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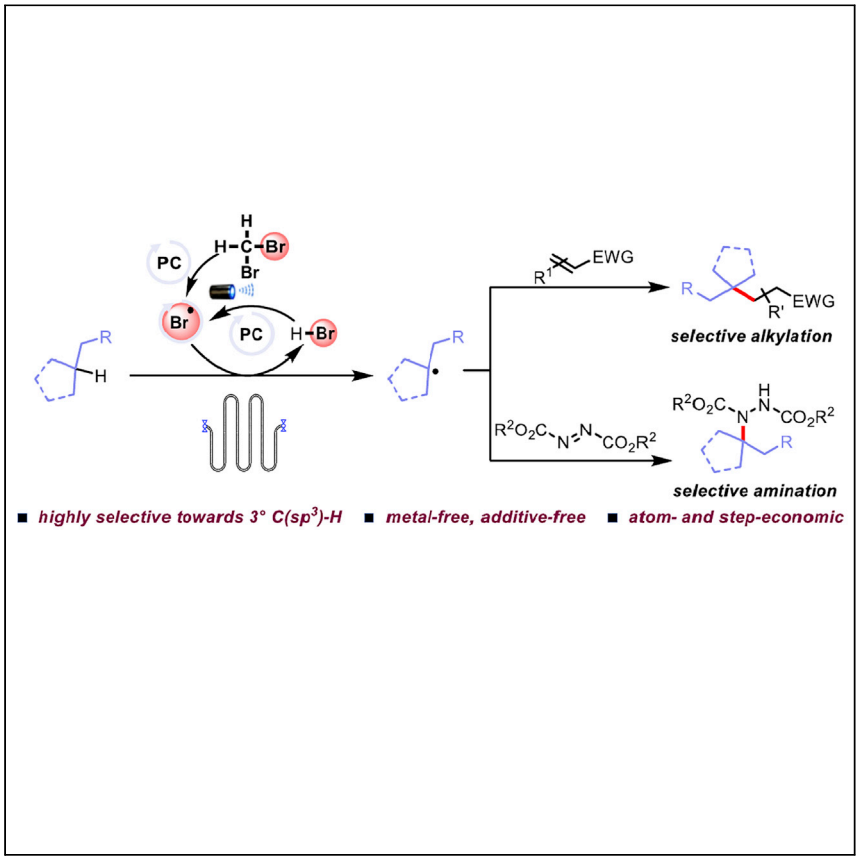
Light-Promoted Bromine-Radical-Mediated Selective Alkylation and Amination of Unactivated C(sp^3)–H Bonds



A visible-light-induced highly selective alkylation and amination of unactivated C(sp^3)–H bonds via the synergistic effects of an organo-photoredox catalyst and a bromine-based hydrogen atom transfer agent has been developed by applying CH_2Br_2 as both the solvent and the bromine radical source. Our study offers a new paradigm for the direct synthesis of valuable compounds from abundant alkane feedstocks in a convenient and metal-free manner.

Penghao Jia, Qingyao Li, Wei Chuen Poh, Heming Jiang, Haiwang Liu, Hongping Deng, Jie Wu

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HIGHLIGHTS

Photo-mediated selective alkylation and amination of unactivated C(sp^3)–H bonds

Generation of bromine radical as the HAT agent in a catalytic and metal-free manner

Excellent selectivity toward tertiary C(sp^3)–H bonds

Stop-flow microtubing (SFMT) reactors enabling enhanced reactivity

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Light-Promoted Bromine-Radical-Mediated Selective Alkylation and Amination of Unactivated C(sp^3)–H Bonds

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SUMMARY

Substantial effort is currently being devoted to selective C(sp^3)–H bond functionalization, and photocatalysis has presented enormous potential opportunities in this research field. Here, we developed a visible-light-induced functionalization of unactivated C(sp^3)–H bonds via the synergistic effects of an organo-photoredox catalyst and a bromine-based hydrogen atom transfer agent. By applying CH_2Br_2 as both the solvent and the bromine radical source, the alkylation and amination of tertiary C(sp^3)–H bonds were achieved in a highly selective fashion. This study represents the first example of selective activation of unactivated alkanes by bromine radicals in a catalytic and metal-free manner. Good reactivity was achieved by using a sealed microtubing reactor or by adding a proper amount of water. This highly selective C(sp^3)–H functionalization protocol offers a new paradigm for the direct synthesis of valuable compounds from abundant alkane feedstocks in a convenient and green manner.

INTRODUCTION

Methods for C–H functionalization serve as a versatile toolbox for the modification of organic molecules in an atom- and step-economical manner. However, most reported successful approaches are limited to activated C(sp^3)–H bonds (e.g., α-oxy, α-amino, benzylic, and allylic C–H bonds).[1] Because of the intrinsically high bond dissociation energies (BDEs) and the ubiquity of similar inert C–H bonds in unactivated alkanes, the selective functionalization of inert C(sp^3)–H bonds represents one of the most attractive goals in organic synthesis. Strategies involving enzymes,[2] metal complexes,[3,4] carbenoids,[5] and radicals[6–10] have been developed to achieve selective C(sp^3)–H functionalizations. Given that radicals can inherently distinguish aliphatic C–H bonds on the basis of the difference of their BDEs and polarity,[9] they offer unique advantages for selective C–H functionalizations with readily accessible feedstocks under mild conditions.[11–13]

In this context, the emergence of photocatalysis has provided enormous opportunities for C(sp^3)–H functionalization. In general, four fundamental pathways have been applied for photo-promoted C–H functionalization: photoredox catalysis,[14,15] direct hydrogen atom transfer (HAT) photocatalysis,[10,16,17] proton-coupled electron transfer (PCET),[18] and synergistic combinations of photoredox with HAT catalysis[12,13,19–30] (Figure 1A). Among these strategies, the synergistic merger of photoredox with HAT catalysis, which mainly relies on photoredox-induced N,[19–22] O,[12,13,23,24] and S[25,26] radicals to promote subsequent HAT transformations, offers

The Bigger Picture

C–H functionalization has provided new opportunities to construct organic molecules in an atom- and step-economic manner, facilitating the derivatization of complex pharmaceutical compounds. However, because of the intrinsically high bond dissociation energies and the ubiquity of similar C–H bonds in unfunctionalized alkanes, the selective functionalization of inert C(sp^3)–H bonds represents one of the most challenging but attractive goals in chemical synthesis. In this context, we developed highly selective alkylation and amination of tertiary C(sp^3)–H bonds through the combination of a photoredox catalyst and CH_2Br_2 as a hydrogen atom transfer agent. Bromine radical is among the weakest but most selective hydrogen atom transfer (HAT) agents. This mild photocatalytic process will inspire new perspectives for the synthesizing value-added chemicals directly from commodity alkane feedstocks by taking full advantage of the merits of bromine radicals to activate tertiary C(sp^3)–H bonds in a highly selective fashion.

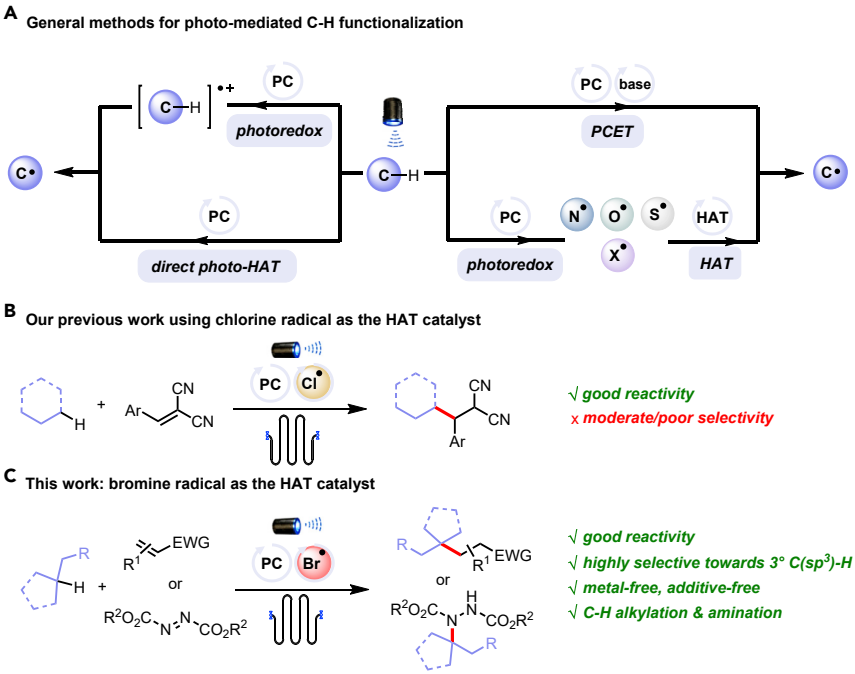

Figure 1. Strategies for C–H Functionalization under Visible-Light Irradiation

the largest reaction scope. Moreover, the use of halogen radicals as HAT agents for C–H functionalization has also been reported. For instance, Doyle's research group and our research group developed catalytic methods for the generation of chlorine radicals by photolysis of a Ni^{III} chloride intermediate to achieve C(sp^3)–H cross coupling[27,28] and selective vinylation[29] with activated C(sp^3)–H substrates, respectively. Our group and Barriault's group recently demonstrated an alternative catalytic pathway for generating chlorine radicals by a single-electron oxidation of chloride ions (Figure 1B).[30,31] The developed chlorine radical-based protocol showed good reactivity toward a series of unactivated C(sp^3)–H bonds, even ethane was efficiently activated. However, when substrates with more than one reactive site were involved, the selectivity was low to moderate probably due to the high reactivity of chlorine radicals.[30] Notably, Barriault et al. have demonstrated an obviously enhanced regioselectivity favoring the activated tertiary C(sp^3)–H bond of a cyclopentyl methyl ether substrate by using pyridine as the solvent to attenuate the high reactivity of the chlorine atom.[31] In classical photo-promoted halogenation reactions, hydrogen atom abstraction based on bromine radicals requires a higher activation energy than that required with chlorine radicals, enabling more selective transformations.[32–34] However, this is limited to bromination using stoichiometric Br_2.[35–38] Recent developments using bromine radicals as a HAT catalyst are mainly based on photo-activation of an *in situ* formed metallic bromide intermediate and the substrates are limited to activated alkanes.[39–41]

In line with our ongoing interest in photo-promoted C–H functionalization,[15,17,29,30,42–44] here, we developed a bromine-radical-mediated highly selective alkylation and amination of unactivated C(sp^3)–H bonds with excellent efficiency in a metal-free and additive-free manner, by using an organo-photoredox catalyst in conjunction with CH_2Br_2, which serves as both the bromine radical precursor and the solvent (Figure 1C). This study represents the first example of functionalization of unactivated alkanes promoted by bromine radicals in a catalytic and metal-free fashion. Excellent selectivity for tertiary

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Table 1. Optimization of the Conditions

Entry	Solvent	HX[a]	Cat.	Combined Yield (%)[b]	Selectivity (2:2′)[c]
1	CH_3CN	HCl	Mes-Acr$^+$$ClO_4^-$	44	1:3
2	CH_3CN	HBr	Mes-Acr$^+$$ClO_4^-$	22	6:1
3	$CHCl_3$	HBr	Mes-Acr$^+$$ClO_4^-$	86	4:1
4	CH_2Br_2	HBr	Mes-Acr$^+$$ClO_4^-$	66	7:1
5	CH_2Br_2	N/A	Mes-Acr$^+$$ClO_4^-$	77	9:1
6	$CHBr_3$	N/A	Mes-Acr$^+$$ClO_4^-$	0	N/A
7	$Br(CH_2)_2Br$	N/A	Mes-Acr$^+$$ClO_4^-$	81	6:1
8	CH_2Br_2	N/A	TPP$^+$$BF_4^-$	76	9:1
9	CH_2Br_2	N/A	[Ir(dF-CF_3ppy)$_2$(dtbpy)]PF_6	0	N/A
10	CH_2Br_2	N/A	4CzIPN	0	N/A
11[d]	CH_2Br_2	N/A	Mes-Acr$^+$$ClO_4^-$	84 (80)[e]	9:1
12[f]	Acetone	N/A	Mes-Acr$^+$$ClO_4^-$	54	6:1
13[g]	CH_2Br_2	N/A	Mes-Acr$^+$$ClO_4^-$	29	9:1
14[g,h]	CH_2Br_2	N/A	Mes-Acr$^+$$ClO_4^-$	76	9:1

Reaction conditions: a mixture of **1** (0.2 mmol), methylcyclopentane (1 mmol), HX (0.04 mmol) and cat. (0.004 mmol) in 2 mL of solvent was injected into a SFMT reactor (volume = 1.5 mL). The reaction was conducted at 50°C under 18 W blue LED irradiation for 48 h, unless otherwise stated.

[a]0.2 M HX solution in CH_3CN was used.

[b]Yields based on analysis of the crude ^{1}H NMR spectra using 1,3,5-trimethoxybenzene as an internal standard.

[c]Selectivity was determined by analysis of the crude ^{1}H NMR spectra.

[d]1 mL of CH_2Br_2 (0.2 M) was used, and the reaction was conducted for 24 h.

[e]Isolated yields.

[f]10 equiv of CH_2Br_2 was used.

[g]Reaction conducted in a sealed batch reactor (10-mL volume).

[h]20 equiv of H_2O was added.

C–H bonds was obtained. Bromine radical is among the weakest but most selective HAT agents because of the low BDE of HBr (87 kcal/mol), and its usage in a catalytic transformation enriches the toolbox of HAT catalysis.

RESULTS

Investigation of Reaction Conditions

We commenced our study by employing the previously established HCl-based HAT protocol.[30] The reaction was more efficient and reliable when taking advantage of our recently developed stop-flow microtubing (SFMT) reactor[45] instead of conventional batch reactors. Benzylidene malononitrile **1**, as the Michael acceptor, and methylcyclopentane, as the C–H coupling partner, were irradiated with an 18 W blue Light Emitting Diode (LED) strip at 50°C in an SFMT reactor (Table 1). With the optimized HCl-based HAT protocol, in which Mes-Acr$^+$$ClO_4^-$ was used as the photoredox catalyst and HCl was used as the HAT catalyst precursor in CH_3CN, moderate reactivity with almost no selectivity between the tertiary and secondary C–H bonds was observed (entry 1). Then, HBr was used in place of the HCl to test the effect of the bromine radical (Table 1, entry 2, and Table S1). A promising selectivity of 6:1 favoring the tertiary C–H bond was observed, but the reactivity was retarded. Using halogenated solvents instead of CH_3CN provided significantly improved results (Table 1, entries 3 and 4, and Table S2). CH_2Br_2[46] turned out to be the optimal choice, as it afforded the products with 66% yield and 7:1 selectivity. Conducting the reaction in CH_2Br_2 without HBr provided an improved outcome, where 77% yield of the products

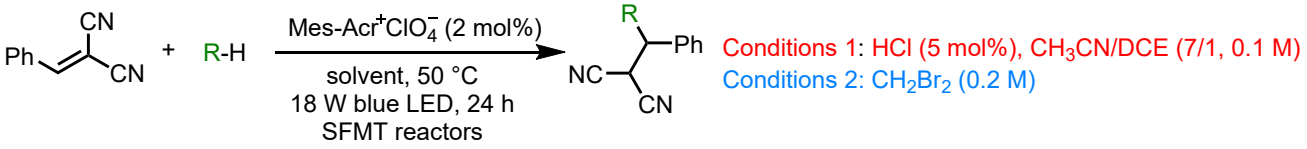
were obtained with a selectivity of 9:1 favoring alkylation of the tertiary C–H bond (Table1, entry 5). Other bromine-containing solvents were evaluated (Table S3). No reaction occurred in $CHBr_3$ (Table 1, entry 6). $Br(CH_2)_2Br$ afforded products in a yield similar to that achieved in CH_2Br_2 with a slightly lower selectivity (entry 7). Examination of other photocatalysts revealed that only photocatalysts with strong oxidative power, such as 2,4,6-tri(*p*-tolyl)pyrylium tetrafluoroborate ($TPP^+BF_4^-$) could effectively promote the reaction (entry 8), whereas no reaction occurred with $[Ir(dF-CF_3ppy)_2(dtbpy)]PF_6$ or 1,2,3,5-tetrakis-(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) (Table 1, entries 9 and 10, and Table S4). Further optimization revealed that the reaction yield could be improved to 80% isolated yield by running the reaction at 0.2 M in CH_2Br_2 for 24 h (Table 1, entry 11, and Table S5). Attempted efforts to use CH_2Br_2 as a reagent instead of a solvent resulted in less effective results. 54% of products was obtained with 6:1 selectivity by using 10 equiv of CH_2Br_2 in acetone (Table 1, entry 12, and Table S3). Notably, when switching the reaction vessel from the SFMT reactor to a sealed batch reactor (10-mL volume), the efficiency decreased significantly (29% yield, Table 1, entry 13), indicating that volatile active species might be involved in the reaction process.[30] However, by adding 20 equiv of water into the reaction mixture in a sealed tube reactor, 76% yield of the products could be obtained (Table 1, entry 14, and Table S6), enabling a convenient batch setup to obtain useful efficiency.

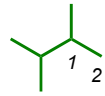
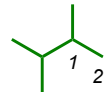
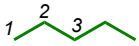
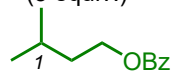
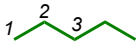
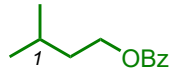
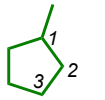
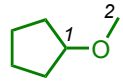
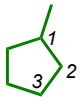
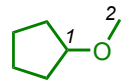
Comparison between the Cl- and Br- Radical-Based Photo-HAT Protocols

To further demonstrate the difference in reactivity and selectivity between the optimized Br-radical-based photo-HAT protocol and the previously established Cl-radical-based method,[30] a series of comparative experiments with various unactivated alkanes were conducted. The results are summarized in Scheme 1. In general, the bromine-radical-based photo-HAT protocol showed no reactivity toward primary C–H bonds and much lower reactivity with secondary C–H bonds compared with the chlorine radical-based protocol (entries 1–4). However, bromine radicals displayed excellent reactivity and selectivity for tertiary C–H bonds, whereas chlorine radicals showed almost no selectivity between different types of C–H bonds (entries 5–10). Even with activated alkanes, such as cyclopentyl methyl ether, the bromine-radical-based protocol still provided much better selectivity for tertiary over primary C–H bonds (entries 11–12).

Substrate Scope for C–H Alkylation

A wide range of unactivated alkanes were effective under the optimal conditions and provided the alkylation products in generally good selectivities (Scheme 2). Both cyclic and acyclic unfunctionalized alkanes afforded the corresponding products in good yields (**2**–**12**). Steric hindrance has little effect on the reactivity, and even 2,3-dimethylbutane gave product **9** in good yield. The selectivity is mainly controlled by the ratio between the number of tertiary C–H bonds and secondary C–H bonds present in the substrate. When there were more secondary C–H bonds present in the substrate, the selectivity was decreased to some extent (**3**, **4**, and **8**). Alkanes bearing remote electron-withdrawing functional groups were subsequently evaluated (**13**–**27**). Different functional groups, such as ester, amide, benzoate, acetate, benzenesulfonate, free acid, bromine, and nitrile groups were well tolerated. Excellent regioselectivity for tertiary C–H bonds was observed in all these cases. Under basic conditions, bromide product **19** underwent a facile intramolecular S_N2-type cyclization to give cyclohexane derivative **20**. To further demonstrate the synthetic value of this protocol, we tested an amino acid derivative and a 3β-androsterone derivative, and alkylation products **26** and **27** were obtained in 63% and 41% yields, respectively, with excellent selectivity. Substrates with multiple reactive sites were also investigated. Several derivatives of dihydrocitronellol with two tertiary C–H sites were applied



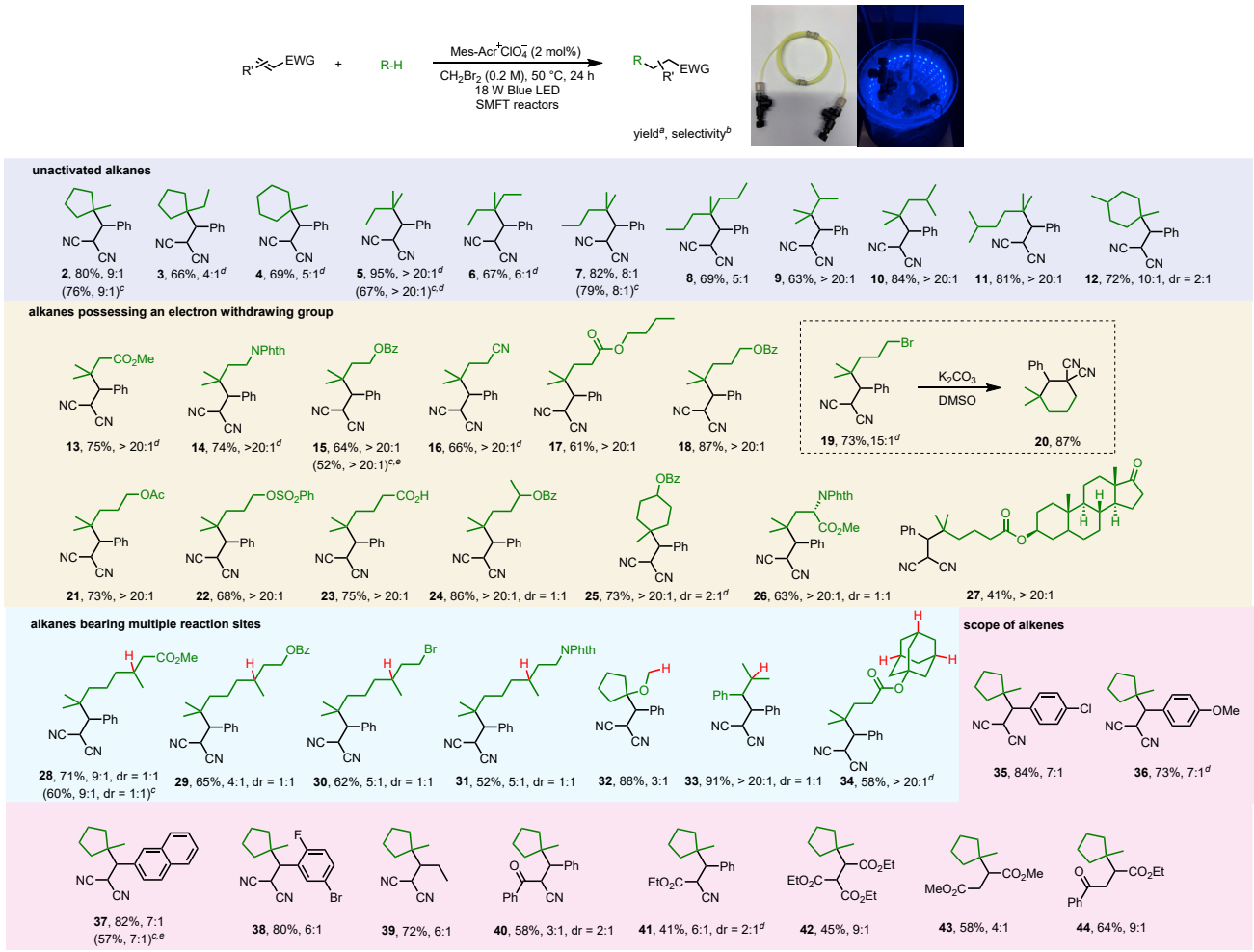
entry	R-H (x equiv.)	conditions	combined yields (%)[a]	selectivity[b]	entry	R-H (x equiv.)	conditions	combined yields (%)[a]	selectivity[b]
1	(2 equiv.)	1	98	-	7	 (5 equiv.)	1	43	C*1*/C*2* = 2/1
2	(10 equiv.)	2	35	-	8	 (5 equiv.)	2	63	C*1*/C*2* > 20/1
3	 (2 equiv.)	1	85	C*1*/C*2*/C*3* = 1/2/1	9	 (5 equiv.)	1	8	nd
4	 (5 equiv.)	2	59	C*1*/C*2*/C*3* = 0/2/1	10	 (5 equiv.)	2	64	> 20:1
5	 (5 equiv.)	1	43	C*1*/C*2*+C*3* = 1/3	11	 (5 equiv.)	1	60	C*1*/C*2* = 1/1
6	 (5 equiv.)	2	80	C*1*/C*2*+C*3* = 9/1	12	 (5 equiv.)	2	89	C*1*/C*2* = 3/1

Scheme 1. Comparison between Cl- and Br-Radical-Based Photo-HAT Protocols

[a]Yields based on analysis of the crude ^{1}H NMR spectra using 1,3,5-trimethoxybenzene as an internal standard.[b]Selectivity was determined by analysis of the crude ^{1}H NMR spectra.

(28–31). Moderate to good selectivities were obtained at the remote and more electron-rich tertiary C–H bonds. A 3:1 selectivity between the tertiary C–H bond and the primary C–H bond adjacent to an oxygen atom was observed when cyclopentyl methyl ether was used as the substrate (32). However, when a substrate bearing both benzylic and tertiary C–H bonds was applied, full selectivity for the benzylic site was observed (33). This protocol was highly selective for the most hydridic C–H bond in the adamantanecarboxylate derivative possessing multiple tertiary C–H bonds (34). For the scope of alkenes, a series of electron-deficient alkenes were tested. Dicyanides containing electron-rich or electron-deficient aryl rings or alkyl chains were all suitable substrates (35–39). Alkenes possessing ketone or ester moieties were good candidates for this transformation, affording the corresponding products (40–44) with moderate to good selectivities. This alkylation could also perform well under the optimized batch conditions (Table 1, entry 14), with slightly lower efficiency obtained than that in the SFMT reactor (2, 5, 7, 15, 28, 37).

Considering the prevalence and importance of nitrogen-containing molecules in natural products and pharmaceutical compounds, developing methods for the direct and selective C(sp^3)–H amination of unactivated alkanes is of great importance.[47] After a simple



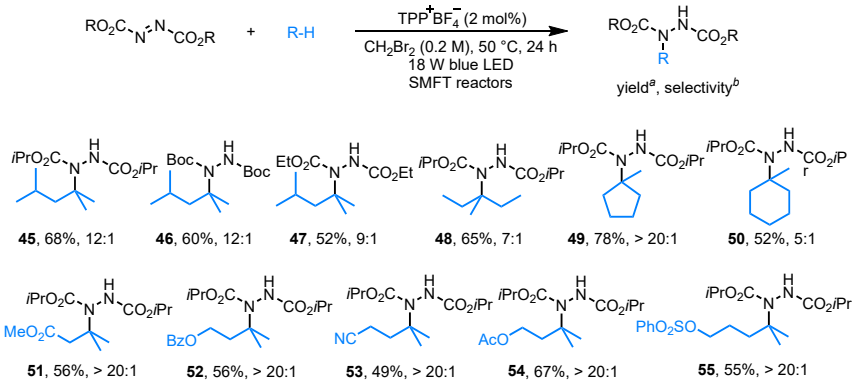
Scheme 2. Scope of the Selective Alkylation of Unactivated C–H Bonds

Reaction conditions: a mixture of the alkene (0.2 mmol), C–H partner (1 mmol), and Acr-Mes$^+$$ClO_4^-$ (0.004 mmol) in 1 mL of CH_2Br_2 (0.2 M) was injected into the SFMT reactors (volume = 0.75 mL). The reaction was performed at 50°C under 18 W blue LED irradiation for 24 h, unless otherwise noted (see Figure S1).

[a]Combined isolated yields of all the isomers.[b]Selectivity of the major isomer relative to all minor isomers, determined by analysis of the crude ^{1}H NMR spectra.[c]Reaction conducted in a sealed batch reactor (10-mL volume) with H_2O (4 mmol) as an additive for 24 h (see Figure S2).[d]10 equiv of the C–H substrate was used.[e]Reaction was conducted for 48 h.

optimization based on the established alkylation protocol, we found that by using TPP^{+}-BF_4^- as the photoredox catalyst, and dialkyl azodicarboxylates as the aminating reagent, a series of unactivated C(sp^3)–H bonds could be aminated in a selective manner (Scheme 3). The amination proceeded well with high selectivity for the tertiary C–H bonds of an alkane substrate with azodicarboxylates bearing different ester groups (**45–47**). Various acyclic and cyclic alkanes were shown to be suitable substrates and afforded hydrazine derivatives **48–50** with good to high selectivities. Excellent selectivities were obtained with alkane substrates bearing remote electron-withdrawing groups (**51–55**). This protocol offers a direct and convenient route for the amination of unactivated C(sp^3)–H bonds with high selectivity toward tertiary C–H bonds in a metal-free, additive-free, and step-economical manner.

To demonstrate the synthetic utility of the established selective alkylation and amination methods, the reactions were conducted on a larger scale, and gram quantities



Scheme 3. Scope of the Selective Amination of Unactivated C–H Bonds

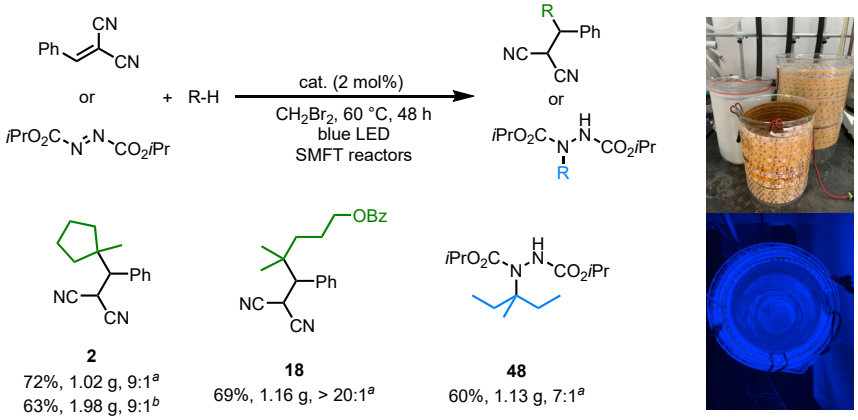
Reaction conditions: a mixture of dialkyl azodicarboxylates (0.2 mmol), C–H partner (1 mmol), and $TPP^+BF_4^-$ (0.004 mmol) in CH_2Br_2 (0.2 M) was injected into an SFMT reactor (volume = 0.75 mL). The reaction was performed at 50°C under 18 W blue LED irradiation for 24 h.[a]Combined isolated yield of all the isomers.[b]Selectivity of the major isomer compared with all minor isomers, determined by analysis of the crude ^{1}H NMR spectra.

of the products were obtained with similar yields and the same high selectivity (Schemes 4 and S1). The scale of the reaction can be further increased by utilizing SFMT reactors with a larger volume (as illustrated in the synthesis of **2**), which highlights the practical utility of this strategy.

DISCUSSION

Mechanism Study

A series of control experiments were performed to elucidate the reaction mechanism. The screening of different photocatalysts (Table S4) demonstrated that the more oxidizing photocatalysts, such as Mes-$Acr^+ClO_4^-$ ($E_{1/2}$(cat*/cat·) = + 2.06 V versus saturated calomel electrode (SCE))[48] and $TPP^+BF_4^-$ ($E_{1/2}$(cat*/cat·) = + 2.31 V versus SCE)[49] could effectively promote the reaction, whereas photocatalysts with higher triplet state energies but lower reductive potentials than Mes-$Acr^+ClO_4^-$ gave no desired product ([Ir(dF-CF_3ppy)$_2$(dtbpy)]PF_6 and *fac*-Ir(ppy)$_3$).[50] These results indicate a redox-initiated process rather than an energy transfer. Radical trapping experiments were conducted to probe the reaction intermediates. When the reaction was performed in the presence of ethene-1,1-diyldibenzene, (2-bromoethene-1,1-diyl)dibenzene (**56**) was generated (Schemes 5A and S3). Product **56** was also formed when ethene-1,1-diyldibenzene was subjected to the standard reaction conditions in the absence of the starting substrates. No reaction occurred in the absence of Mes-$Acr^+ClO_4^-$, which indicated the generation of Br radicals from CH_2Br_2 under photoredox conditions. The Stern-Volmer quenching study further illustrated that CH_2Br_2 could reductively quench the excited photocatalyst Mes-$Acr^+ClO_4^-$ (Figure S4). The strong oxidizing ability of Mes-$Acr^+ClO_4^-$[48] allows it to oxidize CH_2Br_2 ($E_{1/2}^{ox}$ = + 1.62 V versus SCE, Scheme 5B; Figure S5) via a single-electron oxidation. Density functional theory (DFT) calculations (Scheme S6) illustrated that the CH_2Br_2 radical cation generated by the single-electron oxidation of CH_2Br_2 preferentially undergoes cleavage to deliver a bromine radical and a bromomethyl cation, which possesses a much lower free energy barrier (Scheme 5C, 12.6 kcalmol^{-1}, path a) than the generation of a bromo carbon radical and a bromine cation (133.8 kcalmol^{-1}, path b). The transient bromine radical is responsible for the abstraction of the hydrogen atom from the C(sp^3)–H partner to produce a tertiary radical and release HBr. The



Scheme 4. Gram-Scale Reaction of Alkylation and Amination

[a]SFMT reactor (volume = 27.2 mL) was used (see Figure S3).[b]SFMT reactor (volume = 59.3 mL) was used.

generated tertiary radical will undergo nucleophilic addition to the Michael acceptor to furnish a radical adduct, which will be reduced by the reduced form of the photocatalyst. Protonation of the anion will furnish the final product. Notably, because the *in situ* generated HBr ($E_{1/2}^{ox}$ = + 0.76 V versus SCE, Scheme 5B and Figure S6) is more easily oxidized than CH_2Br_2, HBr might act as a more reactive bromine radical source during the reaction process. This could explain why reactions in SFMT reactors were more efficient than those in batch reactors, as SFMT reactors retained the volatile HBr (boiling point: −66°C) within the reaction solution (for more detailed mechanism study, see Schemes S2, S4, S5; Figures S7 and S8).

Conclusion

In conclusion, we have developed visible-light-mediated selective alkylation or amination of unactivated C(sp^3)–H bonds in a highly selective as well as additive- and metal-free manner. By the synergistic effects of photoredox catalysis with CH_2Br_2 as the bromine radical precursor, excellent selectivity for tertiary C(sp^3)–H bonds was achieved with a variety of unactivated C(sp^3)–H partners. Stop-flow microtubing reactors were applied and provided better reactivity than that was achieved with traditional batch reactors. Our study provides a practical strategy for using bromine radicals for HAT in a catalytic and mild fashion, which will shed new light on selective C–H functionalizations using abundant unactivated alkanes as feedstocks.

EXPERIMENTAL PROCEDURES

Full experimental procedures are provided in the Supplemental Information.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.chempr.2020.04.022.

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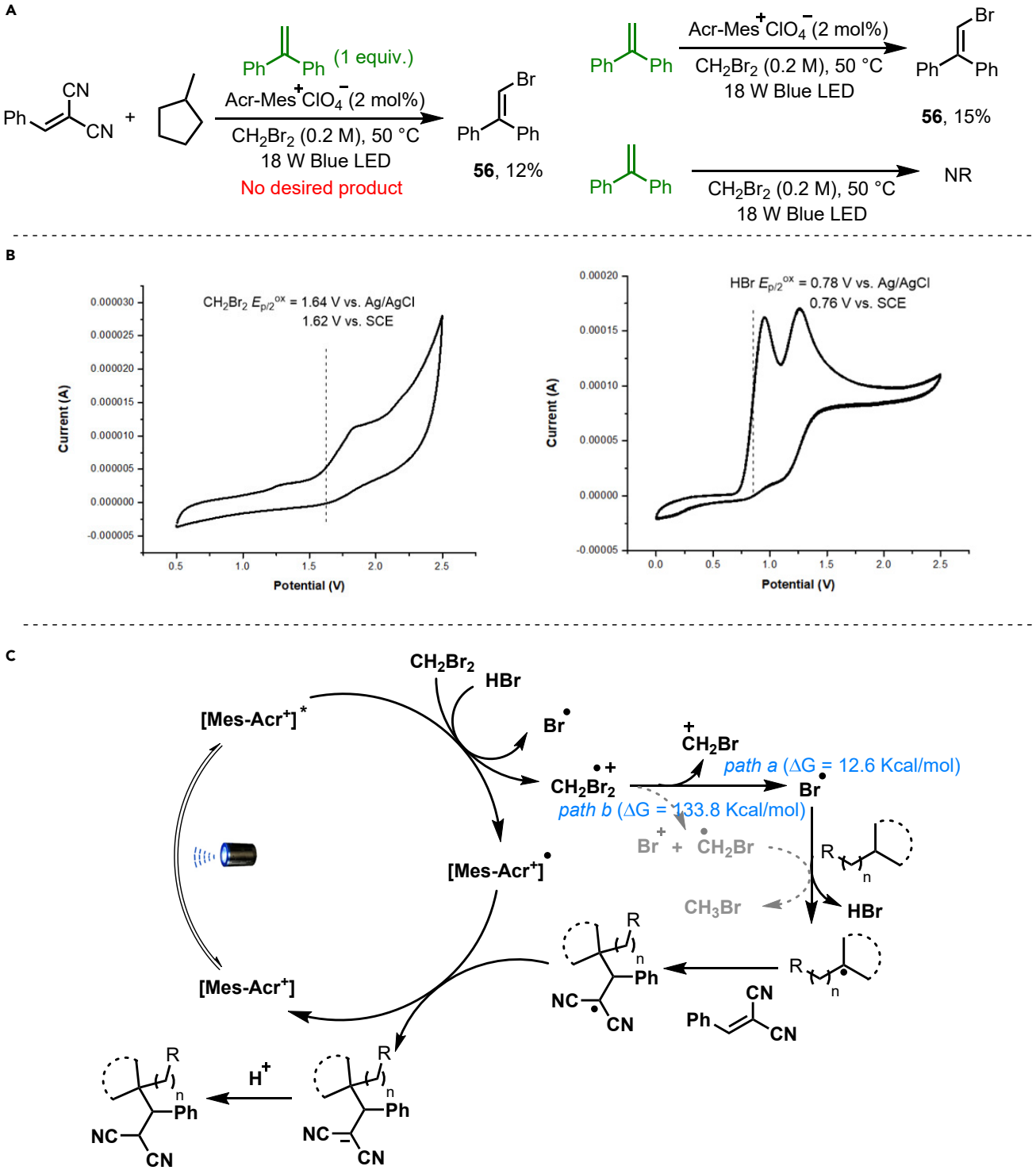

Scheme 5. Plausible Mechanism with Supporting Evidence

(A) Radical trapping experiments.

(B) Cyclic voltammetry measurements of CH_2Br_2 and HBr.

(C) Proposed plausible mechanisms.

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AUTHOR CONTRIBUTIONS

J.W., P.J., and H.D. designed the project and monitored the research progress; P.J., Q.L., and W.C.P. conducted the experiments and analyzed the data; P.J. and H.L. conducted the mechanistic study; H.J. conducted the DFT calculations; J.W. and P.J. wrote the manuscript and Supplemental Information.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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