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# An Air-Stable Nickel(0) Phosphite Precatalyst for Primary Alkylamine C–N Cross-Coupling Reactions

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In this report we describe the design and preparation of a new air-stable nickel phosphite based catalyst for unique C–N bond forming processes. Specifically, (BINAP)Ni- $[P(OPh)_3]_2$ , is presented as an effective catalyst for a range of

## Introduction

Cross-couplings catalyzed by transition metals have evolved to now play a vital role in organic synthesis.<sup>[1]</sup> The use of nickel catalysts in these pivotal bond forming reactions is an attractive and often effective alternative to the more popular and expensive palladium counterparts.<sup>[2]</sup> The most significant advantage of nickel catalysts in this field, are the lower calculated energy barriers for oxidative addition<sup>[3]</sup> allowing a wider and a greater variety of leaving groups to be used.<sup>[4]</sup> Recently, there has been a focus on the design of new nickel catalysts for a range of important cross-coupling reactions.<sup>[5]</sup> In particular, this first row transition metal has been used in cross-coupling processes such as the Heck,<sup>[4c,6]</sup> Suzuki<sup>[4f,7]</sup> and Sonogashira<sup>[8]</sup> reactions.<sup>[2b]</sup>

The pre-catalyst Ni(COD)<sub>2</sub> is routinely used in the majority of nickel-mediated cross-coupling reactions. In these examples the co-ligands, mono- or didentate, such as phosphines,<sup>[4f,9]</sup> N-heterocyclic carbenes (NHCs)<sup>[4e,10]</sup> seem essential.<sup>[11]</sup> Although Ni(COD)<sub>2</sub> has numerous benefits as a precatalyst, the drawbacks of being highly air-sensitive, difficult to transport and challenging to prepare have inspired researchers to find alternatives.

The nickel catalyzed C–N cross-coupling reaction, or the Buchwald–Hartwig amination, has been investigated by several groups including ours.<sup>[10c,12]</sup> A series of reactive

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amination reactions between aryl halides and primary alkylamines. The results are supported by relevant kinetic studies, DFT calculations and a catalytic cycle indicating possible reaction intermediates.

nickel catalysts (Figure 1) have been prepared, and reported very recently, specifically for this cross-coupling process. The group of Buchwald synthesized the air-stable (DPPF)-Ni(*o*-Tol)Cl catalyst (1) for the coupling of aryl chlorides, sulfamates, mesylates and triflates with anilines and second-ary alkylamines.<sup>[13]</sup> Hartwig et al. designed the Ni<sup>0</sup> catalyst (BINAP)Ni( $\eta^2$ -NC-Ph) (2) for the coupling of primary alkylamines in C–N cross-coupling reactions.<sup>[14]</sup> In the same year the group of Garg reported a catalytic combination of



Figure 1. Some recently discovered nickel catalysts for C–N bond formation.

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a Ni<sup>II</sup> precatalyst and the NHC SIPr·HCl (3) for the coupling of aryl chlorides with secondary amines in the green solvent methyl-THF.<sup>[15]</sup> The complex [Ni(allyl)Cl(NHC)] (4) was also described by Nolan for the coupling of anilines and morpholine adding to the range of NHC complexes that show efficacy in this area.<sup>[16]</sup>

Our contribution to this field was initiated to serve as a stable Ni<sup>0</sup> alternative to the Ni(COD)<sub>2</sub> and phosphine catalytic system. In our investigation, (DPPF)Ni[P(OPh)<sub>3</sub>]<sub>2</sub> (**5**) was prepared, without the use of Ni(COD)<sub>2</sub>, and the complex was studied in a series of C–N amination reactions of various aryl chlorides and bromides with anilines or amines.<sup>[12c]</sup> More recently, in ammonia arylation studies, the two nickel catalyst precursors **6** and **7** have been discovered leading to effective C–N bond formation on a range substrates.<sup>[17]</sup>

Prior to our recent contribution, nickel phosphite complexes had shown limited utility in Heck cross-coupling reactions,<sup>[18]</sup> the reaction of allylic acetates with thiols<sup>[19]</sup> and in hydrocyanation reactions.<sup>[20]</sup> Phosphites have also been used with Ni(OAc)<sub>2</sub>·4H<sub>2</sub>O in amino carbonylation reactions with DMF.<sup>[21]</sup> Historically, a seminal investigation in the field of nickel phosphite chemistry was undertaken by Tolman, which led to a further understanding of the effects of cone angles and phosphorus ligand exchange equilibria on nickel zerovalent nickel complexes.<sup>[22]</sup>

It is clear that Ni<sup>0</sup> phosphite complexes are cheaper and more air-stable than both Ni(COD)<sub>2</sub>,<sup>[23]</sup> and nickel(0) phosphine complexes. However, a limitation of our initial catalytic system, using complex 5, were the poor yields associated with less reactive primary alkylamines. Few studies deal specifically with nickel-catalyzed primary alkylamine C-N cross-coupling reactions,<sup>[10c,12h]</sup> and only one previous report, to the best our knowledge, deals with unactivated aryl systems.<sup>[14]</sup> In the development of catalytic conditions using complex 5, we observed varying results depending if additional DPPF ligand was included or not; a result also recently observed with Ni<sup>II</sup> complex (1).<sup>[13]</sup> Furthermore, an issue with our original nickel phosphite catalyst was the extremely poor yields with primary alkylamines. In this current study we sought an air-stable catalyst that would couple primary amines but could also be translated for use in reactions with imines.

### **Results and Discussion**

### **Optimization of the Alkylamine Coupling Reaction**

In our initial test reaction, chlorobenzene (8) was coupled with *n*-hexylamine (9). As a comparison, our previously reported phosphite complex 5 gave less than 10% yield of the desired aniline product 10 (Table 1, Entry 1). This yield was enhanced via the addition of  $(\pm)$ -BINAP to the catalytic system, but only to 32% (Table 1, Entry 2) leaving room for catalyst improvement. This increase in yield prompted us to prepare the (BINAP)Ni[P(OPh)\_3]\_2 complex 11, which may well be forming in this reaction as a precatalyst.

Table 1. Nickel catalyst based screening of C–N coupling between chlorobenzene (9) and *n*-hexylamine (10).



[a] Yields are isolated yields unless in brackets (GC with docosane as internal standard). [b] 1,4-Dioxane was used as the solvent. [c] Under air.

To this end, stirring the tetrakisphosphite complex Ni- $[P(OPh)_3]_4$  (12) with (±)-BINAP afforded the desired complex 11 in 69% yield (Scheme 1) without isolation or detection of any Ni(BINAP)<sub>2</sub>. The precursor, Ni[P(OPh)<sub>3</sub>]<sub>4</sub> (12), is expensive, if obtained from commercial sources, but can be easily prepared in 72% yield from inexpensive Ni-(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O following the procedure of Levison et al.<sup>[24]</sup> From this we estimate the production of Ni[P(OPh)<sub>3</sub>]<sub>4</sub> at US\$0.29/mmol. The crystal structure of complex 11 shows a distorted tetrahedral geometry about the nickel (Figure 2 and Table 2), in which the BINAP bite angle [P(2)-Ni(1)-P(1)] of 94.51° exhibits the greatest deviation from the tetrahedral angle (109.5°) however, is close to the natural bite angle of free BINAP (93°).<sup>[25]</sup> This result is in agreement with comparable nickel complexes, [(R)-BINAP]Ni( $\eta^2$ -NCPh),<sup>[11c]</sup> [(S)-BINAP]Ni(COD)<sup>[26]</sup> and [(S)(BINAP)]-Ni(o-tol)Cl.<sup>[27]</sup> It is also noteworthy that the Ni-P bond lengths between metal center and phosphites are smaller than between metal center and the phosphine (Table 2). A possible consequence of these characteristics regarding ligand dissociation is discussed later in the DFT section of this report.



Scheme 1. Synthesis of (BINAP)Ni[P(OPh)<sub>3</sub>]<sub>2</sub> (11).

Gratifyingly, when subjecting this newly formed complex to the test reaction (Table 1), the aniline product **10** was obtained in an excellent yield of 99% (entry 3), without the need of any additives. Using 1,4-dioxane as an alternative





Figure 2. Molecular representation of the structure of (BINAP)Ni- $[P(OPh)_3]_2$  (11), ellipsoids have been drawn at the 50% probability level; CCDC number 1045787.

Table 2. Comparison of selected bond lengths [Å] and angles [°] for compound 11 from single-crystal X-ray crystallographic and DFT studies, vide infra.

Bond lengths [Å]	X-ray cryst.	DFT
Ni(1)–P(3)	2.1070(9)	2.176
Ni(1) - P(4)	2.1176(10)	2.159
Ni(1) - P(2)	2.2136(10)	2.306
Ni(1) - P(1)	2.2149(10)	2.287
Bond angles [°]		
P(3)–Ni(1)–P(4)	103.11(4)	104.3
P(3)-Ni(1)-P(2)	115.52(4)	114.2
P(4) - Ni(1) - P(2)	122.86(4)	119.6
P(3)-Ni(1)-P(1)	103.32(4)	108.1
P(4) - Ni(1) - P(1)	116.35(4)	113.5
P(2) - Ni(1) - P(1)	94.51(4)	96.9

solvent gave only a moderate yield of 62% (entry 4). Unfortunately, no reaction occurred under ambient conditions (entry 5). Nonetheless, complex **11** proved to be extraordinarily air-stable in its solid form showing no reduction of activity even after six months of regular exposure to air. We also sought to identify alternative, milder, bases to allow this C–N coupling reaction to occur with an enhanced functional group tolerance.<sup>[28]</sup> Fortunately, NaHMDS proved to be a suitable base giving aniline **10** in high 80% yield (entry 6). In contrast, the reaction was low yielding when the potassium variant, KHMDS, was used (entry 7). Unfortunately, no product was formed when the mild base Cs<sub>2</sub>CO<sub>3</sub> was employed (entry 8).

Given the (BINAP)Ni[P(OPh)<sub>3</sub>]<sub>2</sub> (11) complex along with NaOtBu as the base was the most efficient in the primary amine coupling, the optimum catalytic loading and temperature were then determined. These results have been summarized in Table 3. It became apparent that the reaction yield was dependent on the loading of the catalyst. Decreasing the catalytic loading to 3 mol-% (100 °C) still provided a yield of 92%, (entry 3). A series of reactions

with reduced reaction temperatures, decreasing by 20 °C with each step, were also conducted. Remarkably, even at 40 °C, the amination still proceeded in 84% yield (entry 9). Complex 11 was also superior in the coupling of anilines if compared with our previously reported (DPPF)Ni[P(OPh)  $_{3]2}$  (5).<sup>[12c]</sup> The coupling between 4-chloroanisole with *p*-to-luidine, using complex 11, proceeded in quantitative yield forming the corresponding diarylamine (compared to 82% with complex 5; results not shown).

Table 3. Effect of catalyst loading and temperature on C–N coupling between chlorobenzene 8 and *n*-hexylamine 9.

$H_2N$	BINA 8 (BINA + to 9	AP)Ni[P(OPh) <sub>3</sub> ]₂ <b>11</b> DtBu (1.4 equiv.) → Dluene, 18–22h	₩ 10
Entry	Temperature [°C]	Catalyst loading	Yield [%] <sup>[a]</sup>
1	100	5 mol-%	99
2	100	4 mol-%	94
3	100	3 mol-%	92
4	100	2 mol-%	78
5	100	1 mol-%	54
6	100	0.5 mol-%	(13)
7	80	5 mol-%	99
8	60	5 mol-%	93
9	40	5 mol-%	84

[a] Yields are isolated yields unless in brackets (GC determination).

### Scope and Limitations

The scope of the coupling of the aryl chlorides (Table 4) was investigated and found to encompass a large range of electronically differing aryl rings. In all cases, the reaction was carried out using 5 mol-% of the catalyst 11 at 80 °C, and *n*-hexylamine was chosen as the coupling partner. In general, substrates containing electron-withdrawing substituents, such as cyano (13a), trifluoromethyl (13b) and acyl (13j), all coupled in excellent yields.

Similarly, strongly and weekly electron-donating groups also resulted in good to excellent yields of the corresponding alkylaniline 13c-13e. The N-heterocycles pyridine 13f, and quinoline 13k, were produced in reasonable yields, at 68% and 62%, respectively, suggesting this methodology could find utility in derivatization studies favored in medicinal chemistry. Aryl bromides were also successfully employed in this reaction, however lower yielding, affording the products 10, 13d, 13g and 13h. Unfortunately, the less commonly used, but cheap, aryl tosylates gave only modest yields of compounds 10 and 13a. Catalyst 11 was also successful in conducting an intramolecular C-N cross-coupling reaction using ortho-chlorophenethylamine leading to indoline 13i in 76% yield.<sup>[10a]</sup> Gratifyingly, silyl ethers were tolerated as well, and compound 13l was obtained in reasonable 60% yield. Unfortunately, using ortho-substituted hydrocinnamonitrile gave aniline 13n only in low yield. At Table 4. Scope and limitations of the aryl halide coupling partner (0.50 mmol scale).<sup>[a]</sup>



[a] Isolated yields. [b] GC-yield using docosane as internal standard. [c] 100 °C, product contained 10% indole. [d] NaHMDS was used as the base. [e] Corresponding hexylurea formed (44%). 44% carbamate starting material was recovered. [f] NaHMDS was used as the base. Dehalogenation and ring opening of the (thio)acetal. [g] 88% recovery of sulfonamide starting material. <sup>[h]</sup> 50 °C, NaHMDS was used as the base. Amide formation.

this stage, base-sensitive groups appear to be the main limitation of our catalyst system. Thus, acetophenone 130 was obtained in low yield, while the use of a methyl ester did not give compound 13s, but instead resulted in the formation of the corresponding amide. Even lower temperatures (50 °C) and using NaHMDS as the base did not give any desired coupling product. Likewise, in the presence of a Boc-group, only the corresponding hexylurea was isolated in addition to starting material (13m). Moreover, acetals and thioacetals only resulted in the formation of dehalogenated products and ring opening of the acetal moieties (13p, 13q). No coupling reaction to give sulfonamide 13r occurred, and only starting material was isolated.

After establishing the scope of the aryl halides the range of primary alkylamine coupling partners was investigated (Table 5). We were delighted that simple, branched alkylamines and cyclohexylamine could also be employed leading to compounds **14a–b**. Similarly, benzyl- and  $\alpha$ -methylbenzylamine furnished the corresponding anilines **14c–f** in good yields. However, the reaction of allylamine was slightly lower yielding, providing compound **14g**. Similar reactions involving allylamine, catalyzed with palladium, have previously been used in cross-coupling reactions as ammonia equivalents.<sup>[29]</sup> Using 2-picolylamine as the amine coupling partner currently appears to be a limitation of the amine coupling partner scope. The poor yield of compound **14h** (12%) could be due to additional substrate binding to the nickel center affecting the catalytic cycle.

Table 5. Scope of the primary amine coupling partner (0.50 mmol scale).  $^{\rm [a]}$ 



[a] Isolated yields. [b] 60 °C, sealed vessel. [c] Additional ( $\pm$ )-BINAP (5 mol-%) was used.



#### **Competition Experiments**

A short series of competition experiments were then conducted, the first exploring the difference in reactivity of aryl halides containing electron-withdrawing groups compared with electron-donating groups. The reactivity of both the aryl chlorides 15 and 16 (Scheme 2) under the new catalytic methodology at 80 °C with *n*-hexylamine, seems to strongly favor the coupling of the electron poor aryl substrate 15. This result was also mirrored in a similar reaction involving the corresponding aryl bromides 17 and 18. A chemoselectivity experiment between 1-bromo-4-chlorobenzene (19) also revealed a preference for the arvl bromide moiety. In this instance, the reaction with *n*-hexylamine produced 4chloro-*N*-hexylaniline (20) as the sole product (Scheme 2). Higher yields for the C-N cross-coupling Ar-Cl vs. Ar-Br have been observed by the group of Garg with 1-naphthyl halides.<sup>[15a]</sup> Additionally, aryl bromides are often chosen as challenging substrates because of their less reactive nature in nickel based C-N cross-coupling (Table 4).[14,17a]



Scheme 2. Competition experiments of electron-withdrawing group vs. -donating group bearing aryl chlorides/bromides (yields were determined by GC using docosane as an internal standard).

In a second group of competition experiments, we established that the catalyst (BINAP)Ni[P(OPh)<sub>3</sub>]<sub>2</sub> **11** is selective for the primary alkylamine over an aniline (Scheme 3). In this case the 1:1:1 reaction mixture of 4-chlorobenzonitrile (**15**), *p*-toluidine **22** and *n*-hexylamine **9**, under our standard reaction conditions, produced significantly more of the alkylamine product **13a**. This phenomenon is curious considering the reactivity of anilines in C–N cross-coupling reactions is generally considered excellent in comparison to alkylamines. Even when the concentration of the aniline coupling partner was doubled, the reaction was still selective for the alkylamine coupled product **13a** over **23**. Selectivity in C–N amination reactions has been reported previously, for example primary amines over secondary (alkyl, aryl) amines coupling using palladium based catalysts.<sup>[30]</sup>



Scheme 3. Competition experiments of primary alkylamine vs. anilines (yields were determined by GC using docosane as an internal standard).

#### **Imine Coupling Reaction**

Given the successful results for primary alkylamines, we considered, briefly, the ability of complex 11 to catalyze reactions that would incorporate an ammonia equivalent. The reaction was conducted with benzophenone imine (26), similar to reactions catalyzed by palladium.<sup>[31]</sup> The reaction between imine 26 and either *p*-chloro- (24) or *p*-bromotoluene (25) using our nickel-based catalytic conditions provided imine 27 in excellent yields (97% and 88%). Subsequent hydrolysis of the imine resulted in the formation of *p*-toluidine 22 (Scheme 4). This cross-coupling example, as far as we know, is the first nickel catalyzed benzophenone imine coupling. We are currently still investigating whether our catalyst can also be used for direct ammonia arylation reactions as recently reported by the groups of Stradiotto<sup>[17a]</sup> and Hartwig.<sup>[17b]</sup>



Scheme 4. Synthesis of *p*-toluidine **22** through a C–N benzophenone imine coupling (isolated yields).

### NMR and Kinetic Studies

For the further understanding of this nickel-catalyzed C– N cross-coupling process, we were wary of assuming the same intermediates as the equivalent palladium-mediated process, which has been intensively studied. Recently, the group of Hartwig proposed a detailed catalytic cycle for the (BINAP)Ni( $\eta^2$ -NC-Ph) (2) catalyst. This study revealed two interesting aspects, the immediate loss of benzonitrile ligand

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to form Ni(BINAP) and establishing that the oxidative addition of ArX was the rate-limiting step.<sup>[14]</sup> In our case, having a unique catalyst containing two phosphite ligands, we wanted to understand how these would behave alongside the bidentate BINAP, especially in the early stages of the catalytic cycle.

The reaction between 4-chlorobenzonitrile (15) and nhexylamine (9) was first monitored by <sup>31</sup>P NMR (Scheme 5 a; see the Supporting Information for spectra). In this process, it was clear that the concentration of free BINAP increases (resonance at -14.9 ppm) in the early stage of the reaction, suggesting early dissociation of this bidentate ligand. Additionally, no resonance corresponding to free triphenylphosphite was observed ( $\delta = 127.9$  ppm). Also, in this NMR experiment the two signals ( $\delta = 126.3$  ppm and 34.4 ppm) of the parent compound 11 disappeared quickly, while two new signals at  $\delta = 138.7$  ppm and 135.0 ppm appeared. These resonances are assumed to be due to a nickel phosphite species, however due to isolation difficulties they are yet to be identified. These results are consistent with our previous findings in the related (DPPF)Ni[P(OPh)<sub>3</sub>]<sub>2</sub> (5) system.<sup>[12c]</sup> Unfortunately, using <sup>31</sup>P NMR spectroscopy the identification of paramagnetic Ni<sup>II</sup> tetrahedral species is impossible and pathways involving these species cannot be discounted.

For further mechanistic understanding of this reaction, we also decided to conduct a kinetic study using an initial reaction rate approximation. The product formation over time was determined by GC. Again, we chose the reaction between 4-chlorobenzonitrile (15) and *n*-hexylamine (9) (Scheme 5, b) as all reagents readily dissolved, and this re-



Scheme 5. Reaction for a) <sup>31</sup>P NMR monitoring<sup>[a]</sup> and b) Kinetic experiment.<sup>[b]</sup> [a] For the <sup>31</sup>P NMR monitoring study aliquots of the reaction mixture were taken at 0, 2 and 5 min. [b] For the kinetic experiment the product formation at 1, 2, 3 and 4 min time points was determined by GC using docosane as an internal standard.

action was shown to be high yielding (Table 4). The formation of the coupling product *N*-hexyl-4-cyanoaniline (**13a**) with respect to time was fitted with an exponential curve. Differentiation at the first time point gave an approximation of the initial reaction rate, which was plotted against the concentration of reagents/additives. The plots of initial rate vs. concentration of various components in the reaction are illustrated in Figure 3. Further elaboration of this study is available in the Supporting Information.

We established early that in our example, the reaction was first order with respect to the catalyst 11 (Figure 3, a).



Figure 3. Kinetic profile of the reaction between 4-chlorobenzonitrile (15) and *n*-hexylamine (9) (Scheme 5, b). Initial reaction rate vs. varying amount of a) catalyst loading; b) aryl chloride; c) amine; d) base; e) BINAP; f)  $P(OPh)_3$ ; for detailed reaction conditions see the Supporting Information.



Given this series of reactions, modifying the catalytic loading produces a plot which does not intersect the origin, a further reaction without catalyst was carried out. In this case none of the aniline product was produced, discounting the possibility of a S<sub>N</sub>Ar reaction. In the case of aryl chloride 15 the reaction was zero order as seen in the plot initial rate vs. ArCl concentration (Figure 3, b), which indicates that the oxidative addition is fast. This result is in contrast to the aforementioned study of Hartwig with (BINAP)-Ni( $\eta^2$ -NC-Ph) (2).<sup>[14]</sup> The kinetic study further established that the system was first order with respect to the amine (Figure 3, c). The reaction was also first order with respect to the NaOtBu concentration (Figure 3, d). As established earlier with some of our catalyst trials,<sup>[12c]</sup> additional BINAP had a positive influence on the initial rate of the reaction (Figure 3, e). In contrast, in the case of the triphenylphosphite ligand concentration (Figure 3, f), the reaction was zero order, suggesting that the triphenylphosphite ligand does not dissociate.

## **DFT Calculations**

In order to support the experimental observations, density function theory (DFT) was employed to determine the relative energies of various ligand dissociation products arising from the (BINAP)Ni[P(OPh)\_3]\_2 (11) complex. Calculated bond lengths and angles were in good agreement with those determined in the X-ray crystal structure (Table 2). Scheme 6 and Figure 4 summarize the computed enthalpy changes (see Supporting Information for Gibbs free energy changes) for the ligand dissociation reactions.

(BINAP)Ni[P(OPh) <sub>3</sub> ] <sub>2</sub> 11	→ BINAP + Ni[P(OPh) <sub>3</sub> ] <sub>2</sub> 11a	∆ <i>H</i> = +275.3 kJ/mol (1)
(BINAP)Ni[P(OPh) <sub>3</sub> ] <sub>2</sub> <b>11</b>	→ (BINAP)Ni[P(OPh) <sub>3</sub> ] + P(OPh) <sub>3</sub> 11b	$\Delta H = +150.3 \text{ kJ/mol} (2)$
(BINAP)Ni[P(OPh)3]	→ (BINAP)Ni + P(OPh) <sub>3</sub>	∆H = +340.0 kJ/mol (3)
11b	11c	

Scheme 6. Possible dissociation reactions for compound **11** along with computed enthalpy changes.



Figure 4. Computed enthalpy changes for ligand dissociation reactions of complex 9.

The complexes  $(BINAP)Ni[P(OPh)_3]_2$  (11),  $Ni[P(OPh)_3]_2$  (11a),  $(BINAP)Ni[P(OPh)_3]$  (11b), and Ni(BINAP) (11c) are all predicted to be minima on the global potential energy surface. As we are considering ligand dissociation reactions, which do not involve electronic state crossings, aside from a small solvent reorganization effect there should be no substantial transition state between 11 and 11a or 11b, or between 11b and 11c.

The key result from the theoretical treatment is that the enthalpy change for the loss of the BINAP ligand (Figure 4, pathway I) is energetically more feasible than that for the loss of two triphenylphosphite ligands, suggesting that the  $Ni[P(OPh)_3]_2$  (11a) intermediate the more likely candidate to undergo oxidative addition. Although the formation of complex 11b seems energetically favored, considering the significantly higher energy required to lose the second phosphite ligand, we cannot envisage how pathway II would lead to a faster oxidative addition step. The theoretical results are also entirely consistent with the experimental observation (NMR) that the BINAP ligand dissociates rather than triphenylphosphite. A possible explanation for this phenomenon could be the bite angle of the BINAP ligand (94.51°) which deviates considerably from a regular tetrahedral angle around the nickel center (Figure 2, Table 2), potentially releasing strain upon ligand dissociation. Additionally, the shorter bond lengths between phosphite and nickel compared to BINAP and nickel indicate that the phosphite ligands are bound more strongly, favoring the formation of complex 11a over 11c.

### **Mechanistic Details**

From the accumulation of kinetic data, <sup>31</sup>P NMR reaction monitoring, and DFT calculations, we propose the catalytic cycle shown in Figure 5. The <sup>31</sup>P-NMR experiments as well as the DFT calculations clearly suggest that the BINAP ligand dissociates from complex (BINAP)Ni- $[P(OPh)_3]_2$  (11) to form presumed intermediate 11a. As shown in the kinetic experiments, the reaction rate is independent of the aryl halide concentration (Figure 3, b) suggesting a fast oxidative addition to form 11a'. Moreover, we have shown that the reaction rate is also independent of the triphenylphosphite concentration (Figure 3, f), clearly indicating that the triphenylphosphite ligands remain bound to the metal. In contrast, the reaction is dependent on the concentration of base, amine and BINAP, suggesting that the second half of the catalytic cycle (11a' to 11) includes a rate-determining step which is supported by our kinetic studies (Figure 3, c-e). With the first step of the proposed catalytic cycle being the loss of the BINAP ligand, it seems counterintuitive that adding extra BINAP accelerates the reaction (Figure 3, e). However, we propose that extra BINAP assists in the final reductive elimination step to regenerate the parent compound 11. This may compensate for the potential decrease in reaction rate of the first dissociation process from 11 to 11a, where 11a is quickly consumed in the oxidative addition step. A previous example has shown that phosphines assist in the thermal reductive elimination of cross-coupling reactions from platinum complexes,<sup>[32]</sup> however, the unique nature of this nickel catalytic system limits the potential of such direct comparisons with reported reductive elimination reactions in the literature.



Figure 5. Proposed catalytic cycle for the C–N cross-coupling reaction catalyzed by complex 11.

Considering these outcomes, our proposed catalytic cycle is in agreement with the one we suggested for our previously reported (DPPF)Ni[P(OPh)<sub>3</sub>]<sub>2</sub> (5) system,<sup>[12c]</sup> and also shows similarities to mechanisms suggested by other groups.<sup>[10c,14]</sup> However, at this stage we are unsure about which of these processes is the rate-determining step given this preliminary study.

### Conclusions

In summary, we have prepared and characterized a new nickel phosphite/phosphine catalyst, (BINAP)Ni[P(OPh)<sub>3</sub>]<sub>2</sub> (11), that is remarkably air-stable, and can be used to couple primary alkylamines in good to excellent yields. We have shown this new catalyst to be efficient even at 40 °C (5 mol-%). Unfortunately, our catalytic system, like others,<sup>[14]</sup> requires strong bases which, at the moment, does not allow for efficient coupling of substrates containing base-sensitive groups. However, the catalyst was shown to readily couple imines which, to the best of our knowledge, is the first example involving nickel. This catalyst can potentially serve as an alternative to the very sensitive Ni(COD)<sub>2</sub> or many costly palladium reagents. Furthermore, we have gained evidence into mechanistic pathways using kinetic experiments, NMR spectroscopy as well as computational methods.

## **Experimental Section**

(BINAP)Ni[P(OPh)<sub>3</sub>]<sub>2</sub> (11): Ni[P(OPh)<sub>3</sub>]<sub>4</sub> (5.00 g, 3.83 mmol, 1.00 equiv.) and ( $\pm$ )-BINAP (2.38 g, 3.83 mmol, 1.00 equiv.) were placed in a Schlenk flask and dried under high vacuum for 5 min. Toluene (125 mL) was added and the resulting dark orange solution was heated to reflux for 20 h. The solution was concentrated to ca. 20 mL under vacuum (cold trap) and *n*-hexane (100 mL) was added. The solution was cooled on ice for 15 min. and the ensuing

precipitate was filtered under air and washed with hexanes. The solid was then placed in a Schlenk flask along with  $(\pm)$ -BINAP (2.00 g, 3.21 mmol, 0.840 equiv.). Toluene (125 mL) was added and the solution was heated to reflux for further 18 h. The solution was cooled to room temp., triturated with n-hexane (190 mL), and left to stand at room temp. for 30 min. The orange solution was cannula filtered into a second Schlenk flask which was then placed in a freezer for 24 h. Vacuum filtration under air and subsequent drying under high vacuum gave title compound  $[(\pm)$ -BINAP]Ni[P(OPh)\_3]\_2.  $2PhCH_3$  (11) as an orange microcrystalline toluene solvate (3.93 g. 2.64 mmol, 69%). Crystals suitable for X-ray diffraction were obtained via slow vapor diffusion of degassed n-hexane into a degassed toluene solution at r.t. under argon. The excess  $(\pm)$ -BINAP was quantitatively recovered from the second filtration step. Note: The first filtration step is necessary to remove dissociated phosphite. The reaction will otherwise not go to completion, resulting in Ni- $[P(OPh)_3]_4$  to remain which cannot be separated from the product. The compound is not stable in un-degassed solutions but can be weighed out as a solid under air without loss of activity. It should, however, be stored under argon in a fridge. The final product often contained ca. 4% (w/w) BINAP (<sup>31</sup>P-NMR) which did not have an effect on the activity of the catalyst. M.p. 119-121 °C; <sup>1</sup>H NMR  $(500 \text{ MHz}, \text{CD}_2\text{Cl}_2)$ :  $\delta = 7.92$  (br. s, 4 H, Ar-H), 7.43–6.73 (m, 62 H, Ar-H), 6.37 (br. s, 6 H, Ar-H), 2.35 (br. s, 6 H, 2× PhCH<sub>3</sub>) ppm. <sup>13</sup>C NMR (125 MHz, CD<sub>2</sub>Cl<sub>2</sub>): *δ* = 153.8, 138.4, 135.3, 133.2, 132.9, 132.7, 130.2, 129.7, 129.3, 128.7, 128.6, 127.9, 127.2, 126.9, 126.6, 125.6, 125.1, 123.4, 121.9, 121.1, 21.6 ppm. <sup>31</sup>P NMR (121.5 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  = 127.3 [t, J = 21.4 Hz, P(OPh)<sub>3</sub>], 36.2 (t, J = 21.4 Hz, PPh<sub>2</sub>) ppm. IR (ATR):  $\tilde{v} = 3056$ , 1588, 1486, 1435, 1218, 1195, 1157, 1082, 1071, 1024, 1003, 877, 864, 820, 758, 687, 617, 592, 526 cm<sup>-1</sup>. Note: The mass spectrum did not show any peaks resembling the molecular ion or a logical daughter ion. However, the similarity of the <sup>31</sup>P-NMR spectrum to our previously reported  $(DPPF)Ni[P(OPh)_3]_2$ , along with the X-ray crystal structure, unambiguously confirms that the batch sample is indeed the desired title compound.

General Procedure for the Coupling of Primary Alkylamines: A flame-dried Schlenk tube was loaded sequentially with NaOtBu (67 mg, 0.70 mmol, 1.4 equiv.),  $[(\pm)$ -BINAP]Ni[P(OPh)<sub>3</sub>]<sub>2</sub>·2PhCH<sub>3</sub> (11) (37 mg, 25 µmol, 5 mol-%), the corresponding amine (0.60 mmol, 1.2 equiv.), and aryl halide (0.50 mmol, 1.0 equiv.). The mixture was dissolved in toluene (2 mL), placed into a preheated oil bath at 80 °C and stirred for 20 h. Upon cooling, the reaction mixture was purified via flash column chromatography (hexanes/EtOAc, DCM/MeOH, EtOAc/MeOH) to give the desired aniline product.

**Computational Methodology:** Density function theory was employed to determine the relative energies of various ligand dissociation products starting from the (BINAP)Ni[P(OPh)<sub>3</sub>]<sub>2</sub> (11) complex. The calculations were undertaken using the familiar B3LYP functional with the 6-31G\* basis sets for carbon, oxygen, and phosphorus, 6-31G for hydrogen, and the LANL2DZ basis set incorporating an effective core potential (ECP) was used for nickel to reduce the computational burden.

Each complex, and isolated ligand, was fully optimized in the gas phase and subsequently a vibrational hessian calculation was employed in order to determine if the structures were minima, transition states, or higher order stationary points on the potential energy surface. Following on, single point energies were determined using the PCM solvent model for toluene and thermodynamic corrections were estimated at a temperature of 353.15 K which is in line with experimental conditions. Dispersion corrections were applied to the single point energies using the DFT-D3 program.<sup>[33]</sup> Data provided in this paper are the enthalpy changes of ligand dissociation, while free energy changes for these processes are provided in the supplementary information. This level of theory was chosen as it has been shown to be successful in modelling similar systems recently.<sup>[6a]</sup> All quantum-chemical calculations were undertaken using the Gaussian 09 program suite.<sup>[34]</sup>

CCDC-1045787 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data\_request/cif.

**Supporting Information** (see footnote on the first page of this article): Full experimental details, NMR spectra, computational data and procedures for kinetic experiments can be found in the Supporting Information.

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