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Synthetic Methods

Metal-Free 1,3-Boronate Rearrangement to Ketones Driven by Visible Light

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Abstract: Boronate rearrangements, such as the Matteson and Petasis reactions, are valuable metal-free reactions for the transfer of the carbo group on boron to intramolecular electrophilic sites. However, only highly reactive electrophiles are suitable, and ketones are too inactive for those boronate rearrangements due to the high energy barriers. We disclose here the 1,3-boronate rearrangement to ketones, for which a high energy barrier (44.9 kcal/mol) is prohibitory for thermal reactions in the ground state. The reaction is enabled by the key keto-enol-boronate bidentate complex formation in situ, which absorbs visible light to reach the excited state for the chemoselective 1,3-boronate rearrangement to ketones. Experimental and computational investigations exclude free radical intermediates from organoboronates. The aryl, alkenyl, and alkyl boronic acids react with various 1,3-diketones driven by visible light irradiation to construct structurally diverse β-keto tertiary alcohols under metal-free conditions. The reaction demonstrates substrate diversity with 58 examples, yields up to 98%, and it is suitable for gram-scale synthesis.

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Organoboronic acids are readily available and environmental friendly building blocks in organic synthesis.[1] Despite successful transition-metal-catalyzed applications such as Suzuki–Miyaura cross-coupling reactions,[2] significant efforts have been investigated to analogous reactions that use less expensive metals or do not require metals.[3] The intramolecular boronate rearrangements such as Matteson and Petasis reactions provide excellent synthetic appeals under metal-free conditions, in which elimination of trace metal catalysts from reaction residues is not required (Scheme 1a). The boronate rearrangements are initiated with the in situ tetra-coordinated boronate complex formation, followed by the regioselective carbo group migration from boron to intramolecular electrophilic sites such as α-leaving groups or iminium ions.[4] However, the boronate rearrangement to less electrophilic sites such as ketones remains unaccomplished due to the high energy barriers.[5] Recently, organoboronates have been widely explored in photocatalytic reactions to generate carbo radicals from the single-electron oxidation,[6] which further engage in radical additions or cross-coupling reactions.[7] However, the carbo radical addition to ketones is reversible due to the facile β-fragmentation of the resulting alkoxyl radicals, which is especially challenging for intermolecular carbo radical addition to ketones.[8]

β-Keto alcohols are important structural motifs in polyketides, many of which have antibacterial and immunosuppressive activity (Scheme 1b).[9] Mukaiyama aldol reactions have been widely used for the β-keto alcohol synthesis by condensing enolates with aldehydes.[10] Despite great success in constructing β-keto secondary alcohols, the β-keto tertiary alcohols are challenging for aldol reactions due to the low reactivity of ketones. Only activated ketones with adjacent ester or trifluoromethyl groups were suitable for the reaction.[11] Alternatively, the nucleophilic additions to 1,3-diketones may synthesize β-keto tertiary alcohols. However, the protecting-deprotecting sequence was required to obtain the mono-addition adduct rather than the bis-addition adduct, and the use of Grignard reagent may compromise the functional group compatibility of the reaction.[12]

Herein, we report the 1,3-boronate rearrangement to ketones for the first time driven by visible light (Scheme 1c). This metal-free boronate rearrangement to ketones is enabled by the visible-light-excitation of the bidentate keto-enol-boronate complex, which overcomes the prohibitory high energy barrier in the ground state. Aryl, alkenyl, and alkyl boronic acids all engage in the 1,3-boronate rearrange-

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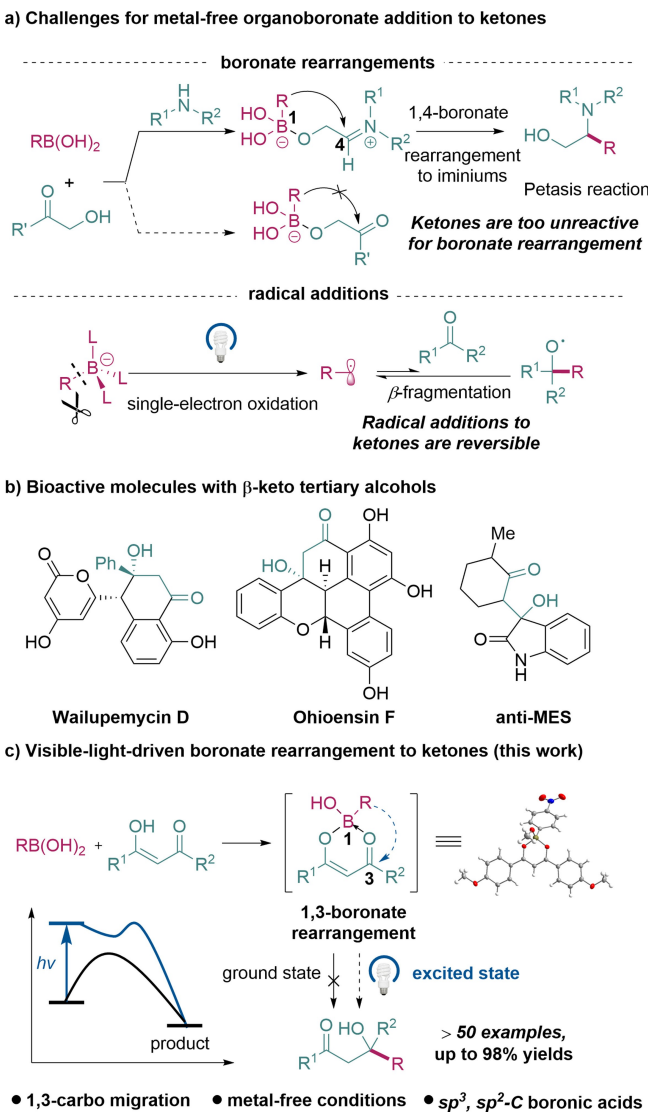

Scheme 1. Boronate rearrangement to ketones driven by visible light.

ment to synthesize various β-keto tertiary alcohols without inducing free carbo-radical intermediates.

Over the past few years, we have systematically investigated the organoboronate complex formation between various ketones and organoboronic acids.[7e] Serendipitously, the mix of the keto-enol **1a**, tautomerized from 1,3-diketone, and p-tolyl boronic acid **1b** in methanol yielded the new boronate complex. The UV/Vis spectrometry shows the bathochromic shift to above 450 nm in the absorption spectra in DCM (Scheme 2a). In addition, the ^{11}B NMR spectra of the **1a**/**1b** mixture showed a new tetra-coordinated organoboronate species at 7.7 ppm in CD_3OD. The HRMS of the complex **1** was 438.1728 for $[M+Na]^+$, consistent with the 1:1 complexation between **1a** and **1b** (Figure S4).

The keto-enol **1a** and p-nitrophenyl boronic acid **2b** demonstrated strong coordination for the boronate complex formation in methanol, which had the association constant K_a as 392.3 M^{-1} by Benesi–Hildebrand analysis.[13] The boronate complex **2**[14] can be further isolated and characterized by X-ray crystallography as the 98% tetrahedral character according to Höpfl's equation (Scheme 2b).[15] The similar B1–O1 (1.53 Å) and B1–O2 (1.52 Å) bond lengths are observed from the bidentate complexation of delocalized keto-enols.[16] The C–O bond lengths (C1–O1 = 1.30 Å, and C2–O2 = 1.30 Å) are shorter than the single bond (C–O as 1.42 Å) and longer than the double bond (C=O as 1.22 Å). Similarly, the C–C bond lengths (C1–C3 = 1.38 Å, and C2–C3 = 1.38 Å) are between the single bond ($C(sp^2)$–$C(sp^2)$ as 1.46 Å) and the double bond ($C(sp^2)$=$C(sp^2)$ as 1.34 Å).[17] These results are together consistent with the delocalized keto-enol form in complex **2**.

As the newly formed boronate complexes absorb blue light, we next irradiated with blue LED to explore their excited-state chemistry. While a range of radical addition, elimination, and fragmentation products were initially expected from the typical reactivity of carbo radicals from organoboronates, the sole product β-keto tertiary alcohols **3** was obtained in 48% yield after 16 h irradiation from the hypothetical 1,3-aryl migration (Scheme 2c). The use of DABCO as the base accelerated the reaction to 8 h and afforded optimal 85% yield (81% isolated yield) of **3** without the detection of other side products.[18] The control experiments indicated that the light irradiation was critical, and heating did not give conversion for the 1,3-boronate rearrangement. The on-off-light experiments demonstrated the light dependence of the reaction (Figure S13).

We next explored the generality of the photochemical boronate rearrangement to 1,3-diketones (Scheme 3). The aryl boronic acids **4b**–**7b** with various electronic properties, including electron-deficient fluorides or electron-rich methoxy substitutions, were all applicable for the 1,3-boronate rearrangement to afford **4**–**7** in 75–84% yields.[7c,d, 19] The esters, ketones, and aldehydes as competing electrophiles on boronic acids **8b**–**10b** did not affect the reaction, giving 84–88% yields of 1,3-carbo migration adducts **8**–**10**. The terminal alkene group in **11b** was tolerated to afford a 60% yield of **11**. The boronate derivative of phenylalanine **12b** engaged in the boronate rearrangement to afford the unnatural amino acid **12** smoothly in 82% yield, which have potential bioconjugation applications.[20] The nitro group did not inhibit the reaction as in other photocatalytic transformations to afford **13** in 82% yield. Noncyclic and cyclic vinyl boronic acids reacted uneventfully to afford **14**–**16** in 70–88% yields, in which the corresponding vinyl boronic acids rarely engaged in other photocatalytic transformations.

The alkyl boronic acids were also suitable for the transformation, in sharp contrast to other previously reported boronate rearrangements in the ground state.[21] The primary alkyl boronic acids **17b**–**21b** with methyl, ethyl, or various aliphatic groups reacted smoothly to afford 63–89% yields of **17**–**21**. The benzyl and allyl boronic acids **22b**–**23b** resulted in quantitative 94–97% yields of **22**–**23**. The terminal alkenes and alkyl bromides in **24b**–**25b** were tolerated in alkyl boronic acids to give 54–71% yields of **24**–**25**. The secondary cyclic- and non-cyclic alkyl boronic acids **26b**–**31b** afforded 74–92% yields of **26**–**31**. The reaction can be easily scaled up to grams to afford β-keto tertiary

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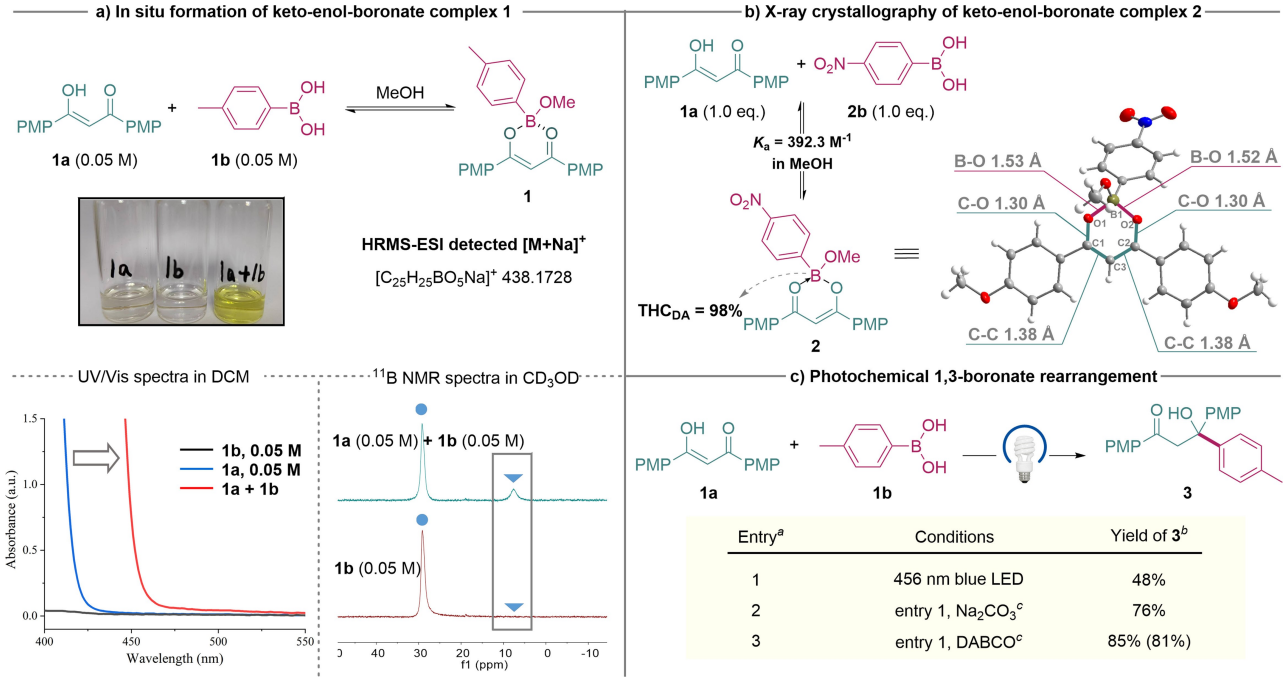

Entry[a]	Conditions	Yield of 3[b]
1	456 nm blue LED	48%
2	entry 1, Na_2CO_3[c]	76%
3	entry 1, DABCO[c]	85% (81%)

Scheme 2. The discovery of keto-enol-boronate complexes and their excited-state chemistry. [a] Reaction conditions: **1a** (0.1 mmol), **1b** (0.3 mmol) in 2.0 mL EtOH under 456 nm blue LEDs for 16 h under nitrogen atmosphere at r.t.. [b] Conversions and yields were determined by ^{1}H NMR analysis. Isolated yields were in parenthesis. [c] Bases (0.2 mmol), 8 h.

alcohols **29** in 1.43 g with 83 % yield. The tertiary alkyl boronic acids **32b**–**33b** gave **32**–**33** in 92–97 % yields in prolonged reaction time, in which two sterically congested quaternary carbon centers were constructed smoothly. The trifluoroborates and boronic esters were also suitable organoboronates to afford similar yields (Tables S10, S13, Figure S15), which was attributed to the solvolysis of trifluoroborates in ethanol and water.[22] When using alkyl boronic acids, the reaction is completed in a few hours with blue LEDs in lower power. In contrast, when using aryl and alkenyl boronic acids in which carbon-boron bonds are more difficult to break, the reaction requires a higher power of blue LED to complete within a few hours.

The substitutions on 1,3-diketones were well tolerated that electron-rich methyl, dimethylamino groups, and electron-deficient bromo, chloro, fluoro, trifluomethyl groups in **34a**–**47a** were all applicable to afford **34**–**47** in up to 98 % yields (Scheme 4). It is worth noting that aryl or alkyl boronic acids with different electronic properties afforded excellent yields consistently. The naphthenyl, furanyl, thiophenyl, and pyridyl substituted 1,3-diketones **48a**–**51a** gave 66–85 % yields of β-heterocyclic alcohols **48**–**51**, which heterocycle components did not affect the bidentate keto-enol-boronate formation.[23]

When 1,3-diketones **52a** bearing unsymmetric substituents with different steric properties were tested,[24] the boronate rearrangement to ketones with less steric hindrance was obtained with 76 % yield of **52**. In contrast, the steric-crowded mesityl ketone rearrangement adduct was not observed. When the steric factor was less significant, the 2.3 : 1 regioisomers of **53** and **54** were obtained from **53a** in a total 92 % yield, favoring the phenyl ketone migration adducts. When ketoesters and phenyl ketones both exist in the molecule, the preferential ketoester rearrangement adduct was observed in 40 % yield of **55**, along with the hydrolysis products from ketoesters. The unsymmetric 1,3-diketones **56a** with both tert-butyl ketones and phenyl ketones yielded the selective phenyl ketone rearrangement adduct **56** in 37 % yield in low conversions, while the tert-butyl ketone rearrangement adduct was not obtained. We also prepared 2-fluoro substituted 1,3-diketones **57a**–**58a**, and found they existed as the diketone form rather than the keto-enol form. However, when they mixed with organoboronates **29b**, the in situ formation of the keto-enol-boronate complex were observed, which underwent 1,3-boronate rearrangement to afford the fluoro-keto alcohols **57**–**58** in 47–57 % yields. It is worth mentioning that these fluoro-keto alcohols could not be obtained directly by other methods, and the fluorination is essential to improve the pharmacological properties of parent molecules significantly.[25]

We next investigated if the radical intermediates occurred as in other light-induced organoboronates transformations (Scheme 5a, left panel). With cyclopropyl methylboronic acid **3b** as the radical clock, the cyclopropyl methyl addition adduct **59** was obtained in 74 % yield, and no detectable ring-opening alkene adducts were detected.[26] When the 1,3-dicyclopropylketones **60a** was used, only the cyclopropyl substituted alcohol **60** was obtained in 51 % yield under the 365 nm irradiation. The cyclopropyl ring-opening adduct from the hypothetical cyclopropyl ketyl radical was not obtained. The addition of radical quenching

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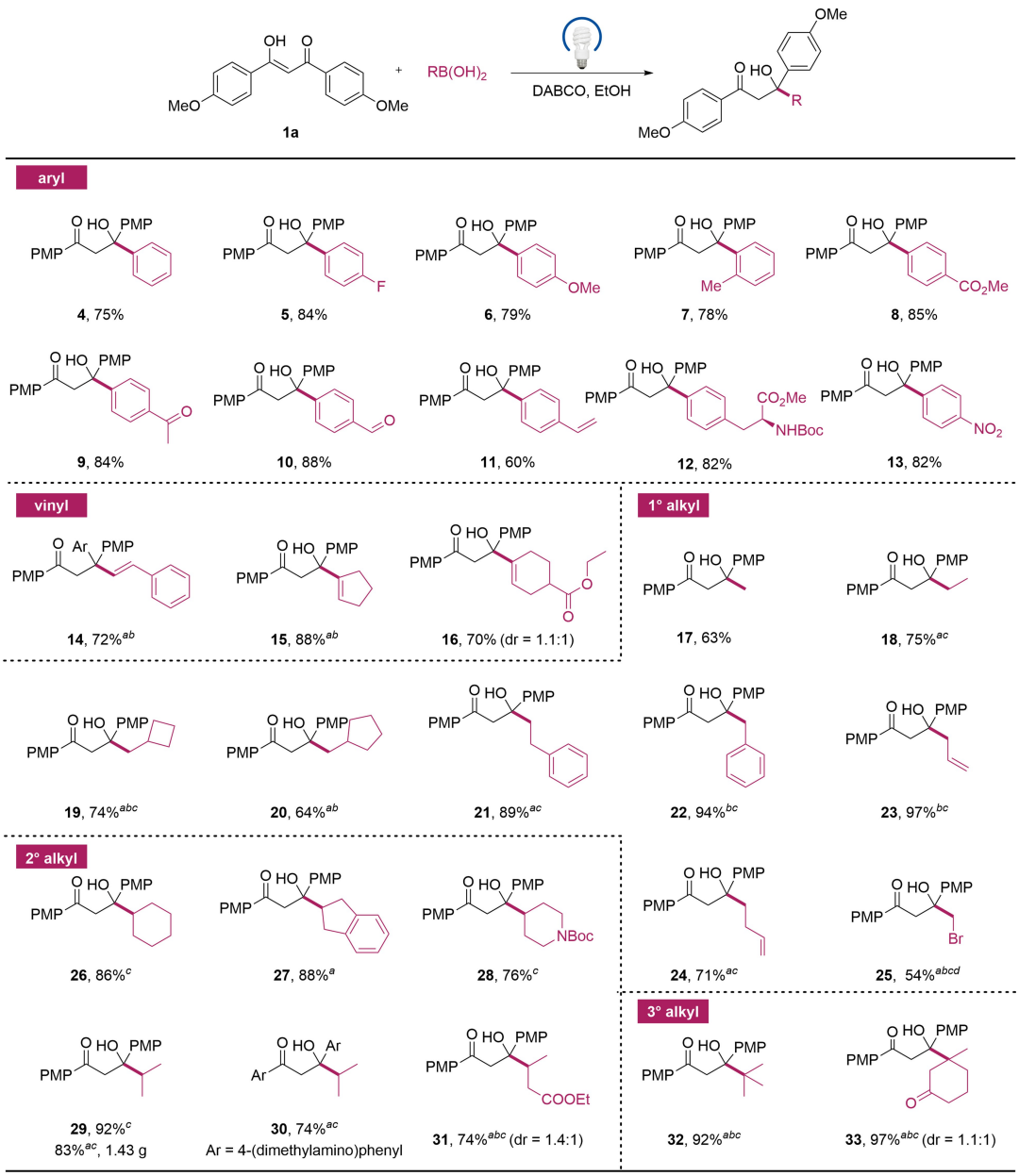

Scheme 3. Scope of organoboronic acids. Reaction conditions: 1,3-diketone (0.1 mmol), boronic acid (0.3 mmol) and DABCO (0.2 mmol) in 2.0 mL EtOH with 80 W blue LEDs irradiation for 8 h under nitrogen atmosphere at r.t., unless otherwise noted. Isolated yields were reported. [a] Irradiation for 12–24 h. [b] RBF_3K instead of $RB(OH)_2$. [c] 2*4 W blue LEDs irradiation. [d] no DABCO addition.

reagent TEMPO to the standard reaction conditions did not affect the reaction to afford boronate rearrangement product **3** in 85 % yield smoothly (Scheme 5a, right panel).[27] In parallel, the addition of BHT had no effect on the boronate rearrangement either. These radical clock and radical quenching results together suggested the intramolecular boronate rearrangement instead of the intermolecular carbo radical addition pathway. We have also tested the effect of oxygen atmosphere on the reaction and found a yield decrease by 10–20 %, which is consistent with the excited-state triplet intermediate (Table S19).

The density functional theory (DFT) calculations were next performed by M06-2X/6-31G* to elucidate the boronate rearrangement to 1,3-diketones (Scheme 5b).[28] In the absence of light, the tetra-coordinated organoboronate complex **I** undergoes a pericyclic 1,3-boronate rearrangement to β-keto tertiary alcohol boronate **II** via a hypothetical transition state **TS1**, which has a prohibitively high energy barrier (44.9 kcal/mol) for thermal reactions. In contrast, the Petasis reaction has only 10–20 kcal/mol of activation energy for the 1,4-boronate rearrangement to iminium ions.[29]

Upon visible light irradiation, the keto-enol-boronate complex **I-S0** is excited to the singlet state **I-S1** with an elevated energy at 69.9 kcal/mol. The **I-S1** undergoes fast intersystem crossing (ISC) to afford the triplet **T1** state **I-T1**

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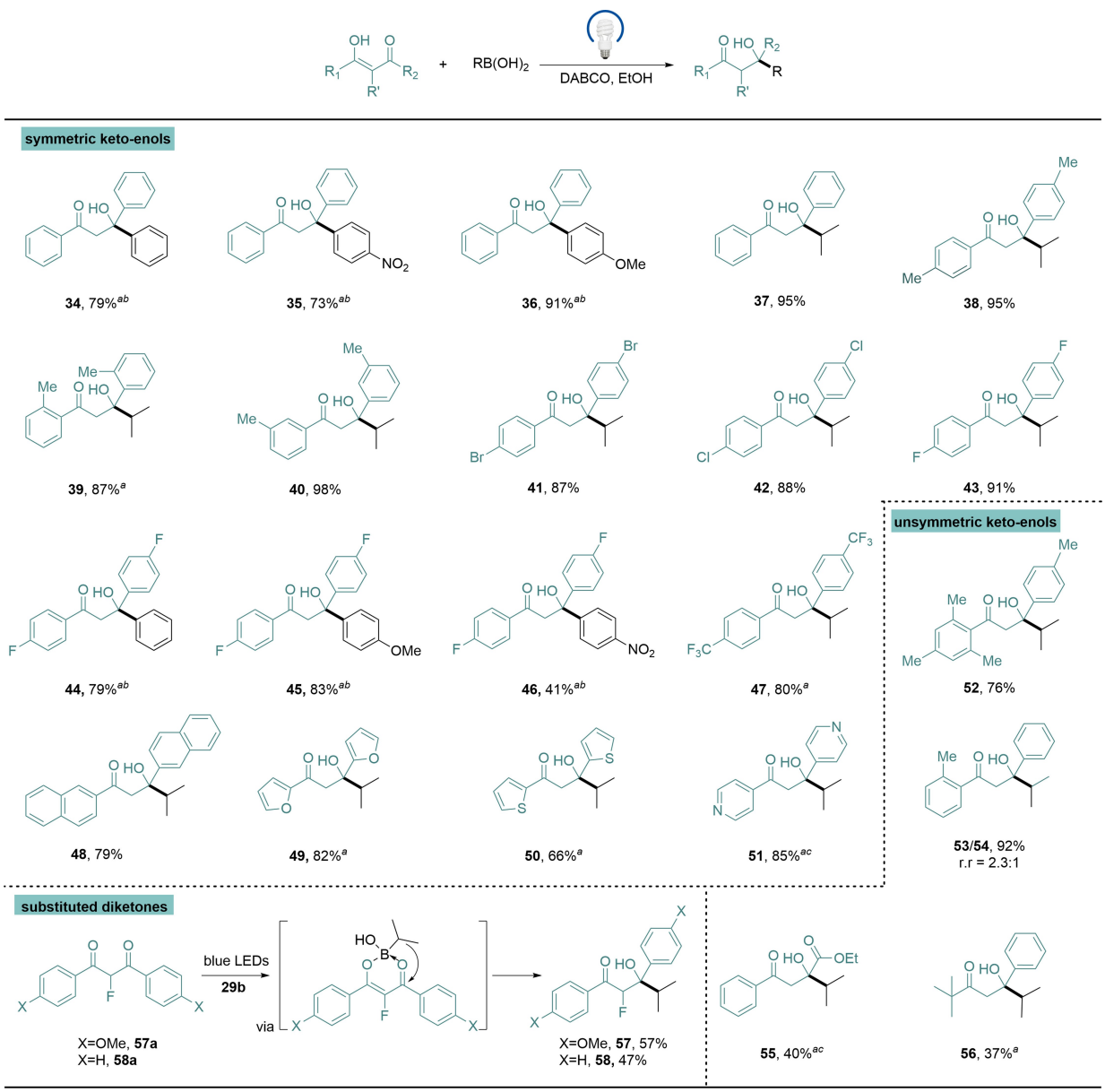

Scheme 4. Scope of diketones. Reaction conditions: 1,3-diketone (0.1 mmol), boronic acid (0.3 mmol) and DABCO (0.2 mmol) in 2.0 mL EtOH with 2*4 W blue LEDs irradiation for 8 h under nitrogen atmosphere at r.t., unless otherwise noted. Isolated yields were reported. [a] Irradiation for 12–48 h. [b] 80 W blue LED. [c] no DABCO addition.

(57.7 kcal/mol). The **I-T1** further forms a partially spin-separated intermediate ^{3}**Int1** at 31.4 kcal/mol via the transition state ^{3}**TS2**. The C/B atom distance at ^{3}**Int1** is 2.90 Å, which is shorter than the van der Waals radius sum of C(1.70 Å) and B(1.92 Å).[30] These results suggest the C–B bond is not completely dissociated to generate the alkyl radical. Subsequently, the open-shell triplet intermediate ^{3}**Int1** is degenerated with the singlet product via a minimal energy crossing point (**MECP**) in the energy surface diagram. **MECP** could be viewed as the structure recombination of the spin-separated intermediate ^{3}**Int1**, in which the carbo group with spin density migrates to the intramolecular ketone with the most abundant spin density. **MECP** is 8.9 kcal/mol higher than that of ^{3}**Int1**, with the C/B atom distance at 3.42 Å for a partial C–B bond cleavage and a partial C–C3 bond formation at 2.68 Å. These results are consistent with the experimental evidences for the lack of carbo radical intermediates in the reaction conditions. Afterwards, the stable β-keto tertiary alcohol boronate **II** is obtained at −15.2 kcal/mol.

Based on experimental and computational investigations above, we propose the photochemical mechanism of 1,3-boronate rearrangement to ketones (Scheme 6). The 1,3-diketones and organoboronic acids dehydrate to form the keto-enol-boronate complex formation in situ,[31] which can be excited by blue light to the excited state. After intersystem crossing and minimal energy crossing point, the 1,3-boronate rearrangement breaks the C–B bond with the

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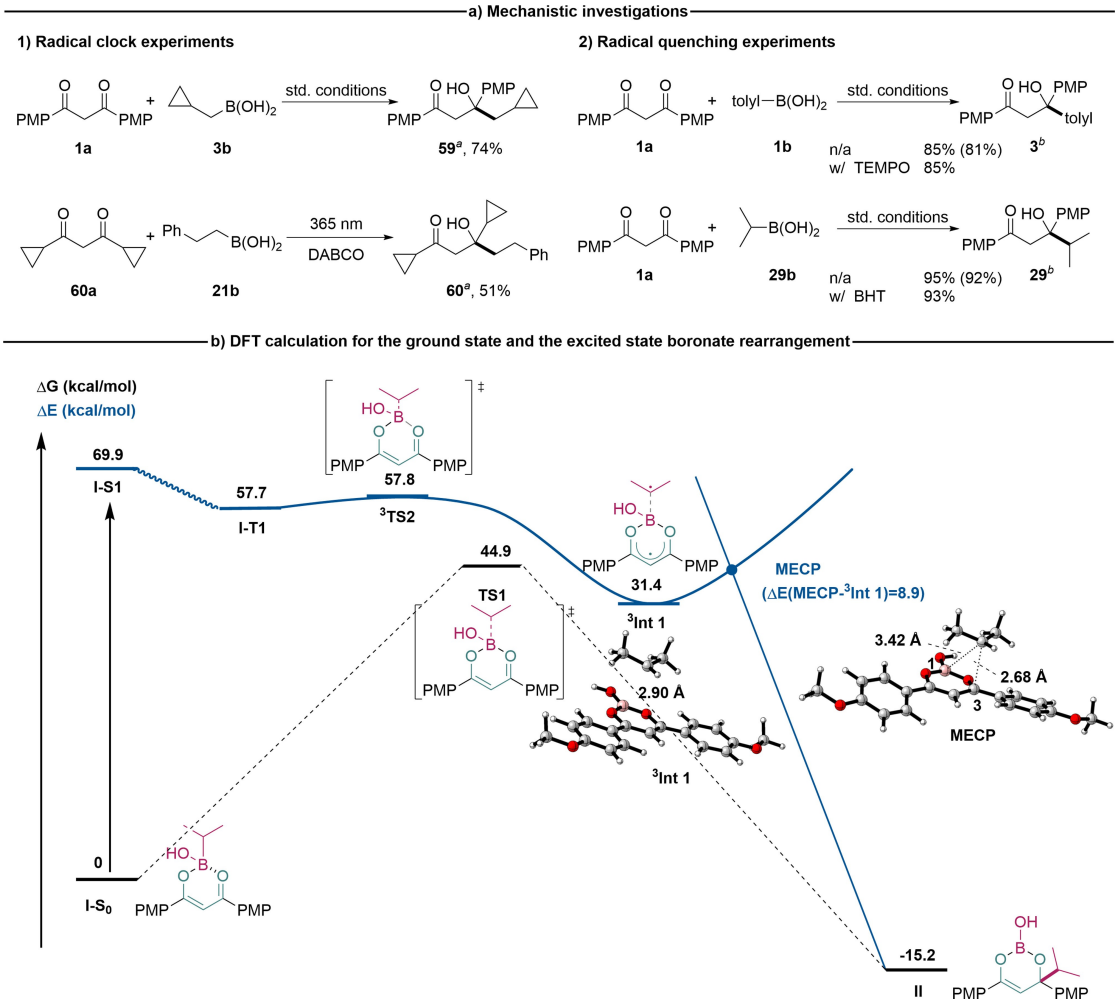
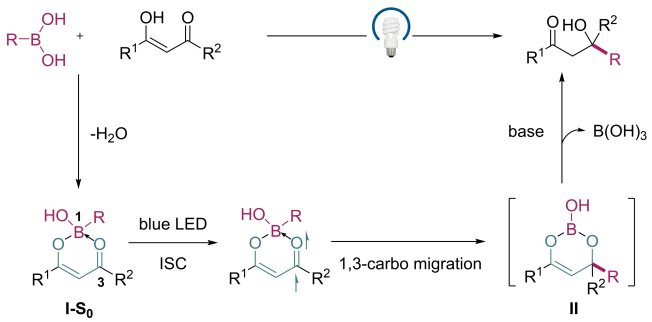


Scheme 5. Experimental and computational investigations on reaction mechanism. Standard conditions: 1,3-diketone (0.1 mmol), boronic acid (0.3 mmol) and DABCO (0.2 mmol) in 2.0 mL of EtOH with blue LEDs irradiation for 8 h under nitrogen atmosphere at r.t., unless otherwise noted. [a] Isolated yields were reported. [b] Yields were determined by ^{1}H NMR analysis, isolated yields were in parenthesis.



Scheme 6. Mechanistic proposal.

concurrent C–C bond formation, in which the alkyl, aryl, and alkenyl radical intermediates are not generated. The β-keto tertiary alcohol boronate then hydrolyzes to afford β-keto tertiary alcohols with the $B(OH)_3$ elimination promoted by the base.

In conclusion, we report a visible-light-driven 1,3-boronate rearrangement to ketones. Various 1,3-diketones react with aryl, alkenyl, and alkyl boronic acids to synthesize β-keto tertiary alcohols under metal-free conditions with excellent regioselectivity, chemoselectivity and functional group compatibility. The computational studies indicate that visible light irradiation overcomes the prohibitory high energy barrier for the boronate rearrangement to ketones. The discovery of boronate rearrangement in the excited state significantly expands current boronate rearrangements by thermal means and will lead to other synthetic applications of organoboronates.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Alcohols · Boron · Photochemistry · Reaction Mechanisms · Rearrangements

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