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Communication

Iron-Catalyzed Highly para-Selective Difluoromethylation of Arenes

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ABSTRACT: Direct functionalization of a C−H bond at either the meta or para position by only changing the catalyst system poses a significant challenge. We herein report the [Fe(TPP)Cl]-enabled, selective, C−H difluoromethylation of arenes using $BrCF_2CO_2Et$ as the difluoromethylation source, which successfully altered the selectivity from the meta to the para position. A preliminary mechanistic study revealed the iron porphyrin complex not only activated the aromatic ring but also induced para selectivity due to the influence of ligand sterics.

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The efficient and selective transformation of a C−H bond into a carbon−carbon or carbon−heteroatom bond has always attracted attention in synthetic chemistry.[1] To control the site-selective functionalization of a C−H bond on an aromatic ring at a remote position is a key challenge. Various directing groups have provided straightforward ways to access ortho,[2] meta,[3] or para[3e,4] position C−H-functionalized products. However, these directing group (template) strategies usually required additional synthetic steps to complete the desired transformations. Recently, noncovalent interaction strategies reported by the Nako,[5] Chattopadhyay,[6] Kuninobu,[7] and Kanai[8] groups offered direct and efficient approaches toward aromatic ring functionalization at the meta or para position. The Phipps[9] group disclosed an ion-pair-directed regioselective C−H borylation using an iridium catalyst in which the interaction between anionic ligand and ammonium salt substrates afforded meta selectivity. The Yu[10] group also smartly designed a bifunctional nitrile template that binds heterocyclic substrates through reversible coordination to achieve meta-selective C−H olefination. A ruthenium catalyst showed promising catalytic ability in promoting the remote selective C−H functionalization. A cyclometalated ruthenium complex not only provided ortho-selective C−H-functionalized products with an electrophilic reagent but also acted as a strong bulk-electronic-transient-metal functional group to realize meta- or para-selective C−H transformations[11] (Figure 1a). Although these methods greatly enriched approaches to meta- or para-selective C−H functionalization, a highly selective installation of a functional group at either the meta or para position to one substrate by only changing the catalyst system remains a significant challenge. Herein we report a [Fe(TPP)Cl]-enabled, selective C−H difluoromethylation of arenes using $BrCF_2CO_2Et$ as the difluoromethylation source, which successfully transformed selectivity from the meta to para position in contrast to previously reported ruthenium catalytic systems (Figure 1c).

Recently, the Ackermann,[12] and Wang[13] groups as well as our group[14] and others[11e,15] have demonstrated that C−H difluormethylation selectively occurs at the meta position of heterocyclic compounds via a cyclometalated ruthenium complex pathway (Figure 1b). The difluoromethylene (CF_2) group is quite important in the agrochemical, pharmaceutical, and life science industries.[16] So the development of new methods to realize para-selective difluoromethylation of heteroaromatic compounds is not only important in synthetic chemistry but also deepens the understanding of site-selective C−H functionalization. Regarding previous reports,[17] steric hindrance usually impacts site selectivity during free radical

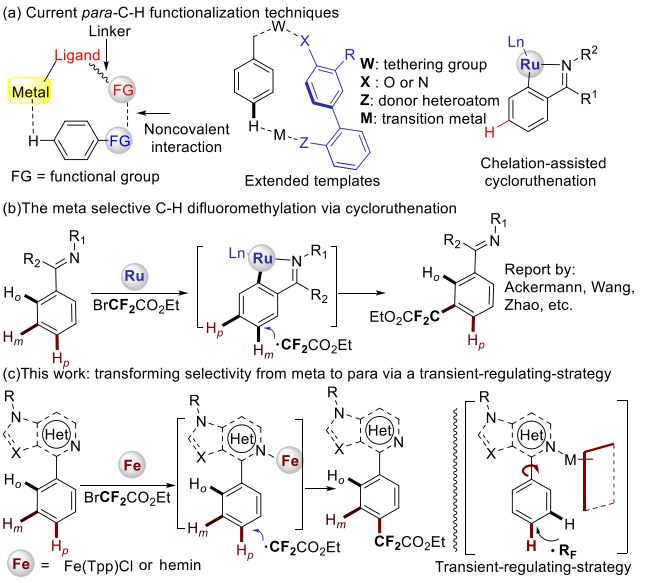

Figure 1. Site-selective C−H activation reactions. (a) Current para-C−H functionalization techniques. (b) Ruthenium(II)-catalyzed meta-C−H difluoromethylation. (c) Our work on Fe(III)-enabled para-selective difluoromethylation.

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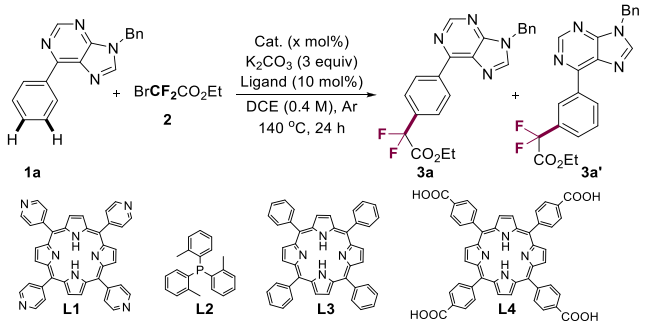
difluoromethyl reactions with aromatic rings; therefore, a transition metal complex with bulky ligands may enable para-selective C−H difluoromethylations.

With these conditions in mind, a sterically hindered porphyrin was selected as the ligand and ruthenium as the catalyst precursor. Initially, 9-benzyl-6-phenylpurine (**1a**) was treated with bromodifluoroacetate (**2**) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), **L1** (10 mol %), and K_2CO_3 (3 equiv) in DCE at 140 °C for 24 h. Mixed meta- and para-difluoromethylated products were obtained in 51% yield (para:meta = 2.7:1; Table 1, entry 1). When PivOH was used instead of **L1**, the meta-difluoromethylated product **3a′** was obtained as the major product (Table 1, entry 2). Various porphyrins were tested; however, neither the yield nor selectivity was improved (Table 1, entries 4, 5). To our great delight, when the hemin was used instead of the ruthenium catalyst, C−H difluoromethylated product **3a** was obtained in 41% yield with high para selectivity (Table 1, entry 6). Encouraged by this result, several metal porphyrin complexes, such as Fe(TPP)Cl, CoTPP, NiTPP, CuTPP, and Mn(TPP)-Cl, were examined (Table 1, entries 7−11). Those results clearly showed that Fe(TPP)Cl was the most effective catalyst and afforded product **3a** in a 78% yield with high para-selectivity (Table 1, entry 7). The difluoromethylated product was not obtained using iron chloride or $Fe(OTs)_3$ as the catalyst (Table 1, entries 12, 13). The control experiment showed that Fe(TPP)Cl is indispensable for this transformation (Table 1, entry 14).

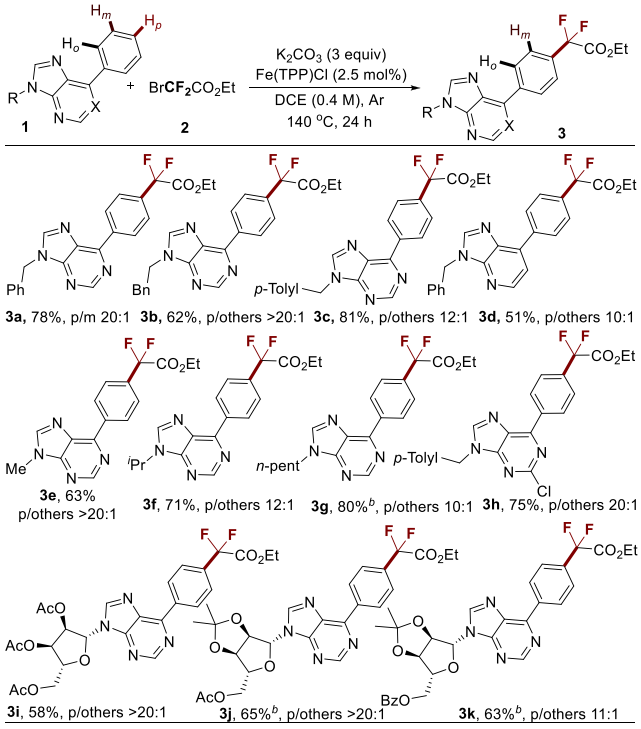
Table 1. Optimized Reaction Conditions[a]



entry[a]	catalyst (*x* mol %)	ligand	(3a+3a′) yield (%)[b]	(3a/3a′) (p/m)[c]
1	$[RuCl_2(p\text{-cymene})]_2$ (5)	**L1**	51	2.7:1
2[d]	$[RuCl_2(p\text{-cymene})]_2$ (5)	PivOH	22	1:1.5
3[d]	$[RuCl_2(p\text{-cymene})]_2$ (5)	**L2**	38	1:1.5
4	$[RuCl_2(p\text{-cymene})]_2$ (5)	**L3**	42	1:3.9
5	$[RuCl_2(p\text{-cymene})]_2$ (5)	**L4**	trace	
6	hemin (5)		41	25:1
7	Fe(TPP)Cl (2.5)		78	20:1
8	CoTPP (5)		trace	
9	NiTPP (5)		trace	
10	CuTPP (5)		trace	
11	Mn(TPP)Cl (2.5)		50	17:1
12	$FeCl_3$ (10)		trace	
13	$Fe(OTs)_3$ (10)		trace	
14			nr	

[a]Reactions were performed with **1a** (0.2 mmol), **2** (1.2 mmol, 160 uL), cat. (*x* mol %), and K_2CO_3 (0.6 mmol, 3 equiv) in DCE (0.5 mL), Ar, 140 °C, 24 h. [b]Yields of product after silica gel chromatography. [c]The ratio of selectivity determined by ^1H NMR spectroscopy. [d]K_2CO_3 (0.4 mmol, 2 equiv) was added at 120 °C.

Scheme 1. Scope of N-Substituted Purines[a]



[a]Reactions were performed in 0.2 mmol scale with **2** (1.2 mmol) in a sealed tube; isolated yields. [b]K_2CO_3 (2 equiv) was added for 48 h.

With the optimized reaction conditions established, we next explored the substrate scope of this reaction. Various N-substituted purines were subjected to the standard reaction conditions; phenemyl, 4-methylbenzyl, methyl, isopropyl, and *n*-pentyl substrates were all well tolerated and afforded para-selective difluoromethylated products in good to excellent yields (**3b−h**). More appealingly, we found that highly reactive nucleosides were all well-tolerated, even those bearing sensitive protecting groups, which led to the para-difluoromethylated products in moderate to good yields (**3i−k**). These results are complementary to the ruthenium-catalyzed meta-difluoroalkylation reaction reported by the Ackermann[12] group and also have potential use for antiviral or anticancer drug screenings.

We expanded this strategy to substrates with strongly coordinating heteroaromatic compounds. For example, various 5-position-substituted 2-phenylpyridines were well tolerated and yielded para-difluoromethylated products in moderate to good yields (**5a** and **5g**). Functional groups (methyl, methoxy, fluoro, chloro, and cyano) were fully compatible with this transformation (**5b−f**). Several 2-arylpyrimidines provided para-selective difluoromethylated products in moderate to good yields, highlighting the importance of this synthetic method (**5i−n**). Interestingly, substrate **4h** yielded product **5h** in good yield with high para selectivity, while 2-fluoro-6-phenylpyridine and 2-methoxy-6-phenylpyridine all gave difluoromethylated products with poor site selectivity. Although the reason is unclear, it might be due to a weak interaction between the chlorine atom in **4h** with the iron

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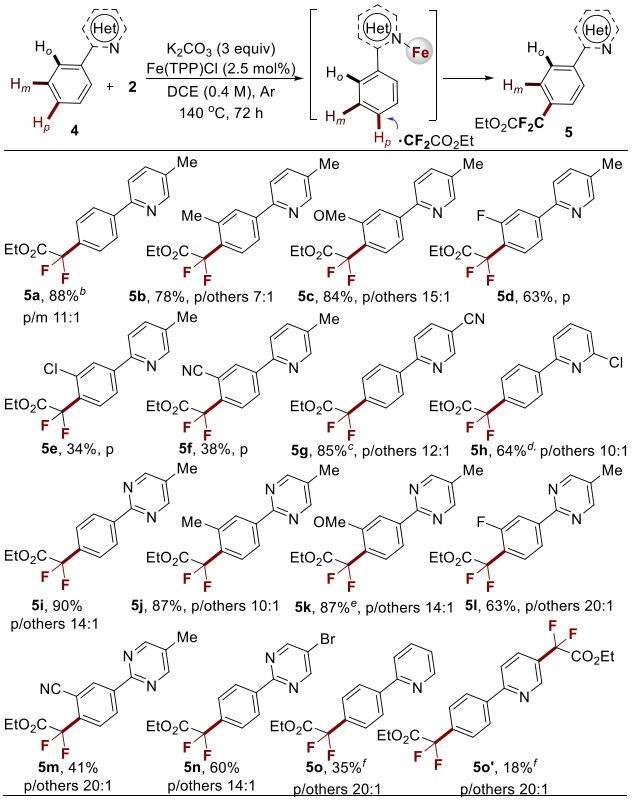
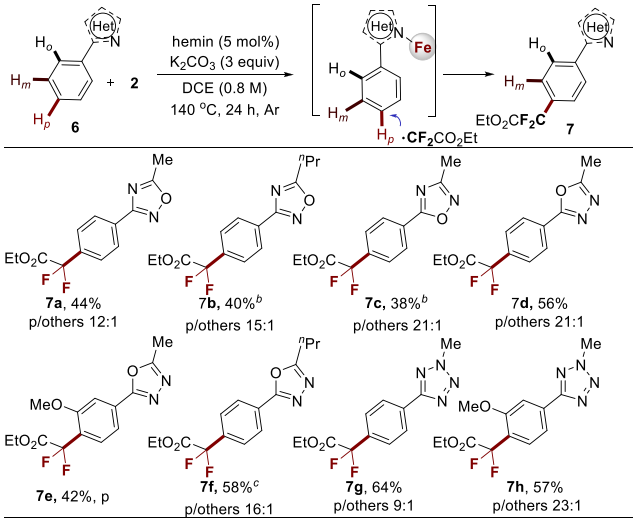
Scheme 2. Arene Substrate Scope[a]



[a]Reactions performed in 0.2 mmol scale with **2** (1.2 mmol) in a sealed tube; isolated yields. [b]Two equiv of K_2CO_3. [c]**2** (0.8 mmol) and K_2CO_3 (0.4 mmol, 2 euqiv) were added. [d]24 h. [e]48 h. [f]**4** (0.2 mmol), **2** (0.6 mmol, 3 equiv), hemin (0.01 mmol, 5 mol %), and K_2CO_3 (0.6 mmol, 3 equiv) in DCE (0.8 M), under Ar, 140 °C for 24 h.

center to form a stable key iron complex and preferentially yield the high para selectivity of **5h**. When 2-phenylpyridine was used, slightly lower selectivity for the difluoromethylated product **5o** was observed, along with side product **5o′**.

Scheme 3. Arene Substrate Scope[a]

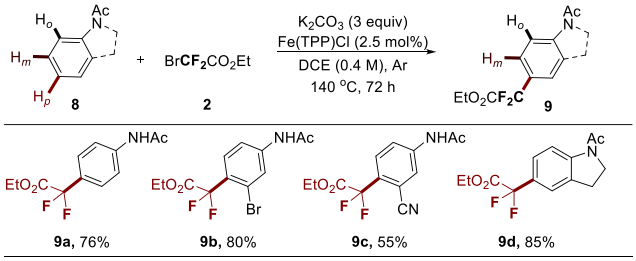


[a]Reactions performed in 0.2 mmol scale with **2** (0.6 mmol) in a sealed tube; isolated yields. [b]48 h. [c]36 h.

A mixture of meta- and para-difluoromethylated mixed products was observed when substrate **6a** was subjected to standard reaction conditions. To further expand the substrate scope, various iron complexes were further explored. We determined that on using hemin as the catalyst instead of Fe(TPP)Cl, para-selective difluoromethylated product **7a** occurred in a synthetically acceptable yield. The scope of substrates was expanded to oxadiazoles and aryltetrazoles, leading to para-selective difluoromethylated products in moderate yields (**7a**–**7h**). It should be noted that monofluoromethylation failed using ethyl bromofluoroacetate as the fluorine source under the optimized standard conditions.

This reaction system also tolerated aniline derivatives, and difluoromethyl products were obtained in excellent yields with only para selectivity (Scheme 4).

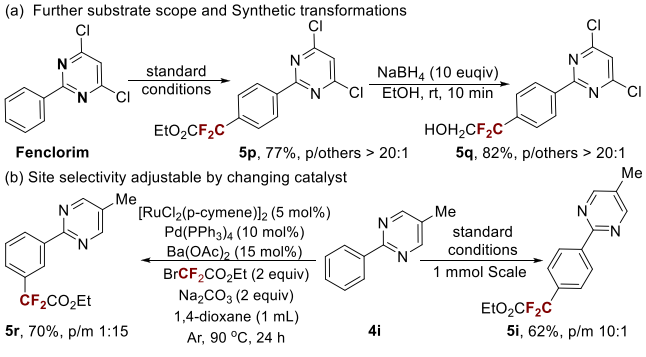
Scheme 4. Para-Selective C–H Difluoromethylation of Anilides[a]



[a]Reactions performed in 0.2 mmol scale with **2** (1.2 mmol) in a sealed tube; isolated yields.

The synthetic utility of this system was further demonstrated by the synthesis of fluorinated fenclorim analogues (Scheme 5a), which are used to protect wet-sown rice from

Scheme 5. Derivation Experiments



pretilachlor.[18] Standard reaction conditions were readily scaled to 1 mmol, yielding the corresponding product **5i** in 62% yield. Interestingly, the meta-difluoromethylated product **5r** was obtained in 70% yield when using a ruthenium catalyst[13] (Scheme 5b).

Several experiments were carried out to explore the reaction pathway of this catalytic system (Scheme 6). The difluoromethylated product was not obtained when the reaction was performed in the presence of the radical scavenger TEMPO.[11c,12a] The radical scavenger 1,1-diphenylethylene trapped $^{\bullet}CF_2CO_2Et$ directly to generate **11** in 65% yield using an iron catalyst. In contrast, product **11** was obtained in less than 5% yield when the reaction took place without Fe(TPP)

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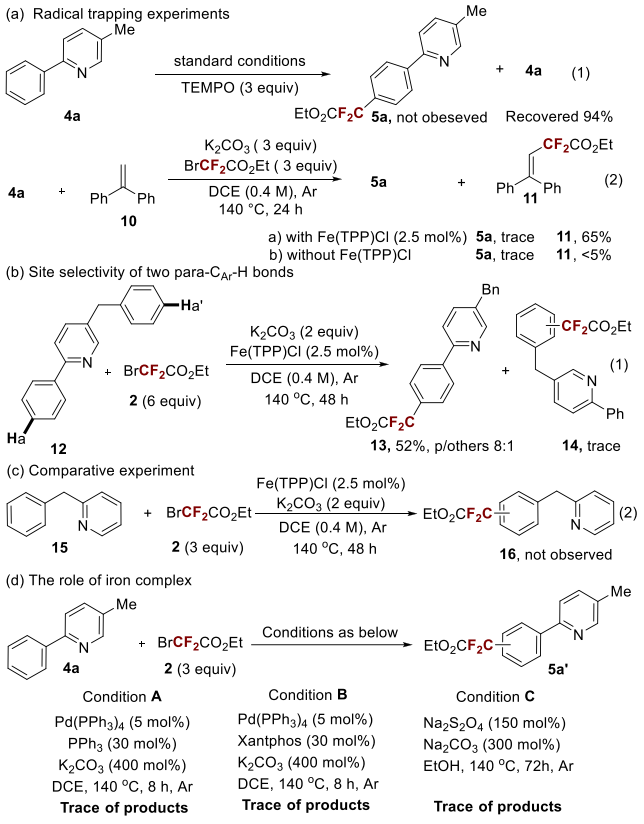
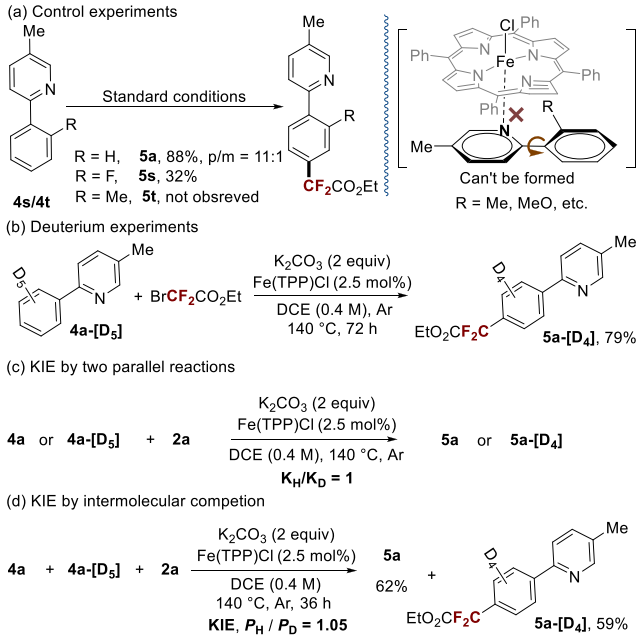
Scheme 6. Preliminary Mechanistic Study



Cl (Scheme 6a). These results indicated the reaction proceeded via a free radical pathway and Fe(TPP)Cl played an important role in generating the $^{\bullet}CF_2CO_2Et$ free radical. Substrate **12**, with two potential reaction sites, was subjected to standard reaction conditions and gave only product **13** in 52% yield (trace amounts of product **14** were obtained; Scheme 6b). Substrate **15** failed to provide the difluoromethylated product under standard reaction conditions, and 2-benzylpyridine was recovered (Scheme 6c). These results indicated the benzene ring adjacent to the nitrogen atom in the heteroaromatic compound was activated by the iron complex. The $^{\bullet}CF_2CO_2Et$ radical forms from 2-bromo-2,2-difluoroacetates and has been reported by the Ackermann,[12] Wang,[13] and Kondratov[19] groups as well as our group.[14] Thus, we directly subjected substrates **4a** and **2** to these reported catalytic systems (Scheme 6d). Unfortunately, **5a′** was not obtained in yields above 5%. These results further suggested the Lewis acid iron complex may coordinate to the nitrogen, which results in an electron-deficient (hence more active) arene core.[20] Meanwhile, the steric hindrance brought by the TPP blocked ortho- and meta-difluoromethylation on the aromatic ring and resulted in high para selectivity.[5a,17,21]

Finally, compared with substrate **4a**, product **5s** was obtained in 32% yield with high para selectivity when fluorine was in the ortho position. Methyl, methoxy, and other functional groups in the ortho position did not yield para-difluoromethylated products, and the only material obtained was the recovered starting material (Scheme 7a). These results suggested that the key intermediate may not be formed with a sterically hindered functional group. Isotopic-labeling experiments indicated that ortho-C−H activation did not occur (Scheme 7b), and a kinetic isotope effect of 1.0 further

Scheme 7. Additional Mechanistic Study Experiments

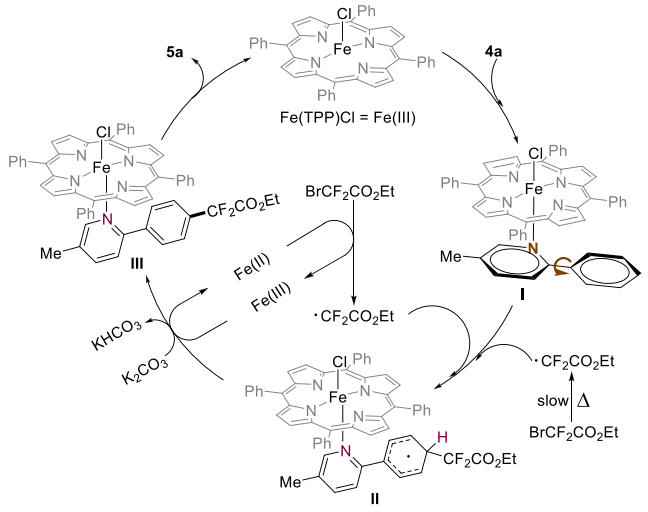


supported the notion that a cyclized iron intermediate was not formed (Scheme 7c and d). Several control reactions were performed, and the catalyst residue was further analyzed by XPS spectroscopy and cyclic voltammetry, which suggested the iron(II) complex might be formed during the catalytic cycle[22] (for details see the Supporting Information).

Based on these results and previous reports,[17,20d,23] a plausible reaction pathway is proposed. The Fe(TPP)Cl cyclized iron coordinated to the substrate led to the formation of intermediate **I**. The free radical $^{\bullet}CF_2CO_2Et$, generated using an iron porphyrin, reacts directly with **I** at the less sterically hindered para position to form intermediate **II**, followed by deprotonation and aromatization to provide the para-difluoromethylated product and an iron complex (Scheme 8).

In conclusion, we developed an [Fe(TPP)Cl]-enabled, para-selective C−H difluoromethylation of arenes using $BrCF_2CO_2Et$ as the difluoromethylation source. A wide variety of heteroaromatic compounds were all compatible, leading to

Scheme 8. Plausible Mechanism



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the corresponding products in moderate to good yields. A preliminary mechanistic study revealed the iron complex not only activates the aromatic ring but also affords the para selectivity by utilizing the steric effect of TPP.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c09545.

^{1}H, ^{13}C, and ^{19}F NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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