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α-FUNCTIONALIZATION OF TETRAHYDROISOQUINOLINES WITH ACTIVATED ALKYL BROMIDE UNDER PHOTOREDOX CATALYSIS

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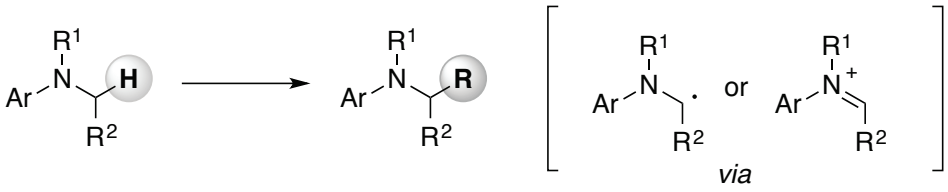
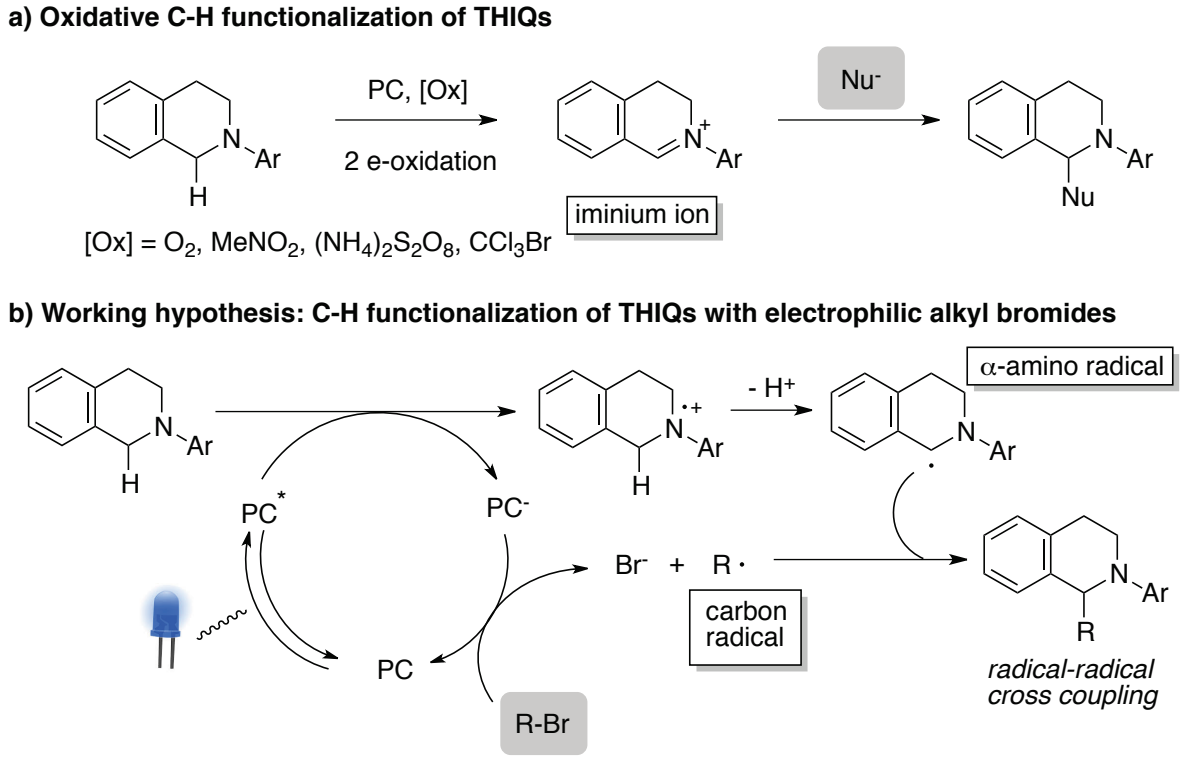
Abstract – Benzylic C-H functionalization of *N*-aryl-tetrahydroisoquinolines (THIQs) with various benzyl bromides was developed using a photoredox iridium (Ir) catalyst under blue LED irradiation, affording arylmethyl group-substituted THIQs in moderate to good yields (up to 82%). This photoredox catalyst-mediated reaction was also applicable to other activated bromides, including allyl bromide, cinnamyl bromide, propargyl bromide, and α-bromoacetate. We propose that photoredox catalyst-mediated electron transfer generates a radical species from the THIQ and another radical from the bromide, and then radical-radical cross-coupling occurs to form a new carbon-carbon bond.

Photoredox catalysis has emerged recently as a powerful strategy to promote organic reactions involving electron transfer processes under mild conditions.[1,2] In particular, direct α-functionalization of amines has attracted attention due to the utility of nitrogen-containing compounds in the pharmaceutical and agrochemical sciences. Tertiary amines are good reducing agents in photocatalysis, and therefore formation of α-amino radicals and/or iminium ions via photoredox catalysis has been widely used for direct α-functionalization of cyclic and acyclic amines (Scheme 1).[3] In 2010, Stephenson and coworkers reported the first example of photoredox catalyst-mediated oxidative aza-Henry reaction of *N*-aryl-tetrahydroisoquinolines (*N*-aryl-THIQs) with nitromethane.[4] Following this pioneering work, many reports have defined the scope of the reaction; currently, this type of oxidative C-H functionalization of THIQs is applicable to addition reactions with a wide variety of (pro)nucleophiles,[5] acylation,[6] and [3+2] cycloaddition reactions[7] (Scheme 2a). In contrast, C-H functionalization with electrophilic compounds, such as alkyl halides, via photoredox catalysis has been less well studied.[8-10]



Scheme 1. General representation of C-H functionalization of tertiary amines



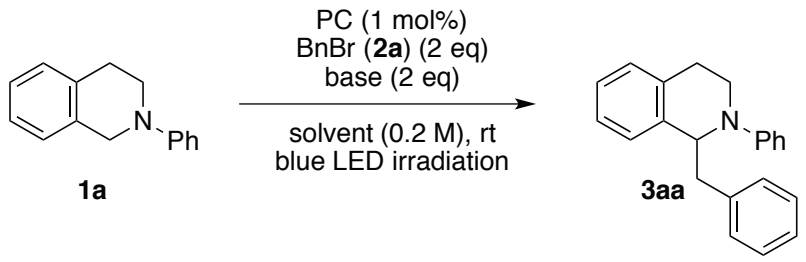
Scheme 2. Oxidative C-H functionalization of THIQs with nucleophiles and redox-neutral C-H functionalization of THIQs with electrophilic alkyl bromides

In general, an α-amino radical of THIQs, generated by reductive quenching of photo-excited catalyst (PC*), readily undergoes further oxidation by reaction with oxidants. When CCl_3Br was used as an oxidant, Stephenson proposed that CCl_3Br oxidizes the α-amino radical intermediate to give the corresponding iminium ion, with concomitant generation of a $\bullet CCl_3$ radical and a bromide anion.[5k] This idea led us to think that the α-amino radical intermediate could participate in a radical-radical cross-coupling reaction, if its oxidation is suppressed by replacing CCl_3Br with a less oxidizing alkyl bromide. Our reaction design is outlined in Scheme 2b. Thus, according to the literature, proton-coupled electron transfer (PCET) would occur to afford an α-amino radical intermediate when *N*-aryl-THIQs react with an excited photoredox catalyst.[11] In conjunction with this oxidation, a carbon radical intermediate would be produced separately via single electron transfer (SET) from the resulting reduced photoredox catalyst (PC^-) to an appropriate alkyl halide, followed by elimination of halide anion. Finally, a

carbon-carbon bond-forming reaction would occur as a result of recombination of the two radical species to give a cross-coupling product. Since radical-radical cross-coupling is hard to achieve in photoredox catalysis, it is common to trap an α-amino radical with C-C multiple bonds,[12] and precursors of the second radical species are limited to cyanobenzene derivatives and ketones.[13] Herein we report α-functionalization of *N*-aryl-THIQs with various activated alkyl halides via photoredox catalysis under blue LED irradiation.

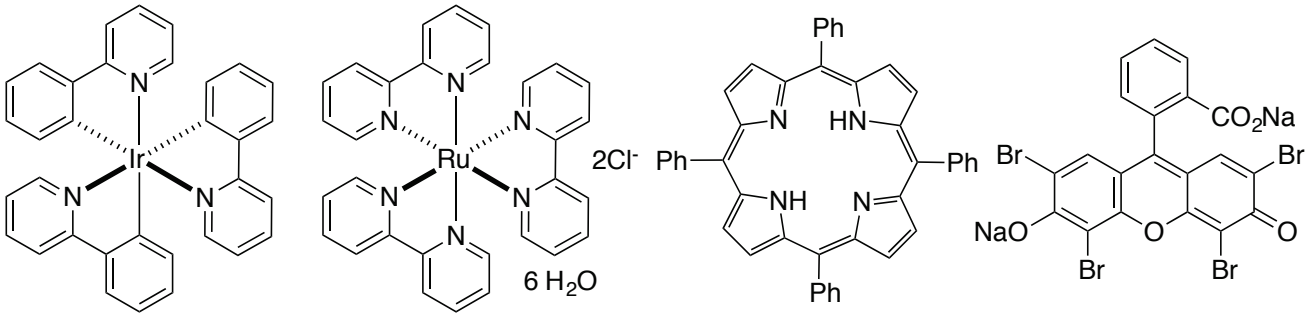
To test our working hypothesis, we selected the reaction of *N*-phenyl-tetrahydroisoquinoline (**1a**) with benzyl bromide (**2a**) as a model reaction, expecting that benzyl bromide would be able to accept a single electron from the reduced catalyst (PC^-), but not oxidize the α-amino radical. We also expected that the balance between the electronic characters of the nucleophilic α-amino radical and the relatively electrophilic benzyl radical would be within an acceptable range for selective cross-coupling. First, photoredox catalysts (PCs) were screened by conducting the model reaction in degassed MeCN with K_2HPO_4 as a base at room temperature under blue LED irradiation (entries 1-4). Among the PCs examined, $Ir(ppy)_3$ (**4**)[14] was found to be the best for this reaction, and the desired **3aa** was obtained in 46% yield after 10 h (entry 1).[15,16] $Ru(bpy)_3Cl_2$ (**5**) gave **3aa** in 14% yield (entry 2), but no or only a trace amount of **3aa** was detected in reactions with other organic photoredox catalyst **6** and **7** (entries 3 and 4). Thus, it seems that an appropriate balance between oxidation and reduction potential of the catalyst is important for promoting the reaction smoothly. We also examined the effect of solvent (entries 5-8) and base[17] (entries 9-12), but no improvement was obtained. Although the starting **1a** was almost completely consumed in many cases, the chemical yield did not exceed 50%, due to the formation of unidentified by-products. We speculated that this might be partially attributed to over-oxidation of **1a** to the iminium ion and decomposition of **3aa**. In contrast, homocoupling of the benzyl radical was negligible as judged from NMR measurement of the crude mixture. In order to suppress undesired reactions, we examined the effect of reaction temperature. As we had hoped, the reaction proceeded more cleanly at 5 °C, at the expense of the reaction rate (entry 13). Further decrease of the reaction temperature completely inhibited the reaction. To our delight, the chemical yield was greatly improved to 75% when the concentration of the reaction mixture was changed to 0.1 M (entry 14). In the absence of the base, the chemical yield was decreased considerably (entry 15). A reference reaction (entry 16) clearly demonstrated that blue LED irradiation is essential for the reaction to proceed. In addition to the reaction temperature and concentration of the reaction mixture, reaction time was also important to maximize the chemical yield. Decomposition of **3aa** could not be neglected in the case of longer reaction times. Unfortunately, benzyl chloride could not be used in this transformation (entry 17).

Table 1. Optimization of reaction conditions for cross coupling of THIQ (**1a**) with benzyl bromide (**2a**)



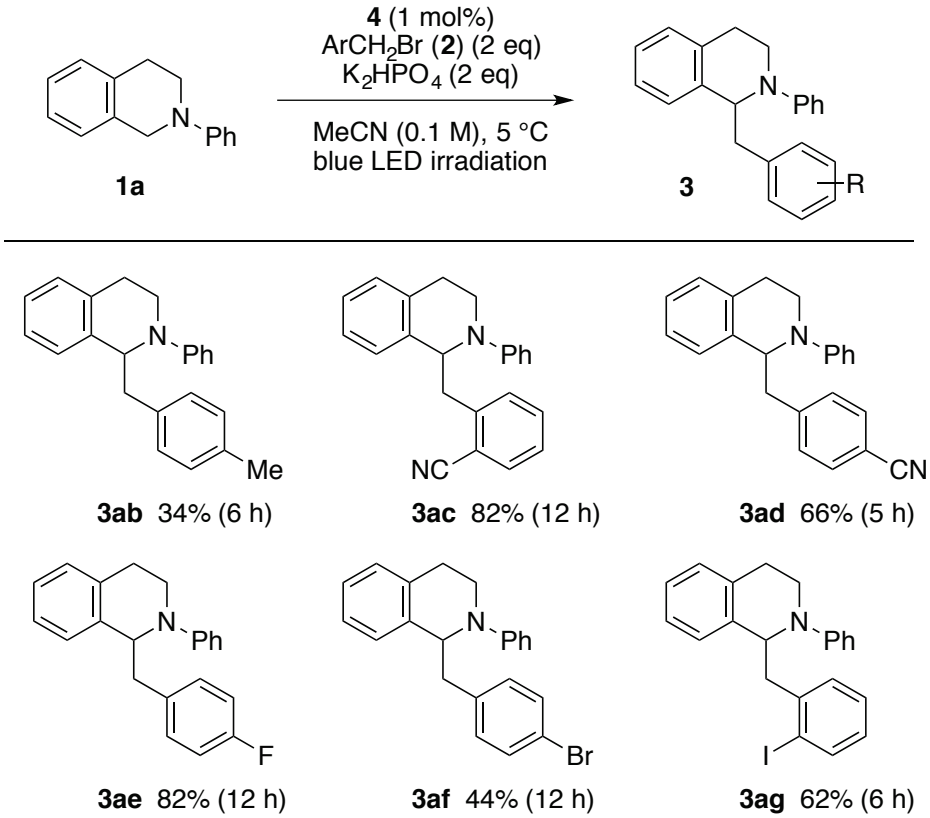
Entry	PC	Solvent	Base	Time (h)	Yield of **3aa** (%)[a]	Recovered **1a** (%)[a]
1	**4**	MeCN	K_2HPO_4	10	46	N.D.
2	**5**	MeCN	K_2HPO_4	10	14	3
3	**6**	MeCN	K_2HPO_4	12	N.D.	N.D.
4	**7**	MeCN	K_2HPO_4	6	Trace	5
5	**4**	DMF	K_2HPO_4	10	17	4
6	**4**	DMA	K_2HPO_4	10	13	15
7	**4**	CH_2Cl_2	K_2HPO_4	10	11	26
8	**4**	THF	K_2HPO_4	10	10	89
9	**4**	MeCN	K_3PO_4	6	26	8
10	**4**	MeCN	K_2CO_3	6	38	15
11	**4**	MeCN	Na_2CO_3	6	10	89
12	**4**	MeCN	KOAc	6	18	50
13[b]	**4**	MeCN	K_2HPO_4	12	56	N.D.
14[b,c]	**4**	MeCN	K_2HPO_4	12	75[d]	8
15[b,c]	**4**	MeCN	—	12	47	N.D.
16[b,c,e]	**4**	MeCN	K_2HPO_4	12	N.D.	92
17[b,c,f]	**4**	MeCN	K_2HPO_4	12	N.D.	97

[a] NMR yield. [b] 5 °C. [c] 0.1 M. [d] Isolated yield. [e] Without blue LED irradiation. [f] Run with benzyl chloride instead of **2a**. N.D.: Not detected.



$Ir(ppy)_3$ (**4**) $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (**5**) TPP (**6**) Eosin Y (Na) (**7**)

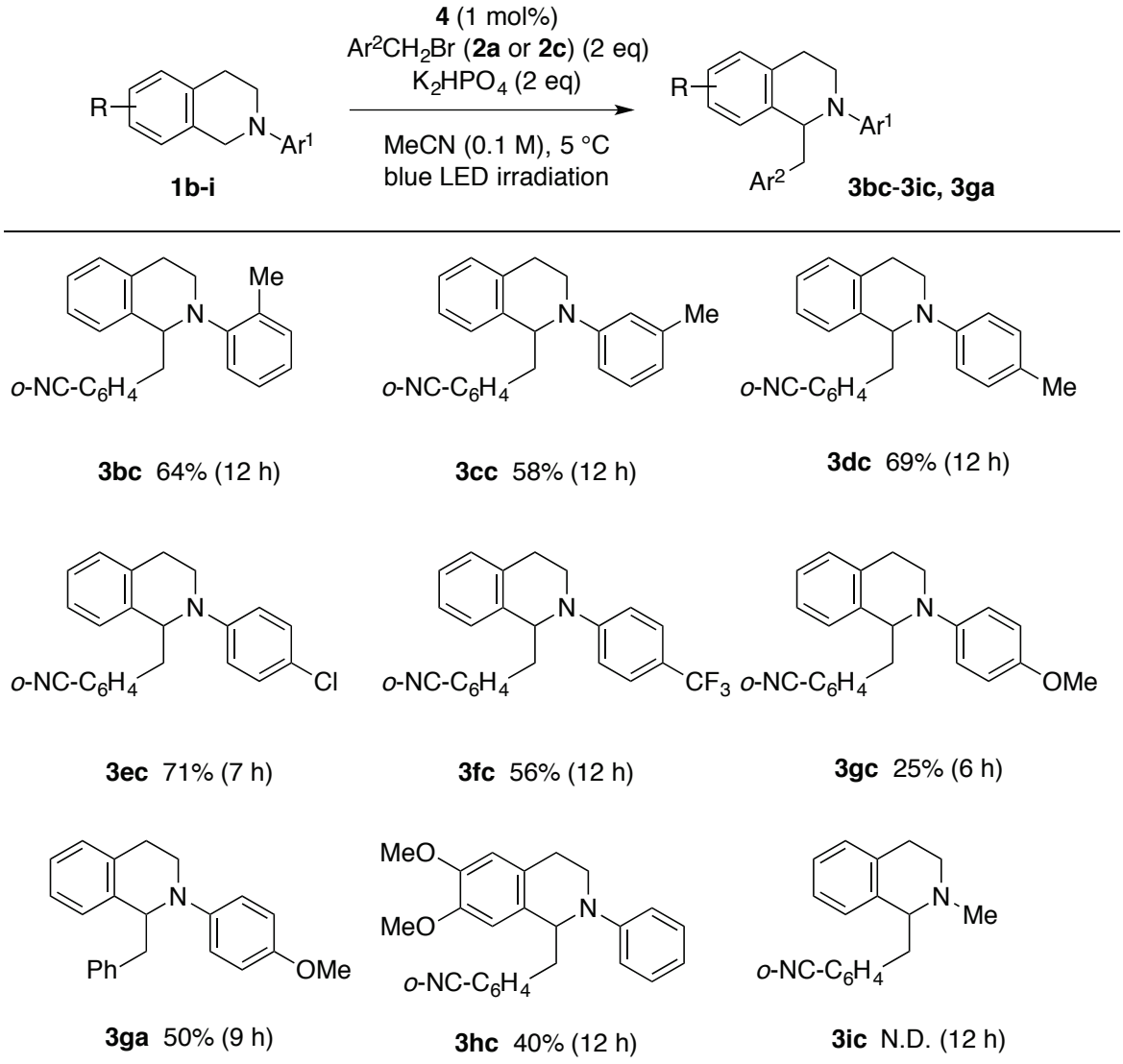
We next investigated the substituent effect of benzyl bromide under the optimized reaction conditions.[18] Electron-donating groups considerably retarded the reaction. For example, the reaction of **1a** with *p*-methylbenzyl bromide (**2b**) gave the coupling product **3ab** in 34% yield. Furthermore, the desired product was not detected in the reactions with *p*-methoxybenzyl or 2,4,6-trimethylbenzyl bromide, resulting in recovery of **1a**. This is probably because SET from the reduced Ir(II) complex to electron-rich benzyl bromides was slow. In contrast, benzyl bromides bearing an electron-withdrawing group tended to undergo the desired reaction more efficiently. When cyano group-substituted benzyl bromides **2c** and **2d** were used under the optimized reaction conditions, C-H substituted products **3ac** and **3ad** were obtained in 82% and 66% yields, respectively. Although the yield was not satisfactory in the case of a brominated compound **2f**, *p*-fluoro and *p*-iodobenzyl bromides (**2e** and **2g**) were converted to the cross-coupling products **3ae** and **3ag** at synthetically useful levels (82% and 62% yields, respectively).



Scheme 3. C-H Functionalization of **1a** with benzyl bromide derivatives under blue-LED irradiation

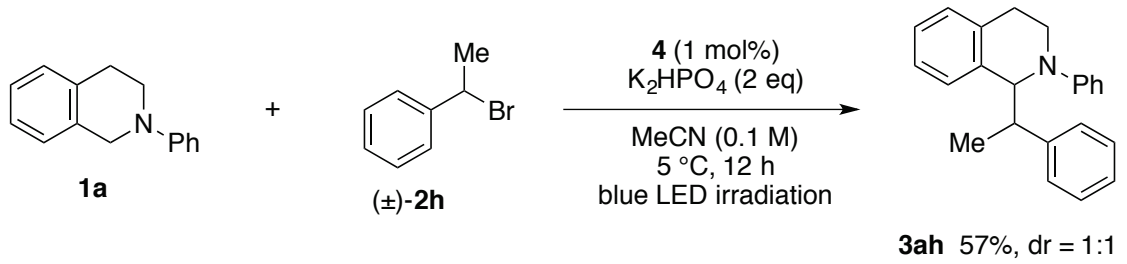
Next, we turned our attention to the generality of THIQs. Various THIQs were subjected to reaction with **2c** under the optimized reaction conditions (Scheme 4). As regards substituents on the *N*-aryl ring, *o*-, *m*-, *p*-methyl, chloro, and trifluromethyl groups were tolerated, and the desired coupling products **3bc**-**3fc** were formed in good yields. While the reaction of *p*-methoxyphenyl-substituted THIQ **1g** with **2c** gave **3gc** in only 25% yield, **1g** reacted with **2a** more efficiently, affording **3ga** in 50% yield. Treatment of

N-pheny-6,7-dimethoxy-THIQ (**1h**) with **2c** under photoredox catalysis afforded **3hc** in 40% yield, indicating that methoxy groups on the aromatic ring on the THIQ side have less impact on the reaction efficiency. Unfortunately, reaction of *N*-methyl-THIQ **3i** with **2c** gave a complex mixture, and no coupling product was observed.



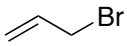
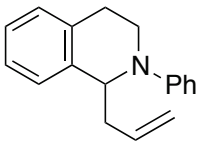
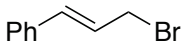
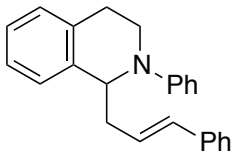
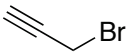
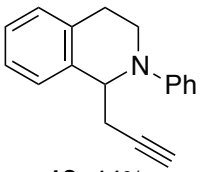
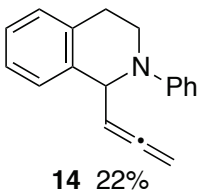
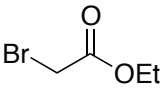
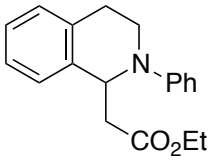
Scheme 4. C-H Functionalization of various THIQs via photoredox catalysis under blue-LED irradiation. N.D.: Not detected.

In addition to the primary benzyl bromides, we next examined the reaction with secondary bromide **2h** (Scheme 5). To our delight, the desired reaction of **1a** with **2h** (2 eq.) proceeded smoothly in spite of the possible steric repulsion, and **3ah** was isolated in 57% yield with a 1:1 diastereomeric ratio.



Scheme 5. Coupling reaction of *N*-phenyl-THIQ (**1a**) with secondary benzyl bromide **2h**

Table 2. Cross coupling reaction of **1a** with other activated alkyl bromides

entry	RBr	time (h)	product / isolated yield
1	 **8**	6	 **9** 62%
2	 **10**	12	 **11** 38%
3	 **12**	12	 **13** 44%  **14** 22%
4	 **15**	12	 **16** 42%

Having confirmed the availability of benzyl bromides for radical-radical cross-coupling with THIQs, we became interested in the reaction with other alkyl bromides (Table 2). Although reaction with 2-bromopropane did not occur, and **1a** was recovered, allyl bromide (**8**) participated in the desired catalytic cycle to give allylated compound **9** in 62% yield (entry 1). Encouraged by this result, we tested other bromides activated by a neighboring unsaturated bond. In the case of cinnamyl bromide **10**, compound **11** was formed as a single regioisomer, albeit in 38% yield (entry 2). This result suggested that

S_N2' attack of the α-amino radical at the γ-position of **10** might not be involved in this reaction. Under the same conditions, propargyl bromide **12** reacted with **1a** without difficulty (entry 3). In this reaction, coupling reaction occurred at the isomeric positions of **12** to deliver **13** (44%) from the propargyl radical and **14** (22%) from the corresponding allenyl radical. Finally, based on the structural similarity with **8**, we examined whether α-bromoacetate would be available as a coupling partner. Gratifyingly, the desired C-H functionalization of **1a** occurred under the same reaction conditions, affording **16** in 42% yield. Since **16** has a β-amino carbonyl substructure, it can be synthesized via oxidative Mannich reaction of **1a** with enol silyl ethers.[5g,o] In contrast, our reaction was performed using electrophilic bromide.

We have developed a direct C-H α-functionalization of *N*-aryl-THIQs using electrophilic activated alkyl halides in the presence of photoredox catalysts. The key to success is likely to be photoredox catalyst-mediated oxidation of tertiary amines coupled with reduction of alkyl bromides to give two different radical species, which then undergo redox-neutral radical-radical cross-coupling. However, we cannot rule out the possibility of other reaction pathways at present. It is noteworthy that electrophilic alkyl bromides were used in the present direct C-H functionalization of THIQs, whereas most of the previous direct C-H functionalizations of THIQs were achieved in an oxidative manner using (pro)nucleophiles as coupling partners. Various alkyl bromides could be employed in this reaction, including benzyl bromides, allyl bromide, propargyl bromide, cinnamyl bromide, and α-bromoacetate. Further investigations of other types of redox-neutral direct α-functionalizations of amines are in progress.

ACKNOWLEDGEMENTS

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15. The desired product was not detected when benzyl phosphonate [$BnOP(O)(OEt)_2$] and benzyl triflate were used under the same reaction conditions.
16. The addition of Lewis acids such as $LiClO_4$ and AgOTf to activate alkyl halides failed, and the desired product was not formed at all.
17. Pyridine derivatives such as 2,6-lutidine were totally ineffective.
18. A typical experimental procedure for photoredox-catalyzed α-functionalization of tetrahydroisoquinolines is given for compound **3ac**: An oven-dried test tube was charged with $Ir(ppy)_3$ (1.3 mg, 1 mol%), *N*-phenyl-tetrahydroisoquinoline **1a** (42 mg, 0.2 mmol), and dry K_2HPO_4 (70 mg, 0.4 mmol). To the tube were added MeCN (2 mL) and 2-cyanobenzyl bromide **2c** (78 mg, 0.4 mmol). The resultant mixture was degassed by freeze-pump-thaw cycling (3 times). The mixture was cooled to 5 °C, then irradiated with blue light for 12 h with stirring. Then, after the light was turned off, water was added to the mixture, and the organic materials were extracted with diethyl ether (2 times). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 10/1) to provide 1-(2-cyanobenzyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline **3ac** (53 mg, 82%) as a yellow oil.