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Preparation of *cis*-2-aminocyclopropanol: [2+1] cycloaddition reaction of bis(iodozincio)methane with α-ketoimine ☆

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Abstract—A reaction of α-ketoimine with bis(iodozincio)methane gave a *cis*-2-aminocyclopropanol derivative via [2+1] cycloaddition. The reaction proceeded via a sequential nucleophilic attack of bis(iodozincio)methane to a couple of carbonyl groups in the substrate, which was fixed into *s-cis* conformation with a couple of zinc atoms in the reagent. The reaction proceeded with high diastereoselectivity.

gem-Dizinc reagents, which possess a couple of nucleophilic sites on a carbon have been used for a variety of characteristic transformations;[1,2] the reagents can form two C–C bonds on one carbon atom. We have reported a preparation of *cis*-cyclopropan-1,2-diol from 1,2-diketone and bis(iodozincio)methane (**1**).[3] This [2+1] reaction could be applied for the preparation of 2-aminocyclopropanol, which has potential for pharmaceutical applications[4] and effective ligand for organometallic chemistry.[5] In addition, even though an example for the preparation of *trans*-2-aminocyclopropanol has been performed via photochemical reaction of β-aminoketone,[6] a preparation of *cis*-isomer has not been reported. Here we wish to report a highly diastereoselective preparation of *cis*-2-aminocyclopropanol from α-ketoimine and bis(iodozincio)methane (**1**).

As shown in Figure 1, tosylimine of benzil **2** (1.0 mmol) in THF, which was prepared following the reported procedure,[7] was treated with bis(iodozincio)methane (**1**) at 25 °C in THF for 1 h. An acidic aqueous work-up gave *cis*-2-aminocyclopropanol diastereoselectively in 97% yield. The quenching reagents such as an acetic anhydride and chlorotrialkylsilane gave the corresponding products.

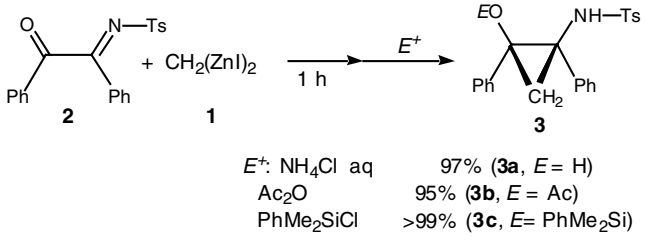

Figure 1. Reaction of tosylimine **2** with bis(iodozincio)methane (**1**).

The stereochemistry of the product was also confirmed by X-ray crystallographic analysis. The ORTEP figure of **3b** was shown in Figure 2.[8] The figure shows *cis*-configuration of the product. As shown in Figure 2, two phenyl groups place parallel on the cyclopropane ring to avoid the steric hindrance.

Other examples are shown in Figure 3. Electron-donating group, methoxy, on benzene ring **4** did not disturb the cyclopropanation reaction. Tosylimine of 1,2-di(2-naphthyl)-1,2-ethandione, **6**, was also converted into *cis*-2-aminocyclopropanol derivative **7** in 92% yield with high diastereoselectivity. An attempt to isolate **7** without a protection with trimethylsilyl group was not possible. The ring opening product, β-hydroxyimide, was isolated quantitatively.

Instead of tosylimine, phenylimine **8** was examined for the cyclopropanation reaction. Aqueous work-up

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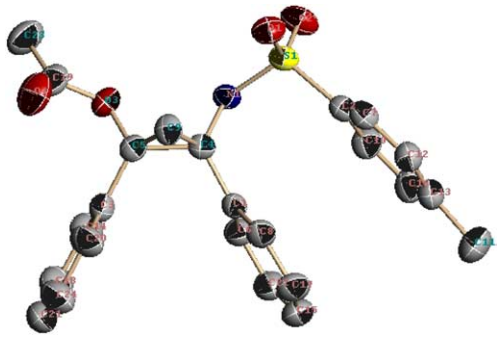

Figure 2. ORTEP of **3b**.[8]

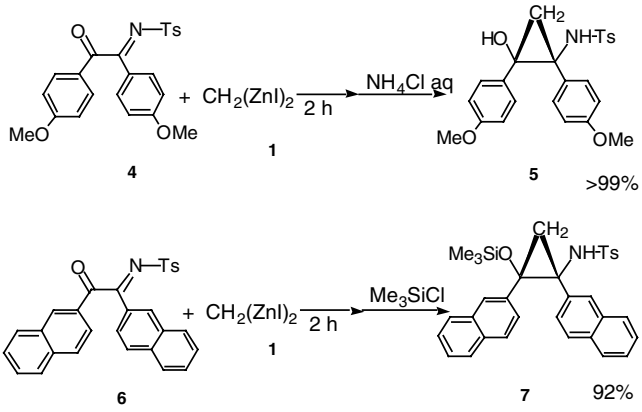

Figure 3. Other examples of reaction of tosylimine with **1**.

afforded *cis*-2-aminocyclopropanol quantitatively (Fig. 4). An attempt to quench with chlorotrimethylsilane afforded only α-methylenated imine **10** as a sole product. The formation of **10** can be explained by a ring opening of the cyclopropane catalyzed with chlorotrimethylsilane as a Lewis acid.

An attempt to prepare 1,2-diaminocyclopropane was also examined using 1,2-diimine derivative as a substrate. The preparation of the substrate, diimine from 1,2-diketone is not easy, but that from glyoxal is not

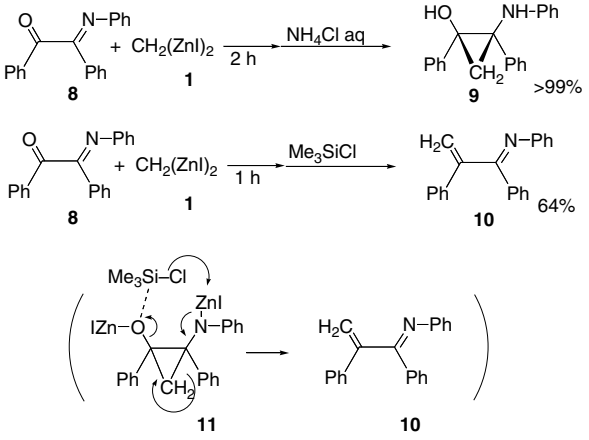

Figure 4. Reaction of phenylimine **8** with bis(iodozincio)methane (**1**).

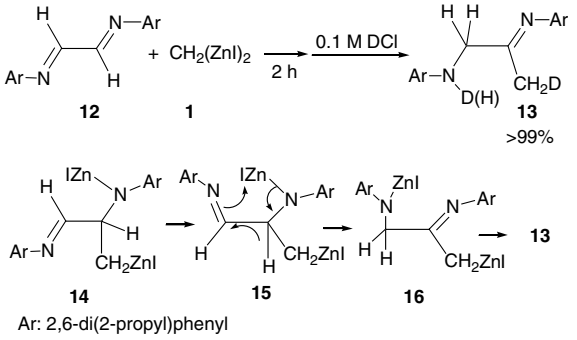

Figure 5. Reaction of diimine **12** with bis(iodozincio)methane (**1**).

difficult. Diimines from glyoxal and aniline, benzylamine and ethylamine were prepared and treated with the dizinc **1**. Those resulted in their decomposition because of Lewis acidity of **1**. On the contrary, the diimine of glyoxal with a bulky amine would not be decomposed with a Lewis acid. Treatment of the diimine **12** from glyoxal and 2,6-di(2-propyl)phenylamine with **1**, however, did not give a cyclopropane derivative (Fig. 5). The product was α-aminoimine **13** after quenching with 0.1 M DCl in deuterium oxide. The precursor before quenching should be the organozinc compound **16**. The formation of **16** can be explained from a hydride shift in **14**, which was formed by an addition of **1** to **12**.

In these reactions, the coordination of bis(iodozincio)methane **1** with α-ketoimine would determine the reaction pathway. In the case of 1,2-diketone, we had profiled the formation of *cis*-1,2-cyclopropanediol by ab initio calculation.[3b] In this case, as an initial complex, we concluded that face-to-face coordination in Figure 6 (left) was favorable as an initial complex. In the present case too, the formation of a sterically disfavored *cis*-2-aminocyclopropanol would be explained by the face-to-face initial complex in the same way. In the case of the reaction with **12**, the bulkiness on nitrogen atom will prevent the formation of face-to-face complex. So, it leads to addition of **1** to imine via simple coordination to *s-trans* substrate, which would not give a cyclopropane product (Fig. 6, right). Although a limitation comes from the preparation of α-ketoimine has not been cleared, the present method gives us a novel route to prepare *cis*-2-aminocyclopropanol.

Bis(iodozincio)methane (**1**): A mixture of Zn (25 mmol), diiodomethane (1.0 mmol) and $PbCl_2$ (0.01 mmol) in THF (2.0 mL) was sonicated for 1 h in an ultrasonic cleaner bath under Ar. To the mixture, diiodomethane

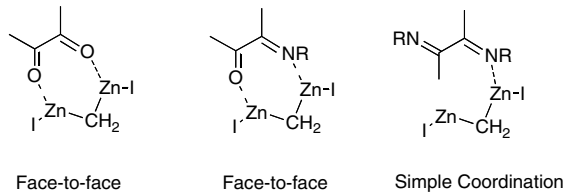

Figure 6. Possible coordination of **1** with diketone, ketoimine and diimine in the initial complex.

(10 mmol) in THF (20 mL) was added dropwise over 15 min at 0 °C with vigorous stirring. The mixture was stirred for 2 h at 0 °C. After the stirring was stopped, the reaction vessel was stood undisturbed for several hours. Excess zinc was separated by sedimentation. ^{1}H NMR spectra of the obtained supernatant showed a broad singlet at −1.2 ppm at 0 °C, which corresponded to the methylene proton of **1**. The supernatant was used for the further reaction as a solution of **1** in THF (0.5–0.6 M). Bis(iodozincio)methane in THF can be kept unchanged at least for a month in the sealed reaction vessel.

General procedure for the preparation of 2-aminocyclopropanol: To a solution of α-ketoimine derivative (1.0 mmol) in THF (4 mL), dizinc **1** (2.0 mmol) was added dropwise at 25 °C. The mixture was stirred 1–2 h. Quenching reagent (2.4 mmol, water, acetic anhydride or chlorotrialkylsilane) was added dropwise and the resulting mixture was stirred for another 30 min. The mixture was poured into satd NH_4Cl(aq) and neutralized with $NaHCO_3$(aq). The mixture was extracted with ether. The combined ethereal phases were washed with brine and dried over Na_2SO_4. Purification on a neutral silica-gel column chromatography gave the corresponding product.

Acknowledgements

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8. For the X-ray diffraction, a crystal was mounted on a glass fibre coated with epoxy resin. Measurements were made on a Rigaku Mercury charge-coupled device (CCD) system with graphite monochromated $Mo_{k\alpha}$ radiation. Crystal data: **3b**, $M = 421.49$, monoclinic, $a = 12.7365(13)$, $b = 10.8102(11)$, $c = 16.3267(17)$ Å, $\beta = 105.936(2)°$, $V = 2161.5(4)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.295$ mg/m^3, $\lambda(Mo_{k\alpha}) = 0.71073$ Å, $T = 296$ K, $2\theta_{max} = 54.0°$, $R = 0.049$ for 4711 reflections ($I > 2\sigma(I)$). ^{1}H NMR ($CDCl_3$): δ 7.41 (d, $J = 8.4$ Hz, 2H), 7.07–6.98 (m, 7H), 6.90–6.83 (m, 5H), 5.83 (s, 1H), 2.39 (d, $J = 8.4$ Hz, 1H), 2.30 (s, 3H), 2.18 (d, $J = 8.4$ Hz, 1H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 171.0, 143.1, 137.9, 135.9, 134.9, 129.3, 129.0, 128.5, 128.0, 127.93, 127.87, 127.4, 127.1, 66.2, 46.7, 22.4, 21.8, 21.7.