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

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Supporting Information

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 was gleaned through studies of the transmetalation 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, which are common motifs in an array of biologically active compounds,[1] including tyrosine and Raf kinase inhibitors,[2a] cardiac-specific myosin activators,[2b] melanin-concentrating hormone receptor 1 (MCH-R1) antagonists,[2c] and antitrypanosomal 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 limited substrate scope, the use of toxic and extremely hazardous reagents (phosgene,[8] azides, carbon monoxide), or otherwise harsh conditions.

While transition-metal-catalyzed C−N 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 a few reports of such reactions to date. A nickel-catalyzed coupling of aryl halides with metal cyanates was reported by Tkatchenko in 1986, but the yields of the corresponding aryl carbamates or ureas ranged from 10 to 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 arylboronic 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.

On first consideration of this transformation, we envisioned two possible catalyst deactivation pathways that had to be avoided in order to access an efficient catalyst system: (1) deactivation of the catalyst by excessive coordination of the cyanate anions to the Pd center, which has previously been shown to occur in the case of other coordinating nucleophiles,[11] and (2) 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 biarylphosphine 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, but 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. To test this, complex **2** was synthesized via treatment of complex **1** [Figure 1a; also see the Supporting Information (SI)] with silver cyanate in CH_2Cl_2. The structure of complex **2** was further confirmed using X-ray crystallography (Figure 1b).

When **2** was heated at 60 °C for 110 min 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 $(2.5 \pm 0.2) \times 10^{-4}$ s^{-1}. Upon completion, only two signals were observed in the $^{31}P\{^1H\}$ NMR (C_6D_6) spectrum of the reaction mixture; they were assigned as the oxidative addition complex (**L1**)Pd(Ph)(Br) (68.0 ppm) (**3**) and its isomeric complex **3a** (82.4 ppm).[15] Furthermore, the reaction exhibited no rate dependence on the concentration of PhBr (1, 2, and 4 equiv of PhBr were used) or on the presence of extra ligand (0.5 equiv of **L1** was used). This is the first reported example of successful reductive elimination from an arylpalladium 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 via an initial isocyanate cross-coupling followed by 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

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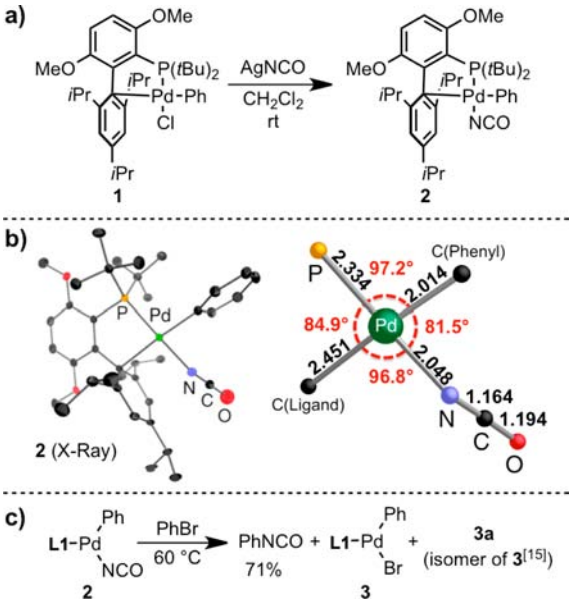
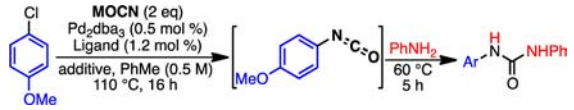


Figure 1. (a) Synthesis of Pd(aryl)isocyanate complex **2**. (b) Crystallographically derived X-ray structure of **2** (thermal ellipsoid plot drawn at 50% probability, H atoms omitted for clarity) and selected bond lengths (Å) and angles (deg) around the metal center. (c) Reductive elimination from complex **2**. The yield of PhNCO was determined by ^{1}H NMR spectroscopy using 1,3,5-tris-(trifluoromethyl)benzene as an internal standard (see the SI). The presence of **3** and **3a** was detected by ^{31}P NMR spectroscopy.

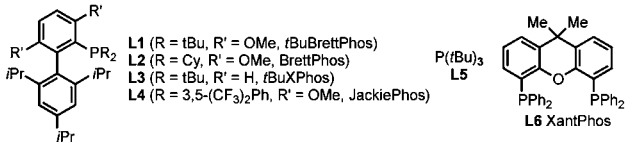
to produce 1-(4-methoxyphenyl)-3-phenylurea (Table 1). An investigation of possible cyanate sources, utilizing a catalyst system based on Pd_2dba_3 and ligand **L1**, demonstrated that while both KOCN and AgOCN were ineffective for this transformation (Table 1, entries 1 and 3), the use of NaOCN did lead to the formation of the desired product, albeit in low yield (Table 1, entry 2). Since the isocyanate anion could potentially inhibit the catalytic activity as mentioned above, we hypothesized that more efficient generation of the active catalytic species prior its introduction into the reaction medium could lead to an increased yield of the urea.[18] In support of this, when Pd_2dba_3 was heated with **L1** at 120 °C for 3 min and then transferred to the reaction medium, the product was obtained in 40% yield (Table 1, entry 4). We further found that the addition of NEt_3 (25 mol %) allowed for an 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 medium for the initial cross-coupling step did not result in competitive aniline arylation in the absence of a base that 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 equiv of a more soluble isocyanate source $[(NBu_4)(NCO)]$ to the reaction mixture under the optimized conditions completely shut down the reaction.

The 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, 7, and 9). Further, use of **L4** and **L6**, which have been used for

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 min. Step 2: aniline (1.2 mmol), toluene (2 mL). [b]For additional studies of the optimization of the reaction conditions, including the use of phase transfer reagents, see the SI. [c]Determined by LC−MS analysis of the crude reaction mixture using biphenyl as an internal standard. [d]The reaction was performed without premixing of $Pd_2(dba)_3$ and the ligand. [e]Isolated yield, average of two runs.

other difficult C−N cross-coupling reactions,[21,22] did not produce any observable amount of the desired urea product (Table 1, entries 8 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% yield. Small ortho substituents on the aryl chlorides were well-tolerated (Table 2, entries **4h** and **4i**), however having an *o*-methyl group resulted in a diminished yield of the aryl isocyanate (51% as 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 that 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*-methylbenzimidazole, could be successfully incorporated into the urea motif by using the corresponding amines in the second step of the reaction sequence (Table 2, entries **4c** and **4h−j**).

It should be noted that the choice of electrophilic and nucleophilic components used in the one-pot, two-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

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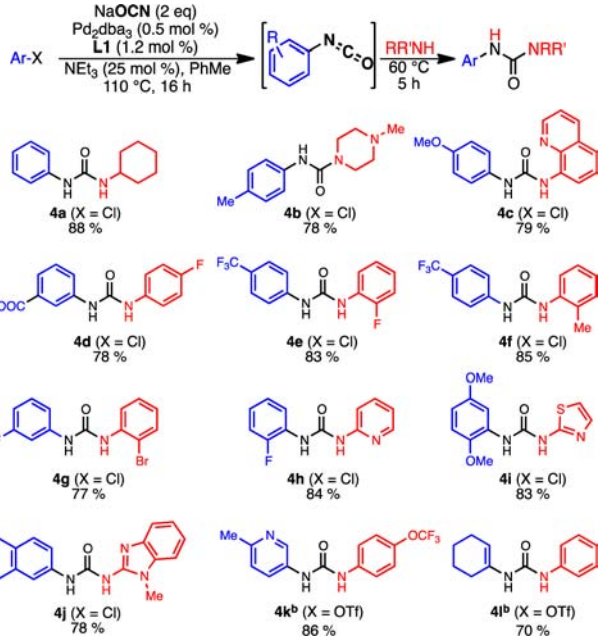
Table 2. Pd-Catalyzed Cross-Coupling of Aryl Chlorides and Triflates with Sodium Isocyanate in a One-Pot Synthesis of Unsymmetrical N,N′-Di- and N,N,N′-Trisubstituted Ureas[a]

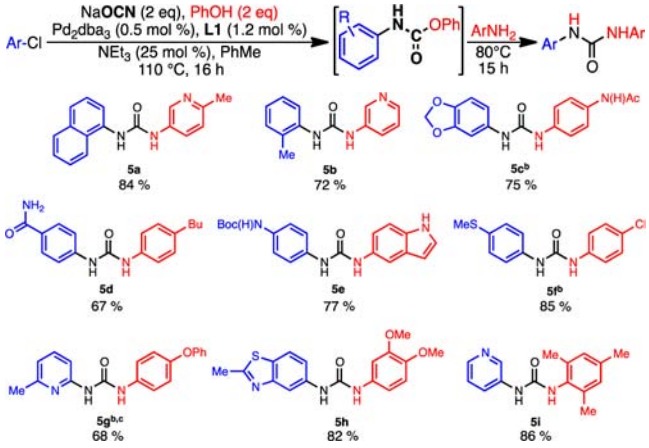


[a]Reaction conditions (isolated yields, average of two runs): Step 1: ArX (1 mmol), NaOCN (2 mmol), PhOH (2 mmol), Pd_2dba_3 (0.5 mol %), **L1** (1.2 mol %), NEt_3 (25 mol %), toluene (2 mL). $Pd_2(dba)_3$ and **L1** were preheated in toluene (2 mL) at 120 °C for 3 min. Step 2: $ArNH_2$ (1.2 mmol), toluene (2 mL). [b]10 mol % NEt_3 was used.

nucleophiles and therefore better facilitate the second step of the sequence. Further, certain chlorinated heterocycles, such as 2-chloropyridine and 8-chloroquinoline, were not efficient coupling partners for the aryl isocyanate formation. However, using the corresponding amines (2-aminopyridine and 8-aminoquinoline) in the second step of the process allowed the desired ureas to be synthesized in 84 and 80% yields, respectively (Table 2, entries **4c** and **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 could 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 efficiently to afford urea **5b** in 72% isolated yield, whereas in the absence of phenol, the coupling provided only a 51% yield of the aryl isocyanate as determined by GC (Table 3). More importantly, the coupling of 3-chloropyridine with sodium cyanate, which did not proceed under our standard conditions, provided the desired urea product in 86% yield when phenol was used as an additive in the cross-coupling step (Table 3, entry **5i**). Thus, with 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–i**) could be coupled efficiently. We were also able to employ substrates with a wider range of functional groups, including primary and secondary amides and a thioether (Table 3, entries **5d–f**).

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 two 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). $Pd_2(dba)_3$ and **L1** were preheated in toluene (2 mL) at 120 °C for 3 min. Step 2: $ArNH_2$ (1.2 mmol), toluene (2 mL). [b]130 °C. [c]1 mol % $Pd_2(dba)_3$ was used.

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 and 2.4 mol % **L1** at 120 °C, we obtained Omecamtiv Mecarbil from methyl 4-(3-chloro-2-fluorobenzyl)piperazine-1-carboxylate (**6**) and 5-aminopicoline in 81% yield in a one-pot procedure (Scheme 1).

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 %), **L1** (2.4 mol %), NEt_3 (10 mol %), toluene (2 mL). $Pd_2(dba)_3$ and **L1** were preheated in toluene (2 mL) at 120 °C for 3 min. Step 2: $ArNH_2$ (1.2 mmol).

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 transmetalation is the rate-limiting step and that rate of Pd–NCO formation decreases in the order Cl > Br > I. Similar reactivity profiles have been demonstrated for other C–N bond-forming processes when a weakly nucleophilic coupling partner is used.[16,22]

In summary, an efficient protocol for the synthesis of unsymmetrical ureas that proceeds via palladium-catalyzed cross-coupling of aryl chlorides and triflates with sodium cyanate has been developed. A second set of conditions allowing for an expanded substrate scope with respect to the

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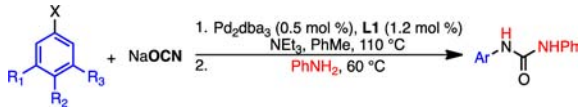
Table 4. Competition Experiments[a]



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). $Pd_2(dba)_3$ and **L1** were preheated in toluene (2 mL) at 120 °C for 3 min. Step 2: $PhNH_2$ (1.2 mmol), toluene (2 mL). [b]Determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

electrophile via introduction of phenol to the reaction mixture was also established. Mechanistic studies conducted on this system suggest that transmetalation is the rate-limiting step. Finally, the first example of reductive elimination from an arylpalladium isocyanate complex has also been demonstrated. Additional studies of the role of phenol in promoting the reaction with more sterically hindered and heterocyclic substrates are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures; characterizations; spectral data for all compounds; complete refs 2b, 2c, and 7b; and X-ray crystallographic data for **2** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): MIT has patents on ligands that are described in the papers from which S.L.B. receives royalty payments.

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