

Review

Bis(iodozincio)methane as a synthetic tool

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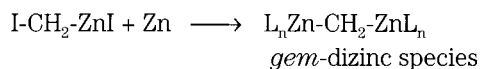
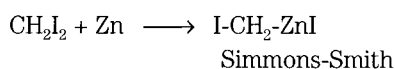
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Abstract: Bis(iodozincio)methane was prepared from diiodomethane and zinc in the presence of a catalytic amount of lead. The compound showed a high potential as an organic synthetic reagent. The reaction with carbonyl compounds proceeded to give methylenated products. The reagent also reacted with a couple of electrophiles sequentially. The function as Lewis acid is also unique. It coordinated with 1, 2-dicarbonyl compounds in face-to-face manner and assisted the stepwise nucleophilic attack on the carbon center of the reagent; the products are *cis*-1, 2-cyclopropanediols. A structural study was also examined.

Key words: Synthetic reaction; organozinc; dimetallomethane; titanium; palladium.

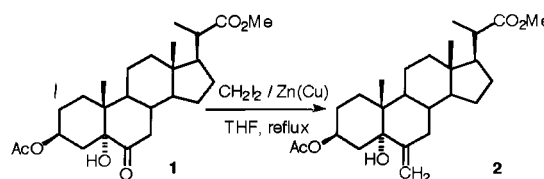
Introduction. *gem*-Dimetallic reagents have attracted considerable attention as versatile reagents in organic synthesis.¹⁾ As a doubly nucleophilic species, they have been treated with electrophiles to form a couple of new bonds. We focused on the corresponding zinc derivatives, as a reasonable stability of C-Zn bond would make their handling easy.²⁾ Through our serial studies for them, the corresponding *gem*-dizinc compounds showed the high characteristic performances in organic transformations. Here we summarize our recent work on the simplest *gem*-dizinc species, bis(iodozincio)methane.

Background. The most direct way to prepare the title compound is the reduction of diiodomethane with zinc metal. The reduction, however, may be much more widely recognized as the preparation of Simmons-Smith reagent that is iodomethylzinc iodide.³⁾ Typical procedure for preparation of Simmons-Smith reagent is an addition of diiodomethane to zinc-copper couple in ether. The choice of the solvent is crucial. When the same procedure was examined in THF, the further reduction to afford *gem*-dizinc species was observed in some cases.



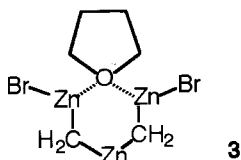
It is well known that Simmons-Smith reagent reacts with alkenes electrophilically as a carbenoid species but does not attack carbonyl compounds nucleophilically. On the other hand, *gem*-dizinc species, which were formed via the further reduction of Simmons-Smith reagent, would be enhanced the nucleophilicity of the crucial carbon by doubly substituted electropositive zinc atoms. An addition of dimetal species to a carbonyl group should lead to Wittig type olefination. In 1966, Fried *et al.* used the *gem*-dizinc species, which is prepared from diiodomethane and zinc-copper couple in THF, to the methylenation of steroid derivatives (**1** to **2**).⁴⁾ In this substrate, a hydroxyl group on the α -position of ketone plays an important role. A chelation enhanced the nucleophilicity of the *gem*-dizinc species.⁵⁾

Not only zinc-copper couple, but also zinc-lead



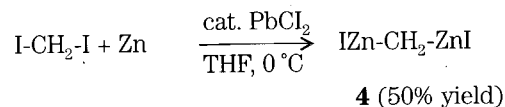
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couple forms the *gem*-dizinc species starting from diiodomethane, according to Nysted's patent in 1975.⁶⁾ He also insisted that treatment of dibromomethane with zinc in THF at 80 °C forms a characteristic *gem*-dizinc species **3**. However, there was no further evidence concerning the structure except ¹H-NMR data. ¹H-NMR spectroscopy was not enough for the determination of this structure. The obtained compound was definitely *gem*-dizinc species, but the written structure **3** is still suspecting. The white solid **3** was obtained as dispersion in THF, and would not dissolve into DMF, and DMI. This THF dispersion is commercially available from Aldrich Co. as Nysted reagent. Nysted also showed that these *gem*-dizinc compounds were effective for the methylation of α -hydroxy ketone moiety in steroid derivatives.



Nozaki, Oshima, and Takai reported in 1978 that the reagent prepared from diiodomethane, zinc, and titanium(IV) chloride was effective for the methylenation of ketones.⁷⁾ The reactive species was considered to be *gem*-dizinc species; titanium salt mediated the methylenation reaction. This method was modified by Lombardo in 1982.⁸⁾ In 1994, Takai and Utimoto showed that the commercially available zinc dust, which was used in their report of 1978, had contained originally a small amount of lead.⁹⁾ The lead had enhanced the reduction rate of diiodomethane into *gem*-dizinc species. This effect was consonant with Nysted's result.⁶⁾ In 1998, we reported a general procedure for the reduction of diiodomethane with zinc powder into dizinc species, which was obtained as THF solution.¹⁰⁾ The detailed structural study of this solution by EXAFS (see next section) implied that the *gem*-dizinc species which was prepared from diiodomethane and zinc, was simple THF solution of bis(iodozincio)methane (**4**). This solution of **4** can be kept unchanged at least for a month in the sealed reaction vessel.

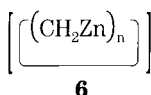
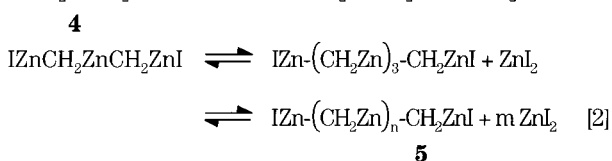
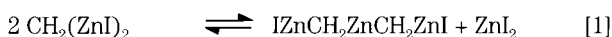
The compound **4** have shown a variety of molecular transformations based on the concept as dianion equivalent. We will introduce our recent examples of these reactions.



Preparation of bis(iodozincio)methane (4). A mixture of Zn (25 mmol), diiodomethane (1.0 mmol), and PbCl₂ (0.01 mmol) in THF (2.0 ml) was sonicated for 1 h in an ultrasonic cleaner bath under Ar. To the mixture, diiodomethane (10 mmol) in THF (10 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. ¹H-NMR spectra of the obtained supernatant showed a broad singlet at -1.2 ppm at 0 °C, which corresponded to the methylene proton of **4**. The concentration was determined by internal standard by ¹H-NMR. The supernatant was used for the further reaction as a solution of **4** in THF (0.4-0.5 M). When the purchased zinc powder is prepared by pyrometallurgy, it contains 0.04-0.07 mol% lead as an impurity (see ref 9)). In this case, an additional lead salt is not necessary.

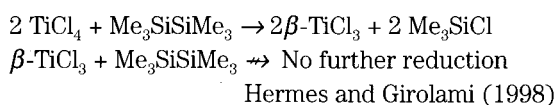
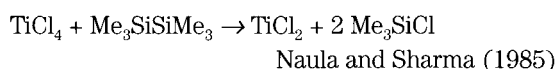
Structure of bis(iodozincio)methane. The structure of bis(iodozincio)methane (**4**) in THF is not so simple, as the possibility of a contribution of Schlenk equilibrium of bis(iodozincio)methane should be considered.¹¹⁾ The equilibrium would be discussed not only by eq. [1] but also by eq. [2], as the equilibrium of **4** induces a polymeric structure such as a linear compound **5** or cyclic compound **6**. Removal of the solvent from the THF solution of **4** *in vacuo* gave a white solid **7**. The solid **7** would not dissolve into THF. During the concentration, the structure had changed. Various other solvents, DMI (1,3-Dimethyl-2-imidazolidinone), CS₂, 1, 2-dichloroethane, pyridine, DMF, and DMSO, were examined to dissolve the solid **7**. Among them, DMSO promoted reasonable solubility. The solid **7** was also obtained by heating **4** in THF at 80 °C for 5 h. The solid was considered to be a polymeric dizinc species (**5** or **6**). An addition of tetrahydrothiophene (THT) changed the situation dramatically. After an addition of the same volume of THT to the THF solution of **4**, the resulting mixture was concentrated *in vacuo* to half volume. In this procedure, THF was removed selectively, and a THT solution of **4** was obtained. The further concentration gave also a white solid. This solid is soluble in THF. An extended X-ray absorption fine structure (EXAFS) spectroscopy of these solutions (**4** in THF, **7** in DMSO, and **4** in THT) was measured to get some information

regarding the structure.¹²⁾ The measurement showed that **4** in THF and THT exists as the monomeric form **4**, whereas the spectrum of **7** in DMSO showed an effect from the polymeric species such as **5** and **6**. The Schlenk equilibrium of eq. [1] in THF and THT may incline to $\text{CH}_2(\text{ZnI})_2$ (**4**), and a concentration or heating of **4** in THF causes a formation of the polymeric species **5** or **6**.

**6**

$\text{CH}_2(\text{ZnI})_2$ in THF $\xrightarrow{\text{in vacuo}}$ **7** (white solid)

Wittig type reaction. Aldehydes were methylenated efficiently by bis(iodozincio)methane (**4**). Methylenation reactions of ketones with **4** required addition of titanium salt. As shown in Table I, 2-dodecanone was treated with **4** in the presence of various titanium salts. As titanium chloride, $\beta\text{-TiCl}_3$, that was prepared from titanium(IV) chloride and hexamethyldisilane with following Girolami's procedure,^{13a)} was shown to be the most effective. This Girolami's report corrected the errors in the Naula and Sharma's result: Naula and Sharma had reported TiCl_2 was formed from the reaction of titanium(IV) chloride and hexamethyldisilane.^{13b)} Girolami pointed out that hexamethyldisilane cannot reduce titanium(III) chloride into titanium(II) or (I) chloride regardless of the stoichiometry. We used the titanium chloride prepared from titanium(IV) chloride and hexamethyldisilane in their olefination with citing Naula and Sharma's report (ref. 13b)). In our reports, the salt was written as TiCl_2 . It should be $\beta\text{-TiCl}_3$ according to Girolami's correction in 1998, although all procedure and results in our olefination reactions are correct.¹⁴⁾



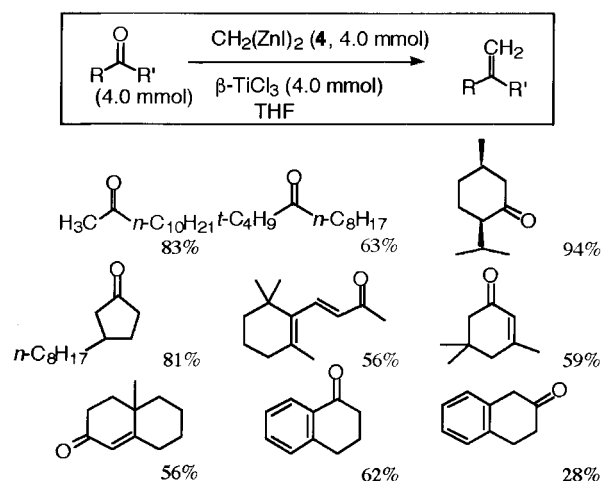
An equimolar mixture of **4** and $\beta\text{-TiCl}_3$ gave reactive

Table I. Titanium salt mediated methylenation of 2-dodecanone with bis(iodozincio)methane (**4**)^{a)}

$n\text{-C}_{10}\text{H}_{21}\text{C(=O)CH}_3 \xrightarrow[\text{Ti salt}]{\text{CH}_2(\text{ZnI})_2 \text{ (4)}} n\text{-C}_{10}\text{H}_{21}\text{C(=CH}_2\text{)CH}_3$				
Entry	Ti salt ^{b)}	4 (eq.)	Alkene (%)	Recovery (%)
1	TiCl_4	1	26	<5
2	TiCl_4	2	78	<5
3	$3\text{TiCl}_3 \cdot \text{AlCl}_3$	2	43	33
4	$\alpha\text{-TiCl}_3$	1	<5	72
5	$\beta\text{-TiCl}_3$	1	83	<5
6	$\beta\text{-TiCl}_3$	2	87	<5
7	TiCl_2	2	<5	86

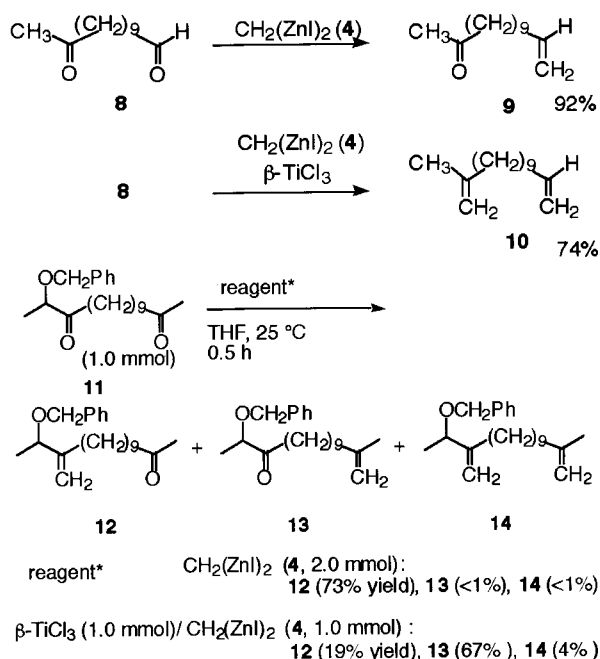
^{a)} S. Matsubara, Y. Yokota, and K. Oshima, unpublished results. ^{b)} $3\text{TiCl}_3 \cdot \text{AlCl}_3$ (Aldrich), $\alpha\text{-TiCl}_3$ (Aldrich), and TiCl_2 (Aldrich).

species for methylenation. As described before, the methylenation procedure by Takai or Lombardo used diiodomethane, zinc, and titanium(IV) chloride. In these procedure, the titanium(IV) chloride would be reduced into titanium(I), titanium(II), or titanium(III). As the higher valent titanium works as the better Lewis acid, use of **4** and $\beta\text{-TiCl}_3$ from the beginning is much desirable. TiCl_4 is also possible mediator with 2 equivalent of **4**, as **4** reduce TiCl_4 into TiCl_3 . The methylenation of other ketones are summarized in the following scheme.



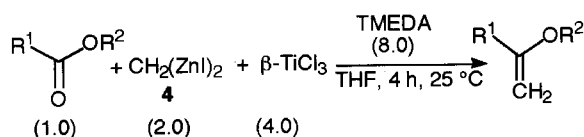
Treatment of ketoaldehyde **8** with **4** resulted in the selective methylenation of aldehyde **9**. Methylenation of α -hydroxy- and α -alkoxy-ketone with **4** proceeded without addition of titanium salt.¹⁵⁾ Treatment of **11**

with **4** resulted in selective methylenation of α -alkoxyketo group. On the other hand, treatment of **11** with **4** and β -TiCl₃ converted simple keto group into alkene much faster than α -alkoxyketo group. Steric hindrance of α -alkoxy group interfered the methylenation with titanium-based reagent.



Treatment of esters with **4** and β -TiCl₃ did not give the desired vinyl ethers.¹⁶⁾ The ethers were decomposed by Lewis acids in the reaction mixture. Addition of TMEDA prevented the decomposition. In Table II, the results of methylenation of esters by **4**, β -TiCl₃, and TMEDA were summarized.

Table II. Methylenation of esters with **4**, β -TiCl₃, and TMEDA



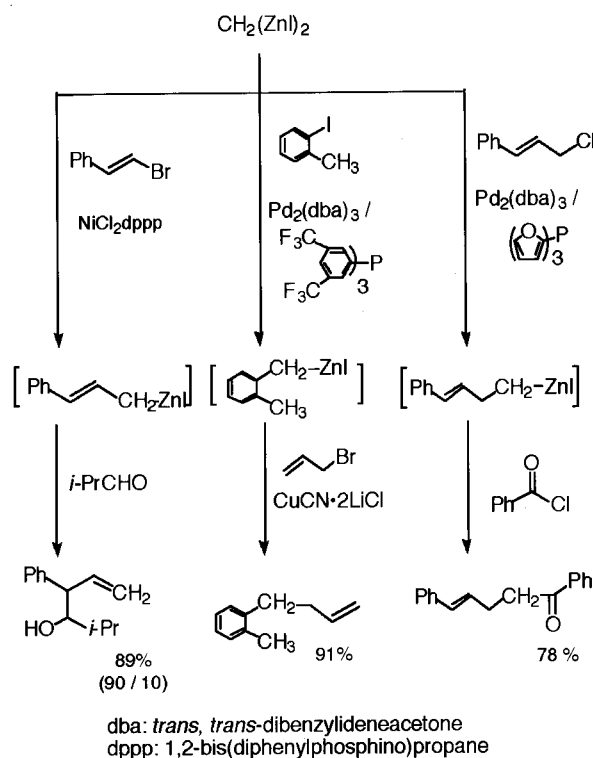
Entry	R ¹	R ²	Vinyl ether (%) ^{a)}
1	<i>n</i> -C ₇ H ₁₅	C ₂ H ₅	75
2	<i>n</i> -C ₉ H ₁₉	CH(CH ₃) ₂	90
3	<i>n</i> -C ₇ H ₁₅	C(CH ₃) ₃	46
4			34 ^{b)}
5	Ph	CH ₃	89
6	Ph	CH ₂ CH ₃	51

^{a)} Isolated yields. ^{b)} The mixture was stirred for 24 h.

Stepwise reaction of bis(iodozincio)methane with two different electrophiles. Bis(iodozincio)methane (**4**), which possesses double nucleophilic sites on one carbon, may react with two different electrophiles sequentially. It will act as a molecular hinge that connects two molecules. The reactivity of C-Zn bond in **4** was much higher than that of methylzinc iodide in the reaction with water or iodine. These results indicated that two C-Zn bonds can be used for a nucleophilic reaction sequentially.



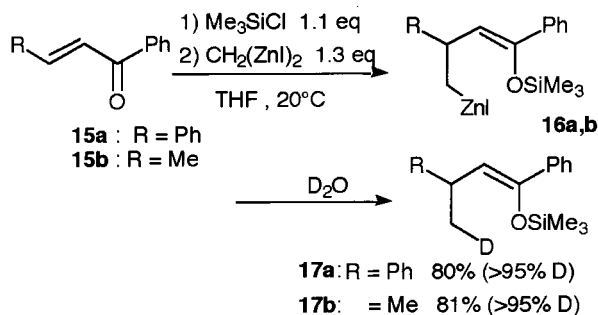
The sequential coupling reactions of **4** with various types of organic halides are summarized in the following scheme. In the case of the coupling with a bromoalkene, a nickel catalyst was more effective than a palladium catalyst.¹⁷⁻²⁰⁾



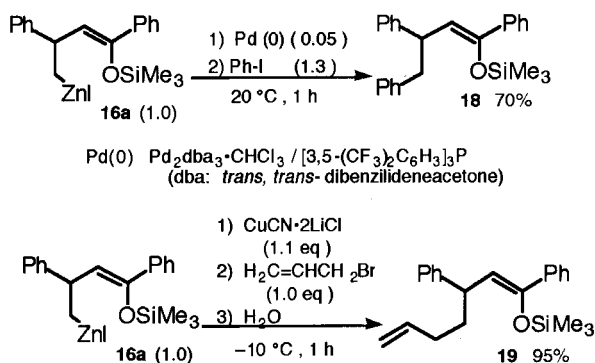
1,4-Addition of bis(iodozincio)methane to α , β -unsaturated ketones. We examined a reaction of bis(iodozincio)methane (**4**) with an α , β -unsaturated carbonyl compound to perform 1,4-addition. This reaction will afford the zinc enolate of β -zinciomethylke-

tone.^{21),22)}

A reaction of **4** with α , β -unsaturated ketone **15** was examined. The zinc enolate being formed *in situ* was trapped with an equimolar amount of chlorotrimethylsilane. The procedure afforded a silyl enolate of organozinc compound **16**. Treatment of **16** with D₂O gave the corresponding silyl enolate **17**.



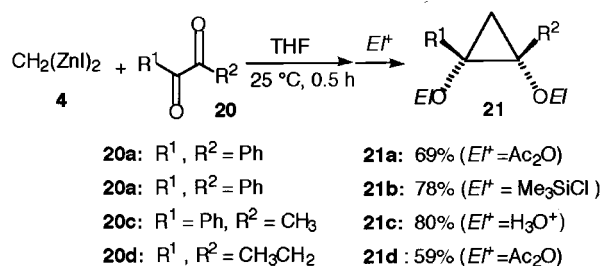
The C-Zn bond in **16** reacted with an organic halide in the presence of transition metal salt. The zinc species **16a** was treated with iodobenzene in the presence of a catalytic amount of Pd(0). The reaction gave **18** in 70% yield. The copper salt-mediated reaction of **16a** with allyl bromide gave the coupling product **19** in 95% yield. It is well known that the silyl enolate reacts with various electrophiles, so the procedure provides us the four-components assembling possibility.



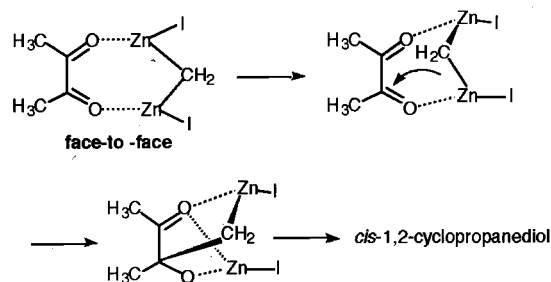
As bidentate Lewis acid. The control of the reaction has been polished up by a combination of catalysts, mediators, and solvents. We should remind the high reactivity of bis(iodozincio)methane (**4**) with α -heteroatom substituted ketone. This means that coordination of the substrate enhances the nucleophilicity of **4**. Along this line, we examined the reaction of **4** with 1,2-dike-

tones. As a result, we found a novel [2+1] reaction which formed cyclopropanediol diastereoselectively.²³⁾

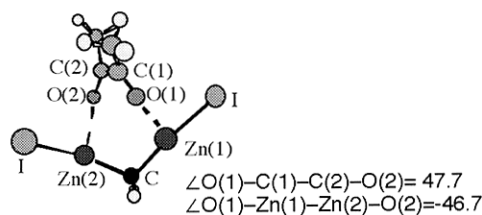
Benzoin (**20a**) was treated with **4** at 25 °C in THF for 0.5 h. Acetic anhydride was added to the reaction mixture, and the whole was stirred for another 30 min at 25 °C. After an aqueous work-up followed by purification with silica-gel column chromatography, *cis*-1,2-diphenylcyclopropane-diol diacetate (**21a**) was obtained in 69% yield. Instead of acylation, an addition of chlorotrimethylsilane to the [2+1] reaction mixture gave bisilyl ether (**21b**). Depending on the substrate, the formed 1,2-cyclopropanediol possesses a reasonable stability that makes the isolation by a silica-gel column chromatography possible (**21c**). In all cases, the reaction proceeded stereoselectively to give *cis*-diol.



The reaction pathway of **4** and 2, 3-diketobutane was profiled by *ab-initio* calculation.²⁴⁾ It was rationalized that the initial complex of this transformation was a face-to-face complex. In this complex, **4** worked as a bidentate Lewis acid.

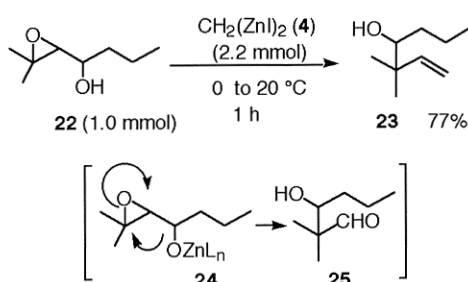


The detailed structural information about the initial complex was shown below. The dihedral angle O(1)-C(1)-C(2)-O(2) was 47.7°. The distortion from flat configuration (i.e. dihedral angle 0 or 180°) suppressed the deprotonation from methyl group, that lead to the unfavourable enolization of the diketone.



Bis(iodozincio)methane (**4**) serves as a bidentate Lewis acid against substrates with hetero atoms at 1, 2 or 1,3-positions as well as 1,2-diketone. We tried to treat 2,3-epoxy alcohols with **4** to find special affinity between them, expecting the pinacolone rearrangement.²⁵⁾

Treatment of a racemic epoxide of 2-methyl-2-hepten-4-ol (**22** as a diastereomeric mixture, *erythro*/*threo* = 84/16, 1.0 mmol) in THF (2.0 ml) with **4** (0.5 M in THF, 2.2 mmol) at 20 °C gave a homoallylic alcohol **23** in 77% yield. The reaction would probably proceed via aldehyde **25** that was formed by pinacolone rearrangement (**24** to **25**), **25** being methylenated by **4** to form **25**.

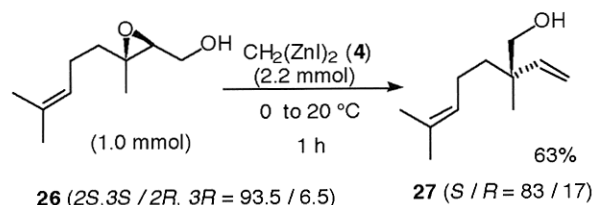


Optically active epoxides were treated with bis(iodozincio)methane **4**. From **26**, **27** was obtained in an optically active form, though a slight decrease of the enantiometric purity was observed. The remarkable point of the transformation is the absolute configuration of the product. The migrating group, -CH₂OH, came from the front side of C-O bond. It is unusual retentive migration reaction.

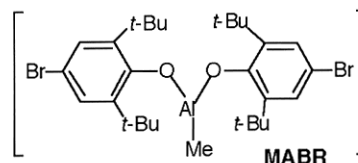
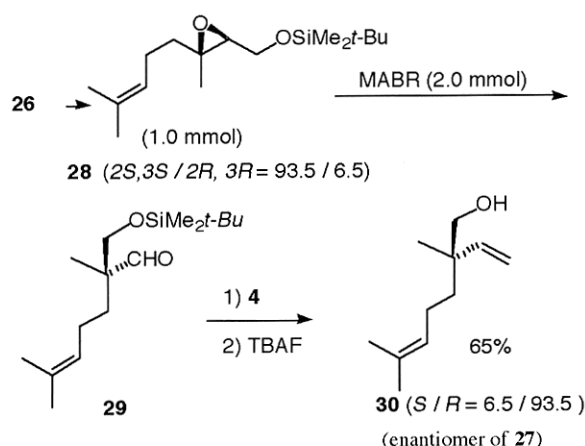
For example, Yamamoto and Maruoka had reported the pinacolone rearrangement of the silyl ether of **26** with MABR (methylaluminum bis(4-bromo-2, 6-di-*tert*-butylphenoxide)).²⁶⁾ The rearranged product was treated with **4** to convert aldehyde into alkene. After desilylation, the obtained homoallylic alcohol **30** was an enantiomer of **27**.

The mechanistic study has not been tried. A possi-

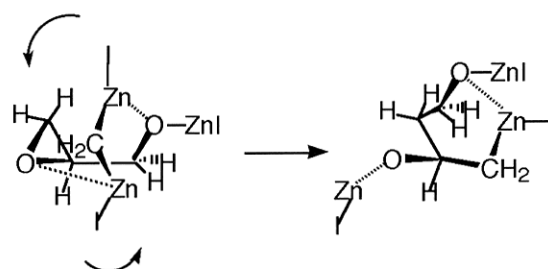
By bis(iodozincio)methane



By MABR (Yamamoto and Maruoka)



ble explanation is formation of a tight face-to-face complex between **4** and substrate. As shown below, the formed complex can be isomerize into the rearranged product by rotation of **4** on the face of the substrate.



Conclusion. Bis(iodozincio)methane (**4**) showed utility in the area of methylenation of carbonyl compounds and also serves as a molecular hinge of two electrophiles. Lewis acid function of **4** was also characteristic

to the 1,2-diketones and 2,3-epoxyalcohols. Our preliminary work for the structural study requires further elaboration, which is underway.

The use of 1, 1-bis(iodozincio)ethane gave rise to a problem of stereoselectivity, as the symmetrical structure of the *gem*-dimetalated species would afford a stereogenic center via desymmetrization.^{20),22)} This will offer a possibility for a new type of stereocontrolled transformation. The heteroatom-substituted *gem*-dizinc reagent (i.e., silyl-, boryl-, and germyl-substituted ones) also offered a novel route to the corresponding alkenyl and allyl derivatives via olefinations and sequential coupling reactions.¹⁸⁾

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