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(*S*)-(+)-$CH_3CH(OH)(CH_2)_5CH_3$, 6169-06-8; (*R*)-glyceraldehyde acetonide, 15186-48-8; 4(*R*)-(1(*S*)-hydroxy-2-(trimethylsilyl)-hept-2(*Z*)-en-1-yl)-2,2-dimethyl-1,3-dioxolane, 102357-26-6; (*S*)-(−)-2-acetoxyheptanol, 75584-25-7.

Supplementary Material Available: Spectral data [IR, ^1H and ^{13}C NMR, and $[\alpha]_D$] for **2–5** and their derivatives (3 pages). Ordering information is given on any current masthead page.

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Calcium in Liquid Ammonia for the Reduction of Benzyl Ethers. Mechanistic Clues Derived from Chemoselectivity Studies

Summary: Extremely high selectivity was provided by calcium in liquid ammonia in the cleavage of the benzylic carbon–oxygen bond in benzyl ethers containing various other functionalities. Results of controlled experiments indicate that the selectivities offered by the $Ca \rightarrow Ca^+ + e^-$ and the $Ca^+ \rightarrow Ca^{2+} + e^-$ processes are 4.6 and 47 times greater, respectively, than that afforded by the $Li \rightarrow Li^+ + e^-$ process.

Sir: Dissolving metals in liquid ammonia have been used extensively to perform reductions for decades.[2a,b,c] The most notable systems are the Birch reduction with sodium, ammonia, and alcohol and the Benkeser reduction with lithium in alkylamines.[3] Calcium metal has also been utilized occasionally.[4] However, studies on its chemoselectivity in reduction have not been carried out.

In general, calcium is considered to be less reactive than the alkali metals.[2d] Its lower oxidation potential in ammonia than that of lithium, sodium, or potassium[5] makes it a more likely candidate for selective reduction of substrates with multiple functional groups. Calcium has two different oxidation potentials in aqueous solution[6] based on the processes $Ca \rightarrow Ca^+ + e^-$ and $Ca^+ \rightarrow Ca^{2+} + e^-$. If similar differences exist in solutions of calcium in liquid ammonia, we deemed it possible to obtain a selective reduction of organic compounds having multiple reduction sites.

The benzyl group is commonly used for protecting the hydroxyl moiety. The resulting benzyl ethers are stable to most acidic, basic, and oxidative conditions.[7] It is also known that the benzyl ether moiety can be readily cleaved by dissolving metals.[7a] Consequently, we chose substrates containing a benzyloxy group in conjunction with other functionalities for the study of chemoselective reduction with calcium metal in liquid ammonia. The results are listed in Table I.

A typical procedure includes the addition of a substrate in a small amount of anhydrous ether or tetrahydrofuran to a blue solution of calcium metal in liquid ammonia. The concentration of the substrate to ammonia was 0.05–0.10 M. After 2 h of being stirred at refluxing ammonia temperature, the reaction was quenched with saturated aqueous ammonium chloride solution followed by a normal workup procedure. The products were analyzed by capillary GLC and purified by column chromatography. We have tried various conditions for the reductions and found that optimal selectivity was obtained when 2.0–2.2 equiv of calcium metal were employed.[8] Use of larger quantities of calcium resulted in lowered selectivity. With shorter reaction times, debenzylation was not always complete.

The benzyloxy alkyne **1a** contains two functional groups, a benzyl ether moiety and a nonterminal carbon–carbon triple bond,[9a,b] that can be reduced under dissolving metal conditions. We found that calcium preferentially reduced the benzyl ether moeity, providing the hydroxy alkyne **1b** in 90% yield. Under similar conditions, aromatic rings such as a phenyl group,[9c] directly attached to an alkyl chain, or a furan nucleus[9d] are resistant to reduction, as evidenced in the conversion of **2a** to **2b** in quantitative yield and **3a** to **3b** in 69% yield. The lower yield of **3b** was due primarily to the instability of the furan ring toward the workup conditions.[10] In the cases where the benzyl ether shares a common oxygen with a 2-furfuryl[9e] or allylic ether,[9f] as in **3a** and **4a**, the only reduction products detected came from cleavage of the benzylic carbon–oxygen bond. In the conversion of **4a** to **4b** and **5a** to **5b**, the carbon–carbon bonds in the cyclobutyl ring and the cyclopropyl ring and the carbon–oxygen bond in the 1-cyclopropylalkoxyl moiety are not cleaved. The reduction of **6a** to **6b** in 93% yield indicates that the oxygen–silicon bond in the *tert*-butyldimethylsilyl ether moiety is resistant to the reduction and workup conditions.

For substrates containing a benzyloxy function and another readily reducible moiety, we determined the susceptibilities of the respective functional groups to cleavage from the ratio of the reduced products. Reduction of the epoxybenzyl ether **7a** resulted in complete cleavage of the benzylic carbon–oxygen bond and partial scission of the oxirane ring[9g,h] at the less substituted carbon–oxygen bond. The alcohols **7b** and **7c** were obtained in 1:1 ratio, indicating that the reduction selectivity for the benzyl ether to the oxirane was on the order of 2:1. Poor selectivity between phenylsulfonyl[9i] and benzyloxy moieties was also found in the reduction of **8a**. Benzene and toluene were detected in the ratio 1:1.6. Even though calcium is a mild reducing agent, we did not find any selectivity between benzyl ether and thiophenyl[9i] or ketone[9j] moieties. The

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(1) Research Fellow of the Alfred P. Sloan Foundation, 1986–1988.

(2) (a) Johnstone, R. A. W.; Wilby, A. H.; Entwhistle, I. D. *Chem. Rev.* **1985**, *85*, 129. (b) Smith, M. In *Reduction: Techniques and Applications in Organic Synthesis*; Augustine, R. L., Ed.; Marcel Dekker: New York, 1968; Chapter 2. (c) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin: Menlo Park, CA, 1972; Chapter 3. (d) See ref 2c, p 191.

(3) Kaiser, E. M. *Synthesis* **1972**, 391.

(4) (a) Benkeser, R. A.; Belmonte, F. G. *J. Org. Chem.* **1984**, *49*, 1662. (b) Benkeser, R. A.; Belmonte, F. G.; Kang, J. *J. Org. Chem.* **1983**, *48*, 2796. (c) Benkeser, R. A.; Kang, J. *J. Org. Chem.* **1979**, *44*, 3737.

(5) (a) Pleskov, V. A.; Monossohn, A. M. *Acta Physicochim. URSS* **1935**, *2*, 615. (b) Pleskov, V. A. *Zh. Fiz. Khim.* **1937**, *9*, 12; *Acta Physicochim. URSS* **1937**, *6*, 1. (c) Lagowski, J. J.; Moczygemba, G. A. In *The Chemistry of Nonaqueous Solvents*; Lagowski, J. J., Ed.; Academic: New York, 1967; Vol. 2, p 341.

(6) (a) *CRC Handbook of Chemistry and Physics*, 67th ed.; Weast, R. C., Ed.; CRC: Boca Raton, FL; 1986–1987, p D-152. (b) Antelman, M. S.; Harris, F. J. Jr. *The Encyclopedia of Chemical Electrode Potentials*; Plenum: New York, 1982; pp 102, 103.

(7) (a) Greene, T. W. *Protective Groups in Organic Synthesis*; Wiley: New York, 1981; pp 29–31 and references therein. (b) Reese, C. B. In *Protective Groups in Organic Chemistry*; McOmie, J. F. W., Ed.; Plenum: New York, 1973; pp 98–100.

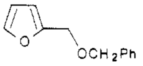
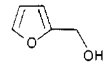
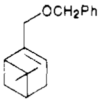
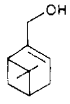
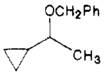
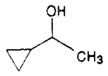
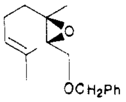
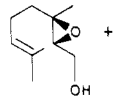
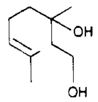
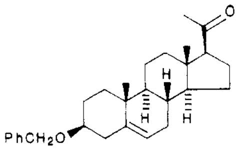
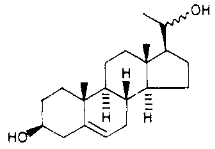
(8) For example, 2.0–2.2 mmol of calcium was used for the reduction of 1.0 mmol of substrate with two reducible functional groups.

(9) For the reduction of this moiety under dissolving metal conditions, see: (a) House, H. O.; Kinloch, E. F. *J. Org. Chem.* **1974**, *39*, 747. (b) see ref 4a. (c) see ref 3 and 4b. (d) Bedenbaugh, A. O.; Bedenbaugh, J. H.; Adkins, J. D.; Bergin, W. A. *J. Org. Chem.* **1970**, *35*, 543. (e) Yamakawa, K.; Satoh, T. *Chem. Pharm. Bull.* **1978**, *26*, 3704. (f) Hallsworth, A. S.; Henbest, H. B.; Wrigley, T. I. *J. Chem. Soc.* **1957**, 1969. (g) Hallsworth, A. S.; Henbest, H. B. *J. Chem. Soc.* **1957**, 4604. (h) Brown, H. C.; Ikegami, S.; Kawakami, J. H. *J. Org. Chem.* **1970**, *35*, 3243. (i) Truce, W. E.; Tate, D. P.; Burdge, D. N. *J. Org. Chem.* **1960**, *25*, 2872. (j) Sondheimer, F.; Mancera, O.; Rosenkranz, G.; Djerassi, C. *J. Am. Chem. Soc.* **1953**, *75*, 1282.

(10) Acheson, R. M. *An Introduction to the Chemistry of Heterocyclic Compounds*; Wiley: New York, 1976; p 126.

0022-3263/86/1951-4731$01.50/0

Table I. Reduction of Benzyl Ethers Containing Various Functional Groups with 2.2 Equivalents of Calcium Metal in Liquid Ammonia

entry	benzyl ether	products	yield, %
1	$CH_3C{\equiv}CCH_2CH_2OCH_2Ph$ **1a**	$CH_3C{\equiv}CCH_2CH_2OH$ **1b**	90
2	$PhCH_2CH_2CH_2OCH_2Ph$ **2a**	$PhCH_2CH_2CH_2OH$ **2b**	100
3	 **3a**	 **3b**	69
4	 **4a**	 **4b**	90
5	 **5a**	 **5b**	96
6	t-$BuMe_2SiOCH_2CH_2OCH_2Ph$ **6a**	t-$BuMe_2SiOCH_2CH_2OH$ **6b**	93
7	 **7a**	 +  **7b** 1:1 **7c**	86
8	$PhSO_2CH_2(CH_2)_2CH_2OCH_2Ph$ **8a**	PhH + $PhCH_3$ 1:1.6	
9	$PhSCH_2(CH_2)_2CH_2OCH_2Ph$ **9a**	(PhSH + PhSSPh) + $PhCH_3$ 1:1	
10	 **10a**	 **10b**	72

ratio of a mixture of thiophenol and diphenyl disulfide[11] to toluene, from the reduction of **9a**, was 1:1, while **10b** was the only major product from the reduction of **10a**.

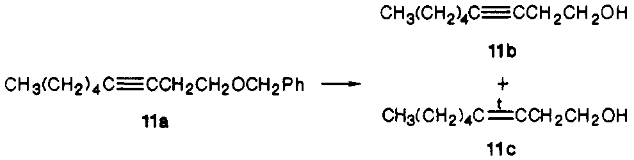
For this complicated calcium–ammonia reduction system, in which calcium metal undergoes two successive monoelectron oxidations, we explored the possibility that each of these oxidation steps provides a different selectivity in the reduction of a bifunctional compound. Consequently a series of controlled experiments on the reduction of **11a** were performed and the results are listed in Table II.

In experiment 1, although electrons from 1.0 equiv of calcium are theoretically sufficient to reduce one functional group, 92% of the starting material was recovered. Similarly, when the dibenzyl ether of 1,4-butanediol, a molecule with high symmetry, was subjected to the same reduction conditions, we were able to recover 88% of the starting material. These experiments indicate that electrons are distributed almost equally between the two functional groups in the substrate and that each functional group receives only one electron, which is insufficient for reduction.

From experiments 2 and 3, we obtained different ratios of **11b** to **11c** when different metals, calcium or lithium, were used. We assumed that the Ca → $Ca^+ + e^-$ process is more easily achieved than the $Ca^+ \rightarrow Ca^{2+} + e^-$ process.[6] After half an hour, a relatively short time interval, the electrons involved in the reduction would come primarily from the Ca → $Ca^+ + e^-$ process, which offers higher selectivity than the Li → $Li^+ + e^-$ process by a factor of 4.6.

In experiment 4, 2.1 equiv of calcium were employed. Since each functional group in the substrate initially receives an electron from the electron pool, as shown in experiment 1, and the electrons from the Ca → $Ca^+ + e^-$ process are assumed to be more readily released than those from the $Ca^+ \rightarrow Ca^{2+} + e^-$ process,[6] they are distributed among the two functional groups first. The second equivalent of electrons necessary for a functionality to be reduced would then have to come from the $Ca^+ \rightarrow Ca^{2+}$

Table II. Selective Reduction of Benzyloxy Alkyne 11a to Hydroxy Alkyne 11b and Hydroxy Alkene 11c with Calcium or Lithium in Liquid Ammonia.



$$\underset{\textbf{11a}}{CH_3(CH_2)_4C{\equiv}CCH_2CH_2OCH_2Ph} \longrightarrow \underset{\textbf{11b}}{CH_3(CH_2)_4C{\equiv}CCH_2CH_2OH} + \underset{\textbf{11c}}{CH_3(CH_2)_4C\overset{t}{=}CCH_2CH_2OH}$$

expt	metal	equiv	time, h	product ratio **11b**/**11c**	yield, %
1	Ca	1.0	4	*a*	*b*
2	Ca	4.2	0.5	5.5:1	92
3	Li	4.2	0.5	1.2:1	90
4	Ca	2.1	2	13.5:1	93
5	Li	4.2	2	1:3.5	90
6	Ca	8.1	3	1:1.1	81
7	Li	8.6	3	1:15.4	82

[a] In this reaction, 92% of the starting material, **11a**, was recovered and trace amounts of **11b** were detected by capillary GLC. [b] Trace.

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[11] The diphenyl disulfide came from the oxidation of thiophenol with oxygen in air, see: Barrett, G. C. In *Comprehensive Organic Chemistry*; Barton, D., Ed.; Pergamon: New York, 1979; Vol. 3, pp 3, 4.

+ e$^-$ process. We believe that this process is more difficult[6], and thus offers better selectivity. Indeed the high selectivity based on the ratio of **11b**/**11c** (13.5:1) obtained from this experiment compared to that obtained by using lithium (1:3.5) in experiment 5 agrees with our prediction. Comparison of these ratios indicates that the selectivity obtained with calcium is 47 times greater than that obtained with lithium for the reduction of **11a**.

In experiments 6 and 7, although excess of both calcium and lithium were used over a longer reaction time, we found that reduction of the alkyne functionality was significantly less for calcium than for lithium. This indicates that calcium is indeed a milder reducing agent than lithium. Therefore consideration must also be given to the origin of the electrons used in dissolving metal reductions.

In summary, we found that calcium metal in liquid ammonia offers better selectivity than lithium for debenzylation of substrates containing a benzyl ether moiety in conjunction with other functionalities.[12] Our experiments clearly indicate that control of the amount of calcium, in order to utilize the electrons from the Ca$^+$ → Ca^{2+} + e$^-$ process, is critical for obtaining very high selectivity.

Acknowledgment. J.R.H. is grateful to Professor Eugene E. van Tamelen (Stanford University) for suggesting that calcium could prove to be a selective reducing agent. We also thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, the American Heart Association—Maryland Affiliate, Inc., and the Research Corporation for the support of this research.

Registry No. **1a**, 98689-60-2; **1b**, 10229-10-4; **2a**, 70770-06-8; **2b**, 122-97-4; **3a**, 16361-14-1; **3b**, 98-00-0; **4a**, 104948-20-1; **4b**, 515-00-4; **5a**, 104948-21-2; **5b**, 765-42-4; **6a**, 104948-22-3; **6b**, 102229-10-7; **7a**, 104948-23-4; **7b**, 62960-04-7; **7c**, 27415-10-7; **8a**, 104948-24-5; **9a**, 64740-57-4; **10a**, 104948-25-6; **10b**, 59042-34-1; **11a**, 104948-26-7; 11b, 31333-13-8; 11c, 10339-61-4; 12a, 104975-83-9; 12b, 104948-27-8; PhCH$_3$, 108-88-3; PhSSPh, 882-33-7; PhSH, 108-98-5; benzene, 71-43-2.

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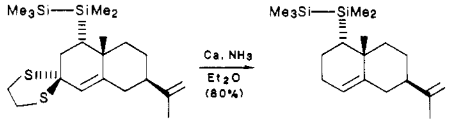
[12] Calcium in liquid ammonia also successfully reduced **12a**, affording **12b** in 80% yield. In contrast, use of sodium in liquid ammonia gave **12b** in only 7% yield with the major product coming from the cleavage of the silicon–silicon bond.



12a **12b**

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Stereoselective Synthesis of 2-[(Trimethylsilyl)methyl]-1,3-butadienes†

Summary: Allylborane **3**, readily prepared from 1,2-bis(trimethylsilyl)-2,3-butadiene by hydroboration with 9-borabicyclo[3.3.1]nonane, smoothly condenses with aldehydes and ketones to afford, after basic or acidic workup, a variety of 2-[(trimethylsilyl)methyl]-1,3-butadienes with the dienes derived from aldehydes having high isomeric purity.

Sir: The synthetic applications of 2-[(trimethylsilyl)methyl]-1,3-butadienes are rapidly expanding.[1] The parent diene exhibited extremely high regioselectivity in the Lewis acid catalyzed Diels-Alder reaction.[1c] It has also been utilized to introduce an isoprenyl group to an electrophilic carbon atom.[1d] However, only a few synthetic methods for these dienes have been reported.[1d,2] We describe here a simple and stereoselective route to these compounds.

It was reported that condensations of trimethylsilyl-substituted allylic boranes with aldehydes showed very high diastereoselectivity.[3] In several cases, the resulting β-trimethylsilyl alcohols contained essentially only the *RS*/*SR* pair (>99%). Treatment of these alcohols with potassium hydride provided the (*Z*)-dienes (98% *Z*) after syn elimination of trimethylsilyl oxide. The (*E*)-dienes (99% *E*) were also obtained by using a catalytic amount of concentrated sufuric acid to induce anti elimination. The ability to obtain both isomers from the same intermediate is especially interesting. We envisioned that by properly attaching an additional (trimethylsilyl)methyl group to the allylic borane, 2-[(trimethylsilyl)methyl]-1,3-butadienes could thus be synthesized. A summary of our reaction sequence is outlined in Scheme I.

Hydroboration of 1,2-bis(trimethylsilyl)-2,3-butadiene (**2**), readily prepared from **1** (40% yield) according to the reported procedure,[4] with 9-borabicyclo[3.3.1]nonane[5] afforded the desired allylborane **3**. The geometry of the double bond in **3** has not been determined.[6] Condensations of **3** with aldehydes and cyclohexanone proceeded smoothly and provided 2-[(trimethylsilyl)methyl]-1,3-butadienes after either basic or acidic workup (Table I). The dienes derived from aldehydes had high isomeric purity (≥97%). Apparently, high diastereoselectivity was also achieved during the condensation step to form **4**. In each case, by simply changing the workup condition, either the *E* or the *Z* isomer of the diene was obtained.

The geometry of the double bond in **5a** and **6a** was determined by comparing the ^{1}H NMR spectra of these two isomers with the reported data.[2c] The chemical shift of the vinylic hydrogen at C(2) of **5a** (δ 6.73) is 0.44 ppm downfield from that of the corresponding hydrogen of **6a** (δ 6.29) and thus allowed easy identification. Such a difference of chemical shifts was also observed for dienes derived from other aldehydes and was utilized to tentatively assign their geometry.[7]

Although cyclohexanone was found to react with **3** at refluxing temperature of THF, 2-pentanone failed to show any significant reactivity even after prolonged heating.

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† Dedicated to Professor George Zweifel on the occasion of his 60th birthday.

[1] (a) Sakurai, H.; Hosomi, A.; Saito, M.; Sasaki, K.; Iguchi, H.; Sasaki, J.-i.; Araki, Y. *Tetrahedron* **1983**, *39*, 883–894. (b) Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1985**, *26*, 5175–5178. (c) Hosomi, A.; Iguchi, H.; Sasaki, J.; Sakurai, H. *Tetrahedron Lett.* **1982**, *23*, 551–554. (d) Hosomi, A.; Saito, M.; Sakurai, H. *Tetrahedron Lett.* **1979** *20*, 429–432.

[2] (a) Wilson, S. R.; Phillips, L. R.; Natalie, K. J. *J. Am. Chem. Soc.* **1979**, *101*, 3340–3344. (b) Vedejs, E.; Campbell, J. B., Jr.; Gadwood, R. C.; Rodgers, J. D.; Spear, K. L.; Watanabe, Y. *J. Org. Chem.* **1982**, *47*, 1534–1546. (c) Djahanbini, D.; Cazes, B.; Gore, J. *Tetrahedron* **1985**, *41*, 867–873.

[3] (a) Tsai, D. J. S.; Matteson, D. S. *Tetrahedron Lett.* **1981**, *22*, 2751–2752. (b) Yamamoto, Y.; Saito, Y.; Maruyama, K. *J. Organomet. Chem.* **1985**, *292*, 311–318.

[4] Montury, M.; Psaume, B.; Gore, J. *Tetrahedron Lett.* **1980**, *21*, 163–166.

[5] Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1977**, *132*, 9–27.

[6] The existence of a rapid allylic rearrangement for allylic borane[5] could allow either the *E* or the *Z* isomer or both to be the reacting species regardless of the geometry of the double bond in 3.

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