Highly Selective Enantiomer Differentiation in Intramolecular Cyclopropanation Reactions of Racemic Secondary Allylic Diazoacetates

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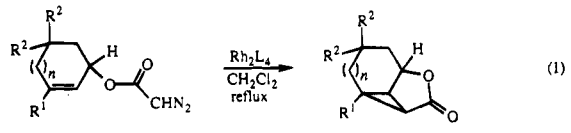
Exceptional enantiocontrol has been achieved in intramolecular cyclopropanation reactions of primary allylic diazoacetates catalyzed by chiral dirhodium(II) carboxamidates, where enantiomeric excesses ≥94% generally accompany high product yields and turnover numbers.[1,2] This methodology has been applied both to the synthesis of 1,2,3-trisubstituted cyclopropanes that have been incorporated into conformationally restricted peptide isosteres, which are potent inhibitors of renin[3] and collagenase,[4] and to the synthesis of presqualene alcohol[5] with notable success. Tetrakis[5(*S*)-(methoxycarbonyl)-2-oxapyrrolidinyl]dirhodium(II) (Rh_2(5*S*-MEPY)$_4$) and its enantiomeric form, Rh_2(5*R*-MEPY)$_4$,[6] are the catalysts of choice for this transformation,[1,2,7] although alternative chiral carboxamide ligands for dirhodium(II) have provided advantages for enantiocontrol in selected cases.[2,8]

Extension of this methodology to secondary allylic diazoacetates is limited by the potential production of two or more sets of diastereoisomeric products from the use of racemic reactants. However, two approaches are suited to generating mainly one stereoisomeric product: (1) the use of chiral secondary allylic diazoacetates and (2) the kinetic resolution of racemic secondary allylic diazoacetates by their differential reactions/reactivities with chiral catalysts. Using enantiomerically pure secondary allylic diazoacetates, Martin and co-workers have demonstrated that high diastereocontrol (up to >20:1) results from the appropriate match of substrate and catalyst configurations.[9] We now report that racemic secondary allylic diazoacetates can be used directly to achieve high enantio- and diastereocontrol in chiral dirhodium(II) carboxamidate-catalyzed cyclopropanation reactions.

Diazo decomposition of racemic 2-cyclohexen-1-yl diazoacetate (**1a**) catalyzed by dirhodium(II) caprolactamate (Rh_2(cap)$_4$) afforded racemic tricyclic cyclopropane **2a** as the sole product in 95% isolated yield (eq 1). When this cyclization was

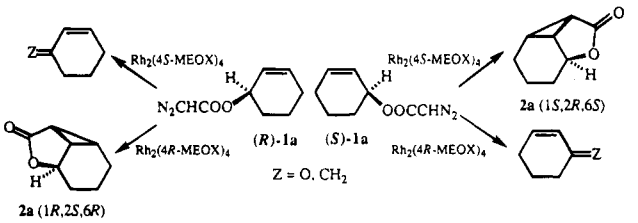


(1)

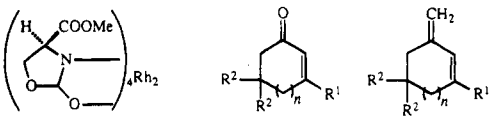
1 **2**

a. n = 1, R^1 = R^2 = H
b. n = 1, R^1 = Me, R^2 = H
c. n = 1, R^1 = R^2 = Me
d. n = 0, R^1 = R^2 = H
e. n = 2, R^1 = R^2 = H

Scheme 1



catalyzed with Rh_2(5*S*-MEPY)$_4$, **2a** was formed in 62% yield, albeit with an enantiomeric excess of only 48%. However, using tetrakis[4(*S*)-(methoxycarbonyl)-2-oxyoxazolidinyl]dirhodium-(II) (Rh_2(4*S*-MEOX)$_4$) as the catalyst led to the production of **2a** in 94% ee, with an isolated yield of 40% based on *rac*-**1a** (78% *ent*-**2a** based on *ent*-**1a**).[10] The byproducts of these



reactions that accounted for the fate of *ent*-**1** were 2-cyclohexenone (**3a**) and diene **4a**, which are suggested to have arisen via intramolecular hydride abstraction from the allylic C−H position α to oxygen, with subsequent elimination of ketene or carbon dioxide.[11] Hydrogenolysis of **2a** (5% Pd/C, HOAc) produced the corresponding bicyclic lactone of known absolute configuration,[12] thus establishing **2a** (1*S*,2*R*,6*S*) as the enantiomer produced in excess from Rh_2(5*S*-MEPY)$_4$- and Rh_2(4*S*-MEOX)$_4$-catalyzed reactions and (1*S*)-cyclohex-2-en-1-yl diazoacetate as the enantiomer that underwent cyclopropanation. Use of Rh_2(4*S*-MEOX)$_4$ with methyl-substituted analogs **1b,c** produced **2b,c** in somewhat lower isolated yields but with similarly high enantiocontrol (Table 1).[13] Similar results were obtained with 2-cyclopenten-1-yl and 2-cyclohepten-1-yl diazoacetates. Thus, formation of **2** occurs via a resolution process in which one enantiomer of **1** undergoes predominantly intramolecular cyclopropanation, and *ent*-**1** reacts mainly through hydride abstraction/elimination (Scheme 1, Z = O, CH_2). Use of Rh_2(4*R*-MEOX)$_4$ provided **2a** in the mirror image configuration with 94% ee, thus demonstrating that this methodology can be used to prepare either enantiomer of **2**. The mass difference between **2** and **3/4** makes them conveniently separable by distillation or chromatography.

With acyclic racemic secondary allylic diazoacetates **5**, enantiomer differentiation in intramolecular cyclopropanation

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(8) Doyle, M. P.; Dyatkin, A. B.; Protopopova, M. N.; Yang, C. I.; Miertschin, C. S.; Winchester, W. R. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 163.
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(10) A solution of the diazoacetate (1.0 mmol) in 10 mL of CH_2Cl_2 was added via syringe pump over 10 h to a solution of the catalyst (1.0 mol %) in 20 mL of CH_2Cl_2 at reflux. The ratios of products were determined by ^{1}H NMR spectral analyses and GC. Enantiomeric excess was measured by GC on a Chiraldex G-TA column with baseline resolution. Isolated yields were of the purified product obtained following distillation and chromatography.
(11) Doyle, M. P.; Dyatkin, A. B.; Autry, C. L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 619. Diketene was detected in reactions performed with Rh_2(4*S*-MEOX)$_4$.
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(13) The structure of each new compound was consistent with its spectral (^{1}H and ^{13}C NMR, IR, and mass) characteristics and with elemental analyses.

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Table 1. Enantiomer Differentiation in Intramolecular Cyclopropanation of Racemic Secondary 2-Cycloalken-1-yl Diazoacetates (**1**)[a]

1	*n*	R^1	R^2	catalyst	2:3:4	yield 2, %[b]	ee 2, %
a	1	H	H	Rh_2(cap)$_4$	100:0:0	95	
				Rh_2(5*S*-MEPY)$_4$	87:13:0	62	48
				Rh_2(4*S*-MEOX)$_4$	50:50:0	40	94
b	1	CH_3	H	Rh_2(cap)$_4$	98:2:0	85	
				Rh_2(5*S*-MEPY)$_4$	51:40:9	52	69
				Rh_2(4*S*-MEOX)$_4$	33:58:9	30	95
c	1	CH_3	CH_3	Rh_2(cap)$_4$	90:10:0	77	
				Rh_2(5*S*-MEPY)$_4$	50:45:5	50	75
				Rh_2(4*S*-MEOX)$_4$	20:66:14	20	95
d	0	H	H	Rh_2(cap)$_4$	100:0:0	86	
				Rh_2(5*R*-MEPY)$_4$	75:15:0	69	59
				Rh_2(4*R*-MEOX)$_4$	56:34:10	34	95
e	2	H	H	Rh_2(cap)	100:0:0	88	
				Rh_2(5*S*-MEPY)$_4$[c]	86:10:4	58	34
				Rh_2(4*S*-MEOX)$_4$[d]	58:40:2	38	83

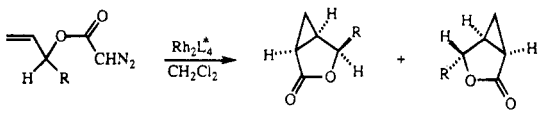
[a] Reactions were performed as described (ref 10). [b] Isolated yields of purified product based on *rac*-**1**. [c] Carbon–hydrogen insertion products (2.4%) and 1,10-dehydro-8-oxabicyclo[5.3.0]decan-9-one (4.0%) were also formed. [d] Same products as in *c*, 7.2% and 6.0%, respectively.

Table 2. Enantiomer Differentiation in Intramolecular Cyclopropanation of Acyclic Racemic Secondary Allylic Diazoacetates (**5**)[a]

5	R	catalyst	yield 6, %[b]	*endo*:*exo* (6)	ee, % *endo*-6	ee, % *exo*-6
a	Me	Rh_2(5*S*-MEPY)$_4$	80	83:17	31	84
		Rh_2(4*S*-MEOX)$_4$	63	70:30	70	30
b	*n*-Pent	Rh_2(5*S*-MEPY)$_4$	69	82:18	47	44
		Rh_2(4*S*-MEOX)$_4$	65	74:26	73	18
c	Ph	Rh_2(5*S*-MEPY)$_4$	63	72:28	56	9
		Rh_2(4*S*-MEOX)$_4$	60	82:18	82	42
d	*c*-C_3H_5	Rh_2(5*S*-MEPY)$_4$	51	87:13	35	89
		Rh_2(4*S*-MEOX)$_4$	65	81:19	79	34

[a] Diastereoselectivities obtained with the use of Rh_2(cap)$_4$ ranged from 90:10 (**5d**) to 93:7 (**5a**). Reactions were performed as described (ref 10). [b] Isolated yields of purified products. Products from hydride abstraction were minor constituents of the reaction mixture.

with chiral dirhodium(II) catalysts occurs through the formation of *exo*- and *endo*-diastereoisomers (eq 2). In the simplest case,

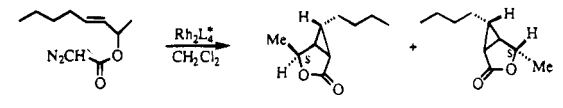


(2)

5 a. R = Me; b. R = *n*-Pent; c. R = Ph; d. R = *c*-C_3H_5 — *endo*-**6** — *exo*-**6**

3-buten-2-yl diazoacetate forms *endo*-**6a** and *exo*-**6a** in high yield and moderate enantioselectivity and diastereoselectivity. The influence of Rh_2(5*S*-MEPY)$_4$ and Rh_2(4*S*-MEOX)$_4$ on selectivity with a series of racemic secondary allylic diazoacetates is summarized in Table 2. With the exception of **5c**, diastereocontrol is higher with Rh_2(5*S*-MEPY)$_4$ than with Rh_2(4*S*-MEOX)$_4$, but these two catalysts show divergent enantiomer preferences in the formation of *endo*-**6** and *exo*-**6**. The absolute configurations of *endo*- and *exo*-**6c** were established by correlations with products from the cyclization of (1*S*)-**5c** with Rh_2(5*R*-MEPY)$_4$ to form enantiomerically pure (4*S*)-*endo*-**6c** and (4*S*)-*exo*-**6c** in a 8.1:1.0 ratio. The predominant enantiomers of the diastereomeric pair from the cyclization of *rac*-**5c** with Rh_2(5*S*-MEPY)$_4$ or Rh_2(4*S*-MEOX)$_4$ have opposite configurations, (4*R*)-*endo*-**6c** and (4*S*)-*exo*-**6c**, demonstrating enantiomer differentiation in which one enantiomer of **5** forms *endo*-**6** predominantly, whereas the other forms mainly *exo*-**6**.

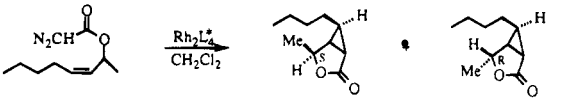
Recognizing the potential influence of olefin substituents on overall stereocontrol, the geometrical isomers of the *rac*-oct-3-en-2-yl diazoacetates **7** and **9** were subjected to diazo decomposition (eqs 3 and 4). The absolute configurations of



(3)

7 — *endo*-**8** — *exo*-**8**

	yield, % *endo*-**8** + *exo*-**8**	*endo*-**8**	*exo*-**8**
Rh_2(cap)$_4$	88	84	16
Rh_2(5*S*-MEPY)$_4$	74	76 (38% ee)	24 (15% ee)
Rh_2(4*S*-MEOX)$_4$	43	71 (92% ee)	29 (56% ee)



(4)

9 — *endo*-**10** — *exo*-**10**

	yield, % *endo*-**10** + *exo*-**10**	*endo*-**10**	*exo*-**10**
Rh_2(cap)$_4$	92	80	20
Rh_2(5*S*-MEPY)$_4$	64	67 (38% ee)	33 (53% ee)
Rh_2(4*S*-MEOX)$_4$	53	59 (67% ee)	41 (69% ee)

endo- and *exo*-**8** and **-10** were established by correlation with the cyclopropane products formed from the optically pure (2*S*)-oct-3-en-2-yl diazoacetates.[9] The predominant enantiomer for both *endo*-**8** and *endo*-**10** possessed the (4*S*)-configuration when these reactions were performed with either Rh_2(5*S*-MEPY)$_4$ or Rh_2(4*S*-MEOX)$_4$. For *exo*-**8**, the (4*R*)-enantiomer predominated in reactions with Rh_2(5*S*-MEPY)$_4$, whereas the (4*S*)-enantiomer was the major product from reactions catalyzed by Rh_2(4*S*-MEOX)$_4$; hydride abstraction products were also observed from diazo decomposition of **7**, and their amounts were proportional to the extent of enantiocontrol that accompanied cyclopropanation.[14] The (4*R*)-enantiomer of *exo*-**10** was the major product from reactions catalyzed by either Rh_2(5*S*-MEPY)$_4$ or Rh_2(4*S*-MEOX)$_4$, and, along with byproducts from hydride abstraction (<3%), limited amounts of a rearrangement product,[15] 5-methyl-4-(*n*-pentyl)-1-oxacyclopent-3-en-2-one (**11**),[16] were formed.

The results reported here demonstrate the versatility of chiral dirhodium(II) catalysts for enantiomer differentiation and suggest their viability for the stereoregulated synthesis of selected cyclopropanes from racemic allylic diazoacetates in high enantiomeric excess. Efforts are continuing to elaborate the scope of enantiomer differentiation and to improve selectivity.

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Supporting Information Available: Experimental details for the synthesis and diazo decomposition of diazoacetates and product characterizations (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(14) *trans*-Oct-3-en-2-one/2-methyl-1,3-octadiene = 7%/3% with Rh_2(5*S*-MEPY)$_4$ and 24%/8% with Rh_2(4*S*-MEOX)$_4$.

(15) A similar product has been reported in intramolecular dirhodium(II)-catalyzed cyclopropanation reactions of 3-methyl-2-buten-1-yl diazoacetate (ref 6).

(16) Amount of 4% **11** from reactions catalyzed by Rh_2(5*S*-MEPY)$_4$ and 10% **11** from those catalyzed by Rh_2(4*S*-MEOX)$_4$.