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Catalytic Enantioselective Synthesis of Prostaglandin E₁ 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 (function-alized) 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 Chan⁸ reached 89% ee using a diphosphite ligand, whereas Pfaltz⁹ enhanced the enantioselectivity in this addition to 94%. Recently Hoveyda¹⁰ 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	<i>n</i> -Bu	Ph	2b	64	87
3	1b	Et	Ph	2c	76	94
4	1b	<i>n</i> -Bu	Ph	2d	69	94
5	1b	Et	<i>p</i> -Br-Ph	2e	69	96
6	1b	<i>n</i> -Bu	<i>p</i> -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 (-)-PGE₁ 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 Bu₄NF (1 M in THF), methylpropionate, DMSO, 80 °C, 20 min; (2) Ac₂O, DMAP, pyridine, 20 min; (b) 5 mol % Pd(CH₃CN)₂Cl₂, THF, 3 h; (c) K₂CO₃, MeOH, 18 h; (d) (NH₄)₂Ce(NO₃)₆, MeCN, borate-HCl buffer (pH = 8), 60 °C, 2 h.

usefulness of this catalytic method by applying it to the synthesis of (-)-PGE₁ 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(BH₄)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 Bu₄NF 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 Bu₄NF 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 Bu₄NF. 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(CH₃CN)₂Cl₂ in THF proceeded with reasonable yield and full retention of configuration¹⁹ to give allylic acetate **11** with the required stereochemistry. After deacetylation in the presence of K₂CO₃ 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 (NH₄)₂-Ce(NO₃)₆ under nearly neutral conditions.²⁰ In this way PGE₁ methyl ester²¹ 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 PGE₁ 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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