ORGANOMETALLICS
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Nickel Hydroxo Complexes as Intermediates in Nickel-Catalyzed Suzuki–Miyaura Cross-Coupling

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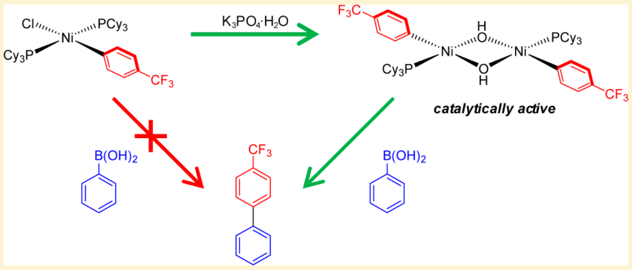
S *Supporting Information*



ABSTRACT: The synthesis, characterization, and reactivity of intermediates formed in the Ni-catalyzed Suzuki–Miyaura cross-coupling (SMC) of an aryl chloride are described. Oxidative addition of 1-chloro-4-trifluoromethylbenzene (**1**) to a mixture of $Ni(cod)_2$ and PCy_3 afforded $NiCl(4\text{-}CF_3Ph)(PCy_3)_2$ (**2**), which then cleanly provided dimeric $[Ni(4\text{-}CF_3Ph)(\mu\text{–}OH)(PCy_3)]_2$ (**3**) by reaction with aqueous KOH. Reactivity studies of **2** and **3** with phenylboronic acid (**4**) revealed that, while **2** affords only traces of the biphenyl coupling product after 24 h, the same reaction with **3** is complete within minutes at room temperature. In contrast, the reaction of **3** with potassium phenyltrihydroxyborate (**6**) is much slower than that with boronic acid **4**, and significantly lower yields of the cross-coupling product are obtained. We show that formation of the hydroxo species **3** is the rate-determining step in the present SMC.

Transition-metal-mediated cross-coupling reactions have transformed the way chemists assemble molecules. While the vast majority of the catalysts used in such transformations are centered around a Pd atom, there has been significant interest in the use of cheaper, more abundant first-row elements[1] such as Ni,[2−10] Fe,[11] Cu,[12−16] Co,[11,17,18] Mn,[19] and Cr[20] as alternatives to Pd. As Suzuki–Miyaura cross-coupling (SMC) is the most heavily used cross-coupling reaction in the pharmaceutical industry,[21] we became attracted by the potential advantages of replacing Pd with Ni in the preparation of pharmaceutically relevant structures. However, despite the plethora of examples documented in a laboratory setting, only a few examples of Ni-catalyzed cross-coupling have been used on a process-relevant scale (>100 mmol),[21] none of which were SMC transformations. There are two major drawbacks to the application of Ni catalysis in SMC on scale: (1) the relatively high catalyst loading that is normally employed (3−10 mol % Ni),[4] which tends to offset the generally lower cost of Ni vs Pd and can potentially complicate the isolation of cross-coupling products with low residual metal content, and (2) the limited substrate scope, particularly for heteroaryl substrates. Importantly, recent advances in catalyst design show encouraging results in broadening the substrate scope while maintaining low catalyst loadings.[4]

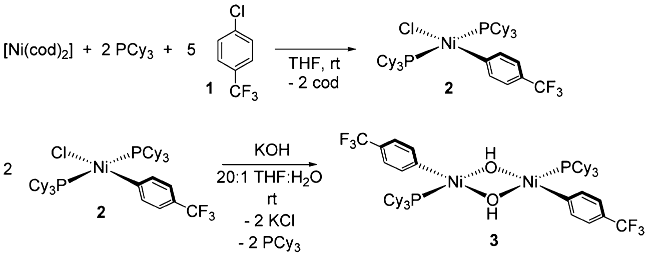
Understanding the mechanism of the Ni-catalyzed SMC is key to improving the efficiency of the reaction and could result in superior catalyst turnover numbers. The mechanism of this reaction is believed to proceed in a way analogous to that for Pd: oxidative addition, transmetalation, and then reductive elimination.[22,23] Of these steps, transmetalation is thought to be the turnover-limiting step in the Ni-catalyzed SMC of aryl halides[22,24] but has remained poorly studied. It has been proposed that complexation of the base anion to the metal center precedes transmetalation during the Ni-catalyzed SMC of aryl halides,[22,25] although observation or isolation of such intermediates has, to the best of our knowledge, not been reported. Convincing reports by Hartwig and Amatore have described the intermediacy of Pd−hydroxo complexes as the species undergoing transmetalation in Pd-catalyzed SMC carried out in the presence of water.[26,27] A similar pathway could be operative for Ni and may explain the differences in yield when anhydrous vs hydrated bases are used.[28] As part of our ongoing efforts to understand the mechanism of Ni-catalyzed SMC for future pharmaceutical applications, we became interested in the potential role of water within this transformation. Herein we report the syntheses of intermediates formed during a Ni-catalyzed SMC of an aryl halide and explore their reactivity toward a typical arylboronic acid and a borate. This study reveals that the role of water in the Ni-catalyzed SMC is to form a Ni−hydroxo complex that undergoes rapid transmetalation with the boronic acid.

As a starting point in our study, we chose $Ni(cod)_2$ and PCy_3 as the catalyst system, given its importance in the SMC of both aryl halides and activated phenols.[25b] We selected 1-chloro-4-trifluoromethylbenzene (**1**) as the electrophile because the electron-withdrawing trifluoromethyl group should facilitate oxidative addition while also serving as a useful NMR handle. Addition of **1** to a red-orange THF solution of $Ni(cod)_2$ and PCy_3 at room temperature caused an instantaneous color

Received: February 5, 2014
Published: April 18, 2014

change to yellow-orange (Scheme 1). Formation of the anticipated $NiCl(4\text{-}CF_3Ph)(PCy_3)_2$ (**2**) was complete within 12 h, as judged by $^{31}P\{^1H\}$ NMR analysis. Complex **2** was isolated in 71% yield after workup; its structure is supported by NMR, X-ray, and combustion analyses. Diamagnetic **2** is indefinitely stable under a dinitrogen atmosphere and is stable for at least 4 months as a solid in air at room temperature, as judged by ^1H and ^{31}P NMR spectroscopy.

Scheme 1. Synthesis of Ni Complexes 2 and 3



X-ray-quality crystals of **2** were obtained by cooling a concentrated diethyl ether solution to −35 °C for 2 days. The asymmetric unit contains one molecule of **2** and one molecule of diethyl ether (Figure 1). Complex **2** adopts a slightly distorted square planar geometry, as evidenced by the C−Ni−Cl and P−Ni−P bond angles of 168.1 and 167.8°, respectively, both of which are significantly shy of the ideal 180°. These angles are nevertheless fully consistent with a related complex recently reported by Standley and Jamison.[29] The remaining bond lengths and angles around the Ni center are similar to those of related complexes.[30]

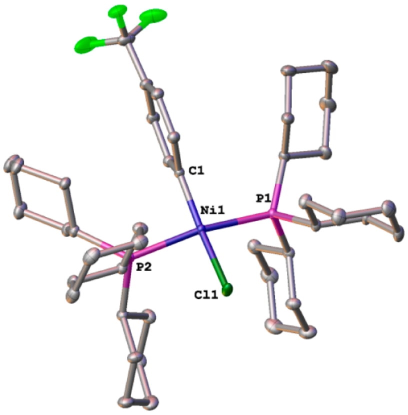


Figure 1. Thermal ellipsoid plot of **2** with ellipsoids at the 50% probability level. Hydrogen atoms and diethyl ether solvent molecule are omitted for clarity. Key bond lengths (Å) and angles (deg): Ni(1)−P(1), 2.2492(3); Ni(1)−P(2), 2.2645(3); Ni(1)−C(1), 1.8844(9); Ni(1)−Cl(1), 2.2295(3); C(1)−Ni(1)−Cl(1), 168.05(3); P(1)−Ni(1)−P(2), 167.840(11); C(1)−Ni(1)−P(1), 91.65(3); C(1)−Ni(1)−P(2), 93.73(3).

Initial attempts to replace the chloride atom within **2** with MOH (M = Li, Na, K, Cs) showed incomplete conversion along with the formation of an unidentified, insoluble black residue after stirring for 24 h at both room temperature and 50 °C (see the Supporting Information). Campora commented on the difficult salt metathesis reaction between NiCl(Me)(dippe) (dippe = 1,2-bis(diisopropylphosphino)ethane) and MOH.[31] We hypothesized that the low solubility of MOH in THF could be responsible for the low conversion observed. Indeed, when a yellow-orange THF solution of **2** was treated with 20 equiv of aqueous KOH (final ratio 20:1 THF:H_2O), a faint color change to yellow was observed after stirring for 2 h at room temperature; conversion to the new diamagnetic product **3** averaged 75% at that time. A prolonged reaction time of 18 h showed complete conversion. As examination of the crude reaction mixture by $^{31}P\{^1H\}$ NMR spectroscopy only revealed free PCy_3 in addition to **3** (1:1 ratio); we propose that **3** is a dinuclear compound of the type $[Ni(4\text{-}CF_3Ph)(\mu\text{-}OH)(PCy_3)]_2$. This structure is supported by NMR, IR, and combustion analyses and is also consistent with previously reported dimeric Ni complexes.[32−34] Scaling up the reaction to 1.5 g of **2** allowed isolation of **3** as a fine yellow powder in 95% yield after workup. The ^1H NMR spectrum of **3** shows a diagnostic resonance for the bridging hydroxo protons at −3.80 ppm in C_6D_6, in good agreement with other Ni complexes containing bridging hydroxo ligands.[32,33] A single, sharp resonance for the hydroxide protons implies that **3** is present only as the anti isomer in C_6D_6.[35] Addition of up to 50 equiv of PCy_3 did not promote anti/syn isomerization or the formation of a monomeric hydroxide complex of the type $Ni(4\text{-}CF_3Ph)(OH)(PCy_3)_2$. Similar results were obtained by Boncella and co-workers for the related $[Ni(Mes)(\mu\text{-}OH)(PMe_3)]_2$.[33] Infrared spectroscopy revealed a strong absorption at 3650 cm^{-1} (Nujol) that we assign to the ν_{O-H} band of **3**.

With complexes **2** and **3** in hand, we wanted to confirm that they are competent catalysts for the SMC of aryl halide **1** and phenylboronic acid (**4**). Thus, formation of 4-trifluoromethylbiphenyl (**5**) was monitored over time using 5 mol % of $Ni(cod)_2/PCy_3$ as a benchmark catalyst system in addition to complexes **2** and **3** (Figure 2). Reactions were carried out at room temperature in THF using 1.5 equiv of **4** and 3 equiv of $K_3PO_4{\cdot}H_2O$. Samples were removed periodically and quenched with DMSO, and the yield of biphenyl **5** was assessed quantitatively by ultraperformance liquid chromatography (UPLC) against an internal standard. With all three catalysts, the yield of biphenyl **5** reaches 75% and 100% at 24 and 48 h, respectively. The rates of formation of biphenyl **5** as a function of time were identical within experimental error for all three

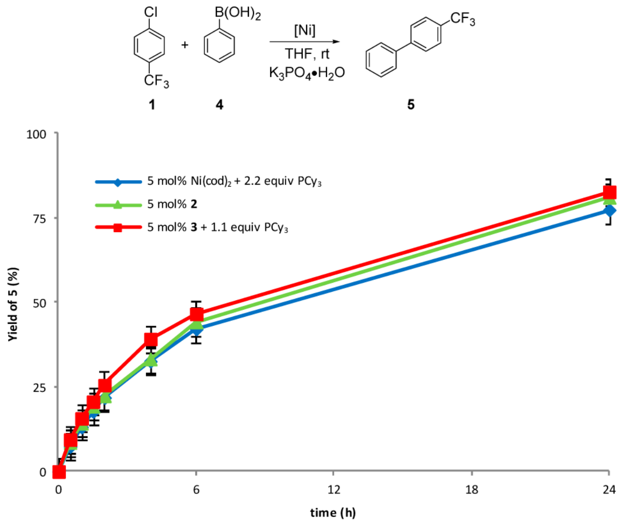


Figure 2. Yield of **5** over time. Conditions: 5 mol % of [Ni], 180 mM **1**, 1.5 equiv of **4**, 3 equiv of $K_3PO_4{\cdot}H_2O$, THF, 22 °C, N_2 atmosphere. Values are ±3% in replicate runs.

catalyst systems. No induction period was noticed with either **2** or **3**, consistent with the presence of both complexes "on" the catalytic cycle.

Having established the ability of **2** and **3** to catalyze a SMC reaction, we next studied the stoichiometric reaction of **2** and **3** with boronic acid **4** to better understand the individual steps of the catalytic cycle (Figure 3). When the halide complex **2** was treated with boronic acid **4** in the absence of base at both room temperature and 60 °C, only a trace amount of biphenyl **5** was detected at 6 h. Longer reaction times did not improve conversions. Similarly, the use of rigorously dried K_3PO_4 led to no observable reaction after 24 h at both room temperature and 60 °C. In sharp contrast to the reactivity of **2**, a quantitative yield of biphenyl **5** was obtained in *less than 2 min* at room temperature when hydroxo complex **3** was treated with boronic acid **4** even in the absence of base and/or added water.[36] Consistent with this observation, the reaction of complex **2** with boronic acid **4** in the presence of 3 equiv of $K_3PO_4{\cdot}H_2O$ reaches full conversion at 6 h at room temperature. These results clearly show the importance of water in promoting the SMC reaction. It has been proposed that water may promote the reaction by formation of a borate species, such as potassium trihydroxyborate **6**, which could then undergo transmetalation with the Ni complex.[22] Our results suggest that this is unlikely as (1) it was previously demonstrated by Lloyd-Jones and coworkers that the equilibrium between the boronic acid and borate favors the former at low water concentration,[37] as is the case here, and (2) reaction of either **2** or **3** with borate **6** and 18-crown 6 (to solubilize **6**) leads to significantly less product than with boronic acid **4** (Figure 3). The reduced reactivity is not due to base-mediated protodeboronation,[37] as analysis of a quenched sample by UPLC showed residual boronic acid but no traces of benzene, the product from protodeboronation of **6**. However, we do note that the color of the reaction mixture changed from the original yellow-orange to a very pale green using borate **6**, potentially signaling the formation of catalytically inactive $Ni(OH)_2$ species.[28]

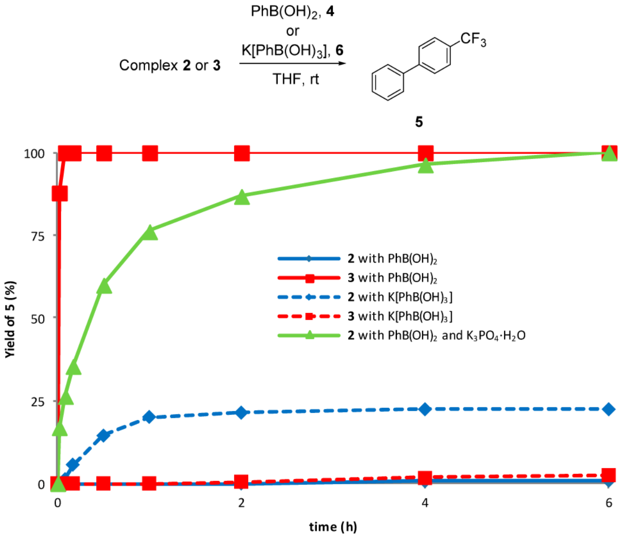


Figure 3. Yield of **5** over time. Conditions: 17 mM [Ni], 1.5 equiv of **4** (solid line) or **6** and 18-crown-6 (dashed line), THF, 22 °C, N_2 atmosphere. Values are ±3% in replicate runs.

The above data suggest that the kinetically more accessible pathway to transmetalation in a Ni-catalyzed SMC involves reaction of a Ni—hydroxo complex with a boronic acid. This result is fully consistent with the results of Hartwig and Amatore using a Pd catalyst.[26,27] The relevance of the hydroxo species **3** during the SMC between aryl chloride **1** and **4** was established by reaction of the oxidative addition product **2** with 15 equiv of $K_3PO_4{\cdot}H_2O$ in THF-d_8. The initially orange solution of complex **2** became slightly paler over 15 h, and $^{31}P\{^1H\}$ NMR analysis revealed the formation of hydroxo **3** in 15% yield (Figure S1, Supporting Information).[38] The only other species detected by ^{31}P NMR spectroscopy were unreacted **2** and free PCy_3, the coproduct from the formation of dimeric **3**. The low yield of **3** obtained using $K_3PO_4{\cdot}H_2O$ is consistent with the large excess of KOH required for its isolation from **2** in good yield (vide supra). The high reactivity of hydroxo **3** with boronic acid **4** (Figure 3) coupled with the observation of halide **2** as the catalyst resting state by $^{31}P\{^1H\}$ NMR spectroscopy (Figure S2) suggests that formation of hydroxo **3** is the turnover-determining step in the catalytic cycle. Moreover, conversion of **2** to **3**, and the formation of **5** from chloride **2** and boronic acid **4** (Figure 3), both occur over a time scale of hours. This supports that formation of **3** accounts for the time scale of catalysis. Thus, strategies targeted at accelerating the chloride to hydroxide ligand exchange, possibly through ancillary ligand design, may help in improving reaction rate and perhaps reducing catalyst loadings.

The foregoing describes high-yield routes to catalytically relevant intermediates in the SMC of aryl halide **1**. Comparison of the reactivities of halide complex **2** and hydroxo **3** revealed that only the latter undergoes transmetalation at an appreciable rate. We also showed that the boronic acid undergoes transmetalation, while the borate is substantially slower and is sometimes unreactive. The present study revealed future avenues to explore such as ways to accelerate the rate of formation of the key Ni—hydroxo complexes through ligand design. Such experiments are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, figures, tables, and a CIF file giving general considerations, synthetic procedures, conversions of **2** to **3**, representative procedures for catalytic reactions and for stoichiometric experiments, $^{31}P\{^1H\}$ NMR spectra of the reaction of **2** with $K_3PO_4{\cdot}H_2O$, $^{31}P\{^1H\}$ NMR spectra of the SMC of **1** with **4**, and crystallographic data for **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge the following Pfizer colleagues: Javier Magano, Chris McWilliams, and Joel Hawkins for helpful discussions, Brian Samas for assistance with the crystallographic analysis, Ronald Morris for assistance with mass spectrometry analysis, and Joshua Denette for analytical support. This work has been influenced through the ongoing efforts of the Non-Precious Metal Catalysis Alliance among Pfizer, Boehringer-Ingelheim, and GlaxoSmithKline.

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(35) In THF-d_8, a 7:1 anti:syn isomeric ratio is observed.

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