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Acid-catalyzed aldol-Meerwein–Ponndorf–Verley-etherification reactions—access to defined configured quaternary stereogenic centers

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ABSTRACT

A novel asymmetric aldol-reduction–etherification process of aliphatic enolizable aldehydes is described. The intermediately formed aldol adducts—β-hydroxyaldehydes—were reduced and transformed into the corresponding 1,3-diol ethers by external secondary alcohols at the same time. Thus, with the help of chiral secondary alcohols an access to optically active 1,3-diol ether is given. Furthermore, asymmetric cross-aldol-Meerwein–Ponndorf reactions of enolizable aldehydes can also be realized under these reaction conditions.

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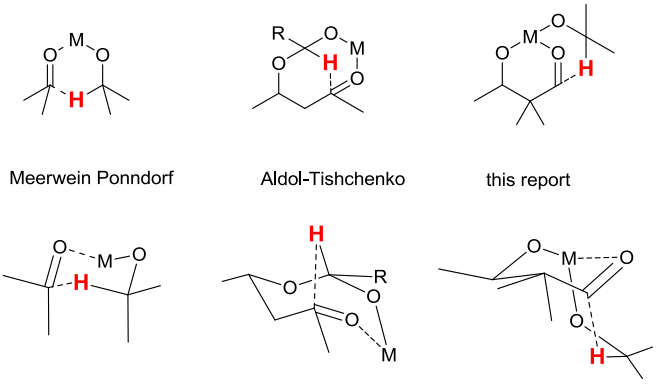
1. Introduction

The Meerwein–Ponndorf–Verley reduction (MPVR) of ketones has a prominent significance and a striking usefulness in organic synthesis. It is reversible, and the reverse reaction is known as the Oppenauer oxidation (OO). Several highly diastereoselective MPV-processes[1] and their extension to the synthesis of chiral 1,3-mercapto alcohols[2] were reported. On the other hand, examples of asymmetric MPV-processes are rare and lacking in general application.[3] Several chiral metal complexes were tested in enantioselective execution of the MPV-reaction but they are mostly devoted to aromatic ketones.[4] Satisfying examples of asymmetric execution in the aliphatic series are still unknown, with the exception of biocatalytical hydrogen transfer reactions.[5] In contrast, several synthetic enlargements of this important redox process have been reported, where the MPV-reaction is incorporated into C–C bond formation processes. These are MPV-aldol condensation processes,[6] and MPV/Brook rearrangement/aldol addition.[7] Also, the formal MPV-alkynylation,[8] MPV-cyanation,[9] MPV-allylation,[10] and MPV-transfer aldol reaction[11] should be mentioned here.

During the Meerwein–Ponndorf–Verley-reaction a 1,5-hydride shift occurs. A metal ion increases the electrophilic nature of the carbonyl group and a 1,5-hydride shift occurs from an external secondary alcohol (mostly isopropanol) to reduce the carbonyl compound.[12] A cyclic six-membered transition state is generally accepted as the mechanism of this hydride transfer.[13]

Also, a similar hydride shift is observed in the aldol-Tishchenko reaction. During this reaction a second molecule of the starting aldehyde generates an acetal intermediate to reduce the ketone by a 1,5-hydride shift. As a consequence corresponding 1,3-diol esters were obtained with extremely high degrees of diastereoselectivity. But again, high enantioselectivities were obtained in these reactions only when used with aromatic ketones as substrates.[14] When starting with corresponding racemic aldol adducts 1,3-diol esters were detected with good enantioselectivities.[15]



Scheme 1. Comparison of 1,5-hydride transfer-reactions.

These findings contrast results we have observed in enantioselective aldol-Meerwein–Ponndorf–Verley-etherification processes of enolizable aldehydes.[16] In these transformations enolizable

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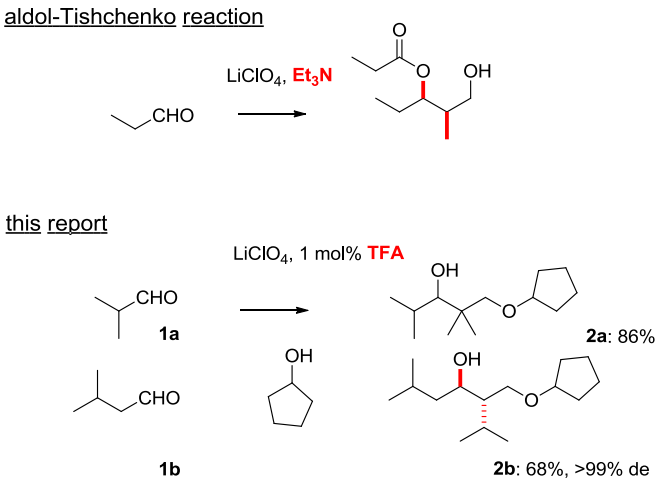
aldehydes react in the presence of catalytic amounts of acids and an external secondary alcohol to give the corresponding 1,3-diol ether—a product derived from an aldol addition, Meerwein–Ponndorf–Verley reduction and etherification sequence. Again, a 1,5-hydride shift, as is shown in Scheme 1, is observed under these reaction conditions. As a consequence, the formation of a primary alcohol followed by etherification is observed. The real reaction mechanism is still unknown so far. A Meerwein–Ponndorf–Verley reduction of intermediately formed hemiacetals to give 1,3-diol ethers cannot be excluded.

Herein we expand this novel transformation to a highly stereoselective intramolecular version with dialdehydes. Furthermore, we describe this transformation for both series—the synthesis of *R*- and *S*-configured 1,3-diol methyl ether. In addition, we provide a mild and useful procedure for the cleavage of resulting methyl ether.

2. Results and discussion

During our ongoing studies of the application of $LiClO_4$ in organic reactions we observed aldol reactions attended by a simultaneous hydride transfer. The type of hydride transfer strongly depends on reaction conditions. When used with bases an aldol-Tishchenko process is observed. The corresponding *syn*-configured 1,3-diol monoesters were detected in this case.[17] In contrast to that an aldol addition/MPV-reduction/etherification reaction sequence is observed by deployment of acids[18] and an external alcohol (cyclopentanol for **2a** and **2b**). The corresponding 1,3-diol cyclopentyl ethers **2a** and **2b** were isolated in high yields. By application of α-unbranched aldehydes extremely high degrees of anti-diastereoselectivity were noticed (**2b**, Scheme 2).



Scheme 2. Comparison of aldol-Tishchenko reaction and aldol-Meerwein–Ponndorf–Verley-etherification reaction.

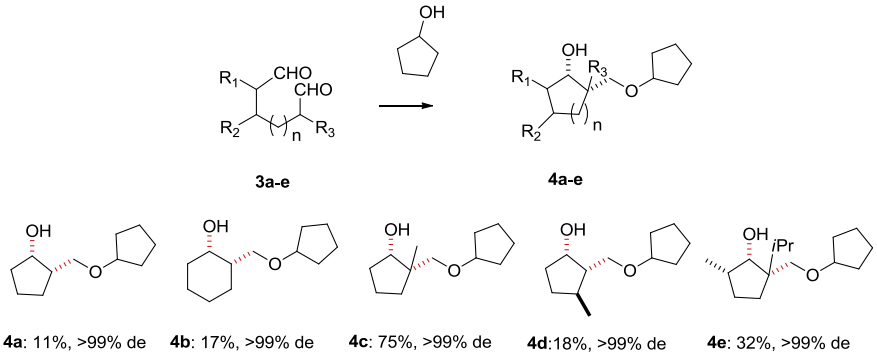
In a following first series we explored the intramolecular version of this reaction. To this end we reacted several enolizable dialdehydes with cyclopentanol in the presence of $LiClO_4$ and catalytic amounts of trifluoroacetic acid (TFA). Extremely high degrees of diastereoselectivities were detected. The 1,3-diol cyclopentyl ethers **4a**–**e** were isolated as a single diastereoisomer (Scheme 3). A typical tendency for preferring the formation of a quaternary carbon atom is observed under these reaction conditions, if one compares the results of intramolecular aldol addition-MPV-etherification of adipaldehyde **3a** (**4a**: 11% yield) and heptanedial **3b** (**4b**: 17% yield) with those of α-methyl adipaldehyde **3c** (**4c**: 75% yield).

To analyze the source and fate of hydride deuterated cyclohexanol was deployed in these reactions. Isobutyraldehyde was reacted with C1-deuterated cyclohexanol in the presence of catalytic amounts of trifluoroacetic acid and lithium perchlorate. The expected 1,3-diol cyclohexyl ether was isolated in addition to equimolar amounts of cyclohexanone (Scheme 4).

One equivalent of C1-deuterated cyclohexanol was oxidized to reduce the assumed intermediate β-hydroxyaldehyde. A second equivalent of C1-deuterated cyclohexanol was used for the etherification. Subsequent analysis revealed the full incorporation of deuterium.[19,20] Again, one single diastereoisomer was detected by ^1H NMR experiments. These interesting findings should offer the possibility of an enantioselective access to optically active 1,3-diol ether. To this end several chiral secondary alcohols were tested in these reactions, but only with moderate success. Racemization of the starting chiral secondary alcohols was observed under the conditions of this aldol-MPV process. At that point we decided to deploy two alcohols in these reactions—one for the etherification process and an additional chiral alcohol for the hydride transfer. To this end we have tested a series or different alcohols in homo-aldol-MPV-etherification reaction of isobutyraldehyde (Scheme 5).

The results clearly indicate the fundamental role played by the alcohols deployed in these reactions. The observed yields correspond to the oxidation enthalpies of the according alcohols.[21] Cyclopentanol, the alcohol with the lowest oxidation enthalpy, is oxidized very easily to give cyclopentanone and thus the highest yields of 1,3-diol ether (**2a**: 86%). On the other hand—methanol is the alcohol with the highest oxidation enthalpy in this series—is nearly resistant against oxidation under these reaction conditions. As a consequence, the 1,3-diol methyl ether was observed in very low yield (**5a**: 12%). Based on these remarkable differences a following comfortable situation appeared: methanol can be used as the etherification-alcohol and optical pure menthol, a secondary and competitive sterically demanding alcohol, should serve as the chiral hydride source.[22] By a careful optimization of the reaction conditions the following protocol was elaborated.

The reactions were carried out in the presence of dry $LiClO_4$[23] and catalytic amounts of trifluoroacetic acid (0.1 mol %) at rt. Best results with regard to yields were obtained in the absence of any



Scheme 3. Intramolecular aldol-Meerwein–Ponndorf–Verley-etherification process. Reaction conditions: rt, neat, 6 equiv $LiClO_4$, 1 mol % TFA, 2 equiv cyclopentanol.

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