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N-Arylation of α-aminoesters with *p*-tolylboronic acid promoted by copper(II) acetate

Patrick Y. S. Lam,* Damien Bonne, Guillaume Vincent, Charles G. Clark and Andrew P. Combs

Bristol-Myers Squibb Company, Experimental Station, PO Box 80500, Wilmington, DE 19880-0500, USA

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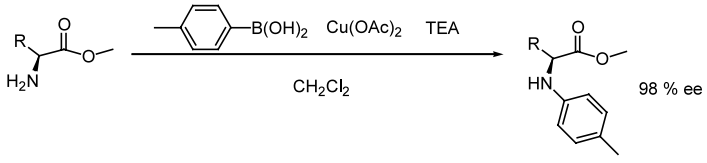
Abstract—Copper-promoted *N*-arylation of α-amino esters with *p*-tolylboronic acid at room temperature was accomplished with little or no racemization. © 2003 Published by Elsevier Science Ltd.

Copper-promoted carbon–nitrogen (C–N) bond cross-coupling reactions of NH-containing substrates with arylboronic acids have emerged as a powerful synthetic method since the initial reports by Chan and Lam.[1] This novel methodology is characterized by the mild reaction conditions (room temperature and weak base) and is useful for the synthesis of nitrogen-containing compounds in pharmaceuticals, crop-protection chemicals and material sciences. Many extensions and applications of this new methodology have been reported.[2–6]



α-Amino acids and their derivatives are important chemical building blocks in organic and biological chemistry. Reactions involving these building blocks should be mild enough so as not to cause epimerization of the chiral centers. Known methods of *N*-arylation of amino acid derivatives are the coupling of α-amino acids with aryl halides under elevated temperature (improved Ullmann reaction)[8,9] and the use of triphenylbismuth diacetate.[10] The drawback of the former reaction is substantial racemization, and for the later it is the lack of commercially available arylbismuth reagents. We would like to report that general *N*-arylation of enantiomerically pure α-amino esters can be achieved with *p*-tolylboronic acid and copper(II) acetate under mild conditions with little or no racemization.

A series of aminoesters were arylated using *p*-tolylboronic acid (Table 1) in 17–67% yield.[12] The general condition for this coupling reaction involves the addition of 2.0 equiv. of *p*-tolylboronic acid and 2.0 equiv. of TEA (triethylamine was found to be a better base than pyridine for amine substrate) to 1.0 equiv. of the α-aminoester followed by 1.1 equiv. of anhydrous copper(II) acetate and 4 Å molecular sieves. The reaction mixture is stirred open to air, protected from atmospheric moisture, at room temperature for 1–2 days.

It is apparent from this study that the length of the alkyl chain has an influence on the yield of these cross-coupling reactions. In general, α-aminoesters with small R groups (Table 1, entries 1 and 2) give poor yields. We believe this is a consequence of the low solubility of the corresponding α-aminoesters. In these cases, the competing conversion of *p*-tolylboronic acid to phenol followed by *O*-arylation is observed. For the proline substrate (entry 15), the poor yield may presumably be due to the steric hindrance of the substrate.

In each reaction we did not observe the formation of the *N*,*N*-bisarylated product.[4a] This suggests that the mono *N*-arylated product is less reactive than the primary amine under these conditions.

We also found that this reaction causes little or no racemization[13,14] (entries 2, 5, 6, 8, 11, 12, 13). L-Aspartic ester is the only substrate that has some racemiza-

* Corresponding author. E-mail: patrick.lam@bms.com

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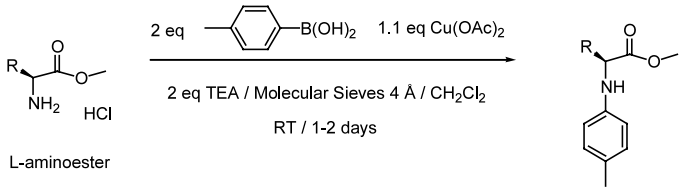
Table 1. C–N bond cross coupling of *p*-methylphenylboronic acid and α-aminoesters

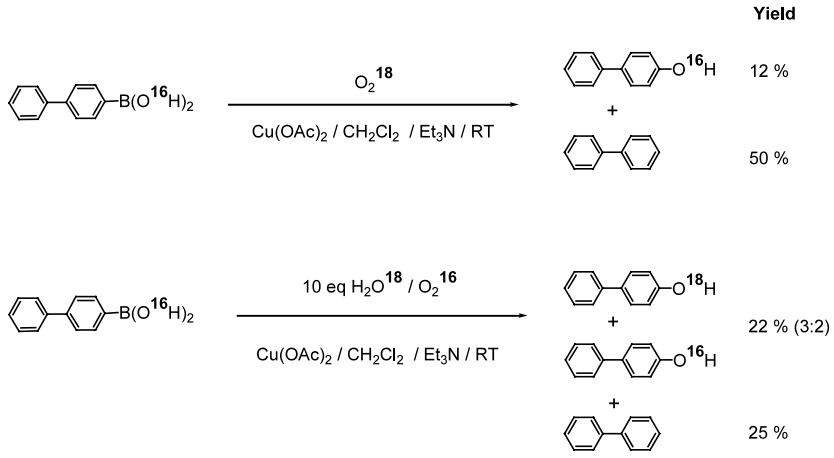


Entry	R	Yield	enantiomeric excess
1	H—	17 %	
2	H_3C—	39 %	99.1 % (98.8 % for D-amino ester)
3		67 %	
4		64 %	
5		53 %	99.0 % (98.2 % for D-amino ester)
6		65 %	98.0 % (98.0 % for D-amino ester)
7		39 %	
8		52 %	99.8 % (98.9 % for D-amino ester)
9		45 %	
10		26 %	
11		44 %	98.6 % (98.3 % for D-amino ester)
12		56 %	98.8 % (98.1 % for D-amino ester)
13		41 %	93.9 % (93.7 % for D-amino ester)
14		49 %	
15	Proline methylester	19 %	

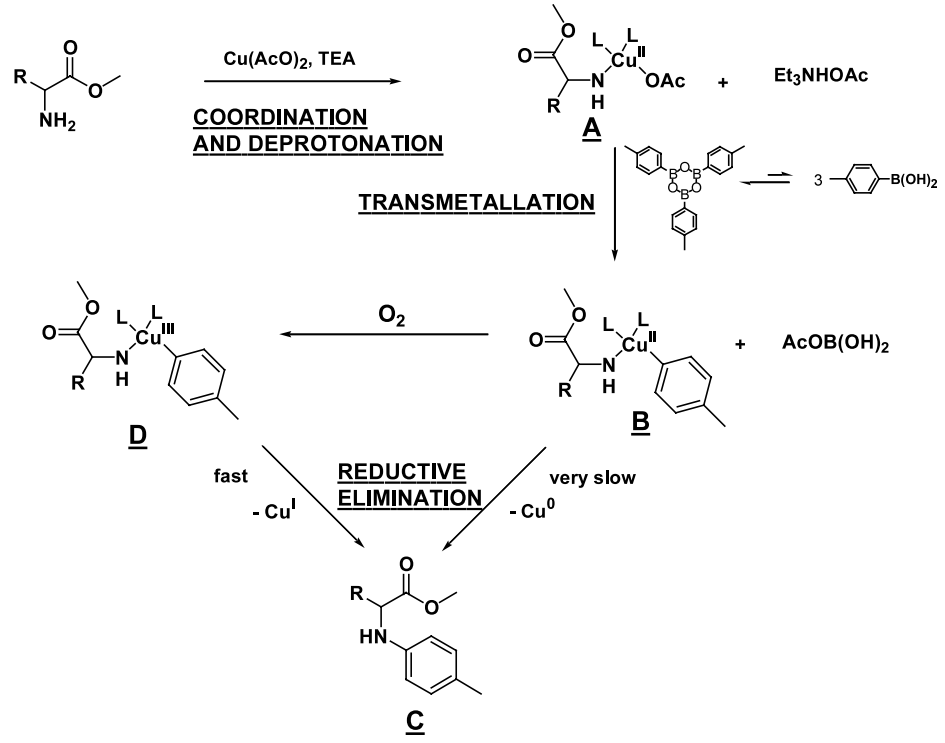
tion (entry 13, 93.8% ee) due to the extra activating α-carbonyl group.

In general, two equivalents of *p*-tolylboronic acid are used for the copper-promoted *N*-arylation reactions to achieve optimal yields. This is due to the competing side reaction of the formation of *p*-cresol from *p*-tolylboronic acid. We decided to investigate the cause of the formation of the undesirable phenol which can serve as a substrate that will undergo *O*-arylation. Biphenylboronic acid was used in the absence of a NH-containing substrate (Scheme 1). When O_2^{18} was used, no isotope incorporation was observed. However, when H_2O^{18} was added to the reaction, O^{18} was incorporated into biphenylphenol. Thus, the source of phenol formation is the *O*-arylation of water. This confirms Evans'[1c] hypothesis which lead to their suggestion of using molecular sieves to sequester water in order to increase the yield. Reduction of biphenylboronic acid to biphenyl was also observed as a side product.

We hypothesized that the first step of the reaction mechanism (Scheme 2) involves the rapid coordination and dissolution of copper(II) acetate by the α-aminoester to form the α-aminoester–copper(II) complex A.[15] The second step involves the transmetallation of the *p*-tolylboronic acid with A to give the α-aminoester-*p*-tolyl–copper(II) complex B. Complex B may very slowly undergo reductive elimination to give C. Alternatively, B can undergo air oxidation to yield the corresponding higher oxidation-state copper(III)[11] complex D which can now more efficiently reductively



Scheme 1. Phenol formation from biphenylboronic acid.



Scheme 2. Possible mechanism of *N*-arylation with *p*-tolylboronic acid.

eliminate to afford C. Quantitative analysis of an analogous reaction mixture shows only trace amount of copper(0) present at the end of the reaction. This suggests that reduction elimination from a copper(II) intermediate is not the major pathway.

In summary, we have successfully *N*-arylated α-aminoesters with little or no racemization using copper(II) acetate and *p*-tolylboronic acid. This reaction works under a very mild set of conditions: room temperature, mild base (triethylamine) and in the presence of air. We continue to explore the mechanism and scope of this powerful copper-promoted C-heteroatom cross-coupling reaction with organometalloids.

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References

1. (a) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Averill, K.; Chan, D. M. T.; Combs, A. P. *Synlett* **2000**, 674–676; (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett*. **1998**, *39*, 2941–2944; (c) For related

O-arylation, see: Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett*. **1998**, *39*, 2937–2940; (d) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett*. **1998**, *39*, 2933–2936.

2. (a) Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. *Tetrahedron Lett*. **2002**, *43*, 3091–3094; (b) Lam, P. Y. S.; Deudon, S.; Hauptman, E.; Clark, C. G. *Tetrahedron Lett*. **2001**, *42*, 2427–2429; (c) Lam, P. Y. S.; Deudon, S.; Kristin, M. A.; Li, R.; He, M.; DeShong, P.; Clark, C. G. *J. Am. Chem. Soc*. **2000**, *22*, 7600–7601.
3. For catalytic copper, see: (a) Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, J. K. *Tetrahedron Lett*. **2001**, *42*, 3415–3418; (b) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett*. **2002**, *4*, 581–584; (c) Collman, J. P.; Zhong, M.; Zhang, C.; Costanzo, S. *Org. Lett*. **2001**, *66*, 7892–7897 and references cited therein.
4. For solid-phase *N*-arylation, see: (a) Combs, A. P.; Tadesse, S.; Rafalski, M.; Haque, T. S.; Lam, P. Y. S. *J. Comb. Chem*. **2002**, *4*, 179–182; (b) Combs, A. P.; Rafalski, M. *J. Comb. Chem*. **2000**, *2*, 29–32; (c) Combs, A. P.; Saubern, S.; Rafalski, M.; Lam, P. Y. S. *Tetrahedron Lett*. **1999**, *40*, 1623–1626.
5. For *S*-arylation, see: (a) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett*. **2002**, *4*, 4309–4312; (b) Herradura, P. S.; Pendola, K. A.; Guy, R. K. *Org. Lett*. **2000**, *2*, 2019–2022. For *O*-arylation, see: (c) Evans, D. A.; Katz, J. L.; Peterson, G. S.; Hinterman, T. *J. Am. Chem. Soc*. **2001**, *123*, 12411–12413; (d) Simon, J.; Salzbrunn, S.; Surya Prakash, G. K.; Petasis, N. A.; Olah, G. A. *J. Org. Chem*. **2001**, *66*, 633–634; (e) Decicco, C. P.; Song, Y.; Evans, D. A. *Org. Lett*. **2001**, *3*, 1029–1032; (f) Petrassi, H. M.; Sharpless, K. B.; Kelly, J. W. *Org. Lett*. **2001**, *3*, 139–142; (g) Jung, M. E.; Lazarova, T. I. *J. Org. Chem*. **1999**, *64*, 2976–2977. For *N*-arylation, see: (h) Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron Lett*. **2000**, *41*, 9053–9057; (i) Mederski, W. W. K. R.; Lefort, M.; Germann, M.; Kux, D. *Tetrahedron* **1999**, *55*, 12757–12770; (j) Cundy, D. J.; Forsyth, S. A. *Tetrahedron Lett*. **1998**, *39*, 7979–7982.
6. (a) Kang, S.-K.; Lee, S.-H.; Lee, D. *Synlett* **2000**, 1022–1024; (b) Fedorov, A. Y.; Finet, J.-P. *Tetrahedron Lett*. **1998**, *39*, 7979–7982; (c) Arnauld, T.; Barton, D. H. R.; Doris, E. *Tetrahedron* **1997**, *53*, 4137–4144; (d) Lopez-Alvarado, P.; Avendano, C.; Menendez, J. C. *J. Org. Chem*. **1995**, *60*, 5678 and references cited therein.
8. Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc*. **1998**, *120*, 12459–12467.
9. Clement, J. B.; Hayes, J. F.; Sheldrake, H. M.; Sheldrake, P. W.; Wells, A. S. *Synlett* **2001**, 1423–1427.
10. Barton, D. H. R.; Finet, J. P.; Khamsi, J. *Tetrahedron Lett*. **1989**, *30*, 937–940.
11. Crystal structure of a related Cu(III) has recently been determined: Hayashi, H.; Pujinami, S.; Nagatomo, S.; Ogo, S.; Suzuki, Y.; Kitagawa, T. *J. Am. Chem. Soc*. **2000**, *122*, 2124–2125.
12. Representative experimental: *N*-*p*-tolylphenylalanine methyl ester. To a 20 mL vial equipped with a $CaSO_4$ drying tube was added in sequence *p*-tolylboronic acid (90.5 mg, 0.667 mmol, 2.0 equiv.), 4 Å molecular sieves (250 mg), 3 mL of dry dichloromethane, triethylamine (93 μL, 0667 mmol, 2.0 equiv.), L-phenylalanine methyl ester hydrochloride (71.5 mg, 0.333 mmol, 1.0 equiv.) and cupric acetate (66.7 mg, 0.367 mmol, 1.1 equiv.). The progress of the reaction was monitored by TLC (eluent: 15% ethyl acetate/hexane). After 15 min, 80% of the starting material was consumed. The reaction was allowed to stir under air at room temperature for 24 h. The reaction was quenched by a solution of 3 mL of 2 M NH_3 in methanol. The solvent was evaporated under reduced pressure and the residue dissolved in 3 mL of dichloromethane and purified by silica gel chromatography (eluent: 15% ethyl acetate/hexane) to give 57.8 mg of *N*-*p*-tolylphenylalanine methyl ester (75% yield) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.21 (m, 5H), 6.98 (d, $J=8.2$ Hz, 2H), 6.52 (d, $J=8.2$ Hz, 2H), 4.36 (t, $J=6.1$ Hz, 1H), 3.68 (s, 3H), 3.12 (t, $J=5.9$ Hz, 2H), 2.22 (s, 3H); MS AP+: 270.5 $[M+H]^+$ (70%), 539.3 $[2M+H]^+$; HRMS calculated for $C_{17}H_{20}NO_2$ $[M+H]^+$ $m/z=270.1494$, found m/z 270.1484. Anal. calcd for $C_{17}H_{19}NO_2$, $0.17H_2O$, C, 74.96; H, 7.16; N, 5.14; found: C, 74.96; H, 7.03; N, 5.14%.
13. Chiral reverse-phase HPLC provided baseline resolution of the enantiomers from which any racemization could be determined.
14. The lack of racemization is in agreement with the findings of Combs and Rafalski (Ref. 4b) for arylation of sulfonamides.
15. Cupric acetate is insoluble in CH_2Cl_2 (colorless solution), the preferred solvent. When the amine substrate is added an instantaneous deep blue color results, suggesting the coordination and dissolution of $Cu(OAc)_2$ as the first step of the reaction.