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New catalysts and methods for highly enantioselective metal carbene reactions

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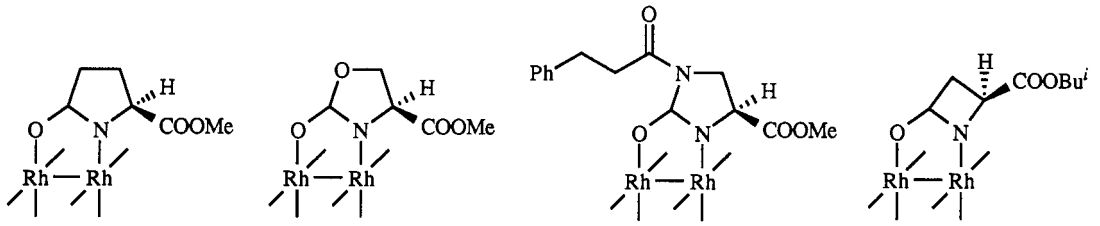
Abstract: Asymmetric catalysis of metal carbene transformations with unique chiral dirhodium(II) carboxamidates provides highly enantioselective, diastereoselective, and regioselective syntheses of lactones and lactams via cyclopropanation, cyclopropenation, carbon-hydrogen insertion, and ylide derived reactions of diazo acetates and diazoacetamides. Constructed from a dirhodium(II) core with bridging chiral pyrrolidone, oxazolidinone, azedinone, or imidazolidinone ligands, these catalysts are especially effective for intramolecular transformations. Reactions characteristically occur with high turnover numbers, and products are formed in high yield with enantiomeric excesses that are generally greater than 90%.

INTRODUCTION

Catalytic generation of metal carbenes from diazocarbonyl compounds is a facile synthetic methodology for the synthesis of organic compounds. Transition metal complexes of copper(I) and dirhodium(II) are the most reactive for diazo decomposition (ref. 1-3), but dirhodium(II) carboxylates and carboxamidates have proven to be the most versatile for highly selective metal carbene transformations that include cyclopropanation, cyclopropenation, insertion reactions, and ylide formation (ref. 1-6). Control of selectivity in these transformations is essential to their synthetic viability, and there is now general understanding that ligand modifications on the metal core induce electronic and steric interactions in product formation that provide substantial control of stereoselectivity, regioselectivity, and chemoselectivity (ref. 7,8).

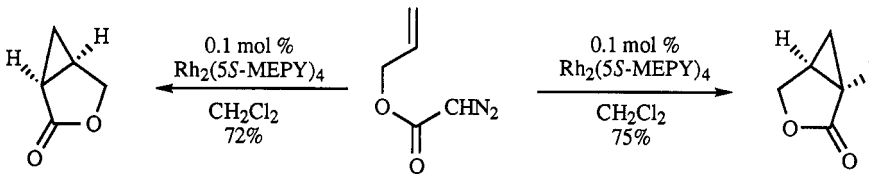
Enantiocontrol in catalytic metal carbene transformations has been a realistic objective since the first report by Nozaki and coworkers in 1966 that asymmetric cyclopropanation could be achieved, albeit with low enantiomeric excess (ee), using a chiral salicylaldimine-ligated copper complex (ref. 9). Advances made by Aratani in the design of chiral salicyclalimines brought this methodology to commercial advantage (ref. 10). The development of chiral semi-corrin ligands for copper by Pfaltz (ref. 11) provided further achievements for asymmetric intermolecular cyclopropanation reactions that were matched by the subsequent introduction of C_2-symmetric chiral bis-oxazolines (ref. 12-14). These copper catalysts were effective for high enantiocontrol in certain intermolecular cyclopropanation reactions with diazoacetates, but they were not generally suitable for intramolecular transformations. Chiral dirhodium(II) carboxamidates, wherein the amide ligands are arranged about the dirhodium(II) core so that two oxygens and two nitrogens are bound to each rhodium and the two nitrogens are adjacent to each other (ref. 15), have made possible exceptionally high enantiocontrol in a vast array of intramolecular transformations (ref. 16-18). A broad selection of these dirhodium(II) catalysts have been prepared based on chiral 2-oxopyrrolidine-5-carboxylates (ref. 15), 2-oxooxazolidine-4-carboxylates (ref. 19), 2-oxoimidazolidine-4-carboxylates (ref. 20), and 2-oxoazetidine-4-carboxylates (ref. 21), the most notable being those whose partial structures are given in Scheme 1. They are prepared by direct ligand exchange from dirhodium(II) acetate, and the (*cis*-2,2) structure is the sole or dominant product.

Scheme 1. Partial Structures of Chiral Dirhodium(II) Carboxamidates



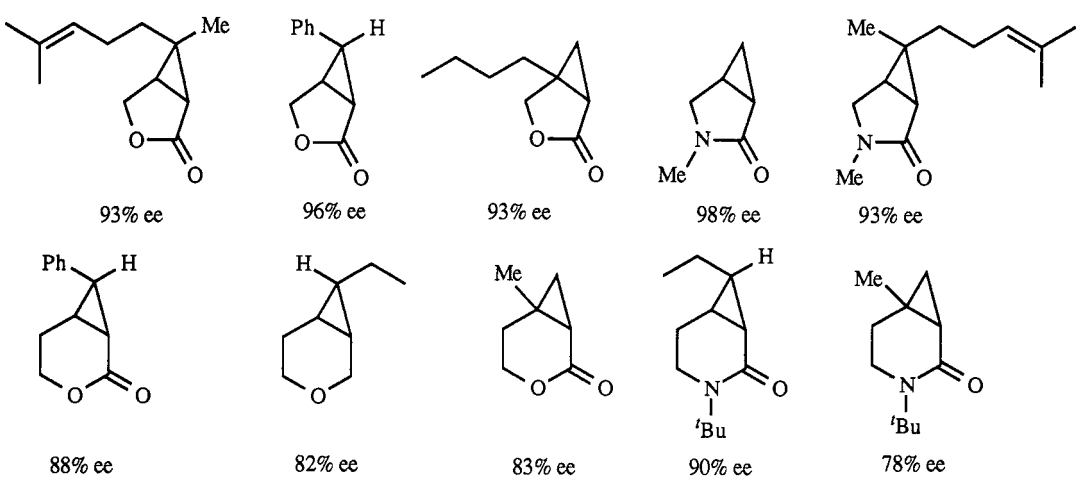
CYCLOPROPANATION

The effectiveness of $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(5R\text{-MEPY})_4$ catalysts for asymmetric induction has been demonstrated by the exceptional enantiocontrol that has been achieved with their uses in intramolecular cyclopropanation reactions of allylic and homoallylic diazoacetates as well as selected *N*-allylic and *N*-homoallylic diazoacetamides (ref. 22,23). With the simplest system, 2-propen-1-yl diazoacetate, use of $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(5R\text{-MEPY})_4$ in catalytic amounts as low as 0.1 mol % (1000 turnovers) causes the formation of the enantiomeric 3-oxabicyclo[3.1.0]hexan-2-ones (**2**) with 95% ee in good yields following distillation (eq. 1). *cis*-Disubstituted diazoacetate systems undergo catalytic cyclopropanation



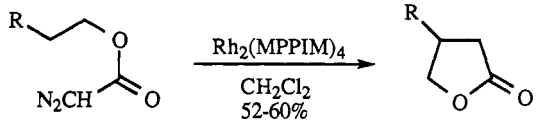
(1S,5R)-2, 95% ee **1** (1R,5S)-2, 95% ee (1)

with such high enantiocontrol that only one enantiomer could be detected by NMR methods with the use ofchiral shift reagents, and this high level of enantiocontrol (≥ 94% ee) was independent of the 3-(*Z*)-substituent. Similar high enantiocontrol characterizes trisubstituted allylic diazoacetates that include those prepared from nerol (93% ee) and geraniol (95% ee), but with *trans*-disubstituted systems use of the $Rh_2(MEPY)_4$ catalysts provides ee's as low as 68%. However, $Rh_2(4S\text{-MPPIM})_4$ offers significant enhancement in % ee so that, even with *trans*-disubstituted allylic diazoacetate ≥ 95% ee's can be uniformly achieved (ref. 24). In addition, significant challenges for selectivity enhancement, such as the 7% ee observed for intramolecular cyclopropanation of 2-methyl-2-propen-1-yl diazoacetate with the use of $Rh_2(5S\text{-MEPY})_4$, can be met by appropriate ligand modification on the dirhodium(II) core so that with the $Rh_2(MPPIM)_4$ catalysts, 89% ee has been realized (ref. 25). Selected products from these asymmetric cyclopropanation reactions are given in Scheme 2.



CARBON-HYDROGEN INSERTION

Dirhodium(II) compounds are the catalysts of choice for intramolecular carbon-hydrogen insertion reactions of diazocarbonyl compounds (ref. 1-5). Although there are notable exceptions, five-membered ring formation is preferred, and regioselectivity is generally subject to defined electronic effects. Early applications of $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(5R\text{-MEPY})_4$ to diazo decomposition of alkyl diazoacetates have demonstrated the feasibility of these catalysts for highly enantioselective and regioselective C-H insertion reactions (ref. 26), and more recent examples using $Rh_2(MPPIM)_4$ catalysts (ref. 27) have suggested the broad versatility of this methodology (eq. 2) that provides convenient entry to lignan lactones (ref. 27) and to β-hydroxy-γ-butyrolactone (ref. 26).

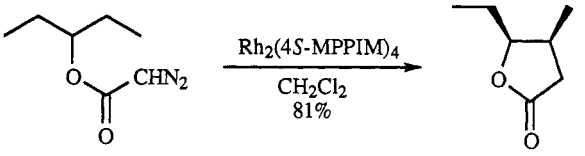


R = Et: 96% ee
R = ^{i}Bu: 95% ee

(2)

8

This methodology has been extended to C-H insertion reactions of secondary cycloalkyl diazoacetates where diastereoselectivity in the formation of *cis*- and *trans*-fused bicyclic lactones is a critical control feature (ref. 28, 29). In these systems the oxoimidazolidine-ligated catalysts exhibit the highest levels of diastereocontrol and enantiocontrol, reaching 99:1 dr and 97% ee respectively. Similar stereocontrol is evident in reactions of acyclic secondary diazoacetates (eq. 3) where diastereoselectivity for the *cis*-

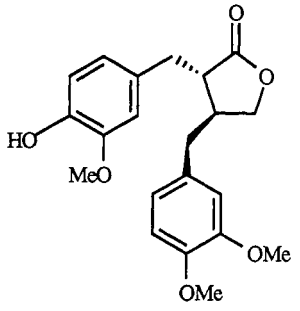


97:3 dr
99% ee

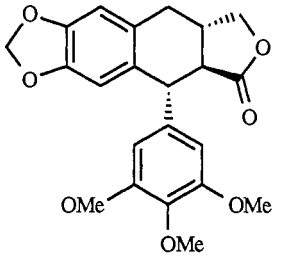
(3)

disubstituted lactone is pronounced (ref. 24). High enantio- and diastereocontrol in C-H insertionreactions of glycerol-derived diazoacetates have also provided a convenient synthesis of pure 2-deoxyxylolactone (ref. 30). Selected products formed from asymmetric C-H insertion reactions are given in Scheme 3.

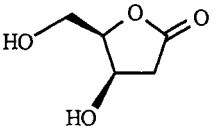
Scheme 3. Selected Products from Carbon-Hydrogen Insertion



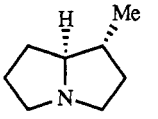
(+)-arctigenin
94% ee (ref. 27)



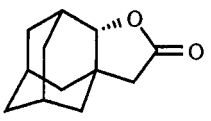
(+)-idodeoxypodophyllotoxin



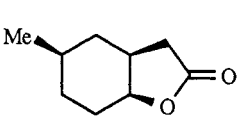
(3R,4R)-2-deoxyxylolactone
94% ee (ref. 30)



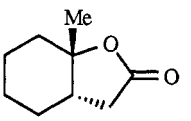
(-)-heliotridane
>99% ee (ref. 31)



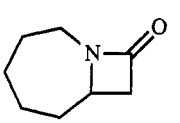
98% ee
(ref. 19)



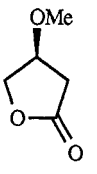
98% ee
(ref. 28)



90% ee
(ref. 32)



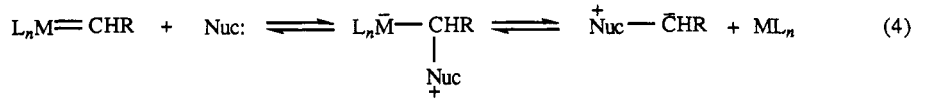
97% ee
(ref. 33)



92% ee
(ref. 19)

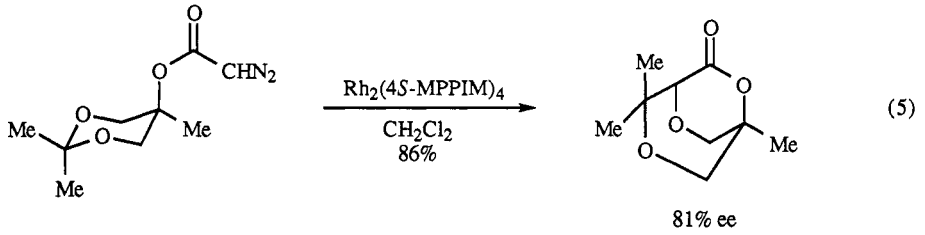
YLIDE FORMATION AND REACTIONS

Catalytic entry to ylide intermediates has provided a useful methodology for complex transformations that are highly valued for organic synthesis (ref. 34). Ylide formation occurs in two stages: initial nucleophilic addition to form a metal stabilized ylide intermediate (eq. 4), followed by dissociation of the metal to form the "free" ylide. A novel approach to enantiocontrolled ylide formation and rearrangement has taken 1,3-



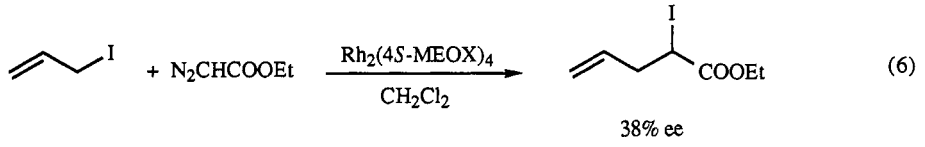
(4)

dioxan-5-yl diazoacetates (ref. 35) via diastereotopic oxygen association to the Stevens rearrangement product (eq. 5).



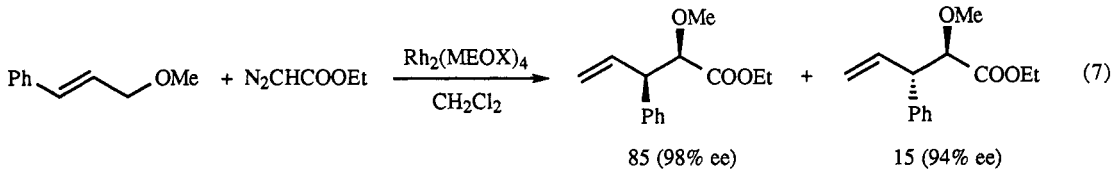
(5)

However, such an example does not distinguish between a metal associated ylide and a free ylide, but several recent examples that involve ylide formation/[2,3]-sigmatropic rearrangement demand that the metal associated ylide is the reactive intermediate (ref. 36). In the first, allyl iodide reacts with ethyl diazoacetate in the presence of $Rh_2(4S\text{-MEOX})_4$ to form the [2,3]-sigmatropic rearrangement product in 38% ee (eq. 6). In the second, cinnamyl methyl ether undergoes oxonium ylide formation with ethyl diazoacetate to



(6)

produce, with high diastereoselectivity, the threo isomer with virtually complete enantiocontrol (eq. 7); diastereocontrol using $Rh_2(OAc)_4$ is reversed (*erythro:threo* = 83:17). These examples demonstrate that



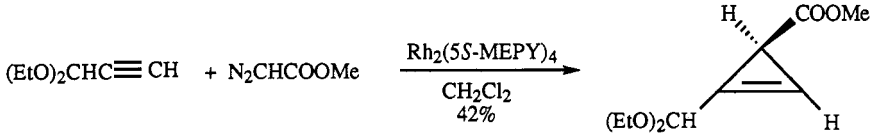
(7)

that the "free" ylide is not a prerequisite for the [2,3]-sigmatropic rearrangement, and they suggest new roles for chiral catalysts in asymmetric transformations previously considered to be inaccessible to the influence of catalysts.

CYCLOPROPENATION

Chiral dirhodium(II) catalysts $Rh_2(5S\text{-MEPY})_4$ are highly effective for intermolecular cyclopropenation reactions of 1-alkynes (but not internal alkynes) with diazoesters and diazoamides (ref. 37). Diastereoselectivities achieved from the appropriate match of catalyst configuration with *d*- or *l*-menthyl diazoacetate are 89:11 to ≥97:3 dr. Enantioselectivities up to ≥94% ee have been obtained with 3-methoxy-1-propyne

(reaction with *N,N*-dimethyldiazoacetamide) and 3,3-diethoxy-1-propyne (eq. 8), but even cyclopropenation of 1-hexyne occurred with 78% ee. *N,N*-Dimethyldiazoacetamide provides a higher



(8)

level of enantiocontrol than do diazoesters, but reactions generally occur in lower yield. The absolute configurations of the cyclopropene products have been established: $Rh_2(5S\text{-MEPY})_4$ produces 1-substituted-1-cyclopropene-3-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, or catalytic hydrogenation, produces the corresponding *cis*-disubstituted cyclopropane esters exclusively in the moderate to high enantiomeric/diastereomeric excesses achieved by cyclopropenation. This catalytic methodology provides a direct route to chiral cyclopropenes and, following reduction, to chiral *cis*-disubstituted cyclopropanes of moderate to high optical purity, neither of which are generally accessible by alternative catalytic routes.

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