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Development and Mechanistic Studies of Iron-Catalyzed Construction of Csp^2–B Bonds via C–O Bond Activation

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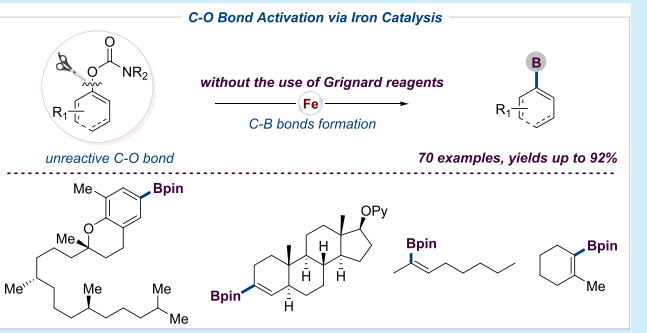
ABSTRACT: Herein we describe an iron-catalyzed borylation of alkenyl and aryl carbamates through the activation of a C–O bond. This protocol exhibits high efficiency, a broad substrate scope, and the late-stage borylation of biorelevant compounds, thus providing potential applications in medicinal chemistry. Moreover, this method enables orthogonal transformations of phenol derivatives and also offers good opportunities for the synthesis of multi-substituted arenes. Preliminary mechanistic studies suggest that a Fe^{II}/Fe^{III} catalytic cycle via a radical pathway might be involved in the reaction.

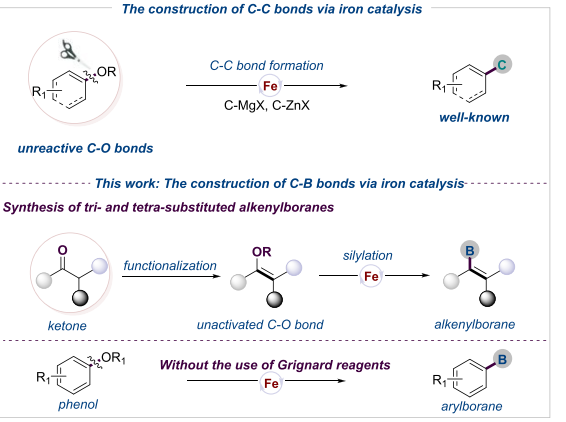


Owing to their cheapness, abundance, and nontoxicity, iron catalysts have been widely used to construct C–C bonds through classical cross-coupling reactions, such as Kumada, Negishi, and Suzuki reactions, using organometallic reagents or organoborons as substrates.[1] However, the formation of carbon–heteroatom bonds by iron catalysis has rarely been explored.[2] Moreover, organohalides are usually used as substrates in iron-catalyzed cross-coupling reactions due to their mild reactivity.[3] Compared with organohalides, oxygen-based electrophiles, such as enolate and phenol derivatives, have become increasingly more attractive as coupling partners because halide-containing waste can be avoided, and ketones and phenols are commercially available and easily produced.[4] Iron-catalyzed C–C bond formation reactions of oxygen-based electrophiles with organometallic reagents were reported by the Nakamura, Garg, Shi, and Cook groups in recent years.[5] To the best of our knowledge, iron-catalyzed carbon–heteroatom bond formation through unreactive C–O bonds has scarcely been developed, even though unreactive C–O bonds have been well studied with nickel and rhodium catalysts.[6−9] This transformation is challenging because it is difficult for the unreactive C–O bonds to undergo oxidative addition with iron catalysts due to their strong bond dissociation energy.[10]

Organoboron compounds are very important and widely employed in organic synthesis, materials science, as well as applications in medicinal chemistry.[11] To date, the transition-metal-catalyzed formation of alkenylboranes has been less reported.[12,13] Thus the construction of Csp^2–B bonds catalyzed by base-metal catalysts using environmentally friendly oxygen-based electrophiles as substrates in a green and highly efficient way is very appealing. With our continuing interest in transition-metal catalysis,[14] herein we describe an example of the iron-catalyzed borylation of alkenyl and aryl carbamates, thus providing a facile and efficient route for the synthesis of tri- and tetra-substituted alkenylboranes (Scheme 1).

Giving the important applications of carbamates in orthogonal transformations and C–H bond functionalization as the directing group,[15] we have a great interest in the exploration of the borylation of alkenyl and aryl carbamates.

Scheme 1. Iron-Catalyzed Construction of C–B Bonds



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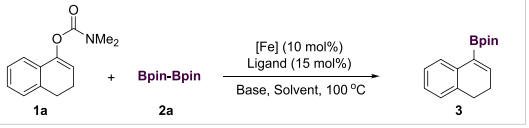
Consequently, we began our investigations by subjecting alkenyl carbamate **1a** to diborane **2a** in the presence of various bases and ligands. (For details, see the Supporting Information.) To our delight, this reaction could proceed when TMEDA was used as a ligand, albeit with poor efficiency (Scheme 2, entries 1 and 2). The bases were crucial for this

Scheme 2. Representative Results for the Optimization of the Iron-Catalyzed Borylation of 1a[a]



Entry	[Fe]	Ligand	Solvent	Base	Yield[b]
1	$Fe(OAc)_2$	TMEDA	MTBE	*t*-BuOLi	5%
2	$Fe(OAc)_2$	TMEDA	MTBE	MeOLi	15%
3	$Fe(OAc)_2$	Phen	MTBE	MeOLi	30%
4	$Fe(OAc)_2$	bpy	MTBE	MeOLi	50%
5	$Fe(acac)_3$	bpy	MTBE	MeOLi	42%[c]
6	$Fe(OTf)_2$	bpy	MTBE	MeOLi	53%[c]
7	$Fe(OTf)_2$	bpy	1,4-dioxane	MeOLi	37%[c]
8	$Fe(OTf)_2$	bpy	toluene	MeOLi	86% (80%)[c]
9		bpy	toluene	MeOLi	0%[c]
10	$Fe(OTf)_2$		toluene	MeOLi	20%[c]
11	$Cu(OAc)_2$	bpy	toluene	MeOLi	0%[c]
12	$Ni(OTf)_2$	bpy	toluene	MeOLi	0%[c]

[a]Reaction conditions (unless otherwise specified): **1a** (0.2 mmol, 1.0 equiv), dilborane **2a** (0.4 mmol, 2.0 equiv), [Fe] (0.02 mmol, 0.1 equiv), ligand (0.03 mmol, 0.15 equiv), solvent (2.0 mL), base (0.8 mmol, 4.0 equiv), 100 °C, 15 h. [b]Determined by ^{1}H NMR using mesitylene as an internal standard. The isolated yield is shown in parentheses. [c]MeOLi (5.0 equiv) was used.

reaction, and strong bases, such as *t*-BuOLi and MeOLi, could promote the reaction. A 15% yield of the desired product could be delivered using MeOLi as the base. Other bases, such as K_2CO_3 and Cs_2CO_3, could not promote this transformation. After testing other ligands, dinitrogen ligands stood out, providing the borylated product in moderate yields (Scheme 2, entries 3 and 4; for details, see the Supporting Information). 2,2-Bipyridine was demonstrated as the best choice, and the desired product **3** was obtained in 50% yield (Scheme 2, entry 4). Then, other iron sources were evaluated. $Fe(OTf)_2$ could slightly improve the reaction efficiency, delivering **3** in 53% yield (Scheme 2, entry 6). Switching the solvent from ethers to toluene provided the borylated product in 86% yield (Scheme 2, entries 7 and 8). Control experiments were conducted, which demonstrated the necessity of both an iron catalyst and ligand. No desired product was observed in the absence of an iron catalyst, and only a 20% yield of **3** was provided without the use of a ligand. These results suggest that an electron-rich ligand, 2,2-bipyridine, plays a crucial role in promoting this transformation. To rule out the trace-metal effect in this reaction, copper and nickel catalysts were tested, and no desired product was observed, which suggested that this reaction was indeed catalyzed by the iron catalysts.

After the optimal conditions were established, the scope of this iron-catalyzed borylation reaction was explored. Alkenyl carbamates could react smoothly, delivering the corresponding products in moderate to good yields (**3**−**32**) (Table 1). Moreover, this reaction exhibited good functional group tolerance. Functional groups such as Cl, F, CF_3, Tips, Opy (2-pyridyloxy), and OBn (**11**, **12**, **13**, **14**, **21**, **22**) were well-tolerated. Thiophene carbamate could also react well, providing the borylated product in 67% yield (**16**). Most remarkably, the alkenyl carbamates without the π-extend conjugated system were demonstrated as good substrates for this borylation, providing the desired products in moderate yields (**19**−**26**, **29**, **32**, 40−71%). Gratifyingly, unreactive linear carbamate was also a suitable substrate, and the corresponding product was isolated in an acceptable yield (**29**, 40%). It should be mentioned that the tetra-substituted alkenyl boronic esters are difficult to synthesize owing to their steric hindrance and could be obtained in moderate yields through our protocol (**30**−**32**, 40−70%). Encouraged by these results, the borylation of aryl carbamates was evaluated as well. When naphthyl carbamates were used as substrates, this reaction proceeded smoothly, providing the borylated products in moderate to excellent yields (**33**−**41**, 66−92%). Functional groups, such as methoxy, trifluoromethyl, morpholyl, and amine, were well-tolerated and afforded the corresponding products in good yields (**36**, **38**, **39**, and **51**). Polycyclic aromatic substrates, such as phenanthryl carbamate, provided **42** in good yield (74%). Furthermore, *N*-heterocyclic ring carbazole carbamate underwent this borylation reaction smoothly as well, producing **44** in a good yield. Additionally, biphenyl substrates also exhibited good reactivity, delivering the borylated products in moderate to good yields (**45**−**47**, 57−71%). Substrates bearing an ortho bulky phenyl group also reacted smoothly, producing **49** in reasonable yield. Importantly, monophenyl carbamates are also applicable to the reaction and provided the corresponding products in moderate to excellent yields (**50**−**60**, 50−86%). This transformation could be conducted on a 6 mmol scale, and a 58% yield was obtained. To explore the scope of this transformation, other oxygen-based electrophiles were evaluated. Oxygen-based groups, such as OTs and OTf, produced the borylated product in a <6% yield, and the OAc and $OPO(OPh)_2$ groups could not undergo this transformation at all, in which a large amount of phenol and protonated product were observed. The OPiv group could react with diborane reagent **2a** with low efficiency, providing the corresponding product in 26% yield. (For details, see the Supporting Information.) Other classical diborane reagents were explored as well, and no transformation occurred. (For details, see the Supporting Information.)

To further evaluate the application of this protocol, the late-stage borylation of biorelevant compounds, such as estrone, vitamin E, epiandrosterone, and stanolone carbamates, was conducted (Scheme 3). The arylboranes and alkenylboranes could be obtained in moderate to good yields (**61**−**65**, 46−76%), which provided a facile access to the diversification of phenol and ketone structures. Furthermore, the ortho- or meta-arylation through C−H bond activation using carbamate as the directing group was also carried out. The ortho-arylation of monophenyl carbamates was conducted using Bedford's method.[16] Furthermore, the ortho-arylated compounds underwent a further transformation, affording the borylated compounds in good yields (**66**−**70**, 55−67%). Similarly, the meta-arylated and borylated compounds could also be delivered in moderate to good yields (**71** and **72**, 50−67%).[17] These results demonstrate the inherent value of our protocol, which provides an efficient method for obtaining the valuable multisubstituted arenes.

To gain insight into the mechanism of this iron-catalyzed borylation reaction, radical inhibition experiments were first

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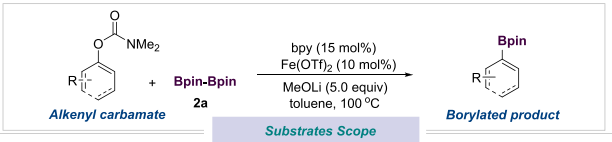
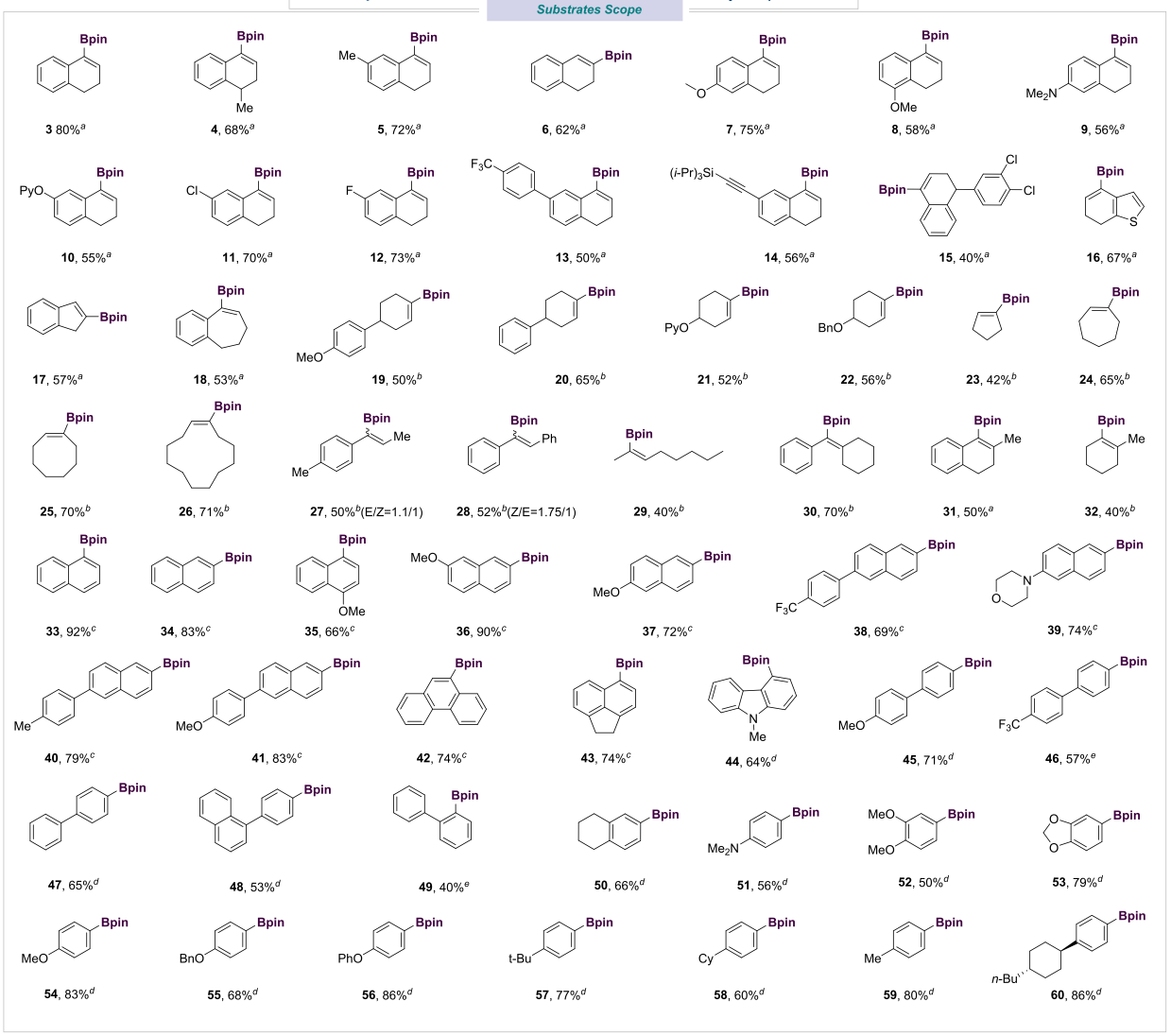
Table 1. Scope of the Iron-Catalyzed Borylation of Alkenyl and Aryl Carbamates[a]





[a]Reaction conditions: Alkenyl carbamates (0.2 mmol, 1.0 equiv), diborane **2a** (0.4 mmol, 2.0 equiv), $Fe(OTf)_2$ (0.02 mmol, 0.1 equiv), bpy (0.03 mmol, 0.15 equiv), toluene (2.0 mL), MeOLi (1.0 mmol, 5.0 equiv), 100 °C, 15 h. [b]Reaction conditions: Alkenyl carbamates (0.2 mmol, 1.0 equiv), $Fe(OTf)_2$ (0.02 mmol, 0.1 equiv), *t*-BuDavephos (0.05 mmol, 0.25 equiv), $PhCF_3$ (2.0 mL), MeOLi (1.0 mmol, 5.0 equiv), 100 °C, 15 h. (For details, see the Supporting Information.) [c]Reaction conditions: Aryl carbamates (0.3 mmol, 1.0 equiv), diborane **2a** (0.6 mmol, 2.0 equiv), $Fe(OAc)_2$ (0.015 mmol, 0.05 equiv), TMEDA (0.03 mmol, 0.1 equiv), *i*-Pr_2O (2.0 mL), *t*-BuONa (0.75 mmol, 2.5 equiv), 120 °C, 15 h. [d]Reaction conditions: Aryl carbamates (0.3 mmol, 1.0 equiv), diborane **2a** (0.6 mmol, 2.0 equiv), $Fe(OTf)_2$ (0.015 mmol, 0.05 equiv), MTBE (2.0 mL), *t*-BuONa (0.75 mmol, 2.5 equiv), 120 °C, 15 h. [e]Reaction conditions: Aryl carbamates (0.3 mmol, 1.0 equiv), diborane **2a** (0.6 mmol, 2.0 equiv), $Fe(OTf)_2$ (0.03 mmol, 0.1 equiv), MTBE (2.0 mL), *t*-BuONa (0.75 mmol, 2.5 equiv), 120 °C, 15 h.

carried out. When a radical scavenger **TEMPO** or a radical inhibitor **BHT** was used as the additive, only a small amount of desired product was generated (Scheme 4A). Furthermore, the radical intermediates were confirmed by EPR experiments. (See the Supporting Information.) To further confirm whether the boron radical or aryl radical participated in this reaction, a radical clock experiment was conducted (Scheme 4B). Instead of the radical ring-opening product **75**, compound **76** was obtained via a plausible β-carbon elimination pathway,[18] which revealed that the boron radical species could be ruled out. Moreover, we also tried to verify the possibility of the aryl radical in this reaction. However, the adduct of **TEMPO** with aryl radical **73** was not observed by LC-MS. The deuterated compound **77** was not obtained as well using d^8-toluene as the solvent. When a large amount of CD_3OD as the additive was added to the reaction to trap the reaction intermediates (see the Supporting Information, Figure S2), only hydrodeoxygenated product **77** was generated, and no deuterated product was observed, which suggested that the aryl-Fe species might not be involved in this catalytic cycle. On the basis of these deuterium experiments, there is the possibility that the aryl radical could not be excluded, which might involve the cage

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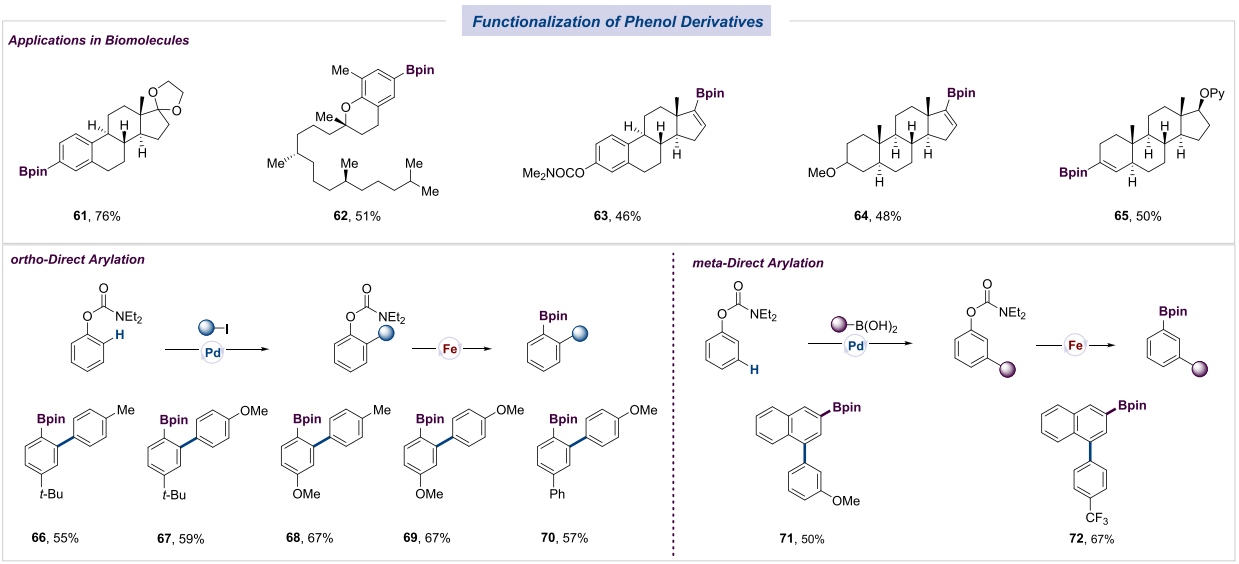
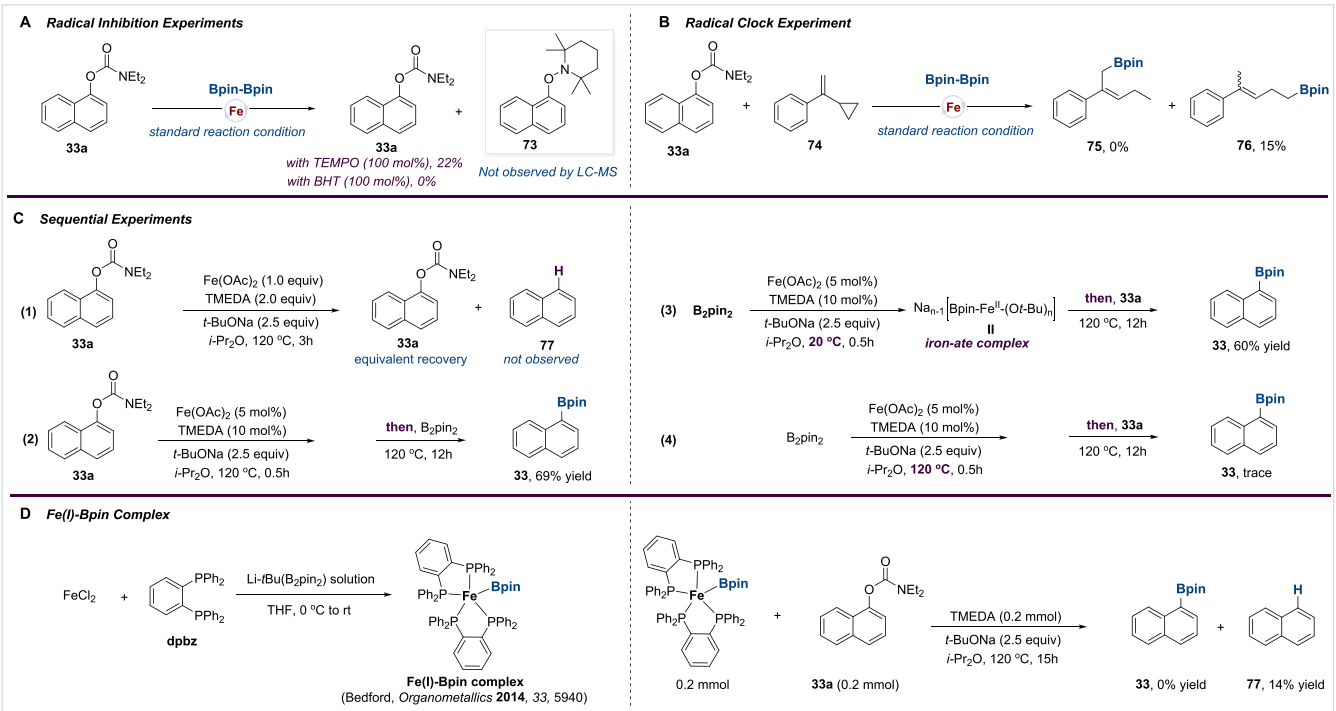
Scheme 3. Late-Stage Functionalization of Biomolecules and Orthogonal Transformations of Phenols



Scheme 4. Mechanistic Studies



effect of the aryl radical. Second, to study how to initiate this reaction, we conducted the sequential experiments. Without the diboron reagent **2a**, the substrate **33a** was fully recovered, and no protonated product was observed in the presence of 1 equiv of $Fe(OAc)_2$, which revealed that the mixture of $Fe(OAc)_2$, TMEDA, and *t*-BuONa could not induce the transformation of the C−O bond (Scheme 4, C1). Instead, 0.5 h later, when diboron reagent **2a** was added to the mixture, the borylated product could be obtained in 69% yield (Scheme 4, C2), suggesting that this reaction might be triggered by the aid of diboron reagent **2a**, and the involvement of an iron−boron intermediate was reasonable. Furthermore, the intermediate was confirmed by ^{11}B NMR. (See the Supporting Information, Figure S4.) The iron−boron complex[19] (^{11}B NMR, δ 22) and *t*-BuOBpin[20] (^{11}B NMR, δ 21) were observed after the mixture of B_2pin_2, $Fe(OAc)_2$, TMEDA, and *t*-BuONa reacted for 4 h. When substrate **33a** was added to the system, the iron−boron complex gradually increased, and a large amount of *t*-BuOBpin was generated. The iron−boron complex could react with aryl carbamate **33a**, providing the corresponding product in 60% yield (Scheme 4, C3). On the basis of these results, we thought that the iron-ate complex was *in-situ*-generated in the mixture of B_2pin_2, $Fe(OAc)_2$, TMEDA, and *t*-BuONa, which could promote this transformation smoothly. Unfortunately, all of the efforts to isolate the iron−boron complex have failed. At the present, the exact structure of the iron−boron complex and its coordination with *t*-BuONa could not be confirmed by high-resolution mass spectrometry (HRMS).

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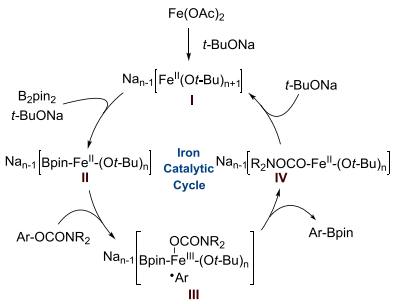
Next, to gain further insight into the nature of the iron-ate complex in the reaction, the reaction mixture of $Fe(OAc)_2$, *t*-BuONa, and diboron was analyzed by X-ray photoelectron spectroscopy (XPS). The XPS experiments suggest that a Fe^{II}/Fe^{III} catalytic cycle might be involved in the borylation reaction. (See the Supporting Information, Figures S7−S10.) Moreover, when 1 equiv of the boron−iron(I) complex was used as the substrate (Scheme 4D),[3b] this reaction could not proceed, and no borylated product was observed, which suggested that the boron−iron(I) species might not be the catalyst of this reaction. On the basis of these preliminary results, a hypothesized mechanism is illustrated in Scheme 5.

Scheme 5. Proposed Mechanism



An iron-ate alkoxide complex **I** could be generated when the ligand exchange occurs between *t*-BuONa and $Fe(OAc)_2$. Subsequently, the resulting iron species **I** transmetalates with diboron to afford an ate complex **II** with a high reduction potential,[21] which would react with aryl carbamate through a single electron-transfer pathway, delivering an iron(III) intermediate **III**.[22] Finally, as a consequence of reductive elimination, the desired product would be afforded, along with the regeneration of the iron(II) species **IV** as well. It should be noted that the iron(IV) species could not be ruled out in this catalytic cycle, even though the iron(IV) species was not observed in the XPS experiments.

In conclusion, we have reported the first example of the iron-catalyzed borylation of alkenyl and aryl carbamates via C−O bond activation. This protocol features simple operation, high efficiency, and a broad substrate scope. It also exhibits excellent applications in the late-stage borylation of bioactive compounds and the synthesis of ortho- or meta-substituted arenes, offering a good platform in drug discovery and development. Studies to further illustrate the mechanism and expand the utilization of this novel transformation are in progress in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01937.

Experimental data and copies of ^1H NMR and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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