Electronic supplementary materials *Mendeleev Commun*., 2011, **21**, 245–246

R-α-Phenylglycinol and *R*-α-phenylglycinamide as novel chiral templates in diastereoselective Ugi reaction

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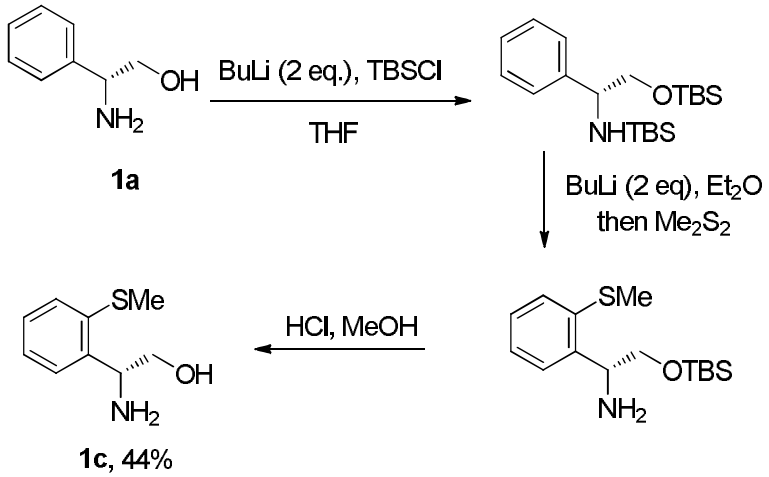
^{1}H and ^{13}C NMR spectra were recorded in deuterated solvents on a Bruker Avance 400 MHz spectrometer. Chemical shifts (δ) are reported in ppm downfield from TMS as internal standard. Deuterated solvent peaks were used as internal references: $CDCl_3$ at 7.25 and 77.00 ppm. Analytical thin layer chromatography (TLC) was performed using 25 DC-Alufolien Kieselgel 60 F254 (Merck). The developed chromatogram was analyzed by UV light and aqueous potassium permanganate ($KMnO_4$). Liquid chromatography was performed using Fluka Silica gel 60 (0.063-0.200 mm). Infrared (IR) spectra were recorded on a Nicolet IR2000 (Thermo Scientific) instrument. High-resolution mass spectra (HRMS) were measured on a Micr OTOF II (Bruker Daltonics) spectrometer. Commercially available reagents and solvents were used without special precautions.

1. Synthesis of phenylglycinols 1b-d

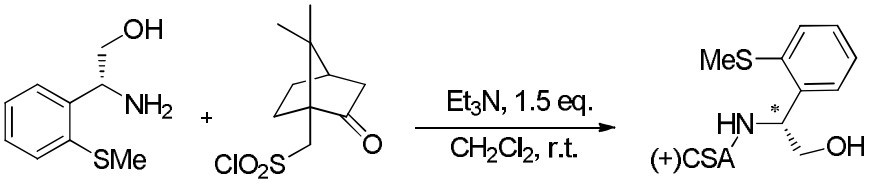
Methyl-α-D-phenylglycinol **1b**[1] and TBS-α-D-phenylglycinol **1c**[2] were synthesized using literature procedures.

(2*R*)-2-amino-2-[2-(methylthio)phenyl]ethanol 1d:



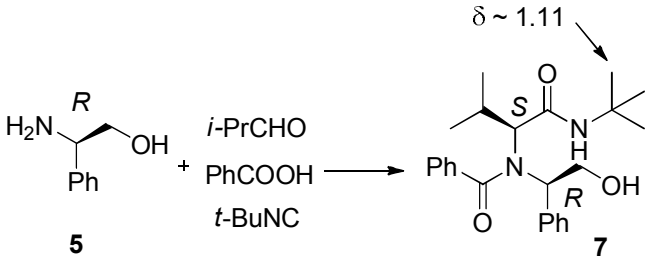
To a suspention of (*R*)-α-methylbenzylamine (1.37 g, 10.0 mmol) in 40 ml of THF n-BuLi (2.5 M solution in hexane, 8 ml) was added dropwise at -78°C. The resulting purple solution was stirred at -78°C for 30 min before a solution of TBSCl (*tert*-butyldimethylsilyl chloride) (3.17 g, 21.0 mmol) in 20 ml of THF was added at the same temperature. The reaction mixture was allowed to reach ambient temperature and was stirred overnight. After removing the THF solvent under reduced pressure, the residue was redissolved in 50 ml of ether. To this solution, n-BuLi (2.5 M solution in hexane, 12 ml) was added dropwise at -78°C. After 30 min Me_2S_2 (40 mmol) was added at -78°C and the mixture was allowed to slowly warm to rt and stirred for 1h. Then 10% $Na_2S_2O_3$ solution (20 ml) was added and the resulting mixture was stirred vigorously for 10 min. The product was extracted with dichloromethane, dried over K_2CO_3 and evaporated *in vacuo* and recrystallized from benzene. The product (800 mg, 44%) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): 2.45 (s, 3H), 3.50-6.60 (m, 1H), 3.73-3.81 (m, 1H), 4.46-4.55 (m, 3H), 7.12-7.24 (m, 3H), 7.40 (d, J = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 140.5, 136.7, 127.8, 126.2, 125.8, 125.4, 66.3, 53.4, 16.2. $[\alpha]^{20}_D$ -81.3 (*c* 12.2 mg/ml in MeOH). Found, %: C, 59.19; H, 7.40. $C_9H_{13}NOS$. Calculated, %: C, 58.98 H, 7.15. This procedure is based on literature data.[3]

Stereochemical purity of amine **1d** was confirmed by the reaction with (1*S*)-(+)-10-Camphorsulfonyl chloride. Formation of one diastereomer was observed.



1d de>98%

2. Search for optimal Lewis acid



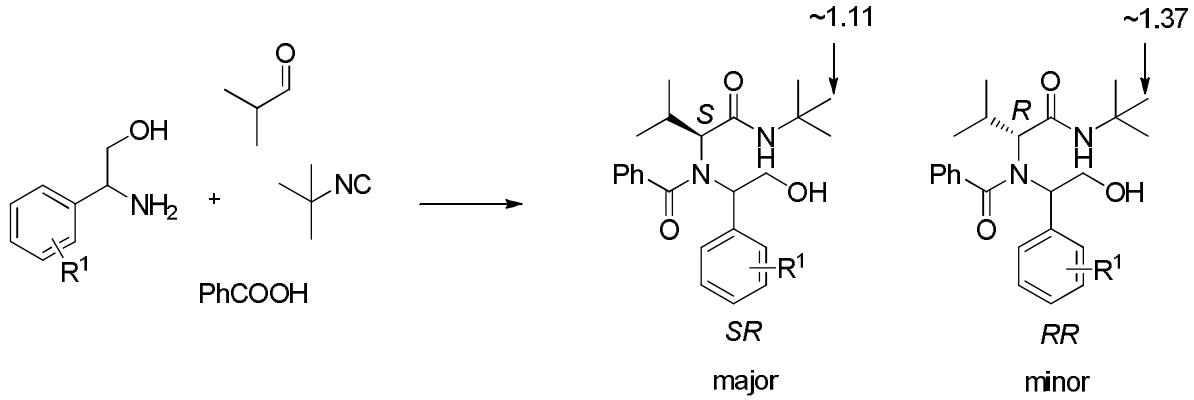
5 **7**

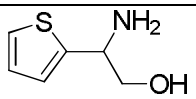
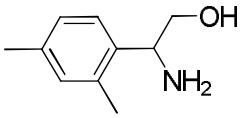
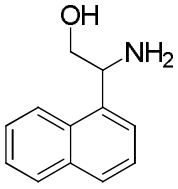
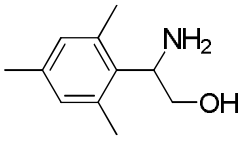
Entry[a]	**Lewis Acid**	**Temp.**	**de**[b]
1	None	-30°C	n.r.
2	$Yb(OTf)_2$, 0.1eq.	-30ºC	~77%
3	BF_3*Et_2O, 1eq.	-30ºC	n.r.
4	$NiCl_2$, 1eq.	-30ºC	n.r.
5	$Al(O\textit{i}\text{-}Pr)_3$, 1 eq.	-30ºC	n.r.
6	$Ti(O\textit{i}\text{-}Pr)_4$, 1eq	-30ºC	n.r.
7	$MgCl_2$, 1eq.	-30ºC	n.r.
8	$Zn(OTf)_2$, 1eq.	-30ºC	~89.5%
9	$ZnBr_2$, 1eq.	-30ºC	~93%
10	$ZnCl_2$, 1eq.	-30ºC	~94%
11[c]	**$ZnCl_2$, 1eq.**	**-38ºC**	**~96%**

[a] THF, 0.1M; [b] de was determined by GC-MS and NMR; [c] Isolated yield 70%

3. Search for optimal amine auxiliary

Amino alcohols (entries 1-4) were obtained by reduction of the corresponding amino acids.



№	Amine	Lewis acid	Conditions	de
1[a]		$ZnCl_2$, 1eq.	THF, -30, 0.1M	~93%[b]
2[a]		$ZnCl_2$, 1eq.	THF, -30, 0.1M	~93%[b]
3[a]		$ZnCl_2$, 1eq.	THF, -30, 0.1M	~92%[b]
4[a]		$ZnCl_2$, 1eq.	THF, -30, 0.1M	~71%[b]

[a] Racemic amines were used; [b] Ration by NMR and GC-MS.

4. General procedure of the Ugi reaction with α-D-phenylglycinol

To a stirred solution of isobutyraldehyde (1 mmol) and α-D-phenylglycinol **1a** (1 mmol) in THF (9 ml), $ZnCl_2$ solution in THF (1 mmol in 1 ml) was added at -38°C. After that, benzoic acid (1 mmol) and *t*-BuNC were subsequently added. The mixture was stirred at this temperature for ~48 h, evaporated *in vacuo* and the residue analyzed by GC-MS and NMR or purified by column chromatography (hexane:EtOAc, 4:1).

Product **2a**, yield 70%, was obtained as a white solid, mp 143-145°C. ^{1}H NMR ($CDCl_3$, 400 MHz) 0.98 (d, J = 5.0 Hz, 3H), 1.07 (d, J = 5.0 Hz, 3H), 1.10 (s, 6H), 2.99 (br.s, 1H), 3.27 (d, J = 9.9 Hz, 1H), 3.80-4.20 (m, 2H), 5.1 (br.s, 1H), 7.00-7.50 (m, 10H), 8.3 (br.s, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz) 19.9, 20.6, 27.3, 28.3, 50.1, 60.6, 64.1, 71.2, 127.1, 127.8, 128.0, 128.5, 128.6, 129.8, 136.4, 136.9, 170.8, 174.5. $[\alpha]^{20}_D$ +28.8 (*c* 0.032 M, MeOH). HRMS (ESI) calculated for $C_{24}H_{32}N_2O_3$ $[M + Na]^+$ 419.2311, found 419.2355.

5. Synthesis of imine 4

Isobutyraldehyde (10 mmol) was added to a solution of α-D-phenylglycinamide **3** (10 mmol) in CH_2Cl_2 at r.t. The mixture was stirred for 12 h at r.t., after that $MgSO_4$ was added, and the mixture was stirred for additional 1 h. The precipitate was filtered off, solution was evaporated and the solid residue was cristallyzed from hexane/acetone mixture. The product was obtained as a white solid in 80% yield, mp 89-90ºC (lit.[4] 91-92ºC). ^{1}H NMR (400 MHz, THF-D_6): 1.10 (s, 3H), 1.12 (s, 3H), 2.44-2.54 (m, 1H), 4.62 (s, 1H), 6.62 (br. s, J = 22.5 Hz, 2H), 7.15-7.25 (m, 3H), 7.4 (d, J = 7.6 Hz, 2H), 7.68 (d, J = 4.0 Hz, 1H). ^{13}C NMR (100 MHz, THF-D_6): 172.1, 141.7, 128.8, 127.8, 78.6, 35.1, 19.2.

6. General procedure of the Ugi reaction with imine 4

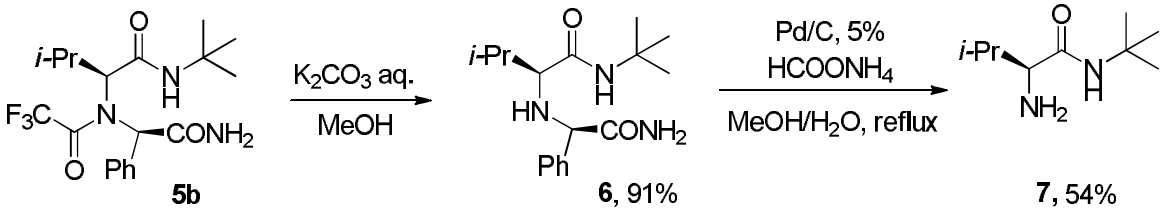
To a stirred solution of **4** (1 mmol) in THF (9 ml), $ZnCl_2$ solution in THF (1 mmol in 1 ml) was added at -38°C. After that, benzoic acid (1 mmol) for **5a** or trifluoroacetic acid (1 mmol) for **5b** and *t*-BuNC were subsequently added. The mixture was stirred at this temperature for ~

48 h, evaporated *in vacuo* and the residue was analyzed by GC-MS and NMR or purified by column chromatography (hexane:EtOAc, 3:1).

Product **5a** was obtained as a white solid in 70% yield, mp 112-116°C. ^{1}H NMR (mixture of rotamers, 400 MHz, $CDCl_3$): 0.5 (d, J = 6.1 Hz, 3H), 0.66 (d, J = 6.1 Hz, 3H), 1.31 (c, 9H), 2.00-2.20 (m, 1H), 3.54-3.76 (m, 1H), 5.30-5.60 (m, 2H), 6.0-6.30 (m, 2H), 7.35-7.40 (m, 9H), 7.60-7.70 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 172.7, 168.4, 166.9, 136.5, 136.4, 129.6, 129.3, 128.8, 128.5, 125.6, 63.4 (m), 60.1, 28.4, 28.1, 20.8, 19.9. $[\alpha]^{20}_D$ +3.3 (*c* 0.03 M, MeOH). HRMS (ESI) calculated for $C_{24}H_{31}N_3O_3$ $[M + Na]^+$ 432.2263, found 432.2296.

Product **5b** was obtained as a white solid in 63% yield, mp 119-122°C. ^{1}H NMR (mixture of rotamers, 400 MHz, $CDCl_3$): 0.95 (d, J = 6.3 Hz, 3H), 1.00 (s, 9H), 1.17 (d, J = 6.3 Hz, 3H), 2.42-2.52 (m, 1H), 3.63 (d, J = 10.4 Hz, 1H), 5.3 (br. s, 1H), 5.54 (s, 1H), 5.8 (br. s, 1H), 6.4 (br. s, 1H), 7.24-7.34 (m, 5H). ^{13}C NMR (mixture of rotamers, 100 MHz, $CDCl_3$): 18.1, 19.3, 28.0, 28.4, 51.8, 63.4, 67.4, 116.0 (q, J = 289.1 Hz, CF_3), 128.3, 128.7, 128.9, 134.5, 155.4, 165.7, 171.1. $[\alpha]^{20}_D$ -32.0 (*c* 73 mg/ml in MeOH). HRMS (ESI) calculated for $C_{19}H_{26}F_3N_3O_3$ $[M]^+$ 424.1823, found 424.1860.

7. Removal of protecting groups



To a stirred solution of **5b** (1 mmol) in MeOH (9 ml), K_2CO_3 in water (1 mmol in 1 ml) is added. The mixture was stirred at this temperature for ~48 h, evaporated *in vacuo* and the residue was purified by column chromatography (hexane:EtOAc, 3:1). The product **6** was obtained as a white solid, mp 99-102°C in 91%. ^{1}H NMR (mixture of rotamers, 400 MHz, $CDCl_3$): 0.82 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H), 1.35 (s, 9H), 1.91 (sept. J = 6.6 Hz, 1H), 2.47 (d, J = 5.8 Hz), 4.12 (s, 1H), 5.7 (br. s, 1H), 6.1 (br. s, 1H), 6.2 (br. s, 1H), 7.30-7.36 (m, 6H). ^{13}C NMR (mixture

of rotamers, 100 MHz, $CDCl_3$): 18.3, 19.5, 28.8, 31.3, 51.1, 65.3, 66.3, 127.8, 128.5, 128.9, 138.2, 172.4, 174.6. $[\alpha]^{20}_D$ -69.6 (*c* 47 mg/ml in MeOH). HRMS (ESI) calculated for $C_{17}H_{23}N_3O_2$ $[M]^+$ 306.2103, found 306.2121.

The solution of $HCOONH_4$ (1g in 5 ml H_2O) was added to a solution of compound **6** (1 mmol) in 10 ml of MeOH. Commercial 10% Pd/C (159 mg, 15 mol%) was added and the mixture was refluxed for 10 h. The mixture was evaporated and treated with aqueous K_2CO_3. The product was extracted with CH_2Cl_2 (3x30 ml), the organic layer was dried (K_2CO_3) and concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2 : MeOH 10:1). The product **7** (valine *N-tert*-butylamide) was obtained as colorless oil in 54% yield. ^1H NMR (mixture of rotamers, 400 MHz, DMSO): 0.73 (d, J = 6.8 Hz), 0.84 (d, J = 6.8 Hz), 1.34 (s, 9H), 1.79-1.87 (m, 1H), 2.47-2.50 (m, 1H), 3.19 (s, 1H), 7.1 (br. s, 1H). ^{13}C NMR (mixture of rotamers, 100 MHz, DMSO): 17.38, 20.03, 29.0, 32.03, 50.1, 60.46, 174.4. $[\alpha]^{20}_D$ +31.2 (*c* 22.3 mg/ml in MeOH). Lit. [5] $[\alpha]^{20}_D$ +32.0 (c 1 M in MeOH). HRMS (ESI) calculated for $C_9H_{21}N_2O$ $[M]^+$ 173.1648, found 173.1644.

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