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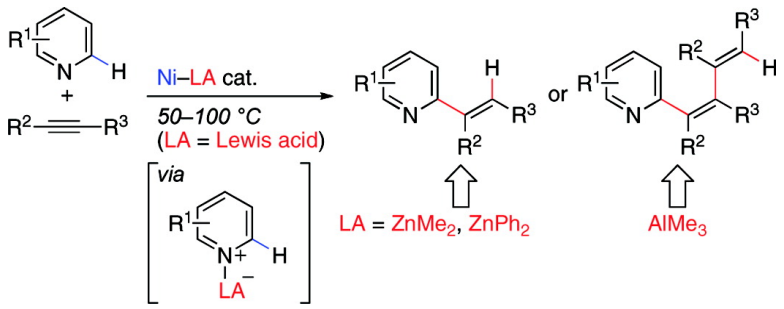

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A Strategy for C−H Activation of Pyridines: Direct C-2 Selective Alkenylation of Pyridines by Nickel/Lewis Acid Catalysis

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A large number of pharmaceuticals, natural products, and optical materials contain a pyridine nucleus. Thus, the functionalization of pyridines is an important transformation in organic synthesis. However, due to the low reactivity of pyridine derivatives toward aromatic electrophilic substitution reactions such as the Friedel−Crafts reaction, additional steps including halogenation and metalation are required to install substituents in a pyridine ring.[1] Accordingly, the development of a direct C−H functionalization[2] of pyridine catalyzed by transition metals has gained significant attention and importance.[3−6] Nevertheless, the limited number of reported examples suffers from harsh reaction conditions of over 150 °C,[3] limited scope of substrates,[4] requires the presence of a directing group,[5] or employs *N*-oxides.[6] We have also recently reported the C-2 alkenylation of pyridine-*N*-oxides by mild nickel catalysis.[6c] Since the enhanced reactivity of pyridine-*N*-oxides, compared with that of parent pyridines, is apparently attributed to an electron-deficient nitrogen that increases the acidity of the C(2)−H bond, we envisioned that a similarly activated pyridine species could be generated *catalytically* in situ by the coordination of the nitrogen to a Lewis acid (LA) catalyst (Scheme 1). Herein, we report that a combination of nickel and LA catalysts allows the direct C-2 alkenylation of pyridines under mild conditions. Moreover, the single or double insertion of alkynes into the C(2)−H bond of pyridines is successfully controlled by simply changing the LA catalyst.

At the onset, we briefly examined effects of various LA catalysts toward the reaction of pyridine (**1a**, 3.0 mmol) and 4-octyne (**2a**, 1.0 mmol) in the presence of $Ni(cod)_2$ (3 mol %) and $P(i\text{-}Pr)_3$ (12 mol %) in toluene at 50 °C and found that zinc and aluminum catalysts with mild Lewis acidity were highly effective (Table 1). Thus, the reaction in the presence of $ZnMe_2$ (6 mol %) afforded C-2 alkenylated product **3aa** highly stereoselectively in 95% yield (entry 1), whereas the absence of the LA or the nickel catalyst gave no trace amount of the adduct. A small amount of C-2 dienylated product **4aa** was also observed, the formation of which was suppressed by running the reaction at 80 °C (entry 2). $ZnPh_2$ was equally effective to give **3aa** in 88% yield after isolation by silica gel chromatography (entry 3). A stronger zinc LA catalyst, $ZnCl_2$, was completely ineffective.[7] Although an equimolar reaction of **1a** with **2a** resulted in a low yield of **3aa** (55% by GC) due to competitive trimerization of **2a**, no trace amount of a C-2 and C-6 dialkenylated product was observed. On the other hand, the use of $AlMe_3$ as a LA catalyst dramatically changed the reaction course, affording **4aa** as a major adduct in 80% isolated yield (based on **2a** as the limiting reagent) together with a small amount of **3aa** (entry 4). The identical reaction at 80 °C, however, gave a mixture of **3aa** and **4aa** (entry 5), suggesting that a higher reaction temperature preferred the formation of **3aa** over **4aa** irrespective of the kind of LA catalysts used (entry 1 vs entry 2 and entry 4 vs entry 5). Again, aluminum LA catalysts with a stronger Lewis acidity were inferior.[7] In either system, the direct C−H functionalization of pyridine by nickel−LA dual catalysis under relatively mild conditions at 50−80 °C is worth noting, compared with the reported ruthenium and rhodium catalysis.[3,8]

Scheme 1. Catalytic Direct C-2 Alkenylation of Pyridines by Nickel−Lewis Acid Cooperative Catalysis

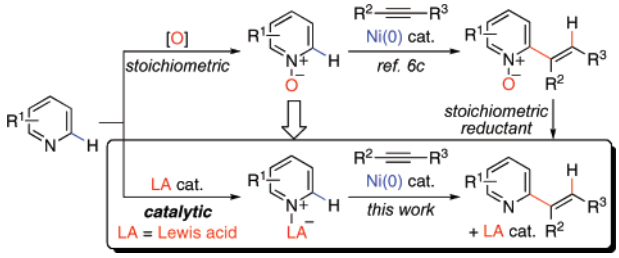
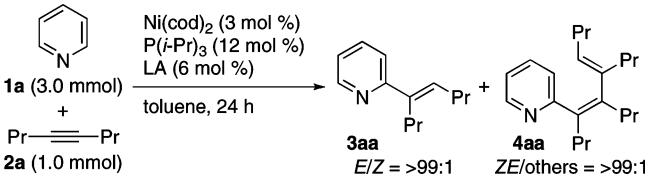


Table 1. Direct C-2 Alkenylation of **1a** with **2a** Catalyzed by Nickel−Lewis Acid[a]



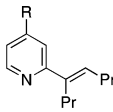
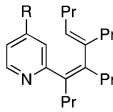
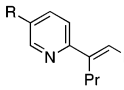
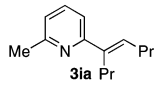
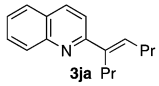
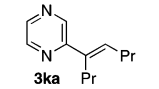
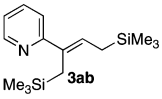
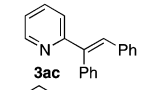
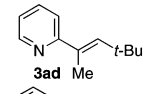
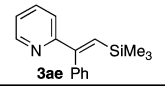
entry	LA	temp (°C)	yield of **3aa**[b] (%)	yield of **4aa**[b] (%)
1	$ZnMe_2$	50	95	3
2	$ZnMe_2$	80	95[c]	<1
3	$ZnPh_2$	50	96 (88)[d]	3
4	$AlMe_3$	50	5	82 (80)[d]
5	$AlMe_3$	80	17[d]	56[d,e]

[a] The reactions were carried out using **1a** (3.0 mmol), **2a** (1.0 mmol), $n\text{-}C_{11}H_{24}$ (internal standard, 0.50 mmol), $Ni(cod)_2$ (3.0 mol %), $P(i\text{-}Pr)_3$ (12 mol %), and a Lewis acid (6.0 mol %) in toluene (2.5 mL). [b] Determined by GC based on **2a** as the limiting reagent. [c] *E*/*Z* = 93:7. [d] Isolated yields. [e] *ZE*/*EE*/others = 52:43:5.

With the binary catalyst systems effective for the C-2 selective alkenylation of pyridines, we further tested the scope of the present transformation (Table 2). A range of electron-withdrawing and -donating substituents on the 4-position of pyridine tolerated the reaction conditions to give the corresponding adducts in good yields (entries 1−5). Some of the substituted pyridines also participated in the dienylation reaction under nickel−$AlMe_3$ catalysis (entries 6 and 7). Excellent regioselectivities were observed with 3-substituted pyridines **1g** and **1h**, which were alkenylated at the C-6 position exclusively (entries 8 and 9). The sensitivity of the reaction toward a steric environment of substrates was also observed with 2-picoline (**1i**), corresponding adduct **3ia** being obtained in a modest yield even at 100 °C (entry 10). Quinoline (**1j**) and pyrazine (**1k**) also underwent the present C-2 alkenylation reaction (entries 11 and 12). The use of other alkynes in this reaction was also briefly examined. Bis(silylmethyl)acetylene **2b** underwent the reaction with **1a** to give pyridyl-substituted allylsilane **3ab** (entry 13), whereas the addition across diphenylacetylene (**2c**) was sluggish (entry 14). The reactions of unsymmetrical internal alkynes, 4,4-dimethyl-2-pentyne (**2d**) and trimethyl(phenylethynyl)silane (**2e**), were highly regioselective to give the corresponding adducts having a smaller

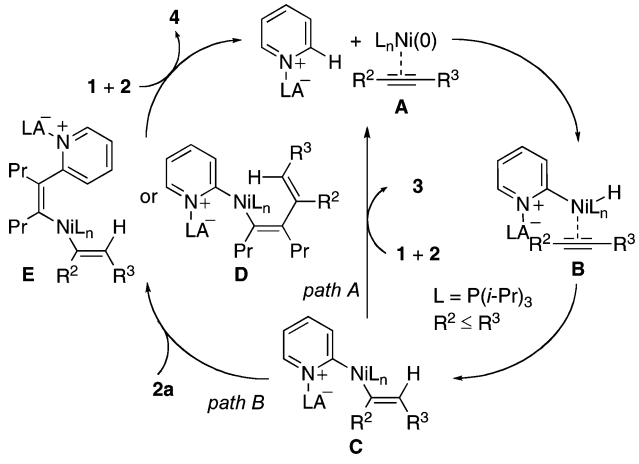
10.1021/ja710766j CCC: $40.75

Table 2. Nickel−Lewis Acid Catalyzed Direct C-2 Alkenylation of Pyridines

entry	1	2	LA	temp (°C)	time (h)	major product	yield (%)[a]	*E*/*Z*[b]
1	**1b**	**2a**	$ZnPh_2$	50	8	 R = Ph (**3ba**)	91	98:2
2[c]	**1c**	**2a**	$ZnPh_2$	50	8	F_3C (**3ca**)	69[d]	96:4
3	**1d**	**2a**	$ZnMe_2$	80	12	***Si***OCH_2 (**3da**)[e]	77	95:5
4	**1e**	**2a**	$ZnMe_2$	50	8	MeO (**3ea**)	84	>99:1
5	**1f**	**2a**	$ZnPh_2$	80	3	Me_2N (**3fa**)	81[f]	97:3
6[g]	**1b**	**2a**	$AlMe_3$	50	30	 R = Ph (**4ba**)	64	>99:1
7	**1e**	**2a**	$AlMe_3$	50	40	MeO (**4ea**)	46[h]	>99:1
8	**1g**	**2a**	$ZnMe_2$	80	10	 R = MeO_2C (**3ga**)	69	93:7
9	**1h**	**2a**	$ZnMe_2$	50	15	(pin)B (**3ha**)	82[d,f]	99:1
10	**1i**	**2a**	$ZnPh_2$	100	12	 **3ia**	42	96:4
11	**1j**	**2a**	$ZnMe_2$	80	10	 **3ja**	65	>99:1
12	**1k**	**2a**	$ZnMe_2$	100	5	 **3ka**	65[d,f]	97:3
13[g]	**1a**	**2b**	$ZnMe_2$	50	24	 **3ab**	61	>99:1
14	**1a**	**2c**	$ZnMe_2$	100	10	 **3ac**	30	>99:1
15	**1a**	**2d**	$ZnPh_2$	50	12	 **3ad**	87	>99:1
16[g]	**1a**	**2e**	$ZnMe_2$	100	24	 **3ae**	56[f]	63:37

[a] Isolated yields of isomerically pure products based on **2** as the limiting reagent. [b] Determined by ^{1}H NMR analysis of a crude product. [c] PMe(*t*-Bu)$_2$ was used as a ligand. [d] About 10% of **4** was also observed. [e] ***Si*** = $SiMe_2$*t*-Bu. [f] Isolated yields of a mixture of stereoisomers. [g] $Ni(cod)_2$ (10 mol %), P(*i*-Pr)$_3$ (40 mol %), and a LA catalyst (20 mol %) were used. [h] About 5% of **3ea** was also observed.

Scheme 2. Plausible Mechanism



substituent on the same side as the pyridyl group (entries 15 and 16), although silyl-substituted adduct **3ae** isomerized under the reaction conditions to give a stereoisomeric mixture.[9] Terminal alkynes were not applicable to this transformation due to rapid oligo- and/or trimerization.

The pyridines activated by coordination to a LA[10] would be responsible for the oxidative addition of the C(2)−H bond to nickel(0) species **A**,[11] a plausible initiation step of the present catalysis (Scheme 2).[12] Hydronickelation across the alkyne coordinating to the nickel center in the direction avoiding a steric repulsion between the bulkier R^3 and the pyridyl group in **B** takes place to give **C**, which upon reductive elimination affords **3** in the presence of zinc LA catalysts (path A). The use of $AlMe_3$, a stronger Lewis acid than diorganozincs,[10] or lower reaction temperature retards the reductive elimination and/or promotes the second insertion of an additional alkyne into either of the C−Ni bonds in **C** to give **D** or **E**, resulting in the formation of dienylated product **4** upon reductive elimination (path B).[13] Another mechanistic scenario involving a metallacycle formation[14] (not shown) could be conceivable. Experimental and theoretical mechanistic analyses will be further investigated in detail.

In conclusion, we have demonstrated the divergent direct C-2 alkenylation of pyridines by nickel−LA cooperative catalysis to synthesize a wide variety of 2-alkenylated pyridines in chemo-, regio-, and stereoselective manners under mild conditions. Development of other C−H functionalizations by nickel−LA dual catalysis is in progress in our laboratories.

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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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(7) See Supporting Information for details.
(8) The mild reaction conditions of the present protocol could also be derived from the higher reactivity of alkynes than that of alkenes.
(9) The *E*/*Z* ratio of **3ae** was 80:20 at 0.7 h.
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