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Sterically Controlled, Palladium-Catalyzed Intermolecular Amination of Arenes

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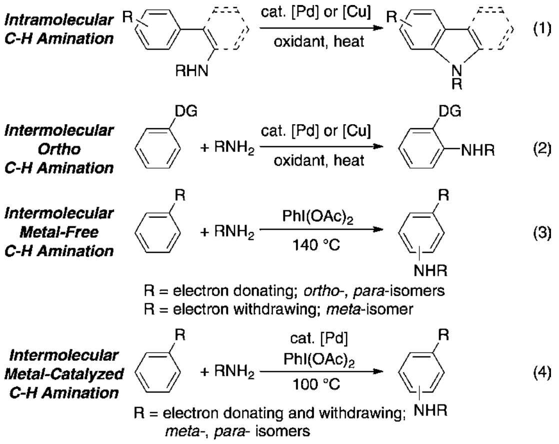
Ⓢ *Supporting Information*

ABSTRACT: We report the Pd-catalyzed amination of arenes to form *N*-aryl phthalimides with regioselectivity controlled predominantly by steric effects. Mono-, di-, and trisubstituted arenes lacking a directing group undergo amination reactions with moderate to high yields and high regioselectivities from sequential addition of $PhI(OAc)_2$ as an oxidant in the presence of $Pd(OAc)_2$ as catalyst. 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 Cu-catalyzed[3] and Pd-catalyzed coupling reactions[4] of amines with aromatic halides or pseudohalides were developed. These approaches have been used widely in academia[5] and industry,[6] but these reactions require prefunctionalization of arenes to aromatic halides. Thus the regioselectivity of the reaction reflects the regioselectivity for halogenation of the arene.

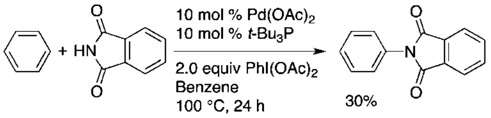
Therefore, a sterically controlled direct amination of aromatic C−H bonds would complement cross-coupling.[7] The direct amination of arenes with Cu[8] and Pd[9] catalysts, as well as under metal-free[10] conditions, has been reported. However, the metal-catalyzed reactions are limited to intramolecular processes (eq 1)[9a−c,11a−d] or intermolecular processes with reactivity and regioselectivity governed by a directing group (eq 2).[9d,e,11a,e,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 borylation[12] 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 Pd-catalyzed intermolecular oxidative amination of mono-, di-, and trisubstituted arenes with regioselectivities guided by steric effects.[14] The selectivity contrasts that for related Pd-catalyzed acetoxylation of arenes,[15] suggesting that a different species cleaves the C−H bond in the two classes of reactions.

Previously, we reported Pd-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. During preliminary studies to develop an intermolecular variant, we observed the formation of *N*-phenyl phthalimide in 30−40% yield in the presence of a Pd catalyst, phthalimide, and $PhI(OAc)_2$ as an oxidant in benzene at 100 °C (eq 5).



(5)

Encouraged by this result, a series of ligands, oxidants, and solvents were investigated by high-throughput experimentation (HTE) methods to identify variable(s) that affect the yield of amination product.[16] The reactions of electron-rich and -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 bidentate N-based ligands, catalytic amounts of $Pd(OAc)_2$ alone, or no catalyst in polar and nonpolar 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; $PhCF_3$ reacted in low yield (10−20%), while PhMe, PhOMe and *t*-BuPh reacted in modest yield (30−50%); (2) reactions of arenes with phthalimide provided the

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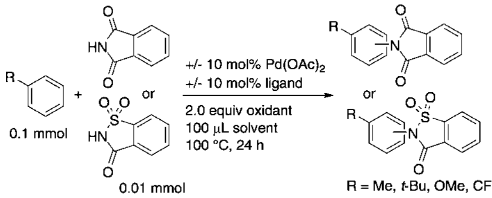


(6)

desired amination product, but the reactions with saccharin gave several byproducts having the same mass as that of the desired amination product;[17] (3) $PhI(OAc)_2$ 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 Pd catalysts as in the absence of catalyst.

With the knowledge gained from HTE, we refined the factors that control reaction yield. The reactions were run using phthalimide as the N-source in neat benzene at 100 °C with catalytic amounts of $Pd(OAc)_2$ and $t\text{-}Bu_3P$, with catalytic amounts of $Pd(OAc)_2$ alone, and without a Pd 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 $t\text{-}Bu_3P$. However, both reactions with and without ligand were complete within 3 h and formed a 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]

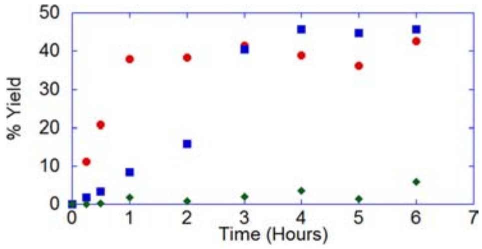


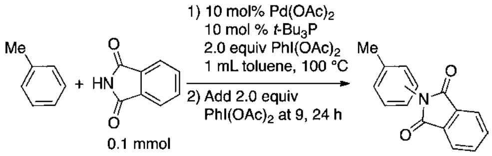
Figure 1. Comparison of amination of benzene with phthalimide in the presence of catalytic amounts of $Pd(OAc)_2/t\text{-}Bu_3P$ (●), catalytic amounts of $Pd(OAc)_2$ alone (■), and without a Pd catalyst (◆).

Due to the shorter reaction time, we focused on reactions catalyzed by the combination of $Pd(OAc)_2$ and $t\text{-}Bu_3P$ 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 Cs_2CO_3, NaOAc, and CsOH) gave the amination product in yields that were comparable to or lower than those for reactions run without these additives, implying that the catalyst was not affected by adventitious water or the acetic acid product.[16] The addition of 10 mol % $Pd(OAc)_2$, 10 mol % $t\text{-}Bu_3P$, or 10 mol % of $Pd(OAc)_2$ and $t\text{-}Bu_3P$ 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 amination product yield.[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 Pd species and increased the amination product yield from 35% to 55% based on phthalimide. Additions of two further portions of 2 equiv of oxidant at 5 h intervals gave an 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, a 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 the catalyst in the absence of ligand occurred in a similar yield and selectivity as reactions run with ligand (entries 2 and 1 respectively). This result is consistent with those observed in HTE.

Table 1. Regioselective Amination of Toluene[a]



entry	change from the standard conditions	yield[b]	selectivity[c] (*o*:*m*:*p*)
1	as above, no change	70%	1:9:8
2	no $t\text{-}Bu_3P$ added	65%	1:6:6
3	no $Pd(OAc)_2$ or $t\text{-}Bu_3P$ added	42%	2:1:1
4	with 8 equiv of $PhI(OAc)_2$ added initially without sequential addition	56%	1:13:13
5	on benchtop	68%	1:7:6
6	with 10 equiv of PhMe in 1 mL of 1,2-DCE	34%	1:3:4
7	with 10 equiv of PhME in 1 mL of MeCN	38%	1:3:3
8	with 10 equiv of PhMe in 1 mL of mesitylene	10%	1:1:1

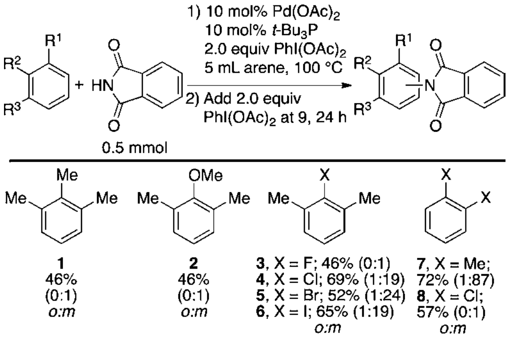
[a] Reactions were assembled in a nitrogen-filled glovebox on 0.1 mmol scale with 1 mL of toluene and run for 33 h total. [b] Corrected GC yield vs dodecane internal standard. [c] Crude GC selectivity.[18]

In contrast, the uncatalyzed reaction with sequential addition of the oxidant occurred in low yield with the selectivity derived from electronic effects (*o*:*m*:*p* = 2:1:1, entry 3).[10] The reaction catalyzed by $Pd(OAc)_2$ and $t\text{-}Bu_3P$ 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 (entry 1 vs 5).[20] Likewise, reactions conducted with 10:1 toluene/phthalimide 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 an *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 sterically controlled direct oxidative amination of a substituted arene in high yield with high regioselectivity.[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 $t\text{-}Bu_3P$, catalytic amounts of $Pd(OAc)_2$, and without a Pd 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-Bu_3P in some cases.

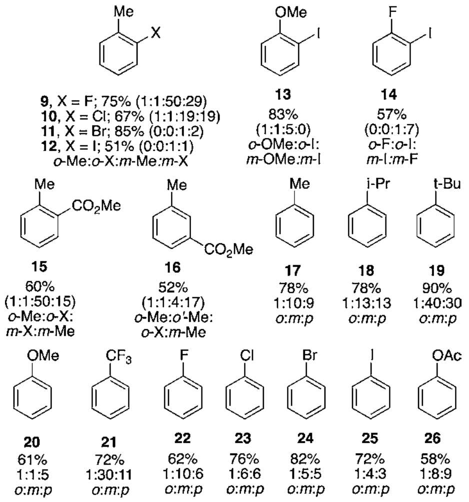
The scope of the reactions of tri-, di-, and monosubstituted arenes under conditions with the catalyst derived from $Pd(OAc)_2$ and t-Bu_3P is shown in Schemes 1 and 2. Reactions of 1,2,3-trisubstituted arenes and symmetric 1,2-disubstituted arenes (**1**–**8**) gave the less hindered products as the 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-Bu_3P 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 Arenes[a]



[a]Reactions were assembled in a nitrogen-filled glovebox in 20 mL scintillation vials on 0.5 mmol scale with 10 mol % $Pd(OAc)_2/t$-Bu_3P in 5 mL of 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]

Scheme 2. Scope of the Sterically Controlled Amination of Unsymmetrical Disubstituted Arenes and Monosubstituted Arenes[a]



[a]Reactions conducted with the conditions of Scheme 1. Yields are of isolated material.

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

In addition, the catalytic amination reaction occurred with electron-rich and -poor monosubstituted arenes (**17**–**26**) to provide monoamination 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 carbon–halogen bonds in mono-, di-, and trisubstituted 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, entry 1 vs 5).

Expansion of the scope of the N-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 anilines[22] 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 arylpalladium 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 4.1 ± 0.1, implying that the C–H bond is cleaved irreversibly.[24] Thus, the species that cleaves the C–H bond in the acetoxylation and 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 the oxidant allows the reactions to occur in good yield in neat arene. This process points to an avenue to develop alternatives to Pd-catalyzed 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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Notes

The authors declare no competing financial interest.

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(16) See Supporting Information (SI) for more details.

(17) More than three products with the *m*/*z* expected for the desired amination product were observed. Currently we hypothesize the byproduct to be arylation of the aromatic ring on saccharin *ortho* to the sulfimide functional group. For the related sulfonamide as a directing group, see: (a) Watanabe, H.; Gay, R. L.; Hauser, C. R. *J. Org. Chem.* **1968**, *33*, 900. (b) Watanabe, H.; Schwartz, R. A.; Hauser, C. R.; Lewis, J.; Slocum, D. W. *Can. J. Chem.* **1969**, *47*, 1543. (c) Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, *41*, 3653.

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(19) Experiments conducted to probe the stability of the *ortho*-amination product suggest that it is stable under the amination reaction conditions. See SI.

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

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