

N-Phenylurea as an inexpensive and efficient ligand for Pd-catalyzed Heck and room-temperature Suzuki reactions

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Abstract—*N*-Phenylurea was found to constitute a highly efficient, yet low-priced, phosphine-free ligand for the Pd-catalyzed Heck and room-temperature Suzuki reactions of aryl bromides and iodides with very high turnover numbers (ca. 10^3 – 10^4).
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Reactions leading to the formation of C–C bonds are central to the synthesis of complex organic molecules. The potent utility of Pd-catalyzed transformations (such as Heck and Suzuki reactions) in this regard has assured their place at the forefront of modern synthetic technologies.¹ These transformations, normally performed with 1–5 mol % of Pd catalyst along with phosphine ligands, have already been widely utilized in the academic institutions. However, industrial applications of these transformations are still rare, mainly due to the following two problems.² First, Pd is expensive, and contamination of the product by Pd has to be tightly controlled. Second, many phosphine ligands are even more expensive, and they are not pleasant to work with as they are poisonous, air sensitive, and prone to degrade at elevated temperatures. Accordingly, one of the current challenges in the field is the development of high turnover-number catalysts (HTC) that utilize inexpensive, preferentially nonphosphine, ligands.

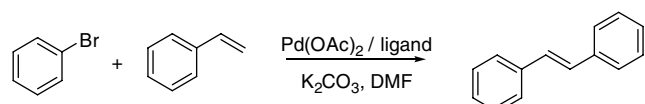
To meet the challenge, a number of phosphine-free catalysts have been examined for the Heck and Suzuki reactions. Previously studied ligands include heterocyclic carbenes,³ oxazolines,⁴ Schiff bases,⁵ diazabutadienes,⁶ pyridines,⁷ hydrazones,⁸ pyrazoles,⁹ phenanthrolines,¹⁰ guanidines,¹¹ quinolines,¹² carbazones,¹³ tetrazoles,¹⁴ imidazoles,¹⁵ amino acids,¹⁶ amines,¹⁷ thioureas,¹⁸ and surfactants.¹⁹ Here we report that *N*-phenylurea can also constitute a highly efficient, yet a low-priced, ligand for the Pd-catalyzed Heck and Suzuki

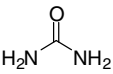
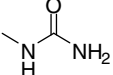
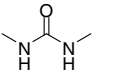
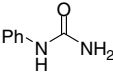
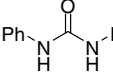
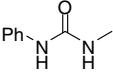
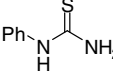
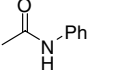
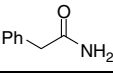
reactions. Compared to many of the previous phosphine-free ligands,^{3–19} an important advantage associated with the *N*-phenylurea ligand is that the catalyzed reactions enjoy very high turnover numbers (ca. 10^3 – 10^4). Moreover, equipped with the *N*-phenylurea ligand we have achieved room-temperature Suzuki reactions, which were accomplished previously either by using complicated phosphine or heterocyclic carbene ligands,²⁰ or by using a relatively high load of Pd (i.e., >1 mol %).²¹

To begin our study, we examined the Heck reaction between bromobenzene and styrene in the absence or presence of ureas (Table 1). It was found that without any ligand the yield of the Heck reaction was as low as 15% after 10 h (entry 1). The addition of un-substituted urea dramatically increased the yield to 73% (entry 2). The addition of *N*-methylurea also increased the yield to 70% (entry 3). Nonetheless, it was found that *N,N'*-dimethylurea was not effective because its corresponding yield was only 8% (entry 4). Surprisingly, we next found that *N*-phenylurea was considerably more active than the un-substituted urea in facilitating the Heck reaction. A nearly quantitative conversion of the starting material to the desired product could be achieved in only 2 h in the presence of *N*-phenylurea (entry 5). Compared to *N*-phenylurea, *N,N'*-diphenylurea, and *N*-phenyl-*N'*-methylurea were not as effective because they required a longer reaction time and their corresponding yields were lower (entries 6–7).

It is worth mentioning that previously Yao et al. reported that Pd(OAc)₂ by itself could effect the Heck reaction at 140 °C after a fairly long reaction time

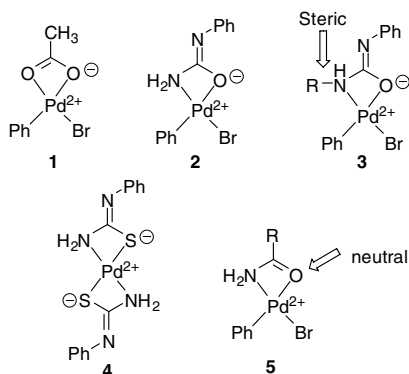
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Table 1. Heck reaction between bromobenzene and styrene^a


Entry	Ligand	Time (h)	GC yield (%)
1	—	10	15
2		10	73
3		10	70
4		10	8
5		2	99
6		10	68
7		10	92
8		10	0
9		10	32
10		10	88

^a Conditions: bromobenzene (0.5 mmol), styrene (0.75 mmol), K₂CO₃ (1 mmol), Pd(OAc)₂ (0.1 mol %), Pd(OAc)₂:ligand = 1:2, DMF (1 mL), 130 °C, under Ar.

(ca. 20–40 h).²² They proposed a mechanism in which the acetate anion acted as a ligand in the rate-determining oxidative-addition step (see **1** in Fig. 1). Compared to Yao's mechanism, it appears that the dramatic effect of *N*-phenylurea is due to the formation of *N,O*-bidentate complex (**2**), in which one of the N–H bond is

**Figure 1.** Proposed Pd intermediates in the catalysis.

deprotonated. This mechanism appears to be consistent with the observation that *N*-methylurea is less effective, because *N*-methylurea is less acidic than *N*-phenylurea by about 5 p*K*_a units.²³ This mechanism may also explain why an additional substituent group on urea decreases the activity because it can cause a steric hindrance in the Pd complex (**3**).

Further experiment revealed that *N*-phenylthiourea completely hampered the Heck reaction (entry 8 in Table 1). This can be explained by the possible formation of a highly stable bis-complex (**4**) due to the strongly-coordinating sulfur atom. Moreover, it was interesting to find that *N*-phenylacetamide and 2-phenylacetamide could also facilitate the Heck reaction, albeit with much less efficiency (entries 9–10). This finding may be explained by the fact that the oxygen in the amide complex (**5**) is neutral, and thereby not effective in stabilizing the cationic Pd intermediate.

Thus, the above results demonstrated that *N*-phenylurea was an efficient, yet inexpensive ligand for the Pd-catalyzed Heck reaction. The addition of *N*-phenylurea not only significantly increased the yield, but also dramatically reduced the reaction time. In order to examine the scope of the *N*-phenylurea mediated Heck reaction, we next performed the Heck reactions between a variety of aryl halide and two representative olefins, namely, styrene and butyl acrylate (Table 2). It was found that both the electron-rich (deactivated) and electron-poor (activated) aryl bromides could be efficiently converted to the desirable products in high yields. The TONs in most of the cases were about 10³, except for 2-bromopyridine where almost no reaction was observed. A possible problem for 2-bromopyridine is that the pyridine nitrogen coordinates to Pd strongly and slows down the turnovers. Besides aryl bromides, aryl iodides could also be successfully used under the same reaction conditions. Nonetheless, Pd/*N*-phenylurea was not active enough to handle an aryl chloride unless it was activated by electron-withdrawing substituents (such as 4-NO₂).

Having demonstrated that Pd/*N*-phenylurea provided excellent conditions for the Heck reactions of various aryl bromides and iodides, we next examined whether *N*-phenylurea could also facilitate the Suzuki reactions. To our great satisfaction, it was found that *N*-phenylurea was active enough to promote the Suzuki reactions at room-temperature (Table 3). Both electron-rich and electron-poor aryl bromides could be successfully converted to the desired product very rapidly (ca. 1–6 h) at room-temperature. The reaction also tolerated both the electron-rich (e.g., 4-MeO-C₆H₄-B(OH)₂) and electron-poor (e.g., 4-MeOC-C₆H₄-B(OH)₂) arylboronic acids. Only 0.01 mol % of Pd was needed and therefore, the turnover numbers were as high as 10⁴. Furthermore, aryl iodides were excellent substrates for the reaction, although aryl chlorides could not be converted effectively. It is worth noting that the room-temperature Suzuki reactions were achieved previously either by using expensive phosphine or heterocyclic carbene ligands,²⁰ or by using a relatively high load of Pd (i.e., >1 mol %).²¹ In comparison, the novel conditions

Table 2. Heck-type reactions between aryl halides and olefins facilitated by the *N*-phenylurea ligand^a






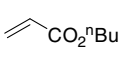
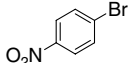

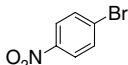
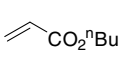



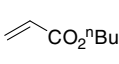
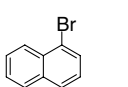
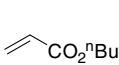
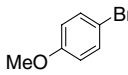

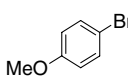
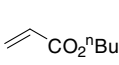
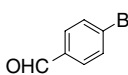

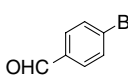
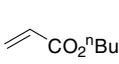
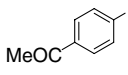

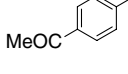
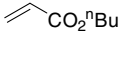
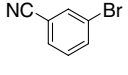

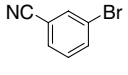
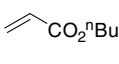
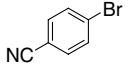

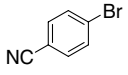
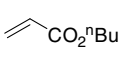
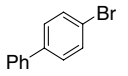

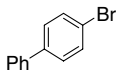
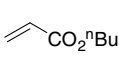
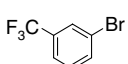

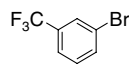
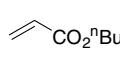



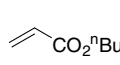



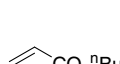



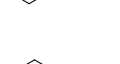
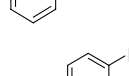

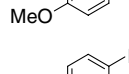
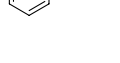
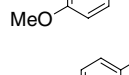

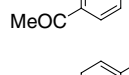
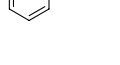


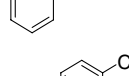

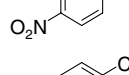
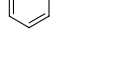
Ar-X + 		Pd(OAc) ₂ (0.1 mol%), 1-phenylurea (0.2 mol%) K ₂ CO ₃ , DMF, 130 °C		Ar- 	
Entry	ArX	R	Time (h)	Yield ^b (%)	
1			2	98	
2			2	99	
3			2	81	
4			2	98	
5			2	85	
6			2	97	
7			2	98	
8 ^c			2	96	
9 ^c			2	99	
10			2	97	
11			2	98	
12			2	97	
13			2	80	
14			2	97	
15			2	93	
16			2	96	
17			2	91	
18			2	86	
19			2	92	
20			2	95	

Table 2 (continued)

Entry	ArX	R	Time (h)	Yield ^b (%)	
21			2	93	
22			20	0	
23			20	<5	
24			2	93	
25			2	98	
26			4	75	
27			2	99	
28			6	84	
29			4	93	
30			2	97	
31			2	99	
32			20	0	
33			20	81	
34			2	90	

^a Conditions: aryl halide (0.5 mmol), olefin (0.75 mmol), K₂CO₃ (1 mmol), DMF (1 mL), under Ar.

^b Isolated yield.

^c In these two reactions, 1 mol % of TBAB was used as the additive.

described here are evidently advantageous from the economic point of view.

To conclude, in the present study we reported an interesting finding that *N*-phenylurea was a highly efficient, yet simple and inexpensive, phosphine-free ligand for the Pd-catalyzed Heck and room-temperature Suzuki reactions of aryl bromide and iodides.^{24,25} Due to the high turnover numbers and mild conditions of the *N*-phenylurea facilitated reactions, we believed that the reaction conditions described here should be both operationally simple and economically competitive in practice. Moreover, the present finding raised interesting

Table 3. Suzuki reactions facilitated by the *N*-phenylurea ligand^a


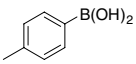

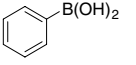

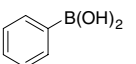

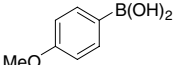
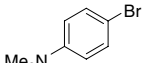
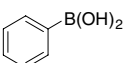
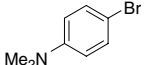
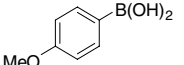

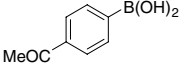

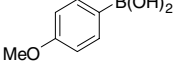

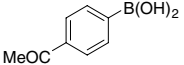

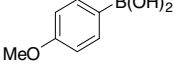

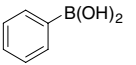

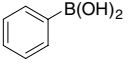

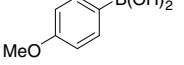

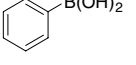

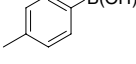

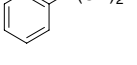

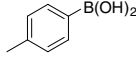
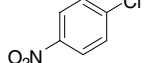
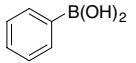
$\text{Ar-X} + \text{R-B(OH)}_2 \xrightarrow[\text{K}_2\text{CO}_3, \text{EtOH/H}_2\text{O}(1:1), \text{r.t.}]{\text{Pd(OAc)}_2 (0.01 \text{ mol}\%), \text{1-phenylurea} (0.02 \text{ mol}\%)} \text{Ar-R}$				
Entry	ArX	R	Time (h)	Yield ^b (%)
1			2	99
2			2	97
3			4	95
4			2	98
5			24	89
6			2	99
7			2	94
8			2	98
9			6	93
10			1	98
11			1	99
12			2	98
13			2	96
14			2	96
15			4	95
16			6	91

Table 3 (continued)

Entry	ArX	R	Time (h)	Yield ^b (%)
17			24	<5
18			24	<5

^a Conditions: aryl halide (5 mmol), arylboronic acid (7.5 mmol), K₂CO₃ (10 mmol), ethanol (7.5 mL), H₂O (7.5 mL), under air.

^b Isolated yield.

questions as to the mechanism and further optimization of urea-based ligands for transition metals. Studies in this regards are actively pursued in our laboratory and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2006.10.124](https://doi.org/10.1016/j.tetlet.2006.10.124).

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24. *Typical experimental procedure for the Heck reaction:* A mixture of phenyl bromide (0.5 mmol, 0.053 mL), styrene (0.75 mmol, 0.087 mL), Pd(OAc)₂ (0.5 × 10⁻³ mmol, 0.11 mg), phenylurea (10⁻³ mmol, 0.14 mg), and K₂CO₃ (1 mmol, 0.138 g) in 1 mL of dry DMF was stirred under Ar at 130 °C for 2 h. After the mixture was washed by water, extracted by ether and condensed, the residue was purified by flash column chromatography (hexane) to afford *trans*-stilbene (89.3 mg, 99%).
25. *Typical experimental procedure for the Suzuki reaction:* A mixture of *p*-methylphenyl bromide (5 mmol, 0.615 mL), phenyl boronic acid (7.5 mmol, 0.915 g), Pd(OAc)₂ (0.5 × 10⁻³ mmol, 0.11 mg), phenylurea (10⁻³ mmol, 0.14 mg), and K₂CO₃ (10 mmol, 1.38 g) in methanol/H₂O (7.5 mL/7.5 mL) was stirred at room-temperature for 2 h. After the mixture was washed by water, extracted by ether and condensed, the residue was purified by flash column chromatography (hexane) to afford biphenyl (75.9 mg, 99%).