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Radical–Polar Crossover Reactions: Oxidative Coupling of 1,3-Dioxolanes with Electron-Deficient Alkenes and Vinylarenes Based on a Radical Addition and Kornblum–DeLaMare Rearrangement

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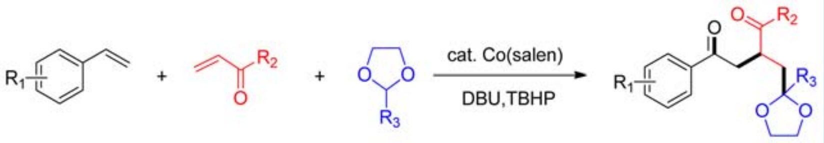
Supporting Information



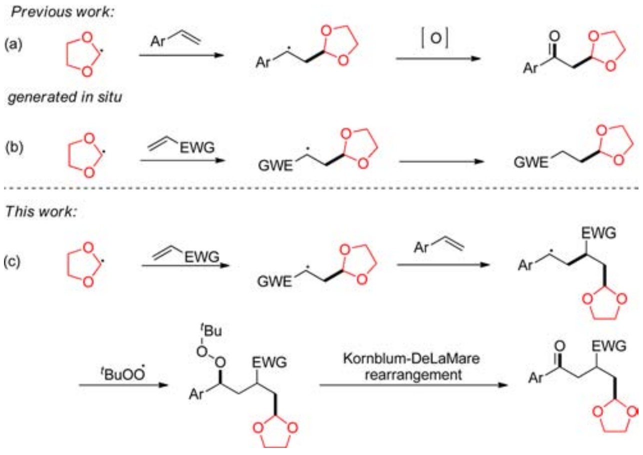
ABSTRACT: A new radical-polar crossover reaction has been developed involving the combination of a tandem radical reaction and Kornblum–DeLaMare rearrangement in a one-pot process. This simple methodology allows for the construction of polyfunctionalized carbonyl compounds via the oxidative coupling of 1,3-dioxolanes with electron-deficient alkenes and vinylarenes in the presence of Co(salen) and TBHP under mild conditions. This reaction also exhibited high functional group tolerance, wide substrate scope, and operational simplicity.

Multicomponent reactions provide a powerful and direct approach for the construction of complex molecules from structurally simple and readily available starting materials in a single-pot process, and many elegant examples of the use of these reactions in both ionic and radical reactions have been reported in the literature.[1] In contrast, there have been very few reports pertaining to the incorporation of radical and ionic reactions into a one-pot process designated as a radical–polar crossover reaction.[2] Differences in the reactivity patterns of radical and ionic intermediates mean that the subtle application of these two mechanisms in the same reaction would be particularly advantageous for the preparation of polyfunctionalized compounds.[3] The transient nature of radical intermediates makes it difficult to exert selectivity over multicomponent radical reactions.[1b,l,2c,4] The Kornblum–DeLaMare rearrangement[5] is a base-promoted reaction used for the construction of carbonyl compounds from peroxide and is generally considered a classic ionic process. In this study, it was envisaged that the combination of a tandem radical reaction with a Kornblum–DeLaMare rearrangement would allow for the construction of polyfunctionalized carbonyl compounds in a one-pot process.

Carbonyl compounds are used extensively in organic chemistry as versatile building blocks.[6] The development of new synthetic strategies for the construction of carbonyl compounds is therefore highly desirable. Ryu et al.[7] recently reported the development of a new method for the synthesis of various carbonyl compounds using CO as a C1 radical synthon. Notably, the potential application of masked aldehydes, such as 1,3-dioxolane, as carbonyl precursors in these reactions has also been recognized in recent years. For instance, Zhang et al.[8] reported the *tert*-butyl peroxide mediated reaction of 1,3-dioxolane with various electron-rich vinylarenes, which afforded the corresponding α-carbonyled β-alkylated aryl products (Scheme 1, path a). Furthermore, Elad et al. reported the radical addition of 1,3-dioxolane to electron-deficient alkenes to give the corresponding alkylated 1,3-dioxolane (Scheme 1, path b).[9]

To the best of our knowledge, there have been no reports in the literature pertaining to the three-component coupling of 1,3-dioxolanes with electron-deficient alkenes and electron-rich

Scheme 1. Radical Reaction of 1, 3-Dioxolane



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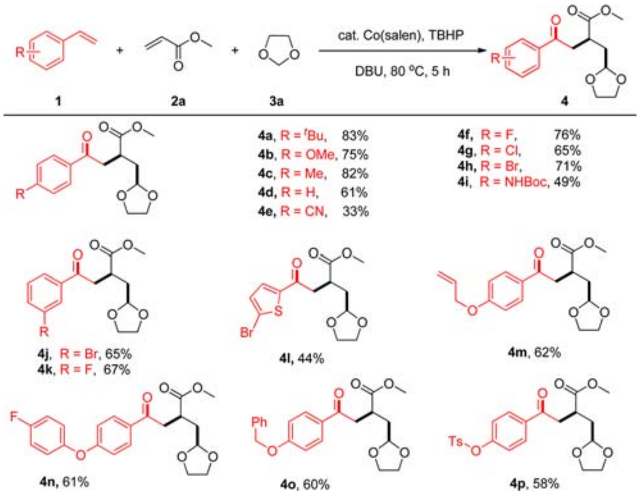
vinylarenes through a radical−polar crossover reaction. We recently developed a novel catalytic approach to the construction of 1,4-dicarbonyl compounds via the combination of a radical reaction with a Kornblum−DeLaMare rearrangement using a Co-catalyst and TBHP as an oxidant.[10] Based on our previous work, it was envisaged that the oxidative coupling of 1,3-dioxolanes to electron-deficient alkenes and vinylarenes would occur via a new radical−polar crossover process (Scheme 1, path c).

After optimizing the reaction conditions (see Table S1 of the Supporting Information for details of the screening experiments), it was established that a high yield of 83% could be obtained by reacting 1-(*tert*-butyl)-4-vinylbenzene and methyl acrylate with 1,3-dioxolane in the presence of 2 mol % Co(salen), 1.0 equiv of DBU, and 7.0 equiv of TBHP at 80 °C for 5 h in air (entry 1). It is noteworthy that the reaction did not proceed in the absence of Co(salen) or TBHP, which demonstrated that these materials play a critical role in the success of this transformation (Table S1, entries 2−3). Several other metal catalysts and oxidants were screened against the reaction with the aim of improving the yield. Unfortunately, however, all of these alternatives were found to be less effective than Co(salen) and TBHP in terms of the extent to which they promoted the process (entries 4−26).

With the optimized reaction conditions in hand, we proceeded to evaluate the scope of the reaction using a wide range of substituted vinylarenes (Scheme 2). Pleasingly, a broad range of vinylarenes were tolerated under the optimized conditions, including those bearing a halogen (**4f−h**), ether (**4b**, **4m−4o**), nitrile (**4e**), Boc-protected aniline (**4i**), methyl (**4c**), or tosyl (**4p**) substituent at the *para*-position of their phenyl ring. Vinylarenes bearing a halogen (**4j**, **4k**) at the *meta*-position of their phenyl ring were also compatible with this reaction. Notably, the heterocyclic vinyl compound 2-vinythiophene reacted smoothly under the optimized conditions to give the corresponding product **4l** in moderate yield.

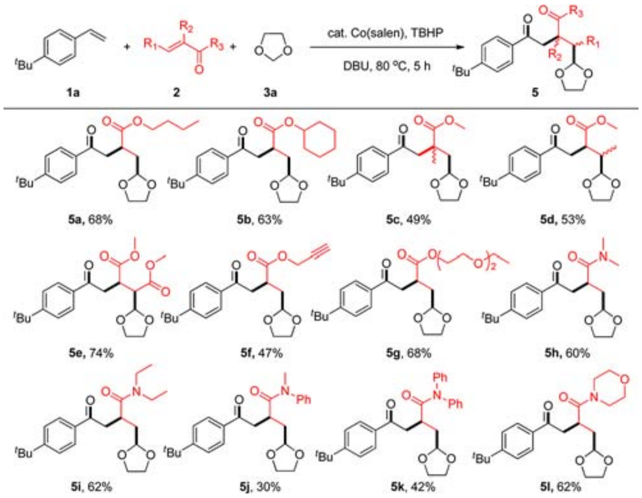
Scheme 2. Scope of Vinylarenes[a]



[a]0.4 mmol of **1**, 0.2 mmol of **2a**, 1.6 mmol of **3a**, 0.004 mmol of Co(salen), 1.4 mmol of TBHP, 0.2 mmol of DBU, 0.5 mL of CH_3CN, at 80 °C for 5 h.

The scope of the reaction was expanded further by reacting 4-*tert*-butylstyrene (**1a**) and 1,3-dioxolane (**3a**) with a variety of different acrylates and acrylamides bearing different substituents (Scheme 3). All of these substrates reacted smoothly under the optimized conditions to provide the desired products in moderate to high yields. Cyclic (**5b**, **5l**) and functionalized acrylates and acrylamides bearing an alkynyl, phenyl, or ether moiety were also found to be compatible with these reaction conditions. Notably, methyl methacrylate and (*E*)-methyl but-2-enoate gave a mixture of the stereoisomers in 49% and 53% yields (**5c**, **5d**), respectively.

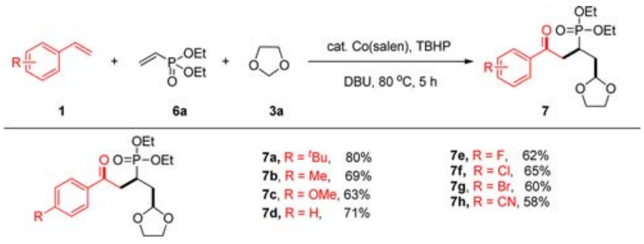
Scheme 3. Scope of Electron-Deficient Alkenes[a]



[a]0.4 mmol of **1a**, 0.2 mmol of **2**, 1.6 mmol of **3a**, 0.004 mmol of Co(salen), 1.4 mmol of TBHP, 0.2 mmol of DBU, 0.5 mL of CH_3CN, at 80 °C for 5 h.

Organophosphorus compounds are ubiquitous in living systems and can also be found in several commercial materials such as fire retardants, fungicides, pesticides, and lubricants.[11] With this in mind, we conducted a series of experiments to assess the validity of using diethyl vinylphosphonate instead of an α,β-unsaturated carbonyl compound in our newly developed transformation (Scheme 4). Pleasingly, vinylphosphonate **6a** reacted smoothly with a wide range of *para*-substituted styrenes, including those bearing a *t*-Bu, methyl, ether, halogen, or nitrile group to furnish the corresponding products (**7a−h**) in good yields.

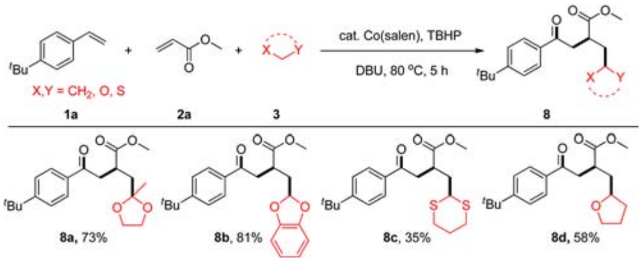
Scheme 4. Diethyl Vinylphosphonate as Substrates[a]



[a]0.4 mmol of **1**, 0.2 mmol of **6a**, 1.6 mmol of **3a**, 0.004 mmol of Co(salen), 1.4 mmol of TBHP, 0.2 mmol of DBU, 0.5 mL of CH_3CN, at 80 °C for 5 h.

The scope of the ether component of this reaction was also evaluated, and the results are shown in Scheme 5. As anticipated, 2-methyl-1,3-dioxolane reacted smoothly under the optimized conditions to give the corresponding product **8a** in good yield, which indicated that the steric effect of the

Scheme 5. Scope of Ethers[a]



[a] 0.4 mmol of **1a**, 0.2 mmol of **2a**, 1.6 mmol of **3**, 0.004 mmol of Co(salen), 1.4 mmol of TBHP, 0.2 mmol of DBU, 0.5 mL of CH_3CN, at 80 °C for 5 h.

methyl group at the 2-position was having very little impact on the outcome of the reaction. 1,3-Dithiane and THF also reacted smoothly under the optimized conditions to give the corresponding products **8c** and **8d**, respectively, in moderate yields.

Several control experiments were conducted to determine the mechanism of this transformation. Interestingly, the addition of the radical scavenger 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) suppressed the reaction, which indicated that free radical intermediates could be involved in this transformation. Furthermore, a series of radical intermediates were formed during the reaction that reacted with TEMPO to give the corresponding adducts shown in Figure 1.

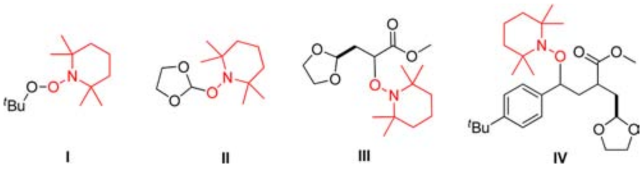
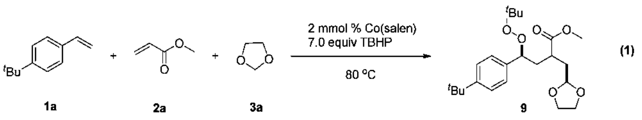
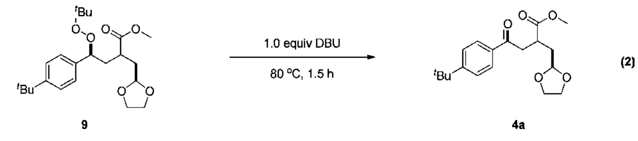


Figure 1. Radical intermediates trapped by TEMPO.

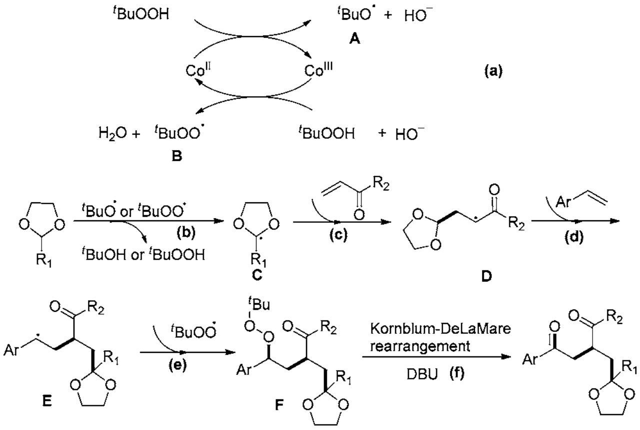
Careful examination of the model reaction mixture revealed that *tert*-butyl peroxide **9** was being formed during this process (eq 1). When a reaction mixture containing *tert*-butyl peroxide **9** and 1.0 equiv of DBU was heated to 80 °C, the corresponding product **4a** was obtained in 98% yield (eq 2). This result strongly suggested *tert*-butyl peroxide generated *in situ* was undergoing a Kornblum−DeLaMare rearrangement to give the desired 1,4-dicarbonyl compound.



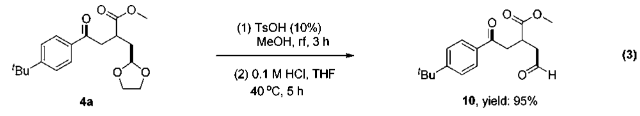


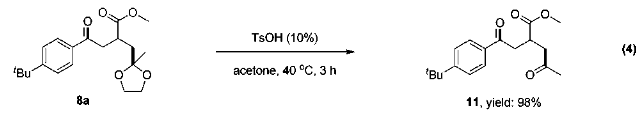
Based on the results of the current study, as well as the results of previous studies from the literature,[8,9] we have proposed a plausible mechanism for this transformation, which is shown in Scheme 6. The initial cobalt-catalyzed homolytic decomposition of TBHP would generate ^{t}BuO· **A** and ^{t}BuOO· **B**.[12] Both of the radical intermediates would then abstract a hydrogen atom from the 2-position of 1,3-dioxolane to give the nucleophilic radical **C**, which would preferentially add to the electron-deficient alkene, leading to the electrophilic radical **D**. The addition of radical **D** to an electron-rich vinylarene would afford the better stabilized benzyl radical **E**, which would be selectively trapped by the ^{t}BuOO· radical to afford *tert*-butyl peroxide intermediate **F**.[13] In the meantime, the oxidation of radical **E** followed by trapping of a carbocation by TBHP to give *tert*-butyl peroxide **F** could not be excluded. In the final step, *tert*-butyl peroxide intermediate **F** would undergo a Kornblum−DeLaMare rearrangement to give the desired product.

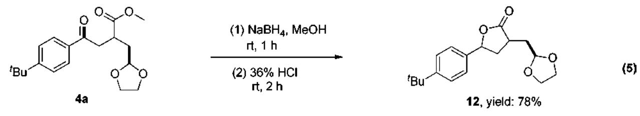
Scheme 6. Proposed Reaction Mechanism

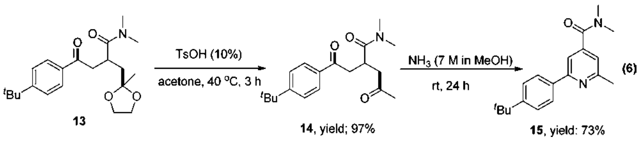


The introduction of the masked formyl group to the alkene represents a promising approach for the introduction of a carbonyl group, because the direct use of formaldehyde would be difficult due to its intractability. Furthermore, the resulting dioxolane moieties could be readily deprotected under acidic conditions to give the corresponding carbonyl compounds (eqs 3−4). Using this new methodology, we successfully synthesized several biologically interesting heterocyclic compounds such as lactone **12** (eq 5) and the 2,4,6-substituted pyridine derivative **15** (eq 6) in only a few steps while avoiding the use of tedious protocols.









In conclusion, we have successfully developed a Co-catalyzed reaction involving the sequential addition of 1,3-dioxolanes to electron-deficient alkenes and vinylarenes with a high degree of selectivity using TBHP as an oxidant. A radical–polar crossover mechanism has been proposed to account for this reaction, where a benzyl radical selectively couples with ^{t}BuOO· to give a peroxide intermediate, which undergoes a subsequent Kornblum–DeLaMare reaction. This protocol uses readily available starting materials, is easy to operate, and exhibits a wide substrate scope. Efforts to develop other multicomponent reactions through the radical–polar crossover mechanism are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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