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AMINOLEAD COMPOUNDS AS A NEW REAGENT FOR REGIOSELECTIVE RING OPENING OF EPOXIDES

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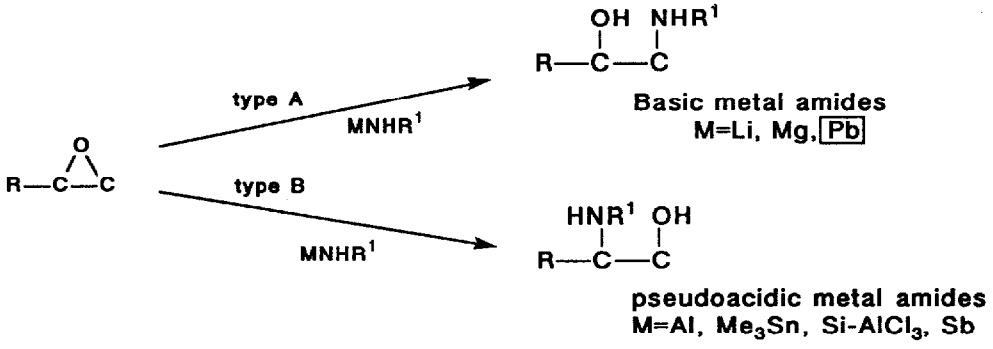
Summary: Regioselective ring opening of epoxides is accomplished by using aminolead compounds; the reagents attack the less hindered carbon of epoxide ring, and the amino alcohols are obtained in good yields.

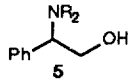
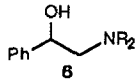
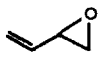
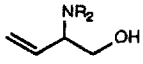
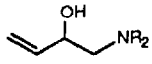
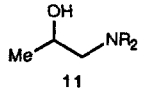
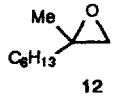
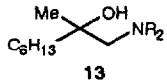
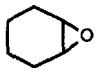
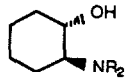
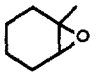
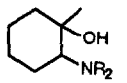
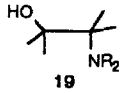
Regioselective ring opening of epoxides with amines is an important procedure for the synthesis of β-amino alcohols. Heating epoxides in the presence of excess amines, the direct reaction, has a number of limitations; 1) low nucleophilicity of amines requires elevated temperatures; 2) sterically bulky amines exhibit poor reactivity, and 3) it is not so easy to control the regioselectivity.[1] To overcome these problems, several metal amides have been developed (Scheme 1). The basic reagents such as lithium[2] and magnesium[3] amides attack the less hindered carbon with moderate regioselectivity (type A). A major drawback associated with lithium amides is that the hydrogen alpha to epoxide ring is abstracted by the amide base and thus the corresponding allylic alcohol is frequently obtained as a major product.[2] Other metal amides, such as aluminium,[4] tin,[5,6] silicon-Lewis acid,[6] and stibium reagents,[7] attack the carbon substituted with an alkyl group either preferentially or very predominantly (type B). In this sense, these reagents may be called as pseudoacidic metal amides.



Scheme 1. Regioselectivity of Metal Amides

We report that regioselective type A ring opening of epoxides is accomplished by using aminolead compounds; no hydrogen abstraction takes place and normally the amino alcohols are obtained with high to good regioselectivity in good chemical yields. The results are summarized in Table 1. Diethylaminoleads, 1 and 2, were prepared from the reaction of lithium diethylamides with Et_3PbBr or with n-Bu_3PbBr in ether under reflux (eq 1).[8] The resultant LiBr was removed by a centrifuge prior to use. The aminoleads 1 and 2 can be stored in dry n-hexane under nitrogen. Benzylaminolead 3 could be prepared by the transamination reaction of diethylaminolead with benzylamine (eq 2).[9]

Table 1. Aminolysis of Epoxides with Aminolead Compounds[a]

Epoxide	Aminolead	Amino alcohol		Reaction time (h)	Product Ratio[b]	Isolated yield (%)
 4		 5	 6			
	1	NR_2=NEt_2	NR_2=NEt_2	(0.5)	6:94	84[c]
	2	NR_2=NEt_2	NR_2=NEt_2	(0.5)	6:94	82[c]
	3	NR_2=$NHCH_2Ph$	NR_2=$NHCH_2Ph$	(2)	19:81	77[c]
 7		 8	 9			
	1	NR_2=NEt_2	NR_2=NEt_2	(3.5)	10:90	74[c,d]
	3	NR_2=$NHCH_2Ph$	NR_2=$NHCH_2Ph$	(6)	23:77	68[c]
 10		 11				
	1	NR_2=NEt_2		(1)		67[c,d]
	3	NR_2=$NHCH_2Ph$		(2)		88[c]
 12		 13				
	1	NR_2=NEt_2		(13)		57[c]
	1	NR_2=NEt_2		(20)		78[e]
	3	NR_2=$NHCH_2Ph$		(14)		66[c]
 14		 15				
	1	NR_2=NEt_2		(14)		73[d,e]
	3	NR_2=$NHCH_2Ph$		(14)		86[e]
 16		 17				
	1	NR_2=NEt_2		(42)		34[e]
	3	NR_2=$NHCH_2Ph$		(72)		65[e]
 18		 19				
	3	NR_2=$NHCH_2Ph$		(62)		trace[e]

[a]All reactions were carried out on 1.0 to 0.5 mmol scales under nitrogen in Et_2O as a solvent. Usually, slightly excess amounts of aminoleads were used (1.5 equiv.). The products were purified by column chromatography on silica gel. [b]Determined by 270 MHz ^{1}HNMR. [c]The reaction was carried out at room temperature. [d]Isolated yield after benzoylation of a mixture of amino alcohols. [e]The reaction was carried out under reflux.

$$Et_2NLi + R_3PbBr \xrightarrow{-LiBr} R_3PbNEt_2 \quad (1)$$

1 : R = Et
2 : R = nBu

$$nBu_3PbNEt_2 + H_2NCH_2Ph \longrightarrow nBu_3PbNHCH_2Ph + HNEt_2 \quad (2)$$

2 3

The aminolysis of the mono-substituted epoxides **4**, **7**, and **10** proceeded smoothly at room temperature, and amino alcohols **6**, **9**, and **11** were obtained either predominantly or as a sole product. On the other hand, the reaction of Et_2AlNEt_2[4] with **4** or with **7** gave a mixture of amino alcohols with low regioselectivity; with **4**, 5:6=43:57; with **7**, 8:9=44:56. It is reported that the reaction of trimethyltin amides with **4** gives **5** with high regioselectivity.[5] Therefore, the regioselectivity of Me_3Sn reagents is completely opposite in comparison with the selectivity of the lead reagent. We repeated the aminolysis with Bu_3Sn reagent. The reaction of **4** with nBu_3SnNEt_2 in CH_2Cl_2 under reflux for 8 hours afforded a mixture of **5** and **6** in a ratio of 20:80 in 21% yield; the regioselectivity is similar to that of the lead reagent. The reason for the difference between Me_3Sn and Bu_3Sn reagent is not clear at present. The reaction of the di-substituted epoxide **12** with **1** was slow at room temperature, but the yield of **13** could be increased upon heating. Always, **13** was obtained as a sole product. Cyclohexene *oxide (**14**) undergoes deprotonation readily upon treatment with lithium diethylamide,*[2] *whereas no hydrogen* abstraction took place with aminolead compounds, **1** and **3**. The stereochemistry of the amino alcohol **15** (NR_2=$NHCH_2Ph$) was determined by the coupling constant of the ring methine protones.[10] The reaction of the tri-substituted epoxide **16** with **1** was sluggish even under reflux for 42 hours, however the reaction with **3** under reflux for 72 hours gave **17** (NR_2=$NHCH_2Ph$) in moderate yield along with trace amounts of the regio-isomer. Unfortunately, the aminolysis of the tetra-substituted epoxide **18** with **3** was very sluggish, and only trace amounts of the desired product was detected after a prolonged reflux.

The following procedure for the aminolysis of styrene oxide is representative. To a solution of **1** (1.5 mmol) in 2 ml of dry ether was added **4** (1 mmol) at room temperature via a syringe under nitrogen. The mixture was stirred at this temperature for 30 min. The reaction was quenched with 6M NaOH. The organic layer was separated and dried over anhyd. K_2CO_3. The products were purified by column chromatography on silica gel with n-hexane/ethyl acetate as an eluent.

In conclusion, we revealed that the ring-opening reaction of epoxides with aminolead compounds proceeded always with the type A regioselectivity in good to high yields. Regioselectivity of epoxide ring opening is often dependent upon not only reagent-types but also substrate structures. As stated above, it is not so easy to predict the

regioselectivity on the ring opening of **4** with ordinary reagents; the Al-reagent gives a 1:1 mixture; type B opening is observed with the Me_3Sn-reagent while type A is obtained with the Bu_3Sn-reagent. However, the lead reagents always produce type A opening regardless of substrate structures. Such predictable regioselectivity is very important to organic synthesis.

References and Notes

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10) ^{1}H-NMR (400 MHz) of **15** (NR_2=$NHCH_2Ph$); δ in $CDCl_3$ 3.08 (C<u>H</u>OH) (ddd, J=4.0, <u>9.4</u>, 9.4 Hz) and 2.35 (C<u>H</u>N) (ddd, J=4.0, <u>9.4</u>, 11,4 Hz). The coupling constant, J=9.4 Hz, indicates trans-geometry.

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