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Amplification of Asymmetric Induction in Sequential Reactions of Bis-diazoacetates Catalyzed by Chiral Dirhodium(II) Carboxamidates

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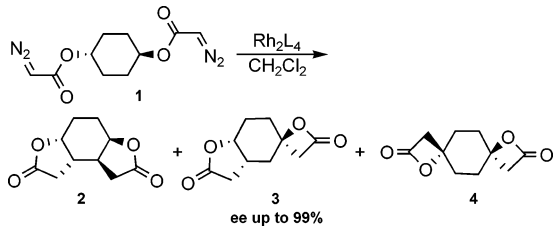
ABSTRACT



Two sequential intramolecular carbon–hydrogen insertion or cyclopropanation reactions of bis-diazoacetates using chiral dirhodium(II) carboxamidate catalysts are reported. The initial metal carbene transformation forms an excess of one enantiomer that with the second transformation further enhances stereocontrol (kinetic amplification). Diastereoselectivity and enantioselectivity for product formation are controlled by the catalyst.

Carbon−hydrogen insertion and cyclopropanation reactions of diazoacetates catalyzed by chiral dirhodium(II) compounds are important methodologies for the formation of lactones. Abundant examples of highly diastereoselective and enantioselective transformations in processes that occur with monodiazoacetates have been published,[1−4] but there are few examples in which double stereodifferentiation is exhibited.[5]

Amplification of asymmetric induction[6] involving sequential reactions at sites in proximity to each other generally results in enhancement of stereocontrol.[7] The first applications with diazoacetates for enhanced selectivity occurred by reacting chiral, nonracemic diazoacetates with chiral catalysts,[8] match/mismatch effects were observed, often with surprising results. More recently, the influence of two chiral centers on the catalyst in close proximity to the metal carbene reaction center was examined.[9] What has yet to be reported is the outcome of two sequential reactions of a bis-

(1) (a) Doyle, M. P. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000. (b) Doyle, M. P. In *Topics in Organometallic Chemistry*; Dotz, K.-H., Ed.; Springer-Verlag GmbH: Berlin, Germany, 2004; Vol. 10, p 203. (c) Doyle, M. P. In *Modern Rhodium-Catalyzed Transformations*; Evans, P. A., Ed.; Wiley-VCH: New York, 2005.

(2) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998.

(3) (a) Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, *57*, 1. (b) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861.

(4) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911.

(5) (a) Davies, H. M. L.; Jin, Q. *Org. Lett.* **2005**, *7*, 2293. (b) Davies, H. M. L.; Venkataramani, C. *Org. Lett.* **2001**, *3*, 1773.

(6) Amplification of asymmetric induction and double stereodifferentiation are discussed in Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; Chapter 12.5.

(7) Examples of the broad applications of double stereodifferentiation include: (a) Heathcock, C. H.; White, C. T. *J. Am. Chem. Soc.* **1979**, *101*, 7076. (b) Starkmann, B. A.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, 725. (c) Togni, A.; Blumer, R. K.; Pregosin, P. S. *Helv. Chim. Acta* **2004**, *74*, 1533.

(8) (a) Martin, S. F.; Spaller, M. R.; Liras, S.; Hartmann, B. *J. Am. Chem. Soc.* **1994**, *116*, 4493. (b) Doyle, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Ruppar, D. A.; Martin, S. F.; Spallar, M. R.; Liras, S. *J. Am. Chem. Soc.* **1995**, *117*, 11021.

(9) Doyle, M. P.; Morgan, J. P.; Fettinger, J.; Colyer, J. T.; Timmons, D. J.; Carducci, M. *J. Org. Chem.* **2005**, *70*, 5291.

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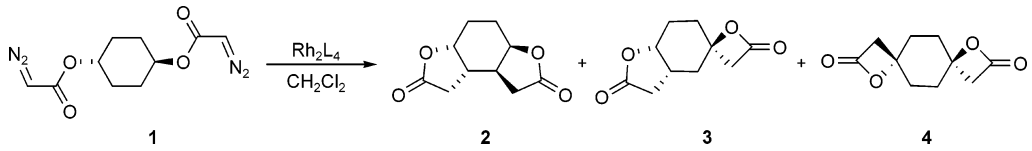
Table 1. Chemoselectivity and Enantioselectivity from Catalytic Reactions of **1**[a]



1 **2** **3** **4**

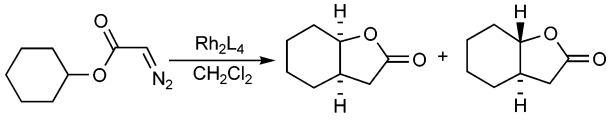
entry	catalyst	procedure	ratio[b] **2**:**3**:**4**	yield[c] (%)	ee of **3**[d] (%)
1	$Rh_2(OAc)_4$[e]	**A**	20:80:0	60	
2	$Rh_2(5S\text{-MEPY})_4$	**B**	11:80:9	58	95
3	$Rh_2(4R\text{-MEOX})_4$[f]	**A**	11:72:17	70	95
4	$Rh_2(4S\text{-MEOX})_4$	**B**	1:65:34	81	99
5	$Rh_2(4S\text{-IBAZ})_4$	**B**	6:94:0	43	96
6	$Rh_2(4S\text{-MPPIM})_4$	**A**	59:41:0	90	99
7	$Rh_2(4S\text{-MPPIM})_4$	**B**	48:52:0	91	
8	$Rh_2(4S,S\text{-BSPIM})_4$	**B**	48:52:0	90	99
9	$Rh_2(4S,R\text{-MNACIM})_4$	**B**	32:68:0	35	99

[a] Reactions were performed by addition of **1** in CH_2Cl_2 to a refluxing CH_2Cl_2 solution of the catalyst (procedure **A**: 1.0 mol % catalyst, addition over 10 h; procedure **B**: 2.0 mol % catalyst, addition over 2 h). [b] Determined by ^1H NMR in $CDCl_3$. [c] Isolated yield after column chromatography. [d] Determined by GC on Chiraldex B-DM column. [e] Racemic mixture of **3** and ***ent*-3** was formed. [f] ***ent*-3** was formed in this case.

diazoacetate in reactions with a chiral dirhodium(II) carboxamidate. In such cases, the first transformation forms an excess of one enantiomer that with the second transformation further enhances stereocontrol (kinetic amplification).

The preference for formation of five-membered rings in carbon−hydrogen insertion reactions is well established.[1−4,10] This preference is exacting and virtually exclusive in C−H insertion reactions that occur with cyclohexyl diazoacetates (Scheme 1).[11] The only significant exception occurred in

Scheme 1



$Rh_2(4S\text{-MACIM})_4$	99 (97% ee)	1 (65% ee)
$Rh_2(5R\text{-MEPY})_4$	86 (>99% ee)	14 (93% ee)
$Rh_2(4S\text{-MPPIM})_4$	100 (92% ee)	0

reactions of 3-substituted steroidal diazoacetates where, when there was a configurational mismatch between substrate and catalyst, four-membered ring β-lactone was the major product.[12] Consider, then, our surprise in encountering three insertion products in varying amounts from reactions of the bis-diazoacetate of *trans*-1,4-cyclohexanediol[13] catalyzed by chiral dirhodium(II) carboxamidates (Table 1). Full characterization of each of these products was provided by their X-ray structures (Figures 2−4)[14] and complimented by

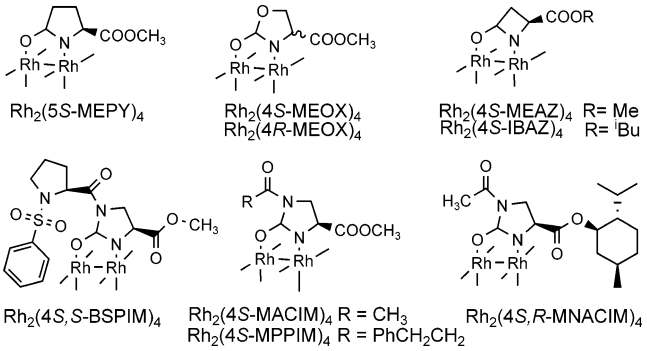


Figure 1. Chiral dirhodium(II) carboxamidate catalysts.

spectroscopic results. The production of **2** was anticipated from the configurational outcome of monodiazoacetates (Scheme 1). This compound is C_2-symmetric, but was formed as the major product only in reactions performed with sterically encumbered oxaimidazolidine−carboxylate catalysts $Rh_2(4S\text{-MPPIM})_4$ and $Rh_2(4S,S\text{-BSPIM})_4$ (Table 1, entries 6−8). Note that the directional outcome of the insertion reactions is consistent with the trans configuration of the reactant bis-diazoacetate.

Spirolactone **3** was the major product from reactions that occurred with the more open catalysts $Rh_2(5S\text{-MEPY})_4$, Rh_2-

(10) Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686.
(11) (a) Doyle, M. P.; Kalinin, A. V.; Ene, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 8837. (b) Doyle, M. P.; Tedrow, J. S.; Dyatkin, A. B.; Spaans, C. J.; Ene, D. G. *J. Org. Chem.* **1999**, *64*, 8907. (c) Doyle, M. P.; Colyer, J. *J. Mol. Catal. A* **2003**, 196. (d) Doyle, M. P.; Yan, M.; Gau, H.-M.; Blossey, E. C. *Org. Lett.* **2003**, *5*, 561.
(12) Doyle, M. P.; Davies, S. B.; May, E. J. *J. Org. Chem.* **2001**, *66*, 8112.
(13) Only products from intermolecular and intramolecular "carbene dimer" formation were observed from reactions of the bis-diazoacetate of *cis*-1,4-cyclohexanediol.
(14) Crystallographic data for **2**, **3**, and **4** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 279653, 279654, 279655. See Supporting Information for X-ray crystal data.

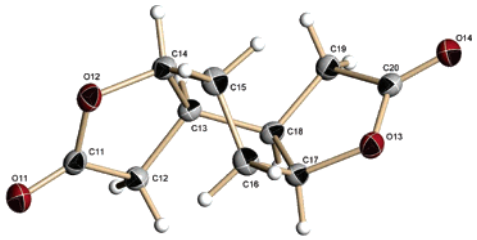


Figure 2. Crystal structure of **2** with selected bond lengths [Å] and angles [deg]: O12−C11 1.347(3), O12−C14 1.465(2), C11−C12 1.496(3), C12−C13, 1.535(3), C13−C18 1.521(3), C13−C14 1.548(3), C14−C15 1.519(3), C11−O12−C14 112.07(17), O12−C11−C12 110.54(17), C11−C12−C13 105.48(17), C18−C13−C14 114.36(16), C12−C13−C14 103.95(16), O12−C14−C13 104.98(15), C15−C14−C13, 113.95(17), C14−C15−C16, 111.16-(17), C17−C16−C15 111.37(17).

(4*S*/*R*-MEOX)$_4$, and Rh$_2$(4*S*-IBAZ)$_4$ (Table 1, entries 2−5), and enantioselectivities associated with its formation were exceptional. The bis-spirolactone product **4** was a minor product only formed in reactions with **1** catalyzed by Rh$_2$-(MEOX)$_4$ and Rh$_2$(5*S*-MEPY)$_4$ (Table 1, entries 2−4), and efforts to increase its production were not successful. The major competing process in these reactions was "carbene dimer" formation, especially with the more reactive catalysts, such as Rh$_2$(OAc)$_4$, Rh$_2$(4*S*-IBAZ)$_4$, and Rh$_2$(5*S*-MEPY)$_4$; only the sterically hindered oxaimidazolidine-ligated catalysts, Rh$_2$(4*S*-MPPIM)$_4$ and Rh$_2$(4*S*,*S*-BSPIM)$_4$, suppressed the formation of these products. Ordinarily, increasing the time of addition of the diazo compound to the reaction mixture containing the catalyst reduces this undesirable reaction. However, in several instances, decreasing the time for addition from 10 h (procedure B) to 2 h (procedure A) led to a reduction in these dimeric and oligomeric products. Furthermore, changes in addition time changed the ratio of **2**:**3**:**4**, indicating that the diazoacetate remaining from the first C−H insertion was being preferentially drawn down this pathway, further suggesting that the rate for diazo

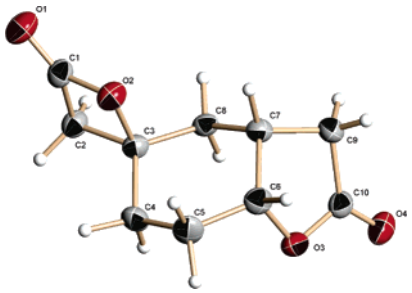


Figure 3. Crystal structure depicting the (3a*R*,5*R*,7a*R*)-**3** enantiomer with selected bond lengths [Å] and angles [deg]: O2−C1 1.359(3), C1−C2 1.509(4), C2−C3 1.524(4), C3−C8 1.502(4), C7−C9 1.516(4), C7−C8 1.527(4), C9−C10 1.508(4), C10−O3 1.348(4), C1−C2−C3 85.2(2), C8−C3−C2 117.0(2), C9−C7−C8 111.0(2), C3−C8−C7 112.5(2), C10−C9−C7 102.2(2).

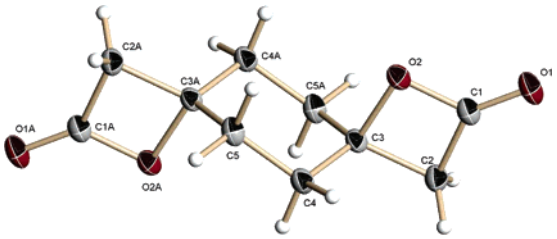
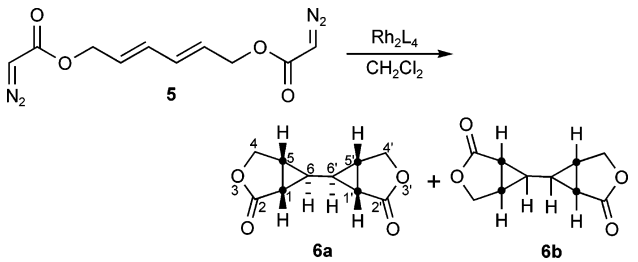


Figure 4. Crystal structure of **4** with selected bond lengths [Å] and angles [deg]: O2−C1 1.3587(15), O2−C3 1.5114(13), C1−C2 1.5025(17), C2−C3 1.5374(17), C3−C4 1.5118(16), C4−C5 1.5251(18), C1−O2−C3 91.11(8), C4−C3−C2 116.60(11), C3−C4−C5 112.03(10).

decomposition of the intermediate monodiazoacetate is slower than that for **1**.

(*E*,*E*)-2,4-Hexadien-1,6-diyl bis-diazoacetate **5** was selected for examination of double diastereoselection in dirhodium(II)-catalyzed intramolecular cyclopropanation reactions (Table 2). Two diastereomeric products were

Table 2. Diastereoselectivity and Enantioselectivity from Catalytic Double Cyclopropanation Reactions of **5**[a]



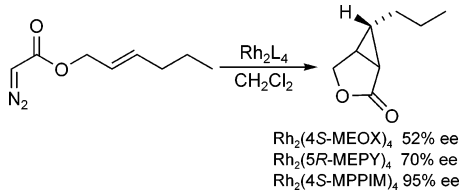
entry	catalyst	yield[b] (%)	**6a**:**6b**[c]	ee of **6b**[d] (%)
1	Rh$_2$(OAc)$_4$	trace		
2	Rh$_2$(CAPY)$_4$	54	48:52	
3	Rh$_2$(R/S-MEPY)$_4$	79	45:55	11
4	Rh$_2$(4*R*-MEAZ)$_4$	21	33:67	82
5	Rh$_2$(4*R*-MEOX)$_4$	78	24:76	86
6	Rh$_2$(5*R*-MEPY)$_4$	91	18:82	96
7	Rh$_2$(4*R*-MPPIM)$_4$	90	7:93	99
8	Rh$_2$(4*S*,*S*-BSPIM)$_4$	79	4:96	99
9	Rh$_2$(4*S*,*R*-MNACIM)$_4$	78	5:95	99

[a] Reactions were performed by addition of **5** in CH_2Cl_2 over 10 h to a refluxing CH_2Cl_2 solution of the catalyst (1.0 mol %). [b] Isolated yield after chromatography. [c] Determined by ^{1}H NMR in CD_3CN. [d] Determined by GC on Chiraldex B-DM column.

formed: **6a** (1*S*,5*R*,6*R*,1′*R*,5′*S*,6′*S*)-[6,6′]bi(3-oxabicyclo-[3.1.0]hexyl)-2,2′-dione, which is the meso product, and a enantiomeric pair of ***R*-6b**, (1*R*,5*S*,6*S*,1′*R*,5′*S*,6′*S*)-[6,6′]bi-[3-oxabicyclo[3.1.0]hexyl]-2,2′-dione, and ***S*-6b**, (1*S*,5*R*,6*R*,1′*S*,5′*R*,6′*R*)-[6,6′]bi[3-oxabicyclo[3.1.0]hexyl]-2,2′-dione. To determine diastereoselectivity for the double cyclopropanation reaction in the absence of the effects related to chiral ligands

on dirhodium(II), reactions with $Rh_2(OAc)_4$ and $Rh_2(CAPY)_4$ were performed. With $Rh_2(OAc)_4$ compounds **6a** and **6b** could only be obtained in trace amounts, but the reaction with $Rh_2(CAPY)_4$ resulted in a modest yield of diastereomers with a product ratio showing no preference for either diastereoisomer, indicating that the influence of the first cyclization on the second cyclization step is relatively small. When "equal" amounts of the enantiomeric $Rh_2(MEPY)_4$ catalysts were used, product diastereoselectivity was the same, but product yields for **6a** + **6b** were dramatically improved.[15] The slight preference for the chiral compound **6b** in this case is probably due to impurities in one of the catalyst enantiomers or to the measurement of unequal amounts of the pure catalysts. The *S*-configured dirhodium(II) catalysts favored the formation of (1*R*,5*S*,6*S*,1′*R*,5′*S*,6′*S*)-**6b** (***S*-6b**), and the (1*S*,5*R*,6*R*,1′*S*,5′*R*,6′*R*)-**6b** (***R*-6b**) was the dominant product of the *R*-configured catalysts. Imidazolidinone-based catalysts gave superior enantioselectivities and low yields of the meso product **6a**. Compared to the model compound, (*E*)-2-hexen-1-yl diazoacetate (Scheme 2),[11c]

Scheme 2

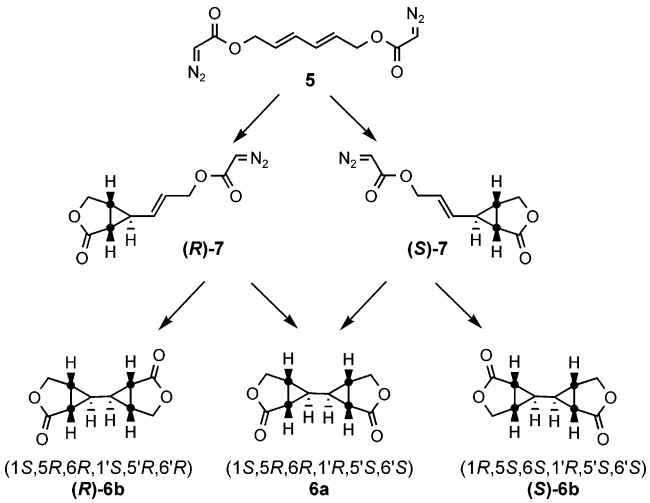


where only monocyclopropanation occurs, all catalysts resulted in an higher enantiomeric excess.

As shown in Table 2, the decrease in the relative yield of the meso product **6a** is linked to the increase of enantioselectivity for **6b**. This relationship can be understood by reference to the stepwise process described in Scheme 3. In the absence of secondary influences, the anticipated ratio of products from reaction with achiral or racemic catalyst is 25:50:25 for ***R*-6b**:**6a**:***S*-6b**, or 50:50 for **6a**:**6b**, and this is what is observed. If, in what is expected from reactions catalyzed by $Rh_2(5R\text{-MEPY})_4$ (Scheme 2), the ratio of ***R*-7** to ***S*-7** is 85:15, then one would expect that product ratio for ***R*-6b**:**6a**:***S*-6b** would be 72:26:2, or 26:74 for **6a**:**6b** and 95% ee for **6b**. Instead, we see from Table 2 that the ***R*-6b**:**6a**:***S*-6b** product ratio is 80:18:2 with 96% ee, which suggests that there is synergistic enhancement of selectivity, but that this enhancement is small.

(15) Similar results were obtained with $Rh_2(R/S\text{-MEOX})_4$.

Scheme 3



In summary, amplification of asymmetric induction in intramolecular metal carbene transformations has provided the first examples of competition for formation of meso and D,L-diastereoisomers. Limiting the formation of the meso isomer provides enhanced enantioselectivity.

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Supporting Information Available: Additional experimental details, ^1H and ^{13}C NMR spectra, tables of positional and thermal parameters, and X-ray crystallographic information in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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