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# Transition-metal free C–C bond cleavage/borylation of cycloketone oxime esters†

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An efficient transition-metal free C–C bond cleavage/borylation of cycloketone oxime esters has been described. In this reaction, the $B_2(OH)_4$ reagent not only served as the boron source but also acted as an electron donor source through formation of a complex with a DMAc-like Lewis base. This complex could be used as an efficient single electron reductant in other ring-opening transformations of cycloketone oxime esters. Free-radical trapping, radical-clock, and DFT calculations all suggest a radical pathway for this transformation.

## Introduction

Alkylboronic esters are very important building blocks in organic synthesis as well as in medicinal chemistry and materials science (Fig. 1).[1,2] For instance, they have been widely used in Suzuki–Miyaura coupling reactions.[3] Thus, many chemists have devoted their efforts to develop facile and efficient methods for the synthesis of alkylborons.[4] The classical method relies on the trapping of highly reactive alkyl-Li or alkyl-Mg reagents with suitable boron compounds.[5] However, this procedure suffers from strict conditions as well as poor functional-group tolerance. In recent years, a number of C–B bond formation reactions, including transition-metal catalyzed borylation of alkyl halides, decarboxylative borylation of aliphatic esters,[6] hydroboration of alkenes and others have emerged as attractive alternatives to classical methods.[7] Nevertheless, noble metal catalysts, strong bases and ligands are usually required in these reactions. Therefore, developing mild borylation reactions to access functionalized alkylboron compounds is still desirable and highly in demand.[4]

Since the pioneering work of Zard and Uemura, C–C bond cleavage of cycloketone oxime derivatives has emerged as an attractive strategy to construct C–C and C–Y (Y = O, S, Se, Te, or X) bonds.[8–10] Recently, an array of radical C–C bond cleavages of cycloketone oxime derivatives have been developed under different catalytic systems including transition-metal catalysis and visible-light photocatalysis (Fig. 2, route a).[9a–h] In addition, the Castle group reported a microwave-promoted C–C bond cleavage of cycloketone oxime ethers.[9i] In this regard, our group presented a series of iron and copper catalyzed C–C bond cleavages of cycloketone oxime esters.[10] These established protocols provided efficient approaches to incorporate the versatile cyanoalkyl moieties into structurally diverse molecules, wherein the iminyl radical was the pivotal intermediate. Although remarkable advances have been made, the C–C bond cleavage/borylation of cycloketone oxime derivatives remains unexplored. Very recently, some elegant transition metal-free borylation reactions have been reported by different research groups.[11] Intriguingly, the diboron species not only served as a boron source but also acted as an electron donor source to generate reactive radical intermediates.[11,12] Inspired by these studies and our previous results, we wish to explore a novel catalytic system to form a reactive iminyl radical and simultaneously to construct C(sp$^3$)–B bonds (Fig. 2, route b). Herein, we report a transition metal free C–C bond cleavage/borylation of cyclobutanone oxime esters through using a diboron reagent as the boron source and activator. This protocol provided a straightforward access to cyanoalkyl boronic esters, a class of versatile building blocks in organic synthesis,[2,13] in good yields.

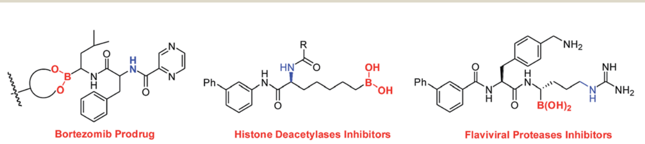


Fig. 1 Biologically active compounds containing alkylboronic moieties.

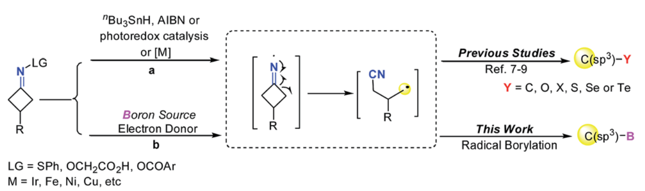


Fig. 2 Transformation of cyclobutanone oxime derivatives.

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† Electronic supplementary information (ESI) available: Experimental procedures and characterization of new compounds are provided. See DOI: 10.1039/c8sc03315c

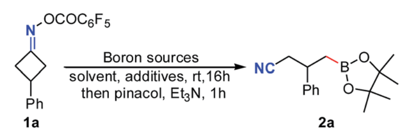
## Results and discussion

To test our hypothesis, cyclobutanone oxime ester **1a** was treated with 1.2 equiv. of bis(pinacolato)diboron ($B_2pin_2$) in DMAc at room temperature under the irradiation of a 23 W CFL bulb. To our delight, the desired pinacol cyanoalkyl boronic ester **2a** was obtained in 7% yield (Table 1, entry 1). When bis(catecholato)diboron ($B_2cat_2$) was used instead of $B_2pin_2$, the yield of **2a** was increased to 54% after workup with pinacol and $NEt_3$ (entry 2). However, the yield of **2a** decreased dramatically when the reaction was conducted in the dark. Satisfactorily, tetrahydroxydiboron $B_2(OH)_4$ showed better reaction efficiency and gave the desired product **2a** in 61% yield (entry 4). Surprisingly, it was found that photoactivation was not essential for the reaction with $B_2(OH)_4$. Treatment of **1a** with 2.0 equiv. of $B_2(OH)_4$ still resulted in a 60% yield of **2a** even in the dark (entry 5). A similar result was also observed under ambient light (entry 6). These results indicated that the reaction was not triggered by a light source. Notably, increasing the amount of $B_2(OH)_4$ to 3.0 equiv. improved the yield of **2a** to 77%, while further increasing the amount of $B_2(OH)_4$ did not improve the yields of **2a** (entries 7 and 8). Solvent screening indicated that other amide-based solvents such as NMP and DMF were less effective (entries 9 and 10). Additionally, other types of solvents such as DCM, acetone and MeCN all furnished worse yields (entries 11–13). It should be noted that the reaction in DCM using 1.0 equiv. of DMAc as the additive only afforded a trace amount of **2a** (entry 14). Finally, other additives such as 4-phenylpyridine, 4-cyanopyridine, DMAP and $Cs_2CO_3$ were also tested, but none of them gave better results than DMAc alone (entries 15–18).

With the optimal conditions in hand, the generality and limitations of cyclobutanone oxime esters were examined (Table 2). A variety of 3-aryl, benzyl and alkyl substituted oxime esters were efficiently engaged in this ring-opening/borylation reaction to provide the corresponding boronic esters **2a–2q** in moderate to good isolated yields. It was found that the nature of the substituents on the aromatic ring has a significant effect on the reaction efficiency (**2e–2g** *vs.* **2h** and **2i**). Satisfactorily, functional groups including halogen (**2d**, **2h**, **2j**), ester (**2i**, **2o**, **2p**) and ether (**2m**, **2q**) in the oxime esters were well-tolerated. Cyclobutanone oxime ester **1r** without any substituent furnished the desired product **2r** in 85% yield. The 3,3-disubstituted substrates **1s** and **1t** also afforded the target products **2s** and **2t** in 76% and 34% yields, respectively.

Notably, besides primary boronic esters, this procedure was also applicable to provide the secondary ones under modified conditions. The 2,3-disubstituted oxime esters **1u** and **1v** underwent the ring-opening/borylation process regioselectively to afford the desired products **2u** and **2v** in acceptable yields by using 1.2 equiv. of $B_2cat_2$ as the boron source at 80 °C under irradiation with 23 W CFL bulbs. It should be noted that the light irradiation, heating and boron source are all important for these reactions, implying that direct photolysis of $B_2Cat_2$

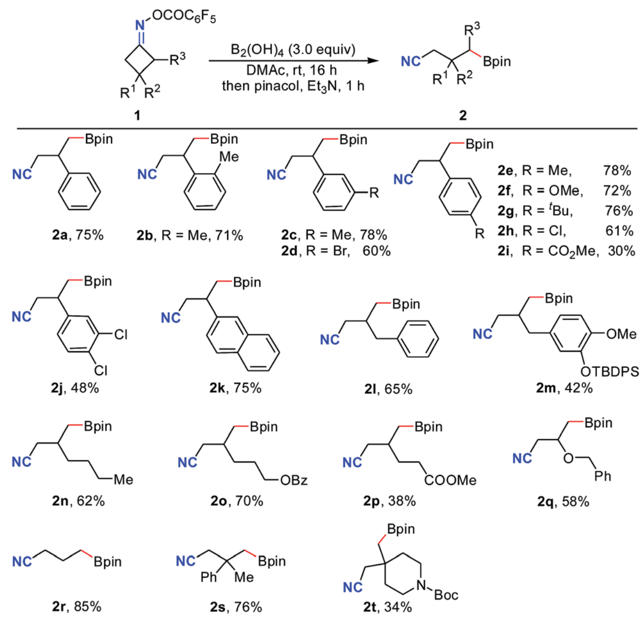
Table 1 Optimization of reaction conditions[a]




| Entry | Boron sources (equiv.) | Solvent | Additives (equiv.) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | $B_2pin_2$ (2.0) | DMAc | | 7[c,d] |
| 2 | $B_2Cat_2$ (2.0) | DMAc | | 54[c] |
| 3 | $B_2Cat_2$ (2.0) | DMAc | | 28[e] |
| 4 | $B_2(OH)_4$ (2.0) | DMAc | | 61[c] |
| 5 | $B_2(OH)_4$ (2.0) | DMAc | | 60[e] |
| 6 | $B_2(OH)_4$ (2.0) | DMAc | | 61 |
| **7** | **$B_2(OH)_4$ (3.0)** | **DMAc** | | 77 |
| 8 | $B_2(OH)_4$ (4.0) | DMAc | | 73 |
| 9 | $B_2(OH)_4$ (3.0) | NMP | | 66 |
| 10 | $B_2(OH)_4$ (3.0) | DMF | | 52 |
| 11 | $B_2(OH)_4$ (3.0) | MeCN | | 20 |
| 12 | $B_2(OH)_4$ (3.0) | Acetone | | 15 |
| 13 | $B_2(OH)_4$ (3.0) | DCM | | n.r.[f] |
| 14 | $B_2(OH)_4$ (3.0) | DCM | DMAc (1.0) | Trace |
| 15 | $B_2(OH)_4$ (3.0) | DMAc | 4-Phenylpyridine (1.0) | 56 |
| 16 | $B_2(OH)_4$ (3.0) | DMAc | 4-Cyanopyridine (1.0) | Trace[g] |
| 17 | $B_2(OH)_4$ (3.0) | DMAc | DMAP (1.0) | 63 |
| 18 | $B_2(OH)_4$ (3.0) | DMAc | $Cs_2CO_3$ (1.0) | 26 |

[a] Reaction conditions: **1a** (0.20 mmol, 1.0 equiv.), boron sources (2.0–4.0 equiv.), additives (1.0 equiv.), in 2.0 mL of solvent at room temperature under $N_2$ for 16 h; then pinacol (0.8 mmol, 4.0 equiv.) dissolved in $Et_3N$ (0.7 mL) was added to the reaction mixture and stirred for 1 h. [b] NMR yields by using $CH_2Br_2$ as the internal standard. [c] Reaction by irradiation with a 23 W compact fluorescent light (CFL) bulb. [d] Without addition of pinacol and $Et_3N$. [e] The reaction was conducted in the dark. [f] n.r. = no reaction. [g] 3-Phenylbutanenitrile was observed as the major product.

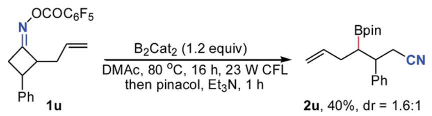
Table 2 Scope of cyclobutanone oxime esters[a]



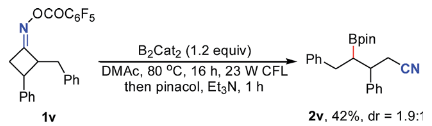

[a] **1** (0.2 mmol), $B_2(OH)_4$ (0.6 mmol), DMAc (2 mL) at room temperature under $N_2$ for 16 h; then workup with pinacol (0.8 mmol) and $Et_3N$ (0.7 mL), isolated yields.

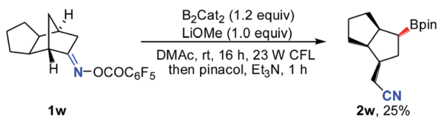
accounts partly for the formation of **2u** and **2v** (eqn (1) and (2)). The tricyclo[5.2.1.0(2,6)]decan-8-one oxime ester **1w** also gave the anticipated secondary boronic ester **2w** as a single diastereomer under the modified conditions, albeit in somewhat low yield (eqn (3)). Unfortunately, the oxime ester derived from 2-substituted cyclopentanone or cyclohexanone could not afford the desired product under the present conditions.




(1)

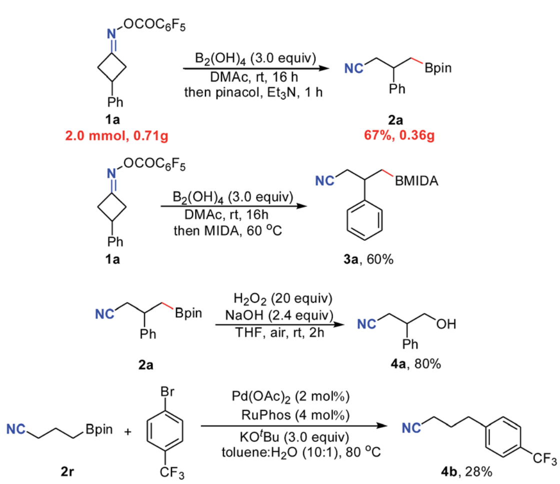



(2)




(3)

Satisfactorily, this metal free C–C cleavage/borylation reaction of cyclobutanone oxime esters could be scaled up. For instance, the reaction of **1a** on a 2.0 mmol scale gave the product **2a** in 67% isolated yield. Furthermore, the product of this reaction was not limited to pinacol boronic ester. Using methyl iminodiacetic acid (MIDA) instead of pinacol for the reaction workup, the corresponding product **3a** was obtained in 60% yield. Moreover, the product **2a** could be oxidized by $H_2O_2$ followed by hydrolysis to deliver the alcohol **4a** in 80% yield (Scheme 1). Finally, treatment of cyanoalkyl boronic ester **2r** with 4-trifluoromethylbromobenzene in the presence of a palladium catalyst afforded the coupling product **4b** in 28% yield (without optimization).




Scheme 1 Synthesis of **2a** on a gram scale and derivatization of the product.

To gain some understanding of the reaction, several control experiments were conducted (Fig. 3). When TEMPO, a typical radical scavenger was subjected to the reaction conditions, only trace amount of **2a** was observed, along with the cyanoalkyl-TEMPO adduct **5a** which was isolated in 50% yield, implying that a radical intermediate was involved in this transformation. In contrast, without $B_2(OH)_4$ or DMAc, the reaction of **1a** with TEMPO did not take place, suggesting that both the diboron reagent and amide-based solvent play a critical role in this ring-opening process (Fig. 3, eqn (4)). Furthermore, the radical-clock substrates **6a** and **6b** furnished the cyclized products **7a** and **7b** *via* a ring-opening/cyclization/borylation cascade, wherein no linear coupling product was detected (Fig. 3, eqn (5) and (6)). Treatment of **6c** under the standard conditions led to the product **7c** in 58% yield as the sole product (Fig. 3, eqn (7)). These results also support a radical pathway.

Based upon the preliminary results and previous reports, a possible mechanism was proposed for this reaction with the further aid of DFT calculation (Scheme 2, for details, see the ESI†). This borylation reaction probably proceeds through a radical chain propagation mechanism. First, cyclobutanone oxime ester **1a** gives the DMAc-stabilized radical intermediate **I** through thermal cleavage of the B–B bond of $B_2(OH)_4 \cdot$DMAc complex.[11,12] Second, N–O bond cleavage of radical **I** affords the iminyl radical **II**, which delivers radical **III** through a β-carbon elimination process.[7–9] Afterward, the alkyl radical **III** reacts with DMAc-ligated $B_2(OH)_4$ to produce the precursor of the desired product **2a′** and DMAc-stabilized boryl radical **IV**.[11,12,14] Finally, the resulting boryl radical **IV** might propagate a radical chain process. It is worth mentioning that $ArCOOB(OH)_2$ can be detected by LCMS during the reaction, which also provided evidence for our proposed catalytic cycle. On the other hand, based on the above result and UV-vis spectrum of **1u** and $B_2Cat_2$ in DMAc, direct light-triggered homolysis of $B_2Cat_2$ might be involved in the reaction of **1u** with $B_2Cat_2$.

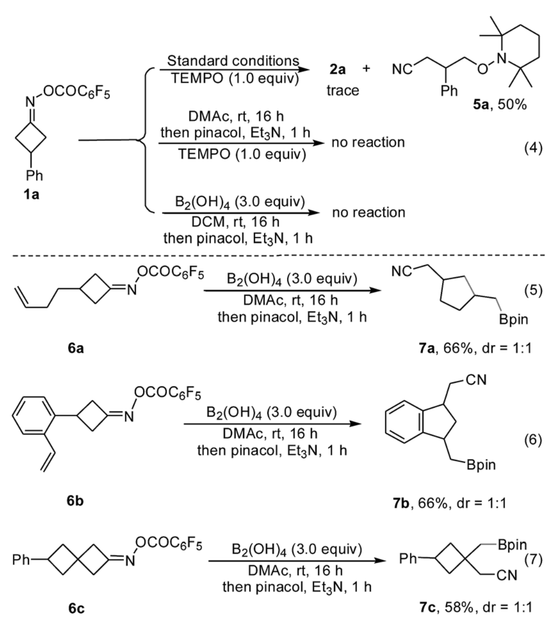
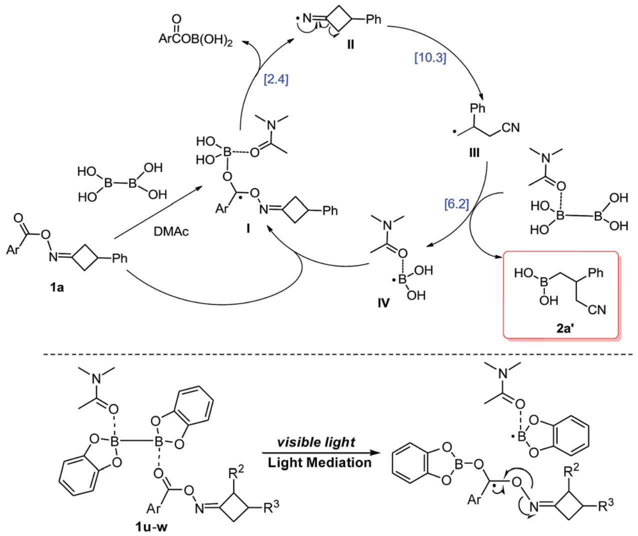



Fig. 3 Control experiments.




Scheme 2 Proposed mechanism.

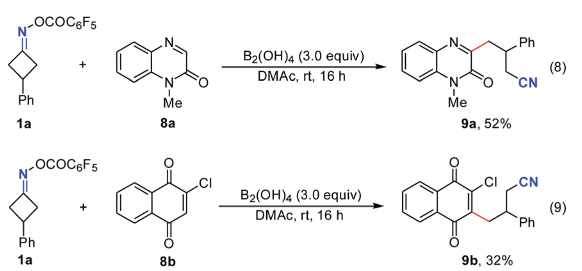



Fig. 4 Reductive cleavage reactions employing the $B_2(OH)_4$/DMAc system.

Remarkably, this simple $B_2(OH)_4$/DMAc system was also applicable to other C–C bond cleavage/C–C bond formations (Fig. 4). The reaction of **1a** with quinoxalin-2(1*H*)-one **8a** and quinine **8b** also worked smoothly to give the cyanoalkylated products **9a** and **9b** in 52% and 32% yields, respectively (without optimization).[10a,b] These results suggested that this new transition metal free system could be used instead of transition metal catalytic systems, further indicating their potential applications in radical chemistry.

## Conclusions

In summary, we have demonstrated the first transition-metal free C–C bond cleavage/borylation of cyclobutanone oxime esters. This protocol is amenable to a variety of cyclobutanone oxime esters, thus providing a facile access to cyanoalkyl boronic esters in good yields. Primary mechanism studies revealed that $B_2(OH)_4$ not only serves as a boron source but also plays a crucial role in the C–C bond cleavage process. Further studies on the mechanistic details are currently underway in our laboratory.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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