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Full Paper

α-Alkoxy Ketones

Direct Synthesis of α-Alkoxy Ketones by Oxidative C–O Bond Formation

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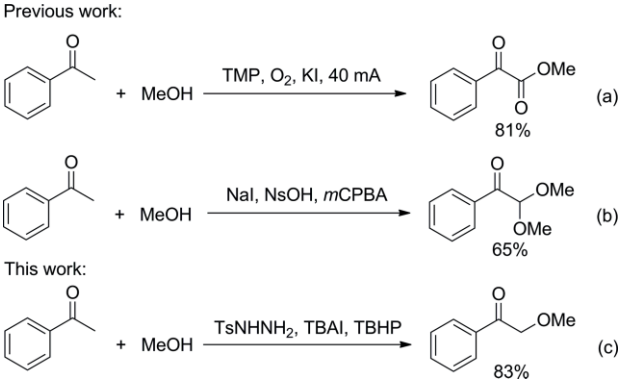
Abstract: A convenient method to prepare α-alkoxy ketones has been developed by oxidative coupling of aryl methyl ketones and alcohols. With aqueous *tert*-butyl hydroperoxide (6.0 equiv.) as the oxidant, tetrabutylammonium iodide (20 mol-%) as the catalyst, and $TsNHNH_2$ (1.0 equiv.) as the additive, ketones underwent direct alkoxylation to give α-methoxy or α-ethoxy ketones in moderate to good yields.

Introduction

α-Alkoxy ketones are important building blocks of many synthetically meaningful compounds, such as ligands for Ru complexes for transfer hydrogenation reactions,[1] or bioactive compounds for drug discovery, such as β-adrenergic blockers and HIV-1 integrase inhibitors.[2] These compounds could also serve as precursors for the preparation of chiral alcohols.[3] As a result of the versatile properties of α-alkoxy ketones, various synthetic methods have been developed. The most frequently used methods included the alcoholysis of enol acetates,[4] silyl enol ethers,[5] or α-diazo ketones,[6] but these methods suffer from disadvantages, such as requiring multiple steps and harsh conditions. Another route to α-alkoxy ketones was the nucleophilic addition of nitriles by α-alkoxy ylides or Grignard reagents, but yields were relatively low, and anhydrous reaction conditions were needed.[7] Thus, development of new and convenient synthetic pathways to α-alkoxy ketones is still in demand.

In recent years, because of its high efficiency and environment-friendly properties, *tert*-butyl hydroperoxide (TBHP)/nBu_4NI system has emerged as an attractive metal-free catalytic system and has been used successfully for the formation of carbon–carbon and carbon–heteroatom bonds.[8] In most cases, these reactions were carried out under mild conditions, and only small molecules such as H_2O and *t*BuOH are released as the main byproducts. With this new method, varied synthetically or pharmaceutically useful compounds have been prepared in good yields. Consequently, we proposed that α-alkoxy ketones might also be synthesized by such an oxidative C–O bond-forming process.[9] Oxone and polystyrene-bound $PhI(OAc)_2$ has been used as an oxidant to convert acetophenone into α-methoxy ketone in MeOH, but yields were poor.[10] Another challenge was that the obtained α-methoxy ketone was sensitive to oxidative conditions and was easily oxidized further to give an ester[11] or α,α-dimethoxy ketone as the final product (Scheme 1a, b).[12] Herein, as a continuation of our efforts on TBHP-mediated oxidative coupling reactions, we report a new tetrabutylammonium iodide (TBAI) catalyzed synthesis of α-alkoxy ketones under mild and metal-free conditions (Scheme 1c).



Scheme 1. Oxidative coupling reaction of a ketone and alcohol. TMP = 2,2,6,6-tetramethylpiperidine; *m*CPBA = *meta*-chloroperoxybenzoic acid.

Results and Discussion

Initially, acetophenone (**1a**) was chosen as the model substrate with which to optimize reaction conditions alongside the additive, catalyst, solvent, and temperature. As shown in Table 1, the reaction of **1a** with TBHP (6.0 equiv., 70 % solution in water) was examined in MeOH (2 mL) with TBAI (20 mol-%) as the catalyst at room temperature, and 16 h later only 15 % of the desired product **3a** was isolated (Table 1, Entry 1). TsOH or $TsNH_2$ (1.0 equiv.) was added to the reaction mixture, but the yield did not improve significantly (Table 1, Entries 2, 3). To our delight, a satisfactory yield (83 %) was obtained with $TsNHNH_2$ (1.0 equiv.) as an additive, and by decreasing the amount of $TsNHNH_2$ to 0.5 equiv. a yield of 69 % was obtained (Table 1, Entry 4). The reaction proceeded less efficiently with other hydrazide additives, such as $NsNHNH_2$, $PhSO_2NHNH_2$, and

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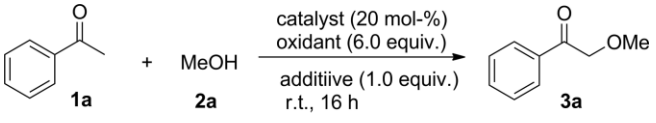
$PhCONHNH_2$ (Table 1, Entries 5–7). Next, a wide range of iodine sources was screened, and TBAI was determined to be the best (Table 1, Entry 8–11). Change of the oxidant to anhydrous TBHP (5 M in decane) or cumene hydroperoxide (CHP) caused lower yields (Table 1, Entry 12–13). When the amount of TBHP was decreased to 4.0 equiv. and 2.0 equiv., the yield of **3a** was decreased to 68 % and 46 %, respectively (Table 1, Entry 14). Furthermore, a higher temperature did not improve the yield of **3a**, and a 53 % yield was observed when the reaction was carried out at 45 °C (Table 1, Entry 15). A 1:1 mixture of MeOH/CH_3CN was tested as solvent, and only 23 % of the product was isolated (Table 1, Entry 16) Thus, the optimized conditions for this reaction are summarized as follows: **1a** (0.5 mmol), $TsNHNH_2$ (0.5 mmol), TBAI (0.1 mmol), and TBHP (3.0 mmol, 70 % solution in water), at room temperature in MeOH (2 mL) for 16 h.

Table 1. Optimization of reaction conditions for α-methoxy ketone.[a]

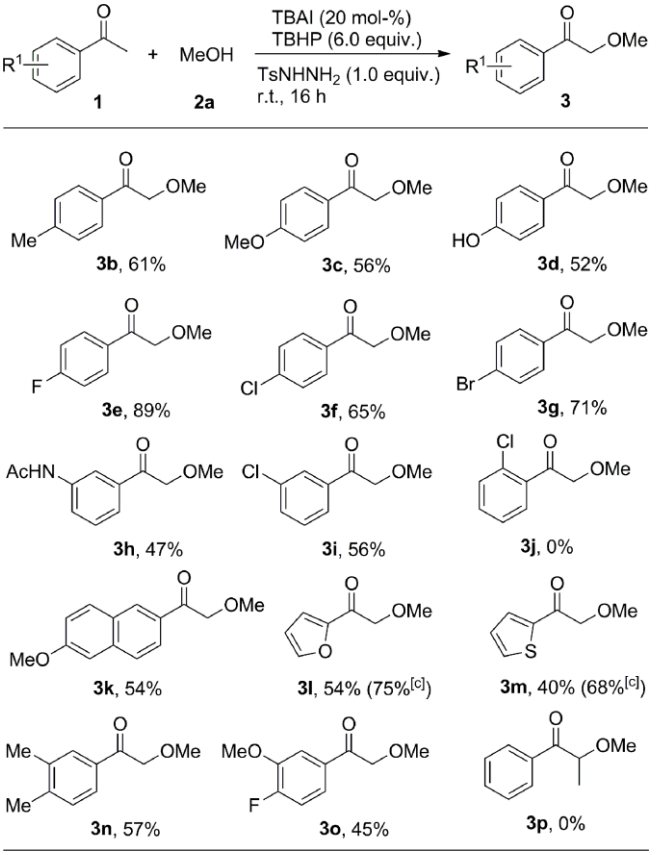


Entry	Additive	Catalyst	Oxidant	Yield[b] [%]
1	–	TBAI	TBHP	15
2	TsOH	TBAI	TBHP	17
3	$TsNH_2$	TBAI	TBHP	20
4	$TsNHNH_2$	TBAI	TBHP	83 (69[c])
5	$NsNHNH_2$[d]	TBAI	TBHP	35
6	$PhSO_2NHNH_2$	TBAI	TBHP	23
7	$PhCONHNH_2$	TBAI	TBHP	20
8	$TsNHNH_2$	I_2	TBHP	48
9	$TsNHNH_2$	NH_4I	TBHP	22
10	$TsNHNH_2$	NaI	TBHP	24
11	$TsNHNH_2$	NIS	TBHP	54
12	$TsNHNH_2$	TBAI	CHP	58
13	$TsNHNH_2$	TBAI	TBHP[e]	75
14	$TsNHNH_2$	TBAI	TBHP	68,[f] 46[g]
15	$TsNHNH_2$	TBAI	TBHP	53[h]
16	$TsNHNH_2$	TBAI	TBHP	23[i]

[a] The reaction was carried out with **1a** (0.5 mmol), **2a** (2.0 mL), oxidant (6.0 equiv.), and MeOH (2.0 mL), at room temperature for 16 h. [b] Isolated yields. [c] $TsNHNH_2$ (0.5 equiv.) was added. [d] $NsNHNH_2$ = *para*-nitrobenzenesulfonyl hydrazide. [e] TBHP (5 M in decane) was used. [f] TBHP (4.0 equiv.) was used. [g] TBHP (2.0 equiv.) was used. [h] Reaction carried out at 45 °C. [i] MeOH/CH_3CN = 1:1.

Under the optimized reaction conditions, the substrate scope was examined, and the results are summarized in Table 2. Different substituted acetophenones were investigated, and the corresponding products were obtained in moderate to good yields regardless of the electron-donating or electron-withdrawing groups on the *para* or *meta* position of the benzene ring (Table 2, **3b**–**i**). Marked steric hindrance effects were observed, and no product was isolated when 2-chloroacetophenone was used as a substrate (Table 2, **3j**). 6-Methoxy-2-acetonaphthone gave the desired product in 54 % yield (Table 2, **3k**). Heterocyclic substrates, such as 2-acetylfuran and 2-acetylthiophene, underwent smooth reactions to provide products, but the isolated yields were low as a result of the volatility of the products (Table 2, **3l**–**m**). Disubstituted acetophenones, such as 3,4-dimethylacetophenone and 4-fluro-3-methoxyacetophenone, were converted into the corresponding products in moderate yields (Table 2, **3n**–**o**). Propiophenone was also tested, but no reaction occurred (Table 2, **3p**).

Table 2. TBAI-catalyzed synthesis of α-methoxy ketone.[a]

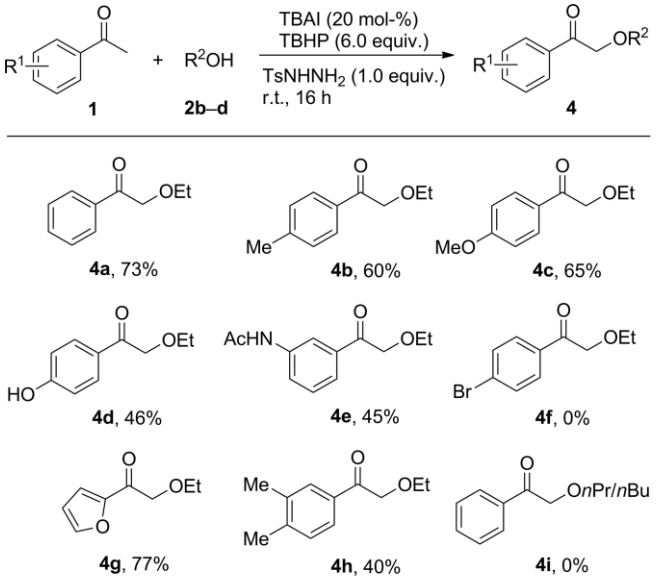


[a] The reaction was performed with acetophenone (0.5 mmol), $TsNHNH_2$ (0.5 mmol), TBAI (0.1 mmol), and TBHP (70 wt.-% in water, 3.0 mmol) in methanol (2.0 mL) at room temperature for 16 h. [b] Isolated yields. [c] Yield determined by NMR spectroscopy.

Encouraged by the facile synthesis of α-methoxy ketones, the scope of the reaction was extended to the formation of α-ethoxy ketones. Reaction of acetophenone and ethanol gave the desired product **4a** in 73 % yield under the optimized reaction conditions (Table 3, **4a**). Different substituted acetophenones were also examined, and the corresponding products were obtained in 45–65 % yields (Table 3, **4b**–**4e**), but no product was found when 4-bromoacetophenone was employed as substrate, which exhibited a reactivity difference of MeOH and EtOH in this reaction (Table 3, **4f**). Heterocyclic substrate 2-acetylfuran gave a 77 % product yield under the optimized reaction conditions (Table 3, **4g**). The disubstituted acetophenone 3,4-dimethylphenyl methyl ketone afforded the corresponding product in 40 % yield (Table 3, **4h**). When other alcohols, such as propanol or butanol, were employed, no desired products were observed because of poor nucleophilicity of the alcohols, and hydrazone was formed as the major product (Table 3, **4i**).

To gain insights into the reaction mechanism, control experiments were carried out, and the results are shown in Scheme 2. A radical pathway was excluded, because the reaction pro-

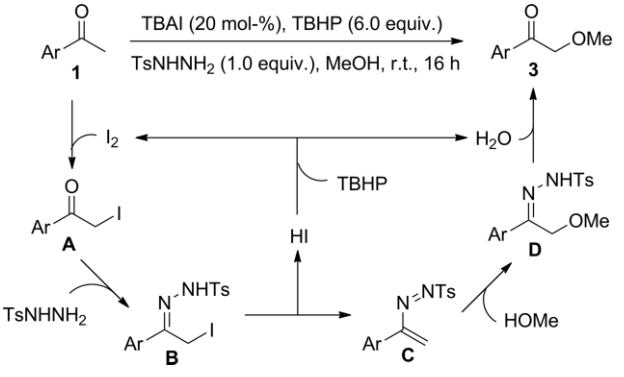
Table 3. TBAI-catalyzed synthesis of α-ethoxy ketones.[a]



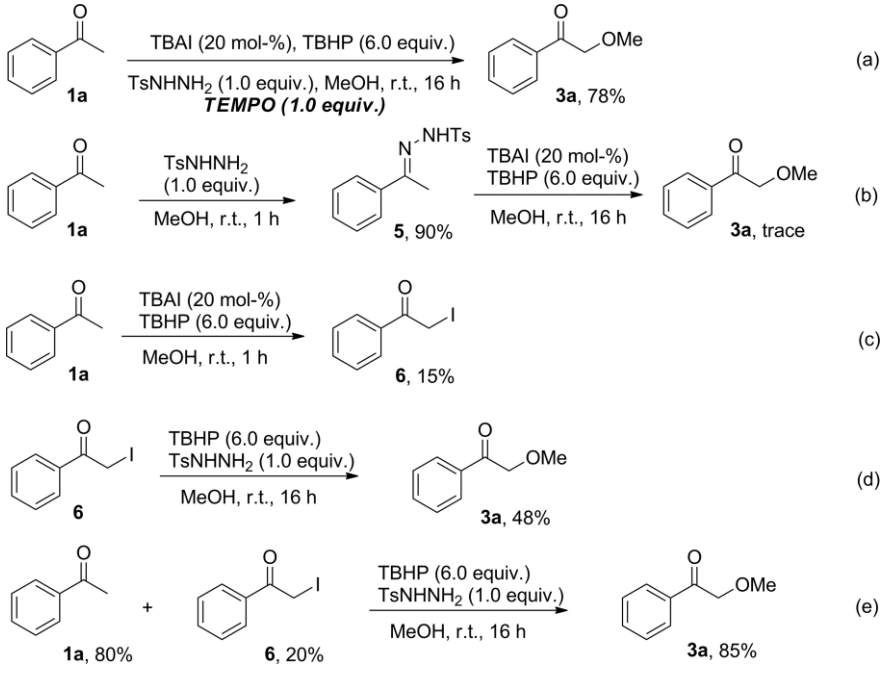
[a] The reaction was performed with acetophenone (0.5 mmol), $TsNHNH_2$ (0.5 mmol), TBAI (0.1 mmol, 20 mol-%), and TBHP (70 wt.-% in water, 3.0 mmol) in ethanol or propanol (2.0 mL) at room temperature for 16 h. [b] Isolated yields.

ceeded well in the present of (2,2,6,6-tetramethyl-1-piperidinyl)oxidanyl (TEMPO, 1.0 equiv.; Scheme 2a). To reveal the role of $TsNHNH_2$ in this reaction, in a two-step one-pot procedure, acetophenone and $TsNHNH_2$ was stirred in MeOH for 1 h and hydrazone **5** was formed in 90 % yield. Subsequent addition of TBAI and TBHP to the resulting solution gave only trace amounts of the product after the mixture had been stirred for 16 h; thus, the possibility of hydrazone **5** as an intermediate was also excluded (Scheme 2b). Next, in the absence of $TsNHNH_2$, acetophenone was treated with TBAI and TBHP in MeOH for 1 h; α-iodoacetophenone (**6**) was isolated in 15 % yield (Scheme 2c). Then α-iodoacetophenone (**6**) was prepared and subjected to the optimized reaction conditions; **3a** was obtained in 48 % yield in the presence of much iodine (Scheme 2d). Finally, a mixture of acetophenone **1a**/α-iodoacetophenone (**6**) (80:20) was stirred in MeOH in the presence of TBHP (6.0 equiv.) and $TsNHNH_2$ (1.0 equiv.) for 16 h. Compound **3a** was isolated in 85 % yield (Scheme 2e). These results indicate that α-iodoacetophenone (**6**) might be a key intermediate of the reaction.

By taking into account the above results, a possible mechanism is proposed in Scheme 3. Iodination of aryl methyl ketone **1** gives α-iodoacetophenone **A**, which reacts with $TsNHNH_2$ to afford α-iodo hydrazone **B**. Then **B** is converted into azoalkene **C** and releases HI, which is oxidized by TBHP to regenerate I_2.[13] Then, addition of MeOH to in situ generated azoalkene **C** gives α-methoxy hydrazone **D**, which is further hydrolyzed to furnish



Scheme 3. Possible reaction pathway.

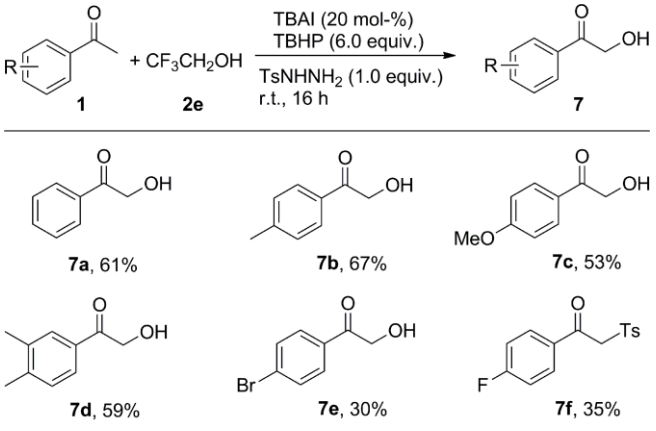


Scheme 2. Control experiments.

the desired product **3**. More details for the mechanism still need further investigation.

Finally, aiming at the formation of α-trifluoroethoxy ketones, the reaction performed in trifluoroethanol (2 mL) was also examined. Interestingly, no expected α-trifluoroethoxy ketone was found, but α-hydroxy ketones were isolated in 30–67 % yields (Table 4, **7a**–**7e**).[14] However, in the case of 4-fluoroacetophenone, only trace amounts of the corresponding α-hydroxy ketone was obtained, and α-tosyl ketone **7f** was formed in 35 % yield as the main product (Table 4).[15]

Table 4. TBAI-catalyzed synthesis of α-hydroxy ketones.[a]



[a] The reaction was performed with acetophenone (0.5 mmol), $TsNHNH_2$ (0.5 mmol), TBAI (0.1 mmol), and TBHP (70 wt.-% in water, 3.0 mmol) in trifluoroethanol (2.0 mL) at room temperature for 16 h. [b] Isolated yield.

Conclusion

We have developed a simple and efficient method for the synthesis of α-alkoxy ketones through a direct alkoxylation reaction mediated by a TBAI/TBHP system. With the aid of $TsNHNH_2$, aryl methyl ketones coupled to methanol and ethanol to give α-methoxy and α-ethoxy ketones, respectively, in moderate to good yields. The reactions could be carried out under environmentally friendly and mild conditions. Further studies to understand the mechanism of this oxidative coupling reaction and to extend this protocol to synthetic applications are still ongoing in our laboratory.

Experimental Section

General Methods: Commercially available reagents were used as received without further purification. Reaction mixtures were magnetically stirred and monitoring was done by thin layer chromatography with silica gel 60 F254 plates, which were visualized by fluorescence quenching at 254 nm. For chromatographic purifications, analytically pure solvents were used with silica gel (300–400 mesh) as the solid support. ^1H and ^{13}C NMR chemical shifts are reported relative to the chemical shift of the residual solvent signal. Reference peaks for chloroform in ^1H and ^{13}C NMR spectra were set at δ = 7.26 ppm and 77.0 ppm, respectively.

Typical Experimental Procedure for the Synthesis of α-Alkoxy Ketones 3a–3p and 4a–4h: A 25 mL Schlenk tube was charged with acetophenone (0.5 mmol), $TsNHNH_2$ (0.5 mmol, 1.0 equiv.), TBAI (0.1 mmol, 20 mol-%), TBHP (70 wt.-% in H_2O, 3.0 mmol, 6.0 equiv.), and the mixture was stirred in MeOH or EtOH (2 mL) at room temperature for 16 h. Then the reaction mixture was diluted with diethyl ether (10 mL), washed with saturated $Na_2S_2O_3$ (1 mL), dried with Na_2SO_4, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography with silica gel by gradient elution with ethyl acetate in petroleum ether to obtain the corresponding product.

2-Methoxy-1-phenylethan-1-one (3a):[16] Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 7.4 Hz, 2 H), 7.59 (t, J = 7.4 Hz, 1 H), 7.48 (t, J = 7.7 Hz, 2 H), 4.73 (s, 2 H), 3.52 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.1, 134.8, 133.5, 128.7, 127.8, 75.2, 59.4 ppm.

2-Methoxy-1-(4-methylphenyl)ethan-1-one (3b):[17] Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, J = 8.2 Hz, 2 H), 7.27 (d, J = 8.0 Hz, 2 H), 4.70 (s, 2 H), 3.51 (s, 3 H), 2.42 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.7, 144.4, 133.5, 129.3, 127.8, 75.1, 59.3, 21.6 ppm.

2-Methoxy-1-(4-methoxyphenyl)ethan-1-one (3c):[18] Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 8.9 Hz, 2 H), 6.94 (d, J = 8.8 Hz, 2 H), 4.66 (s, 2 H), 3.88 (s, 3 H), 3.50 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 194.6, 163.7, 130.2, 127.9, 113.8, 75.1, 59.3, 55.4 ppm.

1-(4-Hydroxyphenyl)-2-methoxyethan-1-one (3d):[18] Yellowish solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, J = 8.8 Hz, 2 H), 6.92 (d, J = 8.8 Hz, 2 H), 4.70 (s, 2 H), 3.51 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 194.8, 160.8, 130.4, 115.6, 75.0, 59.4, 29.6 ppm.

1-(4-Fluorophenyl)-2-methoxyethan-1-one (3e): Yellowish solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.99 (dd, J = 8.8, 5.4 Hz, 2 H), 7.15 (t, J = 8.6 Hz, 2 H), 4.68 (s, 2 H), 3.51 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 194.6, 166.2 (d, J = 248 Hz), 130.7, 130.6, 115.9, 75.2, 59.3 ppm. HRMS (ESI-TOF): calcd. for $C_9H_9FNaO_2$ $[M + Na]^+$ 191.0479; found 191.0479.

1-(4-Chlorophenyl)-2-methoxyethan-1-one (3f):[5a] White solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, J = 8.5 Hz, 2 H), 7.62 (d, J = 8.5 Hz, 2 H), 4.66 (s, 2 H), 3.50 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.3, 133.5, 131.9, 129.4, 128.7, 75.2, 59.4 ppm.

1-(4-Bromophenyl)-2-methoxyethan-1-one (3g):[19] White solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, J = 8.5 Hz, 2 H), 7.62 (d, J = 8.5 Hz, 2 H), 4.66 (s, 2 H), 3.50 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.3, 133.5, 132.0, 129.5, 128.7, 75.3, 59.4 ppm.

***N*-[3-(2-Methoxyacetyl)phenyl]acetamide (3h):** White solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.67 (s, 1 H), 8.10 (s, 1 H), 7.94 (d, J = 7.9 Hz, 1 H), 7.60 (d, J = 7.7 Hz, 1 H), 7.39 (t, J = 7.9 Hz, 1 H), 4.72 (s, 2 H), 3.48 (s, 3 H), 2.23 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.0, 169.2, 138.9, 135.1, 129.3, 125.0, 123.1, 118.7, 75.1, 59.3, 24.3 ppm. HRMS (ESI-TOF): calcd. for $C_{11}H_{13}NNaO_3$ $[M + Na]^+$ 230.0788; found 230.0796.

1-(3-Chlorophenyl)-2-methoxyethan-1-one (3i):[20] White solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.92 (s, 1 H), 7.82 (d, J = 7.8 Hz, 1 H), 7.57 (d, J = 10.9 Hz, 1 H), 7.43 (t, J = 7.9 Hz, 1 H), 4.68 (s, 2 H), 3.51 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.1, 136.2, 135.1, 133.5, 130.0, 128.1, 126.0, 75.4, 59.5 ppm.

2-Methoxy-1-(6-methoxynaphthalen-2-yl)ethan-1-one (3k):[19] White solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.38 (s, 1 H), 7.96 (dd, J = 8.6, 1.6 Hz, 1 H), 7.83 (d, J = 9.0 Hz, 1 H), 7.77 (d, J = 8.6 Hz, 1 H), 7.20 (dd, J = 8.9, 2.5 Hz, 1 H), 7.14 (d, J = 2.3 Hz, 1 H), 4.81 (s, 2

H), 3.94 (s, 3 H), 3.54 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.7, 159.8, 137.4, 131.1, 130.1, 129.3, 127.7, 127.2, 124.1, 119.8, 105.7, 75.2, 59.4, 55.3 ppm.

2-(3-Methoxyprop-1-en-2-yl)furan (3l):[5a] Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, J = 1.0 Hz, 1 H), 7.33 (d, J = 3.6 Hz, 1 H), 6.59–6.55 (m, 1 H), 4.55 (s, 2 H), 3.51 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 185.5, 152.1, 146.5, 117.9, 112.2, 74.7, 59.5 ppm.

2-Methoxy-1-(thiophen-2-yl)ethan-1-one (3m):[5a] Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, J = 3.8 Hz, 1 H), 7.69 (d, J = 4.9 Hz, 1 H), 7.18–7.13 (m, 1 H), 4.56 (s, 2 H), 3.51 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 189.8, 140.9, 134.0, 132.5, 128.1, 75.8, 59.5 ppm.

1-(3,4-Dimethylphenyl)-2-methoxyethan-1-one (3n): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (s, 1 H), 7.66 (dd, J = 7.8, 1.5 Hz, 1 H), 7.22 (d, J = 7.9 Hz, 1 H), 4.70 (s, 2 H), 3.51 (s, 3 H), 2.32 (s, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.9, 143.2, 137.1, 132.7, 129.9, 128.8, 125.5, 77.3, 59.37, 20.1, 19.7, 18.4 ppm. HRMS (ESI-TOF): calcd. for $C_{11}H_{14}NaO_2$ $[M + Na]^+$ 201.0886; found 201.0891.

1-(4-Fluoro-3-methoxyphenyl)-2-methoxyethan-1-one (3o): White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, J = 9.2 Hz, 1 H), 7.71 (dd, J = 11.7, 1.9 Hz, 1 H), 7.01 (t, J = 8.3 Hz, 1 H), 4.63 (s, 2 H), 3.96 (s, 3 H), 3.50 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 194.0, 153.2, 152.2, 150.7, 125.3, 115.7, 112.4, 75.1, 59.3, 56.2 ppm. HRMS (ESI-TOF): calcd. for $C_{10}H_{11}FNaO_3$ $[M + Na]^+$ 221.0584; found 221.0585.

2-Ethoxy-1-phenylethan-1-one (4a):[5a] Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 7.3 Hz, 2 H), 7.58 (t, J = 7.3 Hz, 1 H), 7.47 (t, J = 7.7 Hz, 2 H), 4.75 (s, 2 H), 3.65 (q, J = 7.0 Hz, 2 H), 1.29 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.4, 134.8, 133.3, 128.5, 127.7, 73.4, 67.1, 14.9 ppm.

2-Ethoxy-1-(*p*-tolyl)ethan-1-one (4b): Yellowish solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, J = 8.2 Hz, 2 H), 7.27 (d, J = 4.4 Hz, 2 H), 4.73 (s, 2 H), 3.65 (q, J = 7.0 Hz, 2 H), 2.42 (s, 3 H), 1.30 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl3): δ = 196.16, 144.32, 132.45, 129.77, 129.31, 127.96, 73.45, 67.16, 21.67, 15.05 ppm. HRMS (ESI-TOF): calcd. for $C_{11}H_{14}NaO_2$ $[M + Na]^+$ 201.0886; found 201.0891.

2-Ethoxy-1-(4-methoxyphenyl)ethan-1-one (4c): Yellowish solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, J = 8.9 Hz, 2 H), 6.94 (d, J = 8.9 Hz, 2 H), 4.69 (s, 2 H), 3.88 (s, 3 H), 3.64 (q, J = 7.0 Hz, 2 H), 1.29 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.1, 163.7, 130.2, 128.0, 113.8, 73.4, 67.1, 55.4, 15.10 ppm. HRMS (ESI-TOF): calcd. for $C_{11}H_{14}NaO_3$ $[M + Na]^+$ 217.0835; found 217.0844.

2-Ethoxy-1-(4-hydroxyphenyl)ethan-1-one (4d):[5a] Yellowish solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, J = 8.8 Hz, 2 H), 6.94 (d, J = 8.8 Hz, 2 H), 4.75 (s, 2 H), 3.66 (q, J = 7.0 Hz, 2 H), 1.27 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.7, 161.5, 130.5, 127.1, 115.7, 73.0, 67.3, 14.9 ppm.

***N*-[3-(2-Ethoxyacetyl)phenyl]acetamide (4e):** White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (s, 1 H), 8.05 (s, 1 H), 7.96 (d, J = 8.1 Hz, 1 H), 7.63 (d, J = 7.7 Hz, 1 H), 7.41 (t, J = 7.9 Hz, 1 H), 4.77 (s, 2 H), 3.64 (q, J = 7.0 Hz, 2 H), 2.23 (s, 3 H), 1.27 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.3, 169.0, 138.8, 135.3, 129.3, 124.9, 123.3, 118.8, 73.4, 67.2, 24.4, 15.0 ppm. HRMS (ESI-TOF): calcd. for $C_{12}H_{15}NNaO_3$ $[M + Na]^+$ 244.0950; found 244.0983.

2-Ethoxy-1-(furan-2-yl)ethan-1-one (4g): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, J = 1.6 Hz, 1 H), 7.35 (d, J = 3.6 Hz, 1 H), 6.56 (dd, J = 3.6, 1.7 Hz, 1 H), 4.58 (s, 2 H), 3.65 (q, J = 7.0 Hz, 2 H), 1.30 (t, J = 5.8 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 185.9, 150.9, 146.5, 118.1, 112.1, 73.1, 67.3, 15.0 ppm. HRMS (ESI-TOF): calcd. for $C_8H_{10}NaO_3$ $[M + Na]^+$ 177.0522; found 177.0503.

1-(3,4-Dimethylphenyl)-2-ethoxyethan-1-one (4h): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (s, 1 H), 7.67 (d, J = 7.9 Hz, 1 H), 7.21 (d, J = 7.9 Hz, 1 H), 4.73 (s, 2 H), 3.64 (q, J = 7.0 Hz, 2 H), 2.31 (s, 6 H), 1.29 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.2, 143.0, 137.0, 132.8, 129.8, 128.9, 125.5, 73.4, 67.1, 20.0, 19.7, 15.0 ppm. HRMS (ESI-TOF): calcd. for $C_{12}H_{16}NaO_2$ $[M + Na]^+$ 215.1043; found 215.1065.

Typical Experimental Procedure for the Synthesis of α-Alkoxy Ketones 7a–7e: A 25 mL Schlenk tube was charged with acetophenone (0.5 mmol), $TsNHNH_2$ (0.5 mmol, 1.0 equiv.), TBAI (0.1 mmol, 20 mol-%), TBHP (70 wt.-% in H_2O, 3.0 mmol, 6.0 equiv.), and the mixture was stirred in trifluoroethanol (2 mL) at room temperature for 16 h. Then the reaction mixture was diluted with diethyl ether (10 mL), washed with saturated $Na_2S_2O_3$ (1 mL), dried with Na_2SO_4, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography with silica gel by gradient elution with ethyl acetate in petroleum ether to obtain the corresponding product.

2-Hydroxy-1-phenylethan-1-one (7a):[14a] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 7.5 Hz, 2 H), 7.64 (t, J = 7.4 Hz, 1 H), 7.51 (t, J = 7.7 Hz, 2 H), 4.89 (s, 2 H), 3.56 (s, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.3, 134.2, 133.3, 128.9, 127.6, 65.4 ppm.

2-Hydroxy-1-(*p*-tolyl)ethan-1-one (7b):[14a] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, J = 8.2 Hz, 2 H), 7.30 (d, J = 8.1 Hz, 2 H), 4.86 (s, 2 H), 2.43 (s, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.9, 130.2, 129.6, 129.1, 127.7, 65.2, 21.7 ppm.

2-Hydroxy-1-(4-methoxyphenyl) ethan-1-one (7c):[14a] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, J = 8.9 Hz, 2 H), 6.97 (d, J = 8.9 Hz, 2 H), 4.83 (s, 2 H), 3.89 (s, 3 H), 3.60 (s, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.7, 164.3, 129.9, 126.3, 114.1, 64.9, 55.5 ppm.

1-(3,4-Dimethylphenyl)-2-hydroxyethan-1-one (7d): White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.57 (m, 2 H), 7.28–7.20 (m, 1 H), 4.83 (d, J = 11.0 Hz, 2 H), 2.34 (t, J = 13.2 Hz, 7 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.1, 144.0, 137.4, 131.2, 130.1, 128.7, 125.3, 65.2, 20.1, 19.7 ppm.

1-(4-Bromophenyl)-2-hydroxyethan-1-one (7e):[14a] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, J = 8.5 Hz, 2 H), 7.66 (d, J = 8.5 Hz, 2 H), 4.85 (s, 2 H), 3.46 (s, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.5, 132.4, 132.10, 129.6, 129.1, 65.4 ppm.

1-(4-Fluorophenyl)-2-tosylethan-1-one (7f): White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06–7.95 (m, 2 H), 7.75 (d, J = 8.0 Hz, 2 H), 7.34 (d, J = 7.9 Hz, 2 H), 7.14 (t, J = 8.4 Hz, 2 H), 4.71 (s, 2 H), 2.44 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 186.6, 166.5 (d, J = 249 Hz), 145.5, 135.7, 132.3, 129.9, 128.6, 116.3, 115.9, 63.7, 21.7 ppm. HRMS (ESI-TOF): calcd. for $C_{15}H_{13}FNaO_3S$ $[M + Na]^+$ 315.0467; found 316.0501.

Supporting Information (see footnote on the first page of this article): Synthesis and characterization data and copies of the ^{1}H and ^{13}C NMR spectra.

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Keywords: Synthetic methods · Ketones · C-O bond formation · Oxidation · Oxidative coupling

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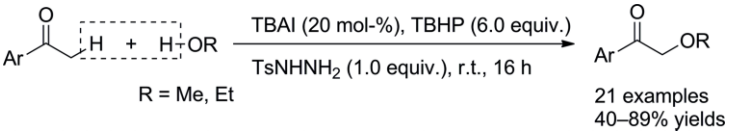

The direct oxidative coupling of aryl methyl ketones and alcohols is described in this paper. With $TsNHNH_2$ (1.0 equiv.) as the additive, aqueous TBHP (6.0 equiv.) as the oxidant, and TBAI (20 mol-%) as the catalyst, aryl methyl ketones undergo a direct alkoxylation process to provide α-methoxy or α-ethoxy ketones in moderate to good yields.

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