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REVIEW

Dirhodium(II) Carbenes : A Rich Source of Chiral Products

Gregory H. P. Roos*[,a] and Conrad E. Raab[b]

[a] Chemistry Department, Sultan Qaboos University, P. O. Box 36, Al Khod 123, Sultanate of Oman

[b] Department of Drug Metabolism, Merck and Co., Inc., RY80R-104, P. O. Box 2000, Rahway, New Jersey 07065, USA

*To whom correspondence should be addressed. E-mail groos@squ.edu.om.

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Abstract

The last decade has witnessed enormous growth in the asymmetric synthetic applications of dirhodium(II) carbenes generated from diazo-precursors. Innovative construction of 'designer' catalysts has played an integral role in extending the breadth of the synthetic cascade of non-racemic products now available through a range of cyclopropanation, C–X insertion, aromatic cycloaddition–rearrangement, and ylide-based reaction types. This review, whilst mindful of importance of the catalytic system, focuses primarily on the latter feature of product diversity.

Keywords: Rhodium, carbenes, diazocarbonyl compounds, asymmetric synthesis.

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1. Introduction: Carbene Reactions

The general group of transformations referred to as “carbene reactions” forms a versatile class of transition metal-catalysed processes. These reactions are characterised by the involvement of a transition metal-stabilized carbene that is formed from the decomposition of a diazo compound in the presence of the transition metal catalyst. Further reaction of the carbene may follow a number of pathways, including insertion and addition reactions as well as ylide generation. Recent investigations have focused on the development of catalysts that control the selectivity of what had traditionally been thought of as non-selective reactions of “free carbenes”. Of these, dirhodium catalysts have emerged as arguably the most versatile for a wide range of stereoselective transformations.[1–11] This review seeks to place the rapid growth within this area of endeavour in context by surveying the published literature through mid-1999. The specific focus of the review is on homochiral catalysts; chiron-based syntheses are excluded, and only pertinent examples of diastereoselectivty *via* chiral auxiliaries are covered. Previous reviews have tended to focus on details of catalyst development, or on the subsequent

reaction types that the carbene undergoes. Outside of essential introductory material, this review seeks primarily to highlight the wealth of diverse enantiomerically enriched chiral products that are available by way of the numerous highly chemoselective, regioselective, and stereoselective transformations brought about by dirhodium(II) catalyst systems. Some of these reactions have a high potential for commercial adaptation. Readers seeking further details on access to diazo compounds, catalyst design and preparation, as well as mechanistic aspects are referred to the alternative specialist reviews cited throughout.

2. Generation of Dirhodium(II) Carbenes

2.1. Diazo Compounds

Diazo compounds are derivatives of diazomethane, and as such have stabilities and reactivities that reflect their substituents. Generally, the stabilities of diazo compounds towards diazo decomposition are increased by electron withdrawing substituents, and decreased by electron donating substituents (Fig. 1). For this reason, the most widely employed diazo compounds for metal catalysed reactions are diazocarbonyl compounds. Numerous synthetic methodologies are now available for the synthesis of diazo compounds, and these have been reviewed by Regitz and Maas,[12] and by Doyle, McKervey and Tao.[5]

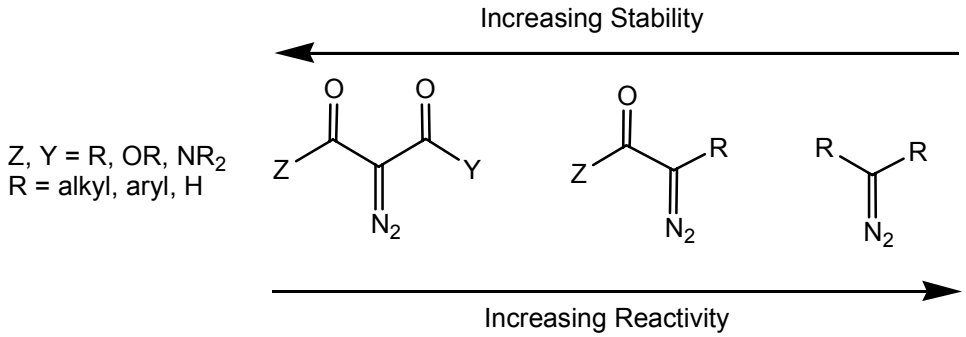


Figure 1 Relative stability/reactivity of diazo substrates.

2.2. Metal-Catalysed Diazo Decomposition, and Rhodium(II) Catalysts

Since diazo decomposition is an acid-promoted process, transition metal complexes that are effective catalysts for diazo decomposition are of necessity Lewis acids.[13] Their catalytic activity depends on the metal centre being coordinatively unsaturated, which allows them to react as electrophiles with diazo compounds. Many metals,

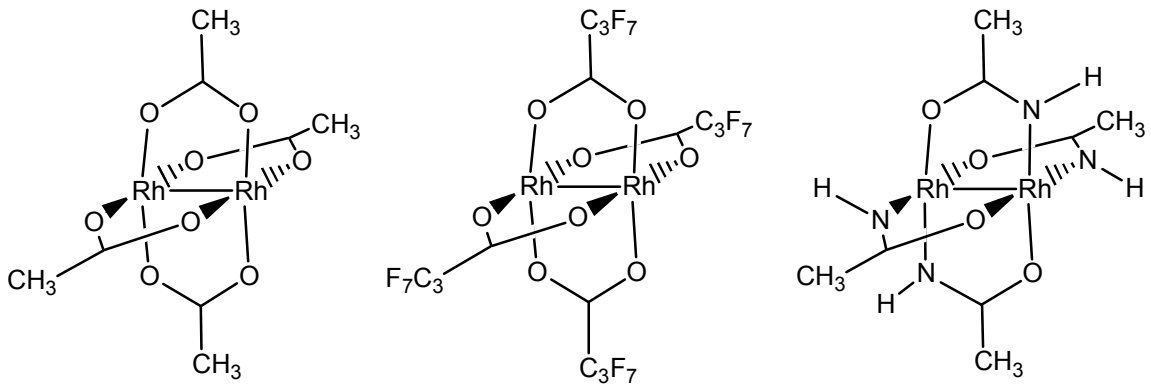
among them copper, cobalt, palladium, ruthenium, osmium, iron, nickel and zinc, have been employed with varying success in catalytic systems.[10,15]

Rhodium and, more specifically, dirhodium(II) complexes have proved to be the most effective and versatile catalysts for diazo decomposition.[9,14–18] Generally, rhodium-mediated carbene reactions proceed under much milder conditions than is common for classical synthetic methods that use copper(II) catalysts.[17] Their versatility arises from the large variety of bridging ligands that can be coordinated to the dirhodium(II) skeleton, and in their marked influence on reactivity and selectivity.

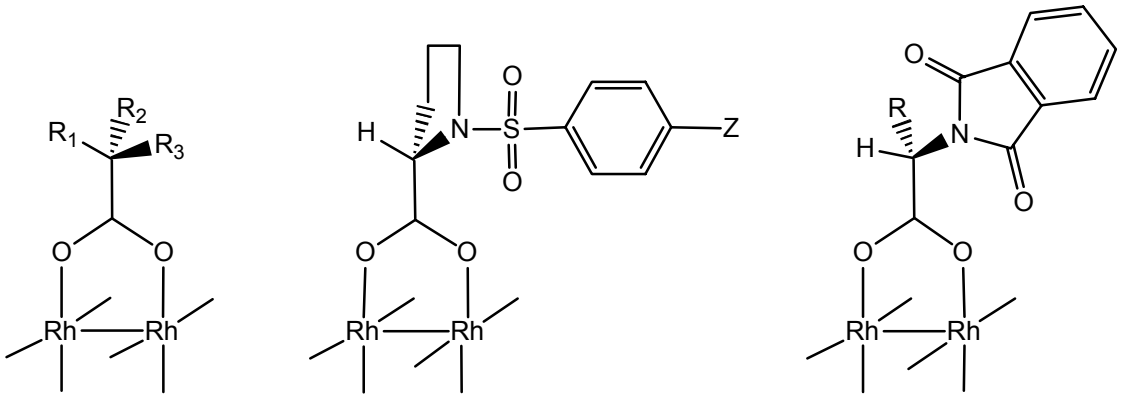
Dirhodium(II) catalyst complexes are divided into two major groups: those bridged with carboxylate ligands, and those bridged with carboxamidate ligands (Fig. 2). It is through the tuning of these ligands that particular catalysts are able to provide appropriate chemical properties as well as specific reactivity and selectivity profiles for desired transformations. The dirhodium(II) catalysts are based on the parent dirhodium(II) tetraacetate, $Rh_2(OAc)_4$ **1**, first introduced in1973.[19] Since that time, this has been the single most widely used catalyst for metal carbene transformations. $Rh_2(OAc)_4$ **1** possesses four bridging acetate ligands and has D_{4h} symmetry, leaving one vacant axial coordination site on each metal for carbene attachment.[20] A multitude of dirhodium(II) catalysts is available by replacement of the acetate ligands with other carboxylate or carboxamidate ligands (see list of abbreviations for ligands). Many of these catalysts have unique properties or synthetic uses.[5,6]

Dirhodium(II) perfluorobutyrate, $Rh_2(pfb)_4$ **2**, is the most reactive dirhodium(II) catalyst, and its selectivity in diazo decomposition reactions is often correspondingly poor.[21] In contrast, dirhodium(II) carboxamidates such as $Rh_2(acam)_4$ **3**, which have two nitrogen and two oxygen donor atoms at each rhodium with the two nitrogen atoms arranged *cis* to each other (a 2,2-*cis* configuration),[22] are less reactive than the dirhodium(II) carboxylates in diazo decomposition, but are often more selective in the subsequent carbene reactions.[23–25]

Homochiral dirhodium(II) carboxylate catalysts **4** for asymmetric carbene reactions were simultaneously developed in three laboratories from enantiomerically pure carboxylic acids.[26–28] More recent refinements have included highly successful prolinate **5**[29–35] and phthalimide **6**[36–38] derivatives.



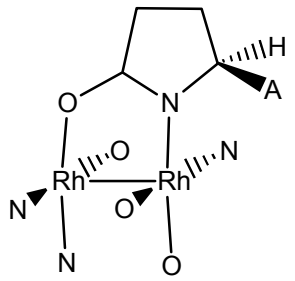
1 $Rh_2(OAc)_4$ **2** $Rh_2(pfb)_4$ **3** $Rh_2(acam)_4$



4 **5** Z = H, NO_2, OMe, Me, ^{t}Bu [= $Rh_2(TBSP)_4$], *n*-$C_{12}H_{25}$ [= $Rh_2(DOSP)_4$] **6** R = $PhCH_2$, ^{t}Bu

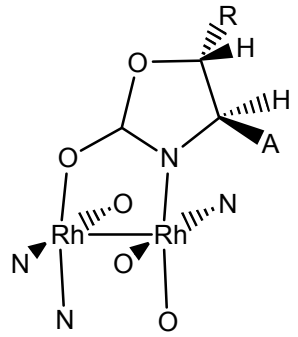
Figure 2 Structures of some rhodium(II)-containing catalysts.

In contrast to the dirhodium(II) carboxylates, the rhodium(II) carboxamidates allow the placement of a stereogenic centre adjacent to nitrogen, which brings it into closer proximity to the axial carbene centre, and hence can lead to a higher degree of asymmetric induction. A series of more than twenty structurally varied homochiral dirhodium(II) carboxamidates derived from chiral cyclic amide ligands has been developed by Doyle and co-workers.[3,39] In general, dirhodium(II) carboxamidate catalysts based on chiral 2-pyrrolidinone **7**,[40,41] 2-oxazolidinone **8**,[42,43] *N*-acylimidazolidin-2-one **9**[44-47] and 2-azetidinone **10**[48] ligands, especially those bearing pendant carboxylate groups, afford the highest levels of enantioselectivity (Fig. 3).



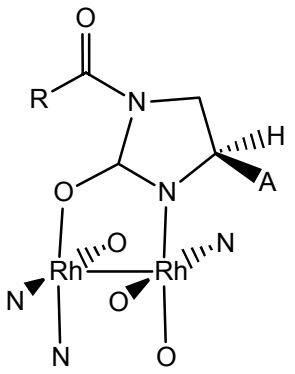
7

a A = CO_2Me; $Rh_2(5S\text{-MEPY})_4$
b A = $CO_2CH_2CMe_3$; $Rh_2(5S\text{-NEPY})_4$
c A = $CO_2(CH_2)_{17}Me$; $Rh_2(5S\text{-ODPY})_4$
d A = $CONMe_2$; $Rh_2(5S\text{-DMAP})_4$



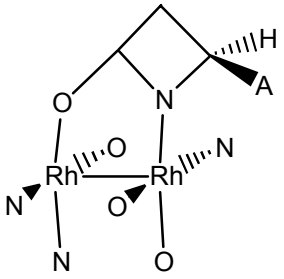
8

a A = CO_2Me, R = H; $Rh_2(4S\text{-MEOX})_4$
b A = CO_2Me, R = CH_3; $Rh_2(4S\text{-THREOX})_4$
c A = CH_2Ph, R = H; $Rh_2(4R\text{-BNOX})_4$
d A = iPr, R = H; $Rh_2(4R\text{-IPOX})_4$
e A = Ph, R = H; $Rh_2(4R\text{-PHOX})_4$



9

a A = CO_2Me, R = CH_3; $Rh_2(4S\text{-MACIM})_4$
b A = CO_2Me, R = Ph; $Rh_2(4S\text{-MBOIM})_4$
c A = CO_2Me, R = $PhCH_2$; $Rh_2(4S\text{-MPAIM})_4$
d A = CO_2Me, R = $PhCH_2CH_2$; $Rh_2(4S\text{-MPPIM})_4$
e A = CO_2Me, R = c-$C_6H_{11}CH_2$; $Rh_2(4S\text{-MCHIM})_4$

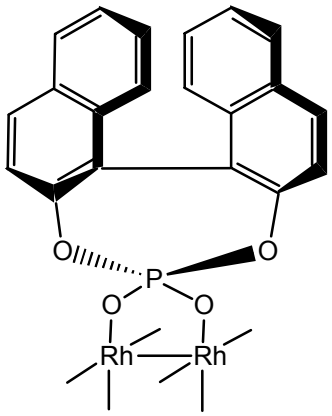


10

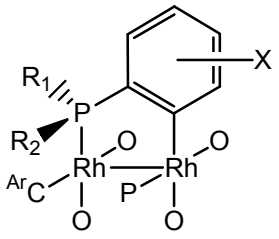
a A = CO_2CH_2Ph; $Rh_2(4S\text{-BNAZ})_4$
b A = $CO_2CH_2CHMe_2$; $Rh_2(4S\text{-IBAZ})_4$

Figure 3 Chiral rhodium(II) carboxamide complexes.

Dirhodium(II) complexes **11** bearing chiral phosphate ligands derived from binaphthol have been reported to provide moderate enantioselectivities in a number of carbene reactions.[49,50] In addition, Estevan and co-workers have prepared a novel set of C_2-symmetric catalysts **12** bearing two *cis* carboxylate ligands along with two *ortho*-metallated phosphine ligands[51] (Fig. 4).



11a Rh_2(*S*-BNHP)$_2$$(HCO_3)_2$
11b Rh_2(*R*-BNHP)$_4$



12 X = H, F, CH_3, CF_3

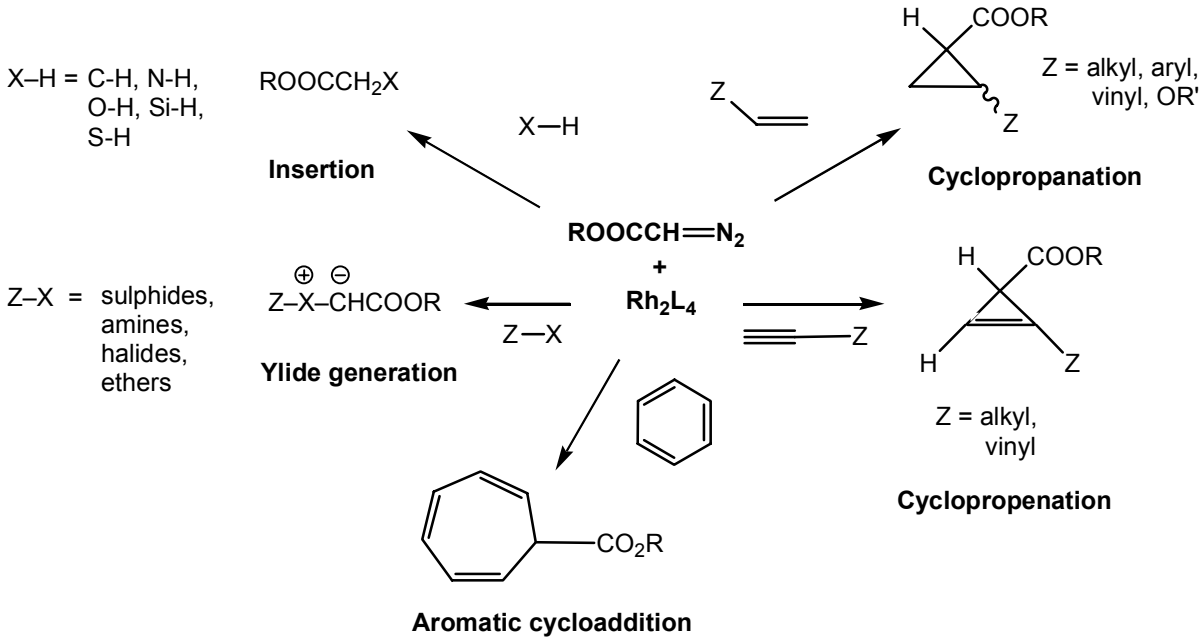
Figure 4 Chiral rhodium(II) complexes with phosphorus-containing ligands.

3. Reaction Products from Dirhodium(II) Carbenes

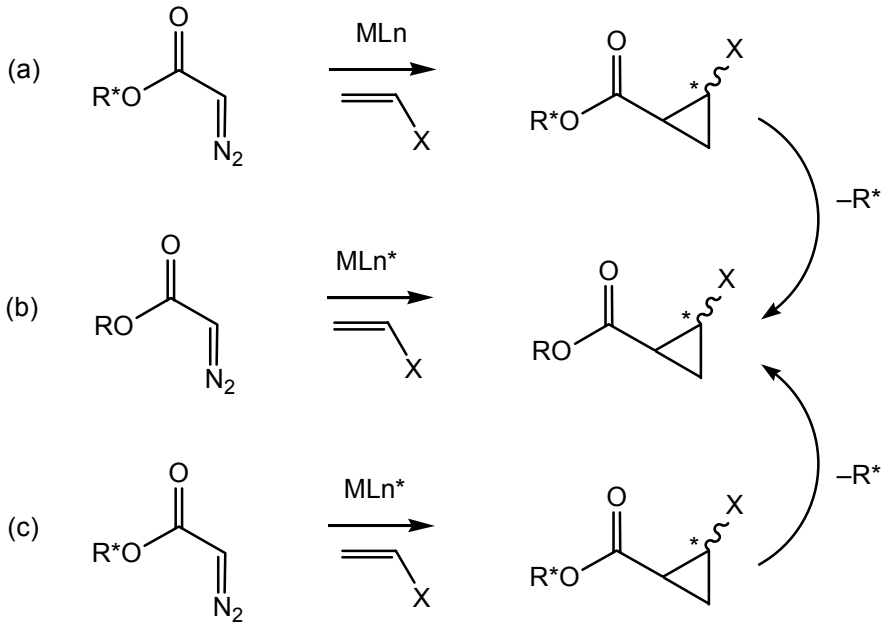
3.1. General Aspects

The metallocarbenes resulting from the diazo decomposition of α-diazocarbonyl compounds by a transition metal catalyst are versatile electrophilic reagents. Dirhodium(II)-catalysed diazo decompositions provide the greatest versatility in subsequent carbene reactions, and lead to many synthetically useful transformations. These include intermolecular and intramolecular reactions as diverse as cyclopropanation, cyclopropenation, insertion, aromatic cycloaddition, and ylide generation (Scheme 1). As a result, the range of stereoselectively generated product types is large.

Researchers in this area have investigated a variety of fundamental approaches to the asymmetric production of chiral compounds *via* dirhodium(II)-catalysed reactions (Scheme 2). The various approaches include (a) diastereoselective reaction of achiral catalysts with diazo substrates containing chiral auxiliaries; (b) enantioselective reaction between chiral catalysts and achiral substrates; and, in a few instances, (c) a double diastereoselective approach with both chiral catalyst and substrate. For the purpose of orderly classification, the range of product molecules surveyed in the following sections has been grouped according to the reaction type by which they are generated.



Scheme 1 Diversity of reactions involving dirhodium(II) carbenes.

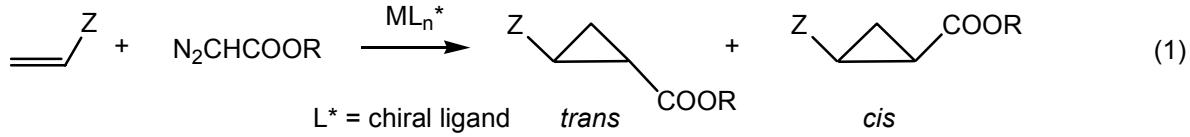


Scheme 2 Approaches to asymmetric synthesis with metallocarbenes.

3.2. Cyclopropanes and Cyclopropenes

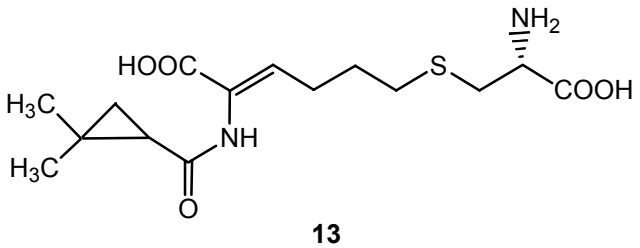
In view of their biological significance and synthetic utility, cyclopropanes and cyclopropenes are extremely important target molecules.[52–55] They are often present as structural sub-units in natural and non-natural products,[52,56–58] are frequently used as mechanistic probes to elucidate reaction pathways,[59–63] and are increasingly valuable as synthetic intermediates.[64–66]

Since the availability of enantiomerically pure cyclopropanes is critical to many applications, a number of useful methods for their enantioselective synthesis have been developed. These include the cyclopropanation of chiral bicyclic lactams to give optically pure di- and trisubstituted cyclopropanes, highly diastereoselective Simmons–Smith cyclopropanation of allylic ethers derivatised with chiral auxiliaries, enantioselective Simmons–Smith cyclopropanation of allylic alcohols using diethylzinc in association with with chiral ligands, and enzymatic resolutions of *meso*-cyclopropanes. In the field of asymmetric synthesis, cyclopropanation of electron-rich olefins by catalytic decomposition of α-diazocarbonyl compounds with chiral catalysts (Eq. 1), particularly copper and rhodium, has become an attractive and important route to optically active cyclopropanes.[1,5,9,14,67,68]



(1)

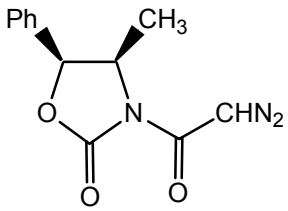
Cyclopropanation may either be performed *intermolecularly* or *intramolecularly*. A successful example of the former is found in the commercial synthesis (by the "Sumitomo process") of optically pure cilastatin **13**, an *in vivo* stabiliser of the antibiotic imipenem.[18] Generally it has been found that copper-based systems are the better catalysts for intermolecular cyclopropanation with traditional diazoacetates, while dirhodium catalysts provide the better results in intramolecular variants.[5,10]



13

3.2.1. Intermolecular Processes

Initial attempts at asymmetric intermolecular cyclopropanations by means of chiral auxiliaries bonded to diazoacetates were largely unsuccessful (Eq. 1, Z = chiral auxiliary). For example, chiral *N*-(diazoacetyl)oxazolidinones **14** and **15** participated in $Rh_2(OAc)_4$-catalysed cyclopropanation with styrene in good yield but with low diastereoselectivity.[69]



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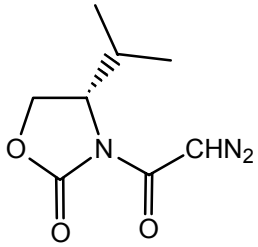
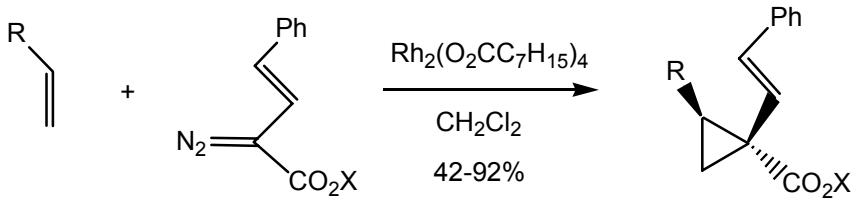
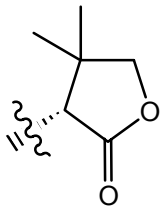
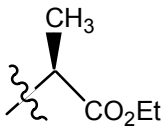


15

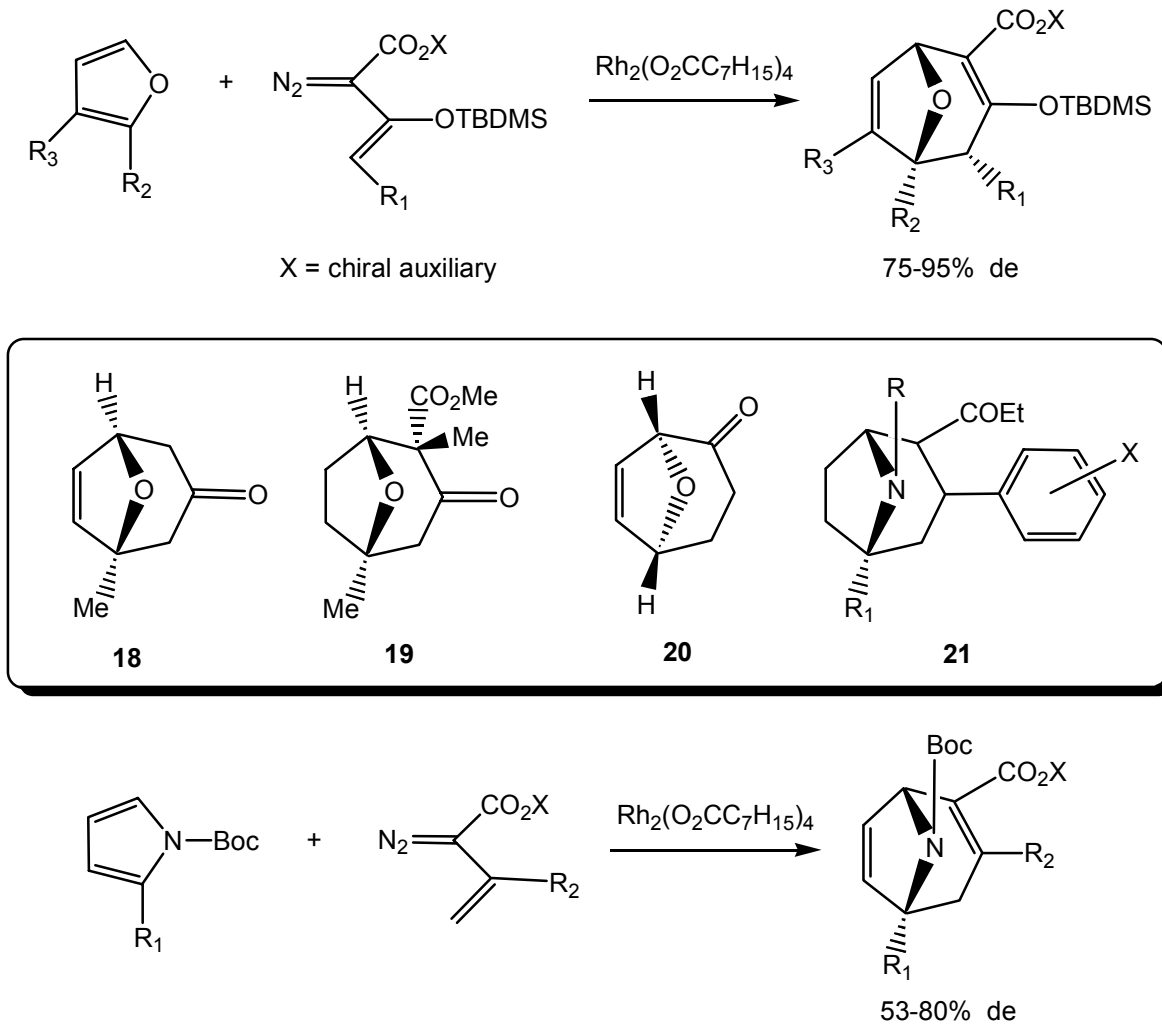
High diastereoselectivities in the catalytic cyclopropanation of diazo compounds bearing chiral auxiliaries have been achieved only in select cases.[70,71] Davies and co-workers have reported diastereomeric excesses of up to 97% in the dirhodium(II) octanoate-catalysed cyclopropanation of styrenes and vinyl ethers with (*R*)-pantolactone- and (*S*)-lactate-substituted vinyldiazomethane **16** to give products **17** (Eq. 2).[70,72] This same group has shown that appropriate choice of vinyldiazo substituent allows ready subsequent transformation of the cyclopropyl products into 2,3-dihydrofurans with high asymmetric induction.[73]



16a,b **17a,b** (2)

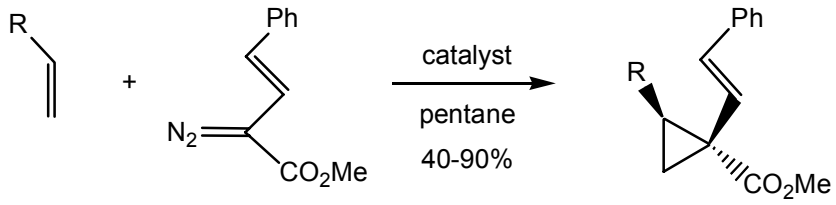
a X =  **b** X = 

This methodology has been extended to diene systems, furans[32] to give 8-oxabicyclo[3.2.1]octan-3-ones, and pyrroles[74] to give tropanes (Scheme 3). The fundamental reaction sequence has allowed the preparation of the oxabicycles **18**–**20** and a series of 2β-acyl-3β-aryltropanes **21**, which are important building blocks in further synthesis.[33,75]



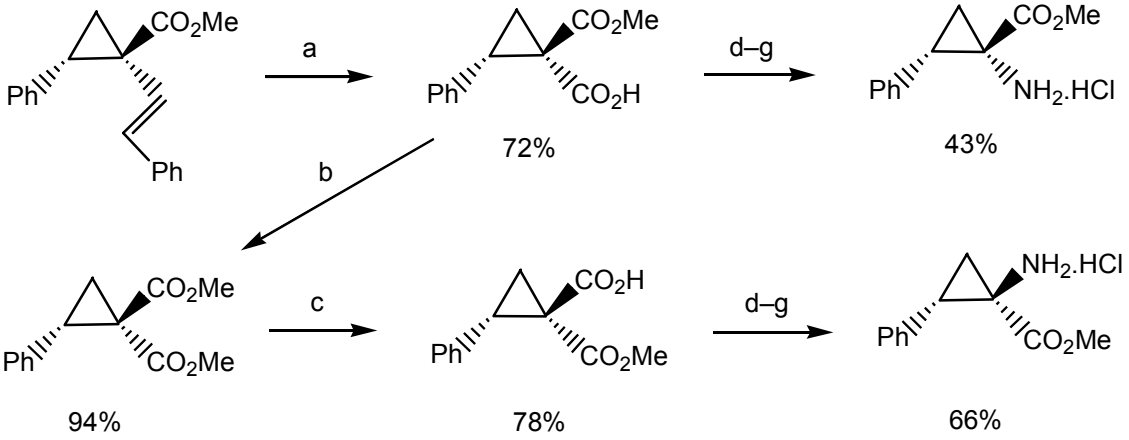
Scheme 3 Diastereoselective synthesis of oxabicyclooctanones and tropanes.

Enantioselective approaches have embraced two distinct types of homochiral dirhodium(II) carboxylates. Brünner and co-workers[26] used carboxylate ligands of the type $R^1R^2R^3CCOO^-$, as in catalysts **4** (substituents included H, Me, Ph, OH, NHAc and CF_3), and Kennedy *et al.*[76] employed the chiral prolinate derivatives **5** (Z = H). They found that enantioselectivities in the cyclopropanation of styrene with ethyl diazoacetate were less than 12% ee and 30% ee, respectively. More recently, the Davies group has used modified prolinate catalysts with vinyldiazoacetates to achieve enantioselectivities of ≥90%, with correspondingly high diastereoselectivities (Eq. 3).[30,32,72,74,77,78] It has further been shown that with suitably fuctionalised vinyldiazoacetates, the cyclopropyl products can afford cyclopentenes with high stereoselectivity.[79] A recent catalyst, based on an axially dissymmetric biphenyl, does as yet not appear to offer any significant advantages over existing examples.[80]



(3)

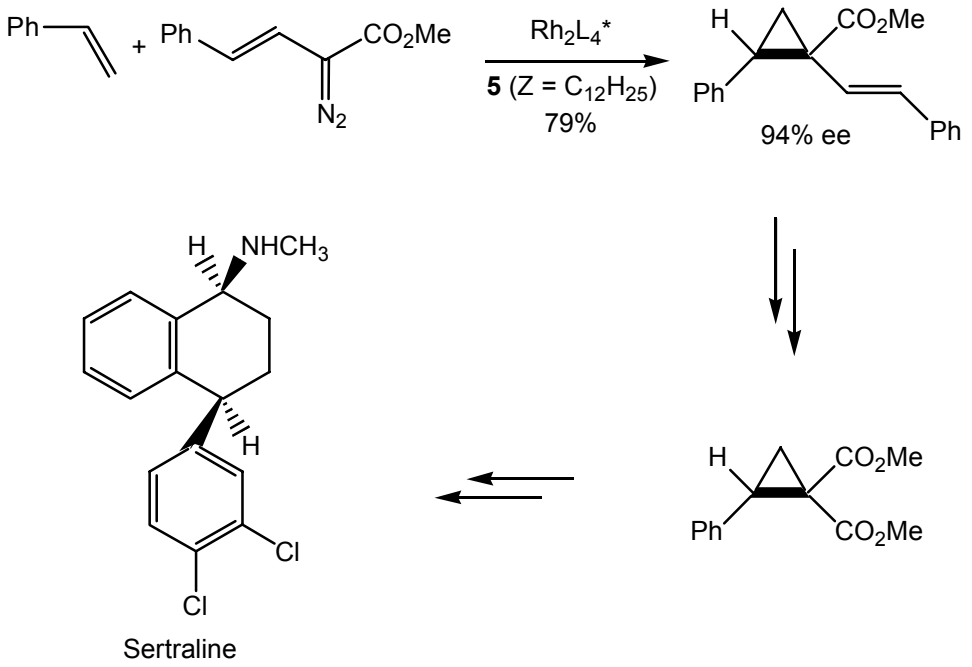
The vinyl functionality that exists in the cyclopropane offers a number of opportunities for further transformations. One generally useful application is for the stereoselective synthesis of cyclopropane-containing amino acid derivatives (Scheme 4).[30,32] This approach has been utilised in a recent synthesis of the antidepressant Sertraline (Scheme 5).[81]



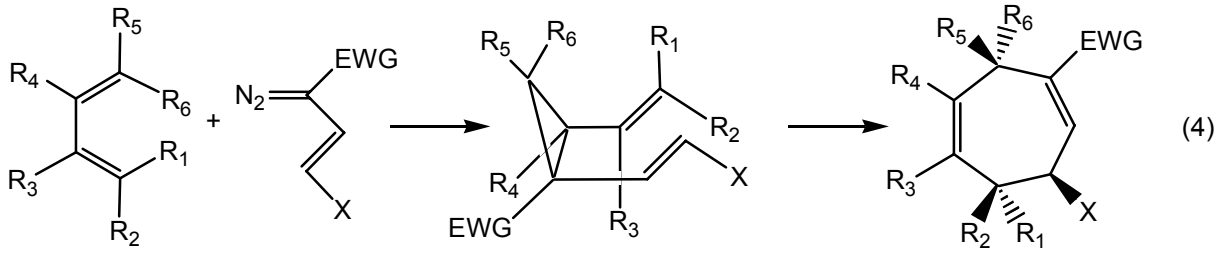
Reagents: a, $RuCl_3/NaIO_4$; b, K_2CO_3, Me_2SO_4; c, LiOH, MeOH; d: NEt_3, DPPA, ^tBuOH; e, $[(CH_3)_3OCO]_2O$; f, $NaOH/H_2O/THF$; g, HCl/EtOAc

Scheme 4 Stereoselective synthesis of cyclopropane amino acids.

The extension of asymmetric vinylcarbenoid cyclopropanation to dienes affords a good general entry into seven-membered rings (Eq. 4).[82] The stereoselectivity that occurs results in a strong preference for the formation of *cis*-divinylcyclopropanes, and the subsequent Cope rearrangement follows with a predictable stereochemical outcome. This methodology, which represents a formal [3 + 4]-cycloaddition, has been well exploited in the enantioselective synthesis of cycloheptadienes (Scheme 6).[82]



Scheme 5 Enantioselective synthesis of the antidepressant Sertraline.

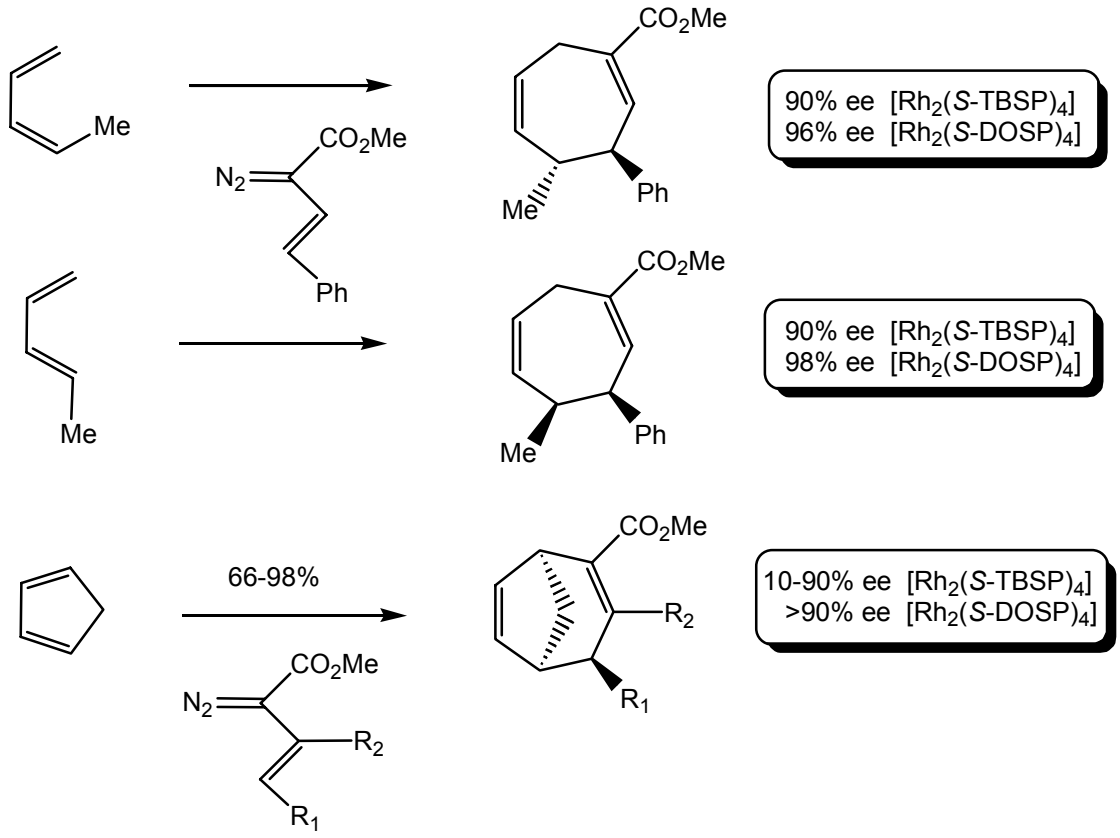


(4)

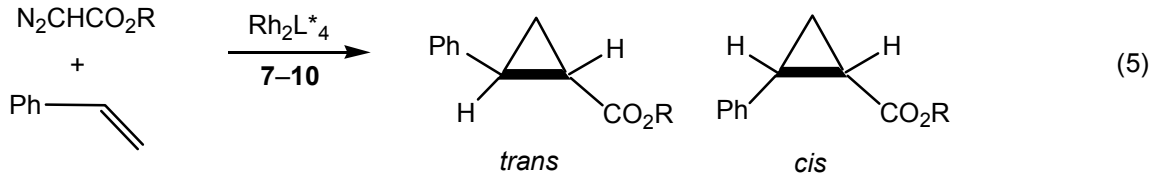
EWG = electron-withdrawing group

Although the dirhodium(II) carboxamidate catalysts **7**–**10** are able to provide substituted cyclopropanes with reasonable levels of enantioselectivity (10-90%), they suffer the drawback of poor diastereoselectivity when diazoacetates are employed; mixtures of *trans*- and *cis*-adducts (ratios 1:1–1:2) are formed (Eq. 5).[42,83,84] Diastereoselectivity can only be effectively induced when sterically demanding diazo esters can be employed. The most noteworthy recent examples have been reported with the catalysts $Rh_2(4S\text{-IBAZ})_4$ **10b**[48] and $Rh_2(S\text{-PTPI})_4$,[85] with which enantioselectivities of up to 95% have been achieved in selected systems. The situation has been somewhat improved by the discovery that methyl

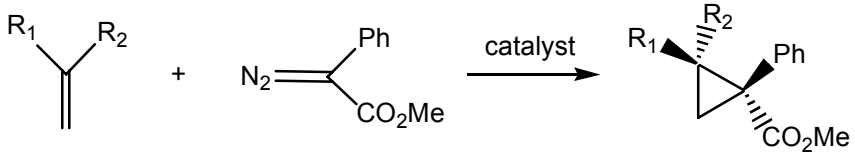
phenyldiazoacetate **22** is an excellent substrate for intermolecular cyclopropanation (Eq. 6).[34,35]



Scheme 6 Enantioselective cycloheptadiene synthesis.



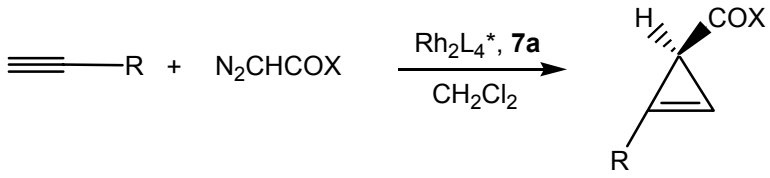
(5)



(6)

R_1 = alkyl; O-alkyl; aryl **22**
R_2 = H; alkyl; aryl

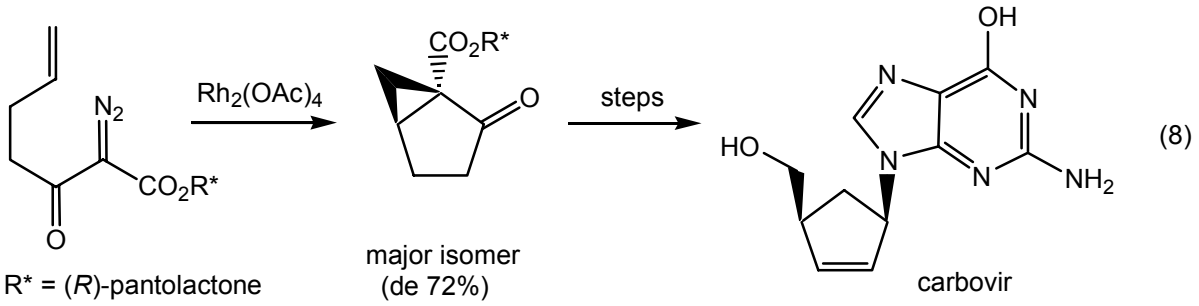
Homochiral dirhodium(II) carboxamidates, in particular **7a**, have proved to be exceptional catalysts for highly enantioselective intermolecular cyclopropenation (Eq. 7).[86] Since the cyclopropene products can be quantitatively reduced to *cis*-cyclopropanes, this provides an alternative route to these products in high enantiomeric purity.



(7)

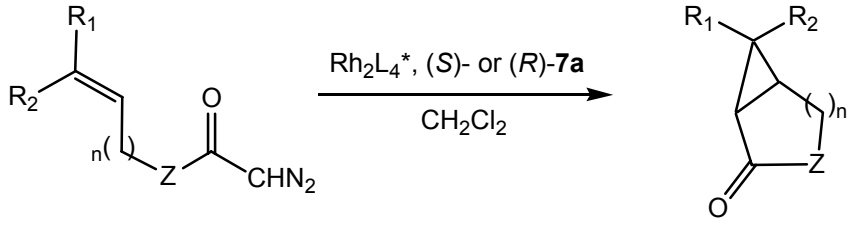
3.2.2. Intramolecular Processes

Because of geometric constraints, intramolecular cyclopropanation of unsaturated diazocarbonyl compounds can produce only one fused bicyclic cyclopropane (the *cis* isomer). Tanimori and co-workers have reported an approach to the intramolecular cyclopropanation of a diazoacetate mediated by a chiral auxiliary in their synthetic route to the carbocyclic moiety of the anti-HIV agent carbovir (Eq. 8).[87] This is, however, a rare diastereoselective approach, since the dirhodium(II) carboxamidate catalysts **7**–**10** have proved to be most efficient and selective for reactions of diazoacetates and diazoacetamides.[44,67,88]



(8)

Excellent enantioselectivities have been reported with allylic diazoacetates **23** (n = 1, Z = O) catalysed by Rh_2(5*S*-MEPY)$_4$, (*S*)-**7a**, and Rh_2(5*R*-MEPY)$_4$, (*R*)-**7a** to give fused cyclopropyl lactones **24** (n = 1, Z = O) (Eq. 9).[44,89,90] Cyclopropanation of homoallylic diazoesters **23** (n = 2, Z = O)[91] and *N*-*tert*-butyldiazoacetamides **23** (n = 2, Z = *N*-^{t}Bu) (Eq. 9)[92] proceeded with moderate to high enantioselectivities with the same catalysts.



23 n = 1,2
Z = O, N-^{t}Bu

24 n = 1,2
Z = O, N-^{t}Bu

(9)

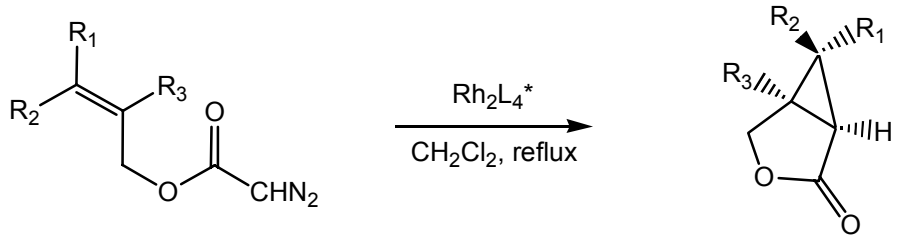
It has further been shown that enantioselectivities obtained in the catalysed cyclopropanation of allylic diazoacetates **25a**–**g** to give the cyclopropyl γ-lactones **26a**–**g** largely depended on the position of vinylic substitution (Table 1).[44] As is shown in Table 1, careful selection of the catalyst becomes necessary in order to optimise the enantioselectivity.[88,93] Application of the enantiomers of the catalysts to the cyclopropanation of these allylic diazoacetates provided the fused cyclopropyl lactone products with the same enantiomeric excesses, but with the opposite absolute configurations. A recent contribution to the area by Martin and Hillier has investigated the complementarity of chiral diazoacetates and chiral catalysts in a form of double diastereodifferention–cyclopropanation.[94]

Several pharmacologically important molecules have been synthesized through the use of the above methodology, using either enantiomer of catalyst **7a**. As outlined in Scheme 7, the Martin group[95,96] synthesized trisubstituted cyclopropanes as conformationally restricted peptide isosteres for renin **27** and collagenase inhibitors, and Rogers and co-workers[97] have synthesizes presqualene alcohol **28**. In addition, the products of these cyclopropanation reactions may serve as synthetic precursors to *cis*-chrysanthemic acid[98] and the pheromone *R*-(–)-dictyopterene C.[99]

With homoallylic diazoacetates **29** (n = 2, R^4 = H)[44,91] and allylic diazopropionates **29** (n = 1, R^4 = Me),[100] there is a moderate reduction in the enantioselectivity (ee 70-90%) with a similar selection of dirhodium catalysts (Eq. 10). Analogous intramolecular cyclopropanation of *N*-allyl diazoacetamides **30** (n = 1)[44,101] and *N*-*tert*-butyl-*N*-homoallylic diazoacetamides **30** (n = 2)[92] to give the fused cyclopropyl lactams **31** have been progressively refined to high yielding, highly enantioselective processes (Eq. 11). The Davies group has demonstrated the applicability of their formal [3+4]-cycloaddition in an intramolecular example of allylic

diazoacetate cyclopropanation as part of a synthesis of 5-epitremulenolide (Eq. 12).[102]

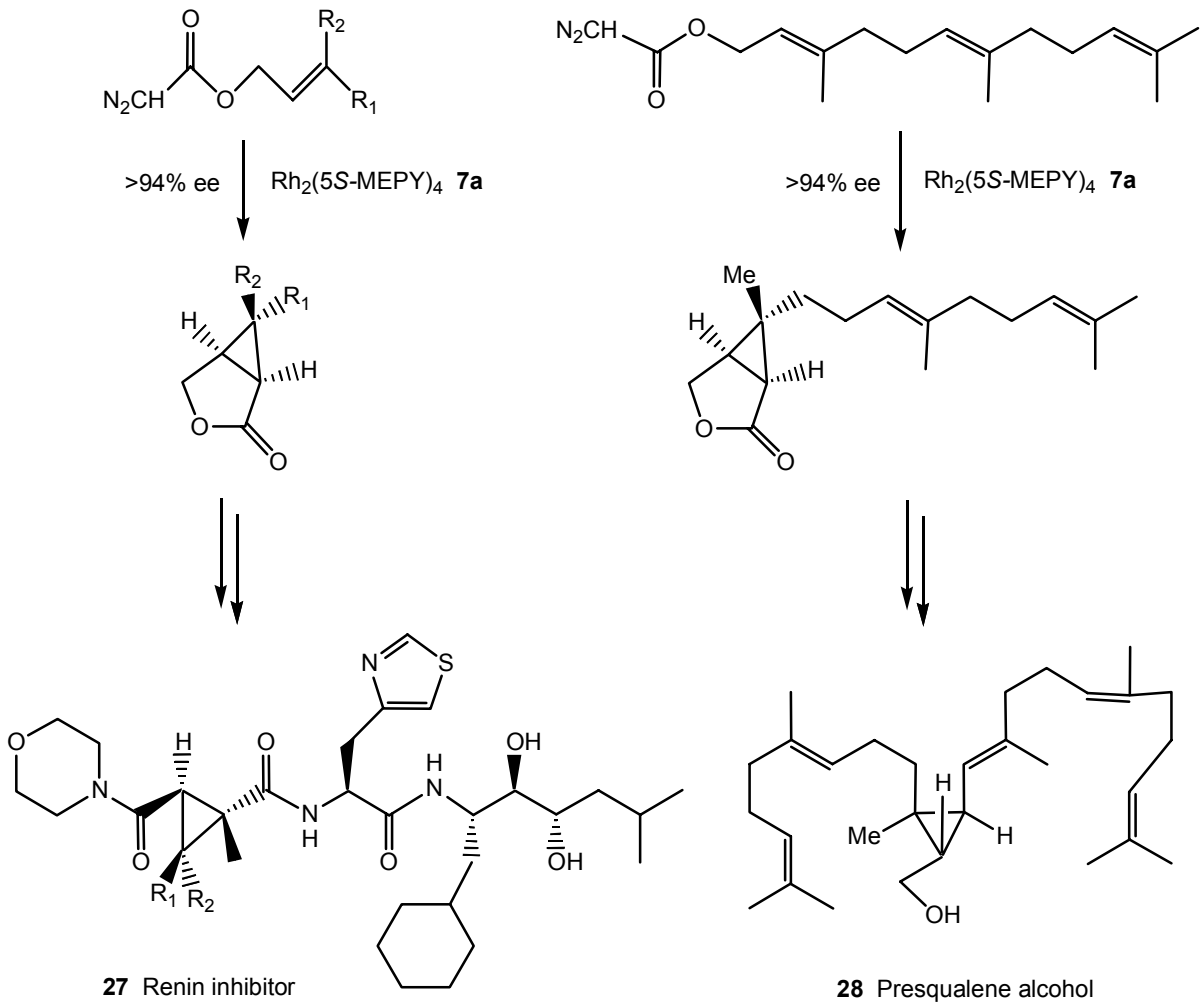
Table 1 Enantioselective intramolecular cyclopropanation of allylic diazoacetates.



25a-g **26a-g**

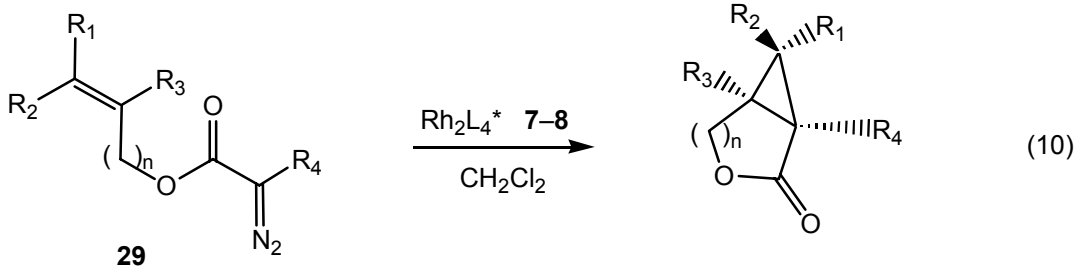
25	R^1	R^2	R^3	Catalyst	Yield, % (ee, %)	Config.
a	H	H	H	**7a**	75 (95)	(1*R*,5*S*)
b	Me	Me	H	**7a**	89 (98)	(1*S*,5*R*)
c	H	H	Me	**7a**	72 (7)	(1*R*,5*S*)
c	H	H	Me	**9d**	75 (89)	(1*S*,5*R*)
d	H	Ph	H	**7a**	70 (≥94)	(1*R*,5*S*)
e	Ph	H	H	**7a**	78 (68)	(1*R*,5*S*)
e	Ph	H	H	**9d**	61 (96)	(1*R*,5*S*)
f	Pr	H	H	**7a**	93 (85)	(1*R*,5*S*)
f	Pr	H	H	**9d**	83 (95)	(1*R*,5*S*)
g	H	*i*Pr	H	**7a**	85 (≥94)	(1*R*,5*S*)

Although diazoacetates and diazoacetamides generally undergo dirhodium(II)-catalysed intramolecular cyclopropanation with high enantiocontrol, the same is not true for diazoketones. Here the best results were obtained from copper-based catalysts.[103]

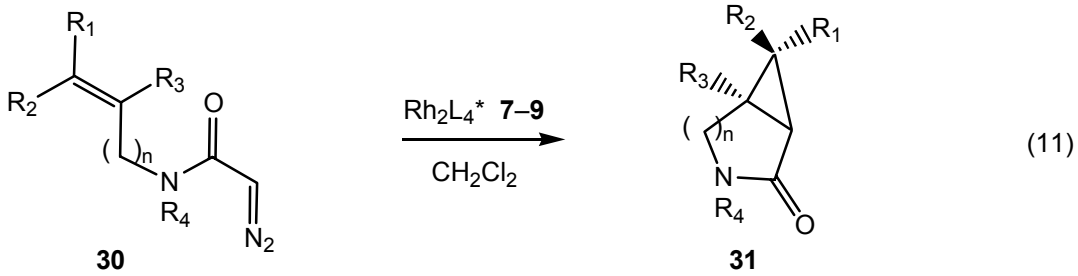


Scheme 7 Applications of enantioselective intramolecular cyclopropanation.

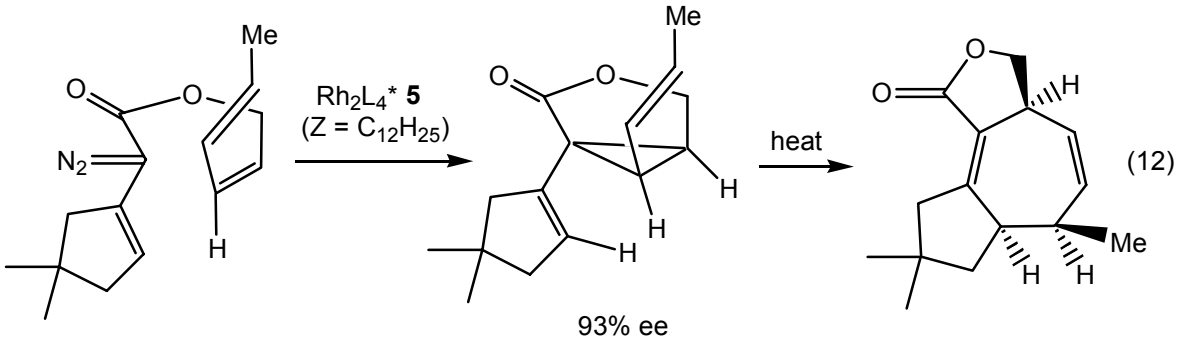
No notable success with intramolecular cyclopropenation has been reported. These reactions generally produce unstable fused cyclopropenes that undergo ring opening to vinylcarbenes that can react by a number of pathways, often giving rise to multiple products.[104,105]



(10)



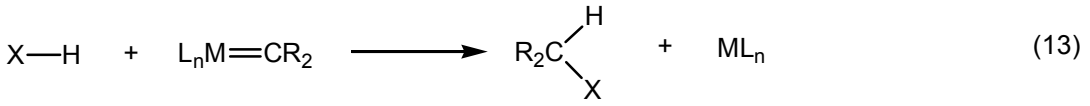
(11)



(12)

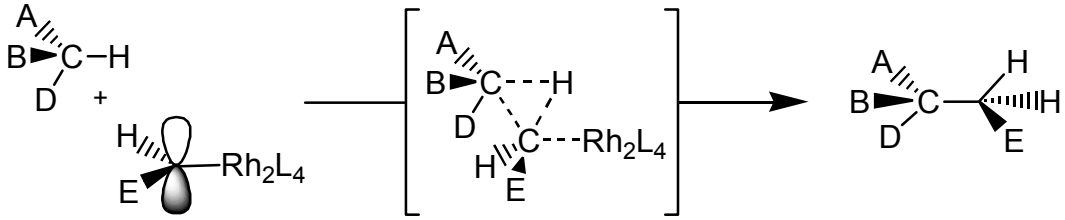
3.3. Insertion Products

Catalytically generated metal carbenes have been shown to be capable of highly versatile insertion into carbon-hydrogen and heteroatom-hydrogen bonds (Eq. 13).



(13)

Although these processes are generally indiscriminate, the advent of dirhodium(II) catalysts provided the required element of control to make these highly attractive C–C bond-forming processes.[9,13,14,18,106] The mechanism of the transition metal catalysed C–H insertion reactions has been the subject of considerable speculation, but there is general agreement that insertion occurs through a metal carbene intermediate.[107,108] Doyle and co-workers have suggested the mechanism depicted below as a suitable model for the C–H insertion process (Scheme 8).[21]



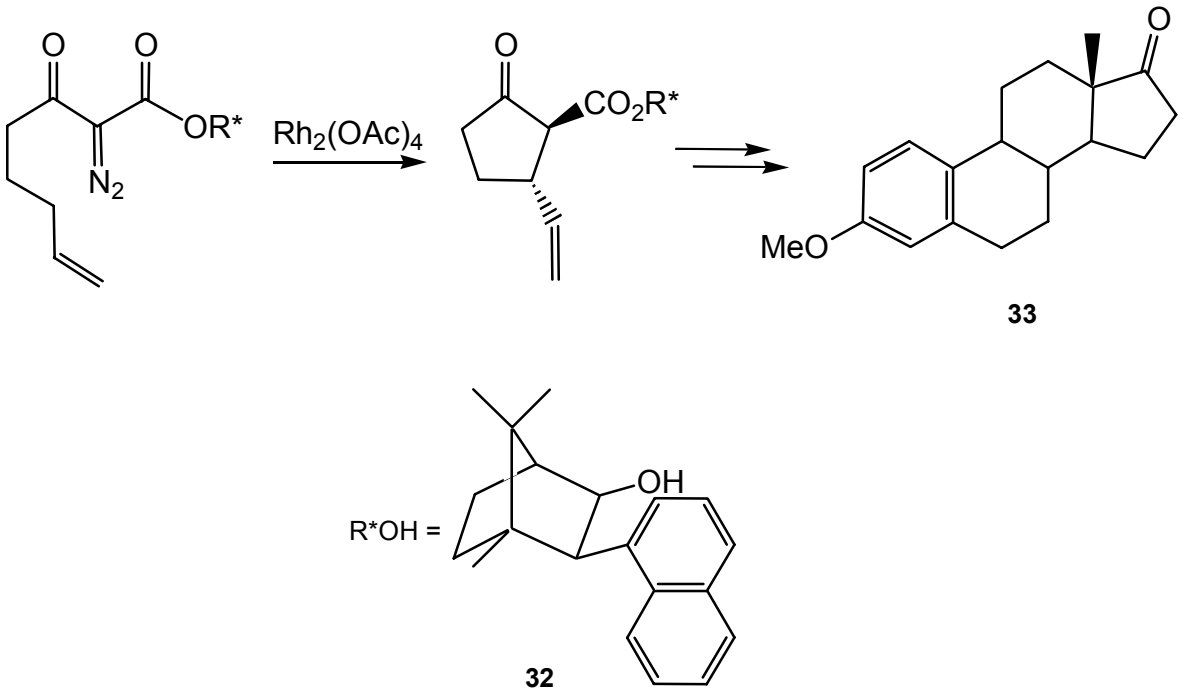
Scheme 8 Mechanism of C-H insertion.

3.3.1. Carbon–Hydrogen Insertion Products

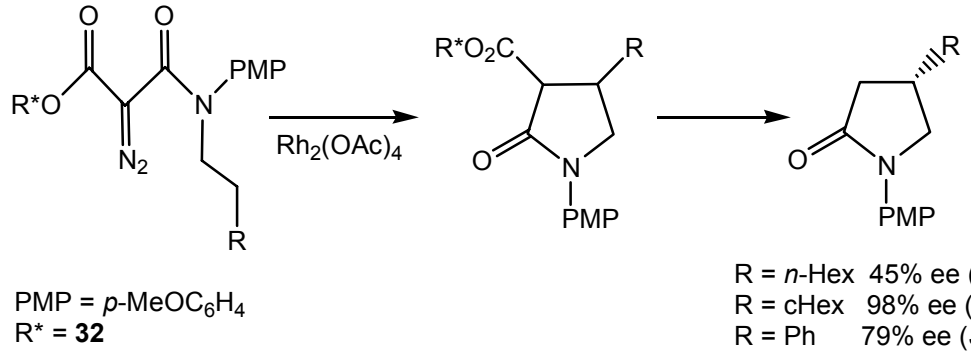
Although examples of dirhodium(II)-catalysed intermolecular C–H insertion reactions are known, they generally lead to multiple products and require highly electrophilic catalysts in order to minimise competitive reactions such as formal carbene dimer formation. The yields and regioselectivities of these reactions are highly dependent on the catalyst employed.[109,110] Intramolecular C-H insertion reactions of diazocarbonyl compounds are more effective and selective, and they have become synthetically relevant, with the dirhodium(II) carboxylates and carboxamidates **5-10** as the catalysts of choice.[2,4,37,111]

Two diastereoselective approaches are worthy of note. In both approaches, 1-naphthylborneol **32** esters were used as the chiral auxiliary for asymmetric induction in C–H insertion reactions.[112-114] Taber and co-workers achieved diastereoselectivities of 83:17–92:8, which corresponds to enantiomeric excesses for the hydrolysed ester of 66% to 84%. This procedure was extended to a synthesis of (+)-estrone methyl ether **33** (Scheme 9). Wee and Liu used the same auxiliary in the C–H insertion reactions of diazomalonamides (Eq. 14).[114]

Enantioselective adaptations have been a more recent development. The McKervey group[4,29,76] and others[27,36,111,115] have utilised dirhodium(II) carboxylates derived from *N*-protected amino acids (catalysts **5** and **6**, respectively) to catalyse the enantioselective C–H insertion of diazoketone derivatives. Enantioselectivities in the C–H insertion reactions of α-diazo-β-ketosulphones catalysed by **5** (Z = H) were low (~12% ee), although yields were high.[76] With a series of methyl diazoketones **34**, the same catalyst yielded the corresponding chromanones with enantioselectivities of 62-82% ee for the major *cis* isomers (Eq. 15).[29]



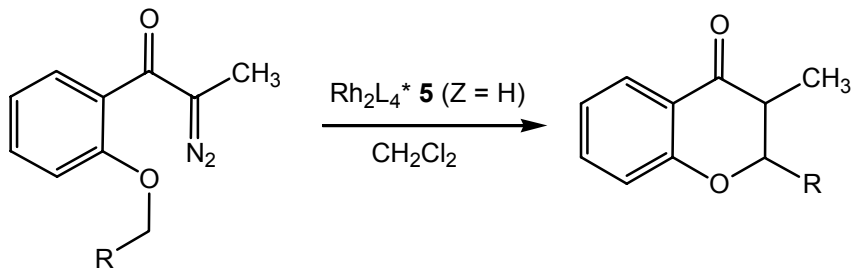
Scheme 9 Diastereoselective route to (+)-estrone methyl ether.



(14)

PMP = *p*-$MeOC_6H_4$
R* = **32**

R = *n*-Hex 45% ee (*R*)
R = cHex 98% ee (*S*)
R = Ph 79% ee (*S*)

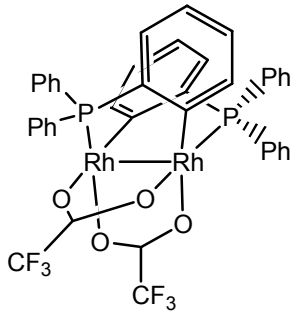


(15)

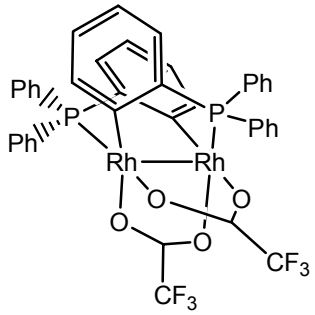
34 R = CH_3, Ph, $CH{=}CH_2$

Major *cis* 62-82% ee

Taber and co-workers have recently published a preliminary report on the preparation of a new type of chiral catalyst **35** (enantiomeric *M* and *P*) that has backbone chirality.[116] Whilst this design strategy may have potential, the initial intramolecular C-H insertions with a diazoketone afforded an enantioselectivity of only 36%. The general trend of moderate enantioselectivity with diazoketone substrates was further confirmed in a recent report by Müller and Maîtrejean.[117]

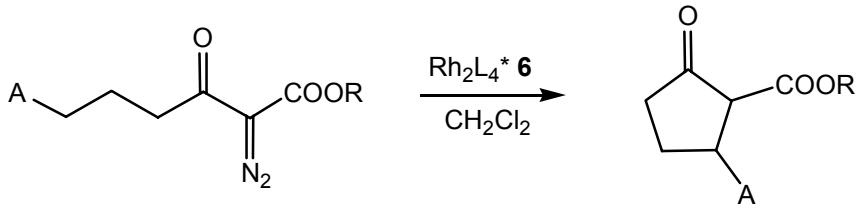


(*M*)-**35**



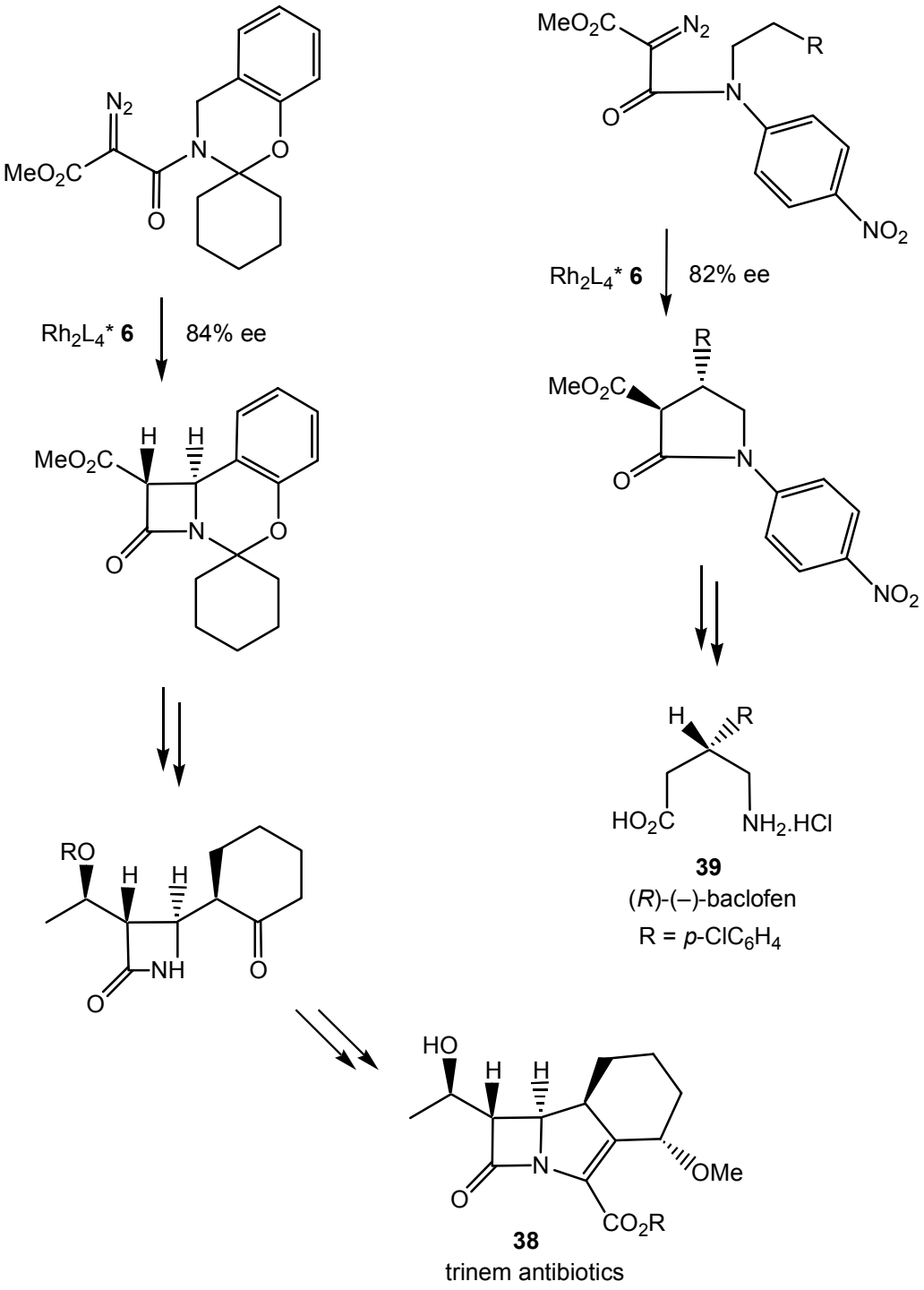
(*P*)-**35**

Hashimoto and co-workers obtained enantiomeric excesses of 24–76% in the intramolecular C–H insertion reactions of α-diazo-β-keto esters **36** catalysed by catalysts of type **6**, to yield β-keto esters **37** (Eq. 16).[27] More recent results with this catalyst line have afforded good enantioselective routes to azetidinones[115] and pyrrolidin-2-ones.[114] These successes are exemplified by their syntheses of intermediates for trinem β-lactam antibiotics **38** and a typical $GABA_B$ receptor agonist (*R*)-(–)-baclofen **39** (Scheme 10).



(16)

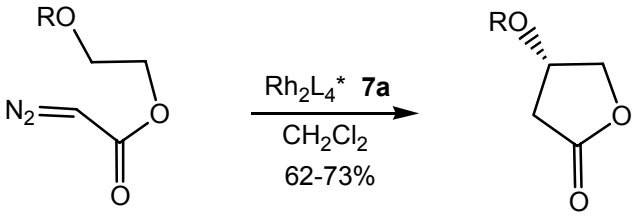
36 A = Me, Ph, C_5H_{11}, $CH=CH_2$ **37** 24-76% ee



Scheme 10 Applications of enantioselective intramolecular C-H insertion.

Doyle and co-workers have applied the homochiral dirhodium(II) carboxamidate catalysts to the enantioselective C–H insertion reactions of diazoesters and diazoamides.[40,43,45] An early application of Rh_2(5*S*-MEPY)$_4$ **7a** was in the diazo decomposition of alkyl diazoacetates such as **40** to give the corresponding γ-lactones

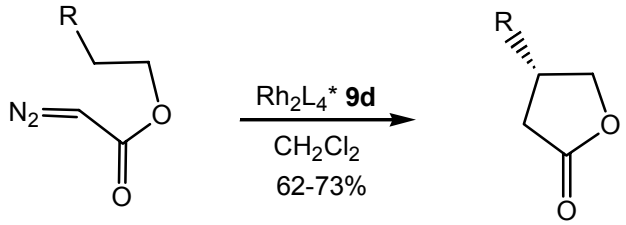
41 in high yield, since insertion into a C–H bond α to an ether oxygen is a ready process (Eq. 17).[118] With primary alkyl diazoacetates other than **40**, C–H insertion reactions catalysed by $Rh_2(MEPY)_4$ proceed with enantiomeric excesses below 70%. However, the introduction of imidazolidin-2-one catalyst variants **9** has led to enhanced enantioselectivities and excellent regiocontrol.[119-124] For example, use of $Rh_2(4S\text{-MPPIM})_4$ **9d** provided γ-lactones **43** from diazoacetates **42** derived from primary alcohols (Eq. 18). This methodology provided simple access to a series of naturally occurring lignans, for example (–) enterolactone **44**, (+)-arctigenin **45** and (+)-isodeoxypodophyllotoxin **46**.[124]



40 **41**

R = Me 91% ee
Et 89% ee
Bn 87% ee

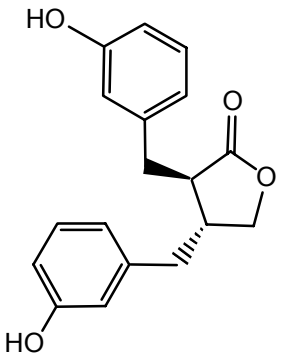
(17)



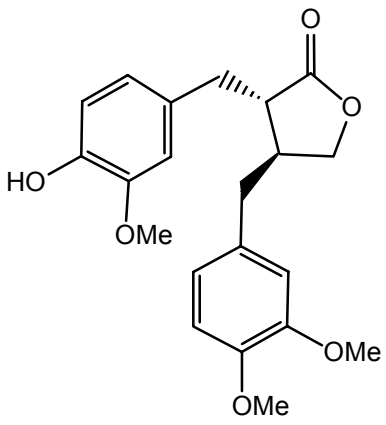
42 **43**

R = Et 96% ee
iBu 95% ee
Bn 89% ee
m-MeOBn 92% ee
3,4-$(MeO)_2$Bn 94% ee

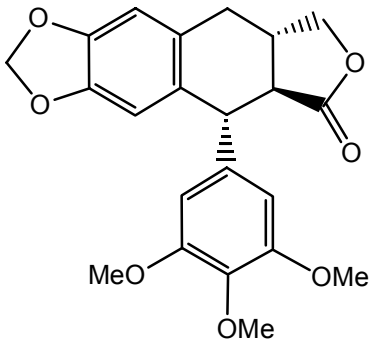
(18)



44



45

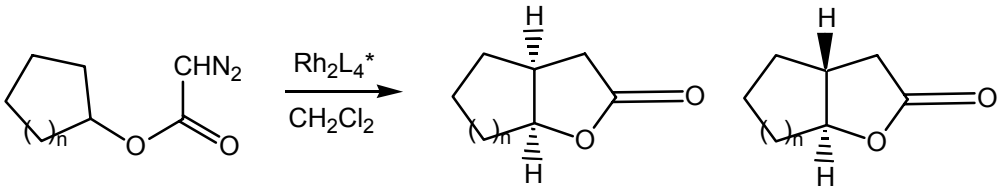


46

Similar methodology has been applied to the C–H insertion reactions of secondary cycloalkyl diazoacetates **47**, where diastereoselectivity in the formation of *cis*- and *trans*-fused bicyclic lactones **48** and **49** is a critical control feature (Table

2).[119] Use of Rh_2(5*S*-MEPY)$_4$ **7a** or Rh_2(4*S*-MEOX)$_4$ **8a** produced insertion products with a high degree of enantiocontrol, but levels of diastereocontrol were far lower. In the formation of the more strained fused cyclopentyl lactone, only the *cis* diastereomer is formed, but the levels of enantioselectivity are lower than those obtained with the larger ring-sizes. However, both high enantiocontrol and almost complete stereocontrol were achieved in the latter with the catalyst Rh_2(4*S*-MACIM)$_4$ **9a** (Table 2).[119]

Table 2 Diastereo- and enantioselective intramolecular synthesis of fused bicyclic lactones.



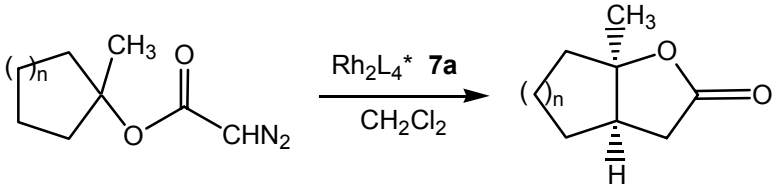
47a-d **48a-d** **49a-d**

a, n = 1; **b**, n = 2; **c**, n = 3; **d**, n = 4

47	Catalyst	**48:49**	**48** (ee, %)	**49** (ee, %)
a	**9a**	100:0	89	—
a	**7a**	100:0	40	—
b	**9a**	99:1	97	65
b	**7a**	75:25	97	91
b	**8a**	55:45	96	95
c	**9a**	99:1	96	61
d	**9a**	99:1	97	59

The enantioselective C–H insertion reactions of tertiary cycloalkyl diazoacetates **50a,b** catalysed by Rh_2(5*S*-MEPY)$_4$ **7a** and Rh_2(4*S*-BNOX)$_4$ **8c** have been investigated (Eq. 19).[123] In contrast to the secondary cycloalkyl analogues above (Table 2), both enantioselectivities and yields obtained in the formation of the bicyclic lactones **51a,b** were poor, although only *cis* products were observed. Again, Rh_2(4*S*-MACIM)$_4$ led to greatly improved results.[120] By contrast, high levels of enantio- and

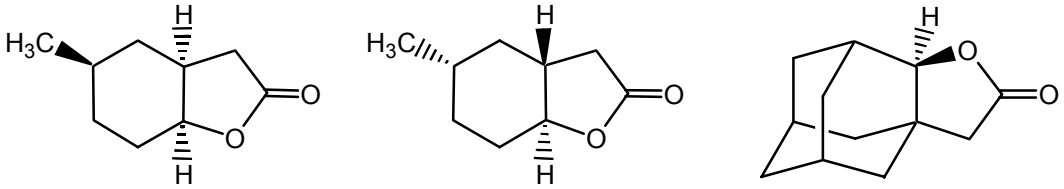
diastereocontrol have been achieved with *cis*- or *trans*-4-alkylcyclohexyl-diazoacetates,[119,123] and with 2-adamantyl diazoacetate[43] in the formation of lactones **52**–**54** respectively.



(19)

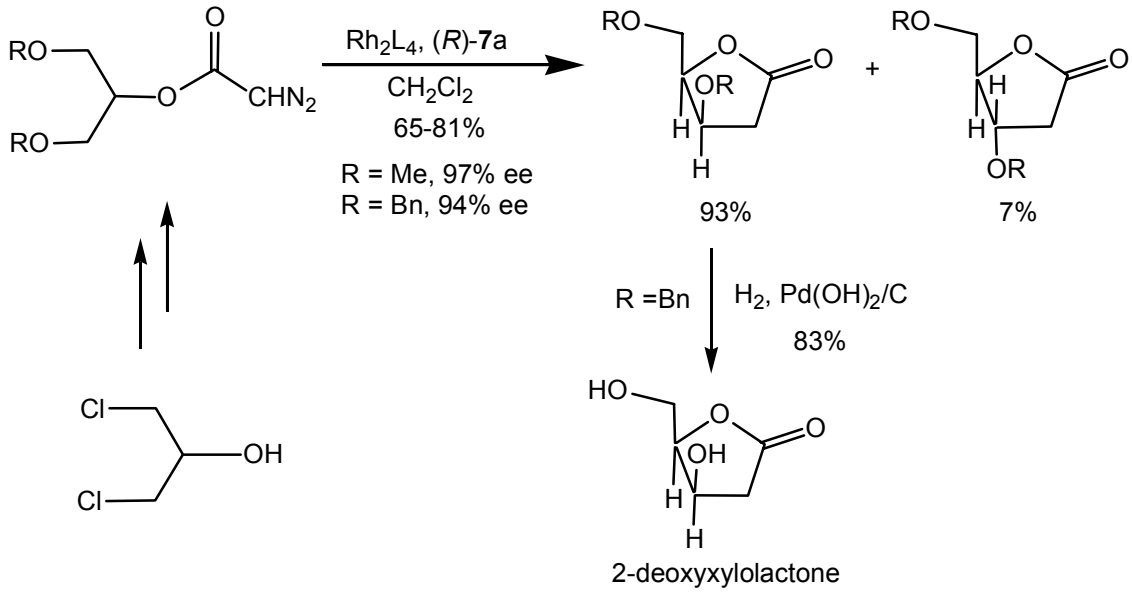
50a n = 1
50b n = 2

51a 85% ee
51b 90% ee



52 98% ee **53** 95% ee **54** 98% ee

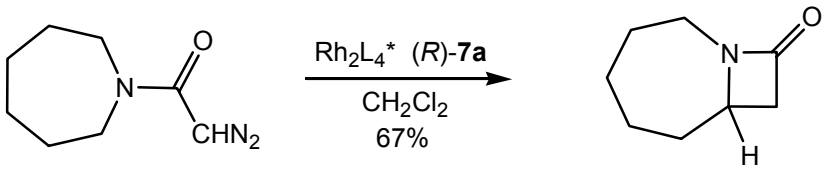
Doyle and co-workers have described the use of $Rh_2(5R\text{-MEPY})_4$ (*R*)-**7a** in the C–H insertion reactions of glycerol derived diazoacetates for the convenient synthesis of pure 2-deoxyxylolactone (Scheme 11).[125]



Scheme 11 Enantioselective synthesis of 2-deoxyxylolactone.

The success of this reaction is probably due to the ether oxygen's electronic activation of adjacent C–H bonds.[126,127] In the absence of the ether oxygen, enantioselectivities in the C–H insertion reactions of alkyl diazoacetates remain high, but diastereocontrol with $Rh_2(MEPY)_4$ catalysts tends to be relatively low.

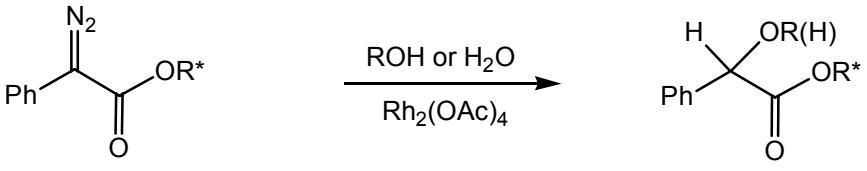
Dirhodium(II) carboxamidate-catalysed C–H insertion reactions of diazoacetamides derived from cyclic amines have been shown to afford β-lactam products preferentially, with a high degree of enantiocontrol (Eq. 20).[128]



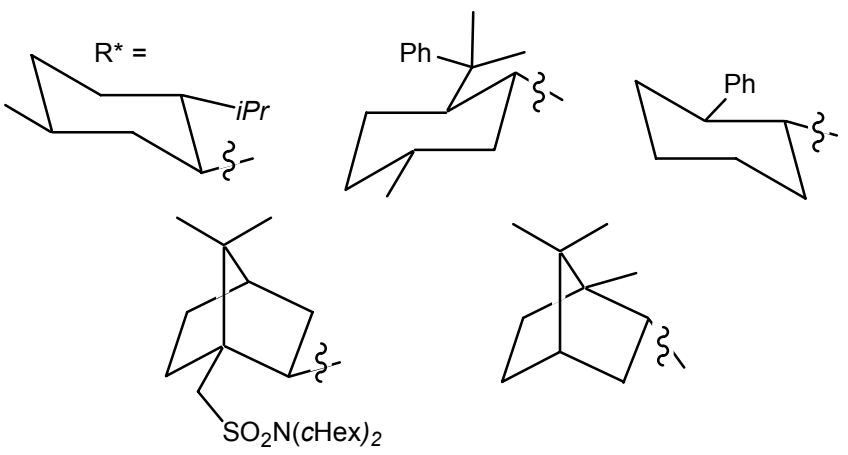
97% ee (20)

3.3.2. Heteroatom–Hydrogen Insertion Products

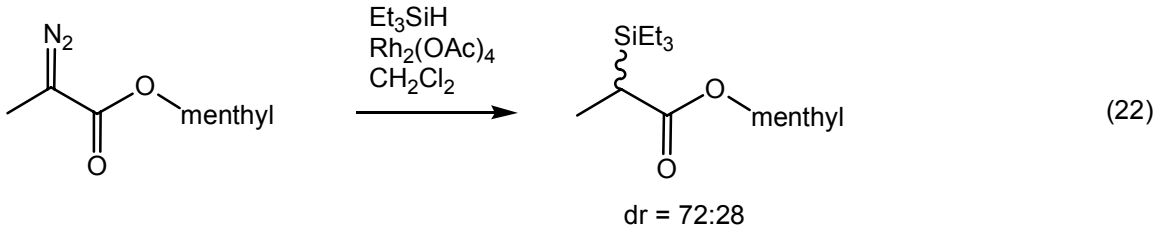
The insertion of transition metal carbenes, particularly those derived from dirhodium(II) carboxylate catalysts, into a variety of nucleophilic heteroatom–H bonds has provided novel routes for the synthesis of many synthetically relevant compounds.[5,9] Of these, insertion into O–H, N–H and Si–H bonds are the most prominent. Asymmetric variants of these reactions, outside of those that are conducted on enantiomerically pure substrates, are still in their infancy. Of the asymmetric variants reported, the diastereoselective chiral auxiliary approach has shown the most success. Recently, Moody and co-workers reported the $Rh_2(OAc)_4$ catalysed intermolecular O–H insertion reactions of chiral auxiliary-bearing diazoacetates with simple alcohols, with diastereomeric excesses of up to 53% being attained (Eq. 21).[129,130]



(21)

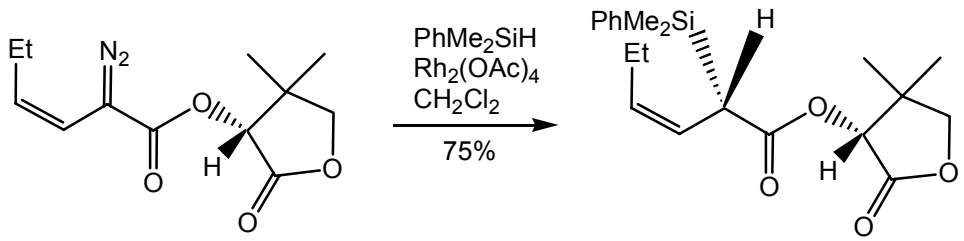


The N–H insertion reactions reported to date have shown disappointing levels of asymmetric induction (<50% ee), and much more research is required before this becomes a useful synthetic tool.[131,132] On the other hand, Si–H insertion has shown greater promise. The Landais group[133] has provided the most significant results by an approach involving chiral auxiliaries (Eqs. 22, 23)[134-136]. Three groups have independently reported the first successful enantioselective approach using chiral dirhodium catalysts, Rh_2(5*S*-MEPY) **7a**[136,137] and Rh_2(*S*-DOSP)$_4$ **5.**[77] The best results (Eq. 24) were obtained with vinyldiazoacetates. The Moody group has reported preliminary results of the screening, by parallel synthesis techniques, of a range of dirhodium(II) carboxylates.[138] Optimisation of the catalyst candidates identified in this study has yet to be published.



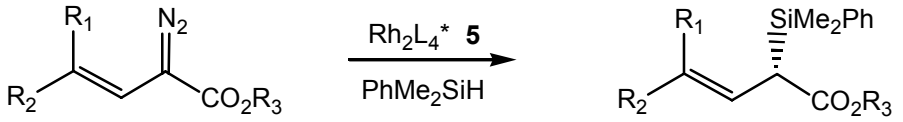
(22)

dr = 72:28



(23)

dr = 85:15



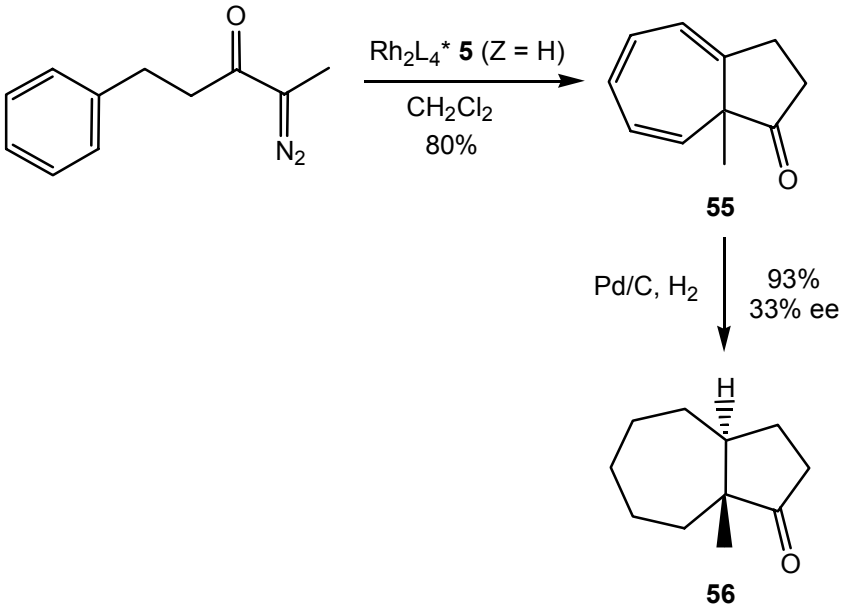
(24)

L = (*S*-DOSP) ee 77-95%
L = *(5S*-MEPY) ee 52-72%

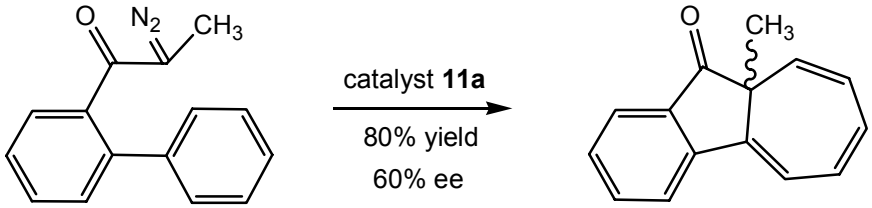
3.4. Aromatic Cycloaddition and Substitution Products

Transition metal-catalysed carbene addition to aromatic rings may be considered a special class of cyclopropanation reaction. The high-yielding dirhodium(II)-catalysed intramolecular reactions of α-diazocarbonyl compounds bearing aryl substituents form fused bicyclic cycloheptatrienes such as **55**. This specific product was reduced to the bicyclo[5.3.0]decanone **56** with a determined enantiomeric excess of 33% (Eq.

25).[76] Successful asymmetric transformations have also been observed with chiral dirhodium(II) phosphates **11a**, and have yielded enantioselectivities of up to 60% ee (*e.g.,* Eq. 26).[49]

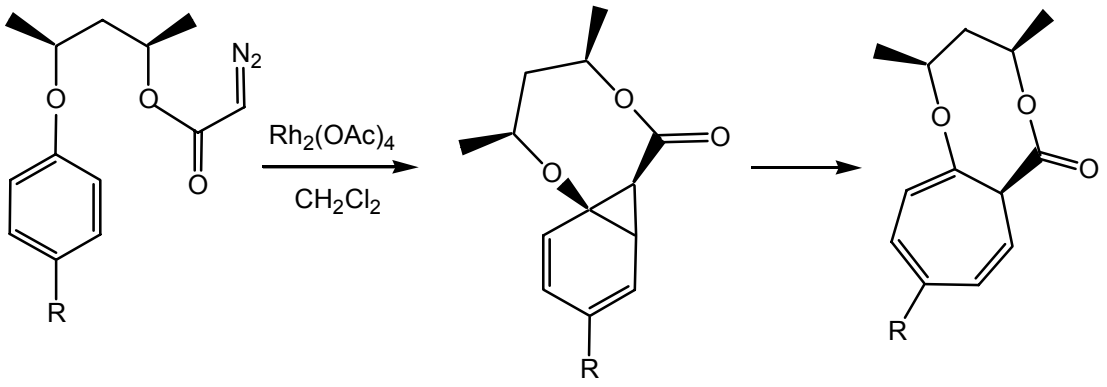


(25)



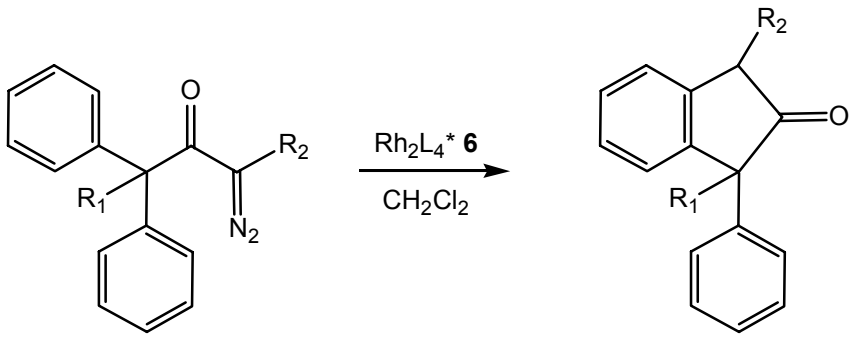
(26)

The only diastereoselective approach to aromatic cycloaddition involves the recent novel use of a chiral diol auxiliary as a tether between the aromatic substrate and the diazo moiety.[139] This has provided entry into a series of potentially useful tropylidenes as chirons for further synthesis (Eq. 27).



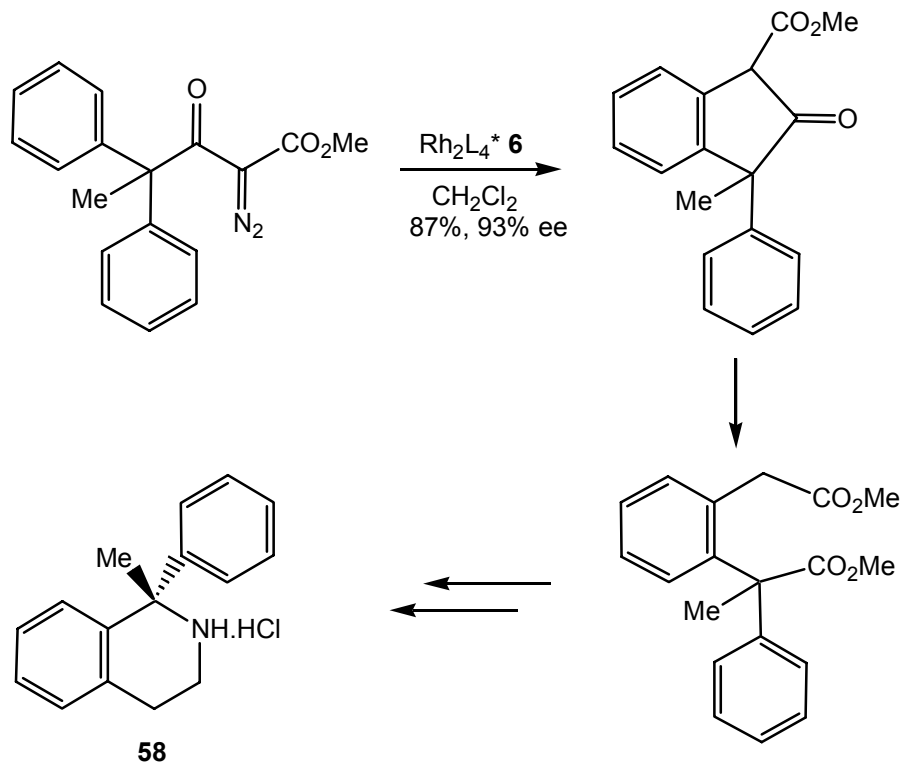
(27)

Intramolecular aromatic substitution by metal carbenes is formally a C–H insertion process. This type of reaction has tremendous potential for asymmetric synthesis if chiral catalysts are used. Although few reports have been published, there is evidence of early success. The Hashimoto group has exploited their amino acid phthalimide catalysts **6** to good effect (ee 88-98%) in the synthesis of a range of indanones **57** (Eq. 28).[37,38] The same workers have adapted this protocol for the synthesis of the aspartate receptor antagonist FR 115427 **58** (Scheme 12).[38] The Doyle group has recently reported early results of related insertions into the naphthalene framework.[140]



(28)

57

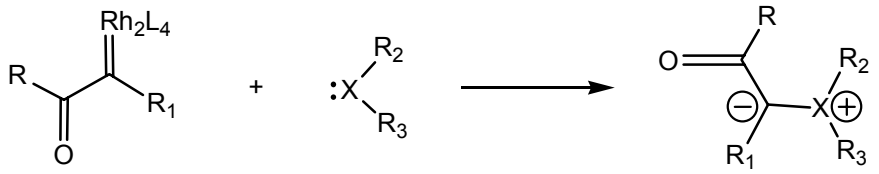


58

Scheme 12 Synthesis of antagonist FR 115427 by intramolecular aromatic substitution.

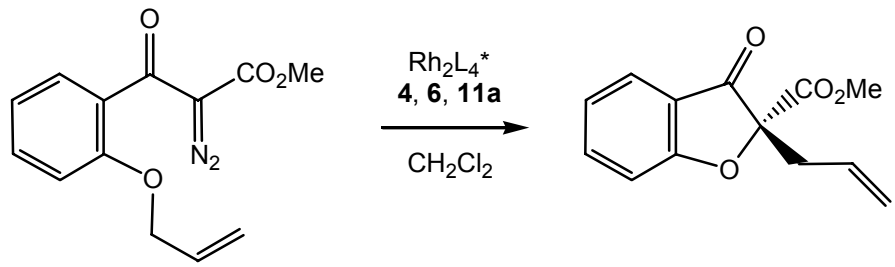
3.5. Ylide Cascade Products

Metal carbenes derived from α-diazocarbonyl compounds are electrophilic enough to add to heteroatoms, thereby forming ylides (Eq. 29). These may then undergo a wide range of reactions including [2,3]-sigmatropic rearrangements, [1,2]-insertion (Stevens rearrangements), hydride elimination, and dipolar cycloaddition.[5,141] This diverse reactivity, along with the often competitive initial formation of the ylides, has relieved what has been a relatively barren landscape in terms of their dirhodium-catalysed asymmetric synthesis.



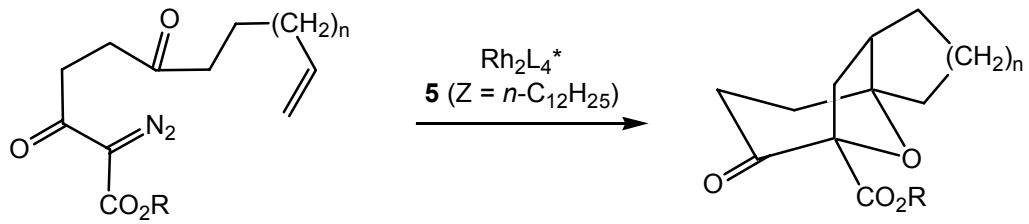
(29)

Successful asymmetric adaptation is only a very recent achievement, and has so far been restricted to oxonium ylide systems. The initial examples were provided by the McKervey group, who exploited a sequence involving tandem ylide formation and [2,3]-sigmatropic rearrangement to produce benzofuranone derivatives with up to 60% ee (Eq. 30).[49,142]

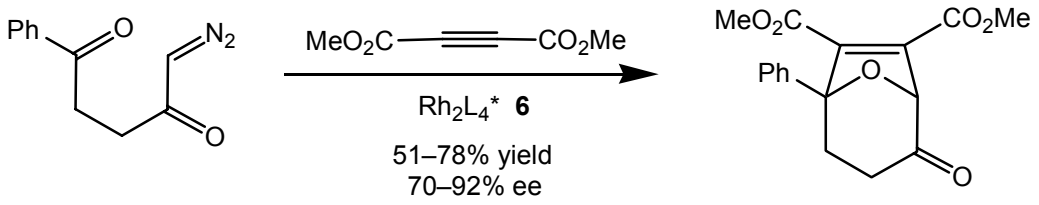


(30)

Chiral dirhodium(II) carboxamidate catalysts were used in initial studies of catalytic asymmetric tandem ylide formation–cycloaddition.[141,143] However, these produced ee values of less than 30%. Very recent developments have produced the first examples with ee values approaching synthetically useful levels. Thus diazo ketoesters were induced to give intramolecular cycloadducts *via* carbonyl ylides with ee's up to 53% (Eq. 31).[144] The Hashimoto group has taken this development further with diazo ketones in the intermolecular cycloaddition to afford bridged bicyclic skeletons in good yield and high enantioselectivity (Eq. 32).[145]

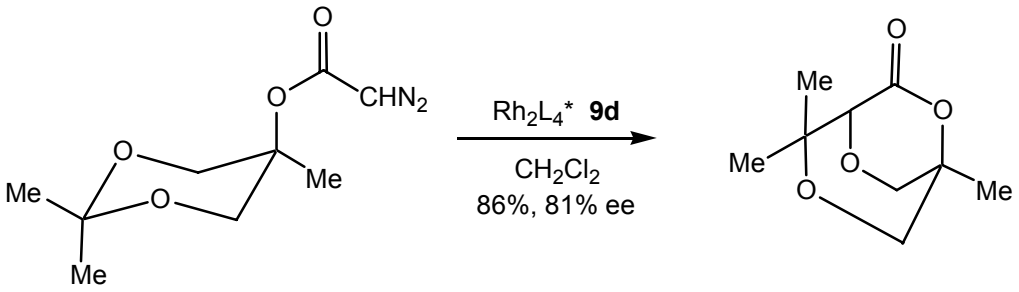


(31)



(32)

The Doyle group has provided the best enantioselective example of ylide formation-[1,2]-insertion (ee up to 88%) in their report on the decomposition of 1,3-dioxane diazoacetates (Eq. 33).[146]



(33)

4. Conclusion

Over the past decade, reports of chiral dirhodium(II) catalyst systems and their applications to asymmetric synthesis have burgeoned. As this technology is applied to a greater diversity of reaction systems, it seems inevitable that the spectrum of dirhodium(II) carbene chemistry will continue to expand. Given the wide range of non-racemic products that can be targeted in this way, these developments augur well for asymmetric organic synthesis and the industries that depend thereon.

Abbreviations for Ligands

BNAZ Benzyl 2-oxoazetidine-4-carboxylate

BNHP 1,1´-binaphthyl-2,2´-diyl phosphate

BNOX 4-benzyloxazolidin-2-one

DMAP 5-(*N,N*-dimethylamido)-2-oxopyrrolidine

DOSP *N*-(4-dodecylphenylsulfonyl)prolinate

IBAZ Isobutyl 2-oxoazetidine-4-carboxylate

IPOX 4-Isopropyloxazolidin-2-one

MACIM Methyl 1-acetyl-2-oxoimidazolidine-4-carboxylate

MBOIM Methyl 1-benzoyl-2-oxoimidazolidine-4-carboxylate

MCHIM Methyl 1-cyclohexylacetyl-2-oxoimidazolidine-4-carboxylate

MEOX Methyl 2-oxooxazolidine-4-carboxylate

MEPY Methyl 2-oxopyrrolidine-5-carboxylate

MPAIM Methyl 1-phenylacetyl-2-oxoimidazolidine-4-carboxylate

MPPIM Methyl 1-phenylpropionyl-2-oxoimidazolidine-4-carboxylate

NEPY Neopentyl 2-oxopyrrolidine-5-carboxylate

ODPY Octadecyl 2-oxopyrrolidine-5-carboxylate

PHOX 4-Phenyloxazolidin-2-one

TBSP *N*-(4-*tert*-Butylphenylsulfonyl)prolinate

THREOX Methyl 5-methyl-2-oxooxazolidine-4-carboxylate

References

1 M.P. Doyle, in *Catalytic Asymmetric Synthesis* (I. Ojima, ed.), VCH, Weinheim, 1993.

2 M.P. Doyle, *Chim. Oggi.,* 1994*,* 13.

3 M.P. Doyle, *Aldrichimica Acta,* 1996, **29**, 3.

4 M.P. Doyle and M.A. McKervey, *Chem. Commun.,* 1997, 983.

5 M.P. Doyle, M.A. McKervey and Y. Tao, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds,* Wiley, New York, 1998.

6 M.P. Doyle, in *Catalysis by Di- and Polynuclear Metal Cluster Complexes* (R.D. Adams and F.A. Cotton, eds.), Wiley–VCH, New York, 1998.

7 M.P. Doyle, *Pure Appl. Chem.,* 1998, **70**, 1123.

8 D.G. Ene and M.P. Doyle, *Chim. Oggi.,* 1998, 37.

9 T. Ye and M.A. McKervey, *Chem. Rev.,* 1994, **94**, 1091.

10 G.H.P. Roos and C.E. Raab, in *Advances in Catalytic Processes, Vol. 2* (M.P. Doyle, ed.), JAI Press, London, 1997.

11 M.P. Doyle, *Enantiomer,* 1999, **4**, 621.

12 M. Regitz and G. Maas, *Diazo Compounds: Properties and Synthesis.* Academic Press, Orlando, 1986.

13 M.P. Doyle, *Chem. Rev.,* 1986, **86**, 919.

14 G. Maas, *Top. Curr. Chem.,* 1987, **137**, 76.

15 A. Padwa and K.E. Krumpe, *Tetrahedron,* 1992, **48**, 5358.

16 H.M.L. Davies, *Tetrahedron,.*1993*,* **49**, 5203.

17 A. Padwa and D.J. Austin, *Angew. Chem., Int. Ed. Engl.,* 1994, **33**, 1797.

18 M.P. Doyle, in *Comprehensive Organometallic Chemistry II, Vol. 12* (L.S. Hegedus, ed.), Pergamon Press, New York, 1995, Ch. 5.1 and 5.2*.*

19 R. Paulissenen, H. Reimlinger, E. Hayez, A.J. Hubert and P. Teyssie, *Tetrahedron Lett.,* 1973, 2233.

20 E.B. Boyar and S.D. Robinson, *Chem. Rev.,* 1983, **50**, 109.

21 M.P. Doyle, L.J. Westrum, W.N.E. Wolthuis, M.M. See, W.P. Boone, V. Bagheri and M.M. Pearson, *J. Am. Chem. Soc.,* 1993, **115**, 958.

22 M.Q. Ahsan, I. Bernal and J.L. Bear, *Inorg. Chem.,* 1986, **25**, 260.

23 M.P. Doyle, J. Taunton and H.Q. Pho, *Tetrahedron Lett.,* 1989, **30**, 5397.

24 M.P. Doyle, V. Bagheri, M.M. Pearson and J.D. Edwards, *Tetrahedron Lett.,* 1989, **30**, 7001.

25 M.P. Doyle, R.J. Pieters, J. Taunton, H.Q. Pho, A. Padwa, D.L. Hertzog and L. Precedo, *J. Org. Chem.,* 1991, **56**, 820.

26 H. Brunner, H. Kluschanzoff and K. Wutz, *Bull. Chem. Soc. Belg.,* 1989, **98**, 63.

27 S. Hashimoto, N. Watanabe and S. Ikegami, *Tetrahedron Lett.,* 1990, **31**, 5173.

28 G.H.P. Roos and M.A. McKervey, *Synth. Commun.,* 1992, **22**, 1751.

29 M.A. McKervey and T. Ye, *J. Chem. Soc., Chem. Commun.,* 1992, 823.

30 H.M.L. Davies and D.K. Hutcheson, *Tetrahedron Lett.,* 1993, **34**, 7243.

31 H.M.L. Davies, G. Ahmed and M.R. Churchill, *J. Am. Chem. Soc.,* 1996, **118**, 10774.

32 H.M.L. Davies, P.R. Bruzinski, D.H. Lake, N. Kong and M.J. Fall, *J. Am. Chem. Soc.,* 1996, **118**, 6897.

33 H.M.L. Davies, L.A. Kuhn, C. Thornley, J.J. Matasi, T. Sexton and S.R. Childers, *J. Med. Chem.,* 1996, **39**, 2554.

34 H.M.L. Davies, P.R. Bruzinski and M.J. Fall, *Tetrahedron Lett.,* 1996, **37**, 4133.

35 M.P. Doyle, Q.-L. Zhou, C. Charnsangavej, M.A. Longoria, M.A. McKervey and C.F. García, *Tetrahedron Lett..* 1996, **37**, 4129.

36 S. Hashimoto, N. Watanabe and S. Ikegami, *Synlett.,* 1994, 353.

37 N. Watanabe, Y. Ohtake, S. Hashimoto, M. Shiro and S. Ikegami, *Tetrahedron Lett.,* 1995, **36**, 1491.

38 N. Watanabe, T. Ogawa, Y. Ohtake, S. Ikegami and S. Hashimoto, *Synlett.,* 1996, 85.

39 M.P. Doyle, *Russ. Chem. Bull.,* 1994, **43**, 1770.

40 M.P. Doyle, W.R. Winchester, J.A.A. Hoorn, V. Lynch, S.H. Simonsen and R. Ghosh, *J. Am. Chem. Soc.,* 1993, **115**, 9968.

41 M.P. Doyle, W.R. Winchester, S.H. Simonsen and R. Ghosh, *Inorg. Chim. Acta,* 1994, **220**, 193.

42 M.P. Doyle, W.R. Winchester, M.N. Protopopova, P. Müller, G. Bernardinelli, D. Ene and S. Motallebi, *Helv. Chim. Acta,* 1993, **76**, 2227.

43 M.P. Doyle, A.B. Dyatkin, M.N. Protopopova, C.I. Yang, C.S. Miertschin, W.R. Winchester, S.H. Simonsen, V. Lynch and R. Ghosh, *Recl. Trav. Chim. Pays-Bas,* 1995, **114**, 163.

44 M.P. Doyle, R.E. Austin, A.S. Bailey, M.P. Dwyer, A.B. Dyatkin, A.V. Kalinin, M.M.Y. Kwan, S. Liras, C.J. Oalmann, R.J. Pieters, M.N. Protopopova, C.E. Raab, G.H.P. Roos, Q.-L. Zhou and S.F. Martin, *J. Am. Chem. Soc.,* 1995, **117**, 5763.

45 M.P. Doyle, Q.-L. Zhou, C.E. Raab, G.H.P. Roos, S.H. Simonsen and V. Lynch, *Inorg. Chem.,* 1996, **35**, 6064.

46 M.P. Doyle, C.E. Raab, G.H.P. Roos, V. Lynch. and S.H. Simonsen, *Inorg. Chim. Acta,* 1997, **266**, 13.

47 G.H.P. Roos, C.E. Raab, N.D. Emslie, M.P. Doyle and V. Lynch, *Aust. J. Chem.,* 1998, **51**, 1.

48 M.P. Doyle, Q.-L. Zhou, S.H. Simonsen and V. Lynch, *Synlett.,* 1996, 697.

49 N. McCarthy, M.A. McKervey, T. Ye, M. McCann, E. Murphy and M.P. Doyle, *Tetrahedron Lett.,* 1992, **33**, 5983.

50 M.C. Pirrung and J. Zhang, *Tetrahedron Lett.,* 1992, **33**, 5987.

51 F. Estevan, P. Lahuerta, J. Pérez-Prieto, S.-H. Stiriba and M.A. Ubeda, *Synlett.,* 1995, 1121.

52 Z. Rappoport, (Ed.), *The Chemistry of the Cyclopropyl Group, Parts 1 and 2,* Wiley, New York, 1987.

53 P. Binger and H.M. Büch, *Top. Curr. Chem.,* 1987, **135**, 77.

54 M.S. Baird, *Top. Curr. Chem.,* 1988, **144**, 137.

55 J. Salaün, *Chem. Rev.,* 1989, **89**, 1247.

56 S.D. Burke and P.A. Grieco, *Org. React.,* 1979, **26**, 361.

57 T. Hudlicky, T.M. Kutchan and S.M. Naqvi, *Org. React.,* 1985, **33,** 247.

58 K. Burgess and T.-L. Ho, *Synlett.,* 1994, 575.

59 C.J. Suckling, *Angew. Chem., Int. Ed. Engl.,* 1988, **27**, 537.

60 R.A. Silverman, C.Z. Ding, J. L. Borrillo and J.T. Chang, *J. Am. Chem. Soc.,* 1993, **115**, 2982.

61 M. Newcomb and D.L. Chestney, *J. Am. Chem. Soc.,* 1994, **116**, 9753.

62 R.A. Caldwell and L. Zhou, *J. Am. Chem. Soc.,* 1994, **116**, 2271.

63 S. Husbands, C.A. Suckling and C.J. Suckling, *Tetrahedron,* 1994, **50**, 9729.

64 H.N.C. Wong, M.-Y. Hon, C.-W. Tse, Y.-C. Yip, J. Tanko and T. Hudlicky, *Chem. Rev.,* 1989, **89**, 165.

65 H.M.L. Davies, in *Comprehensive Organic Synthesis, Vol. 4* (B.M. Trost, ed.), Pergamon Press, New York, 1991, Ch. 4.8, p. 1031.

66 H.-U. Reissig, in *Houben-Weyl Methods of Organic Chemistry, Vol. 21c: Stereoselective Synthesis* (G. Helmchen, R.W. Hoffmann, J. Mulzer and E. Schaumann, eds.), Georg Thieme Verlag, New York, 1995.

67 M.P. Doyle and M.N. Protopopova, *Tetrahedron,* 1998, **54**, 7919.

68 V.K. Singh, A. Dattagupta and G. Sekar, *Synthesis,* 1997, 137.

69 M.P. Doyle, V. Bagheri, T.J. Wandless, N.K. Harn, D.A. Brinker, C.T. Eagle and K.-L. Loh, *J. Am. Chem. Soc.,* 1990, **112**, 1906.

70 H.M.L. Davies, N.J.S. Huby, W.R. Cantrell and J.L. Olive, *J. Am. Chem. Soc.,* 1993, **115**, 9468.

71 M.P. Doyle, M.N. Protopopova, B.D. Brandes, H.M.L. Davies, N.J.S. Huby and J.K. Whitesell, *Synlett.,* 1993, 151.

72 H.M.L. Davies, *Aldrichimica Acta.,* 1997, **30**, 107.

73 H.M.L. Davies, G. Ahmed, R.L. Calvo, M.R. Churchill and D.G. Churchill, *J. Org. Chem.,* 1998, **63**, 2641.

74 H.M.L. Davies, J.J. Matasi, L.M. Hodges, N.J.S. Huby, C. Thornley, N. Kong and J.H. Houser, *J. Org. Chem.,* 1997, **62**, 1095.

75 H.M.L. Davies, E. Saikali, N.J.S. Huby, V.J. Gilliatt, J.J. Matsai, T. Sexton and S.R. Childers, *J. Med. Chem.,* 1994*,* **37**, 1262.

76 M. Kennedy, M.A. McKervey, A.R. Maguire and G.H.P. Roos, *J. Chem. Soc., Chem. Commun.,* 1990, 361.

77 H.M.L. Davies, T. Hansen, J. Rutberg and P.R. Bruzinski, *Tetrahedron Lett.,* 1997, **38**, 1741.

78 H.M.L. Davies and S.A. Panaro, *Tetrahedron Lett.,* 1999, **40**, 5287.

79 H.M.L. Davies, N. Kong and M.R. Churchill, *J. Org. Chem.,* 1998, **63**, 6586.

80 H. Ishitani and K. Achiwa, *Synlett.,* 1997, 781.

81 E.J. Corey and T.G. Grant, *Tetrahedron Lett.,* 1994, **35**, 5373.

82 H.M.L. Davies, Z.-Q. Peng and J.H. Houser, *Tetrahedron Lett.,* 1994, **35**, 8939.

83 P. Müller, C. Baud, D. Ene, S. Motallebi, M.P. Doyle, B.D. Brandes, A.B. Dyatkin and M.M. See, *Helv. Chem. Acta,* 1995, **78**, 459.

84 N. Watanabe, H. Matsuda, H. Kuribayashi and S. Hashimoto, *Heterocycles,* 1996, **42**, 537.

85 S. Kitagaki, H. Matsuda, N. Watanabe and S. Hashimoto, *Synlett.,* 1997, 1171.

86 M.P. Doyle, M.N. Protopopova, P. Müller, D.G. Ene and E.A. Shapiro, *J. Am. Chem. Soc.,* 1994, **116**, 8492.

87 S. Tanimori, M. Tsubota, M. He and M. Nakayama, *Synth. Commun.,* 1997, **27**, 2371.

88 M.P. Doyle, C.S. Peterson, Q.-L. Zhou and H. Nishiyama, *Chem. Commun.,* 1997, 211.

89 M.P. Doyle, R.J. Pieters, S.F. Martin, R.E. Austin, C.J. Oalmann and P. Müller, *J. Am. Chem. Soc.,* 1991, **113**, 1423.

90 M.P. Doyle, W.R. Winchester, M.N. Protopopova, A.P. Kazala and L.J. Westrum, *Org. Synth.,* 1996, **73***,* 13.

91 S.F. Martin, C.J. Oalmann and S. Liras, *Tetrahedron Lett.,* 1992, **33**, 6727.

92 M.P. Doyle, M.Y. Eismont, M.N. Protopopova and M.M.Y. Kwan, *Tetrahedron,* 1994, **50**, 4519.

93 M.P. Doyle, Q.-L. Zhou, A.B. Dyatkin and D.A. Ruppar, *Tetrahedron Lett.,* 1995, **36**, 7579.

94 S.F. Martin and M.C. Hillier, *Tetrahedron Lett.,* 1998, **39**, 2929.

95 S.F. Martin, R.E. Austin, C.J. Oalmann, W.R. Baker, S.L. Condon, E. Delara, S.H. Rosenberg, K.P. Spina, H.H. Stein, J. Cohen and H.D. Kleinert, *J. Med. Chem.,* 1992, **35**, 1710.

96 S.F. Martin, C.J. Oalmann and S. Liras, *Tetrahedron,* 1993, **49**, 3521.

97 D.H. Rogers, E.C. Yi and C.D. Poulter, *J. Org. Chem.,* 1995, **60**, 941.

98 T. Mukaiyama, H. Yamashita and M. Asami, *Chem. Lett.,* 1983, 385.

99 T. Schotten, W. Boland and L. Jaenicke, *Tetrahedron Lett.,* 1986, **27**, 2349.

100 M.P. Doyle and Q.-L. Zhou, *Tetrahedron: Asymmetry,* 1995, **6**, 2157.

101 M.P. Doyle and A.V. Kalinin, *J. Org. Chem.,* 1996, **61**,2179.

102 H.M.L. Davies and B.D. Doan, *Tetrahedron Lett.,* 1996, **37**, 3967.

103 M.P. Doyle, M.Y. Eismont and Q.-L. Zhou, *Russ. Chem. Bull.,* 1997, **46**, 955.

104 A. Padwa, K.E. Krumpe, Y. Gareau and U. Chiacchio, *J. Org. Chem.,* 1991, **56**, 2523.

105 A. Padwa, D.J. Austin, Y. Gareau, J.M. Kassir and S.L. Xu, *J. Am. Chem. Soc.,* 1993, **115**, 2637.

106 O.M. Nefedov, E.A. Shapiro and A.B. Dyatkin, in *Supplement B: The Chemistry of Acid Derivatives* (S. Patai, ed.), Wiley, New York, 1992.

107 D.F. Taber, in *Comprehensive Organic Synthesis, Vol. 3* (B.M. Trost and I. Fleming, eds.), Pergamon Press, New York, 1991, Ch. 4.2

108 M.P. Doyle, in *Homogeneous Transition Metal Catalysts in Organic Synthesis,* (W.R. Moser and D.W. Slocum, eds.), ACS Advanced Chemistry Series 230, American Chemical Society, Washington, 1992, p. 443.

109 A. Demonceau, A.F. Noels, A.J. Hubert and P. Teyssie, *J. Chem. Soc., Chem. Commun.,* 1981, 688.

110 A. Demonceau, A.F. Noels, A.J. Hubert and P. Teyssie, *Bull. Soc. Chim. Belg.,* 1984, **93**, 945.

111 M. Anada and S. Hashimoto, *Tetrahedron Lett.,* 1998, **39**, 79.

112 D.F. Taber, K. Raman and M.D. Gaul, *J. Org. Chem.,* 1987, **52**, 28.

113 D.F. Taber and S.C. Malcolm, *J. Org. Chem.,* 1998, **63**, 3717.

114 A.G.H. Wee and B.S. Liu, *Tetrahedron Lett.,* 1996, **37**, 145.

115 M. Anada and S. Hashimoto, *Tetrahedron Lett.,* 1998, **39**, 9063.

116 D.F. Taber, S.C. Malcolm, J. Pérez-Prieto and M. Angeles Monge, *J. Am. Chem. Soc.,* 1999, **121**, 860.

117 P. Müller and E. Maîtrejean, *Collect. Czech. Chem. Commun.,* 1999, **64**, 1807.

118 M.P. Doyle, A. van Oeveren, L.J. Westrum, M.N. Protopopova and T.W. Clayton, *J. Am. Chem. Soc.,* 1991, **113**, 8982.

119 M.P. Doyle, Q.-L. Zhou, C.E. Raab, G.H.P. Roos, F. Cañas, D.A. Pierson, A. van Basten, P. Müller and P. Polleux, *J. Am. Chem. Soc.,* 1994*,* **116**, 4507.

120 M.P. Doyle, Q.-L. Zhou, C.E. Raab and G.H.P. Roos, *Tetrahedron Lett.,* 1995, **36**, 4745.

121 M.P. Doyle, M.N. Protopopova, Q.-L. Zhou, J.W. Bode, S.H. Simonsen and V. Lynch, *J. Org. Chem.,* 1995, **60**, 6654.

122 M.P. Doyle and A.V. Kalinin, *Russ. Chem. Bull.,* 1995, **44**, 1729.

123 P. Müller and P. Polleux, *Helv. Chim. Acta,* 1994, **77**, 645.

124 J.W. Bode, M.P. Doyle, M.N. Protopopova and Q.-L. Zhou, *J. Org. Chem.,* 1996, **61**, 9146.

125 M.P. Doyle, A.B. Dyatkin and J.S. Tedrow, *Tetrahedron Lett.,* 1994, **35**, 3853.

126 J. Adams, M.-A. Poupart, L. Grenier, C. Schaller, N. Ouimet and R. Frenette, *Tetrahedron Lett.,* 1989, **30**, 1749.

127 P. Wang and J. Adams, *J. Am. Chem. Soc.,* 1994, **116**, 3296.

128 M.P. Doyle and A.V. Kalinin, *Synlett.,* 1995, 1075.

129 E. Aller, D.S. Brown, G.G. Cox, D.J. Miller and C.J. Moody, *J. Org. Chem.,* 1995, **60**, 4449.

130 D.J. Miller, C.J. Moody and C.N. Morfitt, *Aust. J. Chem.,* 1999, **52**, 97.

131 E. Aller, R.T. Buck, M.J. Drysdale, L. Ferris, D. Haigh, C.J. Moody, N. Pearson and J.B. Sanghera, *J. Chem. Soc., Perkin Trans. 1.,* 1996, 2879.

132 C.F. Garcia, M.A. McKervey and T. Ye, *J. Chem. Soc., Chem. Commun.,* 1996, 1465.

133 Y. Landais, *Main Group Chem. News,* 1997, **5**, 20.

134 Y. Landais and D. Planchenault, *Tetrahedron Lett.,* 1994, **35**, 4565.

135 Y. Landais, D. Planchenault and V. Weber, *Tetrahedron Lett.,* 1994, **35**, 9549.

136 P. Bulugahapitiya, Y. Landais, L. Parra-Rapado, D. Planchenault and V. Weber, *J. Org. Chem.,* 1997, **62**, 1630.

137 R.T. Buck, M.P. Doyle, M.J. Drysdale, L. Ferris, D.C. Forbes, D. Haigh, C.J. Moody, M.D. Pearson and Q.-L. Zhou, *Tetrahedron Lett.,* 1996, **37**, 7631.

138 R.T. Buck, D.M. Coe, M.J. Drysdale, C.J. Moody and N.D. Pearson, *Tetrahedron Lett.,* 1998, **39**, 7181.

139 T. Sugimura, S. Nagano and A. Tai, *Chem. Lett.,* 1998, 45.

140 M.P. Doyle, D.G. Ene, D.C. Forbes and T.H. Pillow, *Chem. Commun.,* 1999, 1691.

141 M.P. Doyle and D.C. Forbes, *Chem. Rev.,* 1998, **98**, 911.

142 N. Pierson, C. Fernández-Garciá and M.A. McKervey, *Tetrahedron Lett.,* 1997, **38**, 4705.

143 H. Suga, H. Ishida and T. Ibata, *Tetrahedron Lett.,* 1998, **39**, 3165.

144 D.M. Hodgson, P.A. Stupple and C. Johnstone, *Tetrahedron Lett.,* 1997, **38**, 6471.

145 S. Kitigaki, M. Anada, O. Kataoka, K. Matsuno, C. Umeda, N. Watanabe and S. Hashimoto, *J. Am. Chem. Soc.,* 1999, **121**, 1417.

146 M.P. Doyle, D.G. Ene, D.C. Forbes and J.S. Tedrow, *Tetrahedron Lett.,* 1997, **38**, 4367.