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Nickel/Cobalt-Catalyzed Reductive Hydrocyanation of Alkynes with Formamide as the Cyano Source, Dehydrant, Reductant, and Solvent

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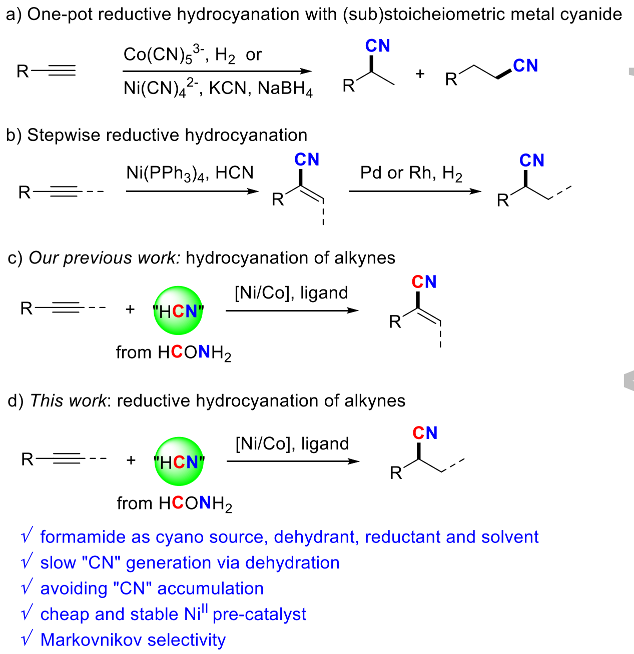
Abstract: A Ni/Co co-catalyzed reductive hydrocyanation of various alkynes was developed for the production of saturated nitriles. Hydrocyanic acid is generated *in situ* from safe and readily available formamide. Formamide played multiple roles as a cyano source, dehydrant, and reductant for the Ni^{II} pre-catalyst and vinyl nitriles, along with acting as the co-solvent in this reaction. Detailed mechanistic investigation supported a pathway via hydrocyanation of C≡C bond and the subsequent reduction of C=C bond. Wide substrate scope, the employment of a cheap and stable nickel salt as pre-catalyst, a safe cyano source and convenient experimental operation render this hydrocyanation practical for the laboratory synthesis of saturated nitriles.

Keywords: hydrocyanation; cyano source; reduction; alkynes; formamide

Introduction

Nitriles are an important compound class, not only due to their prevalence in a variety of natural products, pharmaceuticals and agrochemicals,[1] but also due to their synthetic versatility as powerful precursors for a myriad of functionalities, such as amides, carboxylic acids, amines, and ketones. [2] Therefore, numerous methods have been developed for the generation of nitriles. Among them, the hydrocyanation of alkynes offers a straightforward approach for the preparation of vinyl nitriles using HCN, acetone cyanohydrin, or metal cyanide as the cyano source.[3,4] The generated vinyl nitriles could be hydrogenated to provide saturated nitriles (reductive hydrocyanation of alkynes) via a one-pot[5] or stepwise[6] procedure. Specifically, one-pot reductive hydrocyanation of alkynes without the use of HCN has been accomplished with the use of a stoichiometric amount of $[Co(CN)_5]^{3-}$ under a H_2 atmosphere (Scheme 1a)[5a, 5b] or a sub-stoichiometric amount of $[Ni(CN)_4]^{2-}$ (0.5 equiv) in the presence of excess KCN with $NaBH_4$ or Zn as reducing agents;[5c] meanwhile, stepwise reductive hydrocyanation has been realized through the classic Ni-catalyzed hydrocyanation of alkynes with HCN and subsequent Pd or Rh-catalyzed hydrogenation (Scheme 1b).[6a-6c] However, in these precedents, the hydrocyanation either requires highly toxic and volatile HCN or surrogates thereof, such as acetone cyanohydrin or metal cyanide, while the subsequent reduction of the C=C bond requires the addition of a reductant and noble metal catalyst.



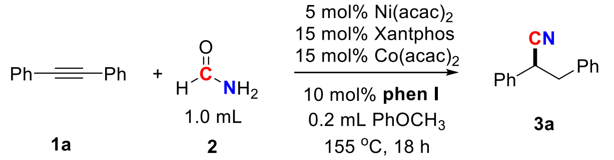
Scheme 1 Reductive hydrocyanation of alkynes with different cyano source.

To avoid the use of toxic metals or metalloid cyanides, a “combined cyano” source strategy has been established, whereby “CN” is generated *in situ* from *N*,*N*-dimethylformamide (DMF) and ammonia, to supply the carbon and nitrogen atoms, respectively, assisted by a Cu or Pd catalyst under oxidative conditions. This has been recognized as a successful strategy for the cyanation of arenes bearing directing groups, indoles, aromatic boronic acids, and aryl iodides, as demonstrated by the pioneering work of Chang *et al*.[7] Subsequently, similar cyanations that employ other compounds as the carbon and nitrogen source were separately reported by Cheng, Yu, Sakai and Jiao.[8] However, multi-step transformations and complex and harsh oxidative reaction conditions are required to convert the carbon and nitrogen source reagents to a “CN”, resulting in diminished yields and limited substrate scope. This drawback of the “combined cyano” source strategy has prompted us to design and develop convenient cyanation reactions with formamide as a green cyano source (Scheme 1c). Thus, the cyanation of (hetero)aryl halides and hydrocyanation of alkynes/alkenes have been successively developed in our group.[9] Our methodology is based on formamide dehydration to produce “HCN” (coordinated to metals), while the released water is consumed by the hydrolysis of another formamide molecule to produce formate as a byproduct. These results further inspired us to devise a possible cascade reduction of vinyl cyanides obtained from the hydrocyanation of alkynes, by harnessing the formate byproduct as the reductant.[10] Herein, we report a Ni/Co co-catalyzed reductive hydrocyanation of alkynes with formamide as the cyano source, dehydrant, reductant and solvent.

Results and Discussion

Based on the above speculation and our recent work,[9] 1,2-diphenylethyne (**1a**) was chosen as the model substrate for exploring our reductive hydrocyanation strategy. Detailed optimization was performed by evaluating Ni^{II} pre-catalysts, phosphorus ligands, cobalt salts, and nitrogen ligands, revealing that the combination of 5 mol% $Ni(acac)_2$ / 15 mol% Xantphos / 15 mol% $Co(acac)_2$ / 10 mol% 3,4,7,8-tretramethyl-1,10-phenanthroline (**phen I**) was the most effective, affording the targeted reductive hydrocyanation product **3a** in 88% isolated yield (Table 1, entry 1). The control experiments indicated that the Ni^{II} pre-catalyst was crucial for this transformation (entry 2); besides $Ni(acac)_2$, $NiCl_2$, and $NiSO_4{\cdot}6H_2O$ could also be utilized, albeit delivering lower yields (entries 3 and 4). In sharp contrast, $Co(acac)_2$ played a supplementary role, and could be replaced by $Ni(OAc)_2$ or ${}^{i}Bu_3Al$ (entries 5-7). The choice of phosphorus ligand likewise significantly influenced this reaction, thus Xantphos[11] with a rigid butterfly structure and a large bite angle of 114° was found to be the optimal match for the $Ni(acac)_2$ catalyst (entries 8-10). The addition of a nitrogenous ligand (**phen I**: 3,4,7,8-tretramethyl-1,10-phenanthroline) had a marginal influence on the reaction, with the yields decreasing slightly in the absence of **phen I**, or when it was replaced with 1,10-phenanthroline or 2,2'-bipyridine (entries 11-13). Compared with our previous study on the hydrocyanation of alkynes,[9a] the introduction of a nitrogen ligand, dosage of the cobalt catalyst, and reaction temperature were important for ensuring the *in situ* reduction of vinyl nitrile intermediates to the corresponding saturated nitriles. It is worth noting that this reductive hydrocyanation generally works well with formamide as the solvent, however its high polarity is unfavorable for the dissolution of non-polar alkyne substrates, thus anisole was added as the co-solvent to increase the compatibility of various alkyne substrates.

Table 1. Optimization of reaction conditions [a]



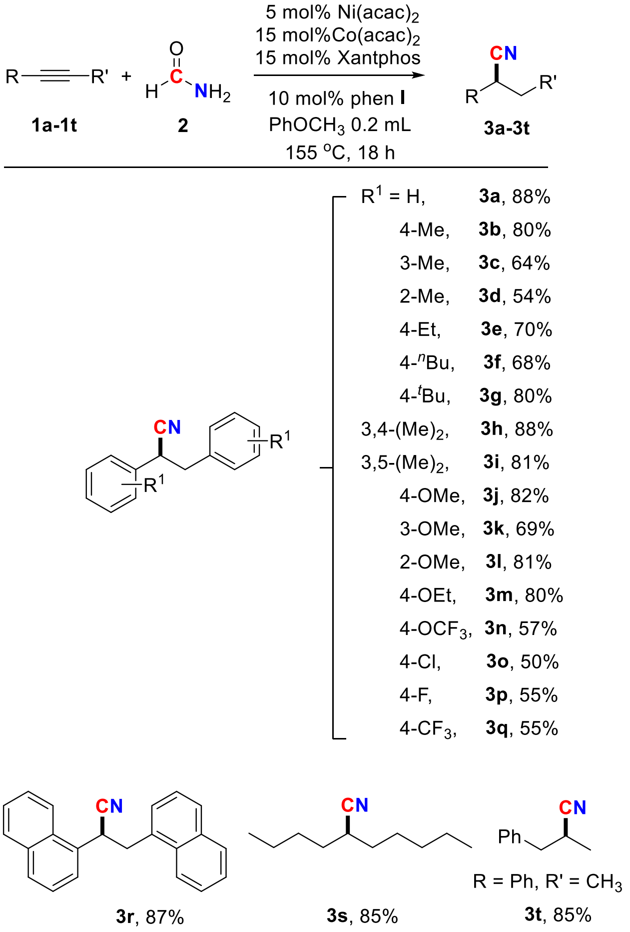
Entry	Change from the “standard conditions”	**3a** (%)
1	none	88
2	without $Ni(acac)_2$	0
3	$NiCl_2$ instead of $Ni(acac)_2$	35
4	$NiSO_4{\cdot}6H_2O$ instead of $Ni(acac)_2$	65
5	without $Co(acac)_2$	18
6	$Co(OAc)_2$ instead of $Co(acac)_2$	80
7	${}^{i}Bu_3Al$ instead of $Co(acac)_2$	43
8	without Xantphos	15
9	dppp instead of Xantphos as the phosphine ligand	56
10	BINAP instead of Xantphos as the phosphine ligand	42
11	without **phen I**	68
12	**phen II** (1,10-phenanthroline) instead of **phen I** as nitrogen ligand	70
13	**bipy** (2,2'-bipyridine) instead of **phen I** as nitrogen ligand	68

[a] Conditions: 1,2-diphenylethyne (**1a**, 0.2 mmol), $Ni(acac)_2$ (0.01 mmol, 5 mol%), Xantphos (0.03 mmol, 15 mol%), $Co(acac)_2$ (0.03 mmol, 15 mol%), **phen I** (3,4,7,8-tretramethyl-1,10-phenanthroline, 0.02 mmol, 10 mol%), formamide (1.0 mL) and anisole (0.2 mL) were reacted at 155 °C (oil bath temperature) for 18 h under argon atmosphere. Isolated Yields.

Under the optimized conditions, symmetrical 1,2-diphenylethynes bearing various types of substituents (**1a-1q**) all underwent the desired reductive hydrocyanation to afford the corresponding nitriles (**3a-3q**) in moderate to good yields (Table 2). Indeed, substrates with alkyl (**1a-1i**), alkoxy (**1j-1n**), halo (**1o**,

1p) and trifluoromethyl (**1q**) substituents were all readily employed. Furthermore, naphthalen-1-yl (**1r**) and *n*-butyl (**1s**) substituted ethynes were also viable substrates for this Ni/Co co-catalyzed reductive cyanation. Unexpectedly, for unsymmetrical internal alkynes, such as 1-phenyl-2-methylacetylene (**1t**), 2-methyl-3-phenylpropanenitrile (**3t**) was detected exclusively by GC-MS and isolated in 85% yield, despite the possibility of the cyano group being installed onto C1 or C2 of the unsymmetrical alkyne to provide two regioisomers.

Table 2. Scope of the 1,2-disubstituted ethynes for this reductive hydrocyanation [a]



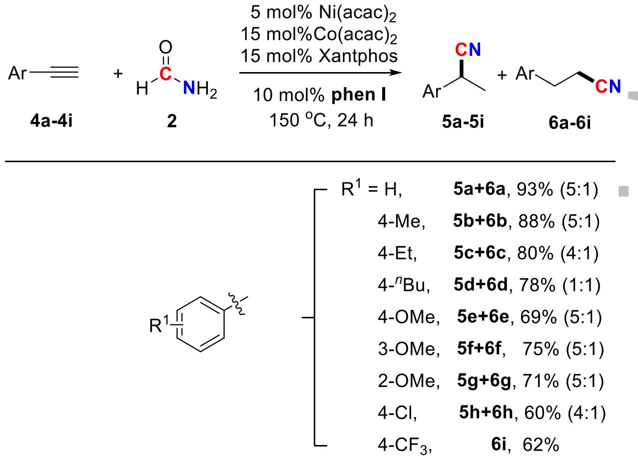
R^1	Product, yield
H	**3a**, 88%
4-Me	**3b**, 80%
3-Me	**3c**, 64%
2-Me	**3d**, 54%
4-Et	**3e**, 70%
4-^{n}Bu	**3f**, 68%
4-^{t}Bu	**3g**, 80%
3,4-(Me)$_2$	**3h**, 88%
3,5-(Me)$_2$	**3i**, 81%
4-OMe	**3j**, 82%
3-OMe	**3k**, 69%
2-OMe	**3l**, 81%
4-OEt	**3m**, 80%
4-OCF$_3$	**3n**, 57%
4-Cl	**3o**, 50%
4-F	**3p**, 55%
4-CF$_3$	**3q**, 55%

3r, 87% **3s**, 85% **3t**, 85%

[a] Conditions: alkyne (**1**, 0.2 mmol), Ni(acac)$_2$ (0.01 mmol, 5 mol%), Xantphos (0.03 mmol, 15 mol%), Co(acac)$_2$ (0.03 mmol, 15 mol%), **phen I** (3,4,7,8-tretramethyl- 1,10-phenanthroline, 0.02 mmol, 10 mol%), formamide (1.0 mL) and anisole (0.2 mL) were reacted at 155 °C (oil bath temperature) for 18 h under argon atmosphere. Isolated Yields.

Encouraged by the above results on the reductive hydrocyanation of symmetrical 1,2-diarylethynes, various terminal aromatic alkynes were then evaluated as substrates for this reaction (Table 3, **4a-1i**). Similarly, various terminal aromatic alkyne derivatives bearing electron-donating or electron-withdrawing substituents on the phenyl moiety underwent this reductive hydrocyanation smoothly to afford saturated nitriles (**5** and **6**) in good yields. Generally, the reaction followed Markovnikov's rule and branched regioisomers were predominantly obtained over the linear isomers, possibly due to the formation of a more stable benzyl nickel intermediate during the hydrocyanation step. In sharp contrast, the trifluoromethyl-substituted alkyne **4i** afforded a single linear product **6i**, because the electron-withdrawing trifluoromethyl group markedly increases the electrophilicity of the terminal carbon.

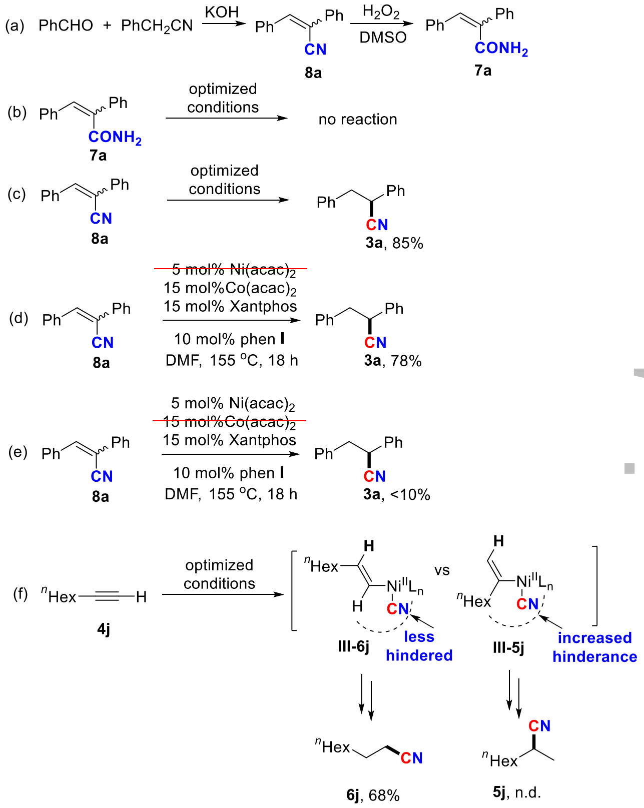
Table 3. Scope of the mono-substituted acetylenes for this reductive hydrocyanation [a]



R^1	Products, yield (ratio)
H	**5a+6a**, 93% (5:1)
4-Me	**5b+6b**, 88% (5:1)
4-Et	**5c+6c**, 80% (4:1)
4-^{n}Bu	**5d+6d**, 78% (1:1)
4-OMe	**5e+6e**, 69% (5:1)
3-OMe	**5f+6f**, 75% (5:1)
2-OMe	**5g+6g**, 71% (5:1)
4-Cl	**5h+6h**, 60% (4:1)
4-CF$_3$	**6i**, 62%

[a] Conditions: alkyne (**4**, 0.2 mmol), Ni(acac)$_2$ (0.01 mmol, 5 mol%), Xantphos (0.03 mmol, 15 mol%), Co(acac)$_2$ (0.03 mmol, 15 mol%), **phen I** (3,4,7,8-tretramethyl- 1,10-phenanthroline, 0.02 mmol, 10 mol%) and formamide (1.0 mL) were reacted at 150 °C (oil bath temperature) for 24 h under argon atmosphere. Isolated Yields. The ratio for the two regio-isomers were determined by GC.

To elucidate the reaction mechanism of this reductive hydrocyanation with formamide as the cyano source, several control experiments were performed. First, two possible intermediates, 2,3-diphenylacrylonitrile (**8a**, *Z* and *E* mixtures) and 2,3-diphenylacrylamide (**7a**, *Z* and *E* mixtures) were prepared by the condensation of benzaldehyde with 2-phenylacetonitrile and subsequent hydrolysis (Scheme 2a). Second, these two potential intermediates were separately subjected to the optimized reaction conditions to demonstrate that 2,3-diphenylacrylamide (**7a**) could not be dehydrated and converted to the desired vinyl product (Scheme 2b), and 2,3-diphenylacrylonitrile (**8a**, *Z* and *E* mixtures) was indeed reduced to provide reductive cyanation product **3a** (Scheme 2c). These results not only ruled out the possibility of a pathway involving the hydroamidation of alkyne **1a** and subsequent dehydration of amide **7a**, but also supported that nitrile **8a** was the intermediate for this reductive hydrocyanation. Third, the exact role of the two transition metals (Ni and Co) was studied. Using 2,3-diphenylacrylonitrile (**8a**) as the starting material, a control experiment in the absence of Ni(acac)$_2$ (at the same time, formamide was replaced by DMF, as no cyano source was needed for the reduction step) provided saturated nitrile **3a** in 78% yield (Scheme 2d). In contrast, a similar reaction in the absence of Co(acac)$_2$ led to a very low yield (Scheme 2e), which strongly supported that the reduction of the C=C bond was chiefly catalyzed by Co(acac)$_2$. In light of the results obtained from reaction optimization (Table 1, entries 2 and 8), which indicated that the Ni(acac)$_2$/Xantphos combination was crucial for the hydrocyanation of alkynes, the Ni and Co salts were determined as being responsible for the hydrocyanation of C≡C bonds and reduction of C=C bonds, respectively. Then, a linear oct-1-yne (**4j**) was further tested as a potential substrate for this reaction to analyze the regioselectivity, which predominately afforded linear saturated nitrile **6j** (Scheme 2f). As the *cis*-addition of the Ni-H bond to the C≡C bond to produce the vinyl nickel intermediate (**III-6j** or **III-5j**) is a crucial step for the hydrocyanation of alkynes, the increased stability of intermediate **III-6j** due to its lower steric hindrance between the hydrogen and phosphorus ligand (compared with intermediate **III-5j**) likely contributes to the linear selectivity. Finally, the reaction progress regarding the generation of product **3a**, intermediate **8a**, and the recovery of **1a** with reaction time was investigated to further support the pathway by which alkynes were directly transformed into acrylonitrile (**8a**), and then reduced to provide saturated nitrile **3a** (Figure 1). As can be seen in Figure 1, byproduct **9a** generated from the direction reduction of alkyne **1a**, accumulated during this reaction, but it was an inactive intermediate in this reductive hydrocyanation, thus excluding the reduction-hydrocyanation pathway.



Scheme 2 Mechanistic experiments.

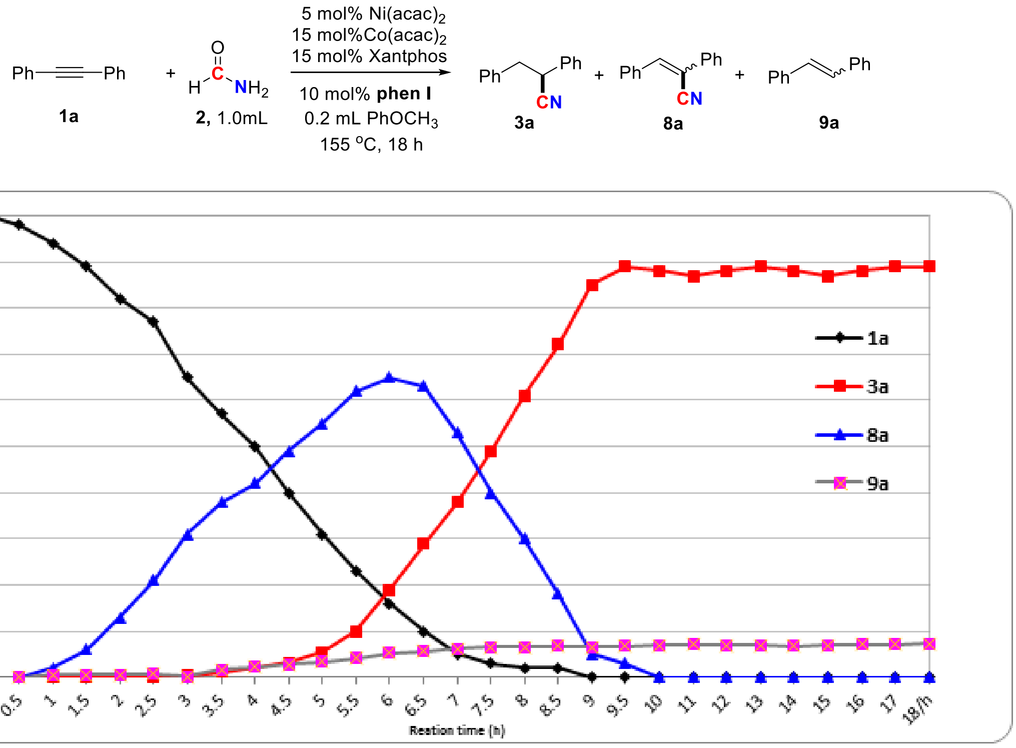
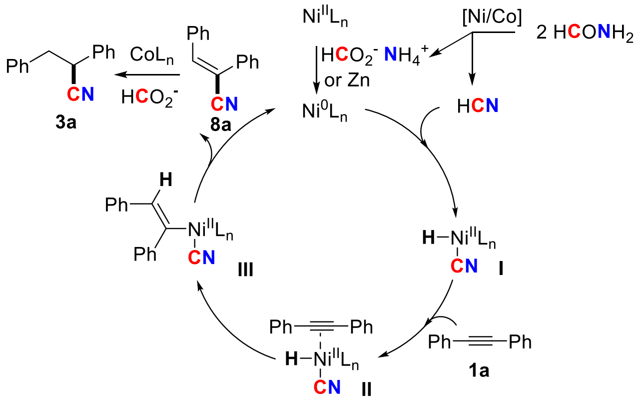


Figure 1 Reaction progress versus reaction time for the reductive hydrocyanation. The values for each measurement were detected by GC (with an internal standard) from independent experiments under the optimized conditions but stopped after the indicated reaction time.

Based on these results and literature reports using metal cyanides as the cyano source,[4] a tentative mechanism for the reductive hydrocyanation of alkenes is proposed, as depicted in Scheme 3, with the reaction of 1,2-diphenylethyne (**1a**) as an example. The first step involves the Ni/Co co-catalyzed dehydration of formamide to form hydrocyanic acid[9a] and hydrolysis of formamide molecules to produce ammonium formate,[10] thus reducing $Ni^{II}L_n$ to provide Ni^0L_n (L = ligand). Then, oxidative addition of hydrocyanic acid to Ni^0L_n generates Ni^{II} intermediate **I**, followed by coordination of alkyne **1a** and the *cis*-addition of the Ni-H bond to the C≡C bond to produce intermediate **III**, which undergoes reductive elimination to provide the hydrocyanation product **8a** in the *E* configuration and regenerates the Ni^0L_n catalyst. Vinyl nitrile **8a** in the *E* configuration is possibly partially converted to its *Z* configuration assisted by Ni or Co at elevated reaction temperatures, and both stereoisomers are reduced by the $Co(acac)_2$/ammonium formate combination to afford saturated nitrile **3a**.



Scheme 3. Proposed mechanism for the reductive hydrocyanation.

Conclusion

We have developed a new protocol for the reductive hydrocyanation of symmetric di-substituted and terminal alkynes utilizing hydrocyanic acid generated *in situ* from safe and readily available forms of formamide. The slow and steady generation of cyano units by the transition-metal-catalyzed dehydration of formamide provided a low concentration of cyanide for hydrocyanation to obviate the possible catalyst deactivation due to coordination saturation between Ni and the cyanide anion. In addition to the cyano source, formamide also acted as the dehydrant, reductant for both the Ni^{II} pre-catalyst and vinyl nitriles, and as co-solvent for this reaction. Detailed mechanistic investigation supported a pathway via hydrocyanation of the C≡C bond and subsequent reduction of the C=C bond. A wide substrate scope, the use of a cheap and stable nickel salt as a pre-catalyst, a safe cyano source, and convenient experimental operation are important advantages of this hydrocyanation protocol for the laboratory synthesis of saturated nitriles.

Experimental Section

2,3-Diphenylpropanenitrile (3a) by Reductive Hydrocyanation of an Alkyne; Typical Procedure:

An oven-dried reaction vessel was charged with 1,2-diphenylethyne (**1a**, 0.2 mmol, 35.6mg), $Ni(acac)_2$ (5 mol%, 2.6 mg), $Co(acac)_2$ (15 mol%, 7.7 mg), Xantphos (15 mol%, 17.4 mg), 3,4,7,8-tetramethyl-1,10-phenanthroline (**phen I**, 10 mol%, 4.7 mg), formamide (1.0 mL) and anisole(0.2 mL) under argon atmosphere. The vessel was sealed, heated and stirred at 155 °C (oil bath temperature) for 18 h. Then the resulting mixture was cooled to room temperature, added with 10 mL brine and extracted with ethyl acetate (3 × 10 mL). The organic layer was combined, washed with brine (2 × 10 mL), dried with anhydrous sodium sulfate and filtered. The filtrate was condensed in vacuum to remove solvent and further purified by column chromatography on silica gel with a mixture of EtOAc/petroleum ether as eluent to give the product (**3a**, 36.4 mg) in 88% yield.

Acknowledgements

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The authors declare no competing financial interest.

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UPDATE

Ni/Co Catalyzed Reductive Hydrocyanation of Alkynes with Formamide as the Cyano Source, Dehydrant, Reductant and Solvent

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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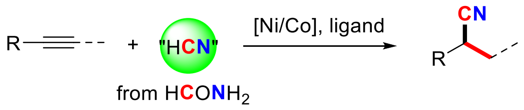

√ formamide as cyano source, dehydrant, reductant and solvent
√ slow "CN" generation via dehydration
√ avoiding "CN" accumulation
√ cheap and stable Ni^{II} pre-catalyst
√ Markovnikov selectivity