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EMERGING AREA

Catalytic methodologies for the β-boration of conjugated electron deficient alkenes

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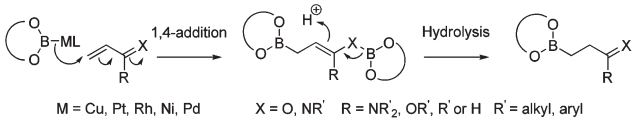
The area of boron conjugate addition *via* diboration (β-boration) has grown rapidly since the first examples appeared in the late 1990s. This article aims to give a comprehensive review of the current advances in β-boration (of electron deficient alkenes), providing a commentary upon the development of the asymmetric version. To date, many mechanistic models have been put forward to explain the experimental observations and this review surveys some of these key ideas. Recently, the development of organocatalytic methodologies that facilitate β-boration have also been demonstrated and current ideas regarding the mechanisms of such processes are examined.

1 Introduction

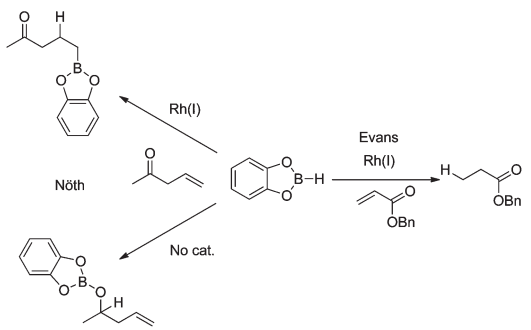
The chemistry of boron is extremely diverse.[1] During the 20th century, chemists unveiled an array of reactions involving boron reagents which demonstrated their utility in organic synthesis. Most notable was the 1997 Nobel prize for Chemistry to H. C. Brown for his work on hydroboration and organoboron chemistry.[2] Hydroboration methodology became of particular interest to synthetic chemists as it allowed the regioselective addition of a boron containing species to the least substituted carbon in olefinic species (*anti*-Markovnikov addition). As a result, the functionalisation at the boron-bearing substituent led to *anti*-Markovnikov-type products. The subsequent transformation of carbon–boron bonds into C–C,[3,4] C–N, C–O, C–X and other transformations[5] have been widely explored[6–8] and organoboron reagents have become key reagents in synthesis.[9–11]

1.1 β-Boration

As part of the endeavour to prepare novel organoboron species, chemists developed a process which is now commonly known as β-boration. This is a process by which a diboron species [*e.g.* B_2pin_2 (pin = $OCMe_2CMe_2O$) **1**, B_2cat_2 (cat = 1,2-$O_2C_6H_4$) **2**, B_2neop_2 (neop = $OCH_2CMe_2CH_2O$) **3**] undergoes a Michael-type addition to an electron deficient alkene, leading to the 1,4-addition adduct, which after work-up, yields the β-boration product (represented by the process outlined in Scheme 1). The first example of this process was reported in 1997 by Marder *et al.*[12] Expanding the known area of metal catalysed diboration of simple alkenes to that of conjugated electron deficient alkenes seemed an attractive prospect.[13] It had been shown previously that the use of a metal catalyst could dramatically modify the chemoselectivity of boron reagents in the presence of substrates with several functional groups. Indeed, Männig and Nöth had demonstrated the hydroboration of simple alkenes using Wilkinson's catalyst ([$RhCl(PPh_3)_3$]) in the presence of other functional groups (Scheme 2).[14] Later, Evans and Fu revealed an elegant conjugate reduction methodology using Wilkinson's catalyst in conjunction with catecholborane (HBcat) (Scheme 2).[15]



Scheme 1 Metal catalysed β-boration (*via* diboration).



Scheme 2 Evans' conjugate reduction and the Nöth hydroboration methodology.

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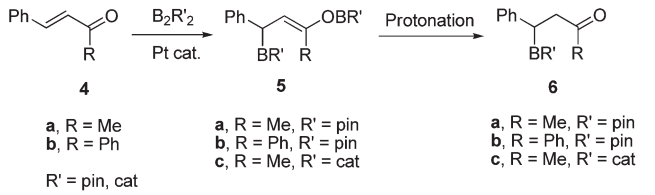
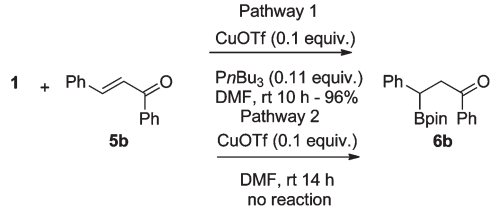
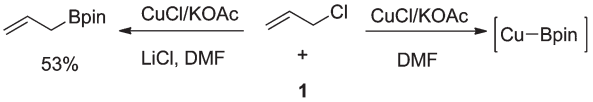


Scheme 3 Diboration followed by aqueous work-up yields β-products **6a–c**.



Scheme 4 Hosomi's Cu-catalysed β-boration protocol for α,β-unsaturated species.



Scheme 5 Evidence for a nucleophilic boron species, as presented by Miyaura *et al.*[22]

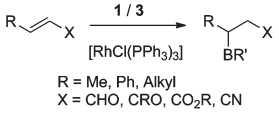
Studies involving the metal catalysed diboration of alkenes were becoming increasingly explored[16,17] due to the products of such reactions finding utility in cross-coupling reactions.[18]

In response to the need for novel routes to organboron reagents, Marder's team demonstrated the diboration of two α,β-unsaturated ketones (**4a** and **4b**) with B_2pin_2 and B_2cat_2 in the presence of a platinum catalysts, $[Pt(C_2H_4)(PPh_3)_2]$ (see Scheme 3). Diboration of α,β-unsaturated ketones **4** yielded the 1,4-diboration product **5**. The addition of water resulted in the β-boration products **6** in stoichiometric conversions. It is interesting to note that there are only two examples in the literature where 1,4-diboration products have been isolated and characterised, likely due to their moisture sensitivity, however, isolation of the 1,4-diboron species also provided valuable mechanistic insights (*vide infra*).[12,19]

These reports also provided a new pathway to β-hydroxy ketones *via* the oxidation of boron functions. Marder *et al.* also noted that reactions between α,β-unsaturated ketones and chiral diboron reagents were possible developments, hinting at the potential of β-boration to be enantioselective, however, it took a further 3 years for this to be developed.

In 2000, Hosomi *et al.* unveiled the first example of a copper-catalysed β-boration on a series of α,β-unsaturated ketones,[20] closely followed by Miyaura *et al.*[21,22] The former report was analogous to their previous work involving the use of disilane reagents, using copper catalysis as a means of introducing silyl substituents into the β-position of electron deficient alkenes.[23] Hosomi's group probed the utility of the copper catalysed system (as developed for use in the disilane case[23]) in the β-boration of chalcone **5b** with B_2pin_2 **1**. Their initial trials failed, however, further attempts showed that the addition of tri-*n*-butylphosphine followed by hydrolysis gave the desired β-boration product **6b** (see Scheme 4). Hosomi *et al.* then probed the optimised of this β-boration methodology using a series of enones, both cyclic and acyclic, resulting in conversions ranging from 67–96%. Interestingly, the reaction was observed to proceed with just the addition of a phosphine ligand, albeit in low yield (7%) (the role of phosphines in β-boration will be discussed later). Miyaura *et al.* further demonstrated the utility of a copper catalysed system[21,22] with the β-boration of a series α,β-unsaturated esters, ketones and nitriles. Interestingly, Miyaura was the first to suggest, and provide evidence for, a boryl-copper species as providing the nucleophilic source of boron in the β-boration reaction.[21] They provided evidence for this by introducing allyl chloride into their copper borane system; the result of which gave an allyl boronate species (Scheme 5). This result is consistent with the assumed presence of a copper–boron species acting as a nucleophilic source of boron.[24] The systems reported by both Hosomi and Miyaura[20–22] had their drawbacks due to relatively high catalyst loadings, especially in the case of Miyaura, who employed stoichiometric amounts of copper. Drawbacks aside, both reports were highly influential in the field and spawned great interest in finding other metal catalysts and more efficient reaction conditions for the β-boration process.

In addition to the work of Hosomi and Miyaura, Kabalka *et al.* demonstrated the use of Wilkinson's catalyst in the β-boration of electron deficient alkenes (esters, ketones and nitriles),[25] as an approach to boronic acids for application in boron neutron capture therapy.[26] They probed the use of Wilkinson's catalyst as a potential means of facilitating the β-boration reaction shown in eqn (1). This work addressed some of the problems associated with the high catalyst loadings reported by Miyaura.[21,22] Typically only 10 mol% of Wilkinson's catalyst was required compared to the stoichiometric copper catalyst loadings in the Miyaura β-boration protocol.[21,22]



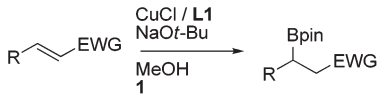
(1)

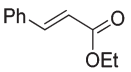
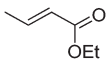
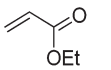
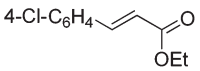
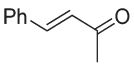
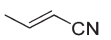
The work of Hosomi *et al.*[20] and Miyaura *et al.*[21,22] were highly influential, however, insufficient activity of their catalytic systems meant applicability was still limited. Yun *et al.* changed this by unveiling a methodology by which a series of α,β-unsaturated esters, ketones and nitriles could undergo β-boration using a copper-based reaction system modified by use of alcohol additives.[27] Yun *et al.* had previously developed an efficient protocol for the conjugate reduction of α,β-unsaturated nitriles[28] using copper catalysis and xanthene-type biphosphine ligands, which were key to improved activity and lower catalyst loadings (Table 1).

When applied to the β-boration reaction, Yun *et al.* showed that xanthene-type biphosphine ligands improved the nucleophilicity of the active copper species (copper-hydride), which resulted in an improved methodology for the chemoselective conjugate reduction of α,β-unsaturated nitriles.[28] Previous evidence[21] suggested that the active copper species in β-boration was a nucleophilic copper-boryl species and hence, Yun *et al.* examined whether the observed increase in nucleophilicity

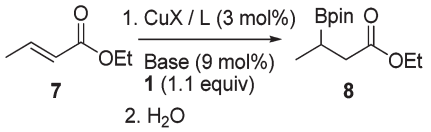
(as observed in the active copper-hydride case) could be applied to the active copper-boryl species in the β-boration of α,β-unsaturated species.[27] They first probed the β-boration of (*E*)-ethyl crotonate **7** using a copper(I) salt, ligand and slight excess of B_2pin_2 [eqn (2)] at RT over 14 h. Their initial attempt used copper(I) acetate and DPEphos **L1** (for all ligands, **L** see Fig. 1) in the absence of base. GC analysis showed a conversion of 26%, which when compared to previous literature examples was poor.[20,21,25] However, by changing to copper(I) chloride with the addition of sodium *tert*-butoxide (9 mol%) the reaction improved and the yield of the β-boration product doubled to 48%. Changing the ligand from DPEphos to Xantphos (**L1** to **L2**, respectively) resulted in a poorer return of the β-boration product. Yun *et al.* had noted in their previous work on the conjugate reduction of α,β-unsaturated nitriles,[28] that the addition of alcohol to their reaction improved yields dramatically. Buchwald *et al.* had shown elsewhere that the addition of ethanol could protonate a copper intermediate and hence, improve reactions yields where the suggested mechanistic pathway proceeded *via* a carbon-bound copper intermediate.[29]

Table 1 Influence of methanol on the β-boration of electron deficient alkenes



Entry	Species	Time (h)	Yield[a,b]
1		11	91
2		14.5	95
3		1.5	98
4		16	93
5		14	95
6		6.5	95

[a] Isolated yield. [b] Reaction conditions: CuCl, 3 mol%; **L1**, 3 mol%; NaO*t*-Bu, 9 mol%; **1**, 1.1 equiv.; MeOH, 2.2 equiv; THF.



Hence, Yun *et al.* used an alcohol additive in their reaction as a means of protonation of the assumed carbon-bound copper intermediate. Indeed, they found that the addition of *tert*-butanol or methanol, dramatically improved yields in their reactions. They found that the use of copper(I) chloride and **L3** (3 mol%), sodium *tert*-butoxide (9 mol%) and methanol (2 equiv.) gave the β-boration products in 98% yield. When methanol was not employed, only 48% product was obtained, highlighting the importance of the alcohol additive. Next, they examined the scope of the β-boration of a series of α,β-unsaturated by probing a series of varied substrates (Table 2). It is clear from Table 2 that the system developed by Yun *et al.* was highly effective and efficient. The dramatic influence of the addition of the alcohol was clear (Table 2 entry 3) giving a higher yields compared to that obtained by Hosomi *et al.* and using a lower catalyst loading (only 3 mol%). Hence, not only was the addition of an alcohol in the copper catalysed β-boration of electron deficient alkenes

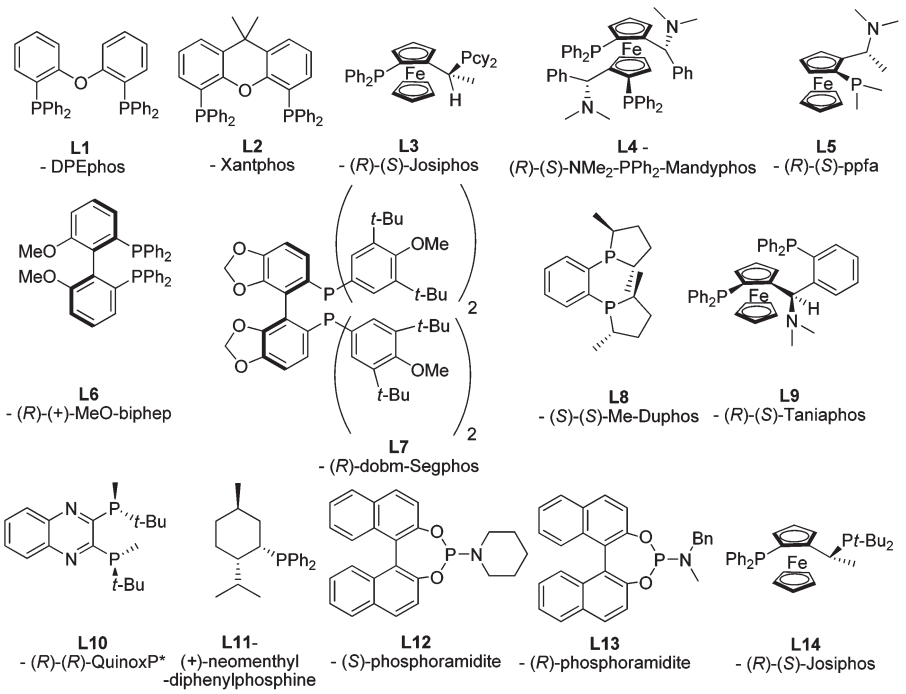
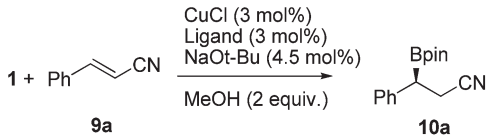


Fig. 1 Ligands employed in catalytic β-boration of electron deficient alkenes.

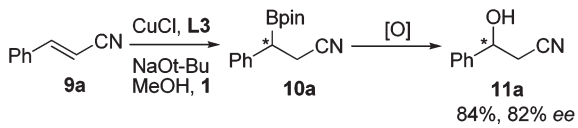
Table 2 Enantioselective β-boration of α,β-unsaturated esters and nitriles



9a **10a**

Entry	Ligand	Yield[a] (%)	ee (%)
1	**L3**	97	94
2[b]	**L4**	96	94
3	**L7**	92	80
4	**L6**	92	3
5	**L5**	93	55

[a] Isolated yield. [b] NaO*t*-Bu (3 mol%).



Scheme 6 Enantioselective β-boration of cinnamonitrile **8a**.

shown to be an important step forward but Yun *et al.* also demonstrated that this protocol had the potential to be enantioselective.[27]

1.2 Enantioselective β-boration: amides, esters and nitriles

During the early days of β-boration development, it was suggested that it had the potential to be enantioselective, perhaps by using chiral diborane reagents.[12] Interestingly, Yun *et al.* developed an enantioselective β-boration protocol which was not based upon chiral diborane reagents, but on a catalytic system involving chiral phosphine ligands.[27] Asymmetric induction in metal-catalysed reactions by the use of chiral phosphine ligands had been reported elsewhere.[30] Having shown that the copper catalysed β-boration of cinnamonitrile **9a** gave the borated product in high yield (95%), Yun *et al.* applied the chiral Josiphos ligand **L3** to their optimised methodology. This was followed by C–B oxidation to yield the chiral β-hydroxy nitrile with the expected complete retention of stereochemistry. This gave the product **11a** in 82% ee and 84% yield (Scheme 6).

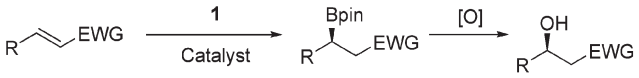
Once it had been shown that enantioselective β-boration could be achieved using chiral phosphine ligands, Yun *et al.* probed the scope of this protocol and the influence of other chiral phosphine ligands, with a series of α,β-unsaturated esters and nitriles (Table 2).[31] All the ligands that were screened induced enantioselectivity, however, it is clear from looking at Table 2, that Josiphos and Mandyphos (**L3** and **L4** respectively) showed the most promise with respect to asymmetric induction. Hence, **L3** and **L4** were employed in the enantioselective β-boration–oxidation sequence of a series of α,β-unsaturated esters and nitriles (Table 3). This protocol also resulted in high yields and high levels of enantioselectivity across a wide range of substrates (see Table 3, entries 1–13), with **L3** providing a higher level of enantioselectivity than **L4** (see Table 3, entries 4 *vs.* 5 and 8 *vs.* 9).

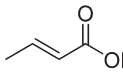
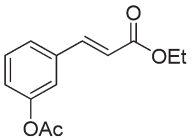
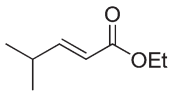
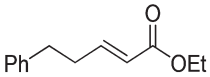
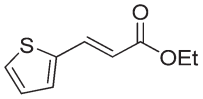
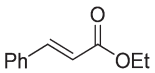
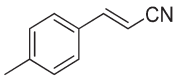
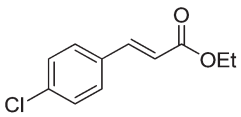
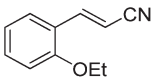
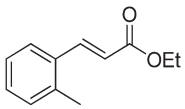
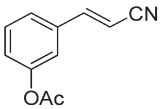
Yun *et al.* also made interesting observations regarding β-substituent effects, electron withdrawing group influence and ester moiety effects on the asymmetric induction of the screened reactions.

Potential β-substituent effects on enantioselectivity can be examined by comparing entries 1–6 and 11–13 (Table 3), whereby the substrates differ only by their β-substituents. The β-substituents differ in terms of both steric and mesomeric effects in each case and the observed ees were remarkably similar, which suggested that the β-substituent did not have a dominant effect on the enantioselectivity of the reaction. The nature of the electron withdrawing group (ester or nitrile in this case) was found to have an influence on the enantioselectivity (Table 2, entry 2 and Table 3, entry 5). When the electron withdrawing group was the α,β-unsaturated nitrile, this resulted in higher enantioselectivity (94% ee) compared to the analogous ester (87% ee).

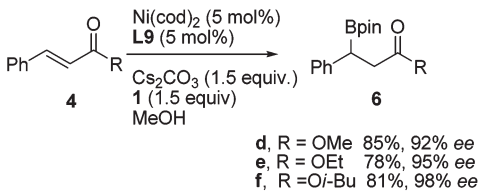
Having established that the nature of the electron withdrawing group plays a important role in stereoselectivity, Yun *et al.* examined this further in the case of esters by varying the alkoxy substituent on the ester. They found that changing the alkoxy substituent from a simple methoxy group to a more sterically demanding substituent (O*t*-Bu) gave no observable effect on the enantioselectivity. Interestingly, Fernández *et al.* were exploring the nickel and palladium catalysed enantioselective β-boration of α,β-unsaturated esters,[32] having previously explored the asymmetric β-boration of α,β-unsaturated esters using a copper catalyst modified with chiral *N*-heterocyclic carbenes (NHC). However, they did not examine the effect on of the ester moiety on the asymmetric induction (see McQuade *et al.* for other work in this area).[33,34] In light of the work by Yun *et al.*,[31] Fernández *et al.* used their nickel-catalysed system to examine whether the enantioselectivity of the catalytic β-boration was indeed independent of ester variation [see eqn (3)] and found that the ester moiety was influencing the enantioselectivity of the reaction. Indeed, this was observed across a range of different chiral ligand systems and the trends were similar in each case, *i.e.* from OMe to Oi-Bu, the asymmetric induction increased with greater steric bulk on the ester moiety. It is important to note that the same trend was also observed in the palladium-catalysed system, also developed by Fernández *et al.*[33] Perhaps more surprisingly, Nishiyama *et al.* also examined the ester effect on enantioselectivity and found an inverse trend to that reported by Fernández *et al.*[35] The rhodium-catalysed β-boration had been reported previously,[25] however, an asymmetric protocol for β-boration was yet to be established. Nishiyama developed a rhodium catalyst that employed a chiral bisoxazolinylphenyl ligand to induce enantioselectivity in the β-boration [see eqn (4)]. Nishiyama *et al.* found that by increasing the steric bulk of the ester moiety, a decrease in enantioselectivity was observed. With different rhodium-bisoxazolinylphenyl systems, the same trend of decreased enantioselectivity with more sterically demanding esters was observed. A point of difference arises here as Yun specifically claimed that the ester moiety had no influence on enantioselectivity;[31] Fernández found this was not the case.[33] It was confirmed by Nishiyama, however, that the trend that was observed by Fernández, was not observed in their systems.[35] On the contrary, they observed an inverse relationship between steric bulk of the ester moiety and asymmetric induction.

Table 3 Enantioselective β-boration–oxidation of a series of α,β-unsaturated species



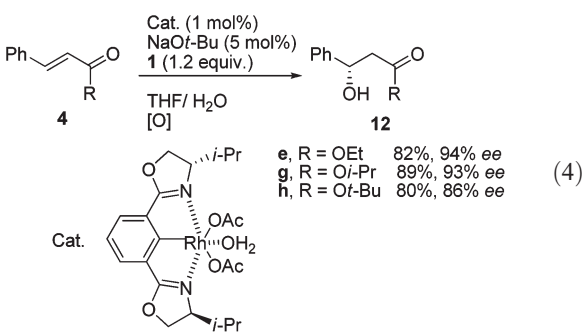
Entry	Substrate	Yield[a] (%)	ee[b] (%)	Entry	Substrate	Yield[a] (%)	ee[b] (%)
1		94[c]	90 (*R*)	8		95[c]	87
2		92[c]	91 (*S*)	9		89[d]	84
3		97[c]	89	10		93[c]	82
4		93[c]	90 (*S*)	11		94[c]	90 (*S*)
5		94[d]	87 (*S*)				
6		90[c]	91(*S*)	12		90[c]	92
7		87[c]	88	13		94[d]	91

[a] Isolated yield of β-boration product. [b] ee of oxidised product. [c] CuCl, 2 mol%; NaO*t*-Bu, 3 mol%; **L3**, 4 mol%. [d] CuCl, 3 mol%; NaO*t*-Bu, 3 mol%; **L4**, 3 mol%.

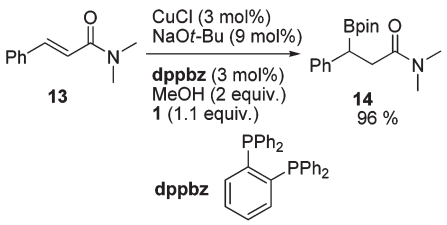


(3)

The work by Yun *et al.* was highly influential as it established for the first time a protocol for enantioselective β-boration that could be applied to a broad range of substrates. It also suggested that β-substituent effects were not influential on enantioselectivity, especially compared to those of the electron withdrawing group. That being the case, Yun *et al.* explored the β-boration of α,β-unsaturated amides as this was another way of gauging the influence of the electron withdrawing group, and to expand the substrate scope of this protocol [see eqn (5)].[36]

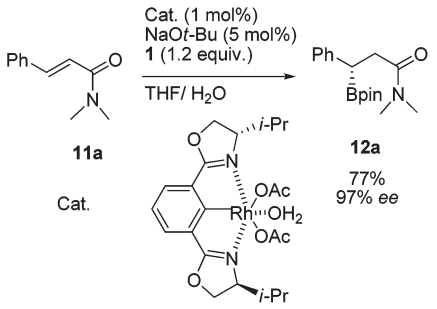


(4)



(5)

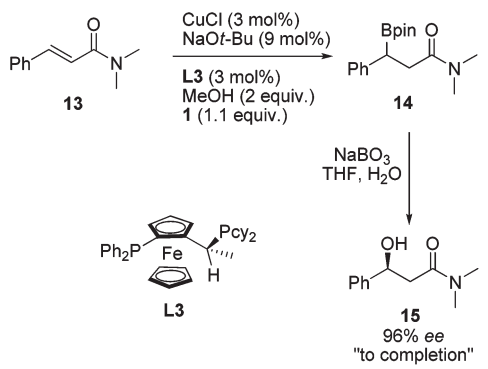
Oshima *et al.* had previously developed an efficient nickel catalysed protocol for the β-boration of α,β-unsaturated esters and amides.[37] Yun *et al.* extended their previously established enantioselective boration protocol from α,β-unsaturated esters and nitriles to the analogous α,β-unsaturated amides. The previous protocol could not be directly applied due to the α,β-unsaturated amides being poorer Michael acceptors compared to the analogous α,β-unsaturated esters and nitriles which resulted in conversions as low as 23%. Unlike their previous examples involving the enantioselective β-boration of α,β-unsaturated esters and nitriles, the system for the α,β-unsaturated amides is limited to a few substrate variants. Nishiyama *et al.* also reported a route to α,β-unsaturated amides *via* their chiral rhodium-bisoxazolinylphenyl system,[35] giving the borated amide in good yield and excellent ee [see eqn (6)]. This, however, was only limited to selected substrates. Molander and Mckee also reported a method of β-borating α,β-unsaturated amides using tetrahydroxydiborane; the analogous asymmetric system has yet to be reported.[38]



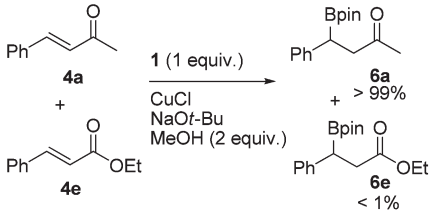
(6)

Exploration into the metal catalysed enantioselective β-boration of α,β-unsaturated esters, nitriles and amides is both fascinating and complex. It offers great insight into the mechanistic pathways that underpin these reactions. However, points of disagreement regarding what influences enantioselectivity have arisen. It is clear that the electron withdrawing group (ester, nitrile or amide) does play a dominant role in asymmetric induction, however, the β-substituent and ester moiety effects also play a subtle role in asymmetric induction, a role that is not fully understood and a point upon which different groups disagree.[31,33,35] It is, therefore, important to examine in depth both the metal catalysed β-boration and enantioselective β-boration of α,β-unsaturated ketones and imines (see tables 4 and 7).

The inherent low reactivity of the copper catalysed protocols of Hosomi and Miyaura *et al.* meant that asymmetric induction was a challenge, even with the use of chiral phosphine ligands. Yun *et al.* had shown that methanol could be used as an additive to dramatically increase catalytic turnover in β-boration-type reactions. This, therefore, allowed the exploitation of potential enantioselective pathways in the β-boration the of α,β-unsaturated ketones.[27] This was explored by Yun *et al.* on the enantioselective β-boration of acyclic α,β-unsaturated ketones.[39] The crucial role of methanol was demonstrated in the β-boration of two analogous α,β-unsaturated species [**4a** and **4e**, eqn (7)]. They combined two α,β-unsaturated carbonyl species and reacted them in parallel, as a means of examining the reactivity of the α,β-unsaturated ketone, **4a** relative to the previously explored α,β-unsaturated ester, **4e**.

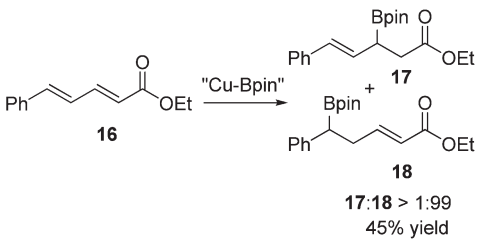


Scheme 7 Yun's enantioselective β-boration–oxidation sequence of α,β-unsaturated amides.



(7)

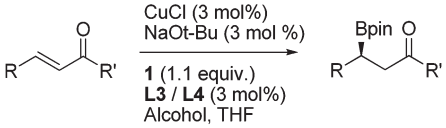
Interestingly, they found that under these conditions, the β-boryl ketone **6a** was formed in near quantitative conversion, whereas the analogous ester **6e** was found in very low yields (<1%). The above reaction [eqn (7)] was achieved without the presence of a ligand and as such, Yun examined whether asymmetry could be induced using chiral phosphine ligands (scheme 7). The use of these chiral ligands (**L3** and **L4**) in the presence of alcohol additives (methanol, *iso*propanol or *tert*-butanol) in varying amounts (1–2 equiv.) resulted in excellent conversions (92–100%) and moderate to good levels of asymmetric induction (37–80%). Interestingly, even without the addition of alcohol additives, high levels of asymmetric induction were achieved (56–77%). However, the alcohol free reactions did not proceed to completion and poorer yields were typically observed (18–54%). Having established, and gained an understanding of the parameters which influence both enantioselectivity and conversion, Yun *et al.* expanded this methodology further by probing several varied substrates using both **L3** or **L4** and different alcohol additives (see Table 4). In light of the experimental evidence outlined in Table 4, Yun *et al.* observed that methanol was the more effective alcohol additive, typically leading to greater levels of conversion and improved enantioselective control.



(8)

Again, as in the case of α,β-unsaturated esters and nitriles,[31] the β-substituent induced subtle changes on the degree of conversion and enantioselectivity of the reaction. Even though it is worth noting that β-substituents do indeed influence these parameters, it is difficult to deduce with any high degree of certainty if there is any trend between β-substituents and enantioselectivity, due to the limited number of substituents (differing in subtle steric and mesomeric properties) probed by Yun *et al.* It is clear, however, that **L3** is certainly more influential in enantioselective induction when compared to **L4**. Indeed, this trend has been shown in the enantioselective β-boration of as in the case of α,β-unsaturated esters and nitriles. It is interesting to note that 1,6-type addition was not observed in any species with extended conjugation (Table 4, entries 1–7 and 13–16). The enantioselective 1,6-conjugate borylation of 2,4-dienoate esters has since been explored by Ibrahem and Córdova *et al.*[40] They noted that regioselectivity was favoured towards 1,4-addition in such reactions [eqn (8)] and hence, they had to devise a protocol that favoured 1,6-addition. Yun *et al.*'s work on the enantioselective

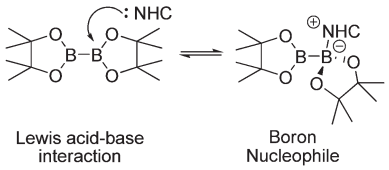
Table 4 Enantioselective β-boration with various substrates, ligands and alcohol additives



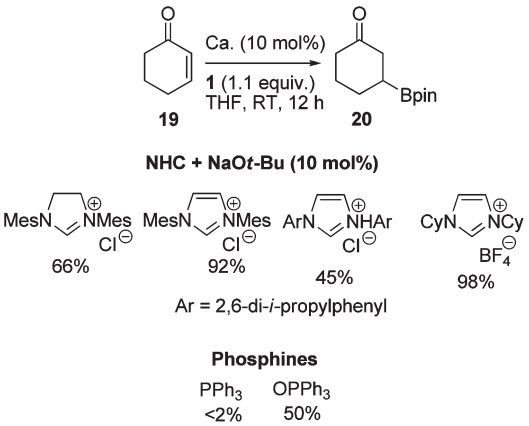
Entry	Substrate	Ligand	Alcohol	Yield[a] (%)	ee[b] (%)
1		**L3**	i-PrOH	94	95
2		**L3**	MeOH	97	89
3	Ph, *i*-Pr	**L4**	MeOH	93	93
4		**L3**	MeOH	89	81
5	Ph, *i*-Bu	**L4**	MeOH	91	88
6		**L3**	MeOH	93	90
7	*n*-Bu	**L4**	MeOH	86	30
8		**L3**	MeOH	95	90
9	Bn	**L3**	i-PrOH	90	88
10		**L4**	MeOH	96	30
11	Ph	**L3**	MeOH	97	97
12	*i*-Pr, Ph	**L3**	MeOH	94	97
13	Ph, O	**L3**	MeOH	72	91
14		**L3**	i-PrOH	72	9
15		**L3**	MeOH	93	96
16	Ph	**L3**	i-PrOH	70	95

[a] Isolated yield. [b] Deduced from the corresponding β-hydroxy ketone.

conjugate boration of α,β-unsaturated ketones complemented their previous work on α,β-unsaturated esters and nitriles. This work set the standard, in terms of high enantiocontrol and efficiency in the β-boration of α,β-unsaturated species.[27] All examples of β-boration, both the asymmetric and symmetric variants, rely upon a metal catalyst to facilitate the conjugate addition of a nucleophilic boron species. However, in early 2009 Hoveyda *et al.* developed the first β-boration of both cyclic and acyclic α,β-unsaturated ketones, using a protocol that did not require a transition metal catalyst.[41] This breakthrough made use of an organic catalyst consisting of an NHC in non-stoichiometric loadings. Interestingly, Sadighi *et al.* had previously isolated a NHC-copper-Bpin species,[42] and had demonstrated its use in the formation of β-boroalkyl complexes (*via* alkene insertion to the NHC-copper-Bpin adduct).[43] Hoveyda *et al.* postulated that the introduction of the NHC resulted in an acid–base interaction between the NHC and the Lewis acidic diboron species; B_2pin_2 in this case. It was suggested that this resulted in a nucleophilic boron species (see Scheme 8) that undergoes conjugate addition to the α,β-unsaturated ketones (mechanistic considerations will be discussed in section 1.5). Hoveyda *et al.* examined this by taking a cyclic α,β-unsaturated ketones and probing the β-boration of this species with various NHC and phosphine salts (Scheme 9). Surprisingly, addition of the



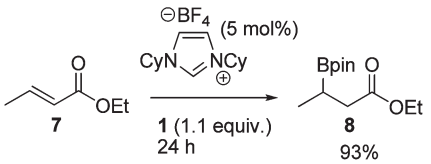
Scheme 8 Hoveyda's proposed nucleophilic adduct in the β-boration of electron deficient alkenes.[41]



Scheme 9 The examined catalytic species in the β-boration of **19**.

catalytic species to a solution of the α,β-unsaturated ketones and diboron reagent resulted in moderate to excellent yields of the β-boration products (45–98%). Interestingly, the catalytic activity of phosphine oxide gave the corresponding β-boryl ketone in moderate yield (50%) without the presence of a transition metal or NHC to facilitate boration. This had been observed before by Hosomi, but the overall conversion was considerably poorer (7%). The importance of this protocol, and the implications for a metal-free variant for a symmetric and asymmetric protocol were clear. Hoveyda *et al.* probed this metal free protocol further by probing both *endo*- and *exo*-cyclic α,β-unsaturated ketones and borated them in excellent yield (88–98%); this methodology was even extended to cyclic α,β-unsaturated esters showing equally excellent yields (95%).

The introduction of a non-metal catalysed protocol for the β-boration of α,β-unsaturated species was a useful contribution to the area. It raised questions regarding the mechanistic understanding of these types of processes, especially the role the phosphine ligands (see Scheme 9).

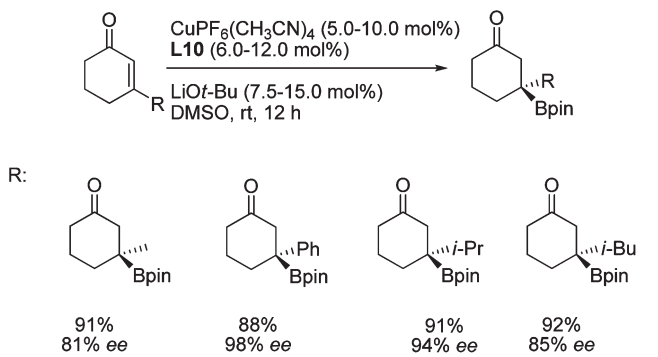


(9)

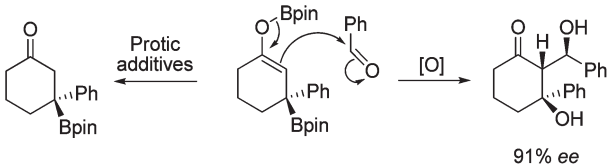
Shortly after Hoveyda *et al.*'s work on metal-free β-boration of cyclic α,β-unsaturated ketones, Shibasaki showed that various β-substituted cyclic α,β-unsaturated ketones could be prepared asymmetrically.[44] Most of the work on β-boration, enantioselective and racemic, was examined using monosubstituted (on the β-carbon) α,β-unsaturated species. These species tend to be more reactive towards β-boration, and also allow for greater

enantioselective induction due to the large steric difference between β-carbon substituents (typically H and R, where R is alkyl, phenyl etc). However, β,β-disubstituted species are not as well explored, despite being suitable prochiral species for enantioselective conjugate boration. As such, Shibasaki *et al.* developed a suitable protocol for the boration of such species. Interestingly, their optimised protocol also did not require alcohol additives and made use of an unexplored (in boron conjugate addition) chiral diphosphine ligand **L10**. The substrate scope of their system was probed on cyclic α,β-unsaturated ketones (Scheme 10). All substrates were obtained in excellent ee and high yield,[44] 70–98% and 80–99%, respectively. As in the case of Hoveyda, Shibasaki *et al.* demonstrated the potential for a stereoselective aldol-type reaction between the diboron intermediate and benzaldehyde. This was possibly due to the lack of protic additives quenching the intermediate boron enolate (Scheme 11). The lack of alcohol additives (*e.g.* MeOH)[27] provided a greater scope of application of the reaction. Not only was it possible to introduce one boron substituent enantioselectively, but this showed that multiple stereocenters could be controlled in one-pot.

Moreover, this further provided evidence that β-boration was indeed a form of diboration that on aqueous work-up gave the β-boration product only. This work overcame some limitations associated with the conjugate addition of boron to β,β-disubstituted α,β-unsaturated species.[45] Perhaps more importantly, this work also provided mechanistic insights by giving examples of the stereoselective aldol-type reaction between benzaldehyde and the intermediate boron enolate. In fact, this work provided mechanistic insights by giving examples of the stereoselective aldol type reaction between benzaldehyde and the intermediate boron enolate. Not content with a protocol limited to the boration of cyclic β,β-disubstituted α,β-unsaturated species, Shibasaki *et al.* developed a protocol for the acyclic β,β-disubstituted α,β-variants (also shown by Yun *et al.*[45] and Hoveyda *et al.*[46])

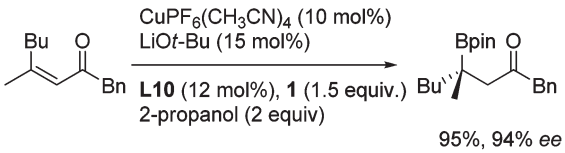


Scheme 10 β-Boration to cyclic β,β-disubstituted α,β-unsaturated species.



Scheme 11 Aldol product formed *via* intermediate enolate.

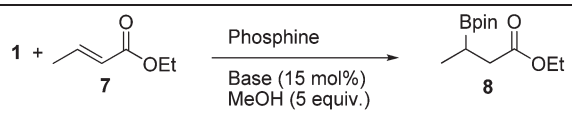
using an adaptation of their protocol for cyclic species.[47] This produced some excellent results, with reaction conversions ranging from 71–95%, with equally high levels of stereocontrol (90–99%). A representative example of this is shown in eqn (10). Effective methodologies for the enantioselective β-boration have been demonstrated across a wide range of substrates by Yun[28] and Shibasaki *et al.*[31,44] The introduction of a non-metal catalysed racemic variant was demonstrated by Hoveyda *et al.*[41] and sparked interest in this area. Indeed, this was further explored by Fernández and Gulyás *et al.* who introduced the first non-metal catalysed enantioselective β-boration of α,β-unsaturated species.[48] Fernández *et al.* knew from the early work of Hosomi *et al.* that phosphines in the absence of transition metal species had the ability to facilitate boron conjugate addition to α,β-unsaturated species. Moreover, chiral phosphine ligands had been shown in numerous examples to induce enantioselectivity with respect to the β-boration of prochiral activated alkenes.[49,50] With this in mind, they probed the ability of various achiral phosphines, bases and alcohols, to facilitate a racemic conjugate boration to ethyl crotonate (some of which are highlighted in Table 5).



(10)

Surprisingly, a whole variety of phosphine species facilitated β-boration of ethyl crotonate in reasonable to excellent yields (Table 5, entries 3 and 4). The addition of base was found to be crucial for the boron conjugate addition, and of the bases that were explored (CsF, NaO*t*-Bu, K_2CO_3 and Cs_2CO_3) Cs_2CO_3 was found to be the most successful. Perhaps more surprisingly is the relatively pure performance of $OPPh_3$ in the facilitation of β-boration. Previously, Hoveyda *et al.* had been unsuccessful in demonstrating the catalytic potential of PPh_3 in β-boration, but had succeeded in demonstrating the potential of $OPPh_3$ (Scheme 9).[41] Indeed, the addition of $OPPh_3$ to their system resulted in the 50% conversion to the β-boration product. It is surprising, therefore, that $OPPh_3$ performed significantly poorer than the corresponding phosphine, PPh_3 in the Fernández *et al.* system.[48] Now that the non-metal catalysed protocol had been optimised for ethyl crotonate, Fernández *et al.* probed the

Table 5 Probing the catalytic potential of phosphines



Entry	Phosphine	Base	Alcohol	Conversion[a] (%)
1	PPh_3		MeOH	0
2	PPh_3	Cs_2CO_3		12
3	PPh_3	Cs_2CO_3	i-PrOH	49
4	PPh_3	Cs_2CO_3	MeOH	99
5	$OPPh_3$	Cs_2CO_3	MeOH	21
6	DPPF	Cs_2CO_3	MeOH	39

[a] Deduced using GC analysis, confirmed using ^{1}H NMR.

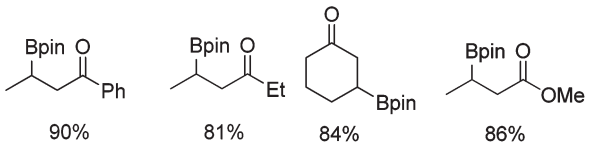
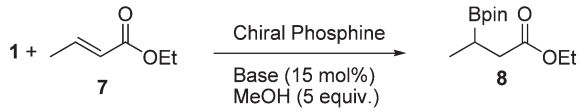


Fig. 2 Products of Fernández *et al.*'s organocatalytic β-boration protocol.[48]

Table 6 Probing chiral phosphine ligands in the development of an asymmetric organocatalytic β-boration protocol



Entry	Chiral phosphine	Base	Conversion[a] (%)	ee (%)
1	**L3**	Cs_2CO_3	99	75 (*S*)
2	**L4**	Cs_2CO_3	58	<5
3	**L9**	Cs_2CO_3	64	72 (*S*)
4	**L11**	Cs_2CO_3	74	<5
5	**L12**	Cs_2CO_3	53	7 (*R*)
6	**L13**	Cs_2CO_3	54	35 (*S*)
7	**L14**	Cs_2CO_3	94	88 (*S*)
8	**L14**	NaO*t*-Bu	59	55 (*S*)
9	**L14**	CsF	72	89 (*S*)

[a] Deduced using GC analysis, confirmed using ^{1}H NMR.

substrate scope on a series of α,β-unsaturated esters and ketones. This protocol was found to be highly effective, with isolated yields ranging from 81–90%. Some of these β-borated products are shown in Fig. 2. Since that it had been demonstrated that this protocol could be applied to a multitude of substrates, Fernández *et al.* attempted to develop an asymmetric variant by the introduction of chiral phosphine ligands.[48] This was done by probing a series of chiral ligands in the β-boration ethyl crotonate (Table 6).

Initially, **L11** was examined as a potential means of inducing enantioselectivity in the reaction. High conversions were observed with this phosphine, but it only provided minimal enantioselectivity in the reaction (<5%, Table 6, entry 4). The phosphoramidite species (**L12–13**) on the other hand gave poorer conversions, but did indeed induce enantioselectivity in the process. However, the more effective phosphines at inducing enantioselectivity proved to be the Taniaphos (**L9**) and the Josiphos (**L3–14**) type species (see Table 6, entries 1, 3 and 7). This demonstrated for the first time that asymmetric β-boration need not be carried out using a metal catalyst with chiral ligands; on the contrary, chiral phosphine ligands, base and a suitable alcohol additive alone, proved sufficient to provide enantioselectivity in the conjugate addition of boron to α,β-unsaturated species. However, this protocol was limited to ethyl crotonate, and as such Fernández *et al.* needed to demonstrate that this non-metal catalysed asymmetric protocol could be applied to a varied substrate class.[48] This was explored using the same substrates as explored in the racemic case. This protocol was found to be applicable to a wide degree of substrates and proved highly effective in terms of both conversion and enantioselectivity. The Josiphos ligand, **L14** proved to be the most successful phosphine species, some of these results are highlighted in Fig. 3. This

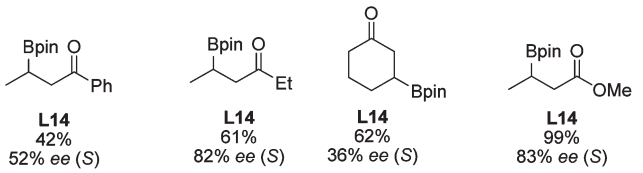


Fig. 3 Products of Fernández *et al.*'s asymmetric organocatalytic β-boration protocol.[48]

demonstrated that this system could be applied to wide range of species. Both cyclic and acyclic α,β-unsaturated ketones and esters were explored, the β-boration products of which showed reasonable to high levels of enantiopurity (36–83%). The utility of the process was clearly demonstrated by the encouraging results, however, more importantly it raised questions regarding the underlying mechanistic principles of the reaction. It is not clear whether the phosphine acts either as a ligand or a catalytically active species in the β-boration of α,β-unsaturated species. Building on their previous work, Fernández and Gulyás *et al.* explored their newly devised non-metal catalysed route to the β-boration of α,β-unsaturated species, and examined the role of iron as an additive as a means of assisting this process.[51] This case will be discussed later (section 1.5), as it provides mechanistic insight to the process of boron conjugate addition.

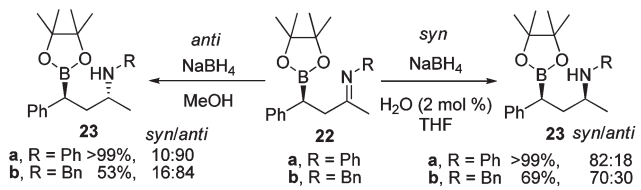
1.3 Enantioselective β-boration: ketones and imines

Most of the literature regarding β-boration is based on the conjugate addition of boron to activated alkenes, typically activated by a carbonyl electron withdrawing moiety, namely amides, ketones and esters.[52] Alkenes activated by nitriles are present in the literature, but α,β-unsaturated imines are under-explored. α,β-Unsaturated imines are more reactive than the analogous carbonyl compounds, and as a result are more difficult to prepare and purify.[53–55] However, they offer scope for boron conjugate addition (functionalisation at the β-carbon), and *via* exploitation of the imine functionality, 1,3-difunctionalisation.[56]

In addition, the previous examples of enantioselective β-boration, and the elegant methods for substrate controlled asymmetric reduction,[57] offered considerable potential for controlling multiple stereocenters in simple organic species. To this end, Fernández and Whiting *et al.* examined whether α,β-unsaturated imines could serve as a suitable platform for a novel asymmetric route to γ-amino alcohols.[58,59] Asymmetric routes to γ-amino alcohols exist,[60] however, Fernández and Whiting *et al.* explored the previously established methods of boron conjugate addition, more specifically the asymmetric variant of, as a means of enantioselectively introducing a boryl substituent at the β-position of the α,β-unsaturated imine substrate.

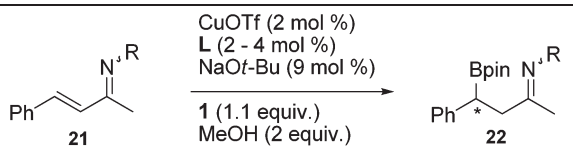
Drawing the expertise of Whiting *et al.*, the resulting β-boryl imine species would be ideally placed for remote asymmetric reduction.[61,62] The potential for remote asymmetric reduction, coupled with established methods for the stereospecific oxidation of boron containing substituents was an intriguing concept that needed to be explored. Hence, Fernández and Whiting *et al.* examined this concept by the asymmetric copper-catalysed β-boration of α,β-unsaturated imines to give **22**, Scheme 12.[58] This involved the screening of multiple chiral phosphine ligands

as a means of devising an efficient protocol for the preparation of chiral β-boryl imines. All the ligands that were screened did indeed induce asymmetry, and moreover, some of the ligands gave the β-boryl imines in excellent conversion and ee (see Table 7). Next, they turned their attention to the asymmetric reduction of the imine functionality. They observed an intramolecular Lewis acid–base interaction (B–N) indirectly by ^{11}B NMR (Scheme 13) which offered potential for the exploitation of previously established reduction methodologies.[61,62] Indeed, on screening various reducing agents and proton-sources, they discovered a means of asymmetrically reducing the imino functionality, and by solvent modification, could tune the selectivity between *syn*- and *anti*-diastereoisomer formation (Scheme 13). This protocol was achieved in a one-pot synthesis, by which the β-boration, reduction and oxidation could be carried out consecutively. This methodology brought together asymmetric conjugate boration and remote asymmetric induction, and fashioned a protocol to access γ-amino alcohols with high levels of stereocontrol across multiple stereocenters. Shortly after this, the protocol was extended to the preparation of γ-hydroxy alcohols and a wider substrate base for the previously established γ-amino alcohols.[63]



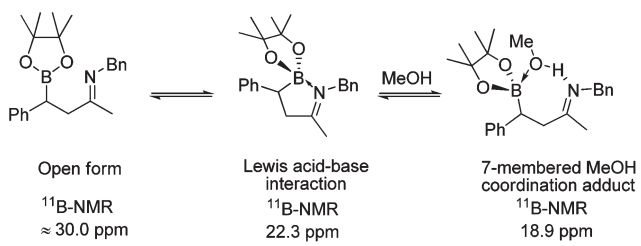
Scheme 12 Tuneable diastereocontrol by solvent modification.

Table 7 Enantioselective β-boration of α,β-unsaturated imines



Entry	R	Ligand	Conversion[a] (%)	ee (%)
1	Ph	**L3**	61	63
2	Ph	**L14**	66	30
3	Ph	**L12**	>99	95
4	Bn	**L3**	>99	91
5	Bn	**L14**	>99	77
6	Bn	**L12**	>99	75

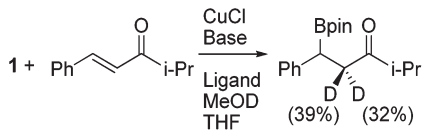
[a] Deduced using ^{1}H NMR.



Scheme 13 ^{11}B NMR evidence for intramolecular Lewis acid–base interaction.[59]

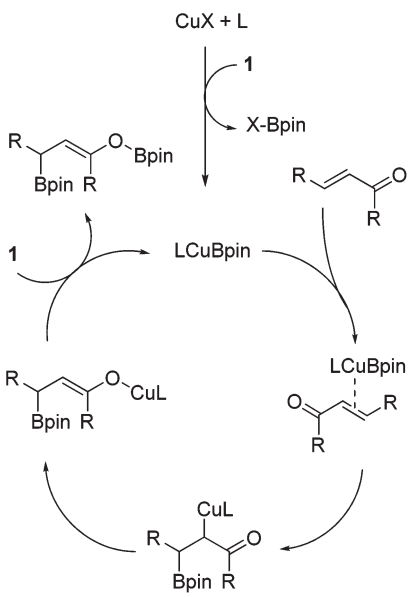
1.4 Mechanistic considerations

Marder *et al.* introduced the first example of 1,4-diboration to activated alkenes,[12,64] which after hydrolysis, gave the corresponding β-boration product. Indirect evidence for 1,4-diboron species has come from other groups, that have used the assumed intermediate 1,4-adduct for the formation of aldol products.[41,44] However, the formation of such species (*e.g.* **5**, Scheme 3) relies upon the presence of a nucleophilic boryl species.[65] Indeed, this idea was put forward by Miyaura *et al*., and substantiated with experimental evidence (Scheme 5).[21] It is interesting to note that nucleophilic boron species have since been reported and isolated.[24] The initial copper-catalysed examples of conjugate boration were plagued by high catalyst loadings. Yun *et al*.'s methodology involving the use of protic additives, *i.e.* alcohols (see Table 2 and Scheme 14),[27] led them to speculate upon a plausible mechanisms and suggested that a diphosphine ligated copper boronate species,[66] similar to the copper boronate species as suggested by Miyaura *et al.*,[21] was key to the conjugate addition of the α,β-unsaturated carbonyl compounds. This results in either a C-bound copper intermediate or an O-bound copper enolate. Yun *et al.* suggested that the equilibrium between the C-bound and the O-bound copper intermediates was more towards the C-bound system and would be this species that the alcohol additive would protonate. This suggested that this copper alkoxide was the active species involved in regenerating the active copper boronate species. Yun *et al.* also provided evidence in the form of isotopic labelling for the protonation of the enolate intermediate, as shown in eqn (11).



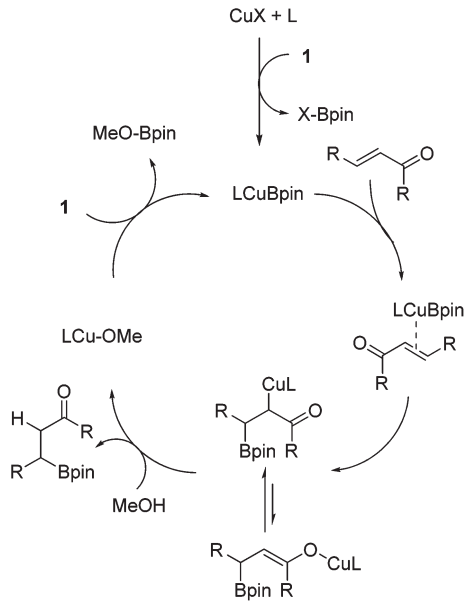
(11)

The groups of Marder and Lin *et al.* jointly carried out extensive DFT studies to try and elucidate some aspects of the



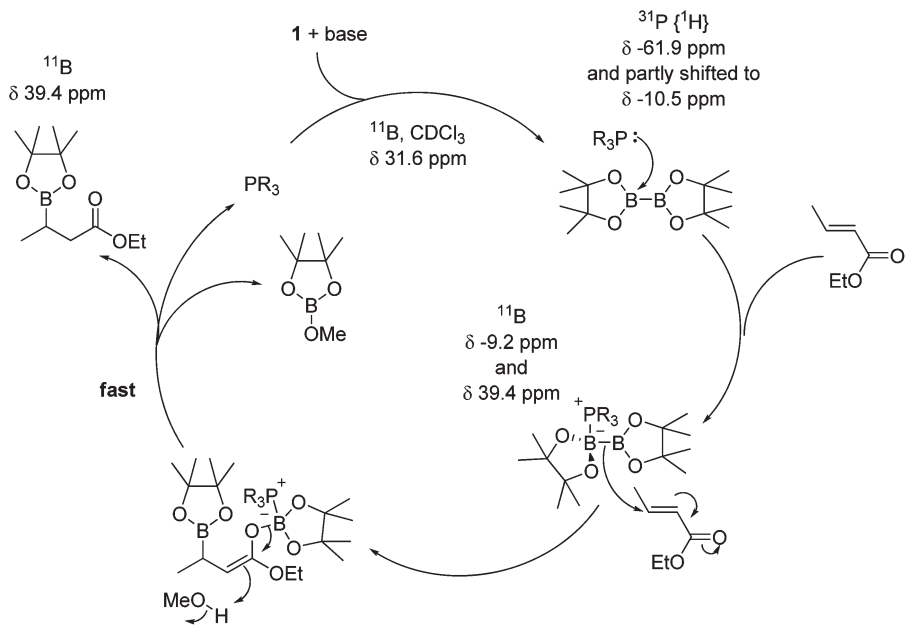
Scheme 14 Mechanism for the copper catalysed β-boration of α,β-unsaturated species.

underlying mechanistic workings of such reactions.[67] As part of this endeavour, studies involving olefinic insertion to copper–boron bonds have been made,[68] and as such led to the DFT study of boron conjugate addition of activated alkenes (namely α,β-unsaturated carbonyl containing species).[69] Their findings support a mechanism similar to that outlined in Scheme 15 by which boration results in the formation of a C-bound copper intermediate which could be protonated by the alcohol forming a ligated copper alkoxide. Such a process provides a barrier-less (as calculated by DFT methods) metathesis between such species and the diboron regent. This work substantiated the suggested mechanistic pathway proposed by Yun and co-workers.[27] In light of this, the mechanistic explanation appears complete; however, the organocatalytic variants of metal catalysed boron conjugate addition cannot be fully understood in this mechanistic framework and brings into question the roll of the constituent reagents in such reactions. Hoveyda put forward a plausible concept by which the NHC species can generate a nucleophilic diboron adduct by the polarisation of the boron–boron bond to form an sp^2–sp^3 type species (Scheme 8). Such species have since been isolated by Marder and Lin *et al.*[70] Hoveyda suggested that this adduct can react with the electrophilic β-carbon of the activated alkenes. However, Marder and Lin *et al.* also note that the from their spectroscopic observations (^{11}B-NMR), the association between the NHC and **1** was weak in solution, which casts doubt on this adduct being involved in the boron conjugate addition process. Perhaps more interesting (as highlighted in Scheme 9) is that a phosphine oxide alone in the presence of **1** can facilitate boron conjugate addition (activation by the nucleophilic oxide coordinating to the diborane species). The ability of phosphines to be active in the metal free conjugate addition was noted by Hosomi *et al.*,[20] but like Hoveyda *et al.*,[41] made no attempt to account for this despite the 50% conversion to the borylated species (in the case of Hoveyda).

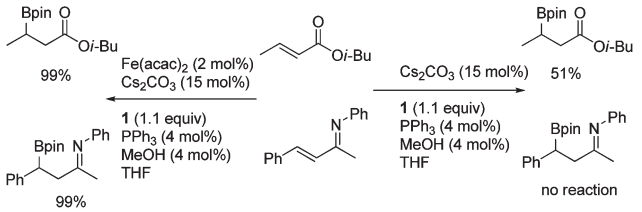


Scheme 15 Mechanism for the copper catalysed β-boration of α,β-unsaturated species as supported by Marder *et al.*'s DFT calculations.[69]

This organocatalytic β-boration, facilitated by phosphines, was probed by Fernández *et al.*[48] to explore the underlying mechanism of such reactions. They suggested that the acid–base interaction between the nucleophilic phosphine forms a nucleophilic adduct which, similarly to that reported by Hoveyda *et al.*, can undergo conjugate addition. This mechanism was deemed consistent with the observed NMR evidence (see Scheme 16), and in particular the loss of the two ^{11}B signals (this suggests the presence of a sp^2–sp^3 diboron adduct) on addition of the activated alkene. Assuming the organocatalytic variant proceeded through this sort of mechanism, Fernández *et al.* examined the influence of Lewis acidic iron salt additives, as a means of activating[71] the Michael acceptor towards conjugate addition.[51]



Scheme 16 Spectroscopic evidence for the proposed organocatalytic route as described by Fernández *et al.*[48]



Scheme 17 Comparison between the influence of iron additives on the β-boration of α,β-unsaturated esters and imines.

Interestingly, in all the examples they examined, carbonyl containing species (esters and ketones) underwent increased conversions when the additive was employed. Intriguingly, the analogous α,β-unsaturated imines only accommodated conjugate boration in the presence of the iron additives (see Scheme 17 for a representative example). This is perhaps unexpected given that α,β-unsaturated imines have been shown previously to be more reactive to nucleophilic diboron adducts than the analagous α,β-unsaturated carbonyl containing species.[58,59] In light of this, it would be interesting to examine the effect of introducing metal salts on other organocatalytic systems, such as that developed by Hoveyda *et al*., because this suggests that activation of the carbonyl should aid conjugate boration when conversions are particularly low.

1.5 Conclusion

The area of boron conjugative addition (β-boration) is not only fascinating, but serves as a valuable synthetic utility for the preparation of simple organic building blocks that represent key structural moieties in many biologically active species and materials. Since the first examples appeared, transition metals have played a crucial role in facilitating this process.[49] Platinum,[12] rhodium,[72] palladium and nickel,[33] have all been shown to facilitate boron conjugate addition, but perhaps due to the work of Yun *et al*., and use of alcohol additives, copper is the now the most used catalytic system in the area.[52] Recently, some groups have developed alternative methods by which β-boration can be achieved by organocatalytic means and they have obtained some excellent results.[48] Such methodologies have not yet displayed results to rival their metal catalysed equivalents, however, it is likely that these organocatalytic routes will develop with the use of additives,[51] resulting in more sustainable chemical processes.[73]

A number of mechanistic theories[69] have been put forward that aim to explain the metal catalysed methodologies, however, when applied to the organocatalytic variants, there are clear inconsistencies. A number of adaptions to these ideas have been made,[41] however, further developments are likely to be made in order to satisfactorily explain all the observed results.[70] To this end, further research is likely to be focused not only on developing new borylation systems, especially organocatalytic protocols and new asymmetric methods, but also on further mechanistic interpretations.

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