Asymmetric Mannich Reactions with α-Silylated Trimethylsilyl Enol Ethers and *N*-Alkoxycarbonyl Imines

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Abstract: The Mannich reaction of enantiomerically pure α-dimethylthexylsilylated trimethylsilyl enol ether (*Z*,*S*)-**2** with titanium complexes of *N*-alkoxycarbonyl imines afforded α´-silylated α,β-disubstituted β-amino ketones (*S*,*R*,*S*)-**4a**–**e** in good to excellent yields (70–92%) and diastereomeric excesses (*de* ≥ 96%). Removal of the directing silyl group gave *N*-protected and *anti*-configured β-amino ketones (*R*,*S*)-**5a**–**e** in excellent yields (90–95%) and stereoselectivities (*de*, *ee* ≥ 96%– > 98%).

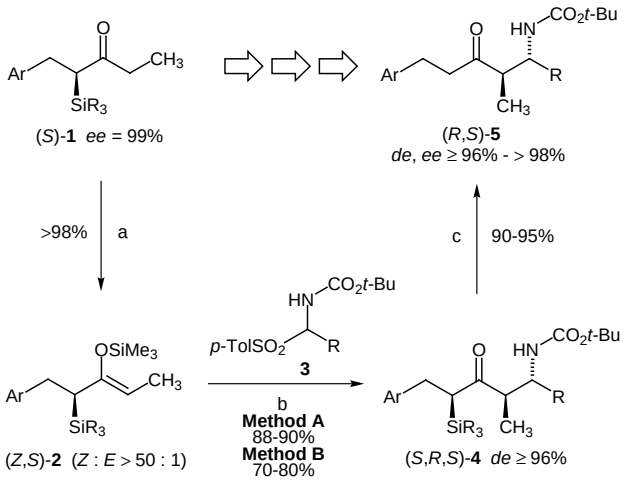
Key words: asymmetric synthesis, Mannich reaction, α-silyl ketones, α-amino sulfones, β-amino ketones

Many nitrogen-containing natural products and pharmacologically active compounds contain the β-amino ketone substructure. In this context asymmetric Mannich reactions have been investigated extensively in recent years to obtain optically active β-amino ketones and esters or derivatives such as γ-amino alcohols because their pharmacological activity usually correlates with the configuration.[1,2]

Acyl- or alkoxycarbonyl imines have been applied in intermolecular asymmetric Mannich reactions for the synthesis of β-amino ketones, esters or acids using chiral nucleophiles (enamines,[3] ketoenolates[4]), chiral electrophiles (α-chloroalkylamides,[5] oxazolidinones[6]), achiral trimethylsilyl enol ethers, keto- or esterenolates[7] or catalytically active chiral metal complexes.[8]

Recently, we reported the immobilization of α-alkoxycarbonylamino sulfones and their application in the solid-phase synthesis of β-amino ketones and sixring carbamates.[9] However, nothing is reported about the Mannich reaction of enantiopure silyl enol ethers with *N*-alkoxycarbonyl imines and their application for the stereoselective synthesis of β-amino ketones. We herein present a successful strategy for the diastereo- and enantioselective synthesis of acyclic *anti*-configured *N*-alkoxycarbonylated α,β-disubstituted β-amino ketones via the α-silyl controlled Mannich reaction.

Enantiomerically pure α-silyl ketones (*S*)-**1** are attractive chiral substrates for various applications in asymmetric synthesis[10] including Mannich reactions[11] and Michael reactions[12]. *N*-Alkoxycarbonylamino sulfones **3** are easily prepared starting from aldehydes, *tert*-butyl carbamate, sodium *p*-toluenesulfinate and formic acid in $MeOH/H_2O$. The carbamates are formed as analytically pure colorless precipitates in good yields (65–85%).[4b,13] The metalation of the acyclic α-dimethylthexylsilyl ketone (*S*)-**1** with LDA in THF/HMPA, followed by the addition of chlorotrimethylsilane at −78 °C yielded the α-silylated trimethylsilyl enol ether (*Z*,*S*)-**2** quantitatively and with a high excess of the *Z*-isomer (Scheme).[11,12,14] The geometrical purity of the *Z*-isomer is crucial to reach high stereoselectivity in the following addition to the *N*-alkoxycarbonyl imines as complete diastereofacial selection arises from the directing dimethylthexylsilyl group.



Scheme *Reagents and conditions*: a) THF, HMPA, LDA, TMSCl, –78 °C → r.t. b) **Method A)** CH_2Cl_2, KH, **3**, 1 h, r.t.; –78 °C, $TiCl_4$, 20 min; –90 °C, then **2**, –90 °C → –78 °C, 75 min. **Method B)** CH_2Cl_2, **3**, –78 °C, $TiCl_4$, 20 min; –90 °C, then **2**, –90 °C → –78 °C, 75 min. c) THF, TBAF, NH_4F, –78 °C → r.t.

β-Elimination with the α-alkoxycarbonylamino sulfones **3** using potassium hydride at room temperature in dichloromethane yields in situ uncharged *N*-alkoxycarbonyl imines. The addition of 1.5 equiv $TiCl_4$ to the solution of the imine at −78 °C results in the formation of a titanium *N*-alkoxycarbonyl imine complex. The reaction with the α-silylated silyl enol ether (*Z*,*S*)-**2** at −90 °C to −78 °C afforded α´-silylated α,β-disubstituted β-amino ketones (*S*,*R*,*S*)-**4a**–**e** in excellent yields (88–92%) and *anti* diastereoselectivities (*de* ≥ 96%) (Table 1, method A, entry 1–5).[15] The addition of 1.1 equiv $TiCl_4$ gave **4a** only in a

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Table 1 Synthesis of α´-Silylated α,β-Disubstituted β-Amino Ketones (*S*,*R*,*S*)-**4a**–**e**

Method	entry	**4**	R	equiv $TiCl_4$	Yield[a] (%)	*de*[b] (%)
A	1	**a**	Ph	1.5	90	≥96
	2	**b**	*p*-MeOPh	1.5	89	≥96
	3	**c**	*p*-*tert*-BuPh	1.5	88	≥96
	4	**d**	2-furyl	1.5	88	≥96
	5	**e**	*p*-MePh	1.5	92	≥96
	6	**a**	Ph	1.1	71	≥96
B	7	**a**	Ph	1.5	77	≥96
	8	**a**	Ph	1.1	70	≥96
	9	**b**	*p*-MeOPh	1.5	80	≥96
	10	**c**	*p*-*tert*-BuPh	1.5	75	≥96

[a] Yields of the analytically pure products after flash chromatography.
[b] Determined by ^1H and ^{13}C NMR spectroscopy.

moderate yield of 71% (Table 1, entry 6). The relative configuration was determined by NOE experiments of compounds **4a** and **4e**. The enantiomerically pure α-silyl ketones (*S*)-**1** are synthesized using the SAMP-hydrazone method. It is known, that the absolute configuration of the stereogenic centre in α-position of **1** is (*S*) as determined by X-ray structure analysis.[10,11] The relative configurations determined by NOE analysis represent the absolute configurations (*S*,*R*,*S*) of the Mannich adducts **4a**–**e**.

Cleavage of the *p*-toluenesulfinate leaving group starting from carbamates **3** is also possible with Lewis acids exclusively. As shown in the Scheme and Table 1, the $TiCl_4$ promoted reaction of carbamates **3** with the α-silylated silyl enol ether (*Z*,*S*)-**2** at −90 °C to −78 °C afforded α´-silylated α,β-disubstituted β-amino ketones (*S*,*R*,*S*)-**4a**–**c** with excellent *anti* diastereoselectivity (*de* ≥ 96%), but only in moderate yields (70–80%) (Table 1, method B, entry 7-10).[15]

As shown in the Scheme and Table 2, the virtually diastereomerically pure α´-silylated α,β-disubstituted β-amino ketones (*S*,*R*,*S*)-**4a**–**e** are easily converted to the *anti*-configured α,β-disubstituted β-amino ketones (*R*,*S*)-**5a**–**e** in excellent yields (90–95%).

Cleavage of the α-dimethylthexylsilyl group could lead to epimerization in α-position of the newly formed stereogenic centre of the β-amino ketones **5**. For the removal of the directing group we used ammonium fluoride as buffer and TBAF at −78 °C.[16] This procedure[11] prevents epimerization in α-position and resulted in the formation of the *anti*-configured α,β-disubstituted β-amino ketones (*R*,*S*)-**5a**–**e** in excellent yields (90–95%), diastereomeric (*de* ≥ 96%–>98%) and enantiomeric excesses (*ee* ≥ 96%–> 98%) as shown by NMR-spectroscopy and HPLC.

Table 2 Synthesis of *anti*-Configured α,β-Disubstituted β-Amino Ketones (*R*,*S*)-**5a**–**e**.

5	R	Yield[a] (%)	*de*[b] (%)	*ee*[c] (%)
a	Ph	95	>98[d]	>98[d]
b	*p*-MeOPh	93	≥96	≥96
c	*p*-*tert*-BuPh	90	≥96	≥96
d	2-furyl	94	≥96	≥96
e	*p*-MePh	92	≥96	≥96

[a] Yields of the analytically pure products after crystallization.
[b] Determined by ^1H- and ^{13}C-NMR spectroscopy.
[c] Related to the diastereomeric excesses established for the α´-silylated α,β-disubstituted β-amino ketones (*S*,*R*,*S*)-**4b**–**e**.
[d] Determined by HPLC on chiral stationary phase (Daicel OD, 250 mm × 4.6 mm).

In summary, an efficient diastereo- and enantioselective synthesis of *N*-alkoxycarbonylated *anti*-configured β-amino ketones in good overall yields and with excellent diastereo- and enantiomeric excesses has been developed employing the α-silyl controlled Mannich reaction and using α-alkoxycarbonyl imines as electrophiles.[17]

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(15) *Asymmetric Mannich Reactions*:
Method A: 1.2 Equiv potassium hydride was added to a solution of 1.1 equiv carbamate **3** in dry CH_2Cl_2 (5 mL/mmol **3**) under argon. After stirring for 1 h at r.t. the reaction mixture was cooled to −78 °C. After addition of 1.1–1.5 equiv $TiCl_4$ (1.0 N in CH_2Cl_2) and stirring for 20 min at this temperature the solution was cooled to −90 °C. 1 equiv Silyl enol ether **2** in dry CH_2Cl_2 (1 mL/mmol **2**) was added dropwise. The reaction mixture was stirred for 75 min at −90 °C → −78 °C, then quenched with a saturated solution of $NaHCO_3$, extracted with CH_2Cl_2 and dried over $MgSO_4$. After evaporation of the solvent, the crude Mannich adducts **4** were purified by flash chromatography (SiO_2, *n*-pentane/Et_2O).
Method B: A solution of 1.1 equiv carbamate **3** in dry CH_2Cl_2 (5 mL/mmol) under argon was cooled to −78 °C. After addition of 1.1–1.5 $TiCl_4$ (1.0 N in CH_2Cl_2) and stirring for 20 min at this temperature the solution was cooled to −90 °C. 1 equiv Silyl enol ether **2** in dry CH_2Cl_2 (1 mL/mmol **2**) was added dropwise. (Further procedure see **Method A**).
Analytical data of compound (*S*,*R*,*S*)-**4a**:
$[\alpha]_D^{24}$ = −93.6 ($CHCl_3$, c = 0.50). ^{1}H NMR [400 MHz, $(CD_3)_2$ CO]: δ = 0.08 (s, 3 H, SiC*H*$_3$), 0.16 (s, 3 H, SiC*H*$_3$), 0.90 (d, 3 H, *J* = 6.8, CHC*H*$_3$), 0.91 (d, 3 H, *J* = 6.9, C*H*$_3$CHCH$_3$), 0.93 (d, 3 H, *J* = 6.9, CH$_3$CHC*H*$_3$), 0.94 (s, 3 H, C*H*$_3$CCH$_3$), 0.95 (s, 3 H, CH$_3$CC*H*$_3$), 1.40 (s, 9 H, OC(C*H*$_3$)$_3$), 1.77 (sept, 1 H, *J* = 6.9, CH$_3$C*H*CH$_3$), 2.77 (m, 1 H, C*H*HC$_6$H$_4$Br), 3.07 (qd, 1 H, *J* = 6.9, 3.3, C*H*CH$_3$), 3.13–3.24 (m, 2 H, CH*H*C$_6$H$_4$Br, SiC*H*), 4.70 (d, 1 H, *J* = 8.3, C*H*NH), 6.00 (m, 1 H, N*H*), 6.66 (m, 2 H, C*H*-Ph), 7.10–7.47 (m, 7 H, C*H*-C$_6$H$_4$Br, *m*/*p*C*H*-Ph) ppm. ^{13}C NMR [100 MHz, $(CD_3)_2CO$]: δ = −3.7 (SiCH$_3$), −2.0 (SiCH$_3$), 13.3 (*C*H$_3$), 18.9 (*C*H$_3$CHCH$_3$), 19.1 (CH$_3$CHCH$_3$), 21.5 (*C*H$_3$CCH$_3$), 21.8 (CH$_3$C*C*H$_3$), 25.7 (CH$_3$*C*CH$_3$), 28.5 (OC(*C*H$_3$)$_3$), 33.7 (*C*H$_2$C$_6$H$_4$Br), 34.9 (CH$_3$*C*HCH$_3$), 47.4 (Si*C*H), 53.1 (*C*HCH$_3$), 56.5 (*C*HNH), 79.1 (O*C*(CH$_3$)$_3$), 120.0 (*C*-C$_6$H$_4$Br), 127.2 (*p*CH-Ph), 127.4 (*C*H-Ph), 128.4 (*m*CH-Ph), 131.2 (*C*H-C$_6$H$_4$Br), 132.0 (*C*H-C$_6$H$_4$Br), 140.4 (*C*-Ph), 142.1 (*C*-C$_6$H$_4$Br), 155.6 (O*C*=O), 211.8 (*C*=O) ppm. MS (CI, isobutane): *m/z* (%): 591(35), 590 (100, M^+ + 1), 589(33), 588(90), 534(47), 533(28), 532(48), 529(8), 526(6), 512(6), 511(22), 510(59), 504(7), 502(6), 491(14), 490(50), 489(14), 488(46), 454(15), 447(20), 446(12), 411(11), 410(36), 368(7), 305(7), 206(20), 150(9), 106(20). Anal. Calcd. for $C_{31}H_{46}NO_3SiBr$ (588.70): C, 63.25; H, 7.88; N, 2.38. Found: C, 63.22; H, 7.75; N, 2.30.
(16) *For removal of the dimethylthexylsilyl group see ref. 11b.*
Analytical data of compound (*R*,*S*)-**5a**:
$[\alpha]_D^{24}$ = −29.0 ($CHCl_3$, c = 0.50). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (d, 3 H, *J* = 6.9, CHC*H*$_3$), 1.41 (s, 9 H, OC(C*H*$_3$)$_3$), 2.15–2.70 (m, 4 H, C*H*$_2$C*H*$_2$), 3.05 (m, 1 H, C*H*CH$_3$), 4.81 (m, 1 H, C*H*NH), 5.87 (m, 1 H, N*H*), 6.87 (d, 2 H, *J* = 8.3, C*H*-Ph), 7.10–7.35 (m, 7 H, C*H*-C$_6$H$_4$Br, *m*/*p*C*H*-Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1 (*C*H$_3$), 28.3 (OC(*C*H$_3$)$_3$), 28.4 (*C*H$_2$C$_6$H$_4$Br), 44.2 (*C*H$_2$CO), 51.0 (CO*C*HCH$_3$), 57.0 (*C*HNH), 79.4 (O*C*(CH$_3$)$_3$), 119.6 (*C*-C$_6$H$_4$Br), 125.9 (*p*CH-Ph), 127.1 (*C*H-Ph), 128.4 (*m*CH-Ph), 129.8 (*C*H-C$_6$H$_4$Br), 131.2 (*C*H-C$_6$H$_4$Br), 139.6 (*C*-Ph), 141.0 (*C*-C$_6$H$_4$Br), 155.3 (O*C*=O), 213.2 (*C*=O) ppm. MS (EI, 70 eV): *m/z* (%): 447 (1, M^+), 390(23), 389(21), 211(4), 207(4), 206(34), 184(4), 182(4), 170(13), 169(13), 151(9), 150(100), 147(4), 134(4), 132(7), 118(15), 117(9), 107(6), 106(70), 104(9), 77(5), 57(59). Anal. Calcd. for $C_{23}H_{28}NO_3Br$ (446.38): C 61.89, H 6.23, N 3.14. Found: C, 61.82; H, 6.30; N, 3.00.
(17) All new compounds showed suitable spectroscopic data (NMR, MS, IR) and correct elemental analyses.