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Elucidating the Mechanism of Aryl Aminations Mediated by NHC-Supported Nickel Complexes: Evidence for a Non-radical Ni(0)/Ni(II) Pathway

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ABSTRACT: Nickel catalysis is gaining in popularity in recent years, mostly within the area of cross-coupling. However, unlike Pd, the mechanisms of Ni-catalyzed C-C and C-heteroatom bond forming reactions have been much less studied, in particular when N-heterocyclic carbenes are used as ligands. Here, we present a thorough study of the mechanism of C-N cross-coupling reaction catalyzed by NHC-Ni complex. Focusing on the coupling of 2-chloropyridines with indole catalyzed by [(IPrNi(styrene)$_2$] (IPr = N,N'-bis-(2,6-diisopropylphenyl)imidazole-2-ylidene), we have examined each of the elementary steps i.e., oxidative addition, ligand substitution and reductive elimination. All relevant catalytic intermediates have been isolated and structurally characterized by both spectroscopic and crystallographic methods. Kinetic studies have revealed that the reductive elimination is the rate-limiting step. Catalyst deactivation is related to the formation of unproductive dinuclear pyridyl-bridged NHC-Ni(II) species, which can be prevented by increasing the size of the heteroaryl chloride. These investigations support a neutral Ni(0)/Ni(II) catalytic cycle. Calculations corroborate the experimental evidence and confirm the influence exerted by the ligands in each of the elementary steps.

INTRODUCTION

The Buchwald-Hartwig amination (BHA) is a powerful synthetic methodology for the construction of C-N bonds.[1] It is particularly useful for the preparation of arylamines, compounds that find important applications in a variety of fields, such as medicinal chemistry, synthesis of natural products, material chemistry and catalysis.[2] Extremely active Pd/phosphine catalysts, which enable the coupling of (hetero)aryl chlorides with primary amines or ammonia under mild conditions and low catalyst loadings, have been reported in the last decade.[3]

Although Pd catalysts still largely dominate the field of BHA, the search for more sustainable catalytic processes based on the use of non-precious metals[4] has turned the attention to its first-row sibling, nickel.[5,6] Remarkably active Ni-based catalyst systems that promote the monoarylation of primary amines[7] and ammonia[8] with aryl chlorides have been reported in recent years. Additionally, since Ni is more electropositive than Pd, it promotes the oxidative addition of electrophiles that are lesser used under Pd catalysis, such as aryl fluorides[9] and phenol derivatives.[10] However, although the number of catalytic applications of Ni in cross-coupling chemistry has grown significantly in the last few years,[5,6] the study of the mechanisms that govern these transformations has been less addressed.[11] The ease availability of odd oxidation states, Ni(I) and Ni(III), introduces the possibility of radical mechanism,[12] uncommon in Pd-catalyzed cross-coupling reactions, adding complexity to the analysis of the reaction pathways.

In the context of Ni-catalyzed BHA, the groups of Hartwig[7a] and Stewart[7c] investigated, independently, the mechanism of the amination of aryl chlorides and bromides with primary aliphatic amines by different (BINAP)Ni(0) precursors. Both studies supported similar non-radical Ni(0)/Ni(II) catalytic cycles but with different rate-limiting steps. The formation of catalytically inactive Ni(I) species, [(BINAP)Ni(μ-Cl)], was identified by Hartwig and co-workers as one of the major route of catalyst decomposition.[7a] However, in a recent report, Stradiotto, Johnson and co-workers compared the activity of (bisphosphine)Ni(I) and (bisphosphine)Ni(II) precursors (bisphosphine = Pad-DalPhos, dppf), in the amination of aryl chlorides with primary and secondary amines and ammonia.[13] Although the catalytic performance of the former lagged behind that of the Ni(II) pre-catalysts in most of C-N cross-coupling studied, they proved to be superior in challenging aminations when combined with dppf ligand. Furthermore, DFT calculations acknowledge the existence of competitive Ni(0)/Ni(II) and Ni(I)/Ni(III) pathways for these aminations.

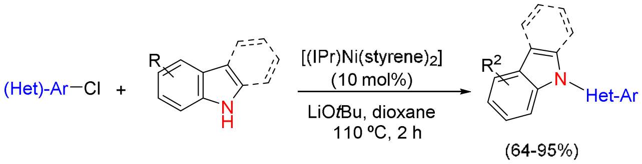
In addition to phosphines, N-heterocyclic carbenes (NHCs) have been widely employed as supporting ligands in Ni-catalyzed BHA.[14] So far, a detailed experimental and computational investigation on the mechanism of the amination reactions catalyzed by Ni/NHC systems has not yet been conducted. We are aware of a single report: the DFT analysis of the nickel-catalyzed BHA of carbamates with secondary amines conducted by Garg and co-workers.[10c] This study supported a Ni(0)/Ni(II) pathway, with rate-limiting reductive elimination. It is worth noting, however, that monovalent (IPr)Ni(I) species have also proven active in the amination of aryl bromides with diphenylamines.[15]

We have been involved in studying the BHA catalyzed by molecularly defined Ni(II) and Ni(0) complexes bearing NHC ligands.[16] Recently, we reported the first amination of (hetero)aryl chlorides with indoles promoted by the Ni(0) pre-catalyst [(IPr)Ni(styrene)$_2$].[17] Given the lack of detailed mechanistic information of C-N bond formation catalyzed by NHC-Ni complexes,[18] we accomplished a systematic experimental investigation of the mechanism of the C-N coupling of 2-chloropyridine with indole catalyzed by a NHC-Ni(0) complex, the results of which are presented herein. We have isolated and structurally characterized all relevant catalytic intermediates and have provided evidence that support a Ni(0)/Ni(II) catalytic cycle. The kinetic studies of the catalytic reaction have revealed that the reductive elimination is the rate-limiting step. The formation of catalytically inactive dinuclear pyridyl-bridged NHC-Ni(II) species has been found to be detrimental for the outcome of the reaction. DFT analysis of the complete catalytic cycle supports the experimentally proposed non-radical pathway.

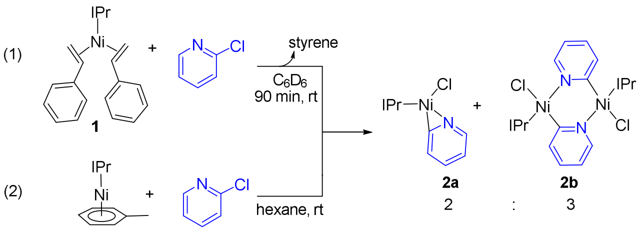
RESULTS AND DISCUSSION

Synthesis and structures of relevant nickel intermediates. In 2015, we described that the pre-catalyst [(IPr)Ni(styrene)$_2$], **1**, efficiently catalyzed the amination of hetero(aryl) chlorides with indoles and carbazoles in short reaction times (2 h), at 110 ºC (Scheme 1).[17]

Scheme 1. Amination of hetero(aryl)chlorides with indoles and carbazoles catalyzed by 1.



We were intrigued by the excellent activity displayed by the (IPr)Ni(0) pre-catalyst in these transformations, particularly when employing hereroaryl chlorides as electrophiles, since the presence of a heteroatom in these substrates could inhibit the catalysis. For that reason, we focused our attention on the reaction of 2-chloropyridine with the parent indole, which proceeded with 80% yield at 10 mol% loading of **1**. We postulated that, instead of impeding the catalytic activity, the presence of a nitrogen atom in the electrophile might help to stabilize the catalytic intermediates by coordination. Thus, we began by examining the oxidative addition reaction of 2-chloropyridine to complex **1** by ^{1}H NMR in C_6D_6 at room temperature (eq 1). After 90 min of reaction, the distinct signals of the vinyl protons of free styrene were clearly observed (ca. 6.53, 5.57 and 5.04 ppm). Integration of these signals revealed that the two molecules of styrene present in **1** were released during the reaction with the 2-chloropyridine. In addition to this, a mixture of two (IPr)Ni compounds **2a** and **2b** in a 2:3 ratio was observed. The minor product **2a** showed only one resonance for the four methine protons (δ 3.21 ppm) and two doublets for the eight methyl groups (ca. 1.06 and 1.44 ppm) of the four isopropyl substituents. However, in the major product **2b** all isopropyl groups of the IPr ligand were in a different chemical environment, giving rise to distinct signals for each of the methine and methyl protons (see Supporting Information).



We scaled up the reaction in an attempt to isolate **2a** and **2b**, but free styrene hampered the workup and the purification of the products. To circumvent this problem, the complex [(IPr)Ni(η^6-toluene)], described by Ogoshi and co-workers,[19] was used instead of **1** (eq 2). Since toluene is a more labile ligand than styrene, the oxidative addition reaction occurred upon mixing the two reagents in hexane at room temperature. The yellow precipitate obtained, constituted by **2a** and **2b** with a composition identical to that previously observed, was recrystallized from toluene. A mixture of yellow and orange crystals was obtained. The former were suitable for X-ray diffraction studies and its molecular structure is shown in Figure 1. This consists of a dimeric Ni(II) complex in which the two square planar nickel units are bridged by the two pyridyl groups in a μ^2-(C,N) fashion. The chlorine atoms are in *trans* position to the α-carbon atom of the pyridyl groups, whereas the positions *trans* to the N atoms of the pyridyl moiety are occupied by the IPr ligands. The long distance of 3.2496(7) Å between the two Ni(II) centers indicates the absence of a metal-metal interaction. This structure is very similar to those described for other pyridyl-bridged containing Ni(II) species.[20]

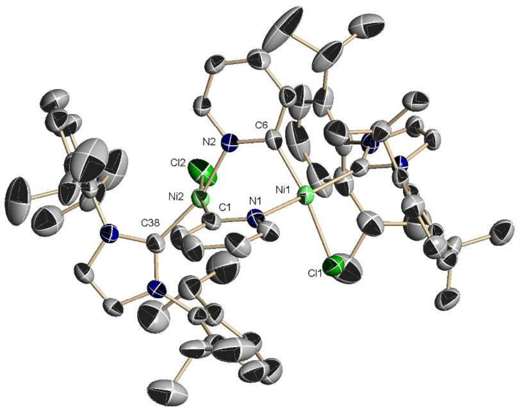
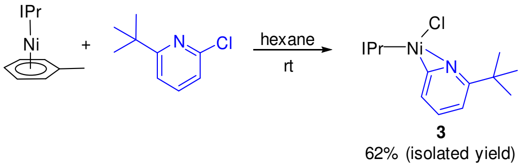


Figure 1. Molecular structure of the dimer complex **2b**. Hydrogen atoms are omitted for clarity. Selected bond distances (Å) and angles (º) for **2b**: Ni1-Cl1, 1.892(4); Ni1-C6, 1.890(4); Ni-N1, 1.926(3); Ni1-Cl1, 2.2143(13), Ni2-C38, 1.888(4); Ni2-C1, 1.878(4);Ni2-N2, 1.938(3); Ni2-Cl2, 2.2234(11); Cl2-Ni2-N2, 89.16(9); Cl2-Ni2-C1, 170.60(11); N2-Ni2-C1, 86.10(14); Cl1-Ni1-C6, 86.63(14); N1-Ni1-C6, 86.63(14); N1-Ni1-Cl1, 89.37(10); N1-Ni1-C11, 162.47(13); C6-N1-C11, 93.21(15); N2-Ni2-C38, 165.36(14), C1-Ni2-C38, 92.81(15).

At this point, we were unable to assign the obtained structure to one of the two compounds **2a** or **2b**, since re-dissolution of the yellow crystals in C_6D_6 furnished again the mixture of **2a** and **2b** in a 2:3 ratio. In this sense, DOSY NMR experiments confirmed the presence of two species with different diffusion coefficients (see Supporting Information). It was clear, however, that the pyridyl-bridged Ni(II) dimer was formed in the oxidative addition reaction. On the other hand, the identity of the second product could not be established, albeit we suspected that it could be the mononuclear [(IPr)Ni(2-pyridyl)Cl] complex, in equilibrium with the dimer.[21]

To test our hypothesis, we focused on the bulkier 2-chloro-6-*tert*-butylpyridine, a substrate that might disfavor the formation of the dimer. First, the suitability of this substrate was examined under catalytic conditions. The amination of 2-chloro-6-*tert*-butylpyridine with indole catalyzed by [(IPr)Ni(styrene)$_2$] afforded the coupling product in 64% isolated yield. Next, the stoichiometric reaction of **1** with 2-chloro-6-*tert*-butylpyridine was monitored by ^{1}H NMR. The mixture was heated at 70 ºC for 90 min, since no reaction occurred at room temperature. The formation of a single product **3** together with free styrene was then observed. The NMR features of **3** resembled those displayed by complex **2a**: the four isopropyl groups of the IPr ligand were equivalent resulting in only one resonance for the methine protons (δ 3.24) and two doublets for the methyl protons (ca. 1.07 and 1.45 ppm). In addition, resonances due to the *tert*-butylpyridyl ligand were observed at δ 1.01, 6.03, 6.49 and 6.65. Complex **3** was prepared in a 62% yield from [(IPr)Ni(η^6-toluene)] following the procedure shown in eq 3.



(3)

Single-crystal analyses of **3** revealed that it is a mononuclear complex (Figure 2). The Ni(II) ion is coordinated in a highly distorted square planar environment by the chloride, the IPr carbene ligand and the pyridyl ligand in a η^2-(N,C) manner. The Ni-Cl and Ni-IPr bond distances are comparable to those found for other (IPr)Ni(II) complexes.[22] The Ni-C(pyridyl) bond of 1.821(3) Å is shorter than the distances in *trans*-[NiF(2-C_5NF_3H)$(PEt_3)_2$][23a] (1.869(4) Å) and *trans*-[NiX(2-C_5F_4N)$(PEt_3)_2$][23b] (X = OTf, 1.851(3) Å; X = OPh, 1.861(6) Å). The angle Ni-C28-N4 of 41.08(14)º is higher than those reported for other η^2-(C,N)-pyridyl metal complexes.[24] The IPr ligand is almost perpendicular to the Ni-C28-N4 plane (dihedrical angle = 84.3(3)º). To the best of our knowledge this is the first example of a group 10 metal complex bearing a η^2-(C,N)-pyridyl ligand.

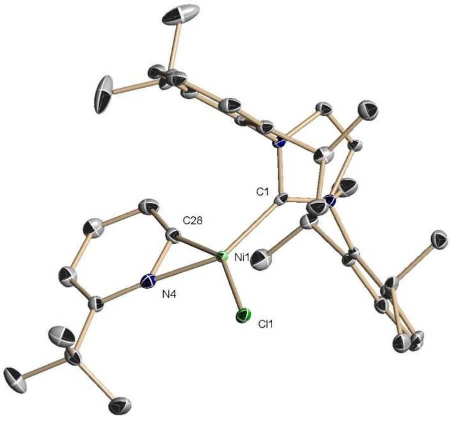
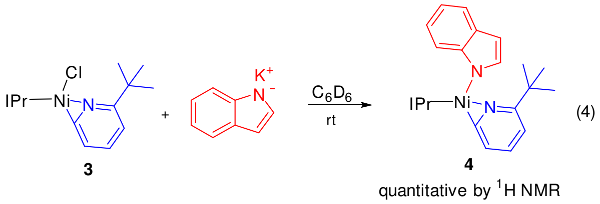


Figure 2. Molecular structure of complex **3**. Hydrogen atoms are omitted for clarity. Selected bond distances (Å) and angles (º) for **3**: Ni-C1, 1.873(3); Ni1Cl1, 2.2115(9); Ni1-C28, 1.821(3); Ni1-N4, 1.928(3); C28-Ni1-N4, 41.08(14); N4-Ni1-C1, 141.79(13).

As mentioned above, **2a** displayed a ^{1}H NMR signal pattern fairly similar to that observed for the mononuclear Ni complex **3.** Therefore, it is reasonable to propose that **2a**, the minor product obtained in the oxidative addition reaction of **1** with 2-chloropyridine, is a mononuclear species with a structure similar to that shown in Fig 2. Consequently, we assign the dimer structure to the major product **2b**. Both complexes form an equilibrium mixture that favors the dinuclear species.

It is interesting to note that the oxidative addition reactions of 2-chloropyridines to the (IPr)Ni(0) complex **1** affords only Ni(II) products. These results contrast to those observed by Louie and co-workers in the reactions of homoleptic Ni(0) complexes (NHC)$_2$Ni with aryl halides.[25] Paramagnetic Ni(I) species [(IMes)$_2$NiX] were formed with the bulky IMes (IMes = N,N'-bis-(2,4,6-trimethylphenyl)imidazole-2-ylidene) ligand, whereas with the less hindered carbene ligand tmiy (tmiy = tetramethylimidazol-2-ylidene) Ni(II) products [Ni(tmiy)$_2$ArX] were isolated. It becomes clear that the N atom in the pyridyl ligand favors the formation of the 16-electron Ni(II) species by coordination. The preference of Ni(II) species with respect to hypothetical Ni(I) alternatives was confirmed by calculations detailed in Figure S24. The Ni(II) intermediate **2a** is more stable than the [IPrNi(I)Cl] alternative complex by 23.6 kcal/mol.

To rule out that radical Ni(I) species formed in the reaction being the key players for these amination reactions, the coupling reaction between 2-chloropyridine and indole catalyzed by **1** was performed in the presence of the radical scavenger 2,6-di-*tert*-butyl-4-methylphenol, BHT,. No adverse effect on the yield of product was observed in the presence of this additive. Thus, this experiment suggests that Ni(I) species, althought they may be formed, do not play a central role in the catalytic formation of the product.



With the oxidative addition product **3** in our hands, we moved to the next step of the catalytic cycle, the nucleophilic attack of the indolate. We examined the reaction of **3** with potassium indolate in C$_6$D$_6$ at room temperature by ^{1}H NMR (eq 4). The immediate and clean formation of compound **4** was observed (see SI). In addition to the signals due to the IPr ligand, the spectrum displayed a new group of resonances at δ 6.80, 6.94, 7.22, 7.76 and 7.92 that were assigned to the indolate group. When the reaction was performed on a preparative scale, **4** was isolated in 76% yield as orange crystals suitable for X-ray crystallography. The molecular structure of **4** is depicted in Figure 3. The complex possesses a distorted square planar geometry, in which the *tert*-butylpyridyl ligand still maintains the η^2-(C,N) coordination mode. The Ni-indolate bond distance of 1.901(3) Å is significantly shorter than those reported for [(dippe)Ni(indolate)$_2$] (1.9307(16) Å and (1.9339(15) Å).[26] The Ni-C(pyridyl) bond (1.823(4)) is almost equal to that found for **3**. The remaining structural features found for **4** are similar to those described for **3** and do not deserve further comments.

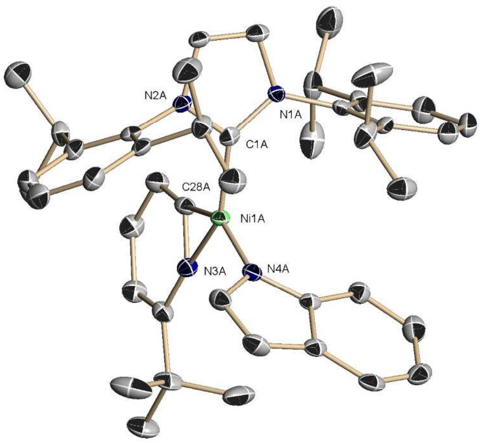
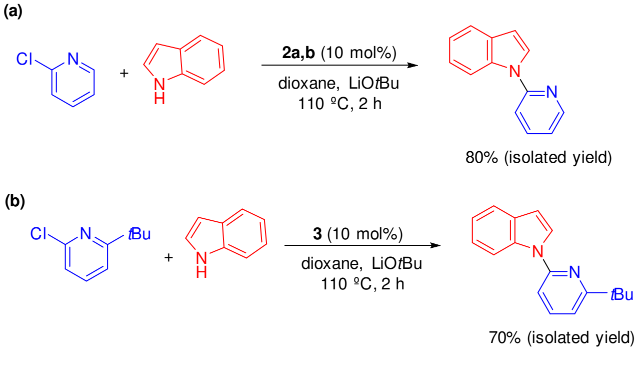


Figure 3. Molecular structure of complex **4**. Hydrogen atoms are omitted for clarity. Selected bond distances (Å) and angles (º) for **4**: Ni1A-C1A, 1.856(4); Ni1A-N3A, 1.884(3); Ni1A-N4A, 1.901(3); Ni1A-C28A, 1.823(4); C28-Ni1A-N3A, 41.39(16); C1A-Ni1A-N4, 109.56(15); C1A-Ni1A-N3A, 146.14(17).

Evaluating the catalytic competence of isolated intermediates in the amination of indole. The mixture of monomer and dimer Ni(II) complexes **2a,b** was tested in the reaction of 2-chloropyridine with indole in the presence of LiO*t*Bu, using 10 mol% of **2a,b** at 110 ºC (Scheme 2a). The reaction afforded the coupling product in 80% isolated yield in 2 h. This result is almost identical to that obtained when [(IPr)Ni(styrene)$_2$] is employed as pre-catalyst.[17] These experiments may show the catalytic competence of the mixture of **2a,b** but, it raises the question about which of these two complexes is more effective in the amination reaction

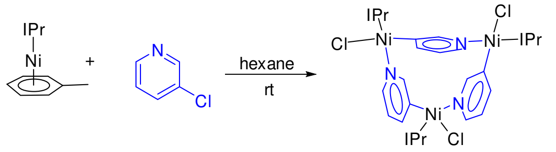
Scheme 2. Amination of (a) 2-chloropyridine and (b) 2-chloro-6-*tert*-butylpyridine with indole catalyzed by the mixture of monomer and dimer complexes, 2a,b and by [(IPr)Ni(η^2-(C,N)6-*t*Bu-pyridyl)Cl], 3, respectively.



Next, we gauged the catalytic activity of the mononuclear complex **3** in the amination reaction of 2-

chloro-6-*tert*-butylpyridine with indole, using same reaction conditions as those applied in the reaction catalyzed by **1** (Scheme 2b). The yield of the amination product was practically the same as that found in the previous experiment with **1** (see above). Thus, [(IPr)Ni(η^2-(C,N)6-*t*Bu-pyridyl)Cl] **3** demonstrates to be a competent intermediate in this catalytic reaction.

We could not measure the catalytic capability of the dimer **2b**, since the monomer/dimer equilibration occurred rapidly in solution. But, we prepared a Ni(II)-pyridyl complex in which the η^2-(C,N) coordination mode of the pyridyl ligand was impeded. This material was obtained by the reaction of [(IPr)Ni(η^6-toluene)] with 1 equiv of 3-chloropyridine under the conditions depicted in eq **5**. Compound **5** was isolated as a yellow crystalline solid in 82% yield. Its ^{1}H NMR spectrum in C_6D_6 exhibited the characteristic lack of symmetry previously observed for the dimer **2b**, i.e. single resonances for each of the CH (δ 1.39, 3.37, 3.67 and 4.94) and CH_3 (δ 0.06, 0.63, 0.84, 1.05, 1.13, 1.63, 1.79 and 1.89) groups of the isopropyl substituents of the IPr ligand.



(5)

5
82% (isolated yield)

Compound **5** was identified by X-ray diffraction studies as the trinuclear Ni(II) macrocycle depicted in Figure 4. The three Ni atoms present a slightly distorted square-planar geometry. Like in the case of **2b** the carbon atoms of the pyridyl groups are in *trans* position to the chlorine atoms, and the NHCs ligands are *trans* to the pyridyl nitrogen atoms. In contrast to **2a** and **3**, the *meta*-position of the nitrogen atom with respect to the pyridyl carbon bonded to the nickel center in **5** prevents the formation of a mononuclear species and, consequently a twelve membered-ring macrocyclic compound by the coordination of bridging pyridyl ligands is formed instead. The three Ni—carbene carbon bond distances for **5** are similar to those reported for other (IPr)Ni(II) complexes[22] and to those described above for **2b** and **4**. Matsubara and coworkers have recently described the formation of a tetranuclear species with similar bridging pyridyl moieties, by the reaction the [Ni(IPr)]$_2$(μ-Cl)$_2$ with 3,5-dichloropyridine.[27] The Ni—pyridyl carbon, 1.901-1.907 Å, Ni—N, 1.930-1940 Å, lengths are similar to those reported by Matsubara for the mentioned tetranuclear species (1.886 and 1.939 Å, respectively).[27]

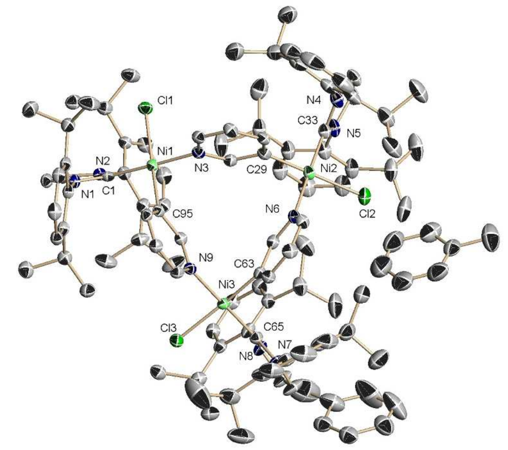
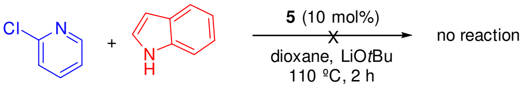


Figure 4. Molecular structure of complex **5**. Hydrogen atoms are omitted for clarity. Selected bond distances (Å) and angles (º) for **5**: Ni1-N3, 1.944(2); Ni2-N6, 1.935(3); Ni3-N9, 1.930(3); Ni1-C1, 1.898, Ni2-C33, 1.896(3); Ni3-C65, 1.886(3); Ni1-C95, 1.905, Ni2-C29, 1.907(3), Ni3-C63, 1.901(3); C1-Ni1-N3, 177.92(12); C95-Ni1-N3, 96.93(12); C29-Ni2-N6, 84.23(12); C33-Ni2-N6, 178.01(13); C65-Ni3-N9, 178.98(13); C63-Ni3-N9, 84.23(12).

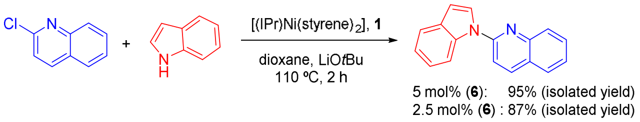
Complex **5** (10 mol%) was used as pre-catalyst in the coupling of 2-chloropyridine and indole at 110 ºC (Scheme 3). No coupling product was detected, which provided evidence of the lack of catalytic activity of the trimer compound **5** in this reaction. It is interesting to note that the reaction of 3-chloropyridine with indole does not proceed in the presence of [(IPr)Ni(styrene)$_2$] as the catalyst either.

Scheme 3. Amination of 2-chloropyridine with indole catalyzed by the trinuclear complex 5.



To further progress on this point, we focused on the amination of 2-chloroquinoline with indole. This reaction proceeded with quantitative yield using 10 mol% [(IPr)Ni(styrene)$_2$] as the precatalyst. We suspected that 2-chloroquinoline could not favor the formation of dinuclear species due to its larger size. So, we checked the nature of the Ni(II) product resulting from the oxidative addition of 2-chloroquinoline to [(IPr)Ni(η^6-toluene)] by ^{1}H NMR. A single species **6**, which exhibited the characteristic pattern of resonances for the isopropyl substituents indicative of the η^2-(N,C)-coordination mode of the 2-quinolyl moiety, was obtained. Complex **6** was isolated in 80% yield following the procedure described in eq 2 and it was characterized by NMR spectroscopy (see SI). Since only the mononuclear Ni(II)-quinolyl species was formed, we re-examined the effect of the catalyst loading in the reaction of 2-chloroquinoline with indole catalyzed by [(IPr)Ni(styrene)$_2$], **1** (Scheme 4). Complete conversion to the coupling product was achieved in 2 h using only 5 mol% of **6**. Even with a lower catalyst loading of 2.5 mol%, the amination product was obtained in 87% isolated yield in same reaction time. However, on lowering the catalyst loading of **1** from 10 mol% to 5 mol% in the coupling of 2-chloropyridine with indole, the yield dropped from 80 to 67%.

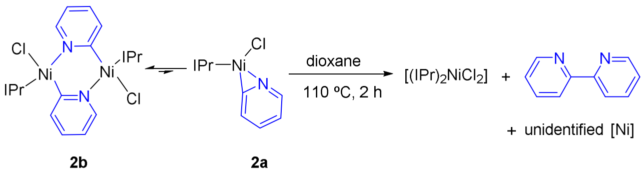
Scheme 4. Amination of 2-chloropyridine with indole in the presence of 6 lowering the catalyst loading.



These observations clearly indicate that mononuclear Ni(II)-[η^2-(C,N)-pyridyl] complexes are chemically and kinetically competent catalytic intermediates in these amination reactions. Furthermore, the formation of catalytically inactive polynuclear Ni(II)-pyridyl complexes are clearly detrimental for the reaction yield, as it removes active species out of the catalytic cycle.

Finally, we examined the stability of the pyridyl complexes **2a,b** and **3**. These compounds are stable in the solid state. However, the mixture **2a,b** slowly decomposed at room temperature in THF-hexane solution yielding crystals of the complex *trans*-[(IPr)$_2$NiCl$_2$], that was identified by comparing its X-ray structure with the previously reported data.[7c,28] On heating a mixture of **2a,b** under the conditions of the catalytic reaction (i.e. dioxane at 110 º for 2 h) the degradation process was accelerated producing *trans*-[(IPr)$_2$NiCl$_2$] and 2,2-bipyridine (observed and quantified by GC), both in 50% yield, together with unidentified Ni species (Scheme 5). The product resulting from the decomposition of **2b**, *trans*-[(IPr)$_2$NiCl$_2$], showed to be catalytically inactive in the amination of 2-chloropyridine with indole. By contrast, when performing the same reaction with mononuclear complex **3** no thermal decomposition was observed, probably due to the steric protection conferred by the tert-butyl group on the pyridyl ligand

Scheme 5. Thermal decomposition of 2a,b.



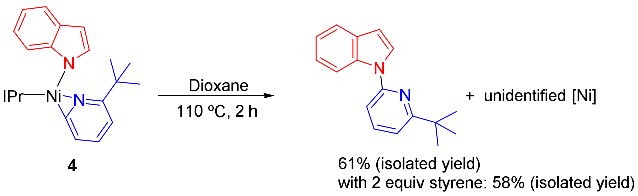
The formation of *trans*-[(IPr)$_2$NiCl$_2$] and 2,2-bipyridine could be the result of dispropotiation of **2b** to di(pyridyl)-Ni(II) and Ni(II)-halides complexes, the former of which undergoes facile reductive elimination of bipyridine with concomitant generation of Ni(0) species.[29]

Kinetics experiments. We decided to examine the influence of the concentration of all the substrates in the rate of the amination of heteroaryl chlorides with indole catalyzed by the Ni(0) complex **1**. The studies were conducted on the reaction of 2-chloro-4-(trifluoromethyl)pyridine with indole in the presence of LiO*t*Bu catalyzed by **1** in toluene-d$_8$ as the solvent, since no significant difference was observed when using toluene or dioxane. The reaction was conveniently monitored by ^{19}F NMR spectroscopy.

Plots of the k_{obs} of the reaction *vs* the concentrations of each of the substrates (i.e. catalyst, indole, chloropyridine, base and styrene) are provided in the Supporting Information. The kinetic studies show that this amination reaction is first order in the catalyst concentration and inverse order in styrene. Additionally, the base, the chloropyridine and the indole concentrations do not have influence in the reaction rate, which implies that none of these substrates is involved in the rate-limiting step.

To verify that reductive elimination was rate determining, we studied the formation of the amination product from complex **4** (Scheme 6). No reaction was detected at 90 ºC but on heating at 110 ºC in dioxane, a brown precipitated was observed. After purification, the coupling product was isolated in 61% yield. It has been demonstrated that olefins facilitate the reductive elimination reaction in Pd-catalyzed C-C couplings,[30] therefore we conducted the reductive elimination process in the presence of 2 equiv of styrene. However, no improvement in the reaction yield was observed under these conditions.

Scheme 6. Study of the reductive elimination reaction from complex 4.



Finally, we questioned about the nature of the catalyst resting state. To address this point, we examined the coupling of 2-chloro-6-*tert*-butylpyridine with potassium indolate in the presence of 10 mol% [(IPr)Ni(styrene)$_2$] at 90 ºC, by ^{1}H NMR (toluene-d$_8$/THF-d$_8$ mixture). The unique nickel species observed in solution after 3 h was the indolate **4.** We believe this should be interpreted as evidence of the role of such species as the feasible resting state of the catalyst during the catalytic transformation.

Mechanistic proposal. On the basis of stoichiometric reactions and kinetic studies discussed above, we propose the non-radical Ni(0)/Ni(II) catalytic cycle outlined in Figure 5 for the amination of heteroaryl chlorides with indole promoted by the [(IPr)Ni(styrene)$_2$], **1**.

The observation that styrene has a negative effect on the reaction rate is consistent with a pre-equilibrium step, whereby the pre-catalyst **1** reversibly dissociates one styrene ligand to form the low-coordinate Ni(0) species **A**. The oxidative addition of the heteroaryl chlorides to **A** leads to the formation of the Ni(II)-η^2-(C,N)-heteroaryl species **B**, in equilibrium with dinuclear species depending upon the steric hindrance of the heteroaryl chloride. The observed first order rate-dependence in catalyst concentration together with studies of the role of such intermediates in the catalytic reaction (see above) strongly suggest that mononuclear Ni(II) complex **B** is the catalytically active species. The substitution of the chloride ligand by the indolate anion in **B** affords **C** from which reductive elimination takes place. The coordination of styrene regenerates the low-coordinate species **A**.

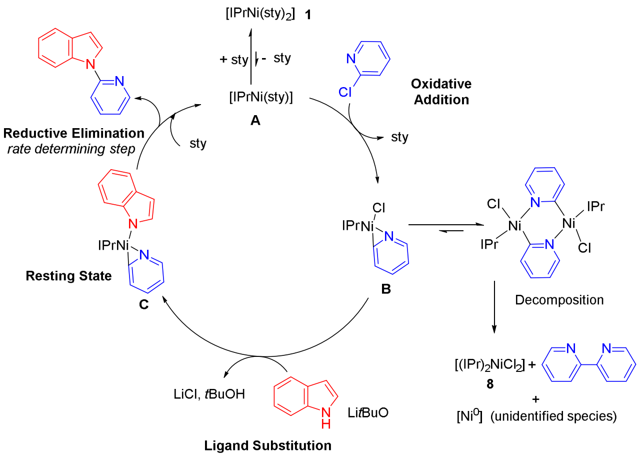


Figure 5. Mechanistic proposal for the amination of heteroaryl chlorides with indole catalyzed by [(IPr)Ni(styrene)$_2$], **1**.

DFT/MM analysis of the mechanism. As a final investigation of the mechanism of this aryl amination reaction, we carried out a QM/MM computational study,[31,32] using the long-range corrected ωB97X-D functional[33] for the QM part and the UFF force field[34] for the MM part (which consisted of the isopropyl groups of the IPr ligand). All the calculations were performed in solution using the SMD method[35] (see the Computational Details in the Supporting Information for a full description of the methods). The singlet spin state has been found to be most stable in all calculations, and all reported energies correspond to this state. The triplet alternative was evaluated in a number of intermediates, and found to be always higher in energy. Further details on spin states are provided in the Supporting Information. A collection of data set of the computed structures is available in the ioChem-BD repository.[36]

The first step of the catalytic cycle i.e., the oxidative addition of 2-chloropyridine (PyCl) to [(IPr)Ni(styrene)$_2$] **1** was computed (the experimentally unidentified species are labelled with a prefix **c**). The reaction started with the dissociation of one molecule of styrene from the initial complex [(IPr)Ni(styrene)$_2$] **1** to form the 14-electron intermediate **c1**, which was 10.2 kcal mol^{-1} above **1** (Figure 6). The dissociation of the second molecule of styrene required a higher activation energy (46.2 kcal mol^{-1}), consequently it remained coordinated to the Ni center. In the following step, 2-chloropyridine was coordinated to **c1** via the nitrogen atom leading to intermediate **c2**. From this intermediate, the activation of the C-Cl bond was not feasible and required the change in the coordination mode of the pyridine ring to η^2-(C,N) fashion to give intermediate **c3**. The oxidative addition proceeded via a S_N2 type transition state **TS c3-c4**, which lied 4.4 kcal mol^{-1} higher than **c3**. Concerted transition states are more common for aromatic systems, but the S_N2 arrangement is not without precedent.[12e] The connectivity for the reported TS was moreover confirmed by IRC calculations (Figure S20). The reaction is quite exergonic, releasing 29.0 kcal mol^{-1} from **c3** and forming irreversibly **c4**. Intermediate **c4** evolved to the experimentally observed **2a** by styrene dissociation, which was in equilibrium with the slightly more stable (by 2.8 kcal mol^{-1}) dinuclear species **2b**.

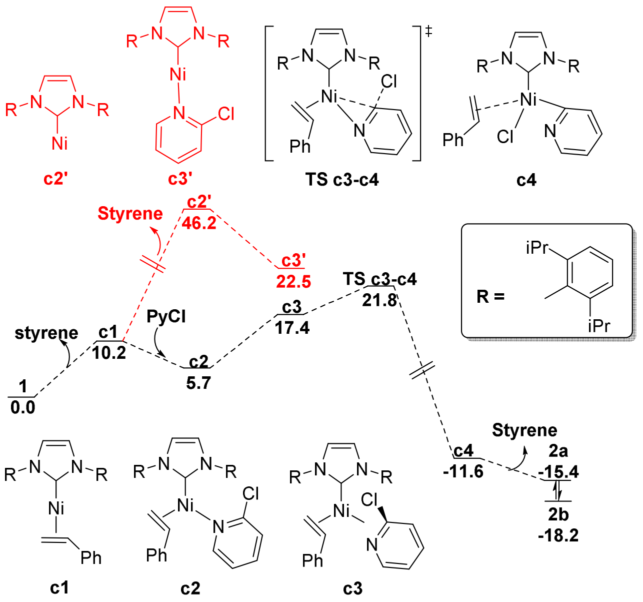


Figure 6. Free energy profile for the oxidative addition of 2-chloropyridine to **1**. Energies in kcal mol^{-1}. 1,4-dioxane used as solvent through SMD model.

The next steps of the catalytic cycle, i.e. the ligand substitution and the reductive elimination, were computed and the free energy profile is shown in Figure 7. The indole reactant is introduced as indolate because its formation must be quantitative in the presence of LiO*t*Bu (see Figure S22 for details). The reaction of **2a** with the indolate reagent produced intermediate **c5**, which lied 4.8 kcal mol^{-1} lower in energy than **2a**. From this point, we explored three different pathways for the reductive elimination step. The most favored one (in black in Figure 7) started with the loss of chloride into the solvent medium and formation of intermediate **c6** (experimentally observed and isolated when using *tert*-butyl-chloropyridine as reactant). This step is exergonic by 5.9 kcal/mol. The formation of the C-N bond of the product occurred via transition state **TS c6-c7** and required free activation energy of 29.8 kcal mol^{-1}. Consistent with the experimental observations, this step was the rate limiting transition state. Finally, the C-N coupling product was released from **c7**, regenerating **1** by styrene coordination. The overall reaction was found to be exergonic by 36.2 kcal mol^{-1}.

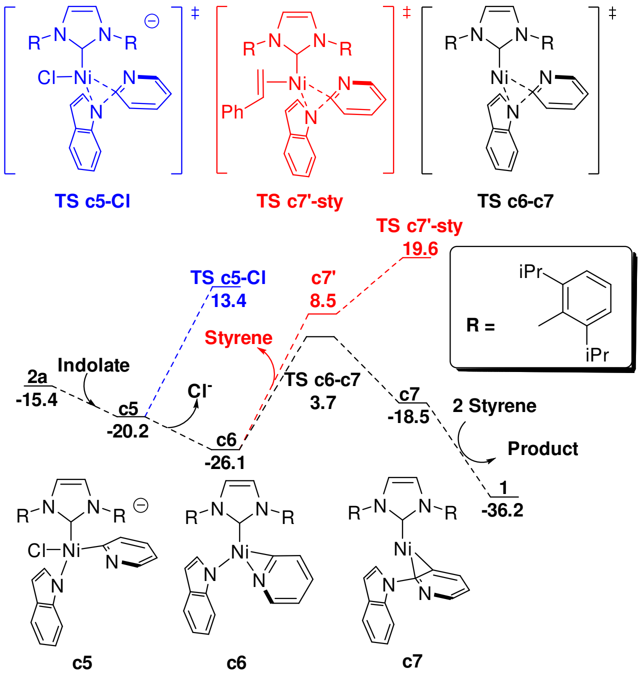


Figure 7. Free energy profile from **2a** to the product. Energies in kcal mol^{-1}. 1,4-dioxane used as solvent through SMD model.

We envisaged two other alternative pathways (in blue and red in Figure 7) for the reductive elimination step, in which either the chloride or the styrene ligands remained coordinated, but both pathways were higher in energy.

The structure of the key transition state **TS c6-c7** is depicted in Figure 8. The indolate ligand is *trans* to the NHC ligand and the Ni-N and Ni-C bond distances are almost identical, 1.88 and 1.87 Å, respectively. The C-N distance in the transition state is only 1.70 Å, close to the product bond length (1.40 Å). We also studied an alternative structure with the pyridine ring *trans* to the NHC ligand, but the transition state optimization always leads to **TS c6-c7**.

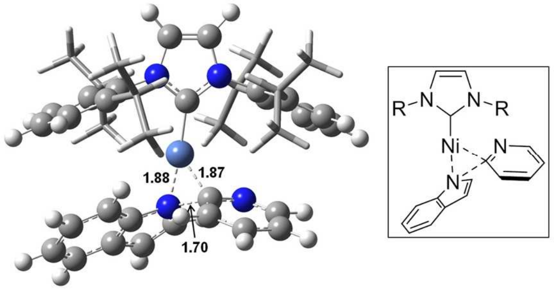


Figure 8. 3D structure of the reductive elimination transition state (**TS c6-c7**). Bond lengths in Å. Ball and sticks for QM part and tubes for MM part.

Finally, we studied the thermodynamics for the decomposition pathway displayed in Scheme 5. The formation of bipyridine product from the dinuclear species **2b** and the transfer of one NHC ligand to the Ni(II) to form *trans*-[(IPr)$_2$NiCl$_2$] was found to be exergonic by 2.2 kcal/mol. The resulting Ni(0)-bpy complex evolved then to form Ni(0) aggregates.

CONCLUSIONS

A detailed experimental mechanistic analysis of the amination of heteroaryl chlorides with indoles catalyzed by [(IPr)Ni(styrene)$_2$] has allowed, for the first time, the isolation and characterization of *all relevant* Ni-based catalytic intermediates proposed for a C-N coupling reaction, demonstrating the involvement of a Ni(0)/Ni(II) catalytic pathway in this amination process. We have found that the oxidative addition of 2-chloropyridine to IPr-Ni(0) species proceeds at room temperature with formation of mononuclear and dinuclear pyridyl-Ni(II) species (**2a** and **2b**, respectively); The coordination of the N atom of the the pyridyl group fashion is key to stabilized the Ni(II) species. The catalytic studies reveal the competence of the mononuclear complex **2a** as intermediate in the C-N coupling, but also the unproductive nature of the dinuclear complex **2b**. The formation of latter withdraws catalytically active species out of the cycle; The suppression of the dinuclear Ni(II) species formation i.e. by increasing the steric hindrance around the metal center using a bulkier NHC ligand might improve the pre-catalyst performance. Kinetic and experimental studies show that the reductive elimination is the rate-limiting step. The calculations provide a complete mechanistic picture, which is consistent with experiment, and confirm the specific role played by the different ligands.

At this stage, we have not experimental evidence to conclude that the Ni(0)/Ni(II) catalytic cycle found in this study is also operative in the amination of simple aryl chlorides with indoles. As others have noted, the mechanism of Ni-catalyzed cross-coupling reactions does not seem to be general and minor changes in the ligand or in the substrates can have a significant effect on the reaction mechanism.[13,18]

ASSOCIATED CONTENT

Supporting Information

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

Data for **2b** (CIF)
Data for **3** (CIF)
Data for **4** (CIF)
Data for **5** (CIF)
Additional experimental details, procedures, and NMR spectra for all new compounds (PDF)

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Notes

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SYNOPSIS TOC. A detailed investigation on the mechanism of aryl amination promoted by [(IPr)Ni(styrene)$_2$] (IPr = N,N'-bis-(2,6-diisopropylphenyl)imidazole-2-ylidene) has been conducted, where all relevant intermediates have been isolated and characterized. Experimental, kinetic and computational studies support a neutral Ni(0)/Ni(II) catalytic cycle.