ORGANIC LETTERS

2000
Vol. 2, No. 8
1101−1104

Palladium-Catalyzed Intermolecular Coupling of Aryl Halides and Amides

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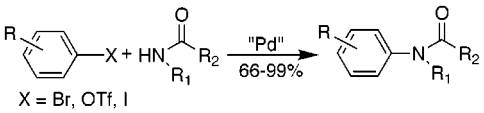
Received February 11, 2000

ABSTRACT



The first general intermolecular C–N bond-forming reactions between aryl halides and amides were realized using a palladium catalyst with Xantphos as the ligand. Aryl triflates, carbamates, and sulfonamides are also viable substrates for the amidations, which proceed at 45–110 °C with 1–4 mol % of Pd catalyst in 66–99% yields and exhibit good functional group compatibility.

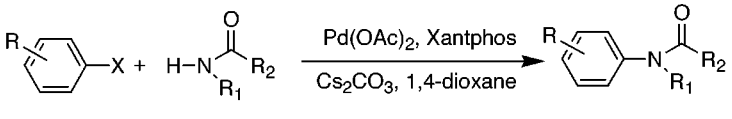
Palladium-catalyzed C−N bond-forming reactions between aryl halides and amines have been extensively studied in the past few years. These reactions can be carried out under mild conditions with a large variety of amines and aryl halide and sulfonate substrates.[1−3] Attempts to perform the analogous coupling reactions using amides or sulfonamides as the nitrogen nucleophile, though desirable, have been less successful.[4−9] Previously, the amidations of aryl halides have been performed using Ullmann-type conditions. Unfortunately these processes usually require stoichiometric amounts of copper salts, high temperatures (> 150 °C), and polar solvents such as DMF, collidine, and pyridine.[4] We recently described the intramolecular coupling of aryl bromides and amides, carbamates, and sulfonamides, but we were unsuccessful in our attempts to achieve the corresponding intermolecular couplings.[7,8] Snider has reported a total synthesis of asperlicin in which the intramolecular Pd-catalyzed coupling of a urethane and an iodoindole was a key step.[9] A recent report by Shakespeare described intermolecular reactions between lactams and aryl bromides. As we had previously found, only the reactions of a five-membered ring lactam were general.[5] In a related process, Hartwig also has reported that the intermolecular combination of *tert*-butyl carbamate with unfunctionalized aryl bromides and chlorides can be effected using sodium phenoxide as base.[6] In this Letter, we describe our discovery of the first general intermolecular C−N bond-forming reactions between aryl halides and primary amides or lactams.

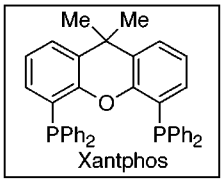
To determine efficient methods for amide coupling processes, we undertook an intensive screening of a variety of ligands and reaction variables using electron-deficient aryl bromides as substrates. We found that a catalyst combination employing Xantphos,[10] a chelating ligand developed by van Leeuwen, with Cs_2CO_3 as the base and THF or 1,4-dioxane as the solvent provided the most generally successful results. These conditions proved to be general for amidations of a large variety of electron-deficient aryl bromides (Table 1).[11] The use of Cs_2CO_3 as the base was particularly advantageous, ensuring that common functional groups such as cyano, nitro,

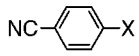
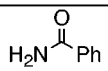
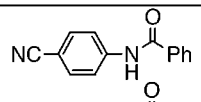
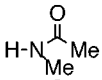
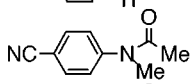
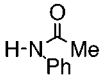
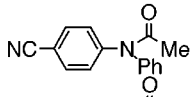
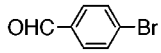
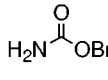
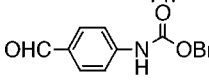
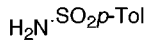
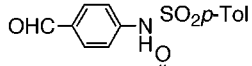
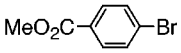
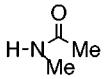
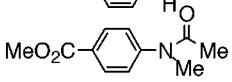
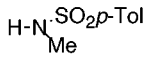
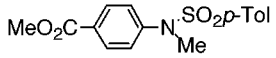
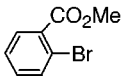
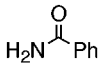
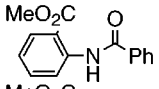
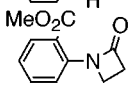
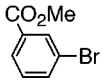
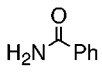
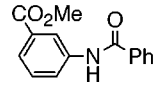
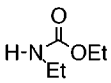
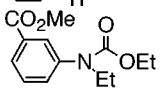
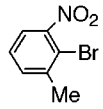
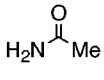
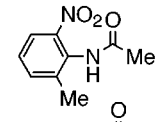
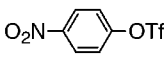
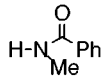
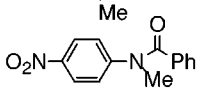
(1) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146.
(2) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818.
(3) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067.
(4) Lindley, J. *Tetrahedron* **1984**, *40*, 1435−1456.
(5) Shakespeare, W. C. *Tetrahedron Lett.* **1999**, *40*, 2035−2038.
(6) Hartwig, J. F.; Kawatsura, M.; Hauck, S. L.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580.
(7) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *21*, 7525−7546.
(8) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35−37.
(9) He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417−6418.
(10) (a) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3081−3089. Previous uses of Xantphos in C−N bond-forming reactions: (b) Guari, Y.; van Es, D. S.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron Lett.* **1999**, *40*, 3789−3790. (c) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251−10263. (d) Harris, M. C.; Geis, O.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 6019−6022.

10.1021/ol005654r CCC: $19.00
Published on Web 03/22/2000

Table 1. Pd-Catalyzed Amidation of Activated Aryl Halides[a]





Entry	ArX	Amide	Product	mol % Pd	temp (°C)	time (h)	yld (%)
1(X=Br) 2(X=I)				1 1	45 45	19 18	93[b] 98[b]
3(X=Br)				1	45	42	97[b]
4(X=Br) 5(X=Cl)				1 1	80 100	33 16	95 74
6				1	45	19	99[b]
7				1	100	6	93[c]
8				1	80	27	99
9				2	100	22	87
10				1	100	16	91[d]
11				1	100	35	78[d]
12				1	100	16	90[d]
13				2	110	44	66[d]
14				1	100	16	82[d]
15				1	80	16	74

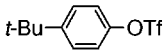
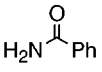
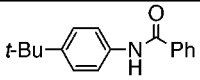
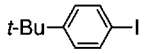
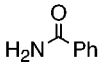
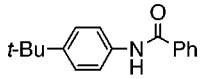
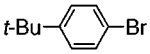
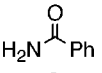
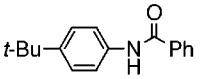
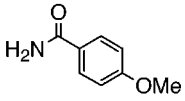
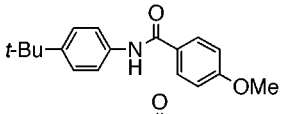
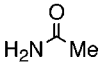
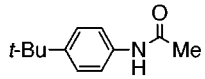
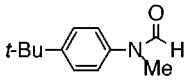
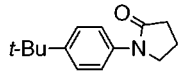
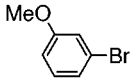
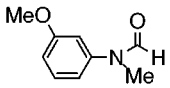
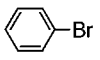
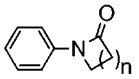
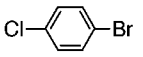
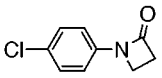
a) Reaction conditions: 1.0 equiv of the aryl halide/triflate, 1.1-1.2 equiv of amide/carbamate/sulfonamide, Xantphos/$Pd(OAc)_2$ = 1.5/1, 1.4-1.5 equiv of Cs_2CO_3, 1,4-dioxane (1mL/mmol halide/triflate); Yields refer to isolated yields (average of two runs) of compounds estimated to be ≥95% pure as determined by ^1H NMR, and GC analysis or combustion analysis; b) THF as the solvent; c) 1.2 equiv of the aryl bromide and 1.0 equiv of the sulfonamide were used; d) $Pd_2(dba)_3$ was used in place of $Pd(OAc)_2$; 1 mol % Pd refers to 0.5 mol % $Pd_2(dba)_3$.

ester, and aldehyde groups were well tolerated. However, due to a competitive ketone arylation process,[12] acyl-substituted aryl bromides could not be used with these conditions. Aryl bromides with electron-withdrawing groups *para* to the bromo group reacted efficiently with various amides at temperatures from 45 to 80 °C using $Pd(OAc)_2$ as Pd(0) precursor (Table 1, entries 1, 3, 4, and 8). Aryl halides with *ortho* or *meta* activating groups were less reactive and

(11) **Typical procedure** (Table 1, entry 11): a flame-dried resealable Schlenk tube was charged with $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol, 1 mol % of Pd), Xantphos (8.7 mg, 0.015 mmol, 1.5 mol %), 2-azetidinone (85 mg, 1.2 mmol), and Cs_2CO_3 (456 mg, 1.4 mmol). The Schlenk tube was capped with a rubber septum, evacuated, and backfilled with argon; this evacuation/backfill sequence was repeated one additional time. Methyl 2-bromobenzoate (0.140 mL, 215 mg, 1.0 mmol) and 1,4-dioxane (1 mL) were added through the septum. The septum was replaced with a Teflon screwcap. The Schlenk tube was sealed, and the mixture was stirred at 100 °C for 35 h until the starting aryl bromide had been completely consumed as judged by GC analysis. The reaction mixture was then cooled to room temperature, diluted with dichloromethane (10 mL), filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel to afford 163 mg (80%) of *N*-(2′-carbomethoxyphenyl)-2-azetidinone as a pale yellow oil.

(12) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360−1370.

Table 2. Pd-Catalyzed Amidation of Unactivated Aryl Halides[a]

Entry	ArX	Amide	Product	mol % Pd	time(h)	yld(%)
1				4	16	94[b]
2				2.5	16	89[b]
3				2.5	16	91[b]
4				2	16	83[b]
5				2	16	87[b]
6				2	16	84[c]
7				2	16	91
8				1	16	99[c]
9 (n=1)				1	16	93
10(n=2)				1	16	96
11(n=3)				1	32	92
12(n=4)				1	22	90
13				1	18	90

a) Reaction conditions: 1.0 equiv of the aryl halide/triflate, 1.2 equiv of amide, Xantphos/$Pd_2(dba)_3$ = 3/1 (L/Pd = 1.5/1), 1 mol % Pd refers to 0.5 mol % $Pd_2(dba)_3$; 1.4 equiv of Cs_2CO_3, 1,4-dioxane (1mL/mmol halide/triflate); 100 °C; Yields refer to isolated yields (average of two runs) of compounds estimated to be ≥95% pure as determined by ^1H NMR, and GC analysis or combustion analysis. b) 2 mL dioxane per mmol halide/triflate was used; c) $Pd(OAc)_2$ was used in place of $Pd_2(dba)_3$.

necessitated the use of higher reaction temperatures and/or higher quantities of catalysts. Moreover, $Pd_2(dba)_3$ was found to be superior to $Pd(OAc)_2$ as the Pd source (Table 1, entries 10−14). We were also able to demonstrate the viability of activated aryl iodide (Table 1, entry 2), aryl chloride (Table 1, entry 5), and aryl triflate (Table 1, entry 15) substrates in these coupling reactions. In addition to amides, both primary and secondary carbamates (Table 1, entries 6 and 13) and sulfonamides (Table 1, entries 7 and 9) could be combined with activated aryl bromides. The reactivity of carbamates appeared comparable to that of amides, while sulfonamides were less reactive, requiring the use of higher temperatures (100 °C).

We next turned our attention to the reactions of amides with unactivated aryl halides. The combination of Xantphos as the ligand, Cs_2CO_3 as the base, and 1,4-dioxane as the solvent also proved to be effective to catalyze the amidation of electron-neutral and slightly electron-rich aryl halides (Table 2). For these processes, the use of $Pd_2(dba)_3$ as the palladium source was critical for the success of amidations. Aryl bromides reacted efficiently with both aromatic and aliphatic primary amides (Table 2, entries 3−5), *N*-methylformamide (Table 2, entries 6, 8), and lactams (Table 2, entries 7, 9−13) at 100 °C. It is worth mentioning that our catalyst system enabled the general coupling between bromobenzene and four- to seven-membered ring lactams at 1 mol % of Pd loading and 100 °C. This complements the work of Shakespeare who found that only a five-membered ring lactam reacted efficiently with bromobenzene. The *N*-arylation of β-lactams is of interest due to the importance of β-lactams in the pharmaceutical industry. We found that the coupling of the β-lactam was fairly general as functional groups such as 2-carbomethoxy (Table 1, entry 11) and 4-chloro (Table 2, entry 13) were well tolerated.

As for the reactions of activated aryl substrates (Table 1, entries 2 and 15), an unactivated aryl iodide (Table 2, entry 2) and aryl triflate (Table 2, entry 1) also underwent amidation with benzamide; 4-*tert*-butylbenzenetriflate required the use of a slightly higher catalyst loading (4 mol % of Pd) than for the corresponding bromide and iodide (2.5 mol % of Pd, Table 2, entries 2 and 3).

While the results presented above represent a significant improvement over those previously reported, the substrate scope of the amidation of unactivated aryl halides still has only a moderate level of generality. To date, the amidations of unactivated aryl chlorides (e.g., *p*-chlorotoluene), *o*-substituted electronically neutral aryl halides (e.g., 2-bromotoluene), and electron-rich aryl halides (e.g., 4-bromoanisole) are not efficient. Additionally, secondary acyclic amides (e.g., *N*-methylacetamide, *N*-methylbenzamide) other than *N*-methylformamide react sluggishly with unactivated aryl halides. We have also been unsuccessful in our attempts to effect the coupling of sulfonamides with electron-neutral or electron-rich aryl halides.

In this work, we found that amidations involving less nucleophilic amides (e.g., sulfonamides and acetanilide) and less electrophilic aryl halides (e.g., unactivated aryl halides) were generally slower, requiring higher temperatures, longer reaction times, and/or higher quantities of catalysts and sometimes resulted in low conversions.[13] For example, both benzamide and 4-methoxybenzamide reacted efficiently with 4-*tert*-butylbromobenzene at 100 °C in 16 h (Table 2, entries 3 and 4). In contrast, under the same conditions as those used for the reaction of benzamide, 4-trifluoromethylbenzamide gave only 50% conversion to product. Amidation of unactivated aryl halides was only effective with primary amides, *N*-methylformamide, and lactams. The relatively higher reactivity of these amides might be explained by the configuration of the deprotonated amide (Figure 1). Binding

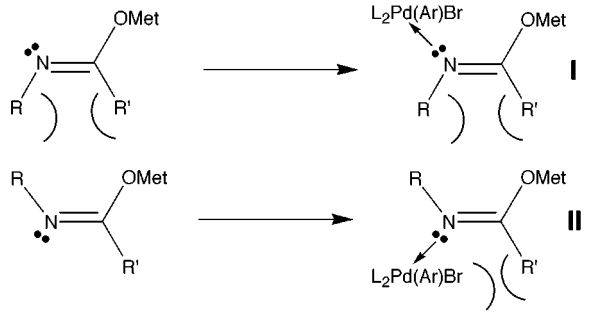


Figure 1.

of the deprotonated amide to the Pd(II) intermediate can occur either via **I** or **II**. In most instances, the steric repulsion between R and R′ would destabilize **I**; in the reactions of lactams, only **I** is possible. Intermediate **II** would be expected to suffer, in most cases, from severe steric interactions between R′ and the Pd complex. For substrates with R′ = H, this is less important. Additionally, when R = H (i.e., for primary amides), the Pd moiety can position itself away from the bulk of R′ with little cost in energy. Consistent with these hypotheses is that when neither R nor R′ is H, the reactions fail to proceed in an efficient manner.

In addition to the desired C−N coupling products, small amounts (2%-8%) of *N*-phenylated amides were also detected in crude reaction mixtures by GC and GC-MS analyses when less reactive aryl halides were used (Table 1, entry 12; Table 2, entries 1−8 and 13). These byproducts, which were removed by flash chromatography, are possibly formed via aryl group exchange between the aryl group bound to Pd(II) and the phenyl group bound to the phosphine ligand[14] followed by C−N bond formation between the amide and the phenyl group. Work is underway to overcome this problem.

In conclusion, use of Xantphos as the ligand, THF or 1,4-dioxane as the solvent, and Cs_2CO_3 as the base allows for the first general intermolecular C−N bond-forming reactions between aryl halides and amides. The amidations proceed at 45−110 °C with 1−4 mol % of Pd catalyst in good to excellent yields, and various functional groups are well tolerated. In addition, aryl triflates, carbamates, and sulfonamides also participate in this process. Further investigations to expand the scope of this and related reactions are currently underway.

Acknowledgment. We thank NIH (Grant GM58160) for support of this work. We are also grateful to Pfizer and Merck for additional unrestricted support.

Supporting Information Available: Experimental procedures and characterization data for amidation products (Tables 1 and 2). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) A substantial influence of the temperature of the reaction or the mol % of catalyst employed on the efficiency of some reactions involving unactivated aryl halides or triflate was also observed. For example, when 1 mol % of Pd catalyst was used, the reactions in entries 1−3 and 7 of Table 2 gave low conversions (<15%). When the reaction in entry 3 of Table 2 was carried out at 120 °C with 5 mol % of Pd catalyst, a product/ArBr ratio of 0.20 was obtained after 19 h. The use of 2 mol % of Pd at the same temperature gave a product/ArBr ratio of 1.1 after 16 h; no further conversion was noted after an additional 26 h. However, when the temperature was lowered to 100 °C, complete conversion was achieved using 2.5 mol % of catalyst after 16 h (Table 2, entry 3). These results suggest that unknown competitive processes leading to decomposition of the catalyst can occur and that changes in reaction parameters may change the relative rates of the desired and unwanted reactions.

(14) Hartwig observed similar aryl group exchange processes in palladium-catalyzed aminations: (a) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 3694−3703. See also: (b) Kong, K.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6313−6315. (c) Segelstein, B. E.; Butler, T. W.; Chenard, B. L. *J. Org. Chem.* **1995**, *60*, 12−13. (d) Herrmann, W. A.; Broβmer, C.; Öfele, K.; Beller, M.; Fischer, H. *J. Organomet. Chem.* **1995**, *491*, C1−C4.