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COMMUNICATION

Metal-free Desulfurizing Radical Reductive C-C Coupling of Thiols and Alkenes

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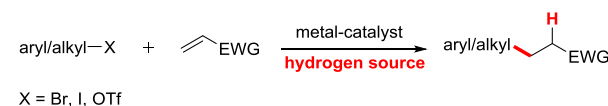
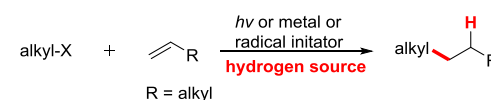
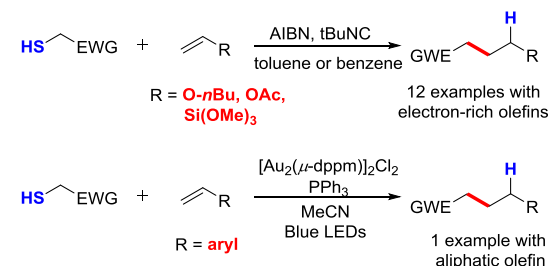
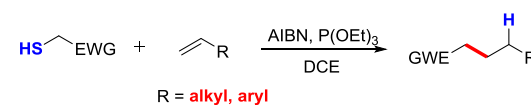
An intermolecular reductive C-C coupling of electrophilic alkyl radicals and alkenes has been developed. Thiols were used as both hydrogen-donating reagents and alkyl radical precursors in the presence of triethyl phosphite and radical initiator. A wide range of alkenes, including styrenes, aliphatic olefins were tolerated well in this transformation. Mechanistic studies indicated that a phosphite promoted radical desulfurization of thiols to access electrophilic alkyl radicals and the radical chain propagation process may be involved in this transformation.

Transition metal catalyzed C-C bond construction have been emerged as a powerful tool for the construction of organic compounds.¹ Of the various type reactions of C-C bond formation, Heck or Heck-type reactions of aliphatic alkenes has been extensively explored and applied for the synthesis of pharmaceuticals and natural products.² Along with the significant progress of Heck reaction, the reductive Heck reaction for the formation C-C single bond has also attracted considerable attentions.³ Since its initial study Cacchi group,⁴ the intramolecular and intermolecular reductive Heck cyclization of alkenes has been well-explored (Scheme 1a).⁵ However, the regioselectivity problem and competitive Heck reaction still limited their further application.⁶ Furthermore, the use of transition metal catalyst and the external hydrogen source are always essential to the reductive process. Therefore, it is highly desirable and attractive to develop new approach for the construction of C(sp³)-C(sp³) bond under mild reaction conditions.

Radical reactions have been widely applied in organic synthesis due to its high efficiency and regioselectivity under mild reaction conditions with the tolerance of many sensitive functional groups. Carbon-centered radicals,⁷ which are usually generated by reduction of alkyl halides, exhibit versatile role in construction of C-C bond formation.⁸ However, reductive electron-deficient alkyl radical addition with styrenes is still rare. Traditional, such process was promoted with tin reagent.⁹

Unfortunately, the high toxicity of organotin compounds limits its application. Recently, photoredox catalysis induced alkyl radical addition with olefins have been widely investigated (Scheme 1b).¹⁰ Despite the significant progress, most of them were proceed with an excess of hydrogen-donating reagent, such as Hantzsch ester, thiol, *N,N*-diisopropylethylamine or formic acid. Thiols are very handy compounds that can be readily synthesized from haloalkanes, alcohols, or their derivatives in manifold ways.¹¹ We therefore envisioned that thiols could act as a clean and efficient alkyl radical precursor. Such concept had been realized by Nanni and coworkers, which performed the reductive C-C coupling with thiols and olefins used *tert*-butyl isocyanide as desulfurization reagent

a) Reductive Heck reaction

b) C(sp³)-C(sp³) coupling via radical approachc) C(sp³)-C(sp³) coupling via desulfurizing approach (previous works) ref. 12 and 13d) Reductive desulfurizing C-C coupling (*this work*)Scheme 1 Methodologies for C(sp³)-C(sp³) Bond Construction.

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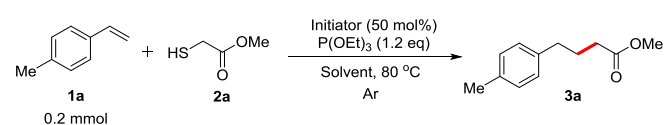
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(Scheme 1c).¹² However, only 12 examples were reported with large excess of alkenes (up to 10.0 equiv) and the substrates were limited to electron-rich aliphatic olefins. Very recently, Hashmi and coworkers reported a gold-catalyzed reductive desulfurizing C–C coupling of electrophilic radicals and styrenes assisted by blue LEDs (Scheme 1c).¹³ Despite the great improvement of desulfurizing addition to styrenes, only one example of aliphatic olefin was exhibited. Herein, we present a reductive desulfurizing C–C coupling of electrophilic radicals and alkenes, which use triethyl phosphite as desulfurization reagent (Scheme 1d). In this work, both styrenes and aliphatic olefins are all tolerated well in moderate to good yields while thiols are used as both hydrogen-donating reagents and alkyl radical precursors, providing a convenient approach to directly C–C bond construction.

Our investigation was initiated by using styrene **1a** and methyl thioglycolate **2a** as the substrates. To our delight, C–C coupling product **3a** was obtained in 77% NMR yield by using triethyl phosphite as the sacrificial reagent and AIBN as the radical initiator in the solvent of DCE under Ar atmosphere at 70 °C (entry 1, Table 1). The use of other radical initiators, such as Benzoyl peroxide (BPO) or dilauroyl peroxide instead of AIBN resulted in lower yields (entries 2–3). Screening the solvents with CH₃CN, PhCl, DMF, EtOH resulted in slightly low yields (entries 4–7). Furthermore, when decreased the loading of AIBN to 25 mol% or even 5 mol%, the yields could be maintained which indicated the radical chain propagation process may be involved in this transformation (entries 8–9). Control experiment showed the essential role of triethyl phosphite (entry 11, Table 1).

Table 1 Reaction Conditions Investigation.^a

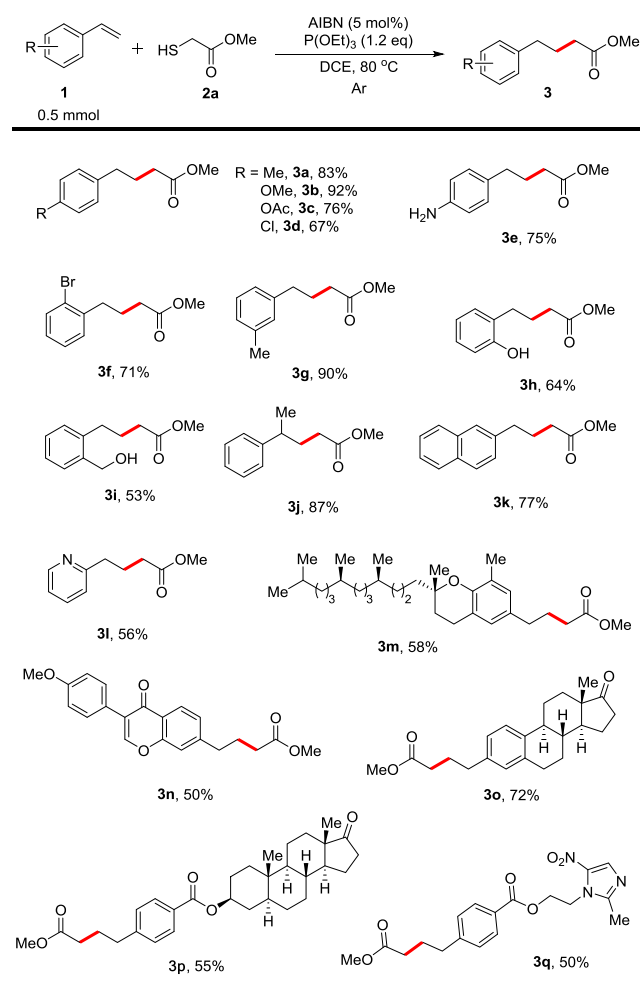


| Entry | Initiator | Solvent | Yield ^b |
|--------------------|--|--------------------|------------------------|
| 1 | AIBN | DCE | 77% |
| 2 | BPO | DCE | 14% |
| 3 | (dodecylCO ₂) ₂ | DCE | 19% |
| 4 | AIBN | CH ₃ CN | 63% |
| 5 | AIBN | PhCl | 65% |
| 6 | AIBN | DMF | 63% |
| 7 | AIBN | EtOH | 72% |
| 8 ^c | AIBN | DCE | 78% |
| 9 ^d | AIBN | DCE | 77% (75%) ^g |
| 10 ^{d, e} | AIBN | DCE | <5% |
| 11 ^{d, f} | AIBN | DCE | Nd |

^a Reaction conditions: **1** (0.2 mmol), **2a** (1.5 equiv), AIBN (50 mol%), P(OEt)₃ (1.2 equiv), DCE (2.0 mL), stirred at 80 °C under Ar for 12 h. ^b Yields were determined by ¹H NMR using Cl₂CH₂CH₂Cl₂ as an internal standard. ^c The loading of AIBN was decreased to 25 mol%. ^d The loading of AIBN was decreased to 5 mol%. ^e The reaction was conducted at 40 °C. ^f No triethyl phosphite added. ^g Isolated yields.

Under the optimized reaction conditions, we next studied the generality of this desulfurizing C–C coupling reaction by exploring the scope of styrenes (Table 2). A variety of electron-rich and electron-deficient alkenes were examined in this transformation. Some functional groups, such as Cl, Br, OAc, NH₂, OH were well tolerated (**3b–3f**, **3h**). It was noteworthy when styrene with a benzyl alcohol group was used as the substrate, which could cause the competitive reactions between deoxygenated and desulfurized, the hydroxyl group was not touched by this protocol, but gave the desired desulfurized C–C coupling product in 53% yield (**3i**). The heteroaromatic substrate also performed well under the standard reaction conditions giving the corresponding product in 56% yield (**3l**). Moreover, five complex alkene substrates bearing varying functional groups could also be employed, affording the desired C–C coupling products in moderate yields (**3m–3q**). These examples clearly suggest that this strategy represents a promising late-stage modification of complex bioactive molecules containing alkene groups.

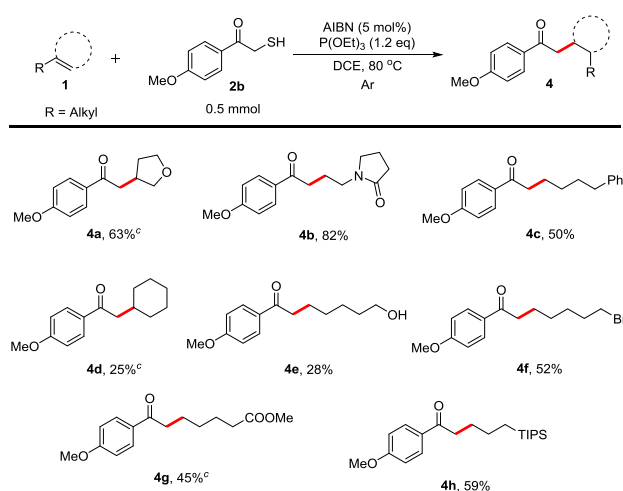
Table 2 Scope of Styrenes Partners for C–C Coupling.^{a, b}



^a Reaction conditions: **1** (0.5 mmol), **2a** (1.5 equiv), AIBN (5 mol%), P(OEt)₃ (1.2 equiv), DCE (4.0 mL), stirred at 80 °C under Ar for 12 h. ^b Yields of isolated products.

Besides of styrenes, a variety of aliphatic olefins were also examined in this desulfurizing C–C coupling reaction (Table 3). Respect of the fact that hydrogen transfer from the thiol to the alkyl radical is much faster than its addition to the olefin. We choose to decrease the concentrations of thiol, setting thiol as one equivalent in the presence of excess of olefins. Electrophilic alkyl radicals are not easily trapped by the thiol due to polar effects in the hydrogen-abstraction reaction, and they can be smoothly generated in the presence of nucleophilic olefins such as 2,3-Dihydrofuran and *N*-Vinyl-2-pyrrolidone, giving the desulfurized C–C coupling products in good yields (**4a–4b**). Furthermore, some other aliphatic olefins bearing versatile functional groups, such as OH, Br, COOMe, TIPS all performed well in this transformation, resulting in moderate yields (**4e–4h**).

Table 3. Scope of Aliphatic Olefins Partners for C-C Coupling.^{a, b}

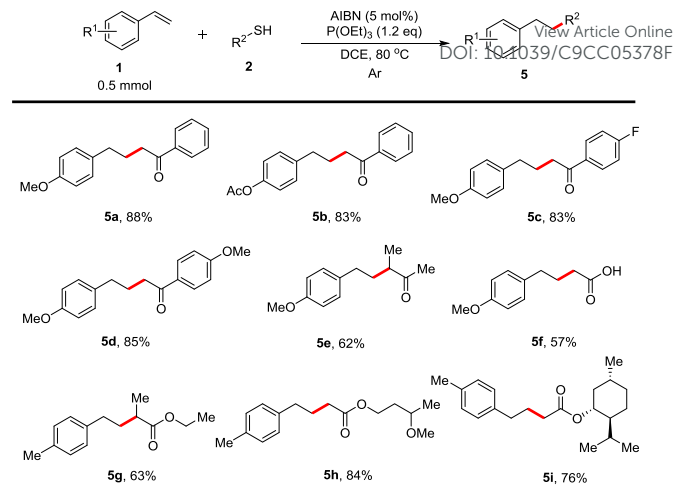


^a Reaction conditions: **1** (1.5 equiv), **2b** (0.5 mmol), AIBN (5 mol%), P(OEt)₃ (1.2 equiv), DCE (4.0 mL), stirred at 80 °C under Ar for 12 h. ^b Yields of isolated products. ^c 4.0 equivalent of alkenes were used.

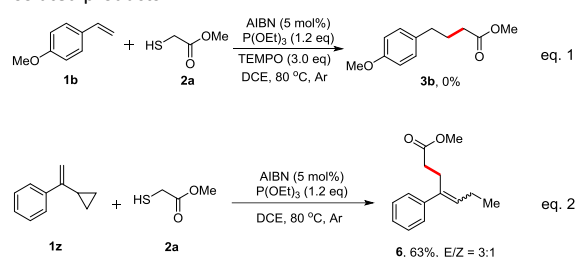
We further investigated the viability of thiols in this desulfurizing C–C coupling reaction (Table 4). Substrates of α -sulfhydryl ketones bearing F or OMe group are competent reaction partners (**5c–5d**). Secondary thiols including α -sulfhydryl ketone and α -sulfhydryl ester also readily underwent this C–C coupling (**5e**, **5g**). Significantly, Mercaptoacetic acid could also be tolerated in the reaction condition, giving the acid derivative in good yield which was not easily accessed in previous reported methods (**5f**). Notably, when D-menthol derivatived thiol was employed, the desired desulfurized C–C coupling product was obtained in 76% yield (**5i**).

To gain mechanistic insight into this desulfurized C–C coupling, radical inhibitor 2,2,6,6-tetramethyl-1-piperidyloxy (TEMPO) was added to the reaction system, no desired desulfurized product **3b** was detected (eq. 1). A radical clock experiment was also performed, using (1-cyclopropylvinyl)benzene **1z** as substrate, the desired ring-open product **6** was obtained in 63% yield, which indicated a radical process may be involved in this transformation (eq. 2).

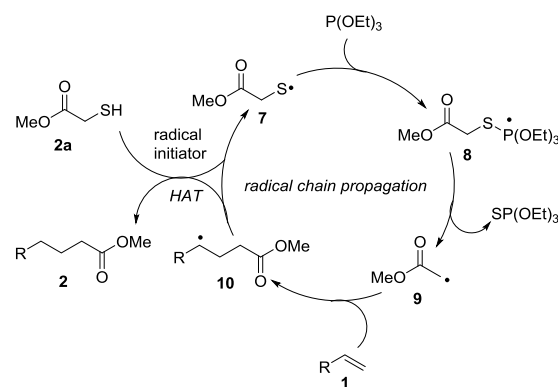
Table 4. Scope of Thiols Partners for C-C Coupling.^{a, b}



^a Reaction conditions: **1** (0.5 mmol), **2** (1.5 equiv), AIBN (5 mol%), P(OEt)₃ (1.2 equiv), DCE (4.0 mL), stirred at 80 °C under Ar for 12 h. ^b Yields of isolated products.



Based on the above experiments and reported works,^{12,13} a possible mechanism is proposed (Scheme 2). Thermal radical initiation is followed by H-atom abstraction from thiol **2a** to produce sulfur radical **7**, which then undergoes reversible addition to triethyl phosphite. The generated phosphoranyl radical **8** undergoes β -scission of C–S bond and radical addition to the alkene to preferentially produce an alkyl radical **10**. The alkyl radical **10** performs a thermodynamically favorable H-atom abstraction from another thiol to afford the desulfurized product **2** and regenerates sulfur radical **7**. In this context, thiol acts as both hydrogen-donating reagent and alkyl radical precursor.



Scheme 2 Proposed Mechanism

In summary, we described a highly efficient reductive C–C coupling of a variety of alkenes and thiols. This catalytic system

enabled a direct desulfurization of thiols to access electrophilic alkyl radicals assisted by commercially inexpensive triethyl phosphite reagent. Styrenes and aliphatic olefins bearing various functional groups were all well tolerated under the mild reaction conditions with high regioselectivity.

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Conflicts of interest

There are no conflicts to declare.

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