Bench-Stable \( \textit{N} \)-Heterocyclic Carbene Nickel Precatalysts for C–C and C–N Bond-Forming Reactions

Felix Strieth-Kalthoff,\textsuperscript{[a, b]} Ashley R. Longstreet,\textsuperscript{[a, c]} Jessica M. Weber,\textsuperscript{[a]} and Timothy F. Jamison*\textsuperscript{[a]}

Homogeneous nickel catalysis has evolved into a powerful and versatile tool for organic synthesis.\textsuperscript{[1]} The particularly attractive properties of nickel extend beyond its low price compared to palladium, and include its ability to undergo facile oxidative addition\textsuperscript{[2]} and high binding affinity towards unsaturated systems,\textsuperscript{[3]} along with flexibility in accessing II oxidation states.\textsuperscript{[1a]} The development of \( \textit{N} \)-heterocyclic carbene (NHC) ligands\textsuperscript{[4]} initiated remarkable progress in this field.\textsuperscript{[5]} Controlled by the electron-rich, highly-shielded metal center, Ni–NHC systems have proven effective in a variety of transformations, including challenging cross-couplings,\textsuperscript{[6]} cycloadditions,\textsuperscript{[7]} C–H activation of olefins\textsuperscript{[8]} and arenes,\textsuperscript{[9]} and (hydro-)functionalization of olefins.\textsuperscript{[10]}

The majority of the abovementioned transformations use [Ni(cod)]\textsubscript{2} (cod = 1,5-cyclooctadiene) as the nickel source. Both [Ni(cod)]\textsubscript{2} and free NHCs demonstrate severe sensitivity towards oxygen and moisture and thus require a glovebox for storage and handling. In order to combat this sensitivity, a number of researchers have investigated various strategies\textsuperscript{[11]} including the formation of stable nickel(II) complexes. Nolan\textsuperscript{[12]} and Snieckus\textsuperscript{[13]} independently demonstrated in 2005 the use of Cowley’s \( \eta^3 \)-cyclopentadienyl NHC-complex 1\textsuperscript{[14]} (Scheme 1a) as an effective, bench-stable Ni-precatalyst for aryl aminations and Kumada cross-couplings, respectively. Matsubara also demonstrated the use of NHC-phosphine Ni-precatalyst 2 for Kumada cross-couplings in 2006.\textsuperscript{[15]} While these precatalysts perform well with reactions such as Suzuki and Kumada cross-couplings\textsuperscript{[16]} and hydroisilylations,\textsuperscript{[17]} reactions are limited when a strong reductant is absent and often require high temperatures. For Ni-catalyzed aminations, Nicasio demonstrated how mild conditions and a broader substrate scope are obtainable with \( \eta^1 \)-allyl complex 3,\textsuperscript{[18]} presumably by opening up an SN2' reaction.

Herein, we introduce a new class of bench-stable \( \textit{N} \)-heterocyclic carbene (NHC) nickel-precatalysts for homogeneous nickel-catalysis. The nickel(II) complexes are readily activated to Ni\textsuperscript{0} in situ under mild conditions, via a proposed Heck-type mechanism. The precatalysts are shown to facilitate carbonyl-ene, hydroalkenylation, and amination reactions.

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pathway for facile precatalyst activation from Ni(II) to Ni(0). However, the stability of the complex in air was sacrificed for this enhancement. The Doyle and Monfette groups reported an air-stable (TMEDA)Ni(o-tolyl)Cl (TMEDA = tetramethylethylenediamine) precatalyst featuring a labile TMEDA that enables a variety of ligands such as phosphines, diimines and NHCs to be used. While this provides a flexible, modular approach to the formation of the active catalyst, the generality of the precatalyst is limited by its inability to be activated at room temperature.

Our group has previously developed a series of Ni-precatalysts (4) bearing phosphine ligands (Scheme 1b). The complexes provide facile access to catalytically active Ni(0) in the presence of silyl triflates. The reduction of 4 from Ni(II) to Ni(0) is suggested to occur by transmetallation with an additional equivalent of 4 followed by reductive elimination, thus only activating 50% of the material (Scheme 1b).

Herein, we describe a new NHC Ni-precatalyst design (5, Scheme 1c) that readily reduces to the catalytically active Ni(0) species for reactions such as the Ni-catalyzed carbonyl-ene, hydroalkenylation, and amination reactions. This design inspired by the previous phosphine complexes (4) by containing an aryl ligand with the addition of a piperidine moiety to satisfy the coordination sphere. An olefin was also appended to the complex to facilitate the reduction of Ni(II) to Ni(0) by an intramolecular Heck reaction.

The investigation began by synthesizing the NHC-Ni complexes with IPr as the NHC and a bidentate aryl ligand (Table 1). The complexes were each prepared by oxidative addition of the corresponding aryl chloride to a pre-formed solution of [(IPr)Ni(cod)]2 in a glovebox. The new complexes were initially synthesized with X-acceptors trans to the strong σ-donating carbene, such as pyridines (8–10), an imine (11), and a phosphite (12), because it was thought necessary for obtaining stable complexes (Table 1, Entries 1–5).

Unexpectedly, stable motifs could also be obtained in the absence of strong X-acceptors using amine ligands trans to the NHC. Whereas acyclic amines did not afford stable complexes (Entry 6), morpholine-12), because it was thought necessary for obtaining stable complexes (Table 1, Entries 1–5). Unexpectedly, stable motifs could also be obtained in the absence of strong X-acceptors using amine ligands trans to the NHC. Whereas acyclic amines did not afford stable complexes (Entry 6), morpholine-12), because it was thought necessary for obtaining stable complexes (Table 1, Entries 1–5). Unexpectedly, stable motifs could also be obtained in the absence of strong X-acceptors using amine ligands trans to the NHC. Whereas acyclic amines did not afford stable complexes (Entry 6), morpholine-12), because it was thought necessary for obtaining stable complexes (Table 1, Entries 1–5).

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15 continued to increase to 30% over seven days. After evaluating a series of complexes with appended olefins with varying linker lengths (Entries 10–12), complex 5a (Entry 12) was determined to be an effective precatalyst for the carbonyl-ene reaction producing 7a in 93 % in situ yield after 48 h.

With the success of complex 5a as a precatalyst, an investigation into the possible modes of precatalyst activation was undertaken. We hypothesized that by appending an olefin to the NHC-complex, activation via an intramolecular Heck-reaction could occur. Indeed, styrene 6 was confirmed to be present by comparing a prepared standard to GC traces and 1H NMR spectra of the crude reaction mixtures (Scheme 2). By-products that would form by an intermolecular Heck or a mechanism of activation similar to precatalyst 4 were not observed by GC/MS. The necessity of the olefin was further verified by the lack of reactivity observed when complex 18 bearing only the alkyl side chain was used (Table 2, Entry 13).

As shown in the product profile for the carbonyl-ene reaction, precatalyst 5a even outperformed the previously reported catalytic system with [Ni(cod)]2/IPr by providing an improved turnover number (TON) at identical catalyst loading (Figure 1). After an induction period for ca. 1 h, the reaction with 5a produced a catalyst with greater catalytic activity than the reaction with [Ni(cod)]2/IPr, which resulted in a higher product yield. Heating the reaction with precatalyst 5a to 50°C did lower the reaction time to 4 h with only a 6–8 % drop in yield (See Supporting Information for details). As an added benefit, no decrease in yield of 7a was observed even after precatalyst 5a was stored on a benchtop at room temperature for over a month. Because cod was demonstrated to impede reaction yields in earlier reports, the carbonyl-ene reaction with precatalyst 5a was performed with cod (0.6 equiv) to determine its effect. Indeed, the product yield was suppressed in the presence of cod, with a dramatic 70 % decrease in yield relative to the use of 5a without cod at the same 48 h time point.

With these findings in mind, a comparison between precatalyst 5a and [Ni(cod)]2/IPr with other substrates was performed under otherwise unaltered reaction conditions (Table 3). In all cases, comparable or improved yields with 5a were observed. While remarkable improvements in yield for electron deficient aldehydes were observed (Table 3, Entries 4–5), substrates from sterically hindered alkenes still proved to be challenging (Entry 6).

After establishing 5a as a valuable precatalyst for the carbonyl-ene reaction, we next aimed to demonstrate its potential in the Ni-catalyzed hydrovinylation of α-olefins (Table 4). For substrates prepared from styrene (19a) or 2-vinylphenylhale (19b), precatalyst 5a provided similar or slightly improved...
Table 3. Reductive, three-component coupling of aldehydes, α-olefins and silyl triflates.

| Entry | Product | R’ | R’’ | Yield of 7 [%] | [Ni(cod)]2/IPr or 5a (30 mol %) | P(OPh)3 (45 mol %) | EtLi (8 equiv) | PhMe, rt; 4 h | + isomers |
|-------|---------|----|-----|--------------|---------------------------------|-------------------|----------------|----------------|-----------|
| 1     | 7a      | n-hexyl | phenyl | 73[a]      | 93[a]                           |                   |                |                |           |
| 2     | 7b      | phenyl  | p-anisyl | 62       | 56                              |                   |                |                |           |
| 3     | 7c      | benzyl  | p-anisyl | 79       | 75                              |                   |                |                |           |
| 4     | 7d      | n-hexyl | 2-furfuryl | 10      | 69                              |                   |                |                |           |
| 5     | 7e      | n-hexyl | p-chlorophenyl | 41     | 78                              |                   |                |                |           |
| 6     | 7f      | t-butyl | p-anisyl | 4        | 5                               |                   |                |                |           |

[a] Determined by 1H NMR against an internal standard (nitromethane).

[b] Determined by GC against a calibrated internal standard (dodecane, 10 mol%).

Table 4. Tail-to-tail hydrovinylation of olefins with [Ni(cod)]2/IPr or precatalyst 5a.

| Entry | Product | R’ | R’’ | Yield of 19 [%] | [Ni(cod)]2/IPr or 5a (6 mol %) | p-anisaldehyde (5 mol %) | 1-ocetene (10 mol %) | Et3SiOTf (10 mol %) | NEt3 (30 mol %) | PhMe, rt; 24 h | + isomers |
|-------|---------|----|-----|--------------|---------------------------------|-------------------------|-------------------|-------------------|----------------|---------------|-----------|
| 1     | 19a     | phenyl | n-hexyl | 81        | 79                              |                         |                   |                   |                |               |           |
| 2     | 19b     | 2-naphthyl | n-hexyl | 53       | 65                              |                         |                   |                   |                |               |           |
| 3     | 19c     | p-fluoro-phenyl | p-fluoro-phenyl | 24   | 65                              |                         |                   |                   |                |               |           |

[a] Isolated yields.

The additions of p-anisaldehyde, 1-ocetene, and Et3SiOTf were doubled.

Scheme 3. Aryl amination with precatalyst 5a.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: homogeneous catalysis · hydroalkenylation · N-heterocyclic carbene ligands · nickel · precatalyst

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