The boron-mediated ketone–ketone aldol reaction

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Abstract—The first examples of the directed, boron-mediated aldol reaction between different ketones are presented. Transformation of a variety of ketones to their corresponding boron enolates with Chx_2BCl/Et_3N, followed by reaction with acceptor ketones in diethyl ether, and oxidation of the resultant boron aldolate (H_2O_2, MeOH/pH 7 buffer), provided the aldol addition products. The reaction was most facile when cyclic ketones were used, with the highest yields obtained for the reaction of boron enolates with cyclohexanone as the acceptor.

The directed aldol reaction is one of the most valuable carbon-carbon bond-forming processes available to the organic chemist.[1] Amid the plethora of available procedures, the aldol reaction of boron enolates with aldehydes has found particularly widespread application in stereoselective organic synthesis.[2] Attractive features of this process include the highly predictable regio- and stereoselective outcomes that can be achieved with a variety of ketones and aldehydes, under mild conditions. The many applications of this reaction to the late-stage coupling of complex molecules in the area of natural product synthesis,[3] serve to highlight the reliability and functional group tolerance of this transformation. However, despite the exemplary nature of the boron-mediated aldol reaction of ketone-derived enolates with acceptor aldehydes, there have been no reports of the reaction of boron enolates with acceptor ketones to give aldol addition products in synthetically useful yields. In contrast to the myriad of procedures available for directed aldol reactions employing aldehydes as acceptors, there are relatively few general procedures for the directed aldol reaction of two different ketones. Reactions of ketone-derived, Sn(II),[4] Ce(III)[5] and Ti(IV)[6] enolates with acceptor ketones have been reported, however, examples of the direct cross-coupling of differing aliphatic ketones have been limited to the last of these procedures.[6a,c]

As part of a program directed toward the synthesis of sterically-congested 1,3-diols, we have investigated the boron-mediated aldol reaction between two different ketones for the construction of highly substituted β-hydroxy ketones. We now report the reaction of dicyclohexylboron enolates, derived from an assortment of aliphatic ketones, with a variety of acceptor ketones, to provide the aldol addition products under mild conditions.

Initial experiments involved the enolisation of cyclohexanone (Chx_2BCl, Et_3N, Et_2O),[7] to give the corresponding boron enolate *in situ*, and subsequent reaction with acetone or 3-pentanone (Et_2O, 5 °C, 16 h), followed by treatment with H_2O_2 in MeOH/pH 7 buffer (Scheme 1). The reaction with acetone afforded the expected aldol product **1a** in low yield (15%), along with a comparable quantity of compound **2** (12%),[8] presumably resulting from the reaction of cyclohexanone with its corresponding dicyclohexylboron enolate. In contrast, attempts to extend this reaction to 3-pentanone failed to give any of the desired aldol product **1b**, providing **2** (11%) as the sole isolated product. Changing the reaction solvent to pentane led to only trace quantities of aldol products.

While the low yields obtained using the simple acyclic ketones, acetone and 3-pentanone, suggested that ketones are relatively unreactive towards boron enolates, as implied by the lack of literature precedence in this regard, we were intrigued by the apparent reactivity of cyclohexanone as an acceptor under these conditions.

Keywords: boron aldol, ketones, sterically congested.

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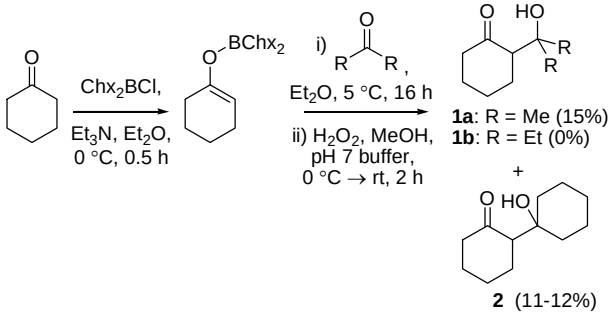
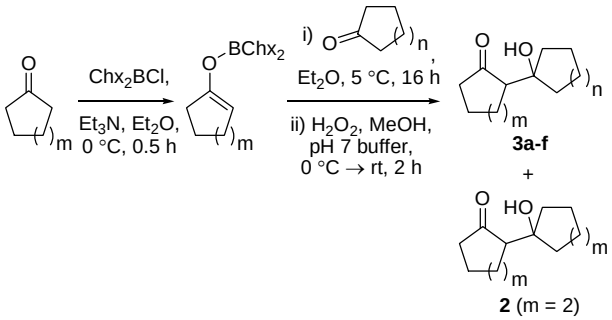


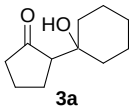
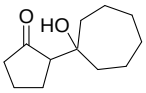
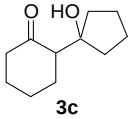
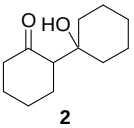
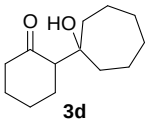
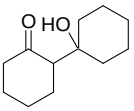
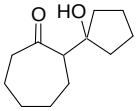
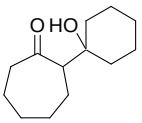
Scheme 1.

The boron-mediated aldol reaction of simple cycloalkanones was systematically studied for five- to seven-membered rings (Table 1).[9] In all cases studied, the desired cross aldol product could be isolated in low to good yields. The highest yields were obtained when cyclohexanone was used as the acceptor ketone (entries 1 and 6, 70% and 64% respectively). The lower yields obtained with cyclopentanone or cycloheptanone as the acceptor under the standard reaction conditions, are attributed to a slower rate of reaction. In the case of the cycloheptanone-derived enolate reacting with cyclopentanone (entry 5), increasing the reaction time from 16 h to 40 h led to a moderate increase in yield (41 → 61%).[10] Furthermore, reactions involving cyclohexanone as the donor ketone (entries 3-4) resulted in the formation of small amounts of **2** (5-8%). In contrast, when cyclopentanone or cycloheptanone were used as the donor ketone, none of the analogous "self-aldol" product was obtained (entries 1-2, 5-6). These findings serve to demonstrate the high reactivity of cyclohexanone as an acceptor ketone in these reactions.

Variation of the reaction conditions, e.g. rate/order of addition, enolisation temperature (–78 °C) and solvent (pentane, CH_2Cl_2), failed to improve the overall yield of aldol product or decrease the quantity of **2** produced in these reactions. Furthermore, the use of the corresponding di-*n*-butylboron enolates, gave lower yields of the desired aldol products (<20%). In these cases, the reactions were conducted in CH_2Cl_2, which we have found to be a greatly inferior solvent for this aldol addition, and therefore the low yields likely illustrate the effect of solvent on the rate of the reaction, rather than the nature of the boron ligands.

Table 1. Boron-mediated aldol reaction between cyclic ketones.



Entry	m	n	Products (yield)[a]	
1	1	2	 **3a** (70%)	–
2	1	3	 **3b** (39%)	–
3	2	1	 **3c** (47%)	 **2** (5%)
4[b]	2	3	 **3d** (8%)	 **2** (8%)
5	3	1	 **3e** (41%)[c]	–
6	3	2	 **3f** (64%)	–

[a]Isolated yields.

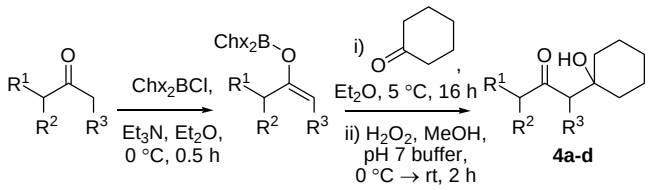
[b]Compounds **2** and **3d** were not separable by flash chromatography.

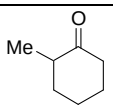
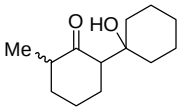
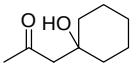
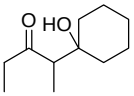
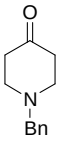
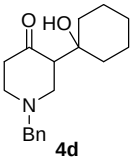
[c]Aldol reaction at 5 °C for 40 h gave a 61% yield of **3e**.

The yields obtained using cyclic ketones as acceptors in these aldol reactions correspond with their rates of reduction with sodium borohydride,[11] reflecting the relative reactivity of each of these ketones toward nucleophilic addition. Molecular mechanics calculations have been used to rationalise the differing reactivity of cyclic ketones according to ring size.[12] Of the acceptor cycloalkanones

studied here, only cyclohexanone has been calculated to be more strained than the corresponding hydrocarbon, cyclohexane. Moreover, the inability to have an alkyl group eclipsing the carbonyl has been used to rationalise the increased strain of cyclohexanone relative to 3-pentanone. Hence, cyclohexanone represents a particularly reactive acceptor ketone for the boron-mediated aldol reaction, due to lack of steric hindrance about the carbonyl group and release of ring strain upon nucleophilic addition.[13] Noting the superior results obtained with cyclohexanone as the acceptor in these boron-mediated ketone-ketone aldol reactions, the scope of this transformation was further explored using a variety of ketone donors and cyclohexanone as the acceptor (Table 2).

Table 2. Boron-mediated aldol reaction between ketones and cyclohexanone.



Entry	Donor ketone	Products (yield)[a]
1		 **4a** (75%, 2:1 *cis*/*trans*-)
2[b]		 **4b** (52%)
3[b]		 **4c** (63%)
4		 **4d** (75%)

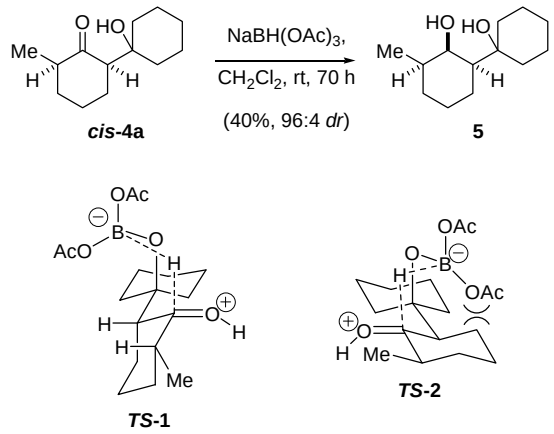
[a]Isolated yields.

[b]Aldol reaction at 5 °C for 40 h.

The aldol reaction proceeded smoothly with 2-methylcyclohexanone as the donor ketone (entry 1), via regioselective enolate formation, providing the aldol product **4a** in good yield (75%), as a 2:1 mixture of *cis* and *trans* diastereomers, respectively. The stereochemistry of each of these were assigned on the basis of ^{1}H NMR coupling constants and NOESY spectra, and confirmed by X-ray crystallographic analysis of a derivative, *vide infra*.

The aldol reaction of acyclic donor ketones, acetone and 3-pentanone, with cyclohexanone proceeded less rapidly, requiring 40 h to yield the corresponding aldol products, **4b** and **4c**, respectively (entries 2 and 3).[14] The aldol reaction with a heterocyclic donor ketone, *N*-benzyl-4-piperidone, provided **4d** (entry 4) in good yield (75%).

The aldol products produced by the methods outlined here could, in principle, be reduced to 1,3-diols by a variety of methods. In order to verify the stereochemical assignments of ***cis***- and ***trans***-**4a** (Table 2, entry 1), the major diastereomer was subjected to $NaBH(OAc)_3$ in dichloromethane (Scheme 2).[15] The corresponding, crystalline 1,3-diol **5** was produced as the major diastereomer (96:4 *dr* by GC and ^{1}H NMR analysis).



Scheme 2. Reduction of ***cis***-**4a**.

The structure and relative stereochemistry of **5** were determined by single crystal X-ray diffraction,[16-21] which confirmed the aldol reaction gave predominantly the *cis*-diastereomer, while reduction occurred via equatorial delivery of hydride to ***cis***-**4a** (Figure 1). This is in contrast to the reduction of *syn*- and *anti*-cyclohexanone–benzaldehyde aldol adducts with $NaBH(OAc)_3$, which provide as the major products, 1,3-diols resulting from axial delivery of hydride.[15]

Inspection of models, in relation to Evans' mechanistic studies on triacetoxyborohydride mediated reduction of hydroxyketones,[22] suggests that the stereoselectivity observed in the reduction of ***cis***-**4a** to **5** may arise by internal delivery of hydride via a boat-like transition state ***TS***-**1**, leading to the axial alcohol.[23] The boat-like transition state, ***TS***-**2**, for internal delivery of hydride in an axial sense suffers from severe 1,4- steric interactions between the acetoxy group on boron and a CH_2 of the cyclohexanone ring. Examination of alternative, chair-like transition states for internal delivery of hydride to either face of the ketone, suggests these are unfavourable in each case due to 1,3-diaxial interactions between an acetoxy group and an axially-oriented CH_2 of one of the six-membered rings.[24]

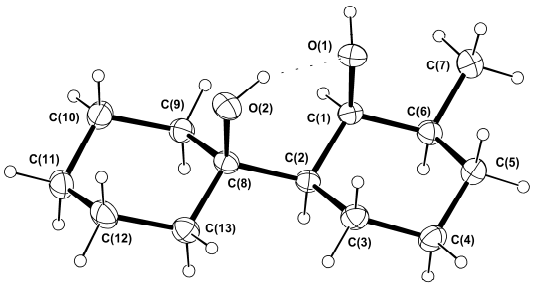


Figure 1. ORTEP[19,25] depiction of **5**, with 50% displacement ellipsoids.

In summary, the boron-mediated ketone-ketone aldol reaction has been shown to be a facile process with cyclic acceptor ketones. In particular, cyclohexanone was found to react with a variety of boron enolates to afford the cross aldol products in good yields. Further efforts to explore the stereoselectivity of this reaction with substituted ketones, and to functionalize the aldol products toward sterically-encumbered 1,3-diols and related compounds, will be reported in due course.

Acknowledgments

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8. All new compounds gave spectroscopic data in agreement with the assigned structures. The data for compound **2** match those reported previously: Yasuda, M.; Hayashi, K.; Katoh, Y.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* **1998**, *120*, 715-721.
9. *Representative procedure*: A solution of Chx_2BCl (241 μL, 234 mg, 1.1 mmol, 1.1 equiv.) in Et_2O (4 mL) at 0 °C was treated with Et_3N (167 μL, 121 mg, 1.2 mmol, 1.2 equiv.) dropwise, followed by cyclopentanone (88 μL, 84 mg, 1.0 mmol) and the resulting mixture was stirred for 45 minutes. Cyclohexanone (114 μL, 108 mg, 1.1 mmol, 1.1 equiv.) was added and the mixture was left at 5 °C for 16 h. A pre-mixed solution of 6:1 MeOH (6 mL) and pH 7 buffer (1 mL) was added at 0 °C, followed by a pre-mixed solution of 2:1 MeOH (2 mL) and 30% H_2O_2 (1 mL), and the mixture was warmed to rt. After 2 hours at rt the mixture was diluted with Et_2O (10 mL) and H_2O (10 mL), the layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (15 mL), and brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 25:75 EtOAc/hexanes) provided **3a** (128 mg, 70%) as a colourless oil: **IR** (NaCl, thin film) 3493, 2934, 2858, 1724, 1448, 1402, 1356, 1321, 1271, 1250, 1209, 1155, 1065, 1034, 1001 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.43 (1H, s), 2.32-2.24 (1H, m), 2.19-1.90 (4H, m), 1.72-1.52 (6H, m), 1.44-1.30 (5H, m), 1.12-1.02 (1H, m); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 222.9, 72.6, 58.3, 39.7, 36.2, 32.6, 25.8, 25.5, 21.2, 21.1, 20.1; **HRMS** (+ESI) Calc. for $C_{11}H_{18}O_2Na$ $[M + Na]^+$: 205.1199, found: 205.1200.
10. In cases where a low to moderate yield of the aldol product was obtained, t.l.c analysis suggested that some unreacted starting materials remained. However, these starting materials were too volatile to recover from the reaction mixtures. Conducting the reaction at temperatures above 5 °C led to lower yields and the production of undesired side products.
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12. Allinger, N. L.; Tribble, M. T.; Miller, M. A. *Tetrahedron*, **1972**, *28*, 1173-1190.
13. No aldol reaction is observed when 2-methylcyclohexanone is used as the acceptor ketone, demonstrating the strong influence of a 2-alkyl substituent on the reactivity of the acceptor. This may be attributed to increased steric hindrance about the carbonyl group, and a diminished contribution from strain relief.
14. The yield of **4c** was also limited by difficulties in isolation, due to the significant volatility of this compound.
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16. *Structure Determination for* ***5***: The crystals fragmented on cutting, accordingly a larger than ideal crystal was used for the data collection. A Bruker SMART 1000 CCD diffractometer with graphite monochromated MoKα radiation from a sealed tube was used to collect data at 150(2) Kelvin, using ω scans. Data integration and reduction were undertaken with SAINT and XPREP[17], and subsequent computations were carried out with the WinGX[18] and XTAL[19] graphical user interfaces. The structure was solved in the space group $P2_1/n$(#14) by direct methods with SIR97,[20] and extended and refined with SHELXL-97.[21] The non-hydrogen atoms were modelled with anisotropic displacement parameters, and the hydrogen atom sites were located and

modelled with isotropic displacement parameters. *Crystal Data*: Formula $C_{13}H_{24}O_2$, *M* 212.32, space group $P2_1/n$(#14), *a* 11.783(2), *b* 6.3284(11), *c* 15.914(3) Å, β 97.095(3), *V* 1177.6(3) $Å^3$, *Z* 4, crystal size 0.628 by 0.088 by 0.049 mm, colour colourless, habit acicular, temperature 150(2) Kelvin, λ(MoKα) 0.71073 Å, μ(MoKα) 0.078 mm^{-1}, $2\theta_{max}$ 56.62, *hkl* range -14 15, -8 8, -20 20, *N* 11150, N_{ind} 2812(R_{merge} 0.0616), N_{obs} 1650(I > 2σ(I)), N_{var} 232, residuals *R*1(*F*) 0.0397, *wR*2(F^2) 0.0921, GoF(all) 1.085, $\Delta\rho_{min,max}$ -0.196, 0.286 e^- $Å^{-3}$. Crystallographic data (excluding structure factors) for **5** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 254676. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or email: deposit@ccdc.cam.ac.uk].

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