

## A Multiligand Based Pd Catalyst for C–N Cross-Coupling Reactions

Brett P. Fors and Stephen L. Buchwald\*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

Received September 7, 2010; E-mail: sbuchwal@mit.edu

**Abstract:** An alternative approach to catalyst development, which led to a Pd catalyst based on two biarylphosphine ligands for C–N cross-coupling reactions, is reported. By effectively being able to take the form of multiple catalysts this system manifests the best properties that catalysts based on either of the two ligands exhibit separately and displays the highest reactivity and substrate scope of any system that has been reported to date for these reactions.

Palladium-catalyzed C–N cross-coupling reactions have become an important technology with widespread use across a variety of disciplines.<sup>1</sup> We have traditionally approached research in this field by identifying an interesting substrate class and then developing a catalytic system that efficiently couples these substrates. Because of this strategy there are currently a large number of catalysts for such processes,<sup>1b,2</sup> which often makes it difficult for the practitioner to decide what system to employ in a specific case. This can lead to a significant amount of effort spent screening various possibilities in order to find the optimum system. This is time-consuming and costly, especially for researchers using these reactions to make libraries of compounds (e.g., medicinal chemists).<sup>3</sup> On this basis, it has been a long-standing goal in our laboratory to find a single catalyst system that would work for all Pd-catalyzed amination reactions. To take a step toward this goal we elected to use an approach to catalyst development, where the focus was to find a catalyst, or catalyst mixture, that incorporates the best features displayed by some, if not all, of our previous systems. It is worth mentioning that different strategies utilizing catalysts based on multiple Pd sources or ligands have been exploited by others.<sup>4</sup> Herein, we disclose a Pd based catalyst comprised of two biarylphosphine ligands that allows for unparalleled substrate scope and reactivity in C–N cross-coupling reactions. This system not only encompasses the reactivity that each of the catalysts based on these two ligands possess separately but also transforms reactions that are inefficient for either of the two systems alone into high yielding processes. We anticipate this multiligand approach to catalyst design will be applicable to other cross-coupling methodologies and will enable the development of more comprehensive catalyst systems.<sup>5</sup>

We have reported that a catalyst based on BrettPhos (**1**)<sup>6</sup> works well for the monoarylation of primary amines but is inefficient for reactions involving secondary amines. Further, a catalyst based on RuPhos (**2**)<sup>7</sup> is highly efficient for the arylation of secondary amines

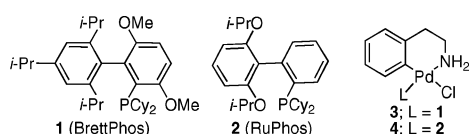


Figure 1. Biarylphosphine ligands and Pd precatalysts.

but is ineffective for cross-coupling reactions of primary amines and gives significant quantities of the undesired diarylation byproduct. Because these two catalysts are complementary we sought a system that would manifest the best properties that each possessed separately (Figure 1).

We began our studies by examining the coupling of 3-bromoanisole and morpholine. As expected, using 1 mol % of the precatalyst **4**, which is based on **2**, a 99% yield of the desired product was obtained after 10 min at 100 °C (Table 1a, entry 1). When this same reaction was run using a mixture of **1** and **4** as the catalyst full conversion to product was also observed after 10 min (Table 1a, entry 2). This demonstrated that **1** does not inhibit reactions of secondary amines when using a catalyst based on **2**. Next, by replacing **4** with precatalyst **3**, which is based on **1**, the yield of the reaction dropped to 17% (Table 1a, entry 3). This was anticipated, as it is well-known that a catalyst based on **1** is unproductive for the arylation of secondary amines. However, it was found that by using a mixture of **2** and **3** as the catalyst the yield was increased to 99%, showing that the efficiency of the reaction did not depend on which ligand began bound to the Pd as long as **2** was in the mixture (Table 1a, entry 4). This result was promising as it suggested that it was possible for a catalyst comprised of multiple ligands to display the same reactivity as a catalyst made up of a single ligand.

Table 1. Effect of Multiple Ligands on Pd-Catalyzed C–N Cross-Coupling Reactions

a)				b)				
Entry	Pd Source	Ligand	GC Yield (%) <sup>a</sup>	Entry	Pd Source	Ligand	Mono-/Diarylation	GC Yield (%) <sup>a</sup>
1	4	--	99	1	3	--	99:1	99
2	4	1	99	2	3	2	97:3	94
3	3	--	17	3	4	1	96:4	92
4	3	2	99	4	4	--	97:3	30
				5 <sup>b</sup>	4	--	89:11	77

<sup>a</sup> Reaction conditions: Pd source (1.0 mol %), ligand (1.0 mol %), 3-bromoanisole (1.0 equiv), amine (1.4 mmol), NaOt-Bu (1.4 mmol), 1,4-dioxane (1 mL/mmol), 100 °C for 10 min. <sup>b</sup> Reaction time of 4 h.

The results described above revealed that the presence of **1** did not affect the productivity of a catalyst based on **2** for the arylation of secondary amines. Of equal importance was that the presence of **2** does not have a deleterious effect on a reaction of a primary amine utilizing a catalyst based on **1**. The reaction of 3-bromoanisole and octylamine using the precatalyst, **3**, gave a 99% yield after 10 min at 100 °C with >99:1 selectivity for monoarylation to diarylation (Table 1b, entry 1). Performing the same reaction using a mixture of **2** and **3** as the catalyst provided a 94% yield of the desired product with an excellent selectivity of 97:3 for monoaryl-

ation/diarylation (Table 1b, entry 2). This indicated that **2** not only had little influence on the yield and rate of the reaction but also led to only minimal degradation in the selectivity for monoarylation. By substituting the combination of **2** and **3** with a mixture of **1** and **4** a nearly identical result was obtained for this transformation, again showing that the success of the process was not dependent on which ligand began bound to the Pd and suggesting that ligand exchange is rapid under the reaction conditions (Table 1b, entry 3). Further, based on the high selectivities observed for monoarylation using this mixed-ligand system we can conclude that the coupling of primary amines with a catalyst based on **1** is faster than the coupling of secondary *N*-aryl alkylamines with a catalyst based on **2**. It is worth noting that when the control reaction was carried out using **4** without any added **1** the yield of the reaction dropped to 30% (after 10 min) demonstrating that **1** had to be present for the catalyst to be effective (Table 1b, entry 4). Combined, these results show that a catalyst based on a mixture of **1** and **2** can take the form of either of the two catalysts and incorporates the best properties from each individual system allowing for the highly efficient arylation of both primary and secondary amines.

We next set out to explore the scope of the mixed-ligand catalyst system for C–N cross-coupling reactions (Table 2). Employing a 1:1 mixture of **2** and **3**, anilines were coupled with aryl chlorides, bromides, and iodides in good to excellent yields. Moreover, only ppm levels of Pd (0.005–0.01 mol %) were used for these reactions, demonstrating that the mixed-ligand system displayed the same catalyst activity and lifetime as the catalyst based solely on **1** for these reactions.<sup>6,7b</sup> A variety of primary aliphatic amines also proved to be excellent substrates using this catalyst system. For example, *n*-hexylamine was successfully combined with 2-chloro-*p*-xylene in 95% yield using only 0.05 mol % Pd. Further, the more sterically hindered branched aliphatic amine, 1-aminoadamantane, was arylated in 81% yield. These results prompted us to employ methylamine as a substrate. Methylamine is the smallest primary aliphatic amine and has typically been a difficult substrate to selectively monoarylate.<sup>6</sup> Utilizing the mixed-ligand system the reaction of methylamine and 4-*n*-butylchlorobenzene provided an 89% yield of the desired product with 98:2 selectivity of monoarylation to diarylation. Lastly, the reaction of a primary amide with 4-chloroanisole yielded the desired product in a nearly quan-

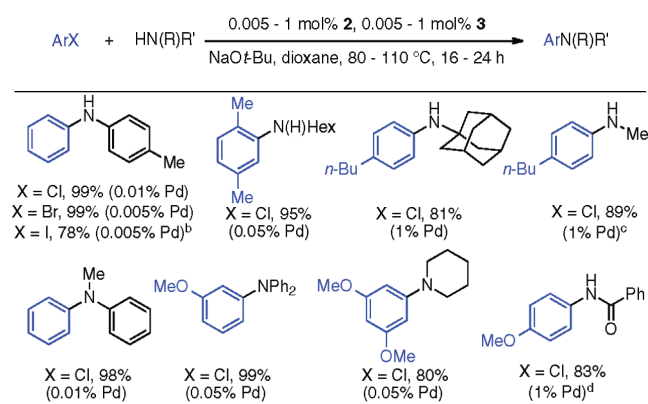
titative yield, further highlighting the diverse range of substrates that can be successfully coupled with this new catalyst system.<sup>8</sup>

The scope for the arylation of secondary amines was next investigated (Table 2). Utilizing the same combination of **2** and **3** as above, an array of secondary amines were successfully coupled with aryl halides. For example, *N*-methylaniline was arylated with chlorobenzene in 98% yield using only 0.01 mol % Pd, the same catalyst loading required when a catalyst based only on **2** is used. Additionally, a secondary diarylamine and a secondary aliphatic amine could be combined with aryl chlorides to give the desired products in good to excellent yields utilizing relatively low levels of Pd in both cases.

We next wanted to extend the scope of this catalyst system to heteroaryl substrates, as well as those containing base-sensitive functional groups (Table 3). Use of Cs<sub>2</sub>CO<sub>3</sub> as the base in *t*-BuOH allowed for substrates with esters, nitriles, ketones, and nitroaromatics to be converted to product in high yield. For example, under these conditions the reaction of ethyl 4-aminobenzoate and chlorobenzene gave a 98% yield of the desired product using only 0.1 mol % of the catalyst mixture. Additionally, this catalyst system allowed for the efficient coupling of an array of aminoheterocycles (i.e. aminopyrazine, aminopyrimidine, aminopyridine, amino-pyrazole, *N*-methylaminopyridine, furan-2-carboxamide), as well as heteroaryl halides all in excellent yields. These structural components are of particular importance because of their prevalence in pharmaceutically interesting molecules.

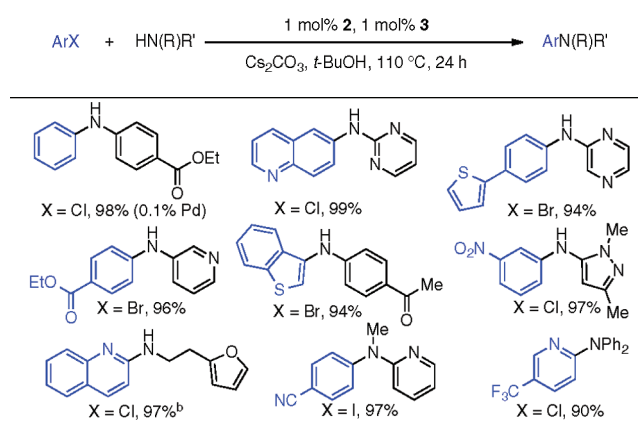
Although this new catalyst system has permitted greater substrate scope and reactivity for these reactions than any of our previous ones, we wanted to further broaden its generality by exploring transformations that could only be done efficiently with the catalyst mixture. We postulated that the synthesis of unsymmetrical triarylamines,<sup>4c,9</sup> which are commonly used in optoelectronic applications,<sup>10</sup> would be one case where the mixed-ligand system could be more effective than catalysts based on either of the two ligands separately. By utilizing the **2/3** combination and taking advantage of the innate relative reactivity of aryl halides we were able to selectively synthesize TPD, a hole transport agent, in 98% yield from simple starting materials in a single step using only 0.2 mol % Pd (Figure 2).<sup>10a</sup> This result corresponds to a 99.5% average yield for each of the four C–N couplings that have taken place.

**Table 2.** Cross-Coupling Reactions Using a Multiligand Based Pd Catalyst<sup>a</sup>

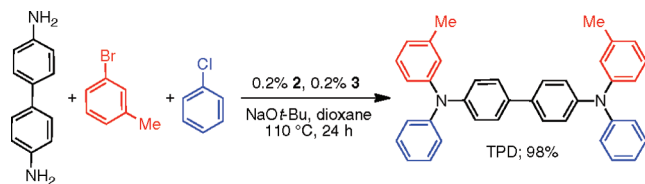


<sup>a</sup> Reaction conditions: **2** (0.005–1.0 mol %), **3** (0.005–1.0 mol %), aryl halide/pseudohalide (1.0 equiv), amine (1.4 mmol), NaOt-Bu (1.4 mmol), 1,4-dioxane (1 mL/mmol), 110 °C. <sup>b</sup> The reaction was run in toluene. <sup>c</sup> A commercial 2 M solution of methylamine in THF was used at 80 °C. <sup>d</sup> K<sub>3</sub>PO<sub>4</sub> was used as the base in *t*-BuOH as the solvent.

**Table 3.** Cross-Coupling Reactions of Substrates Containing Heterocycles and Base Sensitive Functional Groups<sup>a</sup>



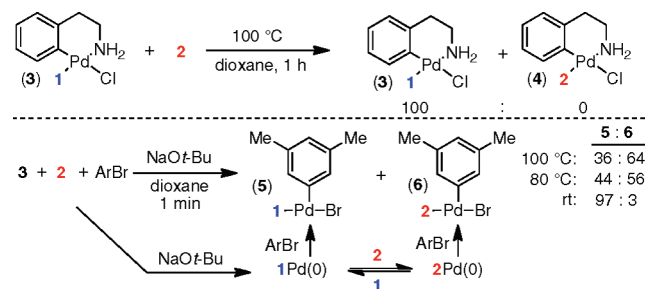
<sup>a</sup> Reaction conditions: **2** (1.0 mol %), **3** (1.0 mol %), aryl halide/pseudohalide (1.0 equiv), amine (1.4 mmol), Cs<sub>2</sub>CO<sub>3</sub> (1.4 mmol), *t*-BuOH (2 mL/mmol), 110 °C. <sup>b</sup> 1 M LHMDS in THF was used as the base and solvent.



**Figure 2.** Synthesis of TPD using a catalyst comprised of 2/3.

It is worth mentioning that although this system shows the highest activity and the broadest substrate scope of any single catalyst system we have developed to date, there are still some limitations. For example, substrates that require catalysts based on highly specialized ligands have not proven to be proficient coupling partners utilizing our mixed-ligand system. Specifically, imidazoles, benzimidazoles, pyrazoles,<sup>11</sup> or secondary acyclic amides<sup>12</sup> have not been successfully employed using the 2/3 combination. Further, this catalyst system does not work well for the monoarylation of ammonia.

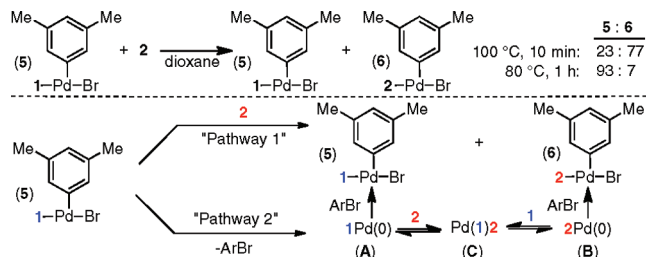
We next set out to gain insight into why the mixed-ligand catalyst system was so effective for C–N cross-coupling reactions. Based on the fact that the reactivity of our system did not depend on which ligand began coordinated to the Pd, we hypothesized that ligand exchange under the catalytic conditions must be facile. To investigate this we conducted studies to elucidate where interchange of the ligands was occurring in the catalytic cycle. First, upon heating stoichiometric quantities of 3 in the presence of 2 at 100 °C for 1 h no formation of 4 via ligand exchange was observed. This demonstrates that the ligand interchange does not occur at the amine bound Pd(II) complex (Figure 3). Next, when 3 was heated to 100 °C for 1 min in the presence of NaOt-Bu, 2, and an aryl bromide, a mixture of both 5 and 6 was observed. This suggested that ligand exchange was facile on a Pd(0) complex (Figure 3). It is worth



**Figure 3.** Ligand exchange studies on the Pd(II) amine bound complex and the Pd(0) complex.

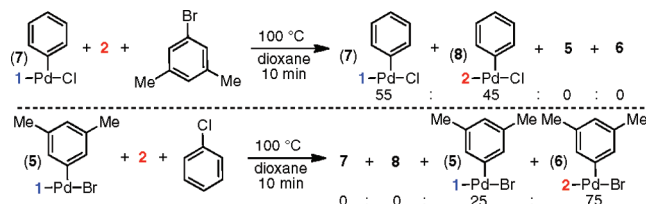
noting that fast ligand exchange at the Pd(0) complex was also observed at 80 °C; however, at room temperature it became slow. This is consistent with our findings that the mixed-ligand catalyst gave optimal results at temperatures  $\geq 100$  °C.

Lastly, we wanted to explore whether ligand exchange could occur at the Pd(II) oxidative addition complex. When a mixture of 5 and 2 were heated in dioxane at 100 °C for 10 min, a mixture of 5 and 6 was observed (Figure 4). We reasoned that two different pathways for ligand exchange could explain this result. First, exchange could be taking place on the Pd(II) oxidative addition complex itself (Figure 4, Pathway 1). Alternatively, complex 5 could undergo reductive reductive elimination to provide the aryl bromide and 1Pd(0) (A).<sup>13</sup> Intermediate A could equilibrate with B via the mixed-ligand complex, C. Subsequent oxidative addition of B with the aryl bromide would afford 6 (Figure 4, Pathway 2). In order to test which pathway was operating a crossover experiment was



**Figure 4.** Ligand exchange studies on the Pd(II) oxidative addition complex.

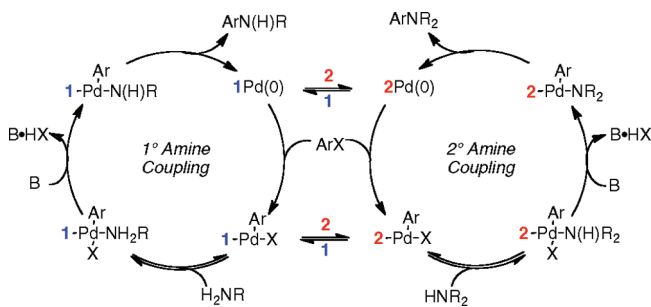
utilized. Heating the aryl chloride oxidative addition complex, 7, in the presence of 2 and 100 equiv of 3,5-dibromobenzene for 10



**Figure 5.** Competition experiment to distinguish between Pathway 1 and Pathway 2.

min resulted in a mixture of 7 and 8 (Figure 5). However, none of the crossover products (5 or 6) were observed, suggesting that ligand exchange was occurring at the Pd(II) center (Pathway 1) and not through a Pd(0) pathway.<sup>14</sup> Moreover, in order to show that the aryl chloride oxidative addition complexes were not just more thermodynamically stable than the corresponding aryl bromide complexes, 5 was heated in the presence of 2 and 100 equiv of chlorobenzene for 10 min. This experiment resulted in a 25:75 mixture of 5 and 6 and no detectable quantities of 7 and 8, which further supports the hypothesis that ligand exchange is occurring via pathway 1. On the basis of these results we propose that this mixed-ligand system is operating via the catalytic cycle shown in Figure 6, where the Pd is being shuttled between the two cycles at both the Pd(0) and the Pd(II) oxidative addition stage.

In summary, we have disclosed a new approach to catalyst design where the goal was to find a catalyst or catalyst mixture that incorporated the reactivity displayed by several of our previous catalyst systems. This strategy led to the development of a Pd catalyst based on two biarylphosphine ligands, which displayed the same substrate scope and catalyst activity in C–N cross-coupling reactions as a catalyst based on either of the ligands separately. For example, an array of both primary and secondary amines, as well as aryl halides/pseudohalides, were successfully coupled utilizing this system in high yields and with low catalyst loadings. Further, this mixed catalyst not only encompassed the substrate scope and activity that each catalyst exhibited alone but also



**Figure 6.** Proposed mechanism of the mixed-ligand catalyst system.

manifested its own reactivity. For example, in the synthesis of triarylaminines the multiligand system was more efficient than a system based on either ligand independently. We not only believe this multiligand catalyst system will see widespread use, especially in industry, but also expect that this approach toward catalyst design will be applicable to other cross-coupling methodologies. We hope that the use of multiligand systems will facilitate the development of more comprehensive catalysts and, ideally, lead to the discovery of a truly “universal” system.

**Acknowledgment.** We thank the National Institutes of Health for financial support of this project (Grant GM58160). B.P.F. thanks Amgen, Boehringer Ingelheim, and the American Chemical Society for graduate fellowships. We are grateful to Professor David W. C. MacMillan for insightful discussions.

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

## References

- (1) (a) Hartwig, J. F. *Nature* **2008**, *455*, 314–322. (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338–6361. (c) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599–1626. (d) Eelkema, R.; Anderson, H. L. *Macromolecules* **2008**, *41*, 9930–9933.
- (2) (a) Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 6586–6596. (b) Lundgren, R. J.; Sapping-Kumankumah, A.; Stradiotto, M. *Chem.—Eur. J.* **2010**, *16*, 1983–1991. (c) Schwarz, N.; Pews-Davtyan, A.; Michalik, D.; Tillack, A.; Krüger, K.; Torrens, A.; Diaz, J. L.; Beller, M. *Eur. J. Org. Chem.* **2008**, 5425–5435. (d) Ackermann, L.; Spatz, J. H.; Gschrei, C. J.; Born, R.; Althammer, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7627–7630. (e) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101–4111.
- (3) Niculescu-Duvaz, I.; Roman, E.; Whittaker, S. R.; Friedlos, F.; Kirk, R.; Scanlon, I. J.; Davies, L. C.; Niculescu-Duvaz, D.; Marais, R.; Springer, C. J. *J. Med. Chem.* **2008**, *51*, 3261–3274.
- (4) (a) Cao, P.; Qu, J.; Burton, G.; Rivero, R. A. *J. Org. Chem.* **2008**, *73*, 7204–7208. (b) Yang, Q.; Ney, J. E.; Wolfe, J. P. *Org. Lett.* **2005**, *7*, 2575–2578. (c) Surry, D. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 10354–10355. (d) Moldoveanu, C.; Wilson, D. A.; Wilson, C. J.; Corcoran, P.; Rosen, B. M.; Percec, V. *Org. Lett.* **2009**, *11*, 4974–4977. (e) Wilson, D. A.; Wilson, C. J.; Moldoveanu, C.; Resmerita, A.-M.; Corcoran, P.; Hoang, L. M.; Rosen, B. M.; Percec, V. *J. Am. Chem. Soc.* **2010**, *132*, 1800–1801. (f) Percec, V.; Golding, G. M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447–3452. (g) Willis, M. C.; Taylor, D.; Gillmore, A. T. *Tetrahedron* **2006**, *62*, 11513–11520. (h) Reetz, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2556–2588.
- (5) (a) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461–1473. (b) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534–1544. (c) Espinet, P.; Echavarran, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704–4734. (d) Negishi, E.; Liu, F. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998.
- (6) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552–13554.
- (7) (a) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686–6687. (b) Fors, B. P.; Davis, N. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 5766–5768.
- (8) Fors, B. P.; Dooleweerd, K.; Zeng, Q.; Buchwald, S. L. *Tetrahedron* **2009**, *65*, 6576–6583.
- (9) Harris, M. C.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5327–5333.
- (10) (a) Sakanoue, K.; Motoda, M.; Sugimoto, M.; Sakaki, S. *J. Phys. Chem. A* **1999**, *103*, 5551–5556. (b) Thayumanavan, S.; Mendez, J.; Marder, S. R. *J. Org. Chem.* **1999**, *64*, 4289–4297. (c) Thelakkat, M.; Hagen, J.; Haarer, D.; Schmidt, H. W. *Synth. Met.* **1999**, *102*, 1125–1128.
- (11) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6523–6527.
- (12) Hicks, J. D.; Hyde, A. M.; Cuezva, A. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 16720–16734.
- (13) For examples of the reductive elimination of Ar–X, see: Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, *23*, 1533.
- (14) When the same experiment was run for 1 h at 100 °C, no crossover product was observed.

JA108074T