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Selective C-4 Alkylation of Pyridine by Nickel/Lewis Acid Catalysis

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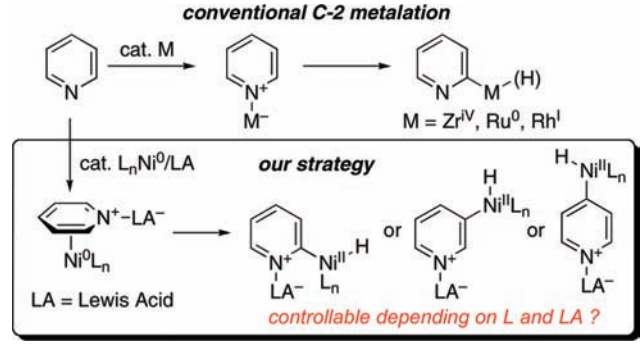
Abstract: Direct C-4-selective addition of pyridine across alkenes and alkynes is achieved for the first time by nickel/Lewis acid cooperative catalysis with an *N*-heterocyclic carbene ligand. A variety of substituents on both alkenes and pyridine are tolerated to give linear 4-alkylpyridines in modest to good yields. The addition across styrene, on the other hand, gives branched 4-alkylpyridines. A single example of C-4-selective alkenylation is also described.

A pyridine core plays a key role in a number of natural products, pharmaceuticals, ligands, and functional materials. Because a wide variety of pyridine derivatives are available, a strategy to install substituents directly into a preformed pyridine core has advantages in terms of step economy as well as versatility. Nevertheless, the low reactivity of pyridine and its derivatives toward aromatic electrophilic substitution reactions such as halogenation and the Friedel−Crafts reaction due to the presence of electron-withdrawing and Lewis-basic sp^2 nitrogen limits a repertoire of methods to decorate the heteroaromatic ring.[1] It has been known that some strong nucleophiles and radicals can react with pyridines at the C-2 position selectively to introduce a C-2 substituent.[1] In addition, the C(2)−H bond can be metalated by a strong base and functionalized by subsequent reactions with electrophile.[1,2] More recently, C-2-selective functionalizations have been effected in a catalytic manner through C(2)−H activation of pyridines by transition metal complexes.[3] The high C-2 selectivity observed in these protocols can be ascribed to the coordination of Lewis-basic sp^2 nitrogen to a metal, which then directs C-2 functionalization due to proximity (Scheme 1). In contrast, direct C-3 and C-4 functionalizations of pyridines have been scarcely achieved, although the acidity of C(2)−H is estimated to be lower than that of C(3)−H and C(4)−H by theoretical calculation.[4] Such transformations have met with limited success using pyridines having a directing group to control both stoichiometric[5] and catalytic[6] metalation at the C-3 or C-4 position. Classically, C-3-selective sulfonation and nitration can proceed under harsh reaction conditions.[1] On the other hand, C-4 functionalization of pyridines has relied on indirect processes that include formation of pyridinium species such as *N*-oxides, *N*-alkyl-, or *N*-acylpyridiniums followed by subsequent reactions with electrophiles or nucleophiles to install a C-4 substituent.[1,7]

We and others have recently uncovered that an electron-rich nickel catalyst can introduce an alkenyl or aryl group into pyridine derivatives selectively at the C-2 position.[8] Our own strategy involves stoichiometric or catalytic activation of pyridines to form pyridinium species, the C(2)−H of which is metalated by a nickel catalyst with an electron-donating phosphine ligand, possibly through oxidative addition.[8a,b] Because η^2-coordination of the activated pyridines to nickel, rather than η^1-coordination of the sp^2 nitrogen atom, precedes the C(2)−H functionalization in our protocol, size and/or electronic factors of the two catalysts can direct regioselectivity of the pyridine metalation (Scheme 1). Herein, we report realization of such control by nickel/Lewis acid (LA) cooperative catalysis. The use of highly bulky *N*-heterocyclic carbene (NHC) ligands allows direct C-4 alkylation and alkenylation of pyridine.[9]

Scheme 1. Strategies for Catalytic Direct Metalation of Pyridine



We first examined C-4 alkylation of pyridine with 1-alkenes (Table 1). The reaction of pyridine (**1a**, 1.0 mmol) and 1-tridecene (**2a**, 1.5 mmol) in the presence of $Ni(cod)_2$ (5 mol %), 1,3-(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr, 5 mol %), and $AlMe_3$ (20 mol %) in toluene at 130 °C for 3 h gave 4-tridecylpyridine (**3aa**) in 70% yield after isolation by flash chromatography on silica gel (entry 1). A small amount of 3-tridecylpyridine was also obtained in 7% yield. Phosphorus ligands including $P(i\text{-}Pr)_3$, a ligand of choice for C-2 alkenylation,[8b] were completely ineffective. Use of other aluminum-based LAs including $AlMe_2Cl$ and $AlMeCl_2$ gave lower yields, whereas BEt_3 and BPh_3 showed comparable activity with slightly decreased yields of **3aa**. Diorganozincs, the best LA catalysts for the C-2 alkenylation,[8b] were ineffective. A reduced amount of the LA catalyst gave lower yields, whereas use of a higher amount showed no significant improvement. While use of other NHC ligands did not improve the regioselectivity (C-4 vs C-3), very bulky $(2,6\text{-}t\text{-}Bu_2\text{-}4\text{-}Me\text{-}C_6H_2O)_2AlMe$ (MAD)[10] as a LA catalyst effected exclusive C-4 alkylation of pyridine, albeit with contamination of branched adduct **3′aa** in a small amount (entry 2). These reaction conditions were examined for aliphatic 1-alkenes having a phenyl-, silyl- or pivaloyl-protected hydroxy group and a terminal or internal double bond as well as a vinylsilane to give respective products in good yields (entries 3−8). No detectable second addition of pyridine was observed across **3ae** and **3af** (entries 6 and 7). On the other hand, branched C-4-alkylated pyridine **3′ah** was obtained exclusively by the addition reaction across styrene (entry 9), probably through migratory insertion of the vinylarene in a manner different from that of aliphatic alkenes to give a stabilized benzylic nickel intermediate (*vide infra*).[11] Use of 1,3-(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes, 5 mol %) instead

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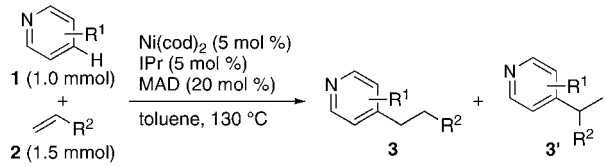
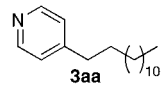
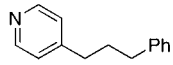
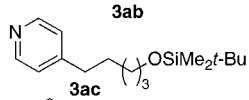
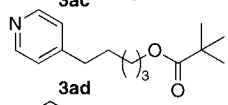
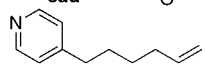
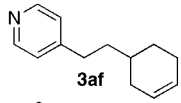
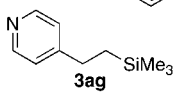
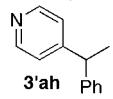
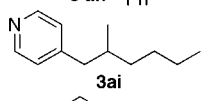
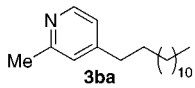
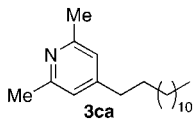
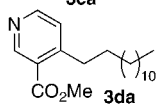
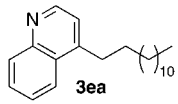
Table 1. C-4 Alkylation of Pyridine Derivatives Catalyzed by Ni/MAD



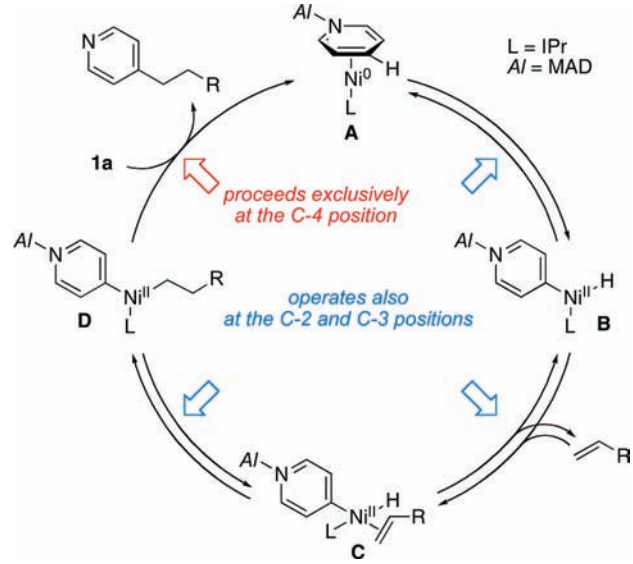
R^1 = H (**1a**); 2-Me (**1b**); 2,6-Me_2 (**1c**); 3-CO_2Me (**1d**)
R^2 = $C_{11}H_{23}$ (**2a**); CH_2Ph (**2b**); $(CH_2)_3OSiMe_2t$-Bu (**2c**); $(CH_2)_3$OPiv (**2d**); $(CH_2)_2CH{=}CH_2$ (**2e**); cyclohexen-4-yl (**2f**); $SiMe_3$ (**2g**); Ph (**2h**)

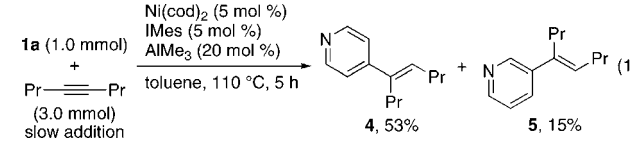
entry	1	2	time (h)	major product	yield of 3+3' (%)[a]	3/3'[b]
1[c]	**1a**	**2a**	3	 **3aa**	70[d]	>95:5
2	**1a**	**2a**	5		87	95:5
3	**1a**	**2b**	9	 **3ab**	85	>95:5
4	**1a**	**2c**	11	 **3ac**	91	94:6
5	**1a**	**2d**	23	 **3ad**	61	90:10
6	**1a**	**2e**	23	 **3ae**	48	94:6
7	**1a**	**2f**	10	 **3af**	91	>95:5
8	**1a**	**2g**	19	 **3ag**	83	>95:5
9[e]	**1a**	**2h**	18	 **3'ah**	95	5:>95
10	**1a**	**2i**[f]	23	 **3ai**	40	>95:5
11	**1b**	**2a**	10	 **3ba**	91	93:7
12	**1c**	**2a**	12	 **3ca**	12	88:12
13	**1d**	**2a**	9	 **3da**	52	>95:5
14	**1e**[g]	**2a**	9	 **3ea**	89	>95:5

[a] Isolated yields based on **1**. [b] Estimated by GC of crude products. [c] Run with $AlMe_3$ (20 mol %) instead of MAD. [d] C-3-alkylated pyridine (7%) was also obtained. [e] Run with IMes as a ligand. [f] 2-Methyl-1-hexene. [g] Quinoline.

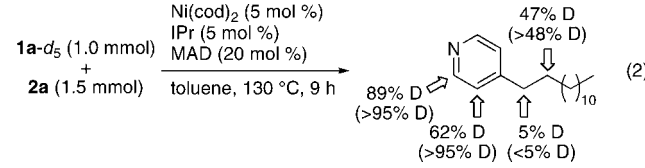
of IPr was found more effective for this particular alkene substrate. The *exo*-methylene of 2-methyl-1-hexene (**2i**) was also hydroarylated with pyridine regioselectively, albeit in modest yield (entry 10). Pyridine derivatives such as 2-picoline (**1b**), 2,6-lutidine (**1c**), methyl nicotinate (**1d**), and quinoline (**1e**) were also alkylated with **2a** at the C-4 position (entries 11−14), while no reaction was observed with pyridines having a C-4 substituent. We also examined C-4-selective alkenylation of pyridine (eq 1). After brief screening of reaction parameters, use of IMes as a ligand and slow addition of an excess amount (3.0 equiv) of 4-octyne were found effective to minimize unwanted tri- and oligomerization of the alkyne, giving a mixture of C-4 and C-3 *cis*-alkenylated pyridines **4** and **5**.

Scheme 2. Plausible Catalytic Cycle





To gain mechanistic insights, the reaction of **1a**-d_5 (>99.5%D) with **2a** was examined under the standard reaction conditions (eq 2).



This reaction for 9 h gave **3aa** with some loss of deuterium at the C-2 and C-3 positions, whereas the identical reaction quenched after 3 min showed almost no incorporation of hydrogen at these positions (values in parentheses). The source of the incorporated hydrogen should be **2a** employed in an excess amount. These results imply a catalytic cycle initiated by oxidative addition of the C(4)−H bond of pyridine coordinating to MAD,[12] which is kinetically favored over that of the C(2)−H and C(3)−H bonds, through η^2-arenenickel species **A** (Scheme 2). Coordination and migratory insertion of alkenes into the Ni−H bond of nickel(II) intermediate **B** takes place to give alkylnickel **D** through **C**, and subsequent reductive elimination gives C-4-alkylated pyridines and regenerates **A**. We observed an equilibrium between **1a**-MAD and **3aa**-MAD in C_6D_6, suggesting that the turnover of the LA catalyst can be operative. The results shown in eq 2 suggest that this catalysis works irreversibly at the C-4 position and that the C-2 and C-3 positions are also activated reversibly to give the corresponding alkylnickel

intermediates like **D**. However, the final irreversible reductive elimination does not operate at these positions, presumably due to steric hindrance and competition with β-hydride elimination, which should account for the observed loss of deuterium. Use of sterically highly demanding NHC ligands and MAD is apparently crucial to induce the C-4 selectivity on both the oxidative addition and the reductive elimination steps, while the exact rationale is under investigation. Regarding the effect of LA on the latter step, Hartwig and Shen have reported that the reductive elimination of aryl(pyridyl)palladium(II) complexes is accelerated by LA with 4-pyridyl derivatives better than with 3- or 2-pyridyl ones.[13]

In conclusion, we have demonstrated that direct C-4-selective alkylation of pyridines is achieved for the first time by nickel/LA catalysis. Combined with our previous report,[8b] we have shown that ligands and LA cocatalyts indeed effect the nickel-catalyzed regioselective functionalizations of pyridines. Current efforts are directed to understanding the reaction mechanism in detail and C-3-selective variants of these transformations.

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Note Added after ASAP Publication. In the version published ASAP September 7, 2010, Table 1, entry 9 contained an error; the correct version reposted September 9, 2010.

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

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