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Nickel(0)-Catalyzed Heck Cross-Coupling via Activation of Aryl C−OPiv Bonds

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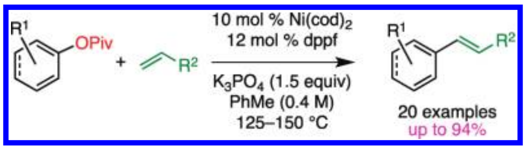
ABSTRACT



Using a Ni(dppf) catalyst generated in situ, Heck cross-coupling of aryl pivalates with a variety of olefin partners has been accomplished. This method represents one of the first examples of a C−C cross-coupling via activation of a strong C−O bond with a nonorganometallic coupling partner. It enables the transformation of phenol-based substrates into styrenyl products without generation of a halogenated byproduct or the use of expensive triflate groups.

The development of greener and less expensive methods is an ongoing challenge in the synthesis of organic compounds. The ubiquity of inexpensive phenols makes them attractive starting materials for the preparation of elaborated aromatic targets. In general, transformation of the C−O bond of such phenol substrates requires activation of the oxygen functional group as a triflate.[1] However, initial reports by Wenkert[2] and more recent efforts in this area have been devoted to nickel-catalyzed activation and subsequent functionalization of the much stronger C−O bonds in aryl ethers, carboxylates, and carbamates, among others.[3] These efforts have resulted in powerful new cross-coupling reactions to form C−C,[4−6] C−N,[7] and C−H[8] bonds using inexpensive oxygen functional groups without generation of a halogenated byproduct. Notably, however, the formation of C−C bonds via activation of such C−O bonds has largely been accomplished with organometallic coupling partners, such as Grignard or boronic reagents (Scheme 1A). Itami recently reported the Ni-catalyzed cross-coupling of azoles with phenol derivatives, including aryl pivalates.[9] However, the compatibility of activating

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(3) For reviews of cross-couplings via C−O bond cleavage, see: (a) Li, B.-J.; Yu, D.-G.; Sun, C.-L.; Shi, Z.-J. *Chem.—Eur. J.* **2011**, *17*, 1728. (b) Rosen, B.; Quasdorf, K.; Wilson, D.; Zhang, N.; Resmerita, A.-M.; Garg, N.; Percec, V. *Chem. Rev.* **2010**, *111*, 1346.

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(5) For examples of aryl and vinyl ethers and alcohols, see: (a) Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4866. (b) Guan, B.-T.; Xiang, S.-K.; Wu, T.; Sun, Z.-P.; Wang, B.-Q.; Zhao, K.-Q.; Shi, Z.-J. *Chem. Commun.* **2008**, 1437. (c) Dankwardt, J. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2428. (d) Hayashi, T.; Katsuro, Y.; Kumada, M. *Tetrahedron Lett.* **1980**, *21*, 3915. (e) Yu, D.-G.; Li, B.-J.; Zheng, S.-F.; Guan, B.-T.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4566. (f) Ueno, S.; Mizushima, E.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2006**, *128*, 16516. (g) Kakiuchi, F.; Usui, M.; Ueno, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2004**, *126*, 2706.

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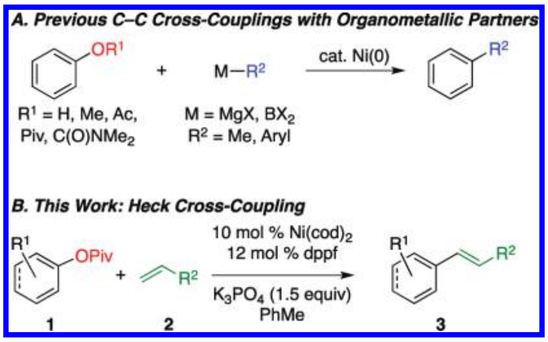
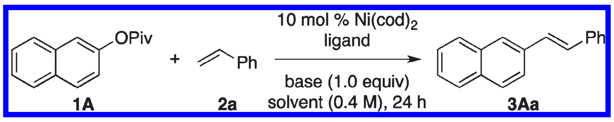
strong C–O bonds with other nonorganometallic partners has not yet been demonstrated, despite its potential utility in both the preparation of synthetic building blocks and late-stage functionalization of complex molecules. To this end, we have developed a Ni(0)-catalyzed cross-coupling of aryl pivalates with olefins (Scheme 1B). This Heck reaction allows facile preparation of 1,2-disubstituted olefins without use of an expensive triflate group or formation of a halogenated byproduct.

Scheme 1. C–C Bond Formation via Activation of Strong C–O Bonds



We selected the reaction of 2-naphthyl pivalate (**1A**) and styrene (**2a**) for optimization studies. Based on conditions reported for other Ni-catalyzed cross-couplings via activation of strong C–O bonds, we anticipated that tricyclohexylphosphine (PCy_3) would be a suitable ligand for our desired Heck cross-coupling.[4,6] However, only a trace amount of product formed when PCy_3 was used with $Ni(cod)_2$ and K_2CO_3 (Table 1, entry 1). A screen of ligands showed that higher yields are obtained with bidentate phosphine ligands, such as racemic 2,2′-bis(diphenylphosphino)-1,1′-binapthyl (BINAP) (entries 2 and 3 vs 4). By changing the base to K_3PO_4, which is more commonly used in Ni-catalyzed C–O activations than K_2CO_3, a further increase in yield was observed (entry 5). Use of organic bases such as Et_3N, pyridine, and *i*-Pr_2NEt led to no reaction. A broader screen of bidentate phosphine ligands under these conditions led to identification of 1,1′-bis(diphenylphosphino)ferrocene (dppf) as the best ligand (entry 6). By increasing the reaction temperature and time, an 82% isolated yield of product **3Aa** was obtained (entry 10).[10] We reinvestigated PCy_3 under these optimized conditions and again found dppf to be superior (entry 7 vs 8).[11] Solvents other than PhMe were less effective in this reaction (entry 9). The cross-coupling can be performed with lower catalyst loading, but a somewhat diminished yield and recovered starting material were observed (entry 11). Lower yields were also observed with less than 2 equiv of styrene (not shown). In addition, we must emphasize that efficient stirring is necessary to achieve a high yield in this heterogeneous reaction.

Table 1. Optimization of Cross-Coupling[a]



entry	ligand (mol %)	base	temp (°C)	solvent	yield (%)[b]
1	PCy_3 (24)	K_2CO_3	110	PhMe	<1
2	PPh_3 (24)	K_2CO_3	110	PhMe	<1
3	bpy[c] (12)	K_2CO_3	110	PhMe	<1
4	BINAP (12)	K_2CO_3	110	PhMe	11
5	BINAP (12)	K_3PO_4	110	PhMe	26
6	dppf (12)	K_3PO_4	110	PhMe	40
7	dppf (12)	K_3PO_4	125	PhMe	56
8	PCy_3 (24)	K_3PO_4	125	PhMe	28
9	dppf (12)	K_3PO_4	125	$(n\text{-Bu})_2O$	12
10[d]	**dppf (12)**	**K_3PO_4**	**125**	**PhMe**	**99 (82)**
11[d,e]	dppf (6)	K_3PO_4	125	PhMe	84

[a] Conditions: Substrate **1A** (0.10 mmol), styrene (**2a**, 0.20 mmol, 2.0 equiv), $Ni(cod)_2$ (0.010 mmol, 10 mol %), ligand, base (1.0 equiv), solvent (0.25 mL, 0.4 M), 24 h, unless otherwise noted. [b] Determined by GC using dodecane as internal standard. Numbers in parentheses are isolated yields. [c] bpy = bipyridine. [d] Reaction mixture was heated for 48 h. [e] 5 mol % $Ni(cod)_2$ used.

We also examined the possibility of activating alternative C–O bonds, which have been successfully cleaved in other Ni-catalyzed cross-couplings (Table 2).[3] No other naphthol derivative was as reactive as pivalate **1A** under the optimized reaction conditions. The reaction of 2-naphthyl tosylate resulted in a 55% yield (GC) of styrene **3Aa** (entry 2).[12] In the reactions of 2-naphthyl mesylate, acetate, and carbamate, yields were substantially less than that with pivalate **1A** (entries 3–5). 2-Napthylmethyl ether failed to react at all (entry 6). In these reactions, the starting material was largely recovered, although a trace amount of naphthol was also observed in the case of the acetate and carbamate.

Under our optimized conditions (Table 1, entry 10), a number of disubstituted olefins can be formed by reaction of naphthyl pivalate **1A** and various olefin partners (Table 3).[13] Styrenes with bulky aromatic groups were well tolerated (entries 2, 3). Good yields were also obtained using electron-poor and -rich styrenes (entries 4–8). Notably, the nitrile functional group is unaffected by this transformation (entry 4). Further, selective activation of the C–OPiv bond occurs in the presence of C–OMe bonds (entry 6). Silyl ethers and amines are also tolerated under

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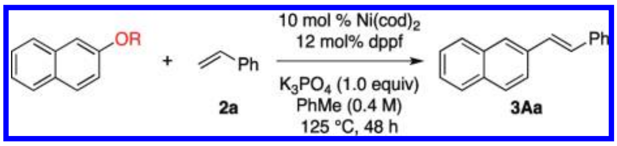
(10) Reactions were conducted in 1-dram vials, capped with Teflon-lined caps, and heated using aluminum heating blocks deep enough to completely enclose the glass of the vial.

(11) Dppf has been used in Ni-catalyzed cross-couplings via activation of benzylic C–OMe bonds. See: (a) Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389. (b) Guan, B.-T.; Xiang, S.-K.; Wang, B.-Q.; Sun, Z.-P.; Wang, Y.; Zhao, K.-Q.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 3268.

(12) The Ni-catalyzed Heck reaction of this tosylate with an enol ether was recently reported. See: Gøgsig, T. M.; Kleimark, J.; Lill, S. O. N.; Korsager, S.; Lindhardt, A. T.; Norrby, P.-O.; Skrydstrup, T. *J. Am. Chem. Soc.* **2012**, *134*, 443.

(13) Increasing the amount of K_3PO_4 to 1.5 equiv led to more reproducible yields.

Table 2. Various Oxygen Functional Groups[a]



entry	R	yield (%)[b]
1	Piv	99
2	Ts	55
3	Ms	26
4	Ac	29
5	C(O)NEt$_2$	25
6	Me	0

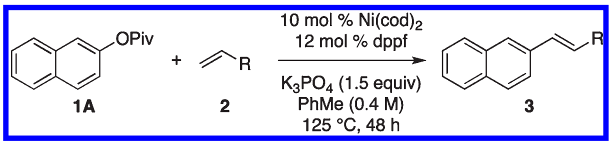
[a] Conditions: Substrate (0.10 mmol), styrene (**2a**, 0.20 mmol, 2.0 equiv), Ni(cod)$_2$ (0.010 mmol, 10 mol %), dppf (0.012 mmol, 12 mol %), K$_3$PO$_4$ (0.10 mmol, 1.0 equiv), PhMe (0.25 mL, 0.4 M), 125 °C, 48 h. [b] Determined by GC using dodecane as internal standard.

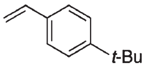
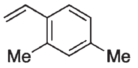
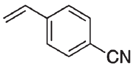
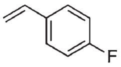
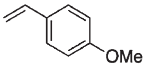
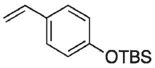
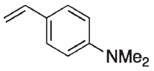
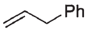
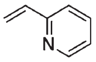
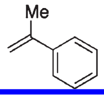
these reaction conditions (entries 7–8). α-Olefins can also be used in this cross-coupling (entry 9). Although olefin isomers of styrene **3Ai** were observed as minor byproducts, an 87% yield of the major isomer was isolated cleanly. However, lower yields are observed with heteroaromatic styrenes, such as 2- or 4-vinylpyridine (2-vinylpyridine shown, entry 10). In these cases, remaining pivalate is observed. α-Methylstyrene was reactive as an olefin partner but resulted in a 1.6:1 mixture of olefin isomers, 1-(2-naphthyl)-2-phenylpropene and 2-phenyl-3-(2-naphthyl)-propene (entry 11). With 1,2-disubstituted olefins, such as cyclohexene, only a trace amount of cross-coupling product was observed, and pivalate **1A** was largely recovered (not shown). Electron-poor methyl vinyl ketone and benzyl acrylate failed to react under these conditions.

Consistent with other Ni-catalyzed cross-couplings via C–O bond activation,[5a,e,8b] we found that the reaction of phenyl pivalate (**1B**) resulted in a lower yield than in the case of naphthyl pivalate (**1A**) (Table 4, entry 1). Longer reaction times were ineffective in substantially increasing the yield of product **3Bb** (entry 2), but increasing the reaction temperature provided synthetically useful yields (entries 3 and 4). Because of difficulties in purification caused by using mesitylene as solvent, we ultimately chose to use PhMe as solvent and heat these reactions at 150 °C in sealed vials. This method enabled a 57% isolated yield of stilbene **3Bb** (entry 4).

At this higher temperature, the Heck cross-couplings of various aryl pivalates were accomplished in moderate to good yields (Table 4). The C–OPiv bond could be selectively activated in the presence of aryl ether bonds and acetals (entries 6–8). Nitrile groups were also tolerated (entry 9). However, pivalates with electron-rich substituents were sluggish in this reaction, resulting in a low yield (entry 10). Finally, vinyl pivalates also underwent reaction using these conditions (entry 12).

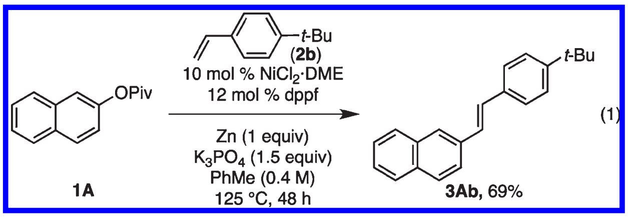
Table 3. Scope of Olefin Partner[a]



entry	2	3	yield (%)[b]
1		**3Aa**	86
2		**3Ab**	89
3		**3Ac**	90
4		**3Ad**	75
5		**3Ae**	85
6		**3Af**	81
7		**3Ag**	94
8		**3Ah**	81
9		**3Ai**	87
10		**3Aj**	44
11		**3Ak + 3Ak’**	64[c]

[a] Conditions: Pivalate **1A** (0.20 mmol), styrene (**2**, 0.40 mmol, 2.0 equiv), Ni(cod)$_2$ (0.020 mmol, 10 mol %), dppf (0.024 mmol, 12 mol %), K$_3$PO$_4$ (0.30 mmol, 1.5 equiv), PhMe (0.5 mL, 0.4 M), 125 °C, 48 h. [b] Average isolated yield from duplicate experiments (±3%), unless otherwise noted. [c] Combined yield of 1.6:1 mixture of 1-(2-naphthyl)-2-phenylpropene (**3Ak**) and 2-phenyl-3-(2-naphthyl)propene (**3Ak′**). Result of a single reaction.

In contrast to cross-couplings with organometallic reagents, our olefins cannot reduce a Ni(II) precatalyst in situ. Although Ni(cod)$_2$ provides a convenient source of Ni(0) for researchers with access to a glovebox, its instability in air limits the utility of our method. However, we have found that this Heck reaction can be set up on the bench by using NiCl$_2$·DME and zinc to form Ni(0) in situ (eq 1).[14] Although the yields are somewhat diminished, this procedure still provides synthetically useful yields of product **3Ab**.



We hypothesize that the mechanism of this Heck reaction follows the general mechanism of oxidative addition, migratory insertion, and β-hydride elimination. However,

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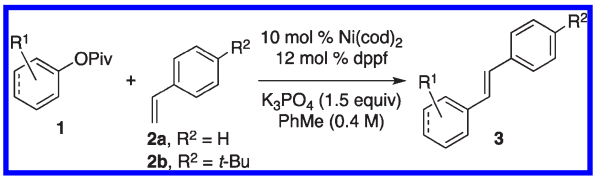
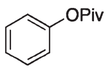
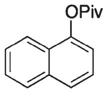
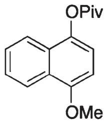
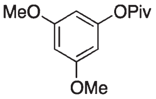
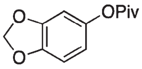
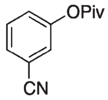
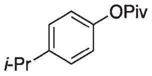
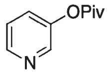
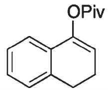
[14] See Supporting Information for full experimental details.

Table 4. Scope of Arylpivalate[a]



entry	1	2	3	temp (° C)	time (h)	yield (%)[b]
1		2b	3Bb	125	48	(22)
2				125	74	(30)
3[c]				150	48	(82)
4				150	48	57
5		2b	3Cb	150	48	50
6		2b	3Db	150	48	76
7		2b	3Eb	150	48	79
8		2b	3Fb	150	48	52
9		2b	3Gb	150	48	57
10		2b	3Hb	150	48	14[d]
11		2a	3Ia	150	48	76
12		2a	3Ja	150	48	85

[a] Conditions: Pivalate (**1**, 0.20 mmol), styrene (**2**, 0.40 mmol, 2.0 equiv), Ni(cod)$_2$ (0.020 mmol, 10 mol %), dppf (0.024 mmol, 12 mol %), K$_3$PO$_4$ (0.30 mmol, 1.5 equiv), PhMe (0.5 mL, 0.4 M), 150 °C, 48 h, unless otherwise noted. [b] Average isolated yield from duplicate experiments (±4%) unless otherwise noted. Numbers in parentheses are GC yields. [c] Reaction conducted in mesitylene. [d] Result of a single experiment.

we do not yet understand why a bisphosphine ligand provides higher yields than a monophosphine ligand.[15] In their computational studies of Suzuki cross-couplings of aryl acetates and aryl carbamates, Liu and Garg have shown that monophosphine nickel(0) complexes undergo oxidative addition more readily than bisphosphine nickel(0).[4d,6b] Further, Liu was unable to computationally locate a pathway for transmetalation of the coordinatively saturated bisphosphine nickel aryl acetate complex. Indeed, the relatively high temperatures required to achieve the Heck coupling are consistent with slower oxidative addition of a bisphosphine nickel catalyst. The higher yields observed with dppf then may be due to its ability to stabilize the resting state of the nickel catalyst and/or to facilitate a different step of the catalytic cycle. It is possible that a bidentate phosphine promotes a cationic mechanism, in which pivalate dissociates from the Ni(II) intermediate after oxidative addition. Such a cationic Ni(II) species would undergo faster olefin coordination and subsequent migratory insertion than a neutral Ni(II) species. Use of a monophosphine ligand would likely favor a neutral Ni(II) intermediate, because the phosphine would dissociate instead of the more tightly bound pivalate.[16] Studies are underway to investigate this interesting observation further.

As discussed above, we have developed the first C–C cross-coupling of an aryl carboxylate with an olefin partner. This Heck reaction enables aryl and vinyl pivalates to be efficiently coupled with both styrenes and α-olefins, providing facile access to 1,2-disubstituted olefin products without generation of a halogenated waste stream or use of triflate groups. Ongoing efforts in our labratory are directed toward expanding the scope of this useful transformation and understanding how the Ni(dppf) catalyst promotes this coupling.

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Supporting Information Available. Experimental procedures, characterization data, and spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] A bisphosphine ligand is also optimal in Itami's cross-coupling of azoles with aryl pivalates. See ref 9.

[16] Lin, B.-L.; Liu, L.; Fu, Y.; Luo, S.-W.; Chen, Q.; Guo, Q.-X. *Organometallics* **2004**, *23*, 2114.

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