Catalytic tert-alkylation on enamides via C-C bond cleavage under photoredox conditions

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Catalytic tert-alkylation on enamides via C-C bond cleavage under photoredox conditions

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Naoki Tsuchiya, Ayane Oku, Takashi Nishikata*

Efficient C-C bond cleavage is recognized as one of the remaining challenges in the field of synthetic methodology. In this study, we found that tertiary alkyl radicals are smoothly formed from tertiary alkylated dienones (BHT adducts) via SET, using PDI as a photocatalyst. The resulting tert-alkyl radicals were able to be applied to the tert-alkylation of enamides. The driving force of this C-C bond cleavage reaction is the mesolytic cleavage of the BHT adducts. Mechanistic study revealed that PDI anion radical is the key active species during the catalytic cycle.

Development of structurally new tertiary alkyl source is challenging issues in construction of all-carbon quaternary centers. Although classical S_N1 reaction using a tertiary-alkyl halide[1] is one of the most promising methodologies to undergo tertiary alkylation, strong cation species generally does not have good functional group compatibilities. Among the various approaches, tertiary alkyl radical reactions have been well-studied in synthetic methodology area[2,3]. For example, tertiary alkyl halides, which generates the radical species via the homolytic cleavage of a weak C−X bond, are one of the most useful precursors[4,5,6]. However, tertiary alkyl halides often suffer from competing H-X elimination to generate the corresponding alkenes or limited choice of radical initiators, such as organotin. In this context, various non-functionalized tertiary alkyl sources other than the halides have been developed (Fig. 1). In 1985, Barton reported tert-alkyl *N*-hydroxypyridine-2-thionyl oxalates as the radical source[7]. Similarly, excellent tertiary alkyl sources including alcohol[8], oxalate[9], and phthalimidoyl oxalate[10], xanthate[11], dithiocarbonate[12], phenyltetrazolyl sulfone[13], trifluoroborate[14], boracene[15], silicate[16], phosphorus compounds[17] and NHC[18] have been reported.

Those reagents described above employed carbon-hetero atom cleavage to generate tertiary alkyl radicals, whereas the generation of tertiary alkyl radical species from a C-C bond cleavage process is much less attention because of strong C-C bond[19]. To generate tertiary alkyl radicals via C-C bond cleavage, a carboxylic acid is one of the best options for the construction of all-carbon quaternary centers, in which radical species generates via CO_2 extrusion. For example, MacMillan,

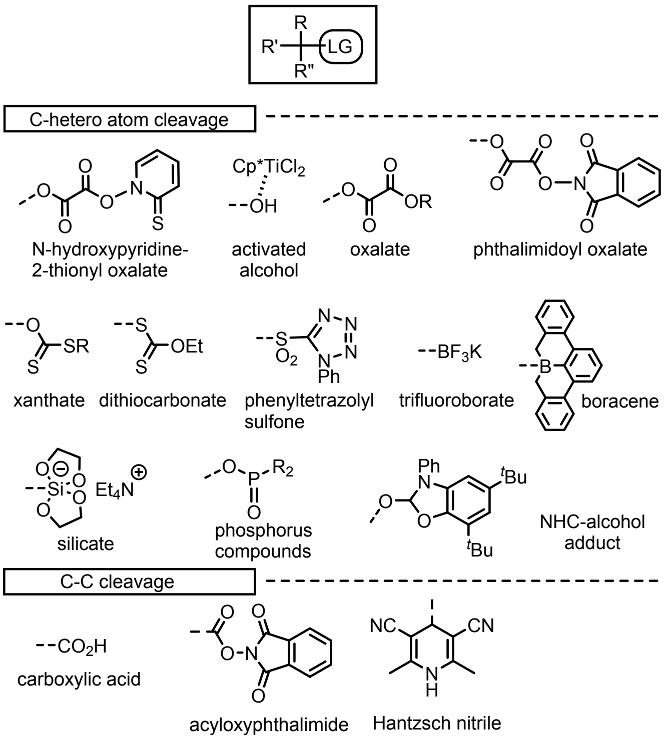

Fig. 1 Various leaving groups.

Wu, Shen, and Glorius recently demonstrated tertiary alkylation in addition or coupling reaction under photoirradiation or a transition-metal catalyzed conditions[20]. Acyloxyphthalimides,

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[a] Graduate School of Science and Engineering, Yamaguchi University 2-16-1 Tokiwadai, Ube, Yamaguchi, 755-8611, Japan

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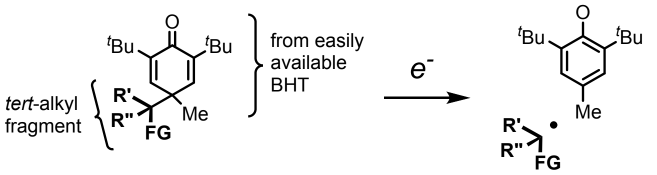
which is carboxylic acid derivatives, are also suitable reagents to undergo tertiary alkylations[21,22]. Ma, Cheng, and Li's group reported the reaction of 4-alkyl Hantzsch nitriles and alkyl bromides under photoredox conditions[23].

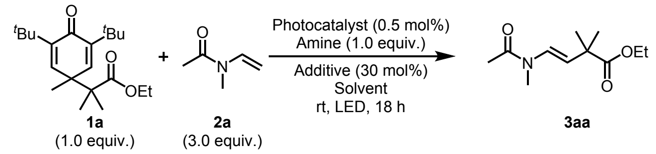
We found that the reaction of BHT with α-bromocarbonyl gave the corresponding tertiary alkylated dienones (BHT adduct) by the corresponding dearomatization[24]. We hypothesized that if the dienone skeleton could act as an electron acceptor under photocatalytic conditions, the tertiary alkylated dienones would be excellent radical donors via mesolytic cleavage (Scheme 1)[25]. Unlike previously reported radical reactions involving C-C cleavage, this reaction is superior in that it can use readily available BHT fragments and a variety of functionalized tertiary alkyl radicals. In this paper, we report on the properties and functions of tertiary alkylated dienones in atom-transfer radical substitution reaction (ATRS).



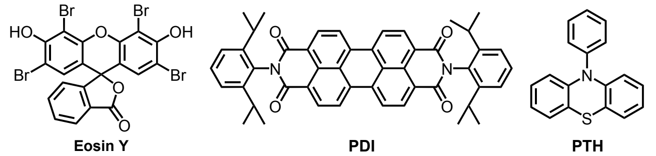
Scheme 1 This work.

At the initial study, we examined some photocatalysts (PC) in the reaction of **1a** and **2a** in DMF (*N,N*-dimethylformamide) (Table 1, Runs 1-3). Eosin Y at 540 nm was not effective. Although PTH was effective to activate α-bromocarbonyls to generate tert-alkyl radicals[26], it was not effective in this case. On the other hand, PDI gave 65% yield of **3aa**. We tested several PC catalysts, including Ru and Ir, but only PDI was effective. The mechanism is discussed later, but the excited PDI anion radicals produced by two visible light excitations starting from PDI[27] might be suitable for the reduction of C-C bonds. Solvent is also important factor. When the reaction was carried out in toluene, the starting material was recovered (Run 4). The reaction in MeCN yielded **3aa** in 44% yield, while the reaction in NMP (*N*-methylpyrrolidinone) gave 81% yield. Amine is also important in this reaction. Tertiary-amines were effective but secondary-amines did not give any products. Among tertiary-amines such as Et_3N, $^nBu_3N$, Hex_3N, and $^iPr_2EtN$, $^nBu_3N$ was the best (Run 7). To further improve the yield, various Lewis acids such as Mg, Al and Zn salts were investigated. Lewis acid has the potential to decrease the LUMO level of **1** and facilitate C-C cleavage[28]. As a result, $MgCl_2$ gave **3aa** in 88% yield (Run 8). $MgCl_2$ gave a slight increase in yield, but was very reproducible compared to other conditions without it, therefore this condition was adopted. Next, we carried out some control experiments (Runs 9-14). We tried the reaction under 365, 540 nm, but 450 nm resulted in the best yield (Runs 9 and 10). Both PC and irradiation were important for the reaction to proceed (Runs 11 and 12). The reaction with 5 mol% amine gave **3aa** in 53% yield, but no product was obtained without the addition of amine (Runs 13 and

Table 1 Optimization

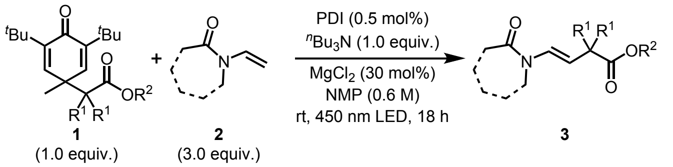


Entry	Photocatalyst (wavelength)	Amine	Additive	Solvent	Yield of **3aa**
1	Eosin Y (540 nm)	$^nHex_3N$	-	DMF	0%
2	PTH (365 nm)	$^nHex_3N$	-	DMF	trace
3	PDI (450 nm)	$^nHex_3N$	-	DMF	65%
4	PDI (450 nm)	$^nHex_3N$	-	Toluene	0%
5	PDI (450 nm)	$^nHex_3N$	-	MeCN	0%
6	PDI (450 nm)	$^nHex_3N$	-	NMP	81% (75%)
7	PDI (450 nm)	$^nBu_3N$	-	NMP	80% (71%)
8	PDI (450 nm)	$^nBu_3N$	$MgCl_2$	NMP	88% (76%)
9	PDI (540 nm)	$^nBu_3N$	$MgCl_2$	NMP	57%
10	PDI (365 nm)	$^nBu_3N$	$MgCl_2$	NMP	76%
11	- (450 nm)	$^nBu_3N$	$MgCl_2$	NMP	0%
12[b]	PDI (450 nm)	$^nBu_3N$	$MgCl_2$	NMP	0%
13[c]	PDI (450 nm)	$^nBu_3N$	$MgCl_2$	NMP	53%
14	PDI (450 nm)	none	$MgCl_2$	NMP	0%

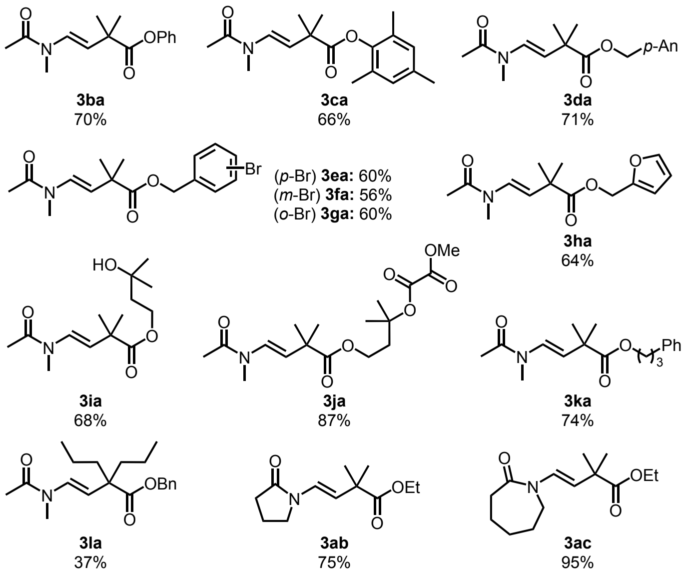


[a] All reactions were conducted with **1a** (1.0 equiv.), **2a** (3.0 equiv.), PC (0.5 mol%), Amine (1.0 equiv.) and additives (30 mol%) in solvent for 18 h at rt under LED irradiation. Yields were determined by ^1H NMR analysis. Isolated yields were shown in parentheses. [b] The reaction was conducted in the dark. [c] 5 mol% of $^nBu_3N$ was used.

Table 2 Substrate scope[a]



Isolated yield of **3**

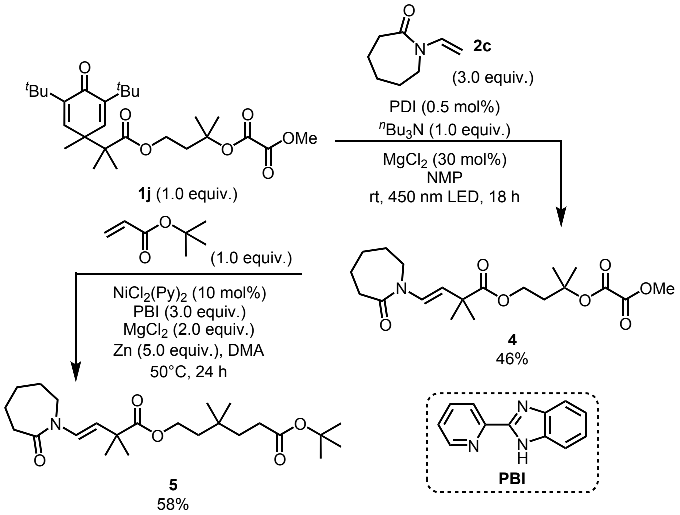


[a] All reactions were conducted with **1** (1.0 equiv.), **2** (3.0 equiv.), PDI (0.5 mol%), $^nBu_3N$ (1.0 equiv.) and $MgCl_2$ (30 mol%) in NMP for 18 h at rt under LED irradiation.

14). Amines are considered to act as sacrificial reducing agents (See later section).

Under the optimal conditions, we screened various functionalized **1** and **2** (Table 2). At first, we examined whether the ester structure of **1** affected the yield. As the result, the yields of phenyl and sterically bulky mesityl groups were 70% (**3ba**) and 66% (**3ca**) respectively. Next, arylmethyl esters (**1d-1h**) were examined. The yield of **3da** was 71% for the *p*-anisyl methyl ester **1d** and the yields of **3ea-3ha** resulting from the other allyl methyl esters were ca.60%. **1** possessing longer and functionalized alkyl chain also reacted smoothly with **2a** to produce **3ja-3ka**. Oxalate is a suitable radical precursor[9]. However, in the case of **3ja**, it remained intact. **1** with two bulky propyl groups at the carbonyl α-position gave **3ia** in 37% yield. In this case, starting materials were recovered. This reaction is sensitive to steric hindrance. Cyclic enamides **2** were also reactive in this reaction. **2** with cyclopentyl or cycloheptyl moiety was reacted with **1a** to produce the corresponding **3ab** and **3ac** in 75% and 95% yield, respectively. Although this reaction is sensitive to the steric hinderance of **1**, functional group compatibility was good.

One of the highlights of this reaction is the chemoselective reaction shown in Scheme 2: **1j** with two different *tert*-alkyl moieties can be applied for sequential *tert*-alkylation. The reaction of **1j** and cyclic enamide **2c** underwent ATRS to produce **4** in 46% yield. Subsequently, **4** reacted with acrylate ester to give **5** in 58% yield under Ni catalyzed conditions[9h]. Overall, two different tert-alkylations were achieved. These transformations show that our reaction system is useful to synthesize diverse tert-alkylated compounds.



Scheme 2 Chemoselective reaction

We investigated the reaction mechanism by carrying out a series of control experiments (Fig. 2). First, the effect of electron transfer inhibitor (1,4-nitrobenzene) was checked to see if this reaction involves SET processes (Fig. 2 #1). As the result, no product was obtained, and both **1** (95%) and 1,4-nitrobenzene (46%) were recovered. When the reaction of **1k** and **2a** was carried out in the presence of alcohol, the three-component coupling product **6** was formed in 40% yield (Fig. 2 #2). This result suggests that the C-C double bond in the target product **3** may be formed in the E1-like reaction through a process in which the generated radical is immediately oxidized to a cationic species. We next conducted Stern–Volmer experiments (See Supporting Figure 6). The quenching tests showed a decrease in photocatalyt's fluorescence with increasing concentrations of **1a**, 2a and ^{n}Bu$_3$N. The most efficient quenching was observed with ^{n}Bu$_3$N. Photo-excited PC may rapidly react with ^{n}Bu$_3$N to generate the corresponding anion radical species of PC. We also performed alternative light/dark experiments that clearly showed that this reaction requires photoirradiation and does not involve a radical-chain mechanism (See Supporting Figure 7).

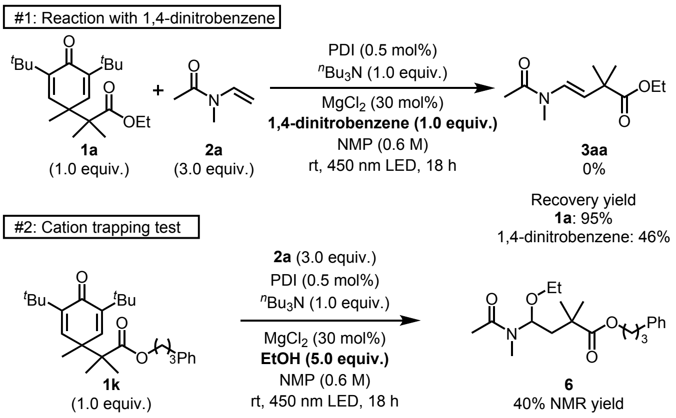


Fig. 2 Control experiments.

Based on above control experiments, we propose the following mechanism shown in Fig. 3. Photo-excited PDI (PDI*) reacts with amine to produce the PDI anion radical (-0.8 V vs Fc in DMF). This anion radical reacts with **1** (-0.8 V vs Fc in DMF) to produce α-radical **A** via mesolytic cleavage of the C–O-bond of **1** (path A). Alternatively, the PDI anion radical is further excited to form a photoexcited PDI anion radical[27] and SET occurs from the resulting highly reactive PDI to **1** (path B). Although there is no evidence for this, the reducing power of photoexcited PDI anion radicals may be much higher than the reducing potential of **1**. The α-radical **A** then reacts with **2** to produce intermediate **B**, which is oxidized to produce cationic species **C**. This cation was able to trap alcohol (Fig. 2#2). Finally, elimination of proton can lead to the formation of **3**.

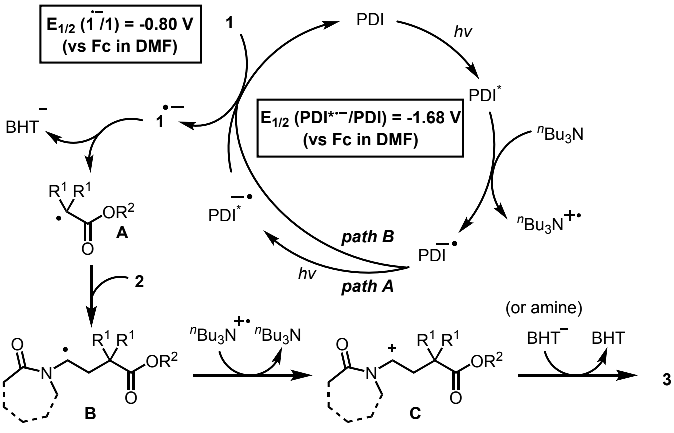


Fig. 3 Proposed mechanism.

In conclusion, we found the efficient C-C bond cleavage of BHT adduct possessing tert-alkyl moiety under photocatalytic conditions. To cleave C-C bond, PDI was the best photocatalyst. Current inexpensive and readily available BHT adducts, tert-alkylation reagents, are useful for the tert-alkylation of enamides. Control experiments revealed that SET first occurs between PDI* and nBu_3N, producing the PDI anion radical; after the formation of the PDI anion radical species, the BHT adduct reacts with the PDI anion radical or the re-photoexcited PDI* anion radical to produce a tert-alkyl radical. This reaction system not only provides a new C-C bond cleavage method from readily available BHT adducts, but also offers a new method of controlling tertiary alkyl radicals.

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Conflicts of interest

There are no conflicts to declare.

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