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meta-Selective C–H Arylation of Fluoroarenes and Simple Arenes

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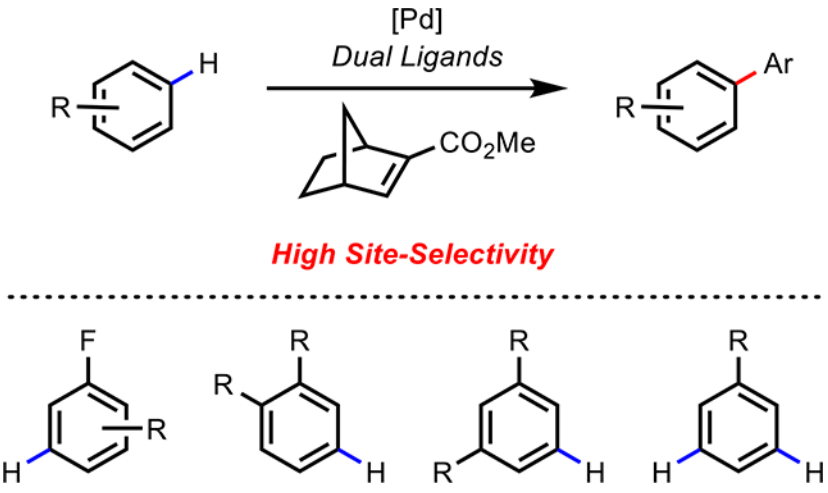
Abstract

Fluorine is known to promote ortho- C–H metalation.[1] Based upon this reactivity, we employed an activated norbornene to trap the ortho-palladation intermediate and relay to the meta-position, leading to a meta-selective C–H arylation of fluoroarenes. Deuterium experiment suggests that this meta-arylation is initiated by ortho C–H activation and the catalytic cycle is terminated by the C-2 protonation. The dual ligand system is crucial for the observed high reactivty and site-selectivity. Applying this approach to simple benzene or other arenes also affords arylation products in good yield and site-selectivity.

Graphical Abstract



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Keywords

arylation; C–H activation; palladium; fluoroarenes

Introduction

Incorporating a fluorine atom into a molecule can significantly influence the lipophilicity, binding affinity, metabolic stability and other properties.[2] Up to 30% of pharmaceuticals currently contain at least one fluorine atom (Scheme 1).[3] Fluoroarene is a particularly important class within fluorinated compounds and their preparation using traditional cross-coupling reactions remains a significant challenge.[4] Hence C–H functionalization of simple and readily available fluoroarenes are highly valuable for medicinal chemistry.

Site-selectivity of C–H activation of arenes are mainly achieved by two complementary strategies: directed metalation; preferential functionalization driven by steric or electronic effects.[5,6] While these two approaches are highly effective, there is still a huge gap where certain arene substrates are not amenable to both of these strategies. For example, *meta*-C–H activation of electron-rich arenes remains a challenge despite the recently developed norbornene relay approach that is limited to phenolethers.[7] In general, arenes lacking strong electron-withdrawing or -donating substituents are challenging substrates due to the absence of electronic bias. Considering the previously observed preferential *ortho*-metalation of fluoroarenes (Scheme 2),[1] we wondered if such reactivity can be exploited to achieve *meta*-selective C–H arylation using our recently established norbornene relay approach (Scheme 3a).[7,8] If successful, this approach could expand our access to *meta*-arylated fluoroarenes as valuable building blocks in medicinal chemistry. Although there are various studies of transition-metal catalyzed *meta* C–H functionalization reactions, many of these precedents are plagued by poor regioselectivity[9] or require the installation of directing groups.[10] Our non-directed protocol could potentially overcome some of these drawbacks and provide an alternative way for *meta*-C–H arylation of arenes.

To reduce this approach to practice, the poor reactivity of fluoroarenes with Pd(II) catalysts points to the search for efficient ligands;[11] on the other hand, the norbornene relay step also needs the assistance from a suitable ligand.[10a, 12] Not surprisingly, applying the recently developed protocol for *meta* C–H arylation of electron-rich arenes via norbornene relay strategy to fluoroarenes or other simple arenes failed to give any desired products. Considering the difficulty of C–H palladation of arenes bearing no electron-donating substituents, we decided to test more ligands to enhance the efficiency of C–H activation. Electron-deficient 2-pyridone could be used as an internal base and was believed to accelerate the C–H cleavage step based on our previous research.[11] Although using 2-pyridones as the sole ligand only gave trace product, significant enhancement in reactivity was observed when 2-pyridones and pyridine-based ligands were used as dual ligand. It is possible that while 2-pyridone accelerates the C–H cleavage step, pyridine ligands can promote subsequent steps in the norbornene relay catalytic cycle.

Results and Discussion

Extensive optimizations were carried out by treating the model substrate (**1d**, 1.0 equiv.) with aryl iodide (methyl 4-iodobenzoate, 2.0 equiv.), $Pd(OAc)_2$ (10 mol%), modified norbornene (NBE-CO_2Me) (1.5 equiv.), and AgOAc (3.0 equiv.) in HFIP (solvent) at 100 °C, using 3, 5-ditrifluoromethyl-2-pyridone (20 mol%) and quinoxaline (20 mol%) as dual ligands. Encouragingly, the desired arylation product was detected in 35% (**entry 1**, Scheme 3), which was improved from less than 20 % when using either 2-pyridone or quinoxaline as the sole ligand. Further extensive screening of ligands identified 3-NHAc-5-CF_3-2-pyridone **(L1**) and 2-methyl-5-trifluoromethylpyridine (**L2**) as the most effective ligands, affording the desired arylation product in 65% yield (**entry 4**, Scheme 3). To further enhance the reactivity, we prepared and tested several modified norbornenes. Although the reactivity of C–H olefination improves when using acrylates with more electron-withdrawing substituents, modified norbornene (**N2** and **N3**) with more electron-withdrawing substituents surprisingly gave lower yields, which is probably due to the steric effect of the bulkier esters (**entry 6 and 7**, Scheme 4).

With the best ligands and optimal reaction conditions established, we set out to explore the scope of arenes. Using 3.0 equiv. of fluorobenzene as the substrate, *meta*-arylated product was obtained as the sole regioisomer in 46% yield (**3a**, Table 1). Further examination of other fluoroaromatics demonstrated the high *meta* site-selectivity of these substrates. 1,3-Difluoronbenzene gave the *meta*-arylation product as the sole regioisomer in 55% yield (**3b**). With 1.0 equiv. of *ortho* and *meta*-fluorotoluene as substrates, the corresponding *meta*-to-fluorine arylation products were obtained in 57% and 65% yields, respectively (**3c**, **3d**). Other *meta*-substituted fluorobenzene such as 3-*n*butyl, 3-*n*pentyl and trimethylsilyl fluorobenzene also afforded desired products in moderate yields and exclusive *meta*-selectivity (**3e**, **3f** and **3g**). Several *ortho* and *meta*-substituted fluorobenzenes containing ester, -OTBS, aryl and -CF_3, -OMe groups were well tolerated by our conditions to give moderate yields (**3h**-**3j**, **3l**-**3n**). Substrates containing moderate electron-withdrawing functional groups such as Cl and Br were also tested to afford the corresponding arylation products with exclusive site-selectivity although a lower reactivity were observed (**3k**, **3o**). Non-directed C–H arylation of 2,3-disubstituted fluorobenzene also proceeded smoothly to afford the corresponding arylation products in 60% yield (**3p**). This protocol could also be applied on other simple arenes.[13] Symmetric 1,2-disubstituted electron-neutral arenes afforded the corresponding arylation products in 54–77% yields and exclusive β-selectivity (**3q**, **3s** and **3t**). Unsymmetric 1,2-disubstituted arene gave a mixture of two regioisomers (**3r**, **3u**) in moderate to good yields. However, dual ligand system of **L1** and **L2** failed to enhance the reactivity of 1,3-disubstituted arenes. Further detailed screening of ligands revealed that using **L3** (quinoxaline) and **L4** (5-trifluoromethylpyridine-3-sulfonic acid) as the ligands could afford the desired product in 46%–67% yields with 1,3-disubstituted arenes as substrates (**3v**-**3x**). Based on our previous study, 2-pyridones accelerated non-directed C–H activation is highly controlled by steric environment and thus always preferably occurs at C-5 of *m*-xylene and the subsequent norbornene relay to C-3 or C-4 will be impeded by steric effect of the methyl groups (See **SI** for detailed explanation).[7,11,14] Notably, β-arylated naphthalene could be afforded as the sole product in 42% yield with

naphthalene as the limiting reagent (**3y**).[15] Site-selective arylation of 2,6-dimethylphenylboronic ester also proceeded in moderate yields (**3z**). With toluene as the substrate, 60% 3,5-diarylated product and 20% *para*-arylated toluene (which is initiated by non-directed *meta*-C–H activation of toluene) were obtained (**3za**). Notably, 1,4-disubstituted arene gave trace amount of product because of steric hinderance (**3zb**).

Besides, preliminary results were obtained in the *meta*-arylation of trifluoromethoxy and difluoromethoxy benzene (**3zc** and **3zd**).[16] Our previous protocol developed for phenyl alkyl ethers only gave the desired products in less than 10 % yields, probably due to the electro-withdrawing effect introduced by -CF_3 or -CF_2H as well as the steric effect imposed on *ortho* C–H bonds. However, this new protocol yielded the desired products in 42% and 45%, respectively. Fluoroarene substrates are stable under these reaction conditions although homocoupling of excess aryl iodides occurred in some cases, thus the moderate yields is most likely due to the palladium catalyst deactivation.

The scope of aryl iodides was examined using **1a**, **1d** and **1p** as the substrates (Table 2). Using fluorine-containing substrates **1a** and **1d**, moderate to good yields and high *meta*-to-fluorine selectivity were observed for a range of (hetero)aryl iodides (**4a**–**4f**). Notably, a fluprofen precursor could be synthesized rapidly in moderate yield starting from the cheap and easily available starting material fluorobenzene, which further showcases the utility of this protocol in streamlining the synthesis of biaryl compounds (**4g**). Other aryl iodides were tested with *o*-xylene (**1p**) as the substrate. The corresponding arylation products were obtained in moderate to good yields and high site-selectivity with a series of aryl iodides regardless of their electronic properties (**4h**–**4p**). Interestingly, when benzene was employed as the substrate, only 1,3-diarylation product was observed in moderate to good yields (**5a**–**5f**, Table 3). Especially, the yields were above 90% when using the aryl iodides bearing *ortho*-ester groups.[12d] The protocol is also well applied to ethylbenzene and isobutylbenzene (**5g** and **5h**).

To distinguish the roles of pyridone and pyridine ligands, we used ethyl acrylate instead of modified norbornene to test the ligand effect on C–H olefination reaction (modified norbornene will not give olefination product). Dual ligand system gave similar reactivity with using pyridone ligand **L1** as the sole ligand, which suggests that pyridine ligand **L2** neither promotes nor reduces the olefination reactivity. However, compared to **L1** alone, dual ligand significantly enhanced the reactivity of arylation reaction. Thus, it's likely that pyridine ligand **L2** could promote oxidative addition step (See **SI** for more information).

To better understand the origin of the *meta* site-selectivity, deuteration experiment was performed using **1d** as the substrate. The presence of 57% deuterium incorporation at exclusively the *ortho*-position (C-2) suggests that this *meta*-arylation product was derived from *ortho* C–H activation and the catalytic cycle is terminated by the C-2 protonation (deuterium incorporation step) of the arylpalladium intermediate (Scheme 5). A plausible catalytic cycle is outlined in Scheme 6.

Conclusion

In conclusion, we have developed a non-directed *meta*-C–H arylation of fluoroarenes and simple arenes with good reactivity and high site-selectivity. This protocol provides a useful method for the synthesis of *meta*-arylated fluoroarenes. The reactivity is also exploited to achieve arylation of simple arenes to give site-selective arylated products.

Acknowledgements

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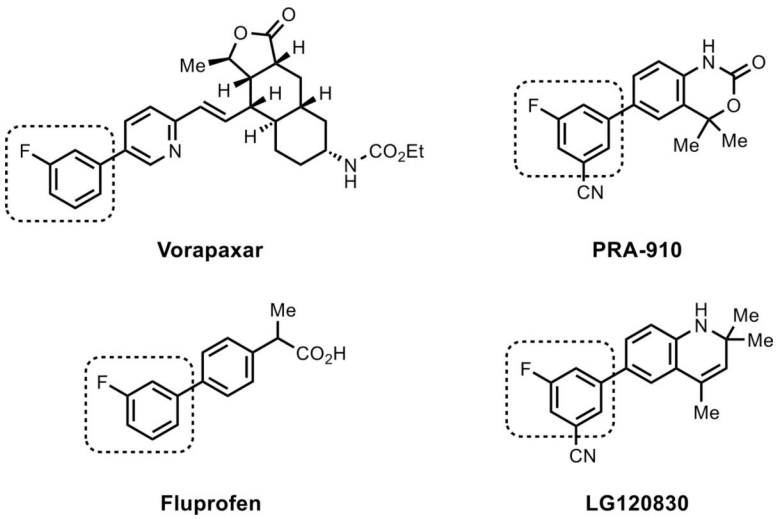
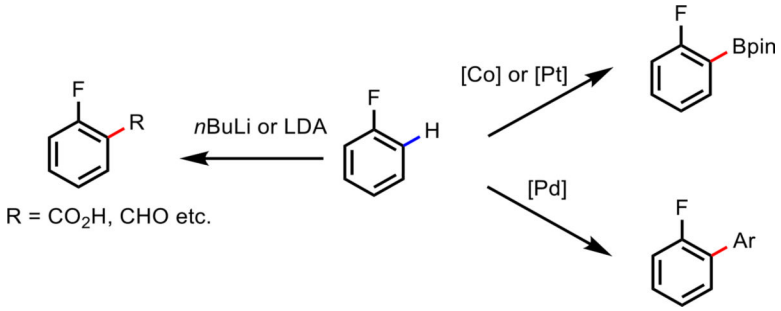


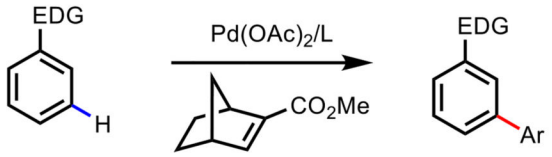
Scheme 1.

Examples of fluorobiaryl motifs in pharmaceuticals

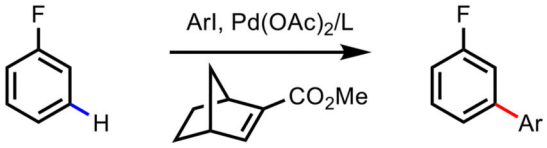


Scheme 2.
ortho C–H Functionalization of Fluoroarene

(a) meta C-H Arylation of Electron-Rich Arene (ref 7)

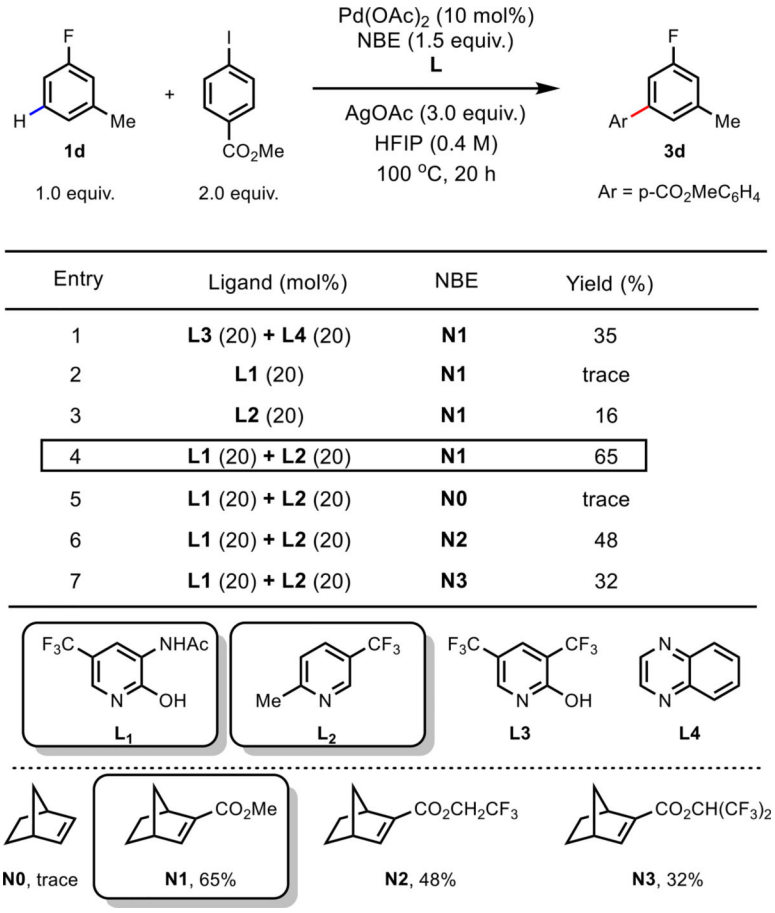


(b) This work: meta C-H Arylation of Fluoroarene



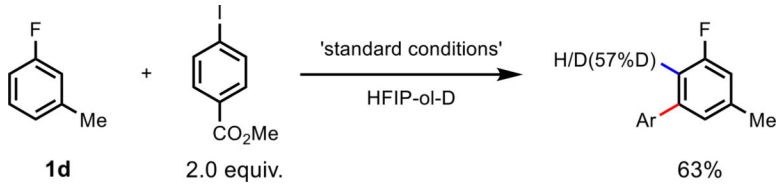
Scheme 3.

Non-Directed C–H Arylation of Arene via Norbornene Relay Strategy

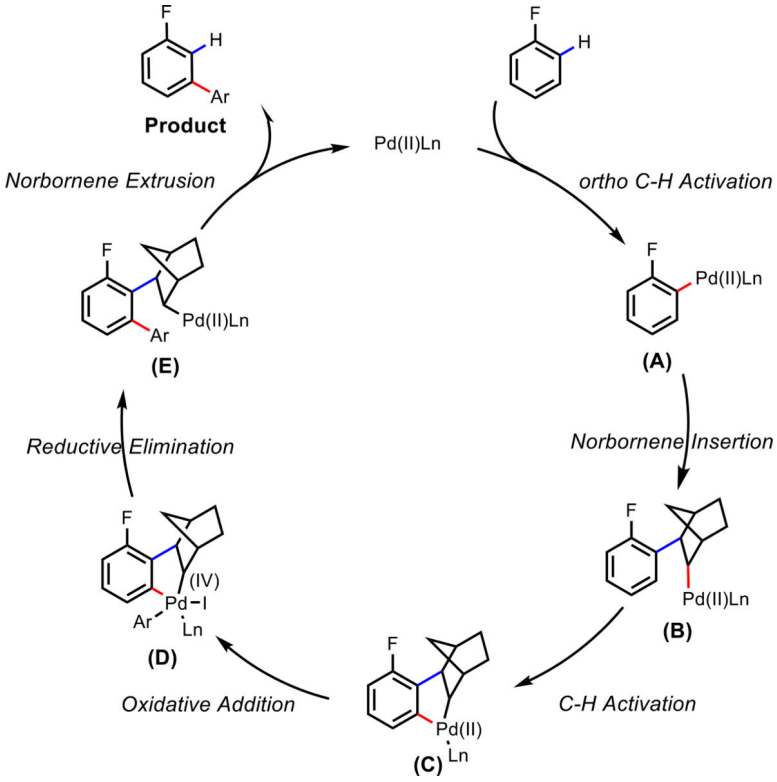


Entry	Ligand (mol%)	NBE	Yield (%)
1	**L3** (20) + **L4** (20)	**N1**	35
2	**L1** (20)	**N1**	trace
3	**L2** (20)	**N1**	16
4	**L1** (20) + **L2** (20)	**N1**	65
5	**L1** (20) + **L2** (20)	**N0**	trace
6	**L1** (20) + **L2** (20)	**N2**	48
7	**L1** (20) + **L2** (20)	**N3**	32

Scheme 4.
Ligand and Norbornene Effect



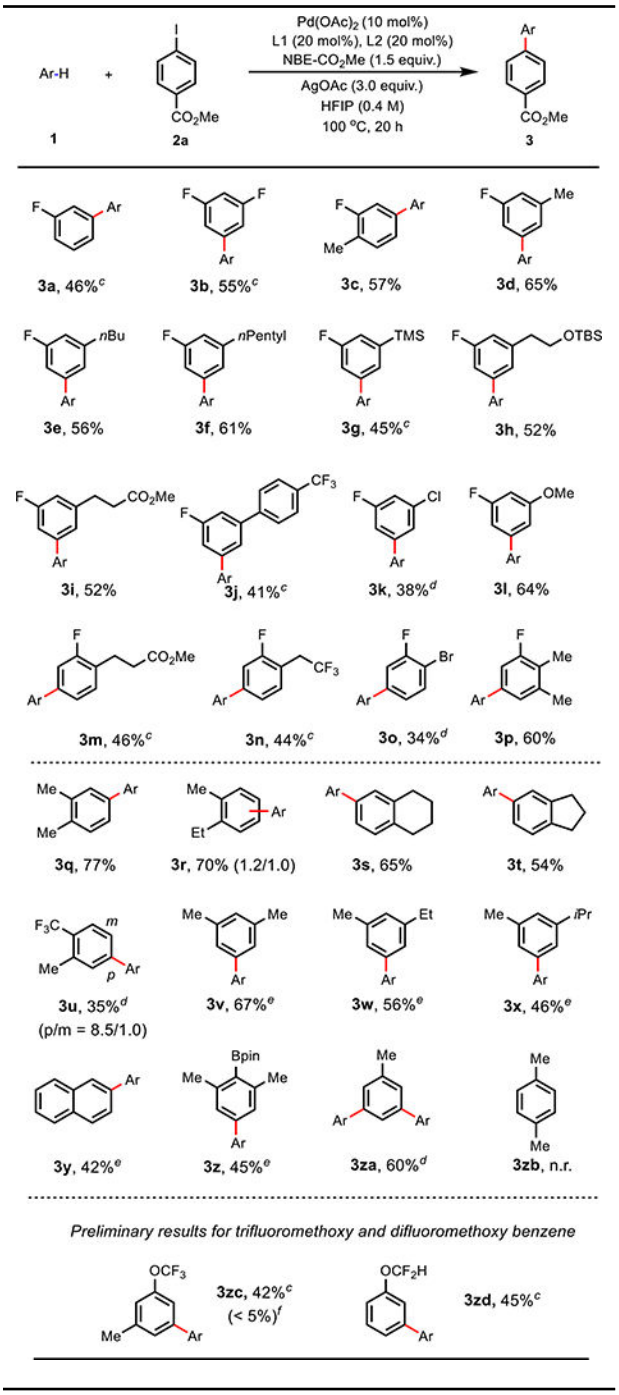
Scheme 5.
Deuteration Experiment



Scheme 6.
Proposed Catalytic Cycle

Table 1.

Scope of Arene [a,b]



[a]Conditions: **1** (0.1 mmol), aryl iodides (2.0 equiv.), $Pd(OAc)_2$ (10 mol%), NBE-CO_2Me (1.5 equiv.), **L1** (20 mol%), **L2** (20 mol%), AgOAc (3.0 equiv.), HFIP (0.25 mL), 100 °C, under air, 20 h;. See SI for work up procedures.

[b]Isolated yields.

[c] Aryl iodide was used as the limiting reagent (1.0 equiv.), 3.0 equiv. of arene was used.

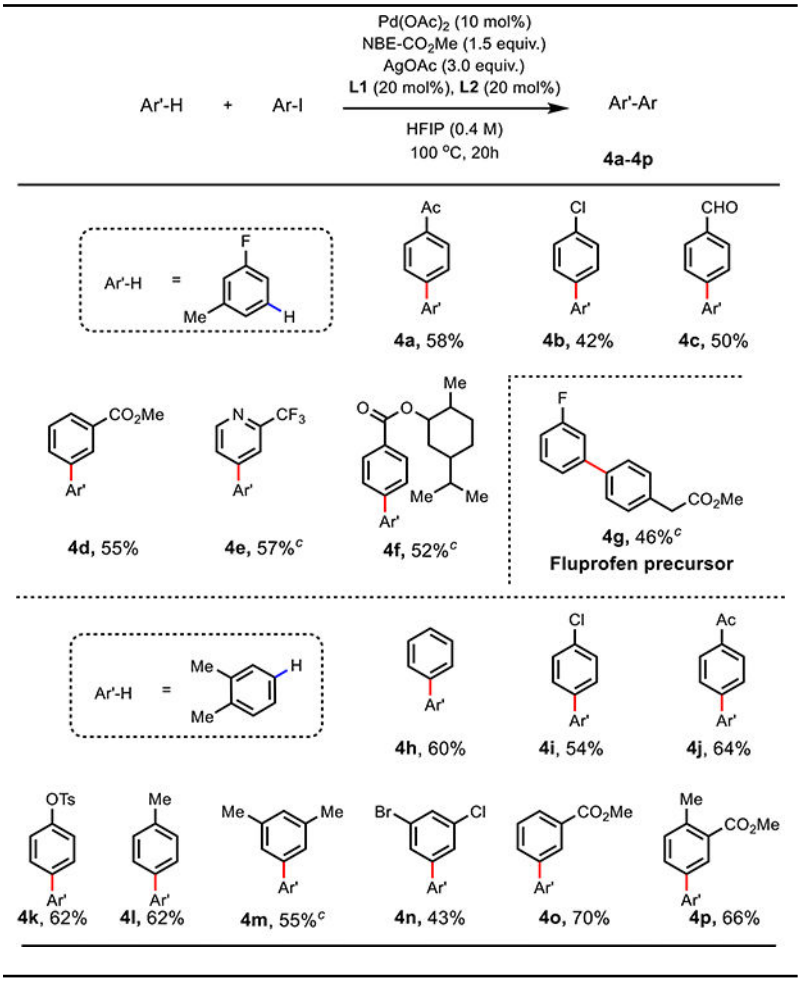
[d] 10.0 equiv. of arene was used. For **3za**, 20% 4-arylated product was also observed.

[e] 20 mol% **L3** (quinoxaline) and 20 mol% **L4** (5-trifluoromethylpyridine-3-sulfonic acid) were used as ligands.

[f] Under the optimal conditions for phenyl ethers substrates reported in ref 7.

Table 2.

Scope of Aryl Iodides Coupling Partners [a,b]



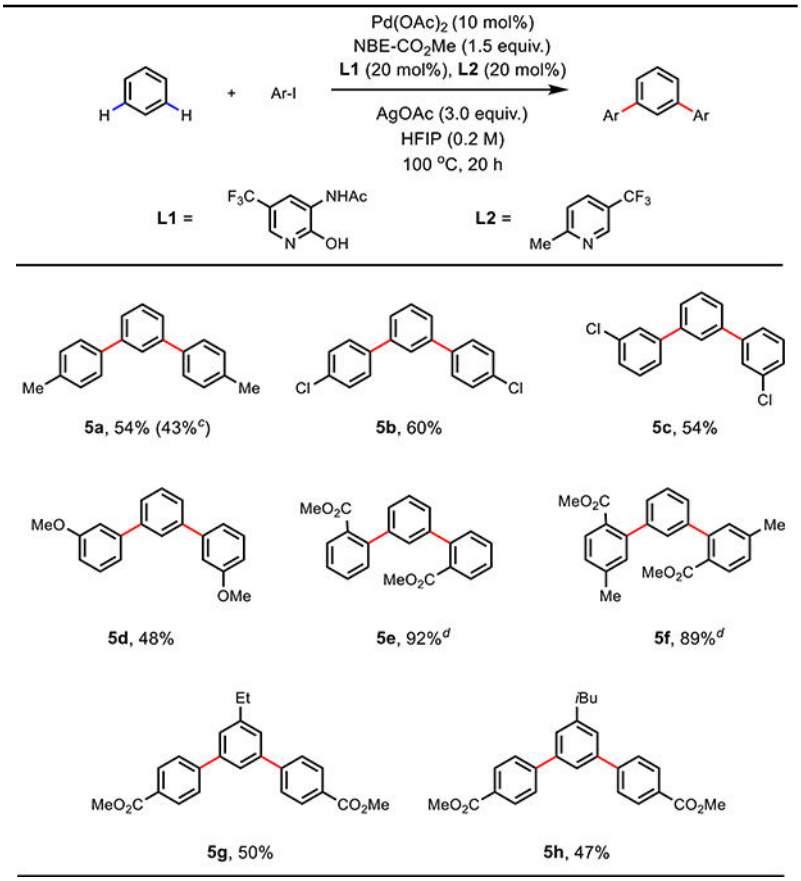
[a]Conditions: for **1** (0.1 mmol), aryl iodides (2.0 equiv.), $Pd(OAc)_2$ (10 mol%), NBE-CO_2Me (1.5 equiv.), **L1** (20 mol%), **L2** (20 mol%), AgOAc (3.0 equiv.), HFIP (0.25 mL), 100 °C, under air, 20 h; See SI for work up procedures.

[b]Isolated yields.

[c]Aryl iodides were used as limiting reagents (1.0 equiv.), 3.0 equiv. of arene was used.

Table 3.

1,3-Diarylation of Benzene



[a]Conditions: aryl iodides (0.2 mmol), arene (10.0 equiv., 2.0 mmol), $Pd(OAc)_2$ (10 mol%), NBE-CO_2Me (1.5 equiv.), **L1** (20 mol%), **L2** (20 mol %), AgOAc (3.0 equiv.), HFIP (0.5 mL), 100 °C, under air, 20 h. See SI for work up procedures.

[b]Isolated yields, based on aryl iodides, *para*-arylation products did not included in the table.

[c]1.0 equiv. of benzene was used.

[d]NBE-$CO_2CH_2CF_3$ (1.5 equiv.) was used instead of NBE-CO_2Me, **L1** (20 mol%) was used as ligand.