Forschung, Wissenschaft

Nitroaliphatic Compounds – Ideal Intermediates in Organic Synthesis?*

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Dedicated to Professor *E.J. Corey*, on the occasion of his fiftieth birthday.

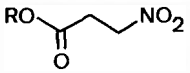
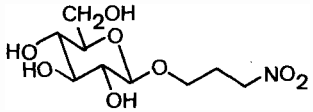
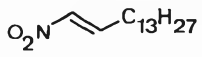
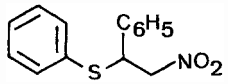
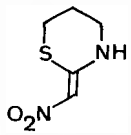
Abstract

Because of improved methods for the conversion of nitroaliphatics into amines, alcohols, and carbonyl compounds, carbon-carbon bond forming processes involving this class of substrate are of increasing importance. This article reviews the work of ourselves and others, and demonstrates that nitroaliphatic compounds can show either electrophilic or nucleophilic reactivity at the α-, β-, γ-, and δ-positions.

Contents

On reading the current literature, one notices a considerable increase in the use of aliphatic nitrocompounds, sought primarily as intermediates towards more complex, nitro-free structures, and rarely as target molecules in their own right; indeed, there are few examples of naturally occuring nitro-aliphatic compounds, or of synthetic products which have found significant biological use (see Table 1).

Table 1: Some Selected Naturally Occurring and/or Biologically Active Aliphatic Nitrocompounds. For further examples, see ref. [1d].

		Reference
	ubiquitous in plants	[1d]
	Miserotoxin – occurs in vetches, causes livestock poisoning	[2]
	Cuban termite soldier defensive compound	[3]
	Fungicide and acaricide	[1d]
	Insecticide	[4]

It is the purpose of this article to highlight some of these more recent applications. Existing reviews [1] either do not stress the broad synthetic utility of aliphatic nitrocompounds, or are devoted to more specialised areas of the field.

To make any claim for extensive utility of a particular class of compound, one must first demonstrate not only a ready availability by a variety of routes, but also a breadth in the scope of subsequent interconversions.

A. Preparation of Aliphatic Nitrocompounds without C–C Bond Formation

Scheme 1 surveys general routes to nitroaliphatic compounds. It is evident that all of the classical organic

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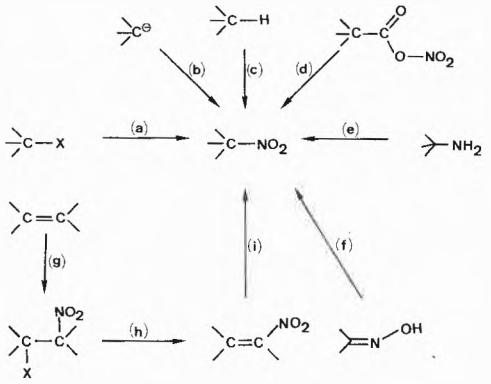
reactions, such as nucleophilic substitution, electrophilic addition, and oxidation processes can be used to good effect. Nitrocompounds are accessible from substrates such as alkylhalides (a), carbanionoids (b), hydrocarbons (c), carboxylic acids (d), amines (e), oximes (f) and alkenes (g → i).

All the illustrated methods have been known [1] for some time, and many have undergone recent improvement; a selected range of such improvements is given in Table 2.



Scheme 1: Preparation of Aliphatic Nitrocompounds without C–C Bond Formation

Table 2: Experimental Conditions for Reactions of Scheme 1

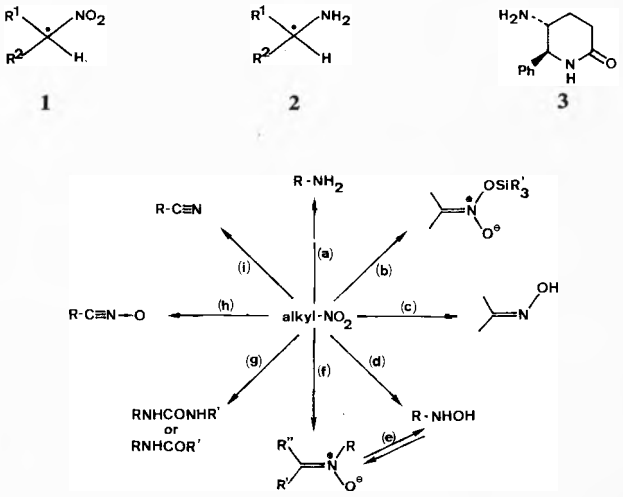
Formal Reaction Type in Scheme 1	Conditions and Range of Yields		References
(a)	MNO_2-18-crown-6	35–70%	[5]
	$R_4N^{\oplus}NO_2^{\ominus}$		[6]
	$NaNO_2$-$(CH_3)_2SO$	40–70%	[7]
(b)	KNH_2-liquid NH_3- $RONO_2$	40–70%	[8]
	$FC(NO_2)_3$	89%	[9]
	$NO_2^{\oplus}BF_4^{\ominus}$	45–90%	[10]
	$LiN[CH(CH_3)_2]_2$–$RONO_2$	50–65%	[11]
(c)	HNO_3		[1a]
(d)	200 °C	25–65%	[12]
(e)	SiO_2–O_3	44–70%	[13]
	$KMnO_4$	30–50%	[14]
	3-$ClC_6H_4CO_3H$	58%	[15]
(f)	Cl_2; O_3; H_2–Pd	40–90%	[16]
	CF_3CO_3H	30–50%	[1a]
(g)	X = I, N_2O_4–I_2	80–90%	[17]
	X = F, $NO_2^{\oplus}BF_4^{\ominus}$-HF-Pyridine	45–70%	[18]
	X = NO, NO		[19]
	N_2O_3		[20]
	X = $OCOCH_3$, $NO_2^{\oplus}BF_4^{\ominus}$-$(CH_3CO)_2O$	45%	[21,42]
(h)	X = OSO_2CH_3, $(C_2H_5)_3N$	70–80%	[22]
(h) → (i)	X = ONO_2, $NaBH_4$–C_2H_5OH	60–90%	[23]
	X = $OCOCH_3$, $NaBH_4$–DMSO	40–70%	[24]
(i)	$NaBH_3CN$–C_2H_5OH–HCl	70–90%	[25]
	$NaBH_4$–ROH	70–95%	[26,41]

B. Conversion of Aliphatic Nitrocompounds into other Functionalised Derivatives, without Change of the Carbon Skeleton

1. Nitrogen derivatives

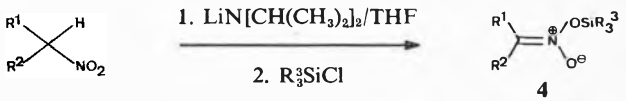
As shown in Scheme 2, nitroalkanes can be reduced to amines (a), amides (g), hydroxylamines (d and e), nitrones (f), oximes (c), nitriles (i), or converted into nitrile oxides (h) or silyl nitronates (b). The conditions required to effect these transformations are described in Table 3.

In anticipation of some of the stereoselective results to be discussed in Chapter D, it is important to mention at this point that the reduction **1** → **2** without epimerisation is best achieved with Fe-acetic acid or catalytically [34]. In this way, the aminopiperidone **3** was obtained [56a].



Scheme 2: Conversion of Nitroalkanes into other Nitrogen Derivatives

The silyl nitronates **4** [(b) in Scheme 2] have been synthesised only recently [36–38], and are best obtained [36] using lithium diisopropylamide and quenching the resulting lithium nitronate with a trialkylsilyl chloride, followed by non-aqueous isolation procedures.



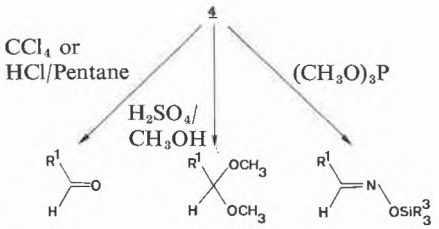
R^1/R^2 = n-C_5H_{11}/H, R_3^3 = $(CH_3)_3$ or $(CH_3)_2$t-C_4H_9
= C_6H_5/H, R_3^3 = $(CH_3)_2$t-C_4H_9
= $H_5C_2OCO(CH_2)_2$/H, R_3^3 = $(CH_3)_3$
= CH_3/CH_3, R_3^3 = $(CH_3)_2$t-C_4H_9
= n-C_6H_{13}/CH_3, R_3^3 = $(CH_3)_2$t-C_4H_9
= -$(CH_2)_5$-/H, R_3^3 = $(CH_3)_2$t-C_4H_9

The yields range from 85–90%, and the products are remarkably stable if kept anhydrous (even at temper-

Table 3: Experimental Conditions for Reactions of Scheme 2

Formal Reaction Type in Scheme 2	Conditions and Range of Yields		References
(a)	H_2-catalyst	50–100%	[27, 56]
	$Al(Hg)—H_2O$		[28, 134]
	$LiAlH_4$	50–100%	[29, 36, 84]
	$Li[(CH_3OCH_2CH_2O)_2AlH_2]—C_6H_6$	75–85%	[30]
	$NaBH_4$—RSH	30–50%	[31]
	$KHFe(CO)_4$		[32]
	Sn—HCl	57%	[33]
	$Fe—CH_3CO_2H$		[34]
	$e^{\ominus}$-H_2SO_4		[35]
(b)	$LiN[CH(CH_3)_2]_2—R^1_3SiCl$	85–90%	[36]
	$(C_2H_5)_3N—(CH_3)_3SiCl$		[37]
	$CH_3C[OSi(CH_3)_3]=NSi(CH_3)_3$		[38]
(c)	$CuOCOCH_3—CO—H_2N(CH_2)_3NH_2$	52–89%	[39]
	$CrCl_2$		[40]
	Zn-CH_3CO_2H	81–88%	[41]
	Fe-CH_3CO_2H		[42]
	HCl gas or HBr		[43]
	$h\nu$		[44]
	n-C_4H_9OH-heat		[45]
(d)	$Al(Hg)$-H_2O		[28, 46]
	Zn-$H^{\oplus}$	20–30%	[47]
	$H^{\oplus}$, $(CH_3CO)_2O$, or $h\nu$		[48]
(e)	conc. HCl	50–70%	[49]
(f)	RMgBr	30–50%	[50]
	Zn-$H^{\oplus}$-intramolecular trapping	50–70%	[51]
(g)	$R^1NHMgBr$-$Fe(CO)_5$	42–99%	[52]
	$R^1COFe(CO)_4^{\ominus}$	71–86%	[53]
(h)	$ArNCO—R^1_2N$		[54]
(i)	PCl_3-pyridine	30–80%	[55a]
	$NaBH_2S_3$	80%	[55b]

atures in excess of 100 °C). This is in marked contrast to the thermal lability of alkyl nitronate esters, which readily fragment into carbonyl compounds and oximes [57].



Scheme 3: Some Transformations of Silyl Nitronates

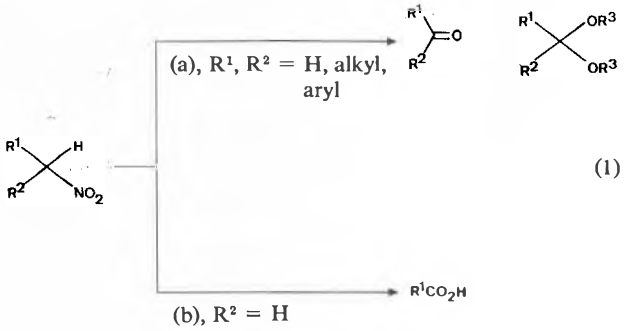
Silyl nitronates show considerable synthetic promise. Preliminary experiments [83] with those derived from primary nitroalkanes show that they can be converted into aldehydes, acetals, and oxime silyl ethers (Scheme 3). For further applications, see Chapter D3.

2. Oxygen Derivatives

The *Nef* reaction [1, 58] (Equation 1a) is one of the most important transformations of nitroalkanes.

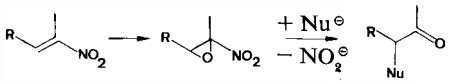
In common with a number of other classical reactions, the method can be capricious, with success often depending on the particular structure of the substrate. Consequently, organic chemists have developed several variations of the original procedure of solvolysis of alkali nitronates with aqueous or alcoholic sulphuric acid. Such variations include reductive [Ti(III), V(II)] and oxidative (O_3, RONO) conditions, as well as the use of sodium methoxide impregnated silica gel (for examples and conditions, see Table 4).

With concentrated mineral acid [1] or $NaNO_2$/RONO/dimethylsulphoxide (DMSO) [79, 84] primary nitroalkanes are converted into carboxylic acids (Equation 1b).



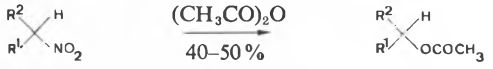
(1)

Equation (2) illustrates sequential nucleophilic substitution and a *Nef* reaction [85] (the nitroolefin is acting as an electrophilic enolate equivalent; see Scheme 4). Equation (3) shows [1a, 86] that the *Nef* reaction can be combined with a *Schmidt* rearrangement, yielding amides. The direct conversion [1a] of nitroalkanes into acetates is alluded to in Equation 4; the scope of this process is at present largely undefined.



(2)

(3)



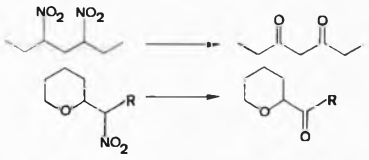
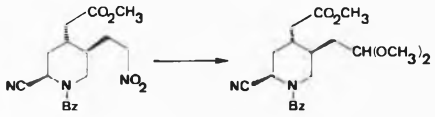
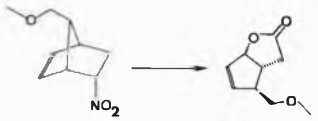
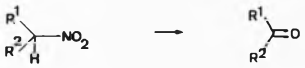
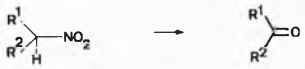
(4)

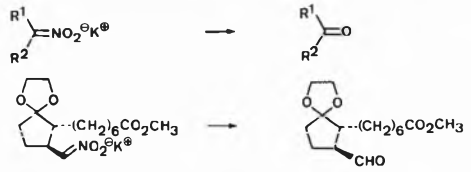
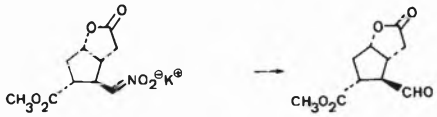
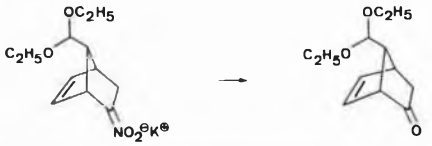
R^1 = H, R^2 = H, CH_3
R^1 = CH_3, R^2 = n-C_6H_{13}
R^1, R^2 = CH_3, -$(CH_2)_5$-

3. Nitrite as a Leaving Group

In addition to being a precursor [84, 87] to almost all of the common organic functionalities (Scheme 2, Tables 3, 4, Equations 2–4), the nitro moiety can also undergo removal under eliminative or reductive conditions (see Table 5).

Table 4: The *Nef* Reaction

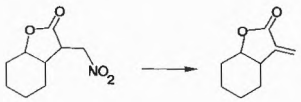
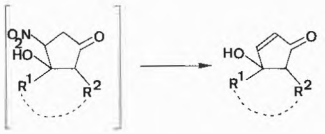
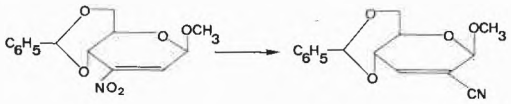
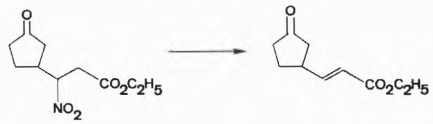
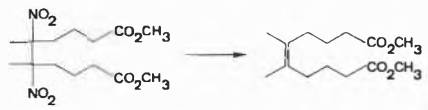
Conditions	Examples and Yields		Refer-ences
1. Solvolytic			
i, $(CH_3)_2NH$; ii, HClaq		39 % 55–65 %	[59]
i, NaOH–C_2H_5OH; ii, HClaq		70 %	[60]
i, $NaOCH_3$–CH_3OH; ii, H_2SO_4–CH_3OH		78 %	[61]
i, NaOH; ii, HCl; iii, $NaNO_2$–$H^{\oplus}$		60–70 %	[62, 63]
i, $NaOCH_3$; ii, H_2SO_4aq		56 %	[62, 64]
i, NaOH–H_2O–THF; ii, H_2SO_4		45 %	[65]
2. Reductive			
i, $NaOCH_3$; ii, $TiCl_3$–NH_4OCOCH_3	 R^2 = alkyl, H	50–90 %	[66]
$TiCl_3$–H_2O	 n = 2, 3	55 %	[67]
i, VCl_2–H_2O–DMF; ii, NaOH	 R^2 = alkyl, H	24–70 %	[68]
$CrCl_2$–CH_3OH		50–75 % (as d. n. p.)	[69]
ascorbic acid-HCl		25–35 %	[70]

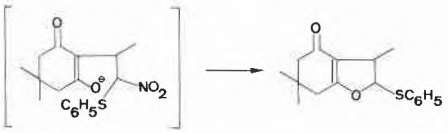
Conditions	Examples and Yields		References
3. Oxidative			
$KMnO_4$—$MgSO_4$		75–95%	[71] [72]
$NaMnO_4$-borate buffer		70%	[73]
$(NH_4)_2S_2O_8$		20–50%	[70, 74]
O_3		65–90%	[75, 76]
$^1O_2$		66%	[77]
Bu^tOOH—$VO(acac)_2$		62%	[78]
4. Neutral			
$NaNO_2$—C_3H_7ONO—DMSO	 R^1/R^2 = alkyl	70–85%	[79, 84]
5. Solid-phase			
SiO_2-NaOMe		80–95%	[80, 81]
SiO_2		35–65%	[70, 82]

C. Synthesis Design and Reactivity Umpolung

The previous two chapters have demonstrated that nitroaliphatic compounds occupy a crucial position in the interconversion of organic functional groups. However, for any class of compounds to have broad synthetic utility, it must also be amenable to C–C bond-forming processes. For this purpose, nitroaliphatic compounds appear to be especially attractive, since they provide an umpolung of reactivity of amines and carbonyl derivatives (Scheme 4). Thus, electrophilic attack on a nitronate anion at carbon, and conversion of the product into an amine, alcohol or carbonyl compound by the processes already dealt with, dem-

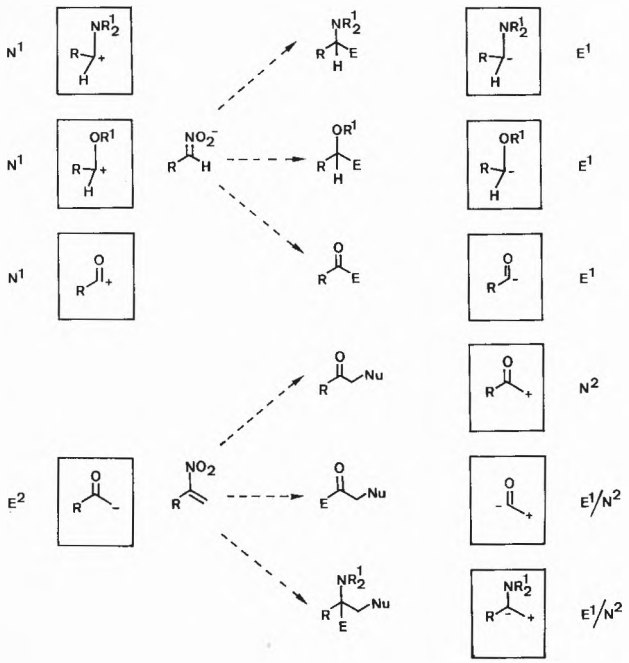
Table 5: Nitrite as a Leaving Group

1,2 Elimination	Conditions and Yields		References
	DBN-DMSO-70 °C or DBN-C_6H_6-25 °C	70–90 %	[88]; see also Chapter G4
	$NaBH_4$		[89]
	*p*H 8 buffer		[90]
	K_2CO_3—CH_3OH	68 %	[91]
	i, $CN^{\ominus}$; ii, $(C_2H_5)_3N$	100 %	[92]
	$AgNO_3$	40–70 %	[93]
	$Cl^{\ominus}$	40–70 %	[94]
	$KOC(CH_3)_3$ or $[(CH_3)_2CH]_2NH$	52 %	[95]
		55–58 %	[95]
	Ca(Hg)-HMPA	65–87 %	[96]
	Na_2S-DMF-hν	80–90 %	[97]
Substitution			
	$NaSCH_3$-DMSO-hν	92 %	[98]

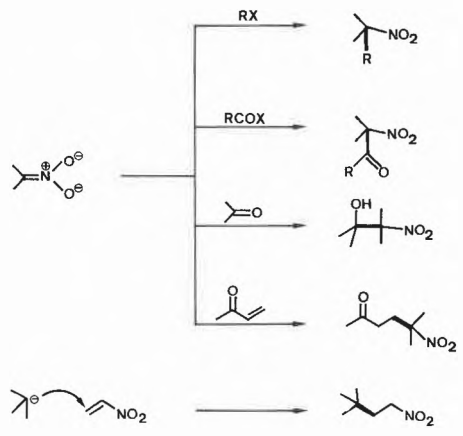
Substitution	Conditions and Yields		References
		55%	[98]
$CH_3NO_2 \longrightarrow CH_3SAr$	$ArS^{\ominus}$	80%	[99]
		71%	[100]

Synthons with normal reactivity

Synthons with reactivity umpolung



Scheme 4: Reactivity Umpolung with Nitroaliphatic Compounds

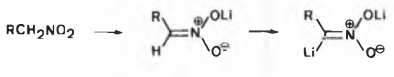


Scheme 5: Carbon-Carbon Bond-Forming Reactions

onstrates that the nitronate ion is synthetically equivalent to the E^1, and not the normal N^1, synthons shown. Likewise, conjugate addition to a nitro-olefin and subsequent transformations illustrate umpolung of reactivity from E^2 to N^2. Such considerations of reactivity umpolung have undoubtedly stimulated much of the recent interest in nitroaliphatic chemistry. The four most important C–C bond-forming reactions with any group of synthetic intermediates are alkylation, acylation, hydroxyalkylation, and conjugate additions. For nitro compounds, these are shown in Scheme 5; the interconnections with Scheme 4 are obvious. Each of these general reactions possesses inherent problems of varying severity, e. g., the reaction of nitronate anions with alkyl halides normally results in O- and not C-alkylation. In the following chapters, the reactions in Scheme 5 will be discussed in detail, with particular emphasis on methods of overcoming such inherent problems.

D. Reactions at the α-Carbon of Nitroalkanes

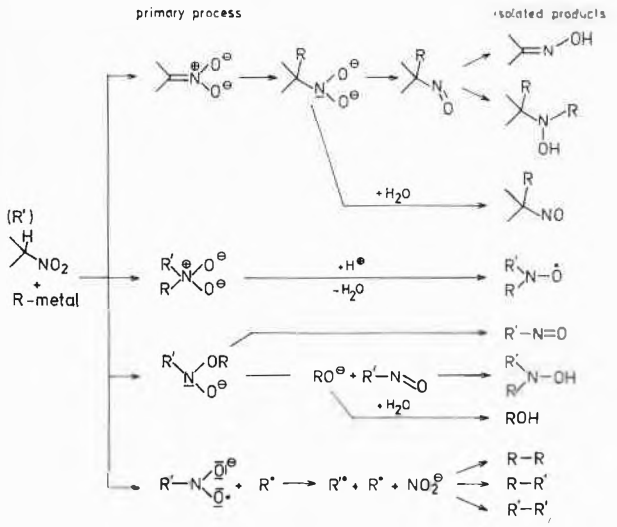
As we have recently found, the poor C-nucleophilicity of nitronate anions **5** can be dramatically improved by formation of the α,α-doubly deprotonated species **6**.



5 **6**

Solutions of the reagents **6** are obtained by rapid addition of two equivalents of n-butyl lithium to a solution of primary nitroalkane in tetrahydrofuran (THF) at − 78 °C in the presence of at least two equivalents of hexamethylphosphoramide (HMPA). While the acidity of nitroalkanes in dipolar aprotic solvents has been determined [102] to be in the range of 15 to 18 pK_a units (aqueous solution [103]: 7.5–10.5), equilibrium studies [83] indicate that the acidity of the remaining nitronate proton of **5** is in the same range as that of diisopropylamine. The relatively high acidity of the proton in **5** has been overlooked until now,

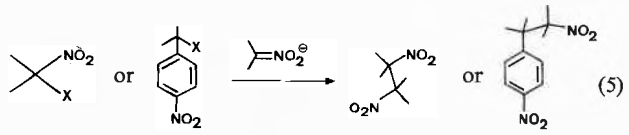
probably due to the plethora of products [1c, 104] which can be isolated from reactions between nitroalkanes and organometallic reagents (Scheme 6) at temperatures ranging from $-40°$ to $+35°C$. Our results constitute yet another example [105] of increasing selectivity with lowering of temperature.



Scheme 6: Reactions of Nitrocompounds with Organometallic Reagents

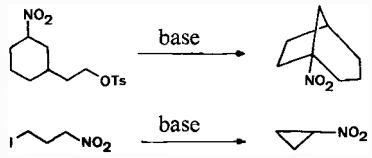
1. Alkylation

Apart from the radical anion chain processes forming highly substituted ethanes (Equation 5) as described by *Kornblum* [1f, 106] there are, to our knowledge, only two cases of C-alkylation of a simple nitronate anion, the intramolecular cyclisations [107] of Equation (6).



(5)

X = Cl, Br, NO_2



(6)

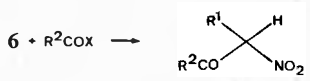
In complete contrast, the dilithio derivatives **6** are smoothly alkylated [108] to the nitroalkanes **7** by primary alkyl and benzyl bromides and iodides in yields of 50–75%.

R^1 = H, C_2H_5, n-C_5H_{11}, C_6H_5, C_6H_5S
R^2 = C_2H_5, n-C_4H_9, n-C_5H_{11}, n-C_6H_{13}, $C_6H_5CH_2$

Some other routes to higher nitroalkanes, most of which are highly specialised, include the electrolysis [109] of boranes in the presence of nitromethane, the palladium/phosphine catalysed reaction [110] between 1,3-butadiene and 2-nitropropane and the trapping of stabilised carbonium ions (tropylium [1a], immonium [1a, 29, 111]).

2. Acylation

As with attempted C-alkylation, most acylating agents attack nitronate anions at oxygen. Some exceptions are methoxy methyl magnesium carbonate (*Stiles'* reagent), aroyl cyanides, and acyl imidazoles (see Table 6). Again, the dilithio derivatives **6** are cleanly acylated [101] to give **8** in isolated yields of 55–80%.

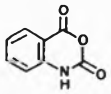
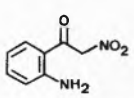


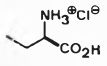
8

R^1 = H, CH_3, C_2H_5, $(CH_3)_2CH$, n-C_4H_9, n-C_5H_{11}, C_6H_5
R^2COX = $(CH_3CO)_2O$, $(C_2H_5CO)_2O$, n-$C_3H_7CO_2CH_3$, $(CH_3)_2CHCO_2CH_3$, $C_6H_5CO_2CH_3$, CH_3OCOCl, $(CH_3O)_2CO$, $(C_2H_5O)_2CO$.

Some of the products **8** have been further transformed by reduction to the α-amino acid **9**, α-hydroxylamino acid esters **10**, α-oximino ketones and esters **11**, or by *Nef* reaction to the α-diketone **12**, and the α-ketoester **13** [83].

Table 6: C-Acylations of Nitroalkanes

Nitroalkane	Acylating Agent	Product and Range of Yields		References
RCH_2NO_2	$CH_3OCO_2MgOCH_3$	$RCH(NO_2)CO_2CH_3$	40–60%	[1a, 112]
$RCH{=}NO_2^-M^+$	R^1COCN	$R^1COCH(R)NO_2$	30–70%	[1a, 113]
$CH_2{=}NO_2^-M^+$	RCOIm	$RCOCH_2NO_2$	50–85%	[114]
$CH_2{=}NO_2^-M^+$				[115]



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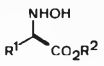
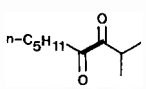


10

R^1/R^2 = C_6H_5/CH_3
= C_6H_5/C_2H_5

11



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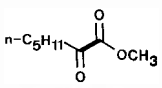
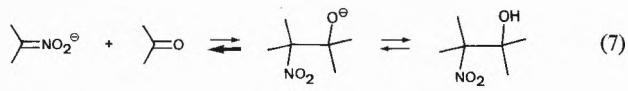


13

R^1/R^2 = n-C_5H_{11}/$CH(CH_3)_2$
= $CH(C_2H_5)C_4H_9$/$CH(CH_3)_2$
= n-C_5H_{11}/OCH_3
= $CH(C_2H_5)C_4H_9$/OCH_3

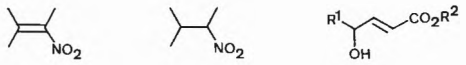
3. Hydroxyalkylation

The addition of nitronates to aldehydes and ketones, the *Henry* [116] or nitro-aldol reaction, is a classical method for C–C bond formation. Due to the ease of its reversibility (Equation 7), it is normally carried out in the presence of only catalytic quantities of base [1a, 117], although in certain cases [118] stoichiometric amounts are used to precipitate the product.



(7)

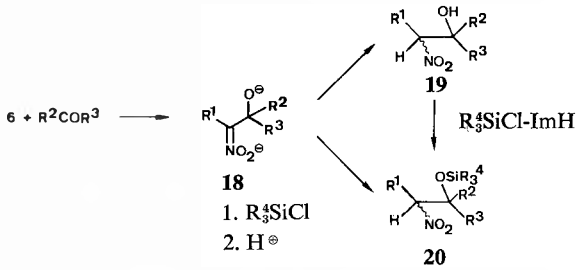
14



15 **16** **17**

A corollary of this reversibility is that yields of isolated nitroalcohols are only high in intramolecularly favoured cases, or with nitromethane and/or aldehydes as reaction partners. The product nitroalcohols can be dehydrated [22,87] to nitro-olefins **15**, which in turn are readily reduced [23–26] to nitroalkanes **16**; this obviously constitutes another way of performing overall C-alkylation of a nitronate anion. Alternatively, base-induced elimination [89] of nitrous acid from suitable nitro-aldols leads to the allylic alcohols [95] **17**; this process was exploited [95] in a recent synthesis of pyrenophorin.

The literature on the *Henry* reaction is vast [1a], and only a few selected recent improvements and applications, with emphasis on our own work, will be given here. Continuing our studies of the dianion **6**, it has been found [83,101,139] that hitherto unavailable nitroalcohols can be readily prepared in yields of 50 to 80%. There is no problem with reversibility, even in the case with benzophenone as electrophile, because in contrast to **14**, **18** is stable, and can be protonated at low temperature to **19**. Alternatively, silylation of **18** and subsequent acidification furnishes the silylated nitro-aldol **20**; this can also be obtained by silylation of **19**. In contrast to nitronates which add to enones exclusively in the 1,4-fashion, **6** furnishes the 1,2-adduct with cyclohexenone [83].



18
1. R^4_3SiCl
2. $H^{\oplus}$

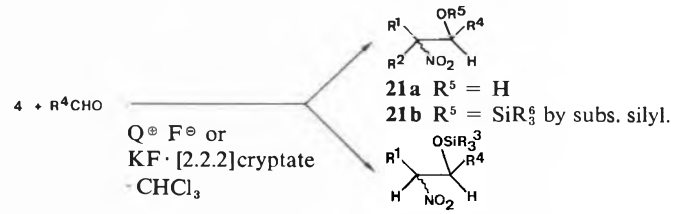
19

R^4_3SiCl-ImH

20

R^1 = C_2H_5, $(CH_3)_2CH$, CH_2=CH, 1-cycloheptenyl, C_6H_5S
R^2 = C_6H_5, R^3 = H; R^2, R^3 = CH_3, $-(CH_2)_5-$, $-[CH{=}CH(CH_2)_3]-$, C_6H_5
R^4_3 = t-$C_4H_9(CH_3)_2$

For the first time, a diastereoselectivity of nitro-aldol formation has been observed [83] in the production of **19** or of **20**; thus, **18** (R^1 = C_2H_5, R^2 = C_6H_5, R^3 = H) on low temperature protonation gives **19** as a 9:1 enriched diastereoisomeric mixture, while quenching with t-butyldimethylsilyl chloride and subsequent acidification gives **20** as a 1:4 mixture of diastereoisomers (unambiguous assignment not yet completed). Another improvement of the nitro-aldol reaction recently accomplished in our laboratories makes use [36] of the silyl nitronates **4**. Such species undergo fluoride ion catalysed reaction with aldehydes (but not with ketones) to give **21a** when silyl nitronates from secondary nitroalkanes are employed, and **22** in those cases with primary nitroalkanes, in good yields in both cases.



Q⊕ F⊖ or
KF · [2.2.2]cryptate
· $CHCl_3$

21a R^5 = H
21b R^5 = SiR^6_3 by subs. silyl.

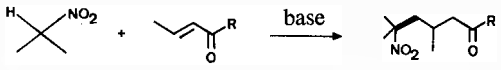
23a R^2 = H, alkyl **23b**

The utility of such silylated nitro-aldols **19**, **21b**, **22** is demonstrated by their facile lithium aluminium hydride (LAH) reduction to 2-aminoalcohols **23**; attempted direct LAH reduction of nitro-aldols such as **21a** results in [36,119] retro-aldol bond scission and subsequent reduction of the original components.

Examples of intramolecular aldol reactions will be found in chapter F, dealing with hetero/homo cyclisation reactions.

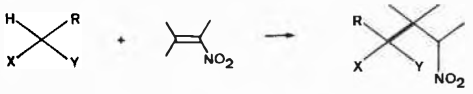
E. Conjugate Addition by α- and at β-Nitro Carbon Atoms

The *Michael* addition of nitroalkanes to α, β-unsaturated aldehydes, ketones, esters, and nitriles, as well as to vinyl sulphones and nitroolefins, is one of the most efficient C–C bond forming reactions (Equation 8) involving nitrocompounds; even nitro-aldols themselves can be added conjugatively to α, β-unsaturated carbonyl compounds under the influence of base [56b]. An exhaustive review is to be found in ref. [1a], pp 182–229, and applications will be discussed in chapter F.



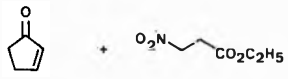
(8)

R = H, alkyl, aryl, O-alkyl
RCO = CN, SO_2R, NO_2



(9)

The same is true of the complimentary addition of active methylene compounds to nitro-olefins (Equation 9), ref. [1a], pp 372–387; this reaction is most successful with well-stabilised anions, yields decreasing with increasing reactivity of the nucleophile, although alkyl groups can be added as dialkyl cuprates [120a] or as cadmium alkyls [120b]. Low temperature addition of alkyl lithium reagents to nitro-olefins, followed by trapping of the resulting nitronate with tetranitromethane provides a route [121] to 1,1-dinitroalkanes. One application of conjugate addition of a nitroalkane to an enone is seen in the use [95] of 3-nitropropanoic acid ester **24** as an acrylate ester β-anion equivalent; the 1,2-addition of **24** to aldehydes was alluded to earlier.



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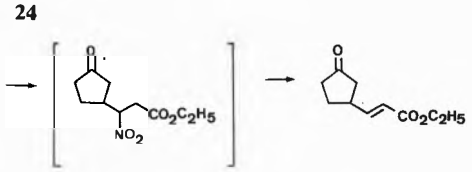
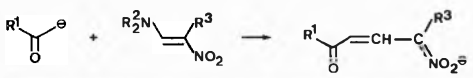
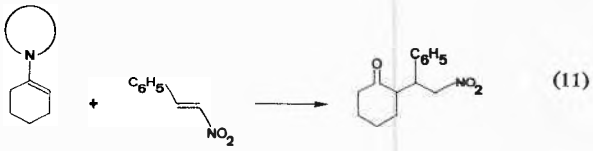


As shown by the work of *Severin* [70,82,122], ester and ketone enolates add smoothly to β-nitroenamines, to give the corresponding *aci*-nitro derivatives (Equation 10), which can be further converted into α, β-unsaturated 1,4-dicarbonyl compounds (see Table 4).



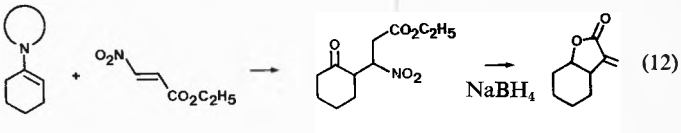
(10)

Enamines themselves react with a variety of nitro-olefins, leading to γ-nitroketones [123] (Equation 11).



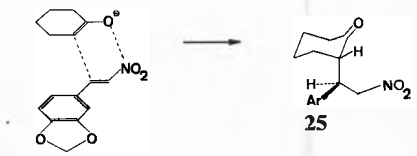
(11)

They also add to 2-nitroacrylate esters [89], ultimately giving α-methylene-butyrolactones (Equation 12).



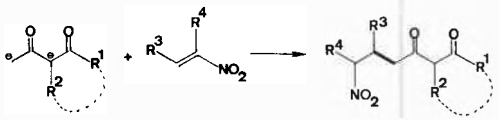
(12)

Our own results indicate that employment of low temperatures can overcome many of the problems of the addition of highly reactive anions; for example, even n-butyl lithium can be successfully added to nitro-olefins if temperatures as low as $-80°$ to $-120°C$ are used [83,84,87,124]. A further example of a highly efficient (93% yield) and stereoselective low temperature addition to an ω-nitrostyrene is seen in the formation of **25** [87,125], exclusively as the *threo* (n) diastereoisomer.



25

A third application of low-temperature conditions is in the conjugate addition of 1,3-dicarbonyl dianions to nitro-olefins, forming 5-nitro-1,3-dicarbonyl compounds **26**; for cyclisation studies with **26**, see Chapter F.



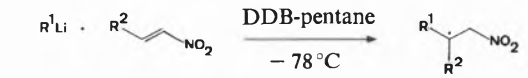
26

Both general conjugate addition processes (Equation 8 and 9) have recently been found to be catalysed by "naked" fluoride ion [100,126,127] use of chiral quaternary ammonium fluorides inducing [127] chirality in the product. Chiral induction can also be attained using DDB [83,128] as co-solvent (Table 7).

F. Carbo- and Heterocyclisation using Nitroaliphatics

Application of the four reaction types so far discussed i. e., alkylation, acylation, hydroxyalkylation, and conjugate additions, leads to a variety of cyclisation possibilities. Thus, while *Robinson* annelation involves 1,5-diketone intermediates, 1,4-diketones are required

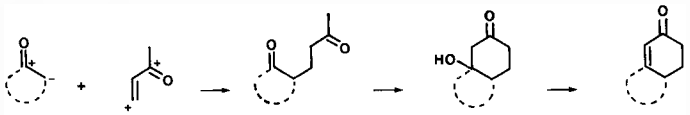
Table 7: Enantioselective Addition of Organolithium, Organocuprate, and Organozincate Reagents to 1-Nitropropene (a) and ω-Nitrostyrene (b)



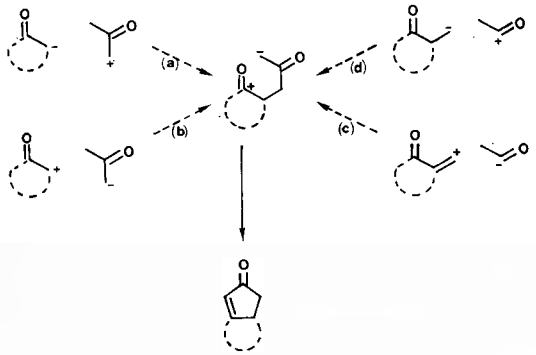
a, $R^2 = CH_3$
b, $R^2 = C_6H_5$

R^1Li		Nitro-olefin	Specific Rotation (c = 5–10, C_6H_6) [% ee] of adduct
$n\text{-}C_4H_9Li$, $(n\text{-}C_4H_9)_2CuLi$, or $(n\text{-}C_4H_9)_3ZnLi$		a	+ 0.82 [28]
$n\text{-}C_4H_9Li$		b	+ 1.22
		a	− 4.3 [43]
		b	+ 0.43
		a	+ 0.05
		a	− 4.25
	R = CH_3	a	− 0.4
	= $C(CH_3)_3$	a	+ 0.12 [6]
	= $N(CH_3)_2$	a	+ 0.64 [12]
		b	+ 1.25 [10]
	= $OC(CH_3)_3$	a	+ 0.10

Robinson Annelation (Cyclohexenone)



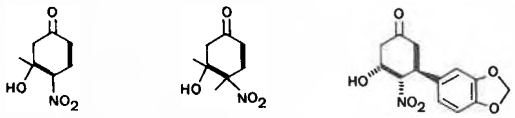
Cyclopentenone Annelation



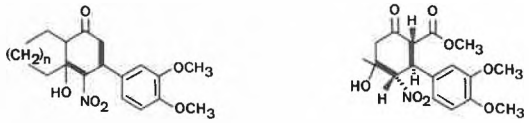
Scheme 7: Ring Forming Reactions with Nitroaliphatic Compounds

for cyclopentenone annelation. Scheme 7 shows the four fundamental modes of construction of such species; each mode contains one synthon with reactivity umpolung, and nitroaliphatic chemistry can readily be used in the conception of three of these, (a) [129], (b) [89], and (c) [66].

Some of the target structures accessible [84, 124] *via* nucleophilic addition to nitro-olefins are shown in Scheme 8. To amplify just one of the reactions shown, the nitrodiketones **26** can be cyclised to highly functionalised six-membered rings **27a–f**; the new bonds formed in the overall process are indicated by heavy lines, and the yields quoted are overall yields from polycarbonyl polyanions and nitro-olefins without isolation of intermediates. Furthermore, the single diastereoisomer formed in each case is easily isolated from the crude reaction product by trituration with dichloromethane.

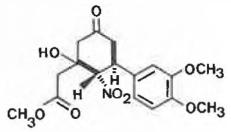


27a (18%) **27b** (45%) **27c** (58%)

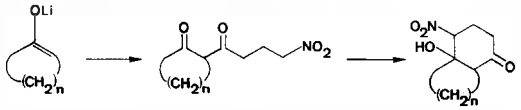


27d, n = 1 (50%)
n = 2 (68%)

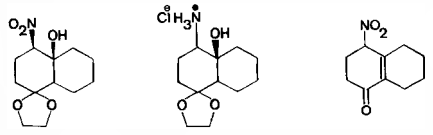
27e (35%)



27f (40%)

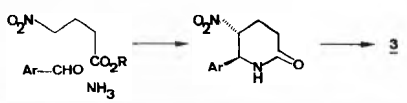


27g, n = 3
27h, n = 9

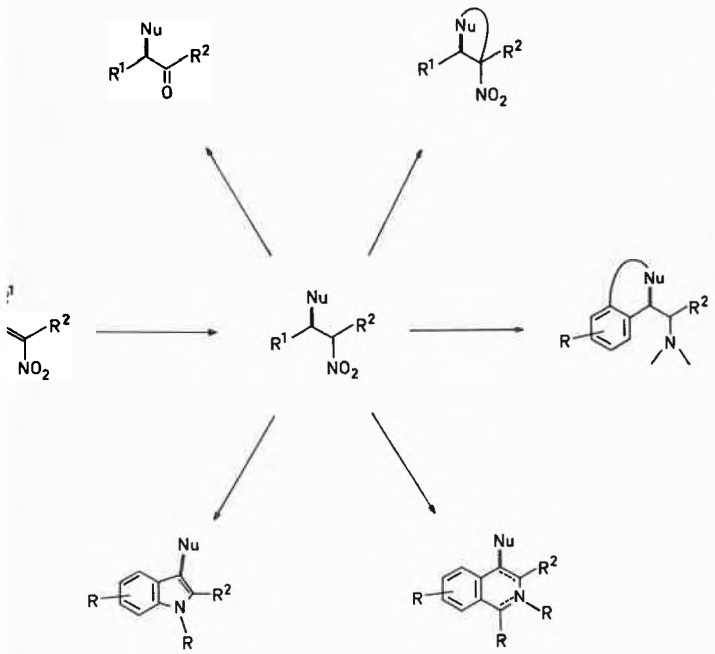


28 **29** **30**

An alternative access to compounds of type **26** is by low temperature acylation [130] of lithium enolates with 4-nitrobutanoyl chloride, followed by cyclisation [83] ($NaHCO_3$/THF) to give, e. g., **27g** and **h**, and the further transformation products **28**, **29** and **30**; Equation (13) shows a further example [56] of the use of 4-nitrobutanoic acid derivatives.

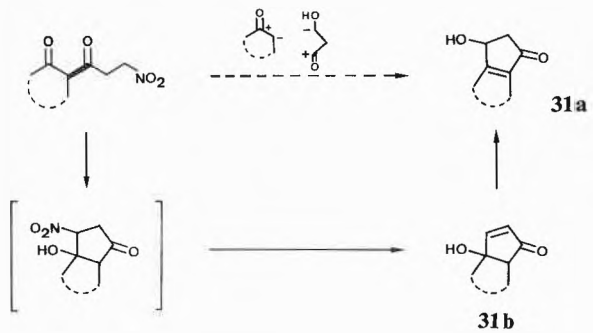


(13)



Scheme 8: Addition and Cyclisation Possibilities with Nitroolefins

A conceptually similar route using 3-nitropropanoyl chloride furnishes a general hydroxycyclopentenone annelation [90,131] of ketones to **31**. The application of this simple two-step reaction to syntheses of prostanoids, rethronoloids and jasmonoids is obvious.



31a

31b

To summarise and further exemplify the usefulness of nitroaliphatic building blocks for ring formation, we have assembled Table 8.

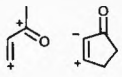
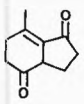
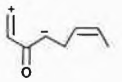
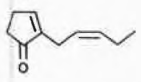
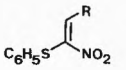
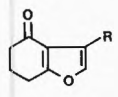
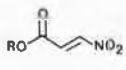
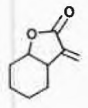
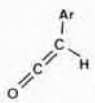
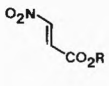
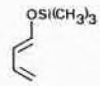
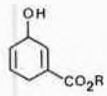
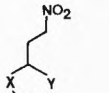
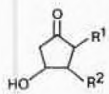
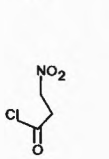
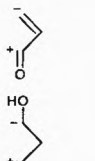
G. Umpolung of Reactivity of Nitroaliphatic Compounds

Nitronate anions are usually considered to be carbon nucleophiles (32b).

a **32** **b**

From **32a**, the nitronate ion should also be an electrophilic carbonyl analogue, although, apart from the *Nef* reaction, few examples of such behaviour are known {see first reaction of Scheme 6 and Equation (14) [1c]; cf. the *Butlerow/Fischer* Formose Reaction [136]}.

Table 8: Nitroaliphatics as Building Blocks for Ring Formation

Nitro-compound	Synthons Nitro-compound	Substrate	Product	Reference
CH_3NO_2				[132]
CH_3NO_2				[65]
				[66]
				[100]
				[89]
				[133]
				[62, 63]
				[91]
				[62, 134]
				[90]
				[129]
				[56a, 83]
				[56b]
				[135]

X = NH
= CH_2

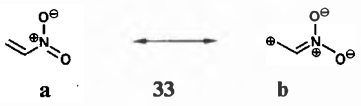
R = $-(CH_2)_4CO_2H$
BIOTIN

$$2\,CH_2NO_2^{\ominus} \rightarrow {}^{\ominus}O{-}N{=}CH{-}CH{=}NO_2^{\ominus} + H_2O \qquad (14)$$

Another unusual type of reactivity is observed in the manganese (III) induced coupling [137] of nitromethane with arenes (Equation 15); the reactive species may be the nitromethyl radical, although its failure to react with nitrobenzene is more suggestive of a radical cation.

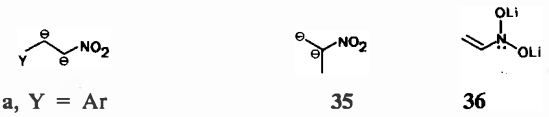
$$CH_3NO_2 + ArH + Mn(OCOCH_3)_3 \rightarrow ArCH_2NO_2 \qquad (15)$$
$$Ar = C_6H_5,\ CH_3C_6H_4,\ CH_3OC_6H_4$$

Nitro-olefins are electrophilic (**33b**) at the β-carbon atom; is it also possible to reverse *this* reactivity?



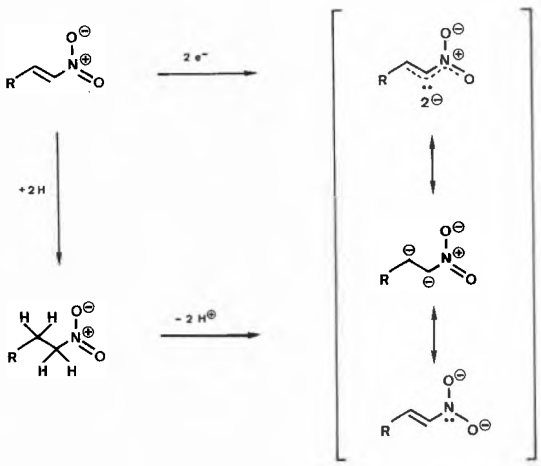
a **33** **b**

A serendipitous discovery in our laboratories has produced an answer [88, 108, 138], to this problem. When we attempted to apply the α, α-double deprotonation (→ **6**) technique to 2-arylnitroethanes, we observed that subsequent reaction with electrophiles led to 2-substituted- 2-arylnitroethanes. The strong base has obviously sequentially abstracted an α- and then a β-proton from the nitroalkane, to give **34a**. The additional acidifying group Y in **34** may also be a vinyl or ester group, but the presence of such a group is not mandatory, as can be seen with 2-nitropropane, which, as it has only one α-proton, gives the α, β-dianion **35** on sequential treatment with n-butyl lithium and t-butyl lithium. We believe that the species actually formed is the dilithio derivative of an N,N-dihydroxyenamine **36** ("superenamine"); this species may also be considered as a reduced form of the nitro-olefin **33a**, see Scheme 9. Formally, the highly electrophilic double bond of a nitro-olefin has become a highly nucleophilic enamine double bond.



34a, Y = Ar
b, Y = $CH_2{=}CH$
c, Y = CO_2CH_3

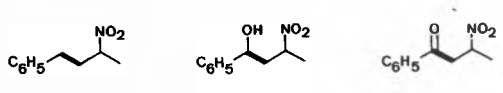
35 **36**



Scheme 9: Equivalence of Nitro-Olefin Two-Electron Reduction with Sequential Hydrogenation and Double Deprotonation to form "Superenamines"

1. α, β-Doubly Deprotonated 2-Nitropropane **35**

The yields of C–C coupling products of the dilithio derivative [83, 138] of **35** are the lowest of this series. Benzylation, hydroxybenzylation, and benzoylation (see Formulae 37a, b and c) proceed in yields of 40, 46 and 30%, respectively.

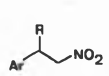


37

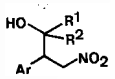
a **b** **c**

2. α, β-Doubly Deprotonated 2-Arylnitroethanes **34a**

Nucleophiles of type **34a** are accessible [138, 139] with a variety of aryl substituents, including chlorine and alkoxy-substituted cases; remarkably, solutions of such nucleophiles are stable for many hours at room temperature. They combine in good to excellent yields with alkyl halides (→ **38**, 60–80%), aldehydes and ketone (→ **39**, 70–90%), and undergo conjugate addi-



38

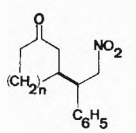


39

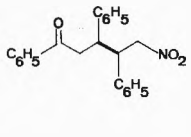
Ar	R
C_6H_5	$C_6H_5CH_2$
1-naphthyl	n-C_4H_9
3,4-$(CH_3O)_2C_6H_3$	n-C_3H_7
4-ClC_6H_4	n-C_6H_{13}

Ar	R^1	R^2
C_6H_5	C_6H_5	H
C_6H_5	4-ClC_6H_4	H
C_6H_5	CH_3	CH_3
C_6H_5	-$(CH_2)_4$-	
1-naphthyl	3,4-$(CH_3O)_2C_6H_3$	H
4-$CH_3OC_6H_4$	3,4-$(OCH_2O)C_6H_3$	H
4-ClC_6H_4	C_2H_5	H
4-ClC_6H_4	C_6H_5	C_6H_5
C_6H_5	$C_6H_5CH{=}CH$	H

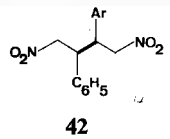
tion to enones (→ **40**, **41**, 50–65%) and to nitro-olefins (→ **42**, 65, 85%); some of these reactions can be performed titrimetrically, using the deep red colour of the dianions as indicator. Other electrophiles such as epoxides (too low reactivity), trimethylsilyl chloride, and acylating agents (attack on oxygen of **34a**?) either do not yield any products at all, or give polymeric materials [88, 139].



40, n = 1,2,3



41

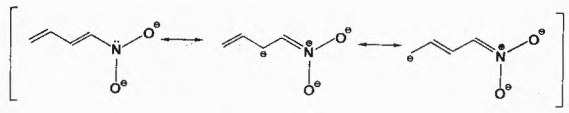


42

Ar = C_6H_5
Ar = 3,4-$(OCH_2O)C_6H_3$

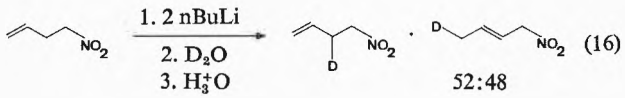
3. 1-Nitrobutadiene Dianion **34b**

4-Nitro-1-butene, when treated with two equivalents of n-butyl lithium in the presence of HMPA, is doubly deprotonated [140] to the dilithio derivative of a dianion **34b**, three further resonance forms of which are shown in **43**; deuterium quenching gives an approximately equal mixture of deuterated isomers (Equation 16, and see **43b** and **c**).



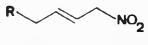
43

a **b** **c**



52:48 (16)

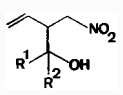
Alkylations of **34b** occur preferentially at the δ-position in yields of 55–75%; the degree of such terminal preference is given in **44**.



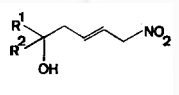
44

R = CH_3 (1.5 : 1)
= $(CH_3)_2CH$ (32 : 1)
= $CH_3CH(OH)CH_2$ (3 : 1)
= $(CH_2)_4CH$ (4 : 1)
= $C_6H_5CH_2$ (4 : 1)
= $C_7H_{15}CH_2$ (7 : 1)

Hydroxyalkylations, on the other hand, show little ambidoselectivity when carried out under conditions of kinetic control (low temperature quenching), giving **45a** and **b** in yields of 60–80%. If however, the reaction mixtures are allowed to warm to room temperature, δ-preferences is greatly enhanced; cyclohexanone and benzaldehyde both then give β/δ ratios of 1 : 9, with no diminution in yield. This proves the reversibility [141] of the addition of **34b** to carbonyl groups, and further emphasises the unusual stability of this dianion (see the dienamine form **43a**).



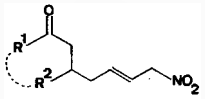
a



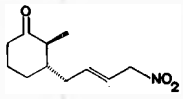
45 **b**

R^1/R^2 = n-C_5H_{11}/H (56 : 44)
= $(CH_3)_3C$/H (52 : 48)
= -$(CH_2)_5$- (50 : 50)
= C_6H_5/H (30 : 70)
= C_6H_5/C_6H_5 (only **45b**)

With enones, we could isolate only products of conjugate addition from the δ-position, giving **46** in yields of 45–70%. Additionally, the primary adduct from cyclohexenone could be trapped with iodomethane to give **47** (enolate trapping, see ref. in [105]).

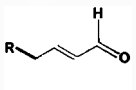


46 R^1/R^2 = -$(CH_2)_n$-, n = 2,3,4
= C_6H_5/C_6H_5

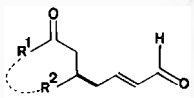


47

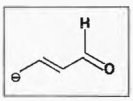
Adducts of type **46** and **47** have been subjected to conditions of the *Nef* reaction ($TiCl_3/H_2O$/THF, see Table 4) to give α,β-unsaturated aldehydes **48** and 1,7-ketoaldehydes **49** respectively; the dianion **34b** may therefore be considered as synthetically equivalent with the enolate **50** of crotonaldehyde, reacting at the δ-position (E^4 synthon).



48



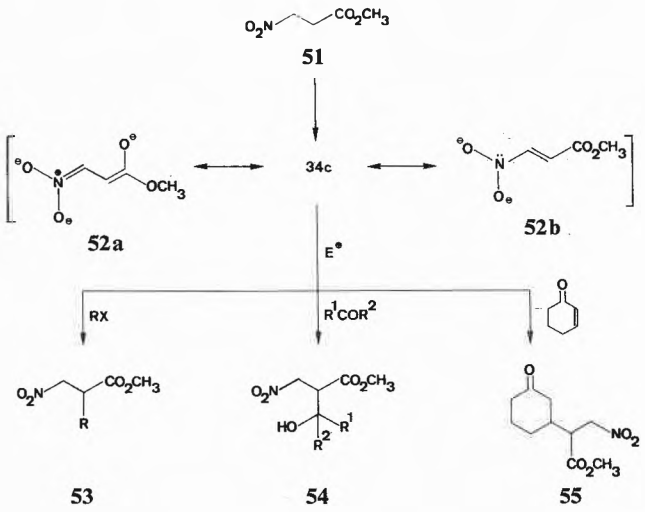
49



50

4. Methyl-3-Nitropropanoate Dianion **34c**

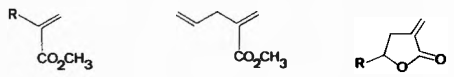
Treatment of methyl-3-nitropropanoate **51** with two equivalents of lithium diisopropylamide in THF/HMPA (5 : 1) at −78 °C generates a clear pale yellow solution of dilithio dianion [108] **34c**, with the nitronate-enolate resonance form **52a** probably contributing more to the overall hybrid than the enamine form **52b**. In common with the other α,β-doubly deprotonated compounds, this dianion combines with electrophiles at the carbon atom which underwent the later deprotonation (*Hauser*'s Rule [142]). In other words, **34c** has the chemical behaviour of the inaccessible enolate of methyl 3-nitropropanoate, the nitro group being "protected" here as its nitronate anion [143]. Some products of alkylation (→ **53**, 70–85%), hydroxyalkylation (→ **54**, 30–60%), and *Michael* addition (→ **55**, 35%) are shown.



R = CH_3, $(CH_3)_2CH$, $CH_2{=}CHCH_2$, n-C_4H_9, n-C_6H_{13}, n-C_8H_{17}, $C_6H_5CH_2$

R^1/R^2 = C_2H_5/H, n-C_5H_{11}/H, C_6H_5/H, 3,4-$(CH_3O)_2C_6H_3/H$ CH_3/CH_3, -$(CH_2)_5$-

Alkylation proceeds well, even with 2-iodopropane, to give products which can be induced to eliminate nitrous acid, yielding 2-substituted acrylate esters such as **56**; of the wide range of bases tested, only 1,4-diazabicyclo [4.3.0] non-4-ene (DBN) [144] is successful, and, remarkably, α-allylated **53** does not undergo further conjugation, but rather is isolated as **57**. The yields in nine cases of this elimination range from 65–90%. Alkylation with vinyl ether-protected 1,2-halohydrins, acid-catalysed lactonisation, and nitrous acid elimination leads to the α-methylene-γ-lactones **58** in modest yields. This alkylation-elimination sequence shows that the dianion **34c** is, *inter alia*, synthetically equivalent with **59** [145]. In addition, the monoalkylated compounds **53** readily undergo a second double deprotonation and alkylation to give, for example, **60a** and **b**.



56 **57** **58** R = H, CH_3

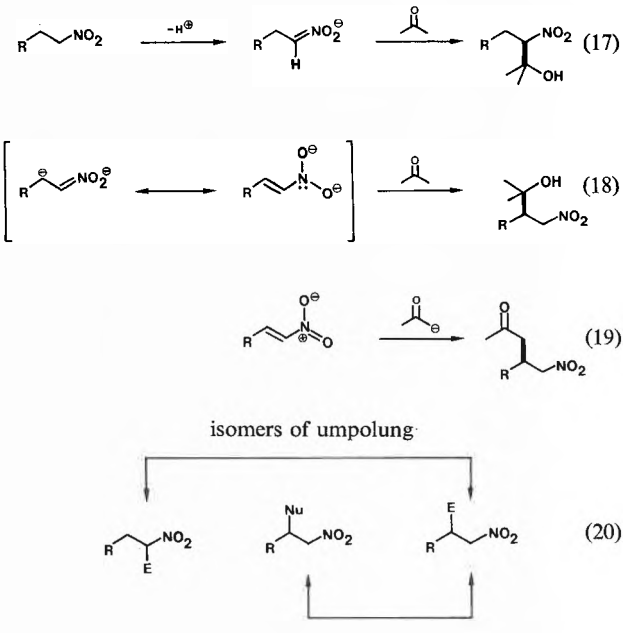
59

60a, $R^1 = CH_3$, $R^2 = C_6H_5CH_2$
60b, $R^1 = C_2H_5$, $R^2 = CH_2{=}CHCH_2$

The primary adducts with carbonyl compounds are apparently formed reversibly. We conclude this from the observation that **54** can only be isolated in the quoted yields by low-temperature quenching; for example, quenching of the benzaldehyde adduct after five hours at $-78\,^{\circ}C$ gives the aldol product in 91% yield, whereas stirring at room temperature overnight results in no observable reaction, the components being re-isolated unchanged. Additionally, benzophenone is unreactive under all conditions tried.

5. Synthetic Implications of α, β-Double Deprotonation in Nitroethane Derivatives

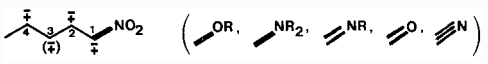
Inspection and comparison of Equations (17), (18), and (19) demonstrates that three entirely different structural types are available from precursors with the same carbon skeletons and functionality patterns but at different levels of oxidation. Acetone combines as an electrophile with the nitronate anion to give a 1,2-nitroalcohol, and with the dianion derivative to give an isomeric 1,3-nitroalcohol, while as its nucleophilic enolate it adds to a nitro-olefin to give a 4-nitroketone. The reactions of **34b** in Chapter G4 illustrate the vinylogous extension of this principle. In (20), we see that the novel dianion reagents **34** are nitro-olefins with reactivity umpolung, having undergone a shift of the familiar attack of electrophiles at the 1-position to the 2-position of the nitroethyl moiety.



H. Conclusions and Future Trends

The ready access to silyl nitronates and to α, α- and α, β-doubly deprotonated nitroalkanes described here should considerably increase the synthetic value of aliphatic nitrocompounds. The recent improvements in conditions for conjugate addition to nitro-olefins, and for non-connective modes of preparation and functional group interconversions with nitroalkanes, will enhance such utility even further. This present survey has attempted to demonstrate that aliphatic nitrocompounds are unique in that they appear to be amenable to both nucleophilic *and* electrophilic attack

at each contiguous carbon atom of their skeleton, **61** – E^3/N^3 attack is under active investigation in our laboratories.



61

Recalling the functional group equivalence of the nitro group with hydroxyl, amino, imino, carbonyl, and nitrile, and the resulting possibilities of reactivity umpolung (Scheme 4), the question provocatively posed in the title may well receive an affirmative answer in the near future.

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Literature

1a *O. v. Schickh, G. Apel, H.G. Padeken, H. H. Schwarz* and *A. Segnitz:* in Houben-Weyl-Müller: Methoden der organischen Chemie, Vol. X/1, Thieme, Stuttgart 1971.
b *G. Baumeyer:* in Methodicum Chimicum, Vol. 6 (C—N-Verbindungen), Thieme, Stuttgart, 1974; Academic Press, New York, N.Y., 1976.
c *P.A.S. Smith,* "The Chemistry of Open-Chain Organic Nitrogen Compounds", Vol II, W.A. Benjamin, Inc. New York 1966.
d *H. Feuer* in *S. Patai:* The Chemistry of the Nitro- and Nitroso-Groups, Parts 1 and 2, Wiley-Interscience, New York 1969/70.
e *T. Urbanski:* Synthesis *1974,* 613.
f *N. Kornblum,* Angew. Chem. *87* (1975) 797; Internat. Edn. p. 734; Organic Reactions, *12* (1962) 101.
g *R. Gottschlich:* Merck-Kontakte 2/76/9.
2 *F. R. Stermitz, F.A. Norris* and *M. C. Williams:* J. Amer. Chem. Soc. *91* (1969) 4599.
3 *J. Vrkoč* and *K. Ubik:* Tetrahedron Lett. *1974,* 1463.
4 *S. B. Soloway, A.C. Henry, W. D. Kollmeyer, W. M. Padgett, J. E. Powell, S.A. Roman, C. H. Tieman, R.A. Corey,* and *C.A. Horne:* Abstracts of Fourth International Congress of Pesticide Chemistry, (IUPAC), Zürich, 1978, p. II 4.
5 *J.W. Zubrick, B. I. Dunbar* and *H. D. Durst:* Tetrahedron Lett. *1975,* 71.
6 *G. Gelbard* and *S. Colonna:* Synthesis *1977,* 113.
7 *K. Baum, D.A. Lerdal* and *J. S. Horn:* J. Org. Cem. *43* (1978) 203.
8 *H. Feuer:* "The Alkyl-Nitrate-Nitration of Active Methylene Compounds", A.C.S. Symposium Series, No. 22, Washington, D.C., 1976, p. 160;
A. I. Fetell and *H. Feuer:* J. Org. Chem. *43* (1978) 497;
H. Feuer and *L.F. Spinicelli:* J. Org. Chem. *41* (1976) 2981;
H. Feuer and *H. Friedman:* J. Org. Chem. *40* (1975) 187;
H. Feuer and *R. P. Monter:* J. Org. Chem. *34* (1969) 991.
9 *M. E. Sitzmann, L.A. Kaplan* and I. *Angres:* J. Org. Chem. *42* (1977) 563.
10 *I. Sh. Shvarts, V. V. Yarovenko, M. K. Krayushkin, S. S. Novikov* and *V. V. Sevost'yanova:* Izv. Acad. Nauk. SSSR, Ser. Khim. *1976,* 1674.
11 *P. E. Pfeffer* and *L.S. Silbert:* Tetrahedron Lett. *1970,* 699.
12 *G. B. Bachmann* and *T. F. Biermann:* J. Org. Chem. *35* (1970) 4229.
13 *E. Keinan* and *Y. Mazur:* J. Org. Chem. *42* (1977) 844.
14 *K.A. Petrov, V.A. Chauzov, I. V. Pastukhova* and *N. N. Bogdanov:* Zh. Obshch. Khim. *46* (1976) 1246.
15 *C. H. Robinson, L. Milewich* and *P. Hofer:* J. Org. Chem. *31* (1966) 524.
16 *M. W. Barnes* and *J. M. Patterson:* J. Org. Chem. *41* (1976) 733.
17 *V. Jäger* and *H. J. Günther:* Angew. Chem. *89* (1977) 253; Internat. Edn. p. 246.
18 *G.A. Olah* and *M. Nojima:* Synthesis *1973,* 785.
19 *J. Tuaillon* and *R. Perrot:* Helv. Chim. Acta *61* (1978) 558.
20 *J. Pfab:* J.C.S. Chem. Commun. *1977,* 766.
21 *S. G. Zlotin, M. M. Krayushkin, V.V. Sevost'yanova* and *S. S. Novikov:* Izv. Akad. Nauk. SSSR, Ser. Khim *1977,* 2286, 2362.
22 *J. Melton* and *J. E. McMurry:* J. Org. Chem. *40* (1975) 2138.
23 *J. M. Larkin* and *K. L. Kreuz:* J. Org. Chem. *36* (1971) 2574.
24 *G. B. Bachman* and *R. J. Maleski:* J. Org. Chem. *37* (1972) 2810;
R. H. Wollenberg and *S.J. Miller:* Tetrahedron Lett. *1978,* 3219.
25 *R. O. Hutchins, D. Rotstein, N. Natale* and *J. Fanelli:* J. Org. Chem. *41* (1976) 3328.
26 *W. Lehnert:* Synthesis *1976,* 827;
A. I. Meyers and *J. C. Sircar:* J. Org. Chem. *32* (1967) 4134.
27 *H.J. Dauben,* Jr., *H.J. Ringold, R.H. Wade* and *A.G. Anderson,* Jr.: J. Amer. Chem. Soc. *73* (1951) 2359;
H.J. Dauben, Jr., *H.J. Ringold, R. H. Wade, D. L. Pearson* and *A.G. Anderson,* Jr.: Org. Synth. Coll. Vol. IV (1963) 221;
R. K. Hill, J. A. Joule and *L. J. Loeffler:* J. Amer. Chem. Soc. *84* (1962) 4951;
J. F. Knifton: J. Org. Chem. *40* (1975) 519;
C. Grundmann and *W. Ruske:* Chem. Ber. *86* (1953) 939;
M. Joseph, T. Leigh and *M. L. Swain:* Synthesis *1977,* 459;
R.J. Sundberg and *P.A. Bukowick:* J. Org. Chem. *33* (1968) 4098;
E. Kaji, H. Kohno and *S. Zen:* Bull. Chem. Soc. Jap. *50* (1977) 928;
S. Zen and *E. Kaji:* Bull. Chem. Soc. Jap. *43* (1970) 2277;
E. Kaji and *S. Zen:* Bull. Chem. Soc. Jap. *46* (1973) 337;
S. Zen, Y. Takeda, A. Yasuda and *S. Umezawa:* Bull. Chem. Soc. Jap. *40* (1967) 431;
S. Zen and *A. Nishikai:* Bull. Chem. Soc. Jap. *42* (1969) 1761.
28 *E. McDonald* and *R.T. Martin:* Tetrahedron Lett. *1977,* 1317;
E.J. Corey, N.H. Andersen, R.M. Carlson, J. Paust, E. Vedejs, I. Vlattas and *R.E.K. Winter:* J. Am. Chem. Soc. *90* (1968) 3245;
E.J. Corey, I. Vlattas, N.H. Andersen and *K. Harding:* J. Am. Chem. Soc. *90* (1968) 3247, 5947;
W. Hückel and *M. Blohm:* Liebigs Ann. Chem. *502* (1933) 114;
C. Shin, Y. Kosuge, M. Yamaura and *J. Yoshimura:* Bull. Chem. Soc. Jap. *51* (1978) 1137.
29 *H.H. Wassermann, M.J. Hearn, B. Haveaux* and *M. Thyes:* J. Org. Chem. *41* (1976) 153.
30 *J. R. Butterick* and *A. M. Unrau:* J.C.S. Chem. Commun. *1974,* 307.
31 *Y. Maki, H. Sugiyama, K. Kikuchi* and *S. Seto:* Chem. Lett. *1975,* 1093.
32 *Y. Watanabe, T. Mitsudo, M. Yamashita* and *Y. Takegami:* Bull. Chem. Soc. Jap. *48* (1975) 1478.
33 *J. E. Baldwin, S. B. Haber, C. Hoskins* and *L. I. Kruse:* J. Org. Chem. *42* (1977) 1239.
34 *N. Kornblum* and *L. Fishbein:* J. Am. Chem. Soc. *77* (1955) 6266.
35 *F. F. Blicke, N.J. Doorenbos* and *R. H. Cox:* J. Am. Chem.

Soc. *74* (1952) 2924;
W. C. Gakenheimer and *W. H. Hartung:* J. Org. Chem. *9* (1944) 85.
36 *E. W. Colvin* and *D. Seebach:* J. C. S. Chem. Commun. *1978*, 689.
37 *K. Torssell* and *O. Zeuthen:* Acta Chem. Scand.: *B 32* (1978) 118.
38 *M. V. Kashutina, S. L. Ioffe* and *V. A. Tartakovskii:* Doklady Acad. Nauk. SSSR *218* (1974) 109.
39 *J. F. Knifton:* J. Org. Chem. *38* (1973) 3296.
40 *J. R. Hanson:* Synthesis *1974*, 1;
J. R. Hanson and *T. D. Organ:* J. Chem. Soc. *(C) 1970*, 1182;
J. R. Hanson and *E. Premuzic:* Tetrahedron Lett. *1966*, 5441;
J. R. Hanson and *E. Premuzic:* Tetrahedron *23* (1967) 4105;
A. Hassner and *C. Heathcock:* J. Org. Chem. *29* (1964) 1350.
41 *H. H. Baer* and *W. Rank:* Canad. J. Chem. *50* (1972) 1292.
42 *P. A. Wehrli* and *B. Schaer:* Synthesis *1977*, 649.
43 *Y. Komeichi, S. Tomioka, T. Iwasaki* and *K. Watanabe:* Tetrahedron Lett. *1970*, 4677.
44 *O. L. Chapman, A. A. Griswold, E. Hoganson, G. Lenz* and *J. Reasoner:* Pure Appl. Chem. *9* (1964) 585;
J. Saito, M. Takami and *T. Matsuura:* Tetrahedron Lett. *1975*, 3155.
45 *P. J. Moles* and *S. T. Reid:* Tetrahedron Lett. *1976*, 2283.
46 *C. Shin, H. Narukawa, M. Yamaura* and *J. Yoshimura:* Tetrahedron Lett. *1977*, 2147.
47 *T. D. Lee* and *J. F. W. Keana:* J. Org. Chem. *41* (1976) 3237;
J. B. Neilands and *P. Azari:* Acta Chem. Scand. *17* Suppl. I (1963) 190;
S. Rogers and *J. B. Neilands:* Biochemistry *2* (1963) 6.
48 *A. Hassner* and *J. Larkin:* J. Am. Chem. Soc. *85* (1963) 2181;
H. O. Larson and *E. K. W. Wat:* J. Am. Chem. Soc. *85* (1963) 827;
F. R. Stermitz and *D. W. Neiswander:* Tetrahedron *31* (1975) 655;
S. T. Reid and *J. N. Tucker:* J. C. S. Chem. Commun. *1971*, 1609.
49 *E. Buehler* and *G. B. Brown:* J. Org. Chem. *32* (1967) 265.
50 *A. Hassner* and *D. R. Fitchmun:* Tetrahedron Lett. *1966*, 1991.
51 *R. F. C. Brown, V. M. Clark* and *A. Todd:* Proc. Chem. Soc., London 1957, 97;
J. J. Tufariello, J. J. Tegler, S. C. Wong and *S. A. Ali:* Tetrahedron Lett. *1978*, 1733 [synthesis of (±)-cocaine].
52 *M. Yamashita, K. Mizushima, Y. Watanabe, T. Mitsudo* and *Y. Takegami:* J. C. S. Chem. Commun. *1976*, 670.
53 *M. Yamashita, Y. Watanabe, T. Mitsudo* and *Y. Takegami:* Tetrahedron Lett. *1976*, 1585.
54 *T. Mukaiyama* and *T. Hoshino:* J. Am. Chem. Soc. *82* (1960) 5339;
A. Barco, S. Benetti, G. P. Pollini, B. Veronesi, P. G. Baraldi, M. Guarneri and *C. B. Vincentini:* Synth. Commun. *8* (1978) 219.
55a *P. A. Wehrli* and *B. Schaer:* J. Org. Chem. *42* (1977) 3956;
b *J. M. Lalancette, A. Frêche, J. R. Brindle* and *M. Laliberté:* Synthesis *1972*, 526.
56a *H. Bhagwatheeswaran, S. P. Gaur* and *P. C. Jain:* Synthesis *1976*, 615;
b *E. Kaji, H. Kohno* and *S. Zen:* Bull. Chem. Soc. Jap. *50* (1977) 928.
57 *H. B. Hass* and *M. L. Bender:* Org. Syntheses, Coll. Vol. *IV*, 1963, p. 932.
58 *W. E. Noland:* Chem. Rev. *55* (1955) 137.
59 *M. Langrenée:* C. R. Acad. Sci. Ser. *C 284* (1977) 153.
60 *D. St. C. Black:* Tetrahedron Lett. *1972*, 1331.
61 *R. M. Jacobsen:* Tetrahedron Lett. *1974*, 3215.
62 *A. Mitra:* The Synthesis of Prostaglandins, Wiley Interscience, New York 1977.
63 *S. Ranganathan, D. Ranganathan* and *A. K. Mehrotra:* J. Am. Chem. Soc. *96* (1974) 5261.
64 *J. Bagli* and *T. Bogri:* Tetrahedron Lett. *1972*, 3815.
65 *P. Dubs* and *R. Stüssi:* Helv. Chim. Acta *61* (1978) 990; for the use of barium hydroxide as base, see *L. Benzing* and *M. B. Perry:* Canad. J. Chem. *56* (1978) 691.
66 *J. E. McMurry:* Acc. Chem. Res. *7* (1974) 281;
J. E. McMurry and *J. Melton:* J. Org. Chem. *38* (1973) 4367.
67 *J. E. McMurry* and *J. Melton:* J. Am. Chem. Soc. *93* (1971) 5309;
T.-L. Ho and *C. M. Wong:* Synthesis *1974*, 196.
68 *R. Kirchhoff:* Tetrahedron Lett. *1976*, 2533.
69 *Y. Atika, M. Inba, H. Uchida* and *A. Ohta:* Synthesis *1977*, 792.
70 *Th. Severin* and *D. König:* Chem. Ber. *107* (1974) 1499 and ref. therein.
71 *H. Shechter* and *F. T. Williams:* J. Org. Chem. *27* (1962) 3699.
72 *F. S. Alvarez* and *D. Wren:* Tetrahedron Lett. *1973*, 569.
73 *F. Kienzle, G. W. Holland, J. L. Jernow, S. Kwoh* and *P. Rosen:* J. Org. Chem. *38* (1973) 3440.
74 *A. H. Pagano* and *H. Shechter:* J. Org. Chem. *35* (1970) 295.
75 *J. E. McMurry, J. Melton* and *H. Padgett:* J. Org. Chem. *39* (1974) 259.
76 *P. Dubs* and *H.-P. Schenk:* Helv. Chim. Acta *61* (1978) 984.
77 *J. R. Williams, L. R. Unger* and *R. H. Moore:* J. Org. Chem. *43* (1978) 1271.
78 *P. A. Bartlett, F. R. Green III* and *T. R. Webb:* Tetrahedron Lett. *1977*, 331.
79 *N. Kornblum* and *P. A. Wade:* J. Org. Chem. *38* (1973) 1418.
80 *E. Keinan* and *Y. Mazur:* J. Am. Chem. Soc. *99* (1977) 3861.
81 *J. L. Hogg, T. E. Goodwin* and *D. W. Nave:* Org. Prep. Proced. Int. *10* (1978) 9.
82 *H. Lerche, D. König* and *Th. Severin:* Chem. Ber. *107* (1974) 1509.
83 Unpublished observations in our laboratories at the ETH and in Giessen: *A. K. Beck, E. W. Colvin, V. Ehrig, J. Gonnermann, R. Henning, M. S. Hoekstra, F. Lehr, G. Protschuk* and *T. Weller*.
84 *D. Seebach, V. Ehrig, H. F. Leitz* and *R. Henning:* Chem. Ber. *108* (1975) 1946.
85 *H. Newmann* and *R. B. Angier:* J. C. S. Chem. Commun. *1969*, 369;
S. Kumazawa, T. Sakakibara, R. Sudoh and *T. Nakagawa:* Angew. Chem. *85* (1973) 992; Internat. Edn. p. 921.
N. A. Sokolov, I. G. Tishchenko and *N. V. Kovganko:* Zh. Org. Khim. *14* (1978) 517;
see also *H. H. Baer* and *C. B. Madumelu:* Canad. J. Chem. *56* (1978) 1177.
86 *L. G. Donaruma* and *M. L. Huber:* J. Org. Chem. *21* (1956) 965.
87 *D. Seebach, H. F. Leitz* and *V. Ehrig:* Chem. Ber. *108* (1975) 1924.
88 Dissertation *R. Henning*, Justus-Liebig-Universität Giessen, 1978.
89 *J. W. Patterson* and *J. E. McMurry:* J. C. S. Chem. Commun. *1971*, 488.
90 *D. Seebach, M. S. Hoekstra* and *G. Protschuk:* Angew. Chem. *89* (1977) 334: Internat. Edn. p. 321
91 *S. Danishefsky, M. P. Prisbylla* and *S. Hiner:* J. Am. Chem. Soc. *100* (1978) 2918.
92 *H. Paulsen* and *W. Greve:* Chem. Ber. *107* (1974) 3013.
cf. a similar process with trialkyl phosphites, *W. E. Krueger, M. B. McLean, A. Rizwaniuk, J. R. Maloney, G. L. Behelfer* and *B. E. Boland:* J. Org. Chem. *43* (1978) 2877 see also.
93 *Th. Severin, I. Bräutigam* and *K. H. Bräutigam:* Chem. Ber. *110* (1977) 1669.
94 *N. Ono, R. Tamura, J. Hayami* and *A. Kaji:* Chem. Letters *1977*, 189.
95 *P. Bakuzis, M. L. F. Bakuzis* and *T. F. Weingartner:* Tetrahedron Lett. *1978*, 2371.

96 *N. Kornblum* and *L. Cheng:* J. Org. Chem. *42* (1977) 2944.
97 *N. Kornblum, S. D. Boyd, H. W. Pinnik* and *R. G. Smith:* J. Am. Chem. Soc. *93* (1971) 4316.
98 *N. Kornblum, S. C. Carlson* and *R. G. Smith:* J. Am. Chem. Soc. *100* (1978) 289.
99 *M. Benn* and *A. C. M. Meesters:* J.C.S. Chem. Commun. *1977*, 597.
100 *M. Miyashita, T. Kumazawa* and *A. Yoshikoshi:* J.C.S. Chem. Commun. *1978*, 362.
101 *D. Seebach* and *F. Lehr:* Angew. Chem. *88* (1976) 540; Internat. Edn. p. 505.
102 *H. F. Ebel:* «Die Acidität der C–H-Säuren», Georg Thieme Verlag, Stuttgart 1969;
F. G. Bordwell, N. R. Vanier, W. S. Matthews, J. B. Hendrickson and *P. L. Skipper:* J. Am. Chem. Soc. *97* (1975) 7160.
103 *A. J. Kresge:* Can. J. Chem. *52* (1974) 1897 and ref. therein.
104 *A. K. Hoffmann, A. M. Feldman* and *E. Gelblum:* J. Am. Chem. Soc. *86* (1964) 646;
S. Wawzonek and *J. V. Kempf:* J. Org. Chem. *38* (1973) 2763.
105 *D. Seebach* and *K.-H. Geiss:* J. Organomet. Chem. Library *1* (1976) 1.
106 *B. L. Burt, D. J. Freeman, P. G. Gray, R. K. Norris* and *D. Randles:* Tetrahedron Lett. *1977*, 3063;
D. J. Girdler and *R. K. Norris:* ibid. *1975*, 2375.
107a *S. J. Etheredge:* Tetrahedron Lett. *1965*, 4527;
b *S. Gabriel:* Chem. Ber. *36* (1903) 570.
108 *D. Seebach, R. Henning, F. Lehr* and *J. Gonnermann:* Tetrahedron Lett. *1977*, 1161.
109 *Y. Takahashi, M. Tokuda, M. Itoh* and *A. Suzuki:* Synthesis *1976*, 616.
110 *T. Mitsuyasu* and *J. Tsuji:* Tetrahedron *30* (1974) 831.
111 *J. Mathieu* and *J. Weill-Raynal:* "Formation of C–C Bonds", Vol. II, S. 149–151, Georg Thieme Verlag, Stuttgart 1973.
112 *H. L. Finkbeiner* and *G. W. Wagner:* J. Org. Chem. *28* (1963) 215;
M. Stiles and *H. L. Finkbeiner:* J. Am. Chem. Soc. *81* (1959) 505.
113 For preparation of RCOCN, see *E. C. Taylor, J. G. Andrade, K. C. John* and *A. McKillop:* J. Org. Chem. *43* (1978) 2280;
F. Pochat: Tetrahedron Lett. *1977*, 3813;
K. E. Koenig and *W. P. Weber:* Tetrahedron Lett. *1974*, 2275;
M. E. Childs and *W. P. Weber:* J. Org. Chem. *41* (1976) 3486;
J. F. Normant and *C. Piechucki:* Bull. Soc. Chim. France *1972*, 2402.
114 *D. C. Baker* and *S. R. Putt:* Synthesis *1978*, 478.
115 *J. Gosteli:* Helv. Chim. Acta *60* (1977) 1980;
see also ref. 1a, p. 166.
116 *L. Henry:* Compt. Rend. *120* (1895) 1265.
117 For use of fluoride ion as base, see *G. Hesse* and *V. Jäger:* Annalen *740* (1970) 79, 85.
118 *H. J. Dauben*, Jr., *H. J. Ringold, R. H. Wade, D. L. Pearson* and *A. G. Anderson*, Jr.: Org. Synth. Coll. Vol. IV, 1963, 221;
W. E. Noland: ibid, Coll. Vol. V, 1973, 833.
119 *A. Dornow* and *M. Gellrich:* Annalen *594* (1955) 177.
120a *S. B. Bowlus:* Tetrahedron Lett. *1975*, 3591;
b *J. Michel* and *E. Henry-Basch:* C. R. Acad. Sc. Paris *262* (1966) 1274.
121 *C. D. Bedford* and *A. T. Nielsen:* J. Org. Chem. *43* (1978) 2460.
122 *Th. Severin, I. Bräutigam* and *K.-H. Bräutigam:* Chem. Ber. *109* (1976) 2897;
Th. Severin, P. Adhikary and *I. Bräutigam:* ibid. p. 1179;
see also *G. Büchi* and *C.-P. Mak:* J. Org. Chem. *42* (1977) 1784.
123 *G. Pitacco, R. Toso, E. Valentin* and *A. Risaliti:* Tetrahedron *32* (1976) 1757 and ref. therein;
G. Pitacco and *E. Valentin:* Tetrahedron Lett. *1978*, 2339.
124 *V. Ehrig* and *D. Seebach:* Chem. Ber. *108* (1975) 1961.
125 *F. P. Colonna, E. Valentin, G. Pitacco* and *A. Risaliti:* Tetrahedron *29* (1973) 3011;
H. Feuer, A. Hirschfeld and *E. D. Bergmann:* ibid. *24* (1968) 1187.
126 *T. Yanami, M. Kato* and *A. Yoshikoshi:* J.C.S. Chem. Commun. *1975*, 726;
T. Yanami, M. Kato, M. Miyashita, A. Yoshikoshi, Y. Itagaki and *K. Matsuura:* J. Org. Chem. *42* (1977) 2779;
S. Hoz, M. Albeck and *Z. Rappoport:* Synthesis *1975*, 162;
I. Belsky: J.C.S. Chem. Commun. *1977*, 237;
F. G. Cowherd, M.-C. Doria, E. Galeazzi and *J. M. Muchowski:* Canad. J. Chem. *55* (1977) 2919;
for use of phosphine catalysts, see *D. A. White* and *M. M. Baizer:* Tetrahedron Lett. *1973*, 3597.
127 *S. Colonna, H. Hiemstra* and *H. Wynberg:* J.C.S. Chem. Commun. *1978*, 238.
128 *D. Seebach, H.-O. Kalinowski, B. Bastani, G. Crass, H. Daum, H. Dörr, N. P. DuPreez, V. Ehrig, W. Langer, C. Nüssler, H.-A. Oei* and *M. Schmidt:* Helv. Chim. Acta *60* (1977) 301.
129 *M. Miyashita, T. Yanami* and *A. Yoshikoshi:* J. Am. Chem. Soc. *98* (1976) 4679;
see also *P. A. Grieco* and *Y. Ohfune:* J. Org. Chem. *43* (1978) 2720.
130 *A. K. Beck, M. S. Hoekstra* and *D. Seebach:* Tetrahedron Lett. *1977*, 1187.
131 X-ray structure determination of **31 b** derived from cycloheptanone shows that the two rings are *cis*-fused: *R. E. Davis*, unpublished results (University of Texas at Austin).
132 *G. A. McAlpine, R. A. Raphael, A. Shaw, A. W. Taylor* and *H. J. Wild:* J.C.S. Chem. Commun *1974*, 834;
J. C. S. Perkin I *1976*, 410.
133 *R. V. Stevens*, in "The Total Synthesis of Natural Products", ed. J. ApSimon, Vol. 3, p. 439 ff., Wiley-Interscience, 1977;
G. Pitacco, A. Risaliti, M. L. Trevisan and *E. Valentin:* Tetrahedron *33* (1977) 3145.
134 *E. J. Corey, I. Vlattas* and *K. Harding:* J. Am. Chem. Soc. *91* (1969) 535.
135 *M. Marx, F. Marti, J. Reisdorff, R. Sandmeier* and *S. Clark:* J. Am. Chem. Soc. *99* (1977) 6754.
136 *J. Lehmann*, «Chemie der Kohlenhydrate», pp 75–77, Georg Thieme Verlag, Stuttgart 1976.
137 *M. E. Kurz* and *R. T. Y. Chen:* J.C.S. Chem. Commun. *1976*, 968;
see also *J.-P. Bégué, C. Pardo* and *J. Sansoulet:* J. Chem. Res. (S) *1978*, 52.
138 *R. Henning, F. Lehr* and *D. Seebach:* Helv. Chim. Acta *59* (1976) 2213.
139 *D. Seebach, R. Henning* and *J. Gonnermann:* Chem. Ber. in press.
140 *D. Seebach, R. Henning* and *F. Lehr:* Angew. Chem. *90* (1978) 479.
141 See also *B. Renger* and *D. Seebach:* Chem. Ber. *110* (1977) 2334.
142 *E. M. Kaiser, J. D. Petty* and *P. L. A. Knutson:* Synthesis *1977*, 509.
143 *D. H. R. Barton, R. H. Hesse, C. Wilshire* and *M. M. Pechet:* J.C.S. Perkin I *1977*, 1075.
144 *H. Oediger, F. Möller* and *K. Eiter:* Synthesis *1972*, 591.
145 For direct generation and use, see *J. P. Marino* and *D. M. Floyd:* Tetrahedron Lett. *1975*, 3897.