JOC The Journal of Organic Chemistry

Article

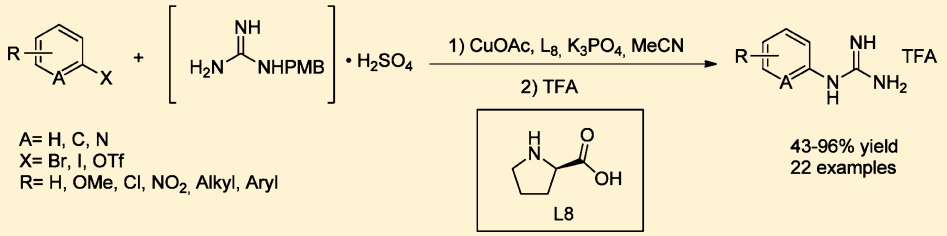
pubs.acs.org/joc

Direct Guanidinylation of Aryl and Heteroaryl Halides via Copper-Catalyzed Cross-Coupling Reaction

Hassan Hammoud, Martine Schmitt,* Frédéric Bihel, Cyril Antheaume, and Jean-Jacques Bourguignon

Laboratoire d'Innovation Thérapeutique, UMR 7200, Faculté de pharmacie, Université de Strasbourg, 74 route du Rhin, BP 60024, 67401 Illkirch, France

Supporting Information



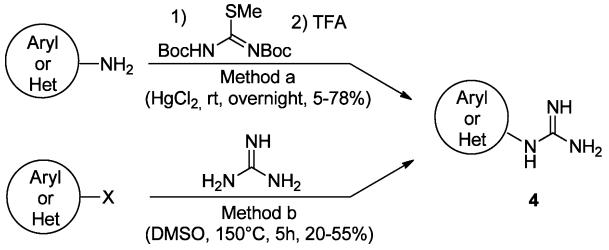
ABSTRACT: A modified Ullmann reaction using *p*-methoxybenzyl (PMB) guanidine as guanidinylation agent yielded various aryl and heteroaryl guanidines in good yields.

INTRODUCTION

The transition-metal-catalyzed formation of carbon−nitrogen bonds via cross-coupling reactions plays an important role in the preparation of numerous products dealing with pharmaceutical sciences,[1] allowing the introduction of various nitrogen-based functions (amine, amide, urea, carbamate, etc.) onto aromatic or heteroatomic cycles. *N*-Aryl and *N*-heteroaryl guanidines represent an important class occurring in both natural and synthetic compounds.[2] The most straightforward route for the synthesis of these compounds involves the reaction of aromatic (or heteroaromatic) amines with electrophilic thiourea derivatives as guanylation reagents, using toxic reagents such as mercury salts.[3]

Although widely used, this methodology suffers from another drawback resulting from poor nucleophilicities of the aromatic amine reagent (anilines bearing electron-withdrawing groups, heteroarylamines). On the basis of the umpolung concept, an alternative approach was developed, as illustrated in Scheme 1.

Scheme 1. Guanylation (Method a) and Guanidinylation (Method b) of Aromatics and Heteroaromatics (Umpolung Concept)



Two examples of direct guanidinylation of aromatics and heteroaromatics have been recently published.[4,5] On one hand, guanidine was reacted with highly electrophilic *ortho*-bromobenzonitrile,[4a] providing easily 4-aminoquinazolines with satisfactory yields. On the other hand, guanidinylation of aryl and heteroaryl halides (X = Br or I) using free guanidine presented limitations resulting from drastic experimental conditions and the possibility to yield *N*,*N*′-diaryl or diheteroaryl guanidines, as the result of the multiple nucleophilic characteristics of guanidine.[4b]

The development of palladium-catalyzed C−N bond forming processes, as efficiently described by Buchwald[6] and Hartwig,[7] opened an avenue for novel synthetic approaches for chemists, especially when compared with the classical Ullmann reaction requiring high temperatures, highly polar solvents, and large amounts of copper reagents as catalyst.[8]

Over the past decade, the copper-catalyzed modified Ullmann reaction has emerged as a powerful approach by means of additive copper chelating agents.[9] Moreover, it could be extended to other nitrogen-containing reagents such as anilines, amides, and carbamates.[10] Progress has been obtained through the use of various copper-chelating agents (α-amino-acids, β-aminoacids, phenolic derivatives, or ethylenediamine derivatives), which dramatically increased the versatility of the reaction (less drastic experimental conditions, higher yields). The objective of this communication is to present a very efficient method of guanidinylation of aromatics and heteroaromatics. A systematic survey of catalysts (Pd *versus* Cu) in different experimental conditions and using different guanidinylation reagents has been carried out, highlighting the most promising system allowing generalization of the reaction to a large panel of aromatics and heteroaromatics.

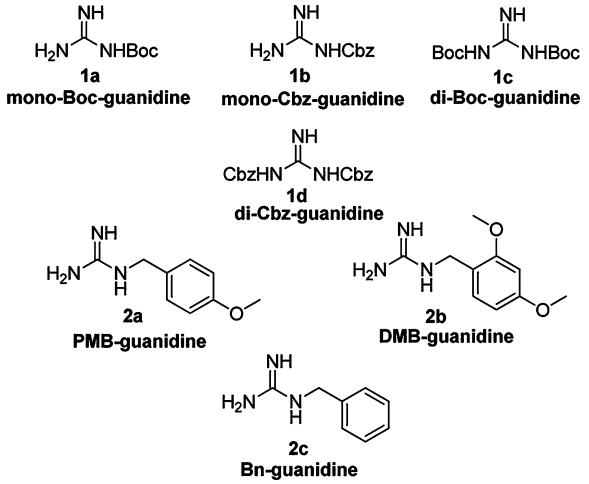
Received: October 6, 2011
Published: November 21, 2011

 © 2011 American Chemical Society

RESULTS AND DISCUSSION

Phenyl iodide was chosen for the model reaction and was reacted with guanidine and guanidine derivatives first in palladium cross-coupling reactions, as earlier described by Buchwald with aniline, amides, ureas, or carbamates. Mono- and diprotected guanidines were first selected for this purpose in order to progressively decrease both the high basicity and multiple nucleophilicity of guanidine (Chart 1).

Chart 1. Protected Guanidines



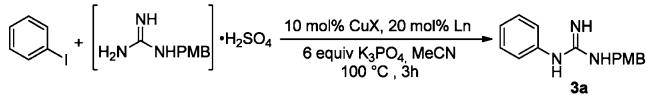
In this work, the benzyl, *p*-methoxybenzyl (PMB), and *o*,*p*-dimethoxybenzyl (DMB) guanidines **2a**–**2c** were first used as alternative ways to modulate both the basicity and the nucleophilicity of guanidine[11] (Chart 1). PMB and DMB protective groups are known to be easily removed in TFA.

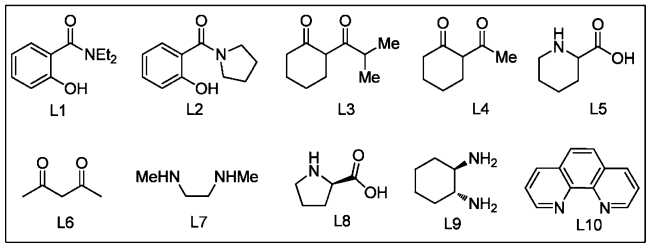
Palladium-catalyzed reactions, as described by Buchwald for amidation of aromatics ($Pd(OAc)_2$, Binap, or Xantphos, Cs_2CO_3, dioxane, 105 °C), were first performed with phenyl iodide. However *N*-carbamate guanidines **1a**–**1d** yielded a complex mixture of products, maybe as the result of the lability of fairly stable carbamates.[12] In addition, *N*-benzylguanidines **2a**–**2c** did not show any significant reactivity in these conditions. During the course of our preliminary studies, an interesting work of Salva et al. dealing with copper-catalyzed guanidinylation of aryl iodides with guanidine was published.[4b] However, due to the double nucleophilicity of unsubstituted guanidine, the authors obtained systematically *N*,*N*′-diarylation. We reinvestigated this approach with PMB-guanidine **2a** expecting a lack of double substitution of guanidine. The role of both the source of copper and the ligand was first evaluated (Table 1).

A series of ligands comprising α-aminoacids (proline L_8, pipecolic acid L_5), β-ketoenols or equivalents (L_1, L_2, L_3, L_4, L_6), ethylenediamines (L_7, L_9), or rigid 1,1-bispyridin (L_{10}) were chosen as reference ligands (Table 1).

Copper I and II acetates and different copper halides (Cl, Br, I) or cyanide or thiophene-2-carboxylate were used as catalysts. Interestingly, in the selected experimental conditions described by Salva et al.[4b] (10 mol % of CuI, 20 mol % of L_1, 6 equiv of K_3PO_4, MeCN, 100 °C, entry 1), *N*-phenyl-*N*′-PMB-guanidine **3a** was obtained with a satisfactory yield (61%) but with still a significant amount of *N*,*N*′-diphenylguanidine, as determined by HPLC.

Table 1. Catalyst and Ligand Effects on Reactivity





entry[a]	catalyst	ligand	yield, %[b]
1	CuI	L_1	61[c]
2	CuI	L_8	58[c]
3	CuI	L_{10}	59[c]
4	CuBr	L_8	41
5	CuCl	L_8	29
6	CuCN	L_8	38
7	$Cu(OAc)_2$	L_8	54
8	CuTc	L_8	71[c]
9	CuOAc	L_1	63[c]
10	CuOAc	L_2	60
11	CuOAc	L_3	12
12	CuOAc	L_4	9
13	CuOAc	L_5	75
14	CuOAc	L_6	5
15	CuOAc	L_7	65
16	CuOAc	L_8	96
17	CuOAc	L_9	70
18	CuOAc	L_{10}	43

[a]The reaction used 1 mmol of PMB-guanidine and 1 mmol of iodobenzene. [b]Isolated yields. [c]Small amount (16 ± 5%) of *N*,*N*′-diarylguanidine could be isolated from the mixture.

The replacement of CuI by CuOAc gave similar results (entry 9), whereas replacement by other copper catalysts provided less reactive systems (entries 4–7), with still a significant amount of starting material after a 3 h reaction period. The reaction using CuTc in place of CuI or CuOAc was already performed by us. However, about 15% of disubstituted adduct was obtained (entry 8). Keeping CuI, and replacing L_1 by other ligands (L_8 or L_{10}), did not improve the reactivity (entries 2 and 3).

Finally, we selected CuOAc for the next set of reactions dealing with the choice of the most suitable ligand (Table 1, entries 9–18).

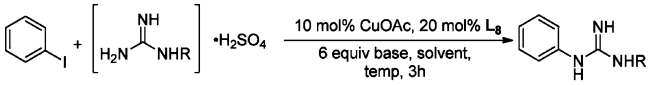
The optimal conditions were obtained with proline L_8 (entry 16), yielding the monosubstitued guanidine in a nearly quantitative yield and with less than 2% of *N*,*N*′-diadduct.

The relative reactivity of *N*-benzyl guanidine derivatives **2a**–**2c** was also evaluated (Table 2, entries 1–3). A nearly quantitative yield was obtained with PMB-guanidine. A 3 h reaction time at 100 °C was found to be optimal (entries 1 and 4–6). The base had a dramatic effect in this reaction, as replacing K_3PO_4 by carbonate salts or triethylamine gave no reaction (entries 8–10). In addition, replacement of MeCN by other solvents was also detrimental for reactivity (entries 11–17).

Table 3 summarizes our attempts to extend the scope of the reaction to various aromatic and heteroaromatic systems.

dx.doi.org/10.1021/jo202018w | J. Org. Chem. 2012, 77, 417–423

Table 2. Optimization of Reaction of *N*-Benzyl Guanidine Derivatives with Iodobenzene



2

entry[a]	R	base	solvent	temp, °C	yield, %[b]
1	PMB	K_3PO_4	MeCN	100	96
2	Bn	K_3PO_4	MeCN	100	90
3	DMB	K_3PO_4	MeCN	100	88
4	PMB	K_3PO_4	MeCN	25	0
5	PMB	K_3PO_4	MeCN	60	63
6	PMB	K_3PO_4	MeCN	80	78
7	PMB	K_3PO_4	MeCN	120	80
8	PMB	Cs_2CO_3	MeCN	100	0
9	PMB	K_2CO_3	MeCN	100	0
10	PMB	Et_3N	MeCN	100	0
11	PMB	K_3PO_4	dioxane	115	13
12	PMB	K_3PO_4	THF	100	0
13	PMB	K_3PO_4	toluene	110	25
14	PMB	K_3PO_4	DMSO	100	0
15	PMB	K_3PO_4	ethanol	90	0
16	PMB	K_3PO_4	DMF	80	10
17	PMB	K_3PO_4	DCM	40	0

[a]The reaction used 1 mmol of PMB-guanidine and 1 mmol of iodobenzene. [b]Isolated yields.

The choice of the leaving group X was checked in our standard experimental conditions (CuOAc, L_8, K_3PO_4, MeCN, 100 °C, 3 h). All of the iodophenyl derivatives reacted smoothly and gave the expected N-substituted compounds **3** in good yields (entries 1−7).

The reaction was still efficient with bromophenyl derivatives bearing either electron-withdrawing or electron-donating groups (entries 8−12). However, with electron-donating groups, the system was found to be relatively more reactive, and the reaction yielded some amounts of *N*,*N*′-guanidine disubstituted adduct (entries 9 and 10). On the other hand, systems bearing electron-withdrawing groups were found to be relatively less reactive, and the reaction time was prolonged to 24 h to obtain completion of the reaction (entries 11 and 12). When considering a benzene ring bearing both chlorine and iodine or bromine atoms (entries 4 and 11), no reaction took place with chlorine. The phenol *O*-triflate was less reactive, giving only 39% conversion after 3 h. Finally, various heteroaromatics bearing different leaving groups (Cl, Br, OTf) were also checked (entries 14−20). 2-Bromo-heteroaromatics (pyridine, pyrimidine, quinoline) showed satisfactory reactivity. A regioselective reaction took place at position 2 of 2,5-dibromopyridine (entry 17). In most cases, chloroaromatics and chloroheteroaromatics (2-chloropyrimidine, 2-chloropyridine, 2-chloro-4-methylquinoline, 2,6-dichloropyridine, 3-chloro-6-methylpyridazine) were not reactive, except for some specific highly reactive systems (entry 19).

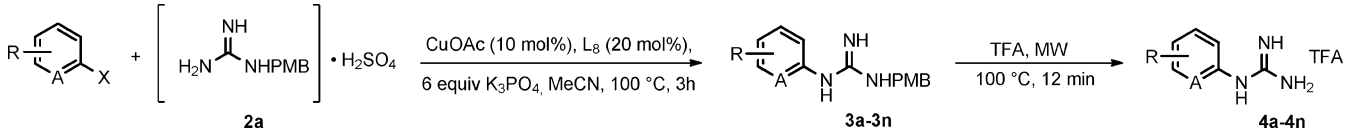
This provided some chemoselectivity to polyhalogenated heteroaromatics (entry 18). The pyridin-2-*O*-triflate showed moderate activity, as already observed in the aromatic series (entries 13 and 20).

The model reaction (entry 1) was applied with success to the preparation of 4 g (19.6 mol) of iodobenzene with similar yields (86%).

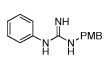
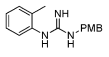
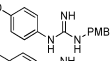
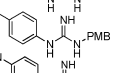
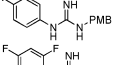
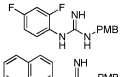
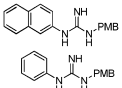
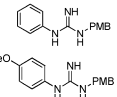
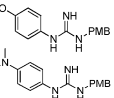
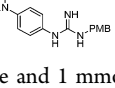
As initially expected, deprotection of aryl and heteroaryl guanidine intermediates **3a**−**3n** was efficiently performed in trifluoroacetic acid in a microwave (100 °C for 12 min) and yielded in all cases the expected aryl or heteroaryl guanidines **4** in good yields[13] (89−97%).

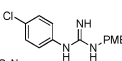
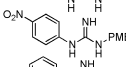
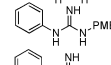
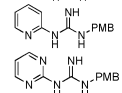
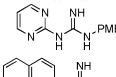
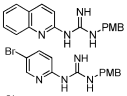
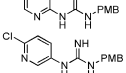
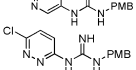
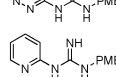
Surprisingly, *ortho*-dibromobenzene was not reactive, whereas *ortho*-diiodobenzene reacted smoothly giving directly *N*-PMB-1*H*-2-aminobenzimidazole **5**, which was further submitted to microwave irradiation in TFA aqueous solution to

Table 3. Copper-Catalyzed Aryl and Heteroaryl Guanidinylation



2a 3a-3n 4a-4n

entry[a]	halide	product	yield 3,%[b]
1		3a 	96
2		3b 	92
3		3c 	74[d]
4		3e 	83
5		3f 	80
6		3g 	87[c]
7		3h 	88
8		3a 	78
9		3c 	84[d]
10		3d 	79[d]

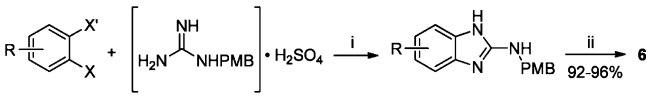
entry[a]	halide	product	yield 3,%[b]
11		3e 	80[e]
12		3f 	72[e]
13		3a 	39
14		3i 	91
15		3j 	73
16		3k 	94
17		3m 	51
18		3l 	85
19		3n 	43[e,f]
20		3i	45

[a]The reaction used 1 mmol of PMB-guanidine and 1 mmol of iodobenzene. [b]Isolated yields. [c]Spectra details available in Supporting Information. [d]*N*,*N*′-Diarylguanidine was observed. [e]Reaction time was increased to 24 h. [f]Presence of starting material.

dx.doi.org/10.1021/jo202018w | *J. Org. Chem.* 2012, 77, 417−423

give 2-aminobenzimidazoles **6a** and **6b**.[13] In good agreement with earlier results in Table 3, *ortho*-dibromobenzene bearing a methoxy group showed a relatively better reactivity (Table 4, entries 1 and 4).

Table 4. Benzimidazole Synthesis with PMB-Guanidine[a]



5a (R=H), **5b** (R=5-OMe)

entry[b]	X	X′	R	yield **5**, %[c]
1	Br	Br	H	0
2	Br	I	H	62
3	I	I	H	90
4	Br	Br	4-OMe	51

[a]Reaction conditions: (i) 10 mol % of CuOAc, 20 mol % of L_8, 6 equiv of K_3PO_4, MeCN, 100 °C, 20 h; (ii) TFA with 0.1 M concentration, MW, 100 °C, 12 min. [b]The reaction used 1 mmol of PMB-guanidine and 1 mmol of iodobenzene. [c]Isolated yields

In conclusion, the use of *N*-PMB-guanidine as a guanidinylation agent is particularly efficient, as it dramatically suppresses double substitution, which generally occurred in a previous method using copper-catalyzed guanidinylation reaction with free guanidine. In addition, the method could be applied to the production of several grams of aryl halides with about the same yield. Easy removal of the PMB protective group in TFA led to versatile substitutions of both aromatics and heteroaromatics. As a first application of the method, a novel preparation of 2-aminobenzimidazoles was proposed.

EXPERIMENTAL SECTION

General Experimental Methods. All reactions were carried out in flame-dried screw cap test tubes with magnetic stirring. Reactions were run under an inert atmosphere of argon gas. Yields refer to isolated compounds, estimated to be >97% pure as determined ^{1}H NMR and HPLC.

^{1}H NMR and ^{13}C NMR were recorded at 400 and 100 MHz, respectively, for $CDCl_3$ solutions. ^{19}F NMR was measured at 373 MHz for $CDCl_3$ solutions with trichlorofluoromethane as an external standard. Chemical shifts (δ) are reported in parts per million (ppm) for ^{1}H and for ^{13}C NMR spectra. The coupling constants, J, are reported in hertz (Hz). TMS was used as the internal reference. High-resolution mass spectra (HRMS) were measured with electrospray ionization (ESI). All microwave reactions were carried out in sealed tubes in an Initiator microwave reactor (Biotage Inc.).

General Procedure for Preparation of Protected Guanidine[13] 2. A solution of 2-methylthiopseudourea sulfate (5.0 g, 1.0 equiv, 35.92 mmol) and substituted benzylamine (2.0 equiv, 71.84 mmol) was dissolved in water (50 mL) and ethanol (50 mL). The mixture was stirred at reflux for 20 h and connected to a series of bleach traps. The mixture was cooled, and solvent was removed under vacuum to give crude product, which was purified by recrystallization from hot water (20 mL). Purified product was collected by filtration and dried in the oven to give the title compound **2** (62−80%).

*1-(4-Methoxybenzyl)guanidine Hemisulfate (PMB-Guanidine), Compound **2a**.* Following the general procedure, the product was obtained by recrystallization to give PMB-guanidine as a white solid: 6.5 g, 80% yield; mp 205.6−207.9 °C; ^{1}H NMR (400 MHz, DMSO) δ 3.72 (s, 3H), 4.18 (s, 2H), 6.88 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H), 7.77 (br s, 4H) 8.89 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 158.4, 157.1, 129.8, 128.5, 113.7, 55.0, 43.1; HRMS (ESI) for $[C_9H_{14}N_3O]$ calcd 180.1131, found 180.1123.

*1-(2,4-Dimethoxybenzyl)guanidine Hemisulfate (DMB-Guanidine), Compound **2b**.* Following the general procedure, the product was obtained by recrystallization to give DMB-guanidine as a white solid: 6.4 g, 69% yield; mp 236.3−238.1 °C; ^{1}H NMR (400 MHz, DMSO) δ 3.74 (s, 3H), 3.79 (s, 3H), 4.13 (s, 2H), 6.50 (dd, J = 2.3 Hz, J = 8.3 Hz, 1H), 6.55 (d, J = 2.3 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 7.76 (br s, 4H), 8.40 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 160.1, 157.6, 157.2, 128.7, 117.4, 104.4, 98.3, 55.4, 55.2; HRMS (ESI) for $[C_{10}H_{16}N_3O_2]$ calcd 210.1237, found 210.1229.

*1-Benzylguanidine Hemisulfate (Bn-Guanidine), Compound **2c**.* Following the general procedure, the product was obtained by recrystallization to give Bn-guanidine as a white solid: 5.5 g, 62% yield; mp 208.2−209.6 °C; ^{1}H NMR (400 MHz, DMSO) δ 4.26 (s, 2H), 7.22−7.25 (m, 1H), 7.31 (d, J = 4.4 Hz, 4H), 7.81 (br s, 4H), 8.97 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 157.2, 137.9, 128.3, 127.1, 127.0, 43.5; HRMS (ESI) for $[C_8H_{12}N_3]$ calcd 150.1025, found 150.1026.

General Procedure for the Cross-Coupling of Aryl or Heteroaryl Halide with PMB-Guanidines 3 and 5. Aryl (or heteroaryl) halide **1** (1 mmol), PMB-guanidine hemisulfate **2a** (228.2 mg, 1 mmol), CuOAc (12.2 mg, 0.10 mmol), L-proline (23 mg, 0.20 mmol), and K_3PO_4 (1.23 g, 6 equiv) were mixed in a flame-dried process vial (10−20 mL) equipped with a magnetic stir bar. The reaction mixture was then capped with a Teflon septum under argon, and anhydrous acetonitrile (6 mL) was added using a syringe. The reaction was microwave heated at 100 °C for 4 h. After complete consumption of the starting material shown by HPLC, AcOEt (30 mL) and H_2O (30 mL) were added. The separated aqueous layer was extracted with AcOEt (2 × 30 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, and concentrated in vacuum. The remaining residue was purified by column chromatography on silica gel to afford the desired product **3** (or **5**).

*1-(4-Methoxybenzyl)-3-phenylguanidine, Compound **3a**.* Following the general procedure, the product was obtained by silica gel chromatography (AcOEt/MeOH/NEt_3 = 9:1:0.1, R_f = 0.38) to give 1-(4-methoxybenzyl)-3-phenylguanidine as a white solid: 244 mg, 96% yield. In the same condition using 4 g of iodobenzene, the reaction gives 4.28 g of **3a**: 86% yield; mp 136.1−138.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H), 4.21 (s, 2H), 6.51 (br s, 2H), 6.72 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 7.5 Hz, 2H), 7.01 (t, J = 7.4 Hz, 1H), 7.11 (d, J = 8.7 Hz, 2H), 7.17 (t, J = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 154.0, 140.9, 129.7, 129.2, 128.7, 125.1, 124.5, 114.2, 55.3, 45.2; HRMS (ESI) for $[C_{15}H_{18}N_3O]$ calcd 256.1444, found 256.1444.

*1-(4-Methoxybenzyl)-3-(o-tolyl)guanidine, Compound **3b**.* Following the general procedure, the product was obtained by silica gel chromatography (AcOEt/MeOH/NEt_3 = 9:1:0.08, R_f = 0.30) to give 1-(4-methoxybenzyl)-3-(*o*-tolyl)guanidine as a white solid: 247 mg, 92% yield; mp 98.1−101.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.06 (s, 3H), 3.72 (s, 3H), 4.09 (br s, 1H), 4.27 (s, 2H), 6.76−6.80 (m, 3H), 6.87 (t, J = 6.5 Hz, 1H), 7.04 (t, J = 6.8 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 7.17 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 151.1, 146.0, 132.0, 130.7, 128.7, 126.8, 123.6, 123.1, 114.1, 55.4, 45.3, 17.9; HRMS (ESI) for $[C_{16}H_{20}N_3O]$ calcd 270.1601, found 270.1602.

*1-(4-Methoxybenzyl)-3-(4-methoxyphenyl)guanidine, Compound **3c**.* Following the general procedure, the product was obtained by silica gel chromatography (AcOEt/MeOH/NEt_3 = 9:1:0.1, R_f = 0.21) to give 1-(4-methoxybenzyl)-3-(4-methoxyphenyl) guanidine as a white solid: 210 mg, 74% yield; mp 158.2−161.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (d, J = 6.3 Hz, 6H), 4.17 (s, 2H), 5.97 (br s, 1H), 6.68−6.76 (m, 6H), 7.09 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 156.2, 153.8, 137.1, 130.2, 128.6, 125.3, 114.8, 114.1, 55.5, 55.3, 44.8; HRMS (ESI) for $[C_{16}H_{20}N_3O_2]$ calcd 286.1550, found 286.1552.

*1-(4-(Dimethylamino)phenyl)-3-(4-methoxybenzyl)guanidine, Compound **3d**.* Following the general procedure, the product was obtained by flash chromatography (H_2O/MeOH = 6:4, R_f = 0.27) to give 1-(4-(dimethylamino)phenyl)-3-(4-methoxybenzyl)guanidine as a white solid: 235 mg, 79% yield; mp 223.1−225.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.83 (s, 6H), 3.64 (s, 3H), 4.40 (s, 2H), 6.51 (d, J = 6.4 Hz, 2H), 6.70 (d, J = 7.2 Hz, 2H), 6.85 (d, J = 6.0 Hz, 2H), 7.18 (d, J = 5.8 Hz, 2H), 9.39 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 156.1, 150.2, 129.1, 127.8, 127.6, 121.4, 114.2, 112.9, 55.3,

dx.doi.org/10.1021/jo202018w | J. Org. Chem. 2012, 77, 417−423

45.4, 40.4; HRMS (ESI) for $[C_{17}H_{23}N_4O]$ calcd 299,1866, found 299,1863.

1-(4-Chlorophenyl)-3-(4-methoxybenzyl)guanidine, Compound ***3e***. Following the general procedure, the product was obtained by silica gel chromatography (AcOEt/MeOH/NEt_3 = 9:1:0.2, R_f = 0.34) to give 1-(4-chlorophenyl)-3-(4-methoxybenzyl)guanidine as a white solid: 240 mg, 83% yield; mp 169.5−171.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53 (br s, 3H), 3.73 (s, 3H), 4.27 (s, 2H), 6.83 (dd, J = 8.7 Hz, J = 3.8 Hz, 4H), 7.16 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 151.4, 147.8, 130.6, 129.4, 128.8, 127.3, 124.7, 114.2, 55.3, 45.6; HRMS (ESI) for $[C_{15}H_{17}ClN_3O]$ calcd 290.1055, found 290.1054.

1-(4-Methoxybenzyl)-3-(4-nitrophenyl)guanidine, Compound ***3f***. Following the general procedure, the product was obtained by silica gel chromatography (AcOEt/MeOH/NEt_3 = 9:1:0.2, R_f = 0.33) to give 1-(4-methoxybenzyl)-3-(4-nitrophenyl)guanidine as a yellow solid: 239 mg, 80% yield; mp 127.8−129.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 4.30 (s, 2H), 4.36 (br s, 3H), 6.82 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 9.0 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 8.05 (d, J = 9.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 157.1, 151.4, 141.9, 130.2, 128.8, 125.5, 123.2, 114.3, 55.3, 45.5; HRMS (ESI) for $[C_{15}H_{17}N_4O_3]$ calcd 301.1295, found 301.1293.

1-(2,4-Difluorophenyl)-3-(4-methoxybenzyl)guanidine, Compound ***3g***. Following the general procedure, the product was obtained by silica gel chromatography (AcOEt/MeOH/NEt_3 = 9:1:0.3, R_f = 0.32) to give 1-(2,4-difluorophenyl)-3-(4-methoxybenzyl) guanidine as a white solid: 252 mg, 87% yield; mp 144.4−146.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.41 (br s, 3H), 3.73 (s, 3H), 4.29 (s, 2H), 6.71−6.86 (m, 5H), 7.21 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 159.4, 159.1, 157.1, 156.9, 156.6, 156.4, 152.6, 132.5, 130.4, 128.7, 126.2, 126.2, 126.1, 126.1, 114.2, 111.4, 111.3, 111.2, 111.1, 104.7, 104.5, 104.2, 55.3, 45.5; HRMS (ESI) for $[C_{15}H_{16}F_2N_3O]$ calcd 292.1256, found 292.1260.

1-(4-Methoxybenzyl)-3-(naphthalen-2-yl)guanidine, Compound ***3h***. Following the general procedure, the product was obtained by silica gel chromatography (AcOEt/MeOH/NEt_3 = 9:1:0.2, R_f = 0.3) to give 1-(4-methoxybenzyl)-3-(naphthalen-2-yl)guanidine as a white solid: 268 mg, 88% yield; mp 145.1−146.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (s, 3H), 4.14 (br s, 2H), 4.28 (s, 2H), 6.79 (d, J = 8.7 Hz, 2H), 7.05 (dd, J = 2.0 Hz, J = 8.7 Hz, 1H), 7.17 (br s, 2H), 7.22 (d, J = 1.9 Hz, 1H), 7.27 (t, J = 8.2 Hz, 1H), 7.34 (t, J = 6.9 Hz, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.68 (dd, J = 3.2 Hz, J = 5.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 152.2, 145.7, 134.6, 130.5, 130.1, 129.3, 128.7, 127.6, 126.9, 126.1, 124.6, 124.2, 119.4, 114.2, 55.3, 45.5; HRMS (ESI) for $[C_{19}H_{20}N_3O]$ calcd 306.1601, found 306.1603.

1-(4-Methoxybenzyl)-3-(pyridin-2-yl)guanidine, Compound ***3i***. Following the general procedure, the product was obtained by silica gel chromatography (AcOEt/MeOH/NEt_3 = 9:1:0.4, R_f = 0.3) to give 1-(4-methoxybenzyl)-3-(pyridin-2-yl)guanidine as a white solid: 234 mg, 91% yield; mp 153.9−154.7.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 4.32 (s, 2H), 6.65 (td, J = 0.8 Hz, J = 6.0 Hz,1H), 6.77−6.82 (m, 3H), 7.22 (d, J = 8.7 Hz, 2H), 7.43 (td, J = 2.0 Hz, J = 8.4 Hz, 1H), 8.03 (dd, J = 1.4 Hz, J = 4.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 159.2, 156.5, 145.6, 137.3, 129.8, 128.3, 119.1, 115.2, 114.3, 55.3, 45.1; HRMS (ESI) for $[C_{14}H_{17}N_4O]$ calcd 257.1397, found 257.1396.

1-(4-Methoxybenzyl)-3-(pyrimidin-2-yl)guanidine, Compound ***3j***. Following the general procedure, the product was obtained by silica gel chromatography (AcOEt/MeOH/NEt_3 = 9:1:0.4, R_f = 0.23) to give 1-(4-methoxybenzyl)-3-(pyrimidin-2-yl)guanidine as a white solid: 189 mg, 73% yield; mp 155.1−157.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (s, 3H), 4.42 (s, 2H), 6.56 (t, J = 4.8 Hz, 1H), 6.80 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 8.7 Hz, 2H), 8.30 (d, J = 4.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 159.1, 158.2, 157.2, 129.7, 128.5, 114.3, 113.9, 112.1, 55.3, 45.1; HRMS (ESI) for $[C_{13}H_{16}N_5O]$ calcd 258.1349, found 258.1347.

1-(4-Methoxybenzyl)-3-(quinolin-2-yl)guanidine, Compound ***3k***. Following the general procedure, the product was obtained by silica gel chromatography (AcOEt/MeOH/NEt_3 = 9:1:0.3, R_f = 0.33) to give 1-(4-methoxybenzyl)-3-(quinolin-2-yl)guanidine as a white solid: 288 mg, 94% yield; mp 116.1−118.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 3H), 4.38 (s, 2H), 6.83 (d, J = 8.7 Hz, 2H), 6.96 (d, J = 8.8 Hz, 1H), 7.20−7.22 (m, 1H), 7.26 (d, J = 8.7 Hz, 2H), 7.45 (td, J = 1.0 Hz, J = 6.7 Hz, 1H), 7.49−7.55 (m, 2H), 7.81 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 159.3, 157.4, 146.1, 137.0, 129.1, 128.4, 127.3, 126.2, 124.4, 123.4, 120.5, 114.4, 113.9, 55.3, 45.1; HRMS (ESI) for $[C_{18}H_{19}N_4O]$ calcd 307.1553, found 307.1551.

1-(6-Chloropyridin-3-yl)-3-(4-methoxybenzyl)guanidine, Compound ***3l***. Following the general procedure, the product was obtained by silica gel chromatography (AcOEt/MeOH/NEt_3 = 9:1:0.4, R_f = 0.29) to give 1-(6-chloropyridin-3-yl)-3-(4-methoxybenzyl) guanidine as a white solid: 246 mg, 85% yield; mp 123.9−124.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 4.02 (br s, 2H), 4.26 (s, 2H), 6.81 (d, J = 8.7 Hz, 2H), 7.07−7.13 (m, 2H), 7.19 (d, J = 8.7 Hz, 2H), 7.88 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 152.2, 145.2, 144.7, 143.7, 133.8, 130.3, 128.8, 124.4, 114.2, 55.3, 45.5; HRMS (ESI) for $[C_{14}H_{16}ClN_4O]$ calcd 291.1007, found 291.1008.

1-(5-Bromopyridin-2-yl)-3-(4-methoxybenzyl)guanidine, Compound ***3m***. Following the general procedure, the product was obtained by silica gel chromatography (AcOEt/MeOH/NEt_3 = 9:1:0.4, R_f = 0.31) to give 1-(5-bromopyridin-2-yl)-3-(4-methoxybenzyl) guanidine as a white solid: 170 mg, 51% yield; mp 201.3−204.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 3H), 4.27 (s, 2H), 5.25 (br s, 2H), 6.63 (d, J = 8.8 Hz, 1H), 6.80 (d, J = 8.7 Hz, 3H), 7.18 (d, J = 8.4 Hz, 2H), 7.43 (dd, J = 2.6 Hz, J = 8.8 Hz, 1H), 8.03 (d, J = 2.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 159.2, 156.7, 146.2, 139.8, 129.4, 128.4, 120.2, 114.3, 110.0, 55.3, 45.0; HRMS (ESI) for $[C_{14}H_{16}BrN_4O]$ calcd 335.0502, found 335.0499.

1-(6-Chloropyridazin-3-yl)-3-(4-methoxybenzyl)guanidine, Compound ***3n***. Following the general procedure, the product was obtained by silica gel chromatography (AcOEt/MeOH/NEt_3 = 9:1:0.3, R_f = 0.21) to give 1-(6-chloropyridazin-3-yl)-3-(4-methoxybenzyl) guanidine as a white solid: 124 mg, 43% yield; mp 156.3−158.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 4.34 (s, 2H), 5.81 (br s, 2H), 6.81 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 9.1 Hz, 1H), 7.14 (d, J = 9.1 Hz, 1H), 7.19 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 159.3, 156.9, 148.3, 129.3, 128.7, 128.4, 127.3, 114.4, 55.3, 45.3; HRMS (ESI) for $[C_{13}H_{15}ClN_5O]$ calcd 292.0960, found 292.0964.

N-(4-Methoxybenzyl)-1H-benzo[d]imidazol-2-amine, Compound ***5a***. Following the general procedure, the product was obtained by silica gel chromatography (AcOEt/heptane = 2:1, R_f = 0.31) to give *N*-(4-methoxybenzyl)-1*H*-benzo[*d*]imidazol-2-amine as a white solid: 227 mg, 90% yield; mp 206.4−208.6 °C; ^{1}H NMR (400 MHz, DMSO) δ 3.72 (s, 3H), 4.44 (d, J = 5.9 Hz, 2H), 6.84−6.87 (m, 3H), 6.89 (s, 1H), 7.02 (t, J = 7.4 Hz, 12.8 Hz, 1H), 7.11−7.13 (m, 2H), 7.32 (d, J = 8.2 Hz, 2H), 10.75 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 180.1, 158.2, 155.4, 132.2, 128.5, 119.0, 118.8, 113.6, 55.0, 45.1; HRMS (ESI) for $[C_{15}H_{16}N_3O]$ calcd 254.1288, found 254.1291.

5-Methoxy-N-(4-methoxybenzyl)-1H-benzo[d]imidazol-2-amine, Compound ***5b***. Following the general procedure, the product was obtained by silica gel chromatography (AcOEt/heptane =2:1, R_f = 0.25) to give 5-methoxy-*N*-(4-methoxybenzyl)-1*H*-benzo[*d*]imidazol-2-amine as a white solid: 145 mg, 51% yield; mp 173.5−175.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.68 (s, 3H), 5.31 (br s, 2H), 6.56 (d, J = 7.4 Hz, 1H), 6.70−6.74 (m, 3H), 7.01 (d, J = 8.5 Hz, 1H), 7.12 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 155.4, 141.6, 139.6, 130.0, 128.5, 114.2, 113.9, 111.9, 108.1, 98.3, 55.9, 55.3, 46.7; HRMS (ESI) for $[C_{16}H_{18}N_3O_2]$ calcd 284.1393, found 284.1391.

General Procedure for the Deprotection of the PMB Group of Guanidines 4 and 6. Compound **3** (0.5 mmol) and trifluoroacetic acid (2 mL) were mixed in a flame-dried process vial (2−5 mL) equipped with a magnetic stir bar. The reaction mixture was then capped with a Teflon septum. The mixture was irradiated at 100 °C in a microwave (3 bar) for 10 min and after cooled to 40 °C. The trifluoroacetic acid was concentrated in vacuum, and the crude sample was triturated with a mixture solvent (heptane/Et_2O 1/1) to provide the desired solid product **4** (or **6**) as the triflate salt.

dx.doi.org/10.1021/jo202018w | *J. Org. Chem.* 2012, 77, 417−423

1-Phenylguanidine Triflate, Compound ***4a***. Following the general procedure, the product was obtained by filtration to give 1-phenylguanidine triflate as a white solid, 118 mg, 95% yield; mp 175.1−177.3 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.23−7.31 (m, 3H), 7.46 (t, J = 7.2 Hz, 2H), 7.61 (br s, 4H), 10.08 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 155.9, 135.4, 129.6, 126.3, 124.4; HRMS (ESI) for [$C_7H_{10}N_3$] calcd 136.0869, found 136.0870.

1-(o-Tolyl)guanidine Triflate, Compound ***4b***. Following the general procedure, the product was obtained by filtration to give 1-(*o*-tolyl)guanidine triflate as a white solid: 118 mg, 90% yield; mp 145.3−146.8 °C; ^{1}H NMR (400 MHz, DMSO) δ 2.22 (s, 3H), 7.20−7.30 (m, 4H), 7.37 (br s, 4H), 9.58 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 155.8, 135.2, 132.6, 131.2, 128.4, 127.5, 127.3, 17.1; HRMS (ESI) for [$C_8H_{12}N_3$] calcd 150.1025, found 150.1020.

1-(4-Methoxyphenyl)guanidine Triflate, Compound ***4c***. Following the general procedure, the product was obtained by filtration to give 1-(4-methoxyphenyl)guanidine triflate as a white solid: 135 mg, 97% yield; mp 157.6−159.1 °C; ^{1}H NMR (400 MHz, DMSO) δ 3.77 (s, 3H), 7.01 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H), 7.36 (br s, 4H), 9.64 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 158.1, 156.3, 127.5, 127.2, 114.8, 55.4; HRMS (ESI) for [$C_8H_{12}N_3O$] calcd 166.0974, found 166.0969.

1-(4-(Dimethylamino)phenyl)guanidine Triflate, Compound ***4d***. Following the general procedure, the product was obtained by filtration to give 1-(4-(dimethylamino)phenyl)guanidine triflate as a white solid: 130 mg, 89% yield; mp 139.7−142.1 °C; ^{1}H NMR (400 MHz, DMSO) δ 6.85 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 7.43 (s, 4H), 9.77 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 156.6, 148.8, 126.6, 124.1, 113.5, 40.4; HRMS (ESI) for [$C_9H_{15}N_4$] calcd 179.1291, found 179.1284.

1-(4-Chlorophenyl)guanidine Triflate, Compound ***4e***. Following the general procedure, the product was obtained by filtration to give 1-(4-chlorophenyl)guanidine triflate as a white solid: 129 mg, 91% yield; mp 139.6−141.0 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.28 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.59 (br s, 4H), 9.95 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 155.9, 134.4, 130.6, 129.6, 126.5; HRMS (ESI) for [$C_7H_9ClN_3$] calcd 170.0479, found 170.0485.

1-(4-Nitrophenyl)guanidine Triflate, Compound ***4f***. Following the general procedure, the product was obtained by filtration to give 1-(4-nitrophenyl)guanidine triflate as a white solid: 133 mg, 90% yield; mp 207.3−209.1 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.47 (d, J = 9.0 Hz, 2H), 8.01 (br s, 4H), 8.29 (d, J = 8.9 Hz, 2H), 10.50 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 155.4, 143.9, 142.9, 125.2, 122.8; HRMS (ESI) for [$C_7H_9N_4O_2$] calcd 181.0720, found 181.0713.

1-(2,4-Difluorophenyl)guanidine Triflate, Compound ***4g***. Following the general procedure, the product was obtained by filtration to give 1-(2,4-difluorophenyl)guanidine triflate as a white solid: 136 mg, 95% yield; mp 125.6−127.8 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.18 (td, J = 2.0 Hz, J = 8.5 Hz, 1H), 7.43−7.49 (m, 2H), 7.64 (br s, 4H), 9.78 (s, 1H); ^{13}C NMR (400 MHz, DMSO) δ 162.7, 162.6, 160.3, 160.2, 158.8, 158.7, 156.2, 130.6, 130.5, 118.6, 118.6, 118.5, 118.5, 112.5, 112.3, 105.5, 105.2, 104.9; HRMS (ESI) for [$C_7H_8F_2N_3$] calcd 172.0680, found 172.0674.

1-(Naphthalen-2-yl)guanidine Triflate, Compound ***4h***. Following the general procedure, the product was obtained by filtration to give 1-(naphthalen-2-yl)guanidine triflate as a white solid: 140 mg, 94% yield; mp 135.3−136.7 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.39 (d, J = 8.7 Hz, 1H), 7.52−7.58 (m, 2H), 7.66 (br s, 4H), 7.79 (s, 1H), 7.95 (t, J = 7.0 Hz, 2H), 8.01 (d, J = 8.8 Hz, 1H), 10.18, (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 155.6, 133.2, 132.2, 131.4, 129.7, 127.6, 127.6, 126.9, 126.4, 123.2, 122.5; HRMS (ESI) for [$C_{11}H_{12}N_3$] calcd 186.1025, found 186.1017.

1-(Pyridin-2-yl)guanidine Triflate, Compound ***4i***. Following the general procedure, the product was obtained by filtration to give 1-(pyridin-2-yl)guanidine triflate as a white solid: 116 mg, 93% yield; mp 159.1−161.2 °C; ^{1}H NMR (MHz, DMSO) δ 7.08 (d, J = 8.3 Hz, 1H), 7.19 (t, J = 6.3 Hz, 1H), 7.89 (t, J = 6.8 Hz, 1H), 8.33 (d, J = 4.3 Hz, 1H), 8.46 (br s, 4H), 11.24 (s, 1H); ^{13}C NMR (MHz, DMSO) δ 155.2, 152.0, 146.6, 139.6, 119.3, 113.3; HRMS (ESI) for [$C_6H_9N_4$] calcd 137.0821, found 137.0819.

1-(Pyrimidin-2-yl)guanidine Triflate, Compound ***4j***. Following the general procedure, the product was obtained by filtration to give 1-(pyrimidin-2-yl)guanidine triflate as a white solid: 113 mg, 90% yield; mp 165.1−167.2 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.32 (t, J = 5.0 Hz, 1H), 8.41 (br s, 4H), 8.74 (d, J = 4.5 Hz, 2H), 11.08 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 158.6, 156.9, 155.1, 117.2; HRMS (ESI) for [$C_5H_8N_5$] calcd 138.0774, found 138.0770.

1-(Quinolin-2-yl)guanidine triflate, Compound ***4k***. Following the general procedure, the product was obtained by filtration to give 1-(quinolin-2-yl)guanidine triflate as a white solid: 143 mg, 95% yield; mp 208.7−210.3 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.22 (d, J = 8.9 Hz, 1H), 7.55 (t, J = 7.4 Hz, 1H), 7.77 (t, J = 7.6 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 8.43 (d, J = 8.8 Hz, 1H), 8.71 (br s, 4H), 11.53, (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 155.5, 151.3, 144.6, 139.7, 130.6, 127.9, 126.9, 125.7, 124.9, 113.6; HRMS (ESI) for [$C_{10}H_{11}N_4$] calcd 187.0978, found 187.0974.

1-(6-Chloropyridin-3-yl)guanidine Triflate, Compound ***4l***. Following the general procedure, the product was obtained by filtration to give 1-(6-chloropyridin-3-yl)guanidine triflate as a white solid: 128 mg, 90% yield; mp 146.2−148.6 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.61 (d, J = 8.5 Hz, 1H), 7.76−7.79 (m, 5H), 8.34 (s, 1H), 10.14 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 156.3, 147.4, 146.4, 136.4, 132.1, 124.9; HRMS (ESI) for [$C_6H_8ClN_4$] calcd 171.0432, found 171.0424.

1-(5-Bromopyridin-2-yl)guanidine Triflate, Compound ***4m***. Following the general procedure, the product was obtained by filtration to give 1-(5-bromopyridin-2-yl)guanidine triflate as a white solid, 150 mg, 91% yield; mp 154.3−157.8 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.07 (d, J = 8.8 Hz, 1H), 8.11 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H), 8.43−8.50 (m, 5H), 11.59 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 155.1, 150.9, 147.1, 141.9, 115.2, 113.7; HRMS (ESI) for [$C_6H_8BrN_4$] calcd 214.9926, found 214.9919.

1-(6-Chloropyridazin-3-yl)guanidine Triflate, Compound ***4n***. Following the general procedure, the product was obtained by filtration to give 1-(6-chloropyridazin-3-yl)guanidine triflate as a white solid: 127 mg, 89% yield; mp 176.5−178.3 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.04 (d, J = 9.9 Hz, 1H), 7.27 (d, J = 9.9 Hz, 1H), 8.13 (s, 4H), 11.13 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 158.9, 154.7, 140.7, 133.1, 128.8; HRMS (ESI) for [$C_5H_7ClN_5$] calcd 172.0384, found 172.0379.

1H-Benzo[d]imidazol-2-amine Triflate, Compound ***6a***. Following the general procedure, the product was obtained by filtration to give 1*H*-benzo[*d*]imidazol-2-amine triflate as a white solid: 117 mg, 95% yield; mp 263.5−264.1 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.20−7.22 (m, 2H), 7.35−7.37 (m, 2H), 8.55 (br s, 2H), 12.80 (s, 2H); ^{13}C NMR (100 MHz, DMSO) δ 150.1, 129.1, 123.3, 111.2; HRMS (ESI) for [$C_7H_8N_3$] calcd 134.0712, found 134.0710.

5-Methoxy-1H-benzo[d]imidazol-2-amine Triflate, Compound ***6b***. Following the general procedure, the product was obtained by filtration to give 5-methoxy-1*H*-benzo[*d*]imidazol-2-amine triflate as a white solid: 128 mg, 92% yield; mp 193.7−195.3 °C; ^{1}H NMR (400 MHz, DMSO) δ 3.77 (s, 3H), 6.79−7.25 (m, 3H), 8.37 (s, 1H), 12.37 (br s, 2H); ^{13}C NMR (100 MHz, DMSO) δ 155.9, 130.8, 129.7, 123.7, 111.8, 109.9, 96.8, 55.7; HRMS (ESI) for [$C_8H_{10}N_3O$] calcd 164.0818, found 164.0812.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mschmitt@unistra.fr.

■ ACKNOWLEDGMENTS

This project was supported by the Alsace region (Région Alsace), the University of Strasbourg (UdS), and the National Center of Scientific Research (CNRS). We thank Mr. Patrick

Wehrung for analytical studies, the ministère de l'économie, des finances et de l'industrie, and OSEO innovation.

REFERENCES

(1) (a) Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027. (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338. (c) Carey, J. S.; Laffan, C.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337. (d) King, A. O.; Yasuda, N. *Top. Organomet. Chem.* **2004**, *6*, 205. (e) Baeza, A.; Burgos, C.; Builla, J. A.; Vaquero, J. J. *Tetrahedron Lett.* **2007**, *48*, 2597. (f) Bauer, D.; Whittington, D. A.; Coxon, A.; Bready, J.; Harriman, S. P.; Patel, V. F.; Polverino, A.; Harmange, J. C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4844.

(2) (a) De Deyn, P. P.; Marescau, B.; Stalon, V.; Qureshi, I. A. *Guanidino Compounds in Biology and Medicine*; John Libbey & Co. Ltd.: London, 1992. (b) Olivier, D. W.; Dormehl, I. C.; Wikberg, J.; Dambrova, M. *Med. Chem. Res.* **2005**, *13*, 427. (c) Rodriguez, F.; Rozas, I.; Ortega, J. E.; Meana, J. J.; Callado, L. F. *J. Med. Chem.* **2009**, *52*, 601. (d) Joossens, J.; Ali, O. M.; Sayed, I.; Surpateanu, G.; Veken, P. V.; Augustyns, K. *J. Med. Chem.* **2007**, *50*, 6638. (e) Bahekar, R. H.; Jain, M. R.; Goel, A.; Patel, D. N.; Jadav, P. A.; Patel, P. R. *Bioorg. Med. Chem.* **2007**, *15*, 3248.

(3) (a) Powel, D. A.; Ramsden, P. D.; Batey, R. A. *J. Org. Chem.* **2003**, *68*, 2300. (b) Katrizky, A. R.; Khashab, N. M.; Bobrov, S. *Helv. Chim. Acta* **2005**, *88*, 1664.

(4) (a) Yang, X.; Liu, H.; Fu, H.; Qiao, R.; Jiang, Y.; Zhao, Y. *Synlett* **2010**, *1*, 101. (b) Salva, M. C.; Nguyen, B. L.; Cuevas, J.; Pennypacker, K. R.; Antilla, J. C. *Org. Lett.* **2010**, *12*, 1316.

(5) (a) Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133. (b) Deng, X.; McAllister, H.; Mani, N. S. *J. Org. Chem.* **2009**, *74*, 5742.

(6) (a) Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 15914. (b) Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505.

(7) (a) Sheng, Q.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 4109. (b) Vo, G. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 11049. (c) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046.

(8) (a) Fanta, P. E. *Synthesis* **1974**, *1*, 9. (b) Wu, Q.; Wang, L. *Synthesis* **2008**, 2007. (c) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581. (d) Wolf, C.; Liu, S.; Mei, X.; August, A. T.; Casimir, M. D. *J. Org. Chem.* **2006**, *71*, 3270. (e) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (f) Evano, G.; Toumib, M.; Costea, A. *Chem. Commun.* **2009**, 4166.

(9) (a) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. (b) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727.

(10) (a) Gavade, S. N.; Balaskar, R. S.; Mane, M. S.; Pabrekar, P. N.; Shingare, M. S.; Mane, D. V. *Chin. Chem. Lett.* **2011**, *22*, 292. (b) Yadav, L. D. S.; Yadav, B. S.; Rai, V. K. *Synthesis* **2006**, *11*, 1868. (c) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

(11) Guery, S.; Schmitt, M.; Bourguignon, J. J. *Syntlett* **2002**, *12*, 2003.

(12) (a) Miel, H.; Rault, S. *Tetrahedron Lett.* **1998**, *39*, 1565. (b) Feichtinger, K.; Sings, H. L.; Baker, T. J.; Matthews, K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 8432.

(13) Geoffrey, C.; Brian, F.; Alan, H.; John, M. T.; Mark, M.; Mahmoud, A.; Alan, K.; Justice, T.; Roger, W. *J. Med. Chem.* **2009**, *52*, 3457.