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Radical Reactions of *N*-Heterocyclic Carbene Boranes with Organic Nitriles: Cyanation of NHC-Boranes and Reductive Decyanation of Malononitriles

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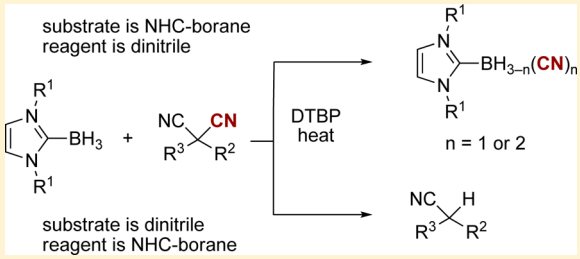
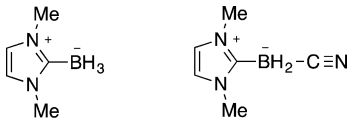
Supporting Information

ABSTRACT: The observation that NHC-boryl radicals abstract cyano groups from various organic nitriles has been parlayed into two complementary transformations. In the main group chemistry aspect, reactions of various NHC-boranes with simple organic dinitriles selectively provide stable NHC-boryl mono- or dinitriles, depending on the nitrile source. In the organic synthesis aspect, reaction of malononitriles and related derivatives with readily available 1,3-dimethylimidazol-2-ylidene borane provides reductively decyanated products in good yields.



INTRODUCTION

N-Heterocyclic carbene boranes (NHC-boranes) are stable compounds that nonetheless have a diverse reaction chemistry that centers around the boron atom and its substituents.[1] They are increasingly useful reagents in organic synthesis because they are easy to handle and because their derived byproducts are readily removed. In radical chemistry (Figure 1), NHC-boranes such as 1,3-dimethylimidazol-2-ylidene borane **1** are hydrogen atom donors that have been used as tin hydride substitutes for various reductions[2] and as co-initiators in photopolymerizations.[3]



1 **2**

Figure 1. Left, 1,3-dimethylimidazol-2-ylidene borane **1**, a useful radical hydrogen atom donor and NHC-boryl radical precursor. Right: 1,3-dimethylimidazol-2-ylidene cyanoborane **2**, first isolated as a minor product from some AIBN-initiated radical reactions. Formal charges are shown on these structures but omitted on subsequent structures.

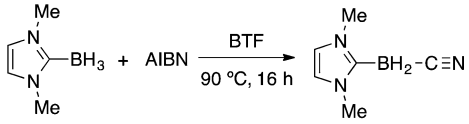
During a study of radical reactions of NHC-borane **1** initiated by azobis(isobutyronitrile) (AIBN), we observed the unexpected formation of NHC-boryl nitrile **2**. Here we describe the discovery of a new cyano group abstraction reaction by NHC-boryl radicals and its application in two complementary directions. From the vantage point of main group chemistry, we report a general method to prepare NHC-boryl cyanides and dicyanides, rare and potentially interesting classes of compounds. From the vantage point of organic synthesis, we report a general way to reductively decyanate malononitriles and related molecules. This is an otherwise difficult reaction; organic nitriles are not typically considered radical precursors.

RESULTS AND DISCUSSION

Reaction Discovery. During some attempted radical hydroboration reactions of unsaturated amides, we isolated by flash chromatography small amounts of a new compound when the column was flushed with 100% ethyl acetate. This compound was tentatively identified by ^{11}B NMR spectroscopy (triplet at −37.8 ppm in $CDCl_3$, J_{B-H} = 92 Hz) and high resolution mass spectrometry as NHC-boryl nitrile **2**. The only possible nitrile precursor in these reactions was AIBN, so this must be the source of the nitrile in **2**, either directly or indirectly.

To verify that boryl nitrile **2** is formed from **1** and AIBN or its thermal decomposition products, we heated **1** and increasing amounts of AIBN in benzotrifluoride ($C_6H_5CF_3$) at 90 °C for 16 h, as shown in Scheme 1. The half-life ($t_{1/2}$) of AIBN under

Scheme 1. Isolated Yields of NHC-Boryl Nitrile 2 in Reactions of 1 with AIBN



1, 1 equiv **2**

AIBN	recovered **1**[a]	yield **2**[a,b]
0.2 equiv	92%	8%
1 equiv	53%	25%
2 equiv	trace	53%

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these conditions is less than 1 h,[4] so no AIBN remains at the stop time. Solvent evaporation and direct flash chromatography of the residue provided nitrile **2** in yields that increased from 8%, to 25%, to 53% as the amount of AIBN increased from 0.2 equiv, to 1 equiv, then finally 2 equiv.

The yield of recovered **1** decreased in parallel with the increase in **2**; only a trace of **1** remained after the reaction with 2 equiv of AIBN. The yield of **2** calculated from converted **1** is consistently about 50% under these conditions. The yield of **2** calculated from the nitrile groups of AIBN on a per-nitrile group basis (AIBN has two nitrile groups) is consistently about 13%.

Substituted boranes NHC-BH_2X are usually robust compounds if the pK_a of the corresponding acid HX is above about 4.[5] The pK_a of HCN is about 9, and indeed **2** is a white solid, mp 101−102 °C, that is neither water- nor air-sensitive. Conversely, if the pK_a of a given acid HX is less than about 2, then an acid/base reaction occurs between NHC-BH_3 and HX to make NHC-BH_2X (and H_2). Thus, boryl nitrile **2** cannot be made by direct acid/base reaction of **1** and HCN. This rules out oxidative degradation of AIBN (via acetone cyanohydrin, for example) as a cyanide source for **2**.

The source of the nitrile in **2** could be AIBN itself or one of the thermal decomposition products of AIBN. The thermal decomposition of AIBN is more complex than generally appreciated, having both in-cage and out-of-cage components.[4] Initial decomposition forms two isobutyronitrile radicals and N_2 in a cage. Cage escape is reasonably efficient, and about 60−70% of the isobutyronitrile radicals are released as free radicals in solution. These in turn are expected to abstract a hydrogen atom from **2** to form an NHC-boryl radical **3** in competition with termination as shown in Figure 2, step (1).

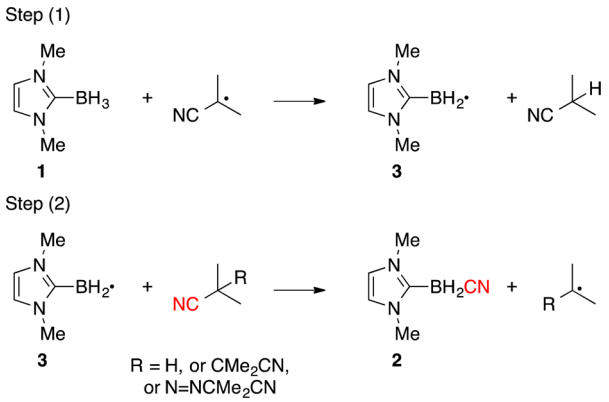
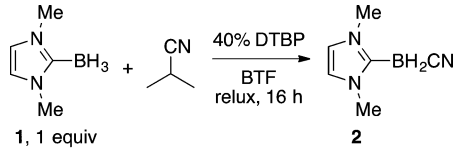


Figure 2. Suggested formation and cyano transfer reactions of NHC-boryl radical **3**.

Thus, the major (but not only) thermal decomposition product of AIBN in the presence of **2** is expected to be isobuyronitrile (R = H). The in-cage recombination products of AIBN are tetramethylsuccinonitrile ($Me_2C(CN)C(CN)Me_2$) and to a lesser extent its isomer $Me_2C(CN)N{=}CMe_2$.[4] Reaction of any of these nitrile-containing compounds with NHC-boryl radical **3** can result in boryl transfer to give **2** and the corresponding radical as shown in Figure 2, step (2). If the radical of step (2) also abstracts hydrogen from **1**, then this is a chain reaction in which AIBN is both the initiator and the (direct or indirect) source of the nitrile.

To test the notion that isobutyronitrile is a competent cyano source, NHC-borane **1** and isobuyronitrile were heated at reflux in benzotrifluoride (bp 103 °C) with di-*tert*-butylperoxide (DTBP, 40 mol %) as a radical initiator. DTBP was chosen because *tert*-butoxy radicals abstract hydrogen atoms rapidly from NHC-boranes.[6] As shown in Scheme 2, the isolated yield

Scheme 2. Isolated Yields of 2 with Increasing Amounts of Isobutyronitrile as the Cyano Source



Me_2CHCN	yield **2**
2 equiv	25%
5 equiv	52%
10 equiv	61%

of **2** increased from 25% with 2 equiv of isobutyronitrile to 52% with 5 equiv, to 61% with 10 equiv. No reaction took place without the DTBP. The experiment with 2 equiv of isobutyronitrile in Scheme 2 gives about the same yield of **2** (25%) as the comparable experiment with 1 equiv of AIBN in Scheme 1.

We also conducted a series of NMR experiments to evaluate the relative performance of acetonitrile, propanenitrile, and 2,2-dimethylpropanenitrile (*tert*-butyl cyanide) as nitrile sources. To determine the yields, 1,1,2,2-tetrachloroethane was added as an internal standard after the reactions were completed. Under standard conditions with 10 equiv of nitrile source, propanenitrile and 2,2-dimethylpropane nitrile gave about half the yield of **2** as isobutyronitrile (NMR yields of 34% and 35% compared to 61%). In contrast, acetonitrile was a poor nitrile donor. Even when it was used a cosolvent (25 vol %, 38 equiv, sealed tube at 120 °C), the estimated yield of **2** by NMR spectroscopy was only 5%.

These results show that isobutyronitrile is a viable cyano source for **2** (without ruling out the coparticipation of AIBN or its other thermal degradation products). They also show that the substituent on the nitrile is important in regulating its ability to transfer a cyano group.

Synthesis of Mono- and Dicyano-NHC-Boranes by Radical Cyanation with Alkane Dinitriles. Because of the scarcity of NHC-borane nitriles,[7] we first targeted this cyano-transfer reaction for the synthesis of new members of the class. Figure 3 shows the three members that preceded **2**, a mononitrile and dinitrile pair made by us (left)[5] and Bertrand's dinitrile (right).[8] Interestingly, Bertrand's dinitrile can be deprotonated by KHMDS to make a boryl anion.[8]

The isolation of **2** suggests that the steric protection afforded by the bulky NHC substituents in the compounds in Figure 3 is not essential for stability of boryl nitriles. Steric protection is

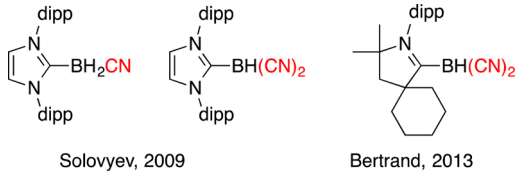


Figure 3. Structures of three known NHC-boryl nitriles (dipp is 2,6-diisopropylphenyl).

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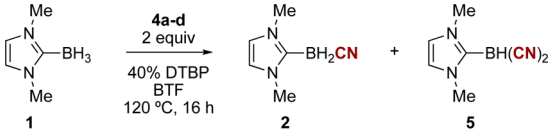
important for other kinds of B-functionalized NHC-boranes. For example, the azide and chloride derivatives of bis-1,3-(2,6-diisopropylphenyl)imidazol-2-ylidene borane are much more stable than the corresponding chloride and azide derived from the smaller 1,3-dimethyl analogue **1**.[9]

These compounds in Figure 3 were made from the corresponding NHC-boranes by reaction with (expensive) triflic acid and (toxic) sodium cyanide. The intermediate boryl triflates are sensitive molecules that must be handled with care. A direct radical substitution reaction that converts B−H bonds to B−CN bonds could be a considerable improvement.

Hypothesizing that the transformation would benefit from polarity matching of the nucleophilic NHC-boryl radical[6b,10] with an acceptor more electrophilic than isobutyronitrile, we studied the reactions of NHC-borane **1** with a series of alkane dinitriles, with key results summarized in Scheme 3. Under

Scheme 3. Reactions of 1 with a Series of Alkane Dinitriles under Standard Conditions



number	dinitrile structure	yield **2**	yield **5**
4a	NC CN	8%	57%
4b	NC CN	66%	tr[a]
4c	NC CN	66%	tr[a]
4d	NC CN	33%	nd[b]

[a]Trace amount detected by ^{11}B NMR spectroscopy, but not isolated. [b]Not detected.

standard conditions, NHC-borane **1** (1 equiv), an alkanedinitrile **4a−d** (2 equiv), and DTBP in BTF were heated at 120 °C in a sealed tube for 16 h, followed by cooling, solvent evaporation, and flash chromatography.

The reaction of **1** with malononitrile **4a** (propanedinitrile) gave a new surprise: the expected boryl nitrile **2** was the minor product (8%), while the major product was the more polar dinitrile **5** (57%). Again **5** is a while solid, mp 182−183 °C. It survives silica chromatography and is not apparently air- or water-sensitive. Reactions with succinonitrile **4b** (butanedinitrile) and glutaronitrile **4c** (pentanedinitrile) with **1** selectively gave the monocyanoborane **2** (66% yield in both cases). Traces of dicyanoborane **5** (<5%) were detected in the crude products by ^{11}B NMR spectroscopy but not isolated. The isolated yield of **2** decreased to 33% when adiponitrile **4d** (hexanedinitrile) was used. No dicyanoborane was detected by ^{11}B NMR analysis in this last experiment. The results with adiponitrile are roughly comparable to those with isobutyronitrile, but the other dinitriles all gave improved yields.

Based on these results, we selected malononitrile **4a** to make boryl dinitriles and succinonitrile **4b** to make boryl mononitriles. The structures and yields of the products of reactions of three other NHC-boranes with this pair of nitrile sources under the standard conditions are shown in Figure 4. Reaction of 1,3,4,5-tetramethylimidazol-2-ylidene borane with succinonitrile **4b** gave 63% of mononitrile **6** alongside 7% of

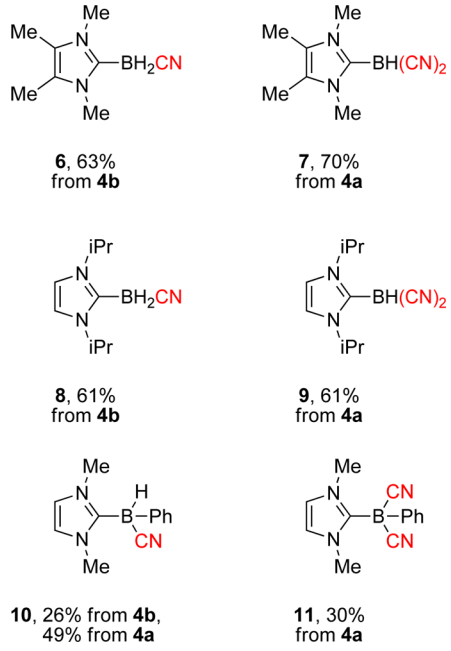


Figure 4. Structures and isolated yields of six new cyano and dicyanoboranes formed under standard conditions: 2 equiv of malononitrile **4a** or succinonitrile **4b**, 20% DTBP, BTF, 120 °C for 16 h.

dinitrile **7**. Malononitrile reversed the product ratio, now giving 70% **7** along with 20% **6**. Similar results were obtained with 1,3-diisopropylimidazoyl-2-ylidene borane. This gave 61% of monocyano borane **8** with **4b** and 61% yield of dicyanoborane **9** with **4a**.

The B-substituted substrate, 1,3-dimethylimidazoyl-2-ylidene phenylborane, was somewhat less reactive than the parent boranes, but exhibited the same trend. Reaction with succinonitrile **4b** gave *B*-cyano-*B*-phenyl borane **10** in 26% yield with no apparent dinitrile **11**. Reaction with malononitrile **4a** now increased the yield of **10** to 49% and also provided 30% of the fully substituted *B*,*B*-dicyano-*B*-phenyl borane **11**.

All of these nitriles are stable, sharp-melting white solids that are easy to handle and store. Crystal structures of three representative compounds, BH_2-mononitrile **2**, BH-phenyl nitrile **10**, and dinitrile **5**, were solved, and the ORTEP representations are shown in Figure 5. These structures confirm the assignments made by ^{11}B NMR spectroscopy that the compounds are boryl nitriles (with a B−C bond), not isomeric boryl isonitriles (with a B−N bond).

To summarize this aspect, the radical cyanation and decyanation of NHC-boranes by alkane dinitriles is a practical route to heretofore rare NHC-boryl nitriles and dinitriles. These compounds are stable and easy to handle, so the door is now ajar to further exploration of their chemistry.

Reductive Decyanation of Malononitriles by NHC-Boranes. In the main group chemistry perspective of this transformation, the NHC-borane is the substrate and the organic nitrile is the reagent. Shifting the focus to organic synthesis, the roles of the two reaction components reverse; the NHC-borane now becomes the reagent, and the nitrile is the substrate. Malononitrile was the most efficient donor to make boryl nitriles, suggesting that substituted malononitriles would be good substrates for reductive decyanations.

The use of nitrile groups as radical precursors in synthesis is rare, and there are only three reports of reductive radical

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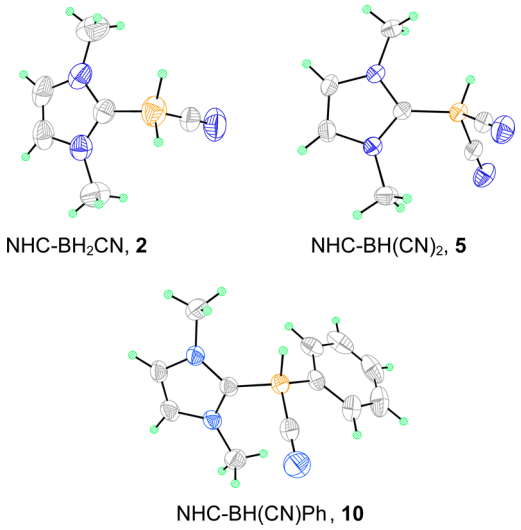


Figure 5. ORTEP representations of X-ray crystal structures of NHC-boryl nitriles **2**, **5**, and **10**.

decyanations of malononitriles, as summarized in Figure 6. Twenty-five years ago, Seong in our group discovered that

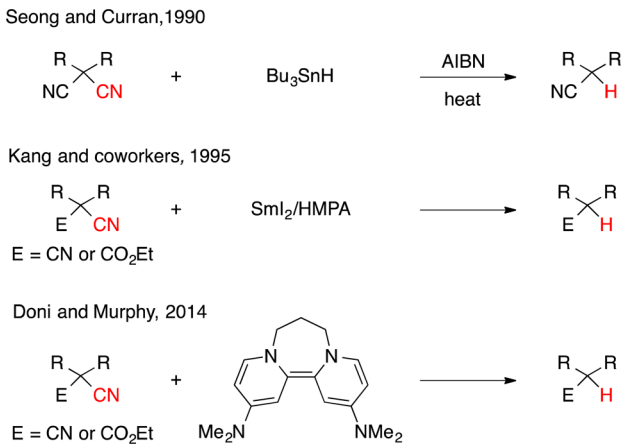


Figure 6. Reductive decyanations of malononitriles and related molecules are valuable but uncommon transformations.

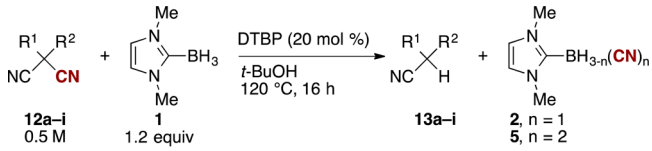
tributyltin hydride could induce reductive decyanations of some geminal dinitriles.[11] There is still no tin-free alternative to this reaction, despite the many tin hydride replacements that have been introduced.[12]

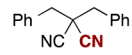
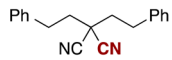
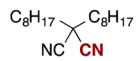
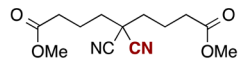
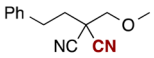
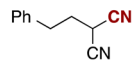
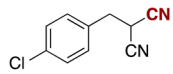
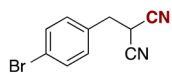
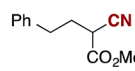
In a complementary approach, reductive decyanations with powerful reductants under electron transfer conditions have also been described. Kang and co-workers used samarium diiodide and HPMA in 1995,[13] while Doni and Murphy modernized this transformation last year with organic super electron donors.[14] No metal or HMPA is needed in these reactions. These electron transfer reactions provide products by protonation of anions, while the tin hydride reaction provides products by radical hydrogen atom transfer. Thus, 2 equiv of the electron transfer agents are needed compared to 1 equiv of tin hydride.

We selected NHC-borane **1** as the reagent for this transformation because it is one of the simplest and therefore lightest NHC-boranes (110 g mol^{-1}, roughly two-thirds lighter than Bu_3SnH). It is a solid that is readily available, stable, and easy to handle. Finally, we expected that the reagent-derived NHC-boryl nitrile product **2** would be easy to remove from target products due to its polarity, an expectation that was borne out in practice.

The results of a series of preparative reductive decyanations are summarized in Table 1. The general procedure is similar to

Table 1. Isolated Yields from Preparative Reductive Decyanations of Malononitriles



entry	12a	series	yield [a] 13	2 [b]	5 [b]
1		a	87%	84%	trace
2		b	97%	90% [c]	7% [c]
3 [d]		c	91%	82%	trace
4 [d]		d	94%	82%	trace
5 [d]		e	74%	82%	trace
6		f	96%	80% [c]	10% [c]
7		g	93%	91%	8% [c]
8 [e]		h	80%	66%	12% [c]
9 [d,f]		i	72%	72%	trace

[a]Isolated yield. [b]Yields were based on **1**. [c]NMR yield was determined using 1,1,2,2-tetrachloroethane as an internal standard. [d]**1** (1.5 equiv) and DTBP (40 mol %) were used. [e]$PhCH_2CH_2CN$ was also obtained in 5% yield. [f]**13f** was also obtained in 12% yield.

that for boryl nitrile synthesis except that now the malononitrile is the limiting reagent. In a typical example (entry 1), a 0.5 M solution of malononitrile **12a**, NHC-borane **1** (1.2 equiv), and DTBP (20 mol %) in *tert*-butanol was refluxed for 16 h, followed by cooling, solvent evaporation, and direct flash chromatography. Elution with hexane/EtOAc 97/3 provided the target nitrile **13a** in 87% yield and good purity. Changing the eluent to EtOAc then provided cyanoborane **2** in 84% yield. There was also a trace of dicyanoborane **5** in the crude product according to ^{11}B NMR analysis, but we did not target this for isolation.

The yields of the target products **13b–i** were also good to excellent, ranging from 72% for the half-malononitrile **13i** (entry 9) up to 97% for **13b** (entry 3). Roughly comparable amounts of boryl nitriles were formed in each case. The dialkylated malononitriles gave boryl mononitrile **2** (82–90%) with only traces of dinitrile **5** (entries 2–5). The monoalkylated

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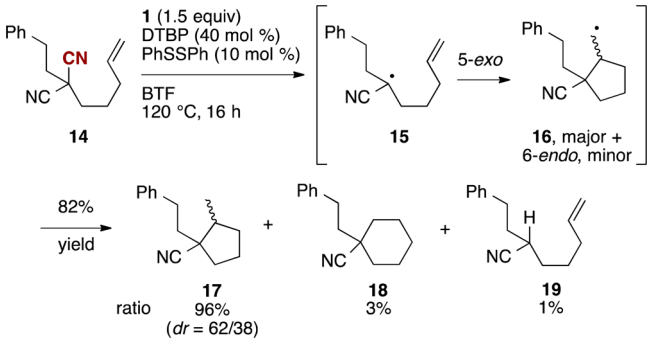
malononitriles still gave mainly **2** (66–91%), but increased amounts of the dinitrile **5** (8–12%) were produced. As an aside, these results also show that disubstituted malononitriles provide yields of monoboryl nitrile **2** that are comparable to or better than succinonitrile under these conditions.

Several of the substrates in Table 1 were selected because they are problematic under conditions currently available. Products **13d** and **13e** are not formed in reductions of **12d** and **12e** with superelectron donors, presumably because intermediate radicals are reduced to anions. In turn, these anions are susceptible to reactions like Dieckmann condensation and β-elimination.[14] Reductions of **12d** and **12e** with **1** occur through radicals not anions, and the expected radical products **13d** and **13e** are formed in good yields (94% and 74%, entries 4 and 5).

Aryl chlorides and more interestingly aryl bromides also survive the reductive decyanation, as shown by the synthesis of **13g** and **13h** (93% and 80% yields, entries 7 and 8), though 5% of the reductively debrominated side product from **13h** was isolated. In contrast, tributyltin hydride reductively debrominates **13h** leaving the malononitrile intact. Further, tributyltin hydride does not react with half-malononitrile **12i**,[11] while the NHC-borane reduces it to ester **13i**.

Finally, to show that the radical intermediates in the reductive decyanation can be used for carbon–carbon bond formation, we synthesized a malononitrile **14** whose derived radical is poised for 5-*exo* cyclization (Scheme 4). Reaction of

Scheme 4. Formation of Radical Cyclization Products

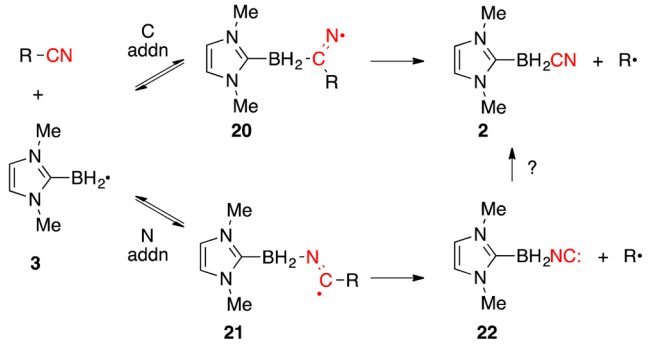


14 and **1** under the standard conditions was rather sluggish, a result that we expected. The sluggishness is caused because the alkyl radical **16** resulting from cyclization of **15** may not react that rapidly with NHC-boranes.[15] Thus, reactions like termination or 1,6-cyclization to the phenyl ring may break chains.[16]

This problem was solved by adding 10% diphenyl disulfide to form thiophenol, a polarity reversal catalyst, in situ.[17] Now reduced products **17**, **18**, and **19** were formed in a combined isolated yield of 82%. The major component by far was the 5-*exo* cyclized product **17** (96%), which was a 62/38 mixture of diastereomers. Minor components were the 6-*endo* cyclized product **18** (about 3%) and the directly reduced product **19** (about 1%). These compounds were separated by HPLC prior to complete characterization.

Mechanism. Figure 7 shows a radical chain mechanism for these reactions that comprises either nitrile or isonitrile abstraction to form an organic radical R$^\bullet$, followed by hydrogen transfer from NHC-borane **1**. Nitrile abstraction occurs by addition of the boryl radical on the nitrile carbon to form nitrogen-centered radical **20**, followed by β-fragmentation. In contrast, isonitrile abstraction occurs by addition of the boryl

(a) nitrile or isonitrile group transfer reaction



(b) hydrogen atom transfer reaction; polarity matched if R• is an α-cyano radical

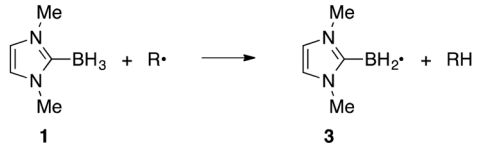


Figure 7. Suggested propagations steps in a radical chain mechanism are nitrile/isonitrile abstraction (by addition/elimination) and hydrogen transfer.

radical on nitrogen to form carbon-centered radical **21**, then α-fragmentation. If the isonitrile abstraction is occurring, then the resulting boryl isonitrile **22** must rearrange to the observed boryl nitrile product **2**.

We suggested in 1990 that tin hydride reductive decyanations probably occur by addition of the tin radical to nitrogen.[11] However, the evidence with boryl radicals points more to addition of the boryl radical to carbon. Roberts observed nitrogen-centered radicals by EPR spectroscopy when borohydride ($BH_3^{\bullet-}$) and cyanoborohydride ($BH_2CN^{\bullet-}$) radical anions were generated in acetonitrile.[18] These borohydride radical anions and NHC-boryl radicals are both nucleophilic, so their addition to the electrophilic carbon of the nitrile is polarity matched.

Supporting the importance of the polar effects in these reactions with NHC-boranes, the more electrophilic dinitriles give better yields of boryl nitriles than simple alkane nitriles. Compare the results of isobutyronitrile (Scheme 2) or adiponitrile **4d** with succinonitrile **4b**, for example. These all produce alkyl radicals on fragmentation, but succinonitrile gives the best yields. Malononitrile **4a** gives even better yields (it even affords the boryl dinitriles), but here the fragmentation step may also be a factor (a resonance stabilized α-cyano radical is formed).

The isolation of the NHC-boryl nitrile **2** rather than the isonitrile **22** also supports the nitrile abstraction path. The one known NHC-boryl isonitrile, bis-1,3-(2,6-diisopropylphenyl)-imidazol-2-ylidine borane isonitrile,[5] is a stable compound and does not rearrange to the derived nitrile at room temperature. Still, this only shows that the rearrangement of a rather hindered boryl isonitrile to the boryl nitrile is not facile. It does not exclude such a rearrangement at the higher temperatures in the less hindered series studied here.

The addition of the boryl radical to the nitrile is potentially reversible, whether it occurs on carbon or nitrogen. Further, when the carbon-centered radical resulting from onward fragmentation is not stable enough, the fragmentation becomes the limiting step. This is shown by the poor results with

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acetonitrile (whose adduct would fragment to give a methyl radical) compared to isobutyronitrile and the dinitriles. An important upshot of these observations is that acetonitrile might not be a good solvent for slower reactions of boryl radicals because it could function as an inhibitor.

Finally, polar effects probably also aid the hydrogen abstraction step when malononitriles are used as substrates. Here α-cyano radicals are formed on fragmentation of the adduct radical **20** or **21** ($R^{\bullet}$ in Figure 7 is $R^1R^2C(^{\bullet})CN$). Here there is matching between the electrophilic α-cyano radical and the nucleophile NHC-borane. This is shown by the poor performance of cyclizable probe substrate **14** when the thiol catalyst is not present. In this reaction, the α-cyano radical **15** cyclizes promptly to an alkyl radical **16**. This degrades chain propagation because it does not react as readily with the NHC-borane.

CONCLUSIONS

In summary, we have discovered that NHC-boryl radicals abstract cyano groups from various organic nitriles and dinitriles. From the standpoint of main group chemistry, we parlayed this reaction into a synthesis of an assortment of new NHC-boryl nitrile and dinitrile compounds, heretofore rare classes of compounds. Access to these compounds allows further exploration of their chemistry.

From the standpoint of organic synthesis, we have parlayed the reaction into a reductive decyanation of malononitriles and half-malononitriles. Here a nitrile group is used as a radical precursor. This is a valuable but uncommon transformation, and the scope of substrates that can be decyanated has been expanded over prior methods. The method is attractive because the reagents are readily available and environmentally friendly, and because reaction and isolation procedures are simple.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization data, copies of NMR spectra, and cif files of the X-ray structure data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04677.

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Notes

The authors declare no competing financial interest.

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