# Ligand-Enabled *Meta*-Selective C–H Arylation of Nosyl Protected Phenethylamines, Benzylamines and 2-Aryl Anilines

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## 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 2-aryl anilines to this protocol lead 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.

## TOC image



Nosyl-protected Amines · Catalytic 2-Norbornene · Broad amine scope
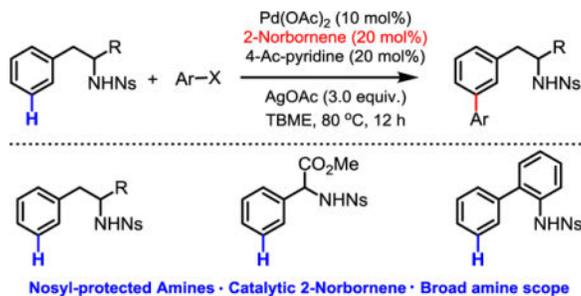
## 1. Introduction

Amino functional groups play important roles in modulating biological systems and cure 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 protected version thereof, can coordinate with a palladium catalyst and direct the functionalization of a

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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 coworkers 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 mono-dentate 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. 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 **3aa** was obtained in 28% yield as determined by ^{1}H NMR, with less than 5% yield of *meta*-monoarylated product. Subsequently, we investigated several commonly used *N*-protecting groups for this *meta*-arylation to evaluate their effect on the reactivity (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 di-substituted *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 di-arylated 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 mono-arylated 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 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 76% 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 in 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 group serve as the most efficient coupling partners affording the desired products (**3ja-je**) 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 1.5 equivalents 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 equivalents 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 tetra-peptides, providing a broad range of corresponding peptides with modified phenylalanine residues.[10] This 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 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 (**9a_{mono}/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]

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 **1** (Scheme 5).[11]

Based on 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. Firstly, 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**. Secondly, *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.

## 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* position, 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 to 24 hours 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, 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) were added. The reaction mixture was heated to 80 °C for 24 hours 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**.

### 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, 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) were added. The reaction mixture was heated to 80 °C for 24 hours 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(sp²)–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, 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) were added. The reaction mixture was heated to 80 °C for 24 hours 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**.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

## References

1. (a) Vitaku E, Smith DT, Njardarson JT. J Med Chem. 2014; 57:10257. [PubMed: 25255204] (b) Hili R, Yudin AK. Nat Chem Biol. 2006; 2:284. [PubMed: 16710330] (c) Lawrence, SA. Amines: Synthesis Properties and Applications. Cambridge University Press; Cambridge: 2004. p. 265-305. (d) Ricci, A., editor. Amino Group Chemistry, From Synthesis to the Life Sciences. Wiley-VCH; Weinheim, Germany: 2007.

2. For select examples of primary and secondary amine directed C–H activation, see:(a) Lazareva A, Daugulis O. Org Lett. 2006; 8:5211. [PubMed: 17078680] (b) Liang Z, Feng R, Yin H, Zhang Y. Org Lett. 2013; 15:4544. [PubMed: 23981087] (c) Liang Z, Yao J, Wang K, Li H, Zhang Y. Chem Eur J. 2013; 19:16825. [PubMed: 24166735] (d) Miura M, Feng CG, Ma S, Yu JQ. Org Lett. 2013; 15:5258. [PubMed: 24098966] (e) McNally A, Haffenmayer B, Collins BSL, Gaunt MJ. Nature. 2014; 510:129. [PubMed: 24870240] (f) Calleja J, Pla D, Gorman TW, Domingo V, Haffenmayer B, Gaunt MJ. Nature Chem. 2015; 7:1009. [PubMed: 26587717] (g) Hu C, Gaunt MJ. Angew Chem Int Ed. 2015; 54:15840.For select examples of tertiary amine directed C–H activation, see:(h) Cai G, Fu Y, Li Y, Wan X, Shi Z. J Am Chem Soc. 2007; 129:7666. [PubMed: 17530847] (i) Gao DW, Shi YC, Gu Q, Zhao ZL, You SL. J Am Chem Soc. 2013; 135:86. [PubMed: 23253097] (j) Feng R, Yao J, Liang Z, Liu Z, Zhang Y. J Org Chem. 2013; 78:3688. [PubMed: 23510158] (k) Tan PW, Haughey M, Dixon DJ. Chem Commun. 2015; 51:4406.

3. For seminal reports of directing groups which have found broad utility in amine directed C–H activation, see:(a) Zaitsev VG, Shabashov D, Daugulis O. J Am Chem Soc. 2005; 127:13154. [PubMed: 16173737] (b) Rodriguez N, Romero-Revilla JA, Fernandez-Ibanez MA, Carretero JC. Chem Sci. 2013; 4:175.(c) Wang C, Chen C, Zhang J, Han J, Wang Q, Guo K, Liu P, Guan M, Yao Y, Zhao Y. Angew Chem, Int Ed. 2014; 53:9884.For examples of Sulfonamide directed C–H activation, see:(d) Li JJ, Mei TS, Yu JQ. Angew Chem Int Ed. 2008; 47:6452.(e) Wang X, Mei TS, Yu JQ. J Am Chem Soc. 2009; 131:7520. [PubMed: 19435367] (f) Mei T-S, Wang X, Yu J-Q. J Am Chem Soc. 2009; 131:10806. [PubMed: 19606861] (g) Vickers CJ, Mei TS, Yu JQ. Org Lett. 2010; 12:2511. [PubMed: 20446711] (h) Chu L, Wang XC, Moore CE, Rheingold AL, Yu JQ. J Am Chem

Soc. 2013; 135:16344. [PubMed: 24151991] (i) Chu L, Xiao KJ, Yu JQ. Science. 2014; 346:451. [PubMed: 25342799] (j) Chan KSL, Wasa M, Chu L, Laforteza BN, Miura M, Yu J-Q. Nat Chem. 2014; 6:146. [PubMed: 24451591] (k) Chan KSL, Fu H, Yu J-Q. J Am Chem Soc. 2015; 137:2042. [PubMed: 25581489] (l) Laforteza BN, Chan KSL, Yu J-Q. Angew Chem Int Ed. 2015; 54:11143. (m) Jiang H, He J, Liu T, Yu JQ. J Am Chem Soc. 2016; 138:2055. [PubMed: 26796676]

4. For a review on meta- and para-C–H activation, see:Li J, De Sarkar S, Ackermann L. Top Organomet Chem. 2016; 55:217.

5. For select examples of template directed meta-C–H functionalization, see:(a) Leow D, Li G, Mei TS, Yu JQ. Nature. 2012; 486:518. [PubMed: 22739317] (b) Tang R, Li G, Yu JQ. Nature. 2014; 507:215. [PubMed: 24622200] (c) Wan L, Dastbaravardeh N, Li G, Yu JQ. J Am Chem Soc. 2013; 135:18056. [PubMed: 24236533] (d) Chu L, Shang M, Tanaka K, Chen Q, Pissarnitski N, Streckfuss E, Yu JQ. ACS Cent Sci. 2015; 1:394. [PubMed: 27162997] For examples of meta-C–H borylation using a non-covalent templating approach, see:(e) Kuninobu Y, Ida H, Nishi M, Kanai M. Nat Chem. 2015; 7:712. [PubMed: 26291942] (f) Davis HJ, Mihai MT, Phipps RJ. J Am Chem Soc. 2016; 138:12759. [PubMed: 27626468] For examples of template directed para-C–H functionalization, see:(g) Bag S, Patra T, Modak A, Deb A, Maity S, Dutta U, Dey A, Kancherla R, Maji A, Hazra A, Bera M, Maiti D. J Am Chem Soc. 2015; 137:11888. [PubMed: 26361337] (h) Patra T, Bag S, Kancherla R, Mondal A, Dey A, Pimparkar S, Agasti S, Modak A, Maiti D. Angew Chem Int Ed. 2016; 55:7751.

6. For pioneering work on the Catellani reaction, see:(a) Catellani M, Frignani F, Rangoni A. Angew Chem Int Ed. 1997; 36:119.For reviews on the Catellani reaction, see:(b) Catellani M. Top Organomet Chem. 2005; 14:21.(c) Martins A, Mariampillai B, Lautens M. Top Curr Chem. 2009; 292:1.(d) Ye J, Lautens M. Nat Chem. 2015; 7:863. [PubMed: 26492005] (e) Della Ca' N, Fontana M, Motti E, Catellani M. Acc Chem Res. 2016; 49:1389. [PubMed: 27333299]

7. (a) Wang XC, Gong W, Fang LZ, Zhu RY, Li S, Engle KM, Yu JQ. Nature. 2015; 519:334. [PubMed: 25754328] (b) Dong Z, Wang J, Dong G. J Am Chem Soc. 2015; 137:5887. [PubMed: 25909445] (c) Shen PX, Wang XC, Wang P, Zhu RY, Yu JQ. J Am Chem Soc. 2015; 137:11574. [PubMed: 26313012] (d) Han J, Zhang L, Zhu Y, Zheng Y, Chen X, Huang ZB, Shi DQ, Zhao Y. Chem Comm. 2016; 52:6903. [PubMed: 27142086] (e) Wang P, Farmer ME, Huo X, Jain P, Shen PX, Ishoey M, Bradner JE, Wisniewski SR, Eastgate MD, Yu JQ. J Am Chem Soc. 2016; 138:9269. [PubMed: 27384126] (f) Wang P, Li GC, Jain P, Farmer ME, He J, Shen PX, Yu JQ. J Am Chem Soc. 2016; 138:14092.

8. For alternative meta-C–H functionalization strategies proceeding via proposed ortho-cyclometalated intermediates, see the following. For examples Ru(II) catalyzed meta-C–H functionalization using ortho-directing groups, see:(a) Saidi O, Marafie J, Ledger AEW, Liu PM, Mahon MF, Kociok-Köhn G, Whittlesey MK, Frost CG. J Am Chem Soc. 2011; 133:19298. [PubMed: 22047022] (b) Hofmann N, Ackermann L. J Am Chem Soc. 2013; 135:5877. [PubMed: 23534668] (c) Li J, Warratz S, Zell D, De Sarkar S, Ishikawa EE, Ackermann L. J Am Chem Soc. 2015; 137:13894. [PubMed: 26418891] (d) Teskey CJ, Lui AYW, Greaney MF. Angew Chem, Int Ed. 2015; 54:11677. (e) Paterson AJ, John Campbell S, Mahon MF, Press NJ, Frost CG. Chem Commun. 2015; 51:12807.(f) Fan Z, Ni J, Zhang A. J Am Chem Soc. 2016; 138:8470. [PubMed: 27181121] For examples of Cu(II) promoted meta-C–H functionalization using ortho-directing groups, see:(g) Phipps RJ, Gaunt MJ. Science. 2009; 323:1593. [PubMed: 19299616] (h) Duong HA, Gilligan RE, Cooke ML, Phipps RJ, Gaunt MJ. Angew Chem, Int Ed. 2011; 50:463.(i) Yang Y, Li R, Zhao Y, Zhao D, Shi Z. J Am Chem Soc. 2016; 138:8734. [PubMed: 27362919]

9. (a) Kan T, Fukuyama T. Chem Comm. 2004:353. [PubMed: 14765207] (b) Fukuyama T, Jow CK, Cheung M. Tetrahedron Lett. 1995; 36:6373.

10. Gong W, Zhang G, Liu T, Giri R, Yu JQ. J Am Chem Soc. 2014; 136:16940. [PubMed: 25384178]

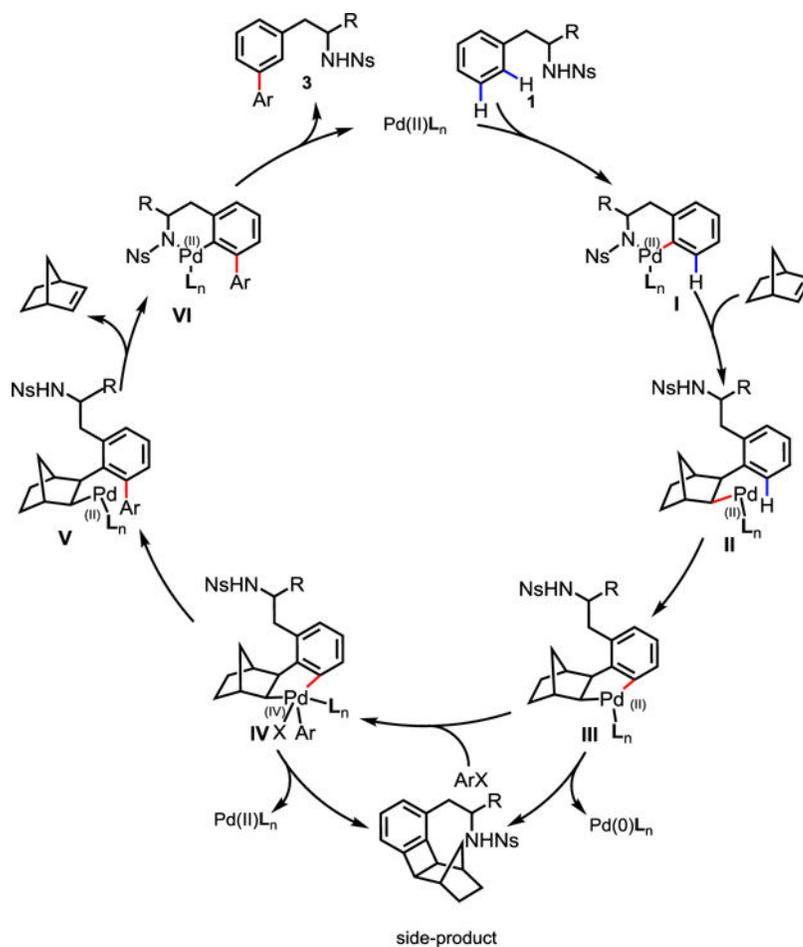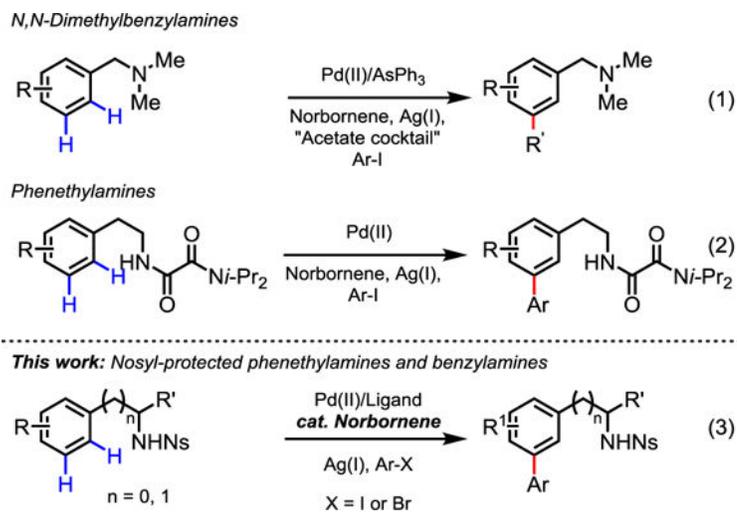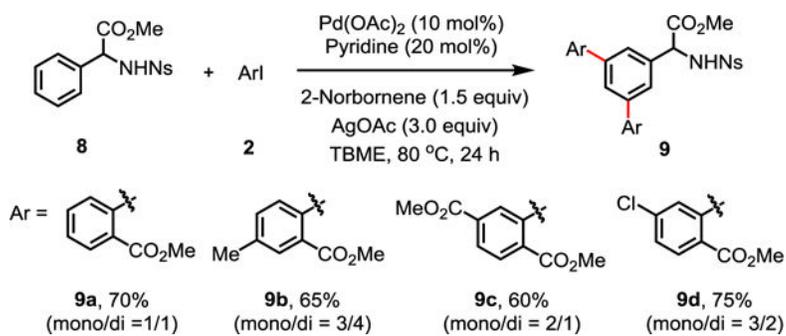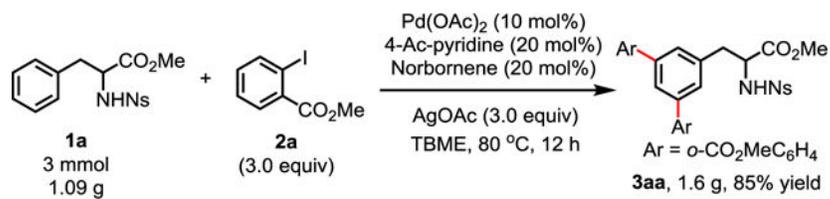11. Tokyama H, Noji T, Okano K, Fukuyama T, Zhang L. Org Synth. 2011; 88:388.

**Figure 1.**
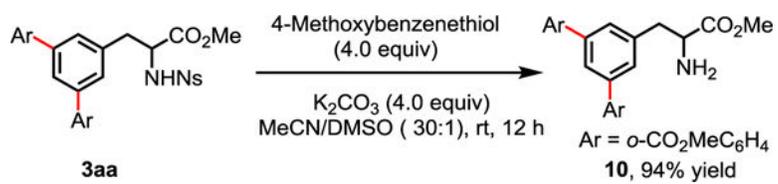Plausible mechanism of directed *meta*-C-H Arylation. **L<sub>n</sub>** = 4-acetylpyridine (**L23**).

**Scheme 1.**
Palladium-Catalyzed *Meta*-C–H Arylation of Amines
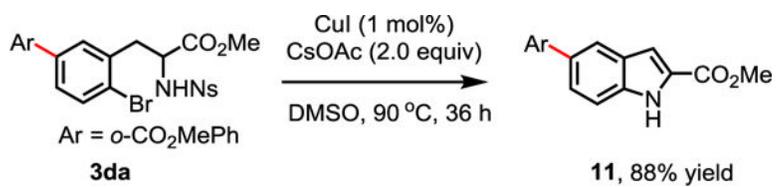
**Scheme 2.**
*Meta*-Arylationof Benzylamine derived Sulfonamide 8 with Aryl Iodides 2

**Scheme 3.**
Gram-Scale Synthesis

**Scheme 4.**
Deprotection

**Scheme 5.**
Application

**Table 1**

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



| PG = | $\overset{O}{\underset{O}{\overset{\|}{S}}}$-CF$_3$ (Tf) | $\overset{O}{\underset{O}{\overset{\|}{S}}}$-Me (Ms) | $\overset{O}{\underset{O}{\overset{\|}{S}}}$-⬡-Me (Ts) | $\overset{O}{\underset{O}{\overset{\|}{S}}}$-⬡-NO$_2$ (Ns) |
|---|---|---|---|---|
| | di 28%; mono <5% | di 13%; mono 22% | di 9%; mono 29% | **di 35%; mono 30%** |

| | S-⬡-CF$_3$ | S-⬡(CF$_3$)$_2$ | S-⬡(O$_2$N)(NO$_2$) | S-⬡F$_5$ |
|---|---|---|---|---|
| | 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.

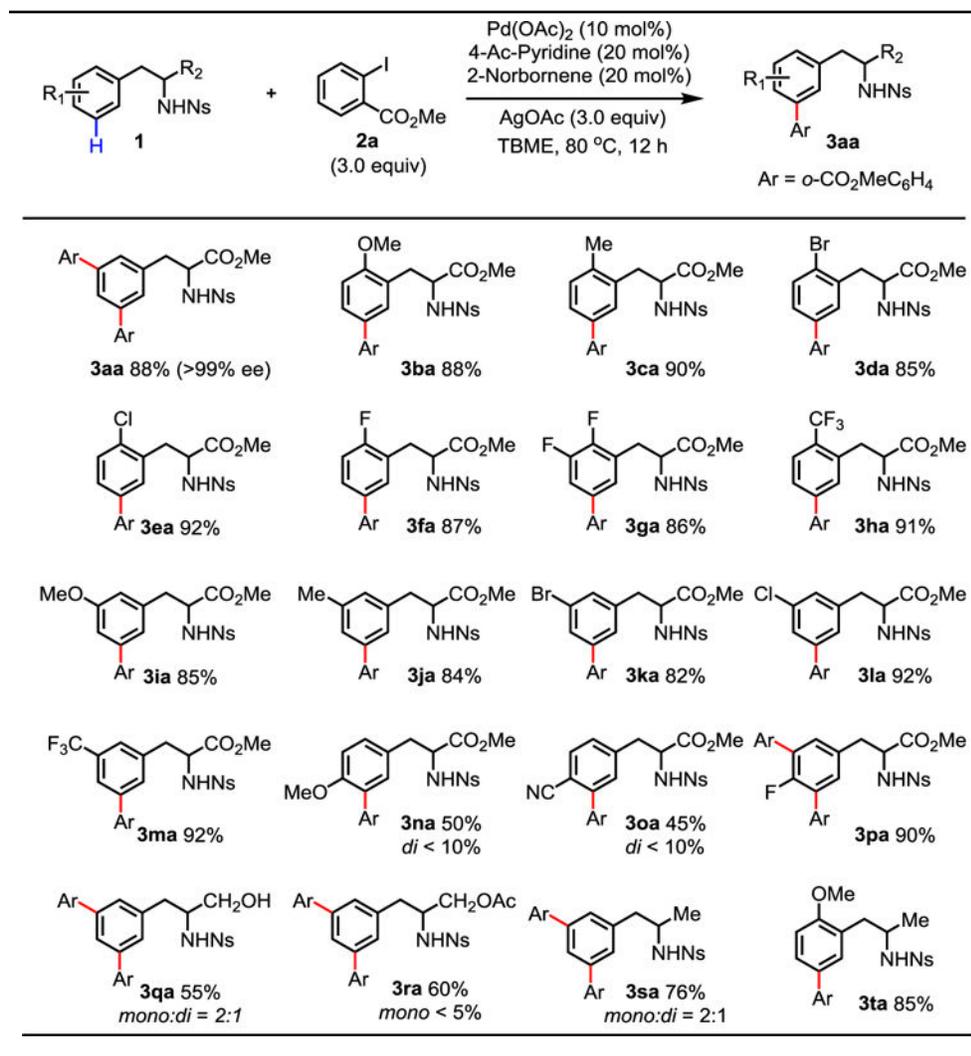[b]Yields of products **3** were determined by ^{1}H NMR using dibromomethane as an internal standard.
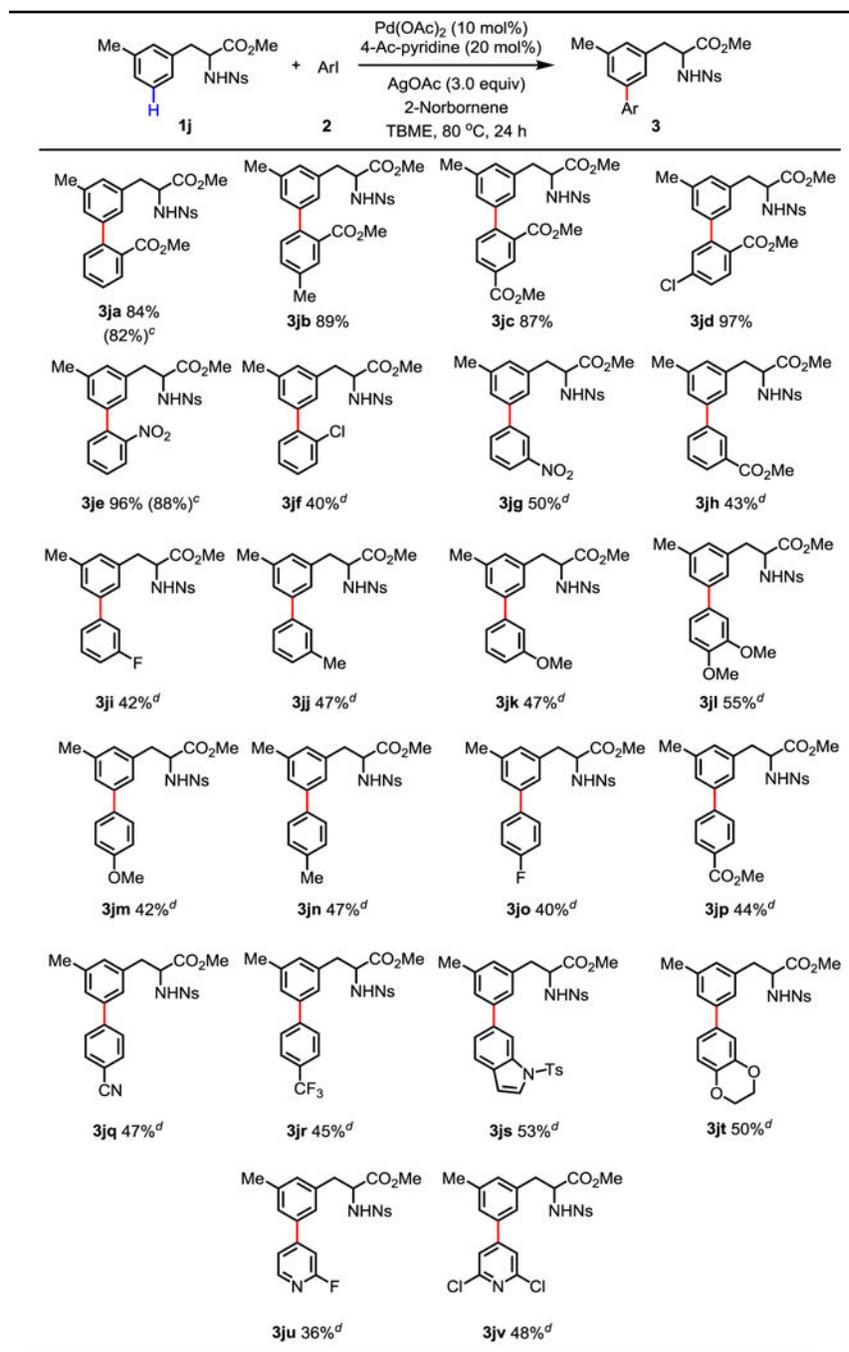
## Table 2

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 ^{1}H NMR using dibromomethane as an internal standard.

**Table 3**

*Meta*-Arylation of Substituted Phenethylamines[a,b]



Ar = o-CO₂MeC₆H₄

Reaction scheme showing:

R₁ (with aryl ring, R₂, NHNs, H) + methyl 2-iodobenzoate 2a (3.0 equiv) →

Conditions: Pd(OAc)₂ (10 mol%), 4-Ac-Pyridine (20 mol%), 2-Norbornene (20 mol%), AgOAc (3.0 equiv), TBME, 80 °C, 12 h → 3aa

Products:

**3aa** 88% (>99% ee)
**3ba** 88%
**3ca** 90%
**3da** 85%

**3ea** 92%
**3fa** 87%
**3ga** 86%
**3ha** 91%

**3ia** 85%
**3ja** 84%
**3ka** 82%
**3la** 92%

**3ma** 92%
**3na** 50%, di < 10%
**3oa** 45%, di < 10%
**3pa** 90%

**3qa** 55%, mono:di = 2:1
**3ra** 60%, mono < 5%
**3sa** 76%, mono:di = 2:1
**3ta** 85%

[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.

**Table 4**

*Meta*-Arylation with Variety of Aryl Halides[a,b]

*c*Isolated yields in parentheses when aryl bromide was used instead of aryl iodide.
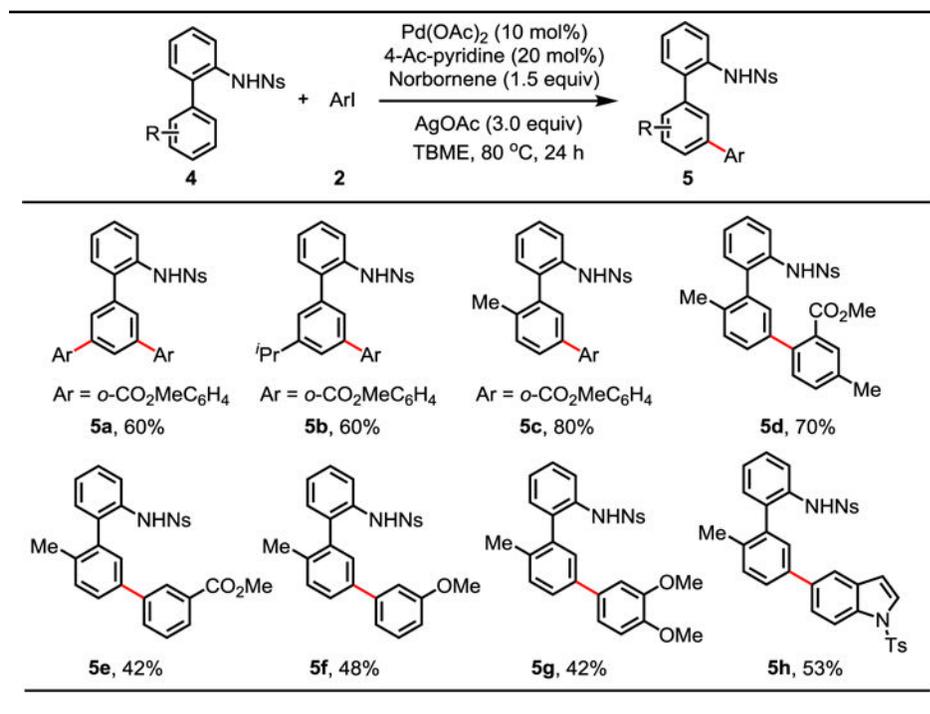
*d*3.0 equiv of 2-norbornene was used.

**Table 5**

*Meta*-Arylation of 2-Aryl Anilines[a,b]

**Table 6**

*Meta*-Arylationof *β*-Aryl Dipeptides 6[a,b]