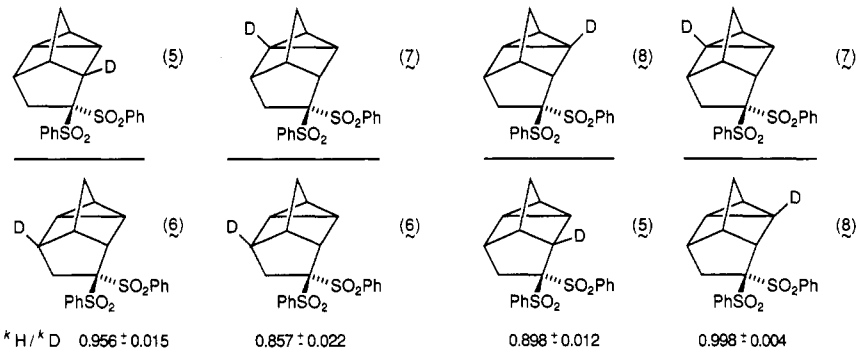

character at the sight of bond formation. The magnitude of the k_H/k_D values reflects the adoption of early transition states where substantive hybridization changes have not yet materialized. For the reaction of DMAD with Q-*1-d*, further progress along the reaction profile is manifested. The kinetic isotope effect for the DMAD/N-2-*d* cycloaddition must be interpreted with greater caution. Since the process is catalyzed, and passaged through a metallacycle has been suggested, the identity of the k_H/k_D's for the matched reactions is perhaps fortuitous. The possibility does exist, of course, that the degree of bond formation for both processes is similar in the respective transition states.

More mechanistically informative yet is the reaction between N and 1,1-bis(phenylsulfonyl)ethylene where four isotope effects are now made available. The **5/6** ratio agrees in direction with preferred bond formation to the more electropositive carbon of the addend.[17] The isotopic fractionation seen here indicates that while the cycloaddition is not synchronous, it is concerted. Product distributions **7/6** and **8/5** reveal a sizeable preference for deuterium incorporation on the proximal five- rather than the distal three-membered ring. This is because the hybridization changes required for cyclopropane construction are much less than those associated with the incipient cyclopentyl centers.[18] In fact, no preference is seen for placement of D at either of the possible $sp^{2.1}$ sites (**7/8** is essentially unity).[19]

The deuterium isotope effects realized from both symmetrical and unsymmetrical addends are consistent with the operation of nonsynchronous, concerted bonding schemes within relatively early transition states. Thus, the $[2_\pi + 2_\pi + 2_\pi]$ reactions of N and $[2_\sigma + 2_\sigma + 2_\pi]$ cycloadditions to Q share similar mechanistic characteristics; moreover, their features compare closely to those observed for the Diels–Alder reaction.[20] Therefore, in the absence of any piece of experimental evidence adduceable as support for a noncerted mechanism, the two processes studied here should be viewed as proceeding in one step, unless exceptionally strong polarization within the addend intervenes.[10]

(17) This phenomenon is extensively precedented. For examples, consult: (a) Brown, P.; Cookson, R. C. *Tetrahedron* **1965**, *21*, 1993. (b) Holder, R. W.; Graf, N. A.; Duesler, E.; Moss, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2929.

(18) Wolfsberg has suggested that the α-D effect is perhaps more accurately correlated with the changes in the H–C–X bending frequencies, which are very sensitive to the extent of C–X bond making or breaking.[11] We do not exclude this point of emphasis in our claims.

(19) The isotope effects for the addition of 1,1-bis(phenylsulfonyl)-ethylene to Q-*1-d* were indeterminable due to an inseparable low-level impurity that exhibited ^{2}H-NMR absorptions that coincidentally overlapped with certain of those arising from the cycloadduct.

(20) Gajewski, J. J.; Peterson, K. B.; Kagel, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 5545 and references cited therein.

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Regioselective Azide Opening of 2,3-Epoxy Alcohols by $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$: Synthesis of α-Amino Acids

Summary: Treatment of 2,3-epoxy alcohols with $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ affords the corresponding 3-azido 1,2-diols, which are readily transformed in two steps to the α-amino acids.

Sir: We have recently reported a mild procedure for the regioselective nucleophilic ring opening of 2,3-epoxy alcohols mediated by $Ti(O\text{-}i\text{-}Pr)_4$.[1] Enhanced rate and C-3 selectivity were observed in the ring opening of *trans*-epoxy alcohol **1** in the presence of the metal alkoxide (Scheme I). In the course of that study, we found that $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ is a safe,[2] mild reagent for azide ring opening of 2,3-epoxy alcohols (Scheme I).[3,4] This reagent had been previously reported to catalyze the opening of isolated epoxides by Me_3SiN_3.[5]

The $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ reagent was routinely prepared on a multigram scale according to the procedure published by Choukroun and Gervais.[6] In a typical experiment, a solution of the epoxy alcohol (1.0 mmol) in 5 mL of dry benzene was added to a suspension of $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$[7,8]

(1) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.

(2) $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ was tested for shock sensitivity by striking a small amount with a hammer; no evidence of decomposition was found. Thermal stability analysis was performed by accelerated rate calorimetry. This material shows a relatively vigorous exotherm starting at 126 °C, which appears to become a detonation at 160 °C. Extrapolation indicates that the same behavior should be expected after 48 h at 97 °C, 30 min at 123 °C, and 30 s at 144 °C (Dr. P. Conrad, Eli Lilly and Co., private communication). It should be noted however, that $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ has been refluxed overnight in xylenes (137–144 °C) without incident.

(3) Another excellent metal-mediated opening of 2,3-epoxy alcohols was recently reported, see: Maruoka, K.; Sano, H.; Yamamoto, H. *Chem. Lett.* **1985**, 599.

(4) Recently, a C-3 selective azide reagent consisting of NaN_3 supported on a calcium zeolite was reported: Onaka, M.; Sugita, K.; Izumi, Y. *Chem. Lett.* **1986**, 1327.

(5) (a) Blandy, C.; Choukroun, R.; Gervais, D. *Tetrahedron Lett.* **1983**, *24*, 4189. (b) Sinou, D.; Emziane, M. *Tetrahedron Lett.* **1986**, *27*, 4423.

(6) Choukroun, R.; Gervais, D. *J. Chem. Soc., Dalton Trans.* **1980**, 1800.

(7) We usually handle $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ under an inert atmosphere (glovebag), although no adverse effects on the yield or selectivity were seen on the few occasions when the reagent was handled quickly in air.

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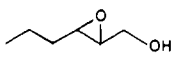
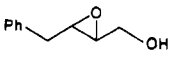
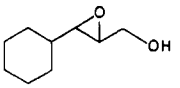
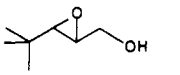
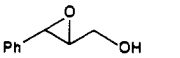
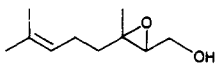
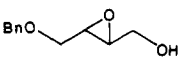
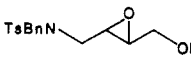
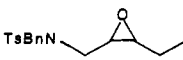
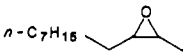
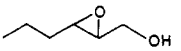
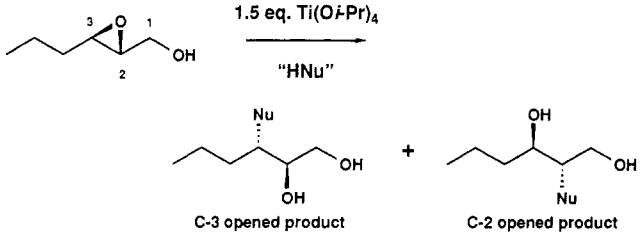
Table I

entry	substrate	conditions	regioselectivity,[a] C-3:C-2	yield,[b] %
1		*c*, 7 h	5.8:1	95[d]
2		*e*, 0.08 h	36:1	88
	1			
3		*f*, 3.5 h	1.4:1	71[g]
4		*e*, 0.16 h	27:1	96
	2			
5		*f*, 10 h	1.7:1	93[g]
6		*e*, 0.25 h	20:1	94
7		*f*, 12 h	1:100[h]	47[g]
8		*e*, 0.75 h	2:1	96
9		*c*, 2.75 h	100:1[h]	100
10		*i*, 0.08 h	100:1[h]	76
11		*e*, 0.16 h	100:1[h]	76[j]
12		*f*, 4 h	1:1	93[g]
13		*e*, 0.25 h	6:1	93
14		*e*, 0.25 h	1.9:1	89
15		*e*, 0.5 h	1:1	78
16		*e*, 0.25 h	1:2	79
17		*e*, 0.08 h	1:1.5	89
18		*e*, 5 h	100:1[h]	40

[a] Determined by ^{1}H NMR analysis of the peracetylated products. [b] Isolated yield. [c] NaN_3/NH_4Cl, 8:1 MeOH:H_2O, 65 °C. [d] See ref 1. [e] $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$, benzene, 70 °C. [f] NaN_3/NH_4Cl, 8:1 $CH_3OCH_2CH_2OH$:H_2O, 124 °C. [g] See ref 12b. [h] Only one regioisomer could be detected by ^{1}H NMR analysis. [i] $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$, ether, 25 °C. [j] Yield of olefin diol was 32%.

Scheme I



(1.2 mmol) in 10 mL of benzene under an inert atmosphere at 75 °C. After being stirred for 5–15 min at 75 °C, the reaction mixture was cooled to room temperature and the benzene was removed in vacuo. The concentrate was diluted with 20 mL of ether, quenched with 8 mL of 5% H_2SO_4, and stirred until two clear phases formed (ca. 1 h). The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were dried (Na_2SO_4) and concentrated to afford the azido diols.[9] The crude products were peracetylated,[10] and the ratio of regioisomers was determined by ^{1}H NMR (250 MHz, C_6D_6). The results are summarized in Table I.

Entries 2, 4, 6, 8, 10, 11, and 13 reveal that *trans*-2,3-epoxy alcohols react with fair to excellent C-3 selectivity upon treatment with $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$. The isolated yields are good to excellent (76–96%). The regioselectivities obtained with this reagent are markedly superior to those obtained in the absence of metal mediation (entries 1, 3, 5, 7, 12), except when the substrate itself exhibits an overwhelming preference for C-3 opening (entry 9). For example, refluxing epoxy alcohol **2** with NaN_3/NH_4Cl in $CH_3OCH_2CH_2OH/H_2O$ (8/1) gave a C-3:C-2 ratio of 1.4:1 (entry 3). Treatment of **2** with 1.2 equiv of $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ in benzene at 75 °C gave an enhanced C-3:C-2 ratio of 27:1 (entry 4). Exclusive C-3 opening is observed in the case of 2,3-epoxygeraniol (entry 11), but here a 24% yield of enediol, the expected rearrangement product,[11] is also obtained. Previous work in this laboratory[12] had shown that although most aliphatic *trans*-2,3-epoxy alcohols display modest C-3 selectivity toward external nucleophiles, the magnitude of this selectivity depends on a delicate balance of steric and electronic factors. For example, increasing steric hindrance at the C-3 position results in decreased C-3 selectivity (entries 5, 7). However, when these substrates were treated with $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$, better C-3 selectivity was observed (entries 6, 8). Fur-

(8) $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ can also be prepared in situ. $Ti(O\text{-}i\text{-}Pr)_4$ and 2 equiv of Me_3SiN_3 were refluxed in benzene under argon or nitrogen for at least 5 h, until the solution became clear. A solution of the epoxy alcohol 1 in benzene was added to the 70 °C solution. ^{1}H NMR analysis of the peracetylated crude product revealed a C-3:C-2 ratio of 36:1 (ca. 2% opening by 2-propanol was also detected).

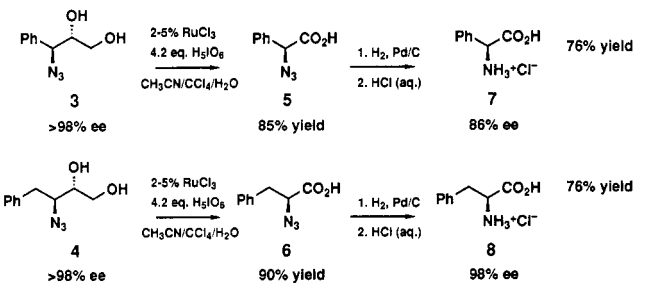
(9) The azido diols isolated in this manner were pure by TLC and ^{1}H NMR analysis.

(10) Acetic anhydride, pyridine, 4-(dimethylamino)pyridine.

(11) Morgans, D. J.; Sharpless, K. B.; Traynor, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 462.

(12) (a) Behrens, C. H.; Sharpless, K. B. *Aldrichimica Acta* **1983**, *16*, 67. (b) Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696. (c) Behrens, C. H. Ph.D. Dissertation, Massachusetts Institute of Technology, Cambridge, MA, 1984.

Scheme II



thermore, entry 8 shows that $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ is powerful enough to achieve neopentyl substitution,[13] overriding the strong C-2 preference of the substrate. Similarly, the presence of electron-withdrawing groups at C-3 also decreases C-3 selectivity (entry 12). Regioselective ring opening at C-3 was possible with $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ (entry 13), although use of this reagent with a nitrogen analogue was not as successful (entry 14). Treatment of *cis*-2,3-epoxy alcohols with $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ gave the corresponding azido diols with no selectivity (entry 15) or slight C-2 selectivity (entries 16, 17).[14]

While the origin of the enhanced rate and C-3 selectivity is not completely understood, coordination of the epoxy alcohol to the metal center in a bidentate manner is believed to play an important role.[15,16] This hypothesis is consistent with the observation that the benzyl ether of 1 is completely consumed only after 5 h at 75 °C. The yield is quite low, due to opening by other nucleophiles present in the reaction (one of which is isopropoxide), but interestingly, no product of C-2 azide opening was detected.

At the outset of this study, we observed that the azide ring opening proceeds at room temperature in less than 5 min in a number of solvents.[17] It was found that regioselectivity increased with temperature in ether and benzene for a number of substrates. For example, epoxy alcohol **2** is opened with a regioselectivity of 11.6:1 in benzene at room temperature; at 75 °C, the C-3:C-2 selectivity increases to 27:1. Thus, thermally labile substrates may be opened with good regioselectivity in benzene or ether at room temperature, but we recommend performing the reaction at elevated temperatures to obtain the maximum selectivity.[18]

The 3-azido 1,2-diols obtained from homochiral epoxy alcohols[19] have many potential uses; in particular they are readily transformed in two steps to the corresponding α-amino acids (Scheme II). RuO_4 oxidation of the 1,2-diol,[20-23] followed by reduction of the azide by catalytic hydrogenation,[24] affords the α-amino acids **7** and **8** in good yields. The enantiomeric excess of the products was determined by chiral stationary phase HPLC of the methyl ester 3,5-dinitrobenzamide derivatives.[25] Such analysis reveals that there is no significant loss in optical purity in the transformation of **4** but a substantial loss of percent ee in the transformation of **3**. Chiral lanthanide shift reagent ^1H NMR experiments[26] on the methyl ester of the intermediate azido acid **5** confirms that the loss of stereochemical integrity occurs during the oxidation, undoubtedly at the aldehyde stage.[27] The poor enantiomeric excess realized for L-phenylglycine **7** is therefore probably a consequence of the presence of an electron-withdrawing phenyl group at the α-carbon. Thus this methodology should be most suitable for the asymmetric synthesis of amino acids that lack electron-withdrawing groups at the α-position.

Acknowledgment. We are grateful to the National Science Foundation (Grant CHE-8308355) and to Merck and Co. for generous support of this work. M.C. thanks the Natural Science and Engineering Research Council of Canada (NSERC) for a postdoctoral fellowship.

Supplementary Material Available: Selected experimental details and spectroscopic data for the transformations described herein, including a procedure for preparation of $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ on a 5-g scale (12 pages). Ordering information is given on any current masthead page.

(13) For an example in which the trans diaxial opening rule is violated to avoid neopentyl substitution, see: Sirat, H. M.; Wallis, J. D. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2885.

(14) Similar results were observed in the $Ti(O\text{-}i\text{-}Pr)_4$-mediated nucleophilic openings of *cis*-2,3-epoxy alcohols (M. Caron, unpublished results.).

(15) (a) See ref 1, especially footnote 21. (b) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560.

(16) There is a favorable change in $T\Delta S^*$ of about 5 kcal mol^{-1} for reduction in the kinetic order by one; this corresponds to an increase in rate of approximately 10^3 at 25 °C (Bruice, T. C.; Benkovic, S. J. *J. Am. Chem. Soc.* **1964**, *86*, 418).

(17) Reaction solvents must be aprotic and dry, and ether and benzene gave the best yields and selectivities. Acetonitrile, pentane, and 1,2-dimethoxyethane gave lower selectivity and/or side products, and THF was partially decomposed by the reagent.

(18) The enhanced regioselectivity at higher temperatures might be due to the dissociation of an oligomeric form of $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$ into a lesser aggregate or monomer exhibiting higher C-3 selectivity. This hypothesis is supported by the observation that, for a number of substrates, when the concentration of reagent is raised above 0.2 M, the regioselectivity of the opening reaction decreases.

(19) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922. (c) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(20) Carlsen, P.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(21) α-Azido acids prepared in this manner decompose gradually on standing; their lability is due to the presence of trace amounts of low-valent ruthenium. We therefore recommend immediate reduction to the amino acid.

(22) Oxidation of mixtures of azido diols derived from **2** highly enriched in the C-3 regioisomer (>20:1) affords essentially pure azido acid **6**; the products of oxidation of the minor regioisomer cannot be detected.

(23) We recommend the use of periodic acid (H_5IO_6) in place of $NaIO_4$ for the stoichiometric oxidant (see ref 15b).

(24) (a) Augustine, R. L. *Catalytic Hydrogenation*; Marcel Dekker: New York, 1965; p 95. (b) Rylander, P. N. *Catalytic Hydrogenation over Platinum Metals*; Academic: New York, 1967; p 494. (c) Moore, A. T.; Rydon, H. N. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 586.

(25) Pirkle, W. H.; Pochapsky, T. C. *J. Am. Chem. Soc.* **1986**, *108*, 352.

(26) (a) Fraser, R. R. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 1, Chapter 9, p 173. (b) McCreary, M. D.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1038.

(27) (a) α-Azido aldehydes are especially susceptible to epimerization (see Kuzuhara, H.; Emoto, S. *Tetrahedron Lett.* **1975**, 1853 and references cited therein). (b) No substantial loss of ee accompanies catalytic hydrogenation of α-azido acids (see Zaloom, J.; Roberts, D. C. *J. Org. Chem.* **1981**, *46*, 5173).

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Highly Enantioselective Solvolyses of L- and D-Phenylalanine *p*-Nitrophenyl Esters by an L-Histidyl Dipeptide in Surfactant Coaggregates Formed by Cholesterol-Containing Amphiphiles

Summary: Highly enantioselective catalysis ($k_{cat}(L)/k_{cat}(D)$ = 98.2) was observed in the solvolyses of *N*-dodecanoyl-L- and -D-phenylalanine *p*-nitrophenyl esters (**2**-L and **2**-D)

