# Catalytic Carbene Insertion into C−H Bonds

Michael P. Doyle,* Richard Duffy, Maxim Ratnikov, and Lei Zhou

*Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742*

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## 1. Introduction

From its earliest observation as an unusual reaction only a half century ago,[1] the insertion of a carbene into a carbon−hydrogen bond has attracted considerable interest because of its potential in forming carbon−carbon bonds (Figure 1). Thermally or photochemically generated carbenes, initially considered to be unselective in insertion reactions,[2–4] have been studied in sufficient detail to distinguish virtually unselective (:$CH_2$) to modestly selective (:$CCl_2$ and PhCCl) carbenes;[4,5] however, few of these reactions have shown potential for synthetically meaningful transformations. How to modify the reactivity of the carbene while still maintaining its reactivity toward carbon−hydrogen insertion was the challenge confronting those desiring to take advantage of what is an efficient and atom-economical transformation.

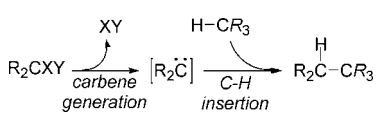
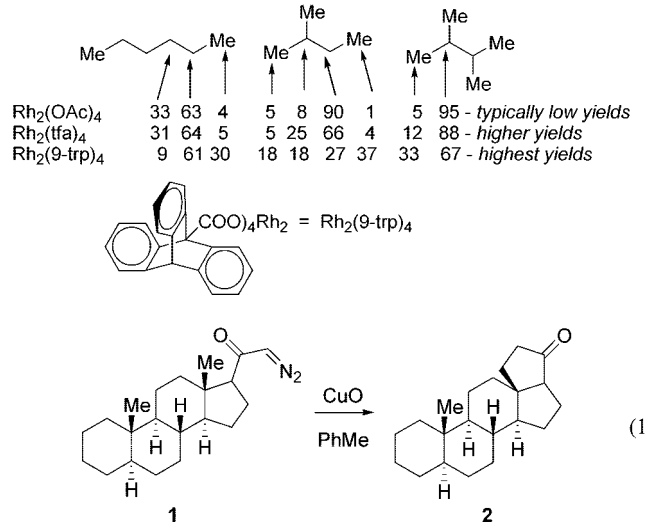



**Figure 1.** Generalized carbene generation and carbon−hydrogen insertion.

Carbene generation can occur from diazoalkanes photochemically and thermally or, as was initially reported in 1958 (eq 1),[6] by the use of a transition metal. Copper and copper compounds were initially employed, but few examples were reported that portrayed generality or synthetic utility except for intramolecular reactions in geometrically rigid systems (e.g., eq 2).[7–9] The breakthrough that brought carbon−hydrogen insertion reactions into the realm of viable synthetic applicability was the report of the Teyssie group of intermolecular carbon−hydrogen insertion reactions of ethyl diazoacetate with alkanes, catalyzed by dirhodium(II) tetraacetate and derivative rhodium carboxylates (for product ratios, see Scheme 1).[10,11] Although limited in selectivity, these initial results showed the influence of catalyst ligand on regioselectivity. Recognizing that intramolecular reactions, had higher potential for success than intermolecular processes, Wenkert[12] and Taber[13] began a series of investigations with diazo carbonyl compounds that demonstrated the synthetic advantages of dirhodium tetraacetate as a catalyst. In these early years, basic understanding of the extraordinary preference for the formation of five-membered cyclopentanone rings emerged,[14] as did regiochemical preference for insertion into a tertiary C−H bond over a secondary C−H bond (insertion into a primary C−H bond was not observed).[15] Insertion into a C−H bond occurred with retention of configuration (eq 3).[16]

**Scheme 1. For Reactions with Ethyl Diazoacetate, Arrows Define Site of C−H Insertion**

*For reactions with ethyl diazoacetate, arrows define site of C-H insertion:*




(1)

A number of reviews have presented carbon−hydrogen insertion reactions over recent years. Several books have included these transformations,[17–21] and reviews have often presented focused aspects relating to reaction selectivity.[22–32]

* Corresponding author e-mail: mdoyle3@umd.edu.

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Michael P. Doyle was born in Minneapolis, MN. He received his B.S. degree from the College of St. Thomas in St. Paul, MN, and obtained his Ph.D. degree from Iowa State University. Following a postdoctoral engagement at the University of Illinois at Chicago Circle, he joined the faculty at Hope College in 1968 where he rose to full professor and was appointed the first Kenneth Herrick Professor in 1982. In 1984, he moved to Trinity University in San Antonio, TX, as the Dr. D. R. Semmes Distinguished Professor of Chemistry, and in 1997 he came to Tucson, AZ, as Vice President, then President, of Research Corporation and Professor of Chemistry at the University of Arizona. In 2003 he moved to the University of Maryland, College Park, as Professor and Chair of the Department of Chemistry and Biochemistry. His research interests are in catalysis, especially reactions catalyzed by paddlewheeled dirhodium compounds, and in the diverse chemistries that surround the dirhodium framework.

Richard J. Duffy was born in Wilmington, Delaware. He received a B.S. degree in chemistry and a B.S. degree in botany in 2001 from the University of Oklahoma. In December of 2007, he received his Ph.D. degree in Chemistry under Professor Daniel Romo at Texas A&M University. His doctoral research focused on the synthesis and application of sprioepoxy-$\beta$-lactones to natural product synthesis and trans-selective cross-couplings of 1,1-dichloroolefins. In 2007 he joined the research group of Professor Michael P. Doyle at the University of Maryland, working with dirhodium Lewis acids. His research interests include transition metal catalyzed reactions and natural product total synthesis.

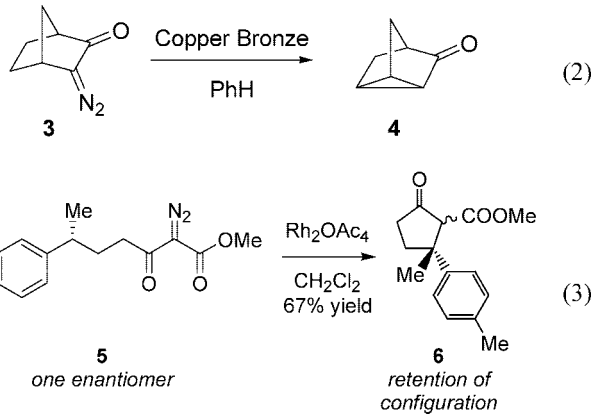
Maxim O. Ratnikov was born in Moscow, Russia, in 1984. In 2007 he received his M.S. degree from the Higher Chemical College in Moscow, participating in a development of polyfluorinated alcohols as a new electrophilic media under Dr. William Smit's supervision and in an elaboration of properties of polynitrogen containing heterocycles under Dr. Alexander Churakov's supervision. After receiving his degree, he moved to University of Kentucky where he worked on investigation of bioinspired nanoparticles under Dr. Marc Knecht's supervision. In 2008, he joined Professor Michael Doyle in University of Maryland where he is currently working towards his doctoral degree. In 2009, Mr. Ratnikov received a Department of Chemistry & Biochemistry Summer Fellowship for excellent academic performance. His research interests are in the development of novel oxidative methods and their applications in synthesis.

Lei Zhou was born and raised in Wuhan, China. He received his M.S. degree from Wuhan University in 2003. In 2004, he began his graduate studies at the University of Oklahoma, working under the direction of Professor Kenneth M. Nicholas. His research focused on the synthesis of tripodal bis(imidazole)thioether ligands and derived copper complexes. Upon obtaining his Ph.D. degree in 2008, he moved to the University of Maryland to carry out postdoctoral research with Professor Michael P. Doyle, undertaking synthesis and structure analysis of bisaryldirhodium(III) compounds. His research interests include the design and development of organometallic compounds and new synthetic methods for heterocyclic compounds.

This review is intended to provide an overview of metal carbene insertion reactions into carbon−hydrogen bonds that encompasses both intra- and intermolecular transformations and is focused on reaction selectivity. Since there is convincing theoretical and experimental evidence for the involvement of metal carbenes in these reactions, we will use that terminology, rather than "metal carbenoid" (*like a metal carbene*), for this transformation. In addition, although popular in current reports, we will not use the terminology "C−H bond activation" to refer to C−H insertion so that clear differentiation can be made between the metal carbene insertion and those reactions in which the metal catalyst forms a complex with a C−H bond,[33,34] activating it for subsequent transformations (Scheme 2).

## 2. Reaction Mechanism

A recent theoretical treatment by Nakamura and coworkers[35] confirmed the mechanistic proposal originally advanced by Doyle (Scheme 3)[36] that C−C and C−H bond formation with the carbene carbon occurs as the ligated metal dissociates at the same time but not necessarily to the same degree.[37] Prior to this density functional theory (DFT) calculation, alternate proposals included transfer of hydrogen from the C−H bond to the metal of the metal carbene,

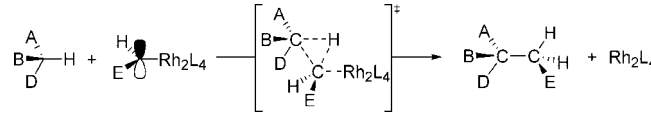



synchronous with carbon−carbon bond formation, then reductive elimination.[38,39] Using rhodium formate in these calculations, carbon−hydrogen insertion was computed to occur in a single step through a three-centered transition state with low activation energy. Overlap of the empty p-orbital on the carbene carbon occurs with the $\sigma$-orbital of the C−H bond. Interestingly, although only one of the two rhodium atoms is the binding site for the carbene, the other rhodium serves as a ligand to the carbene-bound rhodium to enhance the electrophilicity of the bound carbene and to facilitate the cleavage of the rhodium−carbon bond. Neither of the rhodium atoms interacts directly with the carbon−hydrogen bond undergoing insertion.

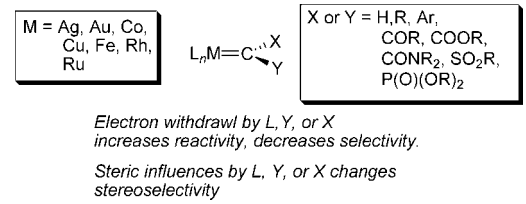
The singular effectiveness of dirhodium(II) for carbene carbon−hydrogen insertion was also suggested from the Nakamura DFT calculations.[35] Copper acetylacetonate,[40] but not the dichlororuthenium(II) pybox complex,[41] are among a number of transition metal compounds known to effect carbon−hydrogen insertion by metal-bound carbenes,[42,43] but none are as effective as those of dirhodium. In the case of dirhodium(II), it is the additional stabilization provided by the second rhodium that accounts for the dramatic lowering of the activation energy for carbon−hydrogen insertion that is found with dirhodium(II) carboxylates.[35] Although possible structural designs for ligands may yet provide less expensive metals with an advantage over dirhodium(II), recent efforts have focused on ligands for dirhodium(II) and diazo compounds whose substituents provide reactivity and selectivity suitable for insertion into carbon−hydrogen bonds with variable electronic demands (Scheme 4).

Dirhodium(II) catalyzed carbon−hydrogen insertion of diazo compounds occurs with retention of configuration at the carbon of the carbon−hydrogen bond,[16] and there is at present no reason to believe that insertion in other metal carbene reactions occurs by a different pathway. Electronic influences that include preferential insertion into tertiary C−H bonds over secondary C−H bonds and secondary C−H bonds over primary C−H bonds,[15,36,44] as well as enhancement of insertion into C−H bonds by adjacent electron-donating groups[45−48] and inhibition of insertion by adjacent electron-withdrawing groups,[49,50] are consistent with the involvement of an electrophilic metal carbene. However, steric effects-based conformational influences can alter

**Scheme 3**



**Scheme 4**




expected electronic influences, and the insertion selectivity of these reactions may be a balance between electronic and steric control.[36,50,51] Although allylic and benzylic C−H bonds were earlier thought to be less reactive than aliphatic C−H bonds,[15] subsequent studies showed that these C−H bonds enhanced C−H insertion.[36,52,53]

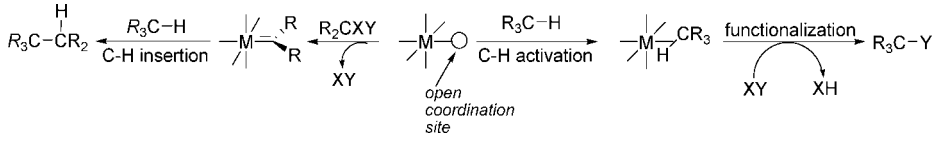
## 3. Catalysts

Carbon−hydrogen insertion is a process that occurs when a carbene associated with a stabilizing entity causes cleavage of a C−H bond concurrent, but not necessarily synchronous, with carbene−carbon and carbene−hydrogen bond formation. As this process requires carbene transfer, the catalysts employed are necessarily those that can stabilize a carbene, and transition metals that form metal carbenes are optimum for this transfer. Some, like those of Fisher carbenes, are so stable that the insertion of the associated carbene into a C−H bond does not occur.[17] Others, like those of some of the coinage metals, are so reactive as to be unselective.[54] Considering the transition metal catalysts that are effective for cyclopropanation with diazocarbonyl compounds,[17] only copper, rhodium, and ruthenium stand out as having high potential for selective reactions, and of these three transition metals only copper and rhodium show generality for C−H insertion. Because of their stability, ruthenium catalysts are generally unreactive for C−H insertion, although there has been a recent report of intramolecular C−H insertion of α-diazoacetoacetamides by $RuCl_2$(*p*-cymene)$_2$.[55] However, the dichlororuthenium(II) pybox complex[41] has not been reported to catalyze C−H insertion.

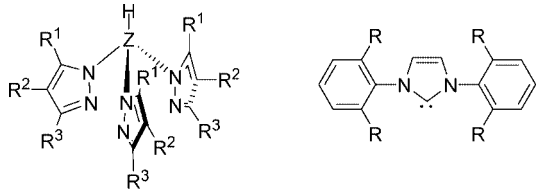
### 3.1. Copper

Copper catalysis dominated the literature that represented catalytic carbene-related carbon−hydrogen insertion before the advent of dirhodium tetraacetate.[8] However, even in those times, silver(I) catalysis of diazo ketone decomposition directed to the Wolff rearrangement process produced C−H insertion products in selected cases.[54,56] This area of metal catalysis has been resurrected recently with extensive investigations by Perez and co-workers of ligated copper, silver, and gold (coinage metals) catalysts of reac-

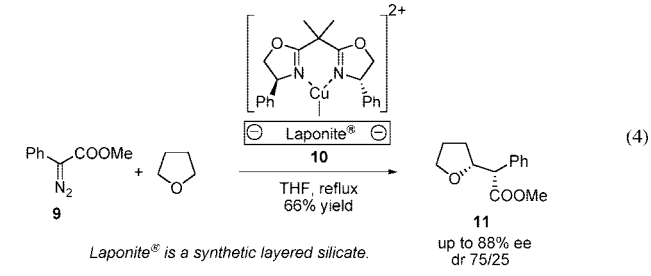
**Scheme 2**



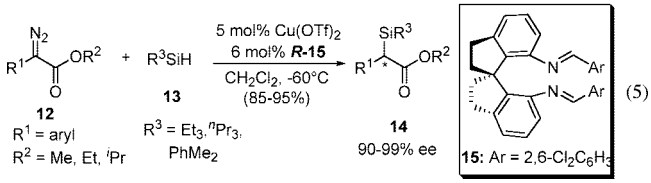
**Scheme 5**




tions with diazoacetates.[57] Ligands that have been employed for these reactions (Scheme 5), which include trispyrazolylborate ($TP^x$), trispyrazoylmethane ($Tpm^x$), *N*-heterocyclic carbenes (NHC), and $\beta$-diketimidate have allowed activation of intermediate metal species for intermolecular C−H insertion.[42,43,58–63] Homogeneous copper(I) catalysts with chiral ligands have also been employed, but enantioselectivities in C−H insertion reactions have been low to moderate, and none exceeded 80% enantiomeric excess (ee).[26] However, copper complexes with chiral bisoxazoline ligands (**10**) immobilized in Laponite have been reported to efficiently catalyze the insertion of the carbene from methyl phenyldiazoacetate into C−H bonds of tetrahydrofuran with high enantioselectivity (up to 88% ee, eq 4).[64] The chiral ligands employed with copper have been mainly $C_2$-symmetric bisoxazoline and salen added to copper(I) triflate or the oxidatively more stable copper(I) hexafluorophosphate.[65] More recently, Zhou and co-workers have published results from their chiral spirodiimine (**15**) copper catalyst that has provided very high enantioselectivity for Si−H insertion (eq 5),[66] which is mechanistically similar to C−H insertion, suggesting that further ligand elaboration on copper may evolve generally applicable chiral copper catalysts for insertion into carbon−hydrogen bonds.




(4)




(5)

## 3.2. Dirhodium

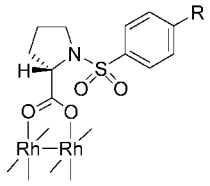
From the time of their initial application to the present, dirhodium(II) compounds have been the most utilized and most versatile catalysts for C−H insertion reactions. Using carboxylate ligands, and recognizing different approaches to the design of the paddlewheel compounds, McKervey,[67] Ikegami and Hashimoto,[68] and Davies[69] developed chiral dirhodium carboxylate catalysts, while Doyle created chiral dirhodium(II) carboxamidate catalysts.[17] The former are built upon N-protected amino acid templates with four carboxylate ligands symmetrically positioned around the dirhodium framework (Scheme 6). Their reactivities toward diazo decomposition are often greater than those of rhodium acetate or rhodium octanoate, with $Rh_2$(*S*-DOSP)$_4$ (**17**) maintaining its catalytic activity even at −78 °C.[24]

Chiral dirhodium(II) carboxamidates are constructed from lactams derived from amino acids. Like the carboxylate structures, each of these compounds has a paddlewheel structure with four bridging carboxamidate ligands about a $Rh_2^{4+}$ core (Figure 2, structure A is shown with the dominant structural geometry).[74,75] Because the chiral carboxamidate ligands are unsymmetrical bridges, four different geometries, based on the positioning of nitrogens and oxygens on each rhodium, are possible: (2,2-*cis*), (2,2-*trans*), (3,1), and (4,0) (see structure B), and examples of each geometry, except for the (2,2-*trans*) isomer, have been isolated and characterized.[76] However, the (2,2-*cis*) isomer is the dominant isomer (>85%) produced by ligand replacement on rhodium acetate, and detailed understanding of the stepwise process for ligand replacement is now available.[77] A formal single bond exists between the two rhodium atoms. Representations of dirhodium(II) tetrakis[methyl 2-oxopyrrolidine-5(*S*)-carboxylate], $Rh_2$(5*S*-MEPY)$_4$, are also presented in Figure 2.

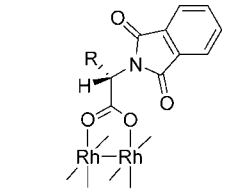
From their first report as ligands in dirhodium(II) metal carbene reactions,[78] four amino acid-derived ligand structures have been developed for chiral dirhodium carboxamidates (Scheme 7). Each has an ester group, generally a methyl ester, at the carbon position adjacent to nitrogen that provides either the S- or R-configuration to the amino acid derived ligand, and the ester is essential for high enantiocontrol in catalytic reactions.[79] The ligands that surround the dirhodium core greatly influence the reactivities and selectivities afforded by their catalytic uses, but as a class, these catalysts are less reactive toward diazo decomposition than are dirhodium(II) carboxylates. The $Rh_2$(MEPY)$_4$ catalysts (**23** for the *S*-enantiomer), although giving high enantiocontrol in several intramolecular C−H insertion reactions,[80] are preferred for intramolecular cyclopropanation reactions.[70,79,81–83] The strain provided by four-membered azetidinone ligands in $Rh_2$(MEAZ)$_4$ and related azetidinone-ligated catalysts lengthens the Rh−Rh bond distance and results in higher reactivities for diazo decomposition.[84–87] The steric bias intrinsic in the design of the imidazolidinone-ligated $Rh_2$(MPPIM)$_4$ catalysts (**30** for the *S*-enantiomer) influences the conformation of attached carbenes derived from diazoacetates and is the preferred catalyst for intramolecular C−H insertion reaction of diazoacetates.[17,88,89]

Lahuerta and co-workers have developed dirhodium(II) complexes that have two cisoid bridging carboxylates (OOCR) and two orthometalated aryl phosphines (PC) with inherent backbone chirality for use as catalysts for C−H insertion reactions of diazo compounds.[100,101] The *cis*-orthometalated phosphines are oriented in a head-to-tail arrangement (*cis-H,T*; **47**, Scheme 8) around the $Rh_2^{4+}$ core or a *cis*-head-to-head arrangement (*cis-H,H*; **48**, Scheme 8). The *cis-H,H*-$Rh_2(OAc)_2(PC)_2$ complexes generally show poor reactivity toward diazo decomposition, but the *cis-H,T* isomers can give high reactivity and selectivity in competitive C−H insertion reactions of selected diazo esters and diazo ketones.[102] Variation of

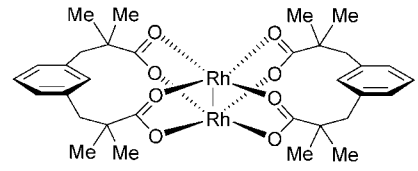
**Scheme 6. Structures of $Rh_2$(*S*-BSP)$_4$ (16),[67] $Rh_2$(*S*-DOSP)$_4$ (17),[70] $Rh_2$(PTTL)$_4$ (18),[71] $Rh_2$(esp)$_2$ (19),[72] Second-Generation Prolinates 20,[73] $Rh_2$(*S*-biTISP)$_4$ (21),[73] $Rh_2$(*S*-biDOSP)$_4$ (22),[73] and Related Dirhodium(II) Carboxylates**



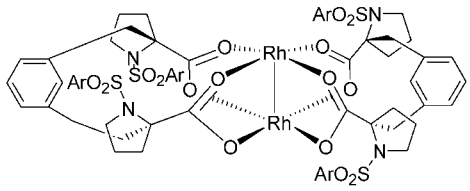
**16**: R = H, $Rh_2$(S-BSP)$_4$
**17**: R = $C_{12}H_{25}$, $Rh_2$(*S*-DOSP)$_4$



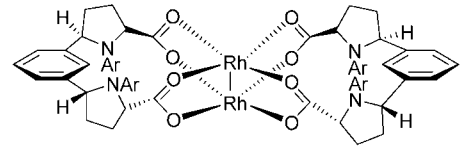
**18:** R = $^t$Bu, $Rh_2$(*S*-PTTL)$_4$
Also: R = Me, $Rh_2$(*S*-PTA)$_4$
$PhCH_2$, $Rh_2$(*S*-PTPA)$_4$
$^i$Pr, $Rh_2$(*S*-PTV)$_4$



$Rh_2$(esp)$_2$
**19**

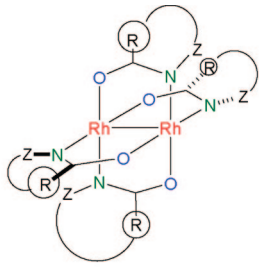


**20**: Ar = *p*-$^t$BuC$_6$H$_4$

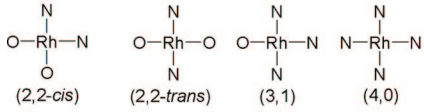


**21**: Ar = 2,4,6-tri-$^i$PrC$_6$H$_2$ $Rh_2$(*S*-biTISP)$_2$
**22**: Ar = *p*-($C_{12}H_{25}$)C$_6$H$_4$ $Rh_2$(*S*-biDOSP)$_2$

carboxylate ligands and of the substituents on the metalated phenyl ring provided dramatic differences in chemoselectivity during C−H insertion and aromatic substitution competition reactions (eq 6), and a high level of selectivity for cyclopropanation has been reported.[100] A recent theoretical analysis of ligand−dirhodium electronic interactions has concluded that reactivity and selectivity differences between carboxylate, carboxamidate, and ortho-metalated arylphosphines are due to electron donation of the ligand to the rhodium atom.[103] Chiral dirhodium(II) binaphtholphosphates have also been developed for metal carbene reactions,[104,105] but they have seen limited use for C−H insertion reactions.

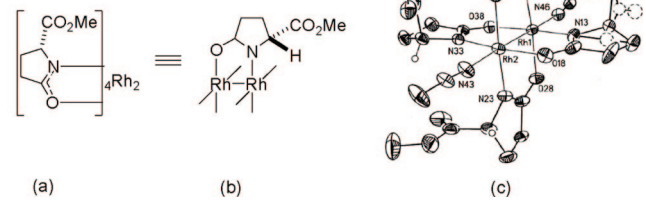


Structure A



(2,2-*cis*) (2,2-*trans*) (3,1) (4,0)

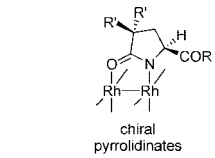
Structures B: Four possible isomers of $Rh_2L_4$



(a) (b) (c)

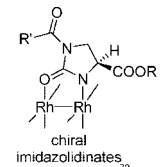
**Figure 2.** Dirhodium(II) tetrakis(methyl-2-oxopyrrolidine-4(*R*)-carboxylate: (a) and (b) are common representations; (c) X-ray structure of bisacetonitrile complex.

**Scheme 7**



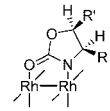
chiral pyrrolidinates

**23** (5*S*)-MEPY (R = OMe, R' = H)[78]
**24** (5*S*)-dFMEPY (R = OMe, R' = F)[90]
**25** (5*S*)-DMAP (R = $NMe_2$, R' = H)[91]
**26** (5*S*)-NEPY (R = $OCH_2CMe_3$, R' = H)[80]
**27** (5*S*)-ODPY (R = $O(CH_2)_{17}CH_3$, R' = H)[92]



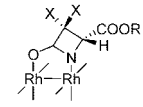
chiral imidazolidinates

**28** (4*S*)-MACIM (R = R' = Me)[79]
**29** (4*S*)-MBOIM (R = Me, R' = Ph)[93]
**30** (4*S*)-MPPIM (R = Me, R' = $PhCH_2CH_2$)[94]
**31** (4*S*)-MCHIM (R = Me, R' = $^cC_6H_{11}CH_2$)[93]
**32** (4*S*)-EPPIM (R = Et, R' = $PhCH_2CH_2$)[95]
**33** (4*S*)-BPPIM (R = $^t$Bu, R' = $PhCH_2CH_2$)[95]



chiral oxazolidinates

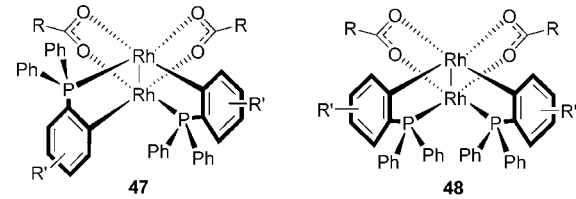
**34** (4*S*)-IPOX (R = $^i$Pr, R' = H)[78]
**35** (4*S*)-PHOX (R = Ph, R' = H)[96]
**36** (4*S*)-BNOX (R = $PhCH_2$, R' = H)[78]
**37** (4*S*)-MPOX (R= $CH_3$, R' = Ph)[97]
**38** (4*S*)-MEOX (R, R' = H)[98]
**39** (4*S*)-THREOX (R = H, R' = Me)[98]



chiral azetidinates

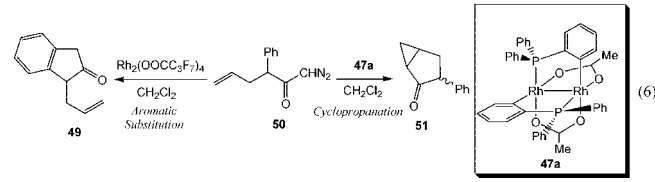
**40** (4*S*)-IBAZ (X = H, R = $^t$Bu)[84]
**41** (4*S*)-BNAZ (X = H, R = $PhCH_2$)[84]
**42** (4*S*)-MEAZ (X = H, R = $CH_3$)[84]
**43** (4*S*)-CHAZ (X = H, R= $^cC_6H_{11}$)[90]
**44** (*S,S/R*)-MENTHAZ (X = H, (R = *S/R*-menthyl)[99]
**45** (4*R*)-dFIBAZ (R = $^i$Pr)[90]
**46** (4*R*)-dFCHAZ (R = $^cC_6H_{11}$)[90]

**Scheme 8**



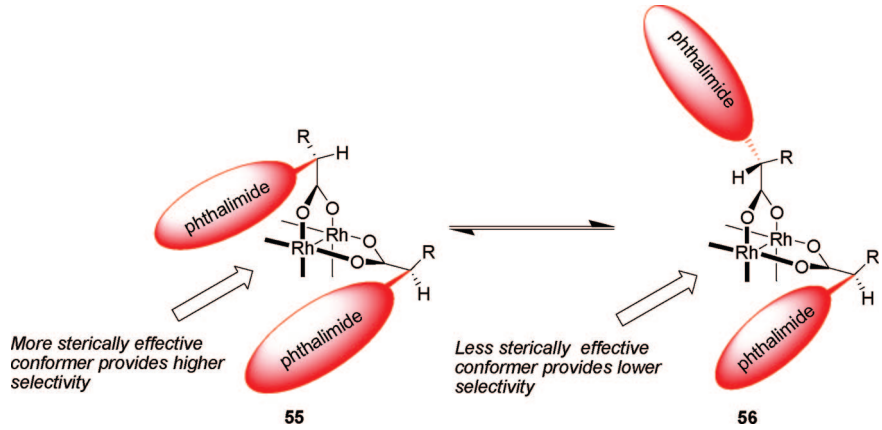
**47** **48**

R' = H, *p*-$CH_3$, *p*-$^t$Bu; R = *m*- or *p*-$CH_3$, $CF_3$, $C_3F_7$

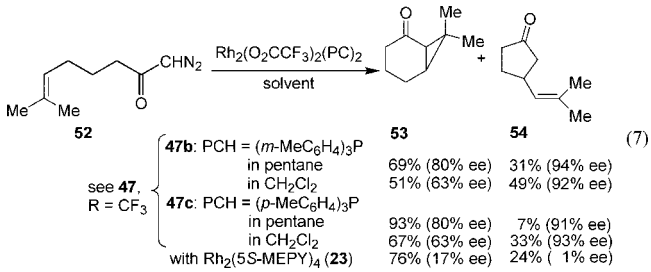


Carbon−hydrogen insertion has been demonstrated in selected stoichiometric reactions of stable metal car-

**Scheme 9**

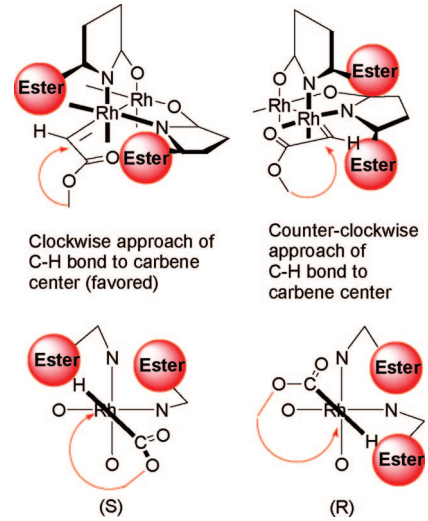



benes.[106] However, efforts to find catalytic alternatives to dirhodium catalysts, especially with less expensive metals and stabilizing porphyrin ligands, for carbon−hydrogen insertion reactions[107–110] have not as yet become evident. Even among dirhodium(II) catalysts there are inherent differences in reactivity and selectivity. Chiral dirhodium(II) carboxamidates, especially the $Rh_2(MPPIM)_4$ (**30**) catalysts, are optimum for highly enantioselective intramolecular C−H insertion reactions of diazoacetates that form $\gamma$-lactams and diazoacetamides that form $\gamma$- and $\beta$-lactams;[18–20,22] they are moderately reactive toward diazo decomposition. The more reactive chiral dirhodium(II) carboxylates are useful for certain intramolecular reactions, but they are most effective for intermolecular C−H insertion reactions of aryldiazoacetates and styryldiazoacetates.[19,26,28] *cis*-Orthometalated arylphosphine dirhodium catalysts (**47**) appear to have unique capabilities for enantioselective C−H insertion reactions of diazo ketones (eq 7),[102] but there are too few examples available from which to make any generalization.




A major difference between chiral dirhodium(II) carboxylates and carboxamidates in their influence on enantiocontrol in C−H insertion reactions resides in their structure. The chiral prolinate ligands on dirhodium(II) can form a chiral cavity that controls the orientation of the carbene and the reacting C−H bond to provide the observed selectivity.[24,111,112] Conformational options for this flexibility in carboxylate ligand attachments were first described by Hashimoto and co-workers for phthalimido groups.[113] Flexible chiral attachments to the dirhodium-bound carboxylate group can be oriented in many conformations, two of which are shown in Scheme 9 using phthalimide as the attachment (**55** and **56**), and each has its own reactivity and selectivity. Enhancement of enantiocontrol by ligand alignment that is evident with the change of reaction solvent to nonpolar pentane or hexane is consistent with this explanation.[111] This flexibility makes modeling and predictions of degree of enantiocontrol uncertain. However, the

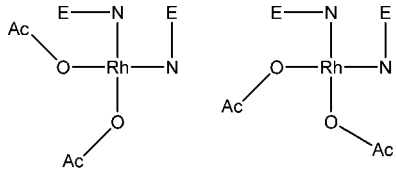
**Scheme 10**



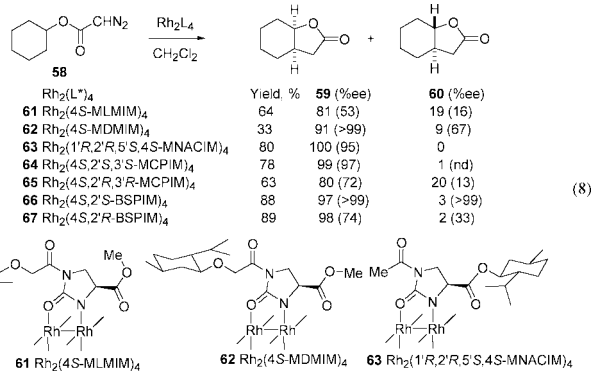

ability of ligand arrangements to adapt to carbene substrate special requirements potentially expands their applicability to a wider range of diazo compounds and substrates for high enantiocontrol.

Chiral dirhodium(II) carboxamidates, on the other hand, have a comparatively rigid structure that, with the ligands portrayed in Scheme 7, is not reported to exhibit solvent effects on stereocontrol. In these catalysts, the ester functionality (E) protrudes from the face of the catalyst and blocks approach of a C−H bond from the regions occupied by the carboxylate groups of the four ligands (Scheme 10); for intramolecular reactions, steric inhibition by the protruding carboxylate groups forces cyclization to occur in a clockwise direction (from the catalyst *R*-enantiomer) or in a counterclockwise direction (from the catalyst *S*-enantiomer). Chiral *N*-acyl groups on imidazolidinone ligands have also been used to explore stereoenhancement in C−H insertion reactions (**57a** and **57b** in Scheme 11, where E is an ester group and Ac is the *N*-acyl attachment).[95,114,115] Here, the chiral *N*-acyl attachments of the imidazolidinone carboxylate catalysts were designed to potentially reinforce the inherent stereocontrol provided by the core ligand system. Use of ligand diastereomers to form $Rh_2(MDLMIM)_4$ (**61**) and $Rh_2(MDMIM)_4$ (**62**) revealed remarkable differences in diastereo- and enantiomeric product selectivity, and the highest diastereocontrol achieved is with the $Rh_2(MNACIM)_4$ catalyst **63** (eq 8).[114] Use of the *S,R*-MENTHAZ catalyst (**44**) was

**Scheme 11**




significantly more selective than its diastereomer *S,S*-MENTHAZ, which itself was less selective than the structure reported as $Rh_2$(IBAZ)$_4$ (**40**).[99]




| $Rh_2(L^*)_4$ | Yield, % | **59** (%ee) | **60** (%ee) |
|---|---|---|---|
| **61** $Rh_2$(4*S*-MLMIM)$_4$ | 64 | 81 (53) | 19 (16) |
| **62** $Rh_2$(4*S*-MDMIM)$_4$ | 33 | 91 (>99) | 9 (67) |
| **63** $Rh_2$(1′*R*,2′*R*,5′*S*,4*S*-MNACIM)$_4$ | 80 | 100 (95) | 0 |
| **64** $Rh_2$(4*S*,2′*S*,3′*S*-MCPIM)$_4$ | 78 | 99 (97) | 1 (nd) |
| **65** $Rh_2$(4*S*,2′*R*,3′*R*-MCPIM)$_4$ | 63 | 80 (72) | 20 (13) |
| **66** $Rh_2$(4*S*,2′*S*-BSPIM)$_4$ | 88 | 97 (>99) | 3 (>99) |
| **67** $Rh_2$(4*S*,2′*R*-BSPIM)$_4$ | 89 | 98 (74) | 2 (33) |

(8)




**61** $Rh_2$(4*S*-MLMIM)$_4$ **62** $Rh_2$(4*S*-MDMIM)$_4$ **63** $Rh_2$(1′*R*,2′*R*,5′*S*,4*S*-MNACIM)$_4$

Results from C−H insertion reactions with two sets of diastereomeric dirhodium(II) complexes using the methyl 2-oxoimidazolidine-4*S*-carboxylate framework have been reported.[115] In **64** and **65**, the *N*-acyl attachment is derived from the enantiomers of *trans*-2-phenylcyclopropanecarboxylic acid, whereas in **66** and **67**, the *N*-acyl attachments are prepared from the *N*-benzenesulfonylprolinate enantiomers. The former were employed because of their structural similarity to $Rh_2$(4*S*-MPPIM)$_4$ (**30**), whereas the latter have a structural relationship to the chiral dirhodium(II) prolinate catalysts (**17**). Viewing the MCPIM catalysts down the rhodium−rhodium bond axis (Figure 3) reveals that these catalysts are configured as shown in Scheme 11. Specifically, $Rh_2$(4*S*,2′*S*,3′*S*-MCPIM)$_4$ (**64**) has its pendant ester and *N*-acyl side chains oriented in the same direction, forming a counterclockwise spiral. This orientation is particularly well-suited to intramolecular reactions in which the active site for reaction is tethered to the dirhodium(II) axial coordination site. Conversely, the ester and *N*-acyl side chains are in configurational opposition in $Rh_2$(4*S*,2′*R*,3′*R*-MCPIM)$_4$ (**65**), and this orientation provides a barrier to stereoselectivity enhancement in intramolecular transformations. When viewed along the rhodium−rhodium bond, the BSPIM catalysts (Figure 3) are also configured according to the depiction offered in Scheme 11. Although the twist of the phenylsulfonyl groups on the ligands makes the determination less clear, $Rh_2$(4*S*,2′*S*-BSPIM)$_4$ (**66**) corresponds to the "matched" case, with the ligands' tetrahydropyrrole rings and pendant methyl esters oriented in the same helical sense (*M*). In the diastereomeric $Rh_2$(4*S*,2′*R*-BSPIM)$_4$ (**67**), the configuration of the pendant methyl esters and *N*-prolinate attachment are opposed to each other, making this catalyst the "mismatched" example. These predictions are borne out in C−H insertion reactions with cyclohexyl diazoacetate (eq 8), cyclopentyl diazoacetate, and 2-methoxyethyl diazoacetate.[115]

## 4. Diazo Compounds

Because of their ease of formation and relative stability, diazo esters and diazo amides are the preferred substrates

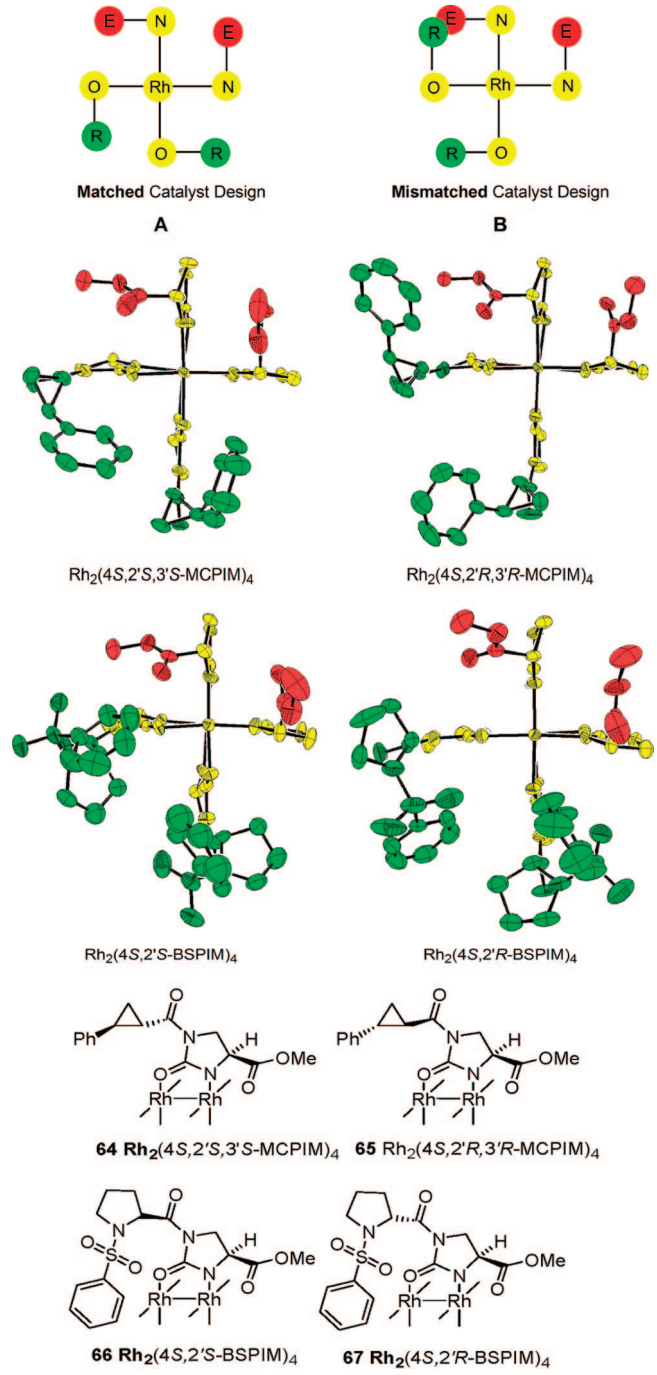
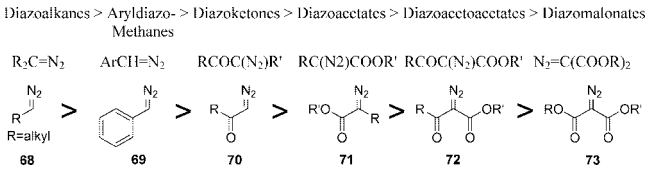


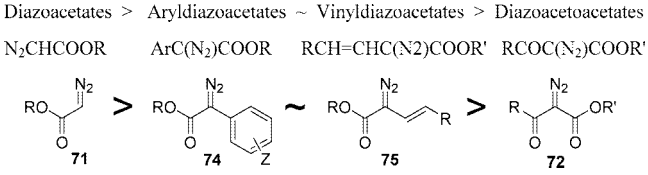

**Figure 3.** Configurational differences with chiral *N*-acyl groups in imidazolidinone-ligated dirhodium(II) carboxamidate catalysts. Each catalyst structure is viewed down the length of the rhodium−rhodium bond. Only the pendant groups around the front rhodium atom are shown; axial ligands are removed for clarity. Figure modified from ref 115. Ligated dirhodium depictions of these structures are given below the colored figures.

for catalytic C−H insertion reactions. Methods for their formation have been reviewed[14,17,116,117] and further elaborated[118–125] so that only comparative information will be presented here regarding their utilization for C−H insertion reactions. Reactivities of diazo compounds toward Lewis acids in diazo decomposition reactions (Scheme 12, B = Lewis base) follow the order of basicity of the diazo compound and are generally in the order:[17]



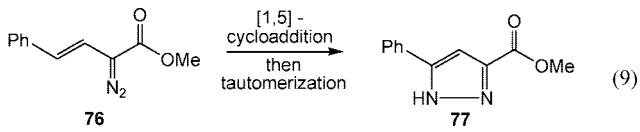

Although suitable procedures are available for their synthesis,[126–128] diazoalkanes other than diazomethane are challenging to prepare, inherently unstable, and even explosive in pure form. In situ generation is a preferred methodology for their preparation.[129] Conjugation with an aromatic ring increases the stability of a substituted diazomethane, but these compounds cannot be stored for long periods of time. In contrast, most diazocarbonyl compounds have much greater stability and are resistant to uncatalyzed decomposition over long periods of time.[116]

Aryldiazoacetates (**74**) are more reactive toward diazo decomposition than diazoacetamides, and among diazoacetates, reactivity follows the order:[17]




However, to place this reactivity in perspective, ethyl diazoacetate is thermally stable below 120 °C and does not decompose when treated with glacial acetic acid at room temperature.

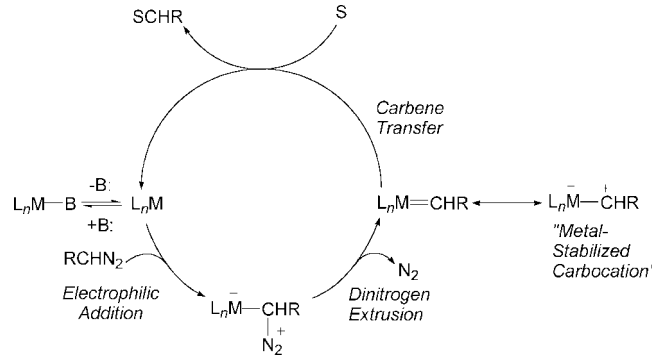
Diazoacetates are traditionally prepared by deacetylation from diazoacetoacetates[130] or with glyoxylic acid chloride *p*-toluenesulfonylhydrazone,[131] and the preparations of diazoacetamides use these same methodologies, as well as diazoacetyl transfer from succinimidyl diazoacetate.[132] These compounds are stable and can be kept under common laboratory conditions for extended periods of time. Aryldiazoacetates are ordinarily prepared from arylacetates by diazo transfer from azides[133,134] and, like diazoacetates, they are stable toward diazo decomposition under common laboratory conditions. In contrast to aryldiazoacetates, most vinyldiazoacetates are unstable, undergoing a spontaneous [1,5]-cycloaddition to yield pyrazoles (e.g., eq 9),[135] and cannot be stored for long periods of time. Even the most used of the vinyldiazoacetates, styryldiazoacetate, has a limited shelf life. However, vinyldiazolactones are stable for long periods of time because they cannot undergo intramolecular cyclization.[136]




(9)

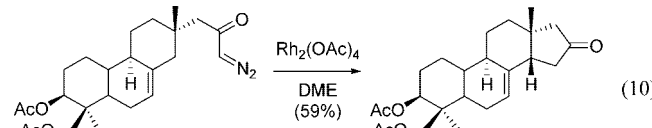
The effectiveness of catalysts toward diazo decomposition is dependent on the relative Lewis acidity of the catalyst and the rates of competitive reactions. For example, most dirhodium(II) carboxamidates are ineffective with vinyldiazoacetates because of the dominance of their competitive intramolecular [1,5]-cycloaddition reaction, and the pyrazole products (e.g., **77**) are catalyst inhibitors.[26] However, in the absence of such competing reactions, catalysts that can cause diazo decomposition are applicable to use for C−H insertion reactions, although those like ruthenium(II)−pybox[137] that exhibit a high degree of stabilization of the intermediate carbene do not effectively undergo C−H insertion.

**Scheme 12**

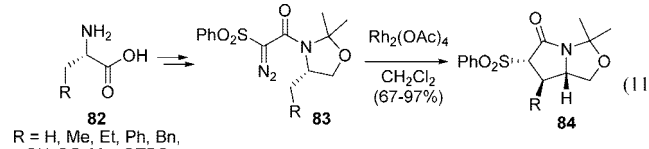



## 5. Intramolecular Reactions

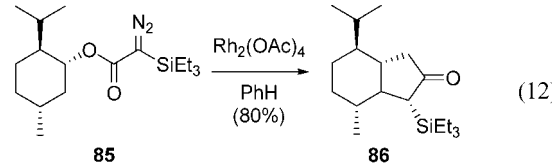
The first successful synthetic applications of diazoesters for C−H insertion reactions were for intramolecular reactions in geometrically rigid systems.[7,9] For such systems that include diazocamphor[7] and 1-adamantyldiazoketone,[138] catalysts of copper, and even nickel(II),[14] are effective. The use of dirhodium(II) acetate for C−H insertion reactions, made visible to synthetic chemists almost simultaneously by Wenkert[12] (eq 10) and Taber,[13] extended the scope of transition metal catalyzed intramolecular cyclopropanation reactions. Preferential insertion into the gamma position to form a five-membered ring dominates examples of reactions with diazo esters, diazo ketones, diazo amides (Scheme 13), and diazo sulfones (eq 11).[139–141] Very few examples can be found of C−H insertion reactions of silyldiazoacetates (eq 12),[142] and, although there is a rich literature record for insertion reactions of diazo phosphonates,[143–146] many of these efforts have been limited to O−H and N−H insertion (ylide-based).[143,144] The greater stability of metal carbenes, particularly those of dirhodium(II), derived from these diazo compounds is one probable cause for their limited utilization in C−H insertion reactions.




(10)




(11)

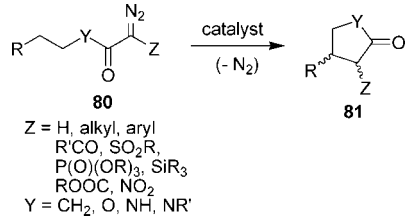



(12)

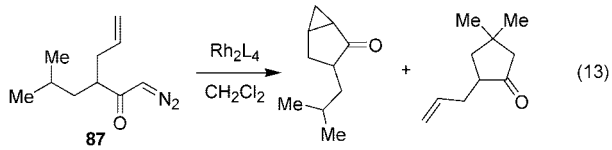
### 5.1. Chemoselectivity

The selectivity for C−H insertion in competition with other carbene-based transformations has been a cause of considerable interest.[36,147–149] Ligands on the metal have been shown

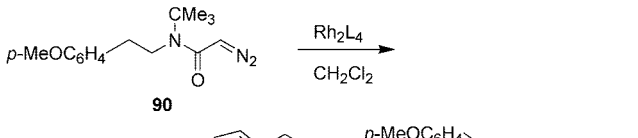
**Scheme 13**




to have significant influences, often leading to a complete change in chemoselectivity (eqs 13 and 14).[37] In general, aromatic substitution ("aromatic C−H insertion") is favored over cyclopropanation, which, in turn, is favored over C−H insertion for catalysts that include dirhodium(II) acetate, which have electron-withdrawing carboxylate ligands.[150] Increasing the electron-withdrawing ability of the ligand, such as replacing acetate by trifluoroacetate on dirhodium(II), increases the electrophilic character of the intermediate metal carbene and leads to an enhancement in the selectivity of the carbene for the more nucleophilic substrates. Decreasing the electron-withdrawing ability of the ligand, such as replacing acetate by acetamide on dirhodium(II), decreases the electrophilic character of the intermediate metal carbene and leads to an enhancement in the selectivity of the carbene for the less nucleophilic substrates.




| | yield, % | 88 | 89 |
|---|---|---|---|
| $Rh_2(pfb)_4$ | 56 | 0 | 100 |
| $Rh_2(OAc)_4$ | 97 | 44 | 56 |
| $Rh_2(cap)_4$ | 76 | 100 | 0 |

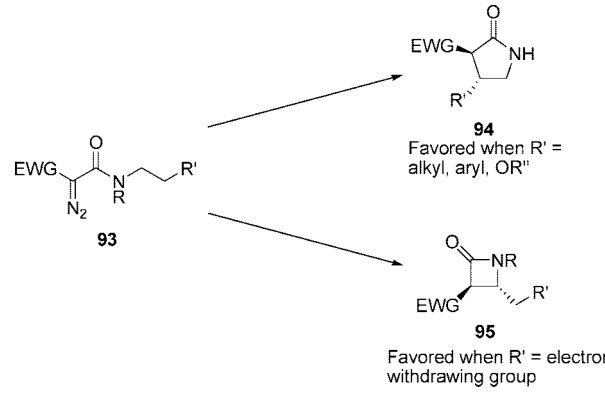



| | yield, % | 91 | 92 |
|---|---|---|---|
| $Rh_2(pfb)_4$ | 93 | 93 | 7 |
| $Rh_2(OAc)_4$ | 90 | 76 | 24 |
| $Rh_2(cap)_4$ | 81 | 14 | 86 |

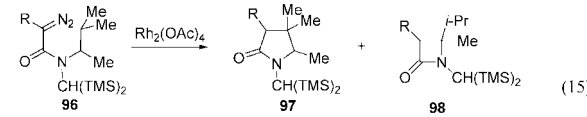
## 5.2. Regioselectivity

As has already been mentioned, regioselectivity in intramolecular C−H insertion reactions occurs overwhelmingly to form five-membered ring compounds (1,5-C−H insertion). However, it has long been known that $\beta$-lactams were formed by C−H insertion reactions of diazoacetoacetamides and diazomalonamides (1,4-C−H insertion),[17,26] but with high selectivity only when access to a $\gamma$-C−H bond is sterically or electronically inhibited (Scheme 14 and eq 15).[55,145,151–157] If both $\beta$-C−H and $\gamma$-C−H bonds of equivalent reactivity are accessible, only $\gamma$-lactam formation occurs. Similar generalizations can be made about C−H insertion reactions of diazoacetates (eq 16) and diazoacetoacetates, but, perhaps because these systems have been less extensively investigated, there appear to be fewer examples of $\beta$-lactones than $\beta$-lactams in C−H insertion reactions.[51,158–160] Wang has reported a surprising example of a previously unreported 1,3-C−H insertion that occurs by

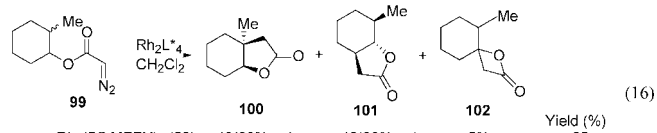
**Scheme 14**



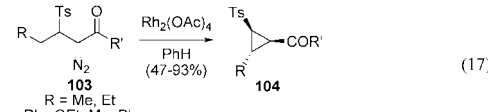

dirhodium(II) tetraacetate catalyzed reactions of $\beta$-tosyl-α-diazo esters and ketones (**103**, eq 17) that he has attributed to conformational influences.[161]



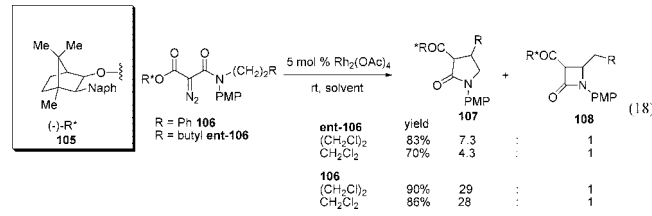

| R = | % | % |
|---|---|---|
| H | 100 | 0 |
| Ac | 67 | 33 |




| | | | | Yield (%) |
|---|---|---|---|---|
| $Rh_2(5S\text{-MEPY})_4$ (**23**) | 49(80% ee) | 40(93% ee) | <5% | 65 |
| $Rh_2(4S\text{-MEOX})_4$ (**38**) | 39(96% ee) | 50(95% ee) | <5% | 75 |
| $Rh_2(4S\text{-MACIM})_4$ (**28**) | 18(87% ee) | 19(49% ee) | 12% | 56 |



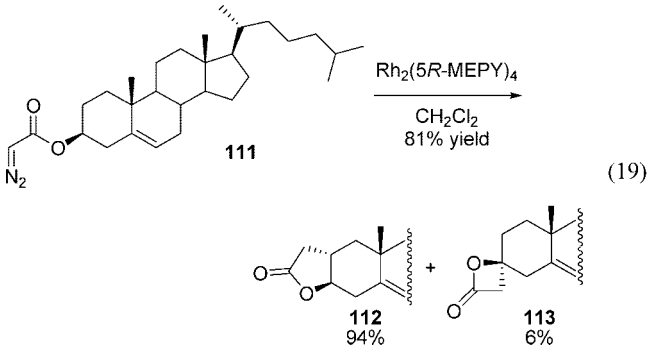

With diazomalonamides having chiral 2-naphthylborneol or 2-naphthylcamphor ester auxiliary, Wee has reported significant differences in regiocontrol for formation of $\beta$- and $\gamma$-lactams (eq 18).[162] Even though the auxiliary is remote from the reaction center, regioselectivity differences from the two diastereomeric compounds are very large. Furthermore, both regioselectivities and diastereoselectivities are dependent on the solvent and temperature, indicating conformational influences on selectivity.




| | yield | 107 | | 108 |
|---|---|---|---|---|
| $(CH_2Cl)_2$ | 83% | 7.3 | : | 1 |
| $CH_2Cl_2$ | 70% | 4.3 | : | 1 |
| $(CH_2Cl)_2$ | 90% | 29 | : | 1 |
| $CH_2Cl_2$ | 86% | 28 | : | 1 |

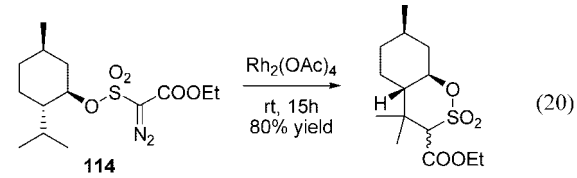
Using chiral dirhodium(II) catalysts, configurational match/mismatch governs C−H insertion reactions. Because of the directional orientation of chiral carboxamidate ligands (Scheme 10), insertion may be directed to take place on opposite sides of the site of diazoacetate attachment so that different products may be produced in high yield and selectivity when enantiomeric catalysts are applied to the same substrate. This is nicely illustrated by the reaction processes with chiral nonracemic 2-methylcyclohexyl diazoacetates in Scheme

15,[160] and additional examples in the steroidal field have also been reported (eq 19).[51] In the steroidal cases such as with **111**, the formation of four-membered ring $\beta$-lactones is a common outcome of configurational mismatch. Applications with racemic alkyl diazoacetates have also been reported, and they show the expected diastereomeric differentiation, but mixtures are obtained because the two reactant enantiomers give different products preferentially.[163] However, the clarity of product differentiation in the reported examples suggests high potential of this methodology for chiral catalyst directed, highly diastereoselective C−H insertion reactions.

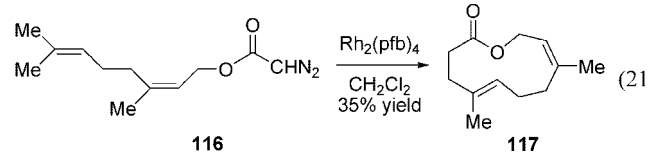


(19)

Few examples can be found for 1,6-C−H insertion reactions of commonly used diazocarbonyl compounds,[17,164] but steric or electronic factors can override the normal preference, as is evident in the insertion step in DuBois' recent synthesis of (−)-tetrodotoxin.[165] However, sulfonate derivatives of diazoacetates (**114** in eq 20)[166] or of their corresponding iodonium ylides[167] have a strong proclivity for insertion into the delta position to form six-membered ring $\delta$-sulfones. The exclusive formation of product from 1,6-C−H insertion is also a characteristic of the now well-established rhodium-catalyzed nitrene insertion reactions[168] and indicates that subtle changes in bond lengths can provide dramatic changes in regiochemical preferences. We are aware of only one example of a C−H insertion reaction that produces a macrolide—the rhodium perfluoroborate catalyzed diazo decomposition of the diazoacetate of nerol (**116**) that produces a 14-membered ring lactone **117** (eq 21).[169]



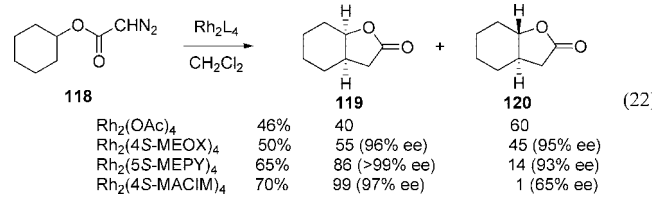
(20)



(21)

## 5.3. Diastereoselectivity

With the availability of multiple sites for intramolecular C−H insertion, the opportunity exists for the formation of more than one stereoisomer with both cyclic and acyclic systems. Beginning with the structurally simple cyclohexyl diazoacetate (**118**), there are four C−H bonds accessible by 1,5-C−H insertion. If the diazoacetate and its corresponding metal carbene are in the equatorial position, insertion into the axial C−H bond gives the cis-stereoisomer of the product bicyclic lactone **119**, whereas insertion into the equatorial C−H bond gives the trans-isomer **120**. As can be seen from the data in eq 22, rhodium acetate shows very low diastereocontrol, but chiral carboxamidate ligands of dirhodium(II) provide significant ligand-dependent stereocontrol.[170] Results from this and complementary studies (Scheme 16) provided the understanding that ligands on the metal had a profound influence on the conformation of the reacting metal carbene, limiting access to one C−H bond in favor of another.[17,22]

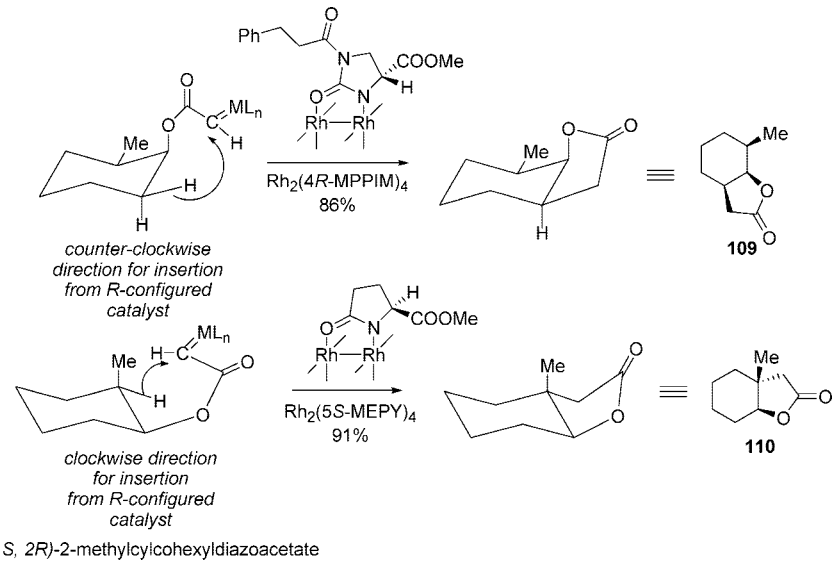



| | | | |
|---|---|---|---|
| $Rh_2(OAc)_4$ | 46% | 40 | 60 |
| $Rh_2(4S\text{-MEOX})_4$ | 50% | 55 (96% ee) | 45 (95% ee) |
| $Rh_2(5S\text{-MEPY})_4$ | 65% | 86 (>99% ee) | 14 (93% ee) |
| $Rh_2(4S\text{-MACIM})_4$ | 70% | 99 (97% ee) | 1 (65% ee) |

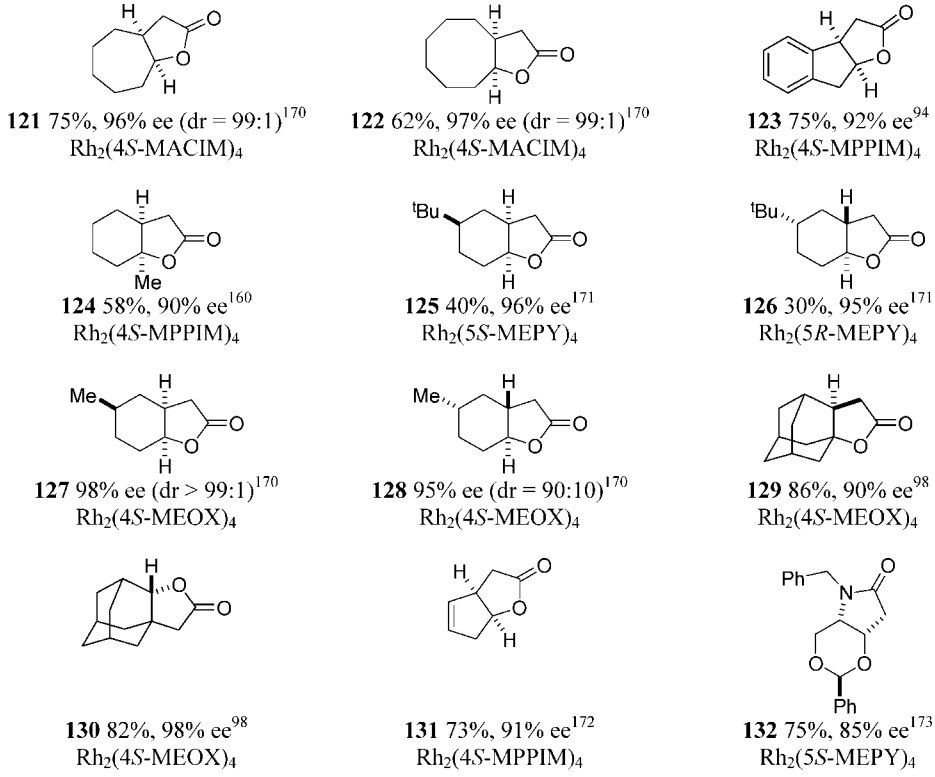
(22)

Taber has looked extensively at diastereoselectivity in intramolecular C−H insertion reactions of diazoketones.[174]

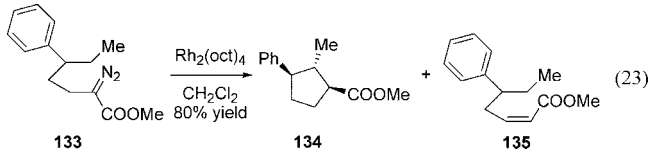
**Scheme 15**



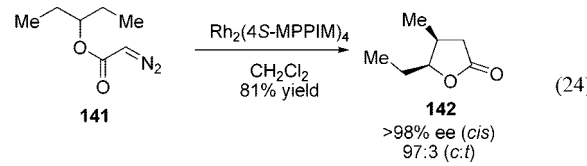
**Scheme 16. Yield, ee (dr)**




In probing C−H insertion reactions, for which eq 23[175] is representative, Taber confirmed that increasing the electron-withdrawing ability of the ligands on dirhodium created a more reactive metal carbene and decreased reaction selectivity, even for reactions performed at low temperatures.[39] The presence of a C−H bond adjacent to the diazo carbon makes possible hydride migration that results in the formation of an α,β-unsaturated ketone; as expected, this competing intramolecular reaction is favored in the order 3° > 2° > 1 °C−H. Steric and electronic factors influence diastereocontrol in the insertion reactions,[176] but carboxylate ligands of dirhodium do not influence stereoselectivity in these cases to nearly the same degree as do carboxamidate ligands of dirhodium with diazoacetates.

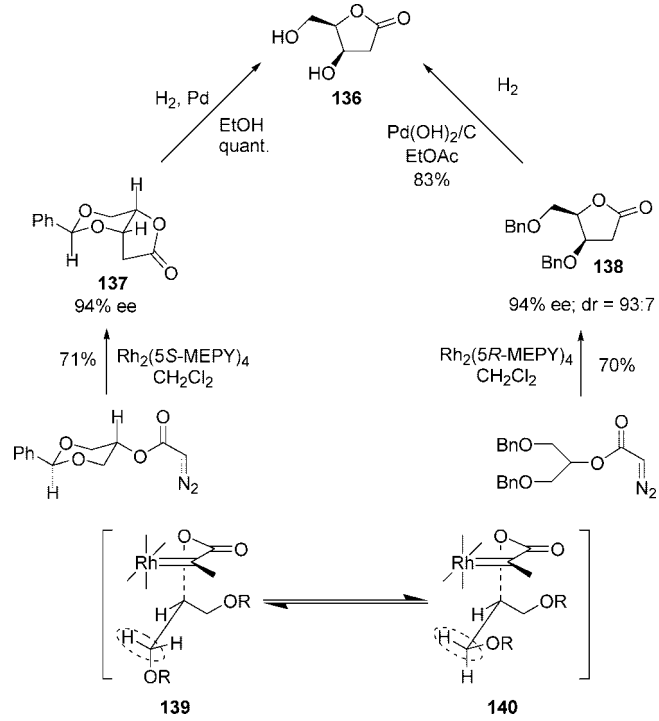



One of the clearest demonstrations of conformational control for diastereoselectivity in C−H insertion reactions is seen in the reactions directed to the synthesis of xylonolactone (Scheme 17).[148] Either in the acyclic case or with the ring-locked cyclic case, the stereoisomer that is dominant appears to arise from the metal carbene conformation **140** rather than **139**. One reason for this diastereoselectivity may be steric and/or electronic interference between the pendent OR group and ligands on the face of the dirhodium catalyst. Similar stereocontrol has been observed with 3-pentyl diazoacetate (eq 24), suggesting the apparent independence of the stereochemical outcome on substituents.[94]

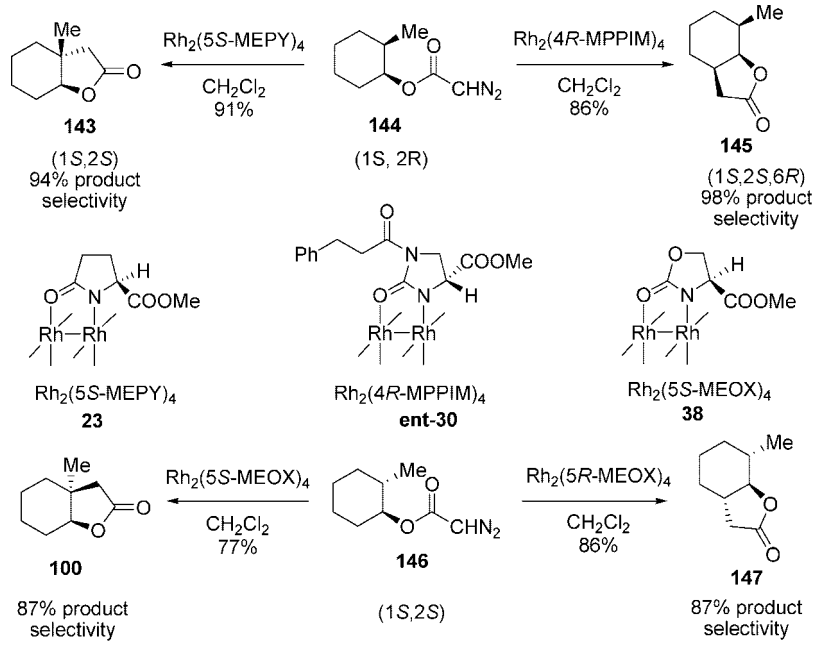



Configurational match/mismatch governs these reactions. Different products may be produced in high yield and

**Scheme 17**



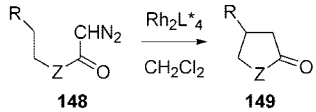
**Scheme 18**



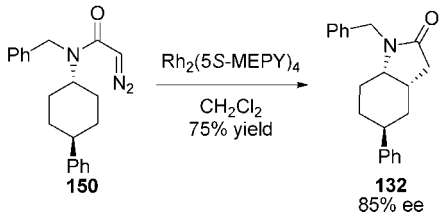

selectivity when enantiomeric catalysts are applied to the same substrate. This is illustrated by reactions with chiral nonracemic 2-methylcyclohexyl diazoacetates in Scheme 18,[160] and additional examples in the steroidal field have also been reported.[51] As has been described in Scheme 15, the configuration of the chiral carboxamide ligands on the catalyst determines the direction for approach of the C−H bond to the carbene center. Different chiral carboxamidate catalysts have different stereoelectronic and steric requirements toward C−H insertion in these cases, and different diastereomeric ratios are produced.

## 5.4. Enantioselectivity

Dirhodium(II) carboxamidates, especially the $Rh_2(MPPIM)_4$ (**30**) catalysts, are exceptionally effective for highly enantioselective intramolecular insertion reactions of diazoacetates and diazoacetamides. These reactions take place with high regioselectivity for $\gamma$-lactone (or lactam) formation (eq 25 and 26), and enantioselectivities greater than 90% ee are commonly achieved



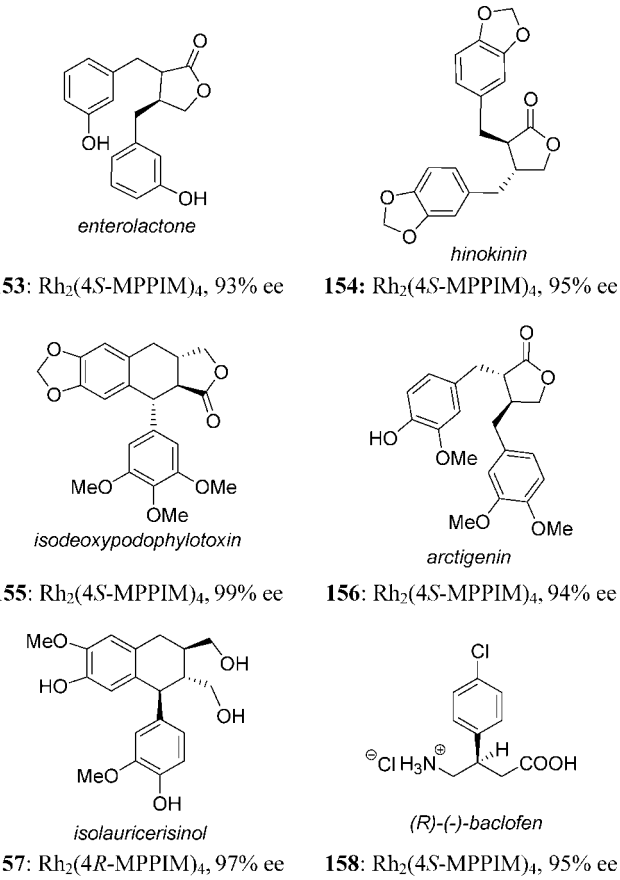

(25)




(26)

for lactone formation. As is expected from the directional influence of chiral carboxamidate ligands on dirhodium(II), in reactions of **118** or **142** (eqs 22 and 24), in reactions with diazoacetates such as **151** (eq 27), use of a *S*-configured dirhodium(II) carboxamidate catalyst yields the lactone having the *S*-configuration, and with the *R*-configured catalyst the *R*-configured product is formed preferentially. Examples of biologically active compounds that have been prepared in greater than 90% ee by this methodology include the lignan lactones (e.g., Scheme 19),[177] the sugar-based 2-deoxyxylolactone **136** (Scheme 17),[148,178] and the GABA receptor agonist (*R*)-baclofen **158** (Scheme 19).[179] This methodology has also been used for the synthesis of naturally occurring

**Scheme 19**

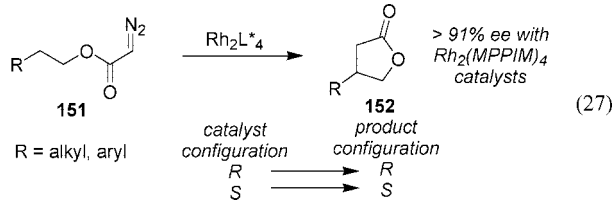



**153**: $Rh_2(4S\text{-MPPIM})_4$, 93% ee **154:** $Rh_2(4S\text{-MPPIM})_4$, 95% ee

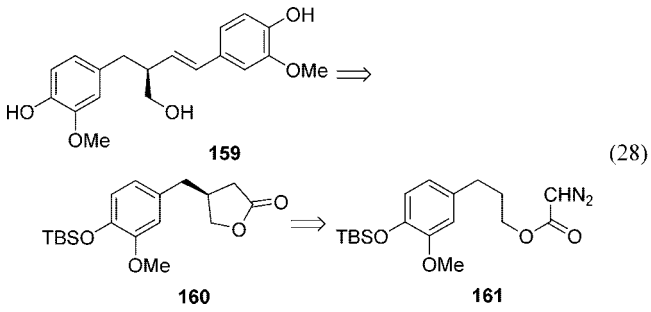
**155**: $Rh_2(4S\text{-MPPIM})_4$, 99% ee **156**: $Rh_2(4S\text{-MPPIM})_4$, 94% ee

**157**: $Rh_2(4R\text{-MPPIM})_4$, 97% ee **158**: $Rh_2(4S\text{-MPPIM})_4$, 95% ee

(*S*)-(+)-imperanene (**159**, eq 28),[180] whose absolute configuration was established in the insertion process ($Rh_2$(5*S*-MPPIM)$_4$, see eq 27). In all cases, selectivities were high with less than 5% insertion into other C−H positions.

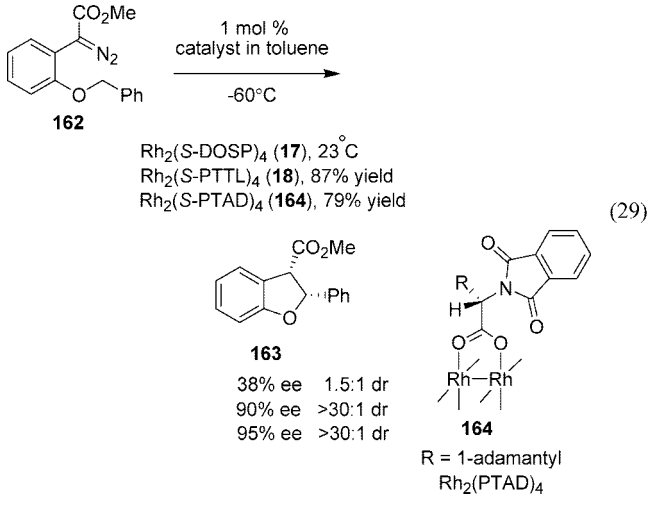



(27)




(28)

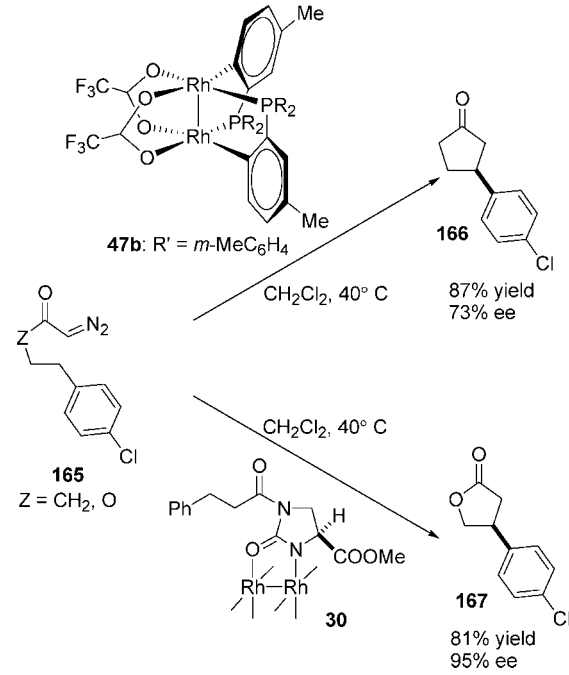
Chiral dirhodium(II) carboxylate catalysts have also been used to effect intramolecular C−H insertion reactions, and high enantiocontrol has been achieved in reactions of aryldiazoacetates that yield 2,3-dihydrobenzofurans (eq 29).[181–183] Selectivities in these reactions are very sensitive to temperature, and the highest levels of enantiocontrol are found when the reaction temperature is at or below −50 °C. Similarly, the chiral prolinate catalysts, especially $Rh_2$(*S*-DOSP)$_4$ (**17**), give higher enantioselectivities in hexane than in dichloromethane. Higher diastereocontrol is obtained with $Rh_2$(*S*-PTAD)$_4$ (**164**) than with $Rh_2$(*S*-DOSP)$_4$ (**17**) in catalytic reactions of **162**.[183] Interestingly, reactions of the structural modification of ArC($N_2$)COOMe to ArCOC($N_2$)R using the chiral dirhodium(II) arylsulfonylprolinate catalysts discovered and developed by McKervey and co-workers yielded the six-membered ring chromanones with good enantiocontrol even in dichloromethane.[184,185]




(29)

Extensive efforts have been undertaken to achieve high levels of enantiocontrol in intramolecular C−H insertion reactions of diazoacetoacetates, diazomalonates, diazophonoacetamides, and α-diazo-β-ketosulfones, but with limited success.[16,25,145,146] Carbon−hydrogen insertion reactions via diazoketones (e.g., **165**, $Z = CH_2$) have also not reached

**Scheme 20**



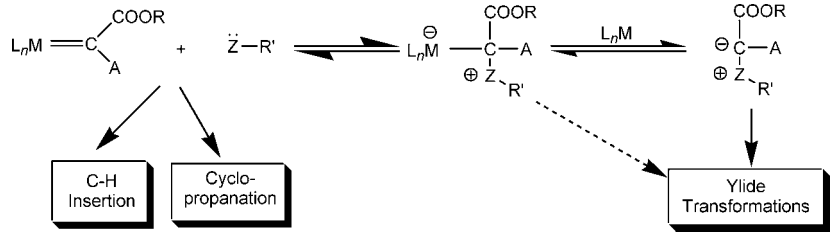

levels of enantiocontrol that are common with diazoacetates (Scheme 20), but Lahuerta's *ortho*-metalated dirhodium catalysts have given the most promising results thus far.[186] Use of the porphyrin complex Fe(TPP)Cl for the diazo decomposition of 2-phenylethyl diazoacetate resulted only in carbene dimer formation, even though this catalyst could effect intermolecular C−H insertion reactions of aryldiazoacetates.[187] Thus, challenges remain to achieve high stereocontrol for intramolecular C−H insertion reactions of most commonly accessible diazocarbonyl compounds; currently, only diazoacetates offer generally exceptional stereocontrol in intramolecular C−H insertion reactions when these reactions are catalyzed by chiral dirhodium(II) carboxamidates, especially the $Rh_2$(MPPIM)$_4$ catalysts.

Nakamura has reported theoretical investigations of stereoselection in dirhodium(II) catalyzed intramolecular C−H insertion reactions, from which he has elucidated the origin of diastereoselectivities and enantioselectivities for 1,5- and 1,4-C−H insertions of diazoacetates.[188] Although precise predictions have not yet been achieved, model structures are provided that are useful in making qualitative predictions. In a review of metal carbene intramolecular C−H insertion reactions, Sulikowski summarized prior models and computational analyses.[23]

## 6. Intermolecular Reactions

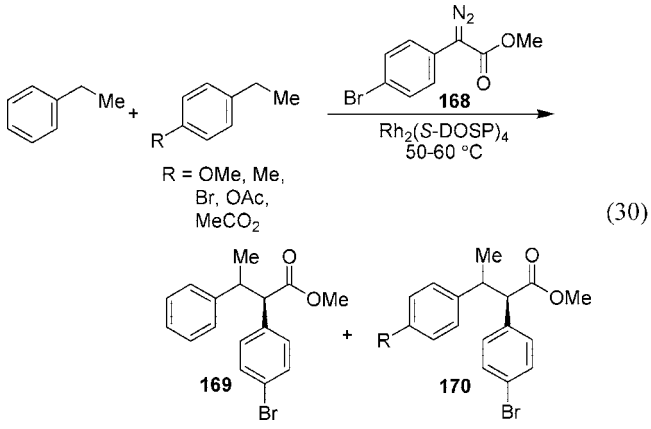
On the basis of early investigations of metal-catalyzed reactions of diazoacetates,[10,11,189] and unreported studies, the conclusion was drawn in a definitive review that "Intermolecular C−H insertion reactions... are not synthetically useful."[17] Subsequent studies with transition metals other than rhodium confirmed this conclusion.[57] However, with demonstration of highly regioselective insertion reactions that could be achieved with aryl- and vinyldiazoacetates in metal carbene reactions,[190] Davies and co-workers embarked on comprehensive investigations of the scope of these reactions.[26,28] The underlying basis for the success of the intermolecular transformations is the balance in activation/stabilization of the intermediate metal carbene (Scheme 4) caused by

**Scheme 21**




contributions from the ligated metal and carbene substituents that are matched with the steric and electronic demands of the C−H bond that is undergoing insertion. To differentiate the effectiveness of aryl- and vinyldiazoacetates in contrast to the relative ineffectiveness of diazoacetates, Davies has called the intermediate metal carbenes "donor−acceptor", although only aryl and selective vinyl "donor" substituents are synthetically accessible and have been employed thus far.

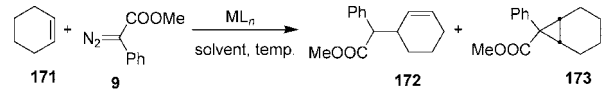
In addition to product yield and selectivity,[44] a measure of the electronic contribution of the aryl group from aryldiazoacetates in the transition state for C−H insertion has been determination of Hammett $\rho$-values (eq 30, 1:1 reactant molar ratio, $\rho = -1.27$ versus $\sigma^+$)[191] that suggest positive charge buildup in the transition state for C−H insertion. Another is kinetic isotope effects[44] that are responsive to substrate ($k_H/k_D = 3.0$ for C−H insertion with THF and 2.0 for C−H insertion with cyclohexane). However, although the kinetic data obtained so far do not portray the proportional contributions from the ligated metal and carbene substituents, indicators of the influence of the carbene carboxylate substituent and the ligated metal have been provided by theoretical analysis.[35] Insertion occurs via a late transition state, in comparison with cyclopropanation that occurs via an early transition state. Phenyl and vinyl groups bound to the carbene carbon further dissipate charge so that the intermediate metal carbene has a later transition state than is possible with diazoacetates.




(30)

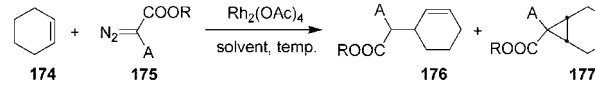
## 6.1. Chemoselectivity

The electrophilicity of metal carbenes and their propensity for their irreversible addition to carbon−carbon multiple bonds generally reduces their suitability for synthetic applications. For example, competition between allylic C−H insertion and cyclopropanation shows dependence on the dirhodium(II) catalyst (eq 31, diastereoselectivity for **172** not reported) but more so on the diazo compound (eq 32, diastereoselectivity not reported).[52] Catalyst chemoselectivity appears to be controlled by both electronic and steric factors, but electronic factors are most evident in variations of the diazo compound, except when exceptionally bulky diazoacetates (e.g., with BHT = 2,6-di-*tert*-butyl-4-methylphenyl)[192] are employed. With 1,4-cyclohexadiene, on the other hand, the product from C−H insertion is the sole outcome from dirhodium(II)-catalyzed reactions with methyl phenyldiazoacetate (**9**) and ethyl diazopropanoate.[52,190]




| | 172 | 173 |
|---|---|---|
| $Rh_2(OAc)_4$ | 75 | 25 |
| $Rh_2(pfb)_4$ | 87 | 13 |
| $Rh_2$(5*S*-PHOX)$_4$ (**35**) | 66 (4% ee) | 34 |
| $Rh_2$(5*S*-MEPY)$_4$ (**23**) | 93 (45% ee) | 7 |
| $Rh_2$(*S*-PTPA)$_4$ (**18**) | 50 (53% ee) | 50 |
| $Rh_2$(*S*-DOSP)$_4$ (**17**) | 80 (75% ee) | 20 |

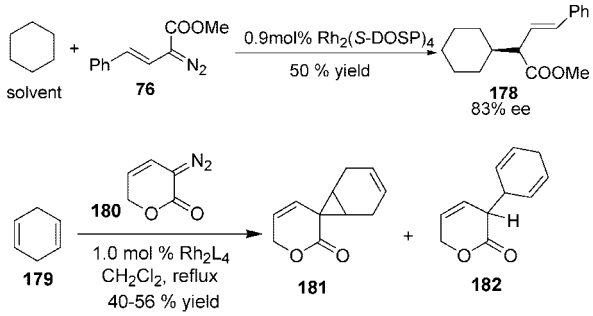
(31)




| | 176 | 177 |
|---|---|---|
| R = Et, A = H | 20 | 80 |
| R = BHT, A = H | 67 | 33 |
| R = Me, A = COOMe | 38 | 62 |
| R = Me, A = Ph (**9**) | 75 | 25 |
| R = Me, A = 4-$NO_2C_6H_4$ | 69 | 31 |

(32)

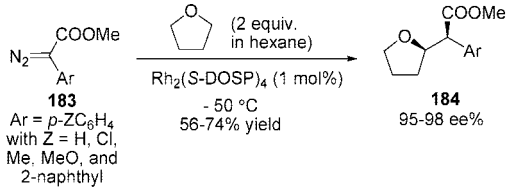
Vinyldiazoacetates also undergo C−H insertion (e.g., eq 33),[193] but these reactions are complicated by competing intramolecular cycloaddition (eq 9) that restricts reactions with this substrate to temperatures near or below room temperature, rather than at lower temperatures at which cycloaddition does not occur, and produce basic compounds that are themselves inhibitors of diazo decomposition. To circumvent this competing reaction, whose rates for conversion have not been quantitatively assessed, Doyle and co-workers constructed vinyldiazolactone **180**, which is stable to dipolar cycloaddition, and applied it to C−H insertion 1,4-cyclohexadiene, which is highly reactive to C−H insertion with methyl phenyldiazoacetate. Surprisingly, especially in comparison with results from methyl phenyldiazoacetate,[52] competition between C−H insertion (**182**) and cyclopropanation (**181**) occurred in all cases examined, but cyclopropanation was most dominant in reactions catalyzed by $Rh_2$(*S*-DOSP)$_4$ (eq 34).[136] In contrast, $Rh_2$(MenthAZ)$_4$ catalysts offered a high degree of chemoselectivity as well as enantioselectivity. Vinyldiazoacetates, especially methyl styryldiazoacetate, are more conducive to cyclopropanation[194] than they are to C−H insertion of 1,4-cyclohexadiene. Recently, Corey and co-workers have obtained high enantiocontrol in Si−H insertion reactions using 6-diazo-2-cyclohexenone catalyzed by a perfluorobutylsulfonyl prolinate analogue of the Davies $Rh_2$(DOSP)$_4$ catalyst.[195]

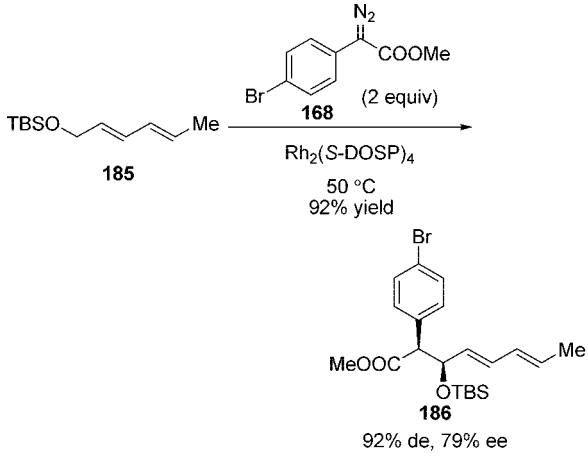



| | | | | |
|---|---|---|---|---|
| $Rh_2$(*S*-DOSP)$_4$ (**17**), 23 °C | 9 | : | 1 | (18% ee) |
| $Rh_2$(5*S*-MEPY)$_4$ (**20**) | 1 | : | 4 | (8% ee) |
| $Rh_2$(5*S*-MEAZ)$_4$ (**39**) | 1 | : | 9 | (60% ee) |
| $Rh_2$(4*S*,*S*-MenthAZ)$_4$ (**41**) | 1 | : | 9 | (79% ee) |
| $Rh_2$(4*S*,*R*-MenthAZ)$_4$ (**42**) | 1 | : | 9 | (80% ee) |

(34)

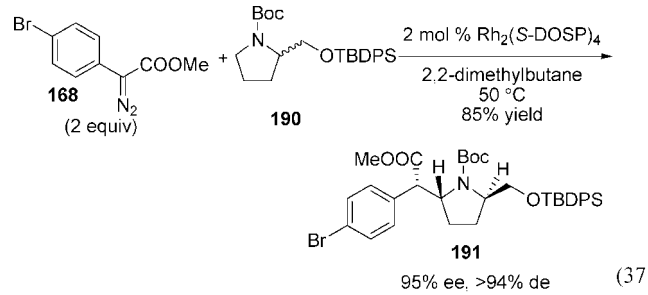
The presence of a heteroatom in the substrate might be expected to capture the carbene as an ylide and afford pathways to product formation from that intermediate (Scheme 21). Indeed, ylide formation and subsequent reactions are common reactions with ethyl diazoacetate,[22,196–201] and their applications are especially evident with aryl- and alkyldiazoacetates.[202–208] Yet catalytic reactions with furan occur in good yield[47] and with high enantioselectivity (eq 35).[44] Davies has successfully employed allyl ethers as substrates[26] even though, if ylides were intermediates, they would be prone to [2,3]-sigmatropic rearrangement as well as cyclopropanation.[196] Allyl ethers and silyloxy allyl ethers undergo C−H insertion in preference to cyclopropanation (e.g., eq 36), and ylide rearrangement products have not been reported, but acetate in place of ether reduces heteroatom activation for C−H insertion and facilitates cyclopropanation (Scheme 22).[209]

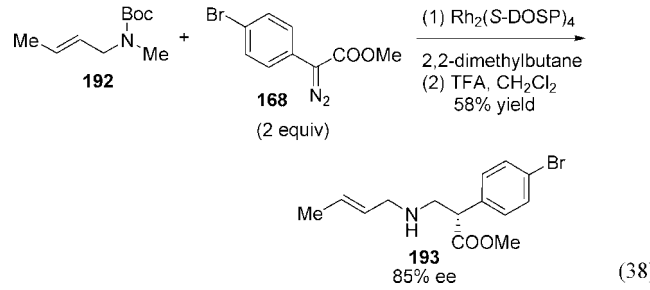



## 6.2. Regioselectivity

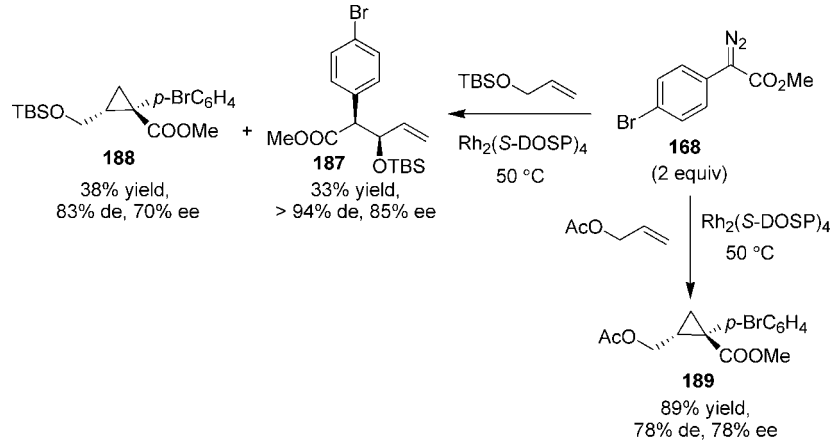
In intramolecular C−H insertion reactions, the preferential formation of five-membered rings dominates regioselectivity, but this is obviously not the case for intermolecular reactions. Here electronic and steric effects are dominant. One of the most informative studies on the factors that influence reactivity in C−H insertion reactions was reported by Davies and co-workers on the relative rates for C−H insertion into various hydrocarbons using methyl phenyldiazoacetate (Scheme 23).[44] This study clearly showed the importance of both electronic and steric factors in intermolecular C−H insertion reactions catalyzed by $Rh_2$(DOSP)$_4$, and 2,3-dimethylbutane was identified as the solvent best suited for these insertion reactions since there was no appreciable insertion reaction into the solvent. As indicated by the reactions in eqs 35 and 36, an ether oxygen activates adjacent C−H bonds for insertion, but reactivity toward a C−H bond adjacent to an ester oxygen is considerably diminished. Silyl ethers appear to be as reactive as alkyl ethers.[210] However, Boc-amides show enhanced reactivity toward C−H insertion by aryldiazoacetates at the carbon adjacent to nitrogen (eq 37);[48,211,212] although amines might be expected to provide further reactivity enhancement, they bind to the catalyst in preference to the diazo compound and reduce overall reactivity; however, insertion into a *N*-methyl group of *N*,*N*-dimethylanilines has been reported.[213] Surprisingly, insertion into a *N*-methyl group takes preference over that into an allylic position activated by nitrogen (eq 38).[214]



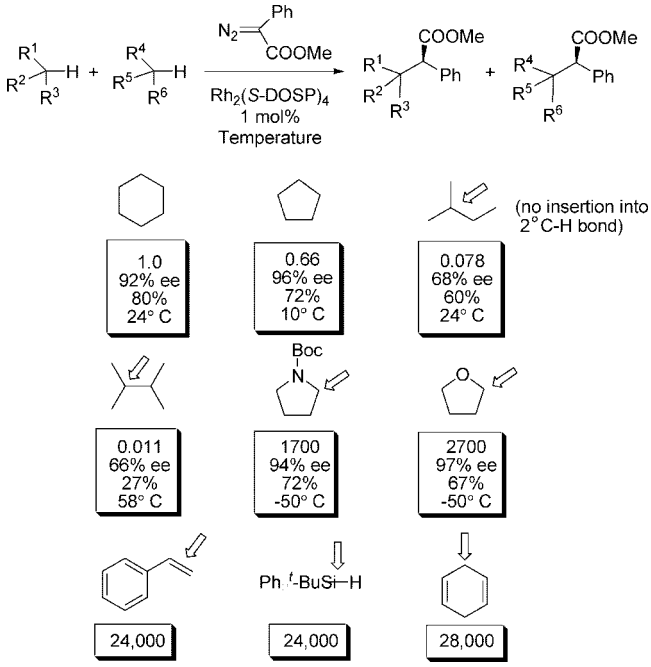




Insertion into benzylic C−H bonds is also favorable, but these reactions are more viable with heteroatom activation and more selective when the systems are fortified by steric encumbrance (e.g., eq 39 OTBS-*t*BuMe$_2$Si).[215] Noteworthy is the advantage in stereoselectivity of $Rh_2$(*S*-PTTL)$_4$ (**18**) over $Rh_2$(*S*-DOSP)$_4$, and relatively subtle changes in catalyst structure (e.g., $Rh_2$(*S*-NTTL)$_4$ (**195**) compared to $Rh_2$(*S*-PTTL)$_4$) have a significant influence on both yield and stereocontrol. Insertion into the 1 °C−H position of toluene occurs, but ethylbenzene exhibits higher reactivity; however, methine C−H insertion into isopropylbenzene occurs in lower yield and with lower enantiocontrol than insertion into the benzylic C−H bond of ethylbenzene.[191] Benzylic C−H insertion occurs in preference to insertion into a methyl C−H bond of an OMe group. In competition between allylic and benzylic C−H insertion, allylic insertion is preferred.[216] There are many examples of cyclopropane formation (bis-

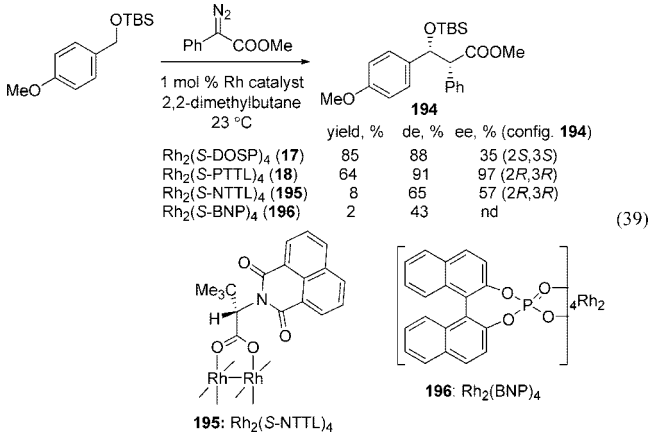
**Scheme 22**




**Scheme 23**



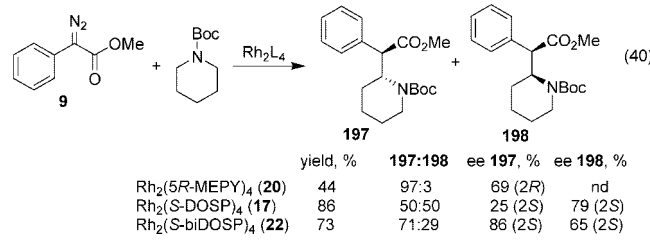

cyclopropanation) in reactions with compounds that can undergo benzylic C−H insertion,[191,209] and the reason for this is not well-understood.

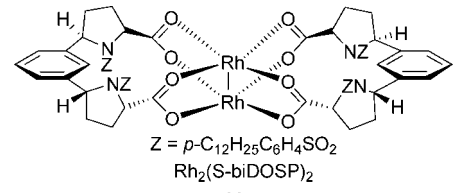



Given the information available regarding intermolecular C−H insertion reactions of aryldiazoacetates and the limited results from vinyldiazoacetates, there are few general predictions that can be made for regiocontrol in benzylic C−H insertion reactions. Steric influences on substrate C−H reactivity that are greatly influenced by the catalyst appear to play a dominant role in determining the preferred site for C−H insertion.

## 6.3. Diastereoselectivity

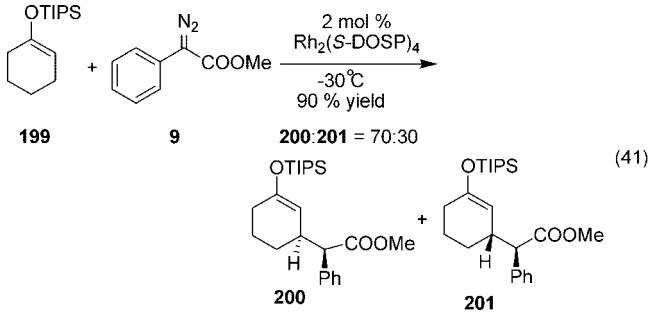
Perhaps the most challenging aspect of intermolecular C−H insertion is diastereocontrol, and the catalyst selected can have enormous control of this selectivity (eq 40).[48,217] In this example, the chiral carboxamidate catalyst exhibits the highest degree of diastereocontrol, but product yield is low and enantioselectivity for the major diastereoisomer is modest; with the more reactive DOSP catalyst (**17**), diastereoselectivity is minimal, but enantioselectivity was sufficiently promising that the modified DOSP catalyst $Rh_2$(*S*-biDOSP)$_4$ (**22**)[73] was prepared and applied successfully to enhance enantioselectivity and improve diastereocontrol.[48] Changing the catalyst and/or substrate,[26,28] using a chiral auxiliary on phenyldiazoacetate,[215] and substituents on the aryl group of aryldiazoacetates[44] can influence diastereoselectivity. However, neither changing the solvent nor lowering the reaction temperature seems to have a significant influence.



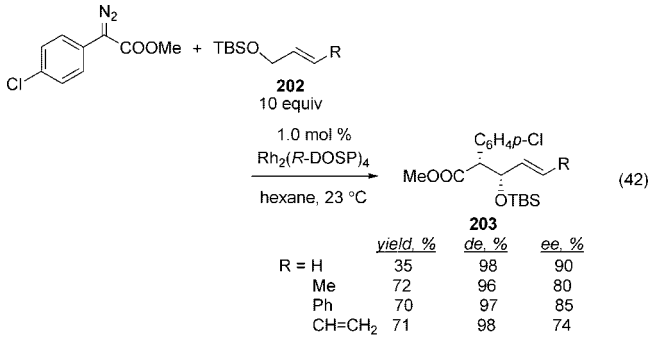

Modest diastereocontrol characterizes carbon−hydrogen insertion reactions at allylic positions catalyzed by $Rh_2$(DOSP)$_4$ catalysts. For example, reactions with cyclic silyl enol ethers (e.g., **199** in eq 41)[218,219] and *N*-Boc-protected amines (eq 40)[48] generally provide high enantioselection, but with limited diastereoselection. This stereocontrol characterizes those

cyclic substrates with an olefinic cis geometry or whose cyclic allylic position is activated by a tri- and tetrasubstituted carbon−carbon double bond. Even lower diastereoselectivity is found from reactions with tetrahydrofuran (THF),[44,193] but relatively high diastereoselectivity occurs in reactions with acyclic silyl ethers.[215] Steric factors influence diastereocontrol.[53] No improvement in diastereoselectivity is achieved by changing the catalyst from $Rh_2(DOSP)_4$ to immobilized copper−bisoxazoline catalysts,[64] and further efforts to increase diastereocontrol may find success using dirhodium catalysts that, like chiral dirhodium carboxamidates, have a (*cis*-2,2) geometry rather than the geometry of the DOSP catalyst that is reported to be akin to that from $C_2$-symmetric chiral ligands.



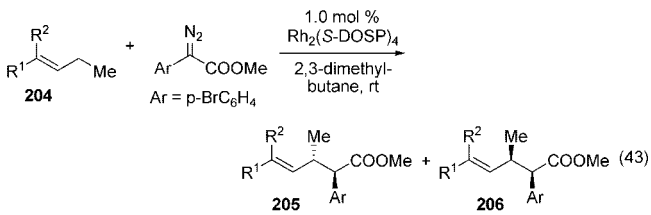
(41)

Although relatively low diastereoselectivity plagues intermolecular C−H insertion with cyclic substrates, insertion into acyclic trans-substituted allylic C−H bonds gives high diastereocontrol. C−H insertion product yields are higher because of less favorable competing cyclopropanation, and the syn products can be formed almost exclusively with good enantiocontrol (compare eqs 42 and 43).[53,210,220] Note that the principal reaction competing with C−H insertion into allyl-OTBS (eq 42) is cyclopropanation. However, there are too few examples available with which to make broad generalizations.



(42)

| | yield, % | de, % | ee, % |
|---|---|---|---|
| R = H | 35 | 98 | 90 |
| Me | 72 | 96 | 80 |
| Ph | 70 | 97 | 85 |
| $CH=CH_2$ | 71 | 98 | 74 |



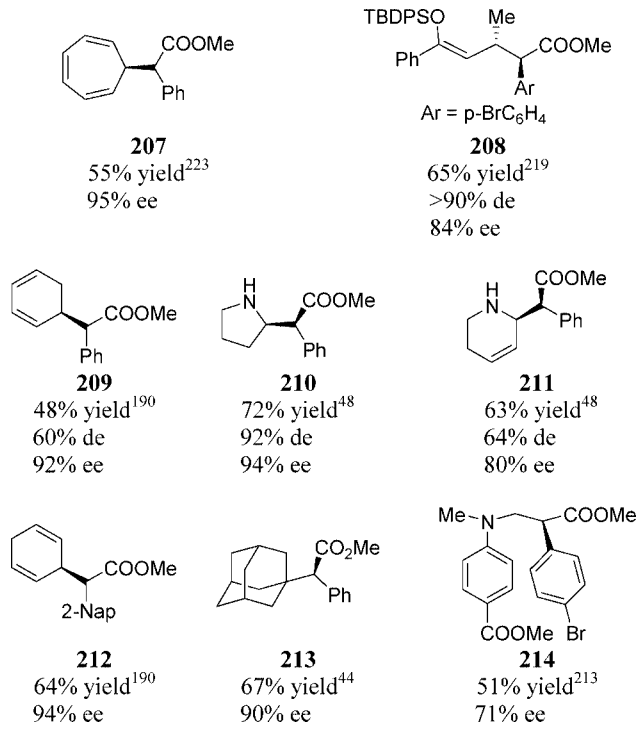
(43)

| | | | |
|---|---|---|---|
| $R_1 = R_2$ = Me | 67% yield | 86% ee | 66% ee |
| | **205**:**206** = 75:25 | | |
| $R_1$ = Et, $R_2$ = H | 56% yield | 92% ee | 80% ee |
| | **205**:**206** = 56:44 | | |
| $R_1 = R_2$ = Ph | 33% yield | 96% ee | 30% ee |
| | **205**:**206** = 85:15 | | |

## 6.4. Enantioselectivity

Enantiocontrol achieved in intermolecular C−H insertion reactions of aryldiazoacetates is generally high (Scheme 24).

**Scheme 24**



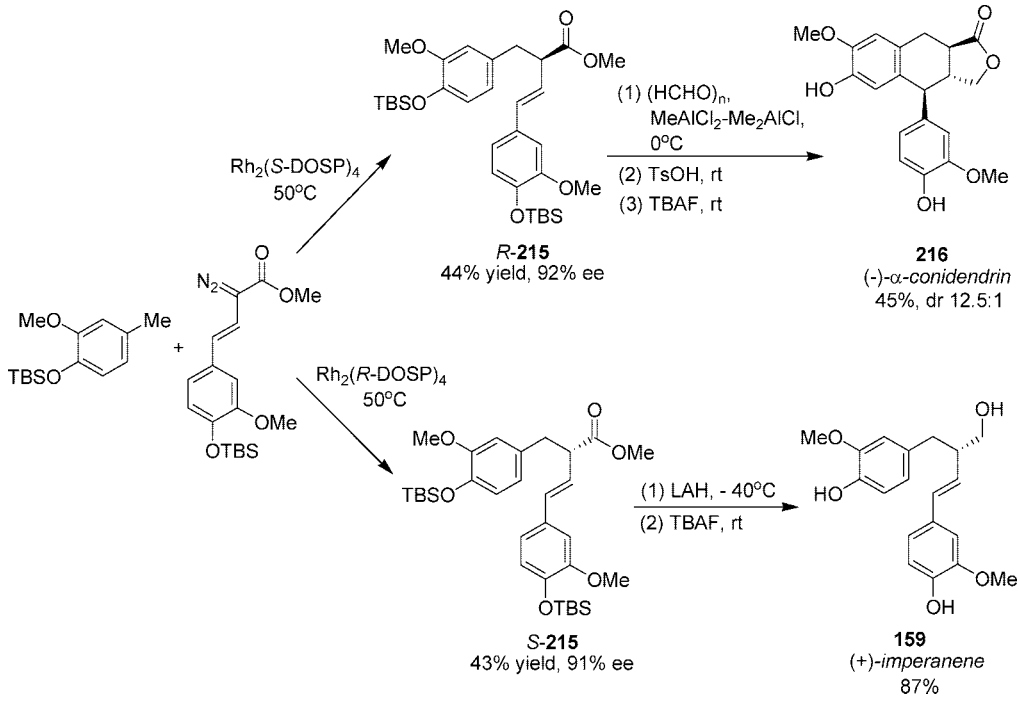

The use of alternatives to the DOSP catalysts, including $Rh_2(TBSP)_4$ (**16**, R = $^t$Bu) and $Rh_2(PTPA)_4$ (**18**),[52,190] have not shown advantages in selectivity, and $Rh_2(DOSP)_4$ is more cost-effective in its applications. Enantiocontrol is generally enhanced at lower temperatures and in hydrocarbon solvents, probably owing to changes in the conformational isomer distribution of the $Rh_2(DOSP)_4$ catalyst. The utility of this methodology has been demonstrated in intermolecular C−H insertion reactions leading to several compounds of pharmaceutical interest.[48,209,221,222]

There are few examples of C−H insertion reactions with vinyldiazoacetates[210] other than those into allylic C−H positions (see next section), but insertion into a benzylic C−H bond has been demonstrated to occur with high enantiocontrol. Examples include the syntheses of (+)-imperanene (**159**) and (−)-α-conidendrin (**216**) (Scheme 25) that occur by intermolecular C−H insertion in high enantiomeric excess.[224] Their further potential has been reported.[28]

### *Catalyst Immobilization*

Since the first report of immobilization of dirhodium(II) catalysts on a solid support,[225] there have been several approaches to immobilization of chiral dirhodium(II) catalysts. One has been to attach the chiral carboxylate or carboxamidate ligand to the polymer and then to exchange that ligand with one (or more) of those on the homogeneous catalyst.[226,227] Immobilized chiral dirhodium carboxamidates with the same[228] or mixed[229] ligands have been prepared in this way with outcomes in limited application that are similar to or beyond results possible with their homogeneous counterparts. A second approach has been to bind the metal to the immobilized phase.[64,218,230,231] In the systems developed by Davies and co-workers, a pyridine attachment from the polymer is used to bind the dirhodium(II) catalyst at the axial position. The catalytic activity/selectivity can be attributed to the detached dirhodium catalyst or to the pyridine-bound catalyst, but the applications presented thus far suggest that

**Scheme 25**

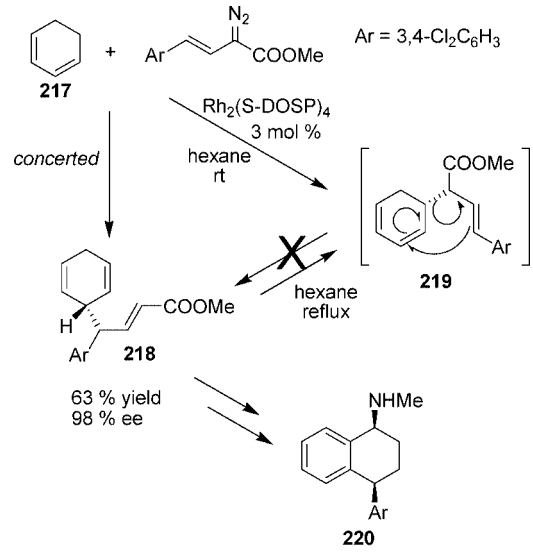



this approach has practical advantages over those in which the chiral carboxylate or carboxamidate ligand is bound to the dirhodium(II) catalyst. In a third alternative, the ligated metal containing a vinyl group was immobilized by copolymerization with 1,4-divinylbenzene.[232] A fourth approach using ionic liquid metal conjugates has recently been reported for dirhodium carboxylates,[233] but its overall applicability has not yet been sufficiently explored to judge its overall promise.

## 6.5. Unusual Behavior of Vinyldiazoacetates in C−H Insertion at Allylic Positions

In undertaking an investigation of the C−H insertion reactions of methyl styryldiazoacetate, Davies and co-workers found that the expected insertion product (**219**) was not formed and, instead, the product from insertion followed by Cope rearrangement was the exclusive product (**218**, Scheme 26).[190] Because the observed insertion/Cope rearrangement product underwent conversion to the initially expected insertion product (**219**) in refluxing hexane and enantiocontrol was higher than expected, the authors concluded that the overall process was concerted. However, additional confirmation will be necessary to more fully certify this unusual transformation. Insertion/Cope rearrangement is a general process with vinyldiazoacetates.[216,234–237] that mimics its counterpart in cyclopropanation chemistry.[238] The synthetic advantages of this transformation are obvious and suffer only from the relative instability of vinyldiazo compounds.

**Scheme 26**




## 7. Summary

Carbon−hydrogen insertion reactions of diazocarbonyl compounds have shown amazing versatility in both intramolecular and intermolecular reactions. Dirhodium(II) carboxylate and carboxamidate catalysts are most effective in these transformations, and new understandings of catalyst structure and reaction selectivity are poised to come from the newest advances in catalyst design.[115,239,240] In intramolecular processes, use of diazoacetates and diazoacetamides have provided exceptional diastereoselectivity and enantiocontrol in reactions catalyzed by chiral dirhodium carboxamidates, especially $Rh_2(MPPIM)_4$; diazo ketones and diazoacetoacetates or diazomalonates have not shown comparable stereocontrol and remain a challenge for catalyst development. For intermolecular processes, aryldiazoacetates and certain vinyldiazoacetates are the preferred substrates for C−H insertion, and high enantiocontrol can be achieved with the use of chiral dirhodium carboxylate catalysts, especially $Rh_2(DOSP)_4$, and new information arrives every month.[241–243] Product yields are generally in the range of 50−70%, although higher yields have also been achieved. Catalyst loading is generally at 1.0 mol %, but 0.1 mol % catalyst has also been used effectively. Diazocarbonyl compounds are, in general, relatively stable to decomposition and can be stored for long periods of time; the exception is vinyl-

diazoacetates that undergo an intramolecular cycloaddition reaction. Applications of this chemistry to the preparation of compounds of biological interest are increasing in number, and the number of research groups reporting results from the use of this chemistry is growing.

## 8. Acknowledgments

The support over the years of the National Institutes of Health and the National Science Foundation for our research in C−H insertion reactions catalyzed by dirhodium catalysts is gratefully acknowledged. Thanks to Yu Liu for providing several drawings for this review and to the many students and colleagues who have participated in this research.

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