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Metal-catalysed Hydroboration of Amide-containing Styrenes

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Abstract

Hydroboration of alkenes is one of the most important methods for preparing alkylboron reagents. While alkylboronic esters are considered to be functional group compatible reagents, methods to prepare them do not always show the same tolerance. In this work, we explore the hydroboration of amide-containing styrenes using catalysts derived from Cu, Ir and Rh. Tertiary amides were found to be compatible with each method we tested. However, secondary amides, with an acidic NH bond, were only successfully hydroborated with Ir and Rh catalysts, but not the Cu-catalyst. The selectivity of hydroboration was consistent with previous findings, with Cu giving only branched products, Ir giving linear only products, and Rh favouring branched products though with variable regioselectivity. Finally, an amide-containing benzylic boronic ester was successfully used in a range of transformations of the boron group, including Cu-catalysed amination, Suzuki-Miyaura cross coupling, and oxidation.

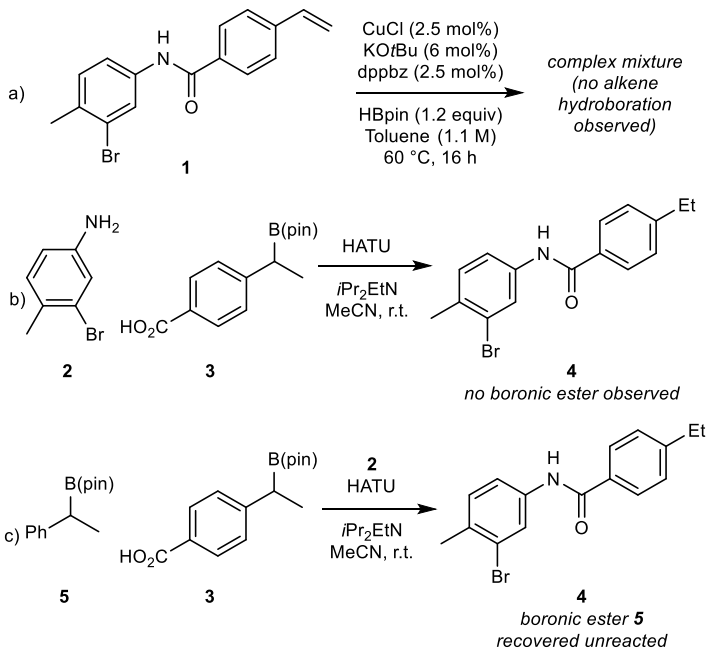
Keywords: boron, catalysis, copper, iridium, rhodium

Introduction:

The hydroboration of alkenes is a classic method to make organoboron reagents. Initially, hydroboration using boranes, such as BH_3, H-9-BBN, and IPC-borane, gave access to alkylborane species, which can be further reacted, predominantly into alcohols and amines.[1,2] A limitation of boranes is that they are generally air and moisture sensitive, and so access to alkylboronic ester are now preferred. Hydroboration of alkenes using pinacol borane (HBpin) can be promoted by a wide range of additives, though often through decomposition of HBpin into BH_3.[3] Metal catalysts, in particular, are advantageous in hydroborations, as they can provide excellent control of both regioselectivity and enantioselectivity.[4]

As part of studies looking at functionalising benzylic boronic esters,[5–7] we have sought to access boronic esters with a wide range of functional groups. The Cu-catalysed hydroboration of styrenes[8,9] developed by Yun and co-workers is one of our methods of choice, due to its reliability, ease of use, and uses an earth abundant first row metal catalyst.

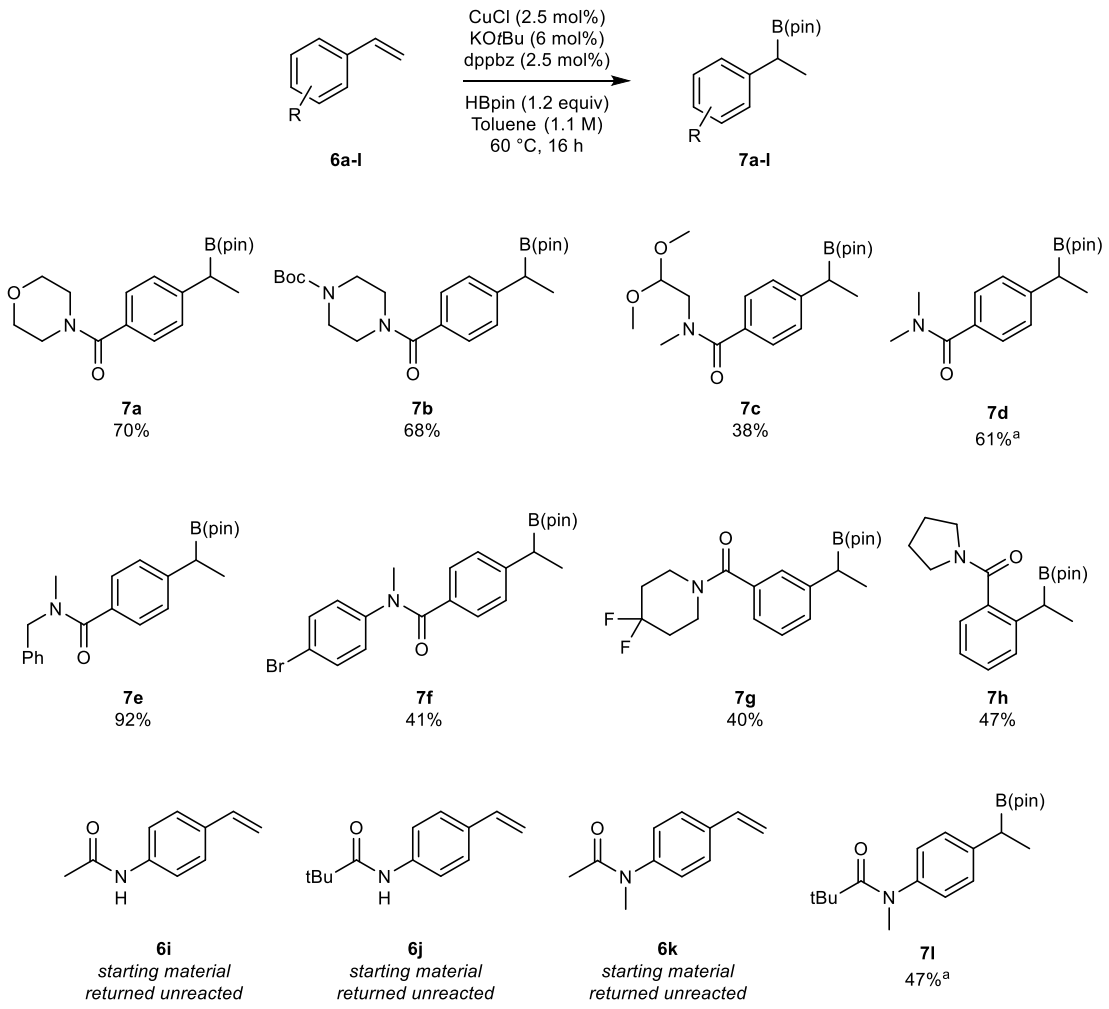
However, when trying to prepare a benzylic boronic ester with an amide group, we found hydroboration was unsuccessful, and a complex mixture was observed. (Scheme 1). Attempts to optimise the reaction, through exploring different ligands, solvents and temperatures were unsuccessful.[10] As an alternative, we looked to form a boronic ester using amide formation from carboxylic acid **3**. While the formation of the amide bond was successful, we found that the boronic ester underwent protoboronation under the reaction conditions to give **4**. A control experiment where boronic ester **5** was added to the reaction showed that **5** was relatively stable to the HATU coupling conditions. These results led us to ask ourselves whether amide-containing benzylic boronic esters are inherently unstable and rapidly undergo protodeboronation,[11] or whether the amide is incompatible with the Cu-catalysed hydroboration.



Scheme 1: Initial attempts to form an amide-containing boronic ester through a) hydroboration, b) amide formation. c) Control to see if benzylic boronic esters are unstable under conditions amide formation. dppbz = 1,2-bis(diphenylphosphino)benzene.

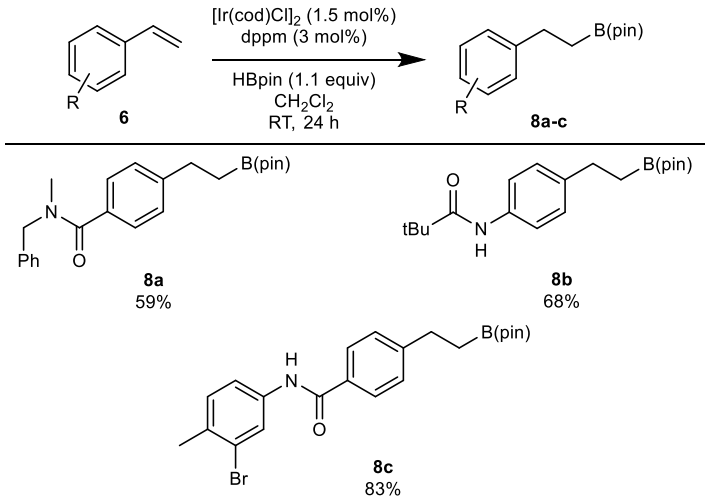
Discussion:

With the aim of probing both the compatibility of the amide group to hydroboration and stability of amide-containing boronic esters, we prepared a series of secondary and tertiary amide-containing styrenes **6a**-**6l**. Using a catalyst derived from CuCl and dppbz,[7] based on the conditions originally reported by Yun and co-workers,[8] we subjected the alkene substrates to hydroboration. Tertiary amides with the carbonyl para to the alkene were found to tolerate the hydroboration conditions, with boronic esters **7a-7f** formed in modest to excellent yield (Scheme 2). Amides formed from both cyclic (**7a**-**7b**) and acyclic (**7c**-**7f**) amines were tolerated. An *N*-aryl amide was also tolerated (**7f**), though the yield of reaction was lower due to competitive protodeboronation of the boronic ester during purification. Having the carbonyl substituent in the meta- (**7g**) and ortho-positions (**7h**) were also tolerated. However, the yield of boronic ester **7g** was low in part due to the styrene showing a tendency to form a polymeric gel during the reaction. In comparison, secondary amides **6i**-**6j**, in addition to **1**, were confirmed to be incompatible with the reaction conditions. An attempt to use an *N*-aryl amide substrate **6k** was also unsuccessful, with unreacted starting material returned. However, changing from an acetamide to a pivalamide did a give a successful substrate for hydroboration (**7l**).



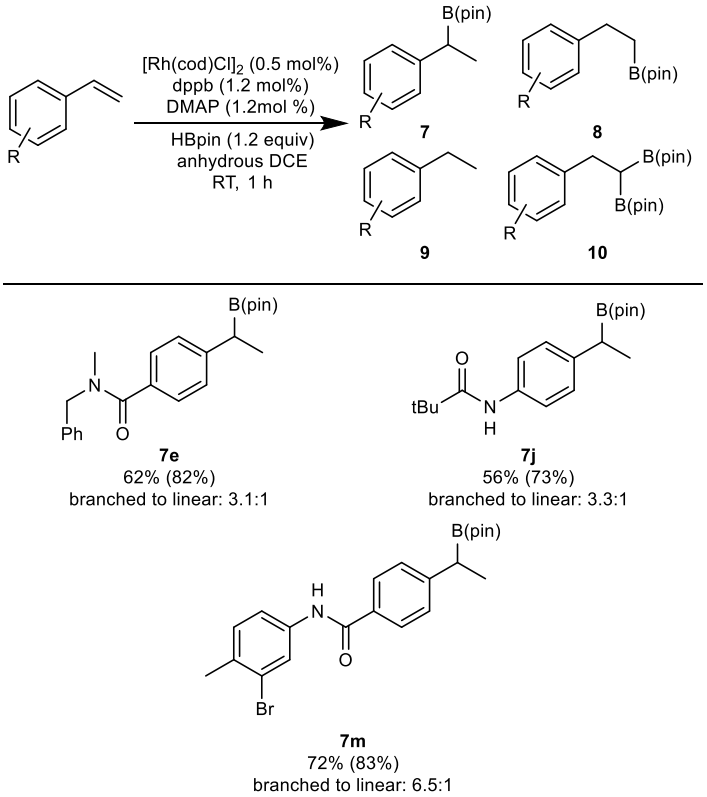
Scheme 2: Cu-catalysed hydroboration of a range of amide-containing styrenes. Yields reported are of isolated material unless otherwise stated. a) NMR yield, using 1,3,5-methoxybenzene as an internal standard. dppbz = 1,2-bis(diphenylphosphino)benzene.

We were interested to compare the Cu-catalysed hydroboration method with complementary Ir-catalysed[12] and Rh-catalysed[13] processes. Using literature conditions from Miyaura and co-workers,[12] alkene **6e** underwent smooth Ir-catalysed hydroboration to give the corresponding linear boronic ester **8a** as the product (Scheme 3). Interestingly, secondary amide boronic esters **8b** and **8c** could also be formed in good yield.



Scheme 3: Ir-catalysed hydroboration of amide-containing styrenes. Yields reported are of isolated material. dppm = Bis(diphenylphosphino)methane.

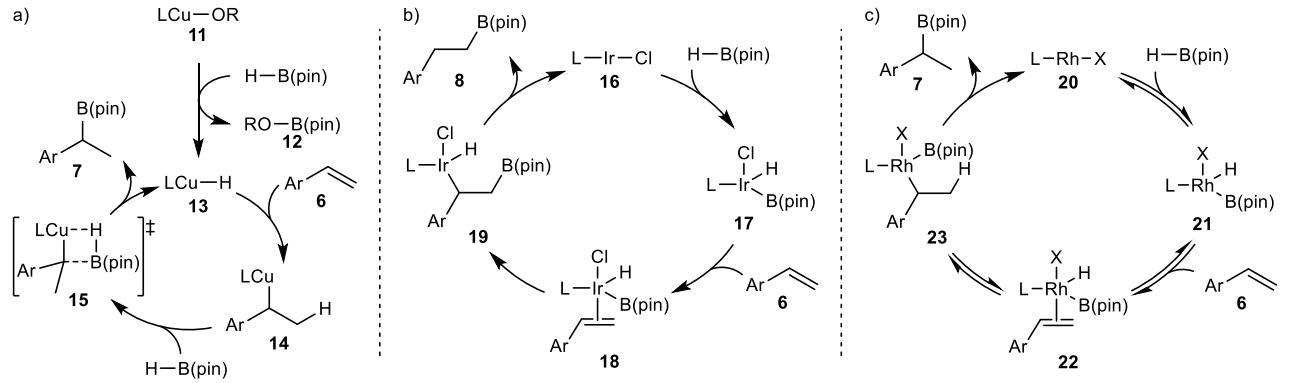
Similarly, Rh-catalysed hydroboration, using conditions reported by Shibata and co-workers,[13] was also successful with alkenes **6e**, **6j** and **1** (Scheme 4). However, in these cases a mixture of branched and linear boronic esters were formed, modestly favouring the branched boronic ester. In the reaction of **1** we also observed formation of the corresponding 2,2-diboronic ester **10**. In all cases alkane **9** made up the mass balance, presumably formed through protodemetallation from either rhodium or boron. The regioselectivity of this reaction has been reported to be sensitive to moisture in the reaction.[14] Attempts to use anhydrous solvent, including from commercial sources, led to an improvement in product specificity in favour of branched boronic ester. However, in our hands, the regioselectivity observed in the reaction of these substrates was not consistently reproducible.[10] Attempts to improve the regioselectivity through trialling a selection of alternative ancillary ligands was unsuccessful.[10]



Scheme 4: Rh-catalysed hydroboration of amide-containing styrenes. Yields reported are of the branched boronic ester determined through ^{1}H NMR analysis using 1,3,5-methoxybenzene as an internal standard. Yields in parentheses are a combination of yields for the branched and linear boronic esters. dppb = Bis(diphenylphosphino)butane.

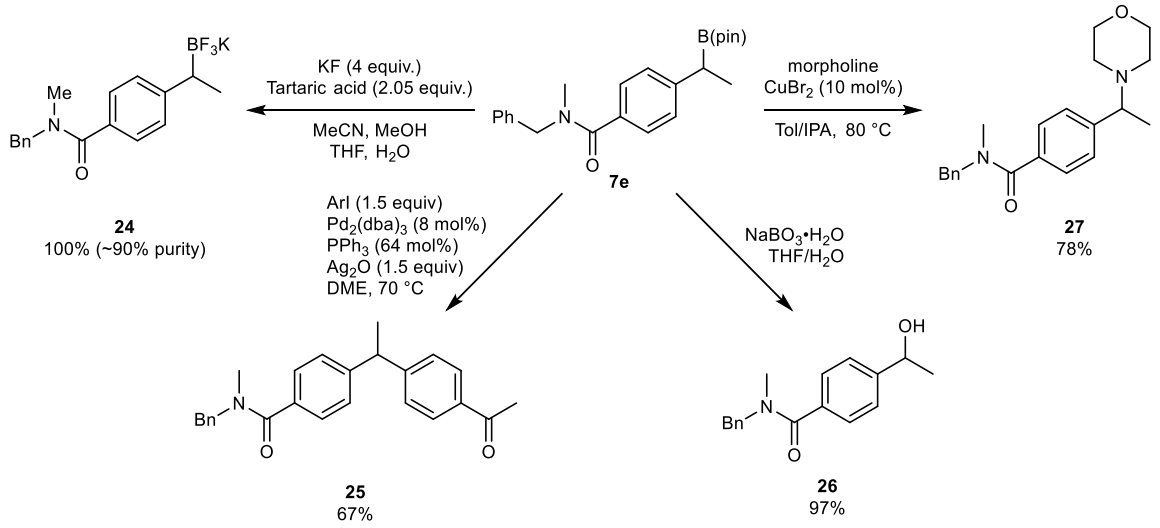
The mechanism of metal-catalysed hydroboration reactions has been widely studied, particularly for Rh-catalysed hydroboration.[4] Unsurprisingly, due to the nature of each metal and the divergence of reactivity, each catalyst is thought to operate under a different general mechanism. The mechanism of Cu-catalysed hydroboration[15,16] is thought to occur through initial transmetallation of an Cu(I) alkoxide complex **11** with pinacolborane to generate Cu hydride **13** and borate **12** as a by-product (Scheme 5). Migratory insertion of complex **13** with a styrene **6** occurs to give alkyl Cu species **14**, with branched regioselectivity thought to arise due charge delocalisation of the Cu-alkyl bond of **14** into the adjacent aryl ring.[15] σ-Bond metathesis (**15**) with pinacol borane give the boronic ester product **7** reforming the activate Cu-hydride catalyst **13**.

In contrast, the reaction of Ir(I) and Rh(I) salts with pinacol borane is thought to occur through oxidative addition, to form the corresponding metal (III) boryl complex (**17** and **21**) which can coordinate to the alkene (**18** and **22**) (Scheme 5). At this point, the mechanism of Rh and Ir catalysts is thought to diverge. In iridium catalysis, it has been proposed that initial migratory insertion of the boryl group[17] in **18** to the alkene occurs to give Ir complex **19**. Reductive elimination to form the C-H bond gives linear boronic ester **8** and reforms Ir complex **16**. In contrast, rhodium is through to undergo migratory insertion of the hydride[13,17] preferentially to give **23**, prior to reductive elimination to give boronic ester **7**. However, hydride insertion when using pinacolborane is thought to be reversible.[18]



Scheme 5: Proposed mechanism for the hydroboration reactions with a) Cu, b) Ir and c) Rh respectively.

To test the synthetic utility of the amide-containing boronic esters, we subjected boronic ester **7e** to a range of reactions of the boronic ester (Scheme 6). Hydroxylation using $NaBO_3$ smoothly occurred in very excellent yield (**26**). Arylation using Pd-catalysed Suzuki-Miyaura conditions[19] from Crudden and coworkers was also successful, giving **25** in 66% yield. Attempts to apply Cu-catalysed amination[5,20] chemistry developed within our group were successful, with the coupling of morpholine occurring in excellent yield (**27**). Finally, formation of trifluoroborate salt **24** was successful.[21] However, due to the poor solubility of **24** in all solvents tested, purification was found to be challenging, with **24** formed in 100% yield but with approximately 90% purity.



*Scheme 6: Exploring the reactivity of boronic ester **7e**.*

Conclusion:

We have found that Cu-catalysed hydroboration of amide-containing styrenes is successful with a range of tertiary amide substrates to give the corresponding benzylic boronic esters. However, secondary amides were found to be incompatible, with the alkene returned unreacted. In contrast, Ir-catalysed hydroboration was successful with both secondary and tertiary amides, giving the corresponding linear boronic ester products. Rh-catalysed hydroboration demonstrated that formation of benzylic boronic esters through the hydroboration of secondary amide-containing styrenes is feasible. However, these reactions were less selective gave a mixture of branched and linear boronic esters, as well as 2,2-diboronic ester and protodeboronation products in some cases. Finally, amide-containing boronic ester **7e** successfully underwent a series of further reactions, including amination, oxidation and Suzuki-Miyaura cross coupling.

Funding Information:

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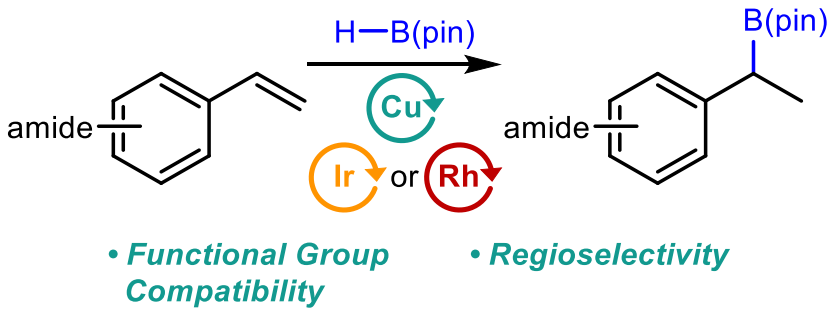

- ***Functional Group Compatibility***
- ***Regioselectivity***