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Rh^{III}-Catalyzed C−H (Het)arylation/Vinylation of *N*-2,6-Difluoroaryl Acrylamides

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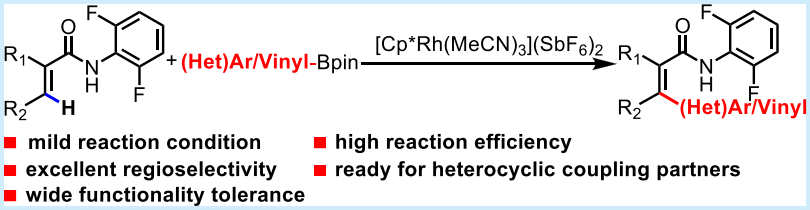
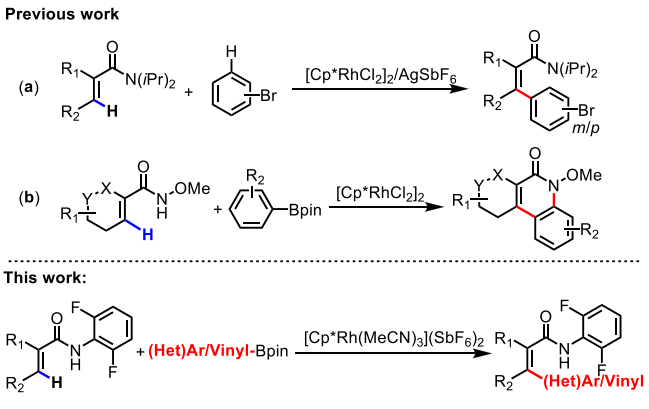


ABSTRACT: Rh^{III}-catalyzed sp^2 C−H cross-coupling of acrylamides with organoboron reactants has been accomplished using a commercially available *N*-2,6-difluoroaryl acrylamide auxiliary. A broad range of aryl and vinyl boronates as well as a variety of heterocyclic boronates with strong coordinating ability can serve as the coupling partners. This transformation proceeds under moderate reaction conditions with excellent functional group tolerance and high regioselectivity.

Cinnamamide derivatives and related substituted dienes are renown for the exhibition of fungicidal and biological activities in agrochemicals as well as their recent specific optical properties as fluorescent probes in organic materials.[1] Therefore, developing efficient and facile protocols for the construction of these compounds is highly desirable. Much effort has been focused on their rapid synthesis from commercially available raw materials under mild conditions with high regioselectivity. Over the past several decades, transition-metal-catalyzed C−H functionalization has demonstrated great potential in building essential structural motifs in a simple and atom-economical fashion.[2,3] Various metal catalysts (for instance, Co,[4] Ir,[5] Pd,[6] Fe,[7] Cu,[8] and Mn[9]) have been explored in this capacity via the cross-coupling reaction between acrylic acid derivatives and organometallic nucleophiles such as aryl halides, organoborons, or Grignard reagents. Despite significant progress in these reactions, heterocycle coupling partners are not compatible.[6c] The heteroarylation of acrylamide derivatives could provide an efficient method for the preparation of diversified heterocyclic drug molecules.[10] However, the strong coordinating ability of hetercycles can often outcompete substrates in binding the metal catalysts, resulting in the inhibition of catalytic turnover in C−H functionalization.

Recently, Rh^{III} salt has been developed as an one of the most effective catalysts to be used for improving the reactivity and site selectivity of the catalytic systems.[11] However, the Rh^{III}-catalyzed C−H (het)arylation of acrylamide derivatives still remains rare so far. In 2013, Glorius' group developed a Rh^{III}-catalyzed dehydrogenative cross-coupling between alkenes and arenes affording *Z*-selective *β*-arylated acrylamide derivatives (Scheme 1a).[12] Quite recently, Zhu's group reported a Rh^{III}-catalyzed C−H functionalization of cycloalkene-1-carboxamides with aryl boronates to synthesize cycloalkaquinolinones (Scheme 1b).[13] Inspired by these pioneering results and our previous work,[14] we demonstrated a facile Rh^{III}-catalyzed sp^2 C−H (het)arylation/vinylation of alkenes with boronates

Scheme 1. Rh^{III}-Catalyzed C−C Cross-Coupling between Acrylamide Derivatives and Organometallic Reagents



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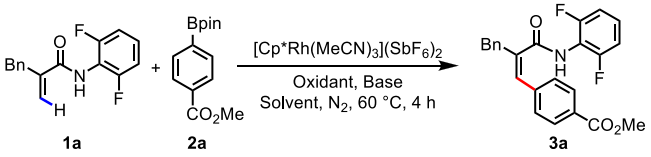
using weakly coordinating *N*-2,6-difluoroaryl acrylamides as directing groups.

We initiated a preliminary investigation by using model substrate *N*-2,6-difluoroaryl acrylamide **1a** and 4-carbomethoxyphenylboronic acid pinacolate **2a** with $[Cp^*Rh(MeCN)_3](SbF_6)_2$ catalyst (Table 1). Encouragingly, we discovered that

Table 1. Optimizations of the Model Reaction[a]



entry	oxidant	base	solvent	yield (%)[b]
1	Ag_2CO_3	K_2CO_3	MeCN	28
2	Ag_2CO_3	Na_2CO_3	MeCN	12
3	Ag_2CO_3	K_3PO_4	MeCN	NR
4	Ag_2CO_3	KF	MeCN	13
5	Ag_2CO_3	CsF	MeCN	11
6	AgOAc	K_2CO_3	MeCN	36
7	Ag_2O	K_2CO_3	MeCN	15
8	AgF	K_2CO_3	MeCN	26
9	Ag_3PO_4	K_2CO_3	MeCN	9
10	AgOTf	K_2CO_3	MeCN	20
11	AgOPiv	K_2CO_3	MeCN	56
12	AgOPiv	K_2CO_3	DCE	19
13	AgOPiv	K_2CO_3	DCM	8
14	AgOPiv	K_2CO_3	THF	45
15[c]	**AgOPiv**	**K_2CO_3**	**MeCN**	**66**
16	-	K_2CO_3	MeCN	NR
17[d]	AgOPiv	K_2CO_3	MeCN	NR
18[e]	AgOPiv	K_2CO_3	MeCN	49

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (0.01 mmol), oxidant (0.2 mmol), and base (0.2 mmol) in dry solvent (2 mL), nitrogen atmosphere, 4 h, 60 °C. [b]Yields were calculated from ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard. [c]AgOPiv(0.3 mmol). [d]Without catalyst. [e]$[Cp^*RhCl_2]_2$(0.005 mmol)/$AgSbF_6$ (0.02 mmol).

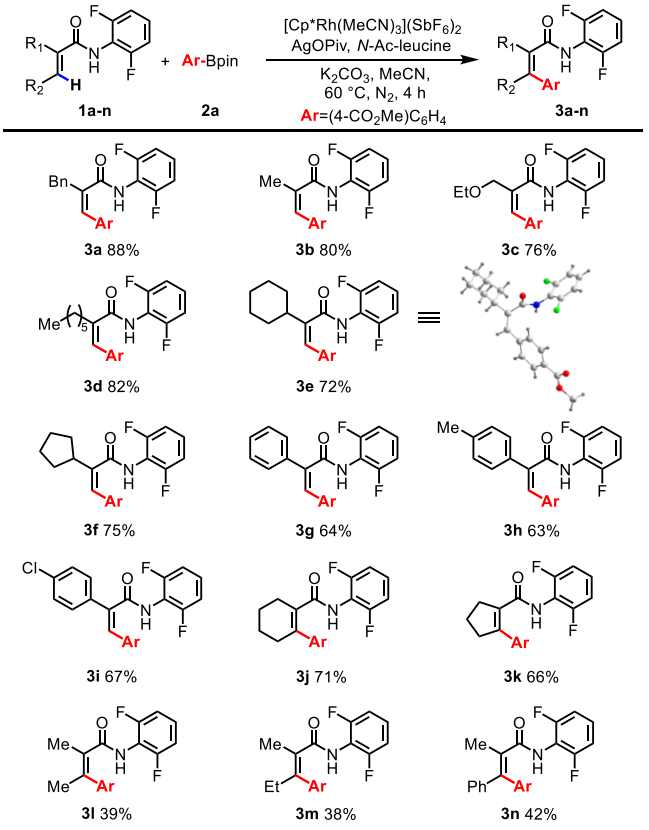
the combination of K_2CO_3, Ag_2CO_3, and MeCN facilitated the desired product **3a** in a 28% yield (entry 1). The *Z* configuration of the desired product **3a** was unambiguously notarized by nuclear Overhauser effect spectroscopy (NOESY) (see the Supporting Information) as well as by X-ray crystallographic studies (CCDC 2017009). Next, we screened the base additives and found K_2CO_3 to be optimal (entries 2−5). Further experiments, including the investigation of various oxidants and solvents (entries 6−14), showed that a combination of AgOPiv and K_2CO_3 gave a 56% yield. Increasing the amount of AgOPiv to 3 equiv enhanced the yield to 66% (entry 15). The control experiments without AgOPiv or the catalyst (entry 16 or 17, respectively) exhibited no transformation, confirming that both of them were crucial to this reaction. Additionally, the application of $[Cp^*RhCl_2]_2$/$AgSbF_6$ as a cocatalyst decreased the yield to 49% (entry 18).

To further ameliorate the reaction efficiency, we attempted to screen various ligands, including MPAAs (mono-*N*-protected amino acids), which could evidently accelerate the C−H cleavage step and promote the subsequent cross-coupling step via potentially regulating the electronic and steric properties of the catalytic center (Table S1).[15] By introducing *N*-acetyl-leucine (Ac-leucine) into the reaction system, the desired product could be obtained in 88% yield (Table S1, entries 2−10). Unprotected amino acids and phosphine ligands were also investigated; however, lower yields were obtained (Table S1, entries 11−16).

To confirm the importance of the *N*-2,6-difluoroaryl acrylamides directing group (**T**), we then investigated the effect of other auxiliaries (Scheme S1). No reaction occurred when acrylic acid (**T1**) and *N*-methoxyacrylamide (**T2**) were applied as the directing groups. Furthermore, the use of the weakly acidic *N*-phenylacrylamide (**T3**) afforded a lower yield of 67%. The previously reported strongly acidic directing group (**T4**) decreased the yield to 56%, which may be due to the weak stability of the substrate in this catalytic system. The *N*-2,6-difluoroaryl acrylamide directing group possesses an optimal balance of electronic properties and substrate stability in this system.

Having identified the optimal reaction conditions for the cross-coupling (Table S1, entry 5), we proceeded to investigate the acrylamide substrate scope using **2a** as the coupling reagent (Scheme 2). Nonactivated acrylate derivatives with alkyl

Scheme 2. Scope of Acrylamides Substrates[a,b]



[a]Reaction conditions: **1a−1n** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (0.01 mmol), AgOPiv (0.3 mmol), K_2CO_3 (0.2 mmol), and *N*-Ac-leucine (0.02 mmol) in dry MeCN (2 mL), nitrogen atmosphere, 4 h, 60 °C. [b]Isolated yield.

substituents at the α position reacted favorably to provide the corresponding products in good yields (**3b−3f**, 72−82%). For the tested α-aryl acrylamides, the desired products were obtained in acceptable yields with good tolerance toward various functional groups at the *para*- position (**3g−3i**). Moreover, the cyclic olefinic substrates readily participated in this transformation, delivering the corresponding arylated

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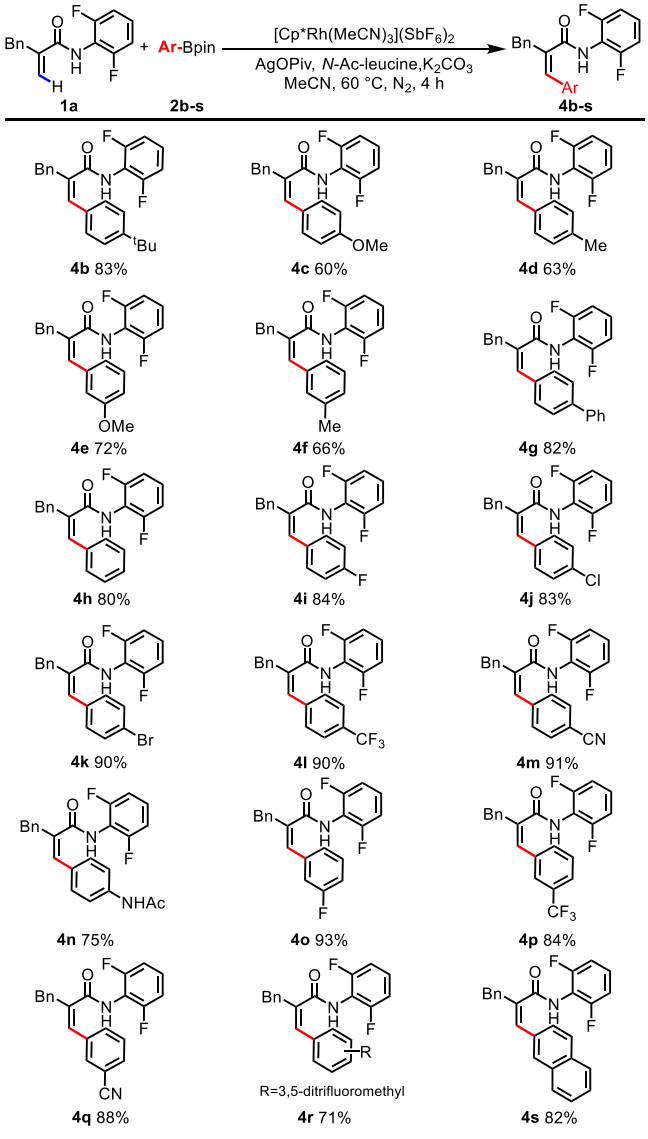
products (**3j** and **3k**) in satisfying yields (71 and 66%, respectively). However, when α,β-dimethyl, α-methyl-β-ethyl, and α-methyl-β-phenyl acrylamides were subjected to the reaction system, lower yields were delivered (38−42%). The steric and electronic effects of the substituents at the β-position of the vinylic C−H bond may lead to the much lower reactivity of the substrates (**1l**−**1n**).

To further scrutinize the scope of this arylation transformation, various functionalized arylboronic acid pinacol esters were then evaluated to determine their influence on the overall reactivity (Scheme 3). In general, this C−H functionalization methodology was appropriate for a large range of arylboronic acid pinacol esters bearing electron-rich and electron-deficient substituents, affording the products in moderate to excellent yields (60−93%). Arylboronic acid pinacol esters bearing *para*- and *meta*- alkyl groups provided yields from 60 to 83% (**4b**−**4f**). 4-Biphenyl- and phenyl-

Scheme 3. Scope of Arylation Reagents[a,b]

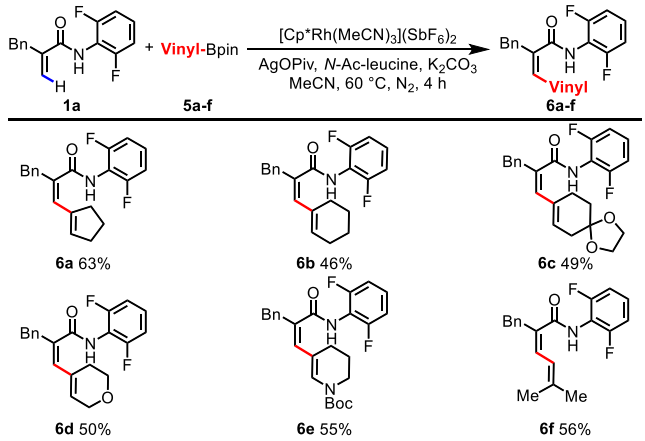


[a]Reaction conditions: **1a** (0.1 mmol), **2b**−**2s** (0.2 mmol), [Cp*Rh(MeCN)$_3$](SbF$_6$)$_2$ (0.01 mmol), AgOPiv (0.3 mmol), K_2CO_3 (0.2 mmol), and *N*-Ac-leucine (0.02 mmol) in dry MeCN (2 mL), nitrogen atmosphere, 4 h, 60 °C. [b]Isolated yield.

boronic acid pinacol esters performed well and gave 82 and 80% yields (**4g** and **4h**), respectively. A variety of electron-deficient *para*-substituted substrates, including the halogen, trifluoromethyl, and nitrile groups, delivered the desired arylated products in excellent yields (**4i**−**4m**, 83−91%). Notably, the coupling partner containing an acetamide group could also undergo the transformation smoothly to achieve the desired product in 75% yield (**4n**). Moreover, the use of *meta*-substituted as well as disubstituted electron-withdrawing arylboronates was allowed in this protocol to give the yields from 71 to 93% (**4o**−**4r**). Additionally, 2-naphthyl boronate also delivered the corresponding product in a yield of 82% (**4s**).

The successful application of arylboronic acid pinacol esters inspired us to examine the compatibility of this transformation to vinylboron reagents. To our delight, the arylation condition was compatible with various vinylboron reagents in the reaction of **1a** (Scheme 4). Cyclic vinyl boronates as coupling

Scheme 4. Scope of Vinylboron Reagents[a,b]



[a]Reaction conditions: **1a** (0.1 mmol), **5a**−**5f** (0.2 mmol), [Cp*Rh(MeCN)$_3$](SbF$_6$)$_2$ (0.01 mmol), AgOPiv (0.3 mmol), K_2CO_3 (0.2 mmol), and *N*-Ac-leucine (0.02 mmol) in dry MeCN (2 mL), nitrogen atmosphere, 4 h, 60 °C. [b]Isolated yield.

partners were also well tolerated in this protocol, which gave the corresponding arylated products **6a**−**6c** in a 46−63% yield. Furthermore, heterocyclic alkenyl boronates **5d** and **5e** gave the desired functionalized products **6d** and **6e** in moderate yields (50 and 56%), respectively. In addition, the disubstituted vinyl boronate **5f** is also suitable for this transformation.

With our highly efficient auxiliary in hand, we were delighted to find that the scope of this reaction can be further extended to the heterocyclic boronates (Scheme 5). In these reactions, the use of $KHCO_3$ as an alternative to the combination of K_2CO_3 and *N*-Ac-leucine is necessary to ensure higher activity. Using the weakly coordinating furan and thiophene hetero-arylboronic acid pinacol esters as the coupling partners, the desired products were selectively afforded in yields from 52 to 73% (**8a**−**8d**). For the strongly coordinating pyridines and 3-substituted pyridines bearing electron-rich and electron-deficient groups, the corresponding heteroarylated products were obtained in a 52−66% yield (**8e**−**8g**). For less strongly coordinating 2-substituted pyridines containing a variety of electron-withdrawing and electron-donating groups, satisfying yields (57−81%) of heteroarylated products could be

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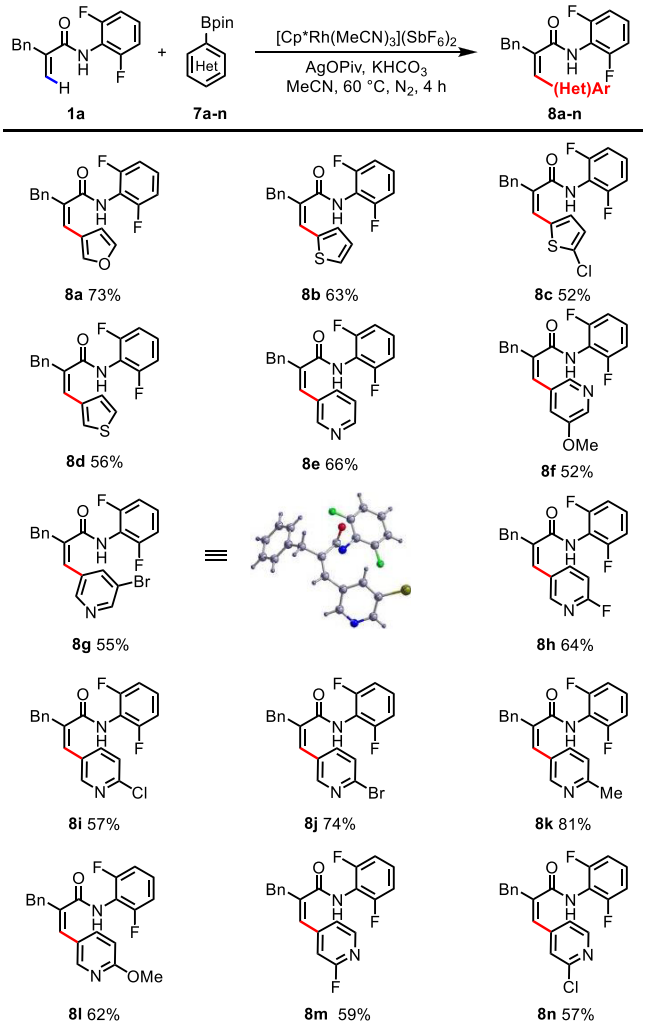
Scheme 5. Scope of Heteroarylation Reagents[a,b]



[a]Reaction conditions: **1a** (0.1 mmol), **7a**–**7n** (0.2 mmol), [Cp*Rh(MeCN)$_3$](SbF$_6$)$_2$ (0.01 mmol), AgOPiv (0.3 mmol), and $KHCO_3$ (0.2 mmol) in dry MeCN (2 mL), nitrogen atmosphere, 4 h, 60 °C. [b]Isolated yield.

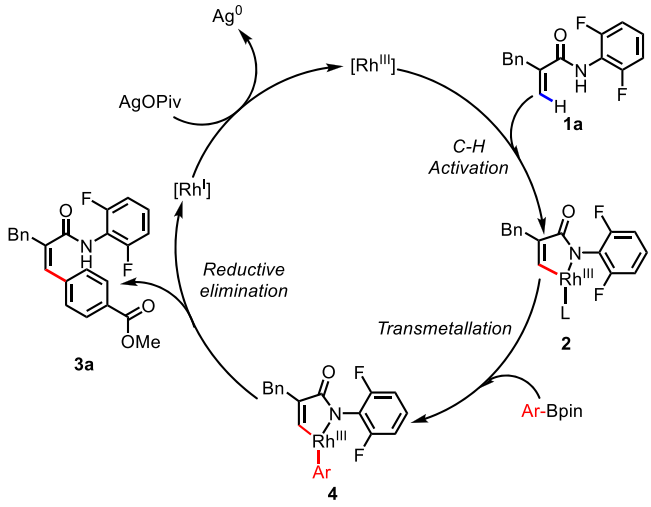
delivered, exhibiting excellent functional group compatibility (**8h**–**8n**).

Furthermore, treatment of the template reaction on a gram scale with the reaction time prolonged to 6 h afforded **3a** in 81% yield, exhibiting the potential large-scale industrial application of this protocol. Meanwhile, the arylated product **4b** obtained in this transformation could readily remove the directing group, converting to the corresponding methyl esters **9b**. (See the Supporting Information.)

A sequence of control experiments has been carried out to explore the possible mechanism of the transformation. 41% Deuterium incorporation was observed for **1a** using excess D_2O, indicating that C–H activation might involve a reversible cyclo-metalation process during the reaction (Scheme S2a). A competitive experiment between **2a** and **2b** was conducted to ascertain the electronic preference of the reaction, which revealed that the electron-deficient coupling partner was more reactive in this reaction with a ratio of 3.2:1 (Scheme S2b). Preliminary kinetic isotope effect (KIE) studies gave an intermolecular KIE value of 2.3, which disclosed that the C–H activation step might be the rate-determining step (Scheme S2c). To confirm the necessity of the *syn*-coplanar C–H bond for activation, we conducted a control experiment using (*Z*)-*N*-(2,6-difluorophenyl)-2-methylbut-2-enamide (**1o**) as the substrate under optimal conditions (Scheme S2d). No corresponding product was obtained, demonstrating that the *syn*-coplanar bond to Rh is necessary for this transformation.

According to the above results and previous reports, a plausible mechanism for this reaction is illustrated in Scheme 6. Initially, the Rh^{III} catalyst coordinates with amide **1a** to give

Scheme 6. Proposed Reaction Pathway



a five-membered rhodacycle species **2** via C–H bond activation. Subsequently, arylboronic acid pinacol esters coordinated to the Rh^{III} center lead to rhodium species **4**. Next, the process of C–C reductive elimination gives the arylated product **3a** and a Rh^{I} species, which could be oxidized to Rh^{III} via AgOPiv.

In conclusion, a Rh^{III}-catalyzed sp^2 C–H functionalization of acrylamide derivatives with organoboron reactants using a commercially available *N*-2,6-difluoroaryl acrylamides auxiliary has been successfully developed. This protocol demonstrates a broad substrate scope with excellent regioselectivity and excellent functional group compatibility. The achievement of heteroarylation could provide a potential application for the synthesis of heterocyclic drug molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03688.

X-ray crystallographic data, characterization data, experimental details, and NMR spectra (PDF)

Accession Codes

CCDC 2017009 (**3a**), 2017010 (**3e**), 2017011 (**4c**) and 2035959 (**8g**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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