Disconnect by the Numbers

A Beginner's Guide to Synthesis

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A perennial problem in teaching organic chemistry is introduction of synthesis and the disconnection method. Sophomores in the midst of the first organic course and first-year graduate students with a single undergraduate organic course have only a limited knowledge of carbon bond forming reactions and functional group interchange reactions. The student often worries more about making the "correct disconnection" rather than focusing attention on the chemical reactions and concepts required to form that bond. When the student makes a reasonable disconnection, the choices to reform that bond are often limited and confusing.

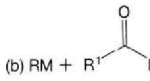
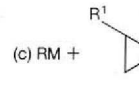
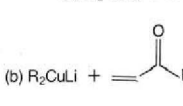
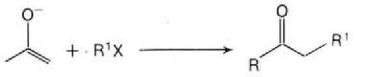
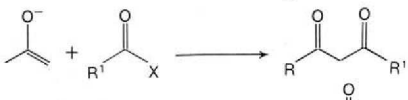
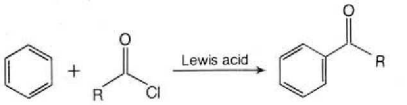
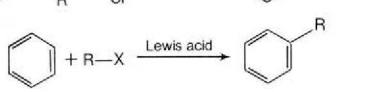
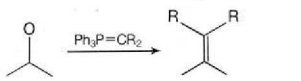
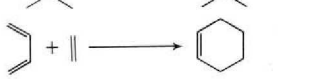
The synthesis of organic molecules dates to the 19th century, but the work of Perkin, Robinson, and others in the early 20th century demonstrated the ability to plan a synthesis (*1*). The work of Woodward, Robinson, Eschenmoser, Stork, and others in the 1940's and 1950's clearly showed how molecules could be evaluated and synthesized in a logical and elegant manner. In the 1960's Corey identified the rationale behind his syntheses, and such logical synthetic plans (termed *retrosynthetic analyses*) have become a common feature of the synthetic literature and form the basis for teaching organic synthesis. Corey formalized this synthetic logic and incorporated it into a computer-based evaluation of synthetic targets called LHASA, described as an interactive program to solve synthetic problems by various strategies (*2*). It relies on the chemical knowledge of the user to choose a strategy (*1*). Orf reported (*3*) the use of LHASA to teach undergraduate organic chemistry, and Stolow (*4*) has successfully used a modified version of LHASA for this purpose. Hendrickson described a noninteractive computer program called SYNGEN, which provides pertinent disconnections and starting materials for a given target (*5*). Warren has several books which describe the "disconnection approach" to synthesis in great detail (*6*), but these are beyond an introductory undergraduate course and at the graduate level become a separate course.

Although each approach is useful, all have limitations for introducing synthesis to undergraduates or first-year graduate students, especially when there is a large class. A simple procedure is needed that does not require sophisticated computations or lengthy study to comprehend. It will be easy to learn and execute, allowing a beginning student to disconnect molecules in a reasonable manner. Perhaps most importantly, it must give a protocol for converting disconnect products to real molecules based on a list of carbon bond forming reactions.

All disconnection approaches assign priorities to bonds in a molecule and disconnect those bonds with the highest priorities, as with Corey's strategic bond analysis (*1*, *2*). In the method described here, we will also assign priorities. To simplify the approach for beginning students, the priorities are based only on the relative ability to chemically form the bond broken in the disconnection. Application of this single criterion to complex molecules is less attractive since it ignores structural and topological features, functional group interactions, protection of key functional groups, and the problems inherent in preparing polycyclic and heterocyclic ring systems. An examination of the structural types encountered in undergraduate courses, however, quickly reveals that such complexity is lacking in most cases and a simple bond-forming strategy is both reasonable and useful.

The protocol described in this work will begin by assigning numbers to each bond, based entirely on the small set of carbon bond forming reactions introduced in a typical two-semester organic chemistry course (*7*). These reactions are listed in Table 1. Tables are provided to assign the numbers, based on the importance of forming carbon bonds in molecules containing a polarized functional group. The procedure assigns priorities based on key regions of a molecule: (1) the bond connected to a functional group X (C—/ /—X), (2) to the second bond from X (C—/ /—C—X) and (3) to the third bond from X (C—/ /—C—C—X). The fourth part of the procedure recognizes the importance of disconnecting bonds attached to chiral centers. This procedure assigns numbers to all bonds and the highest number(s) will be disconnected. The resulting disconnect products are converted to "real reagents" by using a corresponding "synthet-

Table 1. Carbon–Carbon Bond Forming Reactions

1. Cyanide	$RX + CN^{\ominus} \longrightarrow RC{\equiv}N$
2. Acetylides	$RX + R'C{\equiv}C^{\ominus} \longrightarrow R{-}C{\equiv}C{-}R'$
3. Substitution by Organometallics M = MgX, Li, ZnX, . . .	(a) $RM + R^1{-}X \longrightarrow R{-}R^1$
	(b) RM + 
	(c) RM + 
4. Organocuprates	(a) $R_2CuLi + R^1X \longrightarrow R{-}R^1$
	(b) R_2CuLi + 
5. Enolate Alkylation	
6. Enolate Condensation	
7. Friedel–Crafts Acylation	
8. Friedel–Crafts Alkylation	
9. Wittig Reaction	
10. Diels–Alder Cyclization	

ic equivalent". A list of synthetic equivalents for selected disconnect products is given in Table 2. Each synthetic equivalent is based on an S_N2, S_N1, or nucleophilic acyl substitution reaction, any of which are ionic in nature. Two carbons can be joined together by these reactions if one is nucleophilic (donates electrons = donor carbon) and one is electrophilic (accepts electrons = acceptor carbon). This protocol, therefore, assumes the disconnected bond will be reformed by one of these ionic reactions and the disconnect product will be transformed into a "real" ionic synthetic equivalent. The figure provides a conceptually important "reaction wheel" to demonstrate how functional groups are chemically related. This figure can be used to determine functional group exchanges for the disconnect product(s). Jorgenson is developing a program called CAMEO, which is "a mechanistically based, interactive computer program designed to predict the products of organic reactions" (*8*). Such a program will have enormous value in teaching organic chemistry and would be ideal for identifying functional group transforms and carbon bond forming reactions. If such a program is not available, however, the figure provides a simple visual aid to assist the choice of a functional group exchange. The procedure for assigning bond priorities and determining synthetic equivalents will generate the carbon bond forming reactions. The bond priorities, Tables 1 and 2, and the figure constitute a self-contained package for disconnecting a molecule and choosing a rational set of reactions for reassembling the target.

All bonds in a molecule could be disconnected, in turn, and evaluated, but a priority scheme directs attention to those regions of the molecule most likely to yield a useful synthesis. The self-consistent list of reactions, the table of synthetic equivalents, and the priority numbers derived from them will quickly expand as students advance in their studies. They will logically turn to the more advanced reactions and apply them.

Rather than assign complex (and more accurate) priority numbers to bonds, only four priorities will be used.

Table 2. Common Synthetic Equivalents for Disconnect Products

$R_2-C^d(R)-$	$R_3-C-MgX$	R_3-CLi	R_3-Cl_2CuLi, $R_2-C^-(R)-PR_3^+$
$R_2-C^a(R)-$		R_3-C-X	(X = Cl, Br, OTs, OMs, OTf)
$R-C^a(R)$		$-C(=O)-R$	(for Wittig)
$R-C^a(R)-OR$		$-C(=O)-R$ or $-CH(Cl)OR$	
$R-C^a(R)-OH$		$-C(=O)-R$	
$R-C^a(R)-CH_2-C=O$ / $R-C^a(R)-CH_2-C-OH$		or $-CH=CH-C(=O)-R$	
$R_3C-C^d=O$ / R_3C-CH^d-OH	and	R_3C 1,3-dithiane-2-yl (Li)	Acyl Anion Equivalent
$R-C^dR_2C-OH$		epoxide	
$R-C^d(R)-C=O$ / $R-C^d(R)-CHOH$	or	$-CH=C(O^-)-R$	Enolate

(1) + 10 for bonds easily formed
(2) + 7 for bonds formed with moderate ease
(3) + 3 for bonds formed with moderate difficulty
(4) 0 for bonds formed with great difficulty or not at all

To employ this strategy, four regions of the molecule will be examined to assign the 0, 3, 7, or 10 priority numbers to each bond. The four regions are: (1) the C—X bond, (2) the bond α to C—X, (3) the bond β to C—X and (4) the bonds connected to chiral centers. The protocol for assigning bond priorities for these four regions is:

(1) Direct substitution: C—/ /—X—use Table 3. For C = C^{sp^2} and X = C (C=C), assign +7 for C=C. If the C=C is exocyclic to a ring assign +20. Assign 0 for C≡C, C≡N, and aromatic C=C.

(2) α Substitution: C—/ /—C—X—use Table 4. +20 for C—/ /—C—C=C when part of a cyclohexene ring.

(3) β Substitution: C*—/ /—C—C—X.

(a) When X = C=O and C≡N. C* = CH_3, 1°, 2° sp^3, Ar, priority = +7 (−4 for monocyclic). C* = 3°, sp^2, sp, priority = +3 (−3 for monocyclic). For C=N and C≡C, the priority is 0. If "C*" = oxygen, the priority is 0.

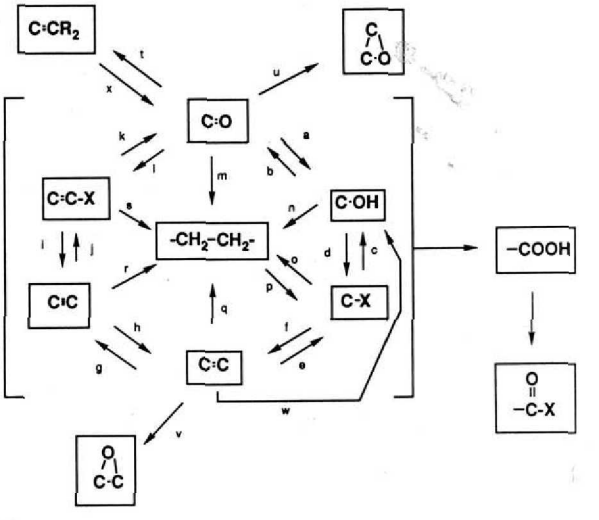
(b) When X = O. C* = CH_3, 1°, 2° 3° sp^3, Ar, C≡N, C≡C, O, N, *priority = +10 (−7 for monocyclic).*

(4) For C^2—C*—X, where C* is the chiral carbon.

(a) Bond connecting C* to X (C*—X). Direct substitution, use Table 3.

(b) Bond attached to C* but not to X (C^2—/ /—C*—X). α Substitution, use Table 4. (c) C^2 is also chiral (C^2—/ /—C*—X). *Double the value from 4a or 4b.*

The bond(s) with the highest priority numbers will be considered most important and will be preferentially disconnected. Typically, only one or two bonds will be considered, and lower priority bonds do not lead to feasible synthetic equivalents, lower



a. $LiAlH_4$ or $NaBH_4$ or H_2 /cat.
b. CrO_3
c. NaOH/ H_2O or Mitsonobu
d. PCl_5, $SOCl_2$ (X = Cl); PBr_3 (X = Br); i. NaH ii. RX (X = OR); i. PBr_3 or RSO_2Cl ii. K-phthalimide iii. hydrolysis or i. NaN_3 ii. H_2/cat. (X = NH_2)
e. HX
f. NaOH/ H_2O or $RO^\ominus$ /ROH
g. i. Br_2 ii. $NaNH_2$
h. H_2 /cat. or Na/NH_3/EtOH
i. $NaNH_2/NH_3$
j. HX
k. $H_3O^\oplus$
l. PCl_5
m. N_2H_4 or Zn(Hg)/HCl
n. i. RSO_2Cl ii. $LiAlH_4$
o. $LiAlH_4$ or H_2 /cat.
p. $X_2/h\nu$ or heat
q. H_2 /cat.
r. 2 H_2 /cat.
s. excess H_2 /cat.
t. $Ph_3P=CR_2$
u. $Me_2S^\oplus$-$CH_2^\ominus$
v. RCO_3H
w. i. B_2H_6 ii. NaOH/H_2O_2 or i. $Hg(OAc)_2$ ii. $NaBH_4$
x. i. O_3 ii. Me_2S or H_2O_2

Functional group exchange reaction wheel.

priority bonds may be important. This requires an evaluation by the student of the fundamental reactions behind each disconnection, a process usually more important to the novice than the actual synthesis. The protocol is:

(a) Assign priorities from Table 3 and 4, based on a modified version of Corey's strategic bond analysis (*1*, *2*), which considers only on the ability to form that bond. The priority numbers will be 0, 3, 7 and 10.
(b) Determine the bond priorities and disconnect the bond(s) with the highest numbers.
(c) Assign each disconnect carbon a donor or acceptor site using Seebach's protocol (*9*) and assume the bond will be formed via an ionic reaction from Table 1.
(d) Using the table of synthetic equivalents (Table 2), transform each donor and acceptor carbon in the disconnect product into a "real" chemical structure.
(e) Using Table 1, determine which disconnect intermediates are realistic and which is best for the problem at hand.
(f) Continue (a)–(e) on the chosen disconnect fragment until a reasonable starting material is obtained.

Region 1 (The Bond Connected to the Functional Group)

The values in Table 3 are used for bonds of the type C—X, where a functional group is attached directly to the carbon of interest (the disconnection is C—/ /—X). Reactions in Table 1 that form this bond are mechanistically based on substitution reactions: S_N2, S_N1, and nucleophilic acyl substitution. Examination of Table 1 shows reactions 1, 2, 3, and 4 are compatible with S_N2 reactions. The S_N1 reaction is most useful for tertiary carbon substrates. A variation of the S_N1 reaction is Friedel–Crafts alkylation (reaction 8, Table 1), which generates the C—/ /—Ar bond but is efficient and controllable only with tertiary carbon groups. Similarly, Friedel–Crafts acylation (reaction 7, Table 1) leads to the Ar—/ /—C=O bond. Each reaction generates a C—X bond, where X is aryl for alkylation and C=O for acylation. For all bonds formed via S_N2 displacement, primary and secondary carbons receive a high priority but tertiary carbon, which does not undergo such displacement, is given a low priority.

Carbon nucleophiles such as Grignards and organolithium reagents (reaction 3, Table 1) do not give good yields of coupling (formation of C—C bonds) without addition of transition metal catalysts (reaction 3a, Table 1). Aryl and vinyl cuprates (*10*) are useful for giving the Ar—C and C=C—C bonds (reaction 4a, Table 1) but disconnection of a C^{sp^3}—C^{sp^3} bond is rarely useful and the priority of zero discourages this route. When the carbon nucleophile is cyanide (reaction 1, Table 1) or acetylide (reaction 2, Table 1), S_N2 displacement of primary and secondary halides give good yields of the C—X bond and the priority is high. The lowered bond priority for secondary carbon reflects the slower rate of substitution and the increased problem of E2 elimination (reaction f, the figure) with basic nucleophiles.

The S_N2 reaction is facile with oxygen nucleophiles (HO^-, RO^-) and substitution gives C—OR with primary and secondary alkyl halides (the *Williamson ether synthesis*, reaction c, figure). The priority numbers for the C—O bond are high, but elimination (reaction f, figure) is competitive for secondary and predominates for tertiary halides, lowering the priorities. An S_N1 pathway can generate the C—OR bond with tertiary carbon but is of limited utility. For the C—N bond, S_N2 displacement with amines on primary and secondary alkyls commonly gives low yields and overalkylation. Displacement with imide anion nucleophiles corrects these deficiencies, and azide is an excellent nucleophile that can be reduced to the amine (*11*). These S_N2 reactions receive the highest priority with primary carbon.

When the carbon in C—X is aryl, coupling to another aryl group (Ar—Ar) is difficult except via Ullman-type reactions involving copper reagents and radical intermediates (*12*) (not shown in Table 1). The bond priority is, therefore, rather low. Similarly, formation of C≡C—C≡C or C≡C—C≡N and coupling of aryl to an oxygen (Ar—O) or nitrogen (Ar—N) is difficult, and all receive low priorities. Oxygenated aryls can be prepared from an aryl diazonium salt but commercially available oxygenated aryls are usually used intact. Formation of Ar—N begins with electrophilic aromatic nitration followed by reduction, but many nitrogen containing aryls are supplied commercially.

Nucleophilic acyl substitution of carbonyls is applicable via in a two-step process. Addition of Grignard reagents or organolithiums (alkyl or aryl) to ketones and aldehydes generates the C—/ /—C—OH bond (see discussion of region 2 bonds). Oxidation of these alcohols to the aldehyde or ketone generates the C—/ /—C=O or Ar—/ /—C=O bond and this important route led to high priorities. Formation of O—C=C, O—C=N, O—C≡C, and O—C≡N bonds are difficult except for the enol (O—C=C), which is usually a reactive intermediate. Similar comments apply for nitrogen-containing compounds such as N—C=C, C—C=N, N—C≡C and N—C≡N. Both O—/ /—C=O and N—/ /—C=O bonds are acid derivatives and considered to be labile functional groups. Disconnection of such functional groups *prior* to the bond analysis is usually preferable.

Disconnection of the C—X bond in monocyclic ketones, ethers, or amines requires an intramolecular cyclization to reform the bond. Such cyclizations are facile for the formation of three→seven membered rings and difficult for eight→twelve membered rings (*13*). Larger rings can be formed using high dilution techniques. Intramolecular ring formation is common and desirable for bicyclic and polycy-

Table 3. Disconnection of C—/ /—X For Region 1 Bonds[a]

C \ X	1°—C	2°—C	3°—C	Ar	C=C	C=O	C≡C	C≡N	O	N
1°—C	—	—	—	3	3	10	10	10	10	10
2°—C	—	—	—	3	3	10	7	7	7	3
3°—C	—	—	—	3	—	7	—	—	3	—
Ar	—	—	—	3	—	10	3	—	3	3
C=C	—	—	—	—	—	3	—	—	—	—
C=O	—	—	—	3	—	—	—	—	10*	10*
C≡C	—	—	—	3	—	—	3	—	—	—
C≡N	—	—	—	—	—	—	—	—	—	—

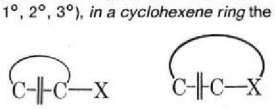
[a] 1° = —CH_2R, 2° = —CHR_2, 3° = —CR_3, (all = sp^3C). For all alkenes (C=C) where C = sp^2C and X = sp^2C (C—X = C=C)—assign +7. If the olefin is *exocyclic*, assign +20.


for monocyclic bonds only (−3 to score from above)

Table 4. Disconnection of C^2—/ /—C^1—X for Region 2 Bonds[a]

C \ X	1°—C	2°—C	3°—C	Ar	C=C	C=O	C≡C	C≡N	O[b]	N[b]
1°—C	—	—	—	10	10	10	10	10	10	7
2°—C	—	—	—	7	7	10	10	10	10	7
3°—C	—	—	—	3	3	3	3	3	7	3
Ar	3	3	3	7	7	3	7	7	10	7
C=C	3	3	—	7	7	—	7	3	10	3
C≡C	10	10	—	10	10	3	10	3	10	3
C≡N	10	10	—	10	10	3	10	7	3	—

[a] 1° = —CH_2R, 2° = =CHR_2, 3° = —CR_3, (all = sp^3C).
[b] For esters and amides (C^2—C^1—O—/ /—C=O or C^2—C^1—N—/ /—C=O), these are *functional group exchanges* and should be disconnected *first*. When X is C=C (C^1 = 1°, 2°, 3°), *in a cyclohexene ring* the priority is +20.


For monocyclic bonds only (−7 from above)


bicyclic (set = 0).

clic molecules. For synthetic problems facing a beginning student it is easier to begin with a functionalized monocyclic compound, taking advantage of the superior stereoselectivity possible in its reactions, than to form a ring from acyclic precursors. Obviously, ring-forming reactions are widely used, but in the first disconnection it is easier to use the intact ring. The rules reflect this by adding a corollary to Table 3 which subtracts 3 (priority 3) if this bond is part of a monocyclic ring.

The *Wittig reaction* (reaction 9, Table 1) generates a carbon–carbon double bond (C=C) by nucleophilic acyl addition of a phosphorous stabilized carbanion to a carbonyl followed by elimination of a phosphine oxide and an alkene (*14*). The bond of interest is C=X (X is C), and a corollary was added to Table 3 giving a priority of +20 *if* C=C is *exocyclic*, suggesting its formation via Wittig methodology. Endocyclic alkenes could be formed via an intramolecular Wittig reaction but this is much less facile.

Region 2 (Second Bond from the Functional Group)

Table 4 generates the numbers for Region 2 bonds and is used to prioritize carbon bonds β to a functional group, X (second bond from X). The disconnection is C—//—C—X. This is probably the most common bond generated by the reactions in Table 1. Mechanistically, S_N2 displacement and nucleophilic acyl substitution account for virtually all the pertinent reactions. With allylic and benzylic carbon, reactions 1–5 (Table 1) apply for S_N2 reactions. Reactions 2, 3, and 6 involve nucleophilic acyl substitution. When X is an sp^3 carbon, the organocuprate reaction (reaction 4, Table 1) will form the bond but requires difficult functionalization, and, as in Table 3, the priority of zero will discourage the disconnection.

To keep Table 4 as simple as possible, only the substitution pattern at C^1 (connected to the functional group, C—//—C^1—X) is considered. In all cases, the highest priorities are given when C^1 is primary or secondary alkyl since these are most compatible with S_N2 displacement. Tertiary alkyl derivatives (C—$C^{3°}$—X) react with difficulty. Carbocation coupling reactions are certainly possible, but the conditions are often harsh and difficult to control. Trisubstituted C^1 derivatives are given reduced priorities in all cases. In this analysis, X is always the functional group and *never* an sp^3 carbon.

For nucleophilic acyl substitution, reaction 3b, Table 1, shows the nucleophile can be alkyl or aryl (RMgX or RLi) and will generate C—//—C—O and Ar—//—C—O. If the nucleophile is an enolate (reaction 6, Table 1), the O=C—C—//—C—O bond will be formed. Acetylide adds to carbonyls to give the C≡C—//—C—O bond. All these facile reactions receive high priorities.

S_N2 displacement of alkyl halides by enolates generates the O=C—C—//—C bond (reaction 5a, Table 1). Similarly, nitriles with an α-hydrogen can form an enolate anion, and reaction with alkyl halides gives C—//—C—C≡N. Nucleophilic acyl substitution of nitrile enolates with carbonyls gives the O—C—//—C—C≡N bond. A related S_N2 reaction is the displacement of α-halo carbonyl derivatives with carbon nucleophiles. Reaction of α-bromoketones with alkyl or aryl Grignards or organocuprates gives the C—//—C—C=O and Ar—//—C—C=O bonds. In all cases the high priorities reflect the ease of forming these bonds.

"Activated" alkyl halides generate high priority numbers for forming this bond via S_N2 reactions with organometallics (reaction 3a, Table 1). Allylic and benzylic halides readily react with cuprates and sometimes with Grignards and organolithiums to give C=C—C—//—C, C=C—C—//—Ar, Ar—C—//—C and Ar—C—//—Ar. This contrasts with region 1 priorities since allylic and benzylic halides are relatively easy to form. Allylic and benzylic halides also react with cyanide, acetylide, alkoxides, and nitrogen nucleophiles to give the C=C—C—//—X and Ar—C—//—X moieties.

As with region 1 priorities, disconnection of monocyclic rings is discouraged. Analysis of region 2 bonds in cyclohexanol and cyclobutanecarboxylic acid shows they have priority bonds *in the ring*. To discourage the intramolecular cyclization, seven is subtracted from the priority number (priority number −7). In Corey's strategic bond analysis (*1, 2*) of cyclic compounds, opening a bond common to two fused primary rings led to a large ring. The difficulty in reforming the rings (*13*) led to a rule which discouraged making such bonds strategic. A corollary was added to Table 4, taken from Corey's strategic bond analysis (*2*), which sets the priority of this bond to *zero*.

There is an important exception to the "monocyclic rule". The *Diels–Alder reaction* is, without question, one of the most important reactions in all of organic chemistry (*15*). The key fragment is a cyclohexene and it is clear that the two-bond "Diels–Alder disconnection" requires cleavage of the allylic bonds, two removed from the olefinic functional group. The corollary to Table 4 increases the priority of such bonds to +20 *when that bond is part of a cyclohexene ring*. This applies to mono- and polycyclic molecules and to bonds that are common to two fused rings (if part of a cyclohexene moiety).

Region 3 (Third Bond from the Functional Group)

Disconnection of a bond that is λ to the X group (third bond from X with the disconnection C*—//—C^2—C^1—X) is generally less important. The only two important mechanistic routes to this bond are conjugate addition of nucleophiles to conjugated carbonyls (reaction 4b, Table 1) and S_N2 opening of epoxides (reaction 3c, Table 1). Conjugate addition will be considered only when X is carbonyl (C=O) or nitrile (C≡N), where 1,4- (Michael) addition of certain nucleophiles to the α,β-unsaturated precursor generates C*—//—C—C—C=O or C*—//—C—C—C≡N (*16*). The "adding group" C* must be a nucleophile species. Conjugate addition of organocuprates (reaction 4b, Table 1) is the preferred reaction to form this bond (*10*). Enolates and some other carbanionic reagents give conjugate additions but heteronuclear nucleophiles usually show reversible addition. The priority is +7 except when C* is tertiary or C^{sp^2} since both cases are significantly more difficult.

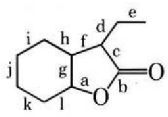
In the second important reaction that generates the C*—C—C—O linkage, C* is also a nucleophilic carbon species. This rule does not apply to the alkene linkage, C*=C—C—O, however. Grignard reagents open epoxides by S_N2 displacement (reaction 3c, Table 1) to generate this bond. It is noted that reactions 1–5 from Table 1 are compatible with nucleophilic ring opening of epoxides and C* can be cyano, alkynyl, primary, secondary, or tertiary alkyl, aryl, oxygen, or nitrogen. Since steric hindrance is a significant problem primarily at the epoxide, high priorities are given for most carbon species. The usual regiochemical problems (which carbon of the epoxide reacts) encountered with ring opening are not reflected in this simple analysis.

Region 4 (Disconnection at Chiral Centers)

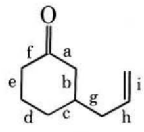
This reflects the importance of disconnections at chiral centers, as stated in Corey's strategic bond analysis (*1, 2, 17*). Disconnection of bonds containing a remote chiral center is discouraged. For the system C^2—C*—X, *C* is the chiral carbon* and there are two bonds to be considered: (1) the bond linking the chiral center to X(C*—//—X, case a) and (2) the bond that is connected to C* but not to X (C^2—//—C*—X, case b). Case a is a region 1 bond, and Table 3 is used to assign priorities to each chiral center. Each chiral center is treated independently. If there is more than one X group (—C*XX′) Table 3 is applied for both functional groups. When X = C^{sp^3}, Table 3 assigns a priority of 0. In most cases this will not be detrimental. Case b is a region 2 bond, and

Table 4 is used to assign priorities for each functional group connected to C*. The net result of this protocol is to double the value from region 1 or region 2, increasing the importance of those bonds, when attached to a chiral center.

1



2



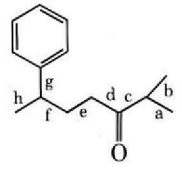
3

There are many cases when C^2 in C^2—C*—X is also chiral. Such a bond is more important, and this is reflected by *doubling the priority from 4a or 4b* (rule 4, case c). Examination of compound 1 reveals bond b is attached to two chiral centers. Since X is C=O, C* and C^2 are labeled accordingly. Bond b receives a priority of 0 by Table 4 since it is part of a bicyclic system. Compound **2**, however, shows that bonds f and g are connected to two chiral centers and receive a priority of 10, which is then doubled (10 × 2). A problem arises when all atoms connected to C* are carbon (X = C^{sp^3}). Which procedure applies, 4a or 4b? Both Table 3 and Table 4 assign a priority of 0, but, if there is a problem, assume this is a region 1 bond, and use Table 3. Bond c in ketone **1** will therefore receive a priority of 0 (C^2 = C* and X = C). Similarly, bonds b, c, and g are connected to a chiral center in **3** and receive priorities of 0 (see Table 7).

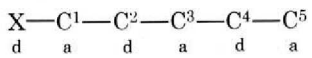
The four bond regions just discussed are the basis for identifying the highest priority bonds. How are these priority numbers used? In the examples discussed below, they will be applied to simple synthetic targets and address the problem of what to do after the priority bond has been disconnected.

Determination of Bond Priorities

Ketone **4** contains two functional groups (carbonyl and phenyl) as well as a chiral center. The bond analysis in Table 5 reveals that bond f has the highest priority, but disconnection leads to fragments that are not obvious reagents. Before these fragments can be evaluated and used in a synthesis, they must be converted to "real" organic synthons. We have seen that reactions 1–9 in Table 1 involve nucleophilic or electrophilic intermediates and form bonds via S_N2, S_N1, or nucleophilic acyl substitution reactions. These reactions involve ionic intermediates or highly polarized transition states. To take advantage of this ionic chemistry, each disconnect product will be converted to an ionic fragment.



4



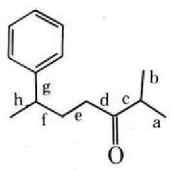
5

The concept of nucleophilic and electrophilic atoms in ionic and polarized intermediates is well known. Polarized bond notation such as $C^{\delta+}$—Br and $C^{\delta-}$—Li are commonly used in describing the reactivity of these bonds. For the nucleophilic and electrophilic centers common to the S_N2 reaction, ΔG_{tr} is approximately zero for highly polarizable anions and a polarizable neutral (*18*). For the nucleophiles, this polarizability is expressed as X^- or X:, where the electrons represent an electron-donating center. The polarizability of various atoms and molecules is reflected in hard/soft acid/base (HSAB) theory (*19*). In his description of Umpolung reagents, Seebach formalized a bond polarization model based on structure **5** (*9*). The sites marked d in **5** represent *donor* sites or *nucleophilic* atoms. The sites marked a are *acceptor* sites and correspond to *electrophilic* atoms. If X is oxygen or nitrogen, for example, donation of two electrons from these nucleophilic atoms to an electrophilic carbon (cation or $\delta+$ carbon) will generate the C—X bond. Bond polarization induced by the heteroatom extends down the carbon chain due to the usual inductive effect which is a combination of "through-space" and "through-bond" effects (*20*). The electrophilic carbon adjacent to X (C^1) is designated a (an *acceptor atom*) since proximity to the electronegative atom (X) induces the opposite polarity. Similarly, C^2 is a donor atom, but weaker than X (this carbon is further away from the electrons that induce the bond polarization), and C^3 is a weak acceptor atom. As a practical matter, the effect is negligible beyond C^4 and will be ignored. With this protocol, disconnection of bond f in **4** leads to two fragments, and each has two polarization modes. There are, therefore, four different synthetic equivalents: **6** + **7** and **8** + **9**.

The *donor carbons* (C^d) in **7** and **8** are *nucleophilic*, and according to Table 1, they correspond to a Grignard reagent, organolithium reagent, or organocuprate. Benzylic fragment **8** can be called the *synthetic equivalent* of α-lithio ethylbenzene or the corresponding organocuprate (Table 2). Similarly, the *acceptor carbons* (C^a) in **6** and **9** are *electrophilic*. The halogen in alkyl halides induces a $\delta+$ charge on the adjacent carbon and C^a in **6** suggests the "real" molecule α-bromoethylbenzene. A list of reagents for a given C^d or C^a is shown in Table 2, based on the reactions shown in Table 1. These ionic "synthetic equivalents" are essential for correlation of C^d or C^a in the disconnect product to a "real" reagent and reaction. Table 2 provides only an introduction to synthetic equivalents and is *not* an exhaustive survey. This list will grow as the student's studies continue. Using Table 2, **7** has an organometallic moiety β- to a carbonyl and will be difficult to form. Fragment **9**, however, is the equivalent of an α,β-unsaturated ketone, and **8** and **9** offer the "easiest" synthesis and are the most logical disconnect products.

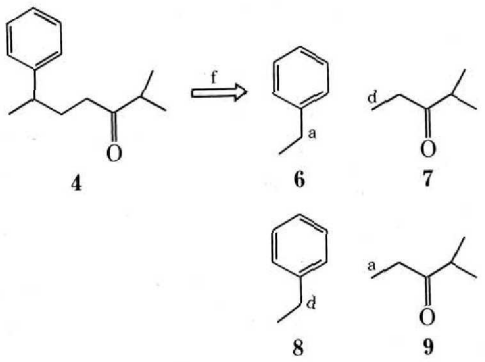
Disconnection f, therefore, points to a cuprate addition (reaction 4, Table 1) as the best reaction. This reaction generates a racemic chiral center since there is no selectivity for one enantiomer. When a chiral center is formed in the presence of a second chiral center diastereomeric products will result. When choosing a disconnection, the ability of the chosen reaction to generate the proper diastereomer in good yield must be taken into consideration. The problem of diastereoselectivity receives little emphasis in the undergraduate course but is obviously critically important to any synthesis. Reactions that give only one specific enantiomer are rare, and the techniques employed to solve this problem are usually beyond the scope of the undergraduate course and are not presented until the first graduate course.

Table 5. Bond Priorities for 4



4

Bond	Region	1	2	3	4	Total
a		—	10	—	—	10
b		—	10	—	—	10
c		10	0	—	—	10
d		10	—	—	—	10
e		—	10	—	—	10
f		**—**	**7**	**7**	**7**	**21**
g		3	—	—	3	6
h		—	7	—	7	14



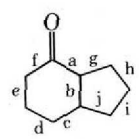
4 6 7 8 9

This analysis did not specify the starting material but relied on the disconnection process to give reasonable precursors. If a starting material is specified, the synthetic route is biased to that molecule and to that key bond or bonds. If 3-bromo-1-propanol is chosen as the starting material for **4**, the first task is *to identify the carbons from the starting material in the target* (highlighted bonds in eq 1). This instantly makes bond f (priority + 21) and bond c (priority + 10) the key bonds, regardless of the analysis in Table 5. Clearly, *the priority scheme is not necessary when the starting material is designated*, but the subsequent conversion to real synthetic equivalents is critically important. Before bromopropanol can be used, the acidic hydrogen must be blocked (protected) as the tetrahydropyranyl (THP) derivative **10**. A variety of other alcohol protecting groups can be used (*21*). Although not covered effectively in the undergraduate organic course, the use of *protecting groups* is common in organic synthesis. The student should be referred to Greene's excellent monograph (*19*).

Functional group exchanges are an integral part of most syntheses. A relatively simple guide to functional group transforms is shown in the figure. Examination of six key functional groups (C=O → C—OH → C—X → C=C → C≡C → C=C—X →) reveals that any given functional group is related to any other by proceeding clockwise or counterclockwise. Common reagents are provided in the figure, but there are *many* reagents to accomplish most of these transforms. These reagents are provided to give the beginner a "first choice", but the student should be referred to any undergraduate organic textbook, graduate text such as March (*7*), or a variety of other useful monographs such as the *Compendium of Organic Synthetic Methods* (*22a*) and *Reagents for Organic Synthesis* (*22b*) for additional and perhaps superior reagents. The figure is valuable to show graphically how functional groups are chemically related to each other. Many undergraduate texts tend to show the uniqueness of a functional group and the "synthetic equivalence" of an alcohol with an alkyl halide or an alkene is often lost on the student. The figure is a strong visual signal of this fact and will allow the student to identify alternative functional groups by known reactions. This signal is lost when a simple list or table of reaction types is presented.

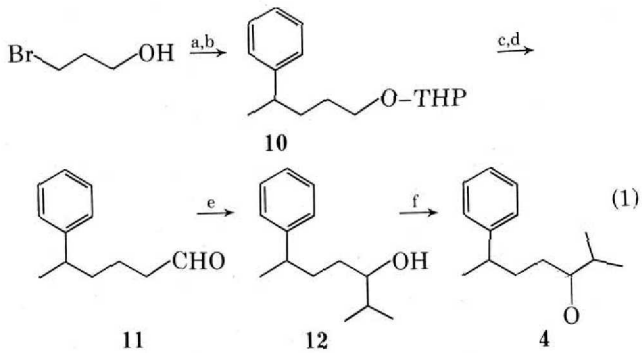
Most other transforms can be derived from these key functional groups. Epoxides, for example, are usually prepared from alkenes (C=C) or ketones and aldehydes (C=O). It is also important to note that all six groups can be reduced to the alkane derivative (—CH_2CH_2—) and oxidized to a carboxylic acid derivative (—COOH). The carboxylic acid family, of course, includes acid halides, anhydrides, esters, lactones, amides, lactams, nitriles, and their reaction products. The figure should be consulted for each disconnect product to choose a functional group for the disconnect product or transform it into one more amenable to a synthesis.

Table 6. Bond Priorities for 1



1

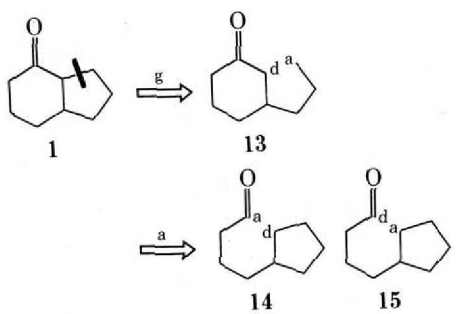
Bond	Region	1	2	3	4	Total
a		**10**	—	—	**10**	**20**
b		—	0	—	0	0
c		—	—	7	0	7
d		—	—	7	—	7
e		—	10	—	—	10
f		10	—	—	—	10
g		—	**10**	—	**10**	**20**
h		—	—	7	—	7
i		—	—	—	—	0
j		—	—	7	0	7



(*a*) dihydropyran, H; (b) $[Ph(Me)CH]_2CuLi$; (c) H_3O^+; (d) PCC; (e) *i*PrMgBr; (f) CrO_3

A synthetic solution for conversion of 3-bromo-4-propanol to **1** is shown in eq 1. 3-Bromopropanol is first converted to the O-tetrahydropyranyl (THP) derivative (**10**), removing the acidic hydrogen and allowing the requisite organocuprate displacement (reaction 4a, Table 1) to generate bond f, the chiral center and insert the phenyl group. The benzylic cuprate is prepared by reaction of α-bromoethylbenzene with lithium, and the bromide is prepared from ethylbenzene by allylic bromination (C—H → CH—Br, reaction p in figure) with *N*-bromosuccinimide (NBS) (*22*). Formation of bond c requires removal of the THP group (*23*), which is followed by oxidation of the resulting alcohol (reaction b, figure) to aldehyde **11**. Reaction of isopropyl magnesium bromide with this aldehyde generates bond c and gives alcohol **12** (reaction 3a, Table 1). The final step in the sequence is oxidation (reaction b, figure) to give the target, **4**.

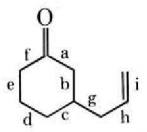
Bicyclic ketone **1** is a more challenging example. Without the corollary in Table 3 for breaking bicyclic bonds, bond b would receive an even higher priority in Table 6. Cleavage of this bond results in a nine-membered ring disconnect product. The corollary to Table 3 assigns a value of 0 to such bicyclic bonds, but only for region 2.



1 13 14 15

Bonds g and a are the priority disconnections. Cleavage of bond g generates disconnect product **13** and bond a leads to

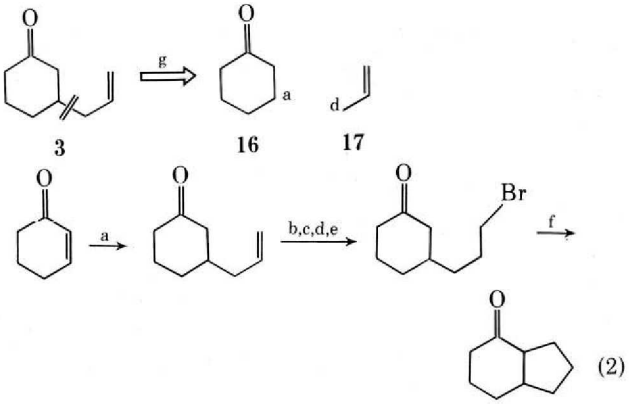
Table 7. Bond Priorities for Disconnect Product 3



3

Bond	Region	1	2	3	4	Total
a		10–3	—	—	—	7
b		—	10–7	—	0	3
c		—	—	7–4	0	3
d		—	—	7–4	—	3
e		—	10–7	—	—	3
f		10–3	—	—	—	7
g		**—**	**10**	**7**	**0**	**17**
h		3	—	—	—	3
i		—	7	—	—	7

14 or 15. In contrast to monocyclic systems, intramolecular cyclization to form a bicyclic moiety is usually preferred. Examination of Table 2 reveals product **13** as a ketone enolate with a pedant primary halide. Intramolecular displacement of the primary halide (reaction 5a, Table 1) will generate the requisite bond in the actual synthesis (eq 2). Disconnect product **14** is rejected since it contains a donor site that will be difficult to generate. Fragment **15** requires an Umpolung reagent (*9*) for the nucleophilic carbonyl (see dithiane anion in Table 2), and fragment **13** appears to be the most easily generated species of all possibilities. *Fragment **13** must be disconnected further since it is not an easily recognized starting material.* The second bond analysis is preceded by a functional group modification. Cleavage of the bond connecting the bromopropyl moiety to the cyclohexanone will give disconnect products that are not synthetically attractive (O=C—C—C^d or Br—C—C—C^d). Rather than a halide (C^a = CH_2Br), the "X" group is converted to an alcohol or an alkene (**3**). Analysis of the alcohol showed that bonds g, h, i, and j have the same priority, and there is no obvious disconnection. The alkene synthon (**3**) analyzed in Table 7, however, clearly shows a preference for bond g and leads to disconnect products **16** and **17**. The allylic anion moiety (**17**) is easily recognized as allyl Grignard or lithium diallyl cuprate. Conjugate addition with diallyl cuprate (reaction 4b, Table 1) leads to a synthetic solution, shown in eq 2. The functional group exchanges are accomplished *after* the carbon bond forming reaction in this case. Clearly, several different functional groups should be examined for each disconnection.



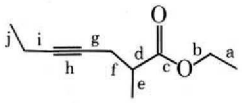
3 16 17

(2)

(a) CH_2=$CHCH_2)_2CuLi$ (b) H^+, $HOCH_2CH_2OH$

(c) BH_3; H_2O_2/HO^- (d) PBr_3 (e) H^+ (f) LDA/THF

Table 8. Bond Priorities for 18[a]

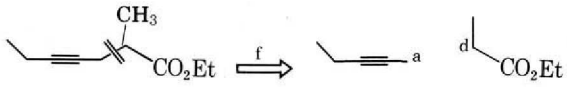


18

Bond	Region	1	2	3	4	Total
d		10	—	—	10	20
e		—	10	—	10	20
f		**—**	**10+10**	**—**	**10**	**30**
g		10	—	3	—	17
h		—	—	—	—	0
i		10	—	—	—	10
j		—	10	—	—	10

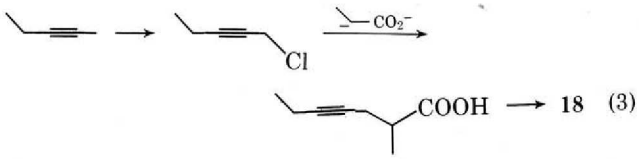
[a] Disconnect the ester moiety (bond c) prior to analysis. The analysis on the resulting acid ignores bonds a, b, c.

Alkynyl ester **18** introduces a labile functional group, the ester. The priority bonds could be applied directly, but the acid → ester functional group interconversion (breaking bond c) does not receive a realistic priority. This labile functional group is usually cleaved *before* determination of the bond priority, as in Table 8. The analysis shows bond f to have the highest priority.



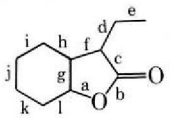
18 19 20

Fission of bond f gives fragments **19** (an allylic halide by Table 2) and **20** (an acid or ester enolate). This bond could be formed by enolate alkylation (reaction 5a, Table 1). If **19** is a synthetic equivalent of 1-chloro-2-pentyne, the synthesis requires a functional group exchange (—CH_3 → CH_2Br). A synthetic solution is shown in eq 3 (2-pentyne → 1-chloro-2-pentyne → **18**). The allylic halide is coupled to an ester enolate and initial allylic chlorination is accomplished with *N*-chlorosuccinimide, NCS (*23*).



(3)

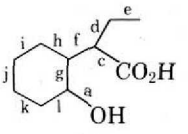
Table 9. Bond Priorities for 2



2

Bond	Region	1	2	3	4	Total
a		7	—	—	7	14
b		10	—	—	—	10
c		10	—	—	10	20
d		—	10	—	10	20
e		—	—	7	—	7
f		**—**	**10**	**10**	**10×2**	**40**
g		—	0	7	0	7
h		—	—	10+7	0	17
i		—	—	—	—	0
j		—	—	—	—	0
k		—	—	10	—	10
l		—	10	—	10	20

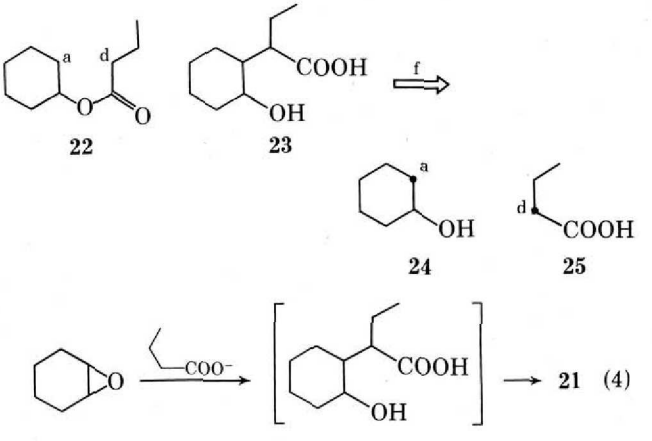
Table 10. Bond Priorities for Disconnect Product 23



23

Bond	Region	1	2	3	4	Total
a		10	—	—	7	20
b		—	—	—	—	—
c		10	—	—	10	20
d		—	10	—	10	20
e		—	—	7	—	7
f		**—**	**10**	**10**	**10×2**	**40**
g		—	10-7	7-4	3×2	12
h		—	—	7-4	0	6
				10-7		
i		—	—	—	—	0
j		—	—	—	—	0
k		—	—	10-7	—	3
l		—	10-7	—	3	6

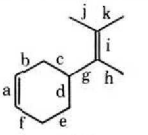
An analysis of the bicyclic target **2** in Table 9 leads to a preference for bond f with a priority of +40 and disconnection gives **22**. Disconnection of fragment **22** at the labile ester group produces two synthons which are easier to identify (**24**, *an epoxide equivalent, and* **25**, *an enolate equivalent*). This simplification can be introduced earlier by cleaving the lactone ring to **24** prior to the bond analysis, shown in Table 10, which leads to bond f as the most likely disconnection. Cleavage to the fragments **24** (cyclohexene oxide) and **25** (butanoic acid enolate) leads to the straightforward synthetic route shown in eq 4, utilizing displacement of the epoxide with an acid (or ester) enolate (reaction 3, 5a in Table 1).



22 23 24 25

Diene **26** illustrates a molecule in which the priorities are biased to both the Wittig and Diels–Alder reactions. It also introduces the problem of which diconnection takes precedent. The bond analysis is in Table 11, and bonds i, c, and e are highest priority. Disconnection of bond i leads to the ketone equivalent **27** and the ylid equivalent **28**. The two-bond disconnection of c, e leads to butadiene (**29**) and diene **30**. A Diels–Alder reaction of **29** and **30** is ambiguous since either fragment could be the dienophile or the enophile. This ambiguity suggests disconnection of bond i *before* the two-bond disconnection. Fission of bond i gives before **31**. The "Diels–Alder" disconnection can be applied directly, or **31** can be analyzed to give the same disconnection to **29** and methyl vinyl ketone (**32**). This final example illustrates that analysis may lead to two excellent disconnections, but the reactions for one may be difficult if the other is done first. It

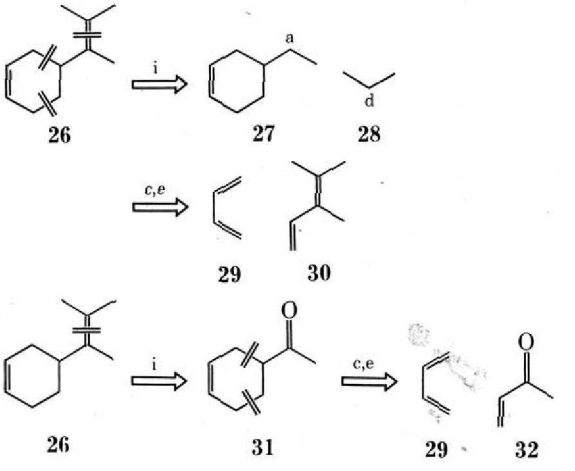
Table 11. Bond Priorities for 26



26

Bond	Region	1	2	3	4	Total
a		7	—	—	—	7
b		3	—	—	—	3
c		**—**	**20+(7-7)**	**—**	**20**	**40**
d		—	7-7	—	7	7
e		—	20+(7-7)	—	—	20
f		3	—	—	—	3
g		3	—	—	3	6
h		3	—	—	—	3
i		7	—	—	—	7
j		3	—	—	—	3
k		3	—	—	—	3

is important to test both reaction sequences in these cases to determine which disconnection takes priority.



26 27 28 29 30 31 32

Conclusion

Conclusion

The simplification of previous bond priority schemes to use only four numbers and assign priorities based only on the *ability to form* a bond has led to a scheme that is easy to use. Students can quickly identify the priority bond(s). The use of Seebach's donor/acceptor scheme and a relatively short list of reactions allows the student to develop the disconnect products into real synthetic precursors that can be evaluated for their utility. The functional group exchanges in the figure allow simple manipulation of both disconnect products and the initial target to facilitate various pathways. This sequence is easily learned and applied. The student begins to think about how and why molecules are dissected and will focus more attention on the reactions that construct the target than in identifying the *correct* disconnection. The method handles the two-bond Diels–Alder disconnections as a simple corollary to region 2 bonds. Similarly, the "Wittig" disconnection is handled as a corollary to region 1 bonds. Even with its oversimplified priority rules, this method can be used to introduce synthesis to first-year graduate students, especially those who will not continue in organic chemistry. These protocols will get the student started in synthesis, even with a limited knowledge of reactions and structural and electronic interactions. The student quickly learns to identify key functional groups, carbon bond form-

ing reaction types, and functional group interchanges and those regions of a molecule that lead to the best syntheses. An elementary disconnection approach becomes a part of how students think about molecules, and they focus on how molecules are put together. This introduction provides a strong foundation for the advanced concepts of the graduate course. When more detailed synthetic concepts and more complex targets are introduced with a discussion of the approaches of Corey, Hendrickson, and others, this foundation allowed the rapid assimilation of synthetic strategies. Classroom experience with undergraduates as well as graduate students in chemistry, medicinal chemistry, and pharmacy has shown this technique to be an invaluable aid to teaching synthesis.

Acknowledgment

I am indebted to the graduate and undergraduate students at the University of Connecticut for both inspiring this work and making many suggestions during its development. I also thank the reviewers of this manuscript, who made many insightful and useful suggestions for the presentation of this work in its final form.

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