α-Silyl Controlled Asymmetric Michael Additions of Acyclic and Cyclic Ketones to Nitroalkenes

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Received 5 March 1999

Abstract: Virtually enantiopure α-*t*-butyldimethylsilyl ketones (*R*)-**1** and (*S*)-**5** are converted regioselectively to the corresponding trimethylsilyl enol ethers (*R*)-**2** and (*S,Z*)-**6**. Subsequent asymmetric Michael addition to nitroalkenes in the presence of $SnCl_4$ affords the 1,4-adducts **3** and **7** in good yields and high diastereo- and enantiomeric excesses. Removal of the *t*-butyldimethylsilyl group with *n*-Bu_4NF, THF, NH_4F/HF leads to the α,β-disubstituted γ-nitro ketones (*S,R*)-**4** (*de* = 91-92 %, *ee* > 98 %) and (*R,S*)-**8** (*de* > 96 %, *ee* > 98 %) in very good overall yields.

Key words: asymmetric synthesis, Michael addition, α-silyl ketones, nitroalkenes, nitro ketones

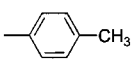
The Michael addition is one of the most important methods for C-C-bond formation in synthetic chemistry[1] and a great variety of asymmetric versions of this name reaction have been developed in recent years.[2]

Nitroalkenes are of special interest as excellent Michael acceptors due to their low tendency for 1,2-addition and the strong anion-stabilizing effect of the nitro group.[3] The latter is an important functional group which can be transformed into other functionalities, such as the carbonyl group via Nef reaction or the amino group by reduction.[4]

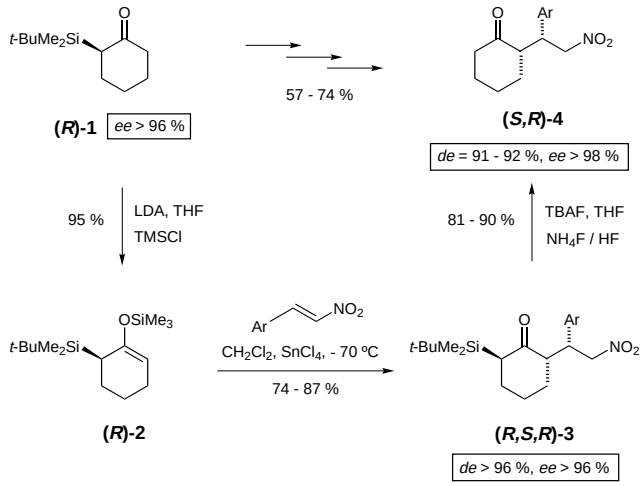
We now wish to report a new efficient method for the diastereo- and enantioselective synthesis of α,β-disubstituted γ-nitro ketones with high diastereomeric and enantiomeric excesses via α-*t*-butyldimethylsilyl ketones, which can be easily prepared based on the SAMP/RAMP-hydrazone methodology.[5] The synthetic utility of the concept of α-silyl ketone control in asymmetric synthesis has already been demonstrated by us in various other applications.[6]

As is depicted in Scheme 1, initially the silyl ketone **1** was converted regioselectively to the corresponding silyl enol ether **2** by deprotonation with lithium diisopropylamide and treatment with chlorotrimethylsilane. Deprotonation at the stereogenic centre and thus racemisation did not occur, because the approach of the amide is hindered by the bulky silyl group resulting in formation of the desired, enantiomerically pure silyl enol ether in almost quantitative yield (95%). Due to the cyclic structure of silyl ketone **1**, the procedure leads to the (*R*)-configuration of **2**, which was used as nucleophile in the asymmetric Michael addition to nitroalkenes. It was found necessary to employ Lewis acids in order to promote the 1,4-addition in dichloromethane.[7] Accordingly, a variety of Lewis acids were screened, with $AlCl_3$ and $LiClO_4$ resulting in no product formation, $TiCl_4$ affording many by-products and BF_3•OEt_2 causing partial removal of the α-silyl group. Best results were obtained by the use of $SnCl_4$, with Michael additions taking place with little by-product formation. After simple workup and isolation, the silyl nitro ketones **3** were obtained in good yields and excellent diastereo- and enantiomeric excesses (*de*,*ee* > 96 %). The absolute configuration of crystalline **3a** could be determined by X-ray structure analysis. The (*R,S,R*)-configuration obtained indicates the expected *trans* orientation of the silyl group and the introduced nitroalkane moiety at the six-membered ring and is assumed for all compounds **3a-c**. The final step required the removal of the *t*-butyldimethylsilyl directing group with *n*-Bu_4NF and NH_4F/HF as a buffer system, resulting in the formation of α,β-disubstituted γ-nitro ketones **4** in very good yields. Desilylation with *n*-Bu_4NF alone caused epimerisation at the α-position, which was dramatically reduced in the presence of NH_4F/HF. Nevertheless, partial epimerisation could not be avoided. The very high diastereomeric excesses (*de* = 91-92 %) were determined by NMR and the excellent enantiomeric excesses (ee > 98 %) by HPLC on chiral stationary phases (Table 1).

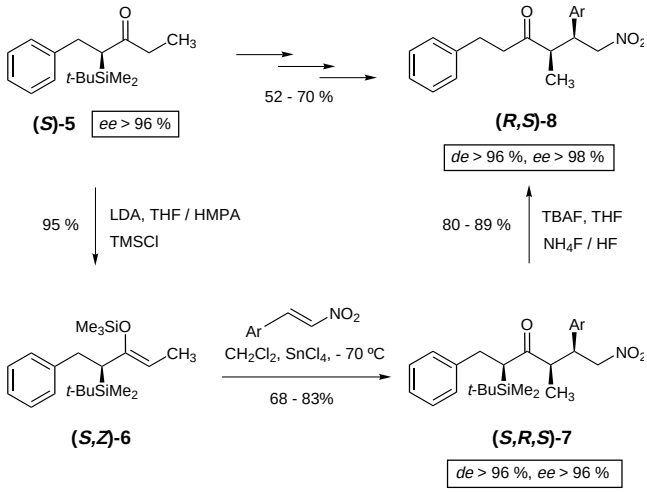
Table 1 α-Silyl Controlled Asymmetric Michael Addition of Cyclic Ketones to Nitroalkenes

4	Ar	overall yield [%]	*de* [a] [%]	*ee* [b] [%]
(*S,R*)-4a		74	91	> 98
(*S,R*)-4b		69	92	> 98
(*S,R*)-4c		57	92	> 98

[a] Determined by NMR. [b] Determined by HPLC on chiral stationary phases : Chiralpak AD (4.6 x 250 mm), (*S,S*)-Whelk-0 1 (4 x 250 mm)



Scheme 1

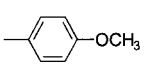


Scheme 2

Starting from acyclic ketones such as **5** (Scheme 2) for the preparation of silyl enol ethers leads to the selectivity problem of *E*/*Z*-geometry. Metalation with lithium diisopropylamide and treatment with chlorotrimethylsilane generates both the *E*- and *Z*-silyl enol ethers. However, to obtain high inductions in asymmetric reactions it is essential to employ stereochemically uniform enol ethers.

Thus, metalation in the presence of HMPA[8] as a strong cation solvating compound allowed regio- and stereoselective access to the pure (*S*,*Z*)-silyl enol ether **6** in excellent yield (95%). Subsequent $SnCl_4$ promoted asymmetric Michael additions to nitroalkenes yielded the virtually diastereo- and enantiomerically pure 1,4-adducts **7** (*de*, *ee* > 96 %) in good yields (Scheme 2). The absolute configuration could be determined by X-ray structure analysis of crystalline **7a** as (*S*,*R*,*S*) indicating the all *syn* orientation.[9] Removal of the *t*-butyldimethylsilyl group with *n*-Bu_4NF and NH_4F/HF gave the α,β-disubstituted γ-nitro ketones **8** in very good yields and high diastereo- and enantiomeric excesses (*de* > 96 %, *ee* > 98 %).[10] It is noteworthy that in this case no epimerisation was observed as was in case of nitroketones **4** (Table 2).

Table 2 α-Silyl Controlled Asymmetric Michael Addition of Acyclic Ketones to Nitroalkenes

8	Ar	overall yield [%]	*de* [a] [%]	*ee* [b] [%]
(*R*,*S*)-8a		52	> 96	> 98
(*R*,*S*)-8b		68	> 96	> 98
(*R*,*S*)-8c		70	> 96	> 98

[a] Determined by NMR. [b] Determined by HPLC on chiral stationary phases : Chiralpak AD (4.6 x 250 mm), (*S*,*S*)-Whelk-0 1 (4 x 250 mm)

General procedures:

Synthesis of silyl enol ether (S,Z)-6: To a solution of 12 mmol diisopropylamine in 50 ml dry THF was added 12 mmol *n*-butyllithium (1.6 M in *n*-hexane) at 0 °C. After stirring for 20 min 14 ml of HMPA were added and the yellow solution was cooled to −80 °C. A solution of the α-silyl ketone **5** (10 mmol)[5] in 10 ml dry THF was added slowly and the reaction mixture was stirred at this temperature for 30 min. After addition of 16 mmol Me_3SiCl the solution was allowed to warm to room temperature over 30 min. The mixture was quenched with a saturated solution of $NaHCO_3$ (25 ml). The aqueous layer was separated, extracted with *n*-pentane and the combined organic layers washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. To remove the residue of HMPA the crude *Z*-silyl enol ether was dissolved in a little *n*-pentane and eluated with *n*-pentane through a small column of neutral Al_2O_3 and the solvent removed *in vacuo*. The obtained silyl enol ether (3.3 g, 95%) was used for the preparation of the Michael adducts.

Asymmetric Michael addition: A solution of 7.5 mmol $SnCl_4$ in dry CH_2Cl_2 (20 ml) was cooled to −70 °C. A solution of 7.5 mmol nitroalkene in dry CH_2Cl_2 (5 ml) was then added. After stirring for 10 min, the intensely coloured mixture was treated dropwise with a solution of the silyl enol ether **6** in dry CH_2Cl_2 (5 ml) and stirred for 48 hours (24 hours for cyclic silyl enol ether **2**) at −70 °C. The reaction was quenched by pouring the reaction mixture into a well stirred emulsion of diethyl ether and a saturated $NaHCO_3$ solution. The organic layer was separated and the aqueous layer extracted with diethyl ether. The combined organic phase was washed with brine, dried (Na_2SO_4) und concentrated *in vacuo*. The crude product was purified by flash chromatoghraphy (SiO_2, Et_2O/*n*-pentane) and washing with *n*-pentane to afford **7**.

Removal of the t-butyldimethylsilyl group: A solution of 5 mmol Michael adduct **7** in dry THF (50 ml) was cooled to −50 °C. Then 100 mmol NH_4F, 1 ml aqueous 48% HF und

5.5 mmol *n*-Bu_4NF (1M in THF) were added and the solution was allowed to warm. When only a very small residue of starting material could be detected (TLC control) it was hydrolyzed with a saturated $NaHCO_3$ solution, extracted with diethyl ether, washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, Et_2O/*n*-pentane) to give **8**.

In summary, an efficient asymmetric synthesis of cyclic and acyclic α,β-disubstituted γ-nitro ketones in good overall yields and with excellent diastereo- and enantiomeric excesses (*de* = 91 - > 96 %, *ee* > 98 %) has been developed employing 1,4-additions of α-silyl ketones to nitroalkenes.

Acknowledgement

This work was supported by the Deutsche Forschungsgemeinschaft (Leibniz prize) and the Fonds der Chemischen Industrie. We thank Degussa AG, BASF AG, Bayer AG, former Hoechst AG and Wakker Chemie for the donation of chemicals.

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(9) Analytical data of compound **7a**: mp: 115 °C, $[\alpha]_D^{RT}$: −92.5 (*c* = 1.10, $CHCl_3$), IR (KBr): ν = 1681 (C=O) cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.06 (s, 3H, SiC<u>H</u>$_3$), 0.18 (s, 3H, SiC<u>H</u>$_3$), 0.79 (d, ^3J = 7.0 Hz, 3H, C<u>H</u>$_3$CH), 1.02 (s, 9H, C(C<u>H</u>$_3$)$_3$), 2.41 (dq, ^3J = 8.2 Hz, ^3J = 7.0 Hz, 1H, CH_3C<u>H</u>), 2.92 (dd, ^2J = 13.4 Hz, ^3J = 1.8 Hz, 1H, C<u>H</u>$_2$-Ph), 3.00 (dd, ^3J = 12.2 Hz, ^3J = 2.1 Hz, 1H, C<u>H</u>Si), 3.21 (dd, ^2J = 13.4 Hz, ^3J = 12.5 Hz, 1H, C<u>H</u>$_2$-Ph), 3.33 (ddd, ^3J = 9.5 Hz, ^3J = 8.5 Hz, ^3J = 5.5 Hz, 1H, C<u>H</u>Ph), 3.73 (dd, ^2J = 12.8 Hz, ^3J = 9.8 Hz, 1H, C<u>H</u>$_2$NO$_2$), 3.85 (dd, ^2J = 12.8 Hz, ^3J = 5.5 Hz, 1H, C<u>H</u>$_2$NO$_2$), 6.68 (m, 2H, Ph), 7.16 (m, 3H, Ph), 7.18 - 7.26 (m, 3H, Ph), 7.31 (m, 2H, Ph). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = − 6.3 (Si<u>C</u>H$_3$), − 4.7 (Si<u>C</u>H$_3$), 14.8 (<u>C</u>H$_3$CH), 18.3 (<u>C</u>(CH$_3$)$_3$), 27.1 (C(<u>C</u>H$_3$)$_3$), 34.9 (<u>C</u>H$_2$-Ph), 46.1 (<u>C</u>HPh), 47.6 (<u>C</u>HSi), 49.8 (CH_3<u>C</u>H), 77.4 (<u>C</u>H$_2$NO$_2$), 126.8 (C_p^{Ph}),127.5 (C_p^{Ph}),127.9 (C^{Ph}), 128.5 (C^{Ph}), 128.7 (C^{Ph}), 128.9 (C^{Ph}), 137.1 (C_q^{Ph}), 141.9 (C_q^{Ph}), 213.2 (C=O). MS (70eV): m/z (%): 368 (19.6, M^{+-} *t*-Bu), 307 (3.4), 281 (9.7), 247 (33.9), 207 (48.5), 163 (24.1), 149 (100), 131 (30.5), 91 (39.1), 69 (51.2), 57 (71.0).
$C_{25}H_{35}NO_3Si$ calc.C 70.55 H 8.29 N 3.29
(425.65)found 70.24 8.463.17

(10) Analytical data of compound **8a**: mp: 92 °C, $[\alpha]_D^{RT:}$ −6.5 (*c* = 1.00, $CHCl_3$), IR (KBr): ν = 1707 (C=O) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, ^3J = 7.2 Hz, 3H, C<u>H</u>$_3$CH), 2.72-2.79 (m, 1H, C<u>H</u>$_2$), 2.84-2.95 (m, 4H, 2C<u>H</u>$_2$, C<u>H</u>-Ph), 3.65 (ddd, ^3J = 9.4 Hz, ^3J = 9.4 Hz, ^3J = 4.9 Hz, 1H, C<u>H</u>Ph), 4.45 (dd, ^2J = 12.4 Hz, ^3J = 4.9 Hz, 1H, C<u>H</u>$_2$NO$_2$), 4.52 (dd, ^2J = 12.4 Hz, ^3J = 9.2 Hz, 1H, C<u>H</u>$_2$NO$_2$), 7.10 (m, 2H, Ph), 7.18 (m, 2H, Ph), 7.21 - 7.33 (m, 6H, Ph). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 15.9 (<u>C</u>H$_3$CH), 29.9 (<u>C</u>H$_2$-Ph), 43.6 (<u>C</u>H$_2$CO), 45.9 (<u>C</u>H-Ph), 48.8 (<u>C</u>HCO), 78.1 (<u>C</u>H$_2$NO$_2$), 126.3 (C^{Ph}),127.9 (C^{Ph}), 128.0 (C^{Ph}), 128.4 (C^{Ph}), 128.6 (C^{Ph}), 129.0 (C^{Ph}), 137.5 (C_q^{Ph}), 140.7 (C_q^{Ph}), 212.0 (C=O). MS (70eV): m/z (%): 311 (M^+), 177 (9.5), 159 (4.7), 133 (16.8), 131 (24.6), 105 (84.9), 91(100) 77 (14.3), 65 (8.3).
$C_{19}H_{21}NO_3$ calc.C 73.29 H 6.80 N 4.50
(311.38)found 73.25 6.98 4.42

Article Identifier:
1437-2096,E;1999,0,06,0747,0749,ftx,en;G09099ST.pdf