Diastereoselectivity

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Stereospecific and Stereoselective Preparation of 2-(1-Hydroxyalkyl)-1-alkylcyclopropanols from α,β-Epoxy Ketones and Bis(iodozincio)methane**

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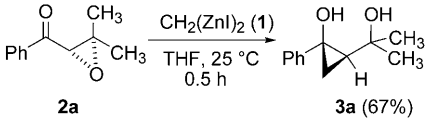
The most common method used to prepare cyclopropane compounds involves the reaction of electrophilic Simmons–Smith-type reagents with alkenes.[1] In contrast to this electrophilic [2+1] reaction, a *gem*-organodimetal compound also has the possibility of participating in a nucleophilic [2+1] reaction because it has two nucleophilic sites on one carbon atom.[2,3] In fact, we have already reported the reaction of bis(iodozincio)methane (**1**) with 1,2-diketone to give *cis*-1,2-cyclopropanediol with high diastereoselectivity.[4] In this transformation, **1** acts as a bidentate Lewis acid and fixes the conformation of the 1,2-diketone in the *s-cis* form.[4c] Thus, a substrate which has two Lewis basic sites may interact at two sites with **1**, and may show some characteristic stereochemical performance during subsequent useful molecular transformations.[5] Following this observation, we treated **1** with α,β-epoxy ketone and found that the reaction resulted in the stereospecific formation of 2-(1-hydroxyalkyl)-1-alkylcyclopropanol.[6]

Treatment of 2-benzoyl-1,1-dimethyloxirane (**2a**) with **1** gives (1*R**,2*R**)-2-(1-methyl-1-hydroxyethyl)-1-phenylcyclopropanol (**3a**) as the sole product (Scheme 1). The stereochemistry of the product was determined by single-crystal X-ray analysis (Figure 1).[7] Other examples of reactions conducted that led to formation of a cyclopropane ring are



2a **3a** (67%)

Scheme 1. Reaction of bis(iodozincio)methane (**1**) with α,β-epoxy ketone **2a**.

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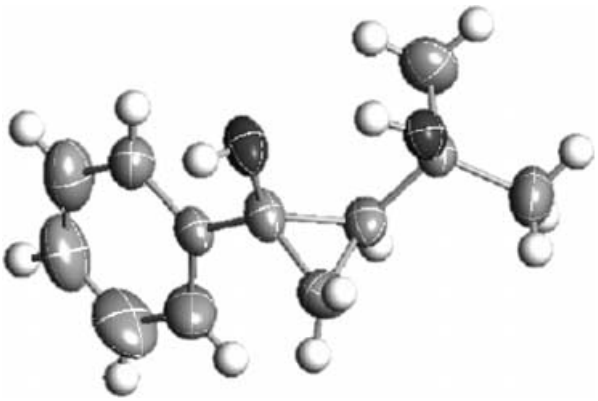
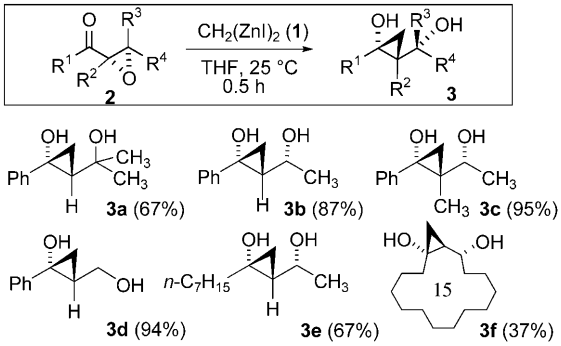


Figure 1. Structure of **3a** as determined by X-ray analysis.



Scheme 2. Preparation of 2-(1-hydroxyalkyl)-1-alkylcyclopropanol **3**.

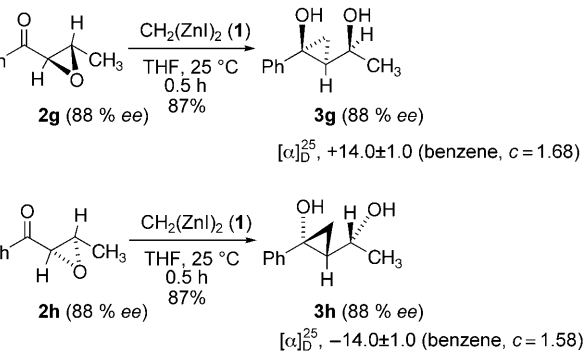
summarized in Scheme 2. In all cases, the reaction yielded a single diastereomer selectively.

An optically active epoxy ketone[8] **2g** was treated with **1** to give (1*S*,2*S*)-2-(*S*-1-hydroxyethyl)-1-phenylcyclopropanol (**3g**) without loss of enantiomeric purity. The reaction involving the enantiomer of **2g** (namely, **2h**) gave the corresponding enantiomer **3h** (Scheme 3).

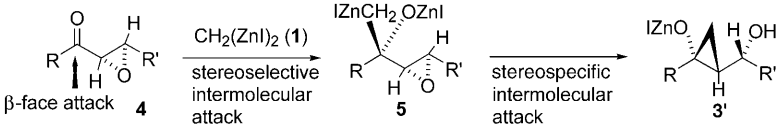
The diastereoselective formation of cyclopropanol **3** can be explained as follows. The reaction starts with the diastereoselective attack of **1** at the carbonyl group as a consequence of the stereogenic center at the α-carbon atom (Scheme 4).[4,9] This step is followed by stereospecific attack on the epoxide.

The explanation shown in Scheme 4 requires diastereoselective attack to the β face of **4**, which needs to be rationalized, since previous reports concerning the diastereoselective metal-mediated nucleophilic attack to an α,β-epoxy ketone occurred from the α face of **4**.[10]

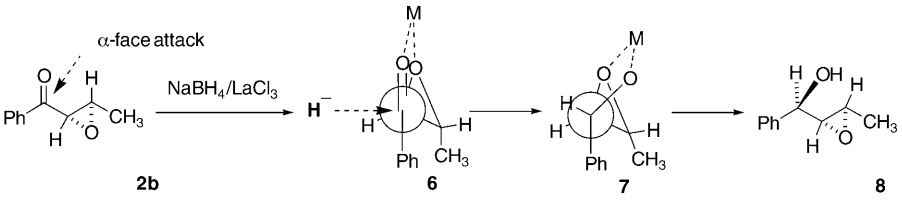
For example, treatment of **2b** with $NaBH_4/LaCl_3$ resulted in the exclusive formation of *erythro*-epoxy alcohol.[11] The diastereoselective reaction was explained by chelation effects to form intermediate **6**, as shown in Scheme 5. Other metal salts, such as $CaCl_2$, $MnCl_2$, and $ZnCl_2$ as well as $LaCl_3$ showed the same effect. Sato et al reported the preparation of 2-(1-hydroxyalkyl)-1-alkylcyclopropanol from an α,β-epoxy ketone and trimethylstannylmethyllithium.[6] Their results did not reveal any diasteromeric selectivity for trisubstituted oxirane substrates such as **3c**. The major isomers were also postulated to be produced by α-face attack of **4** in the case of disubstituted oxirane substrates (namely, **3a**,**b**,**d**–**f**).[6] In the present cyclopropanation reaction, the addition of **1** cannot be explained by a simple chelation intermediate such as **6**,[6,10,11] because the first nucleophilic attack also occurred by β-face attack on **4**. From our ab initio calculations, we propose that coordination of **1** to 2,3-dioxobutane occurs in a face-to-face arrangement, as shown in Figure 2 (**9**: side view; **10**: bottom view).[4c]



Scheme 3. Preparation of optically active 2-(1-hydroxyalkyl)-1-alkylcyclopropanol from optically active α,β-epoxy ketones and bis(iodozincio)methane (**1**).



Scheme 4. Stereochemical requirements for the reaction.



Scheme 5. Diastereoselective reduction of epoxy ketone with $NaBH_4$·$LaCl_3$.

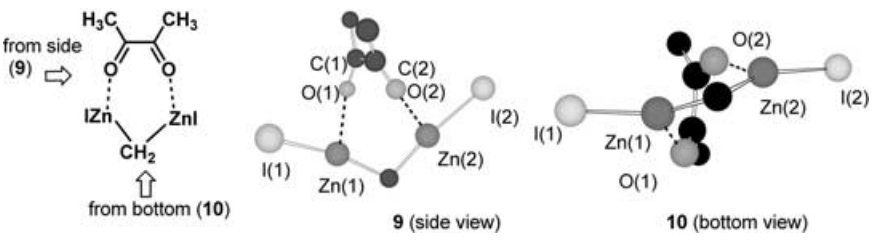


Figure 2. Initial complex formed in the reaction of 2,3-dioxobutane with **1** based on B3LYP/II//B3LYP/I calculations. See ref. [4c].

Such coordination has two characteristic features: first, the dihedral angle of the diketone part ($\measuredangle$O(1)-C(1)-C(2)-O(2) = 47.7°); and second, the mechanism through which the zinc reagent coordinates to the diketone. A line drawn between the two oxygen atoms of the diketone, and another between the two zinc atoms in the initial complex, cross at almost right angles. In the same way, the nucleophilic attack of **1** on epoxy ketone **2h** can be explained via intermediate **11** (Scheme 6). Attack from the other face via intermediate **13** will be constrained by steric hindrance between **1** and the epoxide ring. Thus, face-to-face coordination will promote attack on the opposite face relative to traditional Cram-chelation intermediates such as **6**.

A cyclic substrate such as **14** or **16** (Scheme 7) will experience some difficulty in differentiating between the intermediate corresponding to **11** and **13** because of steric hindrance of the carbocyclic moiety. Treatment of **14** and **16** with **1**, however, gave the spiro compound with good diastereoselectivity. Figure 3 shows the results of the single-crystal X-ray analysis of the diester obtained from **17a** and 3,5-dinitrobenzoyl chloride.[12]

A derivative of 2-(1-hydroxyalkyl)-1-alkylcyclopropanol is an important intermediate structure of some natural products.[13] In our present method, we report a new diastereofacial selective attack of epoxy ketone by utilizing the Lewis acidity of the dizinc reagent **1**. Bis(iodozincio)-methane (**1**), prepared from diiodomethane and zinc powder, exists as monomeric form without aggregation or a contribution of the Schlenk equilibrium.[14,15] This monomeric structure is crucial when demonstrating its function as an effective bidentate Lewis acid in a stereoselective reaction.

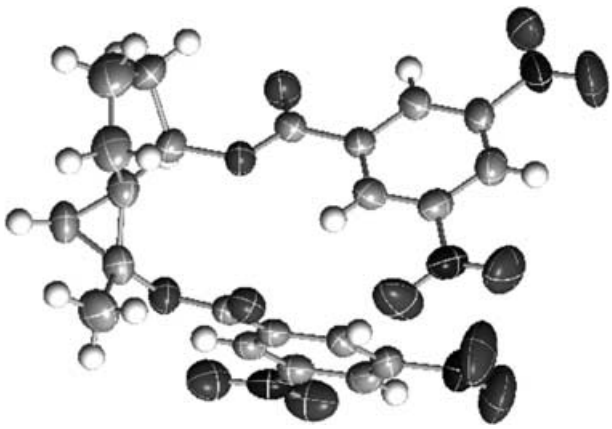
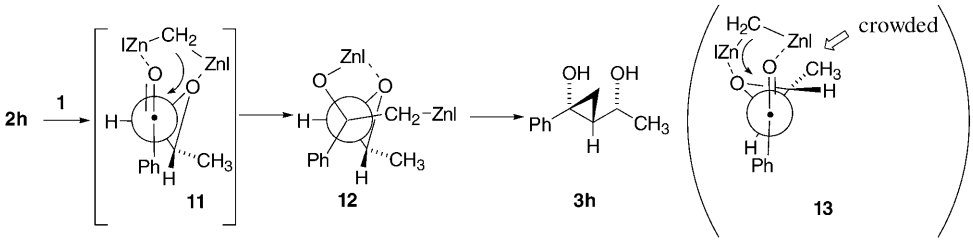


Figure 3. Structure of diester (3,5-dinitrobenzoylester) of **17a** obtained by X-ray analysis.



Scheme 6. Proposal for the stereoselective reaction of **2h** with **1**.

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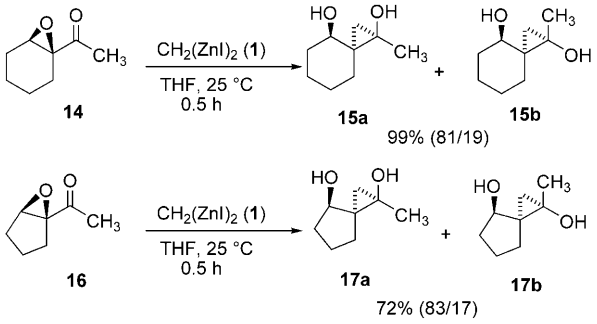

Scheme 7. Formation of spiro derivatives.

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[7] For the X-ray diffraction study, a crystal was mounted on a glass fiber coated with epoxy resin. Measurements were made on a Rigaku Mercury charge-coupled device (CCD) system with graphite monochromated $Mo_{K\alpha}$ radiation. Orthorhombic, a = 6.1690(7), b = 16.0965(17), c = 22.395(2) Å, β = 90.0°, V = 2223.8(4) Å^3, Z = 9, ρ_{calcd} = 1.148 Mg m^{-3}, $\lambda(Mo_{K\alpha})$ = 0.71073 Å,

$T = 296$ K, $2\theta_{max} = 54.1°$, $R = 0.0371$ for 4852 reflections ($I > 2\sigma(I)$).
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