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Modular *ipso/ortho* Difunctionalization of Aryl Bromides via Palladium/Norbornene Cooperative Catalysis

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Supporting Information

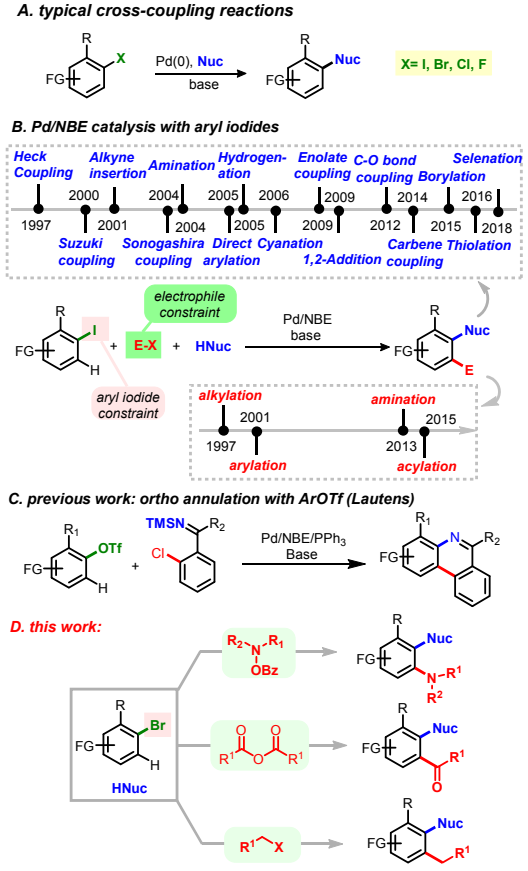
ABSTRACT: Palladium/norbornene (Pd/NBE) cooperative catalysis has emerged as a useful tool for preparing poly-substituted arenes; however, its substrate scope has been largely restricted to aryl iodides. While aryl bromides are considered as standard substrates for Pd-catalyzed cross coupling reactions, their use in Pd/NBE catalysis remains elusive. Here we describe the development of general approaches for aryl bromide-mediated Pd/NBE cooperative catalysis. Through careful tuning the phosphine ligands and quenching nucleophiles, *ortho* amination, acylation and alkylation of aryl bromides have been realized in good efficiency. Importantly, various heteroarene substrates also work well and a wide range of functional groups are tolerated. In addition, the utility of these methods has been demonstrated in sequential cross coupling/*ortho* functionalization reactions, consecutive Pd/NBE-catalyzed difunctionalization to construct penta-substituted aromatics and two-step *meta*-functionalization reactions. Moreover, the origin of the ligand effect in *ortho* amination reactions has been explored through DFT studies. It is expected that this effort would significantly expand the reaction scope and enhance the synthetic potential for Pd/NBE catalysis in preparing complex aromatic compounds.

INTRODUCTION

Poly-substituted aromatics are ubiquitously found in pharmaceuticals[1], agrochemicals[2] and organic materials.[3] During the past decades, cross-couplings[4] and nucleophilic aromatic substitutions[5] (S_NAr) have clearly become indispensable tools for preparing poly-functionalized arenes from readily available aryl halides through introducing a nucleophile at the *ipso* position (Scheme 1A). While powerful, these approaches typically only introduce one substituent at one time and the position of the newly installed functional group (FG) is dictated by the position of the halogen substituent.[6] As a complementary approach for arene functionalization using aryl iodides, palladium/norbornene (Pd/NBE) cooperative catalysis, namely Catellani-type reactions, allows for vicinal difunctionalization of arenes through coupling a nucleophile at the *ipso* position and an electrophile at the *ortho* position simultaneously (Scheme 1B).[7] It can be envisioned that, through using different combinations of nucleophiles and electrophiles, a diverse range of multi-substituted arene products would be easily obtained in one step from simple starting materials, thereby providing a modular approach for *ipso/ortho* difunctionalization. However, there have been some long-lasting constraints in Pd/NBE catalysis that have limited its practical applications in synthesis.

Important contributions by Catellani, Lautens and others have demonstrated that, analogous to the cross coupling reactions, a broad range of nucleophiles can be coupled at the *ipso* position, which include Heck coupling,[7a,8] Suzuki coupling,[9] alkyne insertion,[10] Sonogashira coupling,[11] cyanation,[12] direct arylation,[13] amidation[14]/amination,[15] aryl ether formation,[16] hydrogenolysis,[17] enolate coupling[18], 1,2-addition to carbonyl group,[19] vinylation with hydrazone,[20] borylation,[21] thiolation,[22] and selenation[23] (Scheme 1B). However, compared to the highly versatile *ipso*-coupling, the scope of the electrophiles that can be introduced at the *ortho* position had been primarily restricted to alkyl and aryl halides since the seminal works by Catellani in 1997[7a] and 2001[10a]. In addition, except a single elegant report by Lautens on aryl triflate-mediated annulation reaction[24] (Scheme 1C), the arene substrates in Catellani-type reactions have been limited to aryl iodides, and use of aryl bromides remained elusive.

Scheme 1. Arene Functionalization with Aryl Halides



Such constraints might be better understood from the proposed catalytic cycle (Figure 1). It starts with oxidative addition of Pd(0) into the aryl-iodide bond (Step A), followed by *syn*-migratory insertion[25] into NBE (Step B) and C−H metalation, to generate an aryl-NBE-palladacycle (**ANP**)[26] (Step C), which can react with an electrophile to introduce a FG at the *ortho* position[27] (Step D). The following de-insertion of NBE through β-carbon (β-C) elimination gives a more sterically hindered aryl-palladium species[28] (Step E), which disfavors NBE re-insertion compared to the aryl-palladium species from Step A; thereby, it is persistent enough to be attacked by the nucleophile selectively to furnish the *ipso* functionalization and regenerate the Pd(0) catalyst[7a] (Step F). Thus, to successfully implement the Pd/NBE catalysis, the electrophile employed should selectively oxidize or react with the **ANP** Pd(II) intermediate instead of the electron-rich Pd(0) catalyst (Step G); on the other hand, the aryl halide substrate must selectively react with the Pd(0) instead of **ANP** to avoid self-dimerization (Figure 1B). Given the simultaneous presence of two oxidants (aryl halides and the electrophiles) and two electron-rich Pd species (Pd(0) and **ANP**), developing new *ortho* functionalization with expanded electrophile and aryl halide scopes is not a trivial issue.[7g]

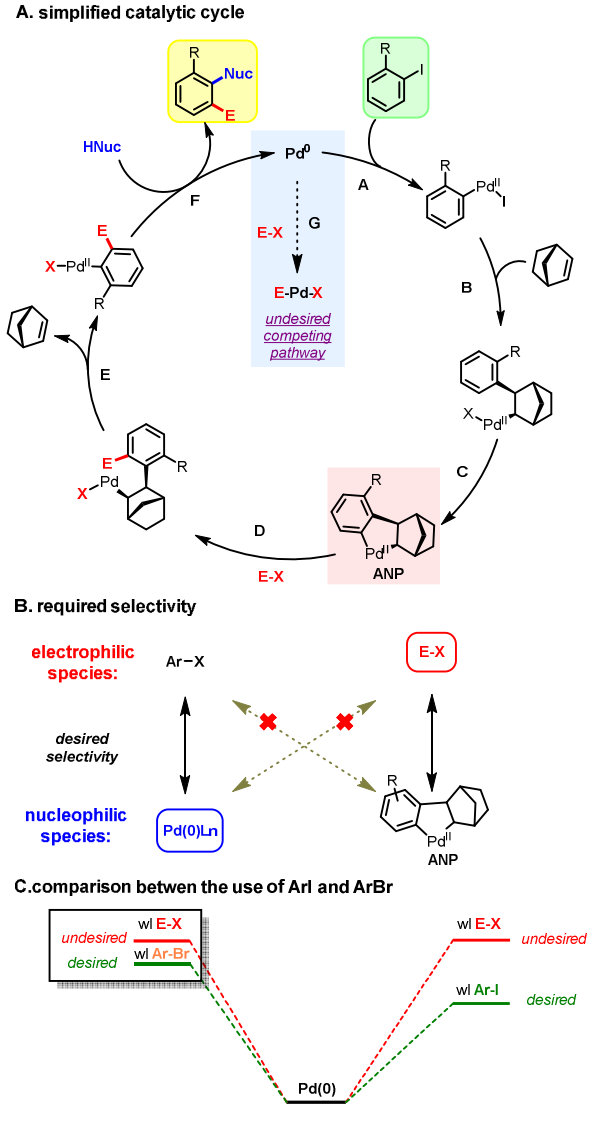


Figure 1. Mechanistic considerations.

To address the challenge of the "electrophile constraint", we hypothesized that electrophiles that have certain coordinating capability with the more Lewis acidic Pd(II) center at **ANP** might be suitable to afford desired selectivity in the Pd/NBE catalysis. In 2013 we reported our preliminary study of developing *ortho* amination using *O*-benzoyl hydroxylamines as the electrophile[29], illustrating that heteroatoms can be introduced to arene *ortho* positions (Scheme 1B). Subsequently, a series of elegant works on *ortho* amination-based different *ipso* functionalization have been disclosed.[21,30] In 2015, the Liang, Gu and our laboratories concurrently described *ortho* acylation using anhydrides as the electrophiles.[31] Recently, *ortho* acylation/*ipso* thiolation with thioesters[22] and *ortho* carboxylation with carbonate anhydrides[32] were reported by Gu and us respectively.

The challenge of the "aryl iodide constraint" may seem to be rather surprising, as aryl bromides have proved to be a suitable coupling partner in the Pd-catalyzed cross-coupling reactions for more than three decades.[33] It is well known that aryl bromides undergo significantly slower oxidative addition with Pd(0) than aryl iodides,[34] which inevitably increases the chance for the "external" electrophile to compete for the oxidation with Pd(0) (Figure 1C). Thus, it is reasonable to imagine the catalytic conditions that work well for aryl iodides may not work for aryl bromides.[35] Hence, fine-tuning of the steric and electronic properties of the Pd(0) catalyst that can selectively accelerate certain steps in the catalytic cycle, e.g. oxidative addition (Step A) and β-C elimination (Step E), would become critical to enable the reactions with aryl bromides.

From a practicality viewpoint, aryl bromides are generally cheaper and more accessible than the corresponding aryl iodides.[36] In addition, for heterocycles and complex nature product derivatives, the aryl bromides are often more stable towards light or heat.[37] Moreover, availing the Pd/NBE catalysis with aryl bromides could also enable sequential cross coupling/*ortho* functionalization reactions or consecutive difunctionalization with polyhaloarenes[38] (*vide infra*, Scheme 9). Therefore, efficient and general methods for *ipso*/*ortho* difunctionalization of aryl bromides via Pd/NBE catalysis would be attractive.

In this article, we describe systematic efforts for developing various *ortho* functionalization reactions with different classes of electrophiles using aryl bromides as substrates (Scheme 1D). Diverse *ipso*–functionalization with different nucleophiles has also been exemplified. These methods have allowed for rapid access of a broad range of poly-substituted arenes and heteroarenes with complete control of site-selectivity.

RESULTS AND DISCUSSION

2.1 *Ortho* amination

In 2004 Johnson and coworkers reported a seminal study on copper-catalyzed electrophilic amination between *O*-benzoyl hydroxylamines and organozinc reagent.[39] Yu and coworkers described the first Pd-catalyzed C−H amination using *O*-benzoyl hydroxylamines in 2011.[40] Inspired by these important works, we found *O*-benzoyl hydroxylamines could serve as an excellent electrophile for Pd/NBE catalysis. In combination with isopropanol as the hydride reductant, the *ortho* amination/*ipso* hydrogenation with aryl iodides was developed in 2013.[29] Using different nucleophiles as quenching reagents, various *ipso* functionalization reactions based on *ortho* amination have been developed (Figure 2), including Mizoroki-Heck reaction with olefins,[30a,f] vinylation with hydrazines,[30b] Suzuki coupling with aryl and alkyl boronic acids,[30c,g] Sonogashira reaction with alkynes,[30d,e] Miyaura borylation with diboranes,[21] cyanation with cyanides,[30h,i] ketone α-arylation with enol equivalents,[30j] dearomatization with phenols[30k] and intramolecular amidation with amides.[30l] It is clear that the *ortho* amination chemistry holds broad applicability and potential for practical utility;[41] however, aryl iodides have been the sole

substrates employed in these reactions except a single example in our *ortho* amination/*ipso* reduction report using a special electron-deficient aryl bromide.[29]

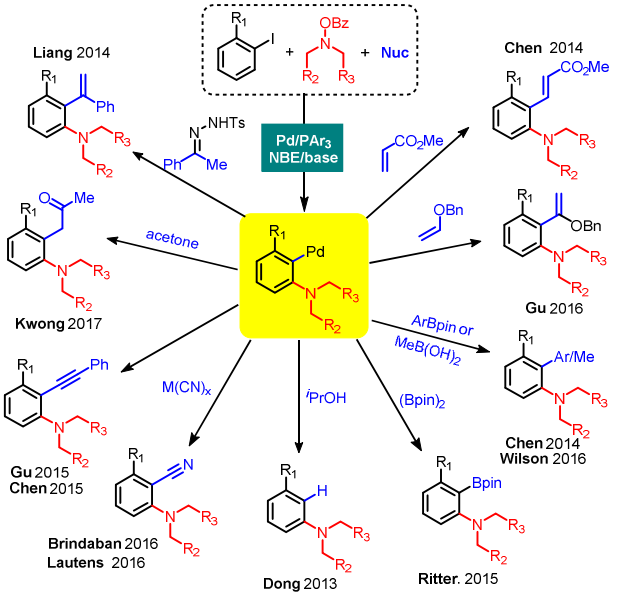
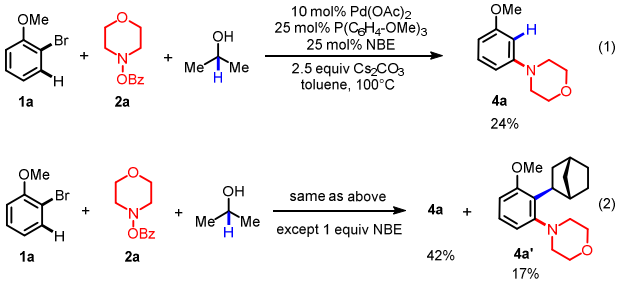


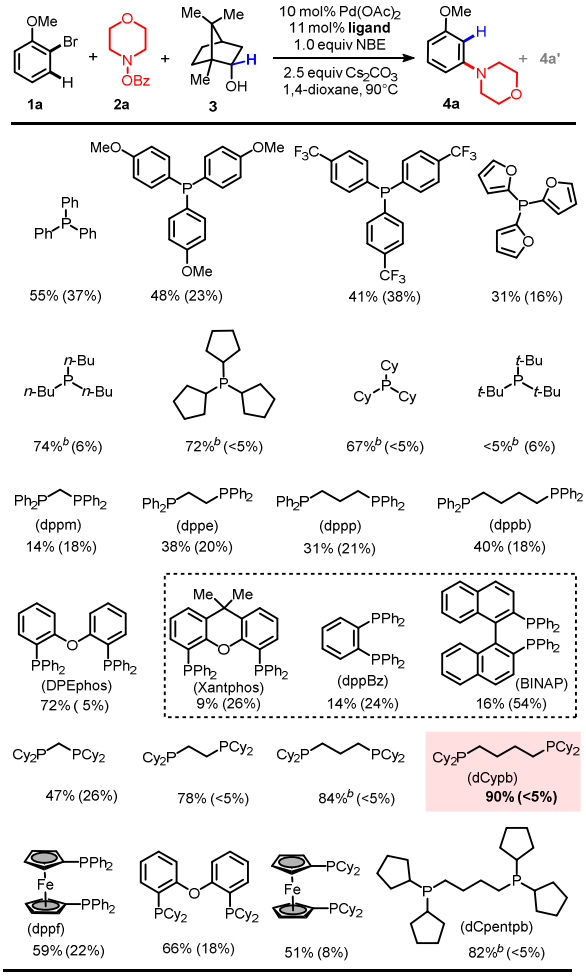
Figure 2. Examples of intermolecular *ortho* amination of aryl iodides.

To explore a general *ortho* amination method with aryl bromides, 2-bromoanisole **1a** was employed as the model substrate and the *ipso* hydrogenation was chosen as the model reaction. Under the previously reported conditions for aryl iodides,[29] poor mass balance of aryl bromide and low yield of desired product **4a** were observed (Eq 1). Further effort to optimize the reaction identified that the major side-product was NBE-attached reduction compound **4a'** (Eq 2). The formation of **4a'** indicated that β-C elimination of NBE from the Pd(II) center was slower than hydride transfer from the alcohol reductant. We proposed that more sterically hindered secondary alcohol could significantly decrease the β-hydrogen (β-H) elimination speed thereby diminishing the side-product formation. After further examining the reaction conditions, bulky (−)-borneol **3** and 1,4-dioxane was found to be a better reductant and solvent combination for a balanced reactivity and selectivity.



Ligand effect: The ligand effect was then carefully investigated. The yields with mono-dentate phosphines were generally moderate with a significant amount of **4a'** formed (Table 1). Compared to triaryl phosphines, trialkyl phosphines appear more selective with minimal **4a'** observed, and by large, electron-rich ligands gave higher yields for the desired product **4a**. Extremely bulky ligands, such as P*t*Bu$_3$, gave a trace amount of desired product. It is rather surprising that bidentate ligands worked well in this case, as they are typically less effective than monodentate ligands when aryl iodides were used as substrates.[7e] In particular, bidentate phosphine ligands with a flexible backbone, such as dppb and DPEphos, gave reasonably good yields. On the contrary, those with a rigid backbone, such as dppBz, Xantphos and BINAP, gave NBE-attached compound **4a'** as the major product, which indicates that rigid phosphine ligands likely disfavored NBE extrusion. Meanwhile, the flexible backbone may allow one phosphine moiety dissociates[42] and leaves a vacant site for NBE coordination and subsequent transformations.[43] Inspired by the fact that PCy$_3$ gave higher yield than PPh$_3$, several bidentate trialkylphosphines were then tested. Gratifyingly, the dCypb ligand gave the desired product in 90% yield, though the same trend was not observed for DPEphos and dppf-type ligands. In addition, the analogous dCpentapb ligand gave a slightly lower yield, which later proved to be more efficient for other substrates.

Table 1. The Ligand Effect for Ortho Amination with Aryl Bromides[a]



[a] Run on a 0.2 mmol scale (0.1 M) for 14 h with 1.6 equiv of **2a** and 1.0 equiv of **3**; yields were determined by ^{1}H-NMR using 1,3,5-trimethoxylbenzene as the internal standard. The number in parentheses refers to the yield of side-product **4a'**. For monodentate phosphines, the loading was 22 mol% instead of 11 mol%. [b] The corresponding HBF$_4$ salts were used. Cy, cyclohexyl.

To investigate the origin of ligands effects on the selectivity between the desired product **4a** and the NBE-attached side-product **4a'**, DFT studies were subsequently carried out (Figure 3). In particular, we focused on the differences between alkyl- and aryl-phosphines as well as the effects of large bite-angle bidentate ligands. Therefore, dCypb, PCy$_3$, and PPh$_3$ were chosen as the model ligands in the computational study. Given that the NBE-attached compound **4a'** is the major side-product, we computed

the competing β-C elimination pathway (product **4a** formation) from carboxylate intermediate **I** and β-H elimination (side-product **4a'** formation) pathway from alkoxide intermediate **II** (Figure 3).[44]

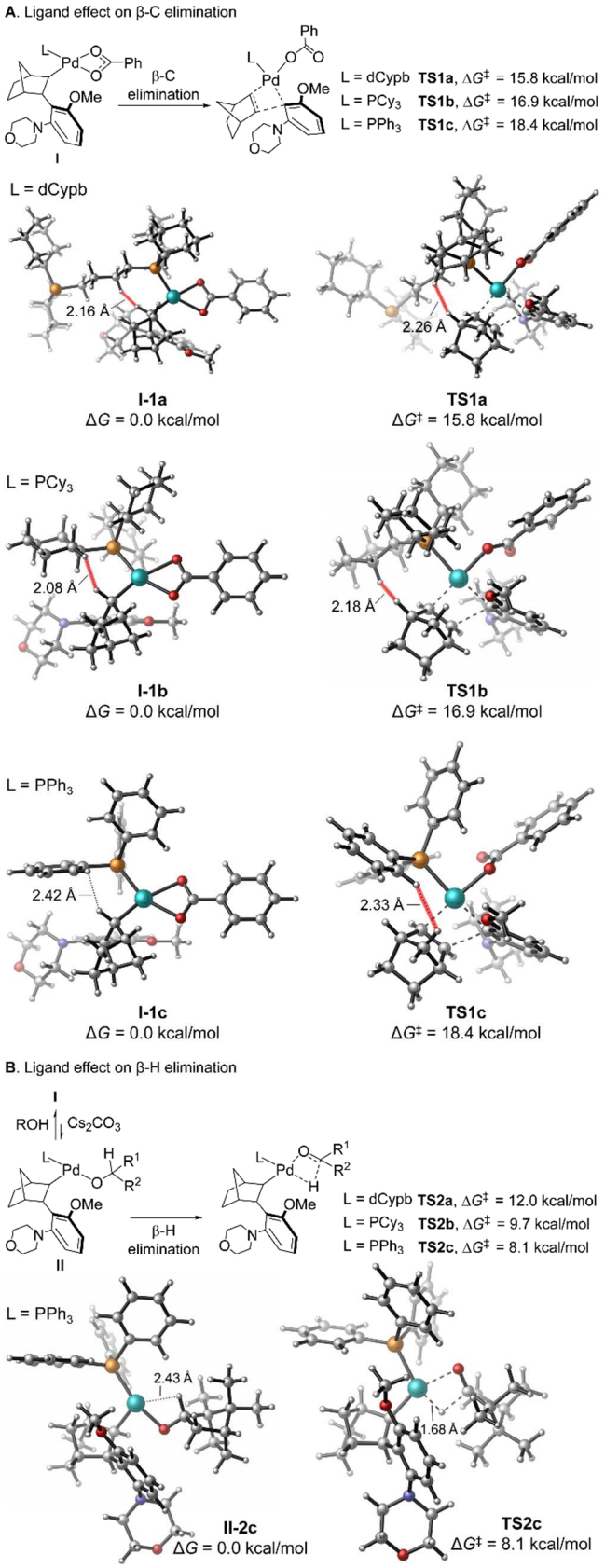


Figure 3. Computed barriers of β-C elimination and β-H elimination from the Pd(II) complexes supported by dCypb, PCy_3, and PPh_3 ligands. Activation free energies of β-C elimination are with respect to complex **I** and activation free energies of β-H elimination are with respect to complex **II**. Calculations were performed at the M06/SDD–6-311+G(d,p)-SMD(1,4-dioxane)//B3LYP/LANL2DZ–6-31G(d) level of theory.

According to the DFT calculations, the activation energies of both the β-C and β-H elimination pathways are affected by the choice of ligand, and the reactivity trends in these pathways are different. The β-C elimination (**TS1a-b**, Figure 3A) is promoted by the use of alkylphosphine ligands (dCypb or PCy_3), consistent with the greater experimental yields of **4a** with these ligands.[45] Here, the larger cone angle of PCy_3 (179°) compared to that of PPh_3 (145°) facilitates the elimination of NBE. This steric effect is evidenced by the short distance between the PCy_3 ligand and the α-hydrogen on the norbornyl group in intermediate **I-1b** (2.08 Å). A similar steric repulsion is observed in intermediate **I-1a** with the monodentate dCypb ligand (2.16 Å), which accounts for the lower barrier for the β-C elimination. It should be noted that bulkier ligands do not always lead to a lower barrier to the β-C elimination, as PCy_3 is slightly less effective than dCypb. In addition, extremely bulky ligands (*e.g.* P(*t*-Bu)$_3$) actually destabilize the β-C elimination transition state by causing severe repulsions with the bridgehead hydrogen on the norbornyl group (see Figure S2 for details). Among the ligands investigated computationally, the monodentate dCypb is the most effective in β-C elimination due to its optimum steric environment. In other words, if the ligand is not sufficiently bulky, the intermediate prior to β-C elimination would be too stable; if the ligand is too sterically hindered, the transition state for the β-C elimination would be of high energy. Thus, both extreme situations lead to a higher activation barrier for β-C elimination.

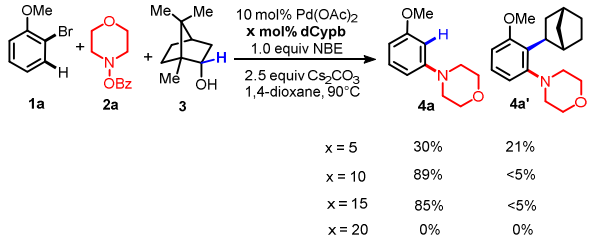
In the β-H elimination pathway, the trend is opposite. The PPh_3 ligand was found to exhibit the lowest activation energy, which is consistent with the relatively high yield of **4a'** with this ligand. Instead of a four-coordinated Pd(II) intermediate (**I**), the β-H elimination was found to occur through a three-coordinated Pd(II) intermediate (**II**) (Figure 3B). The use of sterically hindered and electron-rich ligands (dCypb and PCy_3) stabilizes the three-coordinated alkoxide complex **II**, and thus slows down the β-H elimination.[46] Hence, the β-H elimination from the PPh_3-ligated complex **II-2c** requires the lowest barrier among the three Pd(II) alkoxide complexes. Collectively, the computational study suggests that the reactions with bulky and electron-rich alkyl phosphine ligands, such as dCypb and PCy_3, favor **4a** over **4a'** because these ligands can both promote the β-C elimination and inhibit the β-H elimination.

We also computationally investigated the reactivity of the Pd(dCypb) complex in the oxidative addition of aryl bromide **1a**. In this elementary step, the barrier to the oxidative addition with the Pd(dCypb) catalyst is 8.6 kcal/mol lower than that with Pd(PCy_3)$_2$ (**TS4** vs **TS3**, see details in Figures S5 and S6). The high reactivity with the dCypb ligand in the oxidative addition step is due to the pre-distorted geometry of the Pd(0) catalyst with bidentate phosphine ligands that reduced the catalyst distortion energy in the transition state. Taken together, these DFT calculations indicate the dCypb ligand is effective in controlling the chemoselectivity in the β-C elimination step and enabling rapid oxidative addition of aryl bromides.

The Pd/P ratio also appeared to be important for this transformation. Different loadings of dCypb were tested under the otherwise standard conditions (Scheme 2). When 5 mol% of dCypb ligand was used (Pd/P = 1:1), a complex mixture was formed with a poor conversion of aryl bromide **1a**. The 1:2 and 1:3 Pd/P ratios

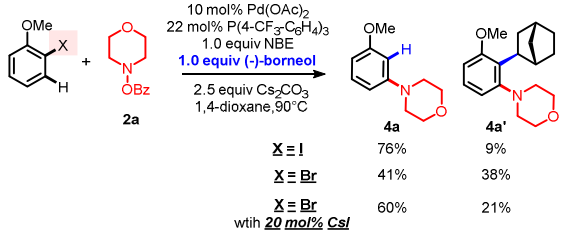
both proved to be efficient giving comparable yields of the desired product. In contrast, a 1:4 Pd/P ratio completely inhibited the reaction, giving nearly no conversion of both starting materials. We reasoned that excess phosphine ligands would suppress formation of the coordinatively unsaturated 14-electron Pd(0) species (*vide supra*, Figure 4), which in turn would inhibit the oxidative addition with aryl bromides.

Scheme 2. The Ligand Ratio Effect



Halide effect: Besides the oxidative addition (Step A, Figure 1A), we found, switching from aryl iodides to aryl bromides, the steps after C−N bond formation could also be affected. For example, 2-iodoanisole gave 76% of the desired amination product **4a** with only 9% NBE-attached side-product **4a'** when using tri(4-trifluoromethylphenyl)phosphine as the ligand. However, 2-bromoanisole gave 41% **4a** and 38% **4a'** under the same reaction conditions (Scheme 3). Considering the large difference of the **4a**/**4a'** ratios in these results, we hypothesized that the halide leaving group from the substrate likely influenced the steps after the reaction of **ANP** with the amine electrophile. To test this hypothesis, 20 mol% CsI was added to the reaction with aryl bromide under the otherwise identical conditions. Indeed, the **4a**/**4a'** ratio was significantly improved from nearly 1:1 to 3:1.[47]

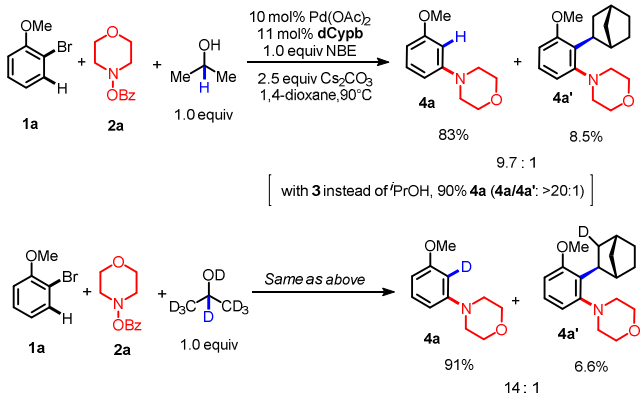
Scheme 3. The Iodide Effect for Aryl Bromide Substrates



Regarding this halide effect, we tentatively propose that the iodide anion may either promote the β-C elimination or inhibit the β-H elimination. It has been known for the reactions with platinum complexes [PtX(alkyl)(diphosphine)] (X = Cl, Br, I) that the one with iodide as the X ligand gives faster β-H elimination than those with bromide and chloride.[48] However, a more detailed mechanistic explanation remains to be disclosed at this stage.[49]

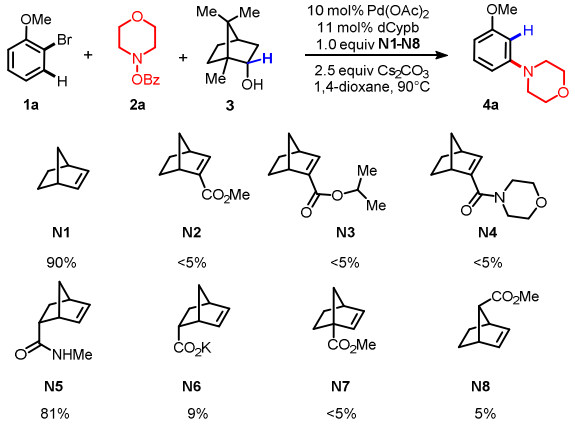
Reductant effect: Clearly, besides promoting β-C elimination, slowing down the β-H elimination should also help to minimize formation of undesired product **4a'**. Indeed, increasing the steric of the reductant (secondary alcohols) from isopropanol to the (−)-borneol **3** decrease formation of **4a'**. More interestingly, using the corresponding deuterated alcohol, i.e. d_8-isopropanol, that should give a slower β-H elimination than the normal isopropanol, the ratio of **4a**/**4a'** was also enhanced (Scheme 4). Altogether, the observed reductant effect is consistent with the hypothesis that slow β-H elimination would inhibit formation of NBE-attached side-product **4a'**.

Scheme 4. The Isotope Effect of the Reductant



NBE Effect: Besides simple NBE, a variety of substituted NBEs have also been examined under the optimal reaction condition (Scheme 5). For example, Yu and coworkers demonstrated that methyl norborne-2-carboxylate (**N2**) is particularly effective in the Pd/NBE-catalyzed *meta* C−H functionalization reactions.[50] In the Catellani-type annulation between aryl iodides and epoxides, we recently found the **N3** was more selective than regular NBE.[51] However, for the reaction with aryl bromide **1a** all the electron-deficient norborne-2-carboxylates (**N2**-**N4**) only gave a trace amount of the desired product **4a**. The *endo*-5-norborne-2-carboxamide **N5**, previously used in the *ortho* acylation,[31b] gave a slightly lower yield. The 5-norbornene-2-carboxylic acid potassium salt (**N6**), recently employed by Zhou and coworkers,[52] led to a low yield probably due to its poor solubility in 1,4-dioxane. Finally, ester substitutions at NBE different positions (**N7** and **N8**) also showed low activity.

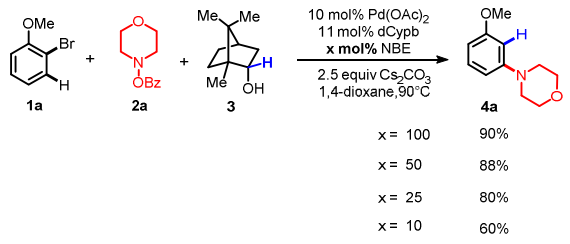
Scheme 5. The NBE Substitution Effect[a]



[a] Run on a 0.2 mmol scale (0.1 M) for 14 h with 1.6 equiv of **2a** and 1.0 equiv of **3**; yields were determined by ^{1}H-NMR using 1,3,5-trimethoxylbenzene as the internal standard.

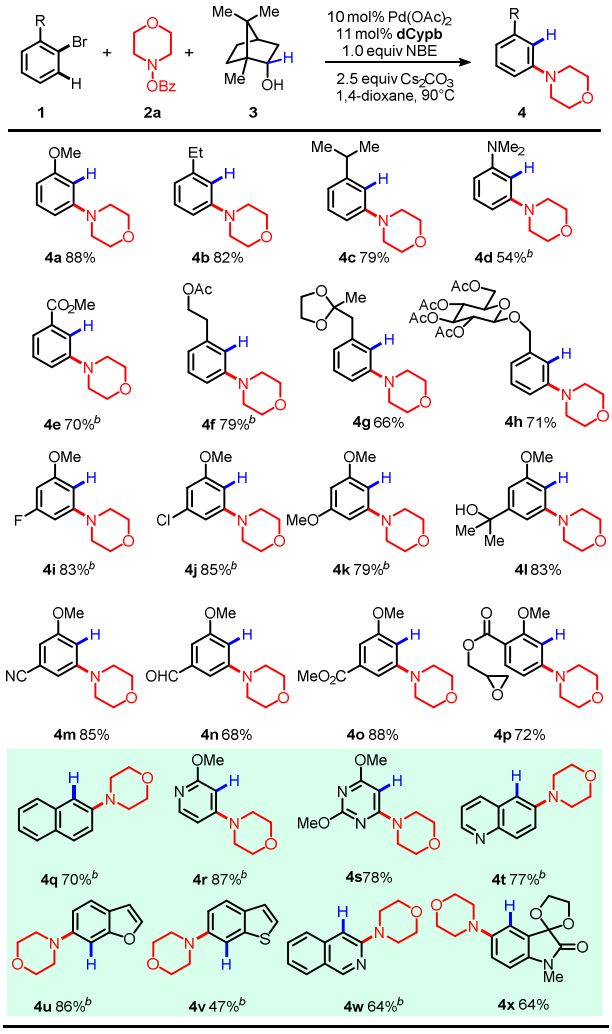
Since simple NBE (**N1**) gave the best result, the use of a catalytic amount of NBE was then attempted under the otherwise standard reaction conditions (Scheme 6). While 1 equiv of NBE gave the highest efficiency, decreasing the loading to 50 or 25 mol% gave similar or comparable yields. Interestingly, when 10 mol% of NBE was used instead (Pd:NBE =1:1), 60% yield of product **4a** was still obtained, suggesting that NBE indeed behaved as a co-catalyst in this transformation. Due to the convenience and low cost of NBE, 1 equiv of NBE was employed subsequently to explore the substrate scope.

Scheme 6. Examination of the NBE Loading [a]



[a] Run on a 0.4 mmol scale (0.1 M) for 14 h with 1.6 equiv of **2a** and 1.0 equiv of **3**; yields were determined by ^{1}H-NMR using 1,3,5-trimethoxylbenzene as the internal standard.

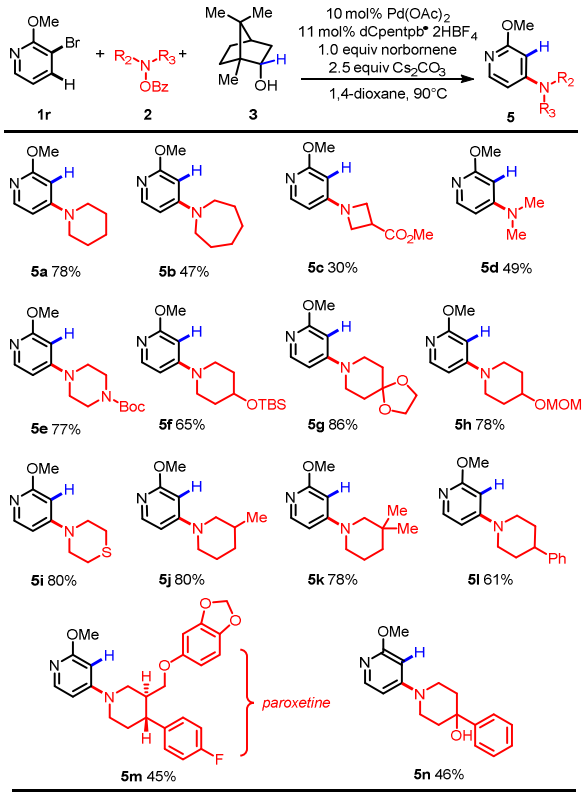
Table 2. Aryl Bromide Scope for *Ortho* Amination[a]



[a] Run on a 0.3 mmol scale (0.1 M) for 14 h with 1.6 equiv of **2a** and 1.0 equiv of **3**. All yields are isolated yields. [b] 11 mol% dCpentapb·2HBF$_4$ was used instead of dCypb.

Substrate scope: With the optimized reaction conditions in hands, the scope of aryl bromides was investigated next (Table 2). We first tested different FGs at the *ortho* position of aryl bromides. Both electron-rich (**4a**, **4d**) and -deficient (**4e**) substrates smoothly gave the desired products in good yields. Bulky substituents at the *ortho* position, such as *iso*propyl (**4c**) and ketal (**4g**), were tolerated. Ester, ketal and glycoside moieties proved compatible under the reaction conditions (**4f-h**). The FG tolerance was further examined with different 2-bromoanisole derived substrates (**4i-p**). A broad range of FGs, including methoxy ether (**4k**), fluoride (**4i**), chloride (**4j**), free tertiary benzyl alcohol (**4l**), nitrile (**4m**), aldehyde (**4n**), methyl ester (**4o**) and epoxide (**4p**), are tolerated. The scope can be further expanded to naphthalene and heteroarenes. Bromo-substituted pyridine (**4r**), pyrimidine (**4s**), quinoline (**4t**), benzo[b]furan (**4u**), benzo[b]thiophene (**4v**), isoquinoline (**4w**) and protected isatin (**4x**) all delivered the desired *ortho* amination products in reasonably good yields, therefore showing promise for medicinal chemistry applications. Note that for certain substrates the dCpentpb ligand gave slightly higher yields.

Table 3. *O*-Benzoyl Hydroxylamine Scope for *Ortho* Amination[a]

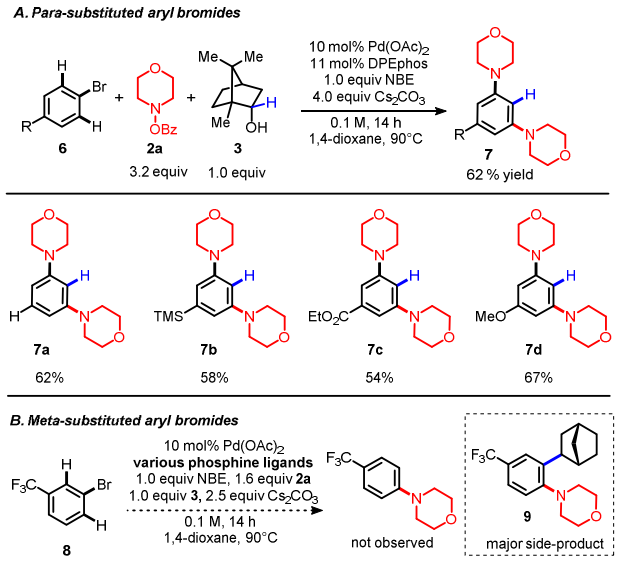


[a] Run on a 0.3 mmol scale (0.1 M) for 14 h with 1.6 equiv of **2** and 1.0 equiv of **3**. All yields are isolated yields.

We then continued to explore the scope of the amine coupling partners, and bromopyridine **3r** was used as the model substrate (Table 3). Piperidine, azepane, dimethylamine, azetidine and Boc-protected piperazine-derived amination reagents all provided the desired products in moderate to good yields (**5a-5e**). Additional FG tolerance was observed with alkyl sulfide (**5i**), tertiary benzylic alcohol (**5n**), TBS and MOM-protected secondary alcohols (**5f** and **5h**), carbamate (**5e**) and benzodioxole (**5m**). The protected 4-piperidone moiety (**5g**) could be converted to free aniline through ketal hydrolysis and retro-aza-1,4-addition.[21,53] The complex *O*-benzoyl hydroxylamine, derived from commercial drug paroxetine, was successfully coupled to give an interesting product (**5m**).

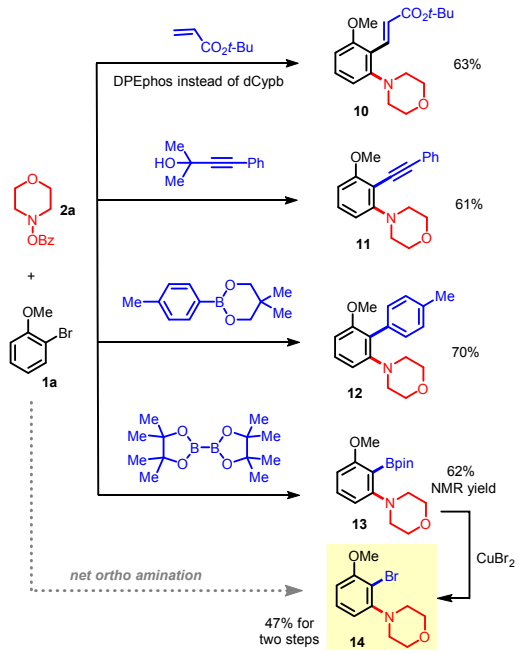
Besides *ortho*-substituted aryl bromides, *para* and *meta*-substituted substrates have also been evaluated (Scheme 7). Similar to the prior observation when using aryl iodides,[29] *para*-substituted aryl bromides afforded the 1,3-diaminated products. It is noteworthy that no mono-amination product was observed in all the cases. *Meta*-substituted aryl bromides, such as the 1-bromo-3-isopropylbenzene and 3-bromobenzotrifluoride **8**, did not give either mono- or di-substituted products; instead, the NBE-attached compound (**9**) was formed as the major side-product.

Scheme 7. *Ortho* Amination of Aryl Bromides without *Ortho* Substitution



Other *ipso* functionalization: Besides coupling with hydride as the nucleophile, other classes of *ipso* coupling with different nucleophiles also worked smoothly using large-bite-angle ligands with flexible backbones (Scheme 8). DPEphos proved to be a better ligand than dCypb for Chen's *ipso* Mizoroki-Heck *ortho* amination reaction.[30a] Sonogashira quench with masked terminal acetylides[30e] afforded the desired alkynylation product. Neopentyl diol-derived boronates were found to be a better coupling partner to deliver *ipso* arylation products.[30c] Finally, Ritter's *ipso* borylation with $B_2(pin)_2$ also provided the desired aryl boronic ester **13**.[21] Due to its instability on column chromatography, compound **13** was further transformed to the corresponding aryl bromide (**14**),[54] offering an intriguing net-*ortho* amination of **1a**.

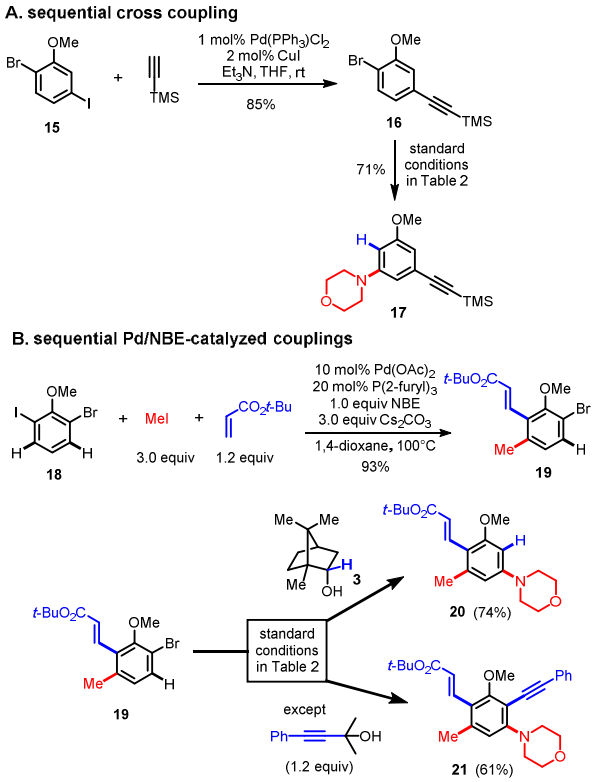
Scheme 8. Different Ipso Functionalization in the Ortho Amination of Aryl Bromidesa



[a] The reactions were operated using the conditions described in Table 2 except replacing alcohol **3** with the corresponding nucleophiles.

Synthetic applications: The synthetic utility of this method was then tested. Sequential cross-coupling[55] plays an important role in synthesis of complex aromatic compounds and is often employed in pharmaceutical research.[56] Using commercially available bromo-iodoarene **15**, selective coupling at the iodide site via Sonogashira reaction afforded alkyne **16**. Subsequently, *ortho* amination occurred smoothly to afford 3,5-disubstituted anisole **17** (Scheme 9A). Hence, the ArBr-based Pd/NBE catalysis offers an additional option for preparing *meta*-substituted arenes.

Scheme 9. Synthetic Utility of ArBr-Based *Ortho* Amination.

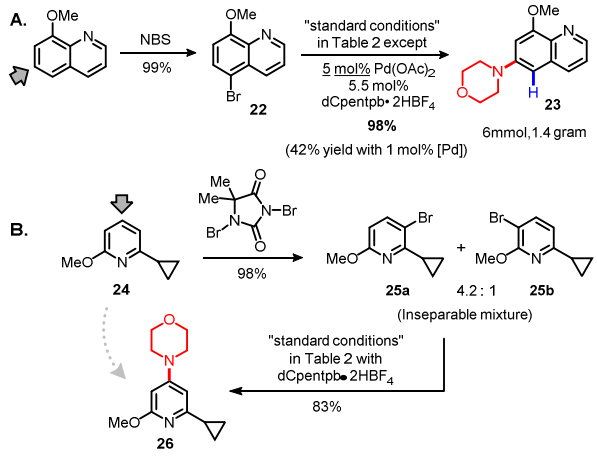


Encouraged by the success of the sequential cross-coupling, we envisioned that merging the classical ArI-based Catellani reaction with the current ArBr-based method would realize a rapid access to multi-and diverse-substituted aromatic compounds from polyhaloarenes. Starting with 2-bromo-6-iodoanisole **18**, *ortho* methylation/*ipso* Heck reaction,[30g] followed by *ortho* amination with either hydride or Sonogashira quench, provided tetra- or penta-substituted arenes efficiently (Scheme 9B). It is noteworthy that for the penta-substituted product (**21**) all the five substituents are different from each other, containing all three hybridized forms of carbons (*sp* to *sp*^{3}), oxygen and nitrogen groups. To the best of knowledge, this represents the first example of combining two different Pd/NBE catalysis reactions into a single arene substrate, showing promise for efficient generation of a diverse range of poly-substituted arenes.

Finally, this method is applied in a two-step *meta*-amination of heterocycles. One merit of this protocol is the avoidance of using directing groups.[50b,f,57] Bromination of the commercially available 8-methoxyquinoline with NBS gave exclusively C5-brominated product **22** in nearly a quantitative yield (Scheme 10A). Subsequent *ortho* amination afforded C6-aminated quinoline **23** in 98% yield on a gram scale with 5 mol% Pd. Further lowering the Pd

loading to 1 mol% still gave the desired product with 42 turnovers. On the other hand, amination of pyridine **24** resulted in an inseparable mixture of 4.2: 1 regio-isomers; however, directly subjecting this mixture to the *ortho* amination conditions provided a *single* regioisomer of the C4-amination product **26** in 83% yield (Scheme 10B). It is worthy to mention that an alternative route to product **26** could be through the Ir-catalyzed C−H borylation of pyridine **24**,[58] followed by electrophilic amination[59] or Chan−Evans−Lam coupling.[60]

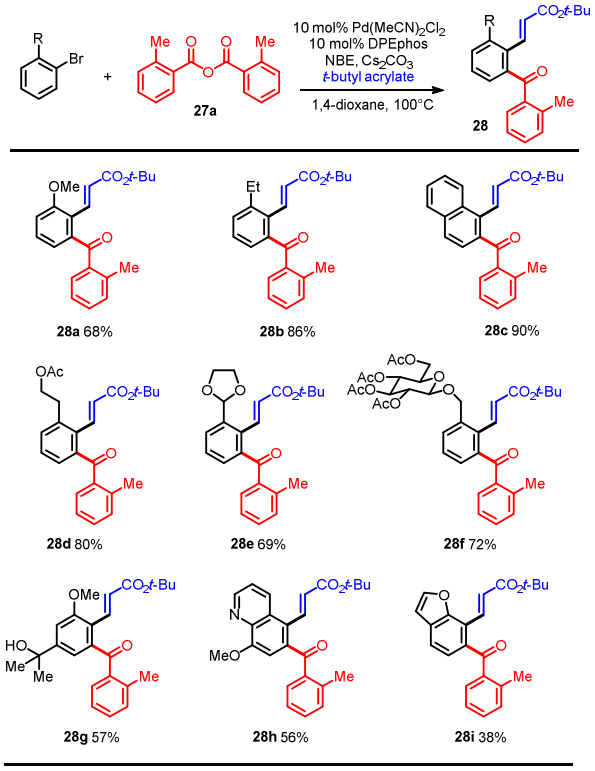
Scheme 10. Stepwise *Meta*-Amination of Heterocycles



2.2 *Ortho* acylation. In 2015, we reported an initial study on *ortho* acylation/*ipso* hydrogenation using a bifunctional mixed anhydride.[31b] Concurrently, the Liang and Gu groups developed *ortho* acylation/*ipso* Heck using symmetrical anhydrides or acyl chlorides as electrophiles.[31a,c] In all these cases, only aryl iodides were used as substrates, and the electron-deficient less bulky trifurylphosphine was found to give the best results.[61] To enable the use of aryl bromides as substrates, *ortho* acylation/*ipso* Heck coupling was chosen as the model reaction. Unsurprisingly, applying the trifurylphosphine conditions directly to aryl bromides led to very low conversion. To our delight, analogous to the *ortho* amination reaction, large bite-angle bidentate phosphine ligands with flexible backbones also worked well for the *ortho* acylation. A survey of ligand effects revealed DPEphos to be optimal.

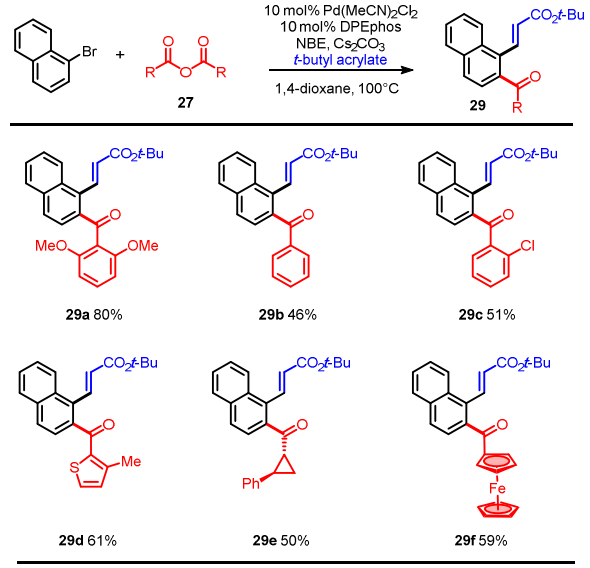
The aryl bromide scope was then explored using anhydride **27a** as the coupling partner (Table 4). A range of substituents and FGs, such as ketals (**28e**) and tertiary alcohols (**28g**), could be tolerated on the arene substrates. Quinoline (**28h**) and benzofuran-derived (**28i**) substrates also participated in this transformation. When 1-bromonaphthylene was used, 90% yield of the desired acylation product (**28c**) was obtained. The acid anhydride scope is also reasonably broad (Table 5). Sterically hindered anhydrides, such as 2-methyl and 2,6-dimethoxyl benzoic anhydrides (**29a**), gave significantly higher yields than the simple benzoic anhydride (**29b**). Aryl chloride (**29c**) is compatible in this reaction. Heteroarenes, such as thiophene (**29d**), and ferrocenes (**29f**) were also tolerated. Besides aromatic acyl groups, the cyclopropyl-derived one was also successfully introduced with aryl bromides (**29e**), in which epimerization was not observed.

Table 4. Aryl Bromide Scope for *Ortho* Acylation/*Ipso* Heck Reaction[a]



[a] Run on a 0.3 mmol scale (0.1 M) for 14 h with 1.8 equiv of **27a**, 1.0 equiv of **3**, 1.5 equiv of *t*-butyl acrylate, 2.0 equiv of NBE and 3.0 equiv of Cs_2CO_3; all yields are isolated yields.

Table 5. Carboxylic Acid Anhydride Scope[a]



[a] Run on a 0.3 mmol scale (0.1 M) for 14 h with 1.8 equiv of **27**; 1.0 equiv of **3**; 1.5 equiv of *t*-butyl acrylate, 2.0 equiv of NBE and 3.0 equiv of Cs_2CO_3; all yields are isolated yields.

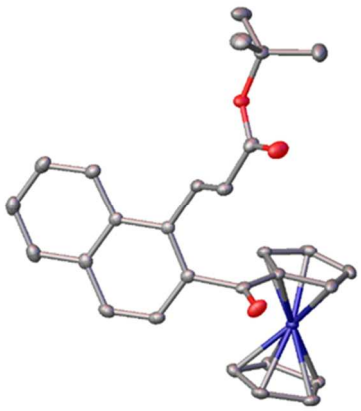
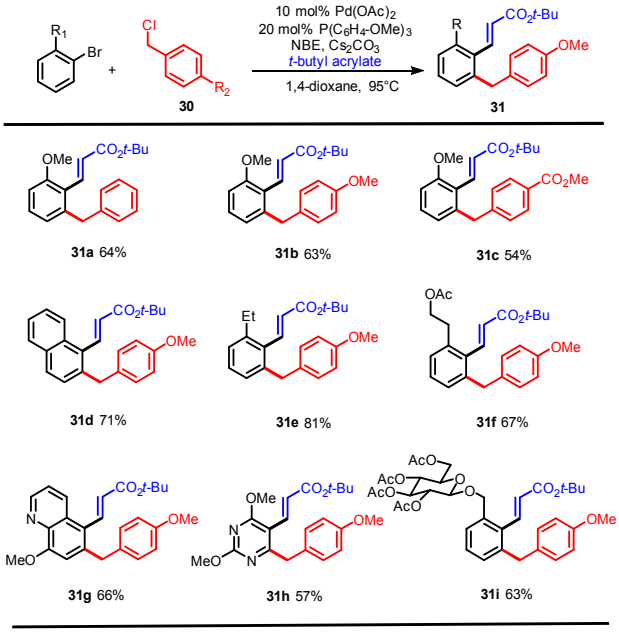


Figure 4. X-ray Crystal structure of compound **29f**.

2.3 *Ortho* alkylation. *Ortho* alkylation with alkyl halides has been the first Catellani reaction reported.[7a] However, the use of aryl bromides for *ortho* alkylation remained to be developed. The feasibility of aryl bromide-mediated *ortho* alkylation was first explored with benzyl electrophiles, in which the corresponding reactions with aryl iodides were reported by Lautens and Liang.[20,62] When benzyl bromides were employed as the electrophile, no desired benzylation product was observed, which is likely due to the strong oxidative ability of benzyl bromides compared to aryl bromides. However, combining benzyl chlorides as the electrophile and tris(4-methoxyphenyl)phosphine as the ligand,[63] the desired benzylation product **31a** was isolated in 64% yield with 2-bromoanisole as the substrate (Table 6). In addition, both electron-rich and -deficient benzyl chlorides gave the desired products in comparable yields (**31b** and **31c**). Moreover, bromoheteroarenes, such as quinoline **31g** and pyrimidine **31h**, are also competent substrates.

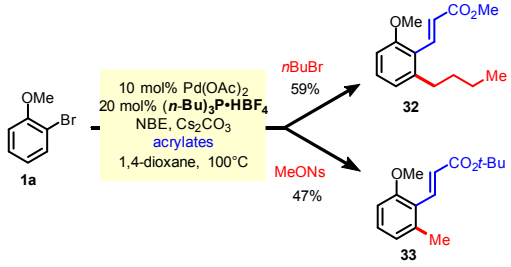
Table 6. *Ortho* Alkylation/*Ipso* Heck Reaction of Aryl Bromides with Benzyl Chlorides[a]



[a] Run on a 0.3 mmol scale (0.1 M) for 14 h with 2.0 equiv of **30**; 1.0 equiv of **3**; 1.5 equiv of *t*-butyl acrylate, 2.0 equiv of NBE and 3.0 equiv of Cs_2CO_3; All yields are isolated yields.

With preliminary success of the reactions using activated benzyl halides as the electrophile, *ortho* alkylation with unactivated alkyl halides,[64] which has been utilized in several elegant total syntheses,[65] was investigated next. 2-Bromoanisole **1a** was again employed as the model substrate. When alkyl iodides (e.g. BuI) were employed as the alkylating reagent, regardless the choice of phosphine ligands, the reaction proceeded with a low conversion without forming any desired product. It is likely that alkyl iodides may react with Pd(0) faster than 2-bromoanisole. Hence, a weaker alkylating reagent, such as alkyl bromides, was tested. To our delight, when BuBr was used as the electrophile, tri-*n*-butylphosphine was found to give optimal results at this stage (Scheme 11). In addition, *ortho* methylation was realized using methyl 4-nitrobenzenesulfonate as the electrophile, given that methyl bromide, a toxic gas, is not convenient to handle. Considering the importance of methylation of arenes[66] and heteroarenes[67] in drug design,[68] this method is expected to be useful for medicinal chemistry research. While the efficiency of these *ortho* alkylation reactions remains to be further improved, they nevertheless show the feasibility of employing widely available aryl bromides as suitable substrates.

Scheme 11. *Ortho* Alkylation of Aryl Bromides with Unactivated Alkyl Electrophiles



CONCLUSIONS

In summary, we describe the efforts of developing general approaches for aryl-bromide-mediated Pd/NBE catalysis, in which *ortho* amination, acylation and alkylation have been realized using *O*-benzoyl hydroxylamines, carboxylic acid anhydrides and alkyl halides respectively as electrophiles. For the *ortho* amination and acylation of aryl bromides, electron-rich bidentate phosphines with large bite angles and flexible backbones generally worked efficiently. For *ortho* benzylation and alkylation, mono-dentate tris(4-methoxyphenyl)phosphine and tributylphosphine were found to be superior than bidentate ligands. The conditions (at least for *ortho* amination) are also general for introducing various substituents, such as vinyl, alkynyl, boryl groups or hydrogen, at *ipso* positions. The high chemoselectivity and tolerance of various heterocycles observed in this study should make these methods attractive for medicinal chemistry research. Allowing aryl bromides for Pd/NBE catalysis also permits development of sequential functionalization strategies for constructing more complex and diverse aromatic compounds, therefore offering new strategic insights for bond disconnection approaches. The knowledge obtained from the DFT study should shed light on the choice of ligands for Pd/NBE catalysis. Further improvement of the catalyst efficiency and efforts towards expanding the substrate scope to more challenging aryl chlorides are ongoing.

Experimental Section

General procedure of palladium/norbornene-catalyzed *ortho* amination of aryl bromides. An oven-dried 4 mL vial was charged with aryl bromide (0.3 mmol, 1.0 equiv), *O*-benzoyl hydroxylamine (0.3 mmol, 1.6 equiv), (−)-borneol (46.2 mg, 0.3

mmol, 1.0 equiv), norbornene (28.2 mg, 0.3 mmol, 1.0 equiv), palladium acetate (6.7 mg, 0.03 mmol, 0.1 equiv) and a magnetic stir bar. The vial was sealed in the air and transferred in a nitrogen-filled glovebox. 1,4-Bis(dicyclo-hexylphosphino)butane (14.9 mg, 0.033 mmol, 0.11 equiv) and cesium carbonate (245 mg, 0.75 mmol, 2.5 equiv) were added to the vial in the glove box. 1,4-Dioxane (3 ml) was added, and the vial was then sealed with PTFE lined cap in the glovebox. The resulting mixture was stirred at room temperature for 10 minutes until the all the palladium acetate was fully dissolved. The vial was subsequently transferred out of glovebox and stirred on a pie-block preheated to 90°C for 14 hours. After completion of the reaction, the mixture was filtered through a thin pad of celite. The filter cake was washed with ethyl acetate, and the combined filtrate was concentrated. The residue was directly purified by flash column chromatography on silica gel to yield the desired product.

General procedure of palladium/norbornene-catalyzed *ortho* acylation of aryl bromides. An oven-dried 4 mL vial was charged with aryl bromide (0.3 mmol, 1.0 equiv), carboxylic acid anhydride (0.54 mmol, 1.8 equiv), *tert*-butyl acrylate (56.7 mg, 0.45 mmol, 1.5 equiv), norbornene (56.4 mg, 0.6 mmol, 2.0 equiv), dichlorobis(acetonitrile)palladium(II) (7.8 mg, 0.03 mmol, 0.10 equiv), bis[2-(diphenylphosphino)phenyl] ether (16.1 mg, 0.03 mmol, 0.10 equiv) and a magnetic stir bar. The vial was sealed in the air and transferred in a nitrogen-filled glovebox. Cesium carbonate (294.0 mg, 0.9 mmol, 3.0 equiv) was added to the vial in the glove box. 1,4-Dioxane (3 ml) was added, and the vial was then sealed with PTFE lined cap in the glovebox. The resulting mixture was stirred at room temperature for 15 minutes until the all the dichlorobis(acetonitrile)palladium(II) was fully dissolved. The vial was subsequently transferred out of glovebox and stirred on a pie-block preheated to 100°C for 14 hours. After completion of the reaction, the mixture was filtered through a thin pad of celite. The filter cake was washed with ethyl acetate, and the combined filtrate was concentrated. The residue was directly purified by flash column chromatography on silica gel to yield the desired product.

General procedure of palladium/norbornene-catalyzed *ortho* benzylation of aryl bromides. An oven-dried 4 mL vial was charged with aryl bromide (0.30 mmol, 1.0 equiv), benzyl chloride (0.60 mmol, 2.0 equiv), *tert*-butyl acrylate (56.7 mg, 0.45 mmol, 1.5 equiv), norbornene (56.4 mg, 0.6 mmol, 2.0 equiv, 2.0 equiv) and a magnetic stir bar ("substrate vial"). Palladium acetate (6.7 mg, 0.03 mmol, 0.1 equiv) and tris(4-methoxyphenyl)-phosphine (21.1 mg, 0.06 mmol, 0.2 equiv) were put in another oven-dried 4 mL vial ("Pd/ligand vial"). Both vials were transferred in a nitrogen-filled glovebox. 1,4-Dioxane (1 ml) was added to the Pd/ligand vial. The resulting mixture was stirred at room temperature for 10 minutes until the all the palladium acetate was fully dissolved to give a bright yellow homogenous solution. 1,4-Dioxane (2 ml) and cesium carbonate (294.0 mg, 0.9 mmol, 3.0 equiv) were added to another vial in the glove box. The palladium/ligand solution was transferred to the substrate vial that was then sealed inside the glovebox. The vial was subsequently transferred out of glovebox and stirred on a pie-block preheated to 95°C for 14 hours. After completion of the reaction, the mixture was filtered through a thin pad of celite. The filter cake was washed with ethyl acetate, and the combined filtrate was concentrated. The residue was directly purified by flash column chromatography on silica gel to yield the desired product.

ASSOCIATED CONTENT

Text, figures, tables, and CIF files giving experimental procedures, kinetics data, and crystallographic information. 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 interest.

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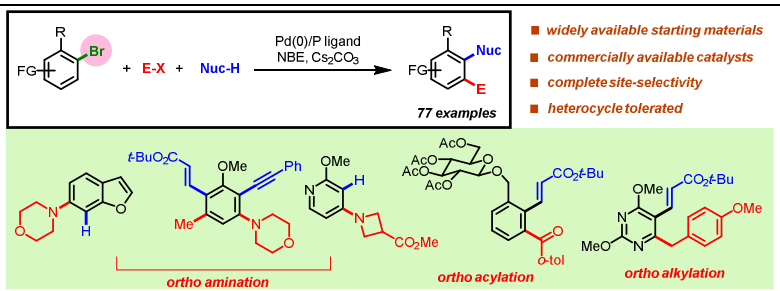
R
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t-BuO2C
OMe
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ortho amination
AcO
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o-tol
ortho acylation
MeO
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