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Traceless Aminoalkyl Radical-Induced Halogen-Atom Transfer for Minisci Reactions

Jin-Song Huang, Zhi-Hui Wang, Xue-Ting Li, Shi-Yu Guo,* Xu-Liang Jiang,* and Qing-An Chen*

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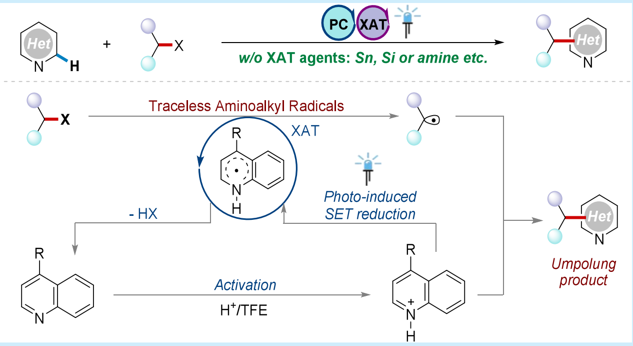
ABSTRACT: Halogen-atom transfer (XAT) provides a viable strategy to convert alkyl halides into the corresponding carbon radicals, but the usage of equivalent XAT reagents and excess oxidants is usually inevitable. Herein, we present a traceless aminoalkyl radical-induced XAT process for the Minisci reaction, especially without the participation of excess XAT reagents under redox-neutral conditions. Mechanistic experiments indicated that the formation of comparable aminoalkyl radicals occurred through the single-electron transfer reduction of protonated heteroaromatics, differing from the conventional oxidation process of amines used to generate α-aminoalkyl radicals.



Due to their wide availability, alkyl halides represent a versatile class of organic compounds with broad applications in organic synthesis.[1] Traditionally, alkyl halides have been recognized as important electrophiles (E^+) owing to the partial positive charge on the carbon atom bonded to the halogen (a result of the halogen's high electronegativity).[2] Taking advantage of the good leaving ability of halogen, alkyl halides undergo substitution reactions with a variety of nucleophiles (Nu^-), including water, alcohols, amines, and other anions, through two primary mechanisms: S_N1 and S_N2. In contrast, it is hard to couple alkyl halides with other electrophiles under redox-neutral conditions. For example, the use of stoichiometric amounts of reductant is usually required for its coupling with aryl halides,[3] protonated heteroaromatics,[4] etc. Therefore, it is of great importance to develop a radical approach to realize the coupling of alkyl halides with electrophiles under redox-neutral conditions (Figure 1a).

Halogen-atom transfer (XAT) has emerged as one of the most important approaches to generate carbon radicals from organic halides in synthetic chemistry.[1a,5] In general, organic tin,[6] silyl,[7] boryl,[8] and phosphorus[9] species have shown good activities in generating the open-shell intermediate by homolytic C−X bond cleavage via XAT under thermal or light irradiation conditions. However, the toxicity, availability issues, or cost concerns associated with these XAT reagents have somewhat impeded further advances in this field. In recent years, visible light photocatalysis represents the state-of-the-art technique to promote various radical reactions[10] and has enhanced the chemists' ability in generating carbon radicals from unactivated alkyl halides. Based on the previous works of Lalevée et al.,[11] Doyle et al.,[12] and Leonori et al.,[13] it has been demonstrated that α-aminoalkyl radicals could promote the homolytic activation of the C−X bond under photoredox catalysis, where aliphatic amines go through oxidation via single-electron transfer (SET) followed by deprotonation to furnish the key α-aminoalkyl radical. They have been widely used in dehalogenation,[13a,14] Giese reaction,[15] Heck-type olefination,[13a] and aromatic C−H alkylation[13a] protocols. Although commercially available amines could be used directly for the generation of α-aminoalkyl radicals, stoichiometric amounts of XAT reagent amines are still required as a reductant or abstractor in those XAT processes (Figure 1b). Therefore, it is still a great challenge to develop a strategy to activate alkyl halides for the generation of carbon radicals using a catalytic amount XAT reagent.[16]

Minisci C−H alkylation is widely used to introduce alkyl groups into heteroaromatics with utilization of diverse alkyl radical precursors,[17] such as aliphatic carboxylic acids,[18] amino acids,[19] primary alcohols,[20] boronic acids,[21] and alkyltrifluoroborates.[22] Unactivated alkyl halides are difficult to be directly reduced through the SET process owing to their highly negative reduction potentials ($E_{1/2}^{red} < -2.0$ V vs SCE).[15d] With the assistance of the XAT strategy, the Minisci reaction using alkyl halides as a carbon radical source could effectively proceed.[4a,17c,23] This process necessitates not only an equivalent amount of XAT reagents but also results in redox imbalance (Figure 1c).[4] Up to now, there is no report on

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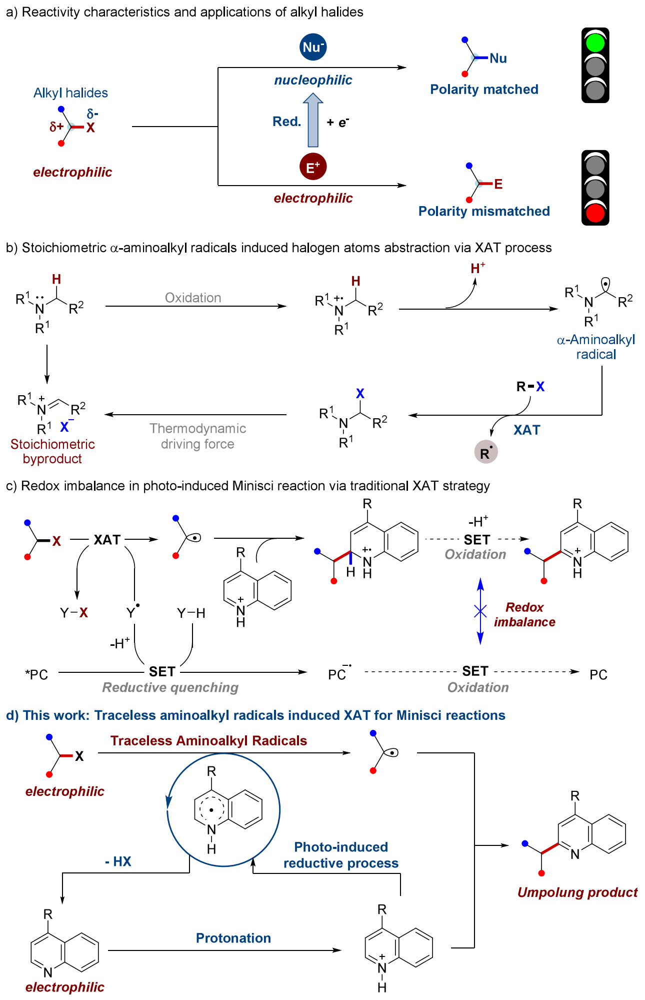
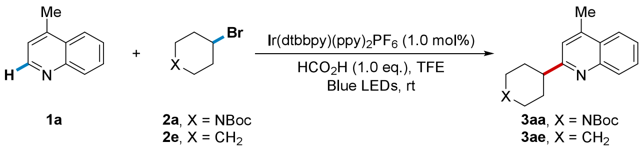


Figure 1. Carbon radicals generated from alkyl halides via XAT.

Table 1. Optimization of Reaction Conditions[a]



entry	alkyl halides	variation from standard conditions	yield of **3aa** or **3ae** (%)
1	**2a**	none	75 (72)
2	**2a**	without PC	0
3	**2a**	in dark conditions	0
4	**2a**	air instead of N_2	0
5	**2a**	oil bath at 80 °C in the dark	0
6	**2a**	HFIP instead of TFE	59
7	**2a**	MeOH instead of TFE	10
8	**2a**	MeCN, DCM, and DMSO instead of TFE	0
9	**2a**	PC-1 and PC-2 instead of Ir(dtbbpy)$(ppy)_2PF_6$	0
10	**2a**	using 2.5 equiv of **2a**	70
11	**2a**	without HCO_2H	71
12	**2e**	without HCO_2H	75[b]
13	**2e**	TFE/H_2O (9:1, v/v), without acid	94[b] (89)

[a] Conditions: compound **1a** (0.20 mmol), compound **2** (0.24 mmol), Ir(dtbbpy)$(ppy)_2PF_6$ (1.0 mol %), HCO_2H (0.20 mmol), TFE (2.5 mL), blue light-emitting diodes (LEDs, λ_{max} = 456 nm, 50 W), N_2 atmosphere, room temperature, and 24 h. Yields were determined by ^1H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. Isolated yields were given in parentheses. [b] Yields were determined by gas chromatography with flame ionization detection (GC−FID) analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. PC-1, $Ru(bpy)_3(PF_6)_2$; PC-2, (Mes-Arc)ClO_4.

visible-light-induced Minisci alkylation between unactivated alkyl bromides and azaarenes via the XAT process just using a catalytic amount of XAT agents under redox-neutral conditions.

Intrigued by these precedents and our previous work,[24] we posed the question whether the radical generated from SET reduction of protonated *N*-heteroarene could serve as an *α*-aminoalkyl radical to promote the XAT process. Herein, this hypothesis has been validated by traceless aminoalkyl radical-induced C−H alkylation of *N*-heteroarenes with unactivated alkyl halides under photocatalysis (Figure 1d). Remarkably, the developed XAT-driven Minisci reaction could proceed smoothly in the absence of extra halogen abstractors under mild and redox-neutral conditions.

As a model reaction, the alkylation of 4-methylquinoline **1a** with *N*-Boc-4-bromopiperidine **2a** was investigated under various conditions (Table 1 and section 2 of the Supporting Information for details). Pleasingly, the desired product **3aa** could be obtained in 75% yield under the optimized conditions (Table 1, entry 1). In the absence of either irradiation or photocatalyst Ir(dtbbpy)$(ppy)_2PF_6$, control experiments resulted in quantitative recovery of 4-methylquinoline **1a** (entries 2 and 3). No desired product **3aa** was observed under thermal conditions or an air atmosphere (entries 4 and 5). The utilization of fluoroalcohol solvents was found crucial for promoting the reaction, and trifluoroethanol (TFE) exhibited better results than hexafluoroisopropanol (HFIP) (entry 6). However, methanol exhibited poor efficiency in promoting the reaction (entry 7). Other aprotic solvents, such as acetonitrile (MeCN), dichloromethane (DCM), and dimethyl sulfoxide (DMSO), were all found to be ineffective (entries 8). The plausible rationale is that fluoroalcohol, as highly polar solvent, can activate *N*-heteroarenes via hydrogen bonding, stabilize radical intermediates, and thereby facilitate the reaction progression.[25] Additionally, Ir(dtbbpy)$(ppy)_2PF_6$ was found to be the best photocatalyst for this transformation, while other photocatalysts exhibited no catalytic ability (entry 9). It is noteworthy that this protocol was highly efficient, requiring only 1.2 equiv of alkyl bromides to give corresponding products with a high yield (entry 10 vs 1). Unexpectedly, a similar reactivity was observed without the addition of external acid, which was usually indispensable for the Minisci reaction (entry 11 vs 1). The investigation of alkylation with cyclohexyl bromide **2e** in the absence of an additional acid was conducted. The alkylation of 4-methylquinoline **1a** with cyclohexyl bromide **2e** could afford the desired product **3ae** with 75% yield in an acid-free system (entry 12). Notably, when the reaction of cyclohexyl bromide **2e** was performed in the mixture solvent TFE/H_2O (9:1), the yield of the desired product **3ae** increased to 94% (entry 13).

With the optimized conditions in hand, the scope of unactivated alkyl halides was explored (Figure 2). It was found that a series of secondary and primary alkyl halides were proven to be feasible, affording C−H alkylation products in moderate to good yields. Cyclic alkyl halides, comprising

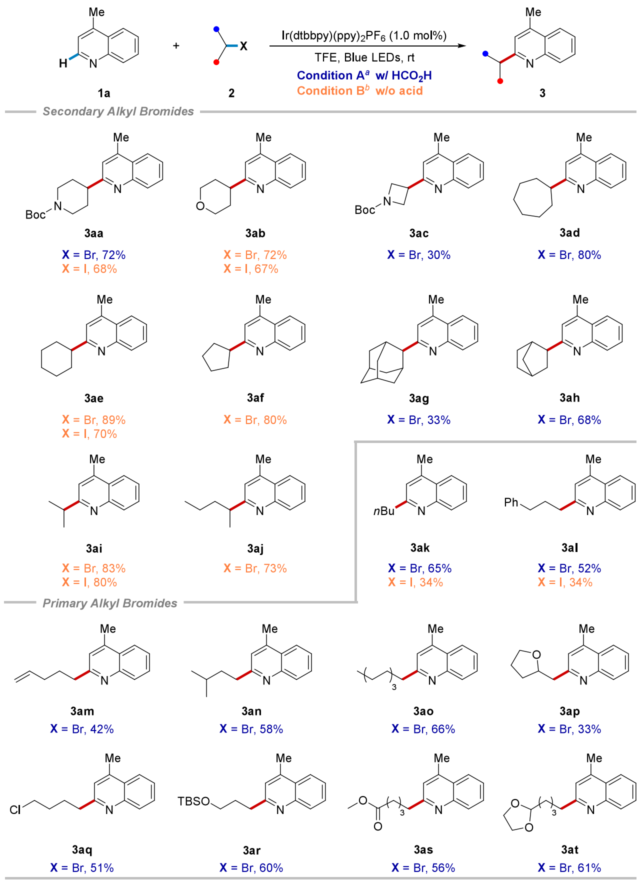


Figure 2. Substrate scope of alkyl halides. [a]Conditions A: compound **1a** (0.20 mmol), compound **2** (0.24 mmol), Ir(dtbbpy)(ppy)$_2$PF$_6$ (1.0 mol %), HCO$_2$H (0.20 mmol), TFE (2.5 mL), blue LEDs (λ_{max} = 456 nm, 50 W), N$_2$ atmosphere, room temperature, and 24 h. [b]Conditions B: without HCO$_2$H, TFE/H$_2$O (9:1, v/v) was used instead of TFE. Isolated yields were given.

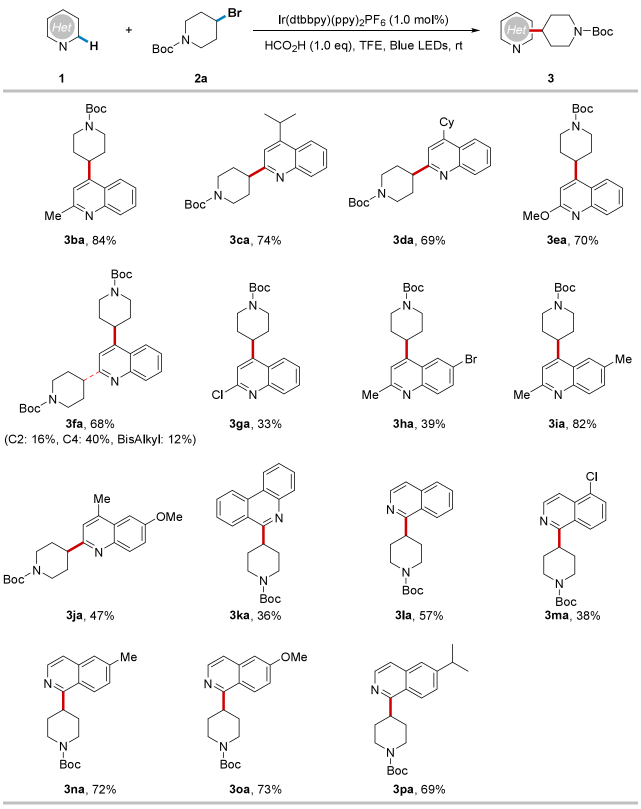


Figure 3. Substrate scope of *N*-heteroarenes. Conditions: compound **1** (0.20 mmol), compound **2a** (0.24 mmol), Ir(dtbbpy)(ppy)$_2$PF$_6$ (1.0 mol %), HCO$_2$H (0.20 mmol), TFE (2.5 mL), blue LEDs (λ_{max} = 456 nm, 50 W), N$_2$ atmosphere, room temperature, and 24 h. Isolated yields were given.

heterocycles (**3aa**−**3ac**) and single (**3ad**−**3af**) and fused (**3ag** and **3ah**) carbocycles, proceeded smoothly. Notably, secondary alkyl halides could still achieve excellent yields even without additional acid (**3aa**, **3ab**, **3ae**, **3af**, **3ai**, and **3aj**), which is difficult to achieve in traditional Minisci protocols. Ring-strained and sterically bulky alkyl halides were also compatible in this protocol but with lower yields (**3ac** and **3ag**). Besides, the reaction still worked well when some of the alkyl bromides were replaced with corresponding alkyl iodides (**3aa**, **3ab**, **3ae**, **3ai**, **3ak**, and **3al**). For primary alkyl halides, a variety of common functionalities, such as alkyl (**3ak**), phenyl (**3al**), alkenyl (**3am**), chlorine (**3aq**), ether (**3ap**), ester (**3ar** and **3as**), and acetal (**3at**), were also well-tolerated to afford the desired alkylated products. Alkyl groups containing acid-labile substituents could be successfully introduced onto *N*-heteroarenes, reflecting the mildness of the protocol. Although alkyl chlorides were not active owing to the high bond energy of the C−Cl bond, this protocol displayed good selectivity on the activation between C−Br and C−Cl bonds (**3aq**).

Next, further exploration of the *N*-heteroarene scope, involving quinolines, isoquinolines, and phenanthridine, was conducted (Figure 3). This C−H alkylation was found to be amenable to a wide range of quinolines bearing electron-donating groups (EDGs), such as methyl, isopropyl, cyclohexyl, and methoxy groups, at either the C-2 or C-4 position (**3ba**−**3ea**). Unsubstituted quinoline showed a slight preference on its C-4 position (**3fa**). The introduction of electron-withdrawing groups (EWGs) onto quinolines decreased the reactivities (**3ga** and **3ha**). Reactions of 2,6-dimethyl- and 4-methyl-6-methoxy-quinolines delivered corresponding products in 82 and 47% yields, respectively (**3ia** and **3ja**). Furthermore, phenanthridine could also be tolerated to incorporate an alkyl group into its C-6 position (**3ka**). For isoquinolines, good regioselectivities were observed to deliver the desired products with C-1 alkylation (**3ma** and **3na**). Other *N*-heteroarenes, like pyridines, were also explored, but the yields were not satisfactory (section 3 of the Supporting Information for details).

To elucidate the mechanism, a series of control experiments were carried out. When 6-bromohex-1-ene **2u** and (bromomethyl)cyclopropane **2v** were employed as substrates, ring-closed cyclization product **3au** and ring-opened linear product **3av** were observed without the formation of products **3au′** and **3av′** (Supplementary Figure 5).[4a] Alcohols could be used for alkylation of heteroarenes though hydrogen-atom transfer (HAT) followed by spin-center shift (SCS) dehydration.[20a] The hydroxyl group and halogen are both EWGs, and the alkyl halide may also undergo a similar process to generate the α-haloalkyl radical. However, radical clock experiments indicate that products **3au** and **3av** are probably not generated through α-haloalkyl radical **A**, ruling out the HAT and SCS pathway (section 6.8.2 of the Supporting Information for details). In addition, Katritzky salts[26] and *N*-benzylpyridinium salts[27] were proven to be good alkyl radical precursors, raising the possibility that the alkyl halides undergo nucleophilic substitution with *N*-heteroarene to generate corresponding salt following carbon radicals. In fact, no corresponding product was observed when *N*-alkyl quinolinium iodide **4ai′** was subjected to the standard conditions, ruling out the possibility of *in situ* generation of *N*-alkyl quinolinium salts (Supplementary Figure 18). This reaction was completely inhibited when radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added, and cyclohexyl-TEMPO adduct **5** was detected by high-resolution mass spectrometry (HRMS) (Supplementary Figure 3). These results indicate the generation of carbon radicals solely from the cleavage of the C−X bond of alkyl halides. Then, light on−off experiments showed that this transformation proceeded only under constant light irradiation, which might exclude the radical chain process (Supplementary Figure 7). In order to deeply understand the mechanism, fluorescence quenching experiments and Stern−Volmer analysis were conducted. The results showed that only the combination of quinoline and acid could quench excited-state Ir(dtbbpy)(ppy)$_2$PF$_6$ (Supplementary Figure 12). The cyclic voltammetry (CV) measurement of 4-methylquinoline **1a** showed that the addition of acid could raise the redox potential $E_{1/2}^{\mathrm{red}}$ (Supplementary Figure 15), which made quinoline more susceptible to be reduced. The experimental $^*E_{1/2}^{\mathrm{ox}}$ of Ir(dtbbpy)(ppy)$_2$PF$_6$ in TFE was measured as $^*E_{1/2}^{\mathrm{ox}}$ = −1.54 V (vs SCE).[24a] These results suggest that protonated quinoline **1** ($E_{1/2}^{\mathrm{red}}$ = − 1.22 V vs SCE in TFE) could be reduced by the excited state of photocatalyst Ir(dtbbpy)(ppy)$_2$PF$_6$ via the SET process. This transformation was proven to result in acid production (section 6.3 of the Supporting Information).

Based on the results above, the mechanism merging oxidative quenching and the XAT cycle was proposed in Figure 4. When the mixture of 4-methylquinoline **1a** and alkyl bromides **2** was taken as an example, initially, the excited photocatalyst *Ir$^{\mathrm{III}}$ is quenched by protonated quinoline **B** to generate oxidized photocatalyst species Ir$^{\mathrm{IV}}$ and the radical intermediate **C**.[28] Then, the XAT process proceeds between intermediate **C** and alkyl bromide **2** to give a carbon radical **D** and a bromine anion afterward. The radical **C** is considered to have the XAT reactivity similar to *α*-aminoalkyl radicals generated from aliphatic amine.[24a,c] Then, the obtained carbon radical **D** undergoes nucleophilic addition onto protonated *N*-heteroarene **1a′** to generate radical cation **E**. Finally, oxidation of radical cation **E** by Ir$^{\mathrm{IV}}$ and then deprotonation gave rise to target protonated Minisci alkylation product **3′** and regenerated photocatalyst Ir$^{\mathrm{III}}$. Hydrohalic acid is the only byproduct of this protocol, which could also activate the *N*-heteroaromatics.

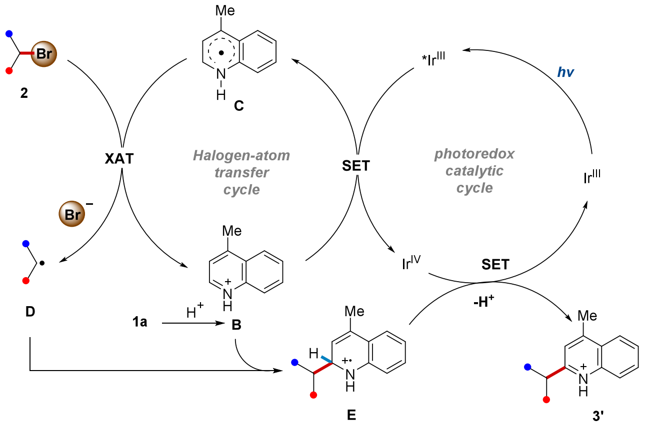


Figure 4. Proposed mechanism.

In summary, we have developed a novel photoredox Minisci reaction through a XAT process realized by traceless aminoalkyl radicals *in situ* generated from the reduction of *N*-heteroarenes, especially under redox-neutral and mild conditions.[29] In this protocol, a variety of unactivated alkyl bromides and iodides could be conveniently converted into the corresponding carbon radicals to couple with *N*-heteroarenes. This protocol could proceed without the addition of traditionally indispensable XAT reagents and oxidant. Mechanistic studies supported the hypothesis that the cyclic aminoalkyl radicals generated from SET reduction of protonated *N*-heteroarenes could induce the XAT catalytic cycle. Such an unprecedented photocatalytic mode for the XAT-induced Minisci reaction contributes to a redox-neutral strategy for coupling of two electrophilic molecules.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c01794.

Detailed experimental procedures, optimization study, mechanism study, complete characterization data, and copies of NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Shi-Yu Guo − *Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China*; Email: carlosguo10@dicp.ac.cn

Xu-Liang Jiang − *School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang 110016, China*; Email: xuliangjiang@syphu.edu.cn

Qing-An Chen − *Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China; University of Chinese Academy of Sciences, Beijing 100049, China*; orcid.org/0000-0002-9129-2656; Email: qachen@dicp.ac.cn

Authors

Jin-Song Huang − *School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang 110016, China; Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China*

Zhi-Hui Wang − *Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China; University of Chinese Academy of Sciences, Beijing 100049, China*

Xue-Ting Li − *Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China; University of Chinese Academy of Sciences, Beijing 100049, China*; orcid.org/0009-0006-4290-5555

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.5c01794

Notes

The authors declare no competing financial interest.

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