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Silylated Pyrrolidines as Catalysts for Asymmetric Michael Additions of Aldehydes to Nitroolefins

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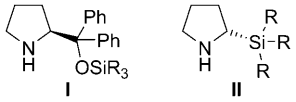
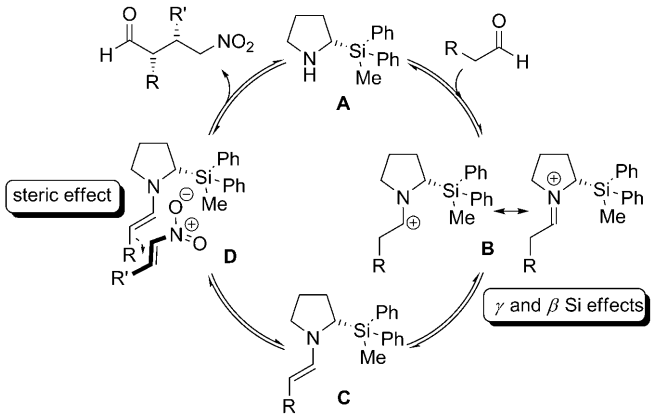
Silicon-containing compounds play an important role in organic chemistry. In the field of organocatalysis the incorporation of silyl groups allows steric and electronic modifications, which lead to catalytic systems with improved properties.[1] The first example of 4-siloxyproline reported by Hayashi et al.[2] and, in particular, the introduction of silylated L-prolinol derivatives **I**, simultaneously developed by the groups of Hayashi and Jørgensen,[3] were major breakthroughs in this field.[4] It is noteworthy that in these catalysts, silicon is always bound through an oxygen atom, thus acting as a sterically demanding protecting group of a hydroxyl function. Many other rationally designed organocatalysts have been described since the pioneering work by the groups of List and MacMillan.[4–6] Herein, we present the synthesis of enantiopure 2-silylated pyrrolidines **II** and the application of such compounds as asymmetric organocatalysts.



I **II**

Our group has focused on the synthesis of α-silyl-α-amino acids[7] and related silicon-containing compounds.[8] In this context it was shown that α-silylated α-hydroxyacetic acids were effective as chiral ligands in aldol-type reactions.[8a] These findings and a thorough analysis of the widely accepted mechanism of the 1,4-conjugate addition of enamine nucleophiles[9,10] led us to hypothesize that a pyrrolidine with a silicon group directly attached in the α position to the nitrogen atom of the heterocyclic core could be an effective organocatalyst. The stabilization of a positive charge in the vicinity of the silicon atom[11] is a key factor, and its use in asymmetric organocatalysis conceptually new. In this scenario (Scheme 1), iminium-type structure **B** is formed from catalyst **A** and the reacting aldehyde. The silicon effects could facilitate this initial, crucial step and thereby promote the catalytic cycle. Enamine **C** is formed from intermediate **B**. Also in this step the silicon group is key, because its bulk affects the preferential formation of the *E* diastereomer. Subsequently, a new C–C bond is formed by the addition of **C** to the unsaturated electrophile, for example, a nitroolefin. Here, the silicon supports the substrate orientation and provides the basis for the enantioselective coupling. Finally, the product is released and the catalyst liberated.



Scheme 1. Proposed mechanism for a 2-silylated pyrrolidine catalyzed Michael addition.

The synthesis of trimethylsilylated *N*-*tert*-butyloxycarbonyl (*N*-Boc)-protected pyrrolidines by asymmetric deprotonation of *N*-Boc-pyrrolidine was first described by Beak et al. and further investigated independently by the groups of O'Brien and Coldham.[12] Their optimized procedure was employed here for the preparation of silylated *N*-Boc-pyrro-

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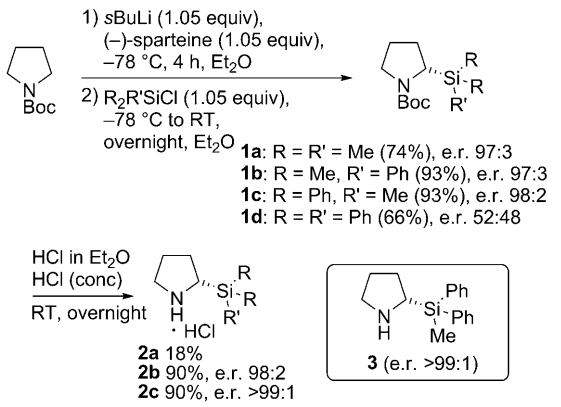
lidines **1a–d** (Scheme 2).[13] In accordance with the literature, products **1a** and **1b** were obtained with high enantioselectivities in good yields.[12] Along the same lines, *N*-Boc-2-



Scheme 2. Synthesis of enantiopure (*S*)-2-(diphenylmethylsilyl)pyrrolidine (**3**).

(diphenylmethylsilyl)pyrrolidine (**1c**) was formed with an enantiomeric ratio (e.r.) of 98:2 in 93% yield. Unexpectedly, silylation with triphenylsilyl chloride gave the corresponding product **1d** only in moderate yield and, furthermore, product **1d** was almost racemic. Deprotection of **1a–c** was effected with hydrochloric acid to give the hydrochloric salts **2a–c**. Whereas (*S*)-2-(trimethylsilyl)pyrrolidine HCl salt (**2a**) was obtained in low yield, compounds **2b** and **2c** were isolated in 90% and quantitative yield, respectively. Recrystallization of **2c** from a mixture of CH_2Cl_2/MeOH afforded the enantiopure HCl salt of (*S*)-2-(diphenylmethylsilyl)pyrrolidine (**2c**) in 90% yield. The e.r. values were determined by HPLC analysis after converting the HCl salts **2a–c** into their benzoyl-protected derivatives.[14] Finally, treatment of **2c** with base afforded the free amine **3** in quantitative yield.

The absolute configuration of (*S*)-**2c** was determined by X-ray analysis by employing Flack's method.[15] (X_{abs} = −0.036(79) for the structure shown in Figure 1).

Next, (*S*)-2-(diphenylmethylsilyl)pyrrolidine (**3**) was applied in catalytic asymmetric Michael addition reactions of propanal (**4a**) and butanal (**4b**) to nitroolefins (Table 1). Solvent screening experiments showed that a mixture of toluene/THF (5:1) gave the best results in terms of stereoselectivity and yield (Table 1, entry 1).[14] To our delight, under the optimized conditions essentially all diastereomeric ratio (d.r.) and e.r. values were on the >90:*x* level, and the yields ranged from 87 to 99%. The only exception was the reaction between propanal and 2-(2-nitrovinyl)furan, which gave the corresponding product **6i** with a lower e.r. (89:11) in a yield of only 88% (Table 1, entry 9). In general, all reactions with propanal (**4a**) were complete within 15–22 h (Table 1, entries 1–9). Although using butanal (**4b**) required longer reaction times (46 and 48 h), the stereoselectivities and yields were on the same level (Table 1, entries 10 and 11).

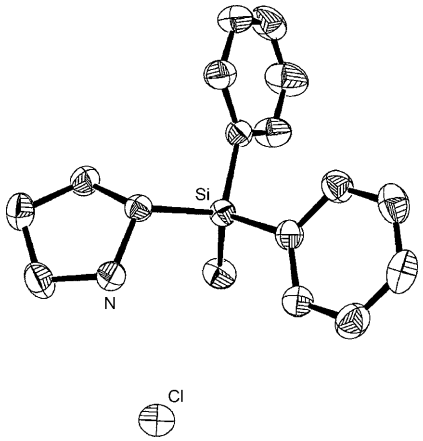


Figure 1. Crystal structure of (*S*)-2-(diphenylmethylsilyl)pyrrolidine HCl salt (**2c**).[16] Ellipsoids at the 50% level.

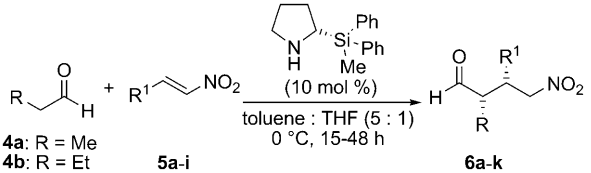
The best overall result was achieved in a Michael addition reaction of propanal to *trans*-4-methyl-β-nitrostyrene, which afforded product **6g** with a *syn*/*anti* ratio of 96:4, an e.r. (for the *syn* diastereomer) of 95:5 in a yield of 98% (Table 1, entry 7).

In conclusion, a conceptually new type of chiral organocatalyst has been found, and its applicability in asymmetric Michael-type addition reactions has been demonstrated. This initial study was performed with (*S*)-2-(diphenylmethylsilyl)pyrrolidine, which is readily accessible in enantiomerically pure form by asymmetric synthesis. Its absolute configuration was determined by X-ray crystal structure analysis of the HCl salt. High stereoselectivities and yields have been achieved in catalyzed enantioselective additions of propanal and butanal to nitroolefins. These promising results form the basis for subsequent studies, which have the goal to introduce new silyl-substituted organocatalysts with improved properties and to find additional applications of the current catalyst system.[17]

Experimental Section

General procedure for the Michael addition: A solution of silylated pyrrolidine **3** (0.05 mmol) and aldehyde (5.00 mmol) in toluene/THF (5:1, 1.5 mL) was cooled to 0°C and stirred for 30 min under an atmosphere of Ar. Then, the nitroolefin (0.50 mmol) was added and the reaction was monitored by TLC. When full conversion was indicated, the reaction was stopped by the addition of a 1 M aqueous solution of HCl. The aqueous layer was extracted with CH_2Cl_2 (3×), and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. After determination of the diastereomeric ratio by ^{1}H NMR spectroscopy, the product was purified by column chromatography. The enantiomeric ratio was measured by HPLC using a chiral stationary phase. The HPLC conditions and spectral data of all compounds are provided in the Supporting Information.

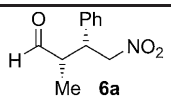
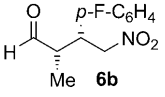
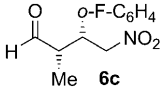
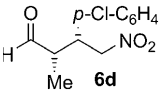
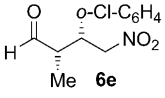
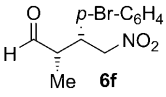
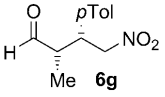
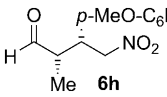
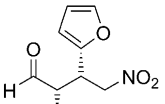
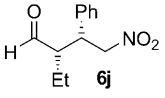
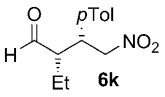
Table 1. Michael addition of aldehydes **4** to nitroolefins **5** catalyzed by (*S*)-2-(diphenylmethylsilyl)pyrrolidine (**3**).[a]



4a: R = Me
4b: R = Et

5a-i

6a-k

Entry	Product	*t* [h]	Yield [%][b]	*syn*/*anti*[c]	e.r.[d]
1	 **6a**	17	96	95:5	94:6
2	 **6b**	22	93	95:5	92:8
3	 **6c**	15	96	97:3	92:8
4	 **6d**	19	99	95:5	93:7
5	 **6e**	15	96	92:8	93:7
6	 **6f**	22	87	97:3	93:7
7	 **6g**	22	98	96:4	95:5
8	 **6h**	22	93	96:4	94:6
9	 **6i**	22	88	96:4	89:11
10	 **6j**	46	95	95:5	94:6
11	 **6k**	48	90	94:6	95:5

[a] Conditions: aldehyde **4** (5 mmol), nitroolefin **5** (0.5 mmol), catalyst **3** (0.05 mmol), solvent (1.5 mL), 0 °C. [b] After column chromatography. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude product. [d] Determined by HPLC analysis using a chiral stationary phase (e.r. values of the *syn* diastereomers are given).[14]

Acknowledgements

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Keywords: asymmetric synthesis · Michael addition · organocatalysis · silicon · silylated pyrrolidines

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[16] Single-crystal X-ray diffraction analysis of **2c**: $C_{17}H_{22}ClNSi$, colorless crystals, space group $P2_12_12_1(19)$, $Z=4$, $a=7.4665(2)$ Å, $b=9.0303(3)$ Å, $c=24.9057(8)$ Å, $V=1679.26(9)$ Å^3, $\rho_{calcd}=1.202$ Mg m^{-3}, $T=293$ K, $Mo_{K\alpha}$, $\lambda=0.71073$ Å, $\Theta_{max}=35.3°$, data collection: Bruker KAPPA APEX II, structure solution: Xtal3.7 (The Xtal 3.7 System, S. R. Hall, D. J. Du Bolay, R. Olthof-Hazekamp, University of Western Australia, **2001**), refinement on F, $R(R_w)=0.054(0.040)$, $S=1.571$, for 265 parameters and 6144 reflections with $I>2\sigma(I)$, hydrogen atoms located and refined isotropically, residual electron density $-0.724/0.599$ e Å^{-3}. CCDC-778923 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] Editorial note: see also closely related paper by C. Strohmann, M. Christmann, and co-workers: J. O. Bauer, J. Stiller, E. Marqués-López, K. Strohfeldt, M. Christmann, C. Strohmann, *Chem. Eur. J.* **2010**, DOI: 10.1002/chem.201002166

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