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Pd-Catalyzed Cross-Coupling Reactions of Amides and Aryl Mesylates

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Abstract

A catalyst, based on a biarylphosphine ligand, for the Pd-catalyzed cross-coupling reactions of amides and aryl mesylates is described. This system allows an array of aryl and heteroaryl mesylates to be transformed into the corresponding *N*-aryl amides in moderate to excellent yields.

Due to the ubiquity of *N*-aryl amides in biologically active molecules the development of efficient methods for their synthesis has been an active area of research for many years. The Goldberg-modified Ullman reaction was the first cross-coupling protocol to synthesize these compounds effectively from aryl iodides and amides using a stoichiometric quantity of copper.² The utilization of diamines as supporting ligands in these reactions has recently allowed the use of catalytic quantities of copper, as well as extended the scope of these processes to include aryl bromides.³ Pd catalysts based on phosphine ligands have also been developed for these transformations. These systems have enabled the coupling of amides with aryl bromides,⁴ chlorides,⁵ triflates,⁶ and tosylates.⁷

Although an array of aryl halides/pseudohalides have been employed in these reactions, there have been no reports of a catalyst system that can effectively couple amides with aryl mesylates. Aryl mesylates are attractive substrates because their use is more atom-economical than that of aryl tosylates. Additionally, they are less expensive and more stable than aryl triflates.⁸

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Supporting Information Available. Procedural and spectral data is available free of charge via <http://pubs.acs.org>.

Because of this, interest in aryl mesylates as substrates has increased, and there have been several reports of catalyst systems that allow their utilization in both C–N⁹ and C–C¹⁰ cross coupling processes.

Herein, we report the first Pd-catalyzed amidation of aryl mesylates. The use of a highly active catalyst system, based on ligand **1**, allows these reactions to proceed in good to excellent yields using a diverse array of coupling partners as substrates.

We started our studies by examining a catalyst comprised of ligand **1** (Figure 1), which we have previously shown to be effective for the coupling of amides with aryl chlorides.^{5a} We began with the reaction of benzamide and 4-*tert*-butylphenyl methanesulfonate using various Pd sources, bases, and solvents. By utilizing our water-mediated catalyst preactivation protocol¹¹ with 1 mol % Pd(OAc)₂, 2.2 mol % **1**, and Cs₂CO₃ in *t*-BuOH the reaction gave a 99% yield (GC) after 1 h at 110 °C (Table 1, entry 1). In contrast, using Pd(OAc)₂ without preactivation or other Pd(II) sources [i.e., (H₃CCN)₂PdCl₂, (PhCN)₂PdCl₂, or Pd(TFA)₂] only trace product was observed (Table 1, entries 2 – 5). These results emphasize the importance of efficiently forming the active catalyst in these reactions. Further, when [(allyl)PdCl]₂ was used, which can be reduced via a nucleophile,¹² a yield of 89% was obtained; this is only minimally less efficient than the conventional preactivation protocol (Table 1, entry 6). Employing Pd(0) sources in this reaction, such as Pd₂(dba)₃ or Pd(dba)₂, resulted in a marked loss in activity (Table 1, entries 7 and 8). Therefore, dba plays a non-innocent role in this particular reaction, which hinders catalysis.¹³ When the reactions were run in the presence of K₃PO₄ or K₂CO₃, instead of Cs₂CO₃, reduced yields of 69% and 39% were obtained, respectively (Table 1, entries 9 and 10). Moreover, the use of other solvents that are commonly used in C–N cross-coupling reactions, such as dioxane, toluene, DME, or DMF, lead to little or no product formation when used in place of *t*-BuOH for these transformations (Table 1, entries 11 – 14).

With optimized reaction conditions in hand we set out to compare **1** to other biarylphosphine ligands that have previously been employed in Pd-catalyzed C–N cross-coupling reactions (Figure 2). By switching to a catalyst comprised of **2**, the dicyclohexylphosphino analogue of **1**, for the reaction of benzamide and 4-*tert*-butylphenyl methanesulfonate a slightly reduced yield of 84% was obtained. This result was expected on the basis of earlier reports that **2** formed an active catalyst for both C–N and Suzuki–Miyaura cross-coupling reactions using aryl mesylates.^{9b,10b} It is also consistent with our prior finding that **1** was a more efficient ligand for the Pd-catalyzed cross-coupling of amides and aryl chlorides than **2**.^{5a} Employing ligand **3**, which has been used for amidation reactions of aryl tosylates,^{7b} led to only trace product formation. This illustrates the large differences in reactivity between aryl tosylates and mesylates in cross-coupling reactions. Further, substituting the 3-methoxy substituent in **1** for a hydrogen or a methyl group (ligands **4** and **5**) resulted in a drop in yield, demonstrating the influence that the substituent in the 3-position of the ligand has on the productivity of the catalyst.

The scope of this reaction using a catalyst system based on **1** was next explored. Both electron-neutral and electron-rich aryl mesylates were transformed into the desired *N*-arylamides in excellent yields with reaction times of less than 4 hours (Table 2, entries 1 – 5). Further, moderately electron-deficient aryl mesylates proved to be highly efficient coupling partners in these reactions (Table 2, entries 6 and 7). For example, the reaction of 3-methoxyphenyl methanesulfonate and benzamide resulted in a nearly quantitative yield in only 20 minutes. An *ortho* methoxy on the aryl mesylate was well tolerated (Table 2, entry 5); however, when the size of the *ortho* substituent was increased (e.g., methyl) the reactions did not proceed.

On the basis of these promising results we set out to investigate more challenging substrates containing heterocycles. Using a catalyst comprised of **1**, amides consisting of heterocycles, such as 2-furamide, nicotinamide or isonicotinamide, were coupled in good to excellent yields with several different aryl mesylates (Table 3, entries 1 – 4). When an aryl mesylate that contained a non-nucleophilic heterocycle [i.e., 4-(1*H*-pyrrol-1-yl)phenyl methanesulfonate] was employed the reaction gave a 94% yield (Table 3, entry 5). However, when heteroaryl mesylates containing nucleophilic groups were used, the yields of product were considerably diminished and significant amounts of phenol formation were observed (Table 3, entries 6 and 7). For example, the coupling of 6-quinolinyl methanesulfonate and isobutyramide yielded only 37% of the desired product. We postulated that the heterocycles could be promoting phenol formation in two ways. First, the aryl mesylates containing these heterocycles are more electron-deficient, which could accelerate sulfonyl transfer. This is consistent with the observation that when the electron-deficient ethyl 3-[(methylsulfonyl)oxy]-benzoate was employed as a substrate a diminished yield of 67% was obtained (Table 3, entry 4). Second, the heterocycles could be acting as nucleophilic catalysts, assisting in desulfonylation. In support of this hypothesis, when 2-methyl-6-quinolinyl methanesulfonate was used as the substrate, which should be less nucleophilic than 6-quinolinyl methanesulfonate, the yield of the desired product was increased to 58% (Table 3, entry 8).

In summary, we have developed a catalyst, based on ligand **1**, for Pd-catalyzed amidation reactions using aryl mesylates. This system allows the coupling of electron-rich, -neutral, and -deficient aryl mesylates in good to excellent yields. Further, benzamides, aliphatic amides, and heterocyclic amides all proved to be excellent coupling partners using our new method. Finally, heteroaryl mesylates were also successfully employed in these reactions, albeit with lower yields than other substrates. Further studies to extend the scope of these reactions to include secondary amides are currently underway in our laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Biarylphosphine ligands.

Figure 2.
Ligand comparison for the Pd-catalyzed amidation of aryl mesylates.

Table 1Optimization of the Pd-Catalyzed Cross-Coupling of Amides and Aryl Mesylates.^a

entry	Pd source	base	solvent	GC yield
1	Pd(OAc) ₂ /H ₂ O Act	Cs ₂ CO ₃	<i>t</i> -BuOH	99%
2	Pd(OAc) ₂	Cs ₂ CO ₂	<i>t</i> -BuOH	1%
3	(H ₂ CCN) ₂ PdCl ₂	Cs ₂ CO ₃	<i>t</i> -BuOH	1%
4	(PhCN) ₂ PdCl ₂	Cs ₂ CO ₃	<i>t</i> -BuOH	1%
5	Pd(TFA) ₂	Cs ₂ CO ₂	<i>t</i> -BuOH	0%
6	[(allyl)PdCl] ₂	Cs ₂ CO ₂	<i>t</i> -BuOH	89%
7	Pd ₂ (dba) ₃	Cs ₂ CO ₂	<i>t</i> -BuOH	1%
8	Pd(dba) ₂	Cs ₂ CO ₂	<i>t</i> -BuOH	1%
9	Pd(OAc) ₂ /H ₂ O Act	K ₃ PO ₄	<i>t</i> -BuOH	64%
10	Pd(OAc) ₂ /H ₂ O Act	K ₂ CO ₃	<i>t</i> -BuOH	39%
11	Pd(OAc) ₂ /H ₂ O Act	Cs ₂ CO ₃	Dioxane	0%
12	Pd(OAc) ₂ /H ₂ O Act	Cs ₂ CO ₃	Toluene	1%
13	Pd(OAc) ₂ /H ₂ O Act	Cs ₂ CO ₃	DME	2%
14	Pd(OAc) ₂ /H ₂ O Act	Cs ₂ CO ₃	DMF	1%

^(a) Reaction conditions: ArOMs (1.0 mmol), benzamide (1.4 mmol), Pd (1 mol %), **1** (2.2 mol %), base (1.4 mmol), solvent (2 mL/mmol), 110 °C, 1 h.

product	time	yield ^b
1 h	90%

product	time	yield ^b
1 h	94%

product	time	yield ^b
2 h	97%
2h	94%

product	time	yield ^b
4 h	92%

product	time	yield ^b
	20 min	99%

product	time	yield ^b
	14 min	93%

product	time	yield ^b
	4 h	87%

amide	product	time	yield ^b
$ \begin{array}{c} \text{R}^1 \\ \\ \text{C(=O)} \\ \\ \text{NH} \\ \\ \text{C}_6\text{H}_4 \\ \\ \text{R}^2 \end{array} $ Reagents: 1 mol % Pd(OAc) ₂ , 2.2 mol % 1 , 8 mol % H ₂ O, t-BuOH, Cs ₂ CO ₃ , 110 °C		4 h	99%
1 h	96%

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product	time	yield ^b
45 min	67%
4 h	91%

side	product	time	yield ^b
24 h	29%

side	product	time	yield ^b
6 h	37%

side	product	time	yield ^b
6 h	58%