proved to be the least selective among all the ring-openings tried.[20]

We have observed in the course of these experiments that the nucleophilic anion of a variety of ammonium salts opened epoxy alcohol 1 when catalyzed by $Ti(O\text{-}i\text{-}Pr)_4$. This is illustrated in entries 21, 22, and 24–27. For example, treatment of 1 with ammonium chloride in dimethyl sulfoxide and 1.5 equiv of $Ti(O\text{-}i\text{-}Pr)_4$ (15 min, room temperature) gave an 84% yield of the chloro diols. The regioselectivity of the reaction was C-3/C-2 = 2.8/1 (entry 21). A longer reaction time (40 h) was required when the reaction was run in THF (entry 22). The ring-opening using ammonium bromide gave identical results (entry 24). A control experiment shows that no reaction takes place in the absence of $Ti(O\text{-}i\text{-}Pr)_4$ (entry 23). Ring-opening of 1 by the ambident nucleophile ammonium thiocyanate (THF, room temperature, 15 min) gave the corresponding thiocyanate diols in 71% yield. A C-3 to C-2 isomer ratio of 5.6/1 was observed (entry 25). Ammonium carboxylates (benzoate or acetate) also proved to be competent nucleophiles. Reactions took place in 15 min in THF at room temperature (entries 26 and 27). The acetylated crude material from the benzoate opening showed only the C-3 isomer by ^1H NMR analysis. The acetate opening gave a C-3 to C-2 isomer ratio estimated to be 65/1 on the basis of the optical rotation of the corresponding triol (see Supplementary Material section).

Carboxylic acids can be used directly and also exhibit regioselective ring-opening at C-3. The epoxy alcohol reacts within 15 min in CH_2Cl_2 with 1.1 equiv of benzoic acid and 1.2 equiv of $Ti(O\text{-}i\text{-}Pr)_4$, affording a 74% yield of the benzoate diol (entry 28). In a similar manner ring-opening of 1 with 1.3 equiv of pivalic acid and 1.5 equiv of $Ti(O\text{-}i\text{-}Pr)_4$ in benzene gives a 59% yield of the pivalate diol (entry 29). We have also extended our list of nucleophiles to include the tosylate anion: highly regioselective ring-opening at C-3 occurs upon treatment of the epoxy alcohol with 1.2 equiv of $Ti(O\text{-}i\text{-}Pr)_4$ and 1.05 equiv of 2,6-lutidinium *p*-toluenesulfonate (LPTS) in CH_2Cl_2 for 15 min. A 64% yield of the *p*-toluenesulfonate diol was obtained (entry 30).

Interestingly, the benzoic acid opening (entry 28) and the tosylate opening (entry 30) demonstrate that large excesses of metal alkoxide and/or nucleophile are not required for these openings. In fact, for most of the reactions described here, a stoichiometric amount of $Ti(O\text{-}i\text{-}Pr)_4$ and nucleophile should suffice to bring the reaction to completion. The amine and alcohol openings, where excess nucleophile is required to achieve reasonable rates, are exceptions.

This study has shown that in the presence of titanium alkoxides, nucleophilic opening reactions of *trans*-2,3-epoxy alcohols occur under extremely mild conditions. Our rationale for these dramatic rate enhancements invokes complexation (via metal alkoxide/hydroxyl group exchange) of the epoxy alcohol to the metal center as shown in Scheme I. While the regioselectivity is generally very good,[21] we cannot yet explain why its magnitude is nucleophile dependent.[22,25] Homochiral 2,3-epoxy alcohols have already proven to be useful in organic synthesis.[23] This new titanium-mediated nucleophilic opening procedure should extend their utility for the synthesis of polyfunctional homochiral organic molecules.

We are presently studying the metal alkoxide assisted openings of the erythro and threo epoxy alcohols which derive from chiral secondary allylic alcohols, and our initial results on $Ti(OR)_4$-mediated openings of glycidic acids and amides appear in the following communication.[24]

Acknowledgment. we are grateful to the National Science Foundation (CHE-8308355) and to Merck and Company 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: Additional experimental details for the $Ti(O\text{-}i\text{-}Pr)_4$-mediated nucleophilic openings of 3-propyloxiranemethanol (1); sequence carried out to assign the ratio of isomers in the ammonium acetate opening; and ^1H NMR data of all peracetylated-opened products prepared in this work (28 pages). Ordering information is given on any current masthead page.

(19) For an example of an unsuccessful attempted cyanide opening of an epoxy alcohol using uncatalyzed conditions (KCN, 18-crown-6, benzene), see: Takatsuto, S.; Yazawa, N.; Ishiguro, M.; Morisaki, M.; Ikekawa, N. *J. Chem. Soc., Perkin Trans. 1* **1984**, 139.

(20) Although disappointing, this result does not mean that a 2,3-epoxy alcohol cannot be opened by cyanide with a reasonable degree of selectivity. For example, when 1 was treated with Nagata's reagent, (Et_2AlCN, 2.3 equiv, toluene, −20 °C, 1 h and then room temperature, 3 h), the corresponding cyano diols were obtained in a C_3/C_2 ratio of 15/1 in a combined yield of 87%. See ref 19 for the utilization of this reagent with another epoxy alcohol. In contrast to Nagata's reagent for opening with cyanide, we found $Al(O\text{-}i\text{-}Pr)_3$ to be inferior to $Ti(O\text{-}i\text{-}Pr)_4$ (regarding both rate and regioselectivity).

(21) At present we can only speculate on the origins of the enhanced C-3 selectivity in openings of the coordinated epoxy alcohols. Examination of the putative intermediate complex in Scheme I suggests one attractive possibility. The bond between C-3 and oxygen (bond a) appears much better oriented to overlap with an empty d orbital on titanium than does the bond between C-2 and oxygen (bond b) which lies nearly in the plane of the five-membered ring.

(22) Whatever the significance, one notices that it is generally the "softer" nucleophiles which are the least regioselective.

(23) (a) Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takatani, M.; Viti, S. M.; Walker, F. J.; Woodard, S. S. *Pure Appl. Chem.* **1983**, *55*, 589; ref 11a, this paper. (b) Finn, M. G.; Sharpless, K. B. in "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 8. (c) Rossiter, B. E. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 7.

(24) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.*, the following communication in this issue.

(25) **Note Added in Proof**: The regioselective (C-3:C-2 > 50:1) openings of 1 with NH_4NO_3 (2 equiv, THF, room temperature) and with CH_3COSH (5 equiv, CH_2Cl_2, room temperature) in the presence of $Ti(O\text{-}i\text{-}Pr)_4$ proceed in excellent yield. For the ambident nucleophile thioacetic acid, it is the C-3 thioacetate which is formed. Gao, Y.; Sharpless, K. B., unpublished results.

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Nucleophilic Openings of 2,3-Epoxy Acids and Amides Mediated by $Ti(O\text{-}i\text{-}Pr)_4$. Reliable C-3 Selectivity

Summary: 2,3-Epoxy acids and amides are opened regioselectively at C-3 by nucleophiles in the presence of $Ti(O\text{-}i\text{-}Pr)_4$.

Sir: As part of continuing efforts to expand the synthetic utility of 2,3-epoxy alcohols, substances readily available in high enantiomeric excess via asymmetric epoxidation,[1] we have examined the openings of these compounds and some of their derivatives.[2] Previous results from these

(1) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

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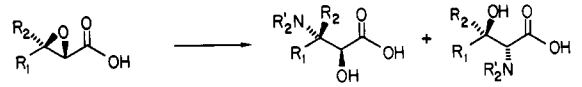
Table I. Reaction of 2,3-Epoxy Acids with Dialkylamines

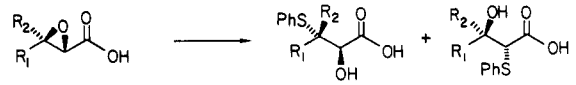


4 5 6

entry	acid	R_1	R_2	conditns[a]	ratio 5:6[b]	yield,[c] %
1	1	n-C_7H_{15}	H	A	>20:1[d]	92
2				B	1:6	95
3	7	H	n-C_7H_{15}	A	>20:1[d]	71
4				B	1.3:1	86
5	8	c-C_6H_{11}	H	A	>20:1[d]	83
6				B	1:7	84
7	9	t-$BuPh_2SiOCH_2$	H	A	10:1	82
8				B	1:>20	84
9	10	H	t-$BuPh_2SiOCH_2$	A	10:1	87
10				B	1:11	86
11	1	n-C_7H_{15}	H	C	>20:1[d]	83
12				D	1:2.5	84
13	7	H	n-C_7H_{15}	C	>20:1[d]	77
14				D	2.4:1	78

[a] A, excess diethylamine, 1.5 equiv of Ti(O-i-Pr)$_4$, room temperature, 4 h; B, excess diethylamine/water (2:1 v/v), reflux, 12 h; C, excess diallylamine, 1.5 equiv of Ti(O-i-Pr)$_4$, room temperature, 4 h; D, excess diallylamine/water (2:1 v/v), reflux, 12 h. [b] As determined by ^{1}H NMR spectroscopy on the derived methyl ester (excess CH_2N_2) acetates (Ac_2O, pyr, DMAP). [c] Determined after purification (flash chromatography) of the methyl ester acetates. [d] The minor isomer was undetectable by ^{1}H NMR spectroscopy.

Table II. Reaction of Epoxy Acids with Thiophenol



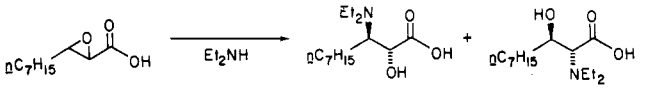
4 11 12

entry	acid	R_1	R_2	conditns[a]	ratio 11:12[b]	yield,[c] %
1	1	n-C_7H_{15}	H	A	1:13	84
2				B	10:1	86
3				C	20:1	80
4	7	H	n-C_7H_{15}	A	1.7:1	77
5				B	*d*	*d*
6				C	20:1	89

[a] A, PhSNa (2 equiv), THF, room temperature, 1 h; B, PhSH (2 equiv), CH_2Cl_2, Ti(O-i-Pr)$_4$ (1.5 equiv), room temperature, 4 h; C, PhSNa (2 equiv), THF, Ti(O-i-Pr)$_4$ (1.5 equiv), room temperature, 0.2 h. [b] As determined by ^{1}H NMR spectroscopy on the esterified (excess CH_2N_2), acetylated (Ac_2O, pyr, DMAP) mixture. [c] Yield of purified, isolated methyl ester acetates. [d] Not determined. The product mixture contained 50% of products derived from opening by isopropyl alcohol.

laboratories[3] have shown that Ti(O-i-Pr)$_4$ facilitates the opening of 2,3-epoxy alcohols with a variety of nucleophiles. We now communicate our preliminary results in opening 2,3-epoxy acids[4] and amides using the same strategy. Specifically, we find that (a) whereas secondary amines open 2,3-epoxy acids preferentially at C-2 in the absence of Ti(O-i-Pr)$_4$ the presence of a stoichiometric amount of Ti(O-i-Pr)$_4$ causes a dramatic shift in regioselectivity to C-3 opening and (b) whereas thiolates tend to open 2,3-epoxy acids and amides at C-2 in the absence of Ti(O-i-Pr)$_4$ there is a high selectivity for C-3 opening in the metal-mediated case.

The ring-opening reaction of *trans*-2,3-epoxydecanoic acid (1) with diethylamine (eq 1) was first examined. In



(1)

the presence of 1.1 equiv of Ti(O-i-Pr)$_4$, ring-opening was complete within 2 h at room temperature. More importantly, only the product of C-3 opening, 3-(diethylamino)-2-hydroxydecanoic acid (2), was detected. In contrast, in the absence of Ti(O-i-Pr)$_4$, only 10% conversion occurred even after 4 days at room temperature, and the products 2 and 3 were formed with little regioselectivity (2:3 = 1:2.2). That a stoichiometric amount of Ti(O-i-Pr)$_4$ is required for facile reaction was shown by the following: when 0.5 equiv of Ti(O-i-Pr)$_4$ was used, reaction proceeded to 52% completion after 48 h, and the products were formed with intermediate regioselectivity (2:3 = 9:1).

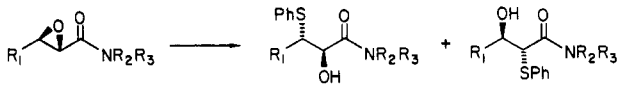
We have allowed a number of other 2,3-epoxy acids to react with diethylamine/Ti(O-i-Pr)$_4$ and have found the observed C-3 selectivity to be quite general. A comparison of the regioselectivities observed in the reaction of some of these acids with diethylamine/Ti(O-i-Pr)$_4$ and with diethylamine/H_2O is shown in Table I. Although it has

(2) (a) Behrens, C. H.; Sharpless, K. B. *Aldrichimica Acta* **1983**, *16*, 67. (b) Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takatani, M.; Viti, S. M.; Walker, F. J.; Woodard, S. S. *Pure Appl. Chem.* **1983**, *55*, 589.

(3) Caron, M.; Sharpless, K. B. *J. Org. Chem.*, preceding paper in this issue.

(4) These compounds may be readily prepared from 2,3-epoxy alcohols by oxidation with RuO_4: Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. See also: Still, W. C.; Ohmizu, H. *J. Org. Chem.* **1981**, *46*, 5242. We have recently found that the use of periodic acid instead of sodium periodate in this procedure provides for a more facile reaction. Typically, use of 2.5 equiv of H_5IO_6 and 2 mol % $RuCl_3$ in the described CCl_4–CH_3CN–H_2O system effects complete conversion to the acid (with no trace of intermediate aldehyde) within 2 h at room temperature. The superiority of periodic acid over sodium periodate in the acetonitrile-modified RuO_4 oxidations of aromatic compounds was brought to our attention by Mr. Kwok Tse and Professor Leon Stock of the University of Chicago: Stock, L. M.; Tse, K. W.-T. *Fuel* **1983**, *62*, 974 and unpublished results. Glycidic acids may also be prepared by tungstate-catalyzed epoxidation of α,β-unsaturated acids. See: Kirshenbaum, K. S.; Sharpless, K. B. *J. Org. Chem.*, in press.

Table III. Reaction of 2,3-Epoxy Amides with Thiophenol



13 14 15

entry	substrate	R_1	R_2	R_3	conditns[a]	ratio 14:15	yield,[c] %
1	16	n-C_7H_{15}	H	$PhCH_2$	A	1:1.2	89
2	16	n-C_7H_{15}	H	$PhCH_2$	B	20:1	95
3	17	c-C_6H_{11}	H	$PhCH_2$	A	1:4	85
4	17	c-C_6H_{11}	H	$PhCH_2$	B	5:1	95
5	17	c-C_6H_{11}	H	$PhCH_2$	C	7:1	95
6	17	c-C_6H_{11}	H	$PhCH_2$	D	20:1	91
7	18	n-C_7H_{15}	$PhCH_2$	$PhCH_2$	A	1:11	84
8	18	n-C_7H_{15}	$PhCH_2$	$PhCH_2$	D	1:7	89

[a] A, PhSNa, THF, room temperature, 1 h; B, PhSH (2 equiv), Ti(O-i-Pr)$_4$ (1.5 equiv), CH_2Cl_2, room temperature, 6 h; C, PhSH (2 equiv), Ti(O-i-Pr)$_4$ (1.5 equiv), THF, room temperature, 6 h; D, PhSNa (1.5 equiv), Ti(O-i-Pr)$_4$ (1.5 equiv), THF, 0.2 h. [b] As determined by ^{1}H NMR spectroscopy on the acetylated (Ac_2O, pyr, DMAP) mixture. [c] Isolated yield of purified (flash chromatography) acetates.

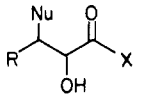
been reported that 2,3-epoxycrotonic acid reacts with aqueous benzylamine to afford exclusively the C-2 opened product,[5] we[2b] and others[6] have not observed such high selectivity in closely related openings but have observed C-3:C-2 opening ratios on the order of 1:5 for *trans*-glycidic acids. With cis 2,3-epoxy acids, there was a small preference for attack at C-3. The regioselectivities in the water-catalyzed cases shown in Table I are typical. In the presence of Ti(O-i-Pr)$_4$, both trans and cis epoxy acids with a simple alkyl substituent at C-3 are attacked by diethylamine apparently exclusively at C-3. Even epoxy acids with an electron-withdrawing group ((*tert*-butyldiphenylsiloxy)methyl; entries 7 and 9) at C-3 are opened at C-3 with reasonable selectivity.

Use of diallylamine in place of diethylamine also gave good selectivity for C-3 in the presence of Ti(O-i-Pr)$_4$ (Table I, entries 11 and 13). The products may be useful precursors to 3-amino-2-hydroxy acids.[7]

The reactions of epoxy acids 1 and 7 with thiophenol were also examined (Table II). In the absence of Ti(O-i-Pr)$_4$, no reaction was observed between either the trans epoxy acid 1 or the cis epoxy acid 7 with thiophenol. In contrast, sodium thiophenoxide reacted rapidly with both epoxy acids; the trans epoxide 1 was opened regioselectively at C-2 (entry 1) whereas the cis epoxide 7 was opened with poor regioselectivity (entry 4). In the presence of Ti(O-i-Pr)$_4$, opening could be effected by using either thiophenol or sodium thiophenoxide. As in the case of amine nucleophiles, there was a shift in regioselectivity in the presence of Ti(O-i-Pr)$_4$ and predominantly C-3 attack was observed. The trans epoxide 1 reacted with the PhSH/Ti(O-i-Pr)$_4$ system to afford a 10:1 (C-3:C-2) mixture of regioisomers (entry 2); the cis epoxide 7, on the other hand, reacted with the same system to afford a mixture of products of opening by thiophenol and isopropyl alcohol (entry 5). Fortunately, competitive opening by isopropyl alcohol was not observed when the PhSNa/Ti(O-i-Pr)$_4$ system was used, and regioselective (C-3:C-2 = 20:1) opening by only thiophenoxide was observed with both the trans epoxy acid 1 and the cis epoxy acid 7.

High selectivity for C-3 opening of secondary 2,3-epoxy amides with thiophenol was also observed when Ti(O-i-Pr)$_4$ was added (Table III). As in the case of the acids, no reaction occured with thiophenol in the absence of Ti(O-i-Pr)$_4$, but regioselective opening at C-3 was observed in the presence of the metal alkoxide (entries 2 and 4–6). This regioselectivity is in contrast to the C-2 selectivity exhibited by sodium thiophenoxide in the absence of Ti(O-i-Pr)$_4$ (entries 1, 3, and 7). Also as in the case of the acids, better regioselectivity was observed by using the PhSNa/Ti(O-i-Pr)$_4$ system than with the PhSH/Ti(O-i-Pr)$_4$ system (entries 5 and 6). Somewhat expectedly, a tertiary amide did not exhibit the same dramatic shift in regioselectivity in the presence of Ti(O-i-Pr)$_4$ (entries 7 and 8).

Of special synthetic importance is our recent finding that both azide and cyanide may also be efficiently introduced highly regioselectively into C-3 of 2,3-epoxy acids. Thus, reaction of epoxy acids **1**, **7**, **8**, and **9** with LiN_3 (3 equiv) in the presence of Ti(O-i-Pr)$_4$ (1.5 equiv) in EtOH at room temperature for 18 h afforded the corresponding ring-opening products in high (88–98%) yields.[8] Furthermore, only the C-3 opened regioisomer (**17**, Nu = N_3) was de-



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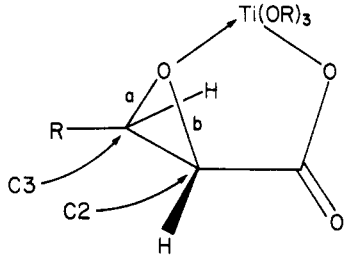
tected in each case, including epoxy acid **9** which contains an electron-withdrawing (*tert*-butyldiphenylsiloxy)methyl group at C-3. Similarly, reaction of epoxy acids **1**, **7**, **8**, and **9** with NaCN (3 equiv) in the presence of Ti(O-i-Pr)$_4$ (1.5 equiv) in Me_2SO at 40 °C for 12 h gave the expected 3-cyano-2-hydroxy acids (**17**, Nu = CN) in very good (87–91%) yields. None of the C-2 opened product was detected in any case.

(5) Liwschitz, Y.; Rabinsohn, Y.; Perera, D. *J. Chem. Soc.* **1962**, 1116.
(6) Zvonkova, E. N.; Mitsner, B. I.; Aksenov, N. E.; Bushnev, A. S.; Evstigneeva, R. P. *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **1976**, *19*, 796; *Chem. Abstr.* **1976**, *85*, 78038t. *trans*-2,3-Epoxyoctadecanoic acid was opened by ammonia with a C-3:C-2 selectivity of 1:6.5.
(7) Laguzza, B. C.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 1483.
(8) This methodology has been used[9] in a short enantioselective synthesis of (2*S*,3*R*)-3-amino-2-hydroxy-5-methylhexanoic acid which is a novel amino acid component of the tetrapeptide amastatin.[10] Thus, asymmetric epoxidation of (*Z*)-5-methyl-2-hexenol (Ti(O-i-Pr)$_4$, (–)-DIPT, TBHP 81%, 91% ee) followed by oxidation with $RuCl_3/H_5IO_6$ afforded the requisite epoxy acid (68%). Opening with azide as described then furnished the 3-azido-2-hydroxy acid (93%) which was readily reduced (H_2, Pd/C, MeOH, 94%) to give (2*S*,3*R*)-3-amino-2-hydroxy-5-methylhexanoic acid; $[\alpha]^{23}_D$ –25.6° (*c* 0.3 AcOH). Recrystallization from EtOH–H_2O followed by drying at 140 °C/0.1 mmHg for 36 h afforded white needles: $[\alpha]^{22}_D$ –29.0° (*c* 0.6, AcOH); mp 213–214 °C. Anal. Calcd for $C_7H_{15}NO_3$: C, 52.16; H, 9.38; N, 8.69. Found: C, 51.92; H, 9.52; N, 8.50 [lit.[10] $[\alpha]^{22}_D$ –28.0° (*c* = 0.5, AcOH); mp 188–189 °C]. Further recrystallization from n-PrOH–H_2O did not affect the rotation or melting point.
(9) Chong, J. M.; Sharpless, K. B., unpublished results.
(10) (a) Tobe, H.; Morishima, H.; Naganawa, H.; Takita, T.; Aoyagi, T.; Umezawa, H. *Agric. Biol. Chem.* **1979**, *43*, 591. (b) Tobe, H.; Morishima, H.; Aoyagi, T.; Umezawa, H.; Ishiki, K.; Nakamura, K.; Yoshioka, T.; Shimauchi, Y.; Inui, T. *Agric. Biol. Chem.* **1982**, *46*, 1865.

While it is unclear exactly why the presence of Ti(O-*i*-Pr)$_4$ provides such a strong tendency for 2,3-epoxy acids and secondary amides to be opened by nucleophiles at C-3, the observed regioselectivities may be rationalized by proposing the formation of an intermediate titanium complex such as **18**. Opening at C-3 occurs preferentially



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for the reasons postulated in the previous communication. Furthermore, the π orbitals of the carbonyl group and bond b are essentially orthogonal, and thus acyl activation for substitution at C-2 is not possible.[11]

It is obvious that the use of Ti(O-*i*-Pr)$_4$ to direct the attack of nucleophiles to C-3 of 2,3-epoxy acids and amides holds considerable promise for the preparation of compounds of general structure **17**. Coupled with asymmetric epoxidation and the facile oxidation of epoxy alcohols to glycidic acids by the catalytic RuO_4/H_5IO_6 system,[4] this approach should provide ready access to these compounds in high enantiomeric purity.

Acknowledgment. We thank the National Science Foundation (CHE-8308355) and Merck and Company for generous support of this research. We are also grateful to the Izaak Walton Killam Memorial Foundation and the Natural Science and Engineering Research Council of Canada (NSERC) for postdoctoral fellowships to J.M.C.

Supplementary Material Available: Procedures for the preparation of epoxy acids **1** and **7–10**; general procedures for the Ti(O-*i*-Pr)$_4$-mediated reaction of epoxy acids with dialkylamines and thiophenol, azide, and cyanide; ^{1}H NMR data for the (a) methyl ester acetates of compounds **5**, **6**, **11**, **12**, and **17** (Nu = N_3 and CN) and (b) acetates of compounds **14** and **15** (15 pages). Ordering information is given on any current masthead page.

(11) (a) Thorpe, J. W.; Warkentin, J. *Can. J. Chem.* **1973**, *51*, 927. (b) Deslongchamps, P. "Stereoelectronic Effects in Organic Chemistry"; Pergamon Press: Oxford, 1983; p 172.

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An Unprecedented Selective Autoxidation of Tertiary Amines to Amine Oxides

Summary: Tertiary amines have been found to react directly with molecular oxygen under high O_2 pressures to give in an unexpected result the corresponding *N*-oxide in high yields.

Sir: During our studies of the oxygen oxidation of tertiary amines,[2] we have discovered a pathway in which the conversion to *N*-oxide is effected directly and selectively with no catalyst. This transformation proceeds, although slowly, in polar solvent media, under high oxygen pressures (~50 bar), and at elevated temperatures (90–130 °C), to afford in some instances >95% yield of the *N*-oxide (Table I). This result is in marked contrast to the previously reported autoxidations of tertiary amines where dealkylation is the predominant pathway. Amine oxides have previously only been observed as minor byproducts arising from the reaction of tertiary amine with an intermediate α-hydroperoxide.[3-5] Further, none of the known amine autoxidation pathways would predict amine oxide yields of >50%.

In a typical procedure a trimethylamine solution in water (2.4 M) was shaken under 71 bar air at 100 °C for 64 h. After this period, >95% conversion to the *N*-oxide resulted as monitored by HPLC and confirmed by isolation of the crystalline $Me_3NO{\cdot}2H_2O$. Non-water-soluble tertiary amines can be similarly oxidized in high yields, but homogeneous aqueous alcohol solutions must be used or a nonselective autoxidation occurs. In the alcohol cosolvent systems only low levels of alcohol oxidation products were observed, indicating that peracids derived from alcohol are not the *N*-oxide-producing oxidants in such systems.[6]

Kinetic data were obtained in aqueous systems to avoid problems with potential solvent oxidation. This necessitated the use of water soluble amines with relatively low volatility. For this reason the oxygen concentration (pressure) dependence was studied in H_2O at 125 °C for the oxidation of *N*-methylmorpholine (0.2 M) over the range of 40–100 bar O_2. At constant oxygen pressure the amine reacts in a pseudo-first-order manner. The rate of conversion to the *N*-oxide was found to be first-order in oxygen during the monitored period (~24 h). Amine oxide yields were >85% of converted amine during this period in all cases.

The structure of the tertiary amine plays a significant role in determining both the reaction rate and types of products obtained in these high-pressure autoxidations. The most selective conversion to *N*-oxides occur with aliphatic amines (Table I, entries 1–4). Phenyl-substituted tertiary amines, such as *N*,*N*-dimethylaniline, react at faster rates than aliphatic amines but afford complex mixtures of products with dealkylations predominating at low conversion. Aromatic amines such as pyridine are unreactive. When the α-carbon is activated, as in *N*,*N*-dimethylbenzylamine, a competitive cleavage of the carbon–hydrogen bond is observed, yielding benzaldehyde, but the pathway yielding *N*-oxide still predominates.

A rational mechanism for this oxidation can be suggested by our data. In the low-pressure oxidation of tertiary amines reported by Beckwich, the yield of amine oxide is limited to 50% by the fact that H_2O_2 or a hydroperoxide, derived from α-oxidation, is required for formation of amine oxide.[3] Our yields in excess of 50% indicate that the mechanism of oxidation changes significantly at the increased temperatures and pressures we employ. We believe that this reaction involves an initial electron

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