Ammonia Coupling Hot Paper

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Nickel-Catalyzed Monoarylation of Ammonia**

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Abstract: *Structurally diverse (hetero)aryl chloride, bromide, and tosylate electrophiles were employed in the Ni-catalyzed monoarylation of ammonia, including chemoselective transformations. The employed JosiPhos/[Ni(cod)$_2$] catalyst system enables the use of commercially available stock solutions of ammonia, or the use of ammonia gas in these reactions, thereby demonstrating the versatility and potential scalability of the reported protocol. Proof-of-principle experiments established that air-stable [(JosiPhos)NiCl$_2$] precatalysts can be employed successfully in such transformations.*

Ammonia ranks among the most widely produced commodity chemicals, and virtually all synthetic nitrogen-containing compounds originate from this inexpensive feedstock chemical.[1] Notwithstanding the wide-ranging industrial-scale processes that successfully utilize ammonia (e.g. the Ostwald process[2] for nitric acid production), the industrial synthesis of amines from ammonia often involves the use of heterogeneous catalysts at relatively high temperatures and pressures, leading to poor product selectivity.

The application of homogeneous transition-metal catalysis for the selective synthesis of amines from ammonia under mild conditions is appealing, however, the development of such transformations is challenging.[3] This is particularly true for the palladium-catalyzed cross-coupling of (hetero)aryl (pseudo)halides with substrates containing N–H groups (i.e. Buchwald–Hartwig amination, BHA[4]). While BHA represents one of the most widely utilized C–N bond-forming protocols for the construction of (hetero)aromatic amines, reports of the successful use of ammonia in such transformations are exceedingly rare,[5] despite the fact that such primary aniline derivatives represent sought-after synthetic intermediates and target compounds in the construction of both biologically active molecules and conjugated functional organic materials.[6] Problems associated with the use of ammonia in BHA and related cross-coupling reactions include catalyst deactivation arising from ammonia-induced ancillary ligand dissociation, as well as uncontrolled polyarylation arising as a result of the ability of the primary aniline product to act as a contending substrate versus ammonia.[5] Nonetheless, in 2006 Shen and Hartwig[7] demonstrated that the judicious choice of the palladium source and the ancillary ligand[8] can afford highly effective catalysts for ammonia monoarylation. This observation and subsequent reports by the groups of Hartwig,[9] Buchwald,[10] Beller,[11] and Stradiotto[12] on the employment of electron-rich and sterically demanding phosphine ancillary ligands established broad substrate scope in the (hetero)aryl (pseudo)halide reaction partner (Figure 1a). The practical utility of the palladium-catalyzed monoarylation of ammonia has recently been demonstrated in the synthesis of pharmaceutically relevant dibenzodiazepines,[10b] and in natural product synthesis.[13]

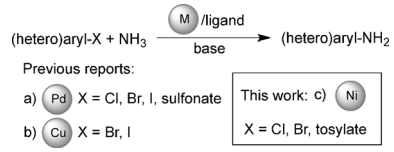

Figure 1. Previous reports of the monoarylation of ammonia catalyzed by a) palladium and b) copper, and c) nickel-catalyzed transformations reported herein.

Notwithstanding the utility of palladium-catalyzed ammonia monoarylation protocols, the significant cost and relatively low abundance of palladium led to the investigation of first-row transition-metal catalysts for such difficult transformations. Beyond economic benefits, the smaller size and distinct electronic properties of the first-row transition metals, relative to the platinum-group metals, may offer new reactivity and thus a means of addressing outstanding challenges in the monoarylation of ammonia. While copper catalysts for ammonia monoarylation have been developed,[14] they exhibit a number of limitations, including poor performance with (hetero)aryl chloride and phenol-derived pseudohalide substrates (Figure 1b). Such limitations are significant, as these substrates represent the least expensive and most widely available aryl electrophile reaction partners.

In an alternative approach, we considered nickel-based catalysts for use in the monoarylation of ammonia. Beyond the fact that nickel is about 1000 times less expensive than palladium, nickel is a privileged metal in myriad challenging cross-coupling applications.[15] Indeed, nickel-based catalysts have proven effective for the arylation of primary as well as secondary amines in combination with synthetically useful

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(hetero)aryl chlorides and phenol-derived pseudohalide (hetero)aryl electrophiles.[15a,16] However, despite this significant progress in C–N cross-coupling chemistry, effective nickel-based catalysts for the monoarylation of the most ubiquitous and important N–H reagent, ammonia, were unknown prior to our work reported herein.

A particularly attractive feature of nickel catalysis, relative to palladium catalysis, is the often successful employment of structurally simple ancillary ligands.[15a] However, lacking prior reports of effective nickel-based catalysts for the monoarylation of ammonia, we screened ligands for the cross-coupling of 4-bromobiphenyl and ammonia to afford 4-aminobiphenyl (**1**), using a range of structurally complex phosphine-based ancillary ligands (Figure 2). For simplicity,

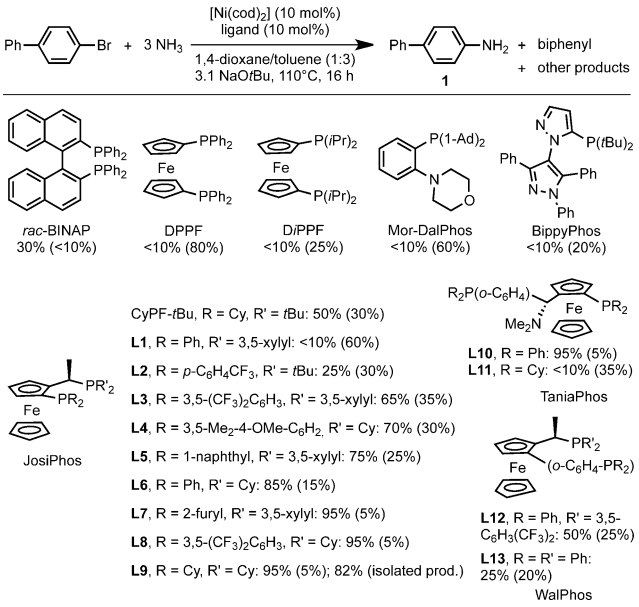

Figure 2. Ligand screen for the nickel-catalyzed monoarylation of ammonia with 4-bromobiphenyl using 0.5 M stock solutions of ammonia in 1,4-dioxane. Conversion determined by GC, reported as % 4-aminobiphenyl (% biphenyl); mass balance attributable to remaining 4-bromobiphenyl and/or unidentified side products.

we intentionally screened catalysts that did not require added nitrile as a co-ligand[16w] or additive,[16y] and employed commercially available ammonia stock solutions (0.5 M in 1,4-dioxane). Our choice of an aryl bromide in this screening process, rather than more sought-after chloride aryl electrophiles, was based on the apparently more challenging nature of aryl bromides in nickel-catalyzed C–N cross-coupling reactions.[17] We initially focussed our attention on the use of *rac*-BINAP and DPPF, given the successful application of nickel catalysts featuring these ligands in C–N cross-couplings of both primary and secondary amines.[16a,w,y] However, these ligands, as well as the more electron-rich D*i*PPF, proved ineffective for the nickel-catalyzed selective monoarylation of ammonia under the screening conditions employed. We then turned our attention to the application of a selection of other commercially available ancillary ligands that have proven effective in the palladium-catalyzed monoarylation of ammonia, including Mor-DalPhos,[12a] BippyPhos,[12d] and the JosiPhos ligand variant CyPF-*t*Bu.[7,9] While none were found to be particularly selective for ammonia monoarylation, the modest success achieved with CyPF-*t*Bu prompted a more detailed survey of structurally related JosiPhos (**L1**–**L9**), TaniaPhos (**L10** and **L11**), and WalPhos (**L12** and **L13**) ligands developed by Solvias. Gratifyingly, ligands **L7**–**L10** proved highly effective, affording high conversion to 4-aminobiphenyl (**1**), which was isolated in 82% yield using **L9**. We are presently unable to rationalize the success of **L7**–**L10**, both in terms of the structural variability found within this successful set of ligands, and between these and structurally similar yet less effective ferrocenyl ligands within the screened set. Nonetheless, we subsequently observed that **L9** was modestly more effective than **L7**, **L8**, or **L10** in a small selection of nickel-catalyzed ammonia monoarylation reactions involving alternative (hetero)aryl halide electrophiles. We thus used **L9** as the ligand of choice in exploring the scope of reactivity with various (hetero)aryl (pseudo)halides more broadly. Given recent evidence for photoinduced Ullmann C–N coupling involving copper-based catalysts,[18] we conducted control experiments employing **L9** in the nickel-catalyzed monoarylation of ammonia with 4-bromobiphenyl with the exclusion of ambient light. No change in catalytic performance was noted relative to reactions conducted without such precautions.

Having identified an effective nickel-based catalyst system for the monoarylation of ammonia, we turned our attention to exploring the scope of reactivity (Figure 3). Preliminary studies confirmed that **L9**/[Ni(cod)$_2$] can accommodate analogous chloride and tosylate electrophiles, affording **1** in 88% and 90% yield, respectively. A selection of *para*-substituted 4-chlorobiphenyl derivatives featuring methyl, cyano, trifluoromethyl, or methoxy substituents were also accommodated (**2**–**5**, 72–92%), as were structurally related pyrrole (**6**, 78%) and pyridine (**7**, 81%) substrates. Chlorobenzenes featuring one or two substituents in the *ortho* position, or alternatively fluoro or methoxy substituents, proved to be compatible substrates (**8**–**12**, 71–85%). We also challenged the **L9**/[Ni(cod)$_2$] catalyst system with chlorobenzene substrates featuring potentially competitive secondary amine functionalities, and observed chemoselectivity for ammonia monoarylation, affording **13** (68%) and **14** (75%). The success of the **L9**/[Ni(cod)$_2$] catalyst system in the monoarylation of ammonia is noteworthy, as no first-row transition-metal catalyst, including the various copper-based catalysts reported to date,[14] was able to promote the cross-coupling of ammonia with unactivated aryl chlorides, or tosylate electrophiles.

Heteroaryl primary aniline derivatives represent particularly attractive synthons in medicinal, biological, natural products and materials chemistry.[6] Therefore, we expanded our studies on the substrate scope to various heteroaryl chlorides and bromides (Figure 3). Remarkably, amino-functionalized pyridine (**15**), pyrimidine (**16**), quinaldine (**17**, **18**), isoquinoline (**19**), quinoline (**20**, **21**), quinoxaline (**22**, **23**), benzothiophene (**24**), and benzothiazole (**25**) heterocycles were prepared efficiently by using our nickel-catalyzed ammonia monoarylation protocol (Figure 3, 68–85%). Only

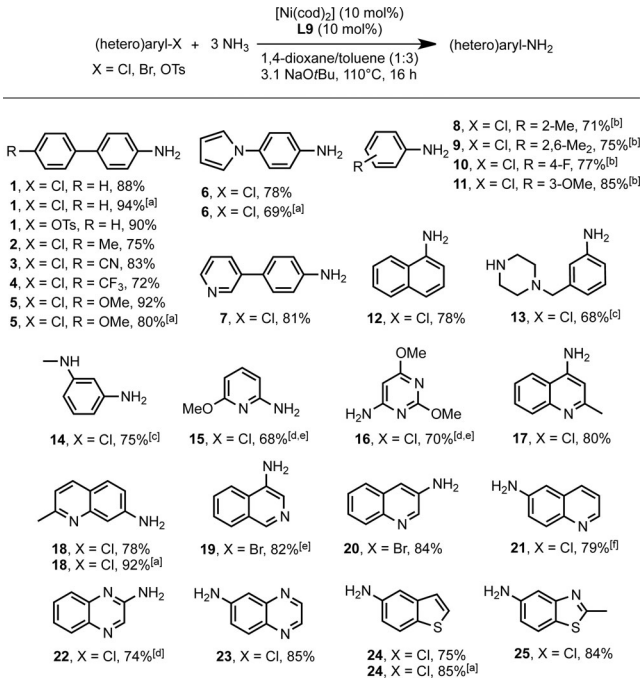

Figure 3. Scope of Ni-catalyzed monoarylation of ammonia with (hetero)aryl (pseudo)halides (yields of isolated products reported). Unless stated otherwise, ammonia was obtained from 0.5 M 1,4-dioxane stock solutions. [a] Ammonia gas employed under similar conditions (114 psi initial pressure, see the Supporting Information for full details). [b] Yield of the corresponding isolated (aryl)NHTs. [c] 7 equiv NH_3. [d] 65 °C. [e] 5 equiv NH_3. [f] Using **L8**.

in the case of 6-chloroquinoline, leading to **21**, did we observe that the performance of **L9** was inferior to that of **L8**. Control experiments involving the formation of **15**, **16**, and **22** in the absence of **L9**/[Ni(cod)$_2$] showed no conversion to the desired product.

In the experiments described thus far, we used commercially available 0.5 M solutions of ammonia in 1,4-dioxane, which is apparently the protocol of choice in analogous palladium-catalyzed reactions.[9–13] While convenient and operationally simple for use in small-scale laboratory syntheses, the use of ammonia gas would appear to be more scalable. Notwithstanding the significant progress that has been achieved in the development of effective palladium catalysts for the monoarylation of ammonia, to the best of our knowledge the use of ammonia gas in such transformations is limited to only two reports by the Hartwig group.[7,9] While the particular reason for this trend is unclear, it is possible that catalyst deactivation arising from ammonia-induced ancillary ligand dissociation may be problematic for some catalyst systems under high pressures of ammonia.[5] Gratifyingly, the **L9**/[Ni(cod)$_2$] catalyst system performed well in selected test reactions employing ammonia gas (114 psi initial pressure), affording the desired (hetero)biaryl (**1**, 94%; **5**, 80%; **6**, 69%), quinaldine (**18**, 92%), and benzothiophene (**24**, 85%) derivatives in high yields that are competitive with those obtained when using 0.5 M solutions of ammonia in 1,4-dioxane (Figure 3).

The air- and moisture-sensitive nature of [Ni(cod)$_2$] prompted us to develop air-stable nickel precatalysts for use in ammonia monoarylation. In a preliminary effort in this regard, we examined the reaction of [$NiCl_2$(dme)] with **L8** and **L9** (Figure 4a). Both reactions were successful and

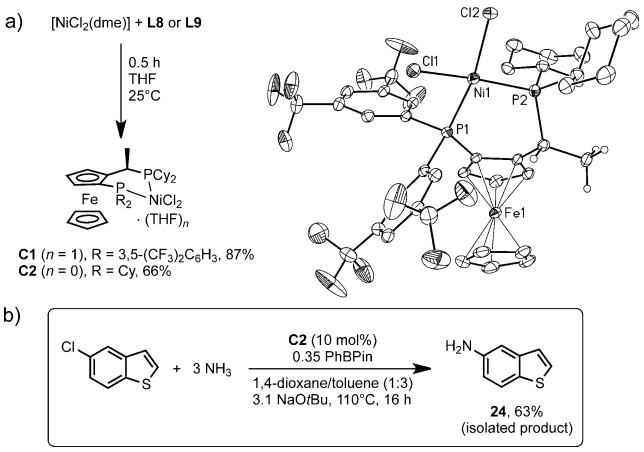

Figure 4. a) Synthesis of the air-stable (JosiPhos)$NiCl_2$ precatalyst complexes **C1** and **C2**, and single-crystal X-ray structure of **C1** (30% ellipsoids; selected hydrogen atoms omitted). b) Successful application of **C2** in the synthesis of **24**.

afforded analytically pure and air-stable [(**L8**)$NiCl_2$·THF] (**C1**, 87%) and [(**L9**)$NiCl_2$] (**C2**, 66%). The established propensity of [$(PR_3)_2NiCl_2$] complexes to exist as equilibrium mixtures of tetrahedral (paramagnetic) and square-planar (diamagnetic) isomers,[19] was confirmed by solution NMR data obtained for **C1** and **C2**, revealing significant paramagnetic broadening at 300 K. However, single-crystal X-ray diffraction analysis of **C1**·2.5 C_6H_6 confirmed the bidentate connectivity in **C1** within a distorted square-planar coordination geometry at the nickel center (Figure 4a).[20] Gratifyingly, in a proof-of-principle transformation employing air-stable **C2** as a precatalyst (with PhBPin as the reductant), 5-chlorobenzothiophene was selectively transformed into the aniline derivative **24** (63% yield, Figure 4b).

In summary, we have identified a JosiPhos/[Ni(cod)$_2$] catalyst system that has enabled the first examples of ammonia monoarylation chemistry employing nickel catalysis. In such cross-coupling chemistry, structurally diverse (hetero)aryl chloride, bromide, and tosylate electrophiles featuring a range of functionalities (e.g. methoxy, cyano, fluoro, trifluoromethyl, pyrrolyl, pyridyl) and heteroaryl motifs (e.g. pyridine, pyrimidine, quinaldine, isoquinoline, quinoline, quinoxaline, benzothiophene, benzothiazole) were successfully accommodated, as were substrates featuring potentially competitive N–H functionalities. Such broad reaction scope, when coupled with the demonstrated efficacy of the reported JosiPhos/[Ni(cod)$_2$] catalyst system when using either commercially available stock solutions of ammonia or ammonia gas, serves to underscore the versatility and potential scalability of the reported protocol. Proof-of-principle experiments established that air-stable (JosiPhos)-$NiCl_2$ precatalysts can also be employed with success in such

challenging transformations. The scope of the nickel-catalyzed ammonia monoarylation reactions reported herein is unprecedented in first-row transition-metal catalysis. Indeed, while not exhaustively demonstrated, the results presented herein establish for the first time the viability of nickel catalysts functioning as first-row competitors to state-of-the-art palladium catalysts, with regard to substrate scope in ammonia monoarylation chemistry. Future work will focus on exploring the mechanism of the transformations reported herein, as well as on applying this and other nickel-based catalysts in addressing challenging cross-coupling chemistry that is traditionally dominated by palladium catalysis.

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[20] CCDC 1028684 contains the supplementary crystallographic data for **C1**·2.5 C_6H_6. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Additional details of the solution and refinement process for **C1**·2.5 C_6H_6 are provided in the Supporting Information.

