

Development of an Operationally Simple, Scalable, and HCN-free Transfer Hydrocyanation Protocol using an Air-Stable Nickel Precatalyst

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ABSTRACT: Hydrocyanation reactions enable access to synthetically valuable nitriles from readily available alkene precursors. However, hydrocyanation reactions using hydrogen cyanide (HCN) or similarly toxic reagents on laboratory scale can be particularly challenging due to their hazardous nature. In addition, such processes typically require air- and temperature-sensitive Ni(0) precatalysts, further reducing the operational simplicity of this transformation. Herein, we report a HCN-free transfer hydrocyanation of alkenes and alkynes that employs commercially available aliphatic nitriles as sacrificial HCN donors in combination with a catalytic amount of air-stable and inexpensive NiCl₂ as a precatalyst and a co-catalytic Lewis acid. The scalability and robustness of the catalytic process was demonstrated by the hydrocyanation of α -methylstyrene on a 100-mmol scale (11.4 g of product obtained) using 1 mol% of the Ni-catalyst. In addition, the feasibility of the dehydrocyanation protocol using the air-stable Ni(II) precatalyst and norbornadiene as a sacrificial acceptor was showcased by the selective conversion of an aliphatic nitrile into the corresponding alkene.

Keywords: transfer reaction, nickel catalysis, homogeneous, hydrocyanation, HCN-free

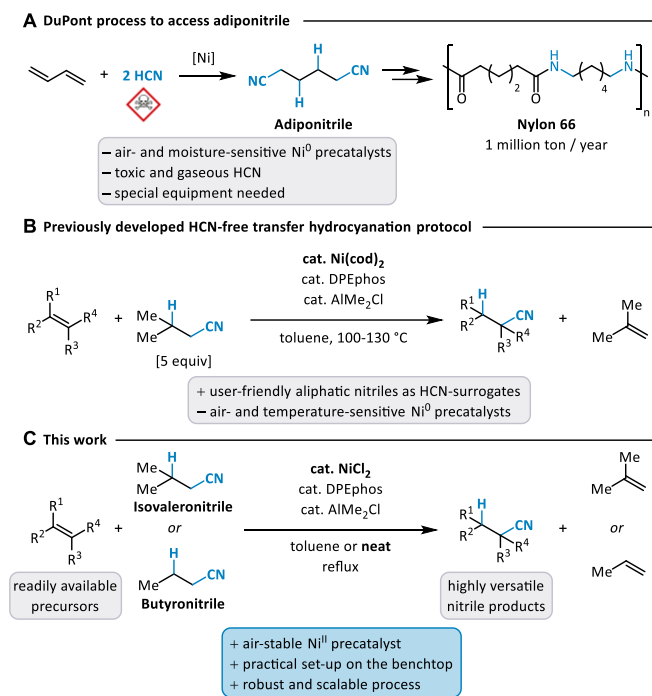
INTRODUCTION

Nitrile groups are versatile functional handles, often harnessed as synthetic intermediates in the construction of more complex molecules. They can be easily transformed into a variety of other fundamentally important functional groups, such as aldehydes, carboxylic acids, esters, ketones, amides, amines, and heterocycles.¹⁻⁴ At the same time, the α -position of aliphatic nitriles can be easily functionalized to introduce additional complexity to organic scaffolds.⁵ Furthermore, the nitrile can also serve as an important functional group in materials,⁶ pharmaceuticals,⁷ fragrances,^{8,9} and agrochemicals.^{10,11}

The hydrocyanation of readily available alkenes is a quintessential strategy for the introduction of nitrile groups.¹² In this transformation, hydrogen cyanide (HCN) is formally added across an alkene or an alkyne yielding the corresponding aliphatic or alkenyl nitriles, respectively.¹³⁻¹⁷ One of the most prominent industrial applications of the hydrocyanation reaction is the DuPont process (Scheme 1A).¹⁸ The catalytic system, relying on a nickel-phosphite catalyst,

has enabled the production of adiponitrile, a common precursor for Nylon 66, by the incorporation of HCN into butadiene on a 1-million-ton scale annually.¹⁹⁻²¹ Despite this notable commercial application of this homogeneously catalyzed hydrocyanation reaction, the use of highly volatile HCN in laboratory-scale settings has been limited due to its extreme toxicity, as well as its explosive and corrosive nature.²²

Scheme 1. Comparison of the traditional hydrocyanation method to the shuttle catalysis approach.



Kilogram-scale reactions relying on the direct use of HCN are feasible providing strict safety regulations to ensure that polymerization or decomposition as well as the release of the reactive and toxic HCN is prevented. Thus highly specialized equipment is required, complicating the implementation of this chemistry on industrial scales.^{23,24} Therefore, alternative strategies that rely on less volatile but similarly toxic surrogates (e.g. TMS-CN, acetone cyanohydrin) have been employed.^{25–34} These reagents partially address these safety concerns but fall short of solving the problem since HCN is usually formed *in situ*.³⁵ Another challenge associated with the use of HCN in traditional nickel-catalyzed hydrocyanation reactions is the demand for careful adjustment of the HCN concentration to avoid catalyst poisoning through the formation of an inactive nickel dicyanide species, a feature that often complicates scale-up campaigns.^{21,36,37}

In recent years, shuttle catalysis^{38–40} has emerged as a useful tool for the introduction of important synthetic functional groups by circumventing the need for directly using toxic and hazardous reagents, such as HMgBr ,^{41–47} HCN,^{48–52} CO ,^{53–58} HCl ,^{59,60} HI ,^{61,62} Cl_2 , and Br_2 ⁶³ in a transfer process. Using this paradigm, a reversible HCN-free transfer hydrocyanation strategy has been developed by our group.⁴⁸ In this protocol, simple, inexpensive, and commercially available aliphatic nitriles are utilized as sacrificial HCN-donor molecules, thereby overcoming the inherent safety concerns associated with traditional hydrocyanation reagents, as well as circumventing catalyst poisoning by limiting cyanide concentration in the reaction (Scheme 1B).⁴⁸ Furthermore, the inherent reversibility of the transfer reaction enables both the functionalization of alkenes and alkynes to generate the corresponding hydrocyanation products, as

well as the defunctionalization of aliphatic nitriles to access alkenes.

In our original report,⁴⁸ the transfer hydrocyanation reaction relied on a $\text{Ni}(\text{cod})_2$, a $\text{Ni}(\text{O})$ precatalyst, and co-catalytic amounts of AlMe_2Cl . The handling of the $\text{Ni}(\text{O})$ precursor is not trivial,^{64,65} since it is especially sensitive towards oxygen and prone to thermal decomposition. Thus, special equipment is necessary for both the storage of the reagent and the reaction set-up, creating a barrier for the widespread adoption of this reaction among synthetic practitioners. We therefore aimed to establish a more user-friendly protocol to enable the reaction set-up on the benchtop. Herein, we report an operationally simple transfer hydrocyanation protocol utilizing an inexpensive and air-stable $\text{Ni}(\text{II})$ precursor in combination with a co-catalytic Lewis acid, which leads to a more robust and scalable hydrocyanation process (Scheme 1C). The reaction could be setup on the benchtop, without the requirement for any special equipment (e.g. glovebox).

EXPERIMENTAL SECTION

Materials. Unless otherwise stated, reagents were used as supplied from commercial sources without any further purification. Isovaleronitrile and butyronitrile were dried and stored over 4 Å activated molecular sieves and were deoxygenated by sparging with nitrogen gas prior to use for 10 minutes. Anhydrous NiCl_2 (98% purity) and DPEphos (99% purity) were purchased from Sigma-Aldrich and Acros Organics respectively and were stored on the bench under a N_2 atmosphere. Extra-dry toluene stored over 4 Å molecular sieves was purchased from Acros Organics and was deoxygenated by sparging with nitrogen gas prior to use. Dimethylaluminum chloride (0.9 M solution in heptane) was purchased from Acros Organics.

All glassware were dried for at least one hour in an oven set at 100 °C prior to use unless stated otherwise. All reactions were carried out in Schlenk tubes connected to a Schlenk line unless stated otherwise and were performed under a positive pressure of nitrogen. ^1H - and ^{13}C -NMR spectra were recorded on a Bruker AVIII 400 MHz or a Bruker Neo 400 MHz spectrometer and are reported in parts per million (ppm). ^1H -NMR spectra are calibrated with respect to the corresponding solvent residual peak (CHCl_3 : 7.26 ppm). ^{13}C -NMR spectra are calibrated with respect to the corresponding solvent residual peak (CHCl_3 : 77.16 ppm). Multiplet signals are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, or combinations thereof. ^{13}C signals are singlets unless otherwise stated. Gas chromatography (GC) was recorded on a Shimadzu GC-2025 (capillary column: Macherey-Nagel OPTIMA 5, 30.0 m × 0.25 × 0.25 μm; carrier gas: H_2). To determine GC yields, calibration curves using *n*-dodecane as an internal standard were generated. Analytical thin-layer chromatography was performed using silica gel 60 F254 coated aluminum sheets (Merck). Visualization was achieved by ultraviolet fluorescence ($\lambda = 254 \text{ nm}$) and/or staining with potassium permanganate (KMnO_4). Flash column chromatography and automated flash column chromatography (Biotage: Isolera

One) were performed using silica gel 60 (pore size = 60 Å, mesh: 40-63 µm from Sigma-Aldrich or SiliCycle).

Precaution. Although highly toxic HCN was never observed in significant amounts under our transfer hydrocyanation conditions, appropriate safety measures should nevertheless be implemented. The handling of all reagents requires the practitioner to wear appropriate safety equipment and all operations should be executed in a well-ventilated fume hood.^{66,67}

General procedure A for the hydrocyanation reaction. On the benchtop, an oven-dried, 10 mL Schlenk tube was charged with NiCl₂ (3.2 mg, 0.025 mmol, 2.5 mol%) and DPEphos (13 mg, 0.025 mmol, 2.5 mol%). The reaction vessel was sealed with a rubber septum and evacuated and refilled with N₂ four times. Subsequently, anhydrous toluene (2.0 mL), isovaleronitrile (0.52 mL, 5.0 mmol, 5.0 equiv), and the substrate (1.0 mmol) were added. The resulting suspension was stirred for 2 minutes at ambient temperature. Then AlMe₂Cl (0.11 mL, 0.9 M in heptane, 0.10 mmol, 10 mol%) was added dropwise. The resulting reaction mixture was stirred at reflux for 18 h (oil bath temperature: 130 °C) under positive N₂ pressure. Afterwards the reaction mixture was allowed to cool to ambient temperature, was quenched by the addition of MeOH (0.2 mL) and stirred for 10 minutes at ambient temperature. The resulting suspension was filtered through a plug of silica using ethyl acetate as an eluent and was concentrated under reduced pressure. The crude product was purified by flash column chromatography.

Remark: With solid substrates, the substrate was added to the Schlenk tube prior to the vacuum-nitrogen cycles (for more details see Supporting Information).

Remark: Control experiments demonstrated that purging the system through vacuum-nitrogen cycles could be omitted. Instead, the reaction vessel can simply be flushed with N₂ gas prior to setting up the reaction (for more details see Supporting Information.)

Procedure B for the hydrocyanation of α -methylstyrene **1a on 100-mmol scale.** On the benchtop, an oven-dried, 250 mL two-necked round-bottom flask equipped with a cooling condenser was charged with NiCl₂ (130 mg, 1.00 mmol, 1.00 mol%) and DPEphos (539 mg, 1.00 mmol, 1.00 mol%). The reaction vessel was sealed with a rubber septum and the system was evacuated and refilled with N₂ four times. Subsequently, butyronitrile (100 mL, 1.15 mol, 11.5 equiv) and **1a** (13.0 mL, 100 mmol) were added and the mixture was stirred for 2 minutes at ambient temperature. Then AlMe₂Cl (4.5 mL, 0.9 M in heptane, 4.0 mmol, 4.0 mol%) was added dropwise, and the suspension was stirred at reflux (boiling point of butyronitrile: 117 °C; oil bath temperature: 140 °C) for 18 h under N₂ atmosphere. Afterwards, the reaction mixture was allowed to cool to ambient temperature, was quenched by the addition of MeOH (10 mL) and stirred for 10 minutes at ambient temperature. The resulting suspension was filtered through a plug of silica using ethyl acetate as an eluent and was concentrated under reduced pressure. The crude product was purified by automated flash column chromatography (Biotage, SiO₂, 0-

20% EtOAc in hexanes) to give the product **3a** as a colorless oil (yield = 11.4 g, 79%). ¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.32 (m, 2H), 7.30 – 7.22 (m, 3H), 3.17 (q, 1H), 2.67 – 2.52 (m, 2H), 1.46 (d, J = 7.0 Hz, 3H).

Procedure C for the dehydrocyanation reaction of α -cyclohexylphenylacetone **6.** An oven-dried, 4 mL screw cap vial was charged with NiCl₂ (3.2 mg, 0.025 mmol, 2.5 mol%), DPEphos (13 mg, 0.025 mmol, 2.5 mol%) and **6** (0.20 g, 1.0 mmol). The reaction vessel was sealed with a rubber septum cap and the system was evacuated and refilled with N₂ four times. Subsequently, anhydrous toluene (2 mL) and norbornadiene (0.15 mL, 1.5 mmol, 1.5 equiv) were added and the mixture was stirred for 2 minutes at ambient temperature. Then AlMe₂Cl (0.11 mL, 0.9 M in heptane, 0.10 mmol, 10 mol%) was added dropwise, and the vial was sealed with electrical tape, and the suspension was stirred at 120 °C for 16 h. Afterwards, the reaction mixture was allowed to cool to ambient temperature, was quenched by the addition of MeOH (0.2 mL) and stirred for 10 minutes at ambient temperature. The resulting suspension was filtered through a plug of silica using ethyl acetate as an eluent and was concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, 0–5% Et₂O in pentanes) to give the product **7** as a colorless oil (yield = 169 mg, 98%). ¹H NMR (400 MHz, CDCl₃) δ 7.35 – 7.27 (m, 2H), 7.24 – 7.15 (m, 3H), 6.24 (s, 1H), 2.38 (m, 1.1 Hz, 2H), 2.30 – 2.23 (m, 2H), 1.70 – 1.54 (m, 6H).

3-Phenylpropionitrile **3b.** Prepared according to the general procedure A using styrene (0.11 mL, 1.0 mmol). Purified by flash column chromatography (SiO₂, 0–20% Et₂O in pentanes) to give product **3b** as colorless oil (yield = 90 mg, 69%). ¹H NMR (400 MHz, CDCl₃) δ 7.27 – 7.21 (m, 2H), 7.20 – 7.11 (m, 3H), 2.86 (t, J = 7.4 Hz, 2H), 2.52 (t, J = 7.4 Hz, 2H).

4-Methyl-3-phenylpentanenitrile **3c.** Prepared according to the general procedure A using (3-methylbut-1-en-2-yl)benzene (146 mg, 1.0 mmol). Purified by flash column chromatography (SiO₂, 0–20% Et₂O in pentanes) to give product **3c** as colorless oil (yield = 125 mg, 72%). ¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.31 (m, 2H), 7.29 – 7.25 (m, 1H), 7.23 – 7.17 (m, 2H), 2.76 – 2.61 (m, 3H), 2.13 – 2.01 (m, 1H), 1.03 (d, J = 6.7 Hz, 3H), 0.78 (d, J = 6.7 Hz, 3H).

3,3-Diphenylpropanenitrile **3d.** Prepared according to the general procedure A using 1,1-diphenylethylene (0.18 mL, 1.0 mmol). Purified by flash column chromatography (SiO₂, 0–10% EtOAc in hexanes) to give product **3d** as white powder (yield = 111 mg, 53%). ¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.32 (m, 4H), 7.30 – 7.23 (m, 6H), 4.39 (t, J = 7.7 Hz, 1H), 3.04 (d, J = 7.7 Hz, 2H).

3-(*o*-Tolyl)butanenitrile **3e.** Prepared according to the general procedure A using 1-methyl-2-(prop-1-en-2-yl)benzene (132 mg, 1.0 mmol) and 1 mL anhydrous toluene. Purified by flash column chromatography (SiO₂, 0–6% EtOAc in hexanes) to give the product **3e** as a colorless oil (yield = 139 mg, 87%). ¹H NMR (400 MHz, CDCl₃) δ 7.25 – 7.11 (m, 4H), 3.44 (dq, J = 7.9, 6.9, 6.1 Hz, 1H), 2.65 – 2.48 (m, 2H), 2.36 (s, 3H), 1.43 (d, J = 6.9 Hz, 3H).

3-(*p*-Tolyl)butanenitrile **3f.** Prepared according to the general procedure A using 4-isopropenyltoluene (132 mg,

1.0 mmol) and 1 mL of anhydrous toluene. Purified by flash column chromatography (SiO₂, 0–10% EtOAc in hexanes) to give the product **3f** as a colorless oil (yield = 106 mg, 67%). ¹H NMR (400 MHz, CDCl₃) δ 7.19 – 7.09 (m, 4H), 3.19 – 3.08 (m, 1H), 2.64 – 2.49 (m, 2H), 2.34 (s, 3H), 1.44 (d, *J* = 7.0 Hz, 3H).

3-(4-Methoxyphenyl)butanenitrile 3g. Prepared according to the general procedure A using 1-methoxy-4-(prop-1-en-2-yl)benzene (148 mg, 1.0 mmol) and 1 mL of anhydrous toluene. Purified by flash column chromatography (SiO₂, 0–7.5% EtOAc in hexanes) to give the product **3g** as a pale green oil (yield = 156 mg, 89%). ¹H NMR (400 MHz, CDCl₃) δ 7.21 – 7.13 (m, 2H), 6.91 – 6.84 (m, 2H), 3.80 (s, 3H), 3.19 – 3.08 (m, 1H), 2.61 – 2.48 (m, 2H), 1.43 (d, *J* = 7.0 Hz, 3H).

3-(1,1'-Biphenyl-4-yl)butanenitrile 3h. Prepared according to the general procedure A using 4-(prop-1-en-yl)-1,1'-biphenyl (194 mg, 1.0 mmol). Purified by flash column chromatography (SiO₂, 0–10% EtOAc in hexanes) to give the product **3h** as a white powder (yield = 210 mg, 95%). ¹H NMR (400 MHz, CDCl₃) δ 7.61 – 7.55 (m, 4H), 7.48 – 7.43 (m, 2H), 7.39 – 7.30 (m, 3H), 3.29 – 3.16 (m, 1H), 2.71 – 2.56 (m, 2H), 1.50 (d, *J* = 7.0 Hz, 3H).

3-Phenyl-3-(pyridine-2-yl)propanenitrile 3i. Prepared according to the general procedure A using 2-(1-phenylvinyl)pyridine (181 mg, 1.0 mmol). Purified by flash column chromatography (SiO₂, 0–30% EtOAc in hexanes) to give the product **3i** as a brownish oil (yield = 94 mg, 45%). ¹H NMR (400 MHz, CDCl₃) δ 8.63 – 8.59 (m, 1H), 7.59 (td, *J* = 7.7, 1.8 Hz, 1H), 7.37 – 7.23 (m, 5H), 7.17 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H), 7.17 – 7.09 (m, 1H), 4.44 (apparent t, *J* = 7.6 Hz, 1H), 3.40 (dd, *J* = 16.7, 7.6 Hz, 1H), 3.09 (dd, *J* = 16.7, 7.6 Hz, 1H).

Cyclooctanecarbonitrile 3j. Prepared according to the general procedure A using cyclooctene (0.13 mL, 1.0 mmol). Purified by flash column chromatography (SiO₂, 0–10% EtOAc in hexanes) to give the product **3j** as a colorless oil (yield = 116 mg, 85%). ¹H NMR (400 MHz, CDCl₃) δ 2.75 (tt, *J* = 8.5, 4.2 Hz, 1H), 2.01 – 1.91 (m, 2H), 1.89 – 1.71 (m, 4H), 1.64 – 1.50 (m, 8H).

4-((*t*-Butyldimethylsilyl)oxy)-4-methylpentanenitrile 3k. Prepared according to the general procedure A using *tert*-butyldimethyl((2-methylbut-3-en-2-yl)oxy)silane (214 mg, 1.0 mmol) and 1 mL of anhydrous toluene. Purified by flash column chromatography (SiO₂, 0–2% EtOAc in hexanes) to give the product **3k** as a pale green oil (yield = 156 mg, 81%). ¹H NMR (400 MHz, CDCl₃) δ 2.46 – 2.39 (m, 2H), 1.83 – 1.76 (m, 2H), 1.24 (s, 6H), 0.85 (s, 9H), 0.09 (s, 6H).

3-Cyclohexylpropionitrile 3l. Prepared according to the general procedure A using vinylcyclohexane (0.14 mL, 1.0 mmol). Purified by flash column chromatography (SiO₂, 0–10% Et₂O in pentanes) to give product **3l** as a colorless oil (yield = 97 mg, 71%). ¹H NMR (400 MHz, CDCl₃) δ 2.34 (t, *J* = 7.4 Hz, 2H), 1.76 – 1.64 (m, 5H), 1.56 (apparent q, *J* = 7.2 Hz, 2H), 1.46 – 1.32 (m, 1H), 1.30 – 1.10 (m, 3H), 0.96 – 0.85 (m, 2H).

3-(Dimethyl(phenyl)silyl)propanenitrile 3m. Prepared according to the general procedure A using dimethyl phenyl vinyl silane (162 mg, 1.0 mmol) and 1 mL of anhydrous

toluene. Purified by flash column chromatography (SiO₂, 0–2% EtOAc in hexanes) to give product **3m** as a light green oil (yield = 159 mg of 78:22 = linear : branched isomer, 84%). *Linear isomer:* ¹H NMR (400 MHz, CDCl₃) δ 7.53 – 7.47 (m, 2H), 7.44 – 7.33 (m, 3H), 2.31 – 2.22 (m, 2H), 1.20 – 1.10 (m, 2H), 0.36 (s, 6H). *Branched isomer:* ¹H NMR (400 MHz, CDCl₃) δ 7.62 – 7.55 (m, 2H), 7.48 – 7.37 (m, 3H), 2.02 (q, *J* = 7.3 Hz, 1H), 1.26 (d, *J* = 7.3 Hz, 3H), 0.52 (d, *J* = 1.4 Hz, 6H).

(*E*)-2-Propylhex-2-enenitrile 3n. Prepared according to the general procedure A using 4-octyne (0.15 mL, 1.0 mmol). Purified by flash column chromatography (SiO₂, 0–15% EtOAc in hexanes) to give the product **3n** as a yellowish oil (yield = 110 mg, 80%). ¹H NMR (400 MHz, CDCl₃) δ 6.34 (tt, *J* = 7.5, 1.2 Hz, 1H), 2.16 (apparent p, *J* = 7.5 Hz, 4H), 1.57 (dq, *J* = 14.7, 7.4 Hz, 2H), 1.52 – 1.38 (m, 2H), 0.93 (apparent td, *J* = 7.4, 5.8 Hz, 6H).

2-Butylhep-2-enenitrile 3o. Prepared according to the general procedure A using 5-decyne (0.18 mL, 1.0 mmol). Purified by flash column chromatography (SiO₂, 0–20% Et₂O in pentanes) to give product **3o** as a yellowish oil (yield = 97 mg, 59%; 94:6 = *E*:*Z*-isomer). ¹H NMR (400 MHz, CDCl₃) δ 6.38 – 6.28 (m, 1H), 2.25 – 2.04 (m, 4H), 1.60 – 1.43 (m, 2H), 1.47 – 1.28 (m, 6H), 0.92 (q, *J* = 7.3 Hz, 6H).

(*E*)-2-Phenyl-3-(trimethylsilyl)acrylonitrile 3p and (*Z*)-2-phenyl-3-(trimethylsilyl)acrylonitrile 3p'. Prepared according to the general procedure A using phenylethynyl-trimethylsilane (0.20 mL, 1.0 mmol). Purified by flash column chromatography (SiO₂, 0–20% EtOAc in hexanes) to give product **3p** as a colorless oil (yield = 87 mg, 43%) and product **3p'** as a colorless oil (yield = 54 mg, 27%). *(Z)-isomer:* ¹H NMR (400 MHz, CDCl₃) δ 7.91 – 7.82 (m, 2H), 7.47 – 7.36 (m, 3H), 7.19 (s, 1H), 0.33 (s, 9H). *(E)-isomer:* ¹H NMR (400 MHz, CDCl₃) δ 7.65 – 7.58 (m, 2H), 7.44 – 7.37 (m, 3H), 7.10 (s, 1H), 0.34 (s, 9H).

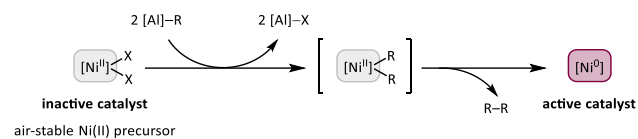
RESULTS AND DISCUSSION

Optimization of the transfer hydrocyanation protocol.

We initially aimed to substitute the air- and temperature-sensitive Ni(0) precursor, used in our previous protocol,⁴⁸ with an air-stable and inexpensive Ni(II) precatalyst. The catalyst could be reduced *in-situ* by either the phosphine ligands,^{68,69} the co-catalytic Lewis acid^{70,71} or an external reductant.^{72,73} In order to keep the reaction set-up as operationally simple as possible, the introduction of an external reductant as an additional component was not considered. Preliminary experiments using phosphine ligands as reducing agents in combination with co-catalytic Lewis acid were unsuccessful. Therefore, we hypothesized that the Lewis acid could potentially fulfill a dual role in the reaction, acting both as a co-catalyst and a reductant. On the one hand, the Lewis acid is required to pre-coordinate to the nitrile group to weaken the C–CN bond and hence to facilitate the nickel mediated C–CN bond activation process.^{74–77} On the other hand, the Lewis acid could also affect the reduction of the Ni(II) precursor for the formation of the active Ni(0) hydrocyanation catalyst.^{78,79} The latter reduction is likely to proceed via two consecutive transmetalation steps from the alkyl-aluminum reagents to the nickel to afford a dialkylnickel(II) complex, which can then undergo reductive

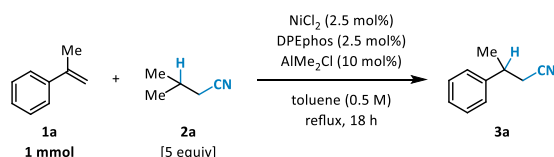
elimination to afford the catalytically active Ni(0) species *in situ* (Scheme 2).^{70,71} The desired catalytic intermediate for hydrocyanation, H–Ni–CN, is then formed via an oxidative addition of the Ni(0) species into the C–CN bond of the donor substrate which is facilitated by the Lewis acid co-coordination to the nitrile moiety, followed by a β -hydride elimination (for details see Supporting Information).

Scheme 2. Mechanistic hypothesis for the Ni(II) reduction by the aluminum Lewis acid

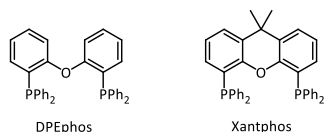


Besides the envisioned *in-situ* reduction of the Ni(II) precatalyst, the reaction set-up, including the weighing of the precatalyst and ligand, should ideally be possible on the benchtop without the requirement for any specialized equipment such as a glovebox. α -Methylstyrene **1a** was chosen as the model substrate using readily available isovaleronitrile **2a** as the sacrificial HCN donor molecule. In an initial set of screening experiments, inexpensive and commercially available Ni(II) precursors, as well as various monodentate and bidentate ligands were evaluated under the previously established reaction conditions (see Supporting Information). Anhydrous NiCl₂ in combination with commercially available DPEphos was highly active in the transfer hydrocyanation reaction using co-catalytic AlMe₂Cl, affording the hydrocyanation product **3a** in quantitative GC-yield in the absence of any additional external reductant (Table 1).⁸⁰

Table 1. Effect of different reaction parameters on the reaction outcome.



Entry	Deviation from standard conditions	Conv. ^a	Yield ^a
1	none	quant.	quant.
2	Ni(acac) ₂ instead of NiCl ₂	95%	91%
3	Xantphos instead of DPEphos	96%	84%
4	PPh ₃ (5 mol%) instead of DPEphos	36%	17%
5	butyronitrile (11.5 equiv) instead of isovaleronitrile ^b	quant.	quant.
6	AlCl ₃ instead of AlMe ₂ Cl	13%	0%



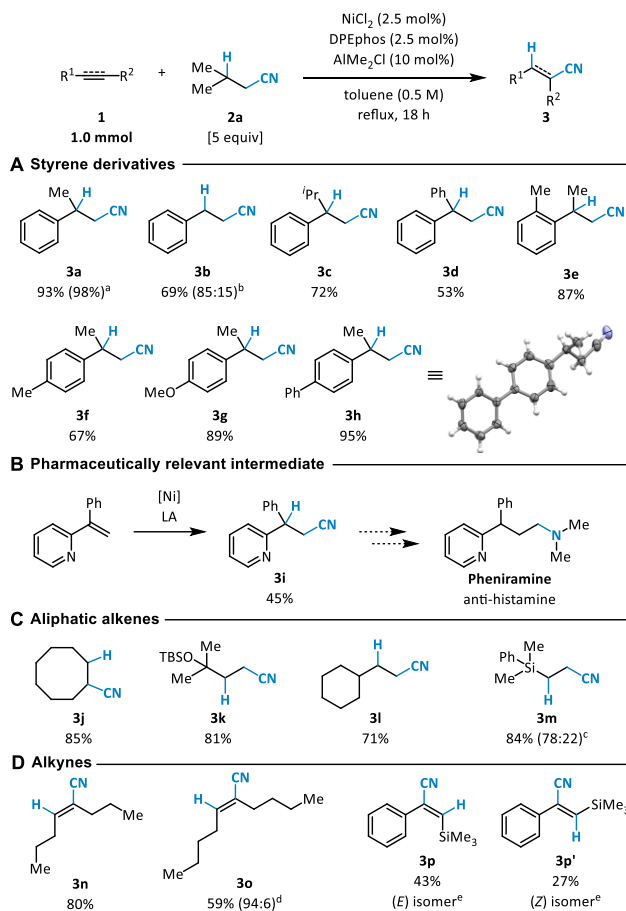
^aGC conversion and GC yields were determined by using *n*-dodecane as an internal standard. ^bThe reaction with butyronitrile was carried out in the absence of toluene.

Besides the use of DPEphos as a ligand, Xantphos was also shown to efficiently facilitate the transfer hydrocyanation reaction. However, slightly diminished GC-conversion and yield were obtained (96% and 84% respectively, Entry 3). Reaction with monodentate PPh₃ gave only poor yields of the desired product (Entry 4). Next, the effect of the sacrificial HCN donor on the overall reaction performance was evaluated. Notably, both isovaleronitrile as well as butyronitrile were shown to be similarly competent HCN donors in this new transfer hydrocyanation protocol (Entry 5). When using more inexpensive butyronitrile as reagent, the need for an additional solvent could be circumvented by increasing the amount of the butyronitrile donor used.

As previously demonstrated,⁴⁸ aluminum-based Lewis acid derivatives are crucial for the transfer hydrocyanation reaction. Additionally, it was shown that only alkyl-aluminum Lewis acids, such as AlMe₂Cl, Al(^{*i*}Bu)₂Cl and Al(^{*i*}Bu)₃ successfully facilitated the transfer hydrocyanation reaction with a NiCl₂ precatalyst. This observation is consistent with the proposed reduction mechanism of the Ni(II) precatalyst by the co-catalytic Lewis acid. By contrast, the use of AlCl₃ did not lead to any product formation (Entry 6), despite proving to be a suitable co-catalyst in our previous work on transfer hydrocyanation using a Ni(0) precatalyst. The inability of AlCl₃ to efficiently reduce the nickel precatalyst further supports the proposed reduction pathway relying on the introduction of two alkyl groups from the aluminum-based Lewis acid via sequential transmetalation steps.

Evaluation of the substrate scope. Next, we evaluated the scope of the transfer hydrocyanation reaction using our optimized reaction protocol. In general, styrene derivatives, aliphatic alkenes as well as alkynes could be successfully transformed into the corresponding hydrocyanation products in good yields (Scheme 3).

Scheme 3. Substrate scope of the hydrocyanation reaction.



All yields are isolated yields. Only one regio- or stereoisomer is obtained in all reactions unless stated otherwise. ^aReaction was run under neat conditions using butyronitrile (11.5 equiv) as the sacrificial HCN donor in the absence of toluene. ^bIsolated yield of the linear product. The ratio of linear to branched isomers was determined by ¹H-NMR of the crude reaction mixture. ^cRatio of linear to branched isomer. ^dThe (*E*) and (*Z*) stereoisomers were obtained in a 94:6 ratio respectively, as determined by ¹H-NMR. ^eThe (*Z*) and (*E*) stereoisomers were formed in a 62:38 ratio respectively, as determined by ¹H-NMR of the crude reaction mixture.

When investigating the positional selectivity in styrene derivatives, we found that hydrocyanation of the unsubstituted styrene afforded a mixture of both the linear and branched hydrocyanation products, similar to the previously developed reaction protocol.⁴⁸ The linear hydrocyanation product **3b** was isolated by column chromatography in 69% yield as a single isomer. However, the reaction with 1,1-disubstituted styrenes exclusively generated the anti-Markovnikov products **3a** and **3c**. Even the sterically demanding 1,1-diphenylethylene was successfully transformed under the reaction conditions to give the 3,3-diphenylpropionitrile **3d** as a single product. Furthermore, *ortho*- as well as *para*-substituted styrene derivatives (**3e**, **3f**, **3g**, **3h**) were tolerated under the reaction conditions.

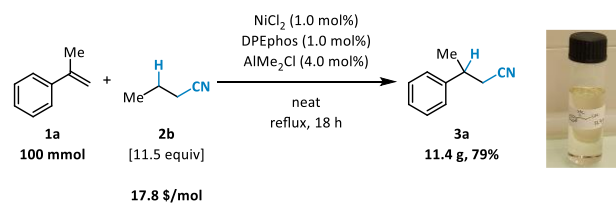
The developed strategy also allowed us to selectively access the precursor **3i** of pheniramine,⁸¹ an anti-histamine drug, in moderate yield (45%). Unactivated aliphatic alkenes

were also transformed efficiently into the corresponding hydrocyanation products **3j**, **3k**, and **3l** in high yield and selectivity. In the case of a vinyl silane, two regioisomers (**3m**) were formed during the reaction and were isolated as a mixture in 84% yield. In addition, alkynes were successfully converted into the corresponding alkenyl nitriles in high yields under the given reaction conditions. For symmetrical alkynes, this transfer hydrocyanation serves as a selective protocol to access the (*E*)-alkenyl nitrile products (**3n** and **3o**) as single stereoisomers. With an unsymmetrical alkyne, 1-phenyl-2-trimethylsilylacetylene, the (*E*) and (*Z*) stereoisomers (**3p** and **3p'**) were obtained in a ratio of 62:38 respectively, which could be separated by column chromatography. In general, the functional group tolerance for this developed protocol is comparable to the more extensive substrate scope we previously reported using the Ni(0) precatalysts.⁴⁸

Scale-up of the transfer hydrocyanation reaction. To evaluate the scalability and robustness of our transfer hydrocyanation protocol, we first conducted test reactions on a 5-mmol scale. Butyronitrile was utilized as the sacrificial HCN donor due to its comparably low-cost. In addition, to reduce solvent waste, we aimed to perform the reaction in the absence of any other solvent.^{82–84} In a pre-evaluation of the reaction parameters, α -methylstyrene **1a** was converted to 3-phenylbutanenitrile **3a** in excellent GC yield using an excess of butyronitrile (23 equiv, corresponds to a 0.50 M solution of the substrate in butyronitrile), 2.5 mol% of Ni-catalyst in combination with 10 mol% of co-catalytic Lewis acid without the need for toluene as a solvent. Having shown that the reaction can be conducted neat, we next aimed at decreasing the catalyst loading to further improve the overall efficiency of the transformation. Initial experiments to reduce the catalyst loading, though, led to a significantly diminished conversion and product yield (see Supporting Information). Gratifyingly, reducing the excess of butyronitrile (11.5 equiv, corresponds to a 1.0 M solution of substrate in butyronitrile) afforded the desired product in excellent GC yields using only 1 mol% of Ni-catalyst.

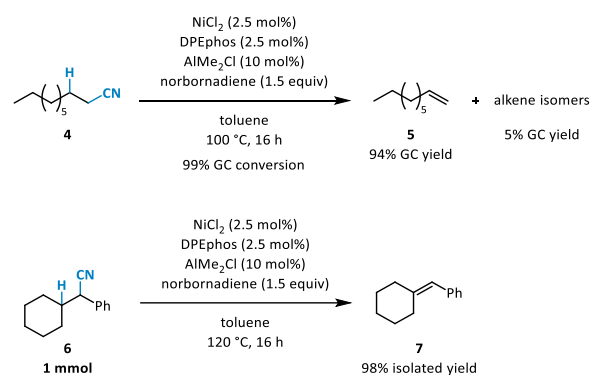
Following the successful scale-up of the hydrocyanation reaction from 1 mmol to 5 mmol, the robustness of the protocol was further challenged on a 100-mmol scale (Scheme 4). The decagram scale reaction was performed on the benchtop under a nitrogen atmosphere using a standard, two-necked round bottom flask. This afforded the desired hydrocyanation product **3a** in 79% isolated yield.

Scheme 4. Scale-up of the transfer hydrocyanation reaction.



Dehydrocyanation of an aliphatic nitrile. Having established a scalable and robust system for the transfer hydrocyanation of alkenes and alkynes using an air-stable Ni(II) precatalyst, we sought to examine whether the defunctionalization reaction to access alkenes from aliphatic nitriles is feasible using our newly developed catalytic protocol. In the model reaction, the transformation of decanenitrile **4** into the desired alkene product **5** was observed using norbornadiene as the sacrificial HCN acceptor (see Supporting Information). The dehydrocyanation of α -cyclohexylphenylacetonitrile **6** was successfully conducted under the optimized reaction conditions on a 1-mmol scale, affording the corresponding alkene **7** with excellent yield (Scheme 5). This demonstrates that our new protocol is also reliable for efficiently catalyzing the transfer dehydrocyanation reaction.

Scheme 5. Transfer dehydrocyanation reactions.



CONCLUSION

In summary, an operationally simple, robust, and scalable HCN-free protocol for the transfer hydrocyanation of alkenes and alkynes to access the corresponding aliphatic and alkenyl nitriles has been developed. The implementation of aliphatic nitriles as sacrificial HCN donors circumvents the use of toxic HCN gas, thereby addressing a major limitation of conventional hydrocyanation reactions. A further advantage of this new protocol is the use of an air-stable, inexpensive NiCl₂ precatalyst in combination with co-catalytic Lewis acid, which simplifies the reaction set-up and the storage of the catalyst. Additionally, the reaction can be conducted neat using inexpensive butyronitrile as a HCN donor and can be performed with reduced catalyst loadings. The scalability and robustness of this protocol were demonstrated on a 100-mmol (decagram) scale for the hydrocyanation of α -methylstyrene to afford the corresponding product, 3-phenylbutanenitrile, in 79% isolated yield. The developed catalytic protocol was also shown to efficiently catalyze the dehydrocyanation reaction. Considering the versatility of nitrile groups and their widespread occurrence in industrially relevant intermediates and products, we believe that the operational simplicity of our new

protocol will provide the impetus for the adoption of this transformation in laboratory-based settings.

ASSOCIATED CONTENT

Supporting Information.

¹H- and ¹³C-NMR spectra, as well as HRMS data for all isolated compounds. Crystallographic data for **3i** (CCDC 2122659). Additional experimental details as well as experimental procedures for the preparation of starting materials, and methods, including photographs of the experimental set-up. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes.

The authors declare the following competing financial interest(s): A patent for transfer hydrocyanation has been granted (US2019031602 (A1)).

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