HHS Public Access

Author manuscript

Angew Chem Int Ed Engl. Author manuscript; available in PMC 2018 June 06.

Published in final edited form as:

Angew Chem Int Ed Engl. 2017 June 06; 56(24): 6874–6877. doi:10.1002/anie.201702686.

Ligand-Enabled Auxiliary-Free *Meta*-C–H Arylation of Phenylacetic Acids

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Abstract

Meta-C–H arylation of free phenylacetic acid has been realized using 2-carbomethoxynorbornene (NBE-CO_2Me) as a transient mediator. Both the modified norbornene and the mono-protected 3-amino-2-hydroxypyridine type ligand are crucial for this auxiliary-free meta-C–H arylation reaction. A series of phenylacetic acids including mandelic acid and phenylglycine react smoothly with various aryl iodides to provide the meta-arylated products in high yields.

Graphical Abstract

Keywords

3-amino-2-hydroxypyridine ligand; *meta*-C–H arylation; phenylacetic acid

Despite the rapid development in transition metal-catalyzed C–H activation, *meta*-C–H functionalization remains limited in scope and efficiency.[1–3] Although sterics or the electronics of the arene substrates can lead to *meta*-selective C–H functionalizations,[3] the successful control of *meta*-selectivity with mono-substituted arenes are rare.[3j] In addition, these approaches are not feasible when polar functional groups are remote to the arenes. The use of a U-shaped template with a tethered nitrile or pyridine directing group demonstrated the feasibility of directing *meta*-selective metal insertion into remote C–H bonds regardless of the substitution patterns.[1] More recently, our group[2a] and others[2b] have combined directed *ortho*-C–H activation with Catellani's norbornene process[4] to achieve *meta*-C–H functionalization.[2] Using this strategy, the design of novel ligands[2a,e] and transient mediators[2c] has enabled a variety of new *meta*-C–H transformations.[2f–g] However, the use of weakly coordinating native functional groups as the directing group to achieve this *meta*-C–H functionalization has not been realized to date, despite the plethora of work concerning

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201xxxxxx.

carboxylic acid directed *ortho*-C−H functionalizations (Scheme 1a).[5–6] Herein we report an auxiliary-free *meta*-C−H arylation of phenylacetic acids, using 2-carbomethoxynorbornene (NBE-CO_2Me) as a transient mediator and *mono*-protected 3-amino-2-hydroxypyridine as the ligand. (Scheme 1c).

Although carboxylic acid directed *ortho*-C−H functionalizations have been developed,[6] we anticipate a number of challenges when using such weakly coordinating directing group for *meta*-C−H functionalizations: 1) The lack of tunability of an external directing group to accommodate the multiple steps of the catalytic cycle is a significant challenge associated with the use of native carboxylic acid; 2) Due to the weak coordination of the carboxylic acid, the Catellani reaction of aryl iodides could outcompete the *ortho*-C−H palladation of phenyl acetic acid to give homo-coupling products; 3) Following the *ortho*-C−H palladation, the undesired *ortho*-C−H arylation is known to take place.[6f]

Despite the aforementioned challenges, the previously observed ligand effect in this catalytic cycle offers a promising handle to overcome these hurdles. For instance, in the *meta*-arylation of phenylacetamide, the quinoline ligand was crucial to achieve the high reactivity[2a,c] (Scheme 1b). We therefore focused on searching for a suitable ligand which can promote both the carboxylic acid-directed *ortho*-C−H activation and the subsequent norbornene-mediated palladation of the *meta*-C−H bonds. Based on our previous findings that *mono-N*-protected amino acid (MPAA) ligands can significantly accelerate the *ortho*-C−H olefination of phenylacetic acid,[6d,f] we initiated our study by stirring the mixture of 2-methyl phenylacetic acid (0.1 mmol), *p*-iodotoluene (2.5 equiv), K_2HPO_4 (2 equiv), Ag_2CO_3 (0.75 equiv), $Pd(OAc)_2$ (10 mol%), NBE-CO_2Me (1.5 equiv) in hexafluoroisopropanol (HFIP) at 100 °C in the presence of MPAA ligands (**L1** and **L2**, Table 1). Unfortunately, no desired products were observed when employing MPAA ligands, indicating that this scaffold does not sufficiently orchestrate the fundamental steps following the carbopalladation of the norbornene mediator. Although quinoline and pyridine ligands have been found to be crucial for norbornene-mediated *meta*-C−H arylation and alkylation of phenylacetamide,[2a,c] no desired products were obtained with phenylacetic acid substrates when ligands **L3–5** were used. Pyridine and quinoline ligands are likely to inhibit the *ortho*-C–H palladation of the phenyl acetic acid.

Next, we turned to *mono*-protected 3-amino-2-hydroxypyridine ligands which were developed for the norbornene-mediated *meta*-C−H functionalization of aniline and phenol derived substrates using a non-native directing group.[2e–f] To our delight, 3-acetylamino-2-hydroxypyridine **L7** orchestrated the fundamental steps of this catalytic cycle and enabled the formation of *meta*-arylated product in 45% yield without detectable formation of the *ortho*-arylated side product. Removal of the 3-acetylamino group caused a decrease in reactivity (**L6**, 23% yield), which indicated the acetyl-protected amino group could enhance the efficiency of the ligand. Further examination of a series of substituted *mono*-protected 3-amino-2-hydroxypyridine ligands was carried out. A methyl group at the 6-position of the pyridine ring resulted in complete loss of reactivity (**L8**), presumably due to the imposed steric hindrance. While the methyl group at either 4- or 5-position gave lower yields (**L9–10**), the electron-withdrawing trifluoromethyl group at 5-position increased the yield to 78% (**L11**). With **L11** identified as promising ligand scaffold, a series of protecting group (PG)

on the amino group (**L11–18**) were evaluated. A benzoyl protecting group decreases the effectiveness of the ligand (**L12**). The strongly electron-withdrawing trifluoroacetyl decreased the yield from 78% to 54% (**L13**), while a slightly electron-withdrawing PG was effective (**L14**). Notably, 1-admantanecarbonyl group (**L18**) afforded the desired products in 85% NMR yield (83% isolated yield). We currently hypothesize that *mono*-protected 3-amino-2-hydroxypyridine ligands are uniquely effective for this transformation because they not only promote the initial carboxylic acid-directed C–H activation and subsequent olefin insertion (much like MPAA ligands), but also promote the remaining steps of the catalytic cycle (unlike MPAA ligands). Control experiments showed that the pyridone-type ligand **L18** can indeed accelerate the carboxylic acid-directed *ortho*-C−H olefination reaction.[7] The loading of $Pd(OAc)_2$ can be reduced to 5 mol% with only a slight decrease in yield (70%). The use of catalytic amount of NBE-CO_2Me is also feasible, albeit leading to lower yield (50 mol% NBE-CO_2Me, 64% yield). In the absence of NBE-CO_2Me, only *ortho*-arylated product was obtained.[6f] The simple norbornene are completely inactive under these conditions.

With the optimal conditions in hand, we examined the reactivity of variety of substituted aryl iodide coupling partners using 2-methyl phenylacetic acid as the model substrate. Both electron-rich and electron-deficient aryl iodides were well-tolerated, affording *meta*-arylated products in good to excellent yields (Table 2). *Ortho*-substituents including methyl, methoxyl, fluoro, and trifluoromethyl groups are compatible with this protocol (**3a–3d**). It is worth-noting that these non-coordinating *ortho*-substitutents were previously found to adversely affect *meta*-C−H arylation reactions.[2e] Surprisingly, methyl 2-iodobenzoate, a superior coupling partner in previous *meta*-C−H arylation reactions, gave the desired product in low yield (45%) under our standard conditions. The use of 1.5 equivalents of Ag_2CO_3 improved the yield to 70% (**3e**). *Para*-substituted aryl iodides gave slightly lower yields (**3l–3r**), especially for electron-deficient aryl iodides (**3o–3r**). 3,5-Disubstituted aryl iodides afforded excellent yields, regardless of their electronic properties (**3s**, **3t**). Although this protocol tolerates various functional groups including nitro, trifluoromethyl, fluoro, chloro, bromo and phosphate (**3f**, **3m–3p, 3r**), coordinating heteroaryl iodides are not reactive under current conditions.

The substrate scope of phenylacetic acids was also examined using 1-iodo-2-nitrobenzene as the coupling partner (Table 3). Substrates containing either electron-withdrawing or electron-donating substituents on the phenyl ring were arylated at the *meta*-position with high efficiency (**5b–5n**). Simple phenylacetic acid afforded a mixture of *mono*- and *di*-arylated products in 85% combined yield with a *mono:di* ratio of 1.2:1.0 (**5a**). Both *ortho*- and *meta*-substituted substrates gave the mono-arylated products in high yields (**5b–5i**). Bromo- and chloro- subsituents remained intact under the reaction conditions (**5g, 5h**), allowing orthogonality with traditional Pd-catalyzed cross coupling reactions. The *mono*-selectivity of *para*-substituted substrates varied. While 4-fluorophenylacetic acid gave a mixture of *mono*- and *di*-arylated products (49% **5j-mono**, 35% **5j–di**), excellent *mono*-selectivity was observed with 4-methoxyphenylacetic acid giving *mono*-arylated product in 60% yield (**5k**). The steric hindrance of the *para*-methoxyl group being adjacent to the *meta*-position is sufficient to prevent the di-arylation.[2e] Disubstituted phenylacetic acids were

compatible substrates, affording moderate to excellent yields (**5l–5n**). 1-Naphthleneacetic acid gave the desired product in 82% yield (**5o**). While α-alkyl substituted phenylacetic acids resulted in poor yields, the rigid bicyclic substrate 1,2,3,4-tetrahydronaphthalene-1-carboxylic acid worked well (**5p**). Notably, derivatives of mandelic acid and α-phenylglycine were compatible with this protocol (**5q, 5r**).

A gram-sale reaction was carried out to demonstrate the robustness of this reaction. Employing 2-methyl phenylacetic acid as substrate, the *meta*-arylated product was obtained in 91% isolated yield under the standard conditions (Scheme 2).

In summary, *meta*-C−H arylation of free phenylacetic acids was achieved by employing 2-carbomethoxynorbornene as the transient mediator and *mono*-protected-3-amino-2-hydroxypyridine as the ligand. Both the pyridone ligand and the modified norbornene mediator are crucial for realizing this auxiliary-free *meta*-C−H arylation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge The Scripps Research Institute and the NIH (NIGMS, 2R01 GM102265) for financial support.

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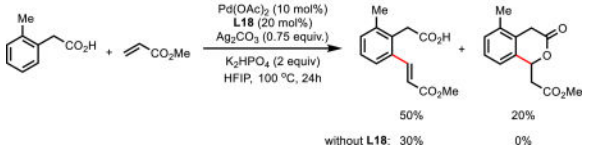
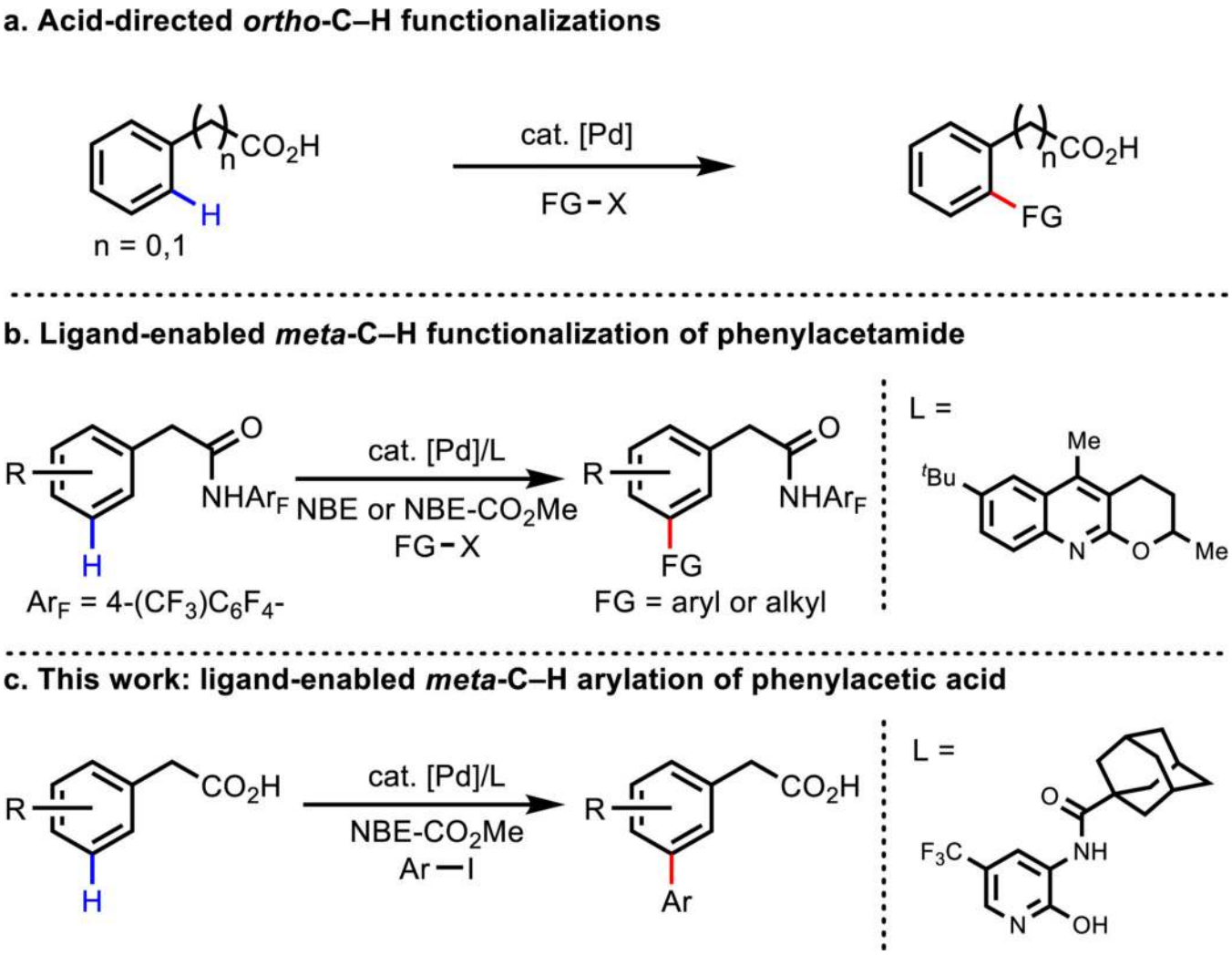
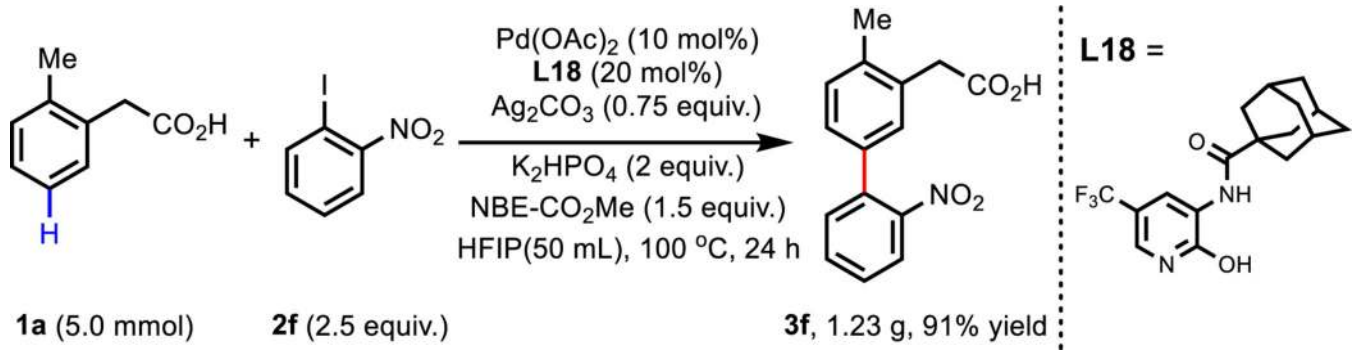
7. The *ortho*-C−H olefination of 2-methyl phenylacetic acid was carried out in the presence of **L18**, 70% combined yield of the *ortho*-olefinated product and cyclized product was obtained under the conditions similar to those used in the *meta*-functionalization reaction. Without ligand **L18**, only 30% olefination product was formed.





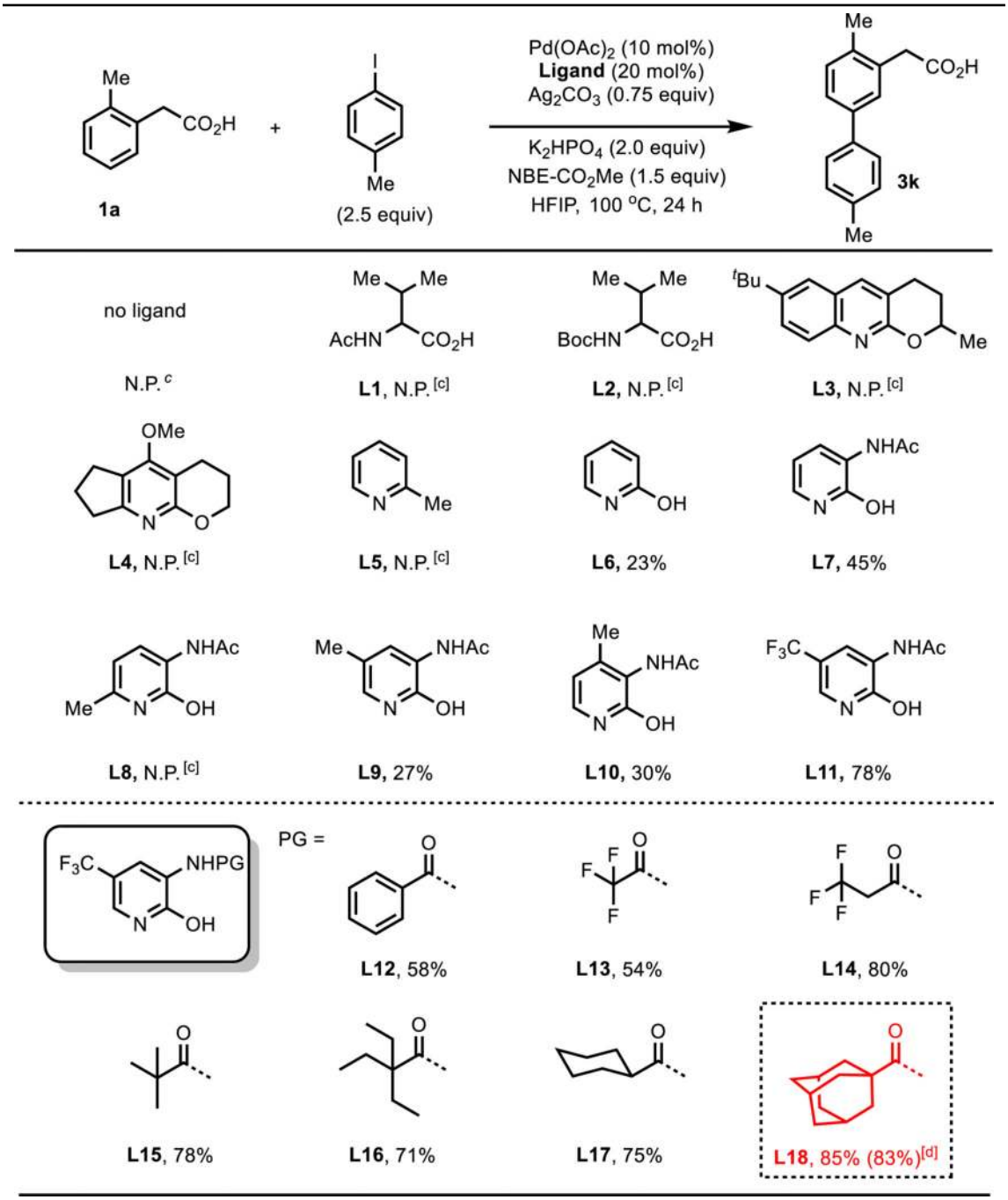
Scheme 1.
Meta-C−H arylation of phenylacetic acid.



Scheme 2.
Gram-scale reaction.

Table 1

Ligand evaluation for *meta*-C–H arylation of phenylacetic acid.[a,b]



[a]Reaction conditions: 2-methyl phenylacetic acid **1a** (0.1 mmol), *p*-iodotoluene (2.5 equiv), $Pd(OAc)_2$ (10 mol %), K_2HPO_4 (2.0 equiv), Ag_2CO_3 (0.75 equiv), NBE-CO_2Me (1.5 equiv), Ligand (20 mol %), HFIP (1.0 mL), 100 °C, 24 h.

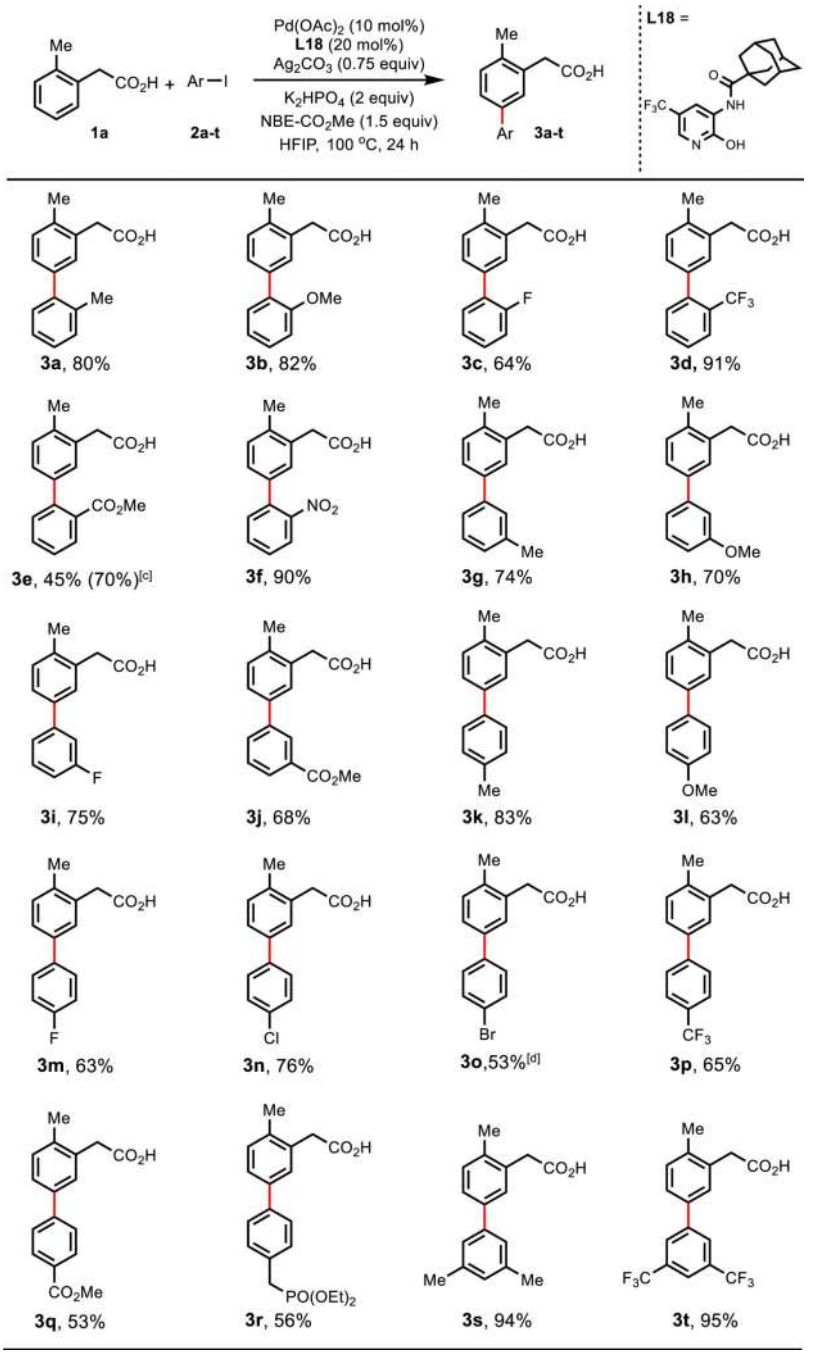
[b]The yield was determined by 1H NMR using CH2Br2 as the internal standard.

[c] N.P.= no desired products.

[d] Isolated yield.

Table 2

Scope of aryl iodides.[a,b]



[a]Reaction conditions: 2-methyl phenylacetic acid **1a** (0.1 mmol), Aryl iodide (2.5 equiv), $Pd(OAc)_2$ (10 mol %), K_2HPO4 (2.0 equiv), Ag_2CO_3 (0.75 equiv), NBE-CO_2Me (1.5 equiv), **L18** (20 mol %), HFIP (1.0 mL), 100 °C, 24 h.

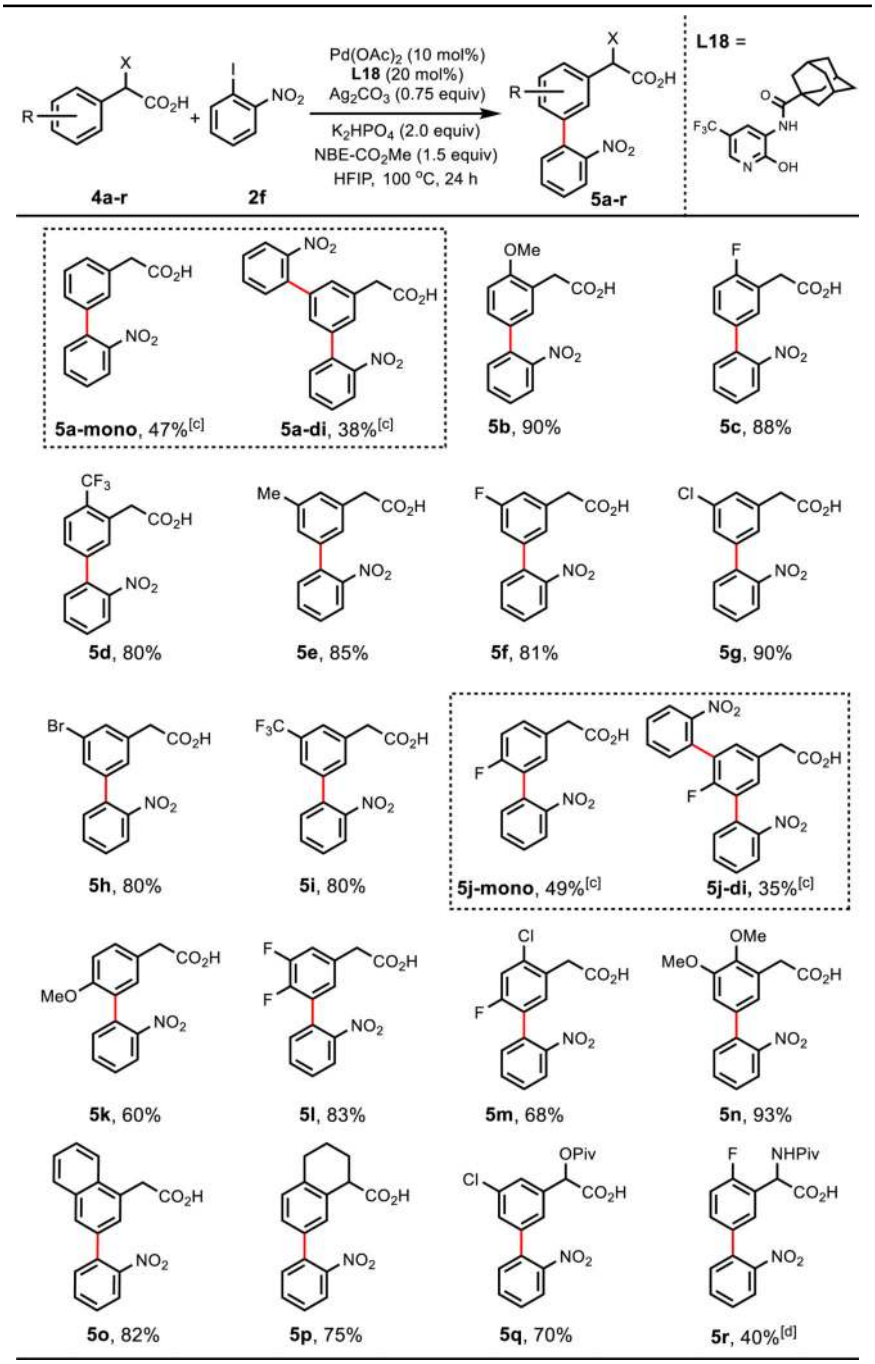
[b]Isolated yield.

[c] Ag_2CO_3 (1.5 equiv) was used.

[d] Isolated as the methyl ester.

Table 3

Meta-arylation of phenylacetic acid.[a,b]



[a]Reaction conditions: phenylacetic acid (0.1 mmol), 2-nitro-iodobenzene (2.5 equiv), $Pd(OAc)_2$ (10 mol %), K_2HPO_4 (2.0 equiv), Ag_2CO_3 (0.75 equiv), NBE-CO_2Me (1.5 equiv), **L18** (20 mol %), HFIP (1.0 mL), 100 °C, 24 h.

[b]Isolated yield.

[c] **2f** (3.0 equiv) was used.

[d] Isolated as the methyl ester.