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Ligand-Enabled *Meta*-C–H Alkylation and Arylation Using A Modified Norbornene

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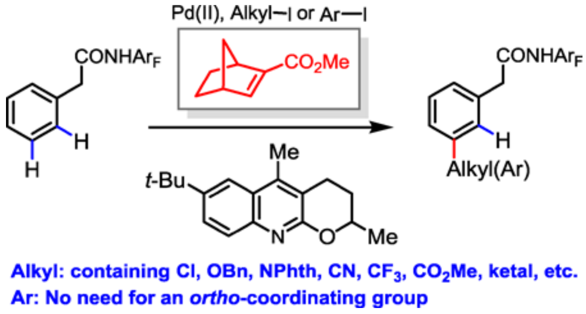
Abstract

2-Carbomethoxynorbornene is identified as a more effective transient mediator to promote a Pd(II)-catalyzed *meta*-C(sp^2)–H alkylation of amides with various alkyl iodides as well as arylation with previously incompatible aryl iodides. The use of a tailor-made quinoline ligand is also crucial for this reaction to proceed.

Graphical abstract



Directed-C–H activation has been largely associated with the functionalizations of *ortho*-C–H bonds.[1] The development of a U-shaped template to direct *meta*-C–H activation has provided a promising solution to this problem.[2] To further improve the efficiency and scope of *meta*-C–H activation reactions, we have established a ligand-enabled catalytic system that combines Pd(II)-catalyzed *ortho*-C–H activation with norbornene-mediated Pd(II)/Pd(IV) catalysis developed by Catellani and Lautens (eq 1)[3,4] to achieve *meta*-selective C–H alkylation and arylation.[5] A related *meta*-C–H arylation adopting similar strategy has also recently appeared in literature.[6] Prior to these developments, an elegant C-2 alkylation of indole using norbornene as the mediator has also been reported by Bach (eq 2).[7] In our amide-directed *meta*-C–H activation reactions,[5] there exist significant limitations. First, alkylation with alkyl iodides containing β-hydrogen is problematic (the use of 6 equiv ethyl iodide is required to give only 21% yield). Second, aryl iodide coupling partners without

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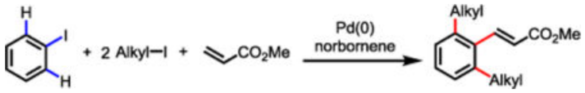
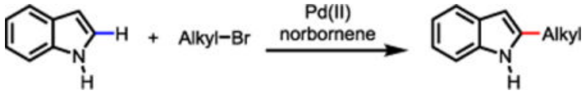
Supporting Information Available: Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

ortho-coordinating groups are not compatible except for a single example with highly reactive 3,5-bis(trifluoromethyl)-iodobenzene.[5] Herein we report the development of a more efficient norbornene-type mediator that can promote efficient *meta*-C–H alkylation with a wide range of alkyl iodides as well as arylation with common aryl iodides in the presence of a quinoline-based ligand. This approach is fundamentally different from other *meta*-selective C–H activation/carbon-carbon bond forming reactions.[8,9,10]



(1)



(2)

Challenges associated with C–H alkylation reactions are anticipated from the extensive studies on transition metal-catalyzed C–C coupling involving alkyl coupling partners.[11] Although a few *ortho*-C–H alkylation reactions have been developed,[12,13] directed *meta*-C–H alkylation with simple alkyl iodides have not been reported to date despite significant synthetic importance. For example, our U-shaped template-directed *meta*-C–H coupling is not compatible with alkyl boron reagents at this stage of development.[2d,2e] Analysis of the catalytic cycle of our norbornene-mediated *meta*-C–H arylation and methylation reactions (Fig. 1) led us to focus on tuning the reactivity of intermediates **III** and **IV** which can potentially participate in multiple reaction pathways, some of which are non-productive. Our preliminary experimental result with ethyl iodide also suggests that the formation of the cyclobutane adduct as the major side product largely outcompetes the ethylation pathway. Reductive elimination from either **III** or **IV** could be responsible for this observation. Considering that norbornene is intimately involved in these competing steps, we envisioned that it is possible to favor the desired oxidative addition of ethyl iodide with **III** or aryl-ethyl reductive elimination from **IV** by systematically modifying the structure of norbornene. Notably, Catellani previously observed that bicyclo[2.1.1]hex-2-ene and bicyclo[2.2.2]oct-2-ene other than norbornene can also react with aryl halides to give benzocyclobutene,[14] albeit without forming the Catellani reaction product.

Prior to the extensive tuning of the norbornene structure, we needed to identify a pyridine- or quinoline-based ligand that will give the optimum reactivity for C–H activation and norbornene insertion steps leading to the formation of intermediate **III**. Guided by our previous extensive studies of these ligands in the *meta*-C–H arylation reaction,[5] a brief survey of a few superior ligands rapidly identified **L1** as the most effective ligand as indicated by the formation of the benzocyclobutene adduct in 85% yield (Table 1). Hence we began to prepare various norbornenes and test them in the *meta*-C–H alkylation reaction with EtI in the presence of ligand **L1** (Table 1).

Since the high reactivity of the norbornene insertion is largely derived from the ring strain, we prepared a number of norbornenes fused with an aryl group at the 5,6-positions (**N2**–**N4**). These structural modifications significantly reduced the formation of the cyclobutane adducts **4**. However, the yield of the *meta*-alkylation product is only moderately improved when the trifluoromethyl group-bearing norbornene derivative **N4** is used. Further tuning the ring strain by replacing the carbon at the 6 position with an oxygen significantly reduced the overall reactivity (**N5**). We then introduced various electron-withdrawing functional groups at the 5, 6 and 7 positions to study the electronic effects (**N6**–**N10**). A noticeable increase in yield was observed with **N7** containing two ester groups. The comparison of the results with **N6** and **N7** is revealing. While the steric hindrance at the 5 and 6 positions of **N7** seems to hamper the undesired reductive elimination pathway leading cyclobutane adduct **4g**, the norbornene insertion step (step 2) is presumably also drastically inhibited compared to **N6** affording lower reactivity.

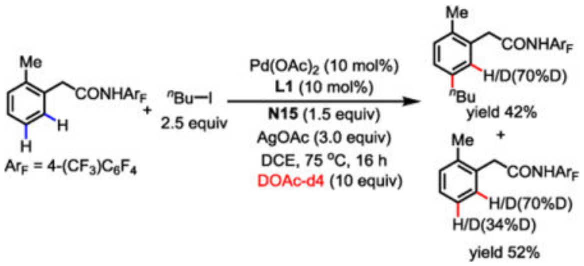
Since the preliminary screening of various readily available norbornenes did not afford significant improvement, we decided to synthesize new norbornenes to accelerate the migratory insertion (step 2) of the arylpalladium species with norbornene. Considering the superior reactivity of styrenes and acrylates in Heck coupling and C–H olefination reactions due to the polarization of the double bond,[15] we introduced phenyl, acetyl, sulfonyl, nitrile, and ester groups to the 2-position in conjugation with the double bond (**N11**–**N15**). Among these modified norbornenes, **N15** was identified to be the most effective mediator affording the *meta*-C–H alkylation product in 97% yield. The use of catalytic amount of **N15** (0.5 equiv) is feasible, albeit affording lower yield (72%, see supporting information). The low reactivity with **N12**–**N14** indicates that the desired reaction pathway is highly sensitive to the electronic and steric effects of the double bond. For example, the carbon-palladium bond α to keto and nitrile group formed from **N12** and **N14** seems to retard the *meta*-C–H activation (step 3). In the presence of DOAc, the fully recovered starting material containing high *ortho*-D-incorporation and no *meta*-D-incorporation supports this hypothesis (see supporting information). It is also important to note that the cyclobutane adduct is not formed with norbornenes **N12**–**N15** even in the absence of EtI, presumably the substitution of electron-withdrawing groups at the 2-position prevents the reductive elimination through both steric hindrance and electronic effect. In addition to being dependent on the structure of norbornene, this reaction is also significantly influenced by the ligands. Replacement of **L1** by other phosphine and carbene ligands also decreases yield of the alkylated product to 10 and 45% respectively (see supporting information).

With these high-yielding conditions in hand, we examined the scope of alkyl iodides (Table 2). Alkyl iodides with long carbon chain afford the *meta*-alkylated products in good yields (**3a**–**3c**). A similar result is obtained with more sterically hindered *i*-butyl iodide (**3d**). Alkyl iodides containing trifluoromethyl, aryl, benzyl and silyl protected hydroxyl, protected amino group, chloro, nitrile and ketal functionalities are all excellent coupling partners rendering this *meta*-alkylation method broadly useful (**3e–3l**). Surprisingly, alkyl iodide containing an ester group gives the product in low yield (40%) under standard conditions, which is improved to 74% by using 3.0 equiv of **N15** (**3m**). *Meta*-ethylation of **1** is also performed in 1 mmol scale to give **3a** in 91% yield (Table 2). Ethyl bromide is also compatible affording **3a** in 40% yield after extending reaction time to 48 h (Table 2). Under current conditions, secondary alkyl iodides or bromides decomposed without giving the desired alkylation product.

This newly established *meta*-alkylation protocol is also extended to other amide substrates derived from phenyl acetic acids using butyl iodide as the coupling partner (Table 3). Substrates containing *ortho*-methoxy, fluoro and chloro groups give the desired *meta*-butylated products in good yields (**6a–c**). *Meta*-methoxy, methyl, fluoro, chloro and trifluoromethyl are also well-tolerated (**6d–6h**). The butylation of the *para*-fluoro and non-substituted phenylacetamides (**5i**, **5j**) under the standard conditions give a mixture of di and mono-butylation products in the ratio of 1:1. However, the di-butylated phenylacetamides **6i-di** and **6j-di** are obtained as the major products in 77 and 65% yields respectively by using 20 mol% Pd catalyst and 5 equiv of butyl iodide. Reducing the butyl iodide to 2 equiv gives the mono-butylated phenylacetamide **6j-mono** as the main product in 44% yield. Naphthalene substrate **5k** is selectively butylated at the 3-position in excellent yield (92%). *Meta*-alkylation of tetralone, dihydrobenzofuran and indoline substrates also proceeds in moderate yields (**6l–n**), even though the amide directing group is out of plane with the *ortho* and *meta*-C–H bonds. However, extending this method to other heterocycles such as pyridines and thiophenes are unsuccessful. Our *meta*-alkylation protocol is also compatible with mandelic acid and phenylglycine substrates affording the desired products **6o** and **6p** in good yields. Unfortunately, substantial racemization occurred during the installation of our amide directing group using previously reported conditions (**5o** is obtained in 67% ee). However, no racemization was observed in this *meta*-alkylation reaction when using mandelic acid derived amide **5o** with 67% ee as the substrate (See supporting information).

The ability of this modified norbornene to enable *meta*-C–H alkylation encouraged us to revisit our previously reported *meta*-arylation reaction (Table 4).[4] This previous protocol is only compatible with aryl iodides bearing an *ortho*-coordinating group or multiple electron-withdrawing substituents. Using norbornene **N15**, *meta*-arylation with broad range of aryl iodides proceeded smoothly, overcoming previous limitation. Phenyl iodide and other aryl iodides containing chloride, trifluoromethyl and ester, as well as methyl, amino and methoxy groups all give good to excellent yields. Notably, 5-iodoindole is also compatible affording the desired product in 57%.

The multiple elementary steps involved in this catalytic cycle add complexity to the investigation of the origin of the beneficial effect of this modified norbornene (Figure 1). A number of mechanistic aspects, however, are worth commenting based on our preliminary studies. First, the stereochemistry of the carbopalladation step (step 2) is mostly likely to be *exo* as established in the stoichiometric reaction of Ph-Pd-I with norbornene.[16] Second, the protonolysis of the arylpalladium bond is crucial for regenerating the Pd(II) catalyst and closing the catalytic cycle. To support our hypothesis, reaction of **1** is performed in the presence of 10 equiv deuterated acetic acid (eq 3). The observed 70% D-incorporation at the *ortho*-position is consistent with the protonolysis pathway. The proton source from the amide substrate and the HOAc generated from the C–H activation step could account for the 30% H-incorporation at the *ortho*-position. Trifluoromethylated amide **5h** was also subjected to the same deuterium labeling experiment to get better separation of aromatic protons on NMR spectrum, which gave similar D-labeling pattern (see supporting information). Finally, the impact of this modified norbornene **N15** is also illustrated in the Catellani arylation reaction. It is well-known that the Catellani *ortho*-arylation using norbornene is limited to aryl iodides bearing *ortho*-substituents.[3c,17] Other aryl iodides only give a series of side-products containing bicyclic structure (eq 4).[18] In contrast, the Catellani *ortho*-arylation followed by Heck reaction proceeds with **N15** to give the standard product **9a–b** in good yield (eq 5).



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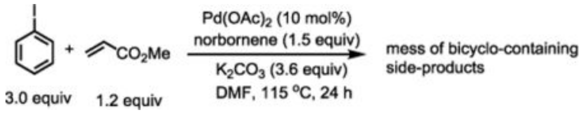

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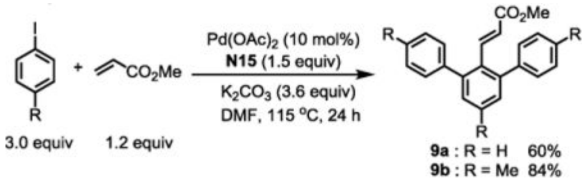

(5)

In summary, we have developed a *meta*-alkylation reaction and significantly improved the scope of *meta*-arylation reaction of phenyl acetamides. The design of a more reactive norbornene analogue and appropriate choice of a quinoline-type ligand are crucial for the success of this development. The acquired insight from this study will guide further development of this emerging *meta*-C–H functionalization strategy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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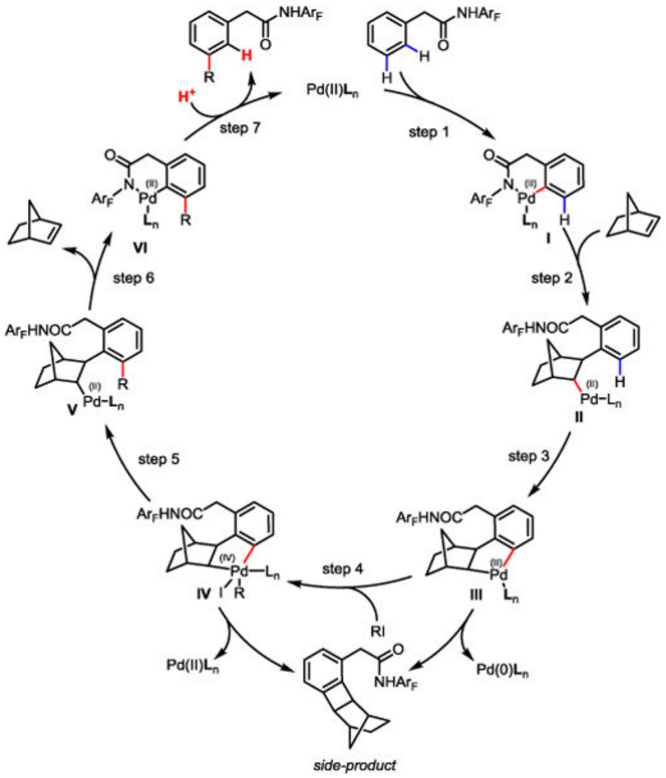
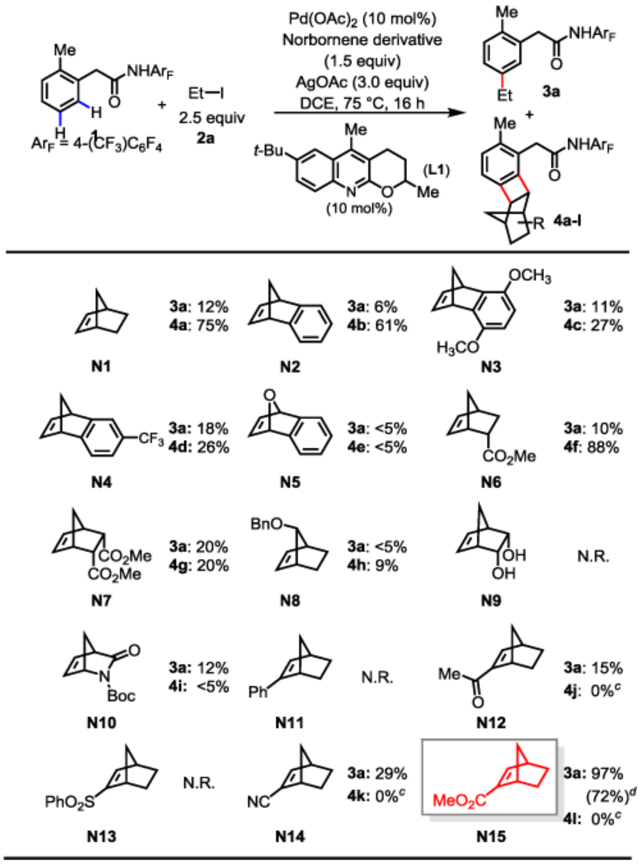


Figure 1.

Plausible Catalytic Cycle for Norbornene-Mediated *Meta*-C–H Alkylation

Table 1

Modified Norbornenes for *Meta*-Alkylation[a,b]



Norbornene	Yields
N1	**3a**: 12% **4a**: 75%
N2	**3a**: 6% **4b**: 61%
N3	**3a**: 11% **4c**: 27%
N4	**3a**: 18% **4d**: 26%
N5	**3a**: <5% **4e**: <5%
N6	**3a**: 10% **4f**: 88%
N7	**3a**: 20% **4g**: 20%
N8	**3a**: <5% **4h**: 9%
N9	N.R.
N10	**3a**: 12% **4i**: <5%
N11	N.R.
N12	**3a**: 15% **4j**: 0%[c]
N13	N.R.
N14	**3a**: 29% **4k**: 0%[c]
N15	**3a**: 97% (72%)[d] **4l**: 0%[c]

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[a] Conditions: **1** (0.1 mmol), **2a** (2.5 equiv), Pd(OAc)$_2$ (10 mol%), **L1** (10 mol%), Norbornene derivative (1.5 equiv), AgOAc (3.0 equiv), DCE (1.5 mL), 75 °C, air, 16 h.

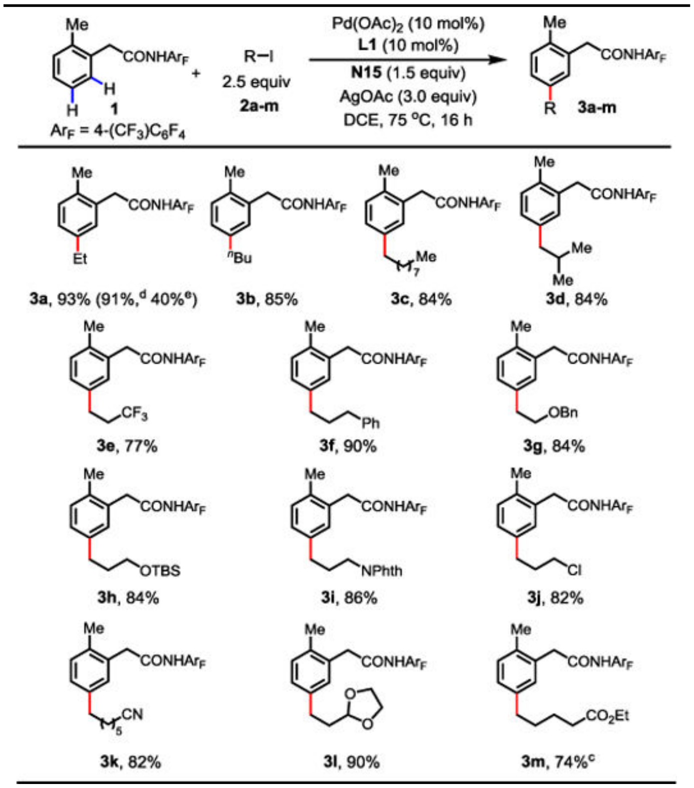
[b] ^{1}H NMR yields, using CH$_2$Br$_2$ as internal standard.

[c] Possible side-product was not observed with or without the addition of **2a**.

[d] Using 0.5 equiv of **N15** instead of 1.5 equiv.

Table 2

Meta-Alkylation with A Variety of Alkyl Iodides[a,b]



3a, 93% (91%,[d] 40%[e])
3b, 85%
3c, 84%
3d, 84%
3e, 77%
3f, 90%
3g, 84%
3h, 84%
3i, 86%
3j, 82%
3k, 82%
3l, 90%
3m, 74%[c]

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[a] Conditions: **1** (0.1 mmol), **2** (2.5 equiv), Pd(OAc)$_2$ (10 mol%), **L1** (10 mol%), **N15** (1.5 equiv), AgOAc (3.0 equiv), DCE (1.5 mL), 75 °C, air, 16 h.

[b] Isolated yields.

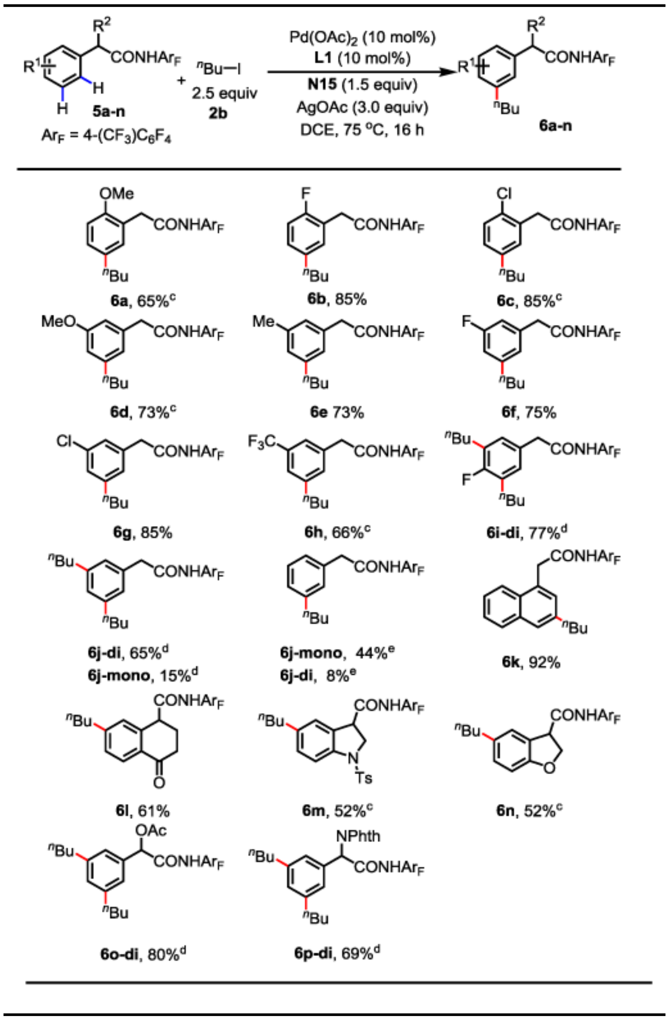
[c] Using 3.0 equiv of **N15** instead of 1.5 equiv.

[d] **1** (1 mmol scale)

[e] Ethyl bromide (2.5 equiv), 48 h; ^{1}H NMR yield measured using CH$_2$Br$_2$ as internal standard.

Table 3

Meta-Alkylation of Substituted Phenylacetamide[a,b]



[a] Conditions: **5** (0.1 mmol), **2b** (2.5 equiv), Pd(OAc)$_2$ (10 mol%), **L1** (10 mol%), **N15** (1.5 equiv), AgOAc (3.0 equiv), DCE (1.5 mL), 75 °C, air, 16 h.

[b] Isolated yields.

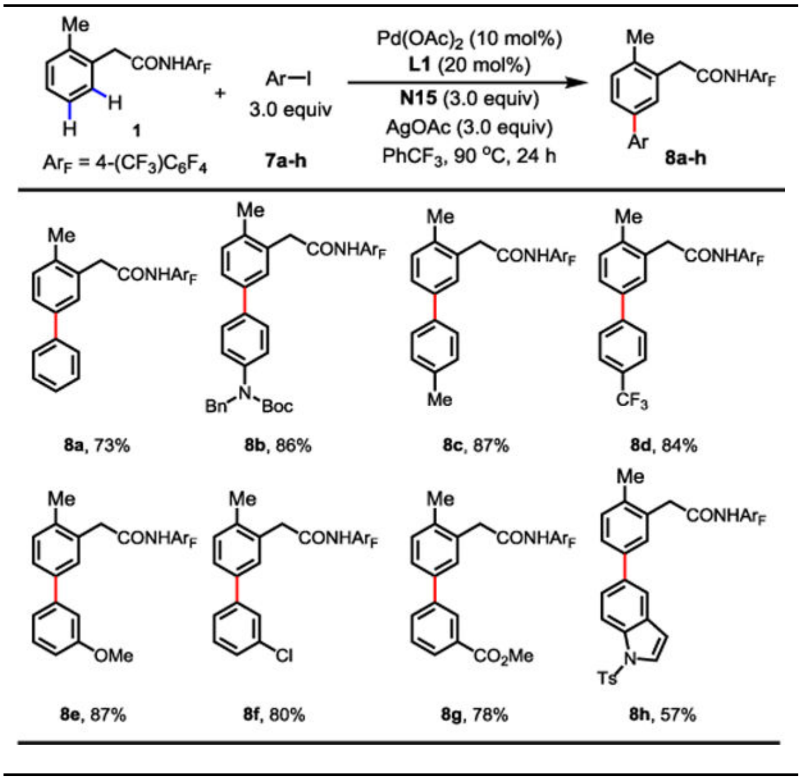
[c] Using 3.0 equiv of **N15** instead of 1.5 equiv.

[d] Using **2b (**5.0 equiv), Pd(OAc)$_2$ (20 mol%), **L1** (20 mol%), **N15** (3.0 equiv), AgOAc (6 equiv), DCE (3.0 ml).

[e] Using **2b** (2.0 equiv), **L1** (20 mol%), 95 °C.

Table 4

Meta-Arylation with A Variety of Aryl Iodides[a,b]



[a] Conditions: **1** (0.1 mmol), **7** (3.0 equiv), Pd(OAc)$_2$ (10 mol%), **L1** (20 mol%), **N15** (3.0 equiv), AgOAc (3.0 equiv), PhCF$_3$ (1.5 mL), 90 °C, air, 24 h.

[b] Isolated yields.