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Direct Alkenylation and Alkylation of Pyridone Derivatives by Ni/AlMe$_3$ Catalysis

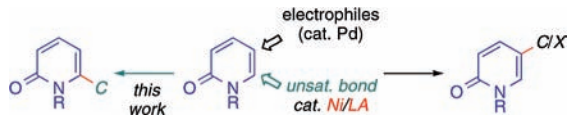
Yoshiaki Nakao,* Hiroaki Idei, Kyalo Stephen Kanyiva, and Tamejiro Hiyama*

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan

Received August 26, 2009; E-mail: yoshiakinakao@npc05.mbox.media.kyoto-u.ac.jp; thiyama@z06.mbox.media.kyoto-u.ac.jp

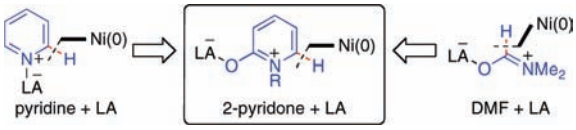
Pyridone derivatives constitute a core of various important biologically active compounds, and therefore, methods for rapid access to the heterocycles substituted at specific positions are of interest to synthetic and medicinal chemists.[1] Whereas significant progress has been made in protocols for constructing the ring systems with a diverse range of substitution patterns,[1a,2] regioselective introduction of substituents to existing pyridone derivatives requires prefunctionalization by stoichiometric metalation or halogenation. On the other hand, an increasing number of direct C−H functionalizations of heterocycles that allow facile and regioselective direct installation of new C−C bonds are available.[3] Nevertheless, related transformations of pyridone derivatives remain elusive. Reactions of pyridones with electrophiles are known to proceed exclusively at the C(5) position (Scheme 1),[4] and this inherent reactivity of the heterocycles has been applied to electrophilic palladation at C(5), allowing a few precedents for C(5) selective direct arylation and oxidative alkenylation in the presence of stoichiometric and catalytic palladium(II).[5,6] We report herein unprecedented C(6)-selective functionalization of pyridone derivatives through inter- and intramolecular insertion of unsaturated bonds into the C(6)−H bond by nickel/Lewis acid (LA) catalysis as a complementary protocol for accessing substituted pyridones.

Scheme 1. Direct Functionalization of 2-Pyridones



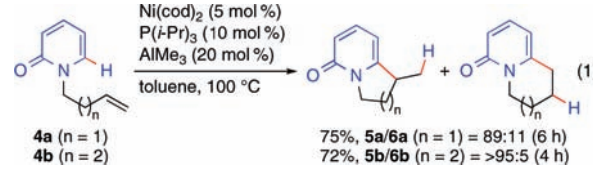
We recently disclosed a direct C−H alkenylation of pyridines and formamides that takes advantage of nickel/LA catalysis.[7] Pyridines and formamides coordinating to a LA cocatalyst through the nitrogen and the carbonyl oxygen are likely responsible for oxidative addition to nickel(0) by C(2)−H and formyl C−H bonds, respectively, that are located α to a formally positively charged nitrogen (Scheme 2). We therefore envisioned that the C(6)−H bond of pyridones could also be activated by nickel(0) upon coordination to a LA catalyst at the more basic carbonyl oxygen.

Scheme 2. Plausible C(6)−H Activation of 2-Pyridones by Ni/LA



To test the above viability, we first examined the reaction of *N*-methyl-2-pyridone (**1a**, 1.0 mmol) and 4-octyne (**2a**, 1.2 mmol) in the presence of Ni(cod)$_2$ (5 mol %), P(*i*-Pr)$_3$ (10 mol %), and AlMe$_3$ (20 mol %) in toluene at 80 °C and found that (*E*)-*N*-methyl-6-octen-4-yl-2-pyridone (**3aa**) was obtained in 90% yield after 6 h through exclusive C(6)−H activation (Table 1, entry 1). The cis stereochemisty of the addition reaction was unambiguously identified by nuclear Overhauser effect experiments on **3aa**.[8] The absence of the LA catalyst gave no trace amount of the adduct.[8] Dialkenylation at the C(4) and C(6) positions was also observed in a small amount (5%).[8] An *N*-benzyl substituent (entry 2) and a methyl group at the C(3) or C(4) position did not affect the reaction (entries 2−4), whereas the C(5) methyl group of **1e** retarded the reaction, presumably because of steric repulsion (entry 5). *N*-Methylisoquinolone (**1f**), -pyrimidone (**1g**), and -quinazolone (**1h**) also participated in the alkenylation, albeit with modest yield or stereoselectivity (entries 6−8).[9] The formal trans adducts observed with **3ga** and **3gh** having α,β-unsaturated imine substructures are likely derived from isomerization of the initial cis adducts, possibly through a phosphine-catalyzed process, given the fact that an isolated sample of (*E*)-**3ha** readily isomerizes to (*Z*)-**3ha** (*E*/*Z* = 57:43 after 1.5 h) under the reaction conditions in the presence of **1a** and **2a**. On the other hand, *N*,*N*-dimethyluracil (**1i**) underwent the alkenylation reaction with a range of alkynes with perfect stereo- and regioselectivities, with the heterocycle being introduced trans to a bulkier alkyne substituent (entries 9−14). Moreover, 1-phenyl-1,3-butadiene (**2g**) reacted with **1i**, albeit in modest yields, and the use of a carbene ligand allowed the insertion of vinyl arene **2h** into the C(6)−H bonds of **1d** and **1i**, giving the corresponding C(6)-alkylated products shown in entries 15−17.

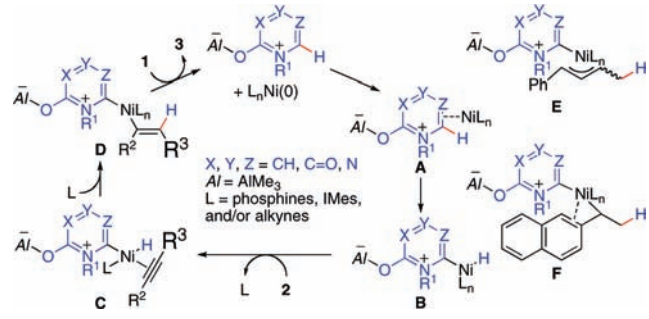
Whereas intermolecular alkylation did not take place with terminal alkenes other than vinyl arenes under these conditions, intramolecular addition across tethered alkenes proceeded mainly in an exo-trig fashion to give bicyclic products **5** and **6** in good yields (eq 1):



The present nickel/LA catalysis is presumably initiated by η^2 coordination (**A** in Scheme 3) followed by oxidative addition of the activated pyridones to give nickel hydride **B**. Coordination of alkynes to the nickel center (**C**) in the direction that avoids steric repulsion between the bulkier R^2 group and the heterocycle, followed by hydronickelation, gives alkenylnickel intermediate **D**, which upon reductive elimination affords **3**. Coordination and subsequent migratory insertion of 1,3-dienes **2g** and vinyl arene **2h** into the H−Ni bond likely give π-allyl- and benzylnickel intermediates **E** and **F**, respectively, which are responsible for the observed regiochemistry of the alkylations (entries 15−17 of Table 1).

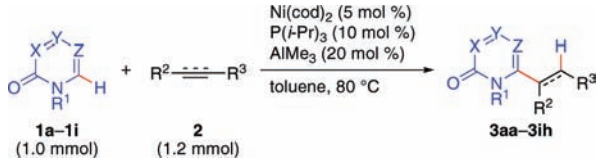
On the basis of the above mechanism, one could imagine the use of a simple enamide (e.g. **7**), a pyridone substructure, as a substrate for these

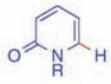
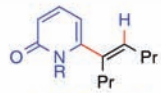
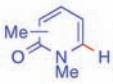
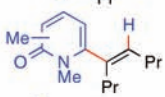
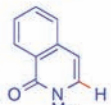
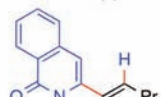
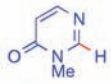
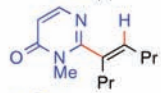
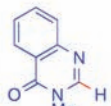
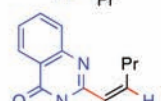
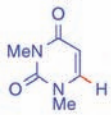
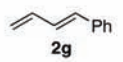
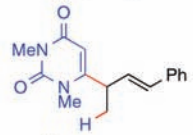
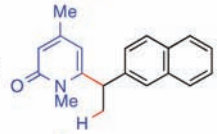
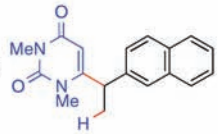
Scheme 3. Plausible Mechanism



10.1021/ja907214t CCC: $40.75

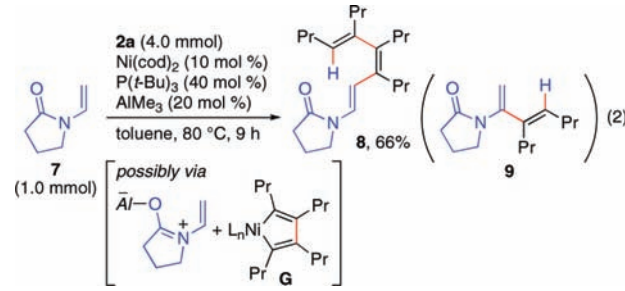
Table 1. Alkenylation and Alkylation of Pyridone Derivatives



entry	1	2	time (h)	major product	yield (%)[a]
1	 **1a** (Me)	**2a**	6		90 (**3aa**)[b]
2	**1b** (Bn)	**2a**	30		62 (**3ba**)[b]
3	 **1c** (3-Me)	**2a**	16		62 (**3ca**)
4	**1d** (4-Me)	**2a**	6		88 (**3da**)
5	**1e** (5-Me)	**2a**	44		29 (**3ea**)[b]
6	 **1f**	**2a**	14		44 (**3fa**)
7	 **1g**	**2a**	3		84 (**3ga**)[c]
8	 **1h**	**2a**	3		99 (**3ha**)[d]
	 R^1—≡—R^2				
	R^1, R^2 =			R^1, R^2 =	
9	**1i** Pr (**2a**)		3	Pr	95 (**3ia**)
10	**1i** CH_2SiMe_3 (**2b**)		3	CH_2SiMe_3	92 (**3ib**)
11	**1i** Me, *i*-Pr (**2c**)		4	Me, *i*-Pr	78 (**3ic**)
12	**1i** Me, *t*-Bu (**2d**)		3	Me, *t*-Bu	97 (**3id**)
13	**1i** Me, $SiMe_2$*t*-Bu (**2e**)		6	Me, $SiMe_2$*t*-Bu	77 (**3ie**)
14	**1i** Ph, $SiMe_3$ (**2f**)		2	Ph, $SiMe_3$	77 (**3if**)[e]
15[f]	**1i**	 **2g**	6		54 (**3ig**)
16[g,h]	**1d**	 2-Np **2h**	12		42 (**3dh**)
17[f,g]	**1i**	**2h**	10		73 (**3ih**)

[a] Isolated yields based on **1**. [b] The 4,6-dialkenylation product was also obtained (entry 1, 5%; entry 2, 4%; entry 5, 1%). [c] *E*/*Z* = 50:50. [d] *E*/*Z* = 38:62. [e] *E*/*Z* = 97:3. [f] Run at 100 °C. [g] Run with 1,3-dimesitylimidazol-2-ylidene (IMes, 10 mol %) as a ligand. [h] Run with 2-vinylnaphthalene (2.0 mmol) at 130 °C.

transformations and expect the formation of dienamide **9**. However, the alkenylation of **7** with **2a** under similar conditions took place exclusively at the β-position with double incorporation of **2a** to give linear trienamide **8** in 66% yield (eq 2):



This particular reaction also required the presence of the LA cocatalyst and likely proceeds through nickelacyclopentadiene **G**, with **7** coordinating to the LA as proposed by Cheng and co-workers[10] for similar reactions using acrylate esters. Therefore, a pyridinium structure in **B** (Scheme 3) would be essential and responsible for the postulated C−H oxidative addition. The LA cocatalyst might make the double bond of **7** electron-deficient, tentatively allowing the enamide to participate in this transformation.

In conclusion, we have demonstrated that regio- and stereoselective alkenylation and alkylation of pyridone derivatives are efficiently catalyzed by nickel/LA. The present transformations allow unprecedented C(6)-selective functionalization of pyridones. Therefore, the protocols are complementary to existing transformations and thus synthetically useful for accessing variously substituted pyridone derivatives. Current efforts are directed extensively to expand the scope of nickel/LA catalysis for new catalytic C−C bond-forming reactions through activation of unreactive bonds.

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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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(8) See the Supporting Information for details.
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