Site-Tunable C_{sp}³–H Bonds Functionalization by Visible-Light-Induced Radical Translocation of *N*-Alkoxyphthalimides

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Supporting Information

Organic



ABSTRACT: Site-tunable functionalization of $C(sp^3)$ -H bonds has been accomplished through radical translocation and cross-coupling. Upon irradiation with visible light, copper-based photocatalyst $[Cu(Xantphos)(dmp)]BF_4$ enabled cross-coupling of *N*-alkoxyphthalimides with amino acid esters or amino acids to provide δ - $C(sp^3)$ -H alkylated alcohols (31 examples, up to 92% yield) with additive BNDHP or α - $C(sp^3)$ -H alkylated alcohols (18 examples, up to 86% yield) with additive DABCO in a highly regioselective fashion.

lcohols are one of the most common and important ${f A}$ synthetic materials in organic and pharmaceutical chemistry.¹ While the hydroxy group can be readily transformed into various functional groups, the $C(sp^3)$ -H bond transformation of alcohols is less investigated but more challenging especially for achieving high site selectivity and chemoselectivity.² Recently, radical approaches for selective functionalization of α -C(sp³)–H and remote C(sp³)–H bonds of alcohols and alcohol derivatives have received more attention due to the development of robust methods for generation of radical intermediates under mild photoredox conditions toward versatile hydrogen atom transfer (HAT) reactivity.3-5 Among these, MacMillan introduced an elegant work based on the visible-light-induced direct α -alkylation/ lactonization of alcohols through the synergistic combination of an iridium-based photocatalyst, a HAT reagent, and a hydrogen-bonding catalyst (Scheme 1a).⁶ While, Chen,⁷ Meggers,^{7b} Hong,^{7c} Zhu,^{7d} Zuo,^{7e} and others,^{7e,f} respectively, developed effective strategies to achieve δ -C(sp³)-H bond activation of free alcohols or their derivates based on the sequence of 1,5-HAT of visible-light-generated alkoxyl radical intermediates⁸ and the follow-up transformations of the resultant alkyl radicals such as radical conjugate additions, Minisci-type reactions, and cross-couplings (Scheme 1b). Besides, photoinduced alkoxyl radicals have led to new advancements in $C(sp^3)$ -H bond cleavage reactions involving HAT and β -fragmentation reactivity by Zhu^{9a} and Zuo.^{9b,6} Although several methods have been established for selective functionalization of alcohols, the use of earth-abundant copper as a photoredox catalyst¹⁰ to achieve the site-tunable $C(sp^3)$ -H bond alkylation of alcohols, to the best of our knowledge, is still unknown.¹¹

Herein, we report the visible-light-induced α -/ δ -selective functionalization of C(sp³)-H bonds of alcohols as shown in

Scheme 1. Visible-Light-Induced Selective Functionalization of C(sp³)–H of Alcohols or Their Derivates

a) Visible-light-induced α-C(sp3)-H bond functionalization



Scheme 1c. This protocol employs simple activating groups, namely *N*-alkoxyphthalimides as recently developed redoxactive radical precursors.^{7a,b,12} It features the advantageous use of a Cu(I) complex as a photocatalyst along with (*R*)-BNDHP or DABCO to assist a challenging switchable alkylation of C– H bond at room temperature. Remarkably, our catalytic manifold is endowed with reaction scalability and a broad substrate scope allowing late-stage functionalization of diverse peptides in good yields.

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We started our investigation with readily prepared heteroleptic Cu(I)-based complex $[Cu(Xantphos)(dmp)]BF_4$ as a photocatalyst.¹³ When *N*-alkoxyphthalimide **1a** reacted with 2-(phenylamino)acetate **2a** in the presence of $[Cu-(Xantphos)(dmp)]BF_4$ (10 mol %) under visible-light irradiation with a 24 W blue LEDs, we were disappointed to not observe even traces of the desired product **3a** (Table 1,

Table 1. Reaction Development^a

o~O phth	+ Ph_N_CO2'Bu (100 action of the solvest solve	$\begin{array}{c} & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ \hline \\ & & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ \end{array} \end{array} \xrightarrow{BF4^{-}} Ph_{N} \overset{N}{H}$	CO2'Bu	
1a	2a 24 W	blue LEDs	3a	4a
entry	additive (equiv)	solvent (M)	3a (%)	4a (%)
1	no	DMA (0.2)	0	0
2	(R)-BNDHP (0.2)	DMA (0.2)	48	0
3	nBu_2PO_2H (0.2)	DMA (0.2)	20	0
4	$PhCO_2H$ (0.2)	DMA (0.2)	14	0
5	PivOH (0.2)	DMA (0.2)	0	0
6	(R)-BNDHP (0.2)	THF (0.2)	trace	0
7	(R)-BNDHP (0.2)	DCM(0.2)	0	0
8	(R)-BNDHP (0.2)	toluene (0.2)	0	0
9	(R)-BNDHP (0.2)	CH3CN (0.2)	20	0
10	(R)-BNDHP (0.2)	DMA (0.1)	53	0
11	(R)-BNDHP (0.2)	DMA (0.05)	60	0
12	DABCO (2.0)	DMA (0.2)	0	74 $(1.5:1)^{c}$
13	Et ₃ N (2.0)	DMA (0.2)	0	trace
14	Na_2CO_3 (2.0)	DMA (0.2)	0	$34(1.5:1)^{c}$
15	NaOAc (2.0)	DMA (0.2)	0	52 (1.5:1) ^c
16 ^d	(R)-BNDHP (0.2)	DMA (0.05)	0	0
17 ^d	DABCO (2.0)	DMA (0.2)	0	0
18^e	(R)-BNDHP (0.2)	DMA (0.05)	0	0
19 ^e	DABCO (2.0)	DMA (0.2)	0	0

"Reaction conditions: *N*-alkoxyphthalimide **1a** (0.40 mmol) and 2-(phenylamino)acetate **2a** (0.20 mmol) with Cu catalyst (10.0 mol %) and additive ((*R*)-BNDHP (0.2 equiv) or DABCO (2.0 equiv)) in DMA (4.0 or 1.0 mL) under light irradiation using 24 W blue LEDs at room temperature for 65 h under a nitrogen atmosphere. ^bIsolated yield. ^cDr value shown in parentheses determined by crude ¹H NMR. ^dNo light. ^eNo Cu catalyst. Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; dmp = 2,9-dimethyl-1,10-phenanthroline; phth = phthalimide; (*R*)-BNDHP = (*R*)-(-)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate; PivOH = pivalic acid; DABCO = 1,4-diazabicyclo[2.2.2]octane.

entry 1). Encouragingly, with the addition of (R)-BNDHP¹⁴ (0.2 equiv), the $C(sp^3)-C(sp^3)$ bond formation product 3a was obtained in 48% yield (entry 2). Other tested acids did not provide satisfactory results (entries 3-5). Further optimization showed that the reaction is very sensitive to solvent effects (entries 6-10), and the best result was obtained by using DMA as solvent with a decreased concentration of 0.05 mol- L^{-1} (entry 11). Interestingly, when DABCO (2.0 equiv) instead of (R)-BNDHP was applied to this system, the reaction afforded the α -alkylation product 4a with a 74% yield and 1.5:1 dr (entry 12). Replacing DABCO with other bases resulted in significantly lower yields (entries 13-15). Control experiments verified that both visible light and a copper-based photocatalyst are essential for product formation (entries 16-19). When [Cu(Xantphos)(dmp)]BF₄ was replaced by other commonly used photocatalysts or dmp and Xantphos were interchanged with other dinitrogen and diphosphine ligands, the reaction proceeded less efficiently (Table S1; see the Supporting Information).

Under the optimized conditions (Table 1, entry 11), we next tested the substrate scope of the photoinduced $C(sp^3)-C(sp^3)$ formation reaction using (*R*)-BNDHP as an additive which is shown in Scheme 2. Primary, secondary, and tertiary *N*-

Scheme 2. Substrate Scope for δ -C(sp³)-H Alkylation Using (*R*)-BNDHP as Additive



alkoxyphthalimides were applied to the reaction, affording the cross-coupling products in moderate to good yields (3a-3e, 2.0:1 dr of 3b and 3c). Notably, the substrates bearing cyclic, heterocyclic, and alkenyl groups were well tolerated (3f-3h). Furthermore, α -sulfur C–H bonds also worked well under standard conditions (3i and 3j). With respect to the coupling partner, various 2-(aromaticamino)acetates with electron-rich or electron-withdrawing aromatic substituents were found to be tolerated (3k-3n). Besides esters, α -amino amide, ketone, and nitrile also exhibited good reactivity to provide the expected products in 40–92% yields (3o-3s). The structure of 3q was determined by X-ray diffraction (CCDC 1923105).

Having obtained the δ -C(sp³)–H alkylation of alcohols, we next investigated the substrate scope of α -C(sp³)-H functionalization using DABCO as an additive. As shown in Scheme 3, under the optimized conditions (Table 1, entry 12), N-alkoxyphthalimides with aliphatic groups reacted smoothly with 2-(phenylamino)acetate to form β -amino alcohols with moderate to good yields as diastereomeric mixtures (44-70% yield, 3.0:1-1.1:1 dr (4b-4f). The conditions clearly enabled the functionalization of the alcohol α -oxy C-H bond in the presence of other functional groups, including thioether (4g) as well as acyclic and cyclic ether (4h-4l). Besides, Nalkoxyphthalimides with aromatic substituents also worked well with 2-(1-naphthylamino)acetate to offer the $C(sp^3)$ - $C(sp^3)$ bond formation products with isolated yields of up to 85% and 2.8:1 dr (4m and 4n). Moreover, heteroaromatics such as furan, thiophene, quinoline, and benzothiazole were successfully applied to this transformation (40-4r). Additionally, tertiary amine N,N-dimethylaniline was also suitable for the reaction albeit with a lower yield (4s).¹⁵

Scheme 3. Substrate Scope for α -C(sp³)–H Alkylation Using DABCO as Additive



 α -Amino acids, well-known radical precursors for decarboxylative radical additions and cross-coupling reactions,¹⁶ reacted quite efficiently under modified reaction conditions (Scheme 4). Without any additives, the reaction of *N*-alkoxyphthalimide **1d** with α -amino acids **5** afforded the decarboxylated radical– radical cross-coupling products **6** in moderate yields.





Given the good regioselectivity, we subsequently examined the δ -C(sp³)-H alkylation of more complex settings, as it represents an attractive approach for late-stage modification of complex molecules (Scheme 5).¹⁷ For example, 2-(phenylamino)acetates, which were prepared from readily available (-)-menthol and (-)-borneol, reacted smoothly with *N*-alkoxyphthalimide **1g** to furnish the products in moderate yields as diastereomeric mixtures (7a and 7b). Dipeptides containing glycine (7c), valine (7d), phenylalanine (7e), and proline (7f) units underwent selective δ -C(sp³)-H alkylation on the Ph-glycine unit with good yields (64–82%). It is worth noting that the presence of a proline unit is beneficial to improve the diastereoselectivity (10.0:1 dr for 7f). The robustness of this method was further demonstrated by the site-selective functionalization of tripeptides in reasonable





yields (7g and 7h). Importantly, the reaction was amenable to scale-up to gram quantity (7i).¹⁸

A plausible mechanism is shown in Scheme 6 and starts with the photoactivation of $[Cu(Xantphos)(dmp)]BF_4 [Cu^I]$ to its

Scheme 6. Proposed Mechanism



excited state [Cu^I]*, which serves as a reducing agent and transfers a single electron to *N*-alkoxyphthalimide **1**.¹⁹ Then the N-alkoxyphthalimide radical anion A fragments to form a carbon-centered radical in two pathways depending on the acid or base additive: (1) In the presence of acid BNDHP, the intermediate A is subsequently protonated and then undergoes a homolytic N-O cleavage under formation of an alkoxy radical B and phthalimide. This intermediate B engages in an intramolecular 1,5-HAT to yield a remote carbon-centered radical C^{7} (2) In the presence of DABCO as a base, intramolecular proton transfer of intermediate A followed by N-O bond homolytic cleavage generates radical anion intermediate D which could exist in its more stable resonance structure α -oxy carbon-centered radical anion D'.²⁰ Simultaneously, [Cu^{II}] oxidizes N-aryl glycine ester 2 to generate an amino radical cation E, along with regeneration of $[Cu^I]^{21}$ The intermediate E is deprotonated to provide an α -amino carbon-centered radical F. Finally, the radical-radical crosscoupling between α -aminoalkyl radical F and alkyl radical C provides δ -functionalized product 3, while the coupling with radical D' and concurrent protonation deliver α -alkylated product 4.²²

Several experiments were performed to probe the mechanism. First, the presence of air or TEMPO (2.5 equiv) completely inhibited the formation of **3a** or **4a**, which might indicate a radical pathway (Scheme 7a). Second, the proposed

Scheme 7. Mechanistic Investigations



carbon-centered radical **C** which formed by 1,5-HAT was verified by a trapping experiment with isoquinoline (Scheme 7b).^{7d} Third, the homocoupling of proposed intermediate α -amino carbon radical **F** (Scheme 7c) and side product aldehyde derived from radical intermediate **D** or **D'** (see the Supporting Information) were isolated under standard conditions. Moreover, deuterium labeling studies involving 1q and 1q-d₂ yielded a KIE value of 6.0 (Scheme 7d), suggesting that cleavage of the α -C(sp³)–H bond is likely the rate-determining step.²³ Finally, the quantum yield $\Phi < 1$ (0.10 and 0.12; see the Supporting Information) indicated the radical chain process might not be involved in the reaction.²⁴

In summary, we demonstrated a visible-light-induced sitetunable functionalization of alcohols by using *N*-alkoxyphthalimides and *N*-aryl glycine esters as redox-active radical precursors. This method features mild radical conditions and employs a Cu(I) complex as a photocatalyst along with BNDHP or DABCO to assist the regioselective aminoalkylation of δ - or α -C(sp³)-H bonds of alcohols. Our catalytic manifold is endowed with a broad substrate scope and reaction scalability. Peptides could also be site-selectively functionalized. The application of this method in asymmetric catalysis is underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b03524.

Experimental procedures, character of new starting materials and products, NMR spectra, and X-ray structure (PDF)

Accession Codes

CCDC 1923105 and 1959513 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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