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Ligand-Promoted *meta*-C−H Amination and Alkynylation

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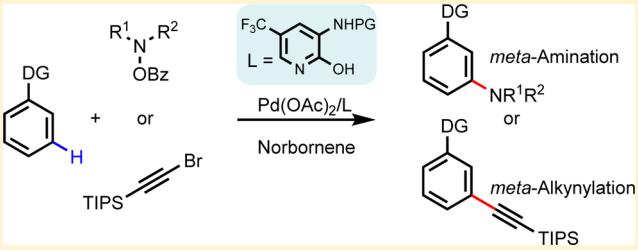
Supporting Information

ABSTRACT: Using a modified norbornene (methyl bicyclo[2.2.1]hept-2-ene-2-carboxylate) as a transient mediator, *meta*-C−H amination and *meta*-C−H alkynylation of aniline and phenol substrates have been developed for the first time. Both the identification of a monoprotected 3-amino-2-hydroxypyridine/pyridone-type ligand and the use of a modified norbornene as a mediator are crucial for the realization of these two unprecedented *meta*-C−H transformations. A variety of substrates are compatible with both *meta*-C−H amination and *meta*-C−H alkynylation. Amination and alkynylation of heterocyclic substrates including indole, indoline, and indazole afford the desired products in moderate to high yields.



1. INTRODUCTION

The *meta*-C−H functionalization of arenes poses a particularly interesting challenge due to the distal and geometric relationship between the *meta*-C−H bond and the existing functional group.[1] Previously, *meta*-selectivity has been obtained using sterically guided catalysts when concerning 1,2- and 1,3-disubstituted arenes.[2] Limited success on *meta*-selective C−H olefination of monosubstituted electron-deficient arenes using electronic bias has also been reported.[3] Inspired by the numerous reports concerning directed *ortho*-C−H activation of arenes, various strategies have been developed that use existing functional groups to direct *meta*-C−H activation.[4−6] For example, by engineering the spatial relationship of a directing group to a *meta*-C−H bond, our group and others have achieved a number of *meta*-C−H functionalization reactions using a U-shaped template.[4] More recently, our group[7a] and Dong's group[7b] have utilized directed *ortho*-palladation to achieve *meta*-C−H activation reactions[7] by synchronizing the palladacycle intermediate with Catellani's norbornene-mediated relay process (Figure 1a).[8] Owing to the development of improved norbornene mediators and ligands, the scope of *meta*-C−H arylation and alkylation using this approach has been substantially expanded.[7c,e] In principle, this approach should be compatible with any substrate containing an effective *ortho*-directing group, thus rendering this approach potentially broadly applicable. However, the transformations which have been reported using this approach are currently limited to either alkylation or arylation. To address the feasibility of overcoming this limitation, we initiated efforts to develop other transformations using this approach. Herein, we disclose the first protocol for *meta*-C−H amination and *meta*-C−H alkynylation (Figure 1b). To date, *ortho*-C−H alkynylation has not been demonstrated in the Catellani-type reactions.[8] Key to the success of these transformations is use of a modified norbornene and monoprotected 3-amino-2-hydroxy pyridine ligands. These results indicate that a transient mediator can be used in combination with the proper ligand and palladium catalyst to achieve a broad range of *meta*-C−H functionalization reactions that are rich with diversity in both substrate and transformation.

2. RESULTS AND DISCUSSION

2.1. *meta*-C−H Amination. Catalytic C−H amination has attracted much attention due to the importance of amines in medicinal and materials chemistry.[9] Several transition metals, such as Ir, Ru, Rh, Pd, Fe, Co, and Cu, have been used for this purpose to afford amines and amides directly from C−H bonds.[10] However, direct C−H amination at remote positions has not yet been reported. Based on the previous finding that 3-acetylamino-2-hydroxy pyridine based ligands can promote the *meta*-arylation of anilines with a broad substrate scope, we chose the aniline **1a** as a model substrate to examine the feasibility of developing a *meta*-C−H amination reaction using norbornene as a transient mediator. 3-Amino anilines provided by this methodology are potentially useful synthetic intermediates for many drug molecules (Figure 2).[11]

Based on our previous work concerning *ortho*-C−H amination using *O*-benzoyl hydroxylmorpholine as the aminating reagent,[12] we found that reaction of **1a** with this aminating reagent in the presence of 10 mol % $Pd(OAc)_2$, 20 mol % 3-acetylamino-2-hydroxy pyridine ligand (**L1**), K_3PO_4 (3.0 equiv), and AgOAc (3.0 equiv) in 1,2-dichloroethane using 2-norbornene as a mediator afforded *meta*-aminated product **3a** in 13% yield. It is worth noting that no *meta*-product was observed in the absence of ligand or base under similar conditions (see SI for more information). Unfortunately,

Received: August 25, 2016
Published: October 7, 2016

DOI: 10.1021/jacs.6b08942
J. Am. Chem. Soc. 2016, 138, 14092−14099

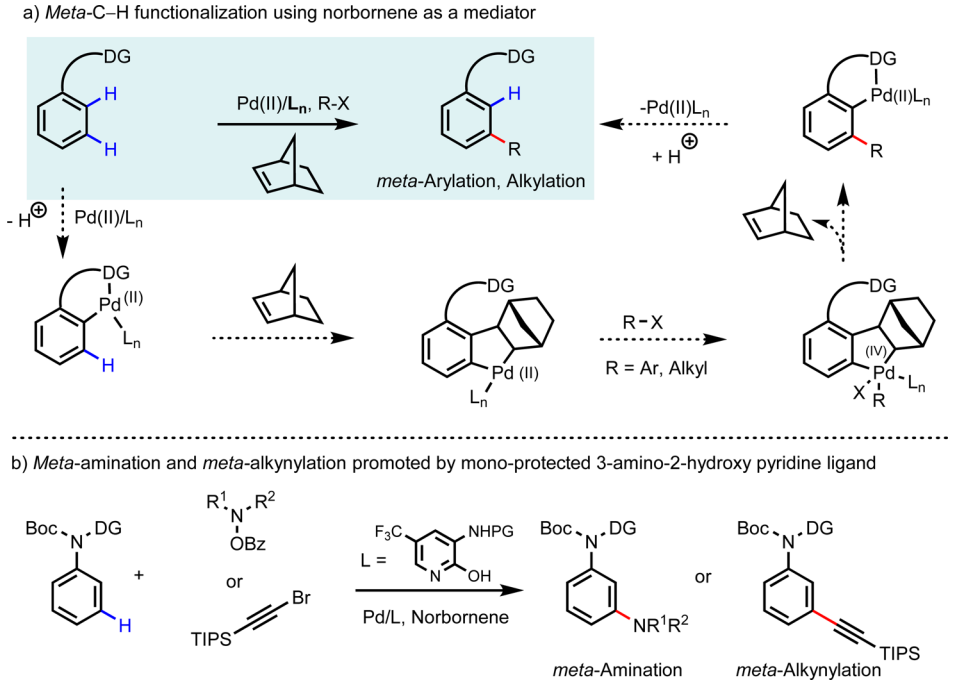


Figure 1. *meta*-C−H amination and alkynylation.

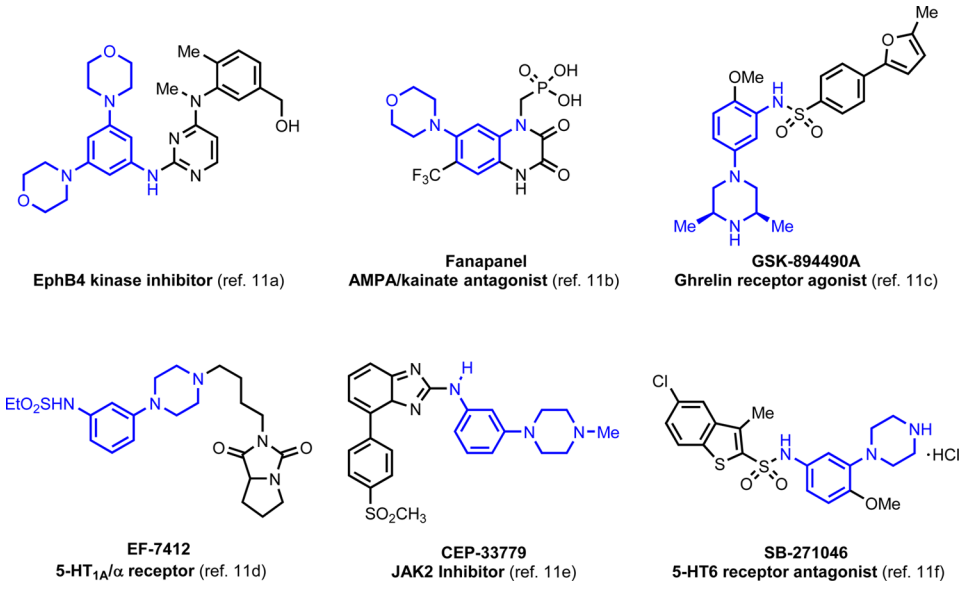


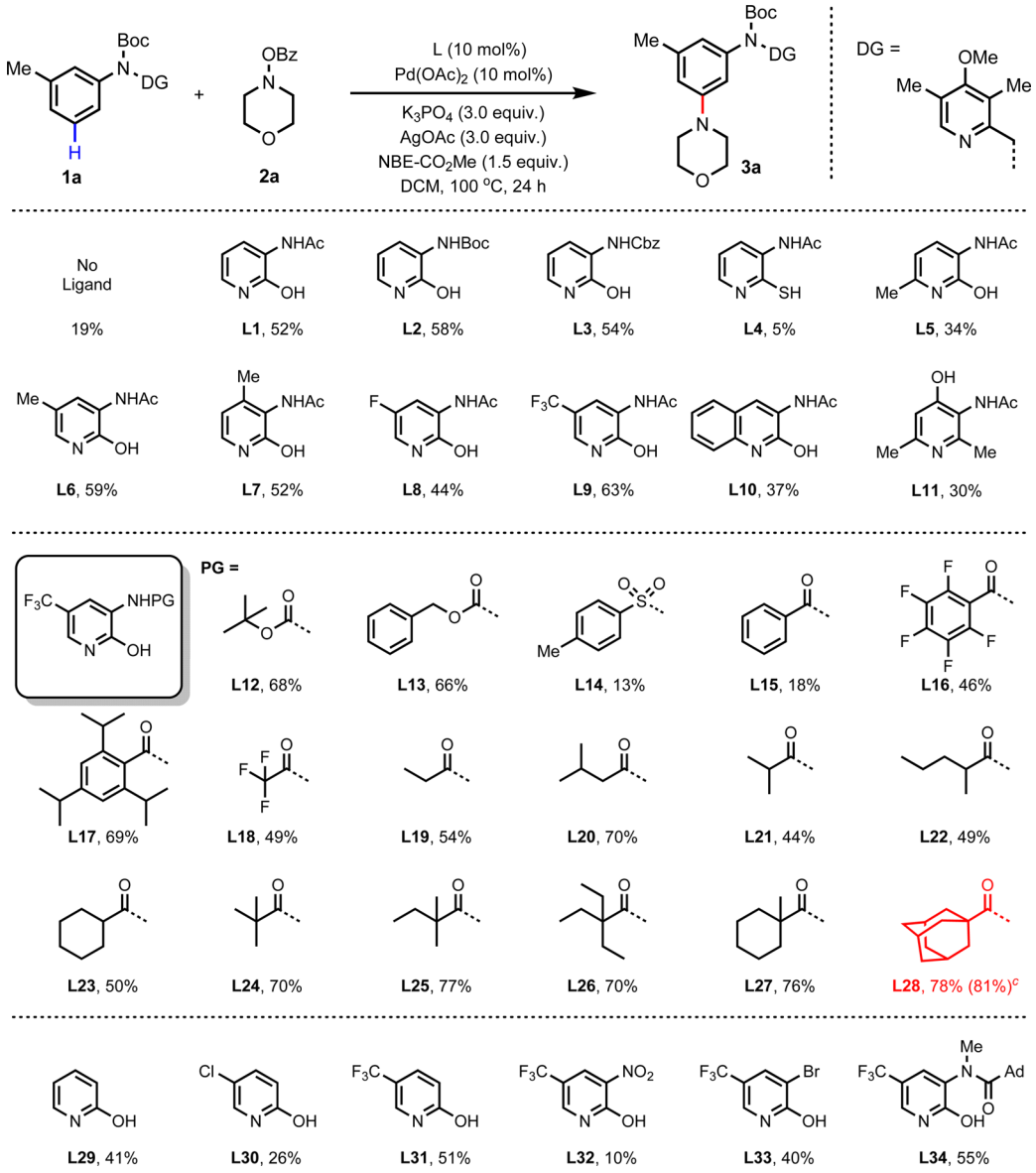
Figure 2. Biologically active 3-amino anilines scaffold.

further screening of bases, solvents, and oxidants did not significantly improve the yield (see SI for more information). Next, we screened various norbornene derivatives in an attempt to improve the efficiency of this reaction and found a modified norbornene, NBE-CO_2Me (methyl bicyclo[2.2.1]hept-2-ene-2-carboxylate),[7c] to be the most efficient mediator. Using this modified norbornene, dichloromethane was found to be a superior solvent affording the amination product **3a** in 52% yield in the presence of 10 mol % of ligand (**L1**, Table 1). The significant increase in yield observed with this modified norbornene is likely due to suppression of the competitively formed benzocyclobutane side product, as previously reported.[7c] Under these newly established conditions, we performed the reaction in the absence of ligand and observed the aminated product **3a** could be obtained in 19% NMR yield. This result clearly demonstrates the 3-acetylamino-2-hydroxy pyridine ligand (**L1**) dramatically increases the efficiency of this reaction.

To facilitate systematic investigations of the influence of 3-amino-2-hydroxy pyridine-based ligands on this reaction, we developed a more practical synthetic procedure to obtain multiple grams of NBE-CO_2Me from 5-norbornene-2,3-dicarboxylic anhydride ($68.75/500 g, from TCI) (see SI, 65% yield over four steps). With the modified norbornene in hand, a wide range of 2-hydroxy pyridine ligands were examined. Replacement of the OH group on the ligand with an SH group (**L4**) gave only 5% yield of the desired product, which we hypothesize is due to the strong coordination of sulfur to palladium. Methyl substitution at the 4- or 5-position of the ligand did not drastically alter the efficiency of the ligand, while substitution at the 6 position (**L5**) led to a significant

DOI: 10.1021/jacs.6b08942
J. Am. Chem. Soc. 2016, 138, 14092−14099

Table 1. Representative Ligand Evaluation[a,b]

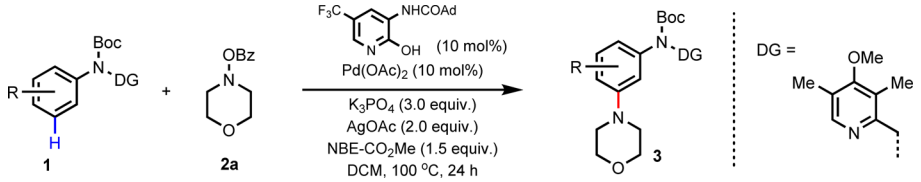


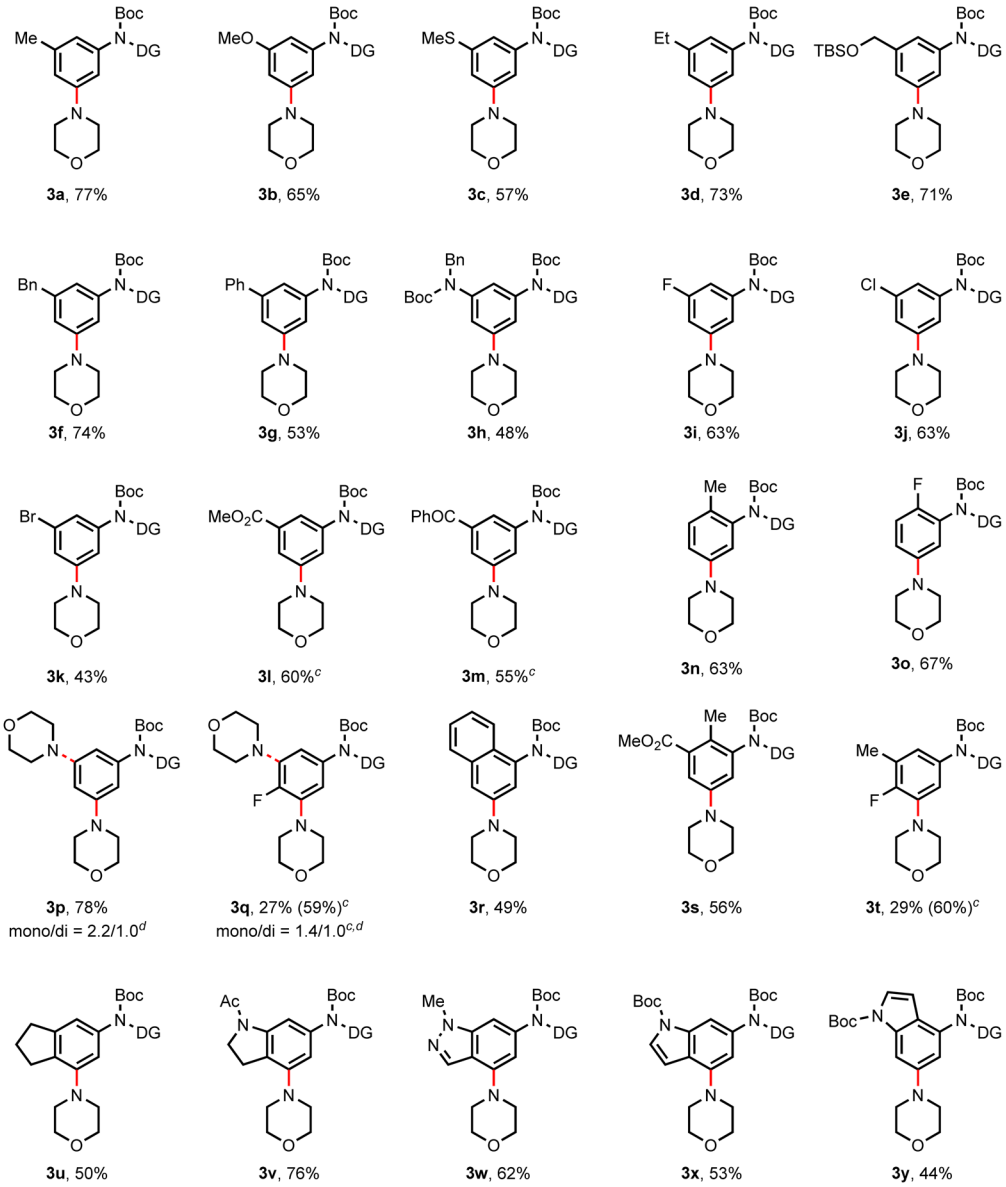
[a]Reaction conditions: **1a** (35.6 mg, 0.1 mmol), **2a** (41.4 mg, 0.2 mmol), $Pd(OAc)_2$ (10 mol %), ligand (10 mol %), NBE-CO_2Me (21.4 mg, 1.5 equiv), AgOAc (50.1 mg, 3.0 equiv), K_3PO_4 (62.8mg, 3.0 equiv), CH_2Cl_2 (1.0 mL), 100 °C, air, 24 h. [b]Yield was determined by ^{1}H NMR using benzyl acetate as internal standard. [c]**2a** (31.1 mg, 0.15 mmol), AgOAc (33.4 mg, 2.0 equiv) were used.

decrease in the activity. A slightly lower yield was observed when the ligand with fluorine at the 5-postion (**L8**) was tested. A trifluoromethyl group at the 5-position of the ligand improved the yield of the reaction to 63% (**L9**). 3-amino-2-hydroxy quinoline (**L10**) afforded the product in 37% yield, presumably due to the steric similarity of **L10** and **L5**, further confirming the intolerance of substitution at the 6-position. Interestingly, 3-acetylamino-4-hydroxy pyridine (**L11**) can also promote this reaction, though to a lesser extent, affording the desired product in 30% yield. Notably, the protecting group on the amine slightly affects the activity of the ligand (**L1** vs **L2** and **L3**). With **L9** being the most promising ligand, we used this scaffold to further screen various protecting groups on the amine. Carbonate-based protecting groups slightly increased the yield (**L12** and **L13**); however, sulfonyl and benzoyl-protected ligands decreased the yield (**L14** and **L15**). Interestingly, introduction of sterics on the benzoyl group restored the ligand's activity (**L17**), which indicates that sterics on the protecting group is important. We next examined a variety of acetyl protecting groups (**L18**–**L28**). Gratifyingly, bulkier acetyl protecting groups such as pivaloyl (**L24**) and 1-adamantanecarbonyl (**L28**) significantly improved the reaction efficiency providing 70% and 78% yields, respectively. With the optimal ligand **L28** identified, we performed a second round of optimizations of the reaction parameters and found that a decrease in the amount of *O*-benzoyl hydroxylmorpholine (**2a**) to 1.5 equiv and silver acetate to 2.0 equiv improves the yield to 81% (77% isolated yield, **3a** in Table 2). Several simple 2-hydroxypyride/pyridone ligands were also investigated (**L29**–**L33**), giving the aminated product in 10–51% yield. Interestingly, protecting the N–H on the best ligand **L28** with a methyl group (**L34**) decreased the yield to 55%, which indicates the N–H is important in this ligand design for the *meta*-C–H amination reaction. The role of the free N–H in the

DOI: 10.1021/jacs.6b08942
J. Am. Chem. Soc. 2016, 138, 14092–14099

Table 2. *meta*-Amination of Anilines[a,b]





[a]Reaction conditions: **1** (0.1 mmol), **2a** (31.0 mg, 0.15 mmol), $Pd(OAc)_2$ (2.2 mg, 10 mol %), **L28** (10 mol %), NBE-CO_2Me (21.4 mg, 1.5 equiv), AgOAc (33.4 mg, 2.0 equiv), K_3PO_4 (62.8mg, 3.0 equiv), CH_2Cl_2 (1.0 mL), 100 °C, air, 24 h. [b]Isolated yield. [c]$Pd(OAc)_2$ (3.4 mg, 15 mol %), **L28** (15 mol %), NBE-CO_2Me (21.4 mg, 1.5 equiv), and AgOAc (50.1 mg, 3.0 equiv) were used. [d]The selectivity of mono- and diproducts was determined by ^{1}H NMR.

ligand is unclear at this stage, though we hypothesize that monoprotected 3-amino-2-hydroxypyridine ligands might coordinate with Pd(II) through the pyridone motif as a carboxylate surrogate in some steps of this reaction and as a bis-dentate ligand (similar to the monoprotected amino acid ligands)[7e] in others.

With the optimized conditions in hand, the generality of the *meta*-C−H amination was investigated. A variety of functional groups, such as MeS, MeO, BnBocN, F, Cl, Br, ester, and ketone, are well tolerated providing the desired *meta*-C−H aminated products in synthetically useful yields (**3b**−**3m**). Substrates bearing functional groups at the *ortho*- and *para*-positions are also compatible with this amination protocol

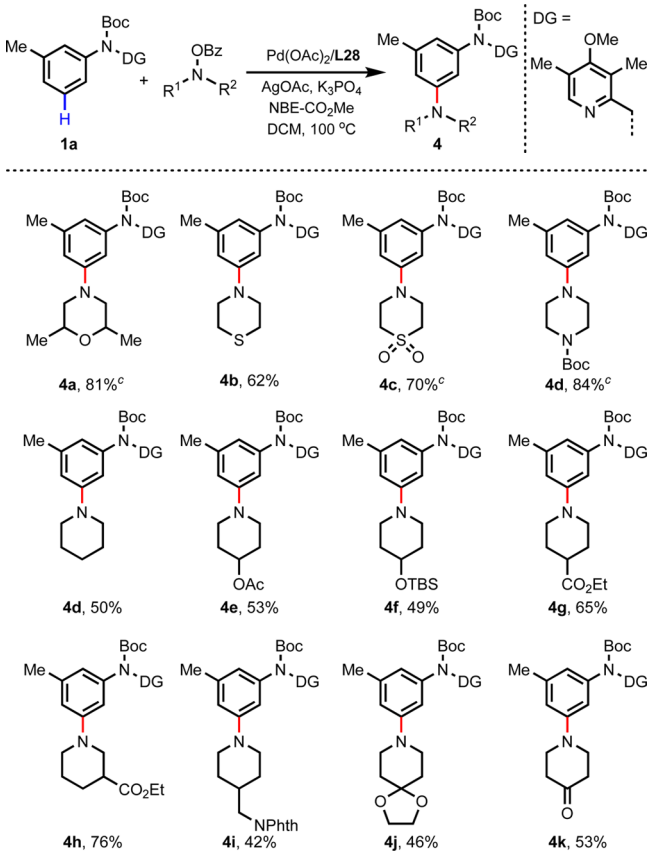
DOI: 10.1021/jacs.6b08942
J. Am. Chem. Soc. 2016, 138, 14092−14099

(**3n**−**3q**), though the *para*-substituted and simple aniline substrates provided both the mono- and diaminated products. 1-Naphthylamine (**3r**) and multiple substituted amines (**3s**−**3u**) are suitable substrates for this transformation. To our delight, heterocyclic amines containing indole, indoline, and indazole scaffolds are tolerated in this reaction, affording the desired *meta*-aminated products in moderate to high yields (**3v**−**3y**).

Having evaluated the substrate scope of aniline derivatives that are compatible with this amination reaction, we next turned our focus toward the scope of aminating reagents (Table 3). Using **1a** as the model substrate, a range of aminating reagents were investigated. Piperazine, thiomorpholine, thiomorpholine 1,1-dioxide, and 2,6-dimethylmorpholine, all of which are privileged motifs in drug discovery, couple smoothly under the reaction conditions to provide the desired products in good yields (**4a**−**4d**). For the medicinally important piperidine moieties, various functional groups were well tolerated on the piperidine backbone including TBS-protected hydroxyl groups, esters, phthalimido (Phth)-protected amino groups, and ketones (**4d**−**4k**). It is worth noting that the piperidin-4-one derived aminating reagent (**4k**) is compatible in this *meta*-amination reaction giving the desired product in 53% yield. The compatibility of this substrate is important, as this motif can be readily transformed to the free amine in one step (see SI for more information). Unfortunately, aminating reagents with pyrrolidine, azepane, and acyclic dialkylamine scaffolds were not effective and resulted in poor yields under the reaction conditions.

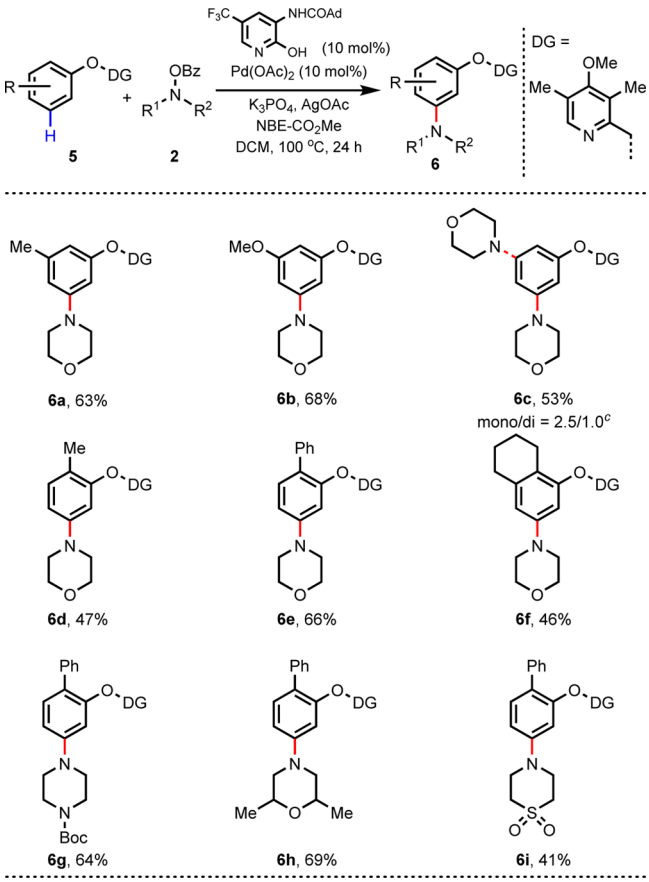
Phenol substrates bearing the same directing group can also be utilized in this *meta*-C−H amination reaction under similar conditions, although the conversions are slightly lower when compared to aniline substrates (**6a**−**6f**, Table 4). A few aminating reagents were tested with phenol substrate **5e**, giving the desired products in moderate to good yields (**6g**−**6i**).

Table 3. Scope of the Amines[a,b]



[a]Reaction conditions: **1a** (35.6 mg, 0.1 mmol), aminating reagent (1.5 equiv), $Pd(OAc)_2$ (15 mol %), **L28** (15 mol %), NBE-CO_2Me (42.8 mg, 3 equiv), AgOAc (50.1 mg, 3.0 equiv), K_3PO_4 (62.8mg, 3.0 equiv), CH_2Cl_2 (1.0 mL), 100 °C, air, 24 h. [b]Isolated yield. [c]$Pd(OAc)_2$ (10 mol %), **L28** (10 mol %), NBE-CO_2Me (21.4 mg, 1.5 equiv), and AgOAc (33.4 mg, 2.0 equiv) were used.

Table 4. *meta*-Amination of Phenols[a,b]



[a]Reaction conditions: **5** (0.1 mmol), **2** (0.15 mmol), $Pd(OAc)_2$ (2.2 mg, 10 mol %), **L28** (10 mol %), NBE-CO_2Me (21.4 mg, 1.5 equiv), AgOAc (33.4 mg, 2.0 equiv), CH_2Cl_2 (1.0 mL), 100 °C, air, 24 h. [b]Isolated yield. [c]The selectivity of mono- and diproducts was determined by ^{1}H NMR.

To demonstrate the utility of this reaction on a laboratory preparative scale, we conducted the reaction on gram scale, and **3a** was obtained in 74% yield (Scheme 1). Although mild oxidative conditions to remove this directing group have been reported,[7e] a simple one-step strategy is always desired. We have demonstrated the removal of the Boc-protecting group and the pyridine directing group simultaneously by treating the aminated product **3i** with hydrobromic acid at 100 °C. This one-step protocol provides the free amine **7** in 83% yield (see SI for more information). Notably, the 3-fluoro-5-morpholinoaniline **7** is a key intermediate in the synthesis of **8**, a BRAF inhibitor.[13]

DOI: 10.1021/jacs.6b08942
J. Am. Chem. Soc. 2016, 138, 14092−14099

Scheme 1. Synthetic Application of *meta*-C−H Amination of Anilines

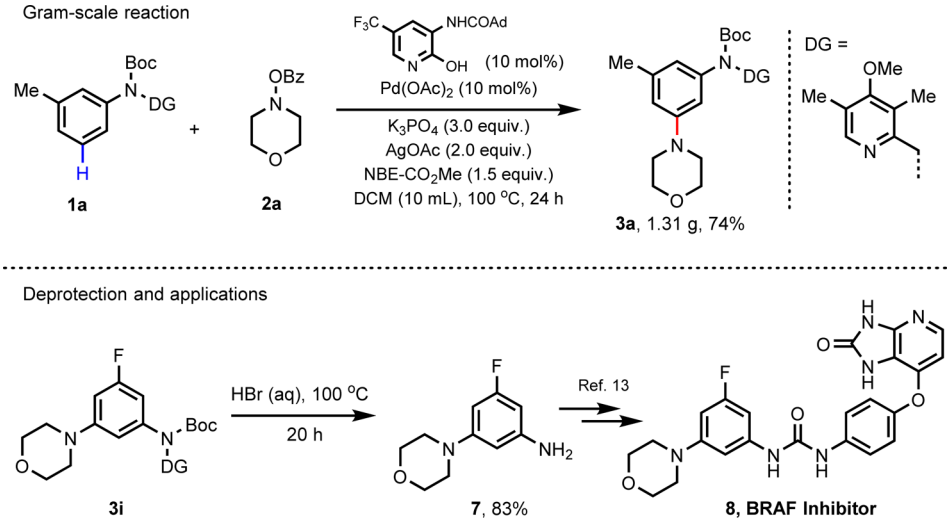
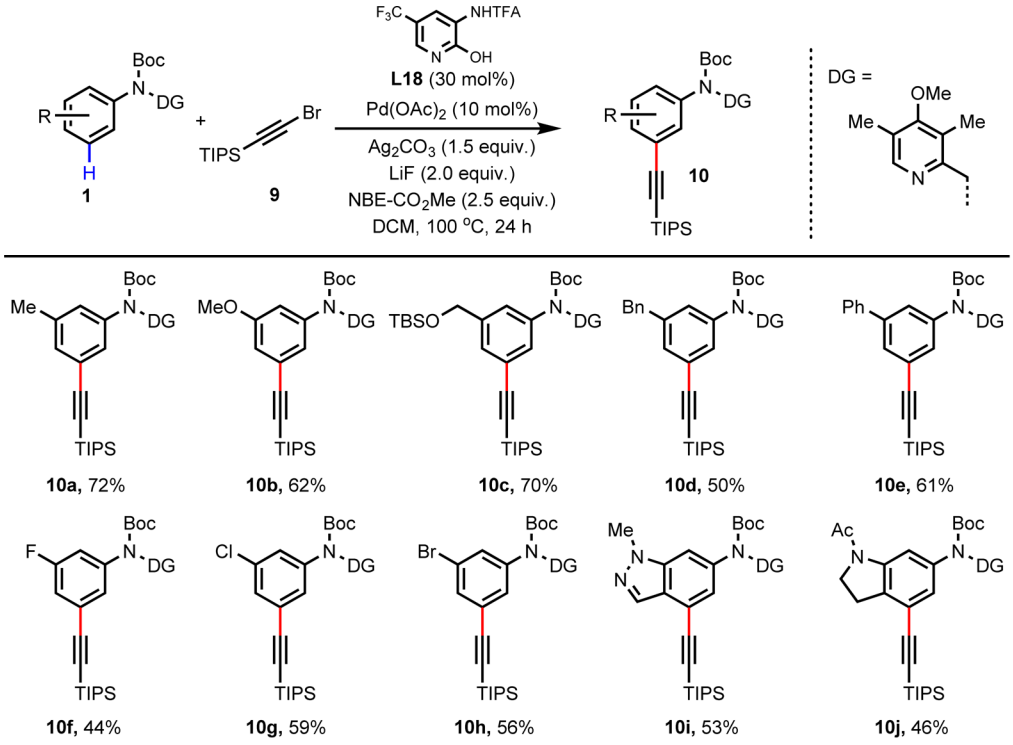


Table 5. *Meta*-Alkynylation of Anilines[a,b]



[a]Reaction conditions: **1** (0.1 mmol), **9** (52.2 mg, 0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 10 mol %), **L18** (8.2 mg, 30 mol %), NBE-CO_2Me (38.0 mg, 2.5 equiv), Ag_2CO_3 (41.3 mg, 1.5 equiv), LiF (5.2 mg, 0.2 mmol), CH_2Cl_2 (1.0 mL), 100 °C, air, 24 h. [b]Isolated yield.

2.2. *meta*-C−H Alkynylation. Aryl alkynes are privileged structural motifs found in natural products, pharmaceuticals, and materials.[14] They also act as valuable precursors participating in many cross-coupling, metathesis, and cycloaddition reactions.[15] In the last few decades, the Sonogashira coupling has been extensively studied and represents one of the most important methods to synthesize aryl alkynes in both academic and industrial settings.[16] Consequently, installation of alkyne groups via C−H alkynylation has attracted significant interest and has been studied using terminal alkynes,[17] alkynyl halides,[18] and hypervalent iodine reagents.[19] However, *meta*-C−H alkynylation has not been reported to date. The lack of precedents using alkynyl coupling partners as electrophiles in the Catellani reaction also attests to the challenge of developing *meta*-C−H alkynylation using norbornene as a transient mediator.[8] Encouraged by the success of *meta*-C−H amination reactions using norbornene as transient mediator, we envisioned that *meta*-alkynylation could be achieved through a Pd(II)/Pd(IV) process using an alkynyl bromide as the electrophile. To our great delight, 25% yield of the *meta*-alkynylated product **10a** was obtained, accompanied by 14% yield of the *ortho*-alkynylated product **10a′** in the presence of 10 mol % $Pd(OAc)_2$, 20 mol % ligand **L9**, alkynyl bromide **9** (2.0 equiv), LiF (2.0 equiv), and Ag_2CO_3 (1.5 equiv) in 1,2-

DOI: 10.1021/jacs.6b08942
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dichloroethane at 95 °C using NBE-CO_2Me as a mediator. Interestingly, the *ortho*-alkynylated product can also be obtained in this protocol due to the high reactivity of alkynyl bromides. After a thorough investigation of solvents, oxidants, additives, and ligands, we found the selectivity of *meta*- to *ortho*-products can be improved to >11:1 using TFA-protected ligand **L18**, allowing the desired *meta*-alkynylated product to be obtained in 71% isolated yield. The yield can be further improved to 75% by increasing the temperature to 100 °C (see SI for more information).

We next evaluated the scope of this *meta*-alkynylation reaction under the optimal conditions (see Table 5). Functional groups such as Me, MeO, Benzyl, Ph, F, Cl, and Br are well tolerated under the reaction conditions affording the *meta*-alkynylated products **10a**−**10h** in moderate to good yields. Indoline and indazole-containing amines are also compatible with this protocol, and the desired products **10i** and **10j** could be obtained in 53% and 46% yield, respectively. The scope of alkyl and aryl alkynes was also investigated. However, only various bulky silyl-protected alkynyl bromides provided *meta*-alkynylated products in good yields. Simple alkyl and aryl alkynyl bromides only led to trace amount of the desired products (see SI).

3. CONCLUSION

In summary, Pd(II)-catalyzed *meta*-C−H amination and *meta*-C−H alkynylation have been developed for the first time, indicating that norbornene-mediated *meta*-C−H functionalization is a highly general platform that is compatible with a wide variety of transformations. Both the monoprotected 3-amino-2-hydroxypyridine ligands and the modified norbornene (NBE-CO_2Me) are crucial to realize these transformations. High yields and a broad substrate scope have been achieved for both *meta*-C−H amination and *meta*-C−H alkynylation reactions using either *N*-benzoyloxyamines or alkynyl bromides as electrophilic reagents. Future efforts will focus on improving the efficiency of these transformations as well as exploring new transformations which have not yet been demonstrated in *meta*-C−H functionalization using this strategy.

4. EXPERIMENTAL SECTION

4.1. General Procedure for Amination of Anilines. Substrate **1** (0.1 mmol), **2a** (0.15 mmol), $Pd(OAc)_2$ (2.2 mg, 10 mol %), **L28** (2.2 mg, 10 mol %), AgOAc (33.4 mg, 0.2 mmol), NBE-CO_2Me (21.6 mg, 0.15 mmol), K_3PO_4 (62.8 mg, 0.3 mmol), and CH_2Cl_2 (1.0 mL) were added to a 2 dram vial. The vial was capped and closed tightly. Then the reaction mixture was stirred at 100 °C for 24 h. After cooling to room temperature, the mixture was passed through a pad of Celite with CH_2Cl_2 as the eluent to remove the insoluble precipitate. The resulting solution was concentrated and purified by preparative TLC to afford the desired product **3**.

4.2. General Procedure for Alkynylation of Anilines. Substrate **1** (0.1 mmol), alkynylating reagent **9** (52.2 mg, 0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 10 mol %), **L18** (8.2 mg, 30 mol %), Ag_2CO_3 (41.3 mg, 0.15 mmol), NBE-CO_2Me (38.0 mg, 0.25 mmol), LiF (5.2 mg, 0.2 mmol), and CH_2Cl_2 (1.0 mL) were added to a 2 dram vial. The vial was capped and closed tightly. Then the reaction mixture was stirred at 100 °C for 24 h. After cooling to room temperature, the mixture was passed through a pad of Celite with CH_2Cl_2 as the eluent to remove the insoluble precipitate. The resulting solution was concentrated and purified by preparative TLC to afford the desired product **10**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08942.

Detailed experimental procedures, characterization of new compounds (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge The Scripps Research Institute and the NIH (NIGMS, 2R01 GM102265) for financial support. Tyler G. St. Denis is thanked for editorial assistance.

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DOI: 10.1021/jacs.6b08942
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