# Diastereocontrol for Highly Enantioselective Carbon–Hydrogen Insertion Reactions of Cycloalkyl Diazoacetates

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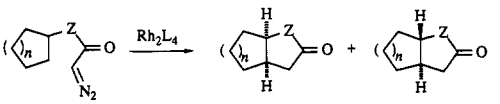
Intramolecular carbon–hydrogen insertion of metal carbenes generated by catalytic diazo decomposition of diazocarbonyl compounds is a facile methodology for carbon–carbon bond formation.[1-3] Although there are notable exceptions,[4-6] five-membered-ring formation is preferred,[7,8] and regioselectivity is generally subject to defined electronic effects.[9,10] Enantiocontrol has recently been achieved with selected substrates through the use of chiral or homochiral dirhodium(II) carboxamides,[11,12] or carboxylates,[13,14] but even with dirhodium(II) tetrakis[methyl 2-pyrrolidone-5(*S*)-carboxylate], $Rh_2(5S\text{-MEPY})_4$ (**1**), and its (*R*)-enantiomer, $Rh_2(5R\text{-MEPY})_4$, enantiomeric excesses only as high as 91% have been reported for C–H insertion with but one set of diazo esters.[11,15] Diastereocontrol in these reactions is even less predictable;[7,14,16] for example, both cis and trans ring fusion results from C–H insertion reactions of cycloalkyl-substituted diazocarbonyl compounds (eq 1, $n > 1$).[7,10,17] We



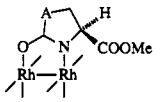

(1)

now report exceptional enantiocontrol and diastereocontrol in C–H insertion reactions of cycloalkyl diazoacetates through the use of a newly designed chiral dirhodium(II) carboxamide catalyst, dirhodium(II) tetrakis[methyl 1-acetylimidazolidin-2-one-4(*S*)-carboxylate], $Rh_2(4S\text{-MACIM})_4$ (**3**).[18]

**Table 1.** Diastereocontrol and Enantiocontrol for Dirhodium(II)-Catalyzed C–H Insertion Reactions of Cycloalkyl Diazoacetates[a]

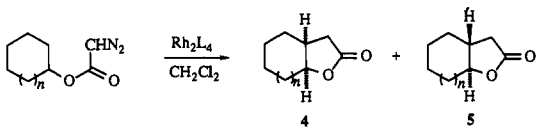
| diazoacetate | catalyst | isolated yield, % | 4:5 | % ee 4[b] | % ee 5[b] |
|---|---|---|---|---|---|
| cyclohexyl | $Rh_2(4S\text{-MACIM})_4$ | 70 | 99:1 | 97 | 65 |
| | $Rh_2(5R\text{-MEPY})_4$[c] | 65 | 75:25 | 97 | 91 |
| | $Rh_2(4S\text{-MEOX})_4$ | 50 | 55:45 | 96 | 95 |
| | $Rh_2(OAc)_4$ | 46 | 40:60 | | |
| cycloheptyl | $Rh_2(4S\text{-MACIM})_4$ | 75 | 99:1 | 96 | 61 |
| | $Rh_2(5R\text{-MEPY})_4$[c] | 80 | 71:29 | 96 | 85 |
| | $Rh_2(4S\text{-MEOX})_4$ | 68 | 58:42 | 97 | 94 |
| | $Rh_2(OAc)_4$ | 29 | 30:70 | | |
| cyclooctyl | $Rh_2(4S\text{-MACIM})_4$ | 62 | 99:1 | 97 | 59 |
| | $RH_2(5R\text{-MEPY})_4$[c] | 80 | 72:28 | 97 | 95 |
| | $Rh_2(4S\text{-MEOX})_4$ | 60 | 57:43 | 99 | 95 |
| | $Rh_2(OAc)_4$ | 33 | 29:71 | | |

[a] Reactions were performed in refluxing dichloromethane containing 0.5 mol % catalyst. [b] Determined on a Chiraldex G-TA GC column with base-line resolution. [c] Reactions performed with $Rh_2(5S\text{-MEPY})_4$ gave identical results but with mirror enantiomer configuration.




1. A = $CH_2$: $Rh_2(5S\text{-MEPY})_4$
2. A = O: $Rh_2(4S\text{-MEOX})_4$
3. A = $NCOCH_3$: $Rh_2(4S\text{-MACIM})_4$

Diazo decomposition of cyclohexyl diazoacetate by $Rh_2(4S\text{-MACIM})_4$ in refluxing dichloromethane resulted in the formation of cis-fused bicyclic lactone **4** ($n = 1$) in a 99:1 excess over the trans isomer **5** ($n = 1$) and with 97% ee (eq 2). With




(2)

$Rh_2(4S\text{-MEPY})_4$ the **4**:**5** ($n = 1$) isomer ratio was 75:25, although enantiomeric excesses were 97% (**4**) and 91% (**5**). The oxazolidinone derivative, dirhodium(II) tetrakis[methyl 2-oxazolidinone-4(*S*)-carboxylate], $Rh_2(4S\text{-MEOX})_4$ (**2**), produced **4**:**5** ($n = 1$) in a 55:45 ratio (96% ee for **4**, 95% ee for **5**) which approached the diastereomeric ratio achieved with $Rh_2(OAc)_4$ (**4**:**5** = 40:60). The absolute configuration of **4** ($n = 1$) formed by catalytic reactions of cyclohexyl diazoacetate with **1**, **2**, and **3** was determined to be (3a*S*,7a*S*); that from catalytic reaction with $Rh_2(5R\text{-MEPY})_4$ was (3a*R*,7a*R*).[19]

Extension of these investigations to cycloheptyl diazoacetate and cyclooctyl diazoacetate demonstrates the generality of this diastereocontrol and enantiocontrol (Table 1). Product yields are those following distillation, and enantiomer separations have been achieved by GC with base-line resolution. The major byproduct of these reactions is that from intermolecular water insertion; carbene dimer formation is controlled by moderating the rate of addition of the diazo compound to the catalyst in $CH_2Cl_2$. β-Lactone products were not observed. Cyclopentyl diazoacetate, whose catalytic diazo decomposition was exceptionally resistant to enantiocontrol (40% ee with $Rh_2[5R\text{-MEPY}]_4$),

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(18) $Rh_2(4S\text{-MACIM})_4$ was prepared from dirhodium(II) acetate and the chiral imidazolidinone according to the same procedure as that for the synthesis of $Rh_2(5R\text{-MEPY})_4$ and $Rh_2(5S\text{-MEPY})_4$.[15] Its cis-(2,2) configuration, with two oxygen and two nitrogen donor atoms at each rhodium arranged cis, was established by NMR analysis.

(19) Bicyclic lactone **4** ($n = 1$): $[\alpha]_D^{26} = -45.8°$ (*c* 0.41, $CH_3OH$) for product from catalytic reaction with $Rh_2(4S\text{-MACIM})_4$. Literature value for (3a*R*,7a*R*)-enantiomer: $[\alpha]_D^{27} = 45.5°$ (*c* 0.43, $CH_3OH$).[20]

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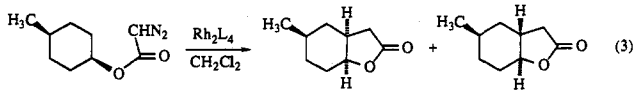
yielded the bicyclic cis-fused lactone product **4** ($n$ = 0) in 89% ee when $Rh_2$(5*S*-MACIM)$_4$ was the catalyst.

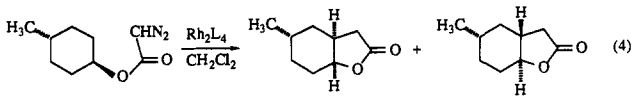
*cis*-4-Methylcyclohexyl diazoacetate was subjected to the same series of catalytic reactions, and unlike the catalyst dependent diastereoselectivity observed with cycloalkyl diazoacetates (Table 1), nearly exclusive cis ring fusion was the outcome for each of the dirhodium(II) catalysts employed (eq 3). A cis:trans ratio




(3)

| | **6** | **7** |
|---|---|---|
| $Rh_2$(4*S*-MACIM)$_4$ | > 99 (95% ee) | < 1 |
| $Rh_2$(5*S*-MEPY)$_4$ | 98 (98% ee) | 2 (84% ee) |
| $Rh_2$(4*S*-MEOX)$_4$ | > 99 (98% ee) | < 1 |

for ring fusion of 94:6 was the result from dirhodium(II) caprolactamate catalyzed reactions. Diazo decomposition of *trans*-4-methylcyclohexyl diazoacetate also provided high diastereocontrol with $Rh_2$(5*S*-MEPY) and $Rh_2$(4*S*-MEOX)$_4$ catalysis, and dominant selectivity was for the trans ring fusion product (eq 4). With $Rh_2$(4*S*-MACIM)$_4$, however, predominant




(4)

| | **8** | **9** |
|---|---|---|
| $Rh_2$(4*S*-MACIM)$_4$ | 63 (93% ee) | 37 (57% ee) |
| $Rh_2$(5*S*-MEPY)$_4$ | 15 (82% ee) | 85 (91% ee) |
| $Rh_2$(4*S*-MEOX)$_4$ | 10 (68% ee) | 90 (95% ee) |

diastereocontrol was for formation of the cis ring fusion product. High enantiocontrol in the production of **9** was achieved with the use of $Rh_2$(5*S*-MEPY)$_4$ and $Rh_2$(4*S*-MEOX)$_4$, but not with $Rh_2$(4*S*-MACIM)$_4$, which exhibited its higher enantioselectivity for **8**. Similarly high enantiocontrol characterized reactions of *cis*- and *trans*-4-*tert*-butylcyclohexyl diazoacetate catalyzed by $Rh_2$(MEPY)$_4$: 96% ee for the *tert*-butyl analog of **6** and 95% ee for the *tert*-butyl analog of **9**; in these cases diastereoisomer **7** or **8** was a trace component or was absent.

The enantioselectivities reported here are the highest that have been achieved in catalytic asymmetric C–H insertion reactions of diazocarbonyl compounds, and the virtually complete diastereocontrol for the formation of ring fused lactones establishes their synthetic potential. The influence of remote substituents on diastereoselection is consistent with preferential conformational alignment of the carbene attachment from the axial position for insertion into an equatorial C–H bond. When axial alignment is prevented, as in the case of *trans*-4-methylcyclohexyl or *trans*-4-*tert*-butylcyclohexyl diazoacetate, reaction can take place with either the equatorial or axial C–H bonds; however, insertion into the equatorial C–H bond is dominant for $Rh_2$(MEPY)$_4$ catalysts.

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**Supplementary Material Available:** Experimental details for catalyst preparation, catalytic reactions and product characterization (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.