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Chemoselective Synthesis of α-Tertiary Hydroxy Oximes via Photochemical 1,3-Boronate Rearrangement

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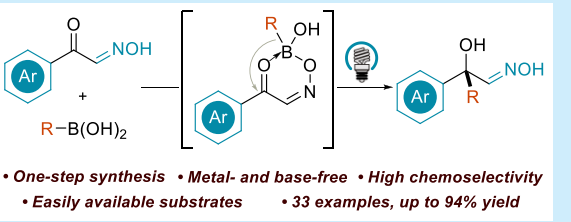
ABSTRACT: Tertiary alcohols with adjacent nucleophilic labile groups are prevalent in bioactive molecules but are challenging to synthesize. Herein we introduce a direct, protecting group-free method to access α-tertiary hydroxy oximes via photochemical 1,3-boronate rearrangement. This reaction delivers high yields (up to 94%) using readily available boronic acids, is scalable to gram quantities, and allows for further derivatization to other nitrogen-containing molecules.



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The construction of quaternary centers holds significant interest due to their increased three-dimensional complexity.[1] Tertiary alcohols are particularly attractive due to their promising bioactivity, such as tyrosinase inhibitors and muscarinic receptor antagonists, which display valuable therapeutic effects in chronic obstructive pulmonary disease and Parkinson's disease (Scheme 1a).[2] Traditional methods for constructing these tertiary alcohols bearing neighboring nucleophilic labile functional groups often rely on multistep protection/deprotection sequences to safeguard the nucleophilic labile groups, hindering their overall efficiency.[3] While direct addition to readily available ketones offers a more concise approach, achieving chemoselectivity becomes a significant challenge.[4] Classical strategies employing Grignard and trimethyl aluminum reagents can achieve chemoselective ketone addition, but limitations in reaction conditions (strong basic environment) and substrate scope (specific types of tertiary alcohols) restrict their broader applicability.[5] Therefore, developing a novel efficient methodology for introducing tertiary alcohols adjacent to nucleophilic labile functional groups remains a critical objective (Scheme 1b).

Organoboron compounds, known for their mild nucleophilicity,[6] have found extensive applications in the transition-metal-free coupling,[7] C−N cross-coupling,[8] borylation,[9] and distal functionalization.[10] Oximes and their derivatives are renowned for their versatile properties, including nucleophilic labilities, making them valuable synthetic handles and fundamental building blocks in diverse bioactive compounds.[11] However, constructing α-tertiary hydroxy oximes presents a unique challenge due to the challenges above.[4,12,13] Inspired by the photosensitivity of tetracoordinate boron,[14] and our previous work on visible-light-driven 1,3-boronate rearrangement to ketones using enols as directing groups,[15] we envisioned incorporating oximes as directing groups to synthesize α-tertiary hydroxy oximes by 1,3-boronate rearrangement. This approach would overcome the limited

Scheme 1. Strategies for the Construction of Tertiary Alcohols Adjacent to Nucleophilic Functional Groups

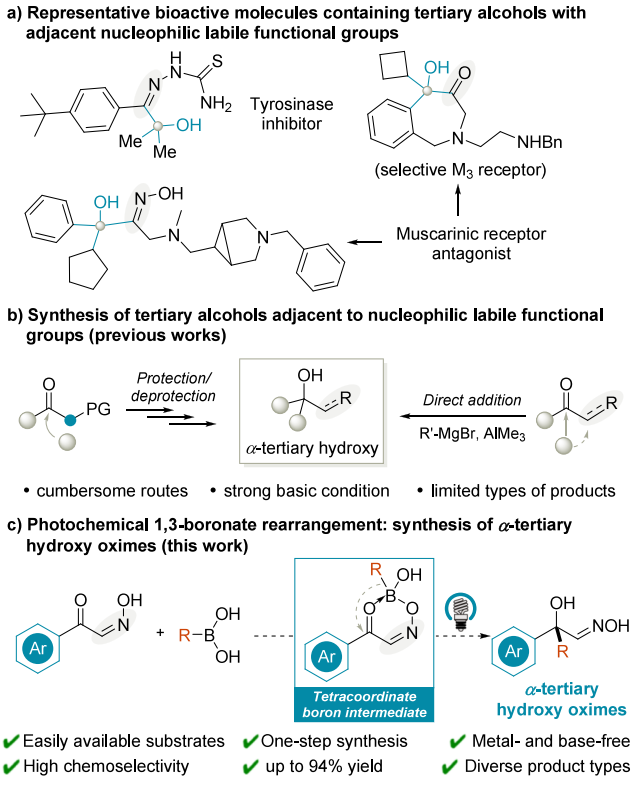

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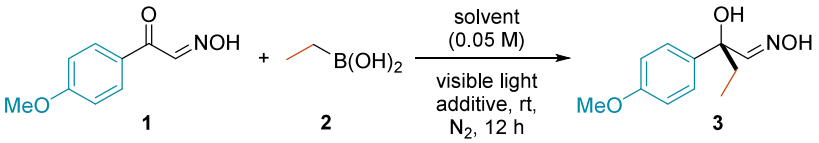
Table 1. Reaction Optimization



Entry[a]	Condition	1 Conv.[b]	Yield of 3[b]
1	427 nm LED, DMSO	10%	<5%
2	427 nm LED, DCM	79%	20%
3	427 nm LED, MeOH	<5%	<5%
4	427 nm LED, HFIP	<95%	60%
5	456 nm LED, HFIP	50%	27%
6	390 nm LED, HFIP	>95%	(79%)[c]
7	Entry 6, DABCO[d]	93%	33%
8	Entry 6, AcOH[e]	87%	64%
9	Entry 6, w/o light	>5%	<5%

[a]Reaction conditions: **1** (0.1 mmol. 1.0 equiv), **2** (0.3 mmol, 3.0 equiv) in 2.0 mL of solvent under N_2 with 20 W LED irradiation at rt for 12 h, unless otherwise noted. [b]Conversions and yields were determined by ^{1}H NMR analysis. [c]Isolated yields are given in parentheses, [d]1,4-Diaza[2.2.2]bicyclooctane, 0.1 mmol. [e]Acetic acid, 0.1 mmol.

substrate scope of the current enol-directed boronate rearrangements to 1,3-diketones (Scheme 1c).

First, we used *p*-methoxy-substituted *α*-keto phenylacetaldoxime (**1**) and ethyl boronic acid (**2**) as model substrates, with 20 W 427 nm LED as the light source, to investigate the effect of reaction solvent (Table 1, entries 1−4; see Table S2 for details). No desired addition product (**3**) was detected in the polar solvent DMSO (entry 1). In the nonpolar solvent DCM, a 20% NMR yield of **3** was obtained, but the conversion of starting material **1** did not match the yield of the product **3** (entry 2). Protic solvent MeOH also failed to produce the desired product (entry 3). Pleasingly, in the more acidic protic solvent hexafluoro isopropanol (HFIP), the desired product **3** was obtained with a 60% NMR yield (entry 4). Optimizations of the light source were subsequently conducted (entries 5−6). The reaction was slowed down under longer wavelengths (456 nm LED, entry 5), whereas a shorter wavelength of 390 nm LED resulted in a significant improvement. **3** was afforded in 79% isolated yield after workup with aqueous NaOH and H_2O_2 (entry 6, see Table S9 for precautions during product purifications).[16] The addition of either acid or base inhibited the conversion of the reactant (entries 7−8, see Table S3 for details). A control experiment confirmed that the reaction requires visible light initiation (entry 9).

With the optimal conditions established, we next investigated the generality of the boronic acids (Scheme 2). Primary alkyl boronic acids, such as *n*-butyl, *n*-hexyl, *n*-hexenyl, and cyclopropylmethyl boronic acids afforded products **4**−**7** in yields ranging from 81% to 88%. Interestingly, when terminal *tert*-butoxycarbonyl (Boc)-substituted ethyl boronic acid was used, the target product underwent *in situ* ester exchange to form *γ*-lactone **8** in 34% yield. Both cyclic and acyclic secondary alkyl boronic acids afforded the target products **9**−**11** in yields of 62%−68%. Expanding the scope of organoboron reagents, we found that bench-stable potassium trifluoroborates can be employed as viable alternatives to boronic acids. Upon activation with a catalytic amount of $Sc(OTf)_3$,[17] these reagents delivered products **12**−**13** containing sterically congested quaternary centers in moderate yields (61% and 43%, respectively). Additionally, benzyl boronic acid afforded **14** in 42% yield. The reaction scope was further extended to include cyclohexenyl boronic acid, affording 1,1-disubstituted allyl alcohol **15** in 49% yield. This broadened substrate scope highlights the versatility of the method for both alkyl and alkenyl boronic acids.

Aryl boronic acids were also compatible under the reaction conditions. *o*-Tolyl boronic acid, with a methyl group at the *ortho* position that could hinder the reaction, provided the product **17** in 85% yield. Notably, aryl halides which normally induce side reactions in traditional transition-metal-catalyzed or Grignard reagent-mediated tertiary alcohol synthesis were well tolerated, affording products **18**−**20** with yields of 72% to 81%. Similarly, aryl boronic acids with strong electron-withdrawing substituents, such as *p*-trifluoromethylphenyl and *p*-nitrophenyl boronic acids, afforded products **21**−**22** in good yields (76% and 65%, respectively). To demonstrate the broad functional group tolerance of this method, propylparaben, indomethacin, and fenofibrate, drugs containing nucleophilic labile esters and ketones, were converted into their corresponding *α*-hydroxybenzaldehyde oxime derivatives (**23**−**25**), followed by the standard reaction conditions. These transformations proceeded in high yields (73−94%, Scheme 2).

Electron-donating substituents on the *α*-keto phenylacetaldoximes improved their reactivity, likely due to their ability to form a more favorable interaction with the electron-deficient boronic acids. This is reflected in the good yields (52%−92%) obtained for substrates with cyclopentyloxy (**26** and **27**), benzyloxy (**28** and **29**), methyl (**30**), and *p*-chlorophenoxy (**31**) substituents at the *para*-position. Even the polysubstituted substrate with a *p*-methoxy and an *o*-fluoro substituent afforded product **32** in 68% yield. Conversely, substrates with electron-withdrawing groups at the *meta*-position of the ketone moiety (**33**−**35**) displayed a clear decrease in yield (from 77% to 26%) as the electron-withdrawing ability increased.[18] This further supports the notion that electron-rich oximes participate in more favorable interactions with organoboronic acids, leading to enhanced reactivity (Scheme 3).

Monitoring the reaction by UV−vis spectrometry indicated the oxime **1** and boronic acid **2** mixture exhibited a bathochromic shift in the absorption spectra beyond 450 nm, while the mixture of the oxime ether **36** and boronic acid **2** showed no significant change. This indicates that the oxime's

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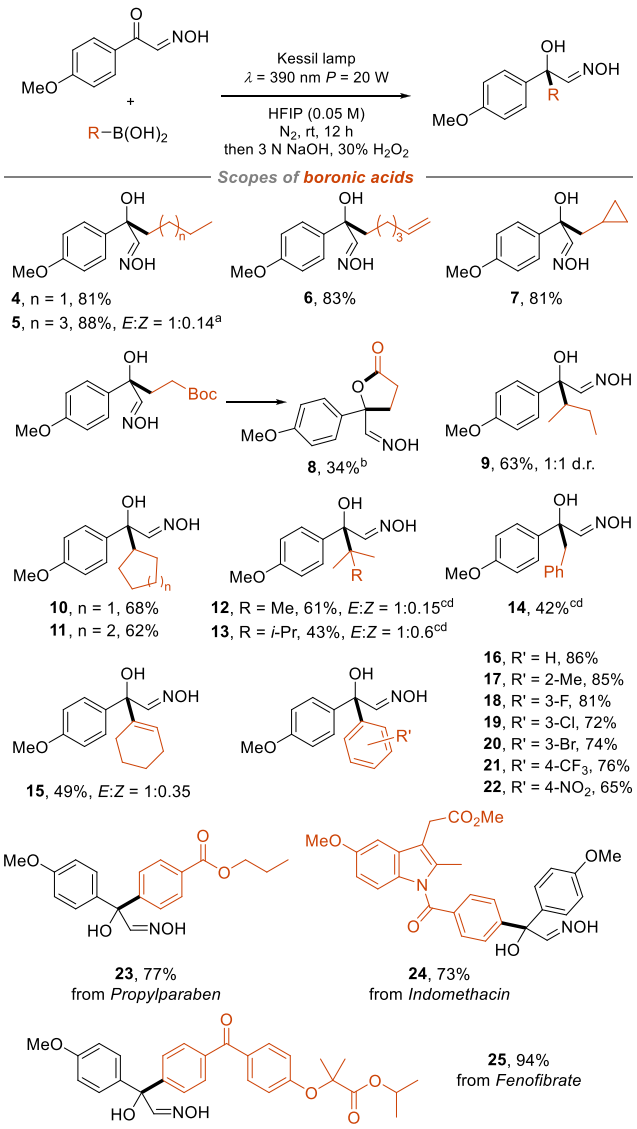
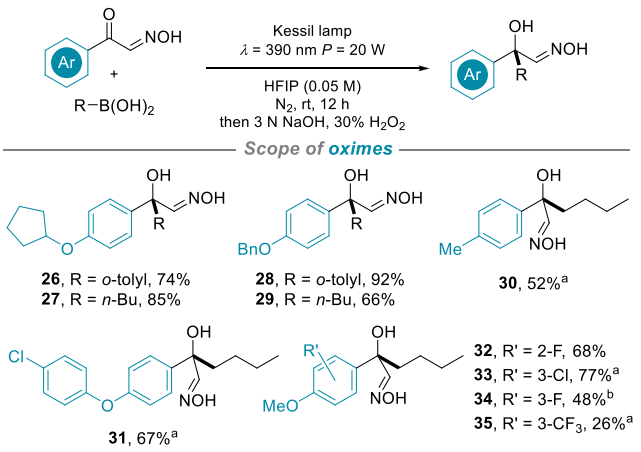
Scheme 2. Scope of Boronic Acids



Reaction conditions: **1** (0.10 mmol) and boronic acid (0.30 mmol) in HFIP (2 mL) with 20 W 390 nm irradiation at room temperature for 12 h under nitrogen atmosphere. Isolated yields were reported. [a]Oximes are in the *E*-configuration unless otherwise noted. [b]20 h. [c]18 h. [d]With 30 mol % $Sc(OTf)_3$ addition, RBF_3K instead of $RB(OH)_2$.

Scheme 3. Scope of Oximes



Reaction conditions: oxime (0.10 mmol), *n*-butylboronic acid or *o*-tolyl boronic acid (0.30 mmol), in HFIP (2 mL) with 20 W 390 nm irradiation at room temperature for 12 h under nitrogen atmosphere. Isolated yields were reported. [a]18 h. [b]20 h. Oximes are in *E*-configuration unless otherwise noted.

hydroxy group is crucial for interactions with boronic acids (Scheme 4a). A control experiment using oxime ether **36** and boronic acid **2** under the standard reaction conditions yielded no product, further confirming the requirement of the oxime hydroxy group for the reaction to proceed (Scheme S8).

To characterize the potential tetracoordinate boron intermediate formed between oximes and boronic acids, we conducted an *in situ* ^{11}B-NMR exchange experiment using oxime **1** and boronic acid **22b** in HFIP. The high-field signal at δ 6.44 ppm confirmed the formation of the intermediate **37** (Scheme 4b). The association constant between the two, calculated using the Benesi−Hilderbrand method, was found to be 4.68 M^{-1} (Figures S4−5). Additionally, high-resolution mass spectrometry detected a positive ion signal corresponding to the complex formed between oxime **1** and boronic acid **4b** after losing a water molecule (Scheme S9). These findings collectively support the formation of a tetracoordinate organoboronate complex during the reaction.

Next, we explored the mechanistic details of the reaction. A thermal initiation experiment at 60 °C without light did not produce any desired product nor with extra AIBN as radical initiator (Schemes S5−6), highlighting the requirement for visible light initiation. To further investigate the possibility of a radical pathway, we included radical scavengers (TEMPO or BHT) under standard reaction conditions. The reaction proceeded smoothly without a significant decrease in yield (Scheme 4c, upper panel). Furthermore, the radical clock experiment using cyclopropylmethyl boronic acid yielded the product **7** in 81% yield, without observing the ring-opening products (Scheme 4c, lower panel, Scheme S7). Moreover, the experiment conducted using a preformed boronate complex (synthesized from oxime **1** and tributyl borane) and another oxime (**30a**) afforded no crossover products (Figures S6−7 and Schemes S10−11).[19] These results suggest that the reaction does not proceed through an intermolecular radical mechanism. Based on the mechanistic investigations above, we propose the following reaction mechanism (Scheme 4d). α-Keto phenylacetaldoxime first forms a tetracoordinate boron complex *in situ* with boronic acids. Visible light irradiation excites this complex to its excited state, facilitating an intramolecular 1,3-migration to the ketone and ultimately generating the α-tertiary hydroxy oxime product.

α-Tertiary hydroxy oxime **4** can be readily obtained on a gram-scale (1.13 g, 68% yield) and further elaborated into structurally diverse molecules, highlighting the versatility of this method (Scheme 5). Treatment with cyanuric chlorides promoted dehydration to afford 1,1-disubstituted alkene **38** in 80% yield. This transformation showcases the potential for introducing unsaturated functionalities, commonly found in bioactive molecules,[20] onto the α-tertiary hydroxy oxime scaffold. Alternatively, selective reduction of the oxime moiety with sodium cyanoborohydride and aqueous HCl furnished hydroxylamine derivative **39** in 80% yield. Hydroxylamine moieties are valuable synthetic handles due to their prevalence in pharmaceuticals and other bioactive compounds.[21] Notably,

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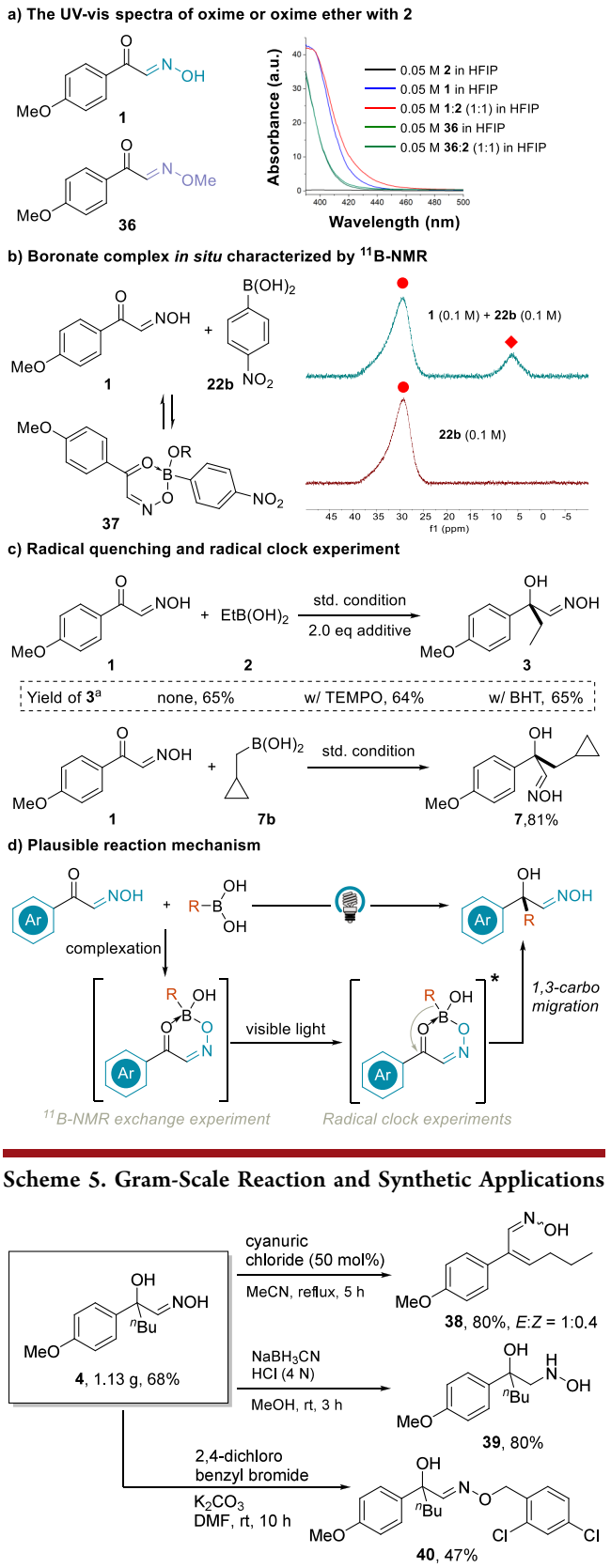
Scheme 4. Mechanistic Investigations and Proposal



Scheme 5. Gram-Scale Reaction and Synthetic Applications

the reaction of **4** with 2,4-dichloro benzyl bromide provided oxime ether **40** (47% yield), a common structural motif encountered in antifungal drugs.[22] The successful transformation of **4** into these valuable building blocks emphasizes the synthetic utility of this method for accessing diverse chemical scaffolds with potential biological applications.

In conclusion, we have established an efficient approach for synthesizing tertiary alcohols with adjacent nucleophilic labile oxime functionalities. This one-step chemoselective method leverages an oxime-directed, photochemical 1,3-boronate rearrangement. The reaction exhibits broad functional group tolerance and delivers high yields. Mechanistic studies support an intramolecular migration pathway, which is consistent with our previous work on a similar paradigm.[15b] This photochemical strategy, initiated by chelation-assisted boronate rearrangement, holds significant promise for expansion.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c02353.

Experimental procedures, reaction optimizations, detailed mechanistic investigations, and new compound characterizations. (PDF)

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Notes

The authors declare no competing financial interest.

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(18) Attempts to apply the reaction to 2-oxopropanal oximes using both ethyl and phenyl boronic acids under standard or shorter wavelength irradiation yielded no desired products (see Table S4 and Figure S1). These results indicate that an α-aryl ketone oxime with a visible light-absorbing aromatic ring is essential for this reaction.

(19) Attempts to isolate the boronate complex formed between oximes and boronic acids were unsuccessful due to its instability.

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