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Sterically Controlled, Palladium-Catalyzed Intermolecular Amination of Arenes

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Supporting Information Placeholder

ABSTRACT: We report the palladium-catalyzed amination of arenes to form *N*-aryl phthalimides with regioselectivity controlled predominantly by steric effects. Mono-, di-, and tri-substituted arenes lacking a directing group undergo amination reactions with moderate to high yields and high regioselectivities from sequential addition of iodosobenzene(diacetate) as oxidant. This sterically derived selectivity contrasts that for analogous arene acetoxylation.

The abundance of amines in medicine, agroscience, and material science makes them valuable synthetic targets.¹ Conventional methods for the synthesis of aromatic amines involve nitration of arenes, followed by reduction.² To mitigate the harsh reaction conditions associated with these early methods, alternative approaches such as copper-catalyzed³ and palladium-catalyzed coupling reactions⁴ of amines with aromatic halides or pseudohalides were developed. These approaches have been used widely in academia⁵ and industry,⁶ but these reactions require pre-functionalization of arenes to aromatic halides. Thus the regioselectivity of the reaction reflects the regioselectivity for halogenation of the arene.





Therefore, a sterically controlled direct amination of aromatic C-H bonds would complement cross-coupling.⁷ The direct amination of arenes with Cu^8 and Pd^9 catalysts, as well

as under metal-free¹⁰ conditions, have been reported. However, the metal-catalyzed reactions are limited to intramolecular processes $(Eq 1)^{9a-c,11a-d}$ or intermolecular processes with reactivity and regioselectivity governed by a directing group $(Eq 2).^{9d-e,11a-f}$ A few uncatalyzed intermolecular reactions with substrates lacking a directing group have been reported.¹⁰ These reactions provide high yields of amination products but require high reaction temperatures and, most relevant to the work reported here, occur with regioselectivity dictated by the electronic effects that control electrophilic aromatic substitution (Eq 3).

One method to conduct sterically controlled aminations of arenes is the combination of arene borylation¹² and Chan-Lam amination of the resulting arylboronate ester.¹³ A direct, intermolecular amination of arenes with this steric control of regioselectivity would avoid the arylboronate intermediate, but such a process has not been reported (Eq 4).

Here, we report a palladium-catalyzed intermolecular oxidative amination of mono-, di- and tri-substituted arenes with regioselectivities guided by steric effects.¹⁴ The selectivity contrasts that for related palladium-catalyzed acetoxylation of arenes,¹⁵ suggesting that a different species cleaves the C-H bond in the two classes of reactions.



Previously, we reported palladium-catalyzed intramolecular aminations of aromatic C-H bonds with oxime esters to form substituted indoles;^{9c} however, an intermolecular version of this reaction has not been observed. As part of studies to develop an intermolecular variant, we observed the formation of *N*-phenyl phthalimide in 30-40% yield in the presence of a palladium catalyst, phthalimide, and iodosobenzene(diacetate) as oxidant in benzene at 100 °C (Eq S).



 $\mathbf{H} = \mathbf{M} \mathbf{e}, \mathbf{r} \mathbf{B} \mathbf{u},$

Encouraged by this result, a series of ligands, oxidants, and solvents were investigated by high-throughput experimenta-

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tion (HTE) methods to identify variable(s) that affect the yield of amination product.¹⁶ The reactions of electron-rich and electron-poor arenes with phthalimide and saccharin as the nitrogen source were conducted in the presence of catalytic amounts of $Pd(OAc)_2$ and mono- and bi-dentate nitrogen based ligands, catalytic amounts of $Pd(OAc)_2$ alone, or no catalyst in polar and non-polar solvents at 100 °C (Eq 6).

Our data from HTE revealed six general features of the reaction: 1) electron-rich arenes reacted in higher yields than electron-poor arenes; trifluoromethylbenzene reacted in low yield (10-20%) while toluene, anisole and *tert*-butylbenzene reacted in modest yield (30-50%); 2) reactions of arenes with phthalimide provided the desired amination product, but the reactions with saccharin gave several byproducts having the same mass as that of the desired amination product;¹⁷ 3) iodosobenzene(diacetate) provided the highest yield of amination product among the oxidants tested, 4) reactions run in neat arene occurred in higher yields and with higher selectivities than those run in a solvent; 5) the observed selectivities were similar in the presence or absence of a ligand; and 6) the selectivities of reactions run in a solvent (1,2-DCE and MeCN providing high yields) were the same when run in the presence of palladium catalysts as in the absence of catalyst.

With the knowledge gained from high-throughput experimentation, we refined the factors that control reaction yield. The reactions were run using phthalimide as the nitrogen source in neat benzene at 100 °C with catalytic amounts of $Pd(OAc)_2$ and *t*-Bu₃P, with catalytic amounts of $Pd(OAc)_2$ alone, and without a palladium catalyst. Figure 1 shows the kinetic profiles of these reactions. The reaction with $Pd(OAc)_2$ alone occurred more slowly than that conducted with $Pd(OAc)_2$ and *t*-Bu₃P. However, both the reactions with and without ligand were complete within 3 h and formed 35-45% yield of the amination product. Upon further heating, no additional amination product formed. Instead, Pd-black formed. Reactions run under metal-free conditions were slow at 100 °C and provided only 10% of the *N*-aryl imide after 6 h.^{10d}



Figure 1. Comparison of amination of benzene with phthalimide in the presence of catalytic amounts of $Pd(OAc)_2/t$ -Bu₃P (•), catalytic amounts of $Pd(OAc)_2$ alone (\blacksquare) and without a palladium catalyst (•).

Due to the shorter reaction time, we focused on reactions catalyzed by the combination of $Pd(OAc)_2$ and t-Bu₃P to determine if catalyst deactivation or consumption of phthalimide or PhI(OAc)₂ in an undesired pathway were responsible for the lack of full conversion. Reactions conducted with activated 3-, 4-, and 5-Å molecular sieves, acetic acid and bases (such as Cs₂CO₃, NaOAc and CsOH) gave the amination product in yields that were comparable to or lower than the reactions run without these additives, implying that the catalyst was not affected by adventitious water or the acetic acid product.¹⁶ Addition of 10 mol % Pd(OAc)₂,

10 mol % t-Bu₃P, or 10 mol % of Pd(OAc)₂ and t-Bu₃P together after Pd-black had formed (5 h reaction time) also did not increase the yield of the amination product.

These results suggested that catalyst deactivation is not responsible for the modest yields. Likewise, addition of an extra equivalent of phthalimide at 5 h did not increase the yield of the amination product.¹⁶ In contrast, addition of an additional 2 equiv of PhI(OAc)₂ after 5 h of reaction time reverted the Pd-black to a soluble palladium species and increased the yield of amination product from 35% to 55% based on phthalimide. Additions of two further portions of 2 equiv of oxidant at 5 h intervals, gave 83% yield of *N*-phenyl phthalimide product.¹⁶

With conditions to form the amination product in high yield, we turned our attention to the primary goal of this work: identifying whether a direct amination could be conducted with sterically controlled regioselectivity. Conditions developed for the amination of benzene were applied to the reaction of toluene (Table 1). With two sequential additions of 2 equiv of PhI(OAc)₂ at 9 and 24 h reaction times, 70% yield of the amination product was observed with a sterically controlled regioselectivity of 1:9:8 (o:m:p, entry 1).^{18,19} Reactions run under similar conditions with Pd(OAc)₂ as catalyst in the absence of ligand occurred in a similar yield and selectivity as reactions run in the presence of ligand (entries 2 and 1 respectively). This result is consistent with those observed in high-throughput experimentation.

Table 1. Regioselective Amination of Toluene*



Entry	Conditions	Yield ^b	Selectivity ^c (o:m:p)
1	As above	70%	1:9:8
2	No <i>t</i> -Bu ₃ P added	65%	1:6:6
3	No $Pd(OAc)_2$ or $t-Bu_3P$ added	42%	2:1:1
4	As entry 1 with 8 equiv $PhI(OAc)_2$ added initially without sequential addition	56%	1:13:13
5	As entry 1, on benchtop	68%	1:7:6
6	As above, with 10 equiv toluene in 1 mL 1,2-DCE	34%	1:3:4
7	As above, with 10 equiv toluene in 1 mL MeCN	38%	1:3:3
8	As above, with 10 equiv toluene in 1 mL mesitylene	10%	1:1:1

^a Reactions were assembled in a nitrogen-filled glove box on 0.1 mmol scale with 1 mL toluene and run for 33 h total. ^b Corrected GC yield vs dodecane internal standard. ^cCrude GC selectivity.¹⁸

In contrast, the uncatalyzed reaction with sequential addition of oxidant occurred in low yield with selectivity derived from electronic effects (o:m:p = 2:1:1, entry 3).¹⁰ The reaction catalyzed by Pd(OAc)₂ and *t*-Bu₃P with 8 equiv of the oxidant at the beginning of the reaction occurred in lower yield (entry 4). Finally, the presence of oxygen or moisture introduced from reactions assembled on the benchtop did not affect the yield of the product, but led to a slightly lower regioselectivity (entries 1 vs 5).²⁰ Likewise, reactions con1

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59 60 ducted with toluene and phthalimide in a 10:1 ratio in 1,2-DCE, MeCN or mesitylene as a solvent at 100 °C occurred in lower yield and with a lower selectivity for *m*-, *p*-isomers vs *o*-isomer (entries 6-8) than reactions run in neat arene. In summary, the reaction conditions described in Table 1 entry 1 lead to the direct oxidative amination of a substituted arene in high yield with high regioselectivity derived from steric effects.¹⁴

Having identified conditions for the amination of a substituted arene with steric control, we examined the selectivity for the amination of a variety of mono-, di-, and trisubstituted arenes with phthalimide using catalytic amounts of $Pd(OAc)_2$ and *t*-Bu₃P, catalytic amounts of $Pd(OAc)_2$, and without a palladium catalyst.¹⁶ In all cases, the yield and regioselectivity of the metal-catalyzed reactions were higher than those observed for the uncatalyzed reactions. Slightly higher yields and selectivities were observed with added *t*-Bu₃P in some cases.

The scope of the reactions of tri-, di-, and monosubstituted arenes under conditions with the catalyst derived from Pd(OAc)₂ and *t*-Bu₃P is shown in Schemes 1 and 2. Reactions of 1,2,3-trisubstituted arenes and symmetric 1,2disubstituted arenes (1-8) gave the less hindered products as the major constitutional isomer. A single isomer was isolated upon purification by silica gel column chromatography. In these cases, the regioselectivity observed with the catalyst derived from Pd(OAc)₂ and *t*-Bu₃P is the opposite of the selectivity from the electronically controlled amination of arenes under uncatalyzed thermal conditions.¹⁰

Scheme 1. Scope of the sterically controlled amination of symmetric arenes⁴



^a Reactions were assembled in a nitrogen-filled glove box in 20 mL scintillation vials on 0.5 mmol scale with 10 mol % $Pd(OAc)_2/t$ -Bu₃P in 5 mL arene and 2.0 equiv of $PhI(OAc)_2$ at the beginning of the reaction. Another 2.0 equiv of $PhI(OAc)_2$ were added at 9, and 24 h of the reaction. The reactions were run for 33 h total. Yield represents isolated yield after silica gel column chromatography. Selectivities are reported based on GC analysis after isolation.¹⁸

The reaction also occurred with unsymmetrical 1,2disubstituted arenes (9-15) to provide good yields of the two amination products containing the phthalimide group *meta* to both the substituents (Scheme 2). Under the developed conditions, 1,2-disubstituted arenes were more reactive than the corresponding 1,3-disubstited arenes (15 vs 16).²¹

In addition, the catalytic amination reaction occurred with electron-rich and electron-poor monosubstituted arenes (17-26) to provide mono-amination products exclusively (Scheme 2). Substrates with larger substituents on the arene reacted with higher selectivity for amination of the less hindered C-H bonds (17 vs 18 vs 19). Arenes containing car-

bon-halogen bonds in mono-, di-, and tri-substituted arenes (3-6, 8-14, 22-25) underwent the C-H amination reaction without any observed proto-dehalogenation or C-X amination.⁴ In all cases, the reactions were selective for the less hindered *meta-*, and *para-*isomers. In some cases, (12, 13, 15, 16, 18, 20, 21, 24,) recrystallization of a mixture of *meta-* and *para-* isomers from MeOH/hexanes allowed for isolation of a single isomer. It is noteworthy that the transformations can be conducted on the benchtop, at the expense of a slight decrease in selectivity (Table 1, entries 1 vs 5).

Scheme 2. Scope of the sterically controlled amination of unsymmetrical di-substituted arenes and mono-substituted arenes⁴



^aSame as in Scheme 1.

Expansion of the scope of nitrogen source has been challenging. Studies of the reactions with imides possessing different electronic properties showed that the reactions of phthalimide and 4-methylphthalimide occurred in similar yields and selectivity, but reactions of the electron-poor imides 4-chlorophthalimide or 3,4,5,6-tetrachlorophthalimide and reactions of maleimide, succinimide or saccharin occurred to low conversion. The reactions of amides or amines in place of imides occurred to low conversion.¹⁶ Nevertheless, our current results demonstrate that commercially available phthalimide can be used to generate a wide range of protected anilines²² from readily available aromatic compounds.

The selectivity of this amination of arenes is clearly distinct from that of the related acetoxylations of arenes.¹⁵ Crabtree showed that the acetoxylation of toluene, phenyl acetate, anisole, chlorobenzene and iodobenzene occurs to form predominantly the *ortho-* and *para*-substituted products.^{15a} Many studies since then have suggested that the C-H bond is cleaved by a concerted metalation-deprotonation (CMD) sequence.²³ For the amination to occur with regioselectivity distinct from that of the acetoxylation process, the species that cleaves the C-H bond in the two reactions must be distinct, or the C-H bond cleavage step must be reversible and the amination step is faster for the less hindered arylpalladium intermediate than for the more hindered arylpalladi intermediate. To distinguish between these possibilities, we measured the kinetic isotope effect (KIE) from the reaction of a mixture of C_6H_6 and C_6D_6 . The KIE from these experiments was 4.10 \pm 0.06, implying that the C-H bond is cleaved irreversibly.²⁴ Thus, the species that cleaves the C-H bond in the acetoxylation and the amination is different. Studies to compare CMD pathways for reactions of phthalimidate and acetate complexes will be the subject of future work.

In conclusion, we have developed a regioselective, intermolecular Pd-catalyzed oxidative amination of arenes with phthalimide. Sequential addition of oxidant allows the reactions to occur in good yield in neat arene. This process points to an avenue to develop alternatives to palladiumcatalyzed amination of aryl halides and the potential to conduct sterically controlled amination without initial borylation of the arene. Further studies to expand the scope of nitrogen sources based on mechanistic data are ongoing.

ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, supplementary tables of data, and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Additional experiments suggest that the decrease in selectivity cannot be attributed to ligand oxidation. See Supporting Information.

(21) This observation was consistent with the reactivity of other 1,3disubstituted vs 1,2-disubstituted arenes reported in Scheme 1. Comparison of the crude GC traces of reactions conducted with a mixture of 1,2disubstituted arenes and 1,3-disubsituted arenes suggest that both reactions produce comparable amounts of acetoxylation products. This observation implies that competitive acetoxylation of 1,3-disubstituted arene is not responsible for the lower yield of amination products with the 1,3disubstituted substrates. See Supporting Information for the primary data.

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(24) The observed KIE is identical to that for acetoxylation reported in ref. 15a and slightly lower than that determined for the acetoxylation product under our reaction conditions with phthalimide (5.7 ± 0.2) . The KIE for the amination of a mixture of protiated and deuterated 1,2-dichlorobenzene with phthalimide under the conditions we developed was 2.8 ± 0.1 .

