A Chiral Benzyl Group as a Chiral Auxiliary and Protecting Group for the Synthesis of Optically Active 1,2-Diols and (+)-Frontalin

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Abstract: Chelation-controlled asymmetric nucleophilic addition of a Grignard reagent to chiral α-benzyloxy ketones gives the corresponding alcohols with high diastereoselectivities (up to 96% de) by 1,4-asymmetric induction. A chiral benzyl group is used as a chiral auxiliary as well as a protecting group for the synthesis of optically active 1,2-diols and (+)-frontalin.

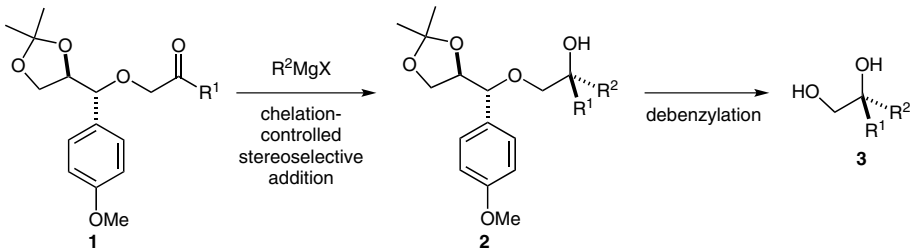
Key words: nucleophilic addition, diols, α-benzyloxy ketones, (+)-frontalin, stereoselective synthesis

The widespread use of 1,2-diols and their derivatives as chiral synthons in organic synthesis has grown in line with advances in methods for their asymmetric synthesis.[1] Sharpless asymmetric dihydroxylation of alkenes is a well-known method for the preparation of optically active 1,2-diols.[2] The nucleophilic addition of a Grignard reagent to α-alkoxy carbonyl compounds offers an alternative and important route to chiral 1,2-diols, especially those not accessible via Sharpless asymmetric dihydroxylation.[3]

Our recent development of a chelation-controlled asymmetric alkylation process that permits efficient syntheses of chiral α-hydroxy esters prompted us to investigate whether this process would be readily adaptable to the synthesis of chiral 1,2-diols.[4] It was envisioned that the chelation-controlled asymmetric nucleophilic 1,2-addition to an α-alkoxy ketone, followed by removal of the chiral auxiliary would provide optically active diols.[5] Our initial attempt toward the synthesis of (+)-flutriafol via a chiral 1,2-diol was found to be successful.[6] Encouraged by this result, we investigated the scope and limitations of our chelation-controlled asymmetric nucleophilic 1,2-addition reaction. Herein, we describe nucleophilic addition to α-alkoxy ketones in which a chiral benzyl group is attached as both a protecting group and a chiral auxiliary in proximity to a prochiral functionality by means of an ether linkage (Scheme 1).

We chose methyl and phenyl ketone derivatives as the α-alkoxy ketones for our investigation. The preparation of α-benzyloxy ketone **1** was simple and straightforward as shown in Scheme 2. Chiral benzyl alcohol **4**, prepared directly from D-glyceraldehyde acetonide, according to the literature method,[7] was converted into the benzyl ethers **6**, in good yields, by O-alkylation using allyl bromides **5**. Ozonolyzis of alkenes **6** produced the corresponding α-alkoxy carbonyl compounds **1a** and **1b** in good yields. O-Alkylation of alcohol **4** with the corresponding α-bromo ketone also provided an alternative and direct entry to ketones **1a** and **1b**.

The feasibility of 1,4-asymmetric induction in this nucleophilic 1,2-addition was first examined using methyl ketone **1a**. The reactions were performed with or without pre-complexation of the ketone, using the respective metal salts as Lewis acids. In addition, the nucleophiles and solvents were varied. The addition of nucleophiles to the carbonyl compounds was performed by utilizing the following standard procedure: a mixture of the ketone and additive (4 equiv, pre-dried with a heat gun under vacuum) in a solvent was irradiated in an ultrasonic water bath for 10 minutes, and then cooled to –78 °C. To this mixture was added dropwise a solution of the appropriate nucleophile (2 equiv). The mixture was quenched after two hours with water to afford, following extraction and chromatography, the respective addition products in good yields



Scheme 1 A chiral benzyl moiety as a chiral auxiliary and protecting group for the synthesis of optically active 1,2-diols

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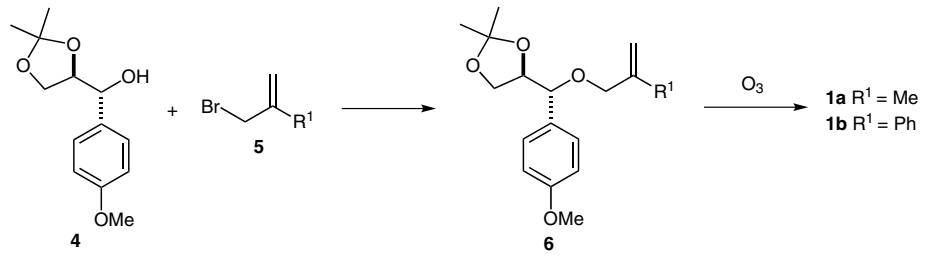
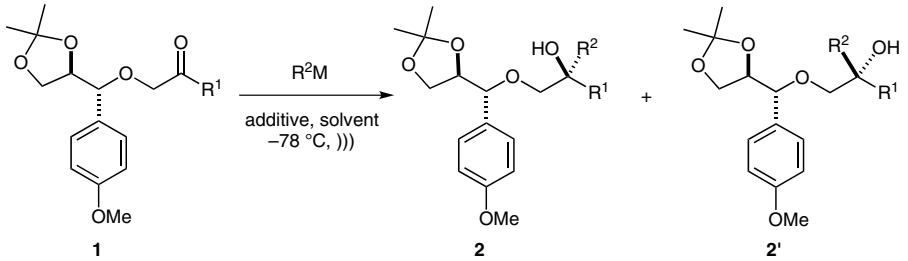


Scheme 2 Synthesis of chiral α-benzyloxy ketones **1a** and **1b**

(75–97%). The stereochemical results of the transformations are summarized in Table 1.

As shown in Table 1, preferential formation of **2** over **2′** was observed, and the ratio was found to be highly dependent on the additive, solvent, and nucleophiles. In the absence of an additive, addition of phenyllithium (PhLi) to the methyl ketone derivative afforded the corresponding alcohol in good yield, but without any diastereoselection (Table 1, entry 1). However, when using phenylmagnesium chloride (Table 1, entry 2), diastereoselective addition occurred under the same conditions. According to the Schlenk equilibrium,[8] two equivalents of RMgX are in equilibrium with R_2Mg and MgX_2. Thus, the MgX_2 species in the phenylmagnesium halide seems to play a pivotal role in inducing the diastereoselective reaction. Even better selectivity was obtained by changing the solvent from tetrahydrofuran to dichloromethane. The solvation ability of tetrahydrofuran or 1,2-dimethoxyethane (DME) seems to be correlated with the stereoselectivity, presumably destroying the chelated complex. The use of Grignard reagents, combined with pre-complexation of

Table 1 Asymmetric Nucleophilic 1,2-Addition to α-Alkoxy Ketones[a]



Entry	R^1	R^2M	Solvent	Additive	**2**:**2′**[b]	Yield (%)[c]
1	Me	PhLi	THF	none	1:1	95
2	Me	PhMgCl	THF	none	8:1	83
3	Me	PhMgCl	DME	none	5:1	85
4	Me	PhMgCl	CH_2Cl_2	none	18:1	80
5	Me	PhMgCl	CH_2Cl_2	LiBr	16:1	97
6	Me	PhMgCl	CH_2Cl_2	$MgCl_2$	16:1	92
7	Me	PhMgCl	CH_2Cl_2	$MgBr_2{\cdot}OEt_2$	50:1	81
8	Ph	MeMgCl	CH_2Cl_2	$MgBr_2{\cdot}OEt_2$	11:1	81
9	Ph	vinylMgBr	CH_2Cl_2	$MgBr_2{\cdot}OEt_2$	11:1	92
10	Ph	allylMgCl	CH_2Cl_2	$MgBr_2{\cdot}OEt_2$	16:1	87
11	Ph	*i*-PrMgBr	CH_2Cl_2	$MgBr_2{\cdot}OEt_2$	10:1	80
12	Ph	*c*-hexMgCl	CH_2Cl_2	$MgBr_2{\cdot}OEt_2$	15:1	90
13	Ph	4-FC_6H_4MgBr	CH_2Cl_2	$MgBr_2{\cdot}OEt_2$	18:1	87
14	Ph	*t*-BuMgCl	CH_2Cl_2	$MgBr_2{\cdot}OEt_2$	35:1	75

[a] Additive (4 equiv) and R^2M (2 equiv) in THF were used based on ketone **1** (1 equiv).
[b] The **2**:**2′** ratios were measured by HPLC analysis.
[c] Combined yield of the two diastereoisomers.

the ketone with magnesium bromide–diethyl etherate ($MgBr_2 \cdot OEt_2$) in a poorly-donating solvent, turned out to represent the best conditions (Table 1, entry 7). Under the optimized conditions, we applied various types of nucleophiles in reactions with phenyl ketone derivative **1b**. The bulkiness of the nucleophile was important to the selectivity. The bulkier the R^2 group, the higher the selectivity attained in the alkylation. When R^2 was a *tert*-butyl group, the selectivity ratio reached up to 35. Overall, methyl ketone **1a** was found to serve as a more efficient substrate than phenyl ketone **1b** (Table 1, entries 7 and 13).

The preferential formation of **2** over **2′** and the high level of stereoselection associated with this asymmetric alkylation can be rationalized by considering the plausible transition state model of a highly organized chelation complex, resulting from tridentate chelation of the three internal oxygens with the magnesium ion (Figure 1). In this model, the five-membered ring containing the carbonyl group is puckered upwards minimizing the steric interaction with the nearby aromatic ring. Therefore, nucleophilic attack is preferred from the convex side of the chelated complex, which is *syn* to the aryl ring.

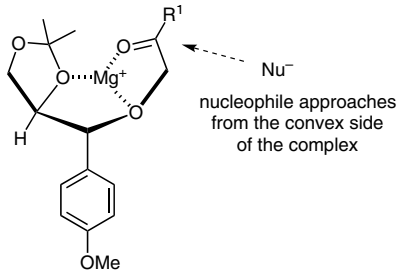
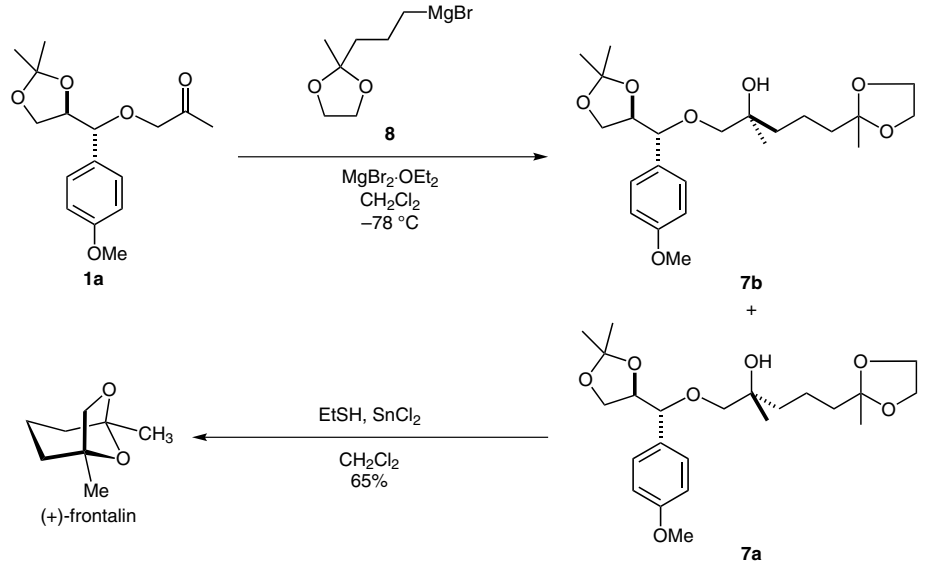


Figure 1 Hypothetical chelated transition state showing the preferred attack by the nucleophile

As shown in Table 1, external polar ligands such as tetrahydrofuran and 1,2-dimethoxyethane could destroy the chelation complex, resulting in lower stereoselectivities. The absolute configurations of the newly created stereogenic centers in **2** and **2′** were assigned after removal of the chiral auxiliary with cerium(IV) ammonium nitrate (CAN) or trimethylsilyl chloride (TMSCl),[9] and comparison of the optical rotations of the resulting 1,2-diols with literature values.[3,10] For example, treatment of a mixture of **2** and **2′** (Table 1, entry 7) with cerium(IV) ammonium nitrate in 10% aqueous acetonitrile at room temperature for five hours afforded (*R*)-2-phenylpropane-1,2-diol $\{[\alpha]_D^{25}$ –5.6 (*c* 1.0, EtOH)$\}$ in 67% yield.[3b,5c] During the removal of the chiral auxiliary on **2** with cerium(IV) ammonium nitrate, intermediate **4** was oxidized into the corresponding ketone, which on treatment with L-Selectride,[11] can be readily recovered for reuse. Encouraged with this result, we applied the present method to the synthesis of optically active (+)-frontalin, as outlined in Scheme 3.

Due to the unique structure and its biological activity, frontalin has attracted intense interest from synthetic chemists, which has led to more than 50 syntheses of the natural and unnatural products.[12] Our diastereoselective synthesis of unnatural (+)-frontalin is simple and straightforward. Only two steps were required to complete the synthesis of the target molecule starting from α-benzyloxy ketone **1a**. Performing the nucleophilic addition of Grignard reagent **8**, pre-complexed with magnesium bromide–diethyl etherate in dichloromethane at –78 °C, to methyl ketone derivative **1a** followed by hydrolysis gave a 15:1 ratio of **7a** and **7b**, isolated in 70% and 4% yield, respectively. Finally, upon exposure of the mixture to ethanethiol (EtSH) and tin(II) chloride ($SnCl_2$) in dichloromethane,[9b] the alcohol **7a** underwent debenzylation and deacetalization, followed by concomitant cyclization to afford (+)-frontalin in 65% yield. This synthetic sample of (+)-frontalin was identical in all respect (^{1}H NMR, ^{13}C NMR, IR), except for the optical rotation, to those reported for natural (–)-frontalin. The specific rotation of the



Scheme 3 Stereoselective synthesis of (+)-frontalin

synthetic sample {$[\alpha]_D^{25}$ +52.3 (*c* 0.5, Et_2O)}[13] was almost identical to that reported previously.[14]

In conclusion, we have shown that optically active 1,2-diols and the natural product, (+)-frontalin, can be prepared efficiently from our chiral auxiliary through a stereoselective nucleophilic 1,2-addition reaction. A high degree of 1,4-asymmetric induction has been realized during the alkylation step via the chelation-controlled mechanism. The chiral benzyl group employed in this reaction was shown to act efficiently as a protecting group as well as a chiral auxiliary. Thus, our synthetic method might offer an alternative route to chiral diols that are not easily accessible through Sharpless asymmetric dihydroxylation.

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