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# Synthesis of novel chiral hydrobenzoin *mono-tert*-butyl ethers derived from *m*-hydrobenzoin and their application as chiral auxiliaries in the diastereoselective reduction of α-keto esters

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Dedicated to Prof. Dr. Fritz Sauter on the occasion of his 75th birthday

**Abstract**—Three *m*-hydrobenzoin derived chiral hydrobenzoin *mono-tert*-butyl ethers were synthesized by a new reaction pathway and tested as chiral auxiliaries in the L-selectride® mediated stereoselective reduction of their corresponding phenyl glyoxylates. As a result, improved stereoselectivities of up to a ratio of 92:8 compared to 84:16 with the initially examined analogous benzyl ether were achieved.


## 1. Introduction

Over the course of our recent studies on novel chiral auxiliaries, which could be attached onto a solid support to serve at the same time as polymer bound enantiomerically pure linkers and chiral auxiliaries,[1] we synthesized chiral hydrobenzoin *mono*-benzyl ethers **5a** and **b** as test systems.[2] These compounds were easily accessible by the desymmetrization of *m*-hydrobenzoin **1** with commercially available anhydro lactols **2a** and **b** as chiral protecting groups,[3] which finally lead to both (*R*)- and (*S*)-substituted hydrobenzoin auxiliaries **5a** and **b** with the benzyl ether moiety symbolizing the linkage of the auxiliary to a polystyrene resin such as Merrifield or Wang (Scheme 1).

Whereas these auxiliaries were only able to induce moderate diastereoselectivities up to 36% de in the alkylation of carboxylic esters,[2] we were surprised to find that when applying auxiliary **5a** in the L-selectride® mediated reduction of phenylglyoxylic acid to mandelic acid, in comparison with the analogous auxiliary derived from (*R*,*R*)-hydrobenzoin, which was reported by Rosini et al. to induce stereoselectivities up to 56% de in this type of reaction,[4] even a slightly increased diastereoselectivity of 68% de with the same (*S*)-absolute configuration on the transformed stereocentre could be achieved (Scheme 2, Table 1).

On the one hand, in the case of Rosini's (*R*,*R*)-auxiliary the resulting stereoselectivities were interpreted to be the result of intramolecular π,π-interactions which force the open chain auxiliary into a conformation where the benzyl ether moiety effectively shields away the *si*-face of the keto carbonyl from the attack of the reducing agent.[4] Thus, by strengthening these π,π-interactions by introducing various substituents into the benzyl ether moiety, Rosini was able to improve the resulting diastereo selectivities significantly[5] (Table 1). On the other hand, we surprisingly found that replacement of the benzyl ether moiety in our *m*-hydrobenzoin derived auxiliary **5a** by the sterically demanding, π,π-non-interacting *i*-butyl group leading to auxiliary **5c** increased the resulting stereoselectivity as well (Table 1). This fact suggested a different mechanistic influence on the auxiliary conformation and prompted us to look out for other sterically more demanding ether moieties such as *tert*-butyl ethers, which might lead to further improvements.

Herein, we report the synthesis of three novel *m*-hydrobenzoin derived chiral hydrobenzoin *mono-tert*-butyl ethers **5d–f** (Scheme 3) via a new synthetic pathway using exclusively basic reaction conditions in the key steps and their application as chiral auxiliaries in the diastereoselective reduction of benzoylformic acid.

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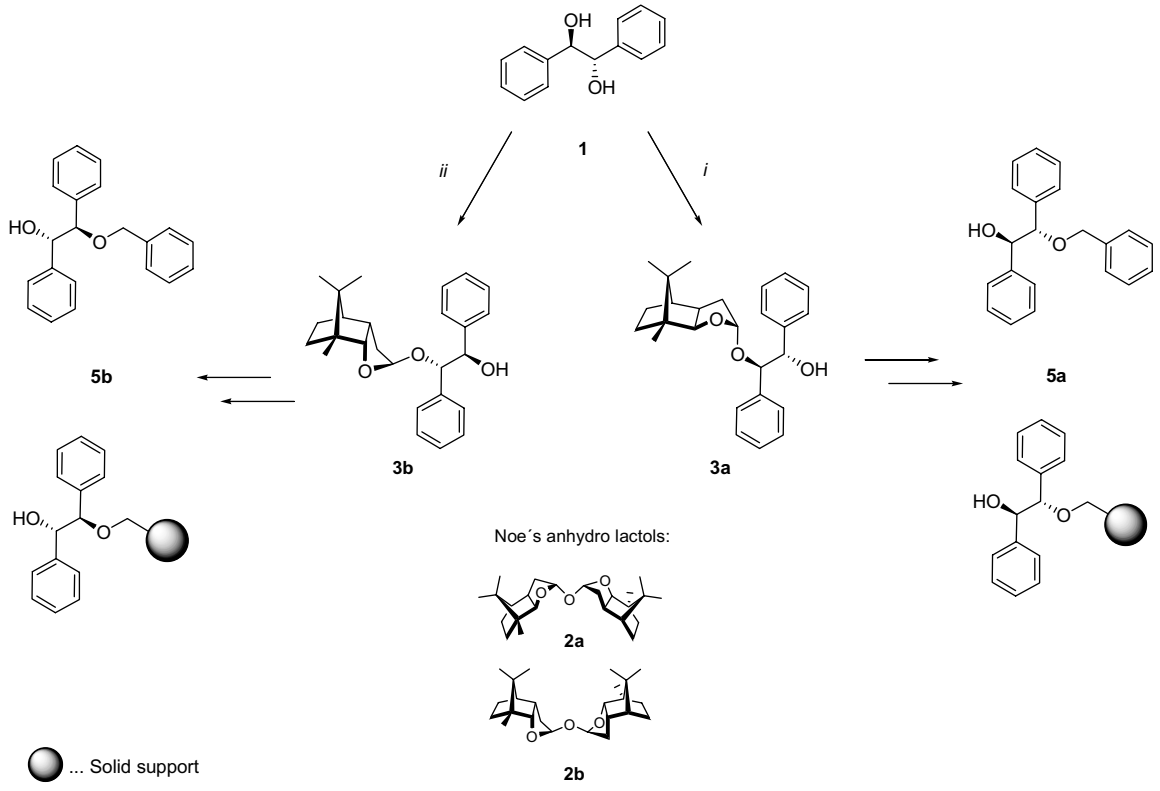
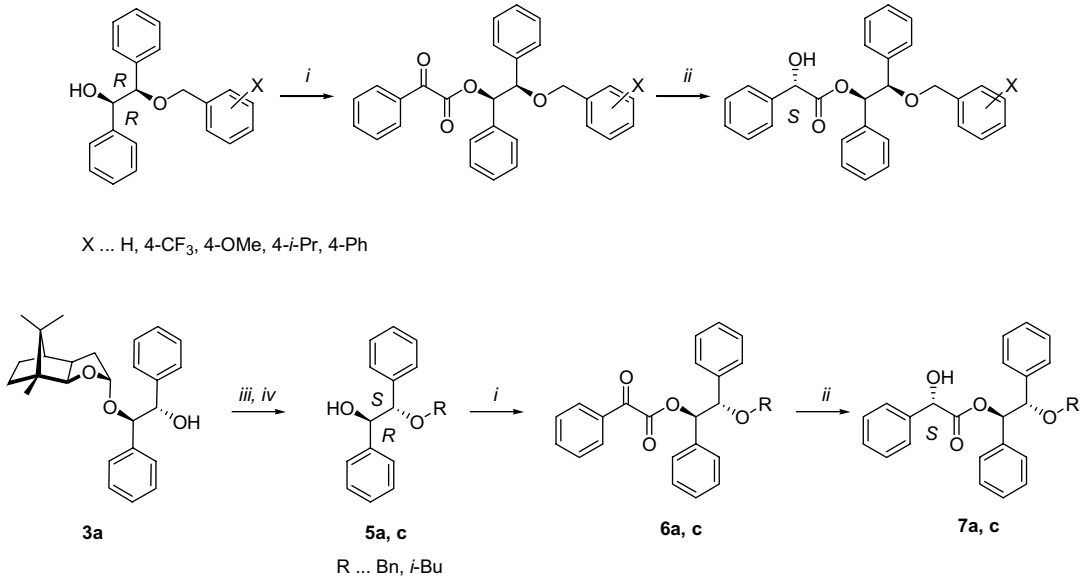



**Scheme 1.** Reagents and conditions: (i) *exo*-anhydro lactol **2a**, *p*-TsOH, $CH_2Cl_2$; (ii) *endo*-anhydro lactol **2b**, *p*-TsOH, $CH_2Cl_2$.




**Scheme 2.** Reagents and conditions: (i) PhCOCOOH, DIC, DMAP, $CH_2Cl_2$; (ii) L-selectride®, −78 °C, THF; (iii) NaH; BnBr or *i*-BuOTs, DMF; (iv) *p*-TsOH, MeOH.

## 2. Results and discussion

Bearing in mind that different kinds of analogous hydrobenzoin *mono-tert*-butyl ethers **5d–f** can be synthesized, we decided to derive these compounds from protected alkoxyacetic acid, *tert*-butyl ester **8** (Scheme 4), which was easily prepared in 98% yield by deprotonating protected, desymmetrized hydrobenzoin **3a** with NaH and refluxing the resulting alkoxide with bromoacetic acid, *tert*-butyl ester in THF in the presence of HMPA. Then ester **8** was methylated with 92% yield by deprotonation with LDA in THF and quenching of the enolate with $CH_3I$ at −20 °C (Scheme 5).

The resulting ester **9** was an approximately 2:1 mixture of diastereoisomers. Trying to increase the stereoinduc-