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Computer-Assisted Mechanistic Evaluation of Organic Reactions. 3. Ylide Chemistry and the Organometallic Chemistry of Lithium, Magnesium, and Lithium Cuprates[1]

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CAMEO, an interactive computer program for the mechanistic evaluation of organic reactions, has been enhanced to encompass ylide chemistry and organometallic reactions involving Li, Mg, and CuLi counterions. Based on literature precedents, alogrithms have been developed to handle the competitions between proton transfer, organometallic addition, and halogen–metal exchange. These processes yield the anionic nucleophiles which are considered for subsequent participation in E1cB, S_N2, E2, and addition reactions. Algorithms to treat the competitions between the latter processes were described previously and remained essentially unchanged. The major modifications for organometallic chemistry involved the routines for pK_a and nucleophile perception. CAMEO is now capable of making sophisticated predictions for a wide variety of synthetically useful base-catalyzed and/or nucleophilic reactions. Sample sequences and a pedagogic flow chart for making logical predictions on the outcomes of such reactions are provided.

I. Introduction

An overview of a new computer program, CAMEO, which predicts products of organic reactions when given starting materials and reaction conditions has recently been presented.[3] A key feature of the program is that it arrives at its predictions by using mechanistic reasoning and fundamental concepts concerning structure and reactivity. Furthermore, the program is interactive and easy to use since the input and output of commands and molecular structures are performed graphically via a computer graphics terminal. The first mechanistic class to be addressed was base-catalyzed and nucleophilic reactions which often involve a proton-transfer prestep. Relative basicities and other data are used to find the best nucleophiles and electrophiles which may subsequently participate in ElcB, E2, S_N2, and addition reactions. Heuristics based on literature precedents then enable evaluation of the competitions between these processes.

As described here, this work has been extended to cover reactions of organolithium, magnesium, and lithium cuprate reagents in which cases proton transfer may not be a valid first step. Instead, the competitions between organometallic addition, proton transfer, and halogen–metal exchange must be considered.[4,5] With relatively minor modifications it has been possible to incorporate the organometallic chemistry into the existing program. In addition, the complementary area of ylide chemistry has also been integrated at the same time. With these enhancements the program is now capable of making sophisticated predictions for most base-catalyzed and nucleophilic reactions which are of particular utility to synthetic organic chemists. Further extensions to electrophilic and pericyclic chemistry are in progress.

To begin, a brief review of reactions for organolithium, Grignard, and lithium cuprate reagents and ylides is provided. The apparent patterns are then organized into heuristics for use by CAMEO. This is followed by a description of the implementation of the new material in the program. A summary of the mechanistic logic used by CAMEO to predict reaction products is then presented with the aid of a pedagogically oriented flow chart. The paper concludes with examples of typical reaction sequences predicted by CAMEO.

The program as described here is now operating on a Harris Corporation H-80 computer equipped with a Tektronix 4010 terminal and electrostatic pen and tablet. This system replaced the original TI 990/10 computer and has significantly enhanced the ease of program development due to its much greater speed and larger word size. The program can now handle molecules with up to 46 explicit atoms and bonds and the response time between reactant input and product display has been reduced to several seconds in typical cases.

II. Review of Reactions

A. Preparation of Organometallic Reagents. The two reactions used in the preparation of organometallics which CAMEO is able to handle at this time are proton transfer and halogen–metal exchange. The former process is facile in many instances in which addition is not competitive. Thus, *N*-methylbenzamide may be metalated as

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[1] Taken in part from the Ph.D. thesis of T. D. Salatin, Purdue University, 1980. For part 2, see B. L. Roos-Kozel and W. L. Jorgensen, *J. Chem. Inf. Comp. Sci.*, 21, 101 (1981).

[2] Camille and Henry Dreyfus Foundation Teacher–Scholar 1978–1983; Alfred P. Sloan Foundation Fellow 1979–1981.

[3] T. D. Salatin and W. L. Jorgensen, *J. Org. Chem.*, 45, 2043 (1980).

[4] (a) B. J. Wakefield, "The Chemistry of Organolithium Compounds", Pergamon Press, Oxford, 1974; (b) For a general review of carbanion chemistry, see J. C. Stowell, "Carbanions in Organic Synthesis", Wiley, New York, 1979.

[5] M. S. Karasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances", Prentice-Hall, New York, 1954; see also ref 4b.

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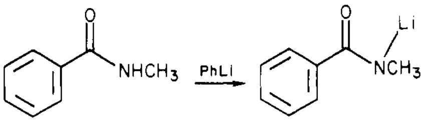
shown below. However, the reaction of cyclohexanone

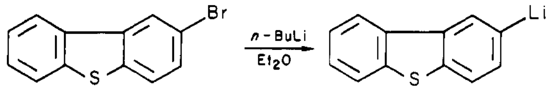


with n-butyllithium leads to predominant addition to the carbonyl group.[6] An additional limitation with simple organometallics is that their basicity is somewhat less than would be expected thermodynamically. For example, n-butyllithium will not metalate butane although this exchange would be thermodynamically equivalent. It is this discrepancy in base strength which has made halogen–metal exchange, discussed below, a very useful method for the preparation of organolithium compounds not available by direct metalation.

Halogen–metal exchange (eq 1) is a fast, equilibrating[7]

$$R\text{-}X + R'\text{-}Li \rightleftharpoons R\text{-}Li + R'\text{-}X \qquad (1)$$

reaction which takes place readily with bromides and iodides, infrequently with chlorides, and not at all with fluorides.[8] It is generally useful only for the preparation of organolithium compounds. Exchange is most often used to metalate a specific position on an aromatic ring, or on a double bond. Poor equilibria and side reactions prevent clean exchange of unactivated alkyl halides,[9] although cyclopropyl systems are a notable exception. Reactions 2 and 3[10] illustrate the utility of this reaction. Exchange is handled in CAMEO in a manner analogous to proton transfer, with a halogen atom being exchanged instead of a proton.



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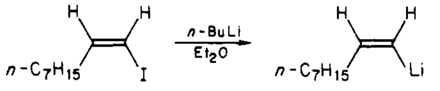
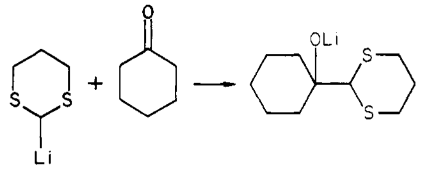


(3)

B. Addition to C–X Activated Systems. A primary characteristic of organometallic reagents is their ability to add to polarized multiple bonds, rather than engage in a proton-transfer operation. In many systems, both 1,2 and conjugate addition are possible. In general, simple alkyllithium reagents add 1,2, while lithium cuprates show a great tendency to add conjugatively. Thus, the two methods are often complementary. Grignard reagents may react in either manner, depending upon steric considerations.

The carbonyl group is the most studied of the functionalities susceptible to addition. Reaction with aldehydes, ketones, esters, amides, acid halides, and anhydrides, among others, has been achieved. For example, reaction 4[11] shows the addition of a lithiated dithiane to a ketone, while reaction 5 is the reaction of a Grignard reagent with an unsaturated system.[12] In general, organolithium additions are faster and less prone to side reactions than Grignard reactions and are therefore usually the reagents of choice. Reaction 6[13] is an example of the use of a lithium cuprate to achieve total conjugate addition.



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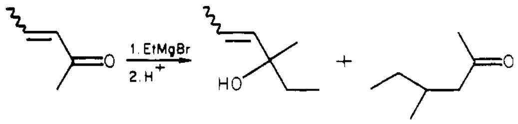

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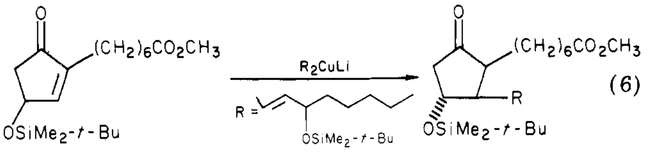
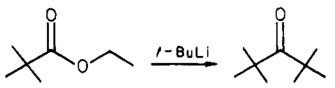


(6)

Reaction of acyl derivatives is straightforward although organolithium compounds often react further to produce tertiary alcohols. This problem is circumvented in reaction 7[14] because of steric hindrance. If the acyl derivative contains two potential leaving groups, as in reaction 8,[15] the most stable base is formed.



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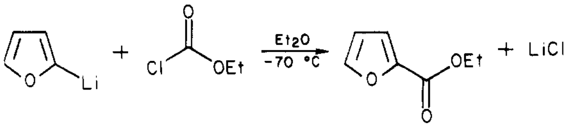
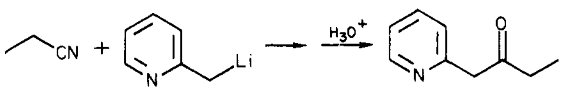


(8)

Nitriles will react with organometallics to form ketones after hydrolysis. Aromatic nitriles react well, while the situation may be complicated by α-metalation with aliphatic compounds. Condensation products are generally observed only with acetonitrile[16] and additionally stabilized compounds. A representative reaction is shown in eq 9.[17] Imines, on the other hand, undergo addition only if there are no α protons available for metalation. Although reactions of this group have been known for many years,[18] few examples have appeared in the literature, partly owing to the susceptibility of imines to metalation.



(9)

The reactions of organolithium and Grignard reagents with S=O containing substrates are quite disparate. The former will metalate sulfones, sulfoxides, and sulfonate esters. Conversely, sulfinate and sulfonate esters react with Grignard reagents to form sulfones and sulfoxides, respectively. The latter reactions are often accompanied by

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[6] J. D. Buhler, *J. Org. Chem.*, **38**, 904 (1973).

[7] (a) H. Gilman, W. Langham, and F. W. Moore, *J. Am. Chem. Soc.*, **62**, 2327 (1940); (b) H. J. S. Winkler and H. Winkler, *ibid.*, **88**, 964 (1966).

[8] R. G. Jones and H. Gilman, *Org. React.*, **6**, 339 (1951); A. P. Batalov, G. A. Rostokin, and I. A. Korshunov, *Trudy Khim. Technol. Iss.*, **2**, 7 (1968).

[9] D. E. Applequist and D. F. O'Brien, *J. Am. Chem. Soc.*, **85**, 743 (1943).

[10] G. Cahiez, D. Bernard, and J. F. Normant, *Synthesis*, 245 (1976).

[11] E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **4**, 1075 (1965).

[12] P. G. Stevens, *J. Am. Chem. Soc.*, **57**, 1112 (1935).

[13] C. J. Sih, J. B. Heather, G. P. Peruzzoti, P. Price, R. Sood, and L. H. Lee, *J. Am. Chem. Soc.*, **95**, 1676 (1973); C. J. Sih, J. B. Heather, R. Sood, P. Price, G. Peruzzoti, L. F. H. Lee, and S. S. Lee, *ibid.*, **97**, 865, (1975).

[14] A. D. Petrov, E. B. Sokolova, and C.-L. Kao, *Zhr. Obsch. Khim.*, **30**, 1107 (1960).

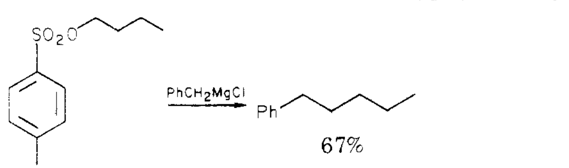
[15] F. H. Pinkerton and S. F. Thames, *J. Heterocycl. Chem.*, **7**, 747 (1970).

[16] J. P. Schaefer and J. J. Bloomfield, *Org. React.*, **15**, 1 (1967).

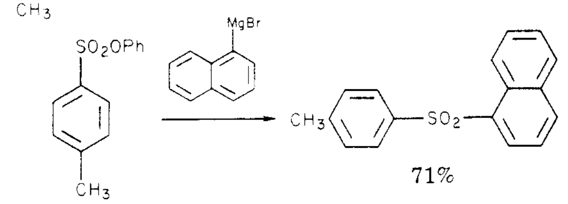
[17] J. Büchi, F. Kracher, and G. Schmidt, *Helv. Chim. Acta*, **45**, 729 (1962).

[18] M. Busch, *Ber. Dtsch. Chem. Ges.*, **37**, 2691 (1904).

substitution. Reactions 10[19] and 11[20] typify these systems.

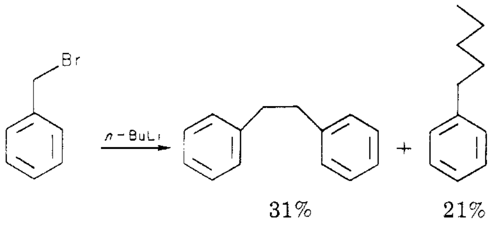


(10)



(11)

C. Alkylation. Although alkylation involving organometallics might seem to be a facile process, competing reactions such as elimination, exchange, and coupling may complicate the situation, e.g., reaction 12.[21] Intramolecular alkylation, however, has been used to synthetic advantage due to kinetic acceleration of the reaction.[22,23] It should be mentioned at this point that lithium cuprates react much more cleanly in alkylation reactions, even when addition is a potential problem as in reaction 13.[24]



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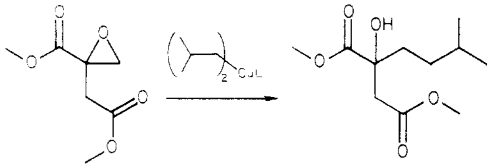
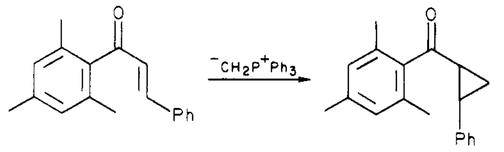


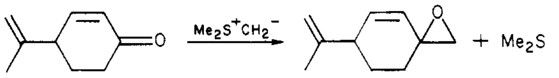
(13)

D. Ylides. Ylides are not organometallics but are considered here since they are frequently generated by these reagents and have not previously been incorporated into CAMEO. At the present time, ylides of phosphorus, sulfur, selenium, and nitrogen are within its scope. Mechanistically, ylides are handled as nonorganometallic reagents. A method has been devised, however, to handle the decomposition of Wittig intermediates to an olefin (or other group) and an oxide of phosphorus. This step is identified in postmechanistic perception of reaction products. Other ylide reactions are handled with no special modifications. Phosphonium ylides may be prepared by proton abstraction with a suitable base, by conjugate addition to vinyl phosphonium salts, or by reaction of active methylene compounds with trialkylphosphine dihalides. Alkylidenephosphoranes react with unsaturated aldehydes and ketones at the carbonyl carbon unless steric hindrance is great, as in reaction 14.[25] Phosphonium ylides have also been acylated with a variety of reagents including acid chlorides,[26-29] chlorocarbonates,[30,31] esters,[32,33] and thioesters[26,34] to form stabilized ylides. They react with isocyanates to yield β-amido ylides or ketimines.[35,36] Ylides may also take part in substitution reactions with common electrophiles such as alkyl halides, halosilanes, and selenium halides.



(14)

As is well-known, sulfur ylides react with aldehydes and ketones to form epoxides and with conjugated systems to form either epoxides or cyclopropanes. Basically, sulfonium ylides react by kinetic control, while stabilized and oxosulfonium species give products of thermodynamic control. This phenomenon is illustrated in eq 15[37] and 16.[38]



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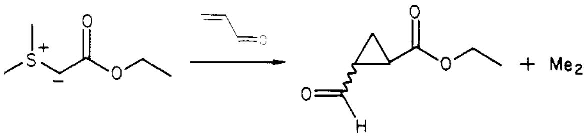

(16)

Selenium ylides react in a manner similar to the corresponding sulfur species although comparatively little work has appeared in this area.[39]

In contrast to the ylides discussed so far, an ammonium group must rely predominantly on electrostatic attraction to stabilize an adjacent carbanion. Consequently, nitrogen ylides are very reactive species. In fact, ammonium ylides with β-hydrogens do not form, rather the ammonium ion undergoes the familiar Hoffmann elimination. They are also very prone to form carbenes. The only generally useful ammonium ylide is trimethylammonium methylide,[40] which has been treated with primary and methyl halides, acid chlorides, aldehydes, and ketones.

III. Kinetic Considerations

Available literature data, a synposis of which is presented above, have been converted into general rules governing these reaction classes. The heuristics have then been incorporated into the existing CAMEO framework, as addressed in section IV. In the past, CAMEO has treated proton transfer as faster than any competing pathway.

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[19] H. Gilman and L. L. Heck, *J. Am. Chem. Soc.*, **50**, 2223 (1928).

[20] H. Gilman, N. J. Baeber, and C. H. Myers, *J. Am. Chem. Soc.*, **47**, 2047 (1925).

[21] H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.*, **66**, 1515 (1944).

[22] D. Seebach, N. R. Jones, and E. J. Corey, *J. Org. Chem.*, **33**, 300 (1968); D. Seebach, *Synthesis*, **1**, 17 (1969).

[23] T. Durst and K.-C. Tin, *Can. J. Chem.*, **48**, 845 (1970).

[24] J. Auerbach, T. Ipaktchi, and S. Weinreb, *Tetrahedron Lett.*, 4561 (1973).

[25] J. P. Freeman, *J. Org. Chem.*, **31**, 538 (1966).

[26] H. J. Bestmann, *Tetrahedron Lett.*, **4**, 7 (1960).

[27] H. J. Bestmann and B. Arnason, *Tetrahedron Lett.*, 455 (1961).

[28] S. Trippett and D. M. Walker, *Chem. Ind. (London)*, 933 (1960); *J. Chem. Soc.* 1266 (1961).

[29] G. Markl, *Chem. Ber.*, **94**, 3005 (1961).

[30] H. J. Bestmann and H. Schulz, *Angew. Chem.*, **73**, 27 (1961); *Justus Liebigs Ann. Chem.*, **674**, 11 (1964).

[31] A. J. Speziale and K. W. Ratts, *J. Org. Chem.*, **28**, 465 (1963).

[32] G. Wittig and U. Schollkopf, *Chem. Ber.*, **87**, 1318 (1954).

[33] S. Trippett and D. M. Walker, *Chem. Ind. (London)*, 202 (1960).

[34] H. J. Bestmann and B. Arnason, *Chem. Ber.*, **95**, 1513 (1962).

[35] R. P. Welcher and N. E. Day, *J. Org. Chem.*, **27**, 1824 (1962).

[36] H. Staudinger and J. Meyer, *Helv. Chim. Acta*, **2**, 635 (1919).

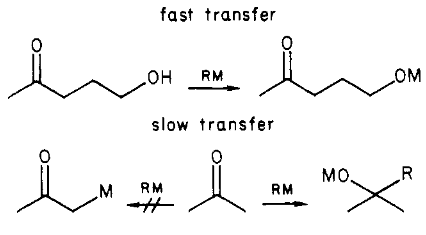
[37] E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).

[38] G. B. Payne, *J. Org. Chem.*, **32**, 3351 (1967); **33**, 1284 (1968); G. B. Payne and M. R. Johnson, *ibid.*, **33**, 1285 (1968).

[39] W. Dumont, P. Bayet, and A. Krief, *Angew. Chem., Int. Edn. Engl.*, **13**, 274 (1974); for reviews of organoselenium chemistry, see Houben-Weyl, "Methoden der Organischen Chemie", Vol. 9, Georg Thieme Verlag, Stuttgart, 1955, p 917; J. Gosselch, *Agnew. Chem., Int. Edn. Engl.*, **2**, 660 (1963).

[40] F. Weygund and H. Daniel, *Chem. Ber.*, **94**, 3147 (1960); H. Gilman and J. W. Morton, *Org. React.*, **8**, 258 (1958).

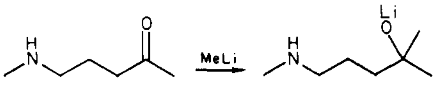
Scheme I



This assumption is obviously false for certain organometallic reactions. Therefore, a new hierarchy of rates has been created. Under certain circumstances, any of the competing processes—proton transfer, addition, or halogen–metal exchange—may be the fastest step. This section details the reaction environment conducive to each pathway and the competitions among them.

A. Competition between Proton Transfer and Addition. Formerly, proton transfer removed the most acidic protons together with those one acidity level (ca. 3–5 pK_a units) less acidic. The resultant anionic sites then became the set of potential nucleophiles. The current treatment of organometallics is the same (i.e., a 2 acidity level nucleophile window) and all algorithms will be discussed with this constraint in mind. Two types of proton transfer—fast and slow—are operative in organometallic reactions. The former process is rapid enough that addition is usually not significant, while the latter is normally slower than addition. Fast proton transfer takes place from nonmetal atoms of groups V, VI, and VII, and from sp-hybridized carbons. Slow transfer occurs with protons attached to sp^2- and sp^3-hybridized carbon atoms. Examples are given in Scheme I. Slow transfer must be further clarified. Addition will take precedence only if a valid additive group exists. This property is dependent upon the counterion in the system. Additive groups for lithium are (1) FG's (functional groups) containing C=O, C≡N, or N=O which do not contain a fast transfer center, (2) FG's containing C=N in which the imine does not activate any α protons, and (3) conjugated withdrawing groups (i.e., Michael acceptors). Simple alkyl or aryl organolithium compounds show a great tendency to add in 1,2 fashion whenever possible. Additive groups for magnesium include those for lithium as well as esters of sulfur. Magnesium organometallics will add either 1,2 or conjugatively, depending on the FG and steric environment present. Lithium cuprates react readily with Michael acceptors but are sluggish in additions to nonconjugated FG's.

The competition between organometallic addition and proton transfer is greatly affected by the relative pK_a values of the conjugate acids of the bases produced by the two processes. Formation of the weakest base is preferred even if the proton transfer is of the "slow" variety. For example, in the reaction of acetylacetone, proton transfer produces a much weaker base (pK_a = 8) than addition to the carbonyl group producing an alkoxide ($pK_a \approx 17$). Thus, proton transfer is the dominant process. Fast transfer is also subject to pK_a considerations. In the following reaction, addition to 1 should be predominant even though the amino group is a fast transfer center since proton transfer from it will produce a much stronger base (pK_a = 35) than addition to the carbonyl group.



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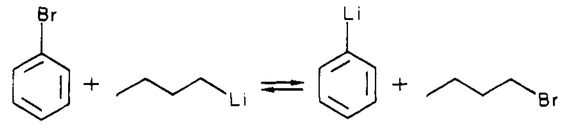
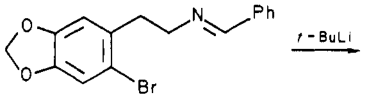
B. Competition between Addition and Halogen–Metal Exchange. Parham and co-workers have obtained data on this competition particularly for haloaryl cyanides and esters such as alkyl *p*-bromobenzoates.[41] In general, they find that the two processes are competitive and complex mixtures often result at temperatures above −78 °C. Lower temperatures (−100 °C) and bulky alkyl groups for the esters favor halogen–metal exchange.

Halogen–metal exchange is formally similar to proton transfer, with a halogen atom being transferred instead of a proton. Since this process is equilibrating, the reaction should be controlled by the strength of the base produced. Therefore, the forward reaction in the following example is favored over the reverse. If an additive group is inserted into this reaction, it is clear that if addition is faster than exchange *n*-butyllithium will be the nucleophile. Likewise, if exchange is fast, phenyllithium is the attacking species. For our purposes, addition will be considered to be competitive with halogen–metal exchange. Thus, both intermediates 5 and 6 would be predicted among the reaction products of 3 with 1 equiv of *tert*-butyllithium. In fact, treatment of 3 with 2 equiv of *tert*-butyllithium has recently been found to yield 4, which reflects both exchange and addition, though their order is uncertain.[42]





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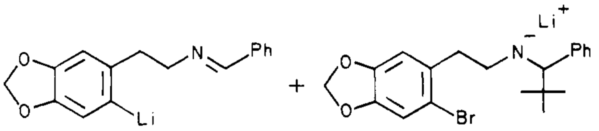

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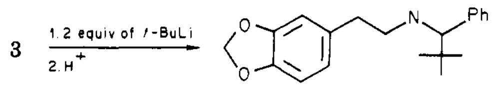

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C. Competition between Proton Transfer and Halogen–Metal Exchange. As Gilman discovered in the 1940's for compounds such as *p*-bromophenol,[43] fast proton transfer is more rapid than halogen–metal exchange with alkyllithiums. Similar results are known for halogenated anilines.[4a] However, there are some isolated, striking exceptions to this rule. Whitlock observed the reaction 17,[44] while Stein and Morton[45] also found a case (eq 18) where exchange appears to be faster than proton transfer from an acid. In both cases special steric or neighboring group effects may be operative. Such subtleties are beyond CAMEO at this time, so it will be assumed for now that fast proton transfer is more rapid than exchange. Acidity considerations normally favor fast proton transfer since the resultant bases are weaker than those obtained from halogen–metal exchange involving alkyl, aryl, or vinyl halides.

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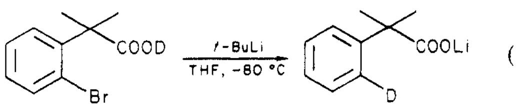
(41) (a) W. E. Parham and Y. A. Sayed, *J. Org. Chem.*, **38**, 2053 (1974); (b) W. E. Parham and L. D. Jones, *ibid.*, **41**, 1187, 2704 (1976).

(42) P. C. Conrad, Ph.D. Thesis, Purdue University, 1980.

(43) H. Gilman and C. E. Arntzen, *J. Am. Chem. Soc.*, **69**, 1539 (1947); H. Gilman and D. S. Melstrom, *ibid.*, **70**, 4177 (1948); H. Gilman and C. G. Stuckwisch, *ibid.*, **63**, 2844 (1941).

(44) R. J. Boatman, B. J. Whitlock, and H. W. Whitlock, Jr., *J. Am. Chem. Soc.*, **99**, 4822 (1977).

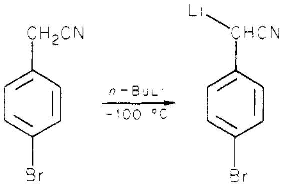
(45) C. A. Stein, and T. H. Morton, *Tetrahedron Lett.*, 4933 (1973).



(17)

(18)

On the other hand, exchange, like addition, is usually faster than slow proton transfer. Thus, 3 is not metalated at the benzylic position even though this would yield a slightly more stable base than the halogen–metal exchange.[42] However, there is a limit, so for reaction 19 the more stable base corresponding to slow proton transfer is the product.[41b]



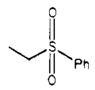
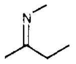
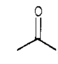
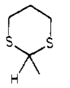
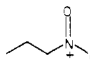
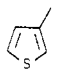
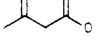
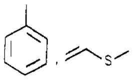
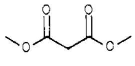
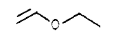
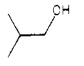
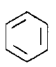
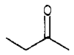
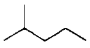
(19)

D. Summary. In general, for the competitions between proton transfer, halogen–metal exchange, and organometallic addition, the weakest bases will be formed. If there are several possible products with comparable stability (within 1–2 acidity levels), then the following hierarchy of rates is usually followed: fast proton transfer > halogen–metal exchange, organometallic addition > slow proton transfer. Thus, organometallic addition to a ketone takes precedence over proton transfer even though an enolate and alkoxide have comparable base strength. And, fast proton transfer forming an alkoxide is faster than addition forming an alkoxide. Following these processes in rate are the reactions discussed previously,[3] E1cB, conjugate E1cB, substitution, E2, and nonorganometallic addition. E1cB is the fastest of this set with the others competitive and therefore requiring more detailed heuristics.[3] The incorporation of the new chemistry into the existing framework in CAMEO will now be addressed.

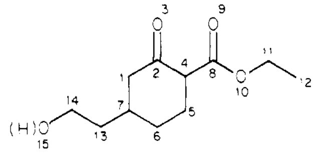
IV. Implementation of Data

An overview of the data storage used in nucleophile selection will first be given. The modified program flow including the processing of organometallic reactions will then be discussed. The general use of very strong bases in organometallic processes has necessitated the expansion of the upper acidity levels in order to achieve greater accuracy in pK_a determinations. Three new acidity levels have been added to the original 15. Levels 14–16 now correspond to acids which may be deprotonated by primary, secondary, and tertiary alkyllithiums, respectively. Levels 17 and 18 contain acids generally too weak to be directly metalated. Examples of compounds in all 18 acidity levels are shown in Table I. Grignard reagents, being more covalently bonded, behave as weaker bases than the corresponding organolithium species. In fact, Grignard reagents do not usually metalate compounds in acidity levels 14–18. Lithium cuprates are also weaker bases than the alkyllithiums and are treated in a manner analogous to the Grignard reagents in CAMEO, i.e., they will not metalate compounds in levels 14–18.

Table I. Examples of Compounds in the 18 Acidity Levels

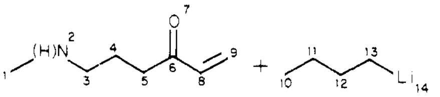
level	example	level	example
1	HCl	10	
2	HF	11	
3		12	LDA, Me$_2$SO
4	PhSH	13	
5		14	
6		15	
7		16	
8		17	
9		18	

A. Data Storage. As presented previously,[3] the recognition of nucleophiles is closely allied with pK_a perception. Atoms containing activated protons are stored along with their activating functional groups. These data are then compared to permanently stored information on which functional group combinations are required to attain each acidity level. For example, the data perceived for the following compound are shown below it. The hydrogen shown is implicit and so it is not given an atom number. As can be seen, atom 1 is activated by a ketone (FGN = 3), atom 4 by a ketone and an ester (FGN = 13), and atom 15 is an alcohol (FGN = 89). The constraint on the data ordering is that the Ith entry in the two arrays must correspond. Any other ordering is fortuitous. Their data are then compared with the activating functionalities for each acidity level until a match is made. In the present example, atom 4, with an acidity level of 6 (pK_a = 11.5), is matched first. Therefore, bit 4 is set in ACIDH, the set of potential nucleophilic sites. Since proton transfer is allowed one level uphill, acidity level 7 is then scanned. There are no available protons which are activated to this level, so ACIDH is unchanged.



PKATM(I)	WDTYP(I,1)	WDTYP(I,2)
1	3	0
4	3	13
15	89	0

The alogrithm for organometallic reactions corresponds in many aspects to that above. For example, consider the data for the reacting system below. Since this is an or-



PKATM(I)	WDTYP(I,1)	WDTYP(I,2)
2	85	0
5	3	0
0	3	0

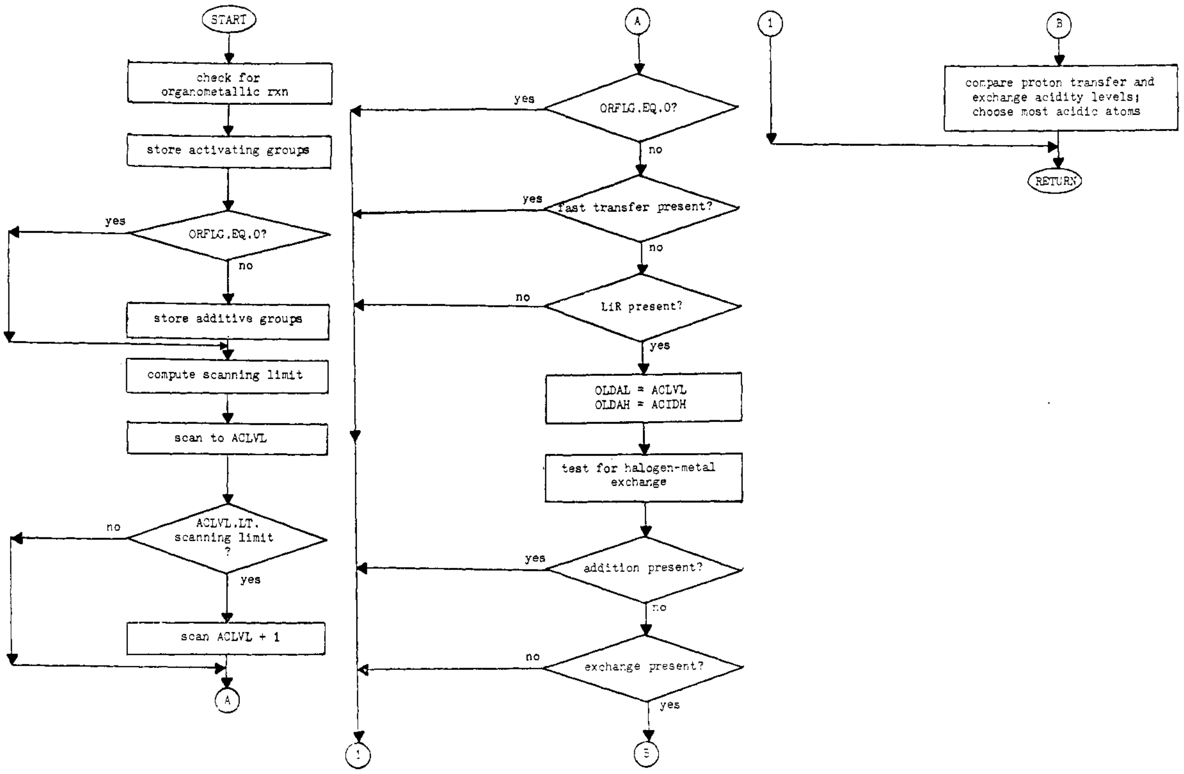


Figure 1. Flow diagram for nucleophile perception including modifications for organometallic reactions.

ganometallic reaction, potential addition must be considered with proton transfer. As can be seen, if an additive group activates a proton, its PKATM is stored in the usual manner (e.g., PKATM(2) = 5, above). In addition, the additive group(s) must also be stored to allow for potential organometallic addition. Therefore, the group is stored, but the corresponding PKATM is zero. When these pK_a data are scanned, the first group to be matched (lowest acidity level) is the ketone activating atom 5. Since organometallic conditions are in effect and a ketone is an additive group for lithium, a check is made and atom 5 is *not* placed in ACIDH. Instead, the original anion, atom 13, is entered in ACIDH. The secondary amine, which is in acidity level 12, does not enter into consideration because it is too weakly acidic relative to the ketone, even though it is a fast transfer center. Thus, at the end of the scan, ACIDH has bit 13 set, so that atom 13 will be treated as the nucleophile in the system. This subtle change enables organometallic additions to be handled efficiently. Specifically, the first pass through pK_a/nucleophile perception handles the competition between proton transfer and organometallic addition. If addition is preferred, the resultant nucleophile is the original organometallic. If proton transfer dominates, it will be performed and the proton-transfer structure(s) then becomes the resultant nucleophile(s). As a further illustration of the efficiency of this procedure, the treatment of sulfonate esters (in the absence of other functionality) is worth noting. If one is treated with an alkyllithium only proton transfer is considered since S=O is not in the set of additive groups for organolithium compounds. However, with a Grignard reagent the proton transfer is disallowed since S=O is now an additive group. So, the Grignard reagent is designated as the nucleophile and can then undergo subsequent addition, substitution, and elimination reactions, depending on the available electrophiles. For organolithiums the competitions between proton transfer or addition and halogen-metal exchange are handled by a second pass through pK_a perception as described in the next section.

B. Program Flow. 1. Nucleophile Perception. Figure 1 is a diagram of the modified program flow for nucleophile perception. It can be seen that the new code is circumvented if organometallic conditions are not in effect. Otherwise, two scans are made through the acidity levels, one for proton transfer and organometallic addition and the other for halogen-metal exchange. The latter is performed whenever a lithium counterion and a bromide or iodide FG are present. Activating groups are first stored along with the corresponding activated atoms, if they exist. When organometallic conditions are operative (ORFLG $\neq 0$), additive groups are stored when found whether or not they activate protons. The scanning limit—the highest acidity level to be scanned—is then computed. If a simple alkyllithium compound is not present, this limit is set at acidity level 13; otherwise, it is 14, 15, or 16, depending upon whether the original anion is primary, secondary, or tertiary, respectively. Acidity levels are scanned sequentially from low to high pK_a until a match with one of the FG combinations present in the system is found, or the scanning limit is reached. If the former condition prevails, the acidity level (ACLVL) is stored and the next acidity level (ACLVL + 1) is scanned, since CAMEO allows a two-level nucleophile range. If ORFLG is zero, nucleophiles found in this scan become the nucleophile set for the reaction (ACIDH).

For organometallic reactions, however, the possibility of halogen-metal exchange and of fast or slow proton transfer distinctions still exists. Nucleophiles from the first scan, together with their acidity level, are stored in the temporary sets, OLDAH and OLDAL. If fast proton transfer is possible, exchange does not have to be considered as discussed above. Since exchange is generally observed only with lithium, the presence of any other counterion also causes CAMEO to exit the alogrithm. If lithium is present, the acidity levels are rescanned, using neutral bromine and iodine atoms as the basis in place of hydrogens. The resulting nucleophile sets from the two scans must then be compared. If addition is predicted in the first scan, ACIDH, the final nucleophile set, will contain the original anion plus any new nucleophiles found from exchange reactions since exchange and addition are usually competitive. If addition is not predicted, two possibilities exist. Nucleophiles from the proton transfer scan become the reactive species if exchange is not possible. Otherwise, the nucleophiles chosen will be those which are the weakest bases.

2. Other Modifications. The majority of changes which have been made in CAMEO to handle organometallic reactions occur in nucleophile perception. In addition, pruning of certain electrophiles may take place. The presence of a lithium cuprate counterion results in the selection of conjugate over 1,2-addition electrophiles, as is commonly observed. Conversely, many organolithium compounds prefer 1,2-addition pathways, so that conjugate electrophiles may be pruned with this counterion. The only other modification of significance is that ADSBST, the routine which actually manipulates the atom and bond table for additions and substitutions, has been altered to allow displacements of vinyl halides by lithium cuprate reagents.

V. Pedagogic Flow Chart

Before sample sequences predicted by CAMEO for organometallic reactions are presented, it is worth reviewing the mechanistic logic the program uses in arriving at products.[3] This will be done by means of a simplified, pedagogically oriented flow chart. One of the primary objectives of the CAMEO project is to search out general organizing principles for organic reactions. The recognition and utilization of such principles is essential in developing an efficient program for predicting reaction products. The analytical scheme for base catalyzed and nucleophilic reactions currently used in CAMEO is summarized in Figure 2. The logic that is followed is discussed below where the numerical headings correspond to the numbered boxes in the flow chart.

1. Check the reacting system for invalid structural features. These include valence violations, trans double bonds or triple bonds in small rings, keto-enol tautomers, and tautomers of aromatic systems.

2. Identify the FG's present and classify them generally as withdrawing, donating, or neutral. Functional groups form the basis for the perception of nucleophiles and electrophiles. Identify the strongest base in the system which will be designated as the initial base. Bases may be anions or neutral atoms containing a lone pair of electrons.

3. If the reaction is not organometallic, proton transfer is the fastest pathway, and is therefore considered before all others. The FG's found in step 2 are used to identify acidic protons. Proton transfer should then be performed, if necessary, to generate the weakest base. This base and others no more than about 5 pK_a units more basic are considered as potential nucleophiles.

4. For organometallic reactions involving alkyllithium, magnesium, and lithium cuprate reagents, competition between proton transfer, addition of the organometallic reagent and halogen–metal exchange must be considered. Generally the processes yielding the weakest bases will dominate. If the resultant bases are similar in stability, the following order of reaction rates then normally determines the favored product(s): fast proton transfer > addition, exchange > slow proton transfer. Also, exchange and addition are often closely competitive. Furthermore, exchange usually takes place only between an organolithium reagent and an iodide or bromide.

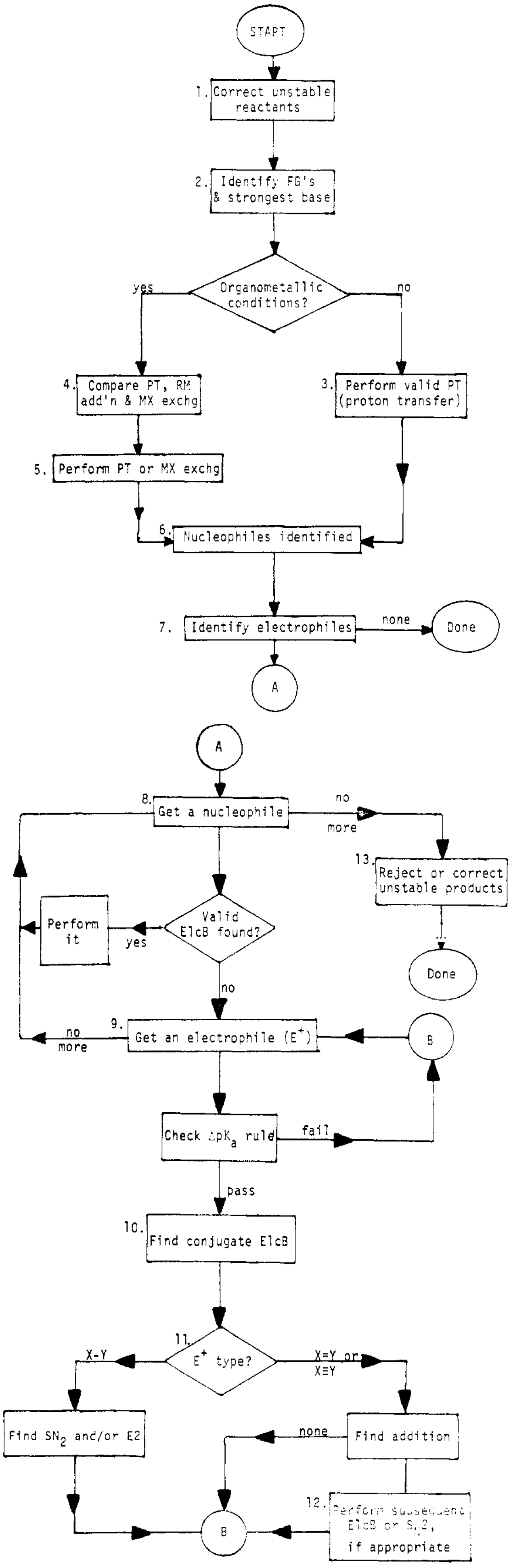


Figure 2. Pedagogic flow diagram for mechanistic evaluation of base-catalyzed and nucleophilic reactions.

5. At this point, the proton transfers or halogen–metal exchanges should be performed if they are the most favorable processes. The resultant anions are placed in the set of potential nucleophiles. If organometallic addition is probable, then the initial base (the organometallic

reagent) is the potential nucleophile.

6. Resonance must be considered for the nucleophiles to obtain all conjugated nucleophilic sites. Standard resonance rules are applied, including the avoidance of 2p–np π bonds for $n > 2$. This completes the identification of the potential nucleophilic sites.

7. The fundamental process in ionic chemistry is bringing nucleophiles and electrophiles together. So, to finish the recognition of reactive sites the electrophiles must now be identified. In general, the atoms in all X—Y, X═Y, and X≡Y bonds where X and Y are carbons or heteroatoms must be considered as potential electrophilic sites. The base strengths of the nucleophiles place some constraints on the electrophiles. Unless a protic solvent is present, the conjugate acid of the leaving group associated with a potential electrophile should not be more than about 5 pK_a units higher than the pK_a of the weakest base in the nucleophile set. If protic conditions prevail, this limitation is waived for multiply bonded electrophiles because of kinetic protonation of the leaving group. Certain electrophiles will participate in E1cB reactions only. These include sulfones, cyclopropyl atoms, and the alkyl origin of esters. Some further pruning of electrophiles may occur under organometallic conditions. Simple alkyl- or aryllithium compounds prefer 1,2 addition to the exclusion of the conjugate path, while the reverse is true with cuprate reagents.

8. The pairing of the nucleophiles and electrophiles along definite mechanistic pathways is considered next. The nucleophiles are processed one at a time. The fastest process is an E1cB reaction, e.g., the elimination of an α-bromo alkoxide ion. If such a reaction is possible for the nucleophile, it is performed and no further processing of the nucleophile is necessary.

9. If an E1cB is not possible, the nucleophile is paired with each electrophile until they are exhausted and then the next nucleophile is processed. The electrophile is rejected if it fails the ΔpK_a rule described above or is in the "E1cB only" class. If it passes, the remaining mechanisms for the nucleophile–electrophile pair are then considered. These are conjugate E1cB, S_N2, addition, and E2 which are all competitive.

10. Conjugate eliminations such as Grob fragmentations or retro-aldol reactions are sought next. These require paths of four or six atoms between the nucleophile and electrophile. All possible paths of these lengths must be considered. Reactions over longer paths are rarely observed.

11. The next mechanisms to consider are addition of the nucleophile to double or triple-bonded electrophiles and S_N2 and E2 reactions for single-bonded electrophiles. For determination of the likely pathways for each pair, several guidelines may be identified. (a) A nucleophile whose conjugate acid has a pK_a greater than 15 is considered a strong base. (b) A nucleophile which is a strong base and has two α tertiary or quaternary attachments (e.g., LDA) will act only as a base. Addition is a viable pathway with all but these species. (c) A strong base containing one α quaternary atom (e.g., KO-t-Bu) will give mixtures of substitution and elimination with primary electrophiles and show total elimination with all others. (d) A nucleophile which is a strong unhindered base will show substitution with primary electrophiles, elimination with tertiary electrophiles, and both processes with secondary species. (e) Nucleophiles which are weak bases will substitute with primary and secondary electrophiles, while eliminating tertiary species. (f) Substitution is always a possibility when a reaction is intramolecular, even with bulky species. (g) An electrophile in a six-membered ring or one which has adjacent bulky groups will show a greater percentage of elimination. (h) The formation of strained substructures such as trans double bonds or triple bonds in small rings or the creation of double bonds at bridgeheads will make a product unfavorable.

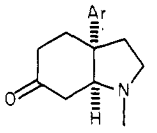
12. All addition products should be allowed to undergo a subsequent elimination or intramolecular substitution reaction, if possible. These processes often complete reactions, such as in the hydrolysis of an ester. However, the one-step addition products should also be retained in many cases.

13. The chemistry of the system has now been defined, at least for the first few reactive steps. Each product should be checked as in step 1 for unstable or tautomeric groups. If further reactions or the continuation of a complex mechanism is desired, add any new reagents which are required and return to step 1.

VI. Sample Sequences

Predictions by the program for a variety of nonorganometallic reactions were presented previously.[3] Consequently, the sequences covered here will focus on organometallic reactions and ylide chemistry. All products predicted by CAMEO are shown in each case below. It should also be noted that the stereochemical capabilities of the program are still limited. Thus, although stereochemistry at asymmetric centers is inverted in S_N2 reactions, the program does not always assign stereochemistry at newly formed double bonds in products.

Scheme II shows selected steps related to a recent synthesis of mesembrine (7).[46] The first step is a simple Grignard addition for which only one product is predicted. The second step is a Horner–Emmons reaction that yields several potential products. **9** is the reported major product[46] which is obtained from elimination of **8**. As always, CAMEO displays the addition intermediates (**8** and **10**) as well as products from a subsequent step (**9** and **11**). This seeming redundancy is necessary in the event that the subsequent step is unlikely and an alternative pathway is followed. **10** results from the resonated nucleophile with the anionic site γ to the phosphorus adding to the ketone, while **11** follows **10** via addition/elimination to the phosphonate ester. From a thermodynamic standpoint **9** is a more likely product than **11** in view of the relative stabilities of the eliminated anions. Along this line, a routine for evaluating ΔH's of reactions has been implemented in the program to provide some guide in selecting products, as will be described in a future publication.



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Addition of n-butyllithium to **9** is then predicted and observed to proceed cleanly to **12**. This compound is quenched with the bromo carbamate to generate four predicted products of which **13** is the principal, observed product.[46] The four products arise from the combinations of the two nucleophilic sites obtained by resonance of the α-imino anion and the carbonyl and bromide electrophiles. The acylations only result in elimination of the more stable

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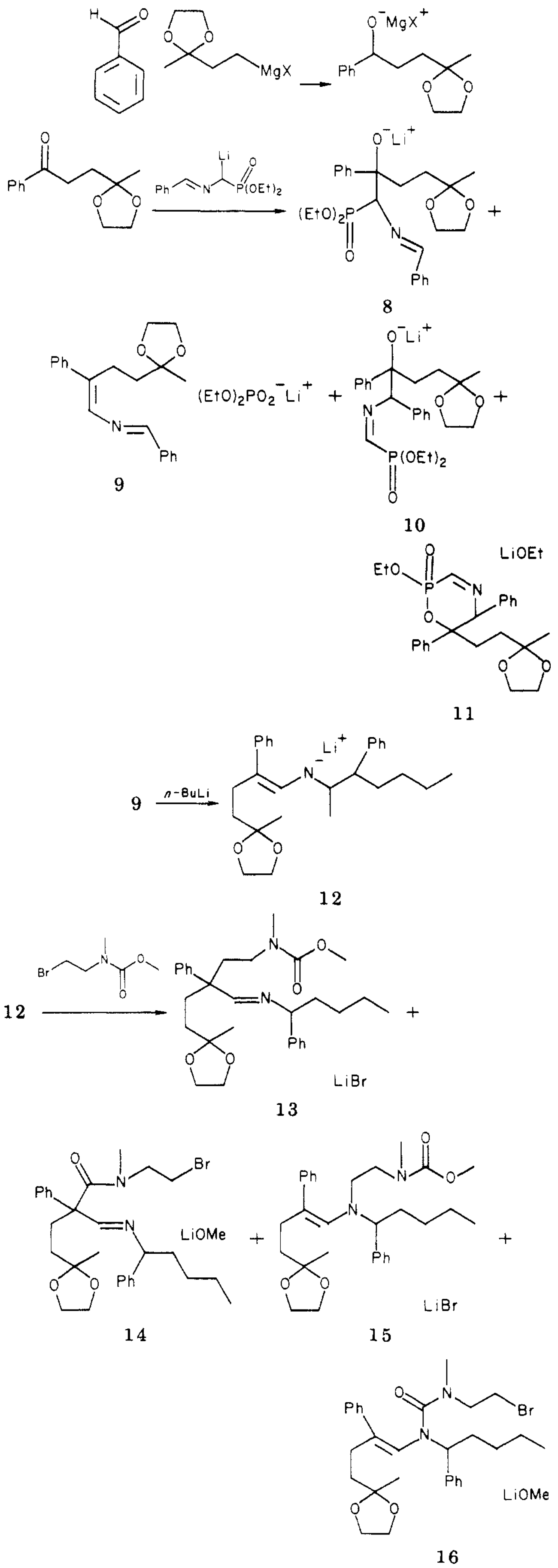
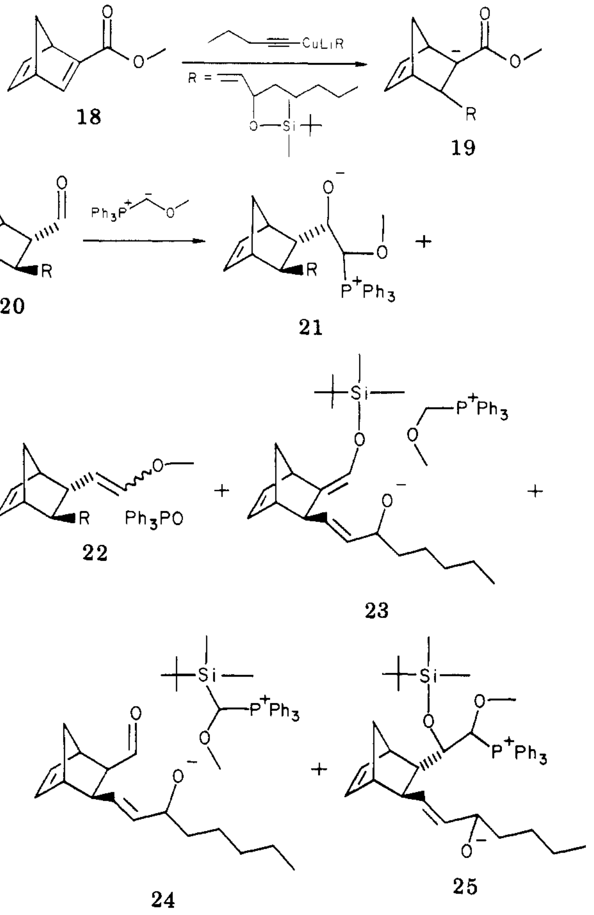
[46] S. F. Martin, T. A. Puckette, and J. A. Colapret, *J. Org. Chem.*, 44, 3391 (1979).

Scheme II

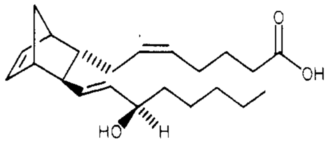


Scheme III



methoxy anion (**14** and **16**) and not the amide anion. The likelihoods of **13** and **15** are increased by the more favorable ΔpK_a for generating bromide ion instead of methoxide.

The second sequence (Scheme III) contains two steps from Corey's synthesis of the prostaglandin endoperoxide analogue, **17**.[47a] The first reaction illustrates CAMEO's ability to correctly avoid breaking the metal-alkynyl bond in a mixed cuprate and to only allow the 1,4 addition (**19**). Subsequent addition of the methoxy ylide to **20** generates **21**–**25** as predicted products. In fact, **22** is observed in 70% yield after hydrolysis.[47a] The betaine **21** is the addition intermediate leading to **22**, while **23**–**25** result from nucleophilic attack on silicon. **23** is a consequence of O-silylation of the enolate formed by proton transfer to the ylide. The product of C-silylation was rejected by the program due to hindrance of the tertiary nucleophile. **24** was formed by substitution of the ylide directly on silicon, which is an unlikely process in the presence of the competing addition. **25** is also unlikely since the elimination of the betaine should be faster than attack at silicon. Of



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[47] (a) E. J. Corey, M. Shibasaki, K. C. Nicolaou, C. L. Malmsten, and B. Samuelsson, *Tetrahedron Lett.*, 737 (1976); (b) A. G. Brook, *Acc. Chem. Res.*, 7, 77 (1974); (c) Y. Torisawa, M. Shibasaki, and S. Ikegami, *Tetrahedron Lett.*, 1865 (1979); G. H. Dodd, B. T. Golding, and P. V. Ioannou, *J. Chem. Soc., Chem. Commun.*, 249 (1975).

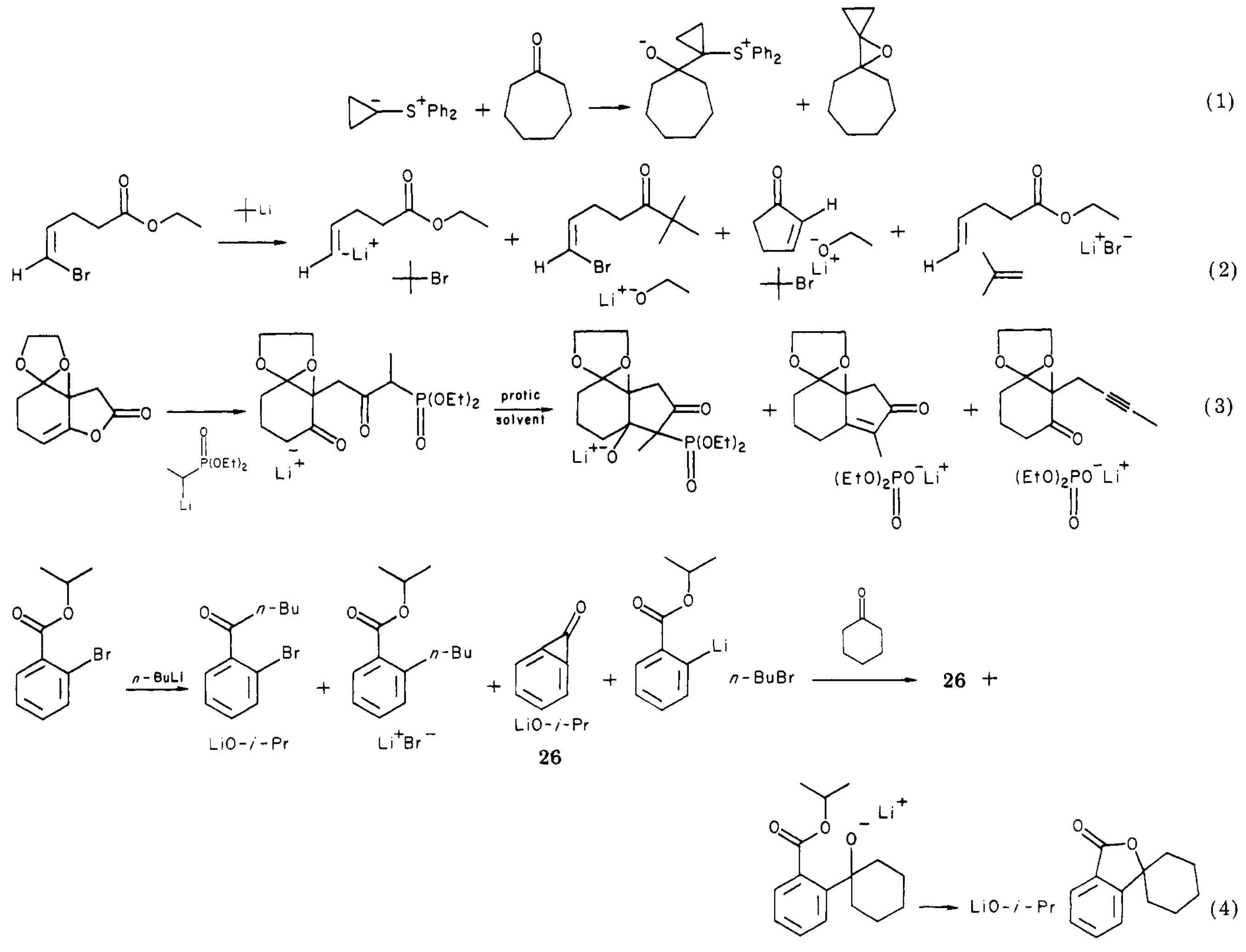

Figure 3. Additional examples of CAMEO predictions.

course, **23**–**25** are all disfavored by the presence of the *tert*-butyl group on the silyl ether which is used just for this purpose. Nevertheless, intramolecular silicon migrations are well-known,[47b] even some involving an OTBDMS group.[47c]

Additional examples that further indicate the variety of reactions and competitions handled by CAMEO are shown in Figure 3. The first reaction is a straightforward addition of a cyclopropyl sulfonium ylide to yield a novel oxaspiropentane.[48] In fact, the program also considered proton transfer from the ketone. However, this did not lead to subsequent products since substitution on the sulfonium ion was deemed improbable. If a second ketone molecule was drawn in, then condensation products would also be output. The presence of extra moles of reagent can always be considered by the program in this manner. The second reaction reflects that halogen–metal exchange and organometallic addition are usually competitive. Exchange may be followed by acylation to lead to cyclopentenone in this case or by elimination of *tert*-butyl bromide to yield isobutylene and the unsaturated ester.

The third example is an elegant Horner–Emmons sequence producing an enone.[49] The only product in the first pass through CAMEO is the β-keto phosphonate ester. A second pass is needed to complete the reaction. Note that the program requires a protic solvent for the second step. This is due to the fact that the phosphonate ester stabilized anion formed by the initial proton transfer to the enolate needs to add back to the ketone in the six-membered ring. However, this is unfavorable from a ΔpK_a standpoint, though the consequent restriction on the selection of electrophiles can be overridden in a protic solvent.[3] In fact, the reaction is reportedly completed by the addition of methoxide/methanol.[49] Nevertheless, in general, the need for the protic conditions is not absolute in such cases experimentally due to the irreversibility of the elimination of the phosphate anion. In addition to the reported product, CAMEO suggests that the β-keto phosphonate anion could decompose by an anologous elimination to yield an acetylene.

Finally, the fourth example is a reaction studied by Parham.[41b] Addition and halogen–metal exchange are again competitive and yield four possible products in the first step. Naturally, the products are all mechanistically possible; however, benzocyclopropenone is unlikely on thermodynamic grounds. Rejecting such structures uniformly can be dangerous in other instances such as in competitions surrounding Favorskii reactions. Two relatively straightforward steps complete the synthesis of the lactone. By careful control of conditions, Parham has achieved overall yields of 50–90% for such sequences.[41b]

These examples help illustrate the scope and sophistication of the program. Clearly, improvements can be made, though caution must be exercised to avoid overly restricting the program to the point where provocative products are too frequently suppressed. For the time being it seems best to err on the side of leniency in predicting

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[48] B. M. Trost, *Acc. Chem. Res.*, 7, 85 (1974).

[49] W. G. Dauben and D. J. Hart, *J. Org. Chem.*, 42, 3787 (1977).

products and to let the chemist/user participate in the screening.

VII. Conclusion

The capabilities of the CAMEO program have been extended to include ylide chemistry and organometallic reactions involving lithium, magnesium, and lithium cuprates. Related literature data were organized with particular attention to the competitions between proton transfer, organometallic addition, and halogen–metal exchange. Overall, the new chemistry merged readily into the existing program for base-catalyzed chemistry. The principal changes were in the routines for the perception of relative acidities and of nucleophiles. The program is constantly evolving and future publications will describe the progress in broadening the scope to other areas of synthetic organic chemistry including electrophilic and pericyclic reactions.

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Exploitation of Solar Energy Storage Systems. Valence Isomerization between Norbornadiene and Quadricyclane Derivatives

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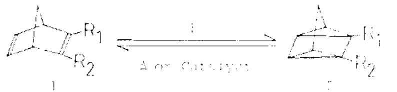
Use of copper(I)–nitrogen ligand catalysts such as $Ph_3PCuCl{\cdot}bpy$ (**3**), $Ph_3PCuCl{\cdot}phen$ (**4**), $Ph_3PCuCl{\cdot}phtha$ (**5**), and $Ph_3PCuBr{\cdot}py$ (**6**) enables the photochemical isomerization of norbornadiene to quadricyclane to be performed at a longer wavelength than 350 nm, at which CuCl catalyst itself cannot induce such an isomerization. Among the norbornadiene derivatives bearing various chromophores, 3-(phenylcarbamoyl)norbornadiene-2-carboxylic acid (**1f**) undergoes a facile and quantitative isomerization into the corresponding quadricyclane derivative (**2f**) in sunlight. The back-isomerization of **2f** to **1f** proceeds quantitatively by use of catalytic amounts of $Rh_2(CO)_4Cl_2$.

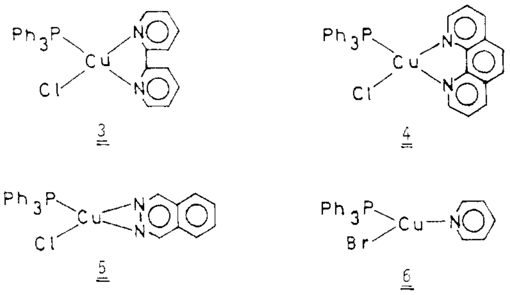
Exploitation of solar energy storage systems based on valence isomerization of organic materials has recently received wide attention.[1] Among many systems examined, norbornadiene[2] derivative (**1**)–quadricyclane[3] derivative (**2**) systems are very hopeful[1a,4–12] because of (i) the relatively large enthalpy change of the isomerization, (ii) quantitative chemical yields, (iii) stability of quadricyclane derivatives,[1a] and (iv) easy and clean back-isomerization of quadricyclane derivatives to the corresponding norbonadienes via various metal complexes.[13–18]



1a, **2a**, $R_1=R_2=H$; $\Delta H_{2a\to 1a} = -26$ kcal/mol [19]

1b, **2b**, $R_1=R_2=CO_2Me$; $\Delta H_{2b\to 1b} = -18.5$ kcal/mol [20]

Chart I



Since norbornadiene (**1a**) itself does not absorb sunlight (>300 nm), the research in this area has been directed toward the efficient photoisomerization of **1** to **2** under sunlight. Hitherto known approaches are divided into two categories: (i) the use of organic sensitizers,[21] polymers,

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(3) Tetracyclo[$3.2.0.0^{2,7}.0^{4,6}$]heptane.

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