A New Approach to (*Z*)-Vinyloxyboranes *via* 1,4 Hydroboration of (*E*)-α,β-Unsaturated Ketones. Synthesis of *syn* Aldols

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(*Z*)-Vinyloxy boranes are obtained *via* 1,4-hydroboration of acyclic disubstituted (*E*)-α,β-unsaturated ketones with dicyclohexylborane or diisopinocampheylborane in tetrahydrofuran, CH_2Cl_2 or $CHCl_3$ at 20 °C; treatment of the hydroboration mixture with an aldehyde allows pure *syn* aldols to be synthesized in good yields, and in excellent enantiomeric excesses, using the latter borane.

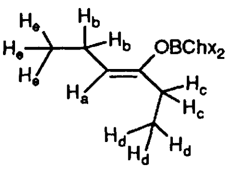
Boron enolates[1] are important tools in achieving stereocontrolled aldol reactions. They are usually prepared *via* enolisation of a carbonyl compound with a base followed by borylation with a suitable dialkylboron chloride or trifluoromethane sulphonate.[2] However, this procedure suffers from a lack of perfect regio- and stereo-control particularly in the case of unsymmetrical ketones.

Here we report a simple one-pot two-step procedure for the synthesis of *syn* aldols involving the reductive condensation of acyclic (*E*)-α,β-unsaturated ketones with aldehydes (Scheme 1). The key step is a 1,4-hydroboration of an (*E*)-α,β-unsaturated ketone with dicyclohexylborane (Chx_2BH)[3] or (−)-diisopinocampheylborane (Ipc_2BH),[4] which can be carried out in tetrahydrofuran (THF), CH_2Cl_2 or $CHCl_3$ at room temperature. The reaction product is a vinyloxyborane which, upon quenching with D_2O, affords the α-deuteriated saturated ketone. This reaction is in sharp contrast with the well known behaviour of 9-borabicyclononane which reduces α,β-unsaturated ketones to allylic alcohols in high yields.[5] For example, when (*E*)-hex-4-en-3-one **1a**, chosen as a model ketone, was added at 20 °C to Chx_2BH in $CDCl_3$ a single hydroboration product was observed by NMR analysis (Varian Gemini-300) of the reaction mixture. The signal at δ 4.58 of H_a appears as a tt multiplet (J_{ab} 7.0 Hz and J_{ac} 1.1 Hz), where the smaller allylic coupling constant J_{ac} is known to be typical of a *cis* arrangement.[6] Moreover, an NOE experiment showed positive enhancements of H_b (1.1%) at δ 1.85, H_c (0.8%) at δ 2.04, H_d (1.9%) at δ 1.02 and H_e (2.0%) at δ 0.92, upon irradiation of H_a. These observations support the assignment of the (*Z*) configuration to the intermediate vinyloxyborane **2a** (Fig. 1). Finally, only two peaks at δ 152.5 and 109.7 in the alkenic region of the ^{13}C NMR spectrum were detected.

Additional evidence supporting the (*Z*) geometry of **2** is given by the diastereoselectivity exhibited in condensation reactions with aldehydes. In fact the formation of *syn* aldols starting from (*Z*)-vinyloxyboranes *via* chair-like transition states (Zimmermann–Traxler model) is reported to be normal.[2] Upon addition of an aldehyde to the hydroboration mixture, a smooth reaction takes place affording *syn* β-hydroxyketones† in good isolated yields and in excellent enatiomeric excess (e.e.) when the chiral (−)-Ipc_2BH is used (Table 1, runs 2–6). This two-step procedure has been successfully applied to β-ionone **1b**, 4-phenyl-but-3-en-2-one **1c**, and 1,3-diphenylpropenone **1d** (Table 1, runs 3–7). In all these cases a single vinyloxyborane was observed in the NMR spectra of the hydroboration mixture, and *syn* aldols were invariably obtained.

The overall stereochemical outcome of the hydroboration–condensation process leads us to propose a concerted pericyclic mechanism for the 1,4 hydroboration reaction,[7] which requires that the α,β-unsaturated ketone adopts a *s-cis* conformation (Fig. 2). Cyclohex-2-enone, which is blocked in an *s-trans* conformation, failed to give the boron enolate under the reported conditions and, in contrast, it underwent C=O and C=C reduction. An alternative reaction pathway such as a regioselective 1,2 hydroboration of the electron-poor C=C bond to give an α-borylated ketone, which then undergoes a 1,3-borotropic C → O shift to a vinyloxyborane, could hardly account for the absolute (*Z*) preference of the enolate C=C bond configuration.

In conclusion, from the synthetic point of view, the reductive condensation process we have described corresponds to a regio- and stereo-controlled condensation of an



2a

Fig. 1

Table 1 Aldol condensations *via* hydroboration[a]

Run	Ketone	Aldehyde	Solv.	*T*/°C	*t*/h	Aldol **3** Yield (%)	Aldol **3** E.e. (%)[b]
1	**1a**	PhCHO	$CHCl_3$	20	4	57[c]	—
2	**1a**	$C_5H_{11}CHO$	THF	−50	24	54	65[d]
3	**1b**	PhCHO	THF	−30	16	77	76[e]
4	**1b**	PhCHO	CH_2Cl_2	−60	2.5	70	62
5	**1b**	MeCHO	THF	−40	12	70	75[f]
6	**1c**	PhCHO	THF	−70[g]	10	91	90[h]
7	**1d**	PhCHO	THF	−30	17	77[c]	—

[a] In a typical procedure, the α,β-unsaturated ketone (10 mmol) is added dropwise at room temperature over a 10 min period to a stirred suspension or solution of (−)-Ipc_2BH (10 mmol) in freshly distilled tetrahydrofuran or chlorinated solvent (30 ml). After 2–3 h, the reaction mixture is cooled to the desired temperature, and treated with the aldehyde (1–1.1 equiv). After stirring at the same temperature for the period reported, the reaction is quenched with water (10 ml) and vigorously stirred at room temperature for 30 min. The crude aldol product is purified by column-chromatography over silica gel and yields refer to isolated products. [b] Determined by ^1H NMR analysis of the corresponding Mosher's esters. [c] Hydroboration carried out with Chx_2BH. [d] $[\alpha]_D^{20}$ +15.4° (*c* 1.07, $CHCl_3$). [e] $[\alpha]_D^{20}$ −57.7° (*c* 1.0, $CHCl_3$). [f] $[\alpha]_D^{20}$ −55° (*c* 0.7, $CHCl_3$). [g] The reaction temperature was allowed to rise to −30 °C. [h] $[\alpha]_D^{20}$ −38.8° (*c* 1.0, $CHCl_3$).

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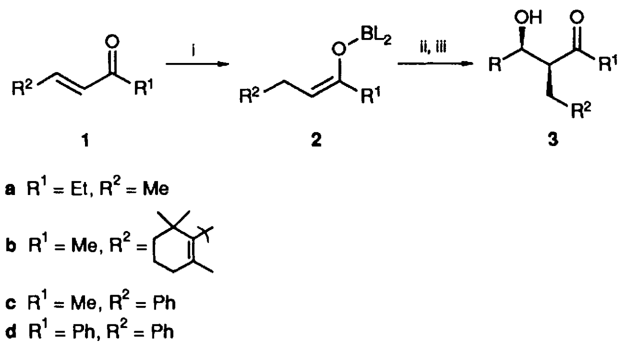
† The relative *syn* configuration of aldols **3** was determined on the basis of the vicinal coupling constant value ($J \leq 6$ Hz) of hydrogens H_α and H_β in the α and β positions relative to the carbonyl group. In fact aldols exist in intramolecularly hydrogen-bonded conformations, where H_α and H_β bear a *gauche* relationship to one another, and $J_{\alpha,\beta}$ is expected to be small. Signals due to the *anti* isomers were never observed.



Scheme 1 *Reagents*: i, HBL_2; ii, RCHO; iii, H_2O

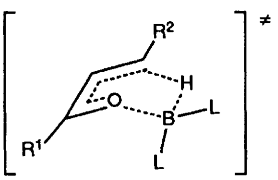


Fig. 2 Proposed transition state for the 1,4-hydroboration reaction

unsymmetrical ketone with an aldehyde, where the regiochemistry is dictated by the original position of the C=C bond. The formation of the enolate **2a** is noteworthy since no direct regio- and stereo-selective enolisation procedure is possible in the case of hexan-3-one. The good yields, the high level of diastereoselection of the aldol condensation step, and the excellent enantiocontrol achieved when working with (−) Ipc_2BH, all make, in our opinion, this simple one-pot procedure a useful integration of the presently available protocols for aldol condensation reactions.

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