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# Contrasting Steric Effects of the Ketones and Aldehydes in the Reactions of the Diisopinocampheyl Enolborinates of Methyl Ketones with Aldehydes

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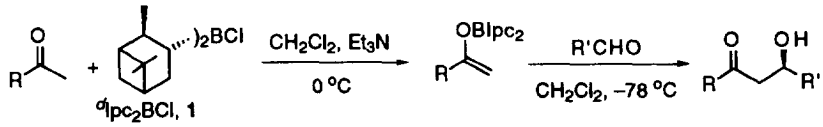
***Abstract:*** Treatment of the diisopinocampheylborinates of a representative series of methyl ketones with a representative series of aldehydes, both of differing steric requirements provides aldols whose enantiomeric purities depend on the steric requirements of both the ketones and the aldehydes. This study has shown that increasing the steric requirements of the R group in the ketones has a pernicious effect on the ee, while increasing the steric requirements of the R group in the aldehydes exerts a beneficial effect on the ee.


The past decade witnessed the art of asymmetric syntheses achieve a high level of sophistication for conformationally nonrigid systems, especially in C-C bond forming reactions, such as is involved in the syntheses of aldols.[2] Of all the elements studied for application in enolization reactions, boron offers special advantages and has been used extensively.[3] We[4] and others[5] have studied the parameters, such as the size of the alkyl groups and the nature of the leaving group on boron, and the steric requirements of the amine used, all of which influence the stereoselectivity in boron mediated cross aldol reactions. Following a systematic study, we developed dicyclohexylchloroborane as an efficient reagent for the synthesis of *anti* aldols.[4] Several researchers developed various chiral auxiliaries to induce diastereoselectivities and enantioselectivities in the reaction.[6] Meyers and coworkers reported the preparation of diisopinocampheylboron triflate ($Ipc_2BOTf$) derived from our super chiral auxiliary, α-pinene,[7] for enantioselective aldol reactions using boron azaenolates.[8] Paterson and coworkers adopted this reagent for the preparation of asymmetric [*Z*]-enolborinates from ketones to carry out aldol reactions in good to excellent diastereo- and enantioselectivity.[9]

In extending our enolboration results with dicyclohexylchloroborane, Paterson demonstrated that *B*-chlorodiisopinocampheylborane (Aldrich: DIP-Chloride, **1**) provides predominantly [*E*]-enolborinates and *anti* aldol products, *albeit* in low enantiomeric excess (ee).[10] However, in the case of methyl ketones, **1** shows excellent regioselectivity toward the methyl group, and the subsequent aldol reactions provide aldols in 56-78% ee.[11] He also studied the double asymmetric aldol reaction of chiral aldehydes with methyl ketone enolates produced with **1** and exploited this aspect in the preparation of Swinholide A synthons.[12] However, Paterson has concluded that diisopinocampheyl enolborinates might not be suitable for the aldol reactions of hindered aldehydes.[9]

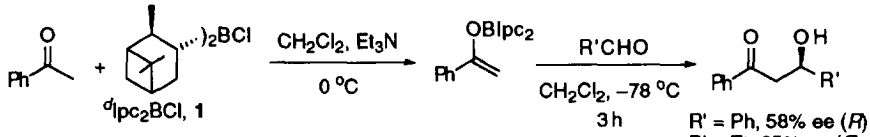
Our experience in the asymmetric reduction of ketones with **1** clearly revealed the strong influence of the steric requirements of the ketone on the stereochemical outcome.[13] For example, 2-butanone is reduced by **1** in only 4% ee, while 3-methyl-2-butanone is reduced in 32% ee, and 3,3-dimethyl-2-butanone is reduced in 95% ee.[13] We were interested in studying whether similar effects, if any, also existed in asymmetric aldol reactions. In this case, we were interested in exploring also the effect of the steric requirements of the aldehydes (Scheme). The commercial availability of both isomers of optically pure **1** and their stabilities simplified our efforts.

**Scheme**




**What are the effects of the steric requirements of R and R' on the stereochemical outcome?**

The aldol reactions of acetophenone enolate with representative aldehydes were first examined. We took advantage of Paterson's search for a proper solvent for such aldolizations and adopted $CH_2Cl_2$ as the preferred solvent for the reactions.[9] The enolizations were carried out at 0 °C ($^{11}$B NMR δ 52 ppm) and the aldol reactions were carried out at –78 °C. The ee's were determined by $^1$H and $^{19}$F NMR spectroscopy of the Mosher esters[14] of the aldols. The reaction of benzaldehyde provides the aldol in 58% ee. However, aliphatic aldehydes show improved enantioselectivity and the % ee increases with increasing steric requirements of the aldehyde. Thus, while the reaction of propionaldehyde provides the corresponding aldol in 65% ee, the reactions of isobutyraldehyde and pivalaldehyde provide the corresponding aldols in 74% and 89% ee, respectively (eq 1). The stereochemistry of the product aldols, determined by comparing their optical rotation with those reported in the literature, is the same, irrespective of the steric or electronic demands of the aldehydes used in the reaction.

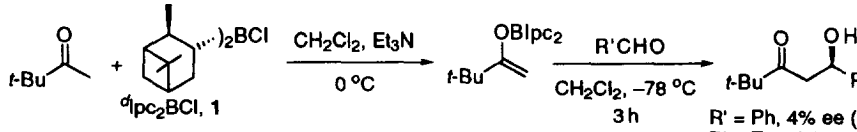



R' = Ph, 58% ee (*R*)
R' = Et, 65% ee (*S*)
R' = *i*-Pr, 74% ee (*R*)
R' = *t*-Bu, 89% ee (*R*)

(1)

Encouraged by this, we carried out the aldol reactions of acetone enolates. Propionaldehyde provides the corresponding aldol in 61% ee. We were surprized to see that isobutyraldehyde provides the aldol of essentially the same % ee.[15] However, once again, pivaladehyde produced the aldol in relatively high ee (83%). Similar results were obtained with 2-butanone as well. While isobutyraldehyde provides the aldol of lower ee (48%), compared to the aldol produced from propionaldehyde (61%), pivalaldehyde provides the corresponding aldol in 81% ee. We obtain 90% ee for the aldol from the enolborinate of 3-methyl-2-butanone and pivalaldehyde.

The aldol reactions of 3,3-dimethyl-2-butanone (pinacolone) with the same series of aldehydes were then studied to ascertain the effect of the steric environment of the ketone. A serious deleterious effect attributed to the larger steric bulk of the group proximal to the carbonyl of the ketone is observed. The ee's of the product aldols are very low (4-26%) (eq 2). Even so, the ee obtained for the aldol from pivalaldehyde is considerably higher than those realized from other aldehydes of lesser steric requirements.




R' = Ph, 4% ee (*R*)
R' = Et, 17% ee (*S*)
R' = *i*-Pr, 13% ee (*R*)
R' = *t*-Bu, 26% ee (*R*)

(2)

The results are summarized in Table 1. It is noteworthy that although the % ees of the aldols are dependent on the steric requirements of the ketones and the aldehydes used, their stereochemistries depend only on the enantiomer of **1** used in the reaction.

**Table 1. Asymmetric Enolboration-aldolization of methyl Ketones with (–)-DIP-Chloride**[a]

| $RCOCH_3$ | R'CHO | $RCOCH_2CH(OH)R'$ | | | |
|---|---|---|---|---|---|
| R | R | % yield[b] | % ee[c] | config.[d] | $[\alpha]_D^{25}$ (*c*, $CHCl_3$) |
| Ph | Ph | 54 | 58 | *R* | +21.3 (*c*, 0.5 MeOH)[e] |
| Ph | Et | 74 | 65 | *S*[f] | +51.10 (*c* 3.5) |
| Ph | *i*-Pr | 70 | 74 | *R* | +68.21 (*c* 1.4)[g] |
| Ph | ***t*-Bu** | 60 | **89** | *R* | +124.4 (*c* 1.6)[h] |
| Me | Ph | | 57 | *R*[i] | |
| Me | Et | 68 | 62 | *S* | +41.9 (*c* 1.6)[j] |
| Me | *i*-Pr | 57 | 61 | *R* | +43.4 (*c*, 1.4)[k] |
| Me | ***t*-Bu** | 63 | **83** | *R* | +82.20 (*c* 0.6)[l] |
| Et | Ph | 73 | 39 | *R*[f] | +35.6 (*c* 1.3) |
| Et | Et | 57 | 61 | *S* | +35.9 (*c* 1.4)[m] |
| Et | *i*-Pr | 69 | 48 | *R*[f] | +33.6 (*c* 2.8) |
| Et | ***t*-Bu** | 65 | **81** | *R*[f] | +48.5 (*c* 0.8) |
| *i*-Pr | ***t*-Bu** | 68 | **90** | *R* | +70.20 (*c* 2.4)[n] |
| *t*-Bu | Ph | 49 | 4 | *R* | +2.4 (*c*, 3.4)[o] |
| *t*-Bu | Et | 75 | 17 | *S*[f] | +13.2 (*c*, 0.6) |
| *t*-Bu | *i*-Pr | 74 | 13 | *R*[f] | +11.9 (*c*, 1.3) |
| *t*-Bu | *t*-Bu | 74 | 26 | *R* | +16.2 (*c* 1.8)[p] |

[a]Enolization was carried out at 0 °C. Aldolization was carried out at –78 °C. [b]Isolated yield after chromatography. [c]Determined by $^1H$ and $^{19}F$ NMR analysis of the MTPA ester. [d]Configuration on the basis of the rotation reported in the literature unless otherwise stated. [e] Literature: $[\alpha]^{25}_D$ = 25.20 (MeOH) for 73% ee (*R*); ref 16. [f]Configuration by analogy. [g]Literature: $[\alpha]^{25}_D$ = 64.9 ($CHCl_3$) for 86% ee (*R*); ref. 17. [h]Literature: $[\alpha]^{19}_D$ = 59.9 ($CHCl_3$) for 74% ee (*R*); ref. 16. [i]From ref. 8. [j]Literature: $[\alpha]^{23}_D$ = 43.2 (*c* 0.3, $CHCl_3$) for 64% ee (*R*); ref. 18. [k]Literature: $[\alpha]^{25}_D$ = –55.0 (*c* 1.4, $CHCl_3$) for (*S*); ref. 19. [l]Literature: $[\alpha]^{24}_D$ = 43.9 (*c* 0.81, $CHCl_3$) for 86% ee (*R*); ref. 20. [m]Literature: $[\alpha]^{25}_D$ = –47.1 (*c* 0.5, $CHCl_3$) for 78% ee (*R*); ref. 18. [n]Literature: $[\alpha]^{25}_D$ = 28.0 (*c* 4.45, $CHCl_3$) for 31% ee; ref. 21. [o]Literature: $[\alpha]^{25}_D$ = 45.9 ($CHCl_3$), for 75% ee (*R*); ref. 16. [p]Literature: $[\alpha]^{25}_D$ = 38.8 ($CHCl_3$) for 62% ee (*R*); ref. 16.

In conclusion, a systematic study of the enantioselective aldol reactions using $Ipc_2BCl$ has revealed a significant influence of the steric environments of both the ketones and the aldehydes. This study has exposed the limits and merits of the isopinocampheyl moiety as the chiral auxiliary in aldol reactions of methyl ketones. This should be of value to synthetic organic chemists. We are currently studying the effect of the steric requirements of the aldehydes on the aldol reactions of different types of ketones.

***Enolboration-aldolization of methyl ketones with (–)-DIP-Chloride.*** All operations were carried out in an inert atmosphere.[22] The reaction of 3-methyl-2-butanone and pivalaldehyde is representative. 3-Methyl-2-butanone (0.43g, 0.5 mL, 5 mmol) dissolved in 5 mL of dichloromethane was added to an ice-cold solution of (–)-DIP-Chloride (1.6 g, 5 mmol) and triethylamine (0.51g, 0.70 mL, 5 mmol) in $CH_2Cl_2$ (5 mL) contained in an oven-dried, 50 mL round-bottom flask equipped with a side-arm, magnetic stirring bar, and a connecting tube, and stirred for 2 h at 0 °C. The $^{11}B$ NMR spectrum of an aliquot (δ 52 ppm) showed the completion of the enolization. The enolate was separated from solid $Et_3N{\bullet}HCl$ and cooled to –78 °C.

Pivalaldehyde (0.54 mL, 5 mmol) in 3 mL of $CH_2Cl_2$ was added and stirred for 3 h at this temperature. Methanol (15 mL) was then added, followed by 30% $H_2O_2$ (4 mL) and the reaction mixture was allowed to warm to room temperature and the stirring was continued for an additional 2 h. The mixture was then poured into water (30 mL) and extracted with $CH_2Cl_2$ (3x30 mL). The combined extracts were sequentially washed with aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. Removal of the solvent and flash chromatography provided 0.59 g (68%) of 3-oxo-2,6,6-trimethylheptan-5-ol. $[\alpha]_D^{21}$ = +70.20 (*c* 2.4, $CHCl_3$) corresponds to 78% ee on the basis of the literature rotation, $[\alpha]^{25}_D$ = 28.0 (*c* 4.45, $CHCl_3$) for 31% optical purity.[21] However, analysis of the $^1H$ and $^{19}F$ NMR of the MTPA ester of this aldol revealed it to be 90% ee. The structure was confirmed by $^1H$ and $^{13}C$ NMR.

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