# Chelation-Controlled Addition of Dialkylzincs to *trans*-α,β-Epoxy Aldehydes

Hirokazu Urabe, Ozden Ozel Evin, and Fumie Sato*

*Department of Biomolecular Engineering,*
*Tokyo Institute of Technology, 4259 Nagatsuta-cho,*
*Midori-ku, Yokohama, Kanagawa 226 Japan*

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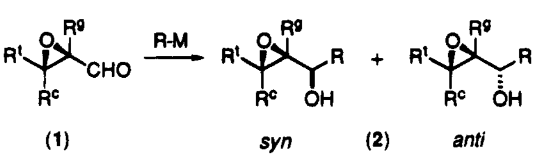
The diastereoselective addition of organometallic compounds to α- and/or β-oxy aldehydes has been well studied and applied many times to critical stages of natural product syntheses.[1] Optically active α,β-epoxy aldehydes, which are now readily available via Sharpless asymmetric epoxidation[2] of allyl alcohols followed by oxidation, are attractive potential substrates for such reactions, as they furnish products having three consecutive stereogenic centers (eq 1).[3−6] Additions of alkylmetals to *trans*- or *cis*-α,β-epoxy aldehydes have been investigated and have revealed moderate to good diastereoselectivities with *anti* adducts always predominating, regardless of the degree of selectivity.[3,7] The Felkin−Anh model[8] (Figure 1, A) would account for these *anti* selectivities. On the other hand, a method that permits the selective preparation of the *syn* adduct has been notably lacking.[9] *Syn* selectivity should stem from the chelation-controlled addition of organometallic compounds to α,β-epoxy aldehydes (Figure 1, B), and the choice of a metal having strong coordination ability seems to improve the *syn* selectivity, this being the common strategy in reactions with other α-oxy aldehydes.[1] However, this means to a *syn* selectivity cannot be applied to α,β-epoxy aldehydes, because strong coordination of a metal cation to an epoxide moiety will result in its destruction via ring opening.[10] We conceived that an organometallic reagent that reacts with a substrate only when it is activated through chelation with the substrate should show high *syn* selectivity, even though the metallic moiety of the organometallic reagent does not have strong Lewis acidity. We found that dialkylzinc nicely fulfills the above requirement.[11,12]



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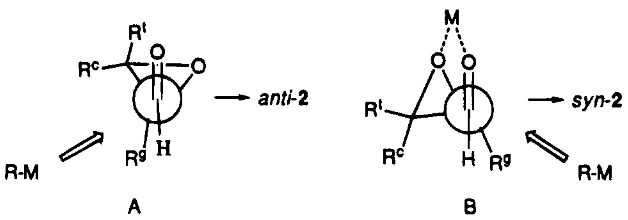

**Figure 1.**

**Table 1. Effect of Solvent, ee of 1a and Number of Equivalents of $Et_2Zn$ on the Diastereoselectivity[a]**

| entry | 1a | $Et_2Zn$ (equiv) | solv[b] | 2a *syn*/*anti* | 2a yield (%)[c] |
|---|---|---|---|---|---|
| 1 | 98% ee | 1.2 | $CH_2Cl_2$ | *syn* major | 3 |
| 2 | 98% ee | 1.2 | THF | ca. 8:2 | ca. 10 |
| 3 | 98% ee | 1.2 | hexane | 91:9 | 82 |
| 4 | 98% ee | 1.2 | $Et_2O$ | 93:7 | 60 |
| 5 | 98% ee | 1.2 | toluene | 93:7 | 77 |
| 6 | 98% ee | 0.5 | toluene | 90:10 | 36 |
| 7 | 98% ee | 2.0 | toluene | 94:6 | 82 |
| 8 | racemic | 1.2 | toluene | 83:17 | 67 |

[a] See eq 2. Reactions were carried out at 0 °C for 13 h. [b] Solvent contains a small volume of hexane coming from a hexane solution of $Et_2Zn$. [c] Yields determined by $^1H$ NMR analysis and based on **1a**.

The reaction of epoxy aldehyde **1a**[5a] and $Et_2Zn$ in various solvents at 0 °C afforded the ethylated product **2a**, always in a *syn*-selective manner (eq 2).[13] However, the degree of *syn* selectivity was dependent on reaction

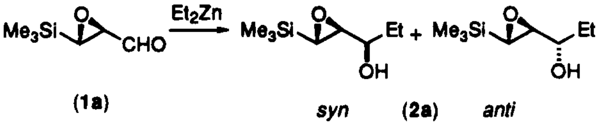

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Table 2. Addition of Dialkylzincs to α,β-Epoxy Aldehydes[a]

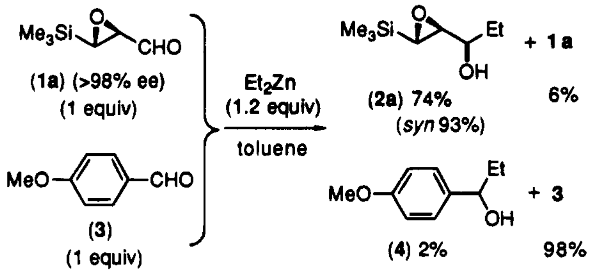
| | 1 | | | | | | | 2 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| entry | $R^t$ | $R^c$ | $R^g$ | | ee; chirality | RM | period (h) | R | | *syn*/*anti*[b] | yield (%)[c] |
| 1 | $Me_3Si$ | H | H | **a** | >98% ee; 2*S*,3*S* | $Et_2Zn$ | 13 | Et | **a** | 93:7 | 70 |
| 2 | | | | | >98% ee; 2*S*,3*S* | $(C_{10}H_{21})_2Zn$ | 14 | $C_{10}H_{21}$ | **b** | 94:6 | 43[b] |
| 3 | | | | | >98% ee; 2*S*,3*S* | (*E*)-$C_6H_{13}CH{=}CHZnEt$[d] | 3 | (*E*)-$C_6H_{13}CH{=}CH$ | **c** | 80:20 | 71 |
| 4 | | | | | racemic | $Et_2Zn$ | 13 | Et | **a** | 83:17 | 67[b] |
| 5 | | | | | racemic | (*E*)-$C_6H_{13}CH{=}CHZnEt$[d] | 3.5 | (*E*)-$C_6H_{13}CH{=}CH$ | **c** | 80:20 | 69 |
| 6 | $C_6H_{13}$ | H | H | **b** | 90% ee; 2*R*,3*S* | $Et_2Zn$ | 14 | Et | **d** | 93:7 | 78[e] |
| 7 | | | | | racemic | $Et_2Zn$ | 14 | Et | **d** | 86:14 | 74 |
| 8 | H | $C_5H_{11}$ | H | **c** | 62% ee; 2*R*,3*R* | $Et_2Zn$ | 22 | Et | **e** | 65:35 | 47[f] |
| 9 | | | | | racemic | $Et_2Zn$ | 22 | Et | **e** | 63:37 | 59[b] |
| 10 | H | H | $C_9H_{19}$ | **d** | racemic | $Et_2Zn$ | *g* | Et | **f** | 1:1 | 11 |

[a] See eq 1. The reactions were carried out with excess diorganozinc (1.2 equiv in most cases) in toluene at 0 °C. [b] Determined by $^1H$ NMR analysis of a crude sample. [c] Isolated yield unless otherwise noted. Yields are not optimized in each case. [d] Reaction was performed in hexane. [e] *syn*-**2d**: 90% ee. [f] Recovered (2*R*,3*R*)-**1c** (32%) was of 62% ee. [g] 0 °C, 15 h; rt, 9 h.

conditions as summarized in Table 1.[14] Toluene is the preferred solvent with respect to both product yields and *syn* selectivity (entries 1–5). The reaction was relatively slow below −10 °C though the degree of *syn* selectivity was unaffected. Surprisingly, changing the aldehyde from optically active material to a racemic sample decreased the diastereomeric ratio of the product from 94:6 to 83:17, under the same reaction conditions (entries 5 and 8). The number of equivalents of $Et_2Zn$ also affected the diastereoselectivity: the use of <1 equiv of $Et_2Zn$ relative to the aldehyde decreased the selectivity (entry 6), but an excess (1.2–2 equiv) showed reliably high *syn* selectivity (entries 5 and 7). These facts suggest that the nature of the reaction intermediate is rather complicated; for example, it could be that ethylzinc alkoxide that is formed during the reaction is involved in the reactive species, despite the simplified illustration in Figure 1B.

This reaction proved to be reasonably general, having been applied to several dialkylzincs and *trans*-α,β-epoxy aldehydes as shown in Table 2.[14] Didecylzinc, prepared by hydroboration of 1-decene followed by boron/zinc exchange,[15,16] performed similarly to diethylzinc (entry 2). An alkenylzinc reagent prepared *in situ* from dicyclohexyl[(*E*)-1-octenyl]borane and $Et_2Zn$ (1:1)[15,17] underwent a selective transfer of the alkenyl group to **1a** and showed *syn* selectivity at a synthetically useful level (entries 3 and 5). For this zinc reagent, the optical activity of **1a**, or lack thereof, did not affect the diastereomeric purity of the product. *trans*-β-Alkyl-α,β-epoxy aldehyde **1b** behaved similarly as did the silyl aldehyde **1a** (cf. entries 1, 4, 6, and 7). Thus optically active **1b** (90% ee) afforded the major product of the same optical purity as the starting material with excellent diastereoselectivity (entry 6), which confirmed that no appreciable kinetic resolution of the starting material had occurred during the reaction. In contrast to the *trans*-substituted epoxy aldehydes, both optically active and racemic *cis*-β-alkyl-α,β-epoxy aldehydes **1c** required a longer period for reasonable conversion and showed *syn*/*anti* ratios as inferior as 65:35 (entries 8 and 9). The reaction of **1d**, which has an alkyl substituent α to the aldehyde, was found to be extremely slow (entry 10).

Another application, as shown in eq 3, is the *chelation-target* delivery[18] of the ethyl group from $Et_2Zn$ to **1a** with retention of excellent *syn* selectivity with respect to the product epoxy alcohol. This experiment clearly shows



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that the alkyl transfer from $R_2Zn$ to the epoxy aldehyde occurs strictly between the chelated partners, as anisaldehyde (**3**) in this reaction mixture does not undergo the alkylation. Note that, when a THF solution of EtMgBr was added to an equimolar mixture of **1a** and **3** in ether, a 1:2 mixture of **2a** and **4** was recovered and, in addition, two diastereomers of the epoxy alcohol (*syn*- and *anti*-**2a**) were formed in a ratio of 42:58.

In conclusion, $R_2Zn$ shows high *syn* selectivity in reactions with *trans*-α,β-epoxy aldehydes, something that had not been achieved with other organometallic reagents. The current shortage of methods for the straightforward preparation of the *syn* epoxy alcohol **2**[19] makes this reaction very useful from the synthetic point of view.

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**Supplementary Material Available:** Typical procedures for the preparation of **2c** and **2d** and structural determination and physical properties of **2a–f** (10 pages).

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[14] Experimental details are described in the supplementary material.

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