Catalytic Enantioselective Synthesis of Prostaglandin E_1 Methyl Ester Using a Tandem 1,4-Addition-Aldol Reaction to a Cyclopenten-3,5-dione Monoacetal

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Conjugate addition reactions are among the most important carbon−carbon bond formation reactions in organic synthesis,[1] and considerable progress has been made in the development of asymmetric Michael additions and 1,4-additions of organometallic reagents.[2] Recently, highly enantioselective copper-catalyzed conjugate addition reactions of diorganozinc reagents to enones have been reported.[3] Among the various chiral ligands introduced for this purpose phosphoramidite **4**, developed in our laboratories, shows nearly complete stereocontrol in the reaction of (functionalized) dialkylzinc (R_2Zn) reagents with six-, seven- and eight-membered cycloalkenones.[4] On the basis of this methodology, catalytic routes are now available to enantiomerically pure products, embedding cyclohexane and larger rings in their structure.[5] In contrast, the catalytic enantioselective 1,4-addition to 2-cyclopentenone is a major challenge, particularly because chiral cyclopentane structures are ubiquitous in natural products. Employing TADDOL-based phosphoramidite ligands we obtained up to 62% ee when the Et_2Zn addition to 2-cyclopentenone was run in the presence of molecular sieves.[6] Furthermore, with using chiral bidentate phosphoramidite ligands, the enantioselectivity improved to 83%.[7] Chan[8] reached 89% ee using a diphosphite ligand, whereas Pfaltz[9] enhanced the enantioselectivity in this addition to 94%. Recently Hoveyda[10] reported ee values up to 97% using a chiral peptide-based phosphine ligand in the 1,4-addition of diethylzinc to 2-cyclopentenone. Although these catalysts give excellent enantioselectivities, the isolated yields for the 3-substituted cyclopentanones are often moderate. Possible reasons are the lower reactivity of 2-cyclopentenone in comparison with other cyclic enones, the side-reactions of the resulting zinc enolate with the starting material and the high volatility of the 1,4-addition product. Performing the reaction in the presence of an aldehyde increases the yield considerably.[4,6,11]

Scheme 1

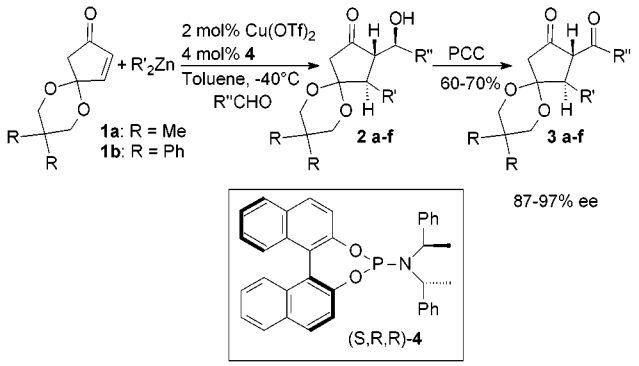

Table 1. Results of Tandem 1,4-Addition-Aldol Reactions According to Scheme 1

entry	enone	R′2Zn	R″CHO	prod.	yield [%][a]	ee **(3a−f)** [%][b]
1	**1a**	Et	Ph	**2a**	67	87
2	**1a**	*n*-Bu	Ph	**2b**	64	87
3	**1b**	Et	Ph	**2c**	76	94
4	**1b**	*n*-Bu	Ph	**2d**	69	94
5	**1b**	Et	*p*-Br−Ph	**2e**	69	96
6	**1b**	*n*-Bu	*p*-Br−Ph	**2f**	64	97

[a] Isolated Yields. [b] Determined with HPLC (Daicel CHIRAL PAK-AD).

We report here the highly enantioselective catalytic tandem 1,4-addition-aldol reaction of dialkylzinc reagents to cyclopenten-3,5-dione monoacetals in the presence of aldehydes. These compounds show a higher reactivity, and the heavily functionalized products are less volatile. The usefulness of this new method is illustrated by the total synthesis of (−)-PGE_1 methyl ester in seven steps using achiral starting materials and only a catalytic amount of a chiral copper complex.

Monoacetals **1a** and **1b** were employed in the tandem 1,4-addition-aldol reaction with various aldehydes and dialkylzinc reagents (Scheme 1).[12] The catalyst was prepared in situ from 2 mol % $Cu(OTf)_2$ and 4 mol % (*S*,*R*,*R*)-phosphoramidite **4**.

Full conversion was reached after 16 h to provide exclusively *trans* substituted cyclopentanones **2a**−**f** in isolated yields up to 76% (Table 1). Excellent stereocontrol is also observed in the subsequent aldol step, as for the hydroxy ketones **2a**−**2f** diastereomeric ratios higher than 95:5 were measured. The configuration of the main product was determined by NOESY-NMR. The adducts **2a**−**f** were converted into the corresponding diketones **3a**−**f** in good yields to give single diastereomers suitable for ee determination by chiral HPLC. The enantioselectivity strongly depends on the acetal moiety present in the starting material as 87% ee for enone **3a** (entry 1) and 94% ee for enone **3c** (entry 3) was obtained. The use of different dialkylzinc reagents, however, has no influence on the selectivity of this reaction (entries 3 and 4). The structure of the aldehyde has a minor influence: the use of benzaldehyde and *p*-bromo benzaldehyde shows ee values of 94% and 97%, respectively (entries 4 and 6).

We have demonstrated therefore, that in the presence of 2 mol % of [(*S*,*R*,*R*)-**4**]$Cu(OTf)_2$ nearly complete stereocontrol over the formation of three consecutive stereocenters in this tandem 1,4-addition-aldol reaction is achieved, providing multifunctional cyclopentanones. These results inspired us to demonstrate the

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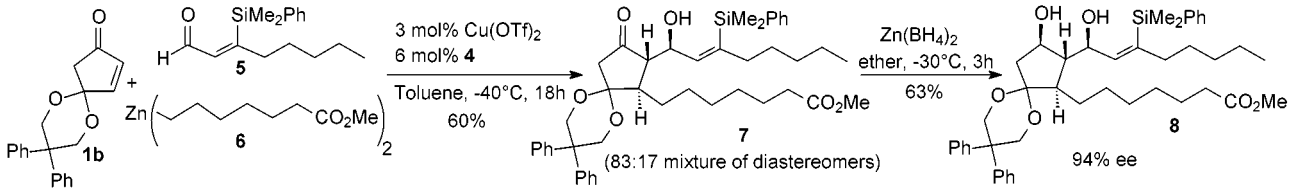
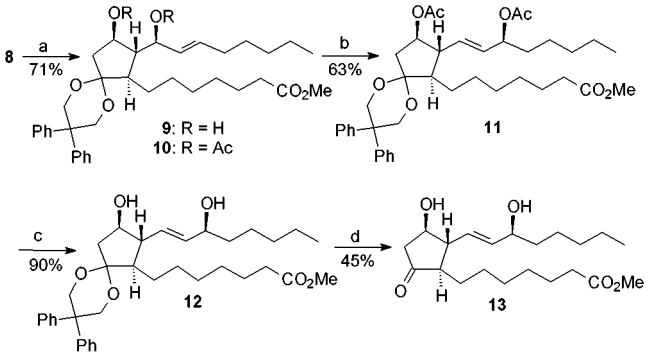
Scheme 2



Scheme 3[a]



[a] Key: (a) (1) 3 equiv Bu_4NF (1 M in THF), methylpropionate, DMSO, 80 °C, 20 min; (2) Ac_2O, DMAP, pyridine, 20 min; (b) 5 mol % $Pd(CH_3CN)_2Cl_2$, THF, 3 h; (c) K_2CO_3, MeOH, 18 h; (d) $(NH_4)_2Ce(NO_3)_6$, MeCN, borate−HCl buffer (pH = 8), 60 °C, 2 h.

usefulness of this catalytic method by applying it to the synthesis of (−)-PGE_1 methyl ester.[13]

The initial approach we followed for this catalytic asymmetric total synthesis is reminiscent of the three component coupling reaction introduced by Noyori et al.,[14] a methodology which gives access to a variety of prostaglandins.[15] However, the use of the required dialkenylzinc reagents instead of the previously used dialkylzincs did not lead to product formation. For this reason we developed a new strategy involving the introduction of the saturated α-chain with a functionalized zinc reagent and the *ω*-chain via an unsaturated aldehyde. The synthesis starts with enone **1b**, aldehyde **5**,[12b,16] and the functionalized zinc reagent **6**[17] (Scheme 2). In the presence of 3 mol % of the catalyst we obtained compound **7** in 60% yield as the only product as a mixture of diastereomers (ratio 83:17) which differ in the configuration at the exocyclic stereocenter bearing the hydroxy functionality. This one-pot procedure is carried out with an enone and an enal. To differentiate between these, the unsaturated aldehyde is equipped with a removable silyl substituent, exploiting the fact that *β*-disubstituted enones are not reactive in the 1,4-addition under these conditions. Reduction of the ketone moiety of **7** proceeds with 95% stereoselectivity using $Zn(BH_4)_2$ in ether at −30 °C. Compound **8** was isolated after chromatography as a single isomer in 63% yield with an ee of 94%. In the next step the silyl substituent was removed using Bu_4NF in THF/DMSO to give compound **9** (Scheme 3). This concept comprises a novel protection and deprotection sequence for enones suitable for the catalytic 1,4-addition with dialkylzincs. The cleavage of vinyl carbon−silicon bonds with Bu_4NF was developed by Nozaki.[18] However, under the normal reaction conditions hydrolysis of compound **9** was observed to be caused by water in the commercial THF solution of Bu_4NF. Adding first sacrificial methylpropionate to remove the water by hydrolysis and only afterwards **8**, the desilylated compound **9** was obtained as the only product and used without further purification. Acetylation of **9** afforded **10** in 71% yield over two steps.

The 1,3-allylic transposition of **10** with a catalytic amount of $Pd(CH_3CN)_2Cl_2$ in THF proceeded with reasonable yield and full retention of configuration[19] to give allylic acetate **11** with the required stereochemistry. After deacetylation in the presence of K_2CO_3 in MeOH, compound **12** was obtained in excellent yield. The last step is the deprotection of the ketone functionality to provide the labile *β*-hydroxy ketone moiety of the prostaglandin. This conversion was realized using a catalytic amount of $(NH_4)_2Ce(NO_3)_6$ under nearly neutral conditions.[20] In this way PGE_1 methyl ester[21] is obtained in 7% overall yield with 94% optical purity in seven steps from **1b**.

In conclusion we have demonstrated that cyclopenten-3,5-dione monoacetals give highly enantioselective tandem 1,4-addition-aldol reactions in the presence of dialkylzinc reagents and aldehydes using a catalytic amount of $Cu(OTf)_2$ and phosphoramidite ligand **4**. Furthermore this reaction is the key step in a short total synthesis of PGE_1 methyl ester, comprising a new route to this natural product.

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Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) The analytical and spectral data (TLC, HPLC, ^1H NMR, ^{13}C NMR, CD, MS) $[\alpha]^{23}_D$ −51° (*c* 1.0, CH_3OH) of **13** were identical with those of authentic material (Sigma) $[\alpha]^{23}_D$ −54° (*c* 1.0, CH_3OH).