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COMMUNICATION

Direct Access to Pentenedinitriles via Ni-Catalyzed Dihydrocyanation of 1,3-Enynes

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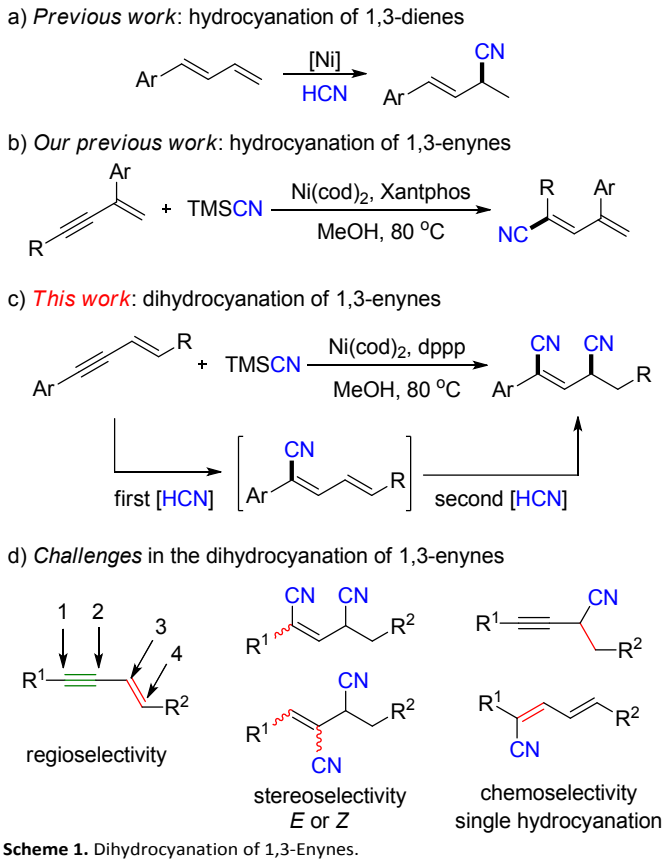
A highly regio- and stereoselective dihydrocyanation of 1,3-enynes was implemented by nickel/diphosphine catalysts. This reaction represents the first example of Ni-catalyzed dihydrocyanation of 1,3-enynes using TMSCN and MeOH as HCN surrogate. In this transformation, the main key feature is a multistep combination by using a single catalyst system. We observed a critical influence of the HCN source on the dihydrocyanation reaction. Moreover, the double hydrocyanation products were conveniently converted to poly-substituted pyridines.

The catalytic hydrocyanation of unsaturated hydrocarbons lead to alkyl nitriles[1], alkenyl nitriles[2] and a valuable array of building blocks[3]. In this context, various reported methods mainly focus on mono-hydrocyanation. However, the development of a complementary platform for the dihydrocyanation of multiple C–C bonds should be pursued intensively in chemical research, as it would increase the scope of product structures. A relevant example is the two steps industrial production of adiponitrile (>10^6 tons per year) from 1,3-butadiene through Ni-catalyzed double hydrocyanation. Adiponitrile is still today one of the most widely used monomers in the chemical industry[4].

We recently reported a highly regio- and stereoselective hydrocyanation of 1,3-enynes implemented by nickel/diphosphine catalysts using TMSCN and MeOH as HCN surrogate (Scheme 1b).[5] In this transformation, a wide range of cyano-substituted 1,3-dienes was prepared. In light of the rapid rise of Ni catalysis that enables the hydrocyanation of 1,3-dienes (Scheme 1a)[6] and 1,3-enynes, this type of system appeared to be a plausible means of achieving multiple hydrocyanations of 1,3-enynes. We envisioned that a single Ni catalyst would play the dual role of converting the 1,3-enynes starting material into a cyano-substituted 1,3-dienes and subsequently performing the hydrocyanation of this alkene intermediate to the desired pentenedinitrile products (Scheme 1c), which are valuable synthetic precursors to polyfunctional pyridine molecules.[7]



Scheme 1. Dihydrocyanation of 1,3-Enynes.

Although theoretically possible, no general catalytic dihydrocyanation process of 1,3-enynes have been so far developed to the best of our knowledge, even though 1,3-enynes were reported as substrates in hydrofunctionalization reaction.[8] A multistep combination through a single catalyst system rather than a combination of different catalysts for each of the steps offers the advantages of operational simplicity, reduced cost and thus renders the protocols eco-friendly. However, an extra difficulty is added as this single

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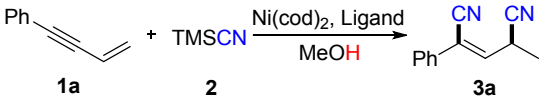
catalyst should exhibit a sufficient reactivity and an accurate selectivity in each of the key steps. Several challenges pertaining to catalyst selectivity and reagent compatibility could be encountered during the development of this protocol. Firstly, the fact that enynes have two unsaturated C–C bonds and four reactive sites may result in additional difficulties in the selectivity control especially for the alkyne substrates (Scheme 1d, left). In fact, the transition-metal-catalyzed selective hydrocyanation of alkynes with hydrogen cyanide (HCN) is challenging.[9] Although an important progress has been made in the hydrocyanation of terminal alkynes,[3a,b] the efficient regio- and stereoselective hydrocyanation of unsymmetrical internal alkynes remains unsolved. Indeed, the alkynes could potentially generate a mixture of regio- and stereoisomers.[10] Secondly, different stereoisomers of the desired product of dihydrocyanation could be formed (Scheme 1d, middle). Finally, the chemoselectivity control between mono-hydrocyanation and dihydrocyanation would be extremely challenging (Scheme 1d, right). In fact, the hydrocyanation of 1,3-dienes mainly focuses either on the aryl or on the alkyl substituted diene (Scheme 1a). The reaction may be stopped after the mono-hydrocyanation since the 1,3-diene conjugated with the cyano group has not been reported so far.[3b] Additionally, the hydrocyanation of 1,3-enynes may occur on the alkene site.

Table 1. Evaluation and Optimization of the Reaction Conditions[a]



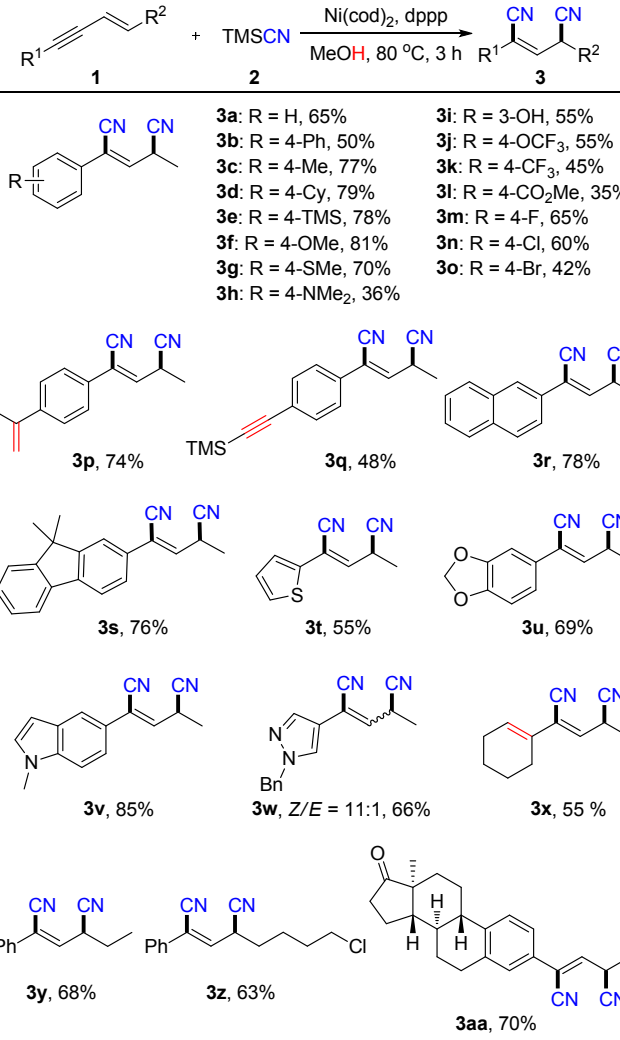
1a **2** **3a**

Entry	Ligand	Temp. (°C)	Time (h)	Conv. **1a** (%)[c]	Yield **3a** (%)[c]
1	/	80	12	0	0
2[b]	PPh_3	80	12	30	trace
3[b]	$P(OPh)_3$	80	12	0	0
4[b]	PCy_3	80	12	10	trace
5	dppp	80	12	100	68
6	dppb	80	12	10	trace
7	BINAP	80	12	10	trace
8	DPEphos	80	12	0	0
9	Xantphos	80	12	0	0
10	dppf	80	12	0	0
11	CyJohnPhos	80	12	0	0
12	dppp	60	12	84	47
13[d]	dppp	80	12	82	53
14[e]	dppp	80	12	47	33
15	dppp	80	3	100	68(65)[f]
16	dppp	80	6	100	68
17	dppp	80	9	100	68

[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.5 mmol, 5.0 equiv.) and MeOH (0.5 mL) in the presence of $Ni(cod)_2$ (20 mol%), ligand (20 mol%). [b]Ligand (40 mol%). [c]Determined by GC analysis using *n*-dodecane as the internal standard. [d]$Ni(cod)_2$ (15 mol%), ligand (15 mol%). [e]$Ni(cod)_2$ (10 mol%), ligand (10 mol%). [f]Isolated yield.

As mentioned above, we recently reported a highly regio- and stereoselective hydrocyanation of 1,3-enynes.[5] In this transformation, both the tethered alkene and the ligand play key roles in the reactivity and selectivity. Based on that work, we envisioned that the regio- and stereoselective hydrocyanation of aromatic 1,3-enynes, such as **1a**, could be achieved by tuning the ligand and changing the type of alkene. Herein, we report the first Ni-catalyzed highly regio- and stereoselective dihydrocyanation of aromatic 1,3-enynes using TMSCN and MeOH as HCN surrogate.

Table 2. Substrate Scope[a]

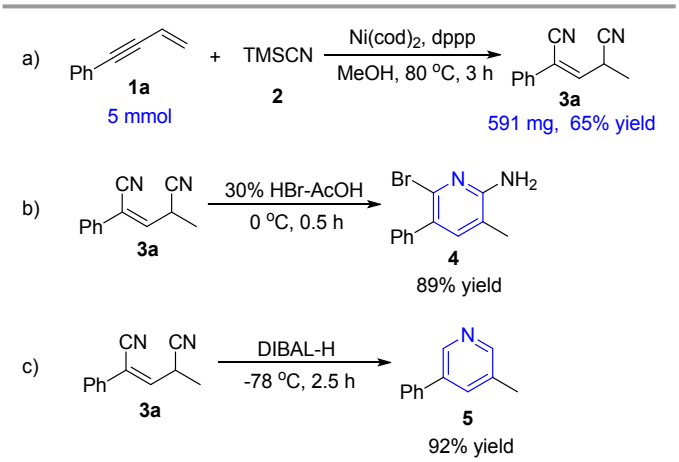


[a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv.), **2** (1.0 mmol, 5.0 equiv.), $Ni(cod)_2$ (20 mol%), and dppp (20 mol%) in MeOH (1.0 mL) at 80 °C under N_2 for 3 h. Yields of isolated products after flash column chromatography.

At the beginning of our studies, we explored the feasibility of our strategy by using **1a** as model substrate and explored the optimum conditions with TMSCN and MeOH under Ni catalysis (Table 1). Based on the previous work, we mainly tested Ni catalysts and various bisphosphine ligands as catalysts. After extensive screening, we surprisingly found that **1a** could react with TMSCN and MeOH to afford **3a**[11], the product of double hydrocyanation, in a 68% GC yield. This result was obtained with a Ni(0)/dppp complex as catalyst (Table 1, entries 1–11 and 15). When lowering the temperature or the catalyst loading, the desired product **3a**

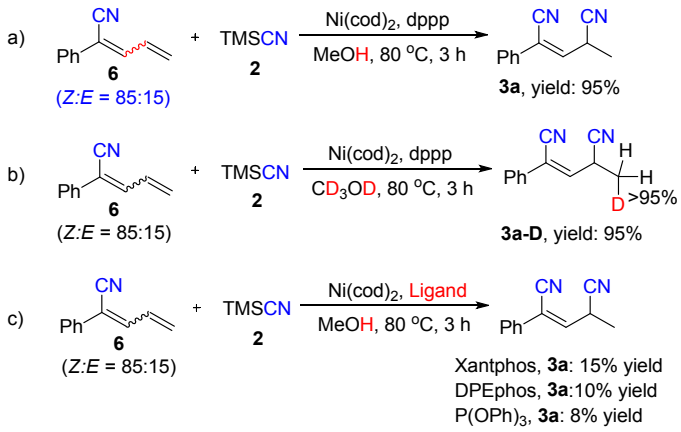
was obtained in lower yields (Table 1, entries 12–14). A longer reaction time has no influence on the yield (Table 1, entries 16–17). We found that the HCN source has a great influence on the dihydrocyanation reaction (see SI, Figure S2). This reaction exhibited a similar character with that of our previous work. The dppp ligand was definitively essential.

With the optimized reaction conditions in hand, we next examined the scope of this reaction. As shown in Table 2, a wide range of 1,3-enynes reacted smoothly with **2** to produce the product of double hydrocyanation (**3a-3aa**). In general, aryl-substituted 1,3-enynes, including electron-neutral, electron-rich, and electron-deficient functional groups, were well tolerated. Substrates with electron-neutral or rich groups (**3a-i**) gave better yields than those with electron-deficient substituents (**3j-l**). Halogen groups, such as fluorine, chlorine and bromine were also compatible with the reaction, providing the desired products with moderate to good yields (**3m-o**). Notably, the vinyl or internal alkynyl groups remained intact in this reaction, suggesting that the reaction is highly chemoselective (**3p-q**). In addition to aryl-substituted 1,3-enynes, both the naphthyl-substituted enyne and fluorene derived enyne were tolerated (**3r-s**). 1,3-Enynes bearing sulfur-, oxygen- and nitrogen-containing heteroaryl substituents also reacted, producing the corresponding products (**3t-w**) in high yield. It is worth noting that pyrazole **3w** is the only example where a mixture of *Z* and *E* products was observed. This strongly suggests that the dihydrocyanation reaction involves an interconversion between the *Z/E* isomers. Moreover, the vinyl substituted 1,3-enyne (**3x**) smoothly underwent this Ni-catalyzed transformation. To our delight, the internal enynes were found to be compatible with the reaction conditions (**3y-z**). To further demonstrate the synthetic value of this reaction, the enyne derived from estrone was subjected to our protocol, leading to **3aa** in 70% yield. The unsuccessful result with enyne as substrate has been introduced in SI.



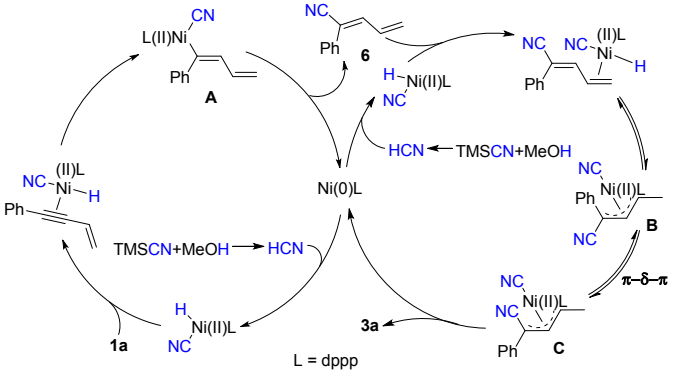
Scheme 2. Large Scale Reaction and Synthetic Applications of **1a**

To demonstrate the practical value of this method, a large scale reaction was conducted, and the double hydrocyanation product **3a** was obtained with preserved yield (Scheme 2a). We then considered that pentenedinitrile was reported as an extremely useful precursor that can be converted to poly-substituted pyridine.[7] Therefore, the experiment was set out to convert the product **3a** to the tetra-substituted pyridine **4** in good yield (Scheme 2b). To our surprise, we found that **3a** could also be easily converted to disubstituted pyridine **5** when using an excess of DIBAL-H (Scheme 2c).[12]



Scheme 3. Preliminary Mechanistic Studies

In order to gain insight about this catalytic transformation, the following control experiments were conducted. Dienenitrile **6** (*Z/E*: 85/15)[13] was prepared and subjected to the model reaction under standard conditions (Scheme 3a), delivering the desired product **3a** in 95% yield with exclusive stereoselectivity. This result highly suggests that the reaction proceeds through the π-allyl-Ni intermediate. Furthermore, deuterated methanol was subjected to the model reaction under standard conditions (Scheme 3b). In this experiment, we observed deuterium incorporation (>95% D) only at the C4 position of **3a-D**, which is consistent with the exclusive formation of the 1,2-addition product. Moreover, in the reaction between dienenitrile **6** and **2**, when using either Xantphos, DPEphos or $P(OPh)_3$ ligands instead of dppp, the product still forms, albeit with low yield. However, the 1,3-enyne **1a** couldn't react with **2** when using such ligands. These results demonstrated that the first step, supposedly the regioselective hydrocyanation of alkynes, is highly dependent on the ligand (Scheme 3c).



Scheme 4. Proposed Catalytic Cycle

Although the detailed mechanism is still under investigation, we suggest the following catalytic cycle based on the above observations and related literature (Scheme 4).[5,14] First, the oxidative addition of hydrogen cyanide to Ni(0) would result in the formation of the H-Ni(II)-CN species, which would insert onto the alkyne via *syn*-addition to afford an (*E*)-alkenyl nickel complex **A**. The steric repulsion of the alkenyl with the nitrile group possibly influences the regioselectivity of this step.[5] Then, the alkenyl nickel complex would give the single hydrocyanation product **6** via reductive elimination. Afterwards, second hydrocyanation would occur to afford the π-allyl-Ni complex **B**. Finally, a second reductive elimination of the more stable π-allyl-Ni complex **C** would lead to the desired product of dihydrocyanation **3a** and to regeneration of the Ni(0) species.

In conclusion, we have developed a highly regio- and stereoselective dihydrocyanation of 1,3-enynes using TMSCN as cyanide source and MeOH as hydrogen source. Through this approach, a wide range of pentenedinitrile products were efficiently prepared with high levels of regio- and stereoselectivity. The dinitrile products were conveniently converted to poly-substituted pyridines. We believe that this finding provides new insight into metal-catalyzed hydrocyanation of internal alkynes. Our approach is also useful for the synthesis of biologically important compounds. Further investigations to elucidate the mechanistic intricacies of this process, to apply this strategy to other reactions and to try to reduce the catalyst loading are currently underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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14 The insertion of H-Ni-CN to alkynes proceeds predominantly in a *syn*-addition manner, see the reference 2b.

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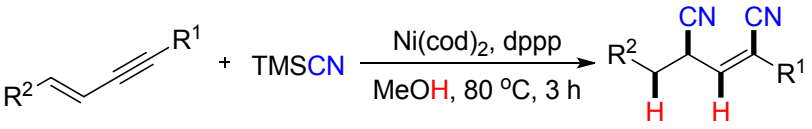

R^1 = aryl or alkenyl
R^2 = H or alkyl

27 examples
up to 85% yield