

New N- and O-Arylations with Phenylboronic Acids and Cupric Acetate¹

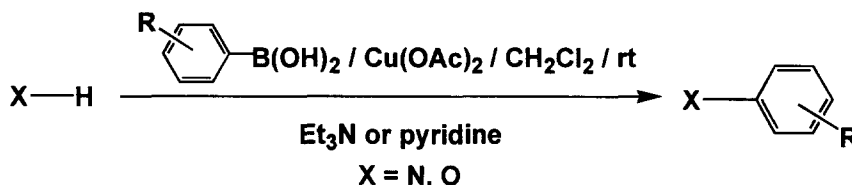
Dominic M. T. Chan*, Kevin L. Monaco, Ru-Ping Wang and Michael P. Winters

Chemical Discovery, DuPont Agricultural Products,
Stine-Haskell Research Center,
Newark, DE 19714, USA

Received 28 January 1998; revised 13 February 1998; accepted 15 February 1998

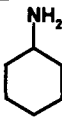
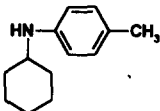
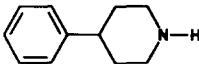
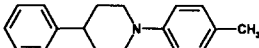
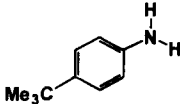
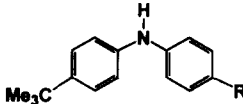
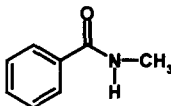
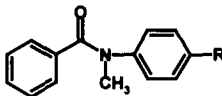
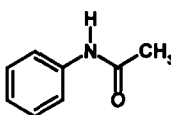
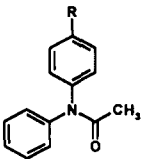
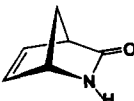
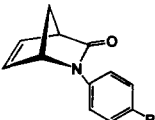
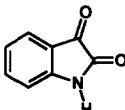
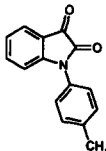
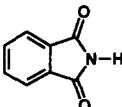
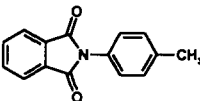
Abstract: A new method of arylating N-H and O-H containing compounds at room temperature with phenylboronic acids and cupric acetate in the presence of a tertiary amine promoter is described. Substrates include phenols, amines, anilines, amides, imides, ureas, carbamates, and sulfonamides. © 1998 Elsevier Science Ltd. All rights reserved.

The application of phenylboronic acids in palladium-catalyzed coupling with aryl halides to produce biphenyls, i.e., the Suzuki coupling reaction, is well known and has gained wide acceptance in the synthetic community as one of the most powerful tools in C-C bond formation. However the use of these boronic acids in forming heteroatom-carbon bonds has not been explored. We have previously reported the tertiary amine promoted reaction of N-H bonds with triaryl bismuth and cupric acetate.² As a continuing effort to develop novel, robust, and convenient methodology to arylate N-H and O-H containing compounds, we wish to report here that phenylboronic acids are also efficient arylating agents.³ Thus, using essentially the same reaction conditions as in the triaryl bismuth arylation,² one can in many cases replace the bismuth reagent with the corresponding arylboronic acid (see Table).

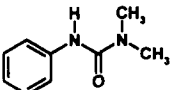
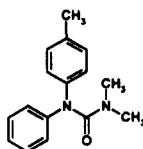
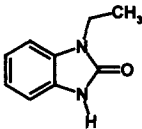
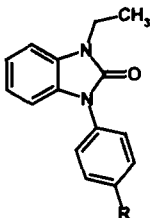


Preliminary results indicate the reaction is broadly applicable to a large variety of substrates and is also very tolerant to many sensitive functional groups. As in the bismuth arylation, it can be performed under very mild conditions, i.e., room temperature and with an amine base. It should be noted that the yield of the reaction can be quite dependent on the nature of the substrate and the substitution on the boronic acid. The choice of the tertiary amine base, i.e., triethylamine vs. pyridine, also plays a critical role in determining the yield of the reaction, but unlike the bismuth arylation reaction,² no clear substrate-based trend for the

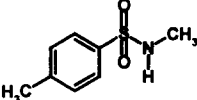
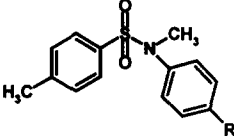
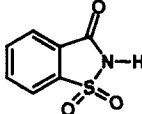
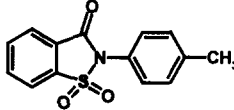
Table: Examples of N- and O-arylation with Phenylboronic acids⁴ and Cupric Acetate.

Entry	Substrate	Product ^a	Tertiary amine	B : Cu : A / time ^b	Yield ^c
<u>Amines</u>					
1			Et ₃ N	2 : 1 : 2 / 45	56%
			Pyridine	2 : 1 : 2 / 45	63%
2			Et ₃ N	2 : 1 : 2 / 48	50%
			Pyridine	2 : 1 : 2 / 48	74%
<u>Aniline</u>					
3			Et ₃ N (R = Me)	2 : 1 : 2 / 24	90%
			Et ₃ N (R = H)	2 : 1 : 2 / 48	58%
			Et ₃ N (R = F)	2 : 1 : 2 / 18	93%
<u>Amide</u>					
4			Et ₃ N (R = Me)	2 : 1 : 2 / 66	17%
			Pyridine (R = Me)	2 : 1 : 2 / 67	4%
			Et ₃ N (R = OMe)	2 : 1 : 2 / 48	5%
5			Et ₃ N (R = H)	2 : 1 : 2 / 48	59%
			Pyridine (R = H)	2 : 1 : 2 / 48	4%
			Et ₃ N (R = OMe)	2 : 1 : 2 / 48	41%
6			Et ₃ N (R = Me)	2 : 1 : 2 / 40	77%
			Et ₃ N (R = H)	2 : 1 : 2 / 64	12%
7			Pyridine	2 : 1 : 2 / 65	72%
			Et ₃ N	2 : 1 : 2 / 65	53%
<u>Imides</u>					
8			Et ₃ N	2 : 1 : 2 / 35	92%
			Pyridine	2 : 1 : 2 / 35	83%

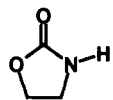
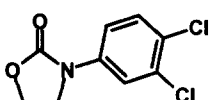
Ureas

9			Et ₃ N	2 : 1 : 2 / 47	45%
			Pyridine	2 : 1 : 2 / 47	7%
10			Et ₃ N (R = Me)	2 : 1 : 2 / 66	96%
			Pyridine (R = Me)	2 : 1 : 2 / 66	52%
			Et ₃ N (R = Cl)	2 : 1 : 2 / 66	37%

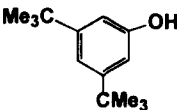
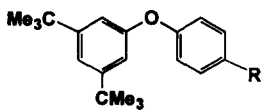
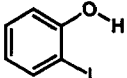
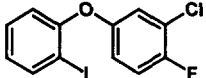
Sulfonamides

11			Et ₃ N (R = Me)	2 : 1 : 2 / 65	72%
			Pyridine (R = Me)	2 : 1 : 2 / 65	23%
			Et ₃ N (R = OMe)	2 : 1 : 2 / 48	67%
12			Pyridine	2 : 1 : 2 / 53	92%
			Et ₃ N	2 : 1 : 2 / 53	23%

Carbamate

13			Et ₃ N	2 : 1 : 2 / 50	60%
----	---	---	-------------------	----------------	-----

Phenols

14			Et ₃ N (R = Me)	2 : 1 : 2 / 24	73%
			Et ₃ N (R = H)	3 : 2 : 2 / 45	40%
			Et ₃ N (R = OMe)	2 : 1 : 2 / 24	73%
15			Et ₃ N	2 : 1 : 2 / 24	78%

a) The spectral data for the new compounds were in accord with the structures assigned.

b) B : Cu : A / time = molar equivalents of ArB(OH)₂ : Cu(OAc)₂ : tertiary amine / reaction time (h).

c) Isolated yields. No optimization was attempted in most cases.

use of either base has emerged from our experimental data. Nonetheless, the use of arylboronic acids in place of triarylbi-muth represents an attractive alternative⁵ in these N- and O-arylations since a large number of phenylboronic acids are either available commercially or their syntheses are well known in the literature. Another advantage of using a phenylboronic acid is that it is in theory a more "aryl-economical" approach since only one of three aryl groups is transferred from the bismuth reagent under normal conditions. Thus this new reaction represents one of the most convenient and efficient ways to effect N- and O-arylations for a wide range of substrates.

We believe the mechanism of this reaction is analogous to that of the bismuth arylations proposed by Barton, with the phenylboronic acid playing a role similar to the triarylbi-muth.⁶ Additional experiments will be performed to help understand the factors that control the reaction. Work on further optimizing the chemistry is also underway and will be reported in due course.

General Procedure for Arylation: A slurry of the substrate, arylboronic acid (2 - 3 equiv), anhydrous Cu(OAc)₂ (1 - 2 equiv), a tertiary amine such as triethylamine or pyridine (2 - 3 equiv) in methylene chloride (~10-12 mL/0.5 g of substrate) was stirred at room temperature for 24-72 h. The progress of the reaction was monitored by TLC. The products were isolated by direct flash column chromatography of the crude reaction mixture with preabsorption on silica gel.

References and Notes

1. Presented in part at the 35th National Organic Symposium, June 22-26, 1997, San Antonio, TX, USA. Abstract M92.
2. Chan, D.M.T. *Tetrahedron Lett.* 1996, 37, 9013-9016.
3. For arylation of heterocycles and phenols see: (a) 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. (b) Evans, D.A.; Katz, J.L.; West, T.R. *Tetrahedron Lett.* **1998**, 39, 2937-2940.
4. All phenylboronic acids were obtained from Aldrich Chem. Co. or Lancaster Synthesis, Inc., and were used without further purification. It should be noted that most commercial samples contain various amounts of the corresponding cyclic boroxine. We have yet to unequivocally determine the nature of the boron species responsible for the arylation.
5. We have not been able to observe any arylation of aliphatic alcohols with our current conditions. However, bismuth reagents have been used in O-arylation of alcohols to generate aryl ethers. (a) For an overview, see: Finet, J.-P. *Chem. Rev.* **1989**, 89, 1487-1501. (b) Sinclair, P.J.; Wong, F.; Staruch, M.J.; Wiederrecht, G.; Parsons, W.H.; Dumont, F.; Wyvratt, M. *Bioorg. Med. Chem. Lett.* **1996**, 6, 2193-2196. (c) Sinclair, P.J.; Wong, F.; Wyvratt, M.; Staruch, M.J.; Dumont, F. *Bioorg. Med. Chem. Lett.* **1995**, 5, 1053-1038.
6. Barton, D.H.R.; Finet, J.-P.; Khamsi J. *Tetrahedron Lett.* **1987**, 28, 887-890.