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Rhodium(II)-catalysed intramolecular C–H insertion α- to oxygen: reactivity, selectivity and applications to natural product synthesis

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The selective functionalisation of C‑H bonds is a powerful strategy for the construction of organic molecules and the Rh(II)-catalysed C‑H insertion reaction is a particularly robust and useful tool for this purpose. This review discusses the insertion of Rh(II) carbenes into C‑H bonds that are activated by α-oxygen substituents, focusing on the trends that have been observed in reactivity and selectivity, and the applications of this reaction to the total synthesis of complex natural products.

Introduction

The selective functionalization of C–H bonds has been an area of great interest and has been extensively studied over the last 30 years. It offers new strategic approaches from simple, readily available precursors, for the synthesis of complex synthetic targets, such as natural products. It is a useful alternative to traditional synthetic transformations offering great potential to improve efficiency in complex molecule synthesis and changing the way that these syntheses are planned.[1]

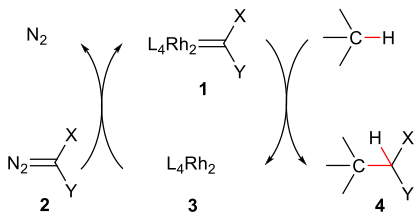
The insertion of a carbene into a C–H bond has attracted considerable interest because of its potential in forming C–C bonds. However, in the early stages of development, carbene chemistry showed limited synthetic utility due to a general lack of selectivity.[2] Nevertheless, with significant progress in the development and understanding of carbene C–H insertion reactions has come major advances in selectivity, making this a powerful tool for the synthetic chemist.[3, 4]

Commonly, carbenes can be generated from diazocompounds, thermally, photochemically or by the use of a transition metal. The latter led to the major breakthrough in this field: in the early 80's, Teyssie and co-workers reported, for the first time, the rhodium-catalysed intermolecular reactions of ethyl diazoacetate with alkanes.[5, 6] Despite modest selectivity, these results showed the synthetic applicability of metal-catalysed C–H insertion and constituted the starting point for decades of subsequent research and improvements. Great advances in intra- and intermolecular catalytic asymmetric C–H activation have been made since then, allowing diastereo- and enantioselective generation of a diverse range of compounds in this fashion.[7-9]

C–H insertion mechanism

The majority of early studies employed copper catalysts, with limited synthetic applications. Since then, rhodium(II) catalysts have generally been established as the most effective and versatile catalysts for diazo decomposition. The ability to form Rh–Rh bonds is thought to be a critical property of rhodium(II) complexes, allowing the formation of dirhodium-bridged cages within a 'paddlewheel' structure.[9]

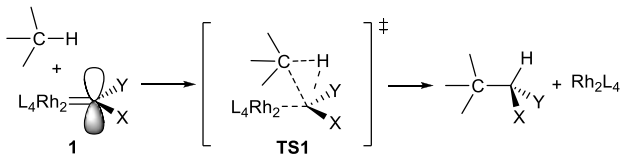
It has generally been assumed that the rhodium(II)-catalysed C–H insertion involves a rhodium carbene complex and that the catalytic cycle consists of three steps (Scheme **1**). The intermediate metal-stabilised carbene **1** is generated by complexation of the α-carbon of diazo compound **2** by the rhodium(II) catalyst, Rh_2L_4 (**3**), then extrusion of nitrogen, followed by C–H insertion with concomitant C–C bond formation, to give the C–H insertion product **4**.



Scheme 1 Catalytic cycle for rhodium(II)-catalysed C–H insertion reactions.

The mechanism of rhodium-catalysed C–H insertion reactions has been the subject of debate. Recent computational studies, by Nakamura and co-workers[10] supported the mechanism originally proposed by Doyle in 1993.[11] The key step proceeds via overlap of the vacant 2p orbital of the strongly electrophilic metal carbene **1** with the σ-orbital of the C–H bond, resulting in C–H activation and C–C bond formation occurring in a single step,

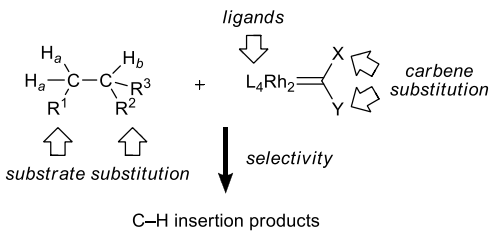
with retention of configuration, through a three-centered transition state **TS1** with a small activation energy (Scheme **2**). These studies also confirmed that only one of the two rhodium atoms acts as a carbene-binding site throughout the reaction. The other rhodium atom assists the C–H insertion reaction acting as a ligand for the first one, enhancing the electrophilicity of the carbene moiety and also facilitating the cleavage of the Rh–C bond.[10]



Scheme 2 Proposed three-centered transition state for rhodium(II)-catalysed C–H insertion reactions.

Factors influencing reactivity and selectivity

The selectivity of rhodium-catalysed C–H insertion is predominantly influenced by stereoelectronic effects and can also be subject to steric influences. Factors, such as the reactivity of the metal carbene, which can be modulated by the carbene substitution and by the ligands on the metal, can have a profound influence on reaction outcomes. Electronic and conformational effects of the substrate, including substitution adjacent to the carbon bearing the hydrogen undergoing insertion, also have a significant influence on the selectivity (Scheme **3**). The electrophilicity of the metal carbene intermediate has a marked influence on the chemo-, regio- and stereoselectivity of C–H insertion. The degree of electrophilicity of the metal-carbene intermediate is governed by the nature of the metal catalyst and the metal carbene substitution.



Scheme 3 Factors that influence selectivity.

Rhodium catalysts: Electronic and steric ligand effects

Ligands on the metal have been shown to have significant influences, often leading to a complete change in chemo-[12, 13] and/or regioselectivity[11] Increasing the electron-withdrawing character of the ligand increases the electrophilicity of the intermediate metal carbene and consequently increases its reactivity, usually to the detriment of selectivity. On the other hand, decreasing the electron-withdrawing ability of the ligand decreases the reactivity of the metal carbene intermediate and often leads to an enhancement of selectivity (Fig. **1**).[14, 15]

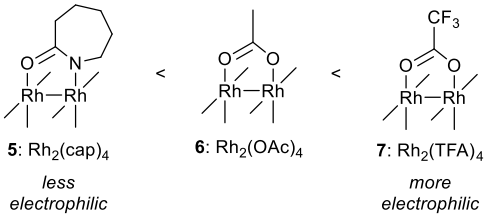


Fig. 1 Electrophilicity of dirhodium tetracaprolactamate (**5**), tetraacetate (**6**) and tetrakis(trifluoroacetate (**7**).

Due to their proximity to the reacting carbene centre, ligands on the metal have an important role to play in determining stereoselectivity in many C–H insertion reactions. Over the last two decades, significant effort has focussed on the development of chiral catalysts for asymmetric C–H insertion, allowing ligand-controlled diastereo- and enantioselectivity. A wide range of chiral rhodium(II) catalysts have been developed. The most extensively used rhodium catalysts belong to the family of rhodium carboxylates and rhodium carboxamidates. Selected examples are shown in Fig. **2**.

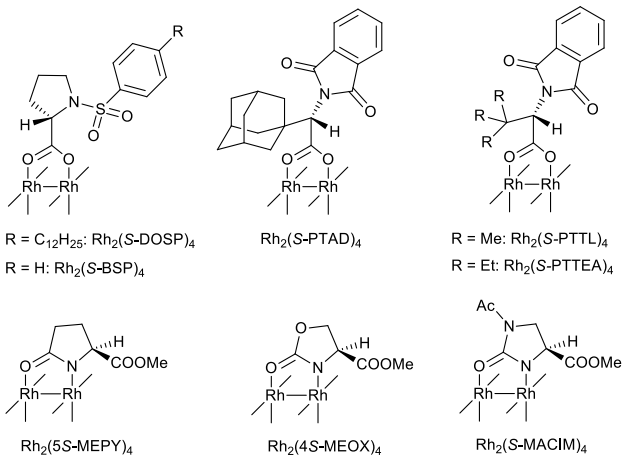


Fig. 2 Examples of chiral rhodium catalysts.

Highly reactive metal carbene intermediates are usually generated by extrusion of nitrogen from diazocarbonyl compounds with a metal catalyst. These metal carbene intermediates can be classified into four major groups according to their functionality (Fig. **3**). The acceptor/acceptor and acceptor metal carbenes, **8** and **9**, respectively, are more reactive than the donor/acceptor metal carbenes **10**, because acceptor groups increase their electrophilicity, whereas the donor group has a stabilizing effect, resulting in increased selectivity. Acceptor/acceptor and acceptor metal carbenes have largely been used for intramolecular reactions where site selectivity can be induced by electronic and conformational biases of the substrate, whereas donor/acceptor metal carbenes allow highly selective intermolecular C–H functionalisation.[8] "Purely donor" rhodium carbenes **11** are relatively rare in the literature, largely owing to the hazards associated with the synthesis of required unstabilised diazo precursors. However, an alternative route to

these intermediates has been reported by Cossy *et al.*, where the rhodium carbene is generated by ring opening of cyclopropenes. Despite reduced electrophilicity, these intermediates underwent facile intramolecular C–H insertion reactions.[16, 17]

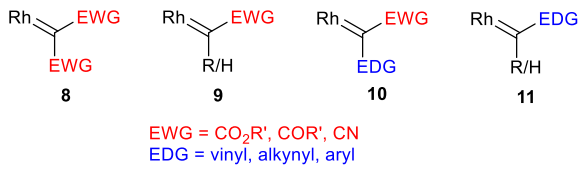


Fig. 3 Classification of intermediate rhodium carbenes.

Electronic and conformational effect of the substrate

From an electronic perspective, C–H insertion preferentially occurs at sites that stabilize the incipient positive charge at carbon. Electronic influences include preferential insertion into tertiary over secondary C–H bonds, and secondary over primary C–H bonds (Fig. **4**),[11, 18, 19] inhibition of insertion into C–H bonds adjacent to electron withdrawing groups (EWG),[20, 21] and promotion of insertion into C–H bonds adjacent to electron donating groups (EDG).[22-24] However, steric and conformational effects, notably steric interactions involving the rhodium catalyst, can override electronic-control and the outcome of reactions is often finely balanced between these factors.[11, 19, 25]

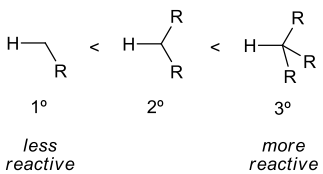


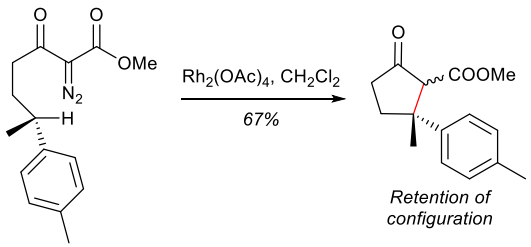
Fig. 4 C–H reactivity increases with substitution.

Intramolecular reactions

In the case of intramolecular reactions, the factors outlined above, including retention of configuration at the site of C–H insertion,[26] remain in force. In addition, there is a strong regioselectivity for 1,5-insertion to form 5-membered rings.[27-29] Due to the challenges of regioselectivity, early C–H insertion research concentrated on intramolecular reactions. The metal carbene and the reacting C–H bond, being connected through a suitable tether, allow a regioselective transformation governed by the preferential formation of 5-membered rings.

Early investigations demonstrated the broad utility of dirhodium tetraacetate and led to increased understanding of chemo- and regioselectivity in systems capable of intramolecular reactions. In 1982, Wenkert and Taber independently described the preference of acceptor/acceptor and acceptor metal carbenes to form cyclopentanone rings via 1,5-insertion.[27, 28] Taber and co-workers subsequently showed the regiochemical preference for insertion into a tertiary C–H bond over a secondary C–H bond[18] and demonstrated that intramolecular insertion occurs with retention of configuration (Scheme **4**).[26] Subsequently, interest in this area has consistently grown, resulting in significant further investigations, notably concerning stereoelectronic effects, enabling control of site- and stereoselectivity of intramolecular cyclisations.[12, 13, 29, 30]

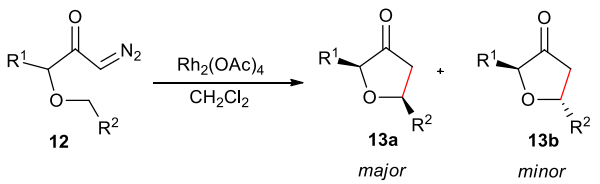
Scheme 4 Retention of configuration in the C–H insertion *en route* to (+)-α-cuparenone.



Intramolecular C–H insertion reactions adjacent to oxygen

Regioselectivity and stereoelectronic effects

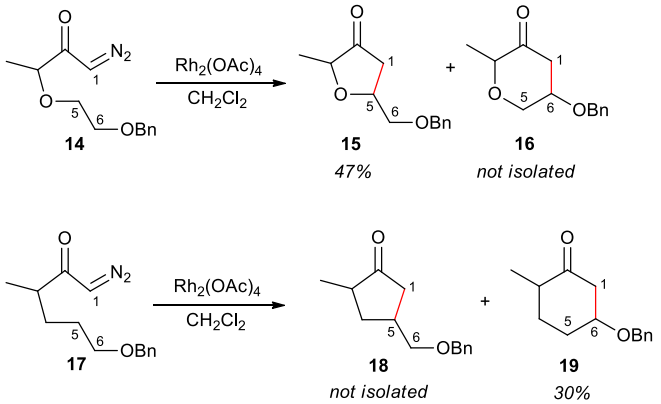
An oxygen atom can have important activating and directing influences on the outcome of intramolecular C–H insertion reactions. The early work of Taber suggested that some stereoelectronic effects are important control elements in C–H insertion reactions. Further studies on stereoelectronic effects, carried out by Adams and co-workers, showed that insertion into a C–H bond adjacent to an ether oxygen was highly favoured compared to unactivated aliphatic C–H bonds.[31] A variety of 3(2*H*)-furanones **13** were synthesised from diazoketones **12**, in modest to good yields with complete



regioselectivity for the C–H bond adjacent to the ether oxygen (Scheme **5**). Stereoselectivity in favour of the 2,5-*cis*-disubstituted products **13a**, was also observed.

Scheme 5 *cis*-Diastereoselectivity in the synthesis of 3(2*H*)-furanones.

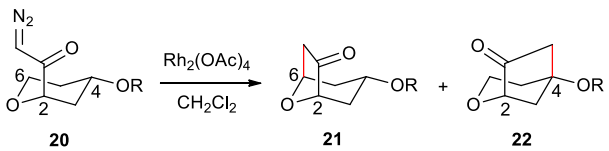
When two ether functionalities are present in a diazo precursor, such as **14**, C–H insertion leading to a 5-membered ring **15** is preferred, with no 6-membered ring **16** isolated (Scheme **6**).[31] However, when only the C–H bond leading to a 6-membered cyclic ether was activated (diazo precursor **17**), none of the cyclopentanone product **18** was isolated. Cyclohexanone **19** and carbene-derived dimer were the only isolated products, showing the dominance of heteroatom activation over the propensity for 5-membered ring formation.



Scheme 6 α-Oxygen activation and 5- vs 6-membered formation.

Subsequently, Adams examined regioselectivity in the transannular cyclisation of 2-diazoketo tetrahydropyrans **20**. They noted that increased electron-withdrawing capacity of the group at C_4 correlated with enhanced selectivity for C_6–H insertion product **21** over C_4–H insertion product **22** (Table **1**).[32] Nevertheless, C–H insertion at the C_6 position is favoured in all cases, owing to the short endocyclic C–O bond of the tetrahydropyran.

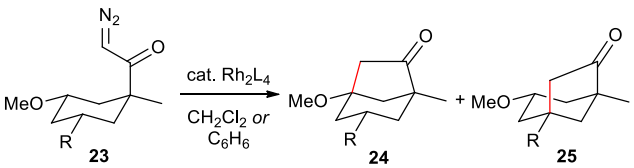
Table 1 Regioselective transannular C–H insertion of 2-diazoketo tetrahydropyrans.



R	Ratio (21/22)
Me	24:1
TBDPS	76:1
Ac	> 99:1
H	5.9:1

To further explore the stereoelectronic influence of substituents with electron donating capabilities, Adams synthesized another series of diazoketones, **23**, where steric and conformational variations were minimised (Table **2**).[22] They demonstrated stereoelectronic control, whereby insertion at the more electron-rich C–H bond is favoured (entry 1), except where steric effects dominate (entry 2). The azido group was shown to be particularly effective at activating the adjacent C–H bond (entry 3) and this selectivity was enhanced by electron-rich ligands on the catalyst, *i.e.* caprolactamate (entry 4).

Table 2 Stereoelectronic control in transannular C–H insertions.

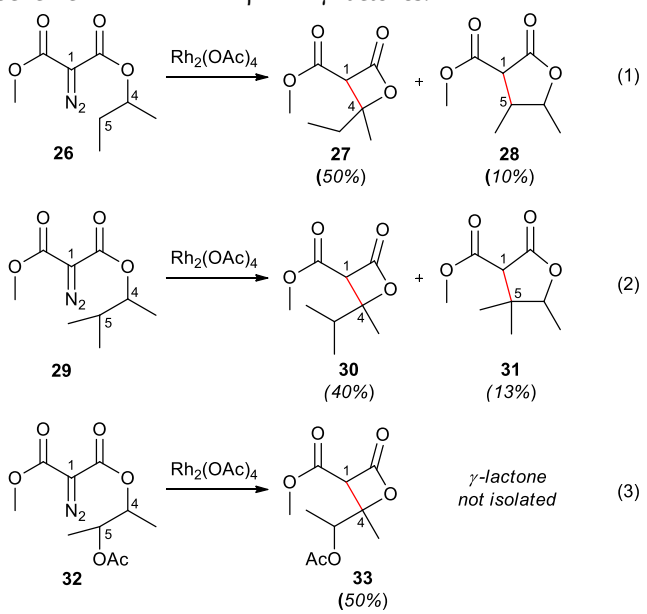


Entry	L	R	Yield (%)	Ratio 24/25
1	OAc	OAc	65	> 99:1
2	OAc	*i*-Pr$_3$SiO	94	6:1
3	OAc	N_3	56	1:8
4	cap	N_3	83	1:30

4-Membered rings: β-lactones

Although the formation of four-membered rings is uncommon, there are examples where activation by oxygen is sufficient to promote 1,4-C–H insertion.[33, 34] Lee and co-workers investigated β- versus γ-selectivity in a lactone formation via $Rh_2(OAc)_4$-catalysed C–H insertion of diazomalonates **26**, **29** and **32**.[35] A preference was observed for 4-membered ring formation leading to **27** in preference to **28**, resulting from the C–H insertion α- to an ester oxygen, when the only methine group in the substrate is located adjacent to oxygen (Scheme **7**, eq. 1).

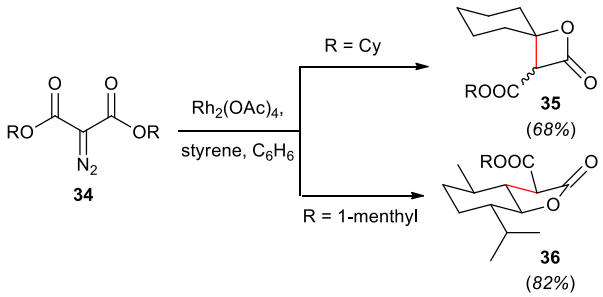
Scheme 7 Formation of β- and γ-lactones.



When both the 4- and 5-positions are tertiary, activation by oxygen still dominates, providing the β-lactone **30** and a smaller quantity of the γ-lactone **31** (Scheme **7**, eq. 2). The complete selectivity for β-lactone formation observed with substrate **32** (Scheme **7**, eq. 3), where both the 4- and 5-positions are activated by oxygen substituents, highlights the difficulty in predicting

product outcomes due to the complex interplay of steric, electronic and conformational factors.

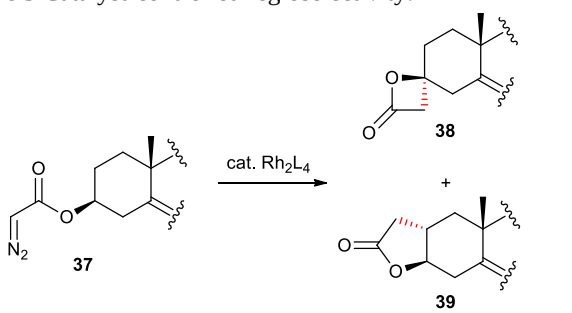
An interesting example of the influence of conformation and sterics on the formation of 4-membered rings is illustrated in the work of Chelucci and co-workers. They observed the formation of bicyclic β- and γ-lactones (**35** and **36)** while investigating the catalytic decomposition of diazomalonic esters **34** in the presence of excess styrene (Scheme **8**). In this case, intramolecular C–H insertion occurs in preference to intermolecular cyclopropanation. Metal carbene insertion into the less hindered methylene C–H bond forming γ-lactones occurs when four-membered ring formation is hindered due to steric and/or conformational effects.[36]



Scheme 8 Steric and conformational effects on 4- vs 5-membered ring formation.

Competition between β- and γ-lactone formation was also reported by Doyle and co-workers for the C–H insertion of cholest-5-en-3β-yl diazoacetate (**37**) and other steroidal diazoacetate derivatives.[25] Regioselectivity was strongly influenced by the choice of catalyst, with (*S*)-configured catalysts promoting selective formation of β-lactone **38** and (*R*)-configured catalysts favouring the formation of γ-lactone **39** (Table **3**).

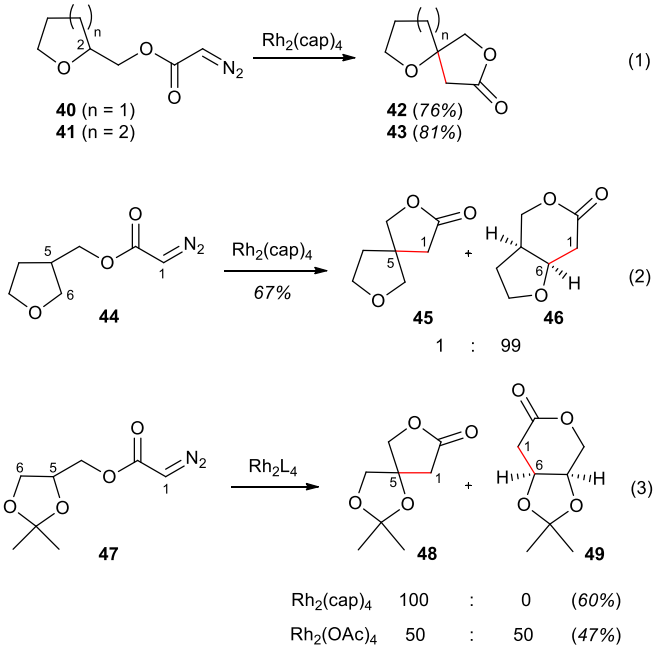
Table 3 Catalyst-controlled regioselectivity.



Entry	Catalyst	Yield (%)	Ratio 38/39
1	Rh_2(5*S*-MEPY)$_4$	74	33:67
2	Rh_2(5*R*-MEPY)$_4$	81	94:6
3	Rh_2(4*S*-MEOX)$_4$	80	10:90
4	Rh_2(4*R*-MEOX)$_4$	81	89:11

5-, 6- and 7-Membered rings

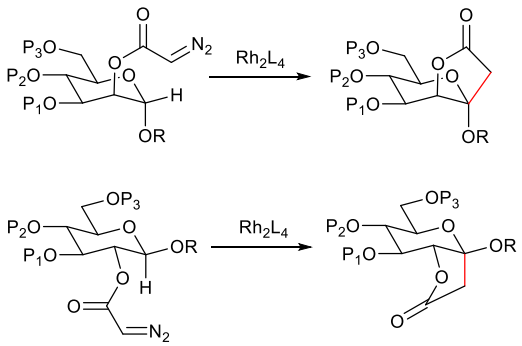
Intramolecular C–H insertion reactions adjacent to an oxygen atom, have been used for the construction of a wide range of carbo- and heterocycles. Doyle and co-workers reported the formation of spirolactones, from dirhodium(II)-catalysed diazo decomposition, with regioselective C–H insertion (Scheme **9**).[23] Rh_2(cap)$_4$-catalysed decomposition of diazoacetates **40** and **41**, derived from tetrahydrofurfuryl alcohol and tetrahydropyran-2-methanol, respectively, provided spirolactones **42** and **43** in good yields (Scheme **9**, eq. 1). Insertion at the C_2 position is particularly favourable due to: (1) five-membered ring formation, (2) activation by the adjacent ether oxygen, and (3) trisubstitution at the reaction site.



Scheme 9 Synthesis of spiro- and bicyclo- compounds via C–H insertion.

In contrast, diazoacetate **44** places the activating oxygen atom one bond further away from the diazo group (eq. 2). Thus, there is competition between tertiary C–H insertion leading to five-membered ring **45** and the α-oxygen activating effect, leading to six-membered ring **46**. The reaction gave very high selectivity for the [4.3.0]-bicyclo compound **46**, with only trace quantities of the 2,7-dioxaspiro[4.4]nonane **45**, demonstrating the dominance of oxygen activation over the usual preference for five-membered ring formation and insertion into a tertiary C–H bond. Interestingly, acetonide **47**, which is activated by α-oxygen for both 5- and 6-membered ring formation, gives equal quantities of **48** and 4**9** using $Rh_2(OAc)_4$ as catalyst, whereas Rh_2(cap)$_4$ catalysis provides exclusively spirolactone **48** via 1,5-C–H insertion (eq. 3). Wood and co-workers also reported the synthesis of spirolactones *via* rhodium(II)-catalysed C–H insertion as part of model studies towards the total synthesis of syringolides.[37]

Lecourt and coworkers reported a rhodium carbene-promoted activation of the anomeric C–H bond of protected carbohydrates, enabling the stereospecific preparation of both α- and β-ketopyranosides (Scheme **10**).[38] In this case, C–H insertion at the anomeric position is facilitated by the formation of a five-membered ring and activation of the tertiary C–H bond by methoxy substitution.



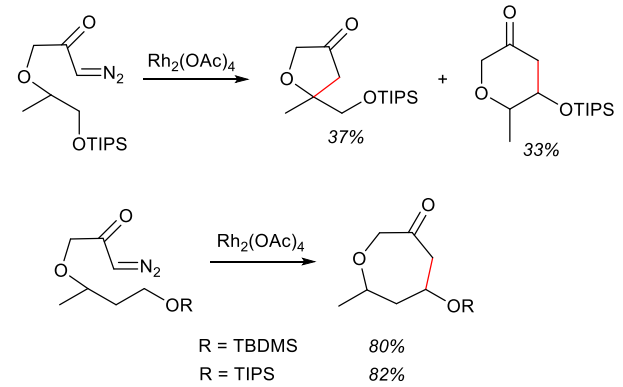
Scheme 10 Synthesis of α- and β-ketopyranosides via C‑H insertion.

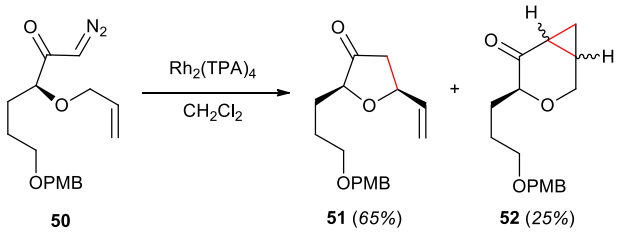
Lee and co-workers developed a method for the synthesis of tertiary alcohols from secondary alcohols (Scheme **11**, eq. 1),[39] proceeding with retention of configuration. Subsequently, Lee reported a related method for the asymmetric synthesis of secondary alcohols from primary alcohols (eq. 2),[40] *via* 3(2H)-furanones. During these studies, Lee observed the preferential formation of 6- and 7-membered rings over 5-membered rings, showing that the intramolecular insertion of a metal carbene into a C–H bond adjacent to trialkylsilyl ether is especially favorable (Scheme **12**).

Scheme 12 Formation of 6- and 7-membered rings via C‑H insertion α- to silyloxy groups.

Anomalous C–H insertion

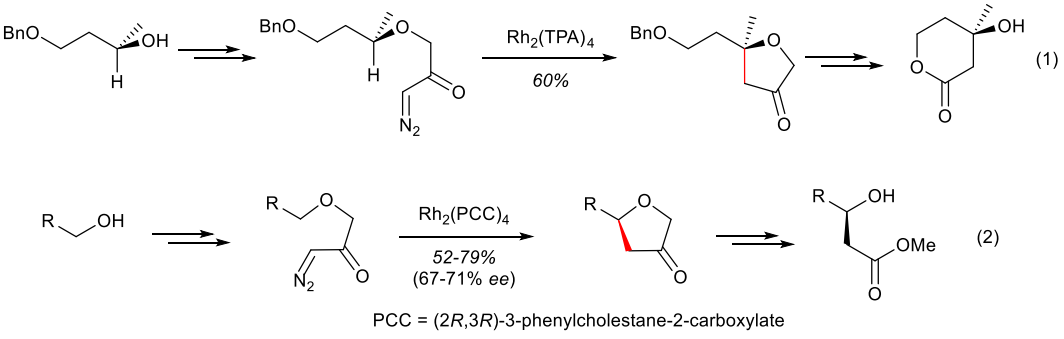
In the course of their studies towards the synthesis of neoliacinic acid,[41] Clark and co-workers treated allyl ether **50** with cat. $Rh_2(TPA)_4$ to give vinyl-substituted 3(2H)-furanone **51** by intramolecular C‑H insertion (Scheme **13**). Although the yield was reasonable, cyclopropanation to give **52**, was a significant competing process.



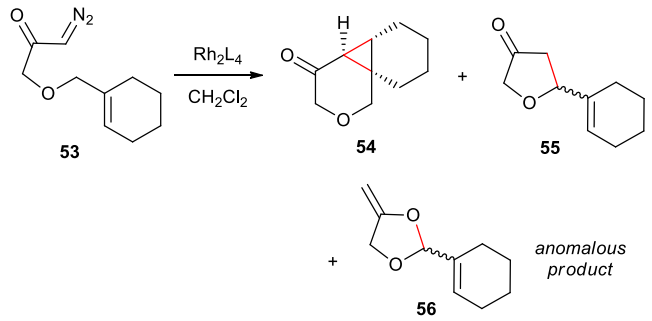


Scheme 13 Competition between allyl ether C‑H insertion and intramolecular cyclopropanation.

In order to improve the selectivity for C–H insertion, Clark investigated cyclisation reactions of some simple substrates related to **50** (Scheme **14**). Rhodium carbenes derived from **53** provided not only the expected cyclopropanation and C‑H insertion products, **54** and **55** respectively, in varying ratios, but also enol acetal **56**. The formation of **56** was particularly favoured by the use of highly electrophilic rhodium catalysts, eg. $Rh_2(TFA)_4$. They also showed that formation of the anomalous product is not restricted to C–H bonds of allylic ethers.[42] Several other groups have also observed this unusual behaviour from metal carbene reactions.[43-45]

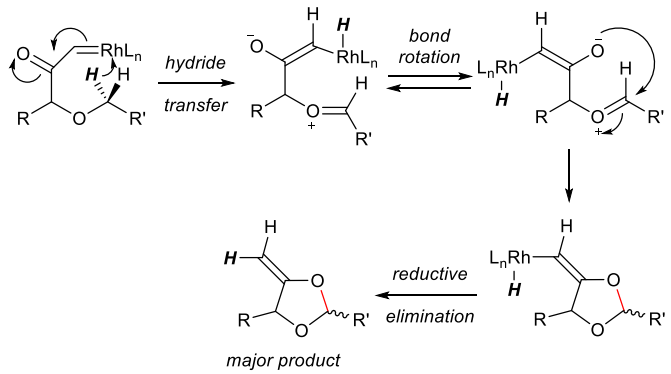


Scheme 11 Synthesis of tertiary alcohols from secondary alcohols and asymmetric synthesis of secondary alcohols from primary alcohols via C–H insertion reactions.



Scheme 14 Formation of an 'anomalous' product.

Clark and co-workers carried out further experiments to better understand and elucidate the mechanism of this anomalous intramolecular C–H insertion reaction. They proposed a mechanism consistent with the results with deuterium-labeled substrates. Firstly, an enolate is formed by oxygen-assisted hydride migration to the rhodium center. Bond rotation then allows C–O bond formation by trapping of the oxonium ion with the enolate oxygen. Subsequent reductive elimination then allows the formation of the acetal product and catalyst regeneration (Scheme **15**).[46, 47]



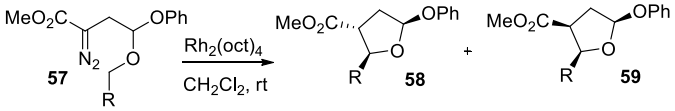
Scheme 15 Mechanism proposed by Clark and co-workers for the 'anomalous' C‑H insertion.

Diastereo- and enantioselectivity of C–H insertion α to oxygen

5-membered rings: 3(2H)-furanones and lactones

McKervey and co-workers demonstrated the synthesis of disubstituted 3(2*H*)-furanones from γ-alkoxy-α-diazo-β-ketoesters with complete regioselectivity and diastereoselectivities up to 61% de, combining a chiral auxiliary in the ester moiety and a chiral catalyst.[48] Taber and co-workers have used the reaction of γ-alkoxy-α-diazo esters (**57**) for the stereoselective synthesis of highly functionalized tetrahydrofurans (**58** and **59**).[49, 50] They observed that the diastereoselectivity of the cyclisation improved as the electron-withdrawing ability of the substituent connected to the ether oxygen increased (Table **4**).

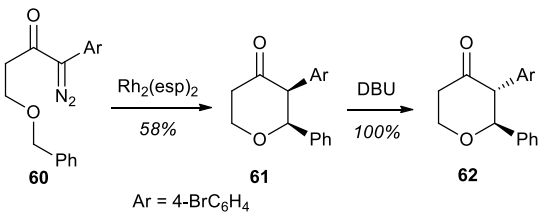
Table 4 Stereoselective synthesis of highly functionalized tetrahydrofuran.



Entry	R	Yield (%)	Ratio (58/59)
1	4-$MeOC_6H_4$	89	1.7:1
2	CH_3	93	4:1
3	$MeOCH_2$	92	8:1
4	$PhOCH_2$	89	11.4:1

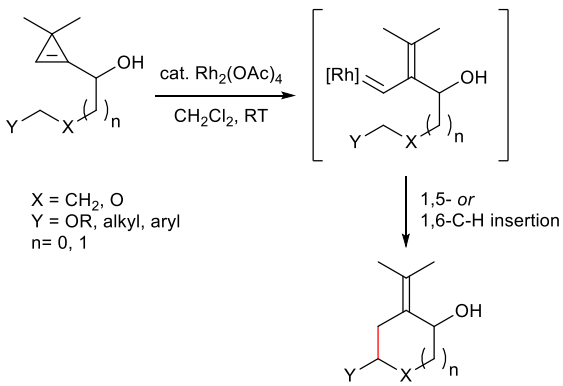
6-membered rings: Diastereoselectivity

While investigating the formation of cyclohexanones by rhodium-mediated C–H insertion, Taber and coworkers observed that donor/acceptor diazoketone **60** produced cis-tetrahydropyranone **61** when treated with $Rh_2(esp)_2$ (Scheme **16**). Equilibration to the thermodynamic trans- product **62** was effected by DBU.[51]



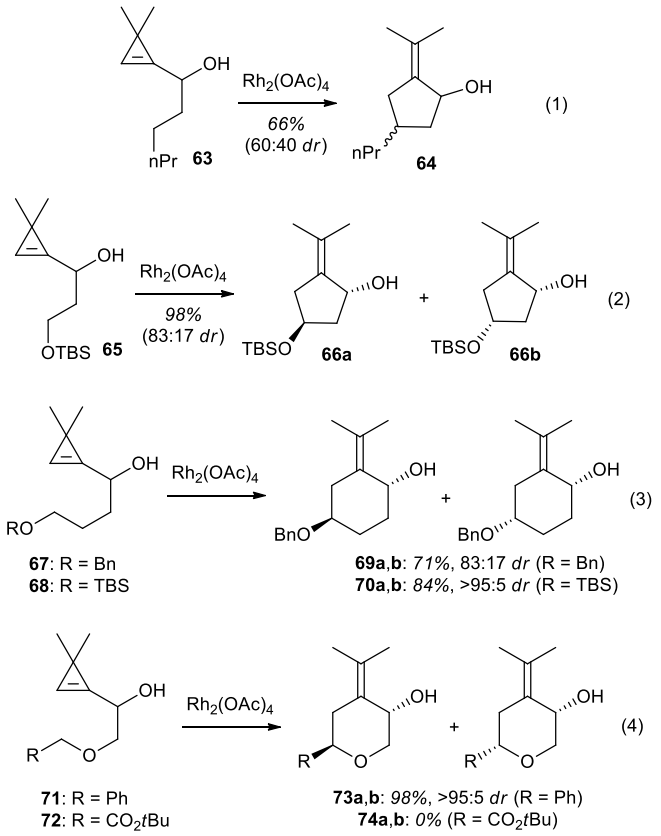
Scheme 16 Synthesis of a 6-membered ring via C‑H insertion of a donor/acceptor metal carbene.

The generation of "purely donor" rhodium carbenes by ring opening of cyclopropenes[16,17] by Cossy and coworkers, allowed investigation of their reactivity within a range of substrates (Scheme **17**).



Scheme 17 C‑H insertion reactions of donor metal carbenes derived from cyclopropenes.

Cyclopropenylcarbinol **63** in the presence of $Rh_2(OAc)_4$ gave a mixture of cyclopentanols **64**, indicating the inherent selectivity of donor metal carbenes to form 5-membered rings in the absence of other, activating effects (Scheme **18**, eq. 1). Furthermore, silyl ether **65**, wherein the 1,5-C–H bond is activated by oxygen, gave an 83:17 mixture of the trans- and cis-cyclopentanols, **66a** and **66b**, respectively, in excellent yield (eq. 2). Using benzyl and TBS ether homologues, **67** and **68**, respectively, cyclohexanols were produced in good yields with high (**69a**,**b** R = Bn) to complete (**70a**,**b** R = TBS) selectivity for the trans- diastereomer (eq. 3). In a related manner, by moving the position of the ether oxygen relative to the cyclopropene, eg. substrate **71**, tetrahydropyran **73a** could be obtained in excellent yield and with complete trans- diastereoselectivity (eq. 4). Notably, however, in substrate **72**, the presence of an electron-withdrawing ester group (-CO_2tBu) at the desired site of C‑H insertion prevented formation of the C‑H insertion products **74a**,**b**.

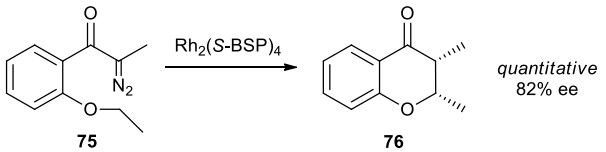


Scheme 18 Regio- and diastereoselectivity in the intramolecular C‑H insertion reactions of donor metal carbenes.

This methodology was extended to the synthesis of a range of substituted tetrahydropyrans and bicyclic compounds that were obtained in moderate to excellent yields with very high trans-diastereoselectivity.

6-membered rings: Enantioselectivity

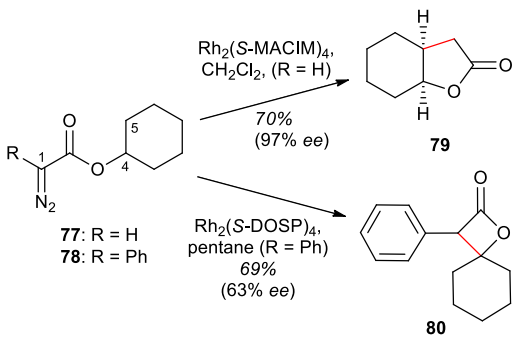
The first application of C–H insertion chemistry for the enantioselective synthesis of a six-membered ring, *via* C–H insertion α- to an oxygen, was published by McKervey and Ye in 1992,[52] and later extended in 1995.[53] They reported the asymmetric synthesis of a range of chromanones from α-diazoketones in the presence of rhodium(II) carboxylates. Enantioselectivities obtained were generally modest, with the best result being obtained for the decomposition of **75** with $Rh_2(BSP)_4$ resulting in the formation of the cis- isomer **76** in 82% *ee* (Scheme **19**).



Scheme 19 Enantioselective chromanone synthesis via asymmetric C‑H insertion.

4-membered rings: regio- and enantioselectivity

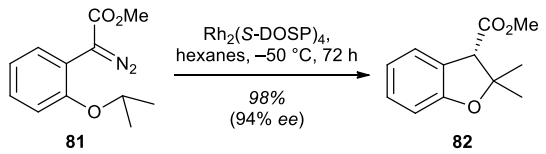
More recently, Doyle and co-workers reported the enantioselective formation of β- and γ-lactones from unsubstitituted and phenyl-substituted diazoacetates, **77** and **78**, respectively (Scheme **20**).[34, 54] Diazoacetate **77** underwent 1,5-C‑H insertion to give γ-lactone **79** in high enantioselectivity (97% *ee*). In contrast, the phenyl-substituted substrate **78** provided β-lactone **80** with modest enantioselectivity (63% *ee*).



Scheme 20 Catalytic enantioselective β- and γ-lactone formation.

Dihydrobenzofurans

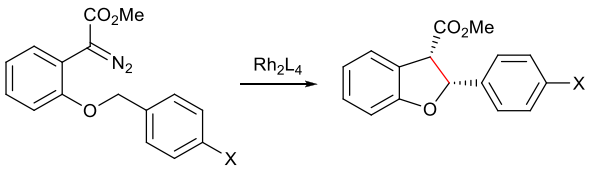
The synthesis of dihydrobenzofurans via rhodium(II)-catalysed C–H insertion has been intensively investigated by several research groups. Davies and co-workers reported the enantioselective intramolecular C–H insertion of aryldiazoacetates (Scheme **21**).[55] The enantioselectivity of Rh_2(*S*-DOSP)$_4$-catalysed C–H insertion of aryldiazoacetates, eg. **81**, leading to dihydrobenzofurans, eg. **82**, is highly dependent on the degree of substitution at the site of the insertion, with the highest enantioselectivities obtained for insertion into methine C–H bonds.



Scheme 21 Enantioselective synthesis of dihydrobenzofurans.

Hashimoto and co-workers reported the enantio- and diastereoselective synthesis of *cis*-2-aryl-3-methoxycarbonyl-2,3-dihydrobenzofurans via rhodium(II) carboxylate-catalysed C–H insertion of aryl benzyl ether substrates (Table **5**).[56] Rh_2(*S*-PTTL)$_4$ was found to be the catalyst of choice for this process, providing exclusively the desired cis- diastereomers in up to 94% *ee* (Table **5**, entry 1).

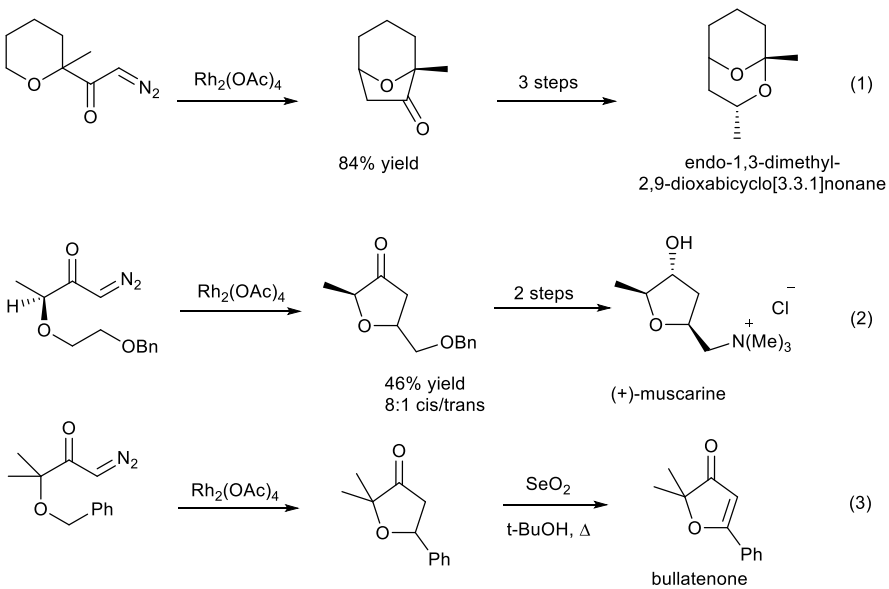
Table 5 Enantioselective synthesis of benzofurans.



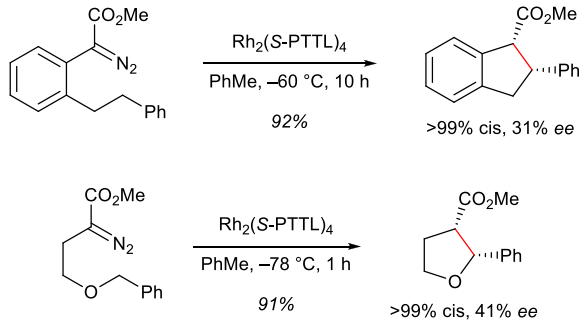
Entry	Catalyst	X	Yield (%)	*ee* (%)
1[a]	Rh_2(*S*-PTTL)$_4$	H	74	94
2[a]	Rh_2(*S*-PTTL)$_4$	Cl	81	94
3[a]	Rh_2(*S*-PTTL)$_4$	Me	80	91
4[a]	Rh_2(*S*-PTTL)$_4$	OMe	81	94
5[b]	Rh_2(*S*-PTAD)$_4$	H	69	95

[a] Experiments carried out by Hashimoto and co-workers.[56]
[b] Experiment carried out by Davies and co-workers.[57]

Substitution with electron-donating or withdrawing substituents at the *para* position of the benzyl substituent had negligible influence on the stereoselectivity of the process (Table **4**, entries 2-4). Davies and co-workers reported the efficiency of Rh_2(*S*-PTAD)$_4$ for the same transformation, giving up to 95% *ee* (entry 5).[57] Hashimoto also highlighted the crucial importance of the aryl diazo substituent and oxygen activation of the C–H insertion site. Removal of either of these features resulted in a dramatic reduction in enantioselectivity (Scheme **22**).



Scheme 23 Total syntheses of three natural products by Adams and co-workers, employing C–H insertion reactions α- to oxygen in key steps.

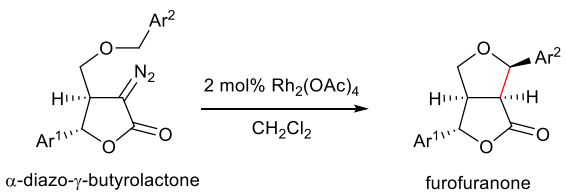


Scheme 22 Substrates that give poor enantioselectivities.

Application to the synthesis of natural products

During their investigations of C–H insertion reactions α- to ether oxygens, Adams and co-workers applied their findings to the synthesis of three natural products – *endo*-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane, an insect attractant, (Scheme **23**, eq 1);[58] (+)-muscarine, a disubstituted 2(*H*)-3-furanone metabolite from the mushroom *Amanita muscaria* (eq 2);[59] and bullatenone, a plant metabolite from *Myrtus bullata*, (eq 3).[31]

Towards the construction of furofuran lignan natural products, Brown used C–H insertion reactions to build the key bicyclic framework. Highly selective ring closure of α-diazo-γ-butyrolactones in the presence of $Rh_2(OAc)_4$ led to the formation of *endo*,*exo*-furofuranones (Scheme **24**). These intermediates were then converted to the corresponding furofurans in 2 steps, to give a number of furofuran lignans – (±)-asarinin[60], (±)-epimagnolin A[61], (±)-fargesin.[62] Using enantiomerically-enriched starting materials, (+)-xanthoxylol, (+)-methylxanthoxylol, (+)-epipinoresinol and (+)-epieudesmin[63] were also synthesised.



Scheme 24 Synthesis of furofuranones *en route* to furofuran lignan natural products.

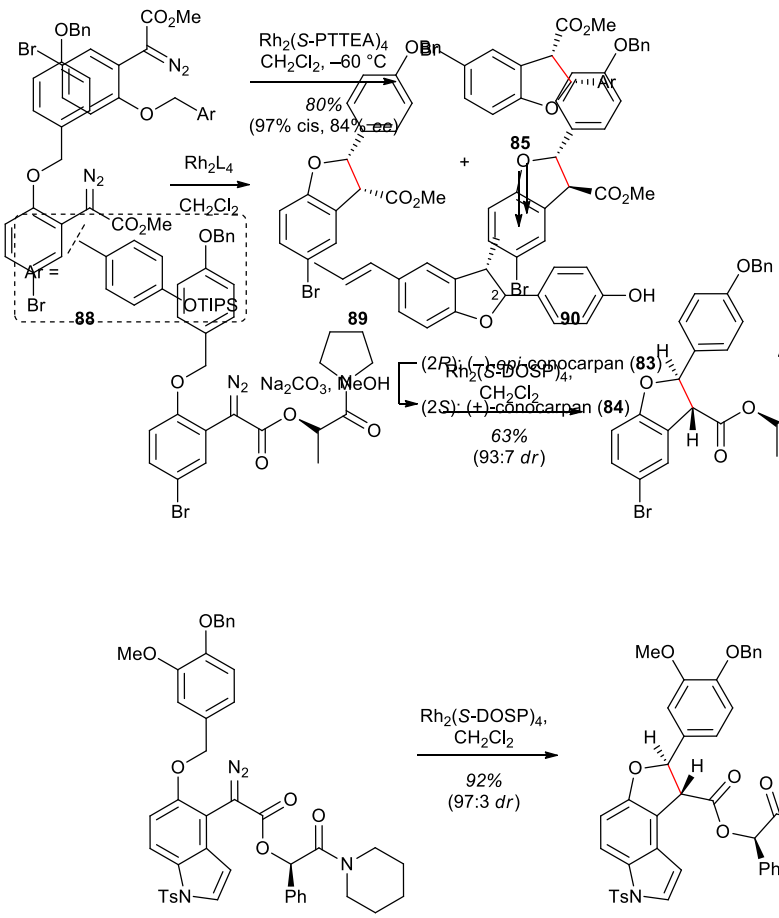
The methodology for the diastereo- and enantioselective synthesis of dihydrobenzofurans[56, 57] has been successfully applied to the asymmetric synthesis of several natural products that incorporate this subunit. Hashimoto and co-workers reported the asymmetric synthesis of neolignans (−)-*epi*-conocarpan (**83**) and (+)-conocarpan (**84**) (Scheme **25**).[64] The key step of this synthesis is construction of the *cis*-2-aryl-2,3-dihydrobenzofuran ring system *via* enantio- and diastereoselective intramolecular C–H insertion, catalysed by the newly developed rhodium(II) carboxylate catalyst Rh_2(S-PTTEA)$_4$, providing the desired *cis* dihydrobenzofuran **85** in 80% yield and 84% *ee*.

Scheme 25 Enantioselective synthesis of (–)-*epi*-conocarpan and (+)-conocarpan.

Fukuyama and co-workers reported a similar synthetic strategy for the dihydrobenzofuran moiety of the macrocyclic spermine alkaloid, (−)-ephedradine A (**86**),[65] and the pentacyclic indole alkaloid, (−)-sorotobenine (**87**) (Scheme **26**).[66] In contrast to the cyclisations carried out by Hashimoto and co-workers, the trans-dihydrobenzofuran was the major diastereomer formed in the key C‑H insertion step in both these total syntheses. In both cases the high level of substrate stereocontrol, afforded by the use of a bulky chiral auxiliary, was reinforced by selection of a chiral catalyst to provide matching reagent control.[67]

The key C–H insertion step in the synthesis of (−)-ephedradine A (**77**) has also been investigated by Davies and co-workers.[57] Using achiral substrate **88**, Davies demonstrated that, in the absence of a chiral auxiliary, the Rh_2(*S*-PTTL)$_4$- or Rh_2(*S*-PTAD)$_4$-catalysed reactions (Table **6**, entries 1 and 2) were considerably more selective than the same reaction using Rh_2(*S*-DOSP)$_4$, as reported by Fukuyama (entry 3).[67] Under optimised conditions, Rh_2(*S*-PTAD)$_4$ provided a 14:1 ratio of the cis- and trans- diastereomers, **89** and **90** respectively. Formation of the cis- isomer proceeded with moderate enantioselectivity (79% *ee*), and this compound can be readily converted to the trans- isomer **90** on treatment with sodium methoxide.[64]

Table 6 Catalytic asymmetric synthesis of a key dihydrobenzofuran intermediate in the synthesis of **86**.



Scheme 26 Total synthesis of (–)-ephedradine A and (–)-serotobenine b

Entry	Catalyst	Yield (%)	Ratio (80/81)	% *ee* (89)	% *ee* (90)
1	Rh_2(*S*-PTTL)$_4$	71	14:1	65	–
2	Rh_2(*S*-PTAD)$_4$	72	14:1	79	–
3	Rh2(S-DOSP)4	72	2:3	–	32

More recently, a total synthesis of (+)-lithospermic acid (**91**), in which a Rh_2(S-DOSP)$_4$-catalysed C–H insertion reaction was used to install the dihydrofuran core, was reported by Yu and coworkers (Scheme **27**).[68] The *trans*-dihydrofuran core was obtained in 85% yield and with 89:11 *dr* when a combination of Rh_2(*S*-DOSP)$_4$ and chiral auxiliary was used.

Conclusions

The intramolecular rhodium(II)-catalyzed C–H insertion of α-diazocarbonyl compounds is extremely useful for a wide variety of synthetic transformations and is highly favoured for the formation of 5-membered rings via insertion at methine and methylene C‑H bonds adjacent to oxygen. When all these conditions are not met, reaction at C–H bonds adjacent to oxygen to yield other ring sizes often over-rides the preference for 5-membered ring formation, allowing for the formation of 4-, 6- and even 7-membered rings. Nevertheless, steric, electronic, and conformational factors inherent to the substrate and the catalyst can lead to unexpected outcomes.

The insertion rhodium(II) carbenes at C–H bonds adjacent to oxygen has been shown to be a powerful tool for the construction of oxygen heterocycles and oxygen-substituted carbocycles. Although activation of a C–H bond by an adjacent oxygen atom has a great influence on the regioselectivity of C–H insertion, there are still relatively few examples of highly diastereo- and enantioselective synthesis. The most highly studied are those leading to dihydrobenzofurans. As new catalysts are developed and the reactivity of metal carbenes continues to be explored, it is likely the utility of metal carbene insertion into α-heteroatom activated C‑H bonds will significantly expand.

Acknowledgements

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Notes and references

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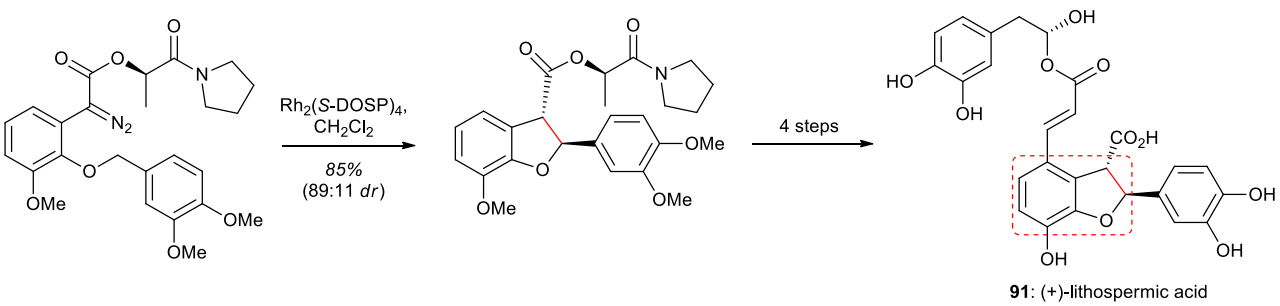

Scheme 27 Asymmetric total synthesis of the anti-HIV integrase natural product lithospermic acid.

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