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## Nickel-catalyzed Cycloaddition of $\alpha,\beta$ -Unsaturated Oximes with Alkynes: Synthesis of Highly Substituted Pyridine Derivatives

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A nickel-catalyzed cycloaddition of  $\alpha,\beta$ -unsaturated oximes with alkynes to afford 2,3,4,6-tetrasubstituted pyridine derivatives has been developed. The reaction involves oxidative addition of the N–O bond of  $\alpha,\beta$ -unsaturated oximes to Ni(0) and subsequent alkyne insertion to an N–Ni bond, followed by intramolecular cyclization. It was also found that  $\beta,\gamma$ -unsaturated oximes participate in the nickel-catalyzed reaction with alkynes to furnish pyridine derivatives.

Despite the large number of synthetic reactions for the construction of the pyridine framework, the development of a new type of reaction that gives direct access to structurally diverse pyridine derivatives remains an important research topic, because of the increasing demand for pyridine derivatives that can function as lead compounds for pharmaceutical drugs and as potential organic functional materials.<sup>1</sup> In this context, we have developed a nickel-catalyzed intermolecular cycloaddition reaction to afford structurally diverse pyridines derivatives. Herein, we report that the cycloaddition of  $\alpha$ , $\beta$ -unsaturated oximes with alkynes is efficiently catalyzed by Ni(0)/IPr to afford highly substituted pyridines. The reaction represents the first example of a nickel-catalyzed formal [4 + 2] cycloaddition of 1,3-azadienes and alkynes to give pyridines.<sup>2,3</sup>

Initially, it was found that the reaction of  $\alpha$ .  $\beta$ -unsaturated oxime 1a with 4-octyne (2a) in the presence of a nickel catalyst, which was prepared in situ from [Ni(cod)<sub>2</sub>] (10 mol%) and IPr (1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) (10 mol%), in toluene at 130 °C for 3 h, provided pyridine 3aa in 22% yield (Table 1, Entry 1, in parentheses). The use of IMes (1,3bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) or phosphine ligands such as PPh<sub>3</sub>, PCy<sub>3</sub>, Pt-Bu<sub>3</sub>, and PMe<sub>3</sub>, in place of IPr resulted in formation of 3aa in lower yields or trace amounts. Among various reaction media examined, toluene gave the best result in providing 3aa. Upon optimization of the reaction conditions, 3aa was obtained in improved yield (Entry 1): addition of *i*-PrOH (5 equiv) was found to be effective in affording 3aa in 75% yield. With the optimized reaction conditions in hand, we next examined the substrate scope of this [4+2] cycloaddition. Oximes such as **1b**, **1c**, and **1d** possessing aliphatic substituents also participated in the reaction to furnish the corresponding pyridine derivatives (Entries 2-4). Furthermore, it was found that  $\alpha,\beta$ -unsaturated oximes with an aryl group were generally effective, regardless of electron-donating or -withdrawing substituents (Entries 5-8). The cycloaddition of 1a with an unsymmetrical alkyne, 4-methyl-2-pentyne (2b), also gave the pyridine 3ab in 71% yield, consisting of regioisomers in a 2/1 ratio (Entry 9).

Table 1. Nickel-catalyzed cycloaddition of 1 with  $2^a$ 



<sup>a</sup>Reactions were carried out using [Ni(cod)<sub>2</sub>] (10 mol %), IPr (10 mol %), **1** (0.3 mmol), and **2** (0.6 mmol) in 1.5 mL of toluene at 130 °C for 3 h in a sealed tube. <sup>b</sup>Isolated yields are given. <sup>c</sup>Without an addition of *i*-PrOH. <sup>d</sup>Ratio of regioisomers.



Table 2. Nickel-catalyzed cycloaddition of 4 with 2<sup>a</sup>



<sup>a</sup>Reactions were carried out using [Ni(cod)<sub>2</sub>] (10 mol %), IPr (10 mol %), 4 (0.3 mmol), and 2 (0.6 mmol) in 1.5 mL of toluene at 130 °C for 3 h in a sealed tube. <sup>b</sup>Isolated yields are given. <sup>c</sup>Ratio of regioisomers.

As shown in Table 2, the present nickel-catalyzed cycloaddition can be applied not only to  $\alpha,\beta$ -unsaturated oximes but also to  $\beta$ ,  $\gamma$ -unsaturated oximes in the synthesis of pyridines. The cycloaddition of  $\beta$ ,  $\gamma$ -unsaturated oxime 4a with 4-octyne (2a) afforded pyridine 5aa in 80% yield under the same reaction conditions: the reaction was performed by addition of *i*-PrOH (5 equiv) in the presence of [Ni(cod)<sub>2</sub>] (10 mol%) and IPr (10 mol %) in toluene at 130 °C for 3 h (Entry 1). The reaction of  $\beta$ ,  $\gamma$ -unsaturated oxime **4b** bearing an electron-withdrawing substituent on the phenyl group with 4-octyne (2a) furnished the correspondingly substituted pyridine 5ba in 67% yield (Entry 2). However, the cycloaddition of 4c possessing an electron-donating substituent resulted in formation of 5ca in lower yield (23%, Entry 3). The reaction of 4a with an unsymmetrical alkyne, 4-methyl-2-pentyne (2b), furnished the pyridine **5ab** with a regioisomer ratio of 5/1 (Entry 4).

Even though the mechanism of this reaction has not been elucidated completely, we propose the following reaction pathway, based on the results that we observed (Scheme 1).<sup>4</sup> The reaction is initiated by the oxidative addition of an oxime N-O bond to an Ni(0) complex, followed by insertion of an alkyne into an N-Ni bond to afford intermediate 7. The subsequent intramolecular insertion of the olefin affords intermediate 8. The methoxy ligand on the nickel would then be replaced with i-PrOH to afford 9. Notably, treatment of 1i with 2a in the presence of the Ni(0)/IPr catalyst in the absence of *i*-PrOH furnished pyridine 3aa in excellent yield (88% yield, Scheme 2). This result suggests that the ligand-exchange reaction of intermediate



Scheme 1. Plausible reaction pathway.



Scheme 2. Effects of *N*-substituent on  $\alpha,\beta$ -unsaturated oxime.

8 with *i*-PrOH to afford intermediate 9 is the rate-determining step in the catalytic process.  $\beta$ -Hydride elimination would give 10, and a second  $\beta$ -hydride elimination, with aromatization of the six-membered heterocycle, would provide pyridine 3aa.<sup>5</sup>

In conclusion, we have demonstrated that  $\alpha,\beta$ -unsaturated oximes reacted with alkynes in the presence of a nickel catalyst to furnish 2,3,4,6-tetrasubstituted pyridines. Furthermore, it was found that the use of  $\beta$ ,  $\gamma$ -unsaturated oximes in place of  $\alpha$ ,  $\beta$ unsaturated oximes also provides 2,3,4,6-tetrasubstituted pyridines.6

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It is reasonable to consider that the NiH2 reacts with alkynes, which exist in 5 the reaction mixture in excess, to regenerate the starting Ni(0) complex via hydrogenation. Indeed, the nickel-catalyzed cycloaddition of 7-tetradecyne with 1a furnished correspondingly substituted pyridine along with tetradecenes.

6 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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