J. Org. Chem. **1994,** *59,* 762–772

Computer Assisted Mechanistic Evaluation of Organic Reactions. 23. Dissolving Metal Reductions with Lithium in Liquid Ammonia Including the Birch Reduction

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Received October 11, 1993[⊛]

The computer program CAMEO, which predicts the products of organic reactions, has been expanded to treat reductions with lithium in liquid ammonia. A comprehensive reactivity table controlling selectivity has been amassed from literature precedents. Individual reactive sites in an input substrate are evaluated using existing routines for calculating pK_as and bond dissociation energies. In the course of processing, charged mechanistic intermediates are explicitly created. When accompanying intramolecular substitutions, additions, and eliminations may occur, the intermediates are automatically submitted to the Basic/Nucleophilic module of CAMEO for further processing. Reaction sequences in the paper illustrate the current predictive capabilities of the program.

I. Introduction

CAMEO is an interactive computer program designed to predict the outcome of organic reactions given the starting materials and reaction conditions.[1] In the course of studying large numbers of reported transformations, reactivity rules based on current mechanistic and theoretical knowledge are developed. Coupled with the ability to estimate fundamental physical data including pK_as and bond dissociation energies, the program essentially attempts to predict the products of organic reactions by mimicking the reasoning of an organic chemist. The mechanistic philosophy of the program is illustrated by its division into modules which deal with individual classes of reactions that often reflect a common type of intermediate, e.g., carbanions or radicals. The classes of reactions that have been implemented include base catalyzed and nucleophilic,[2] acid catalyzed and electrophilic,[3] pericyclic,[4] redox,[5] free radical,[6] carbene,[7] and heterocyclic.[8] A recent addition is the ability to generate and analyze three-dimensional molecular structures that may be further processed by the mechanistic modules to discern stereoselectivity.[9]

CAMEO has recently been expanded to include dissolving metal reductions with lithium in liquid ammonia. The reagent is commonly used for the reduction of benzene derivatives to form 1,4-dihydrobenzenes (the Birch reduction). Since reductive transformations are generally used to effect functional group interconversions in organic syntheses, a comprehensive table of products formed upon lithium–ammonia reduction has been amassed; however, the utility and sophistication of the program does not lie in a simple representation of functional group "A" being reduced to "B". The strength of the program is in the evaluation of adjacent electronic or steric interactions that allows the overall reactivity of a substrate to be fine tuned. Reactivity rankings account for the nuances of a particular substrate by noting the interactions of adjacent groups. And since direct reduction does not always occur in lithium–ammonia reactions, charged mechanistic intermediates are evaluated at each step of the reduction to ascertain the possibility of rearrangements and side reactions occurring before final protonation. When intramolecular substitutions, additions, and eliminations accompany reduction, the intermediates are automatically submitted by the program to the Basic/Nucleophilic module of CAMEO for further processing.

II. Overview of Reduction

The mechanism of reduction with lithium in liquid ammonia is relatively well understood and follows a general sequence of steps that includes the addition of two electrons and two protons to a substrate. The reaction proceeds with the compound accepting the first electron at a site that readily stabilizes negative charge. Polar bonds (carbon–oxygen, nitrogen–oxygen, etc.) are commonly reactive, but even carbon–carbon bond systems are reactive if they are conjugated to a polar group. Depending on the nature of the reduction site, bond fission or bond saturation may take place. The fission of polar single bonds (Scheme 1)[10] occurs with alkyl and aryl halides, arylamines, and benzylic alcohols. Bond saturation of electron-rich, polar multiple bonds (Schemes 2 and 3) occurs with ketones, acetylenes, and aromatic rings. Bond fission produces a radical species and an anionic species, while bond saturation results in a radical–anion intermediate. In both

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[⊛] Abstract published in *Advance ACS Abstracts,* January 15, 1994.

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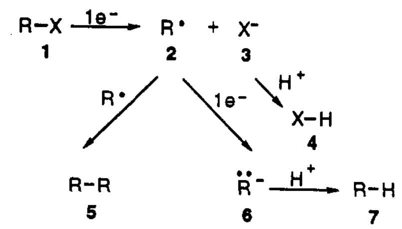
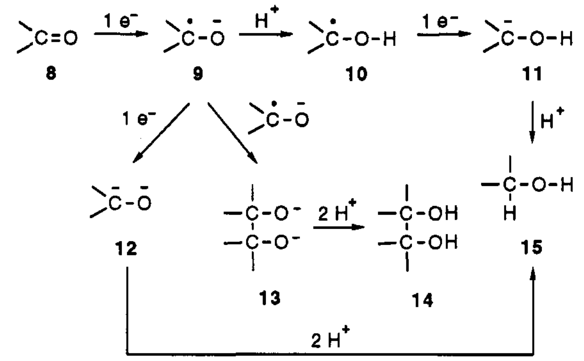
0022-3263/94/1959-0762$04.50/0

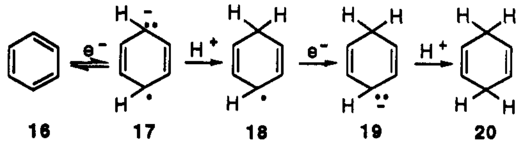
Scheme 1. Mechanism of Bond Fission of Single Bonds with Lithium–Ammonia Illustrated for Alkyl Halides



Scheme 2. Mechanism of Multiple Bond Saturation with Lithium–Ammonia Illustrated for Ketones

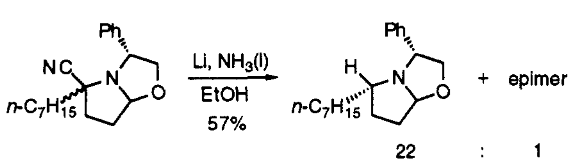


Scheme 3. Mechanism of Birch Reduction of Benzene

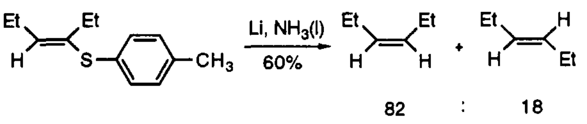


cases, reduction is complete upon addition of a second electron to the radical atom and protonation of the anions. As shown in both Schemes 1 and 2, radical coupling is in competition with reduction; however, it is usually only a significant side reaction when an aprotic solvent is used.

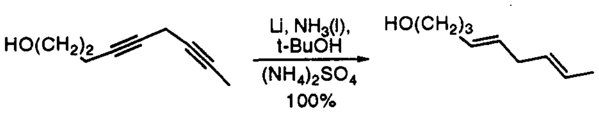
An example of bond fission using lithium–ammonia as the reducing agent is found in the cleavage of tertiary nitriles (eq 1).[11] As shown in eq 2, bond cleavage under Birch-like conditions usually occurs with retention of configuration. In fact, reductive cleavage of sp^2 carbon–sulfur bonds often occurs with greater than 90% retention of configuration;[12] cleavage of vinylic chlorides gives similar results.[13] Stereocontrol is also exhibited in bond saturation reactions. The reduction of acetylenes to form the corresponding *E*-alkenes is generally stereospecific and is shown here in the conversion of a 1,4-diyne to an *E*,*E*-1,4-diene (eq 3).[14] The *E*-isomers may be preferred because maximum separation of charge would be achieved if the dianion corresponding to 12 is formed.



(1)

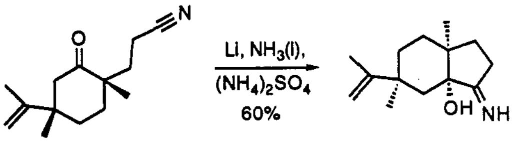


(2)



(3)

While tertiary nitriles act as pseudohalides and are readily cleaved, primary and secondary nitriles undergo some bond saturation to yield amines.[15] In eq 4, the intermediate anion that would have led to the amine is trapped by the electrophilic carbonyl site before complete saturation can take place.[16] Such intramolecular trapping of an intermediate anion is common in alkali metal–ammonia reductions.



(4)

III. Implementation of Li, NH$_3$ Reductions in CAMEO

Program development has been carried out on Digital Equipment Corporation VAX computers, and the graphical interface used is for Tektronix compatible terminals. A more detailed description of the CAMEO program may be found in a review.[1]

To run a reduction reaction, the user draws in the starting material and selects the reducing agent and reaction conditions (<0 °C, basic media, 1 equiv) from the Oxidation/Reduction menu. In CAMEO, the lithium–ammonia reagents are listed as Li/liq NH$_3$ and Li/liq NH$_3$/ROH. With the reaction defined, the user selects a button to start processing. The remainder of the paper deals with the reasoning behind the programming steps taken to enable the user to submit a starting substrate for Li–ammonia reduction and have the correct end products returned. The literature examples of lithium–ammonia reductions shown are handled correctly by the program.

Internally, potential reactive sites are first identified and their relative reactivities evaluated. Since the CAMEO program relies on the application of mechanistic reasoning, the program perceives the correct reactive sites without relying on data tables. The literature survey of lithium–ammonia reductions that is the foundation of the code is, in part, summarized, in Table 1. Of course, organic substrates are generally not as simple as the listing of isolated functional groups in Table 1 would suggest. Further refinement of rankings is necessary in some parts of the program to account for the electronic effects of nearby functional groups. Implementation of the various electron and proton addition steps is used to further evaluate metal–ammonia reductions. Mechanistic evaluation of steps leading to dimerizations, resonations, and intramolecular rearrangements often accounts for product formation. Each intermediate is explicitly formed and automatically resubmitted for processing until the final quenching step is undertaken.

A. Identification of Reactive Sites. The first step in processing is to identify the potential electron addition sites. Any site that can readily accept an electron from the lithium metal is reactive. Systems containing elec-

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Table 1. Reactivity Table of Li, NH_3(l) and Li, NH_3(l), ROH Reductions

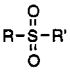
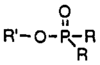
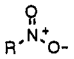
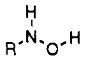
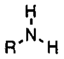
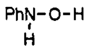
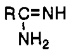
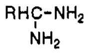
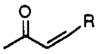
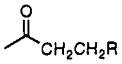
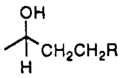
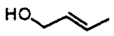
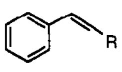
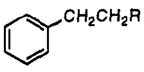
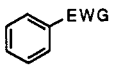
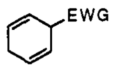
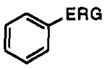
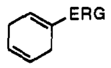
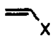
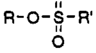
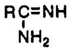
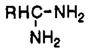
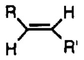
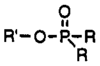
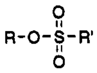
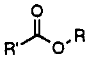
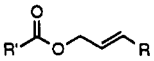
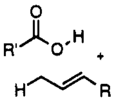
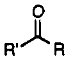
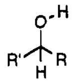
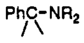
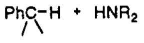
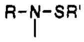
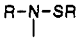
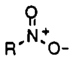
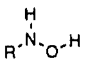
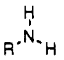
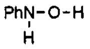
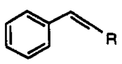
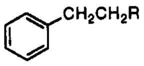
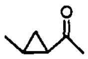
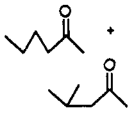
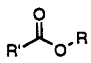
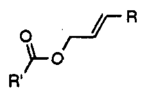
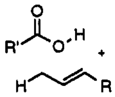
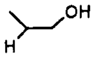
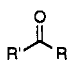
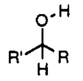
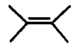
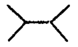
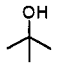
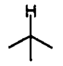
level	functional class	reactive site	product(s)	added proton source only[a]
1	isocyanide	$R-\overset{+}{N}\equiv\overset{-}{C}$	$R-H$	
	sulfones R = $-CH_2Ph$, $-CH_2COR$, $-Ph$	 $R-\overset{O}{\underset{O}{S}}-R'$	$R-H$	
	benzyl ether[b]	$PhCH_2\,OR$	$PhCH_2{\cdot}H$	√
	benzyl sulfide[b] R = alkyl	$PhCH_2{\cdot}SR$	$PhCH_2{\cdot}H$	√
	phosphate ester R = -OEt, -NMe R' = benzyl, allyl, aryl	 $R'-O-\overset{O}{P}(R)-R$	$R'-H$	√
	nitro group R = alkyl			√
	R = unsaturation			
	nitroso	$PhN=O$	 $Ph\underset{H}{N}-O-H$	√
	oxime	$RCH=N-OH$	$RCH_2{\cdot}NH_2$	√
	imine	$RCH=NH$	$RCH_2{\cdot}NH_2$	√
	amidine	 $R\underset{NH_2}{C}=NH$	 $RH\underset{NH_2}{C}-NH_2$	√
2	quarternary ammonium salt	$R'-\overset{+}{N}R_3\overset{-}{X}$	$R'H + NR_3$	
		$R'CH=\overset{+}{N}R_2\overset{-}{X}$	$R'CH_2{\cdot}NR_2$	
	α,β-unsaturated carbonyl R = H, alkyl, benzyl		 or 	√
	conjugated epoxide			
	styrene			√
	aromatic ring[c]			√
				
	halide R = alkyl, benzyl; R' = alkyl, benzyl, H; X = Cl, Br, I	R'_2RC-X	R'_2RC-H	
	vinyl halide			
	disulfide	$RS-SR'$	$RS-H + H-SR'$	
	aryl selenide	$R-SePh$	$R-H + H-SePh$	
	sufonate ester R = benzyl, allyl, aryl R' = CH_3, NR_2, etc.	 $R-O-\overset{O}{\underset{O}{S}}-R'$	$R-H$	√
	alkoxy amines hydroxyl amines R=H, alkyl	$RHN-OR'$	$RNH_2 + HOR'$	√
3	nitrile 3°	$R_3C-C\equiv N$	R_3C-H	
	2°,1°	$R'_2RC-C\equiv N$	$R'_2RC-CH_2NH_2$	
	imine	$RCH=NH$	$RCH_2{\cdot}NH_2$	
	amidine	 $R\underset{NH_2}{C}=NH$	 $RH\underset{NH_2}{C}-NH_2$	
	alkoxy amine hydroxy amine R = H, alkyl	$RHN-OR'$	$RNH_2 \bullet HOR'$	
	phenyl hydrazine	$RNH_2{\cdot}NH_2$	$RNH_2{\cdot}H$	
	oxime	$RCH=N-OH$	$RCH_2{\cdot}NH_2$	
4	alkyne R,R' ≠ H	$R-\equiv-R'$		
	phosphate ester R = -OEt, -NMe R' = benzyl, allyl, aryl	 $R'-O-\overset{O}{P}(R)-R$	$R'-H$	
	benzyl alcohol	$PhCH_2{\cdot}OH$	$PhCH_2{\cdot}H$	
	benzyl thiol	$PhCH_2{\cdot}SH$	$PhCH_2{\cdot}H$	
	sufonate ester R = benzyl, allyl, aryl R' = CH_3, NR_2, etc.	 $R-O-\overset{O}{\underset{O}{S}}-R'$	$R-H$	
	ester		$R'CH_2OH + ROH$	√
				
	aldehyde or ketone R = H, alkyl			√
	weak C-C bond	Ph_3C-CPh_3	Ph_3C-H	
5	benzyl amine	 $Ph\underset{/\backslash}{C}-NR_2$	 $Ph\underset{/\backslash}{C}-H + HNR_2$	
	nitrogen-sulfide bond	 $R-\underset{\mid}{N}-SR'$	 $R-\underset{\mid}{N}-SR'$	
	nitro group[d] R = alkyl			
	R = unsaturation			
	nitroso[d]	$PhN=O$	 $Ph\underset{H}{N}-O-H$	
6	styrene			
	cyclopropane[e] ring with conjugation			
	carbonyl of ester		$R'CH_2OH + ROH$	
				
	epoxide			

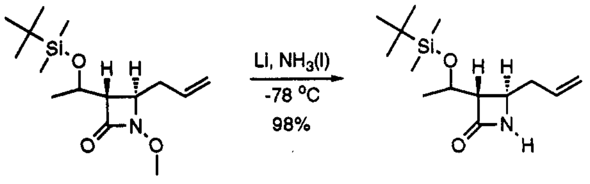
Table 1 (Continued)

level	functional class	reactive site	product(s)	added proton source only[a]	level	functional class	reactive site	product(s)	added proton source only[a]
7	carbonyl of ketone, aldehyde				8	isolated double bond			
	alcohol								

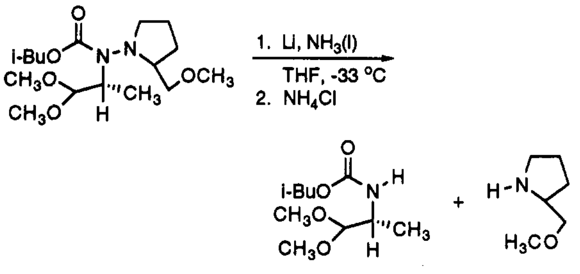
[a] The reactivity level is only valid if an acidic proton source, e.g., an alcohol, is present in the reaction media. [b] Concurrent reduction of a phenyl ring is a minor product in the presence of an added proton source. [c] Some aromatic rings, frequently polyaromatics, are activated toward reduction without the presence of an added proton source, e.g., alcohol. [d] Partial reduction product is isolated only in the absence of an added acidic proton source such as an alcohol. [e] Regioselectivity of reduction depends upon preexisting stereochemistry.

tronegative atoms are most likely to be reduced. Since oxygen is more electronegative than nitrogen, benzyl alcohols are more readily reduced than benzylamines. Lithium metal often adds electrons to π-electron systems. The more readily the π system can delocalize charge, the more stable the radical/anion species formed and the more reactive the π system. Thus, conjugated alkenes and aromatic rings are reactive, while isolated double bonds are seldom reduced. The outcome of the reduction is primarily dependent on the thermodynamic stability of the intermediates.[17] Intermediate anions must be able to effectively stabilize charge, and resonance for radicals and anions needs to be considered. Bond types that are likely to form stable radicals/anions upon reduction fall into three classes: bonds between electronegative atoms, bonds between a carbon and an electronegative atom, and C–C bonds in highly conjugated systems.[18]

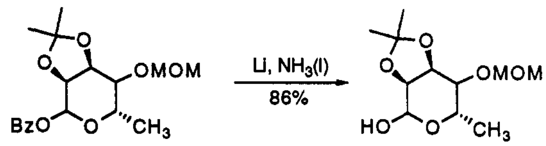
As mentioned, bonds between electronegative atoms are generally very reactive. Since the charged intermediate formed upon electron addition is readily stabilized by the nitrogen and oxygen atoms, the N-oxide bond in eq 5 is easily cleaved in favor of the other polar bonds present.[19] Similarly, the hydrazine linkage in eq 6 is preferentially cleaved to yield an N-protected α-amino acetal.[20] Bonds between a carbon and an electronegative site are also reducible when the carbon is attached to an unsaturated system, e.g., benzylic or allylic. While simple aliphatic ethers are not readily cleaved and are often used as solvents, benzylic ethers are smoothly debenzylated. In eq 7, the benzylic ether is removed to yield a lactol,[21] leaving the remaining C–O linkages untouched. Isolated C–C double bonds are unreactive. In contrast, highly conjugated systems are readily reduced with lithium in liquid ammonia. For example, the diindan in eq 8 is reduced in high yield to the tetraene, which does not react further.[22]



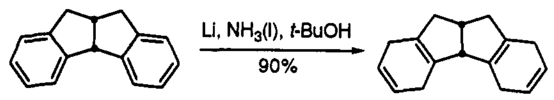
(5)



(6)



(7)



(8)

B. Determination of Reactivity Levels and Construction of Table 1. After perceiving the reactive sites in a substrate, the next two steps are to determine the correct reductive transformations for each functional group in the molecule and the relative chemoselectivities of all the functional groups that comprise the structure. After all, for a functional group interconversion to be useful in organic synthesis, the functional group under consideration must be reduced to the appropriate functionality without other unprotected but reducible functionalities in the substrate being affected. Over 350 experimental transformations from the literature have been assessed to determine reactivity in Li–ammonia reductions. These reactivity trends are summarized in Table 1. The chemoselectivities exhibited in individual literature transformations were the primary means of establishing the reactivity level of each functional class listed in the table; however, where chemoselectivity or simple transformation data were lacking for a reactive site, information was gleaned from the literature in an alternate manner. Sometimes, sodium in liquid ammonia reactions were studied since their reactivity is very similar to that of lithium in liquid ammonia reactions. Reported yields were noted, and any possibility of side products was taken into account. In some cases, an understanding of the mechanism of metal–ammonia reductions helped discern the relative reactivities of functional group classes.

The following reactions illustrate chemoselectivity in lithium–ammonia reductions. For example, the α,β-unsaturated ketone functionality in eq 9 is reduced in the presence of a cyclopropyl ketone.[23] In the reduction of the tosylmethyl isocyanide in eq 10, both the isocyanide and the sulfone group are selectively cleaved in the

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[17] Smith, M. In *Reduction: Techniques and Applications in Organic Synthesis*; Augustine, R. L., Ed.; Marcel Dekker: New York, 1968; pp 95–170.

[18] Ireland, R. E.; Wilcox, C. S.; Thaisrivongs, S. *J. Org. Chem.* **1978**, *43*, 786.

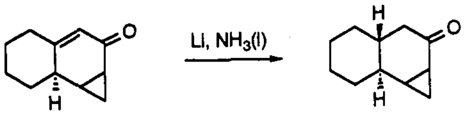
[19] Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1986**, *27*, 4961.

[20] Denmark, S. E.; Nicaise, O. *Synlett* **1993**, *5*, 359.

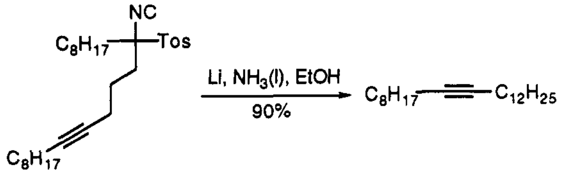
[21] Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988.

[22] Eckrich, R.; Kuck, D. *Synlett* **1993**, No. 5, 344.

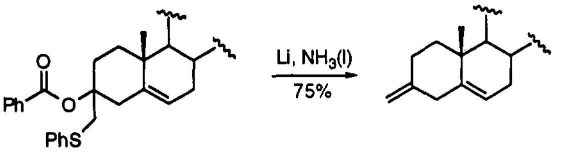
presence of an alkyne.[24] Thus the alkyne functionality is less reactive than either an isocyanide or a sulfone group. Other analogs of the reaction show aromatic rings and isolated double bonds also to be unaffected in the presence of the more reactive tosylmethyl isocyanide functionality.[23] Transformations that show two or more functional groups being simultaneously reduced suggest the groups may be placed in the same reactivity class. However, some caution and mechanistic knowledge are required. For example, though both the ester and the phenyl sulfide are cleaved in the reaction shown in eq 10,[25] the phenyl sulfide is probably first reductively cleaved to yield a carbanion intermediate which undergoes elimination of the ester functionality to produce the exocyclic double bond. A rearrangement, not a second reduction, results in the loss of the ester functionality. The chemoselectivities determined upon evaluating eqs 10 and 11 are shown in Table 1. In the table, reactivity decreases proceeding down a column or with increasing reactivity level number. For example, the alkyne functionality is lower on the table (larger reactivity level number) than an isocyanide or sulfone group.



(9)

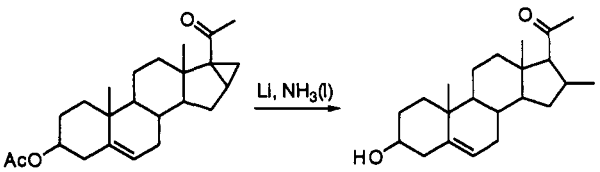


(10)

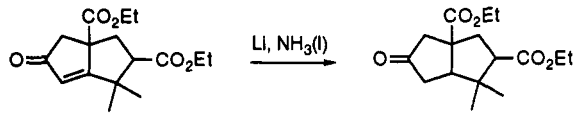


(11)

Since a polyfunctional substrate may not exist for every possible functional group combination, the relative reactivities of some functional groups must be surmised by their reactivity relative to another functional group at the same level in Table 1. The transformation in eq 9 establishes the reactivity ranking: α,β-unsaturated ketone > cyclopropyl ketone; but, suppose a transformation establishing the reactivity of an α,β-unsaturated ketone relative to an ester were not available. In eq 12, a cyclopropyl ketone is cleaved along with the ester functionality present in the steroid system.[26] Since the α,β-unsaturated ketone is more reactive than a cyclopropyl ketone, an α,β-unsaturated ketone should be more reactive than a saturated ester. The following reactivity order is then surmised: α,β-unsaturated ketone > cyclopropyl ketone, saturated ester. Though all such extrapolations cannot be directly verified, the transformation in eq 13 shows the deduced reactivity order to be correct.[27] Note that all three examples occur in the absence of an added proton source. A more acidic proton source can change the relative reactivity levels of two transformations.

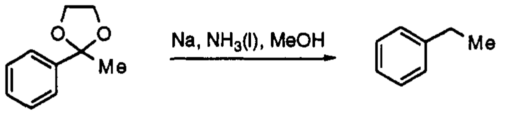


(12)



(13)

Using the information in the reactivity table, the program identifies all possible reactive sites and notes their initial reactivity level. The ranking is then adjusted by considering the effects of adjacent activating or deactivating groups and other mechanistic issues. For example, a benzylic ketal is readily cleaved (eq 14), whereas the corresponding aliphatic ketals and acetals are so unreactive that they can be used as protecting groups.[28] For thermodynamically controlled reactions, the stability of the intermediates plays a major role in determining the reaction paths.



(14)

C. Mechanistic Reasoning. Since the mechanism of the dissolving metal reductions illustrated here is relatively well understood, mechanistic reasoning is used extensively to augment the selectivity data gleaned from the literature. Both processing and reaction display simulate most of the mechanistic steps shown in Schemes 1 and 2. The charged mechanistic intermediates formed in the course of reduction are analyzed internally and then displayed by the program. Two electrons and two protons are added to the substrate in each reduction. After adding the first electron to the substrate, the resulting radical/anion intermediate(s) formed is displayed and automatically resubmitted. Upon evaluation, the first proton and second electron are added, and the second intermediate is formed. This intermediate is an anionic species. In all cases, a final quenching step is performed by adding a proton to form a direct reduction product; however, along with direct reduction, the resulting anion may also undergo resonance and intramolecular reactions. After direct reduction has occurred, the anion precursor is evaluated by the Reduction module for possible intramolecular reactions. When intramolecular reactions are feasible, control is transferred to the Basic/Nucleophilic module of CAMEO.

A simple example of a metal–ammonia reduction that CAMEO processes is illustrated by the transformation shown in eq 15.[18] Though a brief summary of the reaction will be given, the key mechanistic steps in the analyses will be expanded upon in the remainder of the paper. Once the starting material has been perceived by the program, the most reactive site in the furanosyl substrate is found to be the carbon–halogen bond. An electron is added, and the bond is cleaved to form the radical substrate and a halide anion (Figure 1). A proton and an electron are next added to the intermediate just formed to give an anionic species. This intermediate, also displayed by the program, then follows two possible paths to form a mixture of products. The first, a direct reduction product, is formed

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[23] Piers, E.; DeWaal, W.; Britton, R. W. *Can. J. Chem.* **1969**, *47*, 4299.

[24] Yadav, J. S.; Reddy, P. S. *Tetrahedron Lett.* **1984**, *25*, 4025.

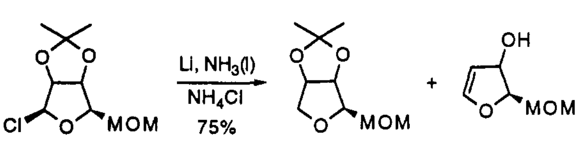
[25] Sowerby, R. L.; Coates, R. M. *J. Am. Chem. Soc.* **1972**, *94*, 4758.

[26] Evans, D. E.; Lewis, G. S.; Palmer, P. J.; Weyell, D. J. *J. Chem. Soc. C* **1968**, 1197.

[27] Stork, G.; Clarke, *J. Am. Chem. Soc.* **1961**, *83*, 3114.

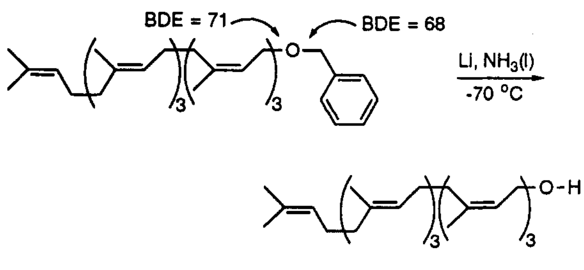
[28] Pinder, A. R.; Smith, H. *J. Chem. Soc.* **1954**, 113.

upon protonation of the carbanion intermediate. Direct reduction is always shown with protonation taking place at the anion site. In the reduction of the furanosyl halide, cleavage of the halide bond to form the tetrahydofuran is also accompanied by a second, elimination path. In the transformation shown in eq 15, the Basic/Nucleophilic module finds an E1cb path particularly favorable; the resulting hemiketal is then recognized as unstable and decomposed to form the glycal (Figures 2 and 3). If the reaction had been transferred to the Basic/Nucleophilic module and a favorable reaction path leading to products had not been found, only the direct reduction product would have been shown. In general, the program does not directly judge the competition between direct reduction and intramolecular reactions. The Reduction module ranks the feasibility of reduction leading to the formation of any anionic intermediate before it is submitted to the Basic/Nucleophilic module. Once submitted to the Basic/Nucleophilic module, that module ranks the feasibility of possible, usually intramolecular, reaction steps.

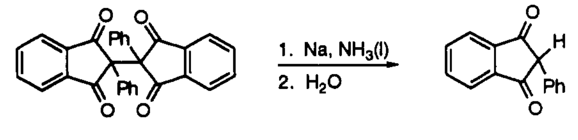


(15)

1. **First Electron Addition.** Once identified, the reducible sites of an input substrate are ranked and arranged into appropriate reactivity levels (Table 1), and the first electron is added. As mentioned, if a single bond is under consideration, electron addition will produce fission and yield a radical and an anion. If a multiple bond is reduced, electron addition will produce a radical–anion. The reactivity of the electron addition sites must be further discerned by gauging the stabilizing effect of adjacent structural features and substituents. In cases where an unsymmetrical substrate may be cleaved in either of two ways, further regioselectivity is often determined by relative bond dissociation energies. For example, the bond dissociation energies of both the allyl and benzyl ether linkages in eq 16[29] are calculated[6] to determine which C–O bond is preferably reduced. The weaker bond is reduced. Another example of the use of bond dissociation energies to predict a site of cleavage is shown in eq 17.[30] The cleaved bond is highly reactive owing to incipient conjugation with both the carbonyl and phenyl groups. Reactivity in other cases may be gauged by anion stability as predicted from pK_a calculations.

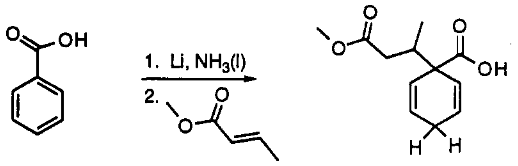


(16)

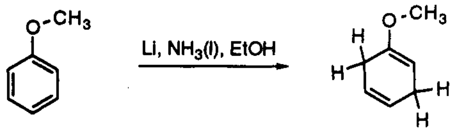


(17)

a. **Regioselectivity in the Reduction of Aromatic Rings.**[31] As shown in Scheme 3, benzene undergoes bond saturation to yield the 1,4-reduction product. The first step in the reduction process is transfer of an electron to the π system of the aromatic ring to form the radical–anion **17**. The radical and anion sites are always para to one another and tend to localize at sites on the ring that stabilize charge. For this reason, regioselectivity in the Birch reduction of benzene derivatives is controlled by the substituents on the ring. Electron-withdrawing groups substituted on the ring stabilize the negative charge incurred in the course of reaction and increase the rate of reaction. By delocalizing charge, electron-withdrawing substituents promote anion formation and subsequent reduction at the position on the aromatic ring bearing the stabilizing group. This may be seen in the metal–ammonia reduction of benzoic acid (eq 18).[32] Quenching the reaction with methyl crotonate leads to a Michael reaction between the methyl crotonate and the anion generated in the reduction. Conversely, electron-donating groups are deactivating and direct protonation toward the unsubstituted 2- and 5-positions, e.g., eq 19.[33]



(18)



(19)

Determining the radical–anion most likely to form, and therefore, the regioselectivity of the reduction is actually a 2-fold process. First, the most reactive aromatic ring must be identified, and second, the most likely site of radical–anion formation within that ring must be determined. Table 2 summarizes factors that influence the relative reactivities of benzene rings in the Birch reduction. Each activating and deactivating substituent type is given a weighting factor that was empirically derived from trends noted in many literature transformations. For example, the Birch reduction in eq 20 demonstrates that the aromatic ring with the most fusions to another aromatic ring is generally the most reactive ring.[34] The regioselective reduction of the unsubstituted ring in eq 21 illustrates that a ring substituted with a hydroxyl group is deactivated.[35] The activation values listed in Table 2 reflect that ring fusions and electron-withdrawing groups are observed to have more influence than electron-donating groups. In CAMEO, a simple calculation using the activation values in Table 2 is performed to determine the most reactive ring. Each ring is assigned a reactivity

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[29] Grigorieva, N. Ya.; Avrutov, I. M.; Semenovsky, A. V. *Tetrahedron Lett.*, **1983**, *24*, 5531.

[30] Beringer, F. M.; Galton, S. A.; Huang, S. J. *Tetrahedron*, **1963**, *19*, 809.

[31] (a) For reviews, see: Harvey, R. G. *Synthesis* **1970**, 161. (b) Zimmerman, H. E.; Wang, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 2205. (c) Birch, A. J.; Hinde, A. L.; Radom. L. *J. Am. Chem. Soc.* **1980**, *102*, 3370, 4074, 6430. (d) Birch, A. J.; Hinde, A. L.; Radom. L. *J. Am. Chem. Soc.* **1981**, *103*, 284.

[32] (a) Subba, Rao, G. S. R.; Ramanathan, H.; Raj, K. *J. Chem. Soc., Chem. Commun.* **1980**, 315. (b) See also: Kuehne, M. E.; Lambert, B. F. *Org. Synth.* **1963**, *43*, 22.

[33] (a) Birch, A. J. *J. Chem. Soc.* **1946**, 593. (b) Dryden, H. L.; Webber, G. M.; Burtner, R. R; Cella, J. A. *J. Org. Chem.* **1961**, *26*, 3237. (c) Wilds, A. L.; Nelson, N. A. *J. Am. Chem. Soc.* **1953**, *75*, 5360. (d) Eastham, J. E.; Larkin, D. R. *J. Am. Chem. Soc.* **1959**, *81*, 3652.

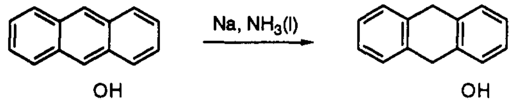
[34] Miller, H. F.; Bachman, G. B. *J. Am. Chem. Soc.* **1935**, *57*, 766.

[35] Gutsche, C. D.; Peter, H. H. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. 4, p 887.

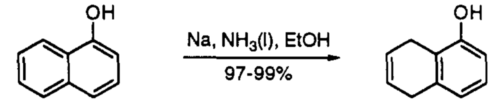
Table 2. Empirical Activation Values Used To Evaluate Relative Reactivities of Benzene Rings for Birch Reductions

activating/ deactivating atom types	activation value
each electron-donating substituent *α* to the ring, e.g., oxygen of alcohols, ethers; nitrogen of amines	−2
each electron-withdrawing substituent *α* to the ring, e.g., carbonyl groups of carboxylic acids, esters, ketones; silicon atoms of $Si(R)_3$ groups	+4
each fusion with another aromatic ring	+4

number based on the sum of the activation values. The ring with the largest net reactivity value is deemed most reactive.

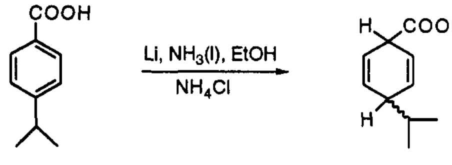


(20)



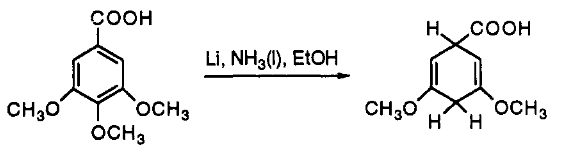
(21)

Once the most reactive ring has been determined, the program, by a series of empirical rules, progressively eliminates less favorable electron addition sites until only the most probable sites for radical–anion formation remain. When a ring has multiple substituents, the directing effects shown in eqs 18 and 19 may be in competition. The radical–anion cannot form at a ring junction with another aromatic ring. As mentioned, the radical–anion is not likely to form *α* to a deactivating group such as oxygen, but will be stabilized if *α* to a site substituted with an electron-withdrawing group. The radical–anion is slightly destabilized if *α* to an alkyl group, but is capable of being formed. In eq 22,[36] the carboxylic acid and the alkyl groups are in opposition, but as in all Birch reductions, the activating electron-withdrawing group has the greater directing effect. Of the electron-donating groups, the directing effects of functional groups containing nitrogen and oxygen outweigh alkyl groups. Thus, the empirical order of directing power is carboxyl > amino, alkoxyl > alkyl. Hydrogen addition is para to an electron-withdrawing group and meta to the most strongly deactivating group, but preferably not at a position occupied by a deactivating substituent.



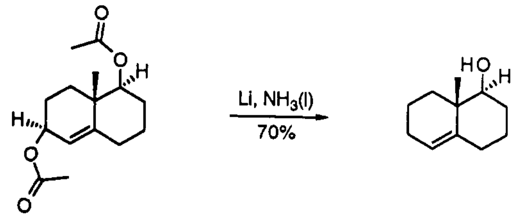
(22)

If necessary, hydrogen will add to a deactivated site, but bond fission will occur if addition takes place at a position occupied by a good leaving group such as an alkoxy or amino substituent. In eq 23, fission of an alkoxy function occurs when gallic acid trimethyl ether is reduced.[37] Regardless of the substituent pattern, the second hydrogen is always directed into a position para to the point of addition of the first in a benzene derivative. If the 1,4-reduction product is allowed to reform the carbanion and isomerize, a conjugated diene susceptible to further reduction will be formed. This is unlikely with the proper choice of proton source and reaction conditions.

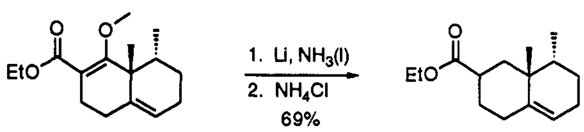


(23)

b. Regioselectivity in the Reduction of Conjugated vs Unconjugated Esters. Unsaturated esters undergo bond fission to form an unsaturated species and an acid, while saturated esters undergo both bond fission and bond saturation to yield alcohols. This reactivity difference is illustrated in the reductive deacylation shown in eq 24.[38] A "double reduction", similar to the Birch reduction in eq 23, occurs when the carbon *β* to the ester carbonyl possesses a good leaving group. Such an elimination is seen with *β*-alkoxy-*α*,*β*-unsaturated esters (eq 25).[39]



(24)



(25)

2. First Protonation and Second Electron Addition. Next, the first protonation and second electron addition steps are undertaken. The ordering of these steps varies with the substrate and reaction conditions. Generally, systems of high electron density that can accommodate resonance through an extended conjugated system are less likely to add a proton before the second electron addition takes place.[18] Instead, the second electron addition directly follows the first electron addition, and in multiple bond reductions, a dianion such as **12** is formed (Scheme 2). Dianions are relatively unstable because of the electrostatic interaction between the negatively charged sites. Unless the charges can be stabilized, a dianion is difficult to form. Consequently, aliphatic ketones probably cannot form stable free dianions, but some diaryl and monoaryl ketones yield dianionic species.[40] Dianion formation is also more likely to occur in the absence of a strongly acidic proton source. As shown in Scheme 2, the order in which the first protonation and second electron addition steps take place does not affect the choice of product. Since the sequence is not important for predictive purposes in CAMEO, for simplicity the steps are combined. Thus, the first intermediate formed internally and displayed by CAMEO corresponds to addition of one electron to the starting material, e.g., **9** and Figure 1. The second intermediate corresponds to addition of two electrons and one proton to the starting material, e.g. **11** and Figure 2.

The ordering of these steps may not be critical, but the acidity of the proton source used in the first protonation step is important to the outcome of the reduction.

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[36] Camps, F.; Coll, J.; Pascual, J. *J. Org. Chem.* **1967**, *32*, 2563.

[37] (a) Birch, A. J.; Hextall, P.; Sternhell, S. *Aust. J. Chem.* **1954**, *7*, 256. (b) Chapman, O. L.; Fitton, P. *J. Am. Chem. Soc.* **1963**, *85*, 41. (c) Harvey, R. G. *Synthesis* **1970**, 161.

[38] Ando, M.; Sayama, S.; Takase, K. *Chem. Lett.* **1981**, 377.

[39] Coates, R. M.; Shaw, J. E. *J. Org. Chem.* **1970**, *35*, 2597.

[40] (a) Caine, D. *Org. React.* **1976**, *23*, 1. (b) Hamrick, P. J.; Hauser, C. R. *J. Am. Chem. Soc.* **1959**, *81*, 493. (d) Murphy, W. S.; Buckley, D. J. *Tetrahedron Lett.* **1969**, 2975.

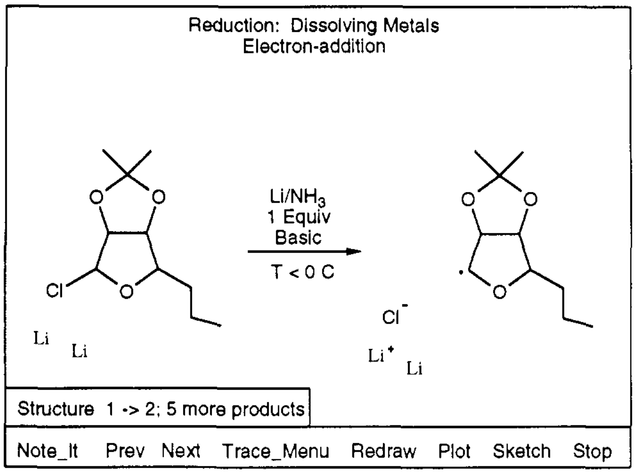


Figure 1. Reaction trace display of first electron addition step.

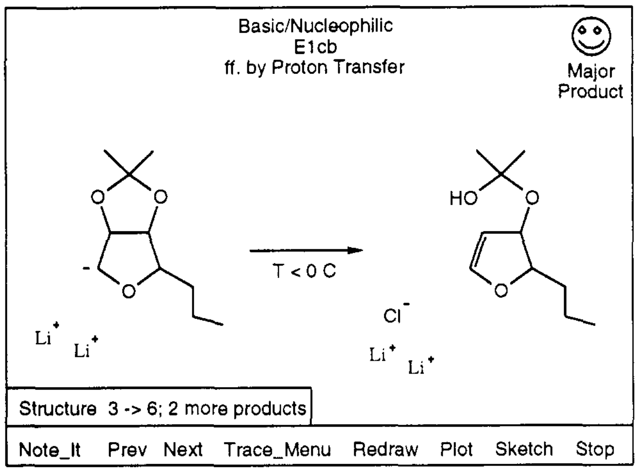


Figure 2. Reaction trace display of elimination step.

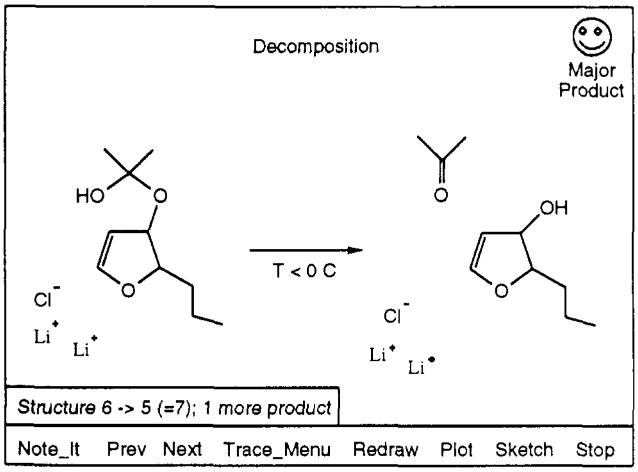
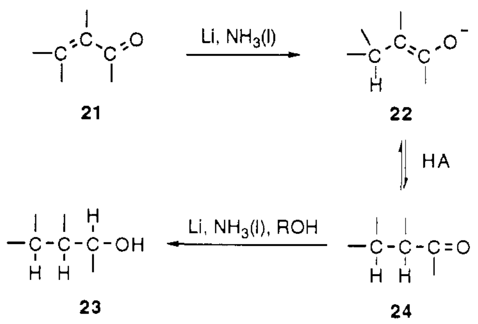


Figure 3. Reaction trace display of decomposition of hemiketal.

Scheme 4. Reduction of an α,β-Unsaturated Ketone in the Presence of an Acidic Proton Source



Naturally, liquid ammonia will be present in the reaction medium; however, an additional, more acidic proton source is sometimes necessary. Ammonia, with an aqueous pK_a of about 34–35, is a significantly weaker acid than the common alcohols (pK_a = 16–19) or ammonium salts (pK_a = 10) that may be added to the reaction mixture.[41] Generally, the more acidic the proton source, the faster the reaction and the easier the reduction. Reaction paths can also depend on the presence or absence of an added proton source.[18] In some cases, liquid ammonia is simply too weak an acid to protonate the intermediate radical–anion. For example, in the absence of an alcohol, the reduction of benzene to form 1,4-dihydro derivatives does not occur. Apparently, the protonation of the radical anion is the rate limiting step.[42] The alcohol may also react with any amide ion that accumulates and could possibly cause isomerization of the 1,4-dihydro compound to the 1,2-dihydro isomer and be further reduced.

In other cases, the desired reduction process not only takes place in the presence of an added proton source but the products are then further reduced before isolation. As shown in Scheme 4, an α,β-unsaturated ketone (**21**) is reduced to the corresponding saturated ketone (**23**) with lithium–ammonia. In the presence of an added proton source, reduction proceeds to the saturated alcohol (**24**). Since ammonia is a relatively weak acid, the enolate of the saturated ketone (**22**) is not protonated unless a stronger acid is present.[40a] Because the simple alcohols have acidity in the same range as the saturated ketones formed in the first stage of the reduction,[40a] the equilibrium is driven forward, and the ketone is reduced further to the alcohol. If excess ethanol or methanol is used, there is complete conversion to form the saturated alcohol. If only 1 equiv of these proton donors is used, then a mixture of the saturated ketone and saturated alcohol results.[43] *tert*-Butyl alcohol or any less acidic proton donor may give poor results with some substrates. The position of the equilibrium depends on the acid/base properties of the intermediates relative to the acidity of the reducing medium.

The acidity of the proton donor may also play a role in controlling regioselectivity. In eq 26, the α,β-unsaturated ketone is reduced to the saturated ketone; however, in the presence of an added proton donor, both the enone and the aromatic ring are reduced (eq 27).[41,44] The enone is reduced to the alcohol. Since an unactivated benzene ring is reduced slowly in the absence of an added proton donor, the selective reduction of the α,β-unsaturated ketone may be achieved in the presence of a benzene ring (eq 26). Considerations such as these are incorporated into the program's processing by treating lithium–ammonia and lithium–ammonia–alcohol as separate reagents with different reactivity level rankings.

3. Dimerization as a Competing Step. Another purpose of adding more acidic proton donors is often to decrease side reactions. Since the initially formed radical anion may be as likely to react with another radical anion

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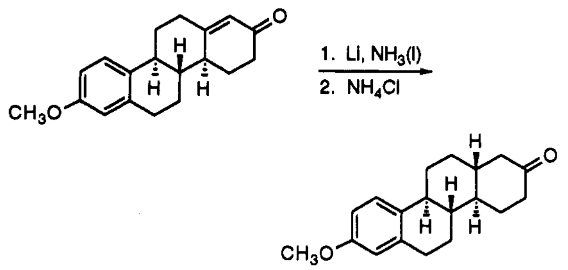
[41] House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin/Cummings: Menlo Park, CA, 1972; p 175.

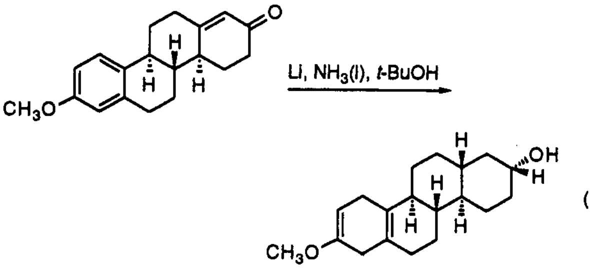
[42] Zimmerman, H. E.; Wang, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 2205.

[43] Hightower, L. E.; Glasgow, L. R.; Stone, K. M.; Albertson, D. A.; Smith, H. A. *J. Org. Chem.* **1970**, *35*, 1881.

[44] Johns, W. F. *J. Org. Chem.* **1963**, *28*, 1856.

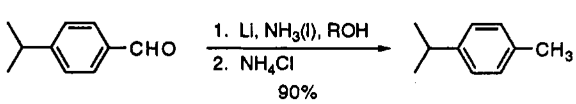


(26)

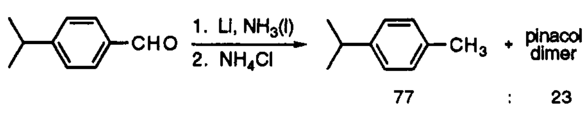


(27)

as to be protonated, undesirable dimerizations and polymerizations may take place if the proton source is not acidic enough (see 13, Scheme 2).[10] Of course, regardless of the proton source, some substrates are better able to produce a stable radical anion that competitively dimerizes before protonation. Aryl ketones are especially prone to form dimeric products. While the reduction of an aliphatic aldehyde or ketone results in the formation of an alcohol, the aromatic analog is further reduced to the hydrocarbon with some dimer formation.[45] In the reduction of aryl aldehydes, dimer formation is likely due to the stability of the intermediates; however, the presence of an acidic proton source suppresses the expected dimerization (eq 28).[45] With ammonia as the only proton source present in the reaction mixture in eq 29,[45] some of the ketyl radical reacts to form the dimer; but, when *tert*-butyl alcohol is added to the system, protonation occurs too rapidly for significant dimerization to occur.[45] After a second electron addition, the benzylic alkoxide produced is further reduced, with the aid of ammonium chloride, to form the hydrocarbon. Though the formation of pinacols (eq 29) may be performed with Li–ammonia reductions, more reliable and higher yielding transformations are usually accomplished with aluminium amalgam or zinc in acetic acid.[46]

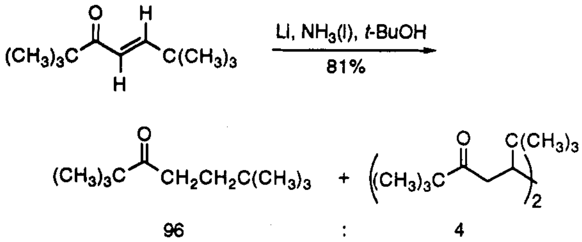


(28)



(29)

Because a proton source such as liquid ammonia or an alcohol inhibits dimer formation, when coupling is desired, the Birch-like reaction conditions are usually not used. Contrast the reduction of an α,β-unsaturated ketone in the presence and absence of a proton donor (eqs 30 and 31).[47] The typical lithium–ammonia–alcohol conditions of eq 30 favor simple reduction; sodium as the reducing metal in the absence of a proton source favors dimer formation in eq 31. Using sodium may also have helped promote dimerization. While benzophenone can be reduced with Li–NH_3 without producing a dimeric product,[45] when reduced with Na–NH_3 some dimerization may occur.[48] Just as pinacol and other coupling reactions can take place under Birch-like conditions, acyloin reduction can also take place. Again, acyloin reductions are more commonly carried out in the absence of a proton source. In eq 32, the diester is treated with sodium in an aprotic solvent to form an acyloin.[49]



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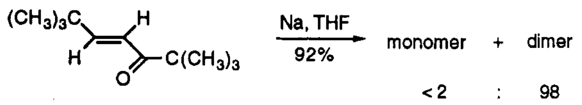

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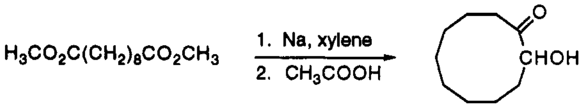

(32)

4. Resonance and/or Intramolecular Reactions. If structural features allow, the final anionic intermediate will rearrange to the more stable anion and/or undergo intramolecular additions, eliminations, or substitutions. In the Reduction module of CAMEO, anionic intermediates formed before the final protonation step are always checked for sites of conjugation. If resonance is possible, the relative stabilities of the resonance structures are determined by a series of simple rules (1° > 2° > 3° carbanions) and by calculating the pK_as of the conjugate acids.[2d] If the resonated anion falls within a suitable range of stability and is more stable than its alternate forms, the more stable resonance structure is explicitly formed and displayed by the program.

Resonance through a chain of unsaturation is common in lithium–liquid ammonia reductions. Under thermodynamic control, the $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl compound shown in eq 33 forms the trans double bond product exclusively after quenching with isopropyl bromide.[50] In the reduction of the conjugated epoxide in eq 34, the allylic C–O bond is cleaved. Charge is initially localized on the tertiary carbon. Resonance to localize negative charge at the primary site results in a more stable intermediate. Experimentally, only the conjugate reduction products are formed, and again the *E*-isomer is stereoselectively favored.[51] The reactions of the silylated compounds in eqs 35 and 36 further illustrate that the ability to recognize the most stable resonance forms is needed for correct product prediction.[52]

The reaction path of an intermediate anion may now branch. After being checked for resonance sites, the intermediate anion is examined for electrophilic sites that would enable additions to occur and for leaving groups

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[45] Hall, S. S.; Bartels, A. P.; Engman, A. M. *J. Org. Chem.* **1972**, *37*, 760.

[46] (a) Newman, M. S. *J. Org. Chem.* **1961**, *26*, 582. (b) Zagumenny, A. *Chem. Ber.* **1881**, *14*, 1402.

[47] Bowers, K. W.; Giese, R. W.; Grimshaw, J.; House, H. O.; Kolodny, N. H.; Kronberger, K.; Roe, D. K. *J. Am. Chem. Soc.* **1970**, *92*, 2783.

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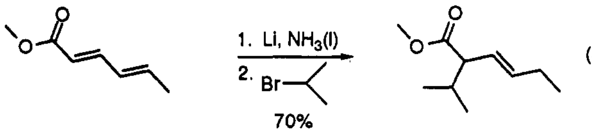
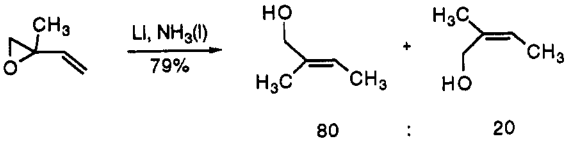
[49] Allinger, N. L. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. 4, p 840.

[50] Birch. A. J.; Slobbe, J. *Aust. J. Chem.* **1976**, *29*, 2737.

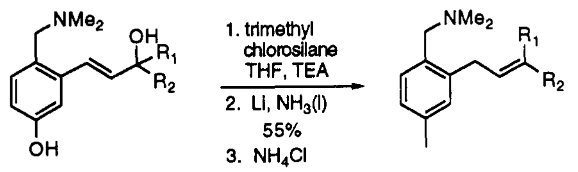
[51] Lenox, R. S.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1973**, *95*, 957.



(33)

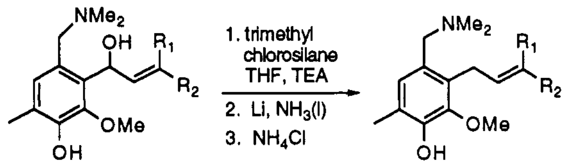


(34)



(35)

E = R_1 = CH_3; R_2 = $-CH_2CH_2CH{=}CH(CH_3)_2$
Z = R_1 = $-CH_2CH_2CH{=}CH(CH_3)_2$; R_2 = CH_3

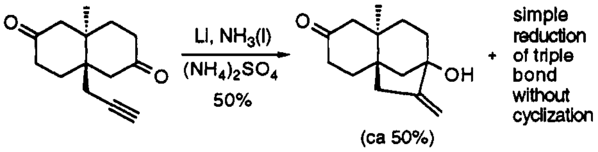


(36)

E = R_1 = CH_3; R_2 = $-CH_2CH_2CH{=}CH(CH_3)_2$
Z = R_1 = $-CH_2CH_2CH{=}CH(CH_3)_2$; R_2 = CH_3

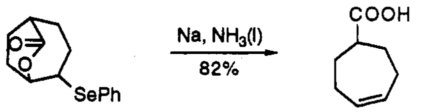
that might promote substitution or elimination reactions. Direct quenching of the anion, as discussed in the next section, is always performed and displayed by the Reduction module; however, if a preliminary check suggests that viable pathways are present, the anionic intermediate is automatically sent to the Basic/Nucleophilic module for further processing.[2] Control is only relinquished for the Reduction module to process additional anionic intermediates.

Since the addition of electrons to a substrate in metal–ammonia reductions often results in intermediates with carbanion character, the Basic/Nucleophilic module is readily able to process the final mechanistic steps of the examples that follow. The addition reaction of an anion typically occurs when an electrophilic carbonyl function is positioned in the substrate such that subsequent intramolecular attack will not violate Bredt's rule. In eq 37, the electron additions and protonation performed by the Reduction module result in the acetylene being converted to a vinylic anion. Since the propargyl group in eq 37 is axial, intramolecular attack of the vinylic anion on the β carbonyl group is favorable.[53] The addition of $(NH_4)_2SO_4$ as a proton source is necessary for the reaction to occur. A similar trapping of an intermediate carbanion by an addition site appears in eq 4.

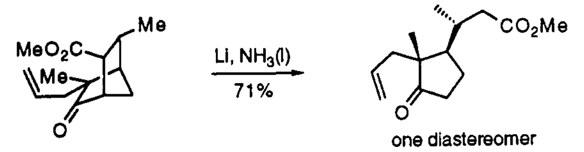


(37)

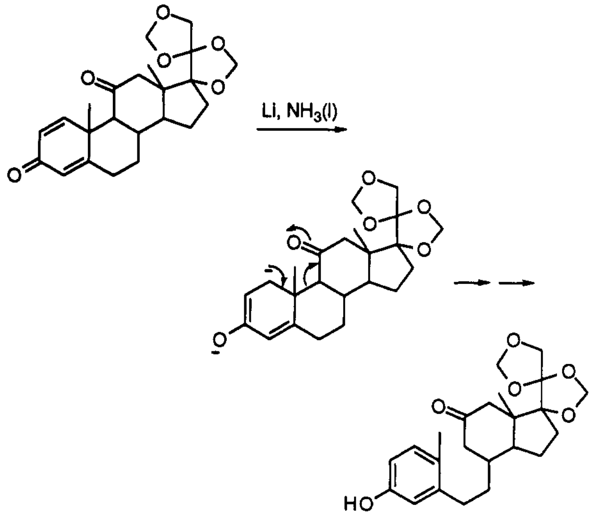
Reductive eliminations are commonly used to synthetic advantage. The fission of the phenyl selenide in eq 38 offers an example of an elimination involving an intermediate anion.[54] The 1,4-dicarbonyl arrangement of eq 39 often leads to bond fission during elimination.[55] In the usual two-electron addition to the α,β-unsaturated ketone of the steroid prednisone, aromatization occurs after conjugate E1cB elimination of an enolate (eq 40).[56]



(38)



(39)



(40)

5. Quenching Anionic Species To Form Products.

After a second electron is added to the radical atom to give the corresponding anion, a final quenching step is necessary to isolate the products. If the anion is protonated by an acid that can establish an unfavorable equilibrium, further reduction may occur and the chemoselectivity of an individual transformation may be changed. For example, if ethanol or methanol is used at the completion of the reduction of an α,β-unsaturated ketone to protonate the anionic intermediates, an equilibrium may be established and the saturated alcohol formed instead of the saturated ketone. When ammonium chloride is used in the quenching step, any excess metal is quickly destroyed and the anionic intermediates are protonated. For practical purposes, the final quenching step in CAMEO is processed as if ammonium chloride was the protonating agent. Though the final quench is automatically performed by showing the addition of a proton, the result of quenching with an alternate reagent, such as an alkyl halide, may be accomplished by the user resubmitting the anionic intermediate with the quenching agent to the Basic/Nucleophilic module.

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(52) Ballester, P.; Capó, M.; Garcías, X.; Saá, J. M. *J. Org. Chem.* **1993**, *58*, 328.

(53) Stork, G.; Malhotra, S.; Thompson, H. *J. Am. Chem. Soc.* **1965**, *87*, 1148.

(54) Nicolaou, K. C.; Sipio, W. J.; Magolda, R. L.; Claremon, D. A. *J. Chem. Soc., Chem. Commun.* **1979**, 83. Similar reductions of phenyl sulfides are also shown.

(55) Nagasawa, K.; Matsuda, N.; Noguchi, Y.; Yamanashi, M.; Zako, Y.; Shimizu, I. *J. Org. Chem.* **1993**, *58*, 1483.

(56) Tanabe, M.; Chamberlin, J. W.; Nishiura, P. Y. *Tetrahedron Lett.* **1961**, 601.

IV. Conclusion

The treatment of reductions with alkali metals in liquid ammonia has been implemented in the Redox module of CAMEO. Key features for the successful prediction of reaction products include the development of an extensive reactivity table from literature precedents that govern selectivity and the explicit generation of anionic intermediates that can be automatically submitted for reaction evaluation by the established Basic/Nucleophilic module.

Acknowledgment. The authors are grateful to Pascal Metivier for early efforts in implementing reductions in CAMEO. We are especially thankful for his contribution toward this work in laying the foundation of the routine responsible for gauging the regioselectivity in reducing aromatic rings. The authors are also grateful to the National Science Foundation for support.