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A New Catalytic Asymmetric Approach to Polyfunctional Aldol Products Mediated by Zinc Organometallics.

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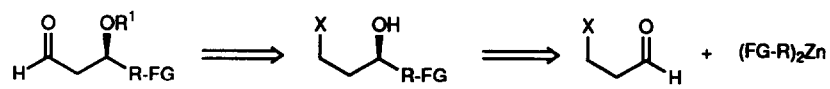
Summary: The catalytic asymmetric addition of functionalized dialkylzincs to β-alkoxyaldehydes provides after a short sequence of functional group interconversions aldol products in 40-99%ee. Their stereoselective transformation to either syn- or anti-1,3-diols has been performed.

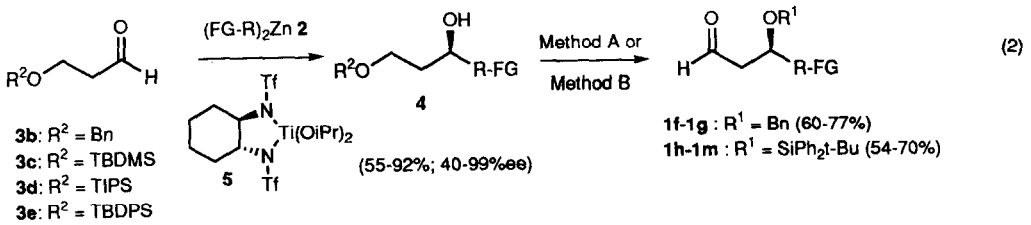
The β-hydroxycarbonyl functionality, characteristic of aldol products, is found in many types of natural products. It is also a key building-block for the preparation of 1,3-diols.[2] The central place of the aldol functionality in organic chemistry explains why its stereocontrolled synthesis has been extensively studied during the last two decades.[3,4] Most enantioselective approaches to aldol products require stoichiometric amounts of a chiral auxiliary[5] and only a few catalytic asymmetric preparations of aldols have been described.[6] We report herein a catalytic enantioselective synthesis of aldols **1** using a new synthetic strategy (eq. 1). The key step being the introduction of the chiral center using a catalytic asymmetric addition of a dialkylzinc **2** to a β-functionalized aldehyde of type **3**.[7,8] The resulting alcohol **4** can then be converted in further steps to the protected aldol product **1** (R^1 = CH_2Ph or SiR_3). In our first experiments, we used 3-(dimethylphenylsilyl)propanal **3a**[9] (X = $SiMe_2Ph$) and found that functionalized dialkylzincs add to this aldehyde in the presence of trans-(1R, 2R)-bis-(trifluoromethanesulfonamido)cyclohexane **5** (8 mol%) with high enantioselectivity (96%ee; entries 1, 2 of Table I).[10,11,12]



1 4 3 2 (1)

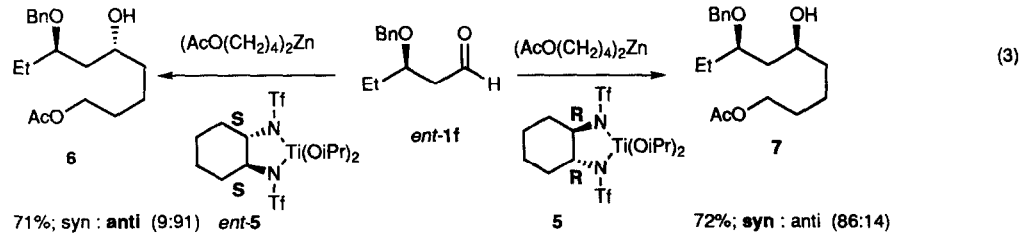
The conversion of **4a** (X = $SiMe_2Ph$) to a 1,3-diol derivative requires an extra oxidation step[13] ((i) KBr, AcO_2H, NaOAc, AcOH, 25 °C, 12h (ii) AcCl, Pyr, 0 °C, 1h) and provides (S)-1,3,8-triacetoxyoctane in 60% yield. The lack of generality of this approach, led us to introduce an oxygen functionality directly into the aldehyde **3** (X = OR^2). This oxygen function has to have a low complexation ability in order to avoid a competitive complexation with the chiral titanium center which would result in a lower enantioselectivity. In an initial experiment, we have reacted 3-benzyloxypropanal **3b** (R^2 = CH_2Ph) under the usual conditions ($Ti(OiPr)_4$ (2 equiv.), **5** (8 mol%), toluene, -20 °C) with Et_2Zn (2 equiv.) providing the alcohol **4c** in 83%ee and 88% yield (entry 3 of Table I). A more bulky oxygen substituent like a t-Bu$(Me)_2Si$ group furnishes a similar enantioselectivity (82-85%ee) but gives lower yields (62-65%; entries 4-5). A triisopropylsilyl protecting group (R^2 = TIPS) proves to give the best results (92%; 93%ee; entry 6) and 3-

triisopropylsilyloxypropanal **3d** reacts successfully with various diorganozincs (entries 6-13). An ester function is tolerated in the zinc reagent if it is separated by more than three carbon atoms from the carbon-zinc bond. Lower yields and enantioselectivities are obtained if the ester function is closer (entry 12) or if a chlorine is present in the carbon chain (59% yield, 66%ee; entry 13). Interestingly, the β-alkoxyaldehyde **3e** (R^2 = TBDPS) allows to add the relatively unreactive zinc reagent di(3-pivaloyloxypropyl)zinc with an excellent enantioselectivity (98%ee) although the yield (35%) still remains to be improved (compare entries 12 and 14). The resulting alcohols **4f-m** are readily converted into the benzyl protected aldol products **1f-h** (method A: (i) NaH, BnBr, THF; (ii) TFA, H_2O-THF or Bu_4NF, THF; (iii) PCC, CH_2Cl_2) in 60-77% overall yields or in TBDPS-ether protected aldol products **1i-m** (method B: (i) t-Bu(Ph)$_2$SiCl, imidazole, DMF, (ii) TFA, H_2O-THF; (iii) PCC, CH_2Cl_2) in 54-70% overall yields (eq. 2).



(2)

The aldehydes **1** can undergo the addition of a second different dialkylzinc affording stereoselectively 1,3-diols. Since both enantiomeric forms of the catalyst are readily available[10], our method allows the preparation of all four stereoisomeric 1,3-diols. The addition of Et_2Zn to **3d** in the presence of the (1S, 2S) - catalyst (*ent*-**5** (8 mol%)) followed by method A furnishes the aldol *ent*-**1f** (70% overall yield; > 95%ee). The treatment of *ent*-**1f** with a dialkylzinc can now afford either the *anti* 1,3-diol **6** or the *syn* 1,3-diol **7** depending if *ent*-**5** or **5** is used.[8] Thus, the reaction of *ent*-**1f** with $(AcO(CH_2)_4)_2Zn$ in the presence of *ent*-**5** (8 mol%) provides mainly the *anti* 1,3-diol **6** (71% yield, *syn:anti* 9:91), whereas the performance of the same reaction using **5** (8 mol%) selectively gives the *syn* 1,3-diol **7** (72%; *syn:anti* 86:14) showing that this catalytic system displays a strong *reagent-controlled* stereoselectivity (eq. 3).



(3)

In conclusion, we have developed a new catalytic enantioselective preparation of functionalized aldol products. The addition of a dialkylzinc to these aldol products proceeds under reagent control and allows the preparation of either *syn* or *anti* 1,3-diols. The study of the scope of this reaction is currently underway in our laboratories.[14]

Table 1. Functionalized protected 1,3-alcohols **4** obtained by a catalytic enantioselective addition of $(FG\text{-}R)_2Zn$ to aldehydes of type **3** and their conversion to aldols **1.**

entry	FG-R	X	4	yield of 4 (%)[a]	(% ee)[b]	R^1	product 1	yield (%)[a]
1	$(CH_2)_5OAc$	$SiMe_2Ph$	**4a**	70	96	-		-
2	$(CH_2)_4Cl$	$SiMe_2Ph$	**4b**	70	96	-		-
3	Et	OCH_2Ph	**4c**	88	83	-		-
4	Et	$OSiMe_2tBu$	**4d**	62	85	-		-
5	Oct	$OSiMe_2tBu$	**4e**	65	82	-		-
6	Et	$OSi(iPr)_3$	**4f**	92	93	CH_2Ph	**1f**	77
7	Pent	$OSi(iPr)_3$	**4g**	83	95	CH_2Ph	**1g**	60
8	Oct	$OSi(iPr)_3$	**4h**	82	93	CH_2Ph	**1h**	64
9	$(CH_2)_5OAc$	$OSi(iPr)_3$	**4i**	71	91	$SiPh_2tBu$	**1i**	70
10	$(CH_2)_5OPiv$	$OSi(iPr)_3$	**4j**	72	91	$SiPh_2tBu$	**1j**	61
11	$(CH_2)_4OAc$	$OSi(iPr)_3$	**4k**	62	99	$SiPh_2tBu$	**1k**	54
12	$(CH_2)_3OPiv$	$OSi(iPr)_3$	**4l**	55	40	$SiPh_2tBu$	**1l**	64
13	$(CH_2)_6Cl$	$OSi(iPr)_3$	**4m**	59	66	$SiPh_2tBu$	**1m**	67
14	$(CH_2)_3OPiv$	$OSiPh_2tBu$	**4n**	35	98	-		-

[a] All yields indicated are isolated yields of analytically pure products; [b] the enantiomeric excess has been determined by preparing the corresponding O-acetyl-mandelates using (S)-(-)-O-acetylmandelic acid (ref. 15)

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References and Notes

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(14) *Typical procedure: Preparation of bis-(4-acetoxybutyl)zinc*: A Schlenk flask equipped with an argon inlet, a septum cap, and a stirring bar was charged with 4-iodobutyl acetate (5.81 g, 24.0 mmol), CuI (ca. 2 mg, 0.01 mmol) and Et_2Zn (4.0 mL, 40 mmol). The reaction mixture was warmed to 50-55 °C (oil bath temperature) and stirred 10 h at this temperature. The flask was then connected to the vacuum (0.1 mm Hg) and the formed ethyl iodide and excess Et_2Zn was distilled over in a trap cooled with liquid N_2 (ca. 2 h at 50 °C). Toluene (8 mL) was added to the prepared zinc reagent and the resulting solution was cooled to -20 °C.
Preparation of the catalyst: A Schlenk flask equipped with an argon inlet, a septum cap, and a stirring bar was charged with the (1R, 2R)-catalyst **5** (120 mg, 0.3 mmol), toluene (2 mL), and $Ti(OiPr)_4$ (3.6 mL, 12 mmol). The reaction mixture was warmed to 40-45 °C and stirred 0.5 h at this temperature.
*Preparation of the alcohol **4k***: To the cooled solution of bis-(4-acetoxybutyl)zinc was added the toluene solution of the catalyst and $Ti(OiPr)_4$, prepared as above, and this mixture was stirred at -20 °C. After 10 min, 3-(triisopropylsilyloxy)propanal **3d** (920 mg, 4.0 mmol) was added and the reaction mixture was stirred at -20 °C overnight. After the usual workup (aqueous NH_4Cl, ether) the crude oil was purified by flash chromatography (hexanes:ether 9:1) to afford the alcohol (860 mg, 62%, 99%ee, $[\alpha]_D^{25}$ = -7.25 (c = 3.86, C_6H_6).
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