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Investigation of the active species in a Michael addition promoted by chirally modified tetrahydroborate

Susan Abraham and G. Sundararajan*

Department of Chemistry, Indian Institute of Technology Madras, Chennai 600036, India

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Dedicated to Professor Robert Moss on the occasion of his 65th birthday

Abstract—For the first time, asymmetric 1,4-addition of various malonates to enones has been carried out using tetrabutylammoniumtetrahydroborate (TBATB) in the presence of a chiral ligand. The Michael adducts were formed in reasonably good yields (61–67%) with moderate ee's at 0 °C. ^{11}B NMR spectroscopic studies explain this unexpected reactivity through the predominant formation of an aminodiol modified borate complex in the presence of a hydride acceptor.
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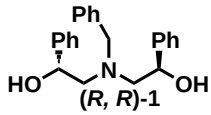
1. Introduction

The Michael addition, being one of the most important C–C bond-forming reactions, has attracted much attention toward the development of enantioselective catalytic procedures in recent years.[1] The current literature abounds with many reports on enantioselective Michael addition catalyzed by chiral complexes of Ru,[2a] Co,[2b] Rh,[2c] Ni,[2d] Cu,[2e] Zn,[2f] Cd,[2g] Al[2h] and other heterobimetallics.[3] Thus far, however, there are not many reports on boron catalyzed asymmetric Michael reactions.[4]

We have earlier shown that chiral aminodiol, (*R*,*R*)-**1**, in combination with $LiAlH_4$ or lanthanum–sodium, can be effectively used for asymmetric Michael additions.[5] As an extrapolation of these findings, we decided to investigate the application of chirally modified borohydrides in promoting the Michael reaction of α,β-unsaturated ketones. Although chirally modified boron has been employed to promote many asymmetric processes[6a] such as Diels–Alder,[6b] allylation[6c] and aldol[6d] reactions, little has been reported on the chirally modified tetrabutylammoniumtetrahydroborate (TBATB) system in such reactions. However, it is known that chirally modified borohydrides are effective in asymmetric reduction processes[7] but, in contrast, to chiral auxiliaries of lithium aluminum hydrides that promote asymmetric Michael addition,[3c,5] chirally modified borohydrides are not known to assist such reactions.[3c] Herein, we give a brief report on the results of Michael additions promoted by a mixture of TBATB/(*R*,*R*)-**1** in THF and attempts to rationalize our observations.



2. Results and discussion

The required ligand (*R*,*R*)-**1** was prepared from the reaction of (*R*)-styrene oxide with benzylamine.[5c] First, a control reaction was performed to study the reduction pattern of cyclic enone with TBATB in the presence of (*R*,*R*)-**1**. As expected the products were alcohol and ketone resulting from an initial 1,4-addition of hydride across the enone to give the enolate, that converts into the ketone (via the enol) and gets reduced further. These findings are in agreement with other literature reports.[8]

Subsequently, (*R*,*R*)-**1** in combination with TBATB was used as a promoter in the Michael addition of cyclic enones with diethyl malonate[9] (Eq. 1). The corresponding Michael adducts from cyclohexenone and cyclopentenone were formed in good yields and with moderate enantioselectivities. The reduced products of cyclic enone were also obtained in minor amounts along with the Michael adduct. In all these cases the yields of Michael adducts remained fairly constant. The results are summarized in Table 1.

Keywords: Borohydride; Michael addition; Malonates.
* Corresponding author. Tel.: +91 44 2257 4213; fax: +91 44 2257 4202; e-mail: gsundar@iitm.ac.in

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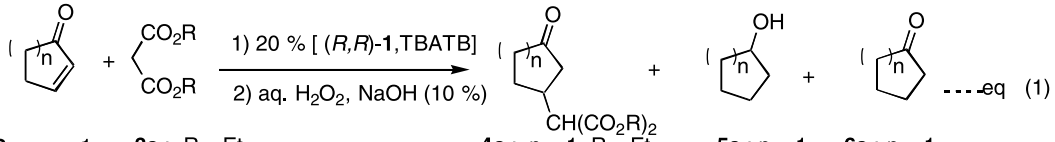
Table 1. Michael addition of various malonates to cyclic enones



2a : n = 1
2b : n = 2

3a : R = Et
3b : R = *t*-Bu
3c : R = Bn

4a : n = 1, R = Et
4b : n = 1, R = *t*-Bu
4c : n = 1, R = Bn
4d : n = 2, R = Et
4e : n = 2, R = t-Bu
4f : n = 2, R = Bn

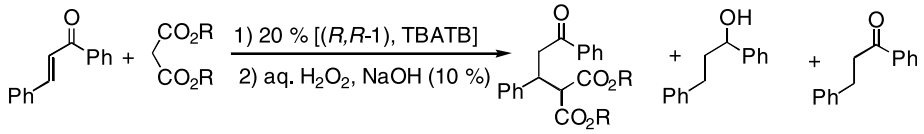
5a : n = 1
5b : n = 2

6a : n = 1
6b : n = 2

Entry	Enone	Michael donor	Time (h)	Product distribution (%)[a]			%ee of **4**[b]
				4	**5**	**6**	
1	**2a**	**3a**	7	**4a**=62	**5a**=24	**6a**=14	**4a**=35
2	**2a**	**3b**	7	**4b**=64	**5a**=22	**6a**=14	**4b**=40
3	**2a**	**3c**	7	**4c**=61	**5a**=25	**6a**=12	**4c**=31
5	**2b**	**3a**	7	**4d**=67	**5b**=22	**6b**=11	**4d**=42
6	**2b**	**3b**	7	**4e**=65	**5b**=25	**6b**=10	**4e**=45
7	**2b**	**3c**	7	**4f**=63	**5b**=22	**6b**=15	**4f**=39

[a] Determined by HPLC.
[b] %ee was determined by HPLC connected to a Chiracel OD. The absolute configuration in all cases were determined by comparison of optical rotation and was found to be *R*.

Table 2. Michael addition of benzylidineacetophenone with malonates



7

3a : R = Et
3b : R = *t*-Bu
3c : R = Bn

8a : R = Et
8b : R = *t*-Bu
8c : R = Bn

9

10

Entry	Enone	Michael donor	Time (h)	Product distribution (%)[a]		
				8	**9**	**10**
1		**3a**	7	**8a**=62	22	16
2	**7**	**3b**	7	**8b**=64	22	14
3		**3c**	7	**8c**=61	23	16

[a] Isolated yields.

In a similar manner benzylidineacetophenone reacts with malonates to give 1,4-adducts with moderate enantioselectivity, along with minor amounts of reduced products. The results are summarized in Table 2.

Thus, in the presence of (*R*,*R*)-**1** and TBATB a mixture of enone and malonate gives reasonable yields of the Michael adducts in moderate enantiomeric excess, suggesting the formation of a chirally modified borohydride, an observation that warranted further scrutiny.

To gain better insight into these findings, we chose to study the reaction by ^{11}B NMR spectroscopy. The ^{11}B NMR spectrum of a solution containing (*R*,*R*)-**1** and TBATB in a 2:1 ratio gave a quintet centered at −57.4 ppm indicating the presence of free borohydride.[10] To this mixture, the addition of cyclohexenone in portions of 0.5 equiv, promoted the formation of a singlet centered at −15.7 ppm alongside the quintet that could be attributed to a free tetraborate anion having a tetrahedral structure,[11,6b] and with 2.1 equiv of cyclohexenone the quintet disappeared completely leaving a sharp singlet at −15.7 ppm (Fig. 1). In the absence of cyclohexenone, a mixture of **1** and TBATB, showed the quintet persisting in the ^{11}B NMR spectrum even after an overnight reflux. Thus, the need for a hydride acceptor to initiate the formation of the tetraalkoxyborate becomes clear.

When the same experiment was performed with cyclohexanone, the quintet did not disappear completely, even after addition of many equivalents of the ketone, indicative of a relatively slow hydride transfer to cyclohexanone. Nevertheless, the appearance of a sharp singlet at −15.9 ppm could be seen here as well. Also as expected, the ^{11}B NMR spectrum of a solution containing (*R*,*R*)-**1**, TBATB and diethyl malonate in the absence of cyclohexenone gave no other signal than the quintet. Not so surprising also was the sudden appearance of the singlet at −15.5 ppm beside the quintet when a small amount of cyclohexenone was added to this solution at

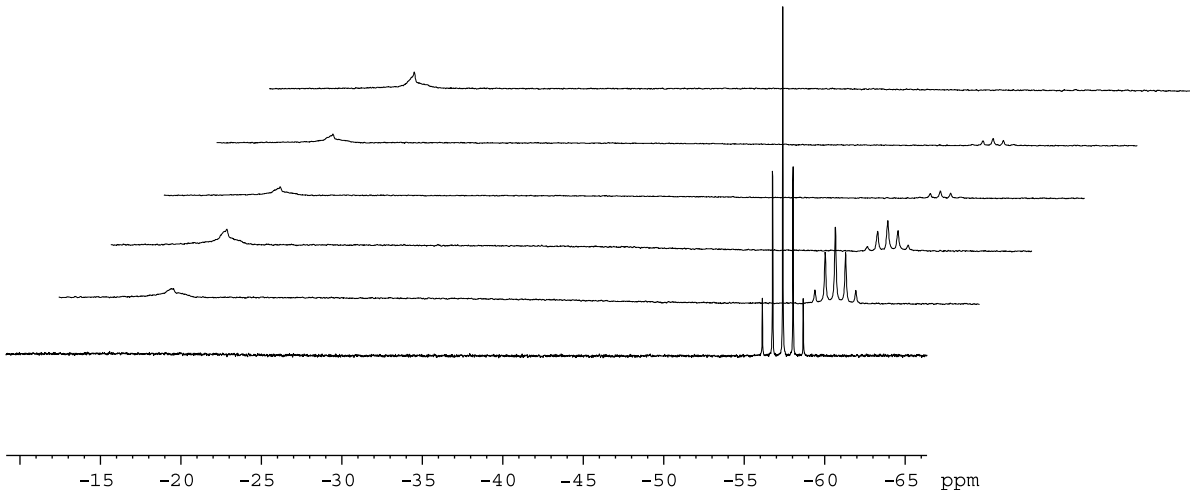
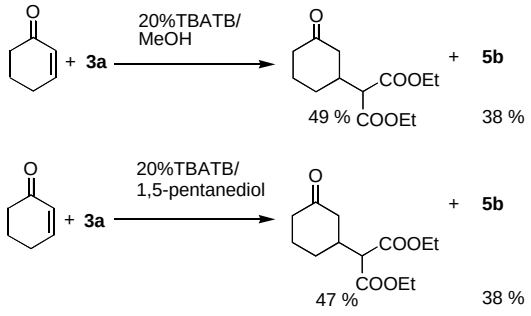


Figure 1. ^{11}B NMR spectra of **1**-TBATB and varying equivalents of cyclohexenone (a) 0 equiv (b) 0.5 equiv (c) 1.0 equiv (d) 1.5 equiv (e) 2.0 equiv (f) 2.1 equiv.

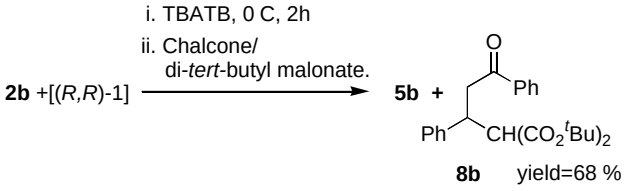
ambient conditions. Thus, the combined role of **1** and cyclohexenone in the generation of the singlet around −15 ppm in ^{11}B NMR needs to be appreciated.

To probe the effect of any interaction of the nitrogen atom in the backbone of (*R*,*R*)-**1** with the boron, the corresponding borate complex was generated from methanol or pentanediol by reacting with TBATB in the presence of the cyclic enone (Scheme 1). The borate complexes generated here, were effective in the Michael addition with product yields hovering around 47–49%, comparable to the earlier observations with (*R*,*R*)-**1** as the chelating ligand, pointing to an unlikely role for the nitrogen atom in the scaffold of **1**. Predictably, the ^{11}B NMR spectral studies of these systems were highly reminiscent of the earlier results.



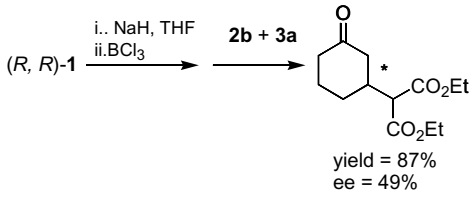
Scheme 1. Michael addition in the presence of achiral alcohols without any ligating atom in the backbone.

In order to confirm the need for a hydride acceptor in the formation of the active catalyst, we deliberately added cyclohexenone as a sacrificial hydride acceptor to the (*R*,*R*)-**1**-TBATB mixture prior to the addition of chalcone as the actual Michael acceptor. Thus, a solution of TBATB, (*R*,*R*)-**1** and cyclohexenone in the ratio 1:2:2 was stirred for a period of 2 h, to which a mixture of chalcone and malonate was added. As expected, we could get the Michael adduct corresponding to chalcone and di-*tert*-butyl malonate as the major product along with the reduction products of cyclohexenone (Scheme 2).



Scheme 2. Use of cyclohexenone as a sacrificial hydride acceptor.

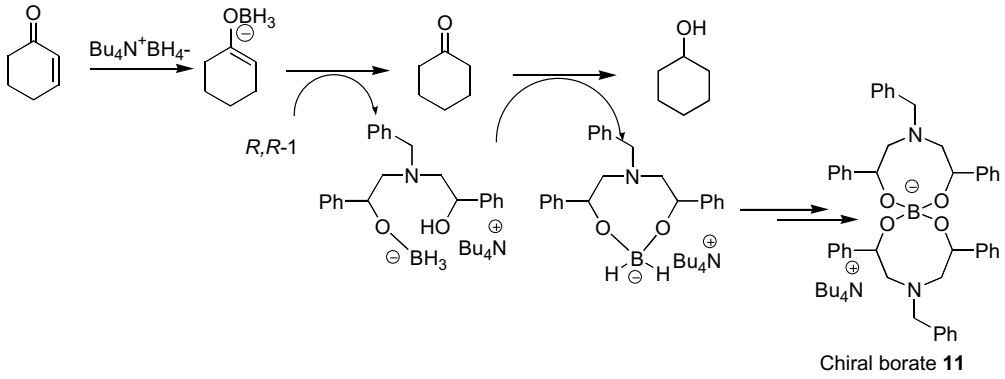
We also examined an alternate possibility for generating the borate, by reacting the disodiated (*R*,*R*)-**1** with BCl_3, to promote the Michael reaction involving cyclohexenone and diethyl malonate which, as expected, gave the Michael adduct in 87% yield with 49% ee (Scheme 3). It was also not surprising that the ^{11}B NMR spectrum of sodium aminodiolate and BCl_3 gave a peak at −16 ppm, implicating strongly the formation of a tetraborate species as in earlier cases.



Scheme 3. Asymmetric Michael addition with chiral borate generated from *R*,*R*-1 and BCl_3.

2.1. Suggested mechanism for the chirally modified borate promoted asymmetric Michael addition

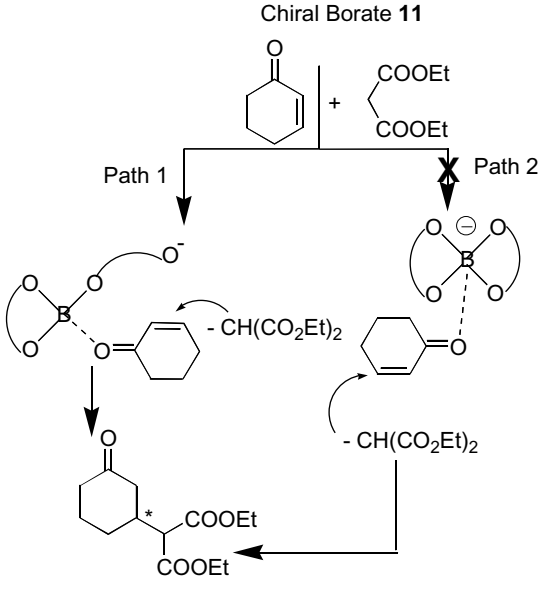
On viewing the above observations collectively, a plausible mechanism for the enantioselective Michael addition emerges (Scheme 4). The less acidic (*R*,*R*)-**1** does not react with TBATB to form the borate complex upon simple



Scheme 4. Suggested mechanism for the formation of the chirally modified borate in the asymmetric Michael addition.

mixing. However, when the enone is added, an initial hydride transfer from TBATB takes place; the enolate so generated undergoes a protic quench with (*R*,*R*)-**1** that converts it to the ketone. Stepwise mediation of boron leads to the eventual formation of the bischelate complex, the catalytically active species in the Michael reaction.

Clearly, the moderate (but tangible!) enantioselectivities observed in all these cases suggest probable coordination of cyclohexenone to a chirally modified borate complex. The possibilities could then be, either a tetracoordinate boron with one arm of the aminodiol acting as a detachable tether or a pentacoordinate hypervalent boron, the half life of which is very short on the NMR timescale[12] (vide Scheme 5). Further NMR spectroscopic investigations performed to detect the catalytically active species involved did not offer positive clues even at low temperatures (−60 °C) when only signals at −57 and −15 ppm could be observed. Since we have no clear proof by boron NMR spectroscopy or otherwise for the occurrence of pentacoordinate boron, we tend to support the former mechanism. The mechanism also explains the fact that the combined yields of the reduced products in the reaction equal a stoichiometric transfer of four hydrides from the borate (Table 1).



Scheme 5. Possible modes of activation of enone.

3. Conclusion

In conclusion, we have shown for the first time that chirally modified TBATB–aminodiol is effective in the Michael addition of α,β-unsaturated ketones with various Michael donors with moderate enantioselectivity. Evidence from ^{11}B NMR spectroscopic studies and other experiments support the formation of chiral tetrahedral borate from aminodiol and borohydride in the presence of a hydride acceptor.

4. Experimental

4.1. General experimental procedures

All operations were carried out under an atmosphere of dry, oxygen-free nitrogen employing vacuum or Schlenk line techniques, unless otherwise noted. Nitrogen was purified by passage through columns of MnO anchored on silica gel catalyst and 4 Å molecular sieves. Solid organometallic compounds were transferred in an argon-filled glove bag. All glassware, syringes and needles were oven dried at 140 °C and cooled to room temperature under nitrogen before use. Tetrahydrofuran was freshly distilled from sodium/benzophenone ketyl under nitrogen atmosphere. Cyclohexenone, di-*tert*-butylmalonate, di-ethylmalonate, di-benzylmalonate and (*R*)-styreneoxide were purchased from Lancaster synthesis and cyclopentenone was purchased from Aldrich and used as received. Tetrabutylammoniumtetrahydroborate (TBATB) was prepared from tetrabutylammonium-hydrogensulphate according to the literature procedure. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ at ambient temperature with TMS as the internal standard and ^{11}B NMR (135 MHz) spectra were recorded with boric acid as an external standard using AV400 Bruker spectrometer ($BF_3 \cdot Et_2O$ signal appeared at −19.38 ppm). Analytical HPLC was performed with Shimadzu LC-8A HPLC instrument equipped with RI detector and chiralcel OD column. Optical rotations were measured on a JASCO DIP-370 Polarimeter. Melting points were determined in a capillary and are uncorrected. Mass spectra were recorded on a Q-TOF mass spectrometer.

4.2. General reaction procedure of malonate addition on conjugate alkenones

To a solution of TBATB (56 mg, 0.214 mmol) in dry THF (3 mL) was added a solution of aminodiol (150 mg, 0.432 mmol) in THF (3 mL). The mixture was stirred under moisture free nitrogen atmosphere for 30 min at 0 °C, then a mixture of α,β-unsaturated ketone (1.06 mmol) and Michael donor (1.06 mmol) were added. The mixture was stirred for 7 h. The reaction was then quenched by the addition of 3% aqueous hydrogen peroxide (2 mL) and 10% aqueous sodium hydroxide (1 mL). The mixture was stirred for 2 h, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2×20 mL). The combined organic layer was dried over anhydrous sodium sulfate, concentrated and the crude product was purified by column chromatography (silica gel 60–120, acetone/hexane 10:90). NMR spectra are identical to those previously reported.[5]

%ee's were determined by HPLC (Daicel Chiralcel OD, 2.0:98.0, 2-propanol/hexane, flow rate = 0.5 mL/min, 254 nm; For example, **4e** had retention times of $t_1 = 28.6$ (*S*), $t_2 = 36.5$ (*R*)). The absolute configuration was established by comparison to the literature.[13]

Acknowledgements

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