# Access to α-Functionalized Glycine Derivatives with Arylboronic Acid via Imino Amides

Liang Zhao, Xiaohong Liao, Chao-Jun Li*

Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, Quebec H3A 2K6, Canada
Fax +1(514)3983797; E-mail: cj.li@McGill.ca

*Received 4 August 2009*

**Abstract:** An efficient approach was developed for the α-arylation of imino amides with arylboronic acids. Different substrates were examined for this arylation reaction. For the α-arylation of *N*-phenylimino amide, due to the electron-withdrawing properties of the phenyl group, the tautomerization between the amide and the iminol is more difficult. Thus, low reaction rate and low conversion were observed. This phenomenon supported our previously proposed mechanism for the arylation of α-amino acid derivatives. Meanwhile, this method provides an alternative approach for the synthesis of α-functionalized glycine derivatives.

**Key words:** α-functionalization, arylation, iminol, imino amide, glycine derivatives

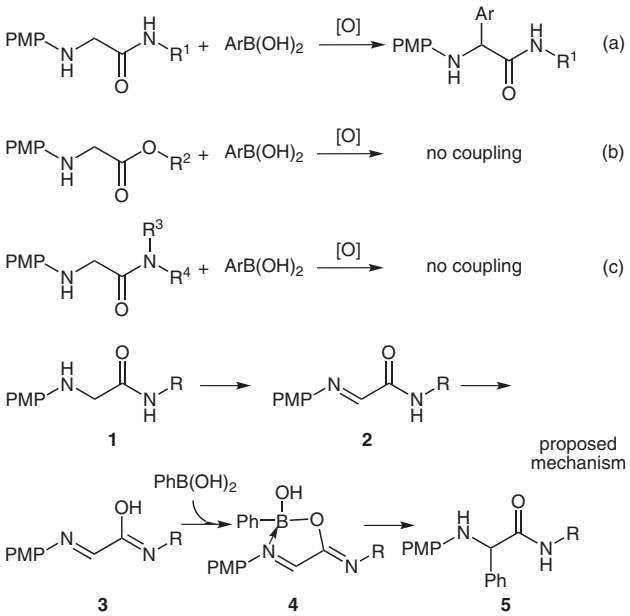
For decades, α-arylation of amino acids and their derivatives has attracted much attention due to their high importance in pharmaceutical compounds (e.g., Ampicillin and Cefachlor) and natural products (such as Vancomycin).[1] The most widely used methods to access these unnatural amino acids are the Strecker reaction,[2] the Ugi reaction,[3] and the Petasis reaction,[4] which are all based on imine chemistry.[5] Arylations of imines with or without a transition-metal catalyst have been extensively studied during the past two decades. Activated imines such as *N*-tosyl imine[6] and even unactivated imines such as PhN=CHPh could be arylated with the ArM[7] (M = Pd, Rh) species which are generated via transmetalation. The Petasis reaction (either with an imine or an iminium precursor[4d,8]) is one of the most well-known catalyst-free approaches. However, arylation of an imino amide (a prototype structure for peptides) has not been explored so far.

Recently, we developed a new approach to achieve the direct α-arylation of glycine and peptide derivatives (Scheme 1, a) under oxidative conditions via functionalization of a C–H bond.[9] During the course of studying the substrate scope, we found that neither the glycine ester nor the tertiary glycine amide undergo the arylation reaction (Scheme 1, b and c). This led us to investigate the mechanism of this novel type of arylation reaction (Scheme 1). We proposed that after formation from glycine derivative **1**, the imino amide **2** will tautomerize to its iminol form **3**. Then, the newly formed hydroxyl group will coordinate with the phenylboronic acid to give intermediate **4**. Subsequently, an intramolecular delivery of the phenyl group will occur to afford the arylation product **5**. Inspired by the iminoamide intermediate **2** and in pursuit of a method which is complementary to, but also beyond the scope of the oxidative coupling reaction, we herein report an alternative synthetic method by utilizing imino amides and nucleophiles such as arylboronic acids to synthesize the α-arylated product (Scheme 2).

To generate the imine precursor for the arylation and to demonstrate proof-of-concept, diethyl tartrate was first converted into dibenzyl tartaric amide by reacting with benzylamine.[10] Oxidative cleavage of the diol by periodic acid[11] generated the glyoxylic amide in situ, which was efficiently transformed into imino amide (Scheme 2).

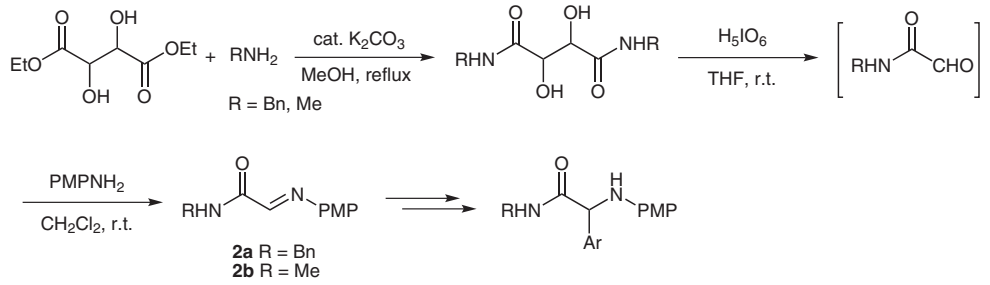
We have optimized this procedure so that it may be easily carried out on multigram scale to make this special imine, with isolation of the reagent accomplished by simple silica gel column filtration followed by recrystallization. With this imino amide in hand, we examined the coupling reaction with arylboronic acids.

Electron-rich arylboronic acids (entries 2, 5, 7, 9, 13–15, Table 1) are generally more reactive than their electron-deficient (entries 3, 8, 16, Table 1) or sterically hindered (entries 4, 12, Table 1) counterparts. The imine substrate with an extra glycine moiety affords good yields as well (entries 11–16, Table 1).



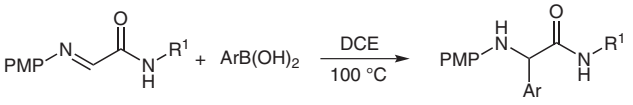

**Scheme 1** Mechanistic studies of the arylation reaction

*SYNLETT* 2009, No. 18, pp 2953–2956
Advanced online publication: 08.10.2009
DOI: 10.1055/s-0029-1218266; Art ID: U08009ST




**Scheme 2** Synthesis of imino amide reagent

**Table 1** Scope of the Arylation Reaction[a]




6 7 8

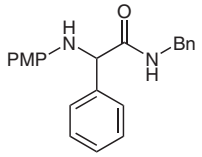
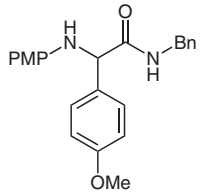
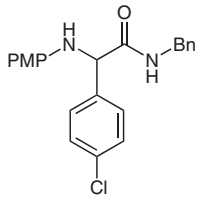
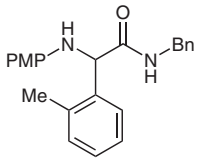
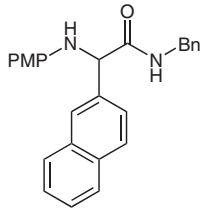
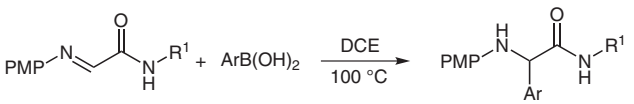
| Entry | Product | Yield (%) |
|---|---|---|
| 1 |  **8a** | 65 |
| 2 |  **8b** | 97 |
| 3 |  **8c** | 78 |
| 4 |  **8d** | 56 |
| 5 |  **8e** | 99 |

**Table 1** Scope of the Arylation Reaction[a] (continued)




6 7 8

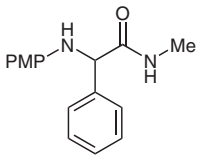
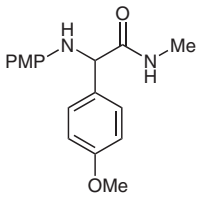
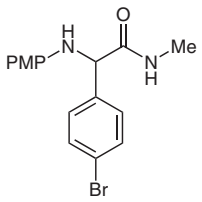
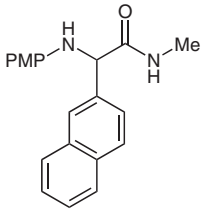
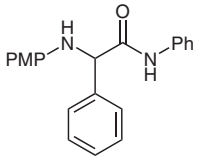
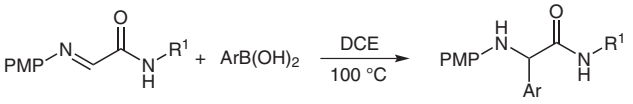
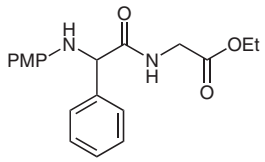
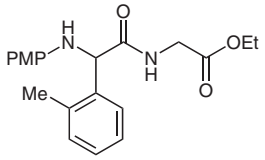
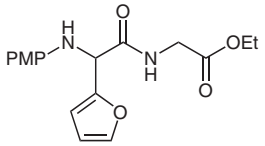
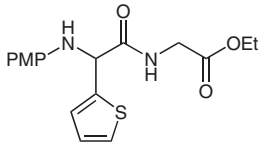
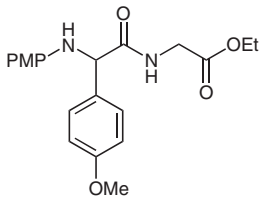
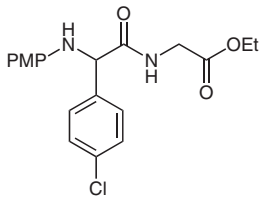
| Entry | Product | Yield (%) |
|---|---|---|
| 6 |  **8f** | 96 |
| 7 |  **8g** | 81 |
| 8 |  **8h** | 82 |
| 9 |  **8i** | 94 |
| 10 |  **8j** | 17 |

**Table 1** Scope of the Arylation Reaction[a] (continued)




**6** **7** **8**

| Entry | Product | Yield (%) |
|---|---|---|
| 11 |  **8k** | 81 |
| 12 |  **8l** | 64 |
| 13 |  **8m** | 73 |
| 14 |  **8n** | 41 |
| 15 |  **8o** | 82 |
| 16 |  **8p** | 50 |

[a] *Reaction conditions*: imino amide (0.10 mmol), arylboronic acid (0.15 mmol), DCE (0.5 mL), 5 h at 100 °C.

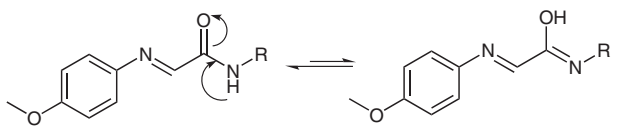



**Figure 1** Tautomerization between the amide and the iminol

It is interesting to note that for the imino amide substrate, *N*-alkyl amides (entries 1–9, and entries 11–16, Table 1) are much more reactive than the *N*-phenyl amide (entry 10, Table 1). This may be due to the fact that the phenyl group of *N*-phenyl amide will withdraw electrons from amide, making the tautomerization to the iminol more difficult compared with *N*-alkyl amides in the current reaction conditions (Figure 1). This reduced activity is consistent with our previously proposed reaction mechanism.

In summary, an alternative route for the synthesis of α-arylated glycine derivatives and dipeptides was described via the α-arylation of imino amides with arylboronic acids. Furthermore, the study supported the mechanism of our previously reported oxidative coupling reaction of glycine amide with arylboronic acids. Further studies on the application of the reaction are in progress.

**General Procedure for the Arylation Reaction of Imino Amide**

The *N*-PMP imine amide (0.10 mmol) and arylboronic acid (0.15 mmol) were added to DCE (0.5 mL) in a test tube. The test tube was sealed and heated at 100 °C for 5 h. After the reaction was completed, DCE was removed in vacuo. Flash chromatography using EtOAc–hexanes (1:4 to 1:2) afforded the arylated product.

**Isolation and Characterization of Compound 8a[12]**

$^1$H NMR (300 MHz, $CD_3Cl$): δ = 7.46–7.36 (m, 5 H), 7.28–7.13 (m, 5 H), 6.77 (d, 2 H, *J* = 9.0 Hz), 6.59 (d, 2 H, *J* = 9.0 Hz), 4.73 (s, 1 H), 4.55 (dd, 1 H, *J* = 14.7, 6.3 Hz), 4.40 (dd, 1 H, *J* = 14.7, 6.3 Hz), 3.75 (s, 3 H) ppm. $^{13}$C NMR (75 MHz, $CD_3Cl$): δ = 171.4, 153.2, 140.6, 138.8, 138.0, 129.2, 128.6, 127.6, 127.4, 127.3, 127.3, 115.1, 114.8, 65.2, 55.7, 43.4 ppm.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

## Acknowledgment

We are grateful to the Canada Research Chair (Tier I) foundation (to C.-J. Li), NSERC, CFI, ACS-Green Chemistry Pharmaceutical Roundtable and McGill University for their support of our research.

## References

(1) (a) Nagarajan, R. *Antimicrob. Agents Chemother.* **1991**, *35*, 605. (b) Perkins, H. R. *Pharmacol. Ther.* **1982**, *16*, 181. (c) Williams, D. H. *Acc. Chem. Res.* **1984**, *17*, 364.

(2) (a) Connon, S. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 1176. (b) Groger, H. *Chem. Rev.* **2003**, *103*, 2795. (c) Yet, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 875.

(3) (a) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3169. (b) Ugi, I. *Angew. Chem.* **1959**, *71*, 386. (c) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 8. (d) Ugi, I.; Steinbruckner, C. *Angew. Chem.* **1960**, *72*, 267.

(4) (a) For a comprehensive review on Petasis reaction, see: Batey, R. A. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, **2005**, 279–304. (b) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583. (c) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445. (d) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798. (e) Petasis, N. A.; Goodman, A.;

Zavialov, I. A. *Tetrahedron Lett.* **1997**, *53*, 16463. (f) Naskar, D.; Roy, A.; Seibel, W. L. *Tetrahedron Lett.* **2003**, *44*, 8861. (g) Koolmeister, T.; Sodergren, M. *Tetrahedron Lett.* **2002**, *43*, 5969.

(5) For other methods to access arylation/allylation of α-amino acids from our laboratory, see: (a) Huang, T.; Li, C.-J. *Tetrahedron Lett.* **2000**, *41*, 6715. (b) Huang, T.; Li, C.-J. *Tetrahedron Lett.* **2000**, *41*, 9747. (c) Huang, T. S.; Li, C.-J. *Org. Lett.* **2001**, *3*, 2037. (d) Huang, T. S.; Keh, C. C. K.; Li, C.-J. *Chem. Commun.* **2002**, 2440.

(6) (a) Wei, D. J.; Shi, Y. L.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092. (b) Dai, H. X.; Lu, X. Y. *Org. Lett.* **2007**, *9*, 3077. (c) Kuriyama, M.; Soeta, T.; Hao, X. Y.; Chen, O.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128. (d) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169.

(7) (a) Krug, C.; Hartwig, J. F. *Organometallics* **2004**, *23*, 4594. (b) Krug, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 2694. (c) Ueura, K.; Miyamura, S.; Satoh, T.; Miura, M. *J. Organomet. Chem.* **2006**, *691*, 2821. (d) Vilaivan, T.; Bhanthumnavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315. (e) Youn, S. W.; Song, J.-H.; Jung, D.-I. *J. Org. Chem.* **2008**, *73*, 5658. (f) Yu, A.; Wu, Y.; Cheng, B.; Wei, K.; Li, J. *Adv. Synth. Catal.* **2009**, *351*, 767. (g) Ding, R.; Zhao, C. H.; Chen, Y. J.; Liu, L.; Wang, D.; Li, C.-J. *Tetrahedron Lett.* **2004**, *45*, 2995.

(8) (a) Lou, S.; Schaus, S. E. *J. Am. Chem. Soc.* **2008**, *130*, 6922. (b) Yamaoka, Y.; Miyabe, H.; Takemoto, Y. *J. Am. Chem. Soc.* **2007**, *129*, 6686. (c) Basle, O.; Li, C.-J. *Org. Lett.* **2008**, *10*, 3661. (d) Selander, N.; Kipke, A.; Sebelius, S.; Szabo, K. J. *J. Am. Chem. Soc.* **2007**, *129*, 13723.

(9) Zhao, L.; Basle, O.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 4106.

(10) Chen, W.; Liu, Y.; Chen, Z. *Eur. J. Org. Chem.* **2005**, 1665.

(11) Bolton, G. L.; Bowles, D. M.; Doyles, D. C.; Howard, W. A. J.; Hutchings, R. H.; Kennedy, R. M.; Park, W. K.-C.; Poel, T.-J.; Song, Y. US 2005239857, **2005**.

(12) Pan, S. C.; List, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 3622.