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Cobalt-catalyzed deoxygenative borylation of diaryl ketones

Longqing Liu[a], Bing Zhang[b], Yu Liu[a], Jinbo Zhao[a,*], Tao Li[b,*], Wanxiang Zhao[b,*]

[a] College of Chemistry and Life Science, Changchun University of Technology, Changchun 130012, China
[b] State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, China

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ABSTRACT

Geminal diboronates and diarylmethyl boronates are versatile building blocks in synthetic chemistry. We here reported a highly efficient approach for the synthesis of *gem*-bisborylalkanes and diarylmethyl boronates *via* cobalt-catalyzed deoxygenative borylation of diaryl ketones. This borylation protocol is compatible with a broad range of functionalized aryl groups, providing access to a wide array of boronic esters. The resulting boronic esters can be further transformed to various cross-coupling products and TPEs that represent important structural motifs in organic chemistry and materials science.

Bisborylalkanes are versatile building blocks in synthetic chemistry and materials science *via* a variety of transformations of C−B bonds [1–4]. The most extensive application of bisborylalkane is to be used as a nucleophile, such as in the Suzuki−Miyaura couplings [5–8] and the boron-Wittig reactions [9–12], in which the 1,1-diboronates undergo deborylation in the presence of an alkoxide base to generate boron-stabilized carbanion intermediates that then react with a series of electrophiles [13–15], such as aldehydes, ketones, carboxylic acids, imines, and aromatic halides. To this end, the synthesis of bisborylalkanes has received lots of attentions from synthetic communities, and recent years we have witnessed great progress in developing synthetic methods of bisborylalkanes [16–29]. For instance, transition metal-catalyzed diboration of alkynes [30] and hydroboration (protoboration) of alkenyl boronic esters [31] provide efficient methods to access 1,1-diboronates (Fig. 1a). The formation of diboronate complexes from B_2pin_2 and alkyl halides (or carbamates) in the presence of a base leads to highly efficient construction of bisborylalkanes *via* 1,2-boron migration (Fig. 1a) [32,33]. Additionally, the Studer group disclosed that B-ate complexes generated from alkyl Grignard reagents and B_2pin_2 can also go through a 1,2-boron shift to give 1,1-diboronates by treatment of UV (365 nm) irradiation and CF_3I [34]. Despite these significant advances, the synthesis of *gem*-diboronates from readily accessible starting materials is still in great demand given their broad applications.

Ketones are among the largest volume platform chemicals in the commodity chemical industry and are incontrovertibly ideal synthetic precursors of bisborylalkanes [35,36]. To date, two strategies are available for converting the ketones to *gem*-diboronates. One of them is to synthesize hydrozones first, which then react with B_2pin_2 in the presence of a base *via* diazo intermediates (Fig. 1b) [37]. Another involves the diboration of ketones, resulting in the formation of *C,O*-bisborylated intermediates, which then undergo a 1,2-Bpin rearrangement with OBpin as a leaving group to deliver bisborylalkane products [38,39]. Of note is that these approaches are applicable to aryl alkyl ketones and dialkyl ketones, but diaryl ketones are incompatible (Fig. 1b). Taking into account that 1,1-diaryl-substituted *gem*-diboronates offer a rapid access to synthetically useful diarylalkanes, which represent an important pharmacophore in drugs and other bioactive molecules as well as materials, such as benadryl, tolpropamine, and tetraphenylethene (TPE, Fig. 1d), the preparation of 1,1-diaryl-substituted *gem*-1,1-diboronates from diaryl ketones is of great significance.

In view of our long interest in organoboron chemistry and our recent success in the deoxygenative borylation of ketones [40,41], here we report a cobalt catalyzed deoxygenative borylation of diaryl ketones under mild reaction conditions, which provides a practical method for the construction of 1,1-diaryl-substituted *gem*-diboronates. Noticeably, the preparation of diarylmethyl boronic ester was also achieved *via* a protodeboration of bisborylalkanes, indicating that the deoxygenative borylation of diaryl ketones can be used selectively to construct *gem*-diboronates or monoboronates *via* fine-tuning the reaction conditions.

Our initial investigation started with the optimization of reaction conditions using diaryl ketone **1a** as the model substrate,

* Corresponding authors.
E-mail addresses: zhaojinbo@ccut.edu.cn (J. Zhao), litao_0922@hnu.edu.cn (T. Li), zhaowanxiang@hnu.edu.cn (W. Zhao).

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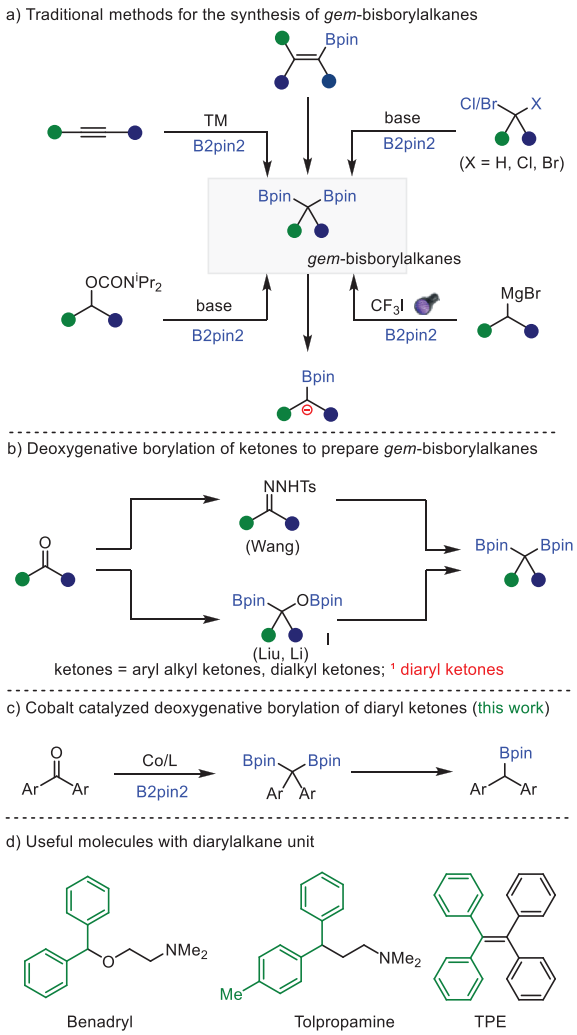
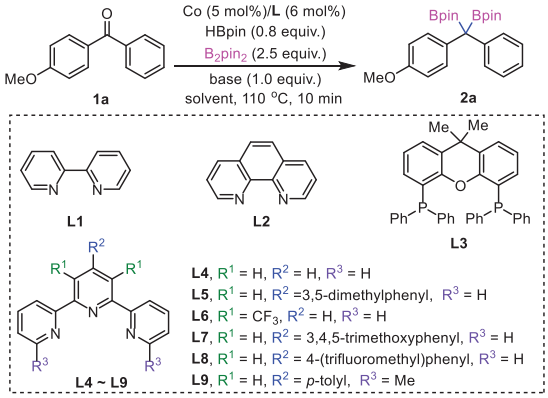


Fig. 1. (a) Traditional methods for the synthesis of *gem*-bisborylalkanes; (b) deoxygenative borylation of ketones to prepare *gem*-bisborylalkanes; (c) cobalt catalyzed deoxygenative borylation of diaryl ketones; (d) useful molecules with diarylalkane unit.

Table 1
Reaction optimization.[a]



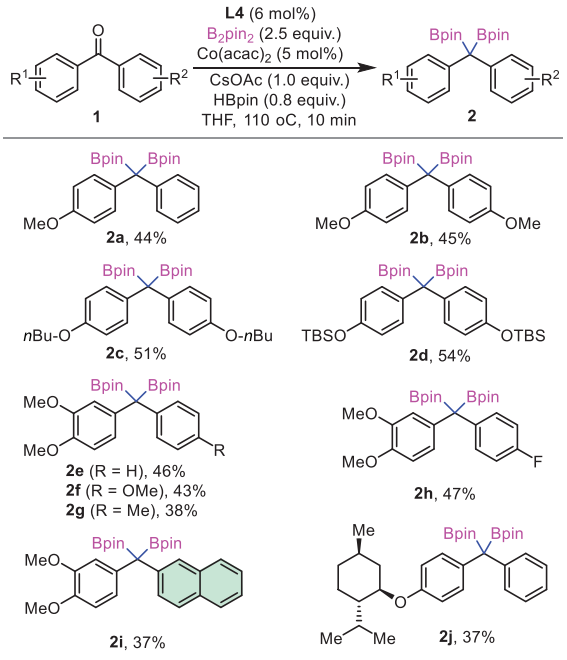
Entry	Co	Ligand	Base	Solvent	Yield (%)
1	$CoCl_2$	**L4**	CsOAc	THF	59
2	$CoBr_2$	**L4**	CsOAc	THF	48
3	$Co(acac)_2$	**L1**	CsOAc	THF	-
4	$Co(acac)_2$	**L2**	CsOAc	THF	-
5	$Co(acac)_2$	**L3**	CsOAc	THF	-
6	$Co(acac)_2$	**L4**	CsOAc	THF	81 (44)[b]
7	$Co(acac)_2$	**L5**	CsOAc	THF	77
8	$Co(acac)_2$	**L6**	CsOAc	THF	65
9	$Co(acac)_2$	**L7**	CsOAc	THF	54
10	$Co(acac)_2$	**L8**	CsOAc	THF	75
11	$Co(acac)_2$	**L9**	CsOAc	THF	-
12	$Co(acac)_2$	**L4**	CsOAc	CyH	6
13	$Co(acac)_2$	**L4**	CsOAc	Tol	Trace
14	$Co(acac)_2$	**L4**	K_2CO_3	THF	-
15	$Co(acac)_2$	**L4**	KOAc	THF	5
16	$Co(acac)_2$	**L4**	LiOAc	THF	Trace
17	$Co(acac)_2$	**L4**	-	THF	-
18[c]	$Co(acac)_2$	**L4**	CsOAc	THF	-
19[d]	$Co(acac)_2$	**L4**	CsOAc	THF	-

[a] Unless otherwise noted, all reactions were carried out with **1a** (0.30 mmol), $Co(acac)_2$ (0.015 mmol), **L** (0.018 mmol), B_2pin_2 (0.75 mmol), HBpin (0.24 mmol), and CsOAc (0.3 mmol) in 2.0 mL of THF at 110 °C, and yields were determined by GC analysis in petroleum ether.
[b] Isolated yield.
[c] No B_2pin_2.
[d] No HBpin.

$Co(acac)_2$ as the catalyst, CsOAc as the base, and B_2pin_2 as the boron source. As shown in Table 1, the ligands were first screened (Table 1, entries 3-11). Although no desired product was observed when 2,2′-dipyridyl (**L1**), 1,10-phenanthroline (**L2**) and Xantphos (**L3**) were employed, the diborylation product **2a** was obtained in 81% yield by treatment with terpyridine (**L4**, Table 1, entries 3-6). Noticeably, the 1,1-diaryl-substituted *gem*-diboronate decomposed moderately on silica gel during column chromatography, leading to the moderate isolated yield. Other terpyridine ligands (**L5**-**L9**) were also evaluated, but none of them gave better result (Table 1, entries 7-11). We next turned our attention to examine the solvents. As depicted, only a trace amount of diborylated product was observed when nonpolar solvents such as cyclohexane and toluene were used (Table 1, entries 12 and 13). The base effect in this reaction was also investigated. The use of K_2CO_3, KOAc and LiOAc resulted in no desired product or forming only a trace amount of **2a** (Table 1, entries 14-16). It is worth noting that no bisborylalkane **2a** was observed in the absence of a base, indicating the important role of a base in the generation of product **2a** (Table 1, entries 17). In addition, control experiments suggested that both B_2pin_2 and HBpin are critical in these deoxygenative borylation reaction, because no desired product **2a** was observed in the absence of either B_2pin_2 or HBpin (Table 1, entries 18 and 19).

With the optimal reaction conditions in hand, we then started to explore the substrate scope for this cobalt catalyzed diborylation reaction. As demonstrated in Scheme 1, a diverse set of diaryl ketones successfully participated in this deoxygenative borylation to give the corresponding diboronate products in moderate to good yields. In addition to unsymmetrical diaryl ketones, symmetrical ketones with OMe, OBu and OTBS groups all proceeded smoothly to afford the bisborylalkane products **2b**-**2d** in 45%-54% yields. Furthermore, disubstituted phenyl groups were also tolerated to furnish the corresponding products **2e**-**2g** in moderate yields. It is worth mentioning that the mild reaction conditions were compatible with a fluorine atom (**2h**). In addition to phenyl groups, naphthalene can be readily introduced into the *gem*-diboronate product, leading to the formation of product **2i**. We were pleased to find that the substrate derived from menthol could undergo the desired pathway to give the deoxygenative borylation product **2j**.

Given that the bisborylalkanes are prone to go through protodeboration to generate mono-borylalkanes on silica gel during column chromatography, we then investigated the deoxygenative mono-boration of diaryl ketones. We first optimized the reaction and determined the optimum condition to generate diarylmethyl boronate. The results indicated that diarylmethyl boronate was dominant in this deoxygenative borylation when the amount HBpin was increasd from 0.8 equiv. to 1.0 equiv. Similar to the de-

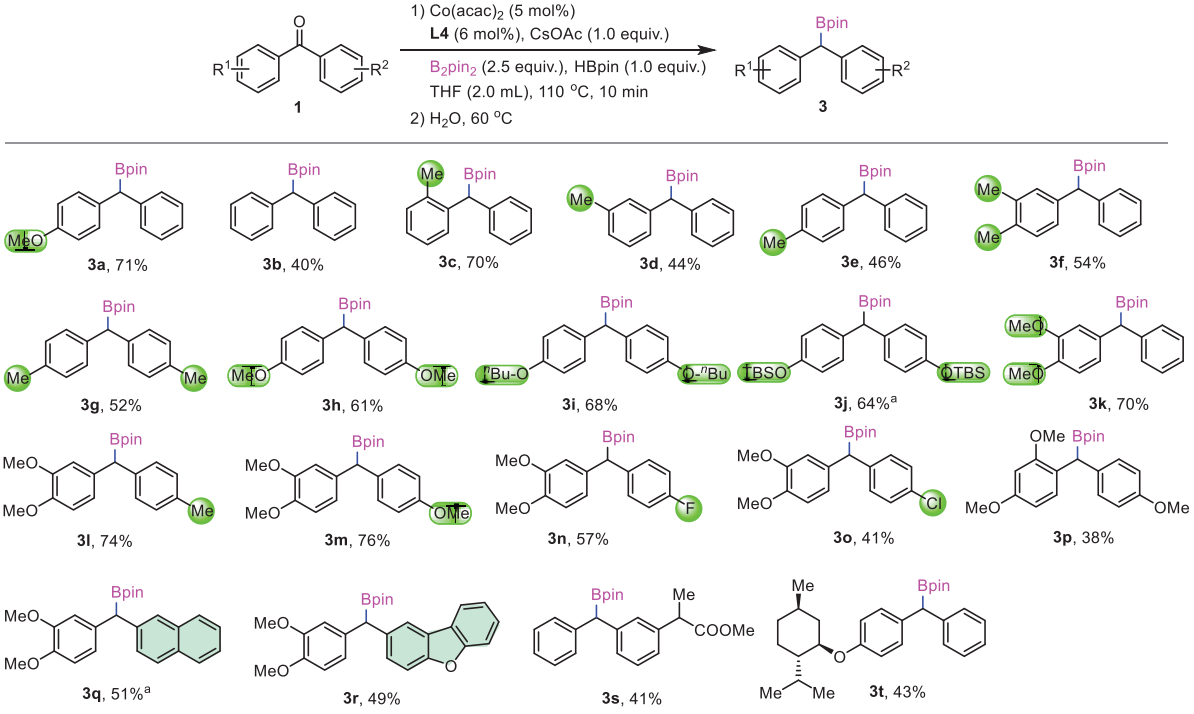


Scheme 1. Synthesis of *gem*-bisborylalkanes. Unless otherwise noted, all reactions were carried out with **1** (0.30 mmol), $Co(acac)_2$ (0.015 mmol), **L4** (0.018 mmol), B_2pin_2 (0.75 mmol), HBpin (0.24 mmol), and CsOAc (0.3 mmol) in 2.0 mL of THF at 110 °C. Isolated yields were reported.

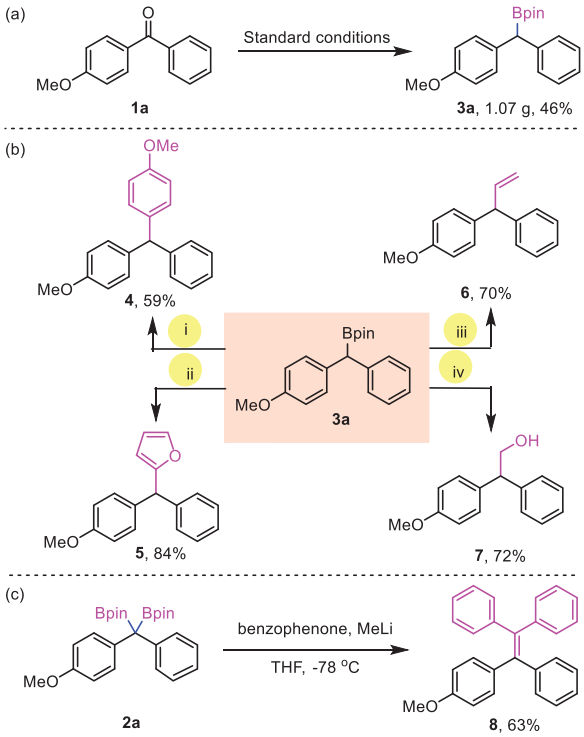
oxygenative diborylation, this reaction tolerated the diaryl ketones with a variety of functional groups including electron-donating or -withdrawing groups (Scheme 2), such as MeO, ^{n}BuO, OBn, OTBS, Cl, and F. Additionally, the substrates with naphthalene and dibenzofuran were capable to afford the borylation products **3q** and **3r**. To get further insight into the applicability of pharmaceutical relevance, ketoprofen methyl ester and (−)-menthol derived diaryl ketone were treated with the established optimal conditions. We were pleased to find that these two substrates were also suitable for this deoxygenative borylation to provide corresponding products **3s** and **3t**.

The gram-scale deoxygenative borylation was conducted to probe the practicability of the developed process (Scheme 3a). The cobalt-catalyzed deoxygenative borylation of diaryl ketone **1a** (1.49 g, 7.0 mmol) with B_2pin_2 under the standard reaction conditions afforded **3a** with a yield of 46% (1.07 g, 3.3 mmol). Bisborylalkanes and diarylmethyl boronates could serve as valuable synthons in various organic transformations and be converted to various functionalized molecules. The obtained momo-borylation product **3a** was employed as the useful building block. For instance, the Suzuki reaction of **3a** with iodobenzene afforded the corresponding triaryl derivative **4** in good yield (Scheme 3b). The addition of an electron-rich aryl lithium reagent (2-lithiofuran) to the boronic ester followed by an elimination generated compound **5**. Furthermore, the introduction of a vinyl group also proved to be efficient by vinylmagnesium bromide. Moreover, **3a** was subjected to the Matteson homologation conditions at low temperature, and the homologated alcohol product was obtained after oxidation in reasonable yield. Meanwhile, aggregation-induced emission molecule TPE **8** could be readily generated by the reaction of diarylmethyl boronate **2a** with benzophenone through boron-Witting olefination (Scheme 3c) [42].

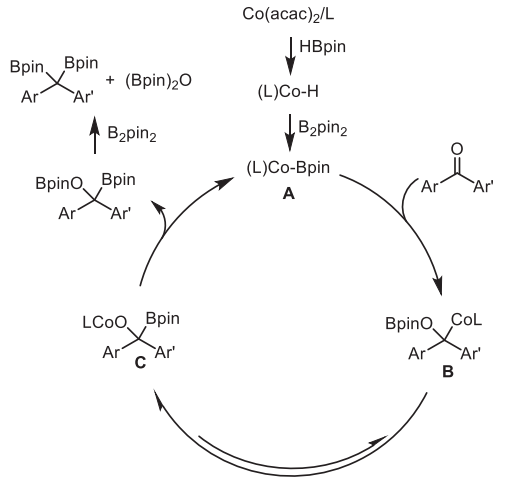
Based on the literature reports and our experimental results [38,39], the mechanism for this deoxygenative borylation reaction is proposed and shown in Scheme 4. The reduction of $Co(acac)_2$ with HBpin in the presence of ligand **L** generates an (**L**)Co(I)−H species [43], which can be converted to a cobalt boryl intermediate (**L**)Co-Bpin **A** *via* σ-bond metathesis with B_2pin_2 [44,45]. Following the coordination of ketone to the cobalt center, the insertion of the C=O group into the Co−B bond forms intermediate **B**, which then goes through 1,2-migration to give intermediate **C** [46,47]. The reaction of species **C** with B_2pin_2 affords the α-OBpin benzylboronic



Scheme 2. Synthesis of diarylmethyl boronates. Unless otherwise noted, all reactions were carried out with **1** (0.30 mmol), $Co(acac)_2$ (0.015 mmol), **L4** (0.018 mmol), B_2pin_2 (0.75 mmol), HBpin (0.3 mmol), and CsOAc (0.3 mmol) in 2.0 mL of THF at 110 °C. Isolated yields were reported. [a]**1q** or **1j** (0.2 mmol) was used.



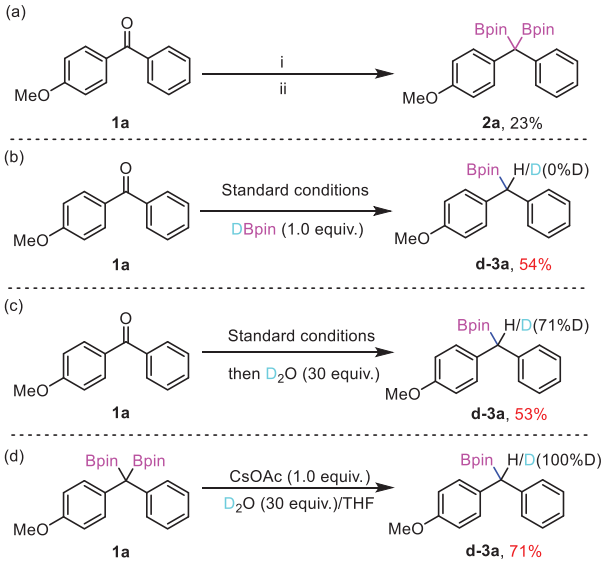
Scheme 3. Synthetic applications. Reaction conditions: (i) 1-iodo-4-methoxybenzene (1.6 equiv.), $Pd(PPh_3)_4$ (20 mol%), K_2CO_3 (1.6 equiv.), Ag_2O (1.6 equiv.), 60 °C, 36 h. (ii) Furan (2.0 equiv.), *n*BuLi (2.0 equiv.), NBS (2.0 equiv.), -78 °C to r.t., 12 h. (iii) Vinylmagnesium bromide (4.0 equiv.), I_2 (4.0 equiv.), -78 °C, 12 h. (iv) Bromochloromethane (2.5 equiv.), *n*BuLi (2.3 equiv.), -78 °C to r.t., 4 h; NaOH (3.0 equiv.), H_2O_2 (3.0 equiv.).



Scheme 4. Proposed mechanism.

ester intermediate and regenerates the cobalt(I) hydride **A**. Subsequently, 1,2-boron migration occurs in the α-OBpin benzylboronic ester to generate *gem*-diboronate [38,39].

To verify the mechanistic hypothesis, we carried out control experiments to confirm the formation of the α-OBpin benzylboronate intermediate. Although we failed to obtain the α-OBpin benzylboronate under the standard conditions probably due to its fast subsequent reaction with B_2pin_2, we prepared the α-OBpin benzylboronate using the procedure reported by Clark [48]. Pleasingly, the treatment of α-OBpin benzylboronate with the standard reaction conditions delivered the desired product **2a** in 23% yield (Scheme 5a). This result indicated that the α-OBpin benzylboronate should be an intermediate in this transformation.



Scheme 5. Control experiments. Reaction conditions: (i) B_2pin_2 (1.0 equiv.), ICyCuCl (3 mol%), *t*-BuONa (20 mol%), C_6D_6, 50 °C, 18 h. (ii) $Co(acac)_2$ (5 mol%), **L4** (6 mol%), CsOAc (1.0 equiv.), B_2pin_2 (1.5 equiv.), THF, 110 °C, 10 min.

As we observed that *gem*-bisborylalkanes could be converted into arylmethyl boronates, we carried out mechanistic studies on the transformations of these two compounds. Using DBpin instead of HBpin under the standard conditions, no deuterium incorporation was found (Scheme 5b). Furthermore, 71% deuterium incorporation at the methylene position was observed when D_2O was used (Scheme 5c). Additionally, when *gem*-bisborylalkane was treated with CsOAc in a mixture solvent of D_2O/THF, the product was isolated in 71% yield with 100% deuteration (Scheme 5d). These results revealed that the mono-borylalkanes was generated *via* the protodeboration of diboronates.

In conclusion, we have developed a cobalt-catalyzed deoxygenative borylation of diaryl ketones, providing a rapid access to a broad range of *gem*-bisborylalkanes and diarylmethyl boronates. The *gem*-bisborylalkanes can be transformed into diarylmethyl boronates with the subtle modification of the reaction conditions, which offers an alternative method for the preparation of diarylmethyl boronates. This reaction is suitable for gram-scale synthesis, and the products are easy-to-handle for further transformations. Further efforts to synthesize diarylmethyl boronates with high stereoselectivity are currently underway in our laboratory.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2023.108631.

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