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A General Method for the Synthesis of Unsymmetrically Substituted Ureas via Palladium-Catalyzed Amidation

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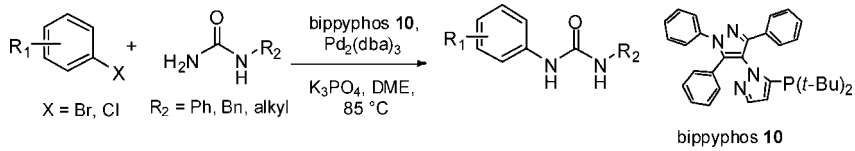
ABSTRACT



A general and practical method for the preparation of unsymmetrically substituted ureas has been developed utilizing palladium-catalyzed amidation. Both aryl bromides and chlorides, as well as heteroaryl chlorides, have been coupled to aryl, benzyl, and aliphatic ureas by using a novel nonproprietary bipyrazole ligand (bippyphos).

N-Aryl- and *N*-heteroaryl-substituted ureas, common pharmacophores in biologically active targets,[1,2] are typically prepared by the coupling of amines with isocyanates, active esters, or activated carbamates. The most utilized of these alternatives, isocyanates,[3] are in turn prepared by the reaction of amines with phosgene. Although widely used, this methodology has numerous deficiencies: most notably, in low reaction yields resulting from instability of the isocyanates, disproportionation leading to symmetrical ureas, and hazards associated with phosgene handling. It is not surprising therefore that numerous modifications have been reported, including the development of phosgene surrogates.[4] The use of cleaner and inherently safer alternatives such as carbonates, carbonyl diimidazole, or reactions of activated carbamates directly with an amine have been reported.[5] Nevertheless, none of these procedures provide a general and practical synthetic method for the preparation of *N*-aryl or *N*-heteroaryl ureas.

Although a significant number of cross-coupling methodologies have been developed for *N*-arylation,[6] few have been applied to the *N*-arylation of ureas.[7−11] It has been reported that electron poor aryl bromides are suitable coupling partners for *N*-arylation of ureas.[7] However, unactivated aryl bromides are less reactive.[8] Aryl and heteroaryl chlorides are generally more attractive from a cost and availability perspective

* Corresponding author.

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(2) For example: (a) Looker, A. R.; Littler, B. J.; Blythe, T. A.; Snoonian, J. R.; Ansell, G. K.; Jones, A. D.; Nyce, P.; Chen, M.; Neubert, B. J. *Org. Process Res. Dev.* **2008**, *12* (4), 666–673. (b) Dai, Y.; Hartandi, K.; Ji, Z.; Ahmed, A. A.; Albert, D. H.; Bauch, J. L.; Bouska, J. J.; Bousquet, P. F.; Cunha, G. A.; Glaser, K. B.; Harris, C. M.; Hickman, D.; Guo, J.; Li, J.; Marcotte, P. A.; Marsh, K. C.; Moskey, M. D.; Martin, R. L.; Olson, A. M.; Osterling, D. J.; Pease, L. J.; Soni, N. B.; Stewart, K. D.; Stoll, V. S.; Tapang, P.; Reuter, D. R.; Davidsen, S. K.; Michaelides, M. R. *J. Med. Chem.* **2007**, *50* (7), 1584–1597.

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(4) Cotarca, L.; Delogu, P.; Nardelli, A.; Sunjic, V. *Synthesis* **1996**, (5), 553–576.

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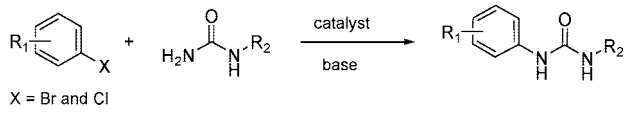
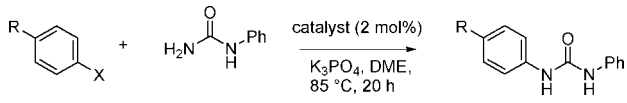
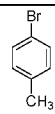
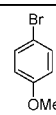
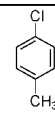
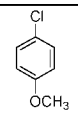


Figure 1. General scheme.

compared to their iodo or bromo analogues. However, we have only found literature precedent for urea coupling to 2-chloropyridine[9] and intramolecular coupling with aryl-chlorides.[10,11] Prompted by the need to prepare nonsymmetric ureas as part of our drug development efforts, we undertook a more comprehensive investigation targeted at identifying a practical and general method for the coupling of substituted ureas with aryl bromides and the more commercially attractive aryl chlorides (Figure 1).[12]

Table 1. Ligands for the Coupling of Aryl Halides and Urea[a]



		conversion[b]			
	catalyst				
1	Xantphos **1** + $Pd_2(dba)_3$	26	37	20	36
2	Pd[Ferrocene **2**]Cl_2	6	22	16	4
3	Davephos **3** + $Pd_2(dba)_3$	69	28	47	29
4	Xphos **4** + $Pd_2(dba)_3$	71	26	65	26
5	Binapthyl **5** + $Pd_2(dba)_3$	99[c]	71	76	46
6	RuPhos **6** + $Pd_2(dba)_3$	43	11	44	12
7	Pd[AmPhos **7**]Cl_2	21	21	14	21
8	Adamantane **8** + $Pd_2(dba)_3$	25	36	27	40
9	Pyrazole **9** + $Pd_2(dba)_3$	23	34	20	36
10[c]	Bippyphos **10** + $Pd_2(dba)_3$	>99	>99	>99	>99
11[c]	Bippyphos **10** + $Pd(OAc)_2$	31	5	19	4

[a] Reaction conditions: 2 mol % of preformed catalyst (entries 2 and 7 available from Johnson Matthey as Pd complex) or 4 mol % of ligand + 1 mol % of $Pd_2(dba)_3$, 1.2 equiv of aryl halide, 1.0 equiv of urea, 1.5 equiv of K_3PO_4, 85 °C and 20 h. [b] Conversion determined by HPLC versus isolated characterized products. Ratio of ((desired)/(SM + desired)). [c] >99% conversion at 2 h.

As an initial probe into the viability of such a urea coupling approach, a series of ligands were screened (Table 1 and Figure 2). Phenylurea was used as one of the coupling partners, as the conversion could be easily monitored by HPLC. Bromo toluenes and anisoles were selected as the benchmark screening compounds as these substrates had

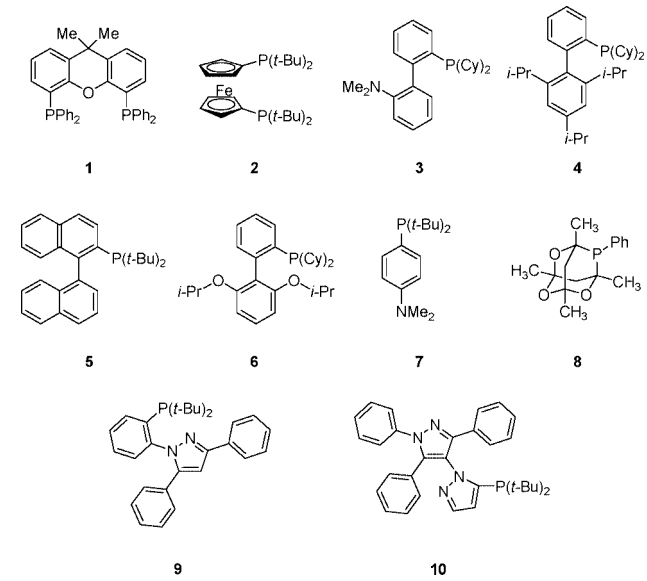


Figure 2. Ligands for urea arylation.

failed to couple with urea under previously reported conditions.[8] Additionally the 4-chlorotoluene and 4-chloroanisole were selected to screen the more attractive chloride couplings.

Earlier reports indicated the reactions of ureas with aryl bromides were catalyzed by palladium complexes of Xantphos.[7,8] In our hands the catalyst generated from bidentate ligand Xantphos **1** + $Pd_2(dba)_3$ (entry 1) gave moderate conversion of 4-bromotoluene and 4-bromoanisole to their respective coupled products. In the case of 4-bromotoluene, biarylmonodentate ligands gave higher conversions (entries 3−6); however, these biaryl ligands are proprietary and their use in further drug development efforts may be encumbered. A search for nonproprietary ligands (entries 7−10) led to the screening of several monodentate phosphine ligands. We found that the recently reported ligand bippyphos **10**[13] + $Pd_2(dba)_3$ resulted in high activity for the coupling (entry 10). In the case of 4-bromoanisole, binapthyl **5** + $Pd_2(dba)_3$ (entry 5) as well as bippyphos **10** + $Pd_2(dba)_3$ (entry 10) gave high conversions. With both 4-bromotoluene and 4-bromoanisole, the bipyphos **10** + $Pd_2(dba)_3$ was significantly better and resulted in complete conversion in only 2 h.

Buoyed by the ease of reaction observed for the unactivated aryl bromides, we anticipated that even aryl chlorides may also be suitable coupling partners for ureas under our experimental conditions. Indeed, both 4-chlorotoluene and 4-chloroanisole with bippyphos **10** + $Pd_2(dba)_3$ (entry 10) gave as high conversions as observed for the reactions of aryl bromides. We then focused our subsequent optimization and development efforts around the bippyphos ligand **10** with aryl chlorides.

The metal precursor as well as the order of addition of ligand and reagents were important for the success of the coupling

(10) McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3311.

(11) Willis, M. C.; Snell, R. H.; Fletcher, A. J.; Woodward, R. L. *Org. Lett.* **2006**, *8*, 5089.

(12) *N*-Aryl urea prep. : Lukin, K. A.; Hsu, M. C.; Fernando, D. P.; Kotecki, B. J.; Leanna, M. R. U.S. Pat. Appl. US2007244178.

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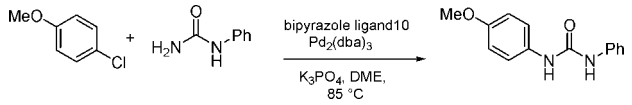
Table 2. Ligand/Metal Ratio and Catalyst Load Effects[a]

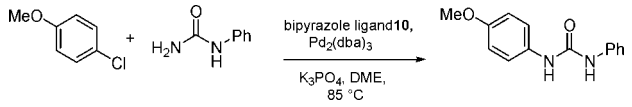


entry	cat. load (mol %)	ligand/metal ratio	conversion[b] at 2 h	conversion[b] at 20 h
1	0.50	2.5to1	76	96
2	0.50	0.8to1	77	95
3	0.25	2.5to1	57	71
4	0.25	2.0to1	57	69
5	0.25	1.2to1	55	66
6	0.25	1.0to1	50	61
7	0.25	0.8to1	46	55

[a] Reaction condition: 1.2 equiv of aryl halide, 1.0 equiv of urea, 1.5 equiv of K_3PO_4, DME, 80 °C. [b] Conversion determined by HPLC versus isolated characterized products. Ratio of ((desired)/(SM + desired)).

reactions. The combination of bippyphos ligand **10** with $Pd_2(dba)_3$ showed higher reactivity (Table 1, entry 10) than bippyphos ligand **10** with $Pd(OAc)_2$ (Table 1, entry 11).[14] The combination of metal, ligand, base, urea, and aryl halide followed then by addition of the solvent and heating afforded variable reaction rates. However, the combination of metal, ligand, base, and the urea followed by addition of solvent and a complexation period,[15] followed then by addition of aryl halide and heating resulted in consistent reaction rates.

Table 3. Base Effects[a]



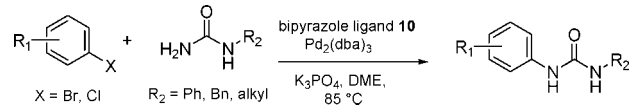
entry	base	conversion[b] at 2 h	conversion[b] at 20 h
1	NaOtBu	57	73
2	K_3PO_4	64	90
3	Cs_2CO_3	67	85
4	K_2CO_3 [d]	92	>99
5	Na_2CO_3	6	20
6	K_2HPO_4	8	17
7	$NaHCO_3$[d]	6	23
8	KOAc	12	14
9	K_3PO_4, milled[c]	>99	>99

[a] Reaction condition: 2 mol % of bippyphos ligand **10**, 0.5 mol % of $Pd_2(dba)_3$, 1.2 equiv of aryl halide, 1.0 equiv of urea, 1.5 equiv of base, DME, and 85 °C. [b] Conversion determined by HPLC versus isolated characterized products. Ratio of ((desired)/(SM + desired)). [c] Milled to mesh size 16. [d] Powdered (available from Aldrich 59,068-1 and 45,161-4)

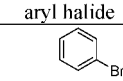
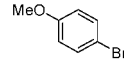
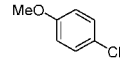
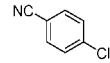
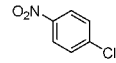
The effect of catalyst loading and the ligand/metal ratio was probed (Table 2). Catalyst loads of 0.5 mol % were typically required to achieve quantitative conversion with

(14) 2 mol % of $Pd(OAc)_2$ complexed with 4 mol % of bippyphos **10**. The 20 h time point indicated 97%, 91%, >99%, and 50%, respectively.

Table 4. Coupling of Aryl Halides with Ureas[a]



X = Br, Cl; R_2 = Ph, Bn, alkyl

entry	aryl halide	R_2	conversion[h] (time (h))	assay yield[d] (%)	isolated yield[f] (%)
1		Ph	>99% (1)	92[e]	92
2		Ph	>99% (1)	92	90
3		Ph	>99% (1)	89	83
4		Ph	>99% (2)	90[e]	90
5		Ph	>99% (1)	86	81
6		Ph	>99% (1)	84	81
7		Ph	>99% (1)	96	86
8		Ph	>99% (2)	96	93
9		Ph	>99% (1)	95	95
10		Ph	29% (20)	--	--
11		Bn	>99% (1)	88	82
12		c-hex	94%[c] (2)	100	87
13		Bu	93%[c] (2)	100	73
14		Ph	86% (20)	58	48[g]
15		Ph	>99% (20)	92	80[g]
16		Ph	38% (20)	36	23[g]

[a] Reaction condition: 4 mol % of bippyphos ligand **10**, 1 mol % of $Pd_2(dba)_3$, 1.1 equiv of aryl halide, 1.0 equiv of urea, and 1.5 equiv of K_3PO_4, 85 °C. [b] Conversion determined by HPLC versus isolated characterized products. Ratio of ((desired)/(urea SM + desired)). [c] Ratio of ((desired/(aryl halide SM)). [d] Solution assay yield utilizing HPLC assay vs isolated product purified by crystallization. [e] Compared to commercially available materials. [f] Isolated yields after crystallization from methanol/water; the products contain up to 3 mol % of bippyphos ligand **10**. Products can be further purified by crystallization/trituration to obtain analytical standards as indicated in the Supporting Information. [g] Product isolated by chromatography.

most substrates (entry 1 and 2). The use of lower catalyst loadings resulted in incomplete reactions (entries 3−7). Ligand to metal ratios ranging between 2.5 to 1 had no significant impact on the apparent reaction rate as indicated by similar conversions at 20 h (entries 3−6). This may suggest bidentate coordination of the bippyphos **10** with metal.[16] Although in our subsequent studies we use a 2 to 1

ratio of ligand to metal, comparable conversions can also be obtained by using a 1 to 1 ratio of ligand to metal.

The effect of different bases on the reaction conversion was investigated (Table 3). The use of the stronger base NaOtBu (entry 1) resulted in degradation and/or disproportionation of the ureas especially when higher temperatures (>90 °C) were used. The use of K_3PO_4, Cs_2CO_3, and K_2CO_3 (entries 2−4) gave conversions >85%. Weaker bases such as Na_2CO_3, K_2HPO_4, $NaHCO_3$, and KOAc (entries 5−8) led to less than 25% conversion. The heterogeneous bases performed better when particle size was reduced by milling or grinding. The highest conversion rate was with milled[17] K_3PO_4 (entry 9) and it was used in subsequent process optimization efforts.

No optimization of solvent was conducted. The use of DME was used as a substitute for dioxane, which was used in the activated aryl bromide couplings previously cited.[7,8]

After the refinement of several of the reaction parameters, we looked to establish the scope of the new method (Table 4). High yields were observed for the reactions of bromobenzene (entry 1) as well as the previously problematic[8] substrates 4-bromotoluene and 4-bromoanisole (entries 2 and 3). Gratifyingly, the unprecidented coupling of urea with chlorobenzene afforded the coupled product in 90% yield (entry 4). High yields were also obtained in the reactions of aryl chlorides with an electron donating group such as 4-chlorotoluene and 4-chloroanisole (entries 5 and 6). Furthermore, the coupling of urea with aryl chlorides was possible in the presence of functional groups such as nitrile (entry 7) and electron-withdrawing nitro (entry 8).

A notable limitation of these reaction conditions is that sterically hindered aryl halides resulted in lower conversions. Moderately sterically hindered aryl chloride (entry 9) afforded the product in high yield, sterically hindered 1-chloro-2,6-dimethylbenzene (entry 10) results in 29% HPLC conversion and was not isolated. In this case the slow reaction time resulted in disproportionation of product, yielding *N*,*N*′-diarylurea and *N*,*N*′-diphenylurea. The formation of these byproduct was also noticed earlier[7] in the case of reactions catalyzed by Xantphos or in the abscense of any catalyst.

The reaction could also be extended to achieve the coupling of aryl chlorides with alkyl ureas such as benzyl, cyclohexyl, and *n*-butyl ureas (entries 11−13). Coupling reactions with pyridyl halides also proceeded efficiently (Table 4, entries 13−15). Not only the couplings of 2-chloropyridines (entry 14) were possible, but also the couplings of more challenging 3-chloropyridines[9] was achieved with 80% yield (entry 15). Unfortunately the reaction of 4-chloropyridine (entry 16) with phenyl urea led to poor conversion and lower isolated yields (entry 16).

We have developed a practical, general, and highly efficient method for the preparation of aryl ureas. The use of a combination of bippyphos ligand **10** with $Pd_2(dba)_3$ offers a relatively inexpensive, nonproprietary ligand system with high reactivity, that enables the coupling of ureas with not only aryl bromides but also aryl and heteroaryl chlorides. We intend to further explore the scope of reaction and the mechanistic detail to elicit a better understanding of the reaction pathway.

Supporting Information Available: Experimental procedures and full characterization for all isolated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) During the complexation period, a noticable color change from purple to amber was observed. Comparable performance was achieved by stirring the catalyst mixture for as little as 15 min to as long as 1 h at ambient temperature. Complexation at 50 °C for between 5 and 60 min also proved effective.

(16) Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *Organometallics* **2007**, *26*, 2183. The metal coordination to bippyphos will be a focus of future investigations.

(17) Milled to mesh size 16.