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Letter

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Development of an Air-Stable, Broadly Applicable Nickel Source for Nickel-Catalyzed Cross-Coupling

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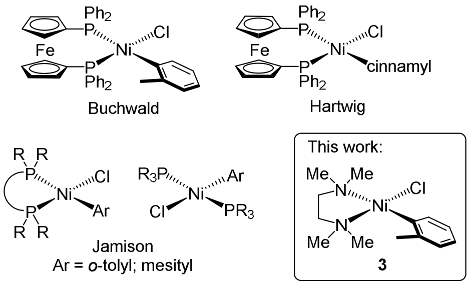
ABSTRACT: The synthesis of NiCl(*o*-tolyl)(TMEDA) (**3**) and its application in coupling reactions is described. In combination with a suitable ligand, precatalyst **3** was applied to a wide range of transformations, such as Suzuki, amination, Kumada, Negishi, Heck, borylation and reductive coupling. Yields of products obtained with **3** are equal or superior to those obtained with common Ni sources such as Ni(cod)$_2$ (**1**) and NiCl$_2$(dme) (**2**). Importantly, and unlike **1**, complex **3** is stable for months in air as a solid, which eliminates the need for a glovebox and greatly facilitates the reaction setup. Thus, complex **3** is the first highly versatile Ni source that combines the broad applicability of **1** with the air stability of **2**.

Transition metal-catalyzed cross-coupling reactions are now well established methods for C–C and C–heteroatom bond formation.[1] Palladium is by far the most prevalent transition metal in cross-coupling chemistry due to its ability to catalyze a broad range of transformations. However, some of the caveats associated with the use of this metal are its high cost,[2] toxicity (which requires stringent controls to minimize its levels in drug manufacturing),[3] and questionable long-term supply.[4] As a result, research on the application of first row metals (Fe, Ni, Cu) in cross-coupling has received considerable attention in recent years. In particular, Ni has been applied to a broad range of transformations[5] and shows great promise as a viable alternative to Pd.[5,6]

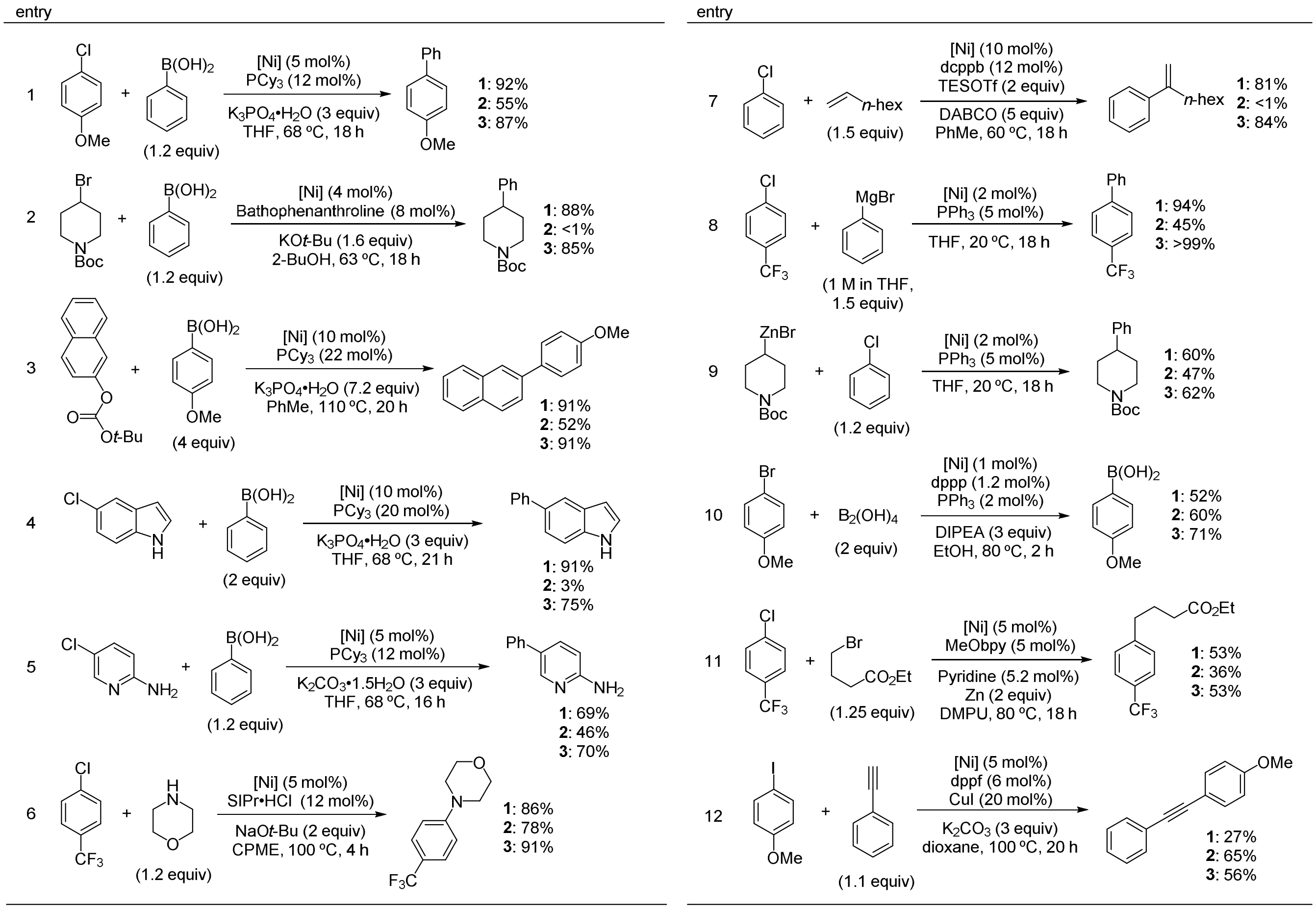
The broad application of cross-coupling chemistry, especially in industrial settings,[7] has been facilitated by the availability of automated equipment. Thus, high-throughput experimentation (HTE) has received increasing attention as a means to solve specific problems by carrying out a very large number of microscale reactions to cover a broad reaction space.[8] Critical for accomplishing this goal is the need for metal sources that, in combination with a large number of ligands, can test a comprehensive set of reaction conditions. Ideally, the metal source should be air, moisture, and thermally stable and readily available from commercial sources. Pd(OAc)$_2$ and Ni(cod)$_2$ (**1**; cod = 1,5-cyclooctadiene) are typically the “go-to” metal sources for cross-coupling screening. However, the high air and thermal sensitivities of **1** are significant drawbacks that limit its use outside of a glovebox environment. In contrast, NiCl$_2$(dme) (**2**) is an air-stable, non-hygroscopic solid that has been used extensively by Fu and co-workers,[9] amongst others.[10] Nevertheless, the low solubility of **2** in many organic solvents, which dramatically slows down its handling by robotic equipment, the necessity to add external reductants in, e.g., amination and Heck reactions, and the uncertainty regarding the extent and timeframe of complexation with an external ligand (given its low solubility) makes **2** unattractive for HTE. Recently the groups of Hartwig, Buchwald, and Jamison have described a series of air-stable Ni-phosphine complexes that catalyze several types of coupling reactions (Chart 1).[11] While these precatalysts show good substrate scope, they are not suitable Ni sources for HTE since the built-in phosphine will inevitably compete with an added external ligand for the Ni center, thereby leading to questionable screening results.

Chart 1. Recently reported well-defined Ni precatalysts



With the intention of facilitating the incorporation of Ni catalysis in the complex cross-couplings prevalent in the pharmaceutical industry, we set out to develop a stable Ni source amenable to HTE that would combine the advantages of complexes **1** and **2**. We set a number of desirable properties for this new Ni source: a) easy to prepare on multi-gram quantities; b) air and moisture stable; c) highly soluble and stable in solution over several hours to allow stock solution preparation and dispensing; d) inexpensive. The recently published precatalysts by the Jamison and Buchwald groups both showcase the “NiCl(*o*-

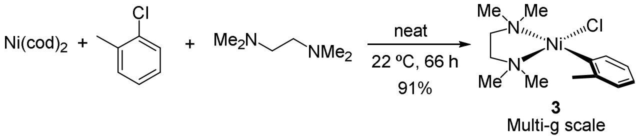
Table 1. Coupling yields[a] using Ni sources **1, 2** and **3**.



[a] Yields determined by ultra-performance liquid chromatography (UPLC) analysis or NMR spectroscopy.

tolyl)" structural element. We therefore sought to conserve these anionic ligands and complete the coordination sphere of the metal by a placeholder ligand that would be readily displaced upon addition of a second ligand, such as a phosphine. Here we report the synthesis and application of NiCl(*o*-tolyl)(TMEDA) (**3**; TMEDA = tetramethylethylenediamine**)** to a variety of cross-coupling reactions of relevance to the pharmaceutical industry. Complex **3** is the first well-defined Ni precatalyst that combines the broad applicability of Ni(0) **1** with the air and moisture stability of Ni(II) **2**.

Scheme 1. Synthesis of complex **3**



Complex **3** was prepared in a manner analogous to that reported by Grushin and coworkers (Scheme 1).[12] Specifically, a suspension of Ni(cod)$_2$ and TMEDA in 2-chlorotoluene was stirred at RT for 3 days under nitrogen over which time the color of the suspension changed to dark orange. Addition of hexanes followed by filtration in air allowed for the isolation of complex **3** in 91% yield as a dark orange, fluffy powder. Importantly, complex **3** will shortly be commercially available.[13] The structure of diamagnetic **3** is supported by NMR and combustion analyses. Complex **3** is indefinitely stable as a solid under a dinitrogen atmosphere at RT and for over six months as a solid under air at RT (*vide infra*). Importantly, and in sharp contrast to the related NiCl(Ph)(TMEDA)[12] for which we observed rapid decomposition and formation of biphenyl (see Supporting Information), complex **3** is stable as a solution in a variety of common organic solvents under nitrogen, including methylene chloride, at RT for at least 24 hours, which is critical to its application in HTE, as noted above.

We next tested the applicability of complex **3** as a metal source in a variety of different coupling reactions (Table 1) and compared the performance of **3** against the established complexes **1** and **2**. We purposely chose *unoptimized* reactions conditions that do *not* provide quantitative yield of the desired product to elicit any differences between Ni sources **1–3**. Assuming that all three precatalysts should funnel toward the same active species during catalysis and that the stabilizing ligand (cod, dme or TMEDA) acts as a spectator, the yields of coupling product should be identical, within experimental error, for complexes **1–3**.[5a,14] All reactions were carried out in a N$_2$-filled glovebox given the high air/moisture sensitivity of complex **1** and the reaction yields were assessed by ultra-performance liquid chromatography (UPLC) analysis or NMR spectroscopy.

Suzuki-Miyaura coupling involving sp^2 (entry 1)[15] and sp^3 (entry 2)[16] halides as well as activated phenols as electrophiles (entry 3)[17] afforded the desired product in equal or superior yields to those reported with either **1** or **2**. The nearly identical yields between **1** and **3** suggests that both phosphine and phenanthroline ligands readily replace the TMEDA ligand within **3**. Importantly, dichloride **2** provided substantially lower yield of the desired biphenyl product (entry 1) and was totally ineffective in the sp^2-sp^3 Suzuki coupling of entry 2. This underscores the dramatic impact of selecting an appropriate Ni source for a given reaction and reinforces the need for a highly versatile Ni source. Precatalyst **3** proved effective for the Suzuki coupling of important pharma-relevant heterocycles such as the *unprotected* indole and 2-aminopyridine in entries 4 and 5 (75% and 70% yield, respectively). Buchwald-Hartwig coupling (entry 6) afforded the expected product in excellent yield. Importantly, the use of dichloride **2** as an air stable Ni source proved effective only when *N*-heterocyclic carbenes were used as ligands (see Supporting Information, Figure S6). Only trace amounts of product, if any, was detected with this Ni source when phosphine ligands were employed whereas several phosphines proved effective with either **1** or **3**. In HTE, this implies that several "hits" could be missed if an inappropriate Ni source (such as dichloride **2**) is employed.

Heck coupling as reported by Jamison and co-workers[18] proceeded smoothly (entry 7). The isolated yield as well as the isomeric ratio of the desired styrenyl product matched very well with the reported values (84%; >99:1 branched/linear). Despite complete consumption of chlorobenzene, no product could be detected using dichloride **2**. Jamison showed that the isomeric ratio for this reaction is very sensitive to the phosphine used. We were thus pleased to find that the branched:linear product ratio obtained upon substitution of dcppb for dppb afforded the same isomeric ratio of products (>99:1 and 4:1 branched:linear for dcppb and dppb, respectively), with both Ni sources **1** and **3**. This shows that the same active species is formed in solution irrespective of the source of Ni used.

Kumada coupling of 4-trifluoromethylchlorobenzene with PhMgBr provided near quantitative yield of the desired biphenyl product with both **1** and **3** (entry 8). The yield is reduced by nearly 50% when complex **2** is used instead. Similarly, sp^2-sp^3 Negishi coupling (entry 9) with **1** and **3** and PPh3 as the ligand afforded good yields (60–62%, respectively) of product after 18 hours at RT; a reduced yield (47%) was again observed employing **2** as the Ni source. Benzene accounts for the mass balance with all three Ni sources.

Boronic acids are an extremely valuable commodity in the pharmaceutical industry. We were thus keen to apply **3** in the borylation reaction between an aryl halide and $B_2(OH)_4$ as reported by Molander and co-workers.[19] To our delight, the reaction afforded the desired boronic acid in 71% yield after two hours at 80 °C using only 1 mol% of **3** (entry 10). Interestingly, the yields with Ni(0) **1** are consistently ca. 20% lower relative to **3**. We hypothesize that the instability of **1** in ethanol may be the cause for the reduced yield of boronic acid.

Cross-electrophile coupling[20] is a powerful methodology that avoids the need for a nucleophile. Using conditions reported by Weix and coworkers,[21] the coupling between 4-trifluoromethylchlorobenzene and ethyl 4-bromobutanoate was carried out in the presence of Zn as the stoichiometric reductant (entry 11). The reaction provided the desired coupling product in 53% yield with **1** and **3**, matching the reported yield.[21] The two different homocoupling products account for the mass balance of material.

Lastly, Sonogashira coupling (entry 12) using **3** with dppf as ligand afforded the desired product in 56% yield while a significantly lower yield (27%) was observed with **1**. Interestingly, this is the only time that dichloride **2** proved marginally superior to **3**. For all three Ni sources investigated, increasing the stoichiometry of phenylacetylene from 1.1 to 2 equiv led to a 10−15% drop in yield of cross-coupled product, possibly due to sequestration of the Ni center by the acetylene moiety.

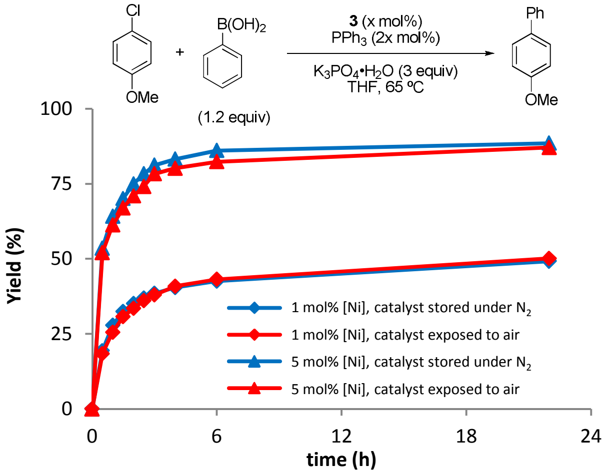


Figure 1. Yield of 4-methoxybiphenyl over time. Conditions: 1 or 5 mol% [Ni], 2 or 10 mol% PPh_3, 0.7 M 4-chloroanisole, 1.2 equiv of phenylboronic acid, 3 equiv $K_3PO_4{\cdot}H_2O$, THF, 65 ºC, N_2 atmosphere. ±3% in replicate runs.

Having established the applicability of **3** to a variety of cross-coupling reactions, we wished to examine the air stability of this new precatalyst. Thus, we exposed a solid sample of complex **3** to air for 2 months. No color or appearance change was observed over this time, providing qualitative evidence for the air stability of complex **3**. In sharp contrast, the notoriously sensitive complex **1** turns black from yellow in less than 30 min when exposed to air, and the resulting solid was totally ineffective in the Suzuki cross-coupling of 4-chloroanisole with phenylboronic acid. To detect any decomposition of **3** upon exposure to air, we obtained the conversion profile for this same reaction (Figure 1). If precatalyst **3** had undergone even partial decomposition in air, we would have expected the conversion profile to be slower relative to a sample of **3** that was kept under an inert atmosphere. We were thus pleased to find identical conversion profiles, within experimental error, with the catalyst generated in situ by combination of **3** and PPh_3 even after the precatalyst was exposed to air for two months. This provides strong evidence for the stability of **3** to air, implying that it can be safely handled outside of a glovebox.

The foregoing describes the synthesis and application of precatalyst **3** in coupling reactions. Complex **3** is the first Ni complex that combines the broad applicability of $Ni(cod)_2$ (**1**) with the air and moisture stabilities characteristic of Ni(II) complexes such as $NiCl_2(dme)$ (**2**). Precatalyst **3** was successfully employed to mediate twelve different cross-coupling reactions with reaction yields matching or exceeding those obtained with the alternative Ni complexes **1** and **2**. Importantly, drastically higher yields are observed when complex **3** is used over dichloride **2** in sp^2-sp^3 Suzuki, Buchwald-Hartwig amination, and Heck couplings. This highlights the importance of choosing an appropriate Ni source for reaction screening and the value of an alternative, air-stable Ni source to replace dichloride **2**. The reason(s) why precatalyst **3** outperforms **2** in several cases remains unclear, however. Given the rapidly expanding area of Ni-catalyzed cross-coupling in both academic and industrial settings and the upcoming commercial availability of **3**,[13] we expect that this novel precatalyst will see rapid uptake and further accelerate the development of the field.

ASSOCIATED CONTENT

Supporting Information

Text, figures, and tables with experimental protocols for the synthesis of **3** and catalytic experiments. 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 interests.

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ABBREVIATIONS

PPh$_3$ = triphenylphosphine; PCy$_3$ = tricyclohexylphosphine; dppp = 1,3-bis(diphenylphosphino)propane; dppf = 1,1’-bis(diphenylphosphino)ferrocene; SiPr•HCl = 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride; dcppb = 1,4-bis-(dicyclopentylphosphino)butane tetrafluoroborate; TESOTf = triethylsilyl triflate; DIPEA = diisopropylethylamine; MeObpy = 4,4’-dimethoxybipyridine; CPME = cyclopentylmethyl ether.

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