A Directive Ni Catalyst Overrides Conventional Site-Selectivity in Pyridine C–H Alkenylation

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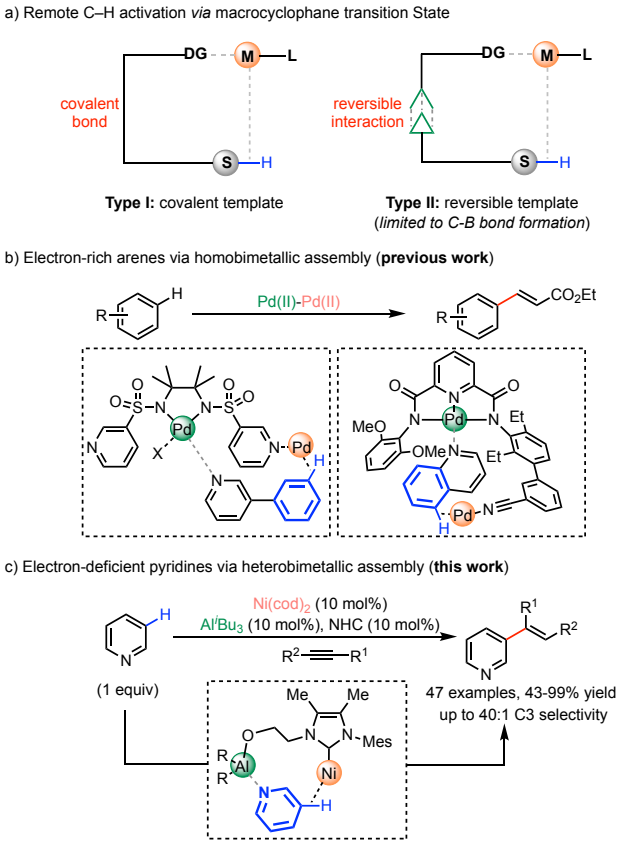
Supporting Information Placeholder

ABSTRACT: A remote C3–H activation of pyridine-containing substrates can be achieved with a directive Ni catalyst. The bifunctional NHC ligand incorporates an Al-binding side-arm that recruits and orients the substrate leading to the assembly of the requisite macrocyclophane transition state through reversible coordination. This assembly not only induces the reactivity of the otherwise unreactive Ni catalyst, but also overrides the intrinsic C2/C4 electronic bias of the Al-bound pyridine substrate, allowing for the first time, the C3 alkenylation of a variety of pyridine and heteroarene substrates as the limiting reagent.

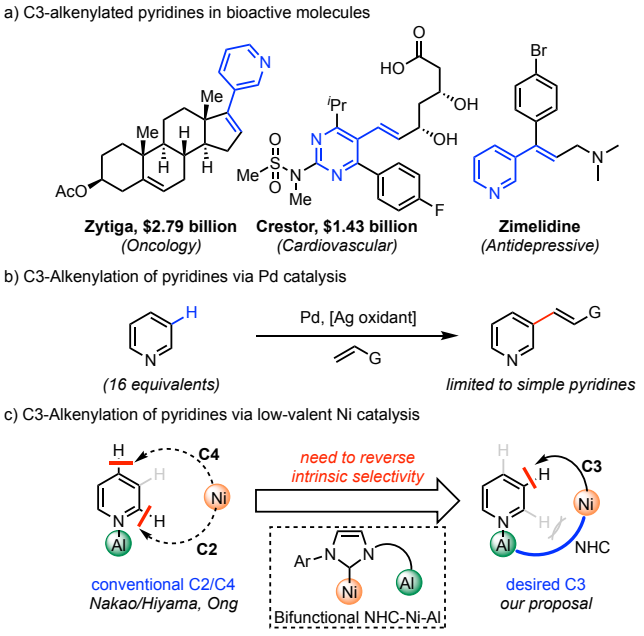
The ubiquity of C–H bonds in organic molecules and their often-marginal chemical differences renders the site-selective activation of C–H bonds an enduring challenge.[1] The directing approach bearing a covalent bond between a directing group and a substrate has proved to be a particularly promising strategy for proximate and increasingly for remote C–H bond activations (Type I, Scheme 1a),[2] In particular, the importance of distance and geometric considerations for tuning the macrocyclophane transition state has been demonstrated for predictable remote C–H activation.[3,4] However, this covalent template strategy faces practical challenges that impede synthetic application, where stoichiometric template use and separate template attachment and removal steps are required. To address these challenges, a reversible template-substrate anchoring strategy has been developed (Type II, Scheme 1a).[5] This strategy merges the role of template and ligand into a single bifunctional scaffold, renders the template catalytic and eliminates the extra steps required for template attachment/removal. Though attractive, this strategy has seen limited applications in the ability to catalyze wide-ranging functionalizations; success has so far been restricted to Ir-catalyzed remote C–H borylation through reversible interactions such as H bonding,[6] ion pairing[7] and Lewis acid coordination.[8] In contrast, direct C–C bond forming reactions of remote C–H bonds has been scarcely explored, partly attributed to lower reactivity and harsher conditions required. Addressing this limitation, our group has recently achieved the first example of remote C–C bond forming reaction *via* Pd–Pd homobimetallic catalysis, furnishing remote C–H alkenylation of relatively electron-rich arenes using the azine nitrogen as the template anchoring group (Scheme 1b).[9] Despite a step forward, the requirements of high loadings of Pd, template, ligand, and super-stoichiometric amounts of metal oxidants for catalyst turnover offer much scope for practical improvement. Moreover, electron-deficient pyridine and related derivatives—challenging substrates widely encountered in natural products and pharmaceuticals—remain incompatible in such a reaction. Herein, we report a Ni–Al heterobimetallic catalyst for the C3–H alkenylation of pyridines with alkynes, providing an atom-economical method for direct C–C bond formation without the need for external oxidants (Scheme 1c). Importantly, this manifold enables the use of pyridines as the limiting reagent for the first time, allowing the late-stage C3–H alkenylation of pyridine motifs in complex molecules. A bifunctional NHC was identified as the critical ligand, which recruits and positions the substrate *via* Al anchorage to the vicinity of the Ni catalyst. This directive ligand not only enables catalytic reactivity through substrate and ligand binding, but also reverses the conventional C2/C4 site-selectivity obtained in low-valent Ni-catalyzed C–H activation processes.

Scheme 1. Remote C–H Activation *via* Macrocyclophane Transition State



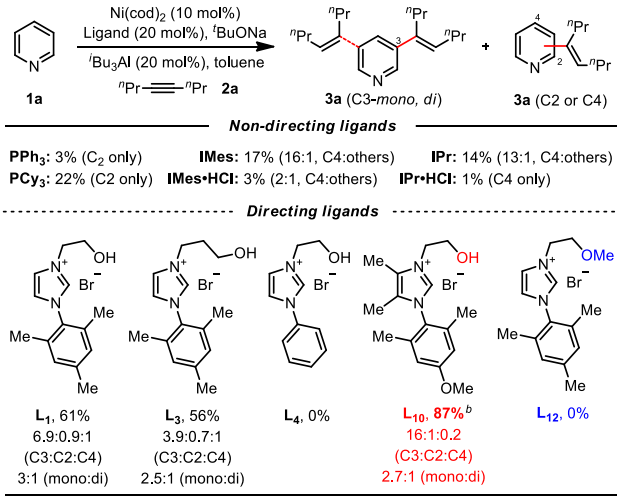
The C3-selective alkenylation of pyridine-containing heterocycles represents a desirable transformation in the realm of medicinal chemistry due to both its prevalence in pharmaceutical agents and its facile entry point to a range of functionalities (Scheme 2a).[10,11] However, the strong σ-coordinative ability of pyridines often poison metal catalysts, rendering the development of catalytic processes a formidable challenge. In 2011, we reported a Pd(II)-catalyzed C3–H alkenylation of pyridines,[12,13] which gave high C3 selectivity arising from an electrophilic palladation process (Scheme 2b). However, a large excess of pyridine substrate (16 equivalents) was required to achieve reasonable reactivity. This drawback also rendered this reaction incompatible with the late-stage functionalization of complex pyridine-containing substrates, where the large excesses required poses unfavorable resource, cost and solubility issues in a synthetic setting. In pioneering studies by Nakao and Hiyama,[14,15] coordination with Al Lewis acids was demonstrated to mask the pyridyl nitrogen, and polarized the pyridine ring to enhance the reactivity of C2/C4 positions towards nucleophilic low-valent Ni C–H oxidative addition. Prompted by this finding, we envisioned that a bifunctional carbene ligand could coordinate to both Ni and Al and form a heterobimetallic catalyst[16] directed towards the C3(5) position, thus achieving the Type II template approach (Scheme 1) and reversing the conventional C2/C4 selectivity (Scheme 2c).

Scheme 2. C3-Alkenylation of Pyridines[a]



We selected non-substituted pyridine (**1a**) and oct-4-yne (**2a**) as the model substrate and coupling partner to explore the necessary ligands and reaction conditions for this transformation. Preliminary results showed that traditional phosphines and NHC ligands were poorly reactive and, as expected, delivered the alkenylated product at the C2 or C4 positions exclusively (Table S1). As expected, the *in situ* formation of NHCs from their precursors led to significant decrease in reactivity, attributed to the generation and deleterious coordination of ^{t}BuOH to the Al Lewis acid. To our delight, we found that ligand $\mathbf{L_1}$ bearing a coordinating alkoxy group provided the desired mono-C3-alkenylated pyridine in moderate yields (33%, Table S1), overruling the intrinsic C2/C4 selectivity of the substrate. Notably, the observed reactivity for $\mathbf{L_1}$ could be obtained through the use of the imidazolium halide precursor, obviating the need for carbene pre-generation required in previous reports.[15a,b] Then we systematically surveyed a range of Al Lewis acids and varied the linker length on the ligand (Table S3 and S6). We found that best results were obtained by using Al^{i}Bu$_3$ as the anchoring Lewis acid, in conjunction with a two-carbon alkoxy side-arm ($\mathbf{L_1}$), improving the combined yield to 61% (Scheme 3). The importance of linker length was affirmed by the use of a homologated side-arm ($\mathbf{L_3}$), which resulted in both a reduction in yield and selectivity. Notably, the use of unsubstituted aryl NHC ligand ($\mathbf{L_4}$) was ineffective, inferring that the assembly of the putative macrocyclophane intermediate may be facilitated by conformational restriction. This observation was reinforced by the further incorporation of methyl groups onto the imidazolium backbone ($\mathbf{L_6}$, Table S6), which elevated the yield to 64% (10:1, C3:others). Additional tuning of the NHC aryl group revealed that the *para*-methoxy substitution was optimal ($\mathbf{L_{10}}$, 87%, *ca.* 16:1, C3:others, Scheme 3). Importantly, methylation of the coordinating alkoxy group completely shut down the reaction ($\mathbf{L_{12}}$, Scheme 3),[17] demonstrating that Al coordination by the ligand side arm was crucial for both the reactivity and the selectivity of this process. Further mechanistic evidence validating such a three-component assembly process was obtained by ^{1}H NMR studies, which showed that 3-phenylpyridine, AlMe$_3$ and ligand ($\mathbf{L_{10}}$) formed a new complex demonstrated by marked downfield shifts of H2, H3, and H6 of 3-phenylpyridine (Page S13 and S14). In addition, heating the aforementioned three-component complex under the reaction conditions led to the C3-alkenylation product in 34% (Page S15), supporting the productive role this ternary complex plays in this reaction.

Scheme 3. Ligand Optimization[a]

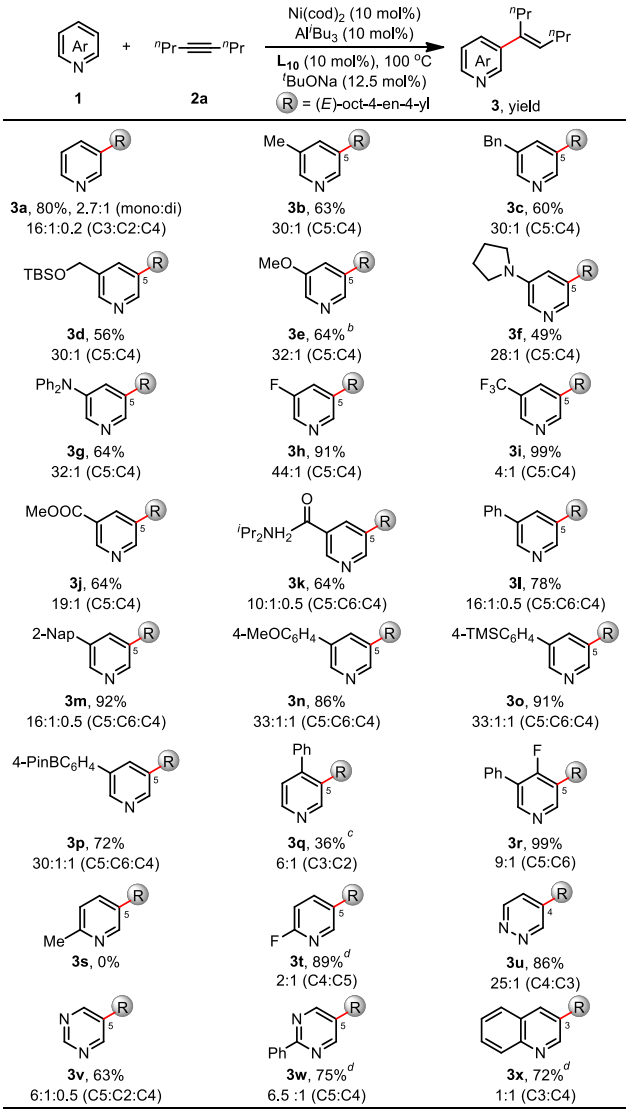


[a]Reaction conditions: **1a** (0.20 mmol), **2a** (0.6 mmol), toluene (0.5 mL); Ni(cod)$_2$, Ligand, ^{t}BuONa and toluene at 80 °C for 30 min, then pyridine, Al^{i}Bu$_3$ and alkyne substrate at 100 °C under N_2 for 12 h; yield of isolated mixed isomers; ratio of isomers determined by ^{1}H NMR. [b]$\mathbf{L_{10}}$ (10 mol%).

With the optimized conditions in hand, we proceeded to examine the scope of pyridines and other heteroarenes for this reaction (Scheme 4). Electron-donating substituents at C3 positions such as alkyls (**3b**, **3c**, **3d**), alkoxyl (**3e**) and amino groups (**3f** and **3g**) were compatible with the reaction, providing the corresponding products in 49% to 64% yield with the desired C5 selectivity (up to 30:1). It was pleasing to observe that increasing the electron density of the pyridine ring system tends to inhibit oxidative addition of the Ni(0) catalyst with C–H bonds. As expected, electron-withdrawing groups such as F (**3h**) and CF$_3$ (**3i**) significantly elevated the yield to 91% (44:1, C5:C4) and 99% (4:1, C5:C4), respectively. Though highly reactive, decreased C5 selectivity was observed for **3i** containing the CF$_3$ group, attributed to poorer binding between the pyridyl group and the Al Lewis acid resultant

of its strongly electron-withdrawing nature. A wide range of functionalities were well-tolerated in this reaction; **3j** and **3k** containing ester or amide groups both gave good yields and high C5 selectivity. In addition, aryl groups (**3l**–**3p**) bearing a range of functional groups such as methoxy (**3n**), silyl (**3o**) and boryl groups (**3p**) are tolerated, giving the desired products in 72–92% yields and excellent C5 selectivity (16:1 to 33:1). The presence of a C4-phenyl group (**3q**) led to decreased reactivity and C3 selectivity, presumably owing to both its electron-donating effect as well as heightened steric hindrance. On the other hand, the smaller C4 fluoro group (**3r**) provided near-quantitative yield and high C5 selectivity (9:1). Consistent with the proposed coordination of pyridine with Al as a crucial mechanistic component, the presence of C2 substituents gave poorer reactivity and selectivity (**3s** and **3t**). Notably, other azaheteroarenes were also compatible (**3u** to **3x**): alkenylation of diazaheteroarenes such as pyridazine (**3u**) and pyrimidines (**3v** and **3w**) afforded the desired products in 63–86% yields (6:1–25:1, C5:others); quinoline gave the alkenylated product in 72% yield, albeit with a lower selectivity (1:1, **3x**) owing to poorer coordination with Al Lewis acid.

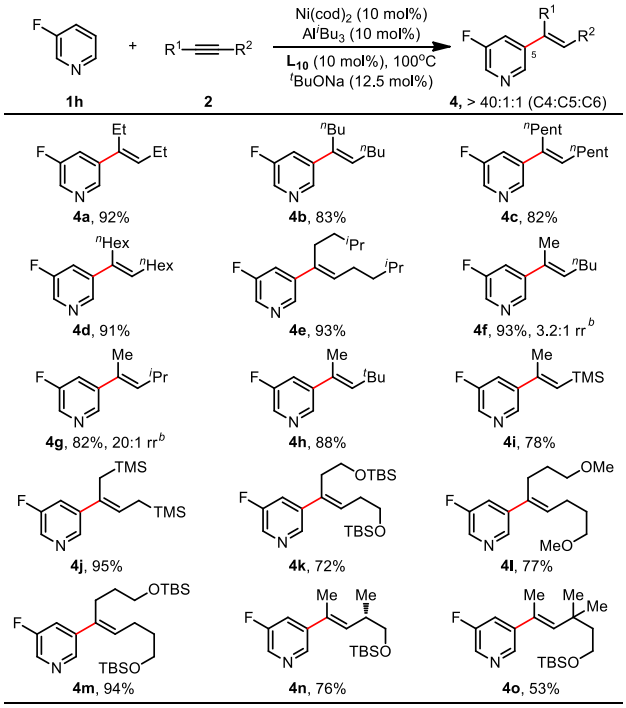
Scheme 4. Scope of Pyridines [a]



[a]Reaction conditions: **1** (0.40 mmol), **2a** (1.20 mmol), toluene (1.0 mL); Ni(cod)$_2$, **L$_{10}$**, ^{t}BuONa and toluene at 80 °C for 30 min, then pyridine, Al^{i}Bu$_3$ and alkyne substrate at 100 °C under N_2 for 12 h; yield of isolated mixed isomers; ratio of isomers determined by ^{1}H NMR. [b]Ni(cod)$_2$ (20 mol%), **L$_{10}$** (20 mol%), Al^{i}Bu$_3$ (20 mol%), and ^{t}BuONa (25 mol%). [c]140 °C. [d]Al^{i}Bu$_3$ instead of AlMe$_3$.

The scope of alkyne coupling partners was next surveyed using 3-fluoropyridine (**1h**) as a model substrate. Considering the synthetic versatility of the olefin motif, it was pleasing to observe that a broad range of alkylalkynes was well-tolerated, affording the trisubstituted alkenylated products with excellent C5 selectivity (Scheme 5, >40:1 C5:others). Both symmetrical dialkylalkynes (**4a** to **4e**) and non-symmetrical alkylalkynes (**4f** to **4h**) afforded the corresponding products in 82–93% yields. For non-symmetrical alkynes, the regiochemical outcomes were governed by the relative steric hindrance between the two alkyne substituents, with larger size differences giving higher alkene regioselectivity. As well, alkylalkynes bearing potentially acid and Lewis acid sensitive groups such as silanes (**4i** and **4j**) and silyl ethers (**4k** to **4o**) were all compatible substrates in this reaction.

Scheme 5. Scope of Alkynes [a]



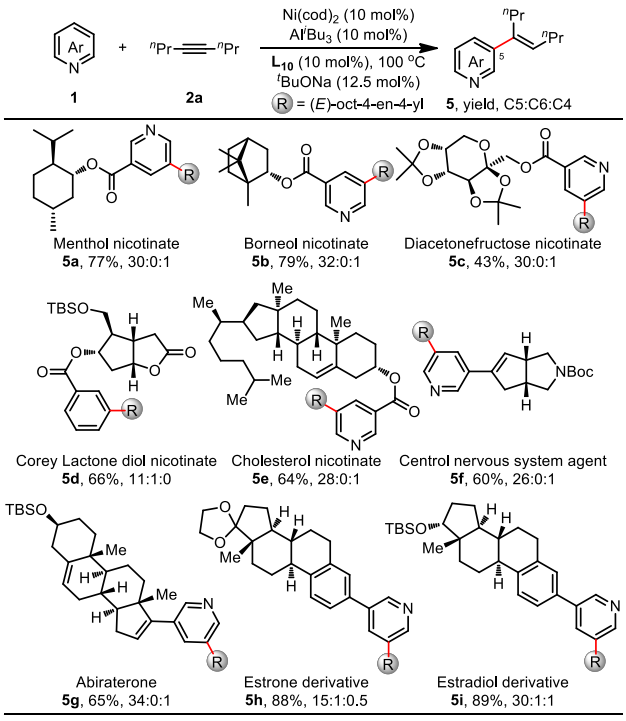
[a]Reaction conditions: **1h** (0.40 mmol), **2** (1.20 mmol), toluene (1.0 mL); Ni(cod)$_2$, **L$_{10}$**, ^{t}BuONa and toluene at 80 °C for 30 min, then pyridine, Al^{i}Bu$_3$ and alkyne substrate at 100 °C under N_2 for 12 h; yield of isolated products; [b]Regioisomer ratio of alkenes determined by ^{1}H NMR.

In contrast to previously reported C–H olefination of pyridines,[12] this newly-developed catalyst allows for the use of pyridine substrates as the limiting agent, thus opening new avenues for the efficient late-stage modification of heterocycle-containing bioactive molecules (Scheme 6). To demonstrate this, we applied our C–H alkenylation reaction to a range of nicotinic acid-derived complex molecules, such as (–)-menthol (**5a**), (–)-borneol (**5b**), diacetonefructose (**5c**), (–)-Corey lactone diol (**5d**), and cholesterol (**5e**). Gratifyingly, the reactions proceeded smoothly, providing the desired products in 43–79% yield and with high C5 selectivity (11:1–32:1). Medicinally relevant compounds were also competent in this process; azabicyclic compound (**5f**), representing an important class of agent active in the central nervous system, was alkenylated in 60% yield (26:1 C5:others). Abiraterone (**5g**), an anticancer drug, was alkenylated in 65% yield (34:1 C5:others). In

addition, bioactive steroid hormones such as estrone (**5h**) and estradiol (**5i**) were also suitable substrates, providing the corresponding alkenylated products in 88% and 89% yield, respectively, both with high C5 selectivity (15:1–30:1).

In conclusion, we have developed a bifunctional Ni catalyst that allows, for the first time, the C3(5)-selective C–H alkenylation of pyridine-containing hetereocycles as the limiting reagent. As the alkene functionality could be readily derivatized, the broad scope and synthetic practicality of this reaction could enable the facile access of diverse C3(5)-functionalized motifs bearing a range of carbon oxidation states. We determined that the assembly of a putative macrocyclophane intermediate through reversible Al coordination was crucial to enable both catalyst reactivity and site-selectivity. As a testament to the strength of the directing effect, the ligand allows for the Ni catalyst to override the intrinsic electronic activation of the C2 and C4 and achieve the selective metalation at the C3–H bond of pyridines. This process further validates the applicability of a merged ligand-template strategy in C–H activation, where we anticipate these design principles applied to a wider range of remote functionalization processes.

Scheme 6. Late-Stage Alkenylation of Pyridine-Containing Bioactive Molecules[a]



[a]Reaction conditions: **1** (0.40 mmol), **2a** (1.20 mmol), toluene (1.0 mL); $Ni(cod)_2$, $\mathbf{L_{10}}$, ^{t}BuONa and toluene at 80 °C for 30 min, then pyridine, Al^nBu_3 and alkyne substrate at 100 °C under N_2 for 12 h; yield of isolated mixed isomers; ratio of C5/C6/C4 determined by ^{1}H NMR. [b]$Ni(cod)_2$ (20 mol%), $\mathbf{L_{10}}$ (20 mol%), Al^nBu_3 (20 mol%), ^{t}BuONa (25 mol%).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures and spectral data for all new compounds (PDF). Metrical parameters for the structure of $\mathbf{L_{10}}$ are available free of charge from the Cambridge Crystallographic Data Centre under reference number CCDC 1434263.

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Notes

The authors declare no competing financial interests.

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