A One-Pot, Single-Solvent Process for Tandem, Catalyzed C–H Borylation–Suzuki–Miyaura Cross-Coupling Sequences

Peter Harrisson,[a] James Morris,[b] Patrick G. Steel,*[a] Todd B. Marder*[a]

[a] Department of Chemistry, Durham University, South Road, Durham, DH1 3LE, UK
Fax +44(191)3844737; E-mail: todd.marder@durham.ac.uk; E-mail: p.g.steel@durham.ac.uk

[b] Syngenta Ltd., Jealott's Hill International Research Centre, Bracknell, Berkshire, RG42 6EY, UK

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Abstract: Methyl *tert*-butyl ether is a suitable solvent for iridium-catalyzed C–H borylation followed, in the same pot, by palladium-catalyzed Suzuki–Miyaura cross-coupling sequences, giving high yields of biaryls.

Key words: biaryls, cross-coupling, homogeneous catalysis, boronate ester, tandem reactions

Aryl and heteroaryl boronates[1] are very important organic intermediates, for example, in applications in a variety of transformations including Suzuki–Miyaura cross-coupling reactions,[2] copper-catalyzed C–O and C–N coupling reactions,[3] and rhodium-catalyzed conjugate additions to carbonyl compounds.[4] Following our observation of substoichiometric arene borylation during the formation of novel [(η^6-arene)Ir(Bcat)$_3$] (cat = 1,2-$O_2C_6H_4$) complexes from reaction of [(cod)Ir(η-indenyl)] with excess HBcat in aromatic solvents,[5] Ishiyama, Miyaura, and Hartwig et al.[6] and Smith et al.[7] have developed in situ Ir catalysts for the borylation of aromatic C–H bonds under mild conditions, employing [(cod)Ir(X)] precursors (X = Cl, OMe, η-indenyl) in the presence of bidentate ligands. The most widely used system at present employs [(cod)Ir(μ-OMe)]$_2$ (**1**) plus 4,4′-di-*tert*-butyl-2,2′-bipyridine.[8] Density functional theory (DFT) calculations by Sakaki and co-workers,[9] in agreement with the experimental data, suggest that the key catalytic intermediate that leads to C–H activation is the sterically encumbered, five-coordinate [Ir(Bpin)$_3$L$_2$]species [Bpin = B(OCMe$_2$CMe$_2$O)]. Steric hindrance in this intermediate accounts for the selectivity observed with these catalyst systems, as borylation typically avoids positions *ortho* to either substituents or to ring junctions. We have taken advantage of this selectivity to prepare novel pyrene-2,7-bis(boronate) and perylene-2,5,8,11-tetra(boronate) esters amongst other polycyclic aryl boronates.[10]

The concept of reducing the number of different operations in a synthesis is a fundamental component in the optimization process.[11] A classic way to achieve this is to run multiple or tandem reactions in a single vessel. Given the versatile nature of aryl boronic acids the direct C–H borylation has become an attractive method in these sequences. A number of 'one-pot' procedures have been described that elaborate the arylboronate ester products of aromatic C–H borylation providing phenols,[12] arylchlorides and bromides,[13] arylboronic acids and trifluoroborates,[14] alkyl- and arylanilines,[15] aryl ethers,[15] arylamine boronate esters,[16] chiral α,α-diaryl methylammonium chlorides[17] and for use in Suzuki–Miyaura cross-couplings.[7,18]

Hindering further development of this 'one-pot' technology is the fact that coordinating solvents, typically employed for Suzuki–Miyaura cross-couplings, are generally incompatible with the iridium-catalyzed borylation reactions, and thus solvents need to be changed between steps. This prompted us to explore alternative solvent systems, which might be compatible with both steps, thus reducing waste and cost in tandem-reaction sequences. We report herein that widely available MTBE is such a solvent, allowing C–H borylation–Suzuki–Miyaura cross-couplings to be conducted in sequence in a single pot and in a single solvent.

We commenced our study by examining the borylation of *m*-xylene in a range of solvents known to be compatible with the Suzuki–Miyaura reaction. However, in line with earlier reports,[6b] those containing coordinating atoms (e.g., DMF, MeCN, dioxane) proved ineffective, with reactions occurring only slowly and leading to poor conversions. Speculating that coordination to the active site in the Ir catalyst was the cause of this inhibition, we then sought solvents in which this could be prevented by simple steric effects and thus explored the use of 2-MeTHF and MTBE. Whilst both proved to be effective for the aromatic C–H borylation reaction, the latter, reflecting its earlier use as a fuel additive and its low tendency to form peroxides, is widely available at low cost and, consequently, we opted to focus on this solvent.

Although, for similar reasons, MTBE has been widely used in process chemistry for a number of years, we are not aware of it having been previously employed in the Suzuki–Miyaura reaction. Consequently, we undertook a simple, preliminary evaluation using purified phenyl boronic acid following the standard Suzuki–Miyaura reaction conditions we have used in our earlier chemistry [PhB(OH)$_2$ (1 mmol), MTBE (2.4 mL), H_2O (0.8 mL), 4-MeC$_6$H$_4$I (1.1 mmol), Pd(dppf)Cl$_2$ (2 mol%), K_2CO_3 (2 mmol)]. Pleasingly, this afforded the desired cross-coupled product, albeit at 75% conversion and contaminated

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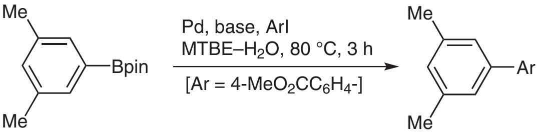
by homocoupled product (Ph–Ph) arising from $PhB(OH)_2$ which was inseparable from the desired material due to the structural similarities of the two molecules.

Having established that the Suzuki–Miyaura reaction could be undertaken in MTBE, we then explored the tandem sequence. Following complete borylation of *m*-xylene at the 5-position to give its pinacolboronate ester (GC-MS), water, methyl 4-iodobenzoate, $Pd(dppf)Cl_2$, and K_2CO_3 were added, and the solution was heated at 80 °C. After 3 hours, minimal amounts of cross-coupled product could be detected, whilst heating for 14 hours afforded 30% of the desired coupled product with the major product being the initial arene arising from protodeborylation. In order to improve the process, we then undertook a simple screen of different bases, catalysts, and stoichiometry, using isolated 3,5-$Me_2C_6H_3$Bpin, as shown in Table 1.

Initial attempts to vary the stoichiometry of the base proved ineffectual, and the first significant success was observed when using $Ba(OH)_2{\cdot}8H_2O$ as the base (entries 9 and 10). However, this reagent led to handling difficulties with a thick slurry being formed during the reaction, complicating product isolation. As a result of this finding, different hydroxide bases were examined, with both NaOH and KOH giving near stoichiometric conversion to the desired product within 3 hours (entries 12–14), the latter proving marginally more effective, giving complete conversion with only 2.5 equivalents as compared to the 5 equivalents required for NaOH. Significantly, the reaction without water present showed no conversion to product with only starting materials present by GC-MS analysis (entry 15).

Table 1 Coupling of 3,5-$Me_2C_6H_3$Bpin with 4-$IC_6H_4CO_2Me$ in 2.4 mL of MTBE



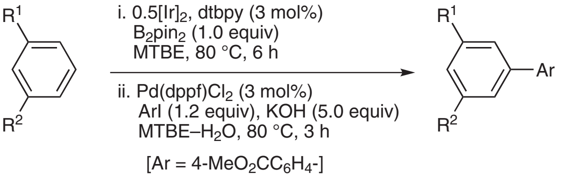
Entry	Catalyst[a]	Base (equiv)	H_2O (mL)	Time (h)	Conversion (%)[b]
1	A	K_2CO_3 (2.0)	1.0	3	0
2	A	K_2CO_3 (2.0)	1.0	12	30
3	A	K_2CO_3 (2.0)	1.0	3	0
4	B	K_2CO_3 (3.5)	1.0	3	0
5	A	K_2CO_3 (4.5)	1.0	3	0
6	B	KF (3.5)	1.0	3	0
7	A	K_3PO_4 (2.5)	1.0	3	29
8	A	NaOH (2.5)	1.0	3	90
9	B	$Ba(OH)_2$ (2.0)[c]	1.0	3	92
10	A	$Ba(OH)_2$ (2.5)[c]	1.0	3	100
11	A	$BaCO_3$ (2.5)	1.0	3	0
12	A	NaOH (5.0)	1.0	3	100
13	A	KOH (2.5)	1.0	3	100
14	A	KOH (5.0)	1.0	3	100
15	A	NaOH (5.0)	0.0	3	0

[a] A: $Pd(dppf)Cl_2$ (3 mol%); B: $Pd(PPh_3)_2Cl_2$ (3 mol%).

[b] GC-MS ratios.

[c] $Ba(OH)_2{\cdot}8H_2O$ used.

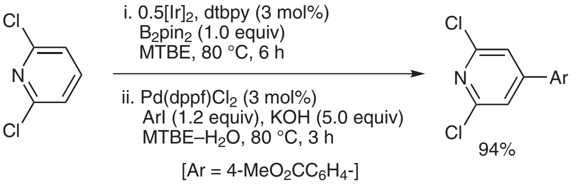
Table 2 One-Pot Borylation of 1-R^1-3-R^2-C_6H_4 followed by Suzuki–Miyaura Coupling with 4-$IC_6H_4CO_2Me$ in MTBE



Entry	R^1	R^2	Yield (%)[a]
1	Me	Me	90
2	Cl	Me	93
3	Cl	CF_3	94
4	Br	CF_3	94
5	Br	MeO	93
6	Cl	MeO	91
7	MeO	MeO	94
8	Br	Br	94
9	Cl	Cl	92
10	MeO	Me	92
11	CN	CF_3	87
12	CN	Br	92
13	CF_3	CF_3	94
14	2,6-$Cl_2C_5H_2N$		94

[a] Yield of isolated, purified products.

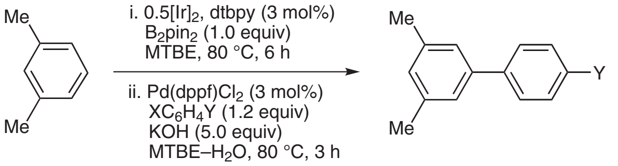
With optimized conditions identified, preparative experiments showed the process to be effective giving high yields across a range of simple 1,3-disubstituted arenes bearing both electron-donating and -withdrawing groups including bromides and chlorides (Table 2). Moreover, this tandem reaction sequence can also be used for suitably substituted heterocycles (e.g., Scheme 1).



Scheme 1 Tandem reaction with 2,6-dichloropyridine and methyl 4-iodobenzoate

Similarly, the cross-coupling partner is not restricted to the more reactive iodoarenes, with both aryl bromides and chlorides being viable (Table 3), the latter being only moderately efficient affording 50% product after a three-hour reaction time. Isolated yields of products (Table 3, entries 1, 3–8, 10) proved to be comparable of those estimated from GC-MS ($\Delta \leq 5\%$). Small amounts of biaryls arising from homocoupling of the boronate ester were observed by GC-MS, and when the products were purified by chromatography on silica gel (entries 1, 3–8, 10), the homocoupling product was isolated in 6% yield, consistent with the amount required for reduction of 3 mol% palladium(II) to palladium(0).

Table 3 One-Pot Borylation of *m*-Xylene Followed by Suzuki–Miyaura Coupling with 4-XC_6H_4Y in MTBE



Entry	X	Y	Yield (%)[a,b]
1	I	CO_2Me	>95 (90)[c]
2	I	Me	>95[d]
3	I	CF_3	>95 (91)[c]
4	I	OMe	92 (90)[c]
5	I	NO_2	94 (93)[c]
6	Br	CO_2Me	>95 (92)[c]
7	Br	CN	92 (92)[c]
8	Br	NMe_2	86 (84)
9	Br	Me	94[d]
10	Cl	CN	50 (50)[c,e]

[a] Yields determined by GC-MS analysis. Isolated, purified yield in parentheses.

[b] Small amounts of biaryl arising from homocoupling of the arylboronate ester detected in all cases by GC-MS.

[c] Homocoupled product (6%) arising from the aryl boronate isolated.

[d] No attempt was made to separate homocoupled byproduct from cross-coupled product.

[e] Unreacted boronate ester (44%) was detected.

In conclusion, MTBE represents an effective and economically viable solvent that permits a truly one-pot tandem C–H borylation–Suzuki–Miyaura cross-coupling to be carried out providing substituted biaryls in high yields.

Typical Procedure for 'One-Pot' Borylation of Bis-1,3-(trifluoromethyl)benzene and Subsequent Suzuki–Miyaura Cross-Coupling to Methyl 4-Iodobenzoate

Under N_2, a catalyst stock solution was prepared by weighing $[Ir(OMe)cod]_2$ (731 mg, 0.4 mmol Ir), dtbpy (105 mg, 0.4 mmol) and B_2pin_2 (713 mg, 2.75 mmol) into a vial and then adding MTBE (26.4 mL). The vial was sealed with a rubber septum and then shaken with the solution developing a deep red color. Under N_2, a Youngs tap tube was charged with B_2pin_2 (200 mg, 0.79 mmol) followed by 1,3-bis(trifluoromethyl)benzene (214 mg, 155 μL, 1.0 mmol). Methyl-*tert*-butyl ether (0.4 mL) was added followed by the catalyst stock solution (2.0 mL; catalyst loading = 3 mol%, 1.0 mmol B_2pin_2). The reaction was heated for 6 h at 80 °C in an aluminum heating block with cooling. Degassed H_2O (1.0 mL) was then added, followed by $Pd(dppf)Cl_2$ (21 mg, 3 mol%), KOH (240 mg, 5.0 mmol), and methyl 4-iodobenzoate (314 mg, 1.2 mmol), and the reaction was heated for 3 h at 80 °C. The solution was then passed through a plug of Celite and washed through with EtOAc (200 mL). The solvent was removed under reduced pressure. The resulting oil was purified by silica flash column chromatography using 5% EtOAc–hexane to afford the cross-coupled biaryl product methyl 4-[3′,5′-bis(trifluoromethyl)phenyl]benzoate (329 mg, 94%); mp 103–104 °C (from hexane). ^{1}H NMR (700 MHz, $CDCl_3$): $\delta = 8.19$ (d, 2 H, $J = 8.2$ Hz), 8.04 (s, 2 H), 7.92 (s, 1 H), 7.69 (d, 2 H, $J = 8.2$ Hz), 3.95 (s, 3 H). ^{13}C NMR (175 MHz, $CDCl_3$): $\delta = 166.9$, 142.8, 142.5, 132.8, 132.6, 130.9, 127.6, 124.4, 122.8, 122.4, 52.7. ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -63.22$. GC-MS (EI): $m/z = 348$ $[M]^+$; all data are in agreement with that previously reported.[19]

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References

(1) *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, **2005**.
(2) Suzuki, A.; Miyaura, N. *Chem. Rev.* **1995**, *95*, 2451.
(3) Chan, D. M. T.; Monaco, K. L.; Li, R.; Bonne, D.; Clark, C. G.; Lam, P. Y. S. *Tetrahedron Lett.* **2003**, *44*, 3863.
(4) (a) Sibi, M. P.; Tatamidani, H.; Patil, K. *Org. Lett.* **2005**, *7*, 2571. (b) Chen, G.; Tokunaga, N.; Hayashi, T. *Org. Lett.* **2005**, *7*, 2885.
(5) Nguyen, P.; Blom, H. P.; Westcott, S. A.; Taylor, N. J.; Marder, T. B. *J. Am. Chem. Soc.* **1993**, *115*, 9329.
(6) (a) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390. (b) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem. Int. Ed.* **2002**, *41*, 3056.
(7) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E.; Smith, M. R. *Science* **2002**, *295*, 305.
(8) Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2003**, *680*, 3.
(9) Tamura, H.; Yamazaki, H.; Sato, H.; Sakaki, S. *J. Am. Chem. Soc.* **2003**, *125*, 16114.
(10) Coventry, D. N.; Batsanov, A. S.; Goeta, A. E.; Howard, J. A. K.; Marder, T. B.; Perutz, R. N. *Chem. Commun.* **2005**, 2172.
(11) Sheldon, R. A. *Chem. Commun.* **2008**, 3352.
(12) (a) Maleczka, R. E.; Shi, F.; Holmes, D.; Smith, M. R. *J. Am. Chem. Soc.* **2003**, *125*, 7792. (b) Shi, F.; Smith, M. R.; Maleczka, R. E. *Org. Lett.* **2006**, *8*, 1411.
(13) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434.
(14) Murphy, J. M.; Tzschucke, C. C.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 757.

(15) Tzschucke, C.; Murphy, J. M.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 761.

(16) Holmes, D.; Chotana, G. A.; Maleczka, R. E.; Smith, M. R. *Org. Lett.* **2006**, *8*, 1407.

(17) Boebel, T. A.; Hartwig, J. F. *Tetrahedron* **2008**, *64*, 6824.

(18) (a) Mkhalid, I. A. I.; Coventry, D. N.; Albesa-Jove, D.; Batsanov, A. S.; Howard, J. A. K.; Perutz, R. N.; Marder, T. B. *Angew. Chem. Int. Ed.* **2006**, *45*, 489. (b) Paul, S.; Chotana, G. A.; Holmes, D.; Reichle, R. C.; Maleczka, R. E.; Smith, M. R. *J. Am. Chem. Soc.* **2006**, *128*, 15552. (c) Ishiyama, T.; Nobuta, Y.; Hartwig, J. F.; Miyaura, N. *Chem. Commun.* **2003**, 2924. (d) Kikuchi, T.; Nobuta, Y.; Umeda, J.; Yamamoto, Y.; Ishiyama, T.; Miyaura, N. *Tetrahedron* **2008**, *64*, 4967.

(19) Blettner, C. G.; König, W. A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* **1999**, *64*, 3885.