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Volume 18 | Number 7 | 7 April 2016 | Pages 1821–2242

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ISSN 1463-9262

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COMMUNICATION

Radical C(sp^3)-H Alkenylation, Alkynylation and Allylation of Ethers and Amides Enabled by Photocatalysis

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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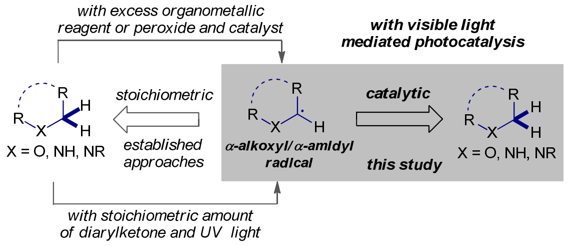
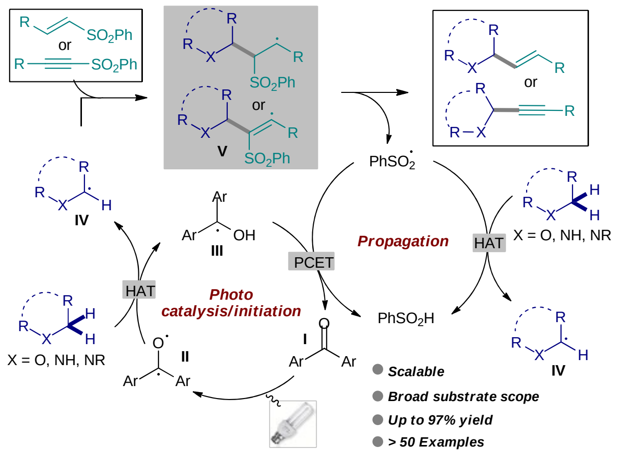
An efficient radical addition/elimination reaction that enables selective incorporation of alkenyl, alkynyl and allyl functional groups at C(sp^3)-H bond under a green reaction condition is developed. The process is based on the catalytic formation of α-alkoxyl/α-amidyl radical via homolytic activation of C(sp^3)-H bond of ether /amide with a catalytic amount of diarylketone in the presence of a household fluorescent light bulb. This simple reaction protocol features good functional group tolerance, scalability, convenient reagents and operating system. Synthetic application of the method has been demonstrated via the preparation of natural product and different valuable synthones.

Catalytic transformation of abundant chemicals to high value compounds via C(sp^3)–H functionalization is of great significance in organic synthesis.[1] In particular, direct C(sp^3)-H alkenylation of ethers and amides receives considerable attention, as alkene[2] would allow further functionalization of such compounds. The existing methods for the direct C(sp^3)-H alkenylation of ethers/amides primarily proceed through α-alkoxyl/α-amidyl radical intermediates.[3,4] These reactive radicals are typically generated in situ via homolytic C(sp^3)-H bond activation of ethers/amides using stoichiometric amount of organometallic reagent/peroxide[3] or diarylketone in the presence of high energy UV light[5] (Scheme 1). Herein, we report an efficient and green method for the direct C(sp^3)-H alkenylation/alkynylation of ethers/amides employing a catalytic amount of diarylketone in the presence of a house hold fluorescent light bulb. This method allows incorporation of alkenyl, alkynyl and allyl functional groups to C(sp^3)-H bond of simple ethers/amides in excellent yield and stereoselectivity avoiding the use of stoichiometric amount of reagent or toxic UV light. Furthermore, a broad range of synthetically useful functional groups particularly UV light sensitive aromatic halides are found to be tolerated in this environmentally friendly C(sp^3)-H alkenylation/alkynylation protocol.



Scheme 1 Different protocols for the generation of α-alkoxyl/α-amidyl radical via homolytic activation of C(sp^3)-H bond



Scheme 2 Proposed reaction pathway

Visible-light mediated photocatalysis has emerged as a new strategy for homolytic activation of C-H bond toward sustainable organic synthesis.[6] Along this line, C-H fluorination[7] and arylation[8] reactions have recently been reported using a catalytic amount of diarylketone and house hold fluorescent light bulb. Being inspired by these work and our recent studies on C-H functionalization[9], we wondered whether a catalytic

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†Electronic Supplementary Information (ESI) available. See DOI: 10.1039/x0xx00000x

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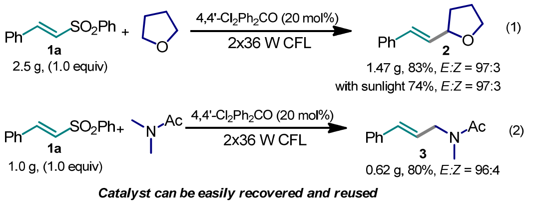
DOI: 10.1039/C7GC00840F

$C(sp^3)$–H alkenylation/alkynylation of ethers and amides can be achieved with diarylketone **I** and visible light. The electrophilic oxyl-radical of the short-lived photoexcited ketone **II** is known to preferentially abstract hydrogen atom adjacent to a heteroatom. [10] The nucleophilic C-centred radical **IV** thus generated is expected to combine with electron deficient conjugated sulfone leading to the *β*-sulfonyl radical intermediate **V**, which upon elimination of a sufinyl radical would enable C-H alkenylation/alkynylation.[11] Reduction of the sulfinyl radical (for $PhSO_2^{\cdot}/PhSO_2Na$, $E_{1/2}^{red}$ = +0.50 V vs SCE) [12] with radical **III** ($E_{1/2}^{red}$ $[Ph_2CO/Ph_2HCO^{\cdot}]$ = -1.68 V vs SCE) [6d] via most likely a proton coupled electron transfer (PCET)[13] would provide sulfinic acid along with the regeneration of **I**. Alternatively, a radical chain mechanism may also be involved, where in situ formed sulfinyl radical could propagate the chain reaction by producing the radical **IV** through homolytic activation of $C(sp^3)$-H bond of ether/amide (Scheme 2).

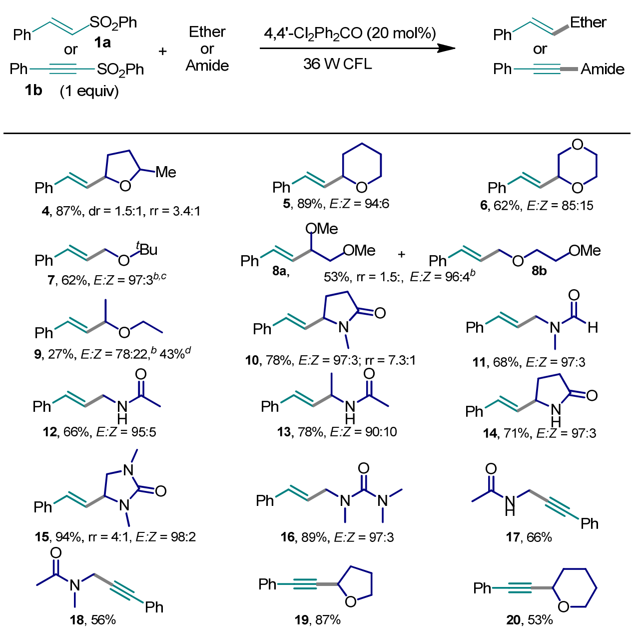
In line with above concept, we began our study by the exposure of THF to vinyl sulfone **1a** in the presence of a catalytic amount of diarylketone and a 36 W white compact fluorescent lamp (CFL). Optimized reaction conditions using 1 equiv of sulfone **1a** and 20 mol% of 4,4'-dichlorobenzophenone in THF at rt, delivered the alkenyl product **2** in 97% yield.[14] The reaction was then performed with 2.5 g of **1a**, which afforded 1.47 g of **2** in 83% yield with 97:3 *E*:*Z* ratio (Eq. 1). The reaction exhibited similar efficiency when carried out in sunlight. The scalability of the reaction was also established using amide coupling partner, delivering the allyl amide **3** in excellent yield and *E*:*Z* ratio (Eq. 2). Notably, the diarylketone could be reused up to five cycles without realizing significant loss of its catalytic activity[15] (see ESI).



We next explored scope of this transformation with respect to ether and amide substrates (Table 1). Accordingly, substituted THF, pyran and 1,4-dioxane could be effectively converted to the vinyl derivatives **4**-**6**. Acyclic ethers were viable substrates to the simple C-H vinylation reaction (**7**-**9**). As like ether, cyclic tertiary amide (**10**) found to be suitable along with acyclic substrate (**11**). Secondary amides could also be converted to the products **12**-**14** in good yields and stereoselectivity. With this simple reaction protocol, vinylation of urea derivatives were achieved (**15**,**16**). Interestingly, the method enabled synthesis of propargyl group substituted amides (**17**,**18**) and ethers (**19**,**20**) in equal efficiency.

Substrate scope was then evaluated using a broad range of functionalized vinyl sulfones (Table 2). Vinyl sulfone having alkyl or phenyl substituent at *p*- or *o*- position of the aryl moiety exhibited good reactivity (**21-25**). The reaction could be carried out in good yield and stereoselectivity with halide substituted vinyl sulfones (**26-33**). Vinyl sulfone bearing electron deficient cyano (**34**), ester (**35**,**36**) and trifluoromethyl (**37**) substituents found to be suitable substrates. Vinyl sulfone with OH or both OMe and OH functional groups at 4 or both 3 and 4 positions of the aromatic ring furnished the products **38-41** in good yields and selectivity; however, an extended reaction time was required. On the contrary, the catalytic C-H vinylation of amide exhibited good reactivity when OH group at phenyl ring of vinyl sulfone was replaced with acetoxy substituent (**42**). The reaction furnished ether **43** in 75% yield with naphthyl substituted vinyl sulfone. Importantly, vinyl sulfones having furan (**44**) and thiophine (**45**) heterocycles were amenable to this protocol. Trisubstituted alkene adducts could be obtained using *β*,*β*-disubstituted vinyl sulfones that introduce aryl-aryl (**46**) and aryl-ester moieties (**47**). The reaction allowed access to ether/amide with ene-yne functionality (**48**,**49**). C-H Allylation could also be achieved with *β*-phenyl allyl sulfone (**50**,**51**). Scope of the reaction is not limited to styrenyl reagent, as sulfonyl methacrylates were found to be viable substrates for this reaction (**52**,**53**).

Table 1 Substrate scope[a]



[a]Reaction conditions: sulfone **1a** or **1b** (1.0 equiv), catalyst (20 mol%) ether/amide (0.02 M), isolated yields, *E:Z* ratio determined by GC analysis, regioisomeric ratio (rr) determined by ^1H NMR analysis. [b]Ph_2CO as catalyst. [c]30 mol% catalyst loading. [d]NMR yield.

To demonstrate synthetic application of the method, a variety of useful compounds (**54**-**56**) were prepared via olefin epoxidation and palladium catalyzed C-C, C-N coupling (see ESI). Furthermore, synthesis of protected chiral *γ*-amino acid **57** was completed by an olefin hydrogenation of amide **47**. A concise total synthesis of (±)-norruspoline[16] (**58**) was achieved by LAH reduction of the amide **42** in good yield (Fig. 1).

To support the proposed activation pathway depicted in Scheme 2, a series of control experiments was carried out (see ESI). When the reaction was performed with *cis* and *trans*

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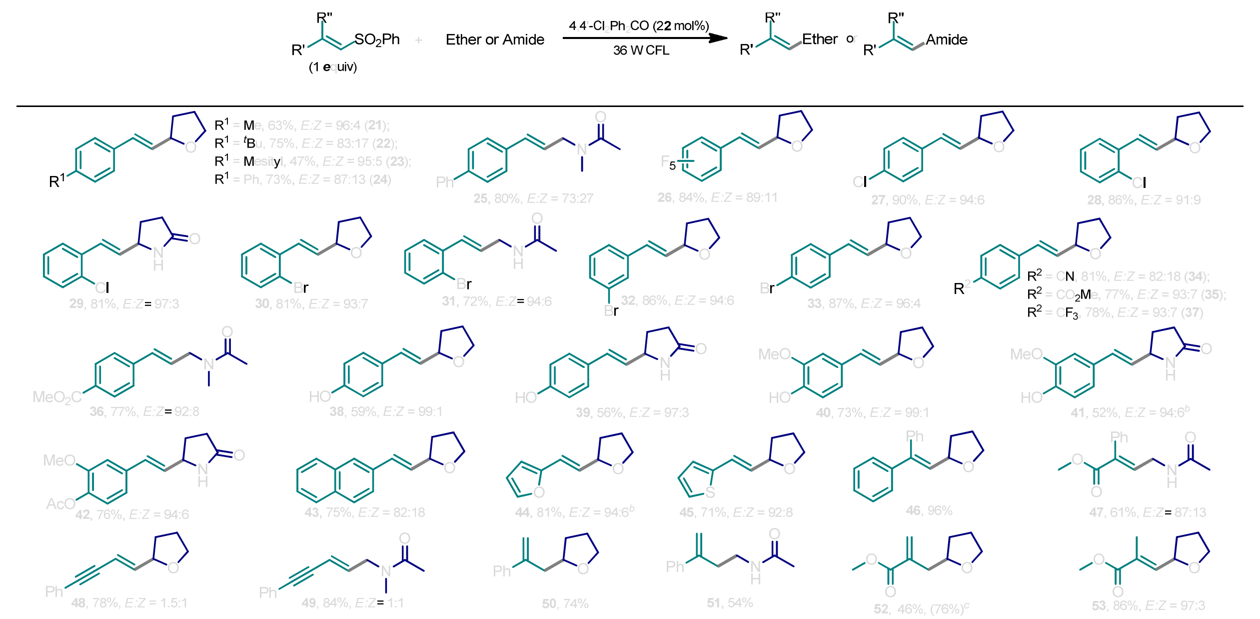
Table 2 Substrate scope[a]



[a]Reaction conditions: sulfone **1a** (0.2 mmol, 1.0 equiv), catalyst (20 mol%) ether or amide (0.02 M, 10 mL), isolated yields, *E:Z* ratio determined by GC analysis. [b]30 mol% catalyst loading was used. [c]NMR yield using mesitylene as internal standard.

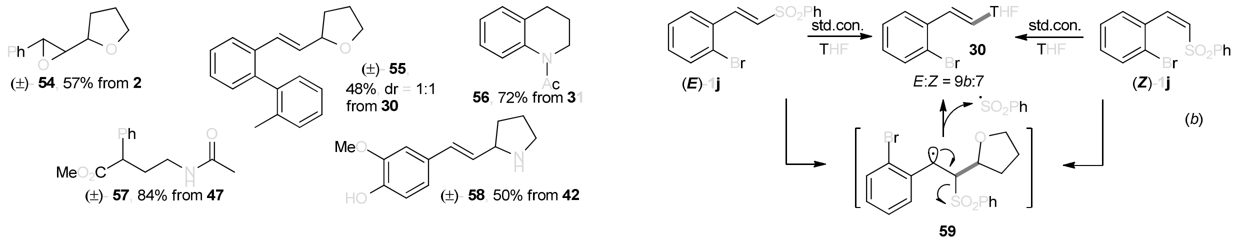


Figure 1 Synthetic application of the C-H alkenylation reaction.

isomer of sulfone **1j** (Eq. 3), both isomers delivered alkene **30** in essentially identical yield with *E*:*Z* ratio. This result suggests that both the reactions may occur through a common intermediate **59**, which upon elimination of a sulfinyl radical[17] affords thermodynamically more stable *trans* alkene as a major product. Furthermore, the reaction exhibited sluggish reactivity in the presence of TEMPO. This result indicates that the reaction may involve a radical mechanism. Additionally, the reaction found to be inefficient in the absence of both ketone **I** and light. No product formation was also realized when the reaction mixture was stirred in dark at 50 °C with or without a catalyst indicating that the reaction did not proceed with thermal energy. By turning light on and off the reaction can be switched on and off, which further proves the necessity of light for the reaction. Complete decomposition of the photocatalyst was observed in absence of sulfone, suggesting that the reduction of sulfinyl radical with ketyl radical **III** of Scheme 2 is essential for the regeneration of ketone. However, the UV-vis absorption spectrum of 4,4'-dichlorobenzophenone reveals very weak absorbance above 400 nm suggesting that the formation of intermediate **II** with white compact fluorescent lamp (CFL) might be inefficient. As a result, the observed reactivity could be attributed via a competing radical chain mechanism, where sulfinyl radical generated after addition/elimination process may contribute in radical chain propagation step (Scheme 2).[18] This was further supported by the observation that the reaction found to be promoted with

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$Ir(ppy)_3$ as photocatalyst, albeit with low yield of the desired product (see Eq. S7 in ESI).

In conclusion, we have developed an efficient method for the direct C(sp^3)-H alkenylation/alkynylation of ethers/amides with household fluorescent light bulb and a catalytic amount of diaryketone. This process allows easy access to alkenyl, alkynyl and allyl substituted ethers/amides in good yield with moderate to excellent stereoselectivity. Furthermore, the ability to perform the reaction with UV light sensitive aromatic halide and alcohol functional groups adds value to this green protocol. This process represents a straightforward entry to different synthetically valuable compounds and natural product such as (±)-norruspoline. Further studies toward reaction mechanism and application of this process with other class of substrates are currently being pursued in our group.

Acknowledgements

We gratefully acknowledge the generous financial support of Science and Engineering Research Board, India (No.SB/S5/GC-08/2014) and CSIR for fellowship to SP.

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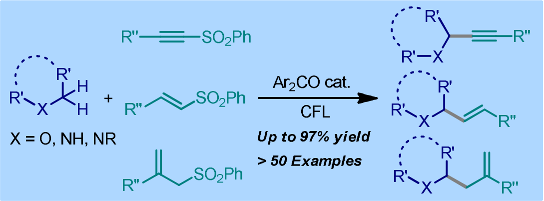

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