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Copper-Catalyzed/Promoted Cross-coupling of *gem*-Diborylalkanes with Nonactivated Primary Alkyl Halides: An Alternative Route to Alkylboronic Esters

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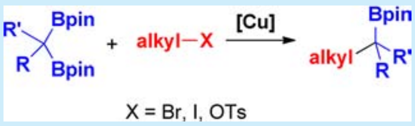
Supporting Information

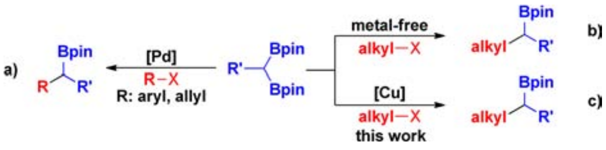
ABSTRACT: The first copper-catalyzed/promoted sp^3-C Suzuki–Miyaura coupling reaction of *gem*-diborylalkanes with nonactivated electrophilic reagents is reported. Not only 1, 1-diborylalkanes but also some other *gem*-diborylalkanes can be coupled with nonactivated primary alkyl halides, offering a new method for sp^{3}C–sp^{3}C bond formation and, simultaneously, providing a new strategy for the synthesis of alkylboronic esters.



Suzuki–Miyaura cross-coupling represents an efficient strategy for the formation of sp^3 C–C bonds.[1] In the past few decades, great progress has been achieved in the cross-coupling reactions between aryl boronate esters and alkyl/aryl electrophiles. In contrast, the coupling of alkylboron reagents with alkyl electrophiles has rarely been reported. As early as 1992, Suzuki et al. found that alkyl 9-BBN reagents react with alkyl iodides in the presence of a Pd-catalyst.[2] Thereafter, Fu et al. developed a Pd-catalyzed coupling reaction of alkyl 9-BBN reagents with more inert alkyl electrophiles.[3] Meanwhile, a Ni-catalyst has also been found to be efficient for the cross-coupling of secondary alkyl halides with alkyl 9-BBN reagents.[4] Recently, our group reported the first Cu-catalyzed cross-coupling reaction of alkyl 9-BBN reagents with primary alkyl electrophiles.[5] It is noteworthy that the 9-BBN reagents used in previous studies are highly reactive species, and thus issues surrounding their preparation (e.g., functional group protection) and purification limit their applications in organic synthesis.[6]

Recently, Shibata et al. successfully realized the coupling between a series of novel alkylboron compounds (1,1-diborylalkanes) and aryl/benzyl/allyl halides with the aid of a Pd-catalyst (Scheme 1a),[7] whereas the Suzuki–Miyaura reaction of unactivated alkyl electrophiles with *gem*-diborylalkanes remains challenging. Lately, Morken et al. described a metal-free reaction of *gem*-diborylalkanes and alkyl electrophiles. However, only a few functional groups were reported in their paper (Scheme 1b).[8]

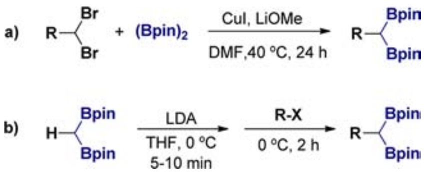
Scheme 1. sp^3-C Suzuki–Miyaura Coupling Reaction



Herein we report the first Cu-catalyzed/promoted sp^3-carbon Suzuki–Miyaura cross-coupling of *gem*-diborylalkanes with nonactivated primary alkyl halides (Scheme 1c). This reaction provides an efficient method for constructing saturated C–C bonds, and an alternative synthesis of alkylboronic esters with a wider range of functional groups,[9,10] and we also present a synthesis of 1,1-diborylalkanes on gram scale.[11]

On the basis of our previous studies[10a] on the Cu-catalyzed borylation of primary/secondary alkyl halides and pseudohalides, we first attempted the synthesis of 1,1-diborylalkanes with the same catalyst system. We found that the reaction occurred smoothly for the preparation of diborylmethane, while 1 equiv of a Cu source was required for the preparation of other 1,1-diborylalkanes. Importantly, these methods enable convenient gram scale synthesis, and the resulting diboryl compounds are readily available for exploring their subsequent transformations. In this context, several 1,1-diborylalkanes, **1a**–**1c** (Scheme 2a; for details, see Supporting Information (SI)), have been synthesized. However, limited availability of 1,1-dibromoalkanes limits the synthesis of different types of 1,1-

Scheme 2. Synthesis Methods of *gem*-Diborylalkanes



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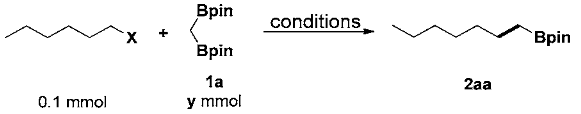
diborylalkanes, but one can efficiently synthesize a variety of 1,1-diborylalkanes with different substituents from diborylmethane using the slightly improved method previously reported by Matteson and Moody.[11b] Thus, we prepared a series of 1,1-diborylalkanes (**1d−1h**) (Scheme 2b; for details, see SI).

Subsequently, we examined the cross-coupling reaction of 1,1-diborylalkanes with primary alkyl halides. The diborylmethane and *n*-hexyl bromide were first selected as the model substrates (Table 1). Similar to our previous study, CuI (10%), DMF, and LiOMe were used as the catalyst, solvent, and base, respectively. However, only 23% GC yield has been gained (entry 1). Adjusting the reaction temperature and increasing the amount of diborylmethane were found to have little influence on the GC yield (<40%, entries 2−4). We next tried to replace LiOMe with *t*-BuOLi and found that the yield improved to ~60% (entry 5).[12] Meanwhile, use of THF or DMSO as solvent results in slightly lower yields (entries 6−8). Significantly, increasing the catalyst loading to 20% or the addition of tetrabutylammonium iodide gives better results (entries 9−10). Accordingly, a 91% GC yield and an 84% isolated yield have been obtained in the presence of 20% CuI and 1 equiv of the additive tetrabutylammonium iodide (entry 11). In addition to alkyl bromide, we also tried some other electrophilic reagents. It was found that 10% CuI, LiOMe, and 40 °C (entry 17, or even rt, entry 18) are appropriate for the couplings of alkyl iodide, and the optimal conditions for alkyl-OTs were the same as those for alkyl bromide (entry 24). What is more important is that the necessity for copper in our reaction conditions was confirmed by the results showing without CuI the reaction does not occur (entry 12) or yields only a small yield of product (entry 20).

Table 1. Various Conditions for the Reaction of *n*-Hexyl Bromide and Diborylmethane[a]

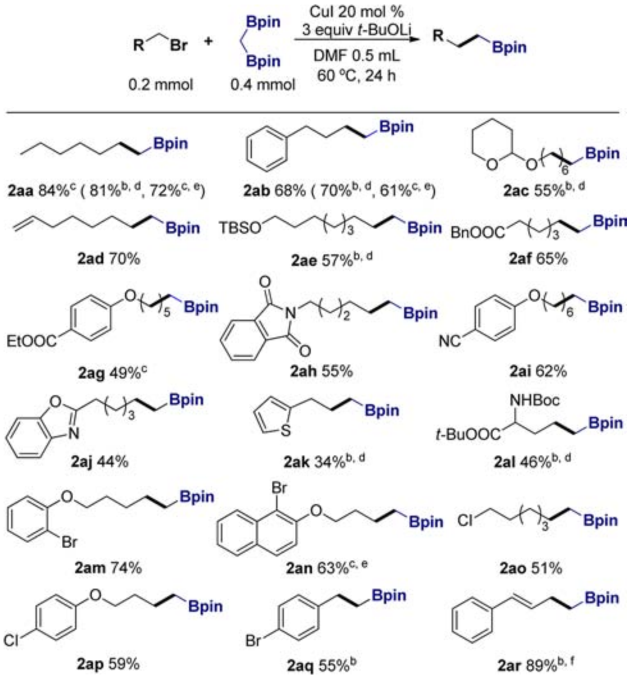


entry	X	*y* (mmol)	base (equiv)	temp (°C)	yield (%)
1	Br	0.15	LiOMe (2)	60	23
2	Br	0.20	LiOMe (3)	60	38
3	Br	0.20	LiOMe (3)	80	10
4	Br	0.20	LiOMe (3)	40	35
5	Br	0.20	*t*-BuOLi (3)	60	58
6[e]	Br	0.20	*t*-BuOLi (3)	60	53
7[b,e]	Br	0.20	*t*-BuOLi (3)	60	25
8[f]	Br	0.20	*t*-BuOLi (3)	60	36
9[b]	Br	0.20	*t*-BuOLi (3)	60	70
10[c]	Br	0.20	*t*-BuOLi (3)	60	85(80)
11[b,c]	Br	0.20	*t*-BuOLi (3)	60	91(84)
12[d]	Br	0.20	*t*-BuOLi (3)	60	trace
13	I	0.15	LiOMe (2)	60	58
14	I	0.15	LiOMe (2)	40	66
15	I	0.15	LiOMe (2)	25	65
16	I	0.15	*t*-BuOLi (2)	40	66
17	I	0.20	LiOMe (3)	40	87(81)
18	I	0.20	*t*-BuOLi (3)	25	84(80)
19	I	0.20	LiOMe (3)	25	64
20[d]	I	0.20	LiOMe (3)	40	12
21	OTs	0.20	LiOMe (3)	60	8
22	OTs	0.20	*t*-BuOLi (3)	60	45
23[c]	OTs	0.20	*t*-BuOLi (3)	60	49
24[b,c]	OTs	0.20	*t*-BuOLi (3)	60	78(72)

[a] All reactions are carried out under 0.1 mmol scale, 10 mol % CuI, and in 0.5 mL of DMF. The yields were determined by GC (average of two GC runs). [b] 1 equiv of tetrabutylammonium iodide was added. [c] 20 mol % CuI was used. [d] CuI was not used. [e] The solvent is THF. [f] The solvent is DMSO.

As shown in Scheme 3, diborylmethane can react with a variety of alkyl electrophiles. Many synthetically important functional groups, including acetal **2ac**, terminal olefin **2ad**, and TBS-protected alcohol **2ae** are tolerated. In addition, alkyl esters (**2af**) and aryl esters (**2ag**) are good substrates for this reaction. Aryl cyanide (**2ai**) and phthalic imide (**2ah**) give moderate yields. The heterocyclic compounds (**2aj**, **2ak**) also give moderate yields under the same conditions, whereas the yield of **2ak** is relatively lower due to elimination of side products. In addition, amino acid derivatives also react with **1a** to give the desired products **2al**. Substrates **2am**, **2an**, **2ao**, **2ap** were examined to explore the chemoselectivity of this reaction. We found that the activity of alkyl bromide and tosylate is higher than that of aryl bromide, and the activity of alkyl bromide is higher than that of aryl and alkyl chloride. Moreover, activated alkyl electrophiles are also good substrates (**2aq**, **2ar**).

Scheme 3. Substrate Scope for the Reaction of Primary Electrophiles with Diborylmethane[a]

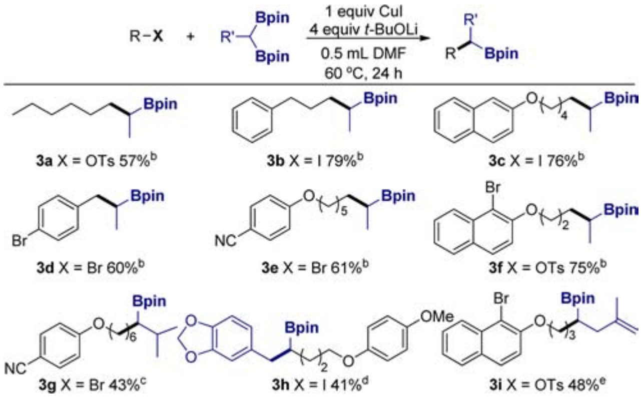


[a] Reactions were carried out under the conditions shown, using alkyl bromides as substrates, and all yields are isolated yields. [b] The reactions were carried out under the optimal condition for the reaction of alkyl iodide and diboryl-methane: 10 mol % CuI, 3 equiv of MeOLi, 0.5 mL DMF and 40 °C; and all yields are isolated yields. [c] The reaction was carried out using 1 equiv of tetrabutylammonium iodide. [d] Alkyl iodide was used as a substrate. [e] Alkyl OTs was used as a substrate. [f] AllylOPO(OEt)$_2$ was used as a substrate.

Unfortunately, the reaction conditions for diborylmethane failed when other substituted 1,1-diborylalkanes were used (the yield is very low). Therefore, we examined the reaction of 1,1-diborylalkane **1b** and *n*-hexyl iodide to reoptimize the reaction conditions. Interestingly, the reaction is very sensitive to the catalyst loading and base. An 89% GC yield was obtained using 1 equiv of CuI and 4 equiv of base (see SI).

Under the newly obtained optimized conditions, we examined the scope of the 1,1-diborylalkanes (Scheme 4). Electrophiles such as alkyl iodides (**3b**, **3c**, **3h**), alkyl bromides (**3d**, **3e**, **3g**), or OTs (**3a**, **3f**, **3i**) all coupled smoothly with **1b**, **1d**, **1e**, **1f** under these conditions.

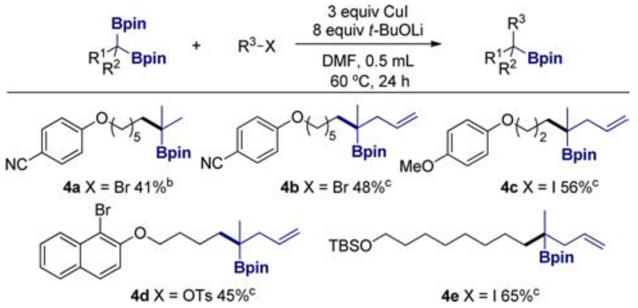
Scheme 4. Substrate Scope for the Reaction of Primary Electrophiles with 1,1-Diborylalkanes[a]



[a]Reactions were carried out under the conditions shown, and all yields are isolated yields. [b] **1b** was used as the substrate. [c] **1f** was used as the substrate. [d] **1e** was used as the substrate. [e] **1d** was used as the substrate.

In addition to synthesizing unactivated primary and secondary alkylboronic esters, we also attempted to synthesize tertiary alkylboronic esters. Thus, we reacted diborylalkane **1i** or **1j** (see SI) with an alkyl halide and successfully obtained the desired products (**4a**−**4e**) (Scheme 5). The reaction requires 3 equiv of CuI and 8 equiv of *t*-BuOLi. If we reduce the loading of copper, the conversion of *gem*-diborylalkane is very low, and the major byproduct is one generated by protodeboronation. We reoptimized the reaction conditions, and some copper sources and ligands were examined (for details, see SI), but to our knowledge, only a few methods have been reported for the synthesis of tertiary alkylboronic esters, and thus our work provides a new strategy for the synthesis of these compounds.[10c−f,13]

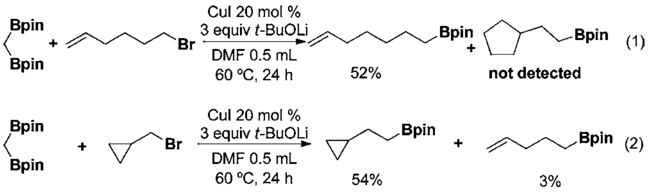
Scheme 5. Synthesis of Tertiary Alkylboronic Ester[a]



[a]Reactions were carried out under the conditions shown, and all yields are isolated yields. [b] **1i** was used as the substrate. [c] **1j** was used as the substrate.

Finally, when 6-bromo-1-hexene was used as a substrate, the terminal olefin was retained, and no cyclized product was detected (Scheme 6, eq 1). Meanwhile, only 3% of the ring-opening product was detected when cyclopropylmethyl bromide was used as the substrate (eq 2). The results are opposed to what would be expected for a radical mechanism usually seen with Ni chemistry.[14,15]

Scheme 6. Selectivity in Ring Closing/Ring Opening Experiments



In summary, we report the first copper catalyzed/promoted Suzuki−Miyaura cross-coupling of *gem*-diborylalkanes with nonactivated primary alkyl electrophiles. The reaction can proceed smoothly in the presence of CuI, *t*-BuOLi, and DMF. Generally, 10−20 mol % CuI is adequate for the reaction of the diborylmethane, while 1 equiv of CuI and 4 equiv of base (*t*-BuOLi) are required for the couplings of substitued 1,1-diborylalkanes. Furthermore, tertiary alkylboronic esters can be obtained using 3 equiv of CuI and 8 equiv of *t*-BuOLi. A radical mechanism has been excluded,[16] and the previously reported S_N2 mechanism seems to be more plausible.[5] Further study on ligand effects is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and spectra data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) Miyaura, N. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., de Meijere, A., Eds.; Wiley-VCH: New York, 2004. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (c) Lloyd-Williams, P.; Giralt, E. *Chem. Soc. Rev.* **2001**, *30*, 145. (d) Darses, S.; Genet, J.-P. *Chem. Rev.* **2007**, *108*, 288. (e) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417.

(2) Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, *21*, 691.

(3) (a) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099. (b) Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945.

(4) (a) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602. (b) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694. (c) Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11908. (d) Lu, Z.; Wilsily, A.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 8154. (e) Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 15362. (f) Wilsily, A.; Tramutola, F.; Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 5794.

(5) Yang, C.-T.; Zhang, Z.-Q.; Liu, Y.-C.; Liu, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3904.

(6) For limited examples of the Pd-catalyzed coupling of an alkyl boronic acid with an alkyl bromide, see: Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662.

(7) (a) Endo, K.; Ohkubo, T.; Hirokami, M.; Shibata, T. *J. Am. Chem. Soc.* **2010**, *132*, 11033. (b) Endo, K.; Ohkubo, T.; Shibata, T. *Org. Lett.* **2011**, *13*, 3368. (c) Endo, K.; Ohkubo, T.; Ishioka, T.; Shibata, T. *J. Org. Chem.* **2012**, *77*, 4826. (d) Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 6534.

(8) Hong, K.; Liu, X.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 10581.

(9) For the Ir-, Rh-, Ru-, and Re-catalyzed C−H activation/borylation of alkanes, see: (a) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2009**, *110*, 890. (b) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995. (c) Waltz, K. M.; Hartwig, J. F. *Science* **1997**, *277*, 211. (d) Shimada, S.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2168. (e) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E.; Smith, M. R. *Science* **2002**, *295*, 305. (f) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *124*, 390.

(10) For some recent examples of the formation of alkylboronic esters from nonactivated alkyl electrophiles, see: (a) Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 528. (b) Yi, J.; Liu, J.-H.; Liang, J.; Dai, J.-J.; Yang, C.-T.; Fu, Y.; Liu, L. *Adv. Synth. Catal.* **2012**, *354*, 1685. (c) Ito, H.; Kubota, K. *Org. Lett.* **2012**, *14*, 890. (d) Dudnik, A. S.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 10693. (e) Bose, S. K.; Fucke, K.; Liu, L.; Steel, P. G.; Marder, T. B. *Angew. Chem., Int. Ed.* **2014**, *53*, 1799. (f) Atack, T. C.; Lecker, R. M.; Cook, S. P. *J. Am. Chem. Soc.* **2014**, *136*, 9521.

(11) For selected examples of the preparation of *gem*-diborylalkanes, see: (a) Matteson, D. S.; Thomas, J. R. *J. Organomet. Chem.* **1970**, *24*, 263. (b) Matteson, D. S.; Moody, R. J. *Organometallics* **1982**, *1*, 20. (c) Abu Ali, H.; Goldberg, I.; Srebnik, M. *Organometallics* **2001**, *20*, 3962. (d) Abu Ali, H.; Goldberg, I.; Kaufmann, D.; Burmeister, C.; Srebnik, M. *Organometallics* **2002**, *21*, 1870. (e) Endo, K.; Hirokami, M.; Shibata, T. *Synlett* **2009**, *2009*, 1331. (f) Li, H.; Shangguan, X.; Zhang, Z.; Huang, S.; Zhang, Y.; Wang, J. *Org. Lett.* **2013**, *16*, 448.

(12) (a) Yang, C.-T.; Zhang, Z.-Q.; Liang, J.; Liu, J.-H.; Lu, X.-Y.; Chen, H.-H.; Liu, L. *J. Am. Chem. Soc.* **2012**, *134*, 11124. (b) Liu, J.-H.; Yang, C.-T.; Lu, X.-Y.; Zhang, Z.-Q.; Xu, L.; Cui, M.; Lu, X.; Xiao, B.; Fu, Y.; Liu, L. *Chem.—Eur. J.* **2014**, *20*, 15334.

(13) Pulis, A. P.; Blair, D. J.; Torres, E.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2013**, *135*, 16054.

(14) (a) Yi, J.; Lu, X.; Sun, Y.-Y.; Xiao, B.; Liu, L. *Angew. Chem., Int. Ed.* **2013**, *52*, 12409. (b) Lu, X.; Yi, J.; Zhang, Z.-Q.; Dai, J.-J.; Liu, J.-H.; Xiao, B.; Fu, Y.; Liu, L. *Chem.—Eur. J.* **2014**, *20*, 15339.

(15) It has been shown both experimentally and computationally that copper alkoxides undergo rapid transmetalation reactions with boronates. Further mechanistic works are ongoing. We thank one reviewer's kind suggestion.

(16) Some Cu reactions show radical behavior, and some do not or are not clear. Ito has suggested that a Cu-catalyzed borylative cyclization of γ-halo alkenes may well NOT be a radical process: Kubota, K.; Yamamoto, E.; Ito, H. *J. Am. Chem. Soc.* **2013**, *135*, 2635. However a radical mechanism is proposed in another work: copper-catalyzed boryl substitution of unactivated alkyl halides (ref 10c), making it even more difficult to understand what is going on. Despite these challenges, by combining the results of ring opening and ring closing experiments, we think the possibility of a radical process is very low.