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Methods of Reactivity Umpolung

By Dieter Seebach[*]

Dedicated to Professor Horst Pommer on the occasion of his 60th birthday

The past decade of organic chemistry may be characterized as a period of violent development of new synthetic methods. This was accompanied by a systematization of the analysis of synthetic problems (synthetic strategy). The planning of the synthesis of an organic target molecule is greatly facilitated by distinguishing between reagents $X(C)_n\ldots$ with normal reactivity (acceptor properties at $C^{1,3,5\cdots}$, donor properties at X, $C^{2,4\cdots}$) and with reactivity umpolung (acceptor properties at X, $C^{2,4\cdots}$, donor properties at $C^{1,3,5\cdots}$). In this context, reactivity umpolung turned out to be useful as a heuristic principle, as a classification scheme, and as an aid for locating so-called strategic bonds (synthon, transform, and antithesis according to *E. J. Corey*). There are six principal methods of umpolung: 1,2*n*-oxidation, heteroatom exchange and modification, homologation and its reversal, the cyclopropane "trick", use of acetylenes, and redox reactions; under certain circumstances none of these techniques is necessary in cases where direct umpolung is possible. Throughout the article, normal reactivity is indicated by green print; reactivity umpolung by red print.

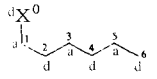
1. Postulates and Nomenclature

Before describing and systematizing the methods of reactivity umpolung, the scope of the discussion, the nomenclature of synthetic methodology and the synthetic problem behind reactivity umpolung must be defined.

1. The reactions most frequently used in organic synthesis are *polar* in nature, *i. e.* nucleophilic or *donor* (**d**) and electrophilic or *acceptor* (**a**) sites are used to make and break bonds (Lewis acid base combinations)[1a, 1b].

2. The large majority of target molecules of organic synthesis contain the heteroatoms *nitrogen* and *oxygen* as functional groups (amino, imino, hydroxy, ether, carbonyl)[1a].

3. These heteroatoms impose an *alternating acceptor and donor reactivity pattern* (*1*) upon the carbon skeleton, *i.e.* acceptor properties or attack by donors at carbons $C^{1.3.5\cdots}$, and donor properties or attack by acceptors at carbons $C^{2.4.6\cdots}$; the heteroatom X^0 itself is a donor center d^{0}[1a].



(*1*), X = O, N

$a^{1,3,5\cdots}$- and $d^{0,2,4,6\cdots}$-reactivity

(*1a*)

In order to clearly distinguish donor and acceptor reactivity from partial charge separation (⊕ or $\delta^{\oplus}$ and ⊖ or $\delta^{\ominus}$) we use the letters **d** and **a** throughout this article [see (*1*) [1c]]. The signs Δ for **d** and o for **a** [see (*1a*)] may also be employed and avoid additional letters to be written in more complex formulas. Green print indicates normal reactivity, red print reactivity umpolung (see definition 1.8).

4. A consequence and synthetic limitation is the fact that combination of components with reactivity (*1*) leads only

[*] Prof. Dr. D. Seebach
Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum
Universitätstrasse 16, CH-8092 Zürich (Switzerland)

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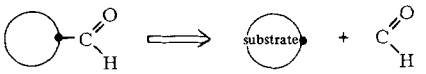
to 1,3-, 1,5- ... 1,(2*n*+1)-disubstituted products (odd number of carbon atoms between the functional groups) [see *(2)* and *(3)*][1a].

a^3/d^0 or a^1/d^2 a^5/d^0, a^3/d^2 or a^1/d^4

(2) *(3)*

direct or vinylogous Prins-, aldol-, Claisen-, Mannich- and Michael reactions [1a, 2]; X, X' = O, N; double bonds where applicable

5. According to the original proposition, *synthons* are "structural units within a molecule which are related to possible synthetic operations"[3a]. Thus, the molecule *(4)* is related

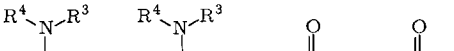


(4) *(5)* *(6)*

with the substrate synthon *(5)* and the formyl synthon *(6)*. This is irrespective of the type of reaction employed (polar, radical[1c], pericyclic, transition-metal mediated, photochemical, electrochemical).

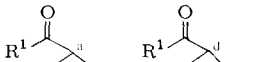
6. An a^n- or d^n-synthon ($n \geq 1$) is, respectively, a synthon with an O- or N-heteroatom at C^1 and an acceptor or donor center at C^n[3b, 4]. Six such synthons are shown in *(7)*–*(9)*. An a^0- or d^0-synthon is an acceptor or donor heteroatom (O or N), respectively.

7. A *reagent* is the compound or intermediate actually used to carry out the synthetic operation. *Synthetically equivalent* reagents or series of reactions perform identical transformations (see Table 1 and definition 1.9)[3c].



a^1 d^1 a^1 d^1

(7a) *(7b)* *(8a)* *(8b)*

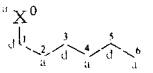


a^2 d^2

(9a) *(9b)*

8. A reagent has normal reactivity if it corresponds to a synthon of general type *(1)*.

Reactivity umpolung is present in a reagent in which **a**- and **d**-centers are reversed as compared to *(1)* [see general representation *(10)*; cf. *(7b)*, *(8b)*, *(9a)*]. Thus, a^{2n+1}- or



$a^{0,2,4,\cdots}$- and $d^{1,3,5,\cdots}$-reactivity

(10), X = O, N

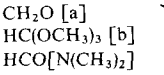
d^{2n}-synthons correspond to reagents of normal reactivity, d^{2n+1}- or a^{2n}-synthons to those with reactivity umpolung (see Table 1).

Umpolung is also present if the alternation of reactivity is violated [see also query 4 in Section 2, and Section 3.5).

Finally umpolung is any *process* by which donor and acceptor reactivity of an atom are interchanged (see Sections 3.2 and 3.6).

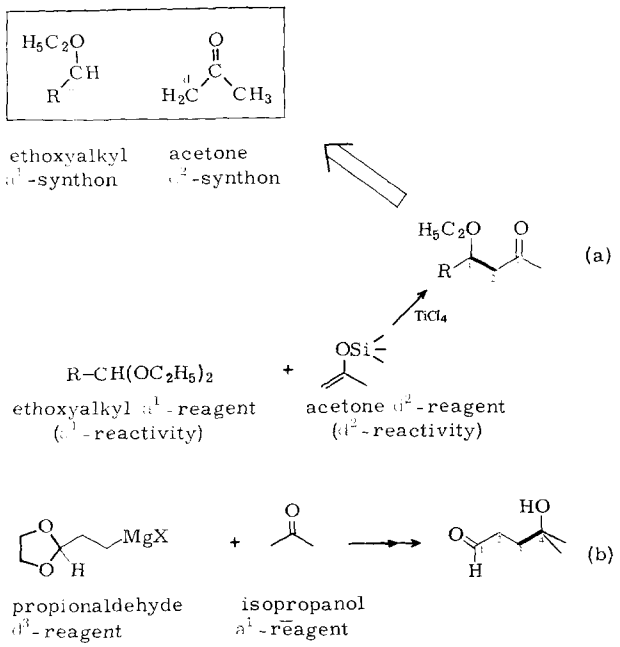
9. When discussing particular transformations, the names of the structural units under consideration are used with the

Table 1. Preparations of an aldehyde R—CH_2—CH_2—CHO (target molecule).

Transformations and synthons leading to target			Reagents			Ref.
R—CH_2—CH_2 **d**	+ a CHO (*the* formyl a^1-synthon)	R—CH_2—CH_2—MgX	+ CH_2O [a]; $HC(OCH_3)_3$ [b]; $HCO[N(CH_3)_2]$; 		*synthetically equivalent reagents* (four of many possible formyl a^1-reagents)	[8]; [4g, 9]
R—CH_2—CH_2 **r**	+ **r** CHO	R—CH=CH_2	+  [c,b]			[10]
R—CH_2—CH_2 **a**	d CHO (d^1)	R—CH_2—CH_2—Br	+  [b]		*synthetically equivalent reagents* (formyl d^1-reagents)	
		R—CH_2—CH_2—OTos	+ NaCN [d]			
		R—CH_2—CHO	+ $CH_3OCH=P(C_6H_5)_3$ [b]			
R—CH_2 **a**	+ d CH_2—CHO (d^2)	R—CH_2X	+  [b];  [d,b]		*synthetically equivalent reagents* (acetaldehyde d^2-reagents)	[11]; [12]
R—CH_2 **d**	+ a CH_2—CHO (a^2)		+ Br—CH_2—$CH(OC_2H_5)_2$ [e, b]		(acetaldehyde a^2-reagent)	
R **a**	+ d CH_2—CH_2—CHO (d^3)	RBr	+  [f,b]		(propionaldehyde d^3-reagent)	[13]
R **d**	+ a CH_2—CH_2—CHO (a^3)	R_2CuLi	+  [d]		(propionaldehyde a^3-reagent)	

[a] Oxidation of the product. [b] Hydrolysis of the product. [c] Radical chain initiator. [d] Reduction of the product. [e] Raney-Ni desulfurization. [f] S-methylation of the primary alkylation product.

corresponding reactivity symbols; newly formed bonds are indicated in **bold type** [see eqs (a)[6] and (b)[7] and Table 1[3c, 5]].

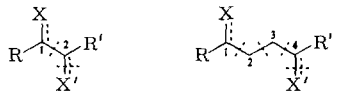


10. A reaction or reagent which differentiates between sites of identical reactivity in a conjugate system of type *(1)* or *(10)* is called *ambidoselective* (see selectivity nomenclature and examples in Table 2).

2. The Synthetic Problem

Four Views of Synthetic Situations Requiring Reactivity Umpolung

1. As stated in Section 1, the normal reactivity *(1)* does not enable us to construct 1,2*n*-disubstituted products (even number of carbon atoms between the functional groups). How are compounds of type *(11)* and *(12)* synthesized?

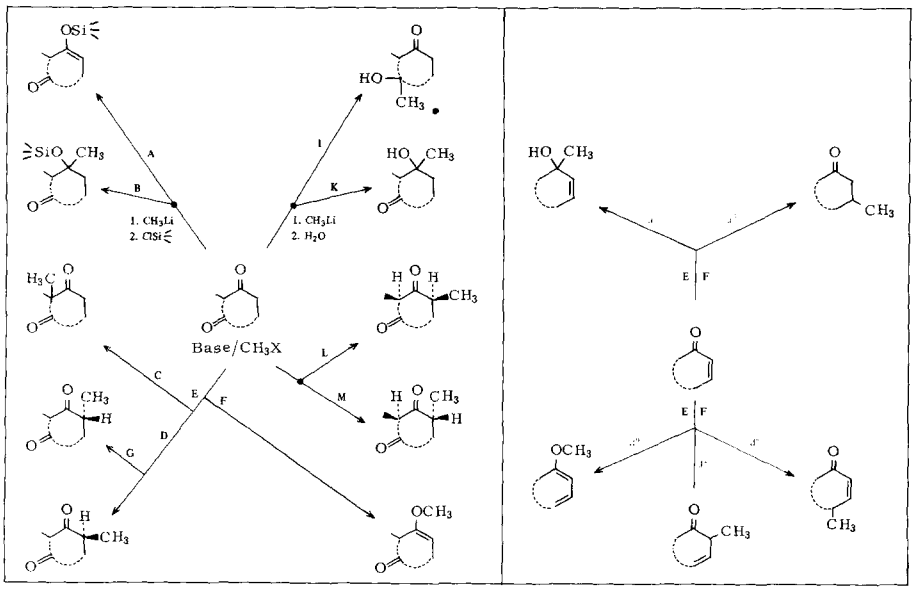


(11) *(12)*

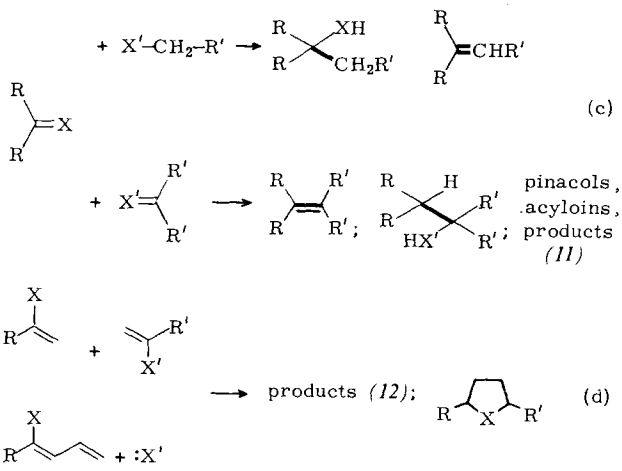
X, X' = NR''_2, OR'', NR'', O

2. We can rephrase this question in the following way: how do we couple two centers of identical polarity or affinity? [see eqs (c) and (d), X/X' = O, N].

Table 2. Structural definition of selectivities.—Three principal selectivities are distinguished [a]: 1. *type* selectivity (*non*-isomeric products, mostly different types of reactions, *i.e.* substitution, addition, elimination, ... A/B); 2. *constitutional* selectivity (same kind of reaction, products are constitutional isomers; C/D, E/F, I/K); 3. *stereo*-selectivity (products are stereoisomers; diastereoselectivity L/M or enantioselectivity G/H [b, c]).—Constitutional selectivity is subdivided into *site* selectivity (differentiates unrelated functional groups in a molecule which can undergo the same type of reaction, I/K), *regio*-selectivity [d] C/D and *ambido*-selectivity E/F (see definition 1.10 [e]).



[a] The term *chemo*selectivity [*B. M. Trost, Th. N. Salzmann, K. Hiroi*, J. Am. Chem. Soc. *98*, 4887 (1976)] is not structurally defined, *stereospecificity* is an often criticized term [*H. E. Zimmermann, L. Singer, B. S. Thyagarajan, ibid. 81*, 108 (1959); *E. Ruch, I. Ugi*, Theoret. Chim. Acta *4*, 287 (1966)]; "specificity" should be dropped altogether. [b] See *Y. Izumi, A. Tai:* Stereodifferentiating Reactions, Academic Press, New York, 1977. [c] Of course, (G) and (H) are only enantioselective routes if the hydrogens of the α-keto CH_2-group are enantiotopic in the starting molecule of the present example; in L/M they must be diastereotopic. [d] See *A. Hassner*, J. Org. Chem. *33*, 2684 (1968). [e] This was part of the original definition of regioselectivity (see [d]). However, the term was rarely used to distinguish between 1,2- *vs.* 1,4-addition to an enone or *O*- *vs.* *C*-alkylation of an enolate [reviews: *J. d'Angelo*, Tetrahedron *32*, 2979 (1976); *R. Gompper, H.-U. Wagner*, Angew. Chem. *88*, 389 (1976); Angew. Chem. Int. Ed. Engl. *15*, 321 (1976); *L. M. Jackman, B. C. Lange*, Tetrahedron *33*, 2737 (1977)]. As evident from the lower part of Table 2, the **a**/**d**-nomenclature is very convenient in this connection.

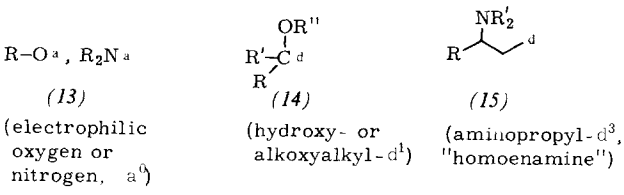


(c)

pinacols, acyloins, products *(11)*

products *(12)*; (d)

3. How can we systematically achieve a reactivity umpolung or construct reagents which correspond to synthons such as *(13)*—*(15)*? [cf. postulates 1.6 and 1.8, *(10)* and Table 1].

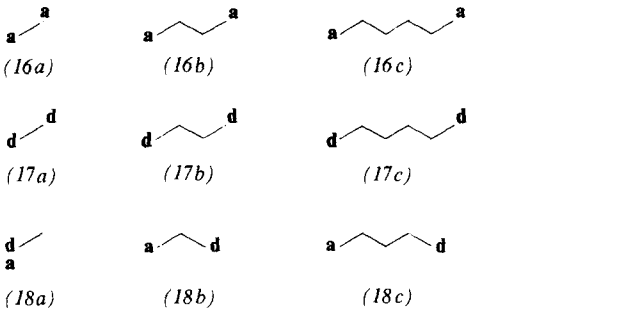


(13) (electrophilic oxygen or nitrogen, a^0)

(14) (hydroxy- or alkoxyalkyl-d^1)

(15) (aminopropyl-d^3, "homoenamine")

4. A fourth way of putting the question is: How do we generate equal reactivity in 1,(2*n*)- or opposite reactivity in 1,(2*n* + 1)-positions of a carbon framework? [see *(16)*—*(18)*].



(16a) *(16b)* *(16c)*

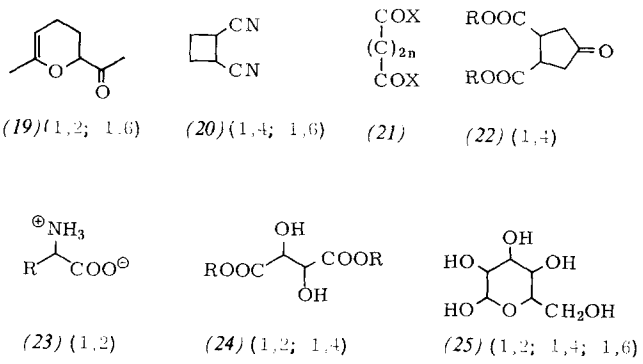
(17a) *(17b)* *(17c)*

(18a) *(18b)* *(18c)*

3. Methods of Reactivity Umpolung

Although the problem has been recognized for a long time[14–16], and although numerous classical solutions are available, an intensive effort has been made in the past decade to answer the four questions in Section 2 in new ways. A confusing variety of apparently independent and unrelated methods has been conceived and demands classification. This is attempted in the following sections.

Prior to doing this, a very important *memo* is appropriate: The preparation of 1,2*n*-bifunctional starting materials such as the [2+4]-dimer *(19)* of methyl vinyl ketone[17] or the head-to-head [2+2]-dimer *(20)* of acrylonitrile[18] is not readily classified in the present context. Also, industrial and biochemical processes furnish readily available and often unusual compounds in large quantities, *e.g.* the dicarboxylic acid derivatives *(21)* (succinic, adipic, fumaric, maleic, phthalic)



(19) (1,2; 1,6) *(20)* (1,4; 1,6) *(21)* *(22)* (1,4)

(23) (1,2) *(24)* (1,2; 1,4) *(25)* (1,2; 1,4; 1,6)

Examples of molecules from the "black magic box".

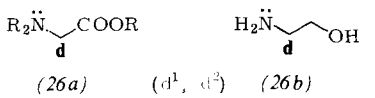
and *(22)* (from fumarate and cyanide[19,20]), furan and its derivatives, amino acids *(23)*, highly functionalized molecules such as tartaric acid *(24)* and carbohydrates *(25)*[21]. These may or may not arise along the lines described below. We might call these sources the "*black magic box*" of the synthetic organic chemist which should never be forgotten when planning the synthesis of a (chiral) molecule with complex functionality[21,22].

3.1. 1,2*n*-Oxidation

A process creating a 1,2*n*-oxygen and/or -nitrogen functionalized carbon skeleton without formation of a C—C bond is an oxidation (conservative conversion, non-connective). Some common transformations of this sort are listed in Table 3. As can be seen, many classical reactions and their recent improvements are among the examples: epoxidation (No. 1, 2), hydroxylation (No. 3, 4, 6, 7), oxygenation (No. 5, 8, 10, 11, 16), amination (No. 4), oximation and imination (No. 9), ozonolysis (No. 18), hydroboration /oxidation (No. 12), the Neber (No. 13), Bayer-Villiger (No. 17), and Criegee-Hock rearrangements (No. 19), the Hofmann-Löffler-Freytag (No. 14), and the Barton reaction (No. 15).

We are dealing with cases in which the heteroatoms oxygen and nitrogen have become acceptor (sextet or septet) sites *(10)* rather than acting as donors *(1)* [umpolung of heteroatom reactivity; a^0-synthons; equal polarity at adjacent heteroatoms R—O—O—R', R_2N—NR'_2, cf. *(17a)*]. Since the methodology of generating and selectively using reagents with electrophilic N or O is rather limited, there are numerous techniques which use other acceptor heteroatoms that are subsequently replaced by oxygen or nitrogen (see Section 3.2).

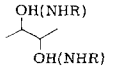
It is evident that all the products in Table 3, like the above mentioned black magic box molecules *(19)*—*(25)*, have a built-in reactivity umpolung: due to the 1,2*n*-functionalization, any of their normal reactions [*(1)*] with respect to one of the functional groups is an umpolung of reactivity [*(10)*] with respect to the other functionality. Thus, the enolate



(26a) (d^1, d^3) *(26b)*

of an amino acid derivative[4d,42] corresponds both to a d^3- *and* a d^1-synthon *(26)* (cf. the use of this type of reagent in the homologative approach, Section 3.3).

Table 3. Some reactions creating 1,2-doubly functionalized carbon skeletons without C—C-formation [23].

No.	Starting material	Reagent [ref.]	Product
1		$R—CO_3H$	
2		*t*-Bu-OOH/Mo V-derivative [24]	
3		OsO_4/R_3NO [25]	
4		OsO_4/chloramine-T [26]	
5		$^1O_2$ [27]	
6		O_2 [28]	
7		MoOPH [29]	
8		$HC(OR)(NR_2)_2/^1O_2$ [30]	
9		$ArN_2^{\oplus}$, $NO^{\oplus}$ [31, 32]	
10		$R—CO_3H$ [6c, 33]	
11		$^1O_2$ [34]	
12		$BH_3(H_2O_2)$ [6c, 35]	
13		NH_2OH/TosCl/base [2]	
		H_2SO_4 [2, 36]	
15		RONO/hv [2, 37]	
16		base/O_2 [38]	
17		H_2O_2 [2, 18, 39]	
18		O_3 or $OsO_4/IO_4^{\ominus}$; $Pb(OAc)_4$ [40]	
19		TosCl [2, 41]	

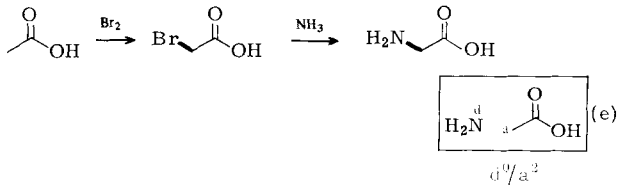
3.2. Exchange and Modification of the Heteroatom

Fortunately, organic chemistry is not restricted to the elements C, H, N, O! We can utilize all the elements of the periodic chart to achieve the goal of synthesizing C, H, N, O-containing products (see postulate 1.2) and to break out of the reactivity pattern *(1)* (see 1.3). The most common and best established systematic way of reactivity umpolung of N- or O-functionalized molecules is the *temporary exchange* of these heteroatoms by others which convey opposite reactivity to the carbon moiety. Thus, we use derivatives of other heteroatoms like a boat to cross a river.

Furthermore, nitrogen, unlike oxygen, has so many oxidation states and occurs in a multitute of bonding situations that it can be "modified" to allow for jumping back and forth between the two reactivity patterns *(1)* and *(10)*.

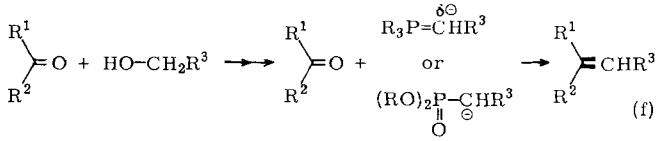
3.2.1. Heteroatom Exchange

As stated above, there is a lack of methods which cleanly introduce nitrogen and oxygen at donor sites. The use of $Br^{\oplus}$ as an electrophilic substitute heteroatom is a classical solution to this problem [see eq. (e)]. When the desired C—N bond is formed, the nitrogen acts as a nucleophile, the α-car-



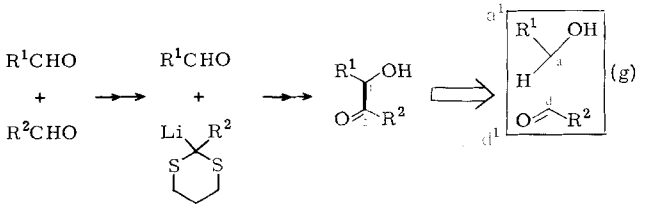
bonyl carbon as an electrophile; therefore the corresponding synthons are d^0 and a^2 (see also the 1,4-oxidation, entry 1 in Table 4). The use of α-chloronitrones (Table 4, entry 2) and of α-heter· ubstituted oximes[43] and hydrazones[44] as ketone a^2-reagents in C—C-bond forming processes has recently been demonstrated. The preparation of Grignard derivatives, the employment of tin-containing intermediates, and the use of certain acyl-metal and acyl-phosphorus compounds for reactivity umpolung are outlined in Table 4 (entries 3—5).

Especially versatile heteroatoms Y for this purpose are phosphorus, sulfur and selenium[4g,45]. They can be readily intro-

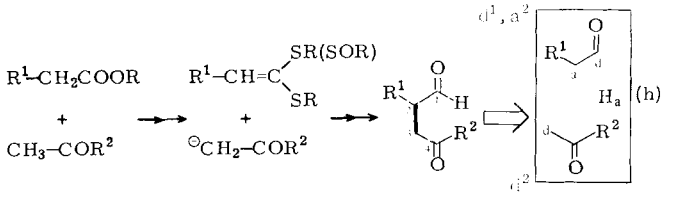


(f)

duced at electrophilic ($+R_nY^{\ominus}$) *and* at nucleophilic sites ($+R_nYX$). Sulfur in particular stabilizes positive *and* negative charges in the α-position, and there are numerous ways of removing all three heteroatoms from a molecule[4g]. Conversions associated with the names of *Wittig*, *Horner*, *Emmons*, *Wadsworth*, *Michaelis* and *Arbuzov*[2] allow the coupling of carbon atoms of the same polarity [cf. eqs. (c) and (f)]; recent improvements and promising developements in this general area are the so called redox condensations with phosphanes[46] and the conversion of NH_2 into the leaving group $N(SO_2R)_2$[47].

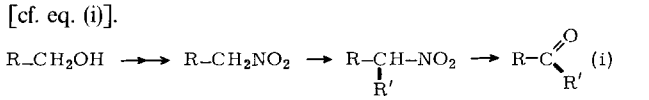


(g)



(h)

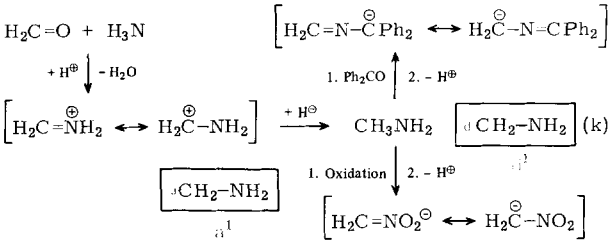
The temporary replacement of the heteroatom oxygen by sulfur for the preparation of 1,2*n*-functionalized products is described in equations (g) and (h) [cf. eqs. (c) and (d); for further examples see Table 4, entries 6—8, and detailed reviews[4b, 4g, h, 12, 45]]. The interconvertibility of oxygen and nitrogen functions (functional group equivalence[13a]) renders the use of N-containing reagents with reactivity umpolung (see Section 3.2.2) a heteroatom exchange method for oxygen [cf. eq. (i)].



(i)

3.2.2. Heteroatom Modification

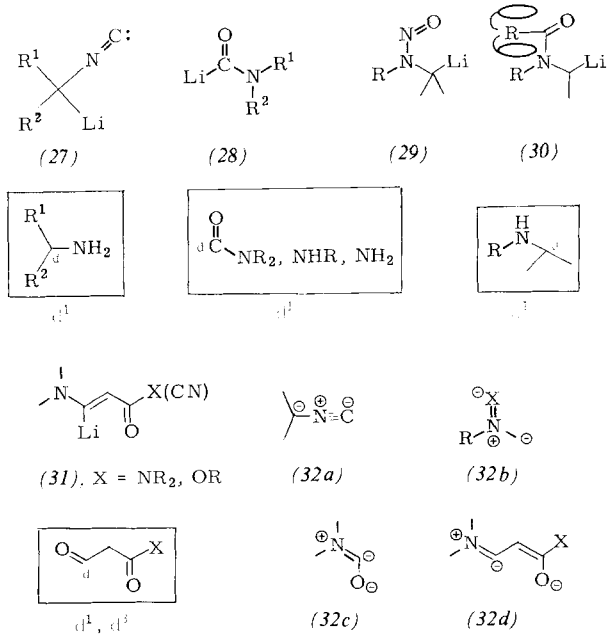
In sharp contrast to oxygen, which can hardly be modified to allow d^1- and a^2-reactivity as in *(10)*[48–50] (see Section 4.1) without the help of heteroatom exchange, nitrogen is a very rich heteroatom in this respect. There are two fundamental reasons for this: nitrogen can 1) make one more bond with carbon and thus be incorporated "in the middle" of conjugated systems, and 2) it has many more oxidation states; it can stabilize $\alpha\text{-}C^{\oplus}$ in the lower ones and $\alpha\text{-}C^{\ominus}$ in the higher ones. Thus, modification of the nitrogen of methylamine in the Schiff-base with benzophenone allows α-N—CH-deprotonation (cf. umpolung of amine reactivity with pyridoxal in Nature[51]) and converts the normal aminoalkylating a^1-



(k)

reactivity of iminium derivatives[52] into d^1-reactivity[53] [see eq. (k)]. On the other hand, we can convert the amine (oxidation state −3) into the nitronate (oxidation state +5) and use this as an aminomethyl d^1-reagent[41].

We need not go all the way to the nitro or diazo group to achieve α-N—CH acidification and α-N—C-donor properties. Any amine derivative which bears an electron-withdrawing group causing a partial positive charge on nitrogen appears to suffice under appropriate conditions [see the isocyanides *(27)*[54], the carbamoyllithium compounds *(28)*[50,55], the nitrosamines *(29)*[4d,56], the amides *(30)* with sterically pro-



tected but electronically effective carbonyl groups[48,49,57], and the vinylogous ureas, urethanes, and cyanamides *(31)*[58]]. It is not entirely clear yet whether the dipolar anion stabilization indicated in *(32)* is the decisive effect causing the ready

Table 4. Exchange and modification of heteroatoms [23].

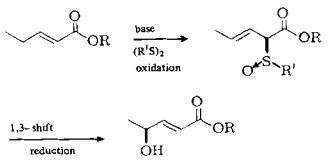
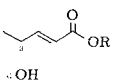
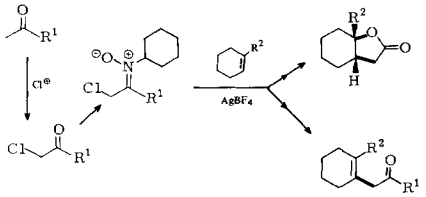
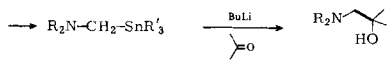
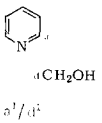
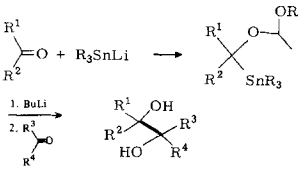
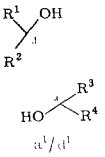
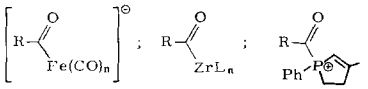
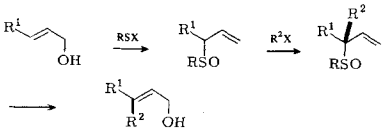
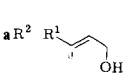
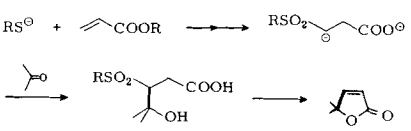
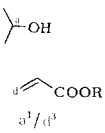
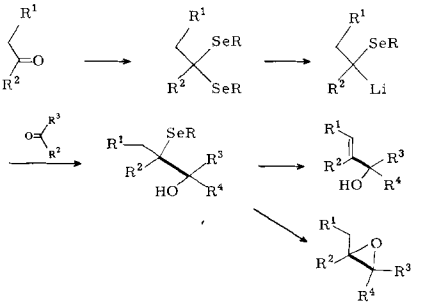
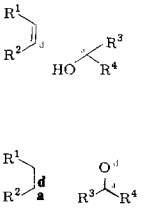
No.	Conversions and Reagents	Synthons	Ref.
1			[61]
2			[62]
3	$R^1\overset{\delta\oplus}{C}H_2OH + HO\overset{\delta\oplus}{C}H_2R^2$ $R^1CH_2OTos + BrMgCH_2R^2 \xrightarrow{Li_2CuCl_4} R^1CH_2{-}CH_2R^2$ $R_2NH + CH_2O + NaHSO_3 \longrightarrow R_2N{-}CH_2{-}SO_3Na$	R^1CH_2 **a** R^2CH_2 **d** $R_2N{-}CH_2$	[63]
			[64]
4	$CH_2O + R_3SnMgCl \longrightarrow HOCH_2SnR_3$ $\xrightarrow{2\ BuLi} LiOCH_2Li$		[65]
			[66]
5			[67—69]
6			[70]
7			[4g, 71]
8			[45] [72]

Table 4 (continued).

No.	Conversions and Reagents	Synthons	Ref.
9	RCOOH, RCH_2OH, RCHO $\xrightarrow{\ominus CN}$ homologous acid, amide, ketone, aldehyde, alcohol, amine, α-amino acid, α-hydroxyamide, -acid, -ketone, -aldehyde, -amine	d^1COOH $d^1$$CONH_2$ d^1CHO d^1COR $d^1$$CH_2OH$ $d^1$$CH_2NH_2$	[2] [23] [73—76]
10	R^1–COOH + $HO–CH_2–CH=CR^2_2$ + RCH(NH$_2$)–COOH →	OH or O; $d^1$$CH_2CH=CR^2_2$	[77]
11	NH_2 $\xrightarrow{SOCl_2}$ N=S=O; 1. Base 2. 3. H_2O	$d^1$$NH_2$	[78]
12	+ $HN(CH_3)_2$; 1. O 2. Raney-Ni or oxidation or hydrolysis; X = H_2, O	d^1N; or HN; OH	[79]
13	NO_2Li; OSi; OH	$d^1$$NH_2$; HO	[41]

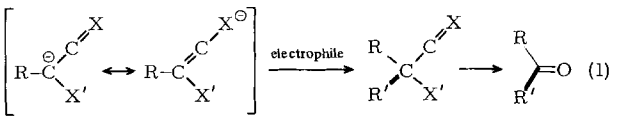
formation and unexpected stability of these systems[4d, 48, 49, 57]. An almost complete list of N-derivatives with nucleophilic α-carbons is found in a previous review (Table 3 in Ref. [4d]). The use of cyanide (Kolbe and Strecker syntheses[2], cyanohydrin formation), a recent example of incorporation of nitrogen into a conjugated system (cf. Section 3.5), and novel derivatives with "dipole stabilization" are listed in Table 4 (entries 9—13).

Examples of simultaneous heteroatom exchange *and* modification for the purpose of reactivity umpolung are the versatile reagent $TosCH_2NC$: (Tosmic[54, 59]) and the thiocarbamoyllithium derivatives $LiCSNR^1R^2$[60].

3.3. Homologation and Its Reversal

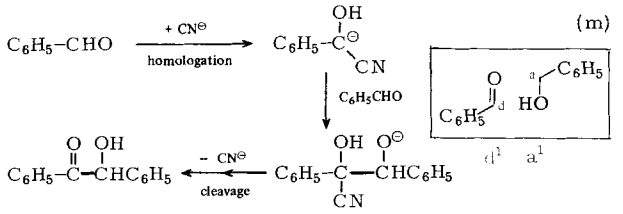
As stated in Section 3.1, any compound with a 1,2*n*-functionalization has the normal reactivity pattern *(1)* with respect to one of the two functional groups and reactivity umpolung *(10)* of the other one [cf. Section 3.1, *(26)*]. After a reaction with an acceptor at C^2, which in this case is at the same time a d^2- *and* a d^{2n-1}-center, the C—C bond leading to C^1 can be cleaved (reversal of homologation, degradation). This procedure then provides a reagent which corresponds to a d^{2n+1}-synthon. The extra functionalized carbon atom (C^1) can be specifically introduced (homologation) for the purpose of reactivity umpolung.

A d^1-reagent of this type has the general formula *(33)* where X and X′ may be oxygen and/or nitrogen, or other heteroatoms, and must fulfil three conditions: the C=X group is essential for anion stabilization, attack of the electrophile must occur on carbon, and the product must be amenable



(1)

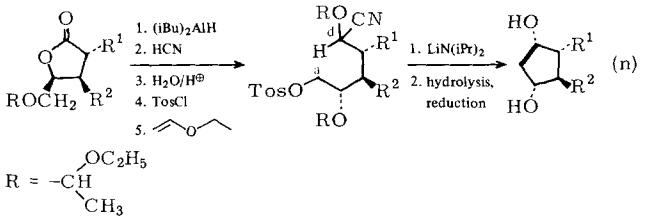
(33)



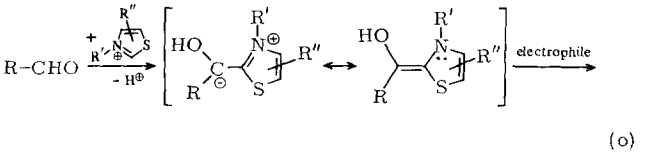
(m)

to cleavage to a carbonyl compound [see eq. (l) and Table 5]. Especially attractive are catalytic processes, the best known

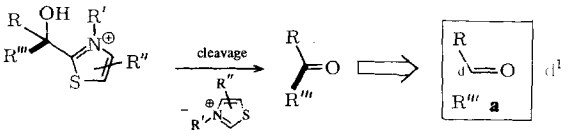
example of which is the benzoin condensation [eq. (m)]. The Stork method[80] is conceived along these lines; it uses lithium derivatives of protected cyanohydrins (see Table 5) and is ingeniously applied to a prostaglandin synthesis as indicated in eq. (n)[81]. The method by which Nature performs nucleophilic acylations again involves a catalytic homologation, with



(n)



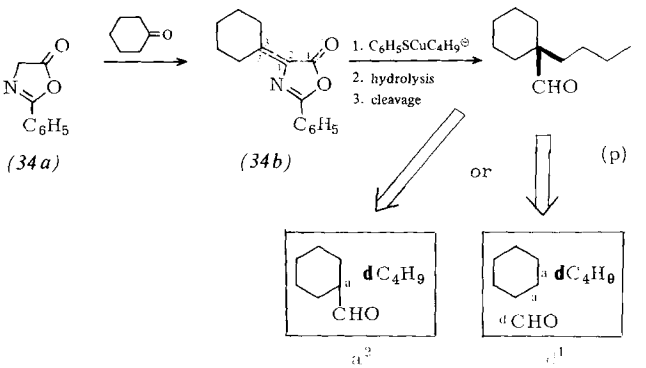
(o)



thiamine pyrophosphate[51,82], and was adopted by *Stetter et al.*[83] for laboratory scale preparations [eq. (o)].

Further examples of devising d^1-reagents by the homologative approach are listed in Table 5.

So far, we have discussed only cases in which d^1-reactions were performed with homologues of the actually required carbon framework. It is equally possible to use this method to supply a^2- and d^3-reagents [see eqs (p)—(r)]. In the first

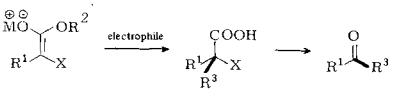
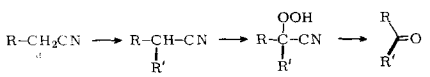
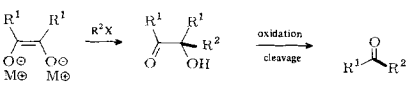
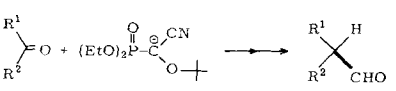
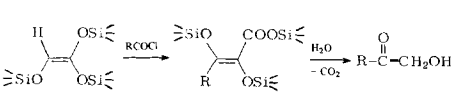


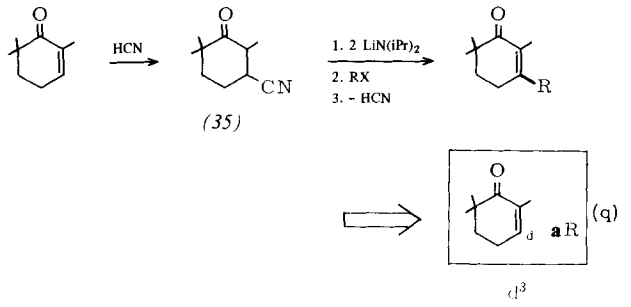
(p)

process a glycine derivative *(34a)* is used as a 1,2-bifunctional molecule[84]. Condensation with cyclohexanone gives a Michael acceptor (a^3) *(34b)*, which also is an enamine derivative (normal reactivity d^2, here a^2); the product obtained from the Gilman reaction[85] is hydrolyzed to the corresponding α-amino acid which is cleaved by lead tetraacetate (retrohomologation; the carbonyl carbon has "done its job"!) to give the final aldehyde product. If we consider the synthesis from cyclohexanone, the oxazolidone *(34a)* is a d^1-reagent (in the Dakin-West reaction[2] it is dCH_2NH_2); comparing *(34b)* with the aldehyde, we see that it is an a^2-reagent.

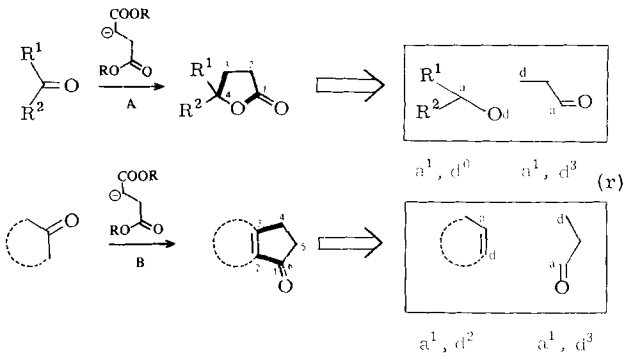
The reversible homologation of equation (q)[86] is vinylogous to the above mentioned use of cyanide for nucleophilic acylation and brings about a β-alkylation of an enone (cf. entries 7 and 9 of Table 4). The reaction sequence in equation (q) employs a 1,4-bifunctional intermediate *(35)*—like the classical Stobbe condensation[2] (and its many recent modifica-

Table 5. Reactivity umpolung by homologative methods [23]. Reagents (or conversions) corresponding to the d^1-synthons 

Reagent (or conversion)	Ref.	Reagent (or conversion)	Ref.
 + electrophiles			
X = OCH(CH3)-OC2H5	[80, 81]	R^2 = metal or alkyl, X = SR	[98]
O-tetrahydropyranyl	[89]	N=CR	[84, 99]
$OSi(CH_3)_3$	[90]	H(→OOH, see above)	[100]
$OCOC_6H_5$	[91]	COOH	[101]
OCOOR'	[92]	Cl (Darzens reaction)	[2]
$SCSN(CH_3)_2$	[93]		
$NR'COC_6H_5$ (Reissert compounds)	[95]		
NR'_2			
	[96]		[102]
 (cf. Darzens reaction [2])	[97]		[103]



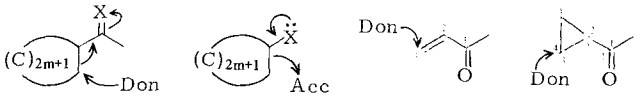
tions[87]; see also Section 3.4). As indicated in equation (r), the enolate derived from succinic ester corresponds to a d^3-synthon; the cyclopentenone annelation (route B) is part of a three carbon ring expansion method[88]. Some further



classical[2] reactions which can be used in homologative reactivity umpolung as defined here are the degradation methods according to *Baeyer-Villiger*, *Beckmann*, *Hofmann-Curtius-Lossen-Schmitt*, *Hunsdiecker* (all RCOR′ or RCOOH→ROH, RNH_2), and *Barbier-Wieland* ($R_2CHCOOH \rightarrow R_2CO$) in which carbon functions as a leaving group and is replaced by a heteroatom (N or O).

3.4. Use of Cyclopropanes

Opening of a cycloalkane with an odd number of carbon atoms and with substituents as indicated in *(36a)* and *(36b)* by donors and acceptors, respectively, constitutes yet another



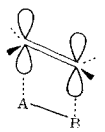
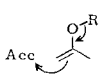
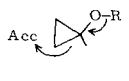
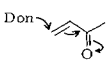
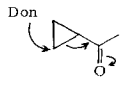
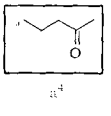
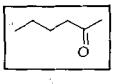
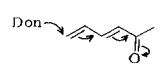
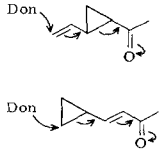
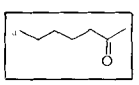
a^{2n}-reactivity d^{2n+1}-reactivity

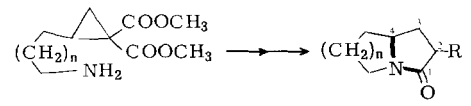
(36a) *(36b)* *(37a)* *(37b)*

principal method of reactivity umpolung. It is related to the homologative method of the previous section by also rendering normal reactivity *(1)* [counting the short distance between the attacked and the functionalized carbon in *(36)*] identical with reactivity umpolung *(10)* [counting around the ring of *(36)*]; the resemblance becomes even closer if we consider that this kind of process is most likely to occur with cyclopropanes (110 kJ/mol strain release), the next higher homologues of "cycloethanes" [see *(37a)* and *(37b)*, and Table 6]. Most of the processes of this scheme were discovered some ten or more years ago[104] (d^3[105a], a^4[105b], a^6[105c]), but only recently have they been exploited systematically for this purpose; improved methodology of cyclopropanation[104, 106] was a prerequisite. A fair coverage of the field is not possible in the present article[107]; only a few illustrative examples will be mentioned.

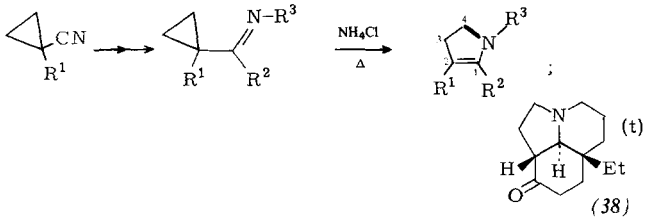
In the field of heterocyclic chemistry and natural product synthesis, the construction of pyrrolines, pyrrolidines, tetrahydrofurans, γ-lactones and γ-lactams is a problem of reactivity umpolung because in all of these five-membered rings, the chain of carbon atoms is 1,4-bifunctionalized. It is therefore not surprising that cyclopropanes have been widely applied in this area. One example each from *Danishefski*'s[108], *Stevens*'[109] and *Wenkert*'s[110] approaches is given in equa-

Table 6. Umpolung of carbonyl reactivity with cyclopropanes.

Synthon	Olefin or "cycloethane"	"Homoolefin" or cyclopropane	Synthon
			
			
			
			

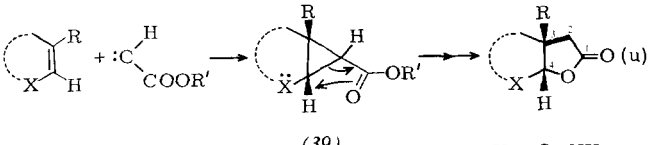


(s)



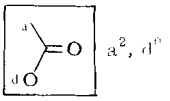
(t)

(38)



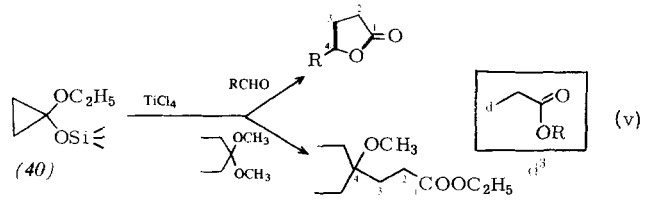
(u)

X = O, $NCOOCH_3$ (39) X = O, NH



tions (s)—(u). In reactions of the type (s)[111] the three-membered ring is opened stereoselectively with inversion; they have been termed homoconjugative additions[108]. The general route outlined in equation (t) was followed in a synthesis of aspidospermine *via (38)*[112]; equation (u) outlines the key step of an eburnamonine synthesis[110,113]. Formally, the 1,4-relationships N—C_4—N and O—C_4—O have been established by an a^4-reaction with a nitrogen or oxygen atom donor in all three cases. The ring enlargements in equations (t) and (u) could also be classified as hetero analogues of the pericyclic vinylcyclopropane → cyclopentene rearrangement. The carbene used in equation (u) [cf. *(18a)*] corresponds to the a^2-synthon drawn underneath it; in *(39)* a pushing (or donor) effect of Ẋ is probably also involved [cf. *(36a) and (36b)*].

Stobbe-type conversions are possible with the cyclopropanone acetal *(40)*[114] [eq. (v)], a^6-reactivity was observed

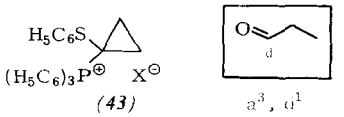


(v)

(40)

(w)

(41) d^3 (42) a^4, d^2

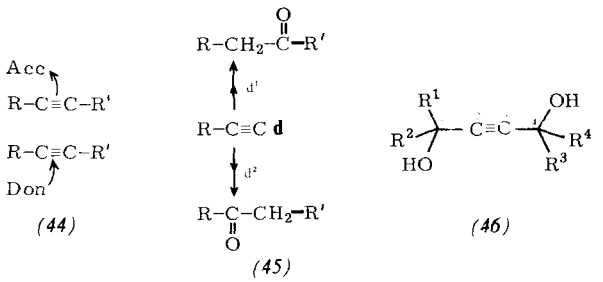


(43) a^3, d^1

with the methyl(vinylcyclopropyl) ketone shown in equation (w)[115], methoxycyclopropyllithium *(41)* is a propionaldehyde d^3-reagent[116], and the phosphonium salts *(42)*[117] and *(43)*[118] are used in cyclopentane annelations to 1,3-dicarbonyl derivatives [cf. the synthons with *(18b)*; see also Section 5, *(77)—(82)*, eq. (av) and Table 9].

3.5. Acetylenes

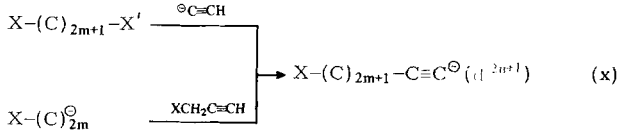
Acetylenes are extremely versatile synthetic intermediates[119]. The highly reactive, "strained" triple bond can be attacked by electrophiles or nucleophiles [see *(44)*, and compare *(18a)*], terminal acetylenes are rather strong CH-acids, and the acetylides obtained by deprotonation are very good, non-hindered nucleophiles [*(45)*] (compare *(18a)*, acyl



(44) (45) (46)

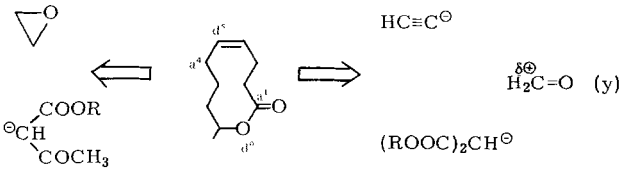
d^1-reagents]. Acetylene itself is therefore a welcome moiety for the synthesis of 1,2*n*-bifunctional systems *(46)* [see *(17a)*]. An advantageous stereochemical aspect is that disubstituted alkynes can be selectively hydrogenated to (*E*) *or* (*Z*)-olefins.

If acetylene is attached to a molecule of normal reactivity (*1*), a carbon framework with reactivity umpolung (*10*) results [eq. (x)]. This principle is used if propiolic acid or propargyl



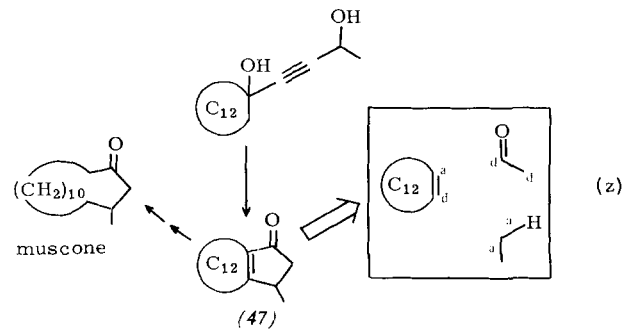
(x)

derivatives (aldehyde, alcohol, bromide) (d^3) or 4-pentynoic acids (d^5) are employed[120]. If one traces back the components of the synthesis of phoracantholide, one finds that the ultimate



(y)

reagents with reactivity umpolung are oxirane (see Section 3.1) and acetylene [see eq. (y)][121]. A recent muscone synthesis



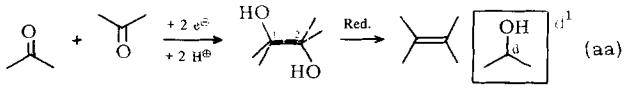
(z)

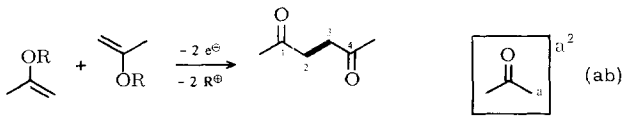
muscone (47)

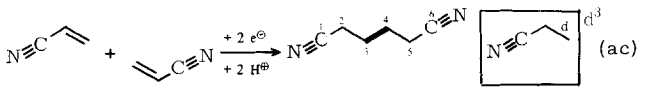
via (47) uses cyclododecanone, acetaldehyde and acetylene as components[122]; these are first joined to a 1,4-diol which is cyclized by sequential Rupe-Meyer-Schuster and Nazarov reactions[2]. Acetylene corresponds to a d^1,d^2-synthon [cf. eq. (z)].

3.6. Redox Reactions

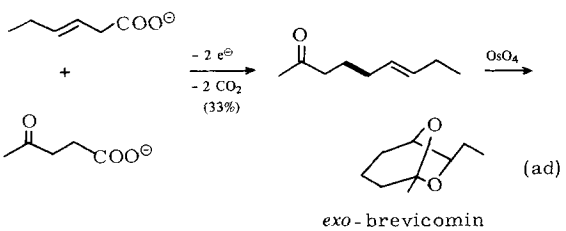
Conceptually, the most simple method of reactivity umpolung is the addition or removal of electrons in a system which is electrophilic or nucleophilic, respectively. This will of course reverse the reactivity of the species (cf. also the formation of a Grignard reagent in Table 4, entry 3). Thus, we can reduce ketones and aldehydes to pinacols [eq. (aa)] and esters to acyloins[123] by electrochemical[124] or photochemical[125] methods or with metals[126]; further reduction leads to olefins which can now be obtained directly from ketones with low-





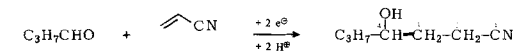
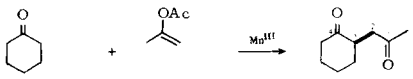
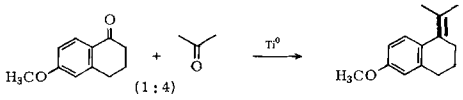
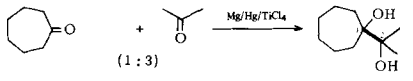
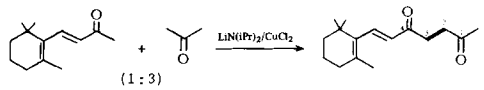


alkali metal, is readily accomplished[126], while we do not normally cleave pinacols and olefins by such simple methods. The products mentioned—except for the olefin—are 1,2*n*-bifunctional and have been made by joining carbon atoms of the same polarity (cf. queries 1 and 3 in Section 2). We formally obtain these products, if we assume that half of the starting molecules are converted into reagents with reactivity umpolung [see the $d^{1,3}$- and a^2-synthons in eqs (aa)—(ac)] and then couple with the other half of normal reactivity. In reality, of course, radical anion or cation coupling (r-reactivity[1c]) furnishes the products in most cases. Therefore, it is difficult to prepare cross-coupling products in better than statistical amounts, unless we carry out intramolecular reactions[137]. Some exceptions to this statement are listed in Table 7; a confirmation is the still very short and efficient synthesis of the pheromone brevicomin[139,140] [equation (ad) (Kolbe carboxylate electrolysis[2])].

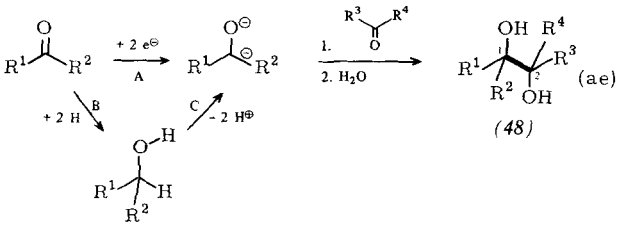


A way out of the problem of "self condensation" or scrambling, when *selective* cross coupling is desired, is being systematically investigated by our group[4f,65,142-148]. The principle

Table 7. Examples for cross-coupling of carbonyl derivatives to olefins, pinacols, and 1,4-dicarbonyl compounds.

Coupling reaction	Yield [%]	Ref.
		[141]
	20—35	[135]
	85	[138]
	75	[130]
	65	[134]

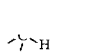
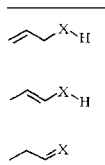
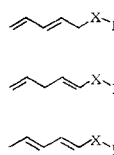
valent titanium[127-131]. Likewise, electrochemical or metal oxidation of enol ethers[132] or enolates[133-135], respectively, furnishes 1,4-dicarbonyl derivatives [eq. (ab)]; electrochemical processes of this type have been called cathodic umpolung[136]. A coupling reaction of industrial importance is the anodic dimerization of acrylonitrile to adiponitrile [eq. (ac)]. The converse of equation (ab), the cleavage of a 1,4-diketone with is described in the accompanying equation (ae). Instead of adding two electrons (A), the π-system is reduced (B) and the resulting dihydro compound is doubly deprotonated (C). The overall result is the same, and no intermediates are involved which could couple with each other. The derivative of the doubly reduced ("LUMO-filled") π-system thus obtained can be added to a different partner to give a "crosslinked



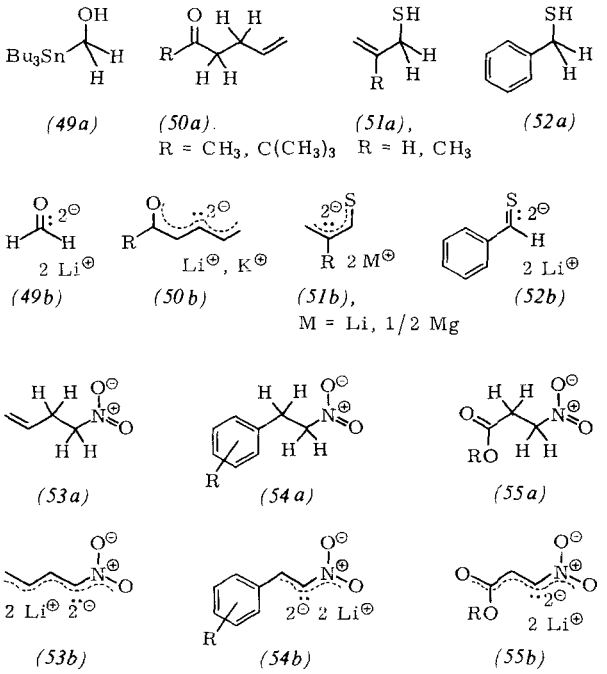
(48) (ae)

dimer", for instance *(48)*. Only a one electron transfer during this latter step could prevent a clean cross-coupling and would lead to scrambling. In the conversion *via* route A, the formerly electrophilic carbonyl carbon has become nucleophilic, an umpolung ("polar reversal", "charge reversal") in the literal sense of the word [see also *(18a)*]. With more extended π-systems, there are several possible hydrogenated precursors to the desired dianion (see Table 8).

Table 8. Doubly reduced π-systems from hydrogenated precursors [see eq. (ae)].

Precursors	"LUMO-filled" π-system	
		2 atoms 4 electrons
		4 atoms 6 electrons
		6 atoms 8 electrons

The smallest system, the formaldehyde dianion *(49b)* could not be generated by double deprotonation of methanol; only tin/lithium exchange in *(49a)* was successful[65] (see also Table 4, entry 4). The other dianion derivatives *(50b)*—*(55b)* are accessible from the "hydrogenated" precursors *(50a)*—*(55a)* and strong base. They preferentially react in the ω-positions with electrophiles. Reagents *(50b)* correspond to d^5-synthons[144b,148]; the lithium compound *(51b)* is attacked at $C^3(d^3)$ by all types of electrophiles[4f,13,142,144], while the magnesium derivative adds to carbonyl compounds with >95 % α-selectivity (d^1); *(52b)* also reacts at the α-S-carbon. The doubly deprotonated nitroalkanes[41] are nitroolefins with reactivity umpolung: while 1-nitro-butadiene is known to accept donors at C^2 or C^4, its dianion *(53b)* (deep-red solution in THF/HMPT, stable at room temperature for a few hours) couples with acceptors (mainly **d^4**-reaction). Similarly, *(54b)* and *(55b)* react with alkyl halides, ketones, and aldehydes at the β-NO_2-position exclusively. It is interesting to note that the nitroolefin dianions *(53b)*—*(55b)* constitute reagents



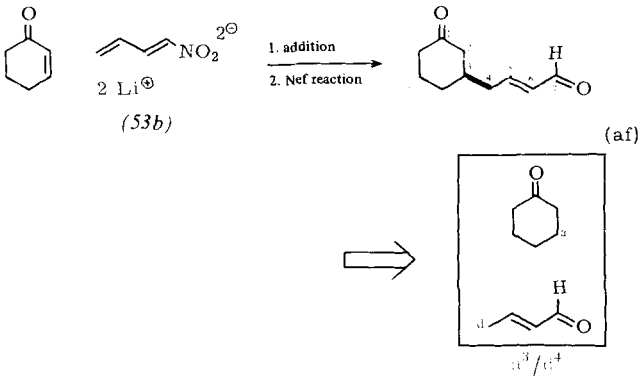
(49a) *(50a)* R = CH_3, $C(CH_3)_3$ *(51a)*, R = H, CH_3 *(52a)*

(49b) *(50b)* *(51b)*, M = Li, 1/2 Mg *(52b)*

(53a) *(54a)* *(55a)*

(53b) *(54b)* *(55b)*

with a double reactivity umpolung if they are used to prepare normal O, N-derivatives (see postulates 1.2—1.4): one is achieved by heteroatom exchange or modification, the other one by the redox method [see eq. (af), cf. eq. (i) and Section 5]. Some amine derivatives with umpolung achieved by going to the doubly reduced state can only be referred to here[149].

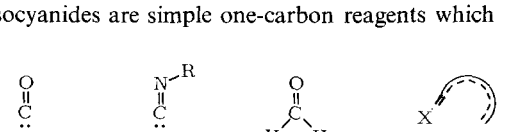


(53b) (af)

4. Direct Umpolung and Substrate Umpolung

4.1. Direct Umpolung

There are of course exceptions to postulate 1.3. If reactivity umpolung is observed without using one of the methods described in Section 3, we call it *direct umpolung*. Carbon monoxide and isocyanides are simple one-carbon reagents which



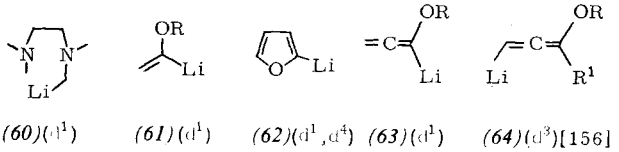
a d **a d** *(56)* *(57)* *(58)* *(59)*

can be attacked by a donor *and* an acceptor [see *(56)* and *(57)* and compare *(18a)*]. Thus, if carbon monoxide, an olefin and water combine to give a carboxylic acid under strongly

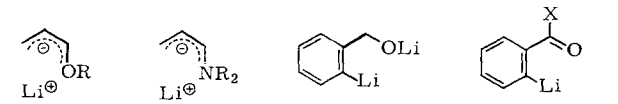
acidic conditions[10b], the CO-carbon atom formally combines with a carbenium ion (**a**/d^1) and $OH^{\ominus}$ (a^1/**d**). Isonitriles are used in the Passerini- and Ugi-reactions (see refs. in [4c]) to prepare α-hydroxy- and α-aminocarboxylic acid derivatives, respectively; given proper substitution in R of *(57)*, Grignard- and lithium-reagents can be added to the carbon atom (a^1) to give an iminoacyl anion derivative; subsequent reaction (d^1) with an electrophile and hydrolysis furnish aldehydes and ketones (Walborsky's method[150]). In the formose reaction[151], formaldehyde *(58)* oligomerizes to give carbohydrates when treated with alkali.

We realize that it is arbitrary to say that CO and CNR are reagents with direct umpolung while we put other, similar compounds [*(27)*—*(31)*, entries 9 and 11—13 of Table 4] into the section on reactivity umpolung by way of heteroatom modification; in *(56)* and *(57)*, not only the carbons but also O and N are in special bonding situations. This is also true of highly conjugated systems such as *(59)*[152]; C^{15} may "not care" whether it is attacked by a nucleophile or an electrophile.

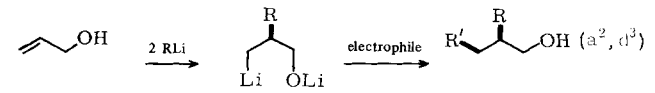
Some unambiguous cases of direct umpolung are the generation of *(60)*—*(68)* directly from the CH-precursors and strong bases, without any of the manipulations described in Section 3. *(60)* is formed by metalation of TMEDA[153] and, like the other α-*O*- and α-*N*-lithium derivatives *(61)*, *(63)*, *(65)* and *(66)*[157], is surprisingly resistant towards Wittig-type rearrangements[154]; *(61)*—*(63)* are also obtained by depro-



(60)(d^1) *(61)*(d^1) *(62)*(d^1,d^4) *(63)*(d^1) *(64)*(d^3)[156]



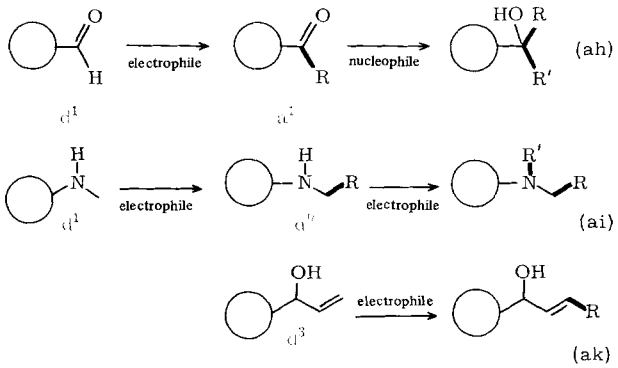
(65)(d^1 or d^3) *(66)*(d^3) *(67)*(d^3) *(68)*(d^3)



tonation[155]; the heterosubstituted allyllithium compounds *(65)* and *(66)* have been discussed in a recent review article[157]. The *ortho*-Li-derivative of benzyl alcohol and a variety of substituted analogues including α-tetralol[158] as well as *(68)*[159] are only two examples of a large number of similar reagents which are formed by direct *ortho*-metalation[160]. Equation (ag) shows a conversion in which allyl alcohol undergoes sequential a^2- and d^3-reactions[161].—It is important to note that in these cases the lithium is bonded to vinylic, arylic (both sp^2), or allylic carbon moieties and/or is internally complexed (chelation).

4.2. Substrate umpolung

By definition, umpolung must be reversible: the final goal is to make O, N-derivatives of normal reactivity. A reversible umpolung is a sequence of operations by which the reactivity of a functional group can be temporarily reversed, and this is not possible with all the methods mentioned in the previous sections. Should we arrive at a certain stage of a synthesis where we need to perform the conversions (ah)—(ak), this would be a task much more difficult than constructing a "small" reagent molecule with reactivity umpolung. We are here concerned with a more complex molecule whose functional groups must be compatible with all operations necessary to achieve the umpolung. Therefore, this may be called a *substrate umpolung*. Of the methods in Section 3 which fulfill this condition, we have to choose the mildest; the ones which require more stringent conditions will be applicable only for reagent umpolung or in the early stages of a synthesis when there is less complexity.

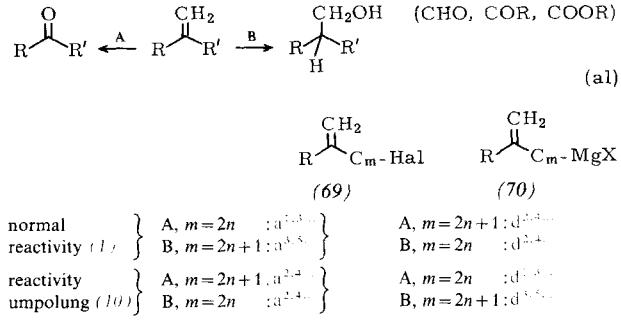


The reversible homologations through cyanohydrins [eq. (n)] and thiazolium derivatives [eq. (o)], and the heteroatom exchange method through thioacetal derivatives[4h] would appear the most promising for the realization of process (ah). The nitrosamine method[4d] [see *(29)*] might be applicable for (ai), and the allyl sulfoxide route[70] (entry 6 in Table 4) for (ak).

5. Analysis of Some Synthetic Methods

There are many possible combinations of the methods described in Sections 3 and 4.1 by which reactivity umpolung can be achieved. An interesting exercise is the analysis of the numerous ways of preparing 1,4-dicarbonyl compounds *(12)*. This has been a very active field because of the importance of jasmonoid, rethrolonoid, and prostanoid synthesis. Extensive review articles on this subject have appeared[113,162]. In the following discussion some reactions will be analyzed which use the six principal methods given in Section 3 in a more or less 'disguised' way.

One such case is the *use of ω-functionalized terminal olefins* (see *Lednicer*'s article on latent functionality in ref. [5])[163]. This method is based on the oxidative cleavage to a carbonyl

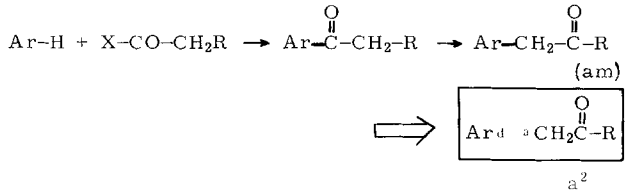


(69) *(70)*

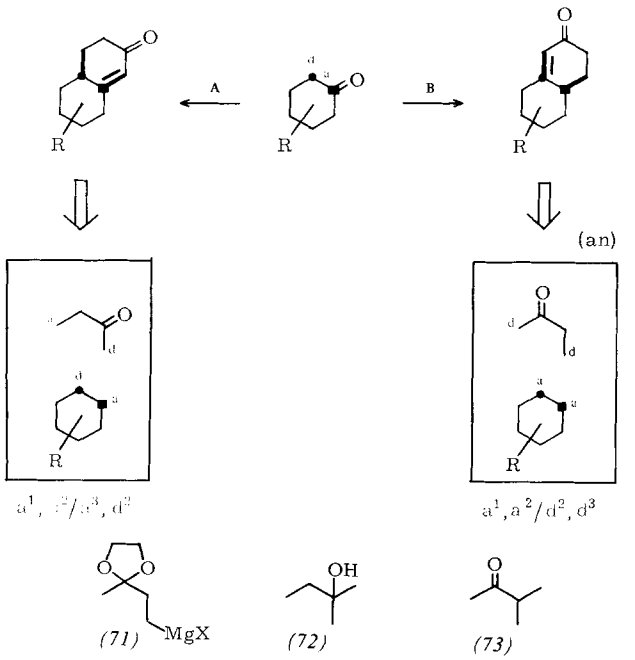
normal reactivity (*11*)	A, $m=2n$: $a^{1,3,5}$	A, $m=2n+1$: $d^{1,3,5}$
	B, $m=2n+1$: $a^{1,3,5}$	B, $m=2n$: $d^{1,3}$
reactivity umpolung (*10*)	A, $m=2n+1$: $a^{2,4}$	A, $m=2n$: $d^{2,4}$
	B, $m=2n$: $a^{2,4}$	B, $m=2n+1$: $d^{2,4}$

compound, [eq. (al), route A], the anti-Markownikoff hydration [eq. (al), route B] or related reactions of olefinic double bonds, which make the halides *(69)* and the corresponding organometallic compounds *(70)* reagents of normal or reversed reactivity at will. If one also takes the preparation of the halides *(69)* into consideration, one realizes that a combination of heteroatom exchange (Section 3.2), homologation and its reversal (Section 3.3) and 1,2*n*-oxidation (Section 3.1) is at work. The same is true of reagents which contain RO-groups instead of the double bond[164].

Another very useful approach is to combine normal reactivity *(1)* with a *1,2n-functionality transposition*[165] [a 1,(2*n*+1)-transposition will only shift reactivity *within* *(1)* or *(10)*, see below]. A simple example is outlined in equation (am): The 1,2-carbonyl transposition converts the product of the Friedel-Crafts acylation (a^1/d-) into the product of an a^2/d-combination (acylmethylation). All transpositions of this type

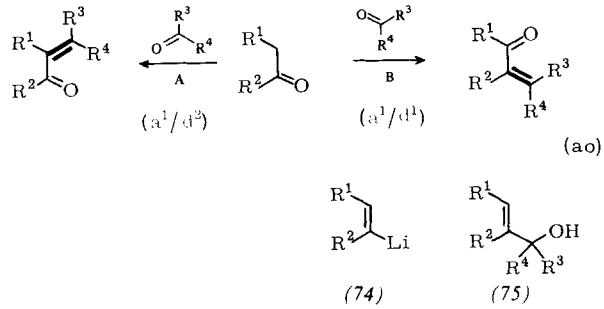


are 1,2*n*-oxidation-reduction processes (see Section 3.1). They either convert the C^1 carbon atom of *(1)* into a donor carbon or they transform d^0 or d^2- into a^0 or a^2-reactivity, respectively (see also Table 3). Two examples are given in equation (an), route B[166], and equation (ao), route B[167a], a "weird" Robinson-annelation [normal: eq. (an), route A][168] and aldol-condensation [normal: eq. (ao) route A][169], respectively. The first sequence of reactions necessitates twofold umpolung. The first one is achieved by heteroatom exchange to *(71)* (Section 3.2), the second one by a 1,2-functionality transposition *(72)* → *(73)* (carried out by dehydration, anti-Markownikoff



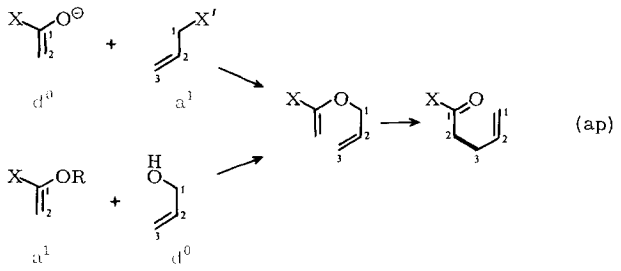
hydration, and oxidation) with an a^0-reagent (BH_3/H_2O_2 corresponds to the HO-a^0 synthon and the H-**d** synthon).

The enone synthesis in equation (ao) uses a reactivity umpolung of the carbonyl carbon [→*(74)*][45,72,167b] with heteroatom exchange methods (Section 3.2) and then a 1,3-transposition of oxygen functionality in *(75)*.



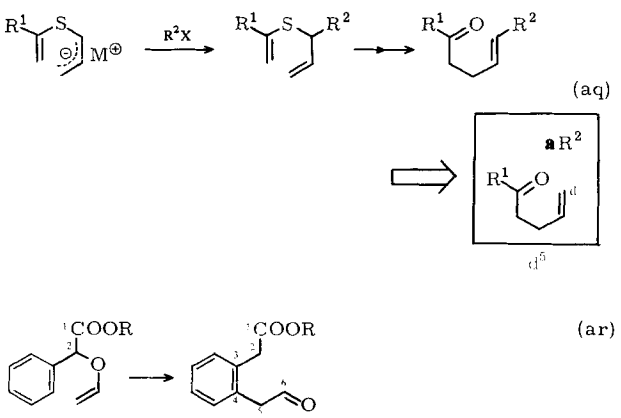
(ao)

Bond shifts with C—C-formation are another important group of synthetic transformations. A [3,3]-shift does not change the relationship (*i.e.* the number of carbon atoms) between functional groups (whether odd or even). The classical Claisen rearrangement[2,170] converts an a^1/d^0- into an a^3/d^2-product [see eq. (ap)]. If a precursor is synthesized with reactivity umpolung [eq. (aq)][171] or from a compound which contains an even number of carbon atoms between the func-



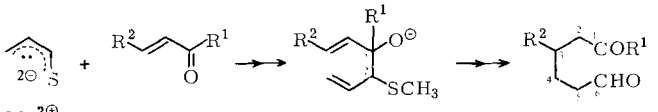
(ap)

tional groups [eq. (ar)[172]], the "even relationship" is preserved in the rearrangement product. The first transformation is realized by the heteroatom exchange method and



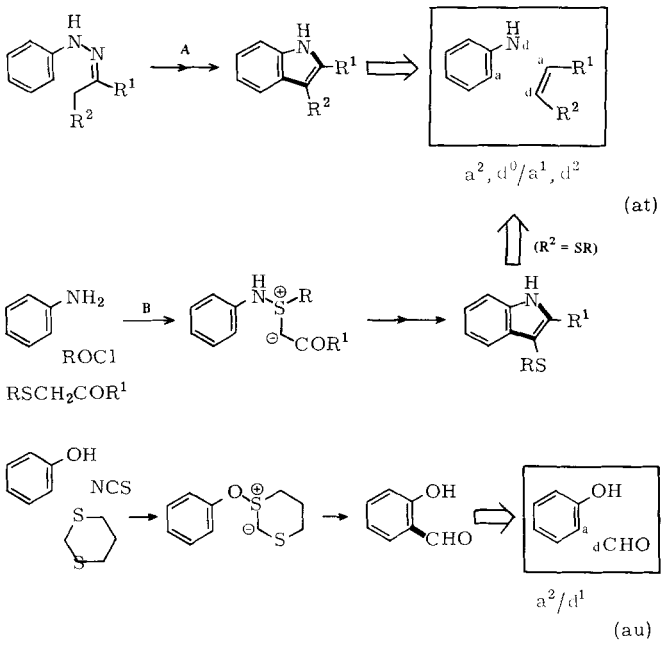
(ar)

a [3,3]-shift which converts the product of a d^1-reaction into that of a d^5-reaction. On the other hand, in equation (ar) one starts with a 1,2-product (see Section 3, "black magic-box" and 1,2*n*-oxidations), a mandelic acid derivative, and furnishes a 1,6-bifunctionalized compound. This is also true of the oxide-Cope rearrangement[2,173] described in equation (as)[4f,142,144]; the reactivity umpolung proceeds *via* heteroatom exchange (Section 3.2).



(as)

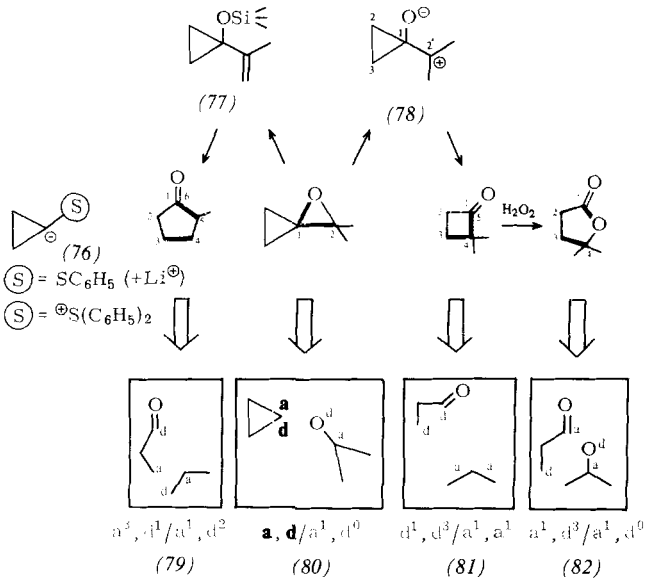
If a molecule contains X—X'-hetero-hetero bonds [R—O—O—R, R—O—NR_2, R—N=O, R_2C=N(O)R, RO—N=CR_2, R_2N—NR_2, R_2C=N—NR_2, RN=NR, ... or heteroatom exchange analogues], it has a built-in 1,2-oxidation (see Section 3.1 and Table 3), and thus a reactivity umpolung. Therefore, we can consider *Fischer*'s indole synthesis[2] and *Gassman*'s recent modification[174] as a^2/d^2-combinations leading to a 1,4-disubstituted carbon framework [see eq. (at), routes A and B]. The Reimer-Tiemann-type[2] reaction in equation (au)[175] is obviously an a^2/d^1-combination; both components have reactivity *(10)*, and we must necessarily obtain a 1,(2*n*+1)-bifunctional system—as in the reactivity pattern *(1)* (cf. postulate 1.4).



(at)

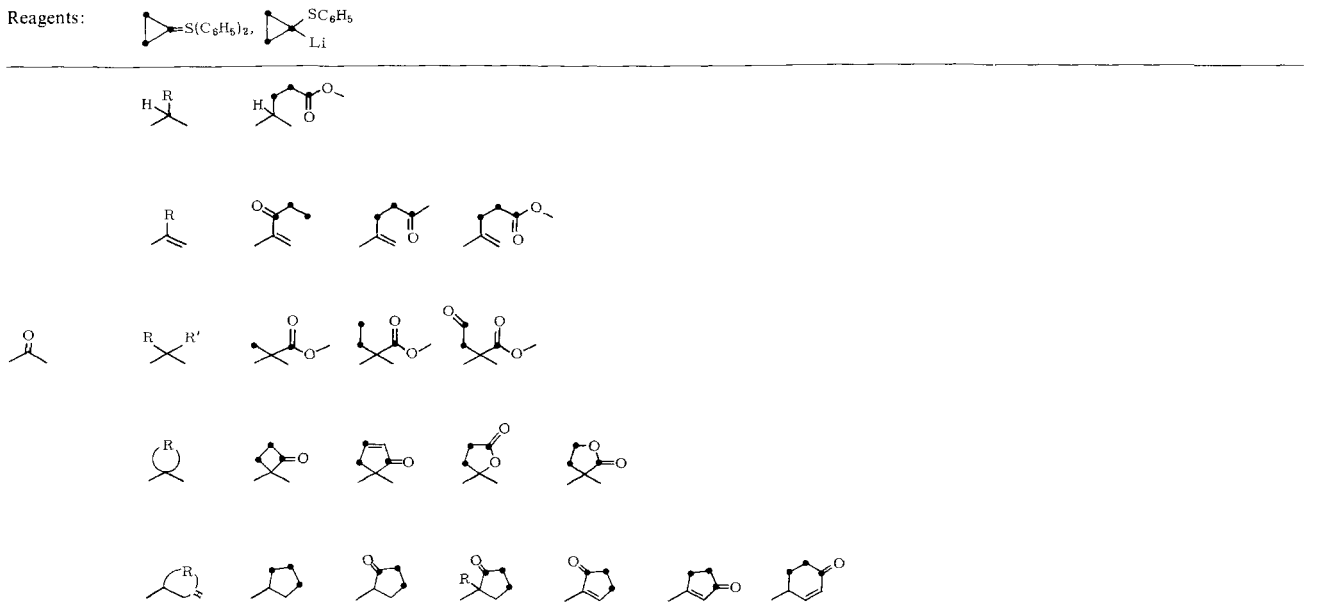
(au)

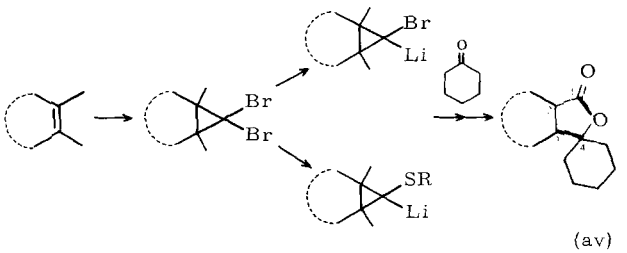
As is evident from Table 9, *Trost*'s cyclopropylidene sulfurane and phenylthiocyclopropyllithium *(76)*[176] are true synthetic chameleons; one can easily count ten different synthon combinations if one compares the products with the starting carbonyl compounds; all of them make at least one bond with reactivity umpolung [see *e.g. (79)—(82)*]. This plethora



of possibilities is obtained by a combination of: 1) heteroatom exchange [Section 3.2, see oxaspiropentane formation *(80)*], 2) the cyclopropane trick [Section 3.4, see *(77)* and *(78)* ($a^{2'}/d^3$)] and 3) the 1,2*n*-oxidation [Section 3.1, see *(82)*]. One limitation of the method, the general lack of availability of substituted reagents *(76)*, can be overcome[39b,177] by starting from dibromo cyclopropanes as outlined in equation (av); they are easily converted into Br/Li-carbenoids or RS-substi-

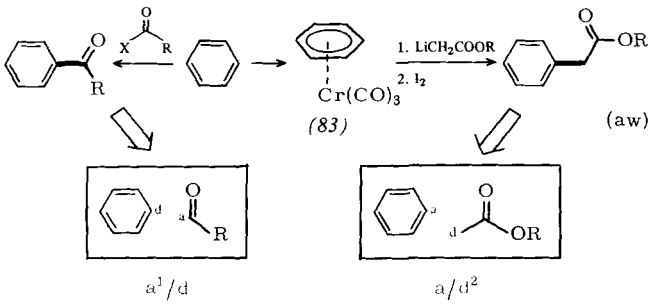
Table 9. Conversions of aldehydes and ketones with sulfur-substituted cyclopropyl nucleophiles of type *(76)*.





(av)

tuted cyclopropyllithium derivatives, which may be up to tetrasubstituted, and which can be used just as the unsubstituted reagent *(76)*. In the overall reaction, the final product in *(46)* is made from cyclohexene, cyclohexanone, and bromoform, which illustrates that this approach constitutes a synthetic elaboration of the ketone *and* of the olefin [39b, 177]. The use of the Trost method for the preparation of 1,6- and 1,8-bifunctionalized carbon skeletons can only be alluded to here[178].



(83) (aw)

a^1/d a/d^2

As last example of a recent, useful development in the field of aromatic substitution with reactivity umpolung, *Semmelhack*'s method[179] is mentioned: formation of the benzene(tricarbonyl)chromium complex *(83)* renders the benzene ring amenable to attack by nucleophiles; instead of the Friedel-Crafts products[2], aryl ketones, α-arylated carbonyl derivatives are formed [see eq. (aw), cf. eq. (am)]. The chromium metal atom decreases the electron density of the benzene ring (lowers the LUMO energy) sufficiently for nucleophilic attack to take place. At least formally, we may say that this is an umpolung by the redox method (Section 3.6).

6. Conclusion

The present article has tried to classify the methods by which reactivity umpolung can be achieved. Hopefully, it will help organic chemists to recognize the necessity of umpolung when planning a synthesis, to see new methods appearing in the literature in a systematic way, and to choose or even discover the best possible reagents for their synthetic problems. Reactivity umpolung is an essential part of synthetic strategy which is now also applied with the aid of computers[180]. It is still a controversial subject among synthetic chemists[181], but highly esteemed in many pharmaceutical and pesticidal industrial laboratories. A most important aspect of organic synthesis, stereochemistry, was naturally excluded from the present discussion, and it is appropriate to stress its importance by quoting: "Stereochemistry rears its ugly head" and "Multistage synthesis: logistics and stereochemistry combine to produce nightmares"[182].

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[23] This is by no means a complete list but a rather deliberate selection of examples.

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