

37. Reversed Stereochemical Course of the *Michael* Addition of Cyclohexanone to β -Nitrostyrenes by Using 1-(Trimethylsiloxy)cyclohexene/Dichloro(diisopropoxy)titanium

Preliminary Communication

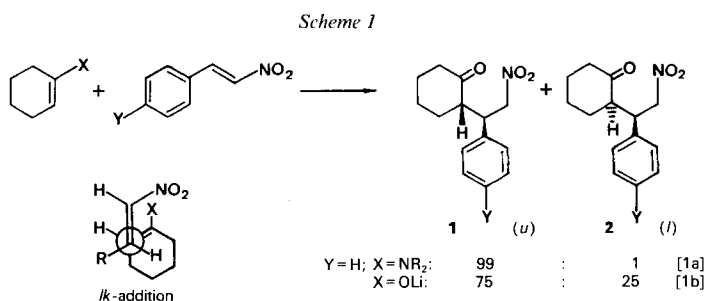
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Induced by a stoichiometric excess of dichloro(diisopropoxy)titanium, 1-(trimethylsiloxy)cyclohexene and *p*-substituted β -nitrostyrenes ($Y = H, CH_3, CH_3O, CN$) combine in CH_2Cl_2 solution at -90° preferentially with relative topicity *ul* – opposite to the corresponding reaction of enolates or enamines. The primary products are the bicyclic nitronates **3–5** which can be separated, and which are cleaved by KF in MeOH to give the aryl(nitroethyl)-substituted cyclohexanones **1** and **2** (Tables 1 and 2, two typical procedures are given). The major products (2:1 to 4:1) are the hitherto not readily available diastereoisomers **2** of *l*-configuration. Instead of being solvolized, the bicyclic nitronate **5** can be used for nitroaldol additions (\rightarrow **6**) and for [3 + 2]-dipolar cycloadditions (\rightarrow **7**), diastereoselectively furnishing products with 4 asymmetric C-atoms (not counting acetal centers). The *Michael* addition described here is yet another example of an *ul*-combination of trigonal centers induced by *Lewis* acids, overriding the influence of the configuration of the donor component.

The *Michael* addition is a powerful method for the construction of C–C bonds. The stereocontrol of this reaction when occurring without ring formation has proven to be a challenge²⁾. In the case of the diastereoselective alkylation of cyclohexanone derivatives by β -nitrostyrenes, many investigations have been described. Thus, *Valentin, Risaliti*, and coworkers [4] have demonstrated that a strong preference for a *lk*-approach³⁾ (*Scheme 1*)



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²⁾ For discussions of diastereoselective and enantioselective cases, see [1–3].

³⁾ For the definition of the *like* (*lk*) and *unlike* (*ul*) descriptors, see [5].

shaken. Neutralization with sat. NaHCO_3 with stirring, extraction with Et_2O , washing of the combined org. layers with H_2O^5 , drying (anh. $\text{MgSO}_4/\text{NaHCO}_3^6$), and evaporation of the solv. at 10 and then at 0.1 Torr lead to the crude crystalline material. The three products **3–5** are separated by flash chromatography using petroleum ether/ Et_2O 2:1 until the first UV-active fraction (**3**) has been eluted and then petroleum ether/ Et_2O 1:2 for elution⁷⁸) of **4** and **5**. The compounds are recrystallized from CHCl_3 /hexanes to give anal. pure materials. The three isomers have very similar $^1\text{H-NMR}$ spectra indicating that they are stereoisomers and not constitutional isomers. The yields of **3–5** are listed in Table 1.

Table 1. Products of the Reaction between 1-(Trimethylsiloxy)cyclohexene and *p*-Substituted β -Nitrostyrenes Induced by (*i*-PrO)₂TiCl₂. See procedure A.

Series	Y in 3, 4, 5	Isolated Yield (% in crude mixture) ^a			Yield	Ratio ul/lk
		3	4	5		
a	H	11 (15)	5 (10)	65 (75)	81% ^b	3:1
b	CH ₃	10 (17)	7 (3)	50 (80)	67%	4:1
c	CH ₃ O	20 (13)	4 (20)	50 (67)	74%	2:1
d	CN	17 (18)	17 (9)	29 (73)	55%	8:3

^a) Determined by $^1\text{H-NMR}$. ^b) The only reaction for which the yield was optimized.

The hydrolysis of the cyclic nitronates **3** and **4** leads to the γ -nitroketones **1**, while the isomers **5** are converted to the epimers **2**, using KF in MeOH, conditions under which epimerization in the α -keto position is not observed⁹). This proves the relative configuration of the newly formed C–C bonds.

In a typical procedure (B), the nitronic ester (0.15 mmol) is dissolved in MeOH (10 ml), and KF (0.01 mmol) is added. After stirring for 2 h at r.t., the soln. is diluted with H_2O , extracted with Et_2O and the org. layer washed

Table 2. Products **1** (*u*-configuration) and **2** (*l*-configuration) of Hydrolysis of the Cyclic Nitronic Esters **3** and **5**. See procedure B.

Starting material	Product ^a)	Yield ^b) [%]	M.p. [°C]	Ref.
3a	1a	86	106.1–106.4	[4] [6]
3b	1b	99	114.2–114.8 ^c)	
3c	1c	93	124.9–125.9 ^d)	[24]
3d	1d	81	124.8–126.2	
5a	2a	96	71.2–71.4	
5b	2b	94	^e)	
5c	2c	83	^e)	
5d	2d	92	110.0–111.0	

^a) The spectroscopic data and combustion analyses are consistent with the proposed structures. ^b) After purification. ^c) The reaction of 1-(morpholino)cyclohexene and *p*-methyl- β -nitrostyrene gave the same product; > 90% yield, m.p. 114.1–114.3°. ^d) The reaction of 1-(morpholino)cyclohexene and *p*-methoxy- β -nitrostyrene gave the same product; > 90% yield, m.p. 125.1–126.5°. ^e) Not crystalline materials.

⁵) The use of sat. NaCl soln. should be avoided.

⁶) The products should not be exposed to acidic conditions.

⁷) In the case of **4d** and **5d**, the silica has to be deactivated with MeOH before use.

⁸) Typically, the AR_f of the major products **3** and **5** is > 0.25 (TLC, silica gel).

⁹) The use of the stronger base, Bu_4NF in THF does lead to epimerization: a 9:1 mixture of **1a/2a** results from either **3a** or **5a**.

with H₂O and brine, dried (MgSO₄), and evaporated at 10 and then 0.1 Torr to give the crude product which is purified by flash chromatography or by recrystallization from CHCl₃/hexanes. The yields of the products **1** and **2** are listed in Table 2. In the ¹H-NMR spectra, all the nitroketones **2** show a pseudo-doublet for CH₂NO₂ (cf. **2a** [4b]), while the isomers **1** exhibit an *ABX* pattern of the corresponding signal (cf. **1a** [4b]). For comparison, samples of **1b** (93% ds) and **1c** (91% ds) were prepared from the morpholino-enamine of cyclohexanone using a modified procedure of Kuehne and Foley [6a] in > 90% yield (cf. [3] [4]).

The *trans*-ring junction of the nitronates **3a** and **5a** (Y = H) was established by NOE (nuclear Overhauser effect) measurements: upon irradiation with the frequency of the (CH₃)₃Si signal, the phenyl signal is enhanced in the latter, but not the former case. Knowing the relative configuration at the newly formed C–C bonds, the ring junction must be *trans* in both cases. By elimination, **4a** must be *cis*-fused. By analogy, the *para*-substituted derivatives **3–5** (Y = CH₃, CH₃O, CN) are assumed to have the same relative configuration at the bridgehead positions.

Preliminary experiments show that the cyclic nitronate **5** can be used for further stereoselective elaboration of the C-skeleton, see the product **6** (m.p. 222.2–224.8° (dec.), yield 66%) obtained by fluoride-catalyzed (Bu₄NF) nitroaldol addition to benzaldehyde (THF, 20°) and the [3 + 2]-cycloadduct **7** (m.p. 143.6–148.6° (dec.), yield 61%) formed with acrylamide (toluene, reflux). For a review on cycloadditions of nitronates see [6b].

There are at least three questions concerning the mechanism of the described reaction of silyl enol ethers with β-nitrostyrenes: *i*) what is the nature of the dependence of the diastereoselectivity on the Lewis acid¹⁰), *ii*) why are 3 equiv. of (i-PrO)₂TiCl₂ required for the reaction to go to completion and, *iii*) why is the stereochemical course¹¹) reversed as compared to the corresponding reactions of β-nitrostyrenes with enamines or enolates? A more detailed discussion of these points must be postponed until our mechanistic investigations have been completed. Some general remarks, however, seem appropriate at this point.

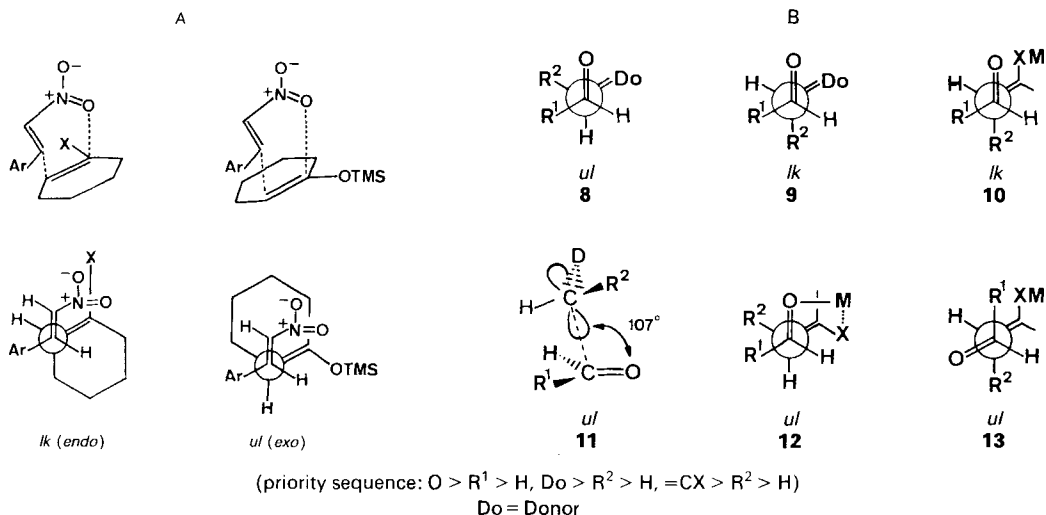
If we consider the reactions of nitroolefins with enol and enamine derivatives as a hetero-Diels-Alder reaction, the use of the Lewis acid in the present modification results in the change-over of an *endo*-(*lk*)¹²) to an *exo*-approach (*ul*) of the reactants, see A in Scheme 3. This suggests that the Lewis acid modifies the reactants in such a way that the normal stereoelectronic effects of the Diels-Alder reaction are overcome [7]. Concerning the diastereoselective C–C bond formation, the reaction may also be considered as a case of addition of two trigonal, prochiral centers, see B in Scheme 3. Generally [1a], this type of reaction occurs preferentially with relative topicity *ul* (**8**), while the opposite steric

¹⁰) Danishefsky and coworkers [7] have described a relationship between the Lewis-acid strength and the diastereoselectivity of the hetero-Diels-Alder reaction between (*E,Z*)-2,4-dimethyl-1-methoxy-3-trimethylsilyloxy-1,3-butadiene and benzaldehyde. With the stronger Lewis acid TiCl₄, a moderate *lk*-selectivity is observed (Mukaiyama reaction [8] [9]). With the weaker Lewis acid MgBr₂, *ul*-addition is preferred. Cf. the present case: non-selective with TiCl₄, *ul*-selective with the weaker Lewis acid (i-PrO)₂TiCl₂.

¹¹) Yoshikoshi and coworkers [10] have described an unstable cyclic nitronic ester from the reaction of 1-(trimethylsilyloxy)cyclohexene and 2-nitropropene. Although not fully characterized, the spectral data of their intermediate are consistent with those of our products **3–5**. The question of the steric course of the reaction was not addressed by Yoshikoshi.

¹²) Many examples of cyclic nitronic esters are known, most of which result from the additions of enamines to substituted nitroolefins (for selected examples see [11]). In all cases for which the diastereoselectivity is known, the products of a *lk*-addition are favored.

Scheme 3



course (9) may be induced by employing donor components of (*E*)-configuration (10). The *Michael* addition under discussion is another example of a growing list of reactions of this type for which the geometry of the donor is relatively unimportant¹³. Most of these reactions are also carried out in the presence of *Lewis* acids, and in all cases the *ul*-approach (8) of the reactants is favored over the *lk*-approach (9). The kinetic advantage of the relative topicity *ul* may be due to [1a], among other things, the optimization of the *Bürgi-Dunitz* approach [21–23], see 11. Although the applicability of this model to the *Lewis* acid induced additions¹³ is uncertain, the proposal of a synclinal, boatlike transition state 12, rather than an antiperiplanar or open transition state 13, is supported by related work, for instance with trichlorotitanium enolates [15b] and allylstannanes [17b].

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¹³) Some selected examples of enolates which undergo the aldol reaction with an *ul*-approach of the reactants, regardless of the enolate geometry are; Sn [12], Si [13], $(Me_2N)_3S^+$ (TAS) [14], Ti [15], and Zr [16] enolates. Analogously, allyl derivatives of Sn [17] and Si [18] add to aldehydes with an *ul*-approach, regardless of the geometry of the olefin, silyl nitronates exhibit a strong preference for an *ul*-addition to aldehydes [19], and the cyclization of linalool to α -terpineol occurs with an *ul*-approach [20].

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