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Nickel-Catalyzed Markovnikov Transfer Hydrocyanation in the Absence of Lewis Acid

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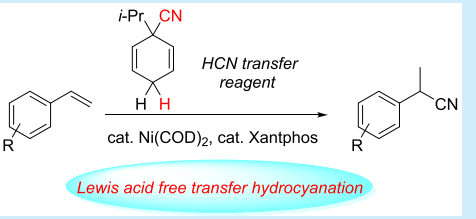
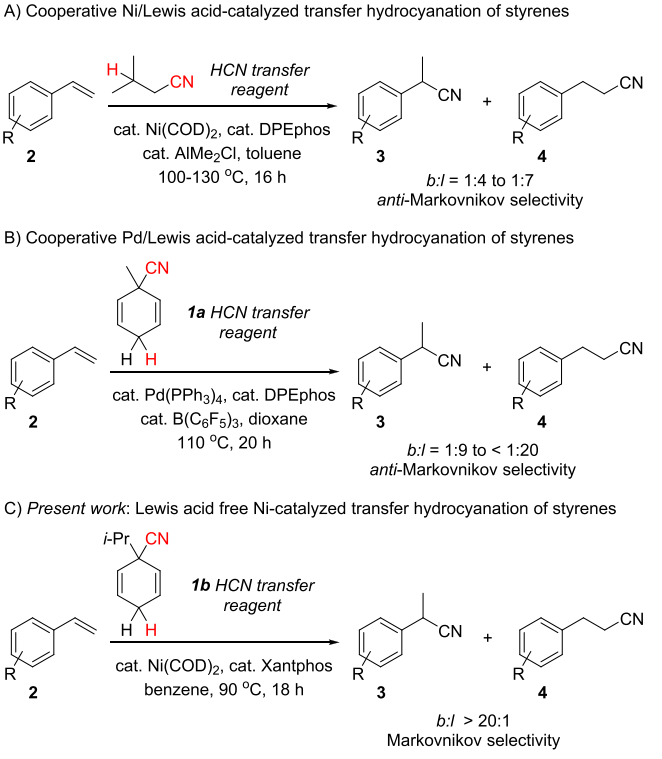
ABSTRACT: Hydrocyanation in the absence of toxic HCN gas is highly desirable. Addressing that challenge, transition-metal-catalyzed transfer hydrocyanation using safe HCN precursors has been developed, but these reagents generally require a Lewis acid for activation, and the control of regioselectivity often remains problematic. In this Letter, a Ni-catalyzed highly Markovnikov-selective transfer hydrocyanation that operates in the absence of any Lewis acid is reported. The readily prepared pro-aromatic 1-isopropylcyclohexa-2,5-diene-1-carbonitrile is used as the HCN source, and the reaction shows a broad substrate scope and high functional group tolerance. Terminal styrene derivatives, dienes, and internal alkynes are converted with good to excellent selectivities. Mechanistic studies provide insights into the origin of the regioselectivity.



The nitrile functional group is an important moiety in synthesis that can be readily transformed into various other functional groups.[1] Moreover, the nitrile entity is also found in natural products.[2] Such alkyl nitriles are generally accessed by substitution reactions using the cyanide anion as the nucleophile[1] and by the transition-metal-catalyzed hydrocyanation of alkenes.[3] The latter important strategy has been successfully applied in industry to the preparation of adipodinitrile.[4] However, a problem in alkene hydrocyanation lies in the necessity of using poisonous HCN gas. To address that critical issue, reagents that generate HCN *in situ* have been introduced. Precursors such as $(Me)_3SiCN$ or acetone cyanohydrin are also not perfect due to their volatility because high reaction temperatures are mostly applied in alkene hydrocyanations.[5] Morandi recently showed that isovaleronitrile can be used as a cheap HCN source in the Ni-catalyzed transfer hydrocyanation of terminal alkenes (Scheme 1A).[6] These hydrocyanations are reversible under the applied conditions, and the formation of gaseous, readily removable isobutylene as the byproduct drives the process. Considering the reversible hydrocyanation of terminal alkenes, control of the regioselectivity is a challenge because the Markovnikov (branched) and *anti*-Markovnikov (linear) alkyl nitriles show similar energies, and accordingly, thermodynamic product control will lead to regioisomeric mixtures.[6]

We have recently introduced 1-methylcyclohexa-2,5-diene-1-carbonitrile **1a**, which is easily prepared via the reductive Birch methylation of benzonitrile, as a valuable HCN donor in Pd-catalyzed *anti*-Markovnikov transfer hydrocyanations (Scheme 1B).[7] Oestreich and coworkers used the same type of reagents in Lewis-acid-catalyzed HCN transfers.[8] Both the Morandi Ni-catalyzed[6] and our Pd-catalyzed transfer hydrocyanation work only in the presence of a Lewis acid for reagent activation,[9] and

Scheme 1. Transition-Metal-Catalyzed Transfer Hydrocyanation of Alkenes



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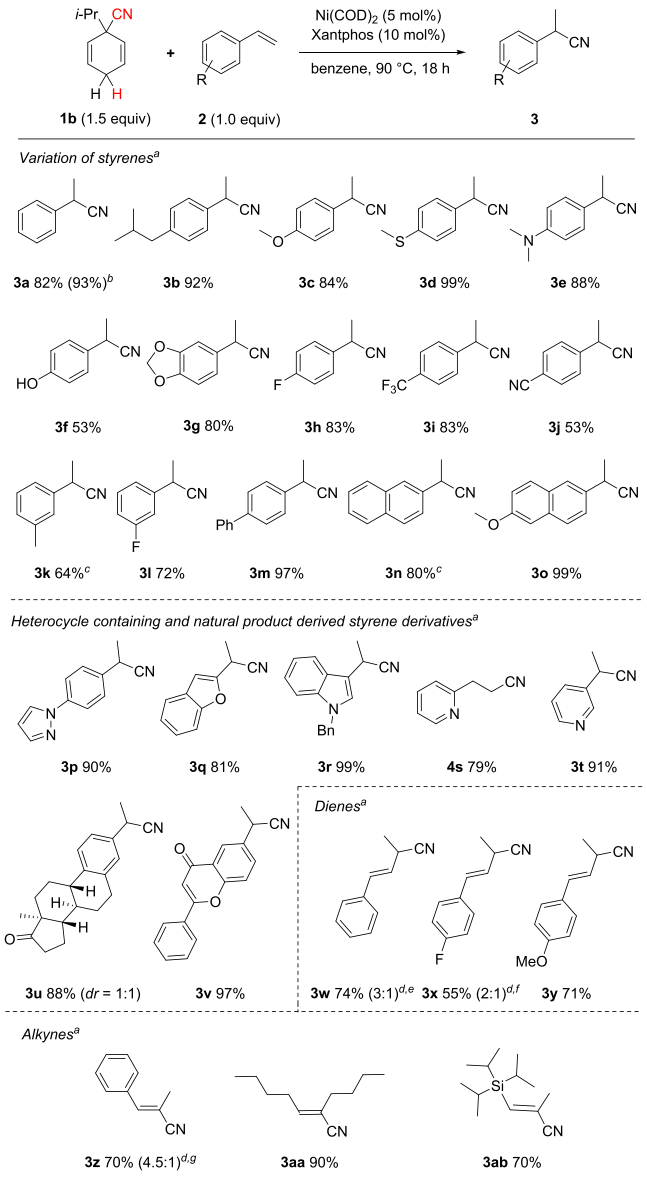
in some cases, the Ni variant delivers only moderate regioselectivity.

Herein we show that cyclohexadienes of type **1** can also be applied to the Ni-catalyzed transfer hydrocyanation of styrene derivatives (Scheme 1C). In contrast with the Pd variant that delivers the linear nitrile, a Lewis acid is not required, and the branched Markovnikov product is obtained with excellent regioselectivity. Mechanistic studies will provide insights into the origin of the high regioselectivity.

Reaction optimization was conducted with styrene (**2a**) as the substrate (Scheme 2). We were pleased to find that the Ni-catalyzed transfer hydrocyanation of **2a** with reagent **1a** can be conducted in the absence of any Lewis acid, significantly simplifying the process. Xantphos (10 mol %) turned out to be the ideal ligand, in combination with $Ni(COD)_2$ (5 mol %) as the catalyst in benzene at 90 °C (18 h), and nitrile **3a** was obtained in 51% isolated yield with complete Markovnikov selectivity (>98:2; for the full reaction optimization, see the Supporting Information). DPEphos as the ligand provided a similar result, and the yield could be further improved to 82% upon switching to reagent **1b** using Xantphos as the ligand without compromising regioselectivity.[10] In addition, we conducted the reaction on a 1.0 mmol scale, increasing the yield to 93%.

Scheme 2. Ni-Catalyzed Transfer Hydrocyanation of Various Styrene Derivatives and Alkynes with Reagent 1b



[a]Reaction was conducted on a 0.5 mmol scale. [b]Reaction was conducted on a 1.0 mmol scale. [c]Reaction was conducted on a 0.2 mmol scale. [d]Ratio of product to its double-bond isomer is given in parentheses. [e]Minor isomer **3w′**: (*E*)-2-methyl-4-phenylbut-2-enenitrile. [f]Minor isomer **3x′**: (*E*)-4-(4-fluorophenyl)-2-methylbut-2-enenitrile. [g]Minor isomer: (*E*)-2-phenylbut-2-enenitrile.

With the optimized conditions in hand, the reaction scope was investigated. The transfer hydrocyanation of styrene derivatives was not very sensitive toward electronic effects because yields obtained for substrates bearing electron-donating substituents such as alkyl (**2b**), methoxy (**2c**), methylthiyl (**2d**), dimethylaminyl (**2e**), and dioxole (**2g**) as well as electron-accepting substituents such as fluoro (**2h**) and trifluoromethyl (**2i**) at the para position did not vary to a large extent with a clear trend. The corresponding products **3b**–**i** were isolated in 80–99% yields with excellent regioselectivity (>98:2; the linear isomer could not be detected by GC analysis on the crude reaction mixture). Substrates with hydroxyl (**2f**) and cyano (**2j**) substituents at the para position reacted moderately, giving the corresponding products **3f** and **3j**, each in 53% yield. Meta-substituted styrenes also engaged in the reaction (**3k**,**l**), but ortho-substituted congeners turned out to be unreactive toward the hydrocyanation. (See the SI.) *para*-Phenylstyrene (**2m**) and *β*-vinyl naphthalenes **2n**,**o** reacted highly efficiently, and the product nitriles **3n**,**o** were isolated in 80–99% yields. Heteroarenes were also tolerated, as documented by the successful transformation of the pyrazole derivative (**3p**), 2-vinylbenzofuran (**3q**), and a 3-vinylated indole (**3r**).

Surprisingly, 2-vinylpyridine (**2s**) gave the *anti*-Markovnikov product **4s** as a major regioisomer in 79% isolated yield (**4s**/**3s** 9:1). We assumed that the N atom of the pyridine ring interacts with the Ni catalyst, leading to a reversal of the regioselectivity. This assumption could be supported by the reaction of 3-vinylpyridine (**2t**), where coordination during hydrocyanation is not likely. As a result, the Markovnikov product **3t** was obtained with high regioselectivity (>98:2) in 91% isolated yield. Hydrocyanation could also be achieved on more complex natural-product-derived alkenes. (See **3u** and **3v**.) Unfortunately, unactivated aliphatic alkenes did not react under the optimized conditions. (See the SI.)

Dienes **2w**–**y** turned out to be eligible HCN acceptors, and the products **3w**–**y** were obtained in moderate to good yields. In all of these transformations, the linear products were not identified, but in two cases, we found isomerization of the double bond to give the corresponding acrylonitrile derivative. For example, the hydrocyanation of diene **2w** occurred with high regioselectivity to afford the desired allylic nitrile **3w**. However, (*E*)-2-methyl-4-phenylbut-2-enenitrile (**3w′**) was formed as a side product, likely via the isomerization of the targeted **3w** (ratio **3w**/**3w′** 3:1; see the SI for more details). A similar reactivity was found for the fluoro-substituted diene **2x**. In contrast, the more electron-rich methoxy congener **2y** afforded the allylic nitrile **3y** with excellent regioselectivity in 71% yield, and isomerization did not occur.

We next tested alkynes in the transfer hydrocyanation with reagent **1b** because acrylonitrile derivatives are valuable substrates in synthesis. Internal alkynes, even unactivated

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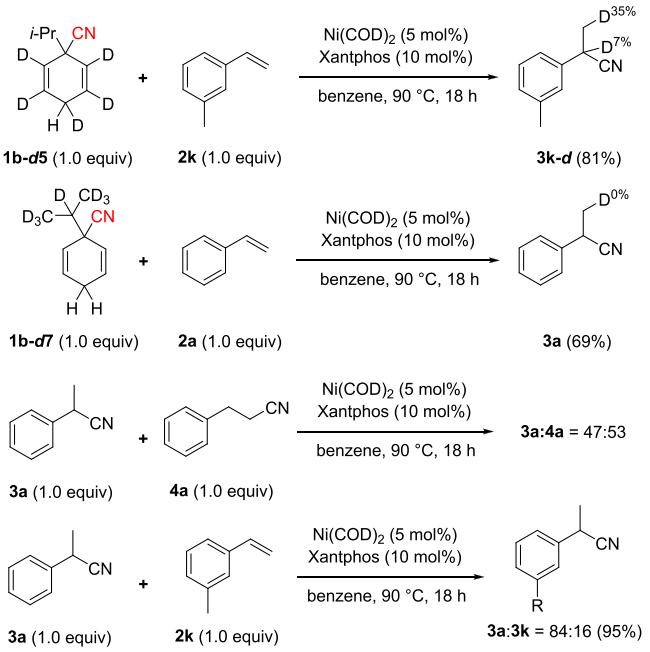
bisalkylalkynes, engaged in the transformation, whereas terminal alkynes did not react under the optimized conditions. (See the SI.) Hence, 1-phenyl-1-propyne (**2z**) provided nitrile **3z** with a 4.5:1 regioselectivity and excellent trans-selectivity (cis-hydrocyanation) for both regioisomers. The symmetric dec-5-yne (**2aa**) afforded the hydrocyanation product **3aa** in 90% yield with excellent trans-selectivity. Propyne protected with the bulky triisopropylsilyl group reacted with excellent regioselectivity to nitrile **3ab** (70% yield, trans/cis > 98:2).

Next, we addressed the mechanism of the transfer hydrocyanation of styrene **2k** by using the perdeuterated reagent **1b**-d_5 (Scheme 3). Nitrile **3k**-*d* was isolated in 81%

Scheme 3. Mechanistic Studies

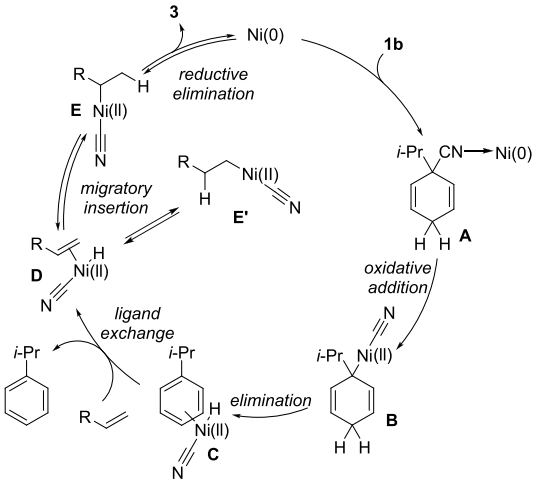


yield with 35% D incorporation at the β-position and 7% D incorporation at the α-position. Upon switching to reagent **1b**-d_7 using styrene as the acceptor, nitrile **3a** was isolated in 69% yield without any deuterium incorporation, and GCMS analysis showed the mass of (propan-2-yl-d_7)benzene as the byproduct. (See the SI for details.) These observations indicate that the H atom that gets transferred to the alkene is derived from the ring methylene group of reagent **1b** and not from the isopropyl group.

In an additional mechanistic experiment, a 1:1 mixture of nitrile **3a** and its regioisomer **4a** was subjected to the reaction conditions in the absence of reagent **1b**. After 18 h, the ratio of **3a**/**4a** remained nearly the same, indicating that the linear regioisomer **4a** is stable under the reaction conditions. To check whether a benzylic nitrile is also stable, we ran the reaction of **3a** with alkene **2k** (1 equiv of each) in the absence of reagent **1b**, and **3k** was identified as product along with **3a** (ratio **3a**/**3k** 84:16). This result clearly shows that the benzylic C−CN bond in **3a** gets activated by the Ni catalyst.

Considering these mechanistic investigations and literature reports,[11] the following mechanism is suggested for the alkene transfer hydrocyanation with **1b** (Scheme 4). The catalytic cycle starts by complexation of the nitrile functionality of reagent **1b** with the Ni(0) catalyst to give **A**, which reacts via oxidative addition to complex **B**. The deuteration experiments

Scheme 4. Proposed Mechanism



revealed that a ring methylene H atom gets transferred to the alkene. Hence **B** can react via direct δ-hydride elimination, considering a boat-shaped conformation with the isopropyl group located in the equatorial position, to **C**.[12] Alternatively, a 1,3-metallotropic shift in **B** followed by β-hydride elimination will also lead to complex **C**.[13] Ligand exchange then affords **D**, which can undergo migratory insertion to complex **E**. Reversible reductive elimination will eventually lead to the final product **3**.

Because the oxidative addition of Ni(0) to the linear product **4a** did not occur (see Scheme 3), linear products of type **4** should never be formed during transfer hydrocyanation. Deuterium incorporation at the benzylic position (see **3a**-*d*) indicates that the migratory insertion does not proceed with perfect regioselectivity. We therefore assume that the migratory insertion is reversible and that reductive elimination proceeds only for the benzylic Ni complex **E**, leading to the branched product **3**, whereas the primary alkyl−Ni(II)CN complex **E′** does not engage in reductive elimination to give **4**. In contrast, Schmalz and coworkers observed no deuterium scrambling in their enantioselective hydrocyanation of styrene-d_8 using HCN at room temperature.[3i] Thus the formation of **E′** seems to be possible only at higher temperatures.

Finally, we tested whether regioselectivity for the transfer hydrocyanation of styrenes using reagent **1a** can be reversed upon running the reaction in the presence of a Lewis acid (Scheme 5).[14] We were pleased to find that with 20 mol % of $AlMe_2Cl$, the hydrocyanation of 4-vinyl-benzonitrile (**2j**) worked under very mild conditions, and the linear *anti*-Markovnikov product **4j** was isolated in 64% yield with 14:1 regioselectivity. In contrast with previous protocols on Lewis-acid-mediated transfer hydrocyanations that operate at 100−130 °C,[6] the current transformation proceeds at room temperature. A lower but still good selectivity (5:1 to 6:1) was noted for styrene and its *para*-fluoro congener (**4a** and **4h**), whereas for the more electron-rich 4-vinylanisole, the regioselectivity dropped to 3:1 (**4c**). Notably, reagent **1b** showed lower efficiency than **1a** in the Lewis-acid-mediated reaction.

In summary, we have presented Ni-catalyzed transfer hydrocyanation of styrenes, dienes, and alkynes using cyclohexadiene **1b** as a readily accessible and storable HCN source. A Lewis acid is not required to activate the cyano functionality in **1b**, and reactions proceed under comparable mild

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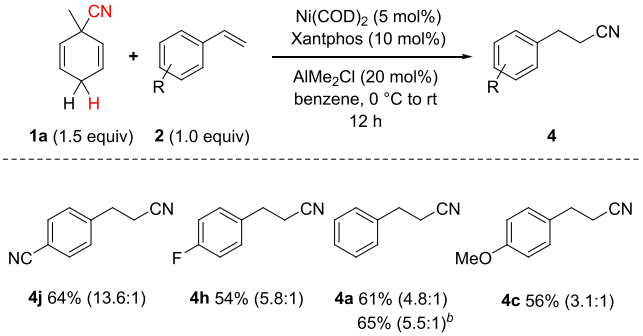
Scheme 5. *anti*-Markovnikov-Selective Transfer Hydrocyanation[a]



[a]Reaction was performed on a 0.2 mmol scale. The ratio of linear to branched product is given in parentheses. [b]Reaction with 40 mol % of $AlMe_2Cl$. The GC yield is reported.

conditions at 90 °C. For styrene derivatives, excellent Markovnikov selectivity is obtained. In the presence of $AlMe_2Cl$ (20 mol %), transfer hydrocyanation can be conducted at room temperature using this type of reagent, and the *anti*-Markovnikov product is formed as a major regioisomer with good to very good selectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01454.

General experimental procedures, reaction optimization, mechanistic experiments, and characterization of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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