Enantiocontrol in catalytic metal carbene reactions

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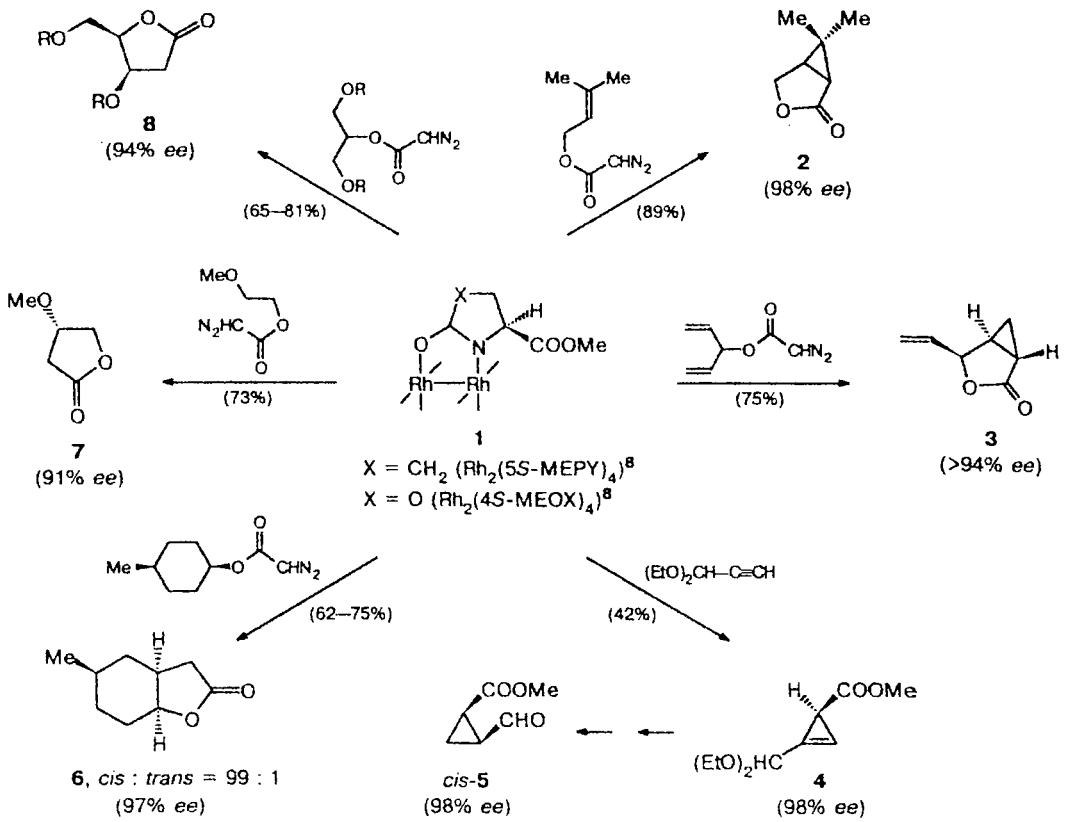
New catalysts and applications for carbon—carbon bond construction are described, providing access to lignan lactones, GABA analogs, and other compounds of biological interest.

Key words: enantiocontrol, enantioselective reactions, metal carbenes, catalysis.

In a previous report we documented the versatility of chiral dirhodium(II) carboxamidates as efficient and effective catalysts for metal carbene transformations.[1] At that time we described ongoing efforts in highly enantioselective cyclopropanation reactions,[2,3] such as in the syntheses of compounds **2** and **3**, in cyclopropanation reactions resulting in the preparation of **4**,[4] and in carbon—hydrogen insertion reactions that are exemplified in the constructions of lactones **6**, **7**, and **8** (Scheme 1).[5–7] Using chiral carboxamidate ligands whose syntheses were derived from common amino acids, a series of chiral dirhodium(II) catalysts was constructed.

Scheme 1



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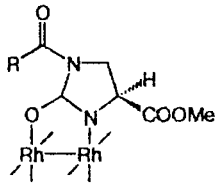
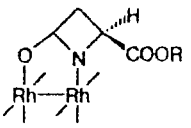
Their characteristic structure has four carboxamidate ligands around the dirhodium(II) core so that two nitrogens and two oxygens are bound to each rhodium(II), and the nitrogens are proximal rather than *anti*.[8,9] These catalysts are air stable, have long shelf lives, and, dependent on the hydrocarbon content of their ester alkyl groups, can even be used in hydrocarbon solvents.

Since our initial report, new catalysts have been constructed, and new processes have been developed directing our efforts towards the syntheses of naturally occurring compounds or their intermediates. Among the new catalysts are a set of *N*-acylimidazolidinone-ligated dirhodium(II) (**9**—**12**) and azetidinone-ligated dirhodium(II) (**13**) complexes.



9—**12**



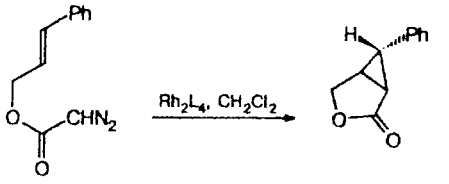
13

9: R = Me (Rh_2(4*S*-MACIM)$_4$)
10: R = Ph (Rh_2(4*S*-MBOIM)$_4$)
11: R = Ph(CH_2)$_2$ (Rh_2(4*S*-MPPIM)$_4$)
12: R = *cyclo*-$C_6H_{11}CH_2$ (Rh_2(4*S*-MCHIM)$_4$)
13: R = Bu^t (Rh_2(4*S*-IBAZ)$_4$)

The ligands are formed from chiral, non-racemic amino acids, asparagine (**14**) and aspartate (**15**), respectively, by efficient procedures, and their syntheses and their structures have been published.[10,11] These catalysts have provided enhanced levels of stereocontrol in selected catalytic metal carbene reactions.

Intramolecular cyclopropanation reactions

Intramolecular cyclopropanation reactions of allylic diazoacetates and homoallylic diazoacetates[12] and diazoacetamides[13] have been achieved with high diastereoselection and exceptional enantiomer differentiation in the presence of catalytic amounts of chiral dirhodium(II) carboxamidate complexes.[14] The Rh_2(5*S*-MEPY)$_4$ catalyst and its *R*-enantiomer have proven to be generally effective in intramolecular cyclopropanation reactions of trisubstituted and *cis*-disubstituted allylic diazoacetates providing cyclopropane-fused lactones (*e.g.*, **2** and **3** in Scheme 1) in high yield and with greater than 94% *ee*.[12] Turnover numbers as high as 1000 have been achieved in small scale reactions, and catalyst efficiency is expected to increase with scaleup. Isolated product yields (after distillation and/or chromatography) are high, and the catalyst can be recovered and reused.[15] In the simplest case, allyl diazoacetate, treatment with 0.1 mol.% of either of the Rh_2(MEPY)$_4$ catalysts, results in either one or the other of the intramolecular cyclopropanation products with an enantiomer ratio of 97.5 : 2.5.[12] Even higher enantiomeric excesses are obtained with *cis*-substituted allyl diazoacetates. However, with the *trans* isomers low enantiocontrol results with the Rh_2(MEPY)$_4$ catalysts, but this is circumvented with the use of Rh_2(4*S*-MPPIM)$_4$ and its mirror image counterpart which, in the example shown in Eq. (1), increases enantiomeric excess from 65 to 96%.[16]

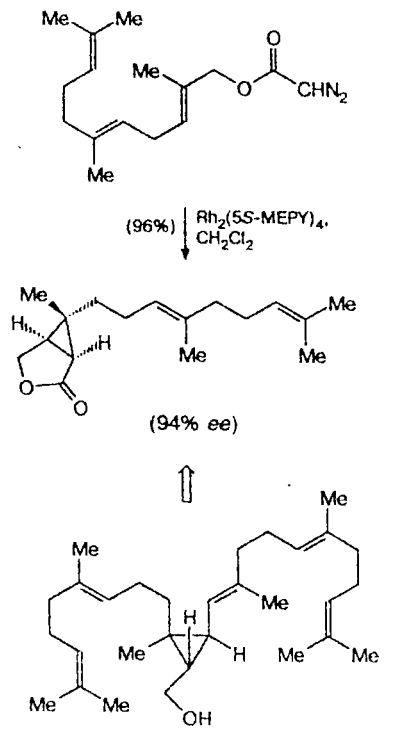


16 **17** (1)

Catalyst	*ee*
Rh_2(5*S*-MEPY)$_4$	65%
Rh_2(4*S*-MPPIM)$_4$	96%

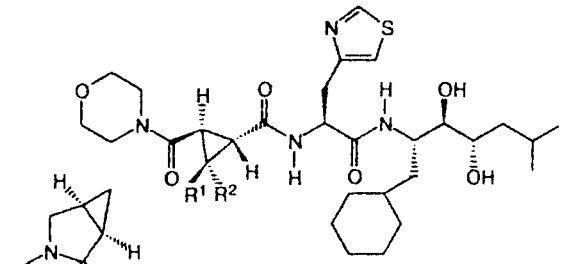
Subsequent to our initial report, this intramolecular catalytic methodology was applied to the syntheses of pharmacologically relevant compounds that include presqualene alcohol (**18**), derived from the product of catalytic cyclization (Scheme 2) of farnesyl diazo-

Scheme 2



18

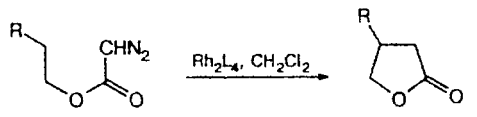
acetate.[17] In other examples, GABA analog **19** [12] was formed from *N*-allyldiazoacetamide in one step and 98% *ee* using $Rh_2(4S\text{-MEOX})_4$, and this methodology has proven to be general for the construction of analogous *N*-methyl bicyclic lactams.[13] Also, the stereoselective syntheses of 1,2,3-trisubstituted cyclopropanes in high optical purity has made possible the construction of conformationally restricted peptide isosters suitable as rennin (*e.g.*, **20**)[18] and collagenase inhibitors.[19]



19 **20**

Intramolecular C—H insertion reactions

Chiral dirhodium(II) carboxamidates are highly effective for asymmetric induction in selected intramolecular carbon—hydrogen insertion reactions of diazoacetates.[20] Catalytic methods favor formation of five-membered rings, and there is considerable precedent for the synthesis of γ-lactones by intramolecular C—H insertion from alkyl diazoacetates. Perhaps the greatest test for catalyst selectivity occurs in the general synthesis of β-substituted-γ-butyrolactones (Eq. (2)), which when R = benzyl or substituted benzyl, provides the key intermediates in the construction of naturally occurring lignan lactones.[21,22]

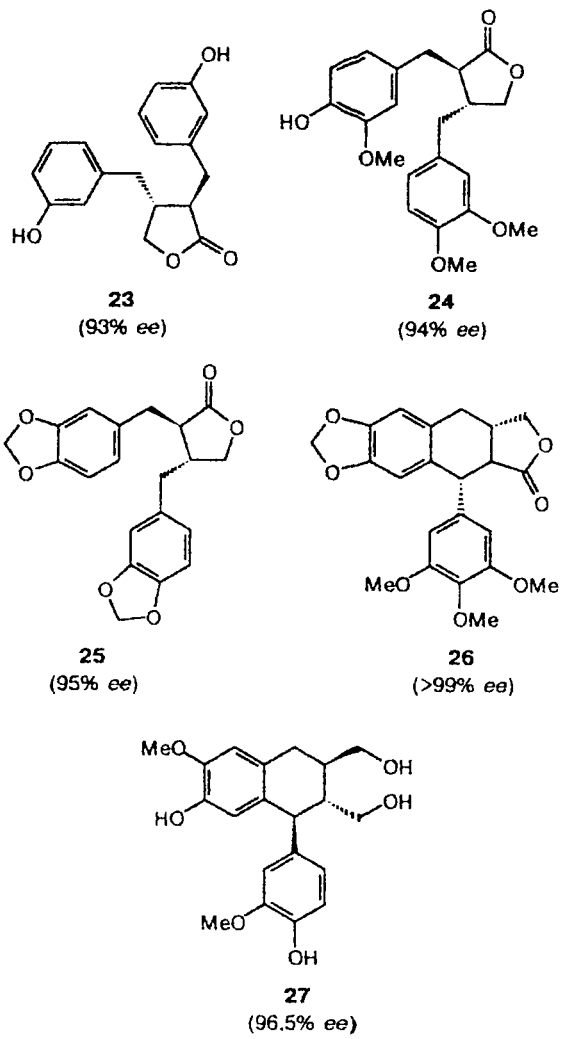


(2)

21 **22**

R = OR′, Et, Bu^t, Ph, $PhCH_2$, $ArCH_2$

In order for this methodology to be effective, however, insertion must occur with high regiocontrol into an inactivated methylene group rather than into the activated methylene groups adjacent to either the oxygen or the aryl group of $ArCH_2CH_2CH_2OCOCHN_2$. The use of $Rh_2(4S\text{-MPPIM})_4$ and its enantiomeric form $Rh_2(4R\text{-MPPIM})_4$ provides exceptionally selective insertion resulting in the total synthesis of a series of natural lignans ((−)-enterolactone (**23**), (+)-arctigenin (**24**), (−)-hinokinin (**25**), (+)-isodeoxyprodophyllotoxin (**26**),



23 (93% *ee*) **24** (94% *ee*)

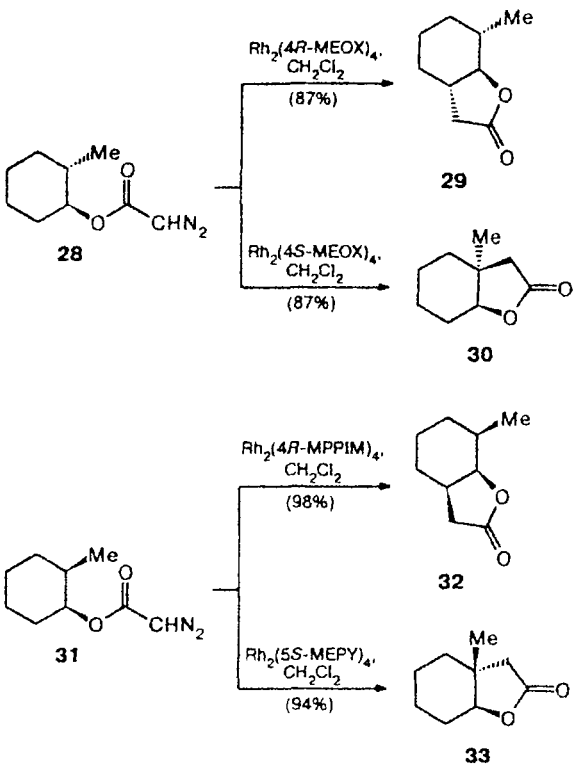
25 (95% *ee*) **26** (>99% *ee*)

27 (96.5% *ee*)

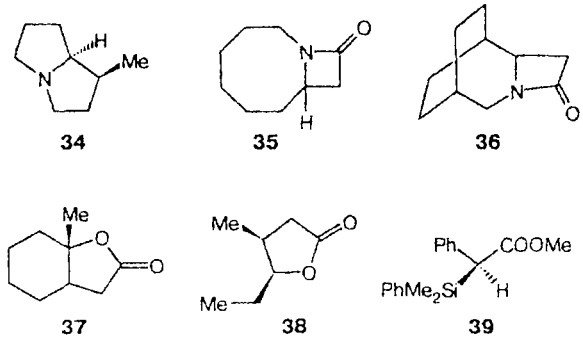
and (+)-isolauricerisinol (**27**)) with 92—97% *ee*. Insertion into the benzylic position to form a six-membered ring was not observed, and insertion into the oxygen-activated methylene group was detected to the extent of less than 5%. This synthetic methodology provides the most convenient access to lignan lactones now available, using 3-aryl-1-propyl diazoacetates prepared from their corresponding cinnamic acids.

Chiral dirhodium(II) catalysts control diastereoselection and regioselection in intramolecular C—H insertion reactions of enantiomerically pure diazoacetates.[14] When optically pure (1*S*,2*S*)-*trans*-2-methylcyclohexyl diazoacetate (**28**) underwent reaction with $Rh_2(4R\text{-MEOX})_4$, lactone **29** was formed predominantly (87% of total) whereas decomposition of **28** in the presence of $Rh_2(4S\text{-MEOX})_4$ resulted in the production of lactone **30** as the major product (87% of total) (Scheme 3). Similarly (1*S*,2*R*)-*cis*-2-methylcyclohexyl diazoacetate (**31**) formed specific products with even higher regio- and diastereocontrol dependent only on the chiral catalyst that is employed.

Scheme 3



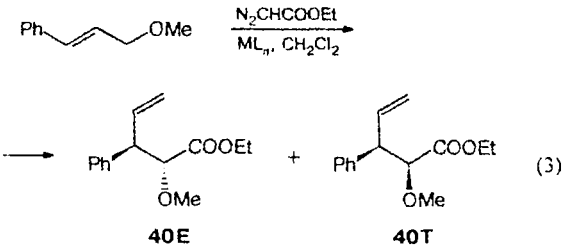
In these and related examples there is a configurational catalyst-substrate match and mismatch with each providing a different C—H insertion product. As might be expected, treatment of racemic diazoacetate,[23] either *rac*-**28** or *rac*-**31**, with the chiral catalyst resulted in the proportional mixture of products (**29** and **30** from *rac*-**28** with $Rh_2(4S\text{-MEOX})_4$, for example). High diastereoselection also characterized carbon—hydrogen insertion reactions of diazoacetamides that led to the preparation of pyrrolizidine base (−)-heliotridane (**34**) with ≥96 : 4 diastereomer ratios (*dr*) favoring the thermodynamically less stable isomer.[24] In an analogous fashion, β-lactams have been produced from cyclic diazoacetamides with high enantiocontrol (**35** in 97% *ee*, **36** in 96% *ee*) and in high isolated yield with $Rh_2(5S\text{-MEPY})_4$.[25]



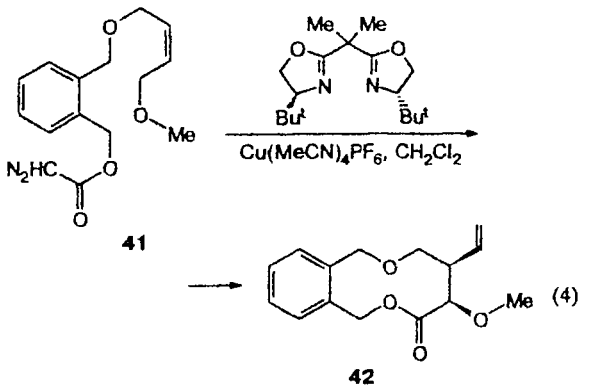
In other operations with chiral dirhodium(II) carboxamidate catalysts tertiary alkyl diazoacetates underwent intramolecular C—H insertion to form lactones such as **37** with high enantiocontrol (90% *ee* with $Rh_2(4S\text{-MACIM})_4$).[26] 3-Pentyl diazoacetate gave the thermodynamically less stable **38** in 90% isolated yield with 98 : 2 *dr* and in 99% *ee* with dirhodium(II) catalyst $Rh_2(4S\text{-MCHIM})_4$.[16] Recently, intermolecular Si—H insertion reactions employed for the synthesis of **39** have proven to be effective with $Rh_2(MEPY)_4$ catalysts[27] but even more so with chiral dirhodium(II) prolinate catalysts.[28]

Asymmetric ylide transformations

Moderate to high enantiocontrol is achieved in reaction products formed from oxonium ylides generated by catalytic diazo decomposition in the presence of chiral dirhodium(II) carboxamidates. The reaction of cinnamyl methyl ether with ethyl diazoacetate in the presence of dirhodium(II) tetrakis[methyl 2-oxooxazolidine-4(*R* or *S*)-carboxylate], $Rh_2(MEOX)_4$, generates the products from ylide generation and subsequent [2,3]-sigmatropic rearrangement (Eq. (3)) chemoselectively with exceptional enantiocontrol (up to 98% *ee*) and with high diastereocontrol (85 : 15) that is the opposite of that obtained with the use of either $Rh_2(OAc)_4$ (17 : 83) or $Rh_2(cap)_4$. An intramolecular counterpart shows 65% *ee* for ylide generation/[2,3]-sigmatropic rearrangement resulting in the formation of a 10-membered ring with the use of $CuPF_6$/chiral bis-oxazoline (Eq. (4)), but the $Rh_2(MEOX)_4$ catalysts were ineffective in this case. That these reactions occur *via* metal-stabilized ylide intermediates has been demonstrated by the high enantioselectivity achieved with allyl iodide/ethyl diazoacetate whose "free" ylide intermediate is achiral.[29]



Catalyst	Ratio	*ee*	
	40E : 40T	**40E**	**40T**
$Rh_2(OAc)_4$	83 : 17		
$Rh_2(4S\text{-MEOX})_4$	15 : 85	94%	98%
$Rh_2(4R\text{-MEOX})_4$	15 : 85	94%	98%



Chiral dirhodium(II) complexes constructed from 2-oxopyrrolidine, oxazolidinone, imidazolidinone, or azetidine ligands are exceptional catalysts for enantioselective metal carbene transformations which provide lactones and lactams *via* cyclopropanation, carbon—hydrogen insertion, and ylide reactions with enantiomeric excesses greater than 90% and in very high yields. These chiral catalysts present high diastereo-, regio- and chemoselectivities, turnover numbers up to 1000, as well as recoverability and reuse.

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