gives all the spanning trees incorporating those atoms with their original links intact. If two linked atoms are removed from *M*, one enumerates all acyclic precursors containing the bond which links them. The normal procedure for evaluating all $|O_1|$ removes any one atom, which is tantamount to counting all acyclic precursors containing that one atom, i.e., all acyclic precursors. If all atoms are removed from matrix *M*, the evaluation is taken as 1.

(24) As noted in ref 19, cleavages which remove carbons not ultimately incorporated in the skeleton (usually as CO_2) are not included in the grid; they may be regarded as functionalizing (or defunctionalizing) reactions. Thus the acceptable bonds indicated for cleavages in this discussion constitute a new ring, and their cleavage is a horizontal ring-opening line on the grid ($\Delta r = -1$; $\Delta k = 0$).

(25) Nearly 30 of the 100 syntheses in ref 4 exhibit such indirect routes in which a skeletal bond, not in the product but useful at an early stage of the sequence, is ultimately cleaved. As examples, in Corey's caryophyllene (p 70), a large ring is formed by cleaving a more accessible bicycle; in the Syntex cecropia horomone synthesis (p 79), two cleavages of a bicycle to an acyclic skeleton are used to create stereochemical control; in Johnson's progesterone (p 288), two ring sizes are changed at the same time by cleavage and recyclization (cf. Figure 6).

(26) It would be misleading, for example, to consider the Barbier-Wieland degradation as an affixation of two six-carbon skeletal synthons followed by cleavage of a 13-carbon unit. The present conception sees it as merely a functionalization of $R{-}CH_2COOR' \rightarrow R{-}COOH$ in which the only skeletal carbons are R–C, i.e., those appearing in the final product.

(27) The idea was proposed for picrotoxin *bio*synthesis years ago by H. Conroy.

Systematic Synthesis Design. IV. Numerical Codification of Construction Reactions

James B. Hendrickson

Contribution from the Edison Chemistry Laboratories, Brandeis University, Waltham, Massachusetts 02154. *Received January 22, 1974*

Abstract: A simple but rigorous system of codification for construction reactions is developed from structural fundamentals, free of mechanistic preconception. The system allows all constructions to be represented with a numerical representation of the involved functionality and skeletal requirements of substrate and product and their interrelation. The scheme is valuable in systematic searching for synthetic routes as well as in cataloging construction reactions and developing new ones.

An essential requirement for the development of systematic synthesis design must be a simple but rigorous numerical codification of the reactions used. Such a system must be free from prejudice about present capabilities or reaction yields. This paper develops such a system for construction reactions from the numerical characterization of structure previously presented.[1]

That constructions are the central reactions of synthesis may be seen from consideration of the ideal synthesis. The ideal synthesis creates a complex skeleton from simpler starting materials[2] and so must link several such synthon molecules via construction reactions. Ideally, the synthesis would start from available small molecules so functionalized as to allow constructions linking them together directly, in a sequence only of successive construction reactions involving no intermediary refunctionalizations, and leading directly to the structure of the target, not only its skeleton but also its correctly placed functionality. If available, such a synthesis would be the most economical, and it would contain only construction reactions. The previous paper in this issue[3] develops mathematically the enumeration of the possible modes of construction of target skeletons. Here the actual chemistry which can be used to effect these constructions will be codified to define all possibilities in terms of their related substrate and product functionalities. Restrictive preconceptions about reaction mechanism are avoided in this development in favor of the more neutral and general conception of the *net structural change* occurring in any reaction.

The net structural change at any single carbon site was previously characterized[1] in terms of four kinds of attachment to that carbon: H for hydrogen, R for σ bond to carbon, Π for π bond to carbon, Z for any bond to heteroatom. In any reaction, the change from one attachment to another was characterized by two letters, the first showing the bond made, the second showing that broken. Thus, of the 16 possible reactions so characterized, the construction reactions are RH, RZ, and RΠ,[4] with respect to either one of the two carbons forming the carbon–carbon σ bond.

A construction requires two partners, the linking carbon of each being characterized by RH, RZ, or RΠ, and these show oxidation state changes of $\Delta x = +1, -1$, and 0, respectively.[1] The RΠ construction necessarily changes the character of a least one other carbon as well, the other carbon of the Π bond undergoing addition, and the oxidation state changes of all must be added to find the net change (Δx) for RΠ constructions. Thus the net change in RΠ constructions is always $\Delta x = \pm 1$. (For $C{=}C \rightarrow R{-}C{-}C{-}Z$, $R\Pi{\cdot}Z\Pi$, $\Delta x = +1$ but, for $C{=}C{-}C{-}Z \rightarrow R{-}C{-}C{=}C$, $R\Pi{\cdot}\Pi\Pi{\cdot}\Pi Z$, $\Delta x = -1$). The overall oxidation state change (the sum of both involved components) can be either oxidative or reductive, or isohypsic,[1] with $\Sigma\Delta x = +2, -2$, or 0, respectively. Oxidative and reductive couplings, however, are rarely useful in synthesis since they are only effective for creating symmetrical dimers in intermolecular reactions (although they can unite dissimilar functionalities in cyclizations). The present treatment largely focuses on isohypsic constructions of one oxidative and one reductive partner. Each partner in a construction will be categorized by reaction type as RH, RZ, or RΠ, depending on the change at the carbon forming the construction link.

The numerical characterization[1] concerns the numbers of each kind of attachment to a single carbon, as summarized in Figure 1. The skeletal value (σ) shows the number of σ bonds to other carbons, i.e., σ = 0–4, and the functional value (f) shows the functionality level at that carbon site, f = 0–4. Since $f = \Pi + Z$, the sum of functional π bonds to adjacent carbon and the number (Z) of heteroatom bonds, a distinction is made by placing one or two bars over an f value to denote the number (Π) of π bonds to adjacent carbon. Thus an enol ether carbon is $f = \bar{2}$, the same functional level as the parent ketone (f = 2), and a chloroacetylene carbon is $f = \bar{\bar{3}}$, while a dichlorovinyl carbon is $f = \bar{3}$, both at the functional level of carboxyl, f = 3.

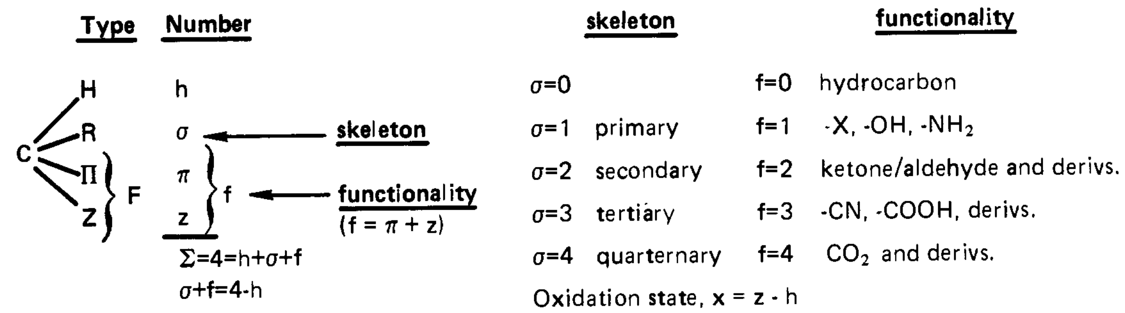


Figure 1. Summary of single carbon characteristics.

In the original outline of this characterization,[1] constructions were defined by the change in f solely at the carbon undergoing construction. However, a full description of a construction on one synthon must involve defining those functionalities (f values) on adjacent carbons which activate the reaction and remain for consideration in the product. This fuller description is developed in the next section.

Basis for Codification. Examination of known construction reactions shows that, in each reacting component, a linear chain of up to three carbons virtually always contains all the functionality necessary to activate the bond-forming carbon site in any particular construction reaction.[5] Thus any generalized construction reaction consists of two partial synthons, each of three (or less) linear carbons variously functionalized, as summarized in eq 1. The three carbons on each side of the forming bond are labeled α,β,γ away from that bond on each side, the α carbon of each synthon being the one at which the construction occurs. Each synthon, as substrate or product, will bear functionality variously (and characteristically for a particular reaction) on sites α, β, and γ and may as well exhibit other carbons also linked to (branched from) the α, β, γ sites, but the central, linear three-carbon unit is the one which bears the minimal obligatory functionality[6] to activate the particular kind of construction.

$$\ldots\overset{\gamma}{C}-\overset{\beta}{C}-\overset{\alpha}{C} + \overset{\alpha}{C}-\overset{\beta}{C}-\overset{\gamma}{C}\ldots \longrightarrow$$

partial synthons as substrates

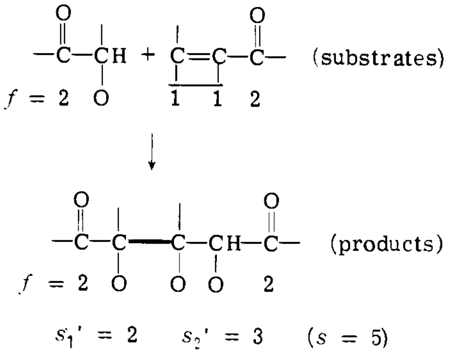
$$\ldots\overset{\gamma}{C}-\overset{\beta}{C}-\overset{\alpha}{C}-\overset{\alpha}{C}-\overset{\beta}{C}-\overset{\gamma}{C}\ldots \qquad (1)$$

product

Each partial synthon may be considered separately and independently. The construction at each may be called a *half-reaction*, defined by the change in functionality from substrate to product on one synthon. Thus any half-reaction on one synthon may be coupled to a whole family of partner half-reactions on the other synthon to make up a construction reaction. The idea is implicit in Grignard or enolate synthons, which may be coupled with ketones, nitriles, vinyl sulfones, epoxides, etc., and the functional change in each half is independent of the other. Furthermore, it is important to observe that the functionality on the substrate and that on the product are specifically related for any given half-reaction since the reactions are defined by their net structural change. Thus not only is the product functionality determined by that of the substrate but also, in reverse, a given product functionality determines that of the substrate for purposes of reasoning backward.

To clarify usage, certain other definitions are adopted. Any linear run or chain of n carbons within a skeleton will be called a *strand*, or *n-strand*, specifying the number (n) of carbons it contains (a *strand* is distinguished here from a *chain* as being specifically linear, since traditionally chains are often described as branched). The *substrate* is understood to refer only to the strand of three (or less) carbons (α, β, γ) of the starting synthon which bear the obligatory[6] functionality for the half-reaction, while the *product* refers to the functionality on the same strand after the half-reaction has taken place. The substrates and products are thus just the reactive strands of two synthons linked by a construction (in a cyclization they are both on the same molecule).[7]

The *span* is the length, or number of carbons, in any strand, defined by and including the carbons at each end. Spans may refer to the distance between two functional groups, between two construction terminals on a synthon, etc. Any half-reaction will be characterized by a *half-span* (s'), the distance from the bond-forming (α) carbon to that of the outermost obligatory function. Values for half-spans are thus $s' = 1$, 2, or 3, for that function at α, β, or γ, respectively. The *construction span* (s) is therefore the number of carbons linking the outermost functions of the two joined synthons after a construction reaction, i.e., $s = s_1' + s_2'$ with values of $2 < s < 6$. The construction span of a Michael reaction, as in eq 2, is $s = 5$, that of cyanohydrin formation $s = 2$. In these cases, the construction span is the same as the span of functionality in the product but, in cases in which one synthon becomes functionless, this is not so. In enolate alkylation, the construction span must incorporate the bond formed and is $s = 3$ even though there are not two functionalized sites remaining to define a span of functionality. In acetylene anion alkylation, $s = 3$, even though the only product carbons remaining functionalized are adjacent, i.e., a functionality span of 2.


$$\begin{array}{l} -\overset{O}{\overset{\|}{C}}-\underset{O}{\overset{|}{CH}} + C{=}C-\overset{O}{\overset{\|}{C}}- \quad \text{(substrates)} \\ f = 2 \quad 1 \quad 1 \quad 2 \\ \downarrow \\ -\overset{O}{\overset{\|}{C}}-\underset{O}{C}-\underset{O}{C}-\underset{O}{CH}-\overset{O}{\overset{\|}{C}}- \quad \text{(products)} \\ f = 2 \quad \quad 2 \\ s_1' = 2 \quad s_2' = 3 \quad (s = 5) \end{array} \qquad (2)$$

The foregoing conceptions are illustrated in the Michael reaction, eq 2, showing the substrates of two synthons each undergoing a half-reaction, the functionalities of both substrates and products noted and interrelated, each independent of the other. The importance of the concept of span is that it shows the relative locus of product functionalities for use in subsequent constructions. Moreover, such a span of

Table I. Possible Combinations of Product Functionality

Half-reaction Labels						
s'	RH	RF	Product f-lists $(\alpha\beta\gamma)^{(a)}$			f'-lists
1	A_1	1_1	000			000
	B_1	2_1	100			100
	C_1	3_1	200	(b)		
	D_1	4_1	3·			
2	A_2	1_2	010	020	03·	010
	B_2	2_2	110	120	13·	110
	C_2	3_2	210	220	23·	
3	A_3	1_3	001	002	003	001
			011	012	013	011
			021	022	023	
	B_3	2_3	101	102	103	101
			111	112	113	111
			121	122	123	
	C_3	3_3	201	202	203	101
			211	212	213	111
			221	222	223	
Σ	10	10		40		8

[a] Any list with $f = 3$ (carboxyl family) must terminate with that carbon. Distinctions of carbon-carbon π-bonds from heteroatom functionalities have not been made here.[11] [b] Pairs differing only in ketone/aldehyde (or related $f = 2$ functions) and carboxyl family, $f = 3$, as the outermost (β- or γ-) functionality.

Table II. Symbols for Construction Half-Reaction Labels

		RF			
Substrate	RH	RZ	RΠ		
f_α	⊖	⊕	⊕	⊖	— Polarities
0	A	–	–	–	
1	B	1	$\overline{1}$	$\overline{1}'$	
2	C	2	$\overline{2}$	$\overline{2}'$	
3	D	3	–	–	
4	–	4	–	–	
Δf_α	0	−1	−1	−1	
Δf_β	0	0	−1	0	
Δf_γ	0	0	0	0	

functionality seen on the total product skeleton can direct attention to particular construction reactions in reasoning backward. This concept was employed by Corey and Wipke[9] as pairwise consideration of functional groups.

The net structural change in each half-reaction is both skeletal and functional. The skeletal change is always simply a unit increase in the value of σ for the α carbon ($\Delta\sigma_\alpha = 1$). It is the change in functionality on the reactive strand which is characteristic of a particular half-reaction. In order to annotate this easily, we have only to list the three (or less) f values for the strand (α, β, γ) in the substrate and the related product. These characteristic *f-lists*, as f_α, f_β, f_γ, then define particular construction half-reactions. The bars over f values for π bonds are linked across two adjacent f values to avoid ambiguity about the location of the π bond. A single barred f value implies the other π bonded carbon is adjacent but off-strand.

For the Michael reaction, eq 2, the f lists are $\overline{11}2 \rightarrow 002$ for the unsaturated acceptor and $02 \rightarrow 02$ for the enolate component. A simple variant of either uses the cyano/carboxyl activating function, as $\overline{11}3 \rightarrow 003$ for the former and $03 \rightarrow 03$ for the latter. Writing the left-hand f list backward, with a dot to symbolize the construction link, the combined product f list is 20.002 (or ⅔0.00⅔), showing both possible carbonyl variants,[10] with a span, $s = 5$. Conjugate addition of Grignard reagents to unsaturated sulfones is $0 \rightarrow 0$ coupled with $\overline{12} \rightarrow 01$, or a product f list 0.01 ($s = 3$), while acetylene anion alkylation is $\overline{\overline{22}} \rightarrow \overline{\overline{22}}$ with $1 \rightarrow 0$, or a product f list 22.0 ($s = 3$). This now provides a basis for cataloging all possible construction reactions in terms of net structural change, without bias from preconceptions of mechanism or current feasibility, using f lists and half-spans for definition.

Catalog of Construction Half-Reactions. It is possible to tabulate systematically all possible functional variants for any three-strand partial synthon in order to encompass all possible constructions in terms of half-reactions. For three-strand construction products, there are 40 structurally possible three-digit *f-lists* ($f_\alpha f_\beta f_\gamma$) since there are three f values ($f = 0, 1, 2$) available to nonterminal carbons and one more ($f = 3$) available only to terminal ($\sigma = 1$) carbons. Thus the number of mathematically possible combinations is $40 = 3^3 + 3^2 + 3^1 + 3^0$. The 40 possible product f lists are shown in the center of Table I. Being simply all possible mathematical combinations, these descriptions must necessarily include not only all known construction products but also all possible ones.[11] A further and useful condensation of functionality information is also shown at the right of Table I as *f' lists*. The simplest view of functionality, its presence or absence at any site, is embodied in the *f' value* of 1 or 0, respectively, i.e., for $f = 0, f' = 0$; for $f \geqslant 1, f' = 1$. Thus there are $2^3 = 8$ f' lists of three binary digits each, as shown. A slightly larger set of f lists can be similarly created for all possible substrates (there are 53 since $f_\alpha = 3, 4$ are structurally allowed for substrates). Half-reactions with no obligatory function beyond the β carbon, i.e., $s' = 2$, are represented in Table I by the group of f lists ending in one zero, while those of $s' = 1$ (only α-carbon functionally involved, as in carbonyl addition, etc.) are those combinations of f lists ending in two zeroes. Subsequently, $s' = 1$ half-reactions will be represented only by one-digit f lists and $s' = 2$ half-reactions by two digit f lists.

From these generated sets of substrate and product f lists, we may formulate the construction half-reactions which interrelate them. To do this, we must define the changes in f value (Δf) at each of the three carbons, α, β, and γ, which are the characteristic substrate-product interrelations for particular types of contruction. The net structural change at the main or bond-forming site (the α carbon) is implicit in the reaction type. For RH half-reactions, there is no functionality change, i.e., $\Delta f_\alpha = 0$ while, for RF reactions (i.e., RZ and RΠ), there is a unit decrease in functionality level at the constructing carbon, i.e., $\Delta f_\alpha = -1$. These definitions therefore relate the f values of substrate and product for the α carbon in any half-reaction. Functionality at the β and γ carbons is obligatory for activation of the construction in half-reactions of $s' = 2$ or 3 but, in the RH and RZ reactions this functionality is unchanged by the construction i.e., $\Delta f_\beta = \Delta f_\gamma = 0$ (e.g., the enolate component of the Michael reaction, eq 2, for which $02 \rightarrow 02$). In addition reactions, RΠ, however, the β carbon also changes functionality from Π to Z or H. In the former case, the functionality *level* is unchanged ($\Delta f_\beta = 0$) although its form changes from Π to Z while, in the latter case, $\Delta f_\beta = -1$ as the β carbon goes from Π to H (e.g., the other half of the Michael reaction, $\overline{11}2 \rightarrow 002$).

These relations allow structural definitions of construction half-reactions. All the primary information about particular half-reactions is contained in the reaction type (RH,

Table III. Examples of Labels for Construction Half-Reactions

Reaction Type	Substrate	Label	Substrate f_α	Substrate s'	Substrate f-list	Product f-list	Polarity
RH	RMgBr(RLi)	A_1	0	1	0	0	⊖
	$R\text{-}\bar{C}H\text{-}CO\text{-}R'$	A_2	0	2	02	02	⊖
	$R\text{-}\bar{C}H\text{-}\overset{+}{P}\phi_3$	B_1	1	1	1	1	⊖
	$R\text{-}C{\equiv}C^-$	C_2	$\bar{\bar{2}}$	2	$\overline{\overline{22}}$	$\overline{\overline{22}}$	⊖
RZ	RCOCl	3_1	3	1	3	2	⊕
	R-CH(O)CH$_2$	1_2	1	2	11	01	⊕
	Cl-CH=CHCOOR	2_3	$\bar{2}$	3	$\bar{2}13$	$\bar{1}13$	⊕
RΠ	$CH_2{=}CH\text{-}NR_2$	$\bar{1}_2'$	$\bar{1}$	2	$\bar{1}2$	02	⊖
	$CH_2{=}CH\text{-}CN$	$\bar{1}_3$	$\bar{1}$	3	$\bar{1}13$	003	⊕

RZ, RΠ), the functional level of the α carbon, and the half-span. Hence simple but systematic labels for all possible construction half-reactions may be developed from this information with a single symbol and a subscript to show the half-span (s'). The symbol will be a letter (A-D) for RH reactions and a number (1-4) for RF (=RZ and RΠ) reactions, the symbol indicating the functionality level at the α carbon, f_α, *in the substrate;* the level in the product is then implicit from the relations above.[12] These RH and RF labels are listed on the left in Table I, as well as the half-spans, s', shown corresponding to their respective product f lists. The corresponding substrates then have the same f lists for RH half-reactions and f lists with one higher f value for the first digit (f_α) in the RF half-reactions. It is the f_α value of the substrate which dictates the label; thus RF reactions 1_1, 1_2, 1_3 all show $f_\alpha = 1$ in the substrate and $f_\alpha = 0$ in the product f list of Table I, while RF reactions 2 yield $f_\alpha = 1$ in the product f lists shown, etc. The RH and RF symbols are also shown in Table II to correspond with the defining values of f_α in the substrate.

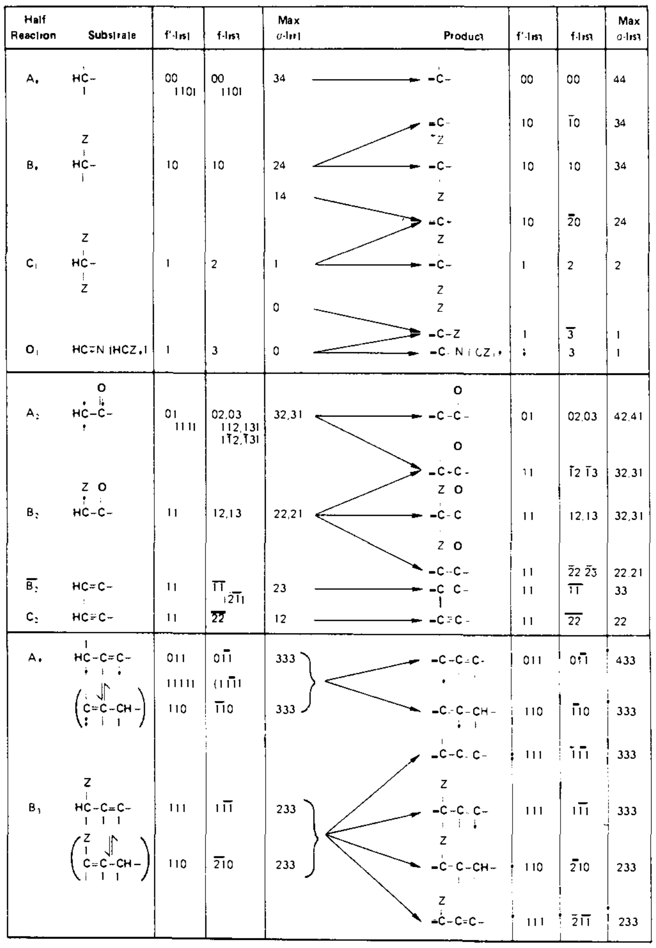
A further distinction of RF half-reactions as RZ or RΠ is still required. The RZ symbols are plain numbers ($=f_\alpha$ in substrate), while RΠ symbols (also f_α numbers) are differentiated with a bar over the number. Furthermore, as noted above, the RΠ reactions must themselves be further divided into those addition reactions in which the β carbon of the π bond broken maintains its functionality level or lowers it. Those RΠ reactions with $\Delta f_\beta = -1$ (i.e., Π to H at β as in the Michael acceptor, eq 2) are labeled normally with barred numbers, while those with $\Delta f_\beta = 0$ are differentiated with primes (i.e., Π to Z or Π at the β carbon).

These symbols described for the half-reaction labels are summarized in Table II, showing their relation to reaction type and f_α of the substrate and the functional changes (Δf at each site) that interrelate substrate and product f lists. Except for the level of activating but unchanging functionalities at β or γ carbons, these simple labels contain all the information necessary to write the structural essentials of substrate and product for any construction half-reaction. These labels and their attendant substrate-product f lists are simple and rigorous, deriving solely from considerations of possible structural changes. However, the families of construction half-reactions which they represent correspond remarkably with current usage in describing half-reactions.[13] Thus the simple alkyllithium or Grignard reagent is an A_1 half-reaction when used for construction: the substrate, R:⊖, acts as RH construction with $f_\alpha = 0$ (hence label A),[14] $\Delta f_\alpha = 0$, and a half-span, $s' = 1$; i.e., only the α carbon bears obligatory functionality. Simple alkylation (R-X → R-R′) is labeled 1_1, hence an RZ type with substrate $f_\alpha = 1$ and $\Delta f_\alpha = -1$, and a half-span, $s' = 1$. The common ketone reactions are A_2, the half-reactions of nucleophilic enolate anion construction, RH with substrate $f_\alpha = 0$, $\Delta f_\alpha = 0$, and $s' = 2$ (f lists of 02 → 02) and carbonyl additions, 2_1 (f lists 2 → 1), RZ with substrate $f_\alpha = 2$, $\Delta f_\alpha = -1$, and $s' = 1$. The two half-reactions in the Michael reaction are $A_2 \cdot \bar{1}_3$, as shown in eq 2. Two labels together show a full construction of two coupled half-reactions with span, $s = s_1' + s_2'$, shown as the sum of the two subscripts. The labels are separated with a dot to indicate the two separate combining synthons (two labels with no dot will subsequently be used to indicate two successive half-reactions on a single synthon). Illustrative examples are provided in Tables III and IV to show that the system is not only simple but

Table IV. Selected Construction Reactions

Half-reactions		Full Reactions	
Grignard Reactions	A_1	Grignard Additions	$A_1 \cdot 2_1$
Wittig Reactions	B_1	Wittig Reactions	$B_1 \cdot 2_1$
Dithianes	C_1	Enolate Alkylations	$A_2 \cdot 1_1$
Enolates	A_2	Aldol Condensations	$A_2 \cdot 2_1$
Friedel-Crafts Reactions	$\bar{B}_2$	Claisen Condensations	$A_2 \cdot 3_1$
Alkylations	1_1	Grignard Carbonations	$A_1 \cdot 4_1$
Epoxide Openings	1_2	Michael Additions	$A_2 \cdot \bar{1}_3$
Carbonyl Additions	2_1	Conjugate Additions/CN$^-$	$D_1 \cdot \bar{1}_3$
Acylations	3_1	Conjugate additions of Alkyl Copper	$A_1 \cdot \bar{1}_3$
Conjugate Additions:			
to Carbonyl	$\bar{1}_3$	Alkyne Alkylations	$C_2 \cdot 1_1$
to Acetylenic Carbonyl	$\bar{2}_3$	Benzoin Condensations	$C_1 \cdot 2_1$
to Nitro, Sulfonyl	$\bar{1}_2$	Pinacol Reductions	$2_1 \cdot 2_1$
Addition-Eliminations:			
to Unsatd. Carbonyl	2_3	Acetylenic Couplings	$C_2 \cdot C_2$
to Unsatd. Sulfonyl	2_2	Claisen Rearrangements	$\bar{1}_2' \cdot \bar{1}_3'$
Electrophilic Additions	$\bar{1}_2'$	Fischer Indole Synthesis	$A_2 \cdot \bar{B}_2$

Table V. RH Half-Reactions and Partial Synthon Characters



Half Reaction	Substrate	f′-list	f-list	Max σ-list	Product	f′-list	f-list	Max σ-list
A_1	HC–	00 1101	00 1101	34	–C–	00	00	44
					=C–Z	10	$\bar{1}0$	34
B_1	Z–HC–	10	10	24	–C(Z)–	10	10	34
				14	=C(Z)–	10	$\bar{\bar{2}}0$	24
C_1	Z–HC–Z	1	2	1	–C(Z)–	1	2	2
				0	–C–Z (Z, Z)	1	$\bar{3}$	1
O_1	HC≡N (HCZ$_3$)	1	3	0	–C≡N (CZ$_3$)	1	3	1
A_2	HC–C(=O)–	01 1111	02,03 112,131 $1\bar{1}2,\bar{1}31$	32,31	–C–C(=O)–	01	02,03	42,41
					=C–C(=O)–	11	$\bar{1}2$ $\bar{1}3$	32,31
B_2	Z–HC–C(=O)–	11	12,13	22,21	–C(Z)–C(=O)	11	12,13	32,31
					=C(Z)–C(=O)–	11	$\bar{2}2$ $\bar{2}3$	22,21
$\bar{B}_2$	HC=C–	11	$\overline{11}$ $(\overline{21}1)$	23	–C=C–	11	$\overline{11}$	33
C_2	HC≡C–	11	$\overline{\overline{22}}$	12	–C≡C–	11	$\overline{\overline{22}}$	22
A_3	HC–C=C– (C=C–CH–)	011 11111 110	$0\bar{1}1$ $(1\bar{1}\bar{1}1)$ $\bar{1}10$	333 333	–C–C=C–	011	$0\bar{1}1$	433
					–C=C–CH–	110	$\bar{1}10$	333
					=C–C=C–	111	$\bar{1}\bar{1}1$	333
B_3	Z–HC–C=C– (Z–C=C–CH–)	111 110	$1\overline{11}$ $\bar{2}10$	233 233	–C(Z)–C=C–	111	$1\overline{11}$	333
					–C(Z)=C–CH–	110	$\bar{2}10$	233
					=C(Z)–C=C–	111	$\bar{2}\overline{11}$	233

Table VI. RZ Half-Reactions and Partial Synthon Characters

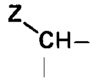
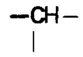
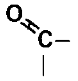
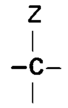
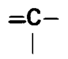
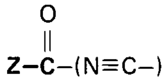
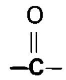
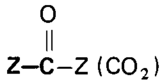
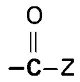
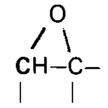
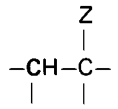
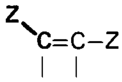
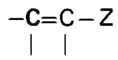
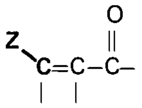
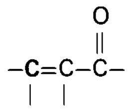
Half Reaction	Substrate	f′-list	f-list	Max σ-list	Product	f′-list	f-list	Max σ-list
1_1		1	1	2	 $-\underset{\vert}{C}H-$	0	0	3
2_1		1	2	2	 $-\overset{\overset{Z}{\vert}}{\underset{\vert}{C}}-$	1	1	3
					 $=\underset{\vert}{C}-$	1	$\overline{1}$	3
3_1	 $Z-\overset{O}{\overset{\parallel}{C}}-(N{\equiv}C-)$	1	3	1	 $-\overset{O}{\overset{\parallel}{C}}-$	1	2	2
4_1	 $Z-\overset{O}{\overset{\parallel}{C}}-Z\ (CO_2)$	1	4	0	 $-\overset{O}{\overset{\parallel}{C}}-Z$	1	3	1
1_2		11	11	23	 $-\underset{\vert}{CH}-\overset{\overset{Z}{\vert}}{\underset{\vert}{C}}-$	01	01	33
2_2		11	$\overline{22}$	22	 $-\underset{\vert}{C}=\underset{\vert}{C}-Z$	11	$\overline{12}$	32
3_2	$Z-C{\equiv}C-$	11	$\overline{\overline{32}}$	12	$-C{\equiv}C-$	11	$\overline{\overline{22}}$	22
2_3		111	$\overline{21}2;\overline{21}3$	232;231	 $-\underset{\vert}{C}=\underset{\vert}{C}-\overset{O}{\overset{\parallel}{C}}-$	111	$\overline{11}2;$ $\overline{11}3$	332; 331

Table VII. RII Half-Reactions and Partial Synthon Characters

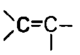
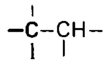
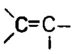
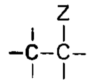
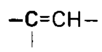
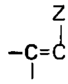
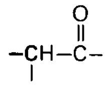
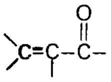
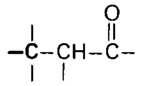
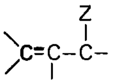
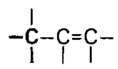
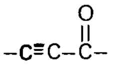
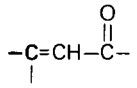
Half reaction	Substrate	f′-list	f-list	Max σ-list	Product	f′-list	f-list	Max σ-list
$\bar{1}_2$		11	$\overline{11}$	33	 $-\overset{\vert}{\underset{\vert}{C}}-\underset{\vert}{C}H-$	00	00	43
$\bar{1}'_2$		11	$\overline{11}$	33	 $-\overset{\vert}{\underset{\vert}{C}}-\overset{\overset{Z}{\vert}}{\underset{\vert}{C}}-$	01	01	43
$\bar{2}_2$	$-C{\equiv}C-$	11	$\overline{\overline{22}}$	22	 $-\underset{\vert}{C}=CH-$	11	$\overline{11}$	32
$\bar{2}'_2$	$-C{\equiv}C-$	11	$\overline{\overline{22}}$	22	 $-\underset{\vert}{C}=\overset{\overset{Z}{\vert}}{C}-$	11	$\overline{12}$	32
					 $-\underset{\vert}{C}H-\overset{O}{\overset{\parallel}{C}}-$	01	02	32
$\bar{1}_3$		111	$\overline{11}2$; $\overline{11}3$	332; 331	 $-\overset{\vert}{\underset{\vert}{C}}-\underset{\vert}{C}H-\overset{O}{\overset{\parallel}{C}}-$	001	002; 003	432; 431
$\bar{1}'_3$		111	$\overline{11}1$	333	 $-\overset{\vert}{\underset{\vert}{C}}-\underset{\vert}{C}=\underset{\vert}{C}-$	011	$0\overline{11}$	433
$\bar{2}_3$	 $-C{\equiv}C-\overset{O}{\overset{\parallel}{C}}-$	111	$\overline{\overline{22}}2$; $\overline{\overline{22}}3$	222; 221	 $-\underset{\vert}{C}=CH-\overset{O}{\overset{\parallel}{C}}-$	111	$\overline{11}2$; $\overline{11}3$	322; 321

Table VIII. Master List of Basic Half-Reactions

⊖	Substrates NoΠ	Substrates βγ-Π	Substrates αβ-Π	Products NoΠ	Products α-Π	Products βγ-Π	Products αβ-Π	Allowed σ_a	Allowed σ_β
$\sigma_a\leqslant 4$:A$_1$	0.			0.				1234	1234
	1.			0.				1234	1234
$\tilde{1}'_2$			$\overline{11}$	01				234	123
A$_3$		$0\overline{11}$				$0\overline{11}$		234	23
		$1\overline{11}$				$0\overline{11}$		234	23
			$\overline{11}0$			$0\overline{11}$		234	23
A$_2$	$0\tfrac{2}{3}$			$0\tfrac{2}{3}$				234	12
	$1\tfrac{2}{3}$			$0\tfrac{2}{3}$				234	12
	$\tilde{1}\tfrac{2}{3}$			$0\tfrac{2}{3}$				234	12
$\tilde{1}'_2$			$\overline{1\tfrac{2}{3}}$	$0\tfrac{2}{3}$				234	12
A$_3$		$0\overline{\overline{22}}$				$0\overline{\overline{22}}$		234	2
		$1\overline{\overline{\overline{22}}}$				$0\overline{\overline{\overline{22}}}$		234	2
$\sigma_a\leqslant 3$:B$_1$	1.			1.				123	1234
	1.				1.			123	1234
B$_2$			$\overline{11}$				$\overline{11}$	23	123
			$\overline{21}$				$\overline{11}$	23	123
A$_3$		$0\overline{11}$					$\overline{11}0$	23	23
			$\overline{11}0$				$\overline{11}0$	23	23
B$_3$		$1\overline{11}$				$1\overline{11}$		23	23
			$\overline{21}0$			$1\overline{11}$		23	23
		$1\overline{11}$			$\tilde{1}\overline{11}$			23	23
			$\overline{21}0$		$\tilde{1}\overline{11}$			23	23
A$_2$	$0\tfrac{2}{3}$				$\tilde{1}\tfrac{2}{3}$			23	12
B$_2$	$1\tfrac{2}{3}$			$1\tfrac{2}{3}$				23	12
	$1\tfrac{2}{3}$				$\tilde{1}\tfrac{2}{3}$			23	12
$\bar{B}_2$			$\overline{1\tfrac{2}{3}}$				$\overline{1\tfrac{2}{3}}$	23	12
$\bar{2}'_2$			$\overrightarrow{2\tfrac{2}{3}}$	$0\tfrac{2}{3}$				23	12
			$\overline{\overline{2\tfrac{2}{3}}}$				$\overline{1\tfrac{2}{3}}$	23	12
$\sigma_a\leqslant 2$:B$_1$	1.				$\bar{2}$.			12	1234
C$_1$	2			2				12	1234
	$\mathbf{2}$				$\bar{2}$			12	1234
B$_3$		$1\overline{11}$					$\overline{21}0$	2	23
			$\overline{21}0$				$\overline{21}0$	2	23
		$1\overline{11}$				$\bar{2}\overline{11}$		2	23
			$\overline{21}0$			$\bar{2}\overline{11}$		2	23
B$_2$	$1\tfrac{2}{3}$					$\bar{2}\tfrac{2}{3}$		2	12
C$_2$			$\overline{\overline{2\tfrac{2}{3}}}$			$\overrightarrow{2\tfrac{2}{3}}$		2	12
$\sigma a = 1$:C$_1$	$\mathbf{2}$–				$\bar{3}$–			1	(None)
D$_1$	$\mathbf{3}$–			3–				1	(None)
	$\mathbf{3}$–				$\bar{3}$–			1	(None)

⊕	Substrates NoΠ	Substrates αβ-Π	Products NoΠ	Products βγ-Π	Products αβ-Π	Allowed σ_a	Allowed σ_β
$\tilde{1}_2$		$\overline{11}$	00			234	1234
$\tilde{1}'_3$		$\overline{11}1$		$0\overline{11}$		234	23
$\tilde{1}_3$		$\overline{11}\tfrac{2}{3}$	$00\tfrac{2}{3}$			234	23
$\bar{1}_2$		$\overline{12}$	01			234	12
$\tilde{1}'_3$		$\overline{12}1$		$0\overline{21}$		234	2
$\tilde{1}_3$		$\overline{12}\tfrac{2}{3}$	$01\tfrac{2}{3}$			234	2
$\bar{1}_2$		$\overline{13}$–	02–			234	1
1$_1$	1		$\mathbf{0}$			123	1234
2$_1$	2		1			123	1234
	2		1			123	1234
1$_2$	11		01			23	123
2$_3$		$\overline{21}\tfrac{2}{3}$			$\overline{11}\tfrac{2}{3}$	23	23
2$_2$		$\overline{2\tfrac{2}{3}}$			$\overline{1\tfrac{2}{3}}$	23	12
$\bar{2}_2$		$\overline{\overline{22}}$			$\overline{11}$	23	12
2$_3$		$\overline{\overline{22}}\tfrac{2}{3}$			$\overline{12}\tfrac{2}{3}$	23	2
$\bar{2}_3$		$\overline{\overline{\overline{22}}}\tfrac{2}{3}$			$\overline{11}\tfrac{2}{3}$	23	2
$\bar{2}_2$		$\overline{\overline{\overline{23}}}$–			$\overline{12}$-	23	1
3$_1$	3		2			12	1234
3$_2$		$\overline{\overline{3\tfrac{2}{3}}}$			$\overline{\overline{2\tfrac{2}{3}}}$	2	12
4$_1$	4–		3–			1	(None)

Notes: Carbons bearing obligatory hydrogens are noted in bold-face. Dots indicate no carbon or no functionality; dashes indicate no carbon possible. The σ-values refer to products.

easily translated to and from real chemistry, and that it correlates closely with traditional reaction descriptions.

The full listings of the construction half-reactions are now cataloged in Tables V–VII for RH, RZ, and RΠ half-reactions, showing the partial synthon structures of substrates and products as well as their reduction to the characteristic numerical f lists for the obligatory activating functionality which defines each half-reaction.[15] Some reactions show multiple substrates and/or products, and a detailed discussion of the individual cases is offered in the Appendix.

Organization of the Catalog for Synthesis Design. In order to present the catalog in a form more suitable for use in comprehensive systems of synthesis design, several further ramifications need to be examined. The variants in the basically defined half-reactions of Tables V–VII, arising from tautomerism, alternate related substrates or products, and extra functionality added onto the basic reactive strand, are all discussed in the Appendix and lead to two reorganized and somewhat expanded summary lists in Tables VIII and IX. These lists are organized in terms of the *skeletal* possibilities or limitations of each half-reaction and in terms of their *polarity*.

The polarity of a half-reaction is its mechanistic expression. Nucleophilic half-reactions deliver the negative electron pair which forms the constructed bond and these are assigned ⊖ polarity. Electrophilic half-reactions are the electron acceptors, assigned ⊕ polarity. In terms of net structural change, the half-reactions of ⊖ polarity all show an increase in oxidation state, and those of ⊕ polarity a decrease.[16] As noted above (and in ref 1), the oxidation state change (Δx) derives directly from the sum of the involved character changes.[17] RH reactions are ⊖ polarity, RZ reactions are ⊕ polarity, and RΠ reactions are ⊕ or ⊖, depending on the character changes of the other involved carbons. Thus, of the RΠ reactions listed, all are ⊕ polarity except for $\bar{1}_2'$ and $\bar{2}_2'$ which are ⊖ polarity (both are RΠ·ZΠ with $\Sigma\Delta x = 0 + 1 = +1$).[18] Since the two half-reactions constituting a construction are to be considered separately, any one chosen for one partial synthon may unite with any partner half-reaction. However, if only isohypsic constructions are considered viable, as noted above, then the two partners must be of opposite polarity.[19] This considerably diminishes the number of possible combinations of half-reactions making up full constructions and significantly lightens the burden of systematic searching. Enumeration of these construction combinations is treated in the next section.

Another significant reduction in the total number of half-reactions actually available for use in a particular synthesis comes from the skeletal limitations imposed by the skeleton (σ values) of the target molecule. Certain skeletal sites are not suited to some half-reactions, e.g., a tertiary ($\sigma = 3$) carbon cannot bear a carbonyl, half-reactions D_1 and 4_1 can only be one-carbon synthons, or a *tert*-butyl skeleton cannot be affixed by half-reactions such as B_1, B_2, C_1, C_2, etc. The allowed σ values for the first two carbons (i.e., σ_α and σ_β) of a partial synthon, as construction product, are listed for the half-reactions assembled in Table VIII. The maximum skel-

Table IX. Substrate and Product Lists of Basic Half-Reactions

Substrate $\alpha\beta\gamma$	Allowed σ_α	Allowed σ_β	Half-reactions ⊖	Half-reactions ⊕
0	0123	01234	A_1	
$\underline{10}$	$01\underline{2\cancel{3}}$	01234	A_1 $(\underline{B_1})$	(1_1)
11	$12\cancel{3}$	123	$\overline{1}'_1$ (B_2)	$\overline{1}_2$
$0\overline{11}$	123	23	A_3	
$\overline{11}0$	123	23	A_3	
$1\overline{11}$	$1\underline{2\cancel{3}}$	23	A_3 $(\underline{B_3})$	
$\overline{11}1$	123	23		$\overline{1}'_3$
$\overline{11}\frac{2}{3}$	123	23		$\overline{1}_3$
$0\overline{22}$	123	2	A_3	
$1\overline{\overline{22}}$	123	2	A_3	
$0\frac{2}{3}$	$12\cancel{3}$	12	A_2	
$1\frac{2}{3}$	$12\cancel{3}$	12	A_2 (B_2)	
$\overline{1}\frac{2}{3}$	23	12	A_2	
$\overline{1\frac{2}{3}}$	$12\cancel{3}$	12	$(\overline{B}_2)$	$\overline{1}_2$
$\overline{12}1$	123	2		$\overline{1}'_3$
$\overline{12}\frac{2}{3}$	123	2		$\overline{1}_3$
11	12	123		1_2
2	$01\cancel{\underline{2}}$	$0\underline{1234}$	$(\underline{C_1})$	2_1
$\overline{21}$	12	123	B_2	
$\overline{21}0$	$1\cancel{2}$	23	B_3	
$\overline{21}\frac{2}{3}$	12	23		2_3
$2\frac{2}{3}$	12	12		2_2
$\overline{2\frac{2}{3}}$	$1\cancel{2}$	12	$\overline{2}'_2$ (C_2)	$\overline{2}_2$
$\overline{22}\frac{2}{3}$	12	2		2_3
$\overline{\overline{22}}\frac{2}{3}$	12	2		$\overline{2}_3$
$\underline{2}$	$0\cancel{1}$	$0\cancel{1}\cancel{2}\cancel{3}\cancel{4}$	(D_1)	3_1
$\overline{\overline{3}}\frac{2}{3}$	1	12		3_2
4	0	0		4_1

Product $\alpha\beta\gamma$	Allowed σ_α	Allowed σ_β	Half-reactions ⊖	Half-reactions ⊕
0	$123\cancel{4}$	01234	A_1	(1_1)
00	234	123		$\overline{1}'_2$
$00\frac{2}{3}$	234	23		$\overline{1}_3$
01	$23\cancel{4}$	123	$\overline{1}'_2$	(1_2), $\underline{\overline{1}_2}$
$0\overline{11}$	234	23	A_3	$\overline{1}'_3$
$01\frac{2}{3}$	234	2		$\overline{1}_3$
$0\frac{2}{3}$	$23\underline{4}$	$1\cancel{2}$	A_2 $\overline{1}'_2$ $\underline{\overline{2}'_2}$	$(\overline{1}_2)$
$0\overline{21}$	234	2		$\overline{1}'_3$
$0\overline{\overline{22}}$	234	2	A_3	
1	123	01234	B_1	2_1
10	123	01234	B_1	2_1
$\overline{11}$	23	$12\cancel{3}$	$\overline{B}_2$	$(\overline{2}_2)$
$\overline{11}0$	23	23	A_3	
$1\overline{11}$	23	23	B_3	
$\overline{1}\,\overline{11}$	23	23	B_3	
$\overline{11}\frac{2}{3}$	23	$2\cancel{3}$		2_3 $(\overline{2}_3)$
$1\frac{2}{3}$	23	12	B_2	
$1\frac{2}{3}$	23	12	A_2B_2	
$\overline{1\frac{2}{3}}$	23	$1\cancel{2}$	$\overline{B}_2\overline{2}'_2$	2_2 $(\overline{2}_2)$
$\overline{12}\frac{2}{3}$	23	2		2_3
2	12	01234	C_1	3_1
$\overline{2}$	12	01234	B_1C_1	
$\overline{21}0$	2	23	B_3	
$\overline{2}\,\overline{11}$	2	23	B_3	
$\overline{2}\frac{2}{3}$	2	12	B_2	
$\overline{2\frac{2}{3}}$	2	12	C_2	3_2
3	1	0	D_1	4_1
3	1	0	C_1D_1	

NOTE: Half-reactions in parentheses exclude σ-values with diagonal slashes and those underlined exclude underlined σ-values; when both are used it implies more than one half-reaction under that label.

etal (σ) value for any carbon is usually $\sigma = 4 - f$, except for cases with implicit obligatory hydrogen (see Figure 1), and these are shown in the partial synthon structures in Tables V-VII.[15]

The master list of 60 construction half-reactions is now presented in Table VIII, divided vertically by polarities and horizontally by the maximum allowed σ_α for the product, and further ordered by allowed σ values at the β carbon. Since the target skeleton is given information in synthesis design, those half-reactions which are skeletally unsuitable are quickly eliminated, e.g., quaternary carbons may only be constructed by half-reactions in the top section ($\sigma_\alpha \leqslant 4$), whereas all but the last ($\sigma_\alpha = 1$) section may construct a secondary site. Examination of the master list shows that, not unexpectedly, it is usually the involvement of π bonds on two carbons which gives rise to half-spans greater than one. The f lists in Table VIII are placed in columns showing where π bonds occur, at $\alpha\beta$ or $\beta\gamma$, or the entry of a barred f_α (α-Π) implying a π bond from the α carbon to an adjacent off-strand carbon for one A_2 substrate, or in products a π bond from α across the constructed link (to α'), further discussed in the Appendix.

Enumeration of Possible Constructions. Just as the previous paper[3] counts the number of components for construction of a target skeleton and the number of ways they may be put together, here we may enumerate the numbers of functional variants possible for any single construction. First, of the 40 possible product f lists of Table I, only those in boldface appear as products in Tables V-VII, i.e., the half-reactions with reasonable real precedent. If the similar pairs with activating β or γ carbonyls as ketone/aldehyde ($f = 2$) or cyano/carboxyl derivative ($f = 3$) are combined (note *b*), i.e., horizontal pairs in the second and third columns (020 and 03-; 120 and 13-: 002 and 003; etc.), there are only 13 *obligatory* product functions (f lists) directly obtainable by construction. Many of the other product f lists of Table I are *possible* construction products, of course, generated with extra (extraneous) functionality beyond an obligatory half span of $s' = 1$ or 2, e.g., a product f list 212 obtained by RZ half-reaction 3_1 from a substrate of f list 312. If more of the product f lists should become primary construction products through the discovery of new reactions they can easily be added, but the extant lists of Tables V-VII render this unlikely because of their general coverage. Also some are unlikely. Thus only seven of the eight f' list categories are represented by real reactions, but the missing f' list (101) is unlikely as it implies obligatory involvement of a γ-carbon function in a construction at the α carbon which leaves an unfunctionalized carbon between them in the product.

The expansion of Table I from 40 to 101 theoretically possible products[11] when the Z/Π differentiation is made raises the 13 viable products to 28 and the number of substrates fortuitously the same, as collected in Table IX. The number of half-reactions linking them (Table VIII) is 60 represented by only 25 labels (10 RH, 8 RZ, 7 RΠ). Table II, taken with the possible half-spans, should yield 28 labels (10 RH, 10 RZ, 8 RΠ), but several are presently without real precedent as separately definable half-reactions, *viz.*, C_3, 1_3, $\overline{2}_3'$.

The 25 labels for half-reactions may be paired all possible ways to obtain $\binom{26}{2} = 325$ possible construction reactions for synthesis. The 325 reactions may be presented as a 25 × 25 matrix in order to assess more clearly which reactions presently have precedent in the literature; the number of known construction reactions appears to be somewhat more

Table X. Enumeration of Skeletal Limitations

σ_α = \ σ_β =		0 (s' = 1)			1 (s' = 1, 2)			2 (s' = 1 − 3)			3 (s' = 1 − 3)			4 (s' = 1)			
		s.→h.r.→p.			s.→h.r.→p.			s.→h.r.→p.			s.→h.r.→p.			s.→h.r.→p.			
0→1	⊖	4	10	7													
	⊕	4	5	5													
	Σ	5	15	7				C_2			C_3			C_4			C_5
		(methyl)															
1→2	⊖				9	21	13	16	33	21	9	21	12	3	7	5	
	⊕				9	12	9	16	17	14	7	9	8	3	3	4	
	Σ				13	33	13	26	50	24	13	30	14	4	10	5	C_6
					(ethyl)			(n-propyl; n-alkyl)			(isobutyl)			(neopentyl)			
2→3	⊖	C_2			9	17	9	15	28	15	8	16	9	2	4	3	
	⊕				7	10	7	14	15	12	7	8	7	2	3	3	
	Σ				12	27	9	25	43	19	13	24	11	3	7	3	C_7
					(isopropyl)			(sec-butyl)			("sec-isoamyl")						
3→4	⊖	C_3			7	7	3	12	12	5	5	6	3	2	2	1	
	⊕				3	3	3	6	6	6	3	3	3	0	0	0	
	Σ				7	10	3	16	18	8	8	9	5	2	2	1	
					(t-butyl)			(t-amyl)			(thexyl)						
		C_4			C_5			C_6			C_7						

Notes: Each square denoting skeletal levels at the α- and β- carbons shows columns of the numbers of substrates (s.), half-reactions (h.r.), and products (p.) which are possible for that skeleton (from Tables 5–7), separated as to − or + half-reactions and the totals (Σ); the total equals the sum for the columns of half-reactions, but less for substrates and products since one f-list may serve as substrate or product for both − and + half-reactions. The enumeration is only for the f-lists of the activating ($\alpha\beta\gamma$) strand and ignores the numbers of variations of extraneous functionality on off-strand carbons. The minimum number of carbons necessary to create the synthon is constant across diagonals and shown by C_2, C_3, C_4, etc. at these diagnoals (dotted lines).

than half of the 325. This discrepancy may serve as a guide and challenge to those who invent new reactions, but the matrix shows that most of the missing reactions in our present collection are oxidative or reductive couplings[19] and intrinsically limited for synthesis (see above). The number of isohypsic constructions is obtained from the polarities. There are 12 $\ominus$ and 13 $\oplus$ half-reaction labels or 156 combinatons, few of which are without good precedent, one of the simplest ($A_1 1_1$) being a good example.

The parallel enumeration for the 60 specific half-reactions of the master list (Table VIII) is $\binom{61}{2}$ = 1830 pairs, i.e., the number of full construction reactions. As there are 40 $\ominus$ and 20 $\oplus$ half-reactions, however, the number of isohypsic constructions is only 800. Similarly, there are $\binom{29}{2}$ = 406 possible pairings of any two of the 28 substrates or products from Table IX. However, there are certain restrictions which reduce these numbers. First, not all substrates or products listed in Table IX are applicable for both $\oplus$ and

$\ominus$ half-reactions. There are in fact only 17 $\ominus$ and 17 $\oplus$ substrates and 22 $\ominus$ and 17 $\oplus$ products. Second, there are 7 products from 12 half-reactions of $\ominus$ polarity which result in a π bond across the constructed link, owing to subsequent elimination, e.g., A_2 (02 → $\bar{1}2$). These products must be coupled only with a similarly π-bonded product of $\oplus$ polarity, for which there is only one case, 2_1 (2 → $\bar{1}$, i.e., carbonyl addition–elimination). These restrictions lower the number of possible isohypsic full products from 406 to only 189 and the number of isohypsic construction reactions ($\ominus$-$\oplus$ half-reaction pairs) from 800 to only 350. The number of full construction products, or of pairs of substrates, is always significiantly less than the number of construction reactions linking them since several reactions may lead to the same product, as with (20.1) being created by $A_2 \cdot 2_1$ (aldol) or by $\bar{1}_2 \cdot B_1$ (e.g., addition to ketene dithioacetals by nitroalkyl carbanions).

Furthermore, as noted above, there is a significant reduction in the numbers of constructions actually available for use on particular target skeletons owing to skeletal limitations on half-reaction *f* lists. These skeletal limitations on reactions are enumerated in Table X, a matrix of the numbers of substrates, half-reactions, and products which are possible for all skeletal situations, as characterized by $\sigma_\alpha/\sigma_\beta$, either for $\ominus$ or $\oplus$ usage. Each block represents one synthon skeletal possibility with respect to σ_α and σ_β and is labeled with the alkyl (functionless) name of the smallest synthon that fits the skeletal ($\sigma_\alpha/\sigma_\beta$) description. Of a total of 60 half-reactions, as many as 50 are viable for affixing *n*-propyl skeletons (or higher linear-chain *n*-alkyl synthons), but only 33 are available for ethyl, 10 for *tert*-butyl, and only the two variants of A_1 for the most substituted skeleton, of which 2,3,3-trimethyl-2-butyl is the smallest example. Thus, not only the viability of the various functional combinations but also the restrictions implicit in the skeletons to be constructed afford sizable reductions in the numbers of possible constructions available to create a given structure.

Simple Synthons as Examples. One way to develop familiarity with the codification scheme is to examine the possible variants of the simple synthon skeletons of Table X as construction reagents and the half-reactions available to them. The respective substrate and product σ lists[15] for the reactive strand of each are fixed by definition: methyl (0 → 1); ethyl (11 → 21); *n*-propyl (121 → 221); *n*-butyl (122 → 222); isopropyl (21 → 31); *sec*-butyl (221 → 321); isobutyl (131 → 231); *tert*-butyl (31 → 41); neopentyl (141 → 241); etc. The traditional mechanism study sequence, methyl, ethyl, isopropyl, *tert*-butyl, is in fact σ_α = 0, 1, 2, 3, respectively (as substrates). Table X affords then the numbers of substrates and products and the half-reactions that convert them (either $\oplus$ or $\ominus$) that are available to affix these synthons; detailed listings of these may be culled from Table VIII, and this is shown as example in Chart I for the one-carbon ("methyl") synthon. The five substrates enumerated in Table X are here illustrated with particular examples, four as substrates for the nine RH(−) half-reactions yielding seven products, four for the five RZ(+) half-reactions; all half-reactions must be $s' = 1$ so that there are no RΠ half-reactions ($s' \geqslant 2$). Only product *f* lists which are all zero, of course, yield the synthon affixed as the actual hydrocarbon group named in the blocks in Table X.[20]

For isobutyl only A_1, 1_1, and $\bar{1}_2$ afford the isobutyl group itself, and the number of half-reactions yielding all functionalized four-carbon synthons of that branched skeleton is still only 30 of the total of 60 in Table VII. The 14 possible products that may be reached by these 30 half-reactions have the structures shown in Chart II, with particular functional groups as examples, as well as the *f* lists and the labels of the half-reactions leading to them. In a similar vein, the 43 half-reactions allowed for the *sec*-butyl skeleton are more but still limited; they include A_1 (from *sec*-butylmagnesium bromide), B_1 (via 2-nitrobutane), but not C_1 or D_1 since the skeleton forbids the required functionality on the α carbon. Also, 1_1 (2-bromobutane) and 2_1 (butanone) are included but not 3_1 or 4_1, B_2 (3-chlorobutanone in Darzens reactions) but not the acetylenic C_2. The small numbers for the heavily substituted *tert*-butyl skeleton and the others in the lowest row are noteworthy, reflecting the few available ways to construct quaternary carbons. The various possible substrate and product *f* lists collected in Table IX, together with their allowed skeletal variations, allow easy gathering of all the possible ways to affix the various synthons enumerated in the blocks of Table X and illustrated in Charts I and II for two of those blocks.

When extraneous functionality is accepted off or beyond the reactive strand, the numbers of reagents and their products (the affixed synthons) increase sharply even for these simplest synthons of Table X, but it is important to note that the skeletons are the same, and the increased off-strand functionality usually is completely acceptable to the basic half-reaction, the major limitation being *f* = 1 functional groups adjacent to carbanions since these are subject to elimination. In illustration of such off-strand extraneous functionality, the *sec*-butyl skeleton is represented by additions to the ketone of oxaloacetates (2_1) or its use as enolate (A_2), or in conjugate addition to acetylene dicarboxylates ($\bar{2}_3$). The *tert*-butyl skeleton is limited to the four half-reactions labeled A_1, A_2, $\bar{1}_2$, and $\bar{1}_2'$, with their several variations, but can occur with more functionalized reagents, such as methyl malonates (A_2) or α-hydroxylmethylenepropionates ($\bar{1}_2'$) or Claisen rearrangements of 2-methyl-1,1,3,3-tetramethoxypropene ($\bar{1}_2'$).

Synthesis Design from Functionality. The codification developed above is well suited for systematic application to problems of synthesis design since it allows easy definition of all possible constructions available from any particular approach to target molecule dissection. The simplest, or best known, heuristic is one of working backward stepwise directed by the functionality of the target;[21] this principle is the main basis of the synthesis design automations developed by Corey[9,22] and Wipke.[9,23] In this approach to synthesis design, the functional groups in the target structure are examined pairwise[9] (or singly) to dictate the last synthesis step as a construction which leaves the particular paired functionalized sites as product.

The half-reactions developed above can provide simple lists of the options available. Thus, lists of product *f* lists can be matched with various functions on the target molecule to determine both the sites of construction and the corresponding substrates. This quickly defines a set of last construction reactions and their starting materials which in turn become targets for a next set of constructions determined in the same fashion. In this way, a synthesis tree is generated from the target molecule and will contain all constructions which do not require intermediate refunctionalization. The possible products in summary Table IX are arranged in an order reflecting the seven possible product *f*′ lists of Table II, with increasing distance of the outermost functionalized site from the bond created (i.e., generally by half-span, s').[24] This affords a list for easy recognition of functions in the given target structure. This list (Table XI) then shows the half-reactions which will produce these particular functionalized strands, as well as the allowed skeletons (maximum σ list),[15] and finally the *f* lists of the corresponding substrates required, divided by polarity.

This organization in terms of product recognition still deals only with half-products, characterized by the seven

Chart I. Examples of One-Carbon Synthon Constructions

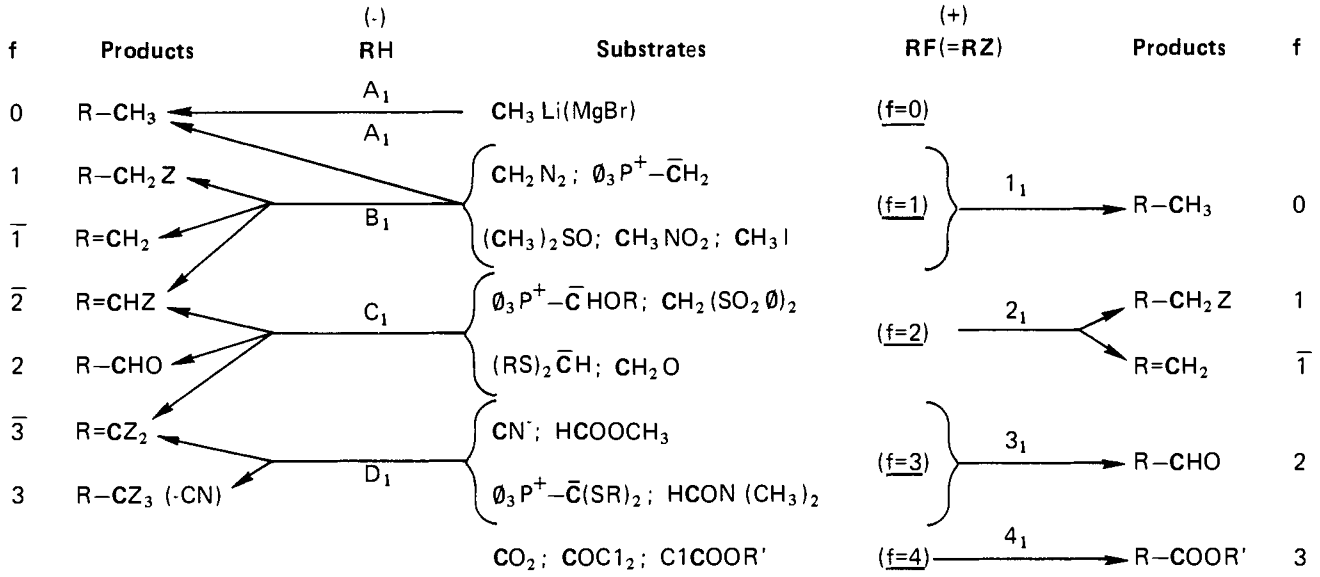
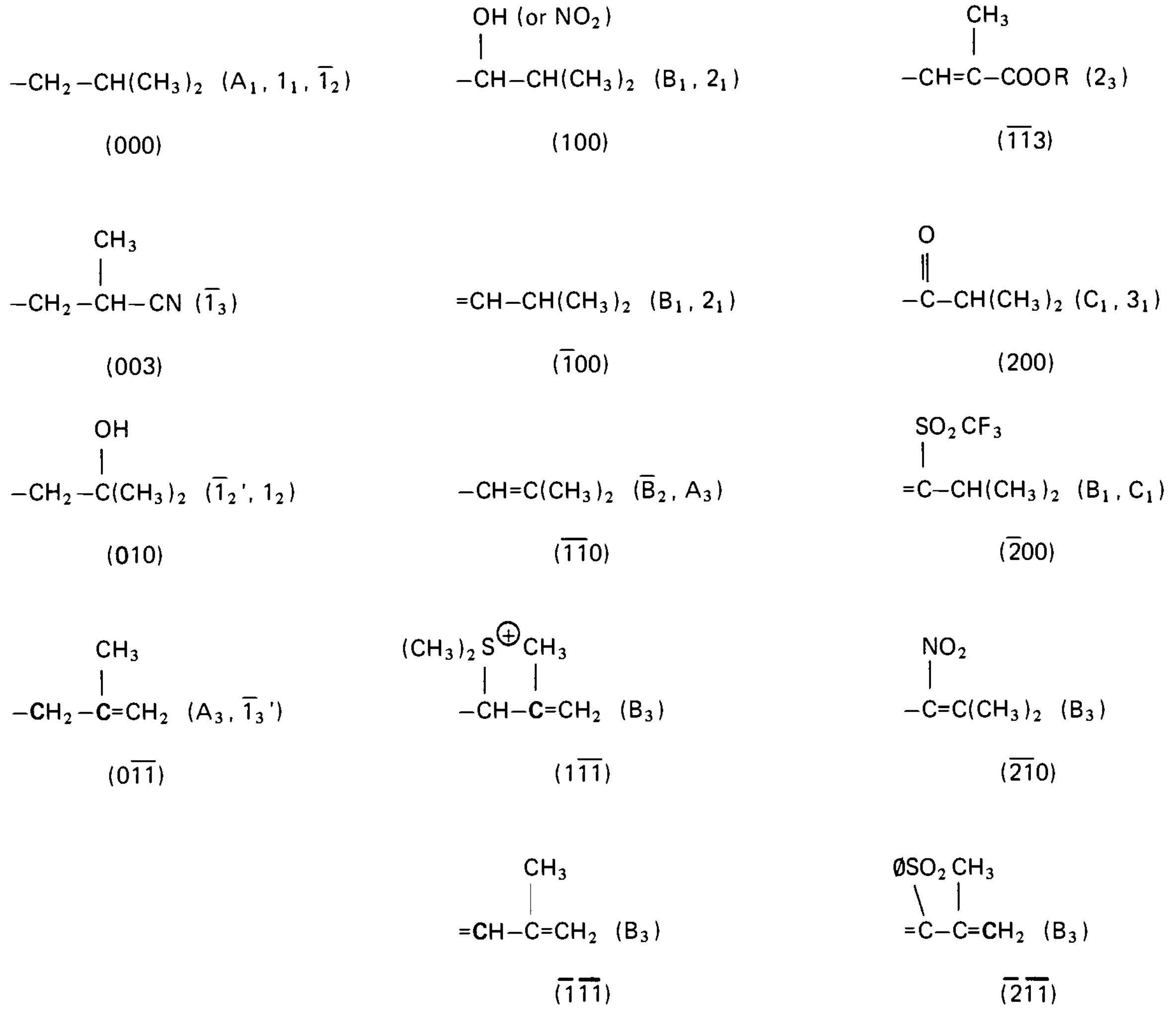


Chart II. Products of the Isobutyl Skeleton



viable f' lists. The full product of a construction is characterized by a six-digit pair of these f' lists, i.e., the 27 combinations[25] collected now in Table XII in terms of the distance between outermost functions (and hence the construction span) as well as the number of functionalized sites (1-6) in the linear strand of functionalized carbons in the full product. Since these six-digit product f' lists identify the construction site (shown with a dot in the lists of Table XII), the two partial synthons are thus identified and can each be located in Table XI, thus identifying in turn the various possible substrates and reactions for their use. Using these two tables, it is an easy matter to recognize any particular functionalized strand (up to six carbons) in the target structure and locate all modes of producing it, often

Table XI. Recognition Table for Functionality Dissection

Product		Max	Half-Reactions		Corresponding Substrates		
f′-list	f-list	σ-list	⊖	⊕	⊖ f-lists		⊕ f-lists
000	0	4	A_1		0	1	
	0	3		1_1			1
	00	43		$\bar{1}_2$			$\overline{11}$
100	1	3	B_1	2_1	1		2
	$\bar{1}$	3	B_1	2_1	1		2
	2	2	C_1	3_1	2		3
	$\bar{2}$	2	$B_1;C_1$		2	3	
	$3\cdot$	1	D_1	4_1	3		4
	$\bar{3}\cdot$	1	$C_1;D_1$		2	3	
010	01	43	$\bar{1}'_2$		$\overline{11}$		
		33		1_2			11
		42		$\bar{1}_2$			$\overline{12}$
	$0\frac{2}{3}$	42	A_2	$\bar{1}_2$	$0\frac{2}{3}$	$1\frac{2}{3}$	$\overline{13}\cdot$
		42	$A_2;\bar{1}'_2$		$\bar{1}\frac{2}{3}$	$\overline{1\frac{2}{3}}$	
		32	$\bar{2}'_2$		$\overline{\overline{2\frac{2}{3}}}$		
110	$\overline{11}$	33	$\bar{B}_2$		$\overline{11}$	$\overline{21}$	
		32		$\bar{2}_2$			$\overline{\overline{22}}$
	$\overline{110}$	333	A_3		$0\overline{11}$	$\overline{110}$	
	$1\frac{2}{3}$	32	B_2		$1\frac{2}{3}$		
	$\bar{1}\frac{2}{3}$	32	$A_2;B_2$		$0\frac{2}{3}$	$1\frac{2}{3}$	
	$\overline{1\frac{2}{3}}$	32	$\bar{B}_1;\bar{2}'_2$	$2_2;\bar{2}_2$	$\overline{1\frac{2}{3}}$	$\overline{\overline{2\frac{2}{3}}}$	$\overline{2\frac{2}{3}}$ $\overline{\overline{23}}\cdot$
	$\overline{21}0$	233	B_3		$1\overline{11}$	$\overline{210}$	
	$\bar{2}\frac{2}{3}$	22	B_2		$1\frac{2}{3}$		
	$\overline{\overline{2\frac{2}{3}}}$	22	C_2	3_2	$\overline{\overline{2\frac{2}{3}}}$		$\overline{\overline{3\frac{2}{3}}}$
001	$00\frac{2}{3}$	432		$\bar{1}_3$			$\overline{11}\frac{2}{3}$
011	$0\overline{11}$	433	A_3	$\bar{1}'_3$	$0\overline{11}$	$1\overline{11}$	$\overline{111}$
						$\overline{110}$	
	$01\frac{2}{3}$	422		$\bar{1}_3$			$\overline{12}\frac{2}{3}$
	$0\overline{21}$	423		$\bar{1}'_3$			$\overline{121}$
	$0\overline{\overline{22}}$	422	A_3		$0\overline{\overline{22}}$	$1\overline{\overline{22}}$	
111	$1\overline{11}$	333	B_3		$1\overline{11}$	$\overline{210}$	
	$\bar{1}\overline{11}$	333	B_3		$1\overline{11}$	$\overline{210}$	
	$\overline{11}\frac{2}{3}$	332		2_3			$\overline{21}\frac{2}{3}$
		322		$\bar{2}_3$			$\overline{\overline{22}}\frac{2}{3}$
	$\overline{12}\frac{2}{3}$	322		2_3			$\overline{22}\frac{2}{3}$
	$\bar{2}\overline{11}$	233	B_3		$1\overline{11}$	$\overline{210}$	

with more than one choice as to which bond is to be constructed, as indicated by the molecular form diagrams in Table XII which show the actual siting of functions and construction link on the skeletons.

Going further, Table XII may be amplified to spell out the particular f lists of full construction products which correspond to these 27 full basic f' lists by simply collecting from Table XI all f list examples for each of the seven product f' lists and coupling them isohypsically to obtain the 189 possible full construction products enumerated above with the corresponding pairs of half-reactions (350) which produce them. Such a list of full construction products and reactions, assembled as Table XIII,[26] is the basic tool for finding quickly the possible reactions and starting materials for any given target, as dictated by its functionality.

Some examples serve to illustrate the functionality approach. A part structure of an intermediate in the Torgov steroid synthesis[27] is shown in Figure 2 and a five strand of functionality selected (boldface) and labeled (C-9 to 14) with f and σ values. In Table XIII, the given f list of $s = 5$ is $\overline{1}\overline{1}0{\cdot}02$ or $\overline{1}\overline{1}{\cdot}002$ depending on which bond is selected to construct. These are taken as full product f lists and their corresponding constructions found in Table XIII are listed, followed ($\Rightarrow$) by the dictated substrates (from Table XI). Several constructions are not viable since they do not fit the skeletal limitations, and these substrates are lined out. Thus, $A_3{\cdot}\bar{1}_2$ requires $\sigma = 1$, not $\sigma = 2$, at C-14 as does $\bar{1}_3{\cdot}\bar{2}_2'$ (which also requires a triple bond in a five-membered ring), and the last three require $\sigma \leqslant 3$ at C-13 (which is given as $\sigma = 4$). Of the two remaining choices, the first ($\bar{1}_3'{\cdot}A_2$) is commonly used,[27] and the second ($\bar{1}_3'{\cdot}\bar{1}_2'$) is illustrated above. It should be noted that another similar construction of the 12-13 bond would be found on examining the single functionality at C-14 (or C-17) alone since, under the f' list, 000·010 would be found 0.02 for constructions 1_1A_2, etc. Applied to the strand of atoms 12-13-14, these create the 12-13 bond with the 9-11 double bond ignored as extraneous. Looking at other functions or pairs of functions in similar fashion can also lead to a number of other bonds as construction links.

As another example of the use of these tables, consider the synthesis of an unsaturated ketone, representing three adjacent functionalized sites which in turn direct construction of any of four bonds, either of $s = 3$ or 4 as shown in Table XII and summarized, along with the nine reactions found in Table XIII,[28] in Figure 3.

Each of the reactions identified also identifies the substrates (Table XI). These in turn may now be probed for their consistency with subsequent dissections. Are they in turn viable products for another dissection without refunctionalization? Application of this criterion of efficiency will stringently reduce the rapid expansion of options on proceeding to subsequent dissections. In the particular cyclic unsaturated ketone in Figure 3, this may be further illustrated by selecting the $A_2{\cdot}2_1$ option for the first dissection and generating the second and third from it; the f lists of successively generated substrates may be listed in order, and the final derived synthons are shown, the net effect a sequence which requires no intermediary refunctionalization.[29,30]

Summary

Any system of reaction description must contain the information available here, *viz.*: (a) f lists (and σ lists) for substrate and product or their equivalent; (b) definition of all possible reactions, not only those presently known; (c) division into separate half-reactions for pairing into full constructions all possible ways; and (d) considerable overlap with traditional categories of thought and mechanism. The correspondence with such categories is illustrated with the examples of half-reactions and full constructions selected for Table IV.

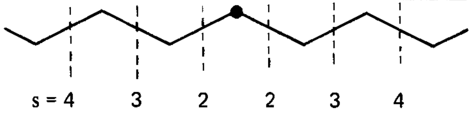
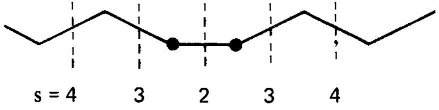
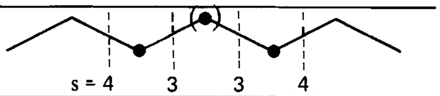
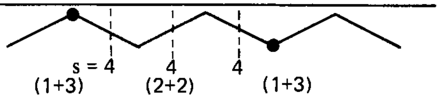
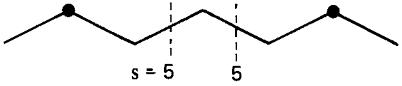
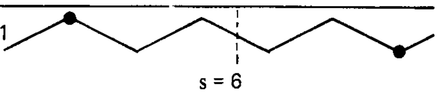
The codification presented here is derived consistently from structural fundamentals, and it is economical in form and easy to learn and use. The labels are brief and simple but nonetheless are easily expanded into familiar partial structures. This codification thus constitutes a systematic nomenclature for construction reactions, comparable to IUPAC nomenclature for structures.

The value of this scheme lies firstly in its application to easy but rigorous cataloging of construction reactions, offering perspective to present synthetic capability as well as direction to the development of new reactions. The classificiation is similarly useful in teaching synthetic methods. Its chief use and intention, however, is to provide a compact numerical tool for systematic search of synthetic routes, readily adaptable to efficent computer use. Such a system for dissection of a target molecule from its functionality is shown above. Dissection by target skeleton (cf. analysis in ref 3) is equally important and amenable to a parallel system currently being developed.[33]

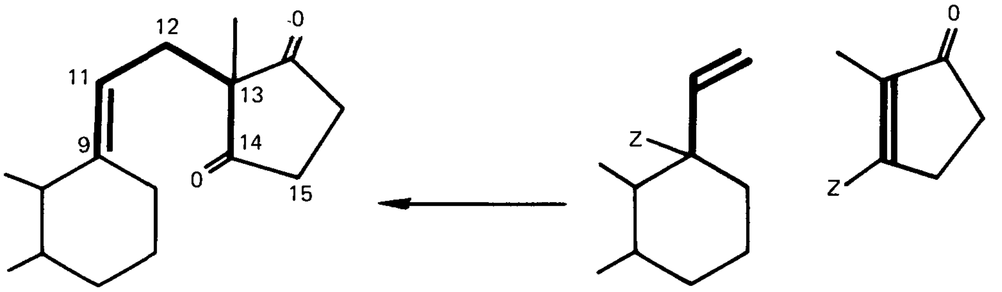
Appendix

Amplification of Individual Half-Reactions. The half-reaction labels do not fully define a single reaction, except for the $s' = 1$ cases. They show reaction type and f_α for sub-

Table XII. Variations of Functionality on Products Strands

Functional Group Span	Construction Span $s = s_1' + s_2'$	PRODUCT f'-LISTS[a]						
		Number of Functional Groups: 1	2	3	4	5	6	Molecular Form[b]
(one only)	2=1+1	000.100						
	3=1+2	000.010						
	4=1+3	000.001						
2	2=1+1		001.100					
	3=1+2		000.110					
	4=1+3		000.011					
3	3=1+2		001.010	001.110				
	4=1+3			000.111				
4	4=1+3		001.001	001.011	001.111			
	4=2+2		010.010	010.110	011.110			
5	5=2+3		010.001	010.011	010.111	011.111		
				011.001	011.011			
6	6=3+3		100.001	100.011	100.111	110.111	111.111	
					110.011			

[a] The 27 *f* '-lists for full strands of six carbons[37] are shown for the product with a dot showing the site of construction. [b] On the linear carbon strand the outermost functionalized sites are shown as heavy dots and the constructed links marked with dashed intersection lines labeled with the construction spans.



PRODUCTS

atoms:	8	9	11		12		13	14	15
σ:	2	3	2		2		4	2	2
f':		1	1		0	•	0	1	0
f:		$\overline{1}$	$\overline{1}$		0	•	0	2	

f':	0	1	1	•	0		0	1	
f:		$\overline{1}$	$\overline{1}$	•	0		0	2	
	0	$\overline{1}$	$\overline{1}$	•	0		0	2	

SUBSTRATES(*)

8 9 11 12 / 13 14

σ: 2 3 2 1 / 3 2

$A_3{\bullet}\overline{1}_2 \Longrightarrow$ ~~$\overline{1\quad 1}$ 0 / $\overline{1\quad 3}$~~

$\overline{1}_3'{\bullet}A_2 \Longrightarrow$ 1 $\overline{1\quad 1}$ / 0 2

$\overline{1}_3'{\bullet}\overline{1}_2' \Longrightarrow$ 1 $\overline{1\quad 1}$ / $\overline{1\quad 2}$(*)

$\overline{1}_3'{\bullet}\overline{\overline{2}}_2' \Longrightarrow$ ~~1 $\overline{1\quad 1}$ / $\overline{\overline{2\quad 2}}$~~

σ: 2 3 1 / 1 4 2

$\overline{B}_2{\bullet}\overline{1}_3 \Longrightarrow$ ~~0 $\overline{1\quad 1}$ / $\overline{1\quad 1}$ 2~~

$A_3{\bullet}\overline{1}_3 \Longrightarrow$ ~~$\overline{1\quad 1}$ 0 / $\overline{1\quad 1}$ 2~~

~~0 $\overline{1\quad 1}$ / $\overline{1\quad 1}$ 2~~

(*) shown above

Figure 2. Functionality dissection: sample steroid intermediate.

Table **XIII.** Product Recognition Table: Full Constructions

FS$^{(a)}$	f'-list	Pr$^{(b)}$	Rx	Product f-lists and corresponding reactions					
–	000.000	1	3	00.00	$A_1\cdot A_1/A_1\cdot 1_1/A_1\cdot\bar{1}_2$ (*)				
	000.100	3	9	00.1	$A_1\cdot 2_1/1_1\cdot B_1$ $\bar{1}_2\cdot B_1$	00.2	$A_1\cdot 3_1/1_1\cdot C_1$ $\bar{1}_2\cdot C_1$	00.3–	$A_1\cdot 4_1/1_1\cdot D_1$ $\bar{1}_2\cdot D_1$
	000.010	2	11	00.01	$A_1\cdot 1_2/A_1\cdot\bar{1}_2$ $1_1\cdot\bar{1}'_2/\bar{1}_2\cdot\bar{1}'_2$	$00.0\tfrac{2}{3}$	$A_1\cdot\bar{1}_2/1_1\cdot A_2/1_1\cdot\bar{1}'_2/1_1\cdot\overline{2'_2}$ $\bar{1}_2\cdot A_2/\bar{1}_2\cdot\bar{1}'_2/\bar{1}_2\cdot\overline{2'_2}$		
	000.001	1	1	$00.00\tfrac{2}{3}$	$A_1\cdot\bar{1}_3$				
2	001.100	9	18	1.1	$B_1\cdot 2_1/B_1\cdot B_1$ $2_1\cdot 2_1$ (*)	$\overline{1.1}$	$B_1\cdot 2_1$	1.2	$B_1\cdot 3_1/2_1\cdot 3_1$ $2_1\cdot C_1$ (*)
				$\overline{1.2}$	$2_1\cdot B_1/2_1\cdot C_1$	1.3–	$B_1\cdot 4_1/2_1\cdot D_1$	$\overline{1.3}$–	$2_1\cdot C_1/2_1\cdot D_1$
				2.2	$C_1\cdot 3_1/C_1\cdot C_1$ $3_1\cdot 3_1$ (*)	2.3–	$C_1\cdot 4_1/3_1\cdot D_1$	–3.3–	$D_1\cdot 4_1$ = trivial
	000.110	6	18	$00.\overline{11}$	$A_1\cdot\bar{2}_2/1_1\cdot\bar{B}_2/\bar{1}_2\cdot\bar{B}_2$			$00.\overline{11}0$	$1_1\cdot A_3/\bar{1}_2\cdot A_3$
				$00.1\tfrac{2}{3}$	$1_1\cdot B_2/\bar{1}_2\cdot B_2$	$00.\overline{1\tfrac{2}{3}}$	$A_1\cdot 2_2/A_1\cdot\bar{2}_2/1_1\cdot\bar{B}_2$ $\bar{1}_2\cdot\bar{B}_2/1_1\cdot\overline{2'_2}/\bar{1}_2\cdot\overline{2'_2}$		
				$00.\overline{21}0$	$1_1\cdot B_3/\bar{1}_2\cdot B_3$	$00.\bar{\bar{2}}\tfrac{2}{3}$	$A_1\cdot 3_2/1_1\cdot C_2/\bar{1}_2\cdot C_2$		
	000.011	4	7	$00.0\overline{11}$	$A_1\cdot\bar{1}'_3/1_1\cdot A_3/\bar{1}_2\cdot A_3$			$00.01\tfrac{2}{3}$	$A_1\cdot\bar{1}_3$
				$00.0\overline{21}$	$A_1\cdot\bar{1}'_3$	$00.0\overline{\overline{22}}$	$1_1\cdot A_3/\bar{1}_2\cdot A_3$		
3	001.010	6	21	1.01	$B_1\cdot 1_2/B_1\cdot\bar{1}_2$ $2_2\cdot\bar{1}'_2$	$1.0\tfrac{2}{3}$	$B_1\cdot\bar{1}_2/2_1\cdot A_2/2_1\cdot\bar{1}'_2/2_1\cdot\overline{2'_2}$		
				2.01	$C_1\cdot 1_2/C_1\cdot\bar{1}_2$ $3_1\cdot\bar{1}'_2$	$2.0\tfrac{2}{3}$	$C_1\cdot\bar{1}_2/3_1\cdot A_2/3_1\cdot\bar{1}'_2/3_1\cdot\overline{2'_2}$		
				–3.01	$D_1\cdot 1_2/D_1\cdot\bar{1}_2$ $4_1\cdot\bar{1}'_2$	$-3.0\tfrac{2}{3}$	$D_1\cdot\bar{1}_2/4_1\cdot A_2/4_1\cdot\bar{1}'_2/4_1\cdot\overline{2'_2}$		
	001.110	22	36	$1.\overline{11}$	$B_1\cdot\bar{2}_2/2_1\cdot\bar{B}_2$	$1.\overline{11}0$	$2_1\cdot A_3$	$1.1\tfrac{2}{3}$	$2_1\cdot B_2$
				$\overline{1.1}\tfrac{2}{3}$	$2_1\cdot A_2/2_1\cdot B_2$	$1.\overline{12}$–	$B_1\cdot\bar{2}_2$	$1.\overline{1\tfrac{2}{3}}$	$B_1\cdot 2_2/2_1\cdot\bar{B}_2$ $2_1\cdot\overline{2'_2}$
				$1.\overline{21}0$	$2_1\cdot B_3$	$\overline{1.2}\tfrac{2}{3}$	$2_1\cdot B_2$	$1.\bar{\bar{2}}\tfrac{2}{3}$	$B_1\cdot 3_2/2_1\cdot C_2$
				$2.\overline{11}$	$C_1\cdot\bar{2}_2/3_1\cdot\bar{B}_2$	$2.\overline{11}0$	$3_1\cdot A_3$	$2.1\tfrac{2}{3}$	$3_1\cdot B_2$
				$2.\overline{1\tfrac{2}{3}}$	$C_1\cdot 2_2/C_1\cdot\bar{2}_2/3_1\cdot\bar{B}_2/3_1\cdot\overline{2'_2}$			$2.\overline{21}0$	$3_1\cdot B_3$
				$2.\bar{\bar{2}}\tfrac{2}{3}$	$C_1\cdot 3_2/3_1\cdot C_2$	$-3.\overline{11}$	$D_1\cdot\bar{2}_2/4_1\cdot\bar{B}_2$	$-3.\overline{11}0$	$4_1\cdot A_3$
				$-3.1\tfrac{2}{3}$	$4_1\cdot B_2$	$-3.\overline{1\tfrac{2}{3}}$	$D_1\cdot 2_2/D_1\cdot\bar{2}_2/4_1\cdot\bar{B}_2/4_1\cdot\overline{2'_2}$		
				$-3.\overline{21}0$	$4_1\cdot B_3$	$-3.\bar{\bar{2}}\tfrac{2}{3}$	$D_1\cdot 3_2/4_1\cdot C_2$		
	000.111	3	5	$00.1\overline{11}$	$1_1\cdot B_3/\bar{1}_2\cdot B_3$	$00.\overline{11}\tfrac{2}{3}$	$A_1\cdot 2_1/A_1\cdot\bar{2}_3$	$00.\overline{12}\tfrac{2}{3}$	$A_1\cdot 2_3$
4	001.001	3	3	$1.00\tfrac{2}{3}$	$B_1\cdot\bar{1}_3$	$2.00\tfrac{2}{3}$	$C_1\cdot\bar{1}_3$	$-3.00\tfrac{2}{3}$	$D_1\cdot\bar{1}_3$
	010.010	3	13	10.01	$\bar{1}'_2\cdot 1_2/\bar{1}'_2\cdot\bar{1}_2$	$10.0\tfrac{2}{3}$	$\bar{1}'_2\cdot\bar{1}_2/1_2\cdot A_2/1_2\cdot\bar{1}'_2/1_2\cdot\overline{2'_2}$ $\bar{1}_2\cdot A_2/\bar{1}_2\cdot\bar{1}'_2/\bar{1}_2\cdot\overline{2'_2}$		
				$\tfrac{2}{3}0.0\tfrac{2}{3}$	$A_2\cdot\bar{1}_2/\bar{1}'_2\cdot\bar{1}_2/\bar{2}'_2\cdot\bar{1}_2/A_2\cdot A_2$ (*)				
	001.011	12	15	$1.0\overline{11}$	$B_1\cdot\bar{1}'_3/2_1\cdot A_3$	$1.01\tfrac{2}{3}$	$B_1\cdot\bar{1}_3$	$1.0\overline{21}$	$B_1\cdot\bar{1}'_3$
				$1.0\overline{\overline{22}}$	$2_1\cdot A_3$	$2.0\overline{11}$	$C_1\cdot\bar{1}'_3/3_1\cdot A_3$	$2.01\tfrac{2}{3}$	$C_1\cdot\bar{1}_3$
				$2.0\overline{21}$	$C_1\cdot\bar{1}'_3$	$2.0\overline{\overline{22}}$	$3_1\cdot A_3$	$-3.0\overline{11}$	$D_1\cdot\bar{1}'_3/4_1\cdot A_3$
				$-3.01\tfrac{2}{3}$	$D_1\cdot\bar{1}_3$	$-3.0\overline{21}$	$D_1\cdot\bar{1}'_3$	$-3.0\overline{\overline{22}}$	$4_1\cdot A_3$
	010.110	12	37	$10.\overline{11}$	$\bar{1}'_2\cdot\bar{2}_2/1_2\cdot\bar{B}_2$ $\bar{1}_2\cdot\bar{B}_2$	$10.\overline{11}0$	$1_2\cdot A_3/\bar{1}_2\cdot A_3$	$10.1\tfrac{2}{3}$	$1_2\cdot B_2/\bar{1}_2\cdot B_2$
				$10.\overline{1\tfrac{2}{3}}$	$\bar{1}'_2\cdot 2_2/\bar{1}'_2\cdot\bar{2}_2/1_2\cdot\bar{B}_2$ $\bar{1}_2\cdot\bar{B}_2/1_2\cdot\overline{2'_2}/\bar{1}_2\cdot\overline{2'_2}$			$10.\overline{21}0$	$1_2\cdot B_3/\bar{1}_2\cdot B_3$
				$10.\bar{\bar{2}}\tfrac{2}{3}$	$\bar{1}'_2\cdot 3_2/1_2\cdot C_2$ $\bar{1}_2\cdot C_2$	$\tfrac{2}{3}0.\overline{11}$	$A_2\cdot\bar{2}_2/\bar{1}'_2\cdot\bar{2}_2$ $\bar{2}'_2\cdot\bar{2}_2/\bar{1}_2\cdot\bar{B}_2$	$20.\overline{11}0$	$\bar{1}_2\cdot A_3$
				$20.1\tfrac{2}{3}$	$\bar{1}_2\cdot B_2$	$\tfrac{2}{3}0.\overline{1\tfrac{2}{3}}$	$A_2\cdot 2_2/\bar{1}'_2\cdot 2_2/\bar{2}'_2\cdot 2_2/\bar{1}_2\cdot\bar{B}_2$ $\bar{1}_2\cdot\bar{2}'_2/A_2\cdot\bar{2}_2/\bar{1}'_2\cdot\bar{2}_2/\bar{2}'_2\cdot\bar{2}_2$		
				$20.\overline{21}0$	$\bar{1}_2\cdot B_3$	$\tfrac{2}{3}0.\bar{\bar{2}}\tfrac{2}{3}$	$A_2\cdot 3_2/\bar{1}'_2\cdot 3_2/\bar{2}'_2\cdot 3_2/\bar{1}_2\cdot C_2$		
	001.111	11	14	$1.1\overline{11}$	$2_1\cdot B_3$	$\overline{1.1}\,\overline{11}$	$2_1\cdot B_3$	$1.\overline{11}\tfrac{2}{3}$	$B_1\ 2_3/B_2\cdot\bar{2}_2$
				$1.\overline{12}\tfrac{2}{3}$	$B_1\cdot 2_3$	$\overline{1.2}\,\overline{11}$	$2_1\cdot B_3$	$2.1\overline{11}$	$3_1\cdot B_3$
				$2.\overline{11}\tfrac{2}{3}$	$C_1\cdot 2_3/C_1\cdot\bar{2}_3$	$2.\overline{12}\tfrac{2}{3}$	$C_1\cdot 2_3$	$-3.1\overline{11}$	$4_1\cdot B_3$
				$-3.\overline{11}\tfrac{2}{3}$	$D_1\cdot 2_3/D_1\cdot\bar{2}_3$	$-3.\overline{12}\tfrac{2}{3}$	$D_1\cdot 2_3$		
	011.110	19	33	$\overline{11}.\overline{11}$	$\bar{B}_2\cdot\bar{B}_2/\bar{B}_2\cdot\bar{2}_2$ (*)	$\overline{11}.\overline{11}0$	$\bar{2}_2\cdot A_3/A_3\cdot A_3$ (*)	$\overline{11}.1\tfrac{2}{3}$	$\bar{2}_2\cdot B_2$
				$\overline{11}.\overline{1\tfrac{2}{3}}$	$\bar{B}_2\cdot 2_2/\bar{B}_2\cdot\bar{2}_2/\bar{2}_2\cdot\bar{B}_2/\bar{2}_2\cdot\overline{2'_2}$			$\overline{11}.\overline{21}0$	$\bar{2}_2\cdot B_3$
				$\overline{11}.\bar{\bar{2}}\tfrac{2}{3}$	$\bar{B}_2\cdot 3_2/\bar{2}_2\cdot C_2$	$\overline{12}.\overline{21}0$	$B_3\cdot B_3$ (*)	$\tfrac{2}{3}\,\overline{1.11}0$	$2_2\cdot A_3/\bar{2}_2\cdot A_3$
				$\tfrac{2}{3}\,1.1\tfrac{2}{3}$	$B_2\cdot B_2$ (*)	$\tfrac{2}{3}\,1.\overline{1\tfrac{2}{3}}$	$B_2\cdot 2_2/B_2\cdot\bar{2}_2$	$\tfrac{2}{3}\,1.1\tfrac{2}{3}$	$B_2\cdot B_2$ (*)
				$\overline{\tfrac{2}{3}}\,1.\overline{1\tfrac{2}{3}}$	$\bar{B}_2\cdot 2_2/\bar{B}_2\cdot\bar{2}_2/\overline{2'_2}\cdot 2_2/\overline{2'_2}\cdot\bar{2}_2$			$\overline{\tfrac{2}{3}\,1.2}10$	$2_2\cdot B_3$
				$\tfrac{2}{3}\,1.\bar{\bar{2}}\tfrac{2}{3}$	$B_2\cdot 3_2$	$\overline{\tfrac{2}{3}}\,1.\bar{\bar{2}}\tfrac{2}{3}$	$\bar{B}_2\cdot 3_2/2_2\cdot C_2$ $\overline{2'_2}\cdot 3_2$	$\tfrac{2}{3}\,\overline{1.2}\tfrac{2}{3}$	$B_2\cdot B_2$ (*)
				$\bar{\bar{\tfrac{2}{3}}}\,2.\overline{11}0$	$3_2\cdot A_3$	$\bar{\bar{\tfrac{2}{3}}}\,2.\bar{2}10$	$3_2\cdot B_3$	$\bar{\bar{\tfrac{2}{3}}}\,2.\bar{\bar{2}}\tfrac{2}{3}$	$C_2\cdot 3_2/C_2\cdot C_2$ (*)

strate and product and the half-span but not the *f* levels at β and γ carbons necessary to activate the reaction. However, in real reactions, there is usually only one activating function corresponding to a given label (B_2 is an exception noted below). This is especially true when carbonyl electron-withdrawing activation is combined, i.e., $f = 2$ (aldehyde/ketone) and $f = 3$ (cyano/carboxyl) functions at β and γ carbons which are not changed in the reaction. The pair are represented as $f = \tfrac{2}{3}$ and reflect their mechanistic commonality (shown in Table I as note *b* and discussed above for

Table XIII (*Cont.*)

FS$^{(a)}$	f'-list	Pr$^{(b)}$	Rx	Product f-lists and corresponding reactions					
5	010.001	2	4	$10.00\tfrac{2}{3}$	$\bar{1}'_2\cdot\bar{1}_3$	$\tfrac{2}{3}\,0.00\tfrac{2}{3}$	$A_2\cdot\bar{1}_3/\bar{1}'_2\cdot\bar{1}_3/\bar{2}'_2\cdot\bar{1}_3$		
	010.011	8	18	$10.0\overline{11}$	$\bar{1}'_2\cdot\bar{1}'_3/1_2\cdot A_3/\bar{1}_2\cdot A_3$			$10.01\tfrac{2}{3}$	$\bar{1}'_2\cdot\bar{1}_3$
				$10.0\overline{21}$	$\bar{1}'_2\cdot\bar{1}'_3$	$10.0\overline{\overline{22}}$	$1_2\cdot A_3/\bar{1}_2\cdot A_3$	$\tfrac{2}{3}\,0.0\overline{11}$	$A_2\cdot\bar{1}'_3/\bar{1}'_2\cdot\bar{1}'_3$
				$\tfrac{2}{3}\,0.01\tfrac{2}{3}$	$A_2\cdot\bar{1}_3/\bar{1}'_2\cdot\bar{1}_3$	$\tfrac{2}{3}\,0.0\overline{21}$	$A_2\cdot\bar{1}'_3/\bar{1}'_2\cdot\bar{1}'_3$		$\bar{2}'_2\cdot\bar{1}'_3/\bar{1}_2\cdot A_3$
					$\bar{2}'_2\cdot\bar{1}_3$		$\bar{2}'_2\cdot\bar{1}'_3$	$-20.0\overline{\overline{22}}$	$\bar{1}_2\cdot A_3$
	011.001	6	7	$\overline{11}.00\tfrac{2}{3}$	$B_2\cdot\bar{1}_3$	$0\overline{11}.00\tfrac{2}{3}$	$A_3\cdot\bar{1}_3$	$0\overline{\overline{12}}.00\tfrac{2}{3}$	$B_3\cdot\bar{1}_3$
				$\tfrac{2}{3}\,1.00\tfrac{2}{3}$	$B_2\cdot\bar{1}_3$	$\overline{\tfrac{2}{3}\,1}.00\tfrac{2}{3}$	$B_2\cdot\bar{1}_3/\bar{2}'_2\cdot\bar{1}_3$	$\overline{\overline{\tfrac{2}{3}\,2}}.00\tfrac{2}{3}$	$C_2\cdot\bar{1}_3$
	010.111	6	15	$10.1\overline{11}$	$1_2\cdot B_3/\bar{1}_2\cdot B_3$	$10.\overline{11}\tfrac{2}{3}$	$\bar{1}'_2\cdot 2_3/\bar{1}'_2\cdot\bar{2}_3$	$10.\overline{12}\tfrac{2}{3}$	$\bar{1}'_2\cdot 2_3$
				$-20.1\overline{11}$	$\bar{1}_2\cdot B_3$	$\tfrac{2}{3}\,0.\overline{11}\tfrac{2}{3}$	$A_2\cdot 2_3/\bar{1}'_2\cdot 2_3/\bar{2}'_2\cdot 2_3$		
				$\tfrac{2}{3}\,0.\overline{12}\tfrac{2}{3}$	$A_2\cdot 2_3/\bar{1}'_2\cdot 2_3/\bar{2}'_2\cdot 2_3$		$A_2\cdot\bar{2}_3/\bar{1}'_2\cdot\bar{2}_3/\bar{2}'_2\cdot\bar{2}_3$		
	011.011	21	29	$\overline{11}.0\overline{11}$	$B_2\cdot\bar{1}'_3/\bar{2}_2\cdot A_3$	$\overline{11}.01\tfrac{2}{3}$	$8'_2\cdot\bar{1}_3$	$\overline{11}.0\overline{21}$	$\bar{B}_2\cdot\bar{1}'_3$
				$\overline{11}.0\overline{\overline{22}}$	$\bar{2}_2\cdot A_3$	$0\overline{11}.0\overline{11}$	$A_3\cdot\bar{1}'_3$	$0\overline{11}.01\tfrac{2}{3}$	$A_3\cdot\bar{1}_3$
				$0\overline{11}.0\overline{21}$	$A_3\cdot\bar{1}'_3$	$0\overline{12}.0\overline{11}$	$B_3\cdot\bar{1}'_3$	$0\overline{12}.01\tfrac{2}{3}$	$B_3\cdot\bar{1}_3$
				$0\overline{12}.0\overline{21}$	$B_3\cdot\bar{1}'_3$	$\tfrac{2}{3}\,1.0\overline{11}$	$B_2\cdot\bar{1}'_3$	$\tfrac{2}{3}\,1.01\tfrac{2}{3}$	$B_2\cdot\bar{1}_3$
				$\tfrac{2}{3}\,1.0\overline{21}$	$B_2\cdot\bar{1}'_3$	$\overline{\tfrac{2}{3}\,1}.0\overline{11}$	$\bar{B}_2\cdot\bar{1}'_3/\bar{2}'_2\cdot\bar{1}'_3$	$\overline{\tfrac{2}{3}\,1}.01\tfrac{2}{3}$	$\bar{B}_2\cdot\bar{1}_3/\bar{2}'_2\cdot\bar{1}_3$
							$2_2\cdot A_3/\bar{2}_2\cdot A_3$		
				$\overline{\tfrac{2}{3}\,1}.0\overline{21}$	$\bar{B}_2\cdot\bar{1}'_3/\bar{2}'_2\cdot\bar{1}'_3$	$\overline{\tfrac{2}{3}\,1}.0\overline{\overline{22}}$	$2_2\cdot A_3/\bar{2}_2\cdot A_3$	$\overline{\overline{\tfrac{2}{3}\,2}}.0\overline{11}$	$C_2\cdot\bar{1}'_3/3_2\cdot A_3$
				$\overline{\tfrac{2}{3}\,2}.01\tfrac{2}{3}$	$C_2\cdot\bar{1}_3$	$\overline{\tfrac{2}{3}\,2}.0\overline{21}$	$C_2\cdot\bar{1}'_3$	$\overline{\tfrac{2}{3}\,2}.0\overline{22}$	$3_2\cdot A_3$
	011.111	15	25	$\overline{11}.1\overline{11}$	$2_2\cdot B_3$	$\overline{11}.\overline{11}\tfrac{2}{3}$	$\bar{B}_2\cdot 2_3/\bar{B}_2\cdot\bar{2}_3$	$\overline{11}.\overline{12}\tfrac{2}{3}$	$\bar{B}_2\cdot 2_3$
				$0\overline{11}.\overline{11}\tfrac{2}{3}$	$A_3\cdot 2_3/A_3\cdot\bar{2}_3$	$0\overline{11}.\overline{12}\tfrac{2}{3}$	$A_3\cdot 2_3$	$0\overline{12}.\overline{11}\tfrac{2}{3}$	$B_3\cdot 2_3/B_3\cdot\bar{2}_3$
				$0\overline{12}.\overline{12}\tfrac{2}{3}$	$B_3\cdot 2_3$	$\overline{\tfrac{2}{3}\,1}.1\overline{11}$	$2_2\cdot B_3/\bar{2}_2\cdot B_3$	$\tfrac{2}{3}\,1.\overline{11}\tfrac{2}{3}$	$B_2\cdot 2_3/B_2\cdot\bar{2}_3$
				$\tfrac{2}{3}\,1.\overline{12}\tfrac{2}{3}$	$B_2\cdot 2_3$	$\overline{\tfrac{2}{3}\,1}.\overline{11}\tfrac{2}{3}$	$\bar{B}_2\cdot 2_3/\bar{B}_2\cdot\bar{2}_3$	$\overline{\tfrac{2}{3}\,1}.\overline{12}\tfrac{2}{3}$	$\bar{B}_2\cdot 2_3/\bar{2}'_2\cdot 2_3$
							$\bar{2}'_2\cdot 2_3/\bar{2}'_2\cdot\bar{2}_3$		
				$\overline{\overline{\tfrac{2}{3}\,2}}.1\overline{11}$	$3_2\cdot B_3$	$\overline{\overline{\tfrac{2}{3}\,2}}.\overline{11}\tfrac{2}{3}$	$C_2\cdot 2_3/C_2\cdot\bar{2}_3$	$\overline{\overline{\overline{\tfrac{2}{3}\,2}}}.\overline{12}\tfrac{2}{3}$	$C_2\cdot 2_3$
6	100.001	0	0	None					
	100.011	2	2	$\tfrac{2}{3}00.0\overline{11}$	$\bar{1}_3\cdot A_3$	$\tfrac{2}{3}00.0\overline{\overline{\overline{22}}}$	$\bar{1}_3\cdot A_3$		
	100.111	1	1	$\tfrac{2}{3}00.1\overline{11}$	$\bar{1}_3\cdot B_3$				
	110.011	7	8	$\overline{11}0.0\overline{11}$	$A_3\cdot\bar{1}'_3/A_3\cdot A_3$ (*)	$\overline{11}0.01\tfrac{2}{3}$	$A_3\cdot\bar{1}_3$	$\overline{11}0.0\overline{21}$	$A_3\cdot\bar{1}'_3$
				$\overline{11}0.0\overline{\overline{22}}$	$\bar{1}'_3\cdot A_3$	$\overline{12}0.0\overline{\overline{22}}$	$\bar{1}'_3\cdot A_3$	$\tfrac{2}{3}10.0\overline{\overline{22}}$	$\bar{1}_3\cdot A_3$
				$\overline{\overline{22}}0.0\overline{\overline{22}}$	$A_3\cdot A_3$ (*)				
	110.111	7	9	$\overline{11}0.1\overline{11}$	$\bar{1}'_3\cdot B_3$	$\overline{11}0.\overline{11}\tfrac{2}{3}$	$A_3\cdot 2_3/A_3\cdot\bar{2}_3$	$\overline{11}0.\overline{12}\tfrac{2}{3}$	$A_3\cdot 2_3$
				$\overline{12}0.1\overline{11}$	$\bar{1}'_3\cdot B_3$	$\tfrac{2}{3}10.1\overline{11}$	$\bar{1}_3\cdot B_3$	$\overline{\overline{22}}0.\overline{11}\tfrac{2}{3}$	$A_3\cdot 2_3/A_3\cdot\bar{2}_3$
				$\overline{\overline{22}}0.\overline{12}\tfrac{2}{3}$	$A_3\cdot 2_3$				
	111.111	4	5	$\overline{111}.1\overline{11}$	$B_3\cdot B_3$ (*)	$\overline{111}.1\overline{11}$	$B_3\cdot B_3$ (*)	$\overline{111}.\overline{11}\tfrac{2}{3}$	$B_3\cdot 2_3/B_3\cdot\bar{2}_3$
				$\overline{111}.\overline{12}\tfrac{2}{3}$	$B_3\cdot 2_3$				

[a] FS = functional group span. [b] Numbers of products (Pr), and reactions (Rx) – overall totals: 196 products and 367 reactions. * Reactions include oxidative or reductive coupling (total of 17).

the Michael reaction).[10] Examination of Table I shows that, with outermost $f = \tfrac{2}{3}$ combined, it is not surprising to find a general 1:1 correspondence of labels and products; the larger number of products for $s' = 3$ still do not turn up more than one real reaction per label. Thus a label prescribes one primary half-reaction with the minimal activating f list.

The primary half-reaction identified by the label, however, has variants which may allow alternate (though closely related) substrates and products, and it is these variants which expand the 25 half-reaction labels to 60 half-reactions. There are two kinds of variants: higher than minimal functionality at β and γ carbons, as already exemplified in the most common coalescence of $f = \tfrac{2}{3}$; and attendant refunctionalizations which commonly occur with certain constructions. The latter include initial reduction to form active reagent, subsequent elimination to a π-bonded construction link, and tautomerism in substrate or product attendant on construction. It should be noted that these variant substrates will not always fit the label description owing to different f_α values, but the primary half-reaction to which they relate always does.[17]

Initial reduction is common to carbanion creation for RH reactions, as in creation of organometallics from halides,[17] an initial R–X → R:⊖ ($f = 1 \rightarrow 0$) refunctionalization (reduction) preceding construction. Subsequent elimination occurs commonly with RH constructions and with carbonyl additions (2_1) and is exemplified in the dehydrative aldol condensation ($A_2 \cdot 2_1$) which proceeds in two steps, $20 + 2 \rightarrow 20\cdot 1 \rightarrow 2\bar{1}\cdot\bar{1}$ or an overall construction, $20 + 2 \rightarrow 2\bar{1}\cdot\bar{1}$; both options are listed in Tables V, VI, and VIII for both half-reactions. Tautomerism of allylic carbanions and enol derivatives to carbonyls are found in reactions such as A_3, B_3, and $\bar{2}_2'$ and discussed below. Discussion of the choices of these variants follows under each reaction type, but most of the variants are with RH half-reactions.

RH Half-Reactions (Table V). RH substrates are nucleophiles, assigned ⊖ polarity ($\Delta x = +1$),[16] and are either carbanions[14] or nucleophilic π bonds, as in electrophilic substitutions. The B_2 half-reaction product can be either $\overline{11}$ or $1\tfrac{2}{3}$ in Table I and is the only case of real conflict of label definition. The simple B_2 label is reserved for $1\tfrac{2}{3} \rightarrow 1\tfrac{2}{3}$ as in α-halocarbonyls for Darzens reaction or stabilized carbanions like nitroacetate or phosphonium enolates (R_3P^+–C(–)–CO–); products with subsequent elimination are common to the last two ($1\tfrac{2}{3} \rightarrow \bar{2}\tfrac{2}{3}$ or $\bar{1}\tfrac{2}{3}$ as in Table V. The substrate and product ($\overline{11}$), however, is a simple π bond undergoing RH substitution and is distinguished as $\bar{B}_2$, with a bar to recall the π bond acting as nucleophile. It should be noted that the notation is fundamentally one of net structural change so that the mechanistically different vinyl carbanions and electrophilic substitutions (of olefins or aromatics) are both $\bar{B}_2$, i.e., RH half-reactions of f list $\overline{11} \rightarrow \overline{11}$.

The different RH labels generally imply different kinds of carbanion stabilization and so follow traditional distinc-

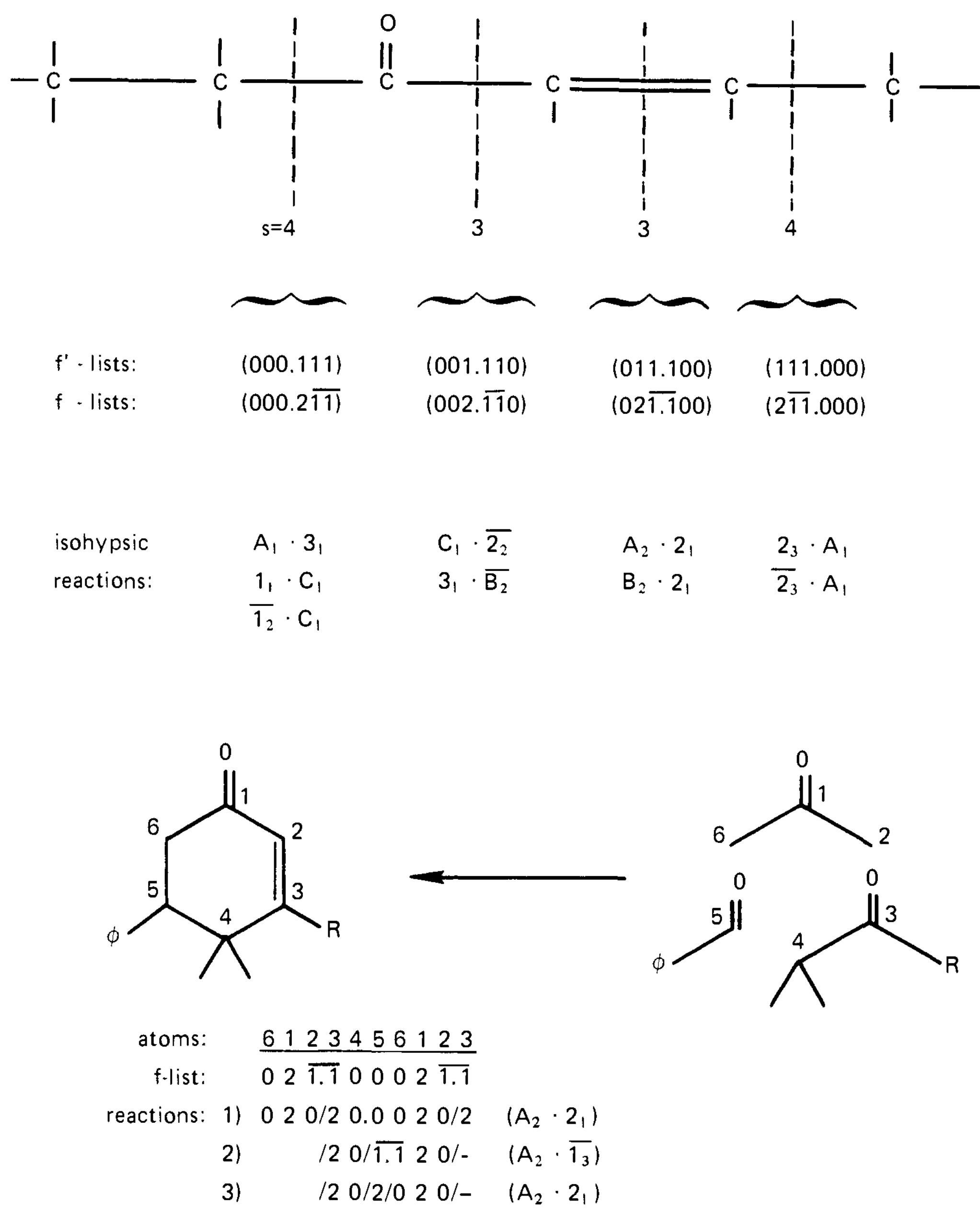


Figure 3. Functionality dissection: unsaturated ketone.

tions of carbanion reagents. Since -Z does not differentiate heteroatoms, the label B_1 includes carbanions stabilized by $-NO_2$, $-SO_2R$, $-S^+R_2$, etc., and Wittig reagents, $-P^+R_3$, while C_1 is the family of carbanions of aldehyde functional level, equivalent to $(R—\bar{C}=O)^-$. Lable D_1 represents the necessarily one-carbon synthon ($\sigma = 0 \rightarrow 1$) of $f = 3$, i.e., cyanide ion and equivalents, $\ominus$:CZ_3 with various different heteroatoms (Z). Half-reactions A_1 and B_1 are annotated with $f_\beta = 0$ even though they are $s' = 1$, as a reminder that extra β functionality would either change the label (see A_2, B_2, B_3, etc.) or be nonviable owing to intervening elimination if $f_\beta = 1$.

Initial reduction to create active carbanions is noted in Table V with variant substrate f lists in parentheses and includes simple organometallics, A_1, from halides (10 → 00), enolates, A_2, by reduction of α-halocarbonyls (1⅔) or unsaturated carbonyls ($\bar{1}$⅔), vinyl carbanions, $\bar{B}_2$ (from $\overline{21}$), and allylic carbanions, A_3 (from 1$\overline{11}$). Subsequent elimination is available as a variant, i.e., alternate product, with B_1, C_1, D_1, A_2, B_2, and B_3. As illustrated by B_1 and C_1, these eliminations can lose either H or Z (i.e., ΠH or ΠZ eliminations[1]) so that two alternate products are available with B_1 as exemplified by nitrocarbanions yielding $=C—NO_2$ ($\bar{2}$) products via ΠH elimination or Wittig reagents yielding $=CH$ ($\bar{1}$) via ΠZ.

The major tautomerism variants occur with the allylic carbanions in A_3 and B_3. In each case, the tautomerism can involve net removal of the α or γ hydrogen, although the parent is labeled for the simplest case of α-hydrogen removal and α construction (RH), as in the upper substrate for both A_3 and B_3, with no tautomeric olefin shifts.[31] The two products for A_3 show the same possible olefinic tautomerism for the product, only the upper one reflecting the simple product predicted by the label, with no tautomerism. The four B_3 products also include subsequent eliminations as with B_1 and B_2. The A_3 reaction generally is more viable at present with an off-strand carbonyl attached at α to activate carbanion formation more effectively. This is the case of carbanions of α,β-unsaturated ketones in alkylations, etc. In designing syntheses with A_3 half-reactions, present chemical experience would dictate the addition of this extra carbonyl (if the synthon skeleton allows it), even though it is not specified by the label.

RZ Half-Reactions (Table VI). RZ substrates are electrophiles, assigned ⊕ polarity ($\Delta x = -1$).[16] They are distinguished by loss of a heteroatom bond at the constructing α carbon, i.e., $\Delta f_\alpha = -1$. They are labeled with number symbols which show directly and recognizably the functional level on the substrate α carbon. Thus the 1_1 family represent the simple alkylation electrophiles, i.e., the alkyl halides, tosylates, etc., of nucleophilic substitution, while 2_1 denotes additions to ketone/aldehyde and 3_1 to carboxyl family groups. The half-reaction 1_2 represents epoxides[32] with the important synthetic distinction of a functionalized β carbon in the product. The other RZ reactions represent addition–elimination modes of construction with β and γ activation. Only eight of the possible ten labels are used, the others (1_3 and 3_3) being regarded as simply 1_1 and 3_2, respectively, with added, but not obligatory, functionality off-strand.

RΠ Half-Reactions (Table VII). RΠ substrates are olefins undergoing addition with construction and may have either polarity depending on the overall change in oxidation state as explained previously. The theoretical number of labels is only four instead of ten since f_α must be $\bar{1}$ or $\bar{2}$ and a half-span of at least 2 is mandatory for π bonds. However, the dependency on Δf_β as well doubles the number possible to eight, four labeled with primes if $\Delta f_\beta = 0$. Of the latter, two ($\bar{1}_2'$ and $\bar{2}_2'$) are nucleophiles (⊖ polarity), while $\bar{1}_3'$ is an electrophile (see above) as in the S$_N$2′ substitution. $\bar{1}_3'$ is also a common allylic synthon in pericyclic reactions such as the Claisen and 2,3-sigmatropic rearrangements. The parallel acetylenic half-reaction $\bar{2}_3'$ was not included[18] so that only seven of the eight possible RΠ reactions are listed.

Extra Functionality. In general the presence of extra functionality beyond the half-span, i.e., off-strand, does not interfere with the operation of these half-reactions. There are, however, a number of combinations of additional functionality possible on the reactive strand itself (within the half-span) above the defined minimal obligatory functionality. Such extra functionality must be on the β and γ carbons (of $s' = 2, 3$ half-reactions) and so does not alter the label, which is defined by f_α. Such combinations represent potentially viable variants of the primary defined half-reactions for each label with $s' > 1$, and some indeed are very important variants.

In the RΠ half-reactions in particular, added functions at β often mechanistically direct the π-bond addition as nucleophilic (cf. $\bar{1}_2$ and $\bar{2}_2$) or electrophilic (cf., $\bar{1}_2'$ and $\bar{2}_2'$), unsaturated sulfones (f list $\overline{1}2$) being acceptors of nucleophiles ($\bar{1}_2$) and enamines or enol ethers (also f list $\overline{1}2$) themselves nucleophiles ($\bar{1}_2'$) but in each case with f_β larger than the minimum 1 of the the definitions in Table VII. These additional f lists, higher than the defining obligatory f lists, have been examined mechanistically and those thought to be viable additions have been added to the lists and constitute the other added variants found in the master list (Table VIII) which do not appear in the three defining lists (Tables V–VII). A number were omitted from RH reactions on grounds of elimination initiated by an α carbanion. An expanded catalog of half-reactions, as an encyclopedia for synthetic use, would include a detailed discussion of the viability of the possible functional attachment of different heteroatoms, Z, at various carbons of the strand. The choices made here in a number of cases are somewhat arbitrary, and the basic list of half-reactions in Table VIII can be slightly altered later, without violence to the concept, if these judgements are changed following further study of various reactions.

References and Notes

(1) J. B. Hendrickson, *J. Am. Chem. Soc.*, **93**, 6847 (1971).

(2) The ultimate, simplest starting materials are the elements themselves, embodied in the classical ideal of a synthesis from "coal, air and water".

(3) J. B. Hendrickson, *J. Am. Chem. Soc.*, previous paper in this issue.

(4) The fourth construction type, RR, involves a concomitant carbon–carbon cleavage (as in skeletal rearrangements) and is ignored in the present treatment, as are the other cleavages, HR, ZR, ΠR. A parallel treatment of these cleavages will be developed later.

(5) Exceptions are few: β-dicarbonyl carbanions involve a branched, not linear (from the construction carbon), three-carbon function unit and unsaturated carbonyl carbanions a branched four-carbon unit, but these can be subsumed for the present as simple enolate anions, i.e., the linear two-carbon unit, –CO—C: ⊖. Since only single constructions are formulated here, Diels–Alder and other pericyclic cycloadditions forming two carbon–carbon bonds at once are a (small but important) special class and must be examined separately. Other pericyclic constructions, however, all conform to the definition here. 1,6 additions invoke more carbons but still linearly arranged, and, though ignored here, can easily be added to the catalog.

(6) Obligatory functions are those which essentially determine a reaction. A carbonyl at the α carbon in the substrate, for example, is obligatory for carbonyl-addition constructions, but a hydroxyl added at the β carbon is virtually extraneous and is thus not obligatory to the mechanism and facility of the additions. Only obligatory functions are considered in the definitions.

(7) The term *synthon*[8] is taken here to mean a particular skeleton followed through successive steps of a synthesis as part of a growing larger molecule, ultimately part of the target molecule. It bears an initial functionality as a starting material, and this changes through the synthesis to the functionality it bears in the target. A partial synthon is similarly a reactive strand passing from substrate to product functionality.

(8) E. J. Corey, *Pure Appl. Chem.*, **14**, 19 (1967).

(9) E. J. Corey and W. T. Wipke, *Science*, **166**, 178 (1969).

(10) The list $^2\!/_3 0.00 ^2\!/_3$ is understood as a strand of five carbons, products of a construction linking the second and third. The first and fifth carbons of the strand, each labeled $^2\!/_3$, bear either $f = 2$ or 3, i.e., are either ketone/aldehyde or cyano/carboxyl family, respectively.

(11) The 40 product f lists here do not distinguish π and Z. Making this distinction, as with one or two bars over f values for π bonds, will of course increase the number of possible combinations (to 101).

(12) Construction reactions were previously[1] grouped into f classes, which correspond to the present symbols.

$$\text{RH: } A = f_{00};\ F = f_{11};\ C = f_{22};\ D = f_{33}$$
$$\text{RF: } 1 = f_{10};\ 2 = f_{21};\ 3 = f_{32};\ 4 = f_{43}$$

(13) Note, for example, that the labels describe the substrates here, and this is also the case with traditional construction descriptions, *viz.*, Grignard, carbonyl addition, enolate reactions, conjugate addition, etc. Other examples are available in Table IV.

(14) The carbanion has the same characteristic and functionality level as its conjugate acid, i.e., free electron pair or metal is the same carbon attachment as H.[1]

(15) It is possible to write σ lists ($\sigma_\alpha\sigma_\beta\sigma_\gamma$) for each half-reaction, paralleling the f lists, but of course each half-reaction has a number of possible σ lists. The minimum σ lists are a function only of half-span, the maximum σ lists are shown in Tables V–VII, and the *number* of possible σ lists is simply calculated from the given maximum σ list ($\sigma_\alpha\sigma_\beta\sigma_\gamma$) as shown:

	minimum σ lists		
s'	sub	→ prod	number of possible σ lists
1	0	1	σ_α
2	11	21	$(\sigma_\alpha - 1)\ \sigma_\beta$
3	121	221	$(\sigma_\alpha - 1)(\sigma_\beta - 1)\ \sigma_\gamma$

(16) Because of the strong tradition of mechanistic thinking common in contemporary chemistry, these polarities are assigned mechanistically, ⊖ for nucleophile and ⊕ for electrophile, but the oxidation state changes are actually of opposite sign, i.e., $\Delta x = +1$ and -1, respectively.

(17) This appears to be untrue for certain half-reactions included as variants in Tables V–VII and discussed in the Appendix. In these cases, however, the actual construction step has the polarity and oxidation state change shown, but the overall change listed includes a separate but common attendant refunctionalization reaction. Thus in the Grignard half-reaction, the common substrate is an alkyl halide, reduced first by metal to a carbanion which then undergoes construction, i.e. $RX \rightarrow R:^- \rightarrow R–R'$, or HZ + RH; f lists = $1 \rightarrow 0 \rightarrow 0$. The $\Sigma\Delta x = -2 + 1 = -1$, but the polarity is still listed as ⊖ since the construction step itself is the parent RH ($\Delta x = +1$) reaction A_1 of ⊕ polarity. Similarly the B_1 half-reaction (cf. Wittig reagent) undergoes a secondary elimination step, i.e., $Ph_3P^+–C:^- \rightarrow Ph_3P–C–R' \rightarrow C{=}R'$, when coupled with carbonyl addition partners (2_1). The steps are RH + ΠZ and the f list change $1 \rightarrow 1 \rightarrow \bar{1}$ with $\Sigma\Delta x = +1 - 1 = 0$. The polarity is still listed as ⊖ for the construction step itself of the parent RH reaction B_1.

(18) The primes on RΠ half-reactions only signify the structural change $\Delta f_\beta = 0$, as noted above, and not the polarity, which is derived from net oxidation state change. Hence half-reactions $\bar{1}_2'$ and $\bar{2}_2'$ are ⊖ polarity, but $\bar{1}_3'$ is ⊕ since there are *three* involved character changes on the 3-strand: RΠ·ΠΠ·ΠZ for $\Sigma\Delta x = 0 + 0 - 1 = -1$. A comparable $\bar{2}_3'$ not shown in the list (although easily added if examples warrant) would also have ⊕ polarity ($C{\equiv}C—C—Z \rightarrow R—C{=}C{=}C$).

(19) With the reaction labeling shown here, oxidative couplings are represented by two letter symbols, reductive couplings by two numbers, and isohypsic constructions by one letter and one number symbol (examples in Table IV).

(20) A single reagent, so counted, is still of course a family of real compounds all of which are characterized by the same f list and may be generated by heteroatom variations. Thus methyl acetate, ethyl acetate,

acetonitrile, acetic anhydride, etc., are treated here as one two-carbon reagent with *f* list 30, yielding an attached two-carbon unit (acetyl) of *f* list 20 in the product of a 3_1 half-reaction (acylation, Tables IV and VI).

(21) R. E. Ireland "Organic Synthesis", Prentice-Hall, Englewood Cliffs, N.J., 1969.

(22) (a) E. J. Corey, W. T. Wipke, R. D. Cramer, and W. J. Howe, *J. Am. Chem. Soc.*, **94**, 421 (1972), and adjacent papers: (b) E. J. Corey, *Q. Rev. Chem. Soc.*, **25**, 455 (1971).

(23) "Computer Representation and Manipulation of Chemical Information", W. T. Wipke, S. R. Heller, R. J. Feldman, and E. Hyde, Ed., Wiley, New York, N.Y., 1974.

(24) There are a few cases in Table V–IX in which the half-span is different in substrate and product, essentially in $\bar{1}_2$ and one variant each of A_3 and B_3. The labeled half-span is always the greater. The *f* lists for A_1 and B_1 are sometimes listed with $f_\beta = 0$ since any function of β is either disallowed or changes the label. See Appendix for discussion.

(25) The eight possible *f* ' lists for half-reactions yield $\binom{9}{2} = 36$ possible combinations of full *f* ' lists of six digits for the full six-carbon product strand. Excluding $f' = 101$, there are only $\binom{8}{2} = 28$ combinations. In Table XII, the rarely accessible $f' = 000.000$ (cf. Wurtz reaction) is omitted.

(26) A few oxidative and reductive couplings with reasonable precedent, as $A_2 \cdot A_2$ or $C_2 \cdot C_2$ (Table IV), have been added to the list of constructions, to make 196 full products and 367 reactions.

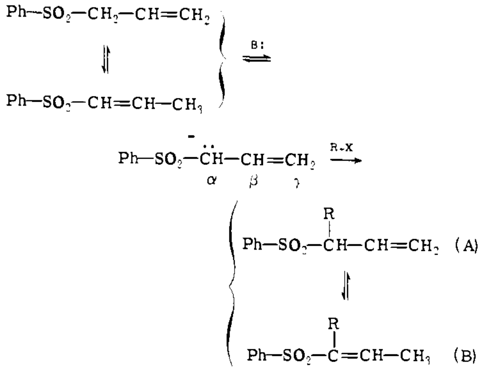
(27) N. Anand, J. S. Bindra, and S. Ranganathan, "Art in Organic Synthesis", Holden-Day, San Francisco, Calif., 1970, provides a convenient summary collection for examining how many syntheses have utilized this principle of functionality dissection; the Torgov and related steroid syntheses are found on pp 96, 170, 177.

(28) The leftmost construction is found in Table XIII only by assuming the double bond to be extraneous off-strand and looking up 000.2 instead of $000.2\bar{1}\bar{1}$.

(29) The sequence includes a Robinson annelation (steps 1 and 2). Another option for step 2, construction of bond 5–6 for the other $A_2 \cdot \bar{1}_3$ (Michael addition), is precluded by the maximum σ list in Table XI which disallows $\sigma = 4$ at the β atom of $\bar{1}_3$ (atom 4).

(30) Cyclization constructions may be further circumscribed by restricting the half-reactions that are viable for given ring sizes; in the particular case in Figure 3, reactions A_1 or $\bar{2}_2$ would presumably be disallowed.

(31) An example of half-reaction B_3 is the alkylation of unsaturated sulfones:



If there were no hydrogen on α, the first tautomer (A) must be the product ($\sigma_\alpha = 3$) but, if (as shown) $\sigma_\alpha = 2$ in the product, then the product structure is expected to be the conjugated (B). Properly the lower substrate should be labeled C_3, but both are subsumed under the B_3 label because they are so clearly one reaction family and both yield the same products.

(32) Reactions 1_1 and 1_2 are further restricted in the tables to $\sigma_\alpha \leqslant 2$ in the substrate, forbidding displacements at tertiary carbons as characteristic of SN2 reactions. The few such constructions which occur at tertiary carbons are usually olefinic cyclizations to tertiary leaving groups. The catalog can be adapted in use to include these but their exclusion here is justified by their rarity: if tertiary 1_1 and 1_2 α carbons were allowed, too many nonviable constructions would turn up in the general sets of routes derived from them in any systematic search protocol.

(33) Presented at the Synthesis Design Symposium, Louvain, Belgium, March 1974; *Top. Curr. Chem.*, in press.

Atomic Oxygen. IV. Rearrangements in the Reactions of Oxygen (^3P) Atoms with Cyclic and Bicyclic Hydrocarbons[1]

James J. Havel* and Kam H. Chan

Contribution from the Department of Chemistry, Rice University, Houston, Texas 77001. Received February 24, 1975

Abstract: The gas phase reactions of ground state (^3P) oxygen atoms with several cyclic and bicyclic hydrocarbons have been examined. The atomic oxygen was produced by the mercury photosensitized decomposition of nitrous oxide. The organic substrates studied were: cyclohexene, norbornene, 1,4-cyclohexadiene, norbornadiene, cyclobutene, and bicyclo[1.1.0]butane. Extensive rearrangements occur during these reactions. Spectra of a novel compound, *endo*-bicyclo[2.1.1]hexane-5-carboxaldehyde, are reported.

The reactions of atomic oxygen are of demonstrated importance in the chemistry of the upper atmosphere[2] and of combustion.[3] Synthetic applications of oxygen atom reactions are also being explored.[1] Cvetanovic has made a number of interesting mechanistic observations about these atomic processes.[4]

Ground state (^3P) oxygen atoms are conveniently produced in the gas phase by the mercury photosensitized decomposition of nitrous oxide (eq 1 and 2).[4,5]

$$\mathrm{Hg}(^1S_0) + h\gamma \longrightarrow \mathrm{Hg}(^3P_1) \qquad (1)$$

$$\mathrm{Hg}(^3P_1) + \mathrm{N_2O} \longrightarrow \mathrm{Hg}(^1S_0) + \mathrm{N_2}(^1\Sigma) + \mathrm{O}(^3P) \qquad (2)$$

While O(^3P) reacts sluggishly with most alkanes, the reaction with alkenes is quite efficient. The reaction of atomic oxygen with acyclic olefins produces approximately equal quantities of epoxides and carbonyl compounds. The latter products are of particular interest, because their formation must involve rearrangement of a substituent of the olefin.

Cvetanovic has proposed[4] that O(^3P) atoms add to olefins to form short-lived 1,3 biradicals (Scheme I). These

Scheme I