DOI: 10.1002/adsc.201100920

# A Metal-Free Oxidative Esterification of the Benzyl C–H Bond

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Received: November 25, 2011; Revised: January 19, 2012; Published online: April 26, 2012

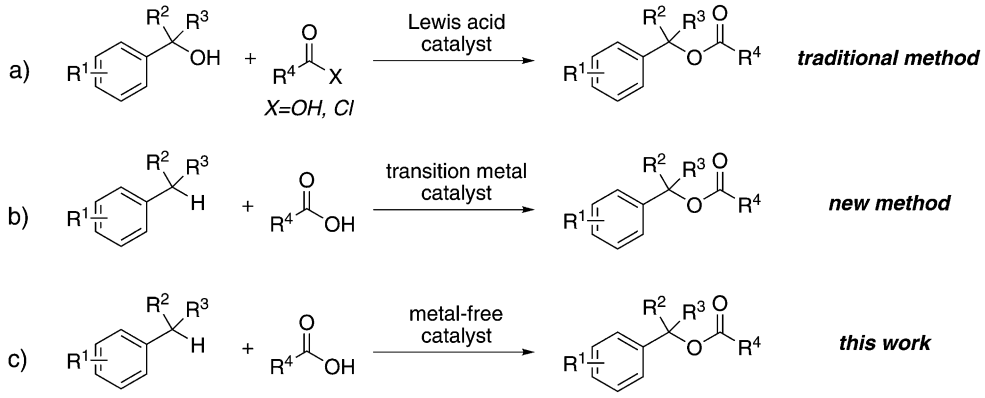
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201100930.

**Abstract:** An efficient metal-free oxidative esterification of benzyl C–H bonds was developed. Using tetrabutylammonium iodide as catalyst and *tert*-butyl hydroperoxide as co-oxidant, benzylic substrates could react smoothly with various carboxylic acids to give the esters with good to excellent yields. The method was also suitable for the *O*-protection of *N*-Boc amino acids. The reaction mechanism was primarily investigated and a radical process was proposed.

**Keywords:** benzyl C–H bond; esterification; metal-free catalyst; protected amino acids; tetrabutylammonium iodide

Benzyl esters are important functional groups in medicinal and natural organic compounds.[1] Meanwhile, they also act as the essential protecting groups in amino acids and their derivatives.[2] Benzyl esters have commonly been prepared by esterification of the corresponding benzyl alcohols with carboxylic acids over the decades (Scheme 1, equation a).[3] With the considerable developments in C–H activation during the last few years,[4] a new method of esterification has been studied widely: esters were synthesized through oxidative coupling reactions from common C–H substrates which served as starting materials.[5] Several types of transition metals, including palladium,[5a–e] copper,[5f] rhodium[5g] and platinum[5h] exhibited excellent catalytic activity in this new C–H activating esterification (Scheme 1, equation b). However, some drawbacks such as toxicity, sensitivity to the environment, and being hard to handle after reactions, are associated with the usage of metal catalysts. Therefore, increasing interest has been focused on metal-free catalysts.

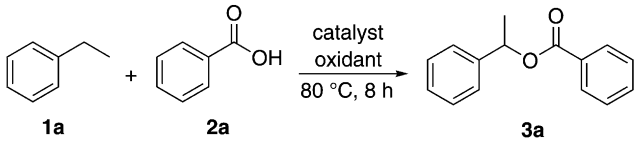
In 2010, Ishihara and co-workers reported a new class of metal-free catalysts based on quaternary ammonium iodides.[6] These reagents were used to catalyze the highly enatioselective intramolecular cycloetherification of ketophenols. After that, Ishihara[7] and Wan,[8] respectively applied such a tetrabutylammonium iodide catalyst to the oxidative esterification of α-C–H bonds of carbonyl and ether substrates. Very recently, Nachtsheim and co-workers reported the oxidative amination catalyzed by $Bu_4NI$ *via* preactivation of acetic acid.[9] These reports revealed that




**Scheme 1.** Different pathways for the synthesis of benzyl esters.

**Table 1.** Optimization of the reaction conditions.[a]



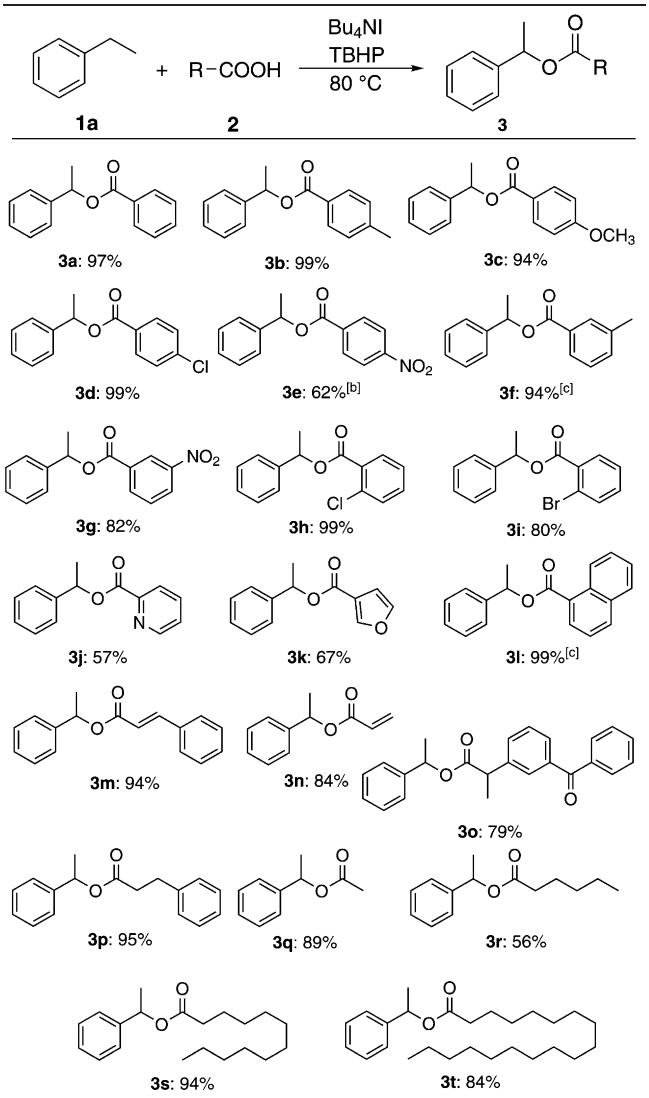

| Entry | Catalyst (mol%) | Oxidant (equiv.)[b] | Yield [%][c] |
|---|---|---|---|
| 1 | $Bu_4NI$ (20) | TBHP (2) | 98 |
| 2 | $Bu_4NI$ (20) | *t*-BuOO-*t*-Bu (2) | N.R. |
| 3 | $Bu_4NI$ (20) | $H_2O_2$ (2) | N.R. |
| 4 | $Bu_4NI$ (20) | DDQ | trace |
| 5 | $Bu_4NI$ (20) | $PhI(OAc)_2$ | 29 |
| 6 | – | TBHP (2) | N.R. |
| 7 | $Bu_4NF$ (20) | TBHP (2) | trace |
| 8 | $Bu_4NCl$ (20) | TBHP (2) | trace |
| 9 | $Bu_4NBr$ (20) | TBHP (2) | trace |
| 10 | NaI (20) | TBHP (2) | trace |
| 11 | CuI (20) | TBHP (2) | N.R. |
| 12 | $Bu_4NI$ (10) | TBHP (2) | 91 |
| 13 | $Bu_4NI$ (5) | TBHP (2) | 78 |
| 14 | $Bu_4NI$ (20) | TBHP (1) | 31 |
| 15[d] | $Bu_4NI$ (20) | TBHP (2) | 52 |

[a] *Reaction conditions:* benzoic acid (1 mmol) and ethylbenzene (20 mmol) at 80 °C for 8 h unless otherwise noted.
[b] Experiments were performed with pure *t*-BuOO-*t*-Bu and TBHP (75% aqueous solution) or $H_2O_2$ (30% in water).
[c] Yield of isolated product.
[d] Reaction was performed with ethylbenzene (5 mmol) in EtOAc as solvent.

the carboxylic acids could be coupled with highly reactive C–H substrates catalyzed by $Bu_4NI$ under oxidative conditions. Herein, we expand the application of the $Bu_4NI$-catalyzed esterification by using benzyl C–H containing substrates (Scheme 1, equation c). These compounds were demonstrated to be suitable for the oxidative coupling with a variety of carboxylic acids including *N*-Boc amino acids, and gave the desired ester products with good to excellent yields.

Benzoic acid and ethylbenzene were chosen as model substrates to optimize the conditions of oxidative coupling, and the results are summarized in Table 1. To our delight, the combination of $Bu_4NI$ (20 mol%) and *tert*-butyl hydroperoxide (TBHP, 2 equiv.) exhibited excellent catalytic activity and gave the desired product **3a** with 98% yield (entry 1). The use of some other peroxides or common oxidants instead of TBHP decreased the yields dramatically (entries 2–5). $Bu_4NI$ is the essential element for the reaction. No reaction happened without the use of $Bu_4NI$ (entry 6), and only traces of product were detected after the change of anions on the quaternary ammonium salts (entries 7–9). Other iodides such as NaI and CuI also showed no catalytic activity (entries 10 and 11). Decreasing the amount of $Bu_4NI$ to 10 mol% led to slightly decreased yield of 91%, while a further reduced yield of 78% was obtained with the use of 5 mol% $Bu_4NI$ (entries 12 and 13). The reaction employing only 1 equiv. of TBHP also gave product **3a** in dramatically decreased yield (entry 14). In addition, ethylbenzene was used as both substrate and solvent in this reaction. The yield dropped to 52% after the decreasing the amount of ethylbenzene and using ethyl acetate as solvent (entry 15).

**Table 2.** The coupling reactions between a variety of carboxylic acids and ethylbenzene.[a]

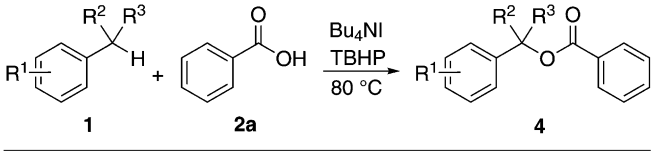



[a] *Reaction conditions:* carboxylic acid (1 mmol), ethylbenzene (20 mmol), $Bu_4NI$ (20 mol%), TBHP (2 equiv., 75% aqueous solution), 80 °C, 8 h.
[b] Reaction time was 10 h.
[c] Reaction time was 3 h.

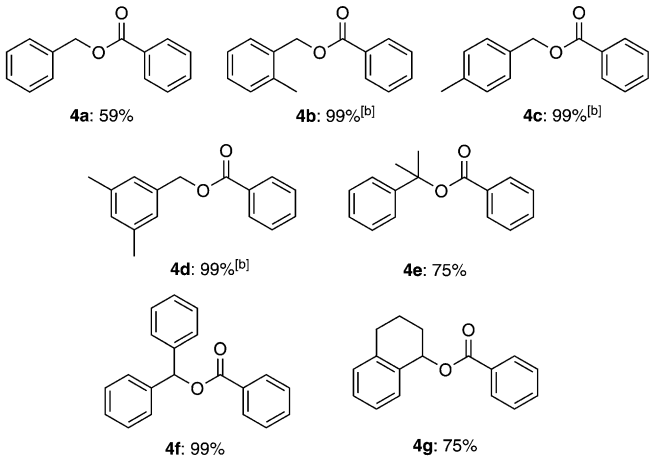
A wide range of carboxylic acids was then employed for oxidative coupling with ethylbenzene under our optimized conditions (Table 2). Various benzoic acids with electron-donating and electron-withdrawing substituents could be converted to the

**Table 3.** The coupling reactions between benzoic acid and hydrocarbons.[a]




1 2a 4

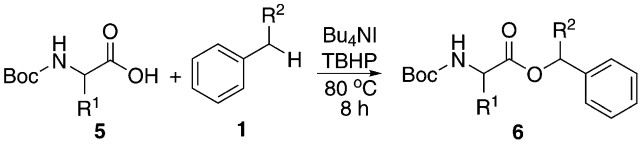



[a] *Reaction conditions:* benzoic acid (1 mmol), benzyl C–H substrate (20 mmol), $Bu_4NI$ (20 mol%), TBHP (2 equiv., 75% aqueous solution), 80 °C, 10 h.
[b] Reaction time was 3 h.

desired products (**3b–3i**) in good to excellent yields. Remarkably, some *ortho*-substituted benzoic acids (**3h** and **3i**) with steric hindrance also gave the products with high yields. 1-Naphthoic acid **2l** could give the ester product almost quantitatively, while heterocyclic carboxylic acids such as α-pycolinic acid **2j** and β-furoic acid **2k** gave the respective products in moderate yields. Some aliphatic carboxylic acids also reacted smoothly with ethylbenzene to give products **3m–3t**. Among these samples, the synthesis of 1-phenylethyl 2-(3-benzoylphenyl)propanoate (**3o**) was an important modification of ketoprofen, a common antiphlogistic drug.[10] Despite the bulky long chain, some fatty acids could give the ester products with good yields (**3s**, **3t**). These results demonstrate the universality of this oxidative esterification method.

Subsequently, different substrates with benzylic C–H bonds were tested for this esterification with benzoic acid. As shown in Table 3, toluene reacted with benzoic acid to give the product **4a** in only moderate yield (59%). But for xylenes (**1b** and **1c**) or mesitylene (**1d**), nearly quantitative yields were obtained. This might be due to the more reactive positions (benzyl C–H bonds) on xylene and mesitylene than those on toluene. Additionally, both xylenes and mesitylene gave only the mono-ester product with high selectivity, and no multi-ester was detected. Other

**Table 4.** The coupling reactions between *N*-Boc amino acids and benzyl C–H substrates.[a]




5 1 6

| Entry | Amino acid derivatives | Substrate **1** | Product | Yield [%] |
|---|---|---|---|---|
| 1 | Boc-Gly | toluene | **6a** | 69 |
| 2 | | ethylbenzene | **6b** | 85 |
| 3 | L-Boc-Ala | toluene | **6c** | 64 |
| 4 | | ethylbenzene | **6d** | 83 |
| 5 | L-Boc-Leu | toluene | **6e** | 80 |
| 6 | | ethylbenzene | **6f** | 99 |
| 7 | L-Boc-Phe | toluene | **6g** | 82 |
| 8 | | ethylbenzene | **6h** | 67 |
| 9 | L-Boc-Pro | toluene | **6i** | 61 |
| 10 | | ethylbenzene | **6j** | 90 |

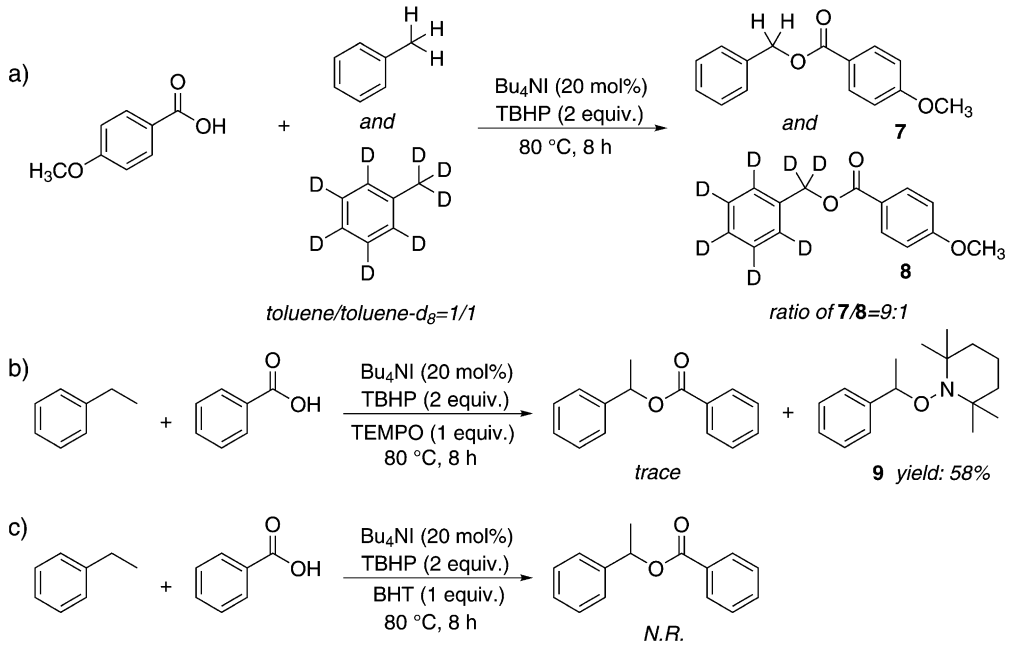
[a] *Reaction conditions:* carboxylic acid (1 mmol), ethylbenzene (20 mmol), $Bu_4NI$ (20 mol%), TBHP (2 equiv., 75% aqueous solution), 80 °C, 8 h.

substrates like cumene **1e**, which has only one benzyl C–H bond, could also react with benzoic acid to give the product **4e** in 75% yield. The quantitative yield from the reaction of diphenylmethane **1f** might be attributed to the more stable intermediate of the coupling. Meanwhile, the polycyclic substrate tetralin **1g** also only gave mono-ester product **4g** with 75% yield.

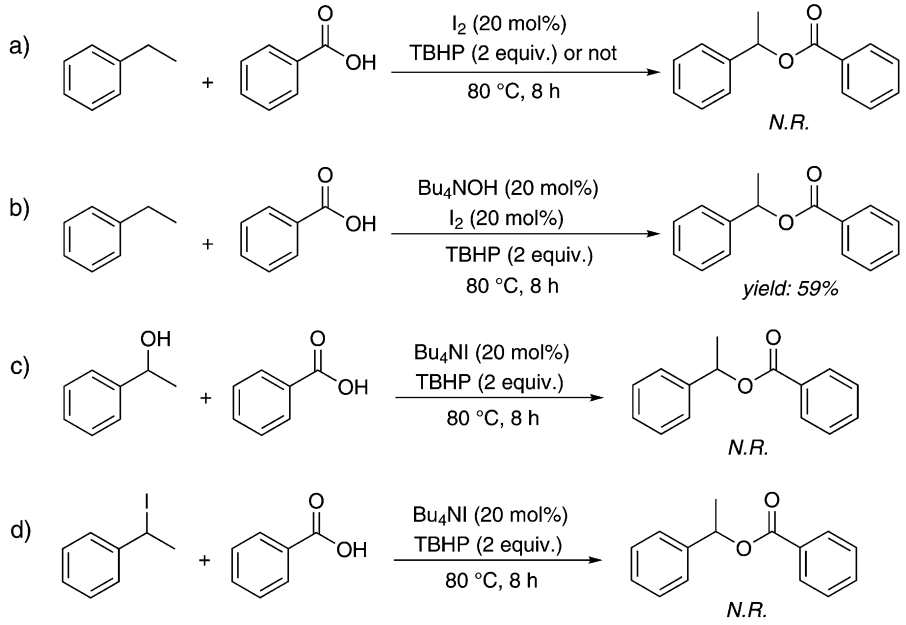
The protection of carboxylic groups on amino acids plays an important role in the synthesis or modification of peptides.[11] The positive results obtained above encouraged us to investigate this metal-free catalytic system toward the protection of amino acids. To our delight, the method was suitable for a series of *N*-Boc-protected amino acids (Table 4). Except phenylalanine, all *N*-Boc-protected amino acids reacted with ethylbenzene to give the ester product in higher yields than those with toluene. It is worth mentioning that the optical rotation measurement and chiral HPLC analysis proved the maintenance of the optical activities of the amino acid derivatives after the reaction (see the Supporting Information). Therefore this method could be an efficient protection method for amino acids. In addition, non-protected amino acids could not give the similar ester product, and this might be attributed to the free amino group which is unfavorable for the reaction.

Several control experiments were performed to probe the reaction mechanism (Scheme 2). Firstly, the competitive esterifications involving toluene and its deuterated derivative toluene-$d_8$ were performed (Scheme 2, equation a). Obvious kinetic isotope effects ($k_H/k_D = 9/1$) was observed, indicating that the cleavage of benzyl C–H bond is involved in the rate-




**Scheme 2.** Investigation of the reaction mechanism. *Reaction conditions:* carboxylic acid (1 mmol), benzyl C–H substrate (20 mmol).

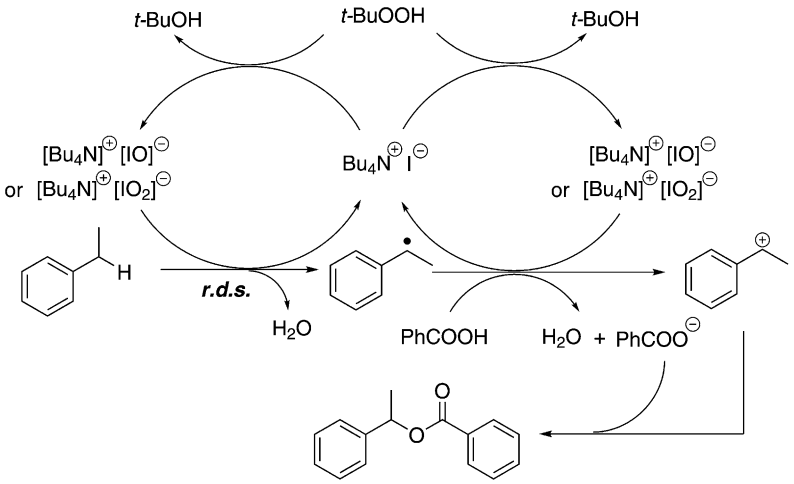



**Scheme 3.** Investigation of the catalytically active species and the reaction intermediate. *Reaction conditions:* benzoic acid (1 mmol), ethylbenzene, 1-phenylethanol or α-iodoethylbenzene (20 mmol).

determining step. Secondly, addition of the radical scavenger 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) decreased the yield of the model reaction (Scheme 2, equations b and c). In the reaction using TEMPO, the oxyamination product **9**, which was formed through the trapping of the benzyl radical by TEMPO, was separated in 58% yield. The results indicates that the benzyl radical was involved in the catalytic cycle of this esterification.[12]

The mechanisms of polyvalent iodine-catalyzed functionalizations were comprehensively discussed in recent reports. Wan and co-workers suggested that the reaction of $Bu_4NI$ with oxidant generates iodine




**Scheme 4.** Proposed reaction mechanism. *Reaction conditions:* benzoic acid (1 mmol) and ethylbenzene (20 mmol) at 80 °C for 8 h.

which further captures the single electron from the reactant.[8,13] Ishihara and other groups speculated an alternative mechanism that involves hypoiodite as the actual oxidant.[7,9,14] Wei and co-workers determined $[IO_2]^-$ as the catalytically active species by ESI-MS analysis, although they could not rule out the possibility of $[IO]^-$ species.[14] Hence, more control experiments were needed to elucidate the reaction mechanism of this transformation. As shown in Scheme 3, replacing $Bu_4NI$ with $I_2$ led to no product (Scheme 3, equation a). However, the combined using of $Bu_4NOH$ and $I_2$ well catalyzed the same esterification in 59% yield (Scheme 3, equation b). This result is similar to those reported by Ishihara,[6] in which the *in situ* generated hypoiodite ($[IO]^-$ or $[IO_2]^-$) plays an important role in the reaction process. To find out whether benzyl alcohol or benzyl iodide was formed *in situ* as active intermediate, the two compounds were applied to the title reaction with benzoic acid respectively (Scheme 3, equations c and d). No ester product was obtained in both reactions.

From the results of the control experiments and the studies reported by Kita[15] and Shi,[4h] we speculate that, during the reaction, the benzyl radical is oxidized by hypoiodite to generate the benzyl cation, leading to subsequent reaction with carboxylic acid. A plausible reaction mechanism was proposed as shown in Scheme 4. Initially, $Bu_4NI$ is oxidized by TBHP to form the $\{[Bu_4N]^+[IO]^-\}$ or $\{[Bu_4N]^+[IO_2]^-\}$ species, which is going to induce the homolysis of a benzyl C–H bond to give a benzyl radical. This is the rate-determining step in the whole reaction. The single electron of hydrogen is captured by hypoiodite which is subsequently reduced to $Bu_4NI$. The benzyl radical is liable to be oxidized by the hypoiodite species to form the benzyl cation. In this redox process, the excess oxygen atom of hypoiodite captures the proton of benzoic acid to give the benzoate anion and a water molecule. The final coupling between the benzoate anion and benzyl cation gives the ester product.

In conclusion, we have described the direct esterification of a benzyl C–H bond catalyzed by tetrabutylammonium iodide and TBHP as co-oxidant. This metal-free catalytic system is suitable for the coupling reactions between a wide range of carboxylic acids and benzyl substrates. It could be conveniently applied to the *O*-benzyl protection of amino acids. Based on the control experiments, a radical catalytic cycle was proposed. Further studies to elucidate the mechanism and to expand the synthetic scope of this reaction are currently in progress.

## Experimental Section

### General Esterification of Carboxylic Acids with Benzyl C–H Substrates

A reaction vessel was charged with tetrabutylammonium iodide (74 mg, 0.2 mmol, 20 mol%), carboxylic acid (1 mmol). After the addition of the benzyl C–H substrate (20 mmol, 20 equiv.) and TBHP (70% wt% in water, 300 μL, 2 mmol, 2 equiv.), the reaction mixture was stirred at 80 °C in the air until fully conversion by TLC observation. After recovering excess benzylic component by distillation, the reaction was quenched by addition of a saturated solution of sodium thiosulfate. The mixture was extracted with ethyl acetate (3×5 mL), the combined organic phases were dried over $Na_2SO_4$ and the solvent was evaporated under vacuum. The crude residue was purified by column chromatography (silica gel, petroleum ether:ethyl acetate, 20:1 v/v) to afford the respective product.

## Acknowledgements

*This work was financially supported by the National Science Foundation of China (Nos. 21021001, 20972104), the Program for Changjiang Scholars and Innovative Research Team in University, the Key Project of Chinese Ministry of Education, and the Scientific Fund of Sichuan Province for Outstanding Young Scientists. We also thank the Sichuan University Analytical and Testing Center for NMR spectroscopic analysis.*

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