Reversibility in the boron-mediated ketone–ketone aldol reaction

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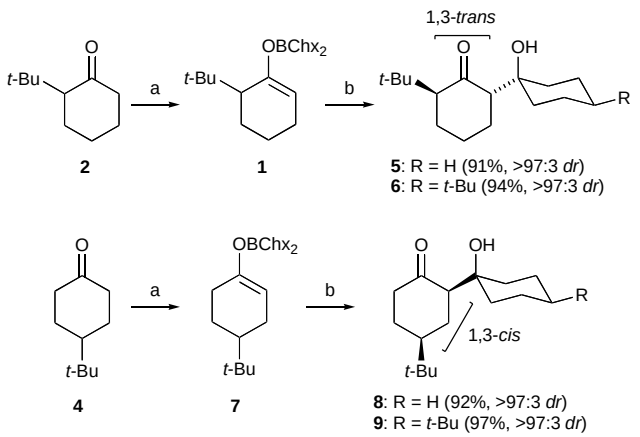
The boron-mediated ketone–ketone aldol reaction is demonstrated, through ^{1}H NMR studies, to be reversible, in contrast to the strictly irreversible aldol reactions of boron enolates with aldehydes.

The directed aldol reaction using boron enolates and aldehydes has often been employed in stereoselective organic synthesis, including the syntheses of several complex natural products, owing in large part to the high levels of chemo-, regio- and stereoselectivity that can be achieved.[1] We have recently reported the first examples of the directed, boron-mediated aldol reaction between non-activated, cyclic aliphatic ketones.[2] In an effort to further explore the utility of this reaction for the stereoselective union of substituted cyclohexanones, the aldol reactions of dicyclohexylboron enolate **1**, derived from 2-*tert*-butylcyclohexanone (**2**) under standard conditions (Chx_2BCl, Et_3N, Et_2O, 0 °C),[3] with cyclohexanone (**3**) or 4-*tert*-butylcyclohexanone (**4**), were examined. Aldol adduct **5** was the sole isolated diastereomer (> 97:3 *dr* by ^{1}H NMR), from the reaction of **1** with **3**, followed by oxidative treatment of the intermediate boron aldolate (H_2O_2, MeOH, pH 7 buffer), demonstrating that very bulky groups at the 2- position of the starting cyclohexanone favour the formation of 1,3-*trans* products (Scheme 1). The reaction of **1** with **4** similarly provided aldol adduct **6** with 1,3-*trans* diastereoselectivity, and with complete selectivity for equatorial attack of the enolate on conformationally locked **4**.



Scheme 1 *Reagents and conditions*: a. Chx_2BCl, Et_3N, Et_2O, 0 °C, 1 h; b. (i) cyclohexanone (**3**) or 4-*tert*-butylcyclohexanone (**4**), 0–5 °C, 24–40 h; (ii) 30% aq. H_2O_2, MeOH, pH 7 buffer, 0 °C to r.t., 2 h.

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The influence of a bulky substituent at the 4- position of the starting cyclohexanone was also examined. Reaction of boron enolate **7**, derived from 4-*tert*-butylcyclohexanone (**4**), with cyclohexanone (**3**), provided **8** with complete 1,3-*cis* stereocontrol (> 97:3 *dr* by ^{1}H NMR). Once again, 4-*tert*-butylcyclohexanone (**4**) reacted as an acceptor in a similar manner, providing the 1,3-*cis* product **9** with complete selectivity for equatorial attack on **4**. The stereochemistry of these four aldol products was assigned on the basis of 2D NOESY experiments and coupling constant data, and confirmed by single crystal x-ray diffraction on **6** and **9** (Figs. S2 and S3, Supplementary Information).‡

In an effort to understand the somewhat surprising nature and extent of diasteroselectivity in these reactions, we sought to determine whether the boron-mediated ketone–ketone aldol reaction is truly irreversible and under kinetic control, in contrast to the well established irreversibility of the analogous reaction with aldehyde acceptors.[4–6]

^{1}H NMR studies of the boron-mediated ketone–ketone aldol reaction were undertaken with a view to gaining information about the nature of the boron aldolate forming step. Rapid formation (< 10 min) of the dicyclohexylboron enolate **1** in d_{10}-diethyl ether was observed upon addition of ketone **2** to Chx_2BCl/Et_3N, as indicated by the appearance of the olefinic boron enolate proton signal at δ 5.03 (app t, J = 3.7 Hz) (Fig. 1a).[7] Formation of the boron aldolate **10** between the pre-formed boron enolate **1**, and cyclohexanone (**3**) as the acceptor ketone (1.1 equiv.), was monitored over a 14 hour period (278 *K*) by the appearance of the distinctive boron aldolate

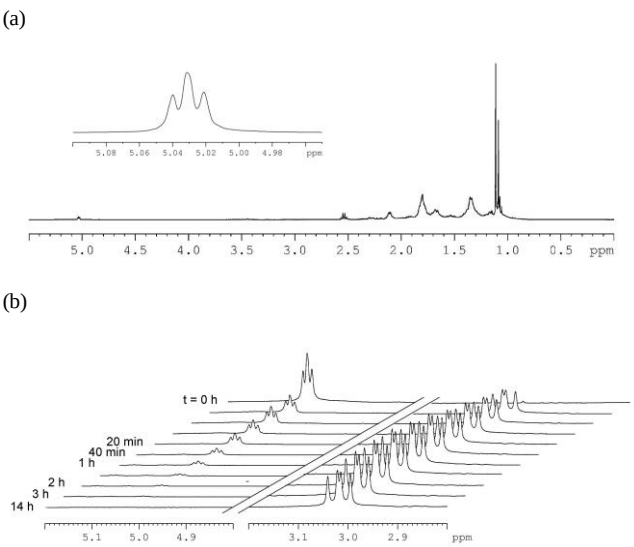

Fig. 1 ^{1}H NMR spectra (400 MHz, d_{10}-diethyl ether, 273 *K*). (a) Boron enolate **1**; (b) cyclohexanone (**3**) added to enolate **1** at t = 0, and 278 K.

H_α signal at δ 3.02 (dd, J = 7.8, 10.5 Hz), in unison with the disappearance of the olefinic boron enolate signal (Fig. 1b).

To test the potential reversibility of this boron aldolate forming step (Scheme 2), a second cyclic acceptor ketone, 4-*tert*-butylcyclohexanone (**4**) (2 equiv.), was introduced into the solution of aldolate **10**, and the appearance of a second boron aldolate H_α signal at δ 3.06 (app t, J = 9.8 Hz) was observed to increase in intensity over the course of 72 h, corresponding to formation of boron aldolate **11** (Fig. 2).

This new signal was confirmed in separate experiments to be due to boron aldolate **11** (Fig. 3a). Additionally, the reverse cross-over experiment was performed, ie. formation of aldolate **11**, followed by introduction of cyclohexanone (**3**) and observation of H_α for aldolate **10** (Fig. 3b). This reversible aldolate formation was also examined using preformed aldol adduct as a starting point. Aldol adduct **5** was treated with Chx_2BCl/Et_3N in d_{10}-diethyl ether to generate the dicyclohexylboron aldolate **10**, as evidenced by the appearance of the H_α signal. On addition of 4-*tert*-butylcyclohexanone (**4**), the appearance of the signal corresponding to the second boron aldolate **11** increases in intensity over time, as expected (Fig. S1, Supplementary Information).[8]

Analogous experiments were carried out using boron enolate **1** and two aldehyde acceptors, propionaldehyde and isobutyraldehyde. Boron aldolate formation was observed by ^{1}H NMR, however, addition of a second aldehyde to these boron aldolate solutions failed to show subsequent formation of new boron aldolate species. These experiments, which exhibit no evidence of boron aldolate equilibration with aldehyde acceptors, support the accepted irreversible, kinetically controlled pathway for the reaction of boron enolates with aldehydes.[6]

Reversibility in the reaction between the dicyclohexylboron enolate **1** and cyclohexanone acceptors has been demonstrated, and can be accounted for by the mechanism illustrated in Scheme 2. Reversible formation of boron ate complexes **12** or **13**, from boron enolate **1** and cyclohexanone (**3**) or 4-*tert*-butylcyclohexanone (**4**), is followed by bond reorganisation to give boron aldolates **10** or **11**, respectively**.** Assuming rapid equilibration, the stereochemical outcome of this C–C bond forming step will be under thermodynamic control.[9] Given that the ate complex is also in equilibrium with free boron enolate (**1**), this then allows formation of a second ate complex and corresponding boron aldolate upon introduction of a second ketone acceptor. Severe steric congestion in these boron aldolates may account for their propensity to undergo retro-aldolisation to boron enolate and ketone, in contrast to the ketone–aldehyde aldolates, which are less sterically congested and do not exhibit analogous reversibility. Further experimental and computational investigations of stereoselectivity in these ketone–ketone aldol reactions will be reported in due course.

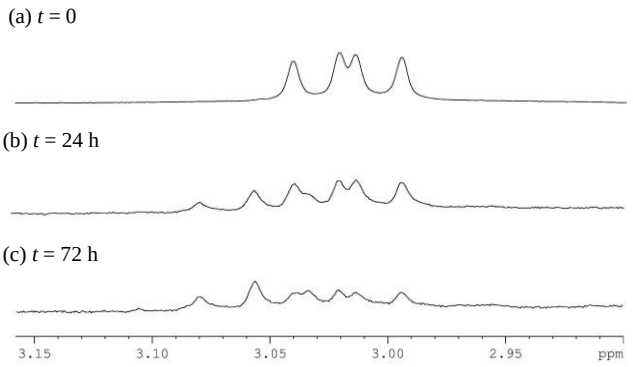

Fig. 2 ^{1}H NMR spectra (400 MHz, d_{10}-diethyl ether, 278 *K*). (a) **10** prior to addition of **4** (t = 0); (b) 24 h after addition of **4**; (c) 72 h after addition of **4**.

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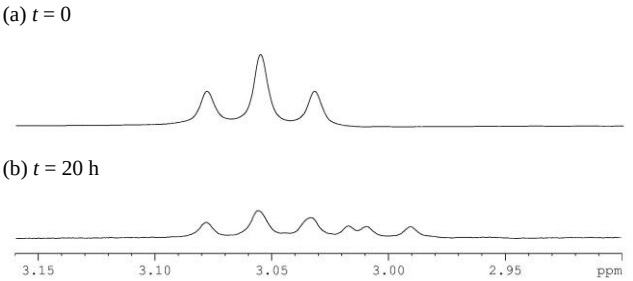
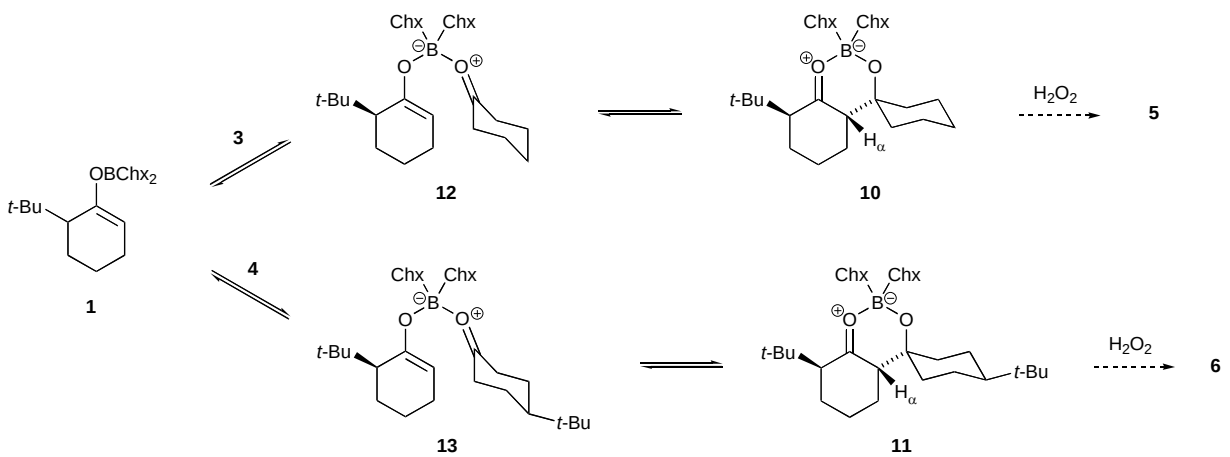


Fig. 3 ^{1}H NMR spectra (400 MHz, d_{10}-diethyl ether, 300 *K*). (a) Boron aldolate **11**; (b) 20 h after addition of **3**.

Notes and references

‡ Crystal structure data for **6**: $C_{20}H_{36}O_2$, M = 308.49, Monoclinic, $P2_1/c$



Scheme 2 Boron aldolate equilibration.

(#14), a = 13.179(1) Å, b = 12.282(1) Å, c = 12.063(1) Å, β = 104.982(1)°, V = 1886.2(3) Å^3, Z = 4, T = 150(2) K, μ(MoKα) = 0.067 mm^{-1}, N = 18394, N_{ind} 4483 (R_{int} = 0.0203), $R1(F)$ = 0.0411 ($I > 2\sigma(I)$), $wR2(F^2)$ = 0.1230 (all data). Crystal structure data for **9**: $C_{20}H_{36}O_2$, M = 308.49, Monoclinic, $P2_1/n$ (#14), a = 11.9035(3) Å, b = 12.7978(4) Å, c = 24.8807(7) Å, β = 96.953(1)°, V = 3762.4(2) Å^3, Z = 8, T = 150(2) K, μ(MoKα) = 0.068 mm^{-1}, N = 80737, N_{ind} 10076 (R_{int} = 0.0696), $R1(F)$ = 0.0447 ($I > 2\sigma(I)$), $wR2(F^2)$ = 0.0848 (all data). CCDC 628475-628476. For crystallographic data in CIF format see DOI:

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3 H. C. Brown, R. K. Dhar, G. Kumaraperumal, B. Singaram, *J. Org. Chem.*, 1992, **57**, 499–504; H. C. Brown, R. K. Dhar, K. Ganesan. K. B. Singaram, *J. Org. Chem.*, 1992, **57**, 2716–2721.

4 Brown and co-workers established that the boron enolate formation is irreversible and under kinetic control, ref. 3.

5 On the assumption of kinetic control, transition state models based on cyclic chair- and boat-like transition states have been highly successful in rationalising the stereoselectivity in these reactions, for examples see: A. Bernardi, A. M. Capelli, C. Gennari, *J. Org. Chem.*, 1990, **55**, 3576–3581; A. Bernardi, A. Comotti, C. Gennari, C. T. Hewkin, J. M. Goodman, A. Schlapbach, I. Paterson, *Tetrahedron*, 1994, **50**, 1227–1242; A. Bernardi, C. Gennari, J. M. Goodman, I. Paterson, *Tetrahedron: Asymmetry*, 1995, **6**, 2613–2636.

6 Evans and co-workers showed that boron-mediated ketone–aldehyde aldol reactions are not reversible, even at high temperature, see: D. A. Evans, J. V. Nelson, E. Vogel, T. R. Taber, *J. Am. Chem. Soc.*, 1981, **103**, 3099–3111.

7 Enolisation was accompanied by the formation of a white precipitate of $Et_3N{\bullet}HCl$, which was compacted by centrifugation.

8 HPLC analysis of product mixtures from separate cross-over experiments of this type support our interpretation of these ^{1}H NMR results.

9 The diastereoselectivities shown in Scheme 1 for formation of aldol adducts **5**, **6**, **8** and **9** could therefore result from differences in the stability of the diastereomeric boron aldolates.