Regiochemical Control in the Reductive Cleavage of 2-Alkylated Oxetanes by Use of Trialkylaluminums. Tertiary Organolithiums with γ-Oxy Functionality

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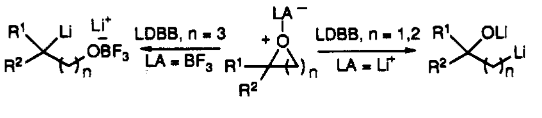
Summary: Whereas 2,2-dialkylated oxetanes are cleaved by lithium 4,4′-di-*tert*-butylbiphenylide to provide the primary organolithium–tertiary oxyanions, the same reaction in the presence of trialkylaluminums gives exclusively the 3-lithio-3,3-disubstituted propoxides, which are trapped by carbonyl compounds in moderate yields.

Epoxides undergo reductive cleavage by lithium 4,4′-di-*tert*-butylbiphenylide (LDBB) in THF at -78 °C to yield β-lithioalkoxides.[1] Oxetanes require a temperature of 0 °C to undergo cleavage to γ-lithioalkoxides.[2] The latter have been shown to be exceptionally useful in the one-pot synthesis of spiroketals.[3] In both cases, the 2-alkylated heterocycles cleave so as to yield predominantly the less substituted organolithium, apparently because the greater stability of the most branched oxyanion outweighs the greater stability of the most substituted radical in the proximate ring-opened product.[4] Tetrahydrofurans, which are reductively cleaved only slowly even at reflux and then in a synthetically useless mode, are cleaved readily at -78 °C in the presence of boron trifluoride; furthermore, the direction of cleavage is the opposite of those of epoxides and oxetanes in the absence of boron trifluoride (Scheme I, LA = Lewis acid, R^1 and/or R^2 = alkyl).[5]

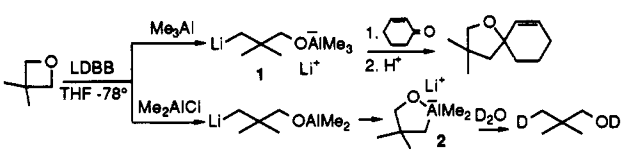
It occurred to us that it may be possible to prepare the useful γ-lithioalkoxides in a regiocontrolled manner from 2-alkylated oxetanes by performing the reductive lithiation in the absence or presence of a strong Lewis acid. The potential products in the latter case, particularly tertiary organolithiums bearing the γ-oxy functionality, are not available by other methods.[6] Since the radical anion reducing agents are prepared in THF, the Lewis acid should meet the requirements that it should selectively complex oxetanes in the presence of the THF solvent and/or its Lewis acid complex with oxetane should undergo C–O bond cleavage faster than its complex with THF. In addition, the Lewis acid must survive the very strong reducing conditions exerted by LDBB.

We now report that trialkylaluminums, when added dropwise to a solution of an oxetane (0.2 M) and LDBB (0.4 M) in THF at -78 °C effect the cleavage of the oxetane with very high chemoselectivity (>99:1 for 3,3-dimethyloxetane), yielding the corresponding lithium (3-lithiopropoxy)trialkylaluminate (1).[7] The Me_2AlCl - LDBB system, although also highly chemoselective, presumably leads to an intermediate that undergoes rapid cyclization to a 5-membered ring ate complex 2, which was found to be completely unreactive in 1,2-additions to aldehydes and 1,4-addition to 2-cyclohexenone[8] and could only be trapped with D_2O (Scheme II). As in the case with the ring-opened product from the THF·BF_3 complex,[5] 1 must be used immediately since it gradually becomes inactive presumably due to organoaluminate formation.

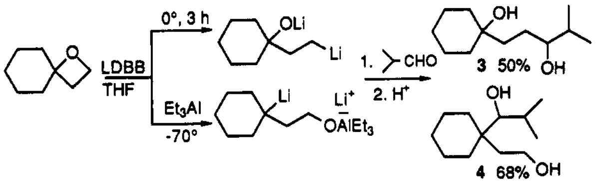
Scheme I



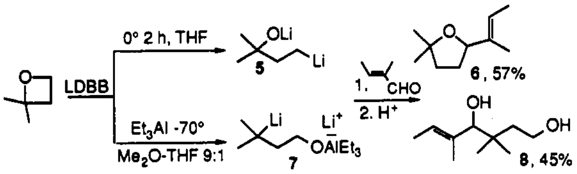
Scheme II



Scheme III



Scheme IV



The reductive lithiation of 2-octyloxetane in the LDBB–Me_3Al system did indeed produce predominantly the most substituted organolithium compound. The secondary and the primary organolithium species were generated in a ratio of 4:1 and yielded with aldehydes the corresponding diols as an inseparable diastereomeric mixture in ~40% yield along with the protonation products, 1- and 3-undecanol. This regioselectivity compares unfavorably with the 15:1 ratio found in the 2-methyltetrahydrofuran·BF_3–LDBB system.[5]

Gratifyingly, 2,2-dialkyloxetanes undergo reductive cleavage by LDBB in the presence of Me_3Al or Et_3Al at -78 °C almost exclusively (>97:3) to tertiary organolithiums. Since the reductive lithiation of 2,2-dialkyloxetanes by LDBB at 0 °C for 1–4 h (depending on substituents) results in predominant formation of the primary organolithium (the minor tertiary one does not survive at 0 °C), full regiochemical control can be attained, yielding, for example, in the case of 1-oxaspiro[3.5]nonane, either 3 or 4 (Scheme III).[9]

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[1] (a) Bartmann, E. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 653. (b) Cohen, T.; Jeong, I.-H.; Mudryk, B.; Bhupathy, M.; Awad, M. M. A. *J. Org. Chem.* **1990**, *55*, 1528.

[2] Mudryk, B.; Cohen, T. *J. Org. Chem.* **1989**, *54*, 5657.

[3] Mudryk, B.; Shook, C.; Cohen, T. *J. Am. Chem. Soc.* **1990**, *112*, 6389.

[4] Dorigo, A.; Houk, K.; Cohen, T. *J. Am. Chem. Soc.* **1989**, *111*, 8976.

[5] Mudryk, B.; Cohen, T. *J. Am. Chem. Soc.* **1991**, *113*, 1866.

[6] The generation of a 3-lithiobutoxide starting from methyl 3-chlorobutanoate has been reported: Barluenga, J.; Flórez, J.; Yus, M. *Synthesis* **1985**, 846.

[7] BF_3-assisted cleavage of oxetane (0.6 M) in THF at -78 °C by LDBB gave products derived from cleavage of both ethers in ≃ 1:1 ratio; $ZnMe_2$ and $Ti(OPr)_4$ underwent reduction by LDBB.

[8] $Ni(acac)_2$ (5 mol %) was used as a catalyst; see: Ashby, E. C.; Heinsohn, G. *J. Org. Chem.* **1974**, *39*, 3297.

[9] All products were chromatographically pure and characterized by ^1H NMR, ^{13}C NMR, and HRMS.

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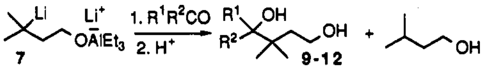
Table I. Reactions of 7 with Aldehydes and Ketones



R^1, R^2	diol, yield (%)[a]	yield of 3-methylbutanol (%)
i-Pr, H	9, 52 (59)	16 (15[b])
t-Bu, H	10, 56	15[b]
$-(CH_2)_5-$	11, (43)	40[b]
Ph, H	12, 38[c]	20[b]

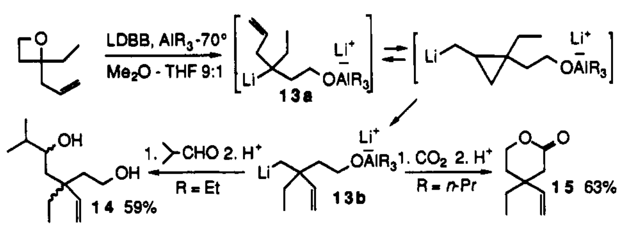
[a] Isolated yields; yields in parentheses refer to 9:1 Me_2O–THF system. [b] GC yields. [c] $PhCH_2OH$ (30%) and $CH_2{=}C(CH_3)CH_2CH_2OH$ (31%) were also isolated.

2,2-Dimethyloxetane[10] undergoes reductive lithiation by LDBB at 0 °C for 2 h to form lithium 4-lithio-2-methyl-2-butoxide (**5**), which was trapped with (*E*)-2-methyl-2-butenal to give, after acidic treatment, the natural product, (±)-ocimenoyl oxide (**6**)[11] in 57% yield. The same oxetane, however, when subjected to reductive cleavage in the Et_3Al–LDBB system followed by treatment with this aldehyde gave the expected diol **8** at first in only 27% yield along with 3-methylbutanol (50%) resulting from the protonation of the tertiary organolithium **7**. The yield of **8** and analogues in the latter process could be improved by changing both the solvent and the electrophile,[12] since both were determined to be proton sources. Dimethyl ether–THF (9:1) was found to be advantageous over pure THF particularly when easily enolizable carbonyl compounds were employed, as exemplified by the increase in the ratio of **8** to 3-methylbutanol from 0.5 to 1.5 and in the yield of **8** to 45% (Scheme IV).

Table I lists the yields of the diols **9**–**12** and 3-methylbutanol obtained by trapping the organolithium **7** with some carbonyl compounds.

The moderate yields of the diols **9**–**12** could result not only from the protonation of **7** but also from other side reactions such as the reduction of the carbonyl compound by **7** to an alcohol which effectively competes with the nucleophilic attack at the carbonyl group in the case of benzaldehyde. The delivery of the β-hydride to the carbonyl carbon has previously been observed for lithium 2-lithioethoxide and is well known for Grignard reagents.[1b]

Scheme V



2-Allyl-2-ethyloxetane[13] in the LDBB–R_3Al system (R = Et or *n*-Pr, −70 °C/Me_2O–THF 9:1) gave an interesting result. It instantaneously underwent the expected exclusive cleavage of the most substituted C–O bond. However, the diol **14** and lactone **15** that were generated by immediate quenching of the intermediate with isobutyraldehyde and CO_2, respectively, followed by the acidic workup, did not result from the reaction of these electrophiles with the initially formed tertiary organolithium **13a** but rather with the rearranged primary organolithium **13b** (Scheme V). All reported cases of homoallylic rearrangements of organolithiums[14] require many hours at room temperature or higher.[15] A systematic study of this unusual rate acceleration is in progress.

Acknowledgment. We thank the National Science Foundation for financial support.

Supplementary Material Available: Sample procedures for the reductive cleavages of 2,2-disubstituted oxetanes in the LDBB–R_3Al system and the spectral data of the products (3 pages). Ordering information is given on any current masthead page.

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[10] Prepared in 65% yield by sequential treatment of 2-chloropropionyl chloride with MeMgBr (2 equiv in ether) and NaH in DMSO, condensing the product in a cold trap in vacuo.

[11] Strickler, H.; Kovacs, E. *Helv. Chim. Acta* **1966**, *49*, 2055.

[12] Since reaction of *t*-BuLi with (*E*)-2-methyl-2-butenal in THF gave a high yield of the addition product, we conclude that triethylaluminum, by complexing the aldehyde oxygen atom, significantly enhances the acidity of its γ-proton.

[13] Prepared in 72% overall yield by addition of allylmagnesium bromide to commercial 1-chloro-3-pentanone followed by cyclization of the tertiary alcohol in the NaH/Et_2O–DMSO 95:5 system.

[14] Review: Grovenstein, E., Jr. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 313–332. Recent examples: Grovenstein, E., Jr.; Black, K. W.; Goel, S. C.; Hughes, R. L.; Northrop, J. H.; Streeter, D. L.; VanDerveer, D. *J. Org. Chem.* **1989**, *54*, 1671.

[15] Maercker, A.; Weber, K. *Liebigs Ann. Chem.* **1972**, *756*, 43.

Carboalumination/Transmetalation/Conjugate Addition: A New Catalytic Cu(I)-Induced Process for the 1,4-Delivery of Vinylic Groups to Enones

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Summary: Exposure of vinylalanes, derived from carbometalations of 1-alkynes, to catalytic amounts of $CuCN{\cdot}2LiCl$ in the presence of an α,β-unsaturated carbonyl group affords products of vinylic ligand transfer in a 1,4-manner.

Transmetalations of a variety of organometallic intermediates, mediated by preformed higher order cyanocuprates, have only recently begun to expand the scope of the intrinsic chemistry of various metals.[1] Thus, vinylic stannanes,[2] tellurides,[3] and zirconates[4] readily exchange

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[1] For some examples, see: Lipshutz, B. H. *Synlett* **1990**, 119.

[2] Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641.

[3] Comasseto, J. V., Berriel, J. N. *Synth. Commun.* **1990**, *20*, 1681.

[4] Lipshutz, B. H.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 7440. Babiak, K. A.; Behling, J. R.; Dygos, J. H.; McLaughlin, K. T.; Ng, J. S.; Kalish, V. J.; Kramer, S. W.; Shone, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 7441.

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