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Organobase-catalyzed 1,1-diborylation of terminal alkynes under metal-free conditions†

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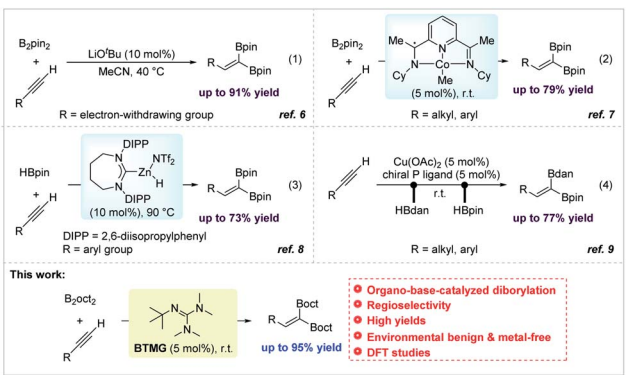
An organobase-catalyzed 1,1-diborylation of terminal alkynes from propargylic derivatives with bis(2,4-dimethylpentane-2,4-glycolato)diboron (B_2oct_2) is first reported, regioselectively providing 1,1-diborylalkene products with high efficiency. The catalytic pathway is well postulated on the basis of DFT calculations.

Organoboron compounds have attracted much attention as versatile building blocks in the synthesis of carbon–carbon and carbon heteroatom bonds,[1] which main features are their stability and ease of handling. Among this important class of reagents, 1,1-diborylalkenes are of particular interest, in part due to that the two geminal boron moieties can be differentiated and transformed *via* Pd-catalyzed cross-coupling reactions in a progressive manner to provide the bioactive and functional polysubstituted alkene motifs.[2,3] Sequent manipulations of 1,1-diborylalkenes with different electrophiles allow for the stereoselective synthesis of challenging unsymmetrically substituted alkenes.[4] What's noteworthy, is that the presence of the geminal boron moiety always has a positive effect on the first cross-coupling reaction. Owing to the significance of 1,1-diborylalkenes as general reaction intermediates in organic synthesis, developing efficient and practical methods for their synthesis is highly desirable.

In comparison with previous multi-step routes, 1,1-diborylation of terminal alkynes with diboron reagents represents one of the most step-economical and atom-economical strategies for synthesis of 1,1-diborylalkenes.[5] In recent years, several elegant works were continuously discovered.[6–9] Sawamura reported a seminal 1,1-diborylation of terminal propargylic derivatives with bis(pinacolato)diboron (B_2pin_2) catalyzed by a strong inorganic base (LiO^{t}Bu) for the preparation of 1,1-diborylalkenes (Scheme 1, eqn (1)).[6] A mild 1,1-diborylation of terminal alkynes with B_2pin_2 catalyzed by a cobalt complex was explored by Chirik and co-workers (Scheme 1, eqn (2)).[7] What's more, stereoselective 1,1-diborylation products with two different boron substituents could be realized using an unsymmetrical diboron reagent pinB–Bdan (dan = naphthalene-1,8-diaminato). After that, Ingleson successfully developed a low-coordinate NHC–zinc hydride complex-catalyzed 1,1-diborylation of terminal alkynes using pinacolborane (HBpin) *via* C–H borylation and hydroboration process (Scheme 1, eqn (3)).[8] In 2020, Engle and co-workers explored a copper-catalyzed protocol for the stereodefined 1,1-diborylation of terminal alkynes, involving a sequential dehydrogenative borylation of the alkyne substrate with 1,8-diaminonaphthalatoborane (HBdan), followed by hydroboration with HBpin (Scheme 1, eqn (4)).[9] Although having achieved such progress, relatively harsh reaction conditions, expensive ligand or preformed catalyst were always involved. Therefore, development of user-friendly and environmental benign protocols for preparation of 1,1-diborylalkenes is still highly desirable to meet the requirements of sustainable development in the field of scientific research and industrial production. In this context, we report on an environmental benign and metal-free protocol for 1,1-diborylation of terminal alkynes with bis(2,4-dimethylpentane-2,4-glycolato)diboron (B_2oct_2) under the catalysis of organobase 2-*tert*-Butyl-1,1,3,3-tetramethylguanidine (BTMG) at room temperature.



Scheme 1 Previous work on 1,1-diborylation and our work.

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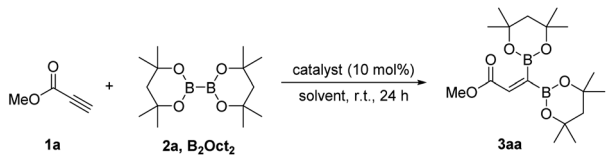
Inspired by Sawamura's strong inorganic base catalyzed 1,1-diborylation strategy[6] and the rapid development of organocatalysis in recent years,[10] we focused on the role of organic base as catalyst in this type of reaction. At the outset, a commercially strong organic base 1,1,3,3-tetramethylguanidine (TMG) was selected as the catalyst to verify its catalytic reactivity in the reaction between methyl propiolate **1a** and B_2oct_2 **2a**. The effect of solvent was initially evaluated and the results indicated that hexane, dichloromethane, 1,2-dichloroethane and toluene all failed to afford the desired *gem*-diborylated product (Table 1, entries 1–4). To our delight, when CCl_4 was used as the solvent, 17% yield of product **3aa** was obtained (entry 5). Whereas, further solvent screening experiments with THF, Et_2O, and EtOAc gave only inferior results (entries 6–8). A slightly higher yield of 35% was obtained utilizing DMF as the solvent (entry 9). Gratifyingly, the yield of **3aa** was dramatically increased to 79%

Table 1 Condition optimization[a]



1a 2a, B_2Oct_2 3aa

Entry	Solvent	Catalyst (mol%)	Yield[b] (%)
1	Hexane	TMG	0
2	DCM	TMG	0
3	DCE	TMG	0
4	Toluene	TMG	0
5	CCl_4	TMG	17
6	THF	TMG	7
7	Et_2O	TMG	5
8	EtOAc	TMG	4
9	DMF	TMG	35
10	MeCN	TMG	79
11	MeCN	Et_3N	95
12	MeCN	BTMG	98 (95)[c]
13	MeCN	TMEDA	77
14	MeCN	TBD	0
15	MeCN	DBU	0
16	MeCN	Pyridine	0
17	MeCN	Quinine	0
18	MeCN	DMAP	12
19	MeCN	2,6-Lutidine	19
20	MeCN	Li_2CO_3	0
21	MeCN	Na_2CO_3	0
22	MeCN	K_2CO_3	0
23	MeCN	Cs_2CO_3	95
24	MeCN	NaOH	95
25	MeCN	LiO^tBu	0
26	MeCN	—	0
27[d]	MeCN	BTMG	96 (94)[c]
28[d]	MeCN	Et_3N	65
29[d]	MeCN	Cs_2CO_3	21
30[d]	MeCN	NaOH	86

[a] Reaction conditions: methyl propiolate **1a** (0.1 mmol), B_2oct_2 **2a** (0.1 mmol), catalyst (10 mol%), solvent (2 mL), rt., 24 h. [b] Yields determined by GC-MS. [c] Isolated yields in parenthesis. [d] 5 mol% of catalyst was employed.

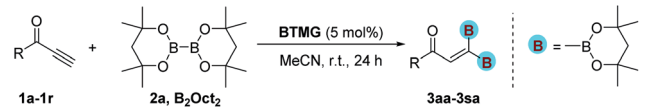
when MeCN was employed as the solvent (entry 10). Then, organobase catalyst screening was performed (entries 11–19), among which organobase like Et_3N, BTMG and TMEDA all proved being effective catalysts, producing **3aa** in yields of 95%, 98% and 77%, respectively (entries 11–13). However, other organobases like TBD, DBU, pyridine and quinine all showed nearly no catalytic activity (entries 14–17). DMAP and 2,6-lutidine were not the proper catalyst because the yields were less than 20% (entries 18–19). Several kinds of inorganic base were also tested to catalyze our reaction, carbonates (K_2CO_3, Na_2CO_3, and Li_2CO_3) all led to the failure of the reaction (entries 20–22), nevertheless, Cs_2CO_3 and NaOH showed excellent performance with formation of product **3aa** in 95% yield (entries 23–24). The strong inorganic base (LiO^tBu), which was employed in Sawamura's work,[6] exhibited no catalytic activity (entry 25) and the high catalytic activity of Et_3N and Cs_2CO_3 indicated that the alkalinity of the base may be not the critical factor for this reaction (entries 11 and 23). When the transformation was conducted in the absence of catalyst, no product was observed (entry 26). It is noteworthy that further lowering the loading of BTMG to 5 mol%, a still high yield of 96% was obtained (entry 27). However, when the loading of other bases (Et_3N, Cs_2CO_3 and NaOH) was also lowered to 5 mol%, an obvious reduction of yields was observed (entries 28–30). Therefore, the catalytic system consisting of 5 mol% BTMG as the catalyst in MeCN performed well as the optimal conditions.

With optimized conditions in hand, we next sought to investigate the scope of this regioselective 1,1-diborylation with respect to the alkyne component (Table 2). A broad array of propargylic derivatives can effectively serve as coupling partners. Linear alkyl ester group of propargyl acid such as methyl, ethyl, *n*-propyl, *n*-butyl and *n*-pentyl were well-tolerated to furnish 1,1-diborylated products in excellent yield (entries 1–5, 88–94% yield). Steric bulk proximal to the ester functionality is compatible, as exemplified by the presence of isopropyl, isobutyl, *tert*-butyl and isopentyl substituents (entries 6–9, 86–91 yield%). We found that benzyl and 1-phenylpropyl propiolate also participated readily to give the corresponding products in a yield of 92% and 78%, respectively (entries 10–11). Moreover, 4-chlorophenethyl propiolate was found to be a competent substrate with the chloro-group remaining unreacted in this transformation (entry 12, 93% yield). Phenyl propionate reacted well to form the desired diborylated product **3ma** in 78% yield (entry 13). Notably, *N*-methyl-*N*-phenylpropiolamide also showed good reactivity towards such diborylation reaction, which provided the desired product **3na** in 53% yield (entry 14).

The diborylation of propiolate esters bearing a terminal alkenyl group all proceeded well to give the diborylated products and kept the alkenyl group untouched (entries 15–17, 89–93% yield). It should be mentioned that diyne substrates demonstrate exceptional chemoselectivity and undergoes 1,1-diborylation exclusively at the site of propiolic acid (entries 18–19, 82–88% yield). Unfortunately, attempts to run the diborylation reaction with other types of alkynes resulted in frustrating results (for more details, please see ESI†).

We also examined the *gem*-diborylation reaction of methyl propiolate **1a** with other types of diboron reagents (Scheme 2).

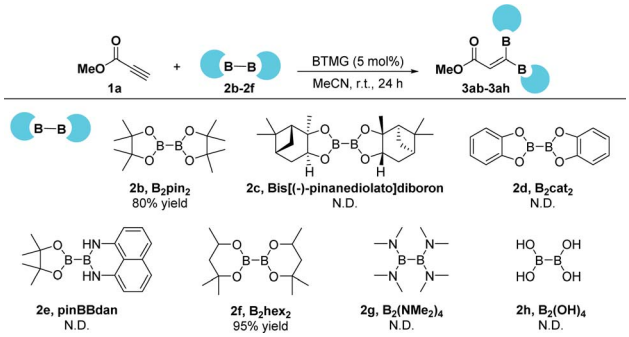
Table 2 Substrate scope for 1,1-diborylation[a,b]



Entry	Alkyne	Product	Yield (%)
1	1a	3aa	94
2	1b	3ba	93
3	1c	3ca	93
4	1d	3da	89
5	1e	3ea	88
6	1f	3fa	91
7	1g	3ga	87
8	1h	3ha	86
9	1i	3ia	90
10	1j	3ja	92
11	1k	3ka	78
12	1l	3la	93
13	1m	3ma	73
14	1n	3na	53
15	1o	3oa	89
16	1p	3pa	93
17	1q	3qa	93
18	1r	3ra	82
19	1s	3sa	88

[a] Reaction conditions: alkyne (0.1 mmol), B_2oct_2 (0.1 mmol), BTMG (5 mol%), MeCN (2 mL), rt., 24 h. [b] Isolated yield.

The 1,1-diborylation reaction proceeded well when B_2pin_2 (**2b**) was used as the diborylating reagent, affording the title diborylated product **3ab** in 80% isolated yield. It should be noted that a comparable yield of 95% was achieved when another six-membered partner B_2hex_2 (**2f**) was employed. However, other diboron compounds, such as Bis[(−)-pinanediolato]diboron (**2c**), B_2cat_2 (**2d**), pinBBdan (**2e**), $B_2(NMe_2)_4$ (**2g**), and $B_2(OH)_2$ (**2h**) proved to be ineffective under this 1,1-diborylation reaction.

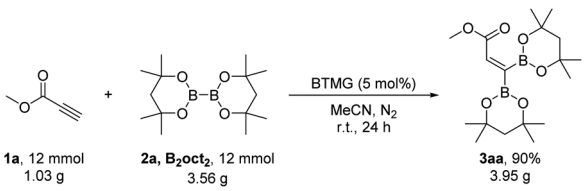


Scheme 2 1,1-Diborylation reaction using other diboron reagents. Reaction conditions: methyl propiolate (0.1 mmol), diboron reagent (0.1 mmol), BTMG (5 mol%), MeCN (2 mL), rt., 24 h. N.D. = not detected.

To demonstrate the practicability and scalability of our methodology, the gram-scale 1,1-diborylation of methyl propiolate **1a** with B_2oct_2 was carried out on 12 mmol to produce **3aa** in 90% yield (3.95 g) (Scheme 3).

To better understand the reaction pathway for organobase-catalyzed 1,1-diborylation of terminal alkynes, DFT studies are performed using methyl propiolate **1a** and B_2oct_2 **2a** as the model substrate and BTMG as the organobase. The calculated energy profile is shown in Fig. 1. The initial step is a concerted three-component proton transfer/borylation process (**TS1**), the base (BTMG) helps to abstract a proton from the terminal alkyne **1a** to give alkynyl anion **I** and protonated base. At the same time, the negatively charged terminal carbon of the alkyne could attack the boron center of the diboron species, leading to a two-component intermediate **II**. Then the negatively charged diboron species would undergo a 1,2-boryl migration process (**TS2**) to generate a 1,1-diborylallene species **III**. Finally, another proton transfer (**TS3**) from protonated base generated in the previous step to the negative-charged oxygen atom of the allene species **II** to give an allene hemiacetal **IV**, which then tautomerizes to the 1,1-diborylated product **3aa**.

Based on the results of previous work[6] and our DFT studies, a plausible reaction pathway was postulated as in Scheme 4. Methyl propiolate **1a** is firstly deprotonated in the presence of an organobase to give an alkynyl anion **I**, which then



Scheme 3 Scale up synthesis.

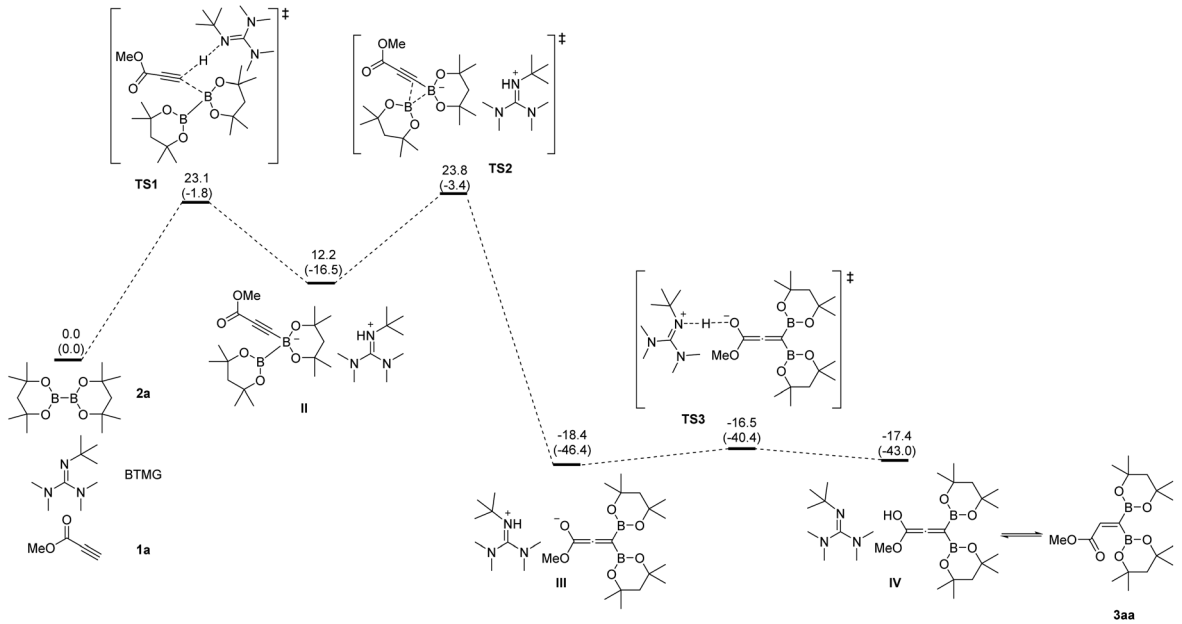
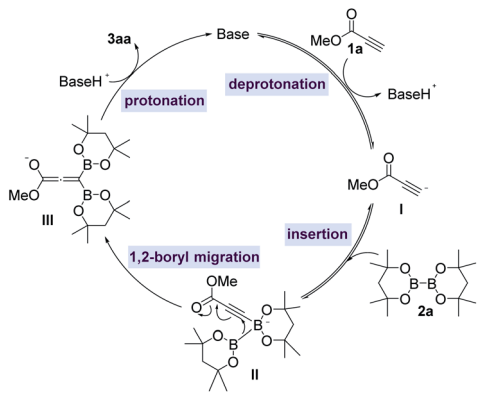


Fig. 1 Energy profile calculated for the organobase-catalyzed 1,1-diborylation of methyl propiolate. Relative free energies and electronic energies (in parentheses) are given in kcal mol^{-1}.



Scheme 4 Proposed catalytic mechanism.

nucleophilically attacks the diboron reagent **2a** to form an alkynyl diboron complex **II**. Complex **II** occurs a 1,2-boryl migration process to produce a *gem*-diborylallene intermediate **III**, followed by a protonation to afford the 1,1-diborylalkene product **3aa** with releasing the organobase catalyst to complete the catalytic cycle.

Conclusions

In conclusion, an efficient and practical methodology for 1,1-diborylation of terminal alkynes were well developed by the catalysis of a commercially available organobase under mild conditions. Employing B_2oct_2 as the diborylating reagent, a series of propargylic derivatives was confirmed to be of high efficiency towards this regioselective 1,1-diborylation reaction. DFT calculations were introduced to well demonstrate the catalytic mechanism. This work provides an alternative approach for the preparation of synthetically important 1,1-diborylalkenes.

Conflicts of interest

There are no conflicts to declare.

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