Asymmetric Synthesis of γ-Amino Ketones and Nitriles via β-Aminoethylation of SAMP-Hydrazones with Tosylaziridine

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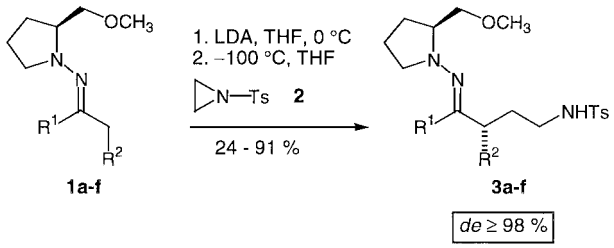
Abstract: The asymmetric synthesis of γ-amino nitriles **4a-c** and γ-amino ketones **5d-f** is described. Key step of the procedure is the diastereoselective β-aminoethylation of metalated SAMP-/RAMP-hydrazones **1a-f** with tosylaziridine **2**. Cleavage of the chiral auxiliary with MMPP leads to γ-amino nitriles **4a-c** in good yields and excellent enantiomeric excesses (*ee* ≥ 98%). Likewise γ-amino ketones **5d-f** (*ee* ≥ 98%) were obtained in good overall yields by cleavage of the hydrazones **3d-f** with aqueous copper(II) chloride solution.

Key words: asymmetric synthesis, hydrazones, ring opening, aziridines, aminoethylation

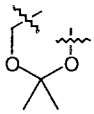
Ring opening reactions of aziridines have considerable value in organic synthesis.[1] Although examples of nucleophilic ring opening reactions of aziridines with organolithium reagents are well known, enolates of simple ketones have rarely been used.[2] The reaction of lithio azaenolates with aziridines has not been published so far.

We now wish to report an extension of our SAMP-/RAMP-hydrazone methodology[3] employing tosylaziridine **2**[4] as electrophile in the asymmetric β-aminoethylation of hydrazones **1a-f**. Representative carbonyl compounds were converted into aldehyde hydrazones **1a-c** and ketone hydrazones **1d-f**. As shown in Scheme 1, lithio azaenolates of SAMP-/RAMP-hydrazones **1b-f** were employed in the ring opening reaction of tosylaziridine **2** to give the aminoethylated compounds **3b-f** in good yields (63 - 91%) and excellent diastereoselectivity (*de* ≥ 98%). Surprisingly the aldehyde hydrazone **3a** was obtained only in 24% yield with recovery of the starting material. In contrast, unsymmetrical as well as symmetrical ketones like dioxanone-SAMP hydrazone **1f**[5] reacted smoothly (Scheme 1 and Table 1).



Scheme 1

Table 1 Synthesis of β-aminoethylated hydrazones **3a-f**

Product	R^1	R^2	Yield (%)	*de*[a] (%)	$[\alpha]_D^{26}$ (*c*, $CHCl_3$)[b]
(*R*,*S*)-**3a**	H	*i*-Pr	24	≥ 98	– 1.7 (1.00)
(*R*,*S*)-**3b**	H	Bn	63	≥ 98	– 39.5 (0.75)
(*R*,*S*)-**3c**	H	3,4-OCH_2O-Ph	88	≥ 98	– 42.9 (1.00)
(*S*,*R*)-**3c**[c]	H	3,4-OCH_2O-Ph	91	≥ 98	+ 44.0 (1.00)
(*S*,*S*)-**3d**	Et	Me	79	≥ 98	+ 174.9 (2.27)
(*S*,*S*)-**3e**	Ph	Me	88	≥ 98	+ 354.7 (1.00)
(*S*,*S*)-**3f**			87[d]	≥ 98	+ 98.6 (0.72)

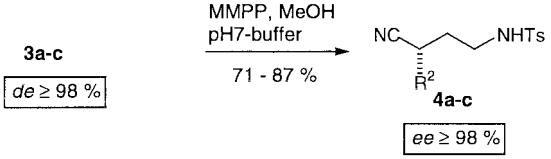
[a] Determined by ^1H NMR and ^{13}C NMR spectroscopy. [b] All optical rotations were measured in Uvasol grade $CHCl_3$ at temperatures T = 26ºC ± 1ºC. [c] RAMP was used as chiral auxiliary. [d] The aza-enolate of **1f** was prepared by addition of 1 equiv *t*-BuLi at −78 °C.

The aminoethylated aldehyde hydrazones **3a-c** were subsequently treated with magnesium monoperoxyphthalate (MMPP)[6] to give γ-amino nitriles **4a-c** in good yields (71 - 87%) and excellent enantiomeric excesses (*ee* ≥ 98%) (Scheme 2 and Table 2).

Table 2 Synthesis of γ-amino nitriles **4a-c** by cleavage of the hydrazones **3a-c** with MMPP

Product	R^2	Yield (%)	*ee* (%)[a]	$[\alpha]_D^{26}$ (*c*, $CHCl_3$)[b]
(*R*)-**4a**	*i*-Pr	87	≥ 98	+ 31.7 (1.23)
(*R*)-**4b**	Bn	84	≥ 98	+ 16.0 (1.12)
(*R*)-**4c**	3,4-OCH_2O-Ph	71	≥ 98	+ 34.5 (1.08)
(*S*)-**4c**	3,4-OCH_2O-Ph	83	≥ 98	– 38.5 (1.32)

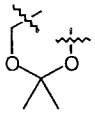
[a] Based on the *de*-value of the corresponding MTPA-amide (HPLC, Chiralpak AD (4.6×250 mm)). [b] All optical rotations were measured in Uvasol grade $CHCl_3$ at temperatures T = 26ºC ± 1ºC.



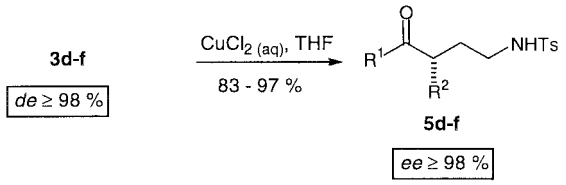
Scheme 2

Cleavage of the chiral auxiliary of ketone hydrazones **1d-f** with a 1 M aqueous solution of copper(II) chloride[7] afforded γ-amino ketones **5d-f** in excellent yields (83 - 97%) and enantiomeric excesses (*ee* ≥ 98%) (Scheme 3 and Table 3).

Table 3 Synthesis of γ-amino ketones **5d-f** by cleavage of the hydrazones **3d-f** with aqueous copper(II) chloride solution

Product	R^1	R^2	Yield (%)	*ee* (%)[a]	$[\alpha]_D^{26}$ (*c*, $CHCl_3$)[b]
(*S*)-**5d**	Et	Me	97	≥ 98	− 9.1 (1.05)
(*S*)-**5e**	Ph	Me	83	≥ 98	− 6.0 (1.00)
(*S*)-**5f**			80	≥ 98	+ 4.4 (1.00)

[a] Based on the *de*-value of the corresponding MTPA-amide (HPLC, Chiralpak AD (4.6×250 mm)). [b] All optical rotations were measured in Uvasol grade $CHCl_3$ at temperatures T = 26ºC ± 1ºC.



Scheme 3

The relative configuration of the new stereogenic centre of the aminoethylated hydrazones **3** was confirmed by NOE experiments on (*S*,*S*)-**3f** (Figure 1).

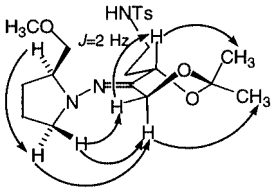


Figure 1 NOE connectivity for **3f**

Assuming uniform reaction pathways, the absolute configuration of hydrazones **3a-e** were assigned by analogy with **3f**. The results as indicated in Table 1 are in accordance with the proposed general mechanism for the α-alkylation of SAMP-/RAMP-hydrazones.[3a] The enantiomeric excesses of γ-amino nitriles **4a-c** and γ-amino ketones **5d-f** were determined by HPLC of the corresponding MTPA-amides.

In conclusion, we have developed an efficient method for the enantioselective β-aminoethylation of SAMP-/RAMP-hydrazones using tosylaziridine as electrophile. Cleavage of the chiral auxiliary affords either γ-amino nitriles or γ-amino ketones in good overall yields and excellent enantiomeric excesses.

General procedure for the aminoethylation of SAMP-/RAMP-hydrazones **1a-e**:

The hydrazones **1a-e** were slowly added to a solution of 1.05 equiv of LDA in THF (5 mL/mmol) at 0 °C and stirred for 4 h. The resulting yellow solutions were cooled to −100 °C and a solution of 1 equiv tosylaziridine **2** in the minimum amount of THF was added dropwise with a syringe pump over 30 min. The temperature was kept at −100 °C for 2 h and the reaction mixtures allowed to reach room temperature overnight. The reactions were quenched by the addition of a saturated aqueous NH_4Cl solution (10 mL). The aqueous phases were extracted with CH_2Cl_2 (3×25 mL). The combined organic phases were washed with H_2O (20 mL) and brine (20 mL) and dried over $MgSO_4$. After removal of the solvent, the residues were purified by flash chromatography (SiO_2; ether/pentane 1:1 containing 2% NEt_3) to afford the aminoethylated products **3a-e**.

General procedure for the cleavage of SAMP-/RAMP-aldehyde hydrazones **3a-c** with magnesium monoperoxyphthalate:

Magnesium monoperoxyphthalate (2 equiv) was dissolved in MeOH (20 mL/mmol) and pH 7-buffer solution (10 mL/mmol). The resulting suspension was cooled to 0 °C and treated with hydrazones **3a-c** dissolved in MeOH (2 mL/mmol). The reaction mixtures were allowed to warm to room temperature, stirred for 4 h and finally H_2O (50 mL) was added. The aqueous phases were extracted with ether (3×50 mL). The combined organic phases were washed with H_2O (20 mL), brine (2×50 mL) and dried over $MgSO_4$. After removal of the solvent, the residues were purified by flash chromatography (SiO_2; ether/pentane 1:2) to afford γ-amino nitriles **4a-c**.

General procedure for the cleavage of SAMP-/RAMP-ketone hydrazones **3d-f** with 1 M aqueous solution of copper (II) chloride:

To an ice cooled solution of the hydrazones **3d-f** in THF (10 mL/mmol) was slowly added a 1 M aqueous solution of copper(II) chloride (1.2 equiv) and the resulting mixtures were stirred for 12 h. Then NH_3 aq (10 mL) was added and the reaction mixtures extracted with ether (3×25 mL). The combined organic phases were washed with brine (2×25 mL) and dried over $MgSO_4$. After removal of the solvent, the residues were purified by flash chromatography (SiO_2; ether/pentane 1:2) to afford γ-amino ketones **5d-f**.[8,9]

Acknowledgement

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References and Notes

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(8) Selected analytical and spectroscopic data of compounds **3**, **4** and **5**:
(*R*,*S*)-**3c**: $[\alpha]^{26}_{D} = -42.9$ (c = 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.75 - 2.10 (m, 6 H, C*H*$_2$CH$_2$NHSO$_2$, NCH$_2$C*H*$_2$C*H*$_2$), 2.42 (s, 3 H, CC*H*$_3$), 2.70 (m, 1 H, NC*H*CH$_2$CH$_2$), 2.95 (m, 2 H, C*H*$_2$NHSO$_2$), 3.25 - 3.60 (m, 5 H, C*H*CH = N, CH$_3$ OC*H*$_2$, NC*H*$_2$CH$_2$CH$_2$), 3.37 (s, 3 H, OC*H*$_3$), 5.30 (s, 1 H, N*H*), 5.92 (s, 2 H, OC*H*$_2$O), 6.50 - 6.60 (m, 3 H, Ar*H*), 6.69 (d, 1 H, *J* = 8.0 Hz, *H*C=N), 7.29 (d, 2 H, *J* = 8.0 Hz, SO$_2$CC*H*), 7.69 (d, 2 H, *J* = 8.0 Hz, H$_3$CCC*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.95, 22.58, 27.07, 34.29, 41.87, 46.57, 50.41, 59.63, 63.76, 75.26, 101.41, 108.59, 108.75, 121.32, 127.59, 130.09, 136.71, 137.86, 138.94, 143.53, 146.71, 148.31; MS (CI, isobutane) m/z 474 (M^++1), 344, 334, 190, 172, 131, 116, 114, 74; IR ($CDCl_3$): 3282, 3018, 2972, 2927, 2879, 1598, 1504, 1487, 1441, 1382, 1328, 1305, 1289, 1247, 1197, 1185, 1160, 1119, 1095, 1040, 971, 934, 865, 815, 757, 708, 666, 551 cm^{-1}; Anal. calcd. for $C_{24}H_{31}N_3O_5S$: C 60.87, H 6.60, N 8.87; found: C 60.64, H 6.55, N 9.02.
(R)-**4c**: $[\alpha]^{26}_{D} = +34.5$ (c = 1.08, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 2.04 (m, 2 H, C*H*$_2$CH$_2$N), 2.44 (s, 3 H, C*H*$_3$), 3.04 (m, 2 H, C*H*$_2$N), 3.87 (t, 1 H, *J* = 7.4 Hz, C*H*CN), 4.95 (t, 1 H, *J* = 6.3 Hz, N*H*), 5.97 (s, 2 H, OC*H*$_2$O), 6.70 - 6.77 (m, 3 H, Ar*H*), 7.32 (d, 2 H, *J* = 8.0 Hz, H$_3$CCC*H*), 7.73 (d, 2 H, *J* = 8.0 Hz, SO$_2$CC*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.52, 33.82, 35.71, 40.26, 101.47, 107.67, 108.70, 120.41, 120.90, 127.14, 128.32, 129.93, 136.38, 143.88, 147.65, 148.34; MS (CI, isobutane) m/z 359 (M^++1), 358, 75; IR ($CDCl_3$): 3280, 3022, 2925, 2895, 2242, 1598, 1505, 1490, 1446, 1368, 1329, 1306, 1291, 1276, 1250, 1186, 1160, 1094, 1040, 932, 858, 814, 757, 707, 667, 552 cm^{-1}; Anal. calcd. for: $C_{18}H_{18}N_2O_4S$: C 60.32, H 5.06, N 7.82; found: C 60.32, H 5.41, N 7.91.
(S)-**5e**: $[\alpha]^{26}_{D} = -6.0$ (c = 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.12 (d, 3 H, *J* = 6.9 Hz, CHC*H*$_3$), 1.59 (m, 1 H, HC*H*CH$_2$NH), 2.03 (m, 1 H, *H*CHCH$_2$NH), 2.36 (s, 3 H, CC*H*$_3$), 2.97 (m, 2 H, C*H*$_2$NH), 3.59 (m, 1H, C*H*CH$_3$), 5.35 (t, 1 H, *J* = 6.2 Hz, N*H*), 7.22 (d, 2 H, *J* = 8.0 Hz, CHCCH$_3$), 7.42 (m, 3 H, Ph), 7.53 (m, 2 H, Ph), 7.71 (d, 2 H, *J* = 8.3 Hz, C*H*CSO$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.59, 21.43, 32.39, 37.70, 41.04, 126.81, 128.18, 128.46, 129.47, 132.89, 135.76, 136.49, 143.09, 203.44; MS (CI, isobutane) m/z 332 (M^++1), 176, 161, 135, 71; IR ($CDCl_3$): 3280, 3063, 2972, 2933, 2875, 1680, 1597, 1495, 1448, 1427, 1379, 1327, 1306, 1291, 1235, 1202, 1184, 1160, 1094, 1002, 975, 816, 796, 707, 686, 664, 574, 552 cm^{-1}; Anal. calcd. for: $C_{18}H_{21}NO_3S$: C 65.23; H 6.39, N 4.23; found: C 64.92, H 6.66, N 4.44.

(9) All compounds showed suitable spectroscopic data (IR, MS, NMR) and correct elemental analyses.

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