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COMMUNICATION

Asymmetric organocatalytic diboration of alkenes†‡

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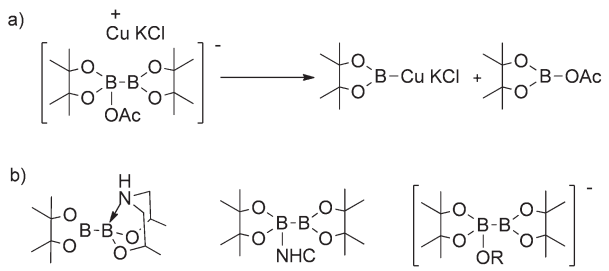
The use of chiral alcohols to form the Lewis acid–base *RO$^-$ → bis(pinacolato)diboron adduct, *in situ*, provides an opportunity to induce asymmetry in the organocatalytic diboration of alkenes and complements the well established transition metal-mediated enantioselective diboration.

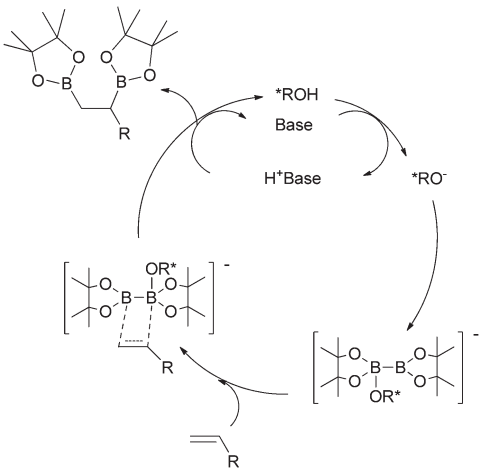
The activation of diboron reagents had generally been attributed to a direct interaction between the reagent and transition metal complexes,[1] until Miyaura and coworkers observed that AcO$^-$ activated diborons by Lewis acid–base interactions.[2] The resulting AcO$^-$ → diboron adduct facilitated the heterolytic cleavage of the B–B bond and the transfer of one boryl moiety to a copper(I) salt (Scheme 1a). Recently, it has been demonstrated that it is possible to activate diboron reagents in the absence of metals, by the sole addition of electron donor reagents (Scheme 1b), such as amines,[3] *N*-heterocyclic carbenes[4] and alkoxides.[5,6] This pre-activation increases the reactivity of the reagent towards both inorganic and organic electrophiles.[7]

We have recently explored the addition of the MeO$^-$ → bis(pinacolato)diboron adduct to non-activated olefins. This was achieved by activation of the diboron reagent by the *in situ* formation of a nucleophilic boryl moiety and represented the first example of a metal free diboration reaction.[8]

Since the catalytic system for the organocatalytic diboration of non-activated olefins is a combination of base and alcohol, we became interested in the extension of this methodology to permit an asymmetric variant by using chiral alcohols as additives (Scheme 2). Chiral alcohols are frequently good "chiral pool" materials due to their ready accessibility from nature. Hitherto the enantioselective diboration reaction has elegantly been accomplished by Morken and coworkers,[9,10] using rhodium and platinum complexes modified with chiral bidentate and monodentate ligands. But, to the best of our knowledge, the asymmetric metal free version has not yet been reported.



Scheme 1 Lewis acid–base adducts: (a) Miyaura first observation, (b) current versions.



Scheme 2 Plausible catalytic cycle for the asymmetric organocatalytic diboration reaction.

To initiate the study on the asymmetric organocatalytic diboration reaction, a small but representative library of alcohols (**1–10**) was selected to induce asymmetry in the addition of bis(pinacolato)diboron to vinylcyclohexane as a model substrate (Scheme 3). The use of 2 equiv. of chiral alcohols **1**, **3**, **4**, **6** and **7** afforded negligible conversion (<10%). Chemoselectivity towards the diborated product *versus* the hydroborated product was expected to be high in accordance with the use of the MeO$^-$ → bis(pinacolato)diboron adduct,[8] however none of the chiral alcohols tested provided quantitative chemoselectivity on the diborated product. The primary alcohol **5**, a pyranose derivative, was rather efficient in transforming the vinylcyclohexane into the diborated product, but the enantioselectivity was low (Table 1, entry 2). Only (*S*)-1-phenylethanol (**10**) induced enantioselectivity up to 24%, although the conversion was low and the chemoselectivity was only moderate (Table 1, entry 5).

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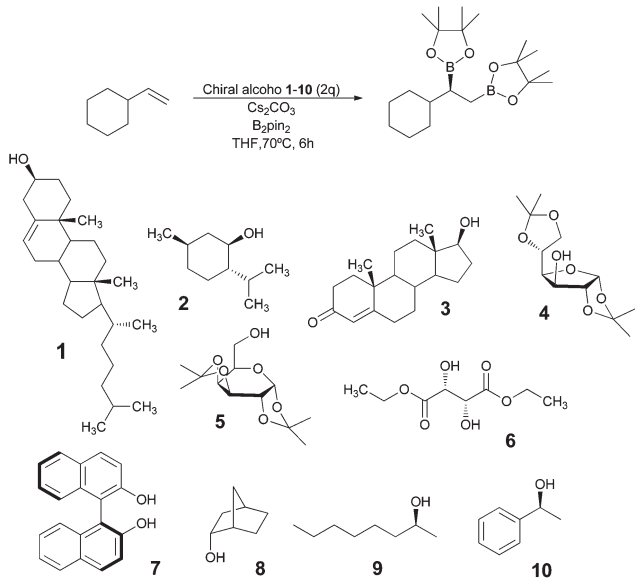
‡This paper is dedicated to Prof. Sergio Castillon on his 60th birthday.



Scheme 3 Set of chiral alcohols used in the organocatalytic diboration of vinylcyclohexane.

Table 1 Asymmetric metal-free diboration of vinylcyclohexane with bis(pinacolato)diboron[a]

Entry	Alcohol	Conv.[b] (%)	Diboron[b] (%)	ee[c] (%)
1	**2**	47	73	13 (*S*)
2	**5**	85	87	10 (*R*)
3	**8**	34	67	9 (*S*)
4	**9**	36	63	9 (*S*)
5	**10**	33	65	24 (*S*)

[a] Standard conditions: substrate (0.25 mmol), B_2pin_2 (1.1 equiv.), Cs_2CO_3 (15 mol%), alcohol (2 equiv.), THF (1 mL), 70 °C, 6 h. [b] Conversion and chemoselectivity of the diborated product determined by GC and ^{1}H NMR spectroscopy. [c] Enantioselectivity was determined from the ketal product by GC-MS.

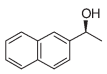
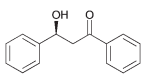
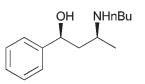
These initial results prompted us to optimise the reaction conditions in order to increase the yield of the diborated product. We did a general screening of the reaction conditions, keeping constant the amount of chiral alcohol for economical reasons. We observed that 16 h of reaction time ensured synthetically useful conversions (Table 2, entry 1). Interestingly, we found that the temperature had a dramatic effect not only on the activity, but also on the chemoselectivity of the reaction. Lower temperature provided better selectivities towards the diborated product, unfortunately without any significant increase of the enantioselectivity (Table 2, entry 2). Increasing the amount of base resulted in a steady increase of the conversion up to 91%, at 1 equiv. of base (with respect to the substrate) (Table 2, entries 3, 4). Replacement of Cs_2CO_3 with sodium alkoxides such as NaOMe or NaO*t*Bu did not affect the chemoselectivity but it decreased the enantioselectivity (Table 2, entries 5, 6). This could be due to the competitive formation of [MeO → Bpin–Bpin]$^-$ or [*t*BuO → Bpin–Bpin]$^-$ which produces the racemic diborated product. The non-polar and polar nature of the solvent hardly affected the reaction outcome under the applied conditions (Table 2, entries 7, 8), although dichloromethane (DCM) provided the highest conversion and chemoselectivity (Table 2, entry 8).

Table 2 Optimisation of the reaction conditions in asymmetric metal free diboration of vinylcyclohexane with bis(pinacolato)diboron and alcohol **10**[a]

Entry	Base (mol%)	*t* (h)	*T* (°C)	Conv. (%)[b] [%][c]	Diboron[b] (%)	ee[d] (%)
1	Cs_2CO_3(15)	16	70	66	61	21 (*S*)
2	Cs_2CO_3(15)	16	45	49	86	23 (*S*)
3	Cs_2CO_3(80)	16	45	78	85	22 (*S*)
4	Cs_2CO_3(100)	16	45	91	83	24 (*S*)
5	NaO*t*Bu(100)	16	45	87	96	17 (*S*)
6	NaOMe(100)	16	45	88	96	10 (*S*)
7[e]	Cs_2CO_3(100)	16	45	83	89	27 (*S*)
8[f]	Cs_2CO_3(100)	16	45	96[72]	91	24 (*S*)

[a] Standard conditions: substrate (0.25 mmol), B_2pin_2 (1.1 equiv.), alcohol (2 equiv.), THF (1 mL), 70 °C, 16 h. [b] Conversion and chemoselectivity of the diborated product determined by GC and ^{1}H NMR spectroscopy. [c] Isolated yield. [d] Enantioselectivity was determined from the ketal product by GC-MS. [e] Solvent: toluene. [f] Solvent: DCM.

Table 3 Screening of secondary chiral alcohols for asymmetric metal free diboration of vinylcyclohexane with bis(pinacolato)diboron[a]

Entry	Alcohol		Conv.[b] (%)	Diboron[b] (%)	ee[c] (%)
1	**11**		83	84	18 (*S*)
2	**12**		50	70	3 (*S*)
3	**13**		90	86	33 (*S*)
4	**14**		70	87	40 (*S*)
5	**15**		75	80	20 (*S*)
6	**16**		18	89	35 (*S*)

[a] Standard conditions: substrate (0.25 mmol), B_2pin_2 (1.1 equiv.), Cs_2CO_3 (1 equiv.), alcohol (2 equiv.), DCM (1 mL), 45 °C, 16 h. [b] Conversion and chemoselectivity of the diborated product determined by GC and ^{1}H NMR spectroscopy. [c] Enantioselectivity was determined from the ketal product by GC-MS.

In order to tune the chiral reagent, we carried out the model reaction using secondary alcohols structurally related to 1-phenyl-ethanol (**10**). These reactions were carried out in DCM, which provided the optimal combination of activity, chemo- and stereoselectivity in the course of the optimization phase. Importantly, α-substituted benzyl alcohols (**11**, **13**–**15**) provided better activities and enantioselectivities than 2-phenyl-ethanol derivative **12**, confirming the beneficial effect of the benzylic position of the hydroxyl group (Table 3). Increasing the steric bulk of the alkyl substituents of the benzyl alcohol, such as the change of the methyl for ethyl, also provided a slight increase of the

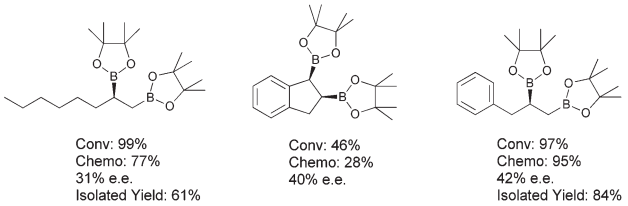


Fig. 1 Asymmetric metal free diboration of alkenes with chiral alcohol **14**.

stereoselectivity (ee up to 40%, Table 3, entry 4). The use of (*S*,*S*) *syn*-γ-amino alcohol provided similar enantioselectivity (ee 35%) combined with high chemoselectivity and low conversion (Table 3, entry 6).

To extend this methodology to other alkenes, we selected the chiral alcohol **14** on the basis of its beneficial influence on the chemo- and stereoselectivity. The substrates tested included a terminal aliphatic alkene (1-octene), a cyclic alkene (indene) and allylbenzene. In the case of the diboration of indene, in THF at 70 °C after 20 h of reaction time, the diborated product was formed in 40% enantiomeric excess, but both the conversion and the chemoselectivity were low (Fig. 1). Temperatures up to 70 °C were required for moderate conversion. Under the same reaction conditions described in Table 3 (45 °C, 16 h), the asymmetric organocatalytic diboration of 1-octene and allylbenzene provided high conversions and chemoselectivities, and enantioselectivities up to 42% ee (Fig. 1).

Conclusions

As a conclusion, we state that the described methodology represents a new concept for inducing enantioselectivity in the diboration of alkenes, in the absence of any transition metal complex, and as such it can potentially be applied in the enantioselective difunctionalization of unsaturated molecules. The simplicity of the method using economically accessible chiral alcohols combined with the obvious advantages in the purification of the products, due to the absence of transition metals, open new perspectives for organic synthetic purposes. The asymmetric induction needs to be improved, therefore we currently work on the experimental and theoretical design of chiral Lewis acid–base $*RO^-$ → bis(pinacolato)diboron adducts to promote the organocatalytic reaction inducing higher levels of asymmetry.

Acknowledgements

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