Catalytic Asymmetric Preparation of Polyfunctional Protected 1,2-Diols and Epoxides

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Summary: α-Trialkylsiloxy aldehydes **4a,b** add functionalized diorganozincs in the presence of catalytic amounts of (1*R*, 2*R*)-bis(trifluoromethanesulfonamido)-cyclohexane (8 mol %), affording protected 1,2-diols in 39–89% yield and 70–94% ee. The conversion of the monosilylated 1,2-diols to functionalized chiral epoxides has been demonstrated.

The enantioselective preparation of scalemic 1,2-diols has been extensively investigated in the past 10 years. 1,2-Diols are versatile chiral building blocks[1] and have found numerous applications as chiral auxiliaries or ligands of metal catalysts.[2] The catalytic asymmetric epoxidation[3,4] and dihydroxylation[5,6] of olefins have been especially successful preparation methods of 1,2-diols. Alternative approaches such as the catalytic enantioselective reduction of α-alkoxy ketones[7] or the catalytic asymmetric addition of an organometallic to an α-alkoxy aldehyde (**1**) have not been extensively investigated (Scheme 1).

Recently, we have shown that functional diorganozincs **2** can be added to various types of aldehydes in the presence of (1*R*,2*R*)-bis(trifluoromethanesulfonamido)-cyclohexane (**3**)[8] leading to polyfunctional secondary[9] or allylic[10] alcohols and aldol products[11] with good to excellent enantioselectivity. Herein, we report that diorganozincs **2** prepared via an iodine–zinc exchange reaction[9] add to α-triorganosiloxy aldehydes **4a,b** in the presence of catalytic amounts of **3** (8 mol %) and titanium(IV) isopropoxide (2 equiv) in toluene (−20 °C, 5–12 h) to provide monosilylated 1,2-diols of type **5** in satisfactory yields (39–89%) and excellent enantioselectivities (up to 94% ee); Table 1 and Scheme 2.

Scheme 1

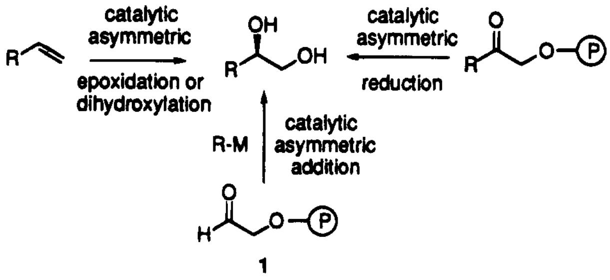
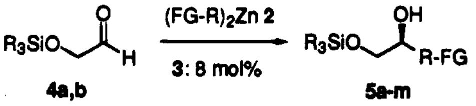


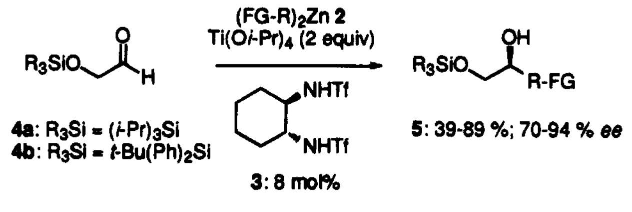
Table 1. Monosilylated 1,2-Diols 5a–m Obtained by the Addition of Dialkylzincs to the Aldehydes 4a,b in the Presence of Catalytic Amounts of 3



entry	aldehyde	(FG-R)$_2$Zn FG-R	product **5**	yield (%)[a]	ee (%)[b]
1	**4a**	Et	**5a**	89	85
2	**4b**	Et	**5b**	78	92
3	**4a**	n-C$_5$H$_{11}$	**5c**	85	75
4	**4b**	n-C$_5$H$_{11}$	**5d**	63	94
5	**4a**	n-C$_8$H$_{17}$	**5e**	79	90
6	**4a**	AcO(CH$_2$)$_4$	**5f**	60	84
7	**4b**	AcO(CH$_2$)$_4$	**5g**	62	86
8	**4a**	PivO(CH$_2$)$_3$	**5h**	74	90
9	**4b**	PivO(CH$_2$)$_3$	**5i**	47	92
10	**4a**	PivO(CH$_2$)$_4$	**5j**	45	93
11	**4a**	PivO(CH$_2$)$_5$	**5k**	75	93
12	**4b**	PivO(CH$_2$)$_5$	**5l**	39	70
13	**4a**	Cl(CH$_2$)$_4$	**5m**	70	85

[a] Isolated yield of analytically pure product. [b] Determined by preparing the corresponding *O*-acetylmandelates using (*S*)-(+)-*O*-acetylmandelic acid (ref 14).

Scheme 2



The protecting group choice of the aldehyde α-hydroxy function is essential for the success of the reaction. [(2,6-Dichlorobenzyl)oxy]acetaldehyde, by allowing metal-chelate formation, adds diethylzinc with only moderate enantioselectivity (40% ee). The triisopropylsilyl (TIPS) or the *tert*-butyldiphenylsilyl (TBDPS) group shields the α-oxygen and therefore gives better results.[12] No complexation to the titanium center leading to the formation of a chelate occurs. (Triisopropylsiloxy)acetaldehyde (**4a**)

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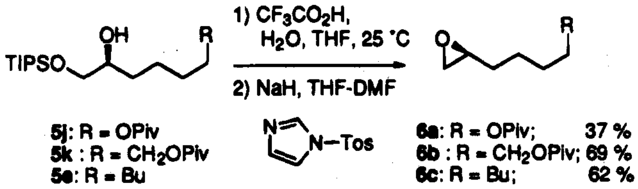
is conveniently prepared in two steps from 1,2-ethanediol (59% overall yield)[13] and adds most diorganozincs with excellent enantioselectivity (75–93% ee). Interestingly, bis(3-pivaloxypropyl)zinc which bears an ester function in proximity to the carbon–zinc bond still smoothly adds to **4a** (entry 8 of Table 1). Diethyl- and dipentylzinc add less selectively to **4a** (entries 1 and 3) and better results are obtained by using the sterically more demanding (*tert*-butyldiphenylsiloxy)acetaldehyde (**4b**) which affords in these cases, respectively, 92 and 94% ee (entries 2 and 4). However, the low reactivity of **4b** due to the bulky silyl substituent leads to low conversions and moderate yields when higher dialkylzincs are used (entries 7, 9, and 12). This shows the importance of the steric environment at the titanium center and the choice of the appropriate triorganosilyl protecting group (TIPS or TBDPS) depends on the size and reactivity of the diorganozinc reagent. The monosilylated 1,2-diols **5** can be stereoselectively converted to epoxides. Thus, treatment of **5e**, **5j**, and **5k** with a 1:3:3 CF_3CO_2H–THF–H_2O mixture affords the corresponding free 1,2-diols which were treated with sodium hydride (2 equiv) in a 1:1 THF–DMF mixture (0–25 °C, 1 h), followed by *N*-tosylimidazole[15] (0–25 °C, 0.5 h) leading to the corresponding epoxides **6a–c** in 37–69% overall yield (Scheme 3). In the case of **6a**, we have verified that no racemization has occurred during the epoxide formation.

In summary, the use of a bulky silyl protecting group allows a catalytic asymmetric addition of various functionalized dialkylzincs to the α-alkoxy aldehydes **4a,b** with excellent enantioselectivities. This method provides an efficient preparation of 1,2-diols bearing a protected primary alcohol function. Further investigations directed toward the enantio- and diastereoselective preparation of secondary 1,2-diols are currently underway in our laboratories.[16]

Scheme 3



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Supplementary Material Available: Typical procedures and characterization data for all new compounds (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(12) For a similar observation see: Soai, K.; Shimada, C.; Takeuchi, M.; Itabashi, M. *J. Chem. Soc., Chem. Commun.* **1994**, 567.

(13) Preparation of **4a**: (i) 1,2-ethanediol, TIPSCl (0.7 equiv), NaH, THF, 25 °C, 4 h; 70% yield. (ii) Dess–Martin oxidation, CH_2Cl_2, 25 °C, 1 h; 84% yield. The aldehyde **4b** was prepared in a similar way giving for the two steps, respectively, 85 and 87% yield. McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B.-D. *J. Org. Chem.* **1986**, *51*, 3388.

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(16) Typical procedure: Preparation of (6*S*)-6-hydroxy-7-(triisopropylsiloxy)heptyl pivalate (**5k**). A 50 mL Schlenk-flask equipped with an argon inlet, a septum, and stirring bar was charged with 5-iodopentyl pivalate (7.40 g, 24 mmol), copper(I) iodide (ca. 14 mg, 0.3 mmol %), and diethylzinc (3.6 mL, 36 mmol). The reaction mixture was warmed to 55 °C and stirred for 12 h. The flask was then connected to the vacuum (0.1 mmHg) and the resulting ethyl iodide and excess diethylzinc were distilled off (ca. 4 h). The resulting bis(5-pivaloxypentyl)zinc was dissolved in toluene (8 mL) and was ready to use. A second 50 mL Schlenk-flask equipped as above charged with (1*R*, 2*R*)-1,2-bis(trifluoromethanesulfonamido)cyclohexane (121 mg, 0.3 mol, 8 mol %), toluene (2 mL), and titanium(IV) isopropoxide (2.4 mL, 8 mmol, 2 equiv) was heated to 50 °C and stirred for 0.5 h at this temperature. The resulting solution was cooled to −40 °C and the toluene solution of bis(5-pivaloxypentyl)zinc was added, followed after 0.25 h by aldehyde **4a** (0.86 g, 4 mmol). The reaction temperature was increased within 1 h to −20 °C, and the reaction mixture was stirred at this temperature overnight. After the usual workup, the resulting crude oil was purified by chromatography (hexanes–ether 4:1) affording the alcohol (**5k**) as a clear oil (1.17 g, 75% yield, 93% ee); $[\alpha]^{25}_D = +0.64°$ (c = 4.71, benzene).