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

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***R*-α-Phenylglycinol and *R*-α-phenylglycinamide as chiral amino components in the Ugi multicomponent reaction provide up to 98% *de* of *S*,*R*-isomer.**

Isocyanide-based multicomponent Passerini and Ugi reactions are efficient methods allowing formation of set of C–C, and C–O or C–N bonds in one step.[1] These methodologies are extremely useful for a construction of new amino and hydroxy acid fragments as well as skeleton of peptides and peptide-like molecules, especially containing artificial α-amino acid.[2]

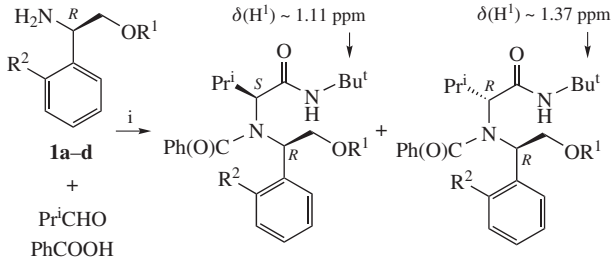
However, the main challenge of the Ugi reaction-based synthesis of peptides and amino acids is a formation of new centre in a stereoselective fashion. Up to days, only chiral amines provided sufficient stereoselectivity, whereas chiral isocyanide, carbonyl compounds and carboxylic acids are usually inefficient.[3]

A variety of chiral amines were tested as chiral auxiliaries for the Ugi reaction. Commercial (α-phenylethyl)amine[4] usually gives low selectivity. Chiral (+)-(α-ferrocenylethyl)amines were also used.[5] However, high molecular weight, conformational instability and multistep synthesis of amine templates are disadvantageous. In 1987 Kunz *et al*.[6] introduced α-D-galactoamine derivatives as a chiral template for this purpose. The reaction proceeds in the presence of Lewis acid ($ZnCl_2$) at low temperatures (up to –78 °C) and provides products in good yields and stereoselectivity of up to 94% *de*.[7] It was found that this stereoselectivity was caused by formation of complex from imine and Lewis acid.[8] Later other amino sugars were tested as chiral templates for the Ugi reaction.[9] Although these templates sometimes had shown good to excellent diastereoselectivity, the removal of sugar moiety from Ugi products was not simple. Moreover, all amino sugar-based templates have limitations with respect to the carbonyl input and relatively high molecular weight (*M* at least 350 g mol^{-1}) and, hence, lack principles of atom-economy. Therefore, development of new efficient and low molecular weight chiral templates is still a great challenge in the Ugi reaction.

Here, we have disclosed employment of α-D-phenylglycinol and α-D-phenylglycinamide as new chiral amino templates for Ugi reactions. The suggested auxillaries are commercially available compounds in both enantiomeric forms.

Initially, we supposed that modification of α-phenylethyl amine molecule with hydroxy group can deliver additional coordination site for the Lewis acid due to chelation of metal atom. As a result, addition of isocyanide should occur from less restricted side to induce a new stereocenter with predictable configuration.

The model Ugi reaction of α-D-phenylglycinol **1a**, isobutiric aldehyde, benzoic acid and *tert*-butyl isocyanide and a number of Lewis acids were tested (Scheme 1). Zn salts were found to be most efficient activators [$Yb(OTf)_2$, $BF_3{\cdot}Et_2O$, $NiCl_2$, $Al(OPr^i)_3$, $Ti(OPr^i)_4$, $MgCl_2$, $Zn(OTf)_2$, $ZnBr_2$ were also tested, but $ZnCl_2$ gave better results; see Online Supplementary Materials]. We found that under optimal conditions the product **2a**,† having *S*-configuration, can be obtained in good yield and 96% *de*. Note that the reaction did not proceed without Lewis acid. We also tried to optimize the structure of chiral template to achieve higher stereoselectivity. Thus, protection of hydroxy group with Me (**1b**) or TBS (**1c**) group, as expected, leads to the decrease in stereoselectivity due to Lewis acid coordination restriction. Insertion of additional coordinating group SMe (**1d**) into the *ortho*-position of benzoic ring also gave no positive result (Scheme 1).‡ The major diastereomer in all cases had *S*,*R* configuration according to the diagnostic chemical shift of Bu^t group in NMR spectra.[4]



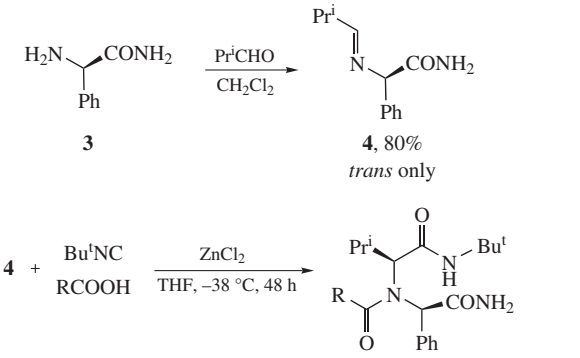
	R^1	R^2	*de*
a	H	H	96%
b	TBS	H	76%
c	Me	H	90%
d	H	SMe	92%

Scheme 1 *Reagents and conditions*: 1 equiv. $ZnCl_2$ (0.1 M solution in THF), –38 °C, 12 h; *de* was determined by GC-MS and NMR techniques.

† To a stirred solution of isobutyric aldehyde (1 mmol) and *R*-α-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 Bu^tNC (1.2 mmol) 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, 4:1). Product **2a**, yield 70%, was obtained as a white solid, mp 143–145 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.98 (d, 3H, *J* 5.0 Hz), 1.07 (d, 3H, *J* 5.0 Hz), 1.10 (s, 6H), 2.99 (br. s, 1H), 3.27 (d, 1H, *J* 9.9 Hz), 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 ($CDCl_3$, 100 MHz) δ: 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, MeOH). HRMS (ESI), *m*/*z*: 419.2355 $[M+Na]^+$ (calc. for $C_{24}H_{32}N_2O_3$, 419.2311).

‡ For synthesis of **1b–d**, see Online Supplementary Materials.

R-α-Phenylglycinamide **3** was used several times as a chiral auxiliary in different reactions, including step of nucleophilic addition to imine.[10] We propose that *R*-α-phenylglycinamide **3** having more constrained amide fragment would be even more efficient in terms of coordination of imine by Lewis acid. For this purpose, chiral imine **4** having *trans*-configuration was easily synthesized from isobutyraldehyde and compound **3**.§ We have found that reaction of imine **4** gave Ugi products **5a**,**b** in good yield and excellent stereoselectivity (>98%) in the presence of 1 equiv. of $ZnCl_2$ (Scheme 2).§ To verify the absolute configuration, compound **5b** was deprotected and hydrolized to known valine *N-tert*-butylamide, which was found to be *S*-enantiomer.



5a R = Ph, yield 70%, *de* > 98%
5b R = CF_3, yield 63%, *de* > 98%

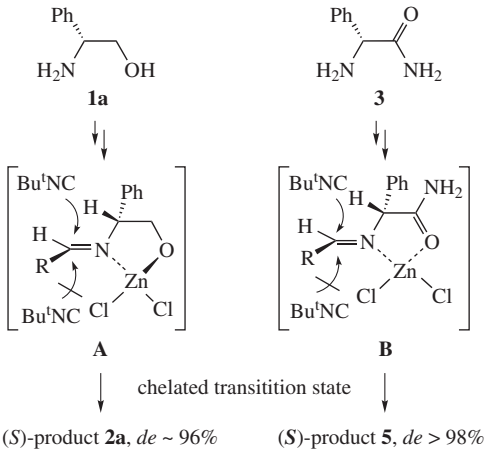
Scheme 2

We proposed that reactions proceed through chelate intermediates **A** and **B** displaying restricted approach of isocyanide from one of the sides (Scheme 3). Slightly higher selectivity in case of *R*-α-phenylglycinamide **3** can be caused by more constrained amide structure of intermediate **B**. These models permit to predict the configuration of major diastereomer in both cases. The approach of isocyanide from upper face gave *S* configuration of new stereocentre formed.

In conclusion, we have tested several derivatives of *R*-α-phenylglycinol as a chiral auxiliary for Ugi multicomponent reaction and found that under optimized conditions reaction can be performed in diastereoselectivity up to 96% *de*. We have also demonstrated that α-D-phenylglycinamide is more efficient template for the Ugi reaction and can be employed for preparation of the products in highly diastereoselective fashion with *de* up to 98%. Note that suggested templates are commercially available in both enantiomeric forms, whereas their residues are readily removed from the target compounds by hydrogenolysis (see Online Supplementary Materials).

§ 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 ButNC (1.2 mmol) were subsequently added. The mixture was then 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, $CDCl_3$, 400 MHz) δ: 0.5 (d, 3H, *J* 6.1 Hz), 0.66 (d, 3H, *J* 6.1 Hz), 1.31 (s, 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, $CDCl_3$) δ: 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, MeOH). HRMS (ESI) *m/z*: 432.2296 (calc. for $C_{24}H_{31}N_3O_3$ [M+Na]$^+$, 432.2263).

For synthesis and characteristics of imine **4**, and characteristics of product **5b**, see Online Suppplementary Materials.



Scheme 3

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2011.09.004.

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