Olefin Carbometalation with (Alkoxy)allylic Lithium and Zinc Reagents. Four-Centered vs Six-Centered Mechanism of Allylmetalation Reaction

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Abstract: Addition of substituted (alkoxy)allyllithium and zinc reagents to cyclopropenone acetal takes place smoothly to give carbometalation products of well-defined regio- and stereochemistry. The pathways of product formation depends on the metal. The (alkoxy)allylzinc reagents add to the cyclopropene in such a manner that the α-carbon attached to the alkoxy group becomes bound to the olefin. The regioselectivity of the (alkoxy)-allylzincation is independent of the allyl substituents, the diastereoselectivity for the newly formed carbon−carbon bond is excellent (>97%), and the geometry of the olefinic bond in the product was always exclusively cis (if applicable). On the other hand, the regioselectivity of the (alkoxy)allyllithiation is dependent on the substituent, while the diastereoselectivity remains constantly high (>97%). Theoretical studies supported this conjecture by revealing that a (hydroxy)allyllithium species of π-allylmetal nature can react with cyclopropene via two [2 + 2]-type four-centered transition states of similar energies leading α- and γ-adducts, while the zinc species of σ-allylmetal nature reacts via a single [2 + 4]-type six-centered transition state leading to an α-adduct.

Nucleophilic reactions of allylic anions are fundamentally more versatile than the reactions of simple alkyl groups. (Alkoxy)allylic anion **1** represents a typical illustration of the utility (eq 1). α-Addition produces a substituted allylic ether, **2**, and γ−addition gives a protected carbonyl compound, **3** (e.g., a homoenolate equivalent).[1] This simple looking chemistry offers complex mechanistic problems, once a metal countercation is considered.[2] The position of the metal atom (π- and σ-coordination, eq 1) is one problem, and the regioselectivity inherent to each organometallic entity[3] is another.[4] Such problems have not been investigated systematically either by experiments or by theory. In the past several years,[5] we have focused our attention on stereocontrol of the addition of organometallics[6] and metal enolates[7] to an isolated olefin (olefin carbometalation) and examined the basic reactivities and the regio- and stereocontrol.[8] In this context, the cyclopropenone acetal **4** has proven not only to be a synthetically viable substrate[9] but also serves as a useful probe for studies on regio- and stereochemistry of carbometalation reactions.[6,7,8a] In the present studies, we have investigated, experimentally and theoretically, the reactions of lithio- (**1Li**) and zincio(alkoxy)-allyl species (**1Zn**) with **4** and found a mechanistically intriguing metal-dependent dichotomy of regioselectivity. The high-level theoretical studies using density functional (DF) theory revealed important insights into the basic stereochemical behavior of the (alkoxy)allylmetals and their reactivities, showing that the observed regioselectivity reflects the contrast in the π- and σ-allylic structures of the lithium and zinc species. An interest-

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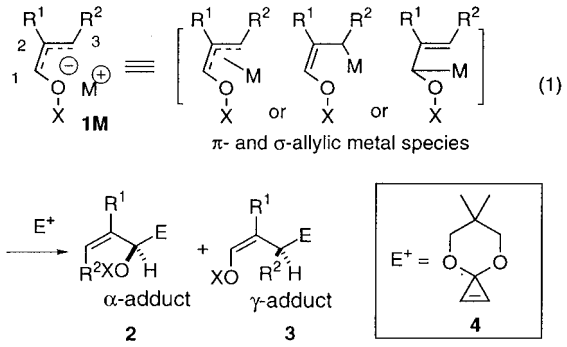
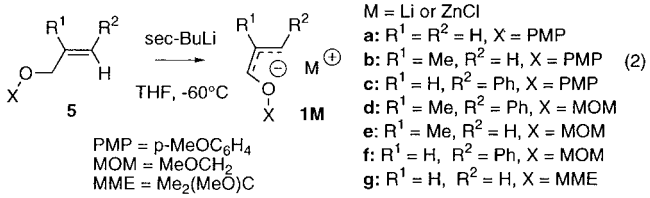
ing, counterintuitive finding in the calculations is that the strong internal chelation in a starting organometallic such as **11** (eq 4) may not be retained during the subsequent reaction course (even under gas-phase assumption).



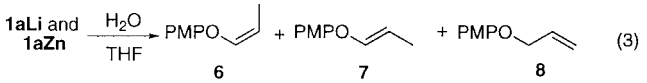
(1)

Results and Discussion

Stereochemistry of (Alkoxy)allylic Metal Species. With an ultimate objective of developing synthetically useful reactions, we have chosen to study representative alkyl-protected allylic metal reagents of some diversity (eq 2; protected with *p*-methyoxyphenyl, methoxymethyl, and 1-methoxy-1-methylethyl). The lithium reagents **1a**−**gLi** were prepared in a straightforward manner by deprotonation of an allylic ether **5** with *sec*-butyllithium at −60 °C (eq 2). The lithium species was then allowed to react with 1 equiv of dry $ZnCl_2$ to prepare the corresponding alkoxy-substituted allylic zinc reagent **1a**−**gZn**. To obtain information on the structure of the allylic metals, we quenched the allylic lithium reagent **1aLi** with water. Protonation occurs 68% at the position γ to the alkoxy substituent and 32% at the α-position. The stereochemistry of the olefinic bond in the former product (**6**) was exclusively in cis geometry. Protonation of the zinc reagent **1aZn** gave a product mixture of similar composition with the same γ-product **6** of cis geometry.



(2)



(3)

M	temp. (°C)	%yield 6	7	8
Li	-70	68	≤2	32
ZnBu	0	45	2	53

While the experiments established that both lithium (**1aLi**) and the zinc allyls (**1aZn**) have the same cis C^2-C^3 geometry, they by no means indicated that the two species have the same structure. A body of previous X-ray crystallographic analyses and theoretical calculations[10] suggests that lithium allyls may have a π-allylic structure[11] owing to simple electrostatic interaction between the lithium cation and the π-allylic center and that zinc allyls may have a σ-allylic structure,[12] because of favorable covalent zinc−carbon bond formation. However, there has been no crystallographic data available for (alkoxy)-allylmetal species. Theoretical study has been reported on free (hydroxy)allyl anion but not on its metal complexes.[13] The paucity of structural information led us to investigate the structure of (alkoxy)allyllithium and zinc reagents by the DF calculations on model (hydroxyl)allylmetal species.

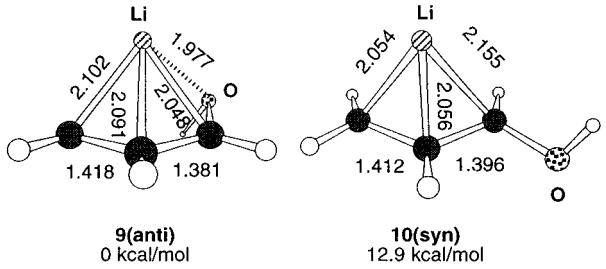


Figure 1. Structures of *syn*- and *anti*-π-allyllithium (B3LYP/631A). The numbers in this and the following figures refer to atomic distances in angstrom.

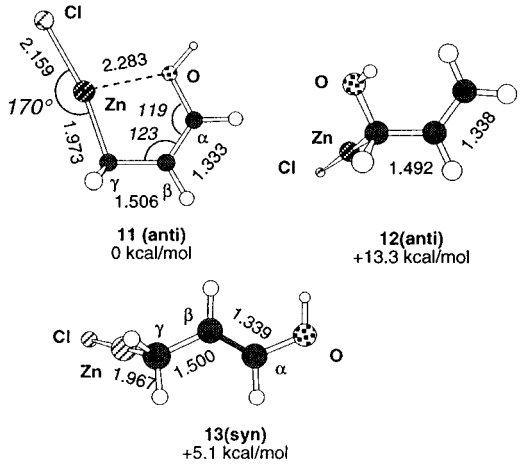


Figure 2. Structures of *syn*- and *anti*-σ-allylZnCl (B3LYP/631A). The numbers in italics refer to bond angles in degrees.

Two geometrical isomers of the π-allylic lithium structure were found (Figure 1). The anti isomer **9** was found to be much more stable than the syn isomer **10**, since the former enjoys extra stabilization due to coordination to the hydroxy oxygen atom. In light of the fully conjugated structure and the resulting large stabilization energy, the anti isomer **9** will likely react without isomerization to the syn isomer **10** (Curtin−Hammett assumption). A similar anti π-allylic structure bearing a neighboring heteroatom is found in the crystals of lithiohydrazone (C═C−N−N·Li).[14]

We could locate three isomeric σ-allylzinc structures **11**−**13**, but failed to find any π-allylic zinc structure, since the zinc

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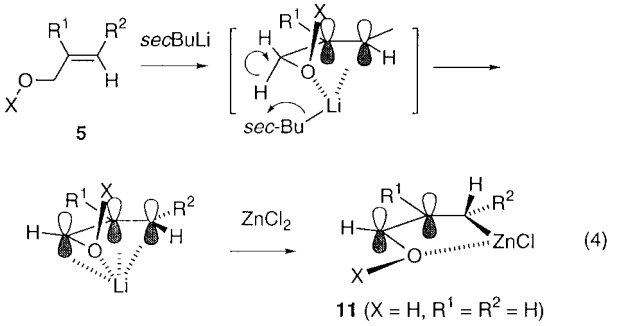
Table 1. Addition of Allylic Lithium **1Li** to **4** in THF (Eq 5)

series	R^1	R^2	X	time (h)	% yield[a]	**14**/**15** (α/γ)	% ds[d]
a	H	H	PMP[b]	0.5	89	91:9	≥97 (**14**)
b	Me	H	PMP[b]	0.5	79	4:96	
c	H	Ph	PMP[b]	2	81	12:88	≥97 (**15**)
d	Me	Ph	MOM[c]	5	91	≤1:≥99	≥97 (**15**)
e	Me	H	MOM[c]	2	83	4:96	
f	H	Ph	MOM[c]	2	78	4:96	≥97 (**15**)

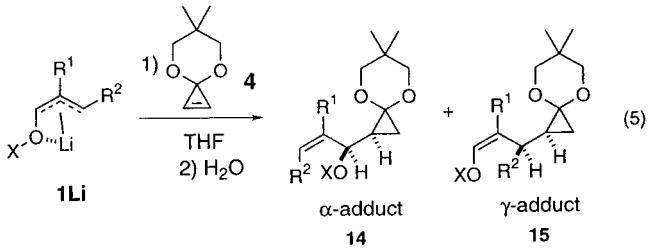
[a] Isolated yield. [b] *p*-Methoxyphenyl. [c] Methoxymethyl. [d] % ds notation stands for % ratio of diastereomer.

metal is prone to become tightly σ-bound to one of the two terminal carbon atoms. The anti isomer **11** was found to be overwhelmingly more stable than other isomers. *The oxygen−zinc chelate in **11** is so strong that the C^3-Zn bond is not conjugated to the C^1-C^2 double bond.* In the alternative less stable regioisomer, **12**, the C−Zn bond is conjugated with the vinyl substituent, and the same is also seen in the syn isomer **13** (Figure 2). In summary, the (alkoxy)allyllithium and zinc species are very different in their bonding scheme, but the overwhelming stability of **9** and **11** in each series strongly suggests that both will be dominant in solution, supporting the experimental findings that the same cis enol ether product **6** was obtained upon γ-protonation of **1aLi** and **1aZn**. Thus, we may consider the process of stereoselective formation of **1Li** and **1Zn** from the ether **5** as shown in eq 4 (transmetalation with retention of stereochemistry is assumed).



(4)

Allylmetalation of Cyclopropenone Acetal. Allyllithiation of the cyclopropenone acetal **4** with **1Li** was investigated first (eq 5, Table 1). *p*-Methoxyphenoxy allyllithium **1aLi** (2 equiv) reacted with **4** at −70 °C in 0.5 h. Quenching the reaction mixture with H_2O afforded an adduct mixture in 89% yield (series **a**). The α-isomer **14a** formed with 91% regioselectivity and, for this isomer, with >97% diastereoselectivity as to the newly formed carbon−carbon bond. With this result in hand, we were surprised to find that other five-substituted allylic reagents (series **b**−**f**) reacted with an opposite regioselectivity to give γ-adduct **15** with 88 to >99% selectivity. The diastereoselectivity for the newly formed bond was also excellent (>97%), and in all entries, the geometry of the olefin bond in α- and γ-adducts **14** and **15** was exclusively cis as determined by ^{1}H NMR. The sense of diastereoselectivity was determined



(5)

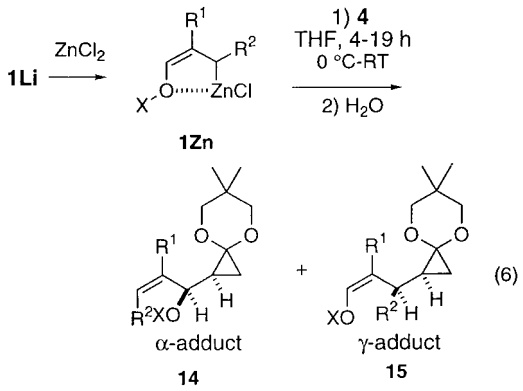
Table 2. Addition of Allylic Zinc **1Zn** to **4** in THF (Eq 6)[a]

series	R^1	R^2	X	% yield	**14**/**15** (α/γ)	% ds for **14**
a	H	H	PMP	79	≥97:≤3	≥97
b	Me	H	PMP	89	≥97:≤3	≥97
c	H	Ph	PMP	90	82:18	≥97
e	Me	H	MOM	82	94:6	≥97
f	H	Ph	MOM	84	80:20	≥97
g	H	H	MME[b]	48	≥97:≤3	≥97

[a] Abbreviations are the same as those used in Table 1. [b] MME: 1-methyl-1-methoxymethyl.

by correlation to known compounds as shown in Scheme 3 (in Experimental Section).

We next investigated the reaction of alkoxy-substituted allylic zinc reagents **1Zn** with **4** (eq 6, Table 2). *p*-Methoxyphenoxy allylzinc chloride slowly reacted with **4** at 0 °C and gave an adduct in 79% yield (series **a**). For various combinations of substituents, the α-adduct **14** predominated with 80 to >97% selectivity. As in the lithium case, the olefinic geometry was always exclusively cis. The diastereoselectivity for the newly formed bond was consistently excellent. The sense of stereoselection was the same as in the lithium case and was not affected by the substitutent variations for R^1, R^2, and X. The excellent diastereoselectivity found for the (alkoxy)allylzinc species with a ZnCl countercation stands in contrast to the fact that, for the previously reported alkyl-substituted allylic zinc reagents,[6c] a bulky countercation such as Zn−*t*-Bu was necessary to obtain high diastereoselectivity. The presence of such a bulky substituent on the zinc atom has been considered necessary to rigidify the flexible half chair conformation of the allylzincation reaction, while, in the present case, a rigid transition state is constructed already by the alkoxy group (vide infra).



(6)

Transition Structures of (Alkoxy)allylmetalation of Cyclopropene. In the above studies, we have established that one can achieve regio- and stereoselective allylmetalation of **4**. The origin of the observed selectivity however was rather difficult to understand since fundamental mechanistic information on the reactivities of allylmetal species is lacking. While there have been recorded some studies on the transitions states (TSs) of allylmetalation reactions,[15] they have neither addressed the issue of metal effects on selectivities nor examined the (alkoxy)-allylmetal species. Since the impact of the chelating alkoxy group on the structure of the metal allyls is so large (vide supra), previous studies on simpler allyls were expected to be rather useless for the mechanistic understanding of the present cases. The role of the chelating oxygen emerged as an interesting target of theoretical analysis. The questions involved were those such

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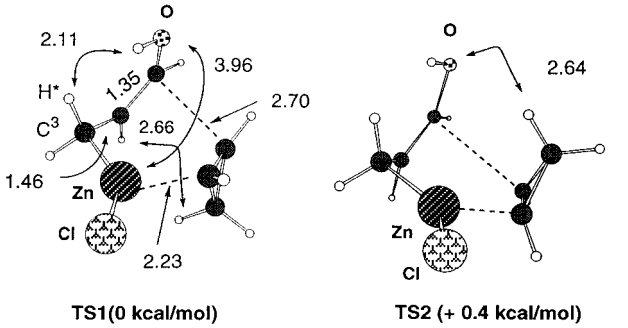


Figure 3. B3LYP/631A TSs leading to endo and exo α-adducts.

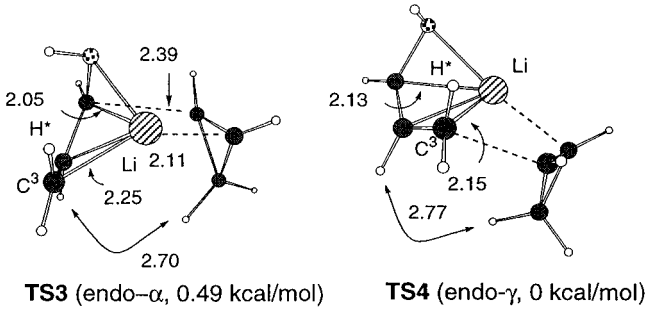
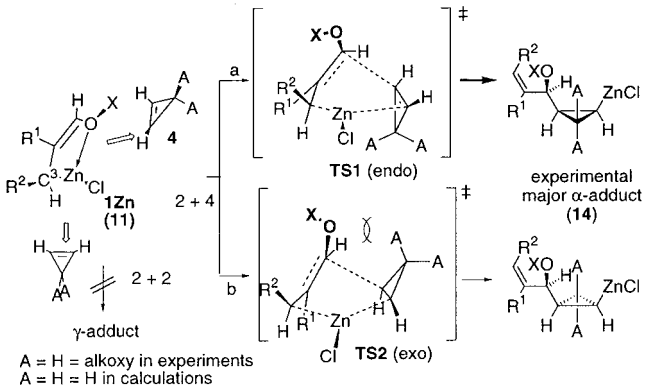
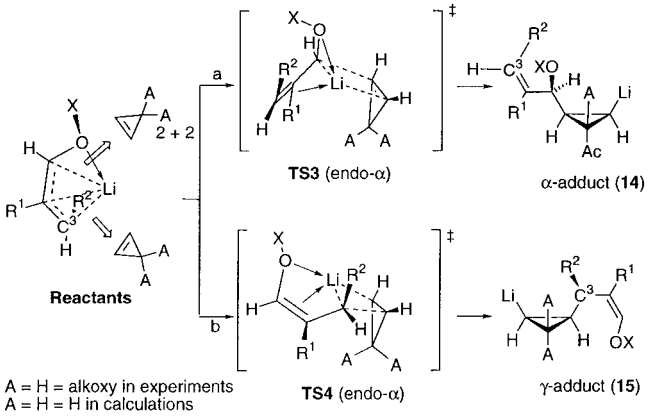


Figure 4. B3LYP/631A TSs leading to α- and γ-adduct.

Scheme 1



Scheme 2



as whether chelation is retained during the addition reaction and how the alkoxy group affects the selectivities. We thus set out to determine the structures and energetics of a model reaction, (hydroxy)allylmetalation of cyclopropene, with the aid of DF calculations. Because of the overwhelming stability of chelated isomers **9** and **11** and the experimental evidence for their existence in THF, we studied only these two species.

Conventional wisdom and previous theoretical studies[15] suggest that the allylzincation of the cyclopropene takes place via a six-centered transition state (TS). Indeed, the DF calculations on a model system ((hydroxy)allylzinc chloride and cyclopropene) at the B3LYP/631A level indicated that the reaction of **11** will take place only through a single set (endo and exo) of TSs (**TS1** and **TS2**, Figure 3), which lead to two diastereomeric α-adducts (Scheme 1). Unlike in the allyllithiation case (vide infra), we could not locate an alternative γ-selective pathway. *Most interestingly (despite gas-phase assumption, which would favor chelation), the chelate structure in the starting material **11** is destroyed in the TSs of allylzincation* (O−Zn = 3.96 Å)[16] because of strong covalent interaction of the metal with the cyclopropene, whose sp^2 carbons have undergone substantial pyramidalization (Figure 2).[17] The anti-geometry of the allylic anion however is still maintained in **TS1**, but the C−Zn bond is now conjugated with the allylic system ($\angle C^1-C^2-C^3-Zn$ = 84−93°). The axially oriented alkoxy group (OX) in **TS1** and **TS2** (Scheme 1) must be serving as a stereochemistry determinant in the real system, where the OX group will push the bulky acetal moiety (A) to the other side of the six-centered transition state (as in **TS2**). This analysis accounts for the experimental diastereoselectivity.[18] **TS1** also accounts for the exclusive cis olefin geometry in the product, since the R^2 group (H* in Figure 3) will take the sterically favorable equatorial orientation (i.e., lack of $A^{1,2}$ strain).

Reflecting the difference of the bonding scheme in the starting material, the TS for the π-allylic lithium species **9** was very different from **TS1** for the σ-allylic zinc species (Figure 4). Starting with **9**, we could locate two regioisomeric pathways leading to α- and γ-adducts (for these, only the TSs leading to the experimentally observed diastereomers were examined; see Scheme 2). *Unlike the zinc allyl case, the π-allylic and oxygen chelate features in **9** are retained even in the TSs.* This is because the metal center interacts with the π-system and the oxygen atom in an electrostatic manner for such a highly electropositive metal cation as lithium cation. The approximate topology of **TS3** (endo α-pathway) is similar to that of **TS1**, which accounts for the formation of the same product **17**. On the other hand, because of the short central Li−C^1 bond coupled with the rather long Li−C^2 and Li−C^3 bonds, ***TS3** is now a four-centered addition of the C^1−Li bond rather than a six-centered TS*. This structural feature was found to be a general feature of alkali metal allyl reactions.[19]

Similarly, the Li−C^3 bond in the γ-pathway (**TS4**) is very short, making now **TS4** a four-centered addition of (2-hydroxyethenyl)methyllithium to the olefin. This endo transition state accounts for the exclusive formation of the cis enol ether products **15**.

In summary, we have shown that the (alkoxy)allylmetal species is a useful nucleophile in olefin carbometalation in that it produces stereodefined allylic alcohol products and that its chelate structure helps to achieve a defined transition state leading to high levels of regio- and stereocontrol. The synthetic

(16) The tendency to break chelation must be larger in the real case of solution chemistry. Note that the use of HF/321A overestimates the electrostatic oxygen−zinc interaction over the metal−carbon interaction in **TS1** and **TS2** (likely the summation of basis set superposition error and lack of electron correlation), and consequently produces TSs keeping the zinc−oxygen chelation.

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(18) Since the acetal group (A) in **4** is lacking in the theortical model substrate, the exact numbers of the energy difference between the two TSs (**TS1** and **TS2**) are of no significance.

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utilities of the cyclopropanone acetal products have already been amply demonstrated.[1,6,9] The theoretical studies revealed the key role of the σ-allylic and π-allylic motifs in the allylmetal species in determining the regio- and stereochemistry of the allylmetalation reactions. Namely, the (alkoxy)allyllithium species is a π-allylmetal in nature and reacts via a [2 + 2]-type four-centered transition state, while the zinc species is a σ-allylmetal and reacts via a [2 + 4]-type six-centered transition state. To our best knowledge, the origin of the regiochemical diversity of allylic metal reactions has not been explicitly considered in terms of the structural dichotomy of the σ- and π-complexation. We speculate that similar principles will operate also in the addition reactions of other allylic metal species. Experimental and theoretical studies of enantioselective allylmetalation are under way.[8,20]

Computational Method

All calculation were performed with the Gaussian 94 program.[21] In the previous theoretical studies on the organozinc[22] and organocuprate reactions,[23] the DF calculations using the B3LYP/631A method gave qualitatively the same structures as those obtained at the MP2(FC) level of theory[24] and the B3LYP energies are quite close to the CCSD(T) values.[19] Therefore, in the present work, geometry optimization was performed (without symmetry assumption) by the B3LYP hybrid functional[25] with the basis set denoted as B3LYP/631A, which consists of the Ahlrichs all-electron SVP basis set[26] for Zn and 6-31G(d)[27] for the rest. Normal coordinate analysis (performed for all TSs) and natural charges[28] are calculated at the same level. The Cartesian coordinates of **TS1**−**4** are given in the Supporting Information.

Experimental Section

General. All ^{1}H NMR spectra were taken at 270, 400, or 500 MHz and ^{13}C NMR spectra at 67.5, 100, or 125 MHz using JEOL GX-270, EX-400, and GSX-500 instruments are reported in ppm (δ). IR spectra recorded on a JASCO IR-800 are reported in cm^{-1}. GC analysis was performed on SHIMADZU GC 8A, 14A, and 14B instruments with a capillary column (0.25 mm i.d. × 25 m) coated with HR-1 or HR-1701. Recycle preparative HPLC was performed on a Japan Analytical Industry LC-908 machine equipped with GPC columns (JAIGEL 1H and 2H) using $CHCl_3$ as an eluent.

Solvent. Anhydrous tetrahydrofuran (THF) and diethyl ether were purchased from Kanto Chemical Co. These ethereal solvents were dried over molecular sieves in a storage flask. The water content of the solvent was confirmed with a Karl Fischer Moisture Titrator (MKC-210, Kyoto Electronics Company) to be less than 10 ppm.

Materials. Unless otherwise noted, materials were purchased from Tokyo Kasei Co., Aldrich Inc., and other commercial suppliers and were either distilled or recrystallized before use. Alkyllithium reagents were purchased from Aldrich Inc. and Kanto Chemical Co. and titrated prior to used. Zinc chloride was purchased from Aldrich Inc., dried by refluxing in thionyl chloride,[29] and storred over P_2O_5 under nitrogen.

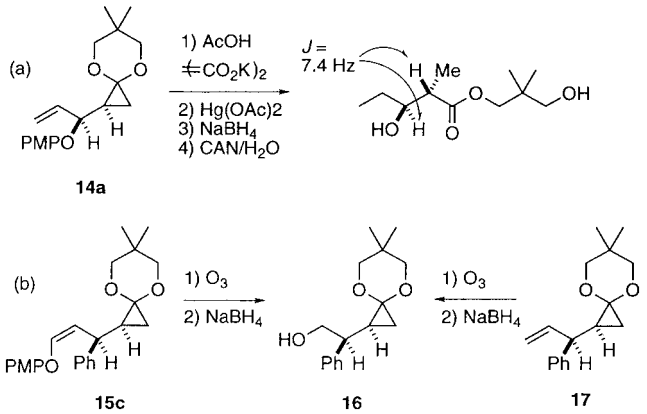
(2*R,1′*R**)-2-[1-(4-Methoxyphenoxy)-2-propenyl]cyclopropanone 1,3-(2,2-Dimethyl)propanediyl Acetal (14a, R^1 = R^2 = H; X = PMP) from 1aLi.** To a solution of *p*-methoxyphenyl allyl ether **5a** (3.0 mL, 20 mmol) in THF (75 mL) was added *sec*-butyllithium in cyclohexane (0.834 M, 24 mL, 20 mmol) at −60 °C. After 30 min, cyclopropenone acetal **4** (1.4 mL, 10 mmol) was added to the allylic lithium reagent. After 20 min, 1/15 N phosphate buffer solution was added to the reaction mixture and the mixture was separated into an aqueous layer and an organic layer. The aqueous layer was extracted with ethyl acetate 3 times. The combined organic layer was washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated in vacuo (5.44 g). The crude mixture was chromatographed on silica gel to obtain the title compound as a 91:9 mixture of regioisomers (assigned by ^{1}H and ^{13}C NMR in this and the following examples) of α-adduct **14a** (≥97% ds) and γ-adduct **15a** (3.04 g, 100%). **14a:** IR (neat) ν 3080, 2955, 2905, 2870, 2058, 1857, 1506, 1227 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75 (dd, J = 7.0, 7.0 Hz, 1 H), 0.80 (s, 3 H), 1.15 (s, 3 H), 1.19 (J = 7.0, 10.5 Hz, 1 H), 1.57 (ddd, J = 7.0, 8.9, 10.5 Hz, 1 H), 3.41 (dd, J = 1.6, 10.5 Hz, 1 H), 3.54 (dd, J = 1.6, 10.5 Hz, 1 H), 3.64 (d, J = 10.5 Hz, 1 H), 3.66 (d, J = 10.5 Hz, 1 H), 3.76 (s, 3 H), 4.09 (dd, J = 6.6, 8.9 Hz, 1 H), 5.17 (dd, J = 1.2, 10.9 Hz, 1 H), 5.22 (dd, J = 1.2, 17.1 Hz, 1 H), 5.92 (ddd, J = 6.6, 10.9, 17.1 Hz, 1 H), 6.80 (d, J = 9.3 Hz, 2 H), 6.86 (d, J = 9.3 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 22.1, 22.7, 29.7, 30.3, 55.6, 76.0 (2 C), 79.1, 90.0, 114.5 (2 C), 116.6, 117.4 (2 C), 136.9, 151.9, 154.0.

Elemental analysis was carried out for the isomeric mixture (as in all other cases). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7,95. Found: C, 70.76; H, 7.92.

The relative stereochemistry of the two chiral centers in **14a** was determined by conversion to an anti aldol followed by ^{1}H NMR analysis as described below according to in Scheme 3a.

2,2-Dimethyl-3-hydroxypropyl (2*R,3*R**)-3-hydroxy-2-methylpropanoate.** To a solution of (2*R**,1′*R**)-2-[1-(4-methoxyphenyl)-2-propenyl]cyclopropanone 1,3-(2,2-dimethyl)propanediyl acetal **14a** (306 mg, 1.2 mmol) in methanol (6.0 mL) was added potassium carbodiimide (3.39 g, 17 mmol) at 0 °C to give a suspension. Acetic acid (1.95 mL,

Scheme 3



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34 mmol) was added to the suspension over 3 min. After being stirred for 8 h, the mixture was washed with saturated sodium carbonate and water and then dried over $MgSO_4$. After evaporation in vacuo, the residual oil was chromatographed on silica gel to obtain (2*R**,1′*R**)-2-[1-(4-methoxyphenyl)propyl]cyclopropanone 1,3-(2,2-dimethyl)propanediyl acetal (318 mg, 85%).

To a solution of (2*R**,1′*R**)-2-[1-(4-methoxyphenyl)propyl]cyclopropanone 1,3-(2,2-dimethyl)propanediyl acetal (318 mg, 1.0 mmol) in methanol (1.5 mL) was added mercury(II) acetate (0.41 g, 1.5 mmol) at room temperature. After the solution was stirred for 5 min, THF (2.4 mL), saturated aqueous sodium chloride (1.2 mL) and 1 N aqueous HCl (1.2 mL) were added to the suspension. After being stirred for 19 h, the mixture was diluted with Et_2O (2 mL) and the mixture was separated into an aqueous layer and an organic layer. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residual oil was chromatographed on silica gel to obtain 2,2-dimethyl-3-hydroxypropyl (2*R**,3*R**)-2-(chloromercuro)methyl-3-(4-methoxy)-phenoxypropanoate (0.57 g, 98%).

To a solution of 2,2-dimethyl-3-hydroxypropyl (2*R**,3*R**)-2-(chloromercuro)methyl-3-(4-methoxy)phenoxypropanoate (0.57 g, 1.0 mmol) in THF (4.5 mL) were added 2 N NaOH in H_2O (3.7 mL, 7.4 mmol) and $NaBH_4$ (52.7 mg, 1.39 mmol) at room temperature. After being stirred for 1 h, the mixture was diluted with Et_2O and separated into an aqueous layer and an organic layer. The organic layer was dried over MgSO4 and concentrated in vacuo. The crude mixture was chromatographed on silica gel to obtain 2,2-dimethyl-3-hydroxypropyl (2*R**,3*R**)-3-(4-methoxy)phenoxy-2-methylpropanoate (0.28 g, 85%).

To a solution of 2,2-dimethyl-3-hydroxypropyl (2*R**,3*R**)-3-(4-methoxy)phenoxy-2-methylpropanoate (0.28 g, 0.86 mmol) in acetonitrile (8.4 mL) and water (2.1 mL) was added cerium ammonium nitrate (1.1 g, 2.1 mmol) at 0 °C, and then the mixture was warmed to room temperature. After 1.5 h, the reaction mixture was diluted with ethyl acetate and water. The mixture was separated into an aqueous layer and an organic layer. The aqueous layer was extracted with ethyl acetate 3 times. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The crude mixture was chromatographed on silica gel to obtain the title compound (169 mg, 90%): IR (neat) 3400, 2955, 2935, 2870, 1718, 1460, 1380, 1260, 1180, 1050 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 0.95 (s, 6 H), 0.99 (t, $J = 7.4$ Hz, 3 H), 1.23 (d, $J = 7.4$ Hz, 3 H), 1.45 (ddq, $J = 7.4$, 7.4, 14.1 Hz, 1 H), 1.61 (ddq, $J = 3.5$, 7.4, 14.1 Hz, 1 H), 2.56 (dq, $J = 7.4$, 7.4 Hz, 1 H), 3.40 (s, 2 H), 3.60 (ddd, $J = 3.5$, 7.4, 7.4 Hz, 1 H), 4.30 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) 9.7, 14.4, 21.5 (2 C), 27.5, 36.3, 45.4, 68.4, 69.7, 74.8, 176.4.

(2*R, ′*R**)-2-(2-Hydroxy-1-phenylethyl)cyclopropanone 1,3-(2,2-Dimethyl)propanediyl Acetal (16).** Into a solution of **15c** (22.6 mg, 0.059 mmol) in MeOH (0.42 mL) and CH_2Cl_2 (0.21 mL) was bubbled ozone at −70 °C. After 10 min, $NaBH_4$ (13.5 mg, 0.357 mmol) was added to a solution. The reaction mixture was warmed to 0 °C and stirred for 30 min. The mixture was concentrated in vacuo to get an oily product. The residual oil was diluted with Et_2O. The solution was washed with 1 N aqueous HCl, saturated NH_4Cl, and saturated NaCl and dried over $MgSO_4$. The organic solution was concentrated in vacuo. The crude mixture was chromatographed on silica gel to obtain **16** as a colorless oil (14.7 mg, 94%): ^1H NMR (400 MHz, $CDCl_3$) 0.65 (s, 3 H), 0.78 (dd, $J = 5.9$, 6.2 Hz, 1 H), 0.97 (s, 3 H), 1.21 (dd, $J = 5.9$, 10.3 Hz, 1 H), 1.59 (ddd, $J = 6.2$, 10.3, 10.3 Hz, 1 H), 1.71 (brs, 1 H), 2.58 (ddd, $J = 4.4$, 6.5, 10.3 Hz, 1 H), 3.07 (d, $J = 10.6$ Hz, 1 H), 3.32 (d, $J = 10.6$ Hz, 1 H), 3.34 (d, $J = 10.0$ Hz, 1 H), 3.46 (d, $J = 10.0$ Hz, 1 H), 3.77−3.92 (m, 2 H), 7.20−7.40 (m, 5 H).

(2*R,1′*R**)-2-[1-(4-Methoxyphenoxy)-2-propenyl]cyclopropanone 1,3-(2,2-Dimethyl)propanediyl Acetal (14a, R¹ = R² = H; X = PMP) from 1aZn.** To a solution of *p*-methoxyphenyl allyl ether **5a** (61 μL, 0.40 mmol) in THF (1.0 mL) was added *sec*-butyllithium in cyclohexane (0.841 M, 0.48 mL, 0.40 mmol) at −60 °C. After 30 min, zinc chloride in THF (1.0 M, 0.40 mL, 0.40 mmol) was added to the allylic lithium reagent and the mixture was warmed to 0 °C. After 30 min, cyclopropenone acetal **4** (28 μL, 0.20 mmol) was added to the allylic zinc reagent. After 12 h, 1/15 N phosphate buffer solution was added to the reaction mixture and the mixture was separated into an aqueous layer and an organic layer. The aqueous layer was extracted with ethyl acetate 3 times. The combined organic layer was washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated in vacuo. The crude mixture was chromatographed on silica gel to obtain the title compound as a single isomer of **14a** (>93% ds, 48 mg, 79%).

(*Z*)-2-[3-Methoxymethoxy-2-methyl-2-propenyl]cyclopropanone 1,3-(2,2-Dimethyl)propanediyl Acetal (15e, R¹ = Me, R² = H, X = MOM) from 1eLi. To a solution of methoxymethyl allyl ether **5e** (54 μL, 0.40 mmol) in THF (1.0 mL) was added *sec*-butyllithium in cyclohexane (0.952 M, 0.42 mL, 0.40 mmol) at −60 °C. After 30 min, cyclopropenone acetal **4** (28 μL, 0.20 mmol) was added to the allylic lithium reagent. After 2 h, 1/15 N phosphate buffer solution was added to the reaction mixture and the mixture was separated into an aqueous layer and an organic layer. The organic layer was extracted with ethyl acetate 3 times. The combined organic layer was washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated in vacuo (77.2 mg). The crude mixture was chromatographed on silica gel to obtain the title compound as a 96:4 mixture (as compared with the product mixture obtained in the next experiment) of the γ-adduct **15e** and the α-adduct **14e** (42.7 mg, 83%). **15e:** IR (neat) ν 2950, 2840, 1680, 1470, 1460, 1380, 1350, 1300, 1270, 1150, 1130, 1080, 1060, 1040 cm^{-1}; 1H NMR (500 MHz, $CDCl_3$) δ 0.56 (dd, $J = 6.2$, 6.2 Hz, 1 H), 0.97 (dd, $J = 6.2$, 9.4 Hz, 1 H), 1.00 (s, 3 H), 1.04 (s, 3 H), 1.29 (dddd, $J = 6.2$, 6.2, 8.6, 9.4 Hz, 1 H), 1.64 (d, $J = 0.5$ Hz, 3 H), 2.18 (dd, $J = 8.6$, 14.7 Hz, 1 H), 2.33 (dd, $J = 6.2$, 14.7 Hz, 1 H), 3.37 (s, 3 H), 3.53 (d, $J = 10.0$ Hz, 2 H), 3.54 (d, $J = 6.2$ Hz, 2 H), 4.74 (s, 2 H), 5.98 (d, $J = 0.5$ Hz, 1 H); 13C NMR (100 MHz, CDCl3) δ 17.3, 17.5, 22.2, 22.5, 23.3, 26.7, 30.6, 55.6, 75.9, 76.4, 90.6, 96.1, 115.5, 137.8.

(2*R,1′*R**)-2-(1-Methoxymethoxy-2-methyl-2-propenyl)cyclopropanone 1,3-(2,2-Dimethyl)propanediyl Acetal (14e, R¹ = Me, R² = H, X = MOM) from 1eZn.** To a solution of methoxymethyl allyl ether **5e** (54 μL, 0.40 mmol) in THF (1.0 mL) was added *sec*-butyllithium in cyclohexane (0.952 M, 0.42 mL, 0.40 mmol) at −60 °C. After 40 min, $ZnCl_2$ in THF (1.0 M, 0.40 mL, 0.40 mmol) was added to the allylic lithium reagent and the mixture was warmed to 0 °C. After 1 h, cyclopropenone acetal (28 μL, 0.20 mmol) was added to the allylic zinc reagent. After 19 h, 1/15 N phosphate buffer solution was added to the reaction mixture and the mixture was separated into an aqueous layer and an organic layer. The aqueous layer was extracted with ethyl acetate 3 times. The combined organic layer was washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated in vacuo (59.8 mg). The crude mixture was chromatographed on silica gel to obtain the title compound as a 96:4 mixture of the (2*R**,1′*R**) and (2*R**,1′*S**) isomers of **14e** (42.2 mg, 82%). anti-**14e**: IR (neat) ν 3075, 2955, 1650, 1470, 1450, 1170, 1140, 1095, 1040, 1020 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.52 (dd, $J = 6.5$, 6.5 Hz, 1 H), 1.02 (s, 3 H), 1.03 (s, 3 H), 1.05 (dd, $J = 6.5$, 10.0 Hz, 1 H), 1.51 (ddd, $J = 6.5$, 10.0, 10.6 Hz, 1 H), 1.76 (s, 3 H), 3.41 (s, 3 H), 3.53 (d, $J = 10.6$ Hz, 1 H), 3.54 (d, $J = 10.6$ Hz, 1 H), 3.58 (d, $J = 10.6$ Hz, 1 H), 3.68 (d, $J = 10.6$ Hz, 1 H), 3.73 (d, $J = 10.6$ Hz, 1 H), 4.65 (s, 2 H), 4.88 (s, 1 H), 4.92 (t, $J = 1.5$ Hz, 1 H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 15.7, 16.9, 22.3, 22.4, 27.6, 30.5, 55.9, 76.0, 76.2, 78.6, 90.4. 93.8, 114.4, 143.3.

Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.31; H, 9.22.

(2*R,1′*S**)-(*Z*)-2-[3-(4-Methoxyphenoxy)-1-phenyl-2-propenyl]cyclopropanone 1,3-(2,2-Dimethyl)propanediyl Acetal (15c, R¹ = H, R² = Ph, X = PMP) from 1cLi.** To a solution of cinnamyl *p*-methoxyphenyl ether **5c** (105.1 mg, 0.44 mmol) in THF (2.2 mL) was added *sec*-butyllithium in cyclohexane (0.811 M, 0.54 mL, 0.44 mmol) at −60 °C. After 30 min, the mixture was cooled to −70 °C and cyclopropenone acetal (28 μL, 0.20 mmol) was added to the allylic lithium reagent. After 2 h, 1/15 N phosphate buffer solution was added to the reaction mixture and the mixture was separated into an aqueous layer and an organic layer. The aqueous layer was extracted with ethyl acetate 3 times. The combined organic layer was washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated in vacuo (198 mg). The crude mixture was chromatographed on silica gel to obtain the title compound as a 88:12 mixture of the γ-adduct **15c** (>97% ds) and the α-adduct **14c** (61.8 mg, 81%): IR (neat) ν 3040, 2960, 2860, 2050,

1950, 1880, 1820, 1670, 1600, 1510, 1470, 1460, 1390, 1295, 1225 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.77 (dd, J = 6.2, 6.6 Hz, 1 H), 0.88 (s, 3 H), 0.94 (s, 3 H), 1.10 (dd, J = 6.2, 10.2 Hz, 1 H), 1.63 (ddd, J = 6.6, 10.0, 10.2 Hz, 1 H), 3.29 (d, J = 10.4 Hz, 1 H), 3.41−3.56 (m, 3 H), 3.62 (s, 3 H), 3.83 (d, J = 10.4 Hz, 1 H), 4.95 (dd, J = 6.2, 10.4 Hz, 1 H), 6.40 (dd, J = 0.8, 6.2 Hz, 1 H), 6.81−6.86 (m, 2 H), 6.90−6.95 (m, 2 H), 7.17−7.47 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 22.2, 22.4, 30.1, 30.4, 38.5, 55.7, 75.9, 76.3, 91.1, 114.6 (2 C), 114.9, 115.8, 117.5 (2 C), 126.0, 127.4 (2 C), 128.4 (2 C), 141.0. 144.5, 151.6.

Anal. Calcd for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42. Found: C, 76.29; H, 7.40.

The relative stereochemistry of the two chiral centers in **15c** was correlated to the known compound **17**[6c] via **16** as shown in Scheme 3b.

(2*R,1′*R**)−(*Z*)-2-[1-(4-Methoxyphenoxy)-2-methyl-2-propenyl]-cyclopropanone 1,3-(2,2-Dimethyl)propanediyl Acetal (14b, R¹ = Me, R² = H, X = PMP) from 1bZn.** To a solution of *p*-methoxyphenyl methallyl ether **5b** (71 μL, 0.40 mmol) in THF (1.0 mL) was added *sec*-butyllithium in cyclohexane (0.952 M, 0.42 mL, 0.40 mmol) at −60 °C. After 40 min, $ZnCl_2$ in THF (1.0 M, 0.40 mL, 0.40 mmol) was added to the allylic lithium reagent and the mixture was warmed to 0 °C. After 1 h, cyclopropenone acetal (28 μL, 0.20 mmol) was added to the allylic zinc reagent and the mixture was warmed to room temperature. After 5 h, 1/15 N phosphate buffer solution was added to the reaction mixture and the mixture was separated into an aqueous layer and an organic layer. The aqueous layer was extracted with ethyl acetate 3 times. The combined organic layer was washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated in vacuo (123 mg). The crude mixture was chromatographed on silica gel to obtain the title compound as a single isomer (>94% ds) of **14b** (56.4 mg, 89%): IR (neat) ν 3075, 2950, 1720, 1650, 1590, 1505, 1460, 1220 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.71 (dd, J = 6.8, 6.8 Hz, 1 H), 0.81 (s, 3 H), 1.17 (s, 3 H), 1.18 (dd, J = 6.8, 10.4 Hz, 1 H), 1.66 (ddd, J = 6.8, 9.6, 10.4 Hz, 1 H), 1.76 (s, 3 H), 3.42 (dd, J = 1.8, 10.4 Hz, 1 H), 3.55 (dd, J = 1.8, 10.6 Hz, 1 H), 3.65 (d, J = 10.6 Hz, 1 H), 3.68 (d, J = 10.4 Hz, 1 H), 3.75 (s, 3 H), 4.06 (d, J = 9.6 Hz, 1 H), 4.90 (s, 2 H), 6.76−6.86 (m, 4 H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 16.3, 17.1, 22.1, 22.7, 28.8, 30.3, 55.6, 76.0 (2 C), 81.7, 90.2. 113.7, 114.5 (2 C), 117.2 (2 C), 143.9, 151.9, 153.9.

Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.48; H, 8.18.

(*Z*)-2-[3-(4-Methoxyphenoxy)-2-methyl-2-propenyl]cyclopropanone 1,3-(2,2-Dimethyl)propanediyl Acetal (15b, R¹ = Me, R² = H, X = PMP) from 1bLi. To a solution of *p*-methoxyphenyl allyl ether **5b** (39 μL, 0.22 mmol) in THF (0.56 mL) was added *sec*-butyllithium in cyclohexane (0.811 M, 0.27 mL, 0.22 mmol) at −60 °C. After 30 min, the mixture was cooled to −70 °C, and then cyclopropenone acetal (28 μL, 0.20 mmol) was added to the prepared allylic lithium reagent. After 30 min, 1/15 N phosphate buffer solution was added to the reaction mixture and the mixture was separated into an aqueous layer and an organic layer. The aqueous layer was extracted with ethyl acetate 3 times. The combined organic layer was washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated in vacuo (87.8 mg). The crude mixture was chromatographed on silica gel to obtain the title compound as a 97:3 mixture of the γ-adduct **15b** and the α-adduct **14b** (50.6 mg, 79%): IR (neat) ν 2950, 2850, 2200, 2050, 1990, 1680, 1505, 1470, 1460, 1380, 1350, 1300, 1220, 1150, 1100, 1080, 1040 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.57 (dd, J = 6.2, 6.2 Hz, 1 H), 0.97 (s, 3 H), 1.01(dd, J = 6.2, 9.7 Hz, 1 H), 1.03 (s, 3 H), 1.29 (dddd, J = 6.2, 6.2, 8.3, 9.7 Hz, 1 H), 1.74 (d, J = 0.5 Hz, 3 H), 2.26 (dd, J = 8.3, 14.2 Hz, 1 H), 2.39 (dd, J = 6.2, 14.2 Hz, 1 H), 3.52 (s, 4 H), 3.78 (s, 3 H), 6.16 (d, J = 0.5 Hz, 1 H), 6.80−6.85 (m, 2 H), 6.87−6.91 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3, 17.6, 22.2, 22.5, 23.3, 26.8, 30.6, 55.7, 75.9, 76.4, 90.5, 114.5 (2 C), 117.0 (2 C), 119.6, 136.5, 151.9, 154.7.

(2*R,1′*S**)-(*Z*)-2-[3-(4-Methoxymethoxy)-2-methyl-1-phenyl-2-propenyl]cyclopropanone 1,3-(2,2-Dimethyl)propanediyl Acetal (15d, R¹ = Me, R² = Ph, X = MOM) from 1dLi.** To a solution of methoxymethyl ether **5d** (74 μL, 0.40 mmol) in THF (1.0 mL) was added *sec*-butyllithium in cyclohexane (0.811 M, 0.495 mL, 0.40 mmol) at −60 °C. After 30 min, the mixture was cooled to −70 °C, and then cyclopropenone acetal (28 μL, 0.20 mmol) was added to the prepared allylic lithium reagent. After 5 h, 1/15 N phosphate buffer solution was added to the reaction mixture and the mixture was separated into an aqueous layer and an organic layer. The aqueous layer was extracted with ethyl acetate 3 times. The combined organic layer was washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated in vacuo (108.7 mg). The crude mixture was chromatographed on silica gel to obtain the title compound as a single isomer (98% ds) of **15d** (60.6 mg, 91%): IR (neat) ν 3050, 3010, 2940, 1960, 1940, 1870, 1800, 1720, 1675, 1595, 1490, 1470, 1450, 1290 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.66 (dd, J = 6.2, 6.2 Hz, 1 H), 0.90 (s, 3 H), 0.95 (s, 3 H), 1.08 (dd, J = 6.2, 10.0 Hz, 1 H), 1.47 (d, J = 1.0 Hz, 3 H), 1.74 (ddd, J = 6.2, 10.0, 10.4 Hz, 1 H), 3.28 (d, J = 10.4 Hz, 1 H), 3.37 (s, 3 H), 3.43 (d, J = 10.4 Hz, 1 H), 3.52 (d, J = 9.0 Hz, 1 H), 3.57 (d, J = 9.0 Hz, 1 H), 3.94 (d, J = 10.0 Hz, 1 H), 4.78 (s, 2H), 6.10 (d, J = 1.0 Hz, 1 H), 7.18 (t, J = 6.8 Hz, 1 H), 7.28−7.33 (m, 2 H), 7.42 (d, J = 7.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 16.7, 22.3, 22.5, 26.7, 30.5, 40.6, 55.7, 75.9, 76.2, 91.5, 96.2, 117.6, 125.8, 127.6 (2 C), 128.2 (2 C), 138.7, 143.2.

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 71.97; H, 8.51.

(2*R,1′*R**)-(*Z*)-2-(3-Methoxymethoxy-1-phenyl-2-propenyl)cyclopropanone 1,3-(2,2-Dimethyl)propanediyl Acetal (15f, R¹ = H, R² = Ph, X = MOM) from 1fLi.** To a solution of cinnamyl methoxymethyl ether **5f** (71 μL, 0.40 mmol) in THF (1.0 mL) was added *sec*-butyllithium in cyclohexane (0.952 M, 0.42 mL, 0.40 mmol) at −60 °C. After 30 min, cyclopropenone acetal **4** (28 μL, 0.20 mmol) was added to the allylic lithium reagent. After 2 h, 1/15 N phosphate buffer solution was added to the reaction mixture and the mixture was separated into an aqueous layer and an organic layer. The aqueous layer was extracted with ethyl acetate 3 times. The combined organic layer was washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated in vacuo (103 mg). The crude mixture was chromatographed on silica gel to obtain the title compound as a 96:4 mixture of the γ-adduct and the α-adduct **15f** (49.5 mg, 78%): IR (neat) ν 3030, 2955, 2900, 1950, 1880, 1810, 1670, 1600, 1495, 1475, 1455, 1380, 1295, 1155, 1040 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.73 (dd, J = 5.6, 6.4 Hz, 1 H), 0.89 (s, 3 H), 0.93 (s, 3 H), 1.08 (dd, J = 5.6, 10.2 Hz, 1 H), 1.58 (ddd, J = 6.4, 10.2, 10.2 Hz, 1 H), 3.31 (d, J = 10.2 Hz, 1 H), 3.35 (s, 3 H), 3.37 (d, J = 10.2 Hz, 1 H), 3.45 (d, J = 10.2 Hz, 1 H), 3.51 (d, J = 10.2 Hz, 1 H), 3.70 (dd, J = 10.2, 10.2 Hz, 1 H), 4.71 (dd, J = 6.2, 10.2 Hz, 1 H), 4.79 (s, 2 H), 6.22 (d, J = 6.2 Hz, 1 H), 7.13−7.20 (m, 1 H), 7.27−7.32 (m, 2 H), 7.39−7.43 (m, 2 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 17.1, 22.2, 22.5, 30.4, 30.5, 38.5, 55.7, 75.9, 76.3, 91.1, 96.3, 111.8, 125.9, 127.4 (2 C), 128.3 (2 C), 142.1, 144.9.

(2*R,1′*R**)-2-{1-(1′-Methoxy-1′-methyl)ethoxy-2-propenyl}-cyclopropanone 1,3-(2,2-Dimethyl)propanediyl Acetal (14g, R¹ = R² = H; X = MME) from 1gZn.** To a solution of 1-methoxy-1-methyl-ethyl allyl ether (0.58 mL, 4.0 mmol) in THF (4.0 mL) was added *sec*-butyllithium in cyclohexane (0.980 M, 4.1 mL, 4.0 mmol) at −60 °C. After 1 h, $ZnCl_2$ in THF (1.03 M, 3.9 mL, 4.0 mmol) at −60 °C was added, and then the mixture was warmed to 0 °C and stirred for 30 min. Cyclopropenone acetal (0.28 mL, 2.0 mmol) was added to the allylic zinc reagent and then warmed to room temperature. After 9 h, 1/15 N phosphate buffer solution was added to the reaction mixture and the mixture was separated into an aqueous layer and an organic layer. The aqueous layer was extracted with ethyl acetate 3 times. The combined organic layer was washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated in vacuo. The crude mixture was chromatographed on silica gel to obtain the title compound **14g** as a colorless oil (0.258 g, 48%): IR (neat) ν 3080, 2960, 2860, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.45 (dd, J = 6.2, 6.2 Hz, 1 H), 0.91 (s, 3 H), 0.99 (dd, J = 6.2, 11.1 Hz, 1 H), 1.09 (s, 3 H), 1.34 (s, 3 H), 1.43 (s, 3 H), 1.46 (ddd, J = 6.2, 8.0, 11.1 Hz, 1 H), 3.27 (s, 3 H), 3.45−3.70 (m, 4 H), 3.92 (dd, J = 8.0, 8.0 Hz, 1 H), 5.03 (br d, J = 10.6 Hz, 1 H), 5.08 (br d, J = 17.7 Hz, 1 H), 5.89 (ddd, J = 8.0, 10.6, 17.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 22.1, 22.6, 25.1, 25.9, 30.2, 30.7, 49.1, 71.1, 75.9, 76.3, 90.4, 100.9, 114.2, 139.9.

Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.44; H, 9.43.

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Supporting Information Available: Cartesian coordinates of **9**−**13** and **TS1**−**TS4** and values of imaginary frequencies for TSs (4 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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