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Simple Nickel Salts for the Amination of (Hetero)aryl Bromides and Iodides with Lithium Bis(trimethylsilyl)amide

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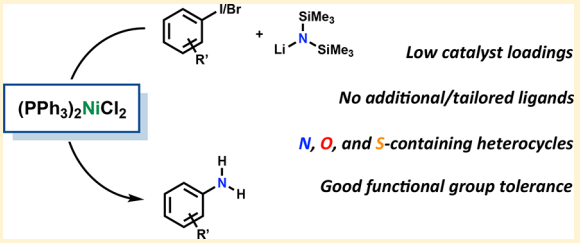
Supporting Information

ABSTRACT: Recent developments in the chemistry of C−N bond formation and the synthesis of anilines have allowed for the use of first-row transition metals to catalyze these transformations. Much of the progress in this area has been driven by comprehensive screening for privileged/tailored ligands, which can be costly and not readily available in a research laboratory setting. In this communication we report a protocol in which simple nickel salts catalyze the C−N cross-coupling reaction between (hetero)aryl bromides and iodides with lithium bis(trimethylsilyl)amide without the need for any additive ligand. This method is amenable to low nickel catalyst loadings (1%) as well as gram-scale reactions. Because of the good functional group tolerance and compatibility with heterocyclic moieties, this method is useful for academic laboratory settings where access to tailored ligands and noble-metal catalysts could be challenging.



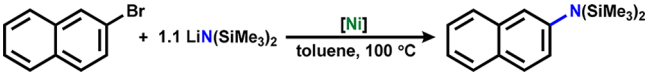
The monoarylation of ammonia is a challenging transformation that has garnered significant interest because of its highly valuable products.[1,2] Since the initial report by Hartwig and co-workers, which featured a Josiphos palladium system, ligand choice has influenced many of the advances in this area.[3] Further work by Hartwig and Stradiotto expanded this cross-coupling to nickel using Josiphos ligand derivatives.[4,5] The development of copper systems for the monoarylation of ammonia has been plagued by harsh reaction conditions; however, a judicious choice of ligands and additives has led to improved results.[6−8] Despite these and other important advances,[9−16] it remains a difficult challenge to develop effective first-row transition-metal catalysts for this coupling reaction.

Lithium bis(trimethylsilyl)amide ($LiN(SiMe_3)_2$), an easy to handle ammonia surrogate, has been effective in the formation of aromatic C−N bonds using palladium.[17,18] More recently, work in our group demonstrated that a simple cobalt catalyst, $(PPh_3)_3CoCl$, could effectively couple $LiN(SiMe_3)_2$ with aryl halides but could not tolerate heterocycles.[19] The reactivity of this cobalt catalyst inspired us to explore this chemistry further with other simple, earth-abundant metal salts. Herein, we report the usage of simple nickel salts ($NiCl_2$ and $(PPh_3)_2NiCl_2$) in C−N coupling reactions of $LiN(SiMe_3)_2$ with (hetero)aryl bromides and iodides to form the corresponding aniline products. This protocol does not require the use of privileged ligands or external reductants for catalysis to occur.

With the goal of using simple, commercially available, and relatively inexpensive nickel compounds, we first probed the competency of nickel(II) chloride in the cross-coupling of 2-bromonaphthalene and $LiN(SiMe_3)_2$. The reaction (100 °C, toluene, 5 mol % $NiCl_2$) resulted in the complete conversion of 2-bromonaphthalene to yield *N*,*N*-bis(trimethylsilyl)-naphthalen-2-amine as the only product (determined by GC-MS). Encouraged by this result, we screened a series of nickel compounds ($NiCl_2$, $NiBr_2$, $(PPh_3)_2NiCl_2$, $(PPh_3)_2NiBr_2$, $NiCl_2py_4$, $(DME)NiCl_2$, and $Ni(COD)_2$, as well as Ni powder (Table 1)). Interestingly, all the nickel reagents screened (except for Ni powder) yielded the cross-coupled product within 3 h at 100 °C.

Intrigued by the competence of $NiCl_2$ in the absence of ancillary ligands,[20] as well as the shorter reaction times required for the more soluble $(PPh_3)_2NiCl_2$, we narrowed our

Table 1. Nickel Source Screening



entry	[Ni] source	loading (%)	time (h)	conversion (%)[a]
1			3	<1
2	$(PPh_3)_2NiCl_2$	1	1	>99
3	$(PPh_3)_2NiBr_2$	1	1	>99
4	$NiCl_2$	5	2	>99
5	$NiBr_2$	5	2	>99
6	$NiCl_2py_4$	1	2	>99
7	$(DME)NiCl_2$	1	3	>99
8	$Ni(COD)_2$	1	3	>99
9	Ni powder	5	3	<1
10	$(PPh_3)_2NiN(SiMe_3)_2$	1	1	>99

[a]Conversion determined by GC-MS.

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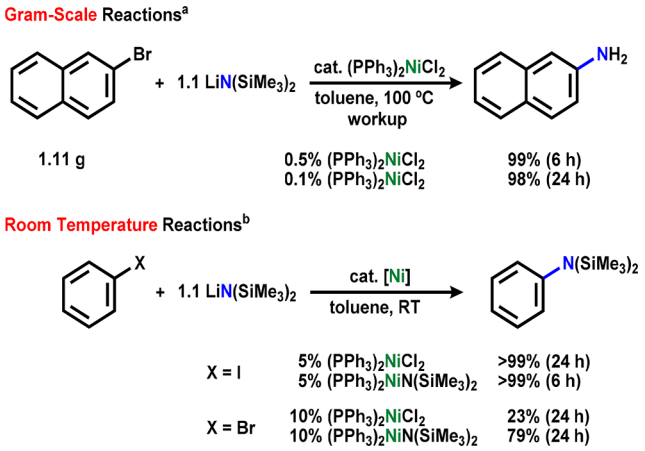
investigation to these two metal salts on the basis of commercial availability and cost. We sought to explore the capability of these two nickel sources to cross-couple PhX (X = Br, I) with $LiN(SiMe_3)_2$ in toluene at room temperature over a 24 h period (Tables S2 and S3). At 10 mol % loading, $NiCl_2$ showed ~3% conversion of PhI to $PhN(SiMe_3)_2$, while the less reactive PhBr resulted in no conversion at all. Conversely, at lower loadings $(PPh_3)_2NiCl_2$ (5 mol %) completely converted PhI to $PhN(SiMe_3)_2$, and at 10% loading it converted 23% of PhBr to the expected product. These results, in combination with the improved performance observed for both $NiCl_2$ and $(PPh_3)_2NiCl_2$ at higher temperatures, suggests that the solubility of the metal salt could be key for the success of the reaction and demonstrates that aryl iodides are more reactive than bromides under these conditions.

The performance of $(PPh_3)_2NiCl_2$ at even lower loadings (0.5 and 0.1 mol %) at 100 °C in the gram-scale coupling of 2-bromonaphthalene with $LiN(SiMe_3)_2$ was tested (Scheme 1).

Scheme 1. Gram-Scale and Room-Temperature Reactions of Aryl Halides

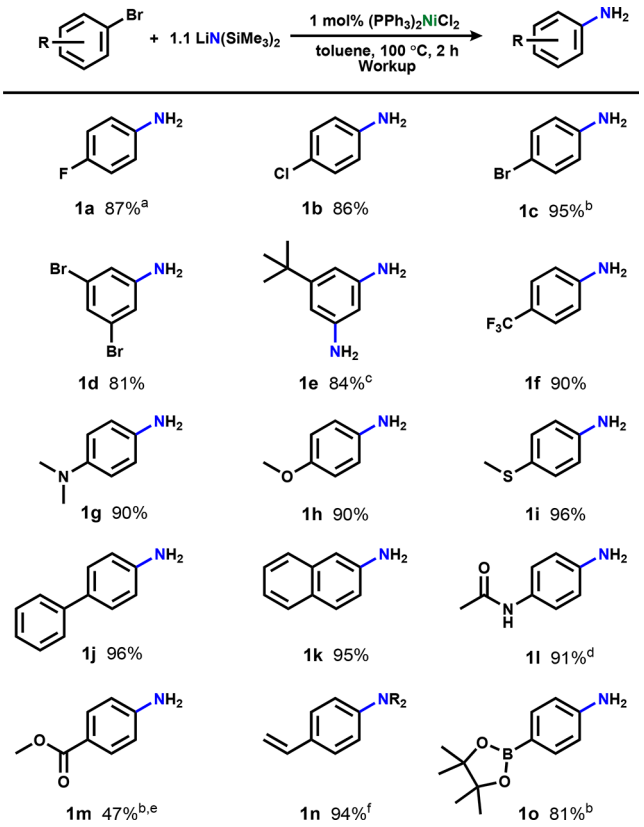


[a]Isolated yield. [b]Conversion determined by GC-MS.

At 0.5 mol % loading, the reaction was complete within 6 h, while 0.1 mol % loading resulted in 62% conversion of the starting material in 6 h and complete conversion within 24 h. Both reactions resulted in the isolation of the desired product in excellent yields.

Initial exploration of functional group tolerance for the cross-coupling of aryl bromides and iodides with $LiN(SiMe_3)_2$ revealed that $(PPh_3)_2NiCl_2$ was a superior catalyst to $NiCl_2$ in terms of both functional group tolerance and reaction time. For these reasons and its commercial availability, $(PPh_3)_2NiCl_2$ was used to develop the substrate scope of this reaction (Scheme 2). At elevated temperatures (100 °C) over the course of 2 h, the reaction of 1-bromo-4-fluorobenzene and 1-bromo-4-chlorobenzene yielded 4-fluoroaniline (**1a**) and 4-chloroaniline (**1b**) selectively after workup, leaving both the fluoride and chloride moieties intact. As observed in the room-temperature reactions, aryl iodides preferentially couple over aryl bromides. When 1-bromo-4-iodobenzene was heated to 70 °C, 4-bromoaniline (**1c**) was formed in excellent yield, leaving the bromide untouched; this allows iodides to be selectively functionalized in the presence of bromides. Subjecting 1,3,5-tribromobenzene to the reaction conditions yielded 3,5-dibromoaniline (**1d**), as opposed to uncontrolled amination

Scheme 2. Scope of Aryl Bromides and Iodides[g]



[a]2% catalyst, 4 h. [b]Aryl iodide starting material, 70 °C. [c]5% catalyst, 18 h, 3 equiv of $LiN(SiMe_3)_2$. [d]2.5% catalyst, 1,4-dioxane. [e]1,4-dioxane. [f]Isolated as the bis(trimethylsilyl)-protected amine. [g]Isolated yields are an average of duplicate runs.

at all bromide sites. However, the reaction can be used to install multiple amine functionalities, as observed by the formation of 5-(*tert*-butyl)benzene-1,3-diamine (**1e**) in good yields. Electron-withdrawing (**1f**) and electron-donating groups (**1g,h**) were also tolerated under the optimized conditions. Furthermore, oxygen-, nitrogen-, and sulfur-containing functionalities (**1g–i**) were tolerated under these reaction conditions. Although 4-bromoaniline did not produce the desired product, the reaction of 4-bromoacetanilide (*N*-acyl-protected aniline) proceeded to form *N*-(4-aminophenyl)-acetamide (**1l**) in great yield. The reaction conditions also tolerated ester (**1m**) and alkene (**1n**) functionalities. Additionally, this amination protocol works in the presence of a boronate ester functionality (**1o**), providing orthogonal reactivity in comparison to palladium-catalyzed methods which require installation of the amine group prior to the boronate ester functionality.[21]

Nitrogen-, oxygen-, and sulfur-containing heterocycles are ubiquitous in natural products and pharmaceuticals, distinguishing them as important moieties to explore.[22] The (hetero)aryl bromides investigated are shown in Scheme 3. The substrates 2-, 3-, and 4-bromopyridine (**2a–c**, respectively) were successfully coupled to form the aminopyridine products, which are of interest because of their promise in treating neurological disorders.[23] Exposing 2-bromo-5-methoxypyridine to the coupling conditions yielded the product 5-alkoxypyridin-2-amine (**2d**) in good yield. The 5-alkoxypyridin-2-amine functionality, found in an oncologically relevant

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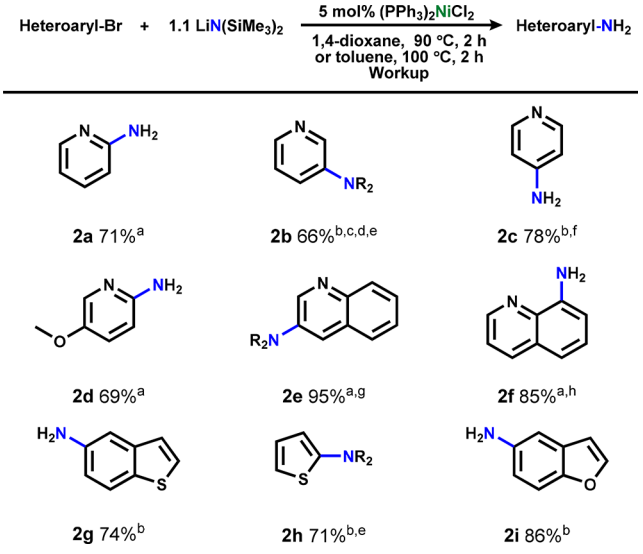
Scheme 3. Scope for Heteroaryl Bromides[i]



[a]1,4-Dioxane. [b]Toluene. [c]2.2 equiv of $LiN(SiMe_3)$. [d]4 h. [e]Isolated as TMS-protected product. [f]3.3 equiv of $LiN(SiMe_3)_2$. [g]Conversion determined by GC-MS. [h]3 h. [i]Isolated yields are an average of duplicate runs.

c-Met inhibitor, was previously transformed from its bromide precursor to the amine by employing $LiN(SiMe_3)_2$, palladium, and a tailored phosphine ligand.[24] Here we have achieved a similar transformation with a simple nickel salt and no tailored ligands. This protocol was also successful with 3-bromoquinoline (**2e**) and even 8-bromoquinoline (**2f**), a substrate not amenable to nickel photoredox coupling conditions.[25] 5-Bromobenzothiophene (**2g**), 2-bromothiophene (**2h**), and 5-bromobenzofuran (**2i**) were also coupled effectively. The compatibility of this protocol with heterocyclic functionalities is exciting for the prospect of its adoption in pharmaceutical and natural product synthesis.

Because many of the reactions for the substrate scope took place in toluene at elevated temperatures with an excess of $LiN(SiMe_3)_2$ versus $(PPh_3)_2NiCl_2$ (1% Ni = 110:1 $LiN(SiMe_3)_2$:$(PPh_3)_2NiCl_2$), we also explored the competency of $(PPh_3)_2NiN(SiMe_3)_2$ to catalyze this reaction. We reasoned that $(PPh_3)_2NiN(SiMe_3)_2$ could be the active species formed under these conditions, considering that its synthesis is achieved in toluene at 80 °C starting from $(PPh_3)_2NiCl_2$.[26] To test its competence, independently prepared $(PPh_3)_2NiN(SiMe_3)_2$ was reacted with 2-bromonapthhalene and $LiN(SiMe_3)_2$, resulting in complete conversion within the first 1 h of the reaction with only the desired product observed by GC-MS (Table 1). Interested in the increased reaction rate, we studied the initial rate kinetics for $(PPh_3)_2NiCl_2$ and $(PPh_3)_2NiN(SiMe_3)_2$; the initial rate of reaction of coupling PhBr and $LiN(SiMe_3)_2$ revealed an induction period of ~3 min for $(PPh_3)_2NiCl_2$ and less of an induction period for $(PPh_3)_2NiN(SiMe_3)_2$, consistent with the solution reaching the final temperature (Figure S4). This finding suggests that the formation of an active Ni(I) catalyst could be responsible for the induction period observed when using $(PPh_3)_2NiCl_2$ as the catalyst. This is further corroborated by the room-temperature reaction of PhI with $LiN(SiMe_3)_2$. At 5 mol % loading of $(PPh_3)_2NiN(SiMe_3)_2$, complete conversion was observed within 6 h, whereas $(PPh_3)_2NiCl_2$ at 5 mol % loading required ~24 h (Scheme 1).

Additional evidence of Ni(I) involvement was provided by monitoring the fate of the catalyst upon reaction completion. Reactions of PhBr with $LiN(SiMe_3)_2$, one catalyzed by $(PPh_3)_2NiCl_2$ and the other catalyzed by $(PPh_3)_2NiN(SiMe_3)_2$, were analyzed by ^1H NMR spectroscopy after filtration and removal of volatiles. The ^1H NMR spectra of both reaction mixtures contained resonances consistent with the independently prepared $(PPh_3)_2NiN(SiMe_3)_2$ (Figures S5 and S6). This suggests that the Ni(I) species $(PPh_3)_2NiN(SiMe_3)_2$ could be involved in catalyzing the reaction and that $(PPh_3)_2NiCl_2$ is reduced over the course of the reaction to form the Ni(I) complex. To ensure that the nickel species present after catalysis was not an inactive decomposition product, the isolated residue was added to more substrate and nucleophile, resulting in coupling to the desired product with no loss in activity. Moreover, no resonances corresponding to $(PPh_3)_2NiX_2$ (X = Cl, Br) were observed in the analyzed mixtures.

In summary, the method presented can be easily adapted in academic laboratories, especially if synthetically advanced ligands and/or palladium sources are not accessible. This method employs simple and inexpensive nickel sources at low loadings for the cross-coupling of aryl bromides and iodides with the ammonia surrogate $LiN(SiMe_3)_2$, without the requirement of ancillary ligands or tailored phosphines. The more soluble Ni sources ($(PPh_3)_2NiCl_2$ and $(PPh_3)_2NiN(SiMe_3)_2$) are competent catalysts even at room temperature, making this method amenable to aminating thermally sensitive substrates. The amination of (hetero)aryl bromides featuring pyridine, quinoline, benzofuran, and (benzo)thiophene moieties, which are ubiquitous in natural products and pharmaceuticals, was also achieved with this simple nickel system.

■ ASSOCIATED CONTENT

Supporting Information

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Synthesis, characterization data, and kinetic data (PDF)

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Notes

The authors declare no competing financial interest.

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