Desymmetrization of Meso Epoxides with Halides: A New Catalytic Reaction Based on Mechanistic Insight

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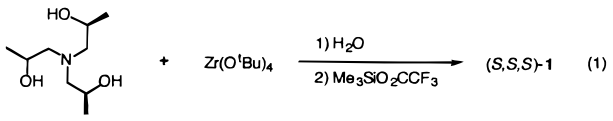
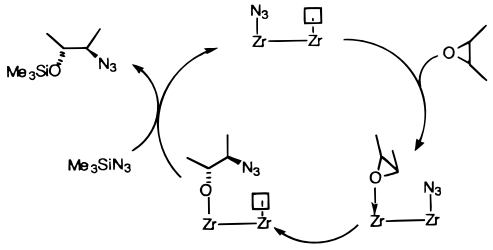
The desymmetrization of meso epoxides via the enantioselective addition of nucleophiles is an efficient strategy for asymmetric synthesis since it simultaneously establishes two contiguous stereogenic centers.[1] Several years ago we introduced[2] precatalyst **1**, a zirconium complex bearing homochiral tri-2-propanol amine[3] ligands, to provide a highly selective catalyst for epoxide desymmetrization. This catalyst promotes the addition of azidotrialkylsilanes to meso epoxides (eq 2, X = N_3) in up to 93% enantiomeric excess. Subsequently several other catalyst systems have been reported which promote epoxide desymmetrization in >90% enantiomeric excess.[4−6]



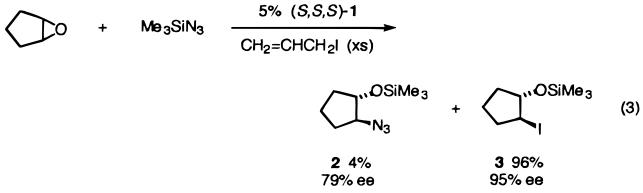
For its success, the desymmetrization strategy requires that epoxide opening occur by exclusive backside attack; however, this also imposes a limitation, namely that the products will necessarily be trans disubstituted.[7] In principle, this limitation could be circumvented by the introduction of a reactive nucleophile such as a halide[8,9] which could be displaced in a subsequent step, thus inverting the stereochemistry at this carbon atom. However, direct addition of trialkylsilyl halides to meso epoxides in the presence of precatalyst **1** (e.g., eq 2, X = Cl, Br, I) invariably gave the products in low or negligible enantiomeric excess.

The mechanism of the enantioselective addition of azidotrimethylsilane to meso epoxides catalyzed by **1** has recently been delineated. A simplified version of the catalytic cycle is shown in Scheme 1; complete details will be reported elsewhere.[10] In common with other catalysts for epoxide desymmetrization,[4,5] the mechanism involves *two* metal centers, one of which activates the azide nucleophile while the other activates the epoxide. Of particular interest is the involvement of a discrete zirconium azide intermediate in which the azide is transferred to the activated epoxide in a relatively slow subsequent step. The implication is that if the azide could be plucked from the zirconium atom and replaced with a different nucleophile and *provided that the replacement process is fast relative to azide transfer*, then the alternative nucleophile might likewise undergo selective transfer to the epoxide.

Scheme 1. Mechanism of Zr-Catalyzed Epoxide Desymmetrization



As a test of this hypothesis the reaction between cyclopentene oxide and azidotrimethylsilane was carried out as usual but with the addition of 2 equiv of allyl iodide.[11] Under these conditions, only 4% of the usual azide product **2** was observed; the remaining 96% of the observed product was the protected β-iodohydrin **3**. Moreover, chiral gas chromatographic analysis showed that **3** was actually formed in significantly higher enantiomeric excess (95%) than was **2** (79%):



Coproduction of allyl azide in an amount equal to that of **3** was confirmed by gas chromatography and by NMR comparison with an authentic sample.[11]

As summarized in Table 1, the reaction could also be extended to the synthesis of protected β-bromohydrins. Because allyl bromide is a less reactive alkylating agent than allyl iodide, a larger excess of allyl bromide was required to suppress formation of the azide side-product. In all cases, 20 equiv of allyl bromide were sufficient to keep the yield of azide <5%. For the desymmetrization of the meso cycloalkene oxides summarized in Table 1, the enantioselectivity appears to decrease monotonically as the ring size is increased from 5 to 8. Of interest from the standpoint of organic synthesis, the reaction proceeds in useful yield and enantioselectivity for functional epoxides containing the ether or ester functional groups.

(1) Review: Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361.

(2) Nugent, W. A. *J. Am. Chem. Soc.* **1992**, *114*, 2768. Although the detailed structure of precatalyst **1** is unknown, it reproducibly analyzes as $L_2(OH)(CF_3CO_2)Zr_2$, where L is the deprotonated tri-2-propanol amine ligand. Upon exposure to azidotrimethylsilane **1** is converted to the discrete unsymmetrical dimer $L_2(N_3)(CF_3CO_2)Zr_2$.

(3) Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1994**, *116*, 6142. See also: Di Furia, F.; Licini, G.; Modena, G.; Motterle, R.; Nugent, W. A. *J. Org. Chem.* **1996**, *61*, 5175.

(4) Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897. Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420. Martinez, L. E.; Nugent, W. A.; Jacobsen, E. N. *J. Org. Chem.* **1996**, *61*, 7963.

(5) Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 4783.

(6) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1668.

(7) For an alternative strategy, see: Schaus, S. E.; Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem.* **1997**, *62*, 4197.

(8) The stoichiometric desymmetrization of meso epoxides with aluminum or boron halides has been reported: Naruse, Y.; Esaki, T.; Yamamoto, H. *Tetrahedron* **1988**, *44*, 4747. Joshi, N. N.; Srebnik, M.; Brown, H. C. *J. Am. Chem. Soc.* **1988**, *110*, 6246. Srebnik, M.; Joshi, N. N.; Brown, H. C. *Isr. J. Chem.* **1989**, *29*, 229.

(9) Very recently Denmark and co-workers have reported the catalytic enantioselective ring-opening of epoxides with $SiCl_4$ to afford optically active chlorohydrins. Interestingly, in contrast with current work, the highest ee's using the Denmark catalyst are obtained with *acyclic* meso epoxides (e.g., 87% ee for *cis*-stilbene oxide). Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 2428.

(10) McCleland, B. W.; Finn, M. G.; Nugent, W. A. Submitted for publication.

(11) No reaction was observed in the absence of zirconium catalyst. Allyl halides react directly with azidotrimethylmethane only in highly polar solvents such as HMPA: Nishiyama, K.; Karigomi, H. *Chem. Lett.* **1982**, 1477.

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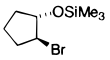
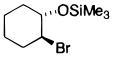
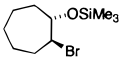
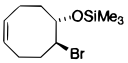
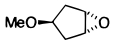
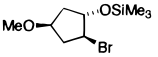
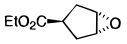
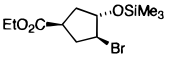
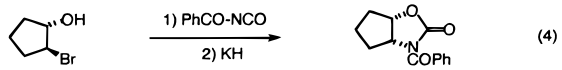
Table 1. Synthesis of Protected β-Bromohydrins via Desymmetrization of Meso Epoxides with Precatalyst (*S,S,S*)-**1**[a]

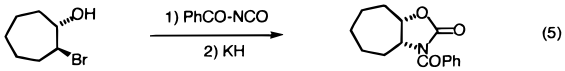
Epoxide	Product	$[\alpha]_D$ (deg)[b]	Yield (%)[c]	e.e. (%)[d]
		+70.0	81	95
		+45.9	86	91
		+28.1	90	89
		+14.5	92	84
		+45.9	89	96
		-38.8	83	~95[e]
		n.d.	[87][f]	84

[a] All runs contain epoxide (2.4 mmol), azidotrimethylsilane (3.0 mmol), and precatalyst **1** (0.12 mg·atom Zr) in chlorobenzene (4 mL) and allyl bromide (4 mL), 25 °C, 48 h. [b] $c = 1$ ($CHCl_3$). [c] Isolated yield after flash chromatography except where indicated. [d] By GLC analysis except as indicated. [e] By NMR with chiral shift reagent. [f] GLC yield (product not isolated).

We anticipate that the enantiopure β-bromohydrins in Table 1 will serve as broadly useful chiral building blocks.[12] One application that we have begun to explore is the conversion of the bromohydrin products to enantiopure cis β-amino alcohols. We examined several literature procedures[13] which were reported to convert racemic bromohydrins to the corresponding amino alcohols; of these, the most efficient proved to be condensation/cyclization with benzoyl isocyanate as reported by Knapp and co-workers.[14] This method has now been applied to nonracemic bromohydrins as exemplified by eqs 4 and 5. The silylated



(4)



(5)

bromohydrins were first desilyated under acidic conditions (Dowex 30/methanol). The deprotected bromohydrins were converted to the corresponding carbamates by treatment with benzoyl isocyanate and were then cyclized (KH/THF/reflux). The bicyclic carbamates were formed with no loss of optical activity. Moreover, in each case a single crystallization[15] from hot toluene was sufficient to increase the enantiomeric excess of the product to >99%. The overall yield of enantiopure product was 78% for eq 4 and 73% for eq 5.

The novel molecular "bait and switch" strategy that was used to redirect Scheme 1 has opened the door to a useful new catalytic transformation. We are currently investigating other catalytic reactions where this strategy may be applied.

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Supporting Information Available: Experimental procedures for the synthesis, isolation, and characterization of the products from Table 1 and eqs 3−5 (5 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(12) However, reactions requiring strongly basic conditions must be avoided because of the potential reversion of these products to the starting epoxides.

(13) Wohl, R. A. *J. Org. Chem.* **1973**, *38*, 3858. Das, J. *Synth. Commun.* **1988**, *18*, 907. Samano, M. C.; Robins, M. J. *Tetrahedron Lett.* **1989**, *30*, 2329.

(14) Knapp, S.; Kukkola, P. J.; Sharma, S.; Dhar, T. G. M.; Naughton, A. B. J. *J. Org. Chem.* **1990**, *55*, 5700. See also: McCombie, S. W.; Nagabhushan, T. L. *Tetrahedron Lett.* **1987**, *28*, 5399. Larsen, R. D.; Davis, P.; Corley, E. G.; Reider, P. J.; Lamanec, T. R.; Grabowski, E. J. J. *J. Org. Chem.* **1990**, *55*, 299.

(15) This useful situation undoubtedly reflects the significantly higher melting points of the enantiopure products versus the corresponding racemates. This difference is 29 °C for the product of eq 4 and 23 °C for the product of eq 5.