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Co-Catalyzed Oxidative Alkylation between Styrenes and Cyclic Ethers via sp^3 C−H Functionalization

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Abstract

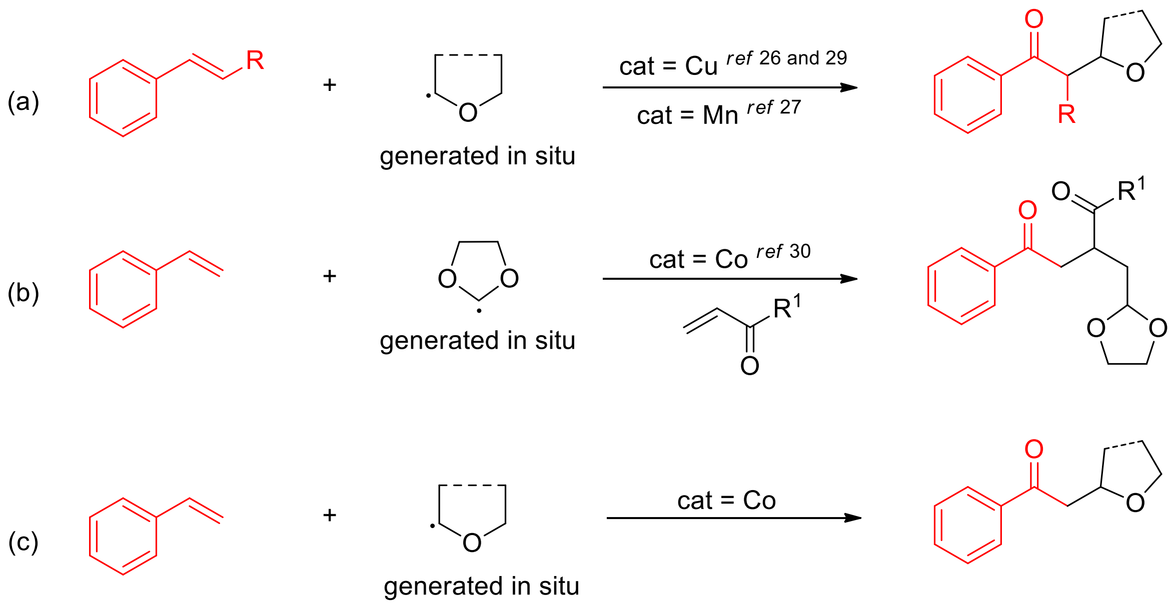
A new cobalt-catalyzed oxidative alkylation from readily available styrenes and ethers has been disclosed for a rapid and highly efficient construction of C−C bond via sp^3 C−H bond functionalization. This methodology was demonstrated by good yields and functional group compatibility with simple operation, easily available starting materials, low catalyst loadings, and mild aerobic conditions.

Keywords

cobalt; oxidative alkylation; styrene; cyclic ether; sp^3 C−H functionalization

Introduction

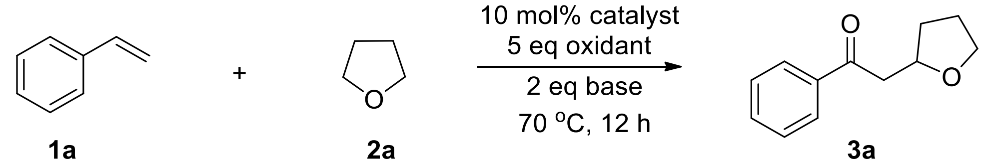
Transition-metal-catalyzed formation of C-C bonds has been one of the active research fields in organic chemistry [1-7]. As one of the most powerful and straightforward synthetic tools for the efficient construction of the assembly of biologically and industrially useful compounds, transition metal catalyzed C-H functionalization has received intense attention [8-12]. Especially in recent years, functionalization of unactivated C(sp^3)-H bond has been considered as one of the most effective strategies in organic synthesis [13-17]. On the other hand, transition-metal-catalyzed oxidative difunctionalization of olefins has been an efficient and rapid tool for the introduction of diverse functional groups, especially which enables the rapid installation of a carbonyl group and a new C−C or C−heteroatom bond on olefins in the presence of reactive radical intermediates [18-22]. For example, significant advances have been made for the oxidative difunctionalization of olefins with radical intermediates to construct a wide variety of substituent ketones [23-25]. However, utilizing this elegant and stepeconomical strategy to realize the synthesis of γ-ether ketone compounds has rarely researched yet. In 2009, the group of Zhang reported copper-catalyzed difunctionalization of styrenes with cyclic ethers to furnish the oxyalkylation products with low to moderate yields. (Scheme 1a) [26]. Subsequently, a regioselective oxyalkylation of styrenes catalyzed by diatomite-supported manganese oxide nanoparticles had been realized by Wang and co-workers [27]. Recently, a copper-catalyzed oxidative cross-coupling reaction between styrenes and chain ethers to form difunctionalization products has been described by Xing and co-workers [28]. In addition, the group of Wan discovered a Co-catalyzed oxidative coupling of 1,3-dioxolanes with electron-deficient alkenes and vinylarenes to afford polyfunctionalized carbonyl compounds (Scheme 1b) [29]. We believe that the generated carbon radicals could directly add to styrene without undergoing the addition of electron-deficient olefins with combination of Kornblum–DeLaMare rearrangement [30] for the construction of oxyalkylation compounds (Scheme 1d).



Results and Discussion

Initially, the reaction conditions for the oxyalkylation reaction were optimized by using styrene **1a** and tetrahydrofuran **2a** as model substrates (Table 1). After extensive screening of different cobalt catalyst, Co(acac)$_2$ was found to be the best catalyst and gave the desired product **3a** in 83% yield in presence of TBHP as the oxidant and DABCO as the base (Table 1, entries 1−5). Moreover, the effect of other common oxidants was also investigated; however, the yield of **3a** decreased significantly (Table 1, entries 6−8). Other common bases were found to not be suitable for this transformation (Table 1, entries 11−16). The control experiment suggested that transition-metal catalyst and base were necessary for this oxyalkylation reaction, which contrasted sharply with Zhang's work (Table 1, entries 13−14). To our delight, with the amount of Co(acac)$_2$ decreased to 1 mol% loading, **3a** was also delivered in 83% separated yield (Table 1, entry 15).

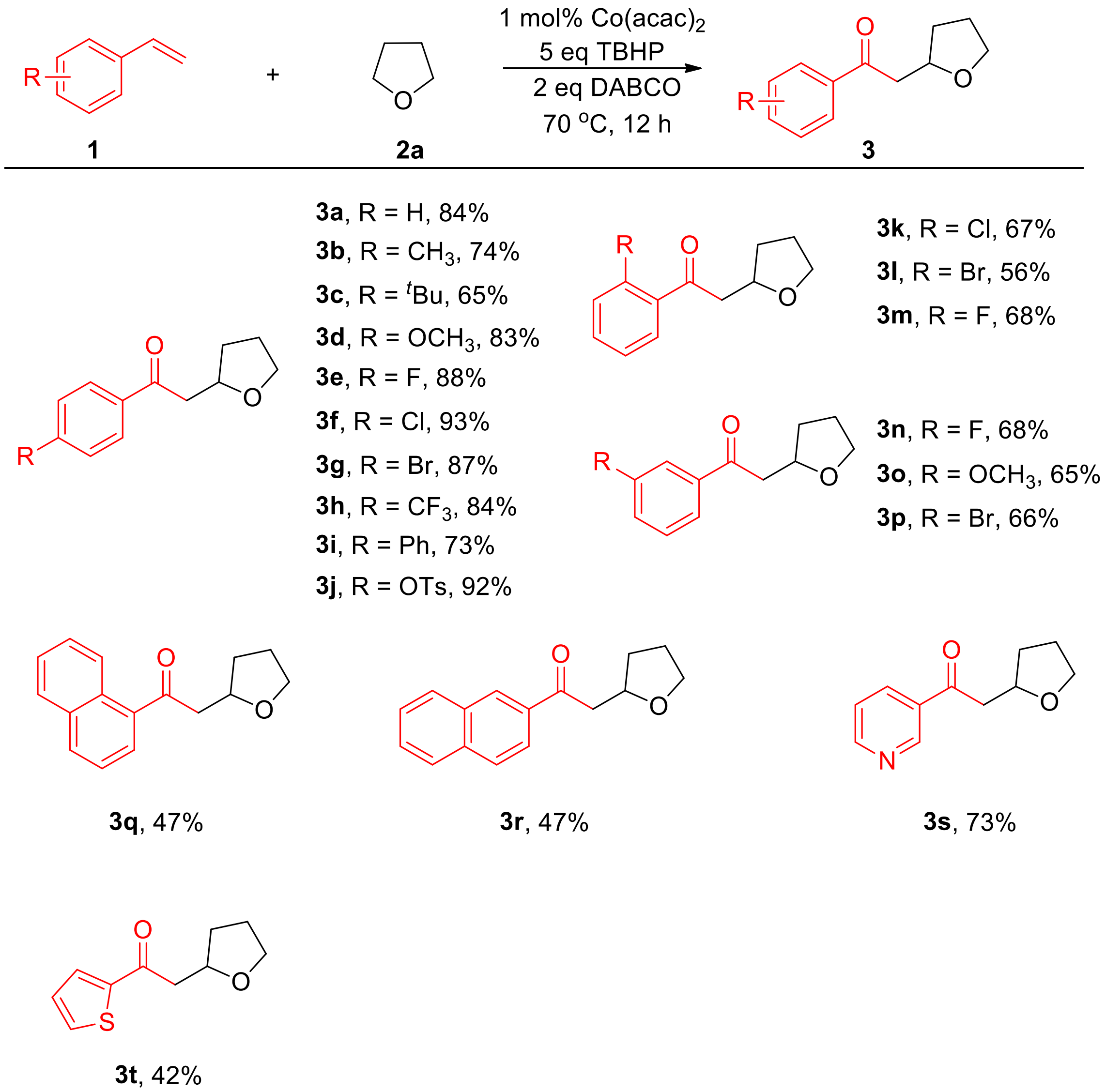
Table 1: Optimization of the reaction conditions^{a}.



entry	catalyst	oxidant	base	yield (%)^b
1	$Co(acac)_2$	TBHP	DABCO	83
2	$Co(acac)_3$	TBHP	DABCO	82
3	$Co(OAc)_2.4H_2O$	TBHP	DABCO	71
4	$CoSO_4.7H_2O$	TBHP	DABCO	56
5	$Co(NO_3)_2.6H_2O$	TBHP	DABCO	38
6	$Co(acac)_2$	DTBP	DABCO	trace
7	$Co(acac)_2$	H_2O_2	DABCO	n. d.
8	$Co(acac)_2$	$K_2S_2O_8$	DABCO	n. d.
9	$Co(acac)_2$	TBHP	DBU	43
10	$Co(acac)_2$	TBHP	NEt_3	10
11	$Co(acac)_2$	TBHP	DMAP	12
12	$Co(acac)_2$	TBHP	K_2CO_3	<5
13		TBHP	DABCO	n. d.
14	$Co(acac)_2$	TBHP		trace
15^c	$Co(acac)_2$	TBHP	DABCO	83

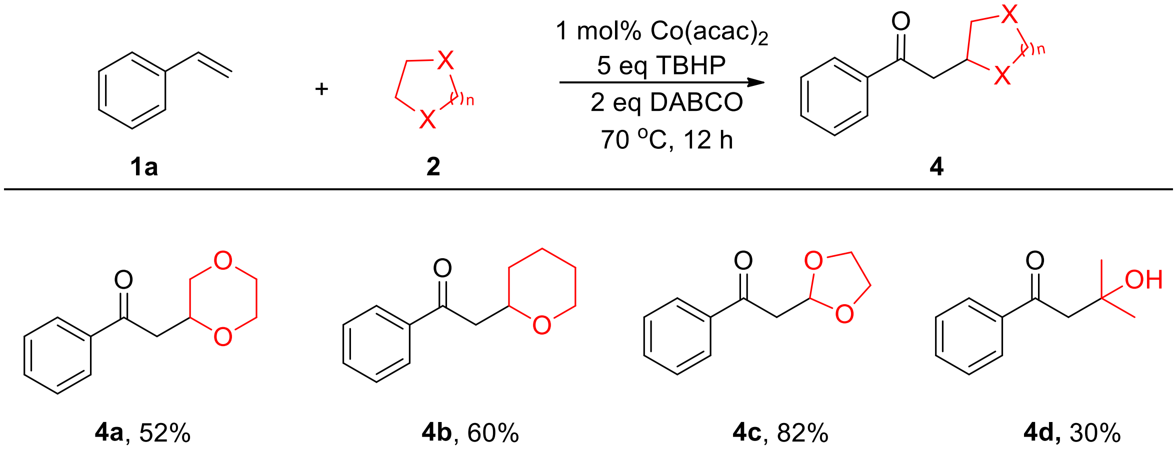
^{a}Reaction conditions: **1a** (0.5 mmol), catalyst (0.05 mmol, 10 mol%), oxidant (2.5 mmol, 5 equiv), base (1.0 mmol, 2 equiv) and THF (2.0 mL) in a test tube. ^{b}Isolated yields. ^{c}catalyst was used in 1 mol%. n.d.= not detected.

With the optimized reaction conditions in hand, we set out to explore the substrate scope of this cobalt-catalyzed intermolecular oxyalkylation reaction. First, different of substituted styrenes were investigated. As shown in Scheme 2, substituted styrenes bearing either electron-donating groups or electron-withdrawing groups on the aromatic ring were proved to be competent candidates in this transformation and provided the corresponding products **3a−3t** in moderate to good yields. It was noteworthy that this transformation showed substituents at the ortho or meta-position on the benzene rings showed little lower reactivity, compared with substituents at the para-position on the benzene rings (**3k-3p**). Meanwhile, Both 1-vinylnaphthalene (**1q**) and 2-vinylnaphthalene (**1r**) shown to be slightly less efficient yet nonetheless suitable substrates, furnishing **3q** and **3r** in moderate yields, respectively. Moreover, replacing benzene ring with pyridine ring and thiophene ring did not prohibit this progress, delivering corresponding target products **3a** and **3t** in 72% and 42% yield, respectively.



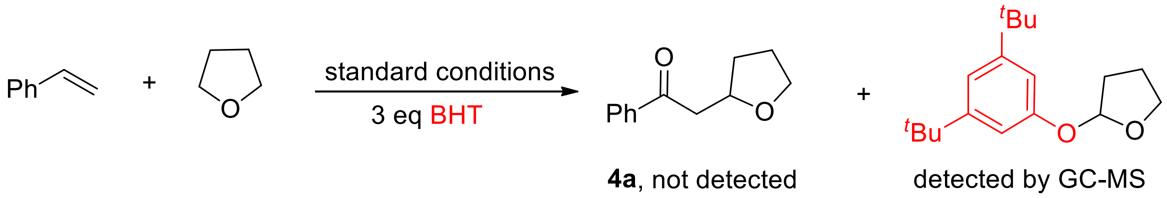
Scheme 2: Scope of styrenes. Reaction conditions: **1** (0.5 mmol, 1.0 equiv), **2a** (2 mL), Co(acac)$_2$ (0.005 mmol, 1 mol%), TBHP (2.5 mmol, 5.0 equiv, 70% in water) and DABCO (1.0 mmol, 2.0 equiv) for 12 h under air.

The scope of this reaction with a variety of cyclic ethers was also investigated as illustrated in Scheme 3. It was found that cyclic ether compounds such as 1,4-dioxane, tetrahydropyran and 1,3-dioxolane all could act as the appropriate components to furnish the corresponding products in moderate to good yields (**4a-4c**). In addition, to our delight, when isopropanol was used as a substrate, the corresponding difunctionalized product could also be obtained, albeit in a lower yield (**4d**).



Scheme 3: Scope of ethers. Reaction conditions: **1a** (0.5 mmol, 1.0 equiv), **2** (2 mL), Co(acac)$_2$ (0.005 mmol, 1 mol%), TBHP (2.5 mmol, 5.0 equiv, 70% in water) and DABCO (1.0 mmol, 2.0 equiv) for 12 h under air.

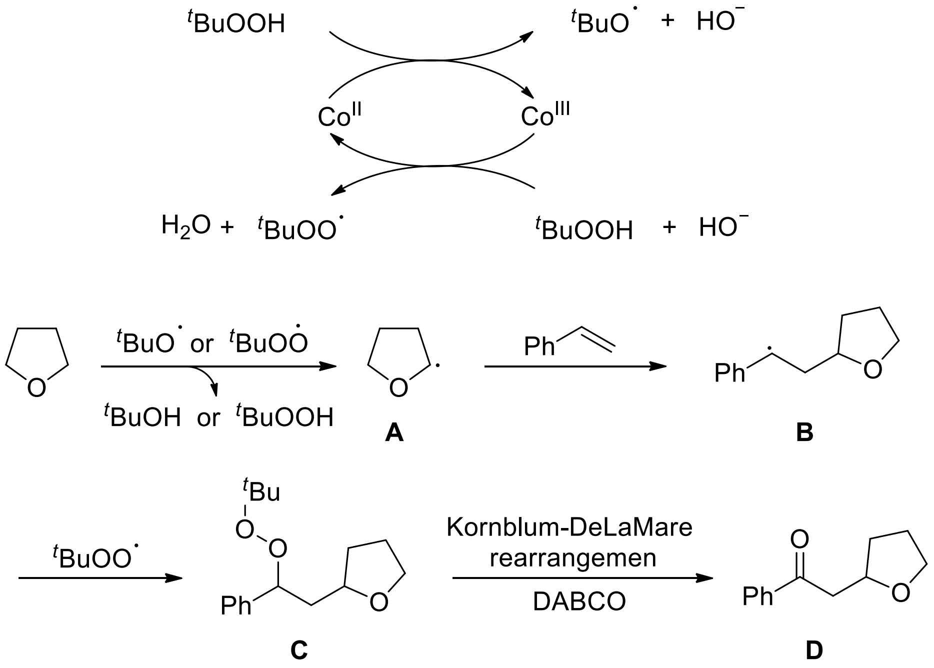
To further understand the mechanism of the reaction, as we predicted, the addition of free radical inhibitor BHT (2,6-di-*tert*-butyl-4-methylphenol) suppressed the reaction under the standard reaction (Scheme 4), which suggested that a free radical process may be involved in this transformation. Moreover, through carefully analyzing the reaction residues, the adduct of α-alkoxy radical with BHT was detected by GC-MS, which served as further evidence for the existence of α-alkoxy radical.



Scheme 4: Preliminary mechanism research.

Based on the results of the current study and the results of previous studies from the literature [31-32], a plausible mechanism for this transformation has been proposed.

As shown in Scheme 5, the initial cobalt-catalyzed hemolytic decomposition of TBHP would generate $^{t}BuO^{\bullet}$ and $^{t}BuOO^{\bullet}$ radical, which would then abstract a hydrogen atom from tetrahydrofuran to give radical intermediate **A**. Then, the addition of radical **A** to styrene would afford the better stabilized benzyl radical **B**, which would be selectively trapped by the $^{t}BuOO^{\bullet}$ radical to afford *tert*-butyl peroxide intermediate **C**. Finally, intermediate **C** would undergo a Kornblum−DeLaMare rearrangement to give the desired product.



Scheme 5: Proposed Mechanism.

Conclusion

In summary, we have successfully developed a cobalt-catalyzed intermolecular oxidative alkylation from readily available styrenes and ethers, which furnished a rapid and highly efficient method for the synthesis of γ-ether ketone compounds. According to the preliminary mechanism studies, we speculated that this transformation may involve a radical process. Our method enjoys good functionality tolerance, simple operation, easily available starting materials, low catalyst loadings and mild aerobic conditions. Further studies on cobalt-catalyzed oxidative coupling reactions are in progress in our laboratory.

Supporting Information

Supporting Information File 1

File Name: Experimental details and characterization data

File Format: pdf

Acknowledgements

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