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# Palladium-Catalyzed Synthesis of *N*-Aryloxazolidinones from Aryl Chlorides

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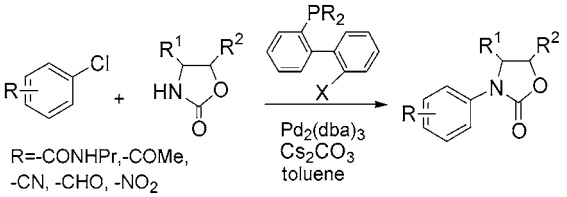
## ABSTRACT




**An efficient method for intermolecular *N*-arylation of oxazolidinones using $Pd_2dba_3$ and various phosphine ligands in the presence of a weak base is reported. The conditions allow the use of cheaper aryl chlorides containing functionalities such as enolizable ketones, amides, etc., which would be incompatible with other coupling methods. The coupling reaction can be used to prepare enantiopure *N*-aryl *β*-amino alcohols. Depending on the stereoelectronic nature of the aryl chloride, careful choice of ligand was necessary for the success of these reactions.**

Fatal infections with vancomycin-resistant enterococci (VRE) among patients with compromised host defenses have magnified the importance of new and improved antimicrobial agents. *N*-Aryl oxazolidinones have recently attracted much attention as a new class of synthetic antimicrobial agents[1] effective against a number of Gram-positive bacteria and have emerged as an approved therapeutic option for VRE. Some *N*-aryl oxazolidinones have also been used as antidepressant agents,[2] and a variety of elegant synthetic approaches have been described in the literature.[3] In a related project, we needed to develop a method for efficient production of *N*-aryl oxazolidinones on large scale. We envisioned that a Pd-catalyzed C−N bond-forming process between aryl halides and oxazolidinones would provide a convergent access to such systems. Moreover, a wide number of *N*-unsubstituted oxazolidinones are readily available in enantiomerically pure form and can also be used as surrogates to produce a diverse array of enantiopure *β*-amino alcohols ready for further synthetic manipulation.

During the past few years, significant progress has been made in the development of Pd-catalyzed cross-coupling of

(1) For a recent review, see: (a) Halle, E.; Majcher-Peszynska, J.; Drewelow, B. *Chemother. J.* **2002**, *11*, 1−11. For some work in this area, see: (b) Tucker, J. A.; Allwine, D. A.; Grega, K. C.; Barbachyn, M. R.; Klock, J. L.; Adamski, J. L.; Brickener, S. J.; Hutchinson, D. K.; Ford, C. W.; Zurenko, G. E.; Conradi, R. A.; Burton, P. S.; Jensen, R. M. *J. Med. Chem.* **1998**, *41*, 3727−3735. (c) Genin, M. J.; Hutchinson, D. K.; Allwine, D. A.; Hester, J. B.; Hemmert, D. E.; Garmon, S. A.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H.; Friis, J. M.; Shobe, E. M.; Adams, W. J. *J. Med. Chem.* **1998**, *41*, 5144−5147. (d) Gleave, D. M.; Brickner, S. J.; Manninen, P. R.; Allwine, D. A.; Lovasz, K. D.; Rohrer, D. C.; Tucker, J. A.; Zurenko, G. E.; Ford, C. W. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1231−1236. (e) Gleave, D. M.; Brickner, S. J. *J. Org. Chem.* **1996**, *61*, 6470−6474.

(2) (a) Keane, P. E.; Kan, J. P.; Sontag, N.; Benedetti, M. S. *J. Pharm. Pharmacol.* **1979**, *31*, 752−754. (b) Moureau, F.; Wouters, J.; Vercauteren, D. P.; Collin, S.; Evrard, G.; Durant, F.; Ducrey, F.; Koenig, J. J.; Jarreau, F. X. *Eur. J. Med. Chem.* **1992**, *27*, 939−948. (c) Moureau, F.; Wouters, J.; Vercauteren, D. P.; Collin, S.; Evrard, G.; Durant, F.; Ducrey, F.; Koenig, J. J.; Jarreau, F. X. *Eur. J. Med. Chem.* **1994**, *29*, 269−277. (d) Mai, A.; Artico, M.; Esposito, M.; Sbardella, G.; Massa, S.; Befani, O.; Turini, P.; Glovannini, V.; Mondovi, B. *J. Med. Chem.* **2002**, *45*, 1180−1183.

(3) (a) Trost, B.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1988**, *110*, 7933−7935. (b) Hayashi, T.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1988**, *29*, 99−102. (c) Schaus, S. E.; Jacobsen, E. N. *Tetrahedron Lett.* **1996**, *37*, 7937−7940. (d) Moreno-Manas, M.; Morral, L.; Pleixats, R.; Villarroya, S. *Eur. J. Org. Chem.* **1999**, 181−186. (e) Larksarp, C.; Alper, H. *J. Am. Chem. Soc.* **1997**, *119*, 3709−3715. (f) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 625−628. (g) Jegham, S.; Nedelec, A.; Burnier, Ph.; Guminski, Y.; Puech, F.; Koenig, J. J.; George, P. *Tetrahedron Lett.* **1998**, *39*, 4453−4454.

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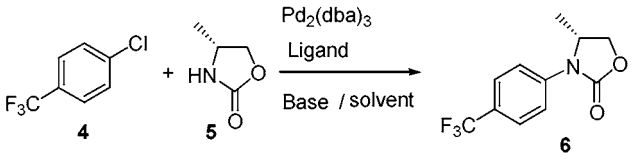
**Scheme 1.** *N*-Arylation of Oxazolidinone




amines and aryl halides.[4] In particular, the ability to utilize readily available and inexpensive aryl chlorides[5] has further enhanced the scope of the process in an industrial sense. Efficient Pd-catalyzed *N*-arylation of amides or amide-type nitrogens, on the other hand, has been less successful. The scope of traditional Cu-catalyzed cross-couplings under Ullmann/Goldberg-type conditions involving stoichiometric copper reagents in a solvent with high dielectric constant and high boiling point (e.g., collidine, DMF, pyridine) is also limited.[6]

Buchwald[7] and Hartwig[8] have independently demonstrated the generality of Pd-catalyzed *N*-arylation involving amides and have extended the chemistry to acyclic carbamates.[9] Interestingly, the first example of intermolecular[10] amidation of an aryl bromide reported by Shakespeare described superior reactivity of five-membered ring lactams compared to four-, six-, or seven-membered congeners.[11] Concurrent with the studies described herein, two independent groups reported that the above conditions were not suitable for oxazolidinones, particularly with more demanding substrates, and that improved conditions with wider applicability needed to be developed.[12] However, both groups used only reactive aryl bromides as the coupling partners. To our knowledge, efficient cross-coupling of aryl chlorides with oxazolidinones has not been reported to date. In this paper, we describe that, with proper choice of conditions, aryl chlorides can be used successfully in the *N*-arylation of five-membered cyclic carbamates.

Our initial attempts to effect *N*-arylation using aryl chlorides met with limited success. However, an intensive screening of a variety of ligands, Pd−ligand combinations, and reaction variables using an electron-deficient aryl chloride **4** and oxazolidinone **5** (Scheme 1) revealed several interesting results (Table 1). With a few exceptions, $Pd_2(dba)_3$ proved to be superior to $Pd(OAc)_2$ and was used as the Pd source for comparison purposes.

**Table 1.** Optimization of Reaction Conditions[a]

| entry | ligand | base | temp (°C) | conv (%)[b] |
|---|---|---|---|---|
| 1 | DPPF | $Cs_2CO_3$ | 100 | 57 |
| 2 | DPEphos | $Cs_2CO_3$ | 100 | 63 |
| 3 | BINAP | $Cs_2CO_3$ | 100 | 57 |
| 4 | Xantphos | $Cs_2CO_3$ | 100 | 60 |
| 5 | IPrHCl | $Cs_2CO_3$ | 110 | 32 |
| 6 | *t*$Bu_3P$ | $Cs_2CO_3$ | 100 | 15 |
| 7 | DIphos | $Cs_2CO_3$ | 100 | tr |
| 8 | **1** | $Cs_2CO_3$ | 100 | 100[c] |
| 9 | **2** | $Cs_2CO_3$ | 100 | 100[c] |
| 10 | **3** | $Cs_2CO_3$ | 100 | 100[c] |
| 11 | **2** | $K_3PO_4$ | 70 | 49[d] |
| 12 | **2** | $Cs_2CO_3$ | 70 | 26[d] |
| 13 | **2** | $K_3PO_4$ | 70 | 19 |
| 14 | **2** | $Cs_2CO_3$ | 70 | 33 |
| 15 | **2** | $K_3PO_4$ | 100 | 63[e] |
| 16 | **2** | $Cs_2CO_3$ | 100 | 66[e] |
| 17 | **2** | $K_3PO_4$ | 100 | 61 |
| 18 | **2** | $Cs_2CO_3$ | 100 | 72 |

[a] Unless otherwise stated, reactions were performed in toluene using the following molar ratios: **4**:**5**:[Pd]:ligand:base = 1:1.1:0.04:0.08:1.4. [b] Judged by NMR and HPLC analysis. [c] Isolated yields are 5−10% lower. [d] Used THF as solvent. Most of the aryl halide (>90%) was recovered intact. [e] Used dioxane as solvent.

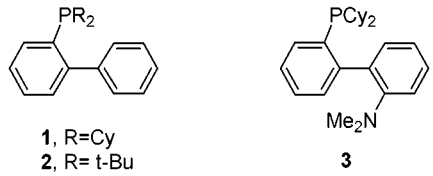



**Figure 1.** Buchwald's biaryl ligands used for optimization.

The Pd/chelating bis(phosphine)ligand combinations, including DPPF, DPEphos, BINAP, or Xantphos,[12a,13,14] as well as several other ligands with $Pd(OAc)_2$ or $Pd_2dba_3$, (Table 1, entries 1−7) were markedly slower compared to Buchwald's biphenyl-derived ligands[14] (Table 1, entries 8−10). Notably, the Xantphos-derived catalyst system was found recently to be the most generally effective catalyst for the coupling of acyclic amides with activated (electron-deficient) or electronically neutral aryl bromides.[7c,d,13c]

(4) (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067. (b) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146. (d) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144−1157. (e) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158−1174 and references therein.

(5) For recent reviews on chloroarene activation, see: (a) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047−1062. (b) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724 and references therein.

(6) Recently, improvements including use of truly catalytic copper salt as well as significantly milder conditions have been described: (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727−7729. For an early report on *intramolecular* amidations under relatively mild conditions, see: (b) Kametani, T.; Ohsawa, T.; Ihara, M. *Heterocycles* **1980**, *14*, 277−280. For a review on Cu-catalyzed cross-coupling reactions, see: (c) Lindley, J. *Tetrahedron* **1984**, *40*, 1435−1456.

(7) (a) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *21*, 7525−7546. (b) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35−37. (c) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101−1104. (d) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043−6048.

(8) Hartwig, J. F.; Kawatsura, M.; Hauck, S. L.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580.

(9) (a) For a related process, see: Wang, Z.; Skerlj, R. T.; Bridger, G. J. *Tetrahedron Lett.* **1999**, *40*, 3543−3546. (b) Arterburn, J. B.; Rao, K. V.; Ramdas, R.; Dible, B. R. *Org. Lett.* **2001**, *3*, 1351−1354.

(10) For intramolecular version, see: Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525−7546.

(11) (a) Shakespeare, W. C. *Tetrahedron Lett.* **1999**, *40*, 2035−2038. Reference 7d also includes an example of oxazolidinone *N*-arylation.

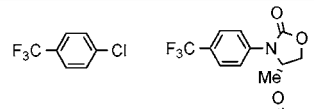
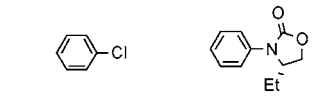
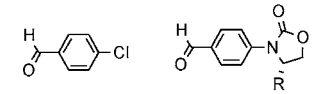
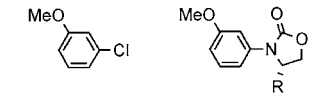
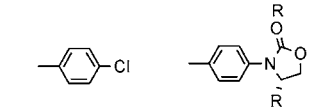
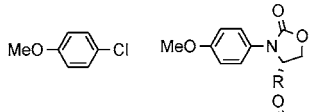
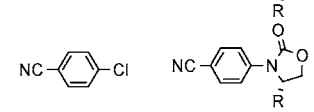
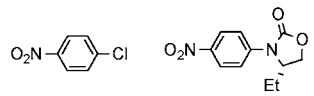
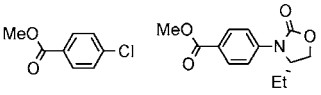
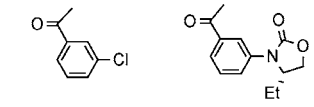
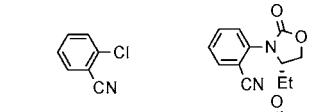
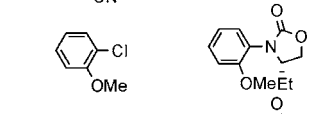
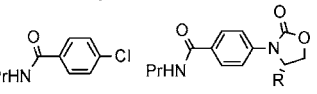
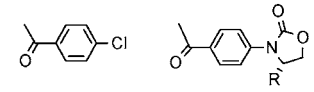
(12) (a) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Zappia, G. *Org. Lett.* **2001**, *3*, 2539−2541. (b) Madar, D. J.; Kopecka, H.; Pireh, D.; Pease, J.; Pliushchev, M.; Sciotti, R. J.; Wiedman, P. E.; Djuric, S. W. *Tetrahedron Lett.* **2001**, *42*, 3681−3684.

An examination of bases, such as sodium carbonate, potassium carbonate, cesium carbonate, potassium phosphate, as well as tertiary and secondary amines, and alkoxides, revealed the two most effective and functional group-compatible[15] bases to be cesium carbonate and potassium phosphate. Although potassium phosphate showed a faster reaction in ethereal solvents (e.g., THF or 1,4-dioxane; Table 1, entries 11, 12, 15, 16), this difference in reactivity was less significant at slightly elevated temperature. Indeed, in toluene, cesium carbonate gave consistently faster reactions (Table 1, entries 13, 14, 17, 18) over a range of temperature (70−115 °C) and proved to be crucial for a cleaner conversion.

As shown in Table 2, a variety of aryl chlorides can be coupled to different substituted oxazolidinones.[16,17] We found that a combination of $Pd_2dba_3$ as the Pd(0) precursor and Buchwald's biaryl ligands (**1**−**3**, preferably **2**) with $Cs_2CO_3$ as the base and toluene or 1,4-dioxane as the solvent provided the most generally successful catalyst for the coupling of oxazolidinone with activated (electron-deficient) aryl chlorides. Electronically neutral or slightly electron-rich aryl chlorides also reacted efficiently under these conditions (Table 2, entries 2, 6−8, 9−11).

Aryl chlorides with electron-withdrawing groups para to the chloro group reacted efficiently with a number of oxazolidinones at temperatures from 100 to 115 °C using $Pd_2dba_3$ as the Pd(0) precursor. *N*-Arylation involving aryl chlorides that possess electron-donating substituents were sluggish, as expected. Interestingly, Pd/BINAP systems turned out to be superior in those cases compared to electron-rich, bulky biaryl ligands **1**−**3** (data not shown). As expected,[18] aryl chlorides containing ortho substitutents are particularly inert to this transformation. Attempts to increase the catalyst loading in Pd/BINAP or Pd/Xantphos combinations led to the formation of varying amounts of *N*-phenyloxazolidinones, presumably via aryl group exchange between the aryl−palladium complex and the phenyl ring of the phosphine (LC and LC-MS analysis). However, removal of these side products from the crude reaction mixtures was straightforward with flash chromatography. Cacchi's *N*-arylation of oxazolidinones of aryl bromides bearing a ketone functional group suffered from a competi-

**Table 2.** Pd-Catalyzed *N*-Arylation of Oxazolidinones[a]

| entry | ArCl | product | mol % Pd | time (h.) | yield[b] |
|---|---|---|---|---|---|
| 1 |  | | 1 | 14 | 99 |
| 2 |  | | 2 | 18 | 81 |
| 3 |  | | 2 | 15 | 99 (R=Et) |
| 4 | | | 2 | 15 | 88 (R=Ph) |
| 5 | | | 2 | 17 | 86 (R=*i*-Pr) |
| 6 |  | | 2 | 17 | 98 (R=Et) |
| 7 | | | 2 | 17 | 82 (R=Bn) |
| 8 | | | 2 | 17 | 52 (R=Ph) |
| 9 |  | | 2 | 14 | 75 (R=Bn) |
| 10 | | | 2 | 17 | 50 (R=Ph) |
| 11 | | | 2 | 15 | 95 (R=Et) |
| 12 |  | | 2 | 17 | 32 (R=Et) |
| 13 | | | 2 | 17 | 15 (R=Ph) |
| 14 | | | 2 | 17 | 11 (R=Bn) |
| 15 |  | | 1 | 16 | 97 (R=Et) |
| 16 | | | 1 | 15 | 99 (R=Bn) |
| 17 |  | | 1 | 17 | 87 |
| 18 |  | | 2 | 17 | 99 |
| 19 |  | | 2 | 17 | 94 |
| 20 |  | | 2 | 17 | 31 |
| 21 |  | | 2 | 17 | 0 |
| 22 |  | | 2 | 18 | 97 (R=Et) |
| 23 | | | 2 | 18 | 98 (R=Ph) |
| 24 |  | | 2 | 17 | 91 (R=Et) |
| 25 | | | 2 | 17 | 61 (R=*i*-Pr) |
| 26 | | | 2 | 17 | 94 (R=Bn) |
| 27 | | | 2 | 17 | 97 (R=Ph) |

[a] Unless otherwise stated, reactions were performed in toluene using the following molar ratios: **4**:**5**:[Pd]:ligand:base = 1:1.1:0.04:0.08:1.4. [b] Yields refer to an average of two runs. The isolated compounds are 95−99% pure as judged by NMR and HPLC analysis.

(13) (a) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3081−3089. For uses of Xantphos in C−N bond-forming reactions, see: (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. For a kinetic study of Xantphos/Pd-catalyzed amine arylation reactions, see: (e) Guari, Y.; van Strijdonck, G. P. F.; Boele, M. D. K.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Chem. Eur. J.* **2001**, *7*, 475−482.

(14) DPPF = 1,1-bis(diphenylphosphino)ferrocene, DPEphos = bis(2-diphenylphosphinophenyl)ether, BINAP = 2,2-bis(diphenylphosphino)-1,1-binaphthyl, Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino) xanthene.

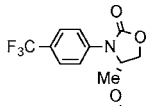
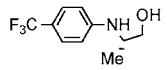
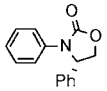
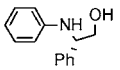
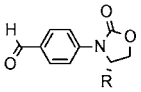
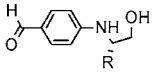
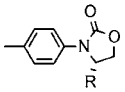
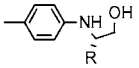
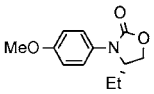
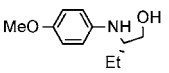
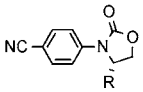
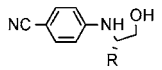
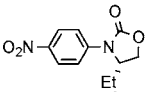
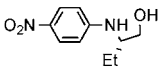
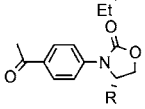
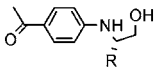
(15) The alkoxide bases showed faster rates. However, lower yields were observed as a result of hydrolytic decomposition of oxazolidinone, as well as undesired *N*-arylation.

(16) Enantiopure oxazolidinones were used for this study. Comparison of products from both antipodes by chiral HPLC (detailed in Supporting Information) showed complete retention of stereochemistry. Preservation of optical purity during Pd-catalyzed arylation of α-substituted amines has been reported by others. See: Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818.

(17) **Typical Procedure.** (Table 2, entry 2) An oven-dried tube was charged with $Pd_2(dba)_3$ (45.6 mg, 0.05 mmol), ligand **2** (29.8 mg, 0.05 mmol), chlorobenzene (132 $\mu$L, 1.3 mmol), oxazolidinone (150 mg, 1.3 mmol), $Cs_2CO_3$ (590 mg, 1.82 mmol), and degassed toluene (1.5 mL). The tube was evacuated and back-filled with nitrogen three times and then heated at 115 °C with stirring for 18 h. The reaction mixture was allowed to cool to room temperature, diluted with MTBE, and filtered through a pad of Celite. The organic layer was washed with saturated $NH_4Cl$, dried with $Na_2SO_4$, and concentrated in vacuo. The crude residue was purified by chromatography on silica gel using mixtures of ethyl acetate/hexanes as the eluent to obtain pure product (81%).

(18) For similar reactivity of aryl bromides, see ref 12a.

**Table 3.** Hydrolysis of *N*-Aryl Oxazolidinones to *N*-Aryl-$\beta$-amino Alcohols

| entry | oxazolidinone | 1,2-amino alcohol | time/temp.(°C) | yield(%) |
|---|---|---|---|---|
| 1 |  |  | 30 min/50 | 92 |
| 2 |  |  | 30 min/50 | 91 |
| 3<br>4<br>5 |  |  | 40 min/50<br>40 min/80<br>40 min/80 | 76 (R=Bn)<br>77 (R=Et)<br>80 (R=Ph) |
| 6<br>7 |  |  | 40 min/80<br>40 min/80 | 84 (R=Ph)<br>91 (R=Et) |
| 8 |  |  | 40 min/80 | 88 |
| 9<br>10 |  |  | 30 min/50<br>40 min/80 | 79 (R=Et)<br>89 (R=Bn) |
| 11 |  |  | 30 min/50 | 88 |
| 12<br>13 |  |  | 30 min/50<br>40 min/80 | 91 (R=Et)<br>94 (R=Bn) |

tive ketone arylation process.[19] Interestingly, such ketone arylation processes were largely suppressed in our conditions (Table 2, entries 19, 24−27). To extend the scope of this transformation, the resulting *N*-aryloxazolidinones were hydrolyzed using ethanolic NaOH to produce the corresponding *N*-aryl $\beta$-amino alcohols (Table 3), which are themselves of current interest.[20]

In summary, the first general intermolecular cross-coupling between aryl chlorides and cyclic carbamates has been developed by using a phosphine/Pd catalyst, $Cs_2CO_3$ as the base, and toluene as the solvent. This *N*-arylation protocol provides a reasonably broad substrate scope and good functional group compatibility. Activated aryl halides that bear electron-withdrawing groups at meta or para positions efficiently underwent C−N bond formation with a variety of oxazolidinones. Unactivated or deactivated aryl halides also reacted with various amides under more carefully controlled conditions.

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**Supporting Information Available:** General experimental details, synthetic procedures, and physical characterization data for *N*-aryloxazolidinones (Table 2, entries 1−19, 22−27). This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3703−3706.