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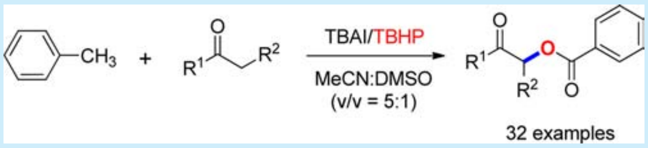
Bu$_4$NI-Catalyzed α-Oxyacylation of Carbonyl Compounds with Toluene Derivatives

Chengliang Li,[†,§] Tao Jin,[†] Xinglu Zhang,[†] Chunju Li,[†] Xueshun Jia,[*,†,§] and Jian Li[*,†,‡]

[†]Department of Chemistry, Innovative Drug Research Center, Shanghai University, 99 Shangda Road, Shanghai 200444, P. R. China
[‡]Shanghai Key Laboratory of High Temperature Superconductors, Shanghai University, Shanghai, 200444, P. R. China
[§]College of Environmental and Chemical Engineering, Shanghai University, Shanghai 200444, P. R. China

Supporting Information

ABSTRACT: A TBAI (tetrabutylammonium iodide)-catalyzed direct α-oxyacylation of carbonyl compounds from readily available toluene derivatives has been developed. The distinguished features of this metal-free protocol include the employment of simple starting material, a wide carbonyl compound scope, and mild reaction conditions.



The selective α-oxygenation of carbonyl compounds constitutes an important reactivity mode in organic synthesis, as the resultant α-oxygenated carbonyl moieties are common structural motifs in many natural products and biologically active molecules.[1] As such, transformations toward the preparation of such skeletons have been extensively investigated in the past decades.[2] Among them, the selective α-hydroxylation of Csp^3−H of ketones seems to provide a direct and efficient approach. For instance, Ritter,[3a] Jiao,[3b] and Schoenebeck[3c] reported the selective and efficient preparation of α-hydroxycarbonyls from ketones using molecular oxygen as the oxidant, respectively. On the other hand, α-oxyacylation of carbonyl compounds has also received considerable attention from the synthetic community. Traditionally, these compounds could be prepared from α-halocarbonyl compounds[4] and the oxidative coupling of carbonyl compounds with highly toxic heavy-metal oxidants.[5] To overcome the drawbacks of traditional methods, hypervalent iodines[6] and other oxidants[7] were widely investigated to promote the α-oxyacylation of ketones. More recently, reactions using other oxyacylative reagents other than carboxylic acids have also been disclosed.[8] Compared with the popularity of ketone α-oxyacylation, successful examples with other carbonyl compounds are still rare. In 2009, Maruoka and co-workers reported the α-oxybenzoylation reaction of aldehyde using benzoyl peroxide as the reagent.[9] In 2011, Ishihara and co-workers reported another intramolecular and intermolecular α-oxyacylation reaction of carbonyl compounds with carboxylic acids.[10] While impressive achievements have been made to date, most of the reported examples suffered from harsh conditions, a limited substrate scope, or highly toxic reagents. As a result, there is still a continuing demand to develop novel and environmentally benign methods with a broad scope as well as simple and readily available starting materials.

As simple and highly valuable starting materials in nature, toluene and its derivatives have found wide application in organic synthesis.[11] Among these transformations, metal-catalyzed benzylic Csp^3−H bond activation[12] of arylmethane was particularly important since it provided a new opportunity for the direct formation of a carbon−carbon and carbon−heteroatom bond in an efficient manner.[13] Additionally, the versatile reactivity of arylmethanes also made them good substrates in cascade processes involving benzylic Csp^3−H bond activation to construct structurally complex heterocyclic compounds.[14] Recently, reactions using toluene derivatives as acyl precursor became another research focus and much progress had been achieved in this area.[15] Stimulated by these fundamental works, we became interested in exploring novel reactions using toluene derivatives as versatile building blocks. Most recently, we have just disclosed a palladium-catalyzed direct synthesis of isoxazoline from toluene derivatives.[16] Our literature survey showed that the reactions between carbonyl compounds and arylmethanes remained underexploited, and only examples on C−C bond formation were reported. Li and co-workers explored an efficient CDC reaction between a benzylic C−H bond and activated ketone to form a new Csp^3−Csp^3 bond (Scheme 1, eq 1).[17] More recently, Song and co-workers developed an interesting Fe-catalyzed double CDC reaction of an arylmethane and a 1,3-dicarbonyl compound (Scheme 1, eq 2).[18] As a continuation of our previous research,[19] herein we report that, in the presence of TBAI (tetrabutylammonium iodide), the reactions between carbonyl compounds and simple arylmethanes could furnish the C−O bond formation using toluene derivatives as an oxyacylative precursor (Scheme 1, eq 3).

We began our reaction optimization using toluene **1a** and propiophenone **2a** as model substrates. As shown in Table 1, no reaction occurred when copper iodide was used as the catalyst (Table 1, entry 1). To our delight, in the presence of a catalytic amount of TBAI, heating the mixture of **1a** and **2a** afforded α-oxybenzolated compound **3a** in 64% yield (Table

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Scheme 1. Representative Transformation of Arylmethane with Ketone

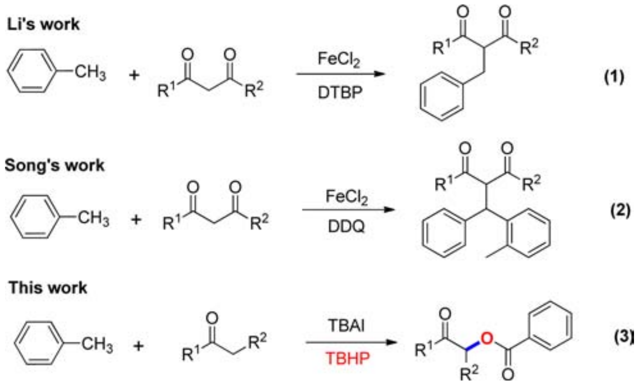


Table 1. Optimization of Reaction Conditions[a]

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

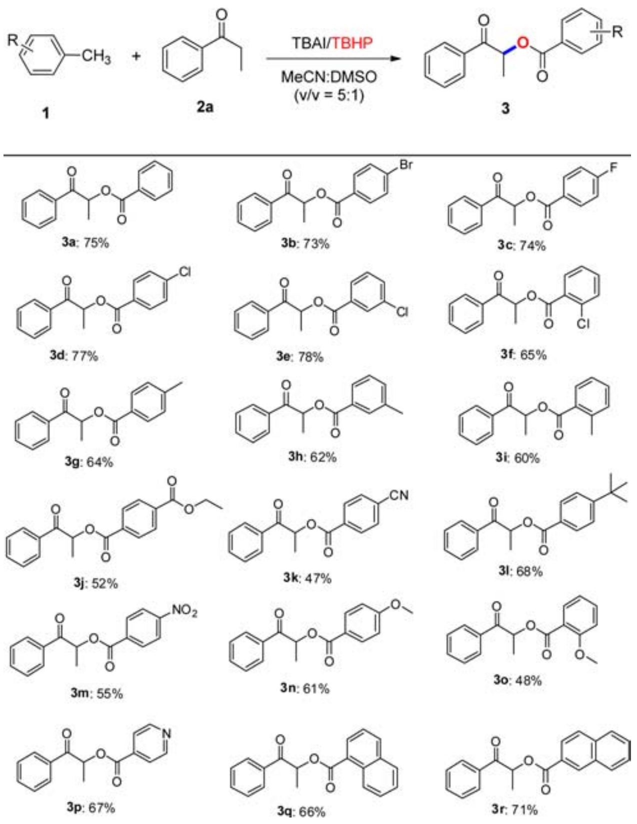
entry	catalyst	solvent	oxidant	yield (%)[b]
1	CuI	EtOAc	TBHP	0
2	NIS	EtOAc	TBHP	0
3	KI	EtOAc	TBHP	<5
4	I_2	EtOAc	TBHP	0
5	TBAI	EtOAc	TBHP	64
6	TBAI	MeCN	TBHP	65
7	TBAI	PhCN	TBHP	51
8	TBAI	PhCl	TBHP	<5
9	TBAI	DCE	TBHP	<10
10	TBAI	THF	TBHP	<5
11	TBAI	MeCN/DMSO	TBHP	75
12	TBAI	MeCN	H_2O_2	0
13	TBAI	MeCN	$K_2S_2O_8$	0
14	TBAI	MeCN	DTBP	<5
15	–	MeCN/DMSO	TBHP	0

[a] Until otherwise noted, all reactions were carried out with toluene **1a** (3 mmol), propiophenone **2a** (1 mmol), catalyst (20 mol %), oxidant (6.0 equiv), solvent (3 mL), 90 °C in sealed tube. [b] Yields of product after silica gel chromatography.

1, entry 5). Encouraged by this experimental result, we then turned our attention to the solvent screening to improve the reaction performance. The experimental outcome showed that mixed solvent MeCN/DMSO (v/v = 5:1) was found to be particularly effective to increase the yield of **3a** from 64% to 75% (Table 1, entry 11). It was also worthy to note that the oxidant also played a key role in the present reaction, and some representative results are summarized in Table 1. For instance, no reaction took place when H_2O_2 and $K_2S_2O_8$ were used (Table 1, entries 12, 13). The employment of DTBP as the oxidant only led to a very poor yield (Table 1, entry 14).

Having the optimized conditions in hand, we turned our attention to the scope and limitations of the present reaction. To establish the feasibility of substituted substrate **1**, toluene derivatives **1** bearing different substitution patterns were subsequently used to react with propiophenone **2a** under optimal conditions. Pleasingly, reactions with arylmethanes **1** having electron-withdrawing and -donating groups on the aromatic rings all worked well to give the desired products **3a**–**3o**. In particular, a wide range of substituents including halide, alkyl, nitro, and cyano groups at the *para*-, *meta*-, and *ortho*-position were well tolerated, and the representative results were summarized in Scheme 2. The experimental results also showed that strong electron-withdrawing groups on the aromatic ring seemed to decrease the reaction reactivity slightly (**3j**, **3k**, **3m**), whereas halide substituents (**3b**–**3f**) favored the formation of products **3**. Notably, the present reaction was not limited to simple benzene-based substrates; arylmethanes containing pyridyl and naphthyl groups were also proven to be compatible in the present transformation (**3p**–**3r**).

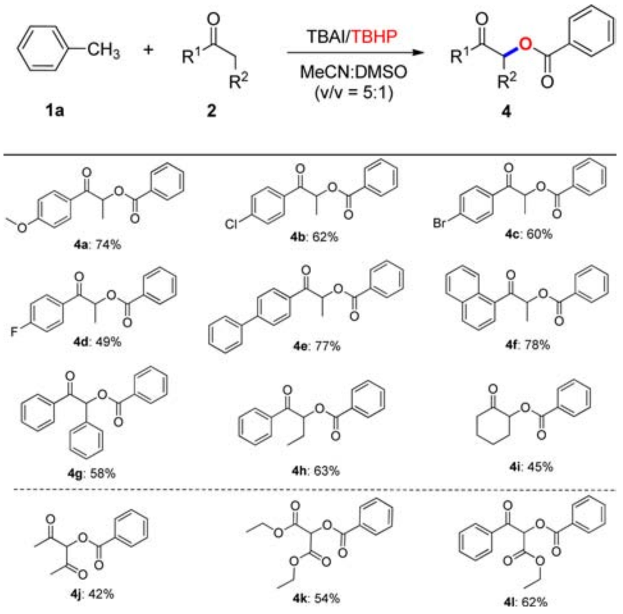
Scheme 2. Scope of the Reaction with Respect to the Arylmethane Substrate 1[a,b]



[a] Reaction conditions: arylmethane **1** (3 mmol), propiophenone **2a** (1 mmol), TBAI (20 mol %), TBHP (6.0 equiv), MeCN/DMSO (v/v = 5:1, 3 mL), 90 °C in sealed tube. [b] Yields of product after silica gel chromatography.

After having demonstrated a broad scope for substituted arylmethane, a series of structurally diverse ketones **2** were next examined to react with toluene **1a** under the optimized conditions. As shown in Scheme 3, all reactions proceeded smoothly to afford the desired products **4a**–**4i**. Upon treatment of ketone **2** bearing diphenyl and naphthyl groups other than the phenyl group, the corresponding *α*-oxy-benzolated compounds (**4e**, **4f**) were also isolated in satisfactory yields. Furthermore, aliphatic ketone was also found to be a good partner in this transformation. The reaction using cyclohexanone furnished compound **4i** in 45% yield. More importantly, 1,3-dicarbonyl compounds including 1,3-diketones, dimethylmalonate, and ketoester, underwent

Scheme 3. Scope of the Reaction with Respect to the Carbonyl Substrate 2[a,b]

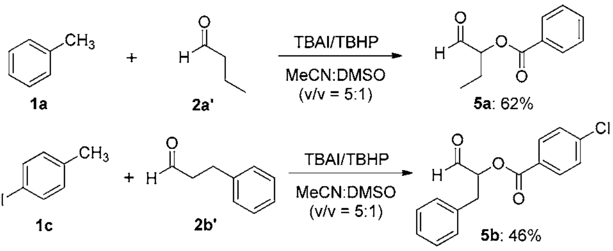


[a]Reaction conditions: toluene **1a** (3 mmol), carbonyl compound **2** (1 mmol), TBAI (20 mol %), TBHP (6.0 equiv), MeCN/DMSO (v/v = 5:1, 3 mL), 90 °C in sealed tube. [b]Yields of product after silica gel chromatography.

the present oxidative coupling to yield the desired products **4j**−**4l** with good performance.

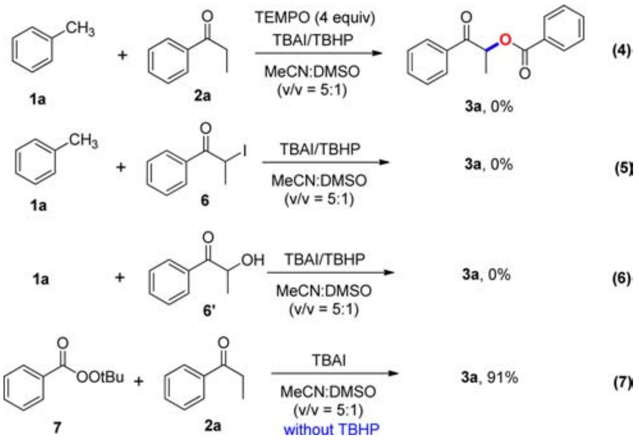
To further explore the versatility of the present reaction, we also briefly tested the possibility of aldehydes. As shown in Scheme 4, butyraldehyde **2a′** and 3-phenylpropanal **2b′** reacted smoothly to give α-oxybenzolated aldehyde **5a** and **5b**, thereby greatly expanding the carbonyl substrate scope.

Scheme 4. Scope of the Reaction with Respect to the Aldehyde



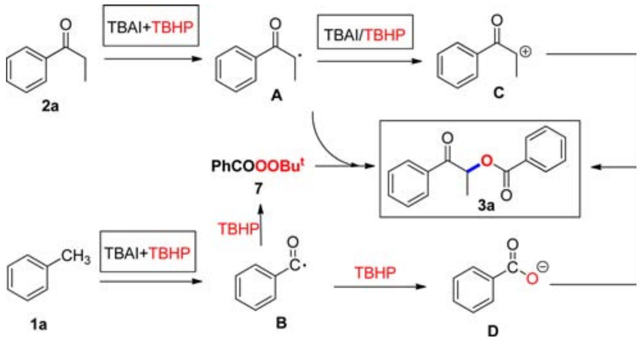
To gain further insight into the aforementioned mechanism, several mechanistic experiments were subsequently performed. First, TEMPO was added as a radical scavenger to the reaction mixture of **1a** and **2a** under optimal conditions (Scheme 5, eq 4). In such case, the desired α-oxyacylative reaction was completely inhibited and no product **3a** was observed.[20] To determine the real reaction intermediate, reactions of **1a** with 2-iodo-1-phenylpropan-1-one **6** and 2-hydroxy-1-phenylpropan-1-one **6′** were also carried out, respectively, which both failed to give the expected product **3a** (Scheme 5, eqs 5 and 6). Thus, the possibility of 2-iodo-1-phenylpropan-1-one **6** or 2-hydroxy-1-phenylpropan-1-one **6′** as the reaction intermediate could be ruled out.[21] Remarkably, the reaction between *tert*-butyl perester **7** and propiophenone **2a** under optimal conditions essentially afforded 91% **3a** in the absence of TBHP, which indicated that perester possibly was the reaction intermediate (Scheme 5, eq 7).

Scheme 5. Preliminary Mechanistic Study



On the basis of previous reports and our experimental observations, a possible reaction mechanism is depicted in Scheme 6 to explain the formation of products **3**−**5**. Initially, the propiophenone was oxidized to α-carbonyl radical **A**,[22] which involved an *in situ* generated oxidant through the oxidation of TBAI by TBHP.[23] On the other hand, toluene **1a** was oxidized by TBHP to perester **7** via intermediate **B**.[24] Coupling of radical **A** and perester **7** essentially led to the formation of product **3a**. Another possibility involved the formation of reactive cation intermediate **C**[8b] from **A**. In this case, reactions between carboxylic anion **D** and cation **C** took place to yield the final product **3a**, which contributed to another alternative route.

Scheme 6. Proposed Mechanism



In conclusion, we have described a TBAI-catalyzed direct α-oxyacylation of carbonyl compounds using simple toluene derivatives as significant building blocks. The present strategy offers several distinguishing features: (1) metal-free oxidation; (2) simplest toluene derivatives as an oxyacylative reagent; (3) a wide carbonyl compound scope, i.e. ketone, aldehyde, and 1,3-dicarbonyl compounds; and (4) mild reaction conditions. Owing to these advantages, the present strategy has the potential to be further applied in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00749.

> Experimental procedures and full characterization of all compounds, spectral data, and ^{1}H and ^{13}C NMR spectra for all products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: xsjia@mail.shu.edu.cn.
*E-mail: lijian@shu.edu.cn.

Notes

The authors declare no competing financial interest.

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