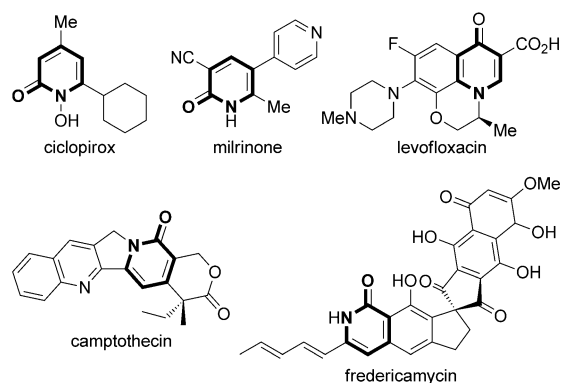


# Alkylation of Pyridone Derivatives By Nickel/Lewis Acid Catalysis\*\*

Ryuichi Tamura, Yuuya Yamada, Yoshiaki Nakao,\* and Tamejiro Hiyama\*

Pyridone derivatives are found in many pharmaceuticals and biologically active natural products (Scheme 1).<sup>[1]</sup> In addition, they often serve as synthetic precursors for nitrogen-containing six-membered-ring compounds, including substituted pyridines and piperidines. Methods for the efficient synthesis of substituted pyridones have thus attracted the interest of synthetic organic and medicinal chemists. In this regard, the



**Scheme 1.** Pyridone derivatives found in pharmaceuticals and natural products.

regioselective and direct functionalization of the pyridone core would be a significantly valuable synthetic method for the rapid access to substituted pyridone derivatives.<sup>[2]</sup> The enaminone substructure of 2-pyridone derivatives, for example, has been amenable to regioselective electrophilic chlorination at the C5-position.<sup>[3]</sup> This type of reactivity has been used for palladium-mediated C–C bond formation at the C5-position, possibly through electrophilic palladation of the enaminone functionality.<sup>[4]</sup> We have previously developed complementary protocols that enable the functionalization of the C6-position of 2-pyridone derivatives. For example, we

have effected C6-alkenylation through regioselective insertion of alkynes into the C(6)–H bond, using electron-rich nickel(0) and Lewis acidic aluminum compounds as cooperative catalysts.<sup>[5]</sup> Additionally, we also reported preliminary results on the alkylation of the C6-position to give branched alkylated pyridones through insertion of 1,3-dienes and vinylarenes into the C<sub>sp<sup>2</sup></sub>–H bond.<sup>[5]</sup> Herein, we wish to report the alkylation of pyridone derivatives with unactivated alkenes that selectively gives pyridones with linear alkyl groups through the use of nickel/Lewis acid cooperative catalysis modulated by N-heterocyclic carbene (NHC) ligands.

Toward finding optimal reaction conditions for the C6-selective alkylation of pyridones with unactivated alkenes, we investigated the reaction of 1-methyl-2-pyridone (**1a**) with 1-tridecene (**2a**) in toluene at 80 °C, in the presence of [Ni(cod)<sub>2</sub>] (5 mol %), a range of ligands, and AlMe<sub>3</sub> (20 mol %) as a co-catalyst (Table 1). When P(*i*Pr)<sub>3</sub>, the ligand of choice in our previously reported alkenylation reaction,<sup>[5]</sup> was used, 1-methyl-6-(tridec-1-yl)-2-pyridone (**3aa**) was indeed obtained, albeit in a low yield (Table 1, entry 1). The use of P(*t*Bu)<sub>3</sub> only led to a slight increase in yield (Table 1, entry 2). We next examined NHC ligands to improve the yield of **3aa**. Although we have previously shown

**Table 1:** C6-Alkylation of 1-Methyl-2-pyridone (**1a**) with tridecene (**2a**).<sup>[a]</sup>

Entry	Ligand	LA	T [°C]	t [h]	Yield of <b>3aa</b> [%] <sup>[b]</sup>
1	P( <i>i</i> Pr) <sub>3</sub>	AlMe <sub>3</sub>	80	6	1
2	P( <i>t</i> Bu) <sub>3</sub>	AlMe <sub>3</sub>	80	6	8
3	IMes	AlMe <sub>3</sub>	80	6	12
4	IPr	AlMe <sub>3</sub>	80	6	76
5	IPr	AlMe <sub>3</sub>	60	12	36
6	IPr	AlEt <sub>3</sub>	60	12	47
7	IPr	AlMe <sub>2</sub> Cl	60	12	34
8	IPr	AlPh <sub>3</sub>	60	12	7
9	IPr	MAD	60	12	62
10	IPr	BEt <sub>3</sub>	80	6	2
11	IPr	none	80	6	1
12	<i>t</i> Bu	AlMe <sub>3</sub>	80	6	7
13	lAd	AlMe <sub>3</sub>	80	6	7

[a] The reactions were carried out using **1a** (0.50 mmol), **2a** (0.55 mmol), *n*C<sub>11</sub>H<sub>24</sub> (internal standard, 125 μmol), [Ni(cod)<sub>2</sub>] (3.0 mol %), ligand (6.0 mol % for phosphines and 3.0 mol % for NHCs), and Lewis acid (12 mol %) in toluene (0.50 mL). [b] Determined by GC based on **1a** as the limiting reagent. cod = 1,5-cyclooctadiene, LA = Lewis acid.

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
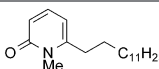

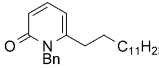

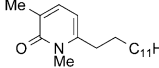

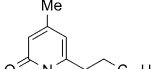

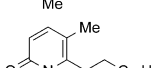

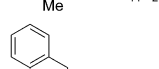

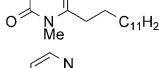

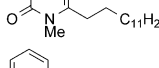

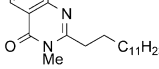
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that the use of 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes) was effective for the alkylation of pyridones with 2-vinylnaphthalene,<sup>[5]</sup> this was not the case here for the alkylation with **2a** (Table 1, entry 3). Instead, we found that 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) was optimal, thus giving **3aa** in 76% yield, as estimated using GC analysis (Table 1, entry 4). We then screened other Lewis acids in the reaction, while maintaining the presence of the ligand IPr. Whereas the use of most of the aluminum-based Lewis acids examined gave similarly modest yields of **3aa** at lower reaction temperatures (Table 1, entries 5–8), the use of (2,6-*t*Bu<sub>2</sub>-4-Me-C<sub>6</sub>H<sub>3</sub>O)<sub>2</sub>AlMe (MAD) afforded **3aa** in 62% yield even at 60 °C (Table 1, entry 9). The reaction in which BEt<sub>3</sub> was used (Table 1, entry 10) and the reaction not containing a Lewis acid co-catalyst (Table 1, entry 11) gave only trace amounts of **3aa**, thus demonstrating the operation of significant cooperative catalysis. When other NHCs, including 1,3-diadamant-1-ylimidazol-2-ylidene (IAd) and 1,3-di-*tert*-butylimidazol-2-ylidene (IrBu), were used only low yields were obtained (Table 1, entries 12 and 13).

With the most favorable combination of catalysts established, we next studied the reaction of various pyridone derivatives with **2a** on a 1.0 mmol scale (Table 2). The preparation of **3aa** on this scale was successful (92%) but the reaction also gave a small amount (2%) of the 4,6-dialkylation product (Table 2, entry 1). However, the C4-monoalkylation product was not observed in an amount detectable by NMR spectroscopy, thus suggesting that the primary reaction occurs at the C6-position exclusively. Furthermore, no branched alkylation product was observed in this particular example. Indeed, linear alkylation products were selectively formed in most reactions in this study. The *N*-benzyl variant **1b** also reacted with **2a**, in the presence of the Ni/IPr/AlMe<sub>3</sub> catalyst, to give **3ba** in 64% yield, together with the 4,6-dialkylation product in 16% yield (Table 2, entry 2). The presence of a methyl substituent at 3-, 4-, or 5-position of the 2-pyridone core did not adversely affect the alkylation reaction and the respective products **3ca–3ea** were obtained in good yields (Table 2, entries 3–5). As anticipated from the observation of minor amounts of the 4,6-dialkylation products of **1a**, **1b**, and **1e**, 1,6-dimethyl-2-pyridone (**1j**) was alkylated at the C4-position when the reaction was conducted at 100 °C [Eq. (1)]. Similarly, 2-quinolone **1k** underwent alkylation at the C4-position [Eq. (2)]. 1-Methylisoquinolone (**1f**),

**Table 2:** Alkylation of pyridone derivatives with **2a** catalyzed by Ni/MAD.

$\begin{array}{c} \text{X} \text{---} \text{Y} \text{---} \text{Z} \\ \diagup \quad \diagdown \\ \text{O} \quad \text{N} \text{---} \text{R}^1 \text{---} \text{H} \\ \text{1 (1.0 mmol)} \quad \text{2a (1.1 mmol)} \end{array} + \text{C}_{11}\text{H}_{23} \xrightarrow[\text{toluene, 80 }^\circ\text{C}]{\begin{array}{l} [\text{Ni}(\text{cod})_2] \text{ (3 mol \%)} \\ \text{IPr (3 mol \%)} \\ \text{MAD (12 mol \%)} \end{array}} \begin{array}{c} \text{X} \text{---} \text{Y} \text{---} \text{Z} \\ \diagup \quad \diagdown \\ \text{O} \quad \text{N} \text{---} \text{R}^1 \text{---} \text{CH}_2\text{C}_{11}\text{H}_{23} \\ \text{3} \end{array}$					
Entry	Starting material <b>1</b>	<i>t</i> [h]	Major product <b>3</b>		Yield [%] <sup>[a]</sup>
1 <sup>[b]</sup>		<b>1a</b>	15		<b>3aa</b> 92 <sup>[c]</sup>
2 <sup>[d,e,f]</sup>		<b>1b</b>	10		<b>3ba</b> 64 <sup>[c]</sup>
3		<b>1c</b>	9		<b>3ca</b> 82
4		<b>1d</b>	8		<b>3da</b> 94
5 <sup>[e,g]</sup>		<b>1e</b>	9		<b>3ea</b> 62 <sup>[c]</sup>
6		<b>1f</b>	16		<b>3fa</b> 83
7 <sup>[g,h,i]</sup>		<b>1g</b>	9		<b>3ga</b> 65 <sup>[c,j]</sup>
8		<b>1h</b>	5		<b>3ha</b> 85
9 <sup>[d]</sup>		<b>1i</b>	5		<b>3ia</b> 80 <sup>[k]</sup>

[a] Yield of isolated product based on **1**. [b] Reaction run at 60 °C.

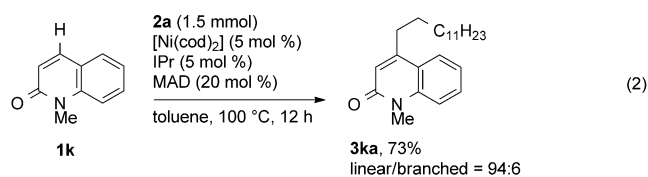
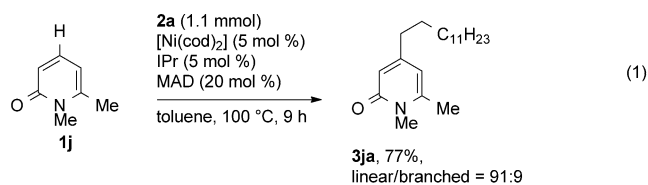
[c] Dialkylation product was also obtained (entry 1: 2%; entry 2: 16%; entry 5: 13%; entry 7: 8%). [d] AlMe<sub>3</sub> was used instead of MAD.

[e] Reaction run with [Ni(cod)<sub>2</sub>] (5 mol %), IPr (5 mol %), and Lewis acid (20 mol %). [f] 1.5 mmol of **2a** was used. [g] Reaction run at 100 °C.

[h] Reaction run with [Ni(cod)<sub>2</sub>] (10 mol %), IPr (10 mol %), and MAD (40 mol %). [i] 1.3 mmol of **2a** was used. [j] The branched isomer was also isolated in 7% yield. [k] linear/branched = 96:4. Bn = benzyl.

1-methyl-pyrimidinone (**1g**), and 1-methyl-quinazolinone (**1h**) all participated in the alkylation reaction with **2a** to give the respective monoalkylation products in good yields (Table 2, entries 6–8). The alkylation of 1,3-dimethyluracil (**1i**) also occurred exclusively at the C6-position to give **3ia** in 80% yield (Table 2, entry 9).<sup>[6]</sup>

The scope of the reaction with respect to variation of the alkene was also explored (Table 3). The presence of other functional groups in the alkene substrate, including silyloxy, ester, and alkenyl moieties, as well as bulky substituents such as *tert*-butyl and trimethylsilyl groups, was tolerated under these reaction conditions (Table 3, entries 1–6). The reaction of hexa-1,5-diene (**2d**) also gave a 40% yield, based on **2d**, of a 1,6-double-addition adduct (Table 3, entry 3). Although terminal double bonds were exclusively functionalized in the presence of more substituted ones, as demonstrated in the

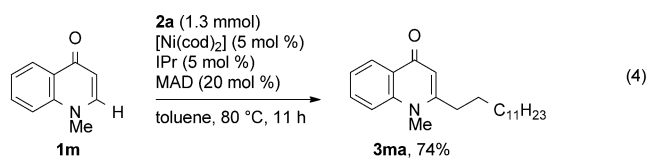
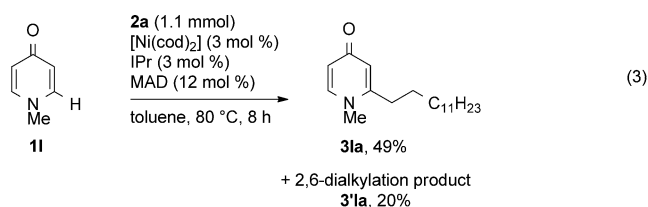


**Table 3:** Alkylation of pyridone **1d** with alkenes, catalyzed by Ni/MAD.

Entry	Alkene	<b>2</b>	<i>t</i> [h]	Major product <b>3</b>	Yield [%] <sup>[a]</sup>
1	R = (CH <sub>2</sub> ) <sub>3</sub> OSiMe <sub>2</sub> tBu	<b>2b</b>	6	<b>3db</b>	84
2	R = (CH <sub>2</sub> ) <sub>3</sub> OPiv	<b>2b</b>	20	<b>3dc</b>	81
3 <sup>[b,c]</sup>	R = (CH <sub>2</sub> ) <sub>2</sub> CH=CH <sub>2</sub>	<b>2d</b>	19	<b>3dd</b>	45 <sup>[d]</sup>
4	R = cyclohexen-4-yl	<b>2e</b>	4	<b>3de</b>	94
5	R = tBu	<b>2f</b>	5	<b>3df</b>	95
6 <sup>[c]</sup>	R = SiMe <sub>3</sub>	<b>2g</b>	19	<b>3dg</b>	88
7		<b>2h</b>	7	<b>3dh</b>	92
8		<b>2i</b>	9	<b>3di</b>	84

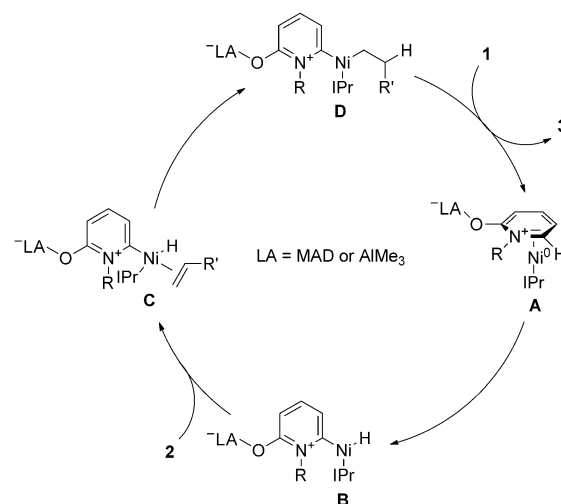
[a] Yield of isolated product based on **1d**. [b] Reaction run with [Ni(cod)<sub>2</sub>] (5 mol %), IPr (5 mol %), and Lewis acid (20 mol %). [c] Reaction run at 100 °C. [d] 1,6-Double-addition product was also obtained in 40% yield based on **2d**. Piv = pivaloyl.

reaction of 4-vinylcyclohexene (**2e**; Table 3, entry 4), the alkylation also proceeded with 1,1-disubstituted ethene **2h** and cyclohexene (**2i**) in good yield (Table 3, entries 7 and 8). In addition to 2-pyridones, 4-pyridone derivatives also reacted selectively; 1-methyl-4-pyridone (**1l**) and 1-methyl-4-quinolone (**1m**), were alkylated directly at the C2-position exclusively through regioselective addition to **2a** [Eqs. (3) and (4)]. Under the newly developed reaction conditions, the C6-

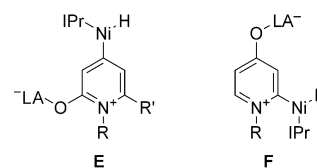


alkylation of **1d** was sluggish when using vinylarenes and 1,3-dienes (< 5% yield); under previously reported reaction conditions, these reactions gave branched alkylation products.<sup>[5]</sup>

A possible catalytic cycle is shown in Scheme 2; it starts with the formation of the η<sup>2</sup>-2-pyridone nickel intermediate


**Scheme 2.** Plausible mechanism.

**A**, wherein the 2-pyridone carbonyl oxygen atom coordinates to the Lewis acidic aluminum catalyst. A related aluminum adduct of an η<sup>2</sup>-pyridine nickel intermediate has recently been identified by Ong et al.<sup>[7]</sup> Oxidative addition of the C(6)–H bond in **A** to a nickel(0) species would give the nickel hydride **B**, to which the alkene substrate could then coordinate, thus giving **C**. Subsequent migratory insertion would afford the alkyl nickel species **D**, which, upon reductive elimination, would give 6-alkyl-2-pyridones; **A** would then be regenerated through ligand exchange reactions, thus completing the catalytic cycle. The selectivity toward oxidative addition at the C6-position, the primary reaction site, could stem from the electrophilicity of this position, which is located α to the formally positively charged nitrogen atom in intermediate **A**. The high selectivity for the linear product could be derived from a regioselective migratory insertion, which would favor the sterically less-hindered primary alkyl nickel **D** rather than the secondary alkyl nickel species. The reaction of 2-vinylnaphthalene has previously been shown to give the opposite regioselectivity, thus giving the branched adduct exclusively,<sup>[5]</sup> presumably because of the high stability of a benzylic nickel intermediate.<sup>[8]</sup> The nickel hydride species **E** and **F**, shown in Scheme 3, would be plausible intermediates responsible for the C4- and C2-selective alkylation reactions of 6-substituted 2-pyridones and 4-pyridones, respectively. The necessity for a highly bulky carbene ligand suggests that it may be crucial in promoting the reductive elimination, which may be a rate-determining step.<sup>[8]</sup> We have yet to undertake mechanistic studies to understand both the proposed catalytic cycle in detail and the high efficiency of the MAD catalyst compared with other aluminum-based Lewis acids.<sup>[9]</sup>


**Scheme 3.** Nickel hydride intermediates **E** and **F**.

In summary, we have developed an alkylation reaction of pyridone derivatives with unactivated alkenes that employs nickel/Lewis acid cooperative catalysis and selectively gives the linear product. The protocols enable the otherwise challenging direct functionalization of the heterocycles that are found in many biologically active substances, in a predictable manner. Efforts to understand the mechanism of the cooperative catalysis and the further application of the reaction toward the functionalization of unreactive substrates are currently in progress.

### Experimental Section

A general procedure for the nickel-catalyzed alkylation of pyridones: In a glove box, pyridone (1.0 mmol), alkene (1.1–1.5 mmol), and undecane or dodecane (internal standard, 0.25 mmol) were placed in a 3 mL vial. A solution of  $[\text{Ni}(\text{cod})_2]$  (8.3 mg, 30  $\mu\text{mol}$ ) and IPr (11.7 mg, 30  $\mu\text{mol}$ ) in toluene (0.50 mL) and a solution of MAD (58 mg, 0.12 mmol) in toluene (0.50 mL) were then added to the mixture. The vial was sealed with a screw-cap, taken out of the glove box, and heated at 80 °C for the time specified in Table 2, Table 3, and Equations (1)–(4). The resulting mixture was filtered through a silica gel pad, concentrated in vacuo, and purified by medium pressure chromatography on silica gel (ethyl acetate/hexane) to give the

corresponding products in yields listed in Table 2, Table 3, and Equations (1)–(4).

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