was stirred for 2 h and then diluted with ether, washed with water, saturated sodium bicarbonate, and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed (5:1 hexanes/EtOAc) and gave 78 mg (94%) of **23**: $[\alpha]^{25}_D$ = +19.2° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1722, 697 cm^{-1}; ^1H NMR (400 MHz) δ 0.85 (m, 6 H, 2 × CH_3), 1.18–1.32 (b m, 28 H), 1.53 (m, 2 H, CH_2), 1.63 (m, 2 H, CH_2), 2.48 (m, 1 H, CHO), 3.65 (m, 2 H, CHO and OH), 3.92 (m, 1 H, CHO), 4.41 (AB, J_{gem} = 12 Hz, 1 H, $ArCH_2O$), 4.58 (AB, J_{gem} = 12 Hz, 1 H, $ArCH_2O$), 5.15 (m, 2 H, $ArCH_2OCO$), 7.3 (m, 10 H, Ar); mass spectrum *m/e* 553, 445, 427, 337, 319, 301. Anal. Calcd for $C_{36}H_{56}O_4$: C, 78.2; H, 10.21. Found: C, 78.01; H, 10.21.

(2*S*,3*S*,5*S*)-2-Hexyl-3-hydroxy-5-(benzyloxy)hexadecanoic Acid (24). To a solution of 475 mg (0.86 mmol) of **23** in 9 mL of ethanol was added 2.6 mL of 1 N sodium hydroxide. The reaction mixture was heated at 50 °C for 4 h, cooled, and then concentrated. The residue was diluted with water, acidified with 1 N hydrochloride acid, and extracted with ethyl acetate. The organic solution was washed with brine, dried ($MgSO_4$), and concentrated. The crude product was chromatographed (1:1 hexanes/EtOAc, 9:1 chloroform/methanol) and gave 392 mg (99%) of **24**: $[\alpha]^{25}_D$ = +12.06° (*c* 0.92, $CHCl_3$); IR ($CHCl_3$) 1747, 1572, 698 cm^{-1}; ^1H NMR (400 MHz) δ 0.87 (m, 6 H, 2 × CH_3), 1.1–1.39 (b, 32 H, CH_2's), 1.5–1.7 (b d, 2 H), 2.3 (b s, 1 H, CHCO), 3.7 (b s, 1 H, CHO), 3.9 (b s, 1 H, CHO), 4.5 (b d, 2 H, $ArCH_2$), 7.28 (s, 5 H, Ar); mass spectrum *m/e* 462, 444, 307, 144.

(2′*S*,3*S*,4*S*)-3-Hexyl-4-[2′-(benzyloxy)tridecyl]oxetan-2-one (25). To a solution of 363 mg (0.78 mmol) of **24** in 10 mL of dry pyridine at 0 °C was added 0.19 mL (1.6 mmol) of benzenesulfonyl chloride. After 17 h at 0 °C, the mixture was added to 20 mL of cold brine. This was extracted with ether, dried ($MgSO_4$), and concentrated. The residue was chromatographed (10:1 hexanes/EtOAc) and gave 239 mg (69%) of **25**: $[\alpha]^{25}_D$ = −3.44° (*c* 0.93, $CHCl_3$); IR ($CHCl_3$) 1818, 698 cm^{-1}; ^1H NMR (400 MHz) δ 0.84 (m, 6 H), 1.2–1.5 (b, 27 H), 1.6 (m, 1 H), 1.65 (m, 2 H), 1.75 (m, 1 H), 1.92 (m, 1 H), 2.15 (m, 1 H), 3.25 (m, 1 H, CHCO), 3.52 (m, 1 H, CHO), 4.43 (m, 1 H, CHOCO), 4.44 (AB, J_{gem} = 12 Hz, 1 H, $ArCH_2$), 4.54 (AB, J_{gem} = 12 Hz, 1 H, $ArCH_2$), 7.32 (m, 5 H, Ar); mass spectrum *m/e* 444, 416, 398, 338, 291. Anal. Calcd for $C_{29}H_{48}O_3$: C, 78.33; H, 10.88. Found: C, 78.61; H, 10.80.

(2′*S*,3*S*,4*S*)-3-Hexyl-4-(2′-hydroxytridecyl)oxetan-2-one (7). To a solution of 224 mg (0.505 mmol) of **25** in 7 mL of THF was added 40 mg of 10% Pd/C. The mixture was stirred under 1 atm of hydrogen. After 3 h, the catalyst was removed by filtration and the filtrate was concentrated. The residue was crystallized from hexane and gave 170 mg (95%) of **7**: mp 63–64 °C (hexanes); $[\alpha]^{25}_D$ = −16.3° (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 3545, 1812 cm^{-1}; ^1H NMR (400 MHz) δ 0.9 (m, 6 H, 2 × CH_3), 1.2–1.38 (b, 26 H, CH_2), 1.43 (m, 1 H), 1.5 (m, 1 H), 1.61 (d, 1 H), 1.7–1.91 (m, 3 H), 2.0 (m, 1 H), 3.32 (m, 1 H, CHCO), 3.8 (s, 1 H, CHO), 4.42 (m, 1 H, CHOCO); mass spectrum *m/e* 354, 336, 292, 270, 252, 199, 181. Anal. Calcd for $C_{22}H_{42}O_3$: C, 74.52; H, 11.94. Found: C, 74.73; H, 12.11.

(1*S*,2′*S*,3′*S*)-*N*-[(Phenylmethoxy)carbonyl]-L-leucine 1-[(3′-Hexyl-4′-oxo-2′-oxetanyl)methyl]dodecyl Ester (26). To a solution of 590 mg (2.22 mmol) of (*S*)-*N*-[(benzyloxy)carbonyl]leucine in 6 mL of dichloromethane at 4 °C was added 228 mg (1.11 mmol) of 1,3-dicyclohexylcarbodiimide. After 15 min, the precipitate was removed by vacuum filtration. The filtrate was concentrated, dissolved in 4.5 mL of dimethylformamide, and then added to a solution of 197 mg (0.55 mmol) of 7 and 8 mg of 4-(*N*,*N*-dimethylamino)pyridine in 2.5 mL of dimethylformamide. After 35 min the reaction mixture was diluted with 15 mL of cold water and extracted with ether. The organic solution was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed (6:1 hexanes/EtOAc) and crystallized from pentane and gave 283 mg (85%) of **26**: mp 47.5–48.5 °C, $[\alpha]^{25}_D$ = −23.86° (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 3335, 1842, 1730, 1692, 697 cm^{-1}; ^1H NMR (400 MHz) δ 0.85 (t, 6 H), 0.95 (t, 6 H), 1.2 (b, 27 H), 1.6 (m, 3 H), 1.7 (m, 3 H), 1.96 (m, 1 H), 2.15 (m, 1 H), 3.2 (m, 1 H, CH), 4.25 (m, 1 H, CHO), 4.35 (m, 1 H, CHO), 5.0 (b s, 1 H, OH), 5.08 (d, 1 H, NH), 5.11 (b s, 2 H, $ArCH_2$), 7.32 (s, 5 H); mass spectrum *m/e* 601, 557, 466, 449, 382, 337. Anal. Calcd for $C_{36}H_{59}NO_6$: C, 71.84; H, 9.88; N, 2.33. Found: C, 71.92; H 9.97; N 2.36.

Tetrahydrolipstatin (4). To a solution of 230 mg (0.382 mmol) of **26** in 6 mL of THF was added 28 mg of 10% Pd/C. The mixture was stirred under 1 atm of hydrogen. After 4 h, the catalyst was removed by filtration and the filtrate was concentrated. The residue was treated with 0.36 mL (0.47 mmol) of formic acetic anhydride. After 5 min, the mixture was diluted with ether. The organic solution was washed with saturated sodium bicarbonate and brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from pentane to provide 137 mg (72%) of **4**: mp 42–43 °C (pentane); $[\alpha]^{25}_D$ −34.58° (*c* 0.96, $CHCl_3$); IR ($CHCl_3$) 3340, 1840, 1722, 1710, 1680, 1668 cm^{-1}; ^1H NMR (400 MHz) δ 0.9 (m, 6 H), 1.0 (m, 6 H), 1.2–1.5 (b, 28 H), 1.52–1.9 (m, 5 H), 2.0 (m, 1 H), 2.15 (m, 1 H), 3.22 (m, 1 H), 4.3 (m, 1 H), 4.7 (m, 1 H), 5.12 (m, 1 H), 5.9 (d, 1 H), 8.22 (d, 1 H); mass spectrum *m/e* 495, 480, 292, 57, 29. Anal. Calcd for $C_{29}H_{53}NO_5$: C, 70.26; H, 10.78; N, 2.83. Found: C, 70.05; H, 10.81; N, 2.78.

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Computer-Assisted Mechanistic Evaluation of Organic Reactions. 18. Reductions with Hydrides

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A reaction module for processing the reduction chemistry of metal hydrides and boranes has been developed for the computer program CAMEO. The general algorithm analyzes and classifies reductive transformations in terms of fundamental mechanistic steps. Central to this algorithm has been the development of general functional group reactivity tables from which competitions between viable reducible sites are assessed. Existing routines for calculating FMO energies, bond dissociation energies, ion stabilities, pK_a's, and Taft E_s parameters have been utilized for the determination of chemo- and regioselectivities. Examples of reaction sequences demonstrating the current predictive capabilities of CAMEO are presented.

I. Introduction

CAMEO, an interactive computer program designed to predict the outcome of organic reactions given the reactants and conditions, is under continuous expansion.[1] Recently, the scope of the program has been enhanced to

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encompass free-radical chain processes[2] and oxidation reactions of transition-metal acetates, metal and nonmetal oxides, peracids, and chromium(VI) oxidants.[3] Other processes currently handled by CAMEO include base-catalyzed and nucleophilic,[4] acid-catalyzed and electrophilic,[5] pericylic,[6] and heterocycle-forming reactions.[7] The development and inclusion of a module that treats the chemistry of hydrides and complex hydrides is addressed in this paper. Though important in their own right, such reductions often provide necessary functional group interconversions in larger synthetic schemes.

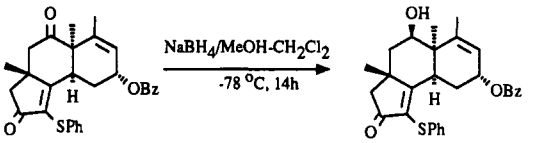
A common key feature of the reaction modules in CAMEO is the application of mechanistic logic in evaluating reactions. The hydride module is no exception since it is principally based on a framework wherein reduction reactions are classified into mechanistic categories. Reaction intermediates are tacitly formed, and crucial information concerning their nature and reactivity is used during reaction evaluation. Mechanistic analyses are not only confined to multipathway transformations but also are utilized throughout the various stages of implementation.

The incorporation of hydride chemistry in CAMEO entailed a systematic organization of the available literature data. Specifically, the important work of Brown and coworkers[8] on relative reactivity has been expanded to include additional synthetically useful chemical conversions. More importantly, some mechanistic patterns have been identified and utilized in the algorithms for processing reactions. This paper begins with a critical analysis of key facets of hydride reduction with emphasis on considerations relevant to reaction implementation in CAMEO. The analysis focuses on the nuances in the reactivity of related hydride reagents such as $LiAlH_4$, $LiAlH(OMe)_3$, $LiAlH(t\text{-}BuO)_3$, $NaBH_4$, $NaCNBH_3$, $NaCNBH_3$, $LiBH_4$, AlH_3, $AlH(i\text{-}Bu)_2$, B_2H_6, and Sia_2BH. Currently accepted mechanisms are presented, and the role of steric and electronic effects on chemo- and regioselectivity is emphasized. The implementation of hydride chemistry in CAMEO is then described. The paper concludes with a presentation of sample reaction sequences predicted by the program.

II. Key Aspects of the Reduction Chemistry of Hydrides and Complex Hydrides

The evolution of hydride derivatives with varying reducing powers and functional-group selectivities has led to new routes and better control in organic syntheses. The implementation of hydride chemistry in CAMEO requires scrutiny of the reducing characteristics of these reagents. Hence, the following analysis of comparative chemical behavior is in order.

A. Reagent and Functional Group Philicity. The classification of hydride reagents as nucleophilic or electrophilic is extremely useful in determining probable sites of attack as well as the subsequent reduction chemistry. Thus, nucleophilic reducing reagents such as lithium aluminum hydride, sodium borohydride, and their corresponding derivatives are attracted to sites with the lowest electron density, whereas electrophilic reducing reagents such as alane, diborane, and their derivatives tend to seek electron-rich sites. Conversely, potentially reactive sites may be classified on the basis of their philicity toward a given reagent. Thus, for the nucleophilic reagent $NaBH_4$, the ease of reduction of carbonyl compounds is directly related to the electrophilicity of the carbonyl group and follows the order acid chlorides > aldehydes > ketones > enones. Due to the mild reducing power of $NaBH_4$, it can selectively reduce ketones in the presence of enones (e.g., eq 1).[9] Electron delocalization in enones renders the



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carbonyl group less susceptible to nucleophilic attack by this reagent. In the same manner, slower reduction is observed for aromatic than aliphatic acids with $NaBH_4$.[10] For the electrophilic reagents alane[11] and diborane,[12] the above reactivity order is reversed, with acid chlorides being less reactive than aldehydes and ketones.

Functional-group philicity may be enhanced or diminished by the electronic effects of substituents.[13-16] Thus, chloral, which contains three α-chloro substituents, is reduced less readily than acetaldehyde by diborane.[13] Philicity for a specific reagent may also vary with pH.[17-19] For example, aldehydes and ketones are practically inert toward the weakly reducing agent $NaCNBH_3$ in basic or neutral media. However, in acidic media, the electrophilicity of the carbonyl group is increased considerably by protonation, thus making aldehydes and ketones reactive at room temperature.[17]

B. Relative Reduction Potentials. $LiAlH_4$ is an exceptionally powerful reducing agent and reacts rapidly with virtually all organic functionalities. $NaBH_4$, on the other hand, is a mild reagent and can be used for the selective reduction of aldehydes, ketones, and acid chlorides. The reducing strengths of these reagents may be altered by hydride substitution or by change of cation. Thus, alkoxyaluminum hydrides such as $LiAlH(t\text{-}BuO)_3$ and $LiAlH(OMe)_3$ as well as $NaCNBH_3$ have markedly lower reactivity and increased chemoselectivity than the corresponding parent hydrides. The single active hydrogen for $LiAlH(OMe)_3$ and $LiAlH(t\text{-}BuO)_3$ contributes to the diminished reactivity, while the lower reactivity of NaCN-

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BH_3 compared to $NaBH_4$ is due to the electron-withdrawing effect of the cyano group. On the other hand, $LiBH_4$ is a stronger reducing agent than $NaBH_4$, presumably because lithium ion is better solvated in the usual ether solvents than sodium ion, thereby making the borohydride anion more nucleophilic.

Alane (AlH_3) is an exceedingly powerful reagent with a reactivity comparable to that of $LiAlH_4$. Its diisobutyl derivative (DIBAL or DIBAH) is less reactive due to the combined steric and electronic effects of the isobutyl groups. Similarly, disiamylborane (Sia_2BH) is less reactive and, therefore, more selective than diborane. It exhibits a higher regioselectivity for the less hindered carbon atom of alkenes as well as alkynes.[12]

The availability of the parent hydrides and their derivatives provides a wide spectrum of reducing potentials applicable to a broad range of functional groups. By proper choice of the reagent and conditions, selective reduction of polyfunctional compounds can be achieved. The philicity of each reagent coupled with its reducing strength define the functional group selectivity for the reagent. To date, only a few attempts to rank the chemoselectivities of the different hydride reagents have been made. Particularly noteworthy is the formulation of a chemoselectivity series comprised of 12 functional groups by Walker[20] and Brown.[8,21] Extension of this series to accommodate a wider variety of functional groups is provided in section III.C. The development of such reactivity tables from literature data is necessary for reaction implementation in CAMEO and constitutes a major part of the present work. These tables should also be of use beyond the context of the program.

C. Mechanisms of Reductions. The reduction of organic compounds by nucleophilic and electrophilic hydrides has generally been considered to proceed via a polar mechanism. However, evidence concerning the existence of a single electron transfer (SET) mechanism has recently emerged. Specifically, the formation of free-radical intermediates has been invoked in the lithium aluminum hydride reductions of alkyl halides,[22] secondary and tertiary aryl alcohols,[23] and diaryl ketones.[24] In this section, reductions involving polar intermediates are discussed first followed by reactions that occur via a SET pathway. Reactions with less common mechanisms are also included for completeness.

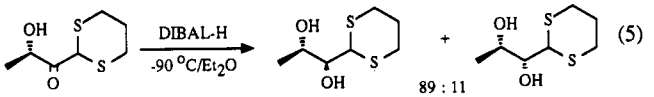
1. Polar Mechanisms. As described next, hydride reductions via polar processes can involve the following steps: 1,2-addition, addition–elimination, 1,4-addition, proton abstraction, intramolecular hydride addition, and S_N2, S_N2', and S_N1 reactions.

(a) 1,2-Addition to Multiple Bonds. This involves the addition of a hydrogen to the less electronegative atom of the multiple bond to form an anionic or neutral intermediate. Hydrolysis of the intermediate leads to the final 1,2-reduced product (e.g., eqs 2–4). Reductions of aldehydes,[25] ketones,[26] N-substituted imines,[27] iminium ions,[28] nitriles,[29] and O-substituted oximes[30] fall under this category. Representative examples are provided in eqs 5 and 6.[26c,28a]

$$4RR'C{=}O \xrightarrow{LiAlH_4} (RR'CHO)_4Al^-Li^+ \xrightarrow{H_2O} 4RR'CHOH + Al(OH)_3 + LiOH \quad (2)$$

$$3RR'C{=}NR'' \xrightarrow{BH_3} (RR'CHNR'')_3B \xrightarrow{H_2O} 3RR'CHNHR'' + B(OH)_3 \quad (3)$$

$$RC{\equiv}N \xrightarrow{LAH} RCH{=}NAlH_3^- \xrightarrow{LAH} RCH_2N(AlH_3)_2^{2-} \xrightarrow{H_2O} RCH_2NH_2 \quad (4)$$



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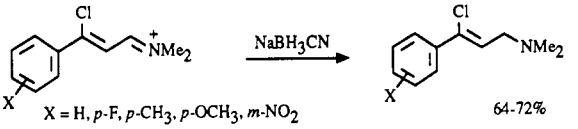

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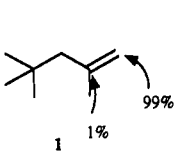
For electrophilic hydrides such as alane and diborane, addition is preceded by complexation with π bonds or electron lone pairs.[25b,31] Addition to nonpolarized bonds such as in alkenes,[31] alkynes,[32] and azo compounds[33] has also been observed with diborane and disiamylborane. The orientation of addition of these reagents to alkenes and alkynes depends on both steric and electronic factors. As a general rule, boron tends to add to the less hindered carbon atom of the double or triple bond or to the carbon atom that is less able to stabilize a cationic charge. Thus, in the reductions of 1 and 2 by diborane, boron adds almost exclusively to the terminal carbon atom in 1 and predominantly to the carbon atom adjacent to the silicon substituent in 2.[31]



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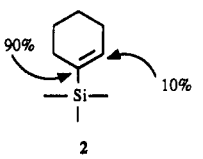

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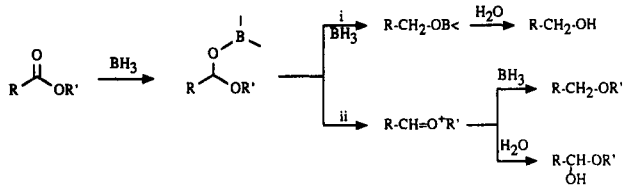
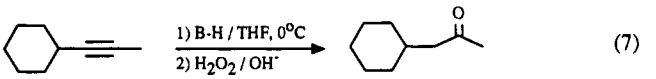
Scheme I



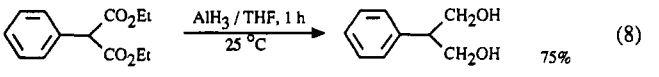
It is interesting to mention that diborane exhibits a higher regiospecificity with alkynes than with alkenes due to more pronounced steric interactions upon double-bond formation, especially in the third stage of hydroboration.[32] An example illustrating regiospecificity for the less hindered carbon atom of a triple bond is given in eq 7.[32] Note that Sia_2BH exhibits a higher regiospecificity than B_2H_6.



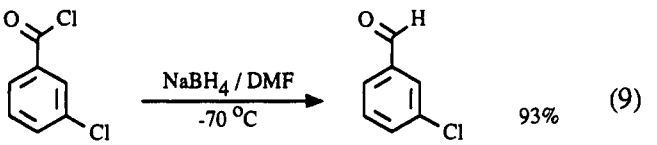
(7)

B-H = B_2H_6 : 74%[a] (70% total yield)
B-H = Sia_2BH : 91%[a] (> 85% total yield)
[a] ketone isomer

(b) Addition–Elimination. Cleavage of bonds to a carbonyl carbon may follow hydride addition during reductions of acid chlorides,[34] esters,[14,33,35] lactones,[33,36] anhydrides,[37] lactams,[38] and acyclic amides.[18,39-41] Thus, acid chlorides and esters are reduced by $LiAlH_4$, $NaBH_4$, $LiBH_4$, AlH_3, and DIBAL to their corresponding alcohols[29c,35] (e.g., eq 8).[35a] Reduction of the former may be quenched at the aldehyde stage below 0 °C (e.g., eq 9).[34] Both B_2H_6 and Sia_2BH react very slowly with acid chlorides and esters; hence, they are not the reagents of choice for reducing these functional groups.

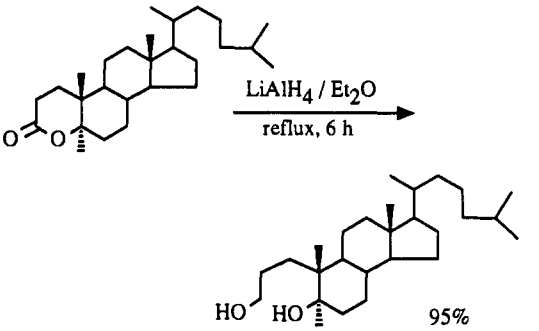


(8)

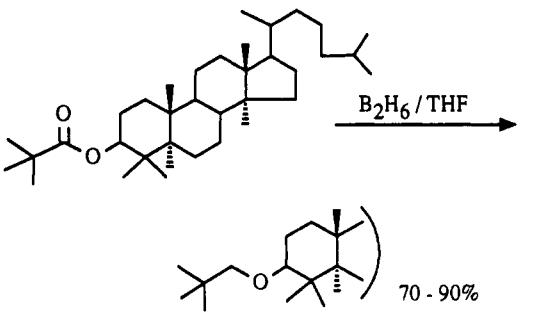


(9)

Lactones undergo reductive cleavage of the C–O bond to form glycols (e.g., eq 10).[36a] With diborane, two modes of cleavage are observed for both esters and lactones. The proposed mechanistic pathways are depicted in Scheme I. In this scheme, path i gives rise to alcohols, while path ii leads to ether formation. The latter seems to be the preferred pathway for esters and lactones with bulky alkyl groups attached to the singly bonded oxygen atom, as in eq 11.[36b] Presumably, oxonium ion formation is favored by steric crowding and electron-donating alkyl groups.

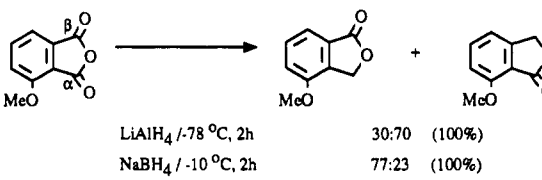


(10)



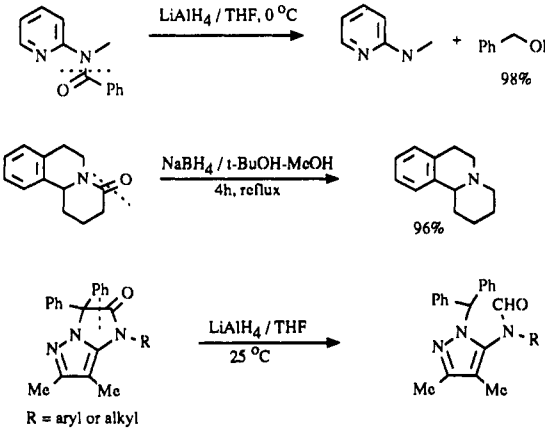
(11)

Anhydrides may undergo deoxygenation at either carbonyl carbon to give a mixture of isomeric lactones. The reaction presumably involves the formation of an oxonium ion intermediate that can undergo further reduction with the hydride. Regioselectivity can be affected by both electronic[37a] and steric[37b-d] factors. Chelation with alkali metal ion can also influence regioselectivity, as in eq 12.[37a]



(12)

Reduction of amides occurs via several reaction pathways involving the following bond cleavages in the *O*-aluminate or *O*-boronate complex: (i) C–N cleavage[38d,39] to form an aldehyde and an amine with the former being further reduced to an alcohol (e.g., eq 13);[39a] (ii) C–O cleavage[38,40] to form an iminium ion which is further reduced to an amine (e.g., eq 14);[38a] and (iii) C–C cleavage[41] to give an alkane and a formamide (e.g., eq 15).[41] C–N



(13)

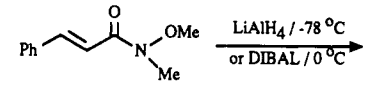
(14)

(15)

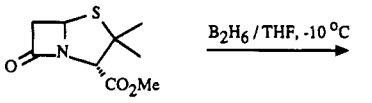
R = aryl or alkyl

(34) Babler, J. H.; Invergo, B. J. *Tetrahedron Lett.* **1981**, *22*, 11.
(35) (a) Choi, Y. M.; Emblidge, R. W. *J. Org. Chem.* **1989**, *54*, 1198. (b) Orellana, G.; Perez-Ossorio, R.; Quiroga, M. L.; Sanchez-Asiain, M. P. *J. Chem. Soc., Perkin Trans. 2* **1987**, 679. (c) Jorgensen, E.; Sydnes, L. K. *J. Org. Chem.* **1986**, *51*, 1926. (d) Kreft, A. *Tetrahedron Lett.* **1977**, 1959. (e) Valverde, S.; Herradon, B.; Martin-Lomas, M. *Tetrahedron Lett.* **1985**, *26*, 3731.
(36) (a) Maione, A. M.; Quaglia, M. G. *Chem. Ind.* **1977**, 230. (b) Dias, J. R.; Pettit, G. R. *J. Org. Chem.* **1971**, *36*, 3485. (c) Ireland, R.; Anderson, R.; Badoud, R. *J. Am. Chem. Soc.* **1983**, *105*, 1988.
(37) (a) Soucy, C.; Favreau, D.; Kayser, M. M. *J. Org. Chem.* **1987**, *52*, 129. (b) Kayser, M. M.; Salvador, J.; Morand, P.; Krishnamurthy, H. G. *Can. J. Chem.* **1982**, *60*, 1199. (c) Kayser, M. M.; Morand, P. *Can. J. Chem.* **1978**, *56*, 1524. (d) Kayser, M. M.; Morand, P. *J. Org. Chem.* **1979**, *44*, 1338.
(38) (a) Mandal, S. B.; Giri, V. S.; Sabeena, M. S.; Pakrashi, S. C. *J. Org. Chem.* **1988**, *53*, 4236. (b) Mandal, S. B.; Giri, V. S.; Pakrashi, S. C. *Synthesis* **1987**, 1128. (c) Cox, B.; Robinson, B. *J. Heterocycl. Chem.* **1988**, *25*, 271. (d) Jackson, M. B.; Mander, L. N.; Spotswood, T. M. *Aust. J. Chem.* **1983**, *36*, 779.
(39) (a) Meyers, A. I.; Comins, D. L. *Tetrahedron Lett.* **1978**, *52*, 5179. (b) Landis, M. E.; Mitchell, J. C. *J. Heterocycl. Chem.* **1979**, *16*, 1637. (c) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
(40) (a) Falorni, M.; Lardicci, L.; Giacomelli, G. *Gazz. Chim. Ital.* **1988**, *118*, 573. (b) See ref 29b. (c) See ref 29c.
(41) Schweizer, E. E.; Lee, K. J. *J. Org. Chem.* **1984**, *49*, 4848.

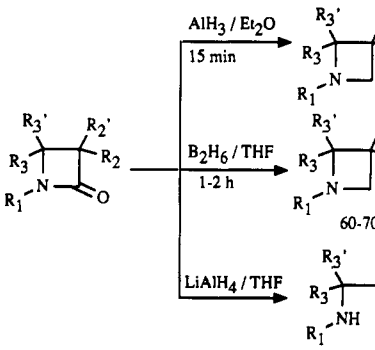
cleavage is generally favored by low reaction temperatures, as shown in eqs 16[39c] and 17.[42] C–O cleavage is more facile with electrophilic hydrides than with nucleophilic hydrides. For example, reduction of amides to amines occurs rapidly and quantitatively with alane[29c] and diborane[29b] at 25 °C. In contrast, C–O cleavage with $NaBH_4$ or $LiAlH_4$ requires elevated temperatures, as shown in eq 14. The contrasting behavior of electrophilic and nucleophilic hydrides is appropriately illustrated in the reduction of azetidin-2-ones by AlH_3, B_2H_6, and $LiAlH_4$ (eq 18).[38d] Finally, C–C



(16)



(17)



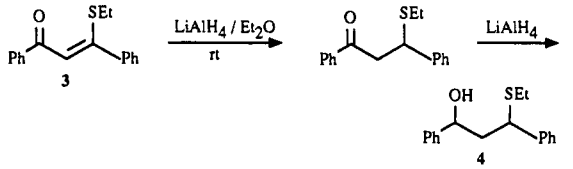
(18a)

(18b)

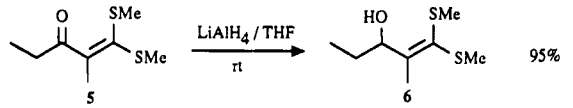
(18c)

cleavage is exceedingly rare and is observed only when a very stable carbanion intermediate can be generated in the elimination step.

(c) 1,4-Addition to Conjugated Systems. Carbon–carbon double bonds are normally not prone to reduction by $LiAlH_4$ and $NaBH_4$. However, their reduction may be facilitated by conjugation with polarized, multiply bonded functionalities such as nitro,[43] cyano,[44,45] sulfone,[46] and carbonyl groups.[47] For α,β-unsaturated carbonyl systems, two modes of hydride attack are possible: 1,2-addition to the carbonyl group and 1,4-addition to the olefinic bond. The latter is regarded as a frontier orbital controlled process that leads to saturated ketones via keto–enol tautomerization. The chemoselectivity of the hydride attack has been suggested to depend on the electronic features of the reducible sites defined in terms of the coefficients of the lowest vacant molecular orbitals.[48] In general, 1,2-addition is more common than 1,4-addition. By making the carbon–carbon double bond more electron deficient, the propensity for 1,4-addition is increased. To illustrate, ketone **3** affords alcohol **4** via 1,4-addition followed by keto–enol tautomerization,[47b] whereas the relatively electron-rich ketone **5** undergoes 1,2-addition exclusively upon treatment with $LiAlH_4$.[47c] Evidently, the phenyl group attached to the olefinic bond in **3** increases its electron deficiency, thereby increasing the likelihood of a 1,4-hydride attack.

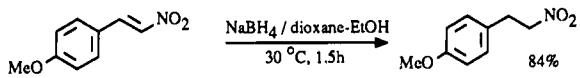


(19)

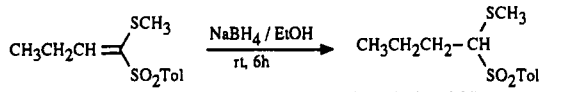


(20)

In addition to electronic factors in the substrates, the nature of the hydride reagent also plays a significant role in determining the course of reduction of conjugated carbonyl compounds. For example, the percentages of 1,4-addition of $LiAlH(OMe)_3$, $LiAlH_4$, and $LiAlH(t\text{-}BuO)_3$ to 2-cyclohexen-1-one are 5, 22, and 95%, respectively.[49] As a rule, hard metal hydrides such as $LiAlH_4$ add preferentially to the 2-position, while softer metal hydrides such as $LiAlH(t\text{-}BuO)_3$ add preferentially to the 4-position.[50] Examples of 1,4-hydride additions involving other conjugated systems are provided in eqs 21[43] and 22.[46]

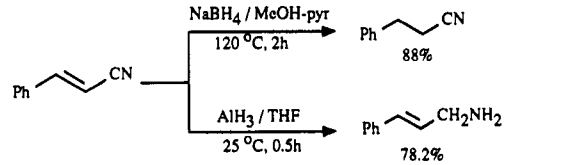


(21)



(22)

While 1,4-addition may constitute a major reaction pathway for nucleophilic hydrides, 1,2-addition predominates for electrophilic hydrides. Thus, α,β-unsaturated amides,[29c] nitriles,[29c] aldehydes,[51a] and ketones[51b] are reduced to their corresponding α,β-unsaturated amines and alcohols by AlH_3. An example highlighting the contrasting behavior of nucleophilic and electrophilic hydrides is shown in eq 23.[44,29c]



(23a)

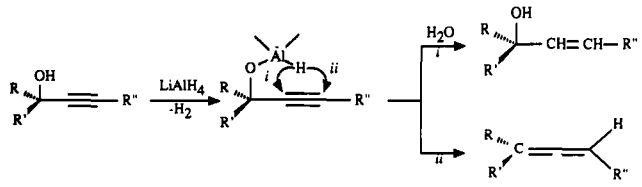
(23b)

(d) Proton Abstraction. An important key step in the hydride reduction of some functionalized organic compounds is the abstraction of a proton by hydride ion. This step often gives rise to a neutral or an anionic complex with concomitant evolution of hydrogen. A typical example is the formation of a *N*-aluminate complex from an unsubstituted imine, as shown in eq 24.

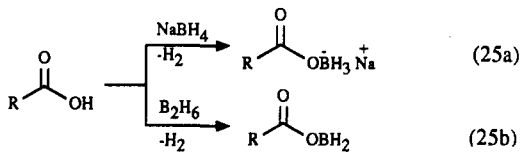
$$>C{=}NH \xrightarrow[-H_2]{LAH} >C{=}NAlH_3^- \xrightarrow{LAH} >CHN(AlH_3)_2^{2-} \xrightarrow{H_2O} >CHNH_2 \quad (24)$$

(42) Sammes, P. G.; Smith, S. *J. Chem. Soc., Chem. Commun.* **1982**, 1143.
(43) Bhattacharjya, A.; Mukhopadhyay, R.; Pakrashi, S. C. *Synthesis* **1985**, 886.
(44) Rhodes, R. A.; Boykin, D. W. *Synth. Commun.* **1988**, *18*, 681.
(45) (a) Kulp, S. S.; Szarko, R. *J. Org. Chem.* **1988**, *53*, 5573. (b) Kulp, S. S.; Caldwell, C. B. *J. Org. Chem.* **1980**, *45*, 171.
(46) Ogura, K.; Ohtsuki, K.; Takahashi, K.; Iida, H. *Chem. Lett.* **1986**, 1597.
(47) (a) Klunder, A. J. H.; Crul, A. A. M.; Houwen-Claasen, A. A. M.; Kooy, M. G.; Zwanenburg, G. *Tetrahedron Lett.* **1987**, *28*, 3147. (b) Nishio, T.; Omote, Y. *J. Chem. Soc., Perkin Trans. 1* **1981**, 934. (c) Gammill, R. B.; Bell, L. T.; Nash, S. A. *J. Org. Chem.* **1984**, *49*, 3039.
(48) (a) Malek, J. *Org. React.* **1985**, Chapter 1. (b) Eisenstein, O.; Lefour, J. M.; Minot, C.; Anh, N. T.; Soussan, G. *C.R. Acad. Sci. Ser.* **1972**, *274*, 1310
(49) Durand, J.; Anh, N. T.; Huet, J. *Tetrahedron Lett.* **1974**, 2397.
(50) Bottin, J.; Eisenstein, O.; Minot, C.; Anh, N. T. *Tetrahedron Lett.* **1972**, 3015.
(51) (a) Jorgenson, M. J. *Tetrahedron Lett.* **1962**, 559. (b) Brown, H. C.; Hess, H. M. *J. Org. Chem.* **1969**, *34*, 2206.

Scheme II



Proton abstraction from other active hydrogen compounds such as alcohols, carboxylic acids, and oximes is also prevalent. Thus, the preliminary step in the reduction of carboxylic acids by $NaBH_4$ and B_2H_6 is given in eq 25.[10]



(25a)

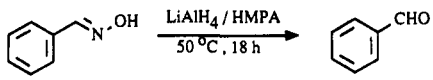
(25b)

Reductions of ketoximes to amines and hydroxylamines by alane[29c] and borane,[33] respectively, are also initiated by a proton abstraction step from the *N*-hydroxy function. Additionally, the reduction of an aldoxime by $LiAlH_4$ proceeds via an initial abstraction followed by effectively a dehydration step (eq 26).[52] Further reduction of the resulting nitrile to an aldehyde occurs in the absence of acidic α-hydrogen atoms.[53] Examples of reduction of aldoximes by $LiAlH_4$ are provided in eqs 27 and 28.[52]

$$RCH{=}NOH \xrightarrow[-H_2]{LiAlH_4} RCH{=}NOAlH_3^-Li^+ \rightarrow$$

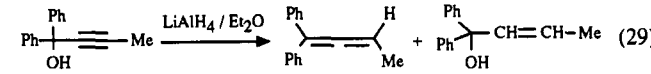
$$RC{\equiv}N \xrightarrow{LiAlH_4} RCH{=}NAlH_3^- \xrightarrow{H_2O} RCH{=}O \quad (26)$$

$$n\text{-}C_{10}H_{21}CH{=}NOH \xrightarrow[50\ ^\circ C,\ 18h]{LiAlH_4/HMPA} n\text{-}C_{10}H_{21}C{\equiv}N \quad (27)$$



(28)

(e) Intramolecular Hydride Addition to Multiple Bonds. Reductions of some organic compounds follow an intra- rather than an intermolecular mechanism. The reductions of allylic, allenic, and propargylic alcohols are typical examples. The initial step involves the formation of an organometallic complex that may undergo intramolecular hydride transfer to either terminal atom of the olefinic or acetylenic bond. Propargylic alcohols, for example, may be reduced by $LiAlH_4$ to yield allenes or olefins. Allenes arise by an intramolecular hydride transfer to the sp carbon that is farther from the hydroxy functionality; olefins result from an intramolecular hydride transfer to the nearer sp carbon (see Scheme II).[54] In both cases, a vinyl carbanion is formed that undergoes either a metal oxide elimination to form an allene (path ii) or a hydrolysis process to form an allylic alcohol (path i). The regioselectivity of hydride attack is largely determined by the relative stability of the incipient carbanions. In eq 29,[54] both hydride transfers are feasible, while in eq 30,[55] hydride delivery to the proximal sp carbon is highly preferred, presumably because of the stabilizing effect of the silicon atom on the incipient adjacent negative charge.

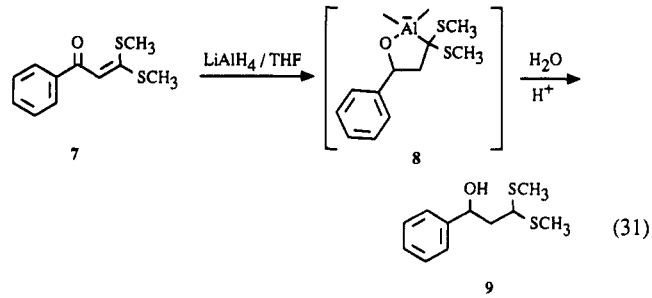


(29)

$$TMSC{\equiv}CC(OH)HCH_3 \xrightarrow[0\ ^\circ C\text{-reflux}]{LiAlH_4/Et_2O} TMSCH{=}CH(OH)HCH_3 \quad (30)$$

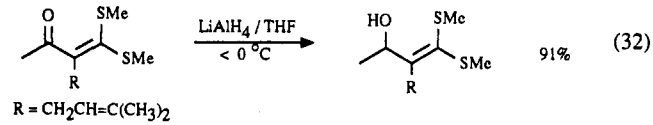
$Z{:}E$ = 70:30

Allylic alcohols may also be reduced via a hydride attack at either terminus of the double bond. Hydride transfer to the proximal sp^2 carbon is exemplified by eq 31.[56]



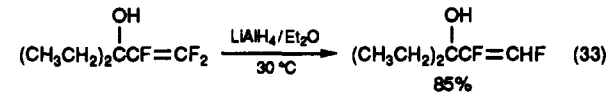
(31)

Reduction, in this case, proceeds by a 1,2-addition process to form an intermediate alcoholate followed by an intramolecular hydroalumination step to give complex **8**. Hydrolysis of **8** then yields the saturated alcohol **9** as the final reduced product. Note that allylic alcohols may be trapped at low temperatures, as in eq 32.[57] Hydride transfer to



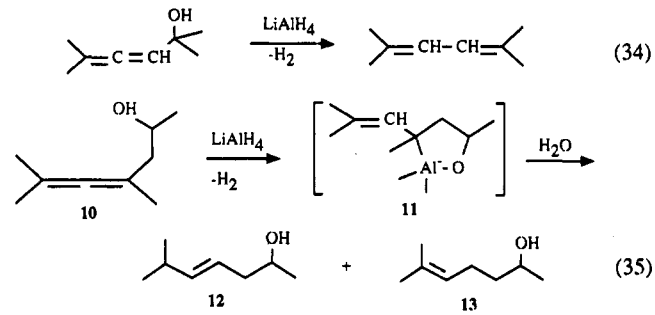
(32)

the remote sp^2 carbon in allylic alcohols is exemplified by eq 33.[58] In this reaction, expulsion of the fluoride ion presumably occurs via a subsequent E1cb elimination.



(33)

Finally, α- and β-allenic alcohols are reduced by $LiAlH_4$ via an intramolecular hydride attack at the central carbon atom of the allene. The former give rise to 1,3-dienes or alkenols (eq 34),[59] while the latter form complexes like **11**, which can be protonated at two sites to give 3-alken-1-ols **12** or 4-alken-1-ols **13** (eq 35).[59]

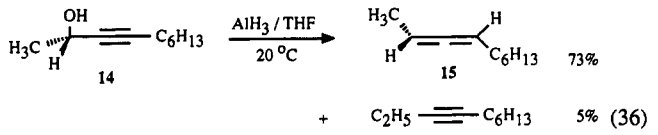


(34)

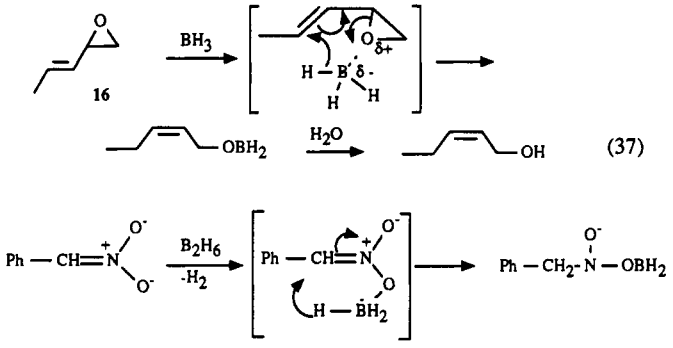
(35)

The above mechanisms are not unique to reductions with $LiAlH_4$. Reduction of propargyl alcohol **14** with alane gives allene **15** via an intramolecular hydride transfer (eq 36).[60] Similarly, borane reduction of α,β-unsaturated

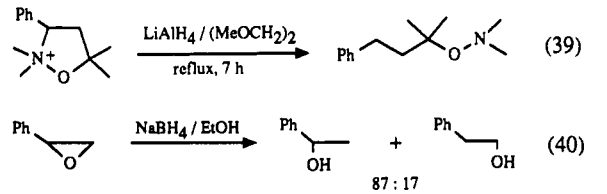
(52) Balachander, N.; Wang, S.-S.; Sukenik, C. N. *Tetrahedron Lett.* **1986**, *27*, 4849.
(53) Wang, S. S.; Sukenik, C. N. *J. Org. Chem.* **1985**, *50*, 5448.
(54) Blunt, J. W.; Hartshorn, M. P.; Soong, L. T.; Munro, M. H. G.; Vannoort, R. W.; Vaughan, T. *Aust. J. Chem.* **1983**, *36*, 1387.
(55) Mancini, M. L.; Honek, J. F. *Tetrahedron Lett.* **1983**, *24*, 4295.
(56) Gammill, R. B.; Gold, P. M.; Mizsak, S. A. *J. Am. Chem. Soc.* **1980**, *102*, 3095.
(57) Gammill, R. B.; Bell, L. T.; Nash, S. A. *J. Org. Chem.* **1984**, *49*, 3039.
(58) Sauvetre, R.; Masure, D.; Chuit, C.; Normant, J. F. *Synthesis* **1978**, 128.
(59) Baudorsy, R.; Gore, J. *Tetrahedron* **1975**, *31*, 383.



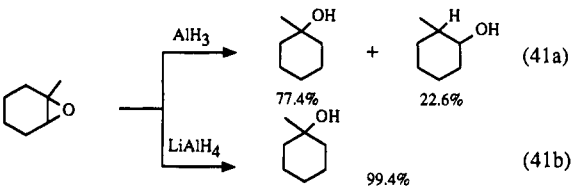
epoxide **16** probably occurs via an intramolecular conjugate hydride transfer, as shown in eq 37.[61] Hydride transfer to sites other than carbon–carbon multiple bonds is illustrated in the reduction of a nitronate by diborane (e.g., eq 38).[62]



(f) S_N2 Displacement. S_N2 displacement by hydride ion typically occurs in alkyl substrates that contain suitable leaving groups. The leaving group may be a part of the substrate, as seen in the ring-opening substitution given in eq 39.[63] Factors that influence the likelihood of S_N2 processes include the nature of the leaving group, the structural features of the substrate, and the nature and strength of the nucleophilic hydride reagent. The reactivity of alkyl halides, as differentiated by $NaBH_4$, is in the order R–I > R–Br > R–Cl ≫ R–F.[64] This order clearly reflects the relative leaving ability of the halogens in accord with the S_N2 mechanism. The preferential reduction of the less substituted carbon atom in unsymmetrical epoxides by $LiAlH_4$ and $NaBH_4$ is also consistent with an S_N2 pathway.[65] Both reagents exhibit high regioselectivities, as shown in eq 40.[65a,c]



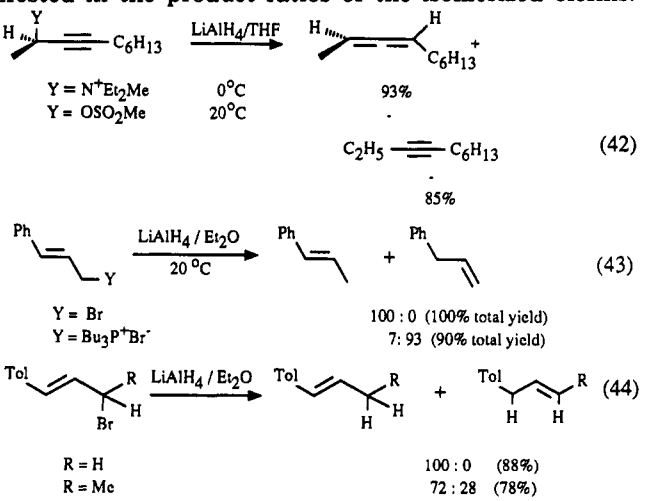
With electrophilic hydrides, reduction of epoxides yields a substantial amount of products derived from hydride attack at the more hindered carbon (e.g., compare eq 41a with eq 41b).[66] The accepted mechanistic rationale for this observation is that complex formation between the reagent and the epoxide leads to significant weakening of the C–O bond prior to S_N2 attack. Thus, the increased



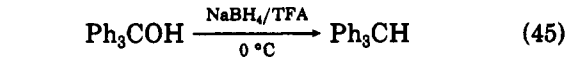
susceptibility of the hindered carbon to hydride attack is due to its greater ability to stabilize the developing positive charge in the complex.

The effect of steric hindrance to bimolecular approach can be demonstrated by the resistance of epoxide rings toward reduction with the bulky reagent $LiAlH(t\text{-}BuO)_3$[67] and by the inertness of hindered epoxides to reduction with $LiAlH_4$.[68]

(g) S_N2' Displacement. Allylic[69] and propargylic[60,70] systems containing potential leaving groups at the α-position may undergo S_N2' displacement with hydrides at the γ-position to give isomerized olefins and allenes, respectively. Competition between S_N2' and S_N2 processes may exist. The preferred orientation of attack by the hydride depends on the nature of the leaving group and the structure of the substrate. S_N2 is generally favored by good leaving groups and primary carbon centers, while S_N2' is favored by poorer leaving groups and hindered carbon centers. In eqs 42[60] and 43,[69b] a change of leaving group leads to a reversal of regioselectivity. In eq 44,[69a] the effect of alkyl branching on the mode of hydride attack is manifested in the product ratios of the isomerized olefins.



(h) S_N1 Displacement. Reductions of certain compounds by $NaBH_4$ and $NaCNBH_3$ in acidic media follow a S_N1 mechanism. Under acidic conditions, the leaving groups are usually protonated hydroxy, alkoxy, or peroxy functionalities. For example, some aryl alcohols are reduced by $NaBH_4$ to their corresponding arylalkanes. The reaction is limited to alcohols that can form sufficiently stable carbocations, as in eq 45.[71] Thus, 1-methylcyclo-

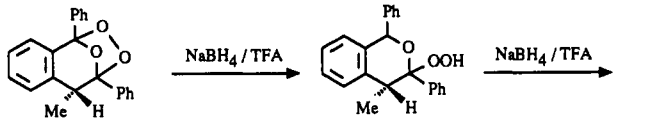


hexanol and benzyl alcohol undergo little or no reduction with $NaBH_4$ in TFA. Reduction of diaryl ketones to diarylmethanes has been suggested to proceed via a 1,2-re-

(60) Claisson, A.; Olsson, L. I. *J. Am. Chem. Soc.* **1979**, *101*, 7302.
(61) Zaidlewicz, M.; Uzarewicz, A.; Sarnowski, R. *Synthesis* **1979**, 62.
(62) Fever, H.; Bartlett, R. S.; Vincent, B. F., Jr.; Anderson, R. S. *J. Org. Chem.* **1965**, *30*, 2880.
(63) Liguori, A.; Sindona, G.; Uccella, N. *Tetrahedron* **1983**, *39*, 683.
(64) Rolla, F. *J. Org. Chem.* **1981**, *46*, 3909.
(65) (a) Ookawa, A.; Kitade, M.; Soai, K. *Heterocycles* **1988**, *27*, 213. (b) Ookawa, A.; Hiratsuka, H.; Soai, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1813. (c) Jones, T. K.; Peet, J. H. J. *Chem. Ind. (London)* **1971**, 995.
(66) Murphy, D. K.; Alumbough, R. L.; Rickborn, B. *J. Am. Chem. Soc.* **1969**, *91*, 2649.
(67) Fukuyama, T.; Vranesic, B.; Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1978**, 2741.
(68) Gurudutt, K. N.; Ravidranath, B. *Synthesis* **1983**, 888.
(69) (a) Hirabe, T.; Tagaki, M.; Muraoka, K.; Nojima, M.; Kusabayashi, S. *J. Org. Chem.* **1985**, *50*, 1797. (b) Hirabe, T.; Nojima, M.; Kusabayashi, S. *J. Org. Chem.* **1984**, *49*, 4084.
(70) Castelhano, A. L.; Krantz, A. *J. Am. Chem. Soc.* **1987**, *109*, 3491.
(71) Gribble, G. W.; Leese, R. M. *Synthesis* **1977**, 172.
(72) Gribble, G. W.; Kelly, W. J.; Emery, S. E. *Synthesis* **1978**, 763.

duction to give a diaryl alcohol followed by a S_N1 pathway.

The S_N1 processes may occasionally be assisted by electron resonance from adjacent functionalities. Examples include the reductions of bicyclic ozonide 17[73] and ketal 18.[74] The leaving groups in these cases are the protonated peroxy and alkoxy groups, respectively. Both transformations have been suggested to involve the formation of intermediate carboxonium ions.[73,74]



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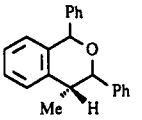

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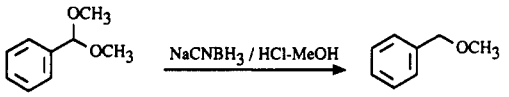
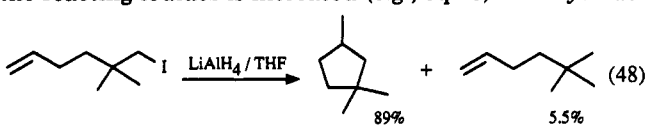


(47)

18 88%

2. Single-Electron Transfer. Evidence for the existence of free-radical intermediates in the hydride reduction of alkyl halides has been presented by Ashby and co-workers.[22b,3] Specifically, the formation of cyclized hydrocarbons has been attributed to intramolecular cyclization of radical intermediates. A reassessment of Ashby's work based on kinetic studies by Newcomb and co-workers led to the conclusion that alkyl iodides are reduced by $LiAlH_4$ primarily through a polar S_N2 pathway in competition with a minor free-radical chain pathway.[22a] However, the latter predominates as the steric bulk near the reacting iodides is increased (e.g., eq 48).[22a] Hydride

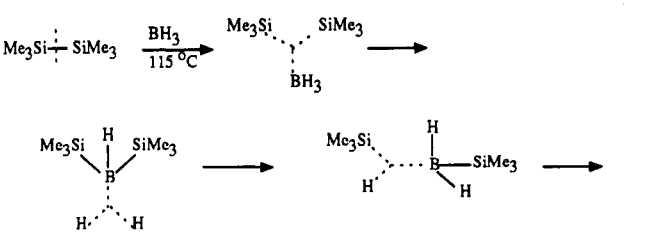


(48)

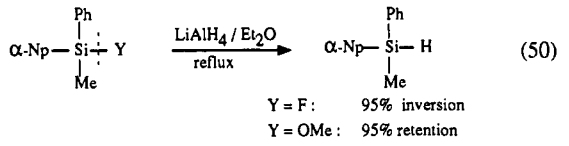
89% 5.5%

reductions of aryl, vinyl, bridgehead, and tertiary halides proceed predominantly by a single electron transfer mechanism. For example, a cyclopropyl radical intermediate inverts to give a racemic mixture.[22c] The SET pathway has also been demonstrated in the reductions of aryl alcohols with $LiAlH_4$.[23] Homolytic cleavage of the C–O bond in the *O*-aluminate complex occurs to give a radical intermediate that is quenched either by the solvent or by the hydride reagent.

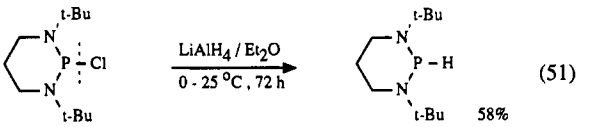
3. Mechanistically Undefined Reductive Transformations. A number of hydride reductions involving hetero–hetero bond cleavages are mechanistically obscure. Although mechanisms have been proposed for some of these reactions, no experiments have been conducted to validate these suggestions. A typical example is the reduction of disilanes by B_2H_6. The reaction has been suggested to proceed by electrophilic attack of the reagent on a Si–Si σ-bond via a two-electron, three-center transition state, as shown in eq 49.[75] However, reduction of disilanes is also feasible with nucleophilic hydrides.[76] The lability of halide and oxygen functionalities attached to silicon[77,78] and phosphorus[79] centers has also been demonstrated (e.g., eqs 50 and 51).



(49)



(50)



(51)

Other examples involving hetero–hetero bond cleavages are reduction of azo compounds to amines by diborane,[33] reduction of nitro compounds to amines by $LiAlH_4$.[80] deoxygenation of sulfoxides to sulfides to diborane,[33] and reduction of N-substituted imines[80,81] and ketoximes[52,53] to their corresponding amines by $LiAlH_4$.

III. General Implementation

A. Program Flow. The executive subroutine, HYDRIDE, directs the processing of reductions by hydrides and complex hydrides in CAMEO. The input and output of chemical structures and reagents are performed interactively at a graphics terminal, as illustrated elsewhere.[1] The program is highly modularized to permit more efficient analyses, as in the present case for related reducing agents. The hydride reagents that have been implemented so far have been classified into four types on the basis of their reducing potentials and philicities: type I, $LiAlH_4$, $LiAlH(OMe)_3$, $LiAlH(t\text{-}BuO)_3$; type II, $LiBH_4$, $NaBH_4$, $NaCNBH_3$; type III, DIBAL; type IV, B_2H_6, Sia_2BH.

The overall program flow is controlled by the type of reagent input by the user. Each type has a corresponding subroutine whose main functions are (1) to analyze and process the reductions elicited by the covered reagents and (2) to encode the structural information necessary for product formation. The stored information is decoded later by the subroutine MPROD, where the actual structural manipulations are performed.

The general procedure for evaluating hydride reductions involves (1) identification of potentially reducible sites, (2) perceiving the relative reactivity of the sites, (3) elimination of less reactive or unreactive sites on the basis of input reaction conditions, (4) mechanistic evaluation of competing pathways, if applicable, and (5) storage of required manipulations for product formation. The treatment of these steps is expanded on in the following text.

B. Perception of Reactive Sites. Prior to perception, the input conditions are examined to ensure the validity of the user's entries. If the specified conditions are unacceptable, a message is issued to the user, and processing of the reaction is discontinued.

Some potentially reducible sites are identified on the basis of reagent philicity (section II.A). Thus, for nu-

(73) Fujisaka, T.; Nojima, M.; Kusabayashi, S. *J. Org. Chem.* **1985**, *50*, 275.
(74) Horne, D. A.; Jordan, A. *Tetrahedron Lett.* **1978**, 1357.
(75) Olah, G.; Field, L. D.; Lammertsma, K.; Pacquin, D.; Suermmerman, K. *Nouv. J. Chem.* **1983**, *7*, 279.
(76) D'Errico, J. J.; Sharp, K. G. *Inorg. Chem.* **1989**, *28*, 2886.
(77) Hosomi, A.; Mikami, M.; Sakurai, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2784.
(78) Corriu, R. J. P.; Fernandez, J. M.; Guerin, C. *Tetrahedron Lett.* **1978**, *36*, 3391.
(79) King, R. B.; Sundaram, P. M. *J. Org. Chem.* **1984**, *49*, 1784.
(80) Puszynski, A.; Rykowski, Z. *Polish J. Chem.* **1984**, *58*, 871.
(81) Hirao, A.; Hattori, I.; Yamaguchi, K.; Nakahama, S. *Synthesis* **1982**, 461.

cleophilic hydrides, the following electrophilic sites are sought:

(1) unsaturated carbon electrophiles ((a) carbonyl carbon atoms of aldehydes, ketones, ketenes, acid halides, carboxylic acids, amides, esters, anhydrides, imides, thiol esters, urea derivatives, carbonates, and thiocarbonates, (b) thiocarbonyl carbon atoms of thioaldehydes, thioketones, thioamides, thioesters, xanthates, and thioketenes, (c) carbon atoms of imines, iminium ions, oximes, and nitriles, and (d) unsaturated carbon atoms in conjugated alkenes and alkynes that are sufficiently electron deficient, as determined by their calculated LUMO energies);[82]

(2) saturated carbon electrophiles (e.g., carbon atoms of oxiranes or carbon atoms with potential leaving groups);

(3) non-carbon electrophiles (e.g., phosphorus atoms of phosphorus(III) halides, silicon atoms of silyl halides, and nitrogen atoms of azides).

The following potentially reactive sites are also identified in view of the mechanistic analyses covered above:

(1) Allylic, allenic, and propargylic alcohols are considered by virtue of their ability to form an organometallic complex that can undergo an intramolecular hydride reduction (section II.C.1.e).

(2) Allylic, allenic, and propargylic systems with appropriate leaving groups at the α-positions are identified as potential sites for S_N2' reductions with AlH_3 and $LiAlH_4$ (section II.C.1.g).

(3) Aryl alcohols capable of forming sufficiently stable carbon free radicals are perceived as potential sites for $LiAlH_4$ reduction (section II.C.2). The stability of free radicals is gauged by employing calculated bond dissociation energies (BDEs).[2] A cutoff value for the radical stability of acceptable sites has been established in the subroutine for $LiAlH_4$ and its alkoxy derivatives.

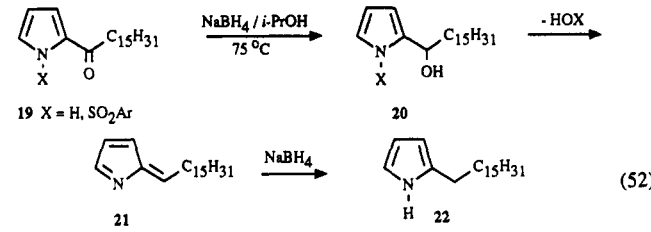
(4) Vinyl, aryl, cyclopropyl, tertiary, and bridgehead halides are considered for reduction with nucleophilic hydrides via a SET pathway (section II.C.2).

(5) Aryl alcohols, ozonides, and acetals are identified as possible sites for reduction with $NaBH_4$ under acidic conditions (section II.C.1.h). These sites form stable carbenium ions via S_N1 pathways. A function "IONSTB", which is part of the module for acid-catalyzed and electrophilic reactions in CAMEO, is invoked on each site. This function returns a number corresponding to the stability of the input cationic site.[5] A cutoff value for cation stability has been established in the subroutine for $NaBH_4$. Shown below is a sample list of calculated carbenium ion stabilities. Note that only the corresponding alcohols of the first two entries are permitted to react with $NaBH_4$.

	IONSTB
Ph_3C^+	256
Ph_2CH^+	214
$PhCH_2^+$	166
Et_3C^+	180

(6) π-Donor sites capable of complex formation with AlH_3 and B_2H_6 through coordination with π-bonds (e.g., olefinic and acetylenic bonds) or with electron lone pairs on heteroatoms (e.g., epoxy and carbonyl oxygen atoms) are perceived as potentially reactive.

(7) Certain sites with specific attachments require special treatment and have to be perceived separately. An example is the carbonyl group in acylpyrrole **19**. Reduction of this group to a methylene unit by $NaBH_4$ under neutral conditions proceeds via a carbinol intermediate (eq 52).[83] The ring nitrogen participates in the reduction through an azafulvene intermediate **21**.[83] Note that the presence of a proton or an easily expelled sulfone group is necessary for the reduction of pyrrolylcarbinol **20**.



(52)

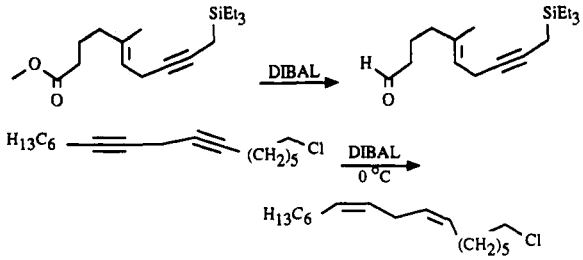
Finally, other sites are perceived on the basis of existing literature precedents. These sites include the hetero–hetero bonds in disilanes, peroxides, disulfides, oxysulfides, and nitro compounds.

C. Ranking of Reactive Sites. Once all possible reducible sites have been identified, the issue of selectivity is addressed. As previously mentioned in section II.B, very few investigations to establish the chemoselectivities of hydride reagents have been carried out. For the program to be reliable, it must be able to generate the correct functional group transformation as well as predict accurately the reactivity order of competitive sites. In this regard, reactivity tables for the selected reagents were developed. The resultant rankings for the parent hydrides are presented in Tables I–IV. The corresponding tables for the hydride derivatives are not shown since they are patterned after those of the parents with slight modifications to reactivity level assignments. In each table, the reactive site, reactivity level, reaction conditions, and reduced product are given. Reactivity decreases with increasing level number, and sites belonging to a lower level can be selectively reduced in the presence of sites belonging to higher levels.

A literature survey of more than 500 reactions was made, and information pertaining to reactivity was collated. Such information includes rate data from reported reaction times and conditions, reductions of polyfunctional molecules, and product yields for competitive reductions and mechanistic considerations. From the condensed information extracted from the literature, competitions between sites were analyzed and the relative reactivity of these sites was deduced iteratively until a "fit" for all experimental data was obtained. Various methods were employed in constructing the functional group reactivity tables. One method orders reactivity based on rate data. For example, reduction of caproic acid with diborane at 0 °C is 100% complete in 15 min, while reductions of the corresponding primary amide and acid chloride are only about 50% complete after 48 h at 0 °C.[33] Reduction of epoxides with diborane proceeds extremely slowly, requiring 2–3 days for completion at 25 °C (e.g., the required reaction times for 1,2-cyclohexene oxide and 1,2-butene oxide are 48 and 72 h, respectively).[33] The above rate data suggest the following relative reactivity: acid > primary amide, acid chloride > epoxide. Note that in Table IV the corresponding reactivity levels for these sites are 2, 4, and 5, respectively.

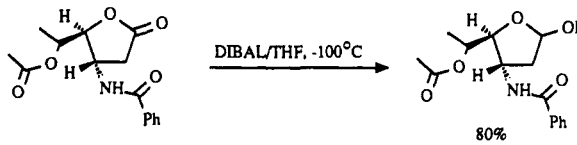
Another method of ranking functional groups involves the use of available data on selective transformations. For example, an ester group can be selectively reduced by DIBAL in the presence of an acetylenic bond (e.g., eq 53).[84] An acetylenic bond, in turn, can be reduced without af-

(82) Paderes, G. D.; Jorgensen, W. L. To be published.
(83) Greenhouse, R.; Ramirez, C.; Muchowski, J. M. *J. Org. Chem.* **1985**, *50*, 2961.
(84) Johnson, W. S.; Elliot, J. D.; Hanson, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 1138.

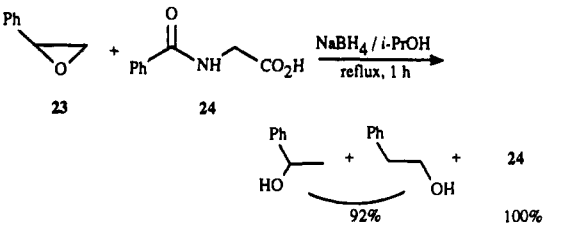


fecting a halide group (e.g., eq 54).[85] Therefore, the following reactivity order is in effect: ester > alkyne > alkyl halide. The initial reactivity level assigned to a functional group may be adjusted depending on the nature of the substituents attached to it. For example, a conjugated double bond may be assigned to different levels based on the electronic effects of its substituents. Since the electron deficiency of conjugated double bonds is reflected in their LUMO energies and since CAMEO is presently able to make accurate predictions on the FMO energies of π-systems,[6b,82] this facility is utilized as a means for estimating the electronic effects of the double-bond substituents. Depicted in Table V are examples of calculated LUMO energies for some representative olefinic sites. The assigned levels as well as the reaction conditions are also given.

Employing selective transformations as a criterion for determining reactivity is extremely useful, especially in cases where the reactive sites involved are reducible under similar conditions. For example, although lactone,[86] ester,[87] and amide[88] groups are all readily reduced by DIBAL at temperatures below 0 °C, the greater reactivity of the lactone group over the latter two is established though selective reductions (eq 55).[89] Thus, for DIBAL, lactone



groups are assigned to reactivity level 1, whereas amide and ester groups are assigned to reactivity level 2. Note that no differentiation in the reactivity of lactone is observed for AlH_3 (see Table III). In general, sites are strongly differentiated with milder reagents, while a leveling of reactivity is observed for stronger reagents. Competitive reductions can occur intermolecularly; hence, product yields are important in determining relative reactivity (e.g., eq 56).[65a] Oftentimes, data on direct com-



petitions for specific sites are absent. In this case, the reactivity relationships between these sites are established by combining the two methods already mentioned. To illustrate, a keto group is reduced selectively by $NaBH_4$ in the presence of an ester group.[90] In a separate study, an oxirane ring is reduced preferentially over an ester group by $NaBH_4$.[65a] Since no examples of direct compe-

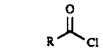
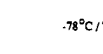
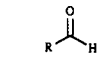
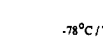
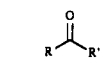
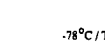
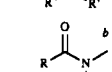
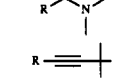
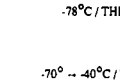
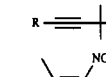
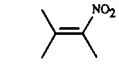
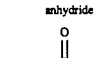
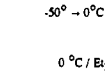
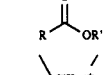
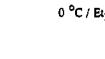
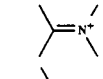
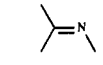
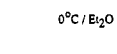
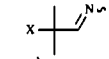
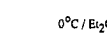
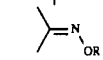
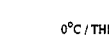
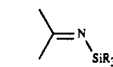
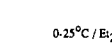
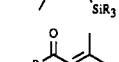
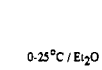
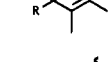
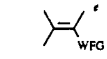
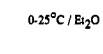
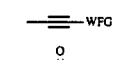
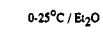
Table I. Reactivity Table for $NaBH_4$ Reductions

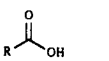
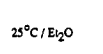
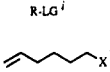
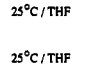
reactivity level	reactive site[a]	reactn condns	product(s)
1		-70°C / DMF	
		-78°C / DMF	
2		-78°C / aq. dioxane or ROH	
	imide	-40°C / EtOH-DMF or abs EtOH or MeOH	hydroxy lactam
	anhydride	0-25°C / i-PrOH	lactone
		0-25°C / TFA	
		0-25°C / MeOH or i-PrOH	
		0-25°C / THF-MeOH	
3	Ar_3C-OH Ar_2CH-OH	0°C / TFA 20°C / TFA	Ar_3C-H Ar_2CH_2
		0-25°C	
		0-25°C / MeOH - CH_2Cl_2	
		DMF 0-25°C / dioxane - EtOH Abs. EtOH	
		0-25°C / Abs. EtOH	
		25°C / EtOH:dioxane[d]	
		25°C / THF	R - NH_2
		25°C / EtOH	
4		H_2O or 25°C / i-PrOH or Aq. dioxane[f]	RCH_2OH + R'OH
	lactone	25°C / EtOH	glycol
	R-X[g]	25°C / EtOH	R-H
	$R-CO_2H$	67°C / THF	$R-CH_2OH$
		reflux / THF - MeOH	R-NH_2
5	lactam	reflux / t-BuOH - MeOH	cyclic amine
	thiolactam	reflux / t-BuOH - MeOH	cyclic amine
		70°C / DMSO - $MeSO_3H$	R - CH_2OH + 
		75°C / i-PrOH	Ar-CH_2-H(R)
6	R-Cl	80°C	R-H
		80°C	
		78°C / EtOH	

[a] R, R' = alkyl or aryl unless specified otherwise. [b] C=C bond may be reduced selectively in pyridine solution. [c] Conjugated FG's such as CO_2H, CO_2R, CONRR', SO_2R, NO_2, CN. [d] HOAc workup. [e] R = $ArSO_2$, RCO, aromatic ring. [f] HCl workup. [g] X = I, Br, OSO_2R. [h] R = alkyl group. [i] Ar = pyrrole. Note: the nitrogen atom in pyrrole participates in the reduction.

(85) Gensler, W. J.; Bruno, J. J. *J. Org. Chem.* **1963**, *28*, 1254.
(86) (a) Corey, E. J.; Ohuchida, S.; Hahl, R. *J. Am. Chem. Soc.* **1984**, *106*, 3875. (b) Baldwin, J. E.; Barden, T. C. *J. Org. Chem.* **1981**, *46*, 2442.
(87) (a) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988. (b) Banfi, L.; Colombo, L.; Gannari, C.; Scolastico, C. *J. Chem. Soc., Chem. Commun.* **1983**, 1112.
(88) (a) Nagao, Y.; Kawabata, K.; Seno, K.; Fujita, E. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2470. (b) Izawa, T.; Mukaiyama, T. *Chemistry Lett.* **1977**, 1443.
(89) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1981**, *46*, 227.
(90) Templeton, J. F.; Sashi Kumar, V. P.; Gupta, R. K.; Friesen, A. M. *Steroids* **1986**, *48*, 339.

Table II. Reactivity Table for $LiAlH_4$ Reductions

reactivity level	reactive site[a]	reactn condns	product(s)
1		-78°C / THF	
		-78°C / THF	
		-78°C / THF	
		-78°C / THF	
		-70° → -40°C / THF	
		-70° → -40°C / THF	
	anhydride	-50° → 0°C / THF	lactone
		0 °C / Et_2O	
		0 °C	
2		0°C / Et_2O	
		0°C / Et_2O	
		0°C / THF	
		0-25°C / Et_2O	
		0-25°C / Et_2O or THF	
		0-25°C / Et_2O	
		0-25°C / Et_2O	
		0°C / THF	
	lactam	25°C / THF	acyclic hydroxy amine
		25°C / THF	
		0 - 35°C / Et_2O	

reactivity level	reactive site[a]	reactn condns	product(s)
3		25°C / Et_2O	
	$(R'_2N)_2P\text{-}X$[g]	0 - 25°C / Et_2O	$(R'_2N)_2P\text{-}H$
	$R_3Si\text{-}SiR_3$	25°C	2 $R_3Si\text{-}H$
	$R_3Si\text{-}X$[h]	25°C	$R_3Si\text{-}H$
	R-LG[i]	25°C / THF	R-H
		25°C / THF	
		20°C / Et_2O	
		35°C / Et_2O	
	cyclic urea	25°C / Et_2O	cyclic 1,3 - diamine
	cyclic carbonate	25°C / Et_2O - CH_2Cl_2	1,2 diol
		35°C / Et_2O	
		25°C / THF	
		35 °C / Et_2O	
		35 °C / Et_2O	
	$Ar_3C\text{-}OH$	THF	$Ar_3C\text{-}H$
	$Ar_2CH\text{-}OH$	THF	$Ar_2CH\text{-}H$
	$R_3Si\text{-}X$[k]	35 °C / Et_2O	$R_3Si\text{-}H$
	$R_3Si\text{-}OR$	35 °C / Et_2O	$R_3Si\text{-}H$
	$Ar\text{-}NO_2$	37 °C / Et_2O	Ar - N = N - Ar[l]
	lactone	35 °C / Et_2O	glycol
		81 °C / C_6H_6	
	imide	67 °C / THF	cyclic amine
	R - LG[j]	35 °C / Et_2O	R - H
	RR'C = N - OH	35-67 °C / Et_2O or THF 50 °C / HMPA	$RR'CHNH_2$ + $RNHCH_2R$ RR'C = O
		50 °C / HMPA	
		35 °C / Et_2O	

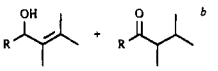
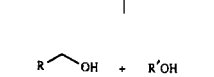
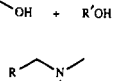
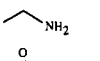
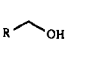
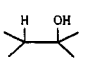
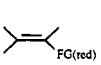
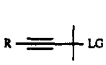
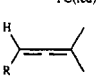
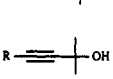
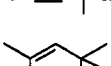
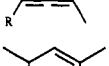
[a] R, R' = alkyl or aryl unless specified otherwise. [b] R = olefinic, alkyl, aryl. [c] Poor leaving group (e.g., $^+NR_3$). [d] Exceptions are cinnamyl systems in which conjugate reductions are observed. [e] Conjugated withdrawing groups (e.g., ester, amide, acetate, nitrile and sulfonate; the latter two are not reduced). [f] WFG(red) = reduced form of WFG. [g] R' = CH_3. [h] X = I, Br. [i] LG = I, Br, Cl, OSO_2R. [j] LG = $^+SR_2$, $^+NR_3$, $^+PR_3$, $PO(OR)_2$. [k] X = F, Cl. [l] Hindered nitro groups are not reduced.

tition between ketones and epoxides are provided in the literature, complementary rate data may be used to assign the reactivity level. From the results of kinetic experiments conducted by Brown and Khrishnamurthy,[8] ketones are much more reactive than epoxides toward $NaBH_4$. Thus, the following reactivity order may be deduced: ketone > epoxide > ester. The corresponding reactivity levels for these sites (Table I) are 2, 3, and 4, respectively. Occasionally, data on both competitive reductions and rate studies are lacking. In this case, reactivity is gauged on the basis of other factors such as the nature of the reagent, reaction conditions, and functional group philicities (section II.A). Thus, if the hydride is an exceedingly powerful reductant (e.g., $LiAlH_4$), then sites that are reduced at temperatures below 0 °C may be assigned to reactivity level 1.

A third method for assessing reactivity relies on the analysis of reaction mechanism. For example, reductions of alkyl halides proceed via a S_N2 mechanism. Thus, saturated carbon electrophiles possessing potential leaving groups are ranked according to the nature of the attached functionalities. In this case, the pK_a's of the protonated leaving groups are utilized to help evaluate the competition between carbon sites. CAMEO is presently equipped with an efficient algorithm for calculating the pK_a's of organic compounds in both aqueous and aprotic media.[4e] Table VI depicts the use of pK_a's in determining the chemoselectivity in the reduction of propargylic systems by $LiAlH_4$ (see section II.A.1.g).

D. Selection of Sites. A hierarchical procedure for site selection is effected by imposition of the user-specified reaction conditions. The choices of conditions that are available to the user are reaction temperature (<0, <50, <100, <200, <300, >300 °C), reagent stoichiometry (1 equiv, first selectivity, excess), and type of media (acidic, neutral, basic). The default stoichiometry is first selectivity, which means that an appropriate number of equivalents of reagent will be used to reduce all sites of

Table III. Reactivity Table for AlH_3 Reductions

reactivity level	reactive site[a]	reactn conds	product(s)
1		-70°C / Et_2O	
		-70°C / Et_2O	
		0 °C / THF	 [b]
		0 °C / THF	
		0 °C / THF	
		0 °C / THF	
	lactone	0 °C / THF	diol
	lactam	0-25°C / THF	cyclic amine
		25 °C / THF	
2		25 °C / Et_2O	
		25 °C / Et_2O	
		0 - 25 °C / THF or Et_2O	
	 [c]	0 - 25 °C / Et_2O	
	 [d]	0-25°C / THF	
		0 - 25 °C / THF	
	 [e]	20 °C / THF	
	R - SO_2R'	25 °C / THF	R - H
		·	
3	RR'C=N - OH	65 °C / THF	RR'CH - NH_2 + R - NH - R'
	R - X	·	R - H
	Het - Het	·	Het - H + H - Het

[a] R, R' = alkyl, aryl. [b] Minor product. [c] FG = CO_2R, CONRR', CO_2H, CN. [d] LG = I, Br, Cl. [e] Y = R_3P^+, $PO(OR)_2$.

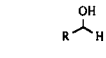
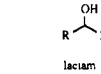
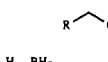
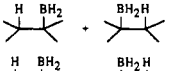
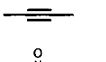
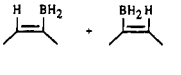
similar reactivity. The default acidity is reagent dependent (e.g., basic for $LiAlH_4$, neutral for B_2H_6), while the default temperature range is <50 °C since most hydride reductions are conducted at room temperature. Selection of a different set of conditions overrides the default options.

The first condition to be imposed in the weeding out of sites is the temperature range. With reference to the reactivity tables, sites that are reduced at temperatures above the user-specified temperature range are removed from consideration. For example, elevated temperatures (80 °C)[91] are required for the reduction of alkyl azides by $NaBH_4$. By selecting the <0 or <50 °C ranges, these sites are eliminated.

The next condition to be imposed is the stoichiometry. With the 1 equiv and first selectivity options, only the sites

(91) (a) Rolla, F. *J. Org. Chem.* **1982**, *47*, 4327. (b) Soai, K.; Yokoyama, S.; Ookawa, A. *Synthesis* **1987**, 49.

Table IV. Reactivity Table for B_2H_6 Reductions

reactivity level	reactive site[a]	reactn condns	products
1		< 0 °C / THF	
2		< 0 °C / THF	
	imide	- 30 °C / THF	lactam
	lactam	- 10 °C / THF	hydroxy amine
		< 0 °C / THF	
		0 °C / THF	
		0 °C / THF	
		25 °C / THF	
	lactone	25 °C / THF	diol or ether
3		25 °C / THF	
		25 °C / THF	R - OH + R'OH
		25 °C / THF	
	[b]	25 °C / THF	
		reflux / THF	
		·	
2	[c]	25 °C	
	Ar - N=N - Ar'	·	Ar - NH_2 + Ar' - NH_2
	RR' S=O	·	R - S - R'
	Ar - N=O	25 °C	Ar - NH_2
4	[d]	·	
		25 °C/ THF	
5		25 °C/ THF, 2 days	mixture [e]
		125 °C	
	R - C≡CN	65 °C/ THF	R - CH_2 - NH_2
		115 °C/ THF	

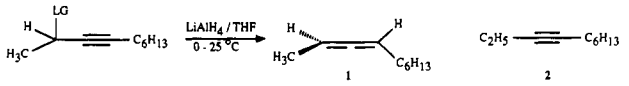
[a] R, R' = alkyl or aryl unless specified otherwise. [b] M^+ = alkali metal ion (e.g., Li^+, Na^+). [c] FG = alkyl, aryl, or acyl. [d] X = halogen. [e] See Scheme IV.

Table V. Substituent Effects on the Relative Reactivity of Alkene toward $NaBH_4$ Reduction

olefin	predicted *E*(LUMO), eV	reactivity level in CAMEO	expl reactn condns	ref
H_2C=CPhNO_2	-2.5	2	0 °C/THF-MeOH	45a
H_2C=CHCOMe	-0.4	3	25 °C/THF-MeOH	45a
PhCH=CHCN	-0.4	3	25 °C/abs EtOH	45c

belonging to the highest reactivity level are permitted to react. With the excess reagent option, all sites belonging to levels that fall within and below the selected temperature block are considered. For clarity, "first selectivity" differs from "1 equiv" in the mode of product formation.

Table VI. Effect of the Leaving Group Ability on the Reduction of Propargylic Systems with $LiAlH_4$



leaving group	predicted pK_a (DMSO)	reactivity level in CAMEO	% yield 1	% yield 2	ref
OSO_2Me	5	2		85	60
Br	1	2		75	60
N^+Et_2Me	15	3	96		60

With the former, similarly reactive sites are reduced simultaneously; with the latter, sites of similar reactivity are reduced one at a time leading to mixtures.

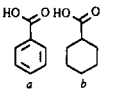
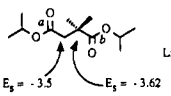
Finally, further pruning of sites is effected by imposing the acidity conditions. For example, aldehydes and ketones are reduced by $NaCNBH_3$[17] under acidic conditions (section II.A). By selecting neutral or basic conditions, the above carbonyl sites are deleted. Once all the reaction conditions have been examined, the final selected sites are subjected to further characterization and mechanistic analysis.

E. Mechanistic Analysis and Generation of Products. Before generating the products, some preparatory steps such as determination of the mode of product display and assignment of yield estimates are carried out. In connection with the former, reactive sites that yield complex mixtures are identified. If such sites are present, they are reduced one at a time regardless of the stoichiometry specified by the user, and an appropriate message is provided. Thus, the display of products showing all possible combinations of reductive transformations is circumvented. With regard to designating yield estimates to the ensuing products, the following are considered: (1) homoselectivity, i.e., competitions between sites of the same functionality, (2) regioselectivity, i.e., the preferred orientation of hydride attack at a given functionality, and (e) pathway selectivity, i.e., competitions among the different mechanistic pathways that may be operative for a given site. Note that homoselectivity has been partly dealt with along with chemoselectivity during the ranking of sites (section III.C).

To facilitate the evaluation of the aforementioned selectivities, it is necessary to characterize the sites in terms of steric and electronic requirements. Recently, a quantitative procedure for evaluating steric effects using the Taft approach[92] has been implemented in CAMEO.[93] The application of this procedure in the determination of homo-, regio-, and pathway selectivities is discussed in the following text.

1. **Homoselectivity.** Homoselectivity can be found in the reductions of acids and esters by nucleophilic hydrides. In these cases, selectivity results from an interplay of steric and electronic effects, with the latter often predominating. The following order of reactivity based on the hybridization of the α-carbon atom has been implemented in CAMEO: aliphatic > aromatic > unsaturated acids and esters.[10] The presence of a heteroatom at the α-position disfavors hydride attack at the adjacent carbonyl atom.[10] In the absence of α-hetero substituents, reduction of the carbonyl group attached to a tertiary carbon center is highly preferred.[37d] Examples illustrating the application of reactivity order and E_s estimates in determining the homoselectivity in the reduction of acids and esters are shown in entries 1–3 of Table VII.

Table VII. Regioselectivity in the Reduction of Organic Compounds by Hydride Reagents

entry no.	substrate	reagent	ratio of hydride attack, a:b[a]	estimated yield in CAMEO[b]	ref
1		$NaBH_4$	7 : 84	a minor b major	10
2	a Cl-CH_2-CO_2H b n-C_6H_{13}-CO_2H	$NaBH_4$	30 : 60	a minor b major	10
3		$LiAlH_4$	b sole product	a minor b major	37d
4		$NaBH_4$	a sole product	a major	94
5		$NaBH_4$	95% : trace (76)	a major b minor	37b
6		$LiAlH_4$	19 : 1 (70)	a major b minor	94, 95
7		$NaBH_4$ $LiAlH_4$ AlH_3 B_2H_6	87 : 13 (97) 98 : 2 73 : 27 0 : 100 (98)	 a major b minor b major	65a 29c 29c 90a
8		B_2H_6	0 : 100	b major	31

[a] Total yield in parentheses. [b] Alcohols for entries 1–3, 6; lactones for entries 4 and 5; boron adduct for entry 7.

2. **Regioselectivity.** High regioselectivity is often exhibited in the reduction of unsymmetrically substituted cyclic anhydrides with nucleophilic metal hydrides. Several factors, which include the electronic effect on the LUMO coefficient of the carbonyl carbon, the steric congestion and topological accessibility of the site, and occasionally, the chelating ability of the substrate, have been invoked in rationalizing the observed selectivities. Despite these complexities, reasonable regiochemical predictions can be made on the basis of the following rules:

(a) Unsaturated α-carbon atoms strongly disfavor hydride attack at the adjacent carbonyl carbon (e.g., entry 4, Table VII). If both α-carbon atoms are aromatic, a check is made to see if chelation is possible. The carbonyl carbon that participates in chelation with a lithium ion is deemed less reactive (e.g., eq 12).

(b) α-Carbon atoms bearing electron-withdrawing substituents disfavor hydride attack at the adjacent carbonyl carbon (e.g., entry 5, Table VII). However, unsaturated α-carbon atoms exert a stronger effect; this is manifested in much lower estimated LUMO energies of carbonyl groups adjacent to unsaturated carbon centers.

(c) In the absence of the electronic features of rules 1 and 2, reduction of unsymmetrical, nonbridged, cyclic anhydrides preferentially occurs at the more hindered carbonyl carbon[37c,94-96] (e.g., entry 6, Table VII). This preference diminishes as the ring size increases due to the increasing conformational flexibility of the anhydride ring. The observed regioselectivity is attributed to the combined,

(92) Unger, S. H.; Hansch, C. *Prog. Phys. Org. Chem.* **1976**, *12*, 91.
(93) Fleischer, J. M.; Gushurst, A. J.; Jorgensen, W. L. To be published.
(94) Bailey, D. M.; Johnson, R. E. *J. Org. Chem.* **1970**, *35*, 3575.
(95) Morand, P.; Kayser, M. *J. Chem. Soc., Chem. Commun.* **1976**, 314.
(96) Bloomfield, J. J.; Lee, S. L. *J. Org. Chem.* **1967**, *32*, 3919.

reinforcing effects of steric and electronic factors (see section II.A.1.b).

(d) For cyclic anhydrides with both α-carbon atoms adjacent to bridgehead atoms in small bridged systems, the regioselectivity is reversed; i.e., hydride attack occurs at the less hindered carbonyl carbon.[37c] Hydride attack occurs at the more accessible convex side of the molecule, i.e., the exo side in the endo-bridged compounds or the endo side in the exo-bridged compounds.

(e) Anhydrides with both α-carbon atoms in a three- or four-membered ring fusion exhibit little or no regioselectivity.[37b]

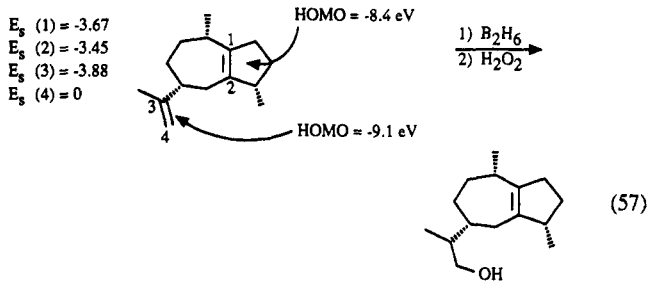
In the algorithm for evaluating the regioselectivity in epoxide reductions, the following considerations are implemented.

(a) Reduction of epoxides with nucleophilic metal hydrides (e.g., $LiAlH_4$ and $NaBH_4$) is essentially an S_N2 process; hence, attack at the less substituted carbon center is highly preferred[29c,65a,97a] (e.g., entry 7, Table VII).

(b) With electrophilic metal hydrides (e.g., AlH_3 and DIBAL), the less hindered carbon sites are preferentially reduced.[29c] However, reduction is less regioselective due to the competitive hydride transfer to the carbon atom that better stabilizes the developing cationic charge (section II.C.1.f).

(c) With boranes (e.g., B_2H_6 and Sia_2BH), regioselectivity in epoxide reductions is dictated by the relative stability of the incipient carbenium ions.[90a,97b] Exceptions are α,β-unsaturated epoxides. With these systems, reduction always occurs at the double bond via an intramolecular pathway with concomitant bond rearrangements (see section II.C.1.e).

In the algorithm for determining the homo-, chemo-, and regioselectivity in the hydroboration of alkenes and alkynes, competition between carbon–carbon multiple bonds, i.e., homo- or chemoselectivity, is evaluated by assessing both the HOMO energies of the reacting bonds and their overall steric requirements. The latter is accorded a higher priority such that highly hindered bonds are not reduced even though they may be electronically favored (e.g., eq 57).[31] Regioselectivity, on the other hand, is dictated more



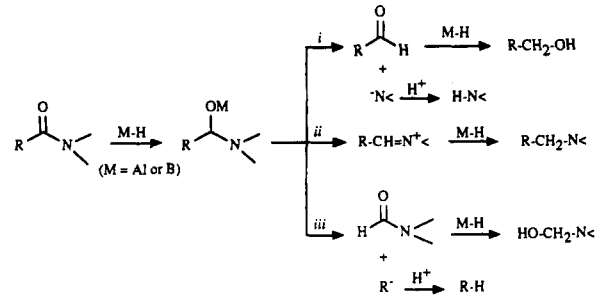
(57)

by the stability of the incipient carbenium ions than by steric accessibility. Separate ranges for ionic stability and steric hindrance have been established to determine the acceptable carbon sites to which boron must be added. Since alkynes tend to exhibit a much higher preference for less hindered carbon atoms, different cutoffs for steric requirements are utilized for alkenes and alkynes. In cases where the carbon atoms comprising the bond in question do not differ much in ionic stability and steric accessibility, then both orientations of addition are permitted. A typical regiochemical prediction from CAMEO for the hydroboration of olefins is provided in entry 8, Table VII.

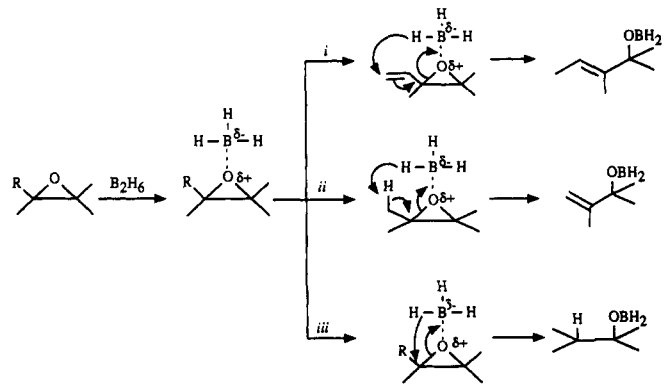
3. Multipathway Evaluation. For reactive sites that involve multipathway transformations, mechanistic analyses are performed to determine the most viable pathways. Determination of the preferred routes can be

(97) (a) Marshall, P. A.; Prager, R. H. *Aust. J. Chem.* **1977**, *30*, 141. (b) *Ibid.* **1977**, *30*, 151.

Scheme III

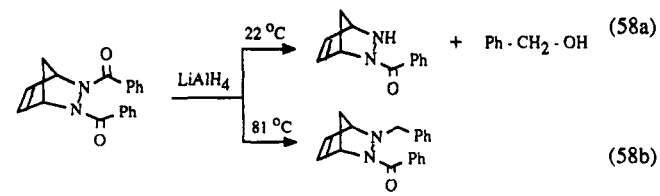


Scheme IV



complicated and may depend on (a) the structural features of the substrates and intermediates, (b) the specified reaction conditions, and (c) the nature of the input reagent. Analysis of pathways requires the implicit presence of the intermediate complex as well as the explicit generation of ionic intermediates. The presence of certain structural and electronic features in both substrate and intermediate may trigger the selection of a reaction pathway.

The above considerations can be demonstrated for the reduction of amides. The algorithm for assessing the pathway competition in this reaction is based on Scheme III.[41] Path i is selected if the specified temperature range is <0 °C (see eqs 13, 16, and 17). The reduced product that is displayed to the user depends on the input stoichiometry. For 1-equiv conditions, the aldehyde product is output, while for first selectivity and excess conditions, the alcohol is shown. In the 0–50 °C range, path ii becomes competitive, and its selection depends on the nature of the input reagent. For electrophilic hydrides, path ii much more facile than path i, presumably because of the greater ease of expulsion of the boronate or aluminate groups in the complex (see eq 18). In such cases, only the product emanating from path ii is formed. For nucleophilic hydrides, products generated via path i and path ii are shown. In the 50–100 °C range, path ii becomes predominant (e.g., eq 58).[39b] Products from path iii are formed only when the required stability of the carbanion intermediate is satisfied.

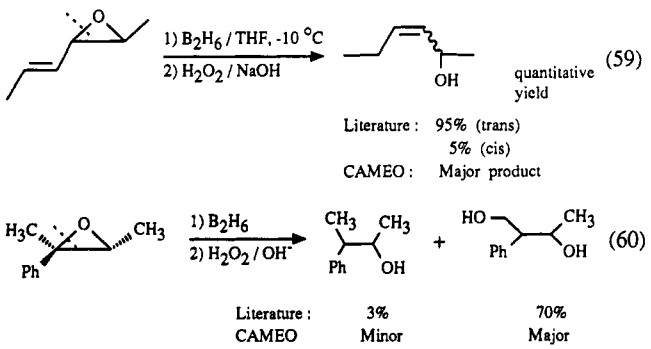


(58a)

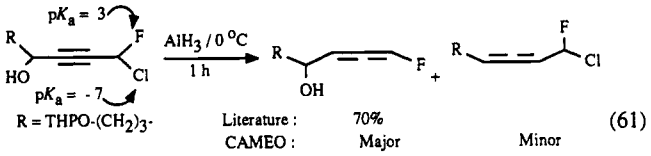
(58b)

Another example that demonstrates pathway competition is the reduction of epoxides by diborane. In Scheme IV, three mechanistic pathways may compete, namely intramolecular hydride addition to double bonds (path i), proton abstraction (path ii), and intramolecular substitution (path iii). Product prediction is simplified by prior evaluation of regioselectivity, i.e., the preferred C–O bond

cleavage (see section III.E.2). A hierarchical search for the presence of an addition site and an abstractable proton α to the carbon atom of the pertinent C–O bond is then carried out. If these sites are present, the corresponding reaction path is selected (e.g., eq 59);[61] if absent, path iii is selected as the major reaction pathway. It should be noted that the allylic alcohols formed from paths i and ii may be subject to further reduction (e.g., eq 60).[97a]



Another interesting example that demonstrates pathway selectivity is shown in eq 61.[70] In this reaction, two mechanistic processes in succession are in operation, proton abstraction to form an organometallic complex and intramolecular hydride addition to a triple bond. The regioselectivity for the latter is dictated by the presence of viable leaving groups at the propargylic position remote from the hydroxy group. The preferential expulsion of the chloride anion over the fluoride anion is determined by the relative leaving ability of the halogens.



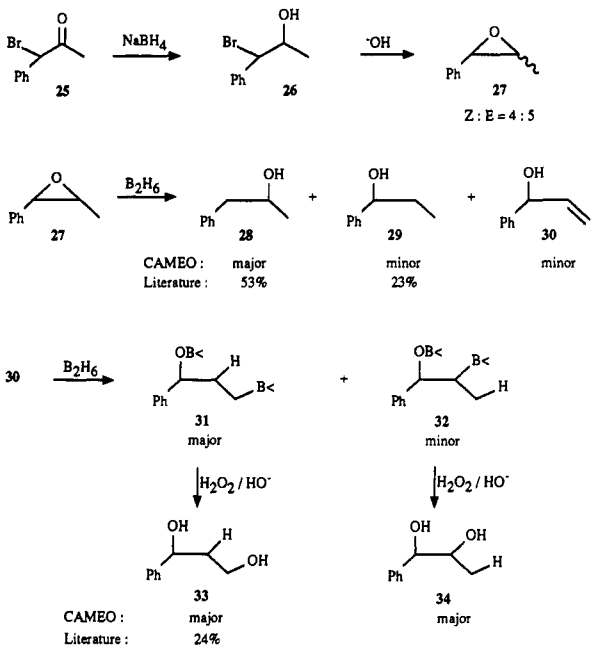
Finally, single-pathway transformations are processed according to their mechanistic categories; i.e., sites with identical reaction mechanisms are evaluated concurrently. This modular processing is highly advantageous since reactions with obscure mechanisms can be treated separately. Although the majority of hydride reductions can be mechanistically rationalized, the existence of undefined reductive transformations cannot be ignored. Thus, an approach that is currently appropriate and amenable to modification and expansion is imperative at this point.

IV. Sample Synthetic Sequences

It has been demonstrated that the CAMEO program can make reliable predictions for a variety of hydride reductions (Table VII). Analysis of complex reactions is made possible by employing mechanistic reasoning during different stages of implementation, from perception of potentially reducible sites to multipathway evaluation. The success of the program relies on outright recognition of the fundamental mechanistic steps involved and on systematic classification of reactions taking into consideration the nature of the reagents. The following representative schemes further illustrate the current predictive capabilities of the program. Each structure in the schemes corresponds to a structure in the reaction tree, as given by the CAMEO program. All input and output structures are stored in this synthetic tree and may be retrieved by the user for further processing.

In Scheme V,[97a] two possible sites of reduction by $NaBH_4$ are recognized for substrate **25**: the halogen-bearing carbon electrophile and the carbonyl carbon atom.

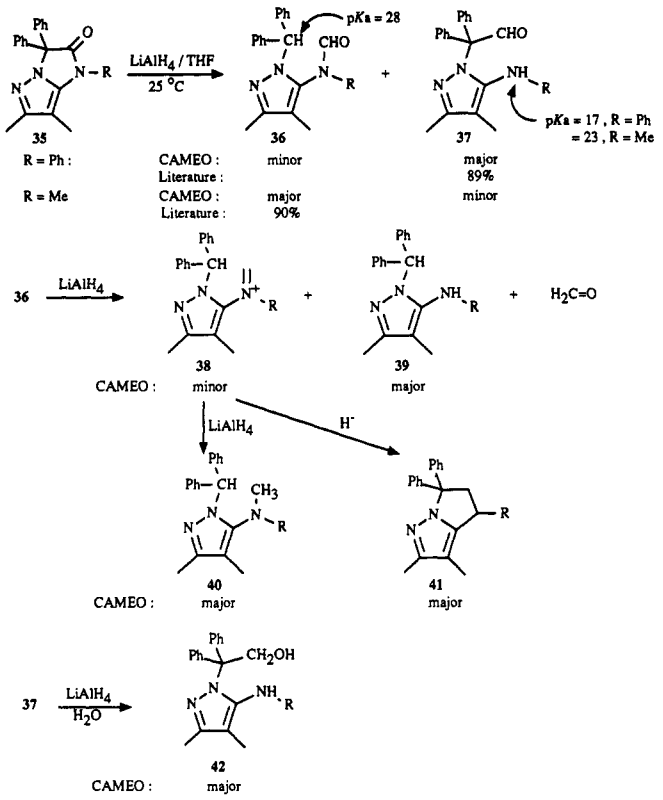
Scheme V



By referring to the reactivity levels in Table I, the former site is considered less reactive under the default stoichiometric conditions. Processing of the latter site using the redox module then gives the corresponding alcohol **26**. Submission of **26** to the nucleophilic module gives epoxide **27** as the major product. Reduction of **27** with diborane yields three products, two of which result from an intramolecular hydride transfer to the epoxy carbon atoms. The designated yields reflect the regioselectivity of hydride attack, i.e., the relative stability of the incipient carbenium ions (section III.E.2). The third product, **30**, results from an intramolecular proton abstraction process and is shown with a minor product designation. Resubmission of **30** to the redox module using the same reagent yields two hydroborated products resulting from stereospecific cis addition of borane to the olefinic bond. Note that CAMEO presently assumes a 1:1 stoichiometry between the reagent and the substrate such that the second and the third stages of hydroboration are not shown. The ratio of the hydroborated products reflects the preferential addition of the boron atom to the terminal olefinic carbon in **30**. Both steric and electronic considerations are utilized in determining the final regiochemistry of the reduction (section III.E.2). Separate submission of **31** and **32** to the redox module using hydrogen peroxide under basic conditions gives the corresponding reported diols. The present scheme demonstrates the ability of CAMEO to simulate the stepwise conversion of an α-bromo ketone to alcohols and diols via the well-known hydroboration–oxidation procedure. Note that the output yield estimates reflect the relative proportion of the products for a given process. Thus, an initial minor product may give rise to a major product upon resubmission.

Scheme VI illustrates the first reported example of carbonyl/α-carbon cleavage in amides with $LiAlH_4$.[41] Under 1-equiv conditions, the cyclic amide **35** is reduced to formamide **36** and oxoamine **37** via an addition–elimination process involving C–C and C–N bond cleavages, respectively. The product ratio reflects the relative stability of the anionic intermediates, as determined by the predicted pK_a values of the corresponding protonated species. In CAMEO, C–C cleavage is performed only if the protonated carbanion has a pK_a of 31 or less. If the difference in the pK_a's of the protonated carbon and nitrogen

Scheme VI



anions is greater than 8, then C–N cleavage is favored; otherwise, C–C cleavage becomes the predominant pathway. Thus, when R is changed from an aryl to an alkyl group, C–C cleavage becomes more favored, and compound **36** is displayed with a major product designation. Resubmission of **36** under 1-equiv conditions yields the iminium ion intermediate **38** and the secondary amine **39** in minor and major amounts, respectively. It must be recalled that with nucleophilic hydrides, iminium ion formation is normally not favored unless an elevated reaction temperature is specified (see section III.E.3). Resubmission of **38** under 1-equiv conditions gives the tertiary amine **40**. The reported products in the literature for the reduction of **36** include the cyclic amine **41** in addition to amines **39** and **40**. The redox module does not output the former product since it arises from a nonreductive process. However, this product may be obtained upon submission of intermediate **38** to the nucleophilic module with hydride anion as the input reagent. Finally, resubmission of **37** to the redox module gives the amino alcohol **42**. Note that with first selectivity conditions, reduction of **35** leads directly to **36** and **42**, and reduction of **36** leads directly to **39** and **40**.

V. Conclusion

The reductive chemistry of a representative variety of synthetically useful hydride reagents has been implemented in the CAMEO program. This required a systematic analysis of numerous reactions in terms of basic mechanistic steps. The recognition of these steps, which are shared by both nucleophilic and electrophilic hydrides, is crucial to the development of efficient algorithms for evaluating reductions. Mechanistic analyses are applied to determine (a) the reactivity of a given site, (b) the chemoselectivity of the hydride reagent, (c) the regiochemistry of hydride attack on specific sites, and (d) the preferred routes in multipathway transformations. Existing algorithms in CAMEO for calculating parameters such as frontier molecular orbital energies, bond dissociation energies, ion stabilities, pK_a's, and Taft E_s parameters are utilized during reaction evaluation. Additionally, reactivity tables with general utility were developed for the covered reagents to address competitions among potentially reactive sites. Finally, a modular approach in the implementation of hydride reductions has been undertaken to accommodate transformations with currently unknown mechanisms.

Acknowledgment. Gratitude is expressed to the National Science Foundation for support of this work. Thanks are also due to Daniel L. Severance for his assistance in the development of algorithms.

Electron-Transfer Reactions. Oxidation of Grignard Reagents in the Presence of an Aminoxyl as a Radical-Trapping Agent

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The indole bisnitrone **1** ($E_{1/2}$red = −0.125 V vs NHE in DMF) reacts with a series of Grignard reagents (RMgX) including primary, secondary, and tertiary alkyls and benzyl and phenyl derivatives, which show different E_{ox}, by single electron transfer to form C-centered radicals corresponding to the Grignard used. The radicals produced in the reaction were trapped by the (arylimino)indolinone nitroxide **5** to form the alkylated hydroxylamines **6**. When the reaction is carried out with a "cyclizing Grignard" such as 5-hexenylmagnesium bromide, the uncyclized (5-hexen-1-yl) **6g** and cyclized (methylcyclopentyl) **6h** alkylated hydroxylamines are both isolated. In all cases, the Marcus theory treatment predicts high electron-transfer rate constants.

The reactions of Grignard reagents with organic substrates have been widely studied from the synthetic point of view,[1] and it can be safely asserted that their role in this respect has not yet been exhausted. During the last

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