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Recent Advances in Asymmetric Catalytic Metal Carbene Transformations

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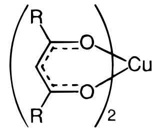
I. Introduction

Catalytic methods to enter the vast array of transformations that take place via metal carbene intermediates are among the most versatile now available to the synthetic organic chemist.[1] Originating in studies of catalytic acceleration of diazo decomposition nearly a century ago,[2] there was rapid recognition that copper and copper salts could facilitate a variety of complex carbon−carbon bond-forming reactions, including addition, insertion, and ylide generation, but early investigations found these transformations to be relatively unselective.[3,4] Parallel development of methods for the preparation of diazocarbonyl compounds[5] advanced the potential of these stabilized diazomethane derivatives as synthetic intermediates and of their catalytic transformations as useful synthetic processes. Ordinarily stable to temperatures above 100 °C, diazocarbonyl compounds undergo dinitrogen extrusion in the presence of a catalyst at considerably lower temperatures.

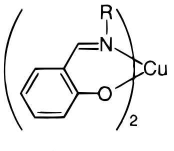
Diazocarbonyl compounds have the general structure depicted in Scheme 1 and include esters, amides, aldehydes, and ketones. When combined with a transition metal compound in an expanding list of catalysts, there is now general agreement that they form metal carbenes that are the reactive intermediates for a broad spectrum of transformation.[6−18] Substituents on the diazocarbonyl unit have a profound influence on reactivity for diazo decomposition so that those with R = H or alkyl are substantially more reactive than those with an electron-withdrawing substituent (COZ, SO_2R, CN, NO_2). The preparation of diazocarbonyl compounds has been thoroughly reviewed[1,5] and will not be elaborated here.

Catalyst development for diazo decomposition reactions began in earnest in the 1960s with the introduction of copper compounds that possessed well-defined ligands. Moser reported phosphite-ligated copper(I) chloride,[19] and Nozaki and co-

$(RO)_3PCuCl$
R = ^{i}Pr, Ph



R = CH_3: Cu(acac)$_2$
R = CF_3: Cu(hfacac)$_2$



R = ^{t}Bu: Cu(TBS)$_2$
R = Bn: Cu(BNS)$_2$

$Cu(OSO_2CF_3)$
[Cu(OTf)]

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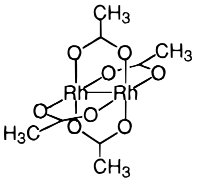
Michael P. Doyle was born in Minneapolis, MN. He received his B.S. degree from the College of St. Thomas in St. Paul, MN, and, working under the direction of Walter S. Trahanovsky, obtained his Ph.D. degree from Iowa State University. Following a postdoctoral engagement with Jan Rocek at the University of Illinois at Chicago Circle, he joined the faulty at Hope College in 1968. In 1984, he moved to Trinity University in San Antonio, TX, as Dr. D. R. Semmes Distinguished Professor of Chemistry, and in 1997, he moved to Tucson, AZ, where he is Professor of Chemistry at the University and Vice President of Research Corp. Professor Doyle has been the recipient of a Camille and Henry Dreyfus Teacher-Scholar Award (1973), a Chemical Manufacturers Association Catalyst Award (1982), the American Chemical Society Award for Research at Undergraduate Institutions (1988), Doctor *Honoris Causa* from the Russian Academy of Sciences (1994), Alexander von Humboldt Senior Scientist Award (1995), and the James Flack Norris Award for Excellence in Undergraduate Education (1995), and he is the coauthor of more than 230 publications. His research interests include asymmetric catalysis and its applications, the design and development of dirhodium(II) compounds, metal carbene chemistry, and new methods for the synthesis of macrocyclic compounds.

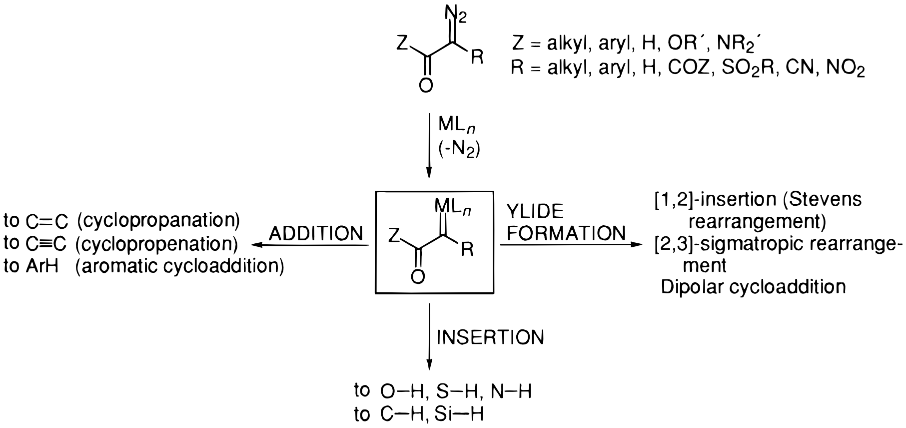
David C. Forbes was born and raised in Chicago, IL. In 1985, he attended the University of Florida, where he participated in research under the advisement of Professor Eric Enholm. There he studied the reactions of samarium(II) iodide with aldimines. Upon receiving his B.S. degree in 1989, he returned to Illinois to begin his graduate studies with Professor Scott Denmark. His studies commenced with an examination of the platinum-catalyzed intramolecular hydrosilylation reaction and the oxone-promoted generation and subsequent reaction of a variety of dioxiranes. Upon completion of his thesis, Dr. Forbes moved south to carry out postdoctoral research with Professor Michael Doyle. Currently, he is undertaking structure/reactivity analyses with chiral dirhodium(II) carboxamidates in the area of ylide generation with diazoacetates. His research interests are in the development of synthetic methodology with emphasis in asymmetric catalysis and understanding structural and stereoelectronic relationships in metal carbene chemistry.

workers described copper(II) acetylacetonate, Cu(acac)$_2$,[20] as an organic solvent soluble alternative to the commonly used copper bronze and copper(II) sulfate. Kochi and Salomon introduced copper(I) triflate, CuOTf (Tf = CF_3SO_2),[21] as a highly active catalyst for cyclopropanation reactions and, in the course of these investigations, drew attention to Cu(I) as the active form, rather than Cu(II), for diazo decomposition. Suggested in earlier investigations of chiral salicylaldimine-ligated copper(II) complexes,[22] Corey and Myers utilized *N*-*tert*-butyl- and *N*-benzylsalicylaldimine complexes [Cu(TBS)^2 and Cu(BNS)^2, respectively] as soluble copper catalysts that were effective for diazo decomposition.[23] Copper(II) supported on Nafion perfluorinated ion-exchange polymer has also been reported to be an efficient catalyst for cyclopropanation reactions.[24]

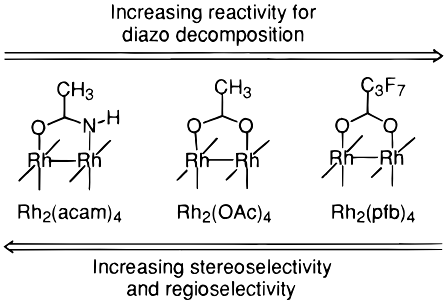
A variety of transition metal compounds have been investigated for their effectiveness as catalysts for diazo decomposition, but only those of rhodium(II) have shown general applicability.[1] Teyssie and coworkers were the first to discover that dirhodium(II) tetraacetate, $Rh_2(OAc)_4$, was highly active for diazo decomposition, initially for O–H insertion reactions[25] but subsequently for cyclopropanation, cyclopropenation, and aromatic cycloaddition



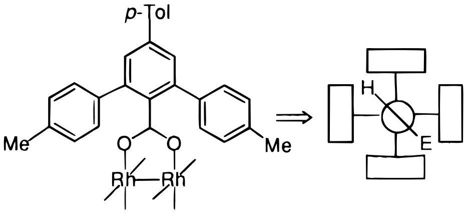
Scheme 1



transformations.[1,6−8] Doyle[26,27] and Padwa[13] and their co-workers established that selectivity in metal carbene transformations could be greatly influenced by the electronic properties of bridging dirhodium(II) ligands. The use of dirhodium(II) perfluorobutyrate, $Rh_2(pfb)_4$,[28] whose ligands are strongly electron withdrawing, showed high reactivity for diazo decomposition, comparable to that for CuOTf, but gave low stereocontrol and regiocontrol in metal carbene transformations. In contrast, dirhodium(II) carboxamidates, including dirhodium acetamidate, $Rh_2(acam)_4$,[26] and dirhodium caprolactamate, $Rh_2(cap)_4$,[27] exhibited lower reactivities and higher selectivities. Although not so well documented, increasing the number of fluorine substituents on the 2,4-pentandionate ligands of $Cu(acac)_2$ also influences catalyst reactivity and reaction selectivity.[29]



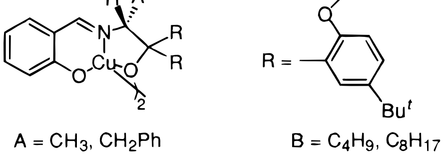
Steric influences on selectivity have received limited attention. Callot prepared dirhodium(II) tris- and tetrakis(tritolylbenzoate) and has investigated them for their steric constraints in catalytic cyclopropanation reactions;[30] the central rhodium of the tetrakis(tritolylbenzoate) is so well enclosed that the bound carbene formed by diazo decomposition of ethyl diazoacetate does not react with alkenes. Hashimoto and co-workers introduced dirhodium(II) tetrakis(triphenylacetate) as an efficient catalyst for C−H insertion reactions;[31] the exact nature of its steric influence on reaction selectivity is not yet clearly defined. Replacement of the acetate ligand of $Rh_2(OAc)_4$ also changes the physical properties of the catalyst. For example, dirhodium(II) octanoate, $Rh_2(oct)_4$, has high solubility in nonpolar solvents[32] and rhodium(II) carboxylates of terminally functionalized polyethylenecarboxylic acids are effective and reusable catalysts for metal carbene transformations.[33]



The importance of catalytic metal carbene transformations for organic synthesis and the high level of investigative activity accorded this research area is suggested by the more than 20 reviews/book chapters that have described progress in the field. The vast majority of them have been written during the past 10 years. We do not intend to duplicate these reports. Instead, we will only survey the use of chiral catalysts for asymmetric metal carbene transformations for which there are currently few summary resources.[1,8,10,34−37] The scope and limitations of these catalytic methodologies are described.

II. Development of Chiral Catalysts for Enantioselective Cyclopropanation: Initial Studies

Nozaki and co-workers were the first to demonstrate that a homogeneous chiral catalyst could provide enantiocontrol for an organic transformation.[22] Using the reaction between ethyl diazoacetate and styrene, a relatively simple salicylaldimine, constructed from salicylaldehyde and enantiopure 1-amino-1-phenylethane, ligated to copper(II) gave low enantioselectivity [6% enantiomeric excess (ee)] for cyclopropane formation. Oxonium ylide rearrangement was also found to occur enantioselectively.[22,38] Subsequent investigations by Nozaki student T. Aratani provided a substantially elaborated salicylaldimine design (**1**) that has proven to be exceptionally effective for intermolecular cyclopropanation reactions, especially with 2,5-dimethyl-2,4-hexadiene (to provide chrysanthemic acid) and isobutylene (eq 1).[39−42] The *R*-configuration of these catalysts produces the (1*R*)-cyclopropane enantiomer, and the *S*-configuration provides the (1*S*)-form. Increasing the size of the substituent A leads to a decrease in enantiocontrol, while increasing the steric bulk of substituents R increases enantioselectivity.[42] A detailed explanation of the factors involved in enantiocontrol with these catalysts has been provided.[34]



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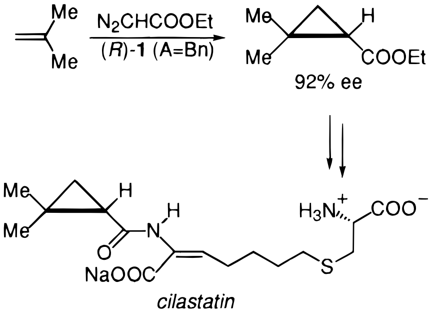
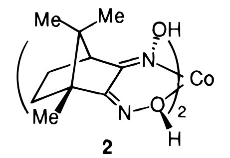


(1)

At about the same time as Aratani's copper catalysts were being reported, Nakamura and co-workers described novel chiral bis(α-camphorquinone-dioximato)cobalt(II) derivatives (**2**) that provided high levels of enantiocontrol in reactions of diazocompounds, including diazomethane, with selected alkenes and dienes.[43,44] Originally interpreted to involve metal carbene intermediates, the available data have



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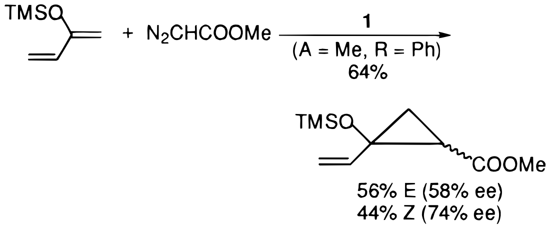
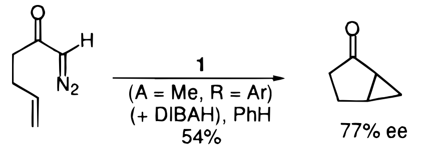
been given an alternative explanation in which a cobalt–olefin complex undergoes electrophilic addition to the diazo compound.[34] Enantiocontrol here resides in the electrophilic addition of the coordinated alkene to the diazo compound.

Other attempts were made to develop chiral catalysts in the late 1960s through the mid-1980s to influence enantiocontrol in catalytic cyclopropanation reactions,[6,7,19,45,46] but none were ultimately successful relative to the Aratani catalyst. A copper(II) chelate of (trifluoroacetyl)-(+)-camphor was reported to give up to 100% ee in the cyclopropanation of styrene using 2-diazodimedone,[47] but this result has not been reproduced; Dauben found that a camphor catalyst of this type was ineffective for asymmetric induction in the intramolecular cyclopropanation of 1-diazo-6-hepten-2-one (2% ee).[48] The Aratani catalyst has been successfully employed by others for both intermolecular[49,50] and intramolecular[48] cyclopropanation reactions (eqs 2 and 3). However, the use of this catalyst system for other metal carbene transformations has not been reported. Major advances beyond those provided with the Aratani catalyst have occurred only during the past 10 years.



(2)[50c]



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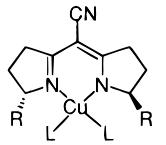
III. Chiral Catalysts for Metal Carbene Transformations

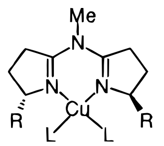
During the past 10 years, major discoveries have been made in the design of chiral ligands for select transition metals and in their catalytic uses for diazo decomposition. Four transition metals—copper, rhodium, ruthenium, and cobalt—will be of concern to us in this review. In this section, we describe those catalyst/ligand combinations that have proven to be effective in transformations that are reported in subsequent sections.

A. Copper/Ligand Combinations

Following the development of the Aratani catalyst, the next major advance in chiral catalyst design and development was provided by A. Pfaltz, who in 1986 described for the first time the construction of chiral semicorrin ligands suitable for coordination with copper(II).[51] Subsequent publications elucidated their effectiveness for cyclopropanation reactions[52,53] and introduced 5-azasemicorrins as suitable alternatives.[54] These catalysts (**3** and **4**) were prepared as stable copper(II) complexes that could be activated by reduction with the diazo compound or, preferably, phenylhydrazine to the copper(I) complex having only one semicorrin ligand.

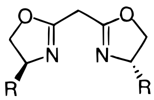


3a: R = CMe_2OH
3b: R = $CH_2OSiMe_2{}^tBu$
3c: R = COOMe

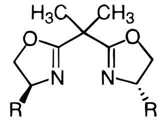


4a: R = $CH_2OSiMe_2{}^tBu$
4b: R = CMe_2OSiMe_3

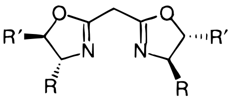
Recognition that C_2-symmetric bis-oxazolines could be prepared from available amino alcohols led Masamune,[55,56] Evans,[57,58] and Pfaltz[59] to construct a series of structures (**5**–**8**) that have been successfully utilized in cyclopropanation reactions. Here Evans recognized that the active copper(I) catalyst could be prepared directly from CuOTf in combination with the bis-oxazoline ligand[57] using the in situ method for catalyst generation that had been widely utilized by Brunner.[60] Structural analogues of these bis-oxazolines (**9** and **10**) have been prepared,[61,62] but



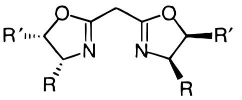
5a: R = $PhCH_2$
5b: R = Me_2CH
5c: R = (*S*)-EtCH(Me)
5d: R = Et
5e: R = Ph
5f: R = ${}^tBu$
5g: R = CH_2OH
5h: R = $Me_2C(OH)$
5i: R = $CH_2OSiMe_2{}^tBu$



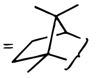
6a: R = ${}^iPr$
6b: R = ${}^tBu$

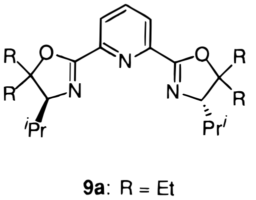


7a: R = Me, R′ = Ph
7b: R = CH_2OH, R′ = Ph

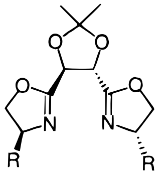


8a: R = Me, R′ = Ph
8b: R = Et, R′ = ${}^tBu$
8c: R = R′ = Ph
8d: R = R′ =





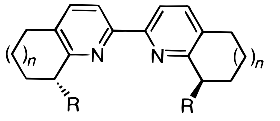
9a: R = Et
9b: R = Ph



10a: R = $PhCH_2$
10b: R = Me_2CH
10c: R = ${}^tBu$
10d: R = Ph

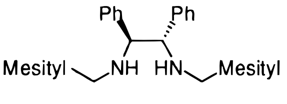
they do not exhibit the same high levels of enantiocontrol as do their parent structures. However, as will be seen (V.B.5), certain variants (**106**) can lead to dramatic improvements.

Ito, Katsuki, and co-workers have prepared chiral bipyridine ligands (**11**) that in combination with CuOTf are effective for formal C−O insertion reactions of diazo esters[63] and for high enantiocontrol in select cyclopropanation reactions.[64,65] The copper complexes of relatively simple diamines (**12** and **13**)[66,67] show promise, with **12** giving high enantiocontrol and enhanced diastereoselectivity for the trans stereoisomer in cyclopropanation reactions.[66] Surprisingly, C_3-symmetric pyrazolylborate (**14**)[68] and the bis(pyrazolyl)pyridine (**15**)[69] afforded low to modest enantiocontrol in catalytic cyclopropanation reactions. None of these ligands for copper yet surpasses the chiral semicorrin or bis-oxazoline ligands in their effectiveness for enantioselectivity in intermolecular cyclopropanation reactions; however, this ligand superiority may not hold for transformations other than cyclopropanation.



a: R = ^{i}Pr
b: R = CMe_2Et
c: R = TMS
d: R = $SiEt_3$

11 (n = 0,1)



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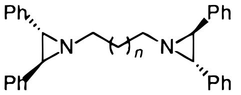
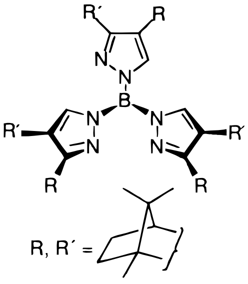


13 (n = 0, 1, 2)



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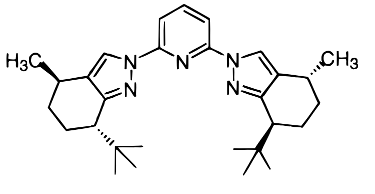

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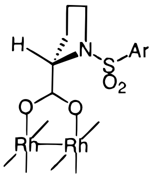
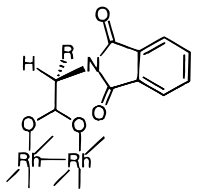
B. Rhodium/Ligand Combinations

Investigations of diazo decomposition reactions following Teyssie's initial discovery of the effectiveness of dirhodium(II) acetate[25] demonstrated broad applicability for this catalytic system.[6−8,12−14] The replacement of acetate by chiral carboxylates was undertaken independently by Brunner, McKervey, and Ikegami with Hashimoto. Brunner used a broad selection of enantiomerically pure aliphatic acids ranging from α-phenylcarboxylic acids to lactic and mandelic acids, but in cyclopropanation reactions between styrene and ethyl diazoacetate, none of them provided selectivities greater than 12% ee.[70] Greater success was achieved with the *N*-sulfonamide−prolinate catalysts (**16**) developed by McKervey[71,72] and with the phthalimide derivatives of phenylalanine[73] and *tert*-leucine (**17**)[74] that were prepared by Ikegami, Hashimoto, and co-workers. As will be seen (vide infra), the effectiveness of these catalysts has been mainly in C−H insertion reactions.

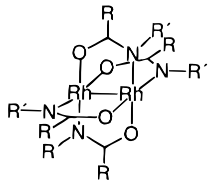


16
(Ar = Ph, C_6H_4X, Nap)



17
(R = $PhCH_2$, ^{t}Bu)

The most universally successful of the catalysts designed for enantioselective metal carbene transformations have been the dirhodium(II) carboxamidates developed by Doyle and co-workers.[1,10,34,37] These catalysts have four bridging amide ligands bound to the dirhodium(II) core with two oxygens and two nitrogens bonded to each rhodium so that the two nitrogens are adjacent to each other (**18**). The chiral center of the ligand is the tetrahedral carbon α to N, and this design places the chiral attachment, usually a carboxylate, in close proximity to the catalytically generated carbene center. The carboxamidate ligands that have been effectively utilized for metal carbene transformations are those derived from 2-oxopyrrolidine (**19**),[75,76] 2-oxooxazolidine (**20**),[77,78] *N*-acyl-2-oxoimidazolidine (**21**),[79,81] and 2-oxoazetidine (**22**),[82] and those generally giving the highest levels of enantiocontrol possess a carboxylate attachment. These catalysts are usually prepared and stored as bis-acetonitrile complexes where the acetonitrile ligands occupy the axial coordination sites of each rhodium.



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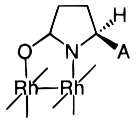
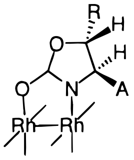
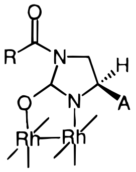
There have been limited reports of dirhodium(II) catalysts bearing chiral phosphate ligands, specifically those with (*S*)-(+)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (**23**). McKervey, McCann, and co-workers have prepared the dirhodium(II) catalyst having two BNHP ligands, $Rh_2(S\text{-BNHP})_2(HCO_3)_2$,



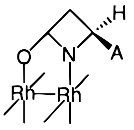
19a: A = COOMe: $Rh_2(5S\text{-MEPY})_4$
19b: A = $COOCH_2CMe_3$: $Rh_2(5S\text{-NEPY})_4$
19c: A = $COO(CH_2)_{17}CH_3$: $Rh_2(5S\text{-ODPY})_4$
19d: A = $CONMe_2$: $Rh_2(5S\text{-DMAP})_4$



20a: A = COOMe, R = H: $Rh_2(4S\text{-MEOX})_4$
20b: A = COOMe, R = CH_3: $Rh_2(4S\text{-THREOX})_4$
20c: A = CH_2Ph, R = H: $Rh_2(4R\text{-BNOX})_4$
20d: A = ^{i}Pr, R = H: $Rh_2(4R\text{-IPOX})_4$
20e: A = Ph, R = H: $Rh_2(4R\text{-PHOX})_4$

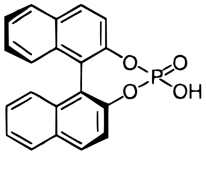


21a: R = CH_3: $Rh_2(4S\text{-MACIM})_4$
21b: R = Ph: $Rh_2(4S\text{-MBOIM})_4$
21c: R = $PhCH_2$: $Rh_2(4S\text{-MPAIM})_4$
21d: R = $PhCH_2CH_2$: $Rh_2(4S\text{-MPPIM})_4$
21e: R = $c\text{-}C_6H_{11}CH_2$: $Rh_2(4S\text{-MCHIM})_4$
21f: R = $p\text{-Bu}^tC_6H_4$; $Rh_2(4S\text{-TBOIM})_4$



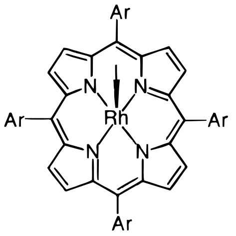
22a: A = $COOCH_2Ph$: $Rh_2(4S\text{-BNAZ})_4$
22b: A = $COOCH_2CHMe_2$: $Rh_2(4S\text{-IBAZ})_4$

from $Na_4Rh_2(CO_3)_4$.[83] Pirrung prepared $Rh_2(S\text{-BNHP})_4$ by ligand exchange with $Rh_2(OAc)_4$.[84]



23
(S-BNHPH)

Kodadek and co-workers have prepared chiral catalysts based on iodorhodium(III) mesotetraarylporphyrins (**24**), whose effectiveness for diazo decomposition originated with Callot.[85] The aryl substituents were chiral binaphthyl ("chiral wall") (**24a**)[86] or pyrenylnaphthyl ("chiral fortress") (**24b**),[87] providing significant steric bias for cyclopropanation reactions. However, enantioselectivities were moderate to low in cyclopropanation reactions, and there have been no further attempts to advance this design for chiral catalyst development.



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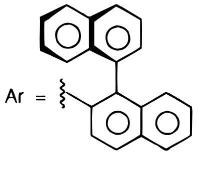
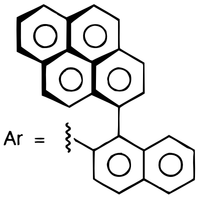
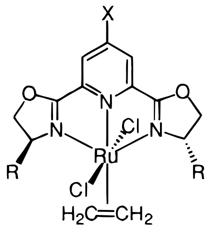




24a **24b**

C. Ruthenium–Pybox Catalysts

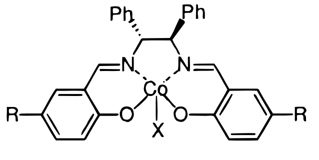
The lower cost of ruthenium, relative to rhodium, and the potential of its compounds as catalysts has drawn increased interest.[88,89] Nishiyama, Itoh, and co-workers have developed ruthenium(II) complexes of chiral C_2-symmetric 2,2-bis(2-oxazolin-2-yl)pyridine (Pybox) as effective catalysts for diazo decomposition (**25**).[90,91] The active catalyst is prepared in situ by the combination of $[RhCl_2(p\text{-cymene})]_2$ and the Pybox ligand in dichloromethane under an ethylene atmosphere. Stable carbene complexes have been formed from **25b**,[92,94] and this stability suggests limited reactivity of the metal carbene toward any but the most reactive nucleophilic substrates. The advantages of these catalysts are their high enantiocontrol and diastereocontrol in intermolecular cyclopropanation reactions. Electron-withdrawing substituents (X) on **25b** increase its catalytic activity and enantioselectivity in intermolecular cyclopropanation reactions.[95]



25a: R = Et
25b: R = ^{i}Pr
25c: R = ^{s}Bu
25d: R = CH_2Ph
25e: R = Ph

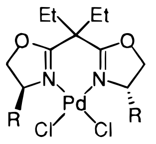
D. Other Chiral Catalysts

Although dioximatocobalt(II) complex **2** was utilized already in the 1970s as an effective catalyst for enantioselective cyclopropanation of alkenes,[43,44] there were no further reports of a potentially useful chiral cobalt catalysts until Katsuki's description of chiral cobalt(III)–salen complexes such as **26**, which has proven to be remarkably effective in several metal carbene transformations.[96,97] The salen ligands are open to a large number of structural variations that may prove to be useful in metal carbene transformations.



26
(R = ^{t}Bu, H)

In an effort to develop catalysts suitable for cyclopropanation with diazomethane, Denmark and co-workers[98] prepared a series of palladium(II) complexes with chiral bis-oxazolines (**27**). Unfortunately, there was a complete absence of asymmetric induction in the cyclopropanation process. One of the reasons for this may be that in Pd(II)-catalyzed reactions cyclopropanation takes place by addition of diazomethane to the alkene that is coordinated to Pd(II) rather than involve an intermediate metal carbene,[1] although partial or complete bis-oxazoline decomplexation, which is the explanation provided by the authors,[98] may also be operative.



27a: R = CH_2Ph
27b: R = ^{i}Pr
27c: R = ^{t}Bu

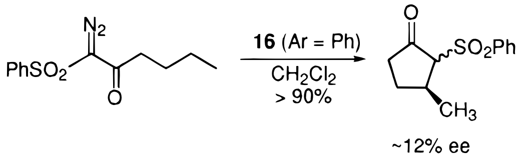
IV. Asymmetric Insertion Reactions

Few chemical transformations provide the breadth and versatility of insertion reactions into single bonds by catalytically generated carbenes. Mechanistic principles cause us to limit treatment here only to those reactions that occur with C—H and Si—H bonds; others, including O—H, N—H, and S—H insertion reactions, are better understood as ylide transformations. The C—H and Si—H insertions occur in a concerted fashion whereby bond-making and bond-breaking into the single bond by the metal carbene occurs in one step.[27] Asymmetric induction is made possible in these reactions because the chiral catalyst undergoes release of the carbene only in the transition state of the product-forming step.

Intermolecular reactions are viable for Si—H insertion,[99] but because of the lower reactivity of C—H bonds, synthetically useful C—H insertion reactions occur only intramolecularly.[1,6–10] Recently, however, Davies and co-workers have shown that intermolecular C—H insertion reactions can occur with high selectivities in select cases,[100] and further investigation is warranted. In intramolecular reactions there is a high preference for formation of five-membered rings, and reactivity for insertion increases dramatically with increasing alkyl substitution: 1° C—H $\ll$ 2° C—H $<$ 3° C—H.[15] Adjacent heteroatoms such as O and N facilitate C—H insertion.[18,101] However, conformational influences based on steric phenomenon can dominate product formation.[27]

A. Enantioselective C–H Insertions

Asymmetric induction in intramolecular C—H insertion reactions was first reported by McKervey and co-workers using their chiral rhodium(II) prolinate catalysts with an α-diazo-β-ketosulfone (eq 4).[71] In this case enantioselection was low, but Hashimoto, Ikegami, and co-workers, using their phthalimide-derivatized phenylalanate dirhodium(II) catalyst (**17**, R = $PhCH_2$) reported higher enantiocontrol with a selection of α-diazo-β-ketoesters (eq 5).[73,102] Increasing the size of the ester substituent R^1 increases enantioselectivity, and with Z = Ph, an enantiomeric excess of 76% was achieved.[102] Lower enantioselectivities for **28** were found with a chiral ferrocenecarboxylate derivative of dirhodium(II) (R^1 = Me),[103] but this catalyst design has not been pursued for metal carbene transformations.



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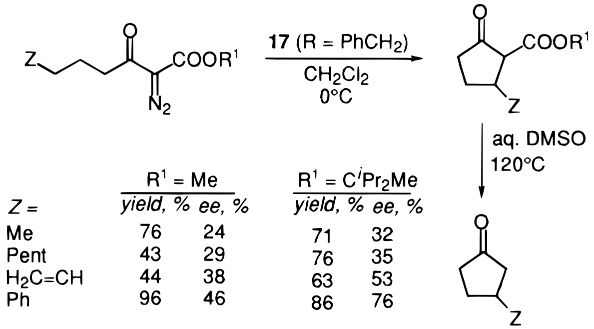
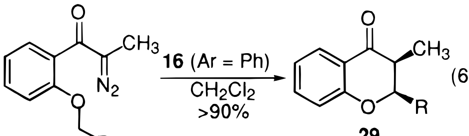


(5)

Z =	R^1 = Me yield, %	ee, %	R^1 = C^iPr_2Me yield, %	ee, %
Me	76	24	71	32
Pent	43	29	76	35
$H_2C{=}CH$	44	38	63	53
Ph	96	46	86	76

28

Diazocarbonyl compounds having a substituent on the diazo carbon generally undergo product formation with lower enantiocontrol than if the substituent is hydrogen. However, the examples of eqs 4–6 demonstrate the potential of chiral dirhodium(II) carboxylates in such cases. With ee values up to 82%, McKervey and co-workers have described C—H insertion in the formation of chromanones (eq 6) with the highest level of enantiocontrol reported thus far for reactions of disubstituted diazomethanes.[104,105] Furthermore, the formation of **29** occurs with high levels of diastereocontrol for the thermodynamically less stable cis-disubstituted chromanone isomer which, as will be further illustrated in later examples, is a characteristic of catalyst ligand influence on the conformation of the reacting carbene.

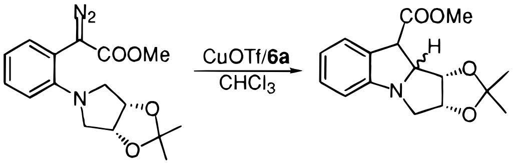


(6)

29

	% ee of *cis*-**29**	cis:trans
R = CH_3	82	75:25
R = Ph	62	89:11
R = $H_2C{=}CH$	79	93:7

The reactivity of the catalyst has an important bearing on the applicability of diazocarbonyl compounds for C—H insertion. Only the most reactive of the chiral catalysts will cause diazo decomposition and subsequent C−H insertion with disubstituted diazomethanes in which one substituent is a carbonyl group. This is amply demonstrated in Sulikowski's examination of catalysts suitable for C−H insertion with **30** (eq 7).[106] Chiral dirhodium(II) carboxamidates were found to be ineffective, but the bis-oxazoline copper(I) catalyst CuOTf/**6a** gave **31** with 48% ee in $CHCl_3$ but only 12% ee in CH_2Cl_2.[106a] Chiral dirhodium(II) carboxylates **16** and **17** were not evaluated, but screening for applicable catalysts by Burgess and Sulikowski uncovered further catalyst and solvent influences on diastereoselectivity in product formation.[107]

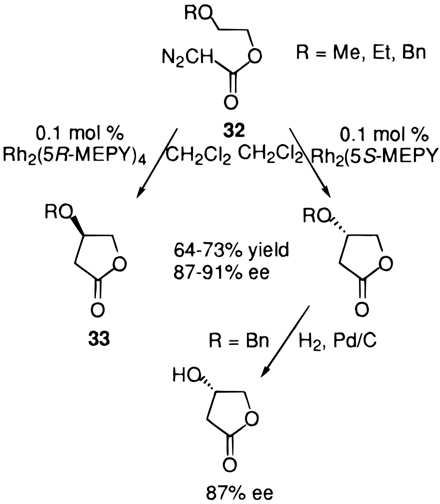


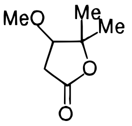
(7)

30 **31** (48% ee)

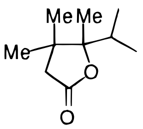
Already in 1991 results were reported with chiral dirhodium(II) carboxamidates that demonstrated their exceptional ability to achieve enantiocontrol in C−H insertion reactions.[108] Capitalizing on Spero and Adams' demonstration that the oxygen heteroatom enhanced the reactivity of adjacent C−H bonds,[18] Doyle and co-workers discovered that $Rh_2(5S\text{-MEPY})_4$ (**19a**) and $Rh_2(5R\text{-MEPY})_4$ caused highly enantioselective insertion with **32** to form alkoxy-substituted γ-lactones in good yield (Scheme 2). As little as 0.1 mol % of catalyst was sufficient to cause complete diazo decomposition. The *S*-catalyst formed the *S*-enantiomer, while the *R*-catalyst produced the *R*-product enantiomer. Other variations in the structure of **32** and other applicable diazo compounds led to products **34**−**36** and modest % ee values from $Rh_2(MEPY)_4$-catalyzed reactions. A polymer-bound $Rh_2(5S\text{-MEPY})_4$ catalyst was used to convert **32** into *ent*-**33**; the issue of recoverability and reuse was addressed when the polymer-bound $Rh_2(5S\text{-MEPY})_4$ was recovered and reused seven times with similar results.[109] Improvements in enantiocontrol for systems such as these can be expected with the use of alternative chiral dirhodium(II) catalysts. For example, *ent*-**33** (R = Et) has been obtained in 92% ee with $Rh_2(4S\text{-MEOX})_4$[77] and 94% ee with $Rh_2(4S\text{-MPPIM})_4$.

Scheme 2

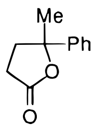




34: 57% ee

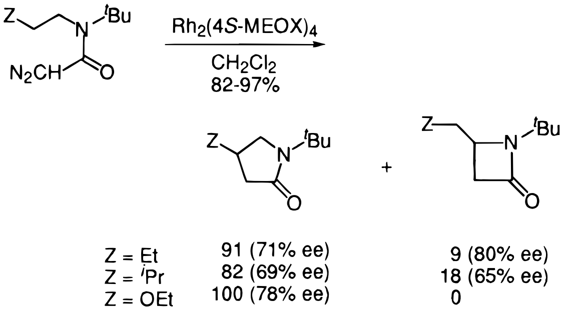


35: 60% ee



36: 79% ee

Modest levels of enantiocontrol were achieved in C−H insertion reactions of acyclic diazoacetamides.[110] Competition between β-lactam and γ-lactam formation complicates these reactions (eq 8), and only when Z = OEt is one product formed. Here the highest ee values were obtained with $Rh_2(4S\text{-MEOX})_4$. These results contrast with those from diazo decomposition of cyclic diazoacetamides where β-lactam formation generally dominates and enantioselectivities are exceptionally high (eqs 9−11).[111] Ring size and conformational influences obviously play significant roles in regioselection and enantioselection in these reactions.



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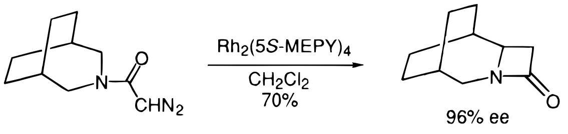

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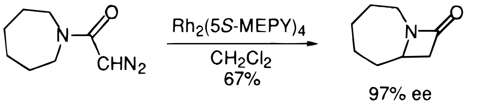

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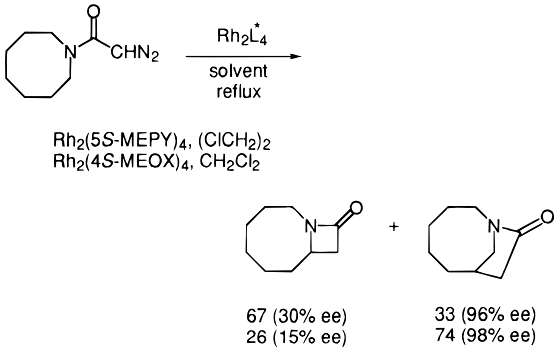
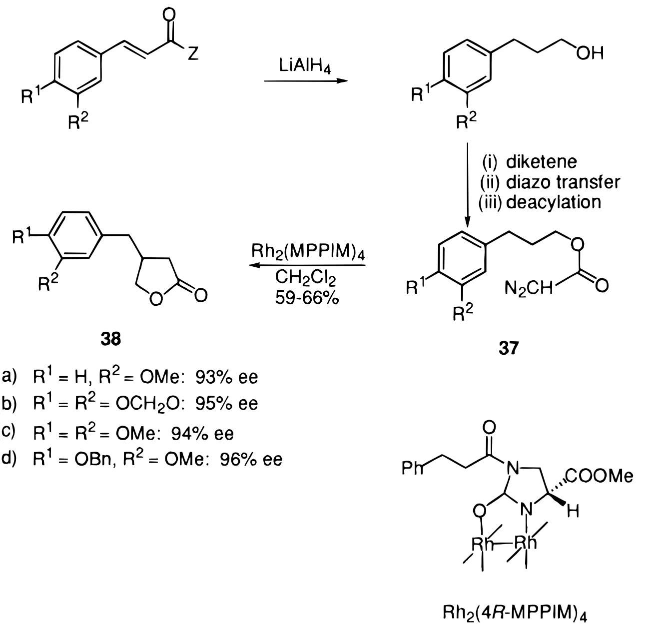


(11)

B. Synthesis of Lignan Lactones: Regio- and Enantiocontrol

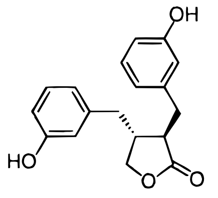
Lignan lactones are a broad class of natural products, many of which have noteworthy biological and medicinal properties.[112] The vast majority of lignan lactones can be synthesized from β-substituted γ-butyrolactones that, using asymmetric C−H inser-

Scheme 3



(a) $R^1 = H, R^2 = OMe$: 93% ee
(b) $R^1 = R^2 = OCH_2O$: 95% ee
(c) $R^1 = R^2 = OMe$: 94% ee
(d) $R^1 = OBn, R^2 = OMe$: 96% ee

tion methodology, are accessible from cinnamic acids.[113,114] The controlling factors in these syntheses are enantiocontrol and regiocontrol in the C−H insertion process and, as can be seen from the general methodology of Scheme 3, this control is achieved with $Rh_2(MPPIM)_4$ (**21d**) catalysts. Regioselectivity is ≥ 95% for the γ-lactone; insertion into the C−H bond adjacent to oxygen is the only competing process (<5%) identified with those substrates included in Scheme 3. Using this methodology, (+)- and (−)-enterolactone (**39**, from **38a**), (−)- and (+)-hinokinin (**40**, from **38b**), (−)-arctigenin (**41**, from **38c**), (+)-isodeoxypodophyllotoxin (**42**, from **38b**), and (+)-isolauricerisinol (**43**, from **38d**) were prepared in high overall yield from their corresponding cinnamic acids.



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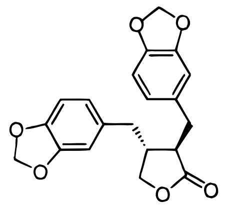

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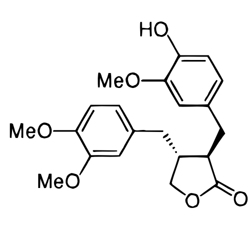

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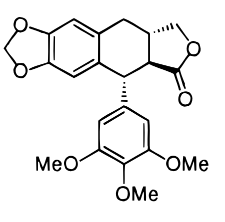

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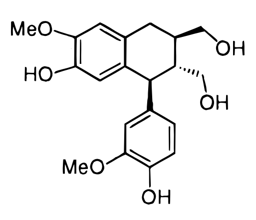
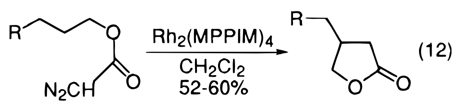


43

The high enantiocontrol and regiocontrol found with the $Rh_2(MPPIM)_4$ catalysts were not limited to their applications with **38**. Indeed, this catalyst provided generally high selectivity for insertion (eq 12) with all primary alkyl diazoacetates that have



44a, R = Ph
44b, R = Me
44c, R = ^{i}Pr

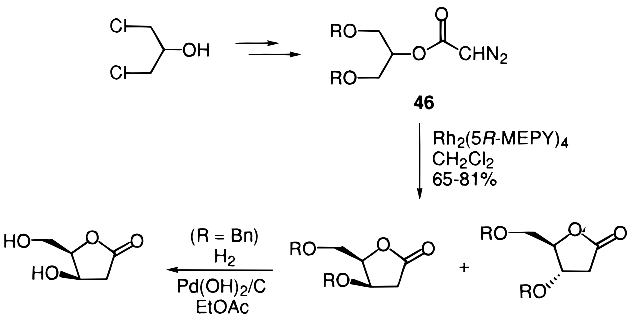
45a, 91% ee
45b, 96% ee
45c, 95% ee

been examined thus far. Much lower enantioselectivities were obtained with the $Rh_2(MEPY)_4$ and $Rh_2(MEOX)_4$ catalysts but, as had been previously established with **32** (Scheme 2), use of the *R*-configured catalysts yielded the *R*-product enantiomer predominantly, whereas with the *S*-catalyst C−H insertion gave the *S*-enantiomer. Detailed analyses of the factors responsible for these high levels of enantiocontrol with use of the $Rh_2(MPPIM)_4$ catalysts—a virtually enzyme-like design—have been reported.[114]

C. Synthesis of 2-Deoxyxylolactone: Diastereo- and Enantiocontrol

A convenient synthesis of 2-deoxyxylolactone from 1,3-dichloro-2-propanol has been reported using the $Rh_2(MEPY)_4$ catalysts.[115] Diazo decomposition of **46** with $Rh_2(MEPY)_4$ (Scheme 4) yielded a mixture of **47a**,**b** with **47a** favored by 93:7. Enantioselectivity for formation of **47a** was high, and chromatographic separation of **47a** from **47b** followed by hydrogenolysis resulted in the formation of (3*R*,4*R*)-**48** with 94% ee. Use of $Rh_2(MEOX)_4$ provided higher enantiocontrol (96% ee for **47a**) but gave lower diastereocontrol (90:10).

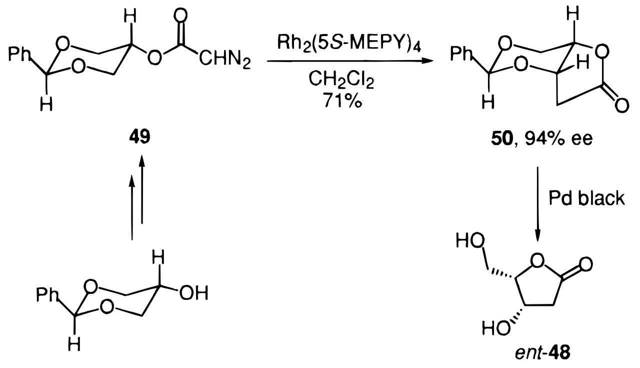
Scheme 4



48	47a	47b
R = Me	93 (97% ee)	7 (50% ee)
R = Et	93 (89% ee)	7 (50% ee)
R = Bn	93 (94% ee)	7 (45% ee)

An alternate methodology has been developed for the synthesis of highly enantiomerically enriched 2-deoxyxylolactone that avoids diastereoisomer formation.[116] The benzal acetal of 1,3-dihydroxy-2-propyl diazoacetate (**49**) undergoes catalytic decomposition in the presence of $Rh_2(MEPY)_4$ (**19a**) to form the axial C−H insertion product (**50**) in high yield with 94% ee (Scheme 5). Simple hydrogenolysis gives the desired product. The formation of **50** was not expected in view of the established preference (vide

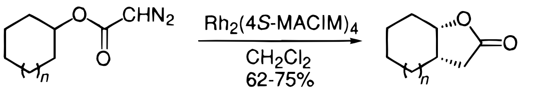
Scheme 5



infra) for equatorial C–H insertion which was observed for the *tert*-butyl acetal corresponding to **49**.

D. Bicyclic Lactones: Diastereo- and Enantiocontrol

Intramolecular insertion into a vicinal C–H bond of cycloalkyl diazoacetates can result in the formation of as many as four products: those with cis and trans ring fusions and their enantiomers. Doyle, Müller, and co-workers have reported that both high diastereoselectivity and high enantioselectivity can be achieved in intramolecular C–H insertion reactions with cycloalkyl diazoacetates.[117,118] With unsubstituted cycloalkyl diazoacetates (**51**), $Rh_2(MACIM)_4$ (**21a**) catalysts effect the highest selectivities for the formation of the *cis*-fused lactone (eq 13).[117] Dirhodium(II) catalysts $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(4S\text{-MEOX})_4$ produce mixtures of diastereoisomers but each with high % ee values. Cyclopentyl diazoacetate gave the corresponding bicyclic lactone with only 89% ee using $Rh_2(4S\text{-MACIM})_4$, but with $Rh_2(4S\text{-MPPIM})_4$, this same product could be formed in 93% ee.[119] The absolute configurations of products formed in these reactions have been established.[117]

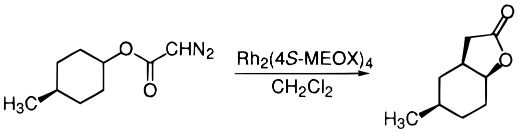


(13)

51: *n* = 1,2,3

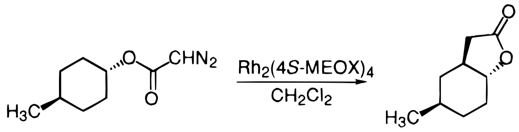
cis:trans = 99:1
96-97% ee

With prochiral 4-substituted cyclohexyl diazoacetates, diastereoselectivity was found to be dependent on the relative configuration of the reactant.[117,118] *Cis* substituted cyclohexyl diazoacetates gave the all-cis products exclusively and in high enantiomeric excess (eq 14). With these systems the most selective catalyst was $Rh_2(MEOX)_4$ (**20a**),[117] and insertion occurred from the axial conformation of the diazoacetate into the equatorial C–H bond. *Trans* substituted cyclohexyl diazoacetates gave the trans-fused lactone product with high diastereocontrol and in high enantiomeric excess using the $Rh_2(MEOX)_4$ catalysts (eq 15). Once again, preferential insertion occurred into the equatorial C–H bond. The $Rh_2(MACIM)_4$ catalysts preferred the cis-fused lactone (63:37 dr) with high enantiomeric excess for the formation of **52** (93% ee).[117] Other lactone systems (e.g., **50** and **53**[77]) have been prepared with similar high stereocontrol. However, enantioselectivity was low for the formation of spirolactone **54**,[120] but chiral dirhodium(II) carboxamidate catalysts currently untested may show improved results.



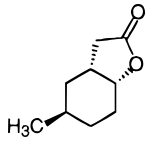
(14)

98% ee
>99:1 dr

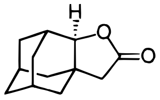


(15)

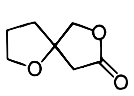
95% ee
90:10 dr



52: 93% ee

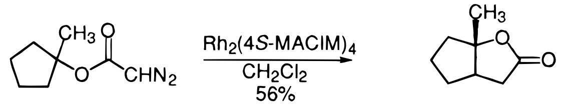


53: 98% ee



54: 24% ee

Tertiary alkyl diazoacetates undergo intramolecular C–H insertion with lower enantiocontrol than do their secondary alkyl diazoacetate counterparts.[121] However, even with 1-methylcyclopentyl diazoacetate (**55**) an 85% ee for the formation of **56** was achieved with $Rh_2(MACIM)_4$ (**21a**) catalysts (eq 16). With the cyclohexyl analogue, the corresponding insertion product was formed in 90% ee. Insertion into a C–H bond of the methyl group was competitive, but regiocontrol was ≥90:10 for **56** and its analogues. Applications to acyclic diazoacetates showed variable selectivities (eqs 17 and 18) that contrast with that from diazo decomposition of 3-pentyl diazoacetate with chiral dirhodium(II) catalyst **21e** (eq 19)[119] and 2,4-dimethyl-3-pentyl diazoacetate with *ent*-**19a** (eq 20).[118] Diazoketone analogues of **55** and its next higher homologue also undergo intramolecular C–H insertion,[118] but enantiocontrol is negligible.



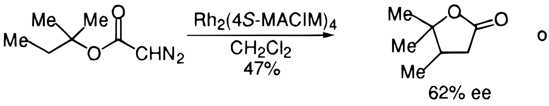
(16)

55

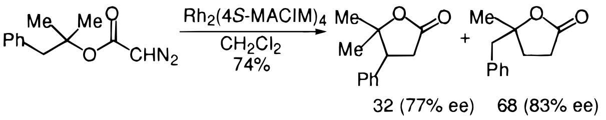
56: 85% ee

E. Enantiomer Differentiation in Intramolecular C–H Insertion Reactions: Diastereo- and Regiocontrol

Unsymmetrical diazoacetates already possess an asymmetric center. When treated with a chiral dirhodium(II) catalyst, one enantiomer gives a specific product while the other yields a diastereoisomer.[122] This is “enantiomer differentiation” by the chiral catalyst so that, ideally, if a racemic reactant is employed, treatment with the chiral catalyst results in the formation of two diastereomers with high enantiomeric excesses for both.[123] For example,



(17)



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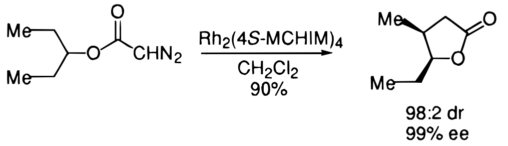
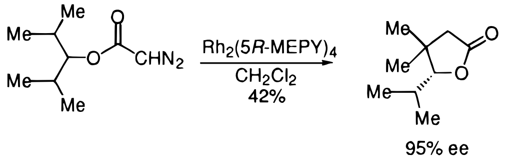
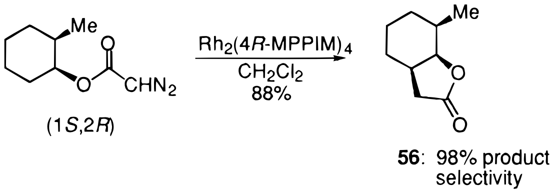


(19)



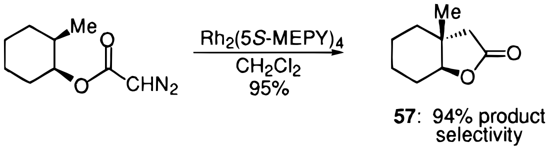
(20)

treatment of (1S,2R)-*cis*-2-methylcyclohexyl diazoacetate with $Rh_2(4R\text{-MPPIM})_4$ (*ent*-**21d**) gives essentially only one insertion product (**56**) and in high yield (eq 21), whereas use of $Rh_2(4S\text{-MPPIM})_4$ produces a complex mixture of C—H insertion products in low yield (46%) of which **56** is only a minor component.[122] With $Rh_2(5S\text{-MEPY})_4$, however, one product predominates (**57**: 94% of total, eq 22), and $Rh_2(5R\text{-MEPY})_4$ produces **56** in lower yield (79%) and 91% product selectivity. Similar results have been reported for *trans*-2-methylcyclohexyl diazoacetate (Scheme 6) and for menthyl and neomenthyl diazoacetates. In all of these examples there is a high preference for insertion into an equatorial C—H bond. There is no obvious regioselectivity (e.g., **56** and **57** or **58** and **59**) in reactions performed with achiral catalysts such as $Rh_2(cap)_4$.



(21)

56: 98% product selectivity

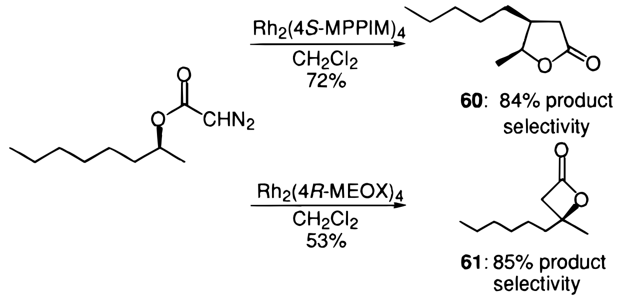


(22)

57: 94% product selectivity

With (R)- or (S)-2-octyl diazoacetate, chiral catalyst selectivity is evident in γ-lactone (**60**) and β-lactone (**61**) formation (Scheme 7). With this system, competition also exists for formation of the trans isomer of **60** and for insertion into a primary C—H bond of the methyl group, so that product selectivity refers to the preference for **60** (or **61**) over all other C—H insertion products. Using racemic diazoacetate, mixtures of products are obtained, but **60** can be formed in greater than 80% ee.[123] Mechanistic details for enantiomer differentiation consistent with these selectivities have been provided.[122] Only the selectivity for the insertion reaction described in Scheme 5 is inconsistent with the conclusions drawn from this study.

Scheme 7



60: 84% product selectivity

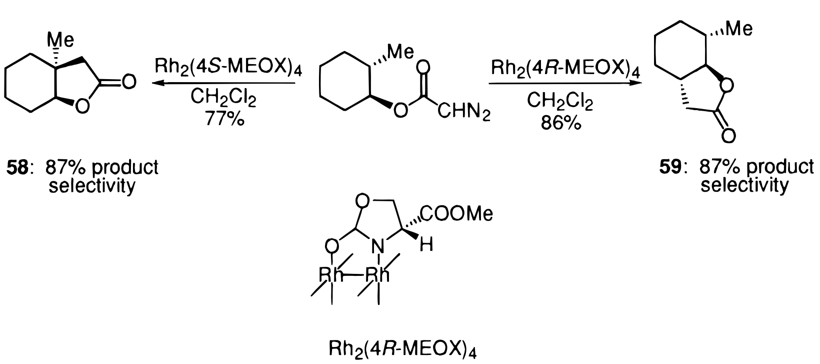
61: 85% product selectivity

Chiral ligands on dirhodium(II) have a remarkable influence on diastereocontrol and regiocontrol in C—H insertion reactions. As is demonstrated by the examples, the appropriate match of catalyst and substrate configurations ensures production of single diastereomers/regioisomers in C—H insertion reactions, and mismatch leads to lower yields and low selectivities. Chiral copper(I)/bis-oxazoline **6b** is not as effective as are chiral dirhodium(II) carboxamidates.

F. Enantioselective Si–H Insertions

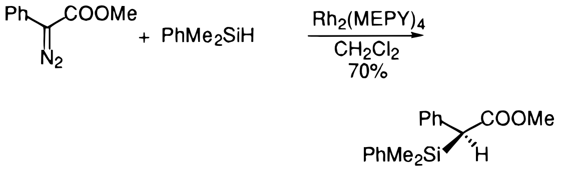
Moody, Doyle, and co-workers were the first to demonstrate that chiral catalysts of dirhodium(II) could induce asymmetry in Si—H insertion reactions of methyl phenyldiazoacetate (eq 23).[124] From a broad selection of dirhodium(II) carboxylates and carboxamidates, the $Rh_2(MEPY)_4$ catalysts proved to give the highest % ee values. Davies and co-workers

Scheme 6



58: 87% product selectivity

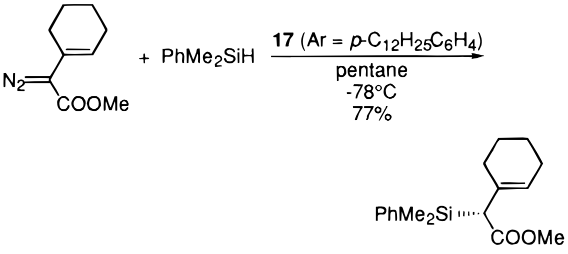
59: 87% product selectivity



(23)

62: 45-47% ee

subsequently reported that vinyl diazoacetates underwent Si−H insertion with even higher % ee's (85% for **62**) with catalysis by chiral dirhodium(II) prolinate **17** (Ar = *p*-$C_{12}H_{25}C_6H_4$) in pentane at −78 °C (eq 24).[125] The first report of Si−H insertion catalyzed by a dirhodium(II) carboxylate appeared only in 1988.[126] Landais has examined diastereocontrolled Si−H insertion using chiral esters of diazocarbonyl compounds.[127] The effects of silicon substituents on enantiocontrol are yet to be examined.



(24)

92% ee

V. Asymmetric Cyclopropanation Reactions

Catalytic reactions involving metal carbenes are best known for cyclopropanation transformations in which formal addition occurs to a carbon−carbon double bond. The development of chiral catalysts has therefore focused on cyclopropanation reactions as a test of their effectiveness. The major targets have been intermolecular and intramolecular processes, and catalyst effectiveness for enantiocontrol differs for each.

A. Intermolecular Cyclopropanation Reactions

Reviews of catalytic cyclopropanation describe the development of this methodology, mainly via intermolecular reactions.[6−11] Significant advances have been made in enantiocontrol for these addition processes during the past decade, initially with diazoacetates and more recently with vinyl- and aryldiazoesters. Effective enantioselective cyclopropanation with diazomethane has been elusive; however, Pfaltz has reported preliminary results of 70-80% ee values for cyclopropanation of 1,2-*trans*-disubstituted olefins with diazomethane using chiral semicorrin copper catalysts.[36]

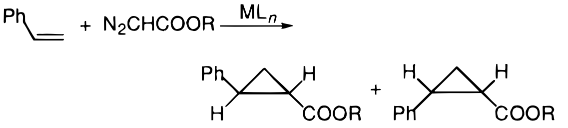
1. Diazoacetates

Comparative evaluation of enantiocontrol for intermolecular cyclopropanation reactions has most often been measured against styrene with ethyl diazoacetate (EDA), *tert*-butyl diazoacetate (*t*-BDA), or *d*- and *l*-menthyl diazoacetates (MDA) as the reactant. Menthyl diazoacetates were originally employed because addition afforded GC-separable diastereoisomers. Results from reactions of styrene and these diazoacetates (eq 25) using a representative spectrum of chiral copper catalysts are given in Table 1. Semicorrin and bis-oxazoline ligands provide the highest levels of enantiocontrol for these cyclopropanation reactions. Increasing the size of R on the diazoacetate generally increases enantiocontrol, but little double diastereoselectivity is observed with the use of *d*- and *l*-menthyl diazoacetates. Diastereoselectivity is relatively low, except when the bulkiest diazoacetates (e.g., BDA) are employed.

Table 1. Enantiocontrol in the Cyclopropanation of Styrene by Diazoacetates Using Chiral Semicorrin and Bis-oxazoline-Ligated Copper Catalysts

copper catalyst	$N_2CHCOOR$	**63t**:**63c**	% ee (config) **63t**	% ee (config) **63c**	ref
3a	EDA	73:27	85 (1*S*,2*S*)	68 (1*S*,2*R*)	53
3b	EDA	75:25	59 (1*S*,2*S*)	45 (1*S*,2*R*)	53
3c	EDA	74:26	23 (1*S*,2*S*)	19 (1*S*,2*R*)	53
3a	*t*BDA	81:19	93 (1*S*,2*S*)	92 (1*S*,2*R*)	53
3a	*l*-MDA	85:15	91 (1*S*,2*S*)	90 (1*S*,2*R*)	53
3a	*d*-MDA	82:18	97 (1*S*,2*S*)	95 (1*S*,2*R*)	53
4a	EDA	75:25	66 (1*S*,2*S*)	43 (1*S*,2*R*)	54
4b	EDA	75:25	94 (1*S*,2*S*)	68 (1*S*,2*R*)	54
4b	*t*BDA	86:14	96 (1*S*,2*S*)	90 (1*S*,2*R*)	54
4b	*d*-MDA	84:16	98 (1*S*,2*S*)	99 (1*S*,2*R*)	54
5a/Cu(I)	*l*-MDA	86:14	19 (1*R*,2*R*)	9 (1*R*,2*S*)	59
5e/Cu(I)	*l*-MDA	83:17	55 (1*R*,2*R*)	50 (1*R*,2*S*)	59
5f/Cu(I)	*l*-MDA	87:13	96 (1*R*,2*R*)	97 (1*R*,2*S*)	59
5f/Cu(I)	EDA	77:23	98 (1*R*,2*R*)	93 (1*R*,2*S*)	57
6b/Cu(I)	EDA	73:27	99 (1*R*,2*R*)	97 (1*R*,2*S*)	57
6b/Cu(I)	*t*BDA	81:19	96 (1*R*,2*R*)	93 (1*R*,2*S*)	57
6b/Cu(I)	BDA[a]	94:6	99 (1*R*,2*R*)		57
11c/Cu(I)	*t*BDA	86:14	92 (1*S*,2*S*)	98 (1*S*,2*R*)	65
12/Cu(I)	EDA	74:26	86 (1*S*,2*S*)	58 (1*S*,2*R*)	66
12/Cu(I)	*l*-MDA	91:9	94 (1*S*,2*S*)		66

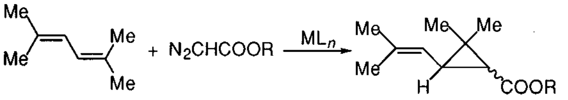
[a] 2,6-Di-*tert*-butyl-4-methylphenyl diazoacetate (ref 27).



(25)

63t **63c**

Cyclopropanation of 2,5-dimethyl-2,4-hexadiene provides a direct route to chrysanthemic acid. Following initial efforts by Aratani and co-workers,[39,40] using chiral salicylaldimines, Masamune and Lowenthal reported the use of chiral bis-oxazolines to effect high enantiocontrol with this normally resistant alkene (eq 26).[56] Representative results from this study are reported in Table 2. The normally favorable *tert*-butyl bis-oxazoline **6b** was relatively ineffective, but multiply substituted bis-oxazolines **7** and **8** led to very high enantiocontrol and, with either BDA or dicyclohexylmethyl (DCM) diazoacetates as the substrate, high diastereoselectivity. Chiral salicylaldimine copper catalysts (**1**) were less effective.[40]



(26)

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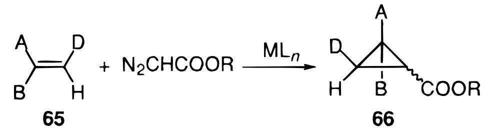
Table 2. Enantiocontrol in the Cyclopropanation of 2,5-Dimethyl-2,4-hexadiene by Diazoacetates with Chiral Bis-oxazoline Copper Catalysts

copper catalyst	$N_2CHCOOR$	**64t:64c**	% ee (config)		ref
			64t	**64c**	
6b/Cu(I)	*l*-MDA	84:16	24 (1*R*,2*R*)	20 (1R,2*S*)	56
7a/Cu(I)	*l*-MDA	90:10	72 (1*R*,2*R*)	60 (1*R*,2*S*)	56
8d/Cu(I)	*l*-MDA	80:20	90 (1*R*,2*R*)	80 (1*R*,2*S*)	56
8c/Cu(I)	BDA	92:8	92 (1*R*,2*R*)		56
8c/Cu(I)	*l*-MDA	92:8	92 (1*R*,2*R*)	84 (1*R*,2*S*)	56
8c/Cu(I)	BDA	94:6	94 (1*R*,2*R*)		56
1 (A = $PhCH_2$)	*l*-MDA	89:11	87 (1*S*,2*S*)	25 (1*S*,2*R*)	40

Table 3. Enantiocontrol in the Cyclopropanation of Selected Alkenes Using Chiral Copper Catalysts

A	B	D	R	copper catalyst	**66t:66c**	% ee		ref
						66t	**66c**	
Me	Me	CH_2Cl	Et	**1** (A = Me)	16:84	51	90	41
Me	Me	CCl_3	Et	**1** (A = Me)	15:85	11	91	41
H	H	$H_2C{=}CH$	*d*-menthyl	**3a**	63:37	97	97	53
Me	Ph	H	*l*-menthyl	**5f**/Cu(I)	89:11	92	79	55
H	H	$(CH_2)_5CH_3$	*l*-menthyl	**5f**/Cu(I)	94:6	99	30	55
Me	Me	$Cl_2C{=}CH$	DCMDA	**8c**/Cu(I)	99:1	92		56
Me	Me	H	Et	**6b**/Cu(I)		>99		57
Me	H	Ph	${}^tBu$	**11c**/Cu(I)	>99:1	73		65
MeO	$H_2C{=}CH$	H	Me	**1** (A = $PhCH_2$)	58:42	61	72	128
MeO	$H_2C{=}CH$	H	Me	**6b**/Cu(I)	55:45	74	>95	129

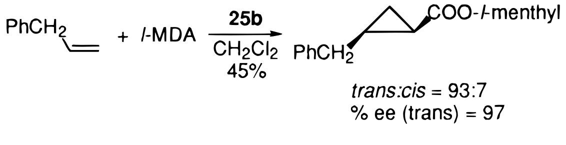
The influence of alkene substituents on enantiocontrol has been determined, and in certain cases there have been surprises (eq 27). For example,



(27)

alkene halogen substituents direct cyclopropanation to the thermodynamically less stable isomer (Table 3), at least with the use of the Aratani salicylaldimine catalyst.[41] Generally, the *trans*-cyclopropane isomer exhibits the higher % ee values with chiral copper catalysts. Reissig and co-workers have examined enantiocontrol in reactions of a broad selection of vinyl ethers with chiral salicylaldimine copper catalysts[128] and with bis-oxazoline copper catalysts;[129] they find that high % ee values with the use of **6b** are limited to 1,1-disubstituted silyl enol ethers.

Diastereocontrol is a major consideration in intermolecular cyclopropanation reactions, and neither the chiral salicyclaldimines, semicorrins, or bis-oxazolines generally offer high selectivity except when bulky diazoacetates (with BHT and DCM) are used (Tables 1 and 2). However, Nishiyama's chiral ruthenium(II) pybox catalyst (**25**) gives high diastereocontrol and high enantiocontrol in reactions with monosubstituted alkenes (eq 28).[91] Higher yields are obtained with substituted styrenes and dienes, both of which are more reactive than unconjugated alkenes toward cyclopropanation with **25**. Kodadek's chiral porphyrin catalysts give unusually high preference for the cis isomer, but % ee values are low.[86,87]



(28)

Chiral dirhodium(II) carboxylate and carboxamidate catalysts are less suitable for intermolecular cyclopropanation reactions than are chiral copper catalysts. The % ee values from the use of chiral dirhodium(II) carboxylate catalysts are exceedingly low,[70,130] and dirhodium(II) carboxamidate catalysts give cyclopropanation products with % ee values less than 90 in reactions with styrene[131] and other substituted alkenes.[37a] With the carboxamidate catalysts, the *cis*-cyclopropane isomer has the higher % ee values. Müller, Doyle, and co-workers have reported a comprehensive analysis of the influence of structure on selectivity for reactions of variously substituted alkenes (eq 27) with diazoacetates using $Rh_2(5S\text{-MEPY})_4$ (**19a**) and $Rh_2(4S\text{-PHOX})_4$ (**20e**) catalysts (Table 4).[78,132] The $Rh_2(4S\text{-PHOX})_4$ catalyst has a preference for the *cis*-cyclopropane isomer in reactions with styrene.

2. Vinyl/Aryldiazoesters

Diazo compounds possessing two carbonyl attachments to the diazo carbon react with most of the chiral catalysts that have been developed, but none provides high enantiocontrol in cyclopropanation reactions. Having significantly developed vinyldiazo chemistry, Davies and co-workers tested their diazo compounds for enantiocontrol in simple cyclopropanation reactions. They chose to use chiral dirhodium(II) prolinate catalysts, originally prepared and developed by M. A. McKervey,[71,133] with vinyldiazoesters and found that use of the prolinate catalysts, especially with a *tert*-butylphenyl substituent to increase solubility in nonpolar solvents, led to high enantio-

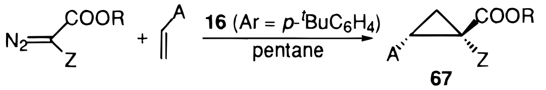
Table 4. Enantiocontrol and Diastereocontrol in the Cyclopropanation of Alkenes by Diazoacetates with Dirhodium(II) Carboxamidate Catalysts[78,132]

				Rh_2(5*S*-MEPY)$_4$			Rh_2(4*S*-PHOX)$_4$		
$N_2CHCOOR$	A	B	D	**66t:66c**	% ee(t)	% ee(c)	**66t:66c**	% ee(t)	% ee(c)
EDA	H	H	Ph	56:44	58	33	34:66	24	57
*t*BDA	H	H	Ph	52:48	56	77	32:68		57
l-MDA	H	H	Ph	52:48	38	80	27:73	40	72
d-MDA	H	H	Ph	57:43	31	88	59:41	4	6
l-MDA	H	H	$H_2C{=}CH$	38:62	72	60	49:51	54	52
EDA	H	H	OAc	52:48	24	60	44:56	50	48
*t*BDA	H	H	PhCOO	63:37	28	78	53:47	76	56
R = Me	Ph	OTMS	H	45:55	30	14	47:53	14	10
R = Me	Me	Me	$Me_2C{=}CH$	49:51	6	20	53:47	16	14

Table 5. Enantiocontrol in the Cyclopropanation of Alkenes by Vinyl- and Aryldiazoesters Catalyzed by Dirhodium(II) Prolinate 16 in Pentane

Z	R	A	temp, °C	**67**, % ee	ref
PhCH=CH	Me	Ph	25	90	134
PhCH=CH	Me	Ph	−78	98	135
PhCH=CH	Me	AcO	25	76	134
PhCH=CH	Me	AcO	−78	95	135
PhCH=CH	Me	EtO	25	59	134
PhCH=CH	Me	EtO	−78	93	135
PhCH=CH	Me	^{n}Bu	25	>90	134
PhCH=CH	Et	Ph	25	84	134
PhCH=CH	^{t}Bu	Ph	25	50	134
Ph	Me	Ph	25	87	136
Ph	Me	EtO	25	66	136
Ph	Me	^{n}Bu	25	77	136

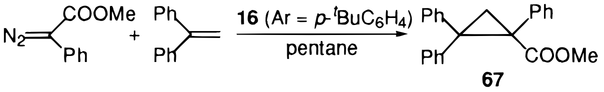
control when the reaction solvent was pentane (eq 29).[134−136] Representative results are given in Table 5. The prolinate catalysts are active toward diazo decomposition at −78 °C, so results obtained at this temperature naturally show enhanced enantiocontrol. Only the (*E*)-cyclopropane isomer is observed from reactions with the *trans*-cinnamyl system, and diastereoselectivity is high even with aryldiazoacetates.



67

(29)

Doyle and McKervey have also examined enantiocontrol for cyclopropanation reactions with phenyldiazoacetate, and they find a similar selectivity enhancement in pentane (e.g., eq 30).[137] More than a 25% increase in enantioselectivity can be seen from changing the reaction solvent from CH_2Cl_2 to pentane. Because this solvent effect is not evident with the rigid dirhodium(II) carboxamidates, and is opposite with the Ikegami/Hashimoto catalyst **17** (R = $PhCH_2$), the conclusion was drawn that, for dirhodium(II) prolinate catalysts, pentane influences the alignment of prolinate ligands on dirhodium(II) to increase enantiocontrol. Although dirhodium(II) carboxamidates are often sluggish in their reactions with substrates such as the phenyldiazoacetates, Rh_2(TBOIM)$_4$ (**21f**) shows promise of being competitive with **16** for high enantiocontrol (addition to styrene: 77% ee vs 85% ee for **16** in pentane).

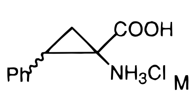


67

97% ee

(30)

Davies has employed this methodology with *trans*-2-diazo-4-phenyl-3-butenoates to construct the four stereoisomers of 2-phenylcyclopropan-1-amino acid (**68**) with high enantiocontrol.[135] Similarly, the asymmetric synthesis of bicyclo[3.2.1]octa-2,6-dienes (**69**) and 1,4-cycloheptadienes (**70**) has been achieved from chiral dirhodium(II) prolinate catalyzed reactions of vinyldiazoacetates with cyclopentadiene and acyclic dienes, respectively.[138] Corey and Grant prepared the antidepressant sertraline using this cyclopropanation methodology (Scheme 8)[139] in high overall yield with organocuprate addition to **71**; enhancement of enantiocontrol was observed to occur when the reaction temperature was 0 °C as opposed to 25 °C originally reported by Davies.[134]



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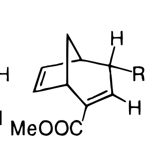
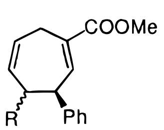


69

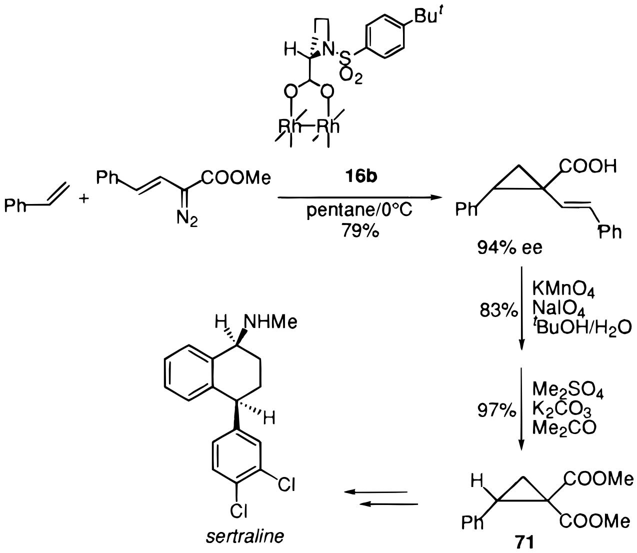
75-91% ee



70

85-90% ee

Scheme 8



B. Intramolecular Cyclopropanation Reactions

Few methodologies have been so effectively optimized for high yield and enantiocontrol as have

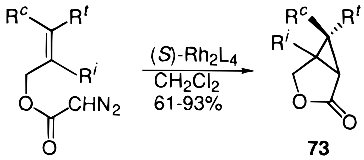
Table 6. Enantiocontrol in Intramolecular Cyclopropanation of Allylic Diazoacetates

R^c	R^t	R^t	(*S*)-Rh_2L_4	% ee (config)	ref
H	H	H	$Rh_2(MEPY)_4$	95 (1*R*,5*S*)	79
CH_3	CH_3	H	$Rh_2(MEPY)_4$	98 (1*S*,5*R*)	79
CH_3	$Me_2C{=}CH(CH_2)_2$	H	$Rh_2(MEPY)_4$	95 (1*S*,5*R*)	79
$Me_2C{=}CH(CH_2)_2$	CH_3	H	$Rh_2(MEPY)_4$	93 (1*S*,5*R*)	79
Ph	H	H	$Rh_2(MEPY)_4$	≥94 (1*R*,5*S*)	79
Et	H	H	$Rh_2(MEPY)_4$	≥94 (1*R*,5*S*)	79
$PhCH_2$	H	H	$Rh_2(MEPY)_4$	≥94 (1*R*,5*S*)	79
^{i}Bu	H	H	$Rh_2(MEPY)_4$	≥94 (1*R*,5*S*)	79
^{i}Pr	H	H	$Rh_2(MEPY)_4$	≥94 (1*R*,5*S*)	79
$(^nBu)_3Sn$	H	H	$Rh_2(MEPY)_4$	≥94 (1*R*,5*S*)	79
I	H	H	$Rh_2(MEPY)_4$	≥94 (1*R*,5*S*)	79
H	H	H	$Rh_2(MEPY)_4$	68 (1*R*,5*S*)	79
H	Ph	H	$Rh_2(MPPIM)_4$	96 (1*R*,5*S*)	119
H	^{n}Pr	H	$Rh_2(MEPY)_4$	85 (1*R*,5*S*)	79
H	^{n}Pr	H	$Rh_2(MPPIM)_4$	95 (1*R*,5*S*)	119
H	I	H	$Rh_2(MEPY)_4$	67 (1*R*,5*S*)	79
H	H	Me	$Rh_2(MEPY)_4$	7 (1*R*,5*S*)	79
H	H	Me	$Rh_2(MPPIM)_4$	89 (1*S*,5*R*)	119
H	H	^{n}Bu	$Rh_2(MEPY)_4$	35 (1*S*,5*R*)	140
H	H	^{n}Bu	$Rh_2(MPPIM)_4$	93 (1*S*,5*R*)	140

intramolecular cyclopropanation reactions. Diazoacetates and diazoacetamides both give ≥93% ee for virtually all allylic systems examined, and their homoallylic counterparts exhibit enantioselectivities that are only moderately less. With few exceptions diazoketones show low enantiocontrol. Recently, intramolecular cyclopropanation onto remote carbon–carbon double bonds has been shown to occur with high enantiocontrol.

1. Diazoacetates: Allylic and Homoallylic

Chiral dirhodium(II) carboxamidates have proven to be the most effective catalysts for highly enantioselective intramolecular cyclopropanation of allylic and homoallylic diazoacetates.[79,119,140–142] Using the $Rh_2(MEPY)_4$ catalysts (**19a**), a broad selection of allylic diazoacetates have been converted to their corresponding bicyclic lactones (eq 31) in high enantiomeric excesses. Trans-substituted allyl diazoacetates give only moderate % ee's with the $Rh_2(MEPY)_4$ catalysts,[141] presumably because of steric interference at the catalyst face,[1] but Rh_2(4*S*-MPPIM)$_4$ (**21d**) increases enantioselectivity to ≥95% ee.[119] With methallyl diazoacetate, % ee values with $Rh_2(MEPY)_4$ or $Rh_2(MEOX)_4$ catalysts are very low, but once again, the Rh_2(4*S*-MPPIM)$_4$ catalyst increases enantiocontrol to respectably high values;[119,140] the absolute configuration of the product is the mirror image of **73**. Representative results are reported in Table 6.



73

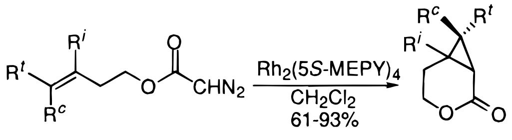
(31)

Table 7. Enatiocontrol in Intramolecular Cyclopropanation of Homoallylic Diazoacetates

R^c	R^t	R^i	(*S*)-Rh_2L_4	% ee (config)	ref
H	H	H	$Rh_2(MEPY)_4$	71 (1*R*,6*S*)	79
CH_3	CH_3	H	$Rh_2(MEPY)_4$	77 (1*S*,6*R*)	79
Ph	H	H	$Rh_2(MEPY)_4$	88 (1*S*,6*R*)	79
Et	H	H	$Rh_2(MEPY)_4$	90 (1*S*,6*R*)	79
c-$C_6H_{11}CH_2$	H	H	$Rh_2(MEPY)_4$	80 (1*S*,6*R*)	79
$PhCH_2$	H	H	$Rh_2(MEPY)_4$	80 (1*S*,6*R*)	79
Me_3Si	H	H	$Rh_2(MEPY)_4$	86 (1*S*,6*R*)	79
H	Ph	H	$Rh_2(MEPY)_4$	73 (1*S*,6*R*)	79
H	E	H	$Rh_2(MEPY)_4$	82 (1*S*,6*R*)	79
H	H	Me	$Rh_2(MEPY)_4$	83 (1*R*,6*S*)	79
H	H	Me	$Rh_2(MPPIM)_4$	78 (1*R*,6*S*)	119

As little as 0.1 mol % of catalyst is effective in these conversions, and scale-up offers no obvious difficulties.[143] Catalyst recovery can be achieved, but optimization of this operation has not yet been reported. Although Cu(I)/bis-oxazoline **6b** provides 87% ee for the cyclopropanation of methallyl diazoacetate, this catalyst system is relatively ineffective with other allylic diazoacetates.[140] Similarly, Nishiyama's Ru(II)/Pybox catalyst **25b** provides 78–86% ee with trans-substituted diazoacetates, but low enantiocontrol is found with cis-substituted diazoacetates; methallyl diazoacetate does not undergo intramolecular cyclopropanation with this chiral catalyst.[140] A detailed account of these differences and rationale for their occurrence have been reported.[1,140]

Homoallylic diazoacetates also undergo intramolecular cyclopropanation in high yield (eq 32) and, using the $Rh_2(MEPY)_4$ catalysts, with 71–90% ee (Table 7).[79,142] Here enantiocontrol is reduced relative to their allylic counterparts, but R^t and R^i substituents do not have as profound an influence on % ee values using $Rh_2(MEPY)_4$ catalysts. Fewer evaluations of factors that control selectivity have been performed with homoallylic than with allylic diazoacetates, and further improvements in enantiocontrol can be expected.

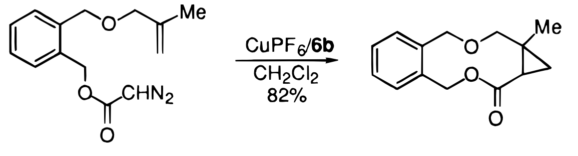


74

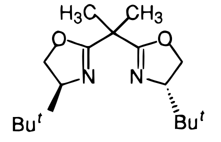
(32)

2. Diazoacetates: Macrocyclization

Doyle and co-workers have reported that high enantiocontrol can be achieved in intramolecular cyclopropanation reactions to remote carbon–carbon double bonds.[144] With the methallyl diazoacetate linked through a 1,2-benzenedimethanol (**75**), CuPF$_6$/**6b** caused macrocyclization to occur in high yield and with 90% ee (eq 33). By using Rh$_2$(5*S*-MEPY)$_4$, which for methallyl diazoacetate resulted in **73** (R^i = Me, R^t = R^c = H) with only 7% ee (Table 6), diazo decomposition of **75** produced **76** with 47% ee (77% yield). Use of CuPF$_6$/**6b** results in higher selectivity for macrocyclization and higher enantiocontrol than is found with chiral dirhodium(II) carboxamidate catalysts. With the (*Z*)-2-buten-1,4-diyl diazoacetate derivative **77**, for which both near and remote cyclopropanation are possible, CuPF$_6$/**6b** preferentially catalyzed formation of the macrocyclic product **78** (Scheme 9), whereas Rh$_2$(5*S*-MEPY)$_4$ produced **79** exclusively. The saturated analogue of **77** also underwent macrocyclization with CuPF$_6$/**6b** (43% yield, 91% ee). The influence of catalyst on regiocontrol in intermolecular cyclopropanation of **77** is consistent with the electrophilicity of the catalyst, CuPF$_6$/**6b** being more reactive in this regard than Rh$_2$(5*S*-MEPY)$_4$.[145,146] A detailed explanation for this regioselectivity has been provided.[1,146]

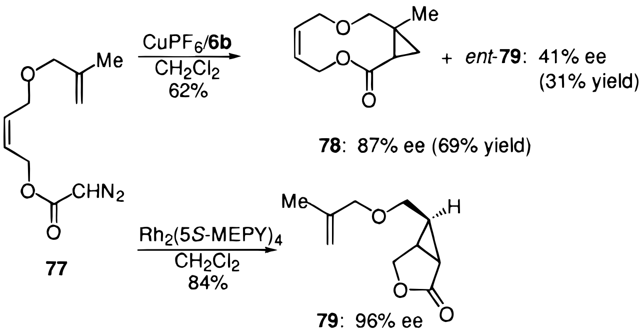


75 **76**: 90% ee (33)



6b

Scheme 9

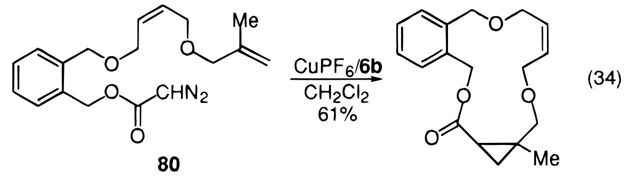


78: 87% ee (69% yield)

77

79: 96% ee

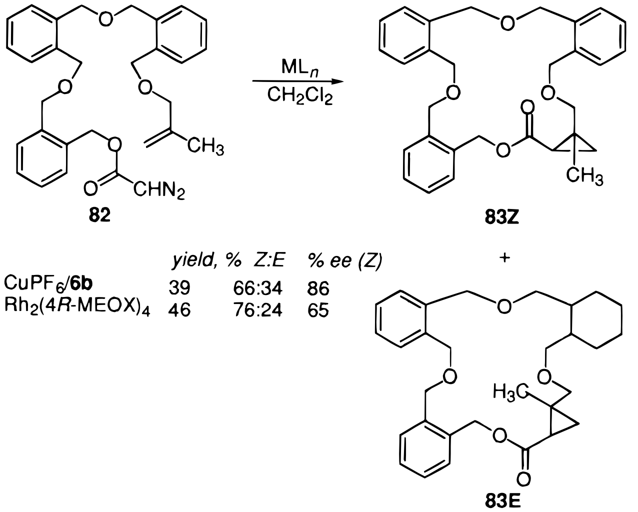
Extension of this methodology to the formation of larger rings has shown relatively constant enantiocontrol with methallyl systems using CuPF$_6$/**6b**. With **80**, for example, application of CuPF$_6$/**6b** produced the (*Z*)-cyclopropane isomer **81** as virtually the sole product in 90% ee (eq 34).[144] Regiocontrol was ≥50:1 for addition to the terminal double bond rather than to the internal double bond. The only other product, formed in <3% yield, was that from ylide formation followed by sigmatropic rearrangement (vide infra). Use of Rh$_2$(4*S*-MEOX)$_4$ resulted in the formation of the product from addition to the internal double bond.[147] With **82** both (*E*)- and (*Z*)-cyclopropane isomers, **83E** and **83Z**, were formed, and the % ee of the *Z*-isomer was 86% with CuPF$_6$/**6b** and 65% with Rh$_2$(4*R*-MEOX)$_4$ (Scheme 10).[148] The % ee values for reactions catalyzed by CuPF$_6$/**6b** remain constant as a function of macrocycle ring size, but those for Rh$_2$(MEOX)$_4$-catalyzed reactions increase with increasing macrocycle ring size.



(34)

80 **81**: 90% ee

Scheme 10

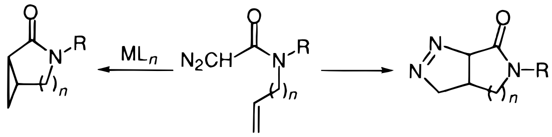


82 **83Z** **83E**

	yield, %	*Z:E*	*% ee (Z)*
CuPF$_6$/**6b**	39	66:34	86
Rh$_2$(4*R*-MEOX)$_4$	46	76:24	65

3. Diazoacetamides

Catalytic decomposition of diazoacetamides occurs in competition with uncatalyzed intramolecular dipolar cycloaddition (eq 35).[149] Cyclopropanation is favored when R is a relatively small substituent (e.g., H, Me) or when $n \geq 2$.[150] Here conformational influences (eq 36) play a significant role in determining the effectiveness of catalytic diazo decomposition in achieving intramolecular cyclopropanation. There is only one example of an intramolecular cyclopropanation when R = H (*N*-allyldiazoacetamide) and although enantiocontrol is exceptional using Rh$_2$(4*S*-MEOX)$_4$ (98% ee), product yield is low (40%).[79] With the *N*-methyl analogue, use of Rh$_2$(5*S*-MEPY)$_4$ re-



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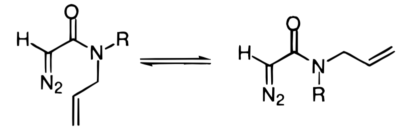
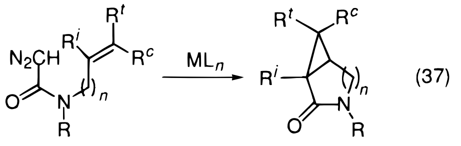


(36)

Table 8. Enantiocontrol in Intramolecular Cyclopropanation of *N*-Allylic- and *N*-Homallylic Diazoacetamides

R	R^c	R^t	R^i	(*S*)-Rh_2L_4	% ee (config)	ref
H	H	H	H	$Rh_2(MEOX)_4$	98 (1*S*,2*S*)	79
$H_2C{=}CHCH_2$	H	H	H	$Rh_2(MEPY)_4$	72 (1*R*,5*S*)	149
Me	H	H	H	$Rh_2(MEPY)_4$	93 (1*R*,5*S*)	150
Me	Me	Me	H	$Rh_2(MPPIM)_4$	94 (1*S*,5*R*)	150
Me	^{n}Pr	H	H	$Rh_2(MPPIM)_4$	95 (1*R*,5*S*)	150
Me	H	^{n}Pr	H	$Rh_2(MPPIM)_4$	92 (1*R*,5*S*)	150
Me	Me	$Me_2CH(CH_2)_2$	H	$Rh_2(MPPIM)_4$	93 (1*R*,5*S*)	150
Et	H	H	Me	$Rh_2(MACIM)_4$	48 (1*S*,5*R*)	150
^{t}Bu	H	H	H	$Rh_2(MEOX)_4$	65	149
^{t}Bu	Me	Me	H	$Rh_2(MEPY)_4$	75	149
^{t}Bu	Et	H	H	$Rh_2(MEPY)_4$	90	149
^{t}Bu	H	Et	H	$Rh_2(MEPY)_4$	67	149
^{t}Bu	H	H	Me	$Rh_2(MEPY)_4$	78	149

sulted in the highest enantiocontrol (93% ee) and isolated yield (62%).[150] Results obtained from a representative series of allylic and homoallylic systems (eq 37) are reported in Table 8.



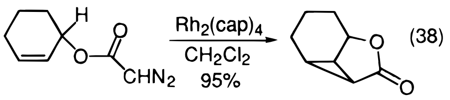
(37)

84 **85**

Enantioselectivities parallel those found with diazoacetates, and isolated yields are generally high. However, minor amounts of byproducts, either from stepwise electrophilic addition to the carbon−carbon double bond[150] or from C−H insertion,[149] can complicate the reaction process. For those results presented in Table 8 these byproducts are unimportant.

4. Enantiomer Differentiation

When racemic allylic diazoacetate **86** was treated with $Rh_2(cap)_4$, racemic tricyclic cyclopropane **87** was formed as the sole reaction product in high yield (eq 38).[151] However, when this same reaction was per-

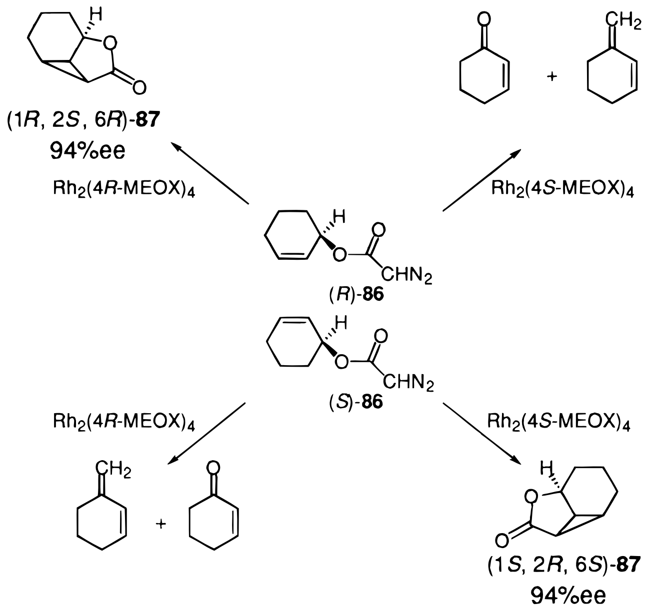


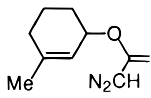
(38)

86 **87**

formed with Rh_2(4*S*-MEOX)$_4$, **87** was formed in 40% yield, after isolation and purification, and with 94% ee; the residual products were 2-cyclohexenone and methylene-2-cyclohexene, the sum of which accounted for the complete conversion of **86** to products. The absolute configuration of the product formed from Rh_2(4*S*-MEOX)$_4$ was (1*S*,2*R*,6*S*)-**87**, which signified that (*S*)-**86** was converted by Rh_2(4*S*-MEOX)$_4$ to (1*S*,2*R*,9*S*)-**87**, whereas (*R*)-**86**, a mismatch of substrate and catalyst configurations, formed 2-cyclohexenone and methylene-2-cyclohexene. The opposite reactant configurations formed the matched and mismatched pairs with Rh_2(4*R*-MEOX)$_4$ (Scheme 11).[151] Similar enantiomer differentiation occurred with methyl-substituted 2-cyclohexen-1-yl diazoacetates (**88** and **89**) and with 2-cyclopenten-1-yl diazoacetate (**90**), all with 95% ee for the tricyclic cyclopropane product. 2-Cyclohexenone and its methylenecyclohexene counterpart were produced by hydride abstraction from the allylic C−H bond by the intermediate metal carbene;[152] similar products were produced from diazo decomposition of **88**−**90**. *β*-Lactone product was not observed in these cases.

Scheme 11





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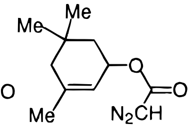

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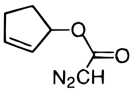
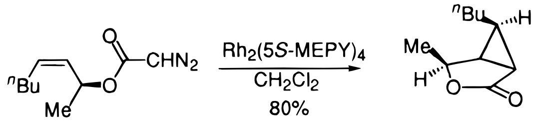


90

Martin and co-workers previously demonstrated that there was a diastereoselective match/mismatch between chiral 2° allylic diazoacetates and chiral Rh_2(MEPY)$_4$ catalysts.[153] Thus, for example, treatment of diazoacetate **91** with Rh_2(5*S*-MEPY)$_4$ produced the endo cyclopropanation product **92** in >20:1 diastereomeric ratio and 80% yield (eq 39). Using Rh_2(5*R*-MEPY)$_4$ **91** was converted to **92** with an endo:exo ratio of 1.0:1.5 but in only 39% yield; this is obviously the mismatch. The trans isomer of **91** also underwent diastereoselective intramolecular cyclopropanation but with a dr of only 6:1 with Rh_2(5*S*-MEPY)$_4$

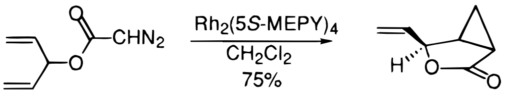


91 ***endo*-92**

> 20:1 dr

(39)

(77% yield). The same catalyst converted prochiral divinyl **93** to **94** in ≥94% ee and with dr > 20:1 (eq 40).



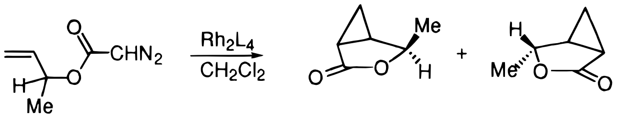
93 **94**

≥ 94%ee

> 20:1 dr

(40)

Starting with racemic secondary diazoacetate **95** and chiral dirhodium(II) carboxamidate catalyst, cyclopropanation products *endo*-**96** and *exo*-**96** were formed in unequal amounts, moderate to high % ee, and good yield (eq 41).[151] Other examples showed similar results. The large difference in enantiocontrol between Rh$_2$(5*S*-MEPY)$_4$ and Rh$_2$(4*S*-MEOX)$_4$ has not been explained.



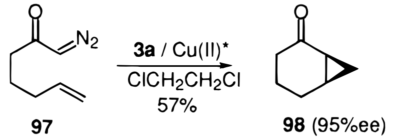
95

	***endo*-96**	***exo*-96**
Rh$_2$(5*S*-MEPY)$_4$	83(31%ee)	17(84%ee)
Rh$_2$(4*S*-MEOX)$_4$	70(70%ee)	30(30%ee)

(41)

5. Diazoketones and Vinyldiazo Compounds

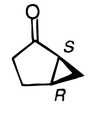
Relative to diazoesters and diazoamides, diazoketones give low levels of enantiocontrol in intramolecular cyclopropanation reactions. However, since the early reports of asymmetric diazoketone cyclization (eq 3), some advances in enantiocontrol and understanding of enantioselectivity have been achieved. Pfaltz has reported that semicorrin **3a**/copper(II) catalyzed the intramolecular cyclopropanation reaction of **97** to **98** in as high as 95% ee (eq 42).[154a] Azasemicorrin **4a** gave similar enantiocontrol, but with bis-oxazoline **5f**/CuOTf, enantioselectivity was only 77%. Extension to other diazoketones with **3a**/Cu(II) showed variable levels of enantiocontrol (**99**−**101**), and no pattern is seen to emerge. In an effort to provide asymmetric intramolecular cyclopropanation leading to the synthesis of the phorbol CD-ring skeleton, Shibasaki and co-workers investigated the bis-oxazoline ligand's influence in diazoketone addition to a silyl enol ether; [154b] up to 92% ee was achieved using CuOTf/**6** (R = CMe$_2$OSiMe$_3$). Doyle and co-workers have found uniformly low enantioselectivities in reactions catalyzed by chiral dirhodium(II) carboxamidates, and they have explained this observation by the conformational alignment of the metal carbene, which is opposite to that found in reactions involving diazoesters and diazoamides.[155]



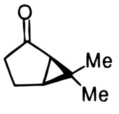
97 **98** (95%ee)

* activated by reduction with PhNHNH$_2$

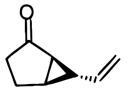
(42)



99 (75%ee)

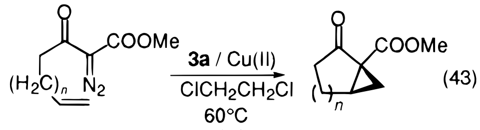


100 (85%ee)



101 (24%ee)

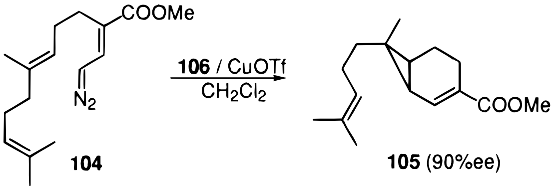
Pfaltz also reported that diazo compounds **102** could cause intramolecular cyclopropanation with **3a**/Cu(II), but enantiocontrol was only 35−40% ee (eq 43).[154] Diazo decomposition of **102** required higher temperatures than for **97** or even diazoesters, but chiral dirhodium(II) carboxamidates were inactive toward **102** even in refluxing dichloroethane. Hassila and Koskinen confirmed these results with the benzyl analogue of **3a** using *tert*-butyl allyl diazomalonate.[156]



102 (*n* = 1,2) **103** (35-40%ee)

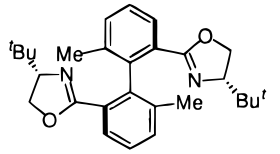
(43)

Corey has recently reapproached the synthesis of sirenin using the diazo decomposition methodology (eq 44).[157] For this synthesis, he designed a new chiral ligand for copper (**106**) that carried with it the binding capabilities of bis-oxazolines linked through a biphenyl. Neither the Doyle nor the classic bis-oxazoline catalysts gave enantioselectivities that could approach that achieved with **106**/Cu(I)OTf for this transformation. Further examples of the use of this catalyst have not yet been reported.



104 **105** (90%ee)

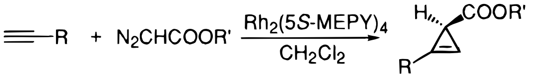
(44)



106

VI. Asymmetric Cyclopropenation Reactions

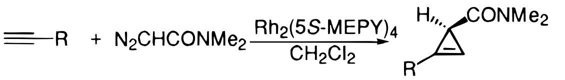
The synthesis of cyclopropenes by metal carbene addition to alkynes occurs under mild conditions with Rh$_2$(OAc)$_4$ catalysis[158] and with diazoesters 3-cyclopropenecarboxylates formed in this process are stable. Addition to 1,3-enynes occurs exclusively at the carbon−carbon triple bond in cases that have been examined, but the resulting vinylcyclopropene products are unstable.[159] Chiral $Rh_2(MEPY)_4$ catalysts have proven to be exceptional in effecting enantiocontrolled synthesis of cyclopropene compounds from diazoacetates (eq 45).[160] Diastereocontrol is particularly high with menthyl diazoacetates, where with *l*-MDA diastereodifferentiation is ≥97:3 when R = CH_2OMe and is 93:7 dr when R = Bu^n with the use of $Rh_2(5S\text{-}MEPY)_4$. Using *d*-MDA and $Rh_2(5S\text{-}MEPY)_4$, however, there is a "mismatch" and dr values of only 70:30 are obtained.



(45)

R =	R'	*yield*, %	%ee
$CH(OEt)_2$	Me	42	>98
CH_2OMe	Me	73	69
Bu^n	Et	70	54
Bu^t	Et	85	57

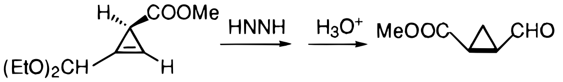
A substantial increase in enantiocontrol is obtained with *N*,*N*-dimethyldiazoacetamide (eq 46). Diazoamides are less reactive and more selective in their catalytic reactions. With *N*-alkyl groups other than methyl C−H insertion reactions become competitive.[1]



(46)

R =	*yield*, %	%ee
CH_2OMe	22	>94
Bu^n	49	78
Bu^t	47	89

One of the benefits of these cyclopropenation reactions is that further reduction by diimide or catalytic hydrogenation produces the cis-disubstituted product (e.g., eq 47). This methodology is highly effective for the formation of those products that are generally the minor components of catalytic cyclopropanation processes. Other cyclopropanation catalysts have not proven to be effective, but further results are required to ascertain the best catalyst for cyclopropenation.

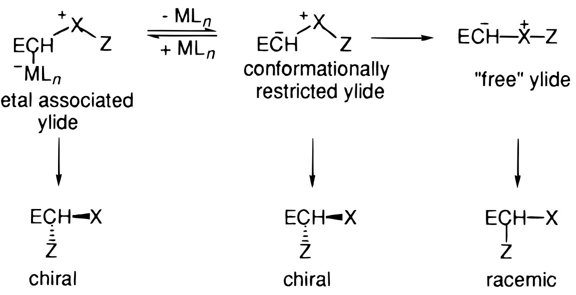


(47)

VII. Asymmetric Ylide Reactions

The availability of new chiral catalysts for diazo decomposition of diazoesters and diazoketones has provided an opportunity to examine their potential for asymmetric catalytic ylide generation and subsequent transformations. Catalytic entry to a nitrogen, oxygen, or sulfur ylide occurs by association of an electrophilic metal carbene with an amine, ether, or sulfide, acting as a Lewis base, followed by dissociation of the ligated metal.[1,10,161] The generation and subsequent transformation of ylides are complex, especially when considering the reaction pathways available for metal carbene transformations. The most critical event is a reversible association of the metal carbene with the heteroatom, and association of the chiral metal catalyst with the ylide is necessary for asymmetric catalysis. Asymmetric induction in ylide transformations can occur if the metal with its chiral ligands remains attached during ylide reaction or if the free ylide formed by metal dissociation retains its chiral conformation during that ylide-derived transformation (Scheme 12). When relaxation of the conformationally restricted ylide is faster than product formation, no asymmetric induction occurs and racemic product results. The most common reactions of catalytically generated ylides include [2,3]-sigmatropic rearrangements, Stevens rearrangements, and dipolar cycloadditions.[162, 163]

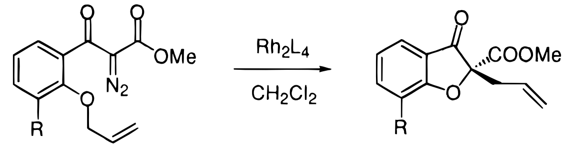
Scheme 12



A. [2,3]-Sigmatropic Rearrangement

Asymmetric diazo decomposition to afford chiral nonracemic [2,3]-sigmatropic rearrangement products by formation of oxonium ylides was first reported by McKervey and McCann (Scheme 13).[164] In the presence of catalytic quantities of homochiral dirhodium(II) carboxylate $Rh_2(S\text{-}BNHP)_2{\cdot}(HCO_3)_2$, where *S*-BNHP (**23**) represents (*S*)-(+)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate, diazoketoester **107** (R = CH_3) afforded furanone **108** in 92% yield and 30% ee. An extensive study reported % ee values for this transformation from the use of eight new chiral dirhodium(II) catalysts.[164b] That derived from *N*-phthaloyl-(*S*)-*tert*-leucinate (**109**) gave the highest enantiocontrol (60% ee). Higher enantiomeric excesses (by 13%) were observed in hexane than in CH_2Cl_2.

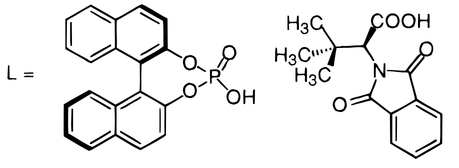
Scheme 13



107 **108**

L = **23** R = CH_3 92% (30%ee)

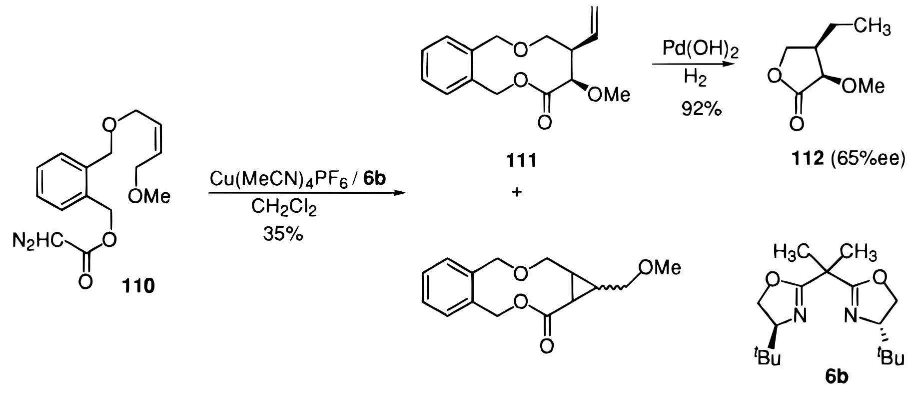
L = **109** R = H 96% (60%ee)



23 **109**

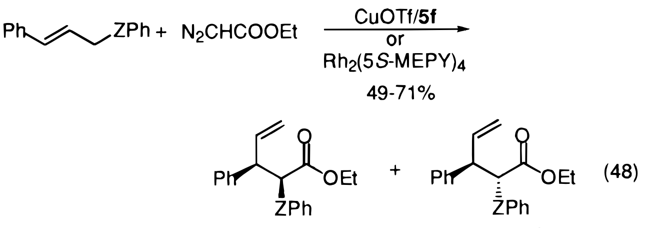
Doyle and co-workers have recently achieved enantiocontrol in intramolecular ylide formation and subsequent [2,3]-sigmatropic rearrangement from macrocyclic templates (Scheme 14).[147] Treatment of

Scheme 14

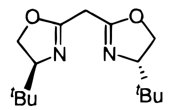


diazoester **110** in the presence of $Cu(CH_3CN)_4PF_6$/bis-oxazoline complex **6b** formed a 13-membered ring oxonium ylide. Products derived both from cyclopropanation and rearrangement (**111**) were observed with high chemoselectivity for ylide-derived product (8:1) in moderate yield. Hydrogenolysis of macrocycle **111** afforded lactone **112** in high yield (65% ee) and confirmed the *cis*-geometry of the macrocyclic product. Unfortunately, dirhodium(II) catalysis resulted in minimal amounts of product formation.

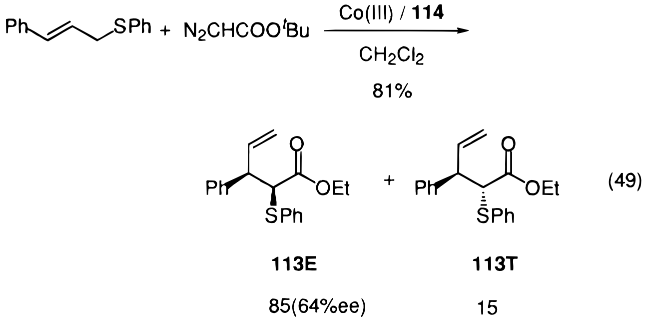
Asymmetric reactions of metal carbenes with heteroatoms containing two or more lone pairs have recently been investigated.[165] Uemura and co-workers were the first to communicate that either chiral copper(I)/bis-oxazoline **5f** or $Rh_2(5S\text{-MEPY})_4$ catalyzed intermolecular generation of sulfonium or selenonium ylide and subsequent [2,3]-sigmatropic rearrangement.[166] Treatment of ethyl diazaoacetate with either *trans*-cinnamyl phenyl sulfide or selenide in the presence of 5 mol % chiral catalyst afforded products **113** in yields ranging from 35 to 68% (diastereomeric ratio < 2:1) and enantioselectivities varying from 6 to 41% (eq 48). Katsuki found up to 64% ee with a similar system using a chiral cobalt(III)–salen catalyst (**114**).[167] Diazo decomposition of *tert*-butyl diazoacetate provided a higher level of diastereocontrol (85:15) and 81% conversion to the [2,3]-sigmatropic rearrangement product (eq 49). Interestingly, these catalysts and those bearing substituents at C-3 and C-3′ positions of the ligand aryl groups showed no catalytic activity toward asymmetric cyclopropanation.

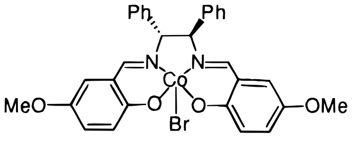


		113E	113T
Rh(II)	Z = S	60(18%ee)	40(17%ee)
Cu(I)	Z = S	65(20%ee)	35(14%ee)
Rh(II)	Z = Se	58(25%ee)	42(41%ee)
Cu(I)	Z = Se	66(22%ee)	34(32%ee)



5f

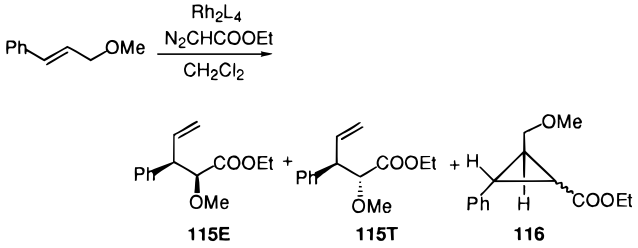




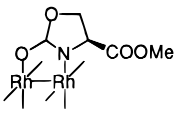
114

Doyle and co-workers have recently examined the role of the metal catalyst in asymmetric oxygen ylide formation. Allylic oxonium ylides, generated by dirhodium(II) acetate catalyzed decomposition of ethyl diazoacetate in the presence of *trans*-cinnamyl methyl ether, undergo [2,3]-sigmatropic rearrangement (92% yield) with a high degree of diastereocontrol, the erythro isomer predominating.[168] Analysis of product distribution revealed the rearrangement-to-cyclopropane ratio being 73:27 (eq 50). However, with $Rh_2(4S\text{-MEOX})_4$ and $Rh_2(4S\text{-MEOX})_4$, diastereoselectivity is reversed (**115E**:**115T** = 15:85), competition from cyclopropanation is diminished (**115**:**116** = 89:11 with **20a**), and each of the ylide-derived diastereomers is formed with exceptionally high enantiocontrol. Isolated yields were 36% and 35%, respectively. Intermediate selectivities and yields were found with other chiral dirhodium(II) catalysts and copper(I) complexes. When unsubstituted dirhodium(II) carboxamidate $Rh_2(cap)_4$ was tested, the level of diastereocontrol matched that from $Rh_2(OAc)_4$ and not carboxamidate-ligated $Rh_2(MEOX)_4$ which further supports the influence of the catalyst ligand in these transformations.[169]

The most compelling evidence for metal association in asymmetric ylide-derived transformations has been reported by Doyle and co-workers through the



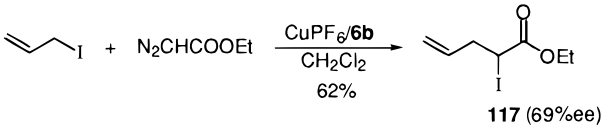
	115E	115T	116
Rh$_2$(OAc)$_4$	83	17	(50)
Rh$_2$(4*S*-MEOX)$_4$ (**20a**)	15 (94% ee)	85 (98% ee)	
Rh$_2$(4*R*-MEOX)$_4$	15 (94% ee)	85 (98% ee)	



20a

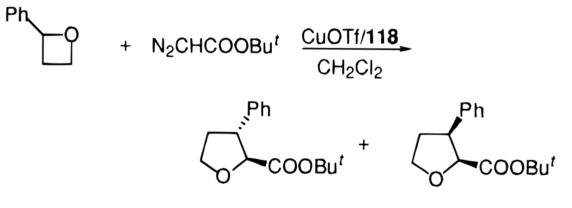
use of allyl halides as achiral intermediates in [2,3]-sigmatropic rearrangements (Scheme 15). Treatment of ethyl diazoacetate with an exess of allyl iodide in the presence of catalytic quantities of CuPF$_6$/**6b** furnished iodo ester **117** in 62% isolated yield and 69% ee. Using Rh$_2$(4*S*-MEOX)$_4$, **117** was formed with 39% ee but only in 20% yield. The only other products were those from carbene dimer formation. At least to the extent of up to 69%, the existence of a metal-associated iodonium ylide and not a free ylide, which is achiral by virtue of the lone pairs, is proposed.

Scheme 15

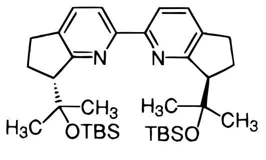


B. Stevens Rearrangement

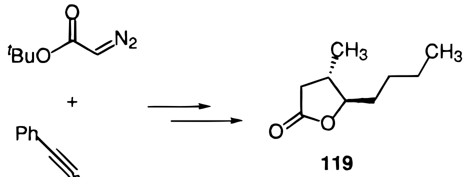
The Stevens rearrangement ([1,2]-insertion), although defined as a stereoelectronically disfavored transformation,[170] has been used in several systems to provide ring expansion products with high levels of enantiocontrol. One of the most important examples of a highly effective [1,2]-insertion process has resulted from the work of Katsuki and Ito, following much earlier results from Nozaki and co-workers, [171] who reported high stereocontrol in reactions of racemic as well as both epimers of 2-phenyloxetane with *tert*-butyl diazoacetate using 1.0 mol % chiral copper(I) complexes (eq 51).[172] The oxonium ylide undergoes rearrangement with preferential retention of configuration. This methodology was next applied to the enantioselective synthesis of *trans*-whisky lactone **119** via enantiospecific ring expansion of the parent oxetane.[173] Key in their synthetic sequence was treatment of chiral racemic oxetane with *tert*-butyl diazoacetate in the presence of the CuOTf/**118** complex to afford the desired tetrahydrofuran in 88% yield (75% ee).



(±) - (36% yield)	59(75%ee)	41(81%ee)	(51)
(*R*) - (89% yield)	89(92%ee)	11(16%ee)	
(*S*) - (85% yield)	25(11%ee)	75(93%ee)	



118

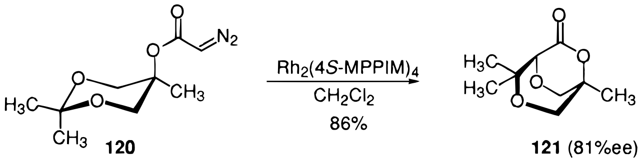


119

trans-whiskey lactone

Doyle and co-workers have taken an alternative approach to those previously used to achieve enantioselection by employing symmetrical 1,3-dioxan-5-yl diazoacetates wherein diastereotopic association of the metal carbene at one of the two oxygens is the source of enantiocontrol (Scheme 16).[174] Diazo decomposition of 2,2,5-trimethyl-1,3-dioxolan-5-yl diazoacetate (**120**) catalyzed by Rh$_2$(4*S*-MPPIM)$_4$ gave the ylide-derived product **121** virtually exclusively in high yield and in 81% ee. Product formation through carbon−hydrogen insertion was competitive in related systems (conformational control) but was observed only in trace amounts in reactions with **120**.

Scheme 16

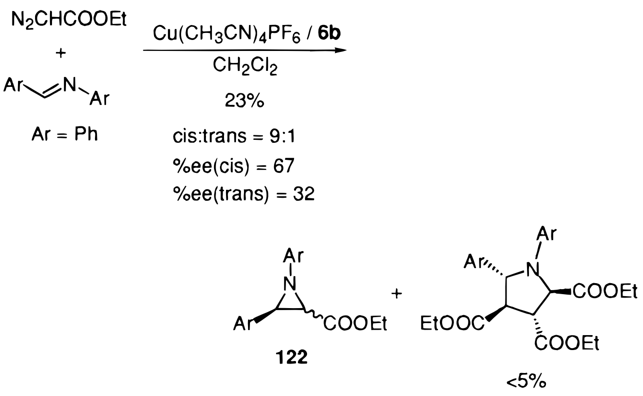


C. Cycloaddition Reactions

1. Azomethine Ylides

In each of the cases cited above involving organochalcogens, the asymmetric transformation could have arisen from the free ylide after dissociation of the metal but before configurational inversion at the onium center. Jacobsen and co-workers have reported asymmetric induction up to 67% ee in aziridine formation (**122**) from benzylidineimines and ethyl diazoacetate catalyzed by chiral copper(I) bisoxazoline complexes (Scheme 17).[175] The product

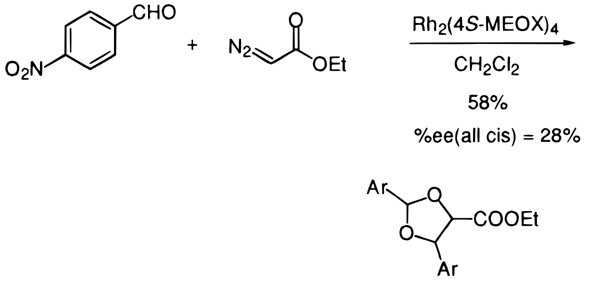
Scheme 17



distribution and selectivity observed demonstrated for the first time that reaction occurred through a metal-associated ylide rather than the free ylide. Aziridination was found to be very sensitive to the electronic properties of the reactant imines, electron-deficient *N*-substituted imines resulting in pyrrolidine formation by way of cycloaddition of the metal-free azomethine ylide with ethyl fumarate.

2. Carbonyl Ylides

The generation of carbonyl ylides and their cycloaddition reactions has received considerable attention due their use in the construction of highly complex polycycles, but until recently, there has been no report of asymmetric induction in a catalytic carbonyl ylide transformation.[1] Doyle and co-workers have recently obtained preliminary data that are promising (eq 52). Treatment of *p*-nitrobenzaldehyde



(52)

123 (Ar = *p*-$NO_2C_6H_4$)

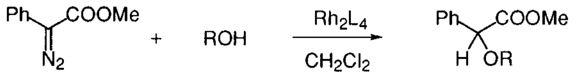
with ethyl diazoacetate gave rise to four 1,3-dioxolane diastereomers **123**, whose relative composition was catalyst-dependent.[176] Reactions that occurred with both Rh_2(4*S*-MEOX)$_4$ and Rh_2(4*R*-MEOX)$_4$ resulted in the all-cis 1,3-dioxolane as the major product (55% all-cis of 58% yield for isolated dioxolanes) and a level of enantiocontrol of 28% ee. Analysis of other chiral dirhodium(II) carboxamidates revealed catalyst ligand influence in both product distribution and enantiocontrol.[169]

3. Sulfur Ylides

An alternative strategy toward the production of chiral products through asymmetric catalytic metal carbenes would be to take advantage of transient ylides within the catalytic cycle itself.[177] Although transfer of chirality was not provided by metal-based catalysts, Aggarwal and co-workers have developed a system which focused on the transfer of chirality by way of chiral sulfur ylides which are employed in catalytic quantities (Scheme 18).[178] A series of epoxides and aziridines have been successfully synthesized using this methodology in excellent yields and in high enantiocontrol. Treatment of phenyldiazomethane with either an aryl aldehyde or SES-substituted aryl imine (SES = β-(trimethylsilyl)ethanesulfonyl)) in the presence of catalytic quantities of both chiral sulfide (20 mol %) and dirhodium(II) acetate (1.0 mol %) afforded the desired cyclized adducts in yields ranging from 64 to 73% for the epoxide and from 44 to 88% for the aziridine. In both series, the trans isomer predominated (96% for epoxidation, 50% for aziridination).

D. X–H Insertion Reactions

In contrast to metal-catalyzed carbene insertions into C–H or Si–H bonds, which are concerted, insertion into polar X–H (X = O, S) bonds has been proposed to occur via a stepwise process which begins with attack of the heteroatom on the electrophilic carbene, ylide formation, and then hydrogen transfer. Exact details, concerted or stepwise, in the transformation remain speculative.[179] However, attempts by Moody and co-workers to induce asymmetry in O–H insertion reactions have been unsuccessful (eq 53).[180] Brunner and co-workers demonstrated that chiral catalysts could affect asymmetry in the S–H insertion reaction of 3-diazo-2-butanone with thiophenol, where up to 12% ee was observed.[181]

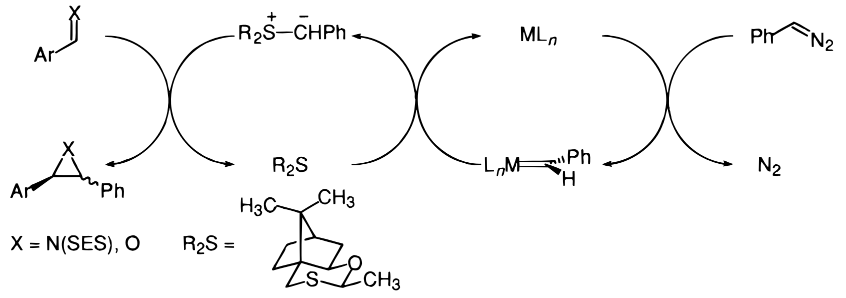


(53)

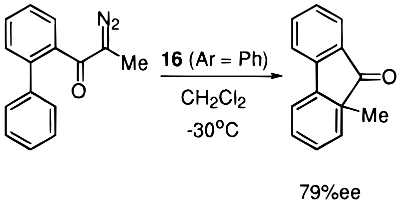
VIII. Conclusions

This review provides a detailed summary of enantiocontrolled sytheses in the major classes of metal

Scheme 18



carbene transformations. We may have overlooked some relevant results, and if so, we apologize. Certain results, because of their unique charatcteristics, including McKervey's highly enantioselective aromatic cycloaddition reactions (e.g., eq 54)[1] and Pirrung's asymmetric dipolar cycloaddition reactions (e.g., eq 55),[84] were not previously described because of the limited information available about their general applicability. However, the overall treatment in this review provides the current state-of-the-art.



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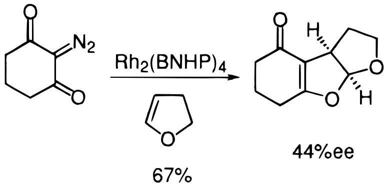

(55)

The accomplishments achieved thus far in asymmetric catalytic metal carbene transformations are impressive, but they are by no means complete. High enantiocontrol is characteristic of reactions with diazoacetates and diazoacetamides, but not diazo ketones or diazo ketoesters. Here, there is need for significant improvemnts, each system requiring a different catalyst design. Furthermore, intermolecular reactions, even with ethyl diazoacetate, are appropriately selective in only a few cases. Cyclopropanation via diazomethane or its equivalent ($TMSCHN_2$) has not received adequate attention, and here again, new asymmetric catalysts are required. Although these transformations are among the oldest to be examined with the use of homogeneous asymmetric catalysts, they still provide opportunity for the insightful investigator.

IX. Acknowledgments

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X. References

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