

Asymmetric Acid-Catalyzed Meerwein–Ponndorf–Verley–Aldol Reactions of Enolizable Aldehydes[†]

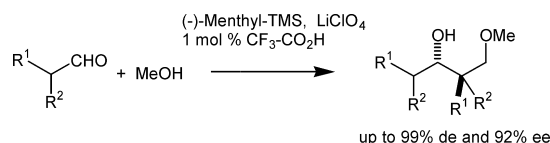
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ABSTRACT



A highly, stereo- and regioselective Meerwein–Ponndorf–Verley–Aldol etherification process of enolizable aldehydes is described. This new transformation is catalyzed by trifluoroacetic acid. The method also allows cross-aldol reactions with α -branched enolizable aldehydes and thus provides access to defined configured quaternary stereogenic centers.

The aluminum alkoxide-catalyzed redox equilibrium of alcohols with various carbonyl compounds is called Meerwein–Ponndorf–Verley reduction (MPV). This transformation generally uses inexpensive 2-propanol as the hydride source.¹ Extensive studies have been carried out to expand the potential of the classical Meerwein–Ponndorf–Verley reduction. Several synthetic enlargements of this important redox process have been reported for the MPV-aldol condensation,² MPV-Michael addition³ and MPV/Brook rearrangement/aldol addition.⁴ Also, the formal MPV-alkynylation,⁵ MPV-cyanation,⁶ MPV-allylation,⁷ and MPV-transfer aldol reaction⁸ should be mentioned here. The purpose of the present communication is to report an enantioselective MPV-aldol

process of enolizable aldehydes giving access even to defined configured quaternary stereogenic carbon atoms.⁹

During our ongoing studies of the deployment of LiClO₄ in stereoselective C–C bond formation processes¹⁰ we have

[†] Dedicated to Pelayo Camps in honor of his 65th birthday.

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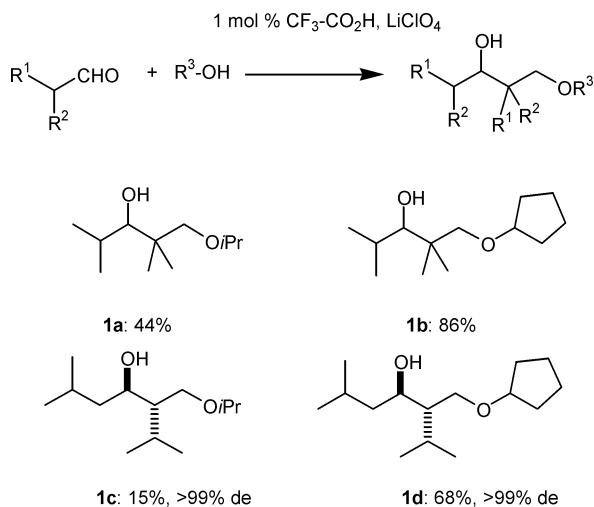
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also demonstrated the successful execution of Prins reactions.¹¹ These transformations were carried out in the presence of catalytic amounts of tartaric acid and tertiary alcohols. By extension of these reaction conditions to secondary alcohols, instead of Prins products corresponding 1,3-diol ethers were obtained, formed by a tandem aldol MPV/etherification process.¹²

During initial studies of this new reaction, the best yields were obtained with no solvents in the presence of dry LiClO₄ and 1 mol % of trifluoroacetic acid at room temperature.¹³ As an example, isobutyraldehyde or isovaleraldehyde reacts with secondary alcohols under these standard conditions to give the corresponding 1,3-diol ethers **1a–d** (Scheme 1). By deployment of isovaleraldehyde, extremely high diastereoselectivities were detected. The isopropyl ether **1c** and cyclopentylether **1d** were isolated as single diastereoisomers. Reactions of unbranched enolizable aldehydes resulted in the expected 1,3-diol ether with very low yields under these reaction conditions (*n*-Pr-CHO, *n*-Bu-CHO < 5%).

Scheme 1. Acid-Catalyzed Meerwein–Ponndorf–Verley–Aldol Etherification Reactions of Enolizable Aldehydes^a

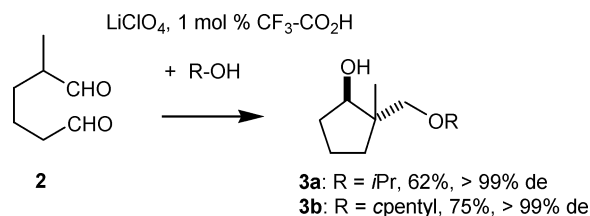


^a Diastereoselectivities were determined by ¹H NMR analysis.

Further, we have investigated the applicability of this protocol in intramolecular aldol/MPV/etherification processes. To this end we reacted α -methyladipaldehyde **2** with 2-propanol or cyclopentanol under these reaction conditions.

In both series, the corresponding 1,3-diol ethers **3a** and **3b** were isolated as single diastereoisomers (Scheme 2).

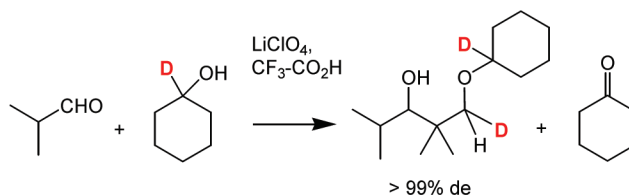
Scheme 2. Intramolecular Meerwein–Ponndorf–Verley–Aldol Etherification Process



These results highlight the crucial role of the choice of alcohol for a successful performance of this transformation. The yields of isolated ethers **1a–d** and **3a,b** are correlated to the secondary alcohols applied. Highest yields were obtained with cyclopentanol (Schemes 1 and 2). This trend matches tendencies of oxidation enthalpies measured for several alcohols.¹⁴ The lowest oxidation enthalpy was calculated for cyclopentanol (stabilization of the corresponding carbocation by hyperconjugation), while the highest enthalpies were found for primary alcohols, in particular for methanol.

In order to analyze the source and fate of hydride in these reactions, we carried out experiments with C1-deuterated cyclohexanol. As depicted in Scheme 3, 1 equiv of C1-deuterated cyclohexanol was oxidized, and deuterium was used for the reduction of the assumed intermediate hydroxy-aldehyde. A second equivalent of C1-deuterated cyclohexanol was used for the etherification. Subsequent analysis revealed the full incorporation of deuterium.^{15,16} Only one diastereoisomer was detected by ¹H NMR experiments, albeit with low yields (Scheme 3).

Scheme 3. Meerwein–Ponndorf–Verley–Aldol Reaction of Isobutyraldehyde with C1-Deuterated Cyclohexanol



During these studies, we detected neither the intermediate aldol adducts nor the corresponding 1,3-diols. Ethers of the secondary hydroxy group of 1,3-diols were not found either. In the absence of alcohols, no reactions occurred at all. And

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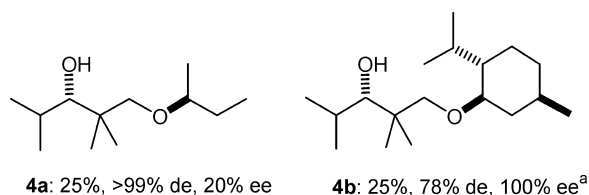
(15) For similar experiments but without any stereoselection, see: Kamitanaka, T.; Matsuda, T.; Harada, T. *Tetrahedron* **2007**, 63, 1429.

(16) See the Supporting Information.

finally, isolated aldol adducts or 1,3-diols cannot be transformed into the corresponding ethers under these reaction conditions. These results prove the assumption that all three theoretical reaction steps must be strongly associated (aldol addition, MPV-process, etherification).

Since these defined configured 1,3-diol ethers are valuable building blocks in natural product synthesis, we strove to realize an enantioselective execution of this transformation.

Scheme 4. Meerwein–Ponndorf–Verley–Aldol Etherification Reactions with Chiral Secondary Alcohols



^a The configuration of the minor diastereoisomer is unknown.

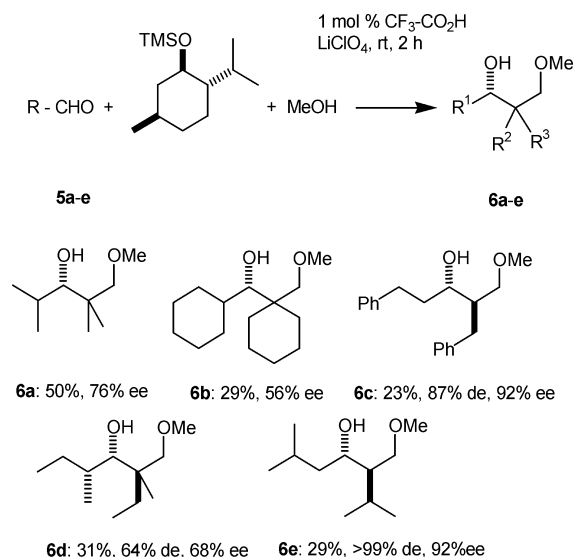
To this end, we tested several chiral secondary alcohols in these reactions. When used with optically pure (*S*)-2-butanol or (–)-menthol the corresponding ethers **4a** and **4b** were isolated with 25% yield. Partial racemization of the chiral secondary alcohols under the conditions of this MPV-aldol process was assumed for lowering of stereoselectivities of the corresponding 1,3-diol ethers (**4a**: 20% ee, **4b**: 78% de, Scheme 4). Also, when used with chiral protonic acids no enantioselectivities could be detected. Racemic 1,3-diol ethers were isolated by deployment of tartaric acid or camphoric acid in low yields.

These problems can be overcome by a strict discrimination between the hydride source and the alcohol that is used for the etherification. This competition can be decided by the considerable difference of oxidation enthalpies of varying alcohols. To this end, methanol was deployed for the etherification (highest oxidation enthalpy).¹⁷ Menthol, a chiral, secondary, and competitive sterically demanding alcohol, served as the chiral hydride source. Under these reaction conditions, we were not able to detect products indicating the formation of formaldehyde. Instead of that menthone, the oxidation product of menthol was isolated in equimolar amounts.

After optimization of reaction conditions, we elaborated the following protocol. The reactions were carried out in the presence of dry LiClO₄ and catalytic amounts of trifluoroacetic acid (1 mol %) at room temperature. Best results with regard to yields were obtained in the absence of any solvents. By application of oxygen-containing solvents no reactions were observed. Furthermore, higher yields and shorter reaction times were obtained by deployment of the trimethylsilyl ether of optically pure menthol. The results of these investigations are shown in Scheme 5.

(17) Application of other primary alcohols such as propanol or benzylic alcohol yielded a more complex reaction mixture.

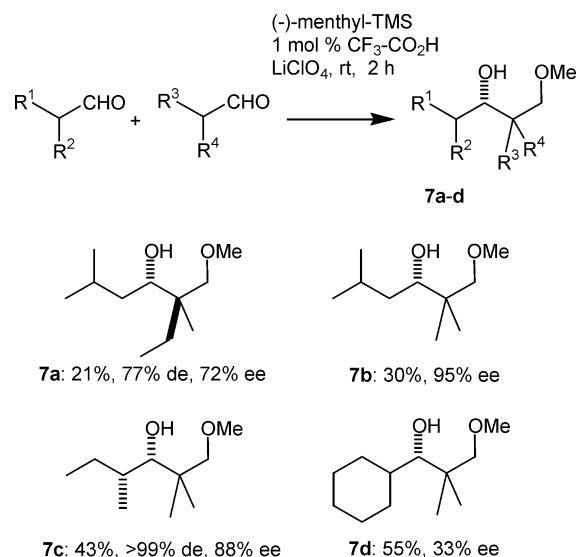
Scheme 5. Asymmetric Meerwein–Ponndorf–Verley–Homo–Aldol Etherification Reactions of Enolizable Aldehydes^a



^a For determination of diastereo- and enantioselectivities see ref 16.

In addition, reactions of two different enolizable aldehydes were investigated. An extremely high differentiation between the deployed aldehydes was observed. The key to the regioselectivity of this reaction is the preferred formation of enolates of α -branched enolizable aldehydes under these reaction conditions. α -Branched enolizable aldehydes act exclusively as ene components in every reaction we tried (**7a** and **7b**, Scheme 6). Even in reactions of two different α -branched enolizable aldehydes an extremely strong dif-

Scheme 6. Asymmetric Meerwein–Ponndorf–Verley–Cross–Aldol Etherification Reactions with α -Branched Enolizable Aldehydes^a



^a For determination of diastereo- and enantioselectivities see ref 16.

ferentiation is observed. In these cases, a less sterically demanding aldehyde acts exclusively as the ene component (**7c** and **7d**, Scheme 6). No other cross-aldol adducts or self-aldol adducts were observed under these reaction conditions. In addition, high enantioselectivities were detected.

In order to confirm the configuration, methyl ethers **6a–e** have been converted into the 1,3 diols by treatment with Me₃SiI in the presence of catalytic amounts of NaI. Subsequent reactions with dimethoxypropane yield the corresponding dimethyl acetals. For details of these investigations, see ref 16.

When used with TMS-ether of (+)-menthol and of isobutyraldehyde in these reactions, similar results with regard to yields and selectivities were obtained.¹⁶ Thus, an access to *R*-configured 1,3-diol methyl ethers is given.

The configurative outcome detected during these investigations is best explained by the transition state models shown in Figure 1. Based on steric interactions in model **A**, a strong preference for structure **B** seems to be likely. The rigid model **B** matches the configurative outcome of reactions when used with the trimethylsilyl ether of (–)-menthol.

In summary, we have developed an asymmetric Meerwein–Ponndorf–Verley–Aldol etherification reaction sequence of enolizable aldehydes. Thus, an access to defined configured quaternary stereogenic centers is given. High regio-, diastereo-, and enantioselectivity were observed. Further optimizations, investigations on the reaction mech-

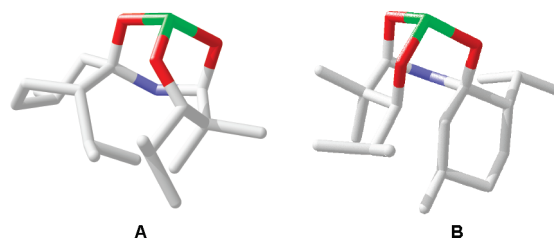


Figure 1. Proposed transition-state models for the configurative outcome of formation of **6a**: green, lithium; blue, C1-hydrogen from (–)-menthol.

anism, and application to natural product synthesis will be reported in due course.

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Supporting Information Available: Experimental details, characterization, and spectra of new products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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