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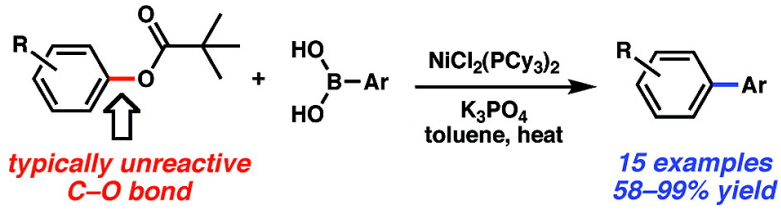

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Cross-Coupling Reactions of Aryl Pivalates with Boronic Acids

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Transition metal catalyzed cross-coupling reactions have emerged as a powerful method for constructing carbon−carbon (C−C) and carbon−heteroatom (C−X) bonds.[1] Whereas methodologies for the cross-coupling of aryl halides have significantly improved,[1,2] less progress has been made toward the coupling of the corresponding phenol derivatives.[1] Given that phenols are cheap and readily available, and that oxygenation can be used to direct the installation of functional groups on an aromatic ring, practical methods that allow for the cross-coupling of phenol derivatives are extremely attractive.

Of the known methods for cross-coupling phenol derivatives,[1,3−5] there are no examples that utilize simple *O*-acylated phenols.[6] Such a process would be of great value, given that *O*-acylated phenols are (a) simple to prepare, (b) among the most affordable phenol derivatives available,[7] (c) stable to a variety of reaction conditions, and (d) able to direct the installation of other functional groups onto an aromatic ring. Furthermore, this cross-coupling would presumably begin by the selective oxidative addition of a metal into the aryl C−O bond of the *O*-acylated phenol (Figure 1), a transformation that has never been achieved.[8] Here, we describe the first cross-coupling reactions of *O*-acylated phenol derivatives, involving the Ni-catalyzed reaction of aryl pivalates.

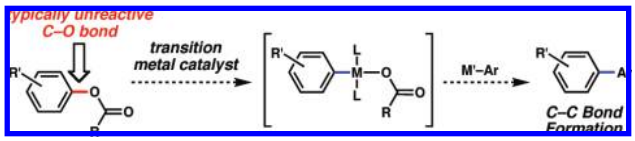


Figure 1. Cross-coupling of *O*-acylated phenol derivatives.

The Suzuki−Miyaura coupling was chosen as our starting point because of the numerous advantages that pertain to using boronic acids (i.e., low toxicity, wide availability, stability to water and air, and high functional group tolerance).[1,9] Several challenges were apparent from the outset of our endeavors. First, the *O*-acylated phenol substrates we intended to employ could be prone to hydrolysis under typical Suzuki−Miyaura conditions involving strong base. Thus, robust pivalate esters (−$OC(O)CMe_3$) were selected as the acylated phenol derivatives of choice. In addition, we postulated that the activation energy for oxidative addition between a transition metal and the aryl C−O bond of an acylated phenol derivative would be fairly high. Since fused aromatic systems are generally activated toward oxidative addition,[1a,4] a naphthol derivative was first examined.

An extensive survey of various reaction parameters (e.g., choice of metal,[10] ligand,[11] solvent, base, additives, and temperature) led to the identification of a catalyst system that facilitates the desired cross-coupling. Under optimal conditions (i.e., $NiCl_2(PCy_3)_2$ (5 mol%) and K_3PO_4 (4.5 equiv) in toluene at 80 °C), coupling of naphthyl pivalate **1** and phenylboronic acid (**2a**)[12] afforded biaryl product **3a** in 92% yield (Scheme 1). The Ni(II) precatalyst[13] of choice is readily available[14] and also shows marked stability to air. Therefore, all reactions are routinely carried out on the benchtop rather than in a glovebox, circumventing a common limitation of related Ni(0) processes.[3b,4]

The scope of this methodology was first examined by varying the aryl pivalate component (Table 1). Cross-coupling of *p*-methoxyphenylboronic acid (**2b**) with the pivalate derivative of 2-naphthol proceeded in 92% yield (entry 1). In addition, the reaction proved tolerant of an electron-withdrawing (−CO_2Me, entry 2) and -donating group (−OMe, entry 3) on the naphthyl ring. The corresponding reactions of non-fused aryl pivalates proved more challenging. Nonetheless, employing additional equivalents of boronic acid and increasing catalyst loading to 10 mol% significantly improved the yields of cross-coupled products. For instance, *p*- and *o*-tolyl pivalates afforded products in 65% and 79% yields (entries 4 and 5), respectively. A non-fused aromatic substrate bearing a *p*-methoxy substituent

Scheme 1

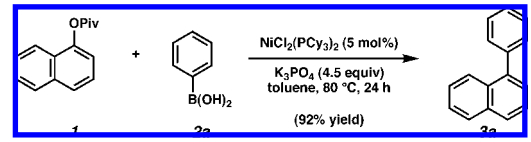
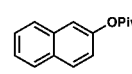
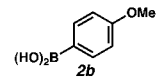
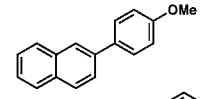
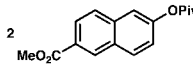
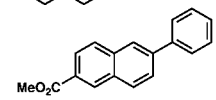
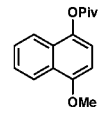
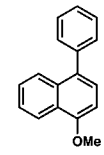
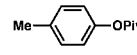
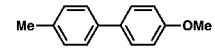
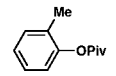
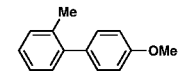
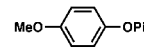
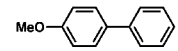
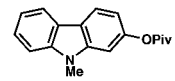
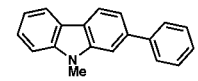
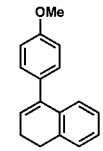


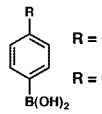
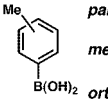
Table 1. Cross-Couplings of Various Aryl Pivalates with Arylboronic Acid **2a** or **2b**[a]

entry	Ar–OPiv	$(HO)_2B$–Ar	product	yield[b]
1				92%
2		**2a**		73%
3		**2a**		83%
4		**2b**		65%[c]
5		**2b**		79%[c]
6		**2a**		58%[c]
7		**2a**		82%
8		**2b**		79%[d]

[a] Conditions: $NiCl_2(PCy_3)_2$ (5 mol%), $ArB(OH)_2$ (4 equiv), K_3PO_4 (7.2 equiv), toluene (0.3 M), 110 °C, 24 h. [b] Isolated yields. [c] Conditions: $NiCl_2(PCy_3)_2$ (10 mol%), $ArB(OH)_2$ (5 equiv), K_3PO_4 (9 equiv), toluene (0.3 M), 110 °C, 24 h. [d] Conditions: $NiCl_2(PCy_3)_2$ (5 mol%), $ArB(OH)_2$ (2.5 equiv), K_3PO_4 (4.5 equiv), toluene (0.3 M), 80 °C, 24 h.

10.1021/ja806244b CCC: $40.75

Table 2. Cross-Coupling of Pivalate **1** with Various Arylboronic Acids[a]

entry	$ArB(OH)_2$		temp (°C)	product	yield[b]
1		R = OMe *2b*	80 °C	*3b*	95%
2		$R = CF_3$ *2c*	120 °C	*3c*	77%
3		*para* *2d*	80 °C	*3d*	91%
4		*meta* *2e*	80 °C	*3e*	99%
5		*ortho* *2f*	130 °C	*3f*	58%

[a] Conditions: Pivalate **1** (1 equiv), $NiCl_2(PCy_3)_2$ (5 mol%), $ArB(OH)_2$ (2.5 equiv), K_3PO_4 (4.5 equiv), toluene (0.3 M), 24 h. [b] Isolated yields.

also participated in the cross-coupling reaction (entry 6). Finally, a substrate derived from *N*-methyl-2-hydroxycarbazole underwent smooth cross-coupling (entry 7), as did a vinyl pivalate derived from tetralone (entry 8).

We have also found that a range of arylboronic acids participate in the Ni-catalyzed cross-coupling of naphthyl pivalate **1** (Table 2). For instance, cross-coupling of electron-rich boronic acid **2b**, bearing a *p*-methoxy substituent, furnished biaryl adduct **3b** in 95% yield (entry 1). Electron-deficient boronic acid **2c** can also be utilitized in the desired cross-coupling reaction (entry 2). Finally, Me-substitution is tolerated at the *p*, *m*, and *o*-positions as demonstrated by the coupling of substrates **2d**−**f** (entries 3−5), respectively, although the *o*-substituted substrate (entry 5) requires elevated temperatures and proceeds in modest yield.

Figure 2 highlights two unprecedented and powerful variations of the cross-coupling methods described herein. As pivalylation protocols typically proceed quantitatively and with minimal byproduct formation, we hypothesized that a one-pot acylation/cross-coupling sequence of phenol derivatives could be possible. Gratifyingly, our efforts to achieve the one-pot conversion of 1-naphthol (**4**) to biaryl adduct **3b** were successful, affording the desired product in 86% yield. Next, to demonstrate the directing ability of aryl pivalates,[15] naphthyl pivalate **1** was selectively brominated at C4 to afford bromopivalate **5** in 84% yield.[16] Postulating that the pivalate functional group of **5** would not be reactive toward Pd(0), orthogonal cross-coupling reactions of the bromide and pivalate groups were attempted next. In the first cross-coupling, treatment of substrate **5** with indolylboronic ester **6** under Pd-catalysis led to the selective reaction of the aryl bromide to afford biaryl product **7**, with the robust pivalate group remaining intact, despite the harsh basic conditions employed (i.e., aqueous K_3PO_4, 90 °C). Next, aryl pivalate **7** underwent smooth cross-coupling under our Ni-catalyzed conditions to afford triaryl product **8** in 88% yield.

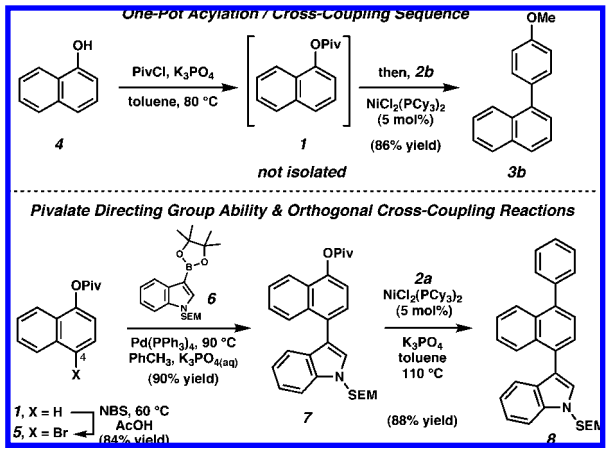


Figure 2. One-pot acylation/cross-coupling sequence and orthogonal cross-coupling reactions.

In summary, we have discovered the first cross-coupling reactions of *O*-acylated phenol derivatives. The method relies on the use of a readily available, air-stable Ni(II) complex to facilitate the Suzuki−Miyaura coupling of aryl pivalates. In addition, a one-pot acylation/cross-coupling sequence has been developed. Moreover, the potential to utilize an aryl pivalate as a directing group has been demonstrated, along with the ability to sequentially cross-couple an aryl bromide followed by an aryl pivalate. Studies aimed at probing mechanistic aspects of these findings are currently underway.

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Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(1) (a) *Metal-Catalyzed Cross-Coupling Reactions;* Diederich, F., Meijere, A., Eds.; Wiley-VCH: Weinheim, 2004. (b) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469. (c) *Top. Curr. Chem.*; Miyaura, N., Ed.; Springer-Verlag: New York, 2002; Vol. 219. (d) Corbet, J.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710. (e) Negishi, E. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 233–257.

(2) For a pertinent review, see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211.

(3) For aryl mesylate and tosylate cross-couplings, see: (a) Zim, D.; Lando, V. R.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2001**, *3*, 3049–3051. (b) Tang, Z.; Hu, Q. *J. Am. Chem. Soc.* **2004**, *126*, 3058–3059. (c) Percec, V.; Golding, G. M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447–3452. (d) Zhang, L.; Meng, T.; Wu, J. *J. Org. Chem.* **2007**, *72*, 9346–9349. (e) Munday, R. H.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 2754–2755, and also references therein.

(4) The Suzuki−Miyaura coupling of electron-deficient aryl methyl ethers was recently reported; see: Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4866–4869.

(5) Of the known methods for phenol coupling, the most common involves formation and reaction of the corresponding aryl triflates. However, these species are somewhat costly to prepare (see ref 7b), unable to serve as directing groups, and susceptible to base-promoted hydrolysis. Aryl mesylates and tosylates can also be utilized, although their utility does not yet appear to be general.

(6) For unsuccessful attempts to effect the cross-coupling of *O*-acetylated phenols using Ni-catalysis, see: Guan, B.; Xiang, S.; Wu, T.; Sun, Z.; Wang, B.; Zhao, K.; Shi, Z. *Chem. Commun.* **2008**, 1437–1439; see also ref 4.

(7) Approximate reagent costs by Aldrich Chemical Co., Inc. are: (a) Trimethylacetyl chloride (pivaloyl chloride) = $10 per mol. (b) Triflic anhydride = $310 per mol. (c) Methanesulfonyl chloride = $10 per mol. (d) Iodomethane = $24 per mol.

(8) For the insertion of Ni(0) into the *acyl* C−O bond of acylated phenols, see: Yamamoto, T.; Ishizu, J.; Kohara, T.; Komiya, S.; Yamamoto, A. *J. Am. Chem. Soc.* **1980**, *102*, 3758–3764.

(9) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Suzuki, A. *Chem. Commun.* **2005**, 4759–4763. (c) Doucet, H. *Eur. J. Org. Chem.* **2008**, 2013–2030.

(10) The more expensive and commonly used d^8 transition metal, palladium, was completely ineffective at promoting the desired transformation under a variety of reaction conditions.

(11) In the presence of Ni(0), other ligands such as PPh_3, dppe, dppf, and dppp provided trace amounts of cross-coupled products.

(12) An excess of the arylboronic acid component is required because the trimeric boroxine, which comprises between 30 and 60% of commercially available arylboronic acids, is completely unreactive under these anhydrous conditions.

(13) In the presence of excess arylboronic acid, $NiCl_2(PCy_3)_2$ is thought to undergo reduction to an active Ni(0) catalyst; see ref 3a.

(14) $NiCl_2(PCy_3)_2$, will soon be commercially available from Strem Chemicals Inc. (catalog #28-0091) or can be prepared in multigram quantities following a simple one-step protocol; see: (a) Stone, P. J.; Dori, Z. *Inorg. Chim. Acta* **1970**, *5*, 434–438. (b) Barnett, K. W. *J. Chem. Educ.* **1974**, *51*, 422–423.

(15) Arenes that possess an−OC(O)R substituent are known to undergo electrophilic aromatic substitution to afford *ortho*/*para* substituted products; see: Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 6th ed.; John Wiley & Sons, Inc.: NJ, 2007; p 668.

(16) The formation of *ortho*-brominated products was not observed, likely because of the steric bulk imposed by the pivalate group.

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