Magnesium Diorganoboronates

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Practical One-Pot Preparation of Magnesium Di(hetero)aryl- and Magnesium Dialkenylboronates for Suzuki–Miyaura Cross-Coupling Reactions**

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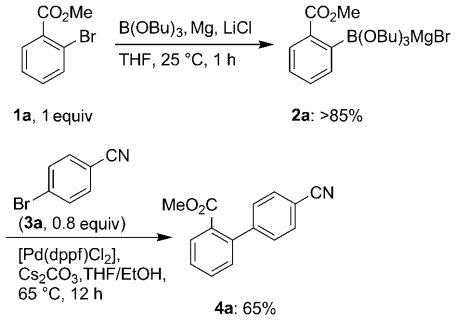
Arylboron derivatives have found broad applications in Suzuki–Miyaura cross-coupling reactions.[1] In particular, various boronic acids,[2] esters, and their derivatives, such as trifluoroborates,[3] MIDA boronates[4] or DAN reagents,[5] have been used very successfully (MIDA = *N*-methyliminodiacetic acid, DAN = 2,3-diaminonaphthalene). In general, most arylboronic compounds are prepared via lithium or magnesium organometallic compounds in a two-step process,[6] although direct transition-metal-catalyzed borylations can also be realized.[7] Furthermore, a one-pot preparation of arylboronic esters by using an iodine/magnesium exchange has been reported.[8]

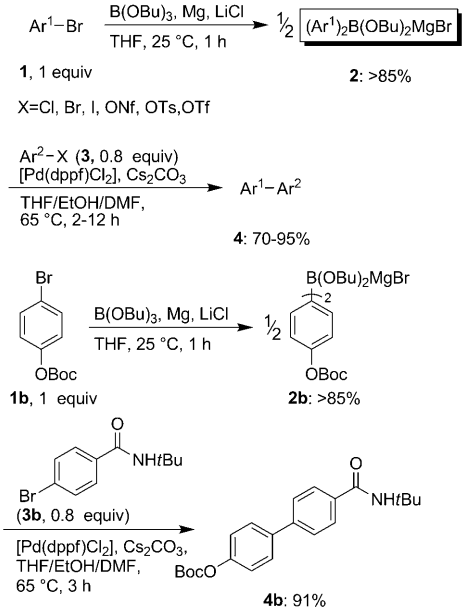
In the search for a convenient, general, atom-economical[9] method for preparing boronic derivatives suitable for cross-coupling reactions, we have investigated a one-pot procedure that uses inexpensive aryl bromides, magnesium as a low-cost reducing agent with low toxicity, and a trialkylborate as a cheap boron source. Preliminary experiments[10] have shown that treatment of methyl 2-bromobenzoate (**1a**) with Mg turnings (1.6 equiv), $B(OBu)_3$ (1.0 equiv), and LiCl (1.1 equiv) in THF at 25 °C leads within 1 h with full conversion to the magnesium arylboronate **2a**. Its cross-coupling with 4-bromobenzonitrile (**3a**) using 4% [Pd(dppf)Cl_2] (dppf = 1,1′-bis(diphenylphosphanyl)ferrocene)[11] and Cs_2CO_3 (2 equiv) in a 1:1 THF/EtOH mixture provides the desired cross-coupling product **4a** in 65% yield (Scheme 1).

Interestingly, the alternative conversion of **1a** into the corresponding zinc reagent by using Mg turnings (1.6 equiv), $ZnCl_2$ (1.0 equiv), and LiCl (1.1 equiv) in THF[12] requires a reaction time of 3 h, which shows that the presence of $B(OBu)_3$ significantly accelerates the Mg insertion. Furthermore, $B(OBu)_3$ was found to be a much better boron source than $B(OMe)_3$ or $B(OEt)_3$ since it did not lead to any transesterification with sensitive substrates such as methyl 2-bromobenzoate (**1a**).



Scheme 1. $B(OBu)_3$-accelerated synthesis of magnesium arylboronate **2a** and subsequent Suzuki–Miyaura cross-coupling.

Further experiments indicate that a better atom economy can be achieved without a loss of yield by using 0.5 equivalents of $B(OBu)_3$, thus forming magnesium diarylboronates of type **2** (Scheme 2).[13] Remarkably, both aryl groups (Ar^1) are transferred under typical Suzuki–Miyaura cross-coupling conditions by using various aryl halides or pseudohalides of



Scheme 2. General synthesis and cross-coupling of magnesium diarylboronates **2**. Boc = *tert*-butoxycarbonyl, ONf = nonaflate, OTf = trifluoromethanesulfonate, OTs = toluene-4-sulfonyl.

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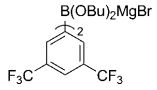
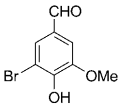
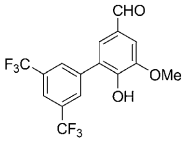
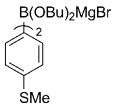
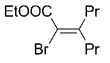
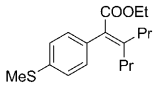
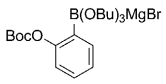
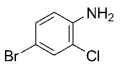
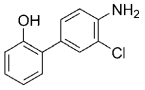
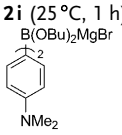
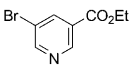
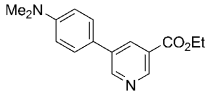
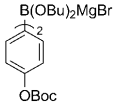
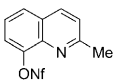
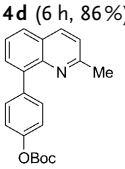
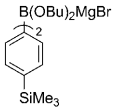
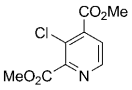
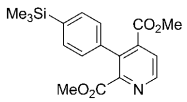
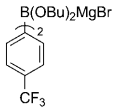
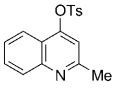
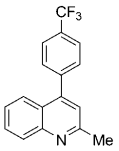
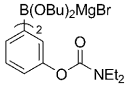
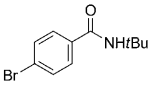
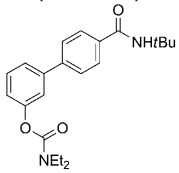
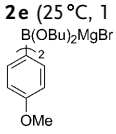
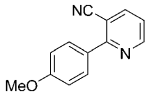
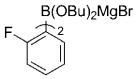
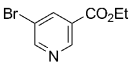
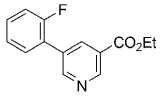
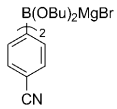
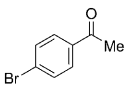
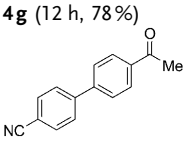
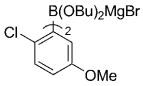
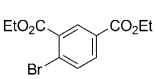
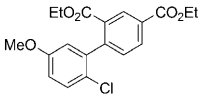
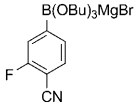
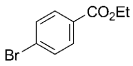
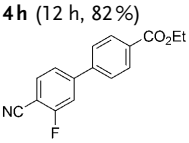
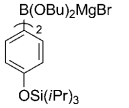
Table 1: Suzuki–Miyaura cross-coupling reactions performed with magnesium diarylboronates of type **2**.

Entry	$Ar_2B(OBu)_2MgBr$ (cond. [*T*, *t*])	Electrophile	Product (*t*, yield[a])	Entry	$Ar_2B(OBu)_2MgBr$ (cond. [*T*, *t*])	Electrophile	Product (*t*, yield[a])
							
1	**2c** (25 °C, 15 min)	**3c**	**4c** (12 h, 83 %)	11	**2i** (25 °C, 1 h)	**3l**	**4m** (12 h, 75 %)
							
2	**2d** (25 °C, 1 h)[b]	**3d**	**4d** (6 h, 86 %)	12	**2j** (25 °C, 1 h)	**3m**	**4n** (2 h, 90 %)
							
3	**2b** (25 °C, 1 h)	**3e**	**4e** (3 h, 78 %)	13	**2k** (25 °C, 1 h)	**3n**	**4o** (12 h, 78 %)
							
4	**2e** (25 °C, 1 h)	**3f**	**4f** (12 h, 70 %)	14	**2l** (25 °C, 1 h)	**3b**	**4p** (7 h, 90 %)
							
5	**2f** (25 °C, 1 h)	**3g**	**4g** (12 h, 78 %)	15	**2m** (25 °C, 1 h)	**3m**	**4q** (3 h, 79 %)
							
6	**2g** (25 °C, 1 h)	**3h**	**4h** (12 h, 82 %)	16	**2n** (25 °C, 1 h)	**3o**	**4r** (6 h, 81 %)
							
7	**2h** (25 °C, 1 h)[b]	**3i**	**4i** (12 h, 72 %)	17	**2o** (25 °C, 1 h)	**3p**	**4s** (3 h, 70 %)
8	**2i** (25 °C, 1 h)	**3j**	**4j** (6 h, 92 %)	18	**2p** (25 °C, 1 h)[b]	**3q**	**4t** (12 h, 89 %)
9	**2i** (25 °C, 1 h)	**3c**	**4k** (6 h, 87 %)	19	**2p** (25 °C, 1 h)[b]	**3r**	**4u** (4 h, 78 %)
10	**2i** (25 °C, 1 h)	**3k**	**4l** (12 h, 81 %)				

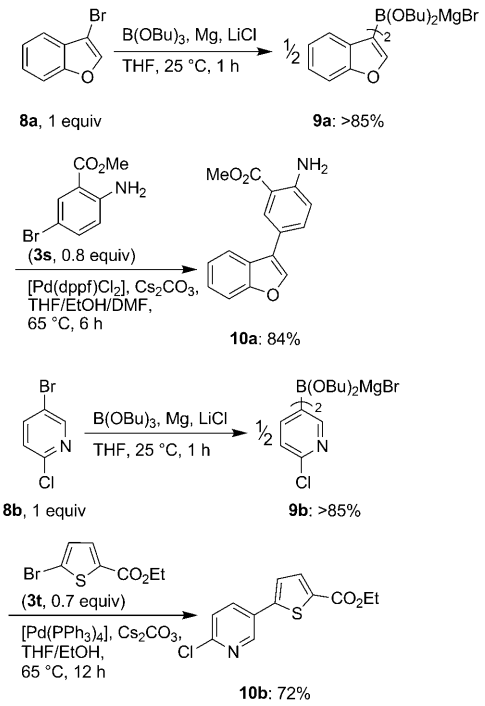
[a] Yield of isolated, analytically pure product. [b] 1 equiv of $B(OBu)_3$ was used.

type Ar^2-X (**3**; X = Cl, Br, I, ONf,[14] OTs,[15] OTf[16]) as the electrophile.

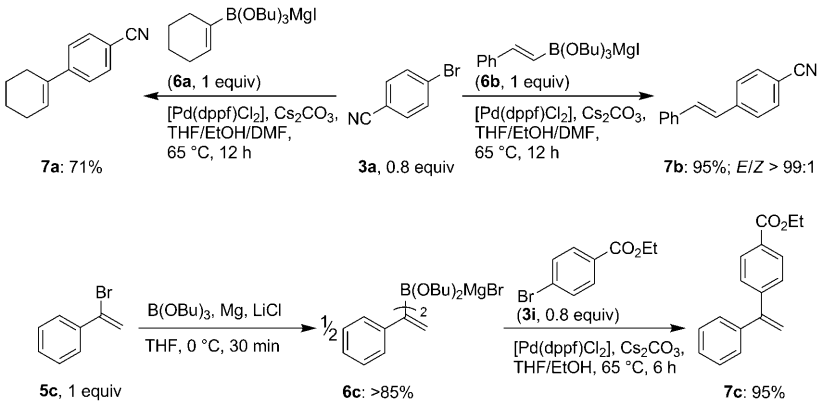
Thus, under typical reaction conditions, the sensitive Boc-protected bromophenol **1b** reacted with $B(OBu)_3$ (0.5 equiv), Mg (1.6 equiv), and LiCl (1.1 equiv) in THF within 1 h at 25 °C to provide the magnesium diarylboronate **2b** (> 85% yield). Its Pd-catalyzed cross-coupling with the bromobenzamide **3b** proceeds within 3 h at 65 °C in the presence of 4% $[Pd(dppf)Cl_2]$ and Cs_2CO_3 (2 equiv) in a 4:4:1 THF/EtOH/DMF mixture and leads to the functionalized biphenyl **4b** in 91% yield. This result clearly demonstrates that both aryl groups of **2b** are available for the cross-coupling. This behavior was general and a wide range of diarylboronates of type **2** bearing various functional groups (ester, cyanide, Boc, (thio)methoxy, amino, or silyl groups) were prepared conveniently at 25 °C within 15 min to 1 h (Table 1). The cross-coupling reaction of the magnesium diarylboronates **2c–p** produces the desired products **4c–u** in 70–92% yield under standard conditions (Table 1, entries 1–19). Although aryl bromides have been used mostly as electrophiles (Table 1, entries 1, 2, 6–9, 12, 14–19), aryl chlorides (Table 1, entries 5 and 13), a nonaflate[14] (Table 1, entry 3), a tosylate (Table 1, entry 4), and a triflate (Table 1, entry 10) readily undergo the cross-coupling without any further optimization. In some cases, when the aryl bromide is sterically hindered (such as in the precursor to **2d**) or strongly electron-deficient (such as in the precursor to **2h**), the preparation of the monoarylboronate ($ArB(OBu)_3MgBr$) was preferable[17] and led to a significant improvement in the yield of the subsequent Suzuki–Miyaura cross-coupling reaction (Table 1, entries 2 and 7).

The method described above also proved to be suitable for alkenyl halides. Suzuki–Miyaura cross-coupling reactions with mono- and dialkenylboronic derivatives such as **6a–c** proceed in high yields (Scheme 3). Thus, the treatment of cyclohexenyl iodide with $B(OBu)_3$ (1 equiv), Mg (1.6 equiv), and LiCl (1.1 equiv) in THF at 25 °C produces the corresponding magnesium alkenylboronate **6a** within 1 h (> 85% yield). Similarly, the reaction of 2-iodostyrene furnishes the desired alkenylboronate **6b** under the same conditions (> 85% yield). The cross-coupling of **6a**,**b** with 4-bromobenzonitrile (**3a**) gives the alkenes **7a**,**b** in 71 and 95% yield, respectively. The magnesium dialkenylboronate **6c** was prepared from 1-bromostyrene (**5c**), $B(OBu)_3$ (0.5 equiv), Mg (1.6 equiv), and LiCl (1.1 equiv). The palladium-catalyzed cross-coupling with ethyl 4-bromobenzoate (**3i**) under standard conditions gives the diarylethylene **7c** in 95% yield (Scheme 3).

Both electron-rich and electron-poor heterocycles such as **8a** and **8b**, respectively, readily react with Mg (1.6 equiv) and LiCl (1.1 equiv) in the presence of $B(OBu)_3$ (0.5 equiv) in THF (0 or 25 °C, 0.5–1 h) to produce the diheterocyclic magnesium boronates **9a**,**b** (> 85% yield). A subsequent Suzuki–Miyaura cross-coupling reaction with the aryl bromides **3s** and **3t** furnishes the corresponding heterocyclic products **10a**,**b** in 72 and 84% yield, respectively (Scheme 4). The related diheterocyclic magnesium boronates **9c–h** are obtained in a similar manner. Suzuki–Miyaura cross-coupling reactions of **9c–h** with aryl chlorides and bromides furnish the expected heterocycles **10c–j** (Table 2, entries 1–8).



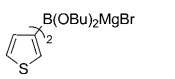
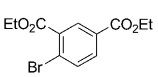
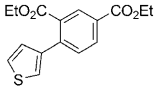
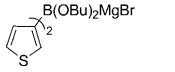
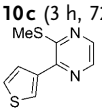
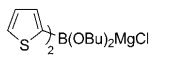
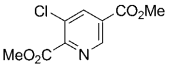
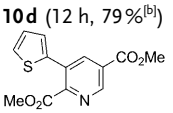
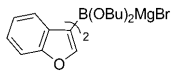
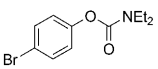
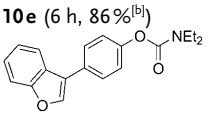
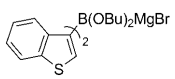
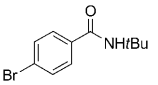
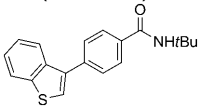
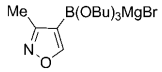
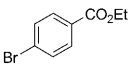
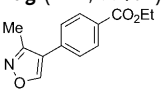
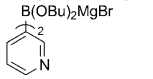
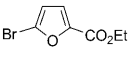
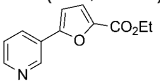
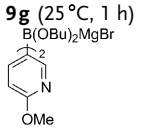
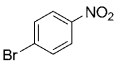
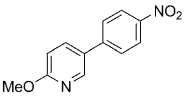
Scheme 4. Synthesis of diheterocyclic boronates **9a**,**b** and subsequent Suzuki–Miyaura cross-coupling reactions.



Scheme 3. Magnesium alkenylboronates **6a–c** and their subsequent Suzuki–Miyaura cross-coupling reactions.

In summary, we have reported a general and low-cost one-step synthesis of new polyfunctional magnesium diorganoboronates that tolerate a wide range of functional groups. This atom-economical synthesis gives ready access to functionalized diaryl- and diheteroaryl- as well as to dialkenylboronates from their correspond-

Table 2: Suzuki–Miyaura cross-coupling reactions performed with magnesium diheteroarylboronates of type **9**.

Entry	$Het_2B(OBu)_2MgBr$ (conditions [*T*, *t*])	Electrophile	Product (*t*, yield[a])
			
1	**9c** (0 °C, 30 min) 	**3o** 	**10c** (3 h, 72 %[b]) 
2	**9c** (0 °C, 30 min) 	**3u** 	**10d** (12 h, 79 %[b]) 
3	**9d** (25 °C, 30 min) 	**3v** 	**10e** (6 h, 86 %[b]) 
4	**9a** (25 °C, 30 min) 	**3w** 	**10f** (3 h, 86 %[b]) 
5	**9e** (0 °C, 1 h) 	**3b** 	**10g** (12 h, 77 %[b]) 
6	**9f** (25 °C, 1 h)[d] 	**3i** 	**10h** (12 h, 60 %[b]) 
7	**9g** (25 °C, 1 h) 	**3x**[e] 	**10i** (24 h, 82 %[c]) 
8	**9h** (25 °C, 1 h)	**3y**	**10j** (12 h, 85 %[b])

[a] Yield of isolated, analytically pure product. [b] Obtained after Pd-catalyzed cross-coupling (4 % $[Pd(dppf)Cl_2]$, Cs_2CO_3 (2 equiv), THF/EtOH/DMF (4:4:1), 65 °C). [c] Obtained after Pd-catalyzed cross-coupling (4 % $[Pd(PPh_3)_4]$, $Na_2CO_3 \cdot 10H_2O$ (1.3 equiv), THF/dioxane/H_2O (4:4:1), 110 °C). [d] 1 equiv of $B(OBu)_3$ was used. [e] 0.7 equiv of electrophile was used.

ing organic bromides. These magnesium diorganoboronates undergo Suzuki–Miyaura cross-coupling reactions with a broad variety of electrophiles in good to excellent yields. Further studies of their reactivity are currently underway in our laboratory.

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[1] a) S. Kotha, K. Lahiri, D. Kashinath, *Tetrahedron* **2002**, *58*, 9633; b) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; c) S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem.* **2001**, *113*, 4676; *Angew. Chem. Int. Ed.* **2001**, *40*, 4544; d) A. Suzuki, *Heterocycles* **2010**, *80*, 15; e) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147; f) *Boronic Acids* (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2005**; g) N. Miyaura in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**, p. 41; h) N. Miyaura in *Cross-Coupling Reactions—A Practical Guide* (Ed.: N. Miyaura), Springer, New York, **2002**, p. 11; i) C. Torborg, M. Beller, *Adv. Synth. Catal.* **2009**, *351*, 3027; j) L. Ackermann, R. Born, *Angew. Chem.* **2005**, *117*, 2497; *Angew. Chem. Int. Ed.* **2005**, *44*, 2444; k) L. Ackermann, *Synlett* **2007**, 507.

[2] a) N. Miyaura, A. Suzuki, *Synth. Commun.* **1981**, *11*, 513; b) T. Ohe, N. Miyaura, A. Suzuki, *J. Org. Chem.* **1993**, *58*, 2201; c) D. Badone, M. Baroni, R. Cardamone, A. Ielmini, U. Guzzi, *J. Org. Chem.* **1997**, *62*, 7170; d) A. Zapf, M. Beller, *Chem. Eur. J.* **2000**, *6*, 1830.

[3] a) G. A. Molander, B. Canturk, *Angew. Chem.* **2009**, *121*, 9404; *Angew. Chem. Int. Ed.* **2009**, *48*, 9240; b) A. Darses, J.-P. Genet, *Chem. Rev.* **2008**, *108*, 288; c) G. A. Molander, N. Ellis, *Acc. Chem. Res.* **2007**, *40*, 275.

[4] a) D. M. Knapp, E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2009**, *131*, 6961; b) E. P. Gillis, M. D. Burke, *Aldrichimica Acta* **2009**, *42*, 17; c) E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2007**, *129*, 6716.

[5] a) H. Noguchi, K. Hojo, M. Suginome, *J. Am. Chem. Soc.* **2007**, *129*, 758; b) H. Noguchi, T. Shioda, C.-M. Chou, M. Suginome, *Org. Lett.* **2008**, *10*, 377; c) N. Iwadate, M. Suginome, *Org. Lett.* **2009**, *11*, 1899.

[6] a) D. D. Winkle, K. M. Schaab, *Org. Process Res. Dev.* **2001**, *5*, 450; b) A. Pelter, K. Smith, H. C. Brown, *Borane Reagents*, Academic Press, London, **1988**; c) D. S. Matteson, *Reactivity and Structure Concept in Organic Synthesis: Stereodirected Synthesis with Organoboranes*, *Vol. 32*, Springer, New York, **1994**; d) M. Vaultier, B. Carboni in *Comprehensive Organometallic Chemistry*, *Vol. 11* (Eds.: G. Wilkinson, F. G. Stone, E. W. Abel), Pergamon, New York, **1995**, p. 191; e) K. Smith, A. Pelter in *Comprehensive Organic Synthesis*, *Vol. 8* (Eds.: B. M. Trost, I. Fleming), Pergamon, New York, **1991**, p. 703; f) M. Zaidlewicz, M. Krzeminski, *Sci. Synth.* **2004**, *6*, 1097; g) M. M. Midland, *Chem. Rev.* **1989**, *89*, 1553; h) C. Ollivier, P. Renaud, *Chem. Rev.* **2001**, *101*, 3415; i) V. Darmency, P. Renaud, *Top. Curr. Chem.* **2006**, *263*, 71.

[7] a) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890; b) C. Kleeberg, L. Dang, Z. Lin, T. B. Marder, *Angew. Chem.* **2009**, *121*, 5454; *Angew. Chem. Int. Ed.* **2009**, *48*, 5350; c) L. Dang, Z. Lin, T. B. Marder, *Chem. Commun.* **2009**, 3987.

[8] E. Demory, V. Blandin, J. Einhorn, P. Y. Chavant, *Org. Process Res. Dev.* **2011**, *15*, 710.

[9] a) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259; b) B. M. Trost, *Science* **1991**, *254*, 1471.

[10] A patent application has been filed.

[11] a) R.-S. *Gan*, T. S. Hor in *Ferrocenes*, (Eds.: A. Togni, T. Hayashi), VCH, Weinheim, **1995**, p. 1–104; b) G. A. Molander, M. R. Rivero, *Org. Lett.* **2002**, *4*, 107; c) G. A. Molander, C.-S. Yun, M. Ribagorda, B. Biolatto, *J. Org. Chem.* **2003**, *68*, 5534.

[12] F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.

[13] NMR experiments indicate that several arylboronates such as $ArB(OBu)_3MgX$, $Ar_2B(OBu)_2MgX$, and $Ar_3B(OBu)MgX$ are in fact formed, and that the formula $Ar_2B(OBu)_2MgX$ only reflects the stoichiometry used.

[14] a) J. Högermeier, H.-U. Reissig, *Chem. Eur. J.* **2007**, *13*, 2410; b) J. Dash, T. Lechel, H.-U. Reissig, *Org. Lett.* **2007**, *9*, 5541; c) J. B. Grimm, K. J. Wilson, D. J. Witter, *J. Org. Chem.* **2009**, *74*, 6390.
[15] a) B. Bhayana, B. P. Fors, S. L. Buchwald, *Org. Lett.* **2009**, *11*, 3954; b) L. Zhang, T. Meng, J. Wu, *J. Org. Chem.* **2007**, *72*, 9346; c) D. Zim, V. R. Lando, J. Dupont, A. L. Monteiro, *Org. Lett.* **2001**, *3*, 3049.
[16] a) A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020; b) G. A. Molander, C. R. Bernardi, *J. Org. Chem.* **2002**, *67*, 8424; c) G. A. Molander, C.-S. Yun, *Tetrahedron* **2002**, *58*, 1465.
[17] This proved to be necessary in less than 10% of all cases studied.

