Palladium-Catalyzed Cross-Coupling of Aryl Chlorides and Triflates with Sodium Cyanate: A Practical Synthesis of Unsymmetrical Ureas

Published in final edited form as:
J Am Chem Soc. 2012 July 11; 134(27): 11132–11135. doi:10.1021/ja305212v.

Palladium-catalyzed cross-coupling of aryl chlorides and triflates with sodium cyanate: A practical synthesis of unsymmetrical ureas

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Abstract

An efficient method for palladium-catalyzed cross-coupling of aryl chlorides and triflates with sodium cyanate is reported. The protocol allows for the synthesis of unsymmetrical N,N'-di- and N,N,N'-trisubstituted ureas in one pot, and is tolerant of a wide range of functional groups. Insight into the mechanism of aryl isocyanate formation is gleaned through studies of the transmetallation and reductive elimination steps of the reaction, including the first demonstration of reductive elimination from an arylpalladium isocyanate complex to produce an aryl isocyanate.

Aryl isocyanates are versatile intermediates in organic synthesis. They serve as precursors to carbamates and ureas, common motifs in an array of biologically active compounds[1] including tyrosine and Raf kinase inhibitors,[2a] cardiac-specific myosin activators,[2b] MCH-R1 (Melanin-concentrating hormone receptor 1) antagonists,[2c] and anti-trypanosomal agents.[2d] Typically, aryl isocyanates are generated via the decomposition of benzoyl azides (Curtius rearrangement),[3] benzamides (Hoffman rearrangement),[4] or carbamates.[5] Other methods for the synthesis of aryl isocyanates include reductive carbonylation of nitroaromatics[6] and the phosgenation of arylamines. [7] Unfortunately, all of these methods either require the formation of difficult-to-access precursors and/or suffer from the limited substrate scope, the use of toxic and extremely hazardous reagents (phosgene,[8] azides, carbon monoxide), or otherwise harsh conditions.

While a transition-metal catalyzed carbon-nitrogen bond formation between a cyanate anion and an aryl electrophile can provide an aryl isocyanate directly and without the need for dangerous reagents, there have been only few reports of such reactions to date. A nickel-catalyzed coupling of aryl halides with metal cyanates was reported by Tkatchenko in 1986, however the yields of corresponding aryl carbamates or ureas ranged from 10–45% in most cases.[9] More recently, Kianmehr reported a synthesis of aryl carbamates that involved a copper-catalyzed oxidative coupling of potassium cyanate with aryl boronic acids in various alcohol solvents.[10]

Herein, we report a method for the palladium-catalyzed cross-coupling of aryl chlorides and triflates with sodium cyanate to generate aryl isocyanates or their phenyl carbamate derivatives. These intermediates were subsequently converted *in situ* to unsymmetrical N,N'-di- and N,N,N'-trisubstituted ureas upon addition of an amine nucleophile.

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SUPPORTING INFORMATION

Experimental procedures, characterizations, spectral data for all compounds, and X-ray crystallographic (CIF) data for **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

On first considering this transformation, we envisioned two possible catalyst deactivation pathways, which needed to be avoided in order to access an efficient catalyst system. First, deactivation of the catalyst by excessive coordination of the cyanate anions to the Pd center; this type of deactivation has been previously shown in the case of other coordinating nucleophiles. [11] Second, reaction of the Pd(0) species with the anticipated aryl isocyanate product to form catalytically inactive diarylisocyanurate palladacycles.[12] We hypothesized that both of these pathways could be suppressed through the use of a bulky biaryl phosphine ligand, which could facilitate the coupling while shielding the active catalytic site from inhibitory coordination.

We initially set out to test the viability of the reductive elimination step to afford the aryl isocyanate. L_nPd(Ar)NCO complexes have been previously synthesized, however, their ability to undergo reductive elimination to afford the aryl isocyanate has not been reported.[13,14] We hypothesized that ligand **L1**, which we have previously shown to facilitate difficult reductive eliminations,[16,17] would help promote this step. Thus, in order to test this, complex **2** was synthesized via treatment of complex **1** (Figure 1a and Supporting Information) with silver cyanate in CH_2Cl_2. The structure of complex **2** was further confirmed using X-ray crystallography (Figure 1b).

Upon heating **2** at 60 °C for 110 minutes in the presence of bromobenzene (used to trap the resulting Pd(0) species), complete conversion was observed and the desired phenyl isocyanate product was formed in 71% yield (Figure 1c). A first order rate constant for this process was observed and was determined to be $(2.5\pm0.2)*10^{-4}$ s^{-1}. Upon completion, only 2 signals were observed in the $^{31}P\{^1H\}$ NMR (C_6D_6) spectrum of the reaction mixture, and were assigned as the oxidative addition complex (**L1**)Pd(Ph)(Br) (68.0 ppm) and its isomeric complex (82.4 ppm), respectively.[15] Further, the reaction exhibited no rate dependence on the concentration of PhBr (1, 2, and 4 equivalents of PhBr were used) or on the presence of extra ligand (0.5 equivalents of **L1** was used). This is the first reported example of successful reductive elimination from an aryl palladium species to efficiently generate an aryl isocyanate.

On the basis of the above results, we next set out to develop an efficient catalytic one-pot synthesis of unsymmetrical ureas, by first effecting an isocyanate cross-coupling, followed by subsequent trapping with an amine nucleophile. For optimization, we chose to investigate the *in situ* formation of 1-isocyanato-4-methoxybenzene from 4-chloroanisole, followed by addition of aniline to produce 1-(4-methoxyphenyl)-3-phenylurea (Table 1).

An investigation of possible cyanate sources, utilizing a catalyst system based on Pd_2dba_3 and ligand **L1**, demonstrated that while both KOCN and AgOCN were ineffective for this transformation (Table 1, entries 1, 3), the use of NaOCN did lead to formation of the desired product, albeit in low yield (Table 1, entry 2). Since the isocyanate anion could potentially inhibit catalytic activity as mentioned above, we hypothesized that a more efficient generation of the active catalytic species prior its introduction into the reaction media could lead to an increased yield of the urea.[18] In support of this, heating Pd_2dba_3 with **L1** at 120 °C for 3 minutes, followed by transferring it to the reaction afforded the product in 40% (Table 1, entry 4). We further found that the addition of NEt_3 (25 mol %) allowed for 80% isolated yield of the desired biaryl urea (Table 1, entry 5).[19] It is worth noting that having the aniline present in the reaction media for the initial cross-coupling step did not result in competitive aniline arylation in the absence of a base which could efficiently promote a C-N cross-coupling reaction, however, the desired isocyanate coupling did not reach full conversion, possibly due to catalyst inhibition via amine binding.[20] Consistent with our belief that excess isocyanate would have a deleterious effect on the reaction outcome, we

found that inclusion of 0.5 equivalents of a more soluble isocyanate source (NBu_4)(NCO) to the reaction mixture under optimized conditions completely shut down the reaction.

Use of catalysts based on **L2, L3** and **L5** in the reaction led to decreased product yields, suggesting that the presence of bulky *tert*-butyl substituents on the phosphorus, in combination with the methoxy group on the top ring of the biaryl ligand, is essential for an efficient catalytic system (Table 1, entries 6–8). Further, use of **L4** or **L6**, which have been used for other difficult C–N cross-coupling reactions,[21,22] did not produce any observable amount of the desired urea product (Table 1, entries 9 and 10).

Having established efficient conditions for isocyanate cross-coupling, followed by urea formation, we set out to explore the substrate scope of this reaction (Table 2). Electron-neutral, -deficient and -rich aryl chlorides and aryl triflates could all be converted into unsymmetrical ureas in 77−88% yields. Small ortho-substituents on the aryl chlorides were well tolerated (Table 2, entries **4h** and **4i**), however, having an ortho methyl group resulted in diminished yield of the aryl isocyanate (51%, determined by GC). A vinyl triflate was also a viable substrate, furnishing 1-(cyclohex-1-en-1-yl)-3-phenylurea in 70% yield (Table 2, entry **4l**). Vinyl isocyanates represent an important class of compounds and are used in a range of cyclization reactions[23] as well as for the construction of highly substituted amines.[24] An investigation of the amine nucleophile demonstrated that both aliphatic and aromatic amines could be used to provide the desired urea products. Moreover, a number of different heterocyclic components, such as quinoline, pyridine, thiazole and N-methyl benzimidazole, could be successfully incorporated into the urea motif through the utilization of the corresponding amines in the second step of the reaction sequence (Table 2, entries **4c, 4h–4j**).

It should be noted that the choice of electrophilic and nucleophilic components used in the one-pot, 2-step synthesis of unsymmetrical ureas is important. Electron-deficient aryl chlorides and triflates are superior coupling partners in the first step, while electron-rich anilines are better nucleophiles and therefore facilitate the second step of the sequence. Further, certain chlorinated heterocycles, such as 2-chloropyridine and 8-chloroquinoline, were not efficient coupling partners in the formation of the aryl isocyanate. However, by utilizing the corresponding 2-aminopyridine and 8-aminoquinoline in the second step of the process, the desired ureas could be synthesized in 84 and 80% yields, respectively (Table 2, entries **4c, 4h**).

We next set out to increase the scope of this process and to overcome the limitations with regard to sterically hindered electrophiles and certain heterocyclic substrates (Table 3). During our studies we discovered that the presence of phenol facilitated the cross-coupling process and afforded the corresponding carbamate as the product after the first step.[25] From this intermediate, unsymmetrically substituted ureas can still be readily obtained via substitution of the phenoxy group upon heating the reaction mixture in the presence of an amine.[26] In this way, 2-chlorotoluene could be coupled efficiency to access urea **5b** in 72% isolated yield, whereas in the absence of phenol the coupling provided only 51% of the aryl isocyanate (determined by GC) (Table 3). More importantly, the coupling of 3-chloropyridine with sodium cyanate, which did not proceed under our standard conditions, provided 86% of the desired urea product when phenol was used as an additive in the cross-coupling step (Table 3, entry **5i**). Thus, by employing this new protocol, more sterically hindered substrates (Table 3, entries **5a** and **5b**), as well as a broader scope of chlorinated heterocycles (Table 3, entries **5g–5i**), could be coupled efficiently. We were also able to employ substrates with a wider range of functional groups including a primary and a secondary amide, and a thioether (Table 3, entries **5d–5f**).

The utility of our method was demonstrated in a synthesis of Omecamtiv Mecarbil, a cardiac myosin activator currently undergoing phase 2 clinical trials.[2b] Using 1 mol % Pd_2dba_3, 2.4 mol % **L1** at 120 °C we obtained Omecamtiv Mecarbil in 81% yield in one-pot from methyl 4-(3-chloro-2-fluorobenzyl)piperazine-1-carboxylate and 5-aminopicoline (Scheme 1).

Finally, to gain further insight into the mechanism of this process an aryl iodide, bromide, chloride and triflate were all subjected to the optimized reaction conditions (Table 4). Reactions using aryl chloride and triflate electrophiles provided the desired products in higher yields than the reaction with aryl bromide, while the corresponding reaction with aryl iodide did not afford any of the urea product. Competition experiments between the aryl chloride and the aryl bromide or iodide gave results suggesting that transmetallation is the rate-limiting step and rate of Pd–NCO formation decreases in the order Cl>Br>I. Similar reactivity profiles have been demonstrated for other CN bond-forming processes when a weakly nucleophilic coupling partner is used.[16,22]

In summary, an efficient protocol for the synthesis of unsymmetrical ureas was developed which proceeds via a palladium-catalyzed cross-coupling of aryl chlorides and triflates with sodium cyanate. A second set of conditions was established which allowed for an expanded substrate scope with respect to the electrophile via introduction of phenol to the reaction mixture. Mechanistic studies conducted on this system suggest that transmetallation is the rate-limiting step. Finally, the first example of reductive elimination from an aryl palladium isocyanate complex was demonstrated. Additional studies on the role of phenol in promoting the reaction with more sterically hindered and heterocyclic substrates are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported, in part, by an educational donation provided by Amgen and by the National Institutes of Health (GM58160). The Varian 300 MHz and 500 MHz NMR spectrometers used for portions of this work was purchased with funds from the National Science Foundation (Grants CHE 9808061 and DBI 9729592). The departmental X-ray diffraction instrumentation was purchased with the help of funding from the National Science Foundation (CHE-0946721). We thank members of the Dincă Laboratory for the help in obtaining IR spectra of complexes **1** and **2**.

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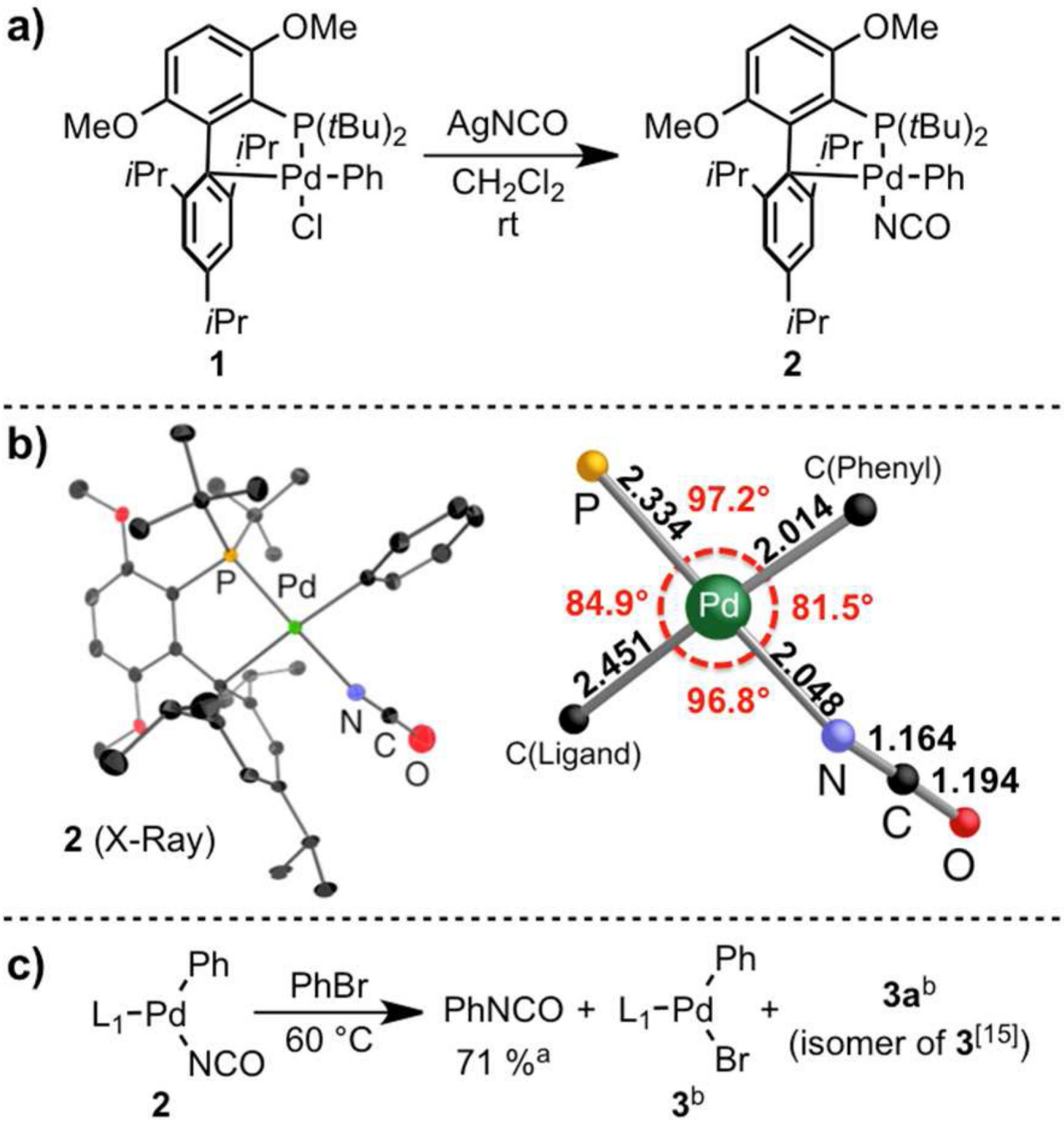
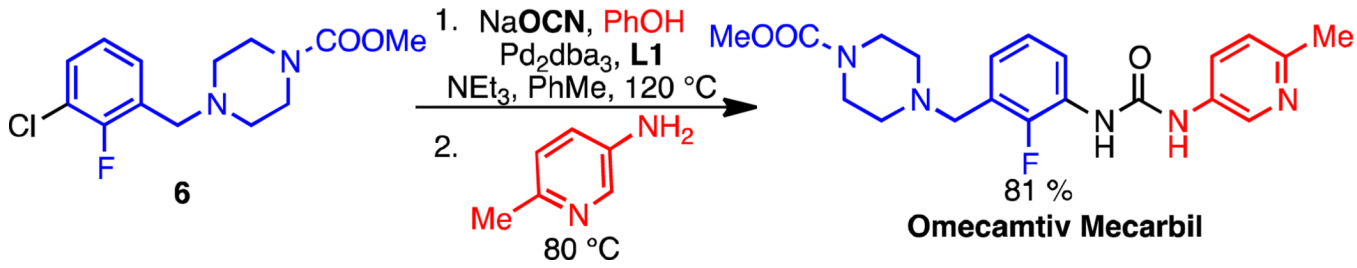


Figure 1.

(a) Synthesis of Pd(aryl)isocyanate complex **2**; (b) crystallographically derived X-ray structure of **2** (thermal ellipsoid plot drawn at 50% probability, hydrogen atoms are omitted for clarity) and selected bond lengths (Å) and angles around the metal center; (c) reductive elimination from complex **2**.

[a]Determined by ^{1}H NMR spectroscopy using 1,3,5-tris(trifluoromethyl) benzene as internal standard (see the Supporting Information). [b]Determined by ^{31}P NMR spectroscopy.

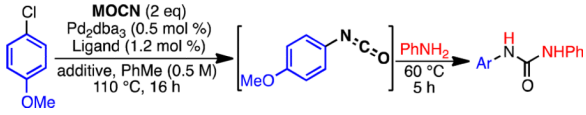


Scheme 1. Synthesis of Omecamtiv Mecarbil.a

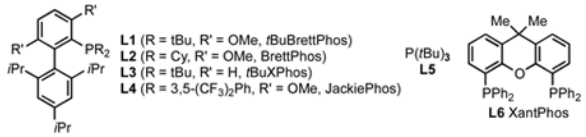
[a] Reaction conditions (isolated yield, average of 2 runs). Step 1: **6** (1 mmol), NaOCN (2 mmol), PhOH (2 mmol), Pd_2dba_3 (1.0 mol %), ligand (2.4 mol %), NEt_3 (10 mol %), toluene (2 mL). The $Pd_2(dba)_3$ and ligand were preheated in toluene (2 mL) at 120 °C for 3 minutes. Step 2: $ArNH_2$ (1.2 mmol).

Table 1

Optimization of the reaction conditions.[a,b]



Entry	MOCN	L (mol %)	Additive (mol %)	Yield, (%)[c]
1[d]	AgOCN	**L1** (1.2)	none	-
2[d]	NaOCN	**L1** (1.2)	none	11
3[d]	KOCN	**L1** (1.2)	none	-
4	NaOCN	**L1** (1.2)	none	40
5	NaOCN	**L1** (1.2)	NEt_3 (25)	80[e]
6	NaOCN	**L2** (1.2)	NEt_3 (25)	<5
7	NaOCN	**L3** (1.2)	NEt_3 (25)	58
8	NaOCN	**L4** (2.4)	NEt_3 (25)	-
9	NaOCN	**L5** (1.2)	NEt_3 (25)	-
10	NaOCN	**L6** (1.5)	NEt_3 (25)	-



[a] Reaction conditions. Step 1: 4-chloroanisole (1 mmol), NaOCN (2 mmol), Pd_2dba_3 (0.5 mol %), ligand (x mol %), additive (y mol %), toluene (2 mL). The $Pd_2(dba)_3$ and ligand were preheated in toluene (2 mL) at 120 °C for 3 minutes. Step 2: aniline (1.2 mmol), toluene (2 mL).

[b] For additional studies on the optimization of the reaction conditions including the use of phase transfer reagents see the Supporting Information.

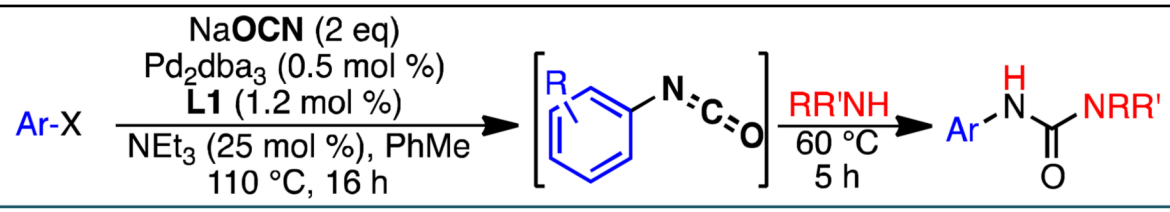
[c] Determined by LC-MS analysis of crude reaction mixture using biphenyl as internal standard.

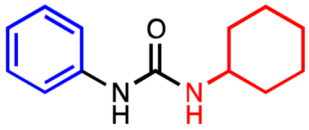
[d] The reaction was performed without premixing of $Pd_2(dba)_3$ and ligand.

[e] Isolated yield, average of 2 runs.

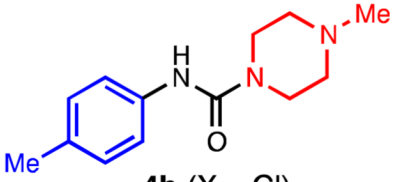
Table 2

Pd-catalyzed cross-coupling of aryl chlorides and triflates with sodium isocyanate in a one pot synthesis of unsymmetrical N,N'-di- and N,N,N'-trisubstituted ureas.[a]

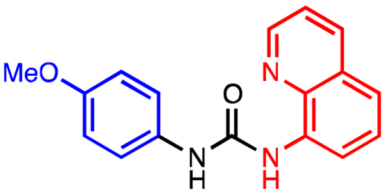




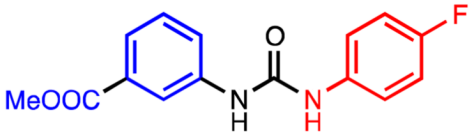
4a (X = Cl)
88 %



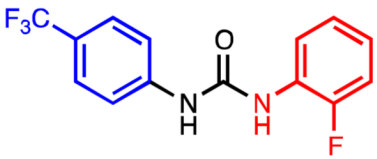
4b (X = Cl)
78 %



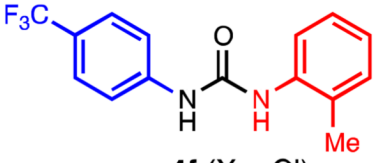
4c (X = Cl)
79 %



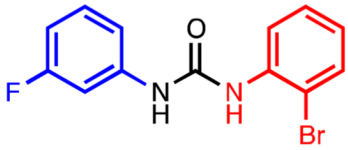
4d (X = Cl)
78 %



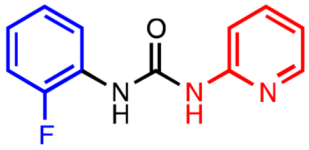
4e (X = Cl)
83 %



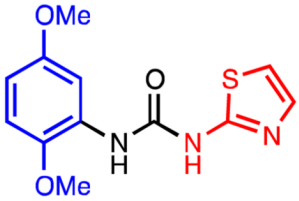
4f (X = Cl)
85 %



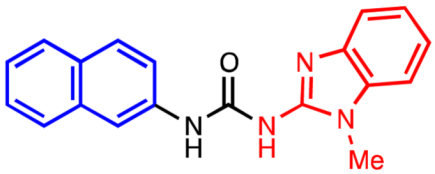
4g (X = Cl)
77 %



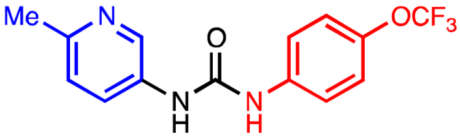
4h (X = Cl)
84 %



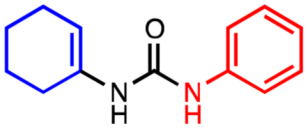
4i (X = Cl)
83 %



4j (X = Cl)
78 %



4k[b] (X = OTf)
86 %



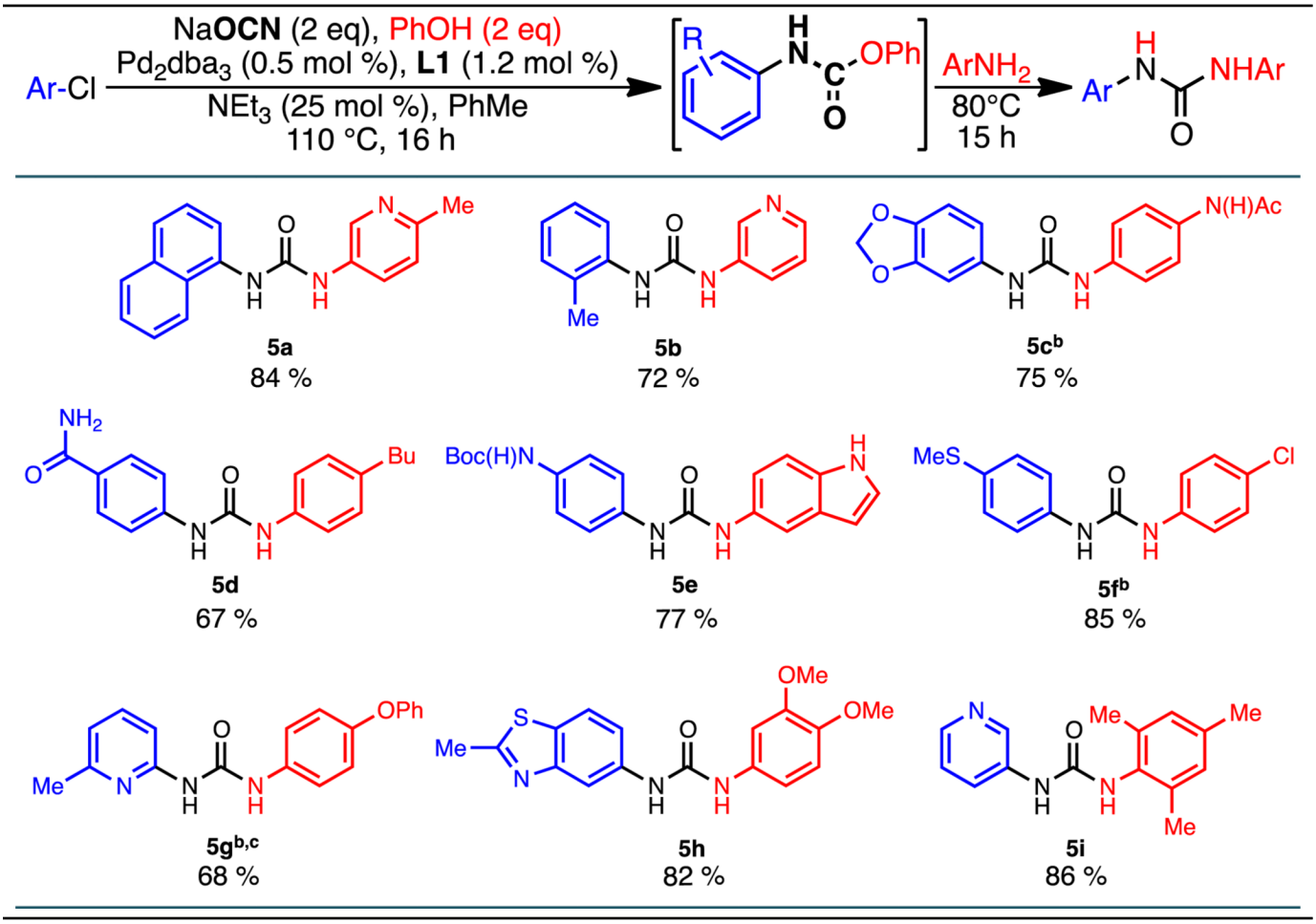
4l[b] (X = OTf)
70 %

[a]Reaction conditions (isolated yields, average of 2 runs). Step 1: ArX (1 mmol), NaOCN (2 mmol), Pd_2dba_3 (0.5 mol %), **L1** (1.2 mol %), NEt_3 (25 mol %), toluene (2 mL). The $Pd_2(dba)_3$ and ligand were preheated in toluene (2 mL) at 120 °C for 3 minutes. Step 2: $ArNH_2$ (1.2 mmol), toluene (2 mL).

[b]10 mol % of NEt_3 was used.

Table 3

Pd-catalyzed cross-coupling of aryl chlorides with sodium isocyanate in the presence of phenol in a one pot synthesis of unsymmetrical N,N'-disubstituted ureas. [a]



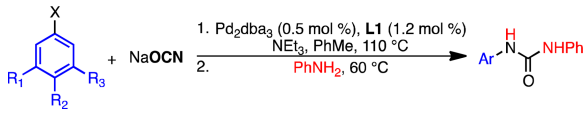
[a] Reaction conditions (isolated yields, average of 2 runs). Step 1: ArX (1 mmol), NaOCN (2 mmol), PhOH (2 mmol), Pd_2dba_3 (0.5 mol %), ligand (1.2 mol %), NEt_3 (25 mol %), toluene (2 mL). The $Pd_2(dba)_3$ and ligand were preheated in toluene (2 mL) at 120 °C for 3 minutes. Step 2: $ArNH_2$ (1.2 mmol), toluene (2 mL).

[b] 130 °C

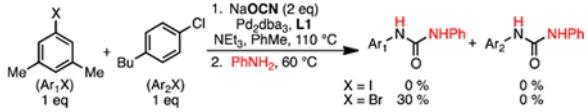
[c] 1 mol % $Pd_2(dba)_3$ was used.

Table 4

Competition experiments[a]



entry	R_1	R_2	R_3	X	Yield[b]
1	CH_3	H	CH_3	I	0 %
2	CH_3	H	CH_3	Br	34 %
3	H	*n*-C_4H_9	H	Cl	93 %
4	CH_3	H	CH_3	OTf	>95 %



[a]Reaction conditions. Step 1: ArX (1 mmol), NaOCN (2 mmol), Pd_2dba_3 (0.5 mol %), **L1** (1.2 mol %), NEt_3 (25 mol %), solvent (2 mL). The $Pd_2(dba)_3$ and ligand were preheated in toluene (2 mL) at 120 °C for 3 minutes. Step 2: $PhNH_2$ (1.2 mmol), toluene (2 mL).

[b]Yields determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.