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Diastereoselective Conjugate Addition and Cyclopropanation Reactions with Nitroalkenes Derived from (*R*)-2,3-Isopropylidene Glyceraldehyde

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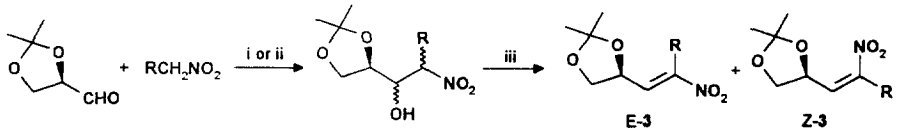
Abstract: In the reactions of functionalized organometallics and of cyclopropanation reagents with chiral nitroalkenes **3** the conjugate addition proceeded with modest to high diastereoselectivity depending on the metal and the substituent R. X-ray analyses showed the nitrocyclopropanes **6**, formed with high stereoselectivity, to be *syn*-derivatives.

Nitroalkenes are versatile synthetic intermediates, being powerful electron-deficient reactants in cycloadditions and conjugate addition reactions. [1] Furthermore the nitro group can be converted into a wide range of functionalities. [2] However, few attempts have been made to use homochiral nitroolefins in asymmetric syntheses. [3] Very recently *Cossio et al.* reported their results on Diels-Alder reactions [4a] and additions of organometallic methyl and phenyl nucleophiles [4b] to γ-chiral nitroalkenes such as E-**3a**. This has prompted us to publish our observations on stereoselective conjugate addition reactions of functionalized carbon nucleophiles and cyclopropanation reactions with nitroolefins derived from (*R*)-2,3-isopropylidene glyceraldehyde **1**.

To prepare the nitroalkenes **3** the diastereomeric mixtures of nitroaldols **2** (accessible from **1** [4b,5]) were dehydrated under mild conditions according to *Seebach*. [6] The (E)- and (Z)-configured nitroalkenes **3** were easily separated by column chromatography.



1 2

3a R=H 90% E/Z = 90 : 10
3b R=CH_3 91% E/Z = 52 : 48

i) KF, ^{i}PrOH, r.t.; ii) NEt_3, r.t.; iii) DCC, CuCl, Et_2O, r.t.

In the non-chiral series many organometallic compounds give 1,4-adducts to nitroalkenes in poor yields. [7] In order to obtain products bearing additional functional groups, we elaborated conjugate addition reactions of various organometallic nucleophiles **4** to the γ-chiral α,β-unsaturated nitro compound (E)-**3a** (see Table 1).

In accordance with the model proposed by *Leonard* and other workers [8] for the conjugate addition of organometallics to enones, the non-chelating zinc-modified copper reagents afforded mainly the *anti*-isomers in modest to high diastereoselectivity (entry 1-3), with the vinyl substituent giving the best result. Remarkably, the vinyl Grignard reagent gave the *syn*-adduct **5'c** (entry 4) with a reversed stereochemistry via a coordinated intermediate. For organolithium compounds the dominant mode of diastereofacial attack in Michael additions

depends on the nature of the organic residue. [8] The observed *anti*-predominance for the alkynyl lithium compounds (entry 5-8) can be rationalized in terms of the soft nucleophilic character of the alkynyl moiety, and thus poor chelation of the lithium atom.

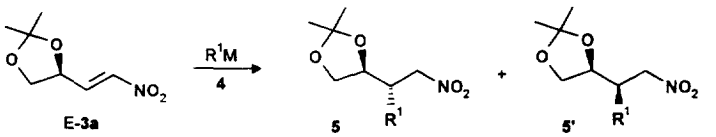


Table 1: Conjugate Addition of Organometallic Nucleophiles to Nitroalkene (E)-**3a**.

Entry	Reagent	Reaction Conditions	Product	Isolated Yield	5 : 5' (*anti* : *syn*)
1	$NC-(CH_2)_3-I$ / Zn / CuCN	- 78°C -> r.t., THF	**5a/5'a**	78 %	60 : 40
2	$CH_2=CH-CH_2-MgBr$ / ZnI_2 / CuCN	- 78°C -> r.t., THF	**5b/5'b**	79 %	70 : 30
3	$CH_2=CH-MgBr$ / ZnI_2 / CuCN	- 78°C -> r.t., THF	**5c/5'c**	57 %	91 : 9
4	$CH_2=CH-MgBr$	- 78°C -> r.t., THF	**5c/5'c**	68 %	10 : 90
5	Ph-C≡C-Li	- 78°C, Et_2O	**5d/5'd**	74 %	67 : 33
6	Ph-C≡C-Li	- 78°C, THF	**5d/5'd**	82 %	73 : 27
7	$Me_3Si-C\equiv C-Li$	- 78°C, THF	**5e/5'e**	71 %	60 : 40
8	$Me_3SiOCH_2-C\equiv C-Li$	- 78°C, THF	**5f/5'f**	40 %	76 : 24

Assignment of the configuration of the products **5** and **5'** followed from ^1H NMR spectroscopic and computational studies. The geometry optimization of the diastereomers **5** and **5'**, using method PM3 of the UniChem® software package, [9] fortunately exhibited a significant preferential conformation for both alternative products. The theoretical coupling constants [10] (3.3 Hz for *syn* and 10 Hz for *anti*-arrangement) correlate well with the data observed (3.3 - 3.4 Hz and 8.9 - 9.5 Hz, respectively) [11] and allow the assignment of *syn*- and *anti*-derivatives.

We also investigated the suitability of nitroolefins **3** for cyclopropanation reactions. Because of the importance of the cyclopropane moiety in biologically active systems, intensive efforts are being made to synthesize optically active cyclopropanes. [12] The nitrocyclopropane moiety is a constituent of biologically active compounds, e.g. nitropyrethroids [13] or the natural peptide-lactone hormaomycin [14], and is a useful intermediate in the synthesis of conformationally restricted aminocyclopropane carboxylic acids. [15] To the best of our knowledge little has been done to obtain enantiomerically pure nitrocyclopropanes, but some are accessible from homochiral sugar-derived nitroalkenes via cyclopropanation. [16] Table 2 summarizes our experimental results with nitroalkene **3** and demonstrates the influence of olefin geometry and cyclopropanation agent on the stereochemical outcome.

In general the cyclopropanation reactions proceeded with good diastereofacial selectivity, obviously caused by steric congestion. Thus the highest asymmetric inductions were observed when the isopropylidene sulfur ylide was reacted with the α-methyl-substituted nitroolefins **3b**. Dibromocarbene, generated in situ via phase transfer catalysis, gave the adduct **6f** in low yield, but only one diastereomer was detected. The isoxazoline N-oxides **7/7'**, observed as a by-product of the cyclopropanation reaction with diphenylsulfonium methylide

(Table 2, entry 4), were formed exclusively if dimethylsulfonium methylide was used (22%, 7 : 7' = 62 : 38). The formation of isoxazoline N-oxides vs. cyclopropanation in the reaction of α-alkylated nitroalkenes with sulfur ylides was recently studied. [17]

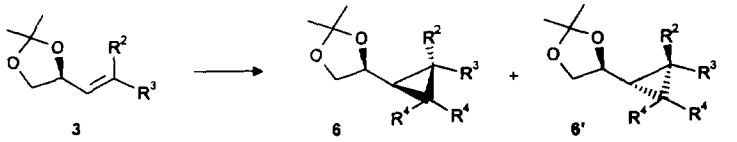


Table 2: Enantiomerically Pure Cyclopropanes 6/6' from Nitroalkenes 3.

Entry	3	Cyclopropanation Conditions	Product	R^2	R^3	R^4	Isolated Yield	6 : 6'
1	E-3a	Ph_2S^+-$C^-(CH_3)_2$ /-78°C	6a/6'a	H	NO_2	CH_3	60 %	70 : 30
2	E-3b	Ph_2S^+-$C^-(CH_3)_2$/-78°C	6b/6'b	CH_3	NO_2	CH_3	89 %	> 95 : 5
3	Z-3b	Ph_2S^+-$C^-(CH_3)_2$/-78°C	6c/6'c	NO_2	CH_3	CH_3	74 %	94 : 6
4	E-3b	Ph_2S^+-CH_2^- /-78°C	6d/6'd	CH_3	NO_2	H	18 % [a]	50 : 50
5	Z-3b	$CHBr_3$/NaOH/TEBA-Cl / r.t.	6f/6'f	NO_2	CH_3	Br	24 %	> 95 : 5

[a] 15 % of 7/7' (1 : 1) was also isolated

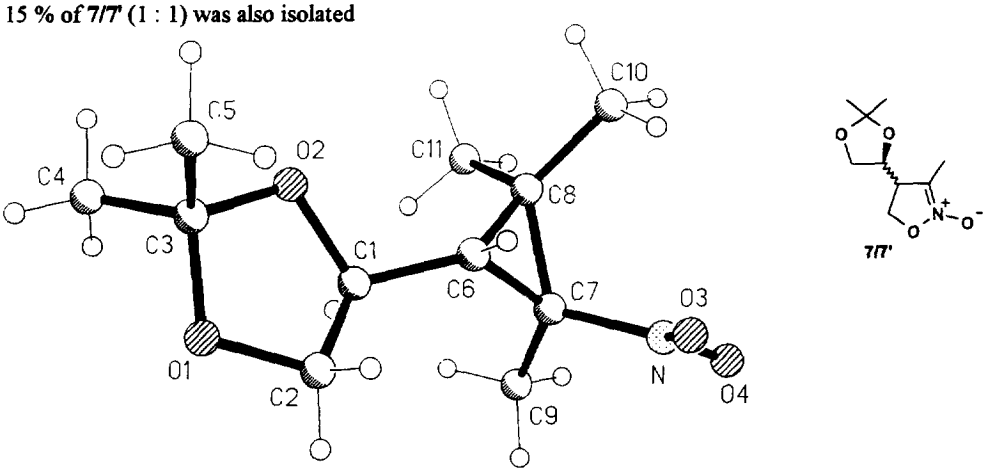


Fig. 1: X-ray structural analysis of nitrocyclopropane 6b

The structural assignment of the isolated cyclopropanes 6 was based on X-ray analyses of compounds 6b (shown in Fig. 1) [18] and 6c. [18] They reveal a *syn*-stereochemistry for the major products arising from the (E)-configured as well as from the (Z)-configured nitroolefin. Hence, the favored approach of the sulfur ylide must take place from the same side of the starting γ-chiral nitroolefin whatever the geometry of its double bond. The same phenomenon has been observed for cyclopropanations of (E)- and (Z)-configured γ-oxygenated α,β-unsaturated esters. [19]

In summary we have demonstrated that the 1,4-addition of methyl and phenyl organometallics to nitroalkenes can be extended to functionalized nucleophiles. This reaction and cyclopropanations of nitroolefins

3 gave comparable results with chiral olefins bearing other electron-withdrawing groups, e.g. COOR and COR, regarding the stereochemical outcome. [8,19] The utilization of the enantiomerically pure nitro compounds **5** and **6** as chiral building blocks for the synthesis of biologically active compounds, such as β-amino acids, is currently under investigation.

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10 . Calculated from measured dihedral angles by means of SpecTool software.
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18 . Crystal Structure Analysis of **6b**: Crystal data: $C_{11}H_{19}NO_4$, space group $P2_1$, a = 663.8 (2), b = 810.71 (14), c = 1206.3 (2) pm, ß = 90.97 (2)°, V = 0.6490 nm^3, Z = 2, T = -130°C. Data collection and reduction: Irregular tablet 0.6 x 0.5 x 0.4 mm, $2\Theta_{max}$ 55° (Mo Kα), Stoe STADI-4 diffractometer; 1337 unique data. Structure solution and refinement: Direct methods, refined anisotropically on F^2 (programm SHELXL-93, G.M. Sheldrick, University of Göttingen). Hydrogen atoms: riding or rigid methyls. Absolute configuration: known at C1). Final $wR(F^2)$ 0.168, for 150 parameters, $R(F)$ 0.060.
Crystal Structure Analysis of **6c** Crystal data: $C_{11}H_{19}NO_4$, space group $P4_1$, a = 1414.4 (3), b = 1414.4 (3), c = 621.97 (12) pm, Z = 4, T = 22°C. Data collection and reduction: colorless needle: 0.6 x 0.18 x 0.15 mm, Stoe IPDS diffractometer; Final $wR(F^2)$ 0.3056, for 146 parameters, $R(F)$ 0.1851. Other details as for **6b**. Full details can be obtained from the Fachinformationszentrum Karlsruhe, Gesellschaft für Wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, Germany. Any request for material should quote a full literature citation and the reference number CSD 405282 (**6b**) and CSD 405288 (**6c**).
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