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Brønsted Acid-Catalyzed Direct C(sp2)-H Heteroarylation Enabling the Synthesis of Structurally diverse Biaryl Derivatives

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Abstract. Biaryl scaffold is an important class of structural frameworks that exists in many natural products and drug molecules. The development of transition metal-catalyzed approaches for the efficient construction of biaryl scaffolds has long been pursued because of the interesting structural features and broad biological profiles of biaryl scaffolds. Herein, we describe the Brønsted acid-catalyzed direct C(sp2)-H heteroarylation that enables the synthesis of biaryl fragments (70 examples) in moderate to excellent yields (up to 99% yield), which was also performed at a gram scale and successfully applied to the privileged quinazoline scaffolds of the first-generation epidermal growth factor receptor (EGFR) inhibitors Gefitinib and Erlotinib, offering rapid access to a series of quinazoline-based biaryl compounds. Additionally, the late-stage diversifications were performed based on the compound **3b**, generating a library of structurally diverse and complex biaryl compounds.

Keywords: Brønsted Acid; C(sp2)-H heteroarylation; Biaryl derivatives

Biaryl scaffolds are prevalent substructures found in a variety of natural products (e.g. Alocasin A, Annomontine, Meridianin D, Farinamycin, etc.) and targeted drug molecules (e.g. Osimertinib, Rosuvastatin, AM-2099, Ibrutinib, etc.) (Figure 1). [1] Analysis of the IEBX database (ca. 6.2 million compounds) by Brown *et al*. have also demonstrated that the biphenyl substructure is one of the three most common functional groups in biologically active molecules. [2] Because of the prevalence of biaryl scaffolds in nature and interesting properties, numerous synthetic strategies for the construction of biaryls have been developed in last decades mainly based on two strategies: transition-metal-catalyzed cross-coupling reactions of aryl halides with aryl metal species [3] and transition-metal-free approaches [4]. New synthetic strategies that could facilitate efficient construction of the biaryl scaffolds are highly desirable.

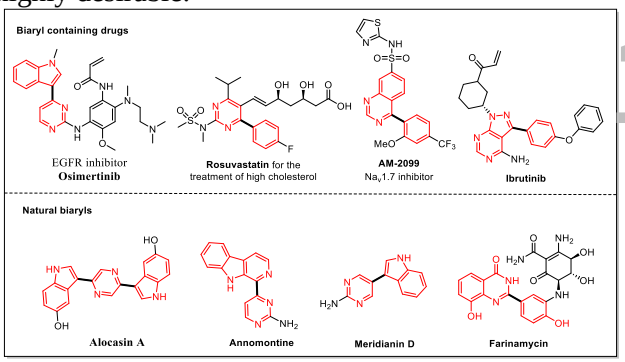


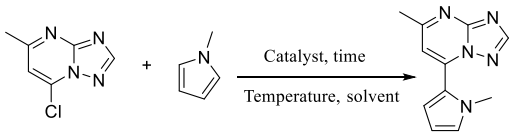
Figure 1. Selected biaryl containing natural products and drugs.

Hexafluoro-2-propanol (HFIP) has been extensively used in organic synthesis, particularly favorable for electrophilic aromatic substitution reactions (e.g. Friedel–Crafts reactions) because of its unique properties such as strong H-bond donating (HBD) ability. [5] Khaledi *et al*. reported that the HFIP-H_2O system can facilitate the electrophilic aromatic substitution of arenes and heteroarenes with benzyl halide to form diaryl alkanes by forming a hydrophobic environment.[6] Very recently, the Aubé group revealed that HFIP can promote intramolecular/intermolecular Friedel−Crafts acylation reactions.[7] Moran *et al*. described that Brønsted acid catalysts can form hydrogen-bonding interactions in HFIP, thereby facilitating Friedel–

Crafts reactions of highly electronically deactivated benzylic alcohols.[8] Given the strong HBD ability and mild acidity of HFIP, herein we speculate that the hydrogen-bonding interactions between Brønsted acid and HFIP could facilitate the direct C(sp2)-H heteroarylation of electron-rich arenes with aryl halides, enabling the efficient construction of structurally novel and biologically interesting biaryl scaffolds.

Initially, 7-chloro-5-methyl-[1, 2, 4]triazolo[1,5-*a*]pyrimidine (**1a**, 0.5 mmol) and 1-methyl-1*H*-pyrrole (**2a**, 1.5 mmol) were used as the model substrates to optimize the reaction conditions. When the reaction was performed for 6 h in solvents such as isopropanol (IPA), MeCN, THF, DCM, $CHCl_3$, Toluene, and Et_2O, no product was observed (Table S1, entry 1). While a trace of compound **3a** was obtained when the reaction was performed in HFIP for 6 h (Table S1, entry 2). When 10% mmol of bis(trifluoromethanesulfonyl)imide (abbreviated as **HTFSI**) was used, compound **3a** was formed in 12 % yield (Table 1, entry 1). To our delight, compound **3a** was obtained in 60% and 66% yield, respectively when the reaction was carried out in HFIP at 60 ℃ or 100 ℃ (Table 1, entries 2 and 3), highlighting the importance of the temperature for the reactivity. When 0.5 or 1.0 mmol of **2a** was used, the yield of compound **3a** decreased to 40% and 56% yield, respectively (Table 1, entries 4 and 5), lower than that of the reaction, in which 1.5 mmol of **2a** was used (Table 1, entry 3). When the reaction was carried out in IPA, toluene, DMF, DMSO, dioxane, and MeCN, the yield decreased correspondingly (Table 1, entries 6-11). In contrast, when Lewis acid such as $AlCl_3$, $ZnCl_2$, CuI, $CuCl_2$, and $Cu(CF_3SO_3)_2$ was employed as the catalyst, the corresponding product was obtained in relatively low yields (Table 1, entries 12-16), significantly lower than that of the reaction catalyzed by HTFSI (Table 1, entry 3). When 10% mmol of TfOH was used, the corresponding product **3a** was formed in 60% yield, comparable to that of the reaction catalyzed by HTFSI. While the reaction was kept for 12h, the product was generated in 69% yield (Table 1, entry 18), comparable to that of the reaction for 6h treatment under the standard condition (Table 1, entry 3).

Table 1. Optimization of reaction conditions [a]



1a **2a** **3a**

Entry	Solvent	Time (h)	T (℃)	Catalyst	Yield[b] (%)
1	HFIP	6	rt	$(CF_3SO_2)_2NH$	12
2	HFIP	6	60	$(CF_3SO_2)_2NH$	60
3	HFIP	6	100	$(CF_3SO_2)_2NH$	66 (53)[c]
4	HFIP	6	100	$(CF_3SO_2)_2NH$	40[d]
5	HFIP	6	100	$(CF_3SO_2)_2NH$	56[e]
6	IPA	6	100	$(CF_3SO_2)_2NH$	38
7	Toluene	6	100	$(CF_3SO_2)_2NH$	46
8	DMF	6	100	$(CF_3SO_2)_2NH$	14
9	DMSO	6	100	$(CF_3SO_2)_2NH$	13
10	Dioxane	6	100	$(CF_3SO_2)_2NH$	37
11	MeCN	6	100	$(CF_3SO_2)_2NH$	54
12	HFIP	6	100	$AlCl_3$	37
13	HFIP	6	100	$ZnCl_2$	20
14	HFIP	6	100	CuI	18
15	HFIP	6	100	$CuCl_2$	42
16	HFIP	6	100	$Cu(CF_3SO_3)_2$	N.D.[f]
17	HFIP	6	100	TfOH	60
18	HFIP	12	100	$(CF_3SO_2)_2NH$	69

[a] Unless otherwise specified, all experiments were conducted in sealed reaction tubes. Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), solvent (1.0 mL), catalyst (0.05 mmol). [b] NMR yields determined by ^1H NMR using the triphenylmethane as an internal standard. [c] Isolated yields. [d] The ratio of **1a**:**2a** is1:1. [e] The ratio of **1a**:**2a** is 1:2.[f] N. D. means Not Detected.

With the optimal reaction conditions established for the Brønsted acid-catalyzed direct C(sp2)-H heteroarylation, we next examined the reactivity of 7-chloro-5-methyl-[1, 2, 4] triazolo [1, 5-*a*] pyrimidine (**1a**) with a wide range of electron-rich arenes. As shown in Scheme 1, 7-chloro-5-methyl-[1, 2, 4] triazolo [1, 5-*a*] pyrimidine (**1a**) reacted well with most of the electron-rich arenes, affording the biaryl fragments in moderate to good yields. In particular, when *α*-naphthol was used, compound **3d** was obtained in a regioselective manner in 91% yield, while for *β*-naphthol, the corresponding product **3e** was generated in only 22% yield. Indole containing biaryl fragments are prevalent in natural products (e.g. Schizandrin) and drug molecules (e.g. Osimertinib), which have shown interesting biological activities. Therefore, we also examined the reactivity of indole derivatives with compound **1a**. Intriguingly, the corresponding biaryl compounds were obtained in moderate to good yields (44-89%), the substituents attached to the indole ring had no remarkable effect on the reactivity. Among these biaryl compounds, compounds **3b** (CCDC number: 1581862) and **3s** (CCDC number: 1581861) were further confirmed by the X-ray crystallographic studies. To examine the scalability, the reaction between 7-chloro-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidine (**1a**, 5.0 mmol) and 1,3,5-trimethoxybenzene (15.0 mmol) was performed under a slightly modified condition, affording compound **3b** in 70% yield.

Scheme 1. Substrate scope of electron-rich arenes [a]

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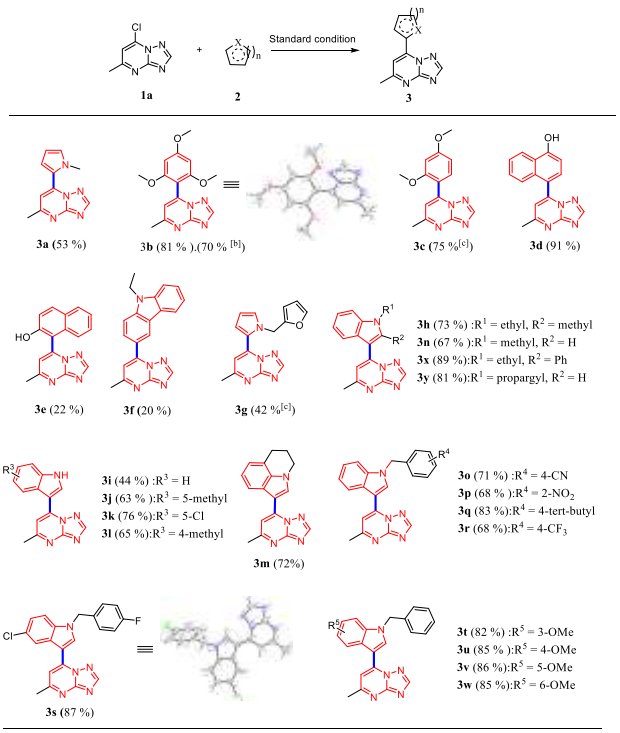
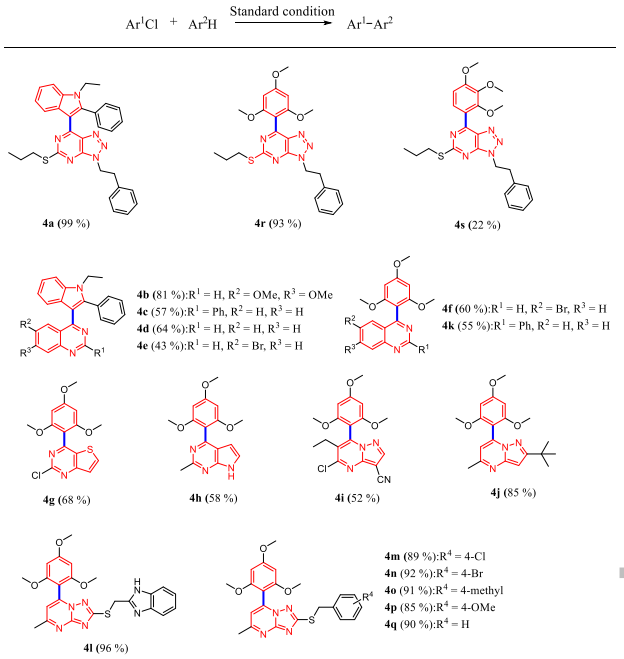


[a] Reaction conditions: **1a** (0.5 mmol), **2** (1.5 mmol), HFIP (1.0 mL), catalyst (0.05 mmol), 6h, 100 °C; [b] **1a** (5 mmol), 1,3,5-trimethoxybenzene (15 mmol), HFIP (3.0 mL), catalyst (1.5 mmol), 6h, 100 °C; [c] **1a** (0.5 mmol), **2** (2.5 mmol), HFIP (1.0 mL), catalyst (0.05 mmol), 6h, 60 °C.

In view of the good reactivity of indole substrates with heteroaryl halide **1a** (Scheme 1), we next examined the reactivity of 1-ethyl-2-phenylindole with substituted 4-chloroquinazolines and [1,2,3]triazolo[4,5-*d*]pyrimidyl-7-chloride **1a**. The corresponding products were obtained in moderate to good yields (43-99% yield) (Scheme 2). Particularly, compound **4a** was formed in 99% yield. As shown in Scheme 2, 1,3,5-trimethoxybenzene reacted smoothly with diverse heteroaryl chlorides regardless of their substituents, giving compounds **4f-k** in 52-85% yields. It should be noted that the left Cl atom in compounds **4g** and **4i** did not react with 1,3,5-trimethoxybenzene further, which may be due to that the introduction of electron-rich 1,3,5-trimethoxybenzene increased the electron density of both compounds, thereby hampering the reaction of both compounds with 1,3,5-trimethoxybenzene. Besides, the triazole fused pyrimidyl chlorides reacted with 1,3,5-trimethoxybenzene quite well, giving the corresponding products **4l-r** in excellent yields (85-96%). While for the 1,2,3-trimethoxybenzene, the corresponding product **4s** was obtained in only 22% yield, which could be attributed to the relatively low electron density of the reactive site.

Scheme 2. Synthesis of structurally diverse biaryl fragments [a]



[a] Reagents and conditions: **1** (0.5 mmol), **2** (1.5 mmol), HFIP (1 mL), catalyst (0.05 mmol), 6h, 100 °C.

In light of the prevalence of the quinazoline scaffold in biologically active molecules and their diverse bioactivities of quinazoline-based analogs, in this work two different 4-chloroquinazoline substrates derived from the first-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) gefitinib and erlotinib for the treatment of advanced non-small cell lung cancer (NSCLC) [9] and several electron-rich arenes were employed to further investigate the reactivity, hoping to construct the quinazoline-based focused library. As shown in Scheme 3, 4-chloro-6,7-bis(2-methoxy ethoxy)quinazoline derived from erlotinib reacted with several different electron-rich arenes, affording compounds **5a-d** in 42-83% yields. While the reactions between 4-chloro-6,7-bis(2-methoxy ethoxy)quinazoline and indole derivatives underwent smoothly, giving the corresponding products **5e-k** in moderate to excellent yields (up to 98% yield). Similarly , 4-chloro-7-methoxy-6-(3-morpholinopropoxy)quinazoline derived from gefitinib also reacted smoothly with indole derivatives, affording compounds **5l-n** in 72-73% yields. Interestingly, this series of compounds showed promising biochemical potency against EGFR (data not shown here), the biology work will be reported in due course. In comparison with the first-generation EGFR-TKIs (e.g. gefitinib and erlotinib), the compounds in Scheme 3 represent new scaffolds for further design of EGFR inhibitors.

Scheme 3. Construction of 4-arylquinazoline derivatives [a]

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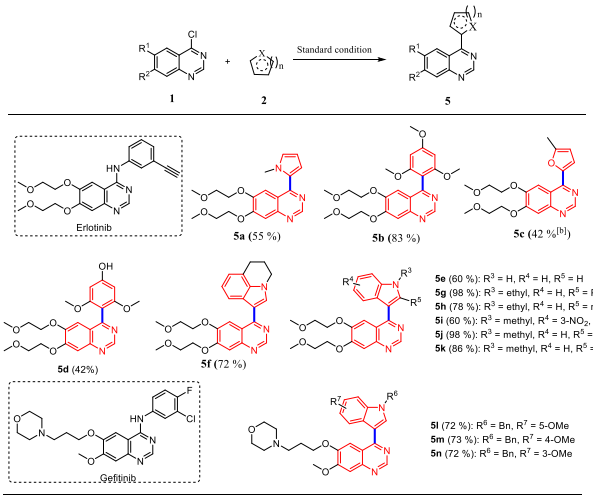
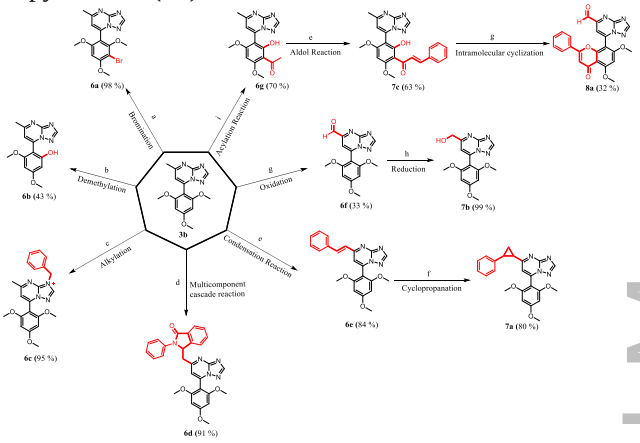


[a] Reagents and conditions: [a] **1b** (0.5 mmol), **2** (1.5 mmol), HFIP (1 mL), catalyst (0.05 mmol), 6h, 100 ℃; [b] **1a** (0.5 mmol), **2** (2.5 mmol), HFIP (1 mL), catalyst (0.05 mmol), 6h, 60 ºC.

With these biaryl compounds in hand, compound **3b** was chosen as a model substrate for late-stage diversification (Scheme 4). Treatment of compound **3b** with NBS in the presence of TMSCl led to the C(sp2)-H bromination, giving compound **6a** in 98% yield, which could be used as a starting point for constructing biaryl-based focused compound collections in the presence of metal catalysts (e.g. Pd, Cu, etc.). $BF_3{\cdot}Et_2O$ treatment led to selective demethylation of compound **3b**, yielding compound **6b** in 43% yield. Treatment of **3b** with benzyl bromide afforded compound **6c** in 95% yield in a regioselective manner. Acetylation of compound **3b** with acetic anhydride in the presence of $BF_3{\cdot}Et_2O$ formed compound **6g** structurally featuring adjacent hydroxy and acyl groups, which then reacted with benzaldehyde in the presence of NaOH to afford the hydroxylated chalcone derivative **7c** in 63% yield. Treatment of compound **7c** with I_2 (0.1 eq) in DMSO gave the flavone derivative **8a** through the Algar-Flynn-Oyamada (AFO) reaction, the methyl group in **7c** was simultaneously oxidized to the formyl group through the catalytic C-H oxidation. Conceivably, the formyl group could be employed as a versatile synthetic handle for further diversity-oriented synthesis (DOS). Similarly, compound **6f** was also obtained through the I_2-mediated oxidation reaction in 33% yield. Subsequent reduction of compound **6f** led to the formation of **7b** in 99% yield. Compound **3b** also reacted with benzaldehyde in the presence of NaOH to give the stilbene analog **6e** in 84% yield. Treatment of **6e** with trimethylsulfoxonium iodide in the presence of NaH yielded compound **7a** in 80% yield *via* the cyclopropanation reaction. Interestingly, 2-carboxybenzaldehyde, aniline, and compound **3b** reacted smoothly in AcOH, affording compound **6d** in 91% yield. In this three-component one-pot reaction, the *N*-Ph isoindolin-1-one ring, two C-N bonds, one C−C bond were formed simultaneously. The method could deserve further investigation for accessing to the *N*-Ph isoindolin-1-one derivatives. Through above-mentioned modifications, we have achieved the late-stage diversification of compound **3b** through chemical controls at multiple sites, generating a structurally novel biaryl-based focused library. Of particular interest is that the methyl group attached to the heterocycle scaffold was used in this work for diverse transformations under common conditions, which provides an example for other C(sp3)-H functionalizations. Conceivably, presented here is just an example illustrating the general strategies for late-stage diversification, further chemical transformations could be done based on the versatile synthetic handles (e.g. -Me, -OH, -CHO, acetyl, *α,β*-unsaturated carbonyl group, etc.) to construct structurally diverse and complex DOS library for biochemical phenotypic screening. Biological evaluation of the synthesized compounds is currently undergoing, some of them have presented interesting bioactivities, and the data will be reported in due course.

Scheme 4. Late-stage diversification based on the 5-methyl-7-(2, 4, 6-trimethoxyphenyl)-[1, 2, 4] triazolo [1, 5-*a*] pyrimidine (**3b**)

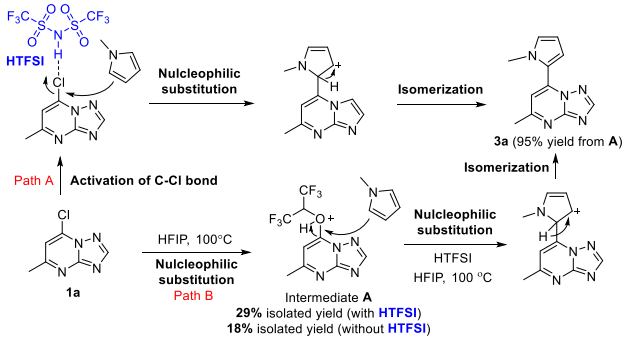


Reagents and conditions: (a) TMSCl (0.1 eq), NBS (1.1 eq), MeCN and *n*-hexane (1:1). (b) $BF_3{\cdot}Et_2O$ (3 eq), DCM, -78 ℃. (c) Benzyl bromide (1.0 eq), MeCN, reflux. (d) Aniline (1.0 eq), 2-carboxybenzaldehyde (1.0 eq), AcOH, 100 ℃, 6h. (e) NaOH (3.0 eq), EtOH, rt 1-12h. (f) trimethylsulfoxonium iodide (1.0 eq), NaH (1.1 eq), DMF, rt, 5-6h. (g) I_2 (0.1 eq), DMSO, reflux, 5-6h. (h) $NaBH_4$ (1.0 eq), MeOH, rt, 15-30 min. (i) $(Ac)_2O$ (16.0 eq), $BF_3{\cdot}Et_2O$ (22.0 eq), DCM, 0 ℃, rt, 48h.

In view of the practicability of the Brønsted acid-catalyzed direct C(sp2)-H heteroarylation, we also proposed the reaction mechanisms (Scheme 5). HTFSI first activated C-Cl bond through forming the H-Cl interaction with **1a**, thus facilitating the subsequent nucleophilic substitution reaction with *N*-methylpyrrole. A similar phenomenon was also observed recently in the Friedel–Crafts benzylation of several arenes and heteroarenes.[10] Further isomerization led to the formation of compound **3a** (Path A). Interestingly, we also found that the intermediate **A** (characterized by NMR and HRMS, please see supplementary information for related spectra.) was formed in 29% and 18% isolated yield, respectively in the presence or absence of HTFSI (Path B). The intermediate **A** reacted smoothly with

N-methylpyrrole under the standard condition, affording **3a** in 95% yield (28% overall yield within two steps in the presence of HTFSI). We speculate that the acidic HFIP or HTFSI first protonated the oxygen atom of the intermediate **A**, thereby promoting the substitution reaction of *N*-methylpyrrole. Further isomerization led to the formation of compound **3a**. To conclude, compound **3a** was formed through at least two distinct pathways as depicted in Scheme 5.

Scheme 5. Proposed reaction mechanism for the Brønsted acid-catalyzed direct C(sp2)-H heteroarylation



Biaryl scaffolds are prevalent substructures found in a variety of natural products and drug molecules. In view of the structural features and their interesting biological profiles, the development of new methods enabling efficient access to such compounds have always been pursued, most of which involve the use of metal catalysts. In this work, we have developed the Brønsted acid-catalyzed direct C(sp2)-H heteroarylation that enables the synthesis of structurally interesting biaryl derivatives. The reactions were also performed at a gram scale and successfully applied to the privileged quinazoline scaffolds of the first-generation EGFR inhibitors Gefitinib and Erlotinib, offering rapid access to a series of new quinazoline-based biaryl compounds. Finally, compound **3b** was used as a starting point to carry out late-stage diversifications based on the versatile synthetic handles, generating a library of structurally diverse biaryl compounds. Biological evaluation of the synthesized compounds against EGFR and epigenetic proteins (e.g. BRD4, LSD1) is currently undergoing in our lab, some of them have presented interesting bioactivities, and the data will be reported in due course.

Experimental Section

General Procedure for the synthesis of biaryl derivatives

To an oven-dried tube were added the heteroaromatic chloride (0.5 mmol), electron-rich arene (1.5 mmol), and bis(trifluoromethanesulfonyl)imide (0.05 mmol), followed by addition of HFIP (1.0 mL). The tube was sealed and stirred at 100 ℃ for 6 h, the solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography (DCM/MeOH as the eluent) to give the pure products **3**, **4**, **5**.

Acknowledgements

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Brønsted Acid-Catalyzed Direct C(sp2)-H Heteroarylation Enabling the Synthesis of Structurally Diverse Biaryl Derivatives

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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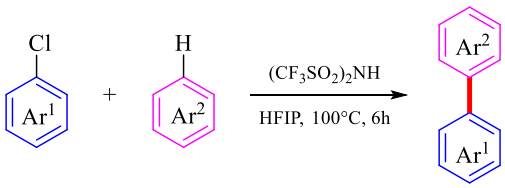

- 70 examples, up to 99% yield
- Transition-metal free direct C(sp2)-H heteroarylation
- Up to gram-scale
- Well functional group tolerance
- Structurally novel biaryl skeleton