130. Synthesis of Open-Chain 2,3-Disubstituted 4-nitroketones by Diastereoselective *Michael*-addition of (*E*)-Enamines to (*E*)-Nitroolefins. A Topological Rule for C,C-Bond Forming Processes between Prochiral Centres

Preliminary communication

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Summary

The *Michael*-additions of aliphatic, alicyclic, and arylsubstituted nitroolefins and enamines lead to γ-nitroketones **3** in good chemical and excellent (>90%) diastereomeric yields (see *Table 1*).

The known *threo*-configuration of one type of adducts **3** (entries 8, 10, and 11 of *Table 1*) can be arrived at by assuming the approach **8** of the *Michael*-acceptor and -donor; the reaction follows a *topological rule*, which is formulated and which is applicable to such diverse reactions as the diene synthesis, cyclopropanations, carbonyl olefinations and methylenations, aldol- and nitroaldol-type additions, as well as additions of lithium, boron, and chromium derivatives to aldehydes (see **9**, **10**, **11**, and *Table 2*).

The availability of diastereoselective modifications of classical C,C-bond forming processes without ring closure is of utmost importance for syntheses of open-chain and macrocyclic target molecules containing numerous centres of chirality[3]). The nitroaldol reaction, giving rise to 1,2-bifunctional structures [3] [4] (see formula **1**), as well as the aldol-/*Reformatzky*-type additions (see **2**), furnishing a *1,3*-functionality pattern [1] [5–11], have been successfully modified to give essentially one diastereomer only. In contrast, the *Michael*-addition, which can produce compounds with *1,4*- or *1,5*-distances of functional groups, is generally considered to be non-selective [1] [10].

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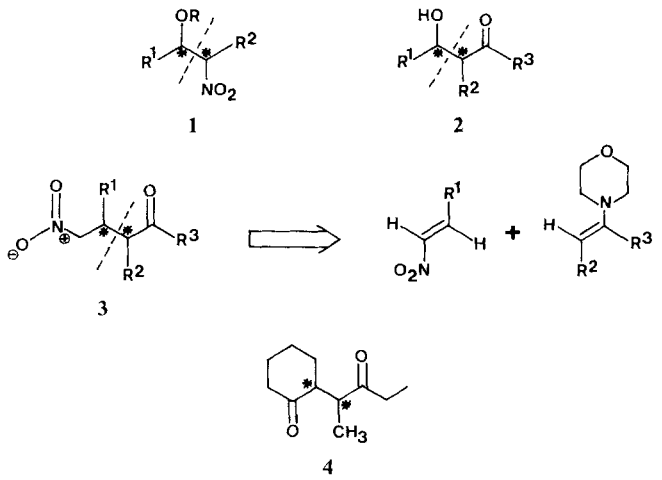
[1]) Postdoctoral research associate; on leave from the *Polish Academy of Sciences*, Warsaw (February–April 1981).

[2]) We thank Dr. *J.N. Hay* (Postdoctoral Fellow under the *NATO* Science Fellowship Scheme, 1979/80) for carrying out some preliminary experiments.

[3]) For a review, *cf.* [1], for recent examples *cf.* [2].

0018-019X/81/5/1413-11$01.00/0



We have now found, that the reaction of *open-chain* nitroolefins [3] [12] (**3a**) with *open-chain* enamines [13] (**3b**) from ketones and morpholine[4]) leads to γ-nitroketones **3** possessing diastereomeric purities of 90–99% (see *Table 1*, entries 1–4, 6, 7, and 12). In a typical procedure [15b], equimolar amounts of the enamine and of the nitroolefin, which have both (*E*)-configuration[5]) [12b] [14] [16] (> 97%) according to NMR. analysis, are dissolved in ether (20 ml per 10 mmol) and kept at room temperature for several hours to several days (TLC. monitoring of the disappearing nitroolefin). The solvent is removed evaporatively, and the residue is stirred in a 1:1 mixture of ethanol and 10% aqueous hydrochloric acid (total volume 60 ml per 10 mmol) for one hour at room temperature before work-up with chloroform. When carried out in ethanol instead of ether, the reaction is much less selective (ratios of diastereomers 2:1 to 3:1 in four cases checked), with essentially unchanged chemical yields.

Inspection of the examples listed in *Table 1* reveals, that both components may be aliphatic, but also alicyclic, or aryl substituted. When 1-nitrocyclohexene [16] is the *Michael*-acceptor of the diethylketone derived enamine (*Table 1*, entry 5), the diketone **4**, resulting from a *Nef*-reaction, is isolated as the main product. The diastereomeric purities of the nitroketones **3** and of the diketone **4** were determined from high performance liquid chromatograms and from capillary gas chromatograms which were qualitatively confirmed by their ^{13}C-NMR. spectra.

While the present results provide a useful diastereoselective route to *vicinally branched, open-chain carbon skeletons*, they also raise a number of important questions which are being studied in our laboratory: *a*) Are the *primary products* – present before hydrolysis – the open-chain enamines **5** [15a–d], the amino-

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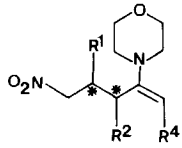
[4]) *Weingarten*'s $TiCl_4$-method was used for the preparation of the morpholinoenamines, following a procedure by *Metzger et al.* [14].

[5]) See references cited in [12a].



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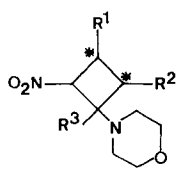

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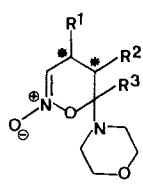
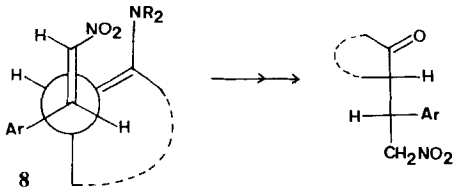


7

nitrocyclobutanes **6** [15a–d] [18] or (4+2)-cycloadducts 7[5])[6])[7]) [15a–d] [21]? *b*) What are the *configurations* of the open-chain products **3**? *c*) Do (E/Z)-*isomeric* enamines [12b] and/or nitroolefins give rise to products **3** of *opposite configuration*? *d*) Will the reaction lead to highly *enantiomerically enriched* 4-nitroketones **3**, when carried out in chiral solvents [22] or with enamines derived from chiral amines [23]? *e*) Which *α,β-unsaturated carbonyl compounds* react with enamines under similarly mild conditions as the nitroolefins, and thus possibly also with high diastereoselectivity?

Previous investigations have shown, that additions of lithium enolates [10] [16] and of silyl enol ethers [21] to aliphatic and aryl substituted nitroolefins are not selective at all. On the other hand, *Risaliti et al.* have published a series of papers [15] which prove that the kinetically controlled *Michael*-additions of enamines derived from *cyclic* ketones (mainly cyclohexanones, *cf.* entries 8–11 of *Table 1*) to nitroolefins (mostly ω-nitrostyrene, *cf.* entries 10 and 11, *Table 1*) occur with (*Re*Re**)-approach of the two components as depicted in the *Newman*-



8

(*anti*-donor/*anti*-acceptor) [*Re*Re**-approach][8])

(*RS,SR*)- or n-diastereomer[9])

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[5]) In the case of (*E*)-1-phenyl-1-morpholino-1-propene (*Table 1*, entry 12), a primary product of type **5** cannot be formed without loss of a centre of chirality. Although conceivable, we do not think, that the selectivity observed here is a result of diastereoselective protonation. We assume, that the process leading to **3** is in all cases a kinetically controlled diastereoselective C,C-bond formation between two prochiral centres (see also discussion, below).

[6]) For a review of 1,4-dipolar cycloadditions see [19].

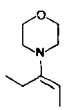
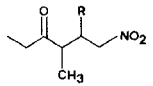
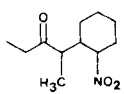
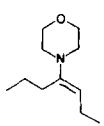
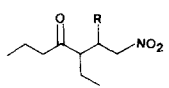
[7]) *Cf.* the chloronitrone derived 1,4-dipoles in [20].

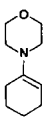
[8]) In most cases (see *Table 2*) the acceptor and the donor groups have priority over the (*R*)-groups in the *CIP*-nomenclature. We therefore prefer to use the *Re, Si*-convention [24] for the *description of the approach* of the prochiral centres rather than *erythro/threo* (*cf.* footnote 7).

[9]) Diastereomers of this type have previously been assigned *erythro*-configuration [15a–d]. In order to avoid the confusion caused by correct [10] [25] and incorrect – or arbitrary [1] [5–9] use of the *Fischer*-projection conventions for assigning *erythro/threo* relative configurations [26], we use here nomenclature based on the (*R, S*)-system [27]. It is unambiguous, albeit it fails to reveal membership to configurational families more often than does the *erythro/threo*-nomenclature (see *Table 2*).

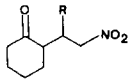
Table 1. *γ-Nitroketones* **3** *from enamines and nitroolefins*

The reactions were conducted as described in the accompanying text. The ratios of diastereomers of purely aliphatic derivatives **3** were determined by capillary GC. (*Carlo-Erba*, carrier gas = H_2, FID-detector, 20 m Column, *Carbowax* 20 M), those of aryl-substituted compounds **3** by HPLC. (Eigenbau, 80–100 bar, reverse phase RP8 column, 20 cm × 0.8 cm, UV.-detector). On GC., the major isomer has the shorter retention time, on the HPLC. column it is the other way around. The IR. and ^{1}H-NMR. spectra of all products are compatible with the structures shown.

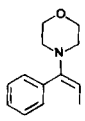
Entry	Starting materials	Products **3**		
		Formula and name	Yield [%]	Diastereo-selectivity
	 *N*-(2-penten-3-yl)-morpholine (enamine from 3-pentanone and morpholine)			
1	+ 1-nitro-1-propene	R = CH_3: 4,5-dimethyl-6-nitro-3-hexanone	81	91:9
2	+ 1-nitro-1-butene	R = C_2H_5: 5-ethyl-4-methyl-6-nitro-3-hexanone	75	92:8
3	+ 3-methyl-1-nitro-1-butene	R = $CH(CH_3)_2$: 5-isopropyl-4-methyl-6-nitro-3-hexanone	24	> 90:10
4	+ 1-nitro-2-phenyl-ethene	R = C_6H_5: 4-methyl-6-nitro-5-phenyl-3-hexanone	84	99:1
5	+ 1-nitro-1-cyclohexene	 2-(1-nitro-2-cyclohexyl)-3-pentanone	7[a])	80:20[b])
	 *N*-(3-hepten-4-yl)-morpholine (enamine from 4-heptanone and morpholine)			
6	+ 1-nitro-1-propene	R = CH_3: 3-ethyl-2-methyl-1-nitro-4-heptanone	65	93:7
7	+ 1-nitro-2-phenyl-ethene	R = C_6H_5: 3-ethyl-1-nitro-2-phenyl-4-heptanone		97:3



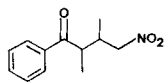
N-(1-cyclohexen-1-yl)-morpholine (enamine from cyclohexanone and morpholine)



8	+ 1-nitro-1-propene	R = CH_3 [15a]: 2-(1′-nitro-2′-propyl)-cyclohexanone	80[c])	> 95:5[c])
9	+ 3-methyl-1-nitro-1-butene	R = $CH(CH_3)_2$: 2-(3′-methyl-1′-nitro-2-butyl)-cyclohexanone	73	> 95:5
10	+ 1-nitro-2-phenyl-ethene	R = C_6H_5 [10] [15a-d] [16]: 2-(2′-nitro-1′-phenylethyl)-cyclohexanone	88	99:1
11	+ 2-(3,4-methylenedioxy-phenyl)-1-nitro-ethene	R = 3,4-(O−CH_2−O)-C_6H_3: 2-[1′-(3′,4′-methylenedioxyphenyl)-2-nitro-ethyl]-cyclohexanone	91	97:3

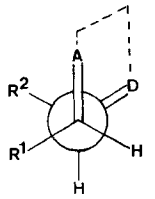


N-(1′-phenyl-1′-propen-1-yl)-morpholine (enamine from 1-phenyl-1-propanone and morpholine)



12	+ 1-nitro-1-propene	2,3-dimethyl-4-nitro-1-phenyl-1-butanone	80	93:7

a) The main product is the diketone **4**, which according to capillary GC. and ^{13}C-NMR. spectrum is > 95% diastereomerically pure.
b) This product contains three centres of chirality, yet we could discover only two diastereomers in the ratio given (GC. analysis).
c) Taken from [15a].



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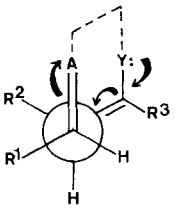
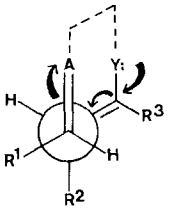
[*Re*Si**-approach][8])



10

(syn-donor) [*Re*Si**-approach[8]), *quasi*-chair]



11

(anti-donor) [*Re*Re**-approach[8]), *quasi*-chair]

projection **8**, and we expect that this is the mode of formation of all the products of *Table 1*.

In fact, the *gauche*-relationship of the donor and acceptor π-systems in the *Michael*-addition **8** follows a *topological rule* applicable to a variety of processes (see the list in *Table 2*). When taking place in poorly anion solvating, *i.e.* aprotic media, under kinetic control, the preferred approach of two prochiral centres RCH=X can be described by the pictures **9**–**11**:

a) with *staggering* of all bonds around the newly formed bond;

b) in a *gauche* (synclinal) arrangement of the *donor* (C=D)-bond between the (C–A)- and the (C–H)-bonds of the *acceptor;*

c) with the *H-atom*, the smaller substituent on the donor component, in an *anti* (antiperiplanar) position with respect to the (C=A)-bond (see **9**);

d) if the components can exist in (*E*/*Z*) (*anti*/*syn*)-isomeric forms (see **8**, **10**, **11**), the *actual donor* and *acceptor* atoms are situated *close* to each other (see A and Y in **10** and **11**; *cf.* NO_2 and NR_2 in **8**).

A formidable array of effects[10]) has been put forward in discussions about the different reactions[11]) of *Table 2*. Yet, not all aspects appear to be fully understood[12]).

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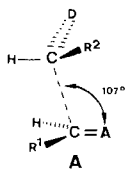
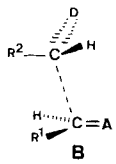
[10]) Steric repulsion (D and D-R^3 in **9**–**11** are normally large and push R^1 to the antiperiplanar position) [1] [4–9] [15], steric attraction (between R^1 and R^2) [28], the *Bürgi-Dunitz* approach [29–31] (of the more readily pyramidalized donor centre might cause the preference of the A=C · · · C–H antiperiplanarity (see rule *c*, **9**, **10** *vs.* **11**, *Table 2* and **A** *vs.* **B**) [30], orbital control ([2a+2s]-cycloaddition [32], A=C LUMO/Y–D=C HOMO interaction [9]), secondary orbital control [28] [32b] [33], metal chelation [5–8] or *Coulomb* attraction [1] [6] [34] [35] (*i.e.* minimalization of charge separation, holding A and D or Y in **9**–**11** together), *London* forces [35].



A



B

[11]) The approach topology is applicable independant of the actual course or mechanism of the reaction, which may lead to a biradical, a betain, a cycloadduct, a chelated metal derivative, *etc.* (see footnotes 10 and 12).

[12]) In spite of many new results and in spite of an improved understanding of reagent approach [29–31], the statement made by *Schlosser* in 1970 [34], that the *cis-*, *syn-* or *erythro*-selectivity of many C,C-bond-forming reactions is 'a fundamental (though rather obscure) principle' still holds to some extent in 1981. – At the time being, we feel that there is not enough evidence to be sure, that **10** and **11** are *mechanisms* rather than *pictures* or *topological rules*; for instance, for the aldol additions with lithium enolates, which are present in solution, and may even react, as tetrameric aggregates [36]. The actual mechanism could be much more complicated than now described [6].

Table 2. *Some examples of reactions following the* (Re*Si*)- (entries 1–6, 8 and 10[a])) *or* (Re*Re*)-*topology* (entries 7, 9, 11, and 12)[a]) **9**/**10** *or* **11**, respectively.

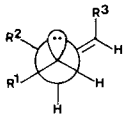
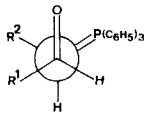
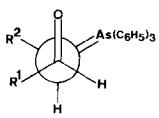
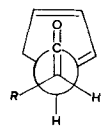
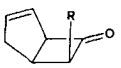
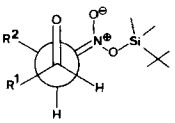
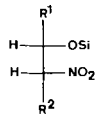
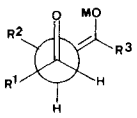
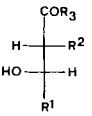
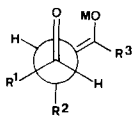
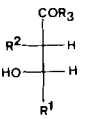
Entry	Starting materials	Topology	Products	Selectivities up to	References
1	Mono- or (*Z*)-disubstituted olefin + carbene precursor[b])		 *cis*-Substituted cyclopropanes	> 95%	[35] [45]
2	Alkylidentriphenyl-phosphane[c]) + aldehyde		 (*Z*)-Olefins	> 98%	[30] [34] [35]
3	Alkylidentriphenyl-arsane[c]) + aldehyde		 *trans*-Dialkyl-oxiranes	> 98%	[49]
4	Ketenes + cyclo-pentadiene		 *endo*-Substitu-ted bicyclo-[3.2.0]-hepte-nones	98%	[32b] [50]
5	(*E*)-Silylnitronates + aldehydes		 *O*-Silylated *erythro*-nitroaldols	> 97%	[3], *cf.* [16] [51] [52]
6	*syn*-Li- and -B-enolates of ketones, esters, and amides[d])[e]) + aldehydes		 *threo*-Aldol adducts	> 98%	[1c] [5–8] [53]
7	*anti*-Li- and -B-enolates of ketones, and esters[d])[e]) + aldehydes		 *erythro*-Aldol adducts	> 95%	[1e] [5–8] [53]

Table 2 (continued)

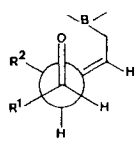
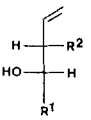
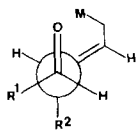
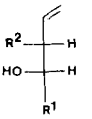
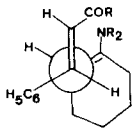
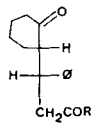
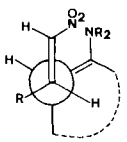
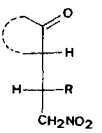
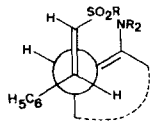
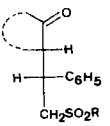
Entry	Starting materials	Topology	Products	Selectivities up to	References
8	(*Z*)-Allyboranes[d][f]) + aldehydes		 *threo*-Homoallylic alcohols	> 95%	[54–56]
9	(*E*)-Alkylborane- or (*E*)-allylchromium derivatives[d]) + aldehydes		 *erythro*-Homoallylic alcohols	99%	[54–58]
10	Enamine from cyclohexanone + cinnamic aldehyde or chalcone		 (*RS; SR*)-Dicarbonyl derivative	> 90%	[42][g])
11	(*E*)-Enamines + (*E*)-nitroolefins		 (*RS; SR*)- or (*RR; SS*)-Nitroketones[a])	99%	[15a–d] and this paper
12	Enamines from cycloalkanones + styryl sulfone		 (*RS; SR*)-Ketosulfone	> 90%	[15e–f]

Table 2 (continued)

a) Although it is of the same family as the reactions in entries 7, 9, 11 and 12, the priority sequence in the particular acceptor of entry 10 *happens* to place this transformation into the (*Re*Si**)-group. The *threo/erythro*-nomenclature is used to describe the configurations of the products in entries 5–9, because in all cases described in the concomitant references, there is no doubt about how to define the carbon chain of the *Fischer*-projection, and therefore, there is no ambiguity of the *threo/erythro*-assignment. In the products of entries 10–12 this is not the case, hence the CIP-nomenclature is employed to describe the relative product configuration, *cf.* footnotes 5 and 6. The product in entry 11 is (*RS; SR*) when R = aryl and (*RR; SS*) when R = alkyl.

b) Instead of the plain lone pair of electrons at the singlet carbene centre, a metal complex (RCH = M^+)[45–47] might be more appropriate here.

c) Sulfur ylids, which are much less stable, do not react selectively under the conditions usually employed [48], *i.e.* in the presence of salts or protic solvents.

d) In agreement with the preference of topology **10** (*syn*-donor) over topology **11** (*anti*-donor), *anti*-enolates (entry 7) furnish lower selectivity [6] and react more slowly [6] (*cf.* [45]), in spite of the fact that their R^2-group is in a *quasi*-equatorial position [6]. – In the case of entries 8 and 9 [R^2 = SR, M = $B(OR)_2$], however, the *anti*-donor is reported to react faster [56], probably because in it the boron has no internal donor ligand.

e) The product configurations of a number of Zn-enolates of esters (*Reformatzky*-reaction, see ref. 21–23 in [35] and ref. 81–85 in [1]) suggest, that the reagents derived from propionic and butyric acid are *syn*-donors fitting topology **10** [R^3 = OR, Y · · · A = OZn(Br)O].

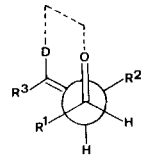
f) *Cf.* the *erythro*-selectivity of the addition of lithiated allyl methyl nitrosamine to benzaldehyde [59].

g) For further examples of diastereoselective *Michael*-additions to enones see also ref. 93–99 in [1].

Some examples suggest that the above rule does not hold, when very bulky groups R^1, R^2 and substituents on Y are present[13]) [5] [6] [9] [37–39]. Also, when the solvent is protic, an *anti*- rather than a *gauche*-relationship, allowing for better solvation of the donor and acceptor heteroatoms, is kinetically preferred[13]) [15f] [40–43].

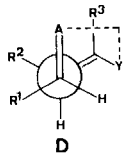
The older [35] and newer literature [1] [44] contains a large number of examples of diastereoselective C,C-bond forming reactions which should be subject to the above topological rule. In many cases, neither the configuration of the reactants, nor that of the products has been determined, more often, the configurations of the products are known while those of reagents generated *in situ* (*cf. syn-* or *anti*-donors) are unknown, so that these reactions could not be included in *Table 2*.

13) Instead of **10** or **11**, the *Re*Re**-topology **C** (*Zimmerman*-approach [9]), or the *Re*Si**-topologies **D**, **E**, **F** may obtain under these conditions.



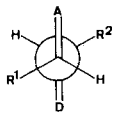
C

(*syn*-donor)
[*Re*Re**, *quasi*-chair]



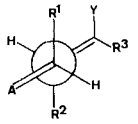
D

(*anti*-donor)
[*Re*Si**, *quasi*-boat]



E

[*Re*Si**, with solvation or complexation at A and D]



F

(*anti*-donor)
[*Re*Si**, with solvation or complexation at A and Y]

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