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ORIGINAL PAPER

Copper-catalyzed demethylative esterification of arylmethylketones: a new route for the synthesis of benzocaine

Sajedeh Maddah Roodan[1] · **Arash Ghaderi**[1]

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Abstract
An efficient method for oxidative cleavage of C(CO)–C bonds of ketones has been developed. This procedure enables activated methyl ketones to react with tetraethyl orthosilicate for generation of the corresponding methyl esters using copper as the catalyst. Primary mechanistic studies revealed that in contrary to other related studies, the involvement of the aldehyde as the intermediate of this reaction is highly probable. Interestingly, this study provides an unprecedented positive effect of the elemental sulfur upon this oxidative esterification reaction. As an application of our method, we have reported a two-step procedure for the synthesis of benzocaine. The second step of this procedure involves a highly selective reduction in nitro group in the presence of ester functionality.

Keywords Esterification · Copper · Ketone · Oxidation · Catalyst

Introduction

Ketones are usually known as relatively stable compounds toward oxidation processes owing to the inertness of their C–C bonds. These compounds could be oxidized only in the presence of very strong oxidants under harsh reaction conditions. Baeyer–Viliger oxidation is an example for doing this function [1, 2]. One of the most susceptible ketones for oxidation reactions involving C(C=O)–C bond cleavage is methyl ketones. A classical oxidative test for identification of methyl ketones is the iodoform test which converts these compounds to carboxylates [3]. Some modifications upon this test have also been reported for the conversion of ketones to carboxylates or amides [4–7]. Studies have shown that pre-functionalization in α-position of methyl ketones with electronegative groups facilitates the oxidation process [8]. In recent years, a few mild and efficient approaches have been reported for the conversion of ketones to carboxylic acids [9, 10], esters [11], amides [12–14], imides [15], nitriles [16] and even aldehydes [17]. Herein, we report our recent findings for direct conversion of ketones to esters.

Experimental section

General

All chemicals were purchased from Merck and Aldrich chemical companies and used as received without further purification. All experiments were run under air atmosphere in an open flask unless stated otherwise. NMR data were determined in Bruker instrument (300 MHz) using $CDCl_3$ or DMSO-d_6 as the solvent.

General procedure for the esterification of ketones

A mixture of ketone (0.5 mmol), tetraethyl orthosilicate (2 mmol, 0.41 g) and KF (2 mmol, 0.116 g) was mixed in the presence of CuI (0.4 mmol, 0.019 g) and 1,10-phenanthroline (0.8 mmol, 0.036 g) in DMF (1.5 mL) under ambient atmosphere at 100 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the product was extracted with ethylacetate/water. The solvent was evaporated, and the product was purified by column

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✉ Arash Ghaderi
aghaderi@hormozgan.ac.ir

[1] Department of Chemistry, College of Sciences, University of Hormozgan, Bandar 'Abbas 71961, Iran

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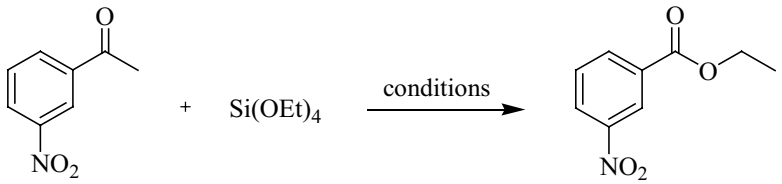
Table 1 Optimization of the reaction conditions



Entry	Copper catalyst	Ligand	Solvent (mL)	Time (h)	Yield (%)
1[a,b]	$Cu(OAc)_2$	Py	DMF	18	Trace
2[a,b]	CuI	Py	DMF	24	33
3[c]	CuI	Py	DMF	4	52
4[c]	CuI	Py	PhCl	4	–
5	CuI	Phen	DMF	4	80
6	CuI	–	DMF	4	Trace
7[d]	CuI	Phen	DMF	4	–
8[e]	CuI	Phen	DMF	4	–
9	CuI	Phen	–	4	20
10	–	Phen	DMF	4	10
11	CuI	Phen	DMSO	4	80
12	CuI	Phen	Toluene	4	–
13	CuI	Phen	1,4-Dioxane	4	–
14	CuI	Phen	PEG400	4	Trace
15	CuI	bipy	DMF	4	Trace
16[f]	CuI	Phen	DMF	4	–

Reaction conditions 3-Nitroacetophenone (0.5 mmol), tetraethyl orthosilicate (2 mmol), catalyst (20 mol%), phenanthroline (0.2 mmol), KF (2 mmol), solvent (1.5 mL), at 100 °C under air

[a]Pyridine (1.5 mmol) was used as the ligand

[b]The reaction was conducted at 60 °C

[c]Pyridine (0.2 mmol)

[d]The reaction was conducted in the absence of KF

[e]The reaction was run under N_2 atmosphere

[f]NaOEt (2 mmol) was used instead of tetraethyl orthosilicate

chromatography over silica gel using *n*-hexane/ethylacetate (8:2) as the eluent.

Ethyl 3-nitrobenzoate ^{1}H NMR (500 MHz, $CDCl_3$) δ; 1.45 (t, J = 7.1 Hz, 3 H), 4.46 (q, J = 7.1 Hz, 2 H), 7.67 (t, J = 7.9 Hz, 1 H), 8.41 (m, 2 H), 8.88 (t, J = 1.9 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ; 14.27, 61.95, 124.55, 127.30, 129.58, 132.21, 135.28, 148.25, 164.47.

Ethyl 4-nitrobenzoate ^{1}H NMR (300 MHz, DMSO-d_6) δ; 1.29 (t, J = 7.1 Hz, 3 H), 4.30 (q, J = 7.1 Hz, 2 H), 8.05–8.10 (m, 2 H), 8.21–8.26 (m, 2 H), ^{13}C NMR (75 MHz, DMSO-d_6) δ; 14.33, 62.09, 124.12, 130.91, 135.58, 150.44, 164.63.

Isoamyl 3-nitrobenzoate ^{1}H NMR (300 MHz, $CDCl_3$) δ; 0.91 (d, J = 6.4 Hz, 6 H), 1.63 (q, J = 6.7 Hz, 2 H), 1.69–1.82 (m, 1 H), 4.35 (t, J = 6.8 Hz, 2 H), 7.58 (t, J = 7.9 Hz, 1 H), 8.28–8.36 (m, 2 H), 8.78 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ; 22.51, 25.20, 37.31, 64.65, 124.55, 127.31, 129.61, 132.28, 135.27, 148.32, 164.56.

Typical procedure for the synthesis of benzocaine

In a reaction vessel, CaH_2 (0.2 mmol, 0.008 g) was added to a solution of $Pd(OAc)_2$ (0.025 mmol, 0.005 g) in DMSO (3 mL) and stirred at 100 °C. In 10 min, the brown color of the mixture turned to black. Then, ethyl 4-nitrobenzoate (1 mmol, 0.195 g), prepared using the above procedure, was added to this mixture followed by $Cu(OAc)_2$ (0.2 mmol, 0.036 g), KF (2.4 mmol, 0.139 g) and HCO_2Na (2 mmol, 0.136 g). After completion of the reaction, the product was extracted with ethylacetate/water. The solvent was evaporated, and the product was purified by column chromatography over silica gel using *n*-hexane/ethylacetate as the eluent.

Ethyl 4-aminobenzoate ^{1}H NMR (300 MHz, $CDCl_3$) δ; 1.26 (t, J = 7.1 Hz, 3 H), 4.05 (s, 2 H), 4.22 (q, J = 7.1 Hz, 2 H), 6.53 (d, J = 8.6 Hz, 2 H), 7.76 (d, J = 8.6 Hz, 2 H), ^{13}C NMR (75 MHz, $CDCl_3$) δ; 14.42, 60.34, 113.77, 119.88, 131.56, 150.97, 166.82.

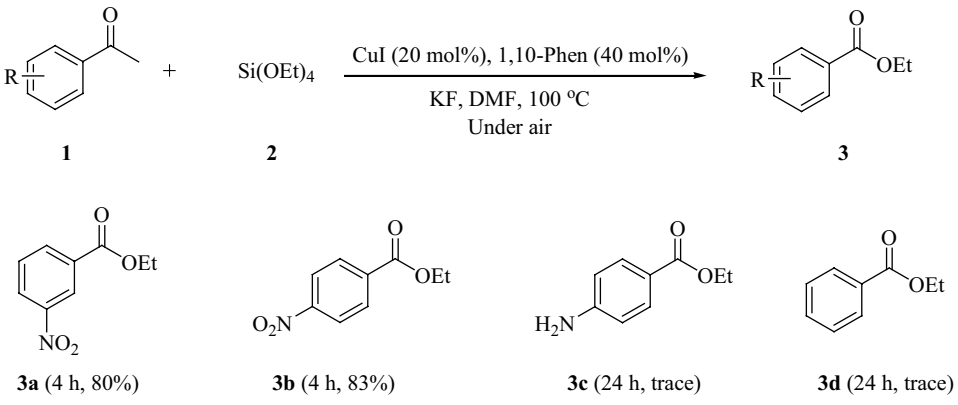
Results and discussion

In order to check the effect of different parameters upon the reaction, we chose the reaction of 3-nitroacetophenone with tetraethyl orthosilicate as the model reaction in the presence of copper salts as the catalysts (Table 1). When the reaction was conducted in the presence of $Cu(OAc)_2$ as the catalyst and pyridine as the ligand in DMF, only a trace amount of the desired product was detected after 18 h reaction time at 60 °C (Table 1, entry 1). Changing the catalyst to CuI under the same conditions gave the product in 33% yield after 24 h (Table 1, entry 2). Increasing the temperature to 100 °C resulted in the formation of the corresponding ester in 52% yield (Table 1, entry 3). The reaction failed employing the conditions similar to the available procedure [11], using CuI/Py in PhCl as the solvent (Table 1, entry 4). By switching the ligand to 1,10-phenanthroline, the yield of the desired product was increased drastically up to 80% within 4 h reaction time in DMF (Table 1, entry 5). The reaction in the absence of this ligand was totally inefficient (Table 1, entry 6). The reaction also failed in the absence of KF (Table 1, entry 7). We have also run the reaction under N_2 atmosphere. No product was obtained under these conditions showing the important role of molecular oxygen in this reaction (Table 1, entry 8). The product was obtained in low yield when the reaction was run in the absence of either DMF or CuI (Table 1, entries 9, 10). Changing the solvent to DMSO gave the same result as DMF, forming the desired product in 80% yield (Table 1, entry 11). Other solvents such as toluene, 1,4-dioxane and PEG400 were inefficient for this reaction (Table 1, entries 12–14). The reaction was failed using bipyridine as the ligand (Table 1, entry 15). No desired product was obtained using NaOEt instead of $Si(OEt)_4$ (Table 1, entry 16). Thus, the conditions mentioned in entry 5 were chosen as the optimum conditions.

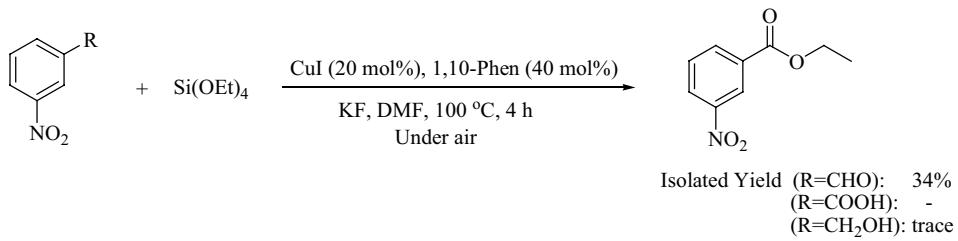
Under the optimized conditions, some other methyl ketones were subjected to the esterification reactions using tetraethyl orthosilicate (Scheme 1). *m*- and *p*-nitroacetophenone gave the desired ethyl esters in 80 and 83% isolated yields, respectively. Unfortunately, our efforts failed for the synthesis of ethyl *p*-aminoacetobenzoate (**3c**). To our surprise, acetophenone was unreactive under the optimum conditions and only a trace amount of ethyl benzoate (**3d**) was detected by GC–MS. In light of these results, we interested in examining the competitive reaction between 3-nitroacetophenone and acetophenone. For this aim, we mixed 3-nitroacetophenone (1 eq.), acetophenone (1 eq.) and tetraethyl orthosilicate (2 eq.) and performed the reaction under the standard conditions. Analysis of the reaction mixture after 4 h revealed that 3-nitroacetophenone selectively converted to the desired product leaving acetophenone intact.

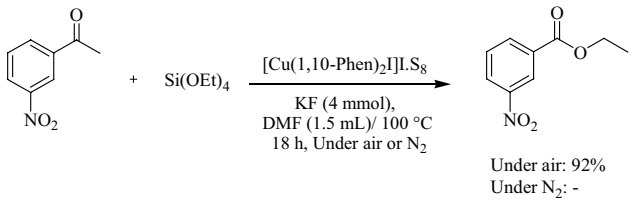
To shed light on the mechanism of the reaction, a series of experiments were conducted. We assumed that

Scheme 1 Esterification reactions under the optimized conditions



Scheme 2 Reaction of possible intermediates with tetraethyl orthosilicate under the optimized conditions

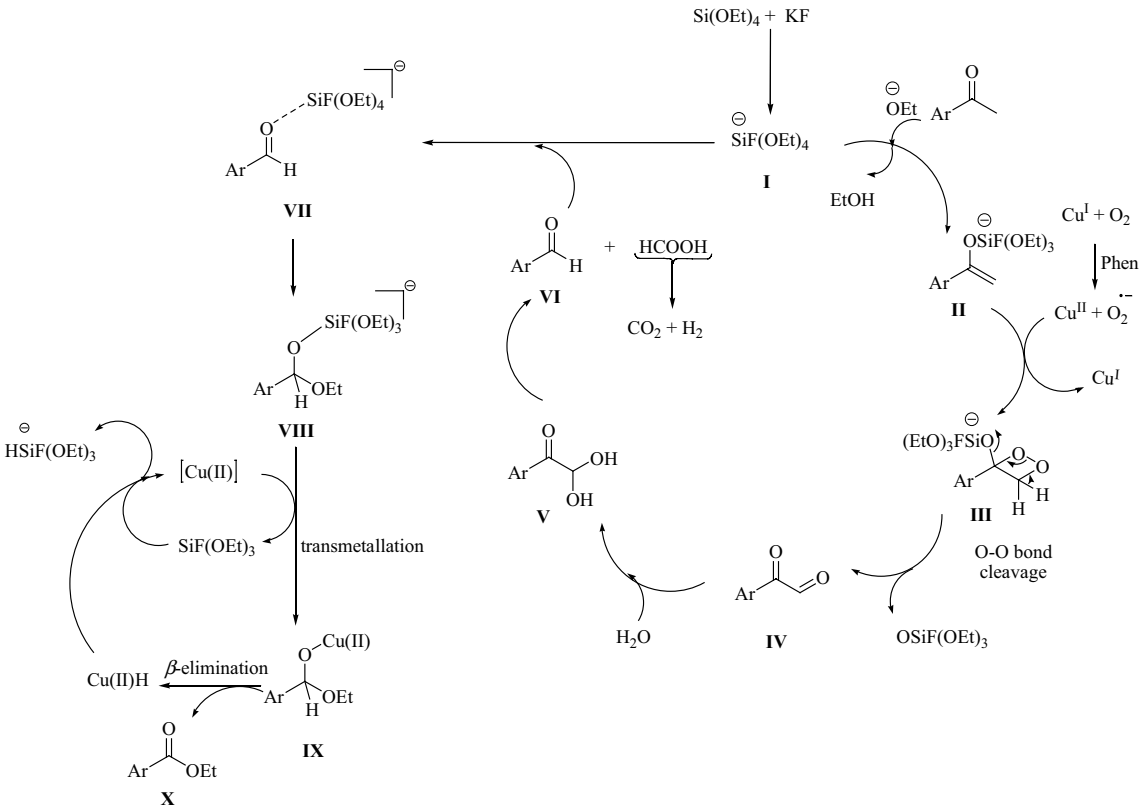




Scheme 3 Oxidative esterification of 3-nitroacetophenone catalyzed by $[Cu(1,10\text{-phen})_2I]I.S_8$

3-nitrobenzaldehyde, 3-nitrobenzoic acid and 3-nitrobenzyl alcohol could be potential intermediates in this reaction. Therefore, we conducted three reactions using these compounds as the starting materials under the optimized conditions. When 3-nitrobenzaldehyde was used as the substrate, the desired ester was isolated in 34% yield showing the possibility of aldehyde to be the actual intermediate (Scheme 2). However, the second experiment including 3-nitrobenzoic acid gave no yield of the product (Scheme 2). Only a trace amount of the product was obtained in our third experiment utilizing 3-nitrobenzyl alcohol (Scheme 2). These results excluded the possibility of 3-nitrobenzoic acid and 3-nitrobenzyl alcohol as the intermediates for this reaction.

In order to check if the reaction involves radical intermediates, we performed the TEMPO test upon the reaction. Interestingly, the reaction was not affected by TEMPO indicating that the process goes through a non-radical pathway. This result is the opposite of that observed by Jiang et al. for oxidative esterification of ketones under CuBr/Py catalysis [11]. The same group also reported that only pyridine was an effective ligand for the reaction and CuBr/1,10-phenanthroline was totally inactive [11]. However, in our case, 1,10-phenanthroline plays the key role increasing the yield of the product drastically while pyridine did not put a significant effect. Therefore, we decided to discover the active catalyst for our reaction. Looking through the literature, we found a report for the synthesis of iodobis(1,10-phenanthroline) copper (II) iodide octasulfur complex, $[Cu(1,10\text{-phen})_2I]I.S_8$, which had been characterized by X-ray diffraction data [18]. We supposed that for our reaction, the same complex is being produced in situ and catalyzes the reaction. Hence, we prepared the complex and used it as the catalyst for the reaction. The reaction proceeded well giving the desired product in 92% yield under the air atmosphere (Scheme 3). However, when the same reaction was conducted under N_2 atmosphere, no product was obtained. This result shows that in our standard conditions (Table 1,



Scheme 4 Plausible mechanism for copper-catalyzed oxidative esterification of ketones

entry 5), oxygen of atmosphere not only cause the conversion of Cu(I) to Cu(II) [19, 20] but also take part in the oxidation of ketone.

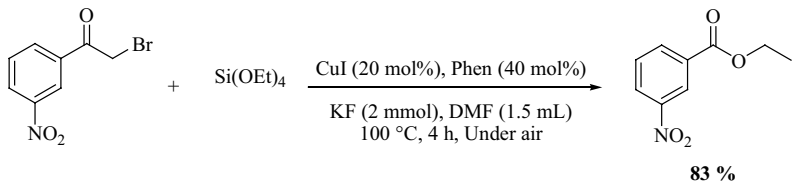
Since this complex involves S_8 which acts as the two-electron ligand, we were interested in checking the effect of this ligand for our reaction. For this aim, the standard reaction (Table 1, entry 5) was conducted in the presence of S_8 as the additive. The result showed that S_8 does not affect the efficiency of the reaction. To understand the fate of the methyl group during the reaction, we connected our reaction vessel to the saturated solution of lime. During the course of the reaction, we observed that the clear lime solution became opaque showing that CO_2 has been evolved under these conditions (Scheme S1).

The probable reaction pathway has been depicted in Scheme 4. The reaction of $Si(OEt)_4$ with fluoride anion which is highly silaphilic reagent generates the pentavalent silicate **I**. This ate complex has reduced electron density on the silicon regardless of its formal charge and coordinates to the oxygen of ketone to form pentavalent species **II** [21]. In this step, extracoordination to hexavalent silicon cannot also be excluded [16]. This oxophilic intermediate promotes enolization of the ketone. Activation of molecular oxygen by copper (I) [19, 20, 22] resulted in the incorporation of dioxygen to form intermediate **III** [23] which converts to intermediate **IV**. Going through the species **V**, the intermediate **IV** undergoes degradation to form the corresponding aldehyde **VI** plus formic acid. This aldehyde reacts with the activated silicon **I** to form intermediate **VII**. This hypervalent organosilicon has increased tendency to transfer an ethoxide group to the electrophilic carbon [22]. After ethoxide transfer, transmetallation followed by β-hydride elimination results in the desired ester **X**. The hydride is abstracted by the silane specious [24] regenerating the active Cu(II). In this final step, molecular oxygen plays no role since we have observed that under N_2 atmosphere, 3-nitrobenzaldehyde gives the corresponding ester smoothly.

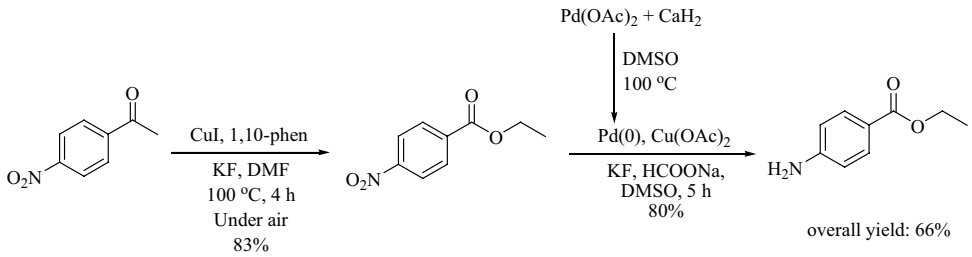
As mentioned above, the model reaction in the absence of the catalyst gives the desired product in 10% isolated yield (Table 1, entry 10 and Scheme S2) indicating that another pathway might be simultaneously involved during the reaction. Interestingly, when the reaction was conducted under copper-free conditions, the lime test showed that CO_2 was not produced in the reaction. Thus, we propose a different mechanism for these conditions (Scheme S3).

We have also used our procedure for the carbon–carbon bond cleavage of α-bromo-3-nitroacetophenone as an activated ketone. Utilizing this starting material, the corresponding ethyl ester was obtained in 83% isolated yield within 4 h reaction time (Scheme 5).

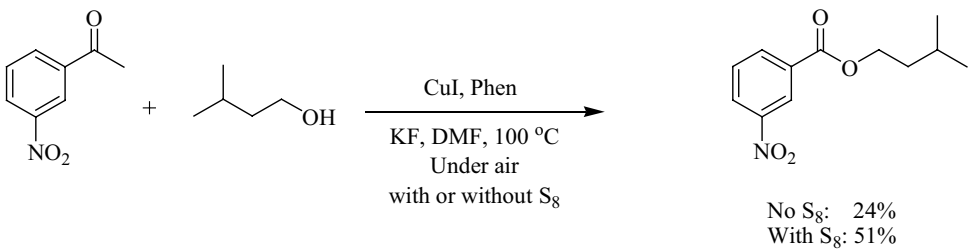
Scheme 5 Preparation of ethyl 3-nitrobenzoate from a bromo-activated methyl ketone



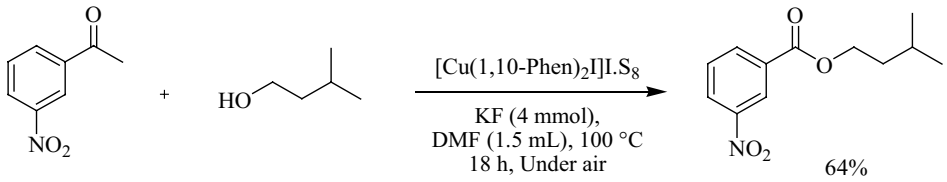
Scheme 6 Synthesis of benzocaine



Scheme 7 Effect of sulfur ligand in the esterification reaction



Scheme 8 Effect of sulfur ligand in the esterification reaction



As an application of this method to organic synthesis, we were interested in preparing the benzocaine as an anesthetic compound [25, 26]. Unfortunately, the direct conversion of 4-aminoacetophenone to benzocaine (**3c**) under our optimized conditions was unsuccessful (Scheme 1). Therefore, we decided to prepare this compound from 4-nitroacetophenone.

In the first step of this reaction, we conducted the oxidative esterification of 4-nitroacetophenone using tetraethyl orthosilicate under the standard conditions (Scheme 1). In the next step, an efficient procedure for selective reduction in nitro group was required so that the ester functionality remains intact. Although a few efficient procedures for this aim are available in the literature [27, 28], we used our own procedure to reduce the nitro group, selectively (Scheme 6). In this novel method, we used Pd(0) as the catalyst generated from the reduction in $Pd(OAc)_2$ by CaH_2 in DMSO at 100 °C. Successively, this mixture plus $Cu(OAc)_2$ as the cocatalyst, HCOONa as the reductant and KF as the additive was added to a vessel containing ethyl 4-nitrobenzoate in DMSO. After 5 h reaction time, the product was isolated in 80% yield. Consequently, we were able to synthesize benzocaine from 4-nitroacetophenone in a two-step reaction in 66% overall yield (Scheme 6). The reaction failed in the absence of sodium format.

Encouraged by these results, we conducted the same esterification reaction using isoamyl alcohol as the starting material instead of $Si(OEt)_4$ (Scheme 7). Under the standard conditions, the desired product was isolated in 24% yield. Intriguingly, when we added S_8 as the additive to this reaction, the yield of the ester improved up to 51%. To the best of our knowledge, this positive effect for S_8 has not been observed in other coupling reactions.

This reaction was repeated using $[Cu(1,10\text{-}Phen)_2I]I.S_8$ as the catalyst, and the desired product was obtained in 64% isolated yield (Scheme 8).

In summary, we have disclosed an efficient procedure for oxidative esterification of methyl ketones using copper as the catalyst in air. Our studies upon the plausible path of the reaction exclude the involvement of carboxylic acids and alcohols as the intermediates. Instead, it suggests that the aldehyde might be involved as the real intermediate. TEMPO test shows that the reaction proceeds through a non-radical pathway. Using this procedure, we have synthesized benzocaine in a two-step reaction.

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