(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) **World Intellectual Property Organization**
International Bureau

(43) **International Publication Date**
8 June 2017 (08.06.2017)

WIPO | PCT

(10) **International Publication Number**
WO 2017/093149 A1

(51) **International Patent Classification**:
C07C 253/30 (2006.01)
C07C 255/03 (2006.01)
C07C 255/07 (2006.01)
C07C 255/19 (2006.01)
C07C 255/31 (2006.01)
C07C 255/33 (2006.01)
C07C 255/34 (2006.01)
C07C 255/37 (2006.01)
C07C 255/46 (2006.01)
C07C 255/47 (2006.01)
C07D 209/76 (2006.01)
C07D 209/86 (2006.01)
C07F 7/08 (2006.01)
B01J 31/14 (2006.01)
B01J 31/24 (2006.01)

(21) **International Application Number**:
PCT/EP2016/078919

(22) **International Filing Date**:
26 November 2016 (26.11.2016)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
15197353.4 1 December 2015 (01.12.2015) EP

(71) **Applicant**: **STUDIENGESELLSCHAFT KOHLE MBH** [—/DE]; Kaiser-Wilhelm-Platz 1, 45470 Mülheim (DE).

(72) **Inventors**: **MORANDI, Bill**; Lembkestr. 4, 45470 Muelheim an der Ruhr (DE). **FANG, Xianjie**; Neudecker Str. 38, 45470 Muelheim an der Ruhr (DE). **PENG, Yu**; Löhberg 68-70, 45468 Muelheim an der Ruhr (DE).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(54) **Title**: Process for the Catalytic Reversible Alkene-Nitrile Interconversion

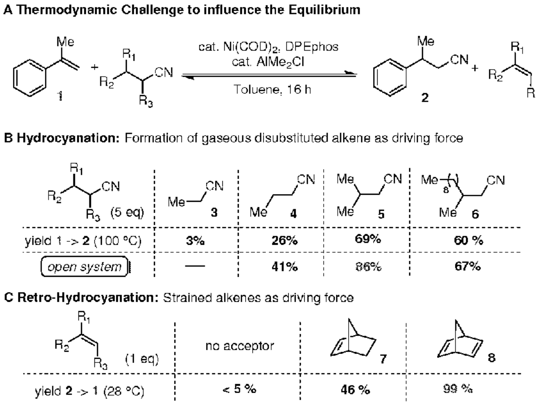


Fig. 2:

(57) **Abstract**: The present invention refers to processes for catalytic reversible alkene-nitrile interconversion through controllable HCN-free transfer hydrocyanation.

WO 2017/093149 A1

Process for the Catalytic Reversible Alkene-Nitrile Interconversion

The present invention refers to processes for catalytic reversible unsaturated carbon-carbon bond--nitrile interconversion through controllable HCN-free transfer hydrocyanation wherein unsaturated carbon-carbon bond stands for a double carbon carbon bond or triple carbon carbon bond.

Organonitriles and alkenes are important synthetic intermediates with orthogonal reactivity that play a central role in the preparation of polymers, pharmaceuticals, cosmetics and agrochemicals. A process to construct or deconstruct nitrile compounds through reversible interconversion with alkenes as desired would provide an exceptionally powerful synthetic tool.

Chemical reactions that can mediate the interconversion between nonpolar functional groups and polar functional groups are of outmost importance due to the orthogonal reactivity profiles of these broad classes of chemical functional groups. The nitrile group is among the most versatile polar functionalities and is widely encountered in the preparation of polymers, pharmaceuticals, cosmetics and agrochemicals, both on industrial and laboratory scale.

Organonitriles can serve as precursors for aldehydes, acids, esters, ketones, amides, amines and heterocycles. Additionally, the electron withdrawing nature of nitriles alters the reactivity profile of a molecule and enables functionalization of neighboring positions (α, but also β in the case of conjugated systems).

The alkene group is a nonpolar functional group that has a distinct and complementary reactivity profile when compared to nitriles. Alkenes are tolerant to a wide range of reaction conditions commonly used to transform polar functional groups. Additionally, they can engage in a number of bond forming reactions (e.g. alkene metathesis reaction) not accessible using polar functional groups. In light of the central role played by the nitrile and alkene groups in chemical synthesis and their complementary reactivity profiles, the ability to directly interconvert nitriles with alkenes using a single catalytic protocol would likely have a broad impact across the molecular sciences.

In the prior art, the development of a broadly applicable hydrocyanation process has been hampered by the mechanistic reliance of previous approaches upon hydrogen cyanide (HCN) (Figure 1A). HCN is an extremely toxic gas (bp 26°C) that is both corrosive and explosive. In fact both scientists and laymen know of HCN as a chemical warfare agent and deadly poison. Although the DuPont Adiponitrile Process produces around 1 million tons/year of adiponitrile (a precursor to the polymer Nylon 6,6) through the catalytic hydrocyanation of butadiene using hydrogen cyanide (HCN) as a reagent, the alkene hydrocyanation reaction has found only very limited synthetic applications beyond the DuPont process. The lack of broad adoption of hydrocyanation is highlighted by the stark contrast to other catalytic reactions of alkenes, such as carbonylation and hydroformylation. While, theoretically, hydrocyanation could have a comparable impact to these analogous alkene transformations, the necessity to use highly toxic HCN as a reagent has greatly impeded a wider application and study of this reaction. Beyond these substantial safety concerns, the thermodynamic instability of HCN renders retro-hydrocyanation processes to produce alkenes from nitriles extremely challenging.

There is currently no catalytic and reversible group transfer reaction that permits both construction and deconstruction of a polar and versatile functional group from alkenes with absolute control over the direction of the equilibrium to selectively form, on demand, either of the functional groups .

In view of the serious hazards and limitations associated with the use of HCN, there is a need of a process for the synthesis of CN-substitued hydrocarbons without relying on the use of HCN.

Starting from the considerations of the inventors that a transfer hydrocyanation between simple alkyl nitriles and alkenes would be a powerful synthetic tool to interconvert these two synthetically versatile functional groups without relying upon

HCN as a reagent, the inventors found that a metal catalyst (M) can mediate a challenging sequence of C-CN oxidative addition, β-hydride elimination, ligand exchange, migratory H-insertion and reductive elimination of C-CN bonds, and thus, a reversible transfer of H and CN can occur between alkyl nitriles and alkenes to reach a thermodynamic equilibrium (Figure 1B). The findings of the inventors is particularly useful because:

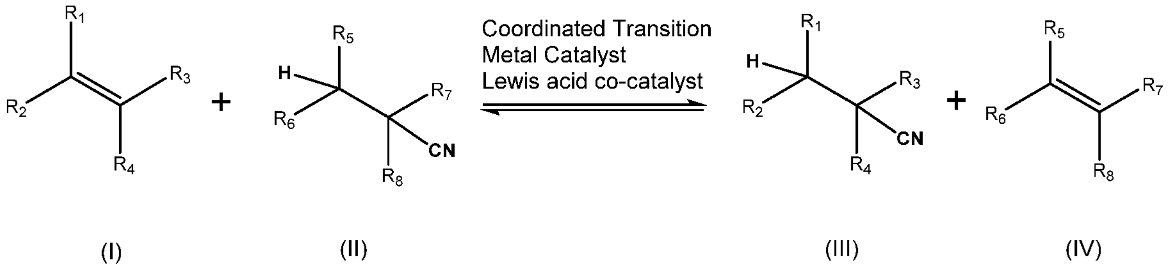
(1) no toxic HCN is needed nor produced;

(2) both the forward reaction, hydrocyanation, and the unknown reverse reaction, retro-hydrocyanation, become accessible;

(3) either reaction pathway can possibly be favored on demand by shifting the equilibrium of the reaction using simple driving forces.

Thus, the present invention provides an HCN-free transition metal, particularly Ni, -catalyzed reversible transfer hydrocyanation between alkyl nitriles and alkenes with tunable control over product selectivity (Figure 1C).

In more detail the present invention refers to a process for the catalytic reversible alkene-nitrile interconversion wherein an unsaturated hydrocarbon (I) is reacted with an alkylnitrile (II) in the presence of a transition metal coordinated to a ligand, as a coordinated transition metal catalyst, and a Lewis acid co-catalyst, preferably in a solvent, to yield an alkylnitrile (III) and an unsaturated hydrocarbon (IV), each being different from the starting compounds, as represented in the following reaction scheme:



wherein

- R^1, R^2, R^3 and R^4 can be the same or different and each independently represents H, straight chain or branched chain alkyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, each being optionally substituted by one or more groups selected from straight chain or branched chain alkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl or a heterosubstituent; or a heterosubstituent, or at least two of R^1, R^2, R^3 and R^4 may each form a cyclic 3 to 20 membered ring structure which may further be substituted by one or more groups selected from straight chain or branched chain alkyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl or a heterosubstituent, and optionally including any of O, S, N in the straight chain, branched chain or cyclic structure; or R^2 and R^4 form a bond; wherein at least one of R^1, R^2, R^3 and R^4 is not hydrogen;

- R^5, R^6, R^7 and R^8 can be the same or different and each independently represents H, straight chain or branched chain alkyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, each being optionally substituted by one or more groups selected from straight chain or branched chain alkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, or a heterosubstituent, or a heterosubstituent; or at least two of R^5, R^6, R^7 and R^8 may each form a cyclic 3 to 20 membered hydrocarbon ring structure which may further be substituted by one or more groups selected from straight chain or branched chain alkyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl or a heterosubstituent, and optionally including any of O, S, N in the straight chain, branched chain or cyclic structure; wherein preferably at least one of R^5, R^6, R^7 and R^8 is not hydrogen;
- the metal of the coordinated transition metal catalyst is selected from a metal of the Iron-group, Cobalt-group, Nickel-group or Copper group;
- the ligand of the coordinated transition metal catalyst is selected from compounds having the ability to coordinate to said transition metal, including phosphorous-, nitrogen- , As-, Sb- or N-heterocyclic based ligands; and
- the Lewis acid co-catalyst is selected from compounds of aluminum, boron, zinc, titanium, scandium.

By choosing the substituents R^1 to R^8 and thus defining the starting compounds of the process, the reaction can be controlled in such way that the reaction equilibrium can be shifted from one side to the other. This can be preferably done by reacting the starting compounds to yield a reaction mixture from which one of the formed products is removed from the reaction system, for example by evaporation of a side-product (eg gas). Alternatively, the introduction of strain (eg ring strain) or steric constraints in one of the reactants can also be used to drive the reaction.

Preferably, R^1, R^2, R^3 and R^4 can be the same or different and each independently represents aryl, heteroaryl, aralkyl, or heteroaralkyl, each being optionally substituted by one or more groups selected from straight chain or branched chain alkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl or a heterosubstituent, or a heterosubstituent, or R^2 and R^4 form a bond; wherein at least one of R^1, R^2, R^3 and R^4 is not hydrogen.

In some embodiments, R^5, R^6, R^7 and R^8 can be the same or different and each independently represents H, straight chain or branched chain alkyl, cycloalkyl, heterocycloalkyl, each being optionally substituted by one or more groups selected from straight chain or branched chain alkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl or a heterosubstituent, or a heterosubstituent, or at least two of R^5, R^6, R^7 and R^8 may each form a cyclic 3 to 20 membered hydrocarbon ring structure which may further be substituted by one or more groups selected from alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl or heterosubstituent, and optionally including any of O, S, N in the straight chain, branched chain or cyclic structure, wherein preferably at least one of R^5, R^6, R^7 and R^8 is not hydrogen.

In further embodiments, R^5, R^6, R^7 and R^8 can be the same or different and each independently represents H, straight chain or branched chain alkyl, or cycloalkyl, or at least two of R^5, R^6, R^7 and R^8 may each form a cyclic 3 to 20 membered aliphatic hydrocarbon ring structure which may further be substituted by one or more groups selected from alkyl, cycloalkyl, heterocycloalkyl, or heterosubstituent, and optionally including any of O, S, N in the straight chain, branched chain or cyclic structure, wherein at least one of R^5, R^6, R^7 and R^8 is not hydrogen.

In some embodiments, the compound of formula (II) is a lower alkyl nitrile having 1 to 6 carbon atoms, optionally substituted by one or more heterosubstituents.

In some embodiments, the compound of formula (I) is preferably a cyclic unsaturated hydrocarbon having 4 to 20, preferably 4 to 12 carbon atoms optionally substituted by one or more heterosubstituents. Unsaturated includes at least one of a double or triple bond.

The inventors have evaluated a range of metals for use as coordinated metalcatalysts to develop the transfer hydrocyanation reaction. Amongst the transition metal catalysts, transition metals and compounds thereof, selected from the Iron-group, Cobalt-group, Nickel-group or Copper group, the groups 8 to 11 of the periodic table, particularly Nickel, Cobalt and Palladium, are preferred. Examples are $Ni(COD)_2$, $Ni(acac)_2$, $Ni(CO)_4$, $Pd(dba)_2$, $Pd(OAc)_2$, $Co_2(CO)_8$ and preferred examples are $Ni(COD)_2$.

Nickel was initially chosen as a metal because Nickel(0) complexes have been shown to be the active species in the oxidative addition of inert bonds, including aliphatic C-CN bonds. However, initial experiments using simple Nickel catalysts alone failed to afford any product formation. Since Lewis Acids can both accelerate some Nickel-mediated reactions, the inventors made use of the addition of a Lewis Acid co-catalyst for facilitating the desired reversible transfer hydrocyanation mechanism.

The inventors also evaluated a range of ligands to increase the activity of the coordinated metal catalyst in the transfer hydrocyanation reaction. The ligand can be selected from compounds having the ability to coordinate to a transition metal, including phosphorous-, nitrogen-, As-, Sb- or N-heterocyclic based ligands. Examples are from the group consisting of phosphine ligands, particularly PPh_3, PCy_3, $P(OPh)_3$, PEt_3, BINAP, Xanthphos, DuPhos, DPEPhos, dppf, dppe, further preferred PPh_3 and DPEPhos, and mixtures thereof. Preferred examples are phosphine ligands, examples of which are DPEPhos, PPh_3, or mixtures thereof with the following meanings:

BINAP: 2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene
Xanthphos: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
DPEPhos: (Oxydi-2,1-phenylene)bis(diphenylphosphine)
dppf: 1,1′-Ferrocenediyl-bis(diphenylphosphine)
dppe: 1,2-Bis(diphenylphosphino)ethane

The coordinated transition metal catalyst can be prepared in situ by addition of said ligands to a solution of the transition metal compound, said metal being selected from the Iron-group, Cobalt-group, Nickel-group or Copper group, the groups 8 to 11 of the periodic table, whereby coordinated transition metal catalysts with the metal Nickel, Cobalt or Palladium are preferred. Examples of such compounds to be added are $Ni(COD)_2$, $Ni(acac)_2$, $Ni(CO)_4$, $Pd(dba)_2$, $Pd(OAc)_2$, $Co_2(CO)_8$ and preferred example is $Ni(COD)_2$.

The Lewis acid co-catalyst can be any known Lewis acid catalyst having sufficient Lewis acid strength and can be selected from compounds of aluminum, boron, zinc, titanium, scandium. Examples are $Al(alkyl)_{3-Z}X_Z$, wherein alkyl is C_1 to C_6, Z is 0 to 3 and X is halogen, preferred chlorine, such as $AlMe_3$, $AlMe_2Cl$, $AlMeCl_2$, $AlCl_3$, BPh_3, $B(C_6F_5)_3$, $Zn(OTf)_2$, $ZnCl_2$, $TiCl_4$, $Sc(OTf)_3$, and preferred examples are $AlMe_3$, $AlMe_2Cl$, $AlCl_3$, BPh_3.

The solvent is not critical and can be selected amongst those which are commonly used for such kind of catalysed reactions, such as aromatic solvents such as toluene, benzene, xylene, cumene, chlorobenzene, dichlorobenzene, or aliphatic hydrocarbon solvents, depending on the specific reaction system.

The reaction temperature is usually in the range from 25 to 150 °C, preferably from 25 to 125°C.

Definition for the substituents as used in the present formulae are given in the following.

A heterosubstituent according to the invention is to be understood as a substituent including heteroatoms, preferentially selected from O, N, S, Si and halogens. It can be preferentially selected from, =O, -OH, -F, -Cl, -Br, -I, -CN, $-N_3$, $-NO_2$, -SO_3H, NCO, NCS, $OP(O)(OR^{S1})(OR^{S2})$, $OP(OR^{S1})(OR^{S2})$, a monohalogenomethyl group, a dihalogenomethyl group, a trihalogenomethyl group, $-CF(CF_3)_2$, $-SF_5$, -$NR^{S1}{}_2$, $-OR^{S1}$, $-OOR^{S1}$, $-OSiR^{S1}R^{S2}R^{S3}$, $-OSi(OR^{S1})R^{S2}R^{S3}$, $-OSi(OR^{S1})(OR^{S2})R^{S3}$, -$OSi(OR^{S1})(OR^{S2})(OR^{S3})$, $-OSO_2R^{S1}$, $-SR^{S1}$, $-SSR^{S1}$, $-S(O)R^{S1}$, $-S(O)_2R^{S1}$, -$C(O)OR^{S1}$, $-C(O)NR^{S1}R^{S2}$, $-NR^{S1}C(O)R^{S2}$, $-C(O)-R^{S1}$, -COOM, wherein M may be a metal such as Na, K or Cs.

R^{S1} R^{S2} and R^{S3} each individually represent H, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, sulfonyl, silyl, each being optionally substituted by one or more alkyl, cycloalkyl, heterocycloalkyl, heteroaryl, aralkyl, heteroaralkyl, sulfonyl or heterosubstituent.

For the reaction system in more detail, alkyl may be C_1-C_{20}-Alkyl which can be straight chain or branched or cyclic and has 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 carbon atoms. Alkyl might particularly be C_1-C_6-alkyl, in particular methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, likewise pentyl, 1-, 2- or 3-methylpropyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl.

Cycloalkyl may be a cyclic alkyl group forming a 3 to 20 membered ring and might be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl.

Heterocycloalkyl may be a cycloalkyl forming a 3 to 10 membered ring and incorporating one or more heteroatoms selected from N, O and S within the cycle. In particular, heterocycloalkyls can be preferentially selected from 2,3-dihydro-2-, -

3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or -5-furyl, tetrahydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetrahydro-2- or -3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-isoquinolyl, 2-, 3-, 5-, 6-, 7- or 8-3,4-dihydro-2H-benzo-1,4-oxazinyl.

Halogen is F, Cl, Br or I.

Aryl might be phenyl, naphthyl or biphenyl and substituted derivatives thereof.

Aralkyl might be benzyl, naphthylmethyl and substituted derivatives thereof.

Heteroaryl may have one or more heteroatoms selected from N, O ,S and Si and is preferably 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, also preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3- or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-Indolyl, 4- or 5-isoindolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 5- or 6-quinoxalinyl, 2-, 3-, 5-, 6-, 7- or 8-2H-benzo-1,4-oxazinyl, also preferably 1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 2,1,3-benzothiadiazol-4- or -5-yl or 2,1,3-benzoxadiazol-5-yl.

Heteroaralkyl might be any of the aforementioned heteroaryl bound to an alkyl group, such as pyridinylmethyl.

Optionally substituted means unsubstituted or monosubstituted, disubstituted, trisubstituted, tetrasubstituted, pentasubstituted, or even further substituted on the respective group.

Thus, the inventors have shown that a reaction pair of a coordinated transition metal catalyst and a Lewis acid co-catalyst can bes used for a nitrile transfer reaction from an hydrocarbon nitrile to an unsaturated hydrocarbon, wherein

- the metal of the coordinated transition metal catalyst is selected from a metal of the Iron-group, Cobalt-group, Nickel-group or Copper group;
- the ligand of the coordinated transition metal catalyst is selected from compounds having the ability to coordinate to said transition metal, including phosphorous-, nitrogen- , As-, Sb- or N-heterocyclic based ligands; and
- the Lewis acid co-catalyst is selected from compounds of aluminum, boron, zinc, titanium, scandium,

so that nitrile compounds are accessible without the need of using hydrogen cyanide.

The invention is further illustrated in the attached drawings and the following experimental section below.

In the attached drawings:

Figure 1 shows the:

(A) Traditional approach to hydrocyanation using HCN.

(B) Proposed HCN-free transfer hydrocyanation reaction and mechanism.

(C) The process of the present invention

Figure 2 shows the:

(A) Model reaction.

(B) Reagent optimization for hydrocyanation 1 -> 2.

(C) Reagent optimization for retro-hydrocyanation 2 -> 1.

Figure 3 shows the:

A. Scope of the hydrocyanation.

B. Scale-up experiment

Experimental Section

After successfully finding initial reactivity using a Nickel catalyst and an Al co-catalyst, the inventors developed the ideas for efficiently manipulating the reaction equilibrium and they have found suitable alkene and alkyl nitrile reagents that allow to selectively drive the forward reaction from **1**->**2** and the reverse reaction from **2**->**1** under appropriate conditions (Figure 2). Considering other metal catalyzed reversible reactions, such as the alkene metathesis reaction, the inventors reasoned that the use of simple driving forces, such as the extrusion of a gaseous side product or the release of ring strain, would efficiently shift the thermodynamic equilibrium to afford the desired product.

In the case of the forward reaction (Figure 2B), hydrocyanation, the inventors evaluated a range of simple aliphatic nitriles (**3**-**6**) as potential hydrocyanating reagents and they found that (1) the degree of substitution of the alkene by-product correlates with the efficiency of the reaction in the order isobutylene > propene > ethylene, and (2) the formation of gaseous alkenes further improves the system, particularly when conducted in an open system. Thus, isovaleronitrile (**5**), which releases isobutylene as a gaseous byproduct, was identified as the best reagent for the hydrocyanation reaction of **1** and gave 86% yield of product **2** in toluene at 100 °C in the presence of catalytic Ni and Al.

Alternatively, alkyl nitrile product **2**, formed in the forward reaction, can be used as test substrate to evaluate the efficiency of diverse alkene traps to drive the retro-hydrocyanation reaction to completion (Figure 2C). A control reaction using no acceptor alkene did not lead to any significant formation of product **1**. This result clearly shows that the formation of HCN and an alkene from an alkyl nitrile is thermodynamically disfavored, emphasizing the need to use an acceptor alkene to drive the process. Both norbornene (NBE, **7**) and norbornadiene (NBD, **8**) were then evaluated since they possess significant ring strain that should help to drive the retro-hydrocyanation reaction. Gratifyingly, NBD proved extremely efficient as a trapping reagent due to its high ring strain, affording good yields of the desired alkene product **1** at room temperature (RT).

Having demonstrated the ability of the inventors´ reaction to be tuned on demand towards either side of the reaction, the inventors studied the scope of the hydrocyanation process (Figure 3A). The transfer hydrocyanation of styrene derivatives gave the products in high yields and good linear to branched ratios (up to 85% for mono-substituted and full linear selectivity in the case of disubstituted styrenes **1** and **19**), a selectivity complementary to previous protocols giving mostly the branched isomer. Non-activated, terminal aliphatic alkenes were also very active substrates in the transformation and gave the linear product as the major product (up to 100% l/b selectivity in the case of sterically congested ^{t}Bu (**30**)). Next, the inventors investigated 1,2-disubstituted substrates. Cycloalkenes (**33**, **35** and **37**) and strained norbornenes (**7** and **43**) were well tolerated and afforded the cyanated products in high yields. Two renewable feedstocks, methyl oleate (**45**) and camphene (**47**), were subjected to the reaction conditions and high yields of the products were obtained. Remarkably, the inventors´ catalytic reaction could also be extended to the efficient hydrocyanation of both conjugated (**23**) and aliphatic alkynes (**21**) in good yields. Finally, the reaction of styrene (**9**) could be performed on a preparative scale (5 g) using inexpensive butyronitrile (**4**) as a reagent and solvent and 2 mol% of Ni catalyst to give the product in 94% yield after distillation (Figure 3B).

The invention is further illustrated by the following non limiting examples.

Examples

Preparation Examples

General procedure for the preparation of nitriles

A: General procedure for the preparation of alkyl nitriles

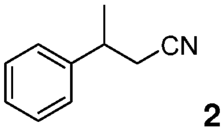
To a 0 °C solution of corresponding alkyl alcohol (5 mmol) in CH_2Cl_2 (5 mL) were added pyridine (2 mL), and 4-toluenesulfonyl chloride (1.06 g, 5.56 mmol). The resultant reaction mixture was stirred at room temperature for overnight. After that time, water was added and the resultant mixture extracted with CH_2Cl_2. The combined organic layers were subsequently washed with a 2M aqueous solution of HCl, a saturated aqueous solution of $NaHCO_3$, and brine and dried over anhydrous Na_2SO_4. After the desiccant was removed, the solvent was distilled off under vacuum to give the corresponding alkyl *p*-toluenesulfonate in quantitative yield and was used without any further purification.

To a solution of alkyl *p*-toluenesulfonate (*ca.* 5 mmol) in DMSO (10 mL) was added powdered NaCN (0.49 g, 10 mmol), and the mixture was stirred at 100 °C for 5 hours. After completion of the reaction, the reaction was cooled down to room temperature and quenched with saturated aqueous solution of Na_2CO_3. The aqueous phase was extracted with methyl tert-butyl ether (3*20 mL), the combined organic layers were washed several times with brine and dried over anhydrous Na_2SO_4. The solution was concentrated *in vacuo*, and purified by flash column chromatography on silica gel (pentane/methyl tert-butyl ether = 10/1) to give the corresponding alkyl nitrile in high yield.

B: General procedure for the preparation of *α*-alkyl benzyl nitriles

Lithium bis(trimethylsilyl)amide (5.5 mL, 5.50 mmol; 1M solution in tetrahydrofuran) was added dropwise to a stirred solution of 2-phenylacetonitrile derivative (5.0 mmol) in anhydrous tetrahydrofuran (20 mL) at −78 °C under an atmosphere of argon. The anion was allowed to form over *ca*. 30 minutes, then corresponding bromide (5.25 mmol) was added dropwise and the reaction allowed to stir for *ca.* 1 hour before being slowly warmed to room temperature and stirred until completion (t.l.c. control). The reaction mixture was then quenched by addition of saturated aqueous ammonium chloride solution and extracted with methyl tert-butyl ether. The organic layers were combined, dried (anhyd. Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude product. Purification by flash column chromatography (silica gel, eluting with hexane/ethyl acetate) afforded the corresponding *α*-alkyl benzyl nitrile.

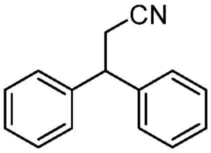
Example 1



2

Isovaleronitrile **5** (0.26 mL, 2.50 mmol), *α*-methylstyrene **1** (65 μL, 0.50 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (0.10 mL, 0.10 mmol) were added sequentially to a solution of $Ni(COD)_2$ (6.9 mg, 5 mol%) and DPEphos (13.5 mg, 5 mol%) in toluene (1.0 mL) prepared in a 10 mL Schlenk tube under an argon atmosphere in a glove box. The Schlenk tube with a reflux condenser was taken out of the glove box, and was then connected to a continuous flow of argon (positive pressure: 0.4 bar) and heated at 130 °C for 16 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel (pentane/methyl tert-butyl ether = 10/1) to give **2** (66.1 mg, yield: 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 2H), 7.26 – 7.21 (m, 3H), 3.13 (h, *J* = 7.0 Hz, 1H), 2.59 (dd, *J* = 16.7, 6.5 Hz, 1H), 2.53 (dd, *J* = 16.7, 7.6 Hz, 1H), 1.43 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.26, 128.99, 127.46, 126.67, 118.72, 36.65, 26.49, 20.80. The spectral data are consistent with those reported in the literature.

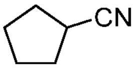
Example 2



Commercial sample **20**

Isovaleronitrile **5** (0.26 mL, 2.50 mmol), 1,1-diphenylethylene **19** (88 μL, 0.50 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (0.10 mL, 0.10 mmol) were added sequentially to a solution of $Ni(COD)_2$ (6.9 mg, 5 mol%) and DPEphos (13.5 mg, 5 mol%) in toluene (1.0 mL) prepared in a 10 mL Schlenk tube under an argon atmosphere in a glove box. The Schlenk tube with a reflux condenser was taken out of the glove box, and was then connected to a continuous flow of argon (positive pressure: 0.4 bar) and heated at 130 °C for 16 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel (pentane/methyl tert-butyl ether = 10/1) to give **20** (54.9 mg, yield: 53%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.36 (m, 4H), 7.32 – 7.26 (m, 6H), 4.42 (t, *J* = 7.7 Hz, 1H), 3.07 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.34, 129.03, 127.66, 127.54, 118.55, 47.26, 24.36.

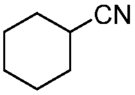
Example 3



34

Isovaleronitrile **5** (0.26 mL, 2.50 mmol), cyclopentene **33** (44 µL, 0.50 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (0.10 mL, 0.10 mmol) were added sequentially to a solution of $Ni(COD)_2$ (6.9 mg, 5 mol%) and DPEphos (13.5 mg, 5 mol%) in toluene (1.0 mL) prepared in a 25 mL pressure tube under an argon atmosphere in a glove box. The pressure tube was taken out of the glove box and heated at 100 °C for 16 hours. After that time, the reaction was cooled down to room temperature, and *n*-dodecane (100 µL) as internal standard was added to the solution. The reaction mixture was analyzed by GC and the yield of **34** determined by comparing their peak areas to that of the internal standard. (Retention time: 6.38 min, GC yield: 83%)

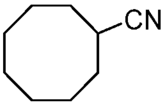
Example 4



36

Isovaleronitrile **5** (0.26 mL, 2.50 mmol), cyclohexene **35** (51 µL, 0.50 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (0.10 mL, 0.10 mmol) were added sequentially to a solution of $Ni(COD)_2$ (6.9 mg, 5 mol%) and DPEphos (13.5 mg, 5 mol%) in toluene (1.0 mL) prepared in a 25 mL pressure tube under an argon atmosphere in a glove box. The pressure tube was taken out of the glove box and heated at 100 °C for 16 hours. After that time, the reaction was cooled down to room temperature, and *n*-dodecane (100 µL) as internal standard was added to the solution. The reaction mixture was analyzed by GC and the yield of **36** determined by comparing their peak areas to that of the internal standard. (Retention time: 7.62 min, GC yield: 91%)

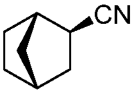
Example 5



38

Isovaleronitrile **5** (0.26 mL, 2.50 mmol), cyclooctene **37** (65 μL, 0.50 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (0.10 mL, 0.10 mmol) were added sequentially to a solution of $Ni(COD)_2$ (6.9 mg, 5 mol%) and DPEphos (13.5 mg, 5 mol%) in toluene (1.0 mL) prepared in a 10 mL Schlenk tube under an argon atmosphere in a glove box. The Schlenk tube with a reflux condenser was taken out of the glove box, and was then connected to a continuous flow of argon (positive pressure: 0.4 bar) and heated at 130 °C for 16 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel (pentane/methyl tert-butyl ether = 10/1) to give **38** (59.7 mg, yield: 87%). ^1H NMR (500 MHz, $CDCl_3$): δ 2.78–2.73 (m, 1H), 1.98–1.92 (m, 2H), 1.87–1.72 (m, 4H), 1.60–1.47 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 123.69, 29.58, 28.87, 26.96, 25.26, 24.39. The spectral data are consistent with those reported in the literature.

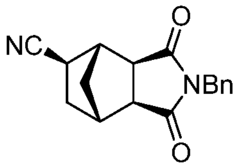
Example 6



42

Isovaleronitrile **5** (0.26 mL, 2.50 mmol), norbornene **7** (47.1 mg, 0.50 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (0.10 mL, 0.10 mmol) were added sequentially to a solution of $Ni(COD)_2$ (6.9 mg, 5 mol%) and DPEphos (13.5 mg, 5 mol%) in toluene (1.0 mL) prepared in a 25 mL pressure tube under an argon atmosphere in a glove box. The pressure tube was taken out of the glove box and heated at 100 °C for 16 hours. After cooling to room temperature, the reaction mixture directly purified by flash column chromatography on silica gel (pentane/methyl tert-butyl ether = 10/1) to give **42** (51.5 mg, yield: 85%). ^1H NMR (500 MHz, $CDCl_3$) δ 2.59 (d, J = 3.5 Hz, 1H), 2.39 (d, J = 3.6 Hz, 1H), 2.35 (ddd, J = 9.1, 4.8, 1.6 Hz, 1H), 1.85 – 1.76 (m, 1H), 1.73 – 1.66 (m, 1H), 1.64 – 1.50 (m, 3H), 1.41 – 1.34 (m, 1H), 1.27 – 1.14 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 123.71, 41.90, 37.30, 36.20, 36.13, 31.18, 28.63, 28.50. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_8H_{11}NNa$, 144.078368; found, 144.078550.

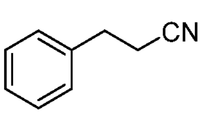
Example 7



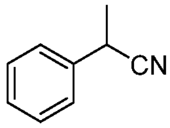
44

Isovaleronitrile **5** (0.26 mL, 2.50 mmol), **43** (126.7 mg, 0.50 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (0.10 mL, 0.10 mmol) were added sequentially to a solution of $Ni(COD)_2$ (6.9 mg, 5 mol%) and DPEphos (13.5 mg, 5 mol%) in toluene (1.0 mL) prepared in a 25 mL pressure tube under an argon atmosphere in a glove box. The pressure tube was taken out of the glove box and heated at 100 °C for 16 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel (pentane/ethyl acetate = 2/1) to give **44** (128.9 mg, yield: 92%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.17 (m, 5H), 4.53 (s, 2H), 2.93 (s, 1H), 2.76 (d, *J* = 3.3 Hz, 1H), 2.55 (q, *J* = 7.1 Hz, 2H), 2.44 (ddd, *J* = 9.1, 4.8, 1.6 Hz, 1H), 1.96 – 1.84 (m, 1H), 1.82 – 1.73 (m, 1H), 1.57 – 1.42 (m, 1H), 1.05 (d, *J* = 11.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.97, 176.36, 135.57, 128.79, 128.76, 128.17, 121.57, 47.49, 47.26, 44.22, 42.68, 39.35, 34.70, 32.24, 29.84. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{17}H_{16}N_2O_2Na$, 303.110396; found, 303.110200.

Example 8



and



Commercial sample

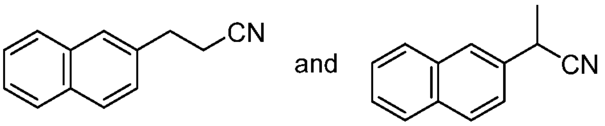
10

Isovaleronitrile **5** (0.26 mL, 2.50 mmol), styrene **9** (57.5 μL, 0.50 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (0.10 mL, 0.10 mmol) were added sequentially to a solution of $Ni(COD)_2$ (6.9 mg, 5 mol%) and DPEphos (13.5 mg, 5 mol%) in toluene (1.0 mL) prepared in a 10 mL Schlenk tube under an argon atmosphere in a glove box. The Schlenk tube was taken out of the glove box, and was then connected to a continuous flow of argon (positive pressure: 0.4 bar) and heated at heated at 100 °C for 16 hours. After cooling to room temperature, the reaction mixture was analyzed by GC and the regioselectivity of **10** determined by comparing their peak areas (l/b: 81/19). The reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel (pentane/methyl tert-butyl ether = 10/1) to give **10** (linear product: 45.9 mg, yield: 70%; branched product: 10.5 mg, yield: 16%).

Linear product: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 2H), 7.22 – 7.17 (m, 1H), 7.17 – 7.12 (m, 2H), 2.86 (t, *J* = 7.4 Hz, 2H), 2.52 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.13, 128.93, 128.34, 127.29, 119.24, 31.60, 19.41.

Branched product: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.31 (m, 5H), 3.90 (q, *J* = 7.3 Hz, 1H), 1.65 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.19, 129.30, 128.19, 126.85, 121.74, 31.41, 21.63.

Example 9



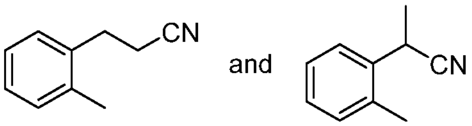
12

Isovaleronitrile **5** (0.26 mL, 2.50 mmol), 2-vinylnaphthalene **11** (77.1 mg, 0.50 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (0.10 mL, 0.10 mmol) were added sequentially to a solution of $Ni(COD)_2$ (6.9 mg, 5 mol%) and DPEphos (13.5 mg, 5 mol%) in toluene (1.0 mL) prepared in a 10 mL Schlenk tube under an argon atmosphere in a glove box. The Schlenk tube was taken out of the glove box, and was then connected to a continuous flow of argon (positive pressure: 0.4 bar) and heated at heated at 100 °C for 16 hours. After cooling to room temperature, the reaction mixture was analyzed by GC and the regioselectivity of **12** determined by comparing their peak areas (l/b: 82/18). The reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel (pentane/methyl tert-butyl ether = 10/1) to give **12** (linear product: 66.1 mg, yield: 73%; branched product: 14.5 mg, yield: 16%).

Linear product: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 – 7.78 (m, 3H), 7.69 (s, 1H), 7.54 – 7.43 (m, 2H), 7.35 (dd, *J* = 8.3, 1.8 Hz, 1H), 3.12 (t, *J* = 7.4 Hz, 2H), 2.70 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.56, 133.59, 132.59, 128.77, 127.80, 127.75, 127.00, 126.48, 126.43, 126.04, 119.26, 31.82, 19.38. The spectral data are consistent with those reported in the literature.

Branched product: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 – 7.79 (m, 4H), 7.56 – 7.48 (m, 2H), 7.43 (dd, *J* = 8.5, 1.9 Hz, 1H), 4.07 (q, *J* = 7.4 Hz, 1H), 1.73 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.44, 133.44, 132.90, 129.27, 127.98, 127.85, 126.87, 126.62, 125.71, 124.54, 121.72, 31.55, 21.57. The spectral data are consistent with those reported in the literature.

Example 10



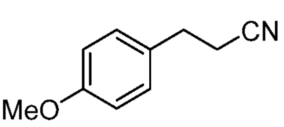
14

Isovaleronitrile **5** (0.26 mL, 2.50 mmol), 2-methylstyrene **13** (65 µL, 0.50 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (0.10 mL, 0.10 mmol) were added sequentially to a solution of $Ni(COD)_2$ (6.9 mg, 5 mol%) and DPEphos (13.5 mg, 5 mol%) in toluene (1.0 mL) prepared in a 10 mL Schlenk tube under an argon atmosphere in a glove box. The Schlenk tube was taken out of the glove box, and was then connected to a continuous flow of argon (positive pressure: 0.4 bar) and heated at heated at 100 °C for 16 hours. After cooling to room temperature, the reaction mixture was analyzed by GC and the regioselectivity of **14** determined by comparing their peak areas (l/b: 86/14). The reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel (pentane/methyl tert-butyl ether = 10/1) to give **14** (linear product: 57.3 mg, yield: 79%; branched product: 9.4 mg, yield: 13%).

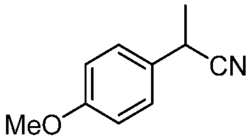
Linear product: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.14 (m, 4H), 2.98 (t, *J* = 7.7 Hz, 2H), 2.59 (t, *J* = 7.7 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.34, 135.91, 130.78, 128.84, 127.50, 126.62, 119.35, 29.01, 19.30, 18.14. The spectral data are consistent with those reported in the literature.

Branched product: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.3, 1.7 Hz, 1H), 7.29 – 7.17 (m, 3H), 4.05 (q, *J* = 7.2 Hz, 1H), 2.37 (s, 3H), 1.61 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.38, 134.90, 131.12, 128.26, 127.13, 126.84, 121.94, 28.30, 20.18, 19.15. The spectral data are consistent with those reported in the literature.

Example 11



and



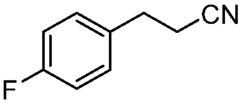
16

Isovaleronitrile **5** (0.26 mL, 2.50 mmol), 4-vinylanisole **15** (66.5 μL, 0.50 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (0.10 mL, 0.10 mmol) were added sequentially to a solution of $Ni(COD)_2$ (6.9 mg, 5 mol%) and DPEphos (13.5 mg, 5 mol%) in toluene (1.0 mL) prepared in a 10 mL Schlenk tube under an argon atmosphere in a glove box. The Schlenk tube was taken out of the glove box, and was then connected to a continuous flow of argon (positive pressure: 0.4 bar) and heated at heated at 100 °C for 16 hours. After cooling to room temperature, the reaction mixture was analyzed by GC and the regioselectivity of **16** determined by comparing their peak areas (l/b: 79/21). The reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel (pentane/methyl tert-butyl ether = 5/1) to give **16** (linear product: 59.6 mg, yield: 74%; branched product: 15.3 mg, yield: 19%).

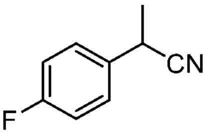
Linear product: ^1H NMR (500 MHz, $CDCl_3$) δ 7.18 – 7.12 (m, 2H), 6.90 – 6.83 (m, 2H), 3.80 (s, 3H), 2.90 (t, *J* = 7.3 Hz, 2H), 2.58 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.85, 130.24, 129.44, 119.38, 114.35, 55.40, 30.87, 19.82. The spectral data are consistent with those reported in the literature.

Branched product: ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.21 (m, 2H), 6.95 – 6.85 (m, 2H), 3.85 (q, *J* = 7.3 Hz, 1H), 3.81 (s, 3H), 1.62 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.43, 129.21, 127.98, 122.01, 114.60, 55.50, 30.61, 21.68. The spectral data are consistent with those reported in the literature.

Example 12



and



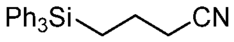
18

Isovaleronitrile **5** (0.26 mL, 2.50 mmol), 4-fluorostyrene **17** (60 μL, 0.50 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (0.10 mL, 0.10 mmol) were added sequentially to a solution of $Ni(COD)_2$ (6.9 mg, 5 mol%) and DPEphos (13.5 mg, 5 mol%) in toluene (1.0 mL) prepared in a 10 mL Schlenk tube under an argon atmosphere in a glove box. The Schlenk tube was taken out of the glove box, and was then connected to a continuous flow of argon (positive pressure: 0.4 bar) and heated at heated at 100 °C for 16 hours. After cooling to room temperature, the reaction mixture was analyzed by GC and the regioselectivity of **18** determined by comparing their peak areas (l/b: 83/17). The reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel (pentane/methyl tert-butyl ether = 10/1) to give **18** (linear product: 56.7 mg, yield: 76%; branched product: 11.2 mg, yield: 15%).

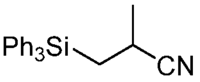
Linear product: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.17 (m, 2H), 7.06 – 6.98 (m, 2H), 2.93 (t, J = 7.3 Hz, 2H), 2.60 (t, J = 7.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.11 (d, $J_{C\text{–}F}$ = 243.75 Hz), 133.81, 129.98 (d, $J_{C\text{–}F}$ = 7.50 Hz), 119.06, 115.84 (d, $J_{C\text{–}F}$ = 21.25 Hz), 30.86, 19.67. The spectral data are consistent with those reported in the literature.

Branched product: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H), 7.10 – 7.04 (m, 2H), 3.89 (q, J = 7.3 Hz, 1H), 1.63 (d, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.47 (d, $J_{C\text{–}F}$ = 245.12 Hz), 132.97, 128.56 (d, $J_{C\text{–}F}$ = 8.25 Hz), 121.53, 116.23 (d, $J_{C\text{–}F}$ = 22.12 Hz), 30.71, 21.65. The spectral data are consistent with those reported in the literature.

Example 13



and



28

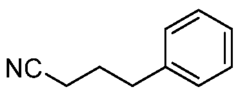
Isovaleronitrile **5** (0.26 mL, 2.50 mmol), allyltriphenylsilane **27** (150.2 mg, 0.50 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (0.10 mL, 0.10 mmol) were added sequentially to a solution of $Ni(COD)_2$ (6.9 mg, 5 mol%) and DPEphos (13.5 mg, 5 mol%) in toluene (1.0 mL) prepared in a 10 mL Schlenk tube under an argon atmosphere in a glove box. The Schlenk tube connected with a reflux condenser was taken out of the glove box, and was subsequently connected to a continuous flow of argon (positive pressure: 0.4 bar) and heated at 130 °C for 16 hours. After cooling to room temperature, the reaction mixture was analyzed by GC (Temperature program: 15°C/min to 180°C; 15°C/min to 300°C; 300°C (15 min)) and the regioselectivity of **28** determined by comparing their peak areas (l/b:

84/16). The reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel (pentane/methyl tert-butyl ether = 10/1) to give **28** (linear product: 127.7 mg, yield: 78%; branched product: 24.5 mg, yield: 15%).

Linear product: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.49 (m, 6H), 7.46 – 7.35 (m, 9H), 2.37 (t, *J* = 6.9 Hz, 2H), 1.88 – 1.78 (m, 2H), 1.57 – 1.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.66, 134.18, 129.90, 128.22, 119.75, 20.94, 20.82, 13.13. HRMS-EI (m/z): $[M]^+$ calcd for $C_{22}H_{21}NSi$, 327.144327; found, 327.144175.

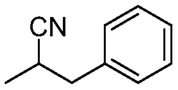
Branched product: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.53 (m, 6H), 7.49 – 7.37 (m, 9H), 2.73 (sext, *J* = 7.0 Hz, 1H), 1.97 (dd, *J* = 15.2, 7.0 Hz, 1H), 1.68 (dd, *J* = 15.2, 7.8 Hz, 1H), 1.27 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.73, 133.45, 130.15, 128.31, 124.07, 21.67, 21.47, 19.19. HRMS-EI (m/z): $[M]^+$ calcd for $C_{22}H_{21}NSi$, 327.144327; found, 327.144029.

Example 14

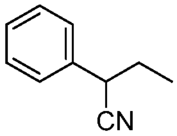


Commercial sample

and



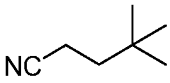
and



26

Isovaleronitrile **5** (0.26 mL, 2.50 mmol), allylbenzene **25** (66 µL, 0.50 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (0.10 mL, 0.10 mmol) were added sequentially to a solution of $Ni(COD)_2$ (6.9 mg, 5 mol%) and DPEphos (13.5 mg, 5 mol%) in toluene (1.0 mL) prepared in a 10 mL Schlenk tube under an argon atmosphere in a glove box. The Schlenk tube connected with a reflux condenser was taken out of the glove box, and was subsequently connected to a continuous flow of argon (positive pressure: 0.4 bar) and heated at 130 °C for 16 hours. After that time, the reaction was cooled down to room temperature, and *n*-dodecane (100 µL) as internal standard was added to the solution. The reaction mixture was analyzed by GC and the yield of **26** determined by comparing their peak areas to that of the internal standard. (GC yield: 88%, ratio of regioisomers: 58/29/13, retention time: 11.48, 10.77, 10.56 min respectively).

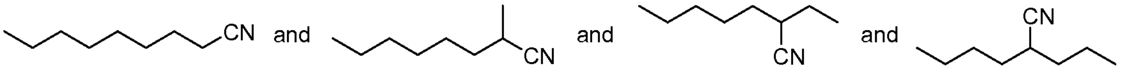
Example 15



30

Isovaleronitrile **5** (0.26 mL, 2.50 mmol), 3,3-dimethyl-1-butene **29** (65 µL, 0.50 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (0.10 mL, 0.10 mmol) were added sequentially to a solution of $Ni(COD)_2$ (6.9 mg, 5 mol%) and DPEphos (13.5 mg, 5 mol%) in toluene (1.0 mL) prepared in a 25 mL pressure tube under an argon atmosphere in a glove box. The pressure tube was taken out of the glove box and heated at 100 °C for 16 hours. After cooling to room temperature, the reaction mixture directly purified by flash column chromatography on silica gel (pentane/methyl tert-butyl ether = 10/1) to give **30** (38.4 mg, yield: 69%). ^1H NMR (500 MHz, $CDCl_3$) δ 2.31 – 2.25 (m, 2H), 1.64 – 1.59 (m, 2H), 0.93 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 120.74, 39.33, 30.48, 28.80, 12.87. The spectral data are consistent with those reported in the literature.

Example 16

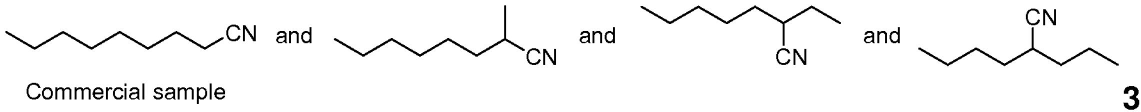


Commercial sample

32

Isovaleronitrile **5** (0.26 mL, 2.50 mmol), 1-octene **31** (78.5 µL, 0.50 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (0.10 mL, 0.10 mmol) were added sequentially to a solution of $Ni(COD)_2$ (6.9 mg, 5 mol%) and DPEphos (13.5 mg, 5 mol%) in toluene (1.0 mL) prepared in a 10 mL Schlenk tube under an argon atmosphere in a glove box. The Schlenk tube with a reflux condenser was taken out of the glove box, and was subsequently connected to a continuous flow of argon (positive pressure: 0.4 bar) and heated at 130 °C for 16 hours. After that time, the reaction was cooled down to room temperature, and *n*-dodecane (100 µL) as internal standard was added to the solution. The reaction mixture was analyzed by GC and the yield of desired product determined by comparing their peak areas to that of the internal standard. (GC yield: 90%, ratio of regioisomers: 48/32/11/9, retention time: 9.70, 8.95, 8.81, 8.71 min respectively).

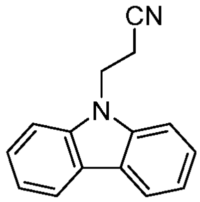
Example 17



32

Isovaleronitrile **5** (0.26 mL, 2.50 mmol), trans-4-octene **39** (78.5 μL, 0.50 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (0.10 mL, 0.10 mmol) were added sequentially to a solution of $Ni(COD)_2$ (6.9 mg, 5 mol%) and DPEphos (13.5 mg, 5 mol%) in toluene (1.0 mL) prepared in a 10 mL Schlenk tube under an argon atmosphere in a glove box. The Schlenk tube connected with a reflux condenser was taken out of the glove box, and was subsequently connected to a continuous flow of argon (positive pressure: 0.4 bar) and heated at 130 °C for 16 hours. After that time, the reaction was cooled down to room temperature, and *n*-dodecane (100 μL) as internal standard was added to the solution. The reaction mixture was analyzed by GC and the yield of desired product determined by comparing their peak areas to that of the internal standard. (GC yield: 98%, ratio of regioisomers: 46/30/12/12, retention time: 9.70, 8.95, 8.81, 8.71 min respectively).

Example 18

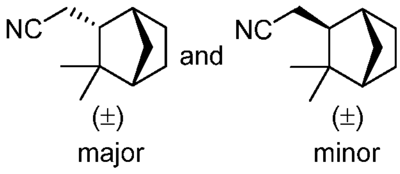


41

Isovaleronitrile **5** (0.26 mL, 2.50 mmol), *N*-vinylcarbazole **40** (96.6 mg, 0.50 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (0.10 mL, 0.10 mmol) were added sequentially to a solution of $Ni(COD)_2$ (6.9 mg, 5 mol%) and DPEphos (13.5 mg, 5 mol%) in toluene (1.0 mL) prepared in a 10 mL Schlenk tube under an argon atmosphere in a glove box. The Schlenk tube connected with a reflux condenser was taken out of the glove box, and was subsequently connected to a continuous flow of argon (positive pressure: 0.4 bar) and heated at 130 °C for 16 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel (pentane/ethyl acetate = 2/1) to give **41** (71.6 mg, yield: 65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.1 Hz, 2H), 7.54 – 7.48 (m, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.33 – 7.27 (m, 2H), 4.65 (t, *J* = 7.2 Hz, 2H), 2.84 (t, *J* = 7.2 Hz, 2H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 139.62, 126.33, 123.48, 120.85, 120.09, 117.46, 108.26, 39.02, 17.39. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{15}H_{12}N_2Na$, 243.089266; found, 243.089470.

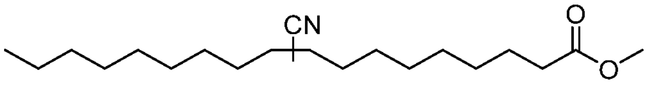
Example 19



48

Isovaleronitrile **5** (0.26 mL, 2.50 mmol), camphene **47** (68 mg, 0.50 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (0.10 mL, 0.10 mmol) were added sequentially to a solution of $Ni(COD)_2$ (6.9 mg, 5 mol%) and DPEphos (13.5 mg, 5 mol%) in toluene (1.0 mL) prepared in a 10 mL Schlenk tube under an argon atmosphere in a glove box. The Schlenk tube connected with a reflux condenser was taken out of the glove box, and was subsequently connected to a continuous flow of argon (positive pressure: 0.4 bar) and heated at 130 °C for 16 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel (pentane/methyl tert-butyl ether = 10/1) to give **48** (62.8 mg, yield: 77%, diastereoselectivity based on ^1H NMR: 7/3). ^1H NMR (500 MHz, $CDCl_3$) δ 2.35 – 2.18 (m, 3.42H), 2.15 – 2.09 (m, 0.84H), 1.84 – 1.79 (m, 2H), 1.76 – 1.74 (m, 0.42H), 1.69 – 1.64 (m, 1.42H), 1.63 – 1.61 (m, 0.42H),1.59 – 1.54 (m, 1H), 1.44 (ddd, *J* = 8.9, 6.7, 1.7 Hz, 0.42H), 1.37 – 1.30 (m, 2H), 1.25 – 1.23 (m, 3.26H), 1.16 (dt, *J* = 10.2, 1.6 Hz, 0.42H), 1.04 (s, 1.28H), 1.02 (s, 3H), 0.94 (s, 1.28H), 0.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 120.36, 50.74, 49.54, 49.02, 47.36, 43.84, 42.13, 37.11, 36.92, 35.61, 32.04, 29.86, 29.49, 27.71, 24.56, 24.47, 23.94, 21.07, 20.11, 19.04, 15.36. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{11}H_{17}NNa$, 186.125318; found, 186.125480.

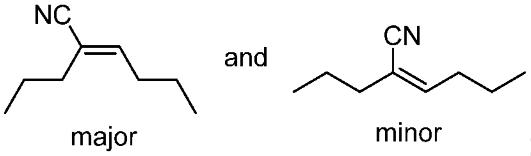
Example 20



46

Isovaleronitrile **5** (0.26 mL, 2.50 mmol), 99% purity of methyl oleate **45** (170 µL, 0.50 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (0.10 mL, 0.10 mmol) were added sequentially to a solution of $Ni(COD)_2$ (6.9 mg, 5 mol%) and DPEphos (13.5 mg, 5 mol%) in toluene (1.0 mL) prepared in a 10 mL Schlenk tube under an argon atmosphere in a glove box. The Schlenk tube connected with a reflux condenser was taken out of the glove box, and was subsequently connected to a continuous flow of argon (positive pressure: 0.4 bar) and heated at 130 °C for 16 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel (pentane/methyl tert-butyl ether = 5/1) to give **46** (137.5 mg, yield: 85%). ^1H NMR (500 MHz, $CDCl_3$) δ 3.77 – 3.60 (m, 3H), 2.57 – 2.41 (m, 1H), 2.36 – 2.24 (m, 2H), 1.65 – 1.50 (m, 7H), 1.46 – 1.37 (m, 2H), 1.31 – 1.24 (m, 19H), 0.98 – 0.84 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.49 ($-CO_2$), 122.63 (-CN). HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{20}H_{37}NO_2Na$, 346.271648; found, 346.271560. It should be noted that the isolated product **46** containing 9 regioisomers which were observed by GC analysis (Temperature program: 15°C/min to 180°C; 15°C/min to 300°C; 300°C (15 min)).

Example 21

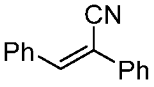


22

Isovaleronitrile **5** (0.26 mL, 2.50 mmol), 4-octyne **21** (73 µL, 0.50 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (0.10 mL, 0.10 mmol) were added sequentially to a solution of $Ni(COD)_2$ (6.9 mg, 5 mol%) and DPEphos (13.5 mg, 5 mol%) in toluene (1.0 mL) prepared in a 4 mL Screw-cap vial under an argon atmosphere in a glove box. The vial was taken out of the glove box, the temperature of which was fixed at 28 °C. The reaction mixture was stirred for 16 hours at 28 °C. After that time, the reaction mixture directly purified by flash column chromatography on silica gel (pentane/methyl tert-butyl ether = 10/1) to give **22** (51.5 mg, yield: 89%, the ratio of *Z*/*E* based on ^1H NMR: 8/1). *Z*- product: ^1H NMR (500 MHz, $CDCl_3$) δ 6.35 (tt, J = 7.6, 1.2 Hz, 1H), 2.20 – 2.13 (m, 4H), 1.57 (sext, J = 7.4 Hz, 2H), 1.45 (sext, J = 7.4 Hz, 2H), 0.96 – 0.91 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.32, 120.37, 115.03, 30.54, 30.51, 21.92, 21.43, 13.85, 13.50. The spectral data are consistent with those reported in the literature.

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_9H_{15}NNa$, 160.109668; found, 160.109800.

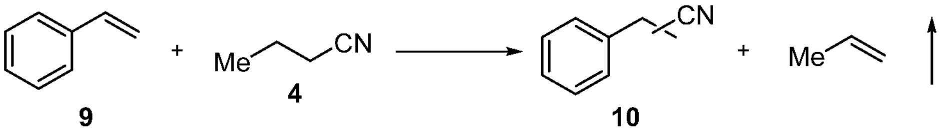
Example 22



24

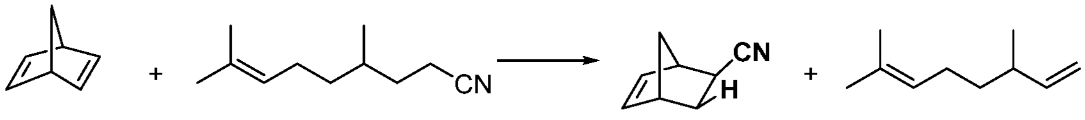
Isovaleronitrile **5** (0.26 mL, 2.50 mmol), diphenylacetylene **23** (89 mg, 0.50 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (0.10 mL, 0.10 mmol) were added sequentially to a solution of $Ni(COD)_2$ (6.9 mg, 5 mol%) and DPEphos (13.5 mg, 5 mol%) in toluene (1.0 mL) prepared in a 25 mL pressure tube under an argon atmosphere in a glove box. The pressure tube was taken out of the glove box and heated at 100 °C for 16 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel (pentane/methyl tert-butyl ether = 10/1) to give **24** (75.9 mg, yield: 74%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 – 7.88 (m, 2H), 7.71 – 7.67 (m, 2H), 7.55 (s, 1H), 7.51 – 7.39 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.39, 134.58, 133.83, 130.67, 129.39, 129.33, 129.19, 129.09, 126.12, 118.13, 111.80. The spectral data are consistent with those reported in the literature.

Example 23



Example 23 refers to a Scale-up experiment as illustrated in Figure 3B. Styrene **9** (4.58 mL, 40 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (3.2 mL, 3.2 mmol, 8 mol%) were added sequentially to a solution of $Ni(COD)_2$ (220.0 mg, 2 mol%) and DPEphos (430.8 mg, 2 mol%) in butyronitrile **4** (80 mL) prepared in a 250 mL round bottle flask under an argon atmosphere in a glove box. The flask with a reflux condenser was taken out of the glove box, and was then connected to a continuous flow of argon (positive pressure: 0.4 bar) and heated at 130 °C for 16 hours. After cooling to room temperature, the reaction was quenched with methanol and the mixture was filtered through celite to remove the solid. The reaction mixture was analyzed by GC and the regioselectivity of **10** determined by comparing their peak areas (l/b: 82/18). The methanol and butyronitrile were distilled off under vacuum. The residue was directly purified by bulb-to-bulb distillation (Büchi Glass oven B-585) to give the desired product in 94% yield (4.95 g).

Example 24

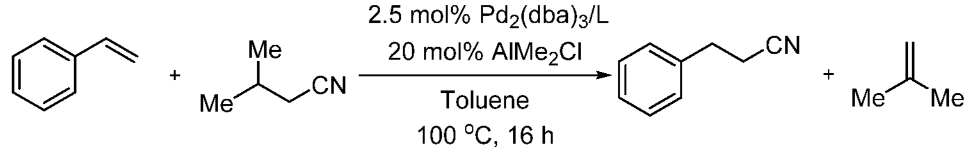


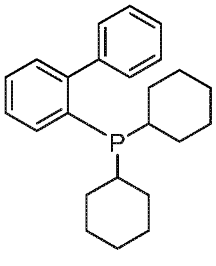
8 **69** **70**

69 (82.6 mg, 0.50 mmol), norbornadiene **8** (51 µL, 0.5 mmol) and 1.0M solution of $AlMe_2Cl$ in hexane (50 µL, 10.0 mol%, 0.05 mmol) were added sequentially to a solution of $Ni(COD)_2$ (3.45 mg, 2.5 mol%, 12.5 µmol) and DPEphos (6.75 mg, 2.5 mol%, 12.5 µmol) in benzene (1.0 mL) prepared in a 4 mL Screw-cap vial under an argon atmosphere in a glove box. The vial was taken out of the glove box, the temperature of which was fixed at 28 °C. The reaction mixture was stirred for 16 hours at 28 °C. After that time, the reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel (100% pentane) to **70** (49.0 mg, yield: 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 – 5.64 (m, 1H), 5.13 – 5.06 (m, 1H), 4.99 – 4.88 (m, 2H), 2.12 (p, *J* = 7.0 Hz, 1H), 2.01 – 1.89 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.35 – 1.26 (m, 2H), 0.99 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.91, 131.44, 124.80, 112.61, 37.51, 36.89, 25.88, 20.30, 17.83.

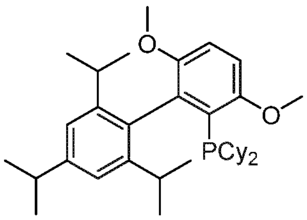
Further experimental work of the inventors evidenced that other reaction systems with different ligands, Lewis acids and/or different metals also lead to satisfying conversion results as illustrated in the following Schemes.

Scheme 1 – Different LIgands

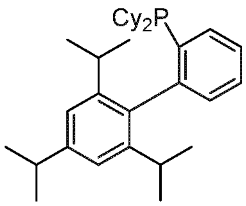




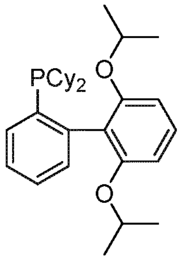
Y: 78%
l/b: 81/19



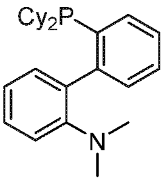
Y: 78%
l/b: 79/21



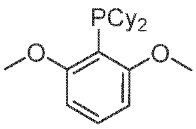
Y: 77%
l/b: 81/19



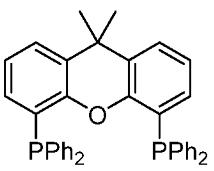
Y: 80%
l/b: 81/19



Y: 81%
l/b: 81/19

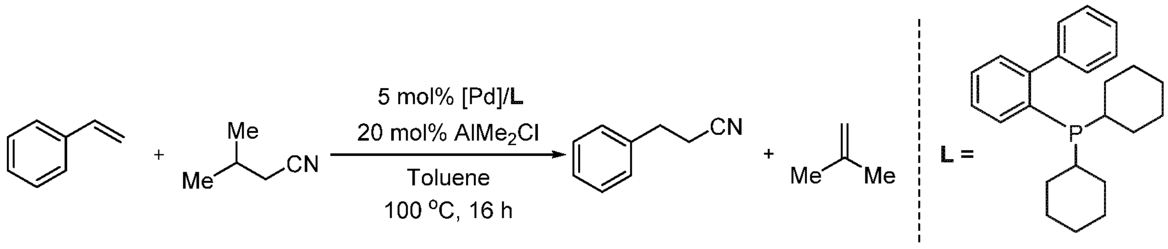


Y: 79%
l/b: 81/19



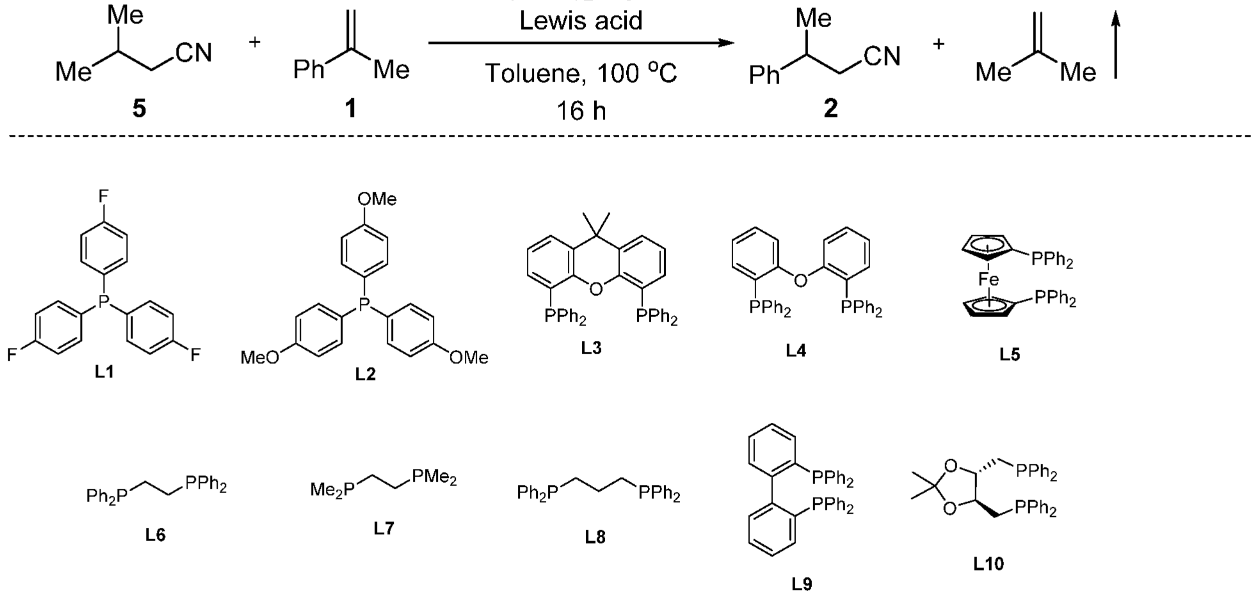
Y: 38%
l/b: 67/33

Scheme 2 – Different Metals



$Pd_2(dba)_3$	$PdCl_2$	$Pd(OAc)_2$	$[PdCl(allyl)]_2$
Y: 78%	Y: 73%	Y: 73%	Y: 71%
l/b: 81/19	l/b: 79/21	l/b: 79/21	l/b: 79/21

Schemes 3 - Different ligands and Lewis acids

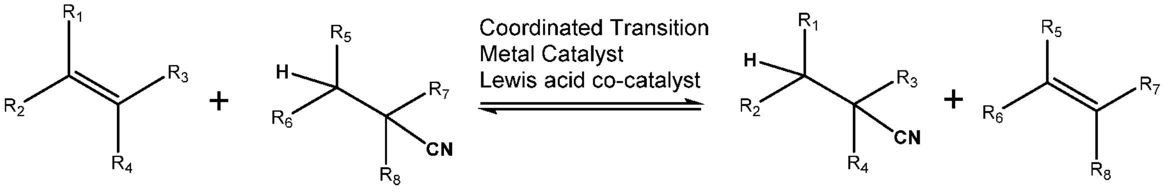


Entry	Catalyst	Ligand	Lewis acid	Conversion	Yield
1	$Ni(COD)_2$	PPh_3	$AlMe_2Cl$	73%	58%
2	$Ni(COD)_2$	L1	$AlMe_2Cl$	71%	59%
3	$Ni(COD)_2$	L2	$AlMe_2Cl$	69%	46%
4	$Ni(COD)_2$	$P(Et)_3$	$AlMe_2Cl$	41%	25%
5	$Ni(COD)_2$	L3	$AlMe_2Cl$	67%	56%
6	$Ni(COD)_2$	L4	$AlMe_2Cl$	75%	69%
7	$Ni(COD)_2$	L4	$AlCl_3$	49%	41%
8	$Ni(COD)_2$	L4	AlMe3	70%	65%
9	$Ni(COD)_2$	L5	$AlMe_2Cl$	65%	49%
10	$Ni(COD)_2$	L6	$AlMe_2Cl$	76%	55%
11	$Ni(COD)_2$	L7	$AlMe_2Cl$	65%	41%
12	$Ni(COD)_2$	L8	$AlMe_2Cl$	80%	52%
13	$Ni(COD)_2$	L9	$AlMe_2Cl$	37%	30%
14	$Ni(COD)_2$	L10	$AlMe_2Cl$	36%	29%

The inventors have shown in the above experimental results that a metal-catalyzed, in particular, Ni-catalyzed transfer hydrocyanation reaction between alkyl nitriles and alkenes can be fully manipulated to produce either product selectively using simple driving forces. This exceptionally powerful synthetic tool could be applied to the catalytic hydrocyanation and retro-hydrocyanation of a wide range of structurally different molecules (>40 examples) without relying on the use of highly toxic HCN. In a broader context, the functional group metathesis strategy delineated in this invention will likely be a milestone in the development of reversible hydrofunctionalization reactions of alkenes that do not rely on the use of hazardous gases.

Claims:

1. Process for the catalytic reversible alkene-nitrile interconversion wherein an unsaturated hydrocarbon (I) is reacted with an alkylnitrile (II) in the presence of a transition metal coordinated to a ligand and a Lewis acid co-catalyst, preferably in a solvent, to yield an alkylnitrile (III) and an unsaturated hydrocarbon (IV), each being different from the starting compounds, as represented in the following reaction scheme:



(I) (II) (III) (IV)

wherein:

- R^1, R^2, R^3 and R^4 can be the same or different and each independently represents H, straight chain or branched chain alkyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, each being optionally substituted by one or more groups selected from straight chain or branched chain alkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl or a heterosubstituent; or a heterosubstituent, or at least two of R^1, R^2, R^3 and R^4 may each form a cyclic 3 to 20 membered ring structure which may further be substituted by one or more groups selected from straight chain or branched chain alkyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl or a heterosubstituent, and optionally including any of O, S, N in the straight chain, branched chain or cyclic structure; or R^2 and R^4 form a bond; wherein at least one of R^1, R^2, R^3 and R^4 is not hydrogen;
- R^5, R^6, R^7 and R^8 can be the same or different and each independently represents H, straight chain or branched chain alkyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, each being optionally substituted by one or more groups selected from straight chain

or branched chain alkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, or a heterosubstituent, or a heterosubstituent; or at least two of R^5, R^6, R^7 and R^8 may each form a cyclic 3 to 20 membered hydrocarbon ring structure which may further be substituted by one or more groups selected from straight chain or branched chain alkyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl or a heterosubstituent, and optionally including any of O, S, N in the straight chain, branched chain or cyclic structure; wherein preferably at least one of R^5, R^6, R^7 and R^8 is not hydrogen;

- the metal of the coordinated transition metal catalyst is selected from a metal of the Iron-group, Cobalt-group, Nickel-group or Copper group;
- the ligand of the coordinated transition metal catalyst is selected from compounds having the ability to coordinate to said transition metal, including phosphorous-, nitrogen- , As-, Sb- or N-heterocyclic based ligands; and
- the Lewis acid co-catalyst is selected from compounds of aluminum, boron, zinc, titanium, scandium.

2. Process according to claim 1, wherein R^1, R^2, R^3 and R^4 can be the same or different and each independently represents H, aryl, aralkyl, heteroaryl, heteroaralkyl, each being optionally substituted by one or more groups selected from straight chain or branched chain alkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl or a heterosubstituent, or a heterosubstituent, or R^2 and R^4 form a bond; wherein at least one of R^1, R^2, R^3 and R^4 is not hydrogen.

3. Process according to claim 1 or 2, wherein R^5, R^6, R^7 and R^8 can be the same or different and each independently represents H, straight chain or branched chain alkyl, cycloalkyl, heterocycloalkyl, each being optionally substituted by one or more groups selected from straight chain or branched chain alkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl or a heterosubstituent, or a heterosubstituent, or at least two of R^5, R^6, R^7 and R^8 may each form a cyclic 3 to 20 membered

hydrocarbon ring structure which may further be substituted by one or more groups selected from alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl or heterosubstituent, and optionally including any of O, S, N in the straight chain, branched chain or cyclic structure, wherein preferably at least one of R^5, R^6, R^7 and R^8 is not hydrogen.

4. Process according to claim 3, wherein R^5, R^6, R^7 and R^8 can be the same or different and each independently represents H, straight chain or branched chain alkyl, or cycloalkyl, or at least two of R^5, R^6, R^7 and R^8 may each form a cyclic 3 to 20 membered aliphatic hydrocarbon ring structure which may further be substituted by one or more groups selected from alkyl, cycloalkyl, heterocycloalkyl, or heterosubstituent, and optionally including any of O, S, N in the straight chain, branched chain or cyclic structure, wherein at least one of R^5, R^6, R^7 and R^8 is not hydrogen.

5. Process according to claim 3, wherein the compound of formula (II) is a lower alkyl nitrile having 1 to 6 carbon atoms, optionally substituted by one or more heterosubstituents.

6. Process according to claim 1 or 2, wherein the compound of formula (I) is a cyclic unsaturated hydrocarbon having 4 to 20, preferably 4 to 12 carbon atoms optionally substituted by one or more heterosubstituents.

7. Process according to any of the afore mentioned claims, wherein the coordinated transition metal catalyst is obtained from a transition metal catalyst precursor selected from $Ni(COD)_2$, $Ni(acac)_2$, $Ni(CO)_4$, $Pd(dba)_2$, $Pd(OAc)_2$, $Co_2(CO)_8$, in particular $Ni(COD)_2$.

8. Process according to any of the afore mentioned claims, wherein the Lewis acid co-catalyst is selected from $AlMe_3$, $AlMe_2Cl$, $AlMeCl_2$, $AlCl_3$, BPh_3, $B(C_6F_5)_3$, $Zn(OTf)_2$, $ZnCl_2$, $TiCl_4$, $Sc(OTf)_3$, and preferably from $AlMe_3$, Al_2Me_2Cl, $AlCl_3$, $B(Ph)_3$.

9. Process according to any of the afore mentioned claims, wherein the ligand is selected from the group consisting of phosphine ligands, particularly PPh_3, PCy_3, $P(OPh)_3$, PEt_3, BINAP, Xanthphos, DuPhos, DPEPhos, dppf, dppe, further preferred PPh_3 and DPEPhos, and mixtures thereof.

10. Use of a reaction pair of a coordinated transition metal catalyst and a Lewis acid co-catalyst for a nitrile transfer reaction from an hydrocarbon nitrile to an unsaturated hydrocarbon, wherein
    - the metal of the coordinated transition metal catalyst is selected from a metal of the Iron-group, Cobalt-group, Nickel-group or Copper group;
    - the ligand of the coordinated transition metal catalyst is selected from compounds having the ability to coordinate to said transition metal, including phosphorous-, nitrogen- , As-, Sb- or N-heterocyclic based ligands; and
    - the Lewis acid co-catalyst is selected from compounds of aluminum, boron, zinc, titanium, scandium.

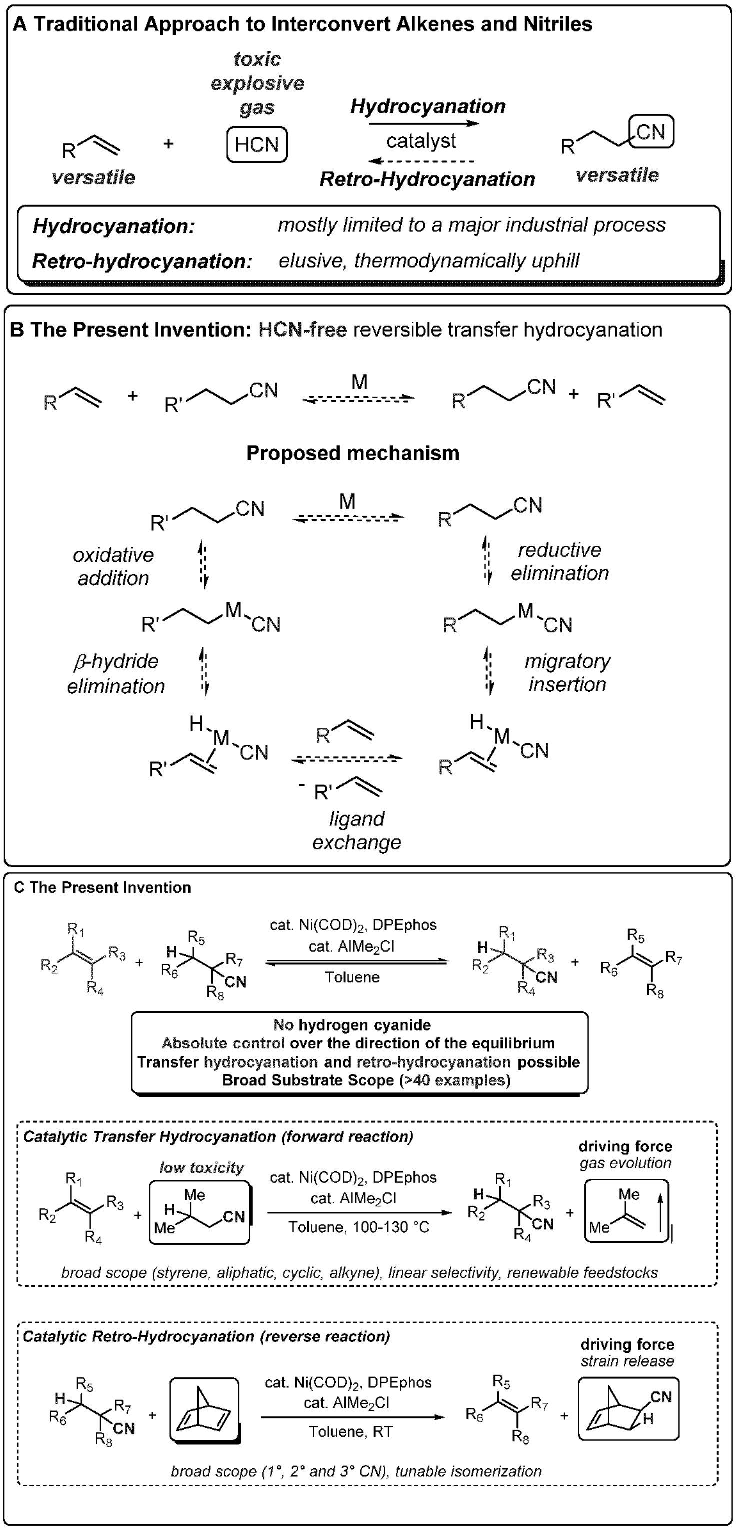

A Traditional Approach to Interconvert Alkenes and Nitriles
toxic explosive gas
Hydrocyanation
catalyst
Retro-Hydrocyanation
R
+
HCN
versatile
CN
versatile
Hydrocyanation: mostly limited to a major industrial process
Retro-hydrocyanation: elusive, thermodynamically uphill
B The Present Invention: HCN-free reversible transfer hydrocyanation
R + R' CN M R CN + R'
Proposed mechanism
oxidative addition
reductive elimination
β-hydride elimination
migratory insertion
H M CN
ligand exchange
- R'
C The Present Invention
R1 R2 R3 R4
R5 R6 R7 R8
H
CN
cat. Ni(COD)2, DPEphos
cat. AlMe2Cl
Toluene
No hydrogen cyanide
Absolute control over the direction of the equilibrium
Transfer hydrocyanation and retro-hydrocyanation possible
Broad Substrate Scope (>40 examples)
Catalytic Transfer Hydrocyanation (forward reaction)
low toxicity
Me
Toluene, 100-130 °C
driving force
gas evolution
broad scope (styrene, aliphatic, cyclic, alkyne), linear selectivity, renewable feedstocks
Catalytic Retro-Hydrocyanation (reverse reaction)
Toluene, RT
driving force
strain release
broad scope (1°, 2° and 3° CN), tunable isomerization

Fig. 1

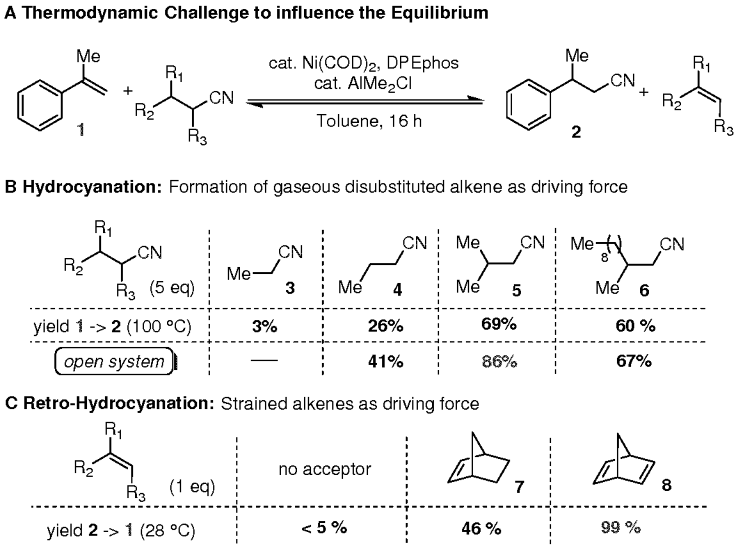

A Thermodynamic Challenge to influence the Equilibrium
Me
R1
CN
R2
R3
1
cat. Ni(COD)2, DPEphos
cat. AlMe2Cl
Toluene, 16 h
2
B Hydrocyanation: Formation of gaseous disubstituted alkene as driving force
(5 eq)
3
4
5
6
yield 1 -> 2 (100 °C)
3%
26%
69%
60 %
open system
—
41%
86%
67%
C Retro-Hydrocyanation: Strained alkenes as driving force
(1 eq)
no acceptor
7
8
yield 2 -> 1 (28 °C)
< 5 %
46 %
99 %

Fig. 2:

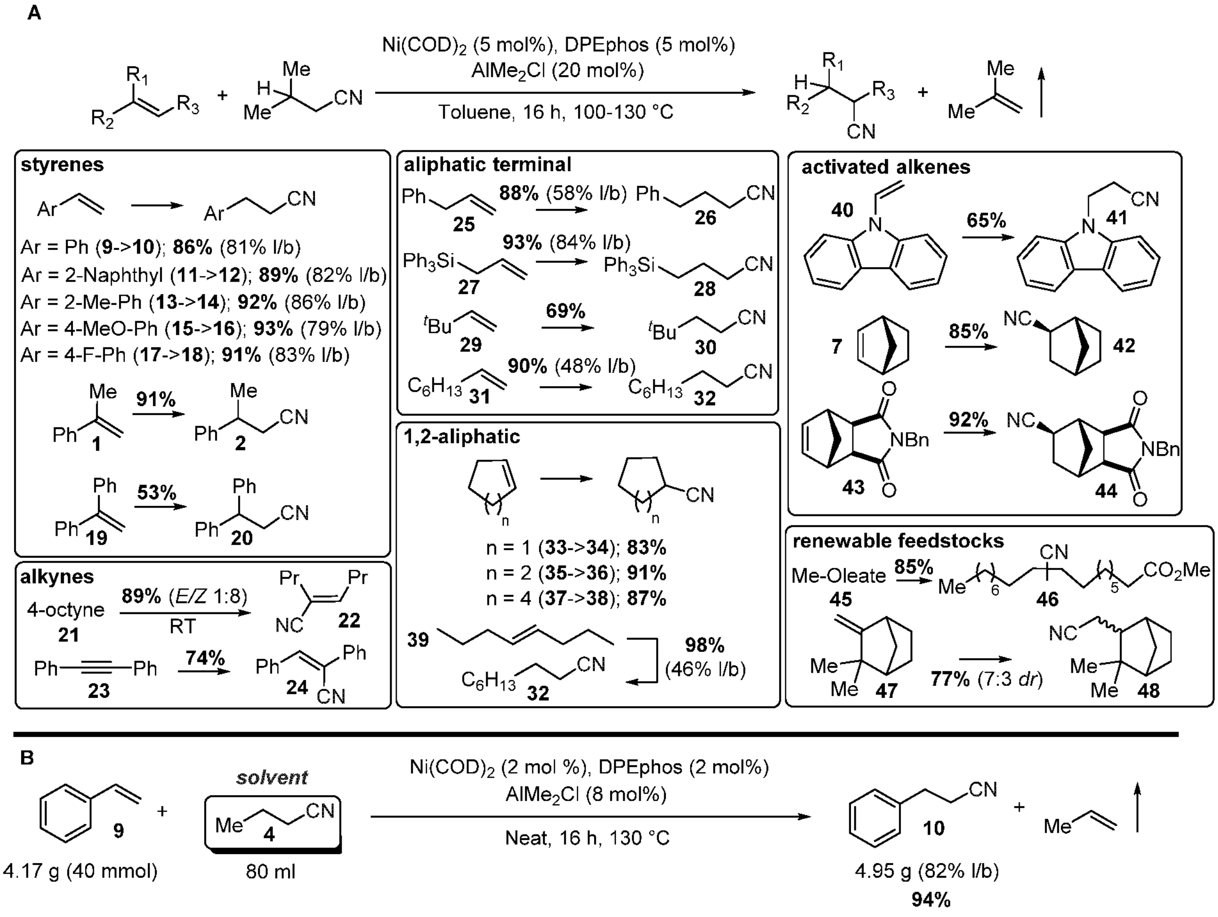

A
Ni(COD)2 (5 mol%), DPEphos (5 mol%)
AlMe2Cl (20 mol%)
Toluene, 16 h, 100-130 °C
styrenes
Ar = Ph (9->10); 86% (81% l/b)
Ar = 2-Naphthyl (11->12); 89% (82% l/b)
Ar = 2-Me-Ph (13->14); 92% (86% l/b)
Ar = 4-MeO-Ph (15->16); 93% (79% l/b)
Ar = 4-F-Ph (17->18); 91% (83% l/b)
91%
53%
alkynes
4-octyne 21
89% (E/Z 1:8)
RT
22
74%
23
24
aliphatic terminal
88% (58% l/b)
25
26
93% (84% l/b)
27
28
69%
29
30
90% (48% l/b)
31
32
1,2-aliphatic
n = 1 (33->34); 83%
n = 2 (35->36); 91%
n = 4 (37->38); 87%
39
98%
(46% l/b)
activated alkenes
40
65%
41
85%
42
43
92%
44
NBn
renewable feedstocks
Me-Oleate 45
85%
46
CO2Me
77% (7:3 dr)
47
48
B
solvent
9
4
Ni(COD)2 (2 mol %), DPEphos (2 mol%)
AlMe2Cl (8 mol%)
Neat, 16 h, 130 °C
10
4.17 g (40 mmol)
80 ml
4.95 g (82% l/b)
94%

Fig. 3:

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/078919

A. CLASSIFICATION OF SUBJECT MATTER

INV.	C07C253/30	C07C255/03	C07C255/07	C07C255/19	C07C255/31
	C07C255/33	C07C255/34	C07C255/37	C07C255/46	C07C255/47
	C07D209/76	C07D209/86	C07F7/08	B01J31/14	B01J31/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D B01J C07C C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	FANG, X. ET AL.: "Catalytic reversible alkene-nitrile interconversion through controllable transfer hydrocyanation", SCIENCE, vol. 351, no. 6275, 19 February 2016 (2016-02-19), pages 832-836, XP055268889, US ISSN: 0036-8075, DOI: 10.1126/science.aae0427 the whole document ----- -/--	1-10

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 23 December 2016	Date of mailing of the international search report 10/01/2017
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Kiernan, Andrea

1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KRANENBURG, M. ET AL.: "Effect of the bite angle of diphosphine ligands on activity and selectivity in the nickel-catalysed hydrocyanation of styrene", JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS, no. 21, 1995, pages 2177-2178, XP055268985, GB ISSN: 0022-4936, DOI: 10.1039/c39950002177 Scheme 2; page 2177; figure 1; table 1 -----	1-10
A	BINI, L. ET AL.: "Lewis Acid Controlled Regioselectivity in Styrene Hydrocyanation", CHEMISTRY - A EUROPEAN JOURNAL., vol. 15, no. 35, 2009, pages 8768-8778, XP055269021, WEINHEIM, DE ISSN: 0947-6539, DOI: 10.1002/chem.200802611 abstract Scheme 1; page 8769; table 1 -----	1-10
A	GOERTZ, W. ET AL.: "Application of chelating diphosphine ligands in the nickel-catalysed hydrocyanation of alk-1-enes and gamma-unsaturated fatty acid esters", CHEMICAL COMMUNICATIONS - CHEMICAL COMMUNICATIONS, vol. 16, 1997, pages 1521-1522, XP002318778, ISSN: 1359-7345, DOI: 10.1039/A702811C reaction schemes; figure 1; tables -----	1-10
A	US 2011/166376 A1 (MASTROIANNI SERGIO [FR]) 7 July 2011 (2011-07-07) abstract; claims; examples 1-10 page 3, paragraph [0052] -----	1-10
A	WILTING, J. ET AL.: "NICKEL-CATALYZED ISOMERIZATION OF 2-METHYL-3-BUTENENITRILE", ORGANOMETALLICS, vol. 24, no. 1, 2004, pages 13-15, XP001235658, ISSN: 0276-7333, DOI: 10.1021/OM049206P abstract Scheme 1; page 13 -----	1-10

-/--

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	VAN DER VLUGT, J.I. ET AL.: "Sterically Demanding Diphosphonite Ligands-Synthesis and Application in Nickel-Catalyzed Isomerization of 2-Methyl-3-Butenenitrile", ADVANCED SYNTHESIS & CATALYSIS, vol. 346, no. 8, 2004, pages 993-1003, XP055269019, ISSN: 1615-4150, DOI: 10.1002/adsc.200303240 abstract page 997, column 2, last paragraph -----	1-10
A	YADA, A. ET AL.: "Nickel/Lewis Acid-Catalyzed Carbocyanation of Alkynes Using Acetonitrile and Substituted Acetonitriles", BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, vol. 83, no. 6, 2010, pages 619-634, XP055268967, ISSN: 0009-2673, DOI: 10.1246/bcsj.20100023 abstract pages 619-620; table 1 -----	1-10

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/078919

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2011166376 A1	07-07-2011	CN 102089275 A	08-06-2011
		EP 2310358 A1	20-04-2011
		FR 2932477 A1	18-12-2009
		JP 2011524394 A	01-09-2011
		KR 20110009248 A	27-01-2011
		RU 2011101416 A	27-07-2012
		SG 191670 A1	31-07-2013
		TW 201004908 A	01-02-2010
		UA 107331 C2	25-12-2014
		US 2011166376 A1	07-07-2011
		WO 2009153171 A1	23-12-2009