Asymmetric syntheses with catalytic enantioselective metal carbene transformations*

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Asymmetric catalysis of metal carbene transformations with unique chiral dirhodium(II) carboxamides provides highly enantioselective and diastereoselective syntheses *via* cyclopropanation, cyclopropenation, and carbon—hydrogen insertion reactions of diazoesters and diazoamides. Constructed from a dirhodium(II) core with bridging pyrrolidone, oxazolidinone, or imidazolidinone ligands, these catalysts are especially effective for intramolecular transformations that occur in high yield with greater than 90 % enantiomeric excess (*ee*) and high diastereocontrol.

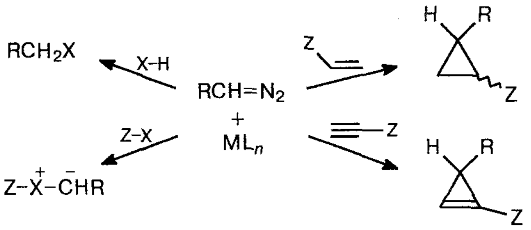
Key words: asymmetric catalysis, metal carbene transformations; dirhodium(II) carboxamides; enantioselective intramolecular cyclopropanation; enantioselective inertmolecular cyclopropenation; enantioselective intramolecular carbon—hydrogen insertion; diazoacetates and diazoacetamides; diastereoselection; regioselection; lactone synthesis; lactam synthesis; 2-deoxyxylolactone synthesis.

1. Introduction

Chiral transition metal catalysts suitable for asymmetric transformations provide potential advantages for enantioselective syntheses that, optimally, include (1) enantiselectivities that are ≥90 % enantiomeric excesses (*ee's*), (2) high turnover numbers and rates, (3) recoverability and reuse, and (4) broad applicability. Their development has been pursued since the first reports of asymmetric catalytic cyclopropanation (1966)[1] and hydrogenation (1968),[2,3] and significant achievements have been made in hydrogenation, epoxydation, dihydroxylation, cyclopropanation, and with a variety of transformations catalyzed by chiral Lewis acids.[4] Generally, synthetically useful chiral catalysts have been designed so that enantiocontrol is achieved through substrate interactions with chiral ligand(s) which surround the metal rather than from metal-centered asymmetry in catalysts. Ligands ranging from chiral phosphines and Schiff bases to C_2-symmetric bis-oxazolines have been constructed to fortify enantioselection in individual transformations.

Transition metal catalyzed reactions of diazo compounds provide a broad diversity of transformations amenable to enantiocontrol, including cyclopropanation, cyclopropenation, X—H (X = C, N, O, Si, S) insertion, and ylide generation and rearrangement (Scheme 1).[5—7]

Scheme 1



In the generally accepted mechanism for these transformations,[7,8] electrophilic addition to the diazo compound by the ligated transition metal catalyst (ML_n) that possesses an open coordination site produces a diazonium ion intermediate which, upon extrusion of dinitrogen, generates a highly electrophilic metal carbene (Scheme 2) whose reactivity resembles of a metal-stabilized carbocation.

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* Based on lectures given at the 1994 International INEOS Workshop, May 21—26, 1994, and at the Nesmeyanov Institute of Organoelement Compounds, Moscow, on May 30, 1994.

** On the occasion of the award of a D. Sc. (*honoris causa*) degree to Prof. M. P. Doyle for his works on catalytic enantioselective syntheses by the Russian Academy of Sciences in 1994.

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 1879—1892, November, 1994.

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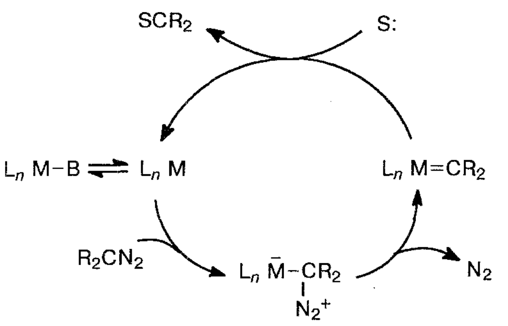
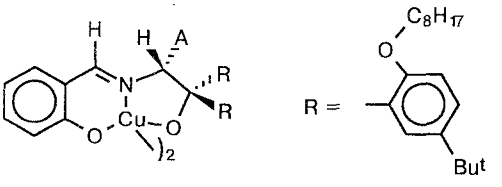
Scheme 2



Transfer of the carbene to the reacting substrate (S) by addition, insertion, or association regenerates the catalyst to complete the catalytic cycle. Lewis bases that include acetonitrile, and with certain catalysts even alkenes, may occupy the open coordination site and thereby inhibit catalytic diazodecomposition. Both copper(I) and dirhodium(II) compounds are highly suitable catalysts for cyclopropanation reactions, but dirhodium(II) carboxylates and carboxamides are the catalysts of choice for insertion, ylide generation, and cyclopropenation. Since diazocarbonyl compounds, especially diazoesters and diazoamides, are readily prepared and are generally stable at temperatures ≤100 °C,[9] they are the preferred substrates for transition metal catalyzed transformations. Palladium(II) catalysts show a special propensity for cyclopropanation reactions of diazomethane that is not exhibited with copper or rhodium catalysts.[10] A significant number of recent reviews have documented the synthetic diversity and versatility of transition metal catalyzed reactions of diazocarbonyl compounds in both intermolecular and intramolecular transformations.[5–7,10–18]

2. Chiral copper catalysts

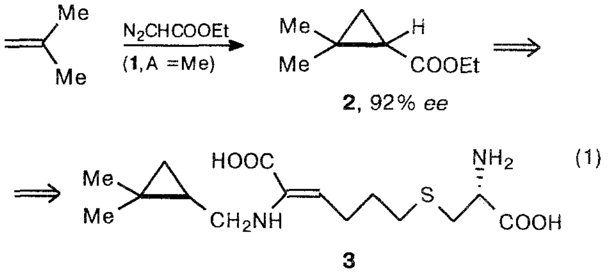
The design and development of chiral copper(I) catalysts for cyclopropanation reactions were initiated by Nozaki and Noyori[1] and extended by Aratani with chiral salicylaldimine ligands (**1**).[19]



1

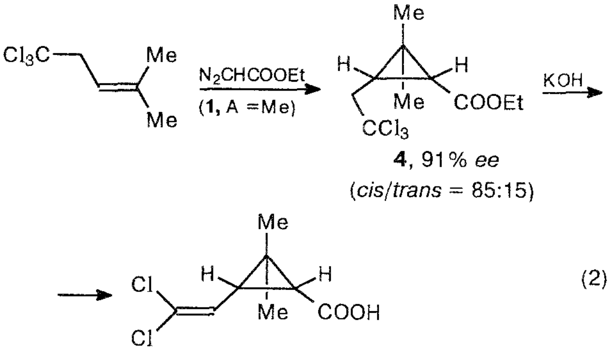
A = Me, PhCH$_2$, Pr^i, Bu^i

The Aratani catalyst has been applied commercially to the synthesis of ethyl 2,2-dimethylcyclopropanecarboxylate (Eq. 1), the key precursor to cilastatin (**3**) — an *in vivo* stabilizer of the antibiotic imipenem.[20]



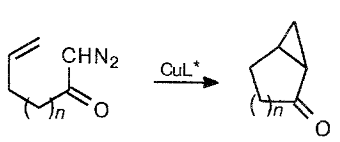
(1)

Generally, moderate to high enantio/diastereocontrol has been achieved for intermolecular cyclopropanation reactions with the use of the Aratani catalysts. The preparation of permethrinic acid (Eq. 2), for example, occurred through a cyclopropanation process in which **4** was formed in 91 % enantiomeric excess and with unusual 85:15 *cis* stereocontrol.



(2)

Not all alkenes exhibit such high enantioselectivity and diastereoselectivity, but mono-, di-, and trisubstituted ethylenes all undergo cyclopropanation with the use of the Aratani catalysts. However, in intramolecular application (Eq. 3) with diazoketones, enantiomeric excesses only as high as 77 % have been achieved.[21]



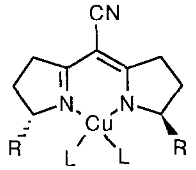
(3)

n	CuL*	% *ee*
1	**1**: A = PhCH$_2$	77
2	**1**: A = PhCH$_2$	34
1, 2	**5**	75–92

Prepared in the copper(II) oxidation state, these catalysts are reduced by the reactant diazo compound to a copper(I) form which is the active catalyst. To achieve 77 % *ee* in Eq. 3, for example, 3 mol. % of **1** (A = PhCH$_2$) was employed and the catalyst was reduced by

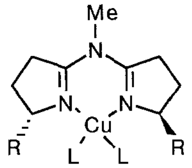
DIBAH (diisobutylaluminum hydride) prior to addition of the diazo compound.[21] Analogous intramolecular cyclopropanation reactions with diazoesters catalyzed by **1** have not been reported.

The introduction of C_2-symmetric semicorrin ligands for copper(I) by Pfaltz (**5**, **6**)[22] provided significant in enantioselectivities for intermolecular cyclopropanation with diazoacetate esters and for intramolecular reactions of diazoketones (Eq. 3) over those achieved with the Aratani catalysts.



R = CMe_2OH

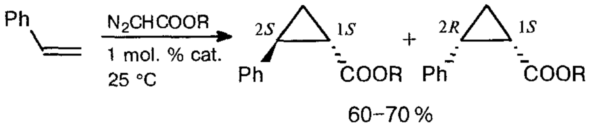
5



R = CMe_2OSiMe_3

6

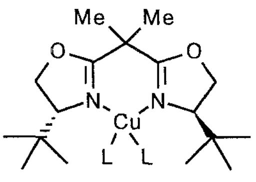
For example, cyclopropanation of styrene with diazoacetates (Eq. 4) could be achieved in modest yields but with high enantioselectivities (Table 1).[23]



(4)

As had been previously reported by Aratani,[19] increasing the size of the alkyl ester (menthyl > *tert*-butyl > ethyl) led to an increase in both enantioselectivity and diastereoselectivity.

Chiral bis-oxazoline ligands, developed independently by Masamune,[26,27] Evans,[28,29] and Pfaltz,[30] on copper (*e.g.*, **7**–**9**) led to even higher enantioselectivities in selected cases, including that of **2** in Eq. 1 (>99 %*ee* with **7**),[28] but none of these catalysts has been successfully applied to processes other than cyclopropanation.



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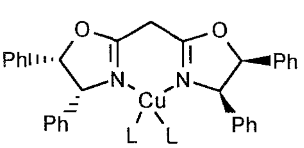

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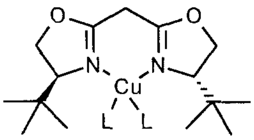


9

The active form of these catalysts is the copper(I) oxidation state; when prepared as the copper(II) complex, phenylhydrazine is generally employed to effect reduction.[22,26] Copper(I) trifluoromethanesulfonate can be combined directly with the chiral bis-oxazoline ligand to form the active catalyst.[28] These catalysts have proven to be generally effective for monosubstituted ethylenes and conjugated dienes but, except for **8**, not for *cis*-di- and trisubstituted olefins. High diastereocontrol could be achieved with the use of 2,6-di-*tert*-butyl-4-methylphenyl diazoacetate (BDA), developed by Doyle and coworkers to enhance stereocontrol,[31] or other diazoesters with bulky substituents. A variety of other chiral ligands for copper has been prepared, including pyrazolylborates[32,33] and bipyridines,[34,35] but enantioselectivities from their use have not generally approached those achieved with **5**–**9**. A chiral ruthenium bis(oxazo-

Table 1. Enantioselective cyclopropanation of styrene with diazoacetate esters ($N_2CHCOOR$) catalyzed by chiral copper complexes

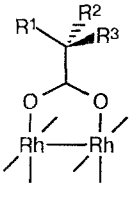
Catalyst	R[a]	*trans/cis*	% *ee* (*de*) *trans*[b]	% *ee* (*de*) *cis*[b]	Ref.
1 (A = Me)	*l*-Menthyl	82:18	81(1R,2R)	78(1R,2S)	19
5	*l*-Menthyl	85:15	91(1S,2S)	90(1S,2R)	24
	d-Menthyl	82:18	97(1S,2S)	95(1S,2R)	24
	Bu^t	81:19	93(1S,2S)	95(1S,2R)	24
	Et	73:27	92(1S,2S)	79(1S,2R)	24
6	*d*-Menthyl	84:16	98 (1S,2S)	99(1S,2R)	25
	Bu^t	86:14	96(1S,2S)	90(1S,2R)	25
	Et	75:25	94(1S,2S)	68 (1S,2R)	25
7	Et	73:27	99(1S,2S)	97(1S,2R)	28
	Bu^t	81:19	96(1S,2S)	93(1S,2R)	28
	BHT[c]	94:6	99(1S,2S)	—	28
9	Et	77:23	98(1S,2S)	93(1S,2R)	28
	Et	75:25	90(1S,2S)	77(1S,2R)	26

[a] *l*-Menthyl = (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl; *d*-menthyl = (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl.
[b] Absolute configuration of cyclopropane product in parentheses. [c] BHT = 2,6-di-*tert*-butyl-4-methylphenyl.

linyl)pyridine catalyst has recently been reported to be highly effective for intermolecular cyclopropanation,[36] but its overall effectiveness awaits further confirmation.

3. Homochiral rhodium(II) carboxylate catalysts

Dirhodium(II) carboxylates are structurally well defined, having D_{2h} symmetry, with axial coordination sites at which carbene formation occurs in reactions with diazo compounds. Homochiral dirhodium(II) carboxylate catalysts derived from enantiomerically pure carboxylate ligands have been prepared, but their applications have met with mixed success. Brünner and coworkers surveyed an extensive series of $(R^1R^2R^3CCOO)_4Rh_2$ catalysts (**10**) for their effectiveness in enantioselective intermolecular cyclopropanation and S—H insertion reactions, finding product optical purities to be less than 12 *%ee*.[37,38]



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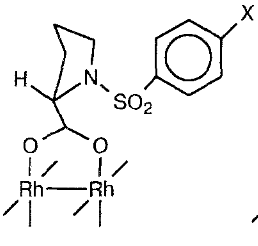

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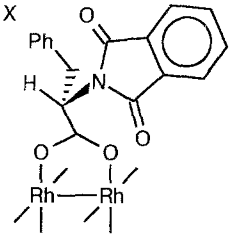
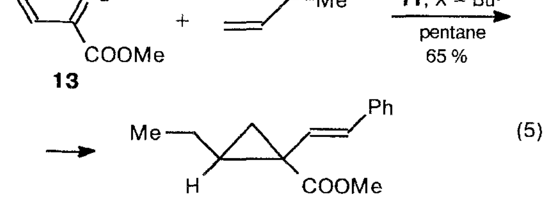


12

Prolinate derivatives of dirhodium(II) (**11**) were developed by McKervey and coworkers, and although product *% ee's* were low in cyclopropanation and insertion reactions of diazoacetate and β-keto-α-diazosulfones,[39] enantioselectivities from intermolecular cyclopropanation reactions of vinyldiazomethane (**13**)[40] reached as high as >95 % (Eq. 5); moderate yields and moderate to high enantiocontrol were also observed with styrene (90 *% ee*), vinyl acetate (76 *% ee*), ethylvinyl ether (59 *%ee*), and 1-hexene (>90 *%ee*). The *E*/*Z* ratios for the cyclopropane products, including **14**, were ≥8:1 which differ greatly from those obtained by cyclopropanation of these same alkenes with ethyl diazoacetate.[31,40] Here vinyldiazomethane **13** exhibits unusual, but very high, stereocontrol.

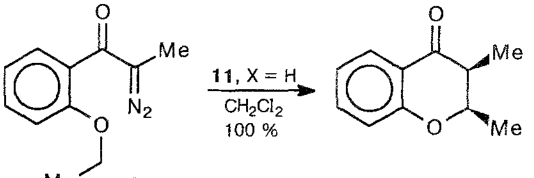


13

(5)

14, >95 % *ee*

Intramolecular C—H insertion reactions of diazoketone **15** yielded chromanone **16** in 82 *%ee* (Eq. 6) in a reaction catalyzed by the McKervey dirhodium(II) prolinate (**11**).[41]

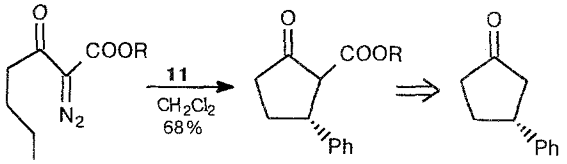


(6)

15

16, 82 % *ee*

The *cis*-isomer is the predominant product, which appears to be a function of the transition state geometry for insertion, and several substrates related to **15** produced similar results. Ikegami and coworkers found that enantioselectivities as high as 76 *%ee* for intramolecular C—H insertion reactions of β-keto-α-diazoesters could be achieved with the use of chiral *N*-phthaloylphenylalanate ligands for dirhodium(II) **12**,[42] but only with substrates that possess a bulky ester group (Eq. 7, R = Bu^t_2CH).

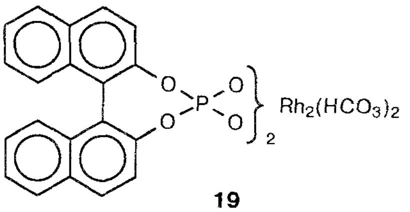


(7)

17

18: 76 % *ee*

The first formed β-ketoester **17** was decarboxylated, and the optical purity of the 3-substituted cyclopentanone **18** was monitored. Chiral binaphthyl phosphate ligated dirhodium(II) catalysts (*e.g.*, **19**) have also been investigated,[43,44] but the enantioselectivities achieved with their use have not rivaled **11** or **12**. Chiral porphyrinatorhodium catalysts, although enhancing *cis*-selectivity in intermolecular cyclopropanation reactions, failed to reach even moderate levels of enantiocontrol.[45]



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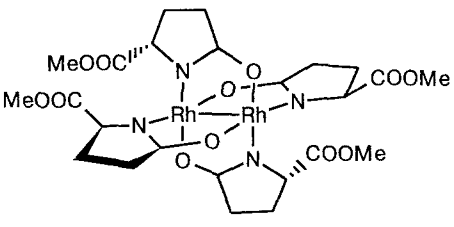
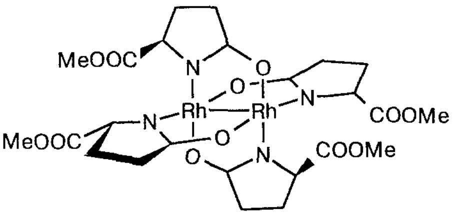
4. Chiral dirhodium(II) carboxamide catalysts

We have developed semiautomated methods for the synthesis of a new class of dirhodium(II) catalysts derived from chiral pyrrolidone, oxazolidinone, and imidazolidinone ligands.[46] Exemplified by dirhodium(II) tetrakis[methyl 2-pyrrolidone-5(*S*)-carboxylate], $Rh_2(5S\text{-}MEPY)_4$ (**20*S***), and its enantiomer

$Rh_2(5R\text{-}MEPY)_4$ (**20*R***), these catalysts were found to be exceptionally effective for highly enantioselective intramolecular reactions of diazoacetate esters.



20*S*



20*R*

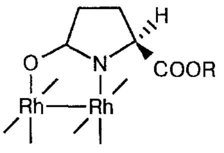
The novel design of these catalysts is revealed in their X-ray structures (*e.g.*, $Rh_2(5R\text{-}MEPY)_4(CH_3CN)_2$ in Fig. 1).[47] The dirhodium(II) core is surrounded by four bridging amide ligands so that the two nitrogen and two oxygen donor atoms bonded to each rhodium are oriented cis. The chiral center of the ligands is the carbon atom directly bonded to nitrogen so that the functional attachment, COOMe in the case of $Rh_2(MEPY)_4$ catalysts, lies in a spacial region that influences both the orientation of the bound carbene and the approach of the substrate to the carbene center.

Dirhodium(II) carboxamides are prepared from $Rh_2(OAc)_4$ by ligands substitution (Eq. 8). Using a Soxhlet extraction apparatus, the liberated acetic acid is trapped by sodium carbonate, thus driving the equilibrium to $Rh_2L^*_4$ and requiring only a modest excess of chiral ligand (L*H) to effect complete substitution.

$$Rh_2(OAc)_4 + 4\,L^*H \longrightarrow Rh_2L^*_4 + 4\,HOAc \qquad (8)$$

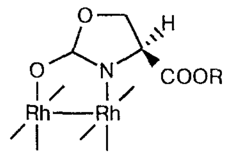
Acyclic amides, such as those derived from amino acids, do not undergo ligand substitution, presumably because syn orientation of the amide carbonyl and N—H are mechanistic requirements.

The dirhodium(II) catalysts that have provided highest levels of enantiocontrol are constructed from pyrrolidone (**21**), oxazolidinone (**22**), and 1*N*-acylimidazolidinone (**23**) ligands that possess a carboxylate group on the chiral adjacent to the amide nitrogen.



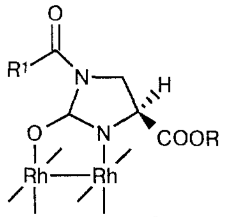
21

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



22

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



23

$Rh_2(4S\text{-}MACIM)_4$ (R = R^1 = Me)

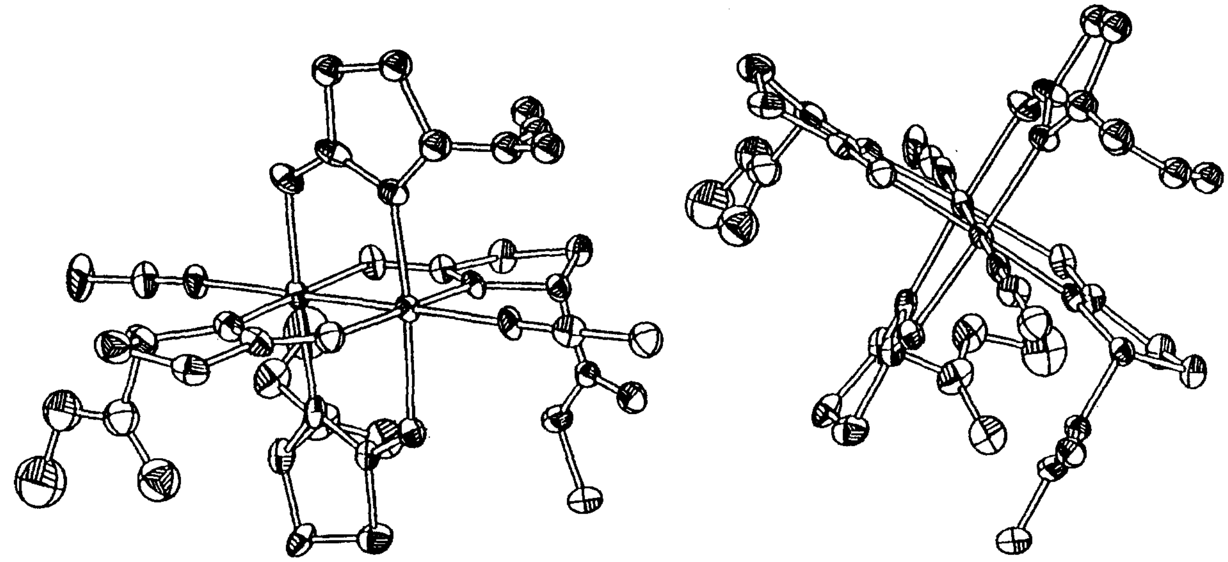
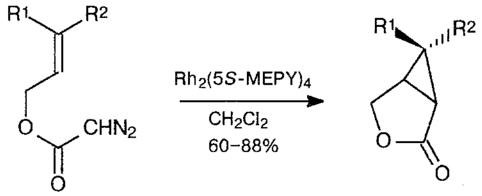


Fig. 1. X-Ray crystal structure of $Rh_2(5R\text{-}MEPY)_4(CH_3CN)_2$.

The carboxylate attachment is believed to provide stabilization to the intermediate metal carbene and further orient the rhodium-bound carbene for a greater degree of enantiocontrol.[47] Changing structure of R from methyl out to octadecyl generally has little effect on enantioselectivity but does change the solubility characteristics of the catalysts; for example, **21** (R = octadecyl) is soluble in pentane.

4.1. Enantioselective intermolecular cyclopropanation reactions

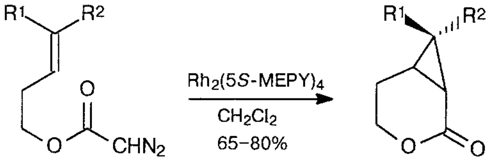
The effectiveness of $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(5R\text{-MEPY})_4$ has been demonstrated by the exceptional enantioselectivities achieved with their use in intramolecular cyclopropanation reactions of allylic diazoacetates (Eq. 9),[48] homoallylic diazoacetates (Eq. 10),[49] and *N*-homoallylic diazoacetamides (Eq. 11).[50]



(9)

24 **25**

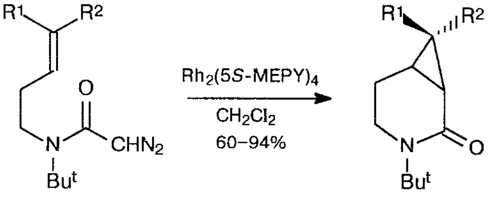
a: $R^1 = R^2 = H$ 95 % *ee*
b: $R^1 = R^2 = Me$ 98 % *ee*
c: $R^1 = Ph, Et, Bu_3Sn$; $R^2 = H$ ≥94 % *ee*
d: $R^1 = H$; $R^2 = n\text{-Pr}$ 85 % *ee*
e: $R^1 = H$; $R^2 = Ph$ 65 % *ee*



(10)

26 **27**

a: $R^1 = R^2 = H$ 71 % *ee*
b: $R^1 = R^2 = Me$ 77 % *ee*
c: $R^1 = Ph, Et$; $R^2 = H$ 88–90 % *ee*
d: $R^1 = H$; $R^2 = Et$ 82 % *ee*

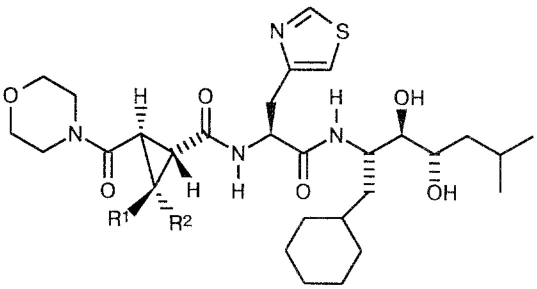


(11)

28 **29**

a: $R^1 = R^2 = H$ 60 % *ee*
b: $R^1 = R^2 = Me$ 75 % *ee*
c: $R^1 = Et$; $R^2 = H$ 90 % *ee*
d: $R^1 = H$; $R^2 = Et$ 67 % *ee*

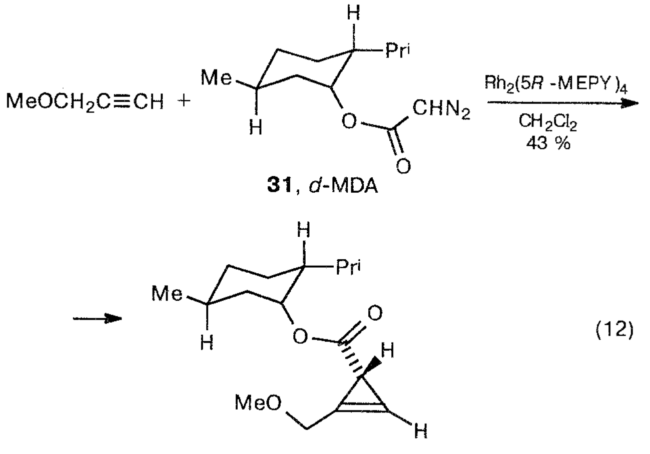
Product yields are generally high, and catalyst turnover numbers greater than 400 have been achieved. The absolute configurations of cyclopropane products have been determined, and they are as shown in the equations. Remarkably, these are relatively clean reactions which yield the pure cyclopropane product in high yield following simple chromatography or distillation. With allylic diazoacetates, trans substituents of the carbon—carbon double bond (R^1 = H, R^2 = alkyl, aryl) lead to lower enantiocontrol than is obtained with cis substituents, but this same effect is less evident in catalytic reactions of homoallylic diazoacetates or diazoacetamides. Furthermore, the placement of a methyl substituent at the β-position of the allyl group (methallyl) led to unexpectedly low enantiocontrol (7 % *ee*) in intramolecular cyclopropanation with the $Rh_2(\text{MEPY})_4$ catalysts. However, this catalytic methodology has been used to prepare highly enantiomerically enriched 1,2,3-trisubstituted cyclopropanes as conformationally restricted peptide isosteres, including those of renin (**30**) and collagenase inhibitors.[51,52]



30

4.2. Enantioselective intermolecular cyclopropanation reactions

$Rh_2(5S\text{-MEPY})_4$ and $Rh_2(5R\text{-MEPY})_4$ are effective catalysts intermolecular cyclopropenation reactions of 1-alkynes (but not internal alkynes) with diazoesters and diazoamides.[53,54] Diastereoselectivities achieved from the appropriate match of catalyst configuration with *d*- or *l*-menthyl diazoacetate are 77 to ≥94 %*de* (*e.g.*, Eq. 12).

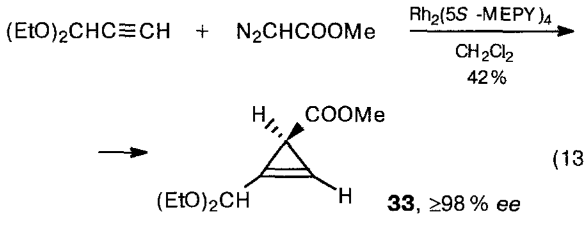


31, *d*-MDA

32, ≥94 % *de*

(12)

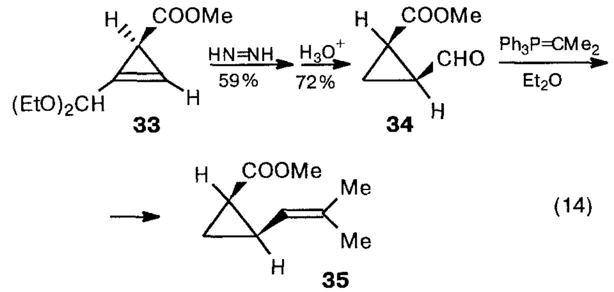
Enantioselectivities up to ≥94 % *de* have been obtained with 3-methoxy-1-propyne (reaction with *N*,*N*-dimethyldiazoacetamide) and 3,3-diethoxy-1-propyne (Eq. 13), but even cyclopropenation of 1-hexyne occurred with 78 %*ee*.



33, ≥98 % *ee*

(13)

N,*N*-Dimethyldiazoacetamide provides a higher level of enantiocontrol than do diazoesters. The absolute configurations of the cyclopropene products have been established;[54] $Rh_2(5S\text{-}MEPY)_4$ produces 2-substituted-2-cyclopropene-1-carboxylates having the (*S*)-configuration, whereas use of $Rh_2(5R\text{-}MEPY)_4$ provides these cyclopropene products in the (*R*)-configuration. Diimide reduction of these enantiomerically enriched cyclopropene compounds produces the corresponding *cis*-disubstituted cyclopropane esters exclusively in the moderate to high enantiomeric excesses achieved by cyclopropenation (Eq. 14);[54] attempts to produce the *cis*-disubstituted cyclopropane compounds directly by enantioselective intermolecular olefin cyclopropanation with chiral porphyrinatorhodium catalysts[45] have not been comparably successful (with styrene and ethyl diazoacetate: *cis*/*trans* = 2.5, *ee* for *cis*-isomer = 15 %).



33 **34** **35**

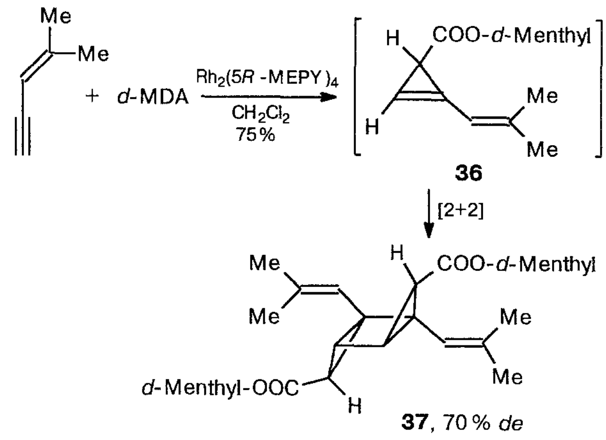
(14)

The use of a chiral semicorrin-copper catalysts (**5**, R = $CH_2OSiBu^tMe_2$) was not effective for enantioselective cyclopropenation reactions (low yields, low % *ee*).[53]

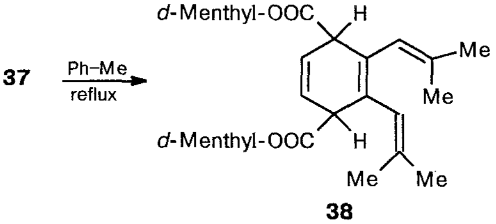
Following from earlier reports of selective cyclopropenation of enynes in $Rn_2(OAc)_4$ catalyzed reactions of methyl diazoacetate,[55,56] diazodecomposition of *d*-menthyl diazoacetate (*d*-MDA) catalyzed by $Rh_2(5R\text{-}MEPY)_4$ was performed in the presence of 4-methylpent-3-en-1-yne. The vinylcyclopropene products derived from these metal carbene reactions are unstable and undergo [2+2]-cycloaddition (Scheme 3). The cycloaddition product **37** was formed in 75 % yield and 70 %*de*.

With *l*-MDA and the same enyne catalyzed by $Rh_2(5S\text{-}MEPY)_4$, the analogous product was formed in 68 % *de* (55 % yield), but the use of *d*-MDA with $Rh_2(5S\text{-}MEPY)_4$ catalysis gave the cycloaddition product corresponding to **37** in only 30 %*de* (53 % yield). The *anti*-divinyl isomers of **37** were not observed, which is consistent with prior observations of methyl ester derivatives[57] and signifies further that the "head-to-head" [2+2]-cyclodimerization occurs between two **(*R*)-36** enantiomers or between two **(*S*)-36** enantiomers but not between **(*R*)-36** and **(*S*)-36**. Thermal decomposition of **37** in refluxing toluene yielded **38** quantitatively (Eq. 15) and with the same % *de* as the reactant.

Scheme 3



37, 70 % *de*



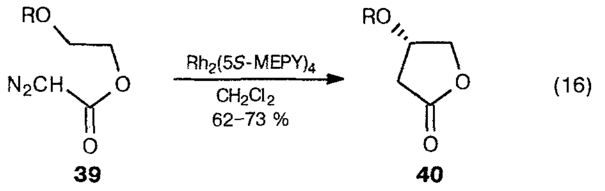
38

(15)

This catalytic methodology provides a direct route to chiral cyclopropenes and, following reduction, to chiral *cis*-disubstituted cyclopropanes, neither of which are accessible by alternative catalytic routes.[45,57] Improvements enantioselection from the use of other chiral dirhodium(II) carboxamide catalysts are under investigation.

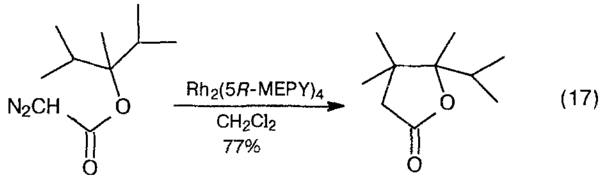
4.3. Enantioselective intermolecular carbon—hydrogen insertion reactions

Dirhodium(II) catalysts are uniquely suitable for intramolecular carbon—hydrogen insertion reactions of diazocarbonyl compounds.[11,15,16] Although there are notable exceptions,[16,58] five-membered ring formation is preferred,[15] and regioselectivity is generally subject to defined electronic effects.[59–61] Early applications of $Rh_2(5S\text{-}MEPY)_4$ and $Rh_2(5R\text{-}MEPY)_4$ to diazodecomposition of alkyl diazoacetates have demonstrated the feasibility of these catalysts for highly enantioselective and regioselective C-H insertion reactions (*e.g.*, Eq. 16).[62] Insertion into a C-H bond a to an ether oxygen is a facile process, and with R = benzyl (Bn) in Eq. 16 hydrogenolysis generated the 4-hydroxy derivative (**40**, R = H).[15]



R = Me (91 % *ee*), Et (89 % *ee*), Bn (87 % *ee*)

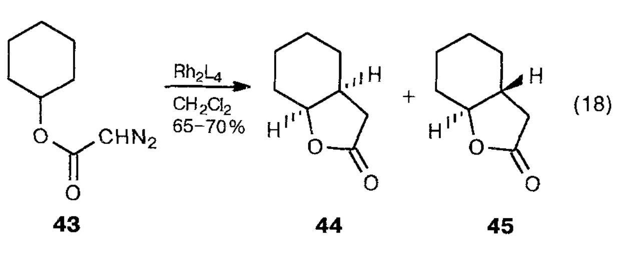
Applications with diazoesters that undergo insertion into a C—H bond vicinal to the incipient chiral center (*e.g.*, Eq. 17) suggested further advantages of this methodology for asymmetric synthesis.



42, 60% *ee*

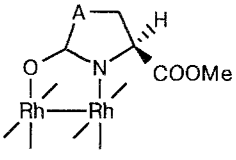
Cumyl diazoacetate underwent insertion into the normally disfavored primary C—H bond of prochiral methyl groups to form the corresponding lactone in 76 % *ee*.[62]

This methodology was recently extended to C—H insertion reactions of cycloalkyl diazoacetates where diastereoselectivity in the formation of *cis*- and *trans*-fused bicyclic lactones is a critical control feature.[63] Prior applications of dirhodium(II) carboxylates indicated limited selectivity (*cis/trans* = 40:60 for cyclohexyl diazoacetate with $Rh_2(OAc)_4$). Use of $Rh_2(5S\text{-MEPY})_4$ or its enantiomer produced insertion products with a high degree of enantiocontrol, but diastereocontrol was only 3:1 (*e.g.*, Eq. 18).



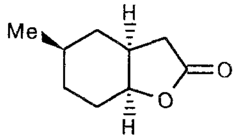
	44	45
$Rh_2(OAc)_4$	40 %	60 %
$Rh_2(5S\text{-MEPY})_4$	75 % (97 % *ee*)	25 % (91 % ee)
$Rh_2(4S\text{-MACIM})_4$	99 % (97 % *ee*)	1 % (65 % *ee*)

However, both high enantiocontrol and nearly complete diastereocontrol were achieved with recently developed dirhodium(II) tetrakis[methyl-1*N*-acetylimidazolidin-2-one-4(*S*)-carboxylate], $Rh_2(4S\text{-MACIM})_4$ (**23**). The oxazolidinone analog of $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(4S\text{-MACIM})_4$, $Rh_2(4S\text{-MEOX})_4$ (**22**), provided high enantiocontrol but significantly lower diastereocontrol: (**44**)/(**45**) = 55:45.

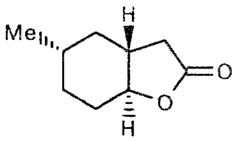


21, A = CH_2: $Rh_2(5S\text{-MEPY})_4$
22, A = O: $Rh_2(4S\text{-MEOX})_4$
23, A = NCOMe: $Rh_2(4S\text{-MACIM})_4$

Similarly high enantio- and diastereoselectivities have been achieved with cyclopentyl through cyclooctyl diazoacetates and with *cis*- or *trans*-4-alkylcyclohexyl diazoacetates where preferential insertion into equatorial C-H bonds (*e.g.*, **46** and **47**) has been demonstrated. Noteworthy is the extent of enantiocontrol in the formation of either *cis*- or *trans*-fused bicyclic lactones.

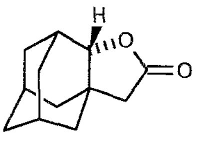


46, 98 % *ee*
(with **22**)

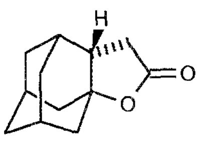


47, 95 % *ee*
(with **22**)

As suggested by the enantiocontrol and diastereocontrol achieved in the formation of **46** and **47**, alkyl substituents fix the transition state geometry and determine the geometrical preference (99 % *cis* for **46**, 90 % *trans* for **47**). Other examples, including the formation of lactones derived adamantanols (**48** and **49**), suggest the generality of this transformation in achieving exceptional enantiocontrol. Product yields of 60—80 %, after distillation or chromatographic purification, are achieved with the use of only 0.5 mol. % catalyst.



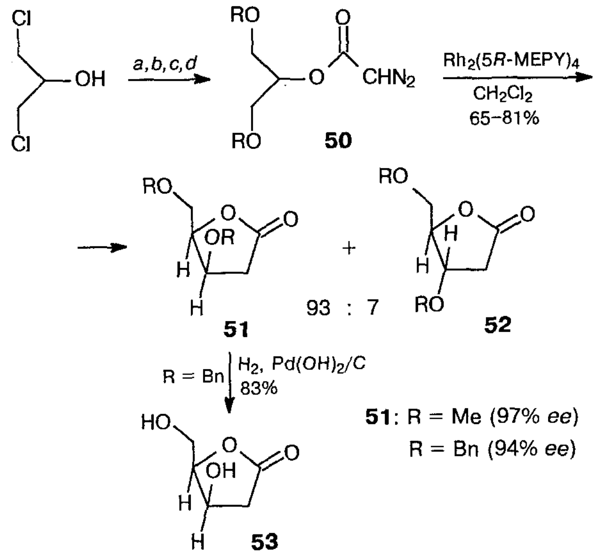
48, 98 % *ee*
(with **22**)



49, 90 % *ee*
(with **22**)

Exceptional enantio- and diastereocontrol in $Rh_2(MEPY)_4$-catalyzed C—H insertion reactions of glycerol-derived diazoacetates have provided a convenient synthesis of pure 2-deoxyxylolactone (**53**, Scheme 4).[64] As little as 0.1 mol. % of catalyst was required to effect complete reaction (1000 turnovers).

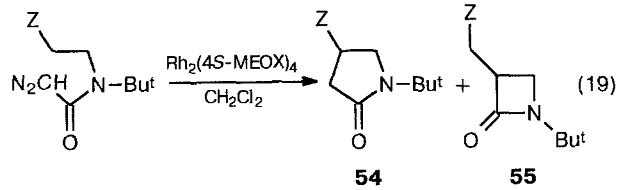
Scheme 4



a) RONa; b) diketene—acetone adduct, xylene, reflux; c) $MeSO_2N_3/Et_3N$; d) $LiOH \cdot H_2O$

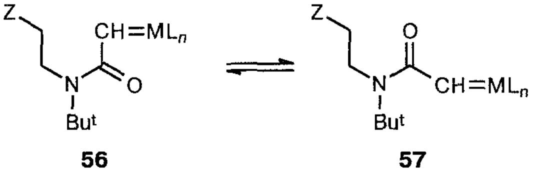
The ether alkyl group has very little influence on diastereoselectivity but, as was found from reactions of 2-alkoxyethyl diazoacetates,[62] the smaller methyl group is conducive to a high degree of enantiocontrol. Formally, 2-deoxyxylolactone is derived from *threo*-3,4,5-trihydroxypentanoic acid and in its reduced form, 2-deoxyxylulose, has been employed for the synthesis of 2-deoxynucleosides.[65–67]

Studies of C—H insertion reactions of *N*,*N*-disubstituted diazoacetamides reveal moderate enantioselectivities for γ-lactam formation (Eq. 19).[68,69]

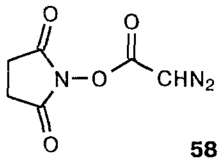


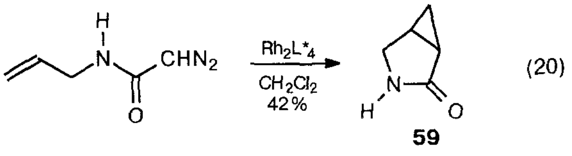
Z	Yield, %	
OEt	100 (78 % *ee*)	0
COOEt	7	93 (46 % *ee*)
Et	91 (71 % *ee*)	9 (80 % *ee*)

For 2-substituted-1-ethyl derivatives, γ-lactam formation is exclusive when the substituent is alkoxy, and β-lactam formation dominates when the substituent is carboxylate. $Rh_2(4S\text{-}MEOX)_4$ offers greater degree of enantiocontrol in γ-lactam formation than does $Rh_2(5S\text{-}MEOX)_4$. The use of *N*-(*tert*-butyl)acetamides was explored in order to facilitate conformational alignment of the was explored in order to facilitate conformational alignment of the reacting carbene with the targeted C—H bond **56**, but this derivatization is not suitable to desired synthetic applications.



The construction of *N*-allyldiazoacetamide, made possible by the use of the diazoacetyl transfer agent *N*-succinimidyl diazoacetate (**58**),[70] has allowed catalytic diazodecomposition resulting in the formation of GABA (γ-amino butyric acid) derivative **59** with up to 98 %*ee* (Eq. 20).



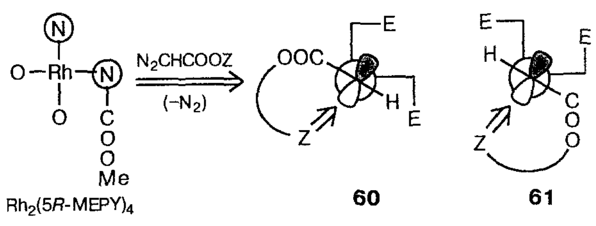


$Rh_2(5S\text{-}MEPY)_4$	97 % *ee*
$Rh_2(4S\text{-}MEOX)_4$	98 % *ee*

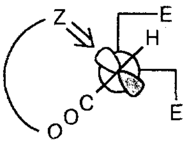
4.4. General view of enantioselection

Looking down the Rh—Rh bond axis, the rhodium face can be divided into four quadrants of which two are occupied by the ligands' chiral attachment (COOMe for **20*R*** or **20*S***). The third quadrant is filled by the carboxylate group of the carbene leaving the fourth open for substrate approach to the carbene center (Scheme 5).

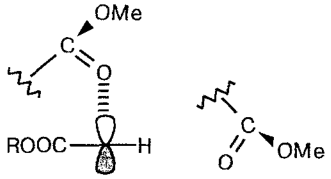
Scheme 5



Calculations have suggested that the preferred conformation of the carbene associated with $Rh_2(5R\text{-}MEPY)_4$ in the transition state for carbenoid transformations is that depicted in **60**.[47] For intramolecular reactions catalyzed by $Rh_2(5R\text{-MEPY})_4$, the reacting substrate bond (Z) approaches the rhodium-bound electrophilic carbene though a counterclockwise movement, whereas with $Rh_2(5S\text{-MEPY})_4$ the movement is clockwise **(61)**. Alternative conformations that model the transition state, especially **62**, have been evaluated by computational methods, and they are higher in energy. The importance of the ligand's carboxylate attachment appears to be associated with both orientation of the carbene and its stabilization by dipolar forces **(63)** since dirhodium(II) catalysts without the carboxylate attachment always give significantly lower enantiocontrol.[47]

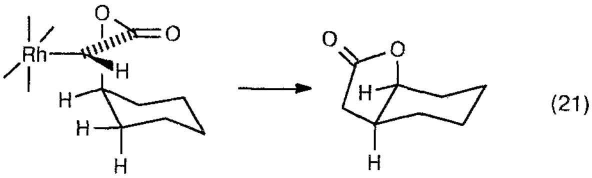


62



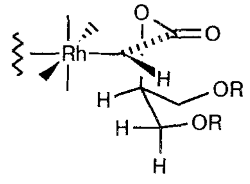
63

Stereochemical preference in C—H insertion reactions of cycloalkyl diazoacetates yielding the *cis*-fused ring corresponds to the conformational alignment of the carbene with the reacting C—H bond depicted in Eq. 21.

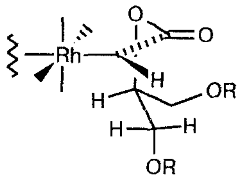


64 **44** (21)

Here axial conformational preference, which may be the unique achievement of $Rh_2(4S\text{-MACIM})_4$, together with preference for insertion into an equatorial C—H bond, dictates the stereochemical selectivity. The high preference for deoxyxylolactone **51** in catalytic diazodecomposition of glycerol-derived diazoacetates **50** is consistent with a transition state conformation **65a** in which the alkoxy group on carbon that is undergoing C—H insertion is *syn* to the carboxylate group rather than *anti*-**65b** which would be sterically less congested.



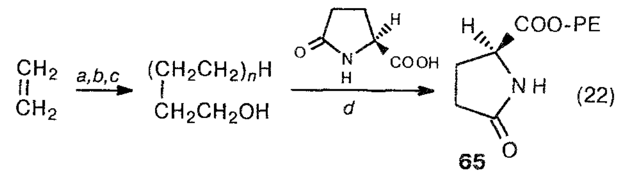
65a



65b

4.5. Structural influences on catalyst effectivenes for enantiocontrol

The development of anionic polyethylene carboxylates for attachment of dirhodium(II), and the successful demonstration that rhodium(II) carboxylate of terminally functionalized polyethylene carboxylic acids are effective and reusable cyclopropanation catalysts,[71] prompted the development of similarly reusable dirhodium(II) catalysts that possess chiral ligands.[72] Consequently, polyethylene oligomers with M_n of 1500—2000 were prepared by anionic oligomerization of ethylene, carboxylated, reduced, and then esterified with 2-pyrrolidone-5(*S*)-carboxylic acid (Eq. 22).

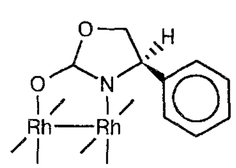


65 (22)

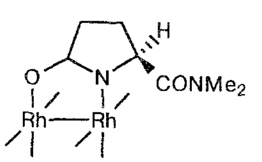
Reagents and conditions: *a*) *n*-BuLi, TMEDA, $n\text{-}C_7H_{16}$; *b*) CO_2 (−78 °C), H_3O^+; *c*) $Me_2S \cdot BH_3$, Ph—Me, 110 °C; *d*) cat. *p*-TsOH, Ph—Me, reflux

Ligand displacement of methyl 2-pyrrolidone-5(*S*)-carboxylate (5*S*-MEPYH) from $Rh_2(5S\text{-MEPY})_4$ by the soluble polyethylene-bound 2-pyrrolidone-5(*S*)-carboxylate produced a recoverable dirhodium(II) catalyst, $PE\text{-}Rh_2(5S\text{-PYCA})_4$, in high yield. The extraordinary effectiveness of this catalyst is demonstrated by high enantioselection for intramolecular cyclopropanation of 3-methyl-2-buten-1-yl diazoacetate **(24a)** in refluxing benzene solution (Eq. 9, 98 *%ee*) and for intramolecular carbon—hydrogen insertion of 2-methoxyethyl diazoacetate **(39)** under the same conditions (Eq. 16, 72 *%ee*). Moderate diastereoselection is obtained from the cyclopropanation of styrene with *d*-menthyl diazoacetate. Although diminished selectivity occurs with catalyst recovery and reuse under standard conditions, retention of catalyst effectiveness is achieved by using 2—3 mol. % of the pyrrolidone ligand in up to seven subsequent runs with recovered, reused $PE\text{-}Rh_2(5S\text{-PYCA})_4$.

Dirhodium(II) tetrakis[4(*S*)-phenyl-2-oxazolidinone], $Rh_2(4S\text{-PHOX})_4$ **(66)**,[73] and dirhodium(II) tetrakis[*N*,*N*-dimethyl-2-pyrrolidone-5(*S*)-carboxamide], $Rh_2(5S\text{-DMAP})_4$ **(67)**,[74] were prepared to offer greater steric bias or stereo electronic control for enantioselective metal carbene reactions.

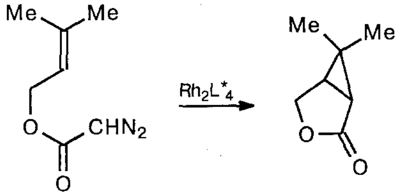


66



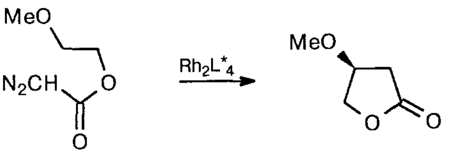
67

Their synthesis, characterization and X-ray structures have been reported. Structure-selectivity comparisons were made for the typical metal carbene transformations, including those of inter- and intramolecular cyclopropanation, intermolecular cyclopropenation, and intramolecular C—H insertion reactions of diazoacetates and, in some cases, diazoacetamides. The enantioselectivity achieved in the $Rh_2(4S\text{-PHOX})_4$ catalyzed reactions was intermediate between that of $Rh_2(5S\text{-MEPY})_4$ and dirhodium(II) tetrakis[4(*R*)-benzyl-2-oxazolidinone], $Rh_2(4S\text{-BNOX})_4$ **(68)** (Fig. 2), and results with $Rh_2(5S\text{-DMAP})_4$ were even lower (*e.g.*, Eqs. 23, 24). Because of its decreased reactivity for diazodecomposition, reactions catalyzed by $Rh_2(5S\text{-DMAP})_4$ were performed in refluxing dichloroethane (83 °C) rather than in refluxing dichloromethane.



(23)

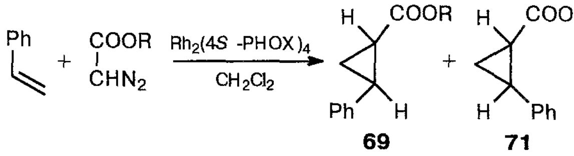
$Rh_2L^*_4$	
$Rh_2(5S\text{-MEPY})_4$	98 % *ee*
$Rh_2(4S\text{-PHOX})_4$	68 % *ee*
$Rh_2(5S\text{-DMAP})_4$	44 % *ee*
$Rh_2(4R\text{-BNOX})_4$	56 % *ee*



(24)

$Rh_2L^*_4$	
$Rh_2(5S\text{-MEPY})_4$	91 % *ee*
$Rh_2(4S\text{-PHOX})_4$	55 % *ee*
$Rh_2(5S\text{-DMAP})_4$	30 % *ee*
$Rh_2(4R\text{-BNOX})_4$	11 % *ee*

Unlike the other dirhodium(II) or copper catalysts, the use of $Rh_2(4S\text{-PHOX})_4$ for intermolecular cyclopropanation reactions results preferentially in the formation of the *cis*-cyclopropane isomer (*e.g.*, Eq. 25).



(25)

R = (–)-Menthyl	27 (40 % *de*) : 73 (72 % *de*)
R = Et	34 (24 % *ee*) : 66 (57 % *ee*)

This unique selectivity has been reported only for cyclopropanation reactions catalyzed by chiral rhodium(III) porphyrin complexes,[45] albeit with low enantiocontrol. However, intramolecular cyclopropanation (Eqs. 9—11) and intermolecular cyclopropenation, followed by reduction (*e.g.*, Eq. 14), remain the most certain methodologies for *cis*-cyclopropane production.

Diazodecomposition by $Rh_2(5S\text{-DMAP})_4$ generally requires mach higher temperatures than those routinely employed with $Rh_2(5S\text{-MEPY})_4$, and this lower activity is commonly attributed to steric effects.[75] The rigidity of this dirhodium(II) compound, defined in its X-ray crystal structure, can be used to rationalize this decreased reactivity. Furthermore, the principal factor responsible for the high level of enantiocontrol observed with $Rh_2(5S\text{-MEPY})_4$ that is, electronic stabilization of the intermediate metal carbene by the pendant carboxylate group **(63)**, is absent in reactions catalyzed by $Rh_2(5S\text{-DMAP})_4$.

Not all catalyst modifications result in lower enantiocontrol, relative to $Rh_2(5S\text{-MEPY})_4$, or its enantiomer. One of the greater challenges in catalyst design has been for the intramolecular cyclopropanation reaction of 2-methyl-2-propen-1-yl diazoacetate (Eq. 26). With

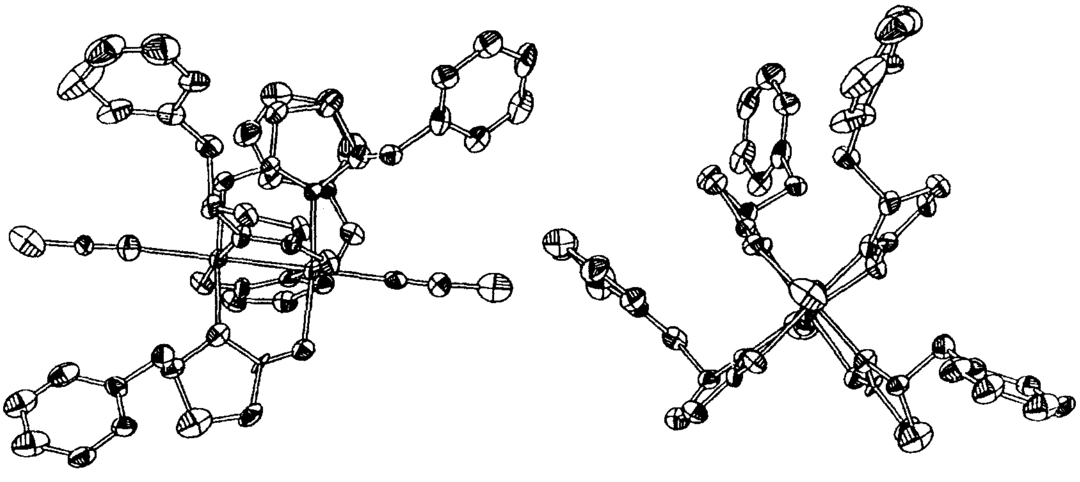
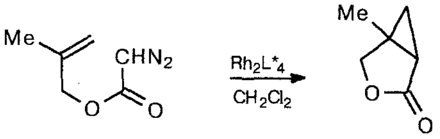


Fig. 2. X-Ray crystal structure of $Rh_2(4S\text{-BNOX})_4(CH_3CN)_2$.[47]

Rh_2(5*S*-MEPY)$_4$, product enantiomeric excess amounted to only 7 %*ee*.



(26)

72

21, Rh_2(5*S*-MEPY)$_4$ 7 % *ee*
23, Rh_2(4*S*-MACIM)$_4$ 67 % *ee*
73, Rh_2(4*S*-MOCIM)$_4$ 78 % *ee*

However, spectacular increases in enantioselectivity have been achieved with the use of the chiral imidazolidinone catalysts; MOCIM = methyl 1*N*-octanoylimidazolidinone-4-carboxylate.

5. Summary

Dirhodium(II) catalysts whose ligands are pyrrolidone-, oxazolidinone-, or imidazolidinone-carboxylates are exceptionally effective for diazodecompositions and carbene addition/insertion of diazoesters and diazoamides. Not only do these catalysts enhance enantiocontrol, routinely reaching >90 % *ee*, but they also achieve significant diastereocontrol. Intramolecular transformations generally occur with mach greater stereocontrol than do intermolecular reactions. No other catalyst or set of catalysts is as selective in metal carbene transformations. The commercial availability of Rh_2(5*S*-MEPY)$_4$ and Rh_2(5*R*-MEPY)$_4$ (Regis Technologies, Inc., Morton Grove, IL 60053, U.S.A.) makes possible applications by other beyond those reported in this review.

Acknowledgment. Our gratitude extends to all postdoctoral associates and undergraduate students who have worked on this project. The long-term collaboration/cooperation that we have had with Academician Oleg M. Nefedov has brought scientists to my laboratory whose exceptional skills and dedication have made this report possible: Marina N. Protopopova, Michail Yu. Eismont, Alexey B. Dyatkin, Evgenii A. Shapiro, and, most recently, Alexey V. Kalinin. Financial support for this research has been provided by the National Institutes of Health, the National Science Foundation, and the Robert A. Welch Foundation.

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Received September 6, 1994