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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.5b02809 • Publication Date (Web): 24 Apr 2015

Just Accepted

Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Simple Amine-Directed *meta*-Selective C−H Arylation via Pd/Norbornene Catalysis

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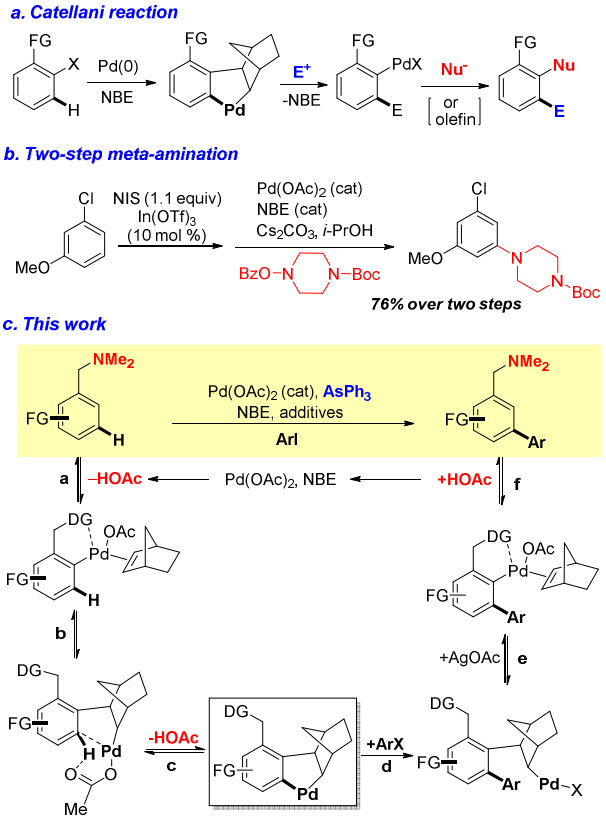
Supporting Information Placeholder

ABSTRACT: Herein we report a highly *meta*-selective C–H arylation using simple tertiary amines as the directing group. This method takes advantages of Pd/norbornene catalysis offering a distinct strategy to control the site-selectivity. The reaction was promoted by commercially available $AsPh_3$ ligand and unique "acetate cocktail". Aryl iodides with an *ortho*-electron withdrawing group were employed as the coupling partner. A wide range of functional groups, including some heteroarenes, can be tolerated under the reaction conditions. In addition, the amine directing group can be easily installed and transformed to other common versatile functional groups. We expect this C–H functionalization mode should have broad implications for developing other *meta*-selective transformations beyond this work.

Site-selective arene functionalization has been continuously impacting the fields of drug discovery, material science and chemical industry.[1] While numerous *ortho*-selective arene functionalization methods have been extensively developed, the *meta*-selective functionalization of an electronically unbiased arene remains a difficult task.[2] Recently, a number of elegant approaches have been developed, including steric-sensitive borylation and silylation,[3] cluster-templated metalation,[4] diaryliodonium salt-mediated arylation,[5] use of a traceless directing group (DG),[6] *ortho*-metalation-triggered ArS_E,[7] use of a U-shape template,[8] and others.[9] Despite these seminal efforts, a broadly applicable C–H functionalization strategy, that is completely *meta*-selective, overrides intrinsic steric and electronic preference of the arene substrates and tolerates a broad range of functional groups (FGs), remains highly sought after.

We foresaw the potential of employing the Pd/norbornene(NBE) catalysis, namely the Catellani reaction,[10] to control the site-selectivity for arene C–H functionalization. The Catellani reaction generally uses aryl halides as the substrates allowing *ipso* and *ortho* di-functionalization of arenes, through a NBE-mediated vicinal C–H metalation reaction (Scheme 1a).[1c,f,10] Seminal work by Catellani and Lautens has shown that various carbon FGs can be installed at the *ortho*-position of the arene,[11] which has been employed to prepare *meta*-substituted arenes.[11j,k] Our group recently demonstrated the first *ortho* C–N bond forming transformations with an electrophilic amination reagent, and further illustrated a two-step *meta*-amination sequence via electrophilic halogenation followed by reductive *ortho*-amination (Scheme 1b).[12] In this communication, we extend our efforts towards developing a direct approach for catalytic *meta*-functionalization of arenes based on the unique features of the Pd/NBE catalysis.[13]

Scheme 1. *meta*-Selective Arene C–H functionalization via Pd/NBE catalysis

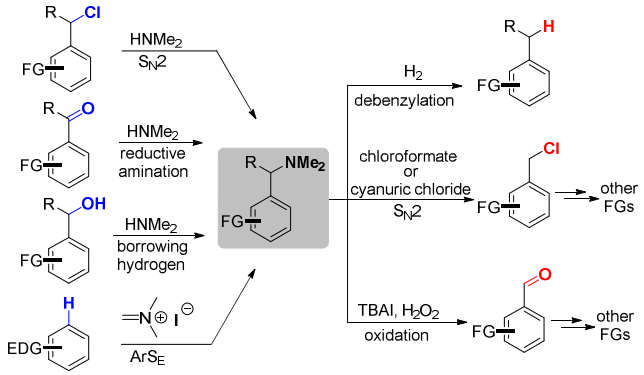


We postulated that the NBE-bridged five-membered palladacycle, the key intermediate in the Catellani reaction, could also be generated via a C–H metalation-initiated pathway.[14] A proposed *meta*-arylation is depicted in Scheme 1c, guided by a DG, *ortho*-metalation should give a Pd(II) intermediate (step a), which should be able to undergo an analogous Catellani reaction pathway (steps b and c). The five-membered palladacycle is expected to react with an electrophile, e.g. an aryl halide, through either a Pd(IV) intermediate or a transmetalation pathway,[15] to generate a *meta*-substituted complex (step d). The resulting Pd(II) intermediate would then undergo β-carbon elimination followed by re-protonation at the *ortho*-position to furnish the desired *meta*-product (steps e and f). However, the challenges of the proposed pathway are three-fold. First, both the *ortho*-metalation-deprotonation (step a), its reverse step (step f, demetalation-

protonation) and the metalation at the *meta*-position (step c) must be accommodated under the same reaction conditions. Second, the electrophile can possibly react with either the *ortho*-palladated arene species or the intermediate after *meta*-metalation. Thus, finding an appropriate ligand to control the relative reactivity of these aryl-palladium intermediates is nontrivial. Finally, for broad applicability purposes, it would be more attractive to utilize a common and versatile FG as the DG.

Stimulated by the aforementioned challenges, we sought the use of a simple tertiary amine, i.e. dimethyl amine, as the DG.[16] A number of benefits with this type of DG can be envisioned: 1) it was demonstrated three decades ago by Ryabov that the dimethylamine can direct a *reversible ortho*-metalation under mildly acidic conditions;[17] 2) amines are widely available and frequently found in bio-active and pharma-interesting molecules; 3) it is small and light (the MW of the Me_2N group is only 44); 4) it can be easily installed from a number of common starting materials, e.g. benzaldehydes and halides, etc (Scheme 2);[18] 5) it is also known that the dimethylamino group at the benzylic position can be easily removed under hydrogenolysis conditions[16b,c,19] or converted to other FGs (*vide infra*, Scheme 3).

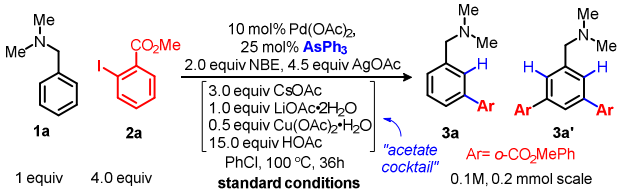
Scheme 2. Availability and versatility of the amine DG



Benzylamine **1a** was employed as the initial model substrate. After extensively examining a range of Pd, ligand, additive and solvent combinations (for detailed optimization studies, see SI), to our delight, the desired *meta*-arylation can be obtained when using $Pd(OAc)_2/AsPh_3$ as the metal/ligand choice, aryl iodide **2a** as the aryl source, and chlorobenzene as the solvent. Given that substrate **1a** has two *meta*-positions, both mono and diarylation are possible; nevertheless, by controlling the amount of the aryl halide used, the diarylation product (**3a'**) can be formed as the dominate product (72% yield, entry 1, Table 1).

A series of control experiments were subsequently conducted to understand the role of each reactant (Table 1). In the absence of either Pd precatalyst or NBE, no desired product was observed (entries 2 and 4). The commercially available $AsPh_3$ proved to be the most efficient ligand for promoting the arylation (entry 3); in contrast, use of more electron-rich ligands, such as PPh_3 or S-Phos, gave significantly lower yields. The silver salt was employed to accelerate the oxidative addition of aryl iodide. In the absence of AgOAc, the mono-arylation product (**3a**) can still be obtained in 6% yield (entry 5). We further discovered that the reaction rate can be improved by using an interesting "acetate cocktail" containing $LiOAc{\cdot}2H_2O$, CsOAc and $Cu(OAc)_2{\cdot}H_2O$ (1: 3: 0.5) in acetic acid (entries 6-8). Although the exact reason remains to be further explored, we speculate that HOAc and LiOAc would help dechelation of the DG from the palladium (through protonation or complexation) after the initial *ortho*-C−H activation, which is required for the second metalation (*vide supra*, step b, Scheme 1c); CsOAc might work as a stronger acetate source to assist the deprotonation/metalation step; the Cu(II) salt may act as an efficient Pd(0) scavenger to minimize Pd(0)-mediated reactions. It should be noted that in the absence of the "acetate cocktail", the desired *meta*-products can be still be formed albeit in lower yields (entry 10). Interestingly, while in the absence of acetic acid the reaction became more sluggish, its use as solvent completely shut down the reaction (entry 11). Finally, shortening the reaction time or using less NBE led to incomplete conversion and more mono-arylation product (entries 12 and 13). Further control experiments showed that no *ortho* and *para*-arylation products were observed during the reaction with **1a**.[20] One major side reaction arises from the self-dimerization of aryl ioide **2a** with NBE.[11j,21]

Table 1. Control experiments for the *meta*-arylation

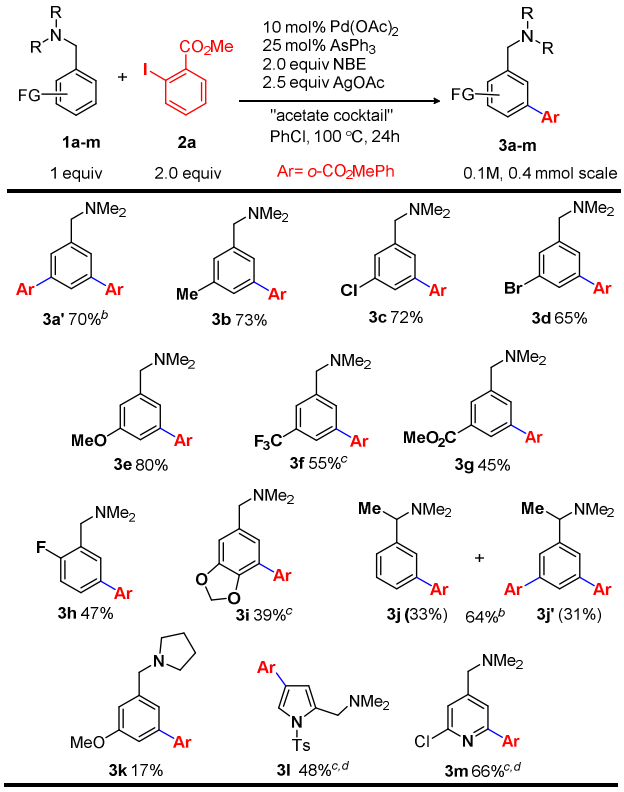


Entry	Change from standard conditions	Yield of 3a[a]	Yield of 3a'[a]
1	None	2%	72%
2	No $Pd(OAc)_2$	0%	0%
3	No $AsPh_3$	11%	7%
4	No NBE	0%	0%
5	No AgOAc	6%	0%
6	No CsOAc	7%	34%
7	No $LiOAc{\cdot}2H_2O$	3%	60%
8	No $Cu(OAc)_2{\cdot}H_2O$	8%	45%
9	No HOAc	19%	14%
10	No acetate cocktail	21%	20%
11	HOAc instead of PhCl	0%	0%
12	12h instead of 36h	23%	29%
13	0.5 equiv of NBE instead of 2.0 equiv	22%	13%

[a] Determined by GC using dodecane as the internal standard.

With the optimal conditions established, we first examined the scope of benzylamine substrates (Table 2). When substituted benzylamines were employed as the substrate, the amount of aryl iodide and AgOAc can be reduced to 2 equiv and 2.5 equiv respectively. To our delight, both electron-rich and deficient arenes provided the desired *meta*-arylated products in moderate to good yields. In particular, the highly electron-rich 3-methoxy substrate, with a strong electron bias on the *ortho* and *para*-positions, still afford the *meta*-product (**3e**) in 80% yield. Substitutions on various positions of the arenes can be tolerated. Moreover, this transformation is compatible with a number of functional groups, including tertiary amines, aryl fluorides, chlorides, bromides, anisoles, trifluoromethyl, methylenedioxy groups and esters. In addition, the substrate with a methyl substituent at the benzylic position still provided the desired mono and diarylation products (**3j** and **3j'**). When enantiopure **1j** was used, no racemization was observed. Besides the dimethylamino group, other tertiary amines[22] can also be employed as the DG (e.g. **3k**) albeit with a lower efficiency. In contrast, use of Ac-protected benzylamines did not lead to the desired products. Further investigation of this transformation with other DGs is ongoing in our laboratory. It is noteworthy that heteroarenes, such as protected pyrrole and pyridine-derived substrates, are also amenable for this transformation (**3l** and **3m**).

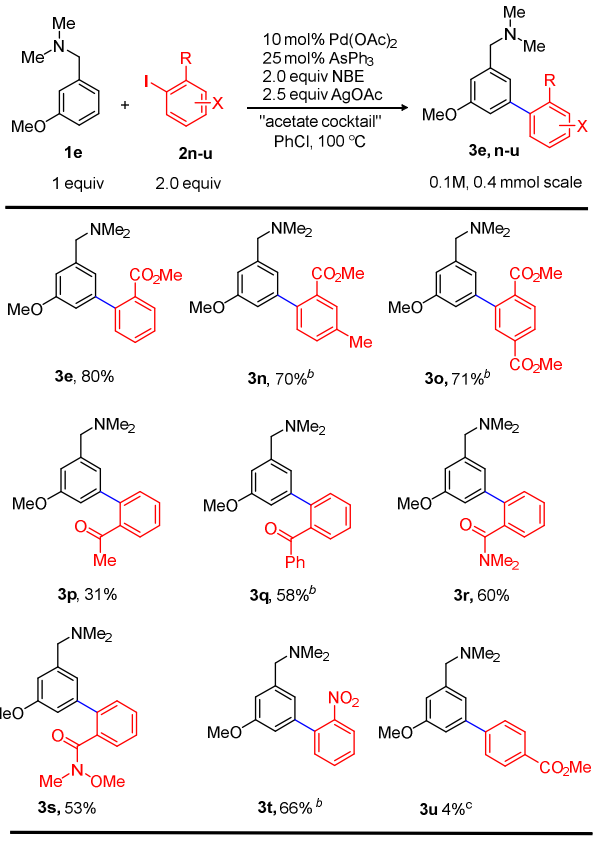
Table 2. Substrate scope with different benzylamines[a]



[a] All yields are isolated yields. [b] The reaction time was 36h; 4.0 equiv of **2a** and 4.5 equiv of AgOAc were used. [c] The reaction was run at 130°C. [d] 3.0 equiv of **2a** and 3.5 equiv of AgOAc were used.

The scope of the aryl halides was investigated next (Table 3). Aryl halides containing an *ortho* electron-withdrawing group (EWG) proved to be most efficient, which is consistent with the previous observation in the typical Catellani arylation reaction.[11g,23] It is likely that the EWGs can accelerate oxidative addition of the aryl iodide (step d, Scheme 1c) through a combined electronic and weak-directing effect. Aryl iodides with only a *para* or *meta*-substituent proved to be much less reactive. For example, when methyl 4-iodobenzoate **2u** was used, a low conversion was observed (<10%) but still giving the desired *meta*-arylation product (**3u**).[24] Nevertheless, besides ester group, amide, Weinreb amide, alkyl and aryl ketone and nitro groups were all found suitable for this transformation.

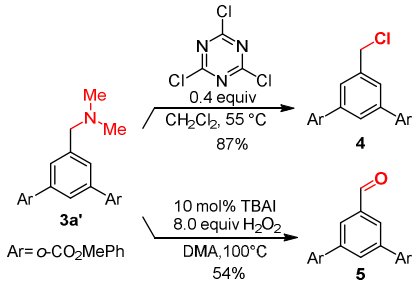
Table 3. Substrate scope with different aryl iodides[a]



[a] All yields are isolated yields. [b] The reaction time was 36h. [c] The reaction was run at 130°C with 4.0 equiv of the aryl iodide and 4.5 equiv of AgOAc.

Finally, as an example to demonstrate the potential usage of this *meta*-arylation reaction, we showed the triaryl product **3a'** can be easily transformed to a benzyl chloride or an aldehyde by using established procedures.[25] Both moieties are well known as versatile synthetic precursors, and can be readily transformed to various other FGs.

Scheme 3. Derivatization of the *meta*-arylation product



In summary, we have developed a distinct highly *meta*-selective arylation using Pd/NBE catalysis. This transformation uses a simple tertiary amine as the DG and commercially available $AsPh_3$ as the ligand. In addition, arenes with various electronic and steric properties can be used as the substrates, and a significant number of FGs, including some heteroarenes, can be tolerated. We expect this mode of reactivity should have high potential to be generalized allowing other *meta*-functionalization, e.g. forming C–X (X≠C) bonds at the *meta*-position. Efforts towards expanding the reaction scope and detailed mechanistic studies to understand the C–C bond formation step (e.g. whether it reacts

through a Pd(IV) intermediate or a transmetalation pathway) are underway.

ASSOCIATED CONTENT

Supporting Information Experimental procedures; spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We thank CPRIT for a start-up fund and the Welch Foundation (F-1781) for research grants. G.D. is a Searle Scholar. We thank Dr. Zhou and Dr. Young for proofreading the manuscript. Mr. Sorey and Ms. Spangenberg are acknowledged for their NMR advice. Johnson Matthey is thanked for a donation of Pd salts.

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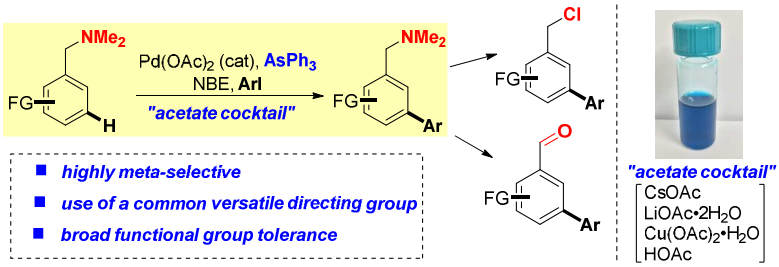
NMe2
FG
H
Pd(OAc)2 (cat), AsPh3
NBE, ArI
"acetate cocktail"
NMe2
FG
Ar
Cl
FG
Ar
O
FG
Ar
highly meta-selective
use of a common versatile directing group
broad functional group tolerance
"acetate cocktail"
CsOAc
LiOAc•2H2O
Cu(OAc)2•H2O
HOAc