# Synthesis of Optically Active α-Arylglycines: Stereoselective Mannich-Type Reaction with a New Chiral Template

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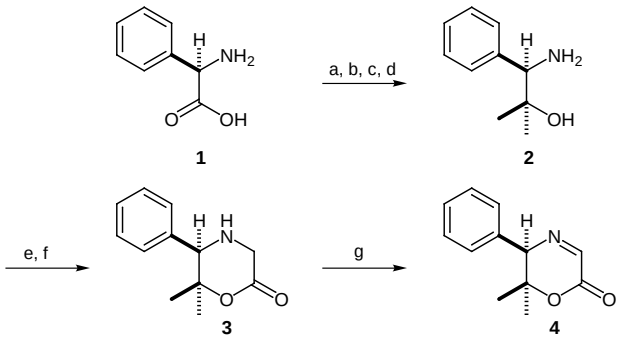
**Abstract:** Mannich-type reaction of phenols with iminolactone **4,** readily prepared from commercially available phenylglycine, proceeded with high stereoselectivity to give α-arylglycine derivatives. The reaction was also applicable to other electron-rich aromatic compounds and aryl boronic acids. These adducts could be readily converted to the corresponding optically active α-arylglycines.

**Key words:** α-arylglycines, Mannich-type reaction, iminolactone, phenol, arylboronic acid

α-Arylglycines constitute an important class of nonproteinogenic α-amino acids.[1,2] These compounds have been found in numerous natural products such as amoxicillin and vancomycin, to name a few. In addition, α-hydroxyarylglycines have been shown to be highly potent agonists or antagonists for the glutamate receptors of the central nervous system.[3,4] The growing need for α-arylglycines has attracted much interests from synthetic chemists.[5,6] It is difficult to synthesize this class of compounds in optically pure form because the benzylic chiral center is prone to racemization. While the methodology reported by Williams appears to be quite attractive, it may not be particularly suited for large-scale preparations of highly functionalized α-arylglycines.[7] During the course of our synthetic study on ecteinascidin 743, we found that an intermolecular Mannich-type reaction of phenol with cyclic imine proceeded with high stereoselectivity.[8] Inspired by this finding, we launched an investigation on the scope of such α-arylglycine synthesis, using simple cyclic imines with readily removable chiral auxiliaries. After preliminary investigation of electrophilic glycine equivalents, lactone **4** was found to be sufficiently robust and suitable for this purpose. Herein we report stereoselective Mannich-type reaction with a new chiral template **4** and its conversion to optically active α-arylglycines.

As illustrated in Scheme 1, iminolactone **4** was readily prepared in a seven-step sequence from phenylglycine (**1**), which is commercially available in both enantiomeric form and relatively inexpensive. After conversion to the *N*-Boc-phenylglycine methyl ester, treatment with MeMgBr followed by removal of the Boc group furnished the alcohol **2**. *N*-Alkylation of **2** with phenyl bromoacetate and subsequent lactonization afforded the desired lactone **3**, which, upon treatment with $Pb(OAc)_4$ smoothly underwent oxidation to provide highly crystalline iminolactone **4**. Because of the geminal dimethyl group, the iminolactone **4** is stable enough to be isolated and thus amenable to large-scale preparations.

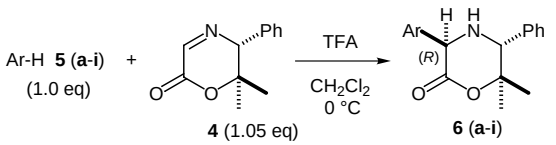



**Scheme 1** Reagents and conditions: a) $SOCl_2$ (5.0 eq), MeOH, r.t.; b) $(Boc)_2O$ (1.0 eq), MeCN, r.t., 88% in 2 steps; c) MeMgBr (3.2 eq), THF, r.t., 82%; d) $SOCl_2$ (5.0 eq), MeOH, r.t., 91%; e) phenyl bromoacetate (1.1 eq), propylene oxide (5.0 eq), MeCN, 50 °C, 81%; f) toluene, Δ, 86%; g) $Pb(OAc)_4$ (1.2 eq), MeCN, r.t., 89%.

With the requisite iminolactone **4** in hand, we then examined the Mannich-type reaction with various phenols (**5a**-**5g**).[9a,b] Under acidic conditions, the addition reactions proceeded with excellent stereoselectivity and in near quantitative yields to give the corresponding phenylglycine derivatives (**6a**-**6g**).[10] The reaction conditions, yields and diastereoselectivities are given in the Table. It is noteworthy that highly substituted phenols such as **5a**,**b**,**g** serve as excellent substrates in this reaction. In addition, the iminolactone **4** reacts with other electron-rich aromatic ethers (**5h** and **5i**). The high stereoselectivity of the addition reactions can be explained by a preferential approach of the nucleophiles from the opposite face of the bulky phenyl group. The stereochemistry of the adduct **6g** was confirmed by X-ray analysis of **7** (Figure).[11]

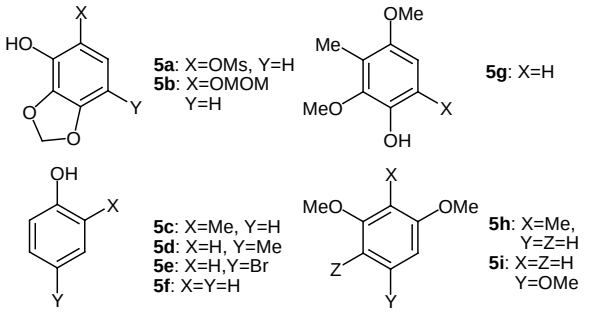
Moreover, the imine **4** was applicable to boronic acid Mannich reaction, which was first reported by Petasis et al.[12] As shown in Scheme 2, treatment of arylbronic acid **8** with trifluoroacetic acid resulted in diastereo- and regioselective addition to **4**, giving **9** in high yield. Since numerous arylboronic acid derivatives can be easily synthesized, this protocol can be applied to synthesis of a wide variety of α-arylglycines.

**Table** Mannich-type reaction of **5** with iminolactone **4**




| ArH | TFA (eq) time (h) | reaction site | dr (*R*:*S*) | yields (%) |
|---|---|---|---|---|
| **5a** | 5 0.5 | Y | 11:1 | 97 (**6a**) |
| **5b** | 2 24 | Y | 12:1 | 83 (**6b**) |
| **5c** | 5 5 | Y | *R* (single isomer) | 88 (**6c**)* |
| **5d** | 5 2.5 | X | >20:1 | 95 (**6d**) |
| **5e** | 10 10 | X | 4:1 | 98 (**6e**) |
| **5f** | 5 3 | X:Y=1:1 | >20:1 | 96 (**6f**) |
| **5g** | 5 0.5 | X | *R* (single isomer) | 93 (**6g**)* |
| **5h** | 5 3 | Z | 10:1 | 96 (**6h**) |
| **5i** | 5 0.5 | X | >20:1 | 98 (**6i**) |

*after recrystallization



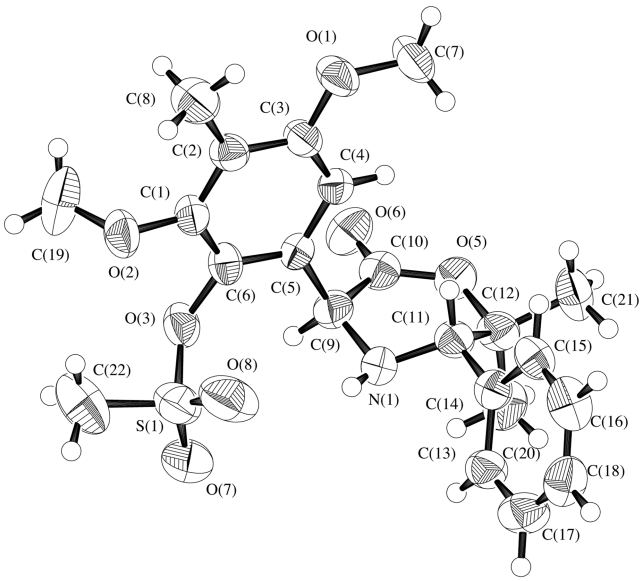
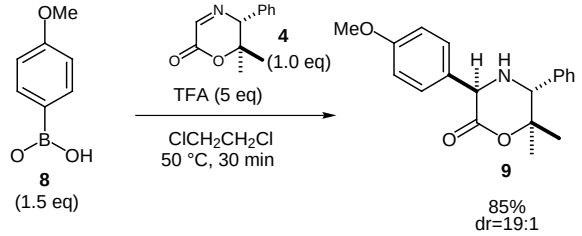
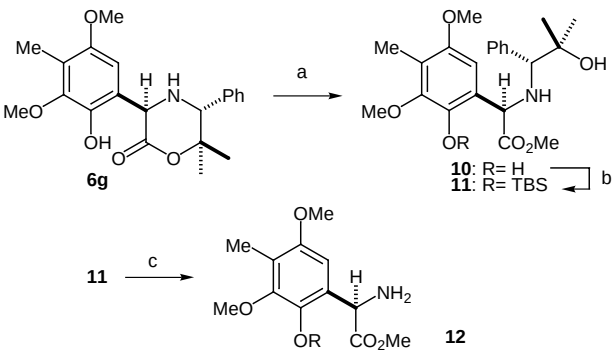




**Figure** ORTEP drawing of adduct **7**




**Scheme 2**

A representative example of the removal of the chiral auxiliary and the conversion to the corresponding α-arylglycine is shown in Scheme 3. Acidic cleavage of aminolactone **6g** with $SOCl_2$ in methanol, followed by protection of the phenol as the TBS ether afforded methyl ester **11**. Oxidative cleavage of amino alcohol **11** with $Pb(OAc)_4$ and the subsequent treatment with hydroxylamine led to aminoester **12**. Examination of the $^1H$ NMR spectra of the corresponding MTPA amide revealed that **12** did not racemize under these reaction conditions.




**Scheme 3** Reagents and conditions: a) $SOCl_2$ (2.0 eq), MeOH, Δ, 92%; b) TBSCl (1.2 eq), imidazole (3.0 eq), DMF, Δ, 93%; c) $Pb(OAc)_4$ (1.5 eq), toluene, 0 °C; $NH_2OH{\cdot}HCl$ (5.0 eq), NaOAc (5.0 eq), EtOH, r.t., 82%.

In conclusion, we have developed a novel synthesis of optically active α-arylglycines by means of stereoselective Mannich-type reaction of a versatile imine **4** with various aromatic compounds. The choice of appropriate aromatic compounds would allows us to synthesize a variety of highly functionalized arylglycines. Further applications of the chiral template **4** to the syntheses of a range of optically active amino acids are under investigation in our laboratories

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## References and Notes


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(9) (a) Preparation of phenols **5a** and **5b**, see: ref 6.
(b) Preparation of phenol **5g**, see: Fukuyama, T.; Sachleben, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 4957.
(10) Typical experimental procedure: To a mixture of 510 mg (3.0 mmol) of **5g** and 650 mg (3.2 mmol, 1.05 equiv) of **4** in 6 ml of $CH_2Cl_2$ was added 0.23 ml (15 mmol, 5 equiv) of TFA at 0 °C. The reaction mixture was stirred at same temperature until **5g** was consumed. The reaction mixture was poured into saturated $NaHCO_3$ solution, and extracted with $CH_2Cl_2$. The extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. Purification of the crude product by recrystallization (AcOEt-Hexane) yielded 1.04 g (2.8 mmol, 93%) of **6g** as white crystal.
(11) Compound **7** was prepared from **6g** by the treatment with MsCl and $Et_3N$ in 85% yield. X-ray crystallographic data for the structure reported in this paper have been deposited with the *Cambridge Crystallographic Data Base* (Deposition No. 162231). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax+44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk).
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