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Copper-Catalyzed Oxidative Three-Component Synthesis of *N*, *N*′,*N*″-Trisubstituted Guanidines

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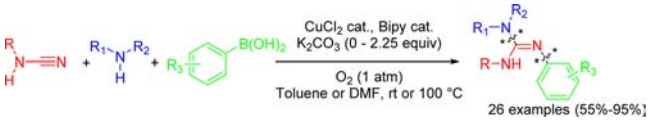
ABSTRACT



A copper-catalyzed three-component synthesis of trisubstituted *N*-aryl guanidines involving cyanamides, arylboronic acids, and amines has been developed. This operationally simple oxidative process, which is performed in the presence of K_2CO_3, a catalytic amount of $CuCl_2 \cdot 2H_2O$, bipyridine, and oxygen (1 atm), allows the rapid assembly of *N*,*N*′,*N*″-trisubstituted aryl guanidines.

Guanidines are important units due to their involvement in essential biological processes through, for example, their presence in arginine-containing peptides and have been found in numbers of molecules of natural origin.[1] As a consequence, they have been actively targeted in medicinal chemistry and therapeutics such as relenza (antiviral), famotidine (antiulcer), and clonidine (anesthetic α2 adrenoceptor agonist) are currently used on the market.[2] In addition, guanidines hold a growing place in the synthetic toolbox, being notably used as organocatalysts or as metal ligands in a number of transformations.[3]

The synthesis of guanidines mostly relies on the condensation between amines and electrophilic guanylating reagents or carbodiimides.[4] Metal-catalyzed functionalizations of guanidines have also been described and provided a useful entry, especially to N-arylated guanidines.[5] In addition, such a strategy is also valuable for the synthesis of heterocyclic structures such as benzimidazoles or quinazolines.[6] While valuable, all these methods leave room for the development of an alternative process especially considering the rapid elaboration of libraries of *N*,*N*′,*N*″-trisubstituted guanidines which requires preparation of a specific reagent/precursor for most cases.[7]

Cyanamides are valuable targets for various applications and have been used as versatile building blocks for further elaboration through nucleophilic addition, cyclocondensation, or radical reactions.[8] In connection with our interest in developing metal-catalyzed transformations for the rapid synthesis of heterocyclic structures[9] through tandem[10] or multicomponent reactions,[11] our attention

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(3) (a) *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts*; Ishikawa, T., Ed.; John Wiley & Sons: West Sussex, U.K., 2009. (b) Taylor, J. E.; Bull, S. D.; Williams, J. M. J. *Chem. Soc. Rev*. **2012**, *41*, 2109–2121.

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was drawn to two Pd-catalyzed reactions involving cyanamides leading to N-arylated cyanamides[12] and benzamidines,[13] respectively (Scheme 1a). Taking into consideration that, besides palladium, copper has been particularly effective for catalyzing C–N bond formation[14] and based on our experience on metal-catalyzed aerobic oxidative transformations,[15] we became interested in building *N*-aryl cyanamides with copper.[16] Indeed, a such process could be valuable considering the cost associated to the metal/ligand couple or provide alternative conditions.

An initial attempt, reacting *N*-(*tert*-butyl)cyanamide (**1a**) with potassium *p*-tolylboronic acid (**6a**) under conditions found previously to be optimum for the N-arylation of amidines,[15c] afforded benzimidamide **7a**, albeit in low yield (< 20%) (Scheme 1b); interestingly, we also identified the presence of urea **8a** among the side products. Such a product, showing a different regiochemical arylation pattern compared to the described Pd-catalyzed reactions, could result from a three-component reaction[17] involving cyanamide, boronic acid, and H_2O (Scheme 1b). From this observation we reasoned that replacing water with a more nucleophilic reagent, namely amine, could offer an entry to guanidines, keeping in mind that N-arylation of the amine could constitute a serious competitive reaction (Scheme 1c). From this study, we now report conditions allowing an easy assembly of multisubstituted guanidines from cyanamides, arylboronic acids, and amines, through a three-component process performed under Cu-catalyzed aerobic conditions.

To evaluate the possible three-component reaction, we chose to react cyanamide **1a**, boronic acid **6a**, and

Scheme 1. Pd- and Cu-Catalyzed Processes Involving Cyanamides

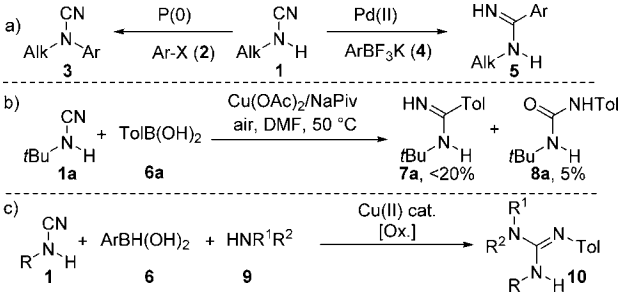
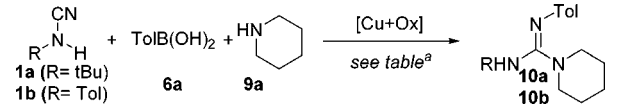


Table 1. Survey of the Reaction Conditions



entry	1	additive/ligand (equiv)	time, temp (°C)	solvent	yield (%)[b]
1[c]	**1a**	NaPiv(0.4)	10 h, 50	DMF	39
2[c]	**1a**	BiPy (0.2)	10 h, 50	DMF	87
3[c]	**1a**	BiPy (0.2)	10 h, 50	toluene	75
4[c]	**1a**	BiPy (0.2)	10 h, 50	DMSO	70
5[c]	**1a**	BiPy (0.2)	10 h, 50	dioxane	52
6[c]	**1a**	BiPy (0.2)	10 h, 50	amlylOH	44
7[c]	**1b**	BiPy (0.2)	10 h, 50	DMF	52
8	**1b**	BiPy (0.2)	10 h, 100	toluene	65
9[d]	**1b**	BiPy (0.2)	0.5 h, 100	toluene	71
10[d]	**1b**	K_2CO_3 (2.25)/BiPy (0.2)	0.5 h, 100	toluene	95
11[d]	**1b**	K_2CO_3 (2.25)	0.5 h, 100	toluene	59
12[d]	**1b**	K_2CO_3 (2.25)/BiPy (0.2)	6 h, rt	toluene	91
13[d]	**1b**	K_2CO_3 (2.25)/BiPy (0.2)	3 h, 50	toluene	91
14[c,d]	**1b**	K_2CO_3 (2.25)/BiPy (0.2)	3 h, 50	toluene	90
15[d,e]	**1b**	K_2CO_3 (2.25)/BiPy (0.2)	3 h, 50	toluene	93
16[f]	**1b**	K_2CO_3 (2.25)/BiPy (0.2)	3 h, 70	toluene	0

[a] Conditions: $Cu(OAc)_2 \cdot H_2O$ (0.2 equiv), additive, cyanamide (1.5 equiv), *p*-TolB(OH)$_2$ (1.5 equiv), piperidine (1.0 equiv), O_2 (1 atm). [b] Isolated yield. [c] Under air instead of O_2. [d] $CuCl_2 \cdot H_2O$ (0.2 equiv) was used. [e] $CuCl_2 \cdot H_2O$ (0.1 equiv). [f] No copper.

piperidine (**9a**) and rapidly found that guanidine **10a** could indeed be obtained under Cu catalysis (table 1). The reaction occurred at 50 °C under air in the presence of a catalytic amount of $Cu(OAc)_2$ and was markedly improved using bipyridine instead of sodium pivalate as an additive/ligand (Table 1, entry 2 vs 1). Various solvents such as toluene and DMSO were a good reaction medium (Table 1, entries 3–4), but the best yields were obtained in DMF allowing isolating guanidine **10a** in 87% yield (Table 1, entry 2).

As *N*-arylated cyanamides were not evaluated under the Pd-catalyzed conditions reported by Louie and Larhed,[12,13] we immediately evaluated the reactivity of *p*-tolylcyanamide and were pleased to obtain the corresponding bis-arylated guanidine **10b** in 52% yield (Table 1, entry 7). Further

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(12) Stolley, R. M.; Guo, W.; Louie, J. *Org. Lett.* **2012**, *14*, 322–325.

(13) (a) Sävmarker, J.; Rydfjord, J.; Gising, J.; Odell, L. R.; Larhed, M. *Org. Lett.* **2012**, *14*, 2394–2397. (b) Rydfjord, J.; Svensson, F.; Trejos, A.; Sjöberg, P. J. R.; Sköld, C.; Sävmarker, J.; Odell, L. R.; Larhed, M. *Chem.—Eur. J.* **2013**, *19*, 13803–13810.

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(15) For reviews, see: (a) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381–3430. (b) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev.* **2013**, *113*, 6234–6458. Our work: (c) Li, J.; Bénard, S.; Neuville, L.; Zhu, J. *Org. Lett.* **2012**, *14*, 5980–5983. (d) Li, J.; Neuville, L. *Org. Lett.* **2012**, *14*, 1752–1755. (e) Piou, T.; Neuville; Zhu, J. *Tetrahedron* **2013**, *69*, 4414–4420.

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(17) (a) *Multicomponent Reaction*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005. (b) ÐSouza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095–1108. (c) Arndtsen, B. A. *Chem.—Eur. J.* **2009**, *15*, 302–312.

investigation of the conditions revealed the following: (1) toluene was a better solvent for *N*-aryl cyanamides (Table 1, entry 8); (2) the reaction was effectively catalyzed by the combination $CuCl_2 \cdot H_2O$ in the presence of O_2 (1 atm) (Table 1, entry 9);[18] (3) the reaction was rather fast at 100 °C, reaching completion in 30 min but could be carried out at rt over 6 h (Table 1, entries 9–12); (4) importantly using a combination of K_2CO_3 (2.25 equiv) and BiPy (0.2 equiv) as the additive/ligand allowed an almost quantitative guanidine formation (Table 1, entry 10).

With the best conditions [cyanamide/boronic acid/amine (1.5/1.5/1.0 equiv), K_2CO_3 (2.25 equiv), O_2 (1 atm), $CuCl_2 \cdot 2H_2O$ (0.1 equiv), Bipy (0.1 equiv), toluene, 100 °C, 30 min], the generality of the reaction was surveyed.

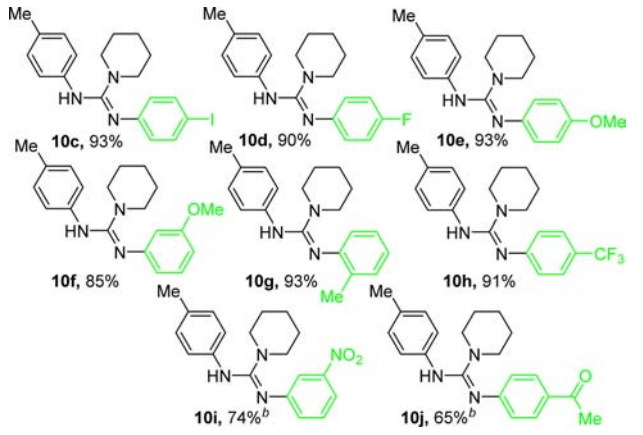

Figure 1. Scope of the Cu-catalyzed synthesis of guanidines: boronic acids.[a] [a] Conditions: *p*-tolyl cyanamide/boronic acid/piperidine (1.5/1.5/1.0 equiv), K_2CO_3 (2.25 equiv), O_2 (1 atm), $CuCl_2 \cdot 2H_2O$ (0.1 equiv), Bipy (0.1 equiv), toluene, 100 °C, 30 min. [b] $CuCl_2 \cdot 2H_2O$ (0.2 equiv), Bipy (0.2 equiv).

The tolerance of the reaction toward the aryl boronic acid component was investigated, and the results are shown in Figure 1. Yields ranged from 65% to 93% demonstrating the tolerance of the reaction to functional groups such as halides including the iodine, ether, ketone, nitro, or trifluoromethyl group. Both electron-rich and -poor as well as sterically demanding aryl boronic acids provided the corresponding guanidines in high yields (**10e**, **10g**, **10h**). For 4-acetyl- and 3-nitro-phenyl boronic acids, a higher catalyst loading of $CuCl_2$ (20 mol %) was required to furnish good yields of products (**10i** and **10j**).

A set of diverse amines was next investigated (Figure 2). Secondary amines, whether cyclic or acyclic, afforded the desired guanidines in high yields uneventfully. Interestingly, the presence of an additional tertiary amine or a free hydroxyl group was well tolerated, as demonstrated with the synthesis of compounds **10r** and **10s**. The process was also viable using primary amines including the sterically demanding *tert*-butyl amine. Anilines were not effective for the process (not shown), but the reaction was not limited to alkyl amines, as benzyl and allyl amine successfully afforded guanidines **10p** and **10q**. In the latter case, performing the reaction at rt greatly improved the reaction's outcome avoiding oxidative degradation of the amine. It should be noted that **10p** and **10q** provide a handle for further deprotection and access to disubstituted guanidines.[19]

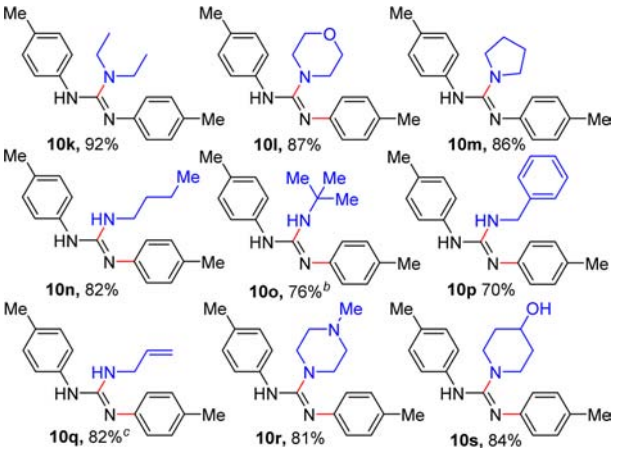

Figure 2. Scope of the Cu-catalyzed synthesis of guanidines: amines.[a] [a] Conditions: *p*-tolyl cyanamide/*p*-tolyl boronic acid/amine (1.5/1.5/1.0 equiv), K_2CO_3 (2.25 equiv), O_2 (1 atm), $CuCl_2 \cdot 2H_2O$ (0.1 equiv), Bipy (0.1 equiv), toluene, 100 °C, 30 min. [b] 70 °C, 30 min. [c] Rt, 24 h.

Substitution at the cyanamide residue was finally evaluated (Figure 3). The presence of a free NH was found to be necessary, as secondary *N*-methyl-*N*-phenylcyanamide did not participate in the process. We were delighted to observe that aryl cyanamides bearing an ortho substituent, electron-withdrawing and -donating groups, all provided good results (**10e**, **t**–**w**, 76–93% yields). Cyanamides bearing a primary, secondary, and tertiary alkyl substituent as well as benzylcyanamide also showed good reactivity (**10w**–**z**). For these compounds we found that the reaction was best accomplished at 50 °C in DMF under base-free conditions.

While targeted for direct use,[1–3] substituted guanidines of type **10** can offer opportunities for building heterocyclic structures by intramolecular cyclization.[5,6] In a preliminary work, we have found that benzimidazoles **11** (Figure 3, box) could be directly assembled through a three-component reaction/C–H functionalization[20] sequence using the same reaction conditions over a prolonged time (100 °C, 24 h), **10b** being an intermediate of the reaction.[21]

It seems reasonable to think that the process is the result of two distinct events, namely a nucleophilic addition of

(18) $Cu(CF_3COCH_2COCH_3)_2$, $CuBr_2$, and $Cu(SO_2CF_3)_2$ were less efficient, furnishing 54%, 69%, and 57% respectively.

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(20) Seminal work: Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932–1934.

(21) Extension of this and related transformations is being pursued.

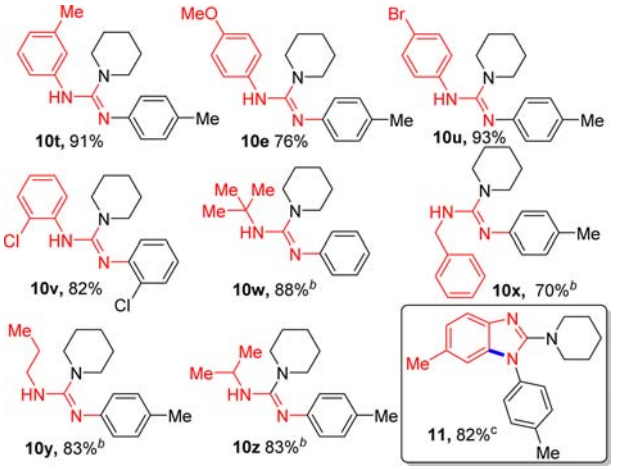

Figure 3. Scope of the Cu-catalyzed synthesis of guanidines: cyanamides.[a] Conditions: cyanamide/aryl boronic acid/piperidine = 1.5/1.5/1.0 equiv, K_2CO_3 (2.25 equiv), O_2 (1 atm), $CuCl_2 \cdot 2H_2O$ (0.1 equiv), Bipy (0.1 equiv), toluene, 100 °C, 30 min. [b] In DMF, without K_2CO_3, at 50 °C, 6 h. [c] At 100 °C, 24 h.

amine to cyanamide to form guanidine **12**,[22] followed by a Cu-catalyzed Chan–Lam–Evans type N-arylation with boronic acid[23] (Scheme 2a). However, control experiments clearly established that guanidine **12** was not formed and that N-arylation did not proceed to a significant level under the present conditions.[24]

Based on this result, a reasonable mechanism accounting for the observed transformation was proposed (Scheme 2b). Transmetalation of boronic acid **6** with a Cu(II) complex would initiate the reaction, and subsequent coordination and deprotonation of the cyanamide **1** would deliver complex **B** which would tautomerize to diimide complex **B′**.[25] Upon oxidation (with a second Cu(II) species or with oxygen), a higher oxidation state Cu(III) complex **C** could next be generated. At this point, a reductive elimination could take place to form the carbodiimide **13**; however, initial results obtained when

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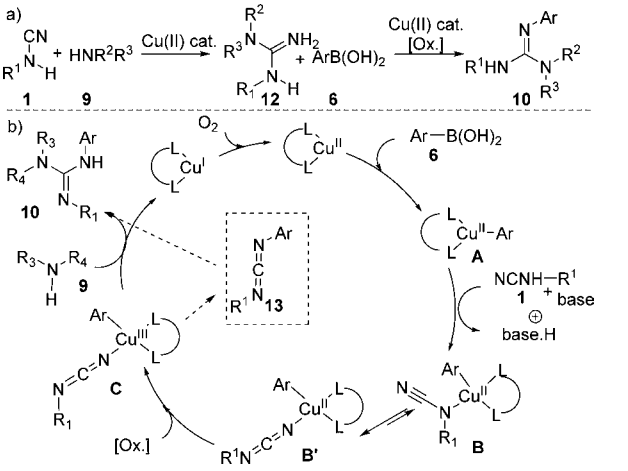
(23) (a) Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011**, 829–856. (b) Rao, K. S.; Wu, T.-S. *Tetrahedon* **2012**, *68*, 7735–7754. Our contribution: (c) Bénard, S.; Neuville, L.; Zhu, J. *J. Org. Chem*. **2008**, *73*, 6441–6444. (d) Benard, S.; Neuville, L.; Zhu, J. *Chem. Commun*. **2010**, *46*, 3393–3395.

(24) See Supporting Information.

(25) Crutchley, R. J. *Coord. Chem. Rev*. **2001**, *219–221*, 125–155.

(26) Arylcyanamides can act as bridging ligands in dinuclear copper complexes; see: Hadadzadeh, H.; Rezvani, A. R.; Esfandiari, H. *Polyhedron* **2008**, *27*, 1809–1817.

Scheme 2. Possible Mechanism



attempting to perform a simple N-arylation of cyanamides in the absence of amine tend to argue against this pathway, as, at least to a significant level, no carbodimiide was observed. Therefore, we propose that a nucleophilic addition of the amine **9** to the highly electrophilic diimide complex **C** (potentially promoted by a second Cu-atom)[26] and a reductive elimination would deliver product **10**. Finally, the Cu(I) complex would be oxidized before reentering the catalytic cycle.

In conclusion, we have disclosed a novel Cu-catalyzed three-component reaction of arylboronic acids, cyanamides, and amines. A broad diversity of symmetrical and unsymmetrical *N*,*N*′,*N*″-trisubstituted guanidines were easily prepared from readily available and simple starting materials using this method. A preliminary mechanistic investigation ruled out a simple nucleophilic addition of an amine to a cyanamide followed by a Cu-catalyzed Chan–Lam–Evans type N-arylation.

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Supporting Information Available. Experimental procedures, product characterization, and copies of the ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.