Stable, Well-Defined Nickel(0) Catalysts for Catalytic C–C and C–N Bond Formation

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Supporting Information Placeholder

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ABSTRACT: The synthesis and catalytic activity of several classes of NHC–Ni(0) pre-catalysts stabilized by electron-withdrawing alkenes are described. Variations in the structure of fumarate and acrylate ligands modulate the reactivity and stability of the NHC–Ni(0) pre-catalysts and lead to practical and versatile catalysts for a variety of transformations. The catalytic activity and efficiency of representative members of this class of catalysts have been evaluated in reductive couplings of aldehydes and alkynes and in *N*-arylations of aryl chlorides.

Nickel catalysis has a long history with many significant developments in C–C and C–heteroatom bond forming processes, and a surge of interest has occurred in recent years.[1] Catalysts with phosphine, amine, or *N*-heterocyclic carbene (NHC) ligands are common, as they are catalyst precursors in the Ni(0) or Ni(II) oxidation state. Ni(II) precursors, such as Ni(acac)$_2$ and nickel halide salts, are commonly employed in combination with phosphine- or amine ligands.[1] Keys to the success of these processes are that the ligands themselves are quite stable, avoiding the additional complexity of deprotonating NHC salts during pre-catalyst activation. In addition to these methods for *in situ* catalyst generation, well-defined Ni(II) complexes of phosphines and amines are commercially available and effectively employed in many catalytic processes.[2,3]

While phosphine and amine ligands promote many classes of nickel-catalyzed processes, NHC–Ni catalysts provide improved catalytic activity and complementary selectivities in many classes of reactions. Ni(0) catalysts of NHC ligands are most commonly prepared *in situ* from Ni(COD)$_2$. Although many NHC–Ni(II) complexes are known, in comparison to amine and phosphine supported Ni(II) pre-catalysts the corresponding NHC complexes are less frequently employed.[2,4] In general, Ni(0) complexes of NHC ligands display greater sensitivity to metal-ligand stoichiometry and catalyst purity than their amine and phosphine counterparts, and the strong σ-donating character of the NHC ligands can lead to inefficiencies in the reduction to catalytically-active Ni(0) or Ni(I) forms. Therefore, discrete NHC–Ni(0) catalysts are highly desirable based on their activity, but current limitations in their accessibility and stability ultimately limit their overall use. In order to address these concerns, we envisioned that a class of air-tolerant, easily accessible, and highly active NHC–Ni(0) complexes with well-defined metal-ligand stoichiometry and structure would be of broad utility. There are currently no catalysts available that meet all of these criteria. Our studies to address this challenge are described herein.

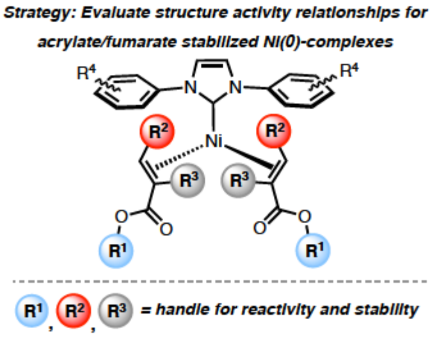

Figure 1. General strategy for pre-catalyst design.

Towards the goal of accessing stable NHC–Ni(0) complexes with high activity, a promising class of catalysts is Ni(0) complexes with a single NHC and two stabilizing dimethyl fumarate (DMFU) ligands.[5] Complexes of this type display remarkable stability, with little degradation upon exposure to air for several months.[5] The IPr variant of this catalyst family has been previously described in the context of alcohol oxidations,[6] but our preliminary studies of DMFU catalysts illustrated that their reactivity in most classes of C-C and C-N bond-forming processes was too sluggish to be preparatively useful (with Kumada couplings being an exception). While other types of NHC–Ni(0) complexes such as bis-olefins like 1,5-hexadiene[7], vinylsilanes,[8] styrene,[9] and norborene[10] as well as

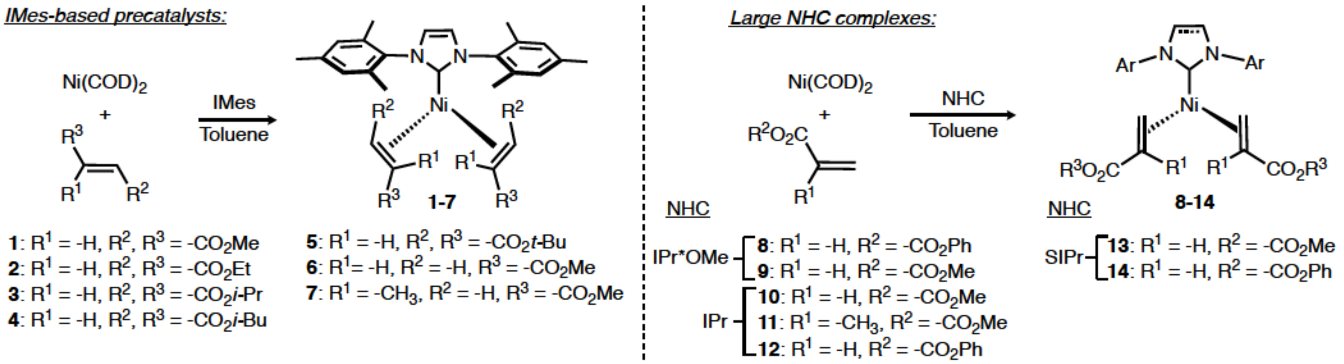

Figure 2. Synthesis and scope of (NHC)Ni(bis(acrylate/fumarate)) complexes.

η^6-arene complexes,[11] display attractive reactivity, we envisioned that carefully tuning fumarate and acrylate ligands might uncover new catalyst types that display improved stability and catalytic performance (Figure 1). Additionally, the key role that π-acidic additives play in governing rate-limiting steps in catalysis suggested that precatalyst properties could be optimized by such an approach.[12,13]

Given the widespread use of IMes-based nickel catalysts, we first assessed how modulating steric and electronic properties of fumarate and acrylate ligands impact stability and reactivity of IMes–Ni(0) complexes (**1-7**, Figure 2). Driven by the hypothesis that steric interactions with IMes at the nickel-center would facilitate dissociation of the π-acidic ligand, a systematic approach was taken to increase the steric bulk of the ester moiety of the fumarate ligands. IMes–Ni(0) fumarate complexes **1-5** and acrylate and methacrylate complexes **6** and **7** were synthesized in good yields as red/orange crystalline solids by ligand substitution from Ni(COD)$_2$ (Figure 2). The structure of **5** was confirmed by X-ray diffraction, and resembles a similar general structural motif as previously described for **1** (Figure 3a).[5] Although acrylate ligands have been reported to form phosphine–Ni(0) complexes in the past,[14] the only prior report of this strategy for NHC–Ni(0) complexes was described by our group. In this work, the benefits of employing discrete methacrylate-stabilized pre-catalysts versus *in situ* protocols was described in the context of skipped diene synthesis.[15]

Although IMes-supported nickel catalysts are useful for a variety of transformations, larger NHC ligands are typically necessary for more challenging cross-coupling reactions. The synthetic protocol for the complexes in the IMes-series could also be applied to complexes bearing a variety of sterically hindered NHC ligands. Specifically, IPr*OMe,[16] IPr, and SIPr complexes were targeted given their value in a broad range of transformations.[4i] Whereas the IMes-series tolerated a range of fumarates, bulkier fumarates were not permitted in the case of the larger NHC ligands, presumably as a result of the increased steric demand at the metal center. Of the larger NHCs tested, IPr was the only ligand to tolerate DMFU,[5,6] whereas these complexes were not cleanly obtained for IPr*OMe and SIPr.

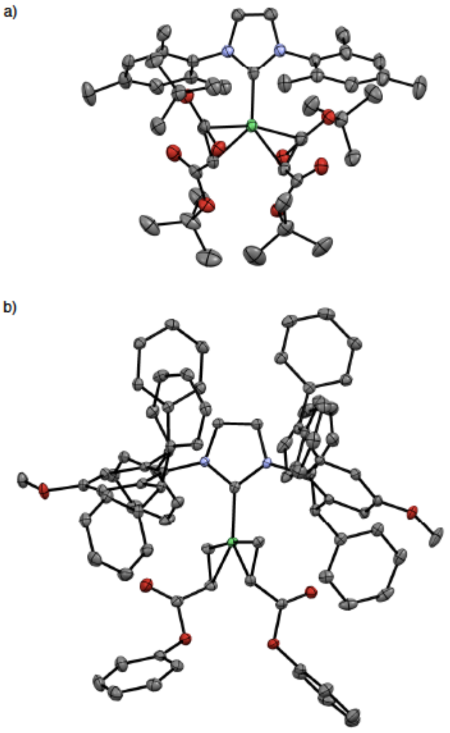

Figure 3. ORTEP diagrams of a) **5** and b) **8** with thermal ellipsoids at 50 % probability. Hydrogens have been omitted for clarity.

With these limitations in mind, a subset of acrylates, including methyl methacrylate, methyl acrylate, and phenyl acrylate were tested as ligands for more sterically demanding NHC ligands. Interestingly, for IPr*OMe, methacrylates were not tolerated for steric reasons, but phenyl and methyl acrylate formed stable crystalline complexes, **8** and **9**, respectively. The steric implications of IPr*OMe can be seen in the X-ray structure of **8** (Figure 3b). Likewise, IPr and SIPr both formed stable complexes of phenyl and methyl acrylate (**10**, **12**, and **14**, Figure 2), but they also formed stable complexes of methyl methacrylate, which was used to prepare IPr complex **11**.

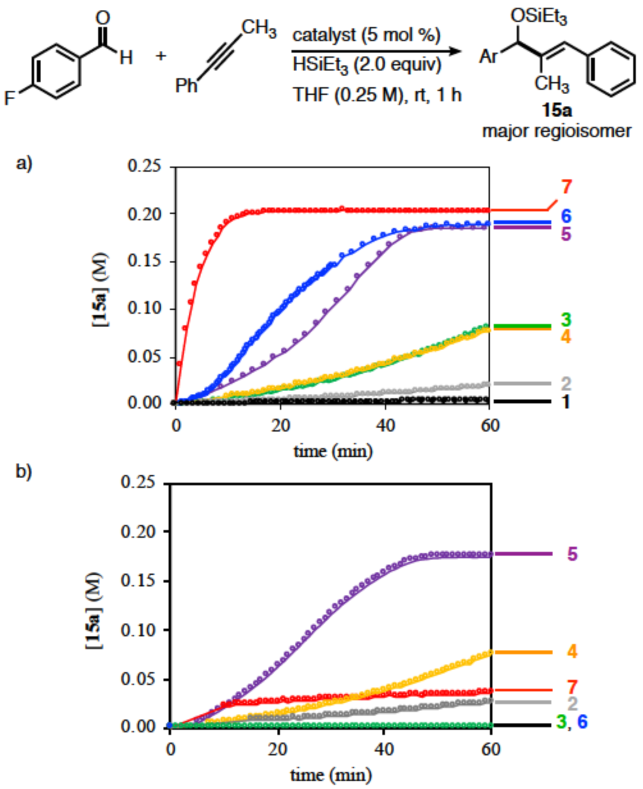

Figure 4. Reaction progression analysis of reductive coupling shown at top: a) Activity for precatalysts **1**-**7**. b) Activity for precatalysts **1**-**7** after being exposed to air for 24 hours. All reactions were monitored by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.

To explore the activity of these new catalysts, the silane-mediated reductive coupling of aldehydes and alkynes was used as an initial model reaction to determine how differentiating the nature of the π-accepting ligands impacted the catalytic activity and stability of complexes **1**-**7**. The mild nature of these reaction conditions represents a challenging environment for pre-catalyst activation compared to examples that include strong nucleophiles, transmetalating agents, or high temperatures, which are often necessary for the activation of other stable nickel pre-catalysts.[3a,f] Furthermore, this transformation has been demonstrated on complex chemical frameworks where well-defined pre-catalysts could have a large impact on the efficiency of these types of reactions.[17] The coupling of 4-fluorobenzaldehyde, 1-phenyl-1-propyne, and triethylsilane was conducted because product (**15a**) formation could be easily evaluated by ^{19}F NMR (Figure 4). Real time monitoring of the reaction allows an evaluation of important metrics including initiation rates and reaction progression.

Complexes **2**-**7** were all competent pre-catalysts for aldehyde-alkyne reductive couplings. However, complex **1**, with DMFU ligands, promoted the formation of only trace amounts of product after 1 hour. This is likely due to the high stability of this complex, which compromises catalytic activity. There is a direct relationship between the rate of product formation and the steric profile for the fumarate series (**1**-**5**, Figure 4a). Among the set of fumarate ligands, complex **5**, possessing di-*tert*-butyl fumarate ligands, exhibited the fastest rates and best overall performance. In the acrylate series (**6** and **7**, Figure 4a), the methyl methacrylate complex **7** exhibited superior performance compared with the acrylate complex **6**. The activity of complex **7** is the highest of any of the IMes-based nickel complexes in this class of reactions.

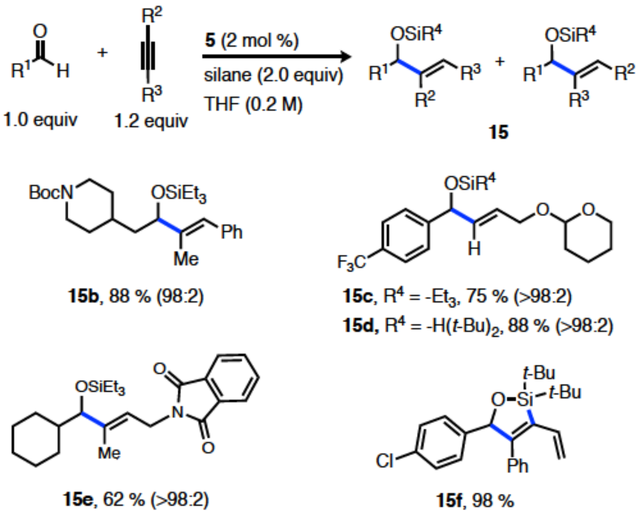

Figure 5. Substrate scope for reductive couplings. All yields are isolated.

Although the long-term air-stability of **1** has been well-documented,[5] as shown in Figure 4a, the stability clearly comes at the expense of catalytic activity. While the catalytic reactions were all performed under an inert atmosphere, the ability to handle and weigh the catalysts on a benchtop open to air is the key determinant of practical utility. To evaluate this key benchmark for catalysts **2**-**7**, the complexes were weighed into reaction vials and left exposed to air for 24 hours. The reactions were then assembled in an inert atmosphere and monitored by ^{19}F NMR (Figure 4b). Interestingly, the fumarates maintained their activity, and in most cases, the reaction progression plots overlay with those obtained with catalysts that were exclusively handled through glovebox manipulations (Figure 4a). However, the catalytic competency of the acrylate complexes was compromised through oxidative decomposition of the catalysts (**6** and **7**, Figure 4b). Based on these results, pre-catalyst **5** is the optimal catalyst in this reaction class where handling and weighing the catalyst in air is an important consideration. Alternatively, when optimum catalyst performance and fast initiation under very mild conditions are the primary considerations, catalyst **7** offers advantages in these respects. Catalyst **7** exhibits higher reactivity than catalysts prepared by a traditional *in situ* protocol using Ni(COD)$_2$, especially at low catalyst concentrations (see Supporting Information).

Several examples of reductive couplings (**15b**-**f**) are shown in Figure 5 to demonstrate the utility of **5** as a pre-catalyst. It should be noted that the catalyst loading can be reduced to 2 mol %, which is a lower than typically used in this reaction class.[18] Aliphatic aldehydes work well as shown in **15b**, which also demonstrates the tolerance of protected amines in this chemistry. Additionally, both triethylsilane and di-*tert*-butylsilane can be used, as shown in **15c** and **15d**. Under these mild reaction conditions aryl chlorides were also tolerated (**15f**), which is interesting as Ni(0) is typically capable of activating aryl chlorides.[1,19]

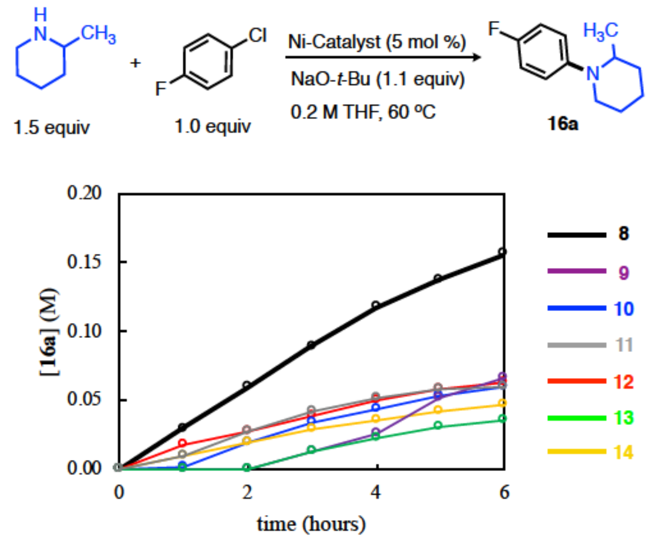

Figure 6. Reaction progression analysis for precatalysts **8-14**. All reactions were monitored by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.

Next, in order to explore the bulkier classes of NHC ligands, which are optimal for C–N couplings,[4b-d,f] complexes **8-14** were tested in the amination of 1-chloro-4-fluorobenzene with 2-methylpiperidine. As shown in Figure 6, complexes **8-14** were all suitable pre-catalysts for aryl chloride amination, but several striking comparisons can be made regarding choice of NHC and stabilizing ligand. It is clear from the graph in Figure 6 that IPr*OMe was optimal for this coupling reaction, but interestingly complex **8** with phenyl acrylate ligands was significantly more reactive than **9,** which possesses methyl acrylate as the stabilizing ligand. Furthermore, there was a significant induction period observed in the reactions using catalyst **9**, **10**, or **13**, all derived from methyl acrylate. Regardless of the NHC ligand used, phenyl acrylate appears to be an optimal choice of stabilizing ligand as the complexes participate in C–N couplings with little to no induction period observed. A similar air-stability test as described for the IMes-Ni(0) series was performed, and it revealed that **8** fully retained its activity after being exposed to air for 1 h then stored under a blanket of nitrogen for 24 h (See Supporting Information). Furthermore, catalysts of IPr and SIPr promoted significant amounts of protodechlorination by-products, whereas IPr*OMe catalysts were more selective for the desired C–N formation. Based on the catalyst stability, fast initiation, excellent rates of catalysis, and selectivity for C–N bond formation over reduction, catalyst **8** is the optimal catalyst among those examined in aryl chloride aminations.

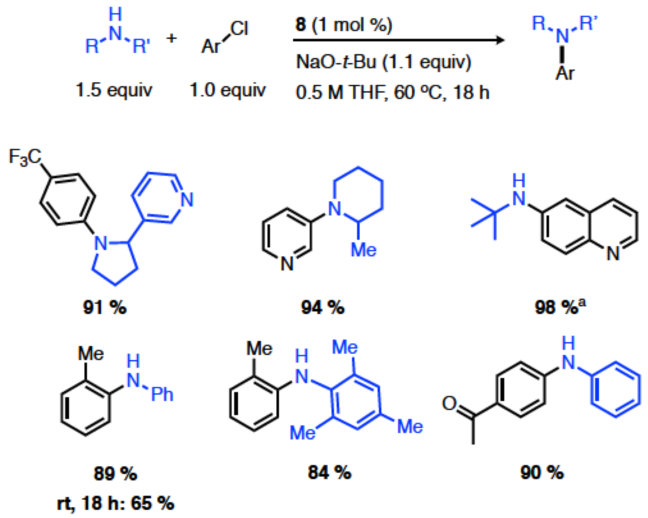

Figure 7. Substrate scope for amination of aryl chlorides. Yields reported are isolated. [a]Reaction run at 45 °C.

The activity of pre-catalyst **8** is highlighted (Figure 7) by the low catalyst loadings (1 mol %) needed to achieve high yields in aminations (**16b**, **d-h**, 84-98 % yield), whereas *in situ* protocols typically require higher loadings due to inefficiencies in assembly of the active catalyst form. As shown in Figure 7, a wide variety of sterically hindered amines were tolerated. Hindered and potentially chelating 2-pyridyl-pyrrolidines could be coupled effectively, although yields drop as the steric profile and electron-rich character of the aryl chloride increases (**16b** versus **16c**). Most notably, amines that lack β-hydrogens were reactive with pre-catalyst **8** (**16d**, **e**, **g**, **h**) even at room temperature (**16d**). This class of substrates is typically challenging for other Ni(II)-based pre-catalysts that rely on β-hydride elimination for pre-catalyst activation.[4d,20,21] Furthermore, *tert*-butyl amine and 2,4,6-trimethylaniline, both sterically hindered and lacking β-hydrogens, participate in *N*-arylations of *ortho*-substituted (**16g**) or N-heterocyclic (**16e**) aryl chlorides. Additionally, our catalyst effects chemoselective *N*-arylation of a substrate containing a methyl ketone (**16h**), which can potentially undergo competitive nickel-catalyzed α-arylation.[4d]

In summary, careful matching of *N*-heterocyclic carbene donor ligands and π-accepting stabilizing ligands leads to a versatile series of stable and highly reactive NHC–Ni(0) pre-catalysts. The catalysts prepared provide rare examples of Ni(0) complexes that tolerate air exposure while retaining a high degree of reactivity in catalytic processes. The modular strategy for catalyst synthesis enables stabilization of a wide range of NHC-Ni(0) complexes, with the continuum of stability and reactivity being easily tuned according to the precise catalyst properties needed for a specific application. While the demonstrations in this study focused on aldehyde-alkyne reductive couplings and C–N bond formations, we anticipate that the catalysts described in this work will be suitable for a wide array of Ni(0)-catalyzed processes.

ASSOCIATED CONTENT

Supporting Information. Experimental and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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