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Iron-catalyzed C-C bond activation / C-O bond formation: direct conversion of ketones to esters

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ABSTRACT

The iron-catalyzed oxidative activation of the (O)C-C bond in ketones has been developed. This method enables direct synthesis of esters by the reaction between ketones and alcohols via conversion of the (O)C-C bond to the (O)C-O bond. The reaction runs selectively: the (O)C- C_{Alkyl} bond is activated, while the (O)C- C_{Aryl} bond remains intact (i.e., iron-catalyzed intermolecular anti-Baeyer-Villiger activation of the (O)C-C bond). The reaction conditions are carefully optimized and allow the production of esters with yields of up to 95%. The method is based on the inexpensive and commercially available catalyst (FeCl₃), oxidant ((NH₄)₂S₂O₈), and solvent (DCE) without using any ligands or additives.

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The C-C bond is fundamental to organic chemistry. The processes involving C-C bond breaking are very common: they take place in hydrocarbon metabolism, the petroleum industry, etc. One of the current global problems is searching for effective environmental waste disposal methods. These processes are directly involved in the modification and refining of petroleum products and plastics.^[11] Furthermore, organic chemists have long been focusing on synthesizing complex molecules from hydrocarbons, their relatively simple precursors. Selective functionalization of molecules with minimal pre-activation can make synthesis simpler and broaden the possibilities for studying the applicability of complex molecules in various fields, from the pharmaceutical industry to materials science. This means that elaboration of new methods for C-C bond activation is today a high-demand and hot-button research area.^[2]

Reactions of transformation of carbonyl compounds hold a central place in modern organic chemistry. Ketones are a fundamental class of organic compounds used in such processes as the Baeyer–Villiger oxidation (Scheme 1, (3) path. B),^[3] the Schmidt reaction,^[4] the Haller–Bauer Reaction,^[5] etc. However, this class of compounds was recently also widely used in metal-catalyzed C-C bond activation, and in particular in the processes involving the new concept known as metal-organic cooperative catalysis (MOCC, Scheme 1, (1)),^[6] intramolecular activation of the (O)C-C bond in ketone, which involve a targeting (chelating)

group (Scheme 1, (2)),^[7] and direct functionalization of (O)C-C bond (Scheme 1, (3) path. A).^[8]



Scheme 1. Approaches to activation of the (O)C-C bond in ketones.

The latter approach is preferred, since no chelating groups, which are often expensive and not commercially available, need to be introduced to the molecule being activated. Furthermore, this approach can also be carried out using inexpensive

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catalysts.^[9] For example, Ning Jiao et al. have conducted copper-catalyzed oxidation of acetophenone derivatives to the corresponding benzoic acid esters.^[10]

In this study, the iron-catalyzed activation of the $(O)C-C_{Alkyl}$ bond in ketones performed with an inexpensive and commercially available catalyst, oxidant, and solvent without using any ligands or additives has been described. This approach allows one to directly cleave the $(O)C-C_{Alkyl}$ bond and form the (O)C-O bond.

The study involved two stages: the reaction conditions were thoroughly optimized at the first stage and the applicability of the reaction to a broad range of substrates was determined at the second stage.

In order to optimize the reaction conditions, an easy-toanalyse model system based on inexpensive and commercially available initial reagents was selected, namely, 4methylacetophenone **1b** and hexanol **2b** (Table 1).

At the first optimization stage, we needed to determine the optimal catalyst/solvent combination ensuring oxidative cleavage of the (O)C-C_{Alkyl} bond and formation of the (O)C-O bond. Salts of inexpensive and commercially available metals (Fe, Cu, Ni, Mn, Co, Cr) as catalysts, solvents of different nature, $(NH_4)_2S_2O_8$ and etc. as oxidant were used (Table 1 and Supporting Information).

Table 1. Examination of reaction conditions.^a

n Me	Me + m	Hex O H So additi 2b	× [M], y [O] I, T (⁰ C), t (h), ves, atmosphere	Me 3b,b	Hex
No.	x[M]	y[O]	Sol	$T\left(^{o}C\right)$	Yield ⁾ (%) ^d
1	0.2FeCl ₃	$2K_2S_2O_8$	DCE	100	30
2	0.2FeCl ₃	$2K_2S_2O_8$	Tol	100	10
3	0.2FeCl ₃	$2K_2S_2O_8$	MeNO ₂	100	5
4	0.2CuCl	$2K_2S_2O_8\\$	DCE	100	0
5	0.2FeCl ₃	$2K_2S_2O_8\\$	DCE	120	35
6	0.3FeCl ₃	$2K_2S_2O_8$	DCE	120	41
7	0.3FeCl ₃	$2(NH_4)_2S_2O_8$	DCE	120	55
8	0.3FeCl ₃	$2(NH_4)_2S_2O_8$	DCE	120	64 ^b
9	0.3FeCl ₃	$2(NH_4)_2S_2O_8$	DCE/CCl ₄	120	71 ^c
10	0.3FeCl ₃	$1(NH_4)_2S_2O_8$	DCE	120	34
11	0.3Fe(ClO ₄) ₃	$2(NH_4)_2S_2O_8$	DCE	120	16

^a Reaction conditions: **1b** (0.299 mmol, 1 eq.), **2b** (0.598 mmol, 2 eq.), catalyst (0.0598 – 0.0897 mmol, 0.2 – 0.3 eq.), oxidant (0.299 – 0.598 mmol, 1 – 2 eq.), and solvent (1.00 mL) were stirred in Schott culture tubes (H × diam. 160 mm × 16 mm) at 100 – 120 °C for 24 h.

^b Reaction conditions: **1b** (0.299 mmol, 1 eq.), **2b** (0.224 mmol, 0.75 eq.), FeCl₃ (0.0897 mmol, 0.3 eq.), $(NH_{4)2}S_2O_8$ (0.598 mmol, 2 eq.), and DCE (0.75 mL) were stirred in Schott culture tubes (H × diam. 160 mm × 16 mm) at 120 °C for 3 h. Further, after adding a solution of **2b** (0.0748 mmol, 0.25 eq.) and DCE (0.08 mL), the reaction mixture was stirred at 120 °C for 3 h (3 times at 3-hour intervals). Next it was stirred at 120 °C for 12 h.

^c Solvent - DCE/CCl₄ = 1/1 (1.00 mL).

 d The yield of **3b,b** was determined by 1H NMR (CDCl₃) after the filtration of the reaction mass through a thin pad (0.4 – 0.5 cm) of silica gel (0.015 – 0.040 mm) using 20 mL of DCM.

Only certain iron salts, such as $FeCl_3$, $FeCl_2$, $Fe(ClO_4)_3$, and $Fe(NO_3)_3$ were found to catalyze oxidative coupling in

organochlorine solvents, such as chlorobenzene (17%), tetrachlormethane (28%), and dichloroethane (30%) (Table 1 and Supporting Information). Subsequent optimization was carried out in dichloroethane in the presence of iron (III) chloride as a catalyst.

At the next stage, optimization was carried out based on the dependence of the yield of product **3b**,**b** on reaction temperature. The initial reagents were converted into the reaction product **3b**,**b** at a temperature as low as 80 $^{\circ}$ C (5%, S. I.); the best yield (35%) was achieved at 120 $^{\circ}$ C (No. 5, Table 1). Further increase in temperature did not raise the yield of the product **3b**,**b** due to the side reactions (Supporting Information).

The yield of **3b**,**b** slightly rose to 41% (No. 6, Table 1) when the molar ratio of FeCl₃/**1b** was increased from 0.2 to 0.3. The decrease in the amount of the catalyst (FeCl₃) to 0.02 eq. abruptly reduced the yield of **3b**,**b** to trace amounts due to incomplete conversion of the initial reagents and the side reactions of oxidation of **1b** (Supporting Information). Further increase in FeCl₃ content to 0.5 and 1 eq. also caused incomplete conversion of **1b** and, as a result, reduced the yield of the reaction product **3b**,**b**. This presumably occurred due to the increased contribution of the side process, viz., intermolecular dehydration of alcohol **2b** to give dihexyl ether that we observed when analyzing the ¹H NMR spectrum.

Next, the oxidant nature was varied. The main focus was placed on simple and inexpensive reagents: *tert*butylhydroperoxide, di-(*tert*-butyl)peroxide, phenyl iodosoacetate, oxygen, ammonium and potassium persulfate, dichlorodicyanoquinone (DDQ), as well as sodium molybdate and tungstate (Supporting Information). The best results were achieved in the presence of DDQ (28%), potassium persulfate (41%), and ammonium persulfate (55%). The higher solubility of ammonium persulfate in organic solvents compared to potassium persulfate was one of the possible reasons why the highest yield was achieved with ammonium persulfate. Only trace amounts of the product **3b,b** (less than 5%) were observed in the presence of other oxidants (Table 1 and Supporting Information).

Further optimization of the reagent ratio has shown the best $1b/2b/FeCl_3/(NH_4)_2S_2O_8$ ratio to be 1/1.5/0.3/2. An abrupt decrease in the yield of product 3b,b was observed when the molar ratio of the substrates 1b/2b was changed. This effect was particularly pronounced when an excess of ketone 1b with respect to alcohol 2b (2/1) was taken. No product formation was observed when the reaction was carried out in alcohol (Supporting Information). Increased and reduced molar ratios of $(NH_4)_2S_2O_8/1b$ differing from (2/1) decreased the yield of product 3b,b (Supporting Information). In addition, the reaction under study is highly sensitive to changes in the amount of solvent: dilution of the reaction mass resulted in a decrease in the reaction rate, while concentration of the reaction mass caused occurrence of oxidative side reactions involving 1b (Supporting Information).

After determining the optimal catalyst, oxidant, temperature, and the molar ratio between the reaction components, the effect of acid, base, free radical scavengers and other additives on the yield of the reaction product **3b**,**b** was studied (Supporting Information). The presence of both basic and acidic additives in the reaction mass was found to drastically reduce the yield of the product **3b**,**b**, in most cases down to 0% (Supporting Information). Such free radical scavengers as γ -terpinene and hydroquinone reduced the yield of the product **3b**,**b** to 5 and 10%, respectively (Supporting Information).

As mentioned previously, the reaction under study is highly sensitive to additives of various nature; hence, it was interesting and important to determine the effect of the atmosphere on the yield of the reaction product **3b,b**. The yield of the product **3b,b**

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for the reaction in the atmosphere of oxygen (37%) and argon (30%) was found to be lower than that for the reaction carried out in air (55%) (Supporting Information). Atmospheric oxygen presumably acts as an oxidant, along with ammonium persulfate. The use of pure oxygen (~99%) resulted in oxidation of the product **3b**,**b** under the reaction conditions as pure oxygen is more reactive compared to atmospheric oxygen.

Studying the effect of the sequence of adding the reagents on the yield of the reaction product was the next key stage in optimizing the reaction (Supporting Information). When 4methylacetophenone **1b**, ammonium persulfate, and the 4methylacetophenone **(1b)**/1.5*hexanol **(2b)** mixture were added in four steps, the yield of the product **3b**,**b** decreased to 8, 19, and 5%, respectively. The fact that the yield of the product **3b**,**b** was increased to 64% by adding hexanol **2b** to the solutions in four steps was an exception (No. 8 ,Table 1, and Supporting Information). Stepwise addition of alcohol **2b** inhibited the intermolecular dehydration of **2b**, which would otherwise give rise to dihexyl ether under these reaction conditions.

Since it has been found (Table 1 and Supporting Information) that the reaction runs best in organochlorine solvents, it was optimized by combining various chlorine-containing solvents (Supporting Information). The optimal solvent combination was DCE/CCl_4 (1/1); the yield of the product increased by 7% (up to 71%) (No. 9, Table 1, and Supporting Information).

Complete conversion of the initial reagents under the optimized conditions takes 24 h (Supporting Information).

Hence, although the reaction conditions were very simple, the reagents were inexpensive and commercially available, the system under study turned out to be very sensitive to various additives, to changes in concentrations of the initial components, and to other parameters.

At the second stage, we tested the applicability of the synthetic method of iron-catalyzed C-C bond activation to reactions of acetophenone derivatives having various substituent moieties on the aromatic ring, 1,3-diketons, and other carbonyl compounds with various alcohols (Table 2).

 Table 2. Substrate scope of esters.^a





^a <u>General method of synthesis of 3a-f,a-d:</u> 1a-h (0.0299 – 0.0532 g, 0.299 mmol, 1 eq.), 2a-d (0.0166 – 0.228 g, 0.224 mmol, 0.75 eq.), FeCl₃ (0.0145 g, 0.0897 mmol, 0.3 eq.), (NH₄)₂S₂O₈ (0.1363 g, 0.598 mmol, 2 eq.), and DCE/CCl₄ (0.75 mL, 1/1) were stirred in Schott culture tubes (H × diam. 160 mm × 16 mm) at 120 °C for 3 h. Further, after adding a solution of 2a-d (0.055 – 0.0763, 0.0748 mmol, 0.25 eq.) and DCE/CCl₄ (0.08 mL, 1 / 1), the reaction mixture was stirred at 120 °C for 3 h (3 times at 3-hour intervals). Next it was stirred at 120 °C for 12 h. The yields of 3a-f,a-d were determined by ¹H NMR (CDCl₃) after the filtration of the reaction mass through a short pad (0.4 – 0.5 cm) of silica gel (0.015 – 0.040 mm) using 20 mL of DCM and evaporation of solvent in vacuum.

It turned out that the proposed synthesis approach can be used for a broad range of acetophenones**1a-e** (Table 2), mostly those having electron-donating substituents in the aromatic ring, as well as for dicarbonyl compounds **1f-h** (Table 2). Acetophenone derivatives **1a-e** (Ar-C(O)-Me) were selectively oxidized to the corresponding benzoic acid esters **3a-e** (Ar-C(O)-OR), while the Ar-C(O) bond remained intact.

Benzophenone, dibenzylidenacetone, benzaldehyde, and derivatives of methyl vinyl ketone were found to be inert in this reaction. Furthermore, secondary, tertiary and aromatic alcohols, amines, thiols, selenols and diorganophosphine oxides did not react with 4-methylacetophenone, which attests to the high selectivity of the reaction under study.

Scheme 2 shows the reaction mechanism in general simplified form. At the first stage of the catalytic cycle, FeCl₃ acts as a Lewis acid and binds to the oxygen in carbonyl group of ketone **1**, giving rise to complex **A**. This process increases electrophilicity of the carbon atom of carbonyl group, thus activating ketone **1** for the nucleophilic attack of alcohol **2**. Further interaction between the alcohol and complex **A** gives rise to complex **B**; further oxidation of the complex **B** results in cleavage of the C-R₂ bond and formation of the reaction product **3** and FeCl₂, which subsequently interacts with the oxidant to be converted back to FeCl₃, thus closing the catalytic cycle.

The catalyst (FeCl₃) acts in this reaction as a Lewis acid and an oxidant in combination with $(NH_4)_2S_2O_8$ and O_2 . Probably, the [Fe] oxidation state under the oxidizing reaction conditions can vary not only in the range of +2 and +3, but also +4, +5, +6 and +7, which, presumably, explains the higher catalytic activity of [Fe] under these reaction conditions in comparison with other catalysts (Supporting Information).

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8.



Scheme 2. The proposed mechanism.

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The proposed method has reversed selectivity in C-C bond oxidation, as opposed to the known Baeyer-Villiger reaction,^[3] where intramolecular oxidation of the (O)C-CAr bond to the (O)C-OCAr bond occurs in the first place. The substituent moieties can be arranged in order of decreasing ease of oxidation of the C-C(O) bond in the Baeyer-Villiger reaction^[3] as follows: $4-Me-C_6H_4-C(O) > C_6H_5-C(O) > 4-Cl-C_6H_4-C(O) > Me-C(O)$ in C_{Ar} -C(O)- C_{Alkvl} . Furthermore, oxidation of the C-C(O) bond in this reaction is usually non-selective and gives rise to a mixture of products of oxidation of the (O)C- C_{Alkyl} and (O)C- C_{Ar} bonds. In addition, this reaction is intramolecular. The approach proposed by us involves selective oxidation of (O)C-Me to (O)C-OR with the (O)C-C_{Ar} bond remaining intact (Table 2) (i.e., ironcatalyzed intermolecular anti-Baeyer-Villiger activation of the (O)C-C bond), which allows one to selectively synthesize derivatives of esters of benzoic and other carboxylic acids,

Thus, we proposed iron-catalyzed activation of the (O)C-C bond in ketones. This method enables a direct synthesis of esters by reactions between ketones and alcohols by converting the (O)C-C bond to the (O)C-O bond. Thorough optimization of the reaction conditions has been carried out. The method is based on the inexpensive and commercially available catalyst (FeCl₃), oxidant ((NH₄)₂S₂O₈), and solvents (DCE, CCl₄) without using any ligands or additives. The reaction runs selectively and involves activation of the (O)C-C_{Alkyl} bond only, while the (O)C-C_{Ar} bond remains intact.

Experimental Section

<u>General method of synthesis of 3a-f,a-d:</u> 1a-h (0.0299 – 0.0532 g, 0.299 mmol, 1 eq.), 2a-d (0.0166 – 0.228 g, 0.224 mmol, 0.75 eq.), FeCl₃ (0.0145 g, 0.0897 mmol, 0.3 eq.), (NH₄)₂S₂O₈ (0.1363 g, 0.598 mmol, 2 eq.), and DCE/CCl₄ (0.75 mL, 1/1) were stirred in Schottculture tubes (H × diam 160 mm × 16 mm) at 120 °C for 3 h. Further, after adding a solution of 2a-d (0.055 – 0.0763, 0.0748 mmol, 0.25 eq.) and DCE/CCl₄ (0.08 mL, 1 / 1), the reaction mixture was stirred at 120 °C for 3 h (3 times at 3-hour intervals). Next it was stirred at 120 °C for 12 h. The yields of 3a-f,a-d weredetermined by ¹H NMR (CDCl₃) after the filtration of the reaction mass through a short pad (0.4 – 0.5 cm) of silica gel (0.015 – 0.040 mm) using 20 mL of DCM and gyadeint flash chromatography (eluent: petroleum ether / ethyl acetate).

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