Pergamon

Tetrahedron 54 (1998) 7919–7946

TETRAHEDRON

Tetrahedron report number 457

New Aspects of Catalytic Asymmetric Cyclopropanation

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Received 4 November 1997

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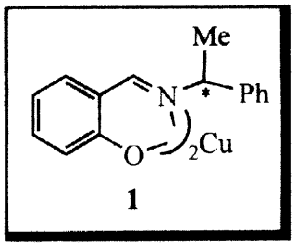
I. Introduction

In 1966 Nozaki, Moriuti, Takaya, and Noyori reported the first enantiocontrolled catalytic intermolecular cyclopropanation reaction.[1] Using a salicylaldimine ligand for copper(II) that possessed a pendant 1-phenethylimine (**1**), 6% enantiomeric excess was obtained in the major product from cyclopropanation of (eq 1) with ethyl diazoacetate (EDA). This was the first reported use of a chiral catalyst



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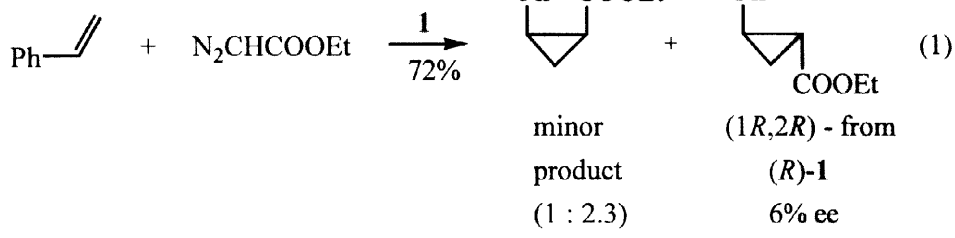

(1)

minor product (1 : 2.3)

(1*R*,2*R*) - from (*R*)-**1** 6% ee

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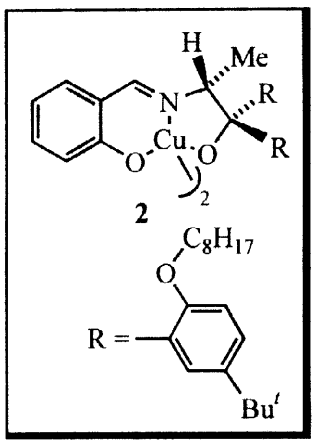
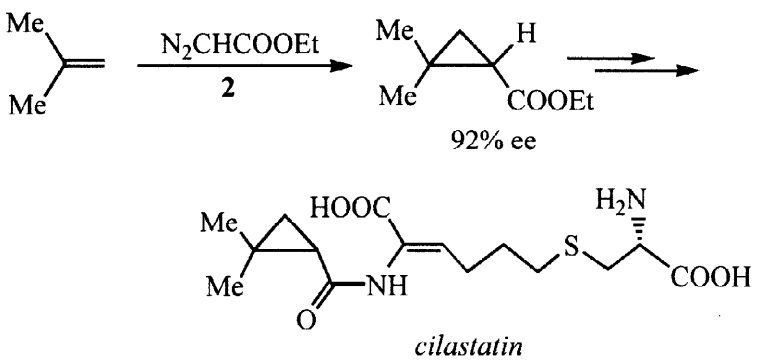
PII: S0040-4020(98)00222-1

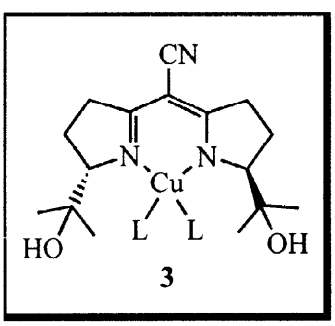
to induce enantiocontrol in a chemical reaction and, although low % ee values were found, this communication, as part of a series,[1-3] initiated further activities that resulted in the development of the elaborated salicylaldimines of Aratani (**2**), a student of Nozaki, whose catalyst applications at Sumitomo[4-6] culminated in the highly enantioselective synthesis of ethyl 2,2-dimethoxycyclopropanecarboxylate (eq 2) that was incorporated into the commercial production (with Merck) of cilastatin.[7]

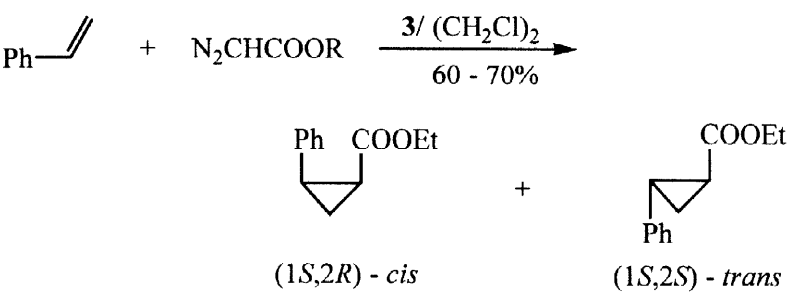




(2)

The next major advance in chiral catalyst design was the contribution of chiral semicorrin ligands (**3**) for copper by Pfaltz.[8] These catalysts were found to provide even greater enantiocontrol for cyclopropanation of monosubstituted olefins (eq 3)[9,10] than did the Aratani catalysts, but, unlike the Aratani





(3)

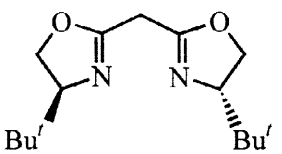
		% ee (cis)	trans : cis	% ee (trans)
R =	Et	80	73 : 27	92
	Bu^t	92	81 : 19	93
	d-menthyl	95	82 : 18	97
	l-menthyl	90	85 : 15	91
with (*R*)-**2**:	*l*-menthyl	54	86 : 14	69
with (*S*)-**2**:	*d*-menthyl	78 (1*R*,2*S*)	84 : 16	81 (1*R*,2*R*)

catalysts, their effectiveness was low with 1,2-disubstituted alkenes or trisubstituted alkenes, presumably for steric reasons.[11] In the course of these investigations, copper(I) was found to be the catalytically active oxidation state, and the catalyst was understood to possess only one, and not two, chiral semicorrin ligands.[10]

The copper(I) oxidation state could be reached directly by reduction of Cu(II)L_2 by the diazo compound or, alternatively, by treatment of the semicorrin-copper(II) precatalyst with phenylhydrazine (eq 4).

$$\text{Cu(I)L*} \xleftarrow{\text{PhNHNH}_2} \text{Cu(II)L}_2\text{*} \xrightarrow{\text{R}_2\text{C=N}_2} \text{Cu(I)L*} \qquad (4)$$

With the advantages of semicorrin ligands for copper firmly established, Masamune,[12] Evans,[13] and Pfaltz[14] independently reported applications using chiral bis-oxazoline ligands (**4-6**), and Evans described



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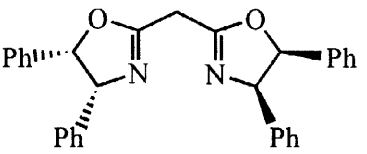

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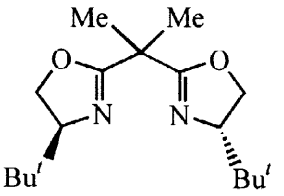
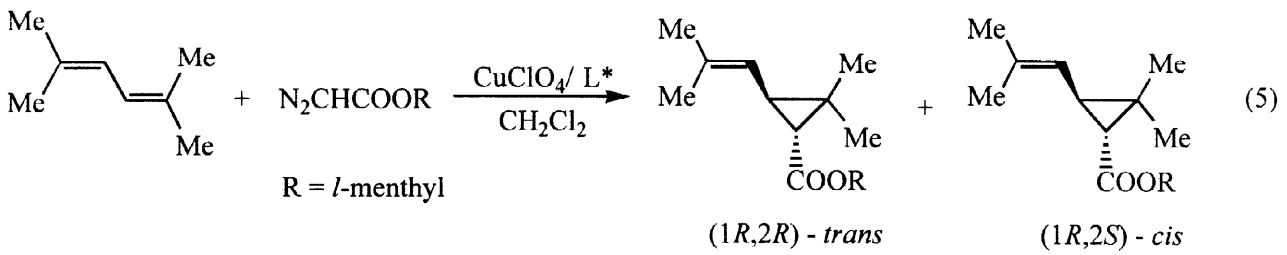


6

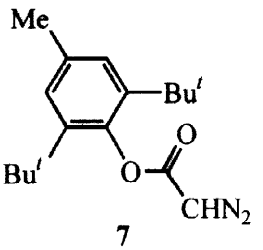
direct access to the (bis-oxazoline)copper catalyst by *in situ* mixing of the ligand with stoichiometric amounts of CuOTf (Tf = CF_3SO_2).[13] The gem-dimethyl derivative **6**, designed by Evans, has proven to be the most widely used chiral bis-oxazoline; with isobutylene and EDA, catalysis with CuOTf/**6** yields ethyl 2,2-dimethylcyclopropanecarboxylate (eq 2) in >99% ee.[13] Masamune has shown that the effectiveness of bis-oxazolines for cyclopropanation of variously substituted olefins depends on the bis-oxazoline substituent (e.g., eq 5).



(1*R*,2*R*) - *trans* (1*R*,2*S*) - *cis* (5)

L*	% ee (*trans*)	*trans* : *cis*	% ee (*cis*)
ent - **4**	24	84 : 16	16
5	92	92 : 8	84
ent - **6**	24	84 : 16	20

Unlike catalytic epoxidation or aziridination reactions of simple alkenes where enantiocontrol is the only stereochemical differentiation, synthetically effective intermolecular cyclopropanation requires both diastereocontrol and enantiocontrol. High diastereoselectivity for the trans isomer can be achieved with the use of bulky diazoacetates such as BDA (**7**)[16] or DCM (**8**);[15] for example, with styrene and BDA catalyzed by CuOTf/**6** the cyclopropane *trans:cis* ratio was 94:6 with 99% ee for the trans isomer.[13] Alternatively, high diastereocontrol is directly provided with the C_2-symmetric 2,6-bis(2'-oxazolin-2'-yl)pyridine (pybox-^{i}Pr) complex of ruthenium (**9**) reported by Itoh, Nishiyama and coworkers (eq 6).[17,18] However, the



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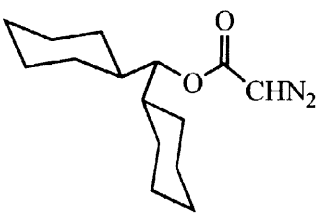

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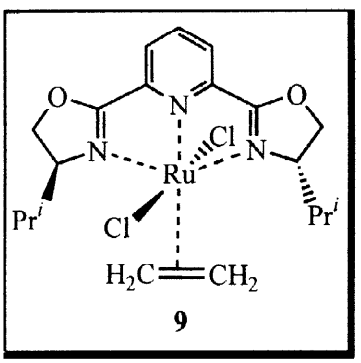
ruthenium catalysts are less active than are copper catalysts towards carbene transfer, and their applications are more limited so that high product yields are achieved only with conjugated alkenes. The enhanced



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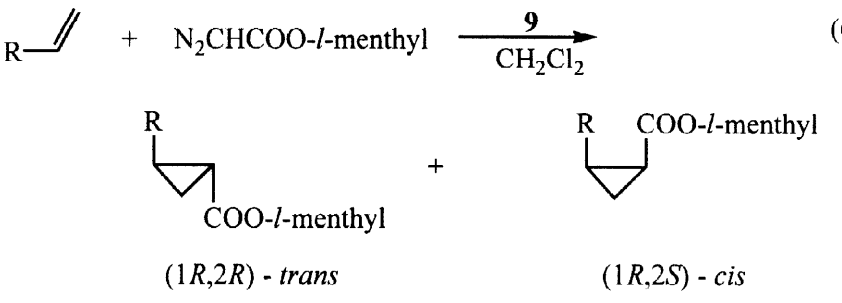
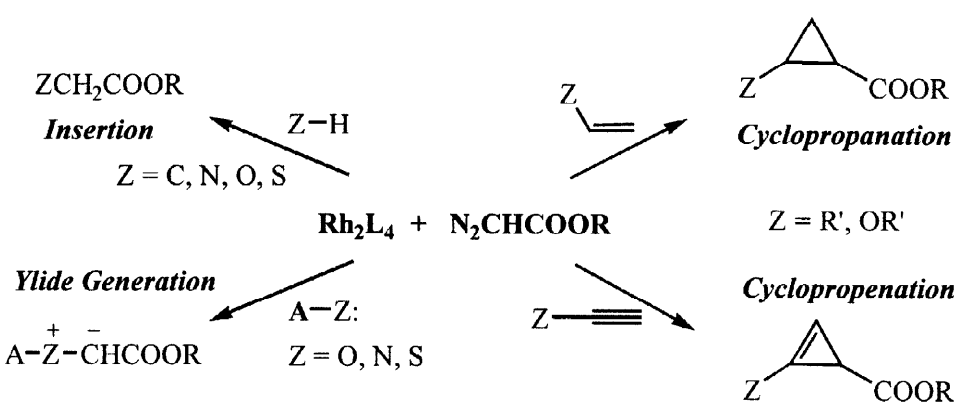


(6)

	yield, %	*% ee (trans)*	*trans : cis*	*% ee (cis)*
R = Ph	87	95	95 : 5	76
CH_2Ph	45	97	93 : 7	-
$^nC_5H_{11}$	54	98	92 : 8	94
Me_2CH=CH	86	98	79 : 21	79

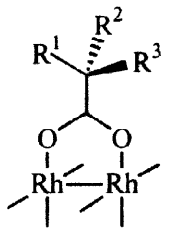
stability of the ruthenium carbenes has allowed the isolation and characterization of stable carbene complexes.[19,20] Because the carbene is transferred from ruthenium to an alkene, the observation of metal carbenes demonstrates that they are intermediates in the catalytic cyclopropanation reaction.

Chiral dirhodium(II) catalysts with carboxylate or carboxamidate ligands have recently been developed to take advantage of their versatility in metal carbene transformations. Since the initial report of the effective

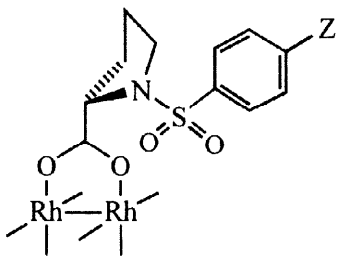


Scheme 1

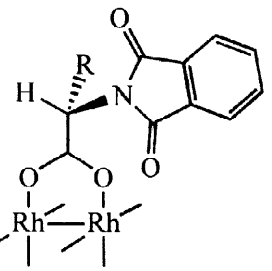
use of $Rh_2(OAc)_4$ for O-H insertion by Teyssie and coworkers,[21] dirhodium(II) carboxylates have become the catalysts of choice for cyclopropanation, cyclopropenation, insertion, and ylide generation (Scheme 1).[22-27] Chiral carboxylate ligands have been independently reported by Brunner (**10**),[28] McKervey(**11**),[29] and Hashimoto/Ikegami (**12**)[30] for tetrasubstitution around the dirhodium(II) core, but their enantioselectivities in intermolecular reactions with simple alkenes have been marginal.



10
R = H, Me, Ph, OH, NHAc, CF_3

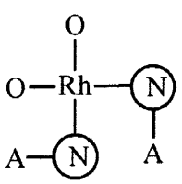


11
Z = H

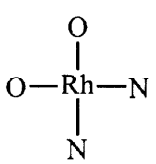


12
R = $PhCH_2$, Bu^t

Chiral carboxamidate-ligated dirhodium(II) compounds have been designed and developed by Doyle and coworkers.[31] In these compounds the dirhodium(II) core is bound to four carboxamidate ligands so that 2N and 2O atoms are bound to each rhodium with a cis array (**13**); the chiral center is the carbon atom adjacent to the ligated nitrogen (**14**), where A is the attachment to the chiral center).[32]



***R*-14**



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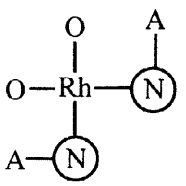
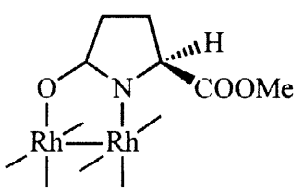
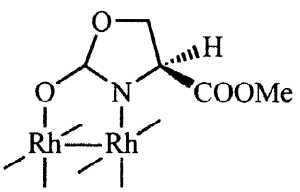


***S*-14**

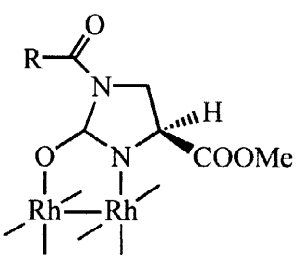
Four different classes of carboxamidate ligands have been reported, the most effective being those with carboxylate ester attachments (A) to amino acid-derived 2-oxopyrrolidines (**15**),[32] 2-oxooxazolidines (**16**),[33]



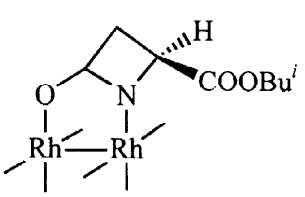
15
Rh_2(5*S*-MEPY)$_4$



16
Rh_2(4*S*-MEOX)$_4$



17
R = Me:
Rh_2(4*S*-MACIM)$_4$
R = $PhCH_2CH_2$
Rh_2(4*S*-MPPIM)$_4$



18
Rh_2(4*S*-IBAZ)$_4$

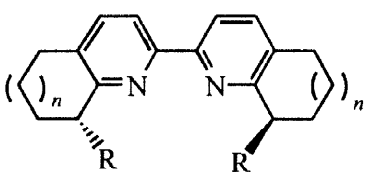
N-acyl-2-oxoimidizolidines (**17**),[34] and 2-oxoazetidines (**18**).[35] Dirhodium(II) catalysts are not oxygen sensitive, and they have long shelf lives. However, initial applications with intermolecular cyclopropanation reactions between styrene and *l*- or *d*-menthyl diazoacetates[31] provided lower stereocontrol than that of the Aratani catalysts (eq 3).

As might be expected, the tests for catalyst effectiveness in intermolecular cyclopropanation reactions have focused on three olefinic substrates, each of which has commercial applications (2,5-dimethyl-2,4-hexadiene, eq 5, and isobutylene, eq 2) or can provide analytically convenient analyses (styrene, eq 3). Chiral copper catalysts, especially those constructed with bis-oxazoline ligands were found to be more effective than those of rhodium in producing the highest levels of enantiocontrol. However, diastereocontrol provided an added complication, except with the use of diazoacetates with bulky ester appendages, that has limited applications of this technology. More recent advances have focused on catalysts and substrates with which total stereocontrol could be achieved. Intramolecular cyclopropanation, which avoids the formation of diastereoisomers, is currently the most advanced methodology for complete stereocontrol.

II. Intermolecular Cyclopropanation Reactions

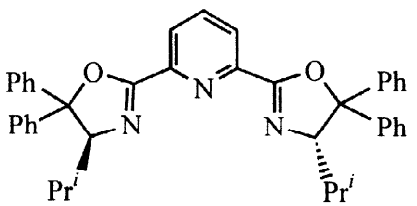
A. Chiral Copper Catalysts

In addition to those derived from salicylaldimines, semicorrins, and bis-oxazolines, chiral copper(I) catalysts have been formulated with optically active bipyridine ligands (**19**)[36-38] the *gem*-diphenyl-bis-oxazoline analogs of the Brunner/Nishiyami Pybox-*ip* (**20**),[39] bis(pyrazolyl)pyridines (**21**),[40] and chiral 1,2-



19 (n = 0,1)

R = Pr^i, CMe_2Et, TMS, $SiEt_3$, CMe_2OTBS



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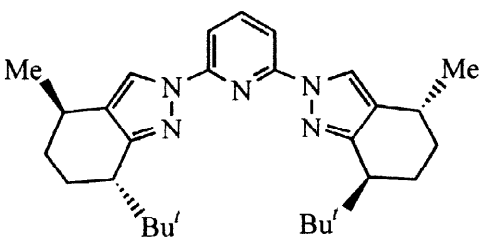

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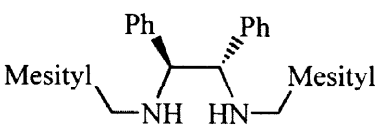
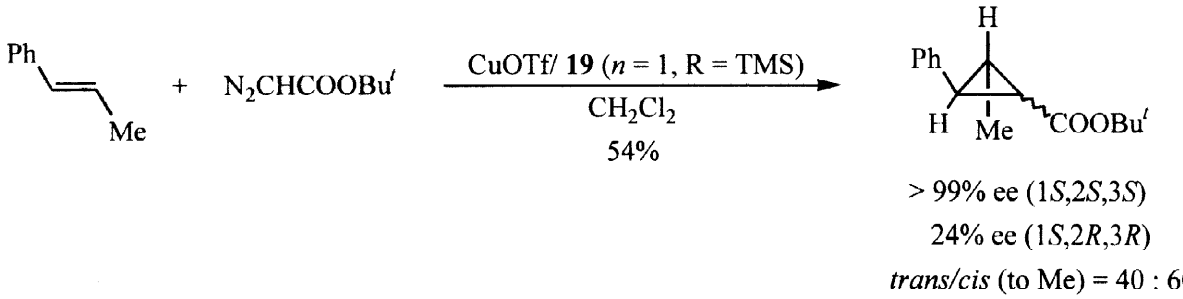


22

diamines (**22**).[41] Katsuki's chiral bipyridines have exhibited the greatest potential with 94% ee observed for the *trans*-cyclopropane isomer formed in the reaction of *tert*-butyl diazoacetate with styrene (*trans*:*cis* = 86:14) using **19** (n = 1, R = TMS).[37] Exceptional enantiocontrol has been achieved in the cyclopropanation of *E*-olefins (eq 7), and even ethyl diazoacetate leads to product with >90% ee.[38] However, diastereo-

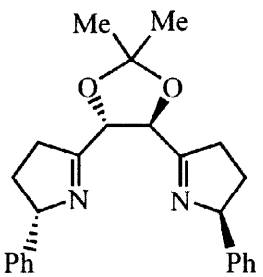
selectivity is modest, and there is no intrinsic factor that might provide improvements; instead, this catalytic system has become more important for ylide generation/insertion.[42,43]



(7)

> 99% ee (1*S*,2*S*,3*S*)
24% ee (1*S*,2*R*,3*R*)
trans/cis (to Me) = 40 : 60

Neither **20**[39] nor its simpler pybox-*ip* ligand[18] or **21**[40] provide stereocontrol that is competitive with **19** or the semicorrin and bis-oxazoline ligands. Similarly, a tartrate-derived bis-oxazoline (**23**) ligand gave only modest enantioselectivity for the cyclopropanation of styrene,[44] but higher levels of enantiocontrol might be observed with more highly substituted alkenes (e.g., eq 5). In addition, ligands having C_3 symmetry are highly specific in alkene cyclopropanation reactions, but they exhibit no advantage thus far for enhanced enantiocontrol.[45, 46] Aza-semicorrin ligands, especially **24**, provide high enantioselectivities in the copper(I)



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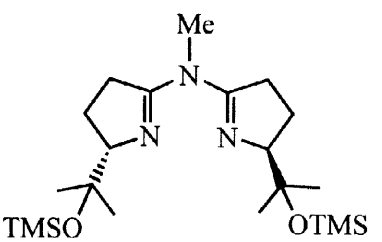
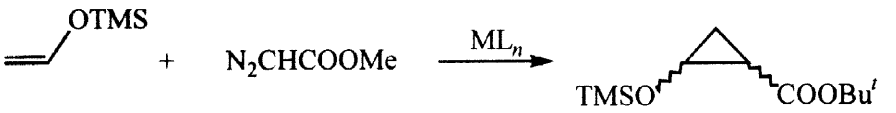


24

catalyzed cyclopropanation of styrene by *d*-menthyl diazoacetate (99% ee for the trans isomer), but diastereocontrol is only modest (*trans: cis* = 84:16).[47] However, C_2 symmetric **22** with $Cu(OTf)_2$ (catalyst activation with phenylhydrazine) has been reported by Kanemasa to give high enantiocontrol (up to 96% ee) and diastereocontrol (*trans:cis* = 93:7) for cyclopropanation of styrene with *d*-menthyl diazoacetate,[41] but with more highly substituted alkenes, including 2,5-dimethyl-2,4-hexadiene, stereocontrol was inferior to that provided by either the Aratani catalyst or Masamune's bis-oxazoline **5** (eq 5). A C_2-symmetric bis(aziridine) was found to be moderately effective for asymmetric cyclopropanation of styrene but not to the level of **22**.[48]

Reissig has examined enantiocontrol for the synthesis of donor-acceptor cyclopropane compounds (eq 8) with a selection of catalysts.[49-51] As seen in these results, the Cu(I)/bis-oxazoline systems provide the highest % ee's or diastereocontrol, but not both. There have been few comparisons among chiral catalysts that allow one to distinguish unique control features appropriate for either or both, enantiocontrol and diastereocontrol.



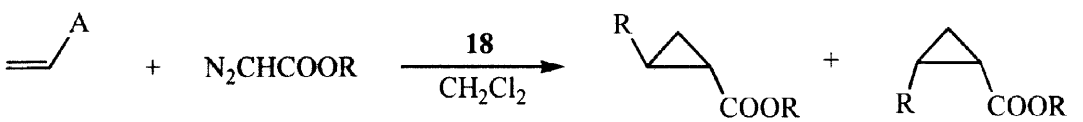
(8)

ML_n	*yield, %*	*trans : cis*	% ee *(trans)*	% ee *(cis)*
3	43	75 : 25	33	12
2[a]	53	72 : 28	30	30
5/ CuOTf	50	>97 : 3	11	-
6/ CuOTf	55	66 : 34	73	76
9	44	72 : 28	41	13
15	35	43 : 57	<5	24

[a]Modified Aratani catalyst with R = 2-$MeOC_6H_4$ and benzyl, rather than methyl, at the chiral center.

B. Chiral Dirhodium(II) Catalysts

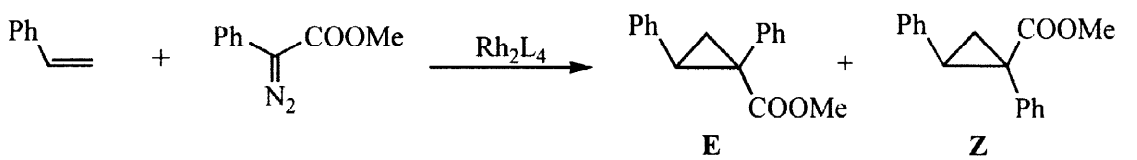
As reported in the Introduction and suggested by the data for **15** [Rh_2(5*S*-MEPY)4] in eq 8, chiral dirhodium(II) catalysts do not provide high levels of enantiocontrol in cyclopropanation reactions of diazoacetates. However, there is a notable exception in the examples given in eq 9. The chiral azetidinone-ligated dirhodium(II) catalyst **18** not only exhibits high enantiocontrol, especially for the cis isomer, but also produces the thermodynamically less stable cis isomer as the preferred product.[35] Curiously, the size of the ester R group has little effect on diastereocontrol.



(9)

R =	A =			
$(c\text{-}C_6H_{11})_2CH$	Ph	77% ee	34 : 66	95% ee
	Me_2C=CH	66% ee	46 : 54	91% ee

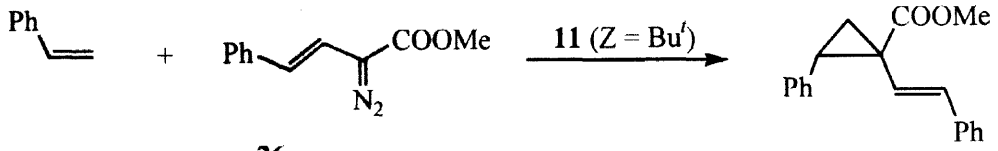
Other notable cases where high levels of enantiocontrol have been achieved are in reactions of aryldiazoacetates (eq 10)[52,53] and of vinyldiazoacetates (eq 11).[54,55] For these substrates the preferred



E **Z**

(10)

Rh_2L_4	*solvent*	*yield, %*	***E**, % ee*	***E : Z***
11 (Z = But)	CH_2Cl_2	77	61	97 : 3
	pentane	73	85	96 : 4
25	CH_2Cl_2	63	77	95 : 5
	pentane	69	75	94 : 6



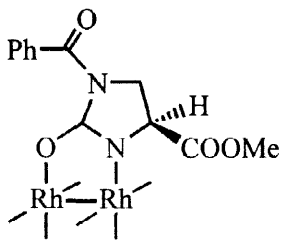
26

CH_2Cl_2 74% ee

pentane 90% ee

(11)

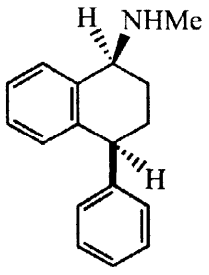
catalyst is the dirhodium(II) *N*-arenesulfonylprolinate, originally reported by McKervey,[29] and modified by Davies by placing *para* substituents on the arenesulfonyl group to increase their solubility. With a *para* ^{t}Bu or *n*-dodecyl group, **11** produces higher product % ee in pentane than in CH_2Cl_2, and because this solvent effect is not observed with the rigid dirhodium(II) carboxamidates, including **25**, Doyle and McKervey concluded that pentane influences the alignment of prolinate ligands on dirhodium(II) to increase enantiocontrol.[52] For reactions of **26** with monosubstituted alkenes, enantiomeric excesses of 59% ($EtOCH{=}CH_2$) and higher, but generally at or greater than 90% ee, are observed at room temperature in pentane; when performed at -78° C, even higher % ee values, including 93% ee for ethyl vinyl ether, are obtained.[55]



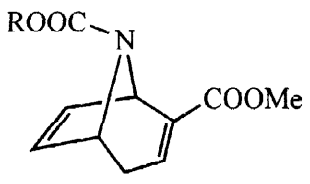
25

Rh_2(4*S*-MBOIM)$_4$

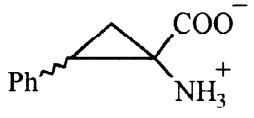
Corey has employed this methodology for the synthesis of the antidepressant sertraline (**27**),[56] and Davies has applied his approach to the enantioselective synthesis of functionalized tropanes (**28**),[57] and to the synthesis of the four stereoisomers of 2-phenylcyclopropan-l-amino acid (**29**).[58]



27: *sertralin*



28



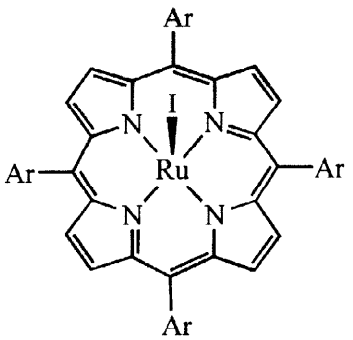
29

C. Other Chiral Catalysts

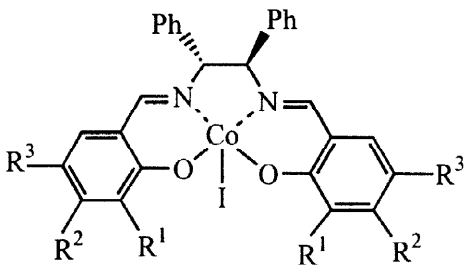
The contributions of Nishiyama and Itoh using $RuCl_2$(Pybox-^{i}Pr) has offered the most significant advance for intermolecular cyclopropanation (eq 6) with both high enantiocontrol and substantial

diastereocontrol for the formation of the trans cyclopropane isomer. However, these reactions are limited by the relatively low reactivity of ruthenium carbenes for addition to conjugated alkenes that are monosubstituted. Electron withdrawing substituents at the 4-position of the pyridine ring increase catalyst reactivity without diminishing diastereoselectivity, but enantioselectivity is affected ($\rho = 0.5$).[59]

Kodadek's "Chiral Wall" (**30a**) and "Chiral Fortress" (**30b**) porphyrins[60-62] have been designed to achieve enantiocontrol in catalytic cyclopropanation reactions, but selectivites were moderate to low (< 60% ee), although turnover numbers were high and diastereoselectivity for cyclopropane formation favored the



30a: Ar = 1,1'-binaphthyl-2-yl
30b: Ar = 1'-pyrenyl-1-naphth-2-yl



31 (R = H, Me, Bu^t)

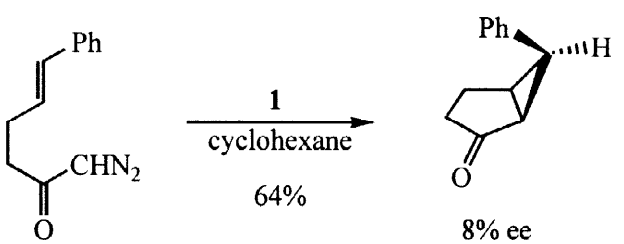
cis/syn isomer. The aryl groups are apparantly too far removed from the carbene to strongly influence enantiocontrol.

Katsuki has reported the use of Co(III)-salen complexes (**31**) for asymmetric intermolecular cyclopropanation.[63] Using *tert*-butyl diazoacetate, styrene yielded, preferentially (>94:6), the trans cyclopropane diastereoisomer in 69-75% ee. With **31** having R^1= ^{t}Bu or Me there was no cyclopropantion, but when R^2 or R^3 = ^{t}Bu or H high diastereocontrol and moderate enantiocontrol were observed. Surprisingly, methanol catalyzed cyclopropane formation, but the reason for this effect has not been established.

III. Intramolecular Cyclopropanation Reactions

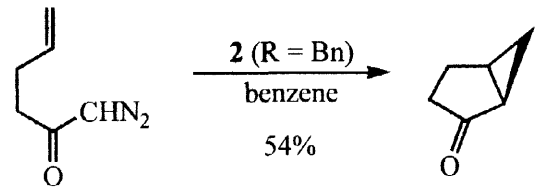
A. Background

Nozaki and coworkers were the first to report enantiocontrol in an intramolecular cyclopropanation reaction.[2] Using a chrial salicylaldimine from phenylethylamine, they achieved 8% ee in the reaction of allyl diazoacetate or a diazoketone (eq 12). Further improvement using a modified chiral salicylaldimine was



(12)

provided by Hirai and Matsui,[64] who were able to achieve 34% optical yield in the construction of dihydrochrysanthemolactone. Dauben employed the Aratani chiral salicylaimine copper catalyst (benzyl instead of methyl in **2**) for intramolecular cyclopropanation of diazoketones and diazoketoesters (e.g., eq 13),[65] and he was able to achieve up to 77% ee with diazoketone **32**. Enantiocontrol with the next higher



(13)

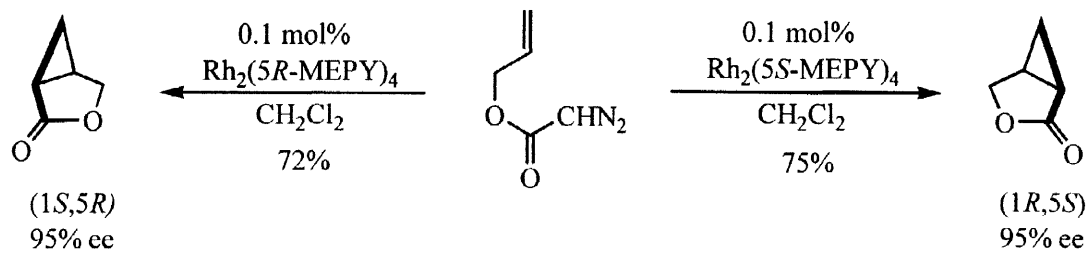
32 77% ee

homolog fell off to 29% ee, and with the corresponding diazoketoester, cyclopropanation products were formed in good yield but low % ee values.

Surprising from the standpoint of their synthetic importance, little attention was given to asymmetric catalytic intramolecular cyclopropanation prior to 1990. Unlike intermolecular cyclopropanation where diastereocontrol is an important but elusive consideration, in the intramolecular process only one diastereoisomer can be formed. Preliminary data using chiral salicylaldimines were disappointing, and even semicorrin-ligated copper(I) complexes were reported to give only moderate levels of enantiocontrol with diazoketones such as **32**.[11]

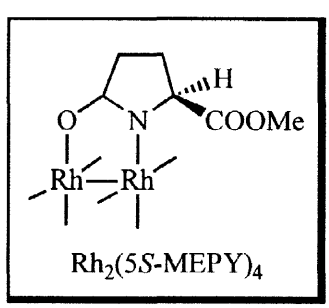
B. Chiral Dirhodium(II) Carboxamidates with Diazoacetates and Diazoacetamides

The dirhodium(II) carboxamidate catalysts **15-17** have proven to be the singularly most selective catalysts for intramolecular cyclopropanation reactions of diazoacetates and diazoacetamides.[66] In the simplest case, allyl diazoacetate, use of $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(5R\text{-MEPY})_4$ in amounts as low as 0.1 mol

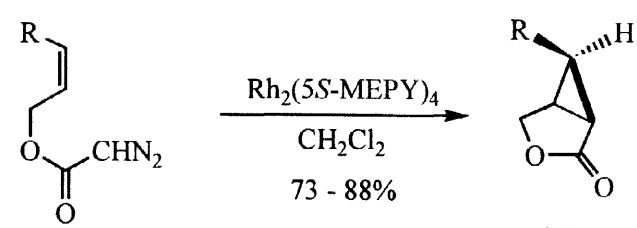


(1*S*,5*R*) 95% ee (1*R*,5*S*) 95% ee

(14)



$Rh_2(5S\text{-MEPY})_4$

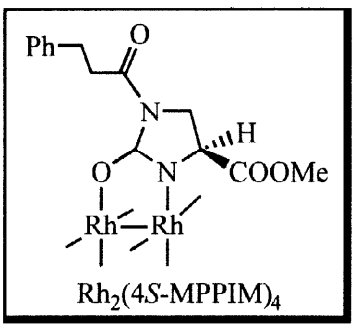


≥ 94% ee

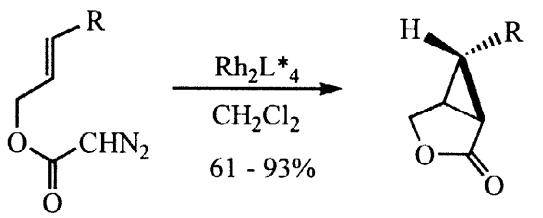
(15)

R = Et, Pr^i, *iso*Bu, Ph, Bn, $(Bu^n)_3Sn$, I

% catalyze the formation of the enantiomeric 3-oxabicyclo[3.1.0]hexan-2-ones in 95% ee and in good yields following distillation (eq 14). These catalysts provide access to both enantiomers with equal facility. Substituted allyl diazoacetates undergo intramolecular cyclopropanation with similar high enantiocontrol. With *cis*-substitution all substituents examined thus far provide ≥ 94% ee (eq 15), independent of size, with catalysis by $Rh_2(5S\text{-MEPY})_4$. The *trans*-substituted allyl diazoacetates show lower % ee values in reactions catalyzed by $Rh_2(MEPY)_4$ catalysts (eq 16), but the sterically more restrictive $Rh_2(4S\text{-MPPIM})_4$ increases enantiocontrol to > 95% ee.[67] High enantiocontrol has also been recorded for trisubstituted allyl



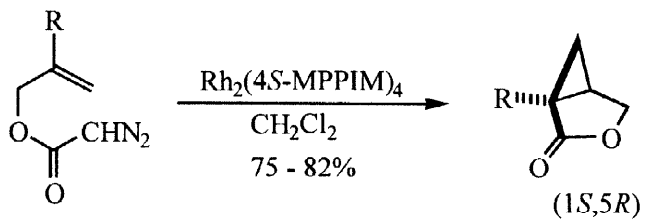
$Rh_2(4S\text{-MPPIM})_4$



(16)

	$Rh_2(5S\text{-MEPY})_4$	$Rh_2(4S\text{-MPPIM})_4$
R = Ph	68% ee	96% ee
Me	85% ee	95% ee

diazoacetates, including those derived from nerol and geraniol.[66] Even methallyl diazoacetate and its ^{n}Bu analog exhibit high enantiocontrol for cyclopropane formation with the use of $Rh_2(4S\text{-MPPIM})_4$ (eq 17),[68] but with these substrates the absolute configuration of the cyclopropane product is opposite (1*S*,5*R*) to that from cyclopropanation of other allylic diazoacetates (1*R*, 5*S*).

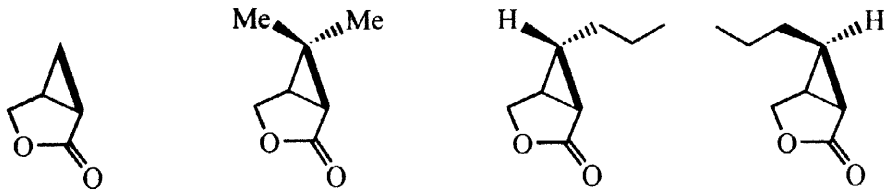


(1*S*,5*R*)

(17)

R = Me	89% ee
^{n}Bu	93% ee

A comparison of chiral catalysts for intramolecular cyclopropanation has demonstrated that dirhodium(II) carboxamidates are superior to copper(I) or ruthenium(II) catalysts (Scheme 2).[68] Methallyl diazoacetate, which undergoes highly enantioselective cyclopropanation catalyzed by $Rh_2(4S\text{-MPPIM})_4$ (eq 17), also undergoes the same highly selective reaction with $CuPF_6$/**6** (87% ee), but Nishiyama's Ru(II) catalyst **9** is unreactive towards this diazo compund. The influence of the metal and its chiral ligands in these reactions has been discussed.[66,68]

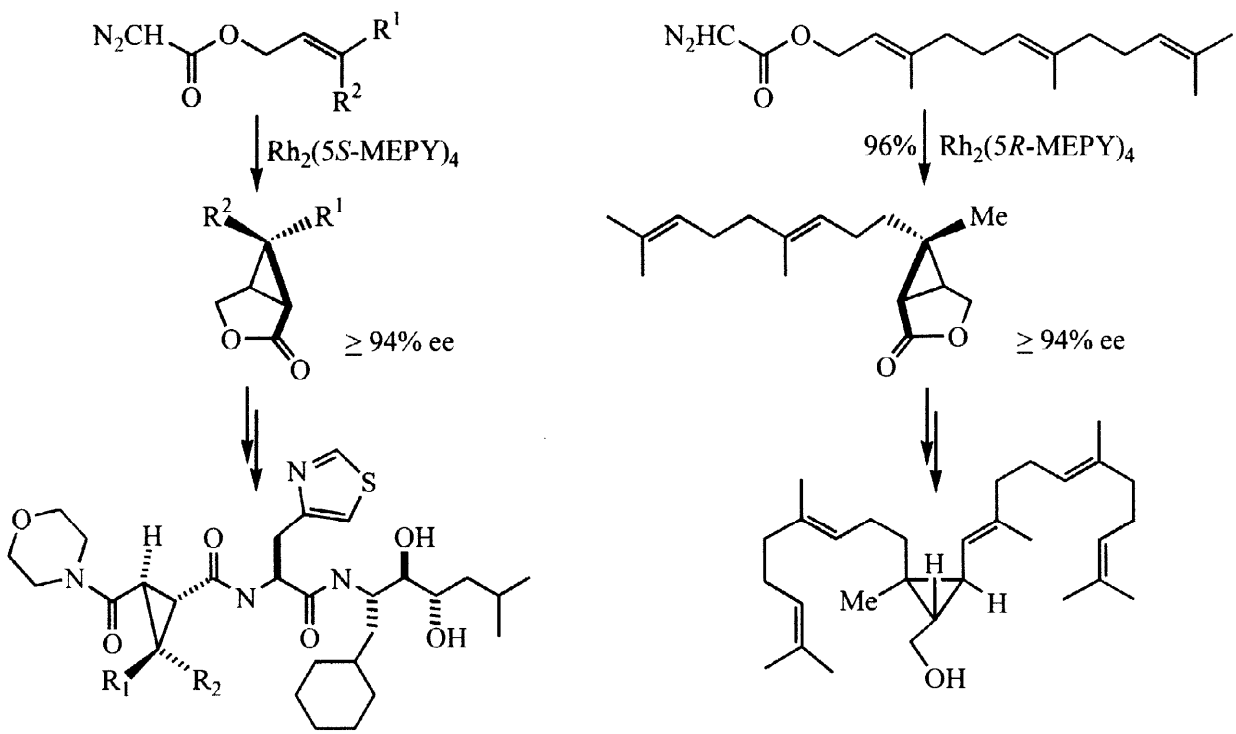


	% ee	% ee[a]	% ee[a]	% ee[a]
$CuPF_6$/ **6**	20	13	(29)	(37)
9	-	(76)	78	21
Rh_2(5*S*-MEPY)$_4$	95	95	85	94
Rh_2(4*S*-MPPIM)$_4$	-	-	95	-

[a]Numbers in parantheses signify enantiomer of opposite configuration

Scheme 2

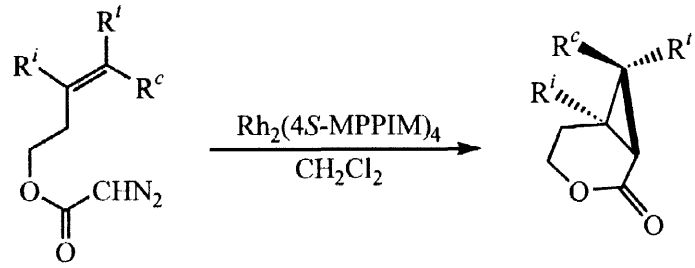
Several pharmacologically relevant compounds have been prepared using this methodology with either or both Rh_2(5*S*-MEPY)$_4$ and Rh_2(5*R*-MEPY)$_4$. Martin has prepared nearly enantiomerically pure 1,2,3-trisubstituted cyclopropanes in conformationally restricted peptide isosteres (Scheme 3) for renin (**33**)[69] and collagenase[70] inhibitors. Poulter has reported the synthesis of optically pure presqualene alcohol (**34**) from farnesyl diazoacetate in high yield. In addition, the products of allylic cyclopropanation reactions are synthetic precursors to *cis*-chrysanthemic acid[72] and to the pheromone *R*-(-)-dictyopterene.[73]



33, *renin inhibitor* **34**, *presqualene alcohol*

Scheme 3

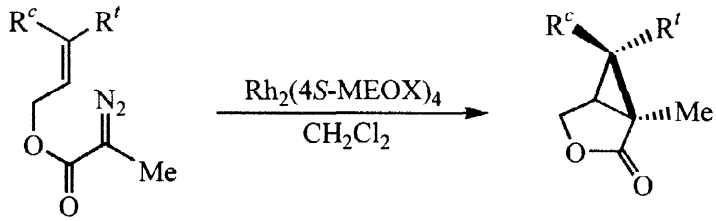
Relative to allylic diazoacetates, there is a moderate reduction in enantioselectivity with the use of the $Rh_2(MEPY)_4$ catalysts in intramolecular cyclopropanation reactions of homoallylic diazoacetates (eq 18).[66,74] However, % ee values are less subject to the substitution pattern of the carbon-carbon double



(18)

R^t	R^c	R^i	*yield, %*	*% ee*
H	H	H	80	71
Me	Me	H	74	77
H	Ph	H	73	88
Ph	H	H	55	73
H	Et	H	80	90
Et	H	H	65	82
H	H	Me	76	83

bond. Furthermore, other chiral dirhodium(II) carboxamidates did not improve enantiocontrol in this system as they did with allylic diazoacetates.[67] With allylic α-diazopropionates lower enantiocontrol was also observed (eq 19),[75] but % ee values in these cases remain the highest for intramolecular cyclopropanation of diazoesters in which the small hydrogen of diazoacetate was replaced by a larger methyl substituent; 1,2-hydrogen migration from the methyl group was the principal competing reaction.

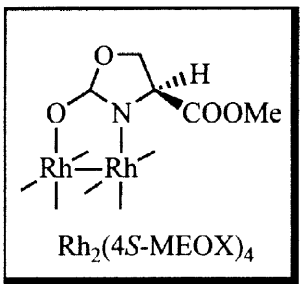


(19)

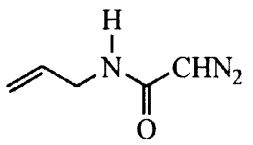
R^t	R^c	*yield, %*	*% ee*
Me	Me	81	71
^{n}Pr	H	62	85
H	^{n}Pr	46	52

N-Allyl- and *N*-homoallyldiazoacetamides also undergo highly enantioselective intramolecular cyclopropanation reactions catalyzed by chiral dirhodium(II) carboxamidates. In the simplest case, *N*-allyldiazoacetamide formed the corresponding cyclopropane GABA analog in 98% ee when the reaction was catalyzed by $Rh_2(4S\text{-}MEOX)_4$ (eq 20).[66] However, further extensions with these simple substrates were limited by competing dipolar cycloaddition.[76] With *N*-methyl substituted *N*-allyldiazoacetates, however,

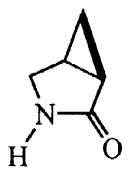
high product yields and high % ee values were uniformly achieved (eq 21);[77] the influence of catalyst ligand structure on enantiocontrol was evaluated. The *N*-methyl substituent maximized catalytic intramolecular cyclopropanation at the expense of intramolecular dipolar cycloaddition.



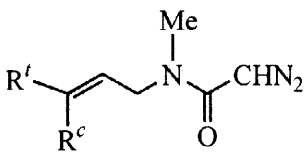
$Rh_2(4S\text{-MEOX})_4$



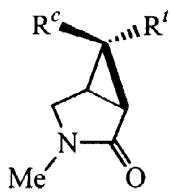
$Rh_2(4S\text{-MEOX})_4$, CH_2Cl_2, 40%



98% ee (20)



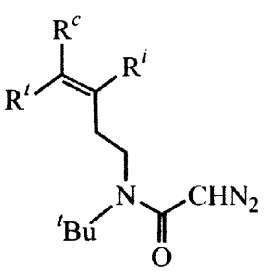
$Rh_2(4S\text{-MPPIM})_4$, CH_2Cl_2



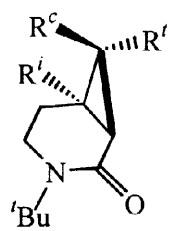
(21)

R^t	R^c	*yield, %*	*% ee*
Me	Me	88	94
^{n}Pr	H	93	92
H	^{n}Pr	88	95

N-tert-Butyl-*N*-homoallylic diazoacetamides gave results that were similar to those achieved with homoallylic diazoacetates (compare eq 18 with eq 22).[76] Only the $Rh_2(MEPY)_4$ and $Rh_2(MEOX)_4$ catalysts



$Rh_2(5S\text{-MEPY})_4$, CH_2Cl_2



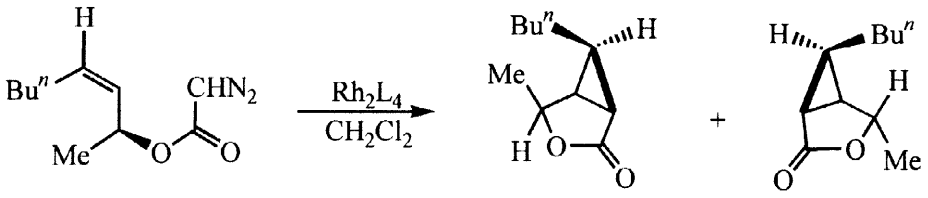
(22)

R^t	R^c	R^i	*yield, %*	*% ee*
H	H	H	60	60
Me	Me	H	75	75
Et	H	H	62	67
H	Et	H	94	90
H	H	Me	87	78

were employed, so it may be possible that higher levels of enantiocontrol can be achieved with the use of chiral imidazolidinone-ligated dirhodium(II). Carbon-hydrogen insertion was a competing reaction.

C. Enantiomer Differentiation in Intramolecular Cyclopropanation

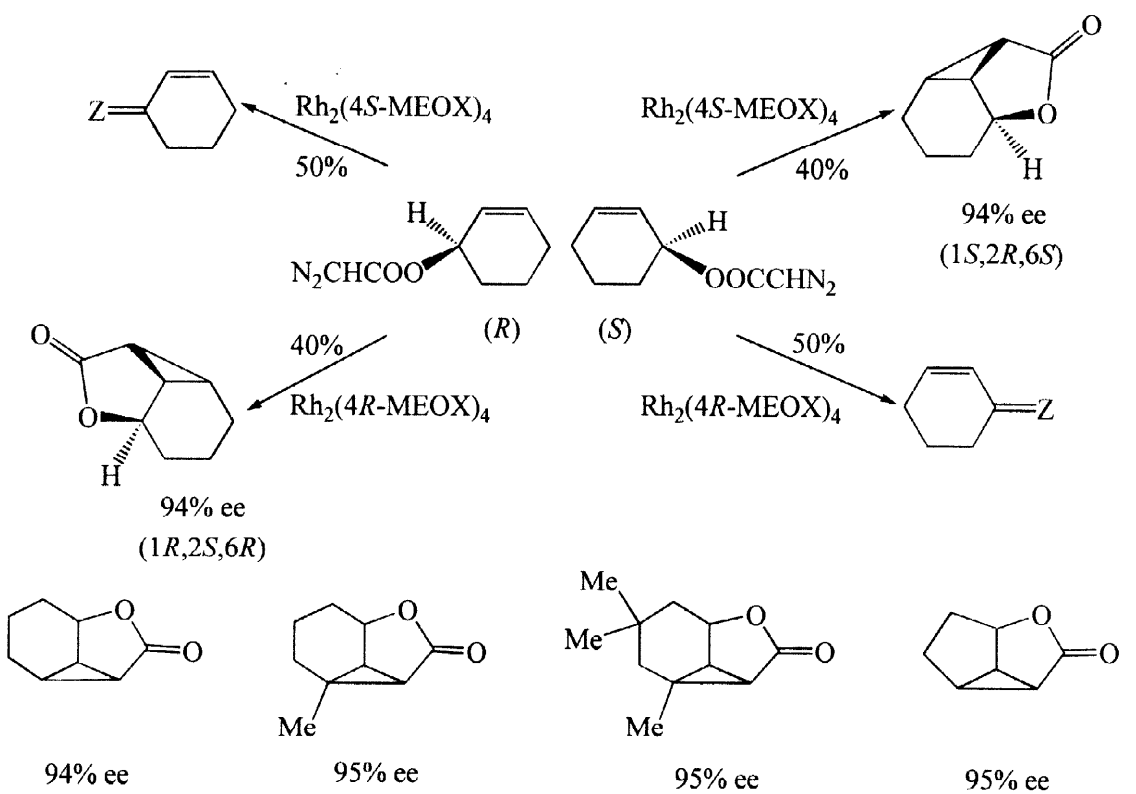
Chiral dirhodium(II) carboxamidates have an amazing ability to react selectively with individual enantiomers of secondary allylic diazoacetates. Martin and coworkers have described the enhanced diastereoselectivity that results from the configurational match between chiral substrate and chiral catalyst (eq 23).[78] A selection of chiral secondary diazoacetates was examined with generally consistent results,



(23)

	endo, %	*exo*, %
Rh_2(5*S*-MEPY)$_4$	>95	<5
Rh_2(5*R*-MEPY)$_4$	40	60

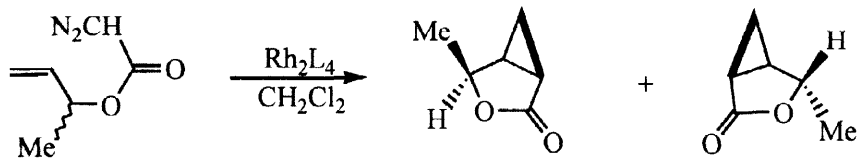
including higher yields with matched pairs than with mismatched pairs (80% versus 39% for eq 23). Enantiomer differentiation from racemic secondary allylic diazoacetates was achieved with cycloalk-2-en-l-yl diazoacetates so that, using Rh_2(MEOX)$_4$ catalysts, one enantiomer underwent intramolecular cyclopropanation whereas the mirror image isomer formed the cycloalk-2-enone *via* a hydride abstraction mechanism.[79] This unique form of enantiomer differentiation is exemplified in Scheme 4 by results from



Scheme 4

reactions of racemic 2-cyclohexen-1-yl diazoacetate catalyzed by Rh_2(4*S*-MEOX)$_4$. The match of catalyst and substrate, *S* with *S* and *R* with *R*, produces the product from intramolecular cyclopropanation. The mismatch allows hydride abstraction to take place preferentially; the mechanism of this reaction has been discussed.[80] Enantiomer differentiation is general for 2-cycloalken-1-yl diazoacetates where 94-95% ee of the intramolecular cyclopropanation products are uniformly achieved.

With acyclic secondary allylic diazoacetates the hydride abstraction pathway is relatively unimportant, and diastereoselection becomes the means for enantiomer differentiation (e.g., eq 24). Here there is significant



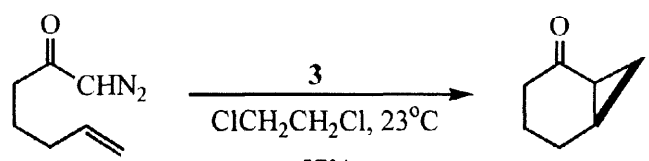
(24)

35	*endo*	*exo*
Rh_2(5*S*-MEPY)$_4$	83 (31% ee)	17 (84% ee)
Rh_2(4*S*-MEOX)$_4$	70 (70% ee)	30 (30% ee)

catalyst dependent diastereoselection and enantiocontrol, but not to the level that has been achieved with 2-cycloalken-1-yl diazoacetates. The endo:exo diastereoselectivity varies over a narrow range when the methyl group of **35** is replaced by *n*-pentyl, phenyl, or cyclopropyl, but enantioselectivity varies widely.

D. Chiral Copper(I) Catalysts with Diazoketones

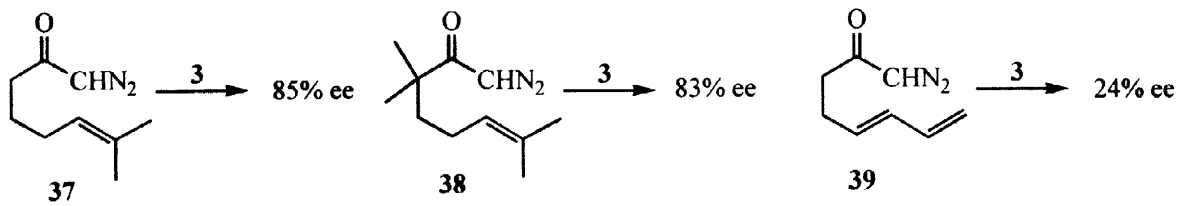
The first application of chiral catalysts to intramoleculaar cyclopropanantion reactions of diazoketones is attributed to Hirai who employed the Aratani catalyst for the synthesis of dihydro-chrysanthemolactone.[64] Dauben subsequently applied these catalysts to systems such as **32** (eq 13) with higher levels of enantiocontrol.[65] It was not until the advent of Pfaltz's semicorrin-ligated copper(II) that high enantioselectivities could be achived. Pfaltz reported that semicorrin catalyst **3** could be used to achieve up to 95% ee with **36** (eq 25);[18] however, % ee increased with increasing mol % of catalyst employed up to



(25)

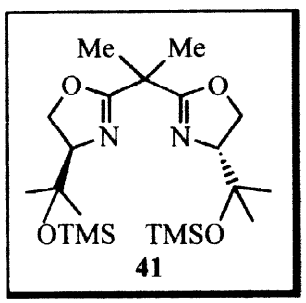
36 95% ee

5 mol %. Surprisingly, the lower homolog of **36** produced the bicyclo[3.1.0]hexan-2-one in only 75% ee; sustitution of alkyl groups onto the carbon-carbon double bond do influence enantiocontrol (**37-39**), but in unpredictable ways. Recently, Doyle and coworkers have communicated the comparable failure of dirhodium(II) carboxamidates to reach even moderate levels of enantioselectivities with **36**, its homolog, or with **37**.[82] Extracting high level of enantiocontrol from diazoketones remains a formidable challenge.



37 38 39

A thorough study of Cu(I)/bis-oxazoline catalysts for enantioselective intramolecular cyclopropanantion of diazoketone **40** (eq 26) has recently been reported.[83] The enantioselective synthesis of



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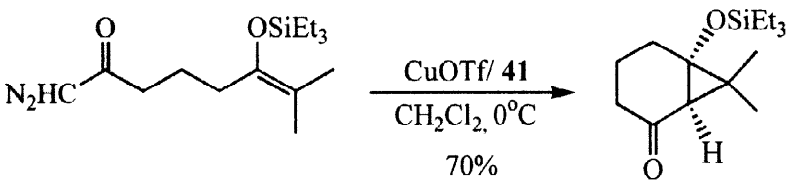
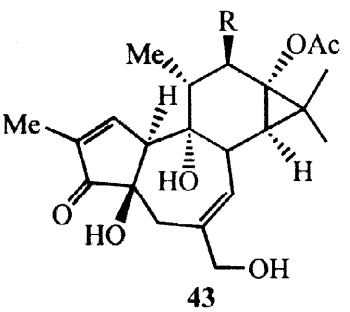


(26)

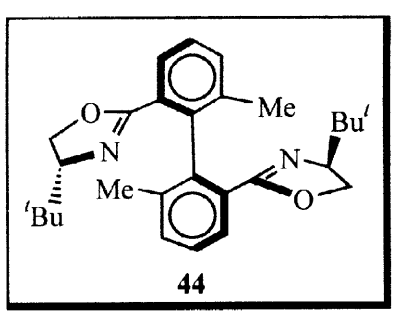
40 **42**, 92% ee

42 was part of the strategy used in construction of the CD-ring of phorbol derivatives **43**. Enantioselectivity increased with increasing size of bis-oxazoline substituents.



43

Corey and coworkers developed a novel bis-oxazoline on a biphenyl backbone (**44**) for the conversion of vinyldiazomethane **45** to **46** (eq 27) in the synthetic scheme for the synthesis of sirenin (**47**).[84] Other



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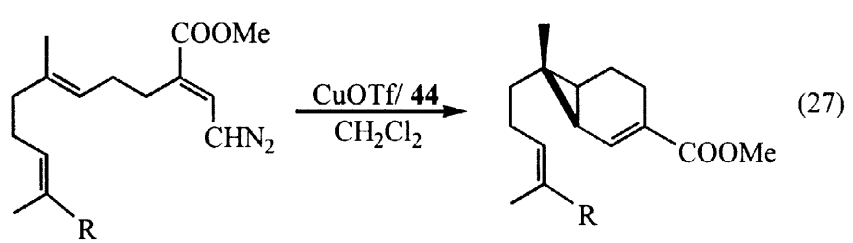
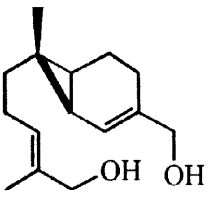


(27)

45 **46**, 90% ee

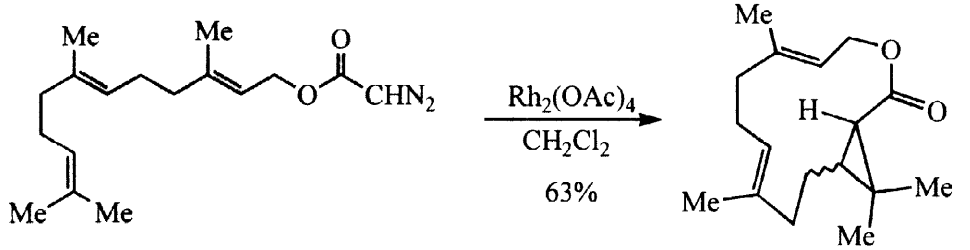


47, *sirenin*

catalysts, including **6** (60% ee) and $Rh_2(5S\text{-MEPY})_4$ (30% ee), gave lower levels of enantiocontrol in the intramolecular reactions of **45**.

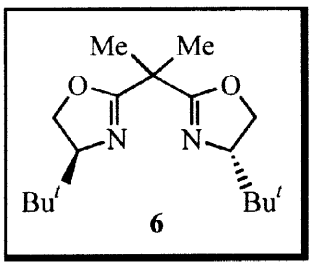
E. Catalytic Enantioselective Macrocyclic Cyclopropanation

Catalytic cyclopropanantion has recently been reported to be a new and effective methodology for the construction of macrocyclic lactones.[85,86] Doyle, Poulter and coworkers have reported that whereas *trans,trans*-farnesyl diazoacetate (**48**) underwent intramolecular cyclopropanantion exclusively at the allylic double bond (Scheme 3) with the use of dirhodium(II) carboxamidates, including those with chiral ligands, with the use of dirhodium(II) carboxylates addition took place solely at the terminal double bond to produce a 13-membered cyclopropane-fused lactone (eq 28).[85] High dilution was not required, and macrocycle **49** was formed in relaltively high yield and with diastereoselectivity that was dependent on the catalyst ligands.



48 **49** (28)

Subsequent investigation revealed that diazoesters derived from 1,2-benzenedimethanol underwent intramolecular cyclopropanantion to form 10-membered ring lactones in high yield and, with catalysis by $Cu(MeCN)_4PF_6$/bis-oxazoline **6**, high % ee (eq 29).[86] With $Rh_2(5S\text{-MEPY})_4$, **51** was also formed in high



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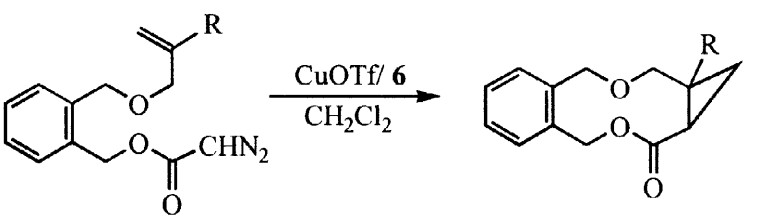
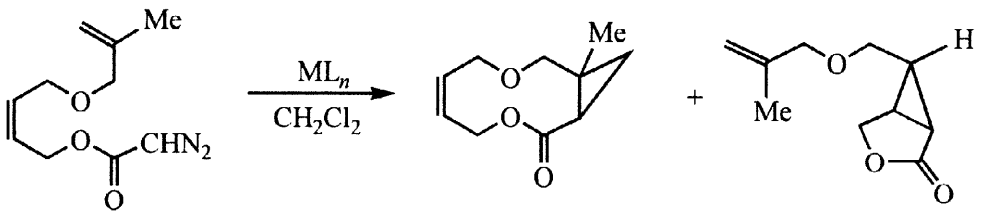


50 **51** (29)

R = Me	82% yield	87% ee
R = H	71% yield	80% ee

yield (77%), but with only 47% ee; still, enantioselectivity in this case is much higher than the 7% ee that was

observed with methallyl diazoacetate.[66-68] When there is competition between allylic cyclopropanation to form a γ-lactone and macrocylization, $Cu(MeCN)_4PF_6$/**6** favors macrocyclization whereas Rh_2(5*S*-MEPY)$_4$ leads to the allylic cyclopropanation exclusively (eq 30). That the success of these macrocyclization reactions is not due solely to entropic factors associated with the *Z* - geometry of **50** and **52**, the ethylene analog of **52** underwent macrocycization in reactions catalyzed by $Cu(MeCN)_4PF_6$/**6** (43% yield) to form the cyclopropane product with 91% ee.

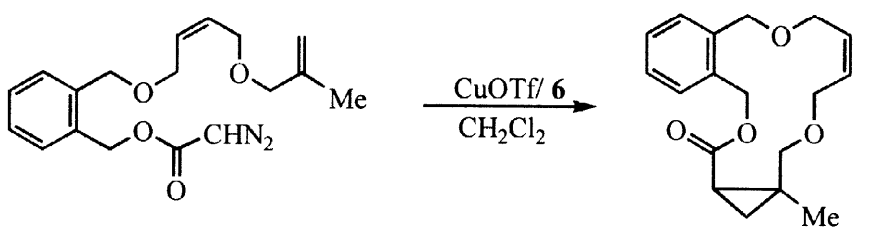


(30)

52 **53** **54**

$CuPF_6$/**6**	43% (87% ee)	19% (41% ee)
Rh_2(5*S*-MEPY)$_4$	0%	84% (96% ee)

Further exploration of the extent of macrocyclization detailed the amazing selectivity achieved in the cyclopropanation of **55** which offered for the reacting carbene competition between formation of 10- and 15-membered rings through cyclopropanantion, *(Z)*- versus *(E)*- cyclopropane geometry, and ennantiomer selection. With catalysis by $Cu(MeCN)_4PF_6$/**6**, however, only one product is formed (eq 31) and in high yield and exceptional chemoselectivity, regioselectivity (>50:1), diastereoselectivity (>50:1), and



(31)

55 **56** 90% ee

enantioselectivity (90% ee).[86] This preference for 15-membered ring formation is due in large part to the difference in relative reactivity between a methallyl double bond and the cis-2-buten-1,4-diyl double bond, but the formation of a 15-membered ring with significant enantiocontrol and in such high yield without resorting to high dilution techniques is extraordinary.

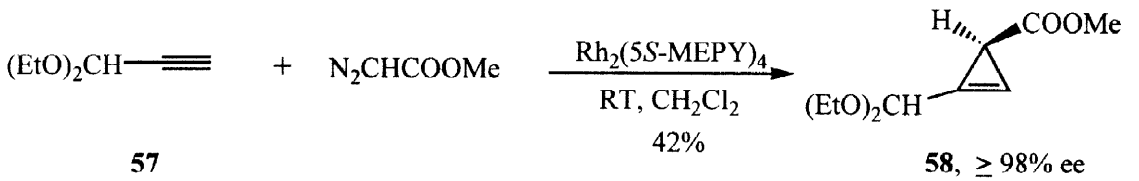
IV. Intermolecular Cyclopropenation Reactions

Catalytic decomposition of diazocarbonyl compouds in presence of alkynes yields cyclopropenes, and this methodology is commonly used for the preparation of cyclopropene-3-carboxylates and their derivatives.[87-89] Due to their high reactivity,[90] cyclopropenes have attracted considerable attention as

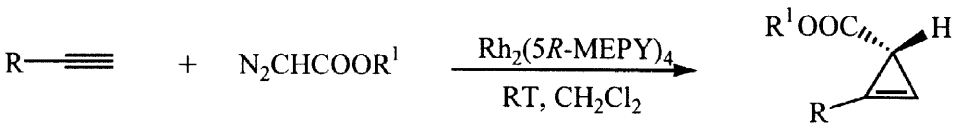
intermediates in syntheses of a wide variety of carbocyclic and heterocyclic compounds,[87-94] and also in the preparation of cyclopropene derivatives of biological importance.[95-101]

Traditionally copper salts were used as catalysts in carbene syntheses of cyclopropenecarboxylates.[89] However, they required high temperatures (90-140°C), and yields of products usually were only moderate. The emergence of $Rh_2(OAc)_4$ as a new and efficient catalyst for diazo decomposition has allowed the synthesis of cyclopropenecarboxylates at room temperature in high yields.[102,103] In addition, recently developed chiral dirhodium(II) catalysts have provided a direct route to chiral cyclopropenes which earlier were obtained *via* chiral resolution,[104,105] by using chiral auxilaries,[106] or from natural sources.[107]

Chiral dirhodium(II) carboxamidates were demonstrated to be exceptional catalysts for highly enantioselective intermolecular cyclopropenation reactions:[108,109] with $Rh_2(5S\text{-MEPY})_4$ or $Rh_2(5R\text{-MEPY})_4$ catalysis cyclopropenecarboxylates were formed from diazoacetates with ee's up to 98% and in good yields (eq 32-34). Both catalysts provided virtually identical results, except for absolute configuration:



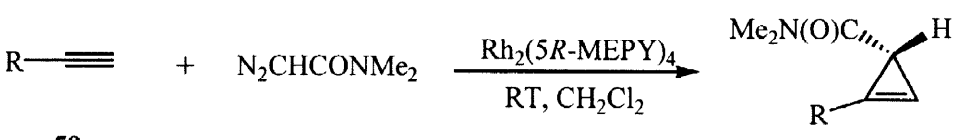
57 **58**, ≥ 98% ee (32)



59 **60** (33)

R	*R*[1]	*yield, %*	*% ee*
CH_2OMe	Et	73	69
CH_2OMe	^{t}Bu	56	78
^{n}Bu	Et	70	54
^{t}Bu	Et	85	57

$Rh_2(5S\text{-MEPY})_4$ was established to produce cyclopropenecarboxylates having predominantely the *(S)*-configuration, whereas use of $Rh_2(5R\text{-MEPY})_4$ gave products in the *(R)*-configuration. Enantioselectivities were observed to increase with the steric size of the diazoester. The polarity of the alkyne also influenced

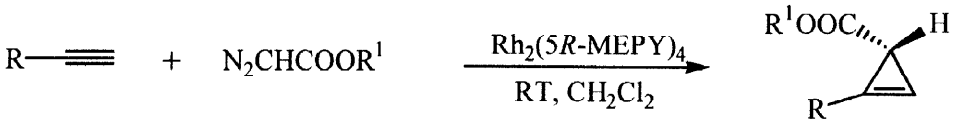


59 **61** (34)

R	*yield, %*	*% ee*
CH_2OMe	22	≥ 94
n-Bu	49	78
t-Bu	47	89

enantiocontrol, perhaps due to an additional polar interaction of the catalyst face with the R substituent in the alkynes **57** and **59** (R = CH_2OMe). *N,N*-Dimethyldiazoacetamide provided a higher level of enantiocontrol (eq 34) than did diazoesters, but reactions generally occurred in lower yields. The use of disubstituted acetylenes in the cyclopropenation reactions with chiral dirhodium(II) carboxamidates gave lower product yields and low enantiocontrol (≤20% ee).

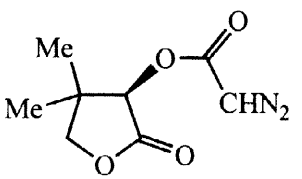
Diastereoselectivities achieved in cyclopropenation reactions with the same set of alkynes and appropriate match of catalyst configuration and *d*- or *l*-menthyl diazoacetate were also high (eq 35). These



59 **60** (35)

R	*R*^{1}	*yield, %*	*dr*
CH_2OMe	*d*-menthyl	43	≥ 97 : 3
CH_2OMe	*l*-menthyl	45	72 : 28
^{n}Bu	*d*-menthyl	46	93 : 7
^{n}Bu	*l*-menthyl	46	60 : 40
^{t}Bu	*d*-menthyl	51	88 : 12
^{t}Bu	*l*-menthyl	50	78 : 22

numbers were unexpectededly high considering that diastereoselectivities in intermolecular cyclopropanation reactions of *d*- or *l*-menthyl diazoacetates provided by these same catalysts were not greater than *dr* 93 : 7.[110] In addition, double diastereoselection in these reactions was also dramatic. Use of diazoacetates of



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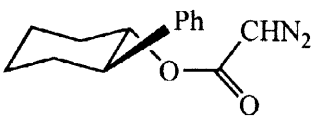

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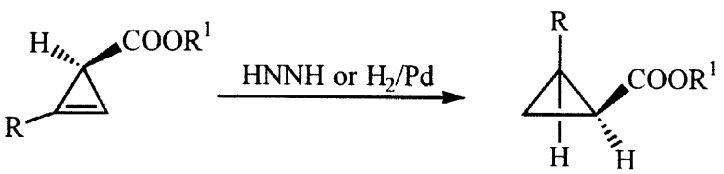
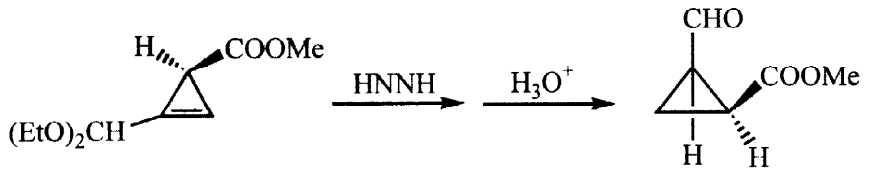
other chiral auxilaries such as **62** and **63** didn't provide enhancement of selectivity.[111] Catalytic hydrogenation or diimide reductions of enantiomerically enriched cyclopropenes, quantitatively yielded the



60 **64** (36)

corresponding *cis*-cyclopropanes **64** and **65** (eq 36, 37), providing a direct route to chiral *cis*-disubstituted of moderate to high optical purity.



(37)

58, ≥ 98% ee **65**, ≥ 98% ee

V. Conclusion

Although a large number of catalysts have been introduced for catalytic asymmetric cyclopropanation reactions, only a few have high potential to achieve enantioselectivities of ≥ 95% ee. For intramolecular cyclopropanation reactions of allylic and homoallylic diazoacetates, chiral dirhodium(II) carboxamidates are clearly superior to all other chiral catalysts, but the jury is still out on relative catalyst effectiveness for the formation of macrocycles. In intermolecular cyclopropanation reactions, copper(I) and bis-oxazoline **6** has given the highest % ee values for cyclopropanation of styrene, isobutylene, and 1,1-diphenylethene, but universal applicability of this catalytic system has been elusive. In addition, diastereocontrol in intermolecular cyclopropanation reactions continues to be a problem, although with the chiral Ru-pybox catalyst **9** some improvement has been achieved. Cyclopropenation is still best performed by chiral dirhodium(II) carboxamidates, but further investigations are warranted.

Acknowledgments

The contributions of the members of our research group whose names are referenced made much of the work described in this report possible. The generous financial support of the National Science Foundation, the National Institutes of Health (GM 46503), and the Robert A. Welch Foundation is gratefully acknowledged.

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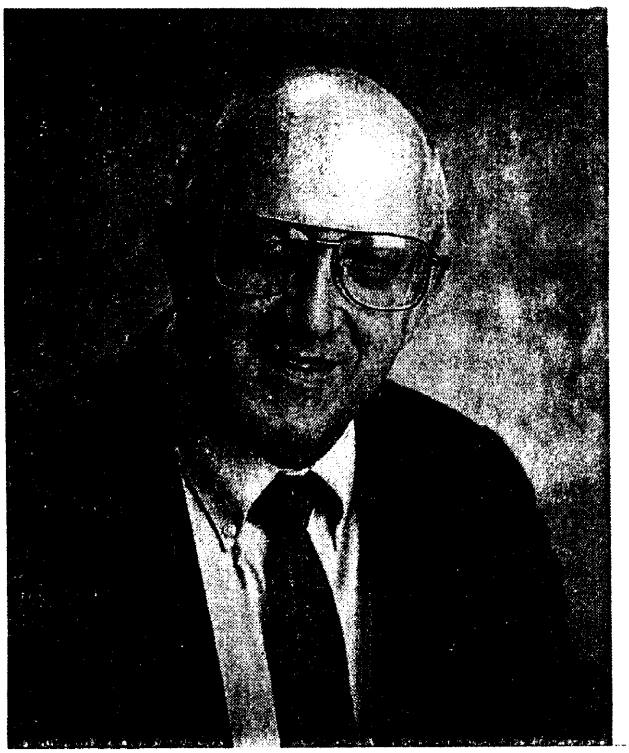
Biographical sketch



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Michael P. Doyle received his B.S. degree from the College of St. Thomas in St. Paul, MN, and his Ph.D. degree from Iowa State University. Following a postdoctoral engagement at the University of Illinois at Chicago Circle, he joined the faculty at Hope College in 1968. In 1984 he moved to Trinity University in San Antonio, TX, as the Dr. D. R. Semmes Distinguished Professor of Chemistry, and in 1997 he moved to Tucson, AZ, where he is Professor of Chemistry at the University of Arizona and Vice President of Research Corporation. The co-author 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.

Marina Protopopova graduated from Moscow State University with a M.S. in Chemistry in 1981. In 1986, she received her Ph.D. from the N. D. Zelinskii Institute of Organic Chemistry of the Russian Academy of Sciences under a supervision of academician Oleg M. Nefedov. In 1990-1992 and 1993-1995 Dr. Protopopova worked as post-doctoral research associate with Professor Michael P. Doyle at Trinity University. Since 1995, she has held a position of Senior Research Scientist at Regis Technologies. Dr. Protopopova is also a part-time faculty member at Columbia College in Chicago where she teaches Computer Models and Virtual Worlds in Science. Her research interests include asymmetric catalysis and all aspects of chiral recognition.