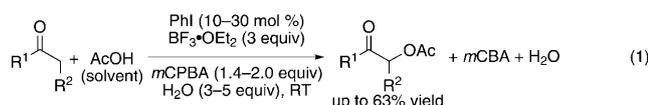


Oxidation

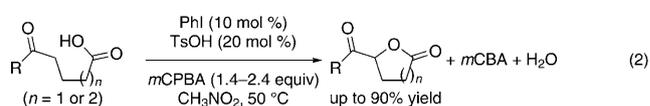
In Situ Generated (Hypo)iodite Catalysts for the Direct α -Oxyacylation of Carbonyl Compounds with Carboxylic Acids**

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α -Acyloxycarbonyl compounds, which are significant building blocks in synthetic organic chemistry, can traditionally be prepared by the substitution reaction of α -halocarbonyl compounds with alkaline carboxylates^[1] or the direct oxidative coupling of carbonyl compounds with toxic heavy metal oxidants (i.e. $\text{Pb}(\text{OAc})_4$, $\text{Tl}(\text{OAc})_3$, $\text{Mn}(\text{OAc})_3$, etc.).^[2] Recently, the chiral amine catalyzed enantioselective α -oxybenzoylation of aldehydes with benzoyl peroxide has also been reported.^[3] However, the substrate scope is still limited. Although hypervalent iodine compounds are environmentally benign alternatives to rare or toxic heavy metal oxidants, their use in catalytic amounts is still limited.^[4] In 2005, the groups of Ochiai^[5a] and Kita^[5b] independently reported the first iodosoarene (ArIL_2)-catalyzed oxidative coupling reactions using *meta*-chloroperbenzoic acid (*m*CPBA) as a co-oxidant. In particular, Ochiai et al. developed the α -oxyacylation of ketones catalyzed by the in situ generated iodine(III) in the presence of an excess amount of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in wet acetic acid [Eq. (1)].^[5a] In 2007,

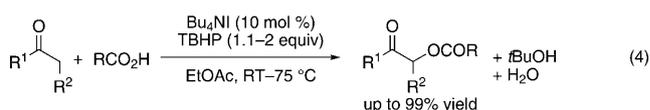
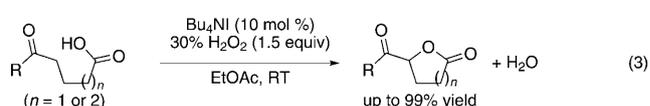


Huang and co-workers reported the same reaction under similar conditions using peracetic acid (generated in situ from Ac_2O and H_2O_2) as a co-oxidant.^[4c,5c] In 2009, we reported the oxylactonization of oxocarboxylic acids to oxolactones catalyzed by the in situ generated PhIL_2 in the presence of a catalytic amount of TsOH [Eq. (2)].^[6] The major drawbacks of these iodosoarene-catalyzed systems are: 1) harsh reaction conditions were required, 2) low chemoselectivity was observed (competing with Baeyer–Villiger oxidation), 3) *meta*-chlorobenzoic acid (*m*CBA) was generated as



waste, and 4) excess amounts of carboxylic acids were required.

We report here intra- [Eq. (3)] and intermolecular [Eq. (4)] oxidative coupling reactions of carbonyl compounds with carboxylic acids catalyzed by in situ generated tetra-



butylammonium (hypo)iodite with either hydrogen peroxide or *tert*-butyl hydroperoxide (TBHP) as an environmentally benign oxidant.^[7,8] The most important features of the present catalytic system are: 1) metal-free oxidation, 2) milder reaction conditions, 3) high chemoselectivity, 4) wide range of substrates, that is ketones, aldehydes, 1,3-dicarbonyl compounds, and carboxylic acids, and 5) water or *tert*-butyl alcohol is the only by-product derived from the co-oxidant used.

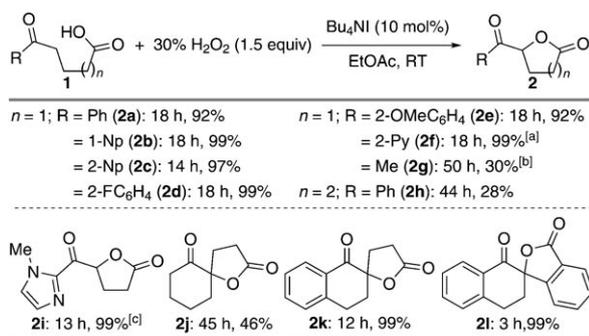
Initially, we found that tetra *n*-butylammonium iodide (*n*Bu₄NI) was highly effective as a pre-catalyst for the oxylactonization of oxocarboxylic acids **1** with commercially available 30% aqueous hydrogen peroxide even at room temperature (Scheme 1).^[9] These results are comparable with our previous results using iodobenzene with *m*CPBA [Eq. (2)].^[6a] Importantly, no Baeyer–Villiger products were obtained under the present reaction conditions. Both γ -arylcarbonyl- γ -butyrolactones (**2a–2e**, **2k**, and **2l**) and γ -heteroarylcarbonyl- γ -butyrolactones (**2f** and **2i**) were obtained in high yield. However, γ -alkylcarbonyl- γ -butyrolactones (**2g** and **2j**) and δ -benzoyl- δ -valerolactone (**2h**) were obtained in moderate yields.

Next, we focused on the intermolecular coupling of ketones with carboxylic acids. The oxidative coupling of propiophenone (**3a**) with benzoic acid (**4a**) under reaction conditions similar to those in Scheme 1 using a catalytic amount of Bu_4NI with 30% aqueous H_2O_2 at room temper-

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Scheme 1. Oxylactonization of oxocarboxylic acids **1**. Reaction times and yields of isolated **2** are shown. For details, see the Supporting Information. [a] 2.5 equiv of H₂O₂ were used. [b] Reaction was performed at 50 °C. [c] Toluene/H₂O (2:1 v/v) was used as a solvent. Np = naphthyl, Py = pyridinyl.

ature or higher temperatures (up to 75 °C) gave α -benzoyloxy ketone **5aa** in low yield (up to 5%), and unreacted starting materials were recovered. Fortunately, we found that a commercial solution of TBHP in anhydrous nonane or decane was much more effective than aqueous hydrogen peroxide as a co-oxidant (Table 1).^[9] Thus, equimolar

Table 1: α -Oxyacylation of propiophenone (**3a**) with carboxylic acids **4**.^[a]

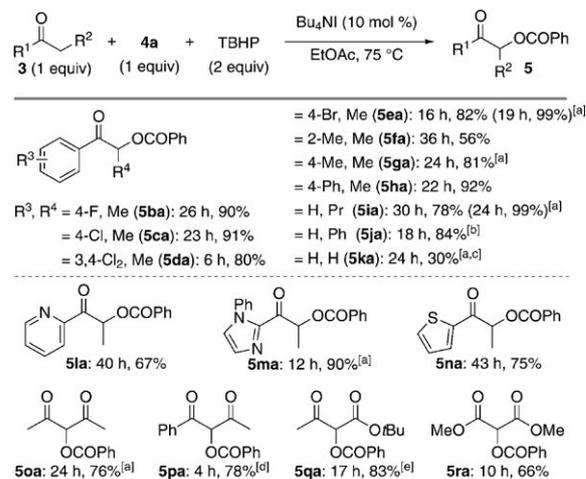
Entry	R (4)	5	t [h]	Yield [%] ^[b]
1	Ph (4a)	5aa	38	79 (84) ^[c]
2 ^[d]	Ph (4a)	5aa	24	99
3 ^[e]	Ph (4a)	5aa	48	76 ^[c]
4 ^[d]	4-MeC ₆ H ₄ (4b)	5ab	23	91
5 ^[d]	4-NO ₂ C ₆ H ₄ (4c)	5ac	53	85
6	Me (4d)	5ad	29	61
7	CH ₂ =CH (4e)	5ae	24	57 (72) ^[d]
8	CH ₂ =C(Me) (4f)	5af	24	61 (72) ^[d]

[a] Unless otherwise noted, an anhydrous solution of TBHP in decane or nonane was used. For details, see the Supporting Information. [b] Unless otherwise noted, yields of isolated **5** are shown. [c] Determined by ¹H NMR analysis. [d] 2 equiv of **3a** were used. [e] A 70% aqueous solution of TBHP was used.

amounts of **3a** and **4a** were heated in the presence of 10 mol % Bu₄NI and 2 equivalents of TBHP in EtOAc to give **5aa** in 79% yield (entry 1). The use of 2 equivalents of **3a** gave **5aa** quantitatively within a shorter reaction period (entry 2). Commercially available 70% aqueous TBHP could also be used instead of anhydrous TBHP (entry 3). The oxidative coupling of **3a** with *p*-toluic acid **4b** also gave **5ab** in good yield (entry 4). However, the coupling reaction with *p*-nitrobenzoic acid **4c** was relatively slow (entry 5). The α -oxyacylation of **3a** gave the corresponding product **5ad** in moderate yield (entry 6). Importantly, polymerizable acrylic acid **4e** and methacrylic acid **4f** could be used as substrates under our reaction conditions, although the yields of the corresponding coupling products **5ae** and **5af** were moderate

(entries 7 and 8). α -Acryloyloxy ketones are used industrially as starting materials for the production of polymers.^[10]

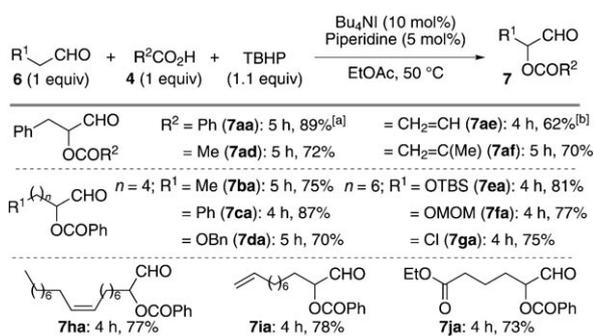
To explore the generality and scope of the present α -oxyacylation, several ketones as well as 1,3-dicarbonyl compounds were examined as substrates to react with benzoic acid (**4a**) under the optimized reaction conditions (Scheme 2). Propiophenones **3b–3h**, which are substituted with electron-donating or electron-withdrawing groups, gave



Scheme 2. α -Oxybenzoylation of ketones (**3b–3n**) and 1,3-dicarbonyl compounds (**3o–3r**). Reaction times and yields of isolated **5** are shown. For details, see the Supporting Information. [a] 2.0 equiv of **3** were used. [b] 5 mol % of Bu₄NI was used. [c] Yield was determined by ¹H NMR analysis. [d] Reaction was performed at 50 °C. [e] Reaction was performed at RT.

the corresponding α -benzoyloxy ketones **5ba–5ha** in good to excellent yields. However, the oxidative coupling of acetophenone (**3k**) gave the desired product **5ka** in only 30% yield. Notably, α -benzoyloxy heteroaryl ketones (**5la–5na**) were obtained in high yields. Oxidative coupling of 1,3-diketones (**5oa** and **5pa**), a ketoester (**5qa**), and dimethylmalonate (**5ra**) gave the corresponding α -benzoyloxy carbonyl compounds in good yields. In general, the reactivity was increased by the excess use of ketones.

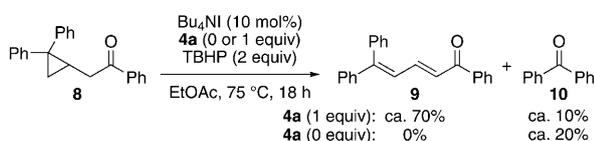
The α -oxyacylation of aldehydes was also examined (Scheme 3). The oxidative coupling of 3-phenylpropanal (**6a**) with **4a** gave a messy reaction mixture under reaction conditions identical to those used for the coupling of ketones **3**. Self-aldol and oxidative dehydrogenation products were obtained along with several unidentified products. We found that the addition of a catalytic amount of piperidine was effective as an additive under milder conditions (50 °C) for enhancing product selectivity (Scheme 3).^[9] Thus, equimolar amounts of **6a** and **4a** were heated in the presence of 10 mol % Bu₄NI, 5 mol % of piperidine, and 1.1 equivalents of TBHP in EtOAc at 50 °C to give α -benzoyloxy aldehyde **7aa** in 89% yield. Several aldehydes (**6**) and acids (**4**) were examined as substrates under the optimized reaction conditions (Scheme 3). Interestingly, the oxidative coupling of **6a** with acetic acid (**4d**) gave the desired **7ad** in higher yield than ketone **3a** (Scheme 3 versus entry 6 in Table 1). Acrylic acid



Scheme 3. α -Oxyacylation of aldehydes **6**. Reaction times and yields of isolated **7** are shown. For details, see the Supporting Information. [a] 2 mol% of piperidine was used. [b] 20 mol% of Bu_4NI was used. Bn = benzyl, TBS = *tert*-butyldimethylsilyl, MOM = methoxymethyl.

(**4e**) and methacrylic acid (**4f**) could be used as coupling partners for **6a** as well as **3a**, and the corresponding **7ae** and **7af** were obtained in good yields. Several functional groups such as terminal or internal alkenyl (**7ae**, **7af**, **7ha**, **7ia**), benzyloxy (**7da**), silyloxy (**7ea**), acetal (**7fa**), halogen (**7ga**), and ester (**7ja**) groups, were tolerated under these conditions.

Several control experiments were run to identify the active iodine species under the present reaction conditions,^[9] and the results suggested that either ammonium hypoiodite ($[\text{Bu}_4\text{N}]^+[\text{IO}]^-$) or iodite ($[\text{Bu}_4\text{N}]^+[\text{IO}_2]^-$), which should be generated in situ from ammonium iodide (Bu_4NI) and a co-oxidant, might be the active species.^[7,11] We conducted additional control experiments to gain insight into the reaction pathway using the well-established fragmentation of cyclopropylmethyl radicals.^[12] The reaction of diphenylcyclopropyl ketone **8** with **4a** under the present reaction conditions gave the rearranged conjugated diene **9** and benzophenone **10** in approximately 70% and 10% yield, respectively, along with several unidentified side products (Scheme 4). The desired α -benzoyloxy ketone was not observed. Interestingly, **10** was obtained as the only isolated product in the absence of **4a** (Scheme 4).^[13] These results suggest that the reaction mechanism most likely includes a radical intermediate.^[12] Additional studies on the reaction mechanism are underway.



Scheme 4. Control experiments with **8**.

In conclusion, we developed a general intra- and intermolecular direct α -oxyacylation reaction catalyzed by an in situ generated ammonium (hypo)iodite species using either hydrogen peroxide or TBHP as an environmentally benign oxidant. The oxidative coupling of several structurally diverse ketones, aldehydes, and 1,3-dicarbonyl compounds with carboxylic acids gave the corresponding α -acyloxycarbonyl compounds in good to excellent yields. Studies to elucidate

the detailed reaction mechanism and achieve enantioselective oxidative coupling are underway in our laboratory.

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