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Distal Amidoketone Synthesis Enabled by Dimethyl Benziodoxoles via Dual Copper/Photoredox Catalysis

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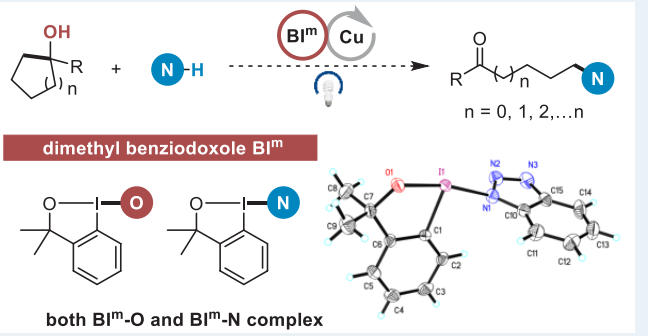
ABSTRACT: Herein, we report distal amidoketone and nitrogen-functionalized ketone syntheses from alcohols and N−H nucleophiles enabled by hypervalent iodine dimethyl benziodoxoles, BI^m. Dimethyl benziodoxoles BI^m dually activate alcohols and various N−H nucleophiles by forming key BI^m−O and BI^m−N complexes in which the BI^m−N complex is characterized by X-ray crystallography and computationally investigated. Readily available N−H nucleophile imides, sulfonamides, carbamates, triazoles, indazoles, and sulfoximines engage in photoredox/copper catalysis to synthesize distal amidoketones and nitrogen-functionalized ketones with excellent regioselectivity and chemoselectivity. This reaction scales up to grams, applies to late-stage complex molecule modification, and streamlines synthetic routes.



KEYWORDS: *hypervalent iodine, ketone, amidation, N−H nucleophiles, alkoxyl radical*

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Site-selective amination is desirable to introduce nitrogen-containing groups to the molecule of interest, and many bioactive molecules have both carbonyl- and nitrogen-containing groups in distal positions (Scheme 1a).[1] Compared to the adjacent functionalization of ketones by Mannich and Michael reactions,[2] the distal amination of ketones is challenging due to the lack of inductive or steric effects from existing ketones. The C(sp^3)-amination is challenging by transition-metal catalysis due to the facile β-hydride elimination of C(sp^3)-alkyl-metal intermediates.[3] To this end, radical-type C(sp^3)-amination by copper catalysis minimizes the β-hydride elimination and provides an attractive alternative.[4] Recently, the remote functionalization of ketones has been achieved from alcohols by alkoxy radical β-fragmentations.[5] However, remote amination from alcohols and N−H nucleophiles has not been achieved.[6]

Our previous studies on hypervalent iodine showed that benziodoxolones (BI) activated alcohols with the covalent I−O bond formation, in which BI−O complex formation reduced the single-electron oxidation of alcohols significantly for the facile alkoxy radical generation (Scheme 1b).[5a] However, the subsequent functionalization from alkoxyl radicals with hypervalent iodines was limited to carbofunctionalizations such as alkynylation, alkenylation, and cyanation.[7] Herein, we report the discovery of dimethyl benziodoxoles (BI^m) for the dual activation of alcohols and N−H nucleophiles with covalent BI^m−O and BI^m−N bond formations, of which the BI^m−N complex is essential for the copper-catalyzed radical-type C(sp^3)-amination. With BI^m, the dual photoredox/copper catalytic system achieved distal amidoketone and nitrogen-functionalized ketone synthesis from alcohols with N−H nucleophile imides, sulfonamides, carbamates, triazoles, indazoles, and sulfoximines (Scheme 1c).

We start the investigation with cyclopentanol **1**, for which ring-opening amination with the pharmacologically active phthalimide **2** would yield the δ-amidoketone **3**.[8] Using the readily available copper salt CuCl and 1,10-phen **L1**, the combination of Ph-Acr-Mes$^+$BF$_4^-$ (E^*_{red} = +2.08 V vs SCE in MeCN)[9] and potassium persulfates afforded no conversion (Table 1, entry 1).[10] Different hypervalent iodine reagents (HIR) BI−OAc **4**, BI−OH **5**, and PhI(OAc)$_2$ **6** were then screened;[5a,7,11] however, no conversion of **2** was observed either (entries 2−4). We hypothesized that these above HIR might not accommodate the copper catalysis for the C(sp^3)-amination due to the carboxylate ligands. We next tested the rarely explored dimethyl benziodoxoles BI^m−OAc **7** with the alkoxy ligand, of which the analogous Togni I reagent has shown compatibility with the copper catalysis for the trifluoromethylation.[12] Unexpectedly, the distal amidation

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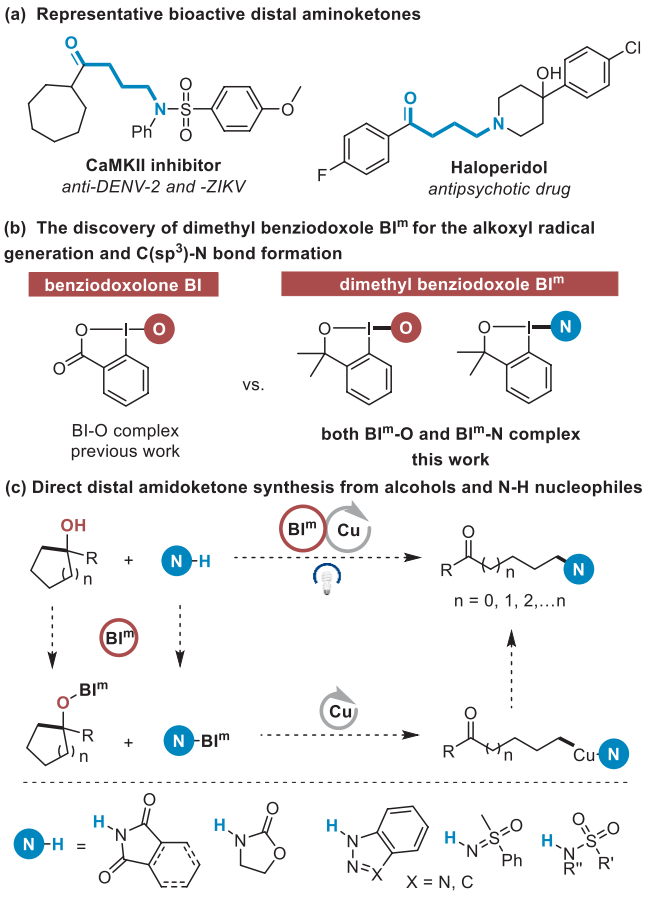
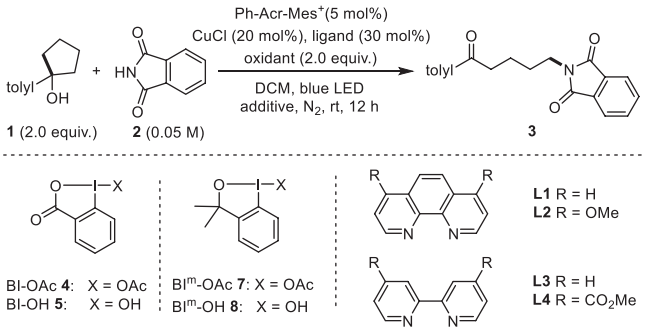
Scheme 1. Distal Amidoketone Synthesis from Alcohols and N−H Nucleophiles



adduct δ-amidoketone **3** was obtained in a modest 30% yield (entry 5). The switch of BI^m−OAc **7** to BI^m−OH **8** increased the yield of **3** to 50% with improved conversion of **2** (entry 6). Different copper salts and ligands **L2**−**L4** were next screened, and 4-CO_2Me-substituted bipyridyl ligand **L4** gave an improved 72% isolated yield of **3** (entries 7−10). The phosphate additive further increased the yield of **3** to an optimal 81% yield (76% isolated yield, entry 11). The control experiments indicated that the photocatalyst, light, and copper salts were all essential for the reaction (entries 12−14). The reaction concentration, oxygen, and light intensity did not significantly affect the reaction (Table S5).

We next explored the substrate scope of the ring-opening amidation (Scheme 2a). The methyl-substituted cyclopentanol **9a** afforded δ-amidoketone **9** in 50% yield. The electron-rich tolyl-, methoxyphenyl-, or biphenyl-substituted cyclopentanols **10a**−**15a** proceeded smoothly to afford δ-amidoketones **10**−**15** in 59−77% yields. The electron-deficient chlorobenzyl and bromobenzyl substitutions gave **16** and **17** in 60−66% yields with an extended 12 h reaction time, which were challenging substrates for alkoxyl radical generation by the PCET mechanism.[5c,13] The mixed aryl-substituted **18a** or naphthyl-substituted **19a** gave excellent 71−79% yields of **18** and **19**. The cyclohexanols obtained the corresponding ε-amidoketones **20** and **21** in 67−79% yields, and the ether linkage in **21a** was tolerated. The medium-sized cycloheptanols and cyclooctanols **22a**−**24a** gave amidoketones **22**−**24** with different linker lengths in 63−79% yields. The 12- and 15-membered cycloalkanols **25a**−**27a** yielded distal amidoketones

Table 1. Optimization of the Reaction Conditions



entry	conditions[a]	conversion (%)	yield[b] (%)
1	**L1**, $K_2S_2O_8$	<5	0
2	**L1**, BI−OAc **4**	<10	<5
3	**L1**, BI−OH **5**	<10	<5
4	**L1**, $PhI(OAc)_2$ **6**	<10	<5
5	**L1**, BI^m−OAc **7**	36	30
6	**L1**, BI^m−OH **8**	>90	50
7	**L2**, BI^m−OH **8**	16	14
8	**L3**, BI^m−OH **8**	>90	56
9	**L4**, BI^m−OH **8**	>90	60
10[c]	**L4**, BI^m−OH **8**	>90	72 (72)
11[d]	**L1**, BI^m−OH **8**	>90	81 (76)
12[d]	no photocatalyst	<5	0
13[d]	no light	<5	0
14[d]	no CuCl	<5	0

[a]Reaction conditions: cyclopentanol (0.2 mmol, 2.0 equiv), *N*-nucleophile (0.1 mmol, 1.0 equiv), oxidants (0.2 mmol, 2.0 equiv), copper salt (0.02 mmol, 0.2 equiv), ligands (0.03 mmol, 0.3 equiv), photocatalyst (0.005 mmol, 0.05 equiv), and in 2.0 mL of DCM under nitrogen with 80 W blue LED irradiation at 25 °C for 12 h, unless otherwise noted. [b]Yields were determined by ^{1}H NMR analysis, and isolated yields are in parentheses. [c]BI^m−OH (0.3 mmol, 3.0 equiv) and Ph-Acr-Mes$^+BF_4^-$ (0.01 mmol, 0.1 equiv). [d]^{n}Bu$_4$P$^+$(OMe)$_2$POO$^-$ (0.02 mmol, 0.2 equiv).

25−**27** in excellent 72−75% yields. The reaction was not limited to cycloalkanols and was applied to linear alcohol **28a** to give **28** in 70% yield with the diphenylketone elimination.

The scope of N−H nucleophiles was next examined (Scheme 2b). The phthalimides **29b**−**31b** with electron-rich methoxy substitutions or electron-deficient chlorides/fluorides all reacted well to give imide-conjugated ketones **29**−**31** in 65−73% yields. The succinimide **32b** afforded succinimide-conjugated ketone **32** in a 67% yield. Sulfonamides have long been a desirable building block in bioactive molecules for improved lipophilicity and antibacterial, anti-inflammatory, and antiviral activity.[14] To this end, sulfonamides with electron-rich tolyl, methoxyphenyl, or electron-deficient pyridyl substitutions were all probed in the reaction and afforded sulfonamide-conjugated ketones **33**−**35** in 65−79% yields. Notably, the reaction scaled up in 5 mmol scales to give **34** in 1.32 g in 73% yield. The cyclic sulfonamide **36b** also reacted to afford **36** in 69% yield.

The alkyl-substituted cyclobutanol **37a** reacted smoothly with sulfonamide to yield γ-amidoketone **37** in 57% yield. When both secondary and primary alkyl radicals could be generated from the ring-opening of cyclopentanol **38a**, amidation preferably occurred at the secondary alkyl site to give **38** in 58% yield. The reaction was also applied to linear alcohol **28a** to give **39** in 50% yield with the diphenylketone

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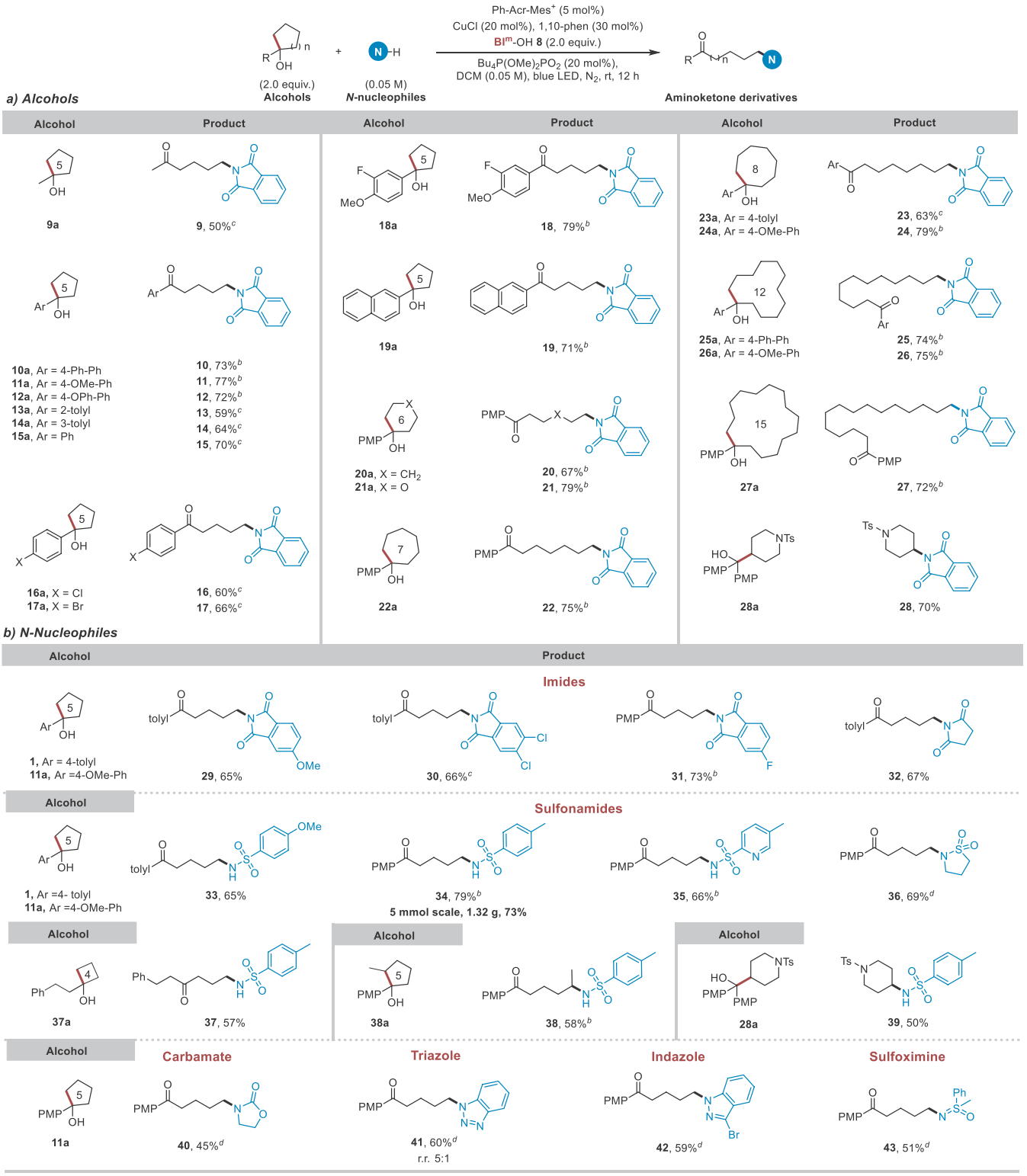
Scheme 2. Substrate Scopes[a]



[a]Reaction conditions: Entry 11, Table 1. Isolated yields were reported. [b]Two h. [c]BI^m−OH (0.30 mmol, 3.0 equiv), **L4** as ligand, Ph-Acr-$Mes^+BF_4^-$ (10 mol %). [d]$Cu(OAc)_2$ as the copper catalyst, 2 h.

elimination. We further found that N−H nucleophile scopes were extremely broad to extend to carbamates, triazoles, and indazoles, which were widely present in drug molecules to obtain the corresponding conjugated amidoketones **40**−**42** in 45−60% yields.[1b,15] Sulfoximines were widely viewed as the sulfone surrogate to improve their water solubility,[16] and they reacted smoothly to give sulfoximine-conjugated ketone **43** in 51% yield.

We next explored the reaction mechanism (Scheme 3). When cyclopentanol **1**, triazole **41b**, and BI^m−OH **8** were

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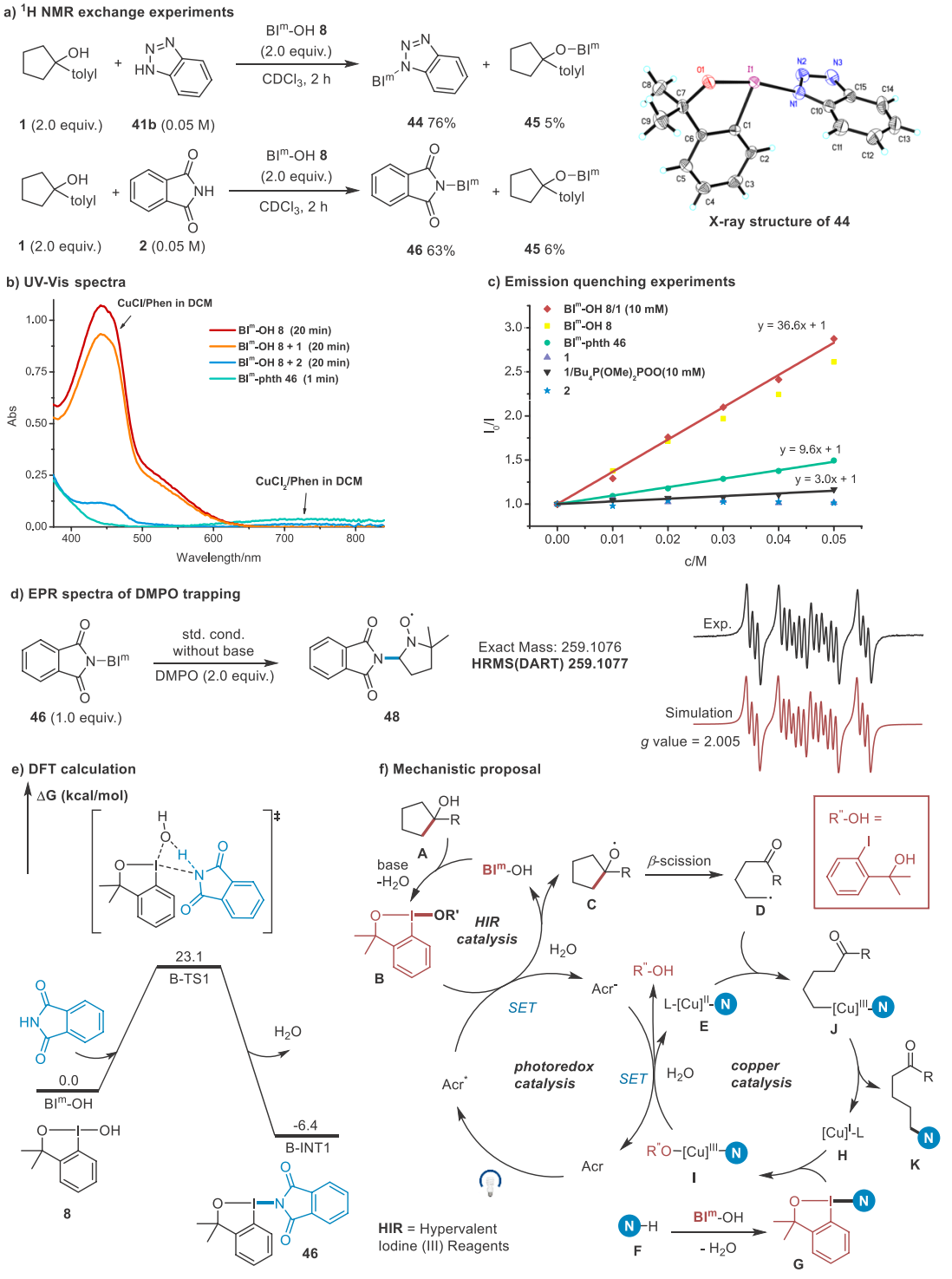
Scheme 3. Mechanistic Investigations



mixed together, the triazole−BI^m complex **44** and cyclopentanol−BI^m complex **45** were observed in 76% and 5% yield, respectively (Scheme 3a, see Figures S1−S6). We further prepared triazole−BI^m complex **44** from BI^m−Cl and potassium benzotriazolate. The X-ray crystallography of triazole−BI^m complex **44** showed the typical T-shape at the iodine center with the I−N bond at 2.204 Å (see the SI for details).[17] This I−N bond formation was also observed from phthalimide **2** and BI^m−OH **8**, in that the phthalimide−BI^m complex **46** was obtained in 56% yield,[18] together with cyclopentanol−BI^m **45** in 5% yield.[5a,7a,19] After the observation of the R_2N−BI^m and RO−BI^m intermediate formation in the reaction mixture, we next investigated how they performed their unique roles in dual photoredox/copper catalysis.

We first measured the UV−vis absorption spectra for Cu(I) at 350−500 nm and for Cu(II) at 650−800 nm (Scheme 3b, see Figures S7−S13).[20] The mixing of BI^m−OH **8** and cyclopentanol **1** resulted in a minor Cu(I) decrease. In contrast, the mixing of BI^m−OH **8** and phthalimide **2** decreased the Cu(I) concentration significantly. When

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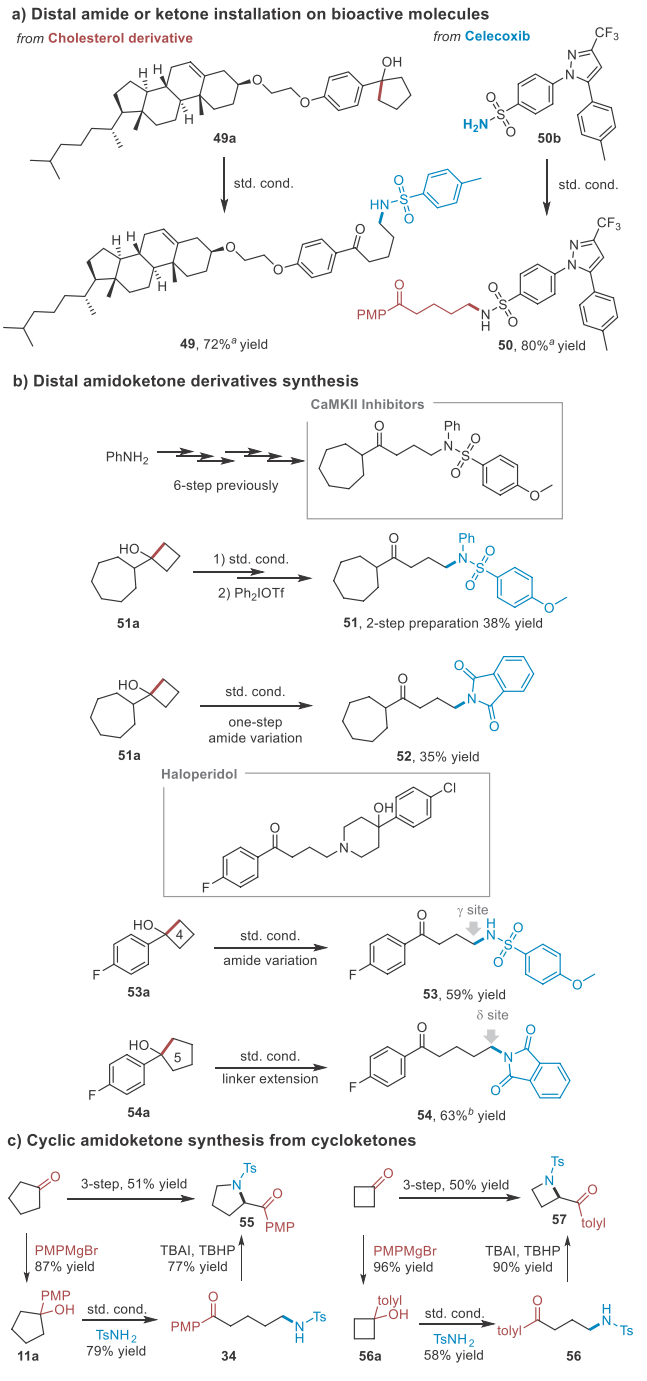
phthalimide−BI^m **46** as the single component was added, a similar Cu(I) decrease and Cu(II) increase were observed. The fluorescence quenching experiments indicated that cyclopentanol−BI^m **45** (red line, Scheme 3c) from the *in situ* mixed cyclopentanol **1** and BI^m−OH **8** quenched the photoexcited Acr* effectively. In contrast, phthalimide−BI^m **46** (green line) quenched Acr* with less than one-third efficiency. Mixing $^nBu_4P^+(OMe)_2POO^-$ with cyclopentanol **1** (black line) insignificantly quenched Acr*, excluding the PCET mechanism.[9] The radical spin trapping reagent 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) was next added to the reaction conditions with phthalimide−BI^m complex **46** and cyclopentanol **11a** (Scheme 3d). The ring-opening TEMPO addition adduct **47** was obtained in 58% yield together with the inhibition of amidoketones (Scheme S1). The EPR signal also indicated **48** as the nitrogen-centered radical trapping adduct by DMPO, which resulted from fragmentation of the Cu(III)−N intermediate.[21]

The DFT calculation was next performed to explore the critical role of dimethylbenziodoxole BI^m for the transformation (Scheme 3e). The formation of phthalimide−BI^m complex **46** from BI^m−OH **8** and phthalimide **2** is exergonic (−6.4 kcal/mol), with activation energy at 23.1 kcal/mol. In contrast, the activation energy for the ligand exchange between benziodoxolone BI−OH **5** and phthalimide **2** is too high (31.5 kcal/mol) to occur at room temperature for the formation of the corresponding BI−phthalimide complex (Figure S37). We also calculated the dissociation energy of I−O in BI^m−OH **8** and BI−OH **5** for the ligand exchange reaction. The dimethyl alkoxyl ligand on BI^m has a strong trans effect (ΔG = +50.6 kcal/mol), which significantly accelerated the ligand exchange reaction compared with BI (ΔG = +68.6 kcal/mol) (Figure S38).[22]

From the mechanistic investigations above, we propose the dual photoredox/copper catalysis mechanism for the distal amidoketone synthesis (Scheme 3f). The alcohol substrate **A** first undergoes the ligand exchange reaction with BI^m−OH to form the BI^m−OR′ complex **B**, in which phosphates as the base accelerate the exchange process. This complex **B** is single-electron-oxidized by the photoexcited Acr* to yield the alkoxyl radical **C** and the reduced Acr−.[23] The amide substrate **F** forms the BI^m−NR_2 complex **G** with BI^m−OH by ligand exchange, and it further reacts with Cu(I) **H** to yield the alkoxyl-Cu(III)−NR_2 complex **I**, which may also be shown as the equilibrium of Cu(II) and the •NR_2 radical.[24] The Cu(III)−NR_2 complex **I** is single-electron-reduced by the reduced Acr$^-$ to yield Cu(II)−NR_2 intermediate **E** and benzyl alcohol. The alkoxyl radical **C** then fragments to yield the alkyl radical **D**, which reacts with Cu(II)−NR_2 **E** to enter the copper catalysis for the alkyl-Cu(III)−NR_2 intermediate **J** formation. The final reductive elimination of the alkyl-Cu(III)−NR_2 **J** yields amidoketone adduct **K** and turns over Cu(I) **H** for the new copper catalytic cycle.

We next explored the synthetic potential of this method for the late-stage modification of complex molecules, which has been increasingly crucial for lead compound optimization in drug discovery.[25] We first tested the distal amide group installation on complex molecules (Scheme 4a). Starting from steroid **49a** with a cyclopentanol moiety, the sulfonamide group can be installed in one step at the terminal position of cholesterol to build cholesterol−sulfonamide conjugate **49** in an excellent 72% yield without affecting other existing functional groups.[26] Similarly, the distal ketone installation

Scheme 4. Synthetic Applications[a]



[a]See the Supporting Information for specific experimental details. (a) 2 h. (b) BI^m−OH (0.30 mmol, 3.0 equiv), **L4** as ligand, and Ph-Acr-Mes$^+BF_4^-$ (10 mol %).

could be achieved on celecoxib **50b**, which is an FDA-proved nonsteroidal anti-inflammatory prescription sulfonamide drug to treat pain.[27] The reaction of celecoxib **50b** with cyclopentanol **11a** yielded the celecoxib−ketone conjugate **50** with a four-carbon linker in an excellent 80% yield, which may serve as a bifunctional celecoxib-related drug candidate.[28]

The CaMKII inhibitor **51** is known to be an effective treatment for dengue and zika fever.[29] Currently, the incorporation of ketones and amides in **51** is stepwise executed, in which six steps are required for its synthesis.[29]

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With our method, the synthesis of **51** is achieved in two steps in a combined 38% yield (Scheme 4b). The sulfonamide group in **51** may be replaced by other N-nucleophiles, such as phthalimides, to obtain **52** from **51a** in 35% yield in one step. Similarly, the tertiary amine group from the antipsychotic drug haloperidol could be replaced by sulfonamide **53** from **53a** in 59% yield in one step. The linker length between the ketone and the amine is known to affect the pharmacological activity of bioactive molecules,[30] and we obtained linker-extended **54** from cyclopentanol **54a** efficiently in 63% yield, which may significantly affect their ligand−receptor interactions.

This distal amidoketone synthesis method, when combined with the C−H oxidative cyclization process,[31] provides a facile approach to the streamlined amidoketone synthesis from cycloalkanones (Scheme 4c). Starting from cyclopentanones, the three-step streamlined sequence afforded the five-membered tetrahydropyrrole derivative **55** in 51% yield, where ketopyrrolidines are essential skeletons in dipeptidyl peptidase IV inhibitors.[32] This approach represents an attractive method for a formal nitrogen atom insertion and ketone extrusion from the cyclopentanone; with this concept, the four-membered azetidine derivative **57** could be obtained similarly in 50% yield from cyclobutanones, the azetidine skeleton of which commonly presents in bioactive molecules.[33]

In conclusion, we have reported distal amidoketone and nitrogen-functionalized ketone syntheses from alcohols with readily available N−H nucleophiles enabled by hypervalent iodines. The dimethyl benziodoxoles (BI^m) formed the key I−O and I−N bonds for the dual activation of alcohols and N−H nucleophiles in dual photoredox/copper catalysis, in which the BI^m−N complex is essential for the copper-catalyzed C−N bond formations. This distal amidoketone synthesis scales up to grams, applies to late-stage complex molecule modification, and streamlines synthetic routes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.3c00230.

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

Crystallographic data for **44** (CIF)

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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