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Selective Cross-Coupling of (Hetero)aryl Halides with Ammonia To Produce Primary Arylamines using Pd-NHC Complexes

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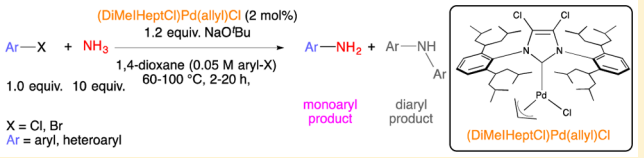
Supporting Information

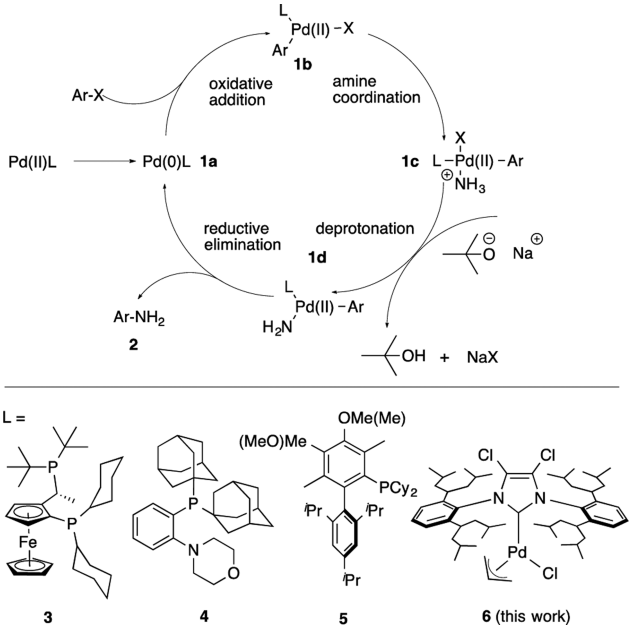
ABSTRACT: Herein we report the first example of (hetero)-arylation of ammonia using a monoligated palladium-NHC complex. The new, rationally designed, precatalyst (DiMeIHept^{Cl})Pd(allyl)Cl featuring highly branched alkyl chains has been shown to be effective in selective aminations across a range of challenging substrates, including nitrogen-containing heterocycles and those featuring base-sensitive functionality. The less bulky Pd-PEPPSI-IPent^{Cl} precatalyst performs well for ortho-substituted aryl halides, giving monoarylated products in high yield with good selectivity.



Palladium-catalyzed amination has become an indispensable method for the construction of carbon−nitrogen (C−N) bonds. In particular, the coupling of ammonia (NH_3) with aryl halides to produce primary arylamines has gained much attention in recent years due to the low cost and atom economy of NH_3 in comparison to NH_3 surrogates previously used.[1−3] The first example of Pd-catalyzed amination with NH_3 was reported in 2006 by Shen and Hartwig.[4] More recently Ni- and Cu-catalyzed aminations have been developed.[5−10] While these catalyst systems appear to be more economical, this can be offset by catalyst loadings of 2−10% in comparison with 0.1−2% with Pd. Other methods can be used to produce primary arylamines such as nitration followed by reduction; however, the utility of these transformations is limited due to problems with regioselectivity and harsh reaction conditions.[11,12]

While the Buchwald−Hartwig amination reaction has been well developed for the coupling of arylamines and alkylamines with aryl halides, NH_3 remains as one of the most challenging amines to couple. This is unfortunate, as primary (hetero)-arylamines are structural units found in many important compounds that are employed in a number of fields, such as medicine, agrochemicals, and materials science.[13−16] Developing a catalyst system that remains catalytically active is perhaps one of the biggest challenges. NH_3 is a good σ donor and can displace many phosphine ligands commonly used in Pd-catalyzed amination reactions.[17] Only ligands that resist displacement by NH_3 are catalytically active. Accessing the primary arylamine selectively is also difficult. The first product of the reaction, $ArNH_2$ (**2**) (Scheme 1), will often couple faster than NH_3 and produce the diarylamine Ar_2NH (not shown). The selectivity for monoarylation depends on a wide number of features, including the ancillary ligand, both electronic and steric properties of the aryl halide, base, temperature, solvent, and amount of NH_3 used.

Scheme 1. Putative Catalytic Cycle and Previously Reported Ligands for the Selective Amination of Primary Arylamines



To date, only a few ligands have been shown to be effective in Pd-catalyzed arylation of NH_3 (Scheme 1).[18−24] Among

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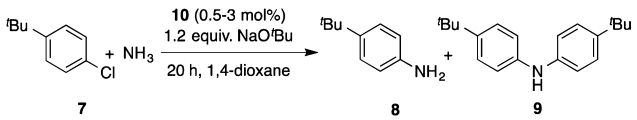
these, the electron-rich and sterically bulky ferrocene-based Josiphos ligand (**3**) was reported by Hartwig and co-workers to be highly reactive, coupling a variety of aryl chlorides, bromides, and iodides with NH_3 in 1,4-dioxane solutions.[18] Stradiotto's Mor-DalPhos ligand (**4**) and Buchwald's dialkylbiaryl phosphine ligand (**5**) have also been shown to couple a variety of aryl halides and six-membered heteroaryl halides with high selectivity for monoarylation using NH_3 1,4-dioxane solutions.[20,21]

As an alternative to Pd phosphine complexes, Pd catalysts featuring N-heterocyclic carbene (NHC) ligands have demonstrated extremely high catalytic reactivity.[25,26] Our group has recently shown the Pd-PEPPSI (PEPPSI = pyridine-enhanced precatalyst preparation, stabilization, and initiation) catalyst family to be effective in a variety of C−N couplings, where increasing the steric bulk around the metal center and chlorination of the NHC backbone dramatically improves both reactivity and selectivity.[27,28] Despite the attractiveness of such Pd-NHC complexes they remain underexplored as catalysts for arylations with NH_3.[29] In this study, Pd-NHC complexes were examined in this challenging coupling in an effort to access valuable primary (hetero)arylamines selectively.

We began our study using Pd-PEPPSI-IPent^{Cl} (**10**) for the amination of 4-*tert*-butylchlorobenzene (**7**) with NH_3 (Table 1), as **10** was recently reported to be highly selective in the Pd-

Table 1. Optimization Study for the Amination of 4-*tert*-Butylchlorobenzene with Ammonia using Pd-PEPPSI-IPent^{Cl} [a]



7 8 9

entry	cat. (mol %)	temp (°C)	LiO^{i}Pr (mol %)	[7] (M)	NH_3 (equiv)	conversn (%)[b]	**8**/**9**[c]
1	1	100		0.05	10	35	5/1
2	3	100		0.05	10	100	2.7/1
3	3	60		0.05	10	15	
4	3	100		0.1	5	100	1.7/1
5[d]	3	100		0.05	5	100	1.4/1
6	1	100	5	0.1	5	100	1.5/1
7	0.5	100	5	0.1	5	100	1.3/1
8	1	100	10	0.05	10	100	2.7/1
9[e]	1	70	10	0.1	5	100	1/1
10[e]	1	30	10	0.1	5	100	0.5/1

[a]Reactions were performed on a 0.25 mmol scale in duplicate. [b]Percentage conversion of **7** to products was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c]Product ratios of **8** to **9** were determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d]Reaction mixture was diluted with 1,4-dioxane to achieve a concentration of 0.05 M. [e]NaO^{t}Bu, **10**, and LiO^{i}Pr were heated to 95 °C for 5 min and then cooled to their respective reaction temperatures before addition of the aryl halide and ammonia.

catalyzed monoarylation of (hetero)aryl halides with aryl and alkyl primary amines.[27] 4-*tert*-Butylchlorobenzene (**7**) is a good model substrate, since it is slightly electronically deactivated for all three steps of the catalytic cycle and thus does not actively undergo monoarylation. Further, it gives rise to electron-rich, sterically unhindered aniline (**8**), which is more likely than NH_3 to navigate the coordination/deprotonation sequence and subsequent reductive elimination to generate **9**. Taken together, this makes it a challenging model reaction and not one that would be expected to preferentially give rise to the monoarylated product. Initial reaction conditions were modified from literature procedures that utilize commercially available 0.5 M solutions of NH_3 in 1,4-dioxane and sodium *tert*-butoxide (NaO^{t}Bu) as base. Using a catalyst loading of 3 mol %, a temperature of 100 °C, and 10 equivalent of NH_3 resulted in complete conversion of **7** with moderate selectivity for **8** (Table 1, entry 2). Decreasing the amount of NH_3 from 10 to 5 equivalent resulted in a decrease in selectivity for **8** (Table 1, entry 4). Since NH_3 comes in a 0.5 M 1,4-dioxane solution, increasing the equivalent requires more solvent to be used, which dilutes the reaction. To determine whether an increase in NH_3 amount or dilution of the reaction mixture was responsible for the increase in selectivity, the reaction concentration was diluted with 1,4-dioxane.[30] Decreasing the concentration from 0.1 to 0.05 M while keeping the equivalent of NH_3 the same resulted in a small decrease in selectivity for **8** (Table 1, entry 4 vs entry 5). This indicates that the observed increase in selectivity is the result of an increase in NH_3 concentration relative to the aryl halide. Both NH_3 and primary arylamine compete for a binding site on Pd. An increase in the ratio of NH_3 to primary arylamine would increase the ratio of Pd-amido (**1c**) to Pd-arylamido complexes in solution.

Next, we examined precatalyst activation. While Pd-PEPPSI precatalysts, such as **10**, reduce rapidly from Pd(II) to Pd(0) in the presence of organometallics, aminations with alkylamines show induction periods that we have attributed to precatalyst activation.[31] We have observed in Pd-catalyzed sulfination that addition of a reducing agent such as lithium isopropoxide (LiO^{i}Pr) helps facilitate precatalyst activation.[32] With this in mind, we examined the addition of LiO^{i}Pr in this transformation and, indeed, this led to full conversion of **7** at 100 °C (Table 1, entry 6). With the addition of LiO^{i}Pr the catalyst loading could also be lowered from 3 to 0.5 mol % (Table 1, entries 4, 6, and 7). As we have observed with aryl sulfinations, precatalyst activation can be done prior to addition of the aryl halide and NH_3. On activation at 95 °C, reactions could proceed at much lower temperatures; however, this was accompanied by a loss in selectivity for **8** (Table 1, entries 9 and 10).

Recently, our group has developed Pd precatalysts with bulkier NHC ligands (**6**, **11**, and **12**), which were evaluated for improved selectivity for monoarylation (Table 2).[33] Increasing the length of the *o*-alkyl chain at the first carbon atom on the aryl ring of the imidazole (i.e., **10** vs **11**) led to a slight increase in selectivity for monoarylation (**8**) (Table 2, entries 1 and 2). However, extending the alkyl chain by one additional carbon unit (i.e., **11** vs **12**) resulted in a drop in selectivity (Table 2, entry 3). Branching at the third carbon atom of the *o*-alkyl chain on the *N*-aryl ring (**6**) resulted in an astounding increase in selectivity to 40:1, dramatically outperforming the less bulky IPent^{Cl} ligand (Table 2, entry 1 vs entry 4). Furthermore, using the π-allyl version of this catalyst obviates the need for a reducing additive such as LiO^{i}Pr, as precatalyst activation may be facilitated by NaO^{t}Bu in this case.[34] Consistent with our group's previous findings, chlorination of the backbone of the NHC ligand led to an increase in reactivity and selectivity.[26,27] For example, when the reaction was performed in the presence of the IPent ligand, the reaction only went to 90% completion and gave almost exclusively the diarylated product (Table 2, entry 1 vs entry 5).

Having identified (DiMeIHept^{Cl})Pd(allyl)Cl (**6**) as the most selective precatalyst, we set out to explore the generality of this

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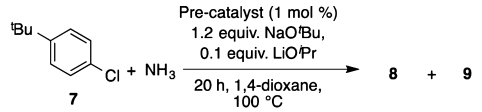
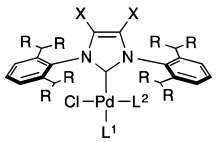
Table 2. Screening of Pd-NHC Precatalysts for the Amination of 4-*tert*-Butylchlorobenzene with Ammonia[a]





6 R = *i*-Bu, $L^1 = L^2$ = allyl, X = Cl
10 R = Et, L^1 = 3-chloropyridine, L^2 = Cl, X = Cl
11 R = *n*-Pr, L^1 = 3-chloropyridine, L^2 = Cl, X = Cl
12 R = *n*-Bu, L^1 = 3-chloropyridine, L^2 = Cl, X = Cl
13 R = Et, L^1 = 3-chloropyridine, L^2 = Cl, X = H

entry	precatalyst	conversn (%)[b]	8/9[c]
1	**10**	100	2.7/1
2	**11**	100	4.6/1
3	**12**	100	3.2/1
4[d]	**6**	100	401
5	**13**	90	1/33

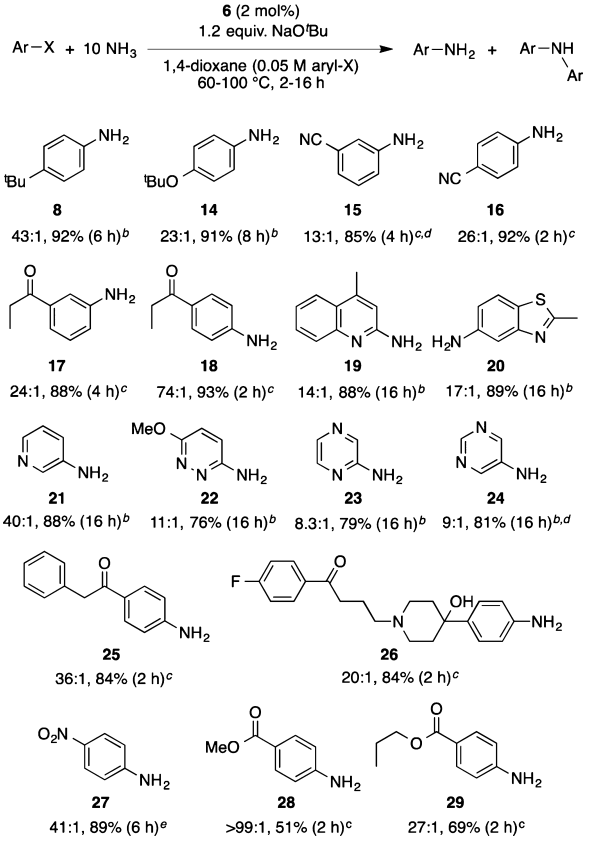
[a]Reactions were performed on a 0.25 mmol scale and in duplicate. [b]Percentage conversion of 7 to products was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c]Product ratios of **8** to **9** were determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d]Reaction performed in the absence of LiO^{i}Pr.

transformation with the aim of preparing a variety of functionalized primary arylamines (Scheme 2). In the presence of 2 mol % of **6**, both electron-rich (**8** and **14**) and electron-deficient aryl halides were coupled with NH_3 in high yield and high selectivity. On comparison of para- and meta-substituted electrophiles with electron-withdrawing groups (e.g., **15** vs **16** and **17** vs **18**), higher selectivities were observed with the para-substituted substrates. Heteroaryl halides could also be successfully coupled with NH_3 using **6** (Scheme 2, products **19**–**24**). Heteroaryl halides possessing multiple heteroatoms, including 2-chloro-6-methoxypyridazine (**22**), 2-chloropyrazine (**23**), and 5-bromopyrimidine (**24**), were successfully coupled with NH_3, generating the monoarylated products in excellent yield and selectivity. This is especially important, as heteroaryl amines serve as valuable synthetic intermediates and are commonly found as structural motifs in many biologically active compounds and organic materials.[13−16]

The majority of reports describing the coupling of NH_3 with aryl halides use an excess of NaO^{t}Bu; however, many substrates cannot tolerate such an aggressive base, especially at elevated temperatures. Aryl halides containing a base-sensitive functionality, such as esters, nitriles, ketones, and nitro groups, tend to undergo reaction at the functional group more quickly than C–N coupling.[27,35] Therefore, Pd-catalyzed NH_3 arylations with these aryl halides containing base-sensitive functional groups are typically avoided when NaO^{t}Bu is employed as the base due to lower yields.[20,22] To the best of our knowledge, only one example in the literature describes conditions that are mild enough to be compatible with base-sensitive functional groups. By replacing NaO^{t}Bu with K_3PO_4, Vo and Hartwig were able to couple aryl halides possessing esters, enolizable ketones, and nitriles in good yield and monoselectivity (>30:1). However, these reactions require very high pressures of NH_3 (200 psi) in order to achieve high selectivities for the monoarylation.[18]

In an effort to couple substrates possessing base-sensitive functional groups, milder bases such as cesium carbonate and sodium 2,2,5,7,8-pentamethylchroman-6-oxide were examined under our optimized conditions; however, a drop in selectivity for monoarylation was observed.[28,35,36] This led us to examine

Scheme 2. Scope of Selective Monoarylation of (Hetero)aryl Halides with Ammonia using Precatalyst 6[a]



[a]Yields of isolated material, X = Cl, mono:di ratio determined by ^{1}H NMR spectroscopy of the crude product mixture. All monoaminated products could be obtained in pure form by simple column chromatography. [b]100 °C, 1.2 equiv of NaO^{t}Bu. [c]80 °C, 1 equiv of NaO^{t}Bu. [d]X = Br. [e]60 °C, 1 equiv of NaO^{t}Bu.

the use of a stoichiometric quantity of NaO^{t}Bu with the aim of mitigating any decomposition starting materials and products, providing the coupling reaction was fast enough with **6**. To our delight, using 1 equiv of base allowed for the efficient and selective coupling of electrophiles containing enolizable ketones (**17**, **18**, **25**, and **26**), nitriles (**15** and **16**), free alcohols (**26**), nitro (**27**), and esters (**28** and **29**) (Scheme 2).

While **6** was also able to couple a selection of ortho-substituted aryl halides (**30**–**35**) with excellent selectivity (Scheme 3), incomplete conversion was typically observed when 2 mol % of catalyst was used. This effect was most pronounced for the substrates leading to **33** and **35**. It may be that the combination of bulky ortho-substituted substrates and an already highly congested Pd center hinders the catalytic process; thus, the additional catalyst bulk is counterproductive. However, using **10** under similar conditions, these substrates were coupled in high yield with moderate to high selectivities (Scheme 3, products **31**–**36**), including more recalcitrant substrates (**33** and **35**). Thus, given the selection of Pd-PEPPSI complexes that are now available, catalyst/substrate pairing can be done as necessary in order to optimize the monoarylation outcome and in some cases, such as these ortho-substituted examples, it is the less hindered catalysts that provide the best outcome.

In summary, we report a Pd-NHC catalyzed arylation of NH_3, using air- and moisture-stable precatalysts **6** and **10**.

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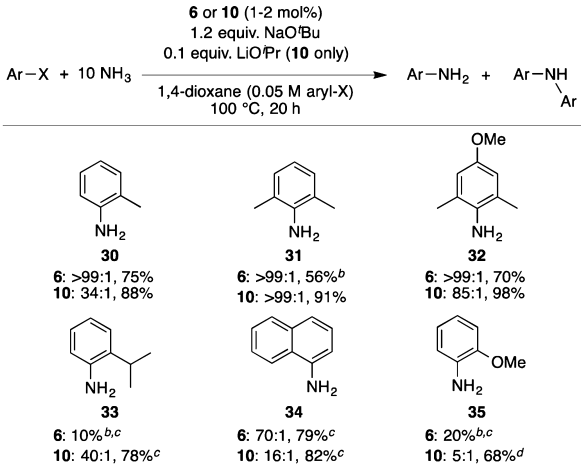
Scheme 3. Scope of Selective Monoarylation of Ortho-Substituted Aryl Halides with Ammonia using 6 and 10[a]



[a]Yields of isolated material, X = Cl, mono:di ratio determined by ^{1}H NMR spectroscopy of the crude reaction mixture. Reactions with **6** were run with 2 mol % catalyst, whereas reactions with **10** used 1 mol % catalyst. [b]Product yield determined by ^{1}H NMR spectroscopy with 1,4-bis(trichloromethyl)benzene internal standard. [c]X = Br. [d]A 2 mol % portion of **10** was used.

Under general conditions, prized (hetero)arylamine products, including those featuring base-sensitive functional groups, may be accessed efficiently with high selectivity using simple protocols.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.6b00830.

General experimental details, details of compound synthesis, and characterization data (PDF)

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Notes

The authors declare the following competing financial interest(s): Some of the catalysts in this manuscript are commercially available and the Principal author receives royalies from their sales.

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(33) (a) Pd-PEPPSI-IHept was first prepared in 2008 and disclosed at the 238th American Chemical Society National Meeting, August 16, 2009: "The Role of Bulkiness in Promoting Pd-NHC-Catalysed Cross-Couplings: A Synergy Between Experiment, Spectroscopy, and Theory" (ORGN-400). Also see: Sayah, M. Ph.D. Thesis, York University, 2013. (b) For another recent preparation of a related IHept complex, see: Meiries, S.; Le Duc, G.; Chartoire, A.; Collado, A.; Speck, K.; Arachchige, K. S. A.; Slawin, A. M. Z.; Nolan, S. P. *Chem. - Eur. J.* **2013**, *19*, 17358−17368.
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