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Ligand-free iron-catalyzed benzylic C (sp³)–H amination of methylarenes with N-fluorobenzenesulfonimide†

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Direct conversion of cheap methylarenes to benzylic amines, which are essential structural units of important drugs, is of great significance. However, the known methodologies suffer from the requirement of noble metal catalysts, heavy metal residues or strong oxidants. Herein, the first biocompatible iron-catalyzed benzylic C (sp^3)–H amination of methylarenes with *N*-fluorobenzenesulfonimide is described. The reactions of methylarenes bearing electron-donating groups and electron-withdrawing groups ran smoothly under ligand and additional oxidant free conditions. Both toluene derivatives and 8-methylquinoline can be aminated by the same iron catalyst.

Benzylic amines are essential structural units of many important drugs, such as imatinib, donepezil, ampicillin, and valsartan (Fig. 1).¹ Direct conversion of benzylic C (sp³)–H bonds to C (sp³)-N bonds to synthesize benzylic amines is of great importance. Intramolecular and intermolecular benzylic amination²⁻⁴ of aliphatic C-H bonds can be realized by Rh, Ru, Ir, Pd, Ag, Cu, Mn or Fe-catalyzed nitrene transfer reactions.^{2,5} In the case of amination of 8-methylquinolines, Pd, Ir, Ru or Rh can be used as catalyst.^{6a-e} This strategy provides a powerful and direct method for the installation of benzylic amines. However, explosive azides or hypervalent iodine reagents need be used to generate nitrenes. The use of hypervalent iodine reagents may result in the generation of stoichiometric amount of environmentally unfriendly iodobenzenes. One alternative way to the benzylic amination is cross-dehydrogenative coupling (CDC) reactions catalyzed by metals or under metal free conditions.⁷ The strategy suffers from the additional oxidants which are essential to activate benzylic C (sp^3) -H. Among the oxidants, potentially explosive peroxides are usually used. Pandey has reported visible-light-catalyzed benzylic amination via CDC procedures under metal and external oxidant free conditions,7e but the substrates could not be totally consumed. Radical addition allows benzylic amination,8 but peroxides need be used in the processes. N-Fluorobenzenesulfonimide (NFSI) is a kind of internal oxidant,9 thus no external oxidant is needed when it is used as amination reagent. Therefore, NFSI is a promising amination reagent. Zhang, Zhang, Liu and coworkers have reported copper-catalyzed benzylic amination by NFSI (Scheme 1a) in the presence of ligand.^{10a} Remote benzylic

amination with NFSI catalyzed by palladium or prompted by hypervalent iodine reagent was also investigated.^{10b-d} Álvarez, Muñiz and co-workers have described Pd-catalyzed amination of 8-methylquinolines with NFSI (Scheme 1b).6f Zheng and coworkers have reported Cu-catalyzed amination of 8-methylquinolines in the presence of ligand and base (Scheme 1b).6g Toluene and xylene are among the cheapest, the most abundant chemical raw materials, but important materials for the production of industrially important chemicals. Their benzylic C-H bonds functionalization¹¹ (including amination) to valueadded products under environment friendly and economic conditions are highly desirable. 8-Methylquinolines are idea substrates for the synthesis of quinolin-8-ylmethanamines, which are building blocks in medicinal chemistry.12 The amination of toluene derivatives and 8-quinolines is significant. However, the known methodologies suffer from noble and or



Fig. 1 Examples of drugs containing benzylic amine units.

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heavy metal catalysts. Their catalytic reactions' applications in the pharmaceutical industry may be limited, for the problem of heavy metal residues must be considered. Iron is abundant, nontoxic, biocompatible, environment-friendly,^{2d} thus it is idea catalyst for the benzylic amination reactions. However, there is no report on iron-catalyzed benzylic amination of methylarenes under additional oxidants and nitrenes free conditions. There is no catalyst which can aminate both toluene derivatives and 8methylquinoline. Herein, we'd like to report the first biocompatible iron-catalyzed benzylic C (sp³)-H amination of methylarenes (including toluene derivatives and 8-methylquinoline) with NFSI under ligand and additional oxidant free conditions (Scheme 1c and d). Our work provides a direct method for preparation of benzylic amines from toluene derivatives and 8methylquinoline without the problem of heavy metal residues. The other advantage is to avoid the use of a large excess amount of methylarenes. Stoichiometric amount of toluene derivatives and 8-methylquinoline were used in this work. The examples of functionalization of stoichiometric amount of methylarenes are still limited.11a

Initially, toluene was chosen as substrate with iron catalyst to optimize the reaction conditions (Table 1). Benzylic C (sp³)-H of toluene was selectively aminated to produce benzylic amine 3a in the presence of C (sp^2) -H bonds. Zero valent diiron nonacarbonyl showed catalytic activity, and 3a was obtained in 27% yield (entry 1). The use of Cp_2FePF_6 as catalyst could slightly increase the yield (from 27% to 28%, entry 2), while the other ferrocenium salt Cp₂FeBF₄ clearly improved the yield (from 27% to 36%, entry 3). With nano Fe₃O₄ as catalyst, the yield became lower (entry 4). Notably, anionic iron also showed catalytic activity (entry 5). Iron(III) salts were investigated. Iron(III) nitrate nonahydrate, iron(m) acetylacetonate (Fe(acac)₃) and iron(m) ptoluenesulfonate hexahydrate (Fe(OTs)₃·6H₂O) were found to be able to catalyze the amination, but they had little effects on the improvement of the yields (entry 7-9). We were pleased to find that iron(III) oxalate hexahydrate ($Fe_2(C_2O_4)_3 \cdot 6H_2O$) gave 3a

Table 1 Optimization of the reaction conditions^a



^{*a*} Reaction conditions: **1a** (0.5 mmol), **2** (1.5 equiv., 0.75 mmol), catalyst (10 mol%) in 10 mL 1, 2-dichlorobenzene under refluxing condition in air. ^{*b*} Isolated yield. ^{*c*} 1.0 equiv. NFSI. ^{*d*} 2.0 equiv. NFSI. ^{*e*} 5 mol% Fe₂(C₂O₄)₃·6H₂O. ^{*f*} Chlorobenzene as solvent.

Table 2 Amination of toluene derivatives with NFSI^a



^{*a*} Reaction conditions: **1** (0.5 mmol), **2** (1.5 equiv., 0.75 mmol), $Fe_2(C_2O_4)_3 \cdot 6H_2O$ (10 mol%) in 20 mL 1, 2-dichlorobenzene under refluxing condition in air.



in 59% yield (entry 10). Iron(II) oxalate was tested. **3a** was afforded in lower yield (entry 11). The results indicate that the catalytic activity of iron(III) salt is higher than of iron(II) salt. The decrease of the amount of NFSI lowered the yield (entry 12). However, the increase of the amount of NFSI almost could not improve the yield (entry 13). The decrease of the amount of the catalyst $Fe_2(C_2O_4)_3 \cdot 6H_2O$ resulted in lower yield (entry 14). With chlorobenzene as solvent, the conversion of C (sp³)–H to C (sp³)–N was limited. **3a** was obtained only in 28% yield (entry 15). With 1,2-dichloroethane (DCE), acetonitrile, 1,4-dioxane or *N*,*N*-dimethylformamide (DMF) as solvent, **3a** could not be detected by thin layer chromatography (TLC). When the reaction was carried out at 120 °C, **3a** could not be detected by TLC.

With the optimized reaction conditions (Table 1, entry 10), we began to investigate the amination of toluene derivatives (Table 2). The amination of o-xylene, m-xylene, p-xylene could be catalyzed by 10 mol% $Fe_2(C_2O_4)_3 \cdot 6H_2O_1$, and the corresponding monoamination products (3b-d) were obtained under the reaction conditions. The amination of both electron-deficient and electron-rich toluene derivatives underwent smoothly to produce the corresponding benzylic amines. Toluene bearing electron-donating substituent tert-butyl at the para position gave **3f** in 80% yield. Notably, primary benzylic C (sp^3)–H was selectively aminated in the presence of secondary benzylic C (sp³)-H, and 3e was afforded. Toluene substrates bearing iodo, bromo, chloro and fluoro substituents were good candidates for the amination, the corresponding products (3h-1 and 3n-p)were obtained in satisfactory yields (from 41% to 76%). Iodo substituent at the ortho, meta or para position of the benzene ring has little effect on the benzylic amination. It is noticed that reactive iodo and bromo substituents remain in the amination products, thus further transformation can be considered. Toluene bearing phenyl substituent at the para position was aminated efficiently to produce 3q in 66% yield. 1-Methyl naphthalene was also suitable substrate. Its amination gave 3r in 43% yield. Electron-withdrawing substituents, such as cyano, sulfonyl, carbonyl, are tolerant, and the corresponding products were obtained (3s-u). 3t was afforded in 46% yield.

The amination of 8-methylquinoline was then studied (Scheme 2). 8-Methylquinoline was successfully aminated, **5a** was obtained in 47% yield.

A possible path of the amination involves cationic iron species. As is known, NFSI is a kind of electrophilic oxidant.^{6f,13} In the amination of 8-methylquinolines with NFSI catalyzed by $Pd(\pi)$, Álvarez and Muñiz proposed a mechanism which involved $Pd(\pi)$ to a cationic $Pd(\pi)$ path.^{6f} As for the interaction of iron(π) catalyst and NFSI, Fu proposed a cationic iron species.¹⁴ On the other hand, iron(π) can be oxidated to iron(ν).¹⁵ Therefore, it is reasonable to assume that $Fe(\pi)$ -catalyzed amination



Scheme 3 Proposed mechanism of amination of methylarenes with NFSI.

of methylarenes proceeds *via* cationic iron(v) path (Scheme 3). The interaction of iron(m) catalyst with NFSI produces cationic iron complex **A**, which is an oxidant to activate benzylic C (sp³)– H to produce benzylic type radical **B**.¹⁶ The following reaction of cationic Fe(w) and anionic C generates radical **D** along with the regeneration of Fe(m). The coupling of radical **B** and **D** gives the amination product.

In summary, we have developed the first biocompatible ironcatalyzed benzylic C (sp³)–H amination of methylarenes with NFSI under ligand and additional oxidant free conditions. The amount of methylarenes is stoichiometric. Both electrondeficient and electron-rich methylarenes are suitable substrates. Electron-withdrawing substituents and electrondonating substituents are tolerant. Both toluene derivatives and 8-methylquinoline can be aminated by the same abundant iron catalyst.

Conflicts of interest

The authors declare no conflict of interest.

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