Tetrahedron Letters, Vol.31, No.12, pp 1665-1668, 1990
Printed in Great Britain

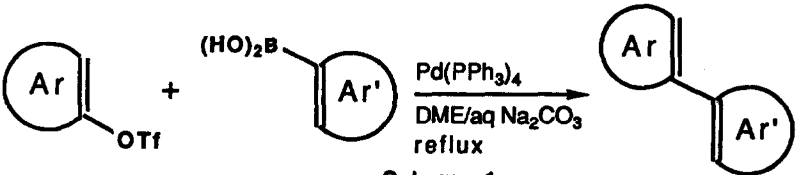
0040-4039/90 $3.00 + .00
Pergamon Press plc

CONNECTIONS TO THE DIRECTED ORTHO METALATION STRATEGY. Pd(0)-CATALYZED CROSS COUPLING OF ARYL BORONIC ACIDS WITH ARYL TRIFLATES†

J.-m. Fu and V. Snieckus*
Guelph-Waterloo Centre for Graduate Work in Chemistry
University of Waterloo, Waterloo, Ontario CANADA N2L 3G1

Summary: A new and general Pd(0)-catalyzed cross coupling reaction of aryl boronic acids with aryl triflates to give biaryls (**Scheme 1**) is reported.

The rapid evolution of preparative methods and applications based on the transition metal-catalyzed cross coupling has been particularly evident in the synthesis of unsymmetrical biaryls and heterobiaryls using aryl halide (Br, I) and aryl MgX,[1] ZnX,[2] $B(OR)_2$, R = H, alkyl,[3] SnR_3,[4] and, most recently, SiR_3,[5] coupling partners. As part of the recent emergence of triflates as versatile synthetic intermediates,[6] their general cross coupling reactions with aryl ZnX[7] and aryl SnR_3[8] intermediates have been described.[9] In the continuation of efforts aimed to develop synthetically flexible directed *ortho* metalation[10] - cross coupling sequences,[3g,3h] we have investigated the aryl boronic acid - aryl triflate variation. Herein we disclose preliminary results[11] which suggest broad utility of this reaction (**Scheme 1**) and demonstrate potentially valuable selectivity of aryl halide versus aryl triflate couplings (**Scheme 2**).



Scheme 1

Cross coupling reactions between aryl boronic acids and triflates[12] were conducted in the presence of $Pd(PPh_3)_4$ (0.05 equiv) in a mixture of dimethoxyethane (DME) and 2M aq Na_2CO_3 at reflux for 8-12 h. Selected results, summarized in the **Table**, indicate that phenyl (entry A), naphthyl (entry B), and phenanthryl[3h] (entries C-E) undergo, with one exception, efficient cross coupling to produce biaryls. In the

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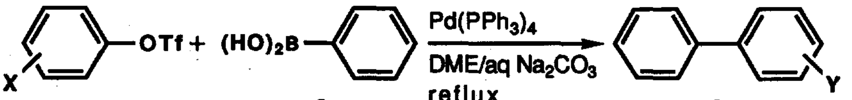
† This paper is dedicated to the memory of John K. Stille.

exception (entry E), steric hindrance to coupling appears to be responsible for the low yield. The high yield of a quinoline triflate coupling (entry F) bodes well for development of a general method for heterobiaryl construction. Aryl boronic acids with *ortho* amide (entries D,[13] F, G) and N-t-BOC (entry B) directed metalation groups smoothly participate in the reaction; in view of the ready availability of diverse aryl boronic acids derived by the directed *ortho* metalation process,[3h,10] this method should find application for the synthesis of a variety of carbon- and heteroatom-functionalized biaryls. Extension to vinyl triflates also appears to be feasible (entry G).



1 **2** **3**

a: *o*-Br; **b**: *o*-I
c: *p*-Br; **d**; *p*-I

a: *o*-OTf; **b**: *o*-OH; **c**: *o*-Ph
d: *p*-OTf; **e**: *p*-OH; **f**: *p*-Ph

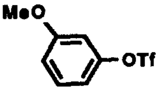
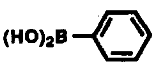
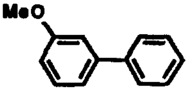
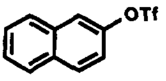
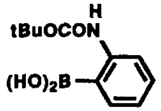
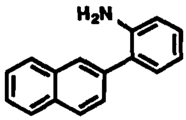
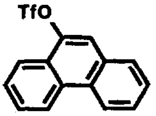
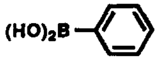
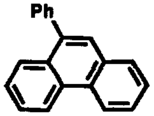
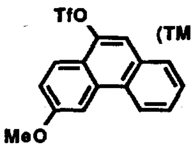
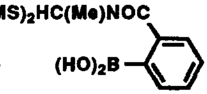
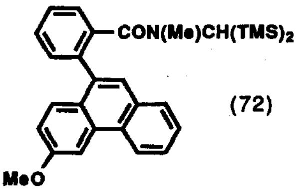
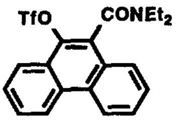
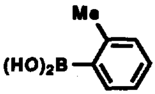
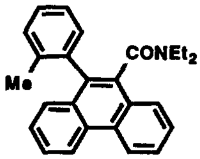
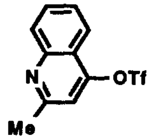
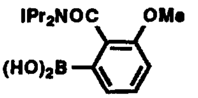
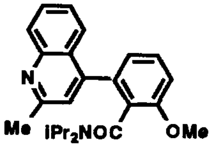
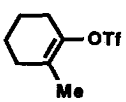
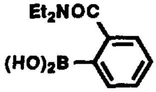
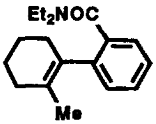
ArOTf	Biphenyl[a] (Yield%)		
1a	3a (33)	3b (21)	3c (20)
1b	3a (14)	3b (40)	3c (34)
1c	3d (0)	3e (22)	3f (37)
1d	3d (0)	3e (28)	3f (59)

[a] Identity of compounds 3b, 3c, 3e and 3f was confirmed by comparison of mp with those of authentic materials reported in the literature (Luttringhaus, A; Saaf, G.V. *Ann.* **1939**, 542, 241; Bachmann, W.E.; Clarke, H.T. *J. Am. Chem. Soc.* **1927**, 49, 2089; Raiford,L. C.; Colbert, J.C. *ibid.* **1925**, 47, 1454; France, H.; Heilbron, I.M.; Hey, D.H. *J. Chem. Soc.* **1938**, 1364.).

Scheme 2

In order to compare relative reactivities[8] of aryl halides and aryl triflates, *ortho*- and *para*-bromo and -iodo phenyl triflates **1a-d** and phenyl boronic acid **2** (1:1.1 ratio) were subjected to the standard cross coupling conditions to give mixtures of isomeric biphenyl triflate **3a**, **3d**, phenols **3b**, **3e**, and terphenyls **3c**, **3f** respectively (**Scheme 2**). The absence of bromo and iodo biphenyls indicates, in agreement with previous work,[8] the order of reactivity I,Br > OTf. The usual I > Br reactivity order[8] is manifested in faster accumulation of **3a** from **1b** than from **1a** which is reflected in higher yields of secondary products (hydrolysis to **3b** or cross coupling to **3c**) in the case of **1b** compared to **1a**. Similar results were obtained in the *p*-X series, **1c** and **1d**, except for the absence of triflate **3d**, an indication of greater steric inhibition to hydrolysis (**3e**) and cross coupling (**3f**) in the *o*-series compared to the *p*-series.

Table. Pd(0)-Catalyzed Cross Coupling of Aryl Triflates with Aryl Boronic Acids

Entry	ArOTf	$ArB(OH)_2$	Product(Yield%)^a	mp (bp)°C
A			 (90)	85-86 (0.15 mmHg)^b
B			 (67)^c	91-93 (hexane)^d
C			 (87)	104-106 (hexane)^e
D			 (72)	118-119 (hexane)
E			 (34)^f	173-175 (hexane) 168-170 (hexane)^g
F			 (87)	161-163 (hexane/ CH_2Cl_2)
G			 (45) (54)^h	62-64 (pentane)

[a] Yields of chromatographed products. [b] Lit bp 159°C (12 mmHg) (Inukai, T.; Kobayashi, K.; Simamura, O. *Bull. Chem. Soc. Jpn.* **1962**, 35, 1576.). [c] After t-BOC deprotection (TFA/reflux/12h). [d] Lit mp 93-95°C (Hanson, P.; Stone, T.W. *J. Chem. Soc. Perkin Trans. I* **1984**, 2429.). [e] Lit mp 104-105°C (Bradsher, C.K.; Schneider, A.K. *J. Am. Chem. Soc.* **1938**, 60, 2960.). [f] N,N-diethyl 9-phenanthrenecarboxamide was isolated in 64% yield. [g] Two diastereomers (2.6:1 ratio), ^1H NMR ($CDCl_3$) δ 2.11 (s, Me), 1.98 (s, Me). [h] In the presence of LiCl (3 equiv), See ref 8.

In summary, the aryl boronic acid - aryl triflate cross coupling reaction constitutes a further permutation in the accumulating repertoire of synthetically valuable transition metal catalyzed C-C bond forming processes.[1-9] The link to the directed ortho metalation strategy[10] and the ready availability of triflates[12] offer particular advantages over other regimens. Generalization and application is in progress.[14,15]

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14. All new compounds show analytical and spectral (IR, NMR, MS) data fully consistent with the assigned structures.
15. We are grateful to NSERC Canada and Merck Frosst Canada for financial support of this research.

(Received in USA 4 January 1990)