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Ligand-Enabled *meta*-Selective C−H Arylation of Nosyl-Protected Phenethylamines, Benzylamines, and 2-Aryl Anilines

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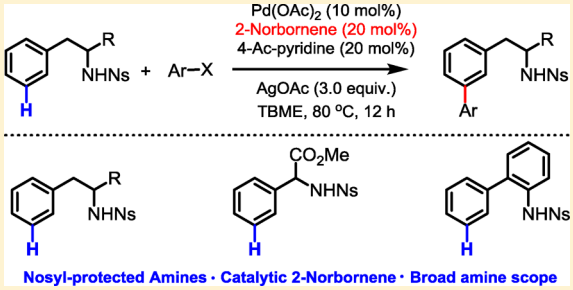
Supporting Information

ABSTRACT: A Pd-catalyzed, *meta*-selective C−H arylation of nosyl-protected phenethylamines and benzylamines is disclosed using a combination of norbornene and pyridine-based ligands. Subjecting nosyl protected 2-aryl anilines to this protocol led to *meta*-C−H arylation at the remote aryl ring. A diverse range of aryl iodides are tolerated in this reaction, along with select heteroaryl iodides. Select aryl bromides bearing *ortho*-coordinating groups can also be utilized as effective coupling partners in this reaction. The use of pyridine ligands has allowed the palladium loading to be reduced to 2.5 mol %. Furthermore, a catalytic amount of 2-norbornene (20 mol %) to mediate this *meta*-C−H activation process is demonstrated for the first time. Utilization of a common protecting group as the directing group for *meta*-C−H activation of amines is an important feature of this reaction in terms of practical applications.



1. INTRODUCTION

Amino functional groups play important roles in modulating biological systems and curing disease.[1] It is therefore of great synthetic value to develop more efficient and versatile methods to rapidly functionalize amine substrates. Palladium-catalyzed C−H functionalization is particularly suited to meet this need as the amine, or the protected version thereof, can coordinate with a palladium catalyst and direct the functionalization of a designated C−H bond that is within an appropriate distance. Indeed, free amino groups,[2] as well as a variety of modified directing groups,[3] have been used to direct transition metal catalysts to *ortho*-C−H bonds which are proximal to the amino group.[4] However, methods which functionalize the distal C−H bonds of these substrates are still somewhat rare. In 2014, our group reported the use of a U-shaped template attached to benzyl amine-derived substrates to direct palladium-catalyzed *meta*-C−H olefination and acetoxylation.[5b] The use of U-shaped templates, originally disclosed by our group in 2012, has led to an array of palladium-catalyzed *meta*-C−H functionalizations.[5] In general, this approach requires the design of a suitable template for a particular class of substrates. More recently, inspired by the Catellani reaction,[6] an alternative *meta*-C−H functionalization strategy has been established by relaying the palladium[6] from a site of *ortho*-cyclometalation to the adjacent *meta*-position.[7] This strategy holds significant promise for the development of highly versatile *meta*-C−H functionalization as it is theoretically compatible with any directing group which can promote *ortho*-cyclometalation.[8] Thus far, two reports have surfaced which concern the use of amine directing groups for *meta*-C−H arylation using norbornene as a transient mediator.[7b,d] The Dong group disclosed the use of *N*, *N*-dimethylamino directing groups for *meta*-arylation of benzylamines, though the scope was relatively limited.[7b] More recently, Zhao and co-workers demonstrated that the bisdentate oxalyl amides derived from phenethylamines are particularly effective substrates for this transformation.[7d] Considering the broad utility of the nosyl protecting group since its disclosure by Fukuyama in 1995,[9] and our long-standing interest in developing amino-group-directed *ortho*-C−H activation,[3] we sought to utilize nosyl-protected amines as simple monodentate directing groups for norbornene-mediated, palladium-catalyzed *meta*-C−H functionalizations of both benzylamines and phenylethylamines. Herein, we report our findings on the use of nosyl-protected phenethylamines, benzylamines, and 2-arylanilines as substrates in palladium-catalyzed *meta*-C−H arylation using norbornene as a transient mediator (Scheme 1). Identification of suitable pyridine-type ligands is crucial for this reaction to proceed. In the case of nosyl-protected phenethylamines, we were able to demonstrate that norbornene can be used in a catalytic amount for the first time in this *meta*-C−H functionalization reaction.

2. RESULTS AND DISCUSSION

Having previously established several sulfonamide-directed C−H functionalization reactions,[3d−m] our initial investigations into amine-directed *meta*-C−H arylation began with triflyl-protected substrate **1** and methyl 2-iodobenzoate **2a**. Under our previously established conditions for *meta*-C−H arylation[7a] using pyridine-based ligand **L1**, the *meta*-diarylated product was obtained in 28% yield as determined by ^{1}H NMR, with less than 5% yield of *meta*-monoarylated product. Subsequently, we

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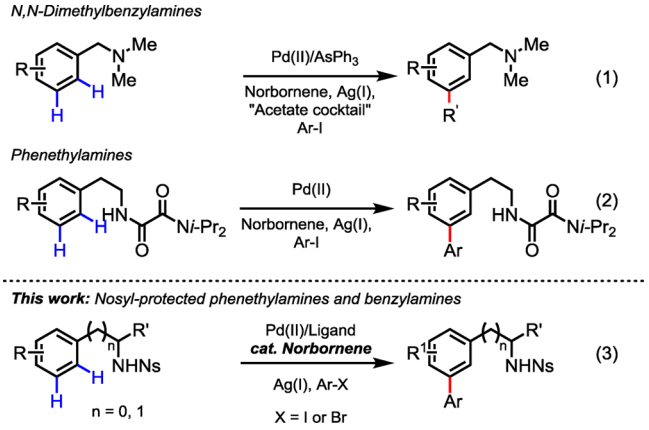
Scheme 1. Palladium-Catalyzed *meta*-C−H Arylation of Amines

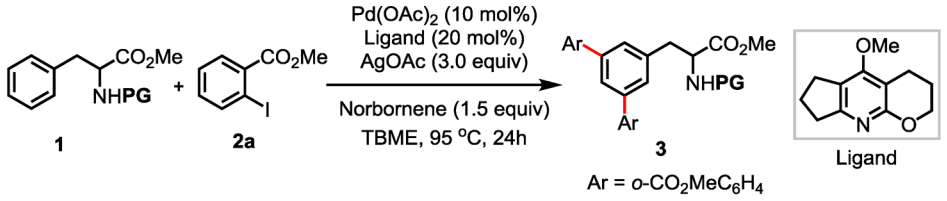


evaluated the utility of several commonly found *N*-protecting groups (Table 1). The data from this table indicates that moderately good yields can be obtained under our previously established reaction conditions by fine-tuning of the electronics of the sulfonamide. Gratifyingly, the optimal yield was obtained when using nosyl (Ns) as both a directing and protecting group. Not surprisingly, *N*-Ac, *N*-TFA, *N*-Boc, and *N*-Cbz gave no desired product as we have previously shown that the N−H acidity of sulfonamide directing groups is critical in enabling them to serve as efficient directing groups.[3d−m]

With preliminary conditions for the *meta*-arylation reaction in hand, we proceeded to systematically re-examine the pyridine ligands in an effort to improve the efficiency of this reaction (Table 2). Prompted by the recent success of **L1** and **L2** to enable *meta*-C−H functionalization of phenylacetic amides using a norbornene relay approach, we began our investigations with **L1** and **L2**.[7a,c] Both ligands only promoted the reaction to a moderate extent, even after substantial optimization. Further evaluation of disubstituted *N*-heterocycles **L3** (2,6-lutidine) and **L4** (2,6-dimethoxypyridine) revealed that these 2,6-disubstituted pyridines do not effectively promote this reaction. Subsequently, we found that 2-alkoxy pyridines (**L5** and **L6**) also were not efficient for this reaction. A further evaluation of pyridines with 2-substitution lead to the realization that pyridines bearing electron-withdrawing substituents at this position (**L7**−**L10**) are completely inactive. In contrast, 2-alkylpyridine (**L11**−**13**) ligands were found to be highly effective in promoting this transformation, affording excellent yields of the desired products (>92%). While the impact of the electron-withdrawing and -donating substituents at the 2-positions are different, a variety of 3- and 4-substituted pyridine ligands (**L14**−**L23**) provided excellent yields (≥95%), with the exception of the highly electron deficient **L18** and 4-(dimethylamino)pyridine **L19**. Among the evaluated ligands, 4-acetylpyridine (**L23**) gave the best result by enabling the desired product to be formed in 99% yield as determined by ^{1}H NMR using dibromomethane as an internal standard. Surprisingly, we found that simple pyridine (**L24**) and pyrazine (**L25**) are also suitable ligands for this reaction allowing formation of the diarylated products in high yields. A key control experiment showed that pyridine-type ligands are crucial for the formation of *meta*-arylated product, as no reaction occurred in the absence of ligand.

Considering that our previous arylation reactions require a high loading of catalyst (10 mol %) and 2-norbornene (NBE, 1.5 equiv),[7a] we attempted to reduce the equivalents of these catalysts. The use of 5 mol % of $Pd(OAc)_2$ provided a mixture of di- and monoarylated products in 85%, and 15% yield, respectively. The catalyst loading could be further reduced to 2.5 mol %, leading to arylated products in 90% yield (di/mono = 1.2/1). We were pleased to find that the loading of NBE could be reduced to 20 mol % without changing the reactivity

Table 1. Investigation of Directing Groups to Direct *meta*-C−H Arylation[a,b]



PG =			
Tf	Ms	Ts	Ns
di 28%; mono <5%	di 13%; mono 22%	di 9%; mono 29%	**di 35%; mono 30%**
di 32%; mono 30%	di 30%; mono 20%	di 32%; mono 15%	di 32%; mono 18%
Acetyl (Ac)	Trifluoroacetyl (TFA)	*tert*-Butyloxycarbonyl (Boc)	Carbobenzoxy (Cbz)
di 0%; mono 0%	di 0%; mono 0%	di 0%; mono 0%	di 0%; mono 0%

[a]Reaction conditions: phenethylamine **1** (0.1 mmol), methyl 2-iodobenzoate **2a** (3.0 equiv), $Pd(OAc)_2$ (10 mol %), ligand (20 mol %), 2-norbornene (1.5 equiv), AgOAc (3.0 equiv), TBME (1.0 mL), 95 °C, air, 24 h. [b]Yields of products **3** were determined by ^{1}H NMR using dibromomethane as an internal standard.

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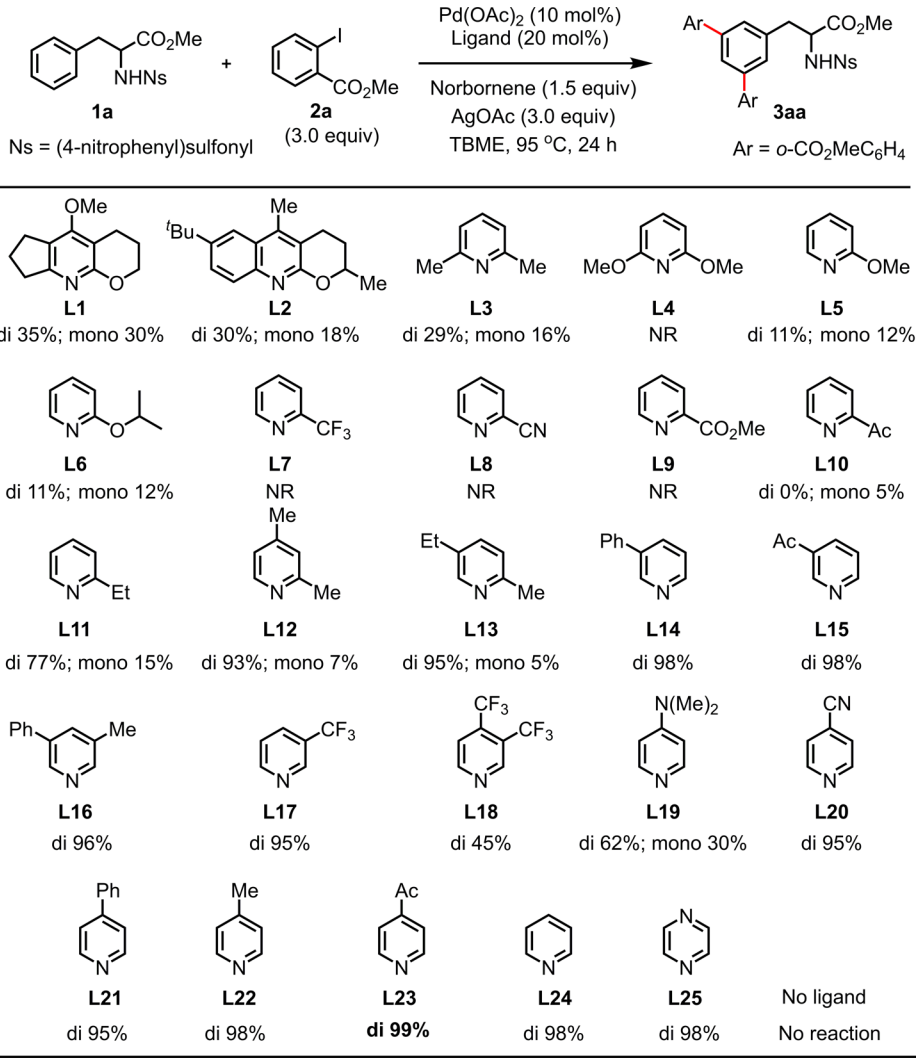
Table 2. Screening of Ligands for *meta*-C−H Arylation of Phenethylamine-Derived Sulfonamide[a,b]



[a]Reaction conditions: substrate **1a** (0.1 mmol), methyl 2-iodobenzoate **2a** (3.0 equiv), $Pd(OAc)_2$ (10 mol %), ligand (20 mol %), 2-norbornene (1.5 equiv), AgOAc (3.0 equiv), TBME (1.0 mL), 95 °C, air, 24 h. [b]Yield of product **3aa** was determined by ^1H NMR using dibromomethane as an internal standard.

and selectivity. Even using 10 mol % NBE could provide the desired product in high yield (93%) with moderate mono/di selectivity (di/mono = 2.9/1). Furthermore, decreasing the reaction temperature to 80 °C did not result in a reduction of efficiency for the reaction, allowing clean formation of the diarylated product **3aa** in nearly quantitative yield (see SI).

Using 10 mol % palladium and 20 mol % NBE, we began to explore the *meta*-arylation reaction of various substrates derived from phenethylamines (**1a**−**1t**) using methyl 2-iodobenzoate **2a** as the coupling partner (Table 3). Both electron-donating and -withdrawing *ortho*-substituents (such as methoxy, methyl, bromo, fluoro, chloro, and trifluoromethyl) on the aryl ring are well-tolerated in this transformation, affording good to excellent yields of the products (**3ba**−**3ha**). Excitingly, the arylation of the *ortho*-bromide-substituted **1d** under the standard conditions gives desired product **3da** in 85% yield, leaving the C−Br bond intact. A range of electron-donating and -withdrawing *meta*-substituted substrates could also be converted to the *meta*-arylated products (**3ia**−**3ma**) in good yields (82−92%). The arylation of *para*-substituted substrates **1n** and **1o** gives the monoarylation products **3na** and **3oa** in moderate yields as the major products, with less than 10% diarylation products. However, the less sterically hindered *para*-fluoro-substituted substrate **1p** is transformed to the diarylation product **3pa** in excellent yield (90%). This *meta*-arylation method is also compatible with phenylalaninol-derived substrates **1q** and **1r** with formation of the desired products **3qa** in 55% yield (mono/di = 2/1) and **3ra** (di) in 60% yield. It is important to note that the unprotected alcohol in **1q** was well-tolerated to provide product **3qa**. This is likely due to a chelate effect whereby bisdentate coordination of the nosyl amine and the free alcohol to Pd(II) prevents oxidation of the alcohol by Pd(II). *meta*-Arylation of amphetamine-derived substrates **1s** and **1t** also proceeds smoothly to give the desired products (**3sa** and **3ta**). Attesting to the mildness of this reaction, no racemization was observed in this *meta*-arylation reaction when L-phenylalanine-derived **1a** (>99% ee) was used as the substrate under the standard reaction conditions (see SI for HPLC data).

To further explore the synthetic utility of this protocol, we proceeded to examine the scope of aryl halides to obtain structurally versatile *meta*-arylated phenethylamines (Table 4). Aryl halides with an *ortho*-coordinating, electron-withdrawing

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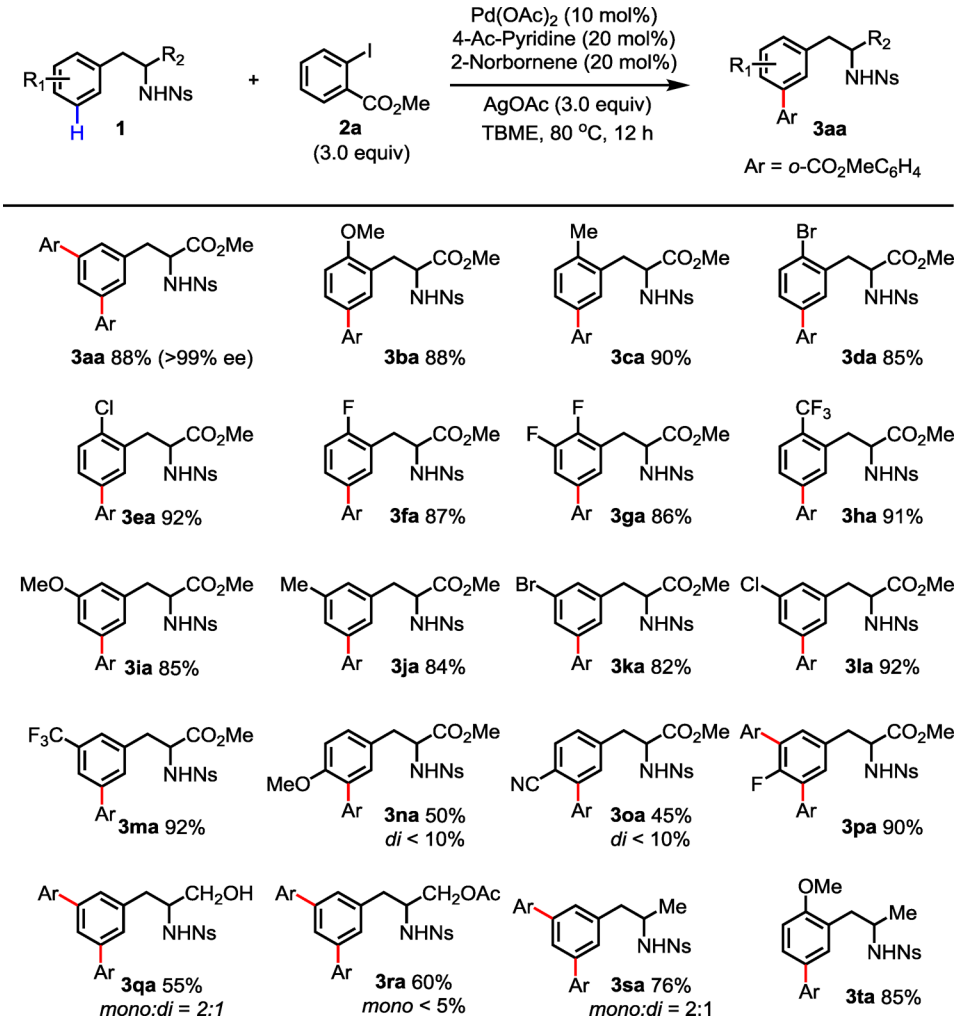
Table 3. *meta*-Arylation of Substituted Phenethylamines[a,b]



[a]Reaction conditions: substrate **1** (0.1 mmol), methyl 2-iodobenzoate **2a** (3.0 equiv), $Pd(OAc)_2$ (10 mol %), 4-acetylpyridine (20 mol %), AgOAc (3.0 equiv), 2-norbornene (20 mol %), TBME (1.0 mL), 80 °C, 12 h. [b]Isolated yield.

group serve as the most efficient coupling partners affording the desired products (**3ja**–**3je**) in good to excellent yields. Importantly, aryl bromides containing *ortho* electron-withdrawing groups are also suitable for this reaction as exemplified by the efficient preparation of **3ja** and **3je**. This constitutes the first demonstration of using aryl bromides as coupling partners when using this *meta*-arylation strategy. Notably, the arylation reaction is compatible with 1-chloro-2-iodobenzene, despite affording a lower yield (**3jf**, 40%). Electron-donating and -withdrawing *meta*- and *para*-substituted aryl iodides are also tolerated in this transformation, affording the desired products (**3jg**–**3jr**) in moderate yields when using 3.0 equiv of NBE. In cases where the aryl iodide is less reactive, the benzocyclobutene side product is also formed. Given the importance of heterocyclic compounds in the pharmaceutical industry, we examined a variety of heterocyclic iodides to prepare compounds which may be of interest in drug discovery. The results showed that *meta*-arylated product **3js** could be obtained in 53% yield when tosyl-protected indolyl iodide was coupled with substrate **1j**. Furthermore, aryl iodides containing dioxane moieties provided the desired product **3jt** in 50% yield. Finally, 4-pyridyl iodides with halogens at the 2-position are also compatible with the protocol leading to **3ju** and **3jv** in moderate yields.

Interested in exploring the generality of NHNs-directed *meta*-C–H arylation using norbornene as a transient mediator, we investigated the feasibility of using 2-aryl anilines as substrates (Table 5). Unlike our prior work on aniline substrates which functionalizes the *meta*-position of the aniline ring,[7e,f] NHNs-directed palladation is expected to occur on the adjacent ring to form a 6-membered palladacycle which would be intercepted by norbornene to provide *meta*-arylation of the adjacent ring. Gratifyingly, Ns-protected 2-phenyl aniline **4a** was smoothly converted to the diarylated product **5a** in 60% yield with a trace amount of monoarylated product and trace benzocyclobutene byproduct when employing 1.5 equiv of norbornene. *meta*-Arylation of substituted 2-aryl anilines **4b** and **4c** gave the corresponding products **5b** and **5c** in 60% and 80% yields, respectively. We were pleased to find that aryl iodides containing both electron-withdrawing and -donating substituents on the *meta*- and *para*-positions are tolerated, affording *meta*-arylated products **5e**–**5g** in moderate yields. Tosyl-protected indolyl iodide is also an effective electrophile, providing the desired product **5h** in 53% yield.

We recently described the site-selective functionalizations of inert C(sp^3)–H bonds of *N*-terminal amino acids in di-, tri-, and tetrapeptides, providing a broad range of corresponding peptides with modified phenylalanine residues.[10] This

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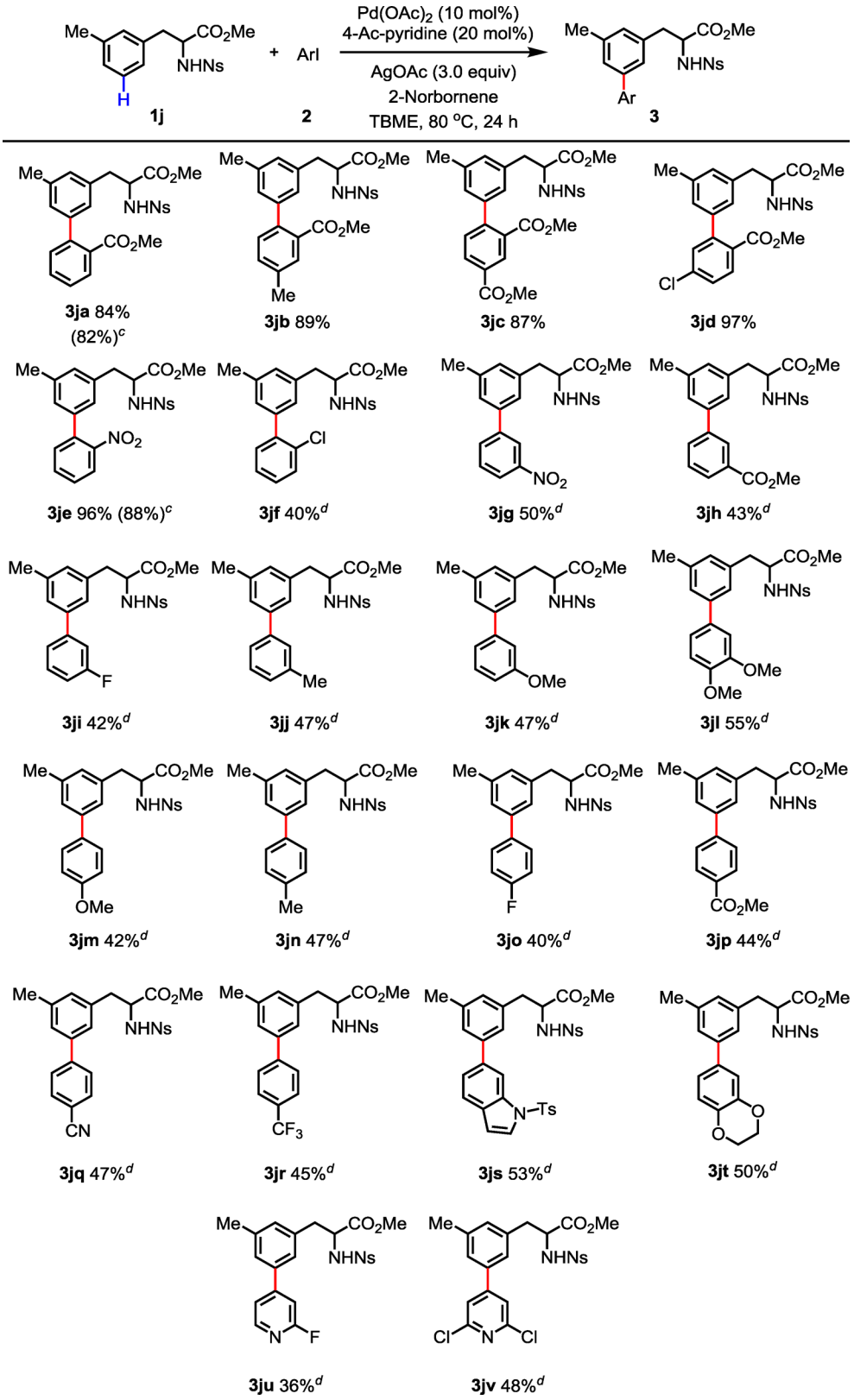
Table 4. *meta*-Arylation with a Variety of Aryl Halides[a,b]



[a]Reaction conditions: **1j** (0.1 mmol), aryl halides **2** (3.0 equiv), $Pd(OAc)_2$ (10 mol %), 4-acetylpyridine (20 mol %), 2-norbornene (20 mol %), AgOAc (3.0 equiv), TBME (1.0 mL), 80 °C, 24 h. [b]Isolated yield. [c]Isolated yields in parentheses when aryl bromide was used instead of aryl iodide. [d]3.0 equiv of 2-norbornene was used.

prompted us to explore the utility of nosyl-protected *β*-aryldipeptides under our standard conditions for NHNs-directed *meta*-C−H arylation (Table 6). Dipeptides **6a** and **6b** derived from L-valine and L-alanine were smoothly arylated

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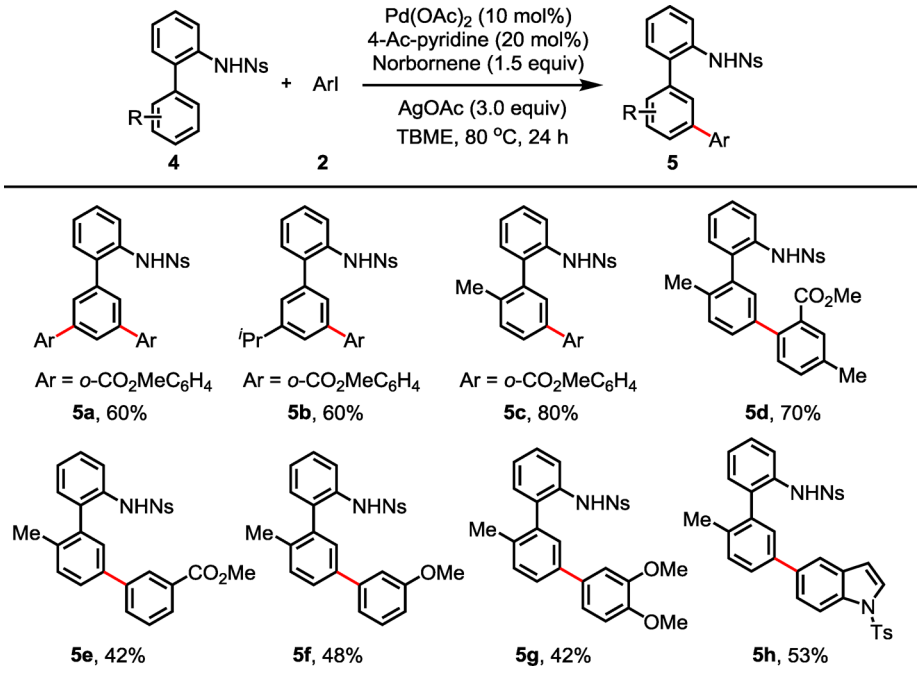
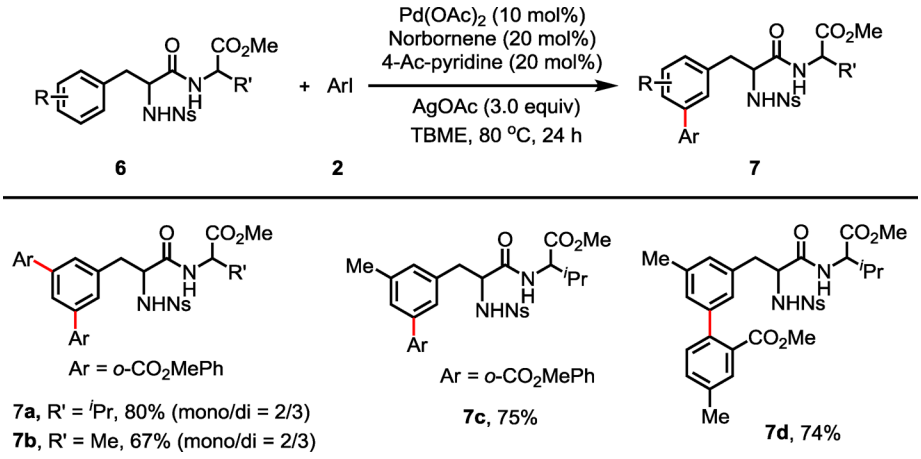
Table 5. ***meta*-Arylation of 2-Aryl Anilines**[a,b]



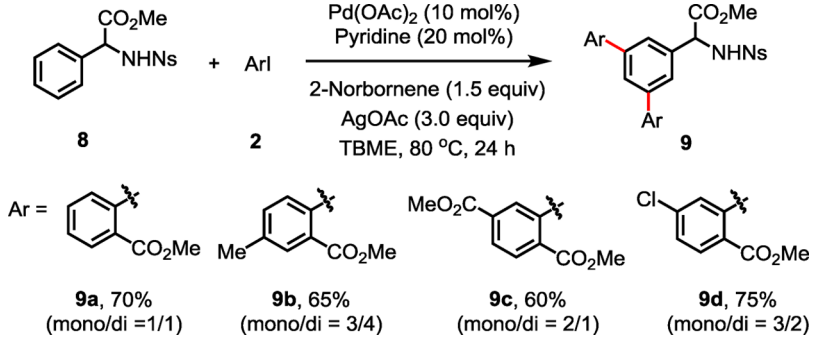
[a]Rection conditions: **4** (0.1 mmol), aryl iodides **2** (3.0 equiv), $Pd(OAc)_2$ (10 mol %), 4-acetylpyridine (20 mol %), 2-norbornene (1.5 equiv), AgOAc (3.0 equiv), TBME (1.0 mL), 80 °C, 24 h. [b]Isolated yield.

Table 6. ***meta*-Arylationof *β*-Aryl Dipeptides 6**[a,b]



[a]Reaction conditions: **6** (0.1 mmol), aryl iodides **2** (3.0 equiv), $Pd(OAc)_2$ (10 mol %), 4-acetylpyridine (20 mol %), 2-norbornene (20 mol %), AgOAc (3.0 equiv), TBME (1.0 mL), 80 °C, 24 h. [b]Isolated yield.

Scheme 2. ***meta*-Arylationof Benzylamine-Derived Sulfonamide 8 with Aryl Iodides 2**



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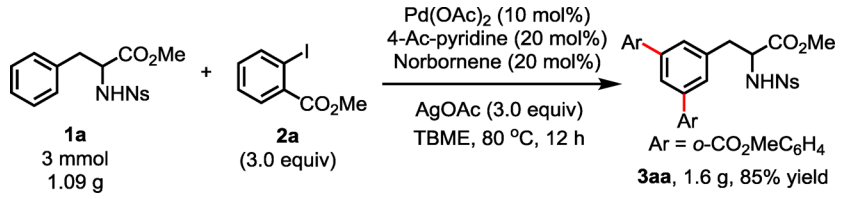
Scheme 3. Gram-Scale Synthesis

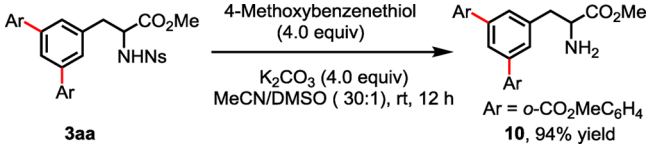


to give the mono- and diarylation products **7a** and **7b** in 80% and 67% combined yields, respectively. *meta*-Arylation of dipeptide **6c** also underwent effective coupling using aryl iodides containing electron-withdrawing groups as coupling partners to provide the desired products **7c** and **7d** in good yields.

Considering the biological importance of *meta*-arylated benzylamines,[1] we also attempted the *meta*-arylation reaction using methyl phenylglycine derivative **8** as a model substrate (Scheme 2). Initially, arylation with methyl-2-iodobenzoate **2a** using 20 mol % 4-acetylpyridine afforded the desired product in low yield (45%). Given the wide range of pyridine ligands that can promote this reaction, we re-evaluated a variety of the best ligands and found that simple pyridine functions as a more efficient ligand when utilizing this substrate, affording the desired products in 70% yield ($\mathbf{9a}_{mono}/\mathbf{9a}_{di}$ = 1/1). Various aryl iodides containing an *ortho*-electron-withdrawing group worked well in the reaction when using this substrate.

To investigate the feasibility of using this reaction on a preparative scale, we carried out a gram-scale *meta*-C(sp^2)−H arylation reaction with substrate **1a** and methyl-2-iodobenzoate **2a** (Scheme 3). The desired product **3aa** could be isolated in 85% yield when the reaction was run on a 3.0 mmol scale. The protecting group (Ns) could also be readily removed by treatment with 4-methoxybenzenethiol and K_2CO_3 in MeCN/DMSO at room temperature to yield the free amine in excellent yield (Scheme 4).[9]

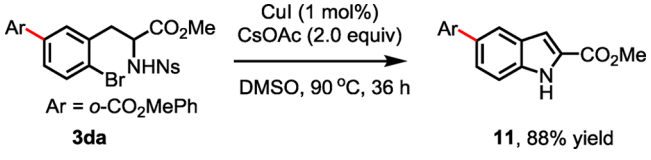
Scheme 4. Deprotection



To showcase the synthetic utility of this reaction, a copper-catalyzed intramolecular amination/oxidation sequence of **3da** has been developed in the presence of CsOAc to give 2,5-disubstituted indole derivative **11** (Scheme 5).[11]

On the basis of previous reports,[6,7] a plausible mechanism for this *meta*-C(sp^2)−H arylation using NBE as a transient mediator is presented in Figure 1. First, palladium(II)-mediated *ortho*-C(sp^2)−H activation of substrate **1** could result in an organopalladium(II) complex **I** which can subsequently react with NBE to generate intermediate **II**. Second, *meta*-C−H activation of intermediate **II** would lead to 5-membered palladacyclic intermediate **III** which can undergo oxidative addition with the aryl halide to form organopalladium(IV) complex **IV**. This palladium(IV) species **IV** can then undergo a new C−C bond forming reductive elimination, which is followed by subsequent *β*-carbon elimination of NBE to afford the *meta*-arylation product and regenerate the palladium(II) catalyst. Importantly, though intermediates **III** and **IV** can undergo reductive elimination to yield the cyclobutane adduct as the major side product, 2-norbornene can effectively be used as a catalyst in this reaction.

Scheme 5. Application



3. CONCLUSION

In summary, we have developed a Pd(II)-catalyzed *meta*-C(sp^2)−H arylation of nosyl-protected aryl ethylamines, 2-aryl anilines, and phenylglycine using norbornene as a transient mediator in combination with pyridine ligands. The use of a catalytic amount of norbornene for this *meta*-C−H functionalization strategy is demonstrated for the first time. The new method is compatible with various aryl iodides containing both electron-donating and electron-withdrawing substituents at the *ortho*, *meta*, and *para* positions, as well as select aryl bromides. In addition, select heteroaryl iodides are tolerated in this transformation. This study suggests that ligand development and reaction tuning is the key to extending this approach to a wide range of substrate classes which use native functionality or common protecting groups as directing groups.

4. EXPERIMENTAL SECTION

4.1. General Procedure for *meta*-C(sp^2)−H Arylation of Nosyl-Protected Phenethylamines. Substrate **1** (0.10 mmol), $Pd(OAc)_2$ (0.01 mmol, 2.2 mg), and AgOAc (0.30 mmol, 50.0 mg) were weighed in air and placed in a sealed tube (10 mL) with a magnetic stir bar. To the reaction mixture, 4-acetylpyridine (0.02 mmol, 2.2 μL), norbornene (0.02 mmol, 1.9 mg), aryl halide **2** (0.3 mmol), and TBME (1.0 mL) were added. The reaction mixture was heated to 80 °C for 12−24 h under vigorous stirring. Upon completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and the resulting residue purified by preparative TLC using an eluent of hexanes/ethyl acetate (2/1 to 4/1) to give the desired products **3**.

4.2. General Procedure for *meta*-C(sp^2)−H Arylation of Nosyl-Protected 2-Aryl Anilines. The starting material **4** (0.10 mmol), $Pd(OAc)_2$ (0.01 mmol, 2.2 mg), and AgOAc (0.30 mmol, 50.0 mg) were weighed in air and placed in a sealed tube (10 mL) with a magnetic stir bar. To the reaction mixture were added 4-acetylpyridine (0.02 mmol, 2.2 μL), norbornene (0.15 mmol, 14.0 mg), aryl iodide **2** (0.3 mmol), and TBME (1.0 mL). The reaction mixture was heated to 80 °C for 24 h under vigorous stirring. Upon completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and the resulting residue purified by preparative TLC using an eluent of hexanes/ethyl acetate (2/1 to 4/1) to give the desired products **5**.

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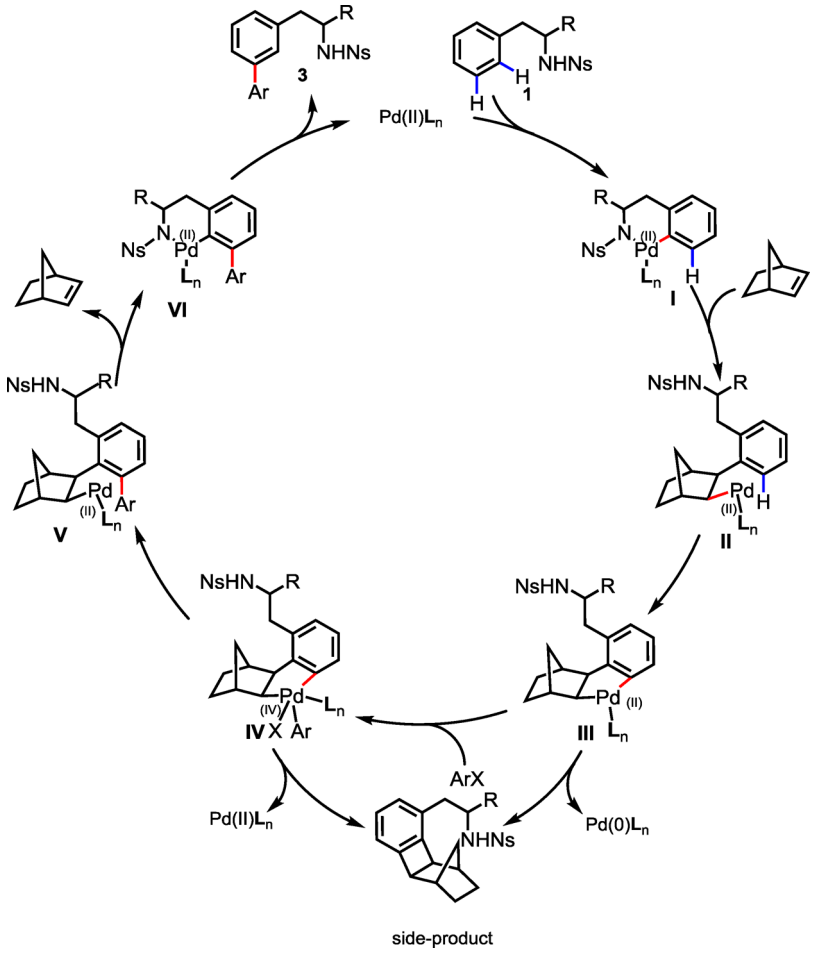

Figure 1. Plausible mechanism of directed *meta*-C−H Arylation. L_n = 4-acetylpyridine (**L23**).

4.3. General Procedure for *meta*-C(sp^2)−H Arylation of Nosyl-Protected *β*-Aryl Dipeptides 6. The starting material **6** (0.10 mmol), $Pd(OAc)_2$ (0.01 mmol, 2.2 mg), and AgOAc (0.30 mmol, 50.0 mg) were weighed in air and placed in a sealed tube (10 mL) with a magnetic stir bar. To the reaction mixture were added 4-acetylpyridine (0.02 mmol, 2.2 μL), norbornene (0.02 mmol, 1.9 mg), aryl iodide **2** (0.3 mmol), and TBME (1.0 mL). The reaction mixture was heated to 80 °C for 24 h under vigorous stirring. Upon completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and the resulting residue purified by preparative TLC using an eluent of hexanes/ethyl acetate (2/1 to 4/1) to give the desired products **7**.

4.4. General Procedure for *meta*-C(sp^2)−H Arylation of Nosyl-Protected Methyl Phenylglycine 8. Phenylglycine **8** (0.10 mmol), $Pd(OAc)_2$ (0.01 mmol, 2.2 mg), and AgOAc (0.30 mmol, 50.0 mg) were weighed in air and placed in a sealed tube (10 mL) with a magnetic stir bar. To the reaction mixture were added pyridine (0.02 mmol, 1.6 μL), norbornene (0.15 mmol, 14.0 mg), aryl iodide **2** (0.3 mmol), and TBME (1.0 mL). The reaction mixture was heated to 80 °C for 24 h under vigorous stirring. Upon completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and the resulting residue purified by preparative TLC using an eluent of hexanes/ethyl acetate (2/1 to 4/1) to give the desired products **9**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b11097.

Detailed experimental procedures and characterization of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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