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Nickel-Catalyzed Dehydrogenative [4 + 2] Cycloaddition of 1,3-Dienes with Nitriles

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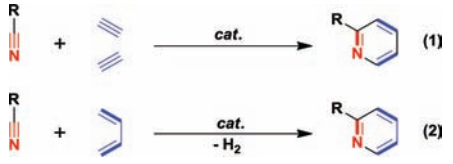
Supporting Information

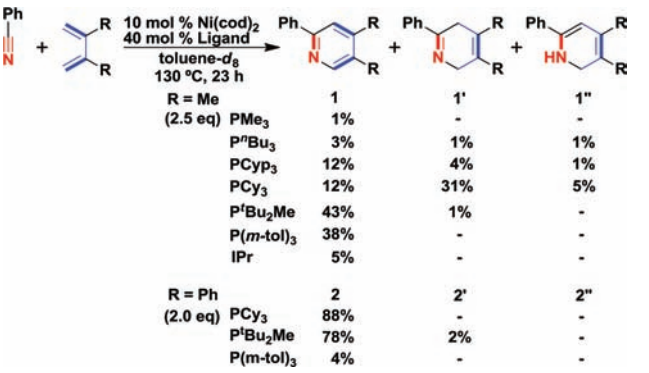
ABSTRACT: Pyridines, which comprise one of the most important classes of the six-membered heterocyclic compounds, are widely distributed in nature, and the transition-metal-catalyzed [2 + 2 + 2] cycloaddition reaction of two alkynes and a nitrile is one of the most powerful methods for preparing versatile, highly substituted pyridine derivatives. However, the lack of chemo- and regioselectivity is still a crucial issue associated with fully intermolecular [2 + 2 + 2] cycloaddition. The present study developed the Ni(0)-catalyzed intermolecular dehydrogenative [4 + 2] cycloaddition reaction of 1,3-butadienes with nitriles to give a variety of pyridines regioselectively.

Transition-metal-catalyzed [2 + 2 + 2] cycloaddition reactions of two alkynes with a nitrile to give pyridine derivatives have received a great deal of attention as a very straightforward method to synthesize pyridines (eq 1).[1] Most of the reported reactions, so far, have used α,ω-diynes, cyanoalkynes, or nitrile-diynes to control regioselectivity and to enhance reactivity.[2] As a result, the obtained pyridines inevitably were either bi- or multicyclic compounds. In contrast, fully intermolecular [2 + 2 + 2] cycloaddition reactions have been demonstrated to attain monocyclic pyridines.[3] However, regioselective intermolecular reactions of unsymmetric alkynes with nitriles are rare. Potentially, the [4 + 2] cycloaddition[4] of 1,3-butadienes with nitriles followed by aromatization would be an efficient method for the regioselective construction of the pyridine skeleton. However, because the elaborate diene, which has a leaving group (X) in its structure, is required to give the pyridine framework by elimination of HX from the corresponding primary product, 2,5-dihydropyridine, only scattered examples have been reported so far.[5,6] Otherwise, either a very high reaction temperature[7] or a highly activated nitrile such as perfluoroalkyl nitrile[8] is required. Furthermore, no catalytic dehydrogenative [4 + 2] cycloaddition reaction of butadienes with nitriles has been reported yet (eq 2).[9]



Recently, we have reported the intramolecular oxidative cyclization of an alkene and a nitrile with nickel(0) to give aza-nickelacycles; however, no intermolecular reaction occurred.[10] Conversely, the intermolecular reaction of an aldehyde and a 1,3-butadiene with nickel(0) species easily took place to give the corresponding oxa-nickelacycle,[11] whereas the intermolecular oxidative cyclization of an aldehyde and a simple alkene with nickel(0) did not proceed at all.[12] The occurrence of an intermolecular reaction with 1,3-dienes might be due to stabilization by the contribution of the η^3-allyl structure. Thus, it seems quite possible that the oxidative cyclization of a 1,3-butadiene and a nitrile with nickel(0) species gave the corresponding η^3-allyl aza-nickelacycle that might have acted as an intermediate for the dehydrogenative [4 + 2] cycloaddition reaction of 1,3-butadienes with nitriles. We report the nickel-catalyzed dehydrogenative [4 + 2] cycloaddition reaction of 1,3-dienes with nitriles to give pyridines. Moreover, the isolation of the reaction of an intermediate nickel complex and a possible reaction path are also discussed.

Scheme 1. Ligand Screening

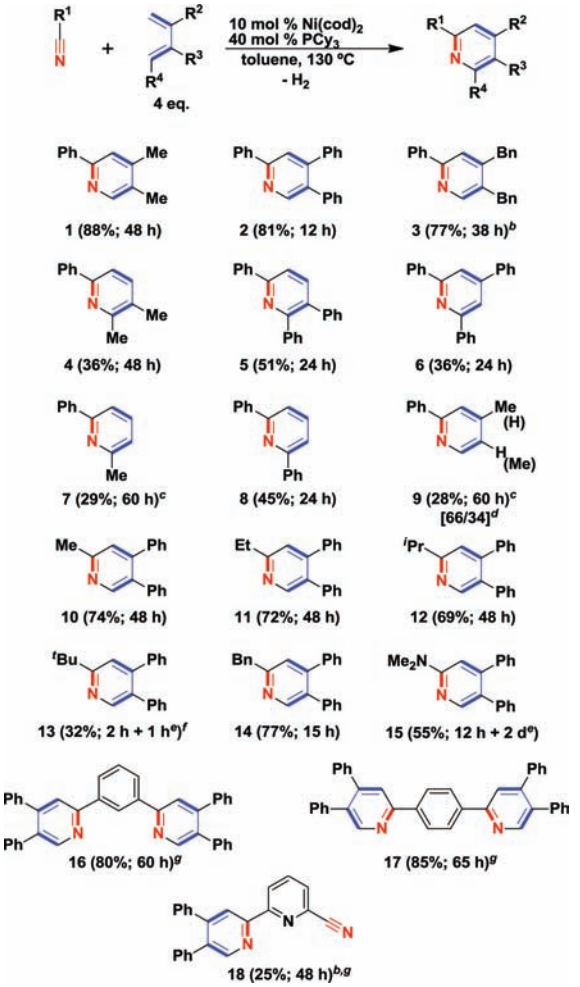


		1	1′	1″
R = Me				
(2.5 eq)	PMe_3	1%	-	-
	P^nBu_3	3%	1%	1%
	$PCyp_3$	12%	4%	1%
	PCy_3	12%	31%	5%
	P^tBu_2Me	43%	1%	-
	$P(m\text{-tol})_3$	38%	-	-
	IPr	5%	-	-
R = Ph		2	2′	2″
(2.0 eq)	PCy_3	88%	-	-
	P^tBu_2Me	78%	2%	-
	$P(m\text{-tol})_3$	4%	-	-

The reaction of 2,3-dimethyl-1,3-butadiene with benzonitrile in toluene-d_8 at 130 °C for 23 h was conducted in the presence of a catalytic amount of $Ni(cod)_2$ and various ligands. The results are summarized in Scheme 1. Although P^tBu_2Me gave the best result for the formation of 4,5-dimethyl-2-phenylpyridine (**1**), the precipitation of nickel black was observed after 8 h. The total yield of **1** and 3,4-dimethyl-6-phenyldihydropyridines (**1′** and **1″**) (48%) in the presence of PCy_3 was better than that in the presence of P^tBu_2Me. Moreover, in the reaction of 2,3-diphenyl-1,3-butadiene with benzonitrile, PCy_3 gave the best result. The formation of a mixture of butenes was observed, which suggests

Received: May 24, 2011
Published: October 17, 2011

Scheme 2. Ni(0)-Catalyzed Dehydrogenative [4 + 2] Cycloaddition of 1,3-Dienes with Nitriles[a]



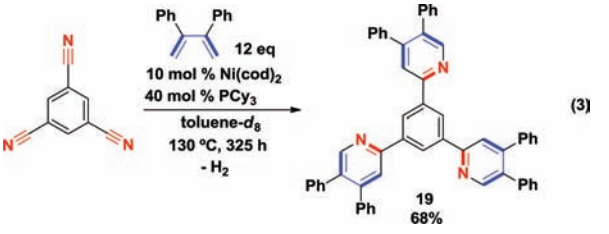
[a] General Condition: nitrile (0.5 mmol). Isolated yield and reaction time in parentheses. [b]Run with 0.25 mmol of nitrile. [c]Run with 1.0 mmol of nitrile. [d]Minor regioisomer in parentheses. [e]The oxidation step was performed under aerobic conditions (in toluene reflux). See also Supporting Information for detailed procedures. [f]Pivalonitrile was used as a solvent. The isolated yield is based on 2,3-diphenyl-1,3-butadiene (1.0 mmol). [g]Run with 8 equiv of 2,3-diphenyl-1,3-butadiene.

the occurrence of the hydrogenation of the 1,3-butadienes. Although styrene and norbornene were examined as hydrogen scavengers, neither of them was hydrogenated. Thus, the catalytic reaction was carried out in the presence of 4 equiv of 1,3-butadienes to avoid a shortage.[13]

A variety of 1,3-butadienes and nitriles could be applied to the reaction. In the presence of a catalytic amount of $Ni(cod)_2$ and PCy_3, the reaction of benzonitrile with 2,3-dimethyl-1,3-butadiene at 130 °C gave **1** in 88% isolated yield (Scheme 2). The reaction of benzonitrile with 2,3-diphenyl-1,3-butadiene and 2,3-dibenzyl-1,3-butadiene afforded 2,4,5-triphenylpyridine (**2**) and 4,5-dibenzyl-2-phenylpyridine (**3**) in 81% and 77% yield, respectively, whereas the reaction with 2,3-dimethoxy-1,3-butadiene or Danishefsky's diene did not give the corresponding pyridine at all. Treatment of benzonitrile with 1,2-disubstituted-1,3-butadiene, such as 3-methylpenta-1,3-diene and 1,2-diphenylbuta-1,3-diene, gave 2,3-dimethyl-6-phenylpyridine (**4**) and 2,3,6-triphenylpyridine (**5**) in 36% and 51% yield, respectively, and the corresponding 2,3,4-trisubstituted pyridines were not generated. In addition, 1,3-diphenylbuta-1,3-diene underwent the dehydrogenative [4 + 2] cycloaddition with benzonitrile in a regioselective manner to yield 2,4,6-triphenylpyridine (**6**) in moderate yield. 1,3-Pentadiene and 1-phenyl-1,3-butadiene also reacted with benzonitrile to yield 2-methyl-6-phenylpyridine (**7**) and 2,6-diphenylpyridine (**8**), respectively, as a sole product. This reaction allowed the regioselective preparation of 2,6-disubstituted pyridines. The reaction of isoprene with benzonitrile gave the corresponding pyridine (**9**) as a mixture of regioisomers. Neither 1,4-diphenyl-1,3-butadiene nor 2,4-hexadiene reacted with benzonitrile under the same reaction conditions. These results clearly indicate that, in this dehydrogenative [4 + 2] cycloaddition reaction, the nitrile carbon is prone to couple with the nonsubstituted terminal carbon of the 1,3-diene.

Acetonitrile, propylnitrile, isobutylnitrile, pivalonitrile, and 2-phenylacetonitrile also underwent dehydrogenative [4 + 2] cycloaddition to give the expected 2,4,5-trisubstituted pyridines as a sole product (**10**−**14**). In addition, *N*,*N*-dimethylcyanamide could take part in the Ni-catalyzed coupling reaction with 1,3-diene to give 2-aminopyridine (**15**) in moderate yield, while acrylonitrile did not afford the corresponding pyridine at all. In the cases of formation **13** and **15**, reduction in reaction time and improvement of product yields were achieved by conducting the oxidation step from dihydropyridines to pyridines under aerobic conditions. Thus, it was demonstrated that a variety of substituents could be introduced into the 2-position of pyridines with complete regioselectivity. Furthermore, di- and tricyano benzenes could be employed as a substrate for the synthesis of di- and tripyridine derivatives. Both isophthalonitrile and terephthalonitrile reacted with 2,3-diphenyl-1,3-butadiene to give the corresponding 1,3-bis(4,5-diphenylpyridin-2-yl)benzene (**16**) and 1,4-bis(4,5-diphenylpyridin-2-yl)benzene (**17**) in 80% and 85% isolated yield, respectively. During the reaction, an increase of monopyridinyl benzene at an earlier stage and its decrease at a later stage were observed. However, 1,2-dicyanobenzene did not react with 2,3-diphenyl-1,3-butadiene under the same reaction conditions due to the formation of a complicated mixture of nickel complexes. We also attempted the reaction of 1,3-dienes with 2,6-dicyanopyridine with the expectation that substituted terpyridines would be formed. However, the reaction with 2,3-diphenyl-1,3-butadiene gave 4′,5′-diphenyl-(2,2′-bipyridine)-6-carbonitrile (**18**) in low yield and the expected terpyridine product was not generated at all.

The reaction could be applied to the synthesis of a 1,3,5-tripyridiylbenzne (eq 3). Under the same reaction conditions, benzene-1,3,5-tricarbonitrile also underwent dehydrogenative [4 + 2] cycloaddition with 2,3-diphenyl-1,3-butadiene to give 1,3,5-tris(4,5-diphenylpyridin-2-yl)benzene (**19**) in 68% isolated yield. The reaction proceeded in a stepwise manner, and the formation of the corresponding mono- and dipyridinyl benzenes was observed.



(3)

dx.doi.org/10.1021/ja208162w |J. Am. Chem. Soc. 2011, 133, 18018–18021

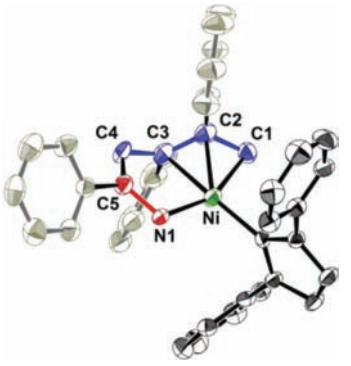
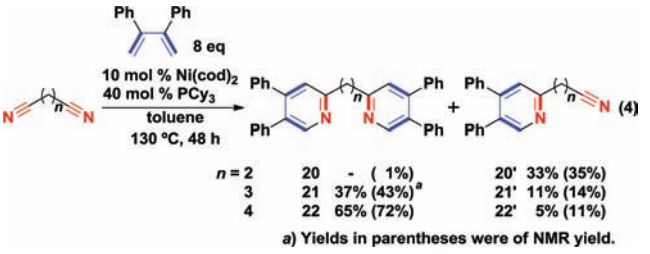


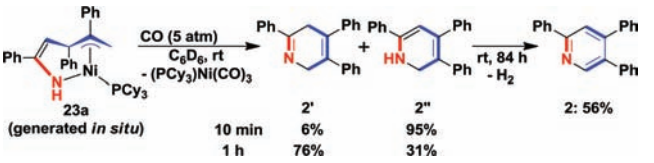
Figure 1. Molecular structure of **23b** with thermal ellipsoids at the 30% probability level. H-atoms and isopropyl groups on IPr are omitted for clarity.

Aliphatic dicyano compounds, such as succino-, glutaro-, and adiponitrile, were also examined as substrates for this reaction. The alkyl chain length is crucial for the reaction, and a longer chain length gave better results (eq 4). The reaction of succinonitrile with 2,3-diphenyl-1,3-butadiene gave a trace amount of the desired dipyridinyl derivative (**20**), and the major product was the corresponding monopyridine (**20′**; 33% isolated yield). The nitriles tethered by a longer alkyl chain (n = 3 or 4) gave dipyridinyl alkanes (**21** and **22**) in 37% and 65% isolated yields, respectively, as a mixture with the corresponding monopyridinyl compound (**21′** and **22′**). The formation of a variety of dipyridine and tripyridine compounds such as **16**, **17**, **19**, **21**, and **22** is a noteworthy feature of this reaction, since, according to previous reports, [2 + 2 + 2] cycloaddition of dicyano compounds with alkynes gave only monopyridine compounds and one cyano group remained intact.[2e,3a,3b,3g,14]

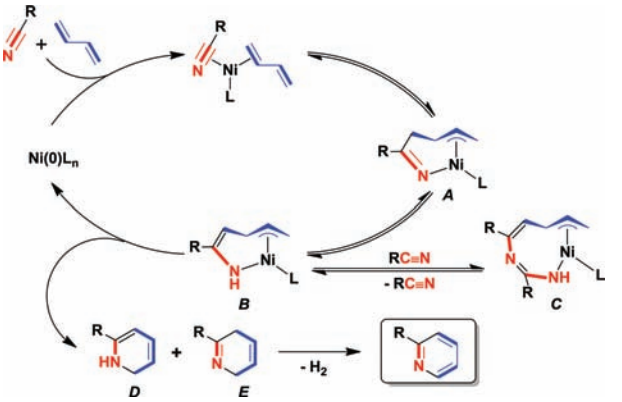


To observe a possible reaction intermediate, the stoichiometric reaction of benzonitrile with 2,3-diphenyl-1,3-butadiene at room temperature in the presence of $Ni(cod)_2$ and PCy_3 was monitored. Although the oxidative cyclization product (**23a**) of benzonitrile and 2,3-diphenyl-1,3-butadiene with nickel(0) was formed as a major product (eq 5),[15] the occurrence of a retro-reaction followed by the oxidative addition of Ph−CN to nickel(0) hampered its isolation.[16] The occurrence of the retro-cyclization was confirmed by treating the oxidative cyclization analogue (**23c**), derived from 2,3-diphenyl-1,3-butadiene and 2-phenylacetonitrile, with benzonitrile, to give **23a**.[17] Whereas IPr was not efficient for the catalytic reaction (Scheme 1), using IPr instead of PCy_3 as a ligand resulted in the formation of the corresponding aza-nickelacylce (**23b**) in 75% NMR yield, and it was isolated in 63% yield. The molecular structure of **23b**, as determined by X-ray crystallography (Figure 1), showed the tautomer of the expected aza-nickelacycle, as shown in Scheme 4. The treatment of **23a** generated *in situ* with carbon monoxide in

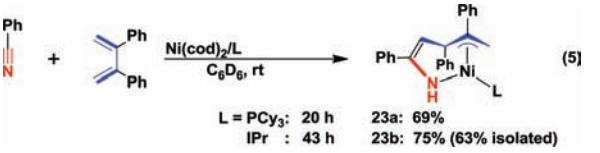
Scheme 3. Treatment of 23a with 5 atm of Carbon Monoxide



Scheme 4. A Plausible Reaction Mechanism

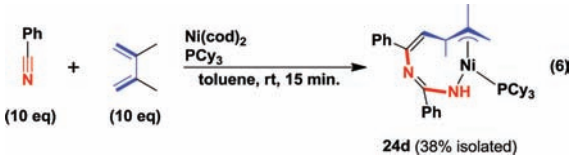


10 min led to the quantitative formation of a mixture of 3,4,6-triphenyl-2,5-dihydropyridine (**2′**) and 3,4,6-triphenyl-1,2-dihydropyridine (**2″**) (Scheme 3; **2′**/**2″** = 6/95).[18] The gradual isomerization of **2″** to **2′** proceeded even at rt and the ratio of **2′** increased from 6/95 to 76/31 in 1 h. The kinetic product of reductive elimination was **2″**. Since the isomerization might occur much more rapidly at 130 °C than at rt, the kinetic product **2″** was not observed at all in the reactions in Scheme 1. After 84 h, **2** was obtained in 56% yield and the generation of a hydrogen molecule (δ_H 4.5) was observed. No hydrogenated 2,3-diphenyl-1,3-butadiene was observed, and the unreacted 2,3-diphenyl-1,3-butadiene remained intact. These observations indicated that the dehydrogenation giving **2** could occur spontaneously, and the hydrogenation of 2,3-diphenyl-1,3-butadiene was catalyzed by a nickel catalyst under the reaction conditions, since $(PCy_3)Ni(CO)_3$ is unreactive under a carbon monoxide atmosphere.



The reaction might proceed as follows (Scheme 4). The oxidative cyclization of a nitrile and a diene with nickel(0) occurred to give an η^3-azaallylnickel intermediate **A** that underwent isomerization to yield the tautomer **B**, which reacted reversibly with a nitrile to form a diazanickelacycle species **C**. Diazanickelacycle (**24d**), generated by the reaction of 2,3-dimethyl-1,3-butadiene with benzonitrile, could be isolated and definitely determined by X-ray diffraction study (eq 6).[17] The reductive elimination from **B** gave rise to 1,2-dihydropyridines **D** followed by isomerization to **E**. Then dehydrogenation of **D** and/or **E** yielded a pyridine. The generated hydrogen molecule was consumed by nickel-catalyzed

hydrogenation of 1,3-butadiene under the reaction conditions. The large difference in reactivity between PCy_3 and IPr is mostly caused by the difference in the stability of the diazanickelacycle **C**. Thermolysis of **24d** for 24 h at 130 °C gave **1** in 48% yield. In contrast, the corresponding IPr analogue (**24e**) was found to be too stable to regenerate the azanickelacycle intermediate **23b**.[19]



In conclusion, we demonstrated the dehydrogenative [4 + 2] cycloaddition of 1,3-butadienes with nitriles to give a variety of pyridines catalyzed by nickel(0) complexes. The prepared pyridines in this report were very difficult to prepare by [2 + 2 + 2] cycloaddition reactions of alkynes with nitriles. Moreover, the reaction can be applied to both di- and tricyano compounds. These polypyridine derivatives were shown to be potentially useful ligands to transition metal complexes. Moreover, the formation of the expected intermediate and its molecular structure were revealed by crystallography.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, analytical and spectral data for all new compounds, and crystallographic data (PDF/CIF) for **23b**, **23c**, and **24d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

This work was supported by Grants-in-Aid for Scientific Research (No. 21245028) and for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis" (No. 23105546) from MEXT.

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(13) Running the catalytic reaction under the *o*-xylene reflux conditions, which would help drive off the H_2 that is generated, could not suppress the formation of the corresponding hydrogenated butene.

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(15) NMR observation of the reaction revealed the formation of a diazanickelacycle complex (**24a**) and *trans*-$(PCy_3)_2Ni(C{\equiv}N)(Ph)$ (**25**) in 8 and 6%, respectively. Details are found in the Supporting Information.

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(17) Detailed procedures for **23c** and **24d**, including the results of X-ray analysis, are found in the Supporting Information.

(18) The treatment of nickel compounds with carbon monoxide can yield $[Ni(CO)_4]$ (extremely toxic) due to the addition of insufficient amounts of ligands, careless handling, or an accident. The reaction mixture must be handled within a well-ventilated fume hood.

(19) See Supporting Information for detail.