidified upon standing (94 mg, 98%). R_f 0.40 (1:1 petroleum ether:Et_2O); m.p. 100−102 °C (CH_2Cl_2); IR 3255 (NH), 2929, 1696 (C=O), 1492, 1373, 1256, 776, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (1H, s, N**H**), 7.35–7.20 (6H, m, Ar**H**), 7.08–7.05 (2H, m, Ar**H**), 6.32 (1H, d, *J* = 15.6 Hz, CH_2CH=C**H**), 5.72 (1H, m, CH_2C**H**=CH), 5.23 (1H, br s, =C**H**$_2$), 5.13 (1H, d, *J* = 1.5 Hz, =C**H**$_2$), 3.47 (2H, d, *J* = 6.7 Hz, C**H**$_2$CH), 2.51 (3H, s, C**H**$_3$C=O), 2.31 (3H, s, ArC**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.0 (C), 169.1 (C), 147.6 (C), 140.2 (C), 136.1 (C), 135.9 (C), 134.2 (C), 133.7 (CH), 131.1 (CH), 129.9 (CH), 128.6 (CH), 128.3 (2 × CH), 128.2 (2 × CH), 127.5 (CH), 127.4 (CH), 116.3 (CH_2), 36.7 (CH_2), 25.6 (CH_3), 19.4 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{21}H_{21}NNaO_2]^+$ $[M+Na]^+$: 342.1464, found: 342.1471.

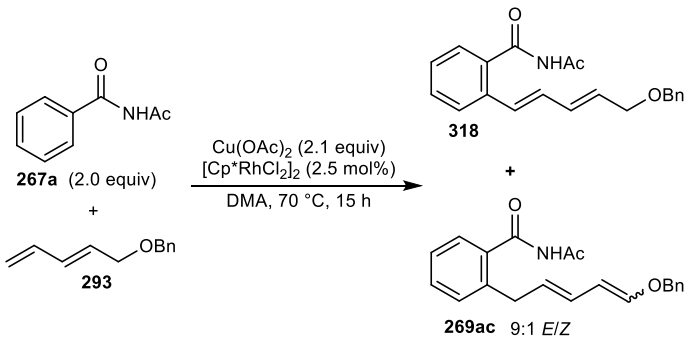


(*E*)-*N*-Acetyl-3-(4-phenylpenta-2,4-dien-1-yl)furan-2-carboxamide (267gb). The title compound was prepared according to General procedure D from *carboxamide* **267g** (46 mg, 0.30 mmol) and 1,3-diene **268b** (87 mg, 0.60 mmol) and was purified by flash column chromatography (1:1 petroleum ether: Et_2O) to give a pale yellow oil (35 mg, 40%). R_f 0.45 (1:1 petroleum ether:Et_2O); IR 3242 (NH), 2928, 1709 (C=O), 1461, 1370, 1259, 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (1H, s, N**H**), 7.41 (1H, d, *J* = 1.7 Hz, Ar**H**), 7.35–7.27 (5H, m, Ar**H**), 6.46 (1H, d, *J* = 1.7 Hz, Ar**H**), 6.41 (1H, d, *J* = 15.6, 0.5 Hz, CHCH=C**H**), 5.74 (1H, dt, *J* = 15.6, 6.9 Hz, CHC**H**=CH), 5.23 (1H, br s, =C**H**$_2$), 5.12 (1H, d, *J* = 1.6 Hz, =C**H**$_2$), 3.73 (2H, dd, *J* = 6.9, 0.8 Hz, ArC**H**), 2.55 (3H, s, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.3 (C), 156.7 (C), 147.7 (C), 144.4 (CH), 140.34 (C), 140.28 (C), 134.9 (C), 133.6 (CH), 129.8 (CH), 128.29 (2 × CH), 128.25 (2 × CH), 127.6 (CH), 116.1 (CH_2), 115.3 (CH), 28.9 (CH_2), 25.6 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{18}H_{17}NNaO_3]^+$ $[M+Na]^+$: 318.1101, found: 318.1108.



(*E*)-*N*-Acetyl-3-(2-methylnona-1,3-dien-5-yl)thiophene-2-carboxamide (269hd). The title compound was prepared according to General procedure D from *carboxamide* **267h** (51 mg, 0.30 mmol), $[Cp^*RhCl_2]_2$ (4.6 mg, 7.5 μmol), $Cu(OAc)_2$ (114 mg, 0.630 mmol) and 1,3-diene **268d** (83 mg, 0.60 mmol) at 70 °C for a reaction time of 12 h and was purified by flash column chromatography (2:1 petroleum ether: Et_2O) to give a pale yellow solid (35 mg, 38%). R_f 0.22 (2:1 petroleum ether:Et_2O); m.p. 45−46 °C (CH_2Cl_2); IR 3392 (NH), 3056, 1690 (C=O), 1461, 1270, 857, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, s, N**H**), 7.45 (1H, d, *J* = 5.1 Hz, Ar**H**), 7.09 (1H, d, *J* = 5.1 Hz, Ar**H**), 6.17 (1H, d, *J* = 15.7 Hz, ArCHCH=C**H**), 5.71 (1H, dd, *J* = 15.7, 7.8 Hz, ArCHC**H**=CH), 4.92 (2H, s, =C**H**$_2$), 4.30–4.24 (1H, m, ArC**H**), 2.56 (3H, s, C(O)C**H**$_3$), 1.80 (3H, br s, C**H**$_3$), 1.76–1.69 (2H, m, C**H**$_2$(CH_2)$_2$$CH_3$), 1.32–1.13 (4H, m, CH_2(C**H**$_2$)$_2$$CH_3$), 0.86 (3H, t, *J* = 7.1 Hz, (CH_2)$_3$C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.7 (C), 160.8 (C), 152.6 (C), 141.6 (C), 133.8 (CH), 132.2 (CH), 129.5 (CH), 129.4 (CH), 129.2 (C), 116.4 (CH_2), 42.1 (CH), 36.0 (CH_2), 29.8 (CH_2), 25.6 (CH_3), 22.7 (CH_2), 20.9 (CH_3), 18.7 (CH_3), 14.1 (CH_3). Exact mass calculated for $C_{17}H_{23}NNaO_2S$ $[M+Na]^+$: 328.1342, found 328.1343.

***N*-Acetyl-2-[(1*E*,3*E*)-5-(benzyloxy)penta-1,3-dien-1-yl]benzamide (318) and *N*-acetyl-2-[(2*E*,4*E*)-5-(benzyloxy)penta-2,4-dien-1-yl]benzamide (269ac)**



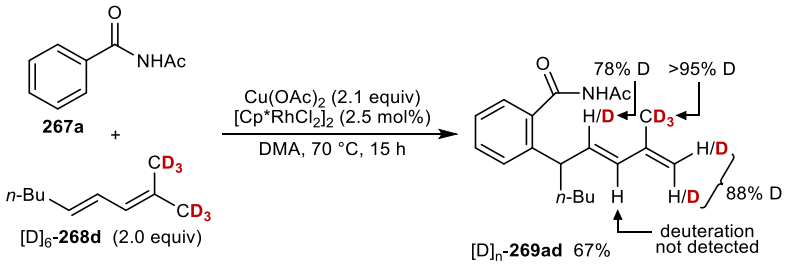
The title compounds were prepared according to General procedure D from benzamide **267a** (98 mg, 0.60 mmol) and 1,3-diene **293** (59 mg, 0.30 mmol) and were purified by preparative TLC (15:5:5 CH_2Cl_2:petroleum ether:EtOAc), followed by a second purification using preparative TLC (3:2 Et_2O:petroleum ether) to give allylated product **269ac** as a 9:1 inseparable mixture of *E*/*Z* isomers as an orange oil (28 mg, 31%) followed by *alkenylated product* **318** as a yellow oil which solidified upon standing (11 mg, 12%).

Data for **269ac** are described above.

Data for **318**: R_f 0.55 (15:5:5 CH_2Cl_2:petroleum ether:EtOAc); IR 3265 (NH), 2923, 1692 (C=O), 1371, 1259, 1018, 746, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (1H, s, N**H**), 7.63 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.52–7.46 (2H, m, Ar**H**), 7.37–7.26 (6H, m, Ar**H**), 6.89 (1H, d, *J* = 15.5 Hz, ArC**H**), 6.78 (1H, dd, *J* = 15.5, 10.2 Hz, ArCH=C**H**), 6.47 (1H, dd, *J* = 15.3, 10.2 Hz, ArCH=CHC**H**), 5.98 (1H, dt, *J* = 15.3, 5.9 Hz, ArCH=CHCH=**CH**), 4.45 (2H, s, C**H**$_2$Ph), 4.13 (2H, d, *J* = 5.9 Hz, C**H**$_2$OBn), 2.59 (3H, s, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.6 (C), 167.7 (C), 138.3 (C), 136.5 (C), 133.1 (C), 132.43 (CH), 132.42 (CH), 132.37 (CH), 131.8 (CH), 128.7 (CH), 128.6 (2 × CH), 127.9 (2 × CH), 127.8 (CH), 127.72 (CH), 127.70 (CH), 126.9 (CH), 72.5 (CH_2), 70.4 (CH_2), 25.6 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{21}H_{21}NNaO_3]^+$ $[M+Na]^+$: 358.1414, found: 358.1412.

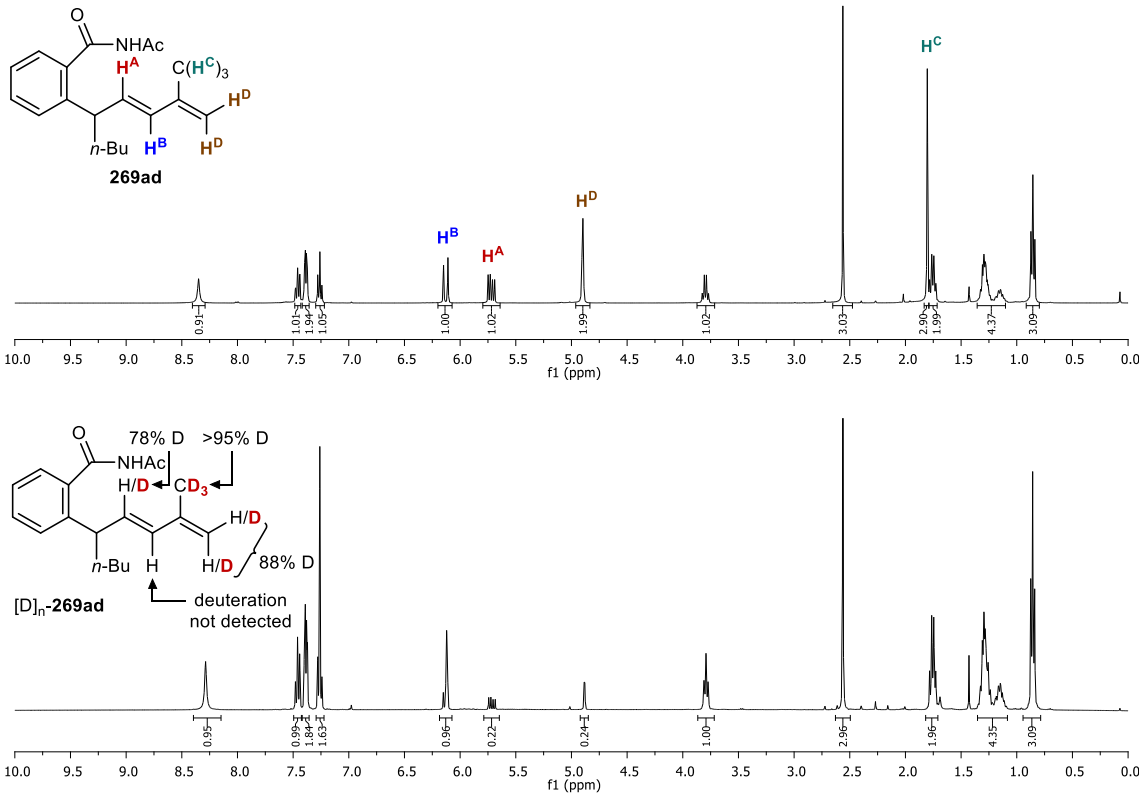
3.1.4 Investigation of deuterium transfer

(*E*)-*N*-Acetyl-2-[2-(methyl-d$_3$)nona-1,3-dien-5-yl-1,1,4-d$_3$]benzamide ([D]$_n$-269ad)

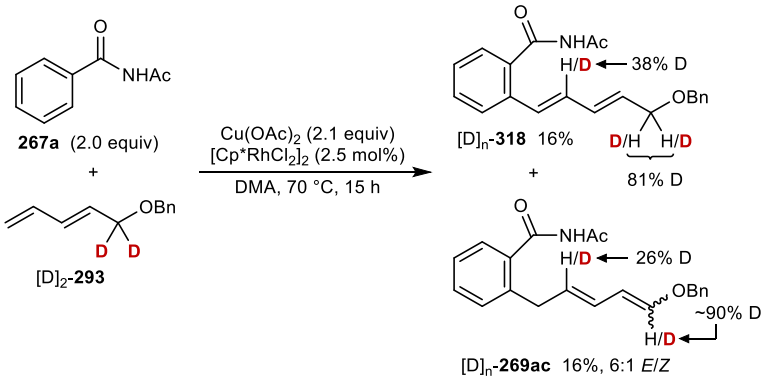


The title compound was prepared according to General procedure D from benzamide **267a** (49 mg, 0.30 mmol) and *1,3-diene* [D]$_6$-**268d** (87 mg, 0.60 mmol) and was purified by flash column chromatography (2:1 petroleum ether: Et_2O) to give a pale yellow oil (61 mg, 67%). R_f 0.43 (2:1 petroleum ether:Et_2O); IR 3261 (NH), 2929, 1694 (C=O), 1466, 1373, 1261, 1019, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (1H, s, N**H**), 7.48–7.44 (1H, m, Ar**H**), 7.40–7.37 (2H, m, Ar**H**), 7.28–7.24 (1H, m, Ar**H**), 6.15–6.12 (1H, m, CHC(D/H)=C**H**), 5.72 (0.22H, dd, *J* = 15.7, 7.8 Hz, CHC(D/**H**)=CH), 4.89 (0.12H, s, =CD**H**; one of the *E*/Z isomers), 4.88 (0.12H, s, =CD**H**; the second of the *E*/*Z* isomers), 3.81–3.77 (1H, m, ArC**H**), 2.56 (3H, s, C**H**$_3$C=O), 1.78–1.73 (2H, m, C**H**$_2$CD/H), 1.33–1.11 (4H, m, CH_3(C**H**$_2$)$_2$), 0.86 (3H, t, *J* = 7.1 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.5 (C), 168.4 (C), 143.5 (C), 141.4 (C), 134.9 (C), 133.4 (CH), 133.3 (CH), 131.5 (CH), 128.2 (CH), 127.0 (CH), 126.3 (CH), 44.2 (CH), 35.8 (CH_2), 29.9 (CH_2), 25.5 (CH_3), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI) Exact mass calculated for $C_{19}H_{21}D_5NNaO_2$ [M+Na]$^+$: 328.2170, found: 328.2165, Exact mass calculated for $C_{19}H_{19}D_6NNaO_2$ [M+Na]$^+$: 328.2154, found: 328.2165.

Comparison of ^{1}H NMR spectra of products **269ad** and [D]$_n$-**269ad**:



***N*-Acetyl-2-[(1*E*,3*E*)-5-(benzyloxy)penta-1,3-dien-1-yl]benzamide ([D]$_n$-318) and *N*-acetyl-2-[(2*E*,4*E*)-5-(benzyloxy)penta-2,4-dien-1-yl]benzamide ([D]$_n$-269ac)**



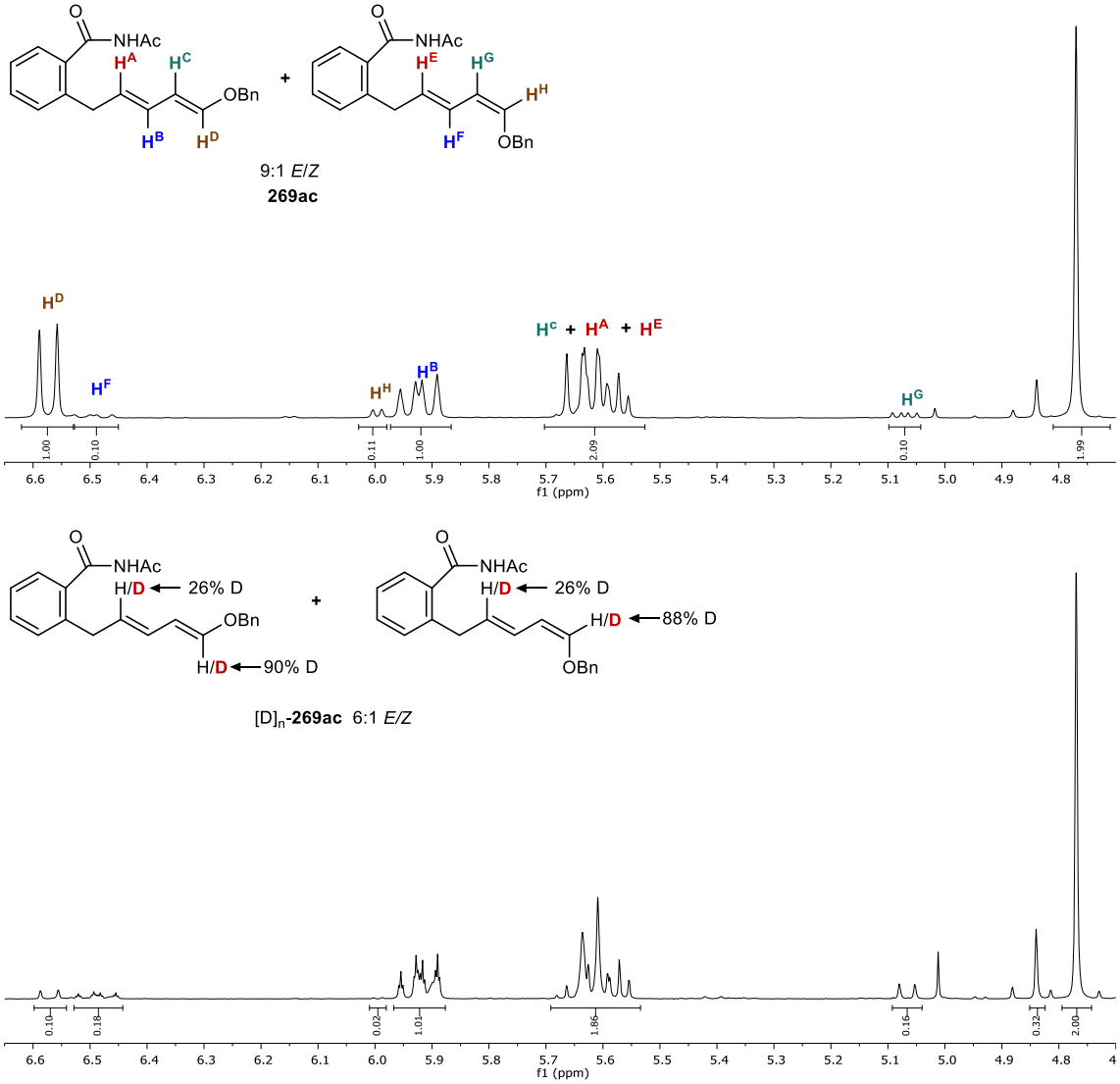
General procedure D was followed using benzamide **267a** (98 mg, 0.60 mmol) and *1,3-diene* [D]$_2$-**293** (58 mg, 0.30 mmol). Purification by preparative TLC (15:5:5 CH_2Cl_2:petroleum ether:EtOAc), followed by a second purification using preparative TLC (3:2 Et_2O:petroleum ether) gave *allylated product* [D]$_n$-**269ac** as a 6:1 inseparable mixture of *E*/*Z* isomers as a pale yellow oil (16 mg, 16%) followed by *alkenylated product* [D]$_n$-**318** as a pale yellow oil (16 mg, 16%).

Data for [D]$_n$-**269ac** (*E*-isomer): R_f 0.65 (15:5:5 CH_2Cl_2:pentane:EtOAc); IR 3278 (NH), 2932, 1692 (C=O), 1376, 1261, 1155, 1018, 974, 733, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (1H, s, N**H**), 7.47–7.42 (2H, m, Ar**H**), 7.37–7.27 (7H, m, Ar**H**), 6.57 (0.10H, d, *J* = 12.4 Hz, C(D/**H**)OBn), 5.92 (1H, ddt, *J* = 15.2, 10.5, 1.5 Hz, $CH_2C(D/H)=C\mathbf{H}$), 5.66–5.55 (1.86H, m, $CH_2C(D/H)=CHC\mathbf{H}$ and $CH_2C(D/\mathbf{H})$), 4.77 (2H, s, C**H**$_2$Ph), 3.58 (2H, d, *J* = 6.4 Hz, C**H**$_2$C(D/H)), 2.56 (3H, s, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.6 (C), 168.0 (C), 149.8 (CH), 139.8 (C), 136.8 (C), 134.3 (C), 131.8 (CH), 131.2 (CH), 128.7 (2 × CH), 128.5 (CH), 128.2 (CH), 127.7 (2 × CH), 127.4 (CH), 126.7 (CH), 126.5 (CH), 106.8 (CH), 71.8 (CH_2), 36.8 (CH_2), 25.6 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{21}H_{20}NNaO_3D]^+$ $[M+Na]^+$: 359.1476, found: 359.1480.

Characteristic signals for *Z*-isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 6.49 (1H, ddt, *J* = 15.4, 10.9, 1.5 Hz, $CH_2C(D/H)=C\mathbf{H}C(D/H)$), 5.99 (0.12H, d, *J* = 6.0 Hz, C(D/**H**)OBn), 5.08 (1H, dd, *J* = 10.9, 6.0 Hz, $CH_2C(D/H)=CHC\mathbf{H}$), 4.84 (2H, s, C**H**$_2$Ph).

Data for [D]$_n$-**318**: R_f 0.50 (15:5:5 CH_2Cl_2:petroleum ether:EtOAc); IR 3263 (NH), 2925, 1691 (C=O), 1373, 1259, 1021, 752, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (1H, s, N**H**), 7.63 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.50–7.46 (2H, m, Ar**H**), 7.37–7.28 (6H, m, Ar**H**), 6.89 (1H, d, *J* = 15.4 Hz, ArC**H**), 6.78 (0.62H, dd, *J* = 15.5, 10.2 Hz, $ArCH=C(D/\mathbf{H})$), 6.47 (1H, m, $ArCH=C(D/H)C\mathbf{H}$), 5.98 (1H, dt, *J* = 15.3, 5.9 Hz, $ArCH=C(D/H)CH=C\mathbf{H}$), 4.55 (2H, s, C**H**$_2$Ph), 4.11 (0.38H, d, *J* = 5.5 Hz, C(D/**H**)OBn), 2.59 (3H, s, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.6 (C), 167.6 (C), 138.3 (C), 136.5 (C), 133.1 (C), 132.6 (CH), 132.5 (CH), 132.4 (CH), 132.3 (CH), 132.2 (CH), 131.8 (CH), 128.7 (CH), 128.6 (2 × CH), 127.9 (2 × CH), 127.8 (CH), 126.9 (CH), 72.40 (CH_2), 72.35 (CH_2), 25.6 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{21}H_{19}NNaO_3D_2]^+$ $[M+Na]^+$: 360.1539, found: 360.1550.

Comparison of ^{1}H NMR spectra of products **269ac** and [D]$_n$-**269ac**:

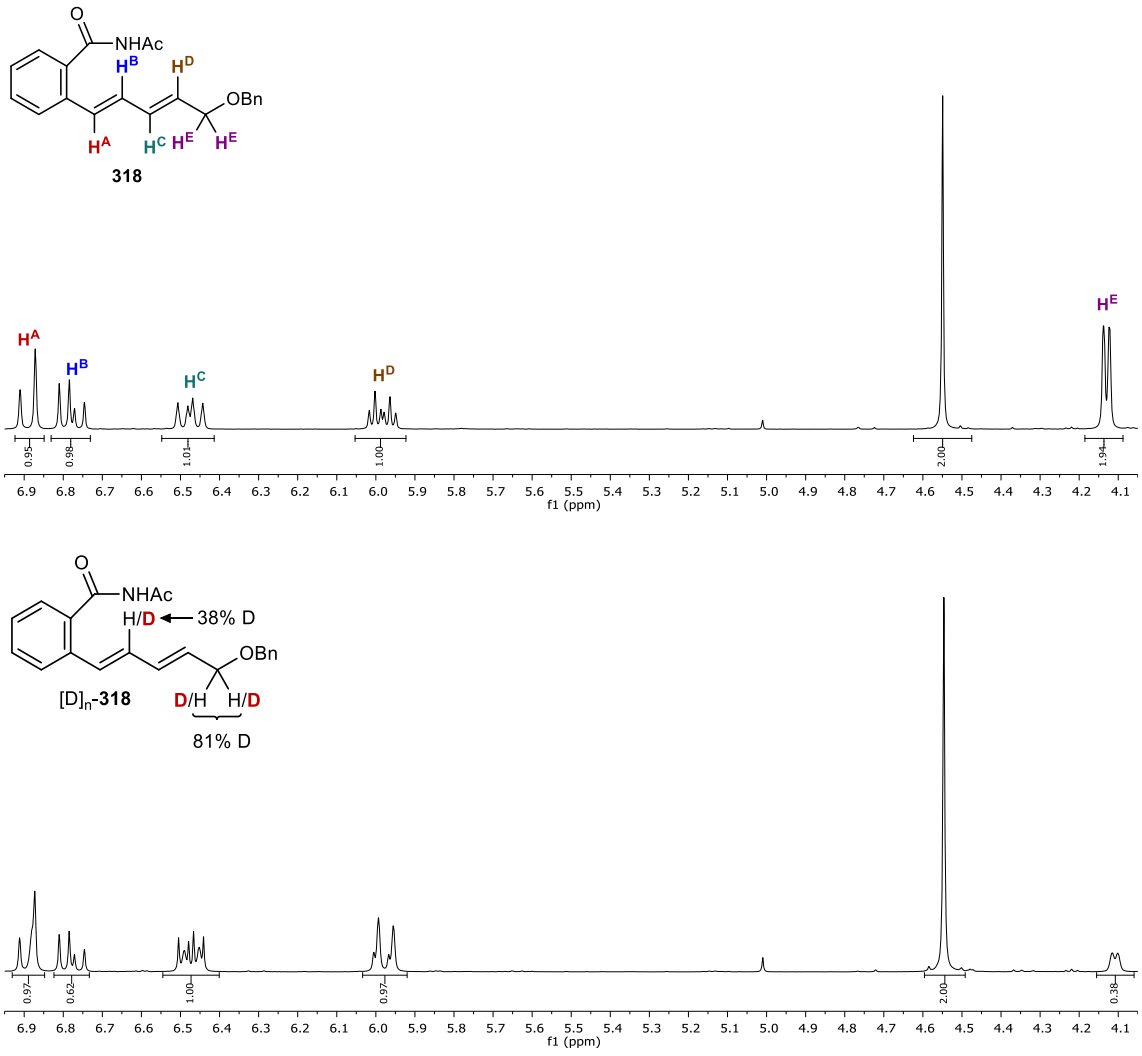


- The %D was calculated to be **90% D** and **88% D** for H^D and H^H, respectively.
  For H^D: %D = (1–0.10)/1 × 100 = 90% D.
  For H^H: %D = (0.16–0.02)/0.16 × 100 = 88% D.

- For H^A and H^E: In a non-deuterated mixture, the multiplet at 5.66–5.55 should integrate to 2.17 (1+1+0.17) (H^C = 1, H^A = 1 and H^E = 0.17 due to the 6:1 *E*/*Z* mixture). Next, subtract H^C to give I_1 = **1.17**, where I_1 is the sum of integrations of H^A and H^E for a non-deuterated 6:1 *E*/*Z* mixture.

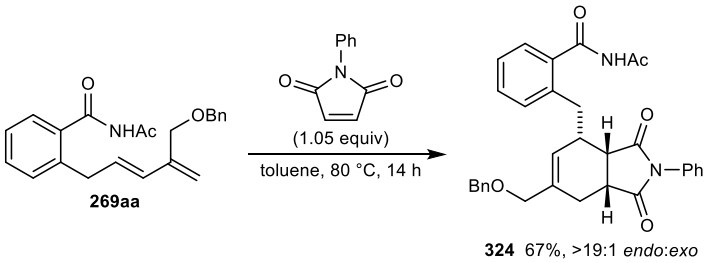
- From the spectrum of the deuterated mixture at sites H_A and H_E: $I_2 = 1.86–1 =$ **0.86** (since $H^C = 1$, which is fully protonated), where I_2 is the sum of integrations of H^A and H^E for the deuterated 6:1 *E*/*Z* mixture.
- Average protonation at H^A and $H^E = P_{AV} = I_2/I_1 = 0.86/1.17 = 0.74$ H
  Average deuteration at H^A and $H^E = 1–0.74 = 0.26$ D
  % Average deuteration at H^A and H^E = **26% D**

Comparison of ^{1}H NMR spectra of products **318** and $[D]_n$-**318**:



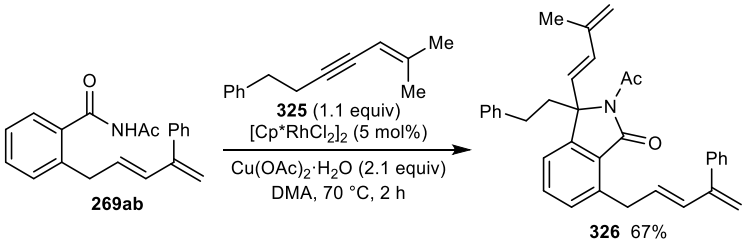
3.1.5 Elaboration of products

(±)-*N*-Acetyl-2-{[(3a*S*,4*S*,7a*R*)-6-[(benzyloxy)methyl]-1,3-dioxo-2-phenyl-2,3,3*a*,4,7,7*a*-hexahydro-1*H*-isoindol-4-yl]methyl}benzamide (324)



To a microwave vial was added diene **269aa** (70 mg, 0.20 mmol) and a solution of *N*-phenylmaleimide (36 mg, 0.21 mmol) in toluene (2.0 mL), and the solution was stirred at 80 °C for 14 h. The reaction was cooled to room temperature, concentrated *in vacuo* and the residue was purified by column chromatography (3:2 EtOAc:petroleum ether) to give *Diels-Alder product* **324** as a white solid (70 mg, 67%). R_f 0.32 (3:2 EtOAc:petroleum ether); m.p. 78−80 °C ($CHCl_3$); IR 3247 (NH), 2927, 1701 (C=O), 1673 (C=O), 1497, 1380, 1286, 1240, 1200, 1089, 719, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.51 (1H, s, N**H**), 7.60–7.58 (1H, m, Ar**H**), 7.48–7.28 (11H, m, Ar**H**), 7.18–7.16 (2H, m, Ar**H**), 5.90 (1H, br s, =C**H**), 4.47 (2H, s, C**H**$_2$Ph), 3.92 (2H, s, BnOC**H**$_2$), 3.58 (1H, dd, *J* = 13.7, 8.0 Hz, PhC**H**$_2$), 3.30–3.21 (3H, m, PhC**H**$_2$ and O=CC**H**C**H**C=O), 2.84–2.76 (2H, m, ArCH$_2$C**H**CHCH and C**H**$_2$CHC=O), 2.52 (3H, s, C**H**$_3$), 2.31–2.24 (1H, m, C**H**$_2$CHC=O); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 178.7 (C), 177.5 (C), 172.7 (C), 168.0 (C), 139.4 (C), 138.1 (C), 137.4 (C), 134.6 (C), 131.94 (C), 131.87 (CH), 131.6 (CH), 129.1 (2 × CH), 128.6 (CH), 128.5 (2 × CH), 128.4 (CH), 127.8 (2 × CH), 127.7 (CH), 127.5 (CH), 126.9 (CH), 126.6 (2 × CH), 72.74 (CH_2), 70.71 (CH_2), 42.7 (CH), 40.7 (CH), 38.5 (CH), 34.3 (CH_2), 26.8 (CH_2), 25.5 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{32}H_{30}N_2NaO_5]^+$ $[M+Na]^+$: 545.2047, found 545.2059.

2-Acetyl-3-[(*E*)-3-methylbuta-1,3-dien-1-yl]-3-phenethyl-7-[(*E*)-4-phenylpenta-2,4-dien-1-yl]isoindolin-1-one (326)



To a microwave vial was added allylation product **269ab** (61 mg, 0.20 mmol), $[Cp^*RhCl_2]_2$ (6.2 mg, 10 μmol), $Cu(OAc)_2{\cdot}H_2O$ (84 mg, 0.42 mmol), and 1,3-enyne **325** (41 mg, 0.22 mmol). The vessel was then sealed, flushed with Ar, and DMA (2 mL) was added. The reaction was then heated at 70 ºC for 2 h, cooled to room temperature, filtered through a short pad of silica using Et_2O (15 mL) as eluent, and concentrated *in vacuo*. Purification of the residue by preparative thin layer chromatography (10:1 petroleum ether:Et_2O) gave the *isoindolinone* as a yellow oil (66 mg, 67%). R_f 0.25 (10:1 petroleum ether:Et_2O); IR 2924, 1699 (C=O), 1373, 1264, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (1H, t, *J* = 7.6 Hz, Ar**H**), 7.37–7.28 (6H, m, Ar**H**), 7.24–7.10 (4H, m, Ar**H**), 6.96–6.93 (2H, m, Ar**H**), 6.45 (1H, d, *J* = 15.5 Hz, CH_2CH=C**H**), 6.10 (1H, d, *J* = 16.1 Hz, =C**H**CCH_3), 5.98 (1H, d, *J* = 16.1 Hz, C**H**=$CHCCH_3$), 5.94 (1H, dt, *J* = 15.5, 7.0 Hz, CH_2C**H**), 5.26 (1H, d, *J* = 1.8 Hz, PhC=C**H**$_2$), 5.14 (1H, d, *J* = 1.8 Hz, PhC=C**H**$_2$), 4.98–4.96 (1H, m, CH_3C=C**H**$_2$), 4.90–4.89 (1H, m, CH_3C=C**H**$_2$), 4.14–4.03 (2H, m, C**H**$_2$CH), 3.29 (1H, ddd, *J* = 13.6, 10.7, 6.3 Hz, PhC**H**$_2$), 2.55 (3H, s, C**H**$_3$C=O), 2.37–2.30 (1H, m, PhC**H**$_2$), 2.16 (1H, ddd, *J* = 13.6, 10.4, 6.3 Hz, $PhCH_2$C**H**$_2$), 1.95 (1H, ddd, *J* = 13.6, 10.7, 4.7 Hz, $PhCH_2$C**H**$_2$), 1.79 (3H, s, =CC**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.9 (C), 168.8 (C), 149.8 (C), 147.8 (C), 141.7 (C), 141.4 (C), 140.8 (C), 140.5 (C), 134.3 (CH), 133.5 (CH), 133.3 (CH), 131.4 (CH), 131.3 (CH), 130.0 (CH), 128.5 (2 × CH), 128.4 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 127.5 (CH), 126.7 (C), 126.1 (CH), 120.8 (CH), 117.9 (CH_2), 115.8 (CH_2), 69.5 (C), 37.5 (CH_2), 34.0 (CH_2), 29.8 (CH_2), 26.7 (CH_3), 18.6 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{34}H_{33}NNaO_2]^+$ $[M+Na]^+$: 510.2404, found 510.2402.

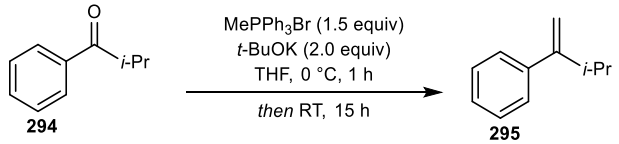
3.2 Rh(III)-catalysed oxidative C–H homoallylation of *N*-acetylbenzamides with 1,3-dienes: migration to a tertiary carbon

3.2.1 General information

Unless specified otherwise, all reactions were carried out under an atmosphere of argon. Unless specified otherwise, all commercially available reagents and solvents were used as received. THF was dried and purified by passage through activated alumina columns using a solvent purification system. All petroleum ether used was 40–60 °C petroleum ether. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates with a fluorescent indicator. Compounds were visualised by exposure to UV light or by dipping the plates into solutions of potassium permanganate or vanillin followed by heating. Flash column chromatography was carried out using silica gel (Fisher Scientific 60 Å particle size 35–70 micron). Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. The solvent of recrystallisation is reported in parentheses. Infra-red spectra were recorded on a Nicolet Avatar 360 FT instrument on the neat compound using the attenuated total refraction technique. NMR spectra were acquired on Bruker DPX300, AV400, AV(III)400, or DPX400 spectrometers at room temperature. ^{1}H and ^{13}C NMR spectra were referenced to external tetramethylsilane *via* the residual protonated solvent (^{1}H) or the solvent itself (^{13}C). All chemical shifts are reported in parts per million (ppm). For $CDCl_3$, the shifts are referenced to 7.26 ppm for ^{1}H NMR spectroscopy and 77.16 ppm for ^{13}C NMR spectroscopy. High-resolution mass spectra were recorded using electrospray ionisation (ESI) or electron impact ionisation (EI) techniques at the School of Chemistry, University of Nottingham.

3.2.2 Substrate synthesis

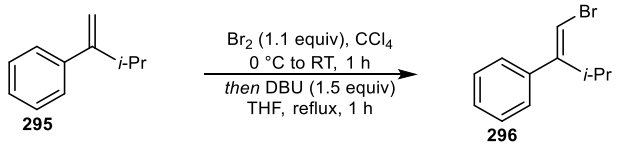
Preparation of (3-methylbut-1-en-2-yl)benzene (295)



294 295

To a solution methyltriphenylphosphonium bromide (17.9 g, 50.0 mmol) in THF (80 mL) was added *t*-BuOK (7.47 g, 66.6 mmol) at 0 °C and stirred for 1 h. Next, isobutyrophenone (5.0 mL, 33 mmol) was added and the resulting mixture was stirred overnight at room temperature. This was filtered through SiO_2 (petrol) which gave alkene **295** (4.68 g, 96%) as a colourless oil without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.27 (5H, m, Ar**H**), 5.15 (1H, s, C**H**$_2$), 5.04 (1H, s, C**H**$_2$), 2.85 (1H, hept, *J* = 7.0 Hz, C**H**$(CH_3)_2$), 1.11 (6H, d, *J* = 7.0 Hz, CH(C**H**$_3)_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.0 (C), 143.0 (C), 128.3 (2 × CH), 127.2 (CH), 126.8 (2 × CH), 110.1 (CH_2), 32.5 (CH), 21.2 (2 × CH_3); Physical and spectral properties were in accordance with the literature.[168]

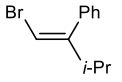
Preparation of (*E*)-(1-bromo-3-methylbut-1-en-2-yl)benzene (296)



295 296

To a solution of alkene **295** (4.68 g, 32.1 mmol) in CCl_4 (32 mL) was added bromine (1.8 mL, 35 mmol) dropwise at 0 °C. The reaction mixture was left for 1 h whilst it gradually reached room temperature. Next, saturated sodium thiosulfate solution was added to remove excessive bromine, separated, extracted with CH_2Cl_2 (20 mL × 3), dried ($MgSO_4$) and concentrated *in vacuo*. The *dibrominated intermediate* was then dissolved in THF (32 mL) and 1,8-diazabicyclo[5,4,0]-udec-7-ene (7.2 mL, 48 mmol) was added and heated to reflux for 1 h. The reaction was quenched by adding brine (15 mL), separated and extracted with EtOAc (15 mL × 3). The combined organic phases were washed with 1.0 M aqueous HCl (50 mL), followed by brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane) gave *alkenyl bromide E*-**296** as a colourless oil (3.20 g, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.31 (3H, m, Ar**H**), 7.16–7.14 (2H, m, Ar**H**), 6.05 (1H, s, **H**CBr), 3.33 (1H, heptd, *J* = 6.9, 1.4 Hz, C**H**$(CH_3)_2$), 1.06 (6H, dd,

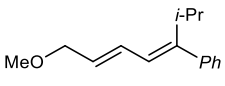
J = 6.9, 1.4 Hz, CH(C**H**$_3$)$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.0 (C), 139.6 (C), 128.7 (2 × CH), 128.0 (2 × CH), 127.6 (CH), 104.5 (CH), 32.3 (CH), 20.6 (2 × CH_3); Physical and spectral properties were in accordance with the literature.[169]



(*Z*)-(1-Bromo-3-methylbut-1-en-2-yl)benzene (*Z*-296)

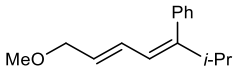
The titled compound was isolated as a pale yellow oil (212 mg, 3%) as the minor isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.31 (3H, m, Ar**H**), 7.17–7.14 (2H, m, Ar**H**), 6.25 (1H, d, J = 1.0 Hz, **H**CBr), 2.71 (1H, heptd, J = 6.9, 1.0 Hz, C**H**(CH$_3$)$_2$), 1.07 (6H, d, J = 6.9 Hz, CH(C**H**$_3$)$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.9 (C), 139.9 (C), 128.5 (2 × CH), 128.2 (2 × CH), 127.4 (CH), 102.5 (CH), 37.1 (CH), 21.5 (2 × CH_3); Physical and spectral properties were in accordance with the literature.[169]

Preparation of 1,3-dienes



((3*E*, 5*E*)-7-Methoxy-2-methylhepta-3,5-dien-3-yl)benzene (297)

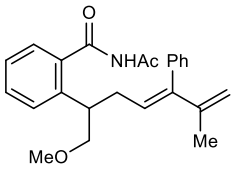
The title compound was prepared according to General procedure C from alkenyl bromide *E*-**296** (113 mg, 0.500 mmol), alkenyl boronate ester **272d** (0.13 mL, 0.60 mmol), Cs_2CO_3 (489 mg, 1.50 mmol) and Pd(PPh$_3$)$_4$ (17 mg, 0.015 mmol) at 80 °C for a reaction time of 15 h and was purified by flash column chromatography (40:1 petroleum ether:Et_2O) to give a pale yellow oil (107 mg, 99%). R_f 0.32 (40:1 petroleum ether:Et_2O); IR 2958, 1490, 1379, 1118, 973, 773, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.23 (5H, m, Ar**H**), 6.75 (1H, ddt, J = 15.1, 11.2, 1.2 Hz, CH=C**H**=CHCH$_2$), 6.00 (1H, d, J = 11.2 Hz, C**H**=CH=CHCH$_2$), 5.82 (1H, dtd, J = 15.1, 6.1, 0.7 Hz, CH=CH=C**H**CH$_2$), 4.06 (2H, dd, J = 6.1, 1.2 Hz, CHC**H**$_2$OMe), 3.41 (3H, s, OC**H**$_3$), 3.27 (1H, hept, J = 7.0 Hz, C**H**(CH$_3$)$_2$), 1.14 (6H, d, 7.0 Hz, CH(C**H**$_3$)$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 149.2 (C), 142.9 (C), 130.0 (CH), 128.5 (CH), 128.4 (2 × CH), 127.8 (2 × CH), 127.3 (CH), 126.7 (CH), 73.2 (CH$_2$), 58.1 (CH$_3$), 29.9 (CH), 22.1 (2 × CH_3); HRMS (ESI) Exact mass calculated for [$C_{15}H_{20}NaO$]$^+$ [M+Na]$^+$: 239.1406, found 239.1405.



((3*Z*, 5*E*)-7-Methoxy-2-methylhepta-3,5-dien-3-yl)benzene (298)

The title compound was prepared according to General procedure C from alkenyl bromide *Z*-**296** (338 mg, 1.50 mmol), alkenyl boronate ester **272d** (0.36 mL, 1.7 mmol), Cs_2CO_3 (1.47 g, 4.50 mmol) and $Pd(PPh_3)_4$ (52 mg, 0.045 mmol) at 80 °C for a reaction time of 15 h and was purified by flash column chromatography (40:1 petroleum ether:Et_2O) to give a pale yellow oil (217 mg, 67%). R_f 0.28 (40:1 petroleum ether:Et_2O); IR 2960, 1492, 1378, 1117, 973, 773, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.28 (3H, m, Ar**H**), 7.16–7.14 (2H, m, Ar**H**), 6.15–6.07 (2H, m, C**H**=C**H**=CHCH$_2$), 5.80–5.74 (1H, m, CH=CH=C**H**CH$_2$), 3.86 (2H, d, *J* = 6.8 Hz, CHC**H**$_2$OMe), 3.28 (3H, s, OC**H**$_3$), 2.72–2.62 (1H, m, C**H**(CH$_3$)$_2$), 1.08 (6H, d, 6.8 Hz, CH(C**H**$_3$)$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 150.9 (C), 140.9 (C), 131.2 (CH), 129.1 (2 × CH), 128.4 (CH), 128.0 (2 × CH), 126.8 (CH), 123.6 (CH), 73.2 (CH$_2$), 57.8 (CH$_3$), 36.0 (CH), 21.8 (2 × CH$_3$); HRMS (ESI) Exact mass calculated for $[C_{15}H_{20}NaO]^+$ $[M+Na]^+$: 239.1406, found 239.1405.

3.2.3 Oxidative C–H homoallylation of benzamides with 1,3-dienes



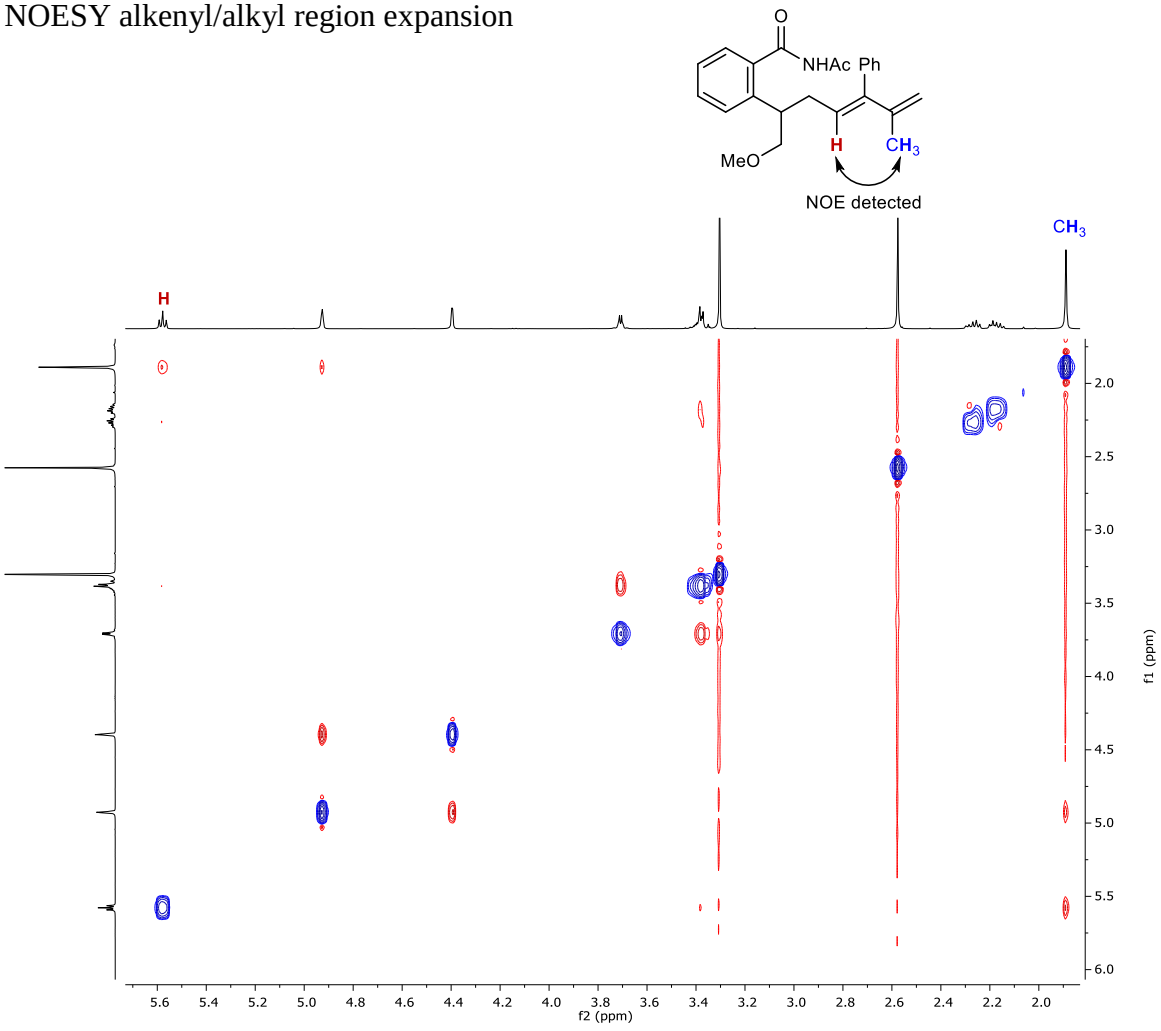
(*E*)-*N*-Acetyl-2-(1-methoxy-6-methyl-5-phenylhepta-4,6-dien-2-yl)benzamide (343)

The title compound was prepared according to General procedure D from benzamide **267a** (98 mg, 0.60 mmol), $[Cp^*RhCl_2]_2$ (4.6 mg, 7.5 μmol), $Cu(OAc)_2$ (114 mg, 0.630 mmol), and 1,3-diene **297** (65 mg, 0.30 mmol) at 70 °C for a reaction time of 15 h and was purified by preparative TLC (10:5:2 CH_2Cl_2: petroleum ether: EtOAc) to give a pale yellow oil (77 mg, 68%). R_f 0.50 (10:5:2 CH_2Cl_2: petroleum ether: EtOAc); IR 3257 (NH), 2927, 1694 (C=O), 1372, 1263, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.90 (1H, s, N**H**), 7.49 (1H, dd, *J* = 7.7, 1.4 Hz, Ar**H**), 7.40 (1H, td, *J* = 7.7, 1.4 Hz, Ar**H**), 7.35–7.27 (4H, m, Ar**H**), 7.05 (1H, d, *J* = 7.7 Hz, Ar**H**), 6.96–6.94 (2H, m, Ar**H**), 5.55 (1H, t, *J* = 7.2 Hz, CH$_2$C**H**=), 4.90 (1H, br s, =C**H**$_2$), 4.37 (1H, br s, =C**H**$_2$), 3.72–3.63 (1H, m, ArC**H**), 3.37–3.34 (2H, m, OC**H**$_2$), 3.27 (3H, s, C**H**$_3$OCH$_2$), 2.55 (3H, s, C**H**$_3$C=O), 2.28–2.11 (2H, m, C**H**$_2$CH=), 1.86 (3H, s, CC**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.5 (C), 168.8 (C), 145.0 (C), 144.3 (C), 140.1 (C), 139.4 (C), 136.9 (C), 131.3 (CH), 129.6 (2 × CH), 128.6 (CH), 128.1 (2 × CH), 126.89 (CH), 126.87 (CH), 126.6 (CH), 125.2 (CH),

116.4 (CH_2), 78.0 (CH_2), 59.1 (CH_3), 42.3 (CH), 32.6 (CH_2), 25.9 (CH_3), 20.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{24}H_{27}NNaO_3]^+$ [M+Na]$^+$: 400.1883, found 400.1884.

Additionally, the title compound was prepared according to General procedure D from 1,3-diene **298** as a pale yellow oil (62 mg, 55%).

NOESY alkenyl/alkyl region expansion



3.3 Rh(III)-catalysed oxidative C–H homoallylation of *N*-acetylbenzamides with 1,4-dienes

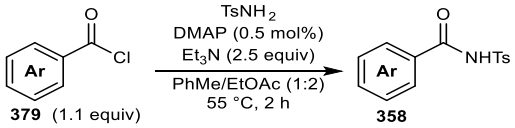
3.3.1 General information

Unless specified otherwise, all reactions were carried out under an atmosphere of argon. Unless specified otherwise, all commercially available reagents and solvents

were used as received. THF was dried and purified by passage through activated alumina columns using a solvent purification system. All petroleum ether used was 40–60 °C petroleum ether. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates with a fluorescent indicator. Compounds were visualised by exposure to UV light or by dipping the plates into solutions of potassium permanganate or vanillin followed by heating. Flash column chromatography was carried out using silica gel (Fisher Scientific 60 Å particle size 35–70 micron). Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. The solvent of recrystallisation is reported in parentheses. Infra-red spectra were recorded on a Nicolet Avatar 360 FT instrument on the neat compound using the attenuated total refraction technique. NMR spectra were acquired on Bruker DPX300, AV400, AV(III)400, DPX400, AV(III)500 or AV500 spectrometers at room temperature. ^{1}H and ^{13}C NMR spectra were referenced to external tetramethylsilane *via* the residual protonated solvent (^{1}H) or the solvent itself (^{13}C). All chemical shifts are reported in parts per million (ppm). For $CDCl_3$, the shifts are referenced to 7.26 ppm for ^{1}H NMR spectroscopy and 77.16 ppm for ^{13}C NMR spectroscopy. High-resolution mass spectra were recorded using electrospray ionisation (ESI) or electron impact ionisation (EI) techniques at the School of Chemistry or at the GSK Carbon Neutral Laboratories for Sustainable Chemistry, University of Nottingham.

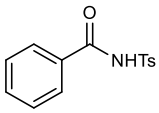
3.3.2 Synthesis of substrates

General procedure E: preparation of *N*-tosylbenzamides



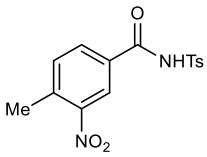
To a solution of *p*-toluenesulfonamide (1.0 equiv), DMAP (0.5 mol%), Et_3N (2.5 equiv) in toluene/EtOAc (1 mL toluene per mmol with respect to *p*-toluenesulfonamide:2 mL EtOAc per mmol with respect to *p*-toluenesulfonamide) was added the appropriate aroyl chloride **379** (1.1 equiv) and the solution heated at 55 °C for 2 h. The resulting mixture was cooled, quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (three times). The organic layers were combined, dried

($MgSO_4$), and concentrated *in vacuo*. Purification of the crude mixture by recrystallisation from *i*-hexane:EtOAc gave the title compound.



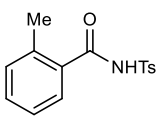
_N_-tosylbenzamide (358a)

The title compound was prepared according to General procedure E from *p*-toluenesulfonamide (8.56 g, 50.0 mmol), DMAP (30.5 mg, 0.250 mmol), Et_3N (17.4 mL, 125 mmol) and benzoyl chloride (6.4 mL, 55 mmol) to give benzamide **358a** as a white crystalline solid (2.25 g, 16%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (1H, br s, N**H**), 8.05 (2H, m, Ar**H**), 7.79–7.77 (2H, m, Ar**H**), 7.59–7.55 (1H, m, Ar**H**), 7.46–7.43 (2H, m, Ar**H**), 7.36 (2H, d, *J* = 8.1 Hz, Ar**H**), 2.44 (3H, s, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.3 (C), 138.6 (C), 135.7 (C), 133.7 (CH), 131.4 (C), 129.8 (2 × CH), 129.1 (2 × CH), 128.9 (2 × CH), 127.8 (2 × CH), 21.9 (CH_3); Physical and spectral properties were in accordance with the literature.[170]



4-Methyl-3-nitro-_N_-tosylbenzamide (358b)

The title compound was prepared according to General procedure E from *p*-toluenesulfonamide (5.34 g, 31.2 mmol), DMAP (19.0 mg, 0.156 mmol), Et_3N (10.9 mL, 78.0 mmol) and 4-methyl-3-nitrobenzoyl chloride (5.0 mL, 34 mmol) to give *benzamide* **358b** as an off-white crystalline solid (6.84 g, 66%). R_f 0.28 (CH_2Cl_2:MeOH 10:0.5); m.p. 169−171 °C (CH_2Cl_2); IR 3277 (NH), 2931, 1698 (C=O), 1531 (NO_2), 1436, 1347 (NO_2), 1166, 1084, 823, 661, 546 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 11.20 (1H, br s, N**H**), 8.49 (1H, d, *J* = 1.9 Hz, Ar**H**), 8.12 (1H, dd, *J* = 8.1, 1.9 Hz, Ar**H**), 8.01–7.99 (2H, m, Ar**H**), 7.63 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.44 (1H, d, *J* = 7.8 Hz, Ar**H**), 2.61 (3H, s, C**H**$_3$C=CNO_2), 2.43 (3H, s, SO_2CH=CHCC**H**$_3$); ^{13}C NMR (100.6 MHz, acetone-d_6) δ 163.7 (C), 150.2 (C), 145.8 (C), 139.2 (C), 137.5 (C), 134.2 (CH), 133.1 (CH), 131.9 (C), 130.3 (2 × CH), 129.3 (2 × CH), 125.0 (CH), 21.5 (CH_3), 20.2 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{15}H_{14}N_2NaO_5]^+$ $[M+Na]^+$: 357.0522, found 357.0522.



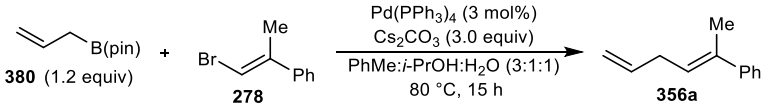
2-Methyl-_N_-tosylbenzamide (358c)

The title compound was prepared according to General procedure E from *p*-toluenesulfonamide (11.93 g, 69.68 mmol), DMAP (46.0 mg, 0.380 mmol), Et_3N (26.7 mL, 192 mmol) and 2-methylbenzoyl chloride (10.0 mL, 76.7 mmol) to give benzamide **358c** as a white crystalline solid (6.47 g, 32%). ^{1}H

NMR (400 MHz, $CDCl_3$) δ 8.73 (1H, br s, N**H**), 8.00 (1H, d, *J* = 8.5 Hz, Ar**H**), 7.40 (1H, d, *J* = 7.6 Hz, Ar**H**), 7.36–7.32 (3H, m, Ar**H**), 7.19–7.16 (2H, m, Ar**H**), 2.44 (3H, s, $SO_2CH{=}CHCC\mathbf{H}_3$), 2.34 (3H, s, $C\mathbf{H}_3CH{=}CHCC{=}O$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.4 (C), 145.3 (C), 138.1 (C), 135.7 (C), 132.3 (C), 131.9 (CH), 131.8 (CH), 129.7 (2 × CH), 128.6 (2 × CH), 127.4 (CH), 126.1 (CH), 21.8 (CH_3), 20.2 (CH_3); Physical and spectral properties were in accordance with the literature.[171]

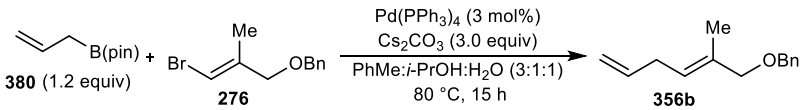
Preparation of 1,4-dienes

(*E*)-Hexa-2,5-dien-2-ylbenzene (356a)



The title compound was prepared according to General procedure C from alkenyl bromide **278** (394 mg, 2.00 mmol), allyl boronate ester **380** (0.45 mL, 2.4 mmol), Cs_2CO_3 (1.96 g, 6.00 mmol) and $Pd(PPh_3)_4$ (69.3 mg, 0.0600 mmol) and was purified by flash column chromatography (pentane) to give a colourless oil (239 mg, 76%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.38 (2H, m, Ar**H**), 7.35–7.29 (2H, m, Ar**H**), 7.24–7.21 (1H, m, Ar**H**), 5.89 (1H, ddt, *J* = 17.1, 10.0, 6.2 Hz, $CH_2{=}C\mathbf{H}$), 5.81 (1H, dq, *J* = 7.3, 1.3 Hz, $CH_2{=}CHCH_2\mathbf{CH}$), 5.10 (1H, dq, *J* = 17.1, 1.7 Hz, $C\mathbf{H}_2{=}$), 5.21 (1H, dd, *J* = 10.0, 1.7 Hz, $C\mathbf{H}_2{=}$), 2.99–2.95 (2H, m, $C\mathbf{H}_2CH$), 2.05 (3H, d, *J* = 1.3 Hz, $C\mathbf{H}_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.9 (C), 136.7 (CH), 136.1 (C), 128.3 (2 × CH), 126.8 (CH), 125.8 (2 × CH), 125.3 (CH), 115.0 (CH_2), 33.1 (CH_2), 15.9 (CH_3); Physical and spectral properties were in accordance with the literature.[172]

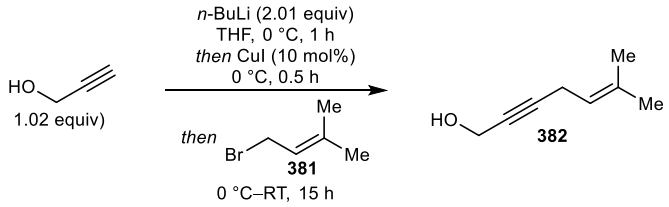
(*E*)-{[(2-Methylhexa-2,5-dien-1-yl)oxy]methyl}benzene (356b)



The title compound was prepared according to General procedure C from alkenyl bromide **276** (482 mg, 2.00 mmol), allyl boronate ester **380** (0.45 mL, 2.4 mmol), Cs_2CO_3 (1.96 g, 6.00 mmol) and $Pd(PPh_3)_4$ (69.3 mg, 0.0600 mmol) and was purified by flash column chromatography (40:1 petroleum ether:Et_2O) to give a pale yellow oil (379 mg, 94%). R_f 0.27 (40:1 petroleum ether:Et_2O); IR 2851, 1452, 1350, 1069, 907, 733, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.32 (5H, m, Ar**H**), 5.82 (1H, ddt,

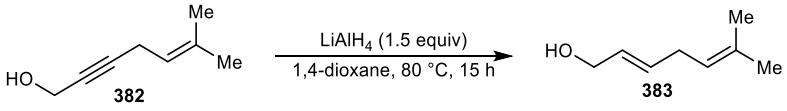
J = 17.1, 10.1, 6.3 Hz, CH_2=C**H**), 5.48 (1H, dq, *J* = 7.3, 1.2 Hz, =CHCH$_2$**CH**), 5.05 (1H, dq, *J* = 17.1, 1.8 Hz, C**H**$_2$=), 4.99 (1H, dd, *J* = 10.1, 1.5 Hz, C**H**$_2$=), 4.47 (2H, s, OC**H**$_2$Ph), 3.93 (2H, d, *J* = 1.1 Hz, C**H**$_2$OBn), 2.84–2.81 (2H, m, C**H**$_2$CH), 1.70 (3H, d, *J* = 1.2 Hz, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.7 (C), 136.8 (CH), 133.5 (C), 128.5 (2 × CH), 127.9 (2 × CH), 127.6 (CH), 125.4 (CH), 114.8 (CH_2), 76.2 (CH_2), 71.7 (CH_2), 32.2 (CH_2), 14.0 (CH_3); HRMS (EI) Exact mass calculated for $[C_{13}H_{16}O]^+$ $[M]^+$: 188.1196, found: 188.1204.

6-Methylhept-5-en-2-yn-1-ol (382)



To a solution of propargyl alcohol (1.19 mL, 20.4 mmol) in THF (50 mL) was added *n*-BuLi (16.1 mL, 2.5 M in hexanes, 40.2 mmol) dropwise at 0 °C over 0.5 h. After 30 min, CuI (389 mg, 2.04 mmol) was added in one portion at 0 °C. After a further 30 min, a solution of prenyl bromide **381** (2.31 mL, 20.0 mmol) in THF (65 mL) was added dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature overnight, quenched with saturated aqueous NH_4Cl (30 mL), extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (gradient elution; 15:1 petroleum ether:EtOAc to 3:2 petroleum ether:EtOAc) to give 1,4-enyne **382** as a pale yellow oil (2.31 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19–5.15 (1H, m, C**H**=), 4.25–4.24 (2H, m, HOC**H**$_2$), 2.91 (2H, d, *J* = 6.7 Hz, C**H**$_2$CH), 1.71 (3H, s, C(C**H**$_3$)$_2$), 1.62 (3H, s, C(C**H**$_3$)$_2$), 1.65 (1H, br s, **H**O); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 134.2 (C), 118.8 (CH), 85.3 (C), 77.8 (C), 51.6 (CH_2), 25.6 (CH_3), 18.0 (CH_3), 17.8 (CH_2). Physical and spectral properties were in accordance with the literature.[173]

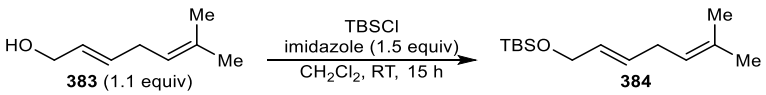
(*E*)-6-Methylhepta-2,5-dien-1-ol (383)



A solution of enyne **382** (2.41 g, 19.4 mmol) in 1,4-dioxane (4 mL) was added dropwise to a suspension of $LiAlH_4$ (1.10 g, 29.1 mmol) in 1,4-dioxane (15 mL) at 0

°C. Next, the reaction mixture was heated at 80 °C for 15 h. The reaction was cooled to 0 °C and quenched carefully with EtOAc (5 mL) followed by *i*-PrOH (2 mL) and saturated aqueous potassium sodium tartrate solution (2 mL), and the mixture was stirred vigorously for 15 min. The mixture was decanted to remove the biphasic liquid layer and the sludgy residue was washed with EtOAc (3 × 5 mL). The washings were combined with the biphasic liquid layer, H_2O (10 mL) was added, and the aqueous layer was separated and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (gradient elution; 10:1 petroleum ether:Et_2O to Et_2O) to give 1,4-diene **383** as a pale yellow oil (2.25 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71–5.59 (2H, m, CH=C**H**CH_2C**H**), 5.14 (1H, ddp, *J* = 8.6, 5.6, 1.3 Hz, C**H**=CHCH_2CH), 4.09 (2H, m, HOC**H**$_2$), 2.75–2.72 (2H, m, C**H**$_2$CH), 1.71 (3H, d, *J* = 1.3 Hz, C(C**H**$_3$)$_2$), 1.61 (3H, s, C(C**H**$_3$)$_2$), 1.35 (1H, br s, **H**O); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 133.1 (C), 132.0 (CH), 128.9 (CH), 121.6 (CH), 63.9 (CH_2), 31.0 (CH_2), 25.8 (CH_3), 17.8 (CH_3). Physical and spectral properties were in accordance with the literature.[173]

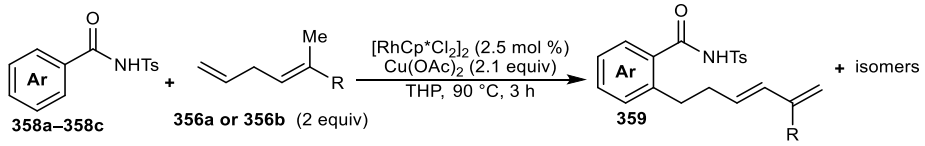
(*E*)-*tert*-Butyldimethyl[(6-methylhepta-2,5-dien-1-yl)oxy]silane (384)



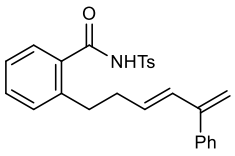
To a stirred solution of alcohol **383** (139 mg, 1.10 mmol) in CH_2Cl_2 (5 mL) was added TBSCl (151 mg, 1.00 mmol) followed by imidazole (102 mg, 1.50 mmol) and stirred at room temperature for 15 h. The reaction mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried (MgSO4), filtered, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (20:1 petroleum ether:Et_2O) gave *1,4-diene* **384** (209 mg, 85%) as a colourless oil. R_f 0.75 (20:1 petroleum ether:Et_2O); IR 2956, 2856, 1253, 1079, 1046, 833, 774 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65–5.50 (2H, m, CH=C**H**CH_2C**H**), 5.14 (1H, tdt, *J* = 7.2, 2.8, 1.4 Hz, C**H**=CHCH_2CH), 4.13–4.11 (2H, m, TBSOC**H**$_2$), 2.73–2.70 (2H, m, C**H**$_2$CH), 1.71 (3H, d, *J* = 1.3 Hz, C(C**H**$_3$)$_2$), 1.61 (3H, d, *J* = 1.3 Hz, C(C**H**$_3$)$_2$), 0.90 (9H, s, Si(C**H**$_3$)$_3$), 0.06 (6H, s, Si(C**H**$_3$)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.7 (C), 130.1 (CH), 129.2 (CH), 122.0 (CH), 64.2 (CH_2), 30.1 (CH_2), 26.2 (3 × CH_3), 25.8 (CH_3), 18.6 (C), 17.8 (CH_3), –4.9 (2 × CH_3). HRMS (ESI) Exact mass calculated for $[C_{14}H_{28}NaOSi]^+$ $[M+Na]^+$: 263.1802, found 263.1808.

3.3.3 Oxidative C–H homoallylation of benzamides with 1,4-dienes

General procedure F: oxidative C–H homoallylation of benzamides with 1,4-dienes



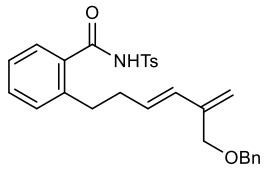
To a microwave vial was added the appropriate *N*-tosylbenzamide (0.05 mmol), $[Cp^*RhCl_2]_2$ (0.8 mg, 1 μmol), $Cu(OAc)_2$[**] (20.0 mg, 0.210 mmol), and the appropriate 1,4-diene (0.1 mmol). The vessel was then sealed, flushed with Ar, and THP (3 mL) was added. The reaction was then heated at 90 ºC for 3 h. The reaction was cooled to room temperature, filtered through a short pad of silica using Et_2O (10 mL) as eluent, and concentrated *in vacuo*. Purification of the residue by flash column chromatography or preparative thin layer chromatography gave the title compound(s). [**]*Note*: $Cu(OAc)_2$ was purified by heating under vacuum with a heat gun to remove residual AcOH and H_2O.



(***E*)-2-(5-Phenylhexa-3,5-dien-1-yl)-*N*-tosylbenzamide** (**359aa**). The title compound was prepared according to General procedure F from benzamide **358a** (13.8 mg, 0.0500 mmol) and 1,4-diene **356a** (15.8 mg, 0.100 mmol). The yield of *homoallylation product* **359aa** was 64%, which was determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. Purification proved to be difficult by flash column chromatography and preparative thin layer chromatography.

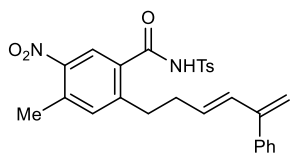
R_f 0.27 (Et_2O:petroleum ether 2:1); 3255 (NH), 2922, 1702 (C=O), 1165, 1083, 884, 810, 733, 706, 547 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (1H, s, N**H**), 8.04–8.00 (2H, m, Ar**H**), 8.00–7.98 (2H, m, Ar**H**), 7.47–7.19 (11H, m, Ar**H**), 6.15 (1H, d, *J* = 15.6 Hz, CH_2CH=C**H**), 5.47 (1H, dt, *J* = 15.6, 6.9 Hz, CH_2C**H**=CH), 5.14 (1H, d, *J* = 1.8 Hz, =C**H**$_2$), 5.10 (1H, d, *J* = 1.8 Hz, =C**H**$_2$), 2.74–2.71 (2H, m, C**H**$_2$CH=CH), 2.39 (3H, s, C**H**$_3$) 2.23–2.18 (2H, m, C**H**$_2$$CH_2$CH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3 (C), 147.9 (C), 145.4 (C), 141.6 (C), 140.5 (C), 135.6 (C), 132.5 (C), 132.8 (CH), 132.3 (CH), 131.8 (CH), 131.2 (CH), 129.7 (2 × CH), 128.7 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 127.5 (CH), 127.2 (CH), 126.4 (CH), 115.2 (CH_2), 34.6 (CH_2), 33.1

(CH_2), 30.5 (CH_3), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{26}H_{25}NNaO_3S]^+$ $[M+Na]^+$: 454.1424, found: 454.1451.



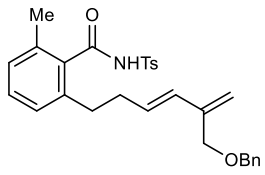
(*E*)-2-{5-[(Benzyloxy)methyl]hexa-3,5-dien-1-yl}-*N*-tosylbenzamide (359ab). The title compound was prepared according to General procedure F from benzamide **358a** (13.8 mg, 0.0500 mmol) and 1,4-diene **356b** (20.2 mg, 0.100 mmol). The yield of *homoallylation product* **359ab** was 74%, which was determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. Purification proved to be difficult by flash column chromatography and preparative thin layer chromatography.

R_f 0.27 (5:2 petroleum ether:EtOAc); IR (mixture) 3258 (NH), 2923, 1702 (C=O), 1430, 1346, 1166, 1067, 746, 670, 572, 548 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (1H, s, N**H**), 8.03–8.01 (2H, m, Ar**H**), 7.37–7.30 (11H, m, Ar**H**), 5.81 (1H, d, *J* = 15.9 Hz, CH_2CH=C**H**), 5.58 (1H, dt, *J* = 15.9, 7.2 Hz, CH_2C**H**=CH), 5.12 (1H, d, *J* = 1.6 Hz, =C**H**$_2$), 5.08 (1H, d, *J* = 1.6 Hz, =C**H**$_2$), 4.41 (2H, s, C**H**$_2$Ph), 4.09 (2H, s, C**H**$_2$OBn), 2.78–2.76 (2H, m, C**H**$_2$CH=CH), 2.43 (3H, s, C**H**$_3$), 2.27–2.22 (2H, m, C**H**$_2$CH$_2$CH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2 (C), 145.1 (C), 141.9 (C), 137.9 (C), 136.0 (C), 135.9 (C), 134.3 (C), 133.8 (C), 131.4 (CH), 130.9 (CH), 130.7 (CH), 130.3 (CH), 129.8 (CH), 129.6 (2 × CH), 128.7 (2 × CH), 128.6 (2 × CH), 128.2 (CH), 128.0 (CH), 116.8 (CH_2), 72.1 (CH_2), 71.2 (CH_2), 34.8 (CH_2), 32.4 (CH_2), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{28}H_{29}NNaO_4S]^+$ $[M+Na]^+$: 498.1715, found: 498.1701.



(*E*)-4-Methyl-5-nitro-2-(5-phenylhexa-3,5-dien-1-yl)-*N*-tosylbenzamide (359ba). The title compound was prepared according to General procedure F from benzamide **358b** (16.7 mg, 0.0500 mmol) and 1,4-diene **356a** (15.8 mg, 0.100 mmol). The yield of *homoallylation product* **359ba** was 68%, which was determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. Purification proved to be difficult by flash column chromatography and preparative thin layer chromatography.

R_f 0.35 (CH_2Cl_2:MeOH 10:0.5); IR (mixture) 3255 (NH), 2924, 1705 (C=O), 1519 (NO_2), 1339 (NO_2), 1167, 1082, 884, 812, 731, 703, 547 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.64 (1H, s, N**H**), 8.04–8.00 (2H, m, Ar**H**), 7.79–7.77 (1H, m, Ar**H**), 7.44–7.41 (1H, m, Ar**H**), 7.36–7.31 (9H, m, Ar**H**), 5.85–5.77 (1H, m, CH_2CH=C**H**), 5.47 (1H, td, *J* = 7.2, 1.3 Hz, CH_2C**H**=CH), 5.04 (1H, dq, *J* = 17.1, 1.7 Hz, =C**H**$_2$), 5.13 (1H, dq, *J* = 10.1, 1.7 Hz, =C**H**$_2$), 2.84–2.81 (2H, m, C**H**$_2$CH=CH), 2.43 (3H, s, C**H**$_3$) 2.25–2.20 (2H, m, C**H**$_2CH_2$CH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.3 (C), 147.7 (C), 147.4 (C), 146.5 (C), 143.8 (C), 143.4 (C), 141.8 (C), 140.4 (C), 135.9 (C), 135.7 (CH), 132.8 (CH), 132.0 (CH), 129.7 (2 × CH), 128.4 (CH), 128.24 (2 × CH), 128.21 (2 × CH), 127.6 (CH), 115.5 (CH_2), 34.1 (CH_2), 33.2 (CH_2), 21.8 (CH_3), 20.9 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{27}H_{26}N_2NaO_5S]^+$ $[M+Na]^+$: 513.1460, found: 513.1447.



(*E*)-2-{5-[(Benzyloxy)methyl]hexa-3,5-dien-1-yl}-6-methyl-*N*-tosylbenzamide (359cb). The title compound was prepared according to General procedure F from benzamide **358c** (14.5 mg, 0.0500 mmol) and 1,4-diene **356b** (20.2 mg, 0.100 mmol). The yield of *homoallylation product* **359cb** was 60%, which was determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. Purification proved to be difficult by flash column chromatography and preparative thin layer chromatography.

R_f 0.25 (5:2 petroleum ether:EtOAc); IR (mixture) 3259 (NH), 2922, 1701 (C=O), 1430, 1346, 1172, 1063, 746, 573 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.36 (1H, s, N**H**), 8.01–7.99 (2H, m, Ar**H**), 7.38–7.20 (10H, m, Ar**H**), 5.93 (1H, d, *J* = 15.9 Hz, CH_2CH=C**H**), 5.63 (1H, dt, *J* = 15.9, 7.1 Hz, CH_2C**H**=CH), 5.10 (1H, s, =C**H**$_2$), 5.06 (1H, s, =C**H**$_2$), 4.31 (2H, s, C**H**$_2$Ph), 4.10 (2H, s, C**H**$_2$OBn), 2.55–2.51 (2H, m, C**H**$_2$CH=CH), 2.44 (3H, s, C=CCH=CC**H**$_3$), 2.36–2.30 (2H, m, C**H**$_2CH_2$CH), 2.34 (3H, s, C**H**$_3$CC=O); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.9 (C), 145.1 (C), 141.8 (C), 138.1 (C), 136.0 (C), 132.3 (C), 131.89 (CH), 131.85 (C), 130.6 (CH), 130.5 (C), 130.5 (CH), 129.9 (CH), 129.7 (CH), 129.6 (2 × CH), 128.7 (2 × CH), 128.6 (CH), 128.5 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 117.1 (CH_2), 71.3 (CH_2), 70.6 (CH_2), 34.3 (CH_2), 32.5 (CH_2), 21.9 (CH_3), 20.2 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{29}H_{31}NNaO_4S]^+$ $[M+Na]^+$: 512.1872, found: 512.1871.

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5 Appendix

Herein is included the relevant publication discussed in the research & discussion section.

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Rhodium-Catalyzed Oxidative C−H Allylation of Benzamides with 1,3-Dienes by Allyl-to-Allyl 1,4-Rh(III) Migration

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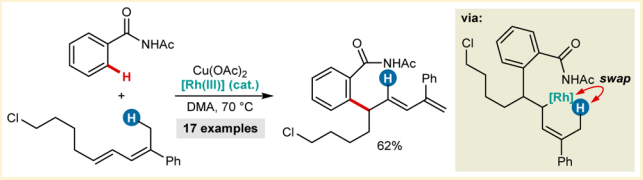
Supporting Information

ABSTRACT: The Rh(III)-catalyzed oxidative C−H allylation of *N*-acetylbenzamides with 1,3-dienes is described. The presence of allylic hydrogens *cis* to the less substituted alkene of the 1,3-diene is important for the success of these reactions. With the assistance of reactions using deuterated 1,3-dienes, a proposed mechanism is provided. The key step is postulated to be the first reported examples of allyl-to-allyl 1,4-Rh(III) migration.

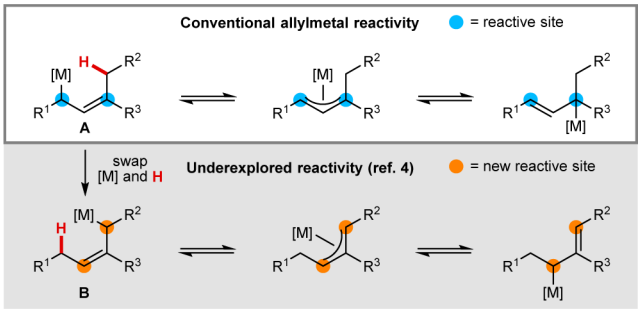


INTRODUCTION

Allylmetal species are important intermediates in organic synthesis.[1,2] For example, π-allylmetal species are usually electrophilic, and can be intercepted by diverse nucleophiles in allylic substitutions.[1] On the other hand, σ-allylmetal species are usually nucleophilic, and can be employed in a huge range of allylations of π-electrophiles.[2] Numerous catalytic, diastereoselective, and/or enantioselective variants of these processes have also been reported.[1,2]

A well-recognized feature of allylmetal reactivity is the often facile 1,3-transposition of the metal from one end of the allylic fragment to the other, which potentially enables new bond-forming reactions at either side (Scheme 1, top). Isomerizations

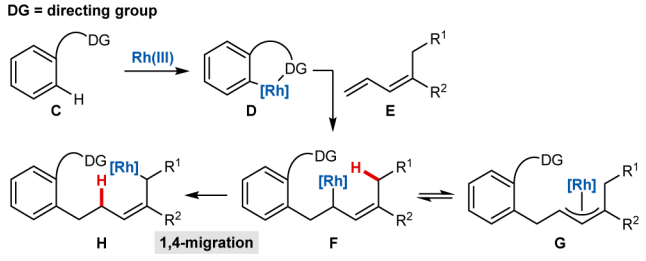
Scheme 1. Allylmetal Reactivity



of allylmetal species that open up reactions at sites *beyond* those resulting from conventional 1,3-allylic transposition would be highly enabling for reaction discovery.[3−5] As part of a program in enantioselective rhodium-catalyzed additions of allylboron reagents to imines,[3,4,6] we have described the allyl-to-allyl 1,4-Rh(I) migration of allylrhodium(I) species (as in **A** to **B**, Scheme 1).[4,7] This isomerization allows subsequent carbon−carbon bond formation at sites not immediately expected from the structure of the allylboron reagents (Scheme 1, bottom). Given the synthetic potential of this underexplored mode of reactivity, its investigation in other classes of reactions is warranted. In particular, demonstration of metals other than Rh(I) to engage in allyl-to-allyl 1,4-migration would be highly valuable.

In connection with our work on Rh(III)-catalyzed C−H functionalization[8,9] in combination with alkenyl-to-allyl 1,4-Rh(III) migration to prepare heterocyclic[10] and carbocyclic[11] products, we became interested in whether allyl-to-allyl 1,4-Rh(III) migrations would be possible.[12] Our design for investigating the feasibility of this migration is shown in Scheme 2. The

Scheme 2. System To Test Allyl-to-Allyl 1,4-Rh(III) Migration



directing-group-assisted cyclorhodation of substrate **C** with a Rh(III) complex to give rhodacycle **D** is well-known.[8] Migratory insertion of **D** with a 1,3-diene **E**, which contains allylic hydrogens *cis* to the less substituted alkene, would give allylrhodium species **F**, which is likely to be in equilibrium with the π-haptomer **G**.[13] If allyl-to-allyl 1,4-Rh(III) migration of **F** were then to occur, a new allylrhodium species **H** would form. Although the final fate of **H** could not be predicted, this process could serve as a valuable addition to the currently limited number of catalytic C−H functionalizations involving 1,3-dienes,[14] provided that high overall chemo-, regio-, and stereoselectivity is exhibited. Herein, we describe the successful

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use of allyl-to-allyl 1,4-Rh(III) migration in the oxidative C−H allylation of benzamides with 1,3-dienes. These reactions are distinct from other metal-catalyzed C−H allylations of arenes, which employ allylic electrophiles,[15] allenes,[16] or terminal alkenes[17] as the reaction partners.

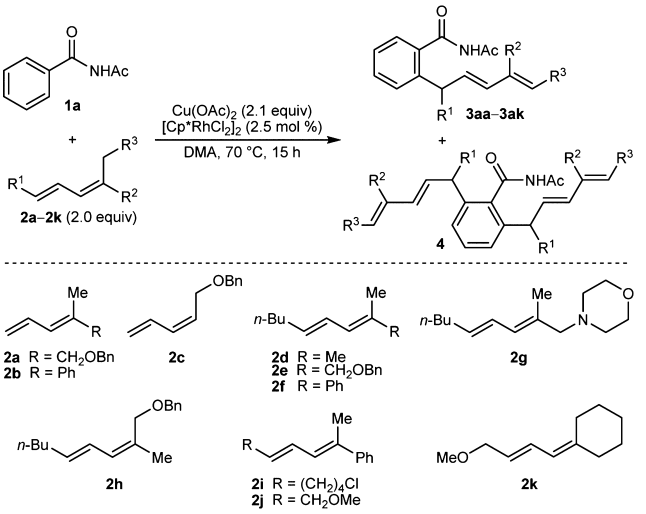
RESULTS AND DISCUSSION

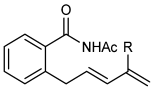
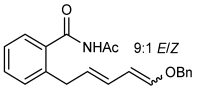
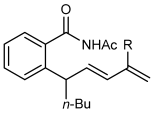
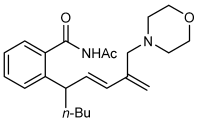
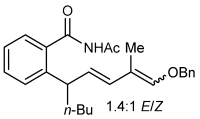
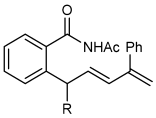
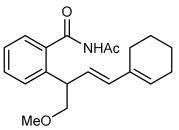
After attempting Rh(III)-catalyzed reactions of various aromatic substrates of type **C** with 1,3-dienes of type **E** (see Scheme 2),[18] we found that *N*-acetylbenzamides **1** gave productive reactions under oxidative conditions to form allylation products **3**. For example, the reaction of *N*-acetylbenzamide **1a** with diene **2a** in the presence of $[Cp^*RhCl_2]_2$ (2.5 mol %) and $Cu(OAc)_2$ (2.1 equiv) in DMA at 70 °C for 15 h gave product **3aa** in 50% yield (Table 1, entry 1). Other dienes **2b**−**2k**, containing either a methyl or a methylene group *cis* to the less substituted alkene, are also effective and gave products **3ab**−**3ak** in 31−82% yield (Table 1, entries 2−11). The mass balance in these reactions was mainly composed of unreacted starting materials. In some cases, a 1:2 ratio of benzamide and diene, respectively, was optimal to maximize the yield of the products **3** (entries 2, 4, 5, 7, 8, and 11). However, in other cases a 2:1 ratio of **1a**:**2** was chosen to minimize the formation of products **4**, which result from C−H functionalization at both *ortho*-positions of **1a** (entries 1, 3, 6, 9, and 10). In one reaction, the diallylated product **4ab** was isolated (entry 2). Dienes containing a terminal alkene are effective (entries 1−3), and hydrogen, phenyl, and various alkyl groups at the alkenes are well-tolerated. With **2a**, the product **3aa** is derived from loss of a hydrogen atom from the methyl substituent *cis* to the vinyl group, rather than from the benzyloxymethyl substituent *trans* to the vinyl group (entry 1). Diene **2c**, which contains a 1,2-disubstituted *Z*-alkene, reacted to give dienol benzyl ether **3ac** as a 9:1 mixture of *E*/*Z* isomers, along with traces of unidentified decomposition products (entry 3). Dienes **2d**−**2k**, which contain a 1,2-disubstituted alkene and a trisubstituted alkene, were also effective (entries 4−11). Here, carbon−carbon bond formation occurs exclusively at the 1,2-disubstituted alkene, at the carbon distal to the trisubstituted alkene. As with diene **2a** (entry 1), when there are different geminal alkyl groups at the trisubstituted alkene, the products are derived from loss of a hydrogen atom at the alkyl group *cis* to the disubstituted alkene (entries 4, 5, 7, and 8). This point is further exemplified by the outcomes with dienes **2e** and **2h**, which are geometric isomers of each other (entries 5 and 8). The reaction with **2h** did not go to completion, but dienol benzyl ether **3ah** was obtained in 31% yield as a 1.4:1 mixture of *E*:*Z* isomers (entry 8). No evidence of **3aa** was detected in this reaction.

Attention was then turned to the scope of the reaction with respect to the *N*-acetylbenzamide (Table 2). Benzamides containing a methyl group at the *para*, *meta*, or *ortho* positions (entries 1, 2, 5, and 6) are tolerated, as are those bearing *p*-methoxy (entry 3) or *p*-nitro substituents (entry 4). Electron-withdrawing substituents on the aromatic ring of the benzamide appear to be beneficial, as shown by the formation of **3dj** in 75% yield compared with a 46% yield for **3cj** (compare entries 3 and 4). C−H functionalization of a furan-containing substrate **5** is also possible, although the yield of the product **6** was modest (eq 1).

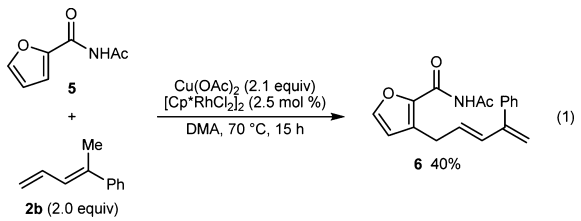
A possible catalytic cycle for these reactions begins with formation of $Cp^*Rh(OAc)_2$ from $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2$ (Scheme 3), which reacts with *N*-acetylbenzamide **1a** to give rhodacycle **7** and AcOH. Coordination and migratory insertion

Table 1. Scope of the 1,3-Diene[a]



entry	1,3-diene	product		R	yield (%)[b]
1[c]	**2a**		**3aa**	CH_2OBn	50
2	**2b**		**3ab**	Ph	69 (27)[d]
3[c]	**2c**		**3ac**		61
4	**2d**		**3ad**	Me	77
5	**2e**		**3ae**	CH_2OBn	77
6[c]	**2f**		**3af**	Ph	63
7	**2g**		**3ag**		60
8	**2h**		**3ah**		31
9[c]	**2i**		**3ai**	$(CH_2)_4Cl$	62
10[c]	**2j**		**3aj**	CH_2OMe	76
11	**2k**		**3ak**		82

[a]Unless stated otherwise, reactions were conducted using 0.30 mmol of **1a** and 0.60 mmol of **2**. [b]Yield of isolated product. [c]Conducted using 0.60 mmol of **1a** and 0.30 mmol of **2**. [d]Values in parentheses refer to the yield of the product **4ab** resulting from reaction at both *ortho* positions of **1a**.



of 1,3-diene **2d** at the less substituted alkene give rhodacycle **8**, in which there is also an allylrhodium(III) moiety. Acetolysis of

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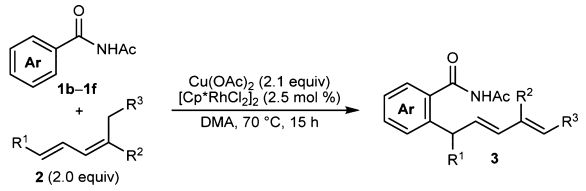
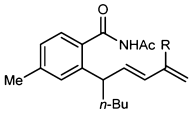
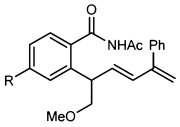
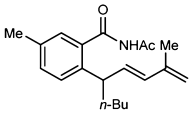
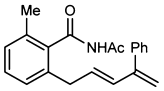
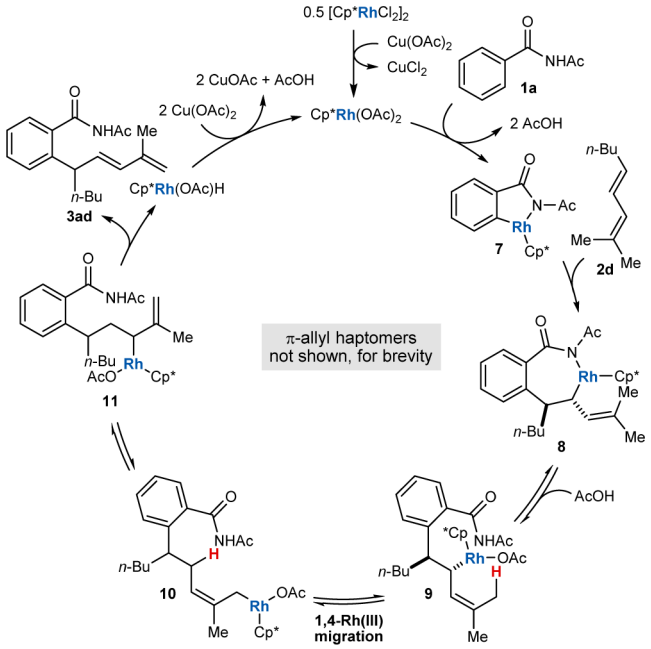
Table 2. Scope of the *N*-Acetylbenzamide[a]



entry	1,3-diene	product		R	yield (%)[b]
1	**2d**		**3bd**	Me	53
2	**2e**		**3be**	CH_2OBn	53
3[c]	**2j**		**3cj**	OMe	46
4[c]	**2j**		**3dj**	NO_2	75
5	**2d**		**3ed**		64
6	**2b**		**3fb**		98

[a]Unless stated otherwise, reactions were conducted using 0.30 mmol of **1** and 0.60 mmol of **2**. [b]Yield of isolated product. [c]Conducted using 0.60 mmol of **1** and 0.30 mmol of **2**.

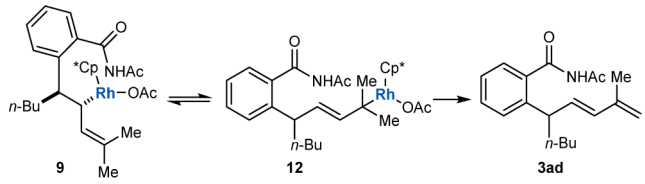
Scheme 3. Postulated Catalytic Cycle



8 gives allylrhodium(III) species **9**, which can undergo 1,4-Rh(III) migration[10−12] to the *cis*-allylic carbon to give a new σ-allylrhodium intermediate **10**. A $\sigma-\pi-\sigma$ isomerization of **10** provides σ-allylrhodium species **11**, which undergoes β-hydride elimination to give product **3ad** and Cp*Rh(OAc)H. Reaction of Cp*Rh(OAc)H with $Cu(OAc)_2$ (2.0 equiv) leads to reductive elimination to give AcOH and Cp*Rh(I), which is oxidized to regenerate $Cp^*Rh(OAc)_2$. Although we have proposed the acetolysis of **8** into **9**, we cannot discount the possibility that the directing group remains coordinated to rhodium in one or more of the subsequent intermediates.

An alternative mechanism involves the isomerization of **9** into σ-allylrhodium species **12**, which undergoes β-hydride elimination to give **3ad** (Scheme 4). If this mechanism was

Scheme 4. Alternative Mechanistic Pathway



operative, it would be expected that dienes **2e** and **2h**, which differ only in the geometry of the trisubstituted alkene, would react to provide similar outcomes. The fact that different products are obtained in their reactions with **1a** (Table 1, entries 5 and 8) suggests this pathway is less likely.

Further support for the mechanism proposed in Scheme 3 is provided by the reaction of **1a** with the hexadeuterated diene $[D]_6$-**2d** (Figure 1A). This experiment gave $[D]_n$-**3ad** in 67% yield, in which there was significant, but incomplete, deuterium transfer (78% D) from one of the CD_3 groups to the alkenyl carbon proximal to the benzene ring. This outcome may be rationalized by considering that $\sigma-\pi-\sigma$ isomerization of $[D]_6$-**10** could provide $[D]_6$-**11a** or $[D]_6$-**11b** (Figure 1B). Deuterium depletion can then occur by β-deuteride elimination of $[D]_6$-**11a** to give $[D]_5$-**3ad**, whereas β-hydride elimination of $[D]_6$-**11b** would give $[D]_6$-**3ad**.

Another outcome of the experiment shown in Figure 1A is partial deuterium depletion (88% D) at the alkenyl methylene of $[D]_n$-**3ad**. This result may be explained by reversible allyl-to-allyl 1,4-migration between $[D]_6$-**10**, $[D]_6$-**9**, and $[D]_6$-**10a**, which leads to deuterium−hydrogen exchange between the two *cis*-allylic substituents (Figure 1C).[4] The $\sigma-\pi-\sigma$ isomerization of $[D]_6$-**10a** would provide $[D]_6$-**11c**, from which β-deuteride elimination would give $[D]_5$-**3ad**, in which there is deuterium depletion at the alkenyl methylene group.

Regarding the actual mechanism of allyl-to-allyl 1,4-Rh(III) migration, there are a number of possibilities (Scheme 5). First, in a manner similar to that proposed for the alkenyl-to-allyl 1,4-Rh(III) migrations we described previously,[10,11] an acetate-promoted, concerted metalation−deprotonation of $[D]_6$-**9** would give rhodacycle **13**, which could undergo acetolysis to give **10**. Alternatively, **9** could undergo a C−H oxidative addition to give a Rh(V) hydride species **14**, which can then form **10** by a C−H reductive elimination. The participation of Rh(V) intermediates has been suggested in various other Rh(III)-catalyzed C−H functionalization reactions[19] and has gained some experimental and theoretical support.[20] Finally, **9** could undergo a σ-complex-assisted metathesis (σ-CAM)[12a,21,22] via **15** to give **10**.

To investigate the possibility of an acetate-assisted concerted metalation−deprotonation pathway to give **13**, the reaction of *N*-acetylbenzamide **1a** with 1,3-diene **2d** was conducted in a 9:1 mixture of DMA/D_2O (eq 2). The presence of D_2O would be expected to provide some of deuterated **3ad** as a result of deuteronolysis of **13**, as we have observed previously in related alkenyl-to-allyl 1,4-Rh(III) migrations.[10,11] In the event, D_2O markedly decreased the efficiency of oxidative C−H allylation. Nevertheless, **3ad** was isolated in 10% yield, but no deuterium

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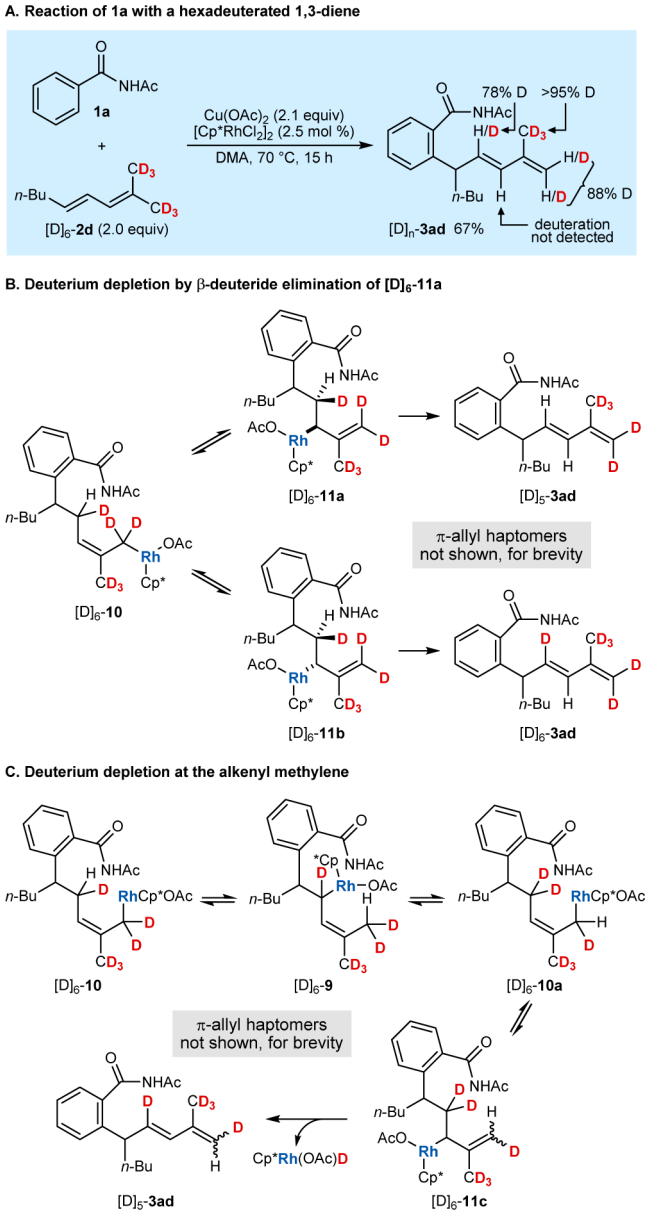
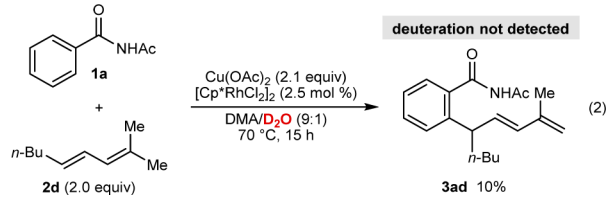


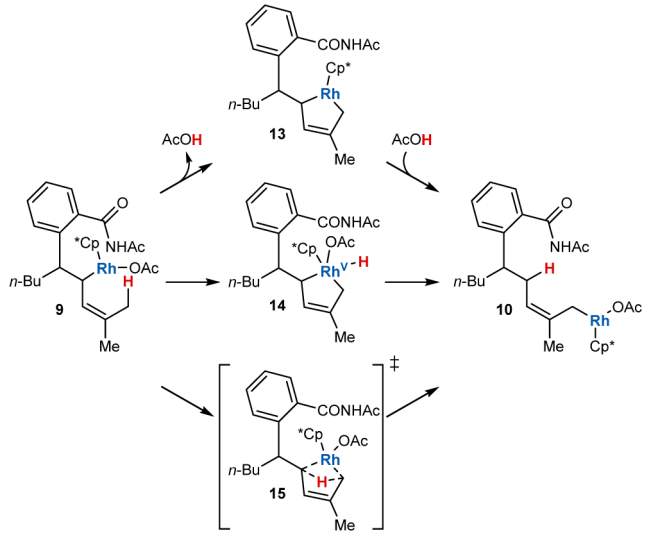
Figure 1. Investigation of deuterium transfer with 1,3-diene $[D]_6$-**3ad** and mechanistic rationale.



incorporation was detected. This result suggests that the intermediacy of **13** is less likely and that C−H oxidative addition/reductive elimination or σ-CAM pathways may be more probable mechanisms for allyl-to-allyl 1,4-Rh(III) migration.

Thus far, all of the 1,3-dienes tested contain allylic hydrogens *cis* to the less substituted alkene, which enables facile allyl-to-allyl 1,4-Rh(III) migration. To test whether 1,3-dienes lacking this structural feature would also be effective substrates, the reaction of **1a** (2.0 equiv) with 1,3-diene **14**, the *E*-isomer of diene **2c** (see Table 1, entry 3), was conducted (Figure 2A).

Scheme 5. Possible Mechanisms for 1,4-Rh(III) Migration



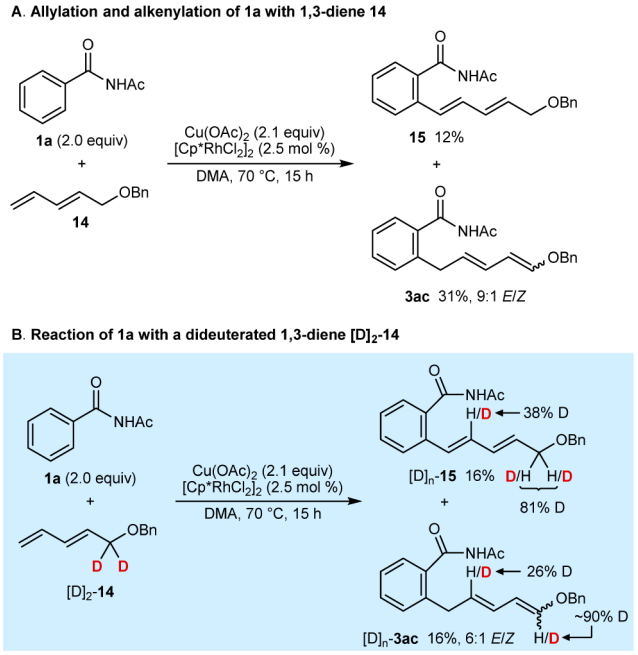


Figure 2. Reaction of a 1,3-diene lacking *cis*-allylic hydrogens.

This experiment did give allylation product **3ac** as a 9:1 mixture of *E*/*Z* isomers, but in a much lower yield of 31% compared with the 61% yield obtained when the corresponding *Z*-diene **2c** was used (Table 1, entry 3). In addition, alkenylation product **15** was isolated in 12% yield, which is notable as analogous alkenylation products were not formed in any of the reactions examined up until this point. The corresponding reaction conducted with dideuterated diene $[D]_2$-**14** gave deuterated products $[D]_n$-**15** and $[D]_n$-**3ac**, each in 16% yield, in which appreciable 1,4-deuterium transfer was observed (Figure 2B). This time, $[D]_n$-**3ac** was obtained as a 6:1 mixture of *E*/*Z* isomers.

The appreciable 1,4-deuterium transfer in both $[D]_n$-**15** and $[D]_n$-**3ac** suggests a complex mechanism is operative, involving the interconversion between numerous allylrhodium(III) species by $\sigma-\pi-\sigma$ isomerization (1,3-allylic transposition), *E*/*Z* isomerization, and allyl-to-allyl 1,4-Rh(III) migration

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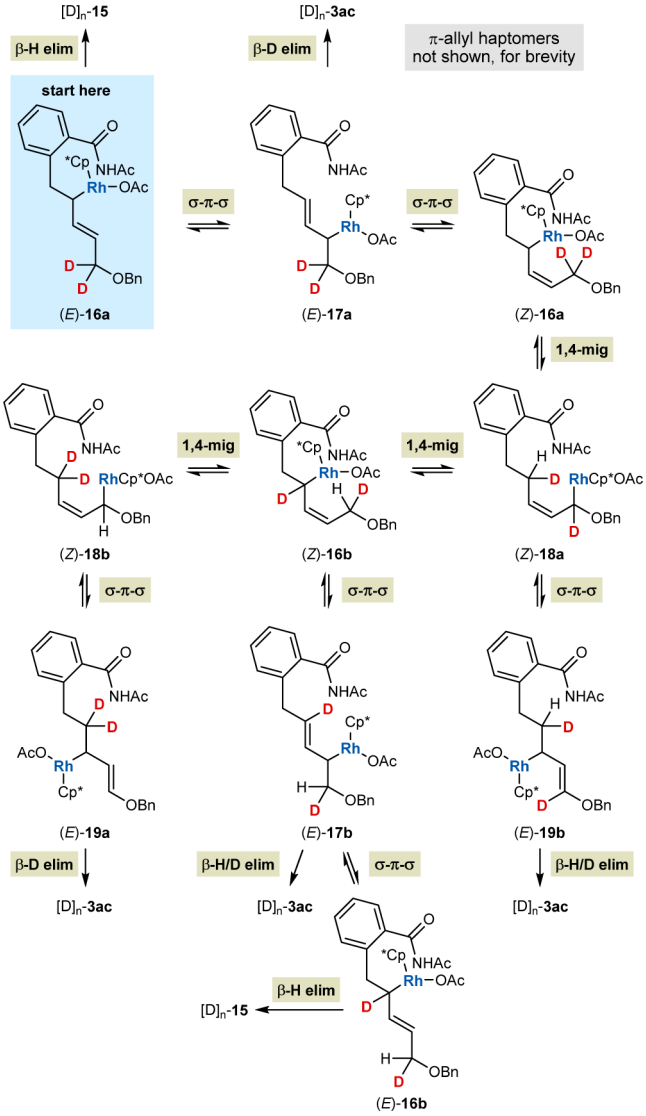
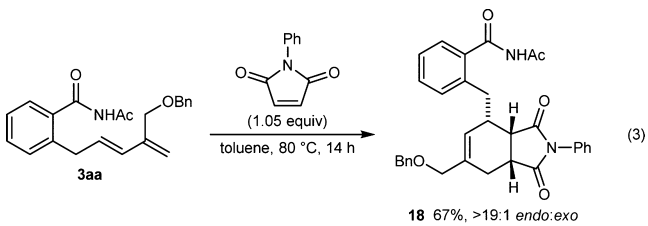
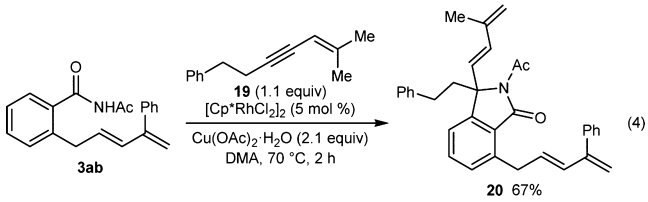
Scheme 6. Mechanistic Rationale To Explain the Outcome of the Reaction of 1a with $[D]_2$-14



pathways (Scheme 6). First, the reaction of **1a**, $[D]_2$-**14**, and $[Cp^*RhCl_2]_2$ following the initial steps of the catalytic cycle shown in Scheme 3 leads to the formation of (*E*)-**16a**, which can give a dideuterated isomer of alkenylation product $[D]_n$-**15** by *β*-hydride elimination. Intermediate (*E*)-**16a** can also undergo *σ*−*π*−*σ* isomerization into (*E*)-**17a**, which, after *β*-deuteride elimination, would give a monodeuterated allylation product $[D]_n$-**3ac**. Alternatively, (*E*)-**16a** can undergo *σ*−*π*−*σ* isomerization with concomitant *E*/*Z* isomerization to give (*Z*)-**16a**, from which a series of reversible allyl-to-allyl 1,4-Rh(III) migrations involving either a 1,4-deuterium or a 1,4-hydrogen shift can give new allylrhodium(III) species (*Z*)-**18a**, (*Z*)-**16b**, and (*Z*)-**18b**. These latter three intermediates can undergo *σ*−*π*−*σ* isomerization to provide (*E*)-**19a**, (*E*)-**17b**, and (*E*)-**19b**, respectively, from which *β*-hydride or *β*-deuteride elimination would give various mono- and dideuterated isomers of $[D]_n$-**3ac**. Finally, *σ*−*π*−*σ* isomerization of (*E*)-**17b** into (*E*)-**16b** followed by *β*-hydride elimination would provide a dideuterated isomer of $[D]_n$-**15**.

To demonstrate the synthetic utility of the allylation products, 1,3-diene **3aa** was heated with *N*-phenylmaleimide in toluene at 80 °C to give Diels−Alder adduct **18** in 67% yield with >19:1 *endo*:*exo* selectivity (eq 3). Furthermore, allylation





product **3a** reacted smoothly with 1,3-enyne **19** in a Rh(III)-catalyzed oxidative annulation to give isoindolinone **20** in 67% yield (eq 4). In this reaction, 1,3-enyne **19** functions as a one-carbon annulation partner as a result of an alkenyl-to-allyl 1,4-Rh(III) migration.[10]

CONCLUSION

In summary, we have described the oxidative C−H allylation of *N*-acetylbenzamides with 1,3-dienes, which involve, to our knowledge, the first reported examples of allyl-to-allyl 1,4-Rh(III) migration. This new mode of Rh(III) reactivity enables reaction at sites not available from conventional 1,3-allylic transposition. The results of reactions of deuterated 1,3-dienes indicate that reversible interconversion of numerous allylrhodium(III) species by *σ*−*π*−*σ* isomerization, *E*/*Z* isomerization, and allyl-to-allyl 1,4-Rh(III) migration pathways occurs on timescales that are rapid compared to product-forming *β*-hydride (or *β*-deuteride) elimination steps. This work suggests that the possibility that these isomerization processes might occur should be taken into consideration in any future design of new reactions involving allylrhodium(III) species. Further investigation of the synthetic potential of allyl-to-allyl 1,4-metal migrations is ongoing in our group.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b06884.

Experimental procedures and full spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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