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Editor's Choice

Nickel-catalyzed Cycloaddition of Aromatic (*O*-Benzyl)ketoximes with Alkynes to Produce Isoquinoline and Isoquinoline *N*-Oxide Derivatives

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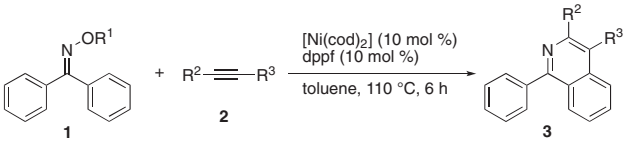
A nickel-catalyzed cycloaddition of aromatic (*O*-benzyl)-ketoximes with alkynes to afford 3,4-disubstituted isoquinoline derivatives has been developed. The reaction involves oxidative addition of N–O bond of *O*-benzylketoxime to Ni(0) and subsequent intermolecular C–H bond activation via elimination of benzyl alcohol. It was also found that ketoximes participate in the nickel-catalyzed reaction with alkynes to furnish isoquinoline *N*-oxide derivatives.

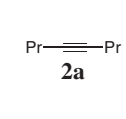
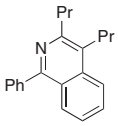
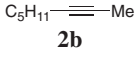
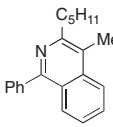
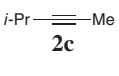
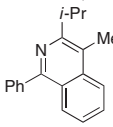
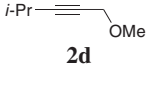
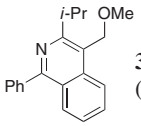
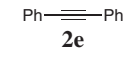
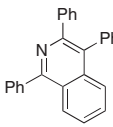
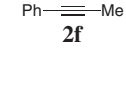
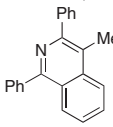
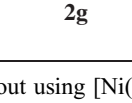
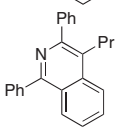
In recent years, transition-metal-catalyzed reactions, which involve C–H bond cleavage as a key reaction step,[1] have been recognized as powerful methodologies for the synthesis of structurally diverse isoquinolines,[2,3] because they allow synthesis of isoquinolines which are difficult to prepare with conventional methods.[4–10] However, the reactions generally need to be performed in the presence of an external oxidant to enable a catalytic process. Herein, we wish to report a catalytic N–O/C–H bond cleavage tandem process for the construction of isoquinolines with cycloaddition of aromatic (*O*-benzyl)ketoximes and alkynes via elimination of benzyl alcohol. The process does not require an additional oxidant.

Initially, when *O*-benzylketoxime **1a** and 4-octyne (**2a**) were treated in the presence of a nickel catalyst, which was prepared in situ from $[Ni(cod)_2]$ (10 mol %) and dppe (10 mol %) in toluene at 110 °C for 6 h, isoquinoline **3aa** was obtained in 48% yield along with benzyl alcohol in 31% yield (Table 1, Entry 1). Upon optimization of the nickel catalyst, **3aa** was obtained in excellent yield; a combination of $[Ni(cod)_2]$ and dppf was found to be effective in affording **3aa** in 80% yield (Entry 4). We then evaluated the effects of the *O*-substituent on an oxime. Oximes consisting of the *O*-methyl and *O*-(mesitylmethyl) group afforded **3aa** in lower yields (Entries 5 and 6), whereas **1d** and **1e** failed to participate in the reaction to afford **3aa** (Entries 7 and 8). The reaction of **1a** with 2-octyne (**2b**) afforded the isoquinoline **3ab** in 76% yield with regioisomer ratio of 1/1 (Entry 9). The reaction of **1a** with unsymmetrical alkynes, such as **2c** and **2d**, also gave the isoquinolines consisting of regioisomers in 1/1 ratio (Entries 10 and 11). The cycloaddition is also compatible with aryl-substituted unsymmetrical alkynes and afforded the corresponding isoquinoline with higher regioselectivity (Entries 13 and 14, Figure 1).

We next examined effects of substituents on *O*-benzylketoxime **1** to gain insight into the cycloaddition. The results of this investigation are summarized in Table 2. Aromatic (*O*-benzyl)ketoxime **1f** consisting of the aryl moiety with electron-withdrawing fluoride substituent, afforded **3fa** in good yield (Entry 2). Whereas *O*-benzylketoximes **1g** and **1h** possessing the aryl moiety with electron-donating substituents reacted with **2a** to afford cycloadducts **3ga** and **3ha** in lower yields of 47% and 26%, respectively (Entries 3 and 4). It was found that

Table 1. Nickel-catalyzed cycloaddition of **1** with **2**[a]



Entry	**1**	R^1	**2**	**3**, Yield[b]/%
1	**1a**	CH_2Ph	 **2a**	 **3aa**, 48[c]
2	**1a**		**2a**	**3aa**, 62[d]
3	**1a**		**2a**	**3aa**, 56[e]
4	**1a**		**2a**	**3aa**, 80
5	**1b**	Me	**2a**	**3aa**, 10
6	**1c**	CH_2Mes	**2a**	**3aa**, 5
7	**1d**	OC(O)Ph	**2a**	**3aa** <1
8	**1e**	$OC(O)C_6F_5$	**2a**	**3aa** <1
9	**1a**	CH_2Ph	 **2b**	 **3ab**, 76 (1/1)[f]
10	**1a**	CH_2Ph	 **2c**	 **3ac**, 60 (1/1)[f]
11	**1a**	CH_2Ph	 **2d**	 **3ad**, 43 (1/1)[f]
12	**1a**	CH_2Ph	 **2e**	 **3ae**, 37
13	**1a**	CH_2Ph	 **2f**	 **3af**, 59 (4/1)[f]
14	**1a**	CH_2Ph	 **2g**	 **3ag**, 66 (5/1)[f]

[a]Reactions were carried out using $[Ni(cod)_2]$ (10 mol %), dppf (10 mol %), **1** (0.6 mmol), and **2** (0.3 mmol) in 1 mL of toluene at 110 °C for 6 h in a sealed tube. [b]Isolated yields are given. [c]dppe (10 mol %). [d]dppp (10 mol %). [e]dppb (10 mol %). [f]Ratio of regioisomers.

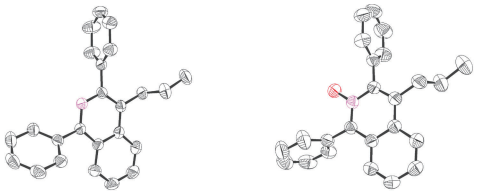
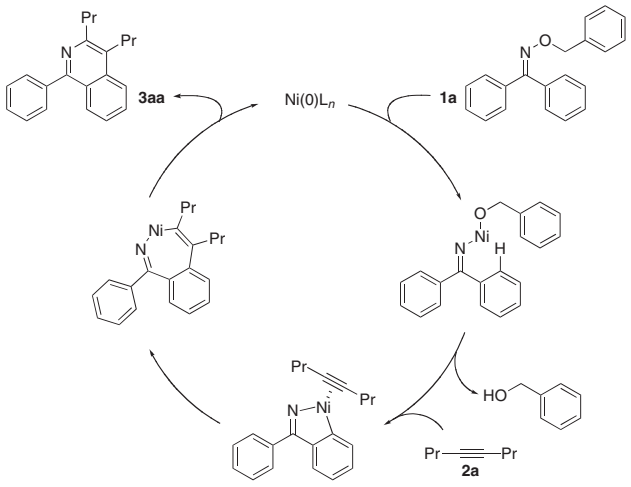


Figure 1. ORTEP drawings of **3ag** and **5ag**.



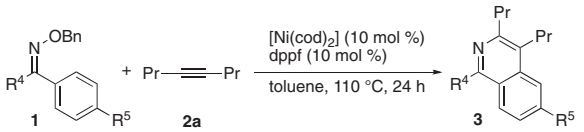
Scheme 1. Plausible reaction mechanism.

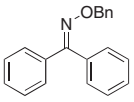
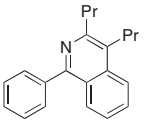
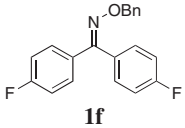
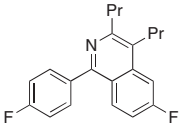
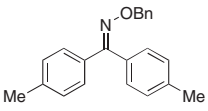
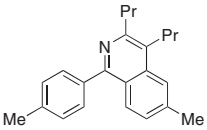
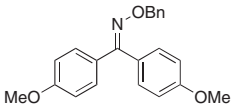
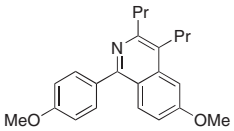
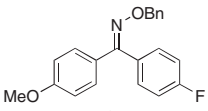
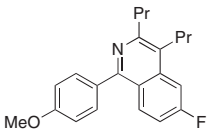
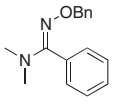
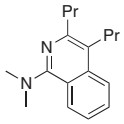
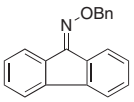
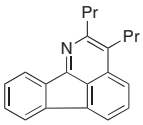
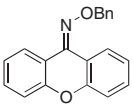
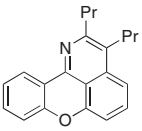
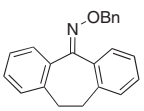
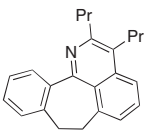
unsymmetrical *O*-benzylketoxime **1i** reacts with alkyne **2a** to give a mixture of regioisomer **3ia** and **3ia′** in a ratio of 1/1 (Entry 5). The reaction of imidamide **1j** with **2a** did not give **3ja** (Entry 6). Neither five-membered-ring nor seven-membered-ring fused *O*-benzylketoximes reacted with **2a** to afford cycloadducts (Entries 7 and 9). However, six-membered-ring fused *O*-benzylketoxime **1l** reacted with **2a** to furnish **3la** in 65% yield (Entry 8).

While 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). It is reasonable to consider that the catalytic cycle of the present reaction should consist of the oxidative addition of an oxime N–O bond to a Ni(0) complex.[11] Subsequent elimination of benzyl alcohol via C–H bond cleavage affords five-membered nickelacycle intermediate. Even though we were not successful in an isolation of the nickelacycle intermediate, we found that treatment of **1a** with stoichiometric amount of Ni(0)/dppf in the absence of alkyne furnished benzyl alcohol.[12] The alkyne would then insert into the C–Ni bond to give seven-membered nickelacycle. With its seven-membered ring strain, Ni can undergo a facile reductive elimination to give **3aa**, and regenerates the starting Ni(0) complex.

Lastly, it should be noted that the use of ketoximes **4** in place of *O*-benzylketoximes with the reaction of alkynes resulted in formation of 3,4-disubstituted isoquinoline *N*-oxides **5** (Table 3). Upon optimization of the nickel catalyst, **5aa** was obtained in good to moderate yield along with **3aa** when $[Ni(cod)_2]$ was used as a catalyst in the absence of ligand (Entry 1). The reaction is also compatible with aryl-substituted alkynes and afforded the corresponding isoquinolines *N*-oxide **5**

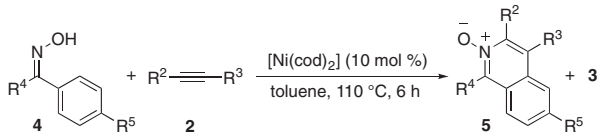
Table 2. Nickel-catalyzed cycloaddition of **1** with **2a**[a]

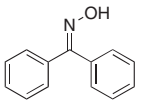
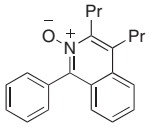
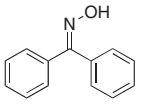
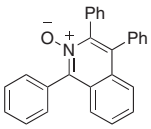
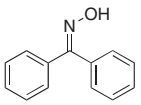
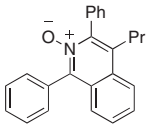
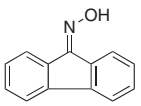
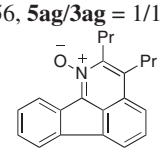
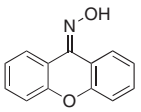
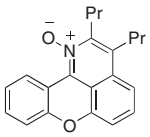
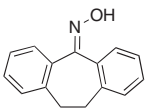
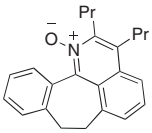


Entry	1	3, Yield[b]/%
1	 **1a**	 **3aa**, 80
2	 **1f**	 **3fa**, 67
3	 **1g**	 **3ga**, 47
4	 **1h**	 **3ha**, 26[c]
5	 **1i**	 **3ia**, 60 (1/1)[d]
6	 **1j**	 **3ja**, <1
7	 **1k**	 **3ka**, <1
8	 **1l**	 **3la**, 65
9	 **1m**	 **3ma**, <1

[a]Reactions were carried out using $[Ni(cod)_2]$ (10 mol %), dppf (10 mol %), **1** (0.6 mmol), and **2** (0.3 mmol) in 1 mL of toluene at 110 °C for 6 h in a sealed tube. [b]Isolated yields are given. [c]Reaction time: 24 h. [d]Ratio of regioisomers.

Table 3. Nickel-catalyzed cycloaddition of **4** with **2**[a]



Entry	4	2	Yield[b]/%, Products
1	 **4a**	**2a**	 57, **5aa/3aa** = 3/1
2	 **4a**	**2e**	 60, **5ae/3ae** = 1.2/1
3	 **4a**	**2g**	 56, **5ag/3ag** = 1/1[c]
4	 **4l**	**2a**	 <1
5	 **4m**	**2a**	 34, **5ma/3ma** = 2/1
6	 **4n**	**2a**	 <1

[a]Reactions were carried out using $[Ni(cod)_2]$ (10 mol %), **4** (0.3 mmol), and **2** (0.9 mmol) in 1 mL of toluene at 110 °C for 6 h in a sealed tube. [b]Isolated yields are given. [c]**5ag**/**5ag′** = 99/1, **3ag**/**3ag′** = 13/1.

along with isoquinolines **3** (Entries 2 and 3, Figure 1). Although **4l** and **4n** did not react with **2a** to afford any cycloadducts **5** (Entries 4 and 6), **4m** reacted with **2a** to furnish **5ma** along with **3ma** (34%, Entry 5).

In conclusion, we have demonstrated that *O*-benzylketoximes reacted with alkynes in the presence of nickel catalyst via elimination of benzyl alcohol to furnish 3,4-disubstituted isoquinolines. It was also found that the use of ketoxime in place of *O*-benzylketoximes resulted in formation of 3,4-disubstituted isoquinoline *N*-oxides as a major product.[13]

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References and Notes

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