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Photochemical 1,3-boronate rearrangement enables three-component N-alkylation for α-tertiary hydroxybenzylamine synthesis

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Hydroxybenzylamines are prevalent in drugs and bioactive molecules, including various antimalarial and anticancer drugs. α-tertiary alkylation of amines impacts drug-target interactions significantly through their influence on basicity and lipophilicity. Traditional *N*-alkylation methods, especially for α-tertiary amines, suffer from limitations due to high energy barriers from steric hindrance. In this work, we leverage visible light irradiation to enable the organoboronic acid addition to sterically hindered ketimines in the excited state. Notably, it overcomes the limitations of the well-explored Petasis reaction, which is restricted to aldimines due to the high energy barrier associated with ketimines (51.3 kcal/mol). This three-component coupling of aliphatic amines, *o*-phenolic ketones, and organoboronic acids delivers diverse α-tertiary *o*-hydroxybenzylamines (77 examples, yields up to 82%) with broad functional group tolerance. The light-driven 1,3-boronate rearrangement introduces quaternary carbon centers adjacent to the amine moiety to enable late-stage functionalization of complex bioactive molecules. This versatile tool for complex amine synthesis holds significant potential for accelerating advancements in drug discovery, chemical biology, and materials science research.

Amines are vital in bioactive molecules and present in over 40% of drug candidates[1]. Among these, *o*-hydroxybenzylamines are prevalent in drugs and bioactive molecules, including the antimalarial drug Amodiaquine, the anticancer drug Topotecan, and the Mdm2-MdmX E3 ligase inhibitor MMRi-64 (Fig. 1a)[2–4]. Previously, these compounds were synthesized via the three-component Mannich reaction involving phenols, amines, and aldehydes, which is also referred to as the Phenolic Mannich reaction. However, it is difficult to prepare α-tertiary *o*-hydroxybenzylamines due to the low reactivity of ketimines. Alternatively, nucleophilic additions to *o*-hydroxyaryl ketimines yield α-tertiary *o*-hydroxybenzylamines. However, this method typically requires the use of highly reactive organometallic reagents and pre-preparation of ketimines, which may complicate the experimental procedure and restrict the substrate scope.

α-tertiary amines offer distinct advantages due to their significant influence on basicity and lipophilicity, ultimately impacting their interaction with biological targets (Fig. 1b)[5–7]. Precise control over the substitution pattern of the amine moiety is crucial for optimal drug-target interactions[8,9]. This is exemplified by a doubled lipophilic efficiency (LE) observed upon incorporating a methyl group into a Bromodomain and Extra-Terminal motif (BET) inhibitor[10,11], and a ninefold anti-cancer potency improvement of the drug Veliparib (PARP1 inhibitor for ovarian cancer) upon introducing a methyl group at the α-position of the amine[12,13]. Notably, the α-tertiary amine structural motif

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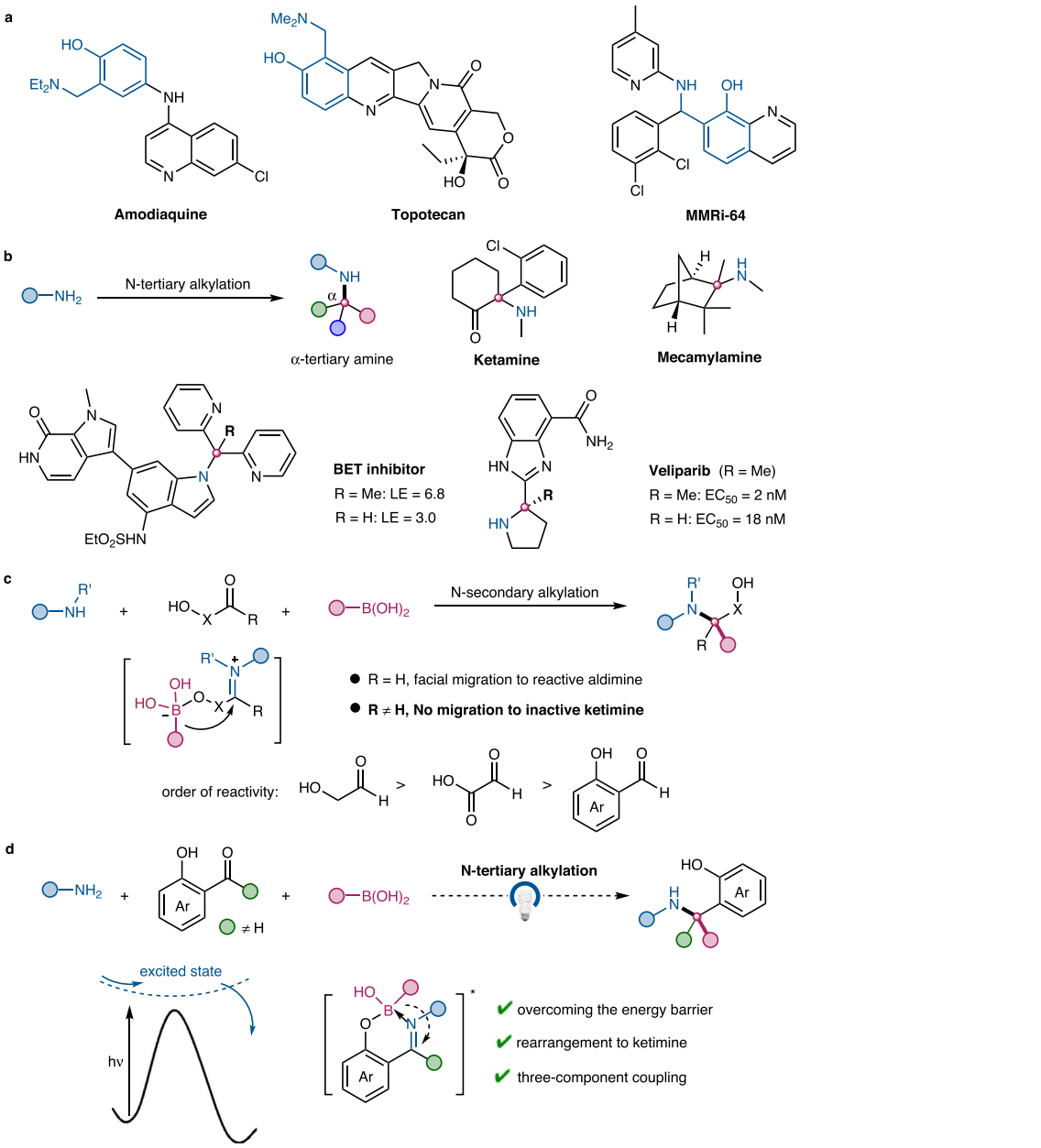

Fig. 1 | Three-component *N*-alkylation via photochemical 1,3-boronate rearrangement to synthesize α-tertiary *o*-hydroxybenzylamines. a The importance of *o*-hydroxybenzylamine motifs. **b** The critical role of *N*-tertiary alkylation of primary amines. **c** The challenge of *N*-tertiary alkylation via Petasis reaction (previous work). **d** Our strategy for *N*-tertiary alkylation via photochemical Petasis-type reaction (this work).

is frequently encountered in established pharmaceuticals such as Ketamine and Mecamylamine[14,15]. Despite the widespread applications of α-tertiary amines in natural products and drug discovery[16–19], established methods for efficient *N*-alkylation often face limitations. A common approach, Hofmann-type alkylation, suffers from steric hindrance issues when employing bulky alkylating agents. This steric hindrance raises the reaction's energy barrier, necessitating the use of highly reactive (and often less versatile) alkylating reagents[20–22]. While a two-step imine formation and alkylation sequence offer a significant advantage over Hofmann alkylation by circumventing steric hindrance and providing greater access in α-tertiary amine synthesis, it often relies on the utilization of highly reactive organometallic reagents such as Grignard and organolithium reagents as alkylating agents, which greatly limits the substrate scope of the reaction[23].

Organoboronic acids have gained prominence in organic synthesis due to their advantageous properties: readily available, air and moisture-stable, exhibiting low toxicity, and demonstrating compatibility with a broad range of functional groups[24,25]. Their prevalence stems from their effectiveness in transition-metal-catalyzed cross-coupling reactions for drug discovery and material science, exemplified by the well-established Suzuki–Miyaura coupling[26,27]. However, the ongoing pursuit of cost-effective and environmentally benign catalysts remains a significant focus in this field[28]. Metal-free processes utilizing organoboronic acids are particularly attractive as they eliminate the need for expensive metal removal procedures and potential catalyst residues within the final product[29–31]. A noteworthy illustration is the Petasis reaction, a metal-free approach for *N*-secondary alkylation that employs organoboronic acids (Fig. 1c)[32,33]. This strategy leverages amines and aldehydes with strategically placed directing groups to facilitate the rearrangement of boronic acids to the in situ generated aldimines. Among the aldehydes with different directing groups, the hydroxy group is the most reactive while the phenol is the least

reactive[33]. Currently, the Petasis reaction has found widespread applications in *N*-secondary alkylation with aldehydes. However, it encounters significant challenges when applied to *N*-tertiary alkylation involving ketones. The sterically hindered nature of ketimines leads to prohibitively high energy barriers associated with the rearrangement, rendering the thermal Petasis reaction unsuitable for *N*-tertiary alkylation, particularly with the less reactive phenols as directing groups[34,35].

To circumvent the inherent limitations associated with current Petasis reactions for α-tertiary *o*-hydroxybenzylamine synthesis, especially the high energy barriers imposed by ketimines, we investigated the potential of light irradiation. Leveraging our established expertise in light-mediated boronate rearrangements to 1,3-diketones[36], we explored the applicability of this strategy to the more challenging scenario of ketimines, known for their inherently lower reactivity[23]. This work presents a three-component photochemical method for the efficient synthesis of α-tertiary *o*-hydroxybenzylamines from readily available aliphatic amines, *o*-phenolic ketones, and organoboronic acids (Fig. 1d). It capitalizes on the utilization of *o*-phenolic ketones and versatile organoboronic acids (unreactive under thermal Petasis conditions), enabling the streamlined synthesis of valuable α-tertiary *o*-hydroxybenzylamines.

Results

The discovery of phenol-ketimine boronate complex and reaction development

To assess the feasibility of light-mediated *N*-tertiary alkylation, we initially explored the reaction using *o*-hydroxy acetophenone imine **1** (Fig. 2a). Treatment of *o*-hydroxy ketimine **1** with triethylborane afforded *o*-hydroxy ketimine boronate complex **2** (details provided later). Notably, under typical Petasis reaction conditions, *o*-hydroxy benzaldimines and triethylboranes form a similarly chelated *o*-hydroxy aldimine boronate complex. However, the current Petasis reaction lacks the ability to drive boronate rearrangement of phenol-directed aldimines, let alone the even less reactive ketimines—a limitation this work aims to address[37].

X-ray crystallographic analysis confirmed the bidentate coordination of the *o*-hydroxy and ketimine functionalities in complex **2** (B–O bond length: 1.50 Å, B–N bond length: 1.60 Å). This observation suggests a covalent B–O bond and a dative B–N bond. Further analysis employing Höpfl's equation revealed a 71% tetrahedral character for complex **2**[38,39]. Building upon our previous success with light-induced boronate rearrangements in 1,3-diketones, we evaluated the light absorption properties of complex **2**. The observed visible light absorbance (Fig. S1) suggested a potential for altered reactivity in the excited state, overcoming the ground-state energy barrier for the desired boronate rearrangement. To test this hypothesis, complex **2** was irradiated with blue light (427 nm). Gratifyingly, this approach triggered a 1,3-ethyl migration, resulting in the formation of *o*-hydroxybenzylamine **3** in 70% yield.

Next, we aimed to streamline the process by directly generating the boronate complex from readily available organoboronic acids rather than trialkylboranes. Treatment of ketimine **1** with cyclohexylboronic acid (**1c**) led to the formation of a new boronate complex, which was confirmed by the appearance of new peaks in the ^{1}H NMR spectrum and a distinct peak at 7.57 ppm in the ^{11}B NMR spectrum (Figs. 2b and S2–S3). Additionally, mass spectrometry analysis (Fig. S4) indicated water elimination upon mixing **1** and **1c**. Notably, subsequent irradiation of this in situ-generated mixture with blue light (427 nm) in methanol afforded compound **5** (68% yield) via a 1,3-cyclohexyl migration. To highlight the versatility of our method, we expanded its scope to include commercially accessible alkyl trifluoroborates and boron pinacol esters. Alkyl trifluoroborates demonstrated comparable reactivity to boronic acids, affording product **5** in 64% yield with catalytic $Sc(OTf)_3$. Although boron pinacol esters required slightly more stringent conditions, such as extended irradiation and the addition of catechol, they produced **5** in respectable yields of 43% (see Table S2 for details). These results underscore the broad applicability of our approach to a variety of organoboron sources.

We further investigated the three-component coupling in one-pot involving amine **1a**, *o*-hydroxy acetophenone **1b**, and organoboronic acid **1c** (Fig. 2c). Gratifyingly, this photochemical *N*-tertiary alkylation in methanol yielded the desired three-component coupling product α-tertiary *o*-hydroxybenzylamines **5** in 65% isolated yield, without undesired two-component product from organoboronic acid addition to ketones[36]. Control experiments confirmed the requirement for light

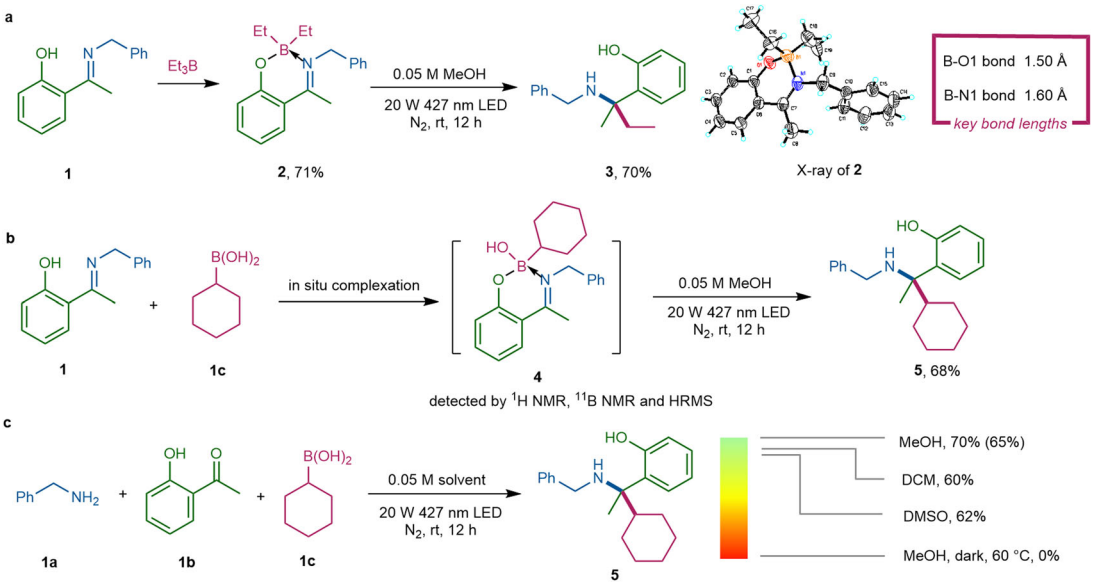

Fig. 2 | The discovery of phenol-ketimine boronate complex and photochemical reactivity. a Two-step ketimine formation and photochemical alkylation with trialkylborane. **b** Two-step ketimine formation and photochemical alkylation with organoboronic acids. **c** Three-component coupling of aliphatic amines, *o*-phenolic ketones, and organoboronic acids. Reaction conditions: amines (0.10 mmol), *o*-phenolic ketones (0.10 mmol), and boronic acids (0.20 mmol) in MeOH (2.0 mL) with 20 W 427 nm LED irradiation at room temperature for 12 h under N_2 atmosphere. Yields were determined by ^{1}H NMR analysis and isolated yields were in parentheses.

irradiation, as heating the mixture without light resulted in no conversion.

Substrate scopes

Having identified the optimal reaction conditions, we explored the versatility of the three-component *N*-tertiary alkylation reaction (Fig. 3). The method readily accommodates a broad range of primary aliphatic amines, as demonstrated by the 75% yield of product **6** obtained from phenylethylamine. Functional group compatibility on the amine substrates was excellent. Unsaturated heterocycles containing furan, thiophene, pyridine, and indole motifs were successfully alkylated (**7**–**10**, yields 70–76%). Saturated heterocycles like morpholine (**11**, 82% yield) and piperazine (**12**, 71% yield) were also well-tolerated (refer to Fig. 3 for details).

This metal-free method offers a significant advantage over traditional approaches by preserving sensitive functional groups susceptible to decomposition with organometallic reagents. Notably, cyano, ester, halide, and acetal groups are all well-tolerated, exemplified by the syntheses of amines **13**–**16** (yields 51–76%). Substrates bearing free hydroxyl and amino functionalities were efficiently transformed (**17**–**19**, yields 62–77%), further demonstrating the method's broad applicability. The compatibility extends to click chemistry precursors, enabling the incorporation of azide and alkyne functionalities (**20**–**21**, yields 70–72%). Remarkably, the reaction tolerated a pharmaceutically relevant difluoromethyl group (**22**, 59% yield). This photochemical strategy also applies to industrially relevant substrates like methylamine, ethylamine, and propylamine, delivering valuable α-tertiary amines **23**–**25** in good yields (67–74%).

The method demonstrates remarkable versatility with a broad range of *o*-phenolic ketones (Fig. 4). It tolerates both electron-withdrawing (fluoro, chloro, and bromo) and electron-donating (methyl, methoxy) substituents on the aromatic ring, as exemplified by the syntheses of amines **26**–**30** in good yields (61–73%). Substitutions at various positions (ortho, meta, and para) proceed smoothly, affording products **31**–**36** (yields 51–72%). Additionally, the reaction accommodates ketones bearing alkyl (ethyl, *n*-propyl, *n*-butyl, and phenylethyl) and benzyl substituents on the aryl group, providing amines **37**–**40** in yields of 53–57%. This broad scope highlights the ability of light irradiation to activate *o*-phenolic ketones, which are unreactive in thermal Petasis reactions, enabling the synthesis of these valuable α-tertiary amine products.

The reaction demonstrates broad applicability with various boronic acids (Fig. 4). Primary alkyl boronic acids (methyl, phenylethyl, *n*-hexyl) were readily incorporated, affording products **41**–**43** in good yields (68–74%). Notably, the method exhibits remarkable tolerance for functional groups within the boronic acid, including terminal alkenes, hydroxyls, and amines (compounds **44**–**47**, yields 51–74%). Using alkyl boronic acids with halogens yielded quaternary carbon-containing pyrroline and piperidine derivatives (**48** and **49**, respectively) in moderate yields (56% and 47%). Nicely, the reaction is

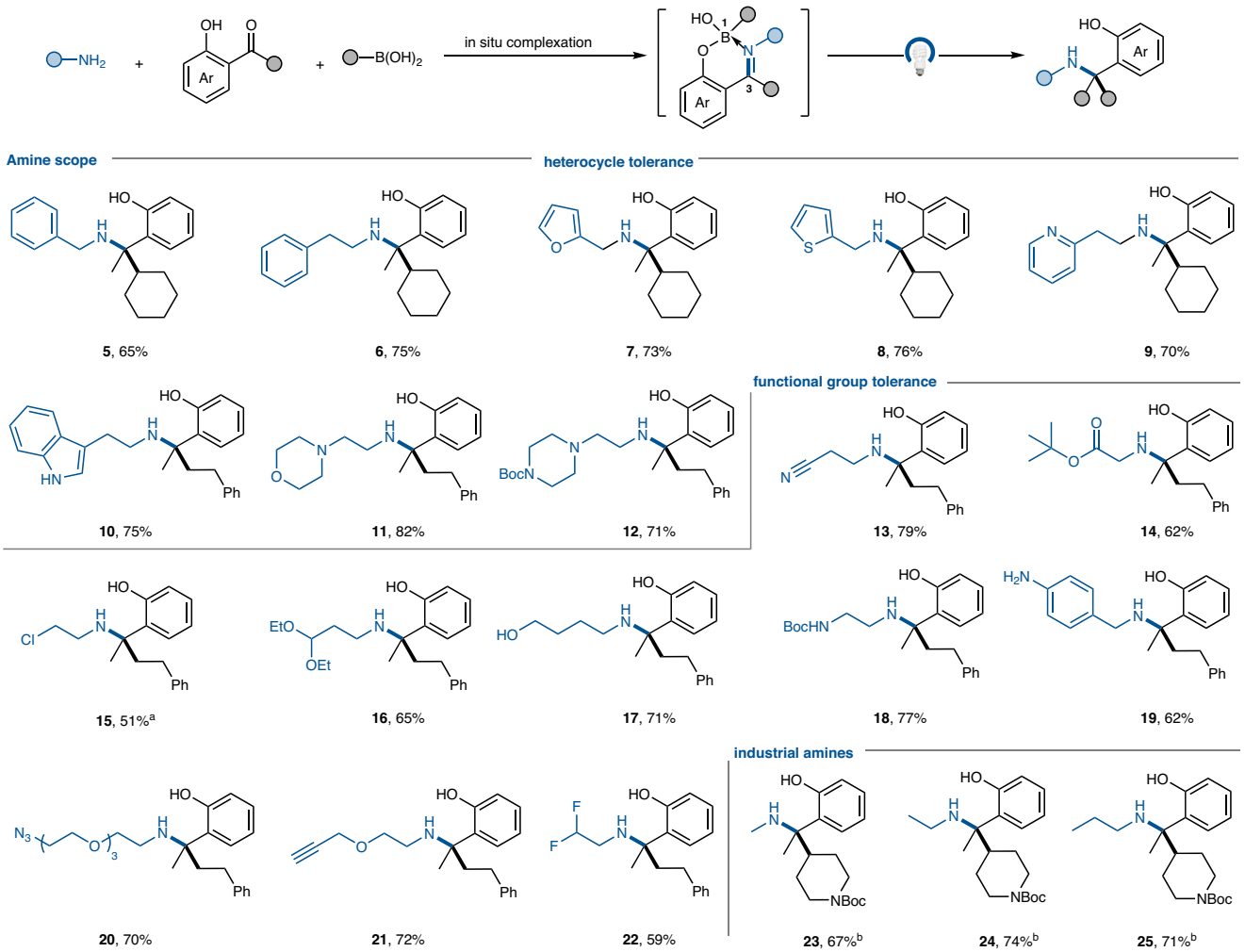

Fig. 3 | Scope of amines. Reaction conditions: amines (0.10 mmol), *o*-phenolic ketones (0.10 mmol), and boronic acids (0.20 mmol) in MeOH (2.0 mL) with 20 W 427 nm LED irradiation at room temperature for 12 h under N_2 atmosphere. Yields are those of isolated products. [a]Amine hydrochloride was used and 1.0 equiv. Et_3N was added. [b]3.0 equiv. amine was used. Boc *t*-butyloxycarbonyl.

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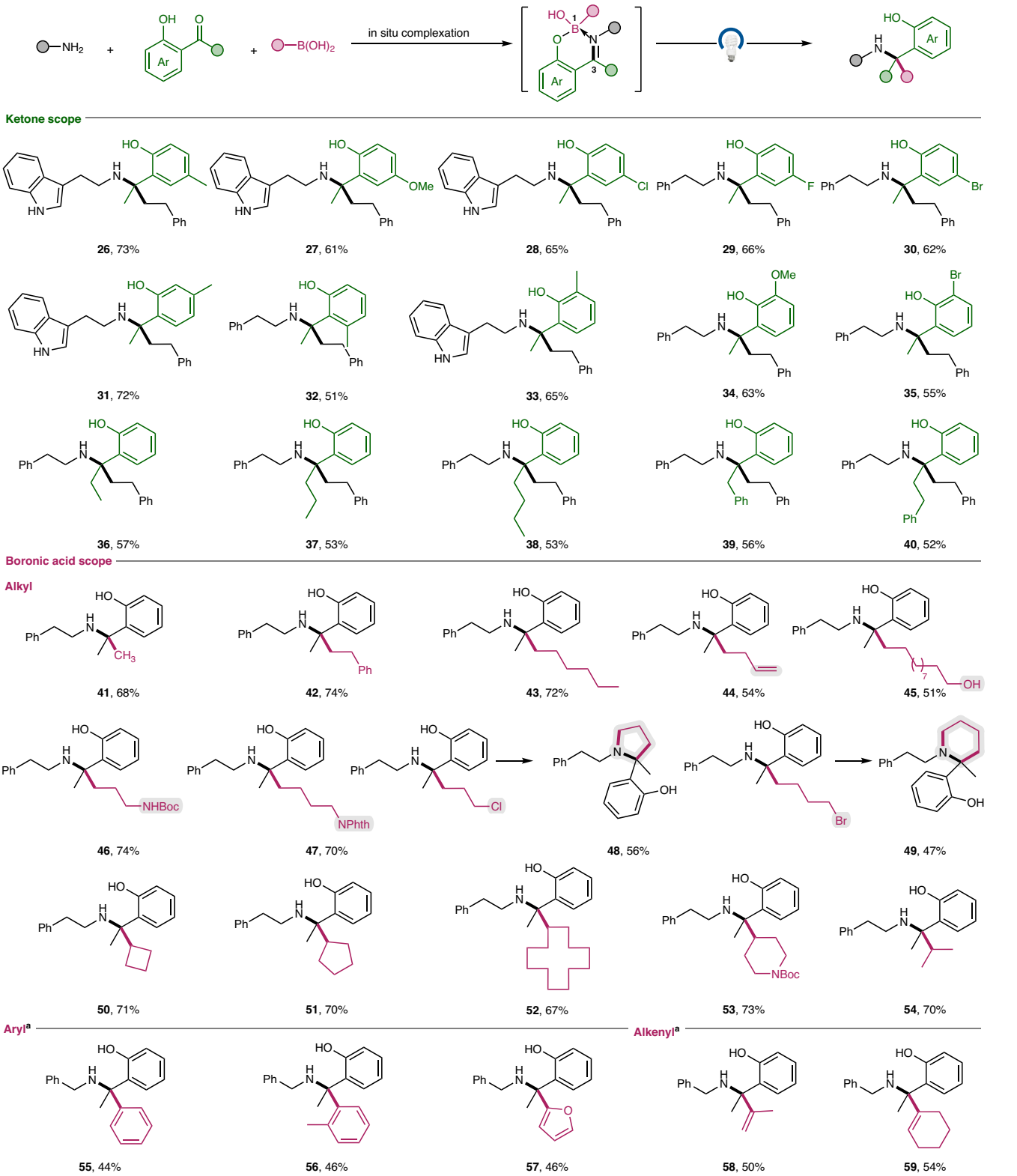

Fig. 4 | Scope of ketones and organoboronic acids. Reaction conditions: amines (0.10 mmol), *o*-phenolic ketones (0.10 mmol), and organoboronic acids (0.20 mmol) in MeOH (2.0 mL) with 20 W 427 nm LED irradiation at room temperature for 12 h under N_2 atmosphere. Yields are those of isolated products. Boc *t*-butyloxycarbonyl. NPhth phthalimidyl. [a]Ketimines and organotrifluoroborates were used as substrates, and 20 mol% $Sc(OTf)_3$ was added.

compatible with secondary cyclic alkyl boronic acids of varying ring sizes (4–12 members), providing products **50**–**53** in yields of 67–73%. Noncyclic alkyl boronic acids were equally well-suited, as exemplified by the 70% yield for product **54**. This scope emphasizes the capacity of light irradiation to activate alkyl boronic acids, typically unreactive in current Petasis reactions, thereby facilitating the synthesis of sp^3-C-rich amine scaffolds.

To expand the substrate scope beyond alkyl boronic acids, we investigated alternative boron derivatives. Aryl trifluoroborates, when combined with $Sc(OTf)_3$ as a Lewis acid, emerged as a promising

alternative. This combination enabled the efficient coupling of aryl trifluoroborates with ketimines, affording the desired *N*-alkylated products **55**–**57** in yields of 44–46%. Moreover, we successfully extended the reaction to alkenyl trifluoroborates, producing compounds **58**–**59** in 50–54% yields. This further demonstrates the versatility of our approach. It is noteworthy that these aryl and alkenyl addition products could not be obtained using radical-type Petasis reactions[40–42]. This highlights the unique advantages of our photochemical strategy, which offers an efficient route from alkyl, aryl, and alkenyl boronates to access these valuable compounds.

Mechanistic studies and proposed mechanism

To elucidate the reaction mechanism of the photochemical boronate rearrangement, we initially investigated the possibility of a radical pathway, common in photocatalytic transformations using organoboronates[43–52]. Interestingly, the presence of radical scavengers like TEMPO or BHT (Fig. 5a) did not affect the reaction yield, with both experiments delivering the desired product **5** in good yields (66% and 68%, respectively). Additionally, no ring-opening product (**61**) was observed when cyclopropyl methylboronic acid (**60c**) was employed as a radical clock (Fig. 5b), suggesting the absence of a free radical mechanism. Further insights came from triplet-state quenching experiments (Fig. 5c). The reaction yield under an oxygen atmosphere dropped significantly, affording product **5** in only 19% yield. The detection of significant singlet oxygen generation using α-terpinene in the reaction mixture under oxygen[53], coupled with the calculated triplet energy of the boronate complex (37.0 kcal/mol), strongly supports the involvement of the triplet state intermediate in the reaction. This triplet energy aligns well with the sensitization of ground-state oxygen to the singlet state (22.7 kcal/mol) (Figs. S6 and S7)[54].

Density functional theory (DFT) calculations at the M06-2X/6-31G level shed light on the mechanism (Fig. 5d)[55]. The rearrangement of the boronate complex **I** to ketimines (product **II**) in the absence of light is thermally unfavorable, requiring a substantial activation energy of 51.3 kcal/mol via transition state **TS1**[36]. This barrier is notably higher than the 44.9 kcal/mol barrier observed for the analogous

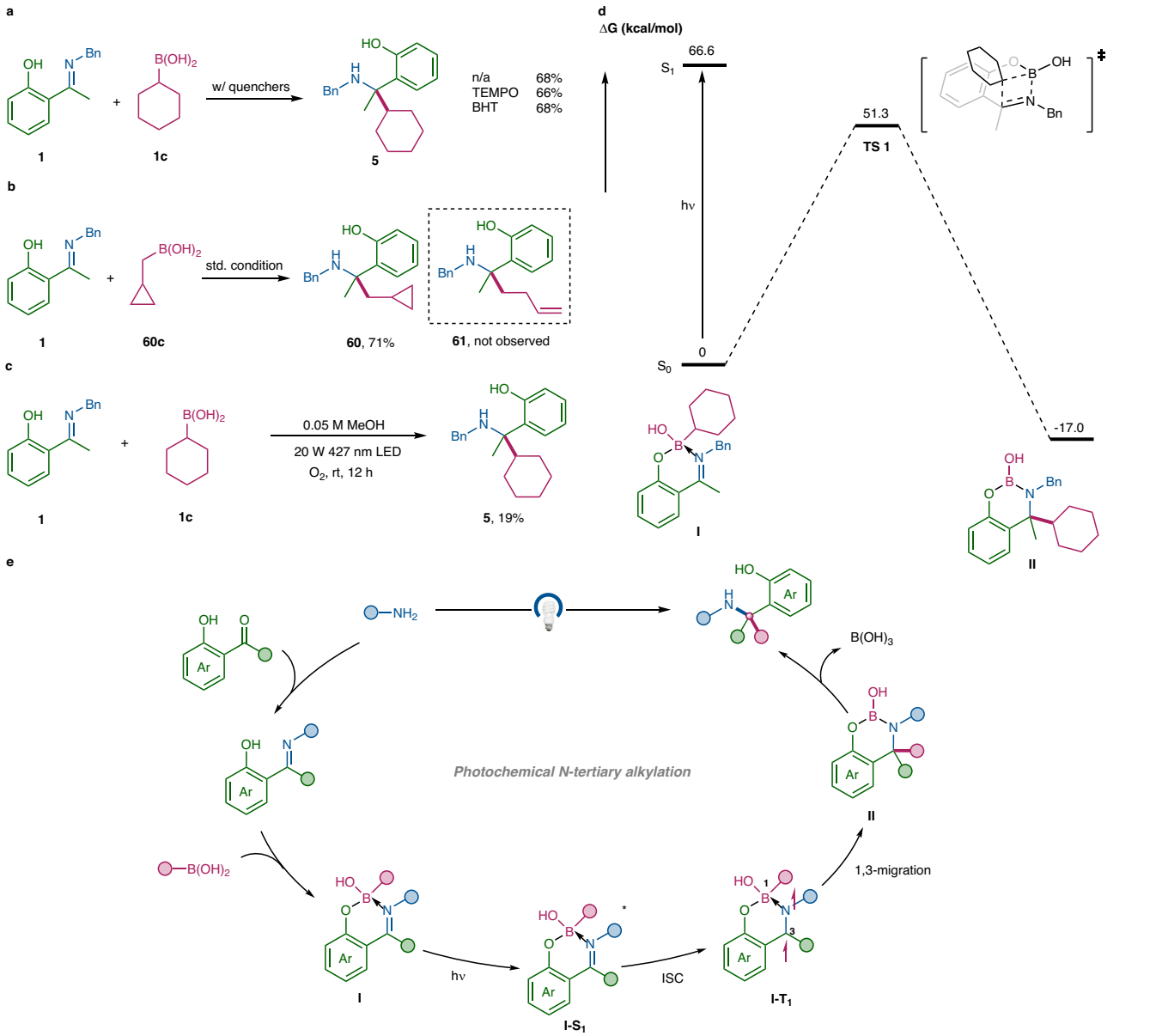

Fig. 5 | Mechanistic studies and proposed mechanism. a Radical quenching experiment. **b** Radical clock experiment. **c** Triplet quenching experiment. **d** DFT calculation. **e** Proposed mechanism.

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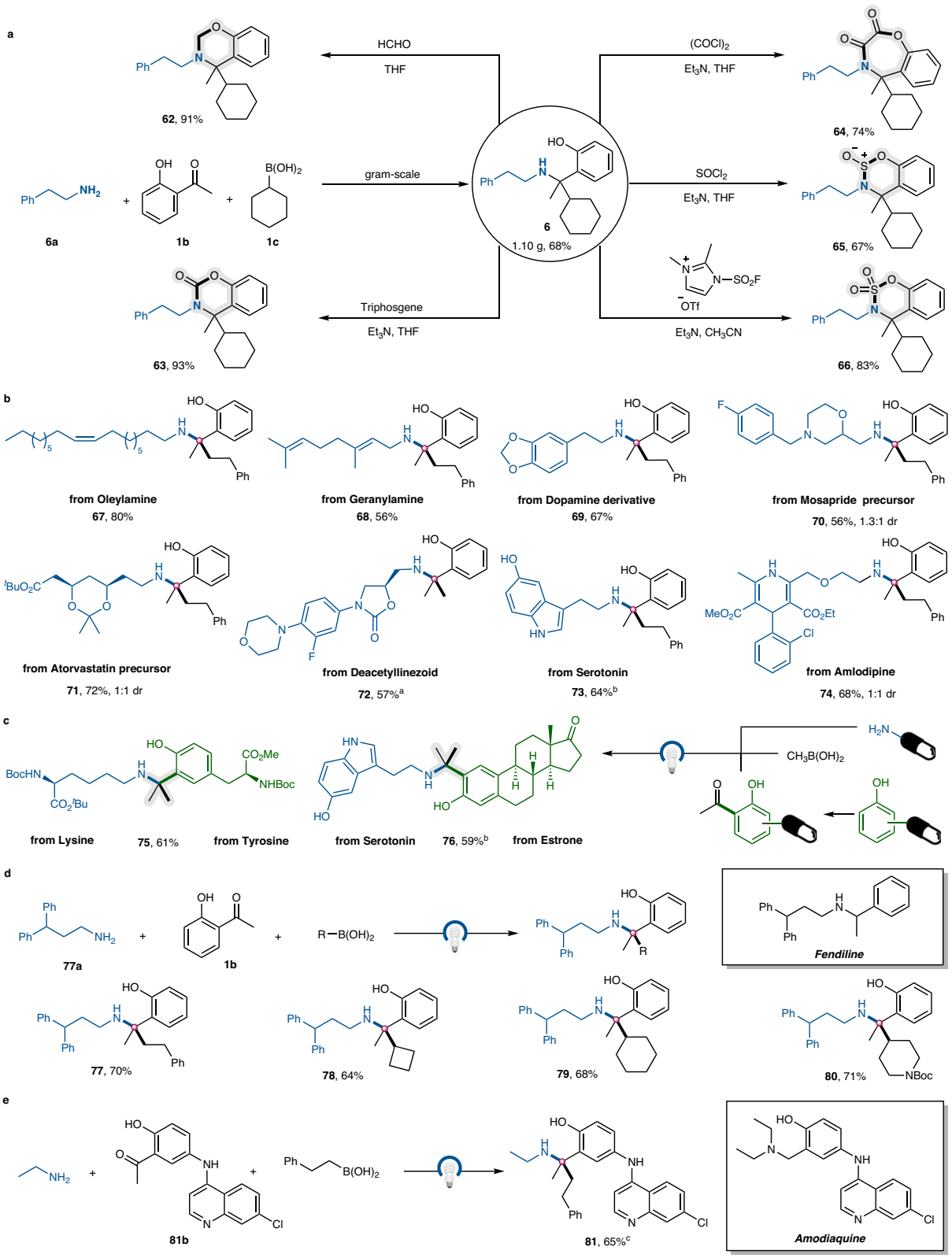

Fig. 6 | Synthetic applications. a Gram-scale reaction and product derivatizations. **b** Late-stage *N*-tertiary alkylation of bioactive amines. **c** Connecting bioactive amines with bioactive phenols via quaternary carbon centers. **d** Synthesis of Fendiline analogs bearing quaternary carbon centers. **e** Synthesis of Amodiaquine analogs bearing quaternary carbon centers. Reaction conditions: amines (1.0 equiv.), *o*-phenolic ketones (1.0 equiv.), and boronic acids (2.0 equiv.) in MeOH (0.05 M) with 20 W 427 nm LED irradiation at room temperature for 12 h under N_2 atmosphere. Yields are those of isolated products. [a]DCM/MeOH (1:1) as the solvent. [b]Amine hydrochloride was used and 1.0 equiv. Et_3N was added. [c]3.0 equiv. amine was used. Boc *t*-butyloxycarbonyl.

rearrangement to ketones, previously reported by us[36]. This disparity underscores the inherent challenge associated with *N*-tertiary alkylation. However, upon visible light excitation, the boronate complex **I** is promoted to an excited singlet state (**S1**) at 66.6 kcal/mol, thereby surmounting the high ground-state energy barrier and enabling the *N*-tertiary alkylation pathway (see Supplementary Data 1 for details).

Drawing on the aforementioned experimental and calculation investigations, we propose the following mechanism for the photochemical three-component *N*-tertiary alkylation (Fig. 5e). Primary amines condense with *o*-phenolic ketones to form ketimines in situ. These *o*-phenolic ketimines then coordinate with organoboronic acids to generate a tetrahedral boronate complex (**I**). Light absorption excites complex (**I**) to its singlet state (**I**–$\mathbf{S_1}$), followed by the intersystem crossing (ISC) to generate the triplet state (**I**–$\mathbf{T_1}$) at the C=N bond, based on quenching experiments. A key step follows through a minimal energy crossing point (MECP) for the structural rearrangement[36]. The carbon bonded to the boron migrates to the adjacent carbon (C3) of the ketimine, forming a new C–C bond and cleaving the C–B bond. This rearrangement yields an *o*-hydroxybenzylamine-coordinated boronate (**II**). Finally, hydrolysis liberates the desired α-tertiary *o*-hydroxybenzylamines product by eliminating $B(OH)_3$.

Synthetic applications

The reaction demonstrates scalability to gram-scale syntheses. For example, product **6** was successfully isolated in a commendable 68% yield (1.10 g) from the reaction of starting materials **6a**, **1b**, and **1c** (Fig. 6a). Importantly, the resulting α-tertiary *o*-hydroxybenzylamine products serve as valuable synthetic building blocks due to their amenability to further transformations with various electrophilic reagents. This allows for the generation of structurally diverse and high-value cyclic amine compounds. The versatility of this approach is exemplified by the efficient conversion (yields 67–93%) of the *o*-hydroxybenzylamine intermediate into compounds **62**–**66** using diverse reagents like formaldehyde, triphosgene, oxalyl chloride, thionyl chloride, and fluorosulfuryl imidazolium salt (Fig. 6a).

To showcase the method's potential for drug discovery[56,57], we employed the *N*-tertiary alkylation protocol for late-stage functionalization of commercially available bioactive molecules containing primary aliphatic amines (Fig. 6b). Under standard reaction conditions, a diverse range of natural products and drugs were efficiently transformed into their complex *N*-tertiary alkyl analogs in good yields (56–80%), which included Oleylamine, Geranylamine, a Dopamine derivative, a Mosapride precursor, an Atorvastatin precursor, Deacetyllinezoid, Serotonin, and Amlodipine (**67**–**74**) (Fig. 6b). Notably, this approach eliminates the need for post-reaction acid-base treatment or laborious heavy metal removal, simplifying the reaction work-up. This streamlined strategy offers medicinal chemists a valuable tool for accessing diverse pharmaceutical analogs through modular late-stage *N*-tertiary alkylation.

By integrating Friedel-crafts acylation of phenols, this approach provides a versatile strategy for constructing quaternary carbon linkages between amines and phenols (Fig. 6c). This approach aligns well with a prominent strategy in medicinal chemistry: exploring potential drug candidates by creating hybrid bioactive molecules from bioactive amines and phenols[58]. Under standard reaction conditions, we efficiently obtained hybrid bioactive molecules **75** and **76** in good yields (61% and 59%, respectively) from the coupling of Lysine and Tyrosine, and Serotonin and Estron, respectively.

Quaternary carbon centers are known to play a crucial role in pharmaceuticals[59]. Our method facilitates the incorporation of these valuable structural elements into drug analogs (Fig. 6d, e). For example, Fendiline, a calcium channel inhibitor to treat coronary heart disease, contains a tertiary carbon in the α-position of its amine group[60]. We demonstrate a streamlined, one-step synthesis of Fendiline analogs (**77**–**80**, yields 64–71%) featuring quaternary carbons using readily available starting materials (Fig. 6d). This approach offers a significant advantage compared to traditional methods. Similarly, Amodiaquine, an antimalarial drug, has a secondary carbon at the α-position of its amine[2]. Our method enables the efficient synthesis (65% yield) of Amodiaquine analog **81** containing a quaternary carbon in one step (Fig. 6e). This analog is expected to exhibit improved interactions with its biological targets due to the altered steric and electronic properties of the quaternary center.

Discussion

This work introduces a versatile, visible-light-driven approach for the efficient synthesis of α-tertiary *o*-hydroxybenzylamines, valuable building blocks in pharmaceutical research. By circumventing the high energy barriers associated with traditional *N*-alkylation methods, especially for sterically hindered ketimines, our metal-free strategy offers mild conditions, excellent functional group tolerance, and chemoselectivity. Leveraging light-induced 1,3-boronate rearrangement, we successfully synthesized 77 examples of α-tertiary *o*-hydroxybenzylamines from a broad range of alkyl, aryl, and alkenyl boronates with yields up to 82%. The introduction of quaternary carbon centers adjacent to the *o*-hydroxybenzylamine moiety opens new avenues for late-stage functionalization, providing medicinal chemists with a valuable tool for developing novel drug analogs. Beyond its applications in medicinal chemistry, this photochemical approach holds significant promise for a variety of research fields, including material science and chemical biology.

Methods

General procedure for photochemical *N*-tertiary alkylation

Amines (0.10 mmol, 1.0 equiv.), *o*-phenolic ketones (0.10 mmol, 1.0 equiv.), and organoboronic acids (0.20 mmol, 2.0 equiv.) were placed in a 4 mL clear-colored glass vial equipped with a magnetic stir bar. After 2.0 mL MeOH was added, the vial was sealed in the N_2 atmosphere and exposed to 20 W 427 nm LED (distance: 8.0 cm, irradiance intensity: 40 mW/cm^2) at room temperature with stirring for 12 h. Then, the reaction mixture was evaporated in a vacuum and purified directly by column chromatography to afford the product.

Data availability

The data that support the findings of this study are available within the article and its Supplementary Information files. Crystallographic data for compound **2** is available free of charge from the Cambridge Crystallographic Data Centre under references CCDC 2343061. The data can be obtained free of charge from the CCDC via https://www.ccdc.cam.ac.uk/structures/. Data supporting the findings of this manuscript are also available from the authors upon request.

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Author contributions

P.Z. and Y.C. designed the research, analyzed the data, and wrote the manuscript. P.Z., H.W., and R.S. performed the experiments. D.F. and Y.L. performed the computational studies. All authors discussed the results and commented on the paper.

Competing interests

The authors declare no competing interests.

Additional information

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