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METAL SALTS AS NEW CATALYSTS FOR MILD AND EFFICIENT AMINOLYSIS OF OXIRANES

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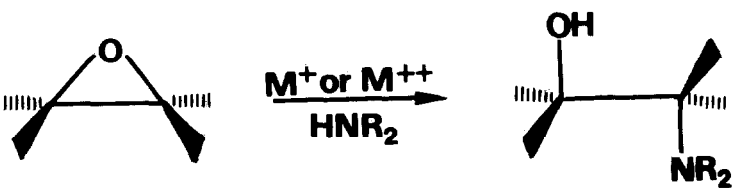
Summary: *A new, simple, efficient, inexpensive, anti stereoselective, highly regioselective method for aminolysis of 1,2-epoxides, by means of metal salts, is described.*

ß-Amino alcohols constitute a large class of well-known organic compounds; the substantial repertory of synthetic approaches to this structural class reflects its broad importance in natural products, medicinal chemistry, and other chemical fields. The ring-opening addition reactions of 1,2-epoxides with ammonia or amines, and their synthetic equivalents, is one of the most widely used methods for ß-amino alcohol synthesis.[1] Several useful modifications of the classical procedures have been demonstrated recently; however, there are still intrinsic limitations on the general utility of epoxide aminolysis.[1-4] Thus, nucleophilic metal amides (aluminum,[4], magnesium,[5a] lithium,[5b] lead,[5c] tin[5d] and silicon[5e]) have been successfully employed in several cases although many functional groups are potentially incompatible with their use and large scale procedures may be costly or difficult. Posner's heterogeneous method[6] employing ammonia or an amine adsorbed on alumina is a useful alternative which, however, requires the use of relatively large excess of the amine reactant. Tetraphenylantimony triflate[7] has recently been demonstrated to catalyze the aminolysis of epoxides under mild, homogeneous reaction conditions but it is not clear whether the expense and difficulty of preparation of this catalyst will justify its widespread synthetic use for this purpose. More recently, it was reported[8] that cobalt (II) chloride mediates a redox type of epoxide aminolysis reaction with relatively non-nucleophilic anilines; however, the method is apparently ineffective with benzylic or aliphatic amines. In this Letter we report conditions for the use of several readily available metal salts that very effectively promote the aminolysis of 1,2-epoxides with a variety of amines. For example, we



have found that the efficient aminolysis of epoxides with an equivalent of amine in acetonitrile solution in the presence of soluble, anhydrous group 1A, 2A or 2B (Zn^{++}) metal salts usually requires only a few hours at room temperature. The results of metal-catalyzed reactions of some representative epoxides (1-8) with structurally diverse primary and secondary amines are summarized in the Table.

Table. Aminolysis of oxiranes in the presence of metal salts.

entry	oxirane[a]	salt	amine	amino alcohol[b]	reaction time(h)[c]	yield[d]
1		$LiClO_4$	H_2NBn		20	95
2		$LiClO_4$	H_2NPh		38	97
3		$LiClO_4$	$HN(i\text{-}Pr)_2$		64(80°C)	86
4		$LiClO_4$	$H_2N(t\text{-}But)$		18	95
5		$Mg(ClO_4)_2$	$HN(Et)_2$		16	97
6	1	$Zn(Tf)_2$[e]	$HN(Et)_2$	9	5	95
7	2	$LiClO_4$	H_2NBn	10	64	80
8		$LiClO_4$	H_2NBn		2	98[f]
9	3	$LiClO_4$	$HN(Et)_2$	11 + 12	0.5	97[f]
10	4	$LiClO_4$	$H_2N(t\text{-}But)$	13	8	90
11		$Mg(ClO_4)_2$	H_2NPh		0.5	98
12		$NaClO_4$	$HN(Et)_2$		1	95
13		$CaCl_2$	$HN(Et)_2$		0.5	94
14		$ZnCl_2$	$HN(Et)_2$			
15	5	$LiClO_4$	$HN(Cy)_2$[e]	14	26	90
16	6	$LiBF_4$	$HN(Et)_2$	15	0.5	94
17	7	$LiClO_4$	$HN(Et)_2$	16	1.5	98
18	8	$LiClO_4$	H_2NBn	17	72(60°C)	95

[a] All the reactions were carried out on racemic material; [b] The amine used determines the nature of the NR_2 group in the formulas of the amino alcohols: for their identification, see General Procedure; [c] With the only exception of entries 3 and 18 all the reactions were carried out at room temperature; [d] Yields based on weight and ^1H NMR examination of the isolated crude product; [e] Cy= cyclohexyl, Tf= triflate; [f] The relative ratio between regioisomers 11 and 12 (almost 40:60 in both the entries 8 and 9) were determined by ^1H NMR (methinic benzylic proton at δ 4.70[g] in 11 and at δ3.90[g] in 12) and by GLC (entry 9).

It appears to be important that the counterion of the metal salt lend acetonitrile-solubility to the catalyst since heterogeneous metal salts (for example, magnesium sulfate) were completely ineffective. Potassium perchlorate or potassium tetrafluoroborate, although readily soluble in acetonitrile, also did not appear to exert any catalytic effect on the aminolysis of 1,2-epoxides. The effective catalytic salts were best employed in mole-equivalent amounts based on the epoxide and amine reactants; the use of fractional equivalents of salt led to considerably longer reaction times at a given temperature. The reaction rate of aminolysis also depends on the structure of the epoxide substrate and on the nucleophilicity of the amine reactant. The aminolysis of unhindered epoxides with nucleophilic primary amines under these conditions may be highly exothermic, in some cases requiring careful control of the reaction temperature. On the other hand, reactions of highly substituted epoxides, especially with aniline or α-branched secondary amines, required fairly long reaction times at room temperature or, in two cases (entries 3 and 18, Table) elevated reaction temperatures. Remarkably, our reaction conditions promoted the facile aminolysis of **1** with diisopropylamine and of **5** with dicyclohexylamine to yield amino alcohols which have not to our knowledge been previously reported (entries 3 and 15, Table). Tetramethylene oxide reacted slowly with benzylamine under our aminolysis conditions to give another new β-amino alcohol (entry 18, Table). In some cases, the metal ion-catalyzed aminolysis procedure could be carried out using toluene, acetone, or ether as the solvent although all of these led to lower reaction rates than the analogous reactions in acetonitrile. The stereoselectivity of the aminolysis reactions was *anti* as demonstrated by the reactions of cyclohexene oxides with several amines which gave exclusively *trans*-2-aminocyclohexanol derivatives. With the exception of styrene oxide (entries 8 and 9, Table), unsymmetric epoxides were attacked at the less substituted oxirane carbon with very high regioselectivity.

It seems probable to us that the observed catalytic effect of Lewis-acidic metal ions on epoxide aminolysis reactions is related in a simple way to the ion ability to coordinate with the oxirane oxygen. The fact that styrene oxide gave an almost equimolar mixture of regioisomeric β-amino alcohols under our conditions is in agreement with a highly polarized reactive form of the epoxide substrate in this example.

In summary, this new method for the aminolysis of 1,2-epoxides appears to be broadly useful, even with amines of low nucleophilicity or hindered epoxides. The reactions proceed under mild conditions in a non-protic solvent to afford β-amino alcohols with complete *anti*-stereoselectivity and generally high regioselectivity. We are continuing to explore applications of the metal salt-catalyzed epoxide aminolysis reaction with the aim of further defining its scope and limitations as a synthetic method.

General Procedure and Identification of the Amino Alcohols 9-17

A solution of the epoxide (10 mmol) in acetonitrile (2 ml) was treated with anhydrous metal salt (10 mmol), then stirred untill complete solution of the salt. The resulting solution was treated under stirring, at room temperature, with the required amount of the amine (10 mmol). The reactions of 1,2-epoxides and amines not particularly hindered, show a strong exothermic effect: in these cases, a control of the reaction by regulating the addition of the amine, may be necessary ,particularly when larger scale reactions are carried out. After the addition of the amine was completed, the reaction mixture was stirred for the time and the temperature indicated in the Table, then diluted with water and extracted with ether. Due to the non complete solubility of some salts, the reactions carried out in the presence of $NaClO_4$, $CaCl_2$, and $ZnCl_2$ were effected in non homogeneous solutions. Evaporation of the washed (water) and dried ether extracts yielded the crude amino alcohol. The purity of the amino alcohol was checked by ^1H NMR and by GLC except for the compounds deriving from primary amines in which it was verified only by ^1H NMR. All the amino alcohols obtained were identified by comparison (^1H NMR, GLC and m.p. in the case of solid compounds) with authentic samples prepared according to literature procedures.[4,5,7,8] In the cases of new compounds (entries 3,15 and 18, Table) the ^1H NMR spectra and the satisfactory microanalytical results on their salts (C,H,N $\pm$ 0.3% of the calculated values) confirm their structures. Compound **9** R=*i*-Pr,liquid, ^1H NMR,δ 3.28-3.11 [m,3H,2 C*H*(CH_3)$_2$ and C*H*OH], 2.41-2.30 (m,1H,CHN),1.06 (d,12H, 4 CH_3); hydrochloride (EtOH), m.p. 207-208°C. Compound **14** R=cyclohexyl, liquid, ^1H NMR,δ 7.46-7.22 and 7.09-6.90 (two multiplets, 2H and 3H respectively, aromatic protons), 4.01-3.84 (m,3H,OCH_2CH), 2.90-2.82 (m,1H,H_A), 2.56-2.45 (m,3H,H_B and 2 CHN); oxalate (EtOH) m.p. 165-166 °C. Compound **17**, R=CH_2Ph, liquid, ^1H NMR, δ 7.40-7.20 (m,5H, aromatic protons), 3.73 (s,2H,Ph*C*H_2), 1.17 (s,6H,2 CH_3), 1.14 (s,6H,2 CH_3); hydrochloride (EtOH) m.p. 188-189°C.

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