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“One-Pot” Tandem C−H Borylation/1,4-Conjugate Addition/Reduction Sequence

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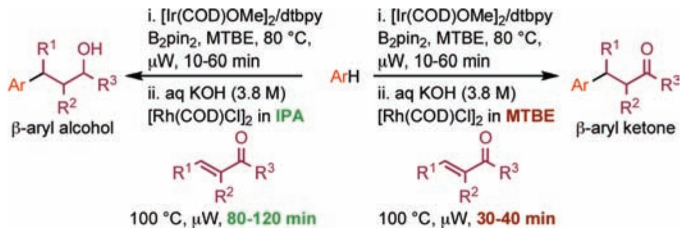
ABSTRACT



A microwave-assisted, one-pot, iridium-catalyzed aromatic C−H borylation/rhodium-catalyzed 1,4-conjugate addition sequence provides a highly robust protocol suitable for high-throughput array synthesis. Selective formation of either *β*-aryl-substituted ketones or the corresponding alcohols can be achieved in good overall yields by simple variation of the reaction conditions.

The use of combinatorial or array chemistry to build chemical libraries for rapid exploration of structure−activity relationships is an important strategy to enhance drug discovery.[1] Effective protocols typically need to be robust and efficient under generalized reaction conditions across a wide range of substrate structures. The direct borylation of aromatic C−H bonds promoted by iridium trisboryl complexes[2] has developed into a popular and powerful method for the functionalization of arenes.[3] This transformation is ideally suited to array chemistry as it avoids the need for specifically functionalized precursors and exploits the diverse chemistry of the resulting boronate ester. This is most effective when carried out in a single vessel, and such in situ elaboration of the initially formed boronate ester can provide rapid access to a variety of functionalized arenes.[4] Recently, we have contributed to this methodological toolbox by developing the use of MTBE (methyl-*tert*-butyl ether) as a compatible solvent for both the borylation and Suzuki−Miyaura cross-coupling reactions and showing that both processes can be efficiently accelerated using microwave irradiation.[5] In this communication, we describe the efficient one-pot conversion of arenes to either *β*-aryl-substituted ketones or the corresponding alcohols through a tandem sequence involving Ir-catalyzed

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(1) Easson, M. A. M.; Rees, D. C. *Medicinal Chemistry: Principles and Practice*, 2nd ed.; King, F. D., Ed.; The Royal Society of Chemistry: Cambridge, 2002; Chapter *16*, pp 359−381.

(2) (a) Nguyen, P.; Blom, H. P.; Westcott, S. A.; Taylor, N. J.; Marder, T. B. *J. Am. Chem. Soc.* **1993**, *115*, 9329. (b) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390. (c) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III *Science* **2002**, *295*, 305.

(3) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.

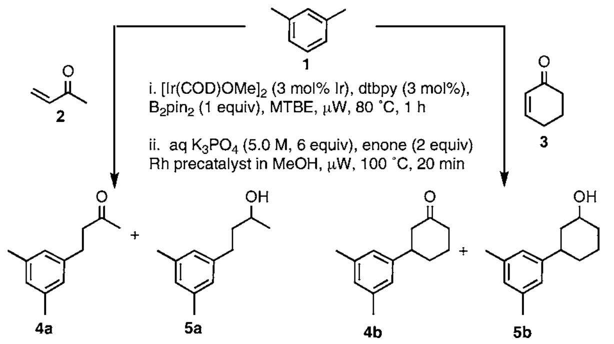
(4) (a) Tzschucke, C. C.; Murphy, J. M.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 761. (b) Holmes, D.; Chotana, G. A.; Maleczka, R. E., Jr.; Smith, M. R., III *Org. Lett.* **2006**, *8*, 1407. (c) Shi, F.; Smith, M. R., III; Maleczka, R. E., Jr. *Org. Lett.* **2006**, *8*, 1411. (d) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434. (e) Maleczka, R. E., Jr.; Shi, F.; Holmes, D.; Smith, M. R., III *J. Am. Chem. Soc.* **2003**, *125*, 7792. (f) Murphy, J. M.; Tzschucke, C. C.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 757.

(5) (a) Harrisson, P.; Morris, J.; Steel, P. G.; Marder, T. B. *Synlett* **2009**, 147. (b) Harrisson, P.; Morris, J.; Marder, T. B.; Steel, P. G. *Org. Lett.* **2009**, *11*, 3586.

10.1021/ol102518v

aromatic C−H borylation followed by the Rh-catalyzed conjugate addition of the arylboronate to enones. While there are many reports describing the conjugate addition of boronic acids to enones,[6] the application of the corresponding pinacol boronate esters is limited to a small number of acrylate and enamide acceptors.[7]

Table 1. One-Pot C−H Borylation/1,4-Conjugate Addition Sequence



entry	Rh precatalyst	enone	yield **4** (%)^{a}	yield **5** (%)^{a}
1	Rh(acac)(CO)$_2$/dppb^{b}	**2**	**4a** (68)	**5a** (0)
2	Rh(acac)(CO)$_2$/dppb^{b}	**3**	**4b** (8)	**5b** (0)
3	[Rh(COD)Cl]$_2$	**2**	**4a** (35)	**5a** (24)
4	[Rh(COD)Cl]$_2$$^{c(i)}$	**2**	**4a** (40)	**5a** (24)
5	[Rh(COD)Cl]$_2$$^{c(ii)}$	**2**	**4a** (37)	**5a** (30)
6	[Rh(COD)Cl]$_2$$^{c(iii)}$	**2**	**4a** (14)	**5a** (51)

[a] Purified isolated yield. [b] No K$_3$PO$_4$. [c] Reaction conditions were modified to: (i) expel H$_2$ from reaction; (ii) extend quenching time; or (iii) combine both H$_2$ expulsion and extend quenching time prior to heating in the second step. See Supporting Information for details.

Initial attempts to explore this sequence involved the use of Rh(acac)(CO)$_2$ and dppb for the 1,4-conjugate addition step as originally reported by Miyaura for ArB(OH)$_2$.[8] Following complete consumption of the arene, the borylation reaction was quenched with aq K$_3$PO$_4$. Subsequent addition of the Rh catalyst and enone in MeOH initiated the 1,4-conjugate addition step. Although the in situ generated Bpin ester proved to be a viable substrate, the transformation was slow. However, microwave heating greatly accelerated the reaction giving complete conversion of ArBpin in minutes rather than hours. To our knowledge, previous microwave acceleration of 1,4-conjugate addition has only been observed using boronic acids with acrylate and enamide acceptors.[9] While this method proved effective with unsubstituted enone MVK (methylvinylketone) **2** as the acceptor (Table 1, entry 1), the yield was substantially lower for substituted enones such as cyclohex-2-enone **3** (entry 2). Additionally, strict precautions were required to exclude oxygen from the reactions, leading us to explore alternative catalyst systems. [Rh(COD)Cl]$_2$ has been reported to be an effective catalyst for the conjugate addition of boronic acids to α,*β*-unsaturated carbonyl compounds.[10] Moreover, functioning in the absence of added ligand, it is ideal for array chemistry. Pleasingly, application of this catalyst to the microwave-accelerated one-pot sequence, using *m*-xylene **1** as the arene and **2** as the acceptor, afforded the desired ketone **4a** in moderate yield (35%) (entry 3). However, a substantial amount of the corresponding alcohol product **5a** (24%) was also isolated, clearly as a result of an unprecedented reduction of the

Scheme 1. Percent Deuterium Incorporation during the Tandem C−H Borylation/1,4-Conjugate Addition Sequence

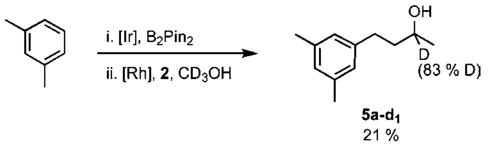


Table 2. [Rh(COD)Cl]$_2$ Catalyzed 1,4-Conjugate Addition of *m*-XylylBpin to MVK **2** in the Presence of Various Ir Complexes

			isolated yield (%)	
entry	solvent	[Ir]^{a}	**4a**	**5a**
1	MeOH	none^{b}	56	0
2	MeOH	A	63	0
3	MeOH	B	66	0
4	MeOH	C	45	10

[a] A = [Ir(COD)OMe]$_2$; B = [Ir(COD)OMe]$_2$ + dtbpy; C = [Ir(COD)-OMe]$_2$ + dtbpy + B$_2$pin$_2$. [b] 1,4-Conjugate addition was carried out following rapid filtration of the borylation reaction mixture through a short plug of silica to remove any Ir complexes.

Table 3. Solvent Effects in the Second Step of One-Pot Tandem C−H Borylation of **1**/1,4-Conjugate Addition to **2** Sequence^{a}

				isolated yield (%)	
entry	solvent	additive^{c}	time (min)	**4a**	**5a**
1	acetone	-	20	73	0
2	MTBE	-	20	71	0
3	THF^{b}	-	20	67	0
4	MeOH	-	150	10	42
5	IPA	-	20	26	49
6	IPA	-	80	0	62
7	MeOH	A	20	47	17
8	MeOH	B	20	7	11
9	MeOH	C	20	0	10
10^{d}	MTBE	-	20	68	0
11^{d}	IPA	-	80	0	61

[a] Conditions: (i) **1** (1 equiv), [Ir(OMe)COD]$_2$/dtbpy (3 mol %), B$_2$pin$_2$ (1 equiv), *μ*W, 80 °C, 60 min; (ii) aq K$_3$PO$_4$ (5 M, 6 equiv), [Rh(COD)Cl]$_2$ in solvent, **2** (2 equiv), *μ*W, 100 °C, stated time. [b] C−H borylation step was also carried out in THF. [c] A = 9,10-dihydroanthracene; B = 1,4-cyclohexadiene; C = ammonium formate. [d] aq KOH (3.8 M, 2 equiv) in place of aq K$_3$PO$_4$ (5 M, 6 equiv).

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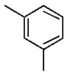
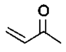
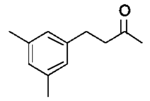
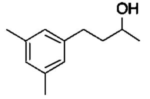
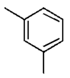
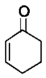
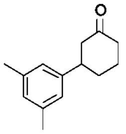
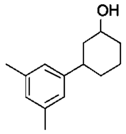
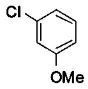
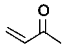
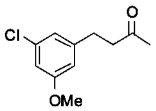
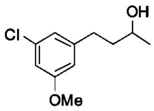
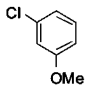
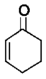
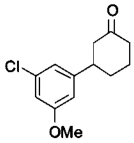
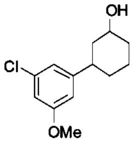
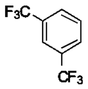
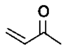
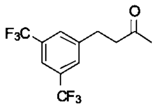
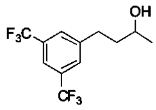
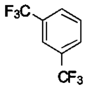
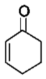
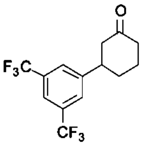
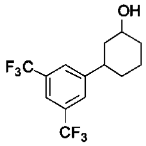
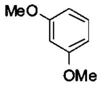
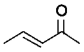
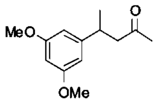
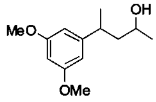
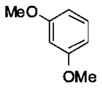
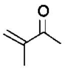
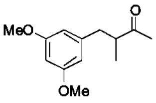
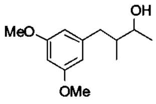
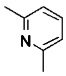
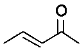
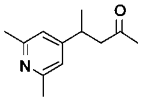
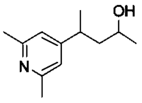
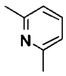
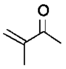
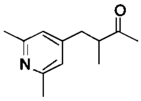
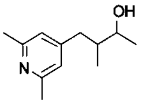
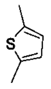
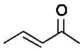
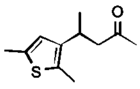
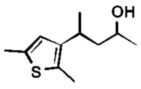
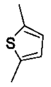
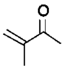
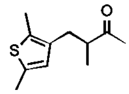
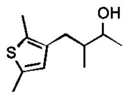
(6) For reviews see. (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

(7) (a) Sakuma, S.; Miyaura, N. *J. Org. Chem.* **2001**, *66*, 8944. (b) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951. (c) Horn, J.; Li, H. Y.; Marsden, S. P.; Nelson, A.; Shearer, R. J.; Campbell, A. J.; House, D.; Weingarten, G. G. *Tetrahedron* **2009**, *65*, 9002.

(8) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229.

(9) (a) Mondiere, A.; Pousse, G.; Bouyssi, D.; Balme, G. *Eur. J. Org. Chem.* **2009**, 4225. (b) Frost, C. G.; Penrose, S. D.; Lambshead, K.; Raithby, P. R.; Warren, J. E.; Gleave, R. *Org. Lett.* **2007**, *9*, 2119. (c) Iyer, P. S.; O'Malley, M. M.; Lucas, M. C. *Tetrahedron Lett.* **2007**, *48*, 4413.

Table 4. Optimized One-Pot C−H Borylation/1,4-Conjugate Addition for Selective Access to β-Arylketone or the Corresponding Alcohol Product and the Corresponding Results under Array Conditions

			non-reducing conditions[a]				reducing conditions[b]			
					isolated yield %				isolated yield % (dr)[e,f]	
entry	arene	enone	product	4	Schlenk[c]	array[d]	product	5	Schlenk[c]	array[d]
1				**4a**	68	45		**5a**	61	46
2				**4b**	65	55		**5b**	58 (1:1)^{e}	53 (1:1)^{e}
3				**4c**	71	69		**5c**	71	68
4				**4d**	68	63		**5d**	68 (1:1.9)^{e}	68 (1:2)^{e}
5				**4e**	53	45		**5e**	53	47
6				**4f**	55	47		**5f**	52 (1:1.7)^{e}	44 (1:1.7)^{e}
7				**4g**	47	36		**5g**	51 (1:1.2)^{f}	47 (1:1.2)^{f}
8				**4h**	45	30		**5h**	52 (1:1.3)^{f}	47 (1:1.3)^{f}
9				**4i**	46	35		**5i**	38 (1:1.2)^{f}	30 (1:1.3)^{f}
10				**4j**	42	30		**5j**	36 (1:1)^{f}	25 (1:1)^{f}
11				**4k**	39	30		**5k**	41 (1:1.7)^{f}	36 (1:1.7)^{f}
12				**4l**	42	37		**5l**	47 (1:1)^{f}	43 (1:1)^{f}

[a] Conditions: (i) arene (1 equiv), B_2pin_2 (1 equiv), 1/2[Ir(COD)OMe]$_2$/dtbpy (3 mol % Ir), MTBE, 80 °C, μW, (ii) aq KOH (2 equiv), [Rh(COD)Cl]$_2$ (2 mol % Rh) in MTBE, enone (1 equiv). [b] Conditions: (i) arene (1 equiv), B_2pin_2 (1 equiv), 1/2[Ir(COD)OMe]$_2$/dtbpy (3 mol % Ir), MTBE, 80 °C, μW, (ii) aq KOH (2 equiv), [Rh(COD)Cl]$_2$ (2 mol % Rh) in IPA, enone (1 equiv). [c] Individually performed reactions with optimized reaction times under a strictly inert atmosphere using Schlenk techniques. [d] Reactions were carried out in parallel in air with common reaction times for each array. [e] (*Syn*:*anti*) as determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture. [f] Diastereoisomers were inseparable and could not be unambigously defined. See Supporting Information for details.

initially formed ketone. Attempts to improve the ketone yield by suppressing the reductive pathway via expulsion from the reaction vessel of H_2, generated in the arene borylation process (entry 4), or prolonged quenching times to ensure complete decomposition of residual HBpin prior to addition of the enone, were unsuccessful (entry 5). Interestingly, the combination of these modifications led to an increased methanol concentration, owing to evaporation of some of the MTBE, resulting in a higher proportion of the alcohol product (entry 6). This suggested that the reduction proceeds via transfer hydrogenation with the MeOH serving as the hydrogen source.

Confirmation of this was achieved using deuterated methanol in the second step of the sequence (Scheme 1). A high level of deuterium incorporation (83%) was observed at the carbinol carbon of the alcohol product **5a**-***d*₁** when CD_3OH was used. Further studies showed that the transfer hydrogenation process requires an iridium complex to be present (Table 2). Reduction was suppressed by filtering the reaction mixture through silica gel prior to the 1,4-conjugate addition step (entry 1). While addition of $[Ir(COD)OMe]_2$ (entry 2) or a combination of this with dtbpy (entry 3) in the Rh-catalyzed 1,4-conjugate addition of *m*-xylylBpin to MVK resulted in no alcohol product being detected, the addition of a premixed solution of B_2pin_2, $[Ir(COD)OMe]_2$, and dtbpy led to the alcohol product being observed once again (entry 4). This suggested that the active species responsible for the transfer hydrogenation process is generated through the quenching of the iridium trisboryl complex $[Ir(Bpin)_3dtbpy]$ formed in the borylation step. In support of this, reaction of purified ketone **4a** with methanol in the presence of the iridium species generated by quenching a mixture of $[Ir(OMe)COD]_2$ (3 mol % Ir), dtbpy (3 mol %), and B_2pin_2 (10 mol %) with aq K_3PO_4 afforded alcohol **5** in 78% yield.

Having identified methanol as the reductant, we then sought to optimize the sequence to obtain either the ketone or alcohol product through solvent selection (Table 3). By replacing the methanol solvent in the second step with a nonoxidizable solvent such as acetone, MTBE, or THF (entries 1−3), selective formation of the ketone product was achieved. Alternatively, extending the reaction time and using isopropanol (IPA) as a more efficient hydrogen source afforded the alcohol product in good yield (entries 4−6). Other hydrogen sources were less effective, suffering from poor conversion of ArBpin due to competitive reduction of the enone and lower reaction rates (entries 7−9). Finally, replacing the K_3PO_4 base used in the reaction with 2 equiv of aq KOH (3.8 M) provided equivalent yields and reactivity but with the practical advantage of a homogeneous reaction mixture (entries 10 and 11).

With these optimized conditions identified, we then explored the general applicability of the reaction sequence, carried out under an inert atmosphere using Schlenk techniques. A wide variety of electron-rich and electron-poor arenes and heteroarenes with α,β-unsubstituted, α-substituted, β-substituted, and cyclic α,β-unsaturated ketones were screened under both nonreducing and reducing conditions (Table 4). Good overall isolated yields were achieved for α,β-unsubstituted and cyclic α,β-unsaturated ketones (entries 1−6). Acyclic enones bearing substitution at either the α- or β-position resulted in slightly lower yields but remain within an acceptable range for a two-step synthesis (entries 7−12). In each case, the remaining mass balance can be accounted for (LCMS analysis) by unreacted ArBpin and arene arising from incomplete borylation or competing protiodeborylation during the conjugate addition step (see Supporting Information). All reactions were repeated under array conditions, i.e., in parallel, with common reaction times and with no precautions to exclude oxygen. Somewhat lower, but still acceptable, isolated yields were observed.

In conclusion, we have developed a highly robust microwave-assisted, one-pot tandem Ir-catalyzed aromatic C−H borylation/Rh-catalyzed 1,4-conjugate addition sequence which is suitable for application in high-throughput array format. Both β-aryl-substituted ketones and the corresponding alcohols can be selectively accessed in good overall isolated yields by employing nonreducing or reducing conditions, respectively. Although the reduction proceeds with low stereoselectivity, this can potentially be addressed by the addition of chiral ligands. Studies in this direction are ongoing and will be reported in due course.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) (a) Xing, C.-H.; Liu, T.-P.; Zheng, J. R.; Ng, J.; Esposito, M.; Hu, Q.-S. *Tetrahedron Lett.* **2009**, *50*, 4953. (b) Martina, S. L. X.; Minnaard, A. J.; Hessen, B.; Feringa, B. L. *Tetrahedron Lett.* **2005**, *46*, 7159. (c) Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000.