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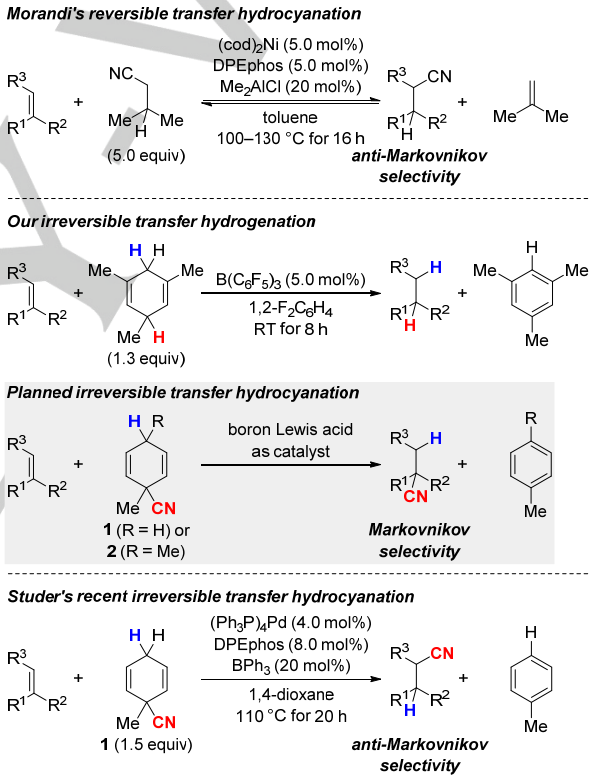
Transfer Hydrocyanation of α- and α,β-Substituted Styrenes Catalyzed by Boron Lewis Acids

Patrizio Orecchia[+], Weiming Yuan[+], and Martin Oestreich*

Abstract: A straightforward gram-scale preparation of cyclohexa-1,4-diene-based hydrogen cyanide (HCN) surrogates is reported. These are bench-stable but formally release HCN and rearomatize when treated with Lewis acids. For BCl_3, the formation the isocyanide adduct $[(CN)BCl_3]^-$ and the corresponding Wheland complex was verified by mass spectrometry. In the presence of 1,1-di- and trisubstituted alkenes, transfer of HCN from the surrogate onto the C–C double bond occurs, affording highly substituted nitriles with Markovnikov selectivity. The success of the transfer hydrocyanation depends on the Lewis acid employed; catalytic amounts of BCl_3 and $(C_6F_5)_2BCl$ are shown to be effective while $B(C_6F_5)_3$ and $BF_3{\cdot}OEt_2$ are not.

Nitriles are synthetically highly versatile as the C≡N functional group is readily converted into amines or various carbonyl compounds directly at the desired oxidation level. On an industrial scale, transition-metal-catalyzed hydrocyanation of alkenes using hydrogen cyanide (HCN) is the prevalent methodology to access nitriles.[1] Conversely, the use of gaseous HCN (b.p. 25.6 °C) in academic laboratories is less appealing despite the atom economy associated with its addition across multiple bonds. The severe toxicity of HCN[2] sparked efforts to identify less volatile surrogates,[3] and acetone cyanohydrin as well as trimethylcyanide (TMSCN) fulfill this role in nickel-catalyzed alkene hydrocyanation.[4–6] Another approach is based on cobalt catalysis, and this radical process makes use of solid tosyl cyanide (TsCN) with $PhSiH_3$ as the source of the hydrogen atom.[7] Morandi and co-workers recently disclosed the *reversible* transfer hydrocyanation of alkenes catalyzed by nickel (Scheme 1, top).[8,9] The equilibrium can be elegantly shifted toward the right by the release of low-boiling isobutylene.

Our laboratory introduced *irreversible* transfer processes catalyzed by $B(C_6F_5)_3$ where the driving force is the rearomatization of cyclohexa-1,4-diene surrogates substituted with an electrofuge at either saturated carbon atom.[10] The general principle behind this strategy is that the boron Lewis acid abstracts a hydride from the other saturated position to generate a Wheland intermediate that eventually releases the electrofuge.[11] With alkenes as π-basic donor molecules, transfer hydrosilylation[12] and hydrogenation[13] as well as the formal transfer of isobutane[14] were realized.[15] As illustrated for the transfer hydrogenation, the hydrogen atom labeled in red is transferred as hydride to the more substituted carbon atom and the hydrogen atom labeled in blue assumes the role of the proton (Scheme 1, middle). Knowing that $B(C_6F_5)_3$ is able to capture isocyanide from activated nitriles,[16] we anticipated that replacement of hydride by cyanide in cyclohexa-1,4-diene-based surrogates could lead to the related transfer hydrocyanation of alkenes (Scheme 1, gray box). We report here the development of such a transition-metal-free transformation using readily available HCN surrogates **1** and **2**. We note here that, while this manuscript was in preparation, a related but complementary methodology employing the same surrogate type was reported by Studer and co-workers (Scheme 1, bottom).[17] However, that transfer hydrocyanation is promoted by a palladium catalyst with the aid of a boron Lewis acid similar to Morandi's approach,[8a] eventually leading to the opposite regioselectivity.



Scheme 1. Transfer hydrocyanation of alkenes.

The preparation of surrogates **1** and **2** was achieved on gram scale in just one synthetic operation (Scheme 2). Birch alkylation of benzonitrile (**3**)[18] and 4-methylbenzonitrile (**4**) with methyl iodide as the alkylating reagent afforded **1** and **2** in isolated yields of 88% and 85%, respectively; **2** is formed as a mixture of diastereomers but this is irrelevant in the subsequent transfer process (see the Supporting Information for details).

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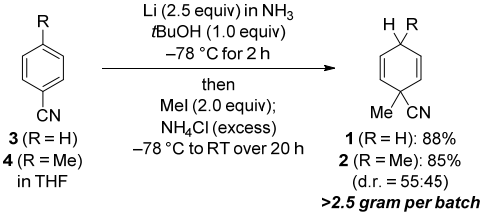
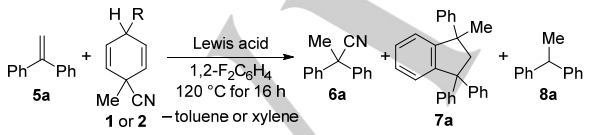


Scheme 2. One-step preparation of the surrogates.

We chose 1,1-diphenylethylene (**5a**) as a model substrate for its propensity to absorb a proton, and stayed with 1,2-$F_2C_6H_4$ as the solvent (Table 1).[13] However, the transfer process required significantly higher temperatures than the transfer hydrogenation[13] and was routinely run at 120 °C (cf. Scheme 1, middle). Initial experiments with $B(C_6F_5)_3$ in catalytic or stoichiometric amounts and employing surrogate **1** were rather disappointing (entries 1 and 2). The target compound **6a** did form but cationic alkene dimerization yielding **7a** prevailed.[19] Competing hydrogenation furnishing **8a** was also seen and is rationalized by competing hydride abstraction from surrogate **1** by either $B(C_6F_5)_3$ or the intermediate carbenium ion[11] (see the Supporting Information for both catalytic cycles). The hydrogenation pathway was efficiently suppressed using surrogate **2** which bears an additional methyl substituent at the former methylene group (entry 3). The use of more Lewis-acidic[20] BCl_3 as catalyst had a dramatic effect on the product distribution, no matter which of the two surrogates was used (entries 4–7). The transfer hydrocyanation proceeded cleanly with 20 mol% catalyst loading, and 10 mol% were also sufficient at prolonged reaction time (36 h instead of 16 h). At lower reaction temperature (80 °C instead of 120 °C), conversion was low and dimerization began to occur, indicating the cyanide release from the assumed isocyanoborate intermediate is probably rate determining. The result with BBr_3 was slightly inferior (entry 8), and $BF_3{\cdot}OEt_2$ behaved similarly to $B(C_6F_5)_3$ (entry 9); $B(OMe)_3$ did not facilitate the activation of the surrogate (entry 10). We briefly examined other Lewis acids such as $AlCl_3$. However, the desired nitrile **6a** and the alkene dimer **7a** were formed in nearly equal amounts (entries 11 and 12). We also note that the choice of the solvent is crucial; there was no conversion in either benzene or toluene (see the Supporting Information for the solvent screening).

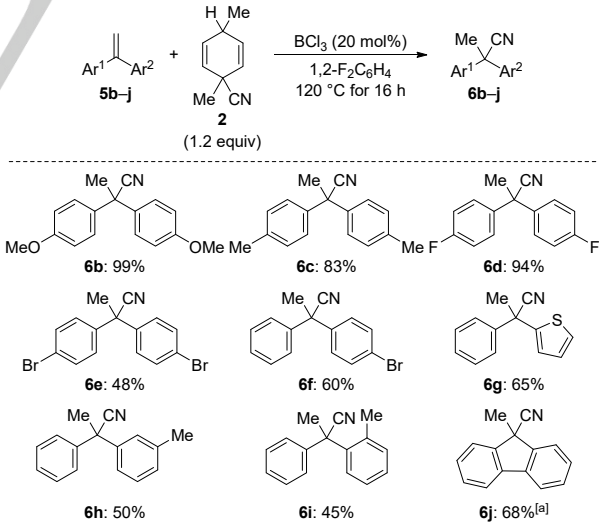
Table 1. Identification of the Lewis acid.[a]



Entry	Lewis acid (mol%)	Surrogate	**6a**:**7a**:**8a**[b]	Conv. [%][c]
1	$B(C_6F_5)_3$ (20)	**1**	42:14:44	>99
2	$B(C_6F_5)_3$ (100)	**1**	20:70:10	>99
3	$B(C_6F_5)_3$ (100)	**2**	18:79:3	>99
4	BCl_3[d] (20)	**2**	99:1:0	>99 (97)[e]
5	BCl_3[d] (20)	**1**	94:3:3	>99
6	BCl_3[d] (10)	**2**	93:7:0	>99 (94)[e]
7	BCl_3[d] (20)	**2**	85:13:2	40
8	BBr_3[d] (20)	**2**	88:11:1	>99 (87)[e]
9	$BF_3{\cdot}OEt_2$ (20)	**2**	38:62:0	85
10	$B(OMe)_3$ (20)	**2**	—	0
11	$AlCl_3$ (20)	**1**	40:49:11	>99
12	$AlCl_3$ (20)	**2**	47:52:1	99

[a] Unless otherwise noted, all reactions were performed on a 0.10 mmol scale at 120 °C for 16 h in a sealed tube, using 1.2 equiv of **1** or **2** in 0.5 mL of 1,2-$F_2C_6H_4$. [b] Estimated by GLC analysis by integration without calibration. [c] Determined by GLC analysis with tetracosane as an internal standard. [d] 1.0 M in CH_2Cl_2. [e] Isolated yield after flash chromatography on silica gel in parentheses.

We then proceeded to investigate other 1,1-diarylethylenes with BCl_3 as catalyst (Scheme 3). Substitution in both *para* positions was generally well tolerated as in **6b**–**d** except for a bromo substituent as with **6e**. We cannot explain this outcome but the effect was less pronounced with just one of the aryl groups brominated as with **6f**. A thienyl group as in **6g** was also compatible though the functional-group tolerance was generally limited. Lewis-basic groups such as nitro (15% NMR yield) and dibenzylamino (33% NMR yield) thwarted high yields, and no reaction was observed with substrates containing carbonyl groups. Moving a methyl group from *para* to *meta* to *ortho* led to a gradual decrease in yield (**6h** and **6i** versus **6c**). We attribute this to increased steric hindrance, hampering cyanide addition to the carbenium-ion intermediate. A rigidified version of parent 1,1-diphenylethylene (**5a**) also reacted smoothly (**5j**→**6j**).



Scheme 3. Scope I: 1,1-Diarylethylenes. All reactions were performed in a sealed tube charged with 0.10 mmol of alkene **5**, 0.12 mmol of surrogate **2** (1.2 equiv), and 20 µL of a 1.0 M solution of BCl_3 in CH_2Cl_2 (20 mol%) in 0.5 mL of 1,2-$F_2C_6H_4$. [a] Determined by NMR spectroscopy using CH_2Br_2 as an internal standard; purification by chromatography failed.

Alkenes other than 1,1-diarylethylenes reacted poorly with BCl_3 as catalyst. We therefore tested $(C_6F_5)BCl_2$[21] and $(C_6F_5)_2BCl$[22] as their Lewis acidity[20] falls between that of BCl_3

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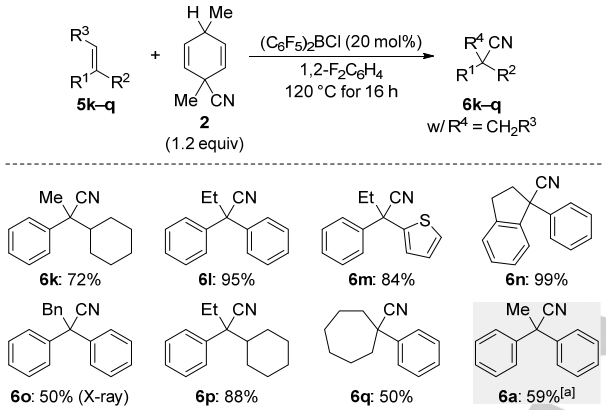
and $B(C_6F_5)_3$ (the role of the substituents at the boron atom is discussed further below). A 1,1-alkyl/aryl-substituted alkene then afforded 45% and 72% yield with $(C_6F_5)BCl_2$ and $(C_6F_5)_2BCl$, respectively (Scheme 4, **5k**→**6k**); other styrenes with a linear alkyl chain in the α position did undergo the aforementioned dimerization (not shown). $(C_6F_5)_2BCl$ as catalyst then enabled the transfer hydrocyanation of several trisubstituted alkenes **5l–q** to form **6l–q** containing a nitrile-bearing quaternary carbon atom (Scheme 4). Yields were consistently high for 1,1-diaryl-substituted alkenes **5l–n**, and triphenylethylene reacted in 50% yield (**5o**→**6o**). Trisubstituted alkenes with just one aryl group participated as well (**5p** and **5q**) yet the yield was lower for **5q** with an endocyclic double bond. For comparison, this setup was also applied to **5a**→**6a** but the reaction was less chemoselective (gray box). As expected for a reaction that involves the formation of carbenium ions, 1,2-disubstituted alkenes and α-olefins did not work.



Scheme 4. Scope II: Various di- and trisubstituted alkenes. All reactions were performed in a sealed tube charged with 0.10 mmol of alkene **5**, 0.12 mmol of surrogate **2** (1.2 equiv), and 20 µL of a 1.0 M solution of $(C_6F_5)_2BCl$ in CH_2Cl_2 (20 mol%) in 0.5 mL of 1,2-$F_2C_6H_4$. [a] The ratio of **6a**:**7a**:**8a** was 68:32:0 (cf. Table 1).

The observed regioselectivity is already convincing evidence for a mechanism involving protonation of the alkene followed by cyanide addition to the carbenium-ion intermediate. The Brønsted acid needed for the protonation step would emerge from abstraction of isocyanide from the HCN surrogate by the boron Lewis acid. Both the ate complex $[(CN)BCl_3]^-$ derived from BCl_3 and the Wheland intermediate $[C_8H_{11}]^+$, that is protonated *para*-xylene from **2**, were detected by mass-spectrometric analysis at room temperature (Figure 1).

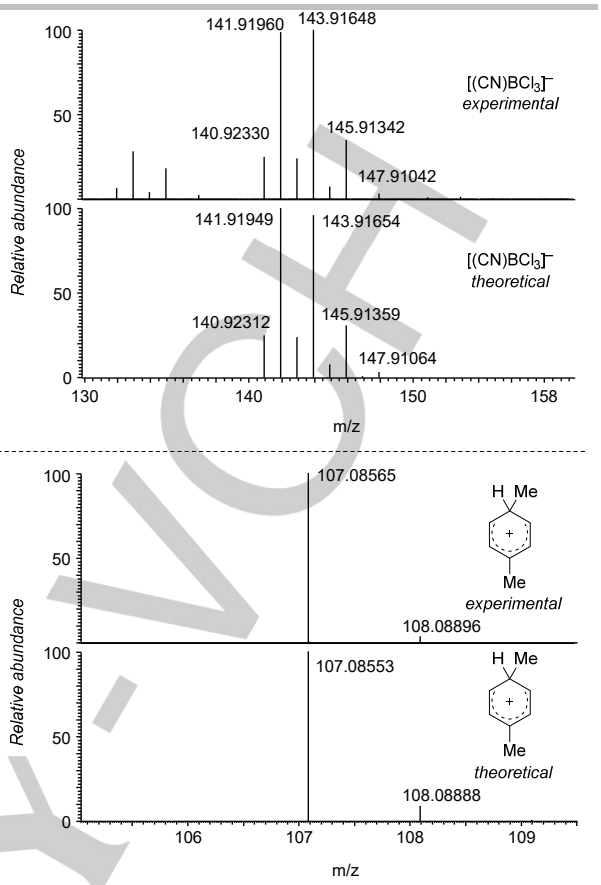
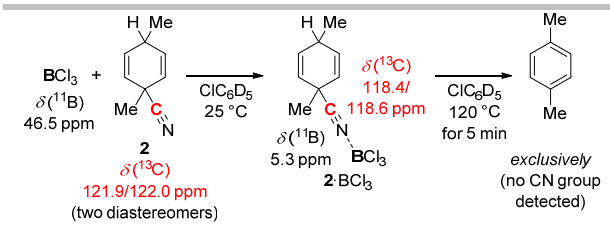


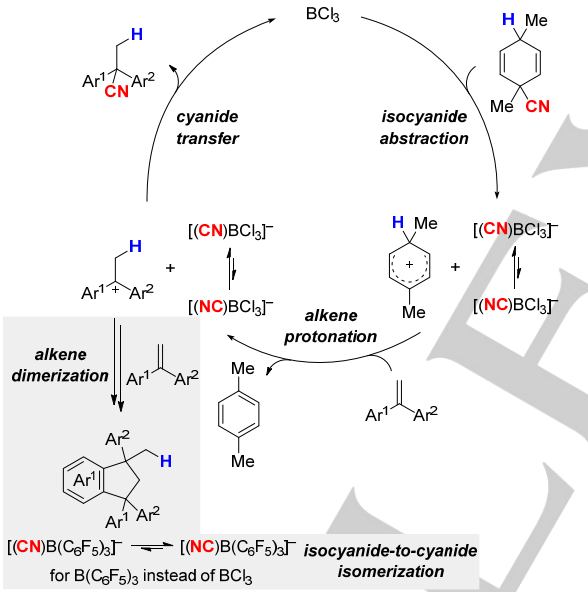
Figure 1. In-situ ESI-MS spectra of $[(CN)BCl_3]^-$ (top) and Wheland intermediate $[C_8H_{11}]^+$ (bottom) at room temperature.

An analysis of the stoichiometric reaction of BCl_3 and HCN surrogate **2** (in form of its two diastereomers) by ^{11}B and ^{13}C NMR spectroscopy at room temperature provided further mechanistic insight (Scheme 5). A diagnostic upfield shift from δ 46.5 ppm for BCl_3 to δ 5.3 ppm for Lewis adduct **2**·BCl_3 was found in the ^{11}B NMR spectrum.[23] Additional support of the nitrile coordination came from the ^{13}C NMR spectra of **2**·BCl_3; the Δδ value of ~3.5 ppm is consistent with those previously described.[23] Heating to 120 °C for a few minutes immediately led to full degradation of **2** into *para*-xylene. Neither HCN nor any isocyano/cyano group could be detected in the ^{13}C NMR spectrum, possibly because of the quadrupolar effect of the boron atom. The ^{11}B NMR spectrum showed several resonance signals at 22.0 and around 5.3 (three) ppm but we could not assign any of the these to $[(CN)BCl_3]^-$. Hence, we could not distinguish between the isocyanide adduct $[(CN)BCl_3]^-$ and the isomeric cyanide $[(NC)BCl_3]^-$. These borates are known to interconvert, and initially formed $[(CN)BCl_3]^-$ could be in equilibrium with $[(NC)BCl_3]^-$. However, the isocyanide isomeric is likely to be favored according to early quantum-chemical calculations in the gas phase.[24]



Scheme 5. Stoichiometric NMR experiment.

Based on the above findings and literature precedent,[23,24] we propose a catalytic cycle with three elementary steps for the transfer hydrocyanation of, e.g., 1,1-diarylethylenes and BCl_3 as catalyst (Scheme 6). The boron Lewis acid abstracts isocyanide from the HCN surrogate to arrive at the corresponding strongly acidic Wheland intermediate and the isocyanoborate $[(CN)BCl_3]^-$ (see Figure 1). Subsequent protonation of the alkene by that strong Brønsted acid leads the more stable carbenium ion paired with the isocyanoborate counteranion. This step is driven by the rearomatization of the Wheland intermediate to form *para*-xylene. $[(CN)BCl_3]^-$ rather than cyanoborate $[(NC)BCl_3]^-$[24] then delivers cyanide to the carbenium to close the catalytic cycle.



Scheme 6. Elementary steps of the catalytic cycle.

The nature of the boron Lewis acid affects both the isocyanide abstraction and the cyanide transfer. Importantly, the substituents at the boron atom also influence the crucial isocyanide/cyanide isomerization that occurs between these steps.[24] A bias away from the isocyanoborate and toward the cyanoborate could retard the final step of the catalytic cycle, at the same time providing the opportunity for the carbenium ion to react with another alkene molecule (Scheme 6, off-cycle dimerization in gray box). For BCl_3 and $(C_6F_5)_2BCl$, isocyanoborate binding is favored whereas the cyanoborate is preferred with $B(C_6F_5)_3$ and $BF_3{\cdot}OEt_2$. Consequently, the dimer is seen in substantial amounts with the latter Lewis acids as well as $AlCl_3$ as catalysts. The recently computed, thermodynamically downhill flip of $[(CN)B(C_6F_5)_3]^-$ to $[(NC)B(C_6F_5)_3]^-$[16] lends further support to this mechanistic picture. These properties of the Lewis acids help rationalize the distribution between nitrile **6a** and dimerized alkene **7a** summarized in Table 1.

We have presented here a new strategy to convert alkenes into nitriles by transfer hydrocyanation. The HCN molecule is delivered stepwise from a bench-stable surrogate to the C–C double bond by the action of Lewis acid catalyst. The HCN surrogates are based on adequately substituted cyclohexa-1,4-dienes that are accessible in gram quantities by Birch reduction of benzonitriles. The boron Lewis acid abstracts cyanide from the surrogate, and the resulting Wheland complex protonates the alkene substrate. The success of the cyanide transfer from the in-situ-generated isocyanoborate to the carbenium-ion intermediate largely depends on the borate's propensity to isomerize to the cyanoborate. In agreement with a cationic mechanism, BCl_3- or $(C_6F_5)_2BCl$-catalyzed addition of HCN across the 1,1-di- and trisubstituted alkenes occurs with Markovnikov selectivity to afford tertiary nitriles.

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Keywords: alkenes • boron • hydrocyanation • homogeneous catalysis • Lewis acids

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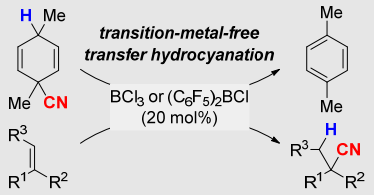

Acid-free! Bench-stable cyclohexa-1,4-diene-based hydrogen cyanide (HCN) surrogates are reported to engage in transfer hydrocyanation of alkenes by treatment with certain boron Lewis acids. The success also depends on the equilibrium position between the intermediate isocyano- and cyanoborate isomers. Tertiary nitriles are obtained with exclusive Markovnikov selectivity (see scheme).

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