Cross-Coupling

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Comparison of dppf-Supported Nickel Precatalysts for the Suzuki–Miyaura Reaction: The Observation and Activity of Nickel(I)

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Abstract: *Ni-based precatalysts for the Suzuki–Miyaura reaction have potential chemical and economic advantages compared to commonly used Pd systems. Here, we compare Ni precatalysts for the Suzuki–Miyaura reaction supported by the dppf ligand in 3 oxidation states, 0, I and II. Surprisingly, at 80°C they give similar catalytic activity, with all systems generating significant amounts of Ni^{I} during the reaction. At room temperature a readily accessible bench-stable Ni^{II} precatalyst is highly active and can couple synthetically important heterocyclic substrates. Our work conclusively establishes that Ni^{I} species are relevant in reactions typically proposed to involve exclusively Ni^{0} and Ni^{II} complexes.*

Cross-coupling reactions, such as the Suzuki–Miyaura reaction, are commonly used to construct carbon–carbon bonds.[1] Currently, the most active systems are based on the precious metal Pd.[1f] The development of catalysts containing earth-abundant first row transition metals such as Ni could result in more affordable systems.[2,3] Furthermore, owing to its smaller size, increased nucleophilicity[3a] and weaker binding to coordinating atoms in heterocycles, there are also often chemical advantages to using Ni. For example, Ni-based systems are superior to Pd for performing Suzuki–Miyaura reactions involving carbamate,[4] carbonate,[4b] sulfamate,[4b,d,5] acyliminium,[6] and sp^3-based substrates.[7] Nevertheless, in general, Ni-catalyzed Suzuki–Miyaura reactions require high temperatures and high catalyst loadings, long reaction times, and have limited substrate scope. Frequently, the cost benefit of using Ni over Pd is offset by one or more of these problems. Additionally, there have been few mechanistic studies of Ni based precatalysts for the Suzuki–Miyaura reaction,[4d,8] which complicates the rational design of improved systems.

Against this background, a remarkable advance was made in 2012, when Ge and Hartwig reported the highly active Ni precatalyst, (dppf)Ni(η^3-cinnamyl)(Cl) (dppf = 1,1′-bis(diphenylphosphino)ferrocene) (**^{Cin}Ni^{II}**),[9] which can perform Suzuki–Miyaura reactions with synthetically useful heterocycles at low catalyst loadings (0.5 mol%) and moderate temperatures (50–80°C). In order to gain further insight into this system, here, we compare the catalytic performance and properties of **^{Cin}Ni^{II}** with a series of related dppf-supported complexes (Figure 1) and study the speciation of Ni during Suzuki–Miyaura reactions. We show that, at elevated temperature, all of the precatalysts form a catalytically active Ni^{I} complex, and propose pathways for the formation of this Ni^{I} species. At high temperatures Ni precatalysts in three different oxidation states, 0, I and II, give comparable activity, whereas at room temperature (RT), a bench-stable Ni^{II} precatalyst is very efficient. It is so active that it is able to perform Suzuki–Miyaura reactions involving heterocyclic substrates relevant to the synthesis of pharmaceuticals at RT; this marks the first time these reactions have been performed under such mild conditions. Overall, our studies establish that Ni^{I} species are relevant in Suzuki–Miyaura reactions previously proposed to solely involve complexes in the Ni^{0} and Ni^{II} oxidation states.[3b,10]

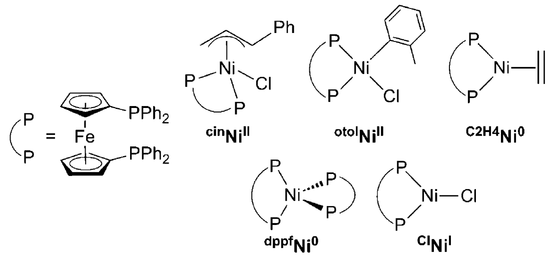

Figure 1. Precatalysts studied in this work.

To compare **^{Cin}Ni^{II}** to other commonly used precatalyst motifs, a family of Ni dppf-supported complexes were prepared using literature methods.[11] The Ni^{II} species (dppf)Ni(*o*-tol)(Cl)[11c] (**^{otol}Ni^{II}**) is a representative example from the commonly used Suzuki–Miyaura precatalyst scaffold $(PR_3)_2Ni(Ar)(Cl)$.[12] It is a particularly attractive precatalyst as, unlike **^{Cin}Ni^{II}**, its synthesis does not require the use of the expensive precursor $Ni(cod)_2$ (cod = 1,5-cyclooctadiene) and it is bench-stable. The air and moisture sensitive Ni^{0} precatalysts $(dppf)Ni(C_2H_4)$[11b] (**^{C2H4}Ni^{0}**) and $(dppf)_2Ni$[11a] (**^{dppf}Ni^{0}**) were synthesized as representative Ni^{0} species and presumably activate via ligand dissociation, whereas **^{Cin}Ni^{II}** and **^{otol}Ni^{II}** most likely activate via transmetalation.[9,13]

Numerous attempts to crystalize **^{Cin}Ni^{II}** under different conditions resulted in the crystallographic characterization of the air and moisture sensitive Ni^{I} complex[14] (dppf)Ni(Cl) (**^{Cl}Ni^{I}**) (see Supporting Information (SI)).[15] Assuming there may be a facile pathway to convert **^{Cin}Ni^{II}** to **^{Cl}Ni^{I}**, we independently synthesized **^{Cl}Ni^{I}** and included it in our

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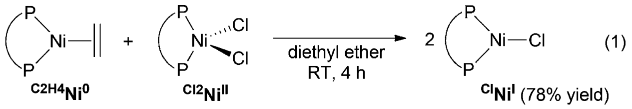
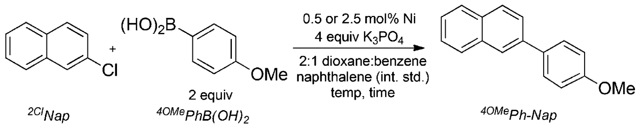
precatalyst comparison. $^{\mathbf{Cl}}\mathbf{Ni^{I}}$ was isolated in good yield (78 %) from the comproportionation of $^{\mathbf{C2H4}}\mathbf{Ni^{0}}$ with (dppf)Ni-$(Cl)_2$ ($^{\mathbf{Cl2}}\mathbf{Ni^{II}}$) in diethyl ether [Eq. (1)]. It was characterized by paramagnetic ^{1}H NMR, UV-Vis and EPR spectroscopy, electrochemistry and elemental analysis (see SI). A similar synthetic route has previously been used to synthesize $(PiPr_3)_2Ni(Cl)$.[16]



The catalytic performance of the family of dppf-supported precatalysts for the Suzuki–Miyaura reaction was compared at a range of temperatures, using 2-chloronaphthalene (^{2Cl}*Nap*) and 4-methoxyphenylboronic acid ($^{4OMe}PhB(OH)_2$) as the substrates (Table 1). Our conditions are related to those reported by Ge and Hartwig,[9] although we find that there is an improvement in catalytic performance using 2:1 1,4-dioxane:benzene as the solvent instead of neat ethereal solvent. At 80 °C all precatalysts give complete conversion within 1.5 h (entries 1–5). In particular, the finding that the Ni^I species $^{\mathbf{Cl}}\mathbf{Ni^{I}}$ gives comparable activity to Ni^0 and Ni^{II} complexes is significant (entry 5), as there are only two previous reports of Ni^I precatalysts that are active for the Suzuki–Miyaura reaction.[8a,17] In both examples complete conversion did not occur even with high catalyst loadings (10 mol %) and the use of a strong base (KO^{t}Bu). Interestingly, $^{\mathbf{Cl}}\mathbf{Ni^{I}}$ has previously been implicated as an inactive species formed in catalytic amination and trifluoromethylthiolation reactions using $Ni(cod)_2$/dppf, suggesting different roles for Ni^I in Suzuki–Miyaura couplings compared to other related reactions.[15,18]

Table 1: Yields[a] of product for the Suzuki–Miyaura reaction[b] catalyzed by dppf-supported Ni complexes.



Entry	T [°C]	Compound	% Yields for precatalysts				
			0.5 h	1 h	1.5 h		
1	80[c]	$^{\mathbf{Cin}}\mathbf{Ni^{II}}$	94	> 99	–		
2		$^{\mathbf{otol}}\mathbf{Ni^{II}}$	66	95	> 99		
3		$^{\mathbf{C2H4}}\mathbf{Ni^{0}}$	81	> 99	–		
4		$^{\mathbf{dppf}}\mathbf{Ni^{0}}$[c]	> 99	–	–		
5		$^{\mathbf{Cl}}\mathbf{Ni^{I}}$	69	> 99	–		
			1 h	2 h	4 h	8 h	12 h
6	RT[d]	$^{\mathbf{Cin}}\mathbf{Ni^{II}}$	11	45	52	> 99	–
7		$^{\mathbf{otol}}\mathbf{Ni^{II}}$	41	57	> 99	–	–
8		$^{\mathbf{C2H4}}\mathbf{Ni^{0}}$	22	55	57	74	> 99
9		$^{\mathbf{dppf}}\mathbf{Ni^{0}}$[c]	66	85	> 99	–	–
10		$^{\mathbf{Cl}}\mathbf{Ni^{I}}$	< 5	< 5	25	66	> 99

[a] Yields were calculated using gas chromatography and are the average of two runs. [b] Reaction conditions: 0.2 mmol 2-chloronaphthalene, 0.4 mmol 4-methoxyphenylboronic acid, 0.8 mmol K_3PO_4, 0.2 mmol naphthalene (internal standard), 0.5 or 2.5 mol % precatalyst, 340 μL 1,4-dioxane and 160 μL benzene. [c] 0.5 mol % catalyst was utilized. [d] 2.5 mol % catalyst was utilized.

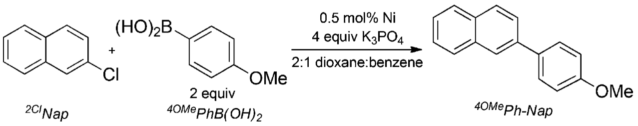
Remarkably, all of the dppf-supported systems are so active that they give complete conversion at RT in 12 h or less when the catalyst loading is increased from 0.5 mol % to 2.5 mol % (Table 1, entries 6–10). These are the mildest conditions reported to date for Ni-catalyzed Suzuki–Miyaura reactions as there are only two other Ni precatalysts that are active for the coupling of aryl halides and boronic acids at RT. However both require significantly higher catalyst loadings and longer reaction times.[12b,19] The Ni^0 complex $^{\mathbf{dppf}}\mathbf{Ni^{0}}$ gives complete conversion faster than any other precatalyst investigated in this study (entry 9). We believe that the improved catalytic activity of $^{\mathbf{dppf}}\mathbf{Ni^{0}}$ compared to $^{\mathbf{C2H4}}\mathbf{Ni^{0}}$ is related to the second dppf ligand in $^{\mathbf{dppf}}\mathbf{Ni^{0}}$ binding less tightly to Ni than the ethylene ligand in $^{\mathbf{C2H4}}\mathbf{Ni^{0}}$ (Table 1, entries 3, 4, 8, 9, see SI).

There is a disparity in the catalytic performance of the Ni^{II} precatalysts $^{\mathbf{Cin}}\mathbf{Ni^{II}}$ and $^{\mathbf{otol}}\mathbf{Ni^{II}}$ at 80 °C (Table 1, entries 1 and 2) despite literature precedent that both activate rapidly.[9,13] This is almost certainly related to the relative stability of $^{\mathbf{Cin}}\mathbf{Ni^{II}}$ and $^{\mathbf{otol}}\mathbf{Ni^{II}}$ at elevated temperature. It was previously noted that $^{\mathbf{otol}}\mathbf{Ni^{II}}$ is unstable in solution,[11c] and decomposition at 80 °C could explain its inferior performance. This hypothesis is supported by RT results, where $^{\mathbf{otol}}\mathbf{Ni^{II}}$ gives significantly better activity than $^{\mathbf{Cin}}\mathbf{Ni^{II}}$ (entries 5 and 6).

Given the exceptional activity of the dppf-supported precatalysts, we probed the species present under catalytic conditions to gain information about their relative performance. Although the finding that precatalysts in three different oxidation states give similar catalytic activity at 80 °C is consistent with all systems forming the same active species, the differences in the relative activity of the precatalysts as a function of temperature (see SI) could be indicative of a more complicated situation. The speciation of Ni both during and at the end of catalysis was probed using paramagnetic ^{1}H NMR spectroscopy (Table 2). In catalytic reactions at 80 °C, under our standard conditions, the predominant Ni species present at the end of the reaction is the Ni^I complex $^{\mathbf{Cl}}\mathbf{Ni^{I}}$, regardless of which precatalyst was utilized (entries 1–5). The identity of the Ni^I complex was unambiguously confirmed using EPR spectroscopy. Furthermore, when reactions using the Ni^0 and Ni^{II} precatalysts were monitored by ^{1}H NMR spectroscopy during catalysis, it is clear that $^{\mathbf{Cl}}\mathbf{Ni^{I}}$ forms while the catalytic reaction is still occurring (entries 1–4, 0.25 h). Interestingly, $^{\mathbf{otol}}\mathbf{Ni^{II}}$ is converted completely to $^{\mathbf{Cl}}\mathbf{Ni^{I}}$ very early in the reaction (entry 2), which presumably explains the near identical catalytic performance of $^{\mathbf{otol}}\mathbf{Ni^{II}}$ and $^{\mathbf{Cl}}\mathbf{Ni^{I}}$ at 80 °C. In contrast for $^{\mathbf{Cin}}\mathbf{Ni^{II}}$ (entry 1), relatively little $^{\mathbf{Cl}}\mathbf{Ni^{I}}$ is formed initially and the concentration of $^{\mathbf{Cl}}\mathbf{Ni^{I}}$ rises drastically at complete conversion.

At RT the Ni^0 and Ni^{II} precatalysts also form Ni^I, but in lower amounts (Table 2, entries 5–10). When $^{\mathbf{Cl}}\mathbf{Ni^{I}}$ was used as the precatalyst, it was detected in essentially unchanged amounts at all stages of the reaction at both RT and 80 °C (entries 5 and 10). These results suggest that the Ni^0 and Ni^{II} precatalysts all have a facile pathway to form $^{\mathbf{Cl}}\mathbf{Ni^{I}}$ under catalytic conditions, but that $^{\mathbf{Cl}}\mathbf{Ni^{I}}$ is relatively stable and does

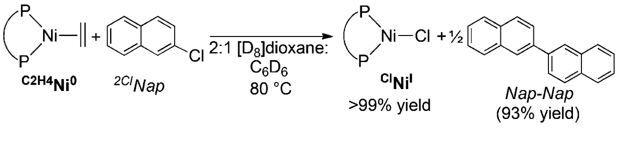
Table 2: Amount[a] of $^{\text{Cl}}\textbf{Ni}^{\text{I}}$ observed both during and at the end of catalysis[b] using different dppf-supported Ni precatalysts.



Entry	T [°C]	Compound	% of total Ni present in the form of $^{\text{Cl}}\textbf{Ni}^{\text{I}}$ 0.25 h	0.5 h	End[d]
1	80	$^{\text{Cin}}\textbf{Ni}^{\text{II}}$	26	23	68 (1 h)
2		$^{\text{otol}}\textbf{Ni}^{\text{II}}$	> 99	> 99	> 99 (1.5 h)
3		$^{\text{C2H4}}\textbf{Ni}^{0}$	51	63	62 (1 h)
4		$^{\text{dppf}}\textbf{Ni}^{0}$[c]	41	85	85 (0.5 h)
5		$^{\text{Cl}}\textbf{Ni}^{\text{I}}$	> 99	> 99	96 (1)
			2 h	End[d]	
6	RT[e]	$^{\text{Cin}}\textbf{Ni}^{\text{II}}$	6	26 (8 h)	
7		$^{\text{otol}}\textbf{Ni}^{\text{II}}$	35	44 (4 h)	
8		$^{\text{C2H4}}\textbf{Ni}^{0}$	34	61 (12 h)	
9		$^{\text{dppf}}\textbf{Ni}^{0}$[c]	12	22 (4 h)	
10		$^{\text{Cl}}\textbf{Ni}^{\text{I}}$	97	94 (12 h)	

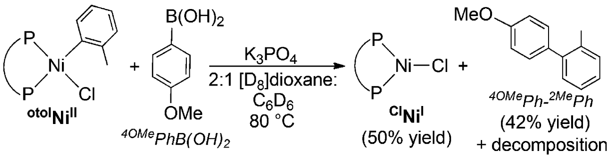
[a] Amounts of $^{\text{Cl}}\textbf{Ni}^{\text{I}}$ were calculated using paramagnetic ^{1}H NMR integrations against a standardized capillary containing Cp_2Co.
[b] Reaction conditions 0.6 mmol 2-chloronaphthalene, 1.2 mmol 4-methoxyphenylboronic acid, 2.4 mmol K_3PO_4, 0.5 or 2.5 mol% precatalyst, 1020 μL 1,4-dioxane and 480 μL benzene. 750 μL of the reaction mixture was removed, evaporated and dissolved in 500 μL C_6D_6. [c] The complex $^{\text{dppf}}\textbf{Ni}^{0}$ formed a different Ni^{I} complex, [(dppf)Ni(Cl)]$_2$(μ-dppf) (see SI). Capillaries were standardized accordingly. [d] Time at which full conversion to product was observed. [e] 2.5 mol% catalyst was utilized.

not form appreciable quantities of Ni^0 or Ni^{II} species (< 5%). To the best of our knowledge, this is the first time that a Ni^I species has been directly observed and quantified during a Ni-catalyzed Suzuki–Miyaura reaction, although Ni^I complexes have been postulated as catalytically relevant intermediates in both Negishi[21] and Kumada[22] reactions. However, notably, there does not appear to be any direct correlation between the amount of Ni^I formed and catalytic activity.



(2)

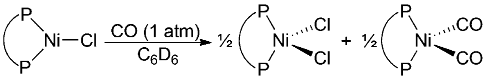
To determine how Ni^I forms during catalysis, a series of stoichiometric reactions were performed. The complex $^{\text{C2H4}}\textbf{Ni}^{0}$ was unreactive towards ^{4OMe}*PhB(OH)$_2$* and/or K_3PO_4 at 80 °C, but $^{\text{Cl}}\textbf{Ni}^{\text{I}}$ formed quantitatively upon addition of 1 equiv ^{2Cl}*Nap* to a 2:1 [D$_8$]dioxane/C_6D_6 solution of $^{\text{C2H4}}\textbf{Ni}^{0}$ at 80 °C [Eq. (2)]. The biaryl 2,2′-binaphthalene (*Nap-Nap*) was also detected (93% yield). At this stage the elementary steps to form $^{\text{Cl}}\textbf{Ni}^{\text{I}}$ and *Nap-Nap* are unclear, possible mechanisms include bimetallic oxidative addition,[23] comproportionation[16] or a radical-based pathway[23a,24] (see SI). However, consistent with this reaction being the route for Ni^I formation during catalysis, a small amount of *Nap-Nap* is also detected in catalytic reactions. Similar reactivity was observed with $^{\text{dppf}}\textbf{Ni}^{0}$ (see Figure S6 in the SI). Our observations are consistent with previous studies demonstrating that the reaction of (NHC)$_2$Ni (NHC = IPr, IMes) with various aryl halides generates Ni^I products and biaryl species,[8a,25] indicating that this observation could be broadly applicable to other ligand sets.



(3)

In contrast, no reaction was observed between $^{\text{otol}}\textbf{Ni}^{\text{II}}$ and ^{2Cl}*Nap*. However, the reaction between $^{\text{otol}}\textbf{Ni}^{\text{II}}$ and 1 equiv of ^{4OMe}*PhB(OH)$_2$* and K_3PO_4 generated $^{\text{Cl}}\textbf{Ni}^{\text{I}}$ in 50% yield by paramagnetic ^{1}H NMR spectroscopy [Eq. (3)]. Additionally, 4′-methoxy-2-methyl-1,1′-biphenyl (^{4OMe}*Ph-*^{2Me}*Ph*) was also formed in 42% yield. Presumably, in this reaction half an equivalent of $^{\text{otol}}\textbf{Ni}^{\text{II}}$ initially undergoes transmetalation and reductive elimination to yield the biaryl product and (dppf)Ni. The latter then comproportionates with the remaining $^{\text{otol}}\textbf{Ni}^{\text{II}}$ to give $^{\text{Cl}}\textbf{Ni}^{\text{I}}$ and (dppf)Ni(Ar), in an analogous fashion to Equation (1) above. Although (dppf)Ni(Ar) was not observed, it is expected to be unstable[11c,26] and some decomposition was noted during the reaction.[27] Further support for this mechanism is provided through the reaction of $^{\text{otol}}\textbf{Ni}^{\text{II}}$ and $^{\text{C2H4}}\textbf{Ni}^{0}$ in C_6D_6 which forms 50% $^{\text{Cl}}\textbf{Ni}^{\text{I}}$ at both RT and 80 °C, as well as decomposition products (see SI).[28] Additionally, when catalysis is performed using $^{\text{otol}}\textbf{Ni}^{\text{II}}$ a small peak correlating to ^{4OMe}*Ph-*^{2Me}*Ph* is observed by GC. The stoichiometric reactivity of $^{\text{Cin}}\textbf{Ni}^{\text{II}}$ was similar to $^{\text{otol}}\textbf{Ni}^{\text{II}}$. The reaction of $^{\text{Cin}}\textbf{Ni}^{\text{II}}$ with 1 equiv ^{4OMe}*PhB(OH)$_2$* and K_3PO_4 formed $^{\text{Cl}}\textbf{Ni}^{\text{I}}$ in 50% yield (see Figure S8). The detection of the related organic fragment was more complicated but products consistent with transmetalation and reductive elimination were observed by GC-MS. As with $^{\text{otol}}\textbf{Ni}^{\text{II}}$, the reaction of $^{\text{Cin}}\textbf{Ni}^{\text{II}}$ with $^{\text{C2H4}}\textbf{Ni}^{0}$ generated 50% $^{\text{Cl}}\textbf{Ni}^{\text{I}}$ and decomposition products.

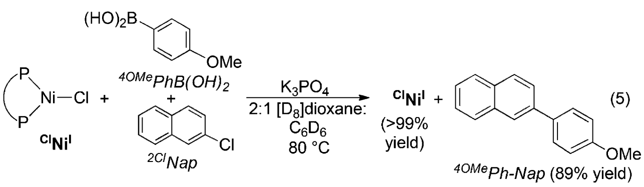
If our proposed pathway for the formation of Ni^I from $^{\text{Cin}}\textbf{Ni}^{\text{II}}$ is correct, then the amount of Ni^I formed in catalysis could be affected by the concentration of the boronic acid. It is plausible that by reducing the concentration of boronic acid, the starting precatalyst will undergo slower transmetalation and is thus more likely to comproportionate with Ni^0 that has been formed via transmetalation and reductive elimination (see SI). When only 1 equiv ^{4OMe}*PhB(OH)$_2$* was used in catalysis with $^{\text{Cin}}\textbf{Ni}^{\text{II}}$ at 80 °C, the amount of $^{\text{Cl}}\textbf{Ni}^{\text{I}}$ produced after 15 min was approximately double than when 2 equiv boronic acid were used (58% and 26%, respectively). The total amount of Ni^I after 1 hour was also elevated in the 1 equiv case vs the 2 equiv case (87% vs 68%). This could have implications for the development of reaction conditions; in systems where Ni^I complexes are formed and are active, it may be possible to reduce the amount of boronic acid and still obtain high conversions. Conversely, in systems where Ni^I is less active, both increasing the equivalency of boronic acid and ensuring it is fully soluble in the reaction mixture could result in more effective catalysis.



(4)

Our stoichiometric reactions confirm that Ni^0 and Ni^{II} precatalysts can be readily converted into $^{\mathbf{Cl}}\mathbf{Ni}^{\mathbf{I}}$. We also wanted to test if $^{\mathbf{Cl}}\mathbf{Ni}^{\mathbf{I}}$ could undergo disproportionation into Ni^0 and Ni^{II} species. Exposure of $^{\mathbf{Cl}}\mathbf{Ni}^{\mathbf{I}}$ to 1 atm of CO[24c] in C_6D_6 resulted in the formation of $(dppf)Ni(CO)_2$ and $(dppf)NiCl_2$ [Eq. (4)]. However, under catalytic conditions, there is no ligand which can π-backbond to Ni^0 as effectively as CO. Treatment of $^{\mathbf{Cl}}\mathbf{Ni}^{\mathbf{I}}$ with dppf, the species present in catalysis that most likely could stabilize Ni^0, did not lead to disproportionation (see SI). This was supported by DFT calculations which indicate that disproportionation of a simplified version of $^{\mathbf{Cl}}\mathbf{Ni}^{\mathbf{I}}$ into simplified versions of $(dppf)_2Ni$ and $(dppf)NiCl_2$ is uphill by 5.0 kcal mol^{-1} (see SI). These results are in agreement with previous studies highlighting the thermodynamic stability of Ni^I complexes formed by comproportionation.[8a,29]

The quantitative detection of $^{\mathbf{Cl}}\mathbf{Ni}^{\mathbf{I}}$ at the end of the reaction when it was used as a precatalyst and the thermodynamic difficulty of disproportionation raises the possibility that Ni^I species may be part of the catalytic cycle. However, no reaction was observed when either 1 equiv $^{2Cl}\mathit{Nap}$ or $^{4OMe}\mathit{PhB(OH)_2}$ and K_3PO_4 were added to a benzene solution of $^{\mathbf{Cl}}\mathbf{Ni}^{\mathbf{I}}$ and heated at 80 °C for 2 h. Consistent with this observation DFT calculations suggest that both oxidative addition of chlorobenzene or transmetallation of $^{4OMe}\mathit{PhB(OH)_2}$ with $^{\mathbf{Cl}}\mathbf{Ni}^{\mathbf{I}}$ are thermodynamically unfavorable (see SI). When 1 equiv of all three of these reagents were present, $^{4OMe}\mathit{Ph\text{-}Nap}$ was formed and $^{\mathbf{Cl}}\mathbf{Ni}^{\mathbf{I}}$ was regenerated in > 99 % yield as determined by paramagnetic ^{1}H NMR spectroscopy [Eq. (5)], in agreement with our catalytic results.



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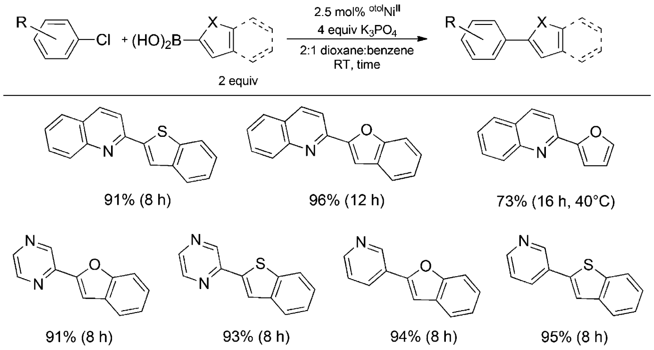
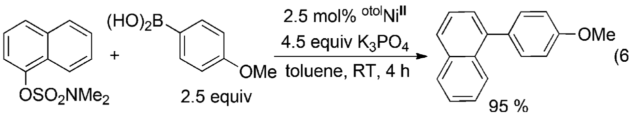


Figure 2. Isolated yields[a] of product for Suzuki–Miyaura reactions[b] at RT catalyzed by $^{\mathbf{otol}}\mathbf{Ni}^{\mathbf{II}}$. [a] Yields are the average of two runs. [b] Reaction conditions: 0.2 mmol ArX, 0.4 mmol $Ar'B(OH)_2$, 0.8 mmol K_3PO_4, 0.005 mmol catalyst, 340 μL 1,4-dioxane and 160 μL benzene.

Finally, to show the utility of our systems, we explored the substrate scope using $^{\mathbf{otol}}\mathbf{Ni}^{\mathbf{II}}$. This precatalyst was selected for three reasons: 1) it is highly active, 2) it is both air and moisture stable, which makes it considerably more practical than other Ni precatalysts such as $^{\mathbf{dppf}}\mathbf{Ni}^{\mathbf{0}}$, and 3) it can be synthesized directly from $NiCl_2$ without using costly $Ni(cod)_2$.[20] A variety of synthetically valuable substrates containing heterocycles were successfully coupled at RT using $^{\mathbf{otol}}\mathbf{Ni}^{\mathbf{II}}$ (Figure 2). This includes 2-benzofuran and 2-benzothiophene boronic acids, and pyridyl and pyrazyl chlorides, which are problematic for Pd-based systems. It should be noted that the more challenging substrate 2-furanylboronic acid still required slightly elevated temperature (40 °C), and gave a slightly lower yield when coupled with 2-chloroquinoline. Furthermore, $^{\mathbf{otol}}\mathbf{Ni}^{\mathbf{II}}$ is competent for Suzuki–Miyaura reactions using aryl sulfamates as the substrate instead of aryl chlorides. The use of aryl sulfamate substrates is of particular interest because they can be selectively functionalized using directed C–H activation prior to cross-coupling.[4b,d,5] Using 2.5 mol % $^{\mathbf{otol}}\mathbf{Ni}^{\mathbf{II}}$, $^{4OMe}\mathit{PhB(OH)_2}$ and naphthalen-1-yl dimethylsulfamate are quantitatively coupled at RT in 4 h [Eq. (6)]. Previous examples of this reaction have typically required catalyst loadings between 5–10 mol %, temperatures ranging from 80–110 °C and extended reaction times.[4b,d,5]



(6)

Overall, although our studies clearly indicate that a Ni^I compound is forming during catalysis, at this stage the exact role of the Ni^I species is unclear. For example, it could be acting as a catalyst resting state, which releases a very small amount of a highly active Ni^0 or Ni^{II} species into the reaction mixture or it may be directly part of the catalytic cycle, with the elementary steps being thermodynamically unfavorable and thus unobservable. Understanding the specific role of Ni^I compounds in Suzuki–Miyaura reactions will be the focus of ongoing work in our laboratory. Nevertheless, we have conclusively established that Ni^0 and Ni^{II} complexes can readily form Ni^I species under the catalytic conditions; the first time this has been demonstrated for Suzuki–Miyaura reactions. In general, the formation of Ni^I species will be problematic in catalytic reactions in which Ni^I species are not active because it is difficult for Ni^I to undergo disproportionation. However, the formation of Ni^I can be suppressed by the addition of a greater number of equivalents of the transmetalating agent. In the case of the Suzuki–Miyaura reactions studied in this work, a Ni^I species that forms readily from Hartwig and Ge's seminal $^{\mathbf{Cin}}\mathbf{Ni}^{\mathbf{II}}$ precatalyst is highly active, however we suggest that the easily accessible $^{\mathbf{otol}}\mathbf{Ni}^{\mathbf{II}}$ is a more active and practical catalyst. In the future we will explore whether our results are relevant to Ni complexes supported by other ligands and ascertain if well-defined Ni^I precatalysts can lead to milder conditions for other cross-coupling reactions.

Acknowledgements

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Keywords: cross-coupling · homogeneous catalysis · nickel · reaction mechanism · Suzuki–Miyaura coupling

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