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Chiral vinyl dioxazaborocines in synthesis: asymmetric cuprate additions to β-boronyl acrylates and vinyl sulfones

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Abstract

The first examples of the addition of organometallic reagents to electron deficient boron-substituted olefins are reported. Thus, copper catalysed addition of Grignard reagents to chiral acryloyl and vinylsulfonyl dioxazaborocines, followed by oxidative removal of the boron, gives β-hydroxy esters and sulfones with asymmetric inductions up to 81 and 95% *ee*, respectively. © 2000 Elsevier Science Ltd. All rights reserved.

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Asymmetric Michael addition of organometallic nucleophiles to electron deficient olefins is an important area of asymmetric synthesis.[1–3] The use of chiral auxiliaries to control absolute stereochemistry in such processes is well documented.[1,2] Significant advances have been made in both reagent and catalyst control of asymmetry through the use of chiral ligands for organocopper reagents, nickel catalysis of organozinc additions, and rhodium catalysis of organoboronate additions.[3,4] The asymmetric addition of organometallics to acyclic Michael acceptors is particularly challenging and most of the systems developed thus far place constraints on the substituents tolerated on either the nucleophile or Michael acceptor if high enantiomeric purities are to be obtained. In this context, efficient chiral auxiliary based strategies still have a role to play in target synthesis.

We and others have been investigating asymmetric additions to olefins bearing chiral boronyl functions as stereocontrol elements. Varying degrees of success have been observed in asymmetric cyclopropanations,[5] cycloadditions (Diels–Alder,[6] nitrile oxide/olefin[7] and nitrone/olefin[7a]) and radical additions.[6e,8] To the best of our knowledge, the addition of organometallic reagents to electron deficient boron substituted olefins has not been investigated, although Negishi has reported an alkoxide promoted Michael-type B–C migration of alkyl groups in β-(dialkylboronyl)acrylates.[9] We were intrigued to see if dioxazaborocines could be used as a stereocontrol element in the addition of organometallics to acrylates and vinyl sulfones (Fig. 1).

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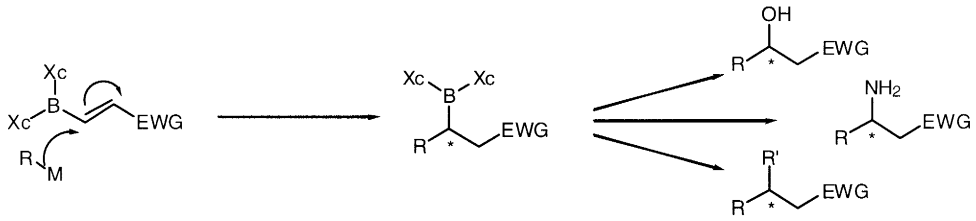
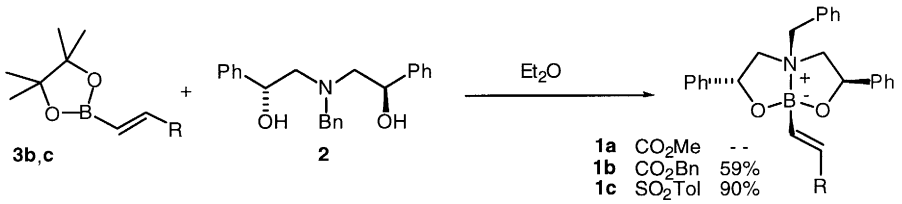


Fig. 1.

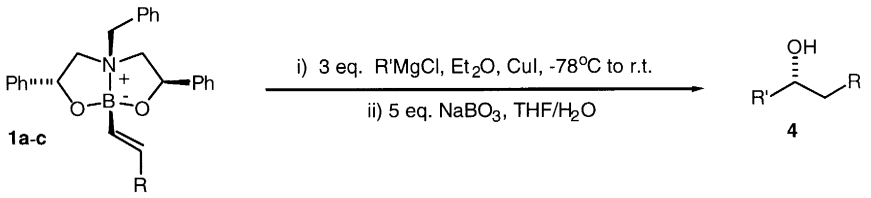
The major attraction of using boron as an anchor point for a chiral auxiliary is that the versatile chemistry of the C–B bond[10] should allow conversion of the intermediate β-boronyl ester/sulfone to the corresponding β-hydroxy, β-amino or β-dialkyl compounds. Thus, a single chiral auxiliary would serve as the synthetic equivalent of a chiral formylacetate,[11] iminoylacetate or 3-substituted acrylate. We report herein the results of our investigations into the addition of cuprates to chiral vinyl dioxazaborocines, leading to enantio enriched β-hydroxyesters and β-hydroxysulfones in good to excellent optical purity.

Vinyl dioxazaborocine **1a** was prepared according to our previous synthesis,[7a] while dioxazaborocines **1b**,**c** were prepared by condensation of diethanolamine **2**[12] with the appropriate pinacolboronates **3b**,**c**[13] in ether at room temperature (Scheme 1). In all cases the product dioxazaborocines precipitated from the solution as microanalytically pure white solids.



Scheme 1.

Initial investigations focused on determining the optimum conditions for the addition of organometallic reagents to the dioxazaborocines. Thus, cyclohexylmagnesium chloride was added to dioxazaborocines **1b**,**c** under the conditions shown and, following aqueous work-up of the reaction, the crude material was treated with sodium perborate to effect the oxidation of the C–B bond to a hydroxyl group. The results of these preliminary investigations are shown in Scheme 2 and Table 1.



Scheme 2.

From these results it can be seen that the additions proceed smoothly either in the presence or absence of tricyclohexylphosphine, provided that the Grignard reagent is added slowly to the mixture. Slightly lower optical purities are obtained in the presence of the phosphine. The use of pre-formed cuprates such as Bu_2CuLi was found to be less effective. Sodium perborate was found to give cleaner oxidations to the alcohol compared to alternatives such as basic hydrogen peroxide. Significantly, we were also able to isolate the intermediate boronic acid (entry 5) which was then readily converted to the alcohol **4** with

Table 1
Optimisation of copper catalysed addition of Grignard reagents to dioxazaborocines **1a–c**

Entry	R'	R	Additives	Yield of **4**	*ee* of **4**
1	Cy	SO_2Tol	DMPU	<5	n.d.
2	Cy	SO_2Tol	PCy_3	54	n.d.
3	Cy	SO_2Tol	PCy_3[a]	69	89
4	Cy	SO_2Tol	PCy_3[b]	0	n.d.
5	Cy	SO_2Tol	PCy_3[a,c]	50	89
6	Cy	SO_2Tol	none[a]	39	95
7	Cy	CO_2Bn	PCy_3[a]	45	52
8	Cy	CO_2Bn	none[a]	60	63

a) reaction was carried out by slow addition of the Grignard reagent to the remaining reagents at -78°C before warming to r.t.; b) reaction was carried out and quenched at -78°C; c) the intermediate boronic acid was isolated (58% yield) and subjected to the oxidation step separately (87% yield).

identical enantiomeric purity to that obtained without isolation. This will be of use when attempting interconversions of the C–B bond other than simple oxidation to the hydroxyl group.

We settled upon the optimum conditions for the addition as being the slow (1 hour) addition of three equivalents of the respective Grignard reagent to the substrate and three equivalents of copper(I) iodide at −78°C in ether, followed by slow warming to room temperature. The results of the addition of a range of Grignard reagents to dioxazaborocines **1a–c** are shown in Table 2.

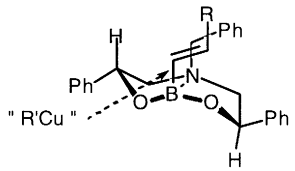
Table 2
Copper catalysed addition of Grignard reagents to dioxazaborocines **1a–c**

Entry	R'	R	Yield of **4**	*ee* of **4**[a]
1	Me	^{n}Pr	41	42
2	Me	Cy	40	57
3	Bn	Me	17	66
4	Bn	^{n}Pr	66	79
5	Bn	^{i}Pr	39	73
6	Bn	^{t}Bu	69	65
7	Bn	Ph	61	18
8	Bn	Bn	34	81
9	Bn	Cy	60	63
10	SO_2Tol	Me	49	95
11	SO_2Tol	^{n}Pr	47	84
12	SO_2Tol	^{i}Pr	50	89
13	SO_2Tol	^{t}Bu	26	76
14	SO_2Tol	Ph	35	67
15	SO_2Tol	Bn	37	83
16	SO_2Tol	Cy	39	95

a) determined by analysis of the ^{1}H or ^{19}F nmr spectrum of the derived Mosher's ester

A number of observations can be made regarding these results. Firstly, the greatest degree of asymmetric induction is observed with vinyl sulfone **1c**, while the benzyl acrylate **1b** performs better than the corresponding methyl ester **1a**. There are no obvious trends regarding the effects of changing the organic function of the Grignard reagent. The sense of asymmetric induction was confirmed as being that shown for entries 1, 3, 4 and 5 by comparison of the sign of the optical rotation of the material obtained with known literature values.[14] The remaining compounds are assigned the same stereochemistry by analogy. The stereochemical outcome can be rationalised in a similar manner to our results in the addition of nitrile oxides to vinyl dioxazaborocines,[7a] namely by assuming the *exo*-approach of the organometallic

reagent to the olefin in the configuration shown below. Compound **1a** has been shown to exist exclusively in this conformation in the solid state.[7a]



In summary, we have demonstrated the first addition of organometallic reagents to electron deficient vinyl boronates, leading to the asymmetric synthesis of a range of β-hydroxyesters and sulfones on oxidative cleavage of the boronyl function. The versatile chemistry of the C–B bond offers the potential for these compounds to act as intermediates for the synthesis of β-amino acids and chiral β-branched acrylates.

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