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Stereoselective intramolecular carbon–hydrogen insertion reactions of metal carbenes

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1. Introduction

The intramolecular formation of a carbon–carbon bond by the metal-catalyzed decomposition of alpha-diazocarbonyl compounds has emerged as a general strategy for the production of various carbocycles and heterocycles. The utility of this approach for ring construction is directly related to the level of site- and stereoselectivity of the carbon–hydrogen insertion process, the former determining the ring size of the carbocycle or heterocycle generated. In order to guarantee high site selectivity, early investigations into intramolecular carbon–hydrogen insertion of carbenoids were restricted to substrates in which the

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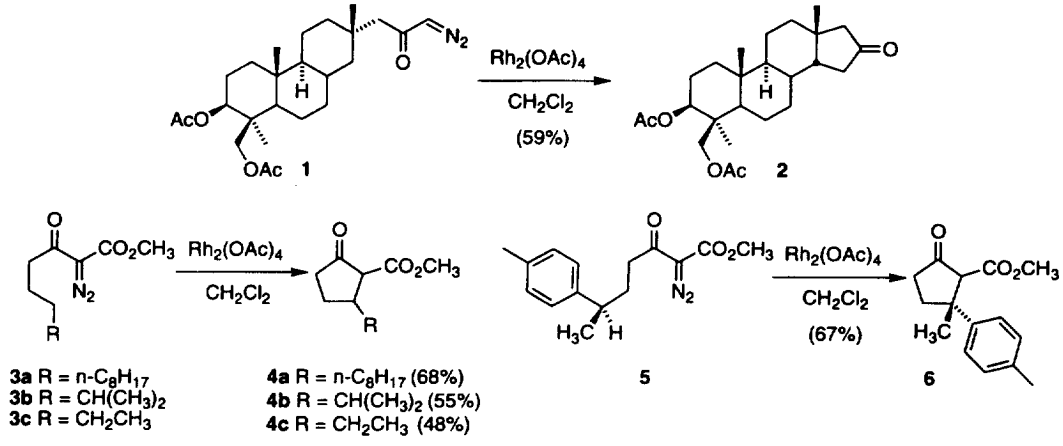
carbon–hydrogen bond and carbenoid center were positioned in close proximity.[1] A second limitation was the almost exclusive use of copper salts to effect diazo decomposition.[2] In 1982, however, Wenkert described the efficient cyclization of **1** to cyclopentanone **2** using rhodium(II) acetate (Scheme 1). The corresponding copper catalyzed cyclization protocol proceeded poorly.[3] In the same year Taber described the rhodium(II) acetate catalyzed decomposition of long-chain diazoketones (**3**) to provide cyclopentanes (**4**) in high yield.[4a] A later report from Taber expanded on the propensity of diazoketones to form five-membered rings, and the order of reactivity of C–H bonds was determined to be methine>methylene>methyl.[4b] Taber also demonstrated that rhodium-catalyzed intramolecular insertion reactions proceed with retention of stereochemistry (**5**→**6**).[5] Subsequent to these early observations, considerable efforts have been made to enable chemists to control site- and stereoselectivity of diazocarbonyl cyclization processes.[6] This review covers advances in the area of asymmetric intramolecular carbon–hydrogen insertions up to 1998.



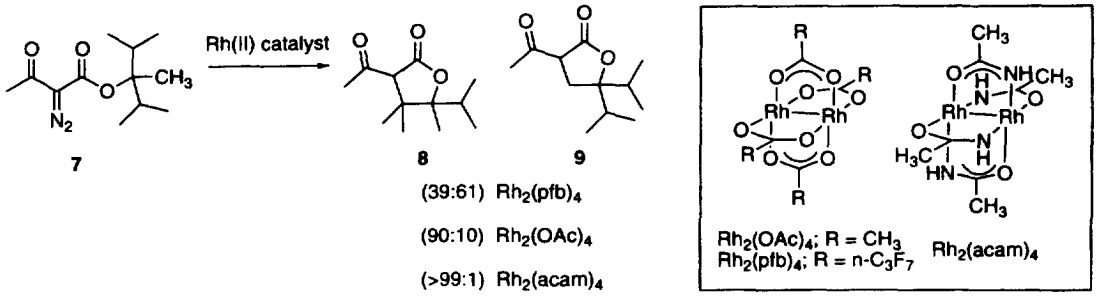
Scheme 1.

2. Regioselectivity

2.1. *Electronic and steric ligand effects*

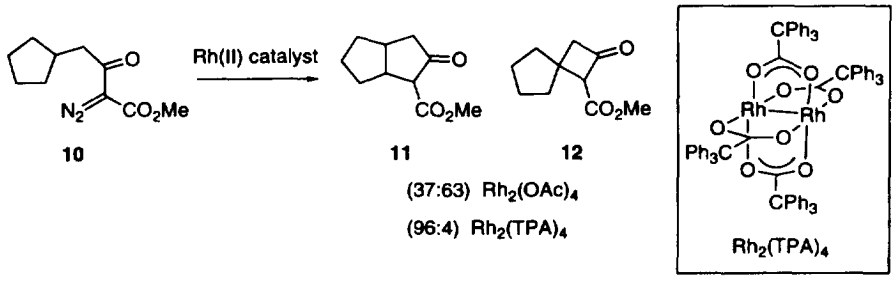
Three major reaction pathways available to metallocarbenes are olefin cyclopropanation, ylide generation, and X–H insertion (X=C, Si, N, O).[6] Thus, for a given substrate, several reaction pathways are sometimes available, and the chemoselectivity of such processes is dependent on the nature of both the substrate and the catalyst. Within the carbon–hydrogen insertion manifold, five-membered ring formation is usually favored. In cases where several chemically inequivalent C–H bonds are positioned equidistant from the diazo moiety the generation of isomeric products may be observed. This type of site (or regio) selectivity is dependent upon steric, conformational, and electronic factors. The choice of catalyst can sometimes improve the selectivity of processes governed by electronic factors, because the catalyst can mitigate the electrophilicity of the intermediate metal carbene. For example, Doyle has examined the cyclization of diazoester **7** which can cyclize to gamma lactones **8** and **9**, the products of insertion into the methine or methyl carbon–hydrogen bond, respectively (Scheme 2).[7] When the cyclization of **7** was effected using $Rh_2(pfb)_4$, a nearly statistical 39:61 mixture of **8** and **9** was observed. When $Rh_2(OAc)_4$ and $Rh_2(acam)_4$ were used to promote the cyclization, the ratios improved to 90:10 and >99:1 respectively. Thus, the more electron deficient carbenoid generated from $Rh_2(pfb)_4$ underwent

C–H insertion in a non-selective manner, while the more electron rich carbenoids provided excellent selectivity for insertion into the C–H methine.



Scheme 2.

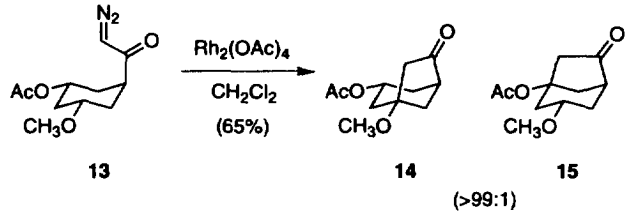
A complementary approach to achieving site selective C–H insertion is to generate sterically demanding metal carbenes. For example, Ikegami has prepared rhodium(II) tetra(triphenylacetate) $Rh_2(TPA)_4$.[8] Cyclization of diazoester **10** using $Rh_2(OAc)_4$ generates a 37:63 mixture of fused cyclopentanone **11** and spiro cyclobutanone **12** (Scheme 3). While five-membered ring formation is generally favored, the electronic preference for methine insertion leads to the competitive generation of cyclobutanone **12**. When cyclization of **10** is carried out using the bulky catalyst $Rh_2(TPA)_4$, a 96:4 mixture of **11** and **12** is produced.



Scheme 3.

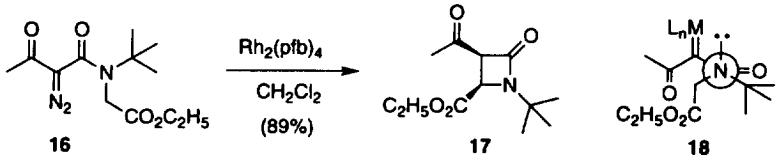
2.2. *Electronic and conformational effects of the substrate*

Heteroatoms capable of donating electron density have an activating influence on adjacent carbon–hydrogen bonds involved in insertion reactions. An interesting example of this effect, reported by Adams, is the cyclization of psuedosymmetric diazoketone **13** which generates exclusively cyclopentanone **14**.[9] The selective formation of **14** is attributed to the electron releasing character of the ether and electron-withdrawing character of the acetate groups.



(1)

As the above examples illustrate, the site selectivity of intramolecular carbon–hydrogen insertion reactions of metal carbenes is influenced by steric, as well as electronic effects. A third factor in determining regioselectivity, in some instances, is conformational effects. For instance, Doyle found the cyclization of diazoketone **16** catalyzed by $Rh_2(pfb)_4$ provided exclusively beta-lactam **17**.[10] The formation of **17** results from insertion into a methylene located alpha to the electron-withdrawing ester group, usually an electronically disfavorable process.[11] The alternative process is insertion into one of the three methyls of the *tert*-butyl group, which would produce a gamma lactam. The preference for **17** is rationalized by invoking conformation **18**, and assuming a faster rate of C–H insertion relative to carbon–nitrogen bond rotation. But insertion into a methyl C–H bond may itself be a slow process because of conformational constraints, even when methyl C–H is in close proximity to a metal carbene.



(2)

3. Mechanism of metal carbene C–H insertion

An understanding of the mechanism of a rhodium(II) mediated carbon–hydrogen insertion reaction of diazocarbonyl compounds would provide a means for predicting the stereochemical course of a cyclization, as well as aid in the design of catalysts capable of inducing asymmetry. Several mechanistic proposals have been advanced, although little is known in terms of the mechanistic detail.[4b,6e,7b,12] The most widely accepted of these proposed mechanisms proceeds by way of either a three-center two-electron transition state (**23**) or a sigma complex (**24**) (Fig. 1). In either case, an intermediate metal carbene (**22**) is generated by complexation of the electron rich alpha carbon of diazoketone **19** with the vacant apical coordination site of rhodium(II) carboxylate **20** to generate **21**. Expulsion of nitrogen produces metal carbene **22**. Viewing the intermediate carbenoid as an ylide-type intermediate (**22a**) reveals an electrophilic p-orbital capable of interacting with a neighboring sigma C–H bond in either a three-center two-electron system (**23**) or a sigma complex (**24**). In general, workers in the area propose that these complexes form reversibly, thus accounting for the observed order of selectivity of methine to methylene to methyl. When complexes **23** and **24** collapse to produce the cyclization product **25**, the catalyst **20** is regenerated.

4. Substrate-induced stereoselectivity

4.1. 1,2-Asymmetric induction

The factors which determine the regioselectivity of intramolecular carbon–hydrogen insertions of metal carbenes are now well documented. On the other hand, the diastereoselectivity of these cyclizations is often less predictable. Generally, the most synthetically useful types of diastereoselection are those involving 1,2-asymmetric induction. For example, cyclization of α-diazoketoester **26** using rhodium(II) acetate as a catalyst yielded exclusively the *trans* cyclopentanone **27**.[13] Cyclization of α-diazoamide **28** provided beta-lactam **29** as the major product along with the corresponding *trans,trans*-isomer **30**.[14] After chromatographic separation, **29** was carried forward to an optically pure bicyclic carbapenem of biological importance.

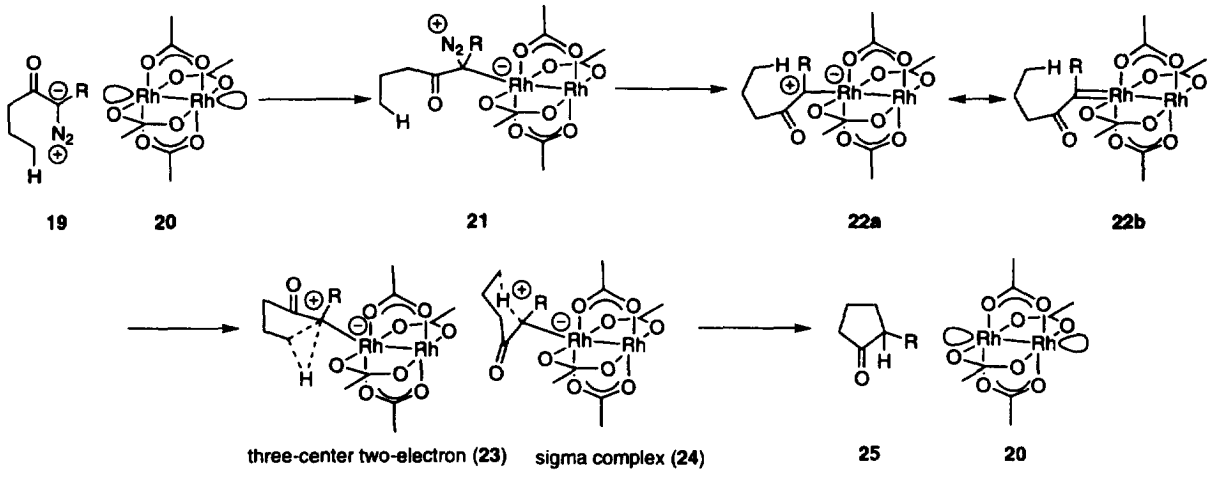
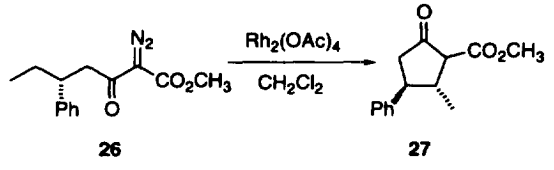
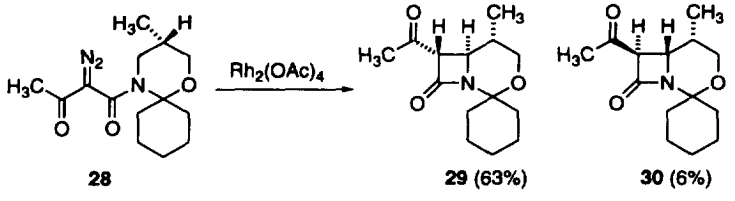


Fig. 1. Proposed mechanisms of the carbon–hydrogen insertion of diazocarbonyl compounds mediated by rhodium(II) catalysis[7b,12]



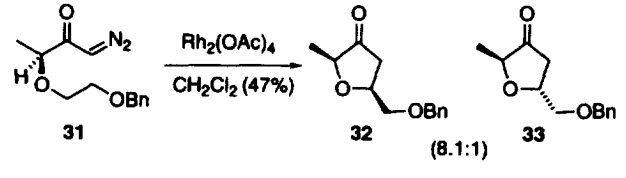
(3)



(4)

4.2. 1,3-Asymmetric induction

The cyclization of chiral alpha alkoxy diazoketones leads to a diastereoselective synthesis of *cis*-2,5-disubstituted 3(2*H*)-furanones. These cyclizations, which rely on 1,3-asymmetric induction, proceed with modest to good *cis* selectivity, and often in moderate chemical yield. An interesting example which also illustrates the preference of five-membered over six-membered ring formation is the cyclization of diazoketone **31**.[15] A copper salt promoted cyclization of diazoketone **34** using copper(II) acetylacetonate proceeded in superior yield and comparable stereoselectivity relative to the corresponding rhodium(II) acetate catalyzed reaction.[16]



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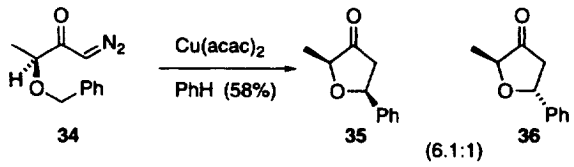
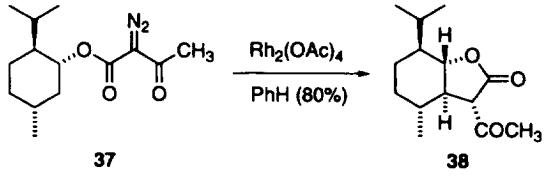


(6)

4.3. Fused ring systems: axial versus equatorial C–H bonds

The intramolecular C–H insertion of cycloalkyl diazoesters is a potentially powerful method for the construction of fused ring systems. The ability to exercise diastereo- as well as regiocontrol in these cyclizations will determine their overall utility. In terms of diastereoselectivity, a propensity for insertion into equatorially positioned C–H bonds has been noted.[7b,17,18] For example, the cyclization of menthyl diazoacetoacetate **37** yielded exclusively *trans* fused lactone **38**.[17] The cyclization of diazoacetate **39** using rhodium(II) acetate caused a loss of regiocontrol resulting in the production of delta lactone **41**, while maintaining diastereoselective insertion into the equatorially oriented C–H bond of the neighboring methylene group.[18] In the case of more flexible cycloalkyl diazoesters (**42**), a loss of diastereocontrol is observed owing presumably to the substrate's ability to access alternative ring conformations, leading to ambiguous definition of axial and equatorial C–H bonds. However, Doyle has found various chiral rhodium(II) catalysts produce not only high levels of enantioselectivity but also diastereoselectivity in the cyclization of diazoacetates **42a–c** (vide infra; Table 1).[17,18]



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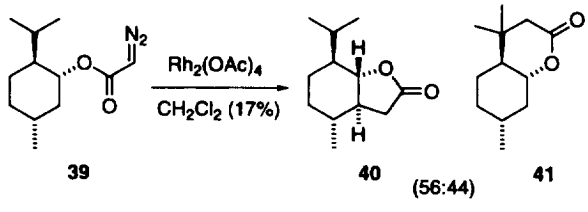
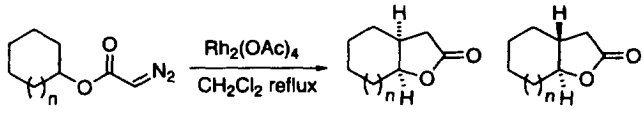


(8)

4.4. Computational methods for predicting stereoselectivity

The cyclization of enatiomerically pure acyclic diazoesters is a useful approach to assembling highly alkylated and enantiopure cyclopentanes.[19] A potential drawback to this strategy is the inability to accurately predict which cyclizations will proceed with high diastereoselectivity.[20] In order to address this issue, Taber has introduced a computational method which predicts which cyclizations will proceed with high diastereoselectivity. The computational model estimates the relative energies of diastereomeric transition states applying a combination of molecular mechanics and ZINDO programs. The assumption made in constructing the estimated transition state structure is that the approach of the appropriate C–H bond to a rhodium carbene will result in a chair-like arrangement. Energy differences greater than 2 kcal/mol between diastereomeric transition state structures suggest a highly diastereoselective

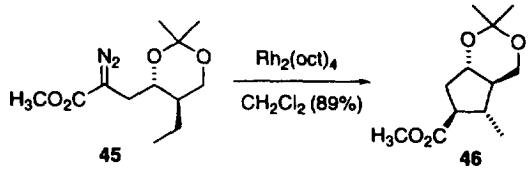
Table 1
Rhodium(II) acetate catalyzed C–H insertion reactions of diazoacetates



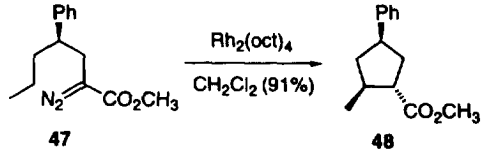
42 43 44

entry	n	isolated yield, %	43:44
a	1	46	40:60
b	2	29	30:70
c	3	33	29:71

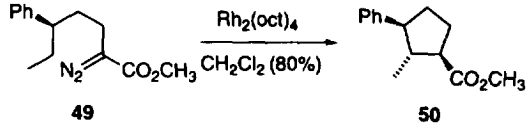
cyclization. This approach accurately predicted the diastereoselectivity of the cyclization of diazoesters **45**, **47**, **49** and **51**.



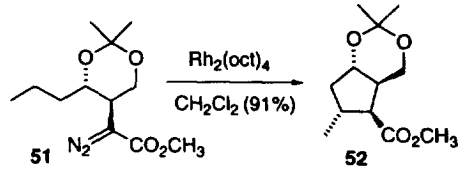
45 46 (9)



47 48 (10)



49 50 (11)

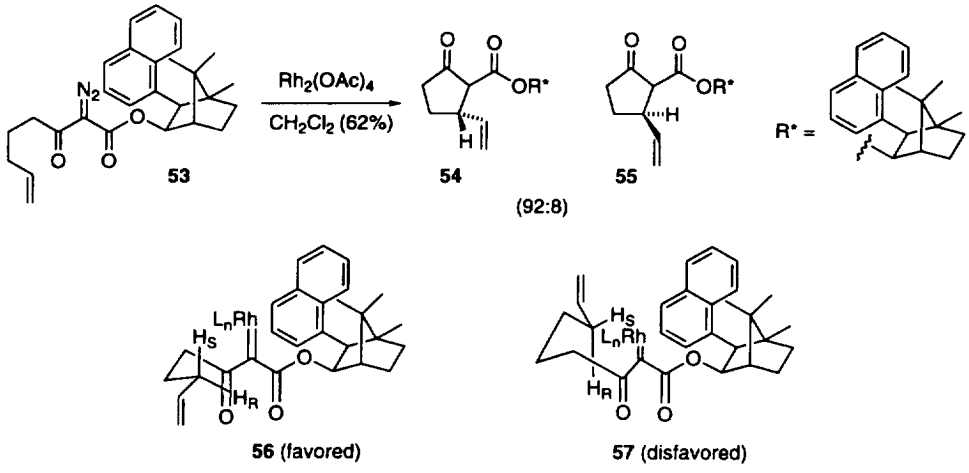


51 52 (12)

5. Auxiliary induced stereoselectivity

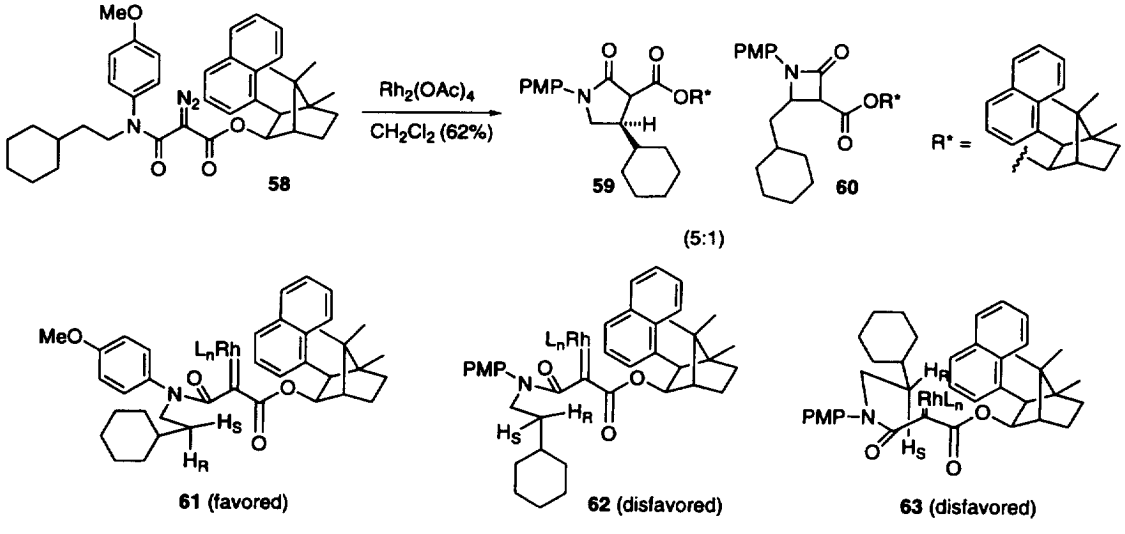
Due in part to advances in the development of highly enantioselective chiral catalysts, chiral auxiliaries have not been routinely used for asymmetric induction in C–H insertion reactions. However, their use has been justified by several practical applications in organic synthesis. One of the first examples is found in the construction of substituted cyclopentanones by Taber and Raman.[21] α-diazo β-keto esters derived from various chiral cyclic alcohols were tested; 1-naphthylborneol esters gave the best results. For example rhodium(II) acetate catalyzed cyclization of **53** provided **54** and **55** in a 92:8 ratio (Scheme 4).

Notably, the diastereomeric esters are separable by flash chromatography providing practical access to optically pure cyclopentanones. The 3-substituted cyclopentanone derived from **54** was later used in an asymmetric synthesis of (+)-estrone methyl ether.[22] The diastereoselectivity of the cyclization of **53** can be explained based on a favored staggered conformation of metal carbene **56** relative to the more congested conformer **57**. Insertion into the psuedo equatorially disposed hydrogen in **56** (with retention of configuration) would lead to the observed production of cyclopentanone **54**.



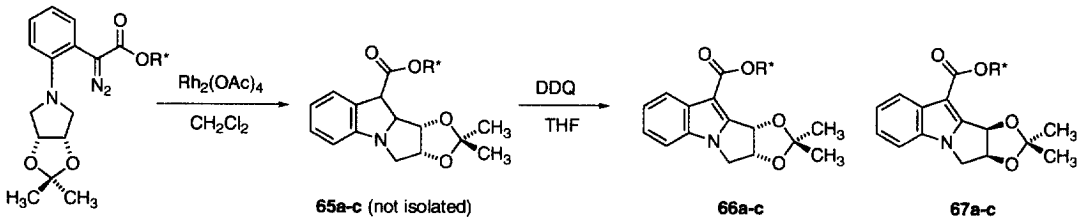
Scheme 4.

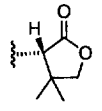
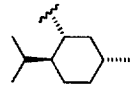
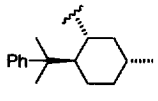
Wee and Liu[23] utilized the naphthyl camphor auxilary in the asymmetric synthesis of 2-pyrrolidinones. A good example is the rhodium(II) acetate catalyzed decomposition of diazoanilide **58** which led to the production of a 5:1 mixture of pyrrolidinone **59** and beta lactam **60** (Scheme 5). Decarboxylation of **59** provided the corresponding pyrrolidinone in 98% enantiomeric excess (depending on the nature of the substrate the reported enantiomeric excesses ranged from 37 to 98%). As these results indicate, the diastereoselectivity of the cyclization of **58** is opposite to that observed by Taber in the cyclization of **53**. To explain the observed selectivity, Wee proposed a favored eclipsed (**61**) rather than staggered conformation (cf. **56**).

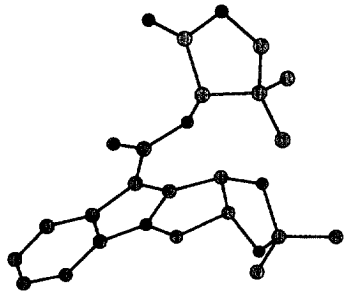


Scheme 5.

Table 2
Rhodium(II) acetate catalyzed C–H insertion reaction of chiral diazoesters



entry	R*	isolated yield, %	66:67
a		82	68:32
b		46	50:50
c		46	53:47



X-ray structure of 66a

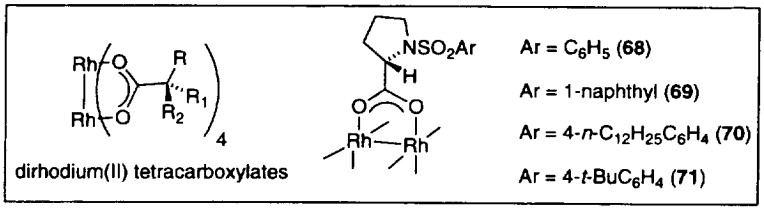
As part of a program directed toward the synthesis of mitomycin antitumor antibiotics, Sulikowski et. al. examined the cyclization of diazoesters **64a–c**[24] (Table 2) which entailed the use of chiral auxilaries. There were eight potential diastereomers that could be generated during the cyclization of **64a–c**; however, no effort was made to analyze the product mixture, but instead the mixture was oxidized with DDQ to generate two diastereomers **66** and **67** whose ratio was determined by HPLC. The ratio of **66** and **67** corresponds to the collective selectivity, vis-à-vis **65**, for insertion into one of the two sets of diastereotopic methylene hydrogens adjacent to the nitrogen atom. Pantolactone ester yielded a 68:32 mixture of **66a** and **67a** which was separable by flash chromatography.[25,26] The structures were assigned based on single crystal X-ray analysis of **66a** (representation of X-ray structure shown). In contrast to the observed diastereoselectivity of this process, neither menthyl ester **64b** nor phenylmenthyl ester **64c** provided selectivity in the cyclization.

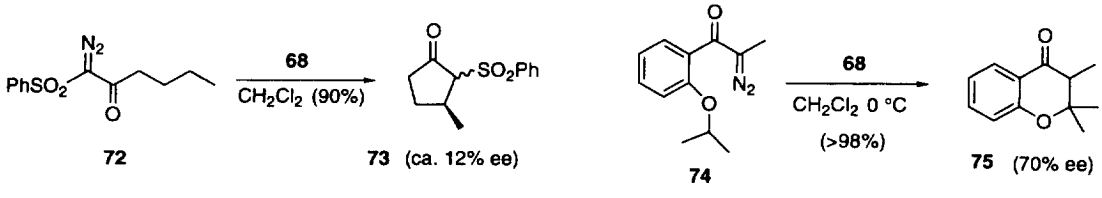
6. Catalyst-induced stereoselectivity

The most active area of investigation for inducing asymmetry in intramolecular carbon–hydrogen insertion of metal carbenes has been the development of chiral catalysts.[27] In the case of enantioselective rhodium(II) catalysts, three types of complexes have been examined. These are the rhodium(II) carboxylates, carboxamidates and to a lesser extent phosphonates. Most of these catalysts are derived from rhodium(II) tetraacetate or rhodium(II) carbonate sodium salt by simple ligand displacement.[28,29] In this section we discuss recent progress in developing enantioselective intramolecular carbon–hydrogen insertions using these three classes of catalyst.

6.1. Dirhodium tetracarboxylates

The first group of catalysts applied to enantioselective carbon–hydrogen insertion reactions of metal carbenes were rhodium(II) tetracarboxylates derived from N-protected L-proline derivatives (**68–71**; Scheme 6).[30–32] In 1990, McKervay reported that the cyclization of diazoketosulfone **72** using the rhodium salt of N-benzenesulfonyl-L-proline provided cyclopentanone **73** as a mixture of *cis*- and *trans*-isomers.[30] The enantiomeric excess of the *trans*-isomer (**73**) was estimated to be 12%, and on recrystallization increased to 30% ee. In a subsequent publication, McKervay found the same rhodium(II) catalyst provided chromanone **75** in near quantitative yield and 70% enantiomeric excess starting from diazoketone **74**.[31] Notably, cyclization of **72** to **73** and **74** to **75** differ in that the latter induces asymmetry at the alpha carbon, while the former induces asymmetry at the beta carbon. In this sense, the cyclization of **74** to **75** is unique relative to other enantioselective cyclizations of metal carbenes.





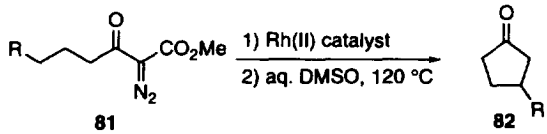
Scheme 6.

Ikegami and Hashimoto have developed a series of rhodium(II) catalysts derived from (*S*)-2-benzyloxyphenylacetic acid (**76**) and N-phthaloyl protected amino acids (**77–80**) (Fig. 2).[33] This series of catalysts has proven to be particularly effective in enantioselective intramolecular C–H insertions of α-diazo β-keto esters leading to the production of 3-substituted cyclopentanones. For instance, cyclization of **81** to **82** provided, following decarboxylation, 3-substituted cyclopentanones (Table 3, entries a–d) with an *R*-configuration and moderate enantiomeric excess. On the other hand, catalyst **76** derived from (*S*)-2-benzyloxyphenylacetic acid provided **82** possessing an *S*-configuration again in low enantiomeric excess (Table 3, entries e–g). The highest enantiomeric excess and chemical yield were observed using the phenylglycine derived catalyst (**77**). In a subsequent study, these workers determined that an increase in the inherent bulk of the alkoxy group of the ester had a favorable effect on enantioselectivity of the cyclization (Table 4).[34] Optimal enantioselectivity and chemical yield were observed in the case of diisopropylmethyl diazoesters (entries d, f–h).

Hashimoto and Ikegami also found the enantioselectivity of the cyclization of α-diazo β-keto esters to be dependent upon the electronic nature of the substituent at the insertion site.[35] In this case, the effect of electron releasing and withdrawing substituents on a phenyl or vinyl group adjacent to the reacting C–H bond was examined. As the results in Table 5 suggest, carbon–hydrogen bonds deactivated by electron-withdrawing groups provided the highest enantioselectivity. On the other hand, electron-withdrawing substituents adjacent to the reacting carbon–hydrogen bond led to higher enantioselectivity (cf. entries f and k).

The application of dirhodium(II) tetrakis[N-phthaloyl-(*S*)-phenylalinate][Rh_2(PTPA)$_4$] catalysis to

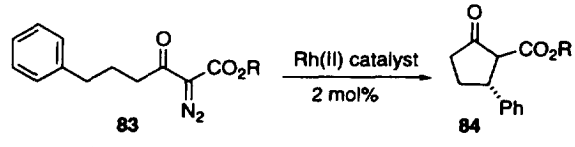
Table 3
Enantioselective intramolecular C–H insertion of α-diazo β-keto esters catalyzed by homochiral rhodium(II) carboxylates



81 82

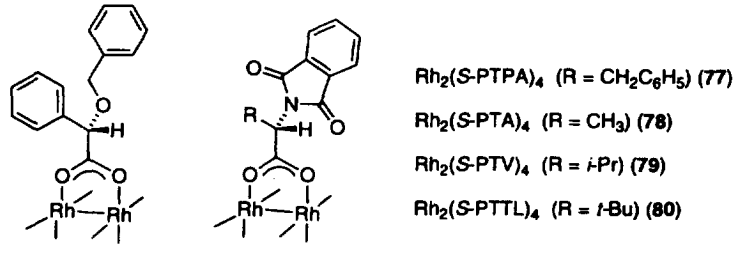
entry	R	catalyst	isolated yield, %	config	% ee
a	CH_3	$Rh_2(PTPA)_4$	76	*R*	24
b	CH_3	$Rh_2(PTA)_4$	73	*R*	24
c	$CH{=}CH_2$	$Rh_2(PTPA)_4$	44	*R*	38
d	C_6H_5	$Rh_2(PTPA)_4$	96	*R*	46
e	CH_3	**76**	75	*S*	10
f	$CH{=}CH_2$	**76**	44	*S*	30
g	C_6H_5	**76**	73	*S*	13

Table 4
Effect of the alkoxy group of the ester on the enantioselectivity of intramolecular C–H insertion reactions of α-diazo β-keto esters



83 84

entry	R	catalyst	isolated yield, %	% ee
a	t-Bu	$Rh_2(PTPA)_4$	60	45
b	c-C_6H_{11}	$Rh_2(PTPA)_4$	91	56
c	Et_2CH	$Rh_2(PTPA)_4$	86	62
d	i-Pr_2CH	$Rh_2(PTPA)_4$	86	76
e	t-Bu_2CH	$Rh_2(PTPA)_4$	68	76
f	i-Pr_2CH	$Rh(PTA)_4$	80	63
g	i-Pr_2CH	$Rh(PTV)_4$	85	64
H	i-Pr_2CH	$Rh(PTTL)_4$	67	53



76

Rh_2(*S*-PTPA)$_4$ (R = $CH_2C_6H_5$) (**77**)

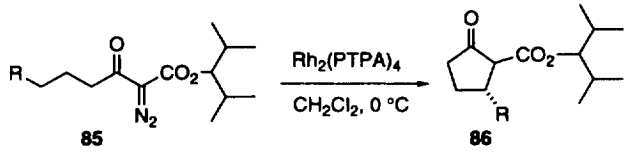
Rh_2(*S*-PTA)$_4$ (R = CH_3) (**78**)

Rh_2(*S*-PTV)$_4$ (R = *i*-Pr) (**79**)

Rh_2(*S*-PTTL)$_4$ (R = *t*-Bu) (**80**)

Fig. 2. Structure of chiral dihrodium(II) tetracarboxylates

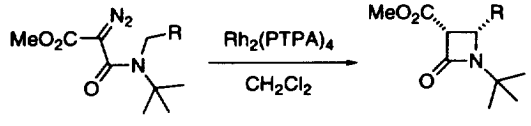
Table 5
Electronic effects of substituents on the enantioselectivity of intramolecular C–H insertion reactions of α-diazo β-keto esters



85 86

entry	R	isolated yield, %	% ee
a	4-$MeOC_6H_4$	86	57
b	4-MeC_6H_4	79	57
c	4-BrC_6H_4	89	70
d	4-$AcOC_6H_4$	80	68
e	4-$MeO_2CC_6H_4$	68	71
f	4-$CF_3SO_3C_6H_4$	84	80
g	CH_2CH	63	53
h	*trans*-MeCHCH	80	30
i	*trans*-ClCHCH	85	64
j	*trans*-MeO_2CCHCH	86	78
k	*trans*-t-BuO_2CCHCH	73	80

the production of optically active 2-azetidinones has also been examined.[36] The optimal substrate for these cyclizations is N-*tert*-butyl diazoacetamides (**87**). Again, dirhodium(II) tetrakis[N-phthaloyl-(*S*)-phenylalaninate] (Rh–PTPA–) proved to be the most selective catalyst.

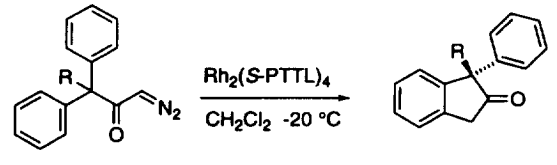


(13)

87a R = C_6H_5
87b R = $CH_2CO_2CH_3$
87c R = $CH_2CH_2CH_3$

88a (94%, 74% ee)
88b (98%, 56% ee)
88c (97%, 60% ee)

A unique enantioselective intramolecular C–H insertion is the cyclization of diazoketones **89** to 1-alkyl-1-phenyl-2-indanones (**90**).[37,38] In this case the catalyst differentiates enantiotopic phenyl rings through an intramolecular aromatic C–H insertion. The reaction proceeds at low temperature and results in the production of optically enriched material bearing a quaternary carbon.



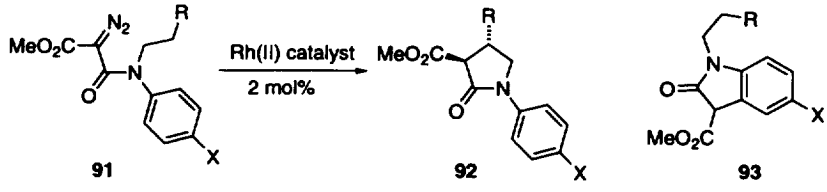
(14)

89a R = CH_3
89b R = CH_3CH_2

90a (84%, 90% ee)
90b (74%,98% ee)

An extension of the studies outlined above is the cyclization of α-methoxycarbonyl-α-diazoacetanilide (**91**) to 4-substituted 2-pyrrolidinone **92**.[39] A competing process in this reaction is the production of 2(3*H*)-indolinone **93** by metal carbene insertion into the aromatic C–H bond. As indicated by entry

Table 6
Effect of vinyl substituents on the enantioselectivity of intramolecular C–H insertion reactions of α-diazo β-keto esters

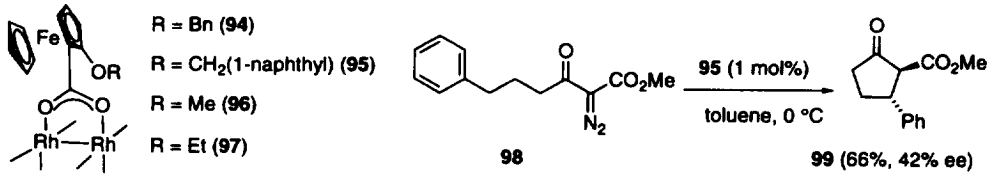


91 92 93

entry	R	X	catalyst	92 yield (% ee)	93 yield (% ee)
a	C_6H_5	CH_3O	$Rh_2(PTPA)_4$	<5 (NA)	68 (NA)
b	C_6H_5	NO_2	$Rh_2(PTPA)_4$	82 (47)	0
c	C_6H_5	NO_2	$Rh_2(PTA)_4$	83 (47)	0
d	C_6H_5	NO_2	$Rh_2(PTV)_4$	82 (26)	0
e	C_6H_5	NO_2	$Rh_2(PTTL)_4$	80 (74)	0
f	p-$MeOC_6H_4$	NO_2	$Rh_2(PTTL)_4$	72 (81)	0
g	C_6H_5	NO_2	$Rh(PTTL)_4$	84 (34)	0

a (Table 6) the electron-releasing *para*-methoxy group favored insertion into the aromatic C–H bond leading to the production of **93**. However, replacement of the methoxy group by an electron-withdrawing nitro group completely shut down this reaction manifold leading to the production of **92** in up to 80% ee.

A series of chiral rhodium(II) tetracarboxylates derived from 2-hydroxyferrocenecarboxylic acid (**94–97**) was prepared by Ito and co-workers.[40] The asymmetric intramolecular C–H insertion of α-diazo β-keto ester **98** was examined using catalysts **94–97**. The highest enantiomeric excess was obtained using rhodium(II) tetracarboxylate **96** to provide cyclopentanone **99** in 66% yield and 42% ee.

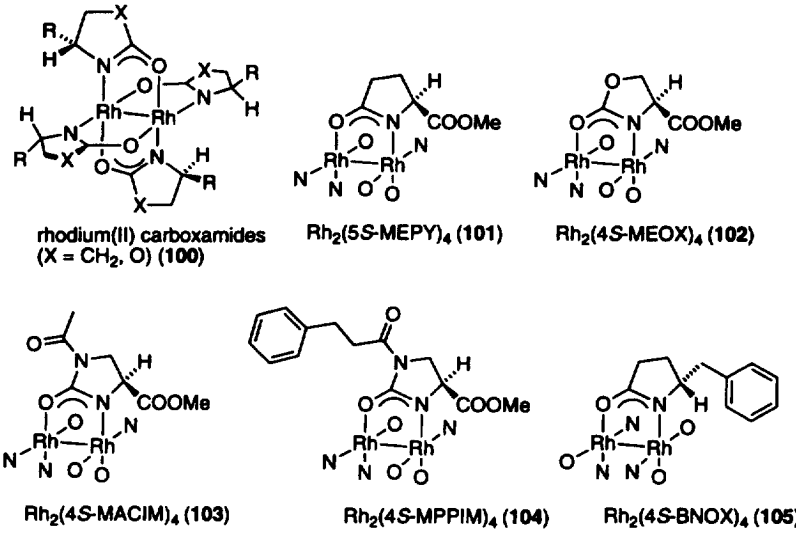


98 99 (66%, 42% ee) (15)

6.2. *Dirhodium carboxamidates*

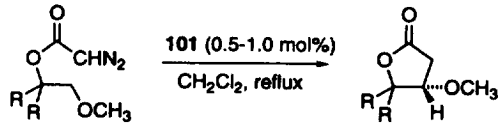
Rhodium(II) carboxamides are typically generated from rhodium(II) tetraacetate by substitution with four chiral pyrrolidone, oxazolidone or imidazolidone ligands. Complexes produced in this way possess two oxygen- and two nitrogen-donor atoms bound to each octahedral rhodium with a *cis* orientation of the nitrogen ligands (cf. **102**). Doyle has synthesized a family of chiral rhodium(II) carboxamide based catalysts (**101–105**; Scheme 7) and explored their use in enantioselective transformations.[41] This family of catalysts include dirhodium tetrakis[methyl 2-oxopyrrolidine-5(*S* and *R*)-carboxylate] Rh_2(5*S*-MEPY)$_4$ (**101**); dirhodium tetrakis[methyl 2-oxazolidine-4 (*R* and *S*)-carboxylate] Rh_2(4*S*-MEOX)$_4$ (**102**); dirhodium tetrakis[methyl 1-acetyl-imidazolidin-2-one-4(*S*)-carboxylate] Rh_2(4*S*-MACIM)$_4$ (**103**); dirhodium tetrakis[methyl 1-(3-phenylpropanoyl)-2-oxoimidazolidine-4(*R* and *S*)-carboxylate] Rh_2(4*S*-MPPIM)$_4$ (**104**) and dirhodium tetrakis(4*S*-benzyloxazolidinone), Rh_2(4*S*-BNOX)$_4$ (**105**). As

the following examples will illustrate, each catalyst (**101–105**) has proven utility with a particular substrate type.



Scheme 7.

Dirhodium(II) carboxamides have proven to be particularly useful in enantioselective intramolecular C–H insertion reactions leading to the production of heterocycles. One of the first reports in this area described the cyclization of alkyl diazoacetates leading to the construction of lactones.[42] Cyclization of diazoacetate **106a** using Rh_2(5*S*-MEPY)$_4$ (**101**) as a catalyst afforded **107a** in 91% ee and 62% isolated yield. In contrast, the cyclization of the tertiary alkyl diazoacetate (**106b**) gave **107b** in only 56% ee. A unique aspect of the conversion of **106** to **107** is that C–H insertion occurs vicinal to the newly formed stereocenter.



106a R = H
106b R = CH_3

107a (62%, 91% ee)
107b (68%, 56% ee)

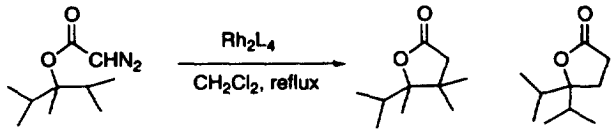
(16)

An enhancement in the enantioselectivity of the cyclization of tertiary alkyl diazoacetates was discovered using dirhodium(II) tetrakis[methyl 1-acetylimidazolidin-2-one-4(*S*)-carboxylate] Rh_2(4*S*-MACIM)$_4$ (**103**).[43] In the case of diazoacetate **108**, Rh_2(5*S*-MEPY) produced a 93:7 ratio of **109** and **110** (Table 7). The former was isolated in only 61% ee. The same cyclization with Rh_2(4*S*-MACIM)$_4$ (**103**) provided an 83:17 ratio of **109** and **110**. In this case **109** was produced in 85% ee. Somewhat surprisingly, Rh_2(4*S*-MEOX)$_4$ (**102**) produced a 70:30 mixture of **109** and **110**, with **109** being produced as a racemic mixture.

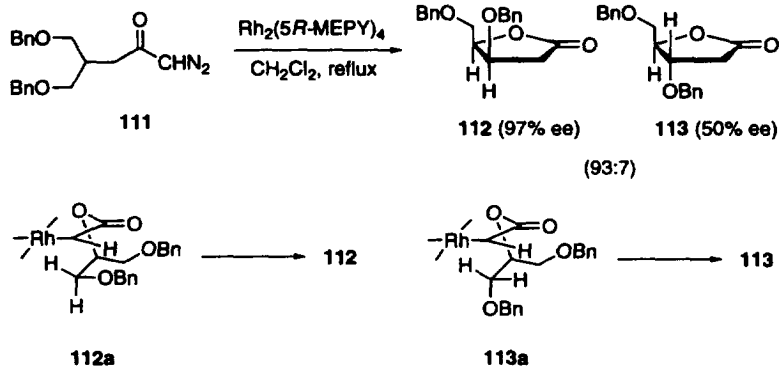
A useful application of an enantio- and diastereoselective carbon–hydrogen insertion reaction is the cyclization of achiral diazoacetate **111** to 2-deoxy ribonolactones **112** and **113** (93:7) using Rh_2(5*R*-MEPY)$_4$ (**101**) (Scheme 8).[44] The reaction requires only 0.1 mol% catalyst and proceeds in 65–70% yield. The major diastereomer **112** was obtained in 97% ee. The high diastereo- and enantioselectivity of the cyclization of **111** to **112** is attributed to transition state **112a** which is favored over **113a**.

In the above cyclization (**111** to **112**) exceptional diastereo- and enantioselectivity was observed when using Rh_2(5*S*-MEPY)$_4$ (**101**) as a catalyst. In some instances, cyclization of similar secondary alkyl

Table 7
Dirhodium(II) carboxamide catalyzed enantioselective carbon–hydrogen insertion reaction of tertiary alkyl diazoacetates



entry	Rh_2L_4	isolated yield, %	109:110	% ee 109
a	Rh_2(5*S*-MEPY)$_4$	66	93:7	61
b	Rh_2(4*S*-MEOX)$_4$	70	70:30	0
c	Rh_2(4*S*-MACIM)$_4$	73	83:17	85



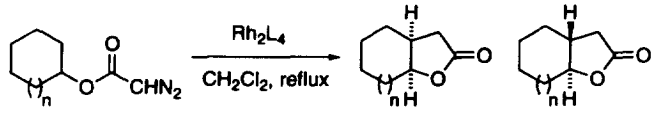
Scheme 8.

diazoacetates (cf. **114** to **115**) using Rh_2(5*S*-MEPY)$_4$ (**101**) provided excellent enantiocontrol but less than satisfactory diastereocontrol (Table 8, entry c).[45] In this cyclization, similar results were obtained using Rh_2(4*S*-MEOX)$_4$ (**102**) (entry d). In the case of Rh_2(4*S*-MACIM)$_4$ (**103**) the cyclization of **114** to **115** proceeded with high diastereoselectivity but provided **115** only in 86% enantiomeric excess. Excellent levels of both regio- and enantioselectivity were observed using Rh_2(4*S*-MPPIM)$_4$ (**104**). The increased level of selectivity was attributed to a tighter orientation of the metal carbene due to the pendant N-alkyl substituent within **104**.

Doyle and Müller have reported on the asymmetric synthesis of bicyclic lactones starting from cycloalkyl diazoacetates (Table 9).[46,47] As in the case of alicyclic diazoacetates (Scheme 8 and Table 8), selectivity for the *cis* isomer (**119**) is observed. Cyclizations using Rh_2(5*S*-MEPY)$_4$ (**101**) proceed with modest diastereoselectivity (ca. 3:1) to provide the *cis* and *trans* fused lactones (**119** and **120**) in high enantiomeric excess (Table 9, entries e, i and m). A further erosion in diastereoselectivity is observed using Rh_2(4*S*-MEOX)$_4$ (**102**) (ca. 1:1). Interestingly, this catalyst also produces **119** and **120** in exceptional enantiomeric excess (entries f, j and n).[47] Dirhodium(II) tetrakis[methyl 1-acetylimidazolidine-2-one-4(*S*)-carboxylate] Rh_2(*S*-MACIM)$_4$ (**103**) provided remarkably high diastereo- and enantioselectivity in the cyclization of cyclohexyl, cycloheptyl and cyclooctyl diazoacetates **118** (n=1, 2, 3) (entries d, h and l). In these cases, 99:1 diastereoselectivity for the *cis* fused lactone **119** was observed in >95% ee. An exception to this trend was cyclopentyl diazoacetate **118** (n=0) which provided **119** in 89% ee (entry b). In this case, dirhodium tetrakis[methyl 1-(3-phenylpropanoyl)imidazolidin-2-one-4(*S*)-carboxylate] Rh_2(4*S*-MPPIM)$_4$ (**104**) provides optimal results affording **119** in 93% ee (entry c).[45]

Doyle has applied the intramolecular cyclization of diazoacetates to the synthesis of natural lignans.[48,49] The core structure of these natural products is a β-benzyl-γ-lactone (cf. **122**) available via the cyclization of 3-phenyl-1-propyl diazoacetate **121** (Table 10). The cyclization of **121** to **122** using either Rh_2(4*S*-MEOX)$_4$ (**102**) or Rh_2(5*S*-MEPY)$_4$ (**101**) proceeded with modest enantioselectivity. As in the case of cyclopentyl diazoacetate **118** (n=0), Rh_2(4*S*-MPPIM)$_4$ (**104**) proved to be the optimal catalyst, in this case providing **122** in 87–91% ee.

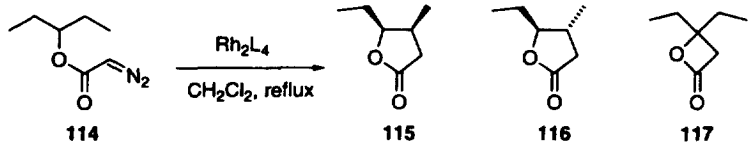
Table 8
Dirhodium(II) carboxamide catalyzed enantio- and regiocontrol in lactone syntheses



118 **119** **120**

entry	n	Rh_2L_4	isolated yield, %	119:120	% ee 119	% ee 120
a	0	Rh_2(5*R*-MEPY)$_4$	54	100:0	40	na
b	0	Rh_2(4*S*-MACIM)$_4$	40	100:0	89	na
c	0	Rh_2(4*S*-MPPIM)$_4$	67	100:0	93	na
d	1	Rh_2(4*S*-MACIM)$_4$	70	99:1	97	65
e	1	Rh_2(5*R*-MEPY)$_4$	65	75:25	97	91
f	1	Rh_2(4*S*-MEOX)$_4$	50	55:45	96	95
g	1	Rh_2(OAc)$_4$	46	40:60	na	na
h	2	Rh_2(4*S*-MACIM)$_4$	75	99:1	96	61
i	2	Rh_2(5*R*-MEPY)$_4$	80	71:29	96	85
j	2	Rh_2(4*S*-MEOX)$_4$	68	58:42	97	94
k	2	Rh_2(OAc)$_4$	29	30:70	na	na
l	3	Rh_2(4*S*-MACIM)$_4$	62	99:1	97	59
m	3	Rh_2(5*R*-MEPY)$_4$	80	72:28	97	95
n	3	Rh_2(4*S*-MEOX)$_4$	60	57:43	99	95
o	3	Rh_2(OAc)$_4$	33	29:71	na	na

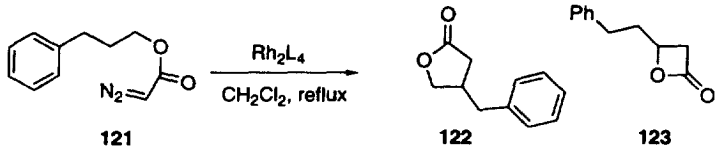
Table 9
Cyclization of secondary alkyl diazoacetates



114 **115** **116** **117**

entry	Rh_2L_4	isolated yield, %	115:116:117	% ee 115	% ee 116
a	Rh_2(4*S*-MPPIM)$_4$	85	92:3:5	99	na
b	Rh_2(4*S*-MACIM)$_4$	83	92:5:3	86	36
c	Rh_2(5*S*-MEPY)$_4$	75	73:20:7	98	71
d	Rh_2(4*S*-MEOX)$_4$	86	60:27:13	98	92

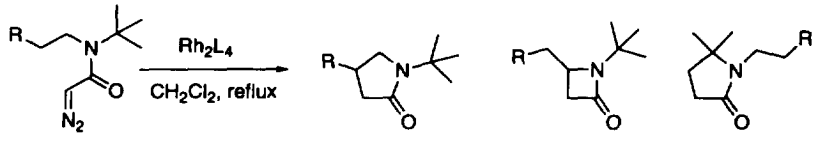
Table 10
Dirhodium(II) carboxamide catalyzed enantio- and regiocontrol in β-benzyl-γ-lactone syntheses



121 122 123

entry	Rh_2L_4	isolated yield, %	122:123	%ee	configuration
a	Rh_2(4*S*-MEOX)$_4$	76	93:7	51	*S*
b	Rh_2(5*R*-MEPY)$_4$	49	94:6	72	*R*
c	Rh_2(4*S*-MPPIM)$_4$	59	93:7	87	*S*
d	Rh_2(4*S*-MPPIM)$_4$	76	93:7	91	*R*

Table 11
Dirhodium(II) carboxamide catalyzed enantio- and regiocontrol in lactam syntheses



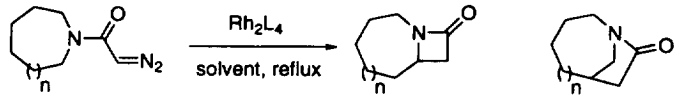
124 125 126 127

entry	R	Rh_2L_4	isolated yield, %	125:126:127	% ee 125	% ee 126
a	C_2H_5	Rh_2(5*S*-MEPY)$_4$	74	88:12:0	63	73
b	C_2H_5	Rh_2(4*S*-MEOX)$_4$	82	91:9:0	71	80
c	i-C_3H_7	Rh_2(5*S*-MEPY)$_4$	91	80:20:0	58	72
d	i-C_3H_7	Rh_2(4*S*-MEOX)$_4$	93	82:18:0	69	65
e	OEt	Rh_2(5*S*-MEPY)$_4$	91	100:0:0	58	na
f	OEt	Rh_2(4*S*-MEOX)$_4$	97	100:0:0	78	na
g	COOEt	Rh_2(5*S*-MEPY)$_4$	64	2:9:89	na	44
h	COOEt	Rh_2(4*S*-MEOX)$_4$	54	2:25:73	na	46

The cyclization of diazoamides using chiral dirhodium(II) carboxamide has been used for the enantioselective production of lactams (Table 11).[50] As an initial investigation, Doyle and co-workers examined the cyclization of a series of N-alkyl-N-(*tert*-butyl)diazoacetamides (**124**). Depending on the regioselectivity of the cyclization, one of three lactams could be produced; azetidones **125** as well as pyrrolidones **126** and **127**. The distribution of the isomeric heterocycles (**125–127**) depended, in part, on the regioselectivity inherent within the substrate. Rh_2(5*S*-MEPY)$_4$ (**101**) and Rh_2(4*S*-MEOX)$_4$ (**102**) were found to produce pyrrolidone **125** as the major isomer in up to 78% ee (Table 11, entries a–f). Incorporation of an electron-withdrawing carboxylate group beta to the amide nitrogen resulted in a shift in the regioselectivity of the cyclization process, pyrrolidone **127** now being the major product (entries g and h). Finally, this study illustrated a modest influence of the catalyst's ligands on the regioselectiviy as well as the enantioselectivity of the insertion reaction (cf. Eq. 14).

Dirhodium(II) carboxamide promoted cyclization of diazoacetamides derived from cyclic amines (**128**) provided beta lactams in high enantiomeric excess (Table 12).[51] The cyclization of diazoacetamides

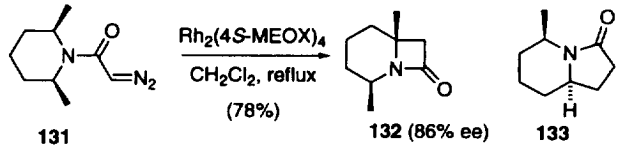
Table 12
Dirhodium(II) carboxamide catalyzed enantio- and regiocontrol in lactam syntheses



128 129 130

entry	n	Rh_2L_4	solvent	isolated yield, %	129:130	% ee 129	% ee 130
a	1	Rh_2(5*S*-MEPY)$_4$	CH_2Cl_2	67	99:1	97	na
b	2	Rh_2(5*S*-MEPY)$_4$	CH_2Cl_2	77	40:60	31	97
c	2	Rh_2(5*S*-MEPY)$_4$	$(CH_2Cl)_2$	67	67:33	30	96
d	2	Rh_2(4*S*-MEOX)$_4$	CH_2Cl_2	95	26:74	15	98
e	2	Rh_2(4*S*-MEOX)$_4$	$(CH_2Cl)_2$	68	49:51	8	96
f	2	Rh_2(4S-MACIM)$_4$	$(CH_2Cl)_2$	81	39:61	66	96

derived from pyrrolidine, piperidine and morpholine were unsuccessful due presumably to redox reactions with the catalyst. Higher cyclic homologs (**128**, n=1, 2) led to favorable results. Notably, Rh_2(5*S*-MEPY)$_4$ (**101**) provided high regio- and enantiocontrol in the azepine derived acetamide (entry a). In other cases, high enantioselectivity was observed in the pyrrolidone isomer (**130**) (entries b–f), although the regioselectivity in these cases was poor. An interesting example was the cyclization of piperidine **131** (Eq. 17) which produced beta lactam **132** in 86% ee.



131 132 (86% ee) 133

89:11

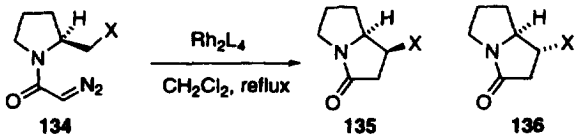
(17)

The preceding examples illustrate the application of chiral dirhodium(II) carboxamidate catalysts in the cyclization of achiral substrates to provide optically enriched heterocycles. A second application of these catalysts is the regio- and diastereocontrolled cyclization of chiral substrates. As discussed in Section 4, chiral substrates display an inherent diastereo- and regioselectivity which varies from poor to very good. As chiral reagents, chiral rhodium(II) carboxamidates display a selectivity which may oppose (mismatched case) or complement (matched case) the inherent selectivity of the substrate.

Doyle has examined the selectivity of metal carbenes derived from 2-substituted pyrolidines and dirhodium(II) carboxamidate catalysts (Table 13).[52] The diazoacetamide derived from the methyl ether of (*S*)-2-pyrrolidinemethanol (entries a–f) and of (*S*)-2-ethylpyrrolidine (entries g–j) were examined. For comparison purposes we note that dirhodium(II) acetate provided **135** and **136** in modest to poor yield and selectivity (entries a and g). In contrast, high yield and diastereoselectivity for the *syn* stereochemistry (**136**) was observed with either dirhodium tetrakis[methyl 1-acetyl-imidazolidin-2-one-4(*S*)-carboxylate] Rh_2(4*S*-MACIM)$_4$ (**103**) or dirhodium tetrakis[methyl 1-(3-phenylpropanoyl)-2-oxoimidazolidine-4(*S*)-carboxylate] Rh_2(4*S*-MPPIM)$_4$ (**104**) (entries e, f, i and j). Finally, we note the dependence of selectivity on the configuration of the starting catalyst (entries b and c).

The regioselectivity of the rhodium(II) carboxamidate catalyzed cyclization of diazoester **137** demonstrated a strong dependence on catalyst configuration (Table 14).[53] For instance, Rh_2(5*S*-MEPY)$_4$ favored formation of gamma lactone **138** while Rh_2(5*R*-MEPY)$_4$ led to production of gamma lactone **139** (entries a and b). Similar catalyst-dependent selectivity was observed for Rh_2(4*S*-MEOX)$_4$ and Rh_2(4*R*-MEOX)$_4$

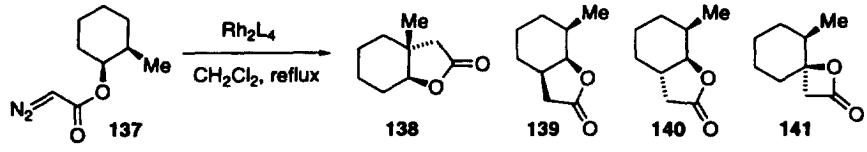
Table 13
Dirhodium(II) carboxamide catalyzed regio- and diastereocontrol in pyrrolizidine syntheses



134 135 136

entry	X	Rh_2L_4	isolated yield, %	135:136
a	OMe	$Rh_2(OAc)_4$	45	53:47
b	OMe	Rh_2(5*S*-MEPY)$_4$	95	90:10
c	OMe	Rh_2(5*R*-MEPY)$_4$	96	73:27
d	OMe	Rh_2(4*S*-MEOX)$_4$	99	89:11
e	OMe	Rh_2(4S-MACIM)$_4$	88	97:3
f	OMe	Rh_2(4*S*-MPPIM)$_4$	97	97:3
g	Me	$Rh_2(OAc)_4$	32	18:82
h	Me	Rh_2(4*S*-MEOX)$_4$	98	71:29
i	Me	Rh_2(4S-MACIM)$_4$	86	98:2
j	Me	Rh_2(4*S*-MPPIM)$_4$	95	96:4

Table 14
Dirhodium(II) carboxamide catalyzed regio- and diastereocontrol in lactone syntheses



137 138 139 140 141

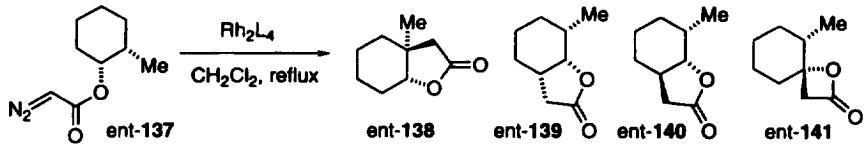
entry	Rh_2L_4	isolated yield, %	relative yield, % 138	139	140	141
a	Rh_2(5*S*-MEPY)$_4$	96	94	1		5
b	Rh_2(5*R*-MEPY)$_4$	79	4	91	3	2
c	Rh_2(4*S*-MEOX)$_4$	82	90	1	0	9
d	Rh_2(4*R*-MEOX)$_4$	91	2	88	7	3
e	Rh_2(4*S*-MPPIM)$_4$	46	28	26		56
f	Rh_2(4*R*-MPPIM)$_4$	88	0	98	0	2

(entries c and d). An exception to this trend was Rh_2(4*S*-MPPIM)$_4$ which displayed modest selectivity for beta lactone **141** (entry e). Interestingly, Rh_2(4*R*-MPPIM)$_4$ selectively produced **139** in line with the MEPY and MEOX series.

In order to further illustrate the dependence of selectivity on catalyst configuration, Doyle and co-workers reported the cyclization of *ent*-**137** using the same series of dirhodium(II) carboxamidate catalysts. [53] As expected, the (*S*)-enantiomer of each set of catalysts selectively provided gamma lactone *ent*-**139** while the (*R*)-enantiomers produced gamma lactone *ent*-**138**.

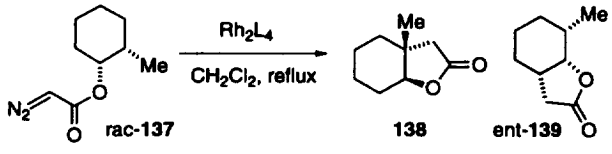
The high regio- and diastereoselectivity of dirhodium(II) carboxamidates provides a unique opportu-

Table 15
Dirhodium(II) carboxamide catalyzed regio- and diastereocontrol in lactone syntheses



entry	Rh_2L_4	isolated yield, %	relative yield, %			
			ent-138	ent-139	ent-140	ent-141
a	Rh_2(5*S*-MEPY)$_4$	86	5	90	3	2
b	Rh_2(5*R*-MEPY)$_4$	74	90	3	0	5
c	Rh_2(4*S*-MEOX)$_4$	89	2	88	7	3
d	Rh_2(4*R*-MEOX)$_4$	86	88	3	0	9
e	Rh_2(4*S*-MACIM)$_4$	90	1	96	1	2
f	Rh_2(4*S*-MPPIM)$_4$	91		98		2

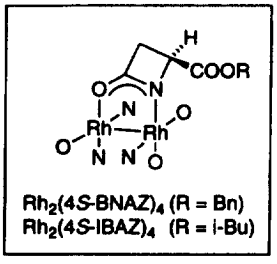
nity to differentiate enantiomers of a racemic mixture. For instance, cyclization of *racemic* diazoester **137** using dirhodium tetrakis[methyl 2-oxopyrrolidine-5(*S*)-carboxylate] Rh_2(5*S*-MEPY) afforded **138** and *ent*-**139** in 91 and 98% ee (Eq. 18).[53] Even higher levels of selectivity were observed in the cyclization of racemic **137** catalyzed by dirhodium tetrakis[methyl 2-oxazolidine-4(*S*)-carboxylate] Rh_2(4*S*-MEOX)$_4$ (Eq. 18). This unusual form of stereocontrol has been termed 'enantiomer differentiation'.



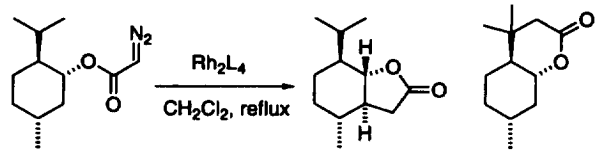
Rh_2(5*S*-MEPY)$_4$	91% ee	98% ee
Rh_2(4*S*-MEOX)$_4$	99% ee	99% ee

(18)

The cyclization of D-(+)-menthyl diazoacetate (**39**) using rhodium(II) acetate yields a 56:44 mixture of **40** and **41** in a combined yield of 17%.[18] In sharp contrast, cyclization of **39** catalyzed by chiral rhodium(II) carboxamidates of the (*S*)-enantiomer series provides high selectivity from **40** in very good yield (Eq. 19).[53] Two new catalysts introduced here are dirhodium(II) tetrakis[benzyl 2-oxaazetidine-4(*S*)-carboxylate] Rh_2(4*S*-BNAZ)$_4$ and tetrakis[*iso*-butyl 2-oxaazetidine-4(*S*)-carboxylate] Rh_2(4*S*-IBAZ)$_4$.



Rh_2(4*S*-BNAZ)$_4$ (R = Bn)
Rh_2(4*S*-IBAZ)$_4$ (R = i-Bu)

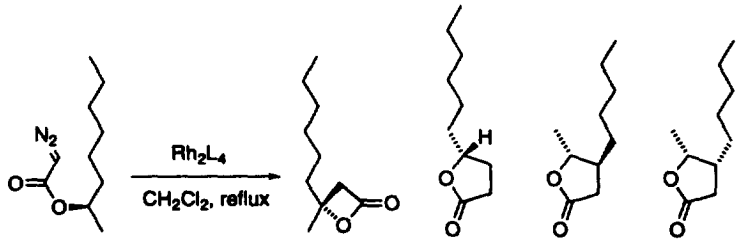


Rh_2(4*S*-MEOX)$_4$	87% yield	(99:1)
Rh_2(4*S*-BINAZ)$_4$	63% yield	(93:7)
Rh_2(4*S*-IBAZ)$_4$	61% yield	(95:5)

(19)

The regio- and diastereocontrol of dirhodium(II) carboxamidate catalyzed cyclization of chiral cyclic diazoesters (Tables 14 and 15) are higher than the selectivity exhibited in the case of chiral *acyclic* diazoesters (Table 16).[53]

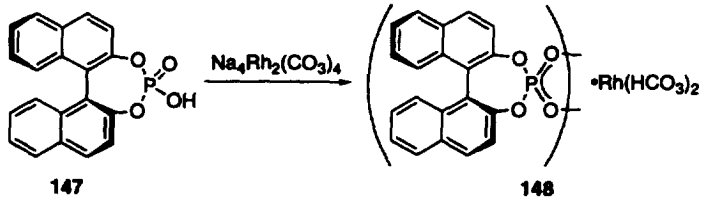
Table 16
Dirhodium(II) carboxamide catalyzed regio- and diastereocontrol in lactone syntheses



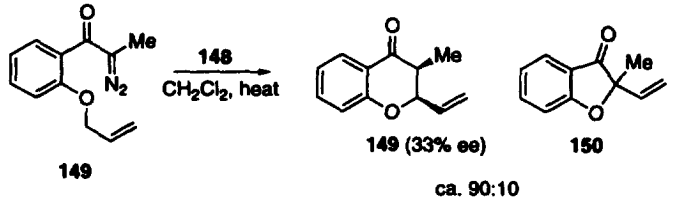
entry	Rh_2L_4	isolated yield, %	relative yield, %			
			143	144	145	146
a	Rh_2(5*S*-MEPY)$_4$	59	66	14	14	6
b	Rh_2(5*R*-MEPY)$_4$	53	43	1	14	42
c	Rh_2(4*S*-MEOX)$_4$	59	83	10	4	3
d	Rh_2(4*R*-MEOX)$_4$	71	57	2	12	9
e	Rh_2(4*S*-MACIM)$_4$	58	39	44	7	10
f	Rh_2(4*S*-MPPIM)$_4$	55	21	61	5	13

6.3. Miscellaneous

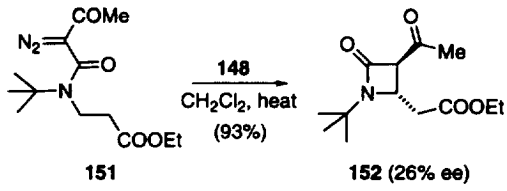
Rhodium(II) catalysts have proven to be the most effective in enantioselective and diastereoselective carbon–hydrogen insertion reactions. The two major groups of catalysts examined to date are dirhodium(II) carboxylates and carboxamidates. McKervey and Pirrung have examined dirhodium(II) phosphates as a new group of chiral catalysts.[54,55] Both catalysts were generated starting from (*S*)-(+)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (**147**). Pirrung prepared tetrakisbinaptholphosphate dirhodium by exhaustive ligand exchange starting from rhodium(II) tetraacetate. McKervay produced a complex formulated as **148** by reaction of **147** with $Na_4Rh_2(CO_3)_4 \cdot 2.5H_2O$. Cyclization of diazoketone **149** using complex **148** afforded an approximate 9:1 mixture of **150** and **151**; products of C–H insertion and sigmatropic rearrangement, respectively. In the case of **149**, the *cis* isomer **150** was the major diastereomer produced in approximately 33% ee. The absolute configuration was not assigned. Similarly, diazoacetamide **152** was cyclized to beta lactam in modest enantiomeric excess and unassigned absolute stereochemistry.



(20)

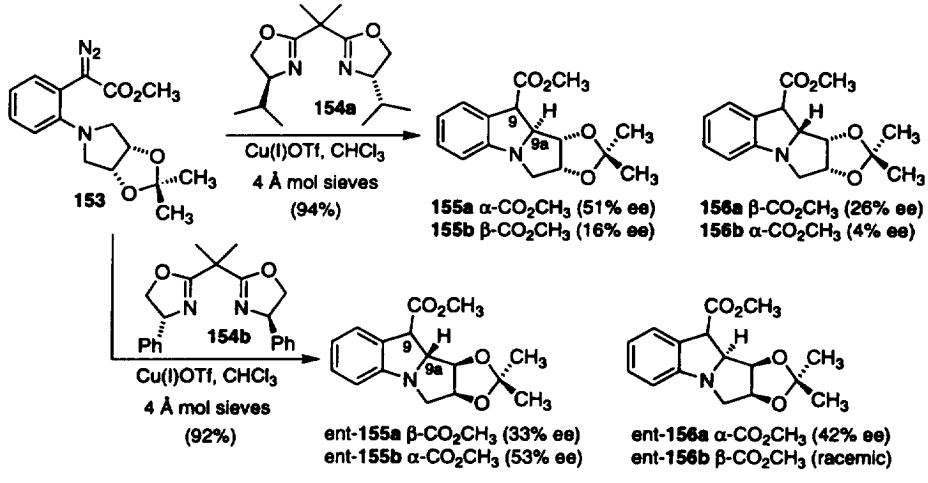


(21)



(22)

As reflected in the contents of this review, rhodium(II) catalysis has been most successful in effecting intramolecular C–H insertion reactions. However, one case in which rhodium(II) catalysis proved inferior to copper(I) catalysis is the cyclization of meso diazoester **154** (Scheme 9).[24,25] Cyclization of **154** using Cu(I)·**155a** complex afforded **156** and **157** in a 3:1 ratio and a combined yield of 90–94%. The *anti* isomer **155** was produced as a 1.7:1 mixture of isomers (**156a** and **156b**), while the corresponding *syn* diastereomers were generated as a 1.3:1 (**157a** and **157b**) mixture. The optical purity of the individual isomers ranged from 51% ee (**156a**) to nearly racemic material (**157b**). In a similar fashion, the antipodal set of isomers (*ent*-**156** to *ent*-**157**) were generated from Cu(I)·**155b**. In this instance, a 3:1 ratio of *ent*-**156** and *ent*-**156** was produced as a 1:3 (*ent*-**156a** and *ent*-**156b**) and 10:1 (*ent*-**157a** and *ent*-**157b**) mixture of epimeric esters, respectively. In this series the *endo–anti* isomer (*ent*-**156b**) and *exo–syn* isomer (*ent*-**157a**) were produced in 53 and 42% ee, respectively.

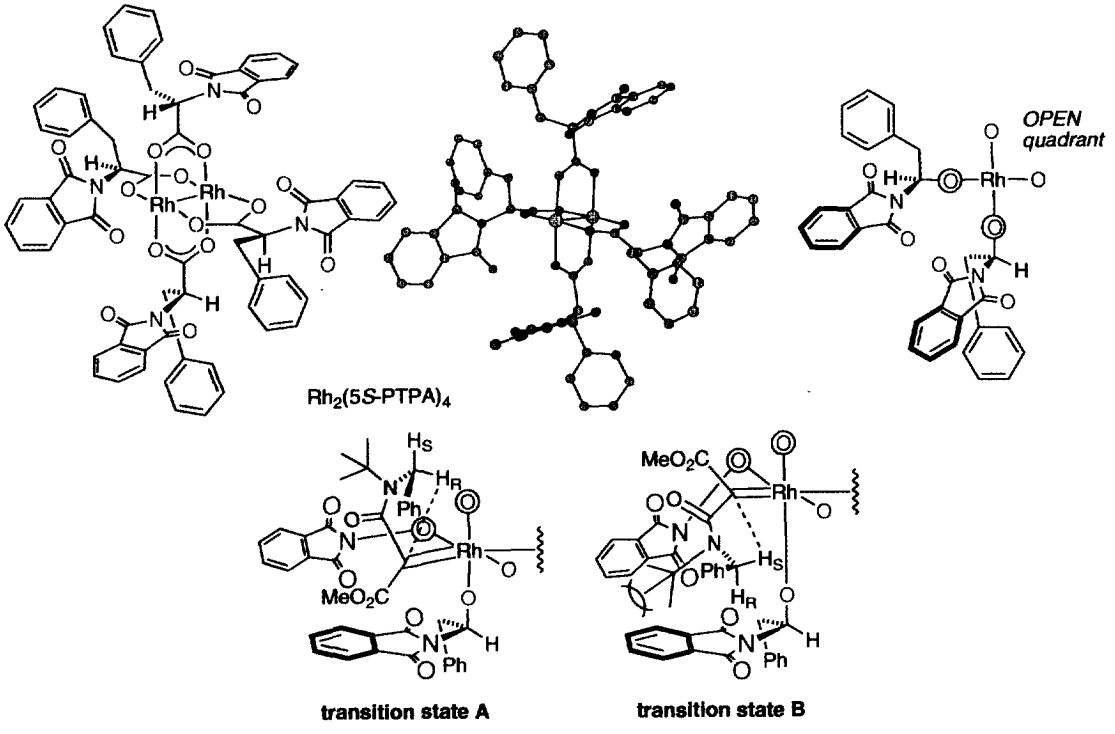


Scheme 9.

7. Models for enantioselection

Models for rationalizing diastereo- and enantioselectivity of chiral rhodium(II) carboxylate and carboxamidate catalysts in intramolecular carbon–hydrogen insertion reactions have been proposed by Hashimoto and Doyle. Hashimoto obtained a single-crystal X-ray analysis of dirhodium(II) tetrakis[N-phthaloyl-(*S*)-phenylalaninate] (**77**) (Scheme 10).[34] This catalyst promoted cyclization of diazoester **87a** to provide beta lactam **88a** in 74% ee. Viewing the complex down the rhodium–rhodium bond axis reveals four quadrants surrounding the vacant apical coordination site of rhodium(II). Two N-phthaloyl groups project into the south eastern coordinate as viewed in Scheme 10. Considering the cyclization of **87a**, the intermediate metal carbene may undergo C–H insertion by one of two transition state structures (A

and B). Transition state A is favored over B since the latter positions a bulky *tert*-butyl group within the sterically crowded southeastern quadrant.

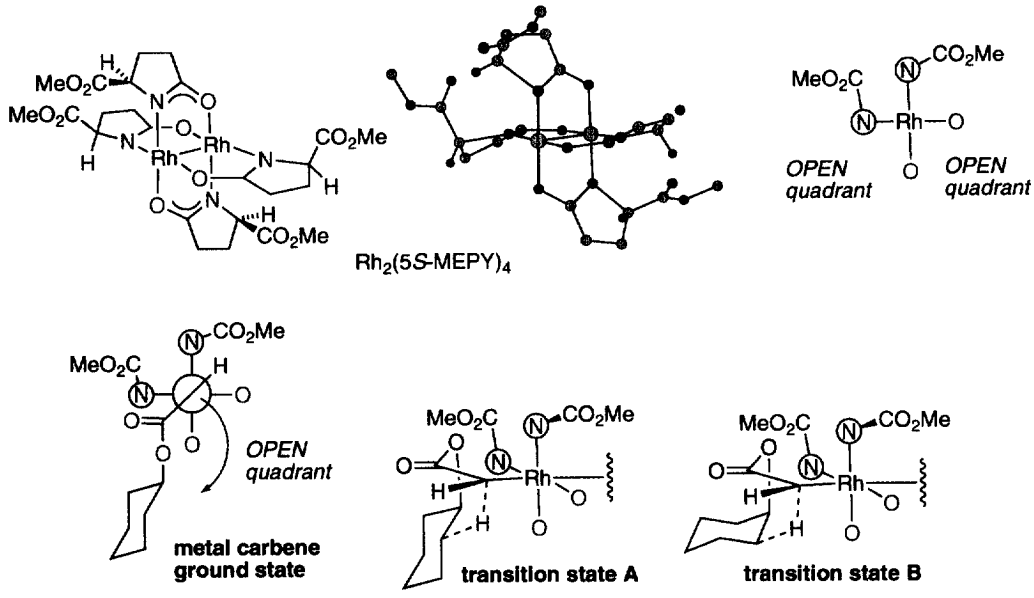


Scheme 10.

The X-ray structures of dirhodium tetrakis[methyl 2-oxopyrrolidine-5(*S* and *R*)-carboxylate] Rh_2(5*S*-MEPY)$_4$ (**101**) and dirhodium tetrakis(4*S*-benzyloxazolidinone), Rh_2(4*S*-BNOX)$_4$ (**105**) viewed down the rhodium–rhodium axis reveal two occupied quadrants (Scheme 11).[41] Cyclization of cyclohexyl diazoacetate produces a 75:25 ratio of *cis*:*trans* lactones **119** (97% ee) and **120** (91% ee) (Table 9, entry 1). Doyle explains this selectivity based on a metal carbene ground state shown in Scheme 11. In this ground state arrangement, the carboxylate group occupies one of the two open quadrants. A clockwise rotation then leads to insertion into one set of diastereotopic methylene hydrogens leading to transition state structures A and B. The latter structure is more sterically encumbered and leads to the minor *trans* fused lactone. Importantly, the conformational mobility of the cyclohexyl ring allows the reacting C–H bond to access equatorial orientations.

8. Conclusion

Considerable progress has been made in the development and application of intramolecular carbon–hydrogen insertion reactions of metal carbenes to construct carbocycles and heterocycles. Limitations do exist in the site and chemoselectivity of these reactions with five and four membered ring systems. A better understanding of the origins of chemoselectivity has been found by fine tuning catalyst reactivity.[6i] In terms of the asymmetric construction of these ring systems, the application of chiral catalysts remains the most efficient method. However, to date no catalyst has achieved high asymmetric induction in the production of both heterocycles and carbocycles. This should encourage future work in the discovery of new catalyst systems.[56]



Scheme 11.

Acknowledgements

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