Oxidative Coupling

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Copper-Catalyzed Oxidative Coupling of Alkenes with Aldehydes: Direct Access to α,β-Unsaturated Ketones**

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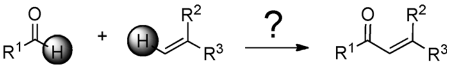
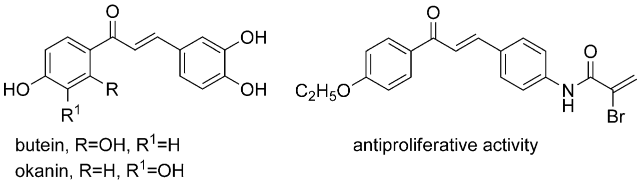
Transition-metal-catalyzed cross-coupling reactions, mainly involving R^1X as an electrophile and R^2M as a nucleophile, have been well-developed for many applications in synthesis. Very recently, remarkable efforts to realize cross-coupling in a green, atom-economic, and sustainable manner have been made. Oxidative coupling of R^1H with R^2H,[1] which avoids the use of halides (or halide equivalents) and organometallic reagents, possesses practical advantages and has attracted much attention. Although some progress has been made in this emerging field, the development of a highly efficient and highly selective oxidative cross-coupling reaction utilizing two different hydrocarbons as the reagents is still a great challenge. One typical example is the oxidative coupling of an aldehyde C–H bond with other C–H bonds. In recent years, significant progress has been achieved, whereby the Csp^2–H bonds of arenes have been activated for the oxidative coupling with an aldehyde C–H bond to afford ketones.[2] Also, alkenes have been widely used in oxidative transformations.[3] However, to the best of our knowledge, up to now, there has been only one example, which involved the direct oxidative coupling between salicylaldehydes and alkenes facilitated by a Rh catalyst.[4] In most cases, the direct addition of aldehyde C–H bonds to alkenes for the construction of saturated ketones[5] or β-peroxy ketones[6] was achieved.

Alkenes and aldehydes are widely used simple chemical feedstock. The oxidative coupling of aldehydes with alkenes would result in the direct construction of α,β-unsaturated ketones (Scheme 1), and represents a highly attractive and sustainable strategy for the synthesis of these types of compounds, as neither the aldehydes nor alkenes need to be prefunctionalized. Moreover, a wide variety of naturally occurring and manmade compounds that exhibit extraordinary biological and pharmaceutical properties (e.g. anticancer, antiinflammatory, antioxidant, antimicrobial) possess α,β-unsaturated ketone core structures (Scheme 2).[7] This class of compounds is also extremely fascinating owing to their versatility for further synthetic transformations, thus enabling the synthesis of compounds such as 1-indanone compounds, 1,4-dihydropyrazole and pyranocoumarin, which are important heterocycles that widely occur in natural products and pharmaceutically molecules.[8] Because of the important biological and pharmaceutical applications of α,β-unsaturated ketones, various methods for their synthesis have been reported.[2c,9] However, the development of an efficient and general synthetic route with high atom economy is highly desirable (Scheme 1). Herein, we document a novel approach for α,β-unsaturated ketones synthesis by the Cu-catalyzed direct oxidative coupling between alkenes and aldehydes.



Scheme 1. Direct synthesis of α,β-unsaturated ketones.



Scheme 2. Examples of important α,β-unsaturated ketone-containing compounds.

Recently, we have demonstrated a Heck-type alkenylation of secondary and tertiary α-carbonyl alkyl bromides with alkenes in the presence of a Ni catalyst.[10] Mechanistically, the reaction was believed to proceed through the α-carbonyl alkyl radical addition to alkenes followed by radical oxidation to generate the desired products. Aldehydes could be easily converted into the corresponding acyl radicals in the presence of peroxides.[2a,d,e,11] Consequently, we decided to convert aldehydes into afford acyl radicals and use these instead of α-carbonyl alkyl radicals to react with alkenes for the direct synthesis of α,β-unsaturated ketones from aldehydes and alkenes. Hence, peroxides in combination with transition-metal catalysts were applied to the oxidative coupling of aldehydes and alkenes to form α,β-unsaturated ketones.

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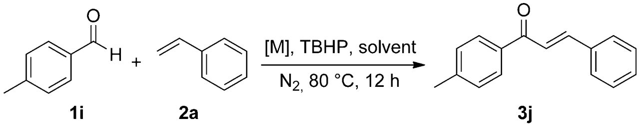
Initially we utilized styrene and 4-methylbenzaldehyde as a model reaction to investigate different reaction conditions. Selected data are listed in Table 1. Firstly, various Ni precursors were screened for the reaction in benzene at 80 °C in the presence of TBHP. Unfortunately, with the use of Ni precursors such as $[Ni(PPh_3)_4]$, $NiCl_2$, or $[Ni(acac)_2]$, no desired product was detected. Conversely, saturated ketones were the major product, thus indicating that the acyl radical could be generated and can react with olefin double bonds under these reaction conditions. However, the benzyl radical, generated by the addition of the acyl radical to styrene, could not be oxidized to result in the desired product **3j** which a Ni catalyst was used (Table 1, entries 1, 2, 3). Therefore, other transition metal catalysts were tested (Table 1, entries 4–8). To our delight, the desired product **3j** was obtained in a 28 % yield, as determined by ^1H NMR spectroscopy (Table 1, entry 8), when $CuCl_2$ was used. When $CoCl_2$, CuCl, $FeCl_2$, or $CuBr_2$ were used, none or only a trace amount of the desired product was detected (Table 1, entries 4–7). The influence of the solvent was also studied. When other solvents, such as CH_3CN, dioxane, and DCE, were applied instead of benzene, a trace or none of the desired product was observed (Table 1, entries 9–11). Decreasing the amount of benzene to 1 mL led to an increased yield (Table 1, entry 12). This promising result encouraged us to do further optimization with regard to the volume of solvent, indeed, the yield of **3j** was improved to 57 % when the reaction was carried out in the absence of solvent (Table 1, entry 13). A lower loading (10 mol %) of $CuCl_2$ resulted in a slower reaction, affording **3j** in 46 % yield (Table 1, entry 14). The desired product **3j** was obtained in 66 % yield, as determined by ^1H NMR spectroscopy, when the amount of $CuCl_2$ was increased to 100 mol % (Table 1, entry 15); this result is similar to that obtained when 20 mol % of $CuCl_2$ was used. Only when the ratio of 4-methylbenzaldehyde and TBHP was 2:1 and the amount of each component was at least 2.5 equivalents of the styrene, the product could be obtained in a satisfactory yield (see the Supporting Information, Table S1). Therefore, the optimized reaction conditions are: $CuCl_2$ (20 mol %), TBHP (2.5 equiv), 80 °C, 12 h (Table 1, entry 16).

Table 1: Impact of reaction parameters on Cu-catalyzed oxidative coupling of aldehydes with alkenes.[a]

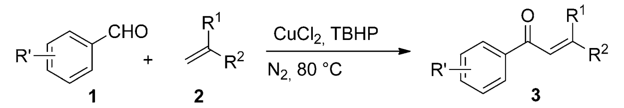


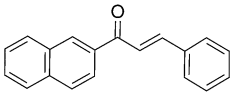
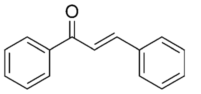
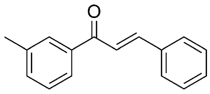
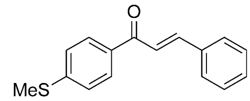
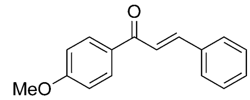
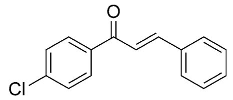
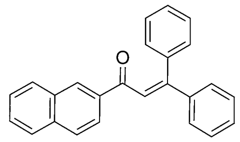
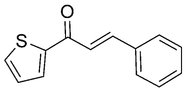
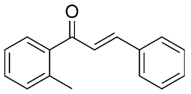
Entry	[M]	Solvent	Yield (**3j**) [%][b]
1	$[Ni(PPh_3)_4]$	benzene	–
2	$NiCl_2$	benzene	–
3	$[Ni(acac)_2]$	benzene	–
4	$CoCl_2$	benzene	–
5	CuCl	benzene	–
6	$FeCl_2$	benzene	–
7	$CuBr_2$	benzene	trace
8	$CuCl_2$	benzene	28
9	$CuCl_2$	CH_3CN	–
10	$CuCl_2$	dioxane	–
11	$CuCl_2$	DCE	trace
12	$CuCl_2$	benzene	38[d]
13	$CuCl_2$	–	57
14	$CuCl_2$	–	46[e]
15	$CuCl_2$	–	66[f]
16	$CuCl_2$	–	76[c]

[a] Reaction conditions: styrene (0.5 mmol), 4-methylbenzaldehyde (1.5 mmol), TBHP (1.0 mmol, 70% aqueous solution), [M] (0.1 mmol), benzene (2.0 mL), 80 °C, N_2, 12 h. [b] Determined by NMR spectroscopy with CH_2Br_2 as the internal standard. [c] styrene 0.5 mmol, 4-methylbenzaldehyde (2.5 mmol), TBHP (1.25 mmol), $CuCl_2$ (0.1 mmol), 80 °C, N_2, 12 h. [d] benzene (1.0 mL). [e] $CuCl_2$ (0.05 mmol). [f] $CuCl_2$ (0.5 mmol). DCE = 1,2-dichloroethane, TBHP = tert-butyl hydroperoxide.

With the optimized reaction conditions established, we studied other substrates in this Cu-catalyzed oxidative coupling of alkenes with aldehydes. Firstly, the scope of the aldehyde substrate was investigated (Table 2). The reaction of

Table 2: Synthesis of α,β-unsaturated ketones from various aldehydes with alkenes.[a]



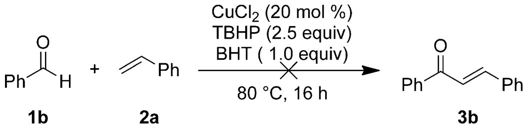
Entry	Product	3	Yield [%][b]
1		**3a**	80
2		**3b**	63
3		**3c**	63
4		**3d**	65
5		**3e**	69
6[c]		**3f**	50
7		**3g**	61
8		**3h**	64
9		**3i**	34

[a] Reaction conditions: **1** (2.50 mmol), **2** (0.50 mmol), $CuCl_2$ (20 mol%), TBHP (1.25 mmol), 80 °C, N_2, 12 h. [b] Yield of the isolated product. [c] **1** (3.00 mmol), **2** (0.50 mmol), $CuCl_2$ (20 mol%), TBHP (1.50 mmol), 90 °C, N_2, 12 h.

2-naphthaldehyde afforded the desired product in 80 % yield (Table 2, entry 1). The reaction of benzaldehyde also proceeded well, giving the coupling product in a 63 % yield (Table 2, entry 2). *meta*-Methyl substituted benzaldehyde was similarly found to be suitable substrate for this transformation and gave the corresponding α,β-unsaturated ketones in good yield (Table 2, entry 3). To our delight, the use of a benzaldehyde with a *para*-SMe substituent, which can be easy oxidized, afforded the desired product in 65 % yield (Table 2, entry 4). Moreover, the reaction of benzaldehyde bearing an electron-donating group also proceeded well (Table 2, entry 5). A C–Cl bond, which provides the possibility for further functionalization, was well tolerated by this transformation (Table 2, entry 6). When thiophene-2-carbaldehyde was used (Table 2, entry 8), the desired product was obtained in a 64 % yield, upon isolation. A 34 % yield was obtained when *ortho*-methylbenzaldehyde was used; this poor yield may be due to steric hindrance (Table 2, entry 9).

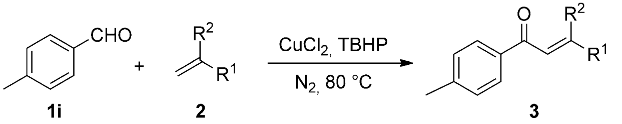
Encouraged by these promising results, we further applied the optimized reaction conditions to examine the substrate scope of alkenes. Styrenes having alkyl substituents, such as methyl and *tert*-butyl, afforded the desired products in good yields (Table 3, entries 2–4). *para*-Fluorostyrene reacted with 4-methylbenzaldehyde under the standard reaction conditions to afford the coupling product in a 75 % yield (Table 3, entry 5). Notably, a chloro substituent on the phenyl ring of styrenes could also be well tolerated (Table 3, entry 6). The desired product was obtained in 30 % yield, upon isolation, when 4-vinylphenyl acetate was used (Table 3, entry 7). The acetyl group is a particularly desirable group owing to the possible use of the deprotected product for further functionalization. 1,1-Diaryl alkenes were shown to couple with 4-methylbenzaldehyde in good yields (Table 3, entries 8 and 9).

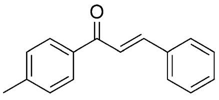
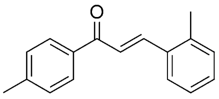
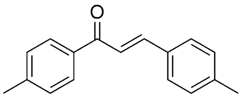
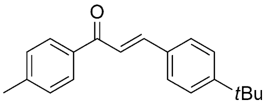
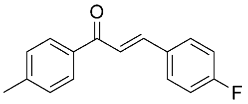
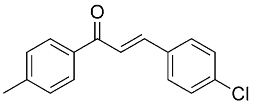
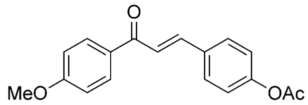
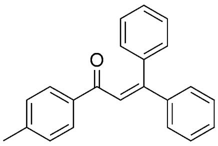
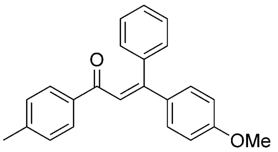
When investigating the reaction mechanism of Cu-catalyzed oxidative coupling of alkenes and aldehydes, single-electron transfer (SET) is an obvious consideration. Therefore, a radical-trapping experiment was carried out. BHT (2,6-di-*tert*-butyl-4-methylphenol) was employed under the standard reaction conditions. The desired reaction did not occur (Scheme 3), thus indicating that this transformation is likely to involve a radical intermediate.



Scheme 3. Investigation into the reaction mechanism.

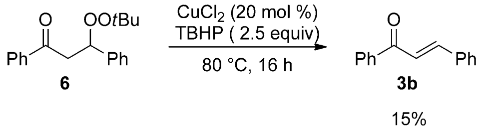
Table 3: Synthesis of α,β-unsaturated ketones from different alkenes with aldehydes.[a]



Entry	Product	3	Yield [%][b]
1		**3j**	73
2		**3k**	57
3		**3l**	60
4		**3m**	65
5		**3n**	75
6[c]		**3o**	54
7		**3p**	30
8		**3q**	64
9[d]		**3r**	70

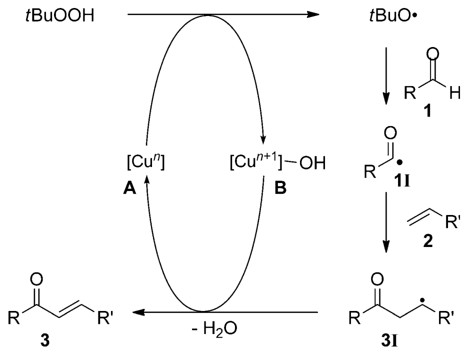
[a] Reaction conditions: **1** (2.50 mmol), **2** (0.50 mmol), CuCl$_2$ (20 mol %), TBHP (1.25 mmol), 80 °C, N$_2$, 12 h. [b] Yield of the isolated product. [c] **1** (3.00 mmol), **2** (0.50 mmol), CuCl$_2$ (20 mol %), TBHP (1.50 mmol), 90 °C, N$_2$, 12 h. [d] $E/Z = 1.6:1.4$.

Furthermore, we postulated that the β-peroxy ketone **6**, which had been reported by the group of Li, maybe an intermediate in the oxidative coupling.[6] To explore the validity of our initial hypothesis, the reaction of β-peroxy ketone **6** under the standard conditions was investigated. Although the desired product **3b** was detected, the isolated yield was only 15 % [Eq. (1)], which is much lower than that of the reaction under the optimized reaction conditions (63 %; Table 2, entry 2). This result indicates that β-peroxy ketone **6** might be involved in this process, but it is probably not an intermediate in the main pathway of this oxidative coupling.



(1)

Based on previous reports[2a,b,d,e,5,6,11] and the above results, a proposed reaction pathway is depicted in Scheme 4. First, the low valent copper species **A** donates an



Scheme 4. Proposed mechanism.

electron to TBHP to generate copper species **B** and the alkyloxy radical, which then abstracts a hydrogen atom from aldehyde **1** to generate the acyl radical **1I**. The radical addition of **1I** to alkene **2** gives the benzylic radical **3I**, which is believed to undergo the direct oxidation by **B** and deprotonation to release the final product **3**. Meanwhile, the low valent copper species **A** was regenerated to continue the catalytic cycle.

In conclusion, we have developed the first Cu-catalyzed oxidative coupling of alkenes with aldehydes. A variety of functional groups were tolerated on both the aldehyde and alkene. This work provides a novel approach for the construction of α,β-unsaturated ketones. Tentative mechanistic studies suggest that this reaction is likely to proceed by a single-electron transfer. Further exploration of the substrate scope and mechanistic studies are currently underway and will be reported in due course.

Experimental Section

General procedure for the synthesis of **3b**: $CuCl_2$ (13.4 mg, 0.1 mmol) was added to a Schlenk tube equipped with a magnetic stir bar, in an argon-filled glove box. **1b** (265.3 mg, 2.5 mmol), **2a** (52.1 mg, 0.5 mmol), and TBHP (112.6 mg, 1.25 mmol) were consecutively injected into the reaction tube. The reaction was then heated to 80 °C and stirred for 12 h. Upon completion, the reaction was quenched with water and extracted with ethyl ether (3 × 10 mL). The organic layers were then combined. The pure product was obtained by flash column chromatography on silica gel (petroleum/ethyl acetate = 200:1). The yield of the isolated product was 63 %.

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Keywords: aldehydes · alkenes · copper · oxidative coupling · α,β-unsaturated ketones

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