ORGANIC CHEMISTRY
FRONTIERS

Cite this: *Org. Chem. Front.*, 2016, **3**, 434

Received 15th December 2015,
Accepted 24th January 2016

DOI: 10.1039/c5qo00426h

rsc.li/frontiers-organic

Synthesis of 1,1-diboronate esters by cobalt-catalyzed sequential hydroboration of terminal alkynes†

Ziqing Zuo and Zheng Huang*

A cobalt complex of iminopyridine-oxazoline catalyzes sequential hydroboration of alkyl and aryl alkynes with pinacolborane to form 1,1-diboronate esters. The reactions proceed under mild conditions with high yields, high regioselectivity, and wide functional group tolerance. The synthetic utility of 1,1-di(boronates) is demonstrated by chemoselective monoarylation and stepwise diarylation through palladium-catalyzed Suzuki–Miyaura coupling reactions.

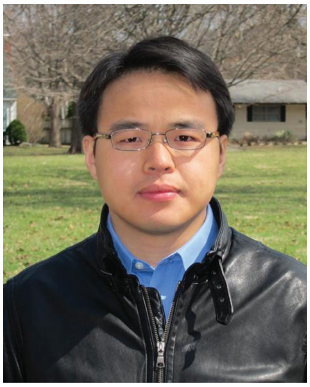
1,1-Organodiboronate esters are valuable synthetic intermediates for preparation of multifunctionalized molecules.[1] Such 1,1-diboryl compounds can be used as coupling reagents for C–C bond formations through Suzuki–Miyaura reactions.[2] Advantages of 1,1-diboronate esters over other 1,1-organodimetallic nucleophiles include their unique stability, operational simplicity, and non-toxicity.[3,4] In addition, the boronate moiety can be readily converted into alcohol, amine, and other functional groups. Conventional, non-catalytic methods for synthesis of 1,1-diboronate esters involve reactions of lithiated reagents with bis(pinacolato)diboron,[5] or hydroboration of terminal alkynes with a mixture of trichloride and trialkylsilane, followed by treatment with a suitable diol reagent.[6] However, these methods suffer from poor functional-group compatibility, formation of waste inorganic salts, and multiple synthetic sequences. Recently, transition-metal-catalyzed methods have gained attention. For example, copper-catalyzed diborylation of 1,1-dibromoethane with bis(pinacolato)diboron formed 1,1-diborylethane in moderate yield.[7,8] Hall[2c] and Yun[9] reported copper-catalyzed enantioselective hydroboration of alkenylboron compounds with a 1,8-naphthalenediaminatoboryl substituent, furnishing 1,1-diboronate esters with high optical purity. Hartwig reported iridium-catalyzed diborylation of benzylic C–H bonds directed by a hydrosilyl group to form 1,1-benzyldiboronate esters.[10] Platinum-catalyzed[11] or metal-free[12] carbene insertions into B–B bonds of diboron compounds have also been developed for preparation of 1,1-diboronate esters.

Due to high atom economy, easy access of starting materials, and mild reaction conditions, the catalytic sequential hydroboration of terminal alkynes is a synthetically useful approach to 1,1-diboronates. However, the sequential, regioselective hydroborations of the alkenylboronate intermediates are rare, and most reactions generate a regioisomeric mixture.[13,14] In 2009, Shibata reported a rhodium-catalyzed sequential hydroboration of alkynes with pinacolborane (HBpin) to afford 1,1-diboronates with high regioselectivity, but in low to moderate yields; monoborylalkanes are formed in noticeable yields (12–24%) as the side-products *via* reduction of the alkenylboronate intermediates (Scheme 1a).[15] More recently, Yun reported a copper(I)-catalyzed selective sequential hydroboration of alkyl alkynes with HBpin to form

---

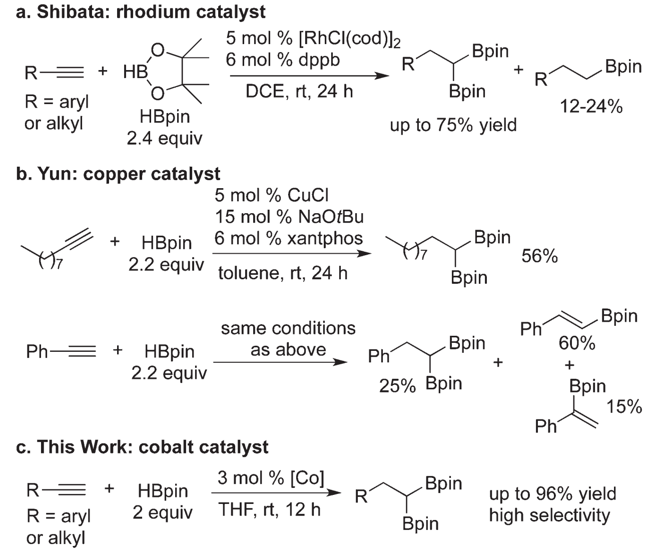
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, 345 Lingling Road, Shanghai, 200032, China.
E-mail: huangzh@sioc.ac.cn

† Electronic supplementary information (ESI) available: Experimental procedures and product characterization. See DOI: 10.1039/c5qo00426h



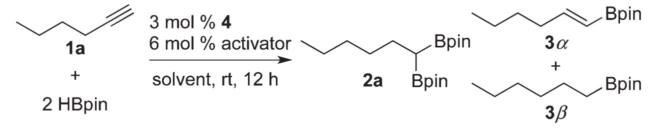
Zheng Huang

Zheng Huang received his B.S. and Master degrees from Nankai University under the direction of Prof. Xianhe Bu. In 2009, he earned his Ph.D. from the University of North Carolina at Chapel Hill under the guidance of Prof. Maurice Brookhart. Upon completion of his postdoctoral research with Prof. John F. Hartwig at the University of Illinois, Urbana-Champaign in 2012, he started his independent career as a professor at the Shanghai Institute of Organic Chemistry. His research focuses on the design of transition-metal complexes with application in catalytic functionalization of alkanes and alkenes, and olefin polymerization. In his spare time, he enjoys reading and the outdoors.

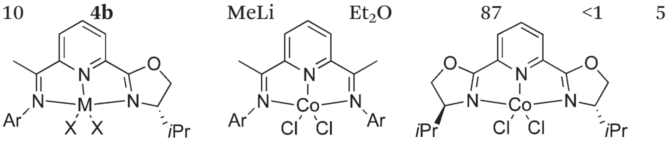


Scheme 1 Transition-metal-catalyzed sequential hydroboration of terminal alkynes.

Table 1 Cobalt-catalyzed sequential hydroboration of 1-hexyne **1a** with HBpin[a]



Entry	Precatalyst	Activator	Solvent	Yield[b] (%)		
				2	**3α**	**3β**
1	**4a**	$NaBHEt_3$	THF	23	28	42
2	**4b**	$NaBHEt_3$	THF	96 (92)	<1	3
3	None	$NaBHEt_3$	THF	0	4	0
4	**4b**	—	THF	0	3	0
5	**4c**	$NaBHEt_3$	THF	11	39	43
6	**4d**	$NaBHEt_3$	THF	89	<1	5
7	**4b**	MeLi	THF	95 (90)	<1	4
8	**4b**	MeLi	Toluene	83	<1	3
9	**4b**	MeLi	*n*-Pentane	87	<1	4
10	**4b**	MeLi	Et_2O	87	<1	5



M = Fe, X = Br, **4a**
M = Co, X = Cl, **4b**
4c
Ar = 2,6-iPr_2-C_6H_4
4d

[a] Reaction conditions: **1a** (0.5 mmol), HBpin (1.0 mmol), **4** (3 mol%), and additive (6 mol%) in THF (2 mL) at RT. [b] GC yields using mesitylene as an internal standard (isolated yields in parentheses).

1,1-diboronate esters, but reactions of aryl alkynes yield monoboryl and diboryl mixtures (Scheme 1b).[16]

Driven by our interest in developing base–metal catalyst systems for alkene hydrofunctionalizations,[17] recently we and Lu independently reported iminopyridine-oxazoline (IPO) cobalt[17e,18] and iron[17g,19] complexes for asymmetric hydroboration/hydrosilylation of 1,1-disubstituted alkenes and ketones. Herein, we report that an IPO cobalt complex catalyzes regioselective sequential hydroboration of alkyl and aryl alkynes (Scheme 1c). Most reactions occur under mild conditions with high isolated yields. The method exhibits a broad substrate scope and wide functional group tolerance.

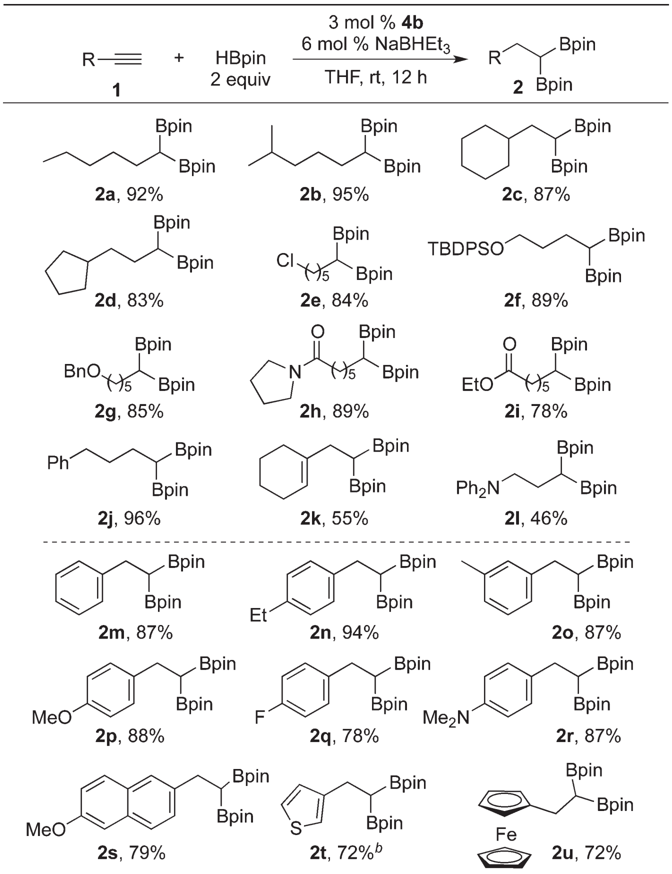
We commenced our studies by examining the reaction of 1-hexyne (**1a**) with HBpin (Table 1). When using 3 mol% of (IPO)$FeBr_2$ (**4a**) as the catalyst precursor and 6 mol% of $NaBHEt_3$ as the catalyst activator, the reaction of **1a** with 2 equiv. of HBpin in THF at room temperature after 12 h gave 23% of the desired dual hydroboration product **2a**, 28% of *trans*-monoborylalkene (**3α**), and 42% of monoborylalkane (**3β**) (entry 1). However, using the cobalt analogue (IPO)$CoCl_2$ **4b** as the precatalyst led to the formation of **2a** with very high selectivity and yield (96%) (entry 2). A control experiment with the catalyst activator, but without the precatalyst only gave 4% of **3α** (entry 3). To evaluate the role of the ligand, reactions using the related cobalt complexes with bis(imino)pyridine (**4c**) and bis(oxazoline)pyridine (**4d**) ligands have been carried out. The former gave the desired product in low yield (11%), along with 39% of **3α** and 43% of **3β** (entry 5), whereas the latter gave 89% of **2a** and 5% of **3β** (entry 6). The addition of the catalyst activator is essential for the catalysis (entry 4), but it is not limited to $NaBHEt_3$. The reaction using MeLi as the activator afforded the dual hydroboration product in a yield close to that using $NaBHEt_3$. The reactions proceeded smoothly in other solvents, such as toluene, *n*-pentane, and diethyl ether, albeit with relatively low yield compared to that in THF (entries 7–10).

We next studied the scope and limitation of the protocol with (IPO)$CoCl_2$ **4b** as the catalyst precursor, $NaBHEt_3$ as the activator, and THF as the solvent (Table 2). Terminal aliphatic alkynes all reacted with HBpin to form the diboryl products selectively. Simple alkynes with linear and branched alkyl groups were converted to the corresponding 1,1-diboronate esters in high yields (**2a–2d**). A wide range of functional groups, such as chloride (**2e**), silicon ether (**2f**), benzyl ether (**2g**), amide (**2h**), ester (**2i**), and internal olefin (**2k**), can be tolerated. Phenyl-protected propargyl amine gave the desired product (**2l**) in moderate yield.

Reactions of terminal aryl alkynes also occurred efficiently. Substrates containing both electron-donating and -withdrawing substituents, such as alkyl (**2n** and **2o**), methoxy (**2p**), fluoride (**2q**), and dimethylamino (**2r**) groups, afforded the 1,1-diboryl products in high isolated yields. Naphthyl- (**2s**), thienyl- (**2t**), and ferrocenyl-substituted acetylenes (**2u**) are suitable substrates for sequential hydroboration with exclusive terminal selectivity.

In situ monitoring of the cobalt-catalyzed reaction of 1-hexyne (**1a**) with 2 equiv. of HBpin provided insight into the catalytic process. As shown in Fig. 1, the reaction at the early stage gave **2a** in low yield, but a substantial amount of **3α** (*e.g.*, 15 min, 67% of **3α**, 8% of **2a**). The intermediate **3α** was gradually converted to **2a** over the course of the reaction. The transform-

Table 2 Cobalt-catalyzed sequential hydroboration of various terminal alkynes with HBpin[a]



[a] Reaction conditions: **1** (0.5 mmol), HBpin (1.0 mmol), **4b** (3 mol%), and $NaBHEt_3$ (6 mol%) in THF (2 mL) at rt. Isolated yields. [b] With 3.0 mmol HBpin.

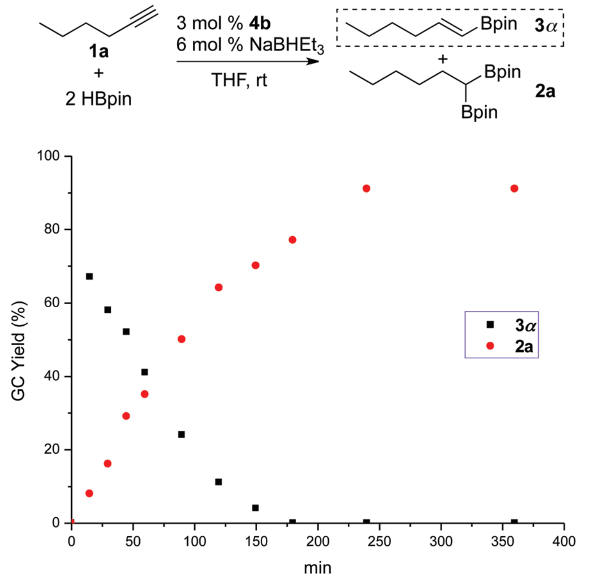


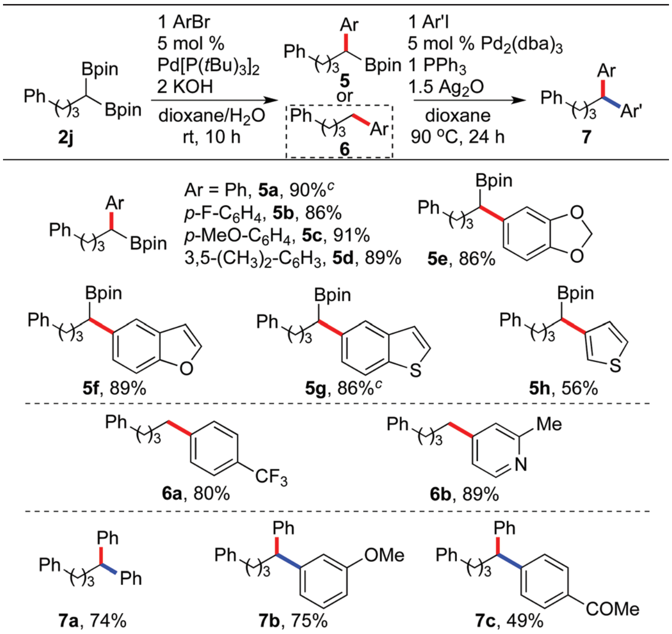
Fig. 1 Profile of sequential hydroboration of 1-hexyne (**1a**) with 2 equiv. of HBpin catalyzed by 3 mol% **4b** and 6 mol% $NaBHEt_3$ in THF at room temperature.

ation was nearly complete in 3 h, furnishing **2a** in 91% yield. Except for **2a**, **3α**, and a trace amount of **3β** (<3%), no other products were detected by GC during the whole process. The results indicate that the reaction occurs *via* formation of *trans*-monoborylalkene (**3α**) as the intermediate, which undergoes subsequent hydroboration to give the 1,1-diboryl product.

The synthetic utility of 1,1-diboronate esters was demonstrated by their applications to palladium-catalyzed Suzuki–Miyaura coupling reactions. Seminal work by Shibata showed that the adjacent boron atom in 1,1-diborylalkanes has a beneficial effect on the transmetallation step for coupling reactions.[2a,8,10] Using $Pd[P(tBu)_3]_2$ as the catalyst and KOH as the base, we found that 1,1-diboryl compound **2j** coupled selectively with various aryl bromides at room temperature, giving the monoarylation products in high yields (Table 3). *O*- and *S*-containing benzoheterocyclic (**5e–5g**) and heterocyclic (**5h**) bromides are also favorable substrates under the reaction conditions. Noteworthily, while the reaction with a *p*-F-substituted aryl bromide gave the benzyl boronate **5b** in 86% isolated yield, under otherwise identical conditions, the coupling with a *p*-CF_3-substituted aryl bromide afforded 80% of the protodeborylation product **6a**. Furthermore, with 4-bromo-2-methylpyridine as the substrate, a similar transformation involving the combination of cross coupling and protodeborylation occurred to form **6b** in 89% yield.[20]

In addition, using a protocol developed by Crudden, the isolated secondary benzylic boronate esters could undergo

Table 3 Coupling of 1,1-diboronate **2j** with aryl bromides[a] and the subsequent coupling with aryl iodides[b]



[a] Reaction conditions: **2j** (0.22 mmol), ArBr (0.2 mmol), $Pd[P(tBu)_3]_2$ (5 mol%), and KOH aq. (40 μL, 10 M in H_2O) in dioxane (1 mL) at RT. Isolated yields. [b] Reaction conditions: **5a** (0.2 mmol), ArI (0.24 mmol), $Pd_2(dba)_3$ (5 mol%), PPh_3 (0.2 mmol), and Ag_2O (0.3 mmol) in dioxane (1 mL) at 90 °C. Isolated yields. [c] Carried out on 0.5 mmol scale.

subsequent cross couplings.[21] For example, the reactions of **5a** with aryl iodides catalyzed by $Pd_2(dba)_2/PPh_3$ in the presence of Ag_2O afforded the diarylation products (**7a–c**) in useful yields. Thus, the sequence of dual hydroboration and two-step cross coupling reactions provides a synthetically efficient approach to diarylmethane derivatives from simple alkynes.

In summary, we have developed a cobalt catalyst system for selective synthesis of 1,1-diboronates from terminal alkyl and aryl alkynes. Featuring the use of low-cost base–metal catalyst, 100% atom economy, mild reaction conditions, high conversion, wide substrate scope, and broad functional group compatibility, the cobalt-catalyzed alkyne sequential hydroboration could be an attractive route to 1,1-organodiboronate esters. We have also demonstrated that the dual hydroboration products are useful synthetic intermediates for chemoselective Suzuki–Miyaura coupling reactions.

Conflict of InterestThe authors declare no competing financial interest.

Acknowledgements

We gratefully acknowledge the financial support from the National Basic Research Program of China (2015CB856600), the National Natural Science Foundation of China (no. 21422209, 21272255, 21432011, and 21421091), and the CAS/SAFEA International Partnership Program for Creative Research Teams.

References

1 (*a*) D. S. Matteson and R. J. Moody, *Organometallics*, 1982, **1**, 20–28; (*b*) K. Endo, M. Hirokami and T. Shibata, *J. Org. Chem.*, 2010, **75**, 3469–3472; (*c*) K. Endo, A. Sakamoto, T. Ohkubo and T. Shibata, *Chem. Lett.*, 2011, **40**, 1440–1442; (*d*) K. Hong, X. Liu and J. P. Morken, *J. Am. Chem. Soc.*, 2014, **136**, 10581–10584; (*e*) Z. Q. Zhang, C. T. Yang, L. J. Liang, B. Xiao, X. Lu, J. H. Liu, Y. Y. Sun, T. B. Marder and Y. Fu, *Org. Lett.*, 2014, **16**, 6342–6345; (*f*) J. R. Coombs, L. Zhang and J. P. Morken, *Org. Lett.*, 2015, **17**, 1708–1711; (*g*) H.-Y. Sun, K. Kubota and D. G. Hall, *Chem. – Eur. J.*, 2015, **21**, 19186–19194.

2 (*a*) K. Endo, T. Ohkubo, M. Hirokami and T. Shibata, *J. Am. Chem. Soc.*, 2010, **132**, 11033–11035; (*b*) K. Endo, T. Ohkubo and T. Shibata, *Org. Lett.*, 2011, **13**, 3368–3371; (*c*) J. C. H. Lee, R. McDonald and D. G. Hall, *Nat. Chem.*, 2011, **3**, 894–899; (*d*) K. Endo, T. Ishioka, T. Ohkubo and T. Shibata, *J. Org. Chem.*, 2012, **77**, 7223–7231; (*e*) K. Endo, T. Ohkubo, T. Ishioka and T. Shibata, *J. Org. Chem.*, 2012, **77**, 4826–4831; (*f*) H. Li, Z. Zhang, X. Shangguan, S. Huang, J. Chen, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2014, **53**, 11921–11925; (*g*) C. Sun, B. Potter and J. P. Morken, *J. Am. Chem. Soc.*, 2014, **136**, 6534–6537; (*h*) J. C. Lee, H. Y. Sun and D. G. Hall, *J. Org. Chem.*, 2015, **80**, 7134–7143; (*i*) S. Xu, X. Shangguan, H. Li, Y. Zhang and J. Wang, *J. Org. Chem.*, 2015, **80**, 7779–7784.

3 (*a*) A. Hirai, M. Nakamura and E. Nakamura, *J. Am. Chem. Soc.*, 1999, **121**, 8665–8666; (*b*) I. Marek, *Chem. Rev.*, 2000, **100**, 2887–2900; (*c*) S. Matsubara, K. Oshima and K. Utimoto, *J. Organomet. Chem.*, 2001, **617–618**, 39–46; (*d*) J. F. Normant, *Acc. Chem. Res.*, 2001, **34**, 640–644; (*e*) V. M. Dembitsky, H. Abu Ali and M. Srebnik, *Appl. Organomet. Chem.*, 2003, **17**, 327–345; (*f*) P. Langer and W. Freiberg, *Chem. Rev.*, 2004, **104**, 4125–4150; (*g*) F. Foubelo and M. Yus, *Curr. Org. Chem.*, 2005, **9**, 459–490.

4 (*a*) M. Shimizu and T. Hiyama, *Proc. Jpn. Acad., Ser. B*, 2008, **84**, 75–85; (*b*) J. Takaya and N. Iwasawa, *ACS Catal.*, 2012, **2**, 1993–2006.

5 (*a*) T. Hata, H. Kitagawa, H. Masai, T. Kurahashi, M. Shimizu and T. Hiyama, *Angew. Chem., Int. Ed.*, 2001, **40**, 790–792; (*b*) T. Kurahashi, T. Hata, H. Masai, H. Kitagawa, M. Shimizu and T. Hiyama, *Tetrahedron*, 2002, **58**, 6381–6395; (*c*) M. Shimizu, C. Nakamaki, K. Shimono, M. Schelper, T. Kurahashi and T. Hiyama, *J. Am. Chem. Soc.*, 2005, **127**, 12506–12507; (*d*) M. Shimizu, M. Schelper, I. Nagao, K. Shimono, T. Kurahashi and T. Hiyama, *Chem. Lett.*, 2006, **35**, 1222–1223.

6 R. Soundararajan and D. S. Matteson, *Organometallics*, 1995, **14**, 4157–4166.

7 H. Ito and K. Kubota, *Org. Lett.*, 2012, **14**, 890–893.

8 C.-T. Yang, Z.-Q. Zhang, H. Tajuddin, C.-C. Wu, J. Liang, J.-H. Liu, Y. Fu, M. Czyzewska, P. G. Steel, T. B. Marder and L. Liu, *Angew. Chem., Int. Ed.*, 2012, **51**, 528–532.

9 X. Feng, H. Jeon and J. Yun, *Angew. Chem., Int. Ed.*, 2013, **52**, 3989–3992.

10 S. H. Cho and J. F. Hartwig, *Chem. Sci.*, 2014, **5**, 694–698.

11 (*a*) H. Abu Ali, I. Goldberg and M. Srebnik, *Organometallics*, 2001, **20**, 3962–3965; (*b*) H. Abu Ali, I. Goldberg, D. Kaufmann, C. Burmeister and M. Srebnik, *Organometallics*, 2002, **21**, 1870–1876; (*c*) A. J. Wommack and J. S. Kingsbury, *Tetrahedron Lett.*, 2014, **55**, 3163–3166.

12 (*a*) H. Li, L. Wang, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2012, **51**, 2943–2946; (*b*) H. Li, X. Shangguan, Z. Zhang, S. Huang, Y. Zhang and J. Wang, *Org. Lett.*, 2014, **16**, 448–451; (*c*) A. B. Cuenca, J. Cid, D. García-López, J. J. Carbó and E. Fernández, *Org. Biomol. Chem.*, 2015, **13**, 9659–9664.

13 (*a*) D. J. Pasto, *J. Am. Chem. Soc.*, 1964, **86**, 3039–3047; (*b*) V. V. R. Rao, S. K. Agarwal, I. Mehrotra and D. Devaprabhakara, *J. Organomet. Chem.*, 1979, **166**, 9–16; (*c*) P. Nguyen, R. B. Coapes, A. D. Woodward, N. J. Taylor, J. M. Burke, J. A. K. Howard and T. B. Marder, *J. Organomet. Chem.*, 2002, **652**, 77–85; (*d*) R. B. Coapes, F. E. S. Souza, R. L. Thomas, J. J. Hall and T. B. Marder, *Chem. Commun.*, 2003, 614–615; (*e*) J. Ramírez, A. M. Segarra and E. Fernández, *Tetrahedron: Asymmetry*, 2005, **16**, 1289–1294.

14 (*a*) H. C. Brown and S. K. Gupta, *J. Am. Chem. Soc.*, 1975, **97**, 5249–5255; (*b*) C. A. Brown and R. A. Coleman, *J. Org. Chem.*, 1979, **44**, 2328–2329; (*c*) C. E. Tucker, J. Davidson and P. Knochel, *J. Org. Chem.*, 1992, **57**, 3482–3485; (*d*) S. Pereira and M. Srebnik, *Organometallics*, 1995, **14**,

3127–3128; (*e*) X. He and J. F. Hartwig, *J. Am. Chem. Soc.*, 1996, **118**, 1696–1702; (*f*) S. Pereira and M. Srebnik, *Tetrahedron Lett.*, 1996, **37**, 3283–3286; (*g*) T. Ohmura, Y. Yamamoto and N. Miyaura, *J. Am. Chem. Soc.*, 2000, **122**, 4990–4991; (*h*) M. Hoshi, K. Shirakawa and M. Okimoto, *Tetrahedron Lett.*, 2007, **48**, 8475–8478; (*i*) D. M. Khramov, E. L. Rosen, A. Joyce, P. D. Vu, V. M. Lynch and C. W. Bielawski, *Tetrahedron*, 2008, **64**, 6853–6862; (*j*) C. Gunanathan, M. Holscher, F. Pan and W. Leitner, *J. Am. Chem. Soc.*, 2012, **134**, 14349–14352; (*k*) B. Sundararaju and A. Furstner, *Angew. Chem., Int. Ed.*, 2013, **52**, 14050–14054; (*l*) H. E. Ho, N. Asao, Y. Yamamoto and T. Jin, *Org. Lett.*, 2014, **16**, 4670–4673; (*m*) J. V. Obligacion, J. M. Neely, A. N. Yazdani, I. Pappas and P. J. Chirik, *J. Am. Chem. Soc.*, 2015, **137**, 5855–5858.

15 K. Endo, M. Hirokami and T. Shibata, *Synlett*, 2009, 1331–1335.

16 S. Lee, D. Li and J. Yun, *Chem. – Asian J.*, 2014, **9**, 2440–2443.

17 (*a*) L. Zhang, D. Peng, X. Leng and Z. Huang, *Angew. Chem., Int. Ed.*, 2013, **52**, 3676–3680; (*b*) Z. Huang and L. Zhang, *Synlett*, 2013, 1745–1747; (*c*) D. Peng, Y. Zhang, X. Du, L. Zhang, X. Leng, M. D. Walter and Z. Huang, *J. Am. Chem. Soc.*, 2013, **135**, 19154–19166; (*d*) L. Zhang, Z. Zuo, X. Leng and Z. Huang, *Angew. Chem., Int. Ed.*, 2014, **53**, 2696–2700; (*e*) L. Zhang, Z. Zuo, X. Wan and Z. Huang, *J. Am. Chem. Soc.*, 2014, **136**, 15501–15504; (*f*) Y. Cao, Y. Zhang, L. Zhang, D. Zhang, X. Leng and Z. Huang, *Org. Chem. Front.*, 2014, **1**, 1101–1106; (*g*) Z. Zuo, L. Zhang, X. Leng and Z. Huang, *Chem. Commun.*, 2015, **51**, 5073–5076; (*h*) L. Zhang and Z. Huang, *J. Am. Chem. Soc.*, 2015, **137**, 15600–15603; (*i*) X. Jia and Z. Huang, *Nat. Chem.*, 2016, **8**, 157–161.

18 (*a*) J. Chen, T. Xi, X. Ren, B. Cheng, J. Guo and Z. Lu, *Org. Chem. Front.*, 2014, **1**, 1306–1309; (*b*) J. Guo, J. Chen and Z. Lu, *Chem. Commun.*, 2015, **51**, 5725–5727.

19 (*a*) J. Chen, T. Xi and Z. Lu, *Org. Lett.*, 2014, **16**, 6452–6455; (*b*) J. Chen, B. Cheng, M. Cao and Z. Lu, *Angew. Chem., Int. Ed.*, 2015, **54**, 4661–4664.

20 Using aryl iodides as the electrophiles, NaOH as the base, THF/H_2O as the solvent, Hartwig and co-workers showed that cross coupling with 1,1-benzyldiboronate esters was accompanied by protodeborylation. Also see ref. 10.

21 D. Imao, B. W. Glasspoole, V. S. Laberge and C. M. Crudden, *J. Am. Chem. Soc.*, 2009, **131**, 5024–5025.