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Nickel-Catalyzed [2+2+2] Cycloaddition of Alkyne-nitriles with Alkynes Assisted by Lewis Acid: Efficient Synthesis of Fused Pyridines

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1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene

Abstract: A Ni/BPh_3 catalyzed [2+2+2] cycloaddition of alkyne-nitriles with alkynes has been developed, which provides an efficient route to fused pyridines under mild reaction conditions. Mechanistic studies indicate that an azanickelacycle via heterocoupling of an alkyne with a nitrile moiety is possibly formed as a key reaction intermediate. The Lewis acid catalyst is crucial to the successful transformation, which is suggested to promote the oxidative cyclization process.

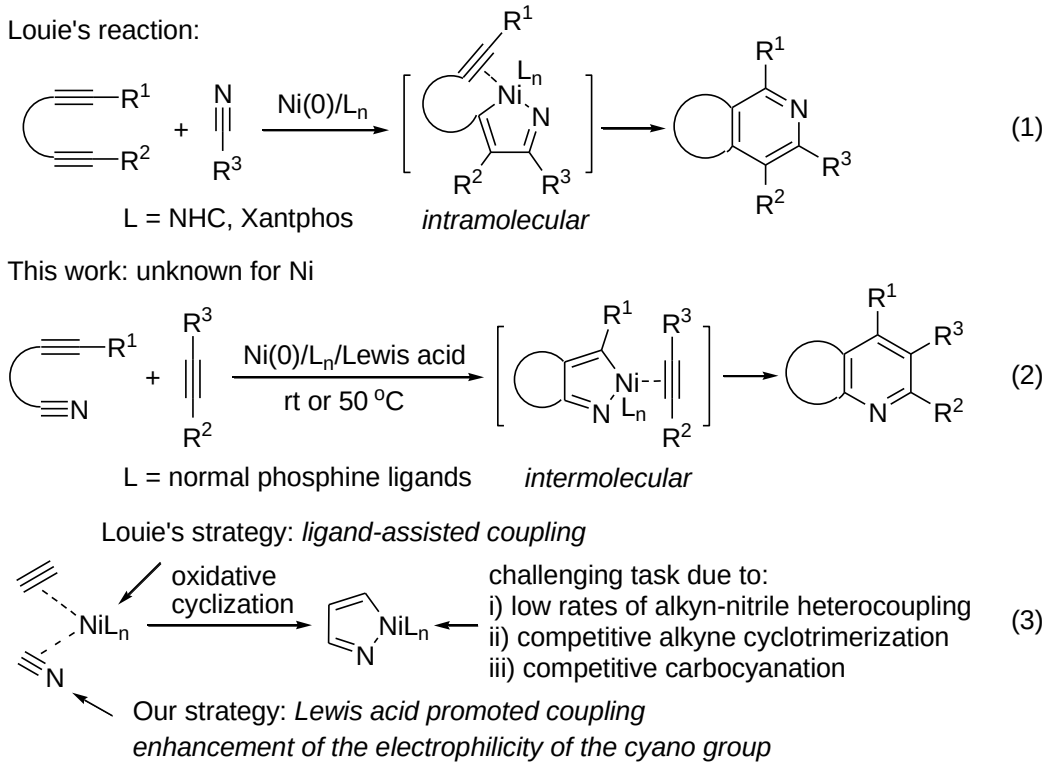
Keywords: nickel ·cycloaddition ·alkynes ·nitriles ·pyridines

Pyridines constitute an important class of heterocycles, which appear as key structural subunits in numerous natural products and pharmaceutical molecules, and also serve as attractive building blocks in organic synthesis.[1] Transition-metal-catalyzed [2+2+2]

cycloaddition of two alkynes with a nitrile represents a powerful and atom-economic strategy for the straightforward synthesis of multi-substituted pyridines.[2] Various transition metal systems such as Co,[3] Ru,[4] Rh,[5] and more recently, Ni,[6] Fe,[7] Ir [8] and Nb[9] have been developed in this field. To solve the regioselectivity issue, the preassembled substrates containing two or three unsaturated units are usually used in these reactions. However, most of the studies concentrated on the cycloaddition of the preassembled diynes with nitriles, while the reactions of alkyne-nitriles with alkynes were less common. So far only two catalytic systems have been developed with Co[3a,c-d,f-g] and Fe-based[7a] transformations, however, they have certain drawbacks. For example, Co-catalyzed reactions usually suffer from elevated temperatures, irradiation conditions, unconvenient manipulations, and most of the reactions restricted to terminal alkyne-nitriles. The only report with Fe catalysis limited to internal alkynes as the alkyne component etc. Therefore, the development of efficient catalytic systems which enable the reaction to occur under mild reaction conditions with wide functional group tolerance is highly desired.

On the other hand, nickel-catalyzed [2+2+2] cycloaddition to pyridines continues to be attractive and challenging due to the low rates of alkyne-nitrile heterocoupling,[10] competitive alkyne cyclotrimerizations,[10] dimerization of nitriles,[10] or carbocyanation of alkynes with nitriles[11]. Several new achievements have recently been developed. Louie et al demonstrated that a combination of $Ni(COD)_2$ with electron-donating *N*-heterocyclic carbene (NHC)[6a-c,e-g] or bulky Xantphos ligands (Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene)[6d] effectively catalyzed the

cycloaddition of diynes with nitriles at room temperature (Scheme 1, eq 1). In contrast to Co-catalyzed [2+2+2] cycloadditions, these reactions were proposed to proceed through the heterocoupling mechanism involving the initial oxidative cyclization of an alkyne and nitrile with nickel(0).[6f] It was found that the ligand played an important role in the achievement of these transformations, which was suggested to promote the formation of an azanickelacycle or the reductive elimination of C-N bond through electronic or steric effects of the ligand. However, the related nickel-catalyzed cycloaddition of alkyne-nitriles with alkynes to pyridines has not been report yet. During our studies, we observed a dramatic effect of a Lewis acid cocatalyst, which facilitated the desired cycloaddition of alkyne-nitriles with alkynes significantly with the use of the normal phosphine ligands, and allowed the reaction to proceed under mild reaction conditions (Scheme 1, eq 2). It is important to note that without the Lewis acid cocatalyst, the desired [2+2+2] cycloaddition cannot proceed even employing the special phosphine or NHC ligands. Compared with the Louie's reaction, here the key intermediate of azanickelacycle is possibly formed via enhancement of the electrophilicity of the cyano group (Scheme 1, eq 3). Interestingly, it is well known that Lewis acid could accelerate the nickel-catalyzed carbocyanation of the alkynes with nitriles via cleavage of the R-CN bond,[11c-f] however, such reaction was not observed in our reaction. Herein, we report these results.

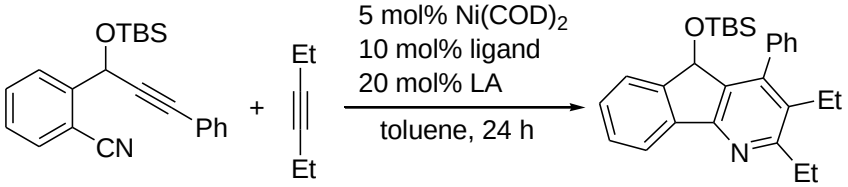


Scheme 1. Nickel-catalyzed [2+2+2] cycloaddition to pyridines.

At the beginning, we chose the Ni(0)-catalyzed cycloaddition of benzene-tethered alkyne-nitrile **1a**[12] with 3-hexyne as the model reaction for the optimization of the reaction conditions (Table 1). It was anticipated that such transformation would afford highly valuable indenopyridines. Treatment of **1a** and one equivalent of 3-hexyne with 5 mol% of $Ni(COD)_2$ and 10 mol% of various phosphine ligands including Xantphos and IPr (1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) in toluene at 50 ^oC for 24 h did not afford the desired cycloaddition product (Table 1, entries 1-3). After a lot of efforts, we found that the desired indeno[1,2-*b*]pyridine **2a** could be obtained at room temperature in 66% yield by adding 20 mol% of $AlMe_2Cl$ (entry 4). Inspired by this result, different Lewis acids were examined in order to improve the yield of **2a**. To our delight, the best yield of **2a** could be achieved using BPh_3 as the Lewis acid and $PMePh_2$ as the ligand

(88%, entry 7). We suggested that Lewis acid might increase the electrophilicity of the cyano group, thereby facilitated the oxidative cyclization of the alkyne and nitrile moiety with Ni(0).[13] A variety of ligands were also screened, among them, PBu_3 shown comparative activity with that of $PMePh_2$, leading to **2a** in 82% yield (entry 14). Other ligands such as PPh_3, Xantphos, bipy, PCy_3 and dppp were less effective (entries 9-13). In the absence of a ligand, the yield of **2a** was sharply reduced to 12% (entry 15). Control experiment run without nickel catalyst resulted in no formation of **2a** (entry 16). A larger scale reaction was also performed (1 mmol scale), and the desired **2a** was still formed in high yield (entry 17).

Table 1. Optimization studies for Ni(0)-catalyzed cycloaddition of alkyne-nitrile **1a** with 3-hexyne.



1a 1.0 equiv **2a**

Entry	Ligand	LA	Temp (^oC)	Yield (%)[a]
1	$PMePh_2$	-	50	- (97)
2[b]	Xantphos	-	50	- (77)
3	IPr	-	50	-[c]
4	$PMePh_2$	$AlMe_2Cl$	rt	66
5	$PMePh_2$	TMSOTf	rt	14
6	$PMePh_2$	$B(C_5F_5)_3$	rt	17

7	$PMePh_2$	BPh_3	rt	88
8[d]	$PMePh_2$	BPh_3	rt	52
9	PPh_3	BPh_3	rt	58
10[b]	Xantphos	BPh_3	rt	7
11[b]	bipy	BPh_3	rt	8
12	PCy_3	BPh_3	rt	41
13[b]	dppp	BPh_3	rt	33
14	PBu_3	BPh_3	rt	82
15	-	BPh_3	rt	12
16[e]	$PMePh_2$	BPh_3	rt	- (92)
17[f]	$PMePh_2$	BPh_3	rt	89

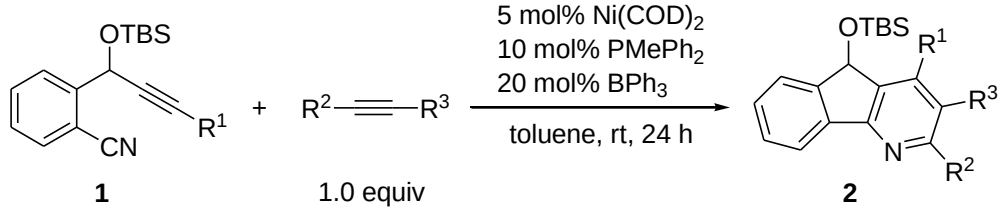
[a] Isolated yields. Unless noted, all the reactions were carried out on 0.3 mmol scale. The yields of recovered **1a** are shown in parentheses. [b] 5 mol% ligand was used. [c] The reaction was not clean and no desired product was formed. [d] 10 mol% BPh_3 was used. [e] In the absence of $Ni(COD)_2$. [f] 1 mmol scale.

In light of the above investigations, we chose entry 7 in Table 1 as the optimized conditions to explore the substrate scope of this reaction. First, the scope of alkynes was examined using **1a** as the reaction partner (Table 2). Under the standard reaction conditions, **1a** underwent cycloadditions smoothly with symmetrically substituted alkynes such as 5-decyne or the alkyne bearing -CH_2OTBS functional groups to give the corresponding indenopyridines **2b** and **2c** in 76% and 82% yields, respectively. However, when diphenylacetylene was used, only 45% of **2d** was obtained at 50 ^oC. Undoubtedly, the reaction of **1a** with a propyl methyl-substituted alkyne afforded **2e** as a 1:1 mixtures of

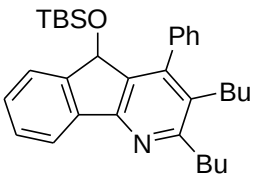
regioisomers. High to excellent regioselectivity were observed for phenyl alkyl alkynes, possibly due to the polarity of these alkynes. The regioselectivity in these cases is opposite to that observed in Fe-catalyzed cycloaddition reactions.[7a] When enyne or butadiynes[3d] were employed, the corresponding **2h**-**2j** were isolated in high yields as a single regioisomer, in which an alkenyl or alkynyl group located at the α-position of the pyridine ring. The high regioselectivity can be explained by the directing effects of these unsaturated groups caused by their coordination with the metal center during the insertion of alkyne to azanickelacycle. To our delight, terminal alkynes bearing normal alkyl, benzyl, cyanoalkyl, chloroalkyl or cyclopropyl functional groups were all compatible to give **2k**-**2p** in 61-89% yields as a mixture of two regioisomers, while the alkyl substituent is located at the α-position of the newly formed pyridine ring in the major regioisomer. Especially, no cycloaddition derived from the reaction of 5-hexynenitrile with the alkyne moiety of **1a** was observed in the case of **2n**. It was important to note that when terminal alkynes were used as the monoalkyne components in metal-catalyzed [2+2+2] cycloaddition reactions, usually low product yields were observed,[3a,c,e,g] possibly due to the rapid trimerization or oligiomerization of these alkynes under the catalytic conditions. In our reaction system, the heterocoupling of an alkyne and a nitrile might be much faster than alkyne trimerization or oligiomerization due to the enhanced electrophilicity of the cyano group through coordination with Lewis acid. It was worth mentioning that both regioisomers obtained in above reactions could be easily separated by column chromatography. The structure and regiochemistry of these indenopyridine products were confirmed by X-ray crystallographic analyses of **2g**, **2h**, **2j**, and the major isomer of **2f**,

2k.[14] Next, the scope of substrates **1** bearing different functionalities at their alkyne terminus were examined. Both of the electron-rich and electron-deficient substituents on the aromatic rings of aryl alkynes were well tolerated. In the case of **2r**, no activation of aryl-halogen bond was observed. 2-Thienyl- or alkenyl-substituted alkyne converted into **2t** and **2u** in good yields. The alkynes bearing linear or cyclic alkyl groups were also well suited. However, when terminal alkyne was employed, only complicated reaction mixture was observed.

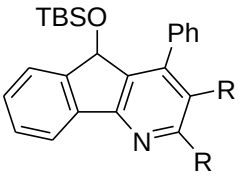
Table 2. Ni/BPh_3-catalyzed cycloaddition of benzene-tethered alkyne-nitriles with alkynes.[a]



1 1.0 equiv **2**

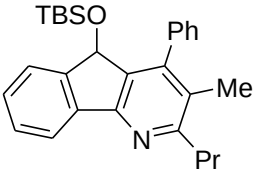


2b, 76%

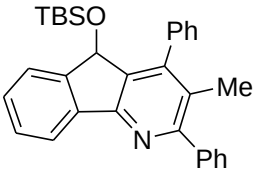


2c, R = CH_2OTBS, 82%

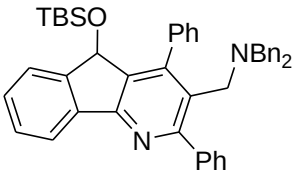
2d, R = Ph, 45%[b]



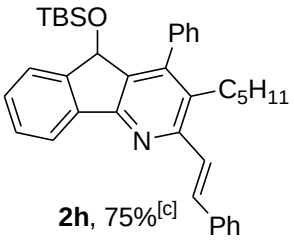
2e, 81% (1:1)



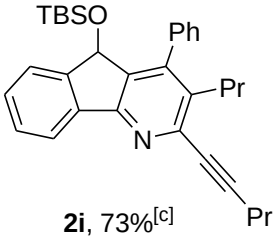
2f, 70% (6:1)



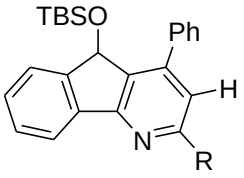
2g, 63%[c]



2h, 75%[c]



2i, 73%[c]



2k, R = Pr, 89% (2:1)

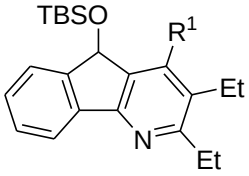
2l, R = Hex, 76% (1.5:1)

2m, R = Bn, 79% (1.8:1)

2n, R = $(CH_2)_3CN$, 66% (2.1:1)

2o, R = $(CH_2)_3Cl$, 61% (1.3:1)

2p, R = cyclopropyl, 89% (8:1)



2q, R^1 = *p*-$MeOC_6H_4$, 81%

2r, R^1 = *p*-ClC_6H_4, 80%[d]

2s, R^1 = *p*-$CF_3C_6H_4$, 86%

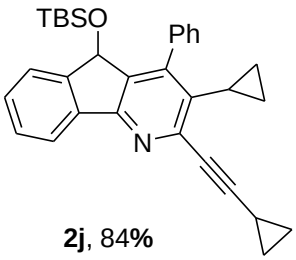
2t, R^1 = 2-thienyl, 80%

2u, R^1 = cyclohexenyl, 77%[d]

2v, R^1 = n-C_3H_7, 64%[d]

2w, R^1 = cyclopropyl, 71%

2x, R^1 = H, messy



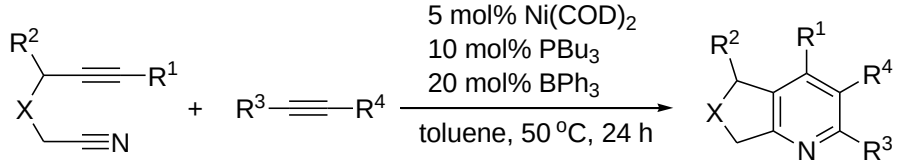
2j, 84%

[a] The yields are given for the isolated products. Only the structure of the major regioisomer is shown. The ratio of two regioisomers is shown in the paretheses. [b] 10 mol% $Ni(COD)_2$, 20 mol% $PMePh_2$, 20 mol% BPh_3 and 1.5 equiv of alkyne were used. The reaction was carried out at 50 °C for 32 h. [c] 10 mol% $Ni(COD)_2$, 20 mol% $PMePh_2$ and 40 mol% BPh_3 were used. [d] 50 °C, 24 h.

The reaction was also successfully expanded to linear alkyne-nitriles using PBu_3 as the ligand (Table 3).[15] A wide variety of C, N or O-linked alkyne-nitriles were compatible. It

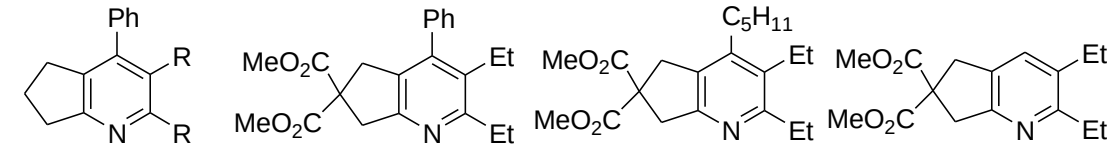
was noted that in some cases, pyridines **5** derived from self-cycloaddition of alkyne-nitrile **3** were also observed. **5** was obtained as a single regioisomer in which phenyl group located at the α-position of the pyridine ring. Internal alkyne substrates, whenever substituted with phenyl or alkyl group reacted with 3-hexyne or diphenylacetylene to afford **4a**-**4d** in 42-74% yields. Terminal alkyne also worked, albeit with a low yield of **4e**. Alkyne-nitriles bearing either a sulphonamide or oxygen tether coupled well with alkynes to give **4f**-**4j** in 44-80% yields. Substrate with a four-atom linkage between the alkyne and cyano group transformed into the pyridine **4k** smoothly. The reaction of (*o*-alkynyl)benzyl nitrile with internal or terminal alkynes proceeded efficiently to afford 9*H*-indeno[2,1-*b*]pyridines **4l** or **4m** in high yields.

Table 3. Scope of the alkyne-nitriles.[a]



3, 1.3 equiv, X = C, N, O

4

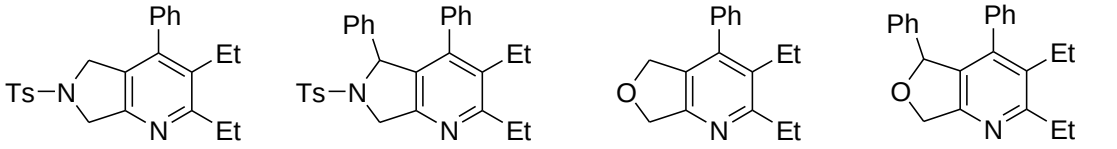


4a, R = Et, 50% (47%)
4b, R = Ph, 42% (49%)[b]

4c, 67% (26%)

4d, 74%

4e,[c] 31%(-)[d]

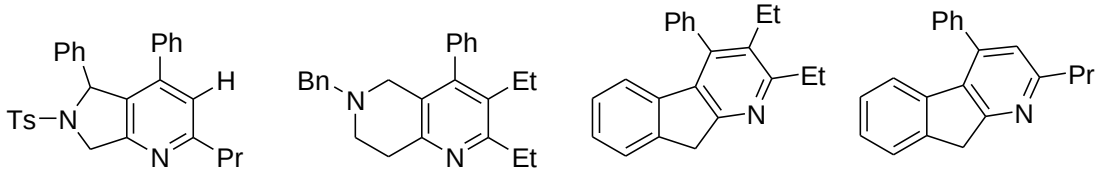


4f, 57% (34%)

4g, 80%

4h,[e] 44% (58%)

4i, 49% (-)[d,e]



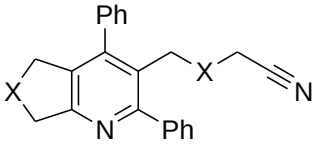
4j, 74%[f]

4k, 42% (-)[d]

4l, 94%[c,g]

4m, 86%[c,f,g]

[a] Isolated yields. The yields of byproduct **5** based on **3** are shown in the parentheses. [b] 60 °C, 24 h. [c] 10 mol% $PMePh_2$ was used as the ligand. [d] The byproducts were not clean. [e] 10 mol% PPh_3 was used as the ligand. [f] Two regioisomers were obtained with a ratio of 1:1. [g] rt, 24 h.

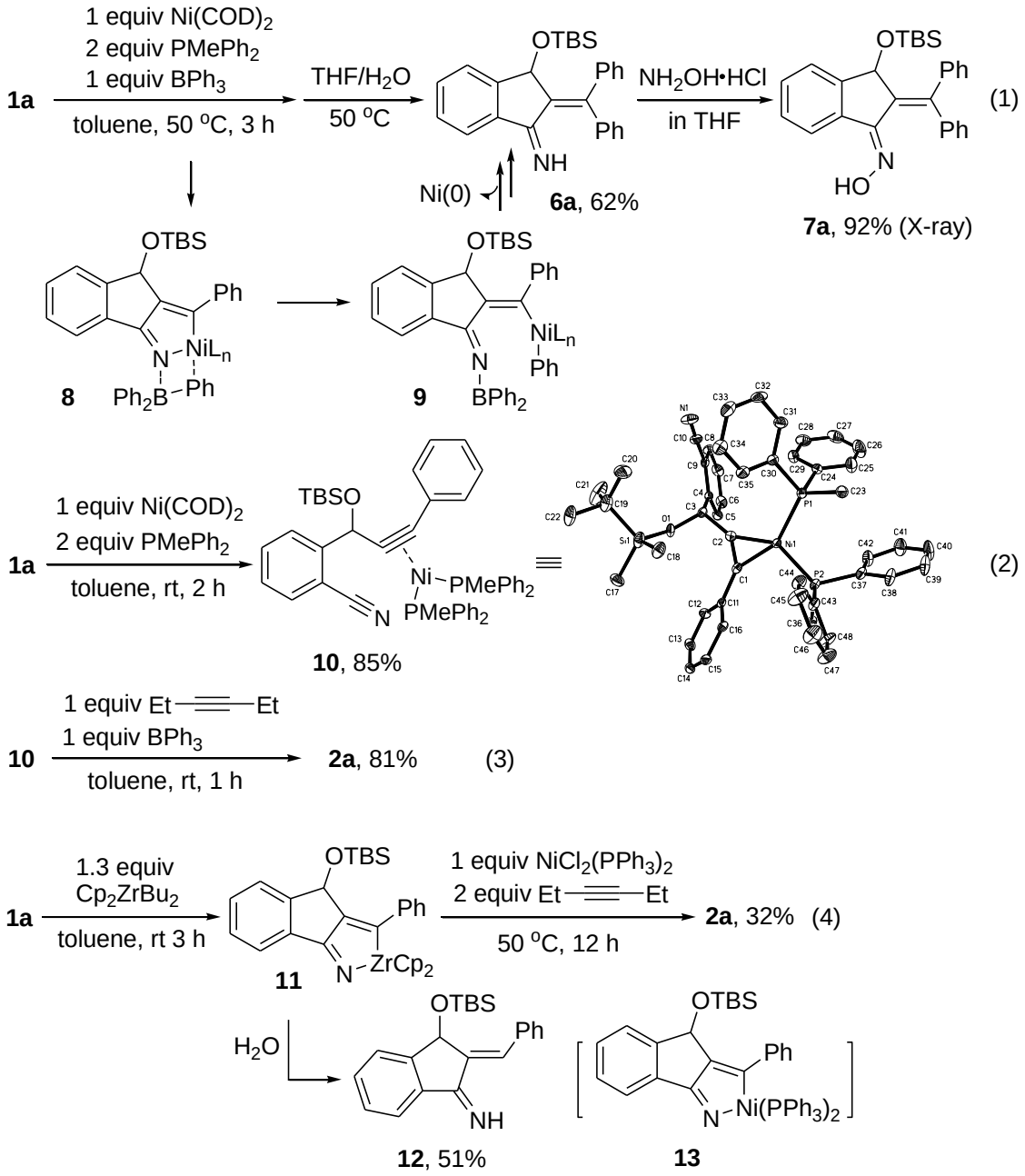


5

To understand the reaction mechanism, we carried out the following experiments. First, we examined the reaction of **1a** with a stoichiometric amount of $Ni(COD)_2$ (1 equiv), $PMePh_2$ (2 equiv) and BPh_3 (1 equiv) (Scheme 2, eq 1). Surprisingly, a cyclized *N*-H imine **6a** was formed in 62% yield after hydrolysis by water. Due to the instability of **6a**, the structure of **6a** was confirmed by X-ray crystal analysis of its derivative **7a**.[14,16] The appearance of one more phenyl group in **6a** indicated that BPh_3 acted not only as a Lewis

acid, but also delivered one of its phenyl group to the product in the stoichiometric reaction. The reaction possibly proceeds by first formation of azanickelacycle **8** followed by transmetalation and reductive elimination, which was not known yet in Ni-catalysis.[17] The results implied that oxidative coupling of the alkyne and the nitrile moiety in **1** could occur in the presence of BPh_3, and in catalytic pyridine formation process, insertion of an alkyne to the resulting azanickelacycle should proceed much faster than transmetalation. The stoichiometric reaction of **1a** with $Ni(COD)_2$ and $PMePh_2$ afforded an orange, air and moisture sensitive $(PMePh_2)_2Ni(\eta^2\text{-alkyne})$ complex **10** in 85% yield, rather than η^2-nitrile[6e] or η^2:η^2-5-en-nitrile[13b] Ni(0) complex (Scheme 2, eq 2). No further cyclization occurred when the reaction was carried out at 50 ^oC. The X-ray crystal analysis[14] of **10** indicates that the metal center adopts a distorted square-planar geometry, and the C≡C bond distances (1.270(8) Å), C≡C-C angles (140.7(6)^o, 144.4(6)^o) are similar to those reported for other nickel(0)-alkyne phosphine complexes.[18] Treatment of **10** with one equiv of 3-hexyne and one equiv of BPh_3 resulted in the formation of **2a** in 81% yield (Scheme 2, eq 3). Without BPh_3, no reaction occurred. The results suggest that the reaction possibly proceeds via formation of a metal π-alkyne complex followed by BPh_3-assisted cycloaddition. Moreover, reaction of the azazirconacyclopentadiene **11** prepared by Zr-meidated alkyne-nitrile coupling of **1a** with $NiCl_2(PPh_3)_2$ and 3-hexyne afforded the same product **2a** in 32% yield. The formation of azazirconacycle **11** was confirmed by the isolation of imine **12** through hydrolysis (Scheme 2, eq 4). In this reaction, azanickelacycle **13** is proposed to be formed through transmetalation from Zr to Ni.[19] The results indicate that a similar azanickelacycle should be generated in Ni-catalyzed reaction, and the

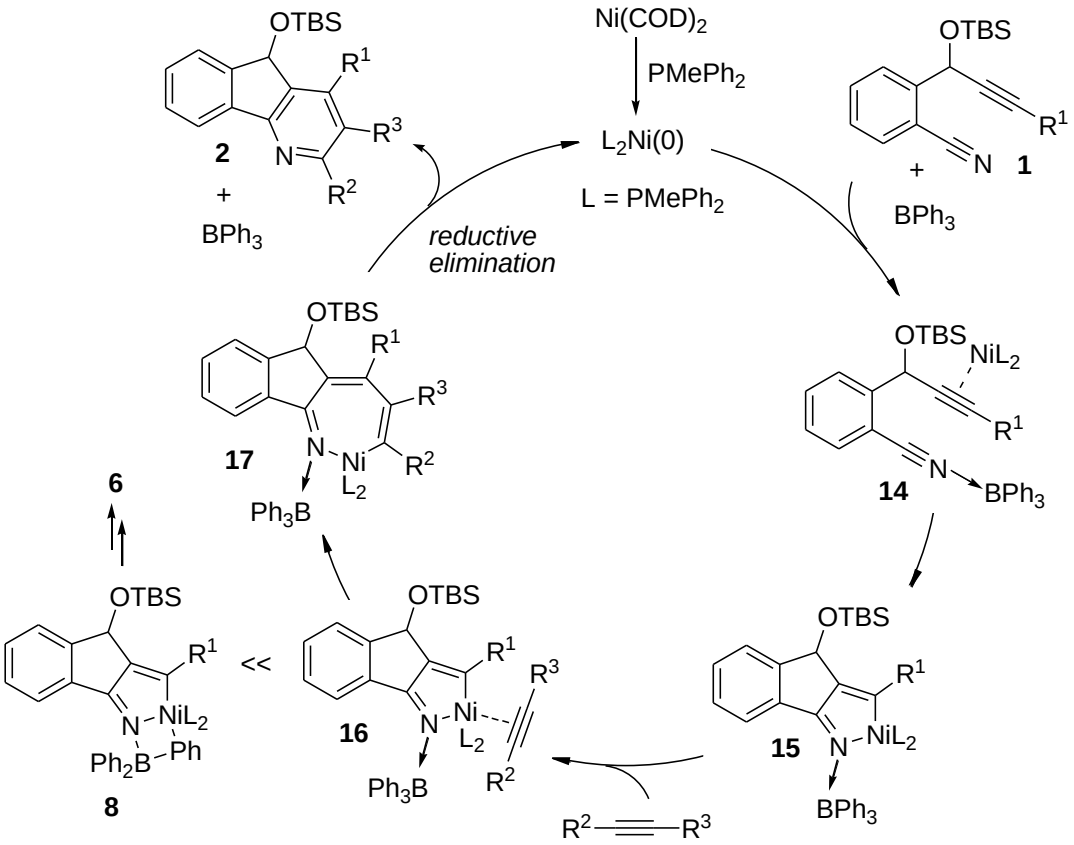
heterocoupling pathway is the most favorable route.[6f] It is also implied that insertion of alkyne to azanickelacycle can proceed without the aid of BPh_3.



Scheme 2. Mechanistic studies

Based on the above observations, we propose the following reaction mechanism for

this cycloaddition reaction (Scheme 3). Initially, a nickel-alkyne complex **14** is formed, in which the cyano group coordinates to BPh_3.[20] Then, oxidative cyclization of the alkyne and nitrile moiety with Ni(0) occurs to give an azanickelacycle **15**. Insertion of an alkyne to Ni-C bond in **15**, which is much faster than transmetalation, results in the formation of seven-membered azanickelacycle **17**. Insertion of an alkyne to Ni-N bond may be unfavored due to the reduced nucleophilicity of nitrogen moiety, which is considered to be coordinated with Lewis acid. Reductive elimination of **17** affords the desired product **2** and regenerates the nickel catalyst. The Lewis acid catalyst is suggested to promote the oxidative cyclization.



Scheme 3. Possible reaction mechanism

In summary, we have demonstrated that Ni/LA dual catalysts are highly effective for [2+2+2] cycloaddition of alkyne-nitriles with alkynes. Not only internal alkynes but also terminal alkynes participate in the cycloaddition very well, allowing the facile access to fused pyridines regioselectively under mild reaction conditions. Mechanistic studies indicated that an azanickelacycle was formed as a key reaction intermediate. The Lewis acid catalyst is crucial for successful transformation, which is suggested to promote the formation of an azanickelacycle. Further investigation of the reaction mechanism and applications of this chemistry are underway in our group.

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[14] CCDC-1434661 (major isomer of **2f**), 1440501 (**2g**), 1434662 (**2h**), 1434663 (**2j**), 1434664 (major isomer of **2k**), 1434665 (**4l**), 1480725 (**5a**), 1440500 (**7a**), 1480813 (*Z*-**7b**), 1480605 (*E*-**7b**) and 1434666 (**10**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

[15] $PMePh_2$ also worked for linear substrates, however, with a slight lower yields of **4** in some cases.

[16] When alkyne-nitrile **1b** substituted with a *p*-$MeOC_6H_4$ group at the alkyne terminus was used, a mixture of double bond isomers of *Z*-**7b** and *E*-**7b** was obtained. This may be explained by double bond isomerization of alkenylnickel species **9** before reductive elimination. For *cis-trans* isomerization of the alkenylnickel species, see: (a) X. Zhang,

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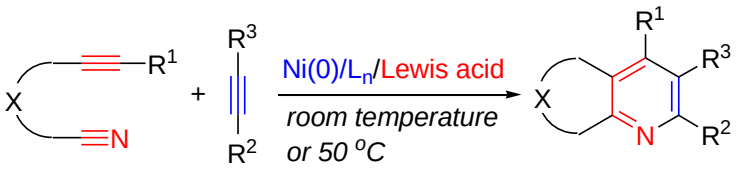

X = C, N, O

36 examples

L = normal phosphine ligands

- *Lewis acid promoted cycloaddition*
- *regio- and chemo-selective*

Ni/LA dual catalysis: A Ni/BPh_3 catalyzed [2+2+2] cycloaddition of alkyne-nitriles with alkynes has been developed, which provides an efficient route to fused pyridines under mild reaction conditions. Mechanistic studies indicate that an azanickelacycle via heterocoupling of an alkyne with a nitrile moiety is possibly formed as a key reaction intermediate. The Lewis acid catalyst is crucial to the successful transformation, which is suggested to promote the oxidative cyclization process.