Chiral Catalyst Controlled Addition of Dialkylzincs to Chiral α-Siloxyaldehydes; Asymmetric Synthesis of either Diastereoisomer of Mono-protected Vicinal Diols

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The extent of the asymmetric addition of dialkylzincs to chiral α-siloxyaldehydes is determined by the configuration of the chiral catalyst and not by the chirality of α-siloxyaldehydes, providing either diastereoisomer of mono-protected vicinal diols in high diastereoisomeric excess.

The direction of diastereoselectivity in the addition of alkylmetal reagents to α-chiral α-alkoxy- and α-siloxy-aldehydes is an important problem.[1] Diastereodivergent alkylation of these carbonyl compounds requires the use of alkylmetal reagents of different structures for different diastereoselectivities.[2] However, regardless of the control of the diastereoselectivity (chelation or non-chelation control), the origin of the sense of the diastereoselectivity comes from the configuration of the α-asymmetric carbon of the aldehydes (1,2-asymmetric induction).

On the other hand, optically active vicinal diols form an important class of compounds as units of naturally occurring compounds and they have also been utilized as chiral auxiliaries for asymmetric syntheses.[3] During our continuing study on the enantioselective 1,2-addition of organozinc reagents to aldehydes,[4] imines[5] and 1,4-addition to α,β-unsaturated ketones,[6] we became interested in the diastereodivergent synthesis of mono-protected vicinal diols.

We now report the asymmetric synthesis of either diastereoisomer of mono-protected vicinal diols by chiral catalyst controlled addition of dialkylzincs to chiral α-siloxyaldehydes. In the reaction, the control of the selectivity comes from the chirality of the catalyst and not from the configuration of the α-asymmetric carbon of α-siloxyaldehyde.

When chiral α-siloxyaldehyde (*R*)-**1a**† was treated with diethylzinc using 5 mol% of (1*S*,2*R*)-**3a** [*N*,*N*-dibutylnorephedrine (DBNE)][7] as a chiral catalyst, (*S*,*R*)-**4a** was formed as the predominant diastereoisomer in high diastereomeric excess (d.e.) (**4a**:**5a** = 95:5) (Table 1, entry 1).‡ However, when the chiral catalyst with the opposite configuration (1*R*,2*S*)-**3a** was used, the other diastereoisomer (*R*,*R*)-**5a** became predominant in high d.e. (**4a**:**5a** = 4:96) (entry 2). Chiral catalyst (*S*)- and (*R*)-**3b** [diphenyl (*N*-methylpyrrolidin-2-yl) methanol (DPMPM)][8] also showed this opposite sense of the selectivities to each other (entries 3 and 4). The reversal of the control of the stereoselectivity by the reversal of the configuration of chiral catalyst was also true for the reactions using a variety of chiral α-siloxyaldehydes with different substituents (**1b**, **c** and **d**) (entries 5, 6, 7, 8, 9, 10 and 11, 12); the d.e.s of the products (**4b–e**:**5b–e**) were very high (up to **4b**:**5b** = 98:2, entry 5).

In the reaction of **1a** with dimethylzinc using (1*R*,2*S*)-**3a** afforded **5d** of which the configuration of alcohol was found to

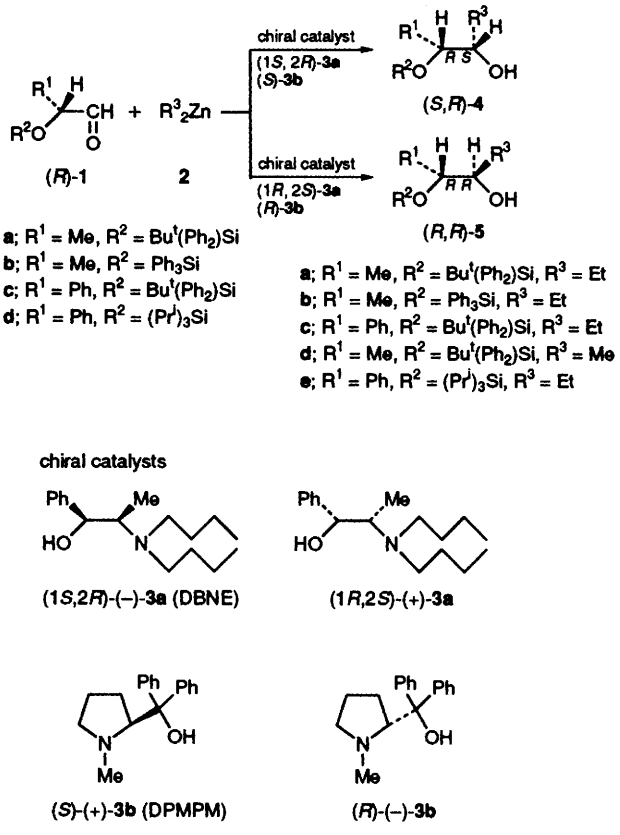

Table 1 Chiral catalyst controlled alkylation of chiral α-siloxyaldehydes

Entry	1	R^3 in 2	Chiral catalyst 3 (mol%)	*T*/°C	*t*/h	4,5	Yield (%)	4:5[a]
1	a	Et	(1*S*,2*R*)-**3a** (5)	0	16	a	46	95:5
2	a	Et	(1*R*,2*S*)-**3a** (5)	0	16	a	56	4:96
3	a	Et	(*S*)-**3b** (5)	0	45	a	30	93:7[b]
4	a	Et	(*R*)-**3b** (5)	0	16	a	54	6:94
5	b	Et	(1*S*,2*R*)-**3a** (20)	Room temp.	20	b	46	98:2
6	b	Et	(1*R*,2*S*)-**3a** (20)	Room temp.	20	b	50	7:93
7	c	Et	(1*S*,2*R*)-**3a** (20)	Room temp.	22	c	46	97:3
8	c	Et	(1*R*,2*S*)-**3a** (20)	Room temp.	23	c	46	8:92
9	a	Me	(1*S*,2*R*)-**3a** (5)	0	26	d	24	85:15
10	a	Me	(1*R*,2*S*)-**3a** (5)	0	26	d	32	7:93
11	d	Et	(1*S*,2*R*)-**3a** (20)	Room temp.	22	e	57	96:4
12	d	Et	(1*R*,2*S*)-**3a** (20)	Room temp.	21	e	68	7:93

[a] Configuration of **5d** (and **4d**) was determined by comparison with an authentic sample [prepared from (2*R*,3*R*)-butane-2,3-diol and *tert*-butyldiphenyl chlorosilane]. Configurations of other **4** and **5** are tentatively assigned. Ratio was determined by HPLC analysis. Conditions: column; eluent; flow rate (ml min^{-1}); retention time (min); UV-detector (254 nm). Chiralpak AD (4.6 × 250 mm); 1% propan-2-ol in hexane; 0.3 ml min^{-1}, 18 min for **4a**, 16 min for **5a**, 24 min for **4d**, 21 min for **5d**. Chiralpak AD (4.6 × 250 mm); 1% propan-2-ol in hexane; 0.2 ml min^{-1}, 55 min for **4b**, 45 min for **5b**. Chiralpak AD (4.6 × 250 mm); 1% propan-2-ol in hexane; 0.1 ml min^{-1}, 58 min for **4c**, 41 min for **5c**. Unisil Q (LQ 340) (4.6 × 300 mm); 0.25% propan-2-ol in hexane; 0.1 ml min^{-1}, 65 min for **4e**, 59 min for **5e**. [b] Ratio was determined with ^1H NMR (270 MHz) analysis.

be *R* [determined by comparison with an authentic sample prepared by the monoprotection of (2*R*,3*R*)-butane-2,3-diol] (entry 10). This direction of attack of dimethylzinc from the *Re*-face of chiral aldehyde (**1a**) using (1*R*,2*S*)-**3a** is in good agreement with the reaction with achiral aldehydes (*Re*-face attack).[7] The direction of the attack changed to the *Si*-face when (1*S*,2*R*)-**3a** was employed (entry 9). The oxygen atom of the siloxy groups hardly coordinates with metal atoms.[9] Thus, the present selectivities are considered to be due to the result of chiral catalyst controlled addition of dialkylzincs to (*R*)-**1**.[10]

Because the silyl ethers are widely used as protecting groups of the hydroxy group,[11] the present method provides a convenient asymmetric synthesis of either diastereoisomer of mono-protected vicinal diols desired by choosing the appropriate configuration of the chiral catalyst.

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Footnotes

† Protection of the hydroxy group of (*R*)-methyl lactate and (*R*)-methyl mandelate with the corresponding silyl chloride and subsequent reduction of the ester with diisobutylaluminium hydride (DIBAL) at −78 °C afforded (*R*)-(**1a–d**).

‡ *General procedure*: To a solution of chiral catalyst **3** (0.025–0.1 mmol) in toluene (0.25 ml), was added a toluene solution (1 mol dm^{-3}, 1.1 ml) of dialkylzinc **2** (0.6 mmol) at 0 °C. Siloxyaldehyde **1** (0.5 mmol) in toluene (2 ml) was added, and the reaction mixture was stirred at 0 °C or at room temp. for the appropriate number of hours. The reaction was quenched by adding saturated ammonium chloride (aq.) (7 ml) and extracted with dichloromethane (3 × 20 ml). The organic layer was dried (sodium sulfate) and evaporated under reduced pressure. The residue was purified by silica gel TLC (developing solvent: hexane–EtOAc = 15:1, v/v).

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