

The First General Palladium Catalyst for the Suzuki–Miyaura and Carbonyl Enolate Coupling of Aryl Arenesulfonates

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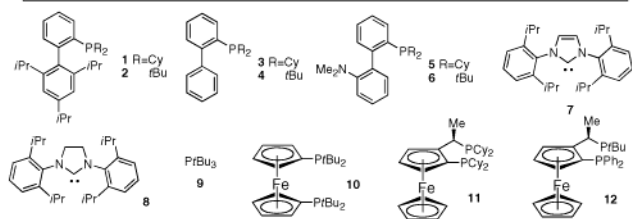
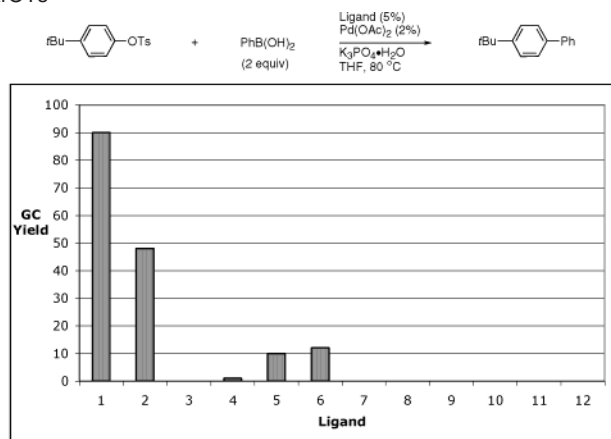
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Cross-coupling methodology to form carbon–carbon bonds has revolutionized organic synthesis.¹ The Suzuki–Miyaura coupling is, arguably, of the greatest practical importance of these methods.² Recently, improved catalyst systems for Suzuki–Miyaura couplings have been described, that allow couplings to be carried out at room temperature,^{3a–c} to handle electron-rich aryl chlorides,^{3a,b} and to prepare highly substituted biaryls.^{3d} Missing is a system capable of handling aryl tosylates. This would be of significant interest as tosylates are more easily handled and considerably less expensive than aryl triflates. Aryl tosylates are relatively unreactive compared to aryl halides and triflates. They have been reported as substrates for other palladium-catalyzed processes, particularly in aromatic amination.⁴ However, for the formation of carbon–carbon bonds little success has been realized, and no general catalyst exists;⁵ some success has been seen with Ni catalyst.⁶ Herein we report on our efforts in this area.

We recently reported that XPhos, **1**,⁷ was an excellent supporting ligand for the Pd-catalyzed amination of aryl benzenesulfonates.^{4a} During this study we also confirmed previous work which had revealed that ferrocenyl ligands **11** and **12** were also moderate to very good in this regard.^{4b} Thus, we were surprised by the results shown in Table 1. While **1** was an effective supporting ligand for this transformation, the use of **11** or **12** provided none of the desired

Table 1. Screening of Ligands for Suzuki–Miyaura Coupling of ArOTs



product. While this is not easily interpretable, one possibility is, as we have previously shown for amination reactions catalyzed by

(BINAP)Pd, that oxidative addition occurs after binding of the amine to Pd(0) intermediate;⁸ such a process is unlikely for coupling reactions involving arylboronic acids.

The use of the catalyst derived from **1** and Pd(OAc)₂ in THF demonstrated a good deal of generality and is successful for a variety of combinations in which neither substrate contains an ortho substituent larger than an OMe group (Table 2). In these cases the reactions were complete in 3 h at 80 °C (80–90% isolated yield). Common functional groups—cyano, aldehyde, nitro and ketone—were tolerated.

Table 2. Suzuki–Miyaura Coupling of ArOTs and VinylOTs in THF^a

Entry	ArOTs or VinylOTs	Ar'B(OH) ₂	Product	Yield (%)
1	<i>t</i> -Bu-C ₆ H ₄ -OTs	(HO) ₂ B-C ₆ H ₄ -OMe	<i>t</i> -Bu-C ₆ H ₄ -C ₆ H ₄ -OMe	91
2	OHC-C ₆ H ₃ (OMe)-OTs	(HO) ₂ B-C ₆ H ₄ -OMe	OHC-C ₆ H ₃ (OMe)-C ₆ H ₄ -OMe	91 ^b
3	1-Naphthyl-OTs	(HO) ₂ B-C ₆ H ₄ -NO ₂	1-Naphthyl-C ₆ H ₄ -NO ₂	93
4	2,3-Dihydrobenzofuran-5-yl-OTs	(HO) ₂ B-C ₆ H ₄ -NO ₂	2,3-Dihydrobenzofuran-5-yl-C ₆ H ₄ -NO ₂	84 ^c
5	2-Pyridyl-OTs	(HO) ₂ B-C ₆ H ₄ -CF ₃	2-Pyridyl-C ₆ H ₄ -CF ₃	92
6	1-Naphthyl-OTs	(HO) ₂ B-C ₆ H ₄ -R	1-Naphthyl-C ₆ H ₄ -R	R = <i>m</i> CF ₃ (90) <i>p</i> C(O)Me (91)
7	Cyclohexyl-OTs	(HO) ₂ B-C ₆ H ₄ -NMe ₂	Cyclohexyl-C ₆ H ₄ -NMe ₂	92 ^d
8	<i>t</i> -Bu-C ₆ H ₄ -OTs	(HO) ₂ B-C ₆ H ₄ -CN	<i>t</i> -Bu-C ₆ H ₄ -C ₆ H ₄ -CN	92 ^d
9	TsO-C ₆ H ₄ -Cl	(HO) ₂ B-C ₆ H ₄ -OMe	TsO-C ₆ H ₄ -C ₆ H ₄ -OMe	88 ^e

^a Reaction conditions: ArOTs or VinylOTs (1 equiv), Ar'B(OH)₂ (2 equiv), K₃PO₄·H₂O (3 equiv), 2 mol % Pd(OAc)₂, 5 mol % **1**, THF, 80 °C, 3 h. Isolated yield (average of two runs). ^b (2-Methoxy-biphenyl-4-yl)-phenylmethanol was also isolated in 3% yield. ^c Reaction time 5 h. ^d Reaction time 1 h. ^e PhB(OH)₂ (1.3 equiv) at room temperature for 2 h.

For difficult substrates, complete conversion of aryl tosylates was achieved when the cross-coupling reaction was performed with a higher catalyst loading (3% Pd(OAc)₂ and 7 mol % **1**) in *t*-BuOH for 6 h (Table 3). We believe that *t*-BuOH probably increases the solubility of the aryl tosylates and arylboronic acids, allowing them to proceed at rates much faster than protodeboronation. For example, with 2,6-dimethoxyphenylboronic acid (Table 3, entry 1), a high yield of coupling product (92%) was obtained. When THF was employed as solvent under similar conditions, conversion of the aryl tosylate was incomplete, and extensive deboration of the

Table 3. Suzuki–Miyaura Coupling of ArOTs in *t*-BuOH^a

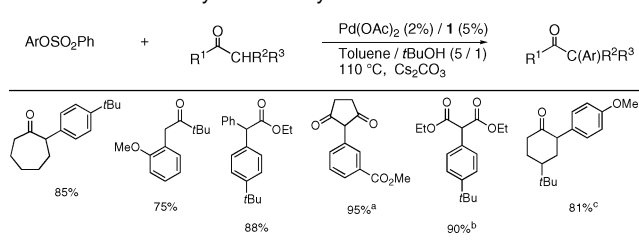
Entry	ArOTs	Ar'B(OH) ₂	Product	Yld (%)
1				92
2				84
3				94
4				88
5				90
6				82
7				94
8				89
9				80 ^b
10				87 ^c

^a Reaction conditions: ArOTs (1 equiv), Ar'B(OH)₂ (2 equiv), K₃PO₄·H₂O (3.0 equiv), 3 mol % Pd(OAc)₂, 7 mol % **1**, *t*-BuOH, 80 °C, 6 h. Isolated yield (average of two runs). ^b Reaction time 9 h, 89–92% conversion of ArOTs. ^c Reaction time 17 h at 110 °C, 88–93% conversion of ArOTs.

boronic acid was observed. We also found that more hindered boronic acids such as 2-methylphenylboronic acid (entries 3 and 4) and 2,6-dimethylphenylboronic acid (entries 6 and 7) could be efficiently utilized as substrates; in THF these reactions failed to proceed to completion. These conditions also worked well to combine 5-(tosyloxy)-1-tetralone and pyridine-3-boronic acid (entry 5). Remarkably, 2,4,6-triisopropylphenylboronic acid, which is exceptionally hindered, could be coupled in high yield (entry 8). These results indicated that the transmetalation step was facile under the conditions studied. In contrast, even a single methyl group at the α -carbon to the tosylate was enough to prevent complete conversion (entries 9 and 10) although very good isolated yields were still obtained. Thus, the standard situation in which transmetalation is rate limiting does not hold here. Moreover, the coupling of 2,4-dimethylchlorobenzene with PhB(OH)₂ proceeded quantitatively in 1 h at 50 °C. Thus, it is tempting to postulate that the transition states for oxidative addition of L_nPd to the tosylate and the aryl chloride have significantly different steric requirements.

We have also demonstrated, as shown in Table 4, for the first time that aryl benzenesulfonates can be utilized as substrates in the arylation of enolates derived from cyclic and acyclic ketones, β -dicarbonyl compounds, and an ester.⁹

In summary, we have disclosed the first palladium catalyst system for the Suzuki–Miyaura coupling of unactivated aryl tosylates. This

Table 4. Enolate Arylation of Aryl Benzenesulfonates

^a K₂CO₃ as base, *t*-BuOH as solvent, from aryl tosylate. ^b Toluene was the solvent. ^c Isolated yield of pure *cis* isomer. Ratio of *cis:trans* in crude product was ~5:1.

system can handle a wide range of substrates, including extremely hindered arylboronic acids, under mild conditions. The same catalyst was also used in the first example of the cross-coupling of carbonyl enolates with aryl arenesulfonates.

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Supporting Information Available: Experimental procedures and characterization data for all unknown compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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