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Bimetallic Nickel Aluminun Mediated *Para*-Selective Alkenylation of Pyridine: Direct Observation of η^2,η^1-Pyridine Ni(0)−Al(III) Intermediates Prior to C−H Bond Activation

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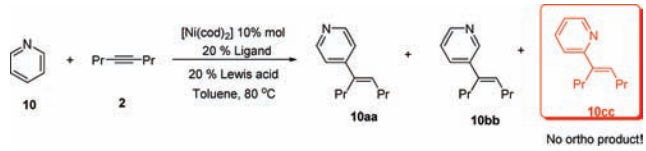
Abstract: We have presented new amino-NHC Ni−Al complex mediated para C−H bond activation for pyridine and quinolin, and isolated for the first time the intermediate structure of a bimetallic η^2,η^1-pyridine nickel aluminum complex prior to its C−H activation, which serves as key evidence for bimetallic catalysis.

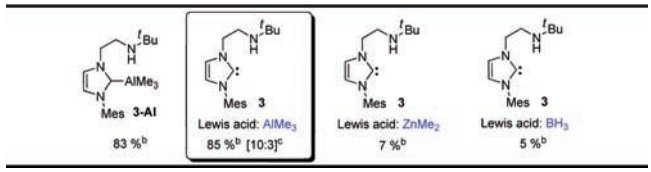
Transition-metal-catalyzed aromatic C−H bond functionalization constitutes a hot area of research,[1] representing an economical and greener synthetic platform for the assembly of biologically and industrially relevant aromatic molecules. Recent elegant work by Hiyama's group utilizes bifunctional catalysts consisting of nickel and a Lewis acid to derivatize the C−H bond of heterocyclic compounds.[2] This is in contrast to the conventional protocol relying on the assistance of directing groups to facilitate C−H bond transformations.[3] Nonetheless, the exact synergistic effect invoked by this bimetallic complex and its reaction pathway remain an enigma. The employment of N-heterocyclic carbenes (NHCs) in metal mediated C−H activation is still very much in its infancy,[4] despite its ubiquity in homogeneous transition metal catalysis. We wish to report the *para* C−H bond activation of pyridine and quinoline using amino-linked NHC **3** as a supporting platform for a Ni−Al bimetallic catalyst. This offers a complementary approach different from the general *ortho*-selectivity observed via directing functional groups.[5] Furthermore, providing a key to unlock the complexity of this chemistry, an intermediate has been successfully isolated prior to the C−H bond cleavage and is characterized as an η^2,η^1-Pyridine Ni(0)−Al(III) complex.

The results of our initial investigation of the alkenylation of pyridine (**10**) by 4-octyne (**2**), using 20 mol % $AlMe_3$-amino-NHC (**3-Al**)[6] in the presence of 10 mol % Ni[COD]$_2$ at 80 °C, are outlined in Table 1. To our delight, the desired coupling products **10** were obtained in good yield (83%). A similar catalytic yield could also be achieved by adding all of the necessary components *in situ* without resorting to the preparation of complex **3-A1**. Detailed NMR spectroscopic analysis into the distribution of the products revealed a 10:3 ratio of **10aa** and **10bb**[7] with no detection of *ortho* product **10cc**. Substitution of $AlMe_3$ for other Lewis acids, such as $ZnMe_2$ and BH_3, yielded only disappointing outcomes.

With the optimized reaction conditions in hand, we further studied the scope and limitations of the dual catalyst Ni-$AlMe_3$ (Table 2). Excellent *para*-regioselectivity was observed for 2-picoline (**11**), 3-picoline (**12**), and methoxypyridine derivatives (**15**) and (**16**). However, diminishing yields were witnessed for 4-picoline

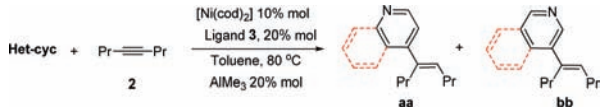
Table 1. Direct *Para* and *Meta* Alkenylation of **10** with **2** Mediated by Nickel-Lewis Acid Supported by Amino Pendant Linked NHC[a]

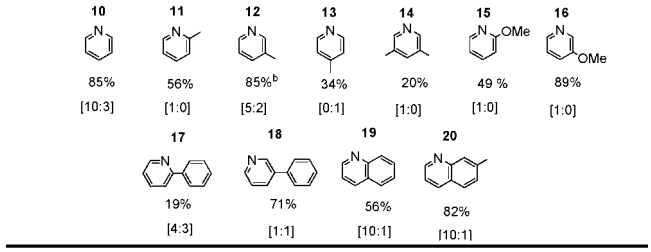




[a] The reactions were carried out using **10** (1 equiv) and **2** (2 equiv) determined by ^{1}H NMR analysis. [b] Isolated yield based on heterocyclic substrate as the limiting reagent. [c] *Para/meta* selectivities are in brackets.

Table 2. Expanded Scope of Nickel-$AlMe_3$ Amino-NHC **3** Mediated C-4/C-3 Alkenylation of Heterocyclic Compounds (Het-cyc)[a]





[a] The reactions were carried out using **1** (1 equiv) and **2** (2 equiv) and determined by ^{1}H NMR analysis. Isolated yields are based on the heterocyclic substrate as the limiting reagent. *para:meta* selectivities are in brackets. [b] 3 equiv of **2** was used in this reaction.

(**13**) and 3,5-lutidine (**14**), suggesting sensitivity of the reaction toward a steric environment. 3-Phenylpyridine (**18**) gave approximately equal amounts of *para* and *meta* functionalization with a satisfactory yield of 71%. The electron-withdrawing effect of the phenyl group may lead to greater *meta* activation. Quinoline (**19**) and 6-methylquinoline (**20**) also participated in the catalytic reaction, giving mostly *para*-alkenylated products in good yields. It is worth noting that the C−H transformations of the phenyl-pyridine and quinoline derivatives proceeded exclusively on the pyridyl ring, which is in sharp contrast to other reported examples.[8]

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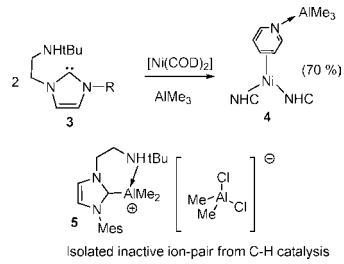
Scheme 1



Isolated inactive ion-pair from C-H catalysis

In order to gain more insight into the regioselectivity and mechanism of this reaction, Ni[COD]$_2$ was treated stoichiometrically with **3-Al** and pyridine at room temperature. **3-Al** was completely consumed within a few hours (Scheme 1), and a new nickel complex (**4**) was formed as a single organometallic product.[9] The structure of **4** was unambiguously confirmed by X-ray crystallography (Figure 1), displaying a three-coordinate nickel (0) σ-bound to two amino-NHCs with normal bond lengths of 1.8949(8) and 1.9224(17) Å. One η^2-bound pyridine (via C3−C4 of the ring) completes the coordination sphere of Ni. The long bond length of C39−C40 (1.455 Å) signifies a high degree of π-back-donation from the metal to the pyridine moiety. Interestingly, $AlMe_3$ is bridged to the nickel complex by coordination at the pyridine nitrogen (Al−N(7) 1.996(2)), illustrating the rationale for the *para*/*meta*-selectivity over *ortho*-selectivity in our system. Performing the reaction with pyridine using **4** in catalytic or stoichiometric amounts generated the alkenylated product in good yield, implying that **4** is not the resting state in the catalytic cycle. To our knowledge, this represents the first structurally isolated example of C−H bond activation via a synergistic effect played by a Ni−Al interaction, a proof of concept that Lewis acids augment the C−H acidity of the pyridine, as proposed by Hiyama.[2]

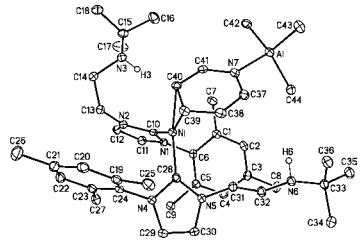
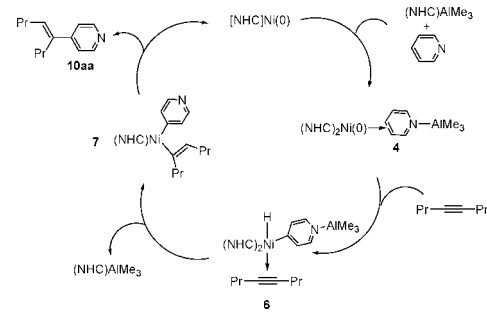


Figure 1. ORTEP diagram of Ni−Al complex **4** with ellipsoids drawn at 30% probability level. All other hydrogen atoms have been omitted for clarity.

Several observations in this reaction are worth mentioning. First, our examination of different Al adducts revealed an inverse relationship between the Al electrophilicity and the yield of the reaction.[10] ^{1}H NMR monitoring of the catalytic reaction employing $AlMe_2Cl$ as a Lewis acid shows the formation of a trace amount of species **5**, an aluminum ion pair that has been confirmed by single crystal X-ray analysis (Scheme 1).[9] Performing the catalytic reaction with **5** under similar conditions furnished a disappointingly low conversion (29%).[10] These findings suggest that the stronger Al-NHC binding and stable ion pair species may retard the formation of Ni-NHC and pyridine-Al species, key ingredients in the catalytic cycle. Second, we hypothesized that the hard donor amino side arm may have acted as a hemilable anchor, briefly stabilizing the reactive nickel center before being displaced by small molecule substrates. Control experiments using a series of classical unsaturated and saturated symmetrical NHCs lacking an amino side arm led to an average yield of 28%,[11] validating the importance of the amino side arm. Finally, a competition experiment was performed in order to obtain the kinetic isotope effect between the pyridine **10** and deuterated-**10**.[11] A small primary KIE of 1.25 indicates that the C−H bond breaking step is not the rate-limiting step of the reaction.[12] The result is consistent with the X-ray diffraction findings (*vide supra*) highlighting the importance of pyridine π-coordination prior to C−H bond activation.[13] On the basis of the above studies and the precedent reports, a mechanistic proposal of the present Ni−Al catalysis is depicted in Scheme 2. It can be assumed that addition of (NHC)$AlMe_3$ and pyridine leads to complex **4**. The following oxidative addition process is proposed to afford the Ni hydride intermediate **6** upon coordination of alkyne. The subsequent alkyne insertion and reductive elimination of the nickel pyridyl **7** would deliver the product **10aa** along with the generation of (NHC)Ni for the next catalytic cycle.

Scheme 2. Plausible Mechanism



In summary, we have presented a new amino-NHC Ni−Al system that mediates *para* C−H bond activation of pyridine and quinoline derivatives and have also isolated the structure of a bimetallic η^2,η^1-pyridine Ni(0)−Al(III) intermediate (**4**) prior to the C−H bond activation step. Further exploration of the synergistic bimetallic catalysis on the scope of the reaction and detailed mechanistic studies are ongoing in our laboratory, to be reported in due course.

Acknowledgment. This communication is dedicated to the memory of Professor Keith R. Fagnou. We are grateful to the Taiwan National Science Council (NSC: 97-2113-M-001-024-MY2) and Academia Sinica for their generous financial support. We also thank Prof. Dr. Pierre Dixneuf (University of Rennes) and Prof. Dr. Jennifer Scotts (Royal Military College of Canada, Kingston, Ontario) for helpful suggestions and discussions.

Supporting Information Available: Detailed experimental procedures, including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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