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FACILE AMINOLYSIS OF EPOXIDES WITH DIETHYLALUMINUM AMIDES

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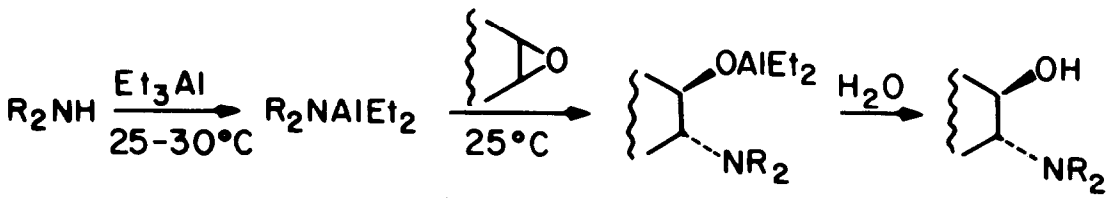
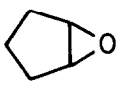
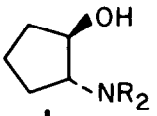
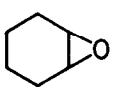
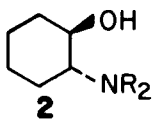
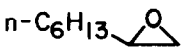
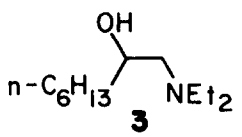
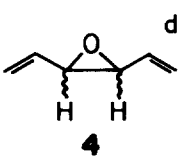
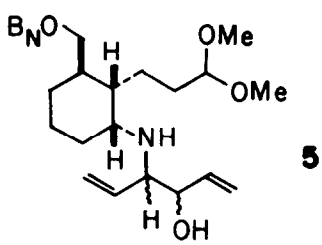
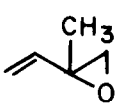
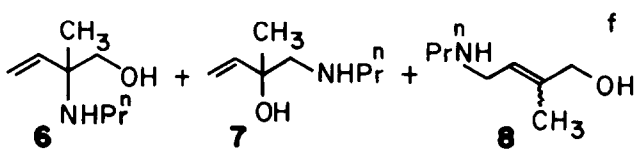
Summary: Treatment of an epoxide with a diethylaluminum amide in dichloromethane at room temperature affords the corresponding β-amino alcohol in good yield.

The classical method for preparing β-amino alcohols involves heating an epoxide in a protic solvent with excess amine.[1] Although this direct reaction is satisfactory in many cases,[1] it has a number of limitations. Non-nucleophilic (e.g., aromatic amines) or bulky amines typically react poorly,[1,2] while the common requirement of using excess amine and elevated temperatures provides further limitations.[1,3] Recent studies in our laboratory[4] required a variety of β-amino alcohols, and in several cases we found classical methods of epoxide aminolysis to be totally ineffectual. Although new methods for promoting the reaction of epoxides with amines have been described,[5] recent studies by Yamamoto[6] and Weinreb[7] suggest that aluminum amides[8] would be uniquely attractive reagents for epoxide aminolysis. An examination of this reaction was consequently undertaken, and in this letter we report that a variety of diethylaluminum amides react stoichiometrically with epoxides at room temperature to give, after hydrolysis, β-amino alcohols in good yield.



The results obtained from the reaction of a variety of diethylaluminum amides with a representative group of epoxides are summarized in the Table.[9] The procedure involved treating the starting primary or secondary amine in dichloromethane with 1 equiv of triethylaluminum (RT, 30 min), followed by reaction with 1 equiv of the epoxide (RT, conveniently overnight). Hydrolysis of the resulting amino aluminate under acidic (excess saturated NH_4Cl, RT, 1-4h), neutral (excess $Na_2SO_4 \cdot 10H_2O$-Celite (1:3), RT, 1-4h), or basic (6M NaOH, RT, 1-2h) conditions afforded the β-amino alcohol product. We found the basic hydrolysis procedure to be most generally satisfactory, and this procedure was employed in the reactions reported in the Table. The success of this reaction with a wide variety of primary and secondary amines is apparent. The advantages of this method over classical procedures are well illustrated by the preparation of 5 in 63% yield,[10] since the starting primary amine could not be induced to react directly with hexatriene 3,4-oxide[11] under prolonged heating at 110 °C, or at 110 °C in the presence of catalytic acid. Similarly 1 [$NR_2 = N(CH_2Ph)_2$] , which was prepared in 78% yield by the aluminum amide procedure, could not be obtained from the direct reaction of dibenzylamine and cyclopentene oxide at 110 °C. That the amino alcohols produced from the reaction of cyclohexene oxide with diethylaluminum amides were the trans isomers was apparent from the 250 MHz ^1H NMR spectra. For example, 2 ($NR_2 = NHPr^n$) showed characteristic signals for the ring methine hydrogens at δ3.39 (ddd, J = 4.3, 9.5, 10 Hz) and δ 3.11 (ddd, J = 3.9, 9.2, 9.5 Hz). The reaction of 1-hexene oxide with diethylaluminum diethylamide occurred exclusively at the terminal carbon, since no trace of a regioisomer could be detected by capillary GC or 250 MHz ^1H NMR analysis. In contrast, the reaction of isoprene oxide with diethylaluminum n-propylamide gave a mixture of products in which the tertiary carbinyl amine 6 predominated. This should be compared with the direct reaction of isoprene oxide with n-propyl amine which gives only 7.[4b] For particularly sluggish reactions the use of the dimethylaluminum amide may be advantageous,[7] since we have observed that the reaction of 1-hexene oxide with dimethylaluminum n-propylamide was essentially complete in 1 h, while reaction with the

TABLE : Aminoalcohols From Epoxides and Diethylaluminum Amides. [a]

Epoxide	Aminoalcohol Product		mp, °c	Yield, % [b]
	 1	$NR_2 = NEt_2$	32 – 33	86
		$= NHPh$	58 – 59	61
		$= NHPr^n$	c	44
		$= N$ 	34.5 – 35.5	58
		$= N(CH_2CH=CH_2)_2$	c	71
		$= N(CH_2Ph)_2$	47.5 – 48.5	78
	 2	$NR_2 = NHPr^n$	48 – 48.5	69
		$= NHPh$	57 – 58	52
		$= N$ 	c	74
		$= N(CH_2Ph)_2$	88 – 89	72
	 3		c	69
 d 4	 5		e	63
	 6 7 8 (72 : 17 : 11)		f	50

[a] All reactions were conducted identically on a 5 mmol scale at RT in CH_2Cl_2 following the general procedure described. No attempt was made to optimize yields. [b] Yield of isolated material, purity ≥ 98% by capillary GLC analysis. [c] Oil, purified by bulb-to-bulb distillation. [d] A mixture of cis and trans isomers.[11] [e] Oil, purified by silica gel chromatography. [f] Structures assigned from the 250 MHz ^1H NMR spectrum of the product mixture, which was not separated.

corresponding diethylaluminum amide required ∿ 4 h.

General Procedure. A stirred solution of the amine (5.0 mmol) and 15 mL of dichloromethane was treated dropwise under nitrogen over ∿ 5 min with 3.2 mL of a 1.55 M solution of triethylaluminum in toluene (Aldrich). Ethane was vigorously evolved and the reaction temperature rose slightly (4-6 °C). After 30 min, 5.0 mmol of the epoxide was added and the reaction was left at room temperature overnight. The aluminate was hydrolyzed by the careful dropwise addition (vigorous gas evolution) at room temperature of 4 mL of 6M NaOH. The resulting two-phase mixture was stirred vigorously for 1-2 h, and the amino alcohol product was isolated by dichloromethane extraction and dried over Na_2SO_4. The crude amino alcohol was purified, as necessary, by bulb-to-bulb distillation, recrystallization, or chromatography.

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References and Notes:

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9. New compounds were fully characterized by IR, ^1H NMR (250 MHz), mass spectra, and combustion analysis.
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