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Iron-Catalyzed Borylation of Aryl Ethers via Cleavage of C−O Bonds

Xiaoqin Zeng, Yuxuan Zhang, Zhengli Liu, Shasha Geng, Yun He, and Zhang Feng*

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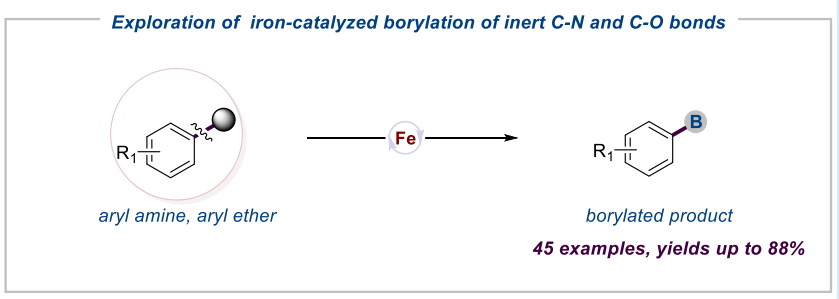


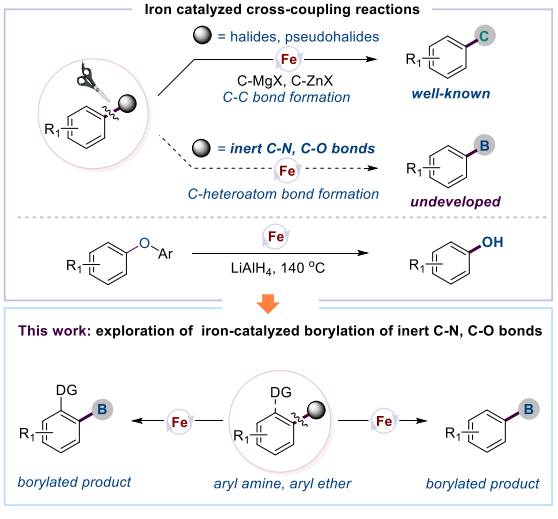
ABSTRACT: Herein, we report the iron-catalyzed borylation of aryl ethers and aryl amines via cleavage of C−O and C−N bonds. This protocol does not require the use of Grignard reagents and displays a broad substrate scope, which allows the late-stage borylation. It also provides facile access to multisubstituted arenes through C−H functionalization using 2-pyridyloxy as the directing group.

The transformation of inert chemical bonds is an attractive and challenging task in synthetic chemistry.[1] It provides a great advantage for orthogonal diversification of complex compounds via the late-stage functionalization.[1] Due to the ubiquitous existence of anilines and phenols, and their valuable applications as synthetic building blocks, numerous protocols have been developed for the diversification of inert C−N[2] and C−O bonds[3] over the past decades (Scheme 1). This area is dominated by nickel catalysis at present,[4] and only a few examples were reported using other transition metals.[5] Iron-catalyzed cross-coupling reactions have received great attention due to their nontoxicity and abundance.[6] Although the iron-catalyzed reactions have been studied for several decades, the exploration of inert bonds catalyzed by iron has been rarely reported.[7] Hence, it is of great interest to develop efficient iron-catalyzed transformations of inert bonds.

Organoboron compounds have been widely employed as intermediates in organic synthesis.[8] Cook, Bedford, and Nakamura reported the iron-catalyzed syntheses of organoboron compounds,[9] in which the halides were used as substrates.[9a,b,e] Moreover, to facilitate the oxidative addition, Grignard reagents were sometimes required to generate the low-valent iron species via *in situ* reductive elimination.[9b,c] In continuation of our interest in transition-metal catalysis,[10] we intended to develop the method for the formation of C−B bond through activation of inert C−N and C−O bonds via iron catalysis, which is operationally simple and without the use of Grignard reagents.

To explore the iron-catalyzed borylation of inert C−N bond, we synthesized a number of potential nitrogen-based electrophiles which were well studied in the nickel-catalyzed transformation of C−N bonds.[4] When $P(Cy)_3$, $P(t\text{-}Bu)_3$, and

Scheme 1. Iron-Catalyzed Functionalization of C−N and C−O Bonds



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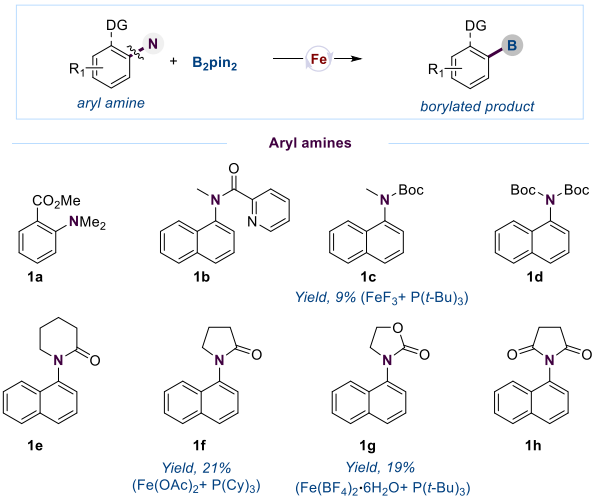
$P(Ad)_3$, common electron-rich ligands, were employed in the presence of $Fe(OAc)_2$, neither aromatic amine **1a** bearing the directing group nor **1b** containing a traceless directing pyridyl group produced the corresponding borylated product. With enhanced reactivity of the C−N bond, the amine **1c** containing an electron-deficient Boc group generated the desired compound in a 9% yield (Scheme 2). Different cyclic amides

Scheme 2. Optimization of the Reaction of Aryl Amine with B_2pin_2[a]

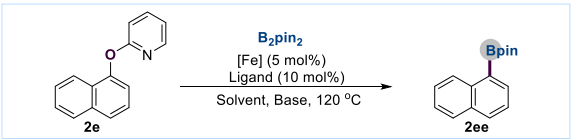


[a]Reaction conditions: for details, please see Supporting Information.

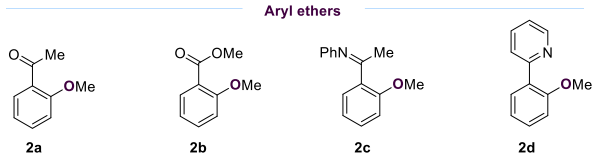
were investigated employing $P(t\text{-Bu})_3$ as the ligand. The five-member ring amide **1f** showed the highest reactivity, resulting in the corresponding product in 21% yield, which was in agreement with those previously reported works (Scheme 2).[4] Installing two electron-deficient groups onto the amine led to the decomposition of substrates **1d** and **1h**, and only trace amounts of the desired products were obtained (Scheme 2). These results suggest that electron-rich ligands could promote the borylation reaction when relatively reactive amides **1c** and **1f** were used as substrates, albeit with low efficiency (Scheme 2; for details, see Supporting Information). It confirms that the borylation of C−N bonds catalyzed by iron is challenging in the absence of Grignard reagents, as the C−N bonds are challenging to undergo oxidative addition owing to the high bond dissociation energy.[11]

Encouraged by these results, we envisioned that the borylation of C−O bonds via iron catalysis should be more feasible. Therefore, we turned our attention to the readily available aryl ethers. The nickel-catalyzed transformation of enol ethers to olefins was demonstrated by the Wenkert group in 1979.[12] To our knowledge, the construction of the C−heteroatom bond from aryl ethers catalyzed by iron was not reported. An important example of reductive cleavage of ether C−O bond by iron catalyst was reported by the Wang group,[13] in which a high temperature of 140−180 °C was required. Inspired by the studies from the Kakiuchi[5] and Snieckus groups,[14] the aryl ethers bearing a directing group, **2a**, **2b**, and **2c**, were first investigated. No desired products were observed after evaluation of some electron-rich phosphine ligands, such as $P(Cy)_3$, $P(t\text{-Bu})_3$, and $P(Ad)_3$ in the presence of $Fe(OAc)_2$ (Scheme 3). When the pyridyl group was used as a directing group,[15] **2d** did not undergo the borylation (Scheme 3). The 2-pyridyloxy group has been commonly used in the C−H bond

Scheme 3. Representative Results for the Optimization of the Iron-Catalyzed Borylation of 2e[a]



entry	[Fe]	ligand	solvent	base	yield[b]
1	FeI_2	$P(Cy)_3$	toluene	*t*-BuONa	32%
2	$Fe(acac)_3$	$P(Cy)_3$	toluene	*t*-BuONa	65%
3	$Fe(OAc)_2$	$P(Cy)_3$	toluene	*t*-BuONa	88%
4	$Fe(OAc)_2$	$P(Cy)_3$	toluene	*t*-BuOLi	57%
5	$Fe(OAc)_2$	$P(Cy)_3$	toluene	*t*-BuOK	trace
6	$Fe(OAc)_2$	$P(Cy)_3$	$(i\text{-Pr})_2O$	*t*-BuONa	59%
7	$Fe(OAc)_2$	$P(Cy)_3$	dioxane	*t*-BuONa	54%
8	$Fe(OAc)_2$	XPhos	toluene	*t*-BuONa	79%
9	$Fe(OAc)_2$	*t*-BuXPhos	toluene	*t*-BuONa	95% (88%)
10	$Fe(OAc)_2$		toluene	*t*-BuONa	0%
11		*t*-BuXPhos	toluene	*t*-BuONa	0%



[a]Reaction conditions (unless otherwise specified): Aryl ether (0.2 mmol), B_2pin_2 (0.4 mmol), [Fe] (5 mol %), Ligand (10 mol %), Base (2.5 equiv), Solvent (2.0 mL), 120 °C, 12 h. [b]NMR yield using mesitylene as an internal standard. The isolated yield is shown in parentheses.

functionalization reactions,[16] but there are no efficient methods to remove the pyridine ring,[17] thus limiting its practical applications. The removal of the pyridine ring from the 2-pyridyloxy moiety usually requires two steps: (i) *N*-methylation with a strong methylating reagent and (ii) cleavage of the C−O bond using a strong base. Therefore, the development of an efficient method for direct borylation of 2-pyridyloxy via iron catalysis would be highly appealing.[18] To our delight, 2-pyridyl ether **2e** indeed underwent the borylation, providing the corresponding product in 32% yield in the presence of $P(Cy)_3$ (Scheme 3, entry 1). Other iron sources were also tested. $Fe(OAc)_2$ and $Fe(acac)_3$ could provide the product in moderate to good yields (Scheme 3, entries 2−3). This reaction was very sensitive to inorganic bases, and only strong bases, such as *t*-BuOLi and *t*-BuONa, could efficiently promote this transformation (for details, see Supporting Information). Other solvents, such as diisopropyl ether and dioxane, also provided the corresponding product in moderate yields, but toluene stood out as the best (Scheme 3, entries 6−8). After investigating various ligands, 88% isolated yield was provided with *t*-BuXPhos (Scheme 3, entry 9). Control experiments demonstrated the importance of both ligand and iron species. No desired product was observed without the use of an iron catalyst or ligand (Scheme 3, entries 10−11).

We then set out to examine the scope of the reaction (Table 1). When naphthyl ethers were employed, the transformation proceeded smoothly and provided the borylated products in moderate to good yields (**2ee**−**13ee**, 47%−88%). Functional groups, such as methoxy, amine, morpholyl, and fluoro, were well-tolerated (**3ee**, **7ee**−**10ee**). Substrate **4e** containing an electron-rich methoxy group at the 4-position on the ring

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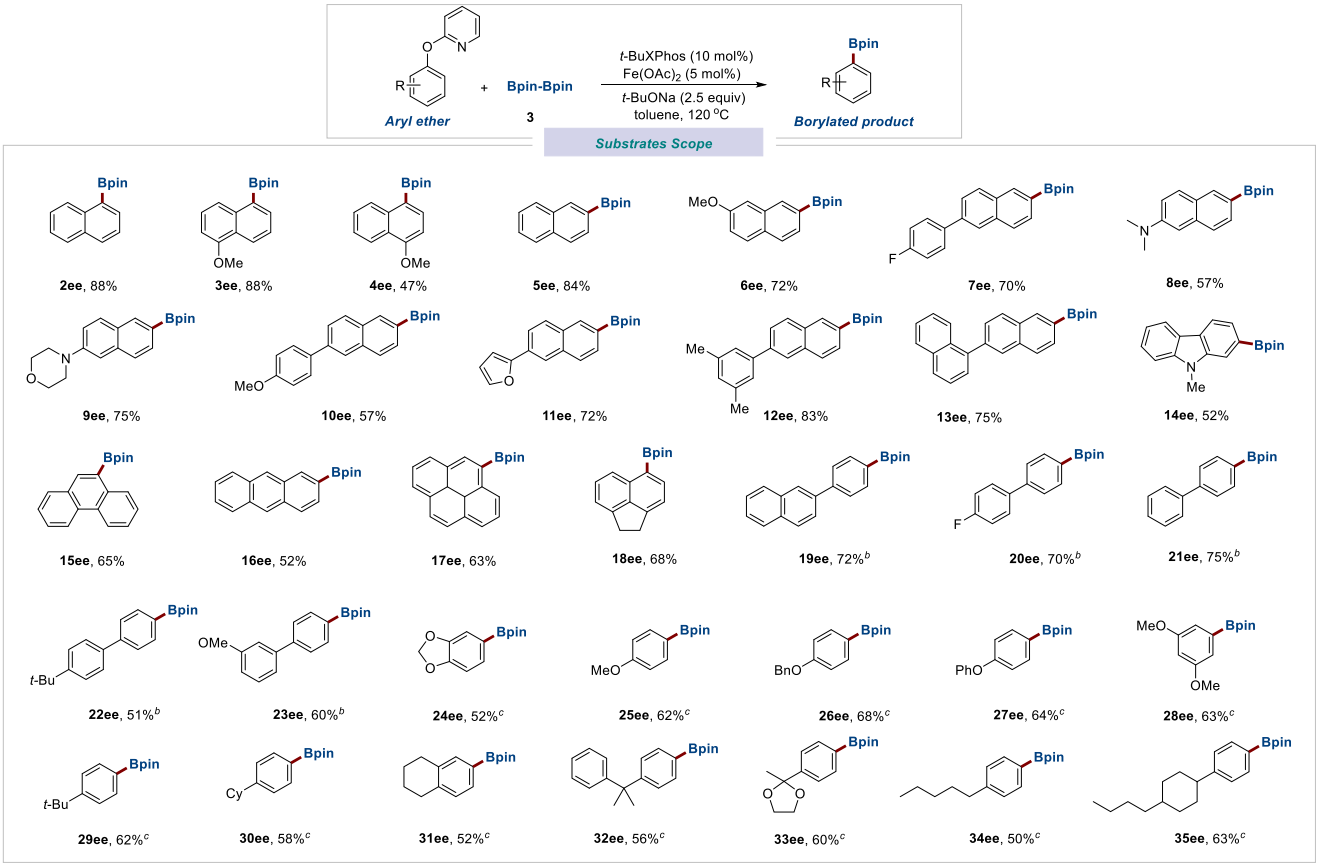
Table 1. Scope of the Iron-Catalyzed Borylation of Aryl Ethers[a]



[a]Reaction conditions: Aryl ether (0.2 mmol), B_2pin_2 (0.4 mmol), [Fe] (5 mol %), Ligand (10 mol %), Base (2.5 equiv), toluene (2.0 mL), 120 °C, 12 h (for details, please see Supporting Information). [b]Aryl ether (0.2 mmol), B_2pin_2 (0.4 mmol), $Fe(OAc)_2$ (10 mol %), *i*-Pr NHC (20 mol %), *t*-BuOK (3.0 equiv), toluene (2.5 mL), 128 °C, 15 h. [c]Aryl ether (0.2 mmol), B_2pin_2 (0.6 mmol), $Fe(OAc)_2$ (10 mol %), *i*-Pr NHC (20 mol %), *t*-BuOK (4.0 equiv), MTBE (3.2 mL), 128 °C, 15 h.

bearing a 2-pyridyloxy group furnished **4ee** in 47% yield, which is in sharp contrast to the borylation of substrate **3e** (**3ee**, 88%). Heteroarene **11e** bearing a furanyl group also reacted well, delivering borylated product in good yield. *N*-Heterocyclic carbazole substrate performed well, leading to product **14ee** in moderate yield. Polycyclic aryl ethers are also suitable substrates for this transformation, delivering the borylated products in moderate yields (**15ee**−**18ee**, 52%−68%). The biphenyl and monophenyl substrates (**19e**−**35e**) were relatively inert reaction partners, and the reaction proceeded sluggishly. To our delight, when the phosphine ligand was switched to a more electron-rich ligand, *N*-heterocyclic carbene (NHC), and the catalyst loading was increased, this reaction could proceed smoothly and yielded the borylated products in moderate to good yields (**19ee**−**35ee**, 50%−75%). Additionally, the borylation reaction could be conducted on a gram scale, and the product **2ee** was obtained in 65% yield.

To further explore the utility of our method, we set out to investigate the late-stage functionalization of biorelevant molecules, such as estrone and vitamin E (Scheme 4). The borylated products were obtained in moderate yields (**36ee**−**37ee**, 51%−52%). The inherent utilities of this protocol were further demonstrated by *ortho*- and *meta*-arylation with the aid of 2-pyridyloxy, followed by iron-catalyzed borylation. The *ortho*-arylated substrates could be easily obtained through a palladium-catalyzed cross-coupling reaction[17] and underwent the borylation reaction smoothly, delivering the corresponding products in moderate yields (**38ee**−**42ee**, 48%−61%). Moreover, a *meta* group could be introduced in the aryl ring,[19] and the corresponding borylated products could be obtained in 48%−60% yields (**43ee**−**46ee**). These results suggest that this protocol could provide a means for orthogonal transformations of aryl ethers and facile access to *ortho*- or *meta*-substituted arenes.

To explore the mechanism of the reaction, the following experiments were conducted. The radical inhibitor **BHT** or radical scavenger **TEMPO** was used as the additive. This reaction was completely shut down. Moreover, no adduct of the aryl radical with **TEMPO** was observed (Scheme 5A). However, a radical signal was indeed observed in this catalytic system by the EPR experiment (Scheme 5A). Furthermore, a radical clock experiment was carried out. Interestingly, *β*-carbon elimination product **47ee** was obtained instead of the common radical ring-opening product **48ee** (Scheme 5B).[20] These results demonstrated that the radical pathway was involved in this reaction. However, it might not be a boron centered radical species. To confirm whether the nitrogen atom on the pyridine ring played a directing role, the control experiments were conducted. As depicted in Scheme 5C, increasing the steric hindrance of the substituent on the 6-position of the pyridine ring diminished yield (Scheme 5C, **2f**), and no desired product was observed when **2g** with a bulky

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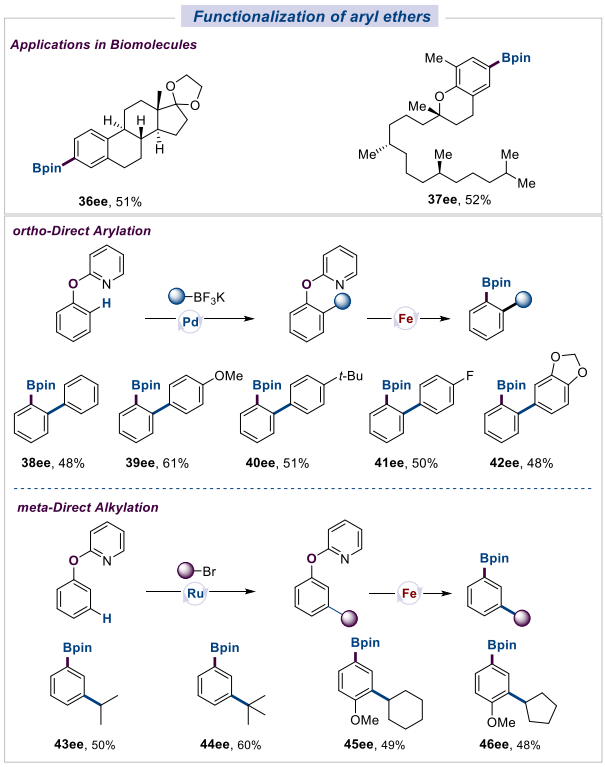
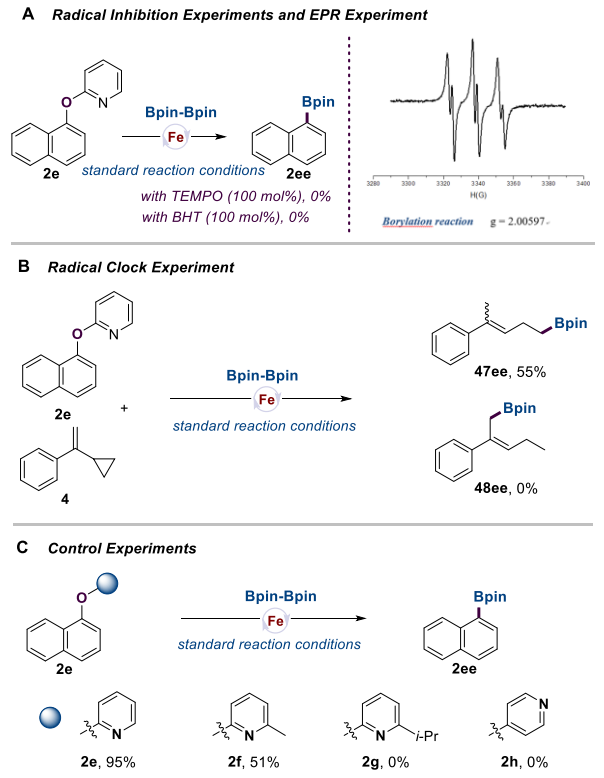
Scheme 4. Functionalization of Biomolecules and Orthogonal Transformation of Aryl Ethers



Scheme 5. Mechanistic Studies

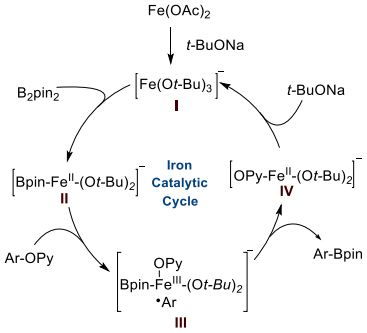


isopropyl group was used as substrate. Moreover, the 4-hydroxy pyridine group could not promote this transformation (Scheme 5C, **2h**). Thus, the nitrogen atom adjacent to oxygen on the pyridine ring may act as an iron-coordinating group and facilitate the oxidative-addition process.

To gain further insight into the nature of iron species in this reaction, the reaction mixture of $Fe(OAc)_2$, *t*-BuONa, *t*-BuXphos, and diboron was analyzed by the X-ray photoelectron spectroscopy (XPS) (for details, see Supporting Information, Figures S2–S3). A peak corresponding to Fe^{II} was observed with the binding energy at 710.3 eV (compared with FeO).[21] Moreover, when the mixture under standard reaction conditions was analyzed by XPS, both Fe^{II} and Fe^{III} were found with the binding energy at 710.3 eV (compared with FeO) and 712.8 eV (compared with $FePO_4$).[22] These results suggest that an Fe^{II}/Fe^{III} catalytic cycle might be involved in this reaction, but the Fe^{II}/Fe^{IV} pathway could not be excluded.

Based on the preliminary results, a probable mechanistic pathway was proposed (Scheme 6). An ate iron alkoxide

Scheme 6. Proposed Mechanistic Pathway



complex **I** was first generated through the reaction of *t*-BuONa with $Fe(OAc)_2$.[23] Subsequent transmetalation of the resulting iron species **I** with diboron afforded complex **II** with high reduction potential,[24] which then reacted with aryl ether through a single electron transfer pathway, delivering an iron(III) intermediate **III**. Finally, the desired product was provided through the reductive elimination, and the iron(II) species **IV** was regenerated.

In conclusion, we have developed a protocol for iron-catalyzed borylation of aryl ether via C–O bond cleavage, which offers late-stage borylation of complex molecules, and also provides a good opportunity to access multisubstituted arenes through the C–H bond functionalization using 2-pyridyloxy as the directing group. Preliminary mechanistic studies suggest that there may be an Fe^{II}/Fe^{III} catalytic cycle in this reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00679.

Detailed experimental procedures, and characterization data for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Zhang Feng − *School of Pharmaceutical Sciences, Chongqing University, Chongqing 401331, P. R. China; School of Preclinical Medicine, North Sichuan Medical College, Sichuan Key Laboratory of Medical Imaging & Department of*

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Chemistry, Sichuan 637000, China; orcid.org/0000-0001-7776-8200; Email: fengzh@cqu.edu.cn

Authors

Xiaoqin Zeng − *School of Pharmaceutical Sciences, Chongqing University, Chongqing 401331, P. R. China*

Yuxuan Zhang − *School of Pharmaceutical Sciences, Chongqing University, Chongqing 401331, P. R. China*

Zhengli Liu − *School of Pharmaceutical Sciences, Chongqing University, Chongqing 401331, P. R. China*

Shasha Geng − *School of Pharmaceutical Sciences, Chongqing University, Chongqing 401331, P. R. China*

Yun He − *School of Pharmaceutical Sciences, Chongqing University, Chongqing 401331, P. R. China;* orcid.org/0000-0002-5322-7300

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00679

Notes

The authors declare no competing financial interest.

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