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Dual visible-light and NHC-catalyzed radical relay trifunctionalization of unactivated alkenes

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Abstract

Radical trifunctionalization of unactivated alkenes remains rare and challenging, although they can provide a robust tool for the construction of molecules with high added value from simple materials. This work presents the relay dual N-heterocyclic carbene organocatalytic and visible-light photocatalytic multi-component trifunctionalization of alkyl alkenes via the merger of remote 1,4-cyano migration and alkylacylation. The method features a broad substrate scope and good compatibility of diverse functional groups. Density functional theory calculations were also carried out to rationalize the origin of this reaction. The cooperative N-heterocyclic carbene and photoredox catalysis enabled reductive single-electron transfer reaction of acyl azolium species and subsequent radical-radical cross-coupling, allowing for the facile construction of three new C–C bonds in one-pot reactions with high regioselectivity.

Keywords: N-heterocyclic carbene, photocatalysis, trifunctionalization, radical, remote CN migration

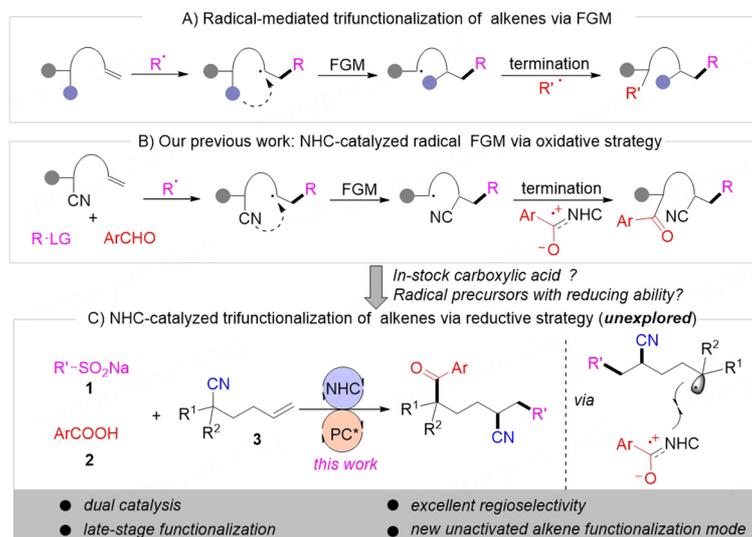
INTRODUCTION

The assembly of molecular frameworks by multi-step relay carbon-carbon bond cleavage and formation in a controlled and efficient manner has been at the heart of organic synthesis. Alkenes are readily available and inexpensive feedstocks that have been widely used for that purpose. Difunctionalization of alkenes presents numerous mature methods for accessing diverse-ranging molecules with high added value and structural complexity^[1-6]. In comparison, the trifunctionalization of alkenes, particularly unactivated alkenes, is less



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Scheme 1. Radical-mediated trifunctionalization of unactivated alkenes. FGM: Functional group migration; NHC: N-Heterocyclic carbene.

explored and still poses a challenge. Recently, the appearance of radical functionalization of unactivated alkenes through the strategy of remote functional group migration (FGM)^[7-10] provides an exceptional chance for the construction of trifunctionalized derivatives that are not accessible by other reactions [Scheme 1A]. Therefore, the discovery of new protocols for FGM reactions remains an important target and continues to be highly desirable for molecular assembly.

N-Heterocyclic carbene (NHC) catalysis^[11-17] has emerged as one of the most powerful catalytic strategies in the field of organocatalysis, usually by means of a polarity-reversal mechanism. With the rapid development of photocatalysis^[18-21], recent advances in single-electron transfer (SET)-based radical reactions have further broadened its reaction modes^[22-28], offering otherwise inaccessible strategies compared to traditional NHC-catalyzed ionic pathways. Radical chemistry by NHC catalysis normally follows two pathways: single-electron oxidation of Breslow intermediates and reduction of NHC-bound acyl azolium intermediates. The oxidative strategy usually involves the employment of single-electron oxidants or some radical precursors with oxidizing ability, which have been well documented by Guin *et al.*^[29,30], Zhang *et al.*^[31-33], Ishii *et al.*^[34-37], Maki *et al.*^[38,39], White *et al.*^[40,41], Chen *et al.*^[42-44], Zhang *et al.*^[45], and others^[46-53], also including our group^[54,55]. The reductive strategy usually requires a well-matched photoredox and NHC catalytic system^[55-68]. The substrate scope enlarges to in-stock carboxylic acids and radical precursors with reducing ability, such as sodium trifluoromethanesulfinate, which brings an important supplement for fluorine chemistry. The pioneering reports on reductive radical NHC-catalysis have enabled the molecular assembly of activated alkenes, giving birth to an array of high value-added aliphatic ketones bearing different functional groups. However, as far as we know, the radical trifunctionalization of alkenes through reductive NHC catalysis has not been documented yet and would be a complementary protocol of our previous work through an oxidative strategy^[69] [Scheme 1B].

As a continuation of our studies on radical NHC-catalysis, our purpose herein is to realize the first reductive radical organocatalytic FGM reactions to fulfill trifunctionalization of hexenenitriles **3**^[70,71] via remote cyano migration^[72-75]. Compared to the previous work using the NHC oxidative radical strategy, the substrate scope can enlarge to in-stock carboxylic acids and much more radical precursors. Thus, this protocol features a compatible dual catalytic system, mild reaction conditions, readily available substrates, excellent

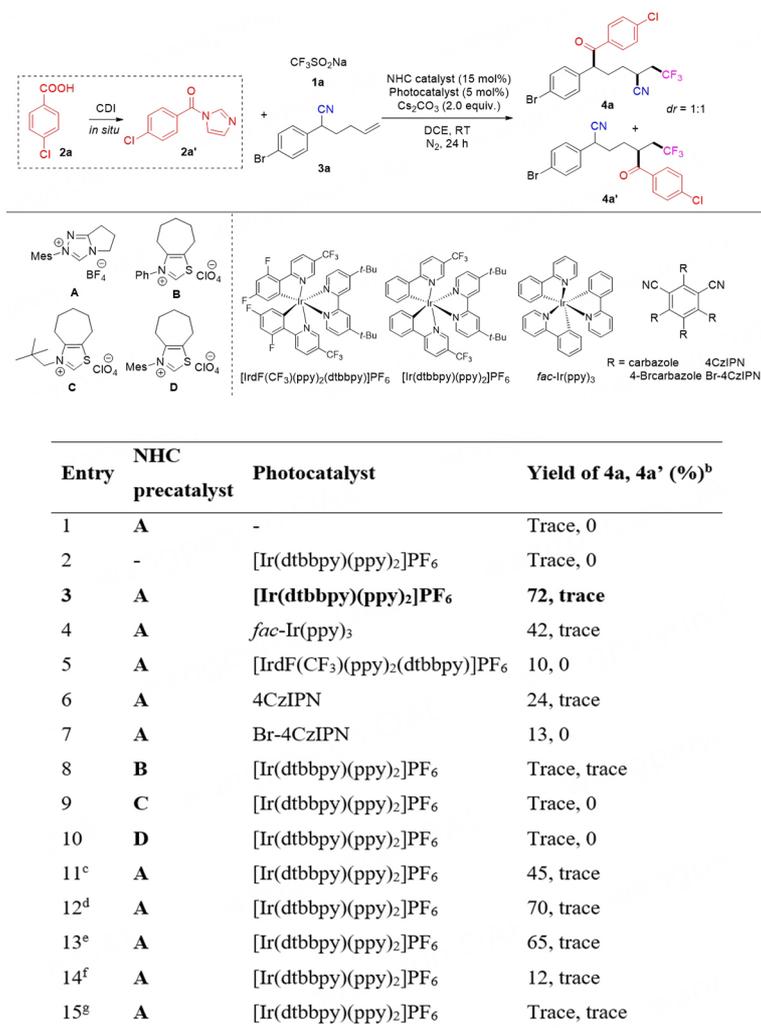


Figure 1. Optimization of the reaction condition^a. ^aUnless otherwise noted, **2a** (0.4 mmol, 2.0 equiv.) and CDI (0.4 mmol, 2.0 equiv.) in DCE (1 mL) were typically stirred for 2 h. Then, the above solution was added to the mixture of **1a** (0.4 mmol, 2.0 equiv.), **3a** (0.2 mmol, 1.0 equiv.), NHC catalyst (0.03 mmol, 15 mol%), photocatalyst (0.01 mol, 5 mol%), and Cs₂CO₃ (0.4 mmol, 2.0 equiv.) in DCE (2 mL) which was irradiated under Blue LED typically for 24 h; ^bIsolated yields based on **2a**, the dr was around 1/1 for all cases, and the dr was determined by ¹H NMR; ^cThe reaction was conducted without N₂ protection; ^d1 mmol scale; ^eK₂CO₃ as a base; ^ftriethylamine as a base; ^gDBU as a base. CDI: 1,1'-carbonyldiimidazole; DBU: N-Heterocyclic carbene.

regioselectivity, and capability of late-stage functionalization, which will be favorable for molecular assembly [Scheme 1C].

RESULTS AND DISCUSSION

To start this work, commercially available sodium trifluoromethanesulfonate **1a** was used as the trifluoromethyl radical precursor to investigate the feasibility of the reaction with 4-chlorobenzoic acid **2a** and hexenenitrile **3a** using DCE as the solvent, Cs₂CO₃ as a base, and Blue LEDs as light sources [Figure 1]. It is worth noting that the acid can be activated to produce benzoylimidazole **2a'** *in situ* with 1,1'-carbonyldiimidazole (CDI). The combination of NHC catalyst and photocatalyst was crucial for this transformation with otherwise trace formation of product **4a** (entries 1 and 2).

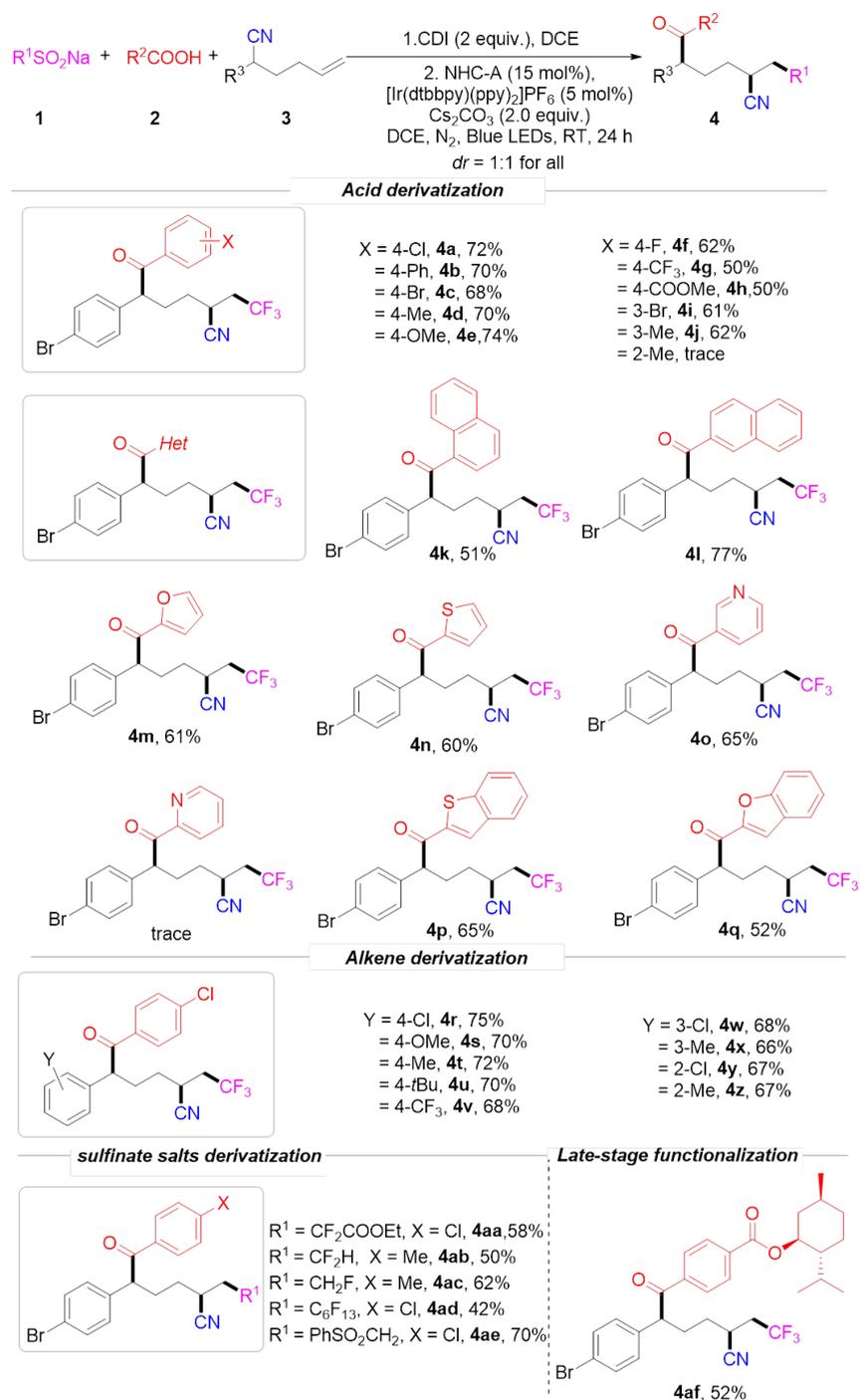
After screening different photosensitizers, it was found that the desired product **4a** was produced in 72% yield with $[\text{Ir}(\text{dtbbpy})(\text{ppy})_2]\text{PF}_6$ as the photocatalyst (entry 3). Other photocatalysts, such as *fac*- $\text{Ir}(\text{ppy})_3$, 4CzIPN, and Br-4CzIPN, were inferior to the $[\text{Ir}(\text{dtbbpy})(\text{ppy})_2]\text{PF}_6$ (entries 4-7). Subsequently, we screened different NHC precursors, and NHC A was selected as the optimal organocatalyst to promote the reaction. Other NHCs B-D did not improve the reaction yields (entries 8-10). The nitrogen atmosphere protection was also essential for this reaction. The yield dropped to 45% when the reaction was conducted in the air (entry 11). Moreover, a scale-up (1 mmol) reaction was taken to afford product **4a** in maintained yield (entry 12). Remarkably, only a trace of byproduct **4a'** was observed along the optimization process. At last, bases were screened, and a slightly decreased yield was observed with K_2CO_3 . Organic bases were not suitable for this transformation.

With the optimal condition in hand, the generality of substrates was explored. We initially tested different acids **2** [Scheme 2]. Substituted benzoic acids bearing either halide or electron-donating groups at *para* positions of the benzoic acid were well compatible with the optimal condition, giving the products **4a-e** in comparable yields. Slightly decreased yields were tracked when benzoic acids bearing electron-withdrawing groups **4f-h**. Benzoic acids bearing *meta* substitution were also well tolerated under the standard conditions **4i-j**. However, the more sterically hindered 2-methylbenzoic acid was not suitable for this reaction. Either 1-naphthoic acid or 2-naphthoic acid was applicable for the optimal condition **4k-l**. A decreased yield of 1-naphthoic acid was probably due to the steric effect. This protocol could also accommodate a variety of heterocyclic aromatic acids (**4m-q**). The reaction of picolinic acid almost did not work, perhaps due to the electronic effect of this substrate. To demonstrate the synthetic potential of this protocol, the late-stage functionalization of benzoic acid derived from menthol was tested, which worked smoothly to afford the corresponding product **4af** in 52% yields. After that, the scope of hexenenitriles was screened. In terms of substituents (Y) at the phenyl ring, the CN migration products **4r-4z** were exclusively produced in satisfying yields and excellent selectivity. The substituents on the phenyl ring have little impact on the yield. Even the more sterically hindered hexenenitriles were found to be suitable substrates for cyano migration, furnishing the expected products **4y** and **4z**, both in a 67% yield.

The feasibility of installation of other radical precursors to the hexenenitrile **3d** was also studied [Scheme 2, bottom]. Several sulfinate salts bearing a fluorinated alkyl group displayed good compatibility with the present system **4aa-ad**. Sulfinate salts bearing a phenylsulfonyl substituted methyl group were also used as effective substrates, enabling the trifunctionalization of **3d** to give product **4ae** in an acceptable yield. However, sulfinate salts, such as sodium methanesulfinate, sodium ethanesulfinate, and other listed aliphatic sulfinate salts, did not deliver the desired products. Density functional theory (DFT) calculations were then taken into account for the possible reasons [Scheme 3]. To our interests, the activating energy of the corresponding radical added to the hexenenitrile significantly contributes to the success of the reaction. The reactions failed to yield the desired product when the activating energy was above 14.1 Kcal/mol. These findings might be helpful for prediction of the reactivity of other sulfinate salts.

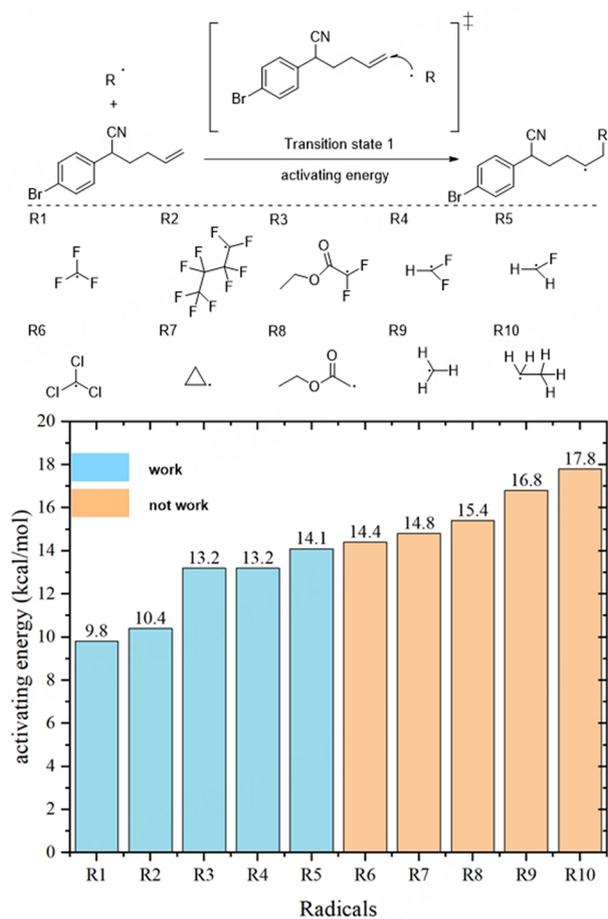
To highlight the utility of this transformation, we undertook the derivatization of the ketone **4a** [Scheme 4]. The alcohol **5** was synthesized using LiAlH_4 as reductant in the yield of 83%. The cyano group within **4a** can transform to amide to yield compound **6** with a mixed acid system (HOAc and H_2SO_4). In addition, the reaction of **4a** with hydrazine could form hydrazone **6** in 80% yield.

Next, DFT calculations have been conducted to further prove the potential reaction mechanism and origin of the regioselectivity for 1,4-cyano migration [Figure 2].

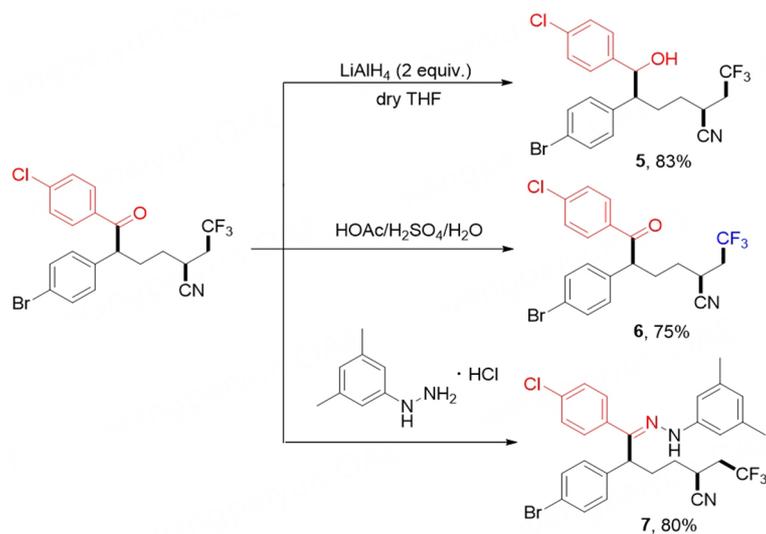


Scheme 2. Substrate scope for trifunctionalization of unactivated alkenes. CDI: 1,1'-carbonyldiimidazole.

The combination of NHC-A (C1) generated from precatalyst A under basic conditions with benzoylimidazole 2a' leads to NHC-bound acyl azolium C2. The SET process between C2 and CF₃SO₂Na proceeds smoothly to give transient trifluoromethyl radical and persistent NHC-bound ketyl radical C3. Subsequent addition of trifluoromethyl radical to hexenenitrile 3a produces intermediate S2 through the transition state TS1 ($\Delta G^\ddagger = 9.8$ kcal/mol). Whether the incident of 1,4-CN migration of TS1 occurs would



Scheme 3. Activating energy calculation with different alkyl precursors.



Scheme 4. Application of the representative product.

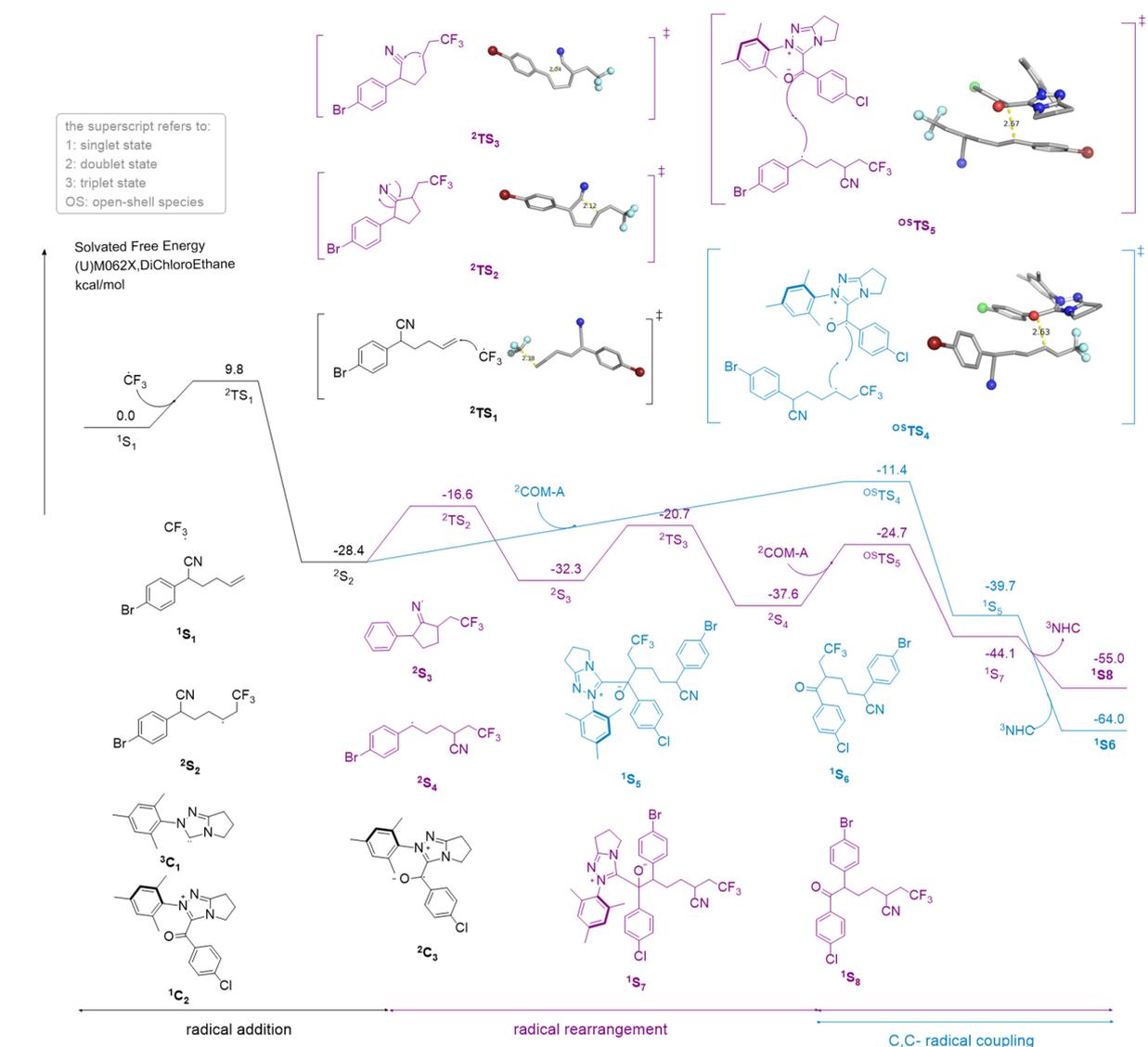
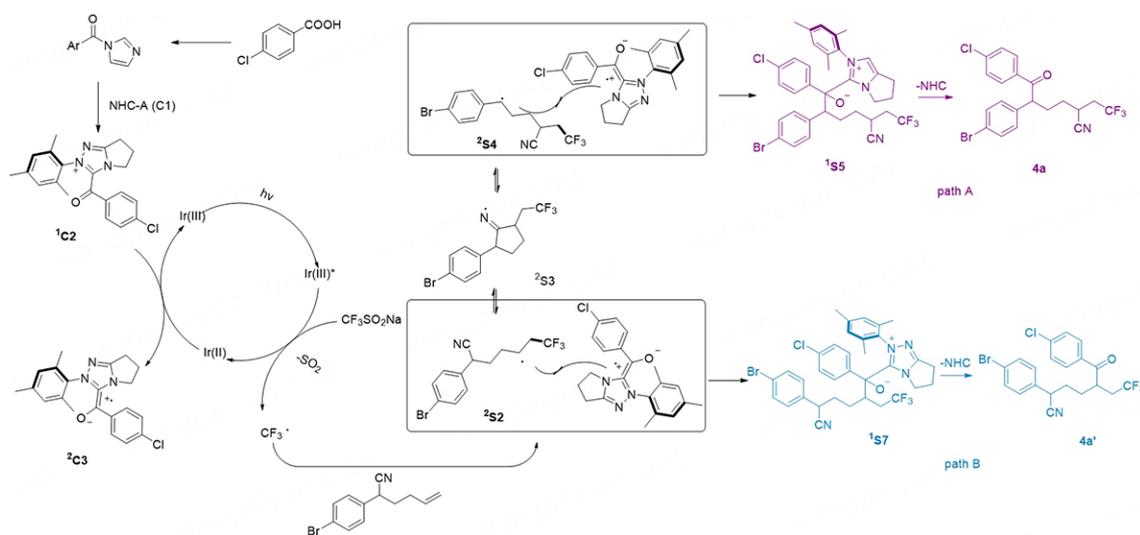


Figure 2. Relative Gibbs free energy profiles of the reaction.

decide the two possible pathways (path A, purple line vs. path B, blue line) for the radical-radical coupling. As described in the blue line, the direct radical-radical coupling of C3 with S2 yields intermediate S5 through transition state TS4 ($\Delta G^\ddagger = 17.0$ kcal/mol). The collapse of S5 gives birth to product 4a' and NHC-A for the next catalytic cycle. In path A (purple line), the intramolecular radical addition of S2 to the cyano group forms a five-member imine radical intermediate S3 through transition state TS2 ($\Delta G^\ddagger = 11.8$ kcal/mol). The following ring-opening of S3 occurs to generate the cyano migrated benzylic radical intermediate S4 through transition state TS3 ($\Delta G^\ddagger = 11.6$ kcal/mol). The subsequent radical-radical coupling of SA-R with intermediate S4 gives intermediate S7 through transition state TS5 ($\Delta G^\ddagger = 12.9$ kcal/mol). At the final step, the C-C bond cleavage leads to the dissociation of the final product 4a along with NHC-A. The calculation showed that benzylic radical S4 generated by cyano migration is more stable than radical S2 without cyano migration. Moreover, the radical-radical coupling of S2 with C3 in path A requires a much higher energy barrier than that in path B, thus disfavouring the direct radical-radical coupling and



Scheme 5. Plausible reaction pathway.

facilitating the cyano migration process. Therefore, high regioselectivity of this protocol can be rationalized by these calculation results.

Based on these results, it can be concluded that the dual photocatalytic and NHC-promoted SET between sodium trifluoromethanesulfonate **1a** and acyl azolium intermediate **SA** could simultaneously produce the NHC-derived radicals **C3** and CF_3 radicals. CF_3 radicals were subsequently triggered by hexenenitriles **3** to obtain **S2**. The generated radical intermediate **S2** may undergo remote 1,4-cyano migration via a cyclic intermediate **S3** to yield radicals **S4**. The radical-radical cross-coupling with the persistent ketyl radical **C3** and **S2** or **S4** would produce intermediate **S5** and **S7**, respectively, which finally afford adducts **4a** and byproduct **4a'** with the loss of NHC for the next catalytic cycle [Scheme 5].

CONCLUSIONS

To sum up, we have described a novel protocol for trifunctionalization of unactivated hexenenitriles *via* merged NHC organocatalytic and photocatalytic radical relay alkylacylation. This reaction offers a generalizable and efficient strategy for molecular framework assembly, which involves multi-step C–C bond cleavage and formation by remote 1,4-cyano migration and alkylacylation. Theoretical calculations were used to both support the possible mechanism and figure out the origin of the regioselectivity for 1,4-CN migration.

DECLARATIONS

Authors' contributions

Supervised the synthesis process: Feng J

Responsible for data collection and analysis: Feng JQ, Li L, Wang J, Ni A Conducted calculations: Wei Z

Led the design and paper-writing efforts: Du D, Feng J

Availability of data and materials

NMR data for all the new compounds can be found in Supplementary Materials, and the data supporting the findings of this study are available within its supplementary materials.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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