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Kinetic-control difunctionalization of olefins to α-hydroxycarbonyls under catalyst-free conditions

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Difunctionalization of olefins is effective in constructing diverse, valuable molecules. However, such a reaction always relies on catalysts to control activity and selectivity. Herein, a catalyst-free difunctionalization of olefins with sulfonyl or alkyl precursors and 1,2-dicarbonyls is reported to synthesize complex α-hydroxycarbonyls under visible light irradiation.

Green foundation

1. Valuable and complex α-hydroxycarbonyls, central motifs in many natural products and pharmaceuticals, are synthesized *via* a catalyst-free difunctionalization of olefins with sulfonyl or alkyl precursors and 1,2-dicarbonyls under mild conditions.
2. A new mechanism is established to control chemo- and regio-selectivity in the absence of a catalyst. The kinetic advantage of the single-electron transfer process between the excited-state 1,2-dicarbonyl substrates and sulfonyl or alkyl precursors, over the Paternò–Büchi reaction between 1,2-dicarbonyls and olefins, determines the chemo- and regio-selectivity of α-hydroxycarbonyls.
3. This reaction is directly driven by visible light without the need for any catalysts or additives, which is greener to achieve pharmaceuticals involving α-hydroxycarbonyl skeletons, beneficial for new drug development.

Difunctionalization of olefins is widely used to install two adjacent functional groups simultaneously to construct diverse, valuable structures from simple molecules.[1–3] Over the past decades, transition metal catalysis,[4–6] N-heterocyclic carbene catalysis[7–9] and photocatalysis[10,11] have been established to activate the substrate and control reaction selectivity. These catalysts activate radical precursors through single electron transfer (SET) or energy transfer (EnT) to generate radicals, which are then added to the β-position of alkenes to produce alkyl radicals.[12–14] The alkyl radicals are then coupled with nucleophiles,[15,16] electrophiles,[17,18] persistent radicals[19,20] or radical acceptors[21,22] to afford difunctionalization products. In the absence of a catalyst, however, the difficulty in substrate activation[23] and the self-coupling of radicals[24] always result in negative effects, especially for a three-component reaction.

Herein, a catalyst-free difunctionalization of olefins with sulfonyl or alkyl precursors and 1,2-dicarbonyls is reported to construct complex α-hydroxycarbonyls, central motifs in many natural products and pharmaceuticals (Scheme 1).[25–27] The key to success is that 1,2-dicarbonyls absorb light to reach spin-polarized diradical triplet states,[28,29] and then interact with radical precursors and alkenes in a kinetic manner. The SET process from sulfonyl or alkyl precursors to the excited 1,2-dicarbonyls is kinetically favorable to generate sulfonyl or alkyl and ketyl radicals. Immediately, the sulfonyl or alkyl radicals are added to olefins, leading to benzyl radicals. By contrast, the Paternò–Büchi reaction between 1,2-dicarbonyls and olefins is too slow to generate oxetanes. Finally, the cross-coupling of the ketyl radicals and benzyl radicals provides α-hydroxycarbonyls. This protocol provides a route to control chemo- and regio-selectivity resulting from the kinetic difference of interaction between the excited-state substrate and the ground-state substrate.

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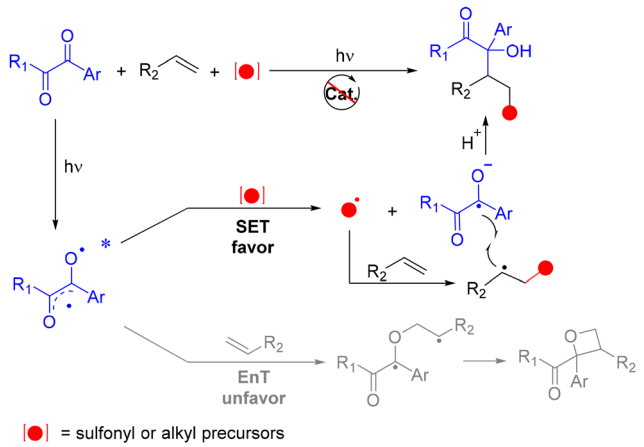
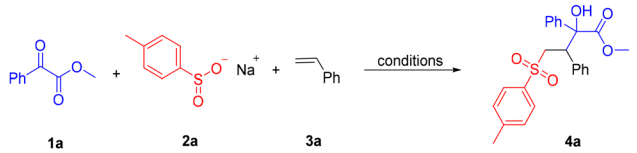


Scheme 1 Catalyst-free difunctionalization of olefins to produce α-hydroxycarbonyls.

Initially, methyl benzoylformate **1a**, sodium 4-methylbenzenesulfinate **2a** and styrene **3a** were allowed to react under 460 nm irradiation in DMF, and the targeted α-hydroxycarbonyl product **4a** was obtained in 46% yield (Table 1, entry 1). LEDs with shorter wavelengths were screened, and 405 nm was determined as the best, giving a yield of 72% (Table 1, entries 2, 4 and 5). When DMF was substituted with a mixed solvent of MeCN and H_2O, the yield was reduced to 56% (Table 1, entry 6). When the concentration of reactants was increased by reducing the volume of DMF, the yield improved to 80% (Table 1, entry 7). This result is equivalent to the yield obtained with a catalyst under blue light (Table 1, entry 3). In control experiments, irradiation and an argon atmosphere proved to be necessary, as no product was detected in the dark (even at high temperature) or in air (Table 1, entries 8 and 9).

Table 1 Optimization of the reaction conditions[a]

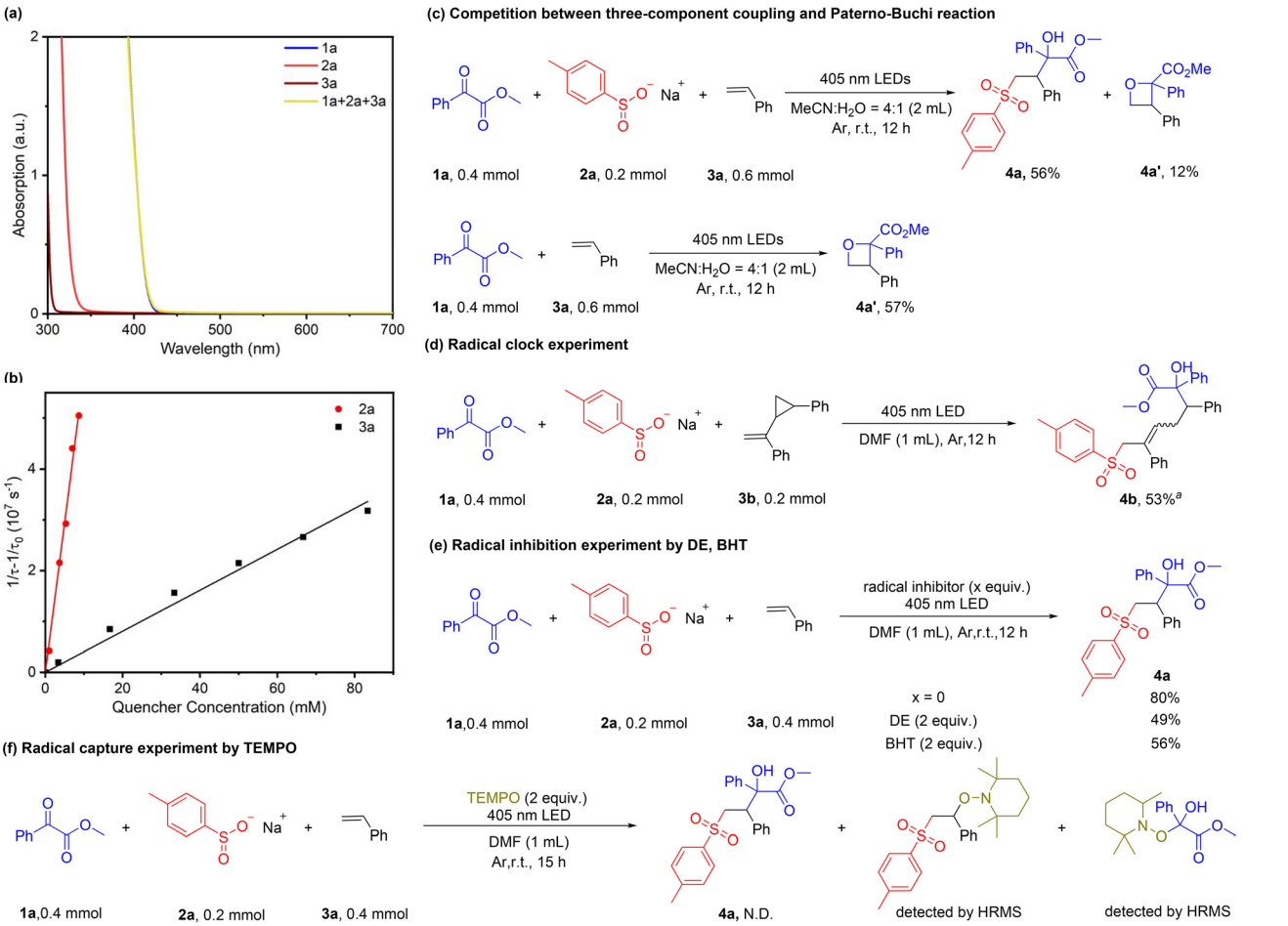


Entry	Light source (nm)	Solvent	Yield[b] (%)
1	460	DMF	46
2	440	DMF	68
3[c]	440	DMF	80
4	405	DMF	72
5	365	DMF	61
6	405	MeCN : H_2O = 4 : 1	56
7[d]	**405**	**DMF**	**80**
8[e]	—	DMF	0
9[f]	460	DMF	0

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol) and **3a** (0.6 mmol) in a solvent (2.0 mL) under LED irradiation for 12 h at room temperature under an Ar atmosphere. [b] ^{1}H NMR yield with 2,2-diphenylacetonitrile as an internal standard. [c] 4CzIPN (2 mol%). [d] **3a** (0.4 mmol), DMF (1.0 mL). [e] Room temperature or 80 °C. [f] In air.

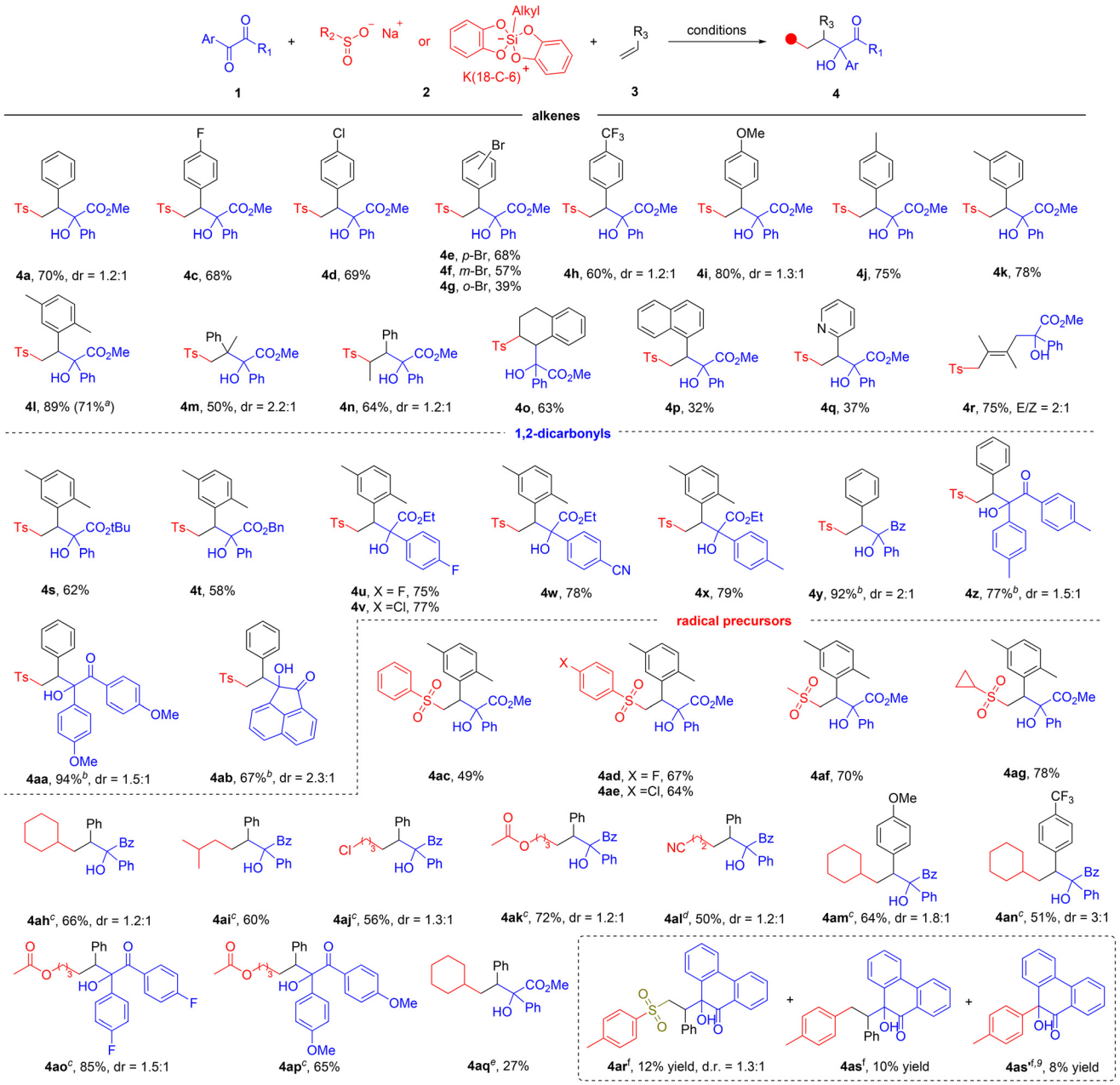
UV–visible (UV–vis) absorption spectra excluded the formation of an electron donor–acceptor (EDA) complex, as neither a bathochromic shift nor a new absorption peak was observed in the reactant mixture (Scheme 2a). The Stern–Volmer plots revealed that the excited **1a*** was quenched by **2a** more efficiently than by **3a** (Fig. S10 and S11). In time-resolved photoluminescence (TRPL) spectra (Fig. S12 and S13), the quenching rate constants of **1a*** by **2a** and **3a** were determined as 5.9×10^9 M^{-1} s^{-1} and 4.0×10^8 M^{-1} s^{-1}, respectively (Scheme 2b), indicating that **1a*** was quenched by **2a** roughly 15 times faster than by **3a**. Based on UV–vis absorption spectra (Fig. S8), photoluminescence spectra and the redox potential of ground state **1a** (E(**1a**/**1a**$^{\bullet-}$) = −1.34 V *vs.* SCE in MeCN),[30] the redox potential of the excited **1a*** [E(**1a***/**1a**$^{\bullet-}$)] can be estimated as +1.64 V *vs.* SCE,[31,32] enabling complete oxidation of **2a** (E(**2a**$^{\bullet+}$/**2a**) = +0.32 V *vs.* SCE in MeCN).[33] Therefore, 75% of **1a*** was intercepted by **2a** (0.1 M) through the SET process and only 15% of **1a*** was intercepted by **3a** (0.3 M) through EnT. Consistent with the above results, 56% of **4a** was obtained through the SET process between **1a*** and **2a**, and the following radical addition of the generated sulfonyl radical to **3a** produced a benzyl radical, which finally underwent cross-coupling with a ketyl radical (Scheme 2c). By contrast, only 12% of oxetane **4a′** was obtained by the direct addition of **1a*** to **3a** and the subsequent intramolecular cyclization. In the absence of **2a**, **4a′** was produced in 57% yield under the same conditions. These results mutually validated that the rate of the SET process between **1a*** and **2a** and the following radical addition and cross-coupling process is faster than that of the Paternò–Büchi reaction between **1a*** and **3a**. In a radical clock experiment, the cyclopropane moiety on (1-(2-phenylcyclopropyl)vinyl)benzene **3b** opened to generate the sole linear product **4b** in 53% isolated yield (Scheme 2d), suggesting that the reaction involved a benzyl radical. When 2 equiv. of 1,1-diphenylethylene (DE) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) were added to the reaction system, the yield of **4a** was obviously decreased (Scheme 2e). Adding 2 equiv. of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), the generation of **4a** was completely inhibited, while the adducts of TEMPO with benzyl and ketyl radicals were detected by HRMS (Scheme 2f). These results supported a possible reaction pathway where sulfonyl radicals were added to alkenes to produce benzyl radicals, which then underwent radical cross-coupling with ketyl radicals to afford our desired α-hydroxycarbonyls.

A range of alkenes, aromatic 1,2-dicarbonyls, sulfinates and bis(catecholato)silicates were used to examine the generality of this protocol (Scheme 3). The different electronic effects and steric effects showed good tolerance when alkenes were tested with **1a** and **2a** as reaction partners. Electron-withdrawing groups including F, Cl, *p*-Br, *m*-Br, *o*-Br and CF_3, and electron-donating groups including MeO, *p*-Me, *m*-Me and 2,5-dimethyl all worked smoothly to provide their products in 39%–89% yields (**4c–4l**). Br substitution at different sites showed an obvious steric hindrance effect (**4e–4g**). Styrenes with larger



Scheme 2 Mechanism studies: (a) UV–vis absorption spectra of **1a** (0.2 M), **2a** (0.1 M), and **3a** (0.2 M) in a mixed solvent of MeCN : H_2O = 4 : 1. (b) Fitting results of TRPL of **1a** (0.1 M) with different concentrations of **2a** and **3a**. (c–f) Competitive reactions and radical experiments. ^{1}H NMR yield with 2,2-diphenylacetonitrile as an internal standard. [a] Isolated yield.

steric hindrance, such as α-,β-methyl styrenes, 1,2-dihydronaphthalene and vinylnaphthalene, gave 32%–64% yields (**4m–4p**). The addition of a sulfonyl radical to **4p** produced an α-naphthalene carbon radical intermediate with a larger electron delocalization range. The smaller difference between the self-coupling reaction rate constant of the α-naphthalene carbon radical and that of the ketyl radical led to lower selectivity for their cross-coupling.[24] 2-Vinylpyridine (**4q**) gave low yields, due to the detrimental electron-withdrawing effect. Alkyl butadiene afforded a distal sulfonylation product (**4r**) in high yield. The α-ketoesters with different alkyl groups on ester moieties and different electronic effects on arenes were all compatible (**4s–4x**, 58%–79%). 1,2-Diketones with different electronic effects were transformed with yields up to 94% (**4y–4ab**). Both aromatic and aliphatic sulfinates were successfully converted to the corresponding products in 49%–78% yields (**4ac–4ag**). Bis(catecholato)silicates were chosen as alkyl precursors,[34] using styrene and benzil as reaction partners. Unstabilized primary and secondary alkyl radicals were converted to target products in 50%–72% yields (**4ah–4al**). Styrenes with strong electron-donating MeO and electron-withdrawing CF_3 groups, as well as benzyls with MeO and F groups, were all suitable (**4am–4ap**, 51%–85%). An α-ketoester offered a low yield (**4aq**, 27%), and methyl mandelate was obtained as a by-product in 28% yield based on **1a**. 4-Iodotoluene and DABSO (1,4-diazabicyclo [2.2.2] octane-sulfur dioxide) were used instead of **2a** in a four-component coupling reaction with phenanthrene-9,10-dione and **3a** in the presence of DIPEA (*N*,*N*-diisopropylethylamine) (Scheme 3). The β-sulfonylated four-component coupling product **4ar**, the β-arylated three-component coupling product **4as**, and the two-component coupling product **4as′** were obtained in 12%, 10% and 8% yields, respectively. This reaction may proceed *via* a halogen atom transfer (XAT) process promoted by *in situ*-generated α-aminoalkyl radicals to afford aryl radicals,[35] which then underwent three different processes including (i) sulfur dioxide insertion[36–39] to form sulfonyl radicals, finally leading to **4ar**, (ii) radical relay with **3a**, finally producing **4as**, and (iii) direct cross-coupling with ketyl radicals, generating **4as′**. This reaction was complicated by the competitive trapping of the aryl radical intermediate by DABSO and **3a**. A gram-scale experiment (3 mmol) afforded **4l** in 71% yield, implying the



Scheme 3 Substrate scope. Standard reaction conditions (Table 1, entry 7). dr = 1 : 1. [a] A gram-scale experiment of **2a** (3 mmol, 1 equiv.) for 18 h. [b] **3** (3 eq.) under 460 nm LED irradiation in EtOH (2 mL). [c] **1** (2.5 eq.) and **3** (4 eq.) in DMF (2 mL) under 460 nm LED irradiation for 9 h. [d] **1** (2.5 eq.), **2** (0.1 mmol), and **3** (4 eq.) under 460 nm LED irradiation for 9 h. [e] **3** (3 eq.). [f] phenanthrene-9,10-dione (2 eq.), 4-Iodotoluene (2 eq.), DABSO (2 eq.) and **3a** (0.2 mmol) with DIPEA (3 eq.) additive in dry MeCN (2 mL) under 460 nm LED irradiation. [g] based on 4-Iodotoluene.

potential of this light-driven difunctionalization of alkene for scaled-up production of complex α-hydroxycarbonyls.

Conclusions

In summary, we constructed complex α-hydroxycarbonyls *via* catalyst-free difunctionalization of olefins under visible light irradiation. Different from the well-studied Paternò–Büchi reaction of 1,2-dicarbonyls with olefins, the SET process from sulfonyl or alkyl precursors to excited 1,2-dicarbonyls is kinetically favorable, generating sulfonyl or alkyl radicals and ketyl radicals. The sulfonyl or alkyl radicals are immediately added to olefins to offer benzyl radicals. Then, the cross-coupling process between benzyl radicals and the ketyl radicals affords α-hydroxycarbonyls. This study achieves an ideal catalyst-free difunctionalization of alkenes based on the kinetic difference of interaction between the excited-state substrate and the

ground-state substrate, showing good chemo- and regioselectivity, a broad substrate scope and potential large-scale synthesis.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data underlying this study are available in the manuscript and its SI: materials, methods, experimental details, additional data, and NMR spectra for all compounds. See DOI: **https://doi.org/10.1039/d5gc02308d**.

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