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Iron-Catalyzed Oxyalkylation of Terminal Alkynes with Alkyl Iodides

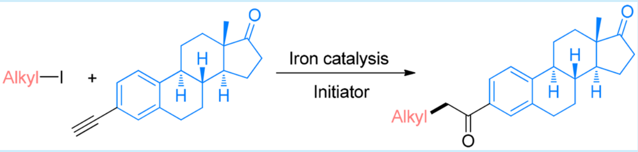
Weili Deng,[†] Changqing Ye,[‡] Yajun Li,[‡] Daliang Li,*[,†] and Hongli Bao*[,‡]

[†]Key Laboratory of Innate Immune Biology of Fujian Province, Biomedical Research Center of South China, College of Life Sciences, Fujian Normal University, 1 Keji Road, Fuzhou 350117, P. R. China

[‡]Key Laboratory of Coal to Ethylene Glycol and Its Related Technology, State Key Laboratory of Structural Chemistry, Center for Excellence in Molecular Synthesis, Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences, 155 Yangqiao Road West, Fuzhou, Fujian 350002, P. R. of China

Supporting Information

ABSTRACT: A general oxyalkylation of terminal alkynes enabled by iron catalysis has been developed. Primary and secondary alkyl iodides acted as the alkylating reagents and afforded a range of α-alkylated ketones under mild reaction conditions. Acetyl *tert*-butyl peroxide (TBPA) was used as the radical relay precursor, providing the initiated methyl radical to start the radical relay process. Preliminary mechanistic studies were conducted, and late-stage functionalizations of natural product derivatives were performed.

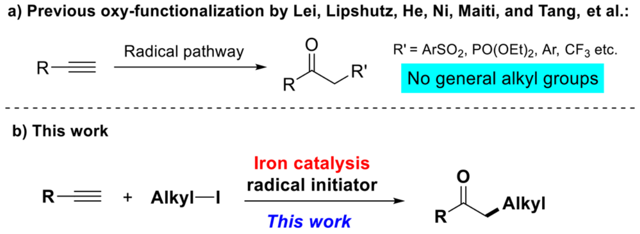


Harnessing free radical as the driving force for chemical transformations has offered a remarkable alternative besides classical synthetic methodologies. The formation of free radical under mild reaction conditions has led to impressive developments for bond formation, such as C−C bond, C−O bond, and C−N bond.[1]

Radical relay is a useful strategy that employs a precursor to generate a new radical species, with more general and useful functionalities from readily available chemicals via a relay process.[2] Many efforts have been dedicated to developing methods for new bond formation enabled by radical relay process.[3] To date, two types of radical relay precursors, nonoxidative[4] and oxidative radical relay precursors,[5] have been published. AIBN,[6] Bu_3SnH, BEt_3/O_2,[7] silylated cyclohexadienes,[8] catechol/Et_3B,[9] and some inorganic compounds like $ZnCl_2$ and SmI_2 are frequently used as nonoxidative radical relay initiators. These initiators are useful for *chain reactions* or *reductive reactions*, but not for *oxidative reactions*. Recently, as a complement to reductive radical relays, oxidative radical relay processes have been developed with oxygen radicals[10] and nitrogen radicals[11] but rarely with carbon radicals. The main obstacles to utilizing a carbon radical to initiate an oxidative radical relay include the lack of convenient methods to generate carbon radicals under mild and oxidative conditions and the undesirable carbon radical side reactions.[12] Despite the difficulties, a carbon radical-initiated oxidative relay is potentially useful because carbon radicals are able to break not only C−H bonds but also C−X (halogen) bonds to generate more versatile radicals from more broadly varied substrate types, which would be impossible with an oxygen or nitrogen radical. Recently, the Studer group discovered that TBAI (tetra-*n*-butylammonium iodide) can be used as a nonoxidative radical relay precursor for electron catalysis.[3b] And Liu group reported an elegant method for copper-catalyzed enantioselective cyanation of benzylic C−H bonds, using high-valent iodine reagent NFSI (*N*-fluorobenzenesulfonmide) as an oxidative radical relay precursor.[3c]

Oxyfunctionalization of alkynes is an ideal strategy to produce α-functionalized ketones, which can serve as core structures in pharmaceuticals, bioactive natural products, and functional materials.[13] Several successful methods to synthesize α-functionalized ketones from alkynes in a radical relay fashion have been developed by Lei, Lipshutz, He, Ni, Maiti, Tang, and others (Scheme 1a).[14] Functionalities such as aryl, trifluoromethyl, sulfonyl, and phosphoryl groups can be incorporated. However, approaches for the introduction of generic alkyl functionalities in a radical relay process are still rare.

Scheme 1. Radical Oxy-functionalization of Terminal Alkynes



Recently, we reported an iron-catalyzed oxyalkylation of terminal alkynes with alkyl peroxides via a radical decarboxylation.[15] Alkyl halides are a kind of important chemical feedstock in organic chemistry in terms of their extensive application.[16] Very recently, in the presence of *t*-butyl perbenzoate (TBPB), an oxidative radical relay precursor, an iron-catalyzed carboazidation of alkenes and alkynes with alkyl

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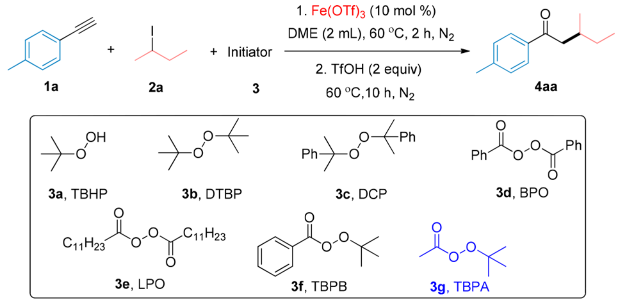
iodides has been successfully developed by our group.[17] Thus, we wondered whether alkyl iodides could serve as the readily available alkyl source for the alkylation of alkynes to afford α-alkylated ketones in the presence of an oxidative radical relay precursor.[18] Herein, we report our latest study on iron-catalyzed oxyalkylation of terminal alkynes via radical relay reaction using alkyl iodides as the alkylating reagents (Scheme 1b).

In order to test the activities of different alkyl peroxides and to find a solution for the above key issue, the initiation reaction was carried out with commercially available 4-ethynyltoluene (**1a**), 2-iodobutane (**2a**), and different alkyl peroxides (**3**). As shown in Table 1, although initiators such as TBHP, DTBP, and DCP could trigger the reaction, the reaction was messy and only a trace amount of the desired product was observed (Table 1, entries 1−3). Then, BPO was examined in the reaction as the initiator. Almost no desired product **4aa** was observed (Table 1, entry 4). To our delight, LPO (**3e**, lauroyl peroxide) afforded the desired product **4aa** in 62% yield (Table 1, entry 5). Other alkyl peroxides were also screened. While perester **3f** delivered the desired product **4aa** in 47% yield, TBPA (**3g**, acetyl *tert*-butyl peroxide) offered a better yield as high as 72% (Table 1, entries 6 and 7). The results implied that the methyl radical generated from the alkyl perester might be the best initiated radical, which is reactive enough to abstract the iodine atom from the alkyl iodide and immune to alkyne. We need to mention that AIBN did not show performance for this radical relay process (Table 1, entry 8). In addition, the influence of the reaction temperature was investigated, and 60 °C was proven to be optimal (Table 1, entries 9 and 10). We speculated that the performance of the radical relay reaction could be enhanced by raising the loading of the iron catalyst. But the yield of **4aa** dropped to 49% with 15 mol % of $Fe(OTf)_3$ (Table 1, entry 11). A low yield was obtained with 5 mol % of $Fe(OTf)_3$ and only 18% yield was obtained when no iron metal was used (Table 1, entries 12 and 13). Without TfOH, the yield of **4aa** decreased to 46% (Table 1, entry 14). Delightfully, when the first step for the alkylation was performed at rt, the highest yield was obtained at 80%. When the amount of the initiator was reduced, the yield of the desired product dropped dramatically (Table 1, entries 16 and 17), and the reaction failed to produce **4aa** without any initiator (Table 1, entry 18).

Table 1. Optimization of the Reaction Conditions[a]

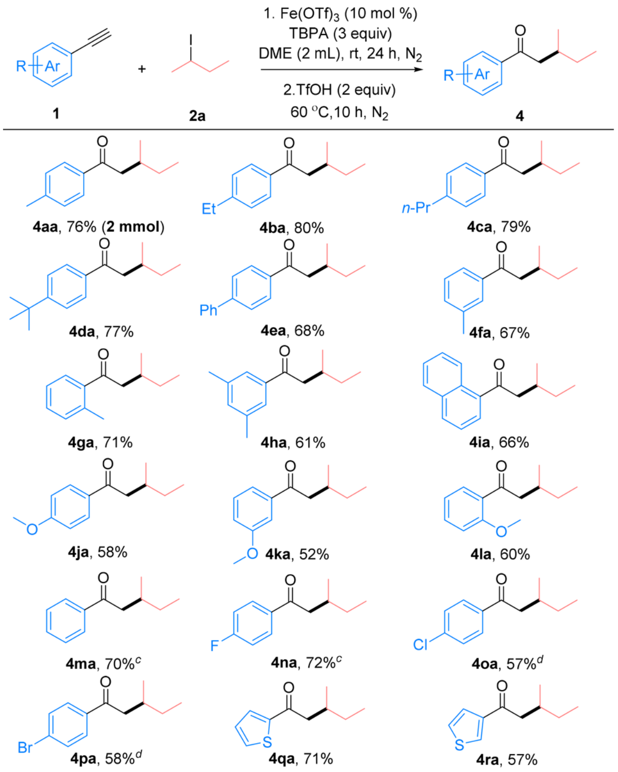


entry	initiator	yield[b] (%)
1	TBHP	trace
2	DTBP	trace
3	DCP	trace
4	BPO	trace
5	LPO	62
6	TBPB	47
7	TBPA	72
8	AIBN	trace
9[c]	TBPA	58
10[d]	TBPA	62
11[e]	TBPA	49
12[f]	TBPA	56
13[g]	TBPA	18
14[h]	TBPA	46
15[i]	TBPA	80
16[i,j]	TBPA	37[k]
17[i,l]	TBPA	8[k]
18[i,m]	none	0

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), $Fe(OTf)_3$ (10 mol %), and initiator (1.5 mmol) in DME (2 mL) at 60 °C for 2 h under nitrogen atmosphere. Then TfOH (1.0 mmol) was added and stirred at 60 °C for another 10 h under nitrogen atmosphere. [b]Yield of the isolated product. [c]The reaction temperature was 80 °C. [d]The reaction temperature was 40 °C. [e]$Fe(OTf)_3$ (15 mol %). [f]$Fe(OTf)_3$ (5 mol %). [g]Without $Fe(OTf)_3$. [h]Without TfOH. [i]24 h at rt for the first step. [j]Initiator (0.5 mmol). [k]GC yield. [l]Initiator (0.25 mmol). [m]Without initiator.

With the identified reaction conditions in hand, the substrate scope was screened (Scheme 2). With the assistance of TBPA and TfOH, various aryl alkynes were able to undergo the reaction and coupled with 2-iodobutane to afford the corresponding oxyalkylation products. The aryl alkynes with an electron-donating group on the benzene ring offered the

Scheme 2. Substrate Scope of the Aryl Alkynes[a,b]

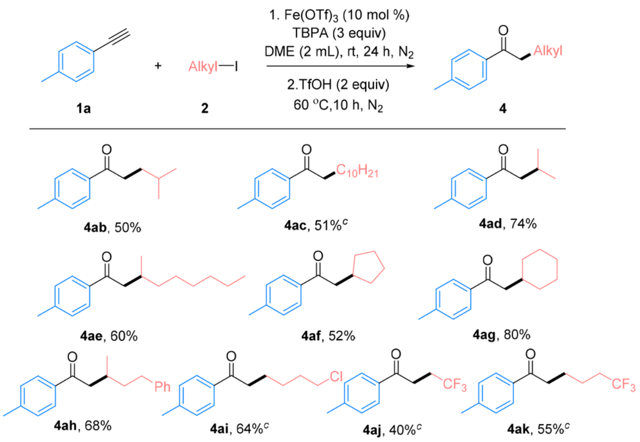


[a]Reaction conditions: **1** (0.5 mmol), **2a** (1.5 mmol), $Fe(OTf)_3$ (10 mol %), and TBPA (1.5 mmol) in DME (2 mL) at rt for 24 h under nitrogen atmosphere. Then TfOH (1.0 mmol) was added and stirred for another 10 h at 60 °C. [b]Yield of the isolated product. [c]100 °C instead of 60 °C. [d]120 °C instead of 60 °C.

corresponding products (**4aa**−**4ia**) with good to high yields. Interestingly, the yield slightly decreased when a methoxy was attached on the benzene ring of the aryl alkynes (**4ja**−**4la**). Reactions of halogen substituent aryl alkynes afforded the corresponding products (**4na**−**4pa**) in relatively low efficiency with elevated temperature. Furthermore, heteroaryl alkynes such as thienyl alkynes could survive and offered the corresponding products **4qa** and **4ra** in 71% and 57% yields, respectively. However, terminal alkyl alkynes and internal alkynes, such as prop-2-yn-1-ylbenzene, oct-1-yne, but-3-yn-2-one, and non-2-yne, failed to afford the corresponding products.

Next, we examined the substrate scope for alkyl iodides, which are commercially available or could be easily synthesized according to reported methods (see the Supporting Information for details). Primary alkyl iodides as well as secondary alkyl iodides provided the corresponding products in moderate yields (Scheme 3, **4ab**−**4ah**). The chloro substituent was tolerated under the reaction conditions, and corresponding product **4ai** was obtained in 64% yield. Interestingly, fluorinated alkyl iodides could also be used as the reaction substrates and delivered the corresponding products **4aj** and **4ak** in 40% and 55% yields, respectively. But, tertiary alkyl iodides, such as 2-iodo-2-methylpropane and 1-iodoadamantane, failed to afford the corresponding products.

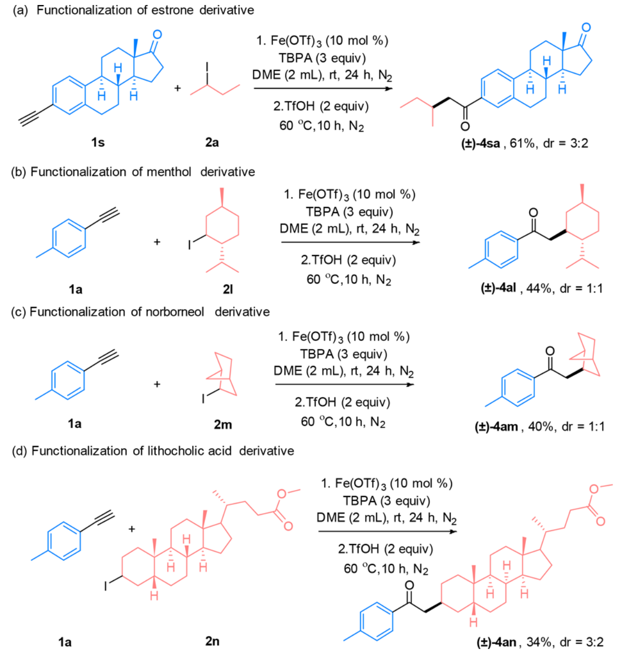
Scheme 3. Substrate Scope of the Alkyl Iodides[a,b]



[a] Reaction conditions: **1a** (0.5 mmol), **2** (1.5 mmol), Fe(OTf)$_3$ (10 mol %), and TBPA (1.5 mmol) in DME (2 mL) at rt for 24 h under nitrogen atmosphere. Then TfOH (1.0 mmol) was added and stirred for another 10 h at 60 °C. [b] Yield of the isolated product. [c] 100 °C instead of 60 °C.

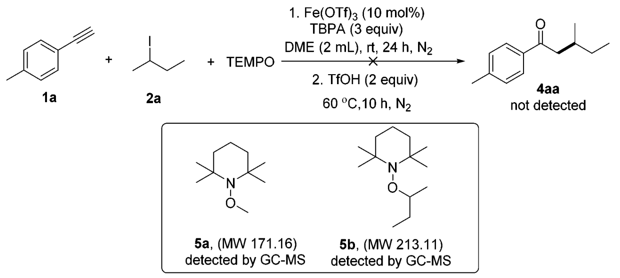
To highlight the synthetic application, late stage functionalizations of natural product derivatives were developed (Scheme 4). Estrone derivative (**1s**) was smoothly transferred into functionalized estrone (**4sa**) in moderate yield under the standard reaction conditions (Scheme 4a). Catalyzed by Fe(OTf)$_3$ and with the assistance of TBPA, the coupling of menthol derivative (**2l**), norborneol derivative (**2m**), and lithocholic acid derivative (**2n**) with terminal alkyne (**1a**) gave the corresponding ketone products **4al**, **4am**, and **4an**, respectively (Scheme 4b−d).

Scheme 4. Functionalization of Natural Product Derivatives



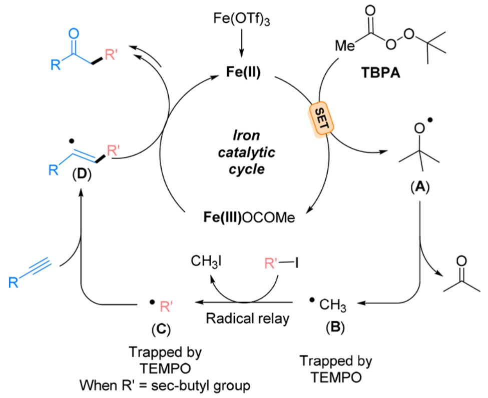
In order to probe the mechanism of this reaction, preliminary mechanistic study was conducted under the standard reaction conditions. When radical scavenger TEMPO was added, the reaction was prevented, and no desired product **4aa** was detected. The methylated TEMPO product (**5a**) and *sec*-butylated TEMPO product (**5b**) could be observed by GC-MS analysis (Scheme 5). This result supports the proposed radical relay process.

Scheme 5. Fundamental Mechanistic Study



In view of the results of the mechanistic experiments, a radical relay-involving catalytic cycle is proposed (Scheme 6). A single electron transfer between Fe(II) and TBPA initiates the reaction by generating a *tert*-butoxyl radical (**A**) and an

Scheme 6. Proposed Catalytic Cycle



Fe(III) species. The *tert*-butoxyl radical (**A**) then decomposed to a methyl radical (**B**, trapped by TEMPO) and a molecular of acetone. A radical relay process then occurs between the methyl radical and alkyl iodide affording a new carbon radical (**C**, trapped by TEMPO when **C** is a *sec*-butyl group) and methyl iodide. This carbon radical adds to the terminal alkyne, generating an internal vinyl radical (**D**). According to our previous work,[15] the radical **D** can deliver the final product and regenerate Fe(II) species.

In conclusion, we have developed an efficient iron-catalyzed oxyalkylation of terminal alkynes with alkyl iodides enabled by a radical relay process. Primary and secondary alkyl iodides could be utilized as alkyl sources to afford a range of α-alkylated ketones under mild reaction conditions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03689.

Typical experimental procedure and characterization of products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*daliangli@fjnu.edu.cn
*hlbao@fjirsm.ac.cn

ORCID

Yajun Li: 0000-0001-6690-2662
Hongli Bao: 0000-0003-1030-5089

Notes

The authors declare no competing financial interest.

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