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I_2/TBHP-Promoted Approach to α-Keto Esters from Trifluoromethyl β-Diketones and Alcohols via C–C Bond Cleavage

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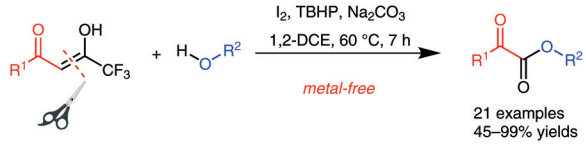

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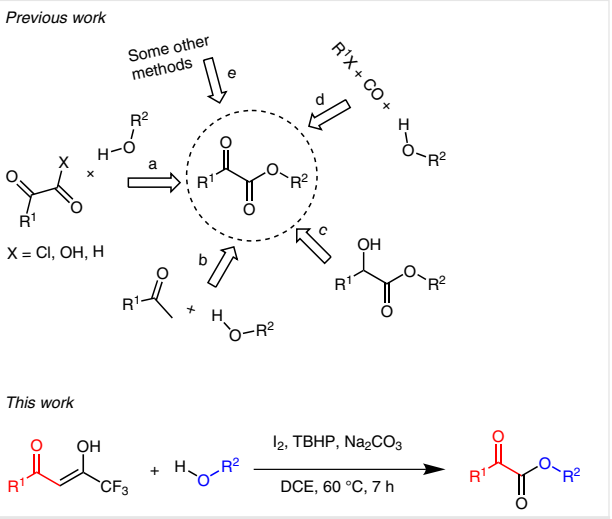
Abstract A metal-free oxidative coupling reaction of trifluoromethyl β-diketones with alcohols for the synthesis of α-keto esters in good to excellent yields has been developed. Preliminary mechanistic studies suggest that an I_2/TBHP promoted sequential iodination, C–C bond cleavage, C–O bond formation and oxidation pathway is involved in this reaction.

Key words trifluoromethyl β-diketones, α-keto esters, C–C bond cleavage, C–O coupling, alcohols

α-Keto esters are widely represented among many biologically active compounds[1] and they are also useful synthetic precursors in organic synthesis,[2] as well as being used in many enantioselective transformations.[3] As a consequence, the development of mild and efficient methods to synthesize α-keto esters is of considerable significance. Although a large number of methods to synthesize such molecules have been established, such as esterification of α-ketoacyl halides, α-carbonyl aldehydes, and α-ketoacids (Scheme 1, a),[4] direct oxidative esterification of aryl ketones with alcohols in the presence of oxidizing agents (Scheme 1, b),[5] oxidation of α-hydroxy esters (Scheme 1, c),[6] palladium-catalyzed double carbonylation of aryl halides (Scheme 1, d),[7] and some other methods (Scheme 1, e),[8] some of these methods suffer from drawbacks such as harsh reaction conditions, difficult preparation for raw materials, and use of toxic transition metals. Therefore, new protocols that can be used to construct α-keto esters from easily available materials under metal-free conditions are still highly desirable.

In recent years, molecular iodine or iodide salt (such as Bu_4NI and TBAI) in combination with *tert*-butyl hydroperoxide (TBHP) as co-oxidant have emerged as efficient protocols for intra- and intermolecular C–O, C–C or C–X (X = heteroatom) bond formation under transition-metal-free conditions.[9–11] Although I_2/TBHP or I_2/DMSO promoted C–H (sp^3) functionalization of arylmethylketones with secondary amines for the synthesis of α-ketoamides has been well studied,[12] the use of the I_2/TBHP system to promote formation of α-keto esters from easily available materials and alcohols has not been reported.

Our group has reported the decarboxylation of trifluoromethyl α-fluorinated gem-diols by cleavage of C–C bonds through a mild release of the trifluoroacetate group.[13] Herein, we want to present our work on I_2/TBHP promoted C–O bond formation between trifluoromethyl β-diketones and alcohols through iodination, C–C bond cleavage, C–O bond formation and oxidation pathway to construct α-keto esters in a one-pot synthetic strategy (Scheme 1).

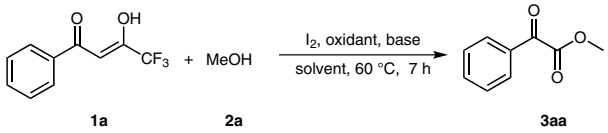


Scheme 1 Strategies for the synthesis of α-keto esters

It is noted that trifluoromethyl β-diketones exist exclusively in the enol form.[14] Initially, the reaction conditions were optimized by using 4,4,4-trifluoro-3-hydroxy-1-phenylbut-2-en-1-one (**1a**) and methanol (**2a**) as model compounds; the results are shown in Table 1. The reaction failed to proceed without TBHP or I_2 (entries 1 and 2). To our delight, methyl 2-oxo-2-phenylacetate (**3aa**) was obtained in 49% yield in the presence of 1.0 equivalent of I_2 and 1.2 equivalents of TBHP (70% aqueous solution) at 60 °C for 7 hours (entry 3). A higher yield of **3aa** (64%) was achieved with 1.0 equiv. of Na_2CO_3 (entry 4), which was attributed to accelerated cleavage of the C–C bond through mild release of the trifluoroacetate unit under basic conditions.[13,15] Variations in the loading of I_2 and TBHP suggested that 1.1 equivalents of I_2 and 2.5 equiv. of TBHP were found to be optimal amounts (entries 5–10). Attempts to improve the yield through the use of other common oxidants, such as DDQ, MnO_2 and H_2O_2, were unsuccessful (entries 11–13). A lower yield of **3aa** (74%) was obtained when the amount of Na_2CO_3 was elevated from 1.0 to 1.2 equivalents (entries 9 and 15). Other bases, such as $NaHCO_3$, NaOH, and NaOAc also were tested, but provided the product **3aa** in low yields (entries 16–18). Subsequently, screening of solvents revealed that 1,2-dichloroethane furnished the highest yield (93%) (entries 9 and 19–23). Although a catalytic amount of iodine in the I_2/TBHP system has been reported,[9–11] the conversion of the reaction was only 40% and a low yield of **3aa** (33%) was achieved with 0.3 equivalents of iodine (entry 24). Elevated reaction temperature and longer reaction time also did not afford any better results (entries 25 and 26).

With optimized conditions in hand, we next sought to define the scope of the reaction with respect to trifluoromethyl β-diketones. As shown in Scheme 2, the reaction between trifluoromethyl β-diketone bearing a methyl on the aryl and methanol showed good reaction efficiency in this protocol (**3ab**, **3ac**). However, notable differences in results were observed depending on the electronic characteristics of the functional groups on the benzene of the trifluoromethyl β-diketones. More specifically, besides the desired α-keto ester products, which were obtained in moderate yields, aryl formic methyl ester by-products (**4ad**, **4ah**, **4ai**) were also afforded in slightly lower yields with substrates bearing electron-donating groups, such as methoxy, phenyl and trifluoroethoxy (**3ad**, **3ah**, **3ai**). However, trifluoromethyl β-diketones substituted with electron-withdrawing groups, such as F, Cl, and Br, afforded the corresponding α-keto ester products in excellent yields (**3ae**, **3af**, **3ag**). A higher yield (99%) was obtained with 3,4-difluoro-substituted substrate (**3ak**). Notably, halogens, such as Br and Cl, usually provide a platform for further transformation. A good yield was achieved when sterically crowed substrate 4,4,4-trifluoro-3-hydroxy-1-(naphthalen-1-yl)but-2-en-1-one was tested (**3aj**). Unfortunately, the desired product was not detected with heterocycle substituted β-diketones as substrates, such as 4,4,4-trifluoro-1-(furan-2-yl)-3-hydroxybut-2-en-1-one (**3al**).

Table 1 Optimization of Reaction Conditions[a]

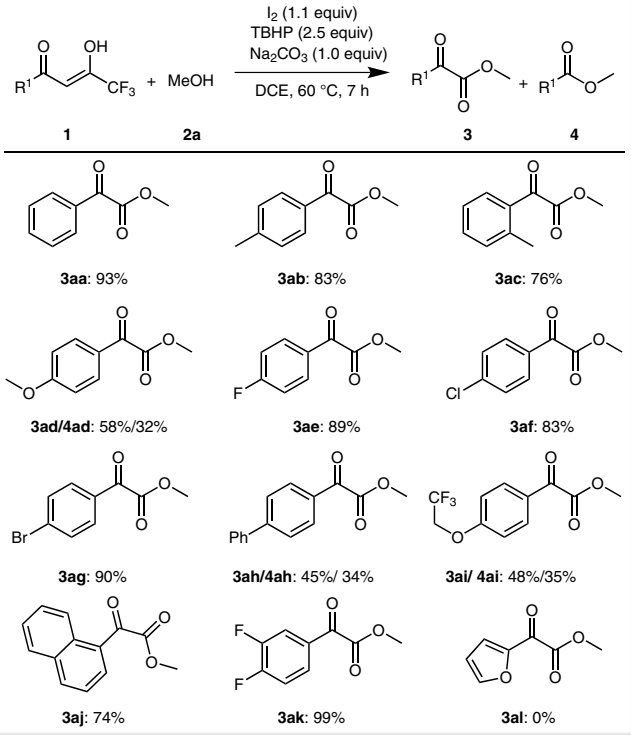


1a **2a** **3aa**

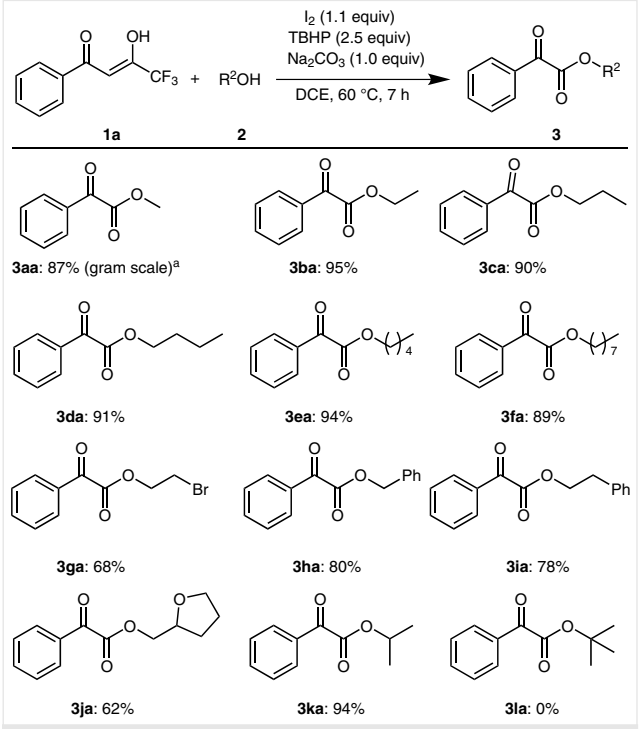
Entry	I_2 (equiv)	Oxidant (equiv)	Base (equiv)	Solvent	**3aa** (%)[b]
1	1.0	–	–	MeOH	
2	–	TBHP (1.2)	–	MeOH	–
3	1.0	TBHP (1.2)	–	MeOH	49
4	1.0	TBHP (1.2)	Na_2CO_3 (1.0)	MeOH	64
5	1.1	TBHP (1.2)	Na_2CO_3 (1.0)	MeOH	76
6	1.2	TBHP (1.2)	Na_2CO_3 (1.0)	MeOH	74
7	1.1	TBHP (1.5)	Na_2CO_3 (1.0)	MeOH	77
8	1.1	TBHP (2.0)	Na_2CO_3 (1.0)	MeOH	82
9	1.1	TBHP (2.5)	Na_2CO_3 (1.0)	MeOH	89
10	1.1	TBHP (3.0)	Na_2CO_3 (1.0)	MeOH	79
11	1.1	DDQ (2.5)	Na_2CO_3 (1.0)	MeOH	trace
12	1.1	MnO_2 (2.5)	Na_2CO_3 (1.0)	MeOH	45
13	1.1	H_2O_2 (2.5)	Na_2CO_3 (1.0)	MeOH	trace
14	NIS (1.1)	TBHP (2.5)	Na_2CO_3 (1.0)	MeOH	80
15	1.1	TBHP (2.5)	Na_2CO_3 (1.2)	MeOH	74
16	1.1	TBHP (2.5)	$NaHCO_3$ (1.0)	MeOH	47
17	1.1	TBHP (2.5)	NaOH (1.0)	MeOH	35
18	1.1	TBHP (2.5)	NaOAc (1.0)	MeOH	41
19	1.1	TBHP (2.5)	Na_2CO_3 (1.0)	DCE	93
20	1.1	TBHP (2.5)	Na_2CO_3 (1.0)	dioxane	44
21	1.1	TBHP (2.5)	Na_2CO_3 (1.0)	CH_2Cl_2	35
22	1.1	TBHP (2.5)	Na_2CO_3 (1.0)	toluene	48
23	1.1	TBHP (2.5)	Na_2CO_3 (1.0)	DMSO	85
24	0.3	TBHP (2.5)	Na_2CO_3 (1.0)	DCE	33[c]
25[d]	1.1	TBHP (2.5)	Na_2CO_3 (1.0)	DCE	92
26[e]	1.1	TBHP (2.5)	Na_2CO_3 (1.0)	DCE	93

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), I_2, TBHP, base and solvent (1.5 mL), 60 °C, 7 h, sealed tube.
[b] Isolated yield.
[c] The conversion of the reaction was 40%.
[d] The reaction mixture was heated at 80 °C for 7 h.
[e] The reaction was carried out at 60 °C for 10 h.

Various alcohols were then examined for this transformation; the results are presented in Scheme 3. We were pleased to find that the reaction between **1a** and various alcohols **2** led to the formation of α-keto ester derivatives in good to excellent yields, and no by-products were detected. Primary alcohols with different length of linear aliphatic



Scheme 2 Scope of the reaction with respect to trifluoromethyl β-diketones for the synthesis of aryl α-keto esters. *Reagents and conditions*: **1** (0.5 mmol), methanol (1.5 mmol), I_2 (0.55 mmol), TBHP (1.25 mmol), Na_2CO_3 (0.5 mmol), 1,2-dichloroethane (1.5 mL), 60 °C, 7 h, sealed tube. Isolated yields are given.

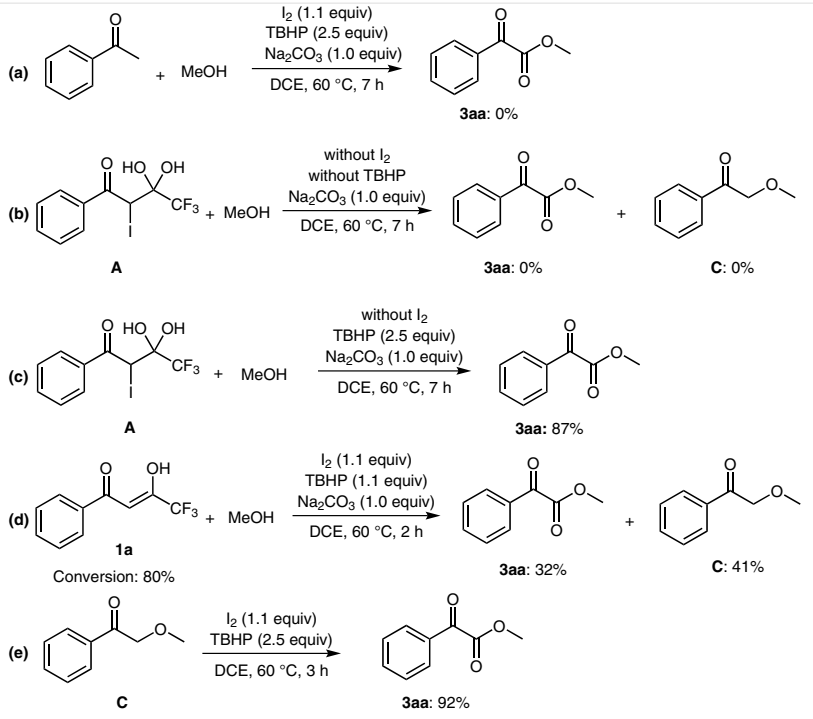


Scheme 3 Scope of the reaction with respect to alcohols for the synthesis of α-keto esters. *Reagents and conditions*: **1** (0.5 mmol), alcohol (1.5 mmol), I_2 (0.55 mmol), TBHP (1.25 mmol), Na_2CO_3 (0.5 mmol), 1,2-dichloroethane (1.5 mL), 60 °C, 7 h, sealed tube. Isolated yields are given. [a] Starting with 0.5 g **1a**.

chain, such as methyl, ethyl, propyl, butyl, pentyl and octyl, all afforded the corresponding products with excellent yields (**3aa–fa**). Moderate to good yields of α-keto esters (**3ga–ia**) were obtained when 2-bromoethanol and aromatic alcohols, such as phenylmethanol (**2h**) and 2-phenylethanol (**2i**) were tested. A moderate yield (60%) was generated when a more complex alcohol (tetrahydrofuran-2-yl)methanol (**2j**) was tested. Subsequently, a secondary alcohol, propan-2-ol (**2k**) also was tested, and excellent yields comparable to primary alcohols were generated. Unfortunately, the protocol was not applicable to tertiary alcohols, such as *tert*-butanol (**2l**). A gram-scale experiment of **3aa** was also conducted with 87% yield, thus demonstrating the scalability of our developed protocol.

To gain insight into the reaction mechanism, a number of control experiments were conducted (Scheme 4). The reaction between acetophenone and methanol did not result in the formation of methyl 2-oxo-2-phenylacetate (**3aa**) under optimized reaction conditions, which suggests that the trifluoroacetate group plays a vital role in the formation of 2-iodo-1-arylethanones (Scheme 4, a). A control experiment revealed that after removing the oxidant TBHP, the reaction between trifluoromethyl α-iodinated gem-diol **A** and methanol gave neither α-keto ester product **3aa** nor α-methoxy ketone **C** (Scheme 4, b). Furthermore, with 2.5 equiv. of TBHP added into the mixture, the reaction between iodinated gem-diol **A** and methanol gave the desired product **3aa** in 87% yield (Scheme 4, c). The TBHP played an important role in the subsequent conversion of **A** into **3aa**. When 1.1 equiv. of TBHP was used in the reaction of **1a** with methanol under the optimized conditions, the conversion of the reaction was 80% and α-keto ester **3aa** was isolated in 32% yield after 2 hours. The key intermediate, α-methoxy ketone **C** was also obtained in 41% yield (Scheme 4, d). Next, α-methoxy ketone **C** can be easily converted into the desired product **3aa** in high yield with 2.5 equiv. of TBHP (Scheme 4, e).

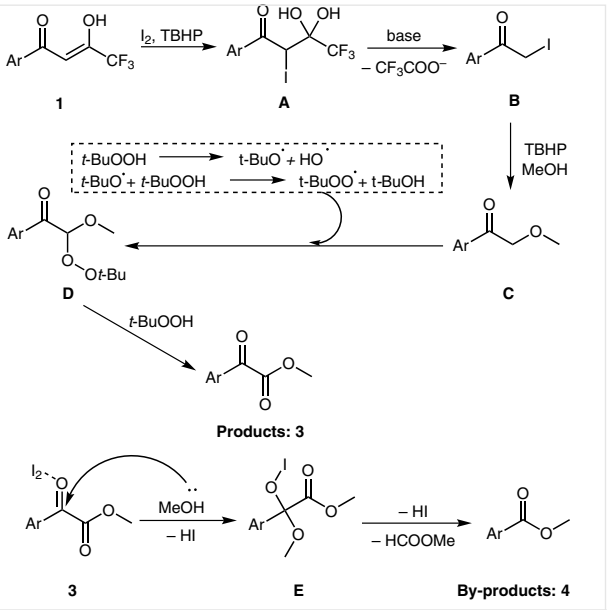
Based on the above results, a plausible mechanism for this reaction is proposed in Scheme 5. Initially, trifluoromethyl β-diketones **1** are converted into iodinated products **A** with addition of I_2/TBHP, followed by release of the trifluoroacetate unit under basic conditions to generate the key intermediate 2-iodo-1-arylethanones **B**.[14,15b] Next, **B** undergoes oxidation by TBHP, and is then attacked by MeOH to afford intermediate α-alkoxy ketones **C**.[16] The generated 2-methoxy-1-arylethanones **C** then proceed to a free radical substitution of its methylene with a *t*-BuOO$^{\cdot}$ generated from homolytic cleavage of *t*-BuOOH to generate **D**, which undergoes further oxidation by *t*-BuOOH to afford the de-



Scheme 4 Related experiments

sired α-keto ester products **3**.[12a,c] For substrates bearing electron-donating functional groups, products **3** could be further activated by molecular iodine and attacked by alcohol to afford intermediates **E**. After loss of molecular HI and release methyl formate, the aryl formic ester by-products **4** are isolated.

In conclusion, we have developed a simple, transition-metal-free, and convenient method for the synthesis of α-keto esters from easy available trifluoromethyl β-diketones and alcohols promoted by I_2/TBHP.[17]



Scheme 5 Proposed mechanism

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588833.

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(17) **Typical Procedure for the Synthesis of 3 from 1**

To a mixture of **1k** (126 mg, 0.5 mmol), methanol **2a** (48 mg, 1.5 mmol), I_2 (140 mg, 0.55 mmol), *tert*-butyl hydroperoxide (112.7 mg, 1.25 mmol) and Na_2CO_3 (53 mg, 0.5 mmol) was added 1,2-dichloroethane (1.5 mL) at room temperature. The reaction mixture was then stirred at 60 °C for 7 h. When the reaction was complete (monitored by TLC), the reaction was quenched with 2 mL of saturated NH_4Cl and 4 mL of saturated $Na_2S_2O_3$ aqueous solution. After extraction with EtOAc and drying with

Na_2SO_4, the organic layer was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using hexanes/EtOAc (100:1 to 50:1) as eluent to afford the desired products **3ak** (99 mg, 99% yield).

Methyl 2-(3,4-Difluorophenyl)-2-oxoacetate (3ak)

White solid; m.p. 38.7–40.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.91 (m, 1 H), 7.90–7.86 (m, 1 H), 7.34–7.28 (m, 1 H), 3.99 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 182.9, 162.9, 154.8 (dd, J_1 = 261.6 Hz, J_2 = 13.1 Hz), 150.5 (dd, J_1 = 253.5 Hz, J_2 = 13.1 Hz), 129.5 (t, J = 4.0 Hz), 127.7 (dd, J_1 = 8.1 Hz, J_2 = 4.0 Hz), 119.3 (dd, J_1 = 18.2 Hz, J_2 = 2.0 Hz), 117.9 (d, J = 18.2 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz): δ = –125.53 to –125.65 (m, 1 F), –134.76 to –134.87 (m, 1 F). EI-MS: *m*/*z* (%) = 63, 93, 113, 141 (100), 142, 153, 172, 184, 200. HRMS: *m*/*z* calcd for $[C_9H_6F_2O_3]^+$: 200.0285; found: 200.028.