62. Diastereoselective Aldol Addition Using Boron Trichloride or Alkoxydichloroborane

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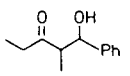
Under carefully controlled conditions, boron trichloride or alkoxydichloroborane/ethyldiisopropylamine in CH_2Cl_2 can be used to effect diastereoselective aldol additions of ethyl ketones to saturated, α,β-unsaturated, or aromatic aldehydes. The C–C bond formation takes place with relative topicity *ul* (*'syn'* configuration of the aldols), in selectivities ranging from 90 to 99% ds *(Tables 1–3)*. Mechanistic aspects of the reaction are discussed.

A) Introduction. – Over the past few years there has been much interest in the development of stereoselective aldol additions [1]. Of the various metal derivatives, boron enolates have been shown to react most selectively with aldehydes [2]. The usefulness of this class of reagents has been demonstrated in a number of complex natural product syntheses (*cf. e.g.* [3] and literature cited therein). Though the stereochemical outcome of this aldol reaction has been thoroughly studied (in most cases, the aldol product of *'syn'*-configuration [4] is formed with relative topicity *ul* [5]), the mechanism of the enolisation of the ketone component as well as the interactions between the base, the boron reagent, and the ketone have not been fully explored. In addition, the reagents required to generate the boron enolate (*e.g.* dialkylboron triflates [2a–c], dialkoxy(chloro)borane [2d], and dichloro(phenyl)borane [2e]) are not readily available[2]) or require tedious preparation and careful handling. In view of this limitation, we started to investigate the use of a much simpler boron derivative, *e.g.* the trichloride, as reagent for generating boron enolates. Here, we describe some of the interesting features of this particular type of alkenyloxyboranes, their reactivity, and stereoselective additions to aldehydes, and we also report an alternative procedure to generate boron enolates under especially mild conditions.

B) Results and Discussions. – 1. *Generation of Boron Enolates.* There is a wide variety of methods for generating boron enolates directly from ketones [2]. Initially, we employed the normal [2a,c] procedure which involves mixing of the boron derivative (here BCl_3) and ethyldiisopropylamine ($Et(i\text{-}Pr)_2N$; *Hünig* base; molar ratio 1:3), followed by the addition of 3-pentanone (1 equiv.) at −78° for 30 min. Surprisingly, we could isolate only a small amount of the aldol **1** (10%), together with starting material, when benzaldehyde (1

[1]) Postdoctoral research associate at ETH 1984/85. We thank the *Swiss National Science Foundation* (Project No. 2.253–0.84) and *Sandoz AG* (Basel) for stipends.

[2]) The sale of the expensive dialkylborane triflates has just been discontinued by one of the major suppliers of research chemicals.



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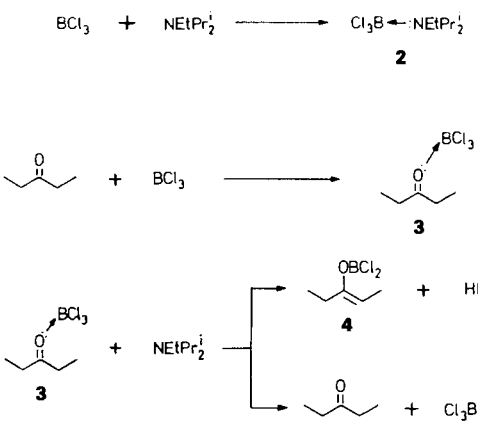
equiv.) was added to the above mixture, followed by quenching with phosphate buffer (pH 7) after 5 h at −78°. Raising the enolisation temperature (0°, 30 min)[3]) or increasing the reaction time (12 h, −78°) did not lead to higher conversions. Another, even more intriguing result was the fact that the 10% of the aldol adduct **1** were formed within the early stage of the reaction (less than 1 min reaction time). Obviously, the enolisation was not complete under these conditions. When we modified the enolisation procedure, it became evident that the order of mixing of the various reagents was of importance. For example, if 3-pentanone and BCl_3 were mixed (1:1 molar ratio) before the addition of *Hünig* base (3.3 equiv., −78°, 1 h), the conversion to the aldol **1** (− 78°, 10 min) was up to 75%. Again, the formation of the enolate could not be further improved, neither by raising the reaction temperature nor by prolonging the reaction time.

^{1}H-NMR experiments showed that a 1:1 complex **2** was formed at 0° when equimolar amounts of BCl_3 and *Hünig* base are mixed *(Eqn. 1)*. Unlike the interaction between dibutylboron triflate and *Hünig* base, where the corresponding complex formation is very slow (and/or reversible) [2c], the reaction with BCl_3 is probably irreversible[4]). (It is well known that tertiary amines and BCl_3 form extremely stable complexes; thus, Cl_3BNMe_3 cannot even be hydrolyzed in boiling water.)

These observations suggest that there are two requirements for the successful generation of boron enolates: *a*) The presence of free BCl_3 acting as a *Lewis* acid to activate the ketone component *(Eqn. 2)*. Ketones are not acidic enough to be deprotonated by amines at −78°, formation of the ketone-BCl_3 complex **3** greatly enhances the acidity of the α-proton. *b*) The presence of free amine acting as the base *(Eqn. 3A)*. The complex **2** of the amine and BCl_3 is ineffective as a proton scavenger.



(1)

(2)

(3A)

(3B)

[3]) Normally, the enolisation of 3-pentanone is complete within 30 min at −78° with other boron reagents [2c,d].

[4]) The low conversion to the product **1** with the initial enolisation procedure is in line with *Evans'* observation that no aldol product is formed when an irreversible reaction occurs between the amine and the boron reagent [2c].

Therefore, when BCl_3 and *Hünig* base (1:3 molar ratio) were mixed before the addition of 3-pentanone (1 equiv.), enolate formation was suppressed since the BCl_3 was complexed with the base. On the other hand, if BCl_3 and the ketone were mixed before the addition of base, there was a dramatic increase in product formation (75%). However, in no way could we drive the enolisation to completion. This has led us to speculate that there are two competitive reactions occurring in the presence of the ketone-BCl_3 complex **3** and the amine. One is a deprotonation *(Eqn. 3A)* to give the boron enolate **4**, and the other is the regeneration of the ketone by the attack of the amine on the B-atom *(Eqn. 3B)*. With excess BCl_3, the regenerated ketone should be activated, and an additional equivalent of amine should convert the rest of **3** into the enolate **4**. Indeed, when 3-pentanone and BCl_3 (molar ratio 1:2) were mixed, followed by the addition of the *Hünig* base (2 equiv.) and benzaldehyde (1 equiv.), a complete conversion to the aldol **1** was realized.

The amount of BCl_3 required to complete the boron-enolate formation depends on the structure of the ketone. In general, the bulkier the ketone, the more BCl_3 was needed. For example, while 3-pentanone, 1-phenyl-2-butanone, and 5-methyl-3-hexanone needed 2 equiv. of BCl_3 to complete the enolate formation, 2-methyl-3-pentanone required 2.5 equiv. and the bulkier propiophenone required 5 equiv. In contrast to the enolisation procedure reported by *Mukaiyama* [2b], *Masamune* [2a], *Evans* [2c], *Gennari* [2d], and *Hamana* [2e], our deprotonation method turns out to be extremely effective (reaction time less than 1 min at −95°). Even in the case of propiophenone, which proved to be particularly sluggish towards enolisation[5]), we could completely generate the boron enolate at −95° within 1 min. The obvious advantages of this enolisation procedure are its mildness and its high selectivity (see *Sect. B2*), which ensure that only kinetically controlled enolate formation takes place[6]). Also the enolisation temperature is so low that the equilibration between the (*E*)- and (*Z*)-enolate does not occur – a process which has been shown to take place at higher enolisation temperatures in the presence of quaternary ammonium salts [2c].

2. *Stereoselective Aldol Reactions with Aldehydes.* The general aldol formation procedure involved the addition of neat aldehydes to the boron enolates in CH_2Cl_2 at −95°. After 15 min the mixture is quenched with phosphate buffer (pH 7). No oxidative workup was necessary, therefore, our method is compatible with a wide variety of oxidisable functionalities. The results are summarized in *Table 1* (for details, see *Exper. Part*).

a) *Reactivity.* The aldol coupling between our boron enolate and the aldehyde is very fast. In one case (coupling of 3-pentanone with benzaldehyde), the reaction was shown to be complete within 15 s at −95°; the reaction can actually be considered as a 'titration' of the boron enolates with aldehydes. The high reactivity of this class of dichloroboron enolates can be attributed to the 2 electron-withdrawing Cl-atoms on the B-atom, which render the latter very electron-deficient and effective in complexing the O-atom of the aldehyde and thus enhancing the reaction rate. This type of boron enolate appears to be

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[5]) For example, the boron enolate of propiophenone could not be formed with ethylene chloroboronate/*Hünig* base [2d].

[6]) In order to further define the structure of our boron enolate, we tried to observe it spectroscopically. However, the high reactivity of this compound precluded its NMR characterization at ambient temperature. Indirect methods, including its attempted conversion to the corresponding silyl enol ether [2c], also failed to give any structural information.

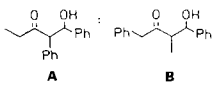
Table 1. *Aldol Additions of Ketones and Aldehydes Using BCl_3*

Entry	Ketone	Aldehyde	Equiv. of BCl_3 used	Yield [%]	*'syn'/'anti'*[a])
1a		PhCHO	2.0	96	95:5
b			2.0	99	(91:9)[b])
2			2.0	87	84:16
3			2.0	88	95:5
4			2.0	79	58:42
5a		PhCHO	2.5	81	93:7
b			2.5	99	(91:9)[b])
6a			2.5	84	75:25
b			2.5	89	(75:25)[b])
7a			2.5	86	85:15
b			2.5	86	(77:23)[b])
8a		PhCHO	5.0	95	92:8
b			5.0	96	(89:11)[b])
9		PhCHO	2.0	95[c])	92:8 for **A** 95:5 for **B**

[a]) Reactions in CH_2Cl_2 at 95° unless otherwise indicated. Aldol ratios were determined by 300-MHz ^{1}H-NMR. For assignments, see [2c].

[b]) Reaction was performed at −105° in $CHCl_3/CH_2Cl_2$ 2:3.

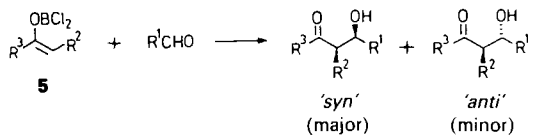
[c]) The ratio of regioisomers **A** and **B** was 1:4.8.



A **B**

the most reactive one so far known. For the same coupling reaction between 3-pentanone and benzaldehyde, other boron enolates (*e.g.* dibutylboron enolates [2c] and dialkoxyboron enolates [2d]) normally require at least 30 min at −78°.

b) *Stereoselectivity.* The dichloroboron enolates **5** derived from acyclic ketones reacted with aldehydes R^{1}CHO to give mainly *'syn'*-aldol adducts in excellent yields *(Table 1)*. The selectivity depends on the nature of R^1 of the aldehyde. For conjugated

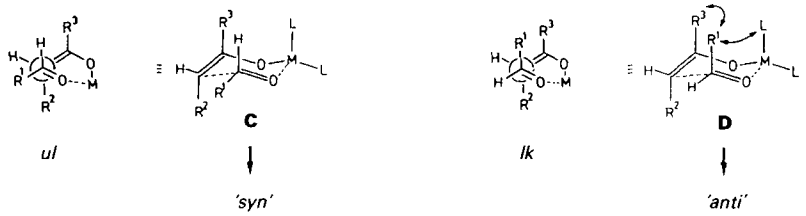


aldehydes, *e.g.* benzaldehyde and tiglaldehyde, selectivities were always greater than 90% *(Entries 1, 3, 5, 7, 8,* and *9)*; with the least hindered butyraldehyde *(Entry 4)*, the selectivity dropped down to 58%, while for the α-branched isobutyraldehyde *(Entries 2* and *6)*, selectivities were *ca.* 80%. The stereoselectivity also depends upon the solvent: consistently lower selectivities *(Entries a vs. b* in *Table 1)* were observed in $CHCl_3/CH_2Cl_2$, even when the reactions were performed at lower temperature (−105°). The regioselectivity of the reaction has not been thoroughly studied, but in general, enolisation takes place at the less hindered side of the ketone component. For example, no regioisomer resulting from enolisation of the isopropyl group was observed for 2-methyl-

3-pentanone. With 1-phenyl-2-butanone, a 1:4.8 ratio of regioisomers *(Entry 9)* in favor of the Et group was observed[7]).

Although we were not able to determine the geometry of our enolate, there seems not to be a good correlation between the enolate geometry and the product configuration in our system[8]). This is particularly evident from the reactions of the dichloroboron enolate derived from 3-pentanone (the (*E*)/(*Z*) ratio of the enolate must be the same in *Entries 1–4*), which gave different degrees of selectivity (58–95%) with different aldehydes. Previous literature indicate that direct enolisation of open-chain ketones with boron triflates [2a–c] or chloroboranes [2d,e] in the presence of *Hünig* base resulted in the preferential formation of (*Z*)-enolates. There is no reason to believe that our system (BCl_3/Et(i-Pr)$_2$N) should be different in this respect from the others. If we assume that our boron enolates have (*Z*)-configuration, the question arises how we can explain the change of stereoselectivity from one aldehyde to another. In the *Zimmerman* model [6] normally applied to discuss the mechanism of aldol additions (*Scheme 1*, only the

Scheme 1



(*Z*)-enolate is shown), there are three 1,3-diaxial interactions in transition state **D** (R^1/R^3, and R^1/L and R^3/L) which make transition state **C** more favorable than **D**. In cases where L is small, we should expect a less pronounced difference between **C** and **D** and hence more *lk*-coupling product would be observed. Our boron enolate (M = B, L = Cl) is probably one of this kind, when the Cl-atom (*A*-value: 0.4) is compared with alkyl groups of corresponding alkyl boron enolates (*e.g.* L = butyl [2c], *A*-value: 2.1). Therefore, we expect the stereoselectivity to depend rather strongly on the relative size of R^1 (on the aldehyde component) in accordance with our observations.

3. *The Effect of 'Additives' on the Stereoselectivity of the BCl_3-Mediated Aldol Reaction.* The presence of 2 Cl-atoms at the boron enolate makes the metal centre sterically less bulky. On the other hand, the electron-withdrawing effect of these Cl-atoms enhances the *Lewis* acidity of the B-atom and makes the enolates extremely reactive. From the synthetic viewpoint, it would be most desirable to have simple modified boron reagents in which the B-atom bears substituents which could increase the stereoselectivity of the aldol reaction. Thus, we replaced one of the Cl-atom by an alkoxy group (see *Scheme 2*).

This is easily achieved by mixing alcohols (ROH) and BCl_3 [7] *(Eqn. 4)*. It is known that the stability of alkoxydichloroboranes **6** depends on the nature of the R group [7]. For

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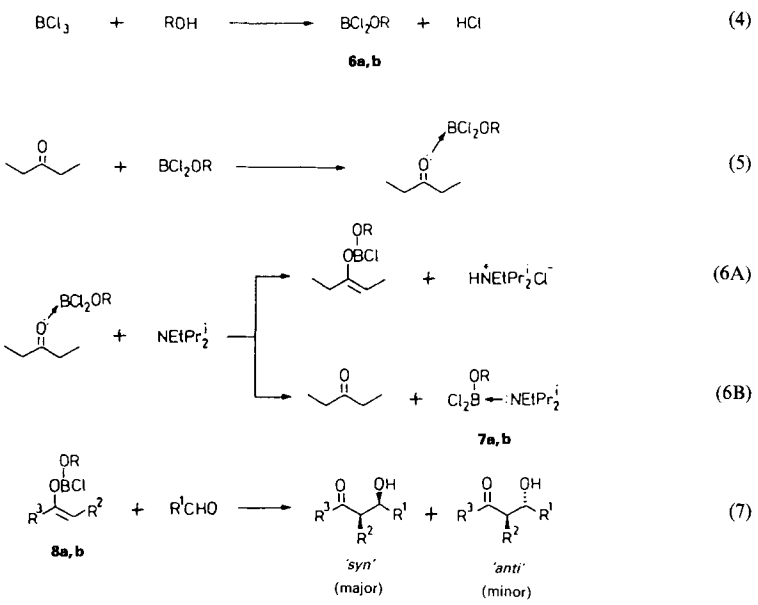
[7]) The corresponding boron enolate derived from dichlorophenyl borane, on the other hand, gave a 1:0.7 mixture of regioisomers [2e].

[8]) Normally, boron (*Z*)-enolates give *'syn'*-aldols and (*E*)-enolates give *'anti'*-aldols [2c], irrespective of the aldehyde used.

Scheme 2



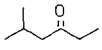
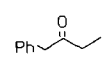
a R = *t*-BuCH$_2$ **b** R = i-Pr

example, when R is a *t*-Bu group, the corresponding derivative decomposes rapidly even at −80°. Alkoxydichloroboranes with a secondary R group are marginally stable at −80° and those with a primary R group are stable at room temperature.

a) *Use of Neopentyl Alcohol.* In the first attempt, we selected neopentyl alcohol as the alcohol component (*Scheme 2*, R = *t*-BuCH$_2$). The alcohol and BCl_3 were mixed at −75° (*Eqn. 4*), the HCl generated was either pumped off (0°) immediately or after the addition of ketone, or trapped as the quaternary ammonium salt with *Hünig* base. Similar to the previous case using BCl_3, the order of addition of the various reagents is very important: the ketone and **6a** must be mixed before the addition of the base (*Eqn. 5*). Enolisation was essentially complete at −75° after 2 min (*Eqn. 6*). Although the replacement of a Cl-atom by an alkoxy group should decrease the *Lewis* acidity of **6a,** we found that an excess of this reagent was required to effect complete conversion to the aldol[9]). Aldol additions (*Eqn. 7*) between the preformed boron enolates **8a** and aldehydes were conducted at −75°, and the results are summarized in *Table 2* (for details, see *Exper. Part*). The first observation was a decrease in the reactivity of the enolate **8a** – the aldol coupling only proceeded to the extent of 60% after 2 min at −75°. In fact, we preferred to prolong the reaction time to 1 h at −75° to obtain consistent results. The stereoselectivity of the reaction increased dramatically in all cases we studied, and yields were good to excellent for reactions in which benzaldehyde was employed (*Entries 2, 4, 5* and *6* in *Table 2*). However, when saturated aldehydes were used, the main product was the corresponding dineopentyl acetal (*Entries 1* and *3*). The aldol adducts, although formed with good

[9]) This suggested that **6a** irreversibly forms a complex **7a** with the base (*Eqn. 6B*). A very stable 1:1 complex between dichloro(1-methylheptyloxy)borane and pyridine has been isolated and characterized [7b].

Table 2. *Aldol Additions of Ketones and Aldehydes Using Dichloro(neopentyloxy)borane*

Entry	Ketone	Aldehyde	Equiv. of $BCl_2(t\text{-}BuCH_2O)$ used	Yield [%]	*'syn'/'anti'*[a])
1			2.0	33[b])	82:18 (58:42)[c])
2		PhCHO	2.0	94	> 99:1 (95:5)[c])
3			2.0	15[d])	92:8 (84:16)[c])
4		PhCHO	2.5	69[e])	> 99:1 (93:7)[c])
5		PhCHO	2.0	90[f])	> 99:1
6		PhCHO	2.0	63[g])	98:2 for **A** (92:8)[c]) > 99:1 for **B** (95:5)[c])

[a]) Aldol ratios were determined by 300-MHz ^{1}H-NMR.
[b]) The major product was $CH_3CH_2CH_2CH(OCH_2\text{-}t\text{-}Bu)_2$.
[c]) Stereoselectivity of the corresponding aldol reaction (–95 °C) using BCl_3.
[d]) The major product was $(CH_3)_2CHCH(OCH_2\text{-}t\text{-}Bu)_2$.
[e]) Aldol condensation was performed at –78° for 2 h.
[f]) Only one regioisomer $(CH_3)_2CHCH_2CO(CH_3)CH(OH)Ph$ was obtained.
[g]) The ratio **A**/**B** *(cf. Footnote c, Table 1)* was 1:2.6.

selectivities in these latter cases, were produced in unsatisfactory yields. We do not know why acetal formation became the major process here, since there was always an excess of base in the reaction mixture. Although the stereoselectivities were high, this modification is hampered by the side reaction and is, therefore, of limited applicability. However, it was gratifying that the stereoselectivity could indeed be improved by replacing a Cl-atom on the β-atom by an alkoxy group.

b) *Use of i-PrOH.* In view of the problem encountered with neopentyl alcohol, we envisaged that acetal formation might be suppressed by employing a sterically more bulky alcohol. Tertiary alcohols are not applicable in this case, in view of the instability of their dichloroboron derivatives [7]. We, therefore, chose the simplest secondary alcohol, i-PrOH *(Scheme 2,* R = i-Pr).

The procedure for making dichloro(isopropoxy)borane (**6b**; R = i-Pr) was the same as for dichloro(neopentyloxy)borane (**6a**; R = t-$BuCH_2$) except that the HCl formed could not be pumped off because of the lability of **6b** at higher temperatures (0°). Therefore, the HCl was trapped as ammonium salt by use of excess of *Hünig* base. Similar to the neopentyl case, an excess of the boron reagent **6b** was required, and the boron enolate **8b** is also less reactive than the parent dichloroboron enolate **5b**. For optimum results, the aldol addition was carried out at –95° for 2 h.

The general applicability of this modification is summarized in *Table 3.* No acetal formation was observed when saturated, linear and branched aliphatic aldehydes were reacted. The aldol adducts were formed with equal ease and in reasonable yields, although in general the reactions were less clean than those using BCl_3 or the neopentyl derivative (see *Exper. Part*). The stereoselectivities were also high with saturated alde-

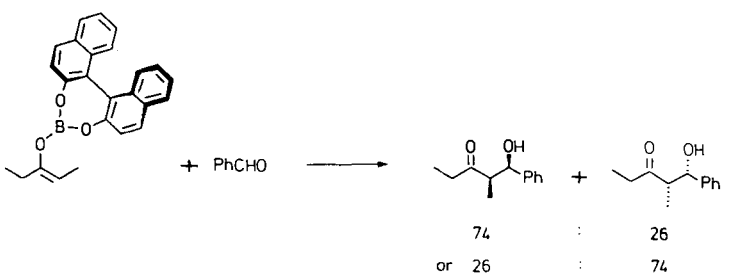
Table 3. *Aldol Additions of Ketones and Aldehydes Using Dichloro(isopropoxy)borane*

Entry	Ketone	Aldehyde	Equiv. of BCl_2(i-PrO) used	Yield [%]	*'syn'/'anti'*[a])
1			2.0	75	90:10 (82:18)[b])
2		PhCHO	2.0	76	98:2 (> 99:1)[b])
3			2.0	65	95:5 (92:8)[b])
4			2.0	59	89:11
5		PhCHO	2.5	80	97:3 (> 99:1)[b])
6		PhCHO	2.0	72[c])	98:2 for **A** (98:2)[b]) 99:1 for **B** (> 99:1)[b])

[a]) Aldol ratios were determined by 300 MHz ^{1}H-NMR.
[b]) Stereoselectivity of the corresponding aldol reaction (−75°) using BCl_2 (*t*-$BuCH_2O$).
[c]) The ratio **A**/**B** *(cf. Footnote c, Table 1)* was 1:1.4.

hydes *(Entries 1* and *3)*. Unfortunately, the regioselectivity diminished in the case of 1-phenyl-2-butanone *(Entry 6)*.

c) *Use of (−)-(P)-1,1'-Bi-2-naphthol.* In a preliminary experiment, we employed optically active (−)-(*P*)-1,1'-bi-2-naphthol as ligand on the *β*-atom (see *Exper. Part*) to see whether an asymmetric aldol addition could be achieved. We found an enatiomeric excess of 47% in the product, as determined by ^{1}H-NMR in the presence of the chiral shift reagent [Eu(hfc)$_3$] (see *Eqn. 8*).



(8)

C) Conclusion. – In summary, we have developed a procedure for diastereoselective aldol additions using a very simple boron reagent, BCl_3. The mildness of the reaction conditions as well as the high selectivities should lead to applications in synthesis. The complicated steric and electronic factors which determine the stereoselectivity and reactivity of the boron enolates were also addressed in this report.

Experimental Part

1. *General.* CH_2Cl_2 and $CHCl_3$ were distilled over P_2O_5 and stored over 4Å molecular sieves under Ar. 5-Methyl-3-hexanone, 2-methyl-3-pentanone, 3-pentanone, 1-phenyl-2-butanone, propiophenone, Et(i-Pr)$_2$N (*Hünig* base), and i-PrOH were distilled over CaH_2 and stored under Ar. Benzaldehyde, butyraldehyde, isobutyraldehyde, and tiglaldehyde (= (*E*)-2-methyl-2-butenal) were distilled under Ar and stored in the refrigerator. Neopentyl alcohol *(Fluka, purum)* (−)-(*P*)-1,1'-bi-2-naphthol *(Aldrich)*, and BCl_3 (1.0M soln. in *Aldrich*) were used without further purification. Buffer solution of pH 7 was prepared by dissolving KH_2PO_4 (5 g) and NaOH (14.5 g) in (1.0 l). All reactions were carried out in oven-dried glassware, under Ar, on a 2.0-mmol scale. Unless otherwise stated, the workup involved addition of phosphate buffer (pH 7; 20 ml) to the vigorously stirred reaction mixture at the temp. indicated. The mixture was extracted with CH_2Cl_2 (2 × 15 ml) and the combined extracts were washed with phosphate buffer (pH 7; 20 ml), dried ($MgSO_4$), filtered and concentrated using a rotary evaporator. Ratios of diastereoisomeric crude aldol adducts were determined by 300-MHz ^{1}H-NMR spectroscopy (*Bruker WM 300;* $CDCl_3$; TMS as internal standard; δ's in ppm; signals marked with an asterisk (*) disappeared on addition of D_2O). The spectral data of the products synthesized resemble those reported in the literature (often from lower-field NMR measurements) [2c,e]. For reactions using BCl_3 *(Table 1)*, the crude product was filtered through a short column (3 × 2 cm, eluant Et_2O) of silica gel (230–400 mesh) to remove 'baseline materials', and then the yields were determined after concentration of the filtrate in a rotary evaporator. For reactions employing BCl_2 (*t*-BuCH_2O) and BCl_2 (i-PrO) (*Tables 2* and *3*, resp.), yields were determined after chromatography of the crude product on silica gel (50 g; hexane/Et_2O, 2:1).

2. *General Procedure for the Aldol Addition Using BCl_3.* BCl_3 (2.0, 2.5, or 5.0 equiv., see *Table 1*) in CH_2Cl_2 (1.0M) was added to a stirred soln. of the ketone (1.0 equiv.) in CH_2Cl_2 (4.0 ml/mmol of ketone) at −95°. After 10 min, Et(i-Pr)$_2$N (2.0, 2.5, or 5.0 equiv., neat) was added over 10 min at −95°. The soln. was stirred at 95° for 1 min, and the aldehyde (1.0 equiv., neat) was added dropwise over 30 s. The mixture was stirred at −95° for 15 min and worked up at 95°. Yields and stereoselectivities: *Table 1.*

(1)-1-Hydroxy-2-methyl-1-phenyl-3-pentanone [2c] *(Table 1, Entry 1).* ^{1}H-NMR (300 MHz): 7.40–7.20 (*m*, 5 arom. H); 5,04 (*d*, *J* = 4.3, H–C(1)); 3.30* (br., OH); 2.85 (*dq*, *J* = 4.3, 7.1, H–C(2)); 2.48 (*dq*, *J* = 18.0, 7.3, H–C(4)); 2.33 (*dq*, *J* = 18.0, 7.2, H–C(4)); 1.09 (*d*, *J* = 7.1, CH_3–C(2)); 0.99 (*t*, *J* = 7.3, CH_3(5)). The corresponding (*u*)-diastereoisomer has a δ at 4.74 (*d*, *J* = 8.3).

(u)-5-Hydroxy-4,6-dimethyl-3-heptanone [2c] *(Table 1, Entry 2).* ^{1}H-NMR (300 MHz): 3.54 (*dd*, *J* = 8.2, 3.2, H–C(5)); 3.10* (br., OH); 2.75 (*dq*, *J* = 3.2, 7.2, H–C(4)); 2.56 (*dq*, *J* = 17.9, 7.3, H–C(2)); 2.51 (*dq*, *J* = 17.9, 7.3, H–C(2)); 1.67 (*dsept.*, *J* = 8.2, 6.7, H–C(6)); 1.12 (*d*, *J* = 7.2, CH_3–C(4)); 1.06 (*t*, *J* = 7.3, CH_3(1)); 1.01 (*d*, *J* = 6.7, CH_3–C(6)); 0.86 (*d*, *J* = 6.7, CH_3–C(6)). The corresponding (*l*)-diastereoisomer gives a signal at 3.47 (*dd*, *J* = 6.9, 4.8).

(E,1)-5-Hydroxy-4,6-dimethyl-6-octen-3-one [2c] *(Table 1, Entry 3).* ^{1}H-NMR (300 MHz): 5.54 (*q*, *J* = 6.8, H–C(7)); 4.27 (*d*, *J* = 4.8, H–C(5)); 3.70* (br., OH); 2.76 (*dq*, *J* = 4.9, 7.1, H–C(4)); 2.60–2.40 (*m*, 2 H–C(2)); 1.61 (*d*, *J* = 6.7, CH_3(8)); 1.58 (*s*, CH_3–C(6)); 1.08 (*d*, *J* = 7.2, CH_3–C(4)); 1.04 (*t*, *J* = 7.3, CH_3(1)). The corresponding (*u*)-diastereoisomer has a *d* at 4.11 (*d*, *J* = 9.0).

(u)-5-Hydroxy-4-methyl-3-octanone [2c] *(Table 1, Entry 4).* ^{1}H-NMR (300 MHz): 3.92 (*ddd*, *J* = 7.9, 4.4, 3.3, H–C(5)); 3.45* (br., OH); 2.59 (*dq*, *J* = 3.2, 7.2, H–C(4)); 2.60–2.42 (*m*, 2 H–C(2)); 1.60–1.24 (*m*, 2 H–C(6), 2 H–C(7)); 1.13 (*d*, *J* = 7.2, CH_3–C(4)); 1.06 (*t*, *J* = 7.3, CH_3); 0.93 (*t*, *J* = 7.1, CH_3). The corresponding (*l*)-diastereoisomer gives a signal at 3.70 (*ddd*, *J* = 10.1, 6.5, 3.3).

(1)-1-Hydroxy-2,4-dimethyl-1-phenyl-3-pentanone [2c] *(Table 1, Entry 5).* ^{1}H-NMR (300 MHz): 7.34–7.20 (*m*, 5 arom. H); 4.97 (*d*, *J* = 4.7, H–C(1)); 4.20* (br., OH); 3.01 (*dq*, *J* = 4.7, 7.1, H–C(2)); 2.56 (*sept.*, *J* = 6.9, H–C(4)); 1.10 (*d*, *J* = 7.1, CH_3–C(2)); 1.04 (*d*, *J* = 6.9, CH_3); 0.95 (*d*, *J* = 6.9, CH_3). The corresponding (*u*)-diastereoisomer gives a signal at 4.76 (*d*, *J* = 7.6.).

(u)-5-Hydroxy-2,4,6-trimethyl-3-heptanone [2e] *(Table 1, Entry 6).* ^{1}H-NMR (300 MHz): 3.46 (*dd*, *J* = 8.2, 3.0, H–C(5)); 3.30* (br., OH); 2.92 (*dq*, *J* = 2.9, 7.1, H–C(4)); 2.78 (*sept.*, *J* = 6.9, H–C(2)); 1.76–1.60 (*m*, H–C(6)); 1.10 (*d*, *J* = 7.4, 3 CH_3); 1.02 (*d*, *J* = 6.5, CH_3); 0.87 (*d*, *J* = 6.8, CH_3). The signal of H–C(5) of the (*l*)-diastereoisomer overlaps with the corresponding signal of the (*u*)-compound. However, the (*l*)-isomer gives 2 well-resolved signals at 0.96 (*d*, *J* = 6.8) and 0.92 (*d*, *J* = 6.7, and the stereoselectivity was determined by the relative integrations at 1.02 and 0.96.

(E,1)-5-Hydroxy-2,4,6-trimethyl-6-octen-3-one [2c] *(Table 1, Entry 7).* ^{1}H-NMR (300 MHz): 5.54 (*q*, *J* = 6.9, H–C(7)); 4.23 (*d*, *J* = 4.8, H–C(5)); 3.80* (br., OH); 2.93 (*dq*, *J* = 4.8, 7.0, H–C(4)); 2.72 (*sept.*, *J* = 6.9, H–C(2)); 1.61 (*d*, *J* = 6.7, CH_3(8)); 1.60 (*s*, CH_3–C(6)); 1.09 (*d*, *J* = 6.8, CH_3); 1.07 (*d*, *J* = 6.8, $CH_3$2); 1.07 (*d*, *J* = 7.0, CH_3). The corresponding (*E,u*)-diastereoisomer shows a *d* at 4.11 (*d*, *J* = 8.8).

(1)-3-Hydroxy-2-methyl-1,3-diphenyl-1-propanone [2c] *(Table 1, Entry 8).* 8.00–7.87 (*m*, 2 arom. H); 7.60–7.20 (*m*, 8 arom. H); 5.22 (*d*, *J* = 3.6, H–C(3)); 3.90* (br., OH); 3.73 (*dq*, *J* = 3.6, 7.2, H–C(2)); 1.12 (*d*, *J* = 7.3, CH_3–C(2)). The corresponding (*u*)-diastereoisomer gives a signal at 5.01 (*d*, *J* = 8.1).

(1)-4-Hydroxy-3-methyl-1,4-diphenyl-2-butanone [2e] (*Table 1, Entry 9,* **B**). ^{1}H-NMR (300 MHz): 7.36–7.18, 7.11–7.07 (2*m*, 10 arom. H); 4.96 (*d*, *J* = 4.6, H–C(4)); 3.85* (br., OH); 3.62 (*s*, 2 H–C(1)); 2.97 (*dq*, *J* = 4.6, 7.1, H–C(3)); 1.09 (*d*, *J* = 7.1, CH_3–C(3)). The corresponding (*u*)-diastereoisomer gives a signal at 4.75 (*d*, *J* = 8.0).

(1)-1-Hydroxy-1,2-diphenyl-3-pentanone [2e] (*Table 1, Entry 9,* **A**). ^{1}H-NMR (300 MHz): 7.36–7.18, 7.11–7.07 (*m*, 10 arom. H); 5.34 (*d*, *J* = 6.6, H–C(1)); 3.97 (*d*, *J* = 6.6, H–C(2)); 3.85* (br., OH); 2.33 (*dq*, *J* = 18.0, 7.3, H–C(4)); 2.13 (*dq*, *J* = 17.9, 7.3, H–C(4)); 1.02 (*t*, *J* = 7.3, CH_3(5)). The corresponding (*u*)-diastereoisomer gives a signal at 5.21 (*d*, *J* = 9.5).

3. *Preparation of Dichloro(neopentyloxy)borane* (**6a**) [7b]. BCl_3 (98 ml, 1.0M, soln. in CH_2Cl_2, 98 mmol) was added into a stirred soln. of neopentyl alcohol (8.54 g, 96,8 mmol) in CH_2Cl_2 (15 ml) at −50° over 15 min. After 5 min, the cooling bath was removed and the mixture warmed to 0° within 20 min. The solvent and HCl were pumped off at 0° (20 Torr) (1 h). The residue was condensed *in vacuo* (0.5 Torr) into a dry-ice/acetone trap to give **6a** (12.43 g, 76%) as a colorless oil, which was diluted to a 1.0M soln. with CH_2Cl_2 (61.6 ml) and stored in a freezer. ^{1}H-NMR (90 MHz, CCl_4): 1.02 (*s*, *t*-Bu); 3.91 (*s*, CH_2).

4. *General Procedure for the Aldol Additions Using BCl_2(t-$BuCH_2O$).* A soln. of **6a** (2.0 or 2.5 equiv., see *Table 2*) in CH_2Cl_2 (1.0M) was added to a stirred soln. of the ketone (1.0 equiv.) in CH_2Cl_2 (4.0 ml/mmol of ketone) at −75°. After 10 min, Et(i-Pr)$_2$N (2.2 or 2.7 equiv., neat) was added over 10 min at −75°. The soln. was then stirred at this temp. for 2 min, and the aldehyde (1.0 equiv., neat) was added dropwise over 1 min. The mixture was stirred at −75° and worked up after 1 h. Yields and diastereoselectivities: *Table 2.*

(1)-1-Hydroxy-2,5-dimethyl-1-phenyl-3-hexanone [2c] *(Table 2, Entry 5).* ^{1}H-NMR (300 MHz): 7.36–7.20 (*m*, 5 arom. H); 5.00 (*d*, *J* = 4.4, H–C(1)); 3.50* (br., OH); 2.81 (*dq*, *J* = 4.5, 7.1, H–C(2)); 2.35–2.16 (*m*, 2 H–C(4)); 2.14–2.02 (*m*, H–C(5)); 1.07 (*d*, *J* = 7.1, CH_3–C(2)); 0.85 (*d*, *J* = 6.6, CH_3); 0.84 (*d*, *J* = 6.6, CH_3). The corresponding (*u*)-diastereoisomer has a signal at 4.72 (*d*, *J* = 8.2).

5. *General Procedure for the Aldol Condensations Using* in-situ-*Prepared Dichloro(isopropoxy)borane* (**6b**). BCl_3 (2.0 or 2.5 equiv., see *Table 3*) in CH_2Cl_2 (1.0M) was diluted with CH_2Cl_2 (4.0 ml/mmol of ketone) at −95°. i-PrOH (2.0 or 2.5 equiv., neat) was added dropwise over 3 min, and the internal temp. was maintained below −90°. The mixture was then stirred at −95° for 15 min and the ketone (1.0 equiv., neat) added over 5 min. After 15 min, Et(i-Pr)$_2$N (4.2 or 5.2 equiv., neat) was added dropwise over 15 min and the solution stirred for another 10 min at −95°. The aldehyde (1.0 equiv., neat) was then added dropwise, and the resulting mixture was stirred at −95° for 2 h before workup. Yields and diastereoselectivities: *Table 3.*

6. *Enantioselective Aldol Addition of 3-Pentanone to Benzaldehyde Using (−)-(P)-1,1'-Bi-2-naphthol as the Chiral Ligand.* BCl_3 (1.0 ml, 1.0M in CH_2Cl_2, 1.0 mmol) was added to a stirred soln. of (−)-(*P*)-1,1'-bi-2-naphthol (286 mg, 1.0 mmol) in CH_2Cl_2 (5.0 ml) at −75°. The cooling bath was then removed and the mixture warmed to 0° over 10 min. After 30 min at 0°, the solvent and HCl were evaporated *in vacuo* (0.5 Torr). The residue was redissolved in CH_2Cl_2 (7.0 ml) and Et(i-Pr)$_2$N (0.20 ml 1.17 mmol, neat) added dropwise at −75°. The mixture was stirred for 5 min and then 3-pentanone (0.10 ml, 0.94 mmol, neat) added. The soln. was stirred at −75° for 30 min and at 0° for 10 min and recooled to −75°. Benzaldehyde (0.10 ml, 1.0 mmol, neat) was added dropwise and the mixture stirred at −75° for 1 h and at 0° for 1.5 h. The mixture was then quenched with phosphate buffer (pH 7; 20 ml) and the org. layer separated. The aq. layer was extracted with CH_2Cl_2 (20 ml) and the combined extracts were washed with phosphate buffer (pH 7; 20 ml), dried ($MgSO_4$), filtered, and concentrated using a rotary evaporator. The residue was chromatographed on silica gel (50 g) eluting with hexane/CH_2Cl_2 1:1 to give *(1)-1-hydroxy-2-methyl-1-phenyl-3-pentanone* (43 mg, 24%) as an oil. The enantiomeric excess of the product was 48% as determined by the use of the chiral shift reagent Eu(hfc)$_3$. The *d* of the Me group α to the carbonyl was split into two *d* at lower field. The signal of the major product was at higher field then the other one.

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