ORGANIC CHEMISTRY FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal

Cite this: DOI: 10.1039/d5qo00549c

Brønsted acid enabled metal-free remote oxygenation and amidation of unstrained C–C bonds *via* 1,4-heteroaryl migration chaperoned radical-polar crossover†

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Received 20th March 2025,
Accepted 12th May 2025

DOI: 10.1039/d5qo00549c

rsc.li/frontiers-organic

C–C bond functionalization has emerged as a powerful tool for the skeleton editing of organic molecules. However, remote C(sp^3)–O and C(sp^3)–N bond formation *via* unstrained C–C bond cleavage in acyclic molecules remains challenging. Herein in this work, a Brønsted acid enabled metal-free remote oxygenation and amidation of NHPI esters *via* 1,4-group migration chaperoned radical-polar crossover has been established, affording a variety of heteroaryl-tethered alcohols, ethers and amides in moderate to good yields. This protocol also features mild conditions, good functional group tolerance and high regioselectivity, representing a novel paradigm for remote C(sp^3)–heteroatom bond construction *via* C–C bond activation.

Introduction

C–C bonds are one of the most fundamental structural units that form the backbone of organic molecules. Selective C–C bond functionalization provides an exceptional opportunity to achieve straightforward structural reassembly of molecules.[1] Particularly, owing to the ubiquity of O- and N-containing molecules in natural products and pharmaceuticals,[2] the C(sp^3)–O and C(sp^3)–N bond formation by C–C bond activation has already drawn a lot of attention. One popular strategy is C–C bond cleavage facilitated by ring-strain release, installing C(sp^3)–O or C(sp^3)–N bonds *via* the ring opening of three- or four-membered ring compounds[3] or strained bicycloalkanes.[4] In comparison, functionalizations of stronger unstrained C–C bonds in massive acyclic molecules are still inadequately explored.

In recent years, 1,*n*-group migration has emerged as a powerful tool for the skeleton editing of unstrained organic compounds.[5] The translocation of various functional groups such as aryl,[6] heteroaryl,[7] alkenyl,[8] alkynyl,[9] amino,[10] and cyano[11] groups could modify the backbone of molecules beyond spatial limitations, which afforded diverse structures difficult to access through conventional synthetic methods. Despite these advancements, synthetic protocols for remote C(sp^3)–O or C(sp^3)–N bond installation *via* group migration have still been rarely reported. A pioneering report from Shi's group demonstrated Ag-catalyzed 1,4-aryl migration of triflic amides to forge distal C(sp^3)–O bonds under oxidative conditions.[12] Very recently, Shu and co-workers have reported the remote oxygenation and nitrogenation of unstrained C–C bonds in *N*-fluorosulfonamides by merging Cu and Ir-photoredox catalysis (Scheme 1a).[13] In the above reports, the aryl group migration is triggered by an electrophilic N-centered radical, which exhibits moderate selectivity between two different aryl moieties. Additionally, the participation of transition metal catalysts may cause issues with metal residues for bioactive molecule synthesis. In this context, remote functionalization *via* unstrained C–C bond activation with improved selectivity and sustainability is still a highly desirable task.

Over the past decades, redox-active *N*-hydroxyphthalimide (NHPI) esters have been employed as versatile synthetic building blocks in organic chemistry.[14] The photoinduced radical-polar crossover strategy has provided an expedient approach for C(sp^3)–heteroatom bond construction between diverse NHPI esters and nucleophiles (Scheme 1b).[15] In contrast to the established decarboxylative *ipso*-functionalization of NHPI esters, decarboxylative remote functionalization of unstrained C–C bonds in NHPI esters *via* the radical-polar crossover process remains underexplored to date. A main challenge is that the alkyl radicals generated by decarboxylation would

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†Electronic supplementary information (ESI) available. CCDC 2416854 and 2416902. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d5qo00549c

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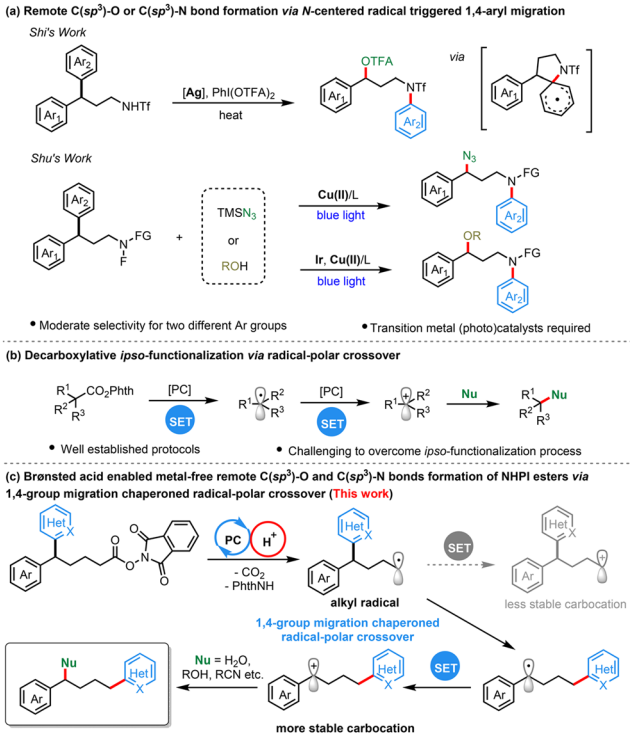


Scheme 1 Remote functionalization of unstrained C–C bonds.

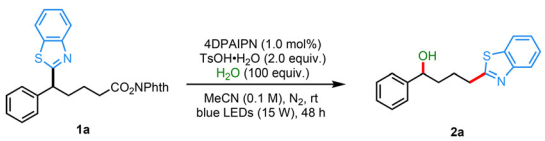
easily undergo SET oxidation to the corresponding carbocations. This process would compete with the radical-triggered 1,*n*-group migration and eventually afford undesired *ipso*-functionalized byproducts instead. We envisioned that the participation of a Brønsted acid might be critical for the selective remote functionalization of NHPI esters. The presence of a Brønsted acid would efficiently activate the NHPI ester moiety *via* a proton-coupled electron transfer (PCET) process, which facilitates the alkyl radical generation.[16] On the other hand, the protonation of distal heteroaryl rings could accelerate the radical-triggered Truce–Smiles rearrangement,[17] which would interrupt the undesired *ipso*-functionalization to provide heteroaryl migration products selectively. With these designs in mind, herein we have developed a Brønsted acid enabled metal-free remote functionalization of unstrained C–C bonds in NHPI esters *via* 1,4-group migration chaperoned radical-polar crossover (Scheme 1c).[18] A variety of heteroaryl-tethered alcohols and ethers are expediently synthesized *via* consecutive C–C bond cleavage and remote C(sp^3)–O bond formation under very mild conditions. In addition, remote Ritter-type amidation products are readily obtained as well by employing nitriles as *N*-nucleophiles instead of *O*-nucleophiles.

Results and discussion

We initiated our research by the optimization of remote C(sp^3)–O bond formation of NHPI ester **1a** with H_2O as the nucleophile. To our delight, after preliminary screening of various reaction parameters (Table S1†), we managed to install the hydroxyl group at the distal site, affording the desired product **2a** in 60% yield with 4DPAIPN as the photocatalyst, TsOH·H_2O as the additive and H_2O (100 equiv.) in a MeCN solution under blue irradiation for 48 h (Table 1, entry 1). The use of the less reductive photocatalyst 4CzIPN diminished the reaction efficiency (Table 1, entry 2). Reactions with H_3PO_4 and HBF_4 could also afford **2a**, albeit in lower yields (Table 1, entries 3 and 4). Other polar solvents such as DMSO, acetone, and EtOAc were verified as inferior choices to CH_3CN (Table 1, entries 5–7). The yield of **2a** was further optimized to 77% when 3.0 equivalents of TsOH·H_2O were employed (Table 1, entry 8). Control experiments revealed that the photocatalyst, acid additive, light irradiation, and N_2 atmosphere were all essential for product generation (Table 1, entries 9–12).

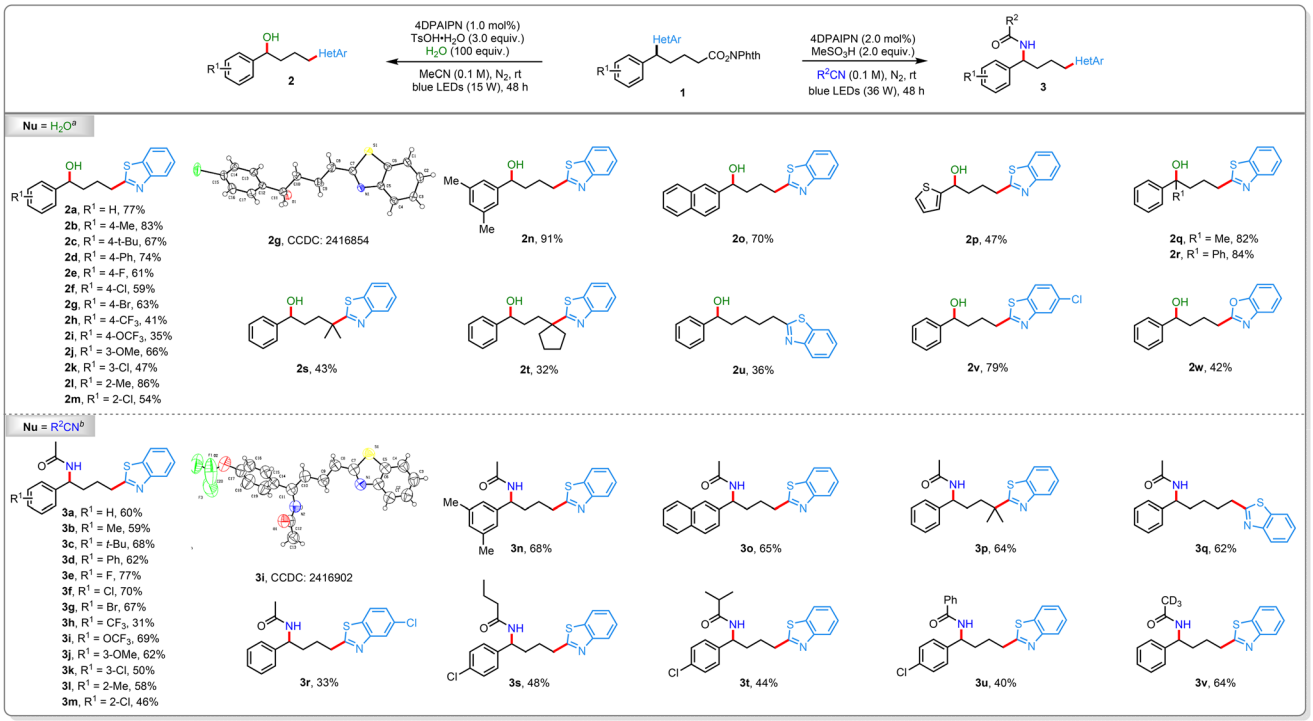
With the optimized reaction conditions in hand, we further investigated the substrate scope of this Brønsted acid enabled remote hydroxylation of NHPI esters (Scheme 2a). A set of NHPI esters with electron-rich or electron-neutral substituents at the *para*-position of the aryl ring worked quite smoothly to afford the corresponding desired products **2a–2d** in good yields. However, substrates bearing electron-deficient aryl motifs only exhibited moderate reactivity (**2e–2i**), which suggested that electron-withdrawing groups would destabilize the carbocation intermediate generated *via* radical-polar crossover. A series of *ortho*- or *meta*-substituted NHPI esters were amenable substrates for this transformation (**2j–2n**). Substrates containing the naphthalene or thiophene moiety were also well tolerated (**2o** and **2p**). NHPI esters with quaternary carbon atoms at the distal benzylic position provided corresponding products **2q** and **2r** in high yields owing to the better stability of tertiary benzylic carbocations. In contrast, substrates bearing quaternary carbon atoms at the proximal

Table 1 Optimization of the reaction conditions[a]



Entry	Variations	Yield[b] (%)
1	None	60
2	4CzIPN instead of 4DPAIPN	42
3	H_3PO_4 instead of TsOH·H_2O	38
4	HBF_4 instead of TsOH·H_2O	48
5	DMSO instead of MeCN	30
6	Acetone instead of MeCN	45
7	EtOAc instead of MeCN	53
8	TsOH·H_2O (3.0 equiv.)	77
9	From entry 8, without acid	n.d.
10	From entry 8, without 4DPAIPN or light	n.d.
11	From entry 8, under an air atmosphere	n.d.

[a] Reaction conditions: **1a** (0.1 mmol), 4DPAIPN (1.0 mol%), TsOH·H_2O (3.0 equiv.), H_2O (100 equiv.), MeCN (1.0 mL), room temperature, N_2, and under blue LED (15 W) irradiation for 48 h. [b] Isolated yields are reported. n.d. = not detected.

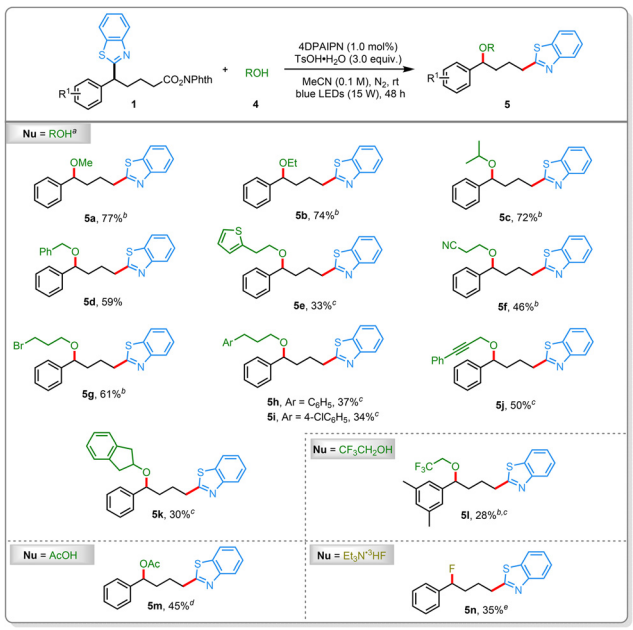


Scheme 2 Substrate scope of remote hydroxylation and amidation of NHPI esters. Reaction conditions: [a] **1** (0.1 mmol), H_2O (10 mmol), TsOH·H_2O (3.0 equiv.), 4DPAIPN (1.0 mol%), MeCN (1.0 mL), room temperature, N_2, and under blue LED (15 W) irradiation for 48 h. [b] **1** (0.2 mmol), $MeSO_3H$ (2.0 equiv.), 4DPAIPN (2.0 mol%), MeCN (2.0 mL), room temperature, N_2, and under blue LED (36 W) irradiation for 48 h. CCDC 2416854 (**2g**) and CCDC 2416902 (**3i**) contain the supplementary crystallographic data for this paper.

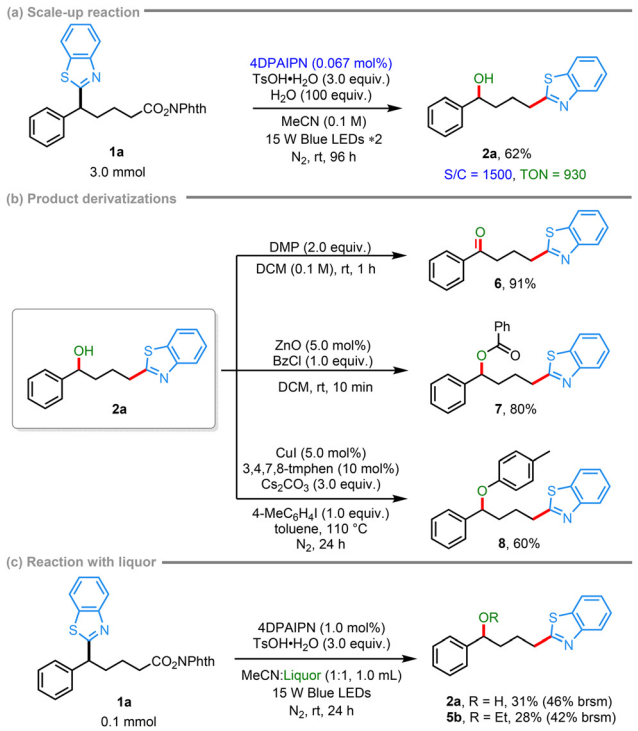
site only led to diminished yields of **2s** and **2t**. The substrate bearing a longer aliphatic chain afforded product **2u** *via* 1,5-heteroaryl migration, albeit in a lower efficiency. Different heterocycles such as Cl-substituted benzothiazole and benzoxazole could also undergo 1,4-migration successfully (**2v** and **2w**).

Furthermore, we were delighted to find that MeCN could be employed as the nucleophile instead of H_2O, which forged the distal C(sp^3)–N bond to afford the remote Ritter-type amidation product **3a** in 60% yield (Table S2†). As exemplified in Scheme 2b, a variety of substrates bearing either electron-rich or electron-deficient aryl moieties were all compatible with this reaction system, affording the corresponding desired products in moderate to good yields (**3b**–**3o**). The variations in the aliphatic chain of NHPI esters did not significantly influence their reactivity in the remote amidation protocol (**3p** and **3q**). The substrate bearing Cl-substituted benzothiazole as the migration group exhibited sluggish performance (**3r**). Remarkably, other aliphatic nitriles, benzonitrile, and deuterated acetonitrile were able to participate in this transformation, affording corresponding amides **3s**–**3v** in promising yields as well.

Inspired by the success of remote functionalization of NHPI esters with H_2O and nitriles as nucleophiles, we continued to extend the nucleophile scope to alcohols for ether preparation (Scheme 3). Feedstock alcohols such as methanol, ethanol and isopropanol were employed as solvents, and the reactions



Scheme 3 Substrate scope of remote alkoxylation of NHPI esters. [a] Reaction conditions: **1** (0.1 mmol), **4** (5.0 equiv.), and TsOH·H_2O (3.0 equiv.), 4DPAIPN (1.0 mol%), MeCN (0.1 M), room temperature, N_2, and under 15 W blue LED irradiation for 48 h. [b] Alcohol **4** (1.0 mL). [c] TsOH·H_2O (1.0 equiv.). [d] AcOH (1.0 mL), 36 W blue LEDs, without TsOH·H_2O. [e] Et_3N·3HF (10 equiv.), and 36 W blue LEDs, without TsOH·H_2O.

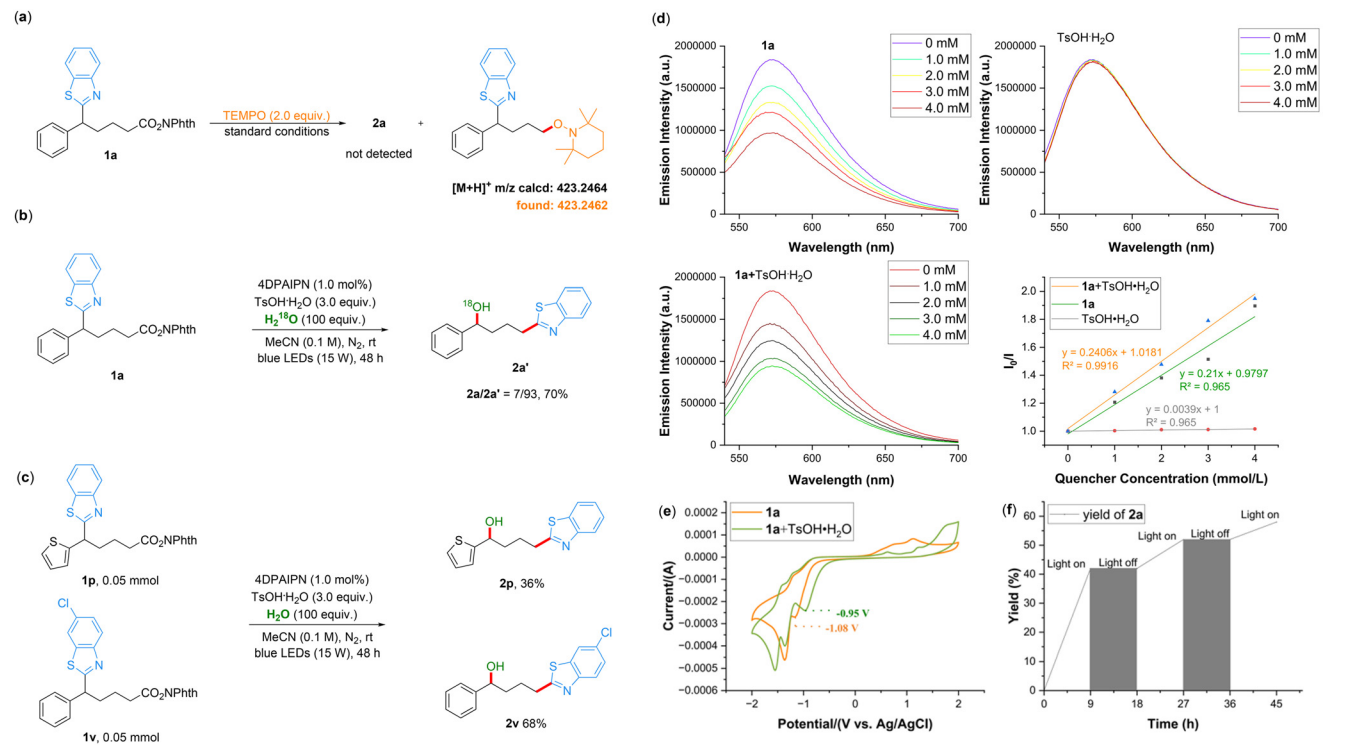


Scheme 4 Synthetic applications.

worked quite smoothly, providing ethers **5a–5c** in good yields. Other primary alcohols tethering various functional groups such as halogen atoms, cyano group, C≡C triple bonds, or (hetero)aryl rings were well tolerated in this transformation (**5d–5j**). The cyclic secondary alcohol performed rather sluggishly owing to the enhanced steric hindrance (**5k**). Notably, fluoro-ether **5l** could be prepared from the less nucleophilic CF_3CH_2OH. A moderate yield of acetate **5m** was obtained in the AcOH solution. Last but not least, nucleophilic remote fluorination was achieved with $Et_3N{\cdot}3HF$ as the fluorine source even though fluorides were known as weak nucleophiles (**5n**).

Moreover, we were glad to find that a scale-up reaction of remote hydroxylation *via* 1,4-group migration chaperoned radical-polar crossover proceeded quite smoothly even under low catalyst loading conditions (S/C = 1500), affording the desired product **2a** in 62% yield and 930 TONs (Scheme 4a). The alcohol **2a** could serve as a versatile synthetic intermediate to realize facile synthesis of diverse derivatives such as ketone (**6**), benzoate (**7**), and aryl ether (**8**) (Scheme 4b). Interestingly, the remote oxygenation of NHPI ester **1a** could be realized with Chinese liquor *Erguotou* (alc/vol: 52%vol) as a binary nucleophile to afford both alcohol **2a** and ether **5b** in one pot, demonstrating the robustness of this transformation (Scheme 4c).

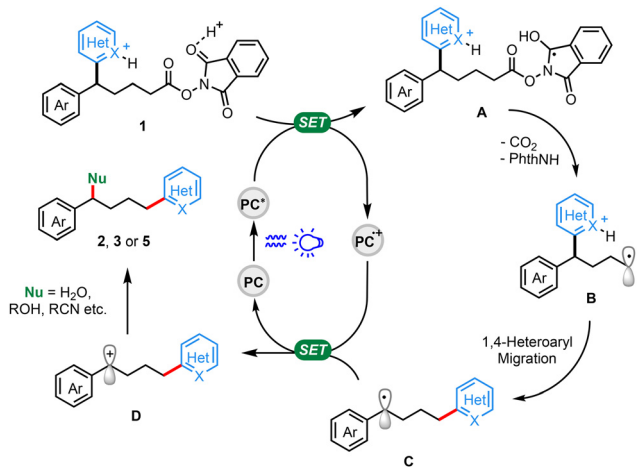
To gain insight into the reaction mechanism, a series of mechanistic investigations were carried out. Upon the addition of the radical scavenger TEMPO, the generation of product **2a** was completely inhibited, and the corresponding trapping adduct was detected by HRMS analysis (Scheme 5a), which indicated that an alkyl radical intermediate could be involved in the mechanism. The isotope labelling experiment with $H_2{}^{18}O$ as the nucleophile resulted in the ^{18}O-labeled product



Scheme 5 Mechanism experiments: (a) radical trapping experiment. (b) $H_2{}^{18}O$ isotopic labelling experiment. (c) Crossover experiment. (d) Stern–Volmer quenching experiments. (e) Cyclic voltammetry measurements. (f) Light on–off profile.

2a′ as the dominant product, suggesting that the hydroxyl group in product **2a** originated from H_2O (Scheme 5b). The crossover experiment between substrates **1p** and **1v** only afforded regular products **2p** and **2v**, respectively, which indicated that the alkyl radical triggered 1,4-heteroaryl migration proceeded in an intramolecular manner (Scheme 5c). Stern–Volmer emission quenching experiments revealed that the redox-active NHPI ester **1a** would undergo oxidative quenching with the photo-excited 4DPAIPN* to initiate the catalytic cycle (Scheme 5d). Notably, the combination of TsOH·H_2O and **1a** enhanced the quenching efficiency. In addition, cyclic voltammetry measurements clearly showed that the reductive potential of **1a** (E_p^{red} = −1.08 V *vs.* Ag/AgCl) shifted towards the positive direction in the presence of TsOH·H_2O (E_p^{red} = −0.95 V *vs.* Ag/AgCl) (Scheme 5e). This evidence supported that the Brønsted acid might engage with NHPI ester **1a** to produce the alkyl radical *via* a proton-coupled electron transfer (PCET) process. Moreover, the light on–off profile illustrated that the generation of product **2a** could only be observed under light irradiation, suggesting that a radical chain process was unlikely to be involved in the mechanism (Scheme 5f).

Based on the results of mechanistic investigations, we described a plausible reaction mechanism as follows (Scheme 6). First of all, the Brønsted acid additive TsOH·H_2O would facilitate the reduction of NHIP ester **1** (E_p^{red} = −0.95 V *vs.* Ag/AgCl) to intermediate **A** by the photo-excited 4DPAIPN* species ($E_{1/2}$ (PC*/PC$^{\bullet+}$) = −1.28 V *vs.* SCE)[19] *via* a PCET pathway. The subsequent decarboxylation resulted in the generation of alkyl radical intermediate **B**. Then, a rapid Truce–Smiles rearrangement of the protonated heteroaryl moiety took place, affording a distal benzylic radical intermediate **C**.[17] The benzylic radical **C** ($E_{1/2}^{ox}$ = 0.37 V *vs.* SCE)[20] was further oxidized by 4DPAIPN radical cation species ($E_{1/2}$ (PC$^{\bullet+}$/PC) = 1.34 V *vs.* SCE)[19] to form a benzylic carbocation **D** and meanwhile regenerate the ground state 4DPAIPN. Finally, carbocation **D** was trapped by different types of nucleophiles to furnish the corresponding remote functionalized products.



Scheme 6 Proposed reaction mechanism.

Conclusions

In summary, we have developed a Brønsted acid enabled metal-free remote oxygenation and amidation of NHPI esters *via* 1,4-group migration chaperoned radical-polar crossover. A broad range of heteroaryl-tethered alcohols, ethers and amides are readily forged with good functional group tolerance and high regioselectivity under very mild conditions. The scale-up reaction with low catalyst loading proceeds quite smoothly to achieve relatively high TONs. Moreover, Chinese liquor could also serve as a binary nucleophile to afford both alcohol and ether products in one pot, which exhibits the robustness of this protocol. Mechanistic studies have revealed that the presence of the Brønsted acid TsOH·H_2O would influence the reactivity of NHPI esters.

Author contributions

Xiaofei Xie: methodology, validation, data curation, investigation, and writing – original draft; Yun Shi: methodology, data curation, and investigation; Yukun Li: methodology, data curation, and investigation; Jinge Gui: data curation and investigation; Yingguang Zhu: conceptualization, project administration, supervision, and funding acquisition; Kang Chen: conceptualization, project administration, supervision, writing – review & editing, and funding acquisition.

Data availability

The data underlying this study are available in the published article and its ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the National Natural Science Foundation of China (No. 22101135 and 21502096), the Natural Science Foundation of Jiangsu Province (BK20150652), the Fundamental Research Funds for the Central Universities (KYQN2022058, KJQN201629, and XUEKEN2022032) and the "333 High Level Talent Project" of Jiangsu Province for financial support.

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