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).

Fig. 1Biologically active compounds containing alkylboronic moieties.

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.
Results and discussion

To test our hypothesis, cyclobutanone oxime ester 1a was treated with 1.2 equiv. of bis(pinacolato)diboron (B2pin2) 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 (B2cat2) was used instead of B2pin2, the yield of 2a was increased to 54% after workup with pinacol and NET3 (entry 2). However, the yield of 2a decreased dramatically when the reaction was conducted in the dark. Satisfactorily, tetrahydroxydiboron B2(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 B2(OH)4. Treatment of 1a with 2.0 equiv. of B2(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 B2(OH)4 to 3.0 equiv. improved the yield of 2a to 77%, while further increasing the amount of B2(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-cyano-pyridine, DMAP and Cs2CO3 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 B2cat2 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 B2Cat2

Table 1 Optimization of reaction conditionsa

| Entry | Boron sources (equiv.) | Solvent | Additives (equiv.) | Yield (%) |
|-------|------------------------|---------|-------------------|-----------|
| 1     | B2pin2 (2.0)           | DMAc    |                   | 7*         |
| 2     | B2Cat2 (2.0)           | DMAc    |                   | 54*        |
| 3     | B2Cat2 (2.0)           | DMAc    |                   | 28*        |
| 4     | B2(OH)4 (2.0)          | DMAc    |                   | 61*        |
| 5     | B2(OH)4 (2.0)          | DMAc    |                   | 61*        |
| 6     | B2(OH)4 (2.0)          | DMAc    |                   | 61        |
| 7     | B2(OH)4 (3.0)          | DMAc    |                   | 77        |
| 8     | B2(OH)4 (4.0)          | DMAc    |                   | 73        |
| 9     | B2(OH)4 (3.0)          | DMAc    |                   | 66        |
| 10    | B2(OH)4 (3.0)          | DMAc    |                   | 52        |
| 11    | B2(OH)4 (3.0)          | DMAc    |                   | 20        |
| 12    | B2(OH)4 (3.0)          | Acetone |                   | 15        |
| 13    | B2(OH)4 (3.0)          | DCM     |                   | n.r.      |
| 14    | B2(OH)4 (3.0)          | DCM     | DMAc (1.0)        | Trace     |
| 15    | B2(OH)4 (3.0)          | DCM     | 4-Phenylpyridine (1.0) | 56        |
| 16    | B2(OH)4 (3.0)          | DCM     | 4-Cyanopyridine (1.0) | Trace* |
| 17    | B2(OH)4 (3.0)          | DCM     | DMAP (1.0)        | 63        |
| 18    | B2(OH)4 (3.0)          | DCM     | Cs2CO3 (1.0)      | 26        |

* 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 N2 for 16 h; then pinacol (0.8 mmol, 4.0 equiv.) dissolved in Et3N (0.7 mL) was added to the reaction mixture and stirred for 1 h. c NMR yields by using CH3Br2 as the internal standard. d Reaction by irradiation with a 23 W compact fluorescent light (CFL) bulb. e Without addition of pinacol and Et3N. f The reaction was conducted in the dark. g n.r. = no reaction. h 3-Phenylbutanenitrile was observed as the major product.

Table 2 Scope of cyclobutanone oxime estersa

| Solvent | Additives | Yield (%) |
|---------|-----------|-----------|
| DMAc    | 3.0 equiv. | 100%      |
| DCM     | 3.0 equiv. | 75%       |
| NMP     | 3.0 equiv. | 65%       |
| DMF     | 3.0 equiv. | 50%       |
| Acetone |            | 20%       |
| DCM     | 1.0 equiv. | 15%       |
| DCM     | 1.0 equiv. | 10%       |

* 1 (0.2 mmol), B2(OH)4 (0.6 mmol), DMAc (2 mL) at room temperature under N2 for 16 h; then workup with pinacol (0.8 mmol) and Et3N (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.

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 H₂O₂ 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).

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 B₂(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 1 through thermal cleavage of the B–B bond of B₂(OH)₄–DMAc complex.¹¹,¹² Second, N–O bond cleavage of radical 1a affords the iminyl radical II, which delivers radical III through a β-carbon elimination process.¹⁷–⁹ Afterward, the alkyl radical III reacts with DMAc-ligated B₂(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 B₂Cat₂ in DMAc, direct light-triggered homolysis of B₂Cat₂ might be involved in the reaction of 1u with B₂Cat₂.

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

Fig. 3 Control experiments.
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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 B₂(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.
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