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A Concise and Atom-Economical Suzuki–Miyaura Coupling Reaction Using Unactivated Trialkyl- and Triarylboranes with Aryl Halides

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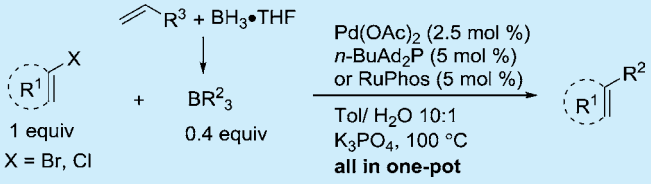
Supporting Information

ABSTRACT: A concise and atom-economical Suzuki–Miyaura coupling of trialkyl- and triarylboranes with aryl halides is described. This new protocol represents the first general, practical method that efficiently utilizes peralkyl and peraryl groups of the unactivated trialkyl- and triarylboranes for the Suzuki–Miyaura coupling reaction.



The sp^2–sp^2 Suzuki–Miyaura cross-coupling reaction of organoboron compounds is one of the most powerful methods for C–C bond formation in modern organic synthesis due to its mild reaction conditions, broad functional group tolerance, and nontoxic byproducts.[1] In contrast, the sp^2–sp^3 Suzuki–Miyaura cross-coupling of alkylboron reagents, despite recent progress, has proven more difficult to develop due to inherently higher kinetic barriers for the transmetalation and reductive elimination steps, and a facile β-hydride elimination side pathway.[1−3]

Trialkylboranes represent potentially attractive reagents for sp^2–sp^3 Suzuki–Miyaura coupling reactions.[4] Despite their lower cost and ease of synthesis, symmetrical trialkylboranes have not found common use in sp^2–sp^3 Suzuki–Miyaura coupling, likely owing to the inefficiency of transfer of all three alkyl groups from the boron center, the sensitivity to oxygen, and the flammable nature of the reagents for storage, thus

Scheme 1. Strategies for the Suzuki–Miyaura Cross-Coupling Reactions of Trialkyl- and Triarylboranes

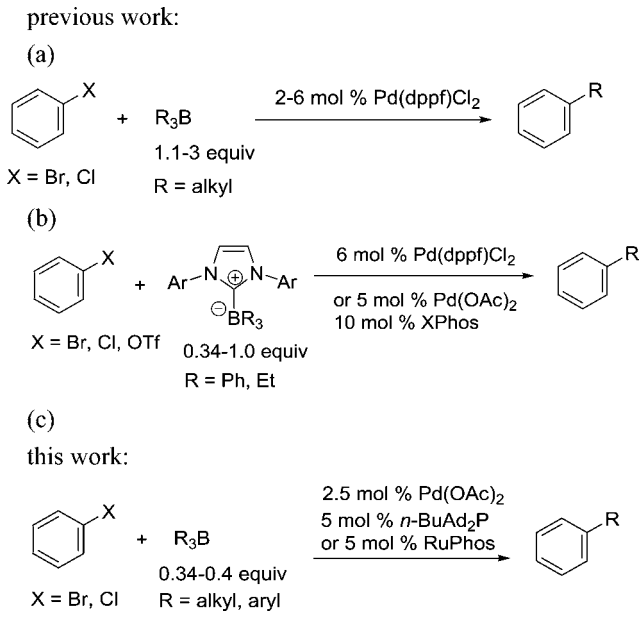
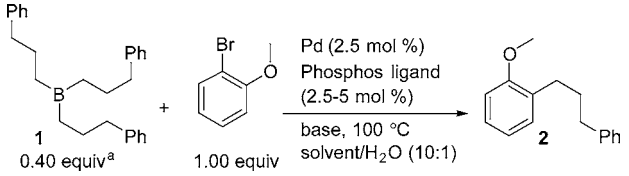


Table 1. Optimization of the Reaction Conditions



entry[b]	catalyst	ligand[c]	base	solvent	yield (%)
1	$Pd(OAc)_2$	dppf	K_3PO_4	Tol/H_2O	74
2	$Pd(OAc)_2$	S-Phos	K_3PO_4	Tol/H_2O	81
3	$Pd(OAc)_2$	JohnPhos	K_3PO_4	Tol/H_2O	61
4	$Pd(OAc)_2$	dpePhos	K_3PO_4	Tol/H_2O	81
5	$Pd(OAc)_2$	Q-Phos	K_3PO_4	Tol/H_2O	64
6	$Pd(OAc)_2$	P^tBu_3•HBF_4	K_3PO_4	Tol/H_2O	55
7	$Pd(OAc)_2$	X-Phos	K_3PO_4	Tol/H_2O	63
8	$Pd(OAc)_2$	RuPhos	K_3PO_4	Tol/H_2O	88
9	$Pd(OAc)_2$	n-$BuAd_2P$	K_3PO_4	Tol/H_2O	86
10	$Pd_2dba_3.CH_2Cl_2$	n-$BuAd_2P$	K_3PO_4	Tol/H_2O	83
11	$Pd(OAc)_2$	n-$BuAd_2P$	K_3PO_4	2-MeTHF/H_2O	74
	$Pd(OAc)_2$	n-$BuAd_2P$	K_3PO_4	DMF/H_2O	69
13	$Pd(OAc)_2$	n-$BuAd_2P$	Cs_2CO_3	Tol/H_2O	75
14	$Pd(OAc)_2$	n-$BuAd_2P$	K_2CO_3	Tol/H_2O	70
15	$Pd(OAc)_2$	n-$BuAd_2P$	KOAc	Tol/H_2O	52
16	$Pd(OAc)_2$	n-$BuAd_2P$	$NaHCO_3$	Tol/H_2O	74
17	$Pd(OAc)_2$	n-$BuAd_2P$	NaOH	Tol/H_2O	59

[a]Generated *in situ* using 1.2 equiv of allylbenzene with 0.45 equiv of borane in THF solution. [b]The reaction was run with **1** (0.040 mmol), 2-bromoanisole (0.10 mmol), and 1 mL of solvent at 100 °C for 12 h, unless otherwise noted. [c]The mole ratio of Pd/P is 1:2. [d]Yield obtained by HPLC using biphenyl as an internal standard.

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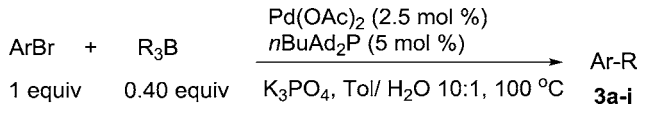
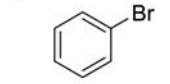
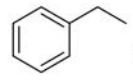
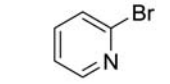
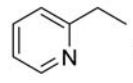
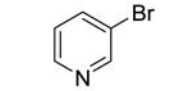
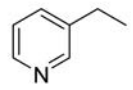
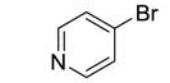
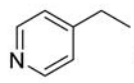
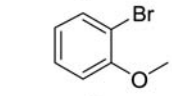
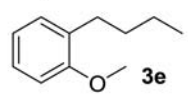
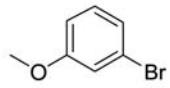
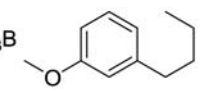
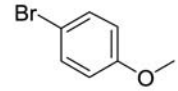
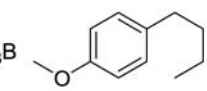
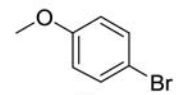
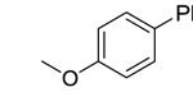
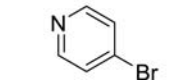
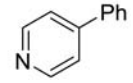
Table 2. Suzuki–Miyaura Coupling with Commercially Available Trialkyl- and Triarylboranes



entry	substrate	R_3B	product	yield (%)
1		Et_3B	 **3a**	90[a]
2		Et_3B	 **3b**	78[a]
3		Et_3B	 **3c**	70[a]
4		Et_3B	 **3d**	91[a]
5		n-Bu_3B	 **3e**	87[b]
6		n-Bu_3B	 **3f**	91[b]
7[c]		n-Bu_3B	 **3g**	94[b]
8[c]		Ph_3B	 **3h**	99[b]
9		Ph_3B	 **3i**	98[b]

[a]HPLC yield refers to quantitative HPLC analysis employing an analytical standard. [b]Isolated yield. [c]0.34 equiv of borane reagents (n-Bu_3B and Ph_3B) was used for the coupling reaction. There are no differences between 0.40 and 0.34 equiv of the borane reagents for the coupling in terms of their conversions and isolated yields.

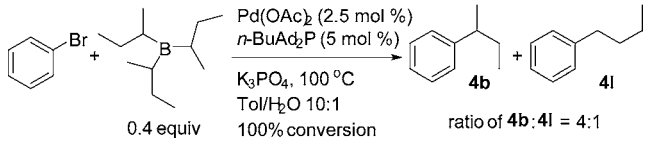
requiring excess amounts of trialkylboranes and handling concerns (Scheme 1a).[5] Recently, Lacote[6] reported that efficient transfer of all three groups can be achieved in the Suzuki–Miyaura coupling with trialkyl- and triarylboranes, but requires activation with *N*-heterocyclic carbenes (e.g., bis-2,6-diisopropylphenyl imidazolylidinene) (Scheme 1b). Herein we report a concise and atom-economical Suzuki–Miyaura coupling of trialkyl- and triarylboranes with aryl halides (Scheme 1c). To the best of our knowledge, this new protocol represents the first general method that efficiently transfers all three alkyl and aryl groups of the unactivated trialkyl- and triarylboranes and does not require stoichiometric quantities of an activating reagent.

We initially investigated the sp^2–sp^3 Suzuki–Miyaura coupling reaction using 1 equiv of 2-bromoanisole and 0.40 equiv of tris(3-phenylpropyl)borane, which is generated *in situ* through hydroboration of 1.2 equiv of allylbenzene and 0.45 equiv of BH_3·THF. As shown in Table 1, using 2.5 mol % of a Pd catalyst formed *in situ* from $Pd(OAc)_2$ and a phosphine ligand, moderate to good yields of the desired product were obtained with many ligands when toluene was employed as solvent using aqueous K_3PO_4 as the base (Table 1, entries 1–9). The ligands RuPhos (entry 8) and n-$BuAd_2P$ (entry 9) gave the highest yields.

Encouraged by these initial results, the generality of these sp^2–sp^3 Suzuki–Miyaura coupling conditions was examined by employing 0.40 equiv of commercially available trialkyl- and triarylboranes along with a series of substituted bromobenzene and bromopyridine derivatives. As shown in Table 2, a variety of aryl bromides, including bromobenzene (entry 1), electron-rich 2-, 3-, and 4-Br anisoles (entries 5, 6, and 7), and hetero-aromatic 2-, 3-, and 4-bromopyridines, reacted smoothly with triethylborane and tributylborane to provide cross-coupling products in good to excellent yields. The coupling reaction proceeded to a near-quantitative yield when triphenylborane was used as a nucleophile (entries 8 and 9). The high isolated yields of the Suzuki–Miyaura coupling product obtained with a substoichiometric amount of trialkylboranes in entries 8 and 9 of Table 1 indicated that all three alkyl groups of the unactivated trialkylboranes were efficiently transferred.[7]

When commercially available tri-*sec*-butylborane was used for this coupling reaction with bromobenzene in the presence of 2.5 mol % catalyst, the reaction provided the expected *sec*-butylbenzene product as well as *n*-butylbenzene with a ratio of 4:1 (Scheme 2). Similar phenomena were also observed

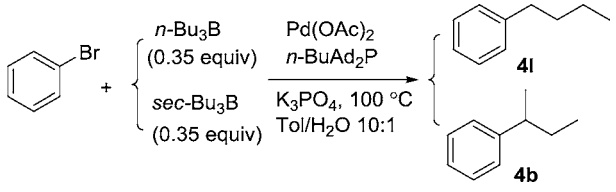
Scheme 2. Suzuki–Miyaura Coupling of Bromobenzene with Tri-*sec*-butylborane



in the cross-coupling using *sec*-butylboronic acid[4c] and *sec*-alkyltrifluoroborates.[3a,8]

To examine the relative rates of primary and secondary alkyl group transfer from trialkylboranes, a competition study was conducted[9] using bromobenzene with 0.35 equiv of primary tri-*n*-butylborane and 0.35 equiv of tri-*sec*-butylborane in the presence of 1 mol % catalyst. As shown by the time course data in Table 3, there is no *sec*-butylbenzene formed below ~70% conversion of the aryl halide, and only a small amount (2–5%)

Table 3. Competition Reaction of Bromobenzene with Primary and Secondary Tributylboranes



		1 mol % catalyst	
entry	t (h)	conversion (%)	ratio of **4l**/**4b**[a]
1	0.5	10	100/0
2	1	17	100/0
3	2	34	100/0
4	3	50	100/0
5	4	77	100/0
6	6	100	98/2

[a]In a separated reaction, the competition reaction was run in a mixture of 10 equiv of n-Bu_3B and 10 equiv of sec-Bu_3B. The ratio of **4l** with **4b** is still 98:2 at the end of the reaction.

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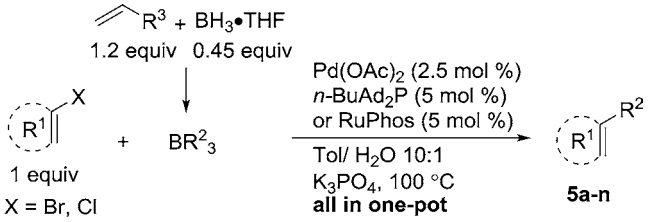
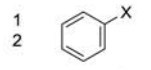
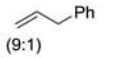
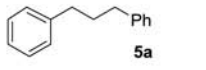
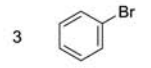
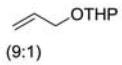
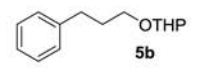
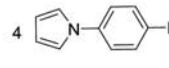
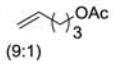
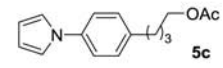
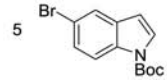
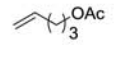
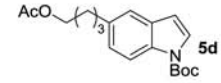
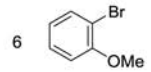
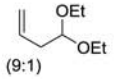
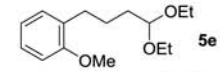
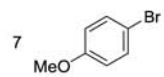
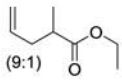
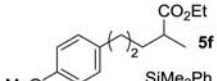
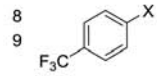
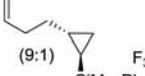
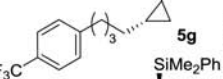
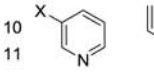
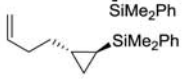
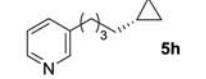
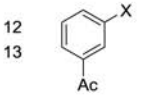
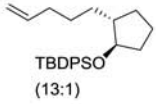
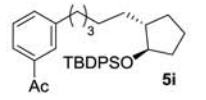
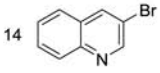
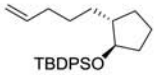
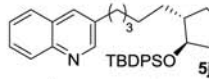
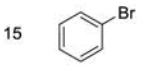
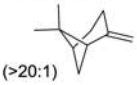
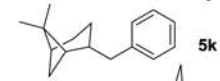
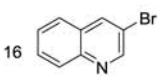
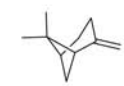
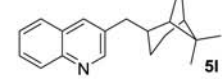
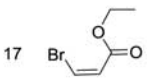
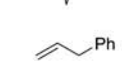
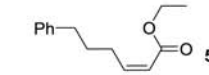
Table 4. Suzuki–Miyaura Cross-Coupling Reaction with Functionalized Trialkylboranes



entry	ArX	alkene (1°:2°)	product	yield (%)
1 2		 (9:1)	 5a	X = Br 86 X = Cl 76
3		 (9:1)	 5b	98
4		 (9:1)	 5c	76
5			 5d	94[a]
6		 (9:1)	 5e	98[a]
7		 (9:1)	 5f	88[a]
8 9		 (9:1)	 5g	X = Br 92 X = Cl 87
10 11			 5h	X = Br 77 X = Cl 63
12 13		 (13:1)	 5i	X = Br 83 X = Cl 81
14			 5j	75
15		 (>20:1)	 5k	74
16			 5l	82 (84[a])
17			 5m (*cis:trans* = 9:1)	52[a,b]
18			5n	60[a]

[a]5 mol % of RuPhos instead of *n*-BuAd$_2$P was used. [b]Isolated yield of *cis*-product.

of *sec*-butylbenzene is formed by the end of the reaction. This result indicates that all the primary alkyl groups of *n*-Bu$_3$B transfer much faster than the secondary alkyl groups of *sec*-Bu$_3$B. On the other hand, the reaction has clearly demonstrated synthetic practicality for selective couplings.

The applicability of this reaction system to the synthesis of functionalized compounds using complex trialkylboranes was then examined. Cross-coupling reactions were conducted under optimal conditions with a variety of aryl and alkenyl halides and 0.40 equiv of trialkylboranes generated *in situ* from hydroboration of terminal alkenes with 1.0 M borane in THF solution (Table 4). Upon exposure of 1.2 equiv of the terminal alkenes to 0.40 equiv of borane in THF solution, a near-quantitative yield of trialkylboranes was obtained, with typically ≥9:1 regioselectivity for anti-Markovnikov hydroboration. The resulting mixture was not isolated, but was directly subjected to optimized Suzuki–Miyaura cross-coupling reaction conditions. Consistent with the previous observation that 1° trialkylborane reacts faster than 2° trialkylborane, only linear coupling products were observed. The desired products were obtained with good to excellent isolated yield in this one-pot hydroboration/Suzuki–Miyaura coupling protocol. A variety of electron-rich and electron-deficient aryl bromides and chlorides performed very well under these coupling conditions, including phenyl (entries 1–2 and 15), indole (entry 5), pyridine (entries 10–11), and quinoline (entries 14 and 16). Similarly, trialkylboranes with various functional groups, including acetate (entries 4–5, 7 and 13), acetal (entries 3 and 6), *trans*-cyclopropane (entries 9–11), and *trans*-cyclopentane (entries 12–14), were nicely tolerated, providing functionalized cross-coupling products in good to excellent yield. Hydroboration of β-pinene gave only primary trialkylborane which also efficiently transferred and coupled in the Suzuki–Miyaura reactions (entries 15–16). The cross-coupling reaction of triakylboranes with vinyl bromides (entries 17–18) also afforded desired products in moderate yields.

In conclusion, a practical, chemoselective, and atom-economical method for the Suzuki–Miyaura coupling of symmetrical trialkyl- and triarylboranes with aryl halides has been developed. The trialkylboranes could be generated in situ from hydroboration of terminal alkenes with borane, and the cross-coupling reaction of the resulting trialkylboranes with aryl halides was run in a one-pot fashion. The reported conditions give efficient utilization of the trialkylborane reagent and are broadly tolerant of functional groups and heterocycles, making them particularly useful in the context of complex molecule synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, and NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01720.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Burkhardt, E. R.; Matos, K. *Chem. Rev.* **2006**, *106*, 2617. (c) Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, *43*, 412. (d) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *2004*, 2419. (e) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461. (f) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (g) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6723. (h) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 3565. (i) Hassan, Z.; Patonay, T.; Langer, P. *Synlett* **2013**, *24*, 412.

(2) (a) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544. (b) Molander, G. A.; Canturk, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9240. (c) Sandrock, D. L. *Science of Synthesis, Cross Coupling and Heck-Type Reactions*; Thieme: Stuttgart, 2013; Vol. 1, p 323. (d) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461. (e) Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, *43*, 412. (f) Bonet, A.; Odachowski, M.; Leonori, D.; Essafi, S.; Aggarwal, V. K. *Nat. Chem.* **2014**, *6*, 584. (g) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Sato, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314. (h) Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405. (i) Kondolff, I.; Doucet, H.; Santelli, M. *Tetrahedron* **2004**, *60*, 3813. (j) Feuerstein, M.; Berthiol, F.; Doucet, H.; Santelli, M. *Synlett* **2002**, *2002*, 1807. (k) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553. (l) Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405. (m) Littke, A.; Dai, C.; Fu, G. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (n) Doucet, H. *Eur. J. Org. Chem.* **2008**, *2008*, 2013. (o) Miyaura, N.; Ishiyama, T.; Ishikawa, M.; Suzuki, A. *Tetrahedron Lett.* **1986**, *27*, 6369. (p) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Sato, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314.

(3) (a) Molander, G. A.; Sandrock, D. L. *J. Am. Chem. Soc.* **2008**, *130*, 15792. (b) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288. (c) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393. (d) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275. (e) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302. (f) Molander, G. A.; Yun, C.-S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 5534. (g) Molander, G. A.; Canturk, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9240. (h) Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867. (i) Molander, G. A.; Petrillo, D. E.; Landzberg, N. R.; Rohanna, J. C.; Biolatto, M. *Synlett* **2005**, 1763. (j) Molander, G. A.; Felix, L. A. *J. Org. Chem.* **2005**, *70*, 3950. (k) Dreher, S. D.; Lim, S. E.; Sandrock, D. L.; Molander, G. A. *J. Org. Chem.* **2009**, *74*, 3626. (l) Duncton, M. A. J; Singh, R. *Org. Lett.* **2013**, *15*, 4284. (m) St. Denis, J. D.; Scully, C. C. G.; Lee, C. F.; Yudin, A. K. *Org. Lett.* **2014**, *16*, 1338.

(4) (a) Chemler, S. R.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 2695. (b) Kawada, H.; Iwamoto, M.; Utsugi, M.; Miyano, M.; Nakada, M. *Org. Lett.* **2004**, *6*, 4491. (c) Seidel, G.; Furstner, A. *Chem. Commun.* **2012**, *48*, 2055.

(5) (a) Sun, H.-X.; Sun, Z.-H.; Wang, B. *Tetrahedron Lett.* **2009**, *50*, 1596. (b) Wang, B.; Sun, H.-X.; Sun, Z.-H.; Lin, G.-Q. *Adv. Synth. Catal.* **2009**, *351*, 415.

(6) Monot, J.; Brahmi, M. M.; Ueng, S.-H.; Robert, C.; Murr, M. D.-E.; Curran, D. P.; Malacria, M.; Fensterbank, L.; Lacote, E. *Org. Lett.* **2009**, *11*, 4914.

(7) *n*-Bu(BOH)$_2$, the likely intermediate formed after two successive alkyl transfers, was shown to react efficiently under the standard conditions to generate the desired product at a rate comparable to, or faster than, the typical conversion rates seen with tri-*n*-butylborane. See Figure 1 in Supporting Information.

(8) Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. *J. Am. Chem. Soc.* **2008**, *130*, 9257.

(9) Competitive rate studies for trialkylboranes vs alkylborinates; see: Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461.

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