Enantio- and Diastereoselectivity in the Intramolecular Cyclopropanation of Secondary Allylic Diazoacetates

Stephen F. Martin,* Mark R. Spaller, Spiros Liras, and Benoît Hartmann

Department of Chemistry and Biochemistry
The University of Texas, Austin, Texas 78712

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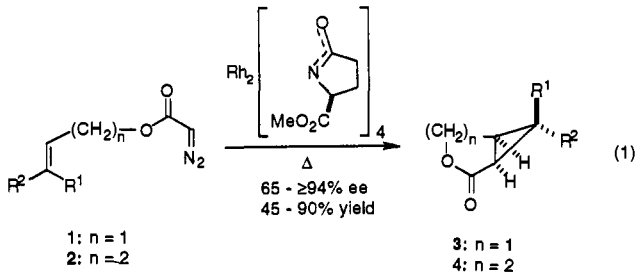
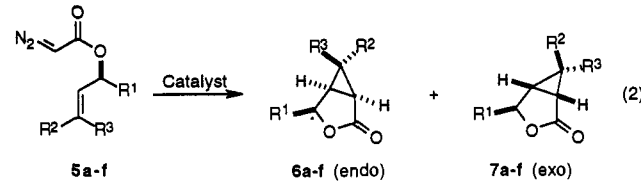
The design and development of efficient methods for the stereoselective and asymmetric syntheses of substituted cyclopropanes have been the subjects of a myriad of investigations because of the presence of such subunits in a number of natural products and their use as mechanistic probes of organic transformations.[1] We have recently discovered that trisubstituted cyclopropanes may be incorporated as novel isosteric replacements of dipeptide arrays to enforce an extended, β-strand conformation on biologically active mimics of oligopeptides.[2] At the outset of our investigations in this area, it was apparent that the available methods for the asymmetric synthesis of highly substituted cyclopropanes suffered from a number of deficiencies, and we therefore set to the task of inventing new routes to these important compounds. These early efforts featured the cyclization of primary allylic and homoallylic diazoacetates such as **1** and **2** catalyzed by the chiral rhodium complex dirhodium(II) tetrakis-[methyl 2-pyrrolidone-5(*S*)-carboxylate] $[Rh_2((5S)\text{-MEPY})_4]$[3] to give the cyclopropyl lactones **3** and **4**, respectively, in high yield and enantioselectivity (eq 1).[4] In the context of extending



(1)

such transformations to more highly substituted substrates, we wondered whether the diazoacetates of secondary allylic alcohols might also undergo cyclizations with high levels of enantio- and diastereoselectivity to give cyclopropyl lactones, and some results emerging from this inquiry constitute the substance of the present report.[5]

Three key questions emerged at the outset of these investigations: (1) What is the diastereoselectivity inherent in the cyclization of chiral secondary allylic diazoacetates **5a–f** to give the isomeric cyclopropyl lactones **6a–f** and **7a–f** (eq 2), and can the selectivity that is dictated by the resident chiral center be overcome through the agency of a chiral rhodium catalyst?



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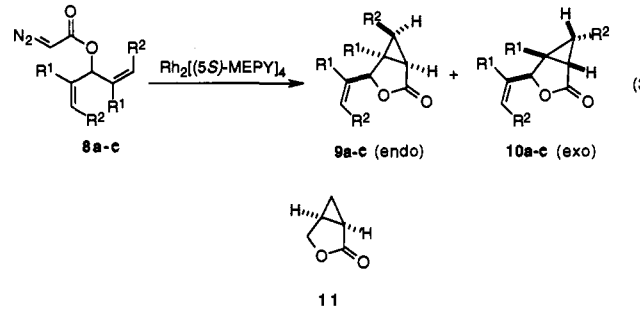
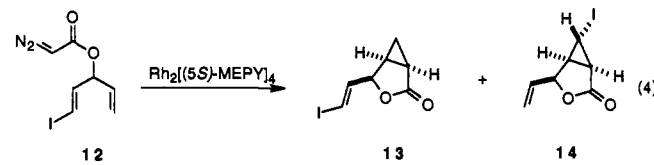
(2) What is the enantio- and diastereoselectivity in the cyclizations of prochiral secondary divinyl diazoacetates **8a–c** to give **9a–c** and **10a–c** (eq 3)?



(3)

(3) Can racemic divinyl diazoacetates such as **12** be kinetically resolved (eq 4)?



(4)

To address the first question, the metal-catalyzed cyclizations of a series of enantiomerically pure, secondary allylic diazoacetates were examined (Table 1).[6,7] The diazoacetates **5a–d** were synthesized from the corresponding homochiral secondary allylic alcohols[8] by the one-step procedure of Corey and Myers (TsNHNCHCOCl, *N,N*-dimethylaniline, CH_2Cl_2; Et_3N).[9] However, this simple technique could not be applied to the syntheses of the diazoacetates **5e,f**, which were prepared by reaction of the corresponding allylic alcohols[10] with diketene and methylsulfonyl azide followed by hydroxide-induced cleavage of the 1,3-

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(5) (a) This work was presented at the 49th Southwest Regional Meeting of the American Chemical Society, Austin, TX, October 24–27, 1993; ORGN 34. (b) For related work, see: Guay, D.; Labine, S.; Sprules, T. J. *Abstracts of Papers*, 207th National Meeting of the American Chemical Society, San Diego, CA, March 13–17, 1994; ORGN 77.

(6) A solution (0.02–0.04 M) of the diazo ester was added via syringe pump over the course of 8–16 h to a solution of the catalyst (0.01–0.05 equiv) in the appropriate solvent [$C_6H_5CH_3$ or C_6H_6 for $Cu(TBS)_2$ and CH_2Cl_2 for $Rh_2((5S/R)\text{-MEPY})_4$] at reflux. The ratios of the cyclized products were determined from the ^1H NMR spectra of the crude reaction mixtures and were based upon integration of the peaks assigned to the methine proton α to the ring oxygen of the cyclopropyl lactones. The methine protons of the endo and exo diastereomers exhibited characteristic splitting patterns ($J_{5,6(exo)} \cong 0$ Hz; $J_{5,6(endo)} = 3.5$–6.5 Hz). The veracity of the stereochemical assignments based upon the ^1H NMR spectra is supported by an X-ray analysis of **6c**. The yields cited represent the combined yield of the *mixture* of exo and endo adducts after all other impurities were removed by flash chromatography.

(7) The structure of each compound was in accord with its spectral (^1H and ^{13}C NMR, IR and mass) characteristics. Analytical samples of all new compounds were obtained by preparative HPLC or flash chromatography, and the molecular composition was determined by high-resolution mass spectrometry.

(8) The allylic alcohols **5a–d** were prepared by stereoselective reduction (H_2, Lindlar, or $LiAlH_4$) of enantiomerically pure propargylic alcohols. See: Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 6129.

(9) Corey, E. J.; Myers, A. G. *Tetrahedron Lett.* **1984**, *25*, 3559.

(10) The allylic alcohols **5e,f** were synthesized by stereoselective reduction (H_2, P-2 nickel boride, or $LiAlH_4$) of the triple bond of the corresponding propargylic alcohol, which was prepared from L-phenylalanine by a straightforward sequence of reactions according to the published method: Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141.

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Table 1. Cyclizations of Diazoacetates of Chiral Secondary Alcohols **5a–f**[6,7]

entry	R^1	R^2	R^3	catalyst	endo:exo	yield (%)
a	CH_3	H	*n*-Bu	$Cu(TBS)_2$	1:2.5	66
				$Rh_2((5S)\text{-MEPY})_4$	>20:1	80
				$Rh_2(5R)\text{-MEPY})_4$	1:1.5	39
b	CH_3	*n*-Bu	H	$Cu(TBS)_2$	1:3.5	81
				$Rh_2((5S)\text{-MEPY})_4$	6:1	77
				$Rh_2((5R)\text{-MEPY})_4$	1:1	42
c	CH_3	H	TMS	$Cu(TBS)_2$	1:1	67
				$Rh_2((5S)\text{-MEPY})_4$	>20:1	74
				$Rh_2((5R)\text{-MEPY})_4$	1:1.7	31
d	CH_3	TMS	H	$Cu(TBS)_2$	1:1.1	69
				$Rh_2((5S)\text{-MEPY})_4$	20:1	76
				$Rh_2((5R)\text{-MEPY})_4$	11:1	47
e		H	Ph	$Cu(TBS)_2$	1:18	49
				$Rh_2((5S)\text{-MEPY})_4$	4.5:1	45
				$Rh_2((5R)\text{-MEPY})_4$	1:>20	33
f		Ph	H	$Cu(TBS)_2$	1:8	67
				$Rh_2((5S)\text{-MEPY})_4$	2.5:1	74
				$Rh_2((5R)\text{-MEPY})_4$	1:3.5	50

dicarbonyl array.[11] The substrate-based stereospecificity for **5a–f** was determined by catalyzing their cyclizations with bis(*N-tert*-butylsalicylamidinato)copper(II) ($Cu(TBS)_2$). For the diazoesters **5a–d**, which have only one stereogenic center, the observed diastereoselectivity using this catalyst was poor as shown in entries a–d, whereas the diastereoselectivity for the amino acid-derived substrates **5e,f** was good. Generally the exo isomer **7a–f** was the major product. The cyclizations of **5a–f** were then induced in the presence of the chiral dirhodium catalysts $Rh_2((5S)\text{-MEPY})_4$ and $Rh_2((5R)\text{-MEPY})_4$. In each instance, $Rh_2((5S)\text{-MEPY})_4$ promoted a reversal in the inherent diastereoselection to provide the endo adduct **6a–f** with good to excellent selectivity. The ability to reverse the facial selectivity in the cyclizations of chiral secondary allylic diazoacetates has significant synthetic applications. Cyclizations of **5a–f** with the enantiomeric catalyst $Rh_2((5R)\text{-MEPY})_4$ appear to represent mismatched pairs, as those reactions were typically less efficient, affording mixtures containing unidentified side products in addition to the desired endo and exo adducts.

The transformation of a prochiral substrate into a single stereoisomer is a powerful technique in asymmetric synthesis.[12] Consequently, we examined the metal-catalyzed cyclizations of the prochiral divinyl diazoacetates **8a–c**, which were prepared from the corresponding divinyl carbinols[13] according to the Corey–Myers protocol. The cyclizations of **8a–c** in the presence of $Cu(TBS)_2$ proceeded with little endo/exo selectivity (Table 2).[6,7,14] Although $Rh_2((5S)\text{-MEPY})_4$ promoted the cyclization of **8a** with high diastereoselectivity *and* enantioselectivity, cyclizations of **8b,c** using $Rh_2((5S)\text{-MEPY})_4$ proceeded with only low diastereoselectivity; the optical purity of the endo adducts from the cyclizations of **8b,c** is superior to that observed for the exo adduct. The absolute configuration of **9a** was determined by converting it into the known,[15] enantiomerically pure lactone **11** by a straightforward sequence of reactions [(a) HNMe(OMe)·HCl, $AlMe_3$; (b) OsO_4, NMO; $NaIO_4$; (c) $NaBH_4$, MeOH; (d) *p*-TsOH, toluene, reflux]. The absolute configuration of **9c** was assigned on the basis of its reduction (Zn, HOAc) to **9a**, and the absolute stereochemistry of **9b** is assumed to follow correspondingly.

Table 2. Cyclizations of Prochiral Secondary Divinyl Carbinols 8a–c[6,7,14]

entry	R^1	R^2	catalyst	endo:exo	ee (%)	yield (%)
a	H	H	$Cu(TBS)_2$	4:1		85
			$Rh_2((5S)\text{-MEPY})_4$	>20:1	≥94 (endo)	75
b	CH_3	H	$Cu(TBS)_2$	1.6:1		78
			$Rh_2((5S)\text{-MEPY})_4$	1:1.2	92 (endo) 91 (exo)	73
c	H	I	$Cu(TBS)_2$	1:1.6		40
			$Rh_2((5S)\text{-MEPY})_4$	2.5:1	84 (endo) 37 (exo)	66

Based upon the results of these experiments, we were intrigued by the prospect that the cyclization of the diazoacetate derived from a racemic divinyl carbinol might be subject to kinetic resolution by the chiral catalyst $Rh_2((5S)\text{-MEPY})_4$. In such a process, the chiral catalyst would be expected to differentiate between the two enantiomers of the substrate by selectively promoting the cyclization of each enantiomer onto a different double bond. To test this hypothesis, we examined the cyclization of racemic **12**, which was prepared from readily available 1-iodopenta-1,4-dienol,[16] in the presence of $Rh_2((5S)\text{-MEPY})_4$ and found that the two endo products **13** (41% yield; 90% de; 87% ee) and **14** (42% yield; 88% de; 91% ee) were formed in excellent yields and enantio- and diastereoselectivities (eq 4). The absolute configurations of the products were determined by correlation with **9a**.[17]

We have thus shown that the inherent diastereoselectivity in the cyclizations of chiral secondary allylic diazoacetates may be effectively reversed using chiral dirhodium catalysts. Moreover, we have demonstrated that prochiral secondary divinyl diazoacetates may be cyclized with high enantio- and diastereoselectivity into vinyl-substituted cyclopropyl lactones using chiral rhodium(II) carboxamide catalysts. The cyclopropanes thus formed are nicely functionalized for subsequent elaboration. Finally, we have established the feasibility of obtaining kinetic resolution of the diazoacetates of racemic divinyl carbinols, a discovery that further expands the synthetic utility of asymmetric cyclopropanations. The applications of these methods to the syntheses of peptide mimics and natural products are in progress, and those results will be reported in due course.

Acknowledgment. We thank the National Institutes of Health, the Robert A. Welch Foundation, The Procter and Gamble Company, and the Texas Advanced Technology Program for support and Dr. Vincent Lynch for performing the X-ray crystallographic analyses of selected compounds.

Supplementary Material Available: ^1H spectra of all new compounds (27 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.

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(13) The alcohol precursor of **8c** was prepared from (Z)-1-iodopent-1-en-4-yn-3-ol (see Marek, I.; Alexakis, A.; Normant, J.-F. *Tetrahedron Lett.* **1991**, *32*, 5329) by iodination (I_2, morpholine) and diimide reduction.

(14) The structures of the exo adducts **10a,b** were verified by X-ray analyses of the diols obtained by treating **10a,b** with excess MeLi. To ascertain the enantiomeric excesses (ees), the diols that were obtained by treating the lactones with excess MeLi were titrated with a chiral shift reagent [$Eu(hfc)_3$ for **9a,b** and $Eu(tfc)_3$ for **10a–c**] in C_6D_6. For the iodolactones in entry c, the iodide group was reduced (Zn/AcOH) prior to reaction with excess MeLi.

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(16) Meyer, C.; Marek, I.; Normant, J.-F. *Synlett* **1993**, 386.

(17) The endo adduct **13** was reduced (*n*-Bu_3SnH, AIBN, toluene) to **9a**, whereas **14** was reduced (Zn, AcOH) to **9a**.