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Catalytic asymmetric C–H insertion reactions of α-diazocarbonyl compounds

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Contents

1. Introduction

Catalytic C–H insertion reactions of α-diazocarbonyl compounds represent a very powerful transformation in organic chemistry, allowing activation of an unactivated C–H bond under very mild conditions, rendering this a very valuable synthetic process. Initial studies examining carbenoid insertions into C–H bonds employed catalytic copper complexes, although few synthetically useful examples were reported during this early period of investigation. In 1981, Teyssié and co-workers reported the first example of successful insertion into a C–H bond in the presence of a rhodium(II) carboxylate catalyst.[1] This report proved to be a turning point in the field of carbenoid chemistry, providing proof of the synthetic utility of C–H insertion reactions for the formation of C–C bonds and leading subsequently to the development of numerous rhodium(II) derived catalysts for application in the decomposition reactions of α-diazocarbonyl compounds.

The potential for asymmetric induction in C–H insertion reactions was first realised in the early 1990s by researchers exploring the decomposition reactions of α-diazoketones[2] and

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α-diazo-β-keto esters.[3] The 20 years following this initial breakthrough have represented a period of vast growth and discovery in the area of enantioselective carbenoid C–H insertions. In excess of 60 chiral catalytic complexes have since been demonstrated to effect enantioinduction in intramolecular and intermolecular C–H insertion reactions. The large majority of these catalysts are rhodium(II)-based systems, but recent reports have indicated the return of copper(I) complexes as viable catalyst choices for asymmetric carbenoid insertion into C–H bonds.[4] In addition, the possibility of broadening the range of available chiral catalysts for enantioselective C–H insertions beyond rhodium(II) and copper(I) complexes has recently been realised with the development of iridium(III)-salen complexes capable of catalysing asymmetric intermolecular C–H insertion reactions.[5]

The importance of this area of organic chemistry is highlighted by the large number of published review articles detailing racemic[6–18] and asymmetric C–H insertion reactions.[8,10,14,15,18–22] The purpose of this review is to provide an overview of the development of asymmetric catalysts for C–H insertion reactions over the past two decades, focusing on the application of these catalysts in the decomposition of α-diazocarbonyl compounds. Given the rapid pace of development in the field of enantioselective C–H insertion chemistry, an up-to-date review of this type is warranted. While recent reviews[22,23] have dissected their content into intramolecular and intermolecular processes, this article is differentiated in extending this division to include classification of C–H insertion reactions according to product type. Thus, catalytic methods for the asymmetric synthesis of carbocyclic compounds, oxygen-containing heterocycles, nitrogen-containing heterocycles and sulfur-containing heterocycles are readily identifiable. Due to the diversity of compounds resulting from intermolecular C–H insertion processes, classification of reactions by product type was not attempted in this section of the review.

2. Copper(I) catalysts

The majority of catalysts employed in early studies of diazo decomposition reactions were copper-based systems,[6,24,25] showing varying levels of success in applied C–H insertion processes. Product yields were at best moderate and synthetic applications of these early copper catalysts were limited mainly to geometrically rigid diazo precursors.[6] The first enantioselective copper-catalysed C–H insertion reaction of α-diazocarbonyl compounds was reported in 1995 by Sulikowski and Lim for the synthesis of 1,2-disubstituted mitosene.[26] Decomposition of aryl diazoacetate **1** in the presence of chiral copper(I)-bis(oxazoline) catalysts was shown to provide the diastereomeric products **2** and **3** with moderate asymmetric induction (Scheme 1).

Bis(oxazoline) complexes have since been employed in several inter- and intramolecular C–H insertion reactions, with enantioinduction of up to 88% ee being achieved.[27–31] To date, in excess of 140 chiral bis(oxazoline) ligands have been synthesised,[32] finding applications in a wide range of asymmetric transformations.[32–34] The success of these catalysts may be attributed to the C_2-symmetry of the ligands, which minimises the number of possible transition states for a given reaction,[35] and also the conformationally constrained metal chelate structure, which places the donor nitrogens in close proximity to the chiral centres, resulting in a strong directing effect on the catalytic site. Selected examples of bis(oxazoline) ligands **4a**-**g** are displayed in Figure 1.

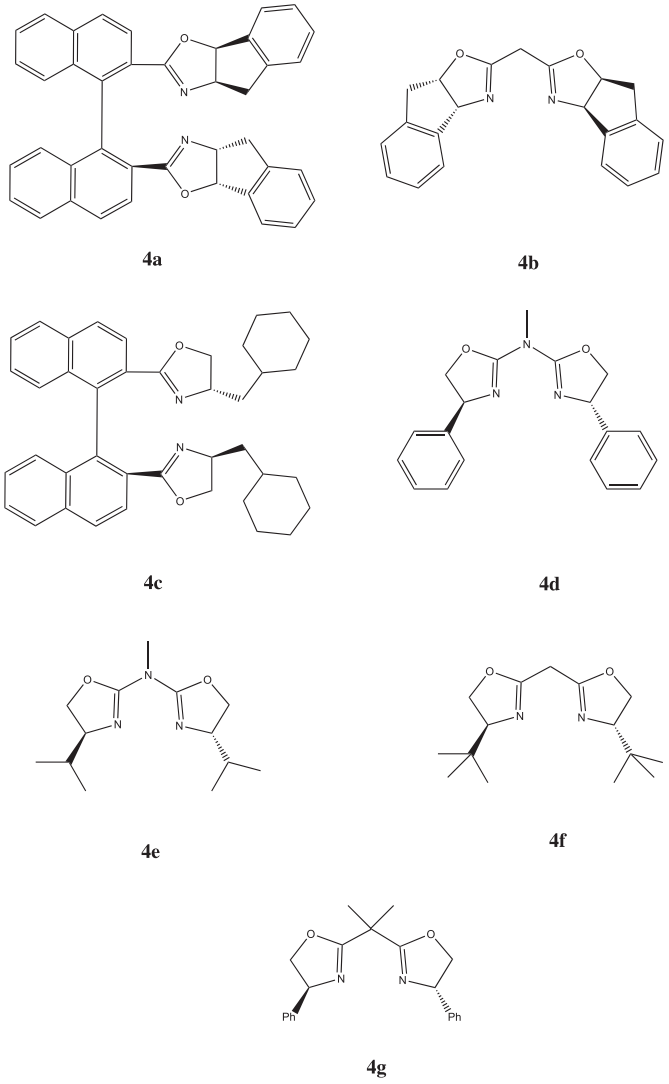
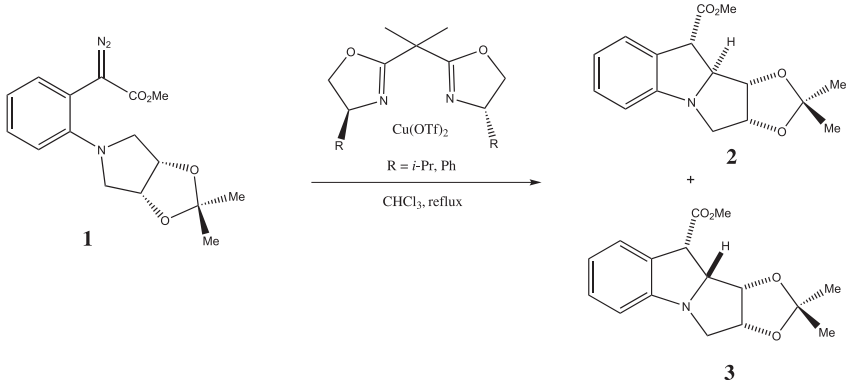
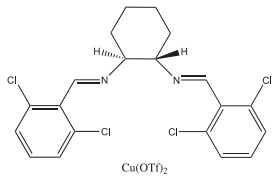


Figure 1.



Scheme 1.

Additional copper(I) catalysts employed in asymmetric C–H insertion processes include copper(I) C_2-symmetric Schiff base complexes such as **5** (Fig. 2), which have shown moderate success in the enantioselective synthesis of D-*threo*-methylphenidate.[36]



5

Figure 2.

The most recent development in the area of copper catalysis for C–H activation chemistry has been the introduction of copper-based catalysts possessing trispyrazolylborate (Tp^X) ligands **6a**–**c** (Fig. 3).[37] Various complexes of general formula Tp^XCu, including complexes where the metal atom is bonded to an *N*-heterocyclic carbene ligand (NHC), have been shown to be efficient catalysts for carbene/diazoacetate insertion into C–H bonds of hydrocarbons.[37–41]

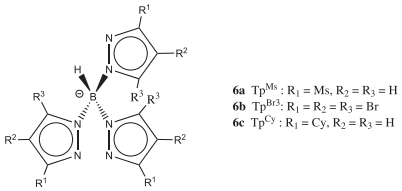


Figure 3.

In general, superior results in terms of catalytic selectivity are observed for those systems in which the metal centre is bonded to a weakly electron-donating ligand, meaning electrophilicity at the metal centre is increased.[42] An asymmetric version of this transformation has yet to be described, but may be achieved in the coming years.

3. Rhodium(II) catalysts

Rhodium(II) complexes have been widely established as the most effective and versatile catalysts for diazo decomposition.[6,7,11,13,16,43] Their popularity may be rationalised by the fact that rhodium(II)-catalysed carbene reactions proceed under much milder conditions than those employed for syntheses with copper(II) catalysts.[16] In addition, a wide variety of rhodium(II) complexes are available, owing to the large number of bridging ligands that can be coordinated to the rhodium(II) skeleton.

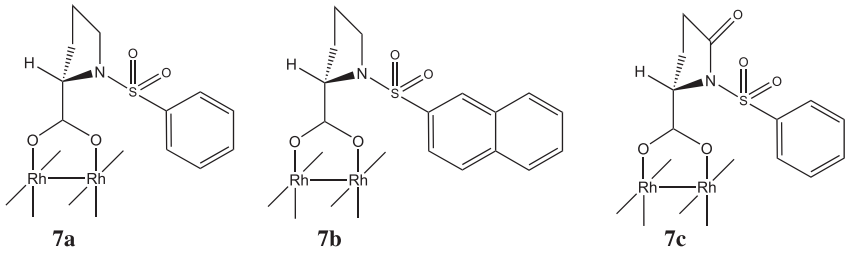
A key property of rhodium(II) is its ability to form Rh–Rh bonds. This property allows the formation of a dirhodium-bridged cage within a 'lantern' structure,[44–46] which is thought to be a critical feature in the success of Rh(II) complexes. It has been suggested that only one of the two rhodium centres functions as a binding site for the carbene generated from diazo decomposition. The second rhodium is believed to aid the reaction by behaving as an electron sink, thereby increasing the electrophilicity of the carbene and facilitating cleavage of the rhodium-carbene bond upon reaction completion.[47]

Rhodium catalysis for C–H insertion processes was first reported by Teyssié and co-workers in 1981.[1] Realisation of the potential of rhodium(II) complexes to induce diazo decomposition led to a significant focus on the development of related catalysts for application in diazo/carbenoid chemistry. Numerous achiral carboxylate and carboxamidate catalysts derived from the parent rhodium(II) tetraacetate [$Rh_2(OAc)_4$] have since been reported for carbenoid transformations.[48–51] Over the past two decades, the focus of study in the area of diazo chemistry has shifted to the development of chiral catalysts for asymmetric diazo decomposition reactions. A vast range of chiral rhodium(II) catalysts now exist, encompassing rhodium(II) carboxylates, rhodium(II) carboxamidates, rhodium(II) phosphonates and rhodium(II) *ortho*-metalated complexes.

3.1. Chiral rhodium(II) carboxylate catalysts

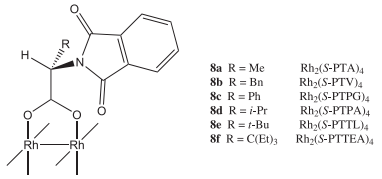
The first use of chiral rhodium(II) catalysts in C–C bond-forming reactions of α-diazocarbonyl compounds was reported by McKervey and co-workers in 1990.[2] Their novel rhodium(II) (*N*-benzenesulfonylprolinate) catalyst [$Rh_2(BSP)_4$] **7a**, (Fig. 4) prepared by treatment of *N*-benzenesulfonyl-L-proline with $Na_4Rh_2(CO_3)_4$, was shown to be an effective catalyst in the intramolecular C–H insertion of an α-diazo-β-keto sulfone precursor (12% ee). Numerous related proline complexes, including **7b** and **7c**, have since been synthesised.[52]

In the same year, Hashimoto and Ikegami reported the use of phthalimide derivatives of amino acid-based chiral rhodium(II) carboxylates as catalysts for enantioselective intramolecular C–H insertion reactions of a series of α-diazo-β-keto esters.[3] These phthalimide catalysts (**8a** and **8b**) displayed considerable enantioselectivity (up to 46% ee) and several related complexes were later prepared to include *tert*-leucinate [Rh_2(*S*-PTTL)$_4$] **8e**, valine [Rh_2(*S*-PTV)$_4$] **8d**, phenylglycine [Rh_2(*S*-PTPG)$_4$] **8c** and triethylalanine [Rh_2(*S*-PTTEA)$_4$] **8f** derived catalysts (Fig. 5), showing improvements in enantiocontrol in many cases, due to the increased steric bulk of



7a 7b 7c

Figure 4.



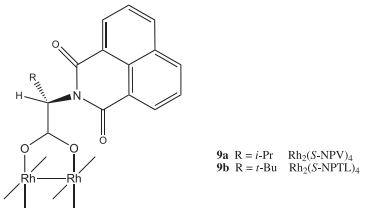


Figure 5.

the alkyl group of the ligand.[53,54] The related catalysts Rh_2(*S*-NPV)$_4$ **9a** and Rh_2(*S*-NPTL)$_4$ **9b** (Fig. 5) have also been developed by Chiu and co-workers, showing moderate enantioselectivity in the C–H insertion reactions of *meso* oxabicyclic compounds.[55]

Subsequent work by Hashimoto and co-workers has included the development of a series of catalysts featuring an extended phthalimido wall (Fig. 6), namely, Rh_2(*S*-BPTTL)$_4$ **10d**, Rh_2(*S*-BPTA)$_4$ **10a**, Rh_2(*S*-BPTPA)$_4$ **10c**, and Rh_2(*S*-BPTV)$_4$ **10b**, derived from *tert*-leucine, alanine, phenylalanine and valine, respectively.[56] These highly structured complexes have displayed improved enantioselectivities for many C–H insertion reactions, compared to the original phthalimide catalysts.[57]

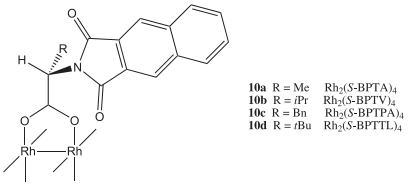


Figure 6.

More recently, halogen-substituted phthaloyl catalysts (Fig. 7) have been introduced.[58] These complexes are characterised by substitution of the phthalimido hydrogens of the parent rhodium (II) species by fluorine (**11a**) or chlorine (**11b**) atoms, resulting in improved reactivity and enantioselectivity, owing to the electron-withdrawing effect of the halide substituents on the chiral ligands. Rh_2(*S*-TFPTTL)$_4$ **11a** has been particularly impressive, achieving an extremely high turnover number (up to 98,000) in the C–H insertion reactions of methyl 4-alkyl-2-diazo-4,4-diphenyl-3-oxo-propionates, with a catalyst loading of just 0.001 mol %.[58]

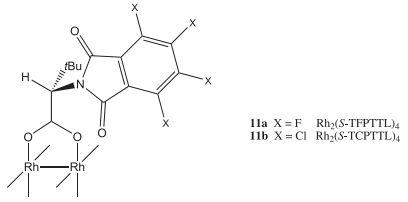


Figure 7.

The catalogue of available proline-based chiral rhodium(II) carboxylates was extended by Davies, who reported the application of rhodium(II) (*S*)-*N*-(*tert*-butylbenzenesulfonyl) prolinate Rh_2(*S*-TBSP)$_4$ **12** and rhodium(II) (*S*)-*N*-(dodecylbenzenesulfonyl)prolinate Rh_2(*S*-DOSP)$_4$ **13** (Fig. 8) for the enantioselective synthesis of vinylcyclopropanes[59] and 2-phenylcyclopropan-1-amino acids,[60] respectively. Despite showing moderate success for asymmetric C–H insertions with traditional diazoacetate substrates, Davies' rhodium (II) prolinate derivatives have become the catalysts of choice for intermolecular C–H insertion reactions with carbenoids substituted with an electron-donating and an electron-withdrawing group.

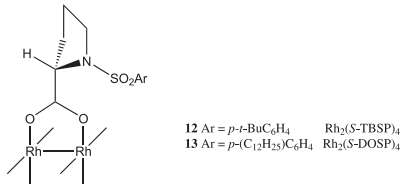


Figure 8.

The bridged prolinate complexes, Rh_2(*S*-biDOSP)$_2$, Rh_2(*S*-biTBSP)$_2$ and Rh_2(*S*-biTISP)$_2$, have also been developed.[61] These rigid catalytic systems have shown success in C–H insertion reactions,[62–65] achieving high asymmetric induction in reactions employing non-hydrocarbon solvents, and in this respect are advantageous over Rh_2(*S*-DOSP)$_4$. Additional developments in the field of prolinate-based catalysis for carbenoid reactions have included the preparation of the fluorous complex, rhodium(II)-(*S*)-*N*-(*n*-perfluorooctylsulfonyl)prolinate [Rh_2(*S*-FOSP)$_4$] **14** (Fig. 9), by Biffis and co-workers.[66] The perfluoroalkyl chains of this novel catalyst allow its facile recovery from the reaction mixture by confining the catalyst in an isolated perfluorinated liquid or solid phase, making this an excellent recyclable asymmetric catalyst. Moderate enantioselectivity has been achieved for this catalyst in the asymmetric C–H bond activation of cyclohexane (61% ee).

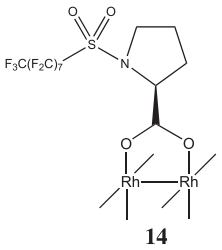


Figure 9.

Recently, Davies and co-workers have prepared a rhodium(II) tetracarboxylate catalyst derived from adamantylglycine Rh_2(*S*-PTAD)$_4$ **15** (Fig. 10).[67] This adamantyl complex has proved to be an effective catalyst for carbenoid reactions, with high asymmetric induction being noted for both intermolecular (92% ee) and intramolecular (94% ee) C–H insertion reactions.[67] High enantioselectivity in the intermolecular C–H insertion of α-aryl-α-diazoketones with cyclohexadiene has also been achieved (89% ee).[68]

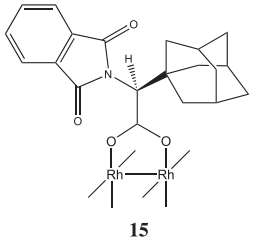
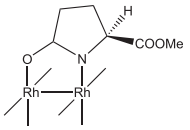


Figure 10.

3.2. Chiral rhodium(II) carboxamidate catalysts

The first preparation of a rhodium(II) carboxamidate was described in 1982 by Dennis and co-workers, who isolated the rhodium(II) tetraacetamidate from a melt of trifluoroacetamide and rhodium(II) tetraacetate.[69] Several isomers of this carboxamidate complex are possible, although the structure in which the two oxygens and two nitrogens are bound to each rhodium in a cis fashion was found to be dominant.[70] In general, decreased reactivity has been observed for catalytic reactions with α-diazocarbonyls in the presence of carboxamidates, compared with the corresponding carboxylates, but higher selectivites are possible, making these complexes a popular catalytic choice for C–H insertion reactions.[71–73]

Doyle's chiral rhodium(II) carboxamidate complexes were first reported for enantioselective cyclopropanation reactions in 1990.[74] These catalysts have since been much exploited and remain today the primary catalysts for enantioselective C–H insertion reactions of electron-withdrawing group-substituted carbenoids derived from diazoacetamides and diazoesters.[6] The carboxamidate derivative Rh_2(MEPY)$_4$ **16** (Fig. 11) was the first of Doyle's catalysts



16

Figure 11.

to be employed for asymmetric C–H insertions.[75] A high degree of enantiocontrol was achieved for this catalyst in the intramolecular C–H insertions of alkyl diazoacetates thereby paving the way for the development of further carboxamidate derivatives.

Numerous rhodium(II) carboxamidate catalysts developed by Doyle have since been employed for C–H insertion reactions including oxazolidinones **17a**–**c**,[27,76–81] azetidinones **18a**–**e**,[36,80,82] and imidazolidinones **19a**–**c**[27,78,80,83–87] complexes (Fig. 12).

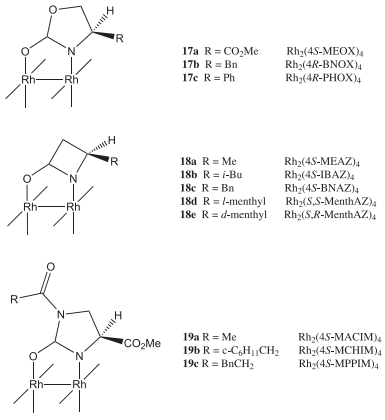
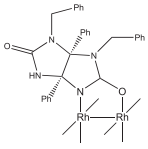


Figure 12.

The diastereomeric azetidinone complexes Rh_2(*S*,*S*-MenthAZ)$_4$ **18d** and Rh_2(*S*,*R*-MenthAZ)$_4$ **18e** have also been shown to be effective catalysts for the enantioselective intermolecular C–H insertion reaction of vinyldiazolactones.[82] Recently, 1,6-bis-(*N*-benzyl)-diphenylglycoluril (1,6-BPGlyc) **20** (Fig. 13) has been reported as a ligand for dinuclear rhodium(II) complexes.[88] This glycouril derivative has been shown to be an effective catalyst for the cyclopropanation of styrene with diazoacetates, displaying reactivities and selectivities in the range of related rhodium(II) carboxamidates and may therefore represent a suitable catalytic choice for future asymmetric C–H insertion reactions.



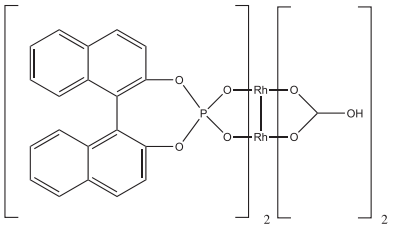
20

Figure 13.

3.3. Chiral rhodium(II) phosphate catalysts

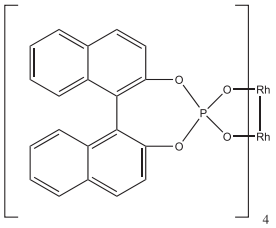
Chiral rhodium(II) binaphthylphosphate catalysts have been developed by both McKervey and Pirrung. McKervey's Rh_2(*S*-BNP)$_2$(HCO$_3$)$_2$ **21** (Fig. 14) complex was first reported in 1992, and was shown to be an efficient catalyst for a range of diazocarbonyl decomposition reactions, including C–H insertions, with moderate-to-good levels of enantioselectivity being achieved.[89]

Pirrung's Rh_2(*R*-BNP)$_4$ complex **22** (Fig. 15), reported in the same year, was also demonstrated to provide good asymmetric induction



21

Figure 14.



22

Figure 15.

in the dipolar cycloaddition of diazo compounds to heterocyclic products.[90]

While some success in asymmetric C–H insertions has since been reported with these chiral rhodium(II) phosphate complexes,[55] their use to date in C–H activation chemistry remains minimal, with their primary application being found in enantioselective ylide formation reactions of α-diazocarbonyls.

3.4. Chiral *ortho*-metalated rhodium(II) complexes

The synthesis and X-ray characterisation of *ortho*-metalated rhodium(II) compounds of general formula $Rh_2(O_2CMe)[(Ph)_2P(C_6H_4)]_2\cdot 2L$ were first described by Cotton in 1985.[91] These novel mixed-ligand bridging systems displayed characteristics not previously observed for rhodium(II) tetracarboxylates or tetraacetamides, including backbone chirality, possession of polarisable aromatic ligands, and the possibility of regulating electronic and steric properties of the catalyst by modification of both carboxylate and phosphine substituents. In 1999, Lahuerta and co-workers reported the synthesis of the first enantiomerically pure *ortho*-metalated rhodium(II) dimer,[92] paving the way for the development of a new series of chiral $Rh_2(OOCR)_2(PC)_2$ catalysts **23a**–**g** (Fig. 16) (PC=orthometalated phosphine).

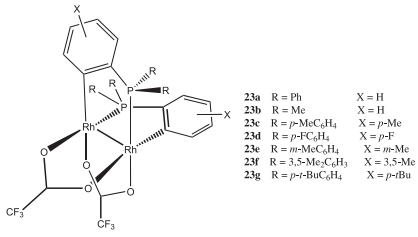


Figure 16.

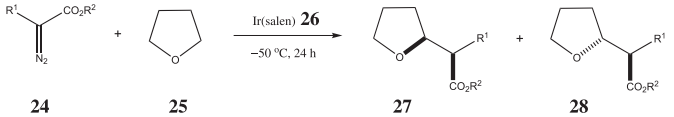
These complexes were subsequently shown to be effective catalysts for the asymmetric C–H insertion reactions of α-diazoketones,[93] producing cyclopentanone products with enantioselectivity as high as 74% ee, representing a significant improvement on previous attempts at enantiocontrol in the decomposition of α-diazoketones.[2] A new series of biscyclometalated Rh(II) compounds of general formula $Rh_2(OOCR)_2(PC)_2\cdot N_2$ have recently been described.[94] These

novel complexes possess different nitrogen donor ligands (N=NH_2Ph, py, 3-MeCO-py and 4-MeCO-py) axially coordinated to both rhodium atoms of the catalyst.

4. Other metal catalysts

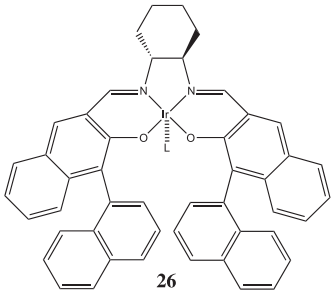
The choice of catalyst for carbene transformation reactions may also comprise a variety of other transition-metal-based complexes including iron,[95] ruthenium,[96] osmium,[97] cobalt,[98] palladium,[99] platinum,[100] molybdenum,[101] iridium,[102] scandium,[103] silver[104] and gold.[105] Several of these catalytic systems have been successfully applied to C–H insertion processes,[95,101,103–106] mainly intermolecular reactions with ethyl diazoacetate, although until recently, none have been reported to induce enantioselectivity. A 2009 report by Katsuki and Suematsu[5] described the first example of iridium(III)-catalysed asymmetric carbenoid insertion (Table 1, entries a–d). This achievement was realised for the intermolecular C–H insertion of various α-substituted α-diazoacetates **24** into tetrahydrofuran **25** in the presence of a chiral iridium(III) salen complex **26**, producing the corresponding α-aryl(tetrahydrofuran-2-yl)acetates **27** and **28** in moderate to high diastereoselectivity and high enantioselectivity (Fig. 17). In addition to representing the first example of enantioselective iridium(III)-catalysed C–H insertion, this report was significant in demonstrating the ability of α-alkyl-α-diazoacetates to undergo efficient intermolecular C–H carbene insertion.

Table 1
Enantioselective C–H insertion of α-substututed α-diazoacetates **24** into tetrahydrofuran



24 **25** **27** **28**

Entry	R^1	R^2	**27**/**28**	Yield (%) **27**	ee (%) **27**
a	Ph	Me	13:1	75	95
b	*p*-$MeOC_6H_4$	Me	>20:1	64	97
c	*m*-$MeOC_6H_4$	Me	9:1	75	97
d	Me	*t*Bu	13:1	70	90



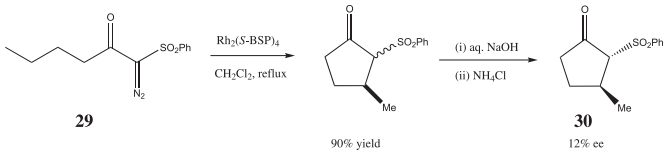
26

L = 4-MeC_6H_4

Figure 17.

5. Intramolecular carbocycle-producing C–H insertion reactions

The first example of asymmetric induction for an intramolecular carbocycle-producing C–H insertion reaction was reported by McKervey and co-workers in 1990 for the Rh_2(*S*-BSP)$_4$-catalysed decomposition of an α-diazo-β-keto sulfone **29** (Scheme 2).[2] In this study, cyclopentanone **30** was obtained as a mixture of cis and trans isomers in >90% yield, with an enantioselectivity of 12% ee being recorded for the trans isomer.

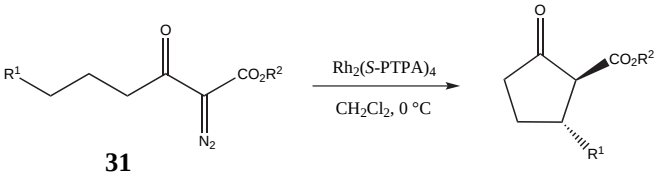


29 90% yield **30** 12% ee

Scheme 2.

The majority of studies exploring the C–H insertion route to five-membered-ring carbocyclic products have employed α-diazo-β-keto ester carbenoid precursors. Early work in this area was carried out by Ikegami and Hashimoto, who demonstrated the ability of *N*-phthaloyl amino acid catalysts to efficiently cyclise a range of α-diazo-β-keto esters **31** (Table 2, entries a–g).[3,53,107]

Table 2
Intramolecular C–H insertion reactions of α-diazo-β-keto esters **31**



31

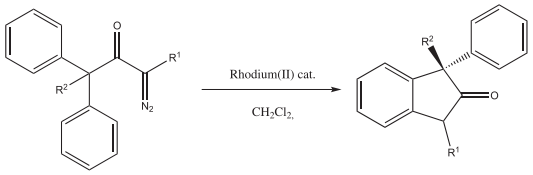
Entry	R^1	R^2	Yield (%)	ee[a] (%)
a	Me	Me	76	24 (3*R*)
b	Ph	Me	96	46 (3*R*)
c	Ph	CH*i*-Pr_2	86	76 (3*R*)
d	Ph	(+)-Neomenthyl	78	53 (3*R*)
e	Ph	CH*i*-Pr_2	81	76 (3*R*)
f	*p*-$CF_3SO_3C_6H_4$	CH*i*-Pr_2	84	80 (3*R*)
g[b]	Ph	(+)-Neomenthyl	79	80 (3*S*)

[a] Enantioselectivity determined following dealkoxycarbonylation.
[b] Catalyst used was Rh_2(*R*-PTPA)$_4$.

Of the catalysts tested, Rh_2(*S*-PTPA)$_4$ was shown to be the catalyst of choice, providing enantioselectivities of up to 80% ee. The extent of asymmetric induction achieved in the cyclisation of the α-diazo-β-keto esters was found to be heavily influenced by both the size of the alkoxy group of the ester moiety and the nature of the substituents adjacent to the target C–H bond. In general, increased steric bulk of the ester group was found to favour improved asymmetric induction, with change of ester moiety from methyl (Table 2, entry b) to CH^iPr_2 (Table 2, entry e) inducing a 30% increase in enantioselectivity. The presence of electron-withdrawing substituents (phenyl, vinyl) adjacent to the C–H insertion site was also proven to enhance asymmetric induction, owing to a decrease in electron density at the target site, which reduced reactivity towards the electrophilic rhodium-carbene species, resulting in an increase in stereoselectivity. Highest enantioselectivities were achieved for substrates possessing electron-withdrawing group-substituted phenyl or vinyl groups at the insertion site (Table 2, entry f), and for substrates containing the chiral ester substituent, (+)-neomenthyl (Table 2, entry g). The high level of enantiocontrol recorded in the latter case was achieved through a process of double asymmetric induction for the matched pair of **31** and Rh_2(*R*-PTPA)$_4$. It is interesting to note in this study that benzylic C–H insertion occurred under the same conditions (CH_2Cl_2, 0 °C) and at the same rate (0.5 h) as the corresponding insertion into methylene sites, despite previous findings by Taber suggesting that benzylic and allylic C–H insertion is less favourable than aliphatic C–H insertion.[108]

Later work by Ikegami and Hashimoto included the examination of enantiotopically selective intramolecular aromatic C–H insertion reactions of α-diazoketones and α-diazo-β-keto esters (Table 3, entries a–h).[58,109,110]

Table 3
Intramolecular aromatic C–H activation of α-diazoketones and α-diazo-β-keto esters



32 **33**

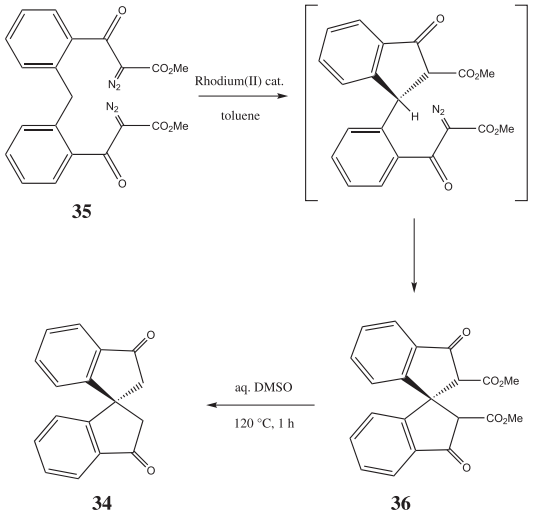
Entry	Rhodium(II) cat.	R^1	R^2	T (°C)	Yield (%) **33**	ee (%) **33**
a	Rh_2(*S*-PTPA)$_4$	H	Me	−20	64	77
b	Rh_2(*S*-PTTL)$_4$	H	Me	−20	84	90
c	Rh_2(*S*-PTTL)$_4$	H	Et	−20	74	98
d	Rh_2(*S*-PTTL)$_4$	H	*n*-Pr	−10	75	88
e	Rh_2(*S*-PTTL)$_4$	CO_2Me	Me	0	89	92[a]
f	Rh_2(*S*-PTTL)$_4$	CO_2Me	Et	0	98	96[a]
g	Rh_2(*S*-TFPTTL)$_4$	CO_2Me	Me	−10	70	98[a]
h	Rh_2(*S*-TFPTTL)$_4$	CO_2Me	Et	0	94	97[a]

[a] Enantioselectivity determined following demethoxycarbonylation.

A high degree of differentiation between the enantiotopic benzene rings was achieved, producing (*S*)-1-alkyl-1-phenyl-2-indanones **33** in up to 98% ee. Dirhodium(II) [*N*-phthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-PTTL)$_4$, was found to be the best-performing catalyst, providing excellent enantioinduction with a variety of R^1 and R^2 substituents (Table 3, entries b–f).[58,109] The fluorine-substituted phthaloyl complex Rh_2(*S*-TFPTTL)$_4$ was also shown to be a successful catalytic choice for asymmetric intramolecular aromatic C–H insertion reactions of **32** (Table 3, entries g and h), providing enantioselectivities comparable to Rh_2(*S*-PTTL)$_4$ with significantly shorter reaction times [2–20 min for Rh_2(*S*-TFPTTL)$_4$ vs 1-2 h for Rh_2(*S*-PTTL)$_4$].[58]

The rhodium(II)-catalysed asymmetric synthesis of 1,1′-spirobi[indan-3,3′-dione] **34** via a double intramolecular C–H insertion process has also been reported (Table 4, entries a–f).[111] Of the rhodium(II) carboxylates tested, the best results were obtained for cyclisation with the bulky *tert*-butyl catalyst Rh_2(*S*-PTTL)$_4$, providing (*R*)-**34** in 78% yield and 80% ee (Table 4, entry e). The use of Rh_2(*R*-PTTL)$_4$ also resulted in high enantioselectivity, producing (*S*)-**34** in 76% yield and 79% ee (Table 4, entry f). The initial decomposition of **35** is thought to be responsible for the stereochemical outcome of the reaction via differentiation of the two enantiotopic hydrogens at the methylene insertion site. The subsequent C–H insertion at the methine C–H bond is believed to proceed with retention of configuration to generate **36**.

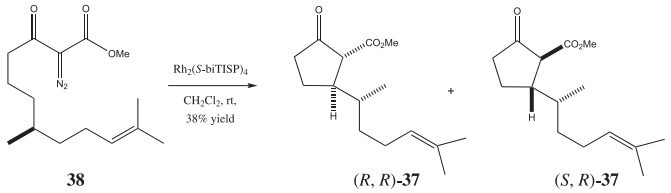
Table 4
Asymmetric synthesis of 1,1′-spirobi[indan-3,3′-dione] **34**



35 **34** **36**

Entry	Rhodium(II) cat.	T (°C)	Yield (%) **34**	ee (%) **34**
a	Rh_2(*S*-DOSP)$_4$	rt	48	8 (*R*)
b	Rh_2(*S*-PTPG)$_4$	0	67	21 (*R*)
c	Rh_2(*S*-PTPA)$_4$	0	71	25 (*R*)
d	Rh_2(*S*-PTTL)$_4$	0	83	68 (*R*)
e	Rh_2(*S*-PTTL)$_4$	−10	78	80 (*R*)
f	Rh_2(*R*-PTTL)$_4$	−10	76	79 (*S*)

The enantioselective synthesis of cyclic β-ketoester **37** was attempted by Taber and Malcolm in 2001.[112] For this purpose, several chiral rhodium(II) catalysts were examined, with Davies' bridged prolinate complex Rh_2(*S*-biTISP)$_4$ found to give the highest level of diastereocontrol (58% de) (Scheme 3).



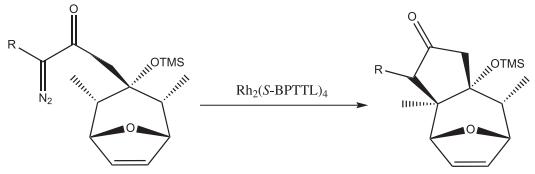
38 (*R*, *R*)-**37** 79 : (*S*, *R*)-**37** 21

Scheme 3.

Interestingly, in contrast to previous observations by Hashimoto and co-workers, increased steric bulk at the ester moiety of **38** via change from the methyl (58% de) to dimethylpentyl (34% de) ester did not improve the level of stereocontrol achieved.[53]

In 2004, Chiu and co-workers described the intramolecular C–H insertion of oxabicyclo[3.2.1]diazoketones **39** to produce oxatricyclic compounds **40**.[55] Eight different chiral rhodium(II) catalysts were tested for their ability to induce enantioselectivity in this desymmetrisation reaction, including two novel catalysts, Rh_2(*S*-NPTL)$_4$ and Rh_2(*S*-NPV)$_4$. The best results were achieved for the Rh_2(*S*-BPTTL)$_4$-catalysed reaction, showing moderate enantioselectivity for the cyclisation of **39** (Table 5, entries a and b).

Table 5
Intramolecular C–H insertion reactions of oxabicyclo[3.2.1]diazoketones **39**



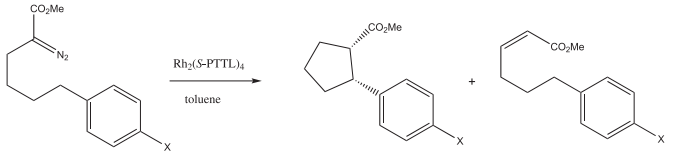
39 **40**

Entry	R	Solvent	T	Yield (%) **40**	ee (%) **40**
a	H	CH_2Cl_2	rt	85	44
b	CO_2Et	$ClCH_2CH_2Cl$	Reflux	73	30

The first highly enantio- and diastereoselective route to 1,2-disubstituted cyclopentanes via rhodium(II)-catalysed C–H insertion reactions of α-diazo esters was reported in 2005 (Table 6, entries a–f).[113] The Rh_2(*S*-PTTL)$_4$-catalysed cyclisation of **41** (X=H) in toluene at −78 °C was found to produce methyl *cis*-2-phenylcyclopentane-1-carboxylate **42** as the sole product in 95% ee, with no evidence of the corresponding trans isomer (Table 6, entry b). The effect of temperature in this study was found to be of great importance, with an increase in reaction temperature corresponding to a decrease in enantioselectivity (Table 6, entry a vs b), as had previously been noted by Hashimoto and co-workers.[110] Solvent choice was also key, with the use of dichloromethane

and ether as reaction solvent resulting in the formation of small quantities of α,β-unsaturated ester **43** via the competing 1,2-hydride shift pathway (Table 6, entry b vs c and d). High enantioselectivity and cis selectivity were also observed for insertions with electron-donating or -withdrawing groups on the *para* position of the benzene ring (Table 6, entries e and f). Surprisingly, reduced asymmetric induction was observed for the Rh_2(*S*-BPTTL)$_4$-catalysed decomposition of **41** at −78 °C in toluene (67% ee), despite the increase in steric bulk of the catalyst.

Table 6
Intramolecular C–H insertion reactions of α-diazo esters **41**



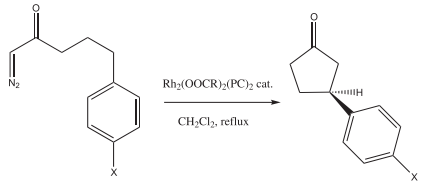
41 **42** **43**

Entry	X	Solvent	*T* (°C)	Yield[a] (%)	**42**/**43**	ee (%) **42**
a	H	Toluene	0	80	82:18	81
b	H	Toluene	−78	85	>99:0	95
c	H	CH_2Cl_2	−78	76	93:7	95
d	H	Ether	−78	73	97:3	94
e	MeO	Toluene	−78	85	>99:0	92
f	Cl	Toluene	−78	81	>99:0	93

[a] Combined yield of **42** and **43**.

The enantioselective production of carbocyclic products via intramolecular C–H insertion reactions has been shown to successfully occur in the presence of rhodium(II) complexes derived from orthometalated arylphosphines, $Rh_2(O_2CMe)_2(PC)_2$. Moderate-to-good asymmetric induction was reported by Lahuerta and co-workers for the $Rh_2(O_2CMe)_2(PC)_2$-catalysed C–H insertion of α-diazoketone **44** (Table 7, entries a–f).[93] The electronic effects of the diazo substrates were of central importance in this study. Addition of an electron-withdrawing substituent (X=F, Cl) to the phenyl ring was shown to correspond to an increase in enantioselectivity (Table 7, entry a vs b and d), while addition of an electron-donating group (X=OMe) provided no significant improvement in enantiocontrol (Table 7, entry a vs f). These results are in accordance with previous findings by Hashimoto and Ikegami.[107]

Table 7
Decomposition of α-diazoketone **44** catalysed in the presence of *ortho*-metalated arylphosphine rhodium(II) complexes

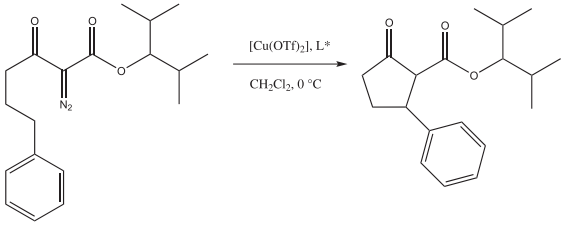


44

Entry	X	Cat.	Yield (%)	ee (%)
a	H	**23a**	73	54 (*S*)
b	F	**23a**	68	60 (*S*)
c	F	**23g**	18	60 (*S*)
d	Cl	**23a**	87	65 (*S*)
e	Cl	**23e**	87	73 (*S*)
f	OMe	**23b**	95	56 (*R*)

The production of cyclopentanone products via C–H insertion reactions is also possible with copper(I) catalysts. Moderate enantioselectivities were reported by Müller and co-workers for the intramolecular C–H insertion of α-diazo-β-keto ester **45** upon exposure to $Cu(OTf)_2$ in the presence of various chiral ligands (Table 8, entries a–c).[31,114]

Table 8
Copper(I)-catalysed C–H insertion reaction of α-diazo-β-keto ester **45**



45

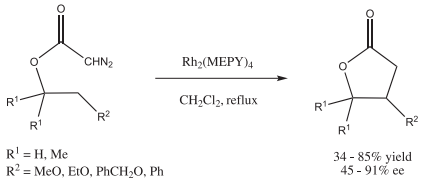
Entry	Ligand (L*)	Yield (%)	ee[a] (%)
a	**4a**	17	51 (*S*)
b	**4b**	14	31 (*S*)
c	**4c**	35	60 (*R*)

[a] Enantioselectivity determined following dealkoxycarbonylation.

6. Intramolecular heterocycle-producing C–H insertion reactions

6.1. Oxygen-containing heterocycle synthesis

6.1.1. Lactone synthesis. The asymmetric synthesis of oxygen-containing heterocycles, including lactones, chromanones and dihydrofurans, may be achieved via intramolecular C–H insertion reactions. Doyle's chiral rhodium(II) carboxamidates have proved to be the catalysts of choice for the generation of lactone products, displaying high enantioselectivities for C–H insertion reactions with a variety of diazoacetates.[75,78,80,86,115,116] Early studies in this area demonstrated the effectiveness of Rh_2(*S*-MEPY)$_4$ and Rh_2(*R*-MEPY)$_4$ in providing an enantioselective route to trisubstituted γ-butyrolactones (Scheme 4).[75] In addition to producing high asymmetric induction, the chiral carboxamidate complexes were advantageous in suppressing competing intermolecular carbene dimer and azine formation with respect to $Rh_2(OAc)_4$-catalysed reactions, a phenomenon also observed in later reports.[79,117]

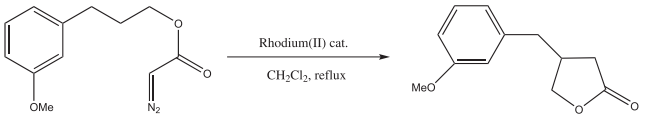


Scheme 4.

A wide variety of Doyle's chiral carboxamidate catalysts have proved to be capable of effecting highly efficient intramolecular C–H activations. The imidazolidinone complex Rh_2(MPPIM)$_4$ has emerged as the superior catalytic choice in many cases, outperforming alternative rhodium(II) carboxamidates in terms of both yield and enantioselectivity (Table 9, entries a–c).[83,86,87,118] It has been suggested that the success of Rh_2(MPPIM)$_4$ may be attributed to its extended *N*-3 phenylpropanoyl chain which causes enhanced steric interactions between the catalyst ligands and the reacting carbene, thereby reducing the number of possible carbenoid orientations and resulting in increased enantioselectivity.[87,118]

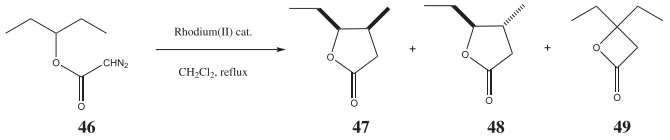
Excellent regio- and diastereocontrol may also be achieved for Rh_2(*S*-MPPIM)$_4$-catalysed C–H insertions. As shown in Table 10 (entries a–d), diazo decomposition of 3-pentyl diazoacetate **46**

Table 9
Intramolecular C–H insertion reaction of 3-(3-methoxyphenyl)propyl 2-diazoacetate in the presence of chiral carboxamidate complexes



Entry	Rhodium(II) cat.	Yield (%)	ee (%)
a	Rh_2(*R*-MPPIM)$_4$	63	93 (4*R*)
b	Rh_2(*S*-MACIM)$_4$	25	84 (4*S*)
c	Rh_2(*R*-MEPY)$_4$	66	68 (4*R*)

Table 10
Intramolecular C–H insertion reaction of diazoacetate **46**



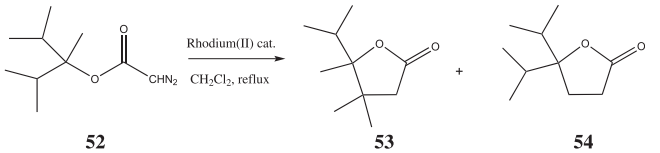
Entry	Rhodium(II) cat.	Yield (%)	Yield (relative %) **47**/**48**/**49**	ee (%) **47**	ee (%) **48**
a	Rh_2(*S*-MPPIM)$_4$	85	92:3:5	99	—
b	Rh_2(*S*-MACIM)$_4$	83	92:5:3	86	36
c	Rh_2(*S*-MEPY)$_4$	75	73:20:7	98	71
d	Rh_2(*S*-MEOX)$_4$	86	60:27:13	98	92

results in three isomeric products (**47**, **48** and **49**). The oxazolidinone complex Rh_2(*S*-MEOX)$_4$ is seen to give the highest level of overall enantiocontrol, but, only Rh_2(*S*-MPPIM)$_4$ provides exceptional control in terms of regio-, diastereo- and enantioselectivity, producing lactone **47** as the major product in high ee.[83]

Rh_2(*S*-MPPIM)$_4$-catalysed C–H insertion reactions have been employed as key steps in the syntheses of the natural lignan lactones, (−)- and (+)-enterolactone, (−)- and (+)-hinokinin, (−)-arctigenin, (+)-isodeoxy-podophyllotoxin, (+)-isolauricerisinol,[86] the necine base, (−)-turneforcidine,[119] and the platelet-aggregration inhibitor, (*S*)-(+)-imperanene **50**.[118] Synthesis of the latter was achieved with excellent enantioselectivity (93% ee) and without any evidence of competing β- or δ-lactone formation (Scheme 5).

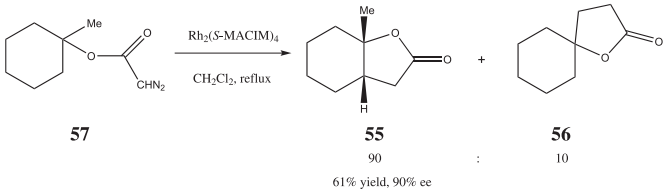
two γ-lactone products (**53** and **54**) resulting from insertion at the methine and methyl sites, respectively.[120] For all catalysts tested, a strong preference for the tertiary insertion product **53** was observed, with Rh_2(*S*-MEPY)$_4$ giving the highest level of regiocontrol, but enantioselectivity in this case was low (61% ee). Despite previously showing success in the C–H insertion reactions of *N*-alkyl-*N*-(*tert*-butyldiazoacetamides),[81] no enantioinduction was recorded for the Rh_2(*S*-MEOX)$_4$-catalysed reaction. The use of Rh_2(*S*-MACIM)$_4$, however, resulted in good regio- and enantiocontrol, although failing to reach the levels of enantioselectivity commonly observed for insertion into methylene C–H bonds.[75,83,115,116] Similar results were obtained for the decomposition of tertiary 2-methyl-1-phenylpropan-2-yl and *tert*-pentyl diazoacetates, with Rh_2(*S*-MACIM)$_4$ again inducing the highest levels of enantioselectivity.[120]

Table 11
Rhodium(II)-catalysed decomposition of 2,3,4-trimethyl-3-pentyl diazoacetate **52**

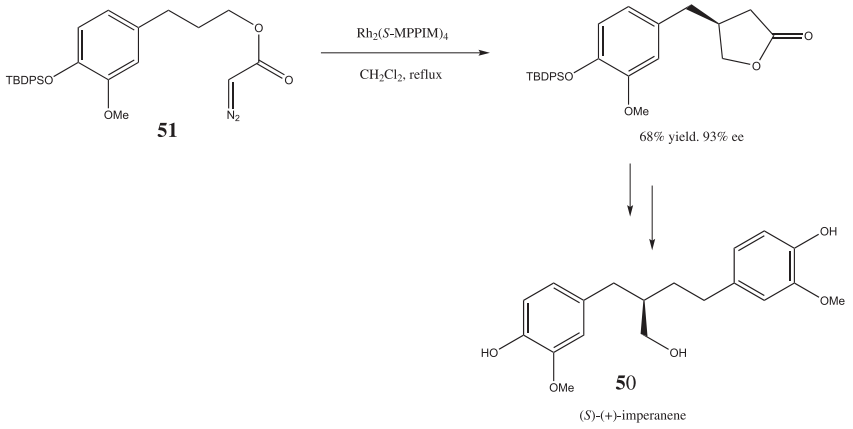


Entry	Rhodium(II) cat.	Yield (%)	**53**/**54**	ee (%) **53**
a	Rh_2(*S*-MACIM)$_4$	73	83:17	85
b	Rh_2(*S*-MEPY)$_4$	66	93:7	61
c	Rh_2(*S*-MEOX)$_4$	70	70:30	0

The C–H activation of tertiary cycloalkyl diazoacetates is also possible;[117,120,121] Rh_2(*S*-MACIM)$_4$ was again found to the optimal catalytic choice for such a process, providing the *cis*-fused bicyclic lactone **55** in 61% yield and 90% ee (Scheme 6).[120] As with the previously described acyclic carbenoid reaction, insertion may occur at more than one site, resulting in both methylene (**55**) and methyl (**56**) insertion products. These results represent an improvement upon previous attempts by Müller and Polleux , who reported a 30% yield



Scheme 6.



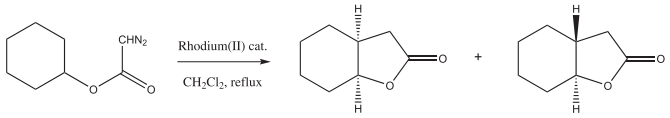
Scheme 5.

In a 1995 report published by Doyle and co-workers, Rh_2(*S*-MACIM)$_4$ was shown to be the optimal catalyst for C–H insertion reactions of tertiary alkyl diazoacetates.[120] As seen in Table 11(entries a–c), decomposition of 2,3,4-trimethyl-3-pentyl diazoacetate **52** gave

and 74% ee for **55** in the Rh_2(*S*-MEPY)$_4$-catalysed decomposition of **57** under similar conditions.[117]

Achievement of higher levels of asymmetric induction is possible for reactions with the related secondary cyclohexyl diazoacetate **58** in which the 1-methyl substituent is absent.[78,117] In this case, production of both *cis*- and *trans*-lactone products (**59** and **60**) was observed, with the greatest overall enantiocontrol being provided by Rh_2(*S*-MEPY)$_4$ and Rh_2(*S*-MEOX)$_4$ and the greatest diastereocontrol being noted for decomposition in the presence of Rh_2(*S*-MACIM)$_4$ (Table 12, entries a–d). The reaction is believed to proceed via equatorial C–H bond insertion, with the *cis*- and *trans*-isomeric products resulting from equilibration between the two possible cyclohexyl chair conformations of the diazoacetate. Such a preference for equatorial C–H bond insertion over axial insertion has been widely observed in carbenoid reactions of cyclohexyl diazoacetates,[10,116,121,122] with only very few exceptions being noted to date.[116,123]

Table 12
Intramolecular C–H insertion reaction of cyclohexyl diazoacetate **58**



58 **59** **60**

Entry	Rhodium(II) cat.	Yield (%)	**59**/**60**	ee (%) **59**	ee (%) **60**
a[a]	Rh_2(*S*-MACIM)$_4$	70	99:1	97	65
b[a]	Rh_2(*R*-MEPY)$_4$	65	75:25	97	91
c[a]	Rh_2(*S*-MEOX)$_4$	50	55:45	96	95
d[b]	Rh_2(*S*-MEPY)$_4$	30	75:25	95	90

[a] Doyle and co-workers.[78]
[b] Müller and Polleux.[117]

As previously discussed, the choice of catalytic system can often be a key decision in determining the regiochemical outcome of intramolecular C–H insertion reactions. This is clearly evident in the decomposition of the bis-diazoacetate of *trans*-1,4-cyclohexanediol **61**, which yields three insertion products (Table 13, entries a–e).[80] The use of the sterically complex imidazolidine catalysts, Rh_2(*S*-MPPIM)$_4$ and Rh_2(*S*-BSPIM)$_4$, in this reaction was seen to produce roughly equal amounts of the predicted bis-lactone **62** and the spirolactone **63**. In contrast, **63** was found to be the dominant product in reactions catalysed by Rh_2(*S*-MEPY)$_4$, Rh_2(*S*-IBAZ)$_4$ and Rh_2(*S*-MEOX)$_4$, which possess a more open catalytic framework by comparison with Rh_2(*S*-MPPIM)$_4$ and Rh_2(*S*-BSPIM)$_4$. The bis-spirolactone **64** was observed as a minor product only in the presence of Rh_2(*S*-MEPY)$_4$ and Rh_2(*S*-MEOX)$_4$. In all cases, two consecutive C–H insertion reactions were seen to occur. The first reaction induces the formation of an excess of one enantiomer over the other. Further enhancement of stereocontrol then occurs in the subsequent insertion reaction. This process of double stereodifferentiation results in extremely high levels of enantioselectivity, with all recorded chiral rhodium(II) carboxamidate-catalysed reactions resulting in ≥95% ee (Table 13). Amplification of asymmetric induction in this way has also been reported by Davies and co-workers for the intermolecular C–H activation of 2-substituted pyrrolidines[124] and dihydronaphthalenes.[125]

A different strategy towards achieving enhanced stereocontrol in C–H insertion reactions was adopted by Doyle and co-workers, in 2005, who examined the application of catalysts possessing two stereogenic centres in the carbenoid reactions of cycloalkyl diazoacetates.[126] For this purpose, two diastereomeric rhodium(II) catalyst pairs (**65**, **66**, **67** and **68**) were prepared by structural alteration of the *N*-acyl substituent of the methyl 2-oxo-imidazolidine-4*S*-carboxylate core structure (Fig. 18).

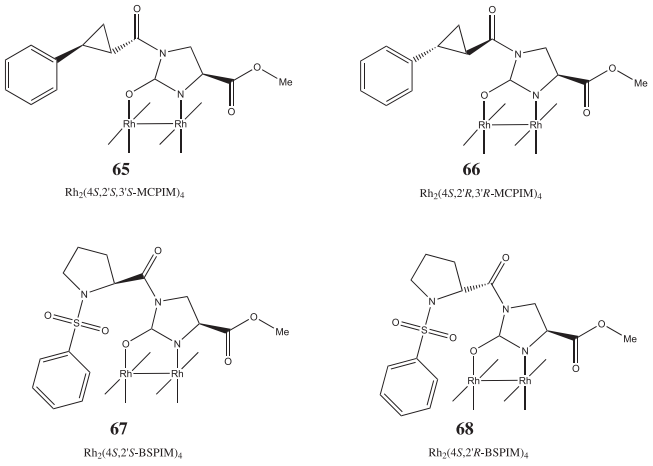
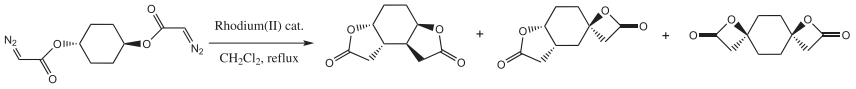


Figure 18.

Employment of these novel rhodium(II) complexes in the decomposition of cyclopentyl and cyclohexyl diazoacetate revealed the occurrence of a distinct 'match/mismatch' phenomenon between the chiral ligand attachments. In 'matched' situations, where orientation of the ligand stereocentres was favourable, enantioselectivities for **69** and **70** were equivalent or improved with respect to those obtained with Rh_2(*S*-MPPIM)$_4$ (Table 14, entries a and f vs b, d and g). In contrast, the 'mismatched' case, defined by unfavourable catalyst orientations, resulted in a dramatic lowering of enantiocontrol (Table 14, entries a and f vs c, e and h). 'Matched/mismatched' effects were observed to the greatest effect with the *N*-benzenesulfonylprolinate-substituted catalysts **67** and **68**, with decreases in ee as large as 71% being recorded.

The propensity for five-membered ring formation in C–H insertion reactions has long been accepted.[6] As seen in the decomposition of **61**, however,[80] this preference is not absolute and the formation of four-membered ring products may also be

Table 13
Bis-lactone versus spirolactone formation in the decomposition of the bis-diazoacetate of *trans*-1,4-cyclohexanediol **61**

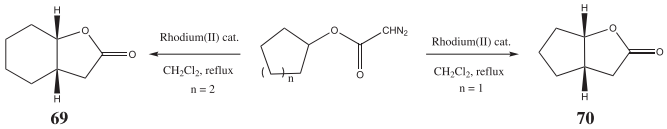


61 **62** **63** **64**

Entry	Rhodium(II) cat.	**62**/**63**/**64**	Yield[a] (%)	ee (%) **63**
a	Rh_2(*S*-MPPIM)$_4$	48:52:0	91	—
b	Rh_2(*S,S*-BSPIM)$_4$	48:52:0	90	99
c	Rh_2(*S*-MEPY)$_4$	11:80:9	58	95
d	Rh_2(*S*-IBAZ)$_4$	6:94:0	43	96
e	Rh_2(*S*-MEOX)$_4$	1:65:34	81	99

[a] Combined yield of **62**, **63** and **64**.

Table 14
Diazo decomposition in the presence of rhodium(II) complexes possessing two stereogenic centres



69 **70**

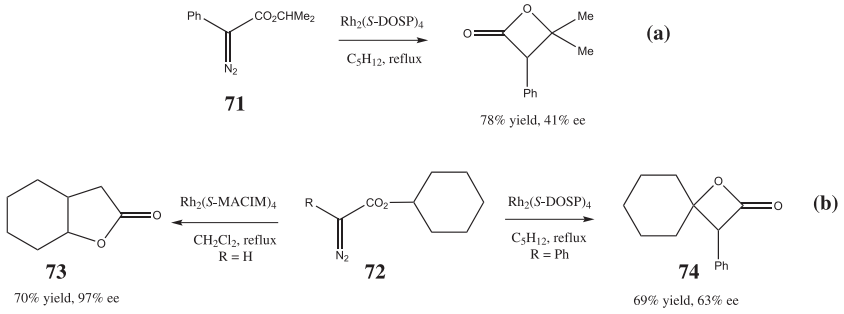
Entry	Rhodium(II) cat.	*n*	Yield (%) **69**/**70**	ee (%) **69**/**70**
a	Rh_2(*S*-MPPIM)$_4$	1	67	93
b	Rh_2(4*S*,2′*S*,3′*S*-MCPIM)$_4$ **65**	1	81	88
c	Rh_2(4*S*,2′*R*,3′*R*-MCPIM)$_4$ **66**	1	75	40
d	Rh_2(4*S*,2′*S*-BSPIM)$_4$ **67**	1	78	98
e	Rh_2(4*S*,2′*R*-BSPIM)$_4$ **68**	1	62	22
f	Rh_2(*S*-MPPIM)$_4$	2	71	92
g	Rh_2(4*S*,2′*S*-BSPIM)$_4$ **67**	2	88	>99[a]
h	Rh_2(4*S*,2′*R*-BSPIM)$_4$ **68**	2	89	74[a]

[a] Minor amounts of the *trans*-lactone also observed.

observed. Such an occurrence has been noted in several intramolecular carbenoid reactions.[83,121,122,127] In 2001, Doyle and co-worker published a report of enantioselective β-lactone formation from phenyl diazoacetates.[127] Despite the introduction of considerable ring strain via its formation and the deactivating effect of the adjacent electron-withdrawing ester group, successful β-lactone formation was observed from isopropyl and cyclohexyl diazoacetate precursors **71** and **72**, respectively [Scheme 7(a) and 7 (b)] In both instances, β-lactone formation was the dominant process over competing γ-lactone formation and moderate enantioselectivities were possible in the presence of Rh_2(*S*-DOSP)$_4$. The phenyl functionality at the α-diazo position of the isopropyl and cyclohexyl substrates is of critical importance in producing the targeted four-membered ring. Replacement of the phenyl group with hydrogen causes a shift in product formation towards the more sterically favourable γ-lactone, as observed in the decomposition of cyclohexyl diazoacetate **72** (R=H), in which production of the γ-lactone **73** is dominant and formation of β-lactone **74** is negligible [Scheme 7(b)].[78]

Competition between γ- and β-lactone formation was again observed for the C–H insertion reactions of 3-substituted steroidal diazoacetates **75** (Table 15).[122] Catalyst selection in this study was seen to have a significant effect on regioselectivity, with *R*-configured catalysts favouring formation of the γ-lactone product **76** (Table 15, entries b and d) and *S*-configured catalysts favouring formation of the β-lactone product **77** (Table 15, entries a and c). In all cases, insertion occurs via equatorial C–H bond insertion. Decomposition of **75** in the presence of chiral bis(oxazoline) copper(I) complexes was also shown to be a viable option, although regioselectivities in this case were poor. As previously observed,[127] changing to the phenyl-substituted diazoacetate carbenoid precursor (R=Ph) resulted in exclusive β-lactone production (Table 15, entries e and f).

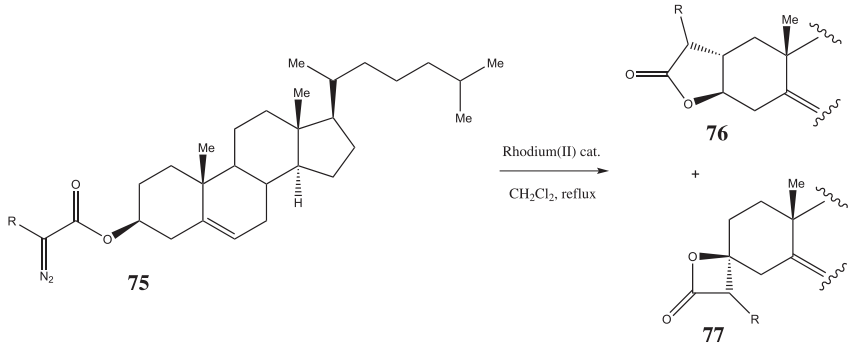
6.1.2. Chromanone synthesis. The first application of C–H insertion chemistry for the enantioselective synthesis of six-membered



71 **73** **72** **74**

Scheme 7.

Table 15
β- versus γ-lactone formation in the C–H insertion reactions of 3-substituted steroidal diazoacetates **75**

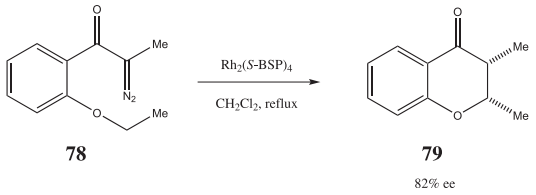


75 **76** **77**

Entry	Rhodium(II) cat.	R	Yield (%)	**76**/**77**
a	Rh_2(*S*-MEPY)$_4$	H	74[a]	33:67
b	Rh_2(*R*-MEPY)$_4$	H	81[a]	94:6
c	Rh_2(*S*-MEOX)$_4$	H	80[a]	10:90
d	Rh_2(*R*-MEOX)$_4$	H	81[a]	89:11
e	Rh_2(*R*-MEAZ)$_4$	Ph	69	0:100
f[b]	Rh_2(*S*-DOSP)$_4$	Ph	58	0:100

[a] Combined yield of **76** and **77** following separation from the catalyst.
[b] Reaction conducted in refluxing pentane.

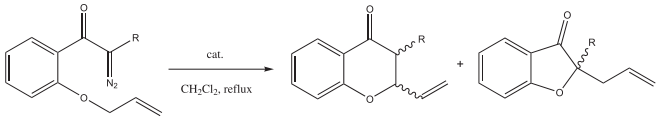
oxygen heterocycles was published by McKervey and Ye in 1992.[128] In this study, the asymmetric production of various chromanones from α-diazoketone substrates in the presence of chiral rhodium(II) carboxylate catalysts was reported. Enantioselectivities obtained were in general moderate, with the best results being noted for the decomposition of **78** with the prolinate catalyst Rh_2(*S*-BSP)$_4$ providing primarily the *cis*-isomer of **79** in 82% ee (Scheme 8).



Scheme 8.

The range of possible diazo precursors for carbenoid chromanone synthesis was later extended to include phenyl and vinyl derivatives of **78**.[52] Decomposition of **80** in the presence of a variety of different chiral rhodium(II) and copper(I) catalysts was shown to result in two isomeric products, arising from C–H insertion (**81**) and oxonium ylide-2,3-sigmatropic rearrangement pathways (**82**), respectively. Reaction with all tested carboxylate catalysts was seen to give predominantly the C–H insertion product **81** (Table 16, entries a–d), while cyclisation under the influence of a chiral copper(I) bis(oxazoline) complex provided solely benzofuranone **82** (Table 16, entries e and f). Rh_2(*S*-BSP)$_4$ was again shown to induce the highest levels of asymmetric induction, producing *cis*-**81** in 60% ee. Improvement of this value to 79% ee was possible by a reduction of the reaction temperature to 0 °C.

Table 16
C–H insertion versus oxonium ylide-2,3-sigmatropic rearrangement in the decomposition of **80**



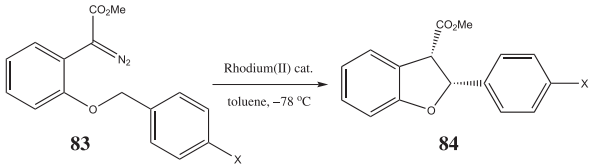
Entry	Cat.	R	**81**/**82**	**81** *cis*/*trans*	ee[a] (%) **81**
a	Rh_2(*S*-BSP)$_4$	Me	97:3	93:7	60
b	Rh_2(*S*-BSP)$_4$	Ph	95:5	[b]	45
c	**7b**	Me	96:4	85:15	31
d	**7c**	Me	82:18	75:25	20
e	Cu/**4f**	Me	0:100	—	—
f	Cu/**4f**	Ph	0:100	—	—

[a] Enantioselectivity for *cis*-**81**.
[b] Values not provided in original report.

6.1.3. Dihydrobenzofuran synthesis. Numerous research groups have undertaken investigations examining the synthesis of dihydrobenzofurans via decomposition of aryl diazoacetates. In 2002, Hashimoto and co-workers reported the enantio- and diastereoselective synthesis of *cis*-2-aryl-3-methoxycarbonyl-2,3-dihydrobenzofurans **83** via rhodium(II) carboxylate-catalysed C–H insertion reactions.[129] The choice of catalyst in this study was seen to be key, with only the phthaloyl catalysts Rh_2(*S*-PTTL)$_4$ and Rh_2(*S*-BPTTL)$_4$, both featuring a bulky *tert*-butyl substituent, providing exclusively the *cis*-isomer **84** with good enantioselectivity (Table 17, entries a–e). This high level of asymmetric induction was found to be preserved for the decomposition of aryl diazoacetates possessing electron-withdrawing or -donating groups in the *para* position on the benzene ring (Table 17, entries c–e).

The presence of both the benzene ring of the aryl diazoacetate and the oxygen adjacent to the C–H insertion site is believed to be

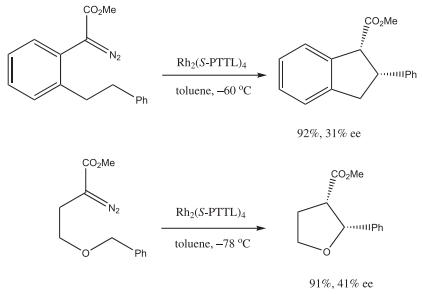
Table 17
Enantio- and diastereoselective synthesis of *cis*-2-aryl-3-methoxycarbonyl-2,3-dihydrobenzofurans via rhodium(II) carboxylate-catalysed C–H insertion reactions



Entry	Rhodium(II) cat.	X	Yield[a] (%) **84**	ee (%) **84**
a	Rh_2(*S*-PTTL)$_4$	H	86	94
b	Rh_2(*S*-BPTTL)$_4$	H	70	91
c	Rh_2(*S*-PTTL)$_4$	Cl	79	94
d	Rh_2(*S*-PTTL)$_4$	Me	84	91
e	Rh_2(*S*-PTTL)$_4$	OMe	89	94

[a] trans Isomer (<1%) observed.

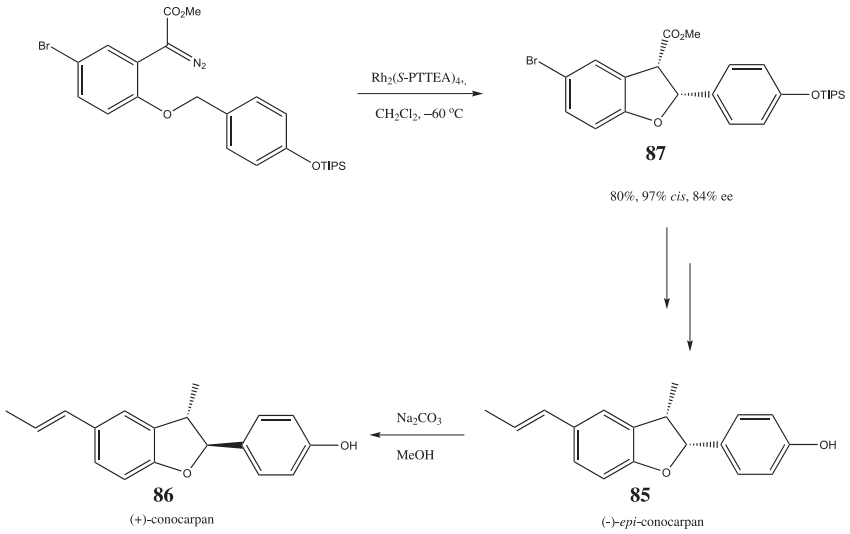
crucial in allowing highly enantioselective reactions to occur. As seen in Scheme 9, loss of either feature results in the destruction of enantiocontrol.[129] This result reinforces previous findings by McKervey, who noted very low asymmetric induction for the synthesis of *cis*-disubstituted dihydrofurans from acyclic diazoacetate precursors.[130]



Scheme 9.

The synthetic methodology described has been successfully applied to the asymmetric synthesis of the neolignans, (−)-*epi*-conocarpan **85** and (+)-conocarpan **86**.[54] For this purpose, the newly developed rhodium(II) carboxylate complex Rh_2(*S*-PTTEA)$_4$ was found to be the most advantageous catalyst choice, providing the desired *cis* isomer of **87** in 80% yield and 84% ee (Scheme 10). A similar synthetic strategy has been adopted by Fukuyama and co-workers for the total syntheses of the macrocyclic spermine alkaloid, (−)-ephedradine,[131,132] and the pentacyclic indole alkaloid, (−)-serotobenine.[133] In contrast to the cyclisations carried out by Hashimoto and co-workers, exclusive formation of the thermodynamically favourable *trans* isomer of the dihydrobenzofuran products was reported for the production of both natural products. Such an outcome was achieved by an increase in steric bulk at the ester moiety of the aryl diazoacetate via attachment of a chiral auxiliary.

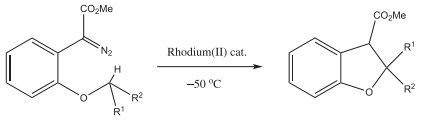
Catalyst choice for the intramolecular C–H insertion formation of dihydrobenzofurans may be extended beyond Hashimoto's phthaloyl complexes to include proline-, adamantylglycine- and imidazolidinone-derived catalysts, namely Rh_2(*S*-DOSP)$_4$, Rh_2(*S*-PTAD)$_4$ and Rh_2(OAc)(DPTI)$_3$ (DPTI=diphenyltriflylimidazolidinone). Aryl diazoacetate decomposition in the presence of the latter complex has been shown to occur with moderate yield (51%) and excellent enantioselectivity (96% ee).[134] Insertion into methine, methylene and methyl sites is possible in the presence of Rh_2(*S*-DOSP)$_4$ or the related bridged complexes Rh_2(*S*-biTISP)$_4$ and Rh_2(*S*-biTBSP)$_4$



Scheme 10.

(Table 18).[135] Greatest enantiocontrol for primary C–H insertion reactions was observed with Rh_2(*S*-biTISP)$_4$ and Rh_2(*S*-biTBSP)$_4$ (Table 18, entries a and b), while cyclisation with Rh_2(*S*-DOSP)$_4$ provided the highest levels of asymmetric induction for reaction at tertiary sites (Table 18, entries f–h). All three catalysts proved to be proficient for C–H insertion into a methylene group (Table 18, entries c–e). The fact that Rh_2(*S*-DOSP)$_4$ and the bridged catalysts Rh_2(*S*-biTISP)$_4$ and Rh_2(*S*-biTBSP)$_4$ provide the opposite sense of asymmetric induction has also been noted in both cyclopropanation[61,136] and intermolecular C–H insertion processes.[63,65]

Table 18
Intramolecular C–H insertion of aryl diazoacetates into methine, methylene and methyl C–H bonds

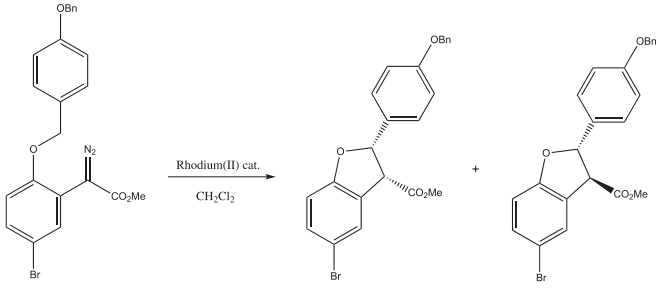


Entry	Rhodium(II) cat.	R^1	R^2	Solvent	Yield (%)	ee (%)
A	Rh_2(*S*-biTISP)$_4$	H	H	CH_2Cl_2	70	43 (–)
B	Rh_2(*S*-biTBSP)$_4$	H	H	CH_2Cl_2	70	68 (–)
c	Rh_2(*S*-DOSP)$_4$	H	Me	Hexane	85[a]	60 (–)[d]
d	Rh_2(*S*-biTISP)$_4$	H	Me	CH_2Cl_2	50[b]	53 (+)[d]
e	Rh_2(*S*-biTBSP)$_4$	H	Me	CH_2Cl_2	70[c]	45 (+)[d]
f	Rh_2(*S*-DOSP)$_4$	Me	Me	Hexane	98	94 (+)
g	Rh_2(*S*-biTISP)$_4$	Me	Me	CH_2Cl_2	48	60 (–)
h	Rh_2(*S*-biTBSP)$_4$	Me	Me	CH_2Cl_2	57	65 (–)

[a] Yield of cis and trans isomers, de (cis)=60%.
[b] Yield of cis and trans isomers, de (cis)=70%.
[c] Yield of cis and trans isomers, de (cis)=75%.
[d] % ee of cis isomer.

The ability of Davies' adamantyl catalyst Rh_2(*S*-PTAD)$_4$ to successfully catalyse enantioselective intramolecular C–H insertions was first demonstrated for the synthesis of *cis*-2-aryl-3-methoxycarbonyl-2,3-dihydrobenzofurans,[67] in which the asymmetric induction obtained was seen to be in the range of previous results recorded by Hashimoto and co-workers for the same transformation.[129] In the same study, a vast improvement in the stereochemical outcome was observed for employment of Rh_2(*S*-PTAD)$_4$ in a key step in the synthesis of the natural product, (–)-ephedradine A.[67] The synthetic route earlier adopted by Fukuyama and co-workers provided low levels of enantioselectivity (32% ee) and diastereoselectivity (20% de) in the presence of Rh_2(*S*-DOSP)$_4$ (Table 19, entry a). Reasonable stereocontrol [86% de (trans)] was obtained only when Rh_2(*S*-DOSP)$_4$ was used in conjunction with a lactamide-type chiral auxiliary.[131,137] In contrast, the Rh_2(*S*-PTAD)$_4$-catalysed decomposition of **88** provided predominantly the *cis* isomeric product **89** in 87% de and 79% ee in the absence of any chiral auxiliary (Table 19, entry b). The desired *trans* isomer **90** could then be easily obtained by equilibration in the presence of sodium methoxide.

Table 19
The key C–H insertion step in the synthesis of (–)-ephedradine A



88 **89** **90**

Entry	Rhodium(II) cat.	*T* (°C)	Yield (%)	**89**/**90**	ee (%) **89**	ee (%) **90**
a[a]	Rh_2(*S*-DOSP)$_4$	23	72	2:3	—	32
b[b]	Rh_2(*S*-PTAD)$_4$	0	72	14:1	79	—

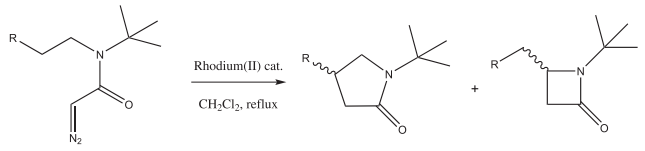
[a] Results reported by the Fukuyama group.[137]
[b] Results reported by the Davies group.[67]

6.2. Nitrogen-containing heterocycle synthesis

6.2.1. Lactam synthesis. Early studies exploring the enantioselective synthesis of nitrogen-containing heterocycles were conducted by Doyle and co-workers, who examined the rhodium(II) carboxamidate-catalysed C–H insertion reactions of *N*-alkyl-*N*-(*tert*-butyl) diazoacetamides.[81] As was observed with the corresponding lactone syntheses, production of both four-(β-lactam) and five-(γ-lactam) membered ring products may occur. Control of such regiochemical variation was shown to be possible by careful choice of *N*-alkyl substituent for the diazoamide precursor (Table 20, entries a–f). Thus, while a mixture of β-(**91**) and γ-(**92**) lactam products was

observed for the C–H insertion reactions of *N*-(*tert*-butyl)-2-diazo-*N*-pentylacetamide and *N*-(*tert*-butyl)-2-diazo-*N*-(4-methylpentyl) acetamide (Table 20, entries a–d), exclusive γ-lactam formation was recorded for decomposition of the ethoxy derivative of **93** (R=OEt), providing pyrrolidinone **92** in high yield and moderate enantioselectivity for cyclisation with both Rh_2(*S*-MEPY)$_4$ and Rh_2(*S*-MEOX)$_4$ (Table 20, entries e and f).

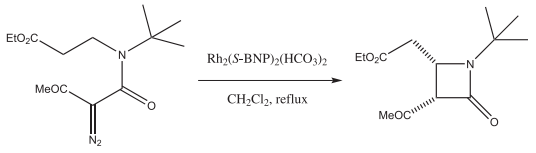
Table 20
Rhodium(II) carboxamidate-catalysed C–H insertion reactions of *N*-alkyl-*N*-(*tert*-butyl)diazoacetamides



93 **92** **91**

Entry	Rhodium(II) cat.	R	Yield (%)	**92**/**91**	ee (%) **92**	ee (%) **91**
a	Rh_2(*S*-MEPY)$_4$	Et	74	88:12	63	73
b	Rh_2(*S*-MEOX)$_4$	Et	82	91:9	71	80
c	Rh_2(*S*-MEPY)$_4$	*i*-Pr	91	80:20	58	72
d	Rh_2(*S*-MEOX)$_4$	*i*-Pr	93	82:18	69	65
e	Rh_2(*S*-MEPY)$_4$	OEt	91	100:0	58	—
f	Rh_2(*S*-MEOX)$_4$	OEt	97	100:0	78	—

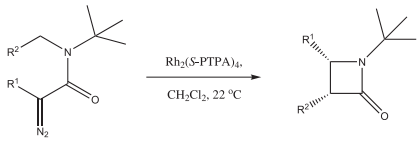
Although the formation of five-membered rings is typically favoured in C–H insertion reactions,[6] generation of β-lactam products is feasible, owing to the activating effect of the adjacent nitrogen atom at the insertion site.[138] In studies employing the achiral $Rh_2(OAc)_4$ catalyst, the *N*-*tert*-butyl group has proved to be superior to other possible substituents in inducing preferential β-lactam formation.[138] Such a trend is preserved for diazoacetamide decomposition in the presence of chiral rhodium(II) complexes. As seen in Scheme 11, β-lactam **94** is the sole product from the Rh_2(*S*-BNP)$_2$(HCO$_3$)$_2$-catalysed C–H insertion reaction of the *N*-*tert*-butyl diazoacetamide **95**.[89]



95 **94**
93%, >99% de, 26% ee

Scheme 11.

Table 21
Intramolecular C–H insertion reaction of *N*-alkyl-*N*-*tert*-butyl-α-methoxycarbonyl-α-diazoacetamides **96**



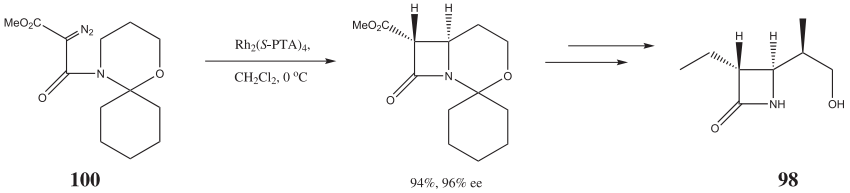
96 **97**

Entry	R^1	R^2	Yield (%) **97**	ee (%) **97**
a	CO_2Me	Ph	94	74 (3*R*, 4*R*)
b	CO_2Me	CH_2CO_2Me	98	56 (3*R*, 4*S*)
c[a]	CO_2Me	$CH_2CH_2CH_3$	97	60 (3*R*, 4*S*)
d	COMe	Ph	64[b]	50 (3*R*, 4*R*)

[a] Reaction was conducted at 16 °C.
[b] *trans* Isomer of **97**.

diazo from the methoxycarbonyl group to the acetyl group resulted in lower asymmetric induction and the formation of the *trans* isomer of **97** (Table 21, entry d). This would seem to suggest that isomerisation of the initial *cis* product of **97** (R^1=COMe) occurs to generate the observed trans stereoisomer. Isomerisation of this type had previously been encountered by Doyle and co-workers in a study of the C–H insertion reactions of *N*,*N*-disubstituted diazoacetoacetamides.[140]

While the ability of the *N*-*tert*-butyl group to induce preferential β-lactam formation in the above examples cannot be doubted, subsequent removal of this *tert*-butyl group may prove problematic. Such an obstacle was encountered by Hashimoto and co-workers in their attempts to produce a key azetidin-2-one for the synthesis of carbapenem antibiotics.[141] Resolution of this issue was possible by replacement of the troublesome *tert*-butyl group with an *N*,*O*-acetal moiety. This strategy was found to maintain exclusive β-lactam formation, whilst also providing high levels of enantiocontrol in the presence of Rh_2(*S*-PTA)$_4$, thus allowing synthesis of the desired carbapenem **98** (Scheme 12). A similar approach was adopted for the generation of a key intermediate required for the synthesis of trinem antibiotics.[142] Interestingly, in this study, Rh_2(*S*-PTA)$_4$-catalysed decomposition of the *N*,*O*-cyclohexylidene acetal **99**, which differs from **100** by the incorporation of a benzene ring, provided predominantly the opposite enantiomer (−)-**101** than that expected from the cyclisation of **100**. Such a result was also observed for catalysis with Rh_2(*S*-PTPA)$_4$, Rh_2(*S*-PTPG)$_4$ and Rh_2(*S*-PTV)$_4$. Enantioselective production of the desired (+)-**101** was, however, found to be possible for reaction in the presence of Rh_2(*S*-PTTL)$_4$, thereby permitting synthesis of the trinem intermediate **102** (Scheme 13).

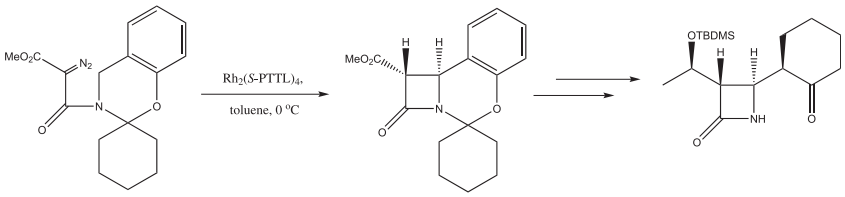


100 94%, 96% ee **98**

Scheme 12.

A similar outcome was observed for the intramolecular C–H insertion reactions of *N*-alkyl-*N*-*tert*-butyl-α-methoxycarbonyl-α-diazoacetamides.[139] Cyclisation of **96** in the presence of the phthaloyl catalyst Rh_2(*S*-PTPA)$_4$ was seen to provide exclusively the *cis* isomer of azetidinone **97** (Table 21, entries a–c). Highest enantioselectivity was noted for the decomposition of the *N*-benzyl-*N*-*tert*-butyl derivative of **96**, producing **97** in 94% yield and 74% ee (Table 21, entry a). Interestingly, change of the substituent α to the

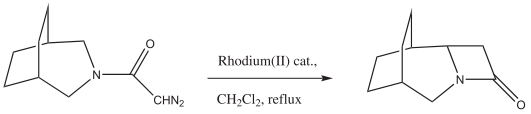
Preferential β-lactam formation may also be observed for the decomposition of diazoacetylazacycloalkanes. The C–H insertion reaction of 3-diazoacetyl-3-azabicyclo[3.2.2]nonane **103** was shown to produce β-lactam **104** as the sole product in high yield and high enantioselectivity (Table 22, entries a and b).[76] It is thought that the conformational rigidity imparted by the cyclic system of **103** is responsible for the observed exclusive β-lactam formation. Thus, reaction of the more flexible diazoamide **105**



Scheme 13.

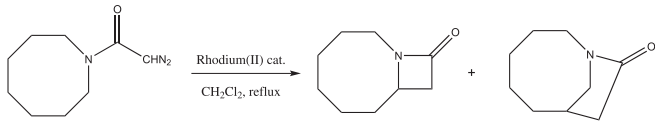
provides both β-(**106**) and γ-(**107**) lactam products (Table 23, entries a and b).

Table 22
Preferential β-lactam formation in the C–H insertion reaction of 3-diazoacetyl-3-azabicyclo[3.2.2]nonane **103**



Entry	Rhodium(II) cat.	Yield (%) **104**	ee (%) **104**
a	Rh_2(*S*-MEOX)$_4$	81	93
b	Rh_2(*S*-MEPY)$_4$	70	96

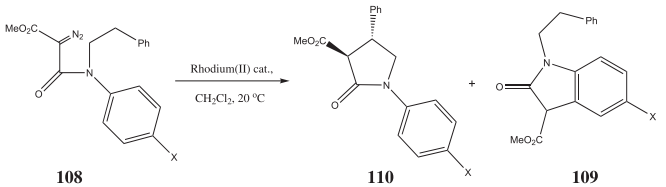
Table 23
β- versus γ-lactam formation in the C–H insertion reaction of **105**



Entry	Rhodium(II) cat.	Yield (%)	**106**/**107**	ee (%) **106**	ee (%) **107**
A	Rh_2(*S*-MEOX)$_4$	95	26/74	15	98
b	Rh_2(*S*-MEPY)$_4$	97	40/60	31	97

The first enantioselective catalytic synthesis of 4-aryl-substituted 2-pyrrolidinones was reported by Hashimoto and Anada in 1998 (Table 24).[143] In this study, aromatic C–H insertion was found to be a competing reaction pathway in the decomposition of the α-methoxycarbonyl diazoacetamide **108** (X=OMe), producing an excess of 2(3*H*)-indolinone **109** over the desired aliphatic C–H insertion product *trans*-pyrrolidinone **110** for the Rh_2(*S*-PTPA)$_4$-catalysed reaction (Table 24, entry a). It is believed that aromatic C–H insertion reactions proceed via a mechanism of electrophilic addition of the rhodium(II) carbenoid carbon to the aromatic ring followed by 1,2-hydride migration to give the aromatic insertion product.[71,144] Therefore, elimination of this competing process may be achieved by attachment of an electron-withdrawing substituent at the *para* position of the aromatic ring. This was indeed found to be true and exclusive production of **110** was observed for the C–H insertion reaction of **108** (X=NO_2) in the presence of various rhodium(II) phthaloyl complexes (Table 24, entries b–e). The success of this method was illustrated in the syntheses of the $GABA_A$ receptor agonist, (*R*)-(−)-baclofen,[143] and the phosphodiesterase type IV inhibitor, (*R*)-(−)-rolipram,[57] both of which feature enantioselective C–H insertion reactions of *N*-4-nitrophenyl-α-methoxycarbonyl-α-diazoacetamides as the key synthetic steps.

Table 24
Enantioselective rhodium(II)-catalysed synthesis of 4-aryl-substituted 2-pyrrolidinones



Entry	Rhodium(II) cat.	X	Yield (%)	**110**/**109**	ee (%) **110**
a	Rh_2(*S*-PTPA)$_4$	OMe	73	5:68	[a]
b	Rh_2(*S*-PTPA)$_4$	NO_2	82	100:0	47
c	Rh_2(*S*-PTV)$_4$	NO_2	82	100:0	26
d	Rh_2(*S*-PTTL)$_4$	NO_2	80	100:0	74
e	Rh_2(*S*-PTA)$_4$	NO_2	83	100:0	47

[a] Value not provided in original report.

The elimination of competing reaction pathways may also be accomplished by careful choice of catalyst system.[123] As seen in Table 25 (entries a–d), decomposition of diazoacetamide **111** may result in both C–H insertion product **112** and aromatic insertion product **113**, arising from two possible orientations of the carbenoid intermediate. Predominant γ-lactam production is achievable by reaction in the presence of Rh_2(*S*-MEPY)$_4$, providing **112** in good yield and high enantioselectivity. Employment of the oxazolidinone, imidazolidinone and azetidinine catalysts, Rh_2(*S*-MEOX)$_4$, Rh_2(*S*-MPPIM)$_4$ and Rh_2(*S*-IBAZ)$_4$, respectively, was, however, found to generate significant amounts of **113**, along with small quantities of the β-lactam product **114**.

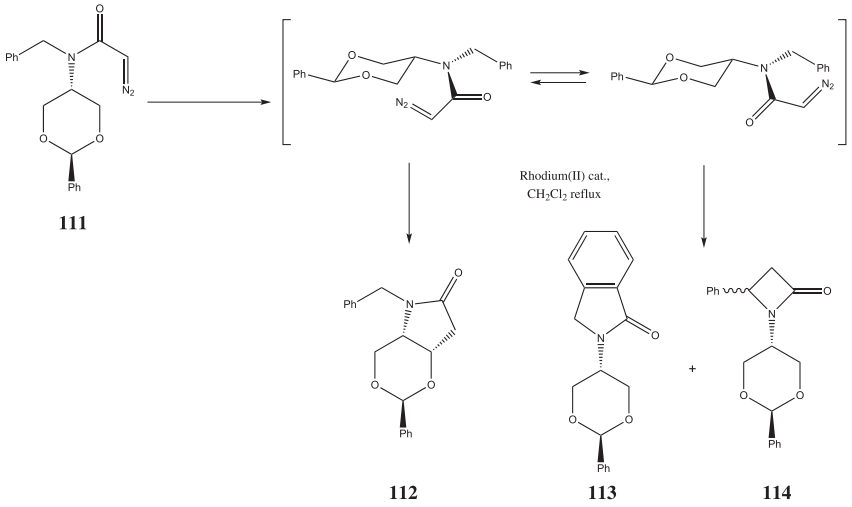
An enhancement in regio- and enantiocontrol is possible for this process by exchange of the *N*-benzyl group for the more sterically demanding *N*-bis(trimethylsilyl)methyl (*N*-BTMSM) moiety.[145] This N-protecting group has previously been shown to deliver effective conformational control for the $Rh_2(OAc)_4$-catalysed intramolecular C–H insertion reactions of various diazoamides, permitting highly regioselective reactions to occur.[146,147] Despite possessing a tertiary C–H bond, the *N*-BTMSM group remains inert towards C–H insertion, due to probable shielding of the methine C–H bond by the two trimethylsilyl groups.[146] For the decomposition of **115** (Scheme 14), use of an *N*-BTMSM diazoamide not only provides exclusive access to the desired γ-lactam product **116**, but also allows the subsequent facile removal of the *N*-silyl substituent, and is thus the optimum route for the production of 2-deoxyxylonolactam.[145]

Such a strategy of *N*-BTMSM protection has been successfully adopted for the synthesis of the GABA analogue, (*R*)-β-benzyl-γ-aminobutyric acid **117** (Scheme 15).[148]

6.3. Sulfur-containing heterocycle synthesis

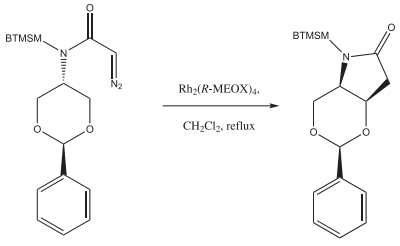
Despite the wide interest in, and application of, sulfur-containing heterocycles in pharmaceutical chemistry,[149] the study of C–H insertion processes generating such compounds has

Table 25
C–H insertion versus aromatic cycloaddition in the rhodium(II)-catalysed decomposition of diazoacetamide **111**



111 **112** **113** **114**

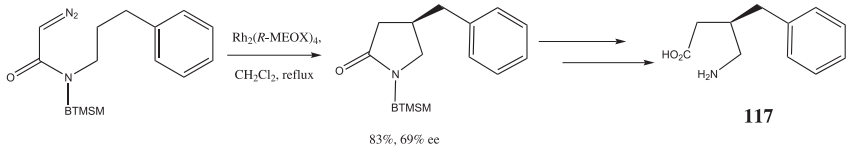
Entry	Rhodium(II) cat.	**112**/**113**/**114**	Yield (%) **112**	ee (%) **112**
a	Rh_2(*S*-MEPY)$_4$	95:5:0	75	85
b	Rh_2(*S*-MEOX)$_4$	74:16:10	61	78
c	Rh_2(*S*-MPPIM)$_4$	53:18:29	48	37
d	Rh_2(*S*-IBAZ)$_4$	49:35:16	45	19



115 **116**

Scheme 14.

reactions of α-diazosulfones (Table 26).[4] In addition to providing a novel enantioselective reaction pathway to such compounds, this report was significant in achieving its goal with the use of copper catalysis. While copper catalysts have previously been employed in C–H insertion processes,[31,114] enantioselectivities achieved have been, in general, moderate, with the highest asymmetric induction being noted for intermolecular C–H insertion in the presence of an immobilised Cu(I) bis(oxazoline) ligand (88% ee).[30] Thus, this publication represents the highest level of enantiocontrol achieved to date in a copper-mediated C–H insertion reaction. As seen in Table 26 (entries a–e), enantioselectivities of up to 98% ee were realised for the decomposition of various substituted α-diazosulfones. The trend towards preferential six-membered-ring formation for carbenoid

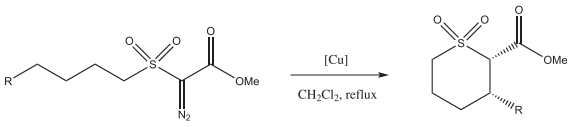


117

Scheme 15.

remained a largely neglected area. Indeed, only a minimum of reports exist documenting the successful synthesis of sulfur heterocycles via carbenoid chemistry and, until recently, such reactions have been realised only in a racemic fashion.[150–153] In 2007, Novikov and co-worker reported the selective formation of six-membered cyclic sulfonates and sulfones by C–H insertion.[152] Such a finding was surprising, given the large preference in diazo decomposition reactions for the formation of five-membered-ring products.[6] This outcome has been rationalised, however, by the difference in bond lengths and bond angles observed around the sulfur atom, which are thought to mimic the geometry of the six-membered ring,[152,153] as was also observed for intramolecular C–H aminations.[154] The first, and only, report of the enantioselective production of sulfur heterocycles employing C–H insertion chemistry was published in 2009 by Maguire and co-workers for the C–H insertion

Table 26
Copper(I)-catalysed C–H insertion reactions of α-diazosulfones **118**



118 **119**

Entry	R	Cat.[a]	Yield (%) **119**	ee (%) **119**
a	Ph	Cu(I)Cl, NaBARF, **4g**	47	98
b	Ph	Cu(MeCN)$_4$PF$_6$, **4g**	19	94
c	*p*-Tol	Cu(I)Cl, NaBARF, **4g**	64	96
d	Bn	Cu(I)Cl, NaBARF, **4g**	42	96
e	Et	Cu(I)Cl, NaBARF, **4g**	68	97

[a] BARF=tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

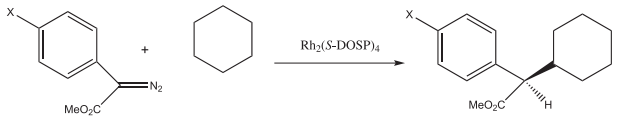
synthesis of sulfur heterocycles, as previously observed by Novikov and co-workers,[152,153] was seen to be preserved, with all thiopyran products forming in a highly enantioselective fashion (94–98% ee) and with cis selectivity.

7. Intermolecular C–H insertion reactions

While the early 1990s represented a period of vast growth and research in the area of intramolecular carbenoid C–H insertion,[2,3,53,75,81] the corresponding intermolecular C–H insertion processes at this time were not generally regarded as being synthetically efficient.[6,7] Such an opinion may be attributed to observed competing dimer formation[25,155] and the typically poor regioselectivities recorded.[25,156–159] Research published by Davies and co-workers in the late 1990s, however, served to provide a renewed interest in this previously neglected area, owing to the discovery that carbenoids substituted with one electron-donating group and one electron-withdrawing group (donor/acceptor-substituted carbenoids) are capable of undergoing highly chemo- and regioselective intermolecular C–H insertions.[160] The presence of a donor group in such species serves to stabilise the donor/acceptor carbenoid with respect to traditional carbenoids derived from alkyl diazoacetates, with the result that insertion into the target C–H bond occurs in a more chemo- and regioselective manner.[161,162]

Highly enantioselective intermolecular C–H insertions can be achieved for donor/acceptor carbenoids when the reactions are catalysed by the chiral rhodium(II) tetraprolinate catalyst Rh_2(*S*-DOSP)$_4$. In 1997, Davies and co-workers reported the first asymmetric intermolecular C–H insertion reaction using metal carbenoid intermediates.[160] Decomposition of various aryl diazoacetates by Rh_2(*S*-DOSP)$_4$ in the presence of cyclohexane (Table 27, entries a–e) and tetrahydrofuran (Scheme 16) as solvents was shown to occur with high levels of enantioselectivity and in excellent yields.

Table 27
Intermolecular C–H insertion reactions of cyclohexane and aryl diazoacetates



Entry	X	*T* (°C)	Yield (%)	ee (%)
a	H	81	83	81
b	H	50	69	88
c	Cl	81	91	86
d	Cl	25	53	93
e	OMe	81	85	67

A number of key trends were identified during this initial study, which have been shown to parallel the results obtained in subsequent investigations into intermolecular C–H insertion processes. Lower reaction temperatures were found to favour increased enantioselectivity.[64,163,164] Improvements in both yields and enantioselectivity were noted upon changing from an electron-donating (X=OMe) to an electron-withdrawing (X=Cl) aromatic substituent for aryl diazoacetate precursors,[67,163,165,166] as had previously been noted in intramolecular C–H insertion studies.[93,107] As seen in Scheme 16, insertion is favoured at positions α to oxygen,[62,167,168] with the same preference also holding true for insertion adjacent to nitrogen,[63,65,124,164,169,170] and at benzylic[64,171] and allylic[20,172–174] sites. The use of hydrocarbon solvents (hexane, 2,2-dimethylbutane) for intermolecular C–H insertion processes has also been found to increase asymmetric induction, compared with the use of polar solvents,[64,173,175] a trend also observed for asymmetric cyclopropanation reactions.[60]

Control of regiochemistry is also possible for intermolecular C–H insertion reactions of donor/acceptor carbenoids in the presence of Rh_2(*S*-DOSP)$_4$.[8,18] In general, insertion into tertiary C–H bonds is preferred over competing secondary and primary insertion, owing to the superior ability of tertiary sites to stabilise the electrophilic metal carbenoid.[6,7] Steric factors may also contribute, however, owing to the bulky nature of the rhodium carbenoid.[8,18] Thus, insertion into secondary C–H bonds is generally favoured for intermolecular diazo decomposition, as this represents the best balance between electronic and steric effects (Fig. 19).[124,166,167,171]

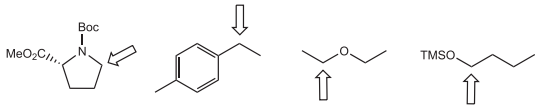
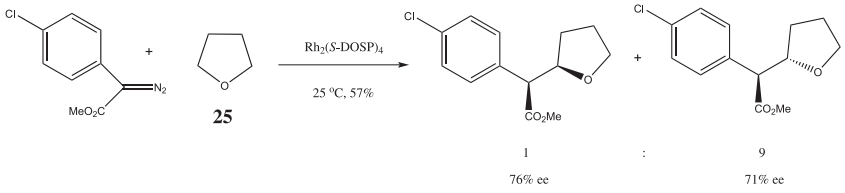


Figure 19.

Nonetheless, selective C–H insertion at primary and tertiary C–H sites may be achieved. The first chemoselective C–H insertion into a methyl site was reported by Davies and co-worker in 2002 for the Rh_2(*S*-DOSP)$_4$-catalysed reaction of methyl *p*-bromophenyldiazoacetate **120** with Boc-protected *N*-methylcrotylamine **121** (Scheme 17).[170] It was suggested that regioselective insertion into the primary site occurs in preference to insertion at the more electronically favourable allylic site, due to the sterically demanding nature of the aryl diazoacetate rhodium carbenoid, which hinders its approach to the competing secondary site.[170]

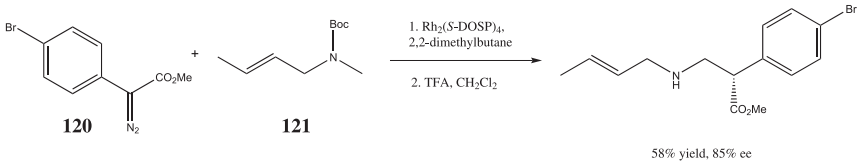
Thus, selective C–H insertion into methyl sites may be achieved when the target primary bond is sufficiently electronically activated and competing insertion sites in the remainder of the molecule are sterically hindered or otherwise electronically deactivated. This was indeed found to be true and various examples of selective C–H insertions at methyl sites are now known (Scheme 18).[163,166]

Preferential C–H insertion is seen to occur at the primary C–H bond of 1,2-dimethoxyethane **122**, due to the deactivating effect of the electron-withdrawing β-oxygen on the competing sec-

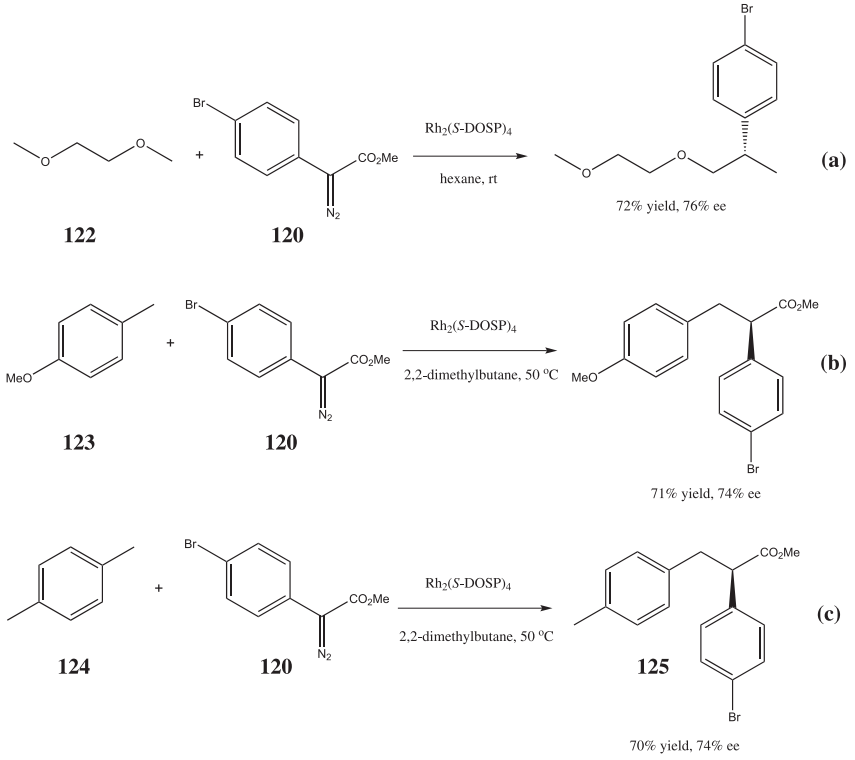


Scheme 16.

ondary insertion site [Scheme 18(a)].[166] No C–H insertion is observed at the methyl group adjacent to oxygen in 1-methoxy-4-methylbenzene **123** [Scheme 18(b)], due to probable delocalisation of the electron lone pairs of oxygen into the benzene ring.[163] The *p*-methoxy group in this reaction serves the function of sterically protecting the ring from possible cyclopropanation, as was observed for the reaction of methyl *p*-bromophenyldiazoacetate



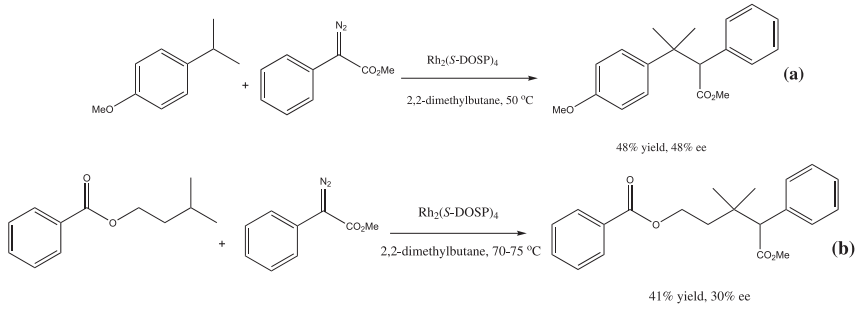
Scheme 17.



Scheme 18.

and toluene. Steric protection of this kind may also be achieved with *p*-alkyl substituents and, accordingly, the reaction of **120** and *p*-xylene **124** generates the corresponding C–H activation product **125** in 70% yield and 74% ee [Scheme 18(c)].[163] This strategy of selective methyl C–H insertion has been successfully applied to the total syntheses of the natural products, (+)-imperanene,[163] and (−)-α-conidendrin,[163] and to the synthesis of the enantiomers of the antidepressant, venlafaxine.[164]

preferential insertion into tertiary C–H bonds were minimal.[67,175] Research by Davies and co-workers, published in 2009,[176] however, has served to broaden the range of known substrates for which functionalisation of tertiary C–H bonds may be achieved (Scheme 19). Although the yields and enantioselectivities obtained for these reactions are moderate, they represent an encouraging platform on which to build future investigations.

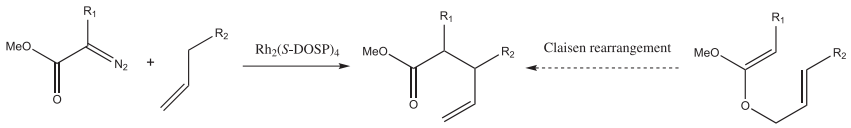


Scheme 19.

Despite the electronic preferences to the contrary,[6,7] regioselective intermolecular C–H insertion into tertiary bonds is a generally difficult process.[168,171,175] Until recently, reports of

Complementary reactions to several classic C–C bond-forming transformations, including the Claisen rearrangement,[173] the aldol reaction,[167,168,177] the Mannich reaction,[65,63] the Claisen

condensation[62] and the Michael reaction,[172,174] may be achieved by intermolecular C–H insertion reactions in the presence of donor/acceptor carbenoids. The synthesis of γ,δ-unsaturated esters, products normally generated by an asymmetric Claisen rearrangement, is possible via allylic C–H activation of alkenes (Scheme 20).[173] Excellent regiocontrol was achieved in these reactions, with high enantioselectivities (up to 95% ee) and moderate diastereoselectivities (up to 88% de) also being recorded.



Scheme 20.

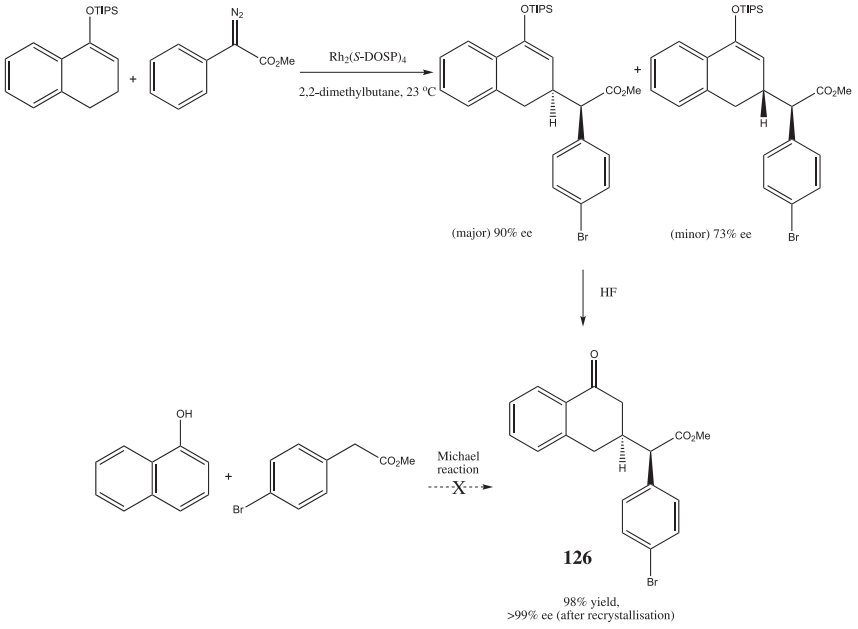
The Rh_2(*S*-DOSP)$_4$-catalysed decomposition of methyl aryl diazoacetates in the presence of silyl enol ethers may be used as an alternative route to typical Michael reaction products.[172] This surrogate reaction is particularly attractive, as it may be employed in the synthesis of compounds not possible with the corresponding Michael reactions. Production of the 1,5-dicarbonyl **126** via the traditional Michael addition route would not be feasible as the necessary enone would be the keto tautomer of 1-naphthol. As seen in Scheme 21, however, **126** may be produced by an intermolecular C–H insertion reaction followed by desilylation with hydrogen fluoride.[172] The enantioselectivity for this reaction was later improved to 97.5% ee for the major diastereoisomer (≥ 98% de) by changing to the TMS protecting group.[174]

An example of each surrogate reaction type is given in Schemes 22a–c.[62,65,167]

A novel reaction pathway was discovered by Davies and co-workers in 1999, during the course of investigations into the asymmetric synthesis of 4,4-diarylbutanoates.[165] The reaction of vinyldiazoacetate **127** and 1,3-cyclohexadiene **128** did not result in the predicted C–H insertion product **129**. Rather, formation of the 1,4-cyclohexadiene **130** was observed in high yield (63%) and high enantioselectivity (98% ee). It was suggested that generation of **130** occurs via a combined C–H activation/Cope rearrangement pathway (Scheme 23).

The direct C–H insertion product **129** was subsequently found to be the more thermodynamically stable product,[165,178] meaning that the reaction likely proceeds via a highly concerted, ordered transition state **131** (Fig. 20), as opposed to a two-step reaction.

Highly enantioselective diazo decompositions have been observed for combined C–H activation/Cope rearrangements in the presence of Rh_2(*S*-DOSP)$_4$. 1,2-Dihydronaphthalenes in particular have proved to be excellent substrates for this type of chemistry, finding application in the synthesis of various naphthalene derivatives (Table 28),[179] Michael addition equivalent products,[174] and double C–H activation



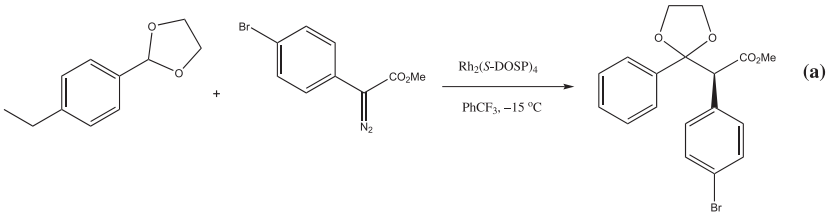
Scheme 21.

The development of surrogate reactions for the Claisen condensation,[62] the Mannich reaction[63,65] and the aldol reaction[167,168,177] has also been described, involving the asymmetric synthesis of β-keto esters, β-amino acid derivatives, and silyl-protected β-hydroxy esters, respectively. These novel reactions feature common C–H insertion at electronically favourable sites adjacent to oxygen or nitrogen, and have been achieved with excellent regiocontrol, and moderate-to-good diastereo- and enantiocontrol.

products.[125] Formation of **132** (Table 28, entries a–e) occurs via a combined C–H insertion/Cope rearrangement pathway, followed by elimination of acetic acid.

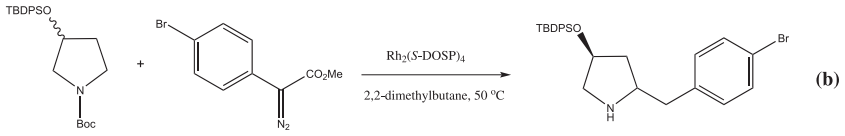
This impressive chemical transformation has also been applied to a formal asymmetric synthesis of the antidepressant, (+)-sertraline,[165] to the synthesis of a series of selective monoamine reuptake inhibitors,[180] and to the synthesis of the diterpene natural products, (−)-colombiasin A,[181] (−)-elisapterosin B,[181] (+)-elisabethadione[182]

Asymmetric Claisen Condensation Surrogate



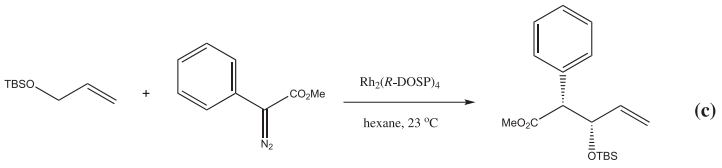
59% yield, 75% ee

Asymmetric Mannich Reaction Surrogate



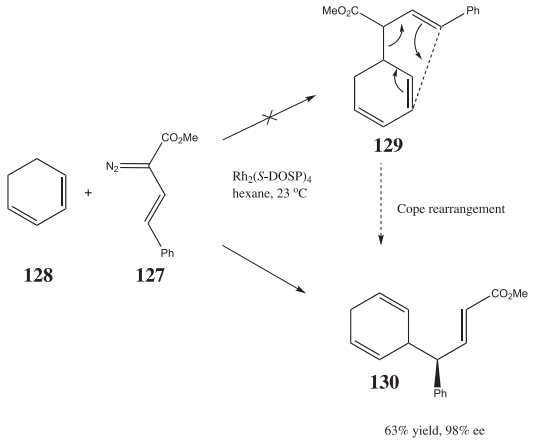
64% yield, >94 % de, >99% ee

Asymmetric Aldol Reaction Surrogate



52% yield, >94% de, 92% ee

Scheme 22.



63% yield, 98% ee

Scheme 23.

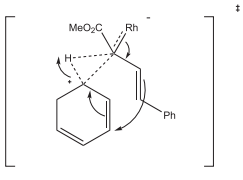


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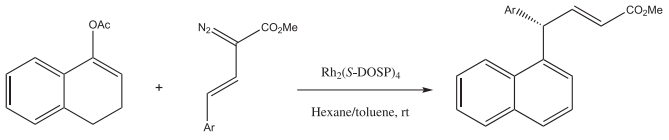
Figure 20.

and (+)-erogorgiaene,[183] all of which feature allylic C–H functionalisation by vinyldiazoacetates as the key step.

While Rh_2(*S*-DOSP)$_4$ is undoubtedly the catalyst of choice for intermolecular C–H insertions employing donor/acceptor carbenoids, in certain cases the reliability of this prolinate catalyst in achieving high levels of asymmetric induction has been seen to fail.[64,65,82] Alternative catalytic systems are, however, available

Table 28
Combined C–H activation/Cope rearrangement reactions



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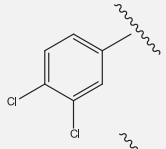
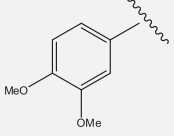
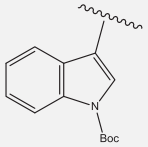
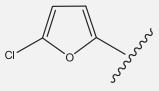
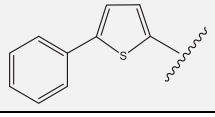
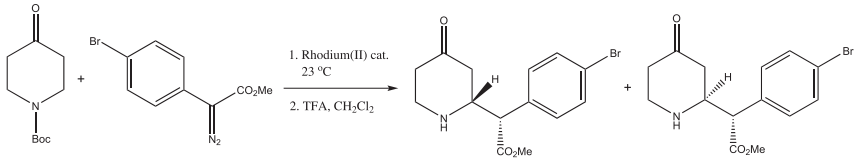
Entry	Ar	Yield (%) **132**	ee (%) **132**
a		79	>98
b		92	99.5
c		82	>98
d		45	99.6
e		66	99.3

which allow the achievement of the desired enantioselective intermolecular reactions. A vast improvement in both enantioselectivity and diastereoselectivity was recorded in the synthesis of *threo*-methylphenidate (Ritalin) upon change of catalyst from Rh_2(*S*-DOSP)$_4$ to Rh_2(*S*-biDOSP)$_2$.[63] A similar trend was observed for the reaction of *N*-Boc-piperidin-4-one **133** and **120**, in which change of catalyst from Rh_2(*S*-DOSP)$_4$ to Rh_2(*S*-biTISP)$_2$ resulted in increased asymmetric induction in the formation of **134** and **135** (Table 29, entries a and b).[65]

Table 29
Rhodium(II) prolinate-catalysed C–H insertion reactions of *N*-Boc-piperidin-4-one **133**

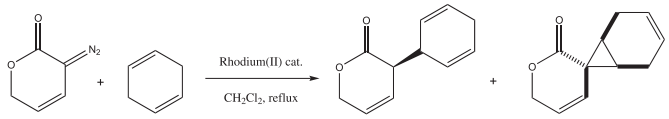


133 **120** **134** **135**

Entry	Rhodium(II) cat.	Yield (%) **134**	**135**	ee (%) **134**	**135**
a	Rh_2(*S*-DOSP)$_4$	31	20	83	53
b	Rh_2(*S*-biTISP)$_2$	46	23	88	76

Chiral rhodium(II) carboxamidate catalysts have been shown to outperform Rh_2(*S*-DOSP)$_4$ in terms of chemoselectivity and enantioinduction in the C–H insertion reactions of vinyldiazolactone **136** (Table 30, entries a–d).[82] For all catalysts screened, a mixture of both C–H insertion (**137**) and cyclopropanation (**138**) products was observed, however, greater chemo- and enantioselectivities were possible for reactions in the presence of the chiral carboxamidate complexes. This example is significant in that the rhodium(II) carboxamidate Rh_2(*S*-MEPY)$_4$ has previously been found to be unsuited to reactions with vinyldiazoacetates[184] and only a very limited number of published reports exist documenting successful chiral rhodium(II) carboxamidate-catalysed intermolecular C–H insertion.[36,185]

Table 30
Intermolecular C–H insertion reaction of vinyldiazolactone **136** and 1,4-cyclohexadiene



136 **137** **138**

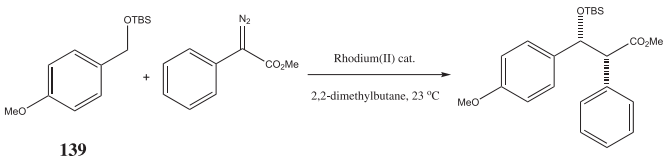
Entry	Rhodium(II) cat.	**137**/**138**	Yield (%) **137**	ee (%) **137**
a	Rh_2(*S*-DOSP)$_4$	1:9	56	18
b	Rh_2(*S*-MEPY)$_4$	4:1	47	8
c	Rh_2(*S*-MEAZ)$_4$	9:1	43	60
d	Rh_2(*S*,*R*-MenthAZ)$_4$	9:1	50	80

Hashimoto's phthalimide catalyst Rh_2(*S*-PTTL)$_4$ was found to be the catalyst of choice ahead of Rh_2(*S*-DOSP)$_4$ for the asymmetric intermolecular C–H functionalisation of *p*-methoxybenzyl *tert*-butyldimethylsilyl ether **139** (Table 31, entries a and b).[64] This result was again significant, given that Rh_2(*S*-PTTL)$_4$ had not previously been reported as an efficient catalyst for either intermolecular C–H insertion or cyclopropanation reactions.

A range of additional chiral complexes have been shown to be efficient catalytic systems for intermolecular C–H insertion processes including a recyclable fluorous chiral rhodium(II) complex,[66] and copper-bis(oxazoline) complexes.[30] More recently, the adamantylglycine-derived chiral tetracarboxylate complex Rh_2(*S*-PTAD)$_4$ has been introduced as an additional catalytic choice for such transformations.[67] While Rh_2(*S*-DOSP)$_4$ has shown exceptional results for the majority of reactions of donor/acceptor carbenoids discussed above, it is not an effective catalytic option when the diazo acceptor group is changed from a methyl ester to another acceptor group.[175] In such cases, the adamantyl complex Rh_2(*S*-PTAD)$_4$ has been found to be an excellent substitute catalyst for Rh_2(*S*-DOSP)$_4$ (Table 32, entries a–e).[67,68]

Rh_2(*S*-PTAD)$_4$ may also be employed to promote C–H insertion over competing cyclopropanation in allylic substrates, as was

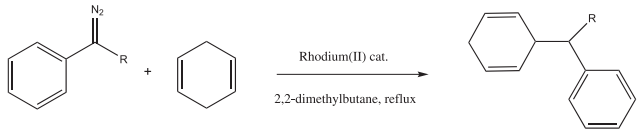
Table 31
Intermolecular C–H insertion reaction of *p*-methoxybenzyl *tert*-butyldimethylsilyl ether **139**



139

Entry	Rhodium(II) cat.	Yield (%)	de (%)	ee (%)
a	Rh_2(*R*-DOSP)$_4$	85	88	35 (2*R*, 3*R*)
b	Rh_2(*S*-PTTL)$_4$	64	91	97 (2*R*, 3*R*)

Table 32
Intermolecular C–H insertion reaction of 1,4-cyclohexadiene

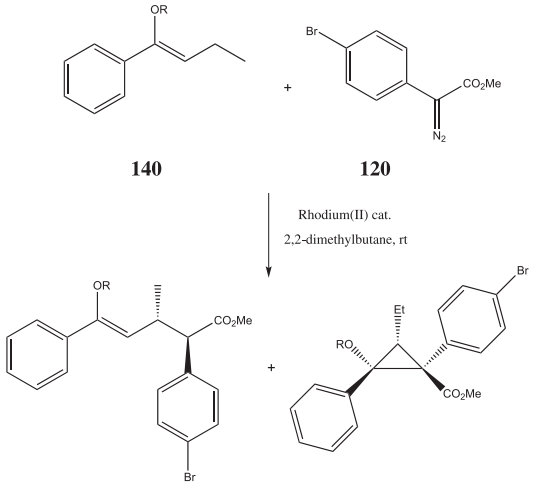


Entry	Rhodium(II) cat.	R	Yield (%)	ee (%)
a	Rh_2(*S*-DOSP)$_4$	$PO(OMe)_2$	62	41
b	Rh_2(*S*-PTAD)$_4$	$PO(OMe)_2$	83	92
c	Rh_2(*S*-PTAD)$_4$	COMe	90	80
d	Rh_2(*S*-PTAD)$_4$	COEt	84	71
e	Rh_2(*S*-PTAD)$_4$	CO*n*-Pr	81	80

observed in the intermolecular reactions of trisubstituted alkenes.[186] As seen in Table 33, intermolecular diazo decomposition of **140** in the presence of Rh_2(*S*-DOSP)$_4$ results in the formation of a 2:1 mixture of allylic C–H insertion (**141**) and cyclopropanation (**142**) products (Table 33, entry a). In contrast, the Rh_2(*S*-PTAD)$_4$-catalysed reaction was seen to produce **141** as the major product (Table 33, entry b). The choice of siloxy group in this study was found to have a significant effect on the reaction outcome. Decreasing the size of the protecting group to TMS in the Rh_2(*S*-PTAD)$_4$-catalysed reaction was seen to correspond to a large

decrease in preference for the C–H insertion product (Table 33, entry c). The enantioselectivity obtained with Rh_2(*S*-PTAD)$_4$ (R=TBDPS) was good (86% ee) and could be improved to 93% ee without loss of yield upon lowering of the reaction temperature to 0 °C.

Table 33
Rh_2(*S*-DOSP)$_4$- versus Rh_2(*S*-PTAD)$_4$-catalysed C–H insertion reaction of **140**



140 **120** **141** **142**

Entry	Rhodium(II) cat.	R	Yield (%)	**141**/**142**	ee (%)**141**	**142**
a	Rh_2(*S*-DOSP)$_4$	TBDPS	87	2:1	65	78
b	Rh_2(*S*-PTAD)$_4$	TBDPS	89	>15:1	86[a]	—
c	Rh_2(*S*-PTAD)$_4$	TMS	63	1:1	83[a]	34

[a] Opposite enantiomer in excess.

8. Concluding remarks

The 20 intervening years between the first reports of asymmetric C–H insertion reactions to the present day have represented a period of rapid growth and learning in the field of enantioselective carbenoid C–H insertion chemistry. Large advances in both intramolecular and intermolecular C–H insertion reactions have been achieved, and the catalogue of possible substrates for both processes continues to grow. Since their initial introduction,[1] rhodium(II) compounds have remained the catalysts of choice for carbenoid insertions into C–H bonds. A wide variety of rhodium(II) catalysts are now known, encompassing carboxylate, carboxamidate, phosphate and *ortho*-metalated complexes. Rhodium(II) carboxylates and carboxamidates have proven themselves the most effective of these catalyst systems, finding applications across a range of intramolecular and intermolecular C–H insertion reactions.

In intramolecular carbocycle-producing C–H insertion reactions, Hashimoto's rhodium(II) phthalimide complexes have emerged as the primary catalytic choice, effecting asymmetric cyclopentanone and cyclopentane synthesis in up to 80 and 95% ee, respectively.[107,113] Chiral copper(I)-bis(oxazoline) and *ortho*-metalated rhodium(II) catalysts have also shown some success in this area,[31,93,114] but the enantioselectivities obtained with these complexes have been moderate.

Catalytic options for the synthesis of heterocyclic products via C–H insertion chemistry may include a range of rhodium(II) carboxylates and carboxamidates. Doyle's chiral rhodium(II) carboxamidates are reliable catalysts for highly enantioselective intramolecular lactone synthesis. The imidazolidinone catalyst Rh_2(*S*-MPPIM)$_4$ has proved to be particularly effective for the carbenoid decomposition reactions of primary and secondary alkyl diazoacetates,[87,83,86,118] while the related compound Rh_2(*S*-MACIM)$_4$ has found success in the C–H insertion reactions of tertiary alkyl diazoacetates.[78,120] For the generation of dihydrobenzofuran products, the choice of catalytic system may include both Hashimoto's phthalimide catalysts and Davies' prolinate- and adamantate-derived catalysts.[67,129,135] Asymmetric chromanone synthesis may be achieved in the presence of the carboxylate catalyst Rh_2(*S*-BSP)$_4$.[52,128] As was observed for the corresponding lactone syntheses, Doyle's chiral carboxamidate complexes are a viable catalytic option for the production of lactam products via intramolecular C–H insertion reactions. In particular, Rh_2(*S*-MEPY)$_4$ and Rh_2(*S*-MEOX)$_4$ have been exploited for this purpose in early studies examining the decomposition reactions of *N*-(*tert*-butyl)diazoacetamides[81] and cyclic diazoacetamides.[76] Very high regio- and enantioselectivities have also been obtained for β-lactam synthesis in the presence of Hashimoto's phthalimide catalysts for C–H insertion reactions with compounds featuring a bulky amide substituent. The only successful example of highly enantioselective thiopyran synthesis has been reported for C–H insertions catalysed by chiral copper (I) bis(oxazoline) complexes.[4]

Intermolecular C–H insertion chemistry has been dominated by catalytic processes employing Davies' rhodium(II) prolinate catalysts. Excellent enantioselectivities have been achieved for the reactions of donor/acceptor-substituted carbenoids in the presence of Rh_2(*S*-DOSP)$_4$, the bridged catalyst Rh_2(*S*-biDOSP)$_4$ and the adamantyl complex Rh_2(*S*-PTAD)$_4$.[20,67] Recently, iridium(III)-salen complexes have also been demonstrated as effective catalysts for the asymmetric intermolecular C–H insertion reactions of donor/acceptor-substituted carbenoids, and as the only catalytic choice to date for the intermolecular decompositions of α-alkyl-α-diazoacetates.[5]

While rhodium(II) complexes remain the dominant catalysts for application in enantioselective C–H insertion reactions, the possibility of extending this choice to include alternative metal catalysts is currently being realised. Nonetheless, development of a catalyst system with general applicability across the spectrum of intramolecular and intermolecular C–H insertion reactions remains elusive, but may be achieved in future years as advances in catalytic techniques for carbenoid C–H insertions continue to grow.

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