Pyridine-N-Oxide Functionalization

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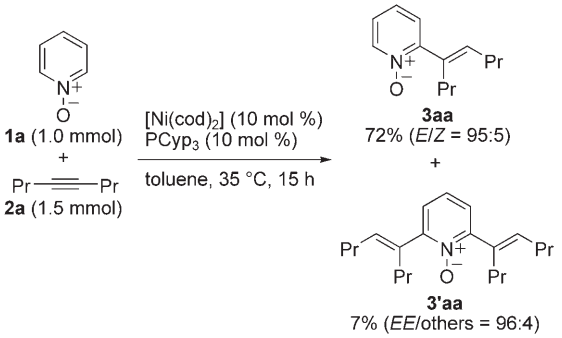
Nickel-Catalyzed Addition of Pyridine-*N*-oxides across Alkynes**

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

Dedicated to Professor Miguel Yus on the occasion of his 60th birthday

Substituted pyridines are important intermediates in the synthesis of pharmaceuticals and functional materials. However, most of the synthetic methods require prefunctionalization, for example by halogenation or metalation, before subsequent coupling reactions owing to the low reactivity of pyridine derivatives towards aromatic electrophilic substitution reactions such as the Friedel–Crafts reaction. Whereas direct C–H functionalization of pyridines catalyzed by a transition-metal complex appears to be ideal, only a few examples are available, and these require a directing group and suffer from harsh reaction conditions or limited substrate scope.[1] On the other hand, pyridine-*N*-oxides have emerged as a promising alternative for the direct C–H functionalization of pyridine rings.[2] Herein we report the nickel-catalyzed *E*-selective alkenylation of pyridine-*N*-oxides at C2 by means of C2–H activation followed by stereoselective insertion of an alkyne under mild conditions. The resulting adducts are readily deoxygenated to give 2-alkenylpyridines, demonstrating that the sequence of reactions provides a novel route for C2 functionalization of pyridine derivatives.

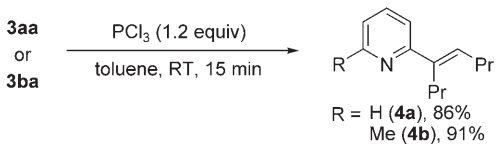
We have recently reported the C–H activation of various five-membered heteroarenes and addition reactions across alkynes in the presence of a catalyst generated from [Ni(cod)$_2$] (cod = cyclooctadiene) and tricyclopentylphosphine (PCyp$_3$) in toluene at 35 °C.[3] Although the reaction conditions were ineffective for addition of pyridine itself across alkynes even at elevated temperatures, we have found that pyridine-*N*-oxide (**1**) undergoes the desired addition reaction exclusively at the C2 position across 4-octyne (**2a**) under the same reaction conditions to give (*E*)-2-(4-octen-4-yl)pyridine-*N*-oxide (**3aa**) in 72 % yield [Eq. (1)].[4] The product (*E*)-**3aa** was contaminated by small amounts of the related *Z* isomer, produced most probably by isomerization of the initially formed *cis* adduct. We suppose this because ^{1}H NMR analysis of the reaction mixture showed gradual formation of (*Z*)-**3aa** during the course of the reaction. A mixture of stereoisomers of the 2,6-dialkenylated product **3′aa** was also isolated in 7 % yield.



(1)

The present conditions were applicable to a diverse range of pyridine-*N*-oxides. The addition of 2-picoline-*N*-oxide (**1b**) gave a 93:7 (*E*/*Z*) mixture of 2-alkenylated products in 67 % yield (entry 1, Table 1); analogous results were obtained with with 3- and 4-methylpicoline-*N*-oxides (entries 2 and 3, Table 1). On the other hand, no trace of the stereoisomeric product was observed with 5-methylpicoline-*N*-oxide (**1e**), probably owing to the steric hindrance of the 5-methyl group (entry 4, Table 1). Whereas the ester functionality of 5-methoxycarbonyl-2-picoline-*N*-oxide (**1f**) was tolerated under the present conditions and the corresponding adduct was obtained in high yield (entry 5, Table 1), the reaction was sluggish with pyridine-*N*-oxides bearing Cl, Br, and NO$_2$ groups.[5] Isoquinoline-*N*-oxide also reacted selectively at the C1 position (entry 6, Table 1). The hydroheteroarylation of other alkynes such as 4-methyl-2-pentyne (**2b**) and 4,4-dimethyl-2-pentyne (**2c**) with **1b** also proceeded smoothly to give the respective adducts, in which the bulkier substituent is *trans* to the pyridyl ring, in excellent regio- and stereoselectivities (entries 7 and 8, Table 1). Terminal alkynes, such as 1-octyne and phenylacetylene, failed to participate in the reaction presumably owing to rapid oligomerization and/or trimerization of the alkynes.

The resulting alkenylated pyridine-*N*-oxides were readily deoxygenated with PCl$_3$ to provide free 2-alkenylpyridines in excellent yields [Eq. (2)]. Furthermore, the deoxygenative functionalizations of the adducts were successfully demon-



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[*] K. S. Kanyiva, Dr. Y. Nakao, Prof. Dr. T. Hiyama
Department of Material Chemistry
Graduate School of Engineering
Kyoto University, Kyoto 615-8510 (Japan)
Fax: (+81) 75-383-2445
E-mail: nakao@npc05.kuic.kyoto-u.ac.jp
thiyama@npc05.kuic.kyoto-u.ac.jp

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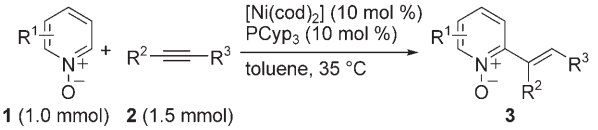
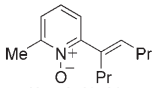
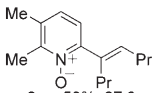
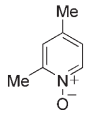
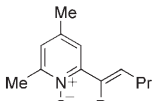
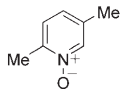
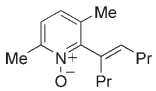
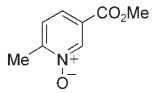
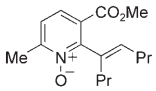
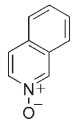
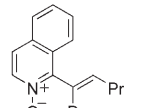
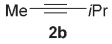
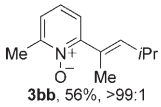
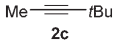
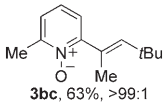
Table 1: Nickel-catalyzed addition of pyridine-*N*-oxides across alkynes.

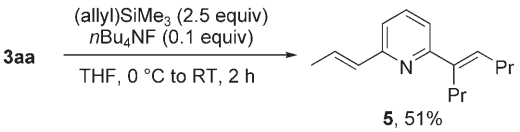


1 (1.0 mmol) **2** (1.5 mmol) **3**

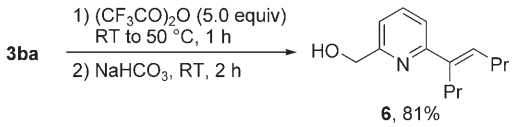
Entry	1	2	*t* [h]	Prod., Yield[a], *E*/*Z*[b]
1	 **1b**	**2a**	15	 **3ba**, 67%, 93:7
2	 **1c**	**2a**	22	 **3ca**, 59%, 97:3
3	 **1d**	**2a**	22	 **3da**, 54%, 94:6
4	 **1e**	**2a**	40	 **3ea**, 66%, >99:1
5	 **1f**	**2a**	24	 **3fa**, 81%, >99:1
6	 **1g**	**2a**	24	 **3ga**[c], 60%, >99:1
7	**1b**	 **2b**	15	 **3bb**, 56%, >99:1
8	**1b**	 **2c**	15	 **3bc**, 63%, >99:1

[a] Yield of isolated product based on **1**. [b] Estimated by ^{1}H NMR spectroscopy. [c] (*E*,*E*)-1,3-Di(4-octen-4-yl)isoquinoline-*N*-oxide (**3′ga**) was also isolated in 5% yield.

strated by the reaction of **3aa** with allyl(trimethyl)silane in the presence of a catalytic amount of nBu$_4$NF to afford **5** in 51% yield [Eq. (3)][6] and by the transfer of the oxygen moiety of **3ba** to the benzylic position, affording **6** in 81% yield [Eq. (4)].[7]

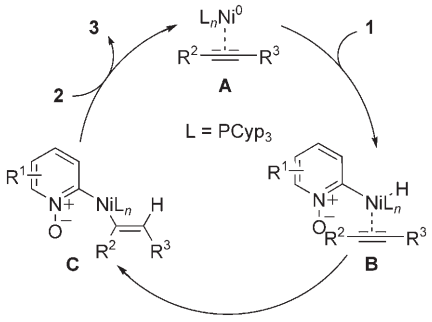


(3)



(4)

A plausible mechanism for this hydroheteroarylation reaction is shown in Scheme 1. We consider that the alkyne-coordinated nickel(0) species **A**[8] undergoes oxidative addition to the C2–H bond,[9,10] giving the pyridyl(hydride)nickel



Scheme 1. A plausible mechanism for the nickel-catalyzed hydroheteroarylation of alkynes using pyridine-*N*-oxides. The steric bulk of R^3 is the same as or greater than that of R^2.

species **B**. Hydronickelation in a *cis* fashion then provides the alkenyl(pyridyl)nickel intermediate **C**. Coordination of the alkyne such that the steric repulsion between the bulkier R^3 and the pyridyl group in **B** is avoided would be responsible for the observed regioselectivities (entries 7 and 8, Table 1). Reductive elimination followed by coordination of an alkyne affords 2-alkenylpyridine-*N*-oxide **3** and regenerates the nickel(0) species **A**. The *N*-oxide moiety plays an important role in directing the metal catalyst to the proximal C2–H bond and/or making the C–H bond acidic enough to undergo the oxidative addition to nickel(0).

In summary, we have demonstrated nickel-catalyzed activation of C2–H bonds of pyridine-*N*-oxides under mild conditions followed by regio- and stereoselective insertion of alkynes to afford (*E*)-2-alkenylpyridine-*N*-oxides in modest to good yields. The resulting adducts are readily deoxygenated to give various substituted pyridines, which are useful intermediates for pharmaceuticals and materials. Current efforts are directed to further development of direct C–H functionalization reactions under the newly disclosed nickel catalysis under mild conditions.

Experimental Section

General procedure: A pyridine-*N*-oxide (1.0 mmol) and an alkyne (1.5 mmol) were added sequentially to a solution of [Ni(cod)$_2$] (28 mg, 0.10 mmol) and PCyp$_3$ (24 mg, 0.10 mmol) in toluene (2.5 mL) in a dry box. The vial was taken outside the dry box and heated at 35 °C for the time specified in Table 1. The resulting mixture was filtered through a pad of silica gel, concentrated in vacuo, and purified by flash chromatography on silica gel to give the corresponding hydroheteroarylation products in the yields listed in Table 1.

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[4] When less catalyst was used (1–5 mol%), **3aa** was obtained in lower yields (37–55% by ^{1}H NMR spectroscopy) even after 24 h.

[5] These pyridine-*N*-oxides were sparingly soluble in toluene.

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