Pergamon

Tetrahedron Letters 39 (1998) 2929–2932

TETRAHEDRON LETTERS

DIASTEREODIFFERENTIATION IN INTRAMOLECULAR CYCLOPROPANATIONS OF CHIRAL SECONDARY ALLYLIC DIAZOACETATES

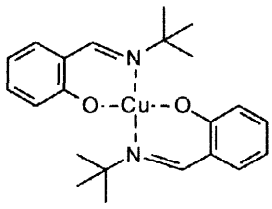
Stephen F. Martin* and Michael C. Hillier

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

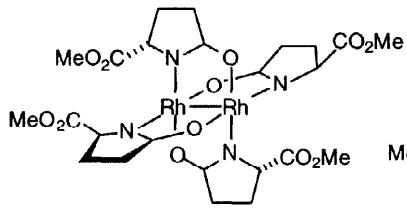
Received 2 January 1998; revised 20 February 1998; accepted 22 February 1998

Abstract. Intramolecular cyclopropanations of diastereomeric, secondary allylic diazoacetates were carried out in the presence of an achiral copper catalyst, $Cu(TBS)_2$, and the chiral rhodium catalysts $Rh_2[5(S)\text{-MEPY}]_4$ and $Rh_2[5(R)\text{-MEPY}]_4$ to give diastereomeric cyclopropyl lactones in ratios that varied with catalyst and stereochemistry of the starting material.

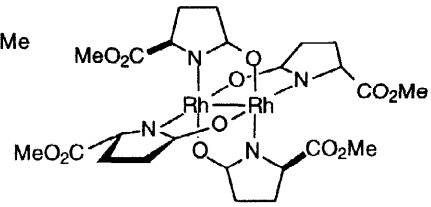
As part of a general program to prepare and evaluate cyclopropane containing pseudopeptides,[1] it has been necessary to develop efficient methods for the asymmetric synthesis of a diverse array of substituted cyclopropanes. One of the best entries to such compounds is via the asymmetric intramolecular cyclopropanations of allylic diazoacetates using the chiral rhodium catalysts $Rh_2[5(S)\text{-MEPY}]_4$ and $Rh_2[5(R)\text{-MEPY}]_4$.[2] During the course of these studies, we became interested in the cyclizations of allylic diazoacetates derived from chiral *secondary* allylic alcohols in the presence of these chiral rhodium catalysts as well as the achiral copper catalyst bis(*N*-*tert*-butylsalicylaldiminato)copper(II) [$Cu(TBS)_2$].[3] We have further extended these latter investigations and now report the findings of a study of the stereoselection in the intramolecular cyclopropanations of the series diastereomeric, secondary allylic diazoacetates **3a,b** and **5a,b** in the presence of [$Cu(TBS)_2$], $Rh_2[5(S)\text{-MEPY}]_4$ and $Rh_2[5(R)\text{-MEPY}]_4$.



$Cu(TBS)_2$



$Rh_2[(5S)\text{-MEPY}]_4$

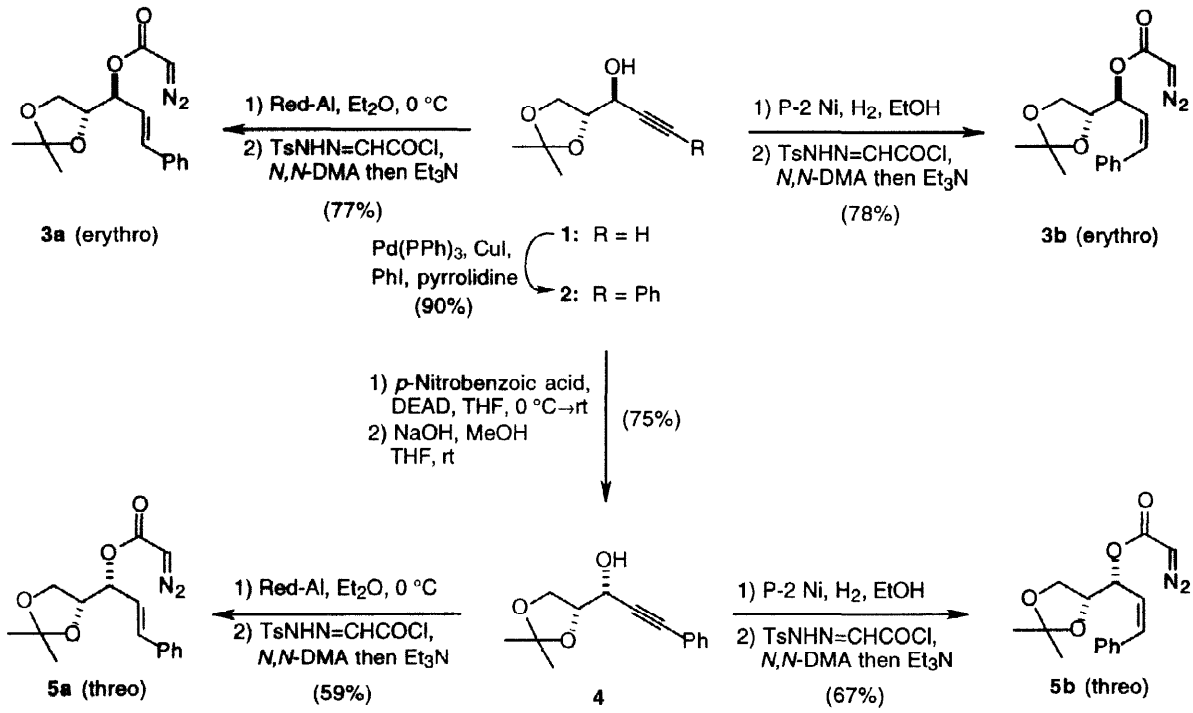


$Rh_2[(5R)\text{-MEPY}]_4$

The synthesis of the starting allylic diazoacetates commenced with the known propargyl alcohol **1**, which is available in three steps and good overall yield from D-arabitol (Scheme 1).[4] The terminal position of the alkyne **1** was arylated with iodobenzene, in the presence of catalytic $Pd(PPh_3)_4$ and CuI in pyrrolidine to give **2**, which was converted into the epimeric alcohol **4** by a modified Mitsunobu protocol developed in our laboratories.[5,6] Stereoselective reduction of **2** with either Red-Al or P2-Ni gave intermediate *E*- or *Z*-alkenes,[7,8] respectively, which were then converted by the Corey-Myers procedure into the corresponding *erythro* allylic diazoacetates

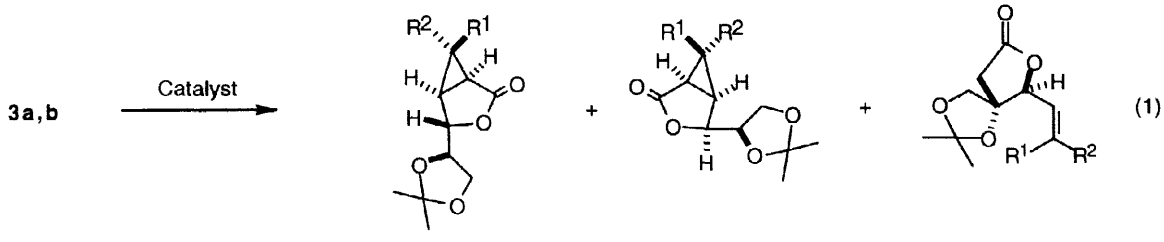
0040-4039/98/$19.00
PII: S0040-4039(98)00501-2

Scheme 1

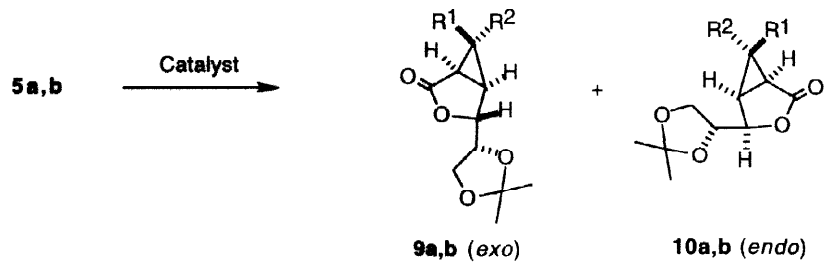


3a,b in good overall yields.[9] Similarly, the alcohol **4** was transformed in good overall yields into the *threo* allylic diazoacetates **5a,b**. With the appropriate substrates in hand, we were then able to examine the intramolecular cyclopropanation reactions.

The allylic diazoesters **3a,b** were first subjected to thermal decomposition in the presence of catalytic amounts of [Cu(TBS)$_2$], Rh$_2$[5(*S*)-MEPY]$_4$ and Rh$_2$[5(*R*)-MEPY]$_4$ to afford mixtures of the corresponding *exo*- and *endo*-adducts **6a,b** and **7a,b** in the combined yields presented in Table 1 (eqn. 1).[10,11] Similarly, the stereoisomeric diazoacetates **5a,b** were cyclized with catalytic amounts of Cu(TBS)$_2$, Rh$_2$[5(*S*)-MEPY]$_4$ or Rh$_2$[5(*R*)-MEPY]$_4$ to furnish mixtures of the *exo*- and *endo*-adducts **9a,b** and **10a,b**, respectively, in the combined yields shown in Table 1 (eqn. 2). The diastereomeric mixtures were separated either by flash chromatography or by HPLC to give the pure adducts. The lactones **8a** and **8b** were formed during the catalyzed decomposition of **3a** and **3b**, respectively, in the presence of Rh$_2$[5(*S*)-MEPY]$_4$. Although **8a** was a minor product from **3a**, **8b** was isolated in 72% yield from **3b**. These lactones arise, at least in part, from a stereochemical "mismatch" between the chiral substrate and the chiral rhodium catalyst via insertion of the putative metallocarbene into the activated carbinol C-H bond, a reaction known to occur in saturated systems.[12]



Series **a**: R^1 = H, R^2 = Ph
Series **b**: R^1 = Ph, R^2 = H



9a,b (*exo*) + **10a,b** (*endo*) (2)

Series **a**: R^1 = H, R^2 = Ph
Series **b**: R^1 = Ph, R^2 = H

The ratios presented in Table 1 reveal a number of trends concerning the cyclopropanation of substrates **3a,b** and **5a,b** in the presence of the achiral copper and chiral rhodium catalysts. When $Cu(TBS)_2$ was employed as the catalyst, the *exo* diastereomer was favored in all cases, suggesting that neither the stereochemistry of the carbon-carbon double bond nor the stereochemical relationship between the two stereogenic centers greatly affects the stereochemical course of the reaction. As we had observed in previous work,[3] the primary determinant of the course of the cyclizations of **3a,b** and **5a,b** in the presence of the chiral rhodium catalysts $Rh_2[(5R)$-MEPY$]_4$ and $Rh_2[(5S)$-MEPY$]_4$ is the stereochemical relationship between the configurations at the stereogenic center in the catalyst and at the allylic center in the diazoacetate. Thus, matched interactions between the chiral catalyst and substrate were observed for the cyclopropanations of **3b** with $Rh_2[(5R)$-MEPY$]_4$ and **5b** with $Rh_2[(5S)$-MEPY$]_4$, while 'mismatched' interactions occurred when the enantiomeric rhodium catalysts were

Table 1. Intramolecular Cyclopropanations of Allylic Diazoacetates 3a,b and 5a,b with $Cu(TBS)_2$, $Rh_2[(5S)$-MEPY$]_4$, and $Rh_2[(5R)$-MEPY$]_4$[a]

Substrate	Catalyst	Exo	Endo	Combined Yield[b]
		6a	**7a**	
3a	$Cu(TBS)_2$	4	1	43
	$Rh_2[(5S)$-MEPY$]_4$	2	1	64[c]
	$Rh_2[(5R)$-MEPY$]_4$	1	4	87
		6b	**7b**	
3b	$Cu(TBS)_2$	4	1	45
	$Rh_2[(5S)$-MEPY$]_4$	1	-	2[d]
	$Rh_2[(5R)$-MEPY$]_4$	1	10	70
		9a	**10a**	
5a	$Cu(TBS)_2$	5	1	89
	$Rh_2[(5S)$-MEPY$]_4$	1	3	83
	$Rh_2[(5R)$-MEPY$]_4$	2	1	66
		9b	**10b**	
5b	$Cu(TBS)_2$	5	1	64
	$Rh_2[(5S)$-MEPY$]_4$	1	20	56
	$Rh_2[(5R)$-MEPY$]_4$	1.5	1	69

[a]Product ratios determined by 500 MHz ^{1}H NMR analysis of the crude product mixtures.
[b]Yields of combined *exo* and *endo* products.
[c]The lactone **8a** was isolated in 30% yield.
[d]The lactone **8b** was isolated in 72% yield.

employed. In some mismatched cases, C-H insertion may become the major reaction pathway as illustrated by the observation that the Rh_2[(5*S*)-MEPY]$_4$-catalyzed cyclization of **3a,b** gave the lactones **8a,b** in significant quantity. This tendency toward C-H insertion was not observed with the *threo* series **5a,b**. The intramolecular cyclopropanations of the *Z*-disubstituted olefinic substrates **3b** and **5b** in the presence of the chiral rhodium catalysts were more selective than those of the corresponding *E*-disubstituted substrates **3a** and **5a**.

In conclusion, the methodology presented here demonstrates that a certain degree of selectivity in the cyclopropanation of secondary allylic diazoesters can be obtained depending upon the stereochemical features of the substrate and the catalyst. Significantly, the stereochemical course of the cyclizations of **3a,b** and **5a,b** in the presence of an achiral catalyst can be reversed with a matched chiral rhodium catalyst. The application of these discoveries to the synthesis of constrained pseudopeptides will be reported in due course.

Acknowledgment. We thank the National Institutes of Health and The Robert A. Welch Foundation for their generous support.

REFERENCES AND NOTES

1. (a) Martin, S. F.; Austin, R. E.; Oalmann, C. J. *Tetrahedron Lett.* **1990**, *31*, 4731-4734. (b) Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Baker, W. R.; Condon, S. L.; DeLara, E.; Rosenberg, S. H.; Spina, K. P.; Stein, H. H.; Cohen, J.; Kleinert, H. D. *J. Med. Chem.* **1992**, *35*, 1710-1721. (c) Baker, W. R.; Jae, H.-S.; Martin, S. F.; Condon, S. L.; Stein, H. H.; Cohen, J.; Kleinert, H. D. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1405. (d) Martin, S. F.; Oalmann, C. J.; Liras, S. *Tetrahedron* **1993**, *49*, 3521.
2. (a) Doyle, M. P.; Pieters, R. J.; Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Müller, P. *J. Am. Chem. Soc.* **1991**, *113*, 1423-1424. (b) Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763-5775
3. (a) Martin, S. F.; Spaller, M. R.; Liras, S.; Hartmann, B. *J. Am. Chem. Soc.* **1994**, *116*, 4493-4494. (b) Doyle, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Ruppar, D. A.; Martin, S. F.; Spaller, M. R.; Liras, S. *J. Am. Chem. Soc.* **1995**, *117*, 11021-11022.
4. (a) Yadav, J. S.; Chander, M. C.; Joshi, V. B. *Tetrahedron Lett.* **1988**, *29*, 2737-2740. (b) Yadav, J. S.; Chander, M. C.; Rao, C. S. *Tetrahedron Lett.* **1989**, *30*, 5455-5458. (c) Yadav, J. S.; Vidyanand, D.; Rajagopal, D. *Tetrahedron Lett.* **1993**, *34*, 1191-1194.
5. The structure assigned to each compound was in accord with its spectral (^{1}H and ^{13}C NMR, IR and mass) characteristics. Yields cited are for compounds judged to be >95% pure by ^{1}H NMR. Analytical samples of all new compounds were obtained by distillation, recrystallization, preparative HPLC or flash chromatography and gave satisfactory identification by high resolution mass spectrometry.
6. Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017-3020.
7. Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403-6406.
8. (a) Marvell, E. N.; Li, T. *Synthesis* **1973**, 457-468. (b) Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, 4595-4597.
9. Corey, E. J.; Myers, A. G. *Tetrahedron Lett.* **1984**, *25* , 3559-3562.
10. For Cu(TBS)$_2$: Substrate (1 mmol) in toluene (10 mL) was added to a refluxing solution of the catalyst (5% mol equiv) in toluene (40 mL) over 12-16 h. For Rh[(5*R* or 5*S*)-MEPY]$_4$: Substrate (1 mmol) in CH_2Cl_2 (10 mL) was added to a refluxing solution of the catalyst (1% mol equiv) in CH_2Cl_2 (90 mL) over 18-24 h.
11. The structure of **6b** was established by X-ray crystallography. The coordinates have been deposited in the Cambridge Crystallographic Data Center.
12. Doyle, M. P.; Dyatkin, A. B. *J. Org. Chem.* **1995**, *60*, 3035-3038.