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ACS Catal., Just Accepted Manuscript • Publication Date (Web): 15 Jan 2019

Downloaded from http://pubs.acs.org on January 15, 2019

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is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

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Iron-Enhanced Reactivity of Radicals Enables C–H Tertiary Alkylations for Construction of Functionalized Quaternary Carbons.

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Iron• SET • C-H alkylation • Tertiary-alkyl group • Radical

ABSTRACT. Iron is one of the most attractive catalysts, especially for aromatic C–H functionalizations. However, stoichiometric amounts of oxidants and strong carbanions are required, and C–H tertiary alkylation, especially electron deficient alkyl groups, is unexplored. In this paper, we describe the development of iron-catalyzed selective C–H tertiary alkylations with heteroaromatics, in which an iron salt acts as a single-electron source and enhances the reactivity of a tertiary alkyl radical generated from α -bromocarbonyl compounds. Our established methodology was demonstrated in the efficient synthesis of various quaternary carbon atoms under very simple conditions.

INTRODUCTION

The synthesis of quaternary carbon atoms is one of the central issues in organic synthesis because the reaction to construct quaternary carbon atoms suffers from the problem of steric hindrance. Although many challenges in the synthesis of complex molecules have been studied so far,^{1,2} the reported methods do not allow the efficient synthesis of functionalized quaternary carbon atoms. In this context, transition-metal-catalyzed reactions are one of the most attractive methodologies to synthesize carbon quaternary centers.² For these reactions, iron catalysts have received considerable attention³ owing to their environmentally benign nature, their inexpensive cost, and the abundance of elemental iron.⁴

Although the possible iron-catalyzed C–H transformations employ excess Grignard reagent and/or an oxidant,³ iron [Fe(0)]⁵ and some Fe(II) complexes⁶ have been known to promote redox-type radical addition reactions through the activation of carbon–halogen bonds. On the other hand, ironcatalyzed reactions involving a redox system are widely used in atom-transfer radical polymerization chemistry,⁷ but the chemistry to construct all carbon quaternary centers through C–H bond transformation has not yet been established.⁸ Generally, a radical species generated from the reaction of an alkyl halide and an iron salt has limited reactivity or too much reactivity for the substrates; specific organic halides, such as poly-halogenated compounds, are applicable to the reaction.⁸ Therefore, the possible variations of the reaction and the structures of the products are limited. This subtle phenomenon is still somewhat controversial^{3,8} but could be one explanation for the limited development of iron-catalyzed organic reactions. Overall, a number of issues in iron-catalyzed C–H bond transformations remain to be addressed, including (1) functional group tolerance, (2) reaction varieties, (3) C–C formations via single-electron transfer (SET) process, and (4) the synthesis of quaternary carbon atoms.

The main strategy to transform C–H bonds by using an iron catalyst requires directed oxidative addition or a concerted metalation–deprotonation (CMD) process in the presence of excess Grignard reagent and oxidant (Figure 1a).^{9,10} On the other hand, our strategy is to use a radical process by single-electron transfer, in which quaternary carbon atoms can be synthesized without special additives (Figure 1b). Recently, there have been some reports of C–H radical alkylation reactions in the presence of Ru or Cu catalysts with/without photoirradiation, but related iron-catalyzed reactions to load tertiary alkyl groups for the synthesis of quaternary carbon atoms



Figure 1. Strategies for the transformation of C–H bonds. DG: directing group.

are rare.^{11,12} During the course of our copper-catalyzed transformation studies using α bromocarbonyl compounds,¹³ we found that an iron catalyst is also effective to generate tertiary alkyl radicals from α -bromocarbonyl compounds for C–H tertiary alkylation reactions.¹⁴ In this reaction, Fe^{II} abstracts Br from the α -bromocarbonyl compound, resulting in the formation of an alkyl radical and a higher oxidation state Fe^{III} complex. We expect that the Fe^{III} complex could enhance the radical reactivity due to the coordination to the carbonyl group of the resulting alkyl radical. As the result, efficient C–H tertiary alkylation could be accomplished. Herein, we disclose the iron-enhanced reactivity of tertiary alkyl radicals for heteroaromatic or vinylic C–H alkylations to construct all carbon quaternary centers.

RESULTS AND DISCUSSION

Heteroaromatic C-H Tert-Alkylations. Optimization studies employed the combination of ethyl 2-bromoisobutyrate (1a, 1 equiv) and benzofuran (2a, 1.5 equiv) in the presence of an Fe catalyst (5 mol%), and a base (2 equiv) at 110 °C (Table 1). The reaction with iPr2NEt gave 2alkylated product **3a** in 45% yield, but the reaction without the Fe catalyst did not proceed (Table 1, entries 1 and 2). Other catalysts, such as Fe(OAc)₂, Fe(OTf)₂, CuI and PdCl₂, were not effective. The reaction was selective and no regioisomers were obtained, unlike the results in previous reports.^{11,12} We expected that ligands would be very important to generate the reactive iron species in situ, but the yields were not improved in the presence of nitrogen or phosphorus ligands (Table 1, entries 3-6). A theoretical study revealed that the coordination of the iron species to the ester group of the generated alkyl radical is important to enhance the reactivity; therefore, ligands retarded the reaction (see mechanism section). We next screened various bases. The reaction did not proceed without a base or with inorganic bases (Table 1, entries 7 and 8). NEt₃ decreased the yield, and iPr₂NH strongly retarded the reaction (Table 1, entries 9 and 10). As a result, iPr₂NEt gave the best yield of product 3a. When the reactions were carried out in various solvents, including MeCN, EtOH, 1,4-dioxane, and toluene, the best result was obtained with 1,4-dioxane (Table 1, entries 11–13). Finally, the reaction with 3 equivalents of **2a** in 1M solution resulted in 75% yield of 3a (Table 1, entries 14 and 15). Several methods for direct C-H alkylation of aromatic compounds with alkyl halides have been reported.^{13,14} However, the alkylation of

 heteroaromatic compounds is quite challenging due to slow C–H substitution and the undesired β -H elimination of alkyl intermediates.¹⁵ Our strategy using reactive radical species can avoid the above-mentioned issues.

Table 1. Optimization^a

1a 2a : 1.5 ec	FeCl ₂ (5 Ligand (1 Base (2) solvent, quiv 22	5 mol%) 0 mol%) 0 equiv) 110 °C th 3a	
Ligand	Base	Solvent (M)	Yield (%) ^b
None	<i>i</i> Pr ₂ NEt	Toluene (0.5)	45
None	<i>i</i> Pr ₂ NEt	Toluene (0.5)	0
2,2-bipyridyl	<i>i</i> Pr ₂ NEt	Toluene (0.5)	32
TPMA	<i>i</i> Pr ₂ NEt	Toluene (0.5)	22
PPh ₃	<i>i</i> Pr ₂ NEt	Toluene (0.5)	46
PCy ₃	<i>i</i> Pr ₂ NEt	Toluene (0.5)	44
None	None	Toluene (0.5)	0
None	Cs_2CO_3	Toluene (0.5)	0
None	NEt ₃	Toluene (0.5)	28
None	<i>i</i> Pr ₂ NH	Toluene (0.5)	0
None	<i>i</i> Pr ₂ NEt	MeCN (0.5)	0
None	<i>i</i> Pr ₂ NEt	EtOH (0.5)	trace
None	<i>i</i> Pr ₂ NEt	1,4-dioxane (0.5)	50
None	<i>i</i> Pr ₂ NEt	1,4-dioxane (1)	57
None	<i>i</i> Pr ₂ NEt	1,4-dioxane (1)	75 ^e
	Br + 1a 2a: 1.5 ec Ligand Ligand None 2,2-bipyridyl TPMA PPh ₃ PCy ₃ None	FeCl ₂ (5 Ligand (1) Br + $2a$: 1.5 equiv Ligand Base None Pr_2NEt None Pr_2NEt 2.2-bipyridyl Pr_2NEt TPMA Pr_2NEt PPh ₃ Pr_2NEt PPh ₃ Pr_2NEt PPh ₃ Pr_2NEt None None None Sc_2CO_3 None NEt_3 None Pr_2NEt None Pr_2NEt	FeCl ₂ (5 mol%) Ligand (10 mol%) Base (2.0 equiv) solvent, 110 °C 2a: 1.5 equiv 24h 3a Ligand Base Solvent (M) None Pr_2NEt Toluene (0.5) None Pr_2NEt Toluene (0.5) 2,2-bipyridyl Pr_2NEt Toluene (0.5) TPMA Pr_2NEt Toluene (0.5) TPMA Pr_2NEt Toluene (0.5) PCy ₃ Pr_2NEt Toluene (0.5) PCy ₃ Pr_2NEt Toluene (0.5) None None Toluene (0.5) None Net_3 Toluene (0.5) None NEt_3 Toluene (0.5) None Pr_2NEt MeCN (0.5) None Pr_2NEt EtOH (0.5) None Pr_2NEt Liduene (0.5) None Pr_2NEt Toluene (0.5) None Pr_2NEt Liduene (0.5) Net Pr_2NEt

^a Reaction conditions: **1a** (0.50 mmol), **2a** (0.75 mmol), FeCl₂ (5 mol%), ligand (10 mol%), base (1.0 mmol) in solvent at 110 °C for 24 h. ^b NMR spectroscopy yield. ^C Without FeCl₂. ^d Using 3 equiv of **2a**. ^e Isolated yield.

Under the optimal conditions, we tried various bromides **1** and heteroaromatic compounds (**2** or **3**) (Table 2). Our optimized conditions can be applied to gram scale C-H alkylation (**4a**), which shows that our reaction conditions are reliable. The bromides **1** possessing alkyl-Br bond and aryl ester gave the corresponding products in good yields (**4b-4e**). The reaction occurred with not only 2-bromoesters but also 2-bromoamides to produce **4f** and **4g** in 64% and 60% yields, respectively. In those cases, the increased amount of **2** was effective to obtain better yields. 2-Bromomalonate ester also reacted with benzofuran to give **4h** but the yield was low due to the decomposition of 2-bromomalonate. 2-Bromoesters possessing various carbon functionalities at α -position resulted in moderate to good yields (**4i-4l**). These results reflect that highly congested quaternary carbons can be synthesized by our methodology. But the corresponding primary- and secondary-alkyl radicals were not reactive due to the radical stabilities (**4m**, **4n**). Substituted benzofuran and furan derivatives possessing bromine, alkyl group, ketone, and even aldehyde gave alkylated products in moderate to good yields without loss of the functional groups (**4o-4v**). We also tried the reaction of thiophens and the corresponding quaternary carbons of thiophens were obtained under the modified conditions (**5a**, **5b**). The reaction did not occur with benzoxazole and benzothiazole.



^a Reaction conditions: **1** (0.50 mmol), **2** or **3** (1.5 mmol), FeCl₂ (5 mol%), iPr₂NEt (1.0 mmol) in 1,4-dioxane at 110 °C for 24 h. ^b 5 equiv of **2** was used. ^c Run at 150 °C.

Mechanistic Consideration. While the exact reaction mechanism is currently unclear, one possibility involves a radical pathway (Scheme 1). The reaction starts with the generation of tertiary-alkyl radical species **A** from the reaction between Fe(II) and **1**. An evidence of this step is the reaction in the presence of radical scavenger such as BHT or TEMPO. This reaction with BHT or TEMPO did not result in the formation of product **4**. After the generation of **A**, addition of **A** to **2** takes place to give the radical intermediate **B**. Then, intermediate **B** reacts with an iron bromide species to produce intermediate **C** with concomitant formation of a Fe(II) species to complete the catalytic cycle. The intermediate **C** undergoes elimination with the amine to give the desired product **4**. During the reaction, there are a few possibilities to produce homocoupling product of **A** and **B**. But such products were not detected.



Scheme 1. Proposed mechanism.

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The formation of cation species from the oxidation of **B** with Fe^{III} cannot be ruled out. The smooth radical addition of **A** to **2** can be explained by comparing the transition states (Scheme 1 bottom). To support the reaction mechanism, we carried out DFT calculations (See supporting information). During the reaction, iron-coordinated species (TYPE I or II) could be generated and favored transition state is to be TYPE I ($\Delta G^{\ddagger}=16.8 \text{ kcal/mol}$). Free radical process (radical chain reaction) is another possibility but energy level was high compared with them. Iron Lewis acidity could enhance the electrophilicity of **A**, in which the life time of the radical might be long enough to react with aromatic C-H bonds. NBO atomic charge of radical carbon in TYPE I was calculated to be 0.135 *e* which showed higher density than that of TYPE II (0.090 *e*). We also calculated the relative Fukui indices, which are calculated by NBO analysis for carbon atoms of **2**. Calculated relative Fukui indices showed that the nucleophilicity of C2 is the highest of all carbons in **2**. This result explains the importance of reactivity enhancement of **A** with iron, in which an electrophilic radical could be generated.

Miscellaneous Reactions. Iron-enhanced alkyl radical species can be applied to various reactions. For example, when the reaction ran in the presence of BHT (**6a**) without benzofuran **2**, the resulting alkyl radical added directly to the aromatic ring to produce dearomatized product **7a** in 73% yield. The reaction of **6b** gave C-H tert-alkylated product **7b** in 61% yield (Scheme 2). These results supported the existence of radical species **A** in Scheme 1. On the other hand, the reaction of **8a-c** underwent similar intramolecular reactions (Scheme 3). The reaction of **8a** possessing a phenol fragment gave dearomatized adduct **9a** and C-H cyclized products (**9b**, **9c**) were obtained from the reaction of **8b** and **8c**. Generally, BHT generates benzyl radical from a phenoxy radical and the resulting benzyl radical could couple with other radical species¹⁶. Those

results showed that the α -radicals generated under our optimized conditions could have broad reactivities.







Scheme 3. Intramolecular reaction.

We next applied our iron-catalyzed conditions to cascade C-H cyclization reactions to produce oxindoles possessing two quaternary carbons which are partly core structure of Indolidan (Table 3). Although intramolecular C-H cyclizations to produce oxindoles have been well studied by using a Pd catalyst¹⁷, the corresponding Fe-catalyzed reactions have not yet been established. The generated α -radicals possessing an ester or an amide under the conditions reacted with the C-C double bond of acrylamide **10** followed by intramolecular C-H radical cyclization radical cyclization to provide the functionalized oxindoles **11** in the yield ranging from 75-94%.





Moreover, our conditions were effective for tert-alkylation of olefins (vinylic C-H substitutions) (Table 4). Unlike previous Fe-, Ni- and Cu-catalyzed related tert-alkylations¹⁸, our reaction system can employ simple styrene derivatives, α -methylstyrene, and β -substituted styrene. The reaction of **1** and styrenes **12** under our iron catalyzed conditions provide Heck like olefination products (**13a-13f**) in moderate to good yields. The reaction of α -methylstyrene and **1** selectively produced exo-methylene product **13e**. In Pd-catalzed reaction, it is very difficult to control exo- and endoselectivity¹⁹. When substrate **12** possessing an internal C-C double bond was employed, the corresponding (E)-tert-alkylated product **13f** was obtained as a single stereoisomer.





CONCLUSION

In conclusion, we found universal iron-catalyzed conditions for 1) heteroaromatic C-H alkylations, 2) C-H cyclizations, 3) dearomative additions of phenols and 4) vinylic C-H alkylations. From the natural resource points of view, finding new aspects of iron chemistry is very important²⁰ and iron is one of the most attractive catalysts. Iron-catalyzed C-H functionalization chemistry have been succeeded with Grignard reagents for the synthesis of substituted arenes, but new iron chemistry for the synthesis of quaternary carbons has not yet been established. Our iron catalyzed radical research revealed that α -radicals generated from the reaction of 2-bromocarbonyls and iron salt can react with various C-H bonds. The theoretical study revealed that iron catalyst enhanced the reactivity of generated alkyl radicals, which enables smooth C-H tertiary-alkylations. Further investigations, including other type of reactions and mechanistic studies, are currently underway.

ASSOCIATED CONTENT

Experimental procedures and spectroscopic data for all new compounds are available free of charge via the Internet at http://pubs.acs.org."

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ACKNOWLEDGMENT

We warmly thank YU and JSPS KAKENHI Grant Number JP 18H04262(TN) in Precisely

Designed Catalysts with Customized Scaffolding.

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Graphical Abstract

