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Four-Component Radical Dual Difunctionalization (RDD) of Two Different Alkenes with Aldehydes and *tert*-Butyl Hydroperoxide (TBHP): An Easy Access to β,δ-Functionalized Ketones

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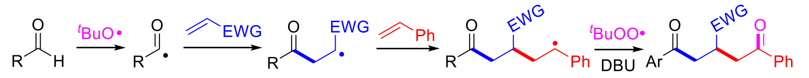
Supporting Information



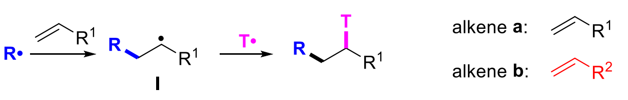
- dual difunctionalization of two different alkenes
- ordered-assembly by the intrinsic nucleo/electrophilicity of radicals and alkenes
- TBHP as radical initiator, terminal oxidant and radical coupling partner
- abundant aromatic/aliphatic aldehydes as radical source
- readily available alkene substrates
- convenient synthesis of chain elongated β,δ-functionalized ketones

ABSTRACT: A convenient Fe-catalyzed four-component radical dual difunctionalization and ordered assembly of two alkenes with aromatic/aliphatic aldehydes and TBHP to provide chain elongated β,δ-functionalized ketones via a one-pot procedure has been developed. Aldehydes were homolytically cleaved to produce acyl radicals and subsequently allowed for the successive construction of $C(sp^2)-C(sp^3)$, $C(sp^3)-C(sp^3)$, and $C(sp^3)-O$ bonds via dual radical insertions and radical−radical coupling, following the intrinsic nucleo/electrophilic reactivity of both the radicals and alkenes.

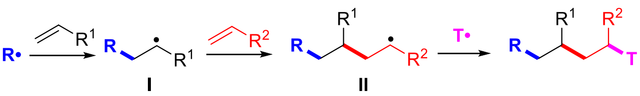
Direct difunctionalization of simple alkenes by incorporating two functional groups across a carbon−carbon double bond is of particular interest to the chemical community, since it converts readily available alkenes into diversified complex molecules in one step.[1] While transition-metal-catalyzed difunctionalizations of alkenes[2] (represented by epoxidation, dihydroxylation, and aminohydroxylation) have been well studied and widely applied in organic synthesis, the radical type difunctionalization of alkenes is expanding and surging in recent years, to introduce both heteroatoms and carbon-centered radicals into the products. Mechanistically, the radical type difunctionalization of alkenes is initiated by a radical addition to the carbon−carbon double bond to produce a new carbon-centered radical (**I**), which could be trapped directly by another suitable radical (precursor) or oxidized into a carbocation prior to the subsequent nucleophilic substitution (Scheme 1a).[1] By careful design, the new generated carbon-centered radical (**I**) might undergo the second radical addition to the carbon−carbon double bond of another alkene, to form the carbon-centered radical (**II**), which then further reacts similarly as a radical (**I**) via radical−radical coupling or an oxidation−substitution pathway to realize the radical dual difunctionalization (RDD) of two different alkenes (Scheme 1b).

Scheme 1. Radical Difunctionalization vs Dual-Difunctionalization of Alkenes

a) Radical difunctionalization of alkenes



b) Radical dual-difunctionalization of two different alkenes



To put this RDD of alkenes into practice, the selectivity of radical addition to carbon−carbon double bond is crucial: (1) for the first radical addition, the initiating radical (R•) prefers alkene **a**, but not alkene **b**; (2) for the second time radical addition, the radical intermediate (**I**) prefers alkene **b**, but not alkene **a** itself to produce oligomers; (3) the radical intermediate (**II**) is stable enough or quenched in time to suppress further copolymerization oligomers. The former two requirements on selectivity might be achieved by the intrinsic nucleophilic/electrophilic reactivity of radicals and alkenes, as exhibited by Ryu and co-workers in the multicompound cascade reactions of alkyl radicals with carbon monoxide and alkenes,[3] and Cheng et al. in the radical polar crossover reaction of dioxolanes with two alkenes.[4] The third challenge might be realized by generating a persistent radical (**II**) for radical−radical coupling with another transient radical, following the "persistent radical effect",[5] as revealed by our recent work on the difunctionalization of styrenes with aldehydes,[6] where a metastable benzyl radical was trapped by the ^{t}BuOO• (from *tert*-butyl hydroperoxide).[6a] In this context,

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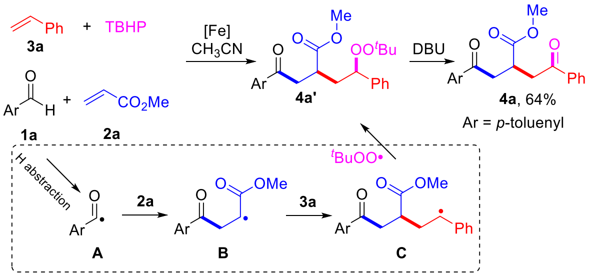
elegant studies on the acylative-peroxidation type difunctionalization of styrenes[7a] or α,β-unsaturated esters[7b] of aldehydes have been reported by Z. Li and co-workers, where the radical reaction was initiated by homolytic cleavage of aldehydes to acyls radicals in the presence of *tert*-butyl hydroperoxide (TBHP). Herein, we report a novel four-component radical dual difunctionalization (RDD) of two different alkenes with aldehydes and TBHP.

Based on the above speculation and our recent work, *p*-tolualdehyde (**1a**), methyl acrylate (**2a**), styrene (**3a**), and *tert*-butyl hydroperoxide (TBHP) were chosen as model substrates to test the radical dual-difunctionalization strategy (Scheme 2).

Scheme 2. Model Reaction for the Radical Dual Difunctionalization (RDD) of Two Different Alkenes[a]

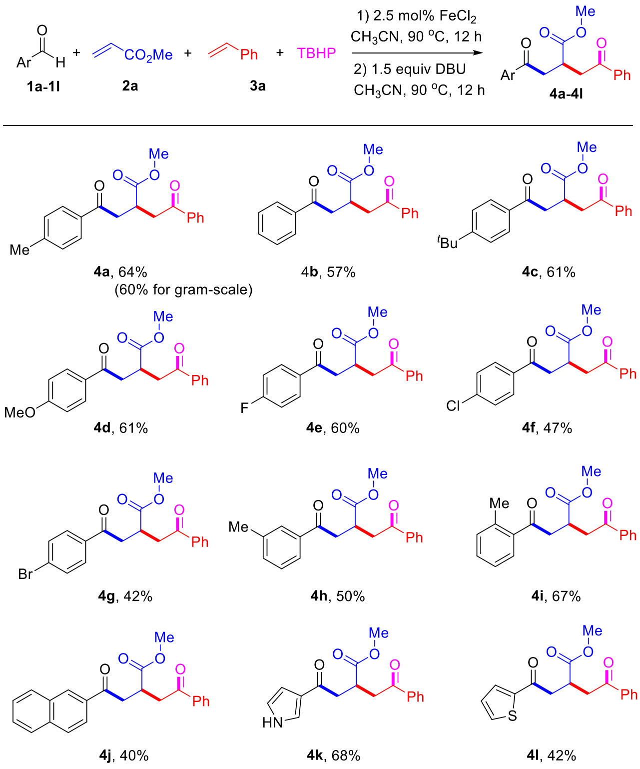


[a]Optimized reaction conditions: **1a** (0.8 mmol, 4.0 equiv), **2a** (0.2 mmol, 1.0 equiv), **3a** (0.4 mmol, 2.0 equiv), TBHP (5.5 M in decane, 1.0 mmol, 5.0 equiv), FeCl$_2$ (0.005 mmol, 2.5 mol %) in CH$_3$CN (1 mL, prepared solution), stirred at 90 °C for 12 h and then DBU (1.5 equiv) was added and stirred at 90 °C for another 12 h.

Assisted by the peroxide, *p*-tolualdehyde (**1a**) can be transformed into an acyl radical (**A**) readily by homolytic hydrogen abstraction.[7] The acyl radical (**A**) is nucleophilic[8] and prefers addition onto the electro-deficient carbon−carbon double bond of methyl acrylate (**2a**),[4,9] to produce another carbon-centered radical (**B**). The rate for addition of an acyl radical to methyl acrylate is around three times faster (depending on the temperature) than that of styrene.[9,10] Obviously, the radical (**B**) is electrophilic due to its α-electron-withdrawing group (an ester group),[11] so it favors the subsequent radical addition to styrene (**3a**) selectively,[12] to provide a metastable benzyl radical (**C**), which would further be trapped by the ^{t}BuOO· (or its precursor) via radical−radical coupling to yield the peroxide **4a′**. The model reaction did yield the expected dual-difunctionalization product in the presence of an iron catalyst. The subsequent detailed optimization on the iron sources, catalyst loading, ratio of the four reactants, solvents, and reaction temperature provided a medium yield of 64%, after a one-pot stepwise conversion of the peroxide **4a′** into β,δ-functionalized ketone **4a** to facilitate the column isolation (since around 5% of the peroxide **4a′** would undergo Kornblum−DeLaMare rearrangement[13] automatically and be transformed into the ketone **4a** even without adding any base.).

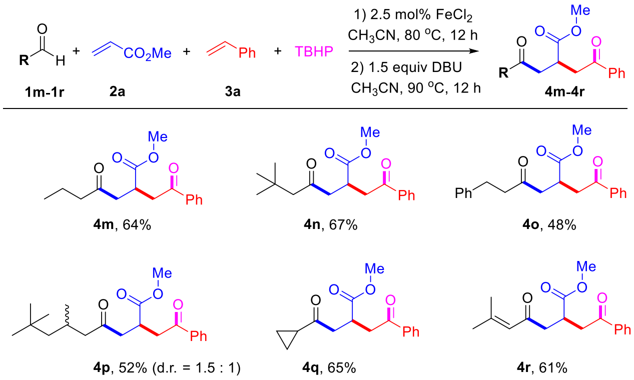
The generality of this radical dual difunctionalization of two different alkenes with aldehydes was subsequently investigated under the optimized conditions. The scope of aromatic aldehydes on this cascade reaction is listed in Scheme 3. Various aromatic aldehydes bearing electron-donating or -withdrawing substituents on the phenyl moiety (**1a**−**1l**) underwent this four-component cascade reaction smoothly to afford the desired β,δ-functionalized ketones in moderate yields, such as methyl (**1a**), *tert*-butyl (**1c**), methoxy (**1d**), and halo (**1e**−**1g**). Furthermore, the optimized reaction conditions could be applied to the aromatic aldehydes with a methyl group substituted at the *para*, *meta*, and *ortho* position (**1a**, **1h**, and **1i**), and similar yields were obtained, which reveal no obvious substituent effect and steric hindrance for the aldehydic unit. Besides substituted benzaldehydes, 2-naphthaldehyde (**1j**), pyrrole-3-carbaldehyde (**1k**), and thiophene-2-carbaldehyde (**1l**) also were suitable substrates for this radical dual difunctionalization and can be transformed into the corresponding β,δ-functionalized ketones (**4j**−**4l**), respectively.

Scheme 3. Scope of (Hetero)aromatic Aldehydes for the RDD



After investigating the scope of aromatic aldehydes, we next tested the generality of aliphatic aldehydes on this radical dual difunctionalization (Scheme 4). Both the linear and branched aliphatic aldehydes (**1m**−**1p**) were tested and compatible with the optimized conditions. Moreover, the cyclopropane-

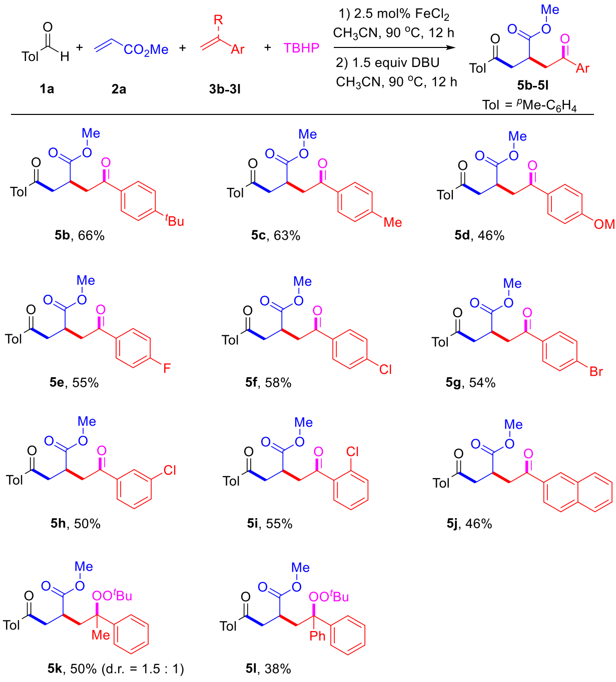
Scheme 4. Scope of Aliphatic Aldehydes for the RDD



carbaldehyde (**1q**) and 3-methylbut-2-enal (**1r**) could also be used as the suitable substrates, with the three-member ring of cyclopropane and the carbon−carbon double bond of enal intact, which might facilitate the further transformation and potential application of these products. To our delight, substrate **1r** (3-methylbut-2-enal) is also a radical Michael acceptor, but it did not compete with methyl acrylate (**2a**) in this radical dual difunctionalization, maybe due to its more hindered *β*-carbon compared with methyl acrylate.

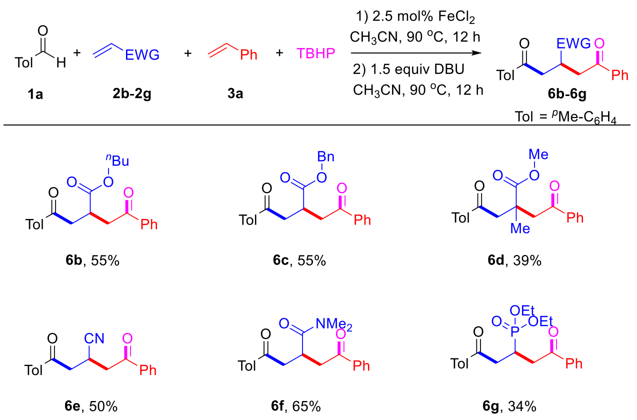
Encouraged by the above results on the wide substrate scope of this radical dual difunctionalization for both aromatic and aliphatic aldehydes, the effect of substituents on the styrene moiety was studied and listed in Scheme 5. Various styrene derivatives bearing electron-donating or -withdrawing substituents on the phenyl moiety (**3b**−**3j**) smoothly underwent this four-component cascade reaction to afford the desired *β*,*δ*-functionalized ketones in moderate yields after the one-pot procedure. However, for the *α*-disubstituted alkenes such as *α*-methylstyrene (**3k**) and 1,1-diphenylethene (**3l**), where the Kornblum−DeLaMare rearrangement (showed in Scheme 2) was impossible for the lack of an *α*-proton of peroxide motif, the radical dual difunctionalization provided the peroxide **5k** and **5l**, respectively, overriding the DBU-promoted rearrangement procedure.

Scheme 5. Scope of Styrene Derivatives for the RDD

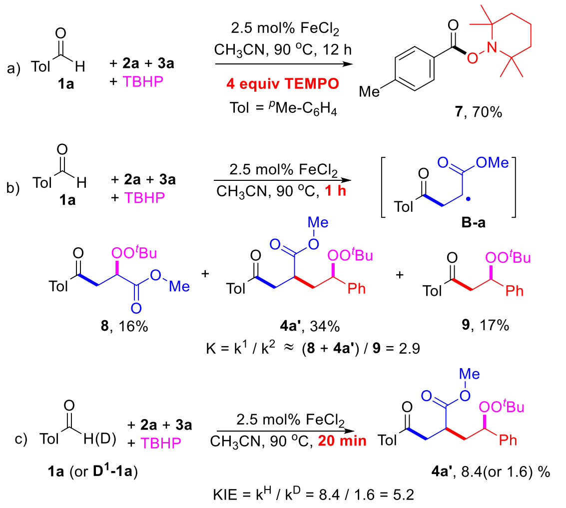


Then, the scope and limitation of electron-deficient alkenes for this radical dual difunctionalization was tested (Scheme 6). Besides methyl acrylate (**2a**), similar *α*,*β*-unsaturated esters such as *n*-butyl acrylate (**2b**), benzyl acrylate (**2c**), methyl methacrylate (**2d**), acrylonitrile (**2e**), *N*,*N*-dimethyl acrylamide (**2f**), and diethyl vinylphosphonate (**2g**) all underwent this cascade reaction with *p*-tolualdehyde (**1a**), styrene (**3a**), and TBHP to yield the targeted ketone successfully under the optimized conditions. It is a pity that currently the chemoselectivity for the radical addition to the two different alkenes was not satisfactory enough, which lowered the yields for this radical dual difunctionalization and produced the byproducts from the acylative peroxidation of the single alkene (styrene or methyl acrylate), as demonstrated in Scheme 7.

Scheme 6. Scope of Electron-Deficient Alkenes for the RDD

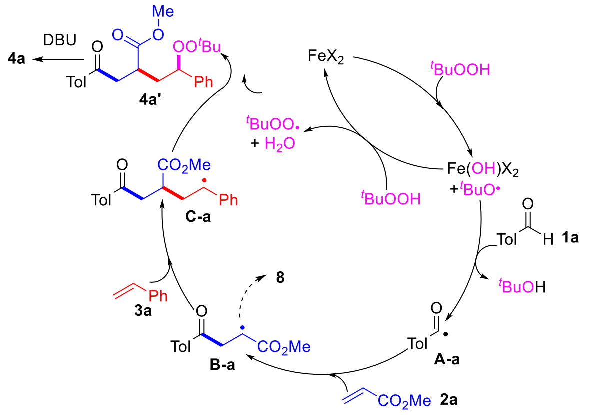


Scheme 7. Mechanistic Experiments

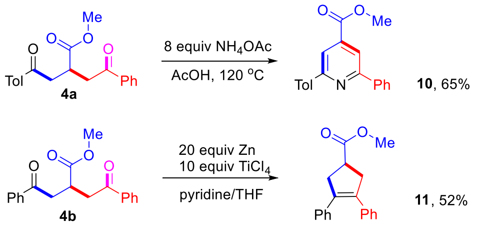


Several mechanistic experiments were carried out to understand this radical dual difunctionalization. First, the model reaction of **1a**, **2a**, **3a**, and TBHP was completely inhibited in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO); instead, the 4-methylbenzoyl radical was captured as 2,2,6,6-tetramethylpiperidin-1-yl 4-methylbenzoate **7**, which was characterized and isolated in 70% yield (Scheme 7a). Second, by shortening the reaction time to 1 h (from the optimized 12 h and overriding the DBU-promoted Kornblum−DeLaMare rearrangement step at the same time) and carefully isolating the reaction mixture, three main-products (**8**, **4a′**, and **9**) were obtained and characterized, and their yields were determined by the ^{1}H NMR using the nitromethane as the internal standard (Scheme 7b). These results supported our speculation (Scheme 2) that the radical cascade reaction was initiated by the 4-methylbenzoyl radical (**A-a**, Scheme 8), which not only was able to add onto the carbon−carbon double bond of methyl acrylate (**2a**) to produce radical intermediate (**B-a**), but also reacted with the styrene (**3a**) similarly. Under the reduced reaction time and in the absence of DBU, the Kornblum−DeLaMare rearrangement of these peroxides to the ketones was almost negligible and indeed the yields of each ketone were below 1% by HPLC analysis, so the

Scheme 8. Proposed Mechanism for the Cascade Reaction



Scheme 9. Synthetic Utility of This Radical Dual Difunctionalization



ratio of reaction rate for addition of the 4-methylbenzoyl radical (**A-a**) to methyl acrylate (**2a**) and that of styrene (**3a**) could be approximatively calculated as dividing the total yield of **8** and **4a′** by the yield of **9**, to provide a value of 2.9. These results on relative reacting rates agreed well with the literature reports, and effectively supported our speculation on radical dual difunctionalization of two different alkenes. Third, the deuterated aldehydes were synthesized and the preliminary isotopic competing experiments gave a KIE value of 5.2 (Scheme 7c), which supported that the cleavage of the aldehydic C−H bond was the rate-determining step for this cascade reaction.

Based on the above mechanistic experiments, our previous studies[6] and literature reports,[7,12] a possible reaction pathway on this radical dual difunctionalization of two different alkenes is depicted in Scheme 8, with the reaction of *p*-tolualdehyde (**1a**), methyl acrylate (**2a**), and styrene (**3a**) as an example. First, reduction of TBHP by Fe(II) salt produces a *tert*-butoxy radical (^{t}BuO·) and Fe(OH)X$_2$. Intermolecular hydrogen abstraction of *p*-tolualdehyde (**1a**) by ^{t}BuO· generates the 4-methylbenzoyl radical (**A-a**), which is a nucleophilic carbon radical that thus preferentially adds to the electron-deficient and less hindered β-carbon of methyl acrylate (**2a**) to produce a radical intermediate (**B-a**). This new generated carbon radical (**B-a**) becomes electrophilic due to its α-electron-withdrawing group (an ester group), so it favors the subsequent addition to the electron-rich and less hindered β-carbon of styrene (**3a**) selectively, to provide a metastable benzyl radical (**C-a**), which would further be trapped by the ^{t}BuOO• (or its precursor) via radical−radical coupling to yield the peroxide **4a′**. On the other hand, reaction of Fe(OH)X$_2$ with TBHP provides the ^{t}BuOO· (and water) to regenerate the Fe(II) catalyst.

To extend the synthetic utility of this radical dual difunctionalization of two different alkenes, the β,δ-functionalized ketones obtained could be readily cyclized into 2,4,6-trisubstituted pyridine **10** or reductively coupled into 1,3,4-trisubstituted cyclopentene **11**, following the literature reported pathway (Scheme 9).[14]

In conclusion, we have developed a convenient Fe-catalyzed four-component radical dual difunctionalization of two different alkenes with aldehydes and TBHP to provide β,δ-functionalized ketones via a one-pot procedure. Radical difunctionalization of alkenes was famous for its ability to synthesize complex molecules from structurally simple and readily available alkenes; this radical dual difunctionalization of two different alkenes has amplified this effect by realizing the difunctionalization and ordered assembly of two different alkenes, to introduce three functionalities and elongate the carbon chain by a one-pot procedure, with TBHP playing a triple role of radical initiator, terminal oxidant, and radical coupling partner. The application of an environmentally benign iron catalyst, cheap and readily available starting materials, wide substrate scope, and versatile synthetic utilities of radical dual-difunctionalization products would render this cascade reaction attractive for organic synthesis and medicinal chemistry.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02264.

> Experimental procedures, detailed optimization, mechanistic studies, compound characterization, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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