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Difunctionalization of ketones *via gem*-bis(boronates) to synthesize quaternary carbon with high selectivity†

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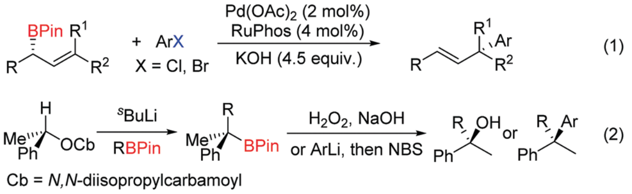
All-carbon quaternary centres are significant and prevalent structural frameworks but their preparation routes are rare and challenging, especially methods with common substrates. Herein, we report a convenient process to construct all-carbon quaternary centres from ketones *via* the diborylation process and Suzuki–Miyaura cross-coupling reaction. This methodology, which simultaneously introduces two different kinds of electrophilic structures, exhibits a large substrate scope and high functional group tolerance. The reaction products with aldehyde and allylic groups have proved to be versatile synthons to prepare complex molecules crucial for natural product synthesis.

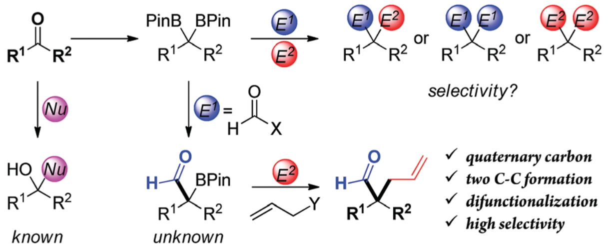
The formation of all-carbon quaternary centres, a widespread structural pattern in biologically active molecules and natural products, is still a challenge for synthetic chemists.[1] The Suzuki–Miyaura cross-coupling reaction, as one of the powerful methods to construct carbon–carbon bonds, has also been applied in the formation of quaternary carbon centres. This reaction commonly relies on tertiary electrophiles rather than tertiary boronic esters, since they are easier to synthesize.[2] Even so, there are only a few examples of the Suzuki–Miyaura reaction with tertiary electrophiles.[3] This is connected to their low ability to oxidatively add to metal complexes, and furthermore, these formed alkyl–metal complexes readily undergo β-hydride elimination. As such, some other methods were developed to form quaternary carbon centres.[4] Allylic secondary boronic esters can be employed to be utilized as tertiary boronate precursors (eqn (1), Scheme 1).[5] In addition, Aggarwal and co-workers have impressively described the enantioselective lithiation–borylation procedure to give tertiary alcohols upon oxidation or other carbon–carbon coupled products (eqn (2), Scheme 1).[6] Nevertheless, to develop a method with common substrates is still of high demand.



Scheme 1 The construction of quaternary carbon from tertiary boronates or precursors.

The facile generation of tertiary boronates faces many issues. Recently, transition-metal catalyzed hydroboration reaction of olefin has provided an efficient route to form boronic substrates. However, it generally takes place in an anti-Markovnikov way to give boronates on the less substituted site of the trisubstituted alkenes.[7] As a result, some other pathways were developed to access tertiary boronic esters, but their application is limited.[8] Herein, we address a transformation of *gem*-bis(boronate) compounds with different electrophiles through a tertiary boronate intermediate to concurrently construct two kinds of carbon–carbon bonds with high selectivity, which provides an efficient and useful protocol to difunctionalize ketones (Scheme 2).

Ketones are ubiquitous and abundant starting materials which play an important role as in organic synthesis. Traditionally, carbonyls react with nucleophiles, such as Grignard reagents, to form the tertiary alcohol products. As a consequence, it would be



Scheme 2 Difunctionalization of ketones with α-boron aldehyde intermediates.

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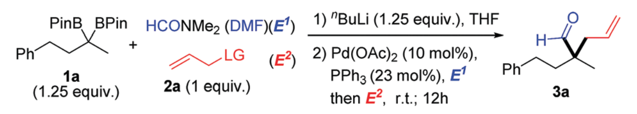
attractive to access the quaternary carbon centres by successively reacting different electrophiles with *gem*-bis(boronates) that can be easily obtained from carbonyls *via* an umpolung (Scheme 2).[9] However, this reaction has a low chemoselectivity, which can be circumvented by stepwise introduction of the respective electrophile.[10] Occasionally, the substitution stops after the first step, leaving behind a monoboronate species.[11] Given this recent success of this approach, we considered introducing aldehyde groups into the diboron species to give α-boron aldehydes, in which the aldehyde functionality helps in activating the second boronate by C/O isomerization, then subsequently facilitates the second substitution.

Though α-boron aldehydes or esters were synthesized, they relied on very special boron structures consisting of chelating groups to stabilize the structure.[12] In general, this method has no downstream synthetic application besides protodeboronation.[13] Recently, Pattison and co-workers reported a tertiary α-boron ketone as an intermediate, which was produced from deprotonated *gem*-bis(boronates) reacting with esters under metal-free conditions, but just introducing the same electrophilic reagent for both substitutions.[14] The Liu and Xia group reported a reaction of diborylalkane with acid compounds to introduce the ketone group without any catalyst but only three examples on the quaternary carbon construction.[15] Furthermore, as a versatile group, the aldehyde group cannot be successfully imbedded through these methods. To the best of our knowledge, tertiary α-boron aldehydes are still little studied in either synthesis or application. The homologation of ketones to introduce an aldehyde group with a boron-Wittig reaction after oxidation was reported; however, it only gave compounds with a tertiary carbon.[16] Therefore, this strategy provides a convenient protocol to construct all-carbon quaternary centres with an aldehyde group.

Initial investigations of this process focused on compound **1a** that was easily prepared from 4-phenylbutan-2-one to react with allylic substrates as electrophiles (E^2) and DMF as an aldehyde group donor (E^1). To facilitate the reaction, the organoboronate **1a** was first lithiated *in situ* by mixing **1a** with ^{n}BuLi in THF (for details, see the ESI†).[17] The reaction with allyl methyl carbonate **2a** proceeded smoothly with $Pd(OAc)_2/PPh_3$ as catalyst at room temperature to give the corresponding product **3a** in 89% NMR yield (entry 1, Table 1). No product or very little was detected in the absence of ^{n}BuLi or with other bases, such as MeLi, NaO^{t}Bu or LiO^{t}Bu (entries 2 and 3, Table 1). Changing the leaving group to Cl, Br, OBz, and OTs decreased the yields (entry 4, Table 1). Different from that previously reported, the use of the esters butyl- and benzylformate showed no product (entry 5, Table 1). The mixed solvent THF/DMF (v/v 10/1) reduced the reactivity; only 18% of the product was observed (entry 6, Table 1). Altering the ligands on the metal complex did not impede the product formation; however, a decrease in reactivity could be detected (entry 7, Table 1). The reaction was much less effective with other metal catalysts, for instance, $NiBr_2$(dme), CuI or $Fe(OAc)_2$ (entry 8, Table 1). Also, no product was found in the absence of catalyst but a moderate yield was given without any ligand (entry 9, Table 1).[18] In addition, the reaction could well take place at a low loading of catalyst (entry 10, Table 1).

Table 1 The optimization of reaction conditions[a]

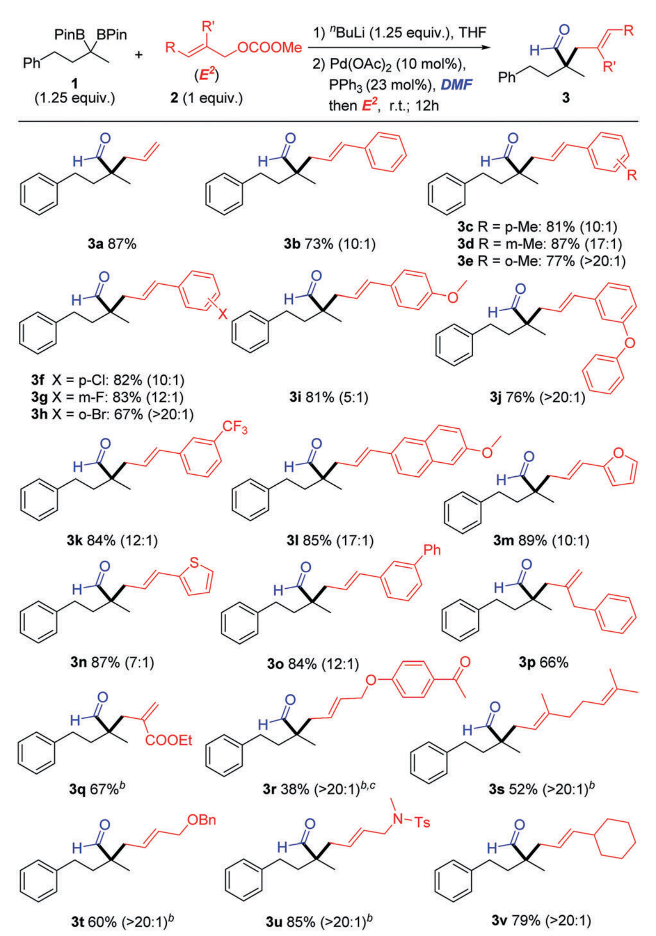


Entry	Changes from the standard conditions	Yield[b] (%)
1	Standard conditions (LG = OCOOMe)	89
2	No pre-active reagent (^{n}BuLi)	0
3	MeLi, NaO^{t}Bu, LiO^{t}Bu as pre-active reagent	4/0/0
4	LG = Cl, Br, OBz, OTs	76/70/88/80
5	HCOO^{n}Bu, HCOOBn as solvent	0/0
6	THF/DMF (v/v 10/1) as solvent	18
7	Bipyridine, Phen, dppe as ligand	44/16/60
8	$NiBr_2$(dme), CuI, $Fe(OAc)_2$ as catalyst	0/0/0
9	No $Pd(OAc)_2$ or no PPh_3	0/30
10	$Pd(OAc)_2$ (5 mol%), PPh_3 (12 mol%)	80

[a] The reaction was conducted on a 0.1 mmol scale. For details on the experimental procedure, see the ESI. [b] The yield was determined by ^{1}H NMR with CH_2Br_2 as an internal standard. Phen = 1,10-phenanthroline. dppe = 1,2-bis(diphenylphosphino)ethane. dme = 1,2-dimethoxyethane.

We next explored the scope of this transformation with a variety of allylic substrates under the optimized reaction

Table 2 The scopes with respect to the allylic substrates[a]

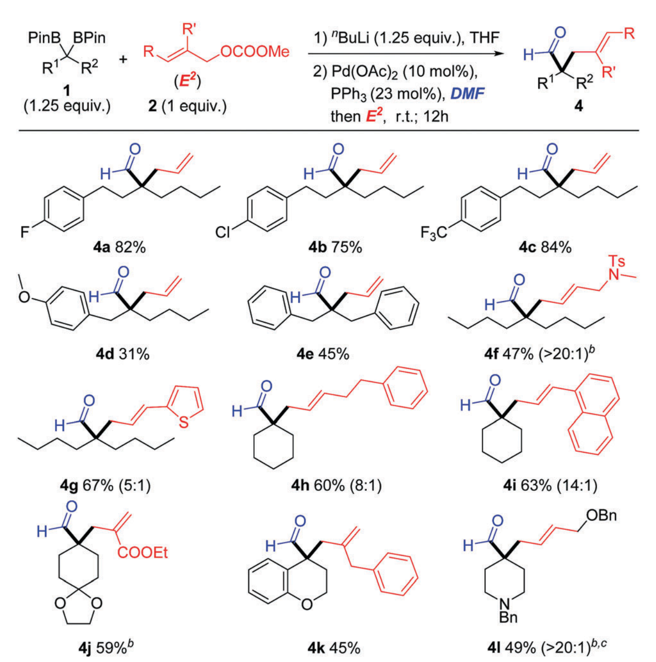


[a] The reaction was conducted on a 0.2 mmol scale under the standard conditions in Table 1. Isolated yields and l-/b-ratios were given. [b] Utilizing Br as a leaving group. [c] The **2r**/**1a** ratio was 3/1.

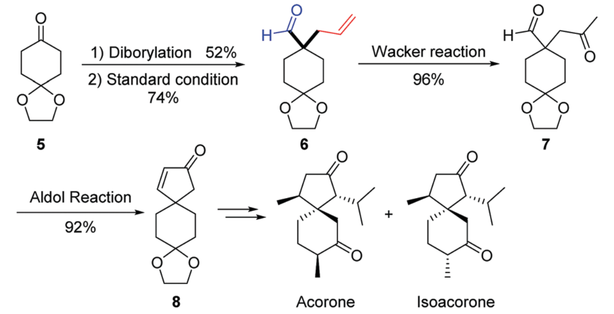
conditions (representative examples are summarized in Table 2).[19] In general, the allylic substrates with either aryl substituents (**3b–3o**) or alkyl groups (**3p–3v**) reacted smoothly to give the corresponding products in high yields and good linear/branched (l-/b-) selectivity. It is reasonable that the substituent at the *ortho* position could give a better l-/b- ratio than that at the *para* or *meta* position (**3c–3e**). Halide functionalities are well tolerated under these conditions (**3f–3h**). The compounds bearing the CF_3 and ether groups remained unchanged (**3i–3l**). Importantly, heterocyclic structures consisting of furan and thiophene were also suitable substrates (**3m, 3n**). The allylic substrates with substituents in the β-position afforded products with acceptable yields (**3p, 3q**). It is worthwhile to mention that although ^{n}BuLi is present in this reaction, strongly base-sensitive functional groups, such as esters and carbonyls, were converted as part of the allylic substrate (**3q, 3r**). Moreover, other functional groups including alkenes, OBn and imines were also successfully coupled (**3s, 3t, 3u**). Furthermore, it was shown that the aliphatic secondary allylic substrate also had good l-/b-selectivity (**3v**).

Then the substrate scope was further extended to a series of substituted ketone compounds (Table 3). To our delight, both the acyclic (**4a–4g**) and cyclic (**4h–4l**) ketone substrates can be converted to the corresponding products in moderate to good yields. In addition, for the ketones including the heterocyclic compounds (**4k, 4l**), the aldehyde and alkene functional groups could also be efficiently introduced at the carbonyl carbon site with this method. With regard to different substituents, it is worthwhile to mention the high functional group tolerance of this reaction. The substrates bearing aryl halide (**4a, 4b**), CF_3 (**4c**), ether (**4d, 4k**), imine (**4f, 4l**), heterocycle (**4g**), ketal (**4j**), ester (**4j**), and OBn (**4l**) groups smoothly generated the corresponding products under these conditions.

Table 3 The scope with respect to ketones[a]



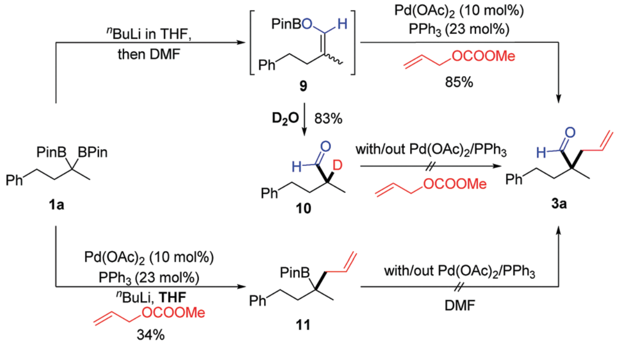
[a] The reaction was conducted on a 0.2 mmol scale under the standard conditions in Table 1. Isolated yields and l-/b-ratios were given. [b] Utilizing Br as a leaving group. [c] The ratio of the *E*/*Z* isomer was 10/1.



Scheme 3 Synthesis of compound **8**.

To further illustrate the utility of this transformation, the method was applied for the formal synthesis of (±)-acorone and isoacorone (Scheme 3). Compound **8** is an important precursor to access these natural products.[20] Despite its previously reported synthesis, a more efficient synthetic pathway was developed using this protocol. Compound **6** could be conveniently obtained from commercial substrate **5**. After the Wacker reaction and Aldol condensation, compound **8** could be obtained in only four steps with a high yield.

In an effort to provide insight into the reaction mechanism, some control experiments were conducted (Scheme 4). In the absence of an allylic substrate, compound **9** was believed to be produced from the isomerization of tertiary α-boron aldehyde, which was corroborated by the boron signal at 23.8 ppm in a ^{11}B NMR spectrum.[21] The chemical shift was consistent with the literature reported on the O-bond BPin isomer of esters.[22] The product was formed after adding an allylic substrate and catalyst to the above reaction. Compound **9** was quenched with D_2O to generate product **10** (97% D) accompanied by the vanishing of the signal at 23.8 ppm and the emergence of a signal at 5.2 ppm that corresponds to the $PinB(OD)^-$ anion. Compound **10** could not give product **3a** under the standard conditions. If the reaction was conducted with THF as a solvent, compound **11** was detected. This substrate also did not proceed to give the quaternary product **3a**. These control experiments proved that the tertiary α-boron aldehyde intermediate provides a vital significance to this transformation (for more details, see the ESI†).



Scheme 4 The mechanistic study.

In summary, herein we report a convenient methodology to difunctionalize ketone compounds through *gem*-bis(boronates), which introduces two significant transformable functional groups simultaneously. This method exhibits a wide substrate scope and high functional group tolerance. The synthetic utility of this method was further demonstrated through producing the intermediate substrate in the synthesis of (±)-acorone and isoacorone. Mechanistic investigations suggest that the tertiary α-boron aldehyde intermediate and C/O isomerization were involved in the process.

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Conflicts of interest

The authors declare no competing financial interest.

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19 Due to their direct commercial availability or easy preparation from commercially available reagents, some substrates with Br as the leaving group were utilized.

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