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Catalytic Asymmetric Access to α,*β* Unsaturated *δ*-Lactones through a Vinylogous Aldol Reaction: Application to the Total Synthesis of the Prelog-Djerassi Lactone

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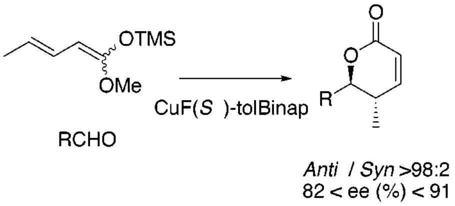
ABSTRACT



A one-step catalytic asymmetric access to α,*β* unsaturated *δ*-lactones is described, using a vinylogous Mukaiyama-aldol reaction between a *γ*-substituted dienolate and various aldehydes in the presence of Carreira catalyst CuF·(S)-tolBinap. This methodology has been further applied to a straightforward access to the Prelog-Djerassi lactone.

The α,*β* unsaturated and saturated *δ*-lactones are found in an impressive number of natural and unnatural products possessing interesting biological activities.[1−9] These compounds are also useful chiral building blocks, such as for example the Prelog-Djerassi lactone.[10,11] Efficient asymmetric syntheses of such lactones have been described but required the use of a stoichiometric amount of chiral auxiliary and/or a multiple-step sequence.[12−18]

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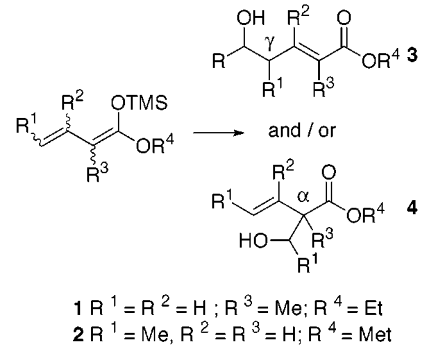
We wish to report herein an efficient catalytic asymmetric one-step protocol to access α,β unsaturated δ-lactones using a vinylogous aldol reaction.[19]

Recently, we have described the efficient formation of vinylogous aldol product using silyl dienolate **1** in good yields, excellent γ: α regioselectivity, and moderate to good enantioselectivity (Scheme 1).[20]

Scheme 1. Vinylogous Mukaiyama-Aldol Reactions

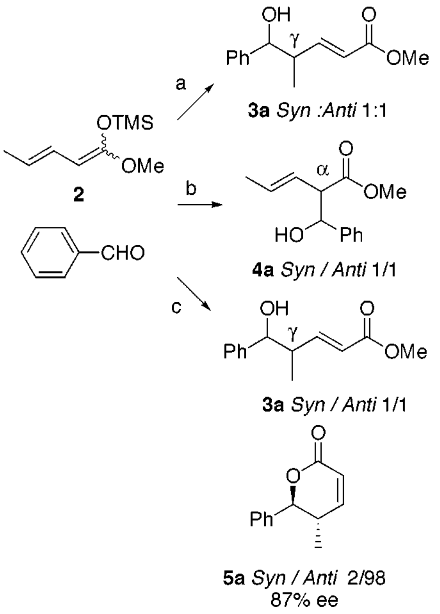


To observe the influence of a γ substituent on the course (α/γ and *syn*/*anti* ratio) of the reaction, we envisioned the reaction of γ-substituted silyl-dienolate **2**[21] with benzaldehyde. Unexpected results were observed depending on the nature of the dienolate activation (Scheme 2).

Using 10% of tetrabutylammonium triphenyldifluorosilicate TBAT as a racemic nonhygroscopic source of fluoride,[22] the expected vinylogous aldol product **3a** was isolated in 45% yield in a disappointing 1:1 *syn*/*anti* ratio. Changing the fluoride source to a chiral nonracemic ammonium fluoride,[20c] we were surprised to isolate only the α aldol product in 68% yield, in a 1:1 *syn*/*anti* mixture.

Moving to the Carreira catalyst CuF•(*S*)-tolBinap,[23] a 14:86 mixture of the vinylogous aldol product **3a** and the lactone **5a** was isolated in 85% yield (Table 1). The vinylogous aldol product **3a** was obtained with no *syn*/*anti* diastereoselectivity and very poor enantioselectivities (<5% ee for both *syn* and *anti* products). On the other hand, the α,β unsaturated lactone **5a** was found to be highly *anti* selective (*syn*/*anti* > 2:98) in 87% ee, suggesting that a more organized transition state had occurred.

Scheme 2[a]



[a] (a) TBAT 10%, THF, rt, 60%; (b) *N*-benzyl cinchodinium fluoride 10%, THF, rt, 60%; (c) CuF•(*S*)-tolBinap, 10%, rt, 85% (**3a**/**5a** 16/84).

Table 1. Vinylogous Mukaiyama Reactions of Dienolate **2** with Various Aldehydes in the Presence of 10% of CuF•(*S*)-tolBinap

entry	aldehyde	yield % (**4** + **5**)	ratio[a] **5**/**4**	lactones **5** no.	lactones **5** *anti*/*syn*[a]	ee
1	benzaldehyde	85	86/14	**5a**	>98/2	87[b], 98[c]
2	2-naphthaldehyde	95	80/20	**5b**	>98/2	85[d]
3	2,3-dimethoxy benzaldehyde	87	81/19	**5c**	>98/2	91[e], 98[c]
4	2-furaldehyde	60	50/50	**5d**	>98/2	86[f]
5	(*E*)-cinnamaldehyde	60	70/30	**5e**	>98/2	82[g]
6	isobutyraldehyde	95	64/36	**5f**	>98/2	91[h]

[a] Determined by ^{1}H NMR on the crude product. [b] HPLC DAICEL-OD, hexane/2-propanol 95/5. [c] After recrystallization (heptane). [d] HPLC DAICEL-OJ, hexane/2-propanol 82/18. [e] HPLC DAICEL-OJ, hexane/2-propanol 95/5. [f] HPLC DAICEL-OJ, hexane/2-propanol 95/5. [g] HPLC DAICEL-OJ, hexane/2-propanol 90/10. [h] HPLC ChiralPAK AD, hexanes/ethanol 99/1.

The reaction with other aromatic aldehydes (Table 1, entries 2−4) was also efficient, leading to lactones with excellent diastereoselectivities (>2:98 *syn*/*anti*) and high enantioselectivities (85−91% ee and even 98% ee for the

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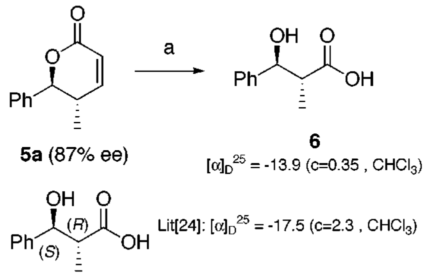
recrystallized lactones **5a** and **5c**). Reaction with 2-furaldehyde proved to be less selective, leading to the lactone with a high ee (86%) but generally in a 1:1 ratio of linear and lactone products. The reactions with unsaturated (entry 5) and aliphatic (entry 6) aldehydes were also efficient in terms of *anti*/*syn* ratio (>98/2) and ee (respectively, 82%, 91%), but the lactone/linear product ratios were somewhat lower (respectively, 70/30, 64/36) compared to aromatic aldehydes.

To determine the absolute configuration of the lactones, lactone **5a** was oxidized to the previously described enantiomerically pure compound **6**.[24] A rotation of −13.9 (for 87% ee) was found, in agreement with the reported rotation of −17.5 described for the enantiomerically pure *anti* (2*R*,3*S*) compound.

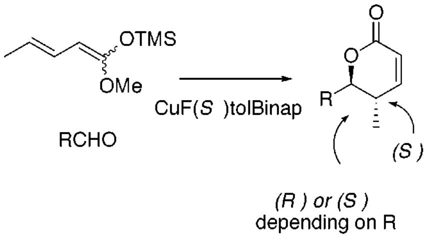
Scheme 3[a]



[a] (a) $RuCl_3$ 6%, $NaIO_4$ 4.2 equiv, $CH_3CN/CCl_4/H_2O$ (1/1/1.5), 50 °C, 24 h, 35%.

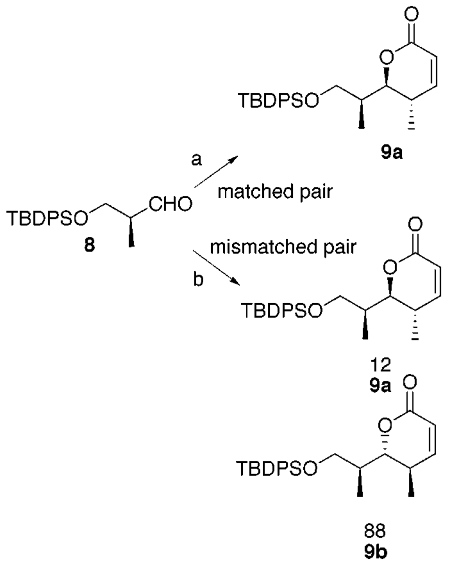
Consequently, asolute configurations of lactones **5**, obtained with CuF•(*S*)-tolBinap, were tentatively assigned as shown in Scheme 4.

Scheme 4



This methodology was then applied to chiral aldehyde **8**.[25] The reaction of chiral aldehyde **8** with the (*S*)-tolBinap ligand (matched pair) led predominantly to the *syn*/*anti* lactone **9a**.[11d,26] The other *anti*/*anti* lactone **9b**[26] could not be observed by ^{1}H NMR of the crude product, and linear products were found to be less than 10% of the mixture. After flash chromatography, lactone **9a** was isolated in a gratifying 60% yield. Using the (*R*)-tolBinap ligand with aldehyde **8** (mismatched pair), an inversion of the diastereoselectivity could be observed: a 9/1 mixture of lactones **9b**[27] and **9a** was obtained (the amount of linear products was again found to be less than 10%). After purification by flash chromatography, the mixture of lactones was isolated in 55% yield.

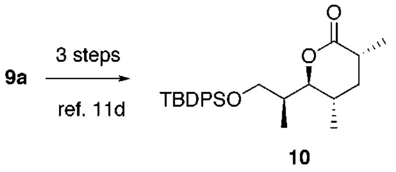
Scheme 5[a]



[a] (a) CuF•(*S*)-tolBinap, 10%, rt, 60%; (b) CuF•(*R*)-tolBinap, 10%, rt, 55%.

According to the procedures described by Cossy,[11d] the lactone **9a** was further transformed in three steps to the Prelog-Djerassi lactone **10**. This procedure constitutes a straightforward (four steps from aldehyde **8**) catalytic asymmetric access to the Prelog-Djerassi lactone (Scheme 6).

Scheme 6



In conclusion, the catalytic asymmetric vinylogous aldol of γ-substituted dienolate constitutes a valuable one-step route to α,β unsaturated lactones, as illustrated by the synthesis of the Prelog-Djerassi lactone. Further optimization

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and applications of this reaction to the synthesis of natural products are currently under investigation.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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