Template Synthesis to Solve the Unreachable *Ortho* C-H Functionalization Reaction of Iodobenzene

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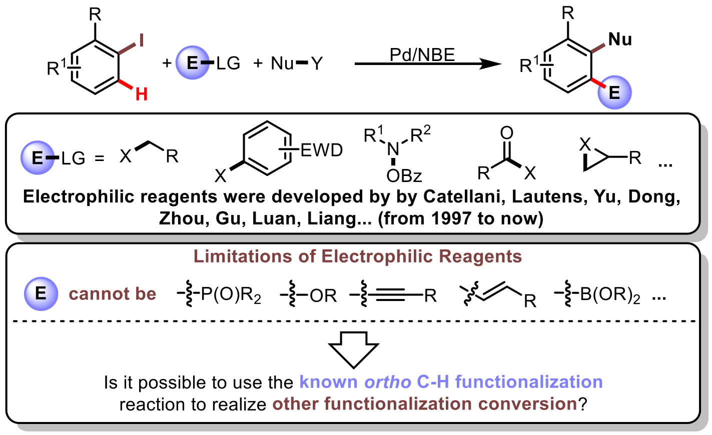
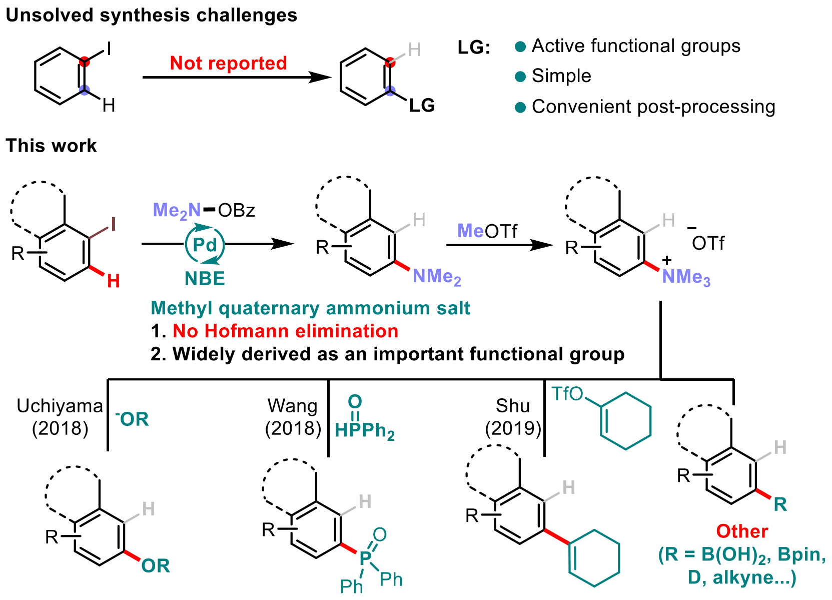
With the development of ortho C-H functionalization in Pd/NBE chemistry, the catalytic systems used are becoming increasingly complex. The increasingly complex catalytic systems may have created technical barriers for researchers in other fields to apply Pd/NBE chemical methods. This report describes the use of a simple Pd/NBE catalytic system to achieve *ortho* C-H oxylation and phosphonylation and other functionalization of iodobenzene through templated conversion reactions. The key point of this method is to explore the previously unknown step of introducing dimethylamine in the ortho position of iodobenzene through C-H amination. Aryl dimethylamine is quickly converted to methyl quaternary ammonium salt precipitation, and methyl quaternary ammonium salt effectively avoids Hofmann elimination in the subsequent functionalization.



Scheme 1. The Electrophilic Reagents of Pd/NBE Chemistry

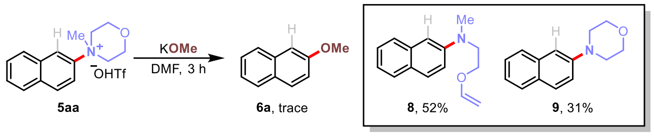
Pd/NBE chemistry, as a one-step *ortho* C-H functionalization method for halobenzene, has been widely used in natural product synthesis, medicinal chemistry and material science.[1-8] In 1982, When Italian chemist Catellani studied the metal complex composed of palladium and norbornene, she found that the complex can undergo oxidative addition and reduction elimination with electrophilic reagents.[9-15] Inspired by this discovery, in 1997, she discovered the first catalytic version of *ortho* C-H alkylation of iodobenzene after her long-term research.[16] This breakthrough reaction established the field of Pd/NBE chemistry. Subsequently, Catellani developed a Pd/NBE co-catalyzed *ortho* C-H arylation reaction of iodobenzene.[17] In 2000, Lautens discovered that adding phosphorus ligands to the reaction system can greatly promote the compatibility of Pd/NBE chemical reactions, providing favorable conditions for the later development of *ortho* C-H functionalization reactions.[18]



Scheme 2. Template Strategy of *Ortho*-C-H Functionalization of Iodobenzene

The development of other *ortho* C-H functionalization reactions was relatively difficult, and it was not until 2013 that Dong's research group reported the first case of iodobenzene *ortho* C-H amination reaction.[19,20] In this report, the electrophilic amination reagent with carboxylic acid oxygen as the leaving group can undergo an oxidative addition process with the Aryl-Norbornyl-Palladacycle (ANP) intermediate, which inspired researchers in this field. Subsequently, C-H acylation[21-23] and thiolation[24,25] were also developed. Even recently, Dong group reported C-H oxylation reaction[26], which was considered impossible in the past due to the large electronegativity of oxygen. These works are of great significance for the theoretical and conceptual development of Pd/NBE chemistry (Scheme 1).

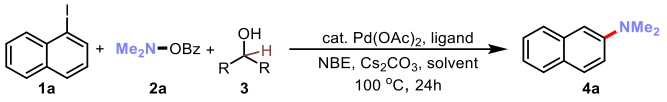
With the development of ortho C-H functionalization in Pd/NBE chemistry, the catalytic systems used are becoming increasingly complex. Especially the synthesis of structurally modified norbornene requires numerous steps. The increasingly complex catalytic systems may have created technical barriers for researchers in other fields to apply Pd/NBE chemical methods. Therefore, whether the most common palladium catalysts and norbornene can indirectly achieve the currently unattainable ortho C-H functionalization is the question we want to solve. Especially by combining previously reported literature, providing researchers in other fields with a universal template synthesis strategy. In addition, although various *ortho* C-H functionalization reactions of iodobenzene have been developed, C-H oxylation (C-H methoxylation has been achieved by Dong), phosphonylation, and alkenylation have not yet been achieved in Pd/NBE chemistry. Based on this, we envision using the simplest Pd/NBE catalytic system to achieve *ortho* C-H oxylation, phosphonylation, and alkenylation of iodobenzene through templated conversion reactions (Scheme 2).



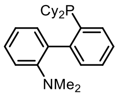
Scheme 3. Non-Methyl Quaternary Ammonium Salt

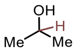
In recent years, quaternary ammonium salts have gradually developed into a good active functional group that can be converted into various functional groups, and these aryl quaternary ammonium salts are limited to trimethyl quaternary ammonium salts.[27-32] This is because when there is hydrogen at *β*-site of nitrogen atom of quaternary ammonium salt, Hofmann elimination will take place preferentially under alkaline conditions (Scheme 3). Therefore, exploring the C-H dimethylamination reaction of iodobenzene under Pd/NBE co-catalysis is the primary task.

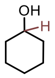
Table 1. Screening of Reaction Conditions[a]

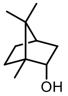


entry	ligand	solvent	**3**	yield (%)
1	PPh_3	toluene	**3a**	36
2	TFP	toluene	**3a**	30
3	P-(2-MeC_6H_4)$_3$	toluene	**3a**	<5
4	DavePhos	toluene	**3a**	33
5	P-(4-OMeC_6H_4)$_3$	toluene	**3a**	45
6	P-(4-OMeC_6H_4)$_3$	DMSO	**3a**	trace
7	P-(4-OMeC_6H_4)$_3$	CH_3CN	**3a**	28
8	P-(4-OMeC_6H_4)$_3$	DME	**3a**	48
9	P-(4-OMeC_6H_4)$_3$	dioxane	**3a**	49
10	P-(4-OMeC_6H_4)$_3$	THF	**3a**	65
11	P-(4-OMeC_6H_4)$_3$	DMF	**3a**	12
12	**P-(4-OMeC_6H_4)$_3$**	**THF**	**3b**	**70**
13	P-(4-OMeC_6H_4)$_3$	THF	**3c**	64


DavePhos


3a

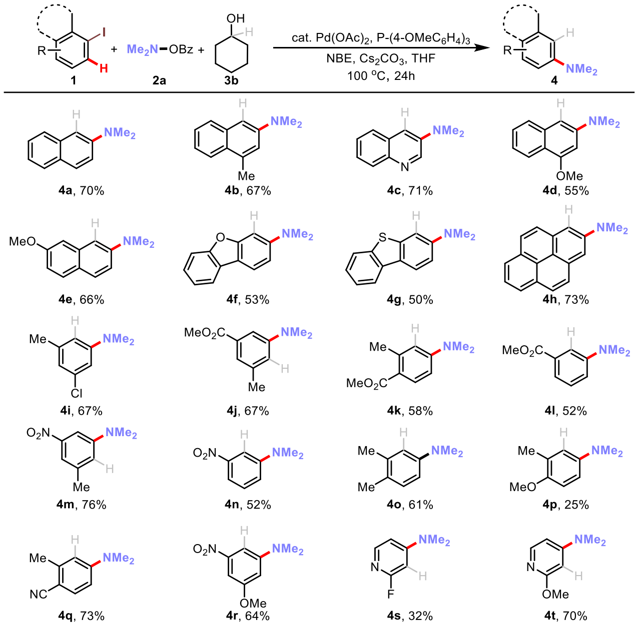

3b


3c

[a]Reaction conditions: substrate **1a** (0.2 mmol), **2a** (0.4 mmol), **3a** (0.24 mmol), $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), NBE (0.8 mmol, 4.0 equiv), Cs_2CO_3 (0.8 mmol, 4.0 equiv), solvent (3.0 mL), 100 °C, 24 h. Isolated yields.

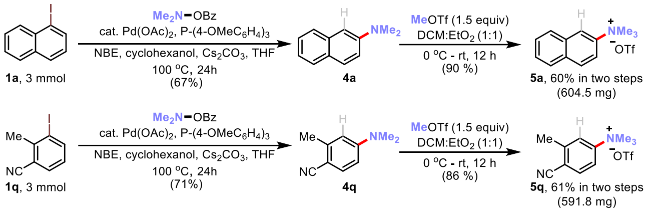
Firstly, we screened the catalytic system using iodine naphthalene as the substrate, NMe_2OBz as the electrophilic dimethylamination reagent, and isopropanol as the hydrogenation reagent (**Table 1**). After screening for base and temperature, the target product **4a** was obtained in 36% yield via *ortho* C-H dimethylamine/*ipso* hydrogenation of iodobenzene using palladium acetate as catalyst, triphenylphosphine as ligand, and cesium carbonate as base. Subsequently, various phosphine ligands were screened, and when P-(4-OMeC_6H_4)$_3$ was used as the ligand, the target product was obtained in 45% yield. Subsequently, we attempted various polar non-proton solvents such as DMSO, acetonitrile, DME, DMF, and tetrahydrofuran, and found that the yield increased to 65% when tetrahydrofuran was used as the solvent. Finally, we further attempted the hydrogenation reagents of cyclohexanol and borneol, and found that the target product **4a** can be obtained in 70% yield when cyclohexanol is used as the hydrogenation reagent.

Table 2. The Scope of Substrate[a]



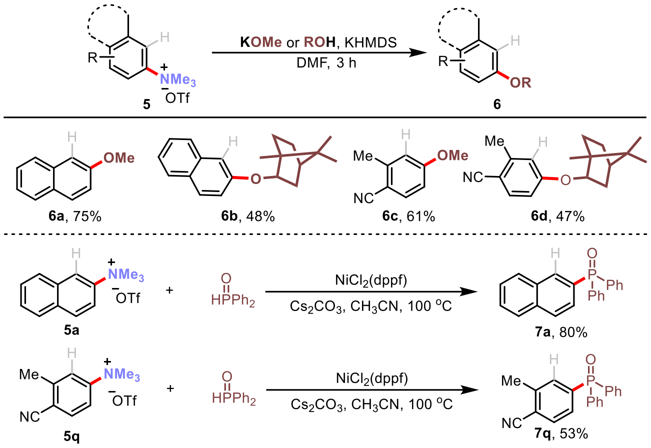
[a]Reaction conditions: substrate **1** (0.2 mmol), **2a** (0.4 mmol), **3b** (0.24 mmol), Pd(OAc)$_2$ (10 mol%), P-(4-OMeC_6H_4)$_3$ (20 mol%), NBE (0.8 mmol, 4.0 equiv), Cs_2CO_3 (0.8 mmol, 4.0 equiv), THF (3.0 mL), 100 °C, 24 h. Isolated yields.

After obtaining the optimal reaction conditions, we investigated the scope of the substrate. Various iodinated naphthalene obtained 2-naphthylamine products (**4a**-**4e**) with high yields, especially heterocyclic 3-aminoquinoline products that also was obtained using 4-iodoquinoline as a substrate. It is worth noting that due to the high reactivity at 1-site of naphthalene, the Friedel-Crafts reaction is difficult to react at the 2-site of naphthalene, so this method is a good supplement. In particular, the electrophilic substitution reaction of pyrene fused rings has poor site-selectivity, surprisingly, this method selectively obtained 2-amino substituted pyrenes. The substrate compatibility of non-fused cyclic iodobenzene is also good, and halogen (-Cl), nitro (-NO_2), ester (-CO_2Me), cyan (-CN), and methoxy (-OMe) were all suitable for this conversion. Importantly, pyridine derivatives (**1r**-**1t**) can also successfully obtain corresponding target products.



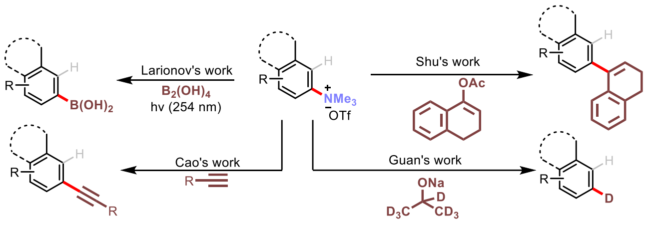
Scheme 4. Gram-level reaction and quaternary ammonium salt conversion

After investigating the substrate range, we conducted a gram-scale reaction. We obtained aryldimethylamine **4a** and **4q** in 67% and 71% yields using 3.0 mmol of iodobenzene as the substrate. Subsequently, by adding MeOTf, trimethyl quaternary ammonium salt precipitation can be directly obtained. This conversion is very simple and convenient, without the need for additional purification. Due to the relatively small amount of quaternary ammonium salts we synthesized, there was some loss during filtration and washing. According to literature reports, if expanded in large quantities, almost equivalent yield can be obtained. In the end, the yield of products **5a** and **5q** can be achieved by two steps of conversion, with a yield of over 60%.



Scheme 5. Oxylation and Phosphorylation

Quaternary ammonium salts can be used as active functional groups for derivatization. Here, we tried the coupling reaction of alcohol and quaternary ammonium salts. This reaction produced various oxoalkyl substituted aromatic products in high yields without transition metal catalysis (Scheme 5). The method is a good supplement to Dong's latest development of iodobenzene *ortho* C-H methoxylation reaction. Subsequently, we also attempted the phosphorylation reaction.



Scheme 6. Other Reported Quaternary Ammonium Salt Derivatization

In addition, the products of this method can also be combined with reported alkenylation, borylation, deuterization, alkynylation, etc of quaternary ammonium salts to solve all unresolved C-H functionalization reactions of Pd/NBE chemistry. For example, boronization, alkenylation, alkynylation and deuterization[27,28,30,31] (Scheme 6).

In summary, this report describes the use of a simple Pd/NBE catalytic system to achieve *ortho* C-H oxylation and phosphonylation and other functionalization of iodobenzene through templated conversion reactions. The key point of this method is to explore the previously unknown step of introducing dimethylamine in the ortho position of iodobenzene through C-H amination. Aryl dimethylamine is quickly converted to methyl quaternary ammonium salt precipitation, and methyl quaternary ammonium salt effectively avoids Hofmann elimination in the subsequent functionalization.

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Data availability

All data are available in the main text or the supplementary materials. Additional data are available from the corresponding authors upon request.

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