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A New Catalytic Cross-Coupling Approach for the Synthesis of Protected Aryl and Heteroaryl Amidines

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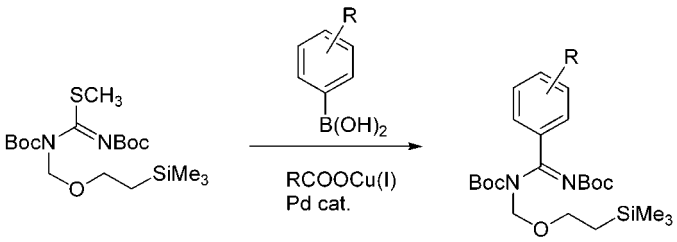
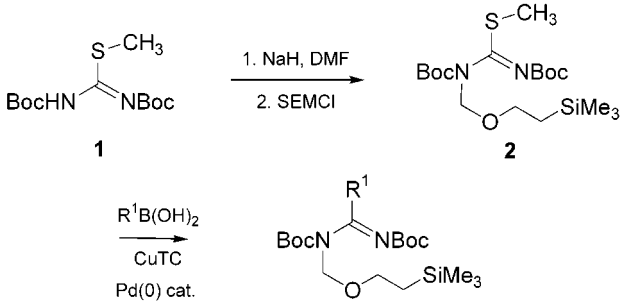
ABSTRACT



A new method for the synthesis of protected benzamidines is described. The commercially available 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea guanidylation reagent, after SEM-protection, functions as an amidine-forming cross-coupling partner under Liebeskind−Srogl conditions. In the presence of copper(I) thiophenecarboxylate (CuTC), the palladium-catalyzed cross-coupling of the SEM-protected thiopseudourea reagent with boronic acids affords fully protected benzamidines in good to excellent yield (40−91%).

The amidine functional group is found in many biological molecules,[1] and the benzamidine variant is often employed as an excellent guanidine surrogate in medicinal chemistry.[2] Consequently, a number of synthetic methods have been developed for the preparation of amidines.[3] Most of these methods rely on the nucleophilic addition of amines or ammonia equivalents to nitriles under forcing conditions, or to suitably activated carboxylate equivalents, such as imidoyl chlorides, imidates, and thioimidates. As a complement to these procedures, we report herein a new and mild method of substituted benzamidine synthesis that involves the cross-coupling of boronic acids with the protected methyl thiopseudourea, **2** (Scheme 1). This new, nonbasic, and general methodology is an extension of the previously described Liebeskind−Srogl thioether cross-coupling protocol.[4] As

Scheme 1



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(1) Patai, S.; Rappoport, Z. *The Chemistry of Amidines and Imidates*, Wiley: New York, 1991; Vol. 27.
(2) Zablocki, J. A.; Miyano, M.; Garland, R.; Pireh, D.; Schretzman, L.; Rao, S. N.; Lindmark, R. J.; Panzer-Knodle, S. G.; Nicholson, N. S.; Taite, B. B.; Salyers, A. K.; King, L. W.; Campion, J. G.; Feigen, L. P. *J. Med. Chem.* **1993**, *36*, 1811. Greenhill, J. V. ; Lue, P. In *Amidines and Guanidines in Medicinal Chemistry*, *Progress in Medicinal Chemistry*; Ellis, G. P., Luscombe, D. K., Eds.; Elsevier: New York, 1993; Vol. 30, Chapter 5, pp 203−326.
(3) For an excellent review, see: Yet, L. A Survey of Amidine Synthesis. Technical Report No. 3, Vol. 4, 2000; Albany Molecular Research, Inc., New York.

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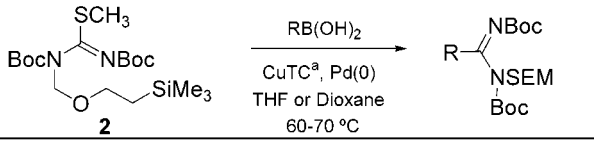
such, it offers a strategic alternative to the aforementioned nucleophilic addition chemistry for the preparation of fully protected aryl and heteroaryl amidines in the presence of a variety of sensitive functionalities.

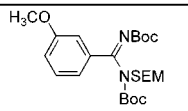
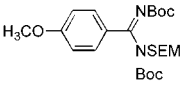
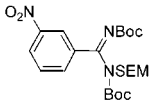
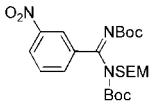
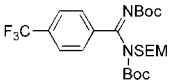
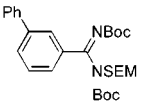
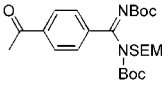
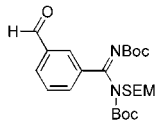
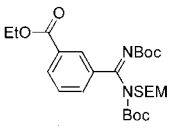
The method takes advantage of boronic acids as readily available, mild, stable and nontoxic reagents that are compatible with a wide variety of functional groups. The cross-coupling partner, amidination reagent **2**, is easily prepared from commercially available guanidylation reagent **1**[5] in one step by deprotonation with sodium hydride followed by treatment with SEM chloride (Scheme 1). Preliminary attempts to use guanidylation reagent **1** as a cross-coupling partner under palladium-catalyzed, copper carboxylate-mediated conditions gave unsatisfactory results.[6] We, therefore, turned our attention to the SEM-protected reagent **2**.

Boronic acids **3**−**10** reacted with amidination reagent **2** in THF or dioxane at 60−70 °C to give fully protected functionalized benzamidines **11**−**18** in good to excellent yields in a palladium-catalyzed ($Pd(PPh_3)_4$ or Pd_2dba_3 and tri-2-furylphosphine (TFP), copper carboxylate (copper(I) thiophenecarboxylate, CuTC)-mediated cross-coupling (Table 1). As described in earlier reports from the Liebeskind laboratory,[4] both the catalytic palladium and stoichiometric copper carboxylate are required for cross-coupling. Of the catalyst systems studied for the amidination cross-coupling, the Pd_2dba_3/TFP system gave the best results.[7] The ability to generate the protected benzamidine products in the presence of aldehyde, ketone, and ester functionality (entries 7, 8, and 9, respectively) is particularly noteworthy. The reaction products are nonpolar materials due to the Boc- and SEM-protecting groups and are easily purified by chromatography on silica gel using hexanes/ethyl acetate mixtures.

Treatment of pyridine-3-boronic acid with amidination reagent **2**, 1.5 equiv of CuTC, and 5−10% Pd catalyst afforded only trace amounts of the desired cross-coupling product. The additive $Zn(OAc)_2$ was shown earlier to have a beneficial effect on these types of cross-coupling reactions with heterocyclic boronic acids such as pyridine-3-boronic acid (possibly by coordinating to Lewis basic sites of the heterocycle).[4a] The addition of 1.2 equiv of $Zn(OAc)_2$ to the pyridine-3-boronic acid reaction mixture did increase the overall conversion to the desired protected amidine product, but in repeated runs, 40−50% starting material still remained after the typical 12−16 h reaction time. We have now found that for the amidination cross-coupling reaction with heterocyclic boronic acids, the use of 3 equiv of CuTC affords much improved results. Table 2 illustrates representative protected heterocyclic amidines that have been prepared by this cross-coupling chemistry. In each case, little or no product was observed under the standard coupling conditions (1.5 equiv of CuTC), with starting amidination reagent **2** recovered unchanged. However, in the presence of 3 equiv of CuTC, all of reagent **2** was consumed within 6−12 h. In each of these heterocyclic cases, 2 equiv of the boronic acid was used to optimize the cross-coupling yields. As is shown for the three examples reported in Table 2, purified yields ranged from 40 to 70%, slightly lower than the aryl cases shown in Table 1. The fate of the mass balance of reagent **2**, which is consumed but does not lead to coupling product, is under investigation at this time.[8]

Table 1. Functionalized Benzamidine Synthesis



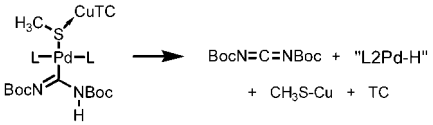
entry	boronic acid, R =		product		%
1	**3**	*m*-MeOPh		**11**	81[b]
2	**4**	*p*-MeOPh		**12**	91[c]
3	**5**	*m*-NO_2Ph		**13**	41[b]
4	**5**	*m*-NO_2Ph		**13**	80[c]
5	**6**	*p*-CF_3Ph		**14**	73[c]
6	**7**	3-Biphenyl		**15**	71[c,d]
7	**8**	4-AcetylPh		**16**	77[c]
8	**9**	3-FormylPh		**17**	68[c]
9	**10**	3-EtO_2CPh		**18**	48[b]

[a] CuTC: Cu(I) thiophene-2-carboxylate. [b] $Pd(PPh_3)_4$/THF. [c] Pd_2dba_3 /TFP/dioxane. [d] 90 °C.

(4) (a) Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979. (b) Savarin, C.; Srogl, J. Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91. (c) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260.

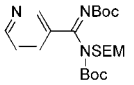
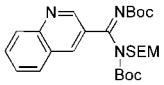
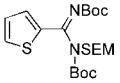
(5) Bergeron, R. J.; McManis, J. S. *J. Org. Chem.* **1987**, *52*, 1700.

(6) Low yields of cross-coupling products have been detected in the palladium-catalyzed copper carboxylate-mediated reactions of reagent **1** with 3-methoxyphenylboronic acid, but the reaction mixtures have proven difficult to optimize. β-Hydride elimination may divert the reaction manifold away from the desired cross-coupling chemistry.



(7) Pd_2dba_3·$CHCl_3$ was purchased from Aldrich Chemical Co. and used as received.

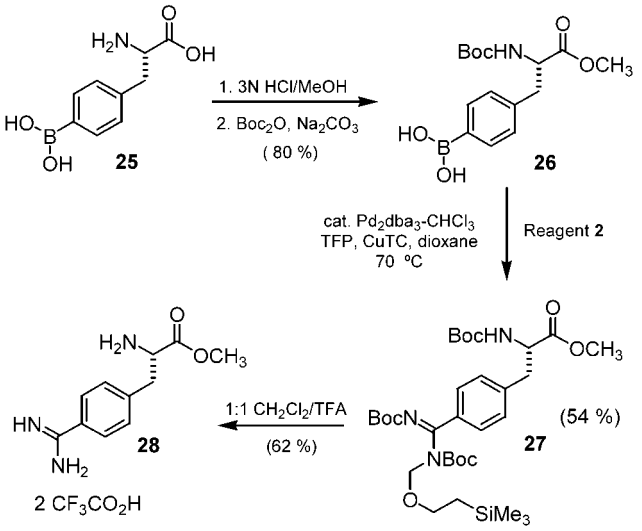
Table 2. Heterocyclic Amidine Synthesis[a]

entry	boronic Acid, R=		product		%
1	**19**	3-pyridyl		**22**	61
2	**20**	3-quinolinyl		**23**	67
3	**21**	2-thienyl		**24**	41

[a] 5% $Pd_2(dba)_3$ /TFP/THF/65 °C/3 equiv of CuTC.

Finally, we report the extension of this new methodology to the preparation of the known 4-amidinophenylalanine methyl ester **28**. Again, this method provides an alternative to the preparation of 4-cyanophenylalanine and subsequent nitrile nucleophilic addition chemistry.[9] As summarized in Scheme 2, the commercially available 4-boronophenylalanine **25** was converted to the *N*-Boc methyl ester derivative **26** under standard conditions. Cross-coupling with amidination reagent **2** under standard conditions proceeded smoothly to afford the fully protected amidinophenylalanine derivative **27** in 54% yield. Deprotection of compound **27** to the free amidine product **28** was accomplished in one step by treatment with a 1:1 solution of TFA in methylene chloride.

Scheme 2. Synthesis of 4-Amidinophenylalanine



In conclusion, the scope and limitations of this new functionalized amidine synthesis via the Liebeskind−Srogl copper carboxylate-mediated, palladium-catalyzed cross-coupling chemisty have been studied. The methodology allows the synthesis of fully protected aryl and heterocyclic amidines in the presence of a range of sensitive functionality.

Acknowledgment. The authors thank Dr. Jiri Srogl of Emory University and Dr. Samuel Tremont of Pharmacia for helpful discussions. We also thank James Doom and David Masters-Moore of the Pharmacia Mass Spectrometry Group for high-resolution mass spectroscopy data.

Supporting Information Available: A complete description of experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

OL025547S

(8) It is possible that the solution aggregation hinders the transmetalation of heterocyclic boronic acids to the oxidative addition product of the Pd catalyst and thiomethyl reagent **2**.

(9) Vieweg, H.; Wagner, G. *Pharm.* **1983**, *38*, 170. Kent, D. R.; Cody, W. L.; Doherty, A. M. *J. Pept. Res.* **1998**, *52*, 201.

(10) **Typical experimental procedure:** The boronic acid (1.2−1.5 equiv), Pd catalyst (5−10 mol %), and CuTC (1.5 equiv) were placed in a 50 mL flask and submitted to 3 vacuum/argon cycles. A sparged solution of the amidination reagent **2** in dioxane was added via syringe. Additional dry degassed dioxane was added as needed, and the mixture was heated at 60−70 °C for 16 h. Following the general procedure, a solution of amidination reagent **2** (5.0 mL of a 45 mg/mL solution in dioxane) was added to 3-nitrophenylboronic acid **5** (110 mg, 0.66 mmol), CuTC (151 mg, 0.80 mmol), Pd_2dba_3·$CHCl_3$ (27 mg, 5 mol %, 10 mol % Pd), and TFP (43 mg, 7 × 5 mol %). Additional dioxane (10 mL) was added, and the reaction was heated at 65 °C for 16 h; after radial chromatography (10/1 hexanes−ethyl acetate), **13** (200 mg, 80% yield) was obtained. Full details are contained in the Supporting Information.