Reductive Arylation of Nitroarenes with Chloroarenes: Reducing Conditions Enable New Reactivity from Palladium Catalysts

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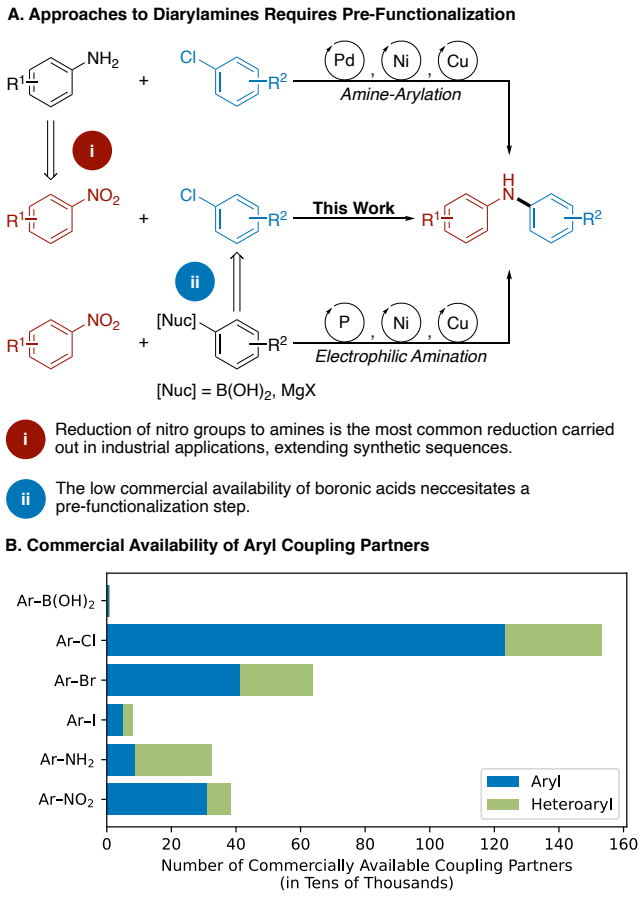
Supporting Information Placeholder

ABSTRACT: Palladium-catalyzed C–N bond forming reactions are a key tool in modern synthetic organic chemistry. Despite advances in catalyst design enabling the use of a variety of aryl (pseudo)halides, the necessary aniline coupling partner is often synthesized in a discrete reduction step from a nitroarene. An ideal synthetic sequence would avoid the necessity of this step while maintaining the reliable reactivity of palladium catalysis. Herein we describe how reducing conditions enable new chemical steps and reactivity from well-studied palladium catalysts, resulting in a new, useful transformation: the reductive arylation of nitroarenes with chloroarenes to form diarylamines. Mechanistic experiments suggest that under reducing conditions, BrettPhos-palladium complexes catalyze the dual *N*-arylation of typically inert azoarenes—generated via the in situ reduction of nitroarenes—via two distinct mechanisms. Initial *N*-arylation proceeds via a novel association-reductive palladation sequence followed by reductive elimination to yield an intermediate 1,1,2-triarylhydrazine. Arylation of this intermediate by the same catalyst via a traditional amine arylation sequence forms a transient tetraarylhydrazine, unlocking reductive N–N bond cleavage to liberate the desired product. The resulting reaction allows for the synthesis of diarylamines bearing a variety of synthetically valuable functionalities and heteroaryl cores in high yield.

Introduction

Palladium-catalyzed amine arylation—the cross-coupling of aryl (pseudo)halide electrophiles with amine nucleophiles to form a new C–N bond (Scheme 1A)—is one of the most-used reactions in medicinal chemistry.[1–3] Buoyed by the importance of amines in pharmaceuticals, the abundance of starting materials, and wide functional group tolerance, the success of amine arylation has made secondary diarylamines a common feature in medicinal and materials chemistry.[4] One key advantage of this chemistry is the ability to access a wide suite of aryl electrophiles; for example, advances in catalyst design have allowed for the use of more widely available chloroarenes instead of aryl bromides (Scheme 1B).[5–10] While there are many commercially available primary anilines, an analysis of industrial chemical reactions reveals that the synthesis of anilines by nitroarene reduction is common.[1,2,11] Indeed, a recent study on the most-used reactions in medicinal chemistry found that reduction of a nitroarene to a primary aniline was the most-used reduction. An obvious, but under-developed, alternative to this synthetic sequence is the direct, reductive arylation of nitroarenes with aryl chlorides (Scheme 1A). Despite its potential

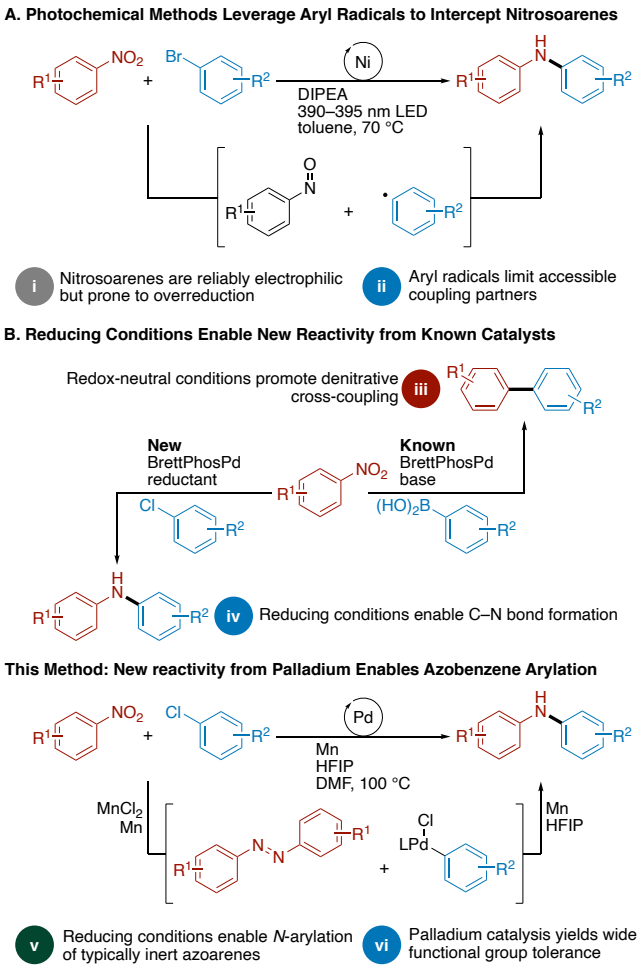
Scheme 1. Synthetic Approaches to Diarylamines.



synthetic utility, this proposed reaction faces numerous challenges, such as managing a net six-electron reduction of the nitro group, resolving the disparate reactivity of the relatively inert chloroarene, and the high electrophilicity of the many possible nitrogen intermediates.

Strategies for the reductive arylation of nitroarenes have thus far relied on the in-situ conversion of the nitroarene to a transient, electrophilic nitrosoarene, which is trapped with a nucleophilic carbon source (Ar-[M]) or aryl radical.[12] In general, the propensity of nitrosoarenes to undergo deleterious over-reduction and dimerization necessitates the use of more reactive nucleophilic carbon sources such as aryl Grignard reagents.[13–17] Despite recent advances enabling the use of less reactive arylboronic acids,[18–25] arylboronic acids are less available than chloroarenes (~180× fewer commercially available,

Scheme 2. Strategies for Nitroarene Arylation.

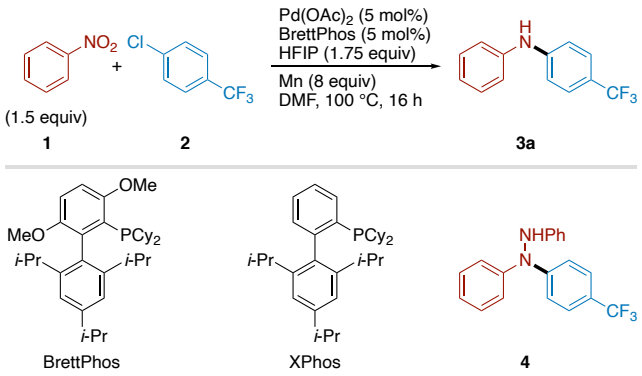


Scheme 1B),[5] adding synthetic complexity. Engagement of aryl chlorides would be simplest via oxidative addition to low-valent palladium or nickel catalysts, but the resulting arylpalladium and arylnickel intermediates are not known to form new C–N bonds with nitroarenes.

Recent work by Xue and coworkers has described the arylation of nitroarenes with bromoarenes via the photo-assisted generation of aryl radicals (Scheme 2A).[26] While an advance over the use of pre-formed aryl nucleophiles, the aryl radical intermediates limit compatibility with heterocycles and even more powerful reductants would be needed to extend this strategy to chloroarenes.[27–33] Harvey and Hu have reported on the reductive acylation of nitroarenes.[34,35] Unlike the known arylation reactions, this reaction proceeds via activation of an intermediate azoarene to form a reactive mixed nickel/zinc-imido complex. While the reactivity of these imido intermediates has been limited to acylation reactions, the intermediacy of an azoarene intermediate offers advantages over nitrosoarenes (vide infra). In contrast to nickel, palladium-catalyzed reductive arylation or acylation of nitroarenes is unknown. Instead, palladium-catalyzed cross-couplings of nitroarenes feature C–NO_2 oxidative addition (Scheme 2B).[36–40]

Herein we demonstrate how the same palladium catalysts that favor C–NO_2 oxidative addition and promote C–N bond formation with amines[39,40] reveal new reactivity when subjected to reducing conditions: catalyzing the *N*-arylation of azoarenes via an association-reductive palladation sequence. The *N*-functionalization of azoarenes using arylpalladium(II)

Table 1. Standard Conditions and Effects of Select Deviations.



entry	deviation	**3a** (%)[b]
1	None	92
2	XPhos instead of BrettPhos	86
3	*rac*-BINAP instead of BrettPhos	1
4	No HFIP	0
5	TFE instead of HFIP	9
6	2-Butanol instead of HFIP	29
7	$PdCl_2$ instead of $Pd(OAc)_2$	81
8	$Pd_2(dba)_3$ instead of $Pd(OAc)_2$	87[c]
9	Zn instead of Mn	89
10	Benchtop setup with no exclusion of air or water (capped)	90[d]

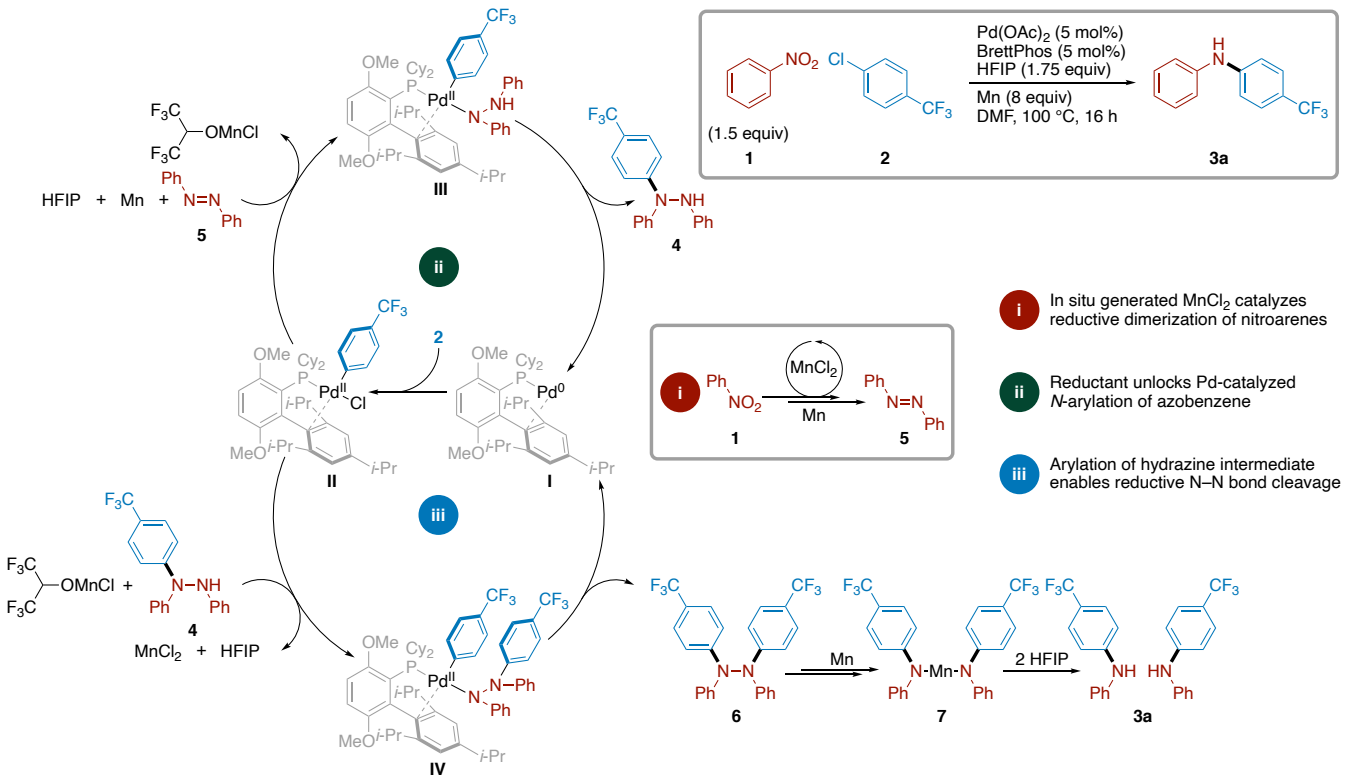
[a]Reactions were assembled in a nitrogen filled glovebox at a 0.25 mmol scale in 0.5 mL of DMF. [b]Yields were determined by SFC-MS analysis. [c]2.5 mol% $Pd_2(dba)_3$ used instead of 5 mol% $Pd(OAc)_2$. [d]Reaction set up at 0.5 mmol scale in 1 mL of DMF.

intermediates is notable because the N=N bond of azoarenes is generally considered inert towards arylpalladium(II) intermediates;[41] even functioning as a useful directing group for C–H bond activation.[42–50] Our studies show that C–N bond formation occurs via reductive dimerization of nitroarenes to azoarenes, followed by diarylation to form a tetra-arylhydrazine, and reductive cleavage of the hydrazine to form two molecules of product. This dimerization-functionalization-cleavage strategy avoids over-reduction that can plague nitrosoarenes, and changes the way that we view reactions of palladium(II) complexes with azo compounds.

Results and Discussion

We began by examining the reductive arylation of nitrobenzene (**1**) with 4-chlorobenzotrifluoride (**2**) (Table 1). Preliminary studies quickly established two key variables in the reaction: the identity of the ligand and the presence of an appropriate proton source. We found that BrettPhos, the same ligand known for promoting C–NO_2 oxidative addition in denitrative cross-couplings, was optimal. While other monodentate, dialkylbiarylphosphines such as XPhos also provided the desired product in good yield, common bidentate phosphines, such as *rac*-BINAP did not. Serendipitously, we found that alcohols modulate the extent of arylation, promoting conversion of intermediates to the desired product and preventing overarylation of the desired diarylamine. Tuning the pK_a of the alcohol is critical, as less acidic additives such as 2,2,2-trifluoroethanol

Scheme 3. Key Aspects of the Proposed Mechanism of the Palladium-Catalyzed Reductive Arylation of Nitroarenes.



(TFE) provided the under-arylated 1,1,2-triarylhydrazine (**4**) as the major arylated product. As will be discussed in more detail below, the alcohol facilitates two proton transfers: mediating the arylation of **4** via association-deprotonation as the conjugate base and providing the desired product from the diarylamide (**7**), thereby preventing overarylation to triarylamine. Besides these two variables, we found that many other components of the reaction conditions were flexible. A variety of palladium(II) and palladium(0) precatalysts provided similar results, although $Pd(OAc)_2$ was chosen due to its high solubility. Manganese powder was optimal, however zinc flake gave similar yields, despite it being a weaker reducing agent. The reactions were generally run under air-free conditions using dry, degassed solvents, but similar yields were obtained using wet DMF, under an air headspace when set up on the benchtop.

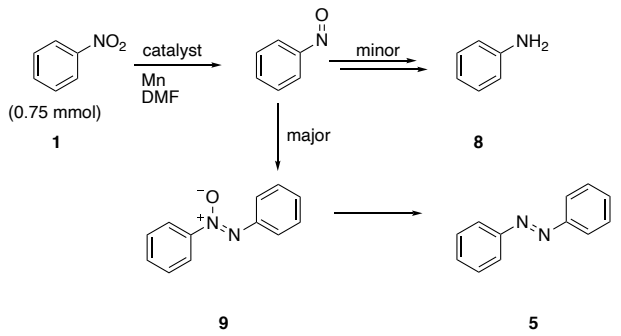
Given the impact of mechanistic understanding on reaction design, the importance of palladium catalysis, and the unique *N*-arylation observed in these conditions, we undertook a mechanistic investigation. We sought to: identify the catalytic species responsible for nitroarene reduction; confirm the identity of the active nitrogenous coupling partner; determine the mechanism by which *N*-arylation occurs; and establish the role of the alcohol in controlling the extent of arylation. Based on observations in catalytic reactions and specific mechanistic experiments described below, we propose the mechanism seen in Scheme 3.

Initial reduction of nitrobenzene occurs via a $MnCl_2$-catalyzed, reductive dimerization to yield azobenzene (**5**). While additional reduction to form hydrazobenzene is possible, experimental evidence suggests that this process is off-cycle and slow in comparison to productive *N*-arylation (Figures S9 and S16). Catalytic *N*-arylation of **5** begins with oxidative addition of **2** to in situ generated Pd^0 (**I**) to form the key oxidative addition intermediate (**II**). We posit that association of the Lewis basic nitrogen of **5** to the Lewis acidic Pd^{II} center forms [(BrettPhos)Pd(Ar^1)Cl(Ar^2N=NAr^2)].[51] This association then enables reduction of the N=N bond of **5** to form a transient mixed palladium(II)/manganese hydrazide which is protonated by HFIP to form palladium(II) aryl hydrazide (**III**) and an alkoxide base. This manganese dependent, reductive palladation could be imagined as analogous to reported reductions of bound ligands, such as dinitrogen.[52] Reductive elimination forms the C–N bond of $Ar^1(Ar^2)$N–NH(Ar^2) (**4**).

The second arylation of **4** occurs via an amine-arylation sequence involving oxidative addition of **2** to **I**, association-deprotonation of **4** to **II,** and C–N reductive elimination from intermediate **IV** to yield a transient 1,1,2,2-tetraarylhydrazine (**6**). The weak N–N bond of **6** then undergoes rapid homolysis,[53,54] followed by reductive capture by Mn, yielding manganese bisdiarylamide (**7**). Final protonation furnishes the desired product (**3a**) and prevents deleterious transmetalation onto **II**, stopping over-arylation to form $Ar^2N(Ar^1)_2$ (over-arylation not depicted in Scheme 3).

We began our mechanistic investigation by determining the conditions necessary for the reduction of nitrobenzene. In contrast to other reductive functionalizations of nitroarenes that employ manganese as the terminal reductant,[34,35,55–59] our conditions did not require the addition of a stoichiometric, oxophilic Lewis acid. We considered whether Pd(0), Pd(II), or residual Mn salts catalyzed the Mn powder reduction step (Table 2). Neither inclusion of the optimal $Pd(OAc)_2$/BrettPhos precatalyst pair (not pictured), nor palladium(0) precursor $(cod)Pd(CH_2TMS)_2$, enabled reduction of nitrobenzene. While the addition of catalytic amounts of oxidative addition Pd(II) complex **II** did allow for reduction of nitrobenzene, the observed induction period led us to conclude that catalyst modification is necessary and **II** is not directly responsible for catalysis. Indeed, addition of catalytic $MnCl_2$—the byproduct of

Table 2. Reduction of Nitrobenzene is Catalyzed by in situ-generated $MnCl_2$



catalyst	Conversion at 15 min (%)[b]	Conversion at 90 min (%)[b] (**9**:**5**:**8**)
(cod)Pd(CH_2TMS)$_2$ and BrettPhos	0	5[c]
(BrettPhos)Pd(Ar)Cl (**II**)	<1	100 (4.7:1.2:1)
$MnCl_2$	18	72 (8.0:1.5:1)

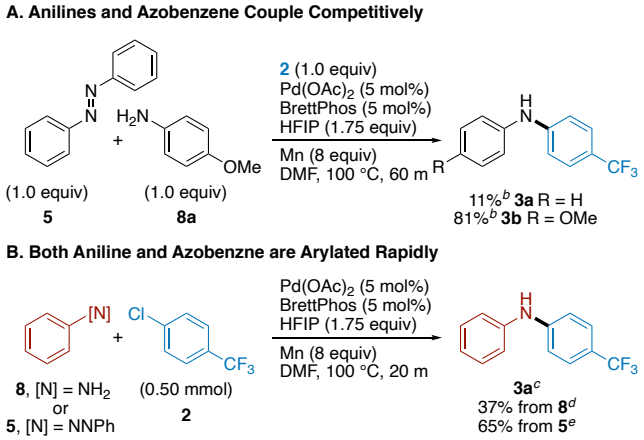
[a]Reactions were assembled in a nitrogen filled glovebox. 0.75 mmol **1**, 3.3 mol% catalyst, 5.33 equiv Mn, 1 ml DMF, 100 °C, 90 m. [b]Concentration was determined by SFC-MS. [c]No Reduction products were observed.

reductive decomposition of **II** by Mn—unlocked reduction of nitrobenzene.[60] Based on these results, we concluded that the coupling reaction is autocatalytic, with initial, slow decomposition of small amounts of **II** turning on the productive pathway, which in turn produces more $MnCl_2$ (Figure S1).

Over the course of catalytic reactions and discrete reduction studies, we observed two probable nitrogenous coupling partners: azobenzene (**5**) and aniline (**8**). While both coupling partners are rapidly arylated under reaction conditions at similar rates (Scheme 4), under these reducing conditions azoxybenzene (**9**) and azobenzene (**5**) form at higher concentration than aniline (Table 2 and Figure S9). Indeed, the reductive dimerization of nitrobenzene to form azobenzene is well known.[56,61,62] These observations, combined with the high rate of *N*-arylation of azobenzene (Scheme 4b, Figure S13), and differences in reaction outcomes between electron-poor anilines and electron-poor nitroarenes (Figure S12) led us to conclude that while reductive amine arylation can occur under these conditions, it is a beneficial, convergent side reaction and that double *N*-arylation of azobenzene is the major pathway.

The N=N bond of azoarenes is typically inert to palladium catalysis, even serving as a directing group for C–H functionalization.[42–46] While limited examples of palladium(0)-mediated reductive functionalization of azo compounds have been reported;[63,64] catalytic, *N*-arylation from palladium oxidative addition complexes is unknown. As such, we sought to determine the elementary step by which arylation occurs, with the aim to better understand this coupling and expand the catalytic schema used to design new reactions. We envisioned 3 possible mechanisms by which palladation of azobenzene might occur: direct migratory insertion of the Pd–C bond across the N=N bond (Scheme 5ii); reduction of **II** to form a reactive palladium(I) intermediate that can capture azobenzene (Scheme 5iii); and association-reduction of azobenzene in a reactive transmetalation process (Scheme 5i).

Scheme 4. Evaluation of Possible Coupling Partners.

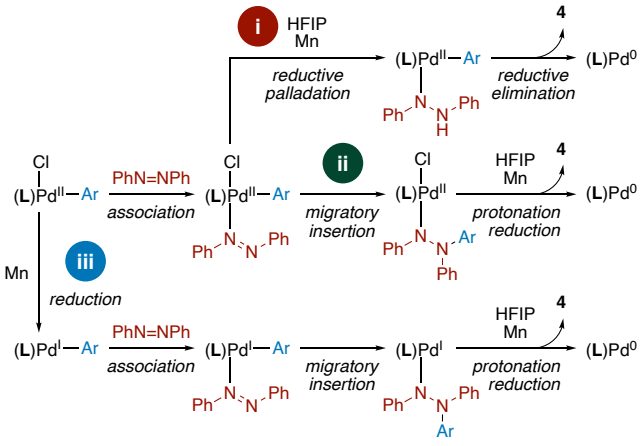


[a]Reactions were assembled in a nitrogen filled glovebox at a 0.50 mmol scale in 1.0 mL of DMF. [b]Yields were determined by ^{19}F NMR. [c]Yields were determined by SFC-MS analysis. [d]0.75 mmol of aniline. [e]0.375 mmol of azobenzene.

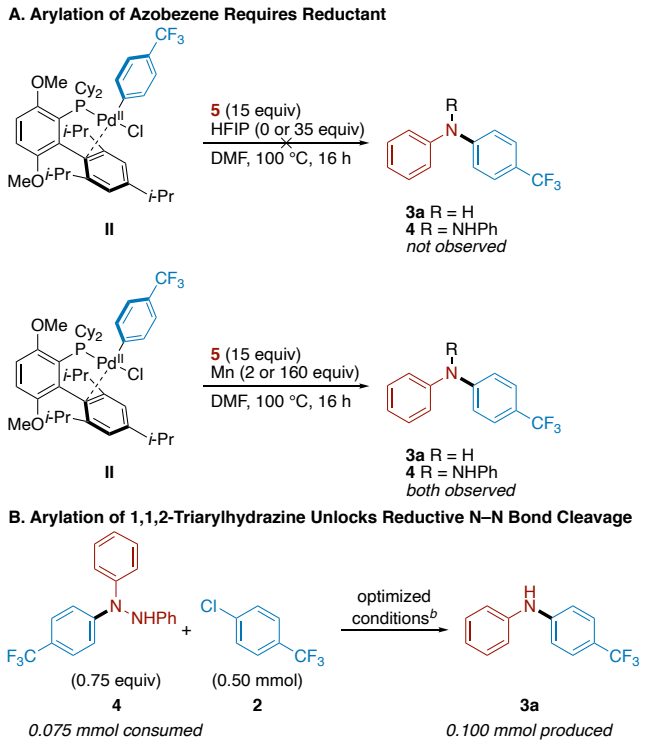
To establish a baseline for reactivity, we reacted **II** with excess azobenzene **5** (Scheme 6A). In the absence of a reductant, no *N*-arylated products were observed (Figure S14), indicating that direct migratory insertion (Scheme 5, pathway ii) is not probable. Only addition of manganese enabled arylation, as **3a** and **4** were observed in reactions containing stoichiometric or excess reductant. These results suggest that either reduction of **II**, azobenzene (**5**), or their association complex is necessary for arylation to occur.

We utilized cyclic voltammetry to distinguish between pathways involving the reduction of **II** and azobenzene **5**. While reductive decomposition of **II** does occur under reducing conditions (Scheme 4A), CV confirmed that irreversible reduction only occurs at very reducing potentials (-2.23 V vs. Fc/Fc^+). Contrastingly, direct, reversable, single-electron reduction of azobenzene is thermodynamically plausible under the reaction conditions (-1.80 V vs. Fc/Fc^+). These data indicate that either direct reduction of azobenzene occurs – the resulting radical anion then exchanging for the chloride ligand on **II** – or that association of azobenzene to the Lewis acidic **II** enables reduction. We predict that association-reduction is the dominant

Scheme 5. Possible *N*-Arylation Pathways to Form Triarylhydrazine (4) from Azoarene and Arylpalladium(II).



Scheme 6. Additional Mechanistic Studies Support Double *N*-Arylationof Azobenzene.



[a]Reactions were assembled in a nitrogen-filled glovebox. Yields were determined by SFC-MS analysis. [b]5 mol% $Pd(OAc)_2$, 5 mol% BrettPhos, 1.75 equiv HFIP, 8 equiv Mn, 1 ml DMF, 100 °C, 16 h.

pathway, as substituting manganese for the much less reducing zinc leads to little change in yield (89% vs 92%) and hydrazobenzene—the product of direct reduction of azobenzene—is not arylated under the optimized conditions (Figure S17).

The intermediacy of **4** was confirmed by replacing nitrobenzene with **4** in the optimized reaction conditions (Scheme 6B). Arylation yielded diarylamine **3a** in excess of the consumption of **4** (0.075 mmol of **4** consumed, 0.1 mmol of **3a** produced). While consumption of **4** was low, this result also confirms that direct reductive cleavage of the N–N bond of **4** (yielding an equivalent of **3a** and aniline **8**) is not operable. We hypothesize that the low conversion was due to the presence of an extra equivalent of protons compared to nitroarene or azoarene arylation reactions. This results in inefficient association-deprotonation of **4** and eventual reductive catalyst degradation.

Finally, we sought to rationalize the role of the alcohol in determining selectivity. As seen in Table 1, the exclusion of a proton source from reactions completely stops the formation of **3a**. However, its exclusion neither prevents reduction of nitrobenzene nor arylation of the resulting azoarene, as **4** is still observed. We propose that balancing the acidity and the steric profile of the alcohol is necessary to manage the protonation of intermediates and the binding of the alkoxide to **II**. Formation of palladium(II) alkoxide complexes is a known intermediate or off-cycle pathway in amine arylation reactions.[65–67] Indeed, we found that **II** is more stable under reducing conditions in the presence of an alcohol (Figure S11). Employing the less acidic and sterically demanding trifluoroethanol in place of HFIP in arylations of nitrobenzene yielded **4** as the major product. We hypothesized that inefficient arylation of **4** is caused by exchange of 2,2,2-trifluoroethoxide for chloride on **II**, yielding an unreactive, stable, palladium(II) alkoxide that prevents association of **4**. Deprotonation of associated **4** is most likely not a limiting factor, as 2,2,2-trifluoroethoxide is more basic than 1,1,1,3,3,3-hexafluoroisopropoxide. Indeed, utilizing 2-butanol as the proton source in place of TFE yields increased conversion of **4** into **3a**. These results indicate that balancing the association of the alkoxide to **II**—via the use of an electron-poor, secondary alcohol—enables arylation of **4**, provides protons to quench the reactivity of the final product, while also stabilizing **II** under reducing conditions.

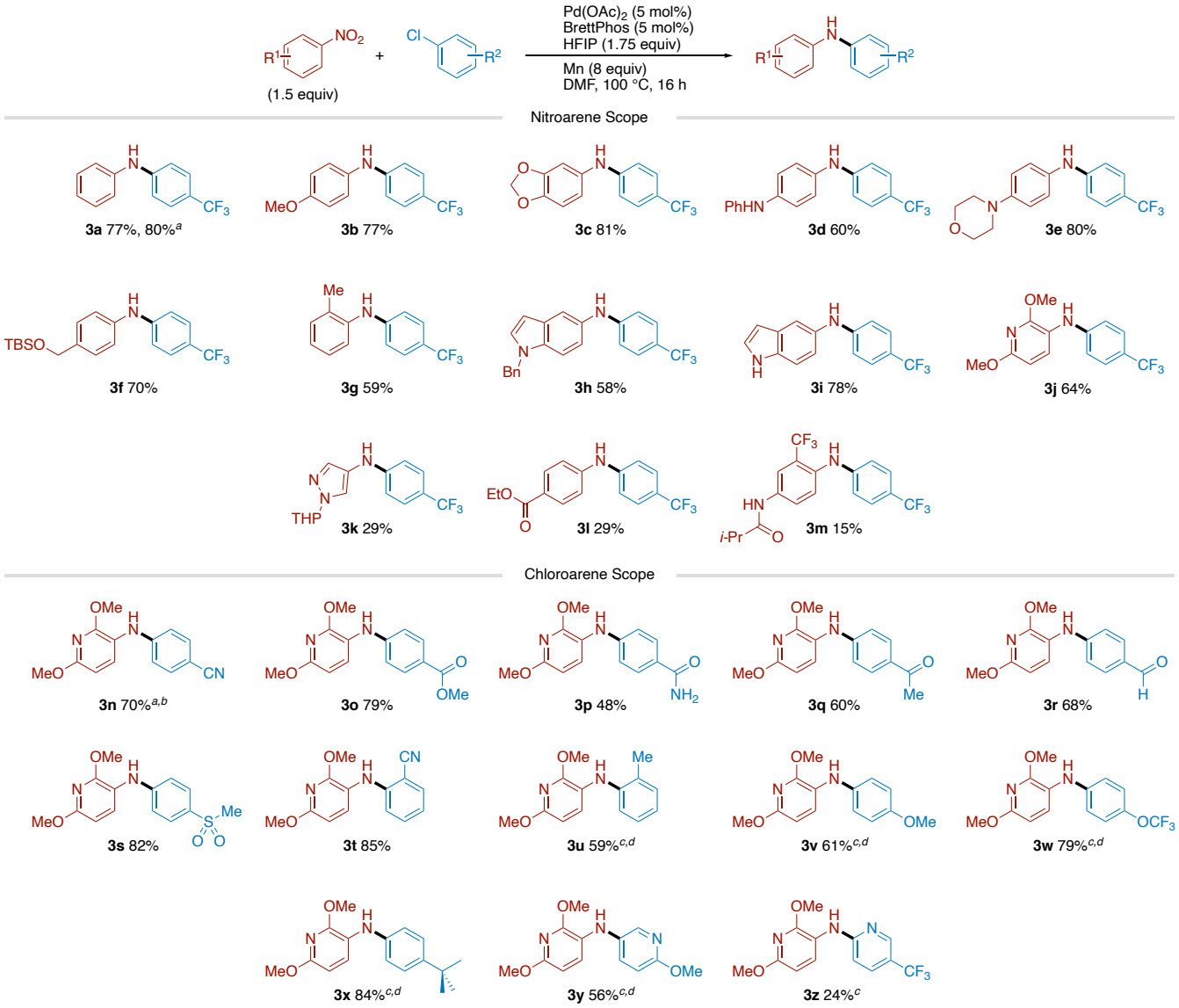
Having an effective understanding of the mechanism by which the reaction proceeds, we proceeded to investigate the scope accessible using these initial conditions (Scheme 7, *next page*). Arylation of nitroarenes bearing synthetically valuable electron-donating groups such as a methyl ether (**3b**), methylenedioxy (**3c**), or an unprotected secondary amine (**3d**) all proceeded in high yield. In contrast to photochemical alternatives to this method,[26] easily oxidized tertiary alkylamines (**3e**) were also well-tolerated. Nitroarenes bearing a silyl protected aliphatic alcohol (**3f**) or substitution in the 2-position (**3g**) were also arylated effectively. Additionally, the optimized conditions enabled the arylation of a variety of nitroheteroarenes, which are not tolerated in photochemical methods due to the reactivity of aryl radicals.[26,28,68–70] We found that common heterocycles such as protected and unprotected indoles (**3h**, **3i**), pyridine (**3j**), and protected pyrazole (**3k**) were all tolerated.

We found that the introduction of an electron-withdrawing ethyl ester (**3l**) significantly decreased the yield of the desired diarylamine. As the major byproduct was the corresponding primary aniline, we hypothesize that direct reduction of an intermediate electron-poor nitrosoarene may occur faster than reductive dimerization. Despite this limitation, the diarylamine derived from arylation of electron-poor chemotherapeutic flutamide (**3m**) was isolated in 15% yield. Again, the primary aniline derived from flutamide was isolated as the major byproduct. These results suggest that modification of the reaction conditions to avoid over-reduction or engage the aniline directly in amine-arylation may be successful in overcoming this limitation.

A variety of electron-poor chloroarenes were effectively engaged using the optimized conditions. We successfully coupled chloroarenes bearing carboxylic acid derivatives including nitriles (**3n**, **3t**), a methyl ester (**3o**), and a primary amide (**3p**). The reaction was amenable to increased scale and a benchtop setup while maintaining good yield (**3n** was synthesized at 2.0 mmol scale on the benchtop using standard air-free technique). Other oxidized functionalities that could be reduced were well tolerated, such as an acetophenone (**3q**), an unprotected benzaldehyde (**3r**), and a sulfone (**3s**). Further, activation of ortho-subsituted chloroarenes yielded secondary diarylamines with either an electron-withdrawing nitrile (**3t**) or electron-donating methyl (**3u**) group in the two-position.

We found that two modifications were necessary to effectively couple electron-rich chloroarenes: increasing the catalyst loading from 5 to 10 mol% and replacing HFIP with the less acidic TFE. These conditions enabled the coupling of chloroarenes bearing electron-donating methyl and trifluoromethyl ethers (**3v**, **3w**), as well as simple alkyl substituents (**3u**, **3x**). We hypothesize that these two changes overcome sluggish arylation of the 1,1,2-triarylhydrazine intermediate afforded from the initial N-arylation of the azoarene and stabilize the critical oxidative addition intermediate (**II**). The decreased Lewis acidity of arylpalladium complexes bearing electron-rich

Scheme 7. Substrate Scope for the Palladium-Catalyzed Reductive Arylation of Nitroarenes with Aryl Chlorides.



Reactions were conducted at 0.5 mmol scale in DMF (1 mL). Isolated yields after purification are shown. [a]Reaction conducted at 2.0 mmol scale. [b]Reaction set up on the benchtop using standard air-free technique. [c]10 mol% each of $Pd(OAc)_2$ and BrettPhos. [c]TFE instead of HFIP.

aryl substituents most likely makes association and deprotonation of the hydrazine intermediate significantly less favorable. Utilizing TFE can have two beneficial effects. First, the more associating 2,2,2-trifluoroethoxide anion may extend catalyst lifetime, forming a reservoir of stable palladium(II) alkoxide. Second, the more basic alkoxide may enable deprotonation of the hydrazine intermediate.

These modified conditions also allowed for the coupling of an electron-rich 3-chloropyridine, yielding diheteroarylamine (**3y**). The increased catalyst loading is also beneficial when coupling other heteroaryl chlorides, regardless of the electron density in the ring (**3z**). Together, these results demonstrate the synthetic utility, functional group tolerance, and electronic and steric limitations of this method.

Conclusions

In conclusion, we developed the first method for the reductive arylation of nitroarenes with chloroarenes. This method relies on a new dimerization-arylation-fragmentation mechanism that avoids deleterious overreduction of reduced nitrogenous intermediates. *N*-arylation of the typically inert azoarene intermediate is unlocked by the reducing conditions. Diarylation of the N=N bond of the azoarene activates it towards reductive cleavage. The resulting reaction tolerates a range of synthetically relevant functionalities, steric crowding, and heterocyclic cores. We expect that the mechanistic results in this study will provide a basis for rapid development of this new approach to diarylamines.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, spectral data, and supplementary tables of data. (PDF)

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ACKNOWLEDGMENT

This work was supported by the NIH (R01GM097243). Analytical data were obtained from the CENTC Elemental Analysis Facility at the University of Rochester, funded by NSF CHE-0650456. Mass spectroscopy and NMR data were obtained in the Paul Bender Chemistry Instrumentation Center. The purchase of the Thermo Scientific Q Exactive Plus in 2015 was funded by the NIH Award 1S10 OD020022-1 to the Department of Chemistry. The purchases of the Bruker Avance III 500 and 400 MHz instruments were funded by a generous gift from Paul J. and Margaret M. Bender in 2012 and NSF CHE-1048642 to the Department of Chemistry in 2010 respectively. We thank Dr. Jiang Wang (UW-Madison) for assistance with initial experiments. We thank Dr. Paige Piszel (UW-Madison) for assistance with electrochemical measurements. We thank Michelle Akana (UW-Madison) for assistance with the preparation of charts and graphs.

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(5) Commercial availability of coupling partners was gathered via a search of the eMolecules database—via Reaxys—performed on 7/18/18. Aryl and heteroaryl coupling partners were specified as ARY–FG and HAR–FG (where FG represents the functional group in question, e.g., Cl, Br, NO2) respectively. While the exact number of commercial coupling partners changes in magnitude depending on the database searched, e.g., PubChem Commercial Substances via Reaxys, Reaxys Commercially Available Filter, etc., the trends observed are consistent.

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