

N-Heterocyclic Carbene Boryl Iodides Catalyze Insertion Reactions of N-Heterocyclic Carbene Boranes and Diazoesters

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Supporting Information

ABSTRACT: Boron-hydrogen bond insertion reactions of Nheterocyclic carbene (NHC) boranes and diazoesters can be catalyzed by NHC-boryl iodides and produce stable α -NHC-boryl esters. The conditions of the reaction resemble the previous rhodium-catalyzed transformations (only the catalyst is different); however, the mechanisms of the two reactions are probably very



different. The new boryl iodide catalyzed method is adept at producing α -substituted- α -NHC-boryl esters, and this has led to a family of NHC-boryl esters with amino acid and amino-acid-like side chains.

Various Rh and Cu salts catalyze the B–H bond insertion reactions of ligated boranes 1 with α -diazo carbonyl compounds 2 (esters, ketones, amides).¹ The products of these reactions are stable ligated α -boryl carbonyl compounds 3 (Figure 1a).² The borane ligands (L) in these reactions must be tightly



Figure 1. Metal-catalyzed reactions of ligated boranes with diazo-carbonyl compounds.

bound—amines, pyridines, phosphines, or N-heterocyclic carbenes—so that reactive boranes are not released during the reaction or purification. Transient metal carbenes are presumed to be catalytic intermediates, as evidenced by asymmetric induction with chiral ligands.^{2,3} These B–H insertion reactions are faster than typical CH insertions, and the ligated boranes are thought to donate a hydride to the metal carbene.^{1a,3} Carbenes generated in other ways also react with ligated boranes.³

In the NHC-borane series, treatment of dimethylimidazol-2ylidene borane 4 and assorted diazoacetates 5 with 1% Rh₂(esp)₂⁴ provides stable α -NHC-boryl esters 6 in varying yields (Figure 1b).¹ The yields tend to be good (60–75%) for unsubstituted diazoesters and for diazoesters substituted with aryl groups or electron-withdrawing groups. However, alkyl-substituted diazoesters provide the corresponding α -NHC-boryl esters in low yields (<30%). In the absence of metal catalysts, diazoesters can function as nucleophiles on carbon.⁵ Ethyl diazoacetate, for example, is a weak neutral nucleophile with an *N* value of 4.91 on the Mayr scale.⁶ Trivalent boranes typically react with diazoesters by addition and 1,2-shift,^{5c,7} a pathway not open to ligated (tetravalent) boranes. However, electrophilic borenium ions or their functional equivalents sometimes express borane-like reactivity.⁸ Thus, we wondered whether there was a pathway to boron–hydrogen bond insertion of diazo compounds involving boryl electrophiles as catalysts rather than transition metals.

We initially studied reactions of 1,3-dimethylimidazol-2ylidene borane 4 with ethyl diazoacetate 5a (Scheme 1). These



^aNo reaction occurs without an activator.

two compounds do not react over 1 day in dichloromethane at rt. However, a rapid transformation occurs when substoichiometric amounts of electrophiles or strong acids are added to NHCborane 4 prior to the addition of the diazoester. Scouting reactions were followed by ¹¹B NMR spectroscopy with results shown in Table S1 of the Supporting Information. Substoichiometric amounts of bromine, iodine, triflic acid, and triflimide all produced substantial amounts of insertion product **5a**, while weaker acids such as camphor sulfonic acid did not.

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For preparative reactions, we selected iodine as an activator because it is convenient to handle and reacts quickly and quantitatively with various NHC-boranes to make NHC-boryl iodides.⁹ NHC-borane **4** (1 mmol) was dissolved in dichloromethane (1 mL), and then diiodine (10 mol %) was added. The iodine color dissipated quickly accompanied by bubbling, presumably due the formation of hydrogen gas. After 5 min, the neat diazo compound **5a** (1.2 equiv) was added. Vigorous bubbling ensued, this time due to formation of nitrogen gas. After 1 h, an ¹¹B NMR spectrum of the reaction mixture showed that starting NHC-borane **4** was absent. Present were monoinsertion product **6a** (t, -28.2 ppm) and the corresponding double insertion product NHC-BH(CH₂CO₂Et)₂ (d, -20.3 ppm) in a ratio of about 80/20. Solvent evaporation and flash chromatog-raphy of the residue provided stable α -boryl ester **6a** in 53% yield.

Table 1 summarizes preparative reactions of 5a with other NHC-boranes under the conditions described in Scheme 1. The





^{*a*}Conditions: 1 mmol of NHC-borane, 10% I₂, 1.2 equiv of **5a**, 1 mL of dichloromethane, 1 h at rt.

stable α -boryl ester products were isolated by concentration and direct flash chromatography. Reaction of 1,3-diisopropylimidazol-2-ylidene borane 7 provided **8** in 57% yield (entry 1). Differentially substituted imidazolium boranes **9** (*N*-Me, *N*-iPr) and **11** (*N*-Me, *N*-Bu) provided products **10** and **12** in 50% and 58% yield, respectively (entries 2, 3). 1,3,4,5-Tetramethylimidazol-2-ylidene borane **13** gave α -boryl ester **14** in 37% yield (entry 4), while the corresponding benzimidazole analog **15** gave **16** in 63% yield (entry 5). In contrast to these successes, a reaction with the hindered 1,3-*bis*-(2,6-diisopropylphenyl)imidazol-2-ylidene borane did not give the corresponding insertion product.

Most of the products in Table 1 are new compounds, though benzimidazole NHC-boryl ester **16** has been made by the rhodium-catalyzed reaction in about the same isolated yield.^{1a} In these reactions, the formation of both the boryl iodide and the boryl ester can be conveniently followed by ¹¹B NMR spectroscopy, if desired. Spectra of most reaction mixtures showed that small amounts (roughly 10%) of double insertion products were formed. These are rather polar and were typically not isolated. The exception was entry 4, the reaction of tetramethylimidazol-2-ylidene borane 13. In this case, the ratio of monoinsertion product 14 to the corresponding double insertion product was 66/34 according to the ¹¹B NMR spectrum of the crude product. Thus, the lower yield in entry 4 is due at least in part to over-reaction of the product 14.

Table 2 summarizes the results of a survey of reactions of various diazoesters **5b**–**5k** with readily available NHC-borane **4**.

Table 2. Isolated Yields in Preparative Reactions of NHC-
Borane 4 with Substituted Diazoacetates ^a



^{*a*}Conditions: 1 mmol of 4, 10% I_2 , 1.2 equiv of 5, 1 mL of dichloromethane, 1 h at rt. ^{*b*}25% conversion of 4. ^{*c*}18 h reaction time. ^{*d*}61% conversion of 4.

The diazo esters were chosen to feature natural or common unnatural amino acid side chains, and they were prepared by literature methods.^{1b,10} These are also the types of diazo compounds that gave low yields in the rhodium-catalyzed reactions.^{1a} The reaction products **6b–6k** are unusual boron analogs of amino esters, with the NHC-boryl group replacing the amine. The standard conditions were used (1 mmol NHC-borane, 10% I₂, 1.2 equiv of diazo ester **5**, 1 mL of dichloromethane, 1 h at rt) unless otherwise noted. Yields are reported after concentration and flash chromatography.

Reactions of 4 with 2-diazopropanoates with methyl (5b) and benzyl (5c) esters provided the corresponding NHC-boryl alanine esters 6b and 6c in 68% and 43% yields (entries 1 and 2). Reaction with methyl 2-diazo-3-methylbutanoate 5d gave the boryl valine analog 6d in only 20% yield (entry 3). However, reactions of diazoesters 5e and 5f with phenylalanine and methionine side chains gave 6e and 6f in 71% and 52% yields (entries 4 and 5). The reaction with 5f was slow and was allowed to progress for 18 h before purification.

Diazoesters with natural (unprotected) tyrosine and tryptophan side chains did not provide insertion products in reactions with 4; however, the corresponding methylated analogs 5g and 5h provided protected tyrosine and tryptophan NHC-boryl esters 6g and 6h in 58% and 46% yields (entries 6 and 7). Finally, 2-phenyldiazoacetates with ethyl (5i), 2,6-dimethylphenyl (5j) and 2,6dichlorophenyl (5k) esters provided the corresponding NHCboryl phenylglycines 6i, 6j, and 6k in 64%, 54%, and 26% yields, respectively.

The progress of these reactions was followed by ¹¹B NMR spectroscopy as usual, and in many cases the conversion of 4 was high (90-100%). Exceptions were the lower yielding reactions in entries 3 and 10. These were not plagued by side-product formation. Instead, they seemed to stop with substantial amounts of NHC-borane 4 remaining (75% and 39%, respectively).

Unlike the crystalline NHC-borane starting materials, many α -NHC-boryl esters in Tables 1 and 2 were clear, free-flowing liquids. Exceptions included benzimidazole derivative 16, tryptophan analog 6h, and the two aryl esters 6j and 6k with the phenylglycine motif. Crystals of the tryptophan analog 6h were grown by vapor phase diffusion. The X-ray crystal structure was solved, and the resulting ORTEP diagram is shown in Figure 2.



Figure 2. ORTEP (left) and standard (right) structures of 6h.

This is the first crystal structure of an NHC-boryl ester, and it confirms the assignment of constitution that was made by NMR methods (specifically, the compounds are α -NHC-boryl esters, not isomeric enol boranes). The molecule adopts an extended conformation from the tryptophan ring on the left through to the NHC-ring on the right. This leaves the bond from the chain to the ester (CH–CO₂Me) as gauche to both the CH₂–tryptophan bond on one side and the BH₂–NHC bond on the other side.

The chiral α -boryl esters in Table 2 are of course racemates. However, we expected that the individual enantiomers would resist racemization. To show this, we resolved the enantiomers of 2,6-dichlorophenyl ester 6k on a chiral HPLC column. These enantiomers proved stable to long-term storage.

Figure 3 shows a plausible mechanism for this reaction that is based on analogies between borane (BH_3) and NHC-borenium



Figure 3. A plausible catalytic cycle.

ions (NHC– BH_2^+), both of which are reactive Lewis acids. It is unlikely that free borenium ions are involved in this reaction, but NHC-boranes bearing excellent leaving groups (NHC– BH_2X) exhibit borenium-like reactivity.¹¹

The probable catalyst, NHC–BH₂I **18**, is formed rapidly and quantitatively by the reaction of NHC–BH₃ **17** with I₂ (Figure 3a).^{9a,12} As mentioned above, this reaction can be verified by ¹¹B NMR spectroscopy if desired. One among several possible catalytic cycles¹³ is shown in Figure 3b. Here C-borylation of diazoester **5** with **18** provides an α -NHC-boryl diazonium iodide **19**. By analogy to borane chemistry,⁶ this can undergo a 1,2-hydride shift from B to C with loss of nitrogen. Collapse of the iodide **00**. This can then exchange iodide for hydride with starting NHC-borane **17** to provide the observed α -boryl ester **6** with return of the catalyst **18**. The hydride/iodide exchange reaction has precedent in 1,2-hydroboration reactions of NHC-boranes, which are also catalyzed NHC-boryl iodides and related molecules.^{9b,11c,14}

The viability of the turnover step was probed by independent generation of an iodide like **20** from one of the α -NHC-boryl ester products (Scheme 2). Pure boryl ester **6a** in DCM was treated

Scheme 2. Demonstration That the Proposed Turnover Step Is Competent



with 0.5 equiv of iodine. As expected, rapid bubbling occurred (H_2) and the ¹¹B NMR spectrum showed disappearance of **6a** with formation of boryl iodide **20a**. Next we added excess NHC-borane **4** (10 equiv) to mimic the catalytic conditions. The ¹¹B NMR spectrum after 1 h showed complete conversion of **20a** back to **6a**. Accordingly, the proposed turnover step is competent under the reaction conditions.¹⁵

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In summary, we have discovered that formal B–H insertion reactions of NHC-boranes with diazoesters can be effected by addition of small amounts of diiodine. The diiodine is a precatalyst that reacts rapidly with the NHC-borane to produce an NHCboryl iodide catalyst.⁹ The reactions are easy to conduct and occur rapidly at room temperature. There is no extractive workup, and the mixture is simply concentrated prior to flash chromatography.

Overall, this B-H insertion reaction resembles the previous Rh-catalyzed transformations,^{1a} and even the reaction conditions are very similar (only the catalyst is different). However, the mechanisms of these two reactions are, generally, opposites of each other. In the Rh-catalyzed reactions, the key catalytic species (a rhodium carbene) comes from the diazo ester and reacts directly with the NHC-borane. In this new transformation, the key catalytic species (NHC-BH₂I) comes from the NHC-borane and reacts directly with the diazoester. In the Rh-catalyzed transformation, the NHC-borane serves as a hydride donor in the leading step with a rhodium carbene serving as an electrophile. Then C-B bond formation follows. In the new transformation, C-B bond formation is leading and involves reaction of the boryl iodide as an electrophile with the diazoester as a nucleophile. Then hydride transfer follows. In short, similarities in reaction components and conditions belie major differences.

These different mechanisms suggest that the two types of reactions might have different features, and indeed at this early point this seems to be the case. The two reactions give comparable yields with unsubstituted and α -aryl-substituted diazoacetates. In contrast, the previous Rh-catalysis method looks superior for electron-poor diazoesters (much better yields with diazomalonates, for example) while the boryl iodide catalysis method looks superior for 2-alkyl-subsituted diazoacetates. Building on this feature, we have produced a number of α -NHC-boryl esters with amino acid side chains in the α -position. This paves the way for study of such molecules as analogs of amino acids where the unusual, electron-donating NHC-boryl group replaces the usual, electron-withdrawing amino group. Many boron analogs of amino acids exist, but typically the boron functionality replaces either the carboxy carbon or the α -carbon of the amino acid.¹⁶

Central to the success of this NHC-boryl iodide catalyzed reaction is the ability of NHC-boranes to donate hydride to NHC-boryl iodides and related borenium ion equivalents. This is also a key step in catalyzed hydroboration reactions.¹¹ The upshot is that while NHC-boranes do not react like trivalent boranes, such "borane-like" reactivity can be expressed with a catalyst that either is a borenium ion or reacts like a borenium ion.^{9b-d,11} In turn, reactions of borenium ions loosely resemble those of boranes. For example, we can say that NHC–BH₂I resembles NHC–BH₂⁺ which in turn resembles BH₃. This is a crude analogy to be sure, but perhaps the deep knowledge of borane chemistry can be tapped to discover new catalytic reactions of boryl iodides and related molecules. If so, then NHC-boranes could become especially valuable since they could exhibit either their own innate reactivity or borane-like reactivity, depending on conditions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01777.

Crystal structure (CIF)

Experimental details; characterization data; spectra (PDF)

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The authors declare no competing financial interest.

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