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Enantioselective synthesis of protected α-aminoketones via electrophilic amination of α-silylketones with an oxaziridine

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Abstract

N-Boc protected α-aminoketones (**4**) of moderate enantiomeric purity were synthesised via N-Boc-3-(4-cyanophenyl)-oxaziridine (**5**) mediated electrophilic amination of enantiopure α-silyl ketones (**2**) followed by removal of the silyl directing group in the aminated products (**3**) with tetrabutylammonium fluoride in a buffer solution.

1. Introduction

The electrophilic α-amination of carbonyl compounds is an important C–N connective process in organic synthesis.[1] This interest in the direct amination of organometallic reagents is reflected in the continuing development of a variety of electrophilic aminating reagents such as hydroxylamine derivatives,[2] sulfonylazides,[3] di-*tert*-butylazodicarboxylate (DBAD),[4] oxaziridines[5] and 1-chloro-1-nitroso reagents.[6] In addition, asymmetric versions of electrophilic aminations have been developed recently, especially those in the α-position of carbonyl compounds.[7]

The synthesis of enantiomerically pure α-aminoketones is of general interest in that it provides a direct route to a large variety of biologically significant compounds.[8] As part of our ongoing project on electrophilic aminations[9] we now wish to describe the synthesis of N-Boc protected α-aminoketones starting from enantiopure α-silylketones and using an oxaziridine as the aminating reagent to transfer the NHBoc group.[5]

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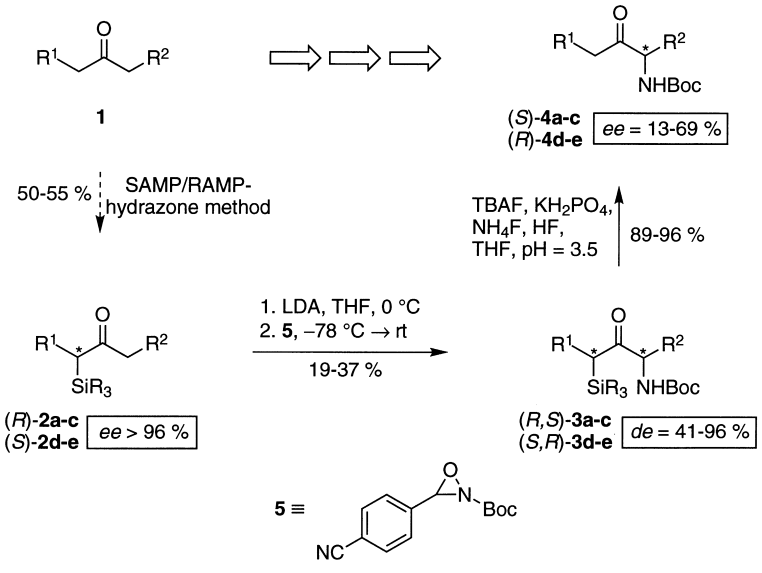
2. Results and discussion

Besides chiral hydrazones, enantiomerically pure α-*tert*-butyldimethylsilyl (TBS) and α-*tert*-hexyldimethylsilyl (TDS) substituted ketones can also serve as a ketone equivalent in asymmetric synthesis, whereby the silyl group functions as the 'traceless' directing group.[10] The synthetic pathway to enantiomerically pure α-silylketones employing the SAMP/RAMP-hydrazone methodology has been well established.[10] They can be regioselectively deprotonated with lithium diisopropylamide (LDA) in the α′-position and are reactive enolate nucleophiles. The first step in the synthesis of the title N-Boc protected α-aminoketones is the transformation of ketones **1** into the corresponding and virtually enantiopure α-silylketone derivatives **2** using the standard procedure.[10a,e] Subsequent metallation with lithium diisopropylamide (LDA) at 0°C generates the enolate, which is trapped by the oxaziridine (**5**) at −78°C or −100°C to yield the α-aminated α′-silylketones **3**. Finally, cleavage of the silyl controlling group with tetrabutylammonium fluoride (TBAF)/NH_4F/HF/KH_2PO_4 yielded the target molecules as N-Boc protected α-aminoketones **4** (Scheme 1).



Scheme 1.

In a typical experimental procedure, the α-silylketones **2** were metallated in THF at 0°C for 4 h and then a pre-cooled solution of the oxaziridine (**5**) was added to the enolate at −78°C. The reaction was continued overnight to room temperature followed by quenching with a pH 7 buffer solution. An extractive work-up followed by purification by column chromatography yielded the N-Boc protected α′-silyl-α-aminoketones (Table 1).

At present, two competing side reactions cause the relatively low chemical yields of the amination reaction. Firstly, hydroxylation to **6** instead of amination and secondly, aldol reaction to form the adduct **7** (Scheme 2). The asymmetric hydroxylation using 2-(phenylsulfonyl)-3-phenyloxaziridine has already been reported by our group.[11] The important factor to be considered here is the electron withdrawing substituent effect on the nitrogen atom which makes it more electrophilic. Efforts to trap the cyanobenzaldehyde formed during the amination with benzylamine in situ in order to prevent the competing aldol addition have not been successful.

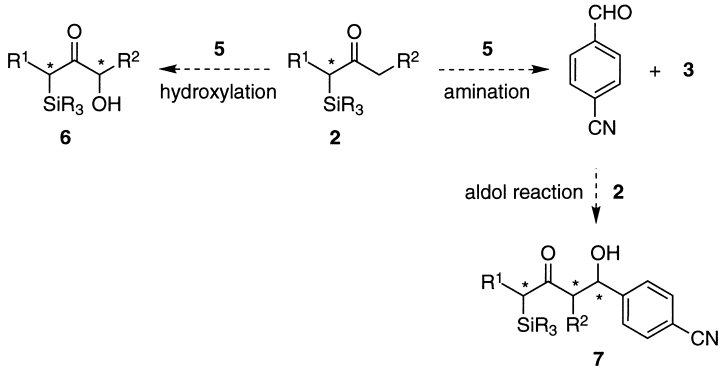
The determination of the diastereomeric excesses was done by ^{1}H NMR spectroscopy. Two dia-

Table 1

3	R^1	R^2	R_3	temp.(°C)	yield(%)[a]	*de* (%)
a	Me	Me	Me_2Bu^t	–100	27	80(96)[b]
b	Et	Et	Me_2Bu^t	–100	37	87(96)[b]
c	*n*-Pr	*n*-Pr	Me_2Bu^t	–100	29	88
d	Bn	Me	Me_2Hex^t	–78	20	83
e	Me	Bn	Me_2Bu^t	–78	19	41

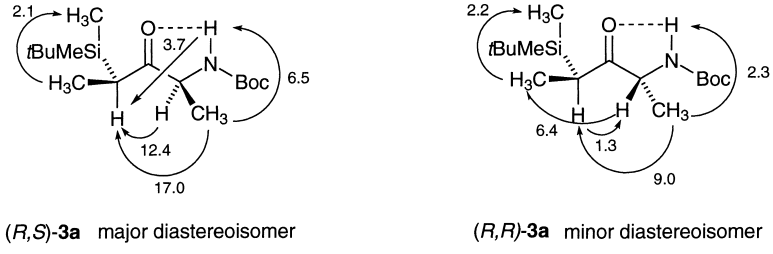
[a] Yield of isolated product after column chromatography.

[b] After preparative HPLC.



Scheme 2.

stereoisomers could be observed. The absolute configurations given are based on NOE experiments of **3a** as is depicted in Scheme 3.



(*R,S*)-**3a** major diastereoisomer (*R,R*)-**3a** minor diastereoisomer

Scheme 3.

The configuration determined for **3a** is (*R,S*) for the major diastereomer and (*R,R*) for the minor one based on the well established (*R*)-configuration of the silyl substituted carbon.[10] During NMR studies we observed that the nitrogen atom, the carbonyl function and the carbon atom α to the carbonyl function are forced into one plane because of hydrogen bonding. The major diastereomer is formed by the attack of the electrophile from the less hindered face of the enolate. The fact that the *de*-value is low for compound **3e** can be explained by a steric effect of the substituent at the α carbon. The reaction proceeded to completion only at higher temperatures which results in low selectivity.

The next step involved was the cleavage of the TBS and the TDS directing group to obtain the desired N-Boc protected α-aminoketones. The easiest cleavage method was to use TBAF. However, this method led to cleavage with complete racemisation of the α-aminoketone. In order to prevent racemisation,

Table 2

4	R^1	R^2	yield(%)[a]	*ee* (%)
a	Me	Me	89	69[b]
b	Et	Et	96	13[c]
c	*n*-Pr	*n*-Pr	96	49[b]
d	Bn	Me	95	42[c]
e	Me	Bn	96	13[b]

[a] Yield of isolated product after column chromatography.

[b] Determined by GC using a chiral stationary phase.

[c] Determined by HPLC using a chiral stationary phase.

temperature and buffer system variations were studied. The best condition found was to carry out the reaction at −78 to −20°C with TBAF and a buffer solution of NH_4F, K_2HPO_4, HF. Neutralisation was carried out with pH 7 buffer. An extractive work-up followed by chromatographic purification yielded, almost quantitatively, the α-aminoketone in moderate enantiomeric excesses, indicating partial racemisation. The results are summarised in Table 2.

In conclusion, we have achieved the asymmetric synthesis of α-aminoketones in moderate yields and *ee*-values using an oxaziridine as the electrophilic aminating reagent.

3. Experimental

The melting points (Büchi apparatus system Dr. Tottoli) are uncorrected. IR spectra: Perkin–Elmer FT 1760 spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR spectra (75 MHz): Varian VXR 300 and Gemini 300 (δ in ppm, TMS as internal standard). Mass spectra were recorded on a Varian MAT 212 (70 eV) and Finnigan SSQ 7000 (70 eV) spectrometer with DEI ionisation and are represented as *m/z* (%). Microanalyses were obtained using a Heraeus CHN–O-Rapid element analyser. Optical rotation values were measured using a Perkin–Elmer P 241 polarimeter.

Chemicals: All reactions were carried out under argon. The reagents were of commercial quality from freshly opened containers or purified prior to use. *n*-BuLi (1.6 N in hexane) was purchased from Merck, Darmstadt. Tetrahydrofuran was freshly distilled from potassium under argon. Flash column chromatography was carried out using Merck silica gel 60. Reactions were monitored by TLC using Merck plates (silica gel F_{254}) and visualised using 5% phosphomolybdic acid solution in ethanol. α-Silylketones **2** were prepared following standard literature procedures.[10]

*3.1. General procedure for amination with the oxaziridine **5***

In a typical reaction procedure, a cooled (−78°C or −100°C) solution of the lithium enolate of the silylketone (formed by the reaction of 1 mmol of the silylketone (**2**) in 2 ml THF with 1.1 mmol of LDA at 0°C for 4 h) was treated with a pre-cooled solution of 1.1 mmol oxaziridine in 2 ml THF via cannula. The reaction was allowed to proceed overnight to room temperature and quenched with a pH 7 buffer solution. An extractive work-up, followed by column chromatography (SiO_2, pentane:ether, 2:1) afforded the aminated product **3**.

In the case of doubled signals, the NMR data of the major diastereomer are marked *.

3.2. (2S,4R)-2-(t-Butoxycarbonylamino)-4-(t-butyldimethylsilanyl)pentan-3-one **3a**

Yield: 85 mg (27%). Viscous liquid. $[\alpha]_D^{28}$ −48 (*c* 1.00; $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.00, 0.01* (s, 3H, $SiCH_3CH_3$), 0.08*, 0.10 (s, 3H, $SiCH_3CH_3$), 0.95 (s, 9H, $Si(CH_3)_3$), 1.25, 1.26* (d, J_3=6.9 Hz, 3H, $CHSiCH_3$), 1.27, 1.32* (d, J_3=7.2 Hz, 3H, $CHNCH_3$), 1.44*, 1.45 (s, 9H, $OC(CH_3)_3$), 2.65*, 2.75 (q, J_3=7.0 Hz, 1H, CHSi), 4.35*, 4.36 (quin, J_3=7.2 Hz, 1H, CHN), 5.00, 5.53* (d, br, J_3=7.2 Hz, 1H, NH) ppm. ^{13}C NMR ($CDC1_3$, 75 MHz): δ −7.5*, −7.2, −6.3*, −5.6, 12.9*, 13.6, 17.1, 17.9*, 17.8, 19.0*, 26.8*, 26.9, 28.3, 28.4*, 34.4, 34.7*, 54.0, 55.6*, 79.3*, 79.7*, 154.9*, 155.2, 212.1, 212.5 ppm. IR ($CHCl_3$, cm^{-1}): 3429, 3362 (NH), 1717 (C=O), 1691 (C=O). MS (70 eV, 80°C) *m/z* (%): 317 (M^++2) (1), 203 (11), 202 (68), 172 (5), 171 (35), 159 (7), 144 (24), 143 (11), 131 (6), 118 (69), 116 (9), 115 (75), 103 (14), 100 (6), 88 (26), 86 (8), 85 (29), 75 (48), 74 (15), 73 (100), 59 (21), 58 (16), 57 (96), 56 (6), 55 (6). $C_{16}H_{33}NO_3Si$ (315.5): calcd C 60.91, H 10.54, N 4.44. Found C 60.34, H 10.55, N 5.29.

3.3. (2S,5R)-3-(t-Butoxycarbonylamino)-5-(t-butyldimethylsilanyl)heptan-4-one **3b**

Yield: 127 mg (37%). Viscous liquid. $[\alpha]_D^{28}$ +220 (*c* 1.00; $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ −0.02, 0.00* (s, 3H, $SiCH_3CH_3$) 0.08*, 0.09 (s, 3H, $SiCH_3CH_3$), 0.85*, 0.88 (dd, 3H, $SiCHCH_2CH_3$, J_3=7.1, 7.4 Hz), 0.96*, 0.97 (dd, 3H, $CHNCH_2CH_3$, J_3=7.1, 7.4 Hz), 0.98 (s, 9H, $SiC(CH_3)_3$), 1.42–1.60 (m, 2H, $SiCHCH_2CH_3$), 1.46*, 1.49 (s, 9H, $OC(CH_3)_3$), 1.70–2.10, 1.90–2.15* (m, 2H, $NCHCH_2CH_3$), 2.58*, 2.74 (dd, J_3=9.37, 1.65 Hz, 1H, CHSi), 4.16, 4.29* (dt, J_3=9.6, 4.4 Hz, 1H, CHN), 4.63, 5.47* (d, br, J_3=9.8 Hz, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ −7.2*, −6.6, −6.2*, −5.0, 9.4*, 10.8, 15.6*, 16.1, 18.0*, 18.5, 21.3*, 22.8, 23.9, 25.1*, 26.8*, 27.5, 28.3*, 28.9, 44.8, 45.1*, 60.6*, 61.0, 79.2*, 80.2, 155.3*, 156.3, 210.6*, 211.7 ppm. IR ($CHC1_3$, cm^{-1}): 3431, 3365 (NH), 1719 (C=O), 1687 (C=O). MS (70 eV, 60°C) *m/z* (%): 344 (M^++1) (1), 272 (4), 271 (8), 239 (99), 231 (17), 186 (15), 185 (84), 158 (27), 129 (33), 118 (51), 115 (66), 113 (18), 102 (60), 99 (8), 85 (9), 75 (27), 74 (13), 73 (100), 59 (18), 58 (83), 57 (77), 55 (7). $C_{18}H_{37}NO_3Si$ (343.6): calcd C 62.92, H 10.85, N 4.08. Found C 61.98, H 10.68, N 4.42.

3.4. (4S,6R)-4-(t-Butoxycarbonylamino)-6-(t-butyldimethylsilanyl)nonan-5-one **3c**

Yield: 107 mg (29%). Viscous liquid. $[\alpha]_D^{28}$ −46.7 (*c* 1.03; $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.01 (s, 3H, $SiCH_3CH_3$), 0.03 (s, 3H, $SiCH_3CH_3$), 0.90–0.97 (m, 6H, $2\times CH_2CH_3$), 0.98 (s, 9H, $SiC(CH_3)_3$, 1.05–1.54 (m, 6H, CH_2CH_2CHSi, CH_2CH_2CHN), 1.46*, 1.49 (s, 9H, $OC(CH_3)_3$), 1.90 (m, 1H, CHHCHN), 2.10 (m, 1H, CHHCHN), 2.69*, 2.89 (dd, J_3=11.8, 1.9 Hz, 1H, CHSi), 4.20, 4.33* (m, 1H, CHN), 4.62, 5.44* (d, br, *J*=8.4 Hz, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ −7.1, −6.2, 13.9, 14.1, 18.0, 18.6, 24.1, 26.8*, 27.0, 28.3, 30.2, 34.6, 42.9, 59.5, 155.3, 210.8 ppm. IR (Et_2O, cm^{-1}): 3430, 3364 (NH), 1719 (C=O), 1688 (C=O). MS (70 eV, 80°C) *m/z* (%): 259 (7), 258 (38), 200 (10), 199 (61), 172 (15), 143 (23), 141 (14), 118 (34), 117 (7), 116 (73), 115 (5), 85 (14), 83 (5), 81 (7), 75 (21), 74 (12), 73 (100), 72 (61), 59 (18), 58 (7), 57 (77), 55 (13). $C_{20}H_{41}NO_3Si$ (371.6): calcd C 64.64, H 11.12, N 3.77. Found C 65.32, H 11.21, N 3.67.

3.5. (2S,4R)-4-t-Butoxycarbonylamino-2-(dimethyl-(1,1,2-trimethylpropyl)-silanyl)-1-phenylpentan-3-one **3d**

Yield: 80 mg (19%). Viscous liquid. $[\alpha]_D^{28}$ −128 (*c* 0.75; $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.04*, 0.05 (s, 3H, $SiCH_3CH_3$), 0.20*, 0.22 (s, 3H, $SiCH_3CH_3$), 0.54*, 0.95 (d, J_3=7.1 Hz, 3H, $CHCH_3$),

0.92–1.02 (m, 12H, SiC(CH_3)$_2$CH(CH_3)$_2$), 1.38, 1.39* (s, 9H, OC(CH_3)$_3$, 1.78 (sept, J_3=10.3 Hz, 1H, SiC(CH_3)$_2$CH(CH_3)$_2$), 2.76–3.28 (m, 3H, CH_2CHSi), 4.13 (m, 1H, CHN), 3.79, 5.42* (d, br, J_3=7.5 Hz, 1H, NH), 7.08 (m, 2H, O–Ar–*H*), 7.13–7.26 (m, 4H, *m/p*-Ar–H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ −4.8, −3.8*, −3.3, 15.7, 16.7*, 18.6, 18.8*, 21.2, 21.4*, 24.9, 25.0*, 28.3, 28.3*, 34.0*, 43.9, 34.6*, 34.6, 44.0, 46.3, 54.2, 55.8*, 79.2*, 79.4, 126.2*, 126.2, 128.2, 128.4*, 128.5*, 128.6, 142.5*, 142.7, 154.8, 209.6*, 210.1 ppm. IR ($CHCl_3$, cm^{-1}): 3425, 3368 (NH), 1716 (C=O), 1693 (C=O). MS (70 eV, 80°C) *m/z* (%): 420 (M^++1) (1), 280 (5), 279 (21), 278 (100), 276 (5), 275 (20), 192 (10), 191 (62), 162 (5), 161 (25), 147 (10), 144 (6), 143 (13), 128 (5), 118 (41), 91 (5), 75 (19), 74 (9), 59 (12), 57 (46). $C_{24}H_{41}NO_3Si$ (419.4): calcd C 68.67, H 9.85, N 3.34. Found C 68.28, H 9.73, N 4.29.

*3.6. (2*S*,4*R*)-4-t-Butoxycarbonylamino)-2-t-(butyldimethylsilanyl)-5-phenyl-pentan-3-one **3e***

Yield: 72 mg (20%). Viscous liquid. $[\alpha]_D^{28}$ +18.8 (*c* 1.25, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.04 (s, 3H, SiCH_3CH$_3$), 0.05 (s, 3H, SiCHCH_3), 0.89*, 0.93 (s, 9H, SiC(CH_3)$_3$), 1.10*, 1.15 (d, ^3J=6.7 Hz, 3H, SiCHCH_3), 1.38, 1.47* (s, 9H, OC(CH_3)$_3$), 2.24 (d, ^3J=6.7 Hz, 1H, CHSi), 1.91 (dd, ^3J=8.4 Hz, ^3J=13.4 Hz, 1H, NCHCHH), 3.10 (dd, ^3J=5.3 Hz, ^3J=13.4 Hz, 1H, NCHCHH), 4.45, 4.58* (ddd, *J*=5.4/8.2/10.7 Hz, 1H, CHN), 5.32, 5.52* (d, br, ^3J=8.1 Hz, 1H, NH), 7.23 (m, 2H, *O*–Ar–*H*), 7.26–7.38 (m, 4H, *m/p*-Ar–*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ −7.4, −6.1, 11.9, 17.8, 26.6, 28.2, 28.3*, 37.0, 40.3*, 41.2, 61.2*, 62.5, 79.4, 126.9, 128.5, 129.3, 136.8, 154.8, 211.1 ppm. IR ($CHC1_3$, cm^{-1}): 3431, 3361 (NH), 1716 (C=O), 1686 (C=O). MS (70 eV, 60°C) *m/z* (%): 392 (M^++1) (0.5), 334 (8), 318 (5), 279 (18), 278 (85), 220 (15), 171 (20), 165 (12), 164 (100), 161 (15), 143 (6), 128 (6), 121 (8), 120 (88), 119 (5), 118 (54), 116 (7), 115 (48), 91, 75 (31), 74 (10), 73 (81), 59 (8), 57(75). $C_{22}H_{37}NO_3Si$ (406.5): calcd C 62.06; H 8.37, N 13.79. Found C 62.80, H 8.38, N 13.83.

3.7. General procedure for the removal of the silyl directing group

In a typical procedure the α-aminated silylketone (**3**) (1 mmol) in 2 ml of THF was subjected to cleavage at −78 to −20°C with 1.5 mmol of TBAF and a buffer solution of NH_4F/KH_2PO_4/HF. The completion of the reaction was monitored by TLC. The reaction was quenched using a pH 7 buffer solution. An extractive work-up followed by column chromatography (SiO_2, pentane:ether, 4:1) yielded the α-aminoketone (**4**).

*3.8. (*S*)-2-t-Butoxycarbonylamino-pentan-3-one **4a***

Yield: 18 mg (89%). Viscous liquid. $[\alpha]_D^{28}$ −24.4 (*c* 0.27; $CHCl_3$), *ee*=69% (CSP, δ-lactone, 80-30-Iso-3-190). GC: R_t=7.1 (OV-17, 80-10-260). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.09 (dd, J_3=7.1 Hz, J_2=7.4 Hz, 3H, CH$_2$CH_3), 1.33 (d, J_3=7.1 Hz, 3H, CHCH_3), 1.44 (s, 9H, C(CH_3)$_3$), 2.41–2.65 (dt, J_3=7.1 Hz, J_4=7.4 Hz, 2H, CH_2CH$_3$), 4.33 (quin, J_3=7.1 Hz, 1H, CHN), 5.28 (s, br, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 7.6, 18.1, 28.4, 32.3, 54.9, 79.7, 154.6, 210.3 ppm. IR ($CHCl_3$, cm^{-1}): 3358 (NH), 1710 (C=O). MS (70 eV, 50°C) *m/z* (%): 201 (M^+) (0.2), 172 (5), 144 (20), 128 (5), 88 (20), 59 (11), 57 (100). $C_{10}H_{19}NO_3$ (201.3): calcd C 59.68, H 9.52, N 6.96. Found C 59.67, H 9.60, N 6.84.

*3.9. (*S*)-3-t-Butoxycarbonylamino-heptan-4-one **4b***

Yield: 16 mg (96%). Viscous liquid. $[\alpha]_D^{28}$ −30.5 (*c* 1.00; $CHCl_3$), *ee*=13% (HPLC, (*S*,*S*)-Whelk-01, CH:isopropanol, 95:5). GC: R_t=8.8 (OV-17, 80-10-260). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, *J*=7.4

Hz, 3H, $CH_2CH_2CH_3$), 0.92 (t, *J*=7.4 Hz, 3H, $CHNCH_2CH_3$), 1.44 (s, 9H, $C(CH_3)_3$), 1.53–1.69 (m, 3H, $CHHCCH_2CH_3$), 1.93 (m, 1H, $CHNCH_2CH_3$), 2.47 (m, 2H, $CHNCH_2CH_3$), 4.29 (ddd, *J*=7.1, 6.7, 5.0 Hz, 1H, CHN), 5.25 (d, br, *J*=6.7 Hz) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 9.2, 13.8, 17.0, 24.8, 28.4, 41.7, 60.2, 79.6, 155.5, 209.4 ppm. IR ($CHCl_3$, cm^{-1}): 3353 (NH), 1710 (C=O). MS (70 eV, 80°C) *m/z* (%): 158 ($M^+-C_4H_7O$) (12), 102 (38), 71(20), 59 (15), 58 (96), 57 (100), 56 (10). $C_{12}H_{23}NO_3$ (229.3): calcd C 62.85, H 10.11, N 6.11. Found C 63.69, H 10.24, N 5.91.

3.10. (S)-4-t-Butoxycarbonylamino-nonan-5-one ***4c***

Yield: 16 mg (92%). Viscous liquid. $[\alpha]_D^{28}$ −30.5 (*c* 1.00; $CHCl_3$), *ee*=49% (CSP, Chirasil-Dex 25 m, 120-30-Iso-1). GC: R_t=6.78 (OV-17, 120-10-260). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.92 (q, J_3=7.1 Hz, 6H, CH_2CH_3, CH_2CH_3), 1.20–1.40 (m, 5H, CH_2CH_3, CH_2CH_3, $CH_2CHHCH_2CH_3$), 1.44 (5, 9H, $C(CH_3)_3$), 1.50–1.63 (m, 2H, $CHHCHHCH_2CH_3$), 1.78 (m, 1H, $CHHCHHCH_2CH_3$), 2.49 (dt, J_3=7.4, 2.4 Hz, 1H, CHN), 5.67 (d, br, J_3=7.1 Hz, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.8, 13.9, 18.5, 22.3, 25.6, 28.3, 33.9, 39.5, 59.1, 79.6, 155.6, 209.9 ppm. IR ($CHCl_3$, cm^{-1}): 3361 (NH), 1710 (C=O), 1645, 1604. MS (70 eV, 60°C) *m/z* (%): 257 (M^+) (0.1), 184 (4), 140 (3), 116 (76), 85 (10), 72 (100), 59 (5), 55 (5), 126 (34), 96 (16), 87 (5), 82 (9), 70 (25), 69 (6), 58 (87), 57 (100), 55 (13). $C_{14}H_{27}NO_3$ (257.4): calcd C 65.33; H 10.57, N 5.44. Found C 65.56, H 10.27, N 6.02.

3.11. (R)-2-t-Butoxycarbonylamino-5-phenyl-pentan-3-one ***4d***

Yield: 25 mg (90%). $[\alpha]_D^{28}$ −12.5 (*c* 0.8; $CHC1_3$), *ee*=42% (HPLC, (*S*,*S*)-Whelk-01, CH:isopropanol, 99:1). ^{1}H NMR ($CDC1_3$, 300 MHz): δ 1.25 (d, J_3=7.1 Hz, 3H, $CHCH_3$), 1.44 (s, 9H, $C(CH_3)_3$), 2.74–2.95 (m, 4H, Ar–CH_2CH_2), 4.29 (m, 1H, CHN), 5.25 (s, br, 1H, NH), 7.15–7.31 (m, 5H, Ar–H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.6, 28.4, 29.6, 40.8, 55.2, 79.8, 126.2, 128.3, 128.5, 140.8, 155.2, 208.7 ppm. IR (Et_2O, cm^{-1}): 3354 (NH), 1709 (C=O). MS (70 eV, 80°C) *m/z* (%): 221 ($M^+-C(CH_3)_3$+H) (3), 144 (10), 105 (6), 91 (10), 88 (22), 57 (54), 44 (100), 41 (11). $C_{16}H_{23}NO_3$ (277.4): calcd C 69.28, H 8.36, N 5.05. Found C 68.79, H 8.42, N 4.87.

3.12. (R)-2-t-Butoxycarbonylamino-1-phenyl-pentan-3-one ***4e***

Yield: 16 mg (96%). Mp: 63°C. $[\alpha]_D^{28}$ +9.0 (*c* 0.7; $CHCl_3$), *ee*=13% (CSP, Chirasil-Dex 25 m, 120-30-Iso-1-190). ^{1}H NMR ($CDC1_3$, 300 MHz): δ 1.01 (dd, J_3=8.0 Hz, 3H, CH_3), 1.40 (s, 9H, $C(CH_3)_3$), 2.38 (m, 2H, CH_2CH_3), 3.00 (m, 2H, Ph-CH_2), 4.53 (m, 1H, CHN), 5.98 (s, br, 1H, NH), 7.13 (m, 2H, O–Ar–H), 7.23–7.35 (m, 4H, *m/p*-Ph–H) ppm. ^{13}C NMR ($CDC1_3$, 75 MHz): δ 7.4, 28.3, 34.1, 38.1, 59.9, 79.9, 127.0, 128.6, 129.2, 136.3, 155.2, 209.8 ppm. IR (KBr, cm^{-1}): 3327 (NH), 1722 (C=O), 1682 (C=O). MS (70 eV, 90°C) *m/z* (%): 277 (M+) (1), 220 (10), 163 (10), 120 (21), 91(4), 57 (100). $C_{16}H_{23}NO_3$ (277.4): calcd C 69.28, H 8.36, N 5.05. Found C 68.81, H 8.52, N 4.69.

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