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Stereoselective Pinacol-Type Rearrangement of 2,3-Epoxy Alcohols with Retention of Configuration Mediated by Bis(iodozincio)methane**

Seijiro Matsubara,* Hiromasa Yamamoto, and Koichiro Oshima

gem-Dizinc reagents that possess two nucleophilic sites on a carbon atom have been used for a variety of molecular transformations based on a repetition of C–C-bond formation on the same carbon atom.[1] To understand and design these characteristic reactions, one should recognize that dimetallic reagents work not only as a double nucleophile but also as a double Lewis acid.[2] The structure of *gem*-dizinc reagents allows them to act as double Lewis acids with substrates that contain heteroatoms at the 1,2- or 1,3-positions. In fact, we reported an example that emphasizes the importance of its double Lewis acidity through the nucleophilic reaction with 1,2-dicarbonyl compounds.[3] Along this line, we treated 2,3-epoxy alcohols with bis(iodozincio)methane (**1**), anticipating a pinacol-type rearrangement.[4, 5] The substrates are readily available in an enantiomerically enriched form by the Sharpless epoxidation.[6]

Treatment of racemic **2a** (diastereomeric mixture, *erythro*/*threo* 84:16, 1.0 mmol) in THF (2.0 mL) with **1** (0.5 M in THF, 2.2 mmol) at 20 °C gave alkenol **3a** in 77% yield (Scheme 1).

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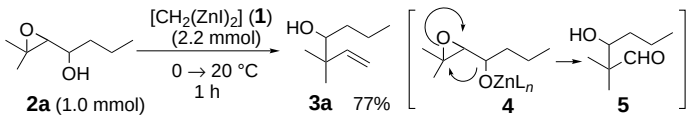
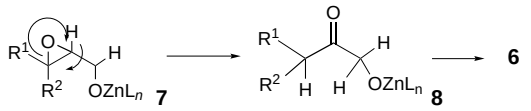


Scheme 1. Reaction of racemic **2a** with **1** to give alkenol **3a**.

The reaction was considered to proceed via aldehyde **5**, which was formed by a pinacol-type rearrangement (**4** to **5**), with subsequent methylenation of **5** to form **3a**.[1a, 7] This type of rearrangement of silyl ethers of 2,3-epoxy alcohols was reported by Maruoka et al.,[5a] who used the highly sterically hindered Lewis acid MABR (methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide)). Jung and Anderson also reported an example induced by $BF_3 \cdot OEt_2$.[5b]

This *gem*-dizinc induced rearrangement/methylenation reaction was applied to other epoxy alcohols to study its limitation and generality. In Table 1, various types of substrates were examined in the reaction. In the reaction of primary alcohols, allylic alcohols **6** were formed as side products, which had not been observed in the reaction of **2a**. As shown in Scheme 2, alcohols **6** were assumed to be formed

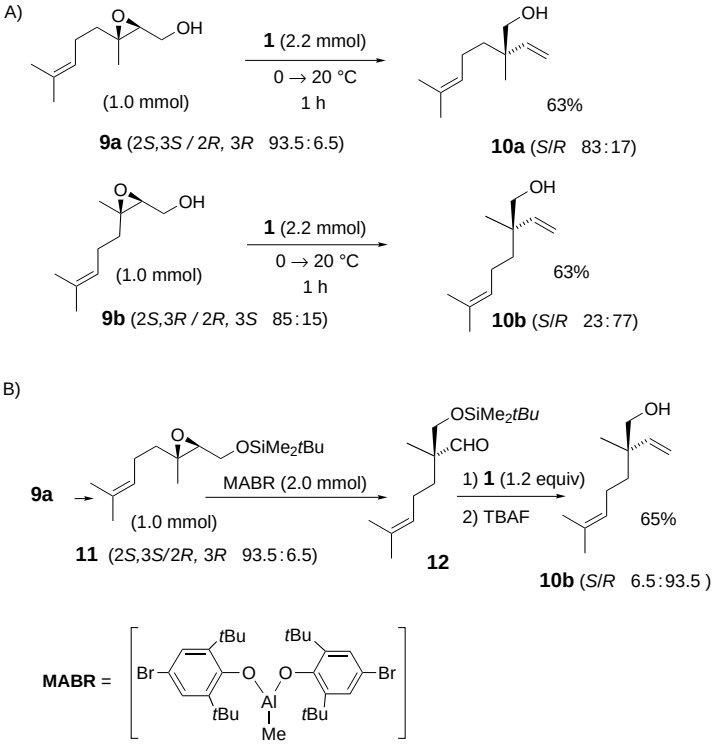


Scheme 2. Possible route for the formation of **6** as a side product.

by methylenation of α-alkoxy ketones **8**, which were formed through a hydride shift. Methylenation of α-alkoxy ketones **8** with **1** was shown to proceed smoothly.[8] The ratio of **3** to **6** varied, depending on the substrate. A disubstituted *cis* epoxide yielded predominantly the hydride-shift-derived product **6** (Table 1, entry 4). The rearrangement did not occur in 2,3-epoxy alcohol substrates with substituents on C2 (Table 1, entries 8 and 9).

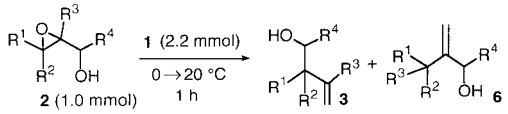
gem-Dizinc **1** reacts with 2,3-epoxy alcohols **2** to give zinc alkoxides (**4** and **7**) before the rearrangement reaction. The free hydroxy group in the substrate is indispensable for the reaction. Treatment of ether derivatives (methyl, trimethylsilyl, and dimethylphenylsilyl ethers) of 2,3-epoxygeraniol resulted in the quantitative recovery of the starting materials.

The wide availability of optically active epoxy alcohols by the Sharpless method prompted us to examine the possibility of chirality transfer in these reactions. This investigation led to the formation of quaternary asymmetric carbon centers.[10] As shown in Scheme 3A, optically active epoxides were treated with bis(iodozincio)methane **1**. Alcohol **10a** was obtained in an optically active form from **9a**, although a slight decrease in enantiomeric purity was observed.[11, 12] The highlight of the transformation is the absolute configuration of the product: the migrating group, $-CH_2OH$, attacks from the front side of



Scheme 3. Formation of alcohols **10** from 2,3-epoxy alcohols **9**. A) Treatment with bis(iodozincio)methane (**1**) results in retention of configuration. B) In contrast, treatment with MABR[5a] gives inversion of configuration. TBAF = tetrabutylammonium fluoride.

Table 1. Treatment of 2,3-epoxy alcohol **2** with **1**.[a,b]



Entry	R^1	R^2	R^3	R^4	**3**	Yield [%]	**6**	Yield
1[c]	Me	Me	H	Me	**d**	74	**b**	< 1 %
2	Me	Me	H	H	**d**	52	**c**	17
3	*n*Pr	H	H	H	**d**	23	**d**	35
4	H	*n*Pr	H	H	**d**	10	**d**	47
5	$(Me)_2C{=}CH(CH_2)_2$	Me	H	H	**e**	67	**e**	17
6	Me	$(Me)_2C{=}CH(CH_2)_2$	H	H	**e**	64	**e**	12
7	Ph	H	Me	H	**f**	30	**f**	< 1
8	Et	H	Me	*n*Bu	**g**	< 1[d]	**g**	< 1
9	Me	Me	Me	H	**h**	< 1[d]	**h**	< 1
10	Ph	H	H	H	**i**	75	**i**	7

[a] **1** (2.2 mmol) and **2** (1.0 mmol) were used. [b] Racemic substrate was used as the starting material. [c] The starting material was used as a mixture of diastereomers (*erythro*/*threo* 80:20). See also ref. [9]. [d] The starting epoxy alcohol was recovered quantitatively.

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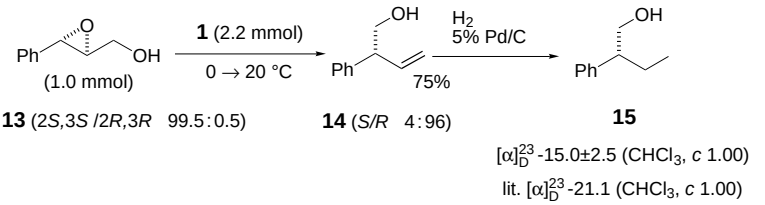
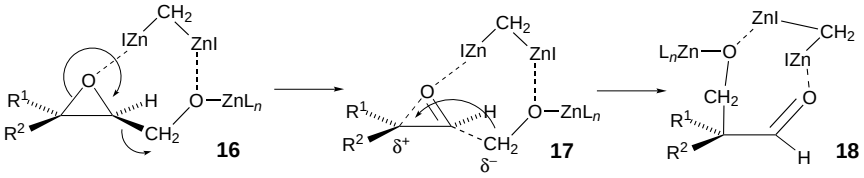
the C–O bond. This is an unusual retentive migration reaction.[13, 14] Similarly, the alcohol **10b** (enantiomer of **10a**) was obtained from **9b** with a slight decrease in the enantiomeric purity. In this case, the rearrangement also proceeded with retention of the configuration at C3 of the 2,3-epoxy alcohol. In contrast, the rearrangement in the reported procedure[5] proceeds with inversion of stereochemistry at C3: Silylation of **9a** provided **11**, which upon treatment with MABR gave **12**. Methylenation of **12** by **1** followed by desilylation with TBAF gave **10b** (Scheme 3B).

In the case of the reaction of a phenyl-substituted substrate **13**, the rearrangement proceeded also with retention of configuration at C3 to give **14** (Scheme 4). The olefin **14** was hydrogenated to give **15** for comparison with an authentic sample[15, 16] to confirm the absolute configuration. Even though the crucial stereogenic center is the benzylic position, only a slight decrease in the enantiomeric purity was observed.

The reaction pathway is not clear enough to rationalize the retention migration. One possible explanation is shown in Scheme 5: the dizinc compound coordinates 2,3-epoxy alcohol as a double Lewis acid (**16**), the Lewis acid induces isomerization into aldehyde, thus providing the negatively charged migrating group (**17**), and the migrating group is transferred to the positively charged carbon atom from the same side of the epoxide oxygen as dizinc coordinates to both oxygen atoms (**18**). The transformation indicate the important character of the dizinc species as a double Lewis acid. At the present stage, we have no evidence for the mechanism outlined in Scheme 5, and detailed investigations are currently underway.



Scheme 4. Reaction of phenyl-substituted substrate **13** to give **14** with retention of configuration at C3.



Scheme 5. Possible mechanism for the dizinc-mediated reaction.

Experimental Section

A solution of epoxy alcohol **2** (1.0 mmol) in THF (2 mL) was added dropwise to a THF solution of bis(iodozincio)methane (**1**, 0.5 M, 2.2 mmol, 4.4 mL) at 0 °C. The mixture was stirred for 1 h at room temperature, and then poured into aqueous HCl (1 M, 20 mL). The resulting mixture was extracted with diethyl ether. The combined ether solutions were washed successively with saturated $NaHSO_3$ and brine and dried over Na_2SO_4. Purification by neutral silica-gel column chromatography (hexane/ethyl acetate 10:1) gave the corresponding product.

10a: Prepared from **9a** (87% *ee*) and **1**. $[\alpha]_D^{23} = -8.06 \pm 1.0$ ($CHCl_3$, $c = 3.10$). ^1H NMR spectroscopic analysis after conversion into the *S* Mosher ester showed that **10a** was obtained with 66% *ee*.

10b: Prepared from **12** and **1**. The aldehyde **12** was prepared from **9a** (87% *ee*) and MABR according to the reported procedure.[5] ^1H NMR spectroscopic analysis after conversion into the *S* Mosher ester showed that **10b** was obtained with 87% *ee*. $[\alpha]_D^{23} = -8.96 \pm 1.0$ ($CHCl_3$, $c = 3.10$). Treatment of **9b** (70% *ee*) with **1** gave **10b** directly with 54% *ee*.

3i: ^1H NMR ($CDCl_3$, 23 °C, 300 MHz): $\delta = 7.4-7.3$ (m, 2H), 7.3–7.2 (m, 3H), 6.02 (ddd, $J = 17.1$, 10.5, 7.8 Hz, 1H), 5.22 (ddd, $J = 10.5$, 1.5, 1.2 Hz, 1H), 5.19 (ddd, $J = 17.1$, 1.8, 1.2 Hz, 1H), 3.84 (dd, $J = 10.8$, 7.2 Hz, 1H), 3.82 (dd, $J = 10.8$, 7.2 Hz, 1H), 3.54 (dd, $J = 7.2$, 7.2 Hz, 1H), 1.60 ppm (bs, 1H); ^{13}C NMR ($CDCl_3$, 23 °C, 75 MHz): $\delta = 141.4$, 139.0, 129.5, 128.7, 127.7, 117.8, 66.8, 53.2 ppm.

14: The enantiomeric purity (*R*/*S* 96:4) was determined by HPLC: Chiralcel-OD (Daicel), 2-propanol/hexane (1:9), 1.0 mL min^{-1}, *R* isomer: 5.93 min, *S* isomer: 7.43 min.

15: ^1H NMR ($CDCl_3$, 23 °C, 300 MHz): $\delta = 7.4-7.3$ (m, 2H), 7.3–7.2 (m, 3H), 3.78 (dd, $J = 10.8$, 6.0 Hz, 1H), 3.73 (dd, $J = 10.8$, 7.8 Hz, 1H), 3.54 (dd, $J = 7.2$, 7.2 Hz, 1H), 2.71 (m, 1H), 1.8–1.5, (m, 2H), 1.25 (bs, 1H), 0.86 ppm (t, $J = 7.5$ Hz, 3H); $[\alpha]_D^{23} = -15.0 \pm 2.5$ ($CHCl_3$, $c = 1.00$), lit.[16]: $[\alpha]_D^{23} = -21$ ($CHCl_3$, $c = 1.00$).

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The Selective Incorporation of Alkenes into Proteins in *Escherichia coli***

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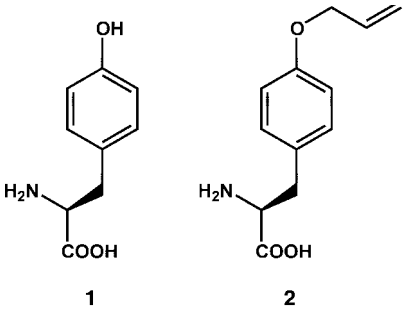
The addition of amino acids with novel functional groups to the genetic code of *Escherichia coli* should greatly enhance our ability to study protein structure and function, as well as generate proteins with novel properties. We recently showed that the unnatural amino acids *O*-methyl-L-tyrosine and L-3-(2-naphthyl)alanine can be site-specifically incorporated into proteins in *Escherichia coli* with high efficiency and fidelity.[1, 2] This result requires the addition of an orthogonal tRNA–codon pair and aminoacyl-tRNA synthetase to the translational machinery of the cell. The new synthetase (and only this synthetase) aminoacylates the orthogonal tRNA (and only this tRNA) with the unnatural amino acid only, which is inserted into proteins in response to the amber codon, TAG.[3] We report here the site-specific incorporation of *O*-allyl-L-tyrosine (**2**) into proteins in *E. coli*. The alkene functional group of this unnatural amino acid should provide new chemical methods for the selective modification of proteins.

Previously we generated an orthogonal tRNA–synthetase pair, $mutRNA^{Tyr}_{CUA}$–TyrRS, in *E. coli* by modifying the $tRNA^{Tyr}$–TyrRS pair of *Methanococcus jannaschii*.[4, 5] This $mutRNA^{Tyr}_{CUA}$ is not aminoacylated by endogenous synthetases in *E. coli*, and functions well in translation. The TyrRS does not aminoacylate *E. coli* tRNAs,[6] but aminoacylates the $mutRNA^{Tyr}_{CUA}$ with tyrosine (**1**); the acylated $mutRNA^{Tyr}_{CUA}$ inserts tyrosine in response to the amber nonsense codon. To change the substrate specificity of the TyrRS so that it aminoacylates the $mutRNA^{Tyr}_{CUA}$ with **2** and not with any common amino acids, a mutant TyrRS library was generated and selected. Based on an analysis of the crystal structure of the homologous TyrRS from *Bacillus stearothermophilus*,[7] five residues (Tyr 32, Glu 107, Asp 158, Ile 159, and Leu 162) in the active site of *M. jannaschii* TyrRS that are within 6.5 Å of the *para* position of the aryl ring of tyrosine were randomly mutated.[1, 8] This mutant library was first subjected to a positive selection based on the suppression of an amber codon introduced at a nonessential position (Asp 112) in the chloramphenicol acetyl transferase (CAT) gene. Cells transformed with the mutant TyrRS libraries, the $mutRNA^{Tyr}_{CUA}$ gene, and the amber mutant CAT gene were grown in minimal media containing 1 mM **2** and 70 μg mL^{-1} chloramphenicol. The survivors must encode a mutant TyrRS that aminoacylates the $mutRNA^{Tyr}_{CUA}$ with either **2** or endogenous amino acids. To remove mutant synthetases with specificities for endogenous amino acids, a negative selection was applied. Three amber codons were introduced at nonessential positions (Gln 2, Asp 44, Gly 65) in the toxic barnase gene.[9] Cells expressing the mutant synthetase from the positive selection, the $mutRNA^{Tyr}_{CUA}$ gene, and the amber mutant barnase gene were grown in Luria–Bertani (LB) media in the absence of **2**. Cells encoding synthetases with specificities for any endogenous amino acids will produce barnase and die. Only those encoding a mutant synthetase with specificity for **2** can survive.



After three rounds of positive selection alternating with two rounds of negative selection, a clone was evolved whose survival in chloramphenicol was dependent on the presence of **2** when the selected mutant TyrRS gene (AL-TyrRS) was coexpressed with the Asp 112amber CAT gene and the $mutRNA^{Tyr}_{CUA}$ gene. Cells can survive in 120 μg mL^{-1} chloram-

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