

The First Suzuki Cross-Couplings of Aryltrimethylammonium Salts

Simon B. Blakey and David W. C. MacMillan*

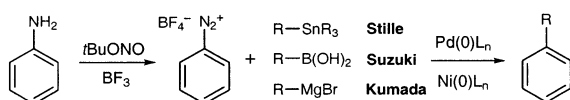
Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

Received February 27, 2003; E-mail: dmacmill@caltech.edu

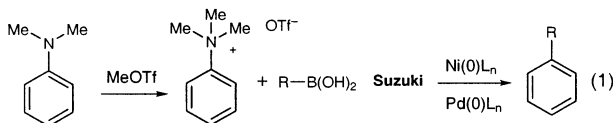
The transition-metal-catalyzed cross-coupling reaction has emerged as one of the most powerful carbon–carbon bond-forming protocols available to practitioners of chemical synthesis.¹ In this context, aryl bromides, iodides, triflates, and, more recently, chlorides² have found broad utility as electrophilic coupling partners in combination with a host of metalobenzene systems. Surprisingly, simple arylamines have yet to be employed directly as oxidative insertion substrates, a notable deficiency in light of their widespread availability and application as π -nucleophiles (Friedel–Crafts, electrophilic aromatic substitution, etc.). While aryl diazonium salts have been utilized in this context,³ the requirement of primary amine precursors and the attendant derivatization conditions (H_2SO_4 , NaNO_2) have restricted their general use.

In 1988, Wenkert and co-workers documented the nickel-catalyzed Kumada reaction of aryltrimethylammonium iodides,⁴ to date the only report of a trialkylammonium-insertion cross-coupling reaction. While the inherent scope and reaction efficiencies were found to be limited, this pioneering study introduced the attractive prospect that dialkylanilines might be utilized as metal insertion precursors via a simple nitrogen-quaternization step. In this Communication, we advance this catalytic concept to describe the first Suzuki cross-coupling reaction of aryltrimethylammonium triflates based on the use of a novel IMes•Ni(0) catalyst complex.⁵ This new Suzuki variant can be accomplished with excellent yield for a broad range of dialkylaniline and boronic acid substrates (eq 1).

Classical Diazotization–Metal Mediated Coupling Sequence



Trialkylammonium Salts Function as Suzuki–Coupling Partners



Our investigation into an effective arylammonium Suzuki reaction began with *p*-butyl-trimethylammonium benzene triflate (**1**), phenyl boronic acid (**2**), and a series of Ni(0) catalyst complexes (Table 1). Nickel catalysts have been successfully employed in a wide range of Suzuki coupling reactions, providing ample precedence for transmetalation with arylboronic acids.⁶ As such, we felt the challenge lay in identifying a catalyst that would readily insert into an aryl–ammonium bond. On the basis of the studies of Wenkert and Miyaura,⁷ we examined Ni(dppp)Cl₂ and Ni(dppf)Cl₂ as catalyst precursors, with the addition of 2 equiv of the bulky electron-rich phosphine ligand **3**; however, in each case, only a trace quantity of the cross-coupled product **5** was observed (entries 1 and 2). Catalyst turnover was accomplished using the 1,3-bis-

Table 1. Optimization of the Catalyst System^a

entry	Ni complex	ligand	base	% yield ^d
1	Ni(dppp)Cl ₂ ^b	3 ^c	K ₃ PO ₄	10
2	Ni(dppf)Cl ₂ ^b	3 ^c	K ₃ PO ₄	11
3	Ni(dppp)Cl ₂ ^b	IMes•HCl	K ₃ PO ₄	20
4	Ni(dppf)Cl ₂ ^b	IMes•HCl	K ₃ PO ₄	27
5	Ni(dppf)Cl ₂ ^b	IMes•HCl	KF	16
6	Ni(COD) ₂	IMes•HCl	K ₃ PO ₄	5
7	Ni(COD) ₂	IMes•HCl	KF	57
8	Ni(COD) ₂	IMes•HCl	CsF	98
9	Ni(COD) ₂	IMes•HCl	CsF	37
10	Ni(COD) ₂	3	CsF	6
11	Pd ₂ (dba) ₃	IMes•HCl	CsF	0

^a Reaction conditions: 1.0 equiv of ArNMe₃X, 1.1 equiv of PhB(OH)₂, 10 mol % catalyst, 10 mol % ligand, 3.0 equiv of base, 80 °C, 12 h. ^b 0.4 equiv of ^tBuLi was used to reduce Ni(II) to Ni(0). ^c 20 mol % ligand used. ^d Yields based on LCMS analysis. ^e Reactions run using the corresponding trialkylammonium iodide resulted in reduced yields.

(2,4,6-trimethylphenyl)imidazole carbene ligand **4** with Ni(dppp)Cl₂ and Ni(dppf)Cl₂; however, reaction efficiencies remained markedly poor (entries 3–5). In an effort to access a phosphine-free catalyst system, we next examined Ni(COD)₂ as a metal source (entries 6–8). To our delight, the catalyst complex arising from Ni(COD)₂ and IMes•HCl,^{8,9} in the presence of CsF as a mild base, gave the desired cross-coupled adduct in 98% isolated yield (entry 8). It is important to note that attempts to perform the analogous Ni(COD)₂ protocol with ligand **3** or in the absence of IMes•HCl resulted in diminished yields (entries 9 and 10). To date, the use of palladium catalysts in this coupling reaction has proven unsuccessful.

The superior reaction efficiencies observed with Ni(0)•IMes in the presence of CsF prompted us to select these catalytic conditions for further exploration.

The scope of this ammonium Suzuki coupling with respect to the aryl boronic acid component has been investigated (Table 2). Gratifyingly, a wide range of boronic acids that incorporate electron-donating groups (entries 1–6) and electron-withdrawing groups (entries 7–10) at the ortho, meta, and para positions are readily tolerated (79–98% yield). Furthermore, both boronate esters (entry 12) and alkenylboranes (entry 13) could be cross-coupled using our standard reaction conditions.

We have also investigated functional group tolerance with respect to the substituents on the aryltrimethylammonium triflate (Table

Table 2. Ammonium Suzuki Couplings of Arylboronic Acids

entry	ArB(OR) ₂	Product	% yield
1			83
2			89
3 ^b			95
4			94
5 ^c			83
6			79
7			82
8			82
9			98
10			87
11			84
12			89
13 ^d			92

^a Reaction times not optimized. ^b 1.1 equiv of boronic acid was used. ^c K₃PO₄ was used in place of CsF. ^d Reaction performed with 4-(carboxylic acid methyl ester)-*N,N,N*-trimethylanilinium triflate.

3). It is well established that electron-rich aromatic systems are generally less susceptible to oxidative addition. As such, we were delighted to find a range of electron-rich ammonium salts efficiently coupled with phenylboronic acid (entries 1–5). As expected, aryl systems with electron-withdrawing substituents performed well under our standard reaction conditions (entries 6–8).

In summary, we have developed a novel catalyst system, capable of activating aryl–ammonium bonds for Suzuki cross-coupling reactions. Full details of this new trialkylammonium Suzuki reaction will be forthcoming.

Acknowledgment. Support was provided by a research foundation grant from Bristol-Myers Squibb.

Table 3. Suzuki Couplings of Aryltrimethylammonium Triflates

entry	ArNMe ₃ OTf	Product	% yield
1			89
2			84
3			96
4			85
5			92
6			93
7			94
8			88

^a Reaction times were not optimized.

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

References

- (1) For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1988.
- (2) (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (b) Wolfe, J. P.; Singer, R. A.; Bryant, H. Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550. (c) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387.
- (3) (a) Darres, S.; Jeffrey, J. P.; Genet, J. P.; Brayer, J. L.; Demoute, J. P. *Tetrahedron Lett.* **1996**, *37*, 3857. (b) Kikukawa, K.; Kono, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* **1983**, *48*, 1333.
- (4) Wenkert, E.; Han, A.-L.; Jenny, C.-J. *J. Chem. Soc., Chem. Commun.* **1988**, 975.
- (5) All of the aryltrimethylammonium triflates described in this Communication were readily prepared from the corresponding dimethylaniline by alkylation with methyl trifluoromethanesulfonate in dichloromethane. See: Langer, O.; Dollé, F.; Valette, H.; Halldin, C.; Vaufrey, F.; Fuseau, C.; Coulon, C.; Ottaviani, M.; Nägren, K.; Bottlaender, M.; Mazière, B.; Cruzel, C. *Bioorg. Med. Chem.* **2001**, *9*, 677.
- (6) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
- (7) Saito, S.; Oh-tani, S.; Miyaura, N. *J. Org. Chem.* **1997**, *62*, 8024.
- (8) Arduengo, J. A., III; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530.
- (9) (a) Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organomet. Chem.* **1988**, *577*, 93. (b) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804. (c) Böhm, V. P. W.; Gstöttmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, *595*, 186. (d) Böhm, V. P. W.; Weskamp, T.; Gstöttmayr, C. W. K.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1602. (e) Fürstner, A.; Leitner, A. *Synlett* **2001**, 290. (f) Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866.

JA034908B