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Controlling First-Row Catalysts: Amination of Aryl and Heteroaryl Chlorides and Bromides with Primary Aliphatic Amines Catalyzed by a BINAP-Ligated Single-Component Ni(0) Complex

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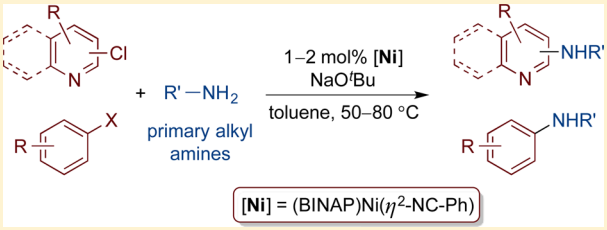
Supporting Information

ABSTRACT: First-row metal complexes often undergo undesirable one-electron redox processes during two-electron steps of catalytic cycles. We report the amination of aryl chlorides and bromides with primary aliphatic amines catalyzed by a well-defined, single-component nickel precursor (BINAP)Ni(η^2-NC-Ph) (BINAP = 2,2′-bis(biphenylphosphino)-1,1′-binaphthalene) that minimizes the formation of Ni(I) species and $(BINAP)_2Ni$. The scope of the reaction encompasses electronically varied aryl chlorides and nitrogen-containing heteroaryl chlorides, including pyridine, quinoline, and isoquinoline derivatives. Mechanistic studies support the catalytic cycle involving a Ni(0)/Ni(II) couple for this nickel-catalyzed amination and are inconsistent with a Ni(I) halide intermediate. Monitoring the reaction mixture by ^{31}P NMR spectroscopy identified (BINAP)Ni(η^2-NC-Ph) as the resting state of the catalyst in the amination of both aryl chlorides and bromides. Kinetic studies showed that the amination of aryl chlorides and bromides is first order in both catalyst and aryl halide and zero order in base and amine. The reaction of a representative aryl chloride is inverse first order in PhCN, but the reaction of a representative aryl bromide is zero order in PhCN. This difference in the order of the reaction in PhCN indicates that the aryl chloride reacts with (BINAP)Ni(0), formed by dissociation PhCN from (BINAP)Ni(η^2-NC-Ph), but the aryl bromide directly reacts with (BINAP)Ni(η^2-NC-Ph). The overall kinetic behavior is consistent with turnover-limiting oxidative addition of the aryl halide to Ni(0). Several pathways for catalyst decomposition were identified, such as the formation of the catalytically inactive bis(amine)-ligated arylnickel(II) chloride, $(BINAP)_2Ni(0)$, and the Ni(I) species $[(BINAP)Ni(\mu\text{-Cl})]_2$. By using a well-defined nickel complex as catalyst, the formation of $(BINAP)_2Ni(0)$ is avoided and the formation of the Ni(I) species $[(BINAP)Ni(\mu\text{-Cl})]_2$ is minimized.



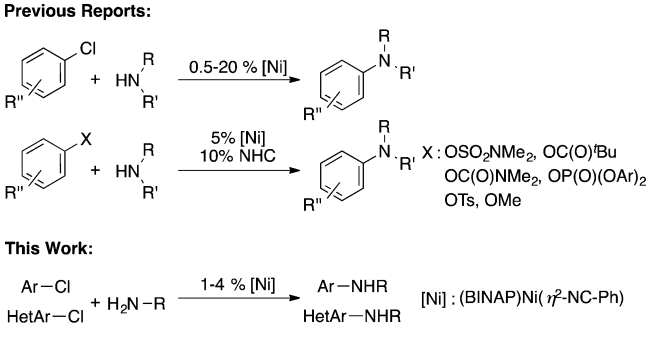
INTRODUCTION

The transition-metal-catalyzed amination of aryl halides has become one of the most powerful methods to construct arylamines.[1] The development of methods to couple aryl halides with amines has been studied extensively in the past decade. Most studies have focused on palladium and copper complexes as catalysts. Palladium-catalyzed reactions occur with a broad scope of both coupling partners, high functional group tolerance, and good selectivity for monoarylation of the amine nucleophile.[2,3] However, this scope is accomplished at a price. Both the palladium metal and the ligands used for this reaction are costly, and the ligand is difficult to recycle.

For these types of reasons, much interest has been paid recently to develop reactions catalyzed by first-row metal complexes that are typically catalyzed by precious metals. For example, copper complexes have been studied extensively for the coupling of aryl iodides, and to a lesser extent aryl bromides, with nitrogen nucleophiles.[4] Yet, the scope of such coupling with electron-rich bromoarenes, ortho-substituted bromoarenes, unactivated aryl chlorides, and heteroaryl halides is limited.

Many of the first-row metals are more electropositive than those of the second row and form electron-rich low-valent species. Indeed, nickel complexes have been shown to catalyze the amination of aryl chlorides and phenol derivatives (Scheme 1).[5−24] Such nickel-catalyzed amination reactions could be more practical than palladium-catalyzed amination reactions on large scale because the metal is much less expensive, and much

Scheme 1. Methods for Nickel-Catalyzed C−N Coupling Reactions



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simpler ligands on the nickel center are needed for the catalyst to react with aryl chlorides. For example, Hidai showed over 40 years ago that $Ni(PPh_3)_4$ adds phenyl chloride at room temperature to form $(PPh_3)_2Ni(Ph)(Cl)$, whereas $Pd(PPh_3)_4$ does not react with aryl chlorides.[25] However, the scope of the nickel-catalyzed amination of aryl halides has been limited to the coupling of secondary alkylamines and arylamines.[11−19] Primary alkylamines, one of the most significant classes of amines for such cross coupling, have been shown to couple only with activated aryl chlorides.[11,17]

In addition to the limitations on the scope of the coupling of aryl halides with amines, the mechanism of the coupling of aryl halides with amines catalyzed by nickel complexes has not been studied. Many papers cite the potential of Ni(I) intermediates,[26] either as part of a one-electron redox event or as part of a mechanism involving Ni(I) and Ni(III) intermediates. In contrast, the mechanism for the palladium-catalyzed amination of aryl electrophiles has been studied in detail, including the kinetic behavior of the catalytic reaction and stoichiometric reactions of isolated intermediates.[27−30] Such studies have not been conducted on nickel-catalyzed couplings to form C−N bonds, but are particularly important if one is to determine how to create catalysts of nickel that are as long-lived as those of palladium and that react with similarly broad scope.

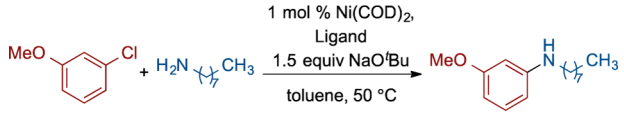
Here, we present the first nickel-catalyzed amination of unactivated aryl chlorides with primary aliphatic amines. The reaction occurs with aryl and heteroaryl chlorides and bromides catalyzed by a single-component BINAP-ligated nickel(0) precursor. Kinetic studies have been conducted on the reaction, and studies on the relative rates of the reaction with various isolated nickel complexes have been conducted. These studies rule out a catalytic cycle occurring through a Ni(I) halide intermediate and are consistent with a Ni(0)/Ni(II) catalytic cycle for the amination of aryl chlorides and aryl bromides, which react with different Ni(0) species.

RESULTS AND DISCUSSION

Evaluation of Ligands for the Ni-Catalyzed Amination Reaction. We initiated our studies of nickel-catalyzed amination of aryl chlorides with primary aliphatic amines by studying the reaction between 3-chloroanisole and octylamine. We investigated nickel complexes generated in situ from $Ni(COD)_2$ and various phosphine ligands as catalysts. These results are listed in Table 1. These reactions were conducted with NaO^{t}Bu as base in toluene at 50 °C. Reactions catalyzed by the combination of $Ni(COD)_2$ and monophosphines, such as PPh_3 and PCy_3, afforded only trace amounts of the desired amine product (entries 1−4). Similar results (<5% conversion and <2% yield) were obtained for reactions catalyzed by the combination of $Ni(COD)_2$ (1 mol %) and DPPE, DPPP, or DPPB (1 or 2 mol %) (Entries 5−10). However, reactions catalyzed by the combination of $Ni(COD)_2$ and DPPF or BINAP gave significant amounts of product (16−67%, entries 11−14). In particular, the reaction catalyzed by the single component catalyst (BINAP)Ni(η^2-NC-Ph) afforded the product in 92% yield (entry 15). An explanation for the high activity of this catalyst will be revealed during the presentation of our mechanistic studies.

Scope of the Ni-Catalyzed Amination of Aryl Chlorides with Primary Aliphatic Amines. With an active catalyst in hand and reliable conditions identified for this Ni-catalyzed amination, we studied the scope of aryl chlorides that undergo these amination reactions, and the results are summarized in Table 2. In general, a range of electron-rich (**2a**−**2e**), electron-neutral (**2h**), and electron-deficient (**2i**−**2l**) aryl chlorides coupled with octylamine in high yields (76−96%) under the developed conditions with 1 mol % of nickel complex

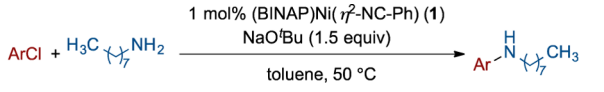
Table 1. Evaluation of Nickel Precursors and Ligands for Amination of 3-Chloroanisole with Octylamine[a]

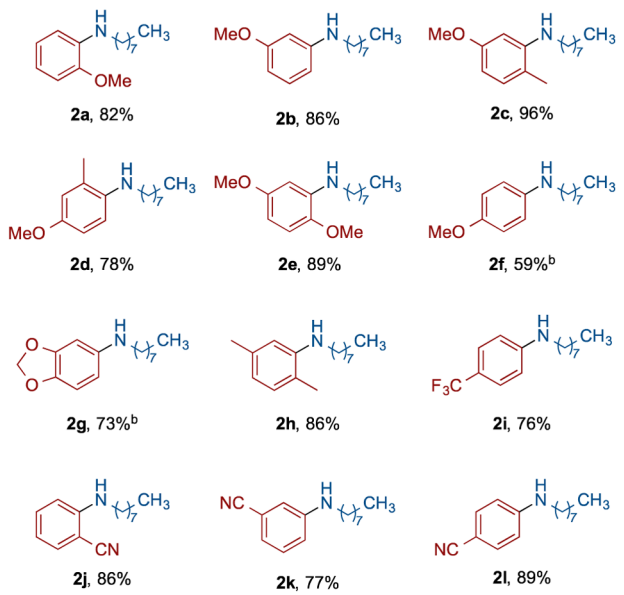


entry	ligand (mol %)	conv (%)	yield (%)
1	PPh_3 (2)	<5	3
2	PPh_3 (4)	<5	<2
3	PCy_3 (2)	<5	3
4	PCy_3 (4)	<5	<2
5	DPPE (1)	<5	<2
6	DPPE (2)	<5	<2
7	PDPP (1)	<5	<2
8	DPPP (2)	<5	<2
9	DPPB (1)	<5	<2
10	DPPB (2)	<5	<2
11	DPPF (1)	31	16
12	DPPF (2)	44	32
13	BINAP (1)	71	66
14	BINAP (2)	75	67
15	[Ni^0] (1)[b]	98	92

[a]Conditions: 3-chloroanisole (0.400 mmol), octylamine (0.600 mmol), NaO^{t}Bu (0.600 mmol), 24 h. Conversion and yield were determined by GC analysis using dodecane as internal standard. [b][Ni^0] = (BINAP)Ni(η^2-NC-Ph).

Table 2. Nickel-Catalyzed Amination: Aryl Chloride Scope[a]





[a]Conditions: ArCl (0.400 mmol), octylamine (0.600 mmol), (BINAP)Ni(η^2-NC-Ph) (4.0 μmol, 1 mol %), NaO^{t}Bu (0.600 mmol), toluene (1 mL); temperature, 50 °C; reaction time, 24 h. [b](BINAP)Ni(η^2-NC-Ph) (16.0 μmol, 4 mol %).

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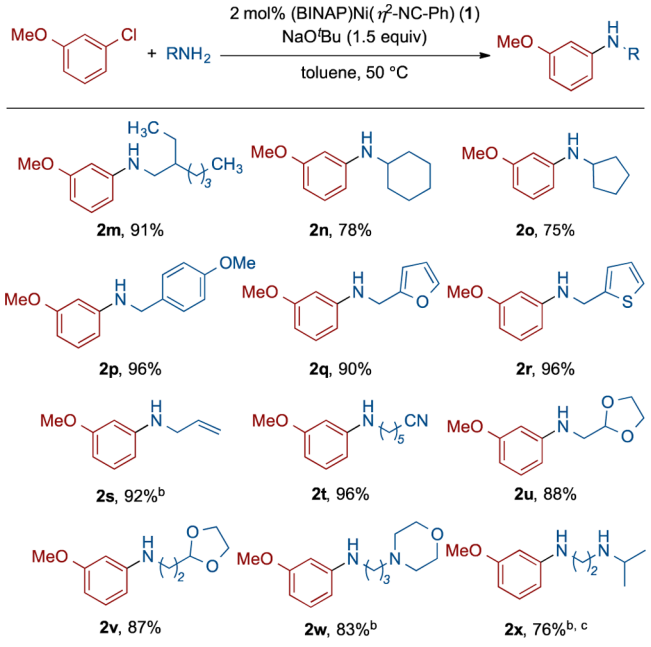
1. For very electron-rich aryl chlorides, 4 mol % of the catalyst was required to obtain modest to good yields (**2f** and **2g**). For these two reactions, aryl chlorides were not fully converted, and only trace amounts (<5%) of biaryl compounds were detected by GC analysis. Mono-*ortho*-substituted aryl chlorides reacted in high yields (**2a**, **2c**−**2e**, **2h**, and **2j**). However, di-*ortho*-substituted aryl chlorides, such as 2-chloro-1,3-dimethylbenzene, did not couple with octylamine under the developed conditions.

The scope of primary amines was studied by conducting the amination reactions of 3-chloroanisole catalyzed by 2 mol % complex **1**. The results of this study are summarized in Table 3. In general, a variety of primary aliphatic amines underwent this amination process in good to excellent isolated yields (75−96%).

Table 3. Nickel-Catalyzed Amination: Primary Amine Scope[a]



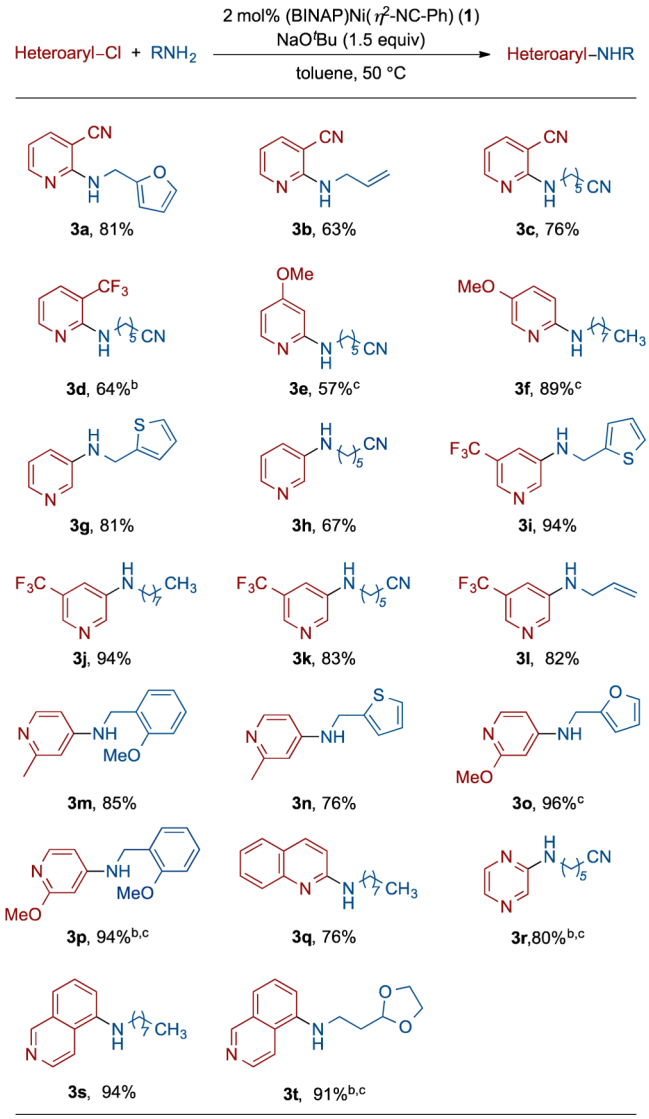
[a]Conditions: 3-chloroanisole (0.400 mmol), primary amine (0.600 mmol), (BINAP)Ni(η^2-NC-Ph) (8.0 μmol, 2 mol %), NaO^{t}Bu (0.600 mmol), toluene (1 mL); temperature, 50 °C; reaction time, 24 h. [b]Temperature, 80 °C. [c](BINAP)Ni(η^2-NC-Ph) (16.0 μmol, 4 mol %).

The steric bulk of the alkyl group of the primary amines significantly influenced the yields of these reactions. The reactions of an amine containing a primary alkyl group (**2m**) afforded the product in higher yield than the reactions of amines containing a secondary alkyl group (**2n** and **2o**), although the primary amines containing a secondary alkyl group still coupled with aryl chlorides in good yield. However, the amination of 3-chloroanisole with primary amines containing a tertiary alkyl group, for example, *tert*-butylamine and amylamine, gave only trace amounts of the desired products. Amines containing aryl (**2p**), heteroaryl (**2q** and **2r**), allyl (**2s**), and cyano (**2t**) groups reacted in high yields (90−96%). Primary amines bearing 1,3-dioxolane (**2u** and **2v**) and morpholine (**2w**) moieties also reacted in high yields (83−88%). The reaction of *N*-isopropylethylenediamine, a substrate containing both a primary and a secondary amine, occurred selectively with the primary amine, leaving the secondary amine intact (**2x**).

Nitrogen-containing heterocycles containing amino substituents are of particular importance for pharmaceutical applications. However, the C−N coupling reactions between nitrogen-containing heteroaryl electrophiles and primary amines are challenging, presumably because of the coordinating properties of both pyridines and primary amines. Such coupling reactions have been achieved only with palladium and copper catalysts.[31−35] Nickel catalysts have been reported for the amination of heteroaryl chlorides, but the amine nucleophiles are limited to secondary amines.[21]

Cross-coupling reactions between nitrogen-containing heteroaryl chlorides and primary amines catalyzed by 2 mol % of complex **1** are summarized in Table 4. The scope of heteroaryl chlorides that underwent this amination reaction encompassed a range of 2-pyridyl (**3a**−**3f**), 3-pyridyl (**3g**−**3l**), and 4-pyridyl

Table 4. Nickel-Catalyzed Amination of Heteroaryl Halides with Primary Amines[a]



[a]Conditions: 3-chloroanisole (0.400 mmol), primary amine (0.600 mmol), (BINAP)Ni(η^2-NC-Ph) (8.0 μmol, 2 mol %), NaO^{t}Bu (0.600 mmol), toluene (1 mL); temperature, 50 °C; reaction time, 24 h. [b]Temperature, 80 °C. [c](BINAP)Ni(η^2-NC-Ph) (16.0 μmol, 4 mol %).

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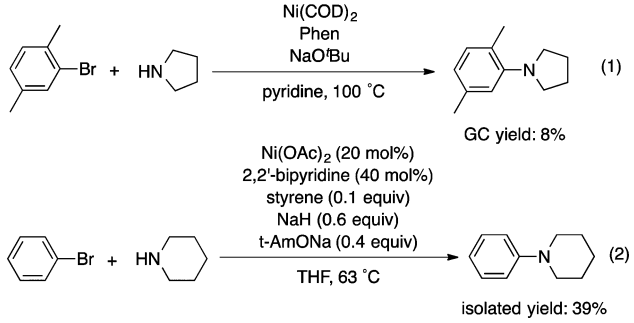
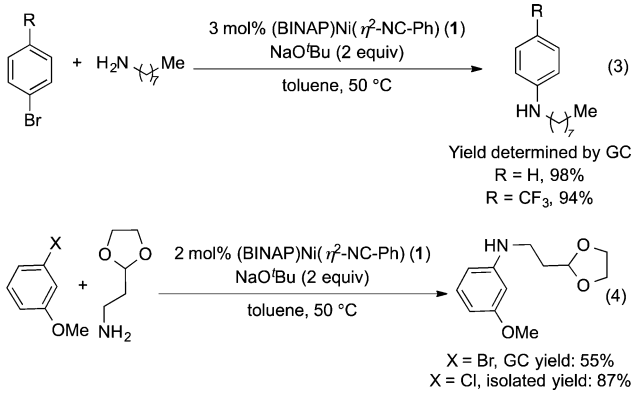
(**3m**−**3p**) chlorides containing electron-donating groups (Me and OMe) and electron-withdrawing groups (CN and CF_3). In general, these reactions afforded the corresponding heteroaryl alkylamine in good to excellent isolated yields (57−96%, average yield: 81%). This amination also occurred in high yields with 2-chloroquinoline (**3q**) and 2-chloropyrazine (**3r**). 5-Chloroisoquinoline also reacted in high yields (**3s** and **3t**). The scope of primary amines that underwent reactions with chloropyridines was similar to that of the reactions of 3-chloroanisole described in Table 3.

Nickel-Catalyzed Amination of Aryl Bromides. Compared to the well-established palladium-catalyzed amination of aryl bromides, the nickel-catalyzed amination of aryl bromides has been less studied, and conditions for coupling of aryl bromides with amines by nickel catalysts have not been identified. Only two examples of nickel-catalyzed amination of aryl bromides have been published,[11,12] and these two reactions occurred in poor yields (eqs 1 and 2). Having identified conditions for the nickel-catalyzed amination of aryl chlorides, we tested these conditions for the coupling of aryl bromides with primary amines.

Prior studies on nickel-catalyzed amination of aryl bromides:



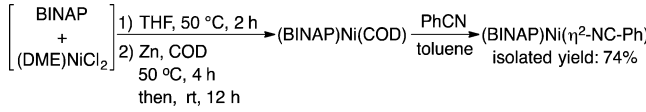
The amination of aryl bromides catalyzed by benzonitrile complex **1** in toluene with NaO^tBu base occurred in good yields in some cases, but the scope of the reaction was limited. Bromobenzene and 4-bromobenzotrifluoride reacted with octylamine in high GC-yields (98% and 94%, repectively) under conditions listed in Table 2 with 3 mol % of complex **1** (eq 3). However, 3-bromoanisole coupled with 2-(1,3-dioxolan-



2-yl)ethan-1-amine in only 55% GC-yield, whereas the reaction of the same amine with 3-chloroanisole afforded the desired product in 87% isolated yield (eq 4). This limited scope for the amination of aryl bromides may stem from the faster thermal decomposition of arylnickel(II) bromide species to nickel(I) bromide, relative to the rate of decomposition of arylnickel(II) chloride species.[36]

Improved Synthesis of (BINAP)Ni(η^2-NC-Ph) from the Air-Stable Nickel Precursor (DME)$NiCl_2$. The catalyst precursor employed in this study is a single-component nickel(0) complex (BINAP)Ni(η^2-NC-Ph) (**1**). Previously, we reported the synthesis of this nickel complex by substitution of the 1,5-cyclooctadiene (COD) in $Ni(COD)_2$ by BINAP, and benzonitrile.[36] To avoid using the thermally labile, air- and moisture-sensitive $Ni(COD)_2$, we developed a new synthesis (Scheme 2) of this complex starting from the air-stable nickel

Scheme 2



precursor (DME)$NiCl_2$. Reaction of (DME)$NiCl_2$ with 1 equiv of BINAP in THF at 50 °C afforded (BINAP)$NiCl_2$, which was then reduced by zinc metal in the presence of COD. ^{31}P NMR analysis of this reaction indicated a clean formation of (BINAP)Ni(COD). The byproduct $ZnCl_2$ was removed by washing the reaction mixture with degassed aqueous NaOH. At this stage, all the volatile components of the reaction mixture were removed under vacuum. The residue was suspended in toluene and then allowed to react with benzonitrile. This reaction sequence afforded (BINAP)Ni(η^2-NC-Ph) in 74% overall yield.

Synthesis of BINAP-Ligated Arylnickel Chloride Complexes by Oxidative Addition of Aryl Chlorides to (BINAP)Ni(η^2-NC-Ph). Arylnickel halide complexes are important intermediates in nickel-catalyzed cross-coupling reactions. In general, arylnickel halides ligated by monophosphines are synthesized by oxidative addition reactions of aryl halides to $Ni(PR_3)_x$ (R = alkyl or aryl),[37−39] but arylnickel halides ligated by bisphosphines are prepared by ligand substitution reactions between monophosphine-ligated arylnickel halide complexes with bisphosphines.[40] The direct oxidative addition of aryl halides to bisphosphine-ligated Ni(0) has rarely been investigated, mainly due to the lack of bisphosphine-ligated Ni(0) precursors that can react with aryl halides at ambient temperature. Recently, we reported the synthesis of BINAP-ligated arylnickel halide complexes by reactions of aryl halides with (BINAP)Ni(COD) in the presence of catalytic amounts of benzonitrile, and we identified (BINAP)Ni(η^2-NC-Ph) as the active Ni(0) species.[36] In our communication on the nickel-catalyzed asymmetric α-arylation of ketones, we reported the single reaction of electron-deficient 4-chlorobenzotrifluoride with this newly defined Ni(0) precursor **1** and no isolation of the products. Here we show the results of the reactions of complex **1** with electronically varied aryl chlorides.

Electron-neutral and electron-deficient aryl chlorides reacted smoothly with Ni(0) complex **1** in THF at room temperature to afford the arylnickel(II) chloride complexes **4**−**7** in 76−89% isolated yields (eq 5). These complexes are stable in the solid state at ambient temperature for at least six months without noticeable decomposition. However, upon standing in THF solution at room temperature for about 48 h, they fully decomposed to [(BINAP)Ni(μ-Cl)]$_2$ (**8**) with concomitant release of biaryls, as detected by GC-MS analysis. The isolated

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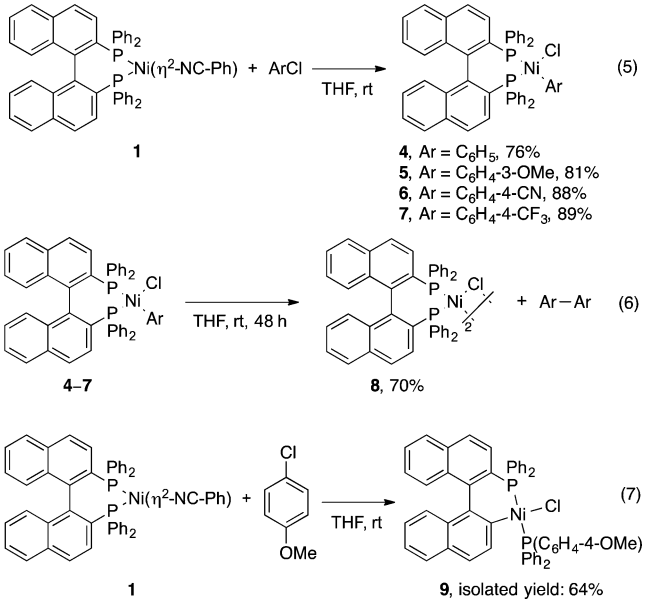
yields for this reaction were about 70% (eq 6). However, the reaction of electron-rich 4-chloroanisole with complex **1** in THF did not form the arylnickel chloride complex resulting from simple oxidative addition, as determined by ^{31}P NMR spectroscopy. Instead, ^{31}P NMR signals corresponding to two mutually *trans* phosphine resonances (doublets at 24.2 and 14.4 ppm with J_{PP} = 352 Hz) were observed.



Single-crystal X-ray diffraction of the isolated material (Figure 1) showed that this product is complex **9** (eq 7). Complex **9** contains a coordinated monophosphine ligand $Ph_2P(C_6H_4$-4-OMe) and a six-membered nickelacyclic structure. Nickelacyclic complex **9** contains a small dihedral angle between the two naphthyl groups of 63°, and the nickel center consists of a distorted square planar geometry. Complex **9** is formed by P−C bond cleavage of the BINAP backbone after the initial formation of BINAP-ligated arylnickel chloride complex (BINAP)NiCl(C_6H_4-4-OMe). Similar P−C bond cleavage of the BINAP backbone in a BINAP-ligated phenylpalladium bromide complex was reported by our group previously.[41]

Complex **9** was tested as a catalyst for the amination of 4-chloroanisole with octylamine under the conditions described in Table 2. Only trace (<5% by GC analysis) amounts of the amination product were formed. Thus, the formation of catalytically inactive complex **9** by the reaction of 4-chloroanisole and nickel precursor **1** explained the high catalyst loading required for the amination of electron-rich 4-chloroanisole.

Identification of Catalytically Active Species: (BINAP)Ni^{II}(Cl)(Ar) or [(BINAP)Ni^{I}(μ-Cl)]$_2$? The oxidation state of the nickel intermediates in the amination of aryl halides with amines has been ambiguous, and pathways involving both Ni(0)/Ni(II) and Ni(I)/Ni(III) couples have been proposed for these reactions.[11,17] With isolated, BINAP-ligated Ni(0), Ni(I) halide, and ArNi(II) halide complexes in hand, we were able to assess precisely the competence of these complexes to be intermediates in the amination reactions.

To do so, we conducted the reaction of the isolated (BINAP)NiCl(C_6H_4-4-CF_3) (**7**) with octylamine and NaO^{t}Bu in the presence of 1 equiv of BINAP to trap a Ni(0) product (A, Scheme 3). This reaction afforded *N*-octyl-4-(trifluoromethyl)aniline in quantitative yield in less than 5 min at room temperature, as indicated by ^{19}F NMR

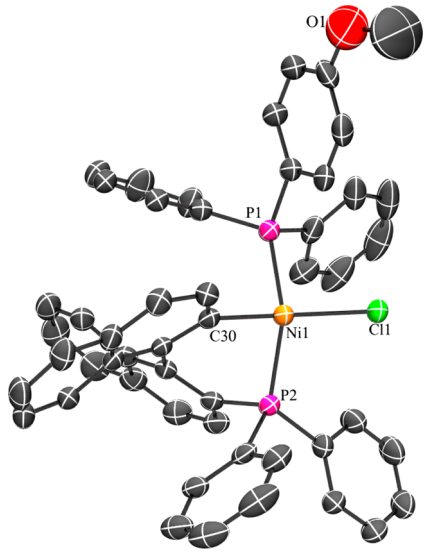
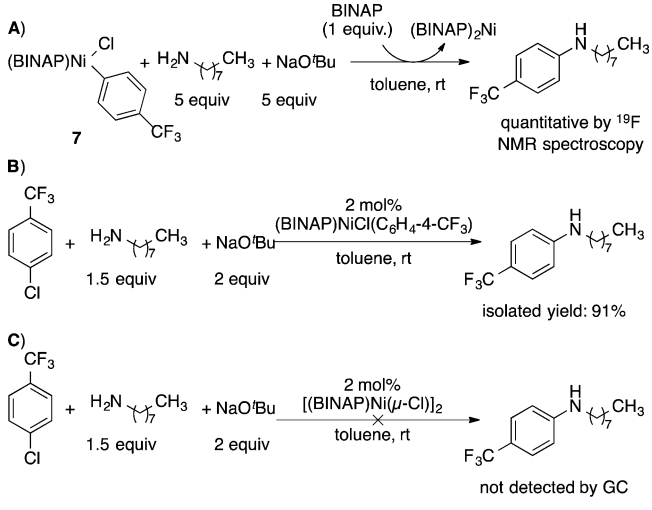


Figure 1. Molecular structure of the nickelacyclic compound **9**. All the ellipsoids are drawn at the 50% probability and all the hydrogen atoms are omitted for clarity.

spectroscopic analysis. In addition, we conducted the amination reaction of 4-chlorobenzotrifluoride with octylamine in the presence of NaO^{t}Bu catalyzed by 2 mol % of (BINAP)NiCl(C_6H_4-4-CF_3) at room temperature (B, Scheme 3). Full conversion of 4-chlorobenzotrifluoride was achieved in 2 h, and this reaction afforded *N*-octyl-4-(trifluoromethyl)aniline in 91% isolated yield. The same reaction catalyzed by 2 mol % of [(BINAP)Ni-μ-Cl]$_2$ did not afford any amination product (C, Scheme 3). These results show clearly that the BINAP-ligated arylnickel(II) chloride compound is kinetically and chemically competent to be an intermediate in the catalytic process and the BINAP-ligated nickel(I) halide is not.

Identity of Nickel Species in the Catalytic Reaction Mixture. To identify the resting state of the catalyst in this nickel-catalyzed amination reaction, we monitored by ^{31}P{^{1}H} NMR spectroscopy the reaction of 4-chlorobenzotrifluoride with octylamine in the presence of NaO^{t}Bu catalyzed by 2 mol % of (BINAP)Ni(η^2-NC-Ph) (**1**) at room temperature. During the first 50% conversion of 4-chlorobenzotrifluoride, only

Scheme 3



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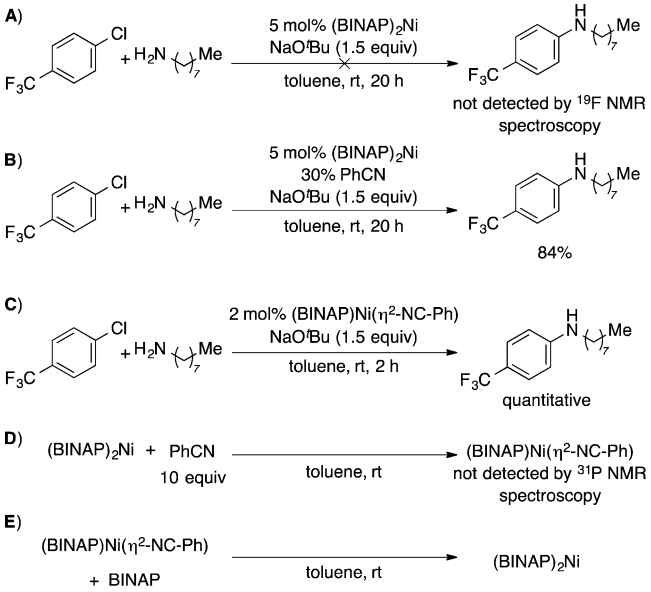
(BINAP)Ni(η^2-NC-Ph) was observed. However, during the second 50% conversion, a new species corresponding to a $^{31}P\{^1H\}$ NMR resonance at δ 31.7 ppm gradually accumulated. This new species is $(BINAP)_2Ni$, as determined by independently preparing this complex by reduction of (DME)-$NiCl_2$ with Zn metal in the presence of 2 equiv of BINAP in THF and comparing the ^{31}P NMR chemical shift.

To test the catalytic activity of $(BINAP)_2Ni$ for this amination process, we conducted the reaction of 4-chlorobenzotrifluoride with octylamine catalyzed by 5 mol % of $(BINAP)_2Ni$ in the presence of NaO^tBu at room temperature. This reaction did not afford detectable amounts of the amination product (A, Scheme 4). This result is consistent with the early report that $(BINAP)_2Ni$ does not undergo oxidative addition with aryl chlorides or bromides at ambient temperatures.[36]

Scheme 4



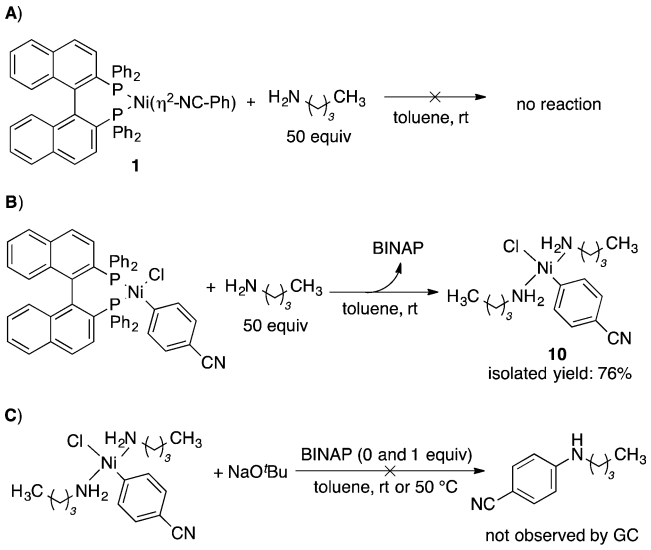
The same reaction catalyzed by 5 mol % $(BINAP)_2Ni$ in the presence of a catalytic amount of PhCN (30 mol %) afforded the amination product in 84% yield in 20 h (B, Scheme 4). For comparison, we conducted the same reaction catalyzed by only 2 mol % (BINAP)Ni(η^2-NC-Ph). This reaction afforded the amination product in almost quantitative yield in 2 h at room temperature (C, Scheme 4). Thus, (BINAP)Ni(η^2-NC-Ph) is a more active catalyst than the combination of $(BINAP)_2Ni$ and PhCN.

To assess the origin of the effect of benzonitrile on the rate of the catalytic reaction, we performed the reaction of $(BINAP)_2Ni$ with benzonitrile and the reaction of (BINAP)-Ni(η^2-NC-Ph) with BINAP. The reaction of $(BINAP)_2Ni$ with 10 equiv of benzonitrile did not form detectable amounts of (BINAP)Ni(η^2-NC-Ph), as determined by ^{31}P NMR spectroscopy (D, Scheme 4). The reaction of (BINAP)Ni(η^2-NC-Ph) with 1 equiv of BINAP afforded $(BINAP)_2Ni$ quantitatively at ambient temperature (E, Scheme 3). Based on these stoichiometric reactions and the catalytic reactions in Scheme 3, we conclude that the formation of $(BINAP)_2Ni$ is reversible in the presence of benzonitrile, but the equilibrium lies largely on the side of $(BINAP)_2Ni$ and free nitrile.

Formation of Bis(amine)-Ligated Arylnickel Chloride. The formation of bis(amine)-ligated palladium complexes was reported as one possible pathway for deactivation of the catalyst in the palladium-catalyzed amination of aryl halides.[42] These bis(amine) complexes have been prepared and well characterized. Formation of analogous bis(amine) complexes of nickel was proposed to explain the much lower reactivity of primary aliphatic amines than that of cyclic secondary aliphatic amines and anilines in the nickel-catalyzed amination reaction.[17] However, these bis(amine)-ligated nickel complexes have never been prepared or characterized. In the nickel-catalyzed amination of aryl chlorides with primary amines catalyzed by (BINAP)Ni(η^2-NC-Ph), we observed the formation of $(BINAP)_2Ni$. The stoichiometry of this conversion indicates that there are nickel complexes lacking BINAP ligand in the reaction mixture. Thus, we studied the ligand substitution reactions between primary aliphatic amines and BINAP-ligated Ni(0) and BINAP-ligated Ni(II) complexes.

The reaction of (BINAP)Ni(η^2-NC-Ph) with 50 equiv of *n*-butylamine in toluene did not form any new nickel species, and free BINAP was not detected by ^{31}P NMR spectroscopy (A, Scheme 5). This result is consistent with the affinity of the

Scheme 5



electron-rich Ni(0) center for softer, π-accepting ligands.[43] However, the reaction of (BINAP)NiCl(C_6H_4-4-CN) with 50 equiv of *n*-butylamine afforded free BINAP and *trans*-(*n*-butylamine)$_2$NiCl(C_6H_4-4-CN) (**10**) (B, Scheme 5). Complex **10** was isolated in 76% yield.

With the bis(amine)-ligated complex **10** in hand, we tested its potential to serve as an intermediate in the amination reaction. We conducted the reaction of **10** with 2 equiv of NaO^tBu in the presence or in the absence of 1 equiv of BINAP (C, Scheme 5). These two reactions did not form the desired amination product. This result indicates that the formation of bis(amine)-ligated nickel complexes is one possible pathway for decomposition of the nickel catalyst.

Kinetic Studies on Nickel-Catalyzed Amination of Aryl Chlorides. After identifying the resting state of the nickel catalyst and possible paths for catalyst deactivation, we sought to identify the rate-limiting step for this nickel-catalyzed amination process. To do so, we measured the dependence of the initial rates of the amination reaction on the

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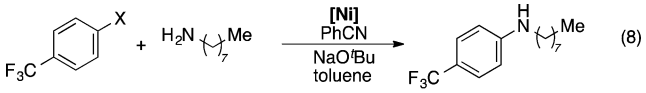
concentrations of each reagent under conditions in which the other reagents were present in large excess.

We chose the reaction of 4-chlorobenzotrifluoride with octylamine in the presence of NaO^{t}Bu for the kinetic studies because this reaction occurred at ambient temperature, and we were able to monitor the reaction conveniently by both ^{31}P and ^{19}F NMR spectroscopy. Furthermore, no background nucleophilic aromatic substitution reaction was observed for this aryl chloride and octylamine in the presence of NaO^{t}Bu.

For the initial rates to be a valid method for kinetic analysis of this reaction, all reagents must be soluble in the reaction medium, and no induction period can be present. The single-component catalyst precursor **1** is only marginally soluble in the reaction medium. Thus, we used (BINAP)NiCl(C_6H_4-4-CF_3) (**7**) as the source of nickel for our kinetic experiments because it dissolves in seconds once mixed with other reagents. Benzonitrile was added to the reaction mixture to trap the BINAP-ligated Ni(0) species to form (BINAP)Ni(η^2-NC-Ph), which had been identified as the catalyst resting state. In the absence of benzonitrile, the irreversible formation of $(BINAP)_2$Ni occurs quickly. Benzonitrile (10 equiv relative to complex **7**) was added so that catalyst decomposition was not observed by ^{31}P NMR spectroscopy over the time of the reaction.

The kinetic behavior was assessed for the coupling of 4-chlorobenzotrifluoride with octylamine catalyzed by the combination of complex **7** in the presence of PhCN and NaO^{t}Bu at room temperature (eq 8). The initial rates were



(8)

X = Cl, **[Ni]** = complex **7**
X = Br, **[Ni]** = complex **11**

measured by ^{19}F NMR spectroscopy using 4-OCF_3-anisole as the internal standard. The rate of the amination reaction was determined by measuring the formation of *N*-octyl-4-(trifluoromethyl)aniline with respect to time. The plots of concentrations of *N*-octyl-4-(trifluoromethyl)aniline vs time at various concentrations of each reagent are shown in Figures S1−S5 in the Supporting Information. The plots of the initial rates of the reaction vs the concentrations of the catalyst, aryl chloride, and benzonitrile are shown in Figure 2. The kinetic analysis showed that this nickel-catalyzed amination reaction of aryl chlorides is first order in the nickel catalyst, first order in aryl chloride, and inverse first order in PhCN. The remaining reagents, NaO^{t}Bu and amine, did not affect the initial rate of the reaction. These data indicate that oxidative addition of the aryl chloride to (BINAP)Ni(0), formed by reversible dissociation of PhCN from the catalyst resting state (BINAP)Ni(η^2-NC-Ph), is the turnover-limiting step in the amination reaction.

Kinetic Studies on Nickel-Catalyzed Amination of Aryl Bromides. The mechanism of palladium-catalyzed cross-coupling reactions with aryl halides as electrophiles has been extensively studied. These studies reveal that the halide identity has a dramatic effect on the mechanism for the oxidative addition of aryl halides to Pd(0) species. The additions of the less reactive aryl chlorides occurs through lower-coordinated Pd(0) intermediate than the additions of more reactive aryl iodides.[44] However, such mechanistic data has not been gained for the nickel-catalyzed amination of aryl halides. For the nickel-catalyzed enantioselective α-arylation of ketones, we found that aryl chlorides react in much higher yields and with much higher enantioselectivities than aryl bromides, and we attributed this dramatic effect of halide on the reaction yield and enantioselectivity to the faster decomposition of the arylnickel(II) bromide intermediate relative to the arylnickel(II) chloride intermediate to their corresponding Ni(I) halide complexes.[36]

Because the Ni(0) complex **1** ligated by BINAP and PhCN catalyzes the amination of both aryl chlorides and aryl bromides, we can compare directly the kinetics and mechanism of the amination reactions of aryl chlorides and aryl bromides catalyzed by this nickel system. To do so, we conducted kinetic experiments on the amination of aryl bromides that were similar to those we conducted on the amination of aryl chlorides.

We monitored by ^{31}P NMR spectroscopy the reaction of 4-bromobenzotrifluoride with octylamine catalyzed by (BINAP)Ni(η^2-NC-Ph) in the presence of NaO^{t}Bu at room temperature. As was the case in the reactions of chloroarenes, (BINAP)Ni(η^2-NC-Ph) was identified as the resting state of the catalyst in the reaction of 4-bromobenzotrifluoride with octylamine.

Kinetic studies were conducted on the reaction of 4-bromobenzotrifluoride with octylamine catalyzed by (BINAP)NiBr(C_6H_4-4-CF_3) (**11**) in the presence of added PhCN (eq 8). The initial rates were measured for various concentrations of each reagent while keeping the other reagents in excess. The plots of concentrations of *N*-octyl-4-(trifluoromethyl)aniline vs time at various concentrations of each reagent are shown in Figures S7−S11. The plots of the initial rates of the reaction vs the concentrations of the catalyst, aryl chloride, and benzonitrile are shown in Figure 3.

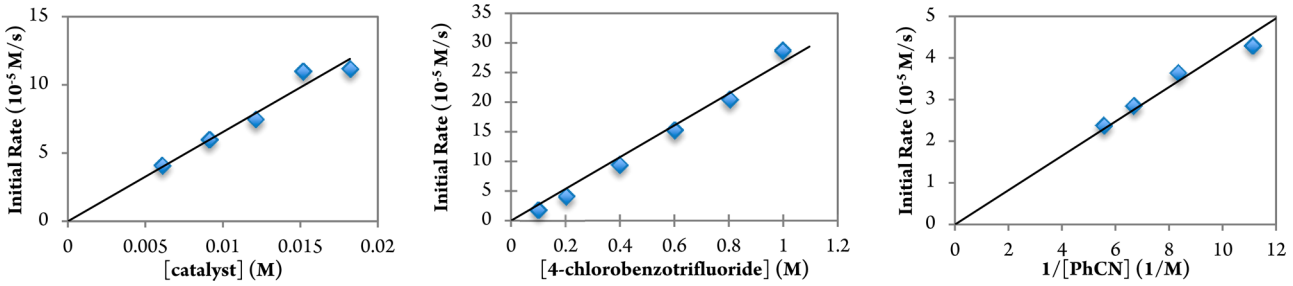


Figure 2. Plots of initial rates vs concentration of catalyst, aryl chloride, and benzonitrile for the amination of 4-chlorobenzotrifluoride (0.10−1.0 M) with *n*-octylamine (0.30 M) catalyzed by (BINAP)NiCl(C_6H_4-4-CF_3) (0.0060−0.018 M) in the presence of benzonitrile (0.090−0.180 M) and NaO^{t}Bu (0.30 M) at room temperature.

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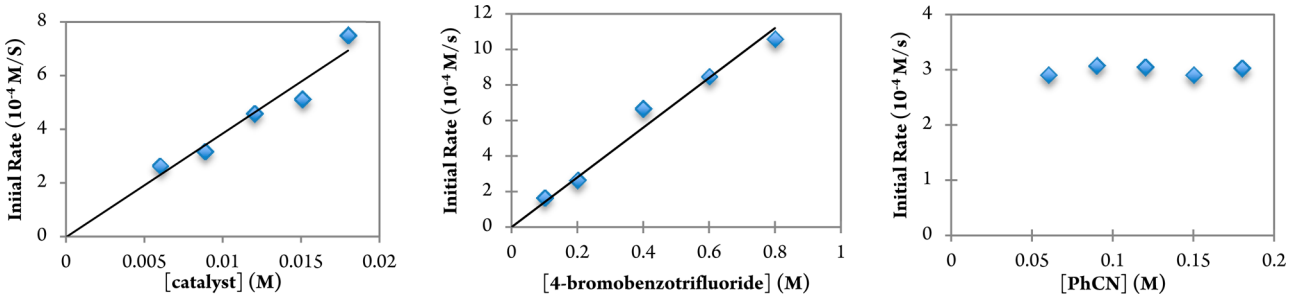
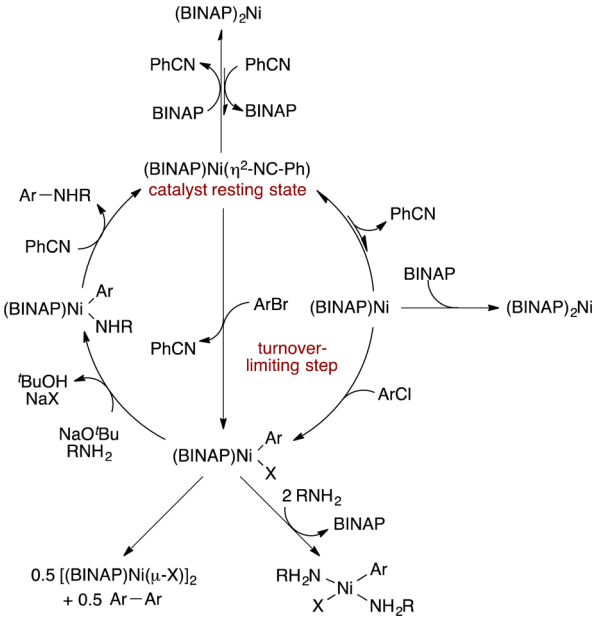


Figure 3. Plots of initial rates vs concentration of catalyst, aryl bromide, and benzonitrile for the amination of 4-bromobenzotrifluoride (0.10−0.80 M) with *n*-octylamine (0.30 M) catalyzed by (BINAP)NiCl(C_6H_4-4-CF_3) (0.0060−0.018 M) in the presence of benzonitrile (0.090−0.180 M) and NaO^{t}Bu (0.30 M) at room temperature.

Like the amination of 4-chlorobenzotrifluoride, the amination of 4-bromobenzotrifluoride with octylamine is first order in the nickel catalyst, first order in aryl halide, zero order in NaO^{t}Bu, and zero order in amine. In contrast to the reaction of 4-chlorobenzotrifluoride, which is inverse first order in PhCN, the amination of 4-bromobenzotrifluoride is zero order in PhCN. This order in PhCN, in combination with the first order in aryl bromide, indicates that the bromoarene reacts directly with (BINAP)Ni(η^2-NC-Ph) during the turnover-limiting step of the amination of the bromoarene without dissociation of PhCN. The different reactivities of aryl halides with BINAP-ligated nickel complexes of different coordination numbers parallels a trend in oxidative addition to Pd(0) complexes noted in the introduction to this section.[44]

Overall Mechanism of Nickel-Catalyzed Amination of Aryl Chlorides and Aryl Bromides. Based on the stoichiometric reactions of the isolated BINAP-ligated arylnickel halides with primary amines in the presence of base and the conducted kinetic studies, we propose a catalytic cycle depicted in Scheme 6 for the nickel-catalyzed amination of aryl chlorides and aryl bromides reported in this paper. The observed first order rate-dependence on the concentrations of both the catalyst and aryl halides indicates that the oxidative addition of aryl halides to BINAP-ligated Ni(0) species to form (BINAP)NiAr(X) (X = Cl or Br) is the turnover-limiting step for both amination processes. This BINAP-ligated arylnickel(II) halide complex subsequently reacts with primary amine and NaO^{t}Bu to form an arylnickel amido complex, followed by reductive elimination of the *N*-alkyl aniline product in the presence of PhCN to regenerate (BINAP)Ni(η^2-NC-Ph), which was confirmed as the catalyst resting state.

Scheme 6. Proposed Catalytic Cycle for the Nickel-Catalyzed Amination of Aryl Chlorides and Bromides



Interestingly, different rate-dependences on the concentration of PhCN were observed for this nickel-catalyzed amination of aryl chlorides and aryl bromides. The reaction of aryl chlorides is inverse first order in PhCN, whereas the reaction of aryl bromides is zero order in PhCN. These reaction orders indicate that aryl chlorides and aryl bromides react with different nickel(0) species. The aryl chlorides react after reversible dissociation of PhCN from (BINAP)Ni(η^2-NC-Ph) to form the lower-coordinate nickel(0) species (BINAP)Ni(0) and ultimately the BINAP-ligated arylnickel(II) chloride complex. However, the aryl bromides react directly with (BINAP)Ni(η^2-NC-Ph) to form BINAP-ligated arylnickel(II) bromide complex and the nitrile dissociates during or immediately after the oxidative addition process. One could imagine the zero-order dependence on added PhCN could indicate that dissociation of this ligand is rate limiting, but the first-order dependence of the reaction on the aryl bromide is inconsistent with this proposal.

In addition to the steps within the catalytic cycle that form the arylamine product, there are several pathways that generate catalytically inactive nickel species. First, the reaction of (BINAP)NiAr(Cl) with amine RNH_2 forms the catalytically inactive $(RNH_2)_2$NiAr(Cl) and free BINAP. The released free BINAP in the reaction mixture traps the (BINAP)Ni(0) fragment generated by dissociation of PhCN from (BINAP)-Ni(η^2-NC-Ph) or reductive elimination of *N*-alkyl aniline from the BINAP-ligated arylnickel(II) amido complex to form $(BINAP)_2$Ni. $(BINAP)_2$Ni does not undergo oxidative addition of the aryl halide and does not catalyze the amination reaction. However, it can be reactivated by PhCN. Second, thermal decomposition of (BINAP)NiAr(X) (Ar = electron-neutral and electron-rich aryl groups) affords the catalytically inactive $[(BINAP)Ni(\mu\text{-}X)]_2$ with concomitant formation of biaryl. Third, for the amination of electron-rich aryl chlorides, P−C bond cleavage of the BINAP backbone is a potential pathway for the deactivation of the nickel catalyst. Indeed, this complex was observed to accumulate (approximately 6.4 mM of the 16 mM concentration of initial catalyst) during the reaction of 4-chloroanisole with octylamine.

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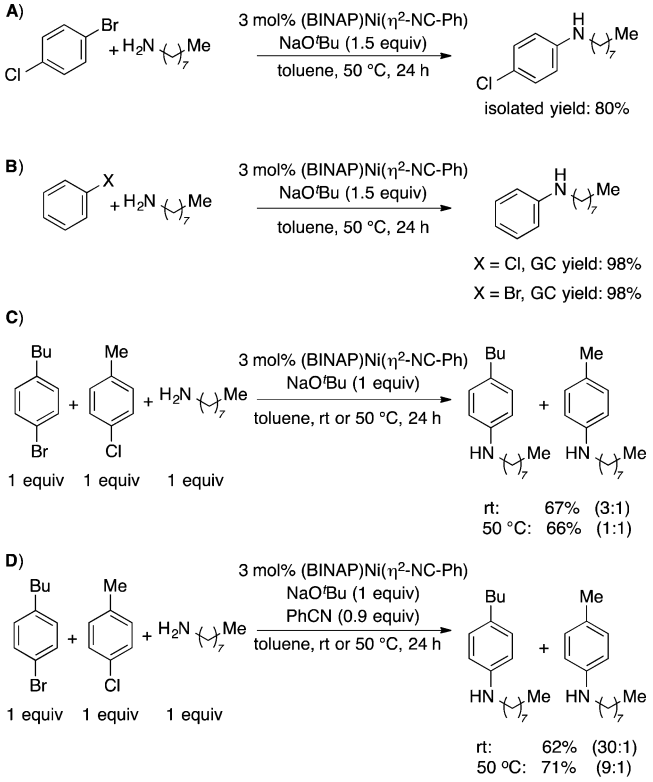
Competition Experiments. To gain information on the relative rates of the amination of aryl chlorides and aryl bromides and the effect of temperature and concentration of PhCN on the selectivity of the amination reaction for an aryl chloride versus an aryl bromide, we conducted a series of reactions with an aryl halide containing both chloride and bromide and a mixture of aryl halides in the presence of various amounts of PhCN at room temperature or 50 °C. The results of these reactions are summarized in Scheme 7.

Scheme 7



The amination of 1-bromo-4-chlorobenzene with octylamine catalyzed by 3 mol % of (BINAP)Ni(η^2-NC-Ph) at 50 °C occurred selectively at the C−Br bond, and the product of the reaction at the C−Cl bond was not detected by GC-MS analysis. The product *N*-octyl-4-chloroaniline was isolated in 80% yield. (A, Scheme 7). However, side-by-side reactions of chlorobenzene and bromobenzene under the same conditions occurred in the same GC yield (98%) (B, Scheme 7).

The amination of equal amounts of 1-bromo-4-butylbenzene and 4-chlorotoluene with octylamine catalyzed by 3 mol % of (BINAP)Ni(η^2-NC-Ph) was conducted at both room temperature and 50 °C (C, Scheme 7). At both temperatures, these reactions occurred in similar yields, but with different selectivity. At room temperature, 1-bromo-4-butylbenzene was converted selectively over 4-chlorotoluene, and a product ratio of 3:1 was obtained. However, at 50 °C, 1-bromo-4-butylbenzene and 4-chlorotoluene converted equally. Compared with the full selectivity for amination of the C−Br bond in 1-bromo-4-chlorobenzene (A, Scheme 7), the decreased selectivity for amination of the C−Br bond over the C−Cl bond in different haloarenes might stem from irreversible or nearly irreversible binding of the haloarene to Ni(0) to form an arene π-complex prior to cleavage of the carbon−halogen bond. This preferential intramolecular oxidative addition has recently been observed for the Ni-catalyzed Kumada cross-coupling reactions that are part of chain-growth polymerizations.[45]

To evaluate the effect of PhCN on the selectivity between the amination of an aryl chloride and an aryl bromide, we conducted the amination of equal amounts of 1-bromo-4-butylbenzene and 4-chlorotoluene with octylamine catalyzed by 3 mol % of (BINAP)Ni(η^2-NC-Ph) in the presence of 0.9 equiv of PhCN (relative to octylamine) (D, Scheme 6). Because our kinetic studies revealed different dependences of the reaction rate on PhCN for this nickel-catalyzed amination (inverse first order and zero order on PhCN for the reaction of aryl chloride and aryl bromide, respectively), we considered that an increased selectivity for the conversion of aryl bromide over aryl chloride would be observed for reactions conducted with higher concentrations of PhCN than for reactions conducted with lower concentrations of PhCN.

Consistent with this prediction, the selectivity was higher (30:1 for the reaction at room temperature and 9:1 for the reaction at 50 °C) for the amination of 1-bromo-4-butylbenzene versus the amination of 4-chlorotoluene for reactions run with higher concentrations (from 0.004 to 0.18 M) of benzonitrile at both room temperature and 50 °C for 24 h. These data show that the difference in Ni(0) species that adds the different aryl halides can be used to beneficially affect selectivity.

Comparison to Prior Ni Systems for Aryl Halide Amination. Several first-row metal complexes catalyze cross coupling reactions, and many catalyze the coupling of certain classes of chloroarenes. However, no first row metal complex has been shown to catalyze the coupling of primary alkylamines with unactivated chloroarenes. Copper complexes couple bromoarenes and iodoarenes with primary amines, but they do not catalyze the coupling of chloroarenes with primary amines.

Previously, the combination of $Ni(COD)_2$ and DPPF was shown to couple an electron-poor chloroarene with a primary amine, but this catalyst did not couple unactivated chloroarenes with primary amines.[11] A set of preliminary studies we conducted have shown that the complexes (DPPF)Ni(COD) or $(DPPF)_2Ni$ generated in situ by the reaction of $Ni(COD)_2$ and DPPF do not add aryl chlorides at ambient temperature, and the reaction of chloroarenes with (DPPF)Ni(COD) or $(DPPF)_2Ni$ at elevated temperatures forms (DPPF)Ni(I)Cl and biaryl.

This formation of $(DPPF)_2Ni(0)$ and (DPPF)Ni(I)Cl at the elevated temperatures required for oxidative addition of chloroarene to occur, likely prevented productive coupling reactions with unactivated chloroarenes. These observations further illustrate the importance of the nitrile-ligated precursor with the general formula $L_2Ni(\eta^2$-NC-Ph).

Nickel complexes of *N*-heterocyclic carbenes have been shown to couple aryl chlorides and sulfonates with secondary amines and with arylamines, but not primary alkylamines. Mechanistic studies on the reactions of secondary amines catalyzed by the complexes of *N*-heterocyclic carbenes are too limited to determine the origin of their lack of reactivity with primary amines, but recent studies have shown that the arylnickel halide complexes containing hindered *N*-heterocyclic carbenes are not formed by the reaction of $(IMes)_2Ni(0)$ with chlorobenzene, bromobenzene, and iodobenzene.[46] Instead, Ni(I) species are formed, and this formation of Ni(I) complexes could either constitute the pathway for catalyst

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decomposition or a mechanism for reaction with this catalyst involving odd-electron nickel intermediates.

CONCLUSIONS

We have shown that nickel complexes containing common aryl bisphosphine ligands can catalyze the coupling of aryl chlorides and bromides with primary amines. In particular, we have shown that the mixed Ni(0) species (BINAP)Ni(η^2-NC-Ph) containing one bisphosphine and one side-bound nitrile is a particularly active catalyst for the coupling of chloroarenes with primary amines and is more active than the related $(BINAP)_2Ni$ catalyst. A range of electronically varied aryl halides and nitrogen-containing heteroaryl chlorides, including pyridine, quinoline, and isoquinoline derivatives, couple with a variety of aliphatic primary amines in high isolated yields. Several aspects of the current system lead to the ability of this first-row metal system to catalyze this class of amination reaction. In general, we attribute the high yields for these amination reactions to the facile oxidative addition of aryl chlorides and heteroaryl chlorides to the (BINAP)Ni(η^2-NC-Ph) precatalyst at ambient temperatures.

Detailed studies on the mechanism of the amination reaction have been conducted. The following conclusions about the mechanism of this coupling process have been drawn from these studies:

(1) The oxidative addition of aryl chlorides to (BINAP)Ni-(η^2-NC-Ph), together with the stoichiometric reactions of (BINAP)NiAr(Cl) with primary aliphatic amines in the presence of base, support a reaction pathway involving a Ni(0)/Ni(II) couple in the catalytic cycle.

(2) The oxidative addition of aryl chlorides and heteroaryl chlorides to the single-component nickel precursor (BINAP)-Ni(η^2-NC-Ph) at ambient temperatures prevents the formation of inactive Ni species.

(3) Ni(I) intermediates, which have been observed in oxidative addition studies to phosphine-ligated Ni(0) complexes, appear to result from decomposition of the Ni(II) product of oxidative addition as opposed to forming from one-electron pathways for oxidative addition to Ni(0).[26]

(4) The reaction of (BINAP)Ni(η^2-NC-Ph) with electron-rich aryl chlorides, such as 4-chloroanisole, leads to the P−C bond cleavage of the backbone of BINAP and forms the nickel complex **9** containing two monophosphine ligands. The formation of the catalytically inactive complex **9** explains the high catalyst loading required for the amination of electron-rich aryl chlorides.

(5) Mechanistic and kinetic studies revealed that the turnover-limiting step of these nickel-catalyzed amination reactions of aryl chlorides is oxidative addition of the aryl chloride to (BINAP)Ni(0), which is formed by dissociation of PhCN from the catalyst resting state (BINAP)Ni(η^2-NC-Ph).

(6) Mechanistic and kinetic studies imply that the turnover-limiting step of the reactions of aryl bromides is also oxidative addition, but that aryl bromides react with a different nickel species, of composition (BINAP)Ni(η^2-NC-Ph) containing a bound nitrile.

(7) The formation of catalytically inactive bis(amine)-ligated Ni(II) species $(RNH_2)_2NiAr(Cl)$, Ni(I) species $[(BINAP)Ni(\mu\text{-}Cl)]_2$, and bis-BINAP-ligated Ni(0) species $(BINAP)_2Ni$ are the major pathways for catalyst inactivation.

Further studies to improve the lifetime of the Ni-bisphosphine catalysts, to determine the mechanism by which the phosphine-ligated Ni(I) species form as a means to prevent this detrimental path, and to determine if Ni(I) complexes are generated during oxidative addition of haloarenes will be the subject of future work.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedure, characterizations of all compounds, and crystallographic data (CIF) for compound **9**. 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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