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Synthesis of Unsymmetrical Diaryl Ureas via Pd-Catalyzed C–N Cross-Coupling Reactions

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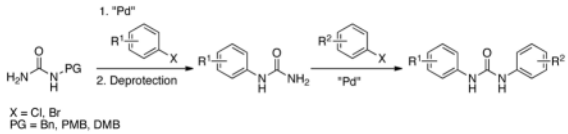
Abstract



A facile synthesis of unsymmetrical *N*,*N*′-diaryl ureas is described. The utilization of the Pd-catalyzed arylation of ureas enables the synthesis of an array of diaryl ureas in good to excellent yields from benzylurea via a one-pot arylation-deprotection protocol, followed by a second arylation.

Unsymmetrical *N*,*N*′-diaryl ureas are found in a variety of biologically active molecules, and their efficient synthesis is of great importance,[1] especially to medicinal chemists.[2] They are most commonly prepared via a nucleophilic attack of an aniline on an isocyanate.[1,3] Unfortunately, isocyanates are unstable and typically require the use of phosgene for their synthesis. To circumvent these issues, several methods have been developed to allow *in situ* generation of the isocyanates from different precursors, such as carbamates,[4] carbamic acids,[5] hydroxamic acids,[6] or acetoacetanilide.[7] However, these methods do not provide general and efficient syntheses of diaryl ureas.

In efforts to develop more general routes to make unsymmetrical diaryl ureas, several metal-catalyzed *N*-arylations of urea or monosubstituted ureas have been reported.[8–10] However, all of these procedures give either symmetrically substituted products (when using urea as the *N*-nucleophile),[8] rely on a commercially available monosubstituted starting material (for which one aryl group is "purchased," e.g., phenylurea)[9] or require the preparation of the monosubstituted urea by traditional methods (*vide supra*).[10]

Herein, we report the development of an efficient and general method for the synthesis of unsymmetrical diaryl ureas based on a two-pot strategy involving two C–N cross-coupling reactions (Scheme 1).

We postulated that we could gain access to diaryl ureas via a Pd-catalyzed arylation of a protected urea, followed by deprotection and then a subsequent second arylation (Scheme 1). We began by looking at the first cross-coupling step of the proposed protocol. Initial studies focused on the reaction of benzylurea with 4-*n*-butylchlorobenzene. It is worth mentioning that benzylurea was chosen because of its commercial availability and low cost.

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Supporting Information Available: Procedural and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

Further, the removal of the benzyl protecting group under hydrogenolysis conditions has previously been reported.[4e,11] We initially examined the catalyst based on **L1** (Figure 1) in conjunction with our water-mediated catalyst preactivation protocol,[12] on the basis of our previous report that this system was optimal for reactions of aryl chlorides with amides.[13] For the coupling of benzylurea and 4-chloro-*n*-butylbenzene, utilizing K_3PO_4 as the base and *t*-BuOH as the solvent, this catalyst provided the desired arylated benzylurea in 50% yield (Table 1, entry 1). Switching to other Pd sources, such as $Pd(OAc)_2$ without preactivation, $[(allyl)PdCl)]_2$, or $Pd_2(dba)_3$, resulted in little or no product formation (Table 1, entries 2–4). A marked increase in conversion was found when replacing *t*-BuOH with THF (Table 1, entry 5). The use of other commonly employed solvents for cross-coupling reactions gave inferior results (Table 1, entries 6–8). The catalyst based on **L1** gave superior results to those based on other biarylphosphine ligands frequently employed for C–N cross-coupling reactions (Table 1, entries 9–12). Lastly, Cs_2CO_3 proved to be the most efficient base for this reaction, giving the desired product in 99% yield (Table 1, entries 13–16).

We next explored the one-pot arylation/hydrogenolysis protocol to afford monoaryl ureas. Utilizing the optimized reaction conditions described in Table 1, 4-chloro-*n*-butylbenzene was reacted with benzylurea at 85 °C for 2 hours. The reaction mixture was then cooled to room temperature and Pd/C (9 mol %), MeOH and concentrated HCl were added. The reaction was placed under an atmosphere of H_2 and allowed to stir for 20 hours, after which time workup and purification afforded the desired monoaryl urea in a 90% isolated yield (Table 2, 2a).

With the optimized one-pot arylation/deprotection protocol in hand, we set out to explore the substrate scope for the synthesis of monoaryl ureas. We found that electron-rich and electron-deficient aryl halides, as well as aryl halides with ortho substituents, were efficient coupling partners and provided good to excellent yields of the desired products (**2a** – **2j**). However, in the case of heteroaryl halides consistently lower yields were obtained under these conditions. Although the *N*-arylation worked efficiently for these heteroaryl substrates, the hydrogenolysis was considerably slower, presumably due to catalyst inhibition; this necessitated higher loadings of Pd/C to achieve acceptable yields (**2k** – **2m**). In addition, the relatively harsh reductive deprotection conditions limited the substrate scope due to possible reduction of functional groups and/or hydrogenation of the heteroarene moieties.

We thus decided to investigate alternative protecting groups, which could be removed under conditions that would be more amenable to hydrogenation-sensitive substrates. We focused on the use of *p*-methoxybenzyl-(PMB) urea. Deprotection by oxidative cleavage with either CAN[14] or DDQ[15] resulted in complex mixtures and no formation of the desired product. However, hydrolysis in acidic media[16] (TFA, 60 °C) resulted in clean conversion to the desired target compounds, providing access to products containing hydrogenation-sensitive functional groups and/or heteroarenes (Table 3). This procedure was also found to be beneficial for heterocycles that caused catalyst inhibition in the hydrogenolysis protocol (compare **2l** and **2m** with **3a** and **3b**, respectively).

Having demonstrated a broad substrate scope in the cross-coupling/deprotection step, we next focused on the second Pd-catalyzed amidation reaction of our proposed process to afford the unsymmetrical diaryl ureas. It was found that the optimized conditions employed for the coupling of benzylurea were also applicable for reactions of monoaryl ureas, although longer reaction times were required (Table 4). Under these conditions both electron-rich (**4a**, **4b**) and electron-deficient (**4c** – **4f**) aryl halides were reacted with monoaryl ureas in good to excellent yields. Further, aryl halides containing a carboxylic acid, ester, nitrile, or amide all proved to be excellent coupling partners (**4c** – **4g**). Lastly, various heteroaryl halides were employed in these reactions. Haloindoles, -pyridazines, -

pyridines, and -thiazoles were all coupled with a monoaryl urea in moderate to excellent yields (**4h** – **4k**). It is worth mentioning that when the electron-deficient 2-chloro-5-trifluoromethylpyridine was subjected to the optimized reaction conditions several byproducts were observed, and the product was isolated in a modest yield (54%). We hypothesized that the byproducts and low yield were due to thermal decomposition of the product to give the isocyanate under the reaction conditions.[17] By lowering the reaction temperature to 60 °C the decomposition pathways could be prevented, and an 84% yield of the product was obtained (**4j**).

Having established a versatile method to synthesize unsymmetrical *N*,*N*′-diaryl ureas, we set out to highlight the utility of this protocol by applying it to the concise syntheses of two pharmaceutical targets. First, *Omecamtiv Mecarbil*,[2a] a cardiac myosin activator currently in phase II clinical trials, was made in a two-pot sequence (Scheme 2). The coupling of benzyl urea with 5-bromo-2-methylpyridine, followed by deprotection afforded the monoaryl urea intermediate **5a** in 74% yield. Urea **5a** was then coupled with **5b**, utilizing a catalyst based on **L1**, to give Omecamtiv Mecarbil in an 81% yield. Second, Sorafenib[18] (Nexavar®), a multikinase inhibitor approved for the treatment of advanced renal cell carcinoma and heptocellular carcinoma, was prepared. The coupling of 2,4-dimethoxybenzyl (DMB) urea with 4-bromo-2-trifluoromethylchlorobenzene, followed by deprotection with HCl provided 76% of the monoaryl urea **5c**. Urea **5c** was then arylated with **5d** to give the target Sorafenib in 86% yield. These two applications display the efficiency and utility of this method.

In summary, we have developed a facile route to unsymmetrical *N*,*N*′-diaryl ureas via Pd-catalyzed C–N cross-coupling reactions. This general protocol allows the coupling of a wide variety of (hetero)aryl halides and ureas in good to excellent yields and gives efficient access to an array of diaryl ureas.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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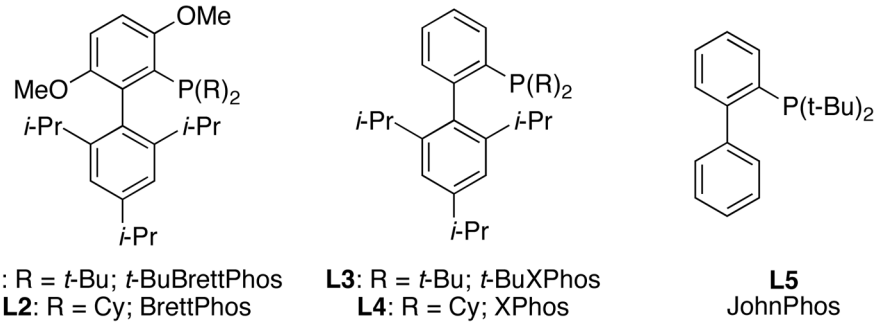
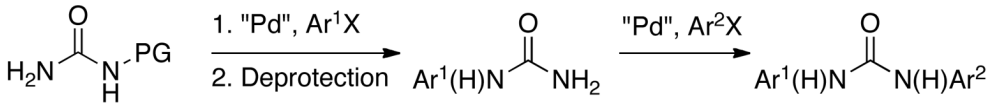


L1: R = *t*-Bu; *t*-BuBrettPhos
L2: R = Cy; BrettPhos

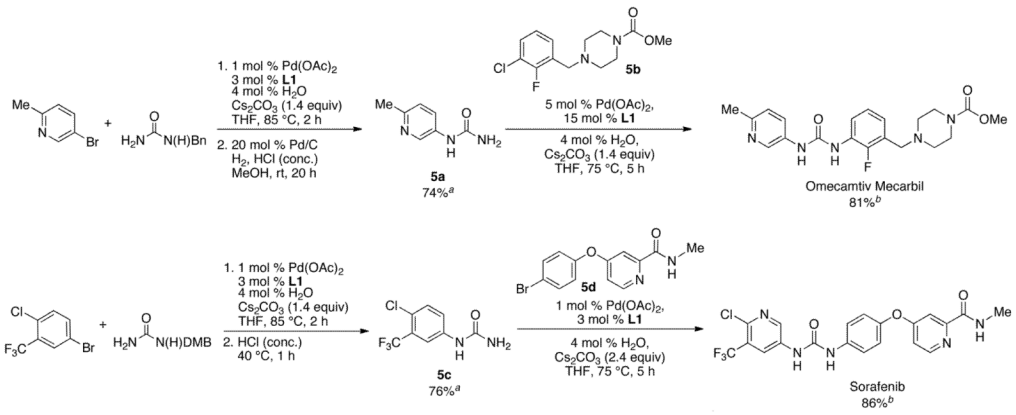
L3: R = *t*-Bu; *t*-BuXPhos
L4: R = Cy; XPhos

L5
JohnPhos

Figure 1.
Biarylphosphine ligands.



Scheme 1.
Proposed synthesis of unsymmetrical diaryl ureas.



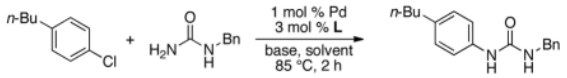
Scheme 2.

Synthesis of Omecamtiv Mecarbil and Sorafenib

[a]isolated yield on 1 mmol scale; average of 2 runs; isolated yield on 5 mmol scale: 78% (**5a**), 81% (**5c**). [b] isolated yield on 0.5 mmol scale; average of 2 runs.

Table 1

Optimization of the Pd-Catalyzed Cross-Coupling Reactions of Benzylurea and Aryl Chlorides[a]



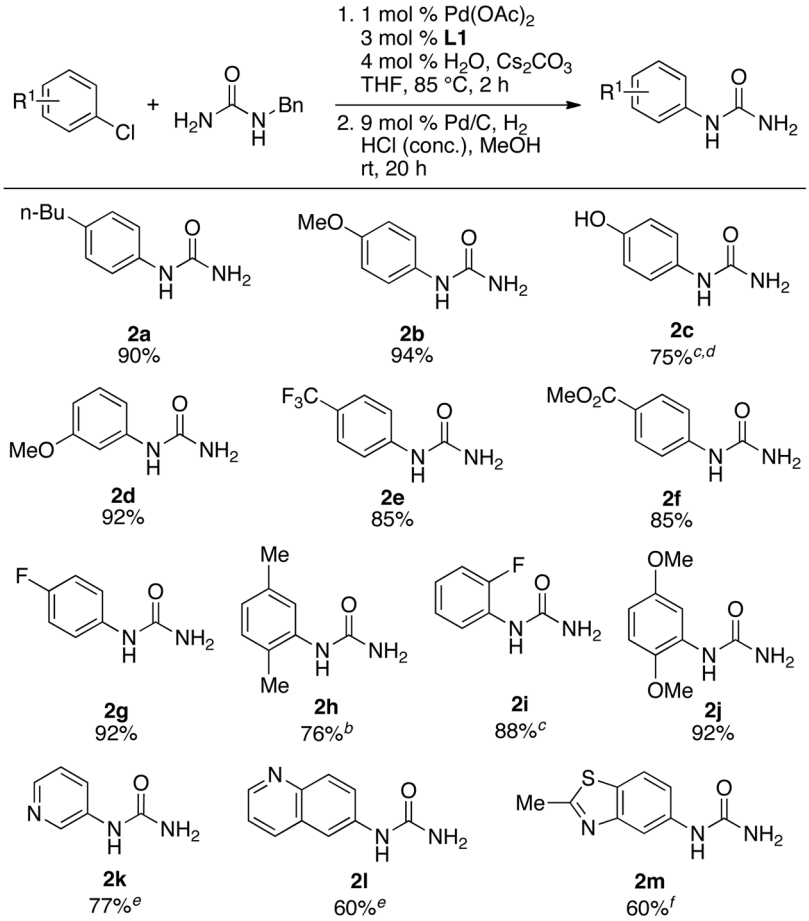
entry	Pd source	L	base	solvent	GC yield (%)
1	$Pd(OAc)_2/H_2O$ Act	**L1**	K_3PO_4	*t*-BuOH	50
2	$Pd(OAc)_2$	**L1**	K_3PO_4	*t*-BuOH	0
3	$[(allyl)PdCl]_2$	**L1**	K_3PO_4	*t*-BuOH	0
4	Pd_2dba_3	**L1**	K_3PO_4	*t*-BuOH	5
5	$Pd(OAc)_2/H_2O$ Act	**L1**	K_3PO_4	THF	79
6	$Pd(OAc)_2/H_2O$ Act	**L1**	K_3PO_4	Toluene	26
7	$Pd(OAc)_2/H_2O$ Act	**L1**	K_3PO_4	DME	0
8	$Pd(OAc)_2/H_2O$ Act	**L1**	K_3PO_4	Dioxane	59
9	$Pd(OAc)_2/H_2O$ Act	**L2**	K_3PO_4	THF	51
10	$Pd(OAc)_2/H_2O$ Act	**L3**	K_3PO_4	THF	48
11	$Pd(OAc)_2/H_2O$ Act	**L4**	K_3PO_4	THF	19
12	$Pd(OAc)_2/H_2O$ Act	**L5**	K_3PO_4	THF	0
13	$Pd(OAc)_2/H_2O$ Act	**L1**	Cs_2CO_3	THF	99
14	$Pd(OAc)_2/H_2O$ Act	**L1**	K_2CO_3	THF	73
15	$Pd(OAc)_2/H_2O$ Act	**L1**	NaO*t*Bu	THF	0
16	$Pd(OAc)_2/H_2O$ Act	**L1**	K_3PO_4	THF	99[b]

[a] Reaction conditions: ArCl (1.0 mmol), benzylurea (1.2 mmol), Pd (1 mol %), **L** (3 mol %), base (1.4 mmol), solvent (2 mL/mmol), 85 °C, 2 h.

[b] Reaction time 6 h.

Table 2

Pd-Catalyzed Cross-Coupling Reactions of Benzylurea with Aryl Chlorides Followed by *In Situ* Hydrogenolysis[a]



[a]Reaction conditions: ArX (1.0 mmol), benzylurea (1.2 mmol), $Pd(OAc)_2$ (1 mol %), **L1** (3 mol %), Cs_2CO_3 (1.4 mmol), solvent (2 mL/mmol), 85 °C, 2 h, then Pd/C (9 mol %), HCl (conc., 12 mmol), H_2 (1 atm), MeOH (6 mL/mmol), rt, 20 h; isolated yield, average of 2 runs.

[b]3 mol % Pd, 9 mol % **L1**, 85 °C, 3 h.

[c]3 mol % Pd, 9 mol % **L1**, 100 °C, 3 h.

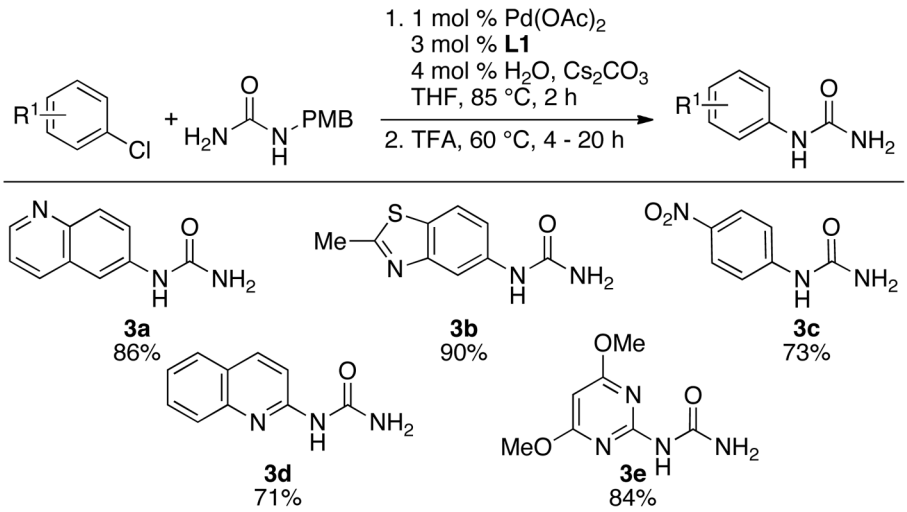
[d]2.4 mmol Cs_2CO_3.

[e]20 mol % Pd/C, HCl (conc., 24 mmol).

[f]60 mol % Pd/C, HCl (conc., 48 mmol), 48 h.

Table 3

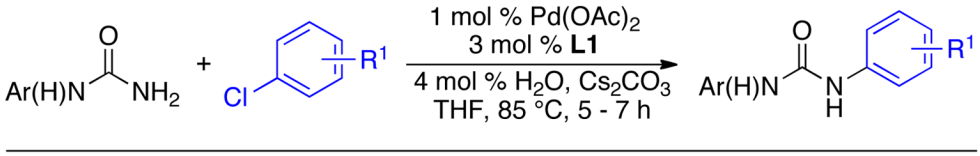
Pd-Catalyzed Coupling Reactions of *p*-Methoxybenzyl Urea[a] and Aryl Chlorides Followed by *In Situ*-Hydrolysis[a]

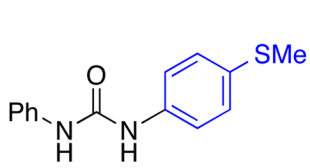


[a]Reaction conditions: ArCl (1.0 mmol), *p*-methoxybenzylurea (1.2 mmol), $Pd(OAc)_2$ (1 mol %), **L1** (3 mol %), Cs_2CO_3 (1.4 mmol), solvent (2 mL/mmol), 85 °C, 2 h, then TFA (8 mL/mmol), 60 °C; isolated yield, average of 2 runs.

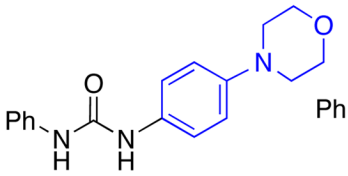
Table 4

Pd-Catalyzed Cross-Coupling Reactions of Monoaryl Ureas and Aryl Halides[a]

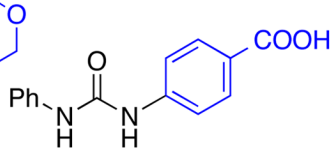




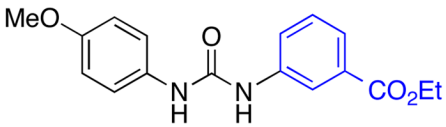
4a, 97%



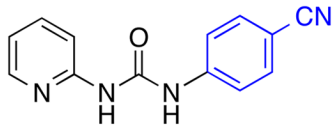
4b, 97%



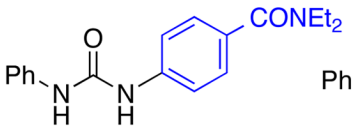
4c, 88%[b]



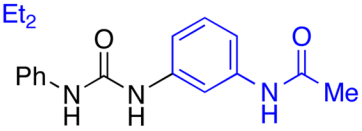
4d, 84%



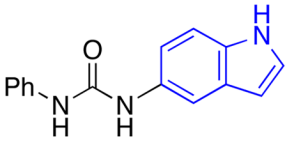
4e, 65%[c]



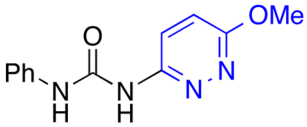
4f, 92%



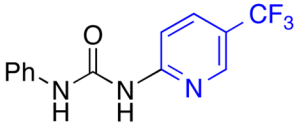
4g, 89%[b]



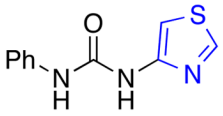
4h, 75%[b]



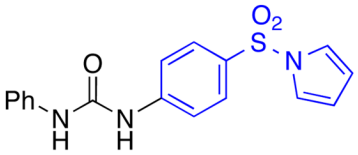
4i, 73%



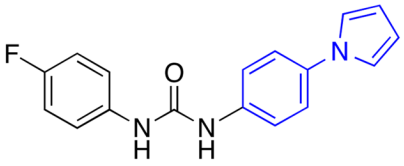
4j, 53% (84%[d])



4k, 87%[e]



4l, 58%



4m, 97%

[a]Reaction conditions: ArCl (1.0 mmol), phenylurea (1.2 mmol), $Pd(OAc)_2$ (1 mol %), **L1** (3 mol %), Cs_2CO_3 (1.4 mmol), solvent (2 mL/mmol), 85 °C, 5 – 7 h; isolated yield, average of 2 runs.

[b]2.4 mmol Cs_2CO_3.

[c]3 mol % Pd, 9 mol % **L1**, 6 h.

[d] 3 mol % Pd, 9 mol % **L1**, 60 °C, 5 h.

[e] 6 mol % Pd, 18 mol % **L1**, 75 °C, 8 h, and the ArBr was used as the substrate.