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Merging Distal Alkynyl Migration and Photoredox Catalysis for Radical Trifluoromethylative Alkynylation of Unactivated Olefins

Yan Xu, Zhen Wu, Jingxing Jiang, Zhuofeng Ke, and Chen Zhu*

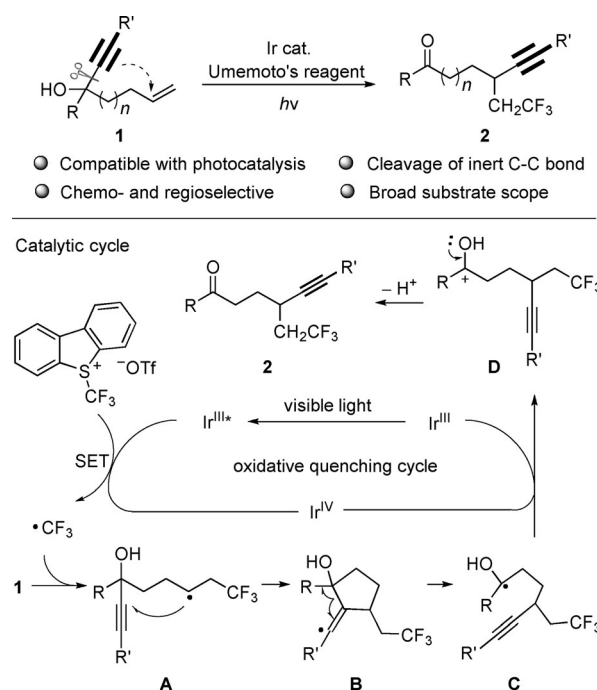
Abstract: Disclosed herein is a novel, redox-neutral protocol for the visible-light-induced radical alkynylation of unactivated olefins. The intramolecular migration of an alkynyl group, by cleaving an inert C–C σ bond, is realized for the first time. A wide range of synthetically useful trifluoroethylated linear alkynes are readily obtained under mild reaction conditions.

Over the last decade we have witnessed a rapidly growing interest in the field of radical-mediated difunctionalization of olefins, as it provides an efficient tool to rationally modulate alkenes by concomitant introduction of two vicinal functional groups.^[1] Mechanistically, the intermolecular addition of a free radical to olefin moiety generates a secondary or tertiary alkyl radical, which could be intercepted by an extrinsic radical-trapping reagent to give the difunctionalized product. The transient alkyl radical is significantly affected by the proximal substituents such that those possessing a π orbital, such as aryl, carbonyl, or heteroatom, stabilizes the radical through a p - π conjugate effect.^[2] In this context, the radical functionalization of unactivated olefins generally remains challenging.

Given the wide applications of alkynes in interdisciplinary fields across organic chemistry, medicinal chemistry, and chemical biology, the development of an efficient alkynylation method has attracted much attention from synthetic chemists.^[3] The radical alkynylation of olefins provides an ideal and divergent strategy for the production of complex substituted alkynes by simple variation of olefin and radical partner, as well as the alkynylating agent. However, the relevant studies remain rare.^[4] Recently, our group became interested in the radical difunctionalization of olefins by means of intramolecular functional-group migration,^[5] and achieved the cyanation and heteroarylation of unactivated alkenes for the first time.^[6] Prompted by these results, we considered the possibility of extending this strategy to the intramolecular migration of an alkyne, thus realizing the

elusive alkynylation of unactivated olefins under mild reaction conditions.

Because of the remarkable effect of the CF_3 group on improvements of metabolic stability and lipophilicity in bioactive molecules, the development of a practical method to incorporate CF_3 into organic molecules is of high importance.^[7] Recently, considerable was been made in the photocatalytic trifluoromethylative difunctionalization of olefins.^[8,9] We envisioned that the combination of photocatalytic trifluoromethylation with alkynyl migration could serve our purposes. As depicted in Scheme 1, the transformation is



Scheme 1. Design of photoinduced trifluoromethylalkynylation of unactivated olefins. Tf = trifluoromethanesulfonyl.

[*] Y. Xu, Z. Wu, Prof. Dr. C. Zhu

Key Laboratory of Organic Synthesis of Jiangsu Province
College of Chemistry, Chemical Engineering and Materials Science
Soochow University
199 Ren-Ai Road, Suzhou, Jiangsu 215123 (China)
E-mail: chzhu@suda.edu.cn

J. Jiang, Prof. Dr. Z. Ke
School of Materials Science and Engineering
Sun Yat-sen University
Guangzhou, Guangdong 510275 (China)

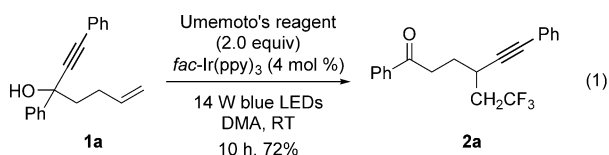
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initiated by visible-light irradiation of the photocatalyst *fac*- $\text{Ir}(\text{ppy})_3$. The strongly reducing excited-state $\text{Ir}^{\text{III}*}$ ($E_{1/2}^{\text{IV/III}*} = -1.73 \text{ V vs. SCE}$)^[10] is quenched by the Umemoto's reagent ($E_{1/2}^{\text{red}} = -0.37 \text{ V vs. SCE}$)^[8c] thus generating a CF_3 radical and Ir^{IV} . The luminescence quenching experiments also explicitly illustrate the single-electron transfer (SET) process between the Umemoto's reagent and $[\text{fac}\text{-Ir}(\text{ppy})_3]^*$.^[8c] The electrophilic addition of the CF_3 radical to the olefin generates the intermediate **A**, which simultaneously undergoes cyclization to form the cyclic radical **B**. The homolysis of the C–C bond of **B** leads to the hydroxyalkyl radical **C** and

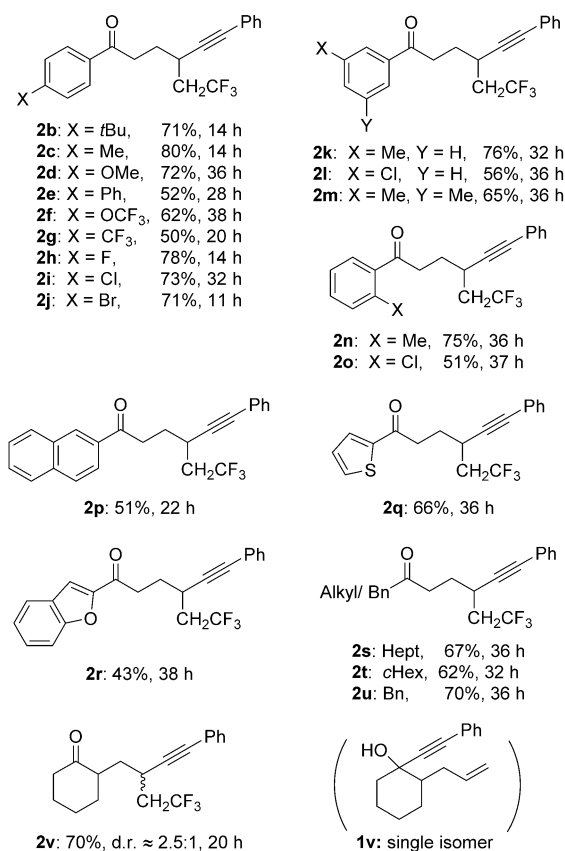
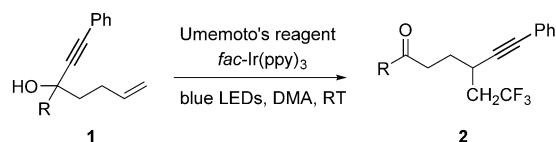
completes the alkynyl migration step. Rapid oxidation of **C** by Ir^{IV} ($E_{1/2}^{\text{IV/III}} = 0.77 \text{ V vs. SCE}$) gives the intermediate **D** and regenerates Ir^{III} .^[10a] Finally, the product is furnished after the deprotonation of **D**.

Herein, we provide concrete support for this hypothesis. A novel protocol of visible-light induced alkynylation and trifluoromethylation of unactivated alkenes is disclosed. The migration of the alkynyl group is reported for the first time. The mild cleavage of an inert C–C σ bond is remarkable, because the C(sp)–C(sp³) bond of propargyl alcohol is generally cleaved with the use of transition metal at high temperature.^[11] A variety of synthetically useful trifluoroethylated linear alkynes are readily obtained under mild reaction conditions. This protocol shows a nontrivial example of mild radical-enabled C–C bond cleavage, and may provide new opportunities in the fields of C–C bond activation and olefin difunctionalization.

We used the alkynyl-substituted tertiary alcohol **1a** as a model substrate to investigate the optimal reaction conditions [Eq. (1); DMA = *N,N*-dimethylacetamide, ppy = 2-phenylpyridine]. The highly conjugated alcohol **1a** is somewhat unstable and prone to dehydration under many reaction conditions which generate the CF_3 radical from either Langlois reagent ($\text{CF}_3\text{SO}_2\text{Na}$) or Togni reagent. Gratifyingly, in the presence of the Umemoto's reagent and *fac*- $\text{Ir}(\text{ppy})_3$, irradiated by blue LEDs, the alkynyl migration product **2a** was readily obtained in DMA (for detailed optimization of reaction conditions; see the Supporting Information). It should be mentioned that the preparation of such distally alkynyl-functionalized alkyl ketones, which could serve as versatile fluoroalkyl-containing building blocks, is usually difficult.^[12]



With the optimized reaction conditions in hand, we set out to evaluate the generality of this protocol (Scheme 2). While most of the electron-rich aryl-substituted alcohols delivered good yields (**2b–d**), the substrates with strong electron-withdrawing groups, such as CF_3 and OCF_3 , afforded the products in modest yields (**2f** and **2g**). Aryl halides, in particular bromide, remained intact in the reaction, thus allowing for further manipulation of products through cross-coupling reactions (**2h–j**). The reaction yield was not significantly compromised by change of the substituent to either the *meta*- or *ortho*-position (**2k–o**). The reaction with naphthyl- and heteroaryl-substituted (e.g., thienyl, benzofuryl) alcohols readily provided the desired products, albeit in moderate yields (**2p–r**). The examples of alkyl- or benzyl-substituted alcohols were noteworthy (**2s–u**), because the reactive olefinic radical intermediate **B**, as shown in Scheme 1, could be easily terminated by the 1,5-H transfer from the proximal alkyl group (R group). The control of the

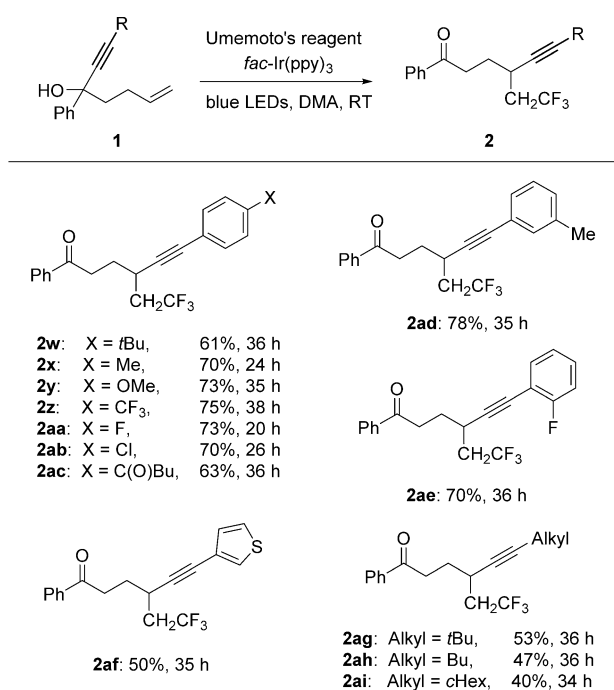


Scheme 2. Scope with respect to the tertiary alcohols. Reaction conditions: **1** (0.2 mmol, 1 equiv), Umemoto's reagent (0.4 mmol, 2 equiv), and *fac*- $\text{Ir}(\text{ppy})_3$ (0.008 mmol, 4 mol%) in DMA (3 mL) at RT with 14 W blue LEDs irradiation. Yields of isolated products are given.

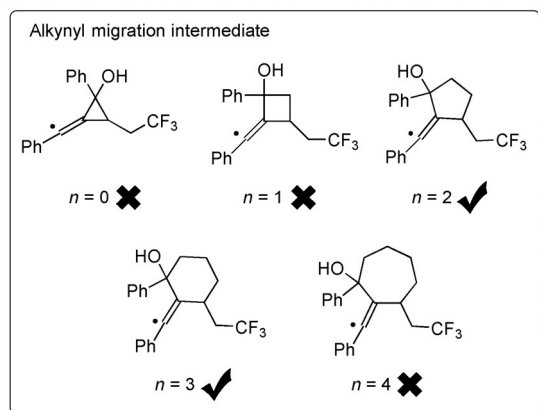
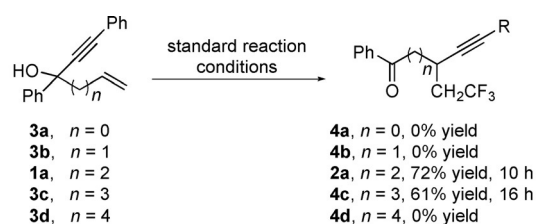
stereochemistry in this radical process is difficult as the reaction with a single isomer of **1v** resulted in two diastereomers of **2v** (d.r. \approx 2.5:1). The 1,1-disubstituted alkenes and internal alkenes were not suitable substrates for the reaction (see Figure S1 in the Supporting Information).

A wide range of alkynes showcased the migration aptitude (Scheme 3). The aromatic alkynes consistently afforded the products in synthetically useful yields regardless of the electronic and steric effects (**2w–ae**). Heteroaryls such as thienyl acetylene also proved to be a suitable migration group (**2af**). Importantly, a variety of aliphatic alkynes could also migrate smoothly to give the corresponding 1,2-dialkyl alkynyl products (**2ag–ai**).

To shed light on the migration step, a set of alkynyl-substituted tertiary alcohols (**1a** and **3a–d**) were tested under the standard reaction conditions (Scheme 4). We found that only **1a** ($n=2$) and **3c** ($n=3$) led to the alkynyl-migrated products **2a** and **4c**, respectively. These results illustrated that the alkynyl migration proceeds via cyclic transition states. The migration prefers the thermodynamically favored five- and



Scheme 3. Scope with respect to the migratory alkynes. Reaction conditions: **1** (0.2 mmol, 1 equiv), Umemoto's reagent (0.4 mmol, 2 equiv), and *fac*-Ir(ppy)₃ (0.008 mmol, 4 mol%) in DMA (3 mL) at RT with 14 W blue LEDs irradiation. Yields of isolated products are given.



Scheme 4. Intermediates of alkyne migration reaction.

six-membered cyclic transition states (*n* = 2, 3) rather than the three-, four-, and seven-membered cyclic transition states (*n* = 0, 1, 4). Moreover, a crossover experiment was carried out with the mixture of **1d** and **1aa**. As expected, only two corresponding products, **2d** and **2aa**, were formed, and no inter-changed products were observed (see Figure S2). This

evidence further supports that the alkynyl migration proceeds in an intramolecular manner. More studies were conducted to elucidate the mechanistic pathways.

We conducted the reaction in the presence of 1.5 equivalents of TEMPO or BHT under the standard reaction conditions. The reaction was significantly inhibited by these radical trap reagents (TEMPO: 31% yield; BHT: 24% yield).^[13] It was found that the transformation is substantially dependent upon photoirradiation. The reaction does not occur in the dark and can be switched on by turning on the light (see Figure S3). Moreover, the quantum yield of this reaction was determined to be 0.94 (see the Supporting Information). These results rule out the possibility of a chain-reaction pathway but support the photocatalytic pathway outlined in Scheme 1.

Computational studies were also carried out to understand the proposed mechanism in Scheme 1, in particular the alkynyl migration step (**B** → **D**). The intermediate **B** (−48.5 kcal mol^{−1}) undergoes decyclization to produce **C** (−44.4 kcal mol^{−1}), which is slightly higher in free energy than **B** by 4.1 kcal mol^{−1}. That means **B** and **C** can be easily tautomerized. The subsequent oxidation of radical **C** (−44.4 kcal mol^{−1}) to **D** (−65.9 kcal mol^{−1}) by Ir^{IV} is exothermic by 21.5 kcal mol^{−1}. This energy may dictate the direction of C–C bond cleavage and provide the driving force for the migration of alkynyl group (for full details, see the Supporting Information).

In summary, we have described a conceptually new approach for the elusive radical-mediated alkylation of unactivated olefins by means of intramolecularly distal alkynyl migration. The alkynyl migration is induced by the addition of a trifluoromethyl radical, which is readily generated by use of the Umemoto's reagent under visible-light irradiation. A broad range of synthetically useful trifluoroethylated linear alkynes are efficiently furnished under mild reaction conditions. This reaction is the first report on the difunctionalization of alkenes with concurrent distal alkynyl migration.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkynes · olefins · photoredox catalysis · radicals · trifluoromethylation

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