C–H Activation

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Ligand-Promoted *meta*-C–H Functionalization of Benzylamines

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Abstract: *Meta-C–H functionalization of benzylamines has been developed using a Pd^{II}/transient mediator strategy. Using 2-pyridone ligands and 2-carbomethoxynorbornene (NBE-CO_2Me) as the mediator, arylation, amination, and chlorination of benzylamines are realized. This protocol features a broad substrate scope and is compatible with heterocylic coupling partners. Moreover, the loading of the Pd can be lowered to 2.5 mol% by using the optimal ligand.*

Meta-C–H functionalization has attracted the attention of many groups within the synthetic community due to the innovative strategies required to achieve high efficiency and selectivity for this process.[1–4] The fundamental challenge associated with this process is the difficulty of delivering a transition metal to the topologically distal *meta*-C–H bond. A direct approach to address this problem in a general manner was first realized in 2012 by the use of a rationally designed, U-shaped nitrile containing template.[2a] This template allowed *meta*-C–H functionalization by facilitating the selective formation of a metallocyclophane-like transition state.[2] Though templating has proven to be a rather general approach, a complementary strategy has recently emerged that leverages the vast body of literature concerning *ortho*-C–H functionalization and translates it to *meta*-C–H functionalization by use of a transient mediator.[3] This is achieved by synchronizing directed *ortho*-palladation with Catellani's norbornene-mediated relay process[5] to provide a net *meta*-functionalized product. Since the disclosure of this approach, the design of both ligands and a new transient mediator (2-carbomethoxynorbornene) has enabled several substrate classes to be functionalized with a variety of partners at the *meta*-position,[3] some of which have no precedent in the Catellani reaction.[3f,g] Given the ease with which this transformation can be implemented and its apparent versatility, it is highly attractive to expand this approach to other useful substrate types to provide the desired *meta*-substituted arenes in a highly efficient and straightforward manner.

Benzylamines are commonly found in natural products and pharmaceutical molecules (Figure 1).[6] Thus, developing general and practical *meta*-C–H transformations of benzylamines will provide synthetic chemists a reliable method for rapid diversification of these important scaffolds. Unlike the well-developed *ortho*-C–H functionalizations of benzylamine substrates,[7] *meta*-C–H functionalizations of benylamines are

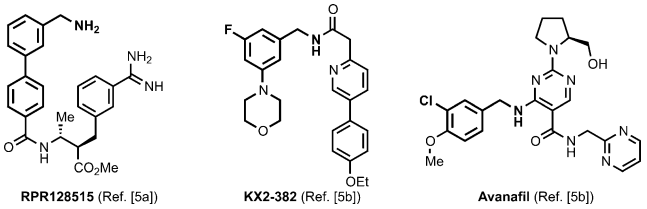
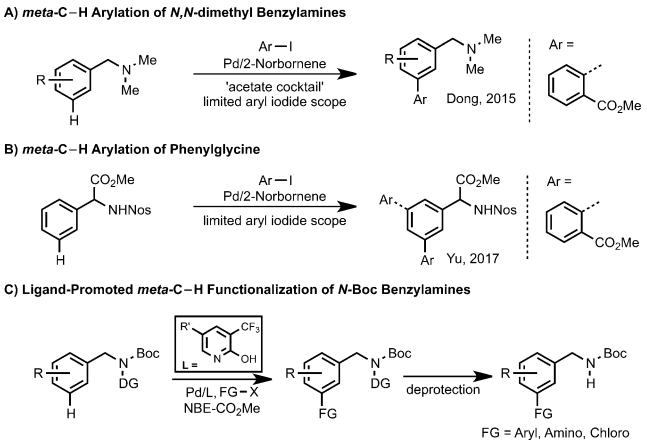


Figure 1. Selected bioactive *meta*-substituted benzylamines.

currently plagued by inefficiencies in both substrate and coupling partner scope. In 2014, our group achieved the *meta*-C–H acetoxylation of *N*-methyl benzylamine using a U-shaped template.[2c] A *meta*-arylation protocol for *N*,*N*-dimethyl benzylamine using a transient mediator has also been developed,[3b] but the coupling partner scope was limited to aryl iodides containing *ortho*-coordinating groups (Scheme 1a). Furthermore, this procedure does not provide



Scheme 1. *Meta*-C–H functionalization of benzylamines.

practical access to free benzylamines due to the difficulty of removing the *N*,*N*-dimethyl groups. Earlier this year, our group reported the compatibility of nosyl protected amines with *meta*-arylation using transient mediators, but only a single substrate (phenylglycine) was reactive and the arene coupling partners were limited to aryl iodides containing *ortho*-coordinating groups (Scheme 1b).[3h] Herein, we report that 2-pyridone ligands can promote palladium-catalyzed *meta*-C–H functionalization of benzylamine substrates. This reaction features a broad substrate scope and good functional group tolerance (Scheme 1c) using 2-carbomethoxynorbornene as a transient mediator. Pd catalyst loading can be reduced to 2.5 mol% for the first time. *Meta*-functionalized *N*-Boc benzylamines can be obtained after

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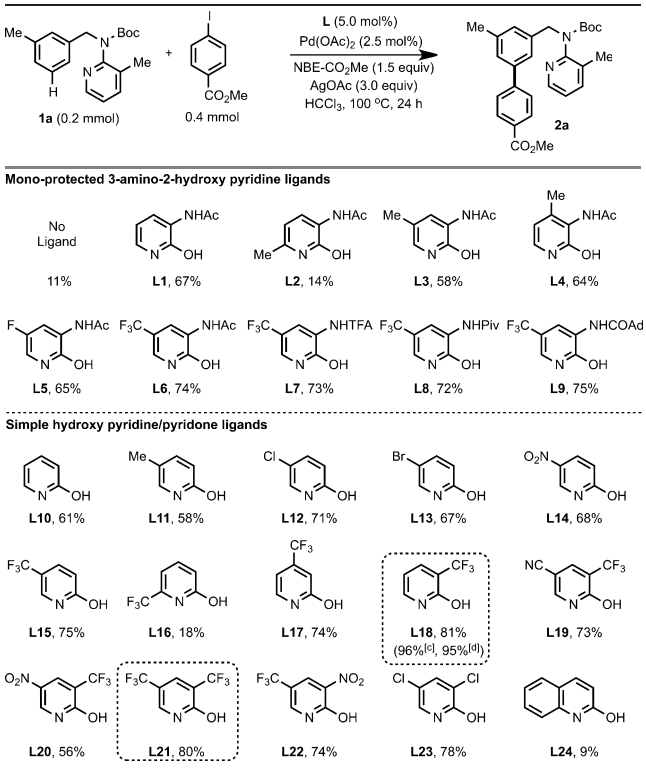
removal of the directing group, providing straightforward access to a wide array of *meta*-functionalized benzylamines.

Our experimental design was guided by the following reasoning: a readily removable directing group is needed to prepare benzyl amines; a 7-membered palladacycle intermediate is known to be advantageous for this norbornene-mediated multi-step catalytic cycle.[3e] Gratifyingly, a newly designed removable pyridine-derived directing group that form a 7-membered palladacycle allowed the formation of the *meta*-arylated product in 25% yield with 10 mol% $Pd(OAc)_2$ (see the Supporting Information (SI) for more information). The presence of a *mono*-protected 3-amino-2-hydroxypyridine ligand **L1** was essential. Notably, these substrates can be easily synthesized in one step using the 2-(Boc-amino)-3-methylpyridine with benzylic halides in the presence of base. After a simple investigation of the substitution on the pyridine directing group, it was found that substitution of the 3-position on the pyridine ring with a methyl group improved the yield to 99%. The efficiency of this reaction prompted us to search for ligands that can reduce the Pd catalyst loading. Hence, we evaluated a variety of ligands in the presence of 2.5 mol% $Pd(OAc)_2$ on 0.2 mmol scale. Based on our previous findings in *meta*-C–H functionalization of anilines and phenols, the *mono*-protected 3-amino-2-hydroxypyridine ligands (**L1**–**L9**) were investigated first (Table 1). The 3-acetylamino-2-hydroxypyridine (**L1**) dramatically improved the reactivity, affording the desired *meta*-arylated product in 67% yield. Methyl substitution at the 6-position (**L2**) of the ligand scaffold led to a significant decrease in the activity probably due to steric encumbrance of the ligand, while methyl substitution at the 4- or 5-position does not drastically alter the effectiveness of the ligand (**L3** and **L4**). Fluorinated ligand (**L5**) provided a slightly lower yield of the desired product. Gratifyingly, the installation of a CF_3 at the 5-position increased the yield to 74% (**L6**). A few acyl protecting groups on amine based on the promising ligand **L6** were evaluated, but no drastic changes in efficiency were noticed (**L7**–**L9**). This is in contrast to our prior publications concerning 3-acetylamino-2-hydroxypyridine ligands wherein the protecting group on the amine can exert a significant influence on the reaction efficiency.[3f] Interestingly, simple 2-hydroxypyridine (**L10**) also promoted this reaction smoothly, providing slightly lower yield compared with the 3-acetylamino-2-hydroxypyridine ligand **L1**. Thus we turned our attention to the evaluation of the simple 2-pyridone ligands (**L10**–**L24**). 5-methyl substituted hydroxypyridine ligand (**L11**) led to a slight decrease of the efficiency of the ligand, while the electron-withdrawing group at the 5-position of the ligand scaffold gave higher yield (**L12**–**L15**). Similar to the ligand **L2**, the 6-CF_3 substituted hydroxypyridine ligand **L16** dramatically decreased the activity, while ligands containing a CF_3 group on the 3, or 4 positions provide promising results (**L16** vs. **L17**–**L18**). To our delight, the 3-CF_3 substituted ligand **L18** improved the yield to 81%. This result demonstrates that the 3-acetylamino group is not likely playing a fundamental role in our previously reported reactions, but instead serves as a tunable substituent whose role is substrate and transformation dependent. More electron deficient hydroxypyridine ligands (**L19**–**L21**) containing the 3-CF_3 substituent were tested and it was found that 3,5-ditrifluoromethyl hydroxypyridine **L21** displays very similar activity with **L18**. 3-Nitro-5-trifluoromethyl-2-hydroxypyridine (**L22**) and 3,5-dichloro-2-hydroxypyridine (**L23**) were also efficient for this transformation, providing the desired product in 74% and 78% yields, respectively. 2-Hydroxyquinoline (**L24**) only afforded the product in 9% yield, probably due to the steric similarity of **L2**, **L6**, and **L24**. The yield of this reaction can be further improved to either 96% or 95% in the presence of **L18** by use of 3.0 equivalents of aryl iodide or increasing the loading of palladium catalyst to 5.0 mol% respectively.

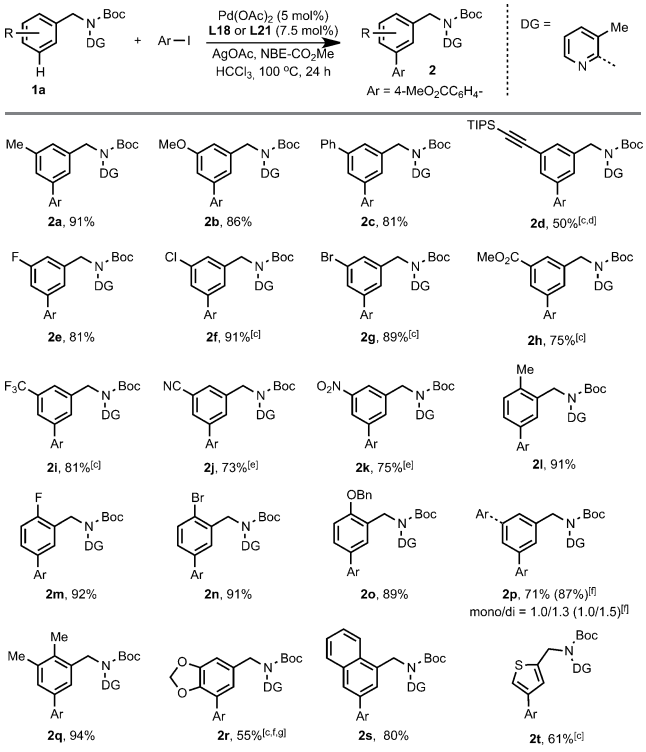
With the optimal conditions in hand, we next examined the scope of benzylic amine substrates. As shown in Table 2, a broad range of functional groups are well tolerated in this reaction. Benzylamines bearing electron-donating substituents at the 3-position (**2a**–**c**), such as methyl, methoxy, and phenyl, are suitable substrates for the process providing the desired products in high yields. Substrate **1d** bearing an alkynyl group on the 3-position afforded lower yield due to the stability of the substrates under the standard conditions. Electron-deficient benzylamines gave lower yields in the presence of **L18** (**2e**–**k**). For example, subjection of the 3-bromo- and 3-trifluoromethyl-benzylamine to the standard conditions afforded the corresponding products in 69% and 61% yields, respectively. Through optimizations of the ligand effects for the electron deficient substrates, we found that the

Table 1: Ligand evaluation for *meta*-C–H arylation of benzylamines.[a,b]



[a] Conditions: **1a** (0.2 mmol), Ar-I (2.0 equiv), $Pd(OAc)_2$ (2.5 mol%), **L** (5.0 mol%), AgOAc (100.2 mg, 3.0 equiv), NBE-CO_2Me (43.0 mg, 1.5 equiv), $HCCl_3$ (1.0 mL), 100°C, air, 24 h. [b] The yields were determined by ^{1}H NMR using acetylene tetrachloride as an internal standard. [c] $Pd(OAc)_2$ (2.5 mol%), **L18** (3.75 mol%), Ar-I (3.0 equiv) were used. [d] $Pd(OAc)_2$ (5 mol%), **L18** (7.5 mol%) were used.

Table 2: *Meta*-C–H arylation of benzylamines.[a,b]



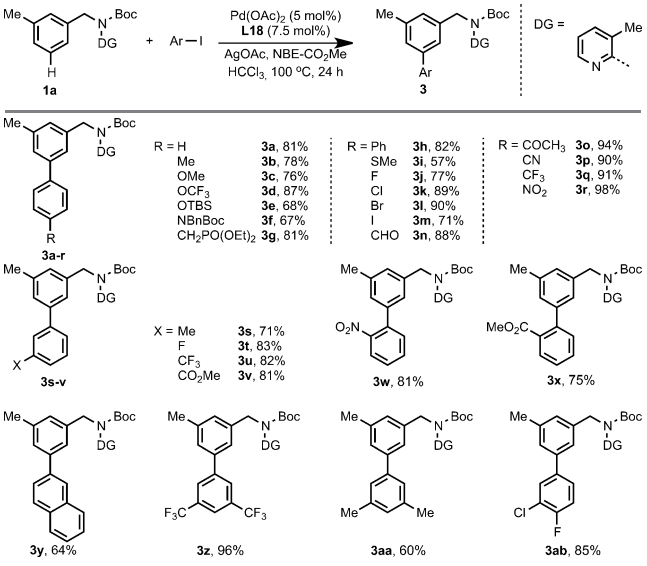
[a] Conditions: $Pd(OAc)_2$ (5 mol%), **L18** (7.5 mol%), Ar-I (2.0 equiv), AgOAc (50.1 mg, 3.0 equiv), NBE-CO_2Me (21.5 mg, 1.5 equiv), $HCCl_3$ (0.5 mL), 100 °C, air, 24 h. [b] Isolated yields. [c] **L21** (7.5 mol%) was used instead of **L18**. [d] **1d** (15%). [e] $Pd(OAc)_2$ (10 mol%), **L21** (15 mol%) were used. [f] Ar-I (3.0 equiv) was used. [g] **1r** (41%).

3,5-ditrifluoromethyl-2-hydroxypyridine (**L21**) was optimal. For example, using **L21** as the ligand, substrate **1g** containing a 3-bromo-substituent afforded the desired product in 89% yield. Under the newly established conditions, a series of electron-withdrawing groups are compatible with this procedure (**2f–k**). C-2 substituted benzylamine derived substrates are suitable substrates for this reaction delivering the desired products in excellent yields (**2l–o**), while the simple benzylamine (**2p**) gave a mixture of *mono*- and *di*-products. Multi-substituted benzylamines (**2q** and **2r**), as well as 1-naphthylmethylamine (**2s**) are also suitable substrates. The tolerance of thiophene substrate (**2t**) also shows the potential applicability of this protocol.

Employing **1a** as a model substrate, the scope of aryl iodides was examined. As shown in Table 3, aryl iodides containing both electron-rich substituents (**3a–i**) and electron-deficient substituents (**3j–r**) are suitable coupling partners. Usually, electron-deficient aryl iodides provided higher yields than electron-rich aryl iodides. Several 3-substituted (**3s–v**), 2-substituted (**3w** and **3x**) as well as multi-substituted aryl iodides (**3z-ab**) were also evaluated and all provided the desired products in high yields, although 2,6-disubstituted aryl iodides cannot be tolerated probably due to the steric hindrance.

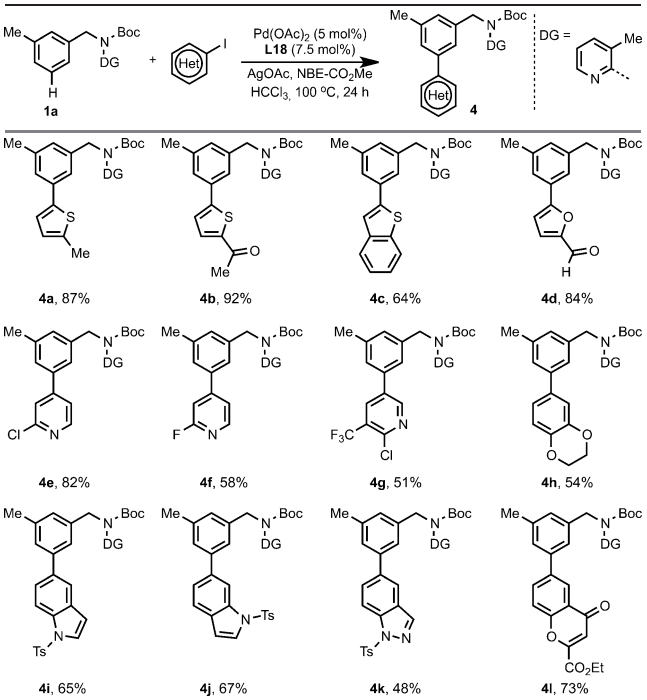
Gratifyingly, heterocyle containing aryl iodides are also compatible in the reaction delivering the desired *meta*-arylated products in moderate to excellent yields (Table 4).

Table 3: Scope of simple aryl iodides.[a,b]



[a] Conditions: $Pd(OAc)_2$ (5 mol%), **L18** (7.5 mol%), Ar-I (2.0 equiv), AgOAc (50.1 mg, 3.0 equiv), NBE-CO_2Me (21.5 mg, 1.5 equiv), $HCCl_3$ (0.5 mL), 100 °C, air, 24 h. [b] Isolated yields.

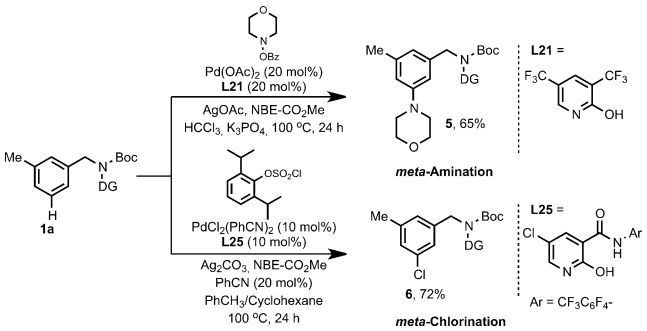
Table 4: Scope of heterocyclic aryl iodides.[a,b]



[a] Conditions: **1a** (0.1 mmol), Ar-I (2.0 equiv), $Pd(OAc)_2$ (5 mol%), **L18** (7.5 mol%), AgOAc (50.1 mg, 3.0 equiv), NBE-CO_2Me (21.5 mg, 1.5 equiv), $HCCl_3$ (0.5 mL), 100 °C, air, 24 h. [b] Isolated yields.

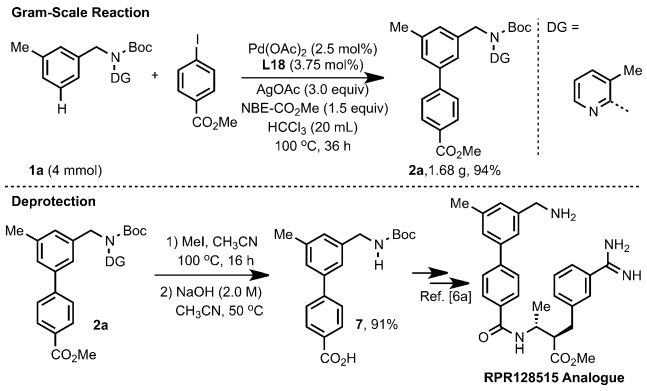
Hetero-aryl iodides containing thiophene, furan, benzothiophene, pyridine,[8] indole, and indazole motifs are all tolerated with this procedure. The compatibility of heterocyclic aryl iodides demonstrated the generality of this protocol as well as the significance of the ligand.

To expand the scope of *meta*-C–H functionalizations using Pd/NBE stragtegy, we also developed other transformations. As shown in Scheme 2, *meta*-C–H amination and chlorination of benzylamines have been realized using *O*-benzoyl hydroxylmorpholine[3f] and aryl chlorosulfate[3g] as electrophiles, respectively.



Scheme 2. Diverse *meta*-C–H functionalizations of benzylamines.

To demonstrate the scalability of this protocol, a gram-scale reaction was conducted under the standard arylation conditions affording the desired arylated product **2a** in 94% yield (Scheme 3). It is worth noting that the loading of Pd catalyst can be reduced to 2.5 mol% at this scale. Importantly, the directing group can be easily removed following a modified known procedure[9] to afford the *N*-Boc benzylamine **7** in 91% yield, a key intermediate to access the RPR 128515 analogues.[6a]



Scheme 3. Gram-scale reaction and deprotection.

In conclusion, Pd^{II}-catalyzed *meta*-C–H functionalizations of benzylaimes have been developed with broad substrate scope and functional group tolerance using 2-carbomethoxy-norbornene as a transient mediator and simple 2-pyridone as the ligands. *Meta*-C–H arylation, amination, and chlorination were all realized using this approach. Importantly, heterocycle containing substrates and coupling partners are compatible with this procedure.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: amination · benzylamines · chlorination · *meta*-C–H arylation · pyridone ligand

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[8] Although 3- or 4-pyridyl iodides (**4e**–**g**) are compatible with this procedure, 2-pyridyl iodides led to low yield (< 10%).

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Communications

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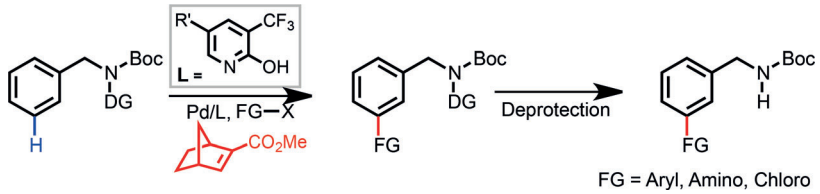
Ligand-Promoted *meta*-C–H Functionalization of Benzylamines



A palladium(II) catalytic system with 2-pyridone ligands and 2-carbomethoxynorbornene (NBE-CO_2Me) as transient mediator enables *meta*-C–H bond activation of benzylamines for arylation, amination, and chlorination (see scheme; DG = directing group). This protocol features a broad substrate scope and is compatible with heterocylic coupling partners. The Pd loading can be lowered to 2.5 mol% by using the optimal ligand.

