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Efficient Photolytic C–H Bond Functionalization of Alkylbenzene with Hypervalent Iodine(III) Reagent

Ryu Sakamoto, Tsubasa Inada, Sermadurai Selvakumar, Shin A. Moteki and Keiji Maruoka[*]

**A practical approach in the radical C–H bond functionalization by the photolysis of hypervalent iodine(III) reagent is presented. The photolysis of [bis(trifluoroacetoxy)iodo]benzene (PIFA) leads to the generation of trifluoroacetoxy radicals that allows the smooth transformation of various alkylbenzenes to the corresponding benzyl ester compounds under mild reaction conditions.**

With growing demands for developing environment-conscious synthetic approaches, hypervalent iodine(III) compounds have attracted great interest in synthetic community due to their low toxicity, environment-friendly, unique reactivity and ready availability. In the last past decades, a wide variety of polar reactions such as oxidations, cyclizations, α-functionalizations of carbonyl compounds and C–H aminations have been successfully achieved by using various hypervalent iodine(III) reagents.[1] In contrast, radical reactions with hypervalent iodine(III) reagents have been less investigated to date, and most of them were achieved by combining use of transition-metal reagents, and/or with relatively high temperature.[2] Thus, the development of milder and metal-free radical reactions using hypervalent iodine(III) reagents is particularly valuable in organic chemistry.[3]

Metal-free generation methods of radical species from hypervalent iodine(III) reagents can be mainly categorized into four groups (Scheme 1); 1) ligand exchange, 2) single-electron transfer (SET) approach, 3) thermal decomposition and 4) photolysis. Among them, the ligand exchange approach is most frequently utilized.[4] This approach can provide radical species under mild conditions by the homolysis of a weak I–Nu bond, which is formed through the ligand exchange on the iodine center (Scheme 1a). However, the ligand exchange has the limitation due to the narrow range of nucleophiles, which can construct weak I–Nu bonds. In SET approach, hypervalent
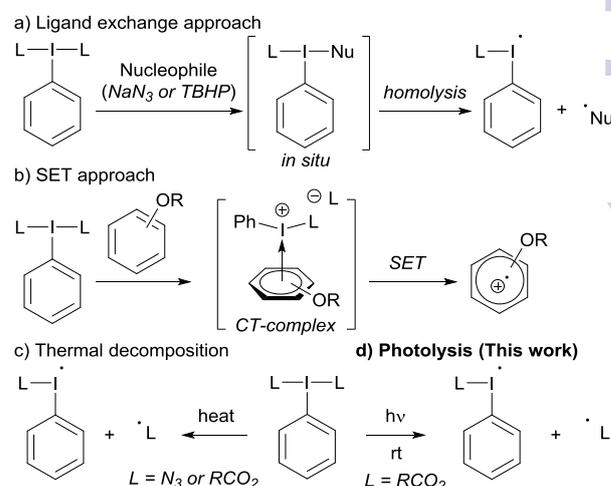
Scheme 1 Generation of Radical Species from Hypervalent Iodine(III) Reagents.
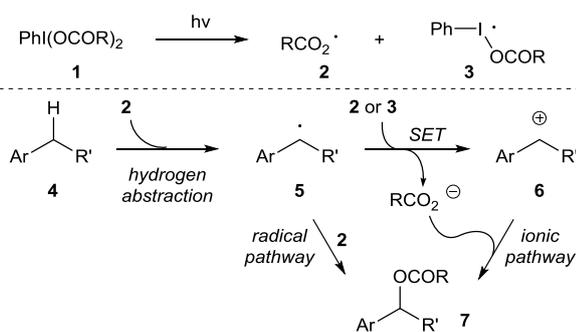
iodine(III) reagents act as efficient SET oxidizing agents for electron-rich aromatic compounds to generate cation radical species (Scheme 1b).[5] In contrast to these two approaches, the thermal decomposition and the photolysis approach can directly provide radical species from hypervalent iodine(III) reagents. The thermal decomposition, however, often requires high temperature, leading to a limited choice of solvent as well as substrate scope (Scheme 1c).[6] On the other hand, the photolysis of hypervalent iodine(III) reagents can readily occur to generate radical species by the irradiation of UV or visible light under mild reaction condition (Scheme 1d). In spite of that kind of advantage, only a few examples of radical reaction by the photolysis of hypervalent iodine(III) reagents have been reported to date with limited success.[7] In this context, we have been interested in the development of photoinduced radical reactions using hypervalent iodine(III) reagents under metal-free conditions.[8] Herein, we describe our recent results on this study, which establishes the direct benzylic C–H bond esterification of alkylbenzenes by the combination of electrophilic hypervalent iodine(III) reagents and visible light irradiation.

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan. E-mail: maruoka@kuchem.kyoto-u.ac.jp;
Fax: +81-75-753-4041; Tel: +81-75-753-4041;
†Electronic Supplementary Information (ESI) available: Experimental Details. See DOI: 10.1039/x0xx00000x

The direct benzylic C−H bond esterification of alkylbenzenes provides an attractive approach toward the construction of benzyl esters, which are valuable building blocks in organic synthesis. Recently, several metal-free direct esterification of benzylic C−H bond have been reported; however, most of them required relatively high temperature (>60 °C) or an excess amount of acid.[9] Therefore, the development of milder and practical methods is still an attractive and a challenging goal. Our strategy for the direct esterification of alkylbenzenes with the photolysis of hypervalent iodine(III) reagent is depicted in Scheme 2. First, the photolysis of hypervalent iodine(III) reagents **1** would generate a carboxyl radical **2** and an iodanyl radical **3**. Then, hydrogen abstraction of alkylbenzene **4** by **2** would afford a benzylic radical **5**. Finally, the radical coupling between **5** and **2** would furnish a desired benzyl ester **7** (radical pathway). Alternatively, ionic reaction between a carboxylate anion and a benzyl cation **6**, which would be formed by single-electron transfer (SET) of **5**, would afford **7** (ionic pathway).

We initially tested hypervalent iodine(III) reagents **1a–d** with ethylbenzene **4a** as a model substrate (Table 1). When the reactions were conducted with (diacetoxyiodo)benzene (DIB)

1a or (dibenzoyloxyiodo)benzene **1b** under the visible light (400 nm), the desired products were not observed, and **1a** or **1b** were almost remained (entries 1 and 2). More electrophilic hypervalent iodine(III) reagent [bis(trifluoroacetoxy)iodo]benzene (PIFA) **1c** or [bis(pentafluorobenzoyloxy)iodo]benzene **1d** provided low yields of **7**, along with the substantial amount of unreacted iodine reagents (entries 3 and 4). The significant increase of the product yield was observed by using benzene as a solvent (entry 5).[10] Use of **1a** in benzene under 400 nm gave the trace amount of the product, and **1a** was recovered quantitatively (entry 6). The use of strong UV light (365 nm) sligthly reduced the yield of **7a** (entry 7), and trifluoromethylbenzene was obtained as a by-product in large quantity, which indicated that the strong UV light further decomposed a trifluoroacetoxy radical via decarboxylation to give the trifluoromethyl radical.[3] In the absence of light, both **4a** and **1c** were recovered (entry 8).

With the optimized conditions in hand, the substrate scope of this reaction was explored, and the results are summarized in Table 2. First, we found that alkyl or aryl substituents at benzylic positions of **4** did not affect the reaction, giving products **7a–d** in good yields. The use of **4e** (R^1, R^2 = H) as a substrate afforded **7e** in low yield. The electronic nature of the aryl group has some effect on the reaction. In the case of **4f–i** with electron-withdrawing groups on the aryl rings, desired

Scheme 2 Proposed Mechanism of the Direct Esterification of Alkylbenzenes.

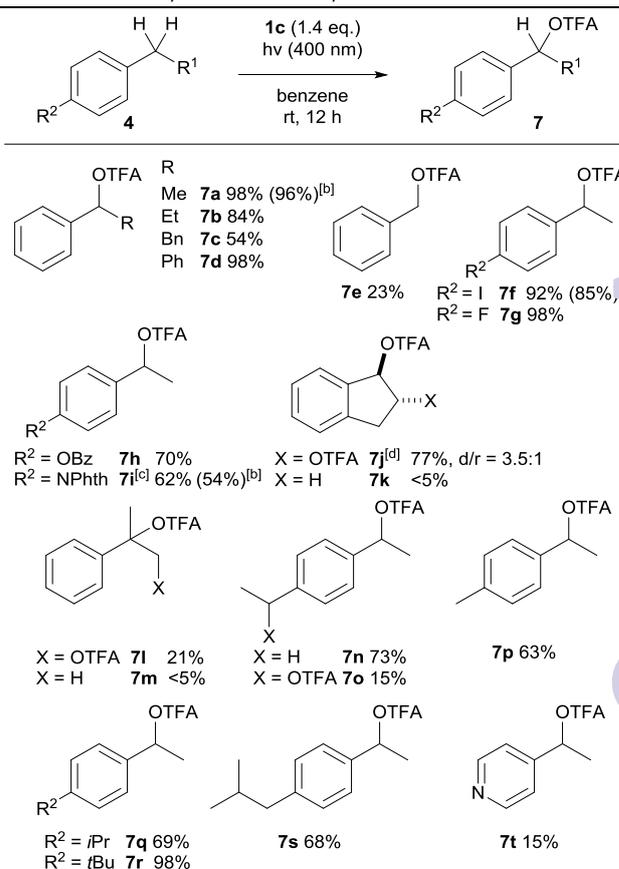**Table 1** Optimization of Reaction Conditions using Ethylbenzene **4a**. [a]

PhI(OCOCH$_3$)$_2$ (**1a**)   PhI(OCOPh)$_2$ (**1b**)
PhI(OCOCF$_3$)$_2$ (**1c**)   PhI(OCOC$_6$F$_5$)$_2$ (**1d**)
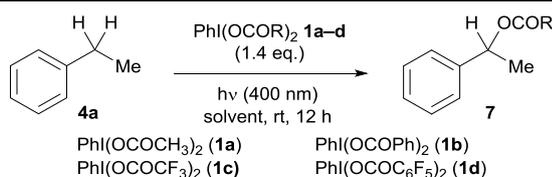
entry	reagent, **1**	solvent	% yield[b]
1	**1a**	MeCN	no reaction
2	**1b**	MeCN	no reaction
3	**1c**	MeCN	16
4	**1d**	MeCN	7
5	**1c**	benzene	98
6	**1a**	benzene	no reaction
7[c]	**1c**	benzene	62
8[d]	**1c**	benzene	no reaction

[a]Unless otherwise specified, reactions were conducted in the presence of **4a** (0.5 mmol), **1** (1.4 equiv.) in solvent (0.5 M) with irradiation by visible light (400 nm). [b] Yield was determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [c] Use of 365 nm black light. [d] The reaction was performed under dark atmosphere.

Table 2 Trifluoroacetoxylation of Various Alkylbenzenes **4**. [a]

R
Me **7a** 98% (96%)[b]
Et **7b** 84%
Bn **7c** 54%
Ph **7d** 98%

7e 23%

R^2 = I **7f** 92% (85%)
R^2 = F **7g** 98%

R^2 = OBz **7h** 70%
R^2 = NPhth **7i**[c] 62% (54%)[b]

X = OTFA **7j**[d] 77%, d/r = 3.5:1
X = H **7k** <5%

X = OTFA **7l** 21%
X = H **7m** <5%

X = H **7n** 73%
X = OTFA **7o** 15%

7p 63%

R^2 = iPr **7q** 69%
R^2 = tBu **7r** 98%

7s 68%

7t 15%

[a] Yield was determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [b] Isolated yield in parentheses. [c] Chloroform was used as a solvent. [d] 2 equiv. of **1c** was used. Bz = benzoyl, Phth = phthaloyl.

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products **7f–7i** were obtained in moderate to high yields. In contrast, introduction of an electron-donating group, such as methoxy group, provided complex mixtures (not shown). Use of indan gave bis(trifluoroacetoxyl) product **7j** in 77% yield, insted of mono-oxidized product **7k**. We assume that the elimination of TFA from **7k** gave inden, and the subsequent olefin bis-trifluoroacetoxylation of inden by PIFA occured to give **7j**.[11] Use of isopropylbenzene also resulted in the formation of bis(trifluoroacetoxy) product **7l** in 21% yield and in the recovery of strating material in 42% yield. Next, we examined disubstituted arenes in this reaction. When 1,4-diethylbenzene was used, mono-oxidized product **7n** was obtained as a major product in 73% yield, along with bis(trifluoroacetoxy) product **7o** in 15% yield. It shoud be noted that the present photolysis reaction using disubstituted arene showed better results in terms of yield and chemoselectivity, in comparison with the similar direct C–H esterification using hypervalent iodine **1a**.[9c] Oxidation reactions with other disubstituted arenes also proceeded smoothly at less hindered secondary benzylic Csp3–H bond to give **7p–s** in good yields.[12] Unfortunately, attempted use of 4-ethylpyridine resulted in decrease in yield of **7r**.[13]
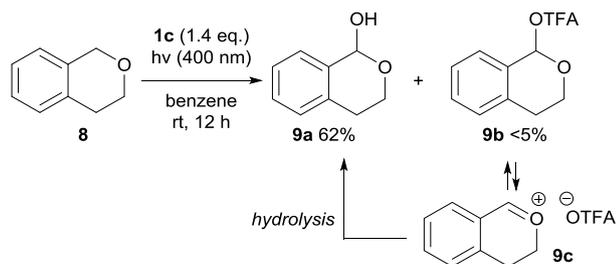

Scheme 3 Photolytic C–H Bond Oxidation of Isochroman.

**Table 3** Direct C–H Functionalization of Isochroman.
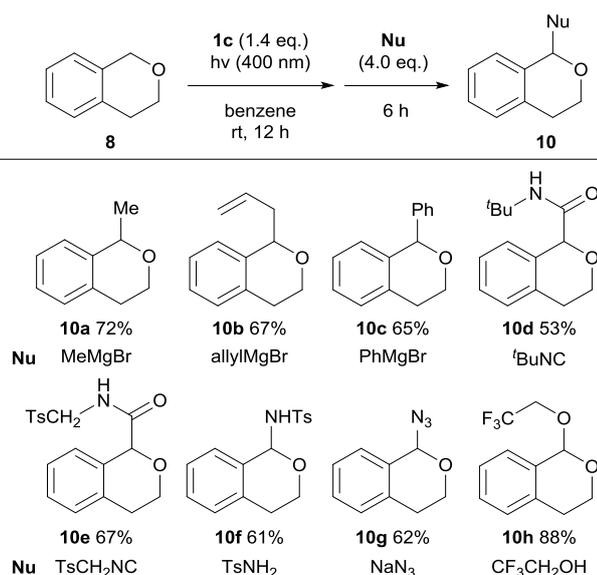
To expand the substrate scope of the reaction, isochroman **8** was used as substrate under the standard reaction conditions, giving a hydroxylated product **9a** in 62% yield, instead of **9b** (Scheme 3). We hypothesized that due to the relatively high leaving ability of the trifluoroacetoxy group, **9b** existed in equilibrium with an oxocarbocation **9c** under the reaction condition, and the hydrolysis of **9c** took place during the work-up to give **9a**. This hypothesis was confirmed by the addition of nucleophiles after the photoreaction with **8** and **1c** (Table 3).[14] Thus, the addition of several Grignard reagents worked well to afford the corresponding alkylation products **10a–c** in moderate yields.[10] Use of isocyanides as nucleophiles gave amide **10d** and **10e**.[15] Nitrogen nucleophiles and an oxygen nucleophile also gave the corresponding products **10f–h** in moderate to good yields. Additionally, the reaction of acyclic benzyl ether derivative **11** proceeded smoothly to afford α-hydroxy carbonyl compound **12** in 54% yield (Scheme 4).
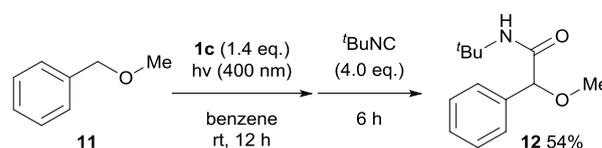
Scheme 4 Direct C–H Functionalization of Benzyl Ether.

Finally, we conducted several control experiments for the understanding of the reaction mechanism (Scheme 5). When the reaction using **4a** under oxygen atmosphere was performed, acetophenone **13** was obtained in 50% yield (Scheme 5a). This implies that a benzyl radical was generated during the reaction. On the other hand, the addition of AcOH in the reaction gave acetoxylated product **14** in 15% yield along with **7a** (Scheme 5b). And also, when the reaction was performed in the presence of 5 equivalent of acetonitrile, the formation of *N*-(1-phenylethyl)-acetamide **15** was observed (Scheme 5c). On the basis of these results, we tentatively considered that the benzyl cation intermediate **6** was formed during the reaction, indicating that C–O bond forming step of **5** proceeded through an ionic pathway to furnish benzyl ester **7** (Scheme 2).
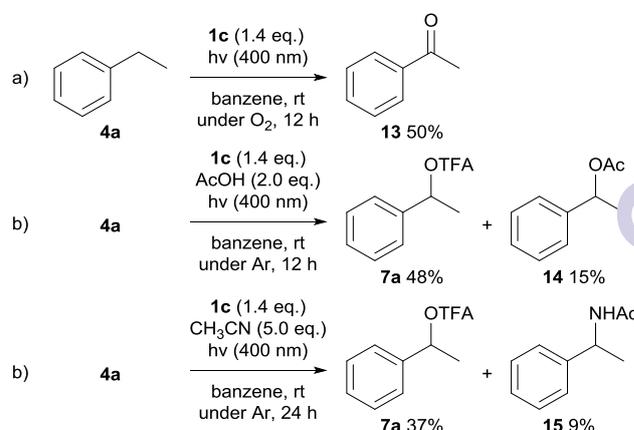
Scheme 5 Control Experiment Reactions.

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In summary, we have succeeded in the development of the direct benzylic C–H bond esterification of alkylbenzenes by the combination of electrophilic hypervalent iodine(III) reagents and visible light irradiation. With this approach, various alkylbenzenes were converted to the corresponding benzyl ester derivatives in good yield. This process represents a rare example of radical reaction from hypervalent iodine(III) reagents induced by photolysis. Further investigations on more detailed mechanism and applications of the present photoreaction for the development of new oxidation reactions is under investigation.

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