Stereochemical and Mechanistic Studies on Conjugate Addition of Organocuprates to Acyclic Enones and Enoates: Simple Rule for Diastereofacial Selectivity

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Systematic studies of organocuprate conjugate additions to three pairs of γ-epimeric and geometrically isomeric γ-chiral acyclic enones (**1a**, **2a**; **1b**, **2b**; and **3**, **4**) and two pairs of γ-chiral acyclic enoates (**5**, **6** and **7**, **8**) allowed us to generalize diastereofacial selectivity of these reactions. The diastereoselectivity depended on the double-bond geometry, the configuration at the γ-position, and the reaction conditions. In reactions without activating additives, cuprate added to the *si*-face of the geometrically isomeric pair of *E*- and *Z*-enones (**1a** and **2a**) with high diastereoselectivity (98%), while their epimers at the γ-position (**3** and **4**) yielded *re*-facial adduct preferentially (86−97%). Addition of TMSCl and HMPA together not only accelerated the addition reaction but also completely changed the pattern of π-facial selectivity. In reactions containing those additives, cuprates added to isomeric *E*- and *Z*-enones with reverse facial selectivity: *E*-enone **1a** gave the *si*-facial adduct exclusively, whereas isomeric *Z*-enone **2a** yielded the *re*-facial adduct with high selectivity (97%). Their γ-epimers gave opposite results; namely, the *E*-isomer **3** reacted with *re*-facial selectivity (97%), while the *Z*-isomer **4** reacted with *si*-facial selectivity (75%). Under conditions where both TMSCl and HMPA were present, even the enoates (**5**−**8**) reacted efficiently with similarly reverse and high facial selectivity. On the basis of these results, we postulate a general and clear-cut rule to predict diastereofacial selectivity of cuprate conjugate additions in which a possibility of *Z*−*E* isomerization of starting enones is taken into account as a crucial determinant.

Conjugate additions of organocuprates to α,β-unsaturated carbonyl compounds are widely applicable versatile C−C bonding-forming reactions in organic synthesis.[1] Addition reactions to conjugated carbonyl compounds having a chiral center at the γ-position are of particular importance both from stereochemical and synthetic viewpoints. Recently, much attention has been focused on developing a diastereoselective version of these reactions.[2] Diastereoselective conjugate addition to chiral cyclic enones has already been used in organic syntheses.[1,3] However, the diastereofacial selectivity of the reaction with *acyclic enones* is difficult to control, due to their greater conformational flexibility and possibility of geometrical isomerization of the double bond under the reaction conditions.[4] Diastereoselectivity of organocuprate conjugate additions to acyclic γ-alkoxy enoates has been extensively studied[2m,n] in which, however, a unified mechanism to explain their stereochemical results has not been presented.

During the synthetic study of conformationally restricted vitamin D analogs,[5] which is part of our research program to clarify the receptor bound conformation of

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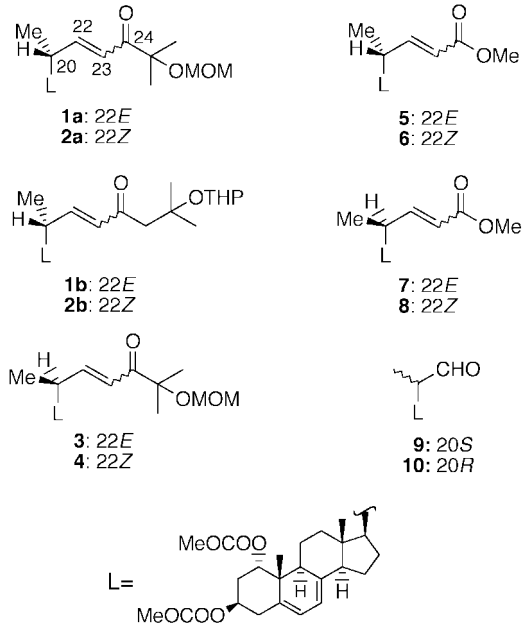
Chart 1



1α,25-dihydroxyvitamin D_3, we found highly diastereoselective conjugate addition of Me_2CuLi to γ-chiral *E*- and *Z*-enones (**1a** and **2a**, Chart 1).[6] The selectivity of these cuprate additions was highly dependent on the reaction conditions and on the geometry of the enones. This type of compounds having a bulky substituent at the γ-position is suitable for studying the effect of the γ-substituent on the facial selectivity of α,β-unsaturated carbonyl compounds. To generalize the diastereoselectivity of organocuprate conjugate addition to γ-chiral α,β-unsaturated carbonyl compounds, we synthesized three *E*,*Z* pairs of γ-chiral enones (**1a**, **2a**; **1b**, **2b**; and **3**, **4**) and two *E*,*Z* pairs of γ-chiral enoates (**5**, **6** and **7**, **8**) and systematically examined the reactions of organocuprates using these compounds mainly under two extreme conditions. These compounds are assumed to be nearly optimum substrates to systematically investigate the facial selectivity of *acyclic enones and enoates* because two enone pairs (**1a**, **2a** and **3**, **4**) are epimers each other at the γ-chiral center and enoate pairs (**5**, **6** and **7**, **8**) are also epimeric at the γ-position. In the present study, we recognized that π-facial selectivity cannot be discussed neglecting *Z*−*E* isomerization of substrates. Here, we report the optimum conditions to achieve highly diastereoselective addition of cuprates and a simple rule to predict diastereofacial selectivity.

Results

Synthesis of γ-Chiral *E*- and *Z*-Enones and *E*- and *Z*-Enoates. Three *E* and *Z* isomeric pairs of enones (**1a**, **2a**; **1b**, **2b**; and **3**, **4**) and two pairs of enoates (**5**, **6** and **7**, **8**), which include epimeric pairs at the γ-chiral center [C(20)], were used as substrates for the cuprate additions in the present study. The *E*-enones **1a**,**b** and **3** were synthesized by aldol condensation of aldehydes **9** and **10** with appropriate ketones, and the corresponding *Z*-enones **2a**,**b** and **4** were prepared from the *E*-enones **1a**,**b** and **3** by photochemical isomerization as reported.[5] *E*- and *Z*-enoates **5**−**8** were synthesized by Horner−Wadsworth−Emmons reaction of the aldehydes **9** and **10**. Reaction of the aldehydes **9** and **10** with trimethyl phosphonoacetate afforded *E*-enoates **5** and **7**, respectively, and with bis(2,2,2-trifluoroethyl)[(methoxycarbonyl)methyl]phosphonate[7] yielded *Z* isomers **6** and **8**, respectively.

Reaction of γ-Chiral Enones with Me_2CuLi·LiI without Activating Additives. The reactions of the three pairs of *E*- and *Z*-enones (**1a**, **2a**; **1b**, **2b**; and **3**, **4**) with various organocuprates were examined under various conditions, and the results are summarized in Table 1 and Scheme 1. Under normal conditions of the Gilman reaction (THF, 0 °C) without any additives, *E*-enones **1a** and **1b** reacted with Me_2CuLi·LiI (prepared from MeLi and CuI) to give methylated products **11a** and **11b**, respectively, in high yield with high diastereoselectivity (98% *si*-face) (Table 1, entries 1 and 2). Under similar conditions, Me_2CuLi·LiI added to the reverse (*re*) face of γ-epimer **3**, giving **15a** in high yield (91%) with high selectivity (97%) (Table 1, entry 3). The *Z*-enones **2a** and **2b** reacted with the same cuprate to give the same products (**11a** and **11b**, respectively) as those from their *E* isomers (**1a** and **1b**) with high facial selectivity (98% *si*-face). γ-Epimeric *Z*-enone **4** showed a similar trend of facial selectivity (86% *re*-face), giving the same product **15a** as from its *E*-isomer **3** (Table 1, entry 6).

Because of steric hindrance, the *Z*-isomers reacted more slowly than the corresponding *E*-enones as the following examples show (Table 1, entries 4−6). In the reactions of isomeric 24-homoenones **1b** and **2b**, which have an active hydrogen at the 24a position (Table 1, entries 2 and 5), *E*-isomer **1b** underwent conjugate addition exclusively (84%), whereas β-elimination predominated in the reaction of *Z*-isomer **2b** (43%), indicating the addition to the *Z*-enone to be sluggish. In the reaction with *Z*-enone **4** (Table 1, entry 6), a large amount (55%) of the starting enone was recovered under the same conditions as for the *E*-isomer **3** (Table 1, entry 3). *E*-Enone **1a** reacted slowly even at −78 °C, but the *Z*-isomer **2a** did not react at all (Table 1, entries 7 and 8).

It should be noted that under conditions without activating additives pairs of *E*- and *Z*-enones (**1a**, **2a**; **1b**, **2b**; and **3**, **4**) gave the same addition products (**11a**, **11b**, and **15a**, respectively) with similarly high facial selectivity (98−86%). Thus, *the diastereofacial selectivity does not depend on the geometry of the enones under these conditions*. This suggests that *Z* isomers (**2a**,**b** and **4**) react after isomerization to the corresponding *E* isomers (**1a**,**b** and **3**, respectively) or that the addition to *E*- and *Z*-enones proceeds via a common intermediate. The former possibility is more probable because the facial selectivity of the *Z* isomers under these conditions is identical with that of the corresponding *E* isomer under the conditions including activating additives (see below). Since the facial selectivity is controlled by the thermodynamically more stable substrate, we tentatively term this type of facial selection *substrate-thermodynamically controlled facial selection*.

Reaction of γ-Chiral Enones with Me_2CuLi·LiI in the Presence of TMSCl. Addition of TMSCl strongly accelerated the cuprate addition. Under these conditions, enone **1a** reacted rapidly with Me_2CuLi·LiI even at −78 °C to give **11a**, after removal of TMS group, in a yield of

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Table 1. Reaction of *E*- and *Z*-Enones 1−4 with R_2CuLi under Various Conditions

		R_2CuLi[a]					
entry	enone	R	CuX	TMSCl[b]	HMPA[b]	T, °C	products, ratio[c] (total isolated yield, %)
1	**1a**	Me	CuI			0	**11a**:**12a**, 98:2 (91)
2	**1b**	Me	CuI			0	**11b**:**12b**, 98:2 (84)
3	**3**	Me	CuI			0	**15a**:**16a**, 97:3 (91)
4	**2a**	Me	CuI			0	**11a**:**12a**, 98:2 (78)
5	**2b**	Me	CuI			0	**11b**:**12b**, 98:2 (35)[d]
6	**4**	Me	CuI			0	**15a**:**16a**, 86:14 (35)[e]
7	**1a**	Me	CuI			−78	**11a**:**12a**, >98:2 (9)[f]
8	**2a**	Me	CuI			−78	(0)[f]
9	**1a**	Me	CuI	5		−78	**11a**:**12a**, 100:0 (91)
10	**1a**	Me	CuI	5	5	−78	**11a**:**12a**, 100:0 (95)
11	**1b**	Me	CuI	5	5	−78	**11b**:**12b**, >98:2 (90)
12	**3**	Me	CuI	5	5	−78	**15a**:**16a**, 97:3 (90)
13	**2a**	Me	CuI	5		−78 to −35	**11a**:**12a**, 48:52 (67)[g]
14	**2a**	Me	CuI	5	5	−78	**11a**:**12a**, 3:97 (62)[h]
15	**2a**	Me	CuI	10	10	−78	**11a**:**12a**, 3:97 (75)[h]
16	**2b**	Me	CuI	5	5	−78	**11b**:**12b**, 3:>97 (72)
17	**4**	Me	CuI	5	5	−78	**15a**:**16a**, 25:75 (60)[i]
18	**1a**	Bu	CuBr·Me_2S			−30 to 0	**11c**:**12c**, 95:5 (37)
19	**2a**	Bu	CuBr·Me_2S			−30 to 0	**11c**:**12c**, 61:39 (21)
20	**1a**	Bu	CuBr·Me_2S	5	5	−78	**11c**:**12c**, >98:2 (86)
21	**2a**	Bu	CuBr·Me_2S	5	5	−78	**11c**:**12c**, 3:>97 (72)[h]
22	**3**	Bu	CuBr·Me_2S	5	5	−78	**15b**:**16b**, 100:0 (88)
23	**4**	Bu	CuBr·Me_2S	5	5	−78	**15b**:**16b**, 3:97 (78)[i]
24	**1a**	vinyl	CuBr·Me_2S	5	5	−78	**11d**:**12d**, 100:0 (91)
25	**3**	vinyl	CuBr·Me_2S	5	5	−78	**15c**:**16c**, 100:0 (73)
26	**4**	vinyl	CuBr·Me_2S	5	5	−78	**15c**:**16c**, 60:40 (14)[j]

[a] Four equivalents of R_2CuLi was used in all reactions except for entry 15 in which 8 equiv was used. [b] Molar equivalents. [c] Ratio was determined by ^1H NMR and HPLC. [d] Cross-conjugate diene **19** was obtained in 43% yield. [e] Starting enone was recovered in 55% yield. [f] Most of the starting enone was recovered without *E*−*Z* isomerization. [g] Starting enone **2a** was recovered in 30% yield. [h] Diene **20** was obtained in 10% yield in entry 14, 13% in entry 15, and 10% in entry 21. [i] Diene **21** was obtained in 17% yield in entry 17 and 8% in entry 23. [j] Diene **22** was obtained in 54% yield.

91% with 100% facial selectivity (Table 1, entry 9).[8] Addition of HMPA in addition to TMSCl further accelerated the reaction and improved the yield of the adduct (95%) (Table 1, entry 10). The effect of TMSCl and HMPA was even more dramatic in the reactions of *Z*-isomers. TMSCl not only accelerated the reaction of the *Z*-enone (**2a**) but also significantly changed the facial stereoselectivity (Table 1, entry 13): *re*-facial adduct **12a** became the major (52% selectivity) product. HMPA in addition to TMSCl further accelerated the reaction and reversed the facial selectivity of *Z*-enones almost completely: **2a** gave a methylated product (**12a**) with 97% *re*-facial selectivity (compare Table 1, entry 15 vs entry 4). HMPA alone (without TMSCl) affected neither the rate nor the diastereoselectivity of the reactions of **1a** and **2a** (data not shown). Under these conditions, γ-epimeric *E*,*Z*-pair **3** and **4** showed similarly reverse facial selectivity: *E*-isomer **3** yielded the *re*-facial adduct **15a** as a major product (97%) (Table 1, entry 12), while *Z*-isomer **4** afforded preferentially (75%) the *si*-facial adduct **16a** (Table 1, entry 17). However, under these conditions, the sterically hindered *Z*-enones (**2a** and **4**) underwent a side reaction (10−17%) where an OMOM group at C(25) was eliminated concomitant with the silylation of the ketone function to afford **20** and **21** (Chart 2), respectively. The stereochemistry at C(22) of the conjugate addition products was unambiguously determined by X-ray crystallographic analysis of the derivative of **11a** as reported.[6]

The diastereofacial selectivity of the cuprate addition under these conditions *is dependent on the geometry of the enones*. Thus, it is clear that *the facial selectivity and the mechanism of cuprate addition under the conditions with activating additives* (*TMSCl and HMPA*) *are distinct from those under the conditions without these additives*. We term this type of diastereofacial selection *kinetically controlled facial selection*.

Reaction of γ-Chiral Enones with Other Organocuprates. Bu_2CuLi·LiI (prepared from *n*-BuLi and CuI) did not react at all with enones **1**−**4** under either the normal or TMSCl−HMPA-containing conditions. But Bu_2CuLi·LiBr·DMS (made from *n*-BuLi and CuBr·Me_2S) added to these enones. Under normal conditions without activating additives, the reaction of enones (**1a** and **2a**) with Bu_2CuLi·LiBr·DMS gave poor results, affording the adduct (**11c**) in low yield (21−37%): The reaction was too sluggish at −30 °C so that the temperature was raised to 0 °C, but at that temperature the reagent seemed to be unstable because the reagent color changed and the reaction yielded precipitates.

In the presence of TMSCl and HMPA, Bu_2CuLi·LiBr·DMS reacted smoothly with all enones (**1a**, **2a**, **3**, and **4**) examined even at −78 °C to give adducts (**11c**, **12c**, **15b**, and **16b**, respectively) in high yield (72−88%) with high stereoselectivity (97−100%) (Table 1, entries 20−23). The facial selectivity with this reagent was the same as with Me_2CuLi·LiI under similar conditions. The cuprate added to the *si*-face of *E*-enone **1a** and the *re*-face of *Z*-enone **2a** with more than 97% selectivity, while with their γ-epimers (**3** and **4**), the cuprate added to the *re*-face of the *E*-enone **3** and the *si*-face of the *Z*-enone **4**. *Z*-Enones (**2a** and **4**) yielded some elimination products (**20** and **21**) as in the reactions with Me_2CuLi·LiI.

$(Vinyl)_2CuLi$·LiBr·DMS similarly added to γ-epimeric *E*-enones **1a** and **3** under the conditions with activating

(8) Under the conditions including TMSCl, all conjugate addition products were obtained as enol silyl ethers and not as free ketones.[5,6] Spectral data of **13a**, **14a**, **17a**, and **18a** have been reported in our previous papers.[5a,d]

Scheme 1

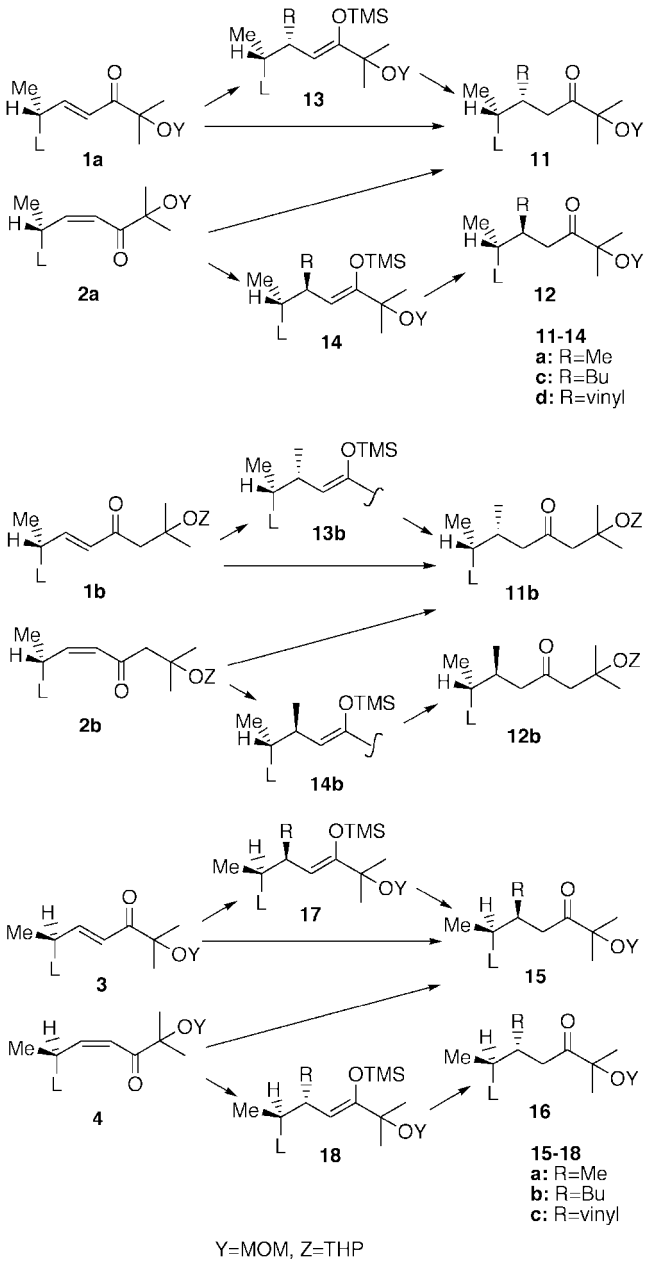
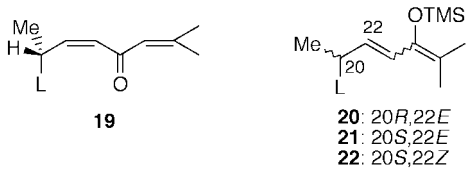


Chart 2



additives providing vinyl adducts **11d** and **15c**, respectively, with 100% *si*- and *re*-facial selectivity, respectively (Table 1, entries 24 and 25). However, the reaction of $(vinyl)_2CuLi\cdot LiBr\cdot DMS$ with sterically most demanding *Z*-enone **4** yielded mainly the elimination product **22** (54%), and the adducts (**15c** and **16c**) were obtained in poor total yield (14%) with low (60%) facial selectivity (Table 1, entry 26).

Interestingly, the *Z*-configuration at C(22) is retained in the byproduct **22**, which was obtained from the reaction with $(vinyl)_2CuLi\cdot LiBr\cdot DMS$, whereas the same double bond in the byproducts **20** and **21**, which were produced from the reaction with $Me_2CuLi\cdot LiI$ and $Bu_2CuLi\cdot LiBr\cdot DMS$, has been isomerized from *Z* to *E*.

Table 2. Reaction of *E*- and *Z*-Enoates 5−8 with R_2CuLi[a]

entry	enoate	R_2CuLi[b] R	product, ratio[c] (total isolated yield, %)
1	**5**	Me	**23a**:**24a**, >97:3 (82)
2	**6**	Me	(0)
3	**5**	Bu	**23b**:**24b**, 94:6 (93)
4	**6**	Bu	**23b**:**24b**, 14:86 (91)
5	**7**	Bu	**27b**:**28b**, 100:0 (92)
6	**8**	Bu	**27b**:**28b**, 21:79 (78)

[a] Enoates **5**−**8** were treated with R_2CuLi (4 equiv) in the presence of TMSCl (5 equiv) and HMPA (5 equiv) at −30 °C for 1 h. [b] Reagents were prepared from $CuBr\cdot Me_2S$. [c] Ratio was determined by ^1H NMR and HPLC.

Reaction of γ-Chiral Enoates with Organocuprates. The reactions of enoates **5**−**8** with cuprates are summarized in Table 2. Generally α,β-unsaturated esters are less reactive toward cuprate addition than the corresponding ketones. Thus, neither $Me_2CuLi\cdot LiI$ nor $Me_2CuLi\cdot LiBr\cdot DMS$ reacted with enoates **5**−**8** at all in the absence of activating additives (TMSCl and HMPA).

In the presence of TMSCl and HMPA, $Me_2CuLi\cdot LiBr\cdot DMS$ reacted with the *E*-enoate **5** (Table 2, entry 1) at slightly higher temperature (−30 °C) to yield **23a** in good yield (82%) with high selectivity (*si*-face, 97%), whereas $Me_2CuLi\cdot LiI$ did not react at all. The *Z*-isomer **6** did not react with $Me_2CuLi\cdot LiBr\cdot DMS$ or $Me_2CuLi\cdot LiI$ under the same conditions (Table 2, entry 2).

$Bu_2CuLi\cdot LiBr\cdot DMS$ was more reactive than $Me_2CuLi\cdot LiBr\cdot DMS$. In the presence of TMSCl and HMPA, both γ-epimeric *E*,*Z*-enoate pairs (**5**, **6** and **7**, **8**) reacted with $Bu_2CuLi\cdot LiBr\cdot DMS$ at −30 °C to give conjugate addition products in high yields (Table 2, entries 3−6).[9] The facial selectivity of these enoates under these conditions was dependent on the geometry and the configuration at γ-position of the starting enoates and was similar to that observed in the reaction with corresponding enones **1**−**4**: *E*-enoate **5** gave *si*-facial adduct **23b** (94% selective), the *Z*-isomer **6** yielded *re*-facial adduct **24b** (86%), γ-epimeric *E*-enoate **7** gave *re*-facial adduct **27b** (100%), and the *Z*-isomer **8** afforded *si*-facial adduct **28b** (79%) (Scheme 2).[10]

Discussion

Diastereofacial Selectivity and Conditions. We studied diastereofacial selectivity of the conjugate additions of organocuprates using γ-epimeric three *E*,*Z*-isomeric pairs of enones (**1a**, **2a**; **1b**, **2b**; and **3**, **4**) and two γ-epimeric *E*,*Z*-pairs of enoates (**5**, **6** and **7**, **8**). Diastereofacial selectivity of these enones and enoates was highly dependent on the reaction conditions and the double-bond geometry and the configuration at γ-position of the substrates.

Under normal conditions of the Gilman reaction, cuprates added preferentially to the *si*-face (98%) of both

(9) The silyl ketene acetals (**25**, **26**, **29**, and **30**) were unstable and were hydrolyzed spontaneously upon a silica gel column chromatography. However, they were detected by ^1H NMR in the extracts after workup.

(10) The configuration at C(22) of the conjugate addition products (**23**, **24**, **27**, and **28**) was assigned by analogy with the facial selectivity of the cuprate addition to enones **1**−**4**. The *E*- and *Z*-geometrically isomeric pair of enoates (**5**−**8**) showed reverse facial selectivity, which was the same as that of enones **1**−**4**, so that both the mechanism and facial selectivity of the reaction with enoates **5**−**8** are assumed to be the same as those of the reaction with enones **1**−**4**.

Scheme 2

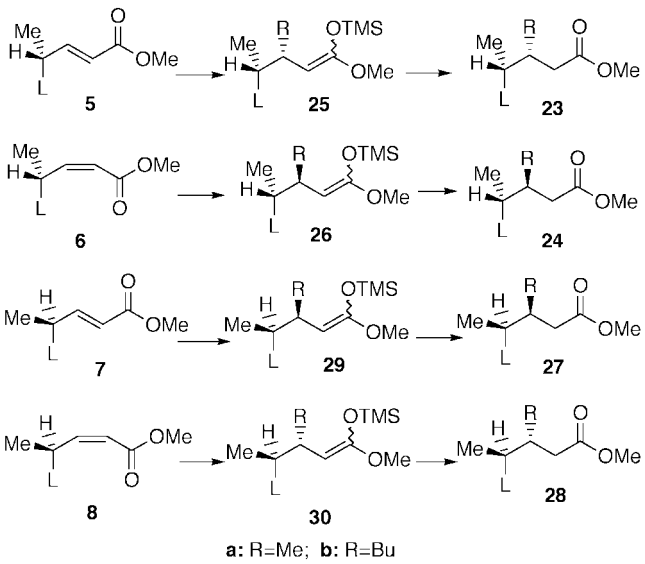


Table 3. Time Course of Reaction of *Z*-Enone 2a with Me_2CuLi·LiI[a]

	compound ratio[b] (%)		
time (min)	*Z*-enone **2a**	*E*-enone **1a**	methyl adduct **11a**
0	100	0	0
5	60	0	40
15	52	0	48
40	40	0	60 (98% selec)

[a] *Z*-Enone **2a** was treated with Me_2CuLi·LiI (2 equiv) at −10 °C. [b] Ratio was determined by HPLC.

E- and *Z*-isomers of 20*R*-enones **1a,b** and **2a,b**, while the same reagent added preferentially to the *re*-face (86−97%) of both geometric isomers of 20*S*-enones **3** and **4**. Thus the geometry of the double bond of enones had no effect on the facial selectivity under these conditions, whereas the configuration at the γ-position had crucial effect reversing the facial selectivity. These results suggest that *Z*−*E* isomerization of the double bond of enones occurs prior to the addition of the nucleophiles.[11a] However, the isomerization of *Z*-enone **2a** to *E*-enone **1a** was not detected even when the reaction of **2a** was investigated in detail (Table 3), most likely because the *E*-isomer **1a** reacts with the cuprate exceedingly faster than the *Z*-isomer **2a**.[11b] Supporting this assumption, when a mixture of the *E*- and *Z*-enones **1a** and **2a** (1:1) was treated with 1 equiv of Me_2CuLi·LiI (THF, −10 °C), the *E*-isomer **1a** rapidly disappeared (within 5 min) but the *Z*-isomer **2a** reacted only after all *E*-isomer **1a** was consumed (Table 4). Under these conditions without activating additives, the diastereofacial selectivity of *Z*-enone **2a** is the same as that of the corresponding *E*-enone **1a** under conditions including activating additives (kinetic conditions) and the opposite of the selectivity of itself (**2a**) under kinetic conditions (see below).

TMSCl and HMPA dramatically accelerated the addition reaction[12] and, furthermore, changed the pattern of diastereofacial selectivity: *the facial selectivity was switched from substrate-thermodynamic control to kinetic control.* HMPA alone did not affect the rate or the selectivity of the addition reaction, but it augmented the

(11) (a) In the conjugate additions of organocuptrates to enones, isomerization of *Z*-enone to *E*-enone has frequently been observed.[2c,d] (b) *Z* to *E* isomerization was observed in byproducts **20** and **21**.

Table 4. Competition Reaction of *E*- and *Z*-Enones (1a and 2a)[a]

	compound ratio[b] (%)		
time (min)	*E*-enone **1a**	*Z*-enone **2a**	methyl adduct **11a**
0	50	50	0
5	0	50	50
15	0	43	57
40	0	40	60 (98% selec)

[a] A mixture of **1a** and **2a** (1:1) was treated with Me_2CuLi·LiI (1 equiv) at −10 °C. [b] Ratio was determined by HPLC.

effect of TMSCl. TMSCl is assumed to increase the electrophilicity of the enones by interacting with the carbonyl oxygen, and HMPA intensifies this effect by removing the lithium ion coordinating with carbonyl oxygen.[13] Under conditions including TMSCl and HMPA, the facial selectivity depended on the geometry of the double bond of substrates. The nucleophile added exclusively to the *si*-face of *E*-enones **1a**,**b**, whereas the same reagent added preferentially to the *re*-face (97%) of *Z*-enones **2a**,**b**. Under these conditions, the facial selectivity was assumed to depend on the conformation of the starting enones. Consequently, we calculated the minimum-energy conformation of enones **1**−**4** using the molecular mechanics method (MMX).[14] These calculations showed that the *E*-enones have two minimum energy conformations, **A** and **B** for **1** and **C** and **D** for **3**, while *Z*-enones have only one, **B** for **2** and **D** for **4** (Scheme 3). Since cuprate additions are nucleophilic reactions, the reagent should approach the double bond on an obtuse angle.[15] Thus, we assumed the favorable transition states of the *E*-enones, **1** and **3**, to be **A′** and **C′** (Felkin−Anh type), respectively, the reagent attacking as shown by the arrow in Scheme 3.[16] Similarly, the transition-state conformations of the *Z*-enones **2** and **4** were considered to be **B′** and **D′**, respectively. Thus, the respective major products derived from **1**−**4** are expected to be **11**, **12**, **15**, and **16**. All the experimental results agree with these postulations.[17] The reactivity of the *Z*-isomers is lower than that of the corresponding *E*-isomers because the reagent must attack the double bond from a sterically more congested direction (arrows in **B′** and **D′** in Scheme 3). Under these conditions, *E*,*Z*-pairs of enoates (**5**, **6** and **7**, **8**) reacted efficiently with similarly reverse facial selectivity.

Effect of Copper(I) Salt. The activity of R_2CuLi has been known to be influenced by the Cu(I) salt used for the preparation of the reagent.[18] Similarly, in the

(12) This effect of TMSCl and HMPA has been previously observed.[2c,d,12a−d] (a) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025−4028. (b) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Ibid*. **1986**, *27*, 4029−4032. (c) Bertz, S. H.; Dabbagh, G. *Tetrahedron* **1989**, *45*, 425−434. (d) Bertz, S. H.; Smith, R. A. J. *Ibid*. **1990**, *46*, 4091−4100.

(13) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868−2877.

(14) MMX (an enhanced version of MM2) was calculated using the software PCMODEL (Serena Software, Bloomington, IN).

(15) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Richard, Y. L.; Loncharich, R. J. *Science* **1986**, *231*, 1108−1117.

(16) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199−2204. Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61−70.

(17) The configuration at C(22) of **11a** was unequivocally determined to be *R* by X-ray analysis of its derivative so that that of **12a** was *S*.[6] The configurations of other cuprate addition products **15**, **16**, **23**, **24**, **27**, and **28** were assigned on the basis of an assumption that those cuprate additions operate via a similar mechanism and hence have similar facial selectivity.

Scheme 3

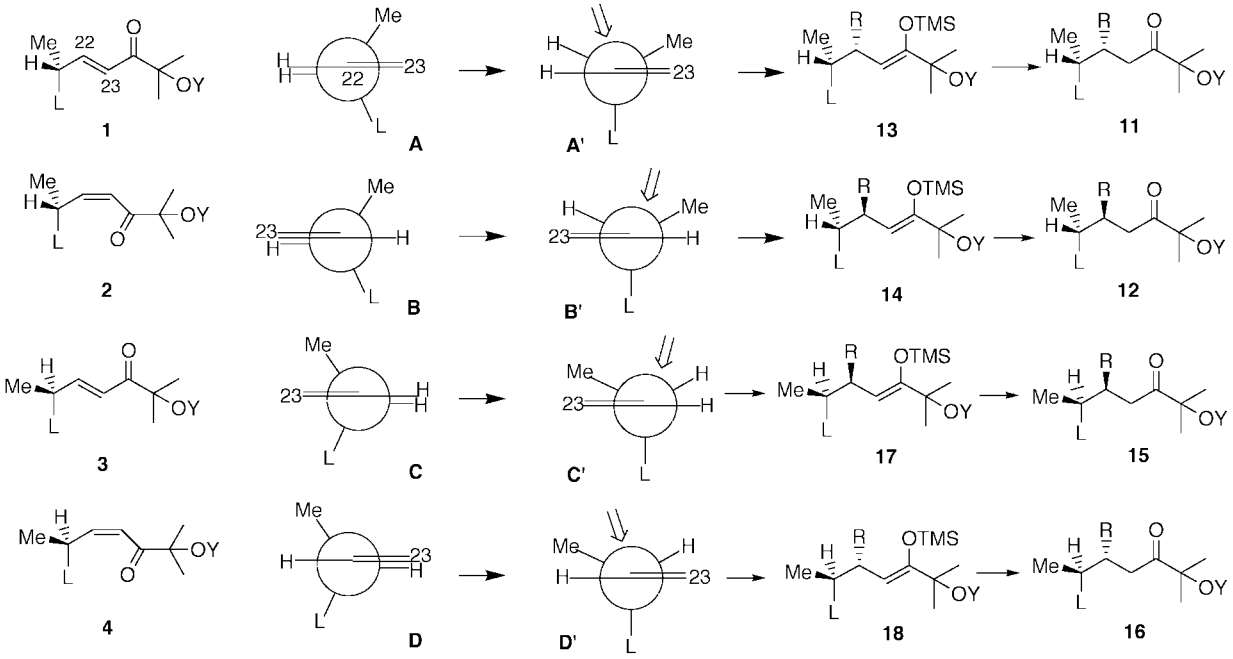


Table 5. Effect of Cu(I) Salt on Cuprate Addition[a]

entry	substrate	R_2CuLi	Cu(I) salt	yield of conjugate addition products (%)
1	**1a**	Me_2CuLi	CuI	95
2	**2a**	Me_2CuLi	CuI	75
3	**5**	Me_2CuLi	CuI	0
4	**6**	Me_2CuLi	CuI	0
5	**5**	Me_2CuLi	CuBr·Me_2S	82
6	**6**	Me_2CuLi	CuBr·Me_2S	0
7	**1a**	Bu_2CuLi	CuI	0
8	**2a**	Bu_2CuLi	CuI	0
9	**5**	Bu_2CuLi	CuI	0
10	**6**	Bu_2CuLi	CuI	0
11	**1a**	Bu_2CuLi	CuBr·Me_2S	86
12	**2a**	Bu_2CuLi	CuBr·Me_2S	72
13	**5**	Bu_2CuLi	CuBr·Me_2S	93
14	**6**	Bu_2CuLi	CuBr·Me_2S	91

[a] Reactions were conducted in the presence of TMSCl and HMPA at −78 °C for enones **1a** and **2a** and at −30 °C for enoates **5** and **6**. Each molar equivalent of R_2CuLi, TMSCl, and HMPA was 8, 10, and 10 in entry 2, and 4, 5 and 5 in others.

present study, the choice of Cu(I) salt used was crucial in the cuprate additions. The effect of Cu(I) salt on the addition to the enones and enoates is summarized in Table 5. Me_2CuLi·LiI reacted with enones **1a** and **2a** to give conjugate addition products in high yield (Table 5, entries 1 and 2) but did not react at all with enoates **5** and **6** (Table 5, entries 3 and 4). However, Me_2CuLi·LiBr·DMS did react with *E*-enoate **5** to give addition product in high yield (Table 5, entry 5), though the *Z*-isomer **6** failed to react. In the case of Bu_2CuLi, CuBr·Me_2S was the choice of Cu(I) salt. Bu_2CuLi·LiI did not react with enones **1a** and **2a** or enoates **5** and **6** (Table 5, entries 7−10), whereas Bu_2CuLi·LiBr·DMS reacted with both enones **1a** and **2a** and enoates **5** and **6** to yield conjugate addition product in high yield (Table 5, entries 11−14). These results confirm that CuBr·Me_2S is superior to CuI.

Effect of the R Group of the Cuprates, R_2CuLi. Conjugate additions of three cuprates (R_2CuLi, R = Me, Bu, and vinyl) were studied. The order of reactivity was R = Bu > Me > vinyl. Bu_2CuLi reacted efficiently with all *E*- and *Z*-enones and *E*- and *Z*-enoates, Me_2CuLi reacted with all enones and *E*-enoate, and $(vinyl)_2CuLi$ reacted smoothly only with *E*-enone. This order is proportional to the order of the nucleophilicity rather than the steric preference of the reagents.

Mechanism of the Reaction. It is generally accepted that organocuprate conjugate addition starts with d−π* complex formation, which has been confirmed by NMR studies.[19] In the next step, the formation of a Cu(III)−β-adduct is generally postulated, though it has never been exemplified.[19,20] Reductive elimination of this Cu(III)−β-adduct gives the final product enolates. In some cases, a radical ion pair was postulated between the d−π* complex and Cu(III)−β-adduct[21] and explains geometrical isomerization of substrate enones.[21a,b]

The results of the present study clearly show that the mechanism is highly dependent on the reaction conditions as the distinct diastereoselectivity shows (Scheme

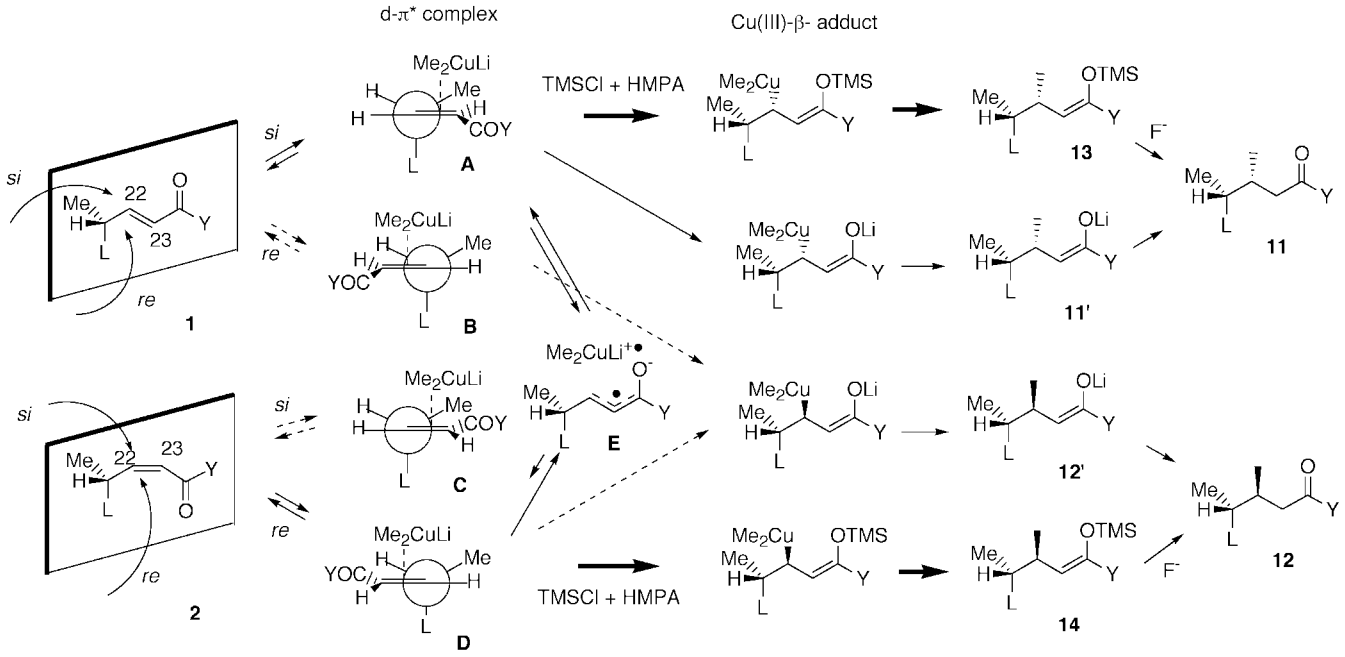
(18) (a) Lipshutz, B. H.; Wilhelm, R. S.; Floyd, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 7672−7674. (b) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005−5038. (c) Bertz, S. H.; Gibson, C. P.; Dabbagh, G. *Tetrahedron Lett.* **1987**, *28*, 4251−4254.

(19) (a) Hallnemo, G.; Olsson, T.; Ullenius, C. *J. Organometal. Chem.* **1985**, *282*, 133−144. (b) Lindstedt, E. L.; Nilsson, M.; Olsson, T. *Ibid.* **1987**, *334*, 255−261. (c) Ullenius, C.; Christenson, B. *Pure Appl. Chem.* **1988**, *60*, 57−64. (d) Christenson, B.; Olsson, T.; Ullenius, C. *Tetrahedron* **1989**, *45*, 523−534. (e) Bertz, S. H.; Smith, R. A. J. *J. Am. Chem. Soc.* **1989**, *111*, 8276−8277. (f) Sharma, S.; Oehlschlager, A. C. *Tetrahedron* **1991**, *47*, 1177−1184. (g) Vellekoop, A. S.; Smith, R. A. J. *J. Am. Chem. Soc.* **1994**, *116*, 2902−2913. (h) Krause, N. *J. Org. Chem.* **1992**, *57*, 3509−3512. (i) Krause, N.; Wagner, R.; Gerold, A. *J. Am. Chem. Soc.* **1994**, *116*, 381−382.

(20) (a) Krauss, S. R.; Smith, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 141−148. (b) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063−3066. (c) Pradilla, R. F.; Rubio, M. B.; Marino, J. P.; Viso, A. *Tetrahedron Lett.* **1992**, *33*, 4985−4988. (d) Nantz, M. H.; Bender, D. M.; Janaki, S. *Synthesis* **1993**, 577−578. (e) Lipshutz, B. H.; Aue, D. H.; James, B. *Tetrahedron Lett.* **1996**, *37*, 8471−8474. (f) Dorigo, A. E.; Wanner, J.; Schleyer, P. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 476−478.

(21) (a) House, H. O.; Wilkins, J. M. *J. Org. Chem.* **1978**, *43*, 2443−2454. (b) House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59−67. (c) Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Am. Chem. Soc.* **1988**, *110*, 617−618. (d) Bertz, S. H.; Dabbagh, G.; Mujsce, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 631−636. (e) Chounan, Y.; Ibuka, T.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 2003−2004.

Scheme 4



The different kinds of arrows are used to show roughly the order of the rate:

fast ⟶ > ⟶ > ⇢ slow

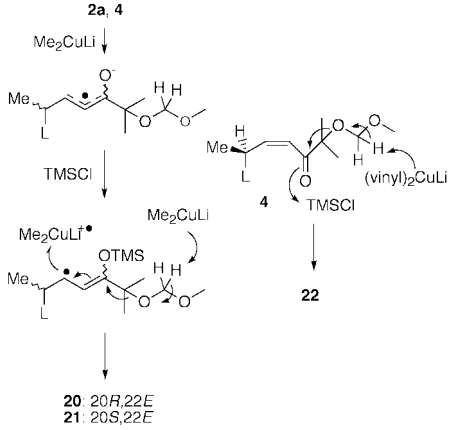
4). In the reaction without additives, *E*- and *Z*-enones **1** and **2** gave the same products in the same ratio (Table 1, entries 1, 4 and 2, 5), which suggests that under these conditions *Z*−*E* isomerization occurred at some stage of the reaction. The isomerization probably occurs at a stage later than the d−π* complex formation[19] because, when this reaction was conducted at −78 °C, the mixture indicated the yellow of a d−π* complex,[2c,19g] but when the reaction was quenched at this stage the starting enone was recovered without detectable *Z*−*E* isomerization (Table 1, entries 7 and 8). Geometrical isomerization has been known to be a sensitive method to detect intermediacy of radical species.[21a,b] In our reactions, evidence of the *Z*−*E* isomerization suggests involvement of a radical ion species. We assume that a radical ion pair (such as **E** in Scheme 4) forms from the d−π* complex, and rapid equilibrium is established between the radical ion pair and d−π* complexes (Scheme 4). However, the addition of cuprates is assumed to occur on the d−π* complex, since the facial selectivity was the same as that of *E*-enone under the kinetic conditions and can be explained by the transition state **A′** in which the reagent is attacking the double bond on an obtuse angle (Scheme 3).[15] If the addition occurs on the radical anion, the facial selectivity should be changed.

In the presence of TMSCl and HMPA, cuprate addition proceeds apparently by a different mechanism (Scheme 4). TMSCl makes the enones more electrophilic by interacting with the carbonyl oxygen. HMPA in addition to TMSCl accelerates the reaction further by removing the Li cation to assist the addition of TMSCl to the carbonyl oxygen. Thus, the electrophilic addition of TMSCl to the carbonyl oxygen and the nucleophilic addition of cuprate to the β-carbon might occur concertedly.[22] As a result, under these conditions, the reaction is kinetically controlled, and the conformation of the starting enones (or enoates) determines the facial selectivity (see above). In reactions of sterically hindered *Z*-enones, diastereoselectivity is lower and the formation of byproducts (elimination products **20**−**22**) becomes significant.[23] The low stereoselectivity indicates that *Z*−*E* isomerization is occurring, and in turn, the formation of radical ion species. Formation of byproducts **20** and **21** provides supporting evidence for *Z*−*E* isomerization in these reactions.[23]

We considered the possibility of Z−E isomerization of enones under sluggish reaction conditions by which we were able to suggest a unified mechanism to explain the observed stereochemical course of cuprate additions.

(22) This mechanism agrees with the mechanism postulated by Bertz et al. in their cuprate addition to cyclohexenone in the presence of TMSCl and HMPA.[27] However, in our case, all conjugate addition products were obtained as enol silyl ethers, and free ketone was never detected in the reactions under these conditions.[8]

(23) Because of steric hindrance at the β-position, the reagent is assumed to attack the 25-OMOM group as shown below to produce the byproducts. In **20** and **21**, isomerization of the 22-double bond was observed, suggesting the formation of radical species.



Conclusions

The conclusions to be drawn from the present study are as follows: (1) To achieve the optimum diastereofacial selectivity, we recommend kinetic conditions including both TMSCl and HMPA.[24] (2) The facial selectivity under these kinetic conditions can be predicted by the Felkin−Anh-type transition state, which is derived readily from the minimum-energy conformation of the substrate calculated using the molecular mechanics method. (3) Under sluggish addition conditions, such as the conditions without activaing additivities, attention must be paid to the geometrical isomerization of the substrates, which results in dramatic changes in the facial selectivity; the facial selectivity under these conditions is tentatively termed substrate-thermodynamic control. (4) This geometrical isomerization is assumed to occur via a radical ion-pair intermediate (such as **E** in Scheme 4), which equilibrates with the d−π* complex. These rules for the prediction of the diastereofacial selectivity of cuprate additions to acyclic compounds were shown to be generally applicable to previous stereochemical results of cuprate additions.[2a,b,k,m,25]

Experimental Section

NMR spectra were obtained in $CDCl_3$ solution at 270 or 400 MHz on a commercially available instrument. IR spectra were obtained on a commercially available Micro FTIR spectrometer. Low- and high-resolution mass spectra were measured at 70 eV. Relative intensities are given in parentheses. Tetrahydrofuran (THF) was distilled from benzophenone ketyl prior to use. All air-sensitive reactions were run under argon atmosphere, and reagents were added through septa using oven-dried syringes. The phrase "dried and evaporated" indicates drying over Na_2SO_4, followed by evaporation of the solvents under house vacuum. The spectral data of **1a**, **2a**, **3**, **4 11a**, **12a**, **15a**, **16a**, and **20** have been reported in previous papers.[5]

(20*R*,22*E*)-1α,-3*β*-Bis[(methoxycarbonyl)oxy]-25-[(tetrahydropyranyl)oxy]-24-homo-5,7,22-cholestatrien-24-one (1b). To a solution of diisopropylamine (3.04 mL, 21.8 mmol) in THF (10 mL) at −78 °C was added dropwise *n*-BuLi (1.6 M in hexane, 13.6 mL, 21.8 mmol), and the solution was stirred at that temperature for 20 min. To this LDA solution was added slowly a solution of 4-hydroxy-4-methyl-2-pentanone tetrahydropyranyl ether (4.36 g, 21.8 mmol) in THF (5 mL), and the mixture was stirred for 40 min at −78 °C. The solution of enolate then added to a solution of 20*S*-aldehyde **9** (5 g, 10.9 mmol) in THF (20 mL), and the mixture was stirred for 1.5 h at −78 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with AcOEt, washed with water, dried, and evaporated. The residue was subjected to next mesylation without purification. The residue was dissolved in methylene chloride, and to this solution at 0 °C triethylamine (6.06 mL, 43.6 mmol) and mesyl chloride (2.53 mL, 32.7 mmol) were added. The mixture was stirred at 0 °C for 45 min, quenched with ice−water, and extracted with methylene chloride. The extracts were washed with water, dried, and evaporated. The residue was subjected to next demesylation without purification. The residue was dissolved in benzene (50 mL) and to this solution DBU (1.92 mL, 12.8 mmol) was added. The mixture was stirred for 40 min at room temperature. The reaction was quenched with water and extracted with AcOEt. The extracts were washed with water, dried, and evaporated. The residue was chromatographed on silica gel (100 g) with 7% AcOEt−benzene to yield 22(*E*)-en-24-one **1b** (4.53 g, 65%): ^{1}H NMR δ 0.65 (3 H, s), 1.01 (3 H, s), 1.10 (3 H, d, J = 6.4 Hz), 1.31 and 1.35 (each 3 H, s), 3.78 and 3.80 (each 3 H, s), 4.80 (1 H, m), 4.84 (1 H, m), 4.91 (1 H, m), 5.38 and 5.68 (each 1 H, m), 6.13 (1 H, d, J = 15.4 Hz), 6.70 (1 H, dd, J = 8.9, and 15.4 Hz); IR (KBr) 2962, 1748, 1657, 1620, 1444, 1282, 1131, 988 cm^{-1}; MS *m*/*z* 490 ($M^+ - CH_3OCO_2H \times 2$, 2), 424 (9), 406 (8), 348 (74), 251 (28), 235 (42), 155 (65), 141 (92), 55 (100); HRMS calcd for $C_{30}H_{40}O_4$ ($M^+ - CH_3OCO_2H - C_5H_{10}O_2$) 464.2926, found 464.2935.

(20*R*,22*Z*)-1α,3*β*-Bis[(methoxycarbonyl)oxy]-25-[(tetrahydropyranyl)oxy]-24-homo-5,7,22-cholestatrien-24-one (2b). A Pyrex vessel containing a solution of the 22(*E*)-enone **1b** (800 mg, 1.25 mmol) and naphthalene (400 mg, 3.13 mmol) in benzene (60 mL) was charged with high quality Ar (99.999%). The solution was irradiated externally with a 100-W high-pressure mercury lamp (Shigemi Standard, Tokyo) at room temperature until the ratio of *E*- and *Z*-enones became approximately 3:1 (analyzed by HPLC). The solvent was evaporated, and the residue was chromatographed on silica gel (30 g, 2% AcOEt−benzene) to give 22(*Z*)-enone **2b** (175 mg, 22%) and starting 22(*E*)-enone **1b** (518 mg, 65%). **2b**: ^{1}H NMR δ 0.67 (3 H, s), 1.01 (3 H, s), 1.02 (3 H, d, J = 4.9 Hz), 1.32 and 1.36 (each 3 H, s), 3.78 and 3.79 (each 3 H, s), 4.81 (1 H, m), 4.84 (1 H, m), 4.93 (1 H, m), 5.36 and 5.68 (each 1 H, m), 5.78 (1 H, t, J = 11.4 Hz), 6.13 (1 H, d, J = 11.4 Hz); IR (KBr) 2958, 1746, 1688, 1620, 1444, 1282, 1257, 1025, 992 cm^{-1}; MS *m*/*z* 490 ($M^+ - CH_3OCO_2H \times 2$, 1), 424 (3), 406 (8), 348 (24), 224 (57), 209 (54), 155 (47), 141 (60), 85 (100); HRMS calcd for $C_{32}H_{46}O_8$ ($M^+ - C_5H_8O$) 558.3193, found 558.3212.

(20*R*,22*E*)-1α,3*β*-Bis[(methoxycarbonyl)oxy]-5,7,22-cholatrien-24-oic Acid Methyl Ester (5). To a solution of sodium hydride (60% oil suspension, 96 mg, 2.4 mmol) in THF (10 mL) at 0 °C was added trimethyl phosphonoacetate (387 μL, 2.39 mmol), and the mixture was stirred for 10 min. To this solution was added a solution of 22-aldehyde **9** (1.0 g, 2.17 mmol) in THF (10 mL), and the mixture was stirred for 1 h. The reaction was quenched by the addition of water, and the mixture was extracted with AcOEt. The extracts were washed with water, dried, and evaporated. The residue was chromatographed on silica gel (50 g) with 0.1% AcOEt−benzene to give 22(*Z*)-enoate **6** (60 mg, 5%) and 22(*E*)-enoate **5** (1.02 g, 91%) in this order. **5**: ^{1}H NMR δ 0.65 (3 H, s), 1.01 (3 H, s), 1.10 (3 H, d, J = 6.4 Hz), 3.72 (3 H, s), 3.78 and 3.80 (each 3 H, s), 4.84 (1 H, m), 4.90 (1 H, m), 5.38 and 5.68 (each 1 H, m), 5.76 (1 H, d, J = 15.8 Hz), 6.84 (1 H, dd, J = 8.9, 15.8 Hz); IR (KBr) 2958, 2876, 1748, 1657, 1441, 1340, 1284, 1151, 994, 791 cm^{-1}; MS *m*/*z* 516 (M^+, 2), 440 (12), 364 (100), 349 (9), 251 (22), 235 (18), 209 (13), 197 (15), 155 (18), 141 (19); HRMS calcd for $C_{25}H_{32}O_2$ ($M^+ - CH_3OCO_2H \times 2$) 364.2402, found 364.2394. Anal. Calcd for $C_{29}H_{40}O_8$: C, 67.42; H, 7.80. Found: C, 67.22; H, 7.74.

(20*R*,22*Z*)-1α,3*β*-Bis[(methoxycarbonyl)oxy]-5,7,22-cholatrien-24-oic Acid Methyl Ester (6). To a solution of bis-(2,2,2-trifuluoroethyl) (methoxycarbonylmethyl)phosphonate (919 μL, 4.35 mmol) and 18-crown-6 (4.6 g, 17.4 mmol) in THF (77 mL) at −78 °C was added potassium bis(trimethylsilyl)-amide (0.5 M in toluene, 8.7 mL, 4.35 mmol), and the mixture was stirred for 20 min. To this solution was added a solution of 22-aldehyde **9** (1.0 g, 2.17 mmol) in THF (3 mL), and the mixture was stirred for 24 h at −78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the mixture was extracted with AcOEt. The extracts were washed with water, dried, and evaporated. The residue was chromatographed on silica gel (40 g) with 0.1% AcOEt−benzene to give 22(*Z*)-enoate **6** (697 mg, 62%) and 22(*E*)-enoate **5** (249 g, 22%) in this order. **6**: ^{1}H NMR δ 0.69 (3 H, s), 1.02 (3 H, s), 1.05 (3 H, d, J = 6.4 Hz), 3.70 (3 H, s), 3.77 and 3.79 (each 3 H, s), 4.84 (1 H, m), 4.92 (1 H, m), 5.38 and 5.68 (each 1 H, m), 5.65 (1 H, d, J = 11.4 Hz), 5.99 (1 H, t, J = 11.4 Hz); IR (KBr) 2960, 2876, 1748, 1721, 1638, 1444, 1346, 1253, 793 cm^{-1}; MS *m*/*z* 516 (M^+, 6), 440 (28), 364 (100), 349 (14), 251 (36), 235 (20), 209 (20), 197 (24), 155 (26), 141 (29); HRMS calcd for $C_{29}H_{40}O_8$ (M^+) 516.2723, found 516.2750. Anal. Calcd for $C_{29}H_{40}O_8$: C, 67.42; H, 7.80. Found: C, 67.53; H, 7.72.

(24) Addition of $BF_3 \cdot Et_2O$ as the Lewis acid in place of TMSCl and HMPA gave unsatisfactory results in our studies.

(25) We have confirmed that this rule can be applicable to almost all known stereochemical results of cuprate additions to acyclic enones and enoates having γ-alkoxy or γ-phenyl substituents. These results will be reported separately.

(20*S*,22*E*)-1α,3*β*-Bis[(methoxycarbonyl)oxy]-5,7,22-cholatrien-24-oic Acid Methyl Ester (7). 20(*R*)-Aldehyde **10** (1.0 g) was treated with trimethylphosphonoacetate anion under similar conditions described in the preparation of **5**, giving 22(*E*)-enoate **7** (0.85 g, 76%) and 22(*Z*)-enoate **8** (0.11 g, 10%). **7**: ^{1}H NMR δ 0.58 (3 H, s), 0.98 (3 H, s), 1.00 (3 H, d, J = 6.4 Hz), 3.74 (3 H, s), 3.77 and 3.79 (each 3 H, s), 4.82 (1 H, m), 4.89 (1 H, m), 5.37 and 5.68 (each 1 H, m), 5.77 (1 H, d, J = 15.8 Hz), 6.87 (1 H, dd, J = 9.9, 15.8 Hz); IR (neat) 2957, 2872, 1745, 1651, 1441, 1251 cm^{-1}; MS m/z 516 (M^+, 1), 440 (11), 364 (100), 349 (7), 251 (18), 235 (17), 209 (10), 197 (12), 155 (12), 141 (16); HRMS calcd for $C_{29}H_{40}O_8$ (M^+) 516.2723, found 516.2703. Anal. Calcd for $C_{29}H_{40}O_8$: C, 67.42; H, 7.80. Found: C, 67.69; H, 7.75.

(20*S*,22*Z*)-1α,3*β*-Bis[(methoxycarbonyl)oxy]-5,7,22-cholatrien-24-oic Acid Methyl Ester (8). 20(*R*)-Aldehyde **10** (1.0 g) was treated with bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate anion under similar conditions described in the preparation of **6**, giving 22(*Z*)-enoate **8** (427 mg, 38%) and 22(*E*)-enoate **7** (480 mg, 43%). **8**: ^{1}H NMR δ 0.55 (3 H, s), 0.97 (3 H, d, J = 6.9 Hz), 0.98 (3 H, s), 3.71 (3 H, s), 3.77 and 3.78 (each 3 H, s), 4.82 (1 H, m), 4.89 (1 H, m), 5.37 and 5.67 (each 1 H, m), 5.66 (1 H, d, J = 11.9 Hz), 6.10 (1 H, t, J = 11.9 Hz); IR (neat) 2957, 2872, 1745, 1722, 1641, 1441, 1251 cm^{-1}; MS m/z 516 (M^+, 2), 440 (13), 364 (100), 349 (8), 251 (20), 235 (13), 209 (13), 197 (14), 155 (17), 141 (17); HRMS calcd for $C_{29}H_{40}O_8$ (M^+) 516.2723, found 516.2741. Anal. Calcd for $C_{29}H_{40}O_8$: C, 67.42; H, 7.80. Found: C, 67.78; H, 7.54.

General Procedure of Cuprate Addition Reactions. 1. Preparation of Me_2CuLi from CuI and MeLi. To a suspension of CuI in THF was added MeLi (1.4 M in ether, 2 equiv for CuI) at 0 °C. The mixture was stirred for 20 min at 0 °C, and then this colorless clear solution was used as Me_2-CuLi in THF.

2. Preparation of Me_2CuLi and Bu_2CuLi from CuBr·Me_2S and Alkyllithium. A flask containing CuBr·Me_2S (Aldrich) was cooled to −30 °C, and to this flask were added THF and then alkyllithium (2 equiv for CuBr·Me_2S). The mixture was stirred for 15 min at −30 °C, and this solution was used as (alkyl)$_2$CuLi in THF. The Me_2CuLi solution was colorless, and the Bu_2CuLi solution was dark green or dark brown.

3. Preparation of (Vinyl)$_2$CuLi from CuBr·Me_2S and Vinyllithium. a. Vinyllithium. *n*-BuLi (2.0 M in pentane, 26.4 mL, 52.8 mmol) was added to a flask containing tetravinyltin (3.0 g, 13.2 mmol) under Ar atmosphere at room temperature, and the mixture was stirred for 3 h. Supernatant of the mixture was discarded with a syringe. The residue was washed with dry pentane (20 mL) five times and dissolved in dry ether (7 mL). The concentration of vinyllithium was determined by a titration using diphenylacetic acid. **b. (Vinyl)$_2$CuLi.** (Vinyl)$_2$CuLi was prepared using CuBr·Me_2S and vinyllithium by a similar procedure used for the preparation of Me_2CuLi and Bu_2CuLi. The (vinyl)$_2$CuLi solution was dark green.

4. Reaction of Enones 1−4 with R_2CuLi in the Absence of TMSCl and HMPA. Enone was added to the solution of R_2CuLi at 0 °C in the reaction of R = Me and at −30 °C in the reaction of R = Bu, and the mixture was stirred for 0.5−1 h. The reaction was quenched with saturated NH_4-Cl and extracted with AcOEt. The extracts were washed with water, dried, and evaporated. At this stage, products ratio was determined by HPLC and/or ^{1}H NMR. The residue was purified by silica gel column chromatography, and then the isolated yield was determined.

5. Reaction of Enones 1−4 with R_2CuLi in the Presence of TMSCl and HMPA. A solution of R_2CuLi in THF was cooled to −78 °C, and then to this cuprate solution were added TMSCl, HMPA, and a solution of enone in THF in this order. The mixture was stirred at −78 °C for 0.5−1 h, and then triethylamine was added. The mixture was diluted with AcOEt and water, and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with water, dried, and evaporated.[26] The residue was dissolved in THF, and to this solution was added 1 equiv of *n*-Bu_4NF (1.0 M in THF) at −78 °C. The mixture was stirred for 30 min at that temperature. The reaction was quenched with saturated NH_4-Cl, and the mixture was extracted with AcOEt. The organic layer was washed with water, dried, and evaporated. At this stage, the product ratio was determined by HPLC and/or ^{1}H NMR. The residue was purified by silica gel column chromatography, and the isolated yield was determined.

6. Reaction of Enoates 5−8 with R_2CuLi in the Presence of TMSCl and HMPA. A solution of R_2CuLi in THF was cooled to −30 °C, and TMSCl, HMPA, and a solution of enoate in THF were added to this cuprate solution in this order. The mixture was stirred at −30 °C for about 1 h, and then triethylamine was added. The mixture was diluted with AcOEt and water, and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with water, dried, and evaporated. ^{1}H NMR of the residue showed production of the silyl ketene acetal. The residue was chromatographed on silica gel, on which the silyl ketene acetal was hydrolyzed spontaneously to give the final product **23**, **24**, **27**, or **28**. Products ratio was determined by HPLC and/or ^{1}H NMR.

(20*R*,22*R*)-1α,3*β*-Bis[(methoxycarbonyl)oxy]-25-[(tetrahydropyranyl)oxy]-22-methyl-24-homo-5,7-cholestadien-24-one (11b): ^{1}H NMR δ 0.62 (3 H, s), 0.82 (3 H, d, J = 6.4 Hz), 0.88 (3 H, d, J = 5.9 Hz), 1.01 (3 H, s), 1.31 and 1.34 (each 3 H, s), 3.77 and 3.79 (each 3 H, s), 4.79 (1 H, m), 4.84 (1 H, m), 4.90 (1 H, m), 5.38 and 5.68 (each 1 H, m); IR (KBr) 2962, 1748, 1444, 1274, 990, 787 cm^{-1}; MS m/z 498 (1), 480 (1), 422 (11), 404 (8), 364 (12), 320 (32) 209 (54), 85 (100); HRMS calcd for $C_{33}H_{50}O_8$ ($M^+ - C_5H_8O$) 574.3506, found 574.3508.

(20*R*,22*R*)-1α,3*β*-Bis[(methoxycarbonyl)oxy]-25-[(methoxymethyl)oxy]-22-butyl-5,7-cholestadien-24-one (11c): ^{1}H NMR δ 0.64 (3 H, s), 0.83 (3 H, d, J = 6.9 Hz), 0.88 (3 H, t, J = 6.4 Hz), 1.01 (3 H, s), 1.34 and 1.36 (each 3 H, s), 3.39 (3 H, s), 3.78 and 3.79 (each 3 H, s), 4.72 (2 H, s), 4.84 (1 H, m), 4.90 (1 H, m), 5.38 and 5.68 (each 1 H, m); IR (KBr) 2962, 1748, 1717, 1444, 1286, 1149, 1035, 791 cm^{-1}; MS m/z 570 ($M^+ - CH_3OCO_2H$, 0.5), 538 (1), 494 (4), 449 (4), 436 (6), 432 (2), 364 (8), 325 (17), 103 (100); HRMS calcd for $C_{34}H_{50}O_5$ ($M^+ - CH_3OCO_2H$-CH_3OH) 538.3659, found 538.3699. Anal. Calcd for $C_{37}H_{58}O_9$: C, 68.70; H, 9.04. Found: C, 68.98; H, 8.90.

(20*R*,22*S*)-1α,3*β*-Bis[(methoxycarbonyl)oxy]-25-[(methoxymethyl)oxy]-22-vinyl-5,7-cholestadien-24-one (11d): ^{1}H NMR δ 0.64 (3 H, s), 0.88 (3 H, d, J = 6.8 Hz), 1.01 (3 H, s), 1.33 and 1.36 (each 3 H, s), 3.40 (3 H, s), 3.78 and 3.79 (each 3 H, s), 4.73 (2 H, s), 4.84 (1 H, m), 4.90 (1 H, m), 4.92 (1 H, d, J = 17.2 Hz), 4.98 (1 H, d, J = 10.4 Hz), 5.38 and 5.68 (each 1 H, m), 5.75 (1 H, ddd, J = 17.2, 10.4, 6.7 Hz); IR (neat) 2957, 2876, 1743, 1718, 1442, 1253 cm^{-1}; MS m/z 616 (M^+ 4), 584 (10), 540 (17), 508 (16), 495 (17), 464 (41), 406 (52), 103 (100); HRMS calcd for $C_{35}H_{52}O_9$ (M^+) 616.3611, found 616.3625. Anal. Calcd for $C_{35}H_{52}O_9$: C, 68.16; H, 8.50. Found: C, 68.38; H, 8.66.

(20*R*,22*S*)-1α,3*β*-Bis[(methoxycarbonyl)oxy]-25-[(tetrahydropyranyl)oxy]-22-methyl-24-homo-5,7-cholestadien-24-one (12b): ^{1}H NMR δ 0.60 (3 H, s), 0.72 and 0.73 (3 H (1:1), d, J = 6.9 Hz), 0.80 (3 H, d, J = 5.9 Hz), 1.00 (3 H, s), 1.30 and 1.35 (each 3 H, s), 3.78 and 3.79 (each 3 H, s), 4.78 (1 H, m), 4.84 (1 H, m), 4.92 (1 H, m), 5.38 and 5.68 (each 1 H, m).

(20*R*,22*S*)-1α,3*β*-Bis[(methoxycarbonyl)oxy]-25-[(methoxymethyl)oxy]-22-butyl-5,7-cholestadien-24-one (12c): ^{1}H NMR δ 0.57 (3 H, s), 0.80 (3 H, d, J = 6.4 Hz), 0.88 (3 H, t, J = 6.9 Hz), 1.00 (3 H, s), 1.33 and 1.36 (each 3 H, s), 3.39 (3 H, s), 3.78 and 3.79 (each 3 H, s), 4.72 (2 H, s), 4.84 (1 H, m), 4.90 (1 H, m), 5.38 and 5.69 (each 1 H, m); IR (KBr) 2958,

(26) In entries 14, 15, 17, 21, 23, and 26 in Table 1, the residue was chromatographed on silica gel at this stage to isolate the byproduct **20**, **21**, or **22**.

(27) Bertz, S. H.; Miano, G.; Rossiter, B. E.; Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11023−11024.

1746, 1717, 1446, 1278, 1147, 1035, 791 cm^{-1}; MS *m*/*z* 570 ($M^+ - CH_3OCO_2H$, 2), 494 (7), 449 (2), 436 (8), 432 (1), 364 (6), 325 (4), 103 (100); HRMS calcd for $C_{35}H_{54}O_6$ ($M^+ - CH_3OCO_2H$) 570.3920, found 570.3965.

(20*S*,22*S*)-1α,3β-Bis[(methoxycarbonyl)oxy]-25-[(methoxymethyl)oxy]-22-butyl-5,7-cholestadien-24-one (15b): ^1H NMR δ 0.64 (3 H, s), 0.75 (3 H, d, *J* = 6.8 Hz), 0.87 (3 H, t, *J* = 6.8 Hz), 1.00 (3 H, s), 1.34 and 1.36 (each 3 H, s), 3.39 (3 H, s), 3.77 (6 H, s), 4.72 (2 H, s), 4.80 (1 H, m), 4.89 (1 H, m), 5.38 and 5.68 (each 1 H, m); IR (neat) 2957, 2872, 1745, 1716, 1442, 1253 cm^{-1}; MS *m*/*z* 646 (M^+, 4), 614 (18), 570 (13), 538 (26), 494 (33), 450 (50), 436 (61), 364 (97), 325 (87), 249 (73), 103 (100); HRMS calcd for $C_{37}H_{58}O_9$ (M^+) 646.4081, found 646.4095.

(20*S*,22*R*)-1α,3β-Bis[(methoxycarbonyl)oxy]-25-[(methoxymethyl)oxy]-22-vinyl-5,7-cholestadien-24-one (15c): ^1H NMR δ 0.66 (3 H, s), 0.81 (3 H, d, *J* = 6.8 Hz), 1.01 (3 H, s), 1.33 and 1.36 (each 3 H, s), 3.39 (3 H, s), 3.77 and 3.78 (each 3 H, s), 4.72 (2 H, s), 4.81 (1 H, m), 4.89 (1 H, m), 4.94 (1 H, d, *J* = 17.0 Hz), 4.97 (1 H, d, *J* = 10.5 Hz), 5.37 and 5.67 (each 1 H, m), 5.68 (1 H, ddd, *J* = 17.0, 10.5, 7.2 Hz); IR (neat) 2959, 2876, 1745, 1716, 1442, 1251 cm^{-1}; MS *m*/*z* 584 ($M^+ - CH_3OH$, 9), 540 (15), 508 (21), 464 (30), 420 (43), 406 (51), 334 (50), 249 (46), 209 (58), 153 (100), 103 (98); HRMS calcd for $C_{35}H_{52}O_9$ (M^+) 616.3611, found 616.3611.

(20*S*,22*R*)-1α,3β-Bis[(methoxycarbonyl)oxy]-25-[(methoxymethyl)oxy]-22-butyl-5,7-cholestadien-24-one (16b): ^1H NMR δ 0.69 (3 H, s), 0.73 (3 H, d, *J* = 6.7 Hz), 0.90 (3 H, t, *J* = 7.1 Hz), 1.01 (3 H, s), 1.34 and 1.37 (each 3 H, s), 3.39 (3 H, s), 3.78 and 3.80 (each 3 H, s), 4.72 (2 H, s), 4.84 (1 H, m), 4.90 (1 H, m), 5.37 and 5.69 (each 1 H, m); MS *m*/*z* 646 (M^+, 3), 570 (14), 538 (16), 494 (25), 450 (20), 436 (22), 364 (27), 325 (25), 249 (37), 183 (100), 103 (39).

(20*R*,22*Z*)-1α,3β-Bis[(methoxycarbonyl)oxy]-24-homo-5,7,22,24a-cholestatetraen-24-one (19): ^1H NMR δ 0.68 (3 H, s), 1.02 (3 H, s), 1.05 (3 H, d, *J* = 6.9 Hz), 1.89 and 2.17 (each 3 H, s), 3.77 and 3.79 (each 3 H, s), 4.84 (1 H, m), 4.90 (1 H, m), 5.36 and 5.68 (each 1 H, m), 5.82 (1 H, dd, *J* = 11.4, 10.4 Hz), 5.98 (1 H, d, *J* = 11.4 Hz), 6.08 (1 H, s); IR (neat) 2957, 2872, 1747, 1628, 1442, 1377, 1356, 1278 cm^{-1}; MS *m*/*z* 540 (M^+, 3), 464 (27), 388 (100), 373 (9), 249 (21), 235 (19); HRMS calcd for $C_{32}H_{44}O_7$ (M^+) 540.3087, found 540.3072.

(20*S*,22*E*)-5,7,22,24-Cholestatetraene-1α,3β,24-triol 1,3-bis(methyl carbonate) 24-trimethylsilyl ether (21): ^1H NMR δ 0.18 (9 H, s), 0.59 (3 H, s), 0.96 (3 H, d, *J* = 6.6 Hz), 0.98 (3 H, s), 1.69 and 1.72 (each 3 H, s), 3.77 and 3.79 (each 3 H, s), 4.81 (1 H, m), 4.89 (1 H, m), 5.37 and 5.67 (each 1 H, m), 5.61 (1 H, dd, *J* = 15.2, 9.5 Hz), 6.19 (1 H, d, *J*= 15.2 Hz); IR (neat) 2961, 2874, 1743, 1695, 1622, 1442, 1342, 1286 cm^{-1}; MS *m*/*z* 600 (M^+, 1), 524 (3), 448 (4), 131 (100), 73 (24); HRMS calcd for $C_{34}H_{52}O_7Si$ (M^+) 600.3482, found 600.3478. Anal. Calcd for $C_{34}H_{52}O_7Si$: C, 67.96; H, 8.72. Found: C, 68.14; H, 8.70.

(20*S*,22*Z*)-5,7,22,24-Cholestatetraene-1α,3β,24-triol 1,3-bis(methyl carbonate) 24-trimethylsilyl ether (22): ^1H NMR δ 0.14 (9 H, s), 0.51 (3 H, s), 0.92 (3 H, d, *J* = 6.5 Hz), 0.99 (3 H, s), 1.57 and 1.63 (each 3 H, s), 3.77 and 3.79 (each 3 H, s), 4.84 (1 H, m), 4.89 (1 H, m), 5.23 (1 H, t, *J* = 10.9 Hz), 5.35 and 5.67 (each 1 H, m), 5.81 (1 H, d, *J* = 10.9 Hz); IR (neat) 2959, 2872, 2856, 1749, 1693, 1614, 1442, 1346, 1286 cm^{-1}; MS *m*/*z* 600 (M^+, 8), 524 (45), 448 (41), 376 (13), 224 (54), 198 (70), 181 (59), 131 (100), 73 (68); HRMS calcd for $C_{34}H_{52}O_7Si$ (M^+) 600.3482, found 600.3479. Anal. Calcd for $C_{34}H_{52}O_7Si$: C, 67.96; H, 8.72. Found: C, 67.84; H, 8.79.

(20*R*,22*R*)-1α,3β-Bis[(methoxycarbonyl)oxy]-22-methyl-5,7-choladien-24-oic acid methyl ester (23a): ^1H NMR δ 0.62 (3 H, s), 0.82 (3 H, d, *J* = 6.4 Hz), 0.93 (3 H, d, *J* = 6.9 Hz), 1.01 (3 H, s), 3.67 (3 H, s), 3.78 and 3.79 (each 3 H, s), 4.84 (1 H, m), 4.90 (1 H, m), 5.38 and 5.68 (each 1 H, m); IR (KBr) 2962, 1746, 1441, 1288, 1007, 963, 791 cm^{-1}; MS *m*/*z* 532 (M^+, 2), 456 (11), 380 (100), 251 (15), 224 (15), 209 (24), 197 (17); HRMS calcd for $C_{28}H_{40}O_5$ ($M^+ - CH_3OCO_2H$) 456.2876, found 456.2866.

(20*R*,22*R*)-1α,3β-Bis[(methoxycarbonyl)oxy]-22-butyl-5,7-choladien-24-oic acid methyl ester (23b): ^1H NMR δ 0.63 (3 H, s), 0.79 (3 H, d, *J* = 6.4 Hz), 0.88 (3 H, t, *J* = 6.9 Hz), 1.01 (3 H, s), 3.66 (3 H, s), 3.78 and 3.79 (each 3 H, s), 4.84 (1 H, m), 4.90 (1 H, m), 5.38 and 5.69 (each 1 H, m); IR (KBr) 2960, 1748, 1444, 1270, 1166, 992, 793 cm^{-1}; MS *m*/*z* 498 ($M^+ - CH_3OCO_2H$, 7), 422 (100), 251 (22), 224 (28), 209 (56), 197 (39); HRMS calcd for $C_{33}H_{50}O_8$ (M^+) 574.3506, found 574.3508.

(20*R*,22*S*)-1α,3β-Bis[(methoxycarbonyl)oxy]-22-butyl-5,7-choladien-24-oic acid methyl ester (24b): ^1H NMR δ 0.60 (3 H, s), 0.81 (3 H, d, *J* = 5.5 Hz), 0.89 (3 H, t, *J* = 6.4 Hz), 1.01 (3 H, s), 3.66 (3 H, s), 3.78 and 3.79 (each 3 H, s), 4.84 (1 H, m), 4.90 (1 H, m), 5.38 and 5.69 (each 1 H, m); IR (KBr) 2960, 1744, 1444, 1284, 1166, 996, 793 cm^{-1}; MS *m*/*z* 574 (M^+, 1), 498 (11), 422 (100), 407 (6), 251 (12), 224 (14), 209 (18), 197 (13); HRMS calcd for $C_{33}H_{50}O_8$ (M^+) 574.3506, found 574.3506. Anal. Calcd for $C_{33}H_{50}O_8$: C, 68.96; H, 8.77. Found: C, 68.90; H, 8.74.

(20*S*,22*S*)-1α,3β-Bis[(methoxycarbonyl)oxy]-22-butyl-5,7-choladien-24-oic acid methyl ester (27b): ^1H NMR δ 0.64 (3 H, s), 0.71 (3 H, d, *J* = 6.9 Hz), 0.88 (3 H, t, *J* = 6.9 Hz), 1.01 (3 H, s), 3.68 (3 H, s), 3.78 and 3.80 (each 3 H, s), 4.82 (1 H, m), 4.90 (1 H, m), 5.38 and 5.68 (each 1 H, m); IR (neat) 2957, 2872, 1745, 1442, 1346, 1253 cm^{-1}; MS *m*/*z* 574 (M^+, 2), 498 (18), 422 (100), 251 (18), 224 (22), 209 (26), 197 (23); HRMS calcd for $C_{33}H_{50}O_8$ (M^+) 574.3506, found 574.3488. Anal. Calcd for $C_{33}H_{50}O_8$: C, 68.96; H, 8.77. Found: C, 69.12; H, 8.83.

(20*S*,22*R*)-1α,3β-Bis[(methoxycarbonyl)oxy]-22-butyl-5,7-choladien-24-oic acid methyl ester (28b): ^1H NMR δ 0.63 (3 H, s), 0.74 (3 H, d, *J* = 5.9 Hz), 0.91 (3 H, t, *J* = 6.9 Hz), 1.01 (3 H, s), 3.66 (3 H, s), 3.78 and 3.80 (each 3 H, s), 4.84 (1 H, m), 4.90 (1 H, m), 5.37 and 5.68 (each 1 H, m); IR (neat) 2958, 2873, 1743, 1444, 1346, 1251 cm^{-1}; MS *m*/*z* 574 (M^+, 1), 498 (13), 422 (100), 251 (16), 224 (20), 209 (22), 197 (18); HRMS calcd for $C_{33}H_{50}O_8$ (M^+) 574.3506, found 574.3508.

Time Course of the Reaction of *Z*-Enone 2a with Me_2CuLi (Table 3). Methyllithium (1.4 M in ether, 486 μL, 0.68 mmol) was added to a suspension of CuI (65 mg, 0.34 mmol) in THF (0.5 mL) at 0 °C, and the solution was stirred for 15 min. To this solution of Me_2CuLi cooled to −10 °C was added *Z*-enone **2a** (100 mg, 0.17 mmol) in THF (0.5 mL), and the mixture was stirred at that temperature. At 5 and 15 min, 20 μL aliquots of the reaction mixture were taken out with a syringe and quenched with water. After 40 min of stirring, the reaction was worked up by the general procedure described above. Compound ratios (**1a**, **2a**, and **11a**) at each time were determined by HPLC (LiChrospher Si60, 4.0 × 250 mm, 2% 2-propanol−hexane).

Competition Reaction of *E*- and *Z*-Enones 1a and 2a with Me_2CuLi (Table 4). Methyllithium (1.4 M in ether, 243 μL, 0.34 mmol) was added to a suspension of CuI (32 mg, 0.17 mmol) in THF (0.5 mL) at 0 °C, and the solution was stirred for 15 min. To this solution of Me_2CuLi cooled to −10 °C was added a THF (0.5 mL) solution of *E*-enone **1a** (50 mg, 0.085 mmol) and *Z*-enone **2a** (50 mg, 0.085 mmol), and the mixture was stirred at that temperature. At 5 and 15 min, 20 μL aliquots of the reaction mixture were taken out with a syringe and quenched with water. After 40 min of stirring, the reaction was worked up by the general procedure described above. Compound ratios (**1a**, **2a**, and **11a**) at each time were determined by HPLC (LiChrospher Si60, 4.0 × 250 mm, 2% 2-propanol−hexane).

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Supporting Information Available: Copies of ^1H NMR spectra for new compounds (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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