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A Remarkable Inversion in Configuration of the Product Alcohols from the Asymmetric Reduction of *ortho*-Hydroxyacetophenones with *B*-Chlorodiisopinocampheylborane[1]

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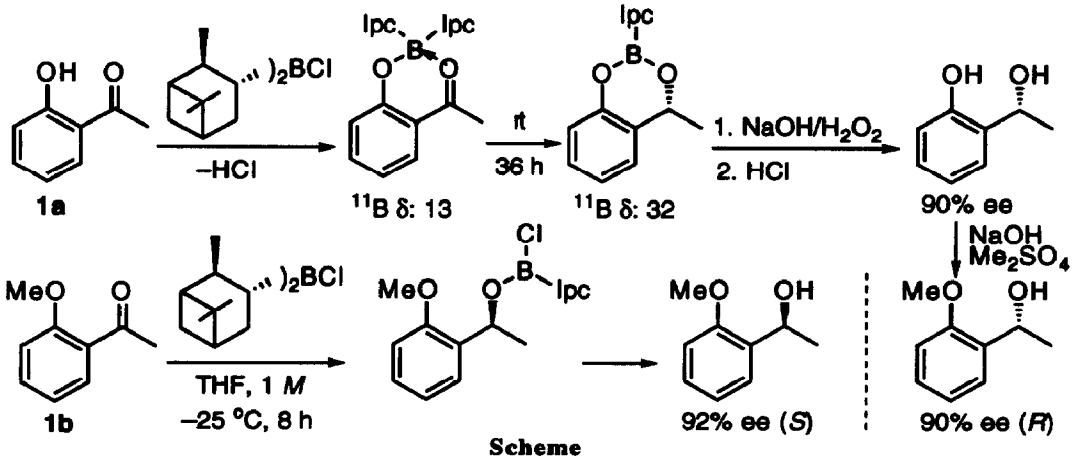
Abstract: Asymmetric reduction of *o*-hydroxyacetophenones with *B*-chlorodiisopinocampheylborane provides product alcohols with the opposite configuration compared to those produced in the reduction of the corresponding *o*-methoxyacetophenones. The implications of this result for organic synthesis are discussed.

Since the introduction of *B*-chlorodiisopinocampheylborane (Aldrich: DIP-Chloride™)[2] for the asymmetric reduction of prochiral ketones, especially aralkyl and α-hindered ketones, the reagent has received a number of applications in organic synthesis.[3] The ready availability of both enantiomers of the reagent in bulk made scaling up possible. A tentative mechanism for the reduction predicts the configuration of the product alcohols.[2] This has been used in synthetic schemes[3] and for the correction of earlier erroneous assignments.[4] Superior reagents were later developed based on this proposed mechanism.[5]

Before turning our attention entirely to modified reagents, we decided to explore DIP-Chloride for the reduction of a considerable number of mono- and disubstituted acetophenones to test the compatibility of the reagent with representative substituents in the phenyl ring.[6] Asymmetric reduction of acetophenones with typical substituents, such as, –OMe, –Me, –F, –Cl, –Br, –I, –COOR, –CN, $-NO_2$, $-CF_3$, etc., in the *ortho*, *meta*, and *para* positions, by DIP-Chloride, gives alcohol products in very high ee whose configurations, we believe, are all consistent with the proposed reduction mechanism.[2] However, we observed that, without exception, all of the 2,6-disubstituted acetophenones react at a considerably slower rate and provide product alcohols in relatively low ee.[6] This brought our attention to Danishefsky's successful application of DIP-Chloride for the asymmetric reduction of a 2-hydroxy-6-carbomethoxyacetophenone derivative[7] and persuaded us to extend our study to include the *ortho*-hydroxy substituent. To our surprise the product from the reduction of the *o*-hydroxyacetophenone (**1a**) revealed the opposite configuration, readily proven by methylating the phenolic –OH and comparing the rotation. The implication of this exceptional behavior of the *o*-hydroxy derivative is readily understood in terms of a modified mechanism required for the reduction of these compounds. The results of a detailed study of the asymmetric reduction of a series of *o*-hydroxyacetophenones with DIP-Chloride are reported herein.

The following scheme outlines a reasonable alternative pathway which can account for the change in the configuration of the product. Addition of one molar equiv of (–)-DIP-Chloride to **1a** in THF at –25 °C liberates one equiv of hydrogen chloride with the concurrent formation of a reddish complex (^{11}B: δ 13 ppm). The reaction was too slow to be monitored at this temperature, so the reaction mixture was warmed to room temperature (rt).[8] Upon completion of the reaction, as noticed by the color change of the reaction mixture from red to pale yellow (36 h), the ^{11}B NMR showed the expected boronate at δ 32 ppm. The usual diethanolamine

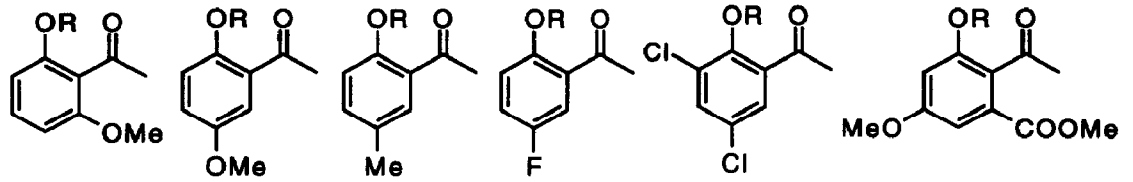
workup[2] failed to transesterify the intermediate with formation of the usual solid complex and liberation of the alcohol product. Treatment of the reaction mixture with acetaldehyde[9] to displace the second equiv of α-pinene was also unsuccessful. Hence we resorted to an alkaline hydrogen peroxide oxidation, followed by acidification to obtain the phenolic alcohol product. Conversion of the phenol to the methyl ether and analysis of the MTPA ester showed the product to be of 90% ee in the *R*-isomer, compared to the *S*-isomer obtained from the reduction of *o*-methoxyacetophenone (**1b**) with (–)-DIP-Chloride.[10]



Scheme

To avoid any possible uncertainities in the chiral outcome arising from the HCl liberated during the initial chelation, the lithio salt of the phenolic acetophenone **1a** was treated with DIP-Chloride to achieve the same result without the liberation of HCl. Moreover, the scheme suggests that diisopinocampheylborane, Ipc_2BH,[11] should be as effective as DIP-Chloride in reducing **1a**. Indeed, this is observed experimentally providing product with the same configuration and % ee as that obtained with the corresponding DIP-Chloride.

The generality of this opposite stereochemistry from an intramolecular reduction was examined for a series of *o*-hydroxyacetophenones (**2a-7a**) and, following methylation of the *o*-hydroxy group, compared with the product alcohols obtained from the intermolecular reduction of the corresponding *o*-methoxyacetophenones (**2b-7b**). In all cases, the configuration realized was opposite.[12]



2a, R = H **2b**, R = Me
3a, R = H **3b**, R = Me
4a, R = H **4b**, R = Me
5a, R = H **5b**, R = Me
6a, R = H **6b**, R = Me
7a, R = H **7b**, R = Me

Based on our earlier results,[2] Danishefsky and coworkers used the reduction of **7a** to assign the configuration of a key intermediate in the synthesis of descarbamoylcalicheamicinone.[7] However, our present results require the opposite configuration. To verify this, we carried out the reductions of the hydroxy ketone **7a** and the corresponding methoxy derivative **7b**.[13] As expected, we obtained a lactone, which when converted to the dimethoxy derivative and compared with the product lactone from the reduction of **7b** showed the

opposite sign of rotation. The % ee was determined by ^1H and ^{19}F NMR of the MTPA derivative of the *o*-hydroxylactone.[14] We believe that we have the product of (*R*)-(+)-configuration for the lactone when (–)-DIP-Chloride is used for the reduction. (+)-DIP-Chloride provides the (*S*)-(–)-lactone. Earlier, we had reduced an *o*-carbomethoxyacetophenone with DIP-Chloride and obtained the expected *S*-alcohol isolated as the lactone showing that the ester group did not control the direction of chiral induction.

Thus, we have shown that the asymmetric reduction of *o*-hydroxyacetophenones with (–)-DIP-Chloride provides the product alcohol of *R*-configuration in very high ee.[15]

Table. Asymmetric Reduction of *o*-Hydroxy- and *o*-Methoxyacetophenones with (–)-DIP-Chloride

ketone	reactn condn	% ee[a]	config	ketone	reactn condn	% ee[a]	config
1a	THF, rt, 36 h	90	*R*[b]	**1b**	THF, –25 °C, 8 h	92	*S*[b]
2a	THF, rt, 48 h	96	*R*[c]	**2b**	THF, 0 °C, 24 h	20	*R*[d]
3a	THF, rt, 48 h	82	*R*[c]	**3b**	THF, –25 °C, 8 h	93	*S*[e]
4a	THF, rt, 48 h	82	*R*[c]	**4b**	THF, –25 °C, 8 h	95	*S*[e]
5a	THF, rt, 12 h	79	*R*[c]	**5b**	THF, –25 °C, 6 h	94	*S*[e]
6a	THF, 0 °C, 6 h	78	*R*[c]	**6b**	THF, –25 °C, 6h	94	*S*[e]
7a	THF, rt, 16 h	90[f]	*R*[c]	**7b**	THF, 0-25 °C, 16 h	20[g]	*S*[e]

[a]Determined by GC analysis as the MTPA ester on a capillary GC. [b]Ref. 10. [c] By analogy with the product from **1a**. [d]Ref. 12. [e]By analogy with the product from **1b**. [f]The % ee determined by ^1H and ^{19}F NMR of the MTPA ester of the *o*-hydroxylactone. The ee was improved to 98% by crystallizing from acetone. [g]By comparison of the rotation with the product derived from **7a**.

Reduction of o-Methoxyacetophenones with (–)-DIP-Chloride. The reductions were carried out using our published procedure.[2] The reduction of **7b** is as follows. All operations were carried out under a nitrogen atmosphere.[16] A solution of **7b** (1.43 g, 6.0 mmol) in 10 mL THF was added dropwise to a solution of (–)-DIP-Chloride (2.12 g, 6.6 mmol) in 10 mL THF at 0 °C, and warmed to rt. The ^{11}B NMR of a methanolized aliquot, which showed two singlets at δ 52 and 32 ppm, was unchanged after 16 h.[17] Workup using diethanolamine provided the crude product which was filtered through silica (CH_2Cl_2 as eluent) to obtain 0.62 g of the dimethoxy lactone (71% yield, based on 0.42 g, 1.8 mmol of the recovered ketone[17]): mp. 141-43 °C, $[\alpha]_D^{21}$ = –9.93 (*c* 0.9, $CHCl_3$), which corresponds to 20% ee based on the rotation of 89% ee material derived from **7a** (below). The structure was confirmed by ^1H and ^{13}C NMR, MS, and elemental analysis.

Reduction of o-Hydroxyacetophenones With (–)-DIP-Chloride. The reduction of **7a** is representative. An oven-dried, 50 mL round-bottom flask equipped with a side-arm, magnetic stirring bar, and a connecting tube was cooled to rt in a stream of nitrogen. (–)-DIP-Chloride (4.97 g, 15.5 mmol) was transferred to the flask in a glove bag, dissolved in THF (25 mL) and added dropwise to the ketone **7a**[12] (3.36g, 15 mmol) at –25 °C. The reaction mixture turned reddish in color immediately and the ^{11}B NMR showed a peak at δ 15 ppm corresponding to a complex. The mixture was warmed to rt and upon completion of the reaction (16 h) as was shown by the change in color to yellow and the ^{11}B NMR spectrum (δ 32 ppm), the product was extracted with aqueous sodium hydroxide (2x15 mL, 2 *N*) and acidified with conc. HCl to pH 1. The product was extracted with ethyl acetate and the combined extracts were dried ($MgSO_4$) and concentrated, passed through a silica gel pad and eluted with EE to provide 2.52 g (87%) of a white solid: mp 239-41 °C, $[\alpha]_D^{21}$ +52.33 (*c* 0.6, MeOH), which corresponds to 90% ee as determined by the ^1H and ^{19}F NMR of the MTPA ester. Upon crystallizing from acetone, the % ee was improved to 98%: mp 244-45 °C, $[\alpha]_D^{21}$ +56.75 (*c* 0.6, MeOH). The structure was confirmed by ^1H and ^{13}C NMR, MS, and elemental analysis.

The uncrystallized hydroxy lactone from above (0.97 g, 5 mmol) in CH_2Cl_2 (25 mL) was treated with an aqueous solution of NaOH (7.5 mmol), $(CH_3)_2SO_4$ (1.58 g, 12.5 mmol) and $PhN(Bu)_3Cl$ (0.1 g) and stirred for 12 h. Treatment with 10 mL of 2*N* aq ammonia and extraction with CH_2Cl_2, drying ($MgSO_4$) and removal

of solvents provided 0.89 g (86%) of the dimethoxy derivative which showed the same ^{1}H, and ^{13}C NMR spectral characteristics of the product from **7b**. But the optical rotation, $[\alpha]_D^{21}$ +43.05 (*c* 0.9, $CHCl_3$) (90% ee), shows that the product is of the opposite stereochemistry.

A similar reaction of **7a** with (+)-DIP-Chloride provided the (*S*)-hydroxy lactone: mp 238-40 °C, $[\alpha]_D^{21}$ –49.66 (*c* 0.6, MeOH) which corresponded to 89% ee by ^{1}H and ^{19}F NMR analysis of the MTPA ester. The ee was increased to 98% upon crystallization from acetone: mp 244-45 °C, $[\alpha]_D^{21}$ –54.78 (*c* 0.6, MeOH). The uncrystallized product was converted to the methoxy lactone as above: $[\alpha]_D^{21}$ = –43.92 (*c* 0.9, $CHCl_3$).

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12. In the case of the reduction of 2,6-dimethoxyacetophenone (**2b**), the analysis of the MTPA derivative of the product alcohol showed two peaks (20% ee) with the major isomer the same as that produced in the reduction of **2a**. We assume that we obtain the *R*-alcohol based on the generality of the reduction of *o*-hydroxyacetophenones.
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15. When Danishefsky was informed of our result and conclusion, he advised us that he had arrived at the conclusion that the product alcohol, originally assigned the *R*-configuration (by reaction with (+)-DIP-Chloride) must have the *S*-configuration, based on an X-ray examination, as discussed in a forthcoming publication in *Angew. Chem.*
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17. The persistence of the peak at δ 52 ppm could probably mean that the ketone exists partially in enol form. Ref. 6. This probably is also confirmed by the recovery of 15% of unreacted ketone.

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