Optimization of Enantiocontrol for Carbon–Hydrogen Insertion with Chiral Dirhodium(II) Carboxamidates. Synthesis of Natural Dibenzylbutyrolactone Lignans from 3-Aryl-1-propyl Diazoacetates in High Optical Purity

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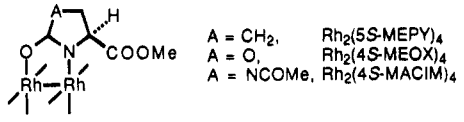
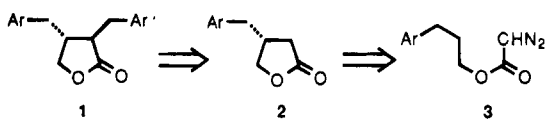
The catalysts of choice for enantioselective intramolecular metal carbene transformations of diazoacetates are chiral dirhodium(II) carboxamidates, particularly dirhodium(II) tetrakis[methyl 2-oxapyrrolidine-5(*S*)-carboxylate], $Rh_2(5(S)\text{-MEPY})_4$, and its enantiomeric form $Rh_2(5(R)\text{-MEPY})_4$,[1–6] and when diastereocontrol is also an important consideration, dirhodium(II) tetrakis-[methyl 2-oxooxazolidine-4(*R* or *S*)-carboxylate], $Rh_2(4(S)\text{-MEOX})_4$ or $Rh_2(4(R)\text{-MEOX})_4$,[7] and dirhodium(II) tetrakis[methyl 1-acetyl-2-oxoimidazolidine-4(*S*)-carboxylate], $Rh_2(4(S)\text{-MACIM})_4$,[8] offer advantages. Enantioselective

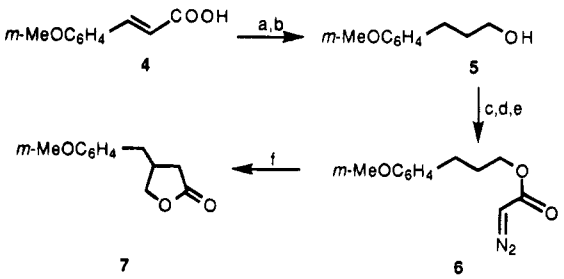


catalytic cyclopropanation reactions have been employed with increased frequency as key steps in the synthesis of natural products and/or physiologically active compounds.[9–11] Similar applications with inherently more complex intramolecular C–H insertion reactions of primary alkyl diazoacetates have not been possible because of limitations in the existing complement of chiral dirhodium(II) carboxamidates for highly enantioselective and regioselective insertion into a remote, unactivated prochiral C–H bond.[12] Because of their general accessibility via this methodology, we have targeted dibenzylbutyrolactone lignans (Scheme 1)[13] and now report their highly enantioselective (and regioselective) syntheses through C–H insertion with the use of chiral oxoimidazolidine carboxylate-ligated dirhodium(II) catalysts that are optimal for this conversion.

Scheme 1



Scheme 2[a]



[a] Key: (a) H_2 (2 atm), 5% Pd/C, MeOH/EtOAc (1:1); (b) $LiAlH_4$, THF, reflux; (c) diketene, THF, reflux; (d) MsN_3, Et_3N, CH_3CN, 25 °C; (e) $LiOH{\cdot}H_2O$ (3 equiv), CH_3CN/H_2O, 1.5 h; (f) $Rh_2L^*_4$ (2.0 mol %), CH_2Cl_2, reflux.

3-(*m*-Methoxyphenyl)prop-1-yl diazoacetate (**6**) was prepared from *m*-methoxycinnamic acid by standard methods in 59% overall yield. Diazo decomposition of **6** in refluxing CH_2Cl_2 containing 2.0 mol % $Rh_2(5(R)\text{-MEPY})_4$ produced the γ-lactone product from C–H insertion (**7**) in 66% isolated yield with 68% ee for the (4*R*)-enantiomer (Scheme 2).[14] The $Rh_2(4(S)\text{-MACIM})_4$ catalyzed reaction provided no advantage; **7*S*** was formed with 84% ee but in only 25% isolated yield. Recognizing that further elaboration of the *N*-acyl group of the MACIM ligand could significantly influence approach of the pendant alkyl group to the carbene center, methyl 1-(3-phenylpropanoyl)-2-oxoimidazolidine-4(*S*)-carboxylate and its 4(*R*) enantiomer were prepared from L- and D-asparagine, respectively (Scheme 3), and the corresponding dirhodium catalysts (**10**) were synthesized from them in 57 and 48% yield, respectively. The X-ray crystal structure of $Rh_2(4(S)\text{-MPPIM})_4(CH_3CN)_2$ (Figure 1) shows the basic stereochemical relationship of the methyl carboxylates and *N*-(3-phenylpropanoyl) groups on each face of this dirhodium(II) catalyst; noteworthy is the relative openness of the area around the ligand labeled a (top) so that the 3-arylpropan-1-yl group of the resident carbene can be expected to orient itself for C-H insertion in this quadrant.

Use of $Rh_2(4(R)\text{-MPPIM})_4$ (2.0 mol %) converted **6** to **7** in 63% yield and in 93% ee. Enantiomer separation was achieved with baseline resolution by GC on a 30-m Chiraldex A-DA column, and % ee values are reported

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(12) 2-Phenyl-1-ethyl diazoacetate underwent $Rh_2(5(R)\text{-MEPY})_4$ catalyzed C–H insertion into the benzylic position to form 4(*S*)-phenyldihydro-2(3*H*)-furanone in 46% ee (42% yield).[5] 1-Butyl diazoacetate gave the corresponding γ-lactone in 69% ee with $Rh_2(5(S)\text{-MEPY})_4$, 63% ee with $Rh_2(4(S)\text{-MEOX})_4$, and 85% ee with $Rh_2(4(S)\text{-MACIM})_4$.
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(14) With 1.0 mol % of $Rh_2(5(R)\text{-MEPY})_4$ the isolated yield of **7** was only 18% and its enantiomeric excess was 65%.

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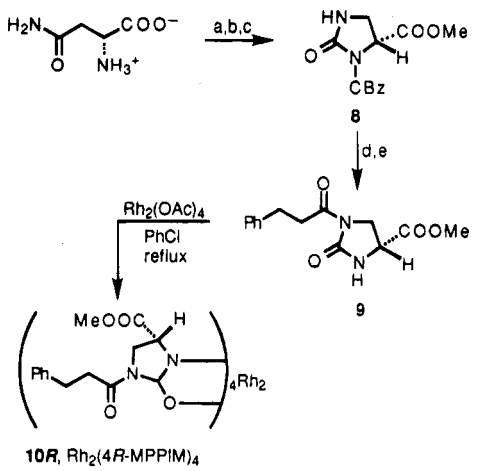
Scheme 3[a]



[a] Key: (a) CBzCl; (b) Br_2, NaOH, 50 °C; (c) MeOH, $SOCl_2$; (d) $PhCH_2CH_2COCl$, pyr, DMAP; (e) H_2, 5% Pd/C, MeOH.

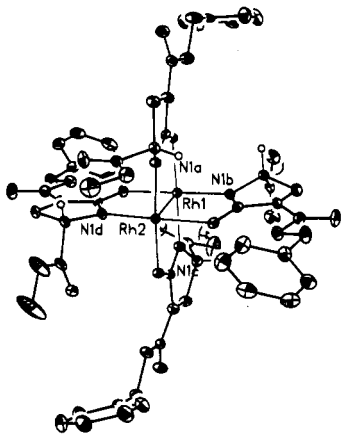
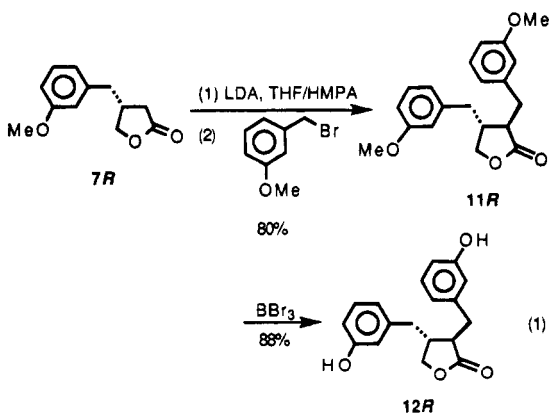


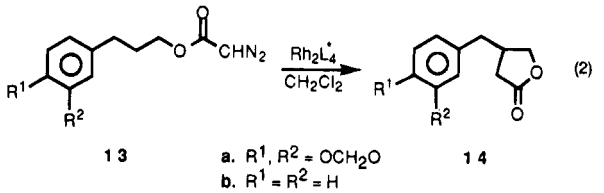
Figure 1. Thermal ellipsoid plot of $Rh_2(4(S)\text{-MPPIM})_4(CH_3CN)_2$ without axial acetonitrile ligands. Thermal ellipsoids are scaled to the 30% probability level. Most hydrogens have been omitted for clarity.

from these analyses.[15] Subsequent alkylation of **7*R*** and removal of the *O*-methyl groups provided (−)-enterolactone (**12*R***) in 70% yield from **7*R*** (eq 1).

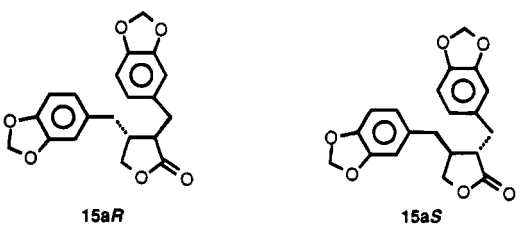


Application of $Rh_2(4(S)\text{-MPPIM})_4$ with the same series of reactions led to (+)-enterolactone in 46% yield (from **6**) with 91 ± 2% ee. The absence of either β-lactone or δ-lactone byproducts in the $Rh_2(MPPIM)_4$ induced conversion of **6** to **7** exemplifies the exceptional regiocontrol provided by these catalysts.

3-Aryl-1-propyl diazoacetates **13** were also prepared from their corresponding cinnamic acids (53% yield, **13a**; 74% yield, **13b**) and subjected to diazo decomposition in the presence of chiral dirhodium(II) carboxamidates (eq 2). Lactones **14** were obtained in good yields (**14a**, 67%



yield; **14b**, 56% yield) and high enantiomeric excesses (94% ee for **14a**; 91% ee for **14b**) with the use of $Rh_2(MPPIM)_4$ catalysts. Thus, this new chiral dirhodium(II) oxoimidazolidinecarboxylate catalyst offers substantial advantages in both chemical yields and % ee over existing catalysts for intramolecular insertion into prochiral C−H bonds of remote unactivated methylene groups. Alkylation of **14a** in its predominant *R*- or *S*-configuration produced (−)- and (+)-hinokinin (**15a*R*** and **15a*S***), respectively, in 76 and 70% yield.



Numerous strategies to achieve stereocontrolled syntheses of the various classes of lignans, which are indigenous in plants but also isolated from mammals, have been developed.[13] For dibenzylbutyrolactone lignans, asymmetric syntheses have focused on diastereoselective alkylation or aldol reactions of monobenzyl-substituted butyrolactones.[16,17] Other routes involving chiral dihydrofuryl ketones or cycloaddition−lipase-mediated resolution have been recently reported.[18] Catalytic carbon−hydrogen insertion with $Rh_2(MPPIM)_4$ is a novel, efficient, highly enantioselective alternative to these methodologies, and its generality is evident in the examples provided.

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Supporting Information Available: Experimental procedures and compound characterizations (11 pages).

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