Enolexo *Aldol Reactions*

Direct Catalytic Asymmetric *Enolexo* Aldolizations**

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The aldol reaction is an exceptionally useful strategic C–C bond-forming reaction for the stereoselective construction of cyclic and acyclic molecules. As a result, several catalytic

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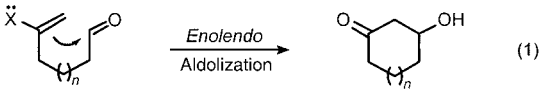
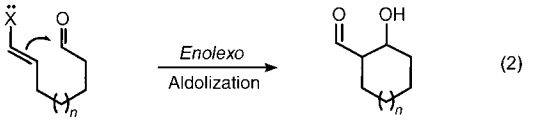
asymmetric intermolecular variants, both indirectly, with preformed enolate equivalents, and directly involving unmodified carbonyl compounds have been described.[1] Remarkably, however, there is still only one catalytic asymmetric intramolecular aldol reaction, the proline-catalyzed Hajos–Parrish–Eder–Sauer–Wiechert reaction.[2] While the usefulness of this process has been illustrated in a broad context,[3] only 6-*enolendo* aldolizations [Eq. (1), $n=1$] have been described so far. Direct catalytic asymmetric *enolexo* aldolizations [Eq. (2)] are unknown. Herein we describe the first and highly enantioselective examples of this process.



(1)



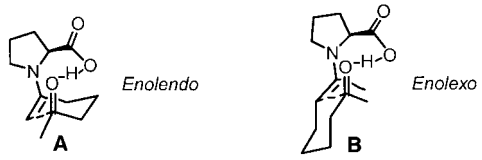
(2)

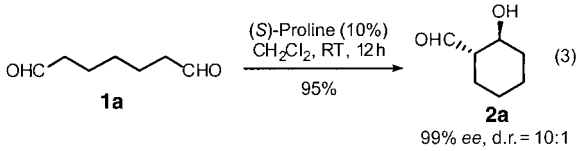
6-*Enolendo* aldolizations are very common and favored according to the Baldwin rules.[4,5] The only catalytic asymmetric variant of this process, the Hajos–Parrish–Eder–Sauer–Wiechert reaction has not been extended to different ring sizes, nor have any proline-catalyzed *enolexo* aldolizations [Eq. (2)] been described.[6] Although Baldwin-favored in the formation of 3–7 membered rings, *enolexo* aldolizations are less studied[7] and direct catalytic asymmetric variants are unknown.[8]

Recently, we discovered the first proline-catalyzed asymmetric intermolecular aldol reactions[9–11] and proposed a unified one-proline enamine catalysis mechanism of both inter- and intramolecular aldol reactions.[12–14] By inspecting possible transition-state models, we realized that in addition to the established 6-*enolendo* aldolizations via transition state **A**, proline should also catalyze corresponding 6-*enolexo* aldolizations via the chairlike assembly **B**. Such reactions should provide a highly stereoselective pathway to useful *trans*-1,2-disubstituted cyclohexanes.

Indeed, the reaction of heptanedial[15] (**1a**) with a catalytic amount of (*S*)-proline in dichloromethane gave aldol **2a** in high yield and diastereoselectivity, and with excellent enantioselectivity [Eq. (3)].[16,17]

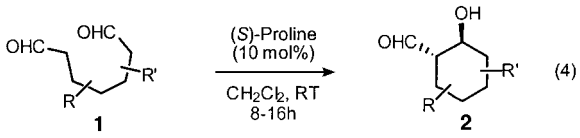
With this encouragement, we decided to study the scope of this





(3)

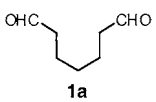
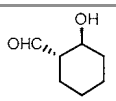
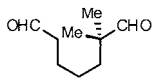
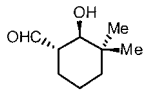
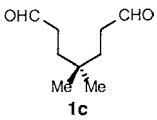
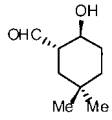
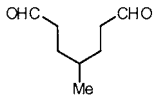
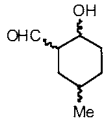
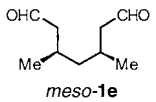
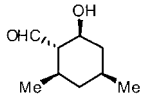
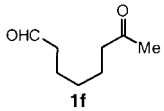
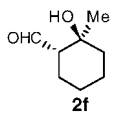
proline-catalyzed 6-*enolexo* aldolization. Various pentane-1,5-dialdehydes (pimelaldehydes; **1**) were prepared[18] and then treated with a catalytic amount of (*S*)- or (*R*)-proline in dichloromethane [Eq. (4), Table 1]. Both **1b** and **1c** provided



(4)

the corresponding cyclic aldols **2b** and **2c** in high yields and excellent diastereo- and enantioselectivities. Surprisingly, we found that a single substituent in the 4-position has an unfavorable effect on the stereoselectivity of the cycloaldo-

Table 1: Proline-catalyzed *enolexo* aldolizations of dicarbonyl compounds. Yields refer to diols obtained after in situ $NaBH_4$ reduction.

Dicarbonyl	Yield [%]	Products	*ee* [%]	d.r. [%]
 **1a**	95	 **2a**	99	10:1
 **1b**	74	 **2b**	98	>20:1
 **1c**	75	 **2c**	97	>20:1
 **1d**	76	 **2d**	75,89,95,8	22:5:5:1
 *meso*-**1e**	88	 **2e**	99	1:1
 **1f**	92	 **2f**	99	2:1

lization. This effect was demonstrated with 4-methyl-substituted **1d**, which provided all four possible diastereomeric aldols of **2d** upon treatment with proline; the resulting aldols were obtained in a 22:5:5:1 ratio and in 75, 89, >95, and 8% *ee*, respectively. Explaining the lowered stereoselectivity in this case is difficult without calculating the relative energies of all reasonable transition states.[12] Even if the enamine is fixed to having *E* geometry, and boat conformations are excluded (as in **B**), the transition states may still vary in an axial versus equatorial 4-substituent and/or enamine double bond, and in the *anti* versus *syn* relationship of the carboxylic acid to the olefin. We also investigated the behavior of the *meso*-configured dialdehyde **1e** under our reaction conditions. Four stereogenic centers may be created simultaneously in a catalytic asymmetric desymmetrization of this substrate. We found the two expected *anti*-configured aldols (**2e** and **2e′**) to be formed in equal amounts and in 99 and 75% *ee*, respectively. That the proline-catalyzed *enolexo* aldolization is not limited to dialdehydes was illustrated in the reaction of ketoaldehyde **1f**, which gave tertiary aldol **2f** (d.r. = 2:1), in 99% *ee* (minor isomer 95% *ee*).

In summary, we have described the first and highly enantioselective proline-catalyzed *enolexo* aldolization of dicarbonyl compounds. This reaction provides β-hydroxy cyclohexane carbonyl derivatives that are of potential widespread usage in target-oriented synthesis. This *anti*-diastereoselective proline-catalyzed *enolexo* aldolization nicely complements alternative methodologies such as the highly enantio- and *syn*-diastereoselective baker's yeast reduction of β-keto esters.[19] An advantage of the aldolization methodology is that both enantiomeric products can be accessed simply by using either (*S*)- or (*R*)-proline, whereas the biocatalysis route is limited to products of a single absolute configuration.[20] Applications in natural product synthesis and further extensions of proline-catalyzed inter- and intramolecular aldolizations are forthcoming.

Experimental Section

Typical aldolization procedure: Dicarbonyl **1** (1 mmol) was dissolved in dry dichloromethane (10 mL) and treated with (*S*)- or (*R*)-proline (12 mg, 0.1 mmol, 10%). The mixture was stirred at room temperature until the starting material had disappeared (8–16 h). Aldols **2** can be isolated after standard aqueous work-up, but are unstable over extended time periods at room temperature. Stable diols are obtained by in situ reduction with $NaBH_4$ followed by an aqueous work-up, as described elesewhere.[11d,21]

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Keywords: aldol reaction · amino acids · asymmetric catalysis · organocatalysis

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[17] The analogous proline-catalyzed 5-*enolexo* aldolization of hexanedial is less selective (d.r. = 2:1; *ee*(*anti*) = 79 %, *ee*(*syn*) = 37 %).
[18] Substituted pimelaldehydes **1** were routinely prepared from commercially available substituted cyclohexanones through α-carbomethoxylation (NaH, $MeOCO_2Me$) and retro-Dieckman condensation using either NaOMe or Cs_2CO_3 (R. G. Salomon, M. F. Salomon, *J. Org. Chem.* **1975**, *40*, 1488 – 1492; P. Tundo, S. Memoli, M. Selva, , WO 02/14257, **2000**.) Diisobutylaluminium hydride reduction (or LAH reduction followed by PCC oxidation) of the resulting diesters then provided the desired pimelaldehydes **1** in acceptable overall yields.
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