Diastereoselectivity of the Conjugate Addition of Organocopper Reagents to γ-Alkoxy α,β-Unsaturated Carbonyl Derivatives. Importance of the Reagent Type and the Double-Bond Geometry

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Received April 21, 1992

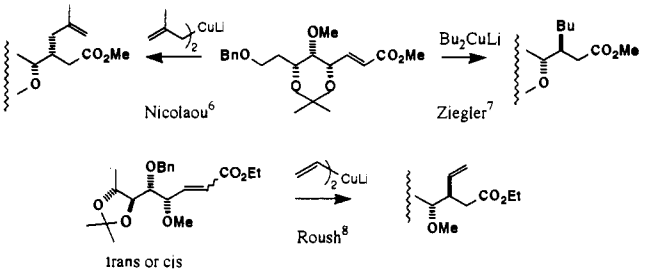
Abstract: Systematic investigations of the diastereoselectivity of organocopper conjugate addition to γ-alkoxy trans enoates (**3**), cis enoates (**4**), and diesters (**5**) revealed that the selectivity highly depended on the substrate structure and the reagent type. The anti-diastereoselectivity was produced in the following combinations: **3** and vinylcopper reagents; **3** and alkylcopper reagents; and **4** and vinylcopper reagents. The syn-diastereoselectivity was obtained in the following reactions: methallylcopper reagents with **3**–**5**; any copper reagents with **5**; alkylcopper reagents with **4**; and a certain vinylcopper reagent with **4**. These diastereoselectivities can be interpreted by either ordinary nucleophilic attack mechanisms (**12**, **15** (or **19**), **16**) or a π-complex mechanism (**13**). π-Complex formation may be involved in the reaction of Michael acceptors having higher reduction potentials or in the reaction of copper reagents having lower oxidation potentials. In a nucleophilic addition mechanism, "inside OR" and "anti R" are proposed for the transition-state model (**12**). Finally, a synthetically useful level of syn-selectivity (~100% de) was obtained in a *t*-Bu-substituted diester (**21**).

The diastereoselectivity of nucleophilic addition to chiral aldehydes can be interpreted and predicted by a Felkin–Anh transition-state model[1] (Figure 1). The model has also been supported by recent calculations.[2] On the other hand, the diastereoselectivity of nucleophilic conjugate addition to chiral Michael acceptors is puzzling. Some additions have been interpreted in terms of a modified Felkin–Anh model, which involves replacement of the carbonyl group of Figure 1 with the conjugated Michael acceptor group (Figure 2). However, in some cases the opposite diastereoselectivity has been observed. Although conjugate addition to chiral Michael acceptors is widely used in organic synthesis, the stereoselectivity has not been studied systematically. We intended to clarify the diastereoselectivity by systematic studies on conjugate addition to simple systems and to present an empirical model.[3] We now detail the results for conjugate addition to γ-alkoxy α,β-unsaturated carbonyl derivatives. Quite recently, the theoretical aspects of conjugate addition have appeared in the literature,[4] and thus it is very interesting to compare our experimental results with the theoretical calculations.

Results and Discussion

Background. Conjugate additions of organometallic reagents of γ-alkoxy α,β-unsaturated carbonyl systems have been investigated by several groups. The diastereoselectivity is dependent upon the substrate and reagent structures. Highly diastereoselective conjugate addition of alkyllithium reagents to γ-alkoxy-α-trimethylsilyl α,β-unsaturated sulfones has been reported by Isobe.[5] The reaction proceeds through a chelated intermediate. Nicolaou has reported that dimethallylcuprate addition to carbohydrate-derived enoates, which produces very high diastereoselectivity, can be explained by chelation control.[6] On the other hand, Ziegler has reported that dibutylcuprate addition to the same enoates proceeds with completely reversed diastereoselectivity.[7] Roush has reported that vinylcuprate addition to carbohydrate-derived enoates and enones gives the anti isomers with very high diastereoselectivity regardless of the geometry of the double bond.[8] The anti-selectivity has been observed with other related reactions

Scheme I. Diastereoselectivity Depending on Reagent Type and Not the Double-Bond Geometry



(Scheme I).[9] Previous results are summarized in Figure 3. Generally speaking, the syn isomer is obtained via the chela-

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(1) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205. Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.

(2) Mukherjee, D.; Wu, Y.-D.; Fronczek, F. R.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3328. Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908. See also: Srivastave, S.; LeNoble, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 5874.

(3) (a) Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 464. (b) Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1572. (c) Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Am. Chem. Soc.* **1988**, *110*, 617.

(4) (a) Dorigo, A. E.; Morokuma, K. *J. Am. Chem. Soc.* **1989**, *111*, 6524. (b) Dorigo, A. E.; Morokuma, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1884. (c) Bernardi, A.; Capelli, A. M.; Gennari, C.; Scolastico, C. *Tetrahedron: Asymmetry* **1990**, *1*, 21.

(5) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1979**, 3465; **1980**, *21*, 4727. See also: Alcarez, C.; Carretero, J. C.; Dominguez, E. *Tetrahedron Lett.* **1991**, *32*, 1385.

(6) (a) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1981**, *103*, 1224; *Tetrahedron Lett.* **1979**, 2327. (b) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 2027.

(7) Ziegler, F. E.; Gilligan, P. J. *J. Org. Chem.* **1981**, *46*, 3874.

(8) Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Lesur, B. M.; Chong, W. K. M.; Harris, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 2984. Roush, W. R.; Lesur, B. M. *Tetrahedron Lett.* **1983**, *24*, 2231. See also: Jako, I.; Uiber, P.; Mann, A.; Taddei, M.; Wermuth, C. G. *Tetrahedron Lett.* **1990**, *31*, 1011.

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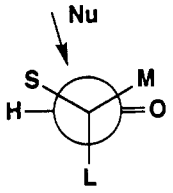


Figure 1. Felkin–Anh model for chiral aldehydes.

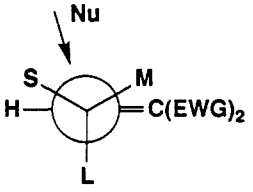
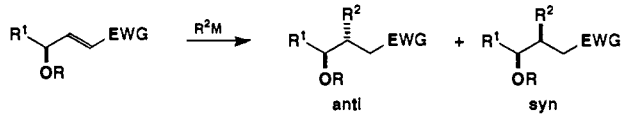


Figure 2. "Modified" Fekin–Anh model for chiral Michael acceptors.

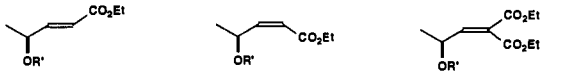


control	R	R^2M	geometry of double bond	product
chelation	Me, Bn, MOM, MEM	R^2Li, R^2MgX, (R^2_2CuLi)	E&Z	syn
non-chelation	TBDMS	R^2CuL_n	E&Z	anti

model "modified" Felkin-Anh (cf) Felkin-Anh

Figure 3. Summary of the previous results.

tion-controlled addition of RLi and RMgX to both *E* and *Z* enoates or enones which have protective groups R, such as Me, Bn, MOM, and MEM. The anti isomer is produced via non-chelation-controlled addition of organocopper reagents to enoates and enones (*E* and/or *Z*) which have a bulky protecting group such as TBDMS. These diastereoselectivities have been explained by the "modified" Felkin–Anh model **1**. Anomalies from the generalization have also been reported: the allylcuprate additions giving the syn isomers,[6,7] the butylcopper and dibutylcuprate additions producing the syn adduct,[9a] and the allyllithium additions which produce the anti isomers.[7] We thought that most of the previous systems, especially carbohydrate-derived substrates, have many oxygen atoms which can chelate the organometallic reagents, and thus the complicated structures might prevent generalization. We chose the simplest systems (**3–5**) to elucidate the diastereoselectivity relationship between substrate structure and reagent type.



3 a; R' = Bn (Bn=CH_2Ph)
b; R' = $SiMe_2$t-Bu

4 a; R' = Bn
b; R' = $SiMe_2$t-Bu

5 a; R' = Bn
b; R' = $SiMe_2$t-Bu

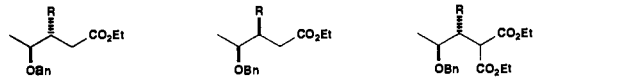
(9) (a) Lenord, J.; Ryan, G. *Tetrahedron Lett.* **1987**, *28*, 2525. (b) Cha, J. K.; Lewis, S. C. *Tetrahedron Lett.* **1984**, *25*, 5263. (c) Salomon, R. G.; Miller, D. B.; Raychaudhuri, S. R.; Avasthi, K.; Lal, K.; Levison, B. S. *J. Am. Chem. Soc.* **1984**, *106*, 8296. (d) Heathcock, C. H.; Kiyooka, S.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214; **1986**, *51*, 3252. (e) Larchevêque, M.; Tamaguan, G.; Petit, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 31. (f) Multzer, J.; Kappert, M. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 63. (g) Honda, Y.; Hirai, S.; Tsuchihashi, G. *Chem. Lett.* **1989**, 255. (h) Burgess, K.; Cassidy, J.; Henderson, I. *J. Org. Chem.* **1991**, *56*, 2050. (i) Yoda, H.; Shirai, T.; Katagiri, T.; Takabe, K.; Kimata, K.; Hosoya, K. *Chem. Lett.* **1990**, 2037.

Table I. Conjugate Additions of Vinylcopper Reagents[a]

entry	substrate	reagent	product ratio anti:syn	tot. isolated yield, %
1	**3a**	$(vinyl)_2CuLi$	72:28	99
2	**3a**	$(vinyl)_2CuLi{\cdot}BF_3$	94:6	58
3	**3a**	$(vinyl)_2Cu(CN)Li_2$	72:28	83
4	**3a**	$(vinyl)_2Cu(CN)Li_2{\cdot}BF_3$	95:5	66
5	**4a**	$(vinyl)_2CuLi$	>99:1	82
6	**4a**	$(vinyl)_2CuLi{\cdot}BF_3$	52:48	63
7	**4a**	$(vinyl)_2Cu(CN)Li_2$	96:4	58
8	**4a**	$(vinyl)_2Cu(CN)Li_2{\cdot}BF_3$	21:79	64
9	**5a**	$(vinyl)_2CuLi$	38:62	91
10	**5a**	$(vinyl)_2CuLi{\cdot}BF_3$	39:61	91
11	**5a**	$(vinyl)_2Cu(CN)Li_2$	29:71	94
12	**5a**	$(vinyl)_2Cu(CN)Li_2{\cdot}BF_3$	31:69	96
13	**5a**	(vinyl)Cu	31:69	45
14	**5a**	$(vinyl)Cu{\cdot}BF_3$	22:78	72
15	**5a**	(vinyl)Cu(CN)Li	30:70	88
16	**5a**	$(vinyl)Cu(CN)Li{\cdot}BF_3$	34:66	83

[a] The starting substrate was recovered when the conjugate adduct was obtained in low yields.

Conjugate Addition of Vinylcopper Reagents. Conjugate additions to **3a–5a** were carried out under the same conditions as those of Roush, and the diastereoisomer ratio was determined by capillary GC. The results are summarized in Table I. From the trans enoate **3a**, the anti isomer **6a** was produced predominantly



6 (anti)
a; R = $CH{=}CH_2$
b; R = Me
c; R = n-Bu
d; R = $CH_2CH(CH_3){=}CH_2$

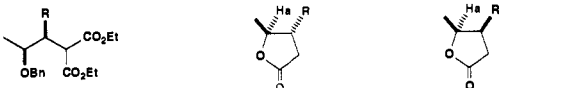
7 (syn)
a; R = $CH{=}CH_2$
b; R = Me
c; R = n-Bu
d; R = $CH_2CH(CH_3){=}CH_2$

8 (anti)
a; R = $CH{=}CH_2$
b; R = Me
c; R = n-Bu
d; R = $CH_2CH(CH_3){=}CH_2$

(entries 1–4). The addition of $BF_3{\cdot}OEt_2$ enhanced the anti-selectivity (entries 2 and 4), although it decreased the chemical yield. The addition of (vinyl)Cu to **3a** was sluggish, but the diastereoselectivity was identical with that of the divinylcuprate reagent.

The cis enoate **4a** produced again **6a** either predominantly or exclusively (entries 5–7). Accordingly, Roush's observation was reconfirmed even in the case of the simple system. In contrast to the trans enoate, the addition of $BF_3{\cdot}OEt_2$ shifted perfect anti-selectivity (entry 5) to very low anti-selectivity (entry 6), and the combination of the Lipshutz's higher order cyanocuprate and $BF_3{\cdot}OEt_2$ gave the syn isomer **7a** predominantly (entry 8). The reason for this influence of $BF_3{\cdot}OEt_2$ is not clear at present. However, as mentioned later, the diastereoselectivity trend of the $(vinyl)CuL_n{\cdot}BF_3$ reagent is similar to that of the $(alkyl)CuL_n{\cdot}BF_3$ reagent which produces predominantly the anti isomer **6b** from **3a** and the syn isomer **7b** from **4a**.

The diester **5a** (cis form) was converted to the syn isomer **9a** predominantly (entries 9–16). Since the reactivity of **5a** is higher than that of the monoesters, even the (vinyl)Cu reagent gave the adduct in an allowable yield (entry 13). The ratio of syn:anti (**9a**:**8a**) was approximately 7:3 regardless of the reagent type.



9 (syn)
a; R = $CH{=}CH_2$
b; R = Me
c; R = n-Bu
d; R = $CH_2CH(CH_3){=}CH_2$

10 a; R = Et
b; R = Me
c; R = n-Bu
d; R = i-Bu

11 a; R = Et
b; R = Me
c; R = n-Bu
d; R = i-Bu

Conjugate Addition of Alkylcopper Reagents. Conjugate additions to **3a** and **4a** did not take place with the ordinary alkylcuprate reagents, but they occurred with the organocopper–BF_3 reagent.[10] The reactions of **3a** and **4a** with R_2CuLi or $R_2CuLi{\cdot}BF_3$ afforded the products of allylic substitution at the α-position as the major product; S_N2'-type substitution took place.[11] Conjugate addition to the disubstituted Michael acceptor

(10) Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 947.

Table II. Conjugate Additions of Alkylcopper Reagents[a]

entry	substrate	reagent	product ratio anti:syn	tot. isolated yield, %
1	**3a**	$MeCu\cdot BF_3$	69:31	60
2	**3a**	$MeCu(CN)Li\cdot BF_3$	95:5	62
3	**3a**	$BuCu\cdot BF_3$	92:8	64
4	**4a**	$MeCu\cdot BF_3$	22:78	30
5	**4a**	$MeCu(CN)Li\cdot BF_3$	26:74	45
6	**4a**	$BuCu\cdot BF_3$	22:78	56
7	**5a**	MeCu	11:89	58
8	**5a**	$MeCu\cdot BF_3$	6:94	54
9	**5a**	Me_2CuLi	37:63	75
10	**5a**	BuCu	30:70	75
11	**5a**	$BuCu\cdot BF_3$	5:95	52
12	**5a**	Bu_2CuLi	32:68	63
13	**5a**	$Bu_2CuLi\cdot BF_3$	19:81	51

[a] See footnote to Table I.

Table III. Conjugate Additions of Methallylcopper Reagents[a]

entry	substrate	reagent	product ratio anti:syn	tot. isolated yield, %
1	**3a**	(methallyl)Cu	40:60	87
2	**3a**	$(methallyl)_2CuLi$	42:58	99
3	**4a**	(methallyl)Cu	18:82	45
4	**4a**	$(methallyl)_2CuLi$	20:80	99
5	**5a**	(methallyl)Cu	7:93	99
6	**5a**	$(methallyl)Cu\cdot BF_3$	3:97	86
7	**5a**	$(methallyl)_2CuLi$	10:90	79
8	**5a**	$(methallyl)_2CuLi\cdot BF_3$	8:92	99
9	**5a**	(methallyl)Cu(CN)Li	17:83	88
10	**5a**	$(methallyl)Cu(CN)Li\cdot BF_3$	4:96	95
11	**5a**	$(methallyl)_2Cu(CN)Li_2$	7:93	99
12	**5a**	$(methallyl)_2Cu(CN)Li_2\cdot BF_3$	24:76	87

[a] See footnote to Table I.

5a proceeded more readily. The results are summarized in Table II.

Reactions of the trans ester **3a** with alkylcopper–BF_3 reagents gave the anti isomers **6b,c** predominantly (entries 1–3), whereas the cis ester **4a** produced the syn isomers **7b,c** preferentially (entries 4–6). It is now clear that the double-bond geometry plays an important role in controlling the diastereoselectivity of conjugate addition to simple systems. The addition to **5a** proceeded smoothly even in the absence of $BF_3\cdot OEt_2$, and the syn isomers **9b,c** were produced predominantly (entries 7–13). The presence of $BF_3\cdot OEt_2$ enhanced the syn-selectivity (entries 8, 11, and 13). In the absence of $BF_3\cdot OEt_2$ the syn:anti ratio was approximately 7:3, similar to the ratio of the vinylcopper addition.

The diastereoisomer ratios of the methyl adducts (**6b** and **7b**) were determined by capillary GC (SE-30), but those of the butyl derivatives (**6c** and **7c**) were obtained by ^1H NMR analyses because the chain-elongated products could not be separated by the capillary column. The adducts (**8** and **9**) of **5a** were decarboxylated upon heating in Me_2SO–H_2O–NaCl, and the resulting monoesters (**6** and **7**) were analyzed by either capillary GC or ^1H NMR spectroscopy.

Conjugate Addition of Methallylcopper Reagents. The results are summarized in Table III. Conjugate addition to **3a** gave a 6:4 mixture of the syn and anti isomers in high yields (entries 1 and 2). The reaction of $(methallyl)_2CuLi\cdot BF_3$ resulted in recovery of the starting material. The addition to **4a** produced the syn isomer **7d** predominantly (entries 3 and 4), and the addition of $BF_3\cdot OEt_2$ to $(methallyl)_2CuLi$ gave trace amounts of the adduct. This observation is in agreement with Lipshutz's result that formation of a 1,4-addition product decreases when $BF_3\cdot OEt_2$ is added to prenylcopper–prenylcuprate.[12] However, the $BF_3\cdot OEt_2$-complexed reagent added to the diester in high yields, presumably owing to the higher reactivity of **5a** compared to **3a** and **4a**. Conjugate addition to **5a** gave an approximately 9:1 mixture of the syn and anti isomers (entries 5–12). In some cases, the addition of $BF_3\cdot OEt_2$ enhanced the syn-selectivity. Consequently, methallylcopper reagents produce the syn isomer predominantly, regardless of the substrate geometry and the reagent type, in good agreement with Nicolaou's observation.

Table IV. Diastereoselectivity Relationships[a]

substrate	reagent: (vinyl)-CuL_n	(alkyl)-CuL_n	(methallyl)-CuL_n
3a (trans ester)	anti (anti)*	anti (anti)*	syn (syn)*
4a (cis ester)	anti [syn] (anti)*	syn	syn
5a (diester, cis)	syn	syn	syn

[a] Key: ()*, diastereoselectivity observed by Nicolaou, Roush, and Ziegler; [syn], syn-selectivity was observed in a certain case.

Allylcopper was prepared by the addition of allyllithium to copper iodide (House's procedure).[13] The reaction of this allylcopper with **5a** did not proceed at all. This is in marked contrast to the case of methallyl reagents in which the House procedure gave the conjugate product in high yields. The addition of allylcopper to **5a** proceeded in high yield by using CuI/LiCl (Lipshutz's procedure)[12] instead of CuI. The allylated product was obtained as a 93:7 mixture of the syn and anti isomers in 99% yield.

Structure Determination of Stereoisomers. The stereochemistries of the products **6–9** were determined by ^1H NMR analyses of the five-membered lactones derived from the adducts. Removal of the benzyl group of **6** and **7** with H_2–Pd/C in ethanol followed by treatment with TsOH gave **10** and **11**, respectively. The H_a of **10** resonated at higher field than the H_a of **11**, owing to the shielding effect of R: **10** H_a δ 4.05 for R = Me and Bu, δ 4.26 for Et, δ 4.17 for *i*-Bu; **11** H_a δ 4.55 for R = Me, δ 4.58 for Bu, δ 4.75 for Et, δ 4.70 for *i*-Bu. This procedure for stereochemical determination of five-membered lactones was used previously and proved to be practical.[14] Decarboxylation of **8b,c** and **9b,c** upon heating in Me_2SO–H_2O–NaCl followed by the acid treatment gave **10b,c** and **11b,c**, respectively, and thus the stereochemistries of **8b,c** and **9b,c** could be correlated with those of **6b,c** and **7b,c**. In the case of **8a,d** and **9a,d**, reduction of the double bond and debenzylation were carried out with H_2–Pd/C before the decarboxylation.

Diastereoselectivity Relationship between Substrates and Reagents. Table IV illustrates a diastereoselectivity relationship between the copper reagents and the Michael acceptors. The diastereoselectivity of each major product is shown in the table; the utmost stereoselectivity was >99% and the lowest was ca. 60%. As evident, the diastereoselectivities observed by Nicolaou, Roush, and Ziegler in conjugate addition to carbohydrate-derived enoates having several oxygen atoms are almost reproducible in the simple systems. The only exception is a pair between **4a** and $(vinyl)_2Cu(CN)Li_2\cdot BF_3$ which produced the syn isomer predominantly (Table I, entry 8). However, direct comparison of this syn-selectivity with Roush's observation is not appropriate, since $BF_3\cdot OEt_2$ is involved in the present system. An interesting feature is that the syn-selectivity is observed in the lower right of the table whereas the anti-selectivity is observed in the upper left.

Explanation of the Diastereoselectivity. New Models. In order to interpret the diastereoselectivity shown in Table IV, we propose two different pathways for conjugate addition: (1) an ordinary nucleophilic attack in which the addition of the copper reagent (Nu) proceeds through a Burgi–Dunitz trajectory from the outside position (**12**); (2) a π-complex mechanism[15] in which Nu attacks from the inside position (**13**). In order to explain the syn-selectivity of the γ-Ph-γ-Me-substituted diester[3b,c] (instead of the present γ-OBn-γ-Me diester **5**), we previously proposed that an electron-transfer mechanism would be involved in the diester system and the resulting $(RCuL_n)^{\cdot+}$ would attack the intermediate

(11) For S_N2' substitution of γ-(methylsulfonyl)oxy α,β-unsaturated esters see: Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4864.

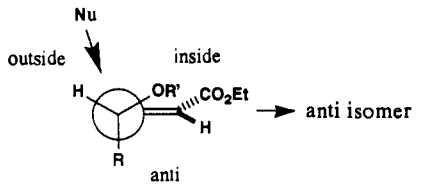
(12) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Smith, R. A. J. *J. Am. Chem. Soc.* **1990**, *112*, 4404.

(13) House, H. O.; Fischer, W. F., Jr. *J. Org. Chem.* **1969**, *34*, 3615.

(14) Yamamoto, Y.; Nishii, S. *J. Org. Chem.* **1988**, *53*, 3597.

(15) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063.

A model for the trans ester



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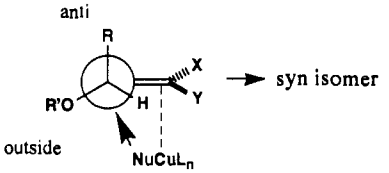
A model for the diester and/or allylic CuL_n addition



13 a; X = Y = CO_2Et
b; X = CO_2Et, Y = H
c; X = H, Y = CO_2Et

(diester)$^{\bullet-}$ from the inside position. In other words, we postulated the angle of attack would be smaller than 90°, although an ordinary nucleophilic attack proceeds with the angle larger than 90°. Later, Dorigo and Morokuma's computations indicated that the angle of methyl radical attack on C_β of the acrolein radical anion is close to 115°, essentially the same value as that calculated for the nucleophilic attack of methylcopper on C_β of enals.[4b] They also carried out the ab initio calculations on a π-complex for the reaction of lithium dimethylcuprate with dicyanoethylene and found that an "acute" angle of attack, that is, attack from the inside position, is expected from the π-complex. Accordingly, we would like to attribute an "acute" angle of attack to the π-complex formation instead of an electron-transfer mechanism, although there is a difference between the γ-Ph-γ-Me diester and the γ-OBn-γ-Me diester. Needless to say, the π-complex formation does not necessarily rule out the possibility of subsequent electron transfer. The full details on the γ-Ph-γ-Me system will be reported in due course.

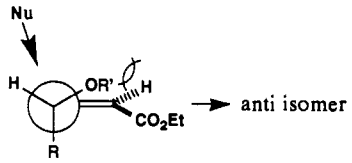
Whether conjugate addition proceeds through an ordinary nucleophilic attack or a π-complex mechanism may depend upon the substrate structure and reagent type. It seems reasonable to assume that either a strong Michael acceptor having higher electron-accepting ability or a reactive copper reagent having higher electron-donating ability is prone to produce a π-complex. The E(red) values vs SCE measured in THF were as follows: **5b** (−2.0 eV), **3b** and **4b** (≪−2.0 eV). Accordingly, it is clear that the diester **5a** possesses much higher electron-accepting ability than **3a** and **4a**.

The oxidation potential of copper reagents must constitute a measure of the electron-donating ability. We attempted to determine the oxidation potential using any physical chemistry methods conceivable at present, but all trials resulted in failure due to instability of copper reagents. We decided to measure the ionization potential of stable $RSnBu_3$, in which R was vinyl, *n*-Bu, and methallyl, assuming a logical extension from $RCuL_n$ to $RSnBu_3$. We expected the ionization potential would be significantly dependent upon the substituent of the organometallic compound, and this was proved to be true.

The photoelectron spectra of the organotins were measured by Professor Katsumata at Iwaki Meisei University. The vertical ionization potential of methallyltributyltin was 8.1 eV, that of tetrabutyltin was 8.7 eV, and that of vinyltributyltin was 8.8 eV, indicating that the order of electron-donating ability is methally ≫ *n*-butyl > vinyltin. Needless to say, there must be an argument against extending this substituent order of ionization potential for organotins to that for organocoppers. However, this is the only procedure available to us to estimate the substituent effect, and we would like to propose this order is more or less valid for organocoppers.

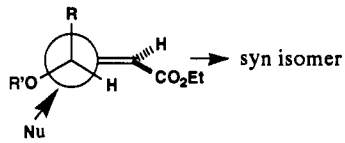
If we consider the above experimental results and their deductive inference, the syn-selectivity in the reactions of (methallyl)CuL_n or of the diester **5a** can be reasonably explained (see Table IV). The reaction must proceed through a π-complex mechanism **13**, giving the syn isomer predominantly. Regardless of mono- and diesters, H is on the inside position because Nu attacks from inside (**13a–c**). The reactions of the monoesters (**3a** and **4a**) with vinyl- or alkylcopper reagents must proceed via an ordinary nucleophilic attack.

The trans ester **3a** prefers a transition-state geometry **12** in which R is on the anti position and OR′ on the inside position. Nucleophiles attack from the outside position, giving the anti isomer predominantly. If the double-bond geometry changes to cis, the inside alkoxy conformation is destabilized due to the steric repulsion between the ester group and OR′ (as shown in **14**), forcing the transition-state geometry **15** to be adopted in order



14

A model for the cis ester and (alkyl)CuL_n

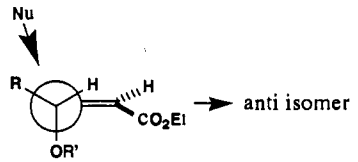


15

to minimize the steric crowding. The syn isomer is produced from **15**, and this mechanism is in good agreement with the diastereoselectivity observed in the reaction between (alkyl)CuL_n and **4a** and with the stereoselectivity switch from anti to syn upon changing the enoate from **3a** to **4a**.

However, the diastereoselectivity in the reaction between (vinyl)CuL_n and **4a** is not simple; both syn- and anti-selectivity were observed. A clear-cut rationale is not possible for this particular combination, but a plausible explanation follows. When the steric bulk of (vinyl)CuL_n is relatively small, the reaction might proceed through **16** to give the anti isomer. On the other hand, a relatively

A model for the cis ester and certain (vinyl)CuL_n



16

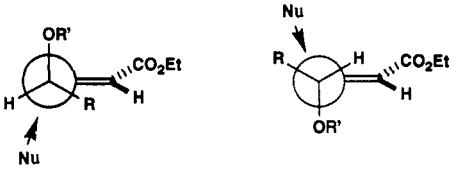
bulky reagent might attack from the OR′ position as shown in **15**. The A-value of CH_3 is 1.70 kcal/mol, whereas that of CH_2=CH is 1.35 kcal/mol.[16] Accordingly, any alkyl reagents are sterically more bulky than vinyl reagents. The A-values of Me, EtO, and MeO are 1.70, 0.98, and 0.6 kcal/mol, respectively,[16] suggesting that the steric bulk of R (Me in the present case) is larger than that of OR′ (OCH_2Ph). Perhaps the geometry **16** may become a favorable transition state in the case of smaller nucleophiles. The BF_3·OEt_2-complexed reagent $(vinyl)_2Cu(CN)Li_2$·BF_3 may be larger in its steric bulk than the other (vinyl)CuL_n, taking an alternative transition-state model **15**.

Inside OR′ and Anti R Groups. A remaining problem is why OR′ is on the inside position and R is on the anti position in **12**. Nucleophilic additions to α-chiral aldehydes have been studied extensively from both experimental and theoretical points of view,

(16) Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199.

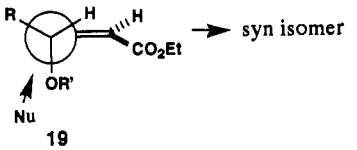
and the following conclusions are widely accepted. In general, the diastereoselectivity for the 1,2-asymmertric induction can be accommodated by the Felkin–Anh model (Figure 1), in which L is a sterically large group. M is a medium sized substituent, and S is the smallest group. Steric factors aside, the best acceptor group is assigned to L since the anti L stabilizes the filled σ_s MO of the forming nucleophile–carbon bond with the vacant σ_L* MO of the C–L bond (Anh–Eisenstein model).[17] Heathcock counted both the σ* orbital electronic effect and the steric effect and pointed out the following order of ligand preferences for the anti position: MeO > *t*-Bu > Ph > iPr > Et > Me > H.[18]

If we directly transfer the model for aldehydes to the present Michael acceptor system, the model **17**[9h] has to be involved as a transition state in the reaction of **3a** which produces the syn isomer. This is inconsistent with the experimental result. If the nonchelation attack in the modified Felkin–Anh model **1** (and **18**) is taken into consideration, the anti-selectivity of the trans



17 18

enoate **3a** can be understood. The nonchelation attack is reasonable from the above experimental results and the observation in the TBDMS system mentioned later. The syn-diastereoselectivity with the cis enoate **4a** may be interpreted as arising via the chelation attack in **1** (and **19**) or via addition to an alternative



19

conformer (**15**). The chelation possibility is negligible, since it is unlikely that the same copper reagent which reacts with **3a** in a nonchelation manner reacts with **4a** through chelation. An important question arises concerning both models **18** and **15** (or nonchelation **19**). Is there any logical reason why **3a** reacts via **18** and **4a** via **15** (or **19**)? The answer is no, because the hydrogen of **18** is already on the inside. When the geometry changes from trans to cis, it is not necessary to rotate the conformation at the γ-carbon in order to minimize the allylic strain. Consequently, the diastereoselectivity dependence upon the double-bond geometry strongly supports the new model **12** for the trans enoate. For the cis enoate, the nucleophile may attack from the direction either between H and OR′ (**15**) or between R and OR′ (**19**). There is experimental support for the inside OR′ (model **12**). The ^{1}H NMR studies of cyclohexylidene enoates reveal that the conformation similar to **12** (inside OR′) is more stable than that similar to **18** (anti OR′) when an electron-withdrawing group is attached to the double bond.[19] Needless to say, the ground-state and the reactive conformer are not necessarily the same. Reaction stereoselectivity depends on the energy of the transition states (including the nucleophile) and may be different from the ground-state structures (in the absence of the nucleophile). However, the inside OR′ is supported at least in the ground state.

The models **12**, **13**, and **15** have the R group on the anti position; that is, the best donor ligand is assigned to L (anti). Accordingly, these geometries correspond to the Cieplak electronic model,[20] in which the anti R conformation is thought to be dominated by mixing of the vacant σ* MO of the forming bond with the filled σ_L MO of the C–L bond, although the anti OR′ model corresponds to the Anh–Eisenstein model.[21]

Table V. Conjugate Additions to TBDMS-Protected Enoates[a]

entry	substrate	reagent	product ratio anti:syn	tot. isolated yield, %
1	**3b**	$MeCu{\cdot}BF_3$	68:32	6
2	**3b**	$Me_2CuLi{\cdot}BF_3$	73:27	26
3	**3b**	$Me_2Cu(CN)Li_2{\cdot}BF_3$	92:8	55
4	**4b**	$MeCu{\cdot}BF_3$	14:86	2
5	**4b**	$Me_2CuLi{\cdot}BF_3$	13:87	12
6	**4b**	$MeCu(CN)Li{\cdot}BF_3$	17:83	17
7	**4b**	$Me_2Cu(CN)Li_2{\cdot}BF_3$	18:82	36
8	**5b**	MeCu	15:85	92
9	**5b**	$MeCu{\cdot}BF_3$	16:84	98
10	**5b**	Me_2CuLi	38:62	89
11	**5b**	MeCu(CN)Li	8:92	92
12	**5b**	$MeCu(CN)Li{\cdot}BF_3$	9:91	94

[a] See footnote to Table I.

Table VI. Conjugate Additions to **20** and **21**[a]

entry	substrate	reagent	product ratio anti:syn	tot. isolated yield, %
1	**20**	MeCu	10:90	72
2	**20**	$MeCu{\cdot}BF_3$	9:91	75
3	**20**	MeCu(CN)Li	8:92	98
4	**20**	$MeCu(CN)Li{\cdot}BF_3$	3:97	57
5	**20**	Me_2CuLi	15:85	94
6	**20**	$Me_2CuLi{\cdot}BF_3$	4:96	75
7	**21**	$MeCu{\cdot}BF_3$	...:100	67
8	**21**	MeCu(CN)Li	...:100	72
9	**21**	Me_2CuLi	...:100	83
10	**21**	$Me_2CuLi{\cdot}BF_3$	...:100	98
11	**21**	n-Bu_2CuLi	...:100	99
12	**21**	n-$BuCu{\cdot}BF_3$	...:100	99

[a] See footnote to Table I.

Inspection of New Models and Accomplishment of a Synthetically Useful Level of Stereoselectivity. As mentioned in Figure 3, it is believed that the chelating ability of organocopper reagents is in general less than that of organolithium or -magnesium reagents. In fact, we have not taken chelation into consideration in the above discussion, although the computation of Dorigo and Morokuma counts the chelation effect.[4] Since there may be the possibility of chelation in the case of the benzyl group, we examined the conjugate addition to TBDMS-protected Michael acceptors (**3b**, **4b**, **5b**). It is widely accepted that TBDMS is a "nonchelating" group.[22] The results are summarized in Table V.

The diastereoselectivity trend of the TBDMS series is identical with that of the benzyl series, indicating that a chelation mechanism is not involved in the present conjugate addition as we expected. However, there are interesting small changes between Table V and Table II. The anti-selectivity of **3b** was slightly lower than that of **3a** (entries 1–3). The lower chemical yields were due to the use of 3 equiv of the copper reagents; 10 equiv of the reagents was used in Table II.[23] The inside OR′ of **12** becomes sterically unfavorable even in the trans geometry when the steric bulkiness of the R′ group increases from CH_2Ph to TBDMS, causing the slight decrease of the anti-selectivity. On the other hand, the syn-selectivity of **4b** was slightly higher than that of

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(18) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353.

(19) Lessard, J.; Saunders, J. K.; Viet, M. T. P. *Tetrahedron Lett.* **1982**, *23*, 2059.

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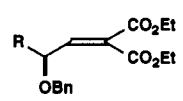
(21) One of the reviewers proposed a different explanation. Some of the cuprate additions are controlled via π-complexation of the cuprate (with the best σ-electron-withdrawing group anti and perpendicular to the double bond and the smallest group in the inside position), giving anti-selectivity. Other cuprates cannot complex, and they tend to give syn products via a Felkin–Anh-like model. With cis double bonds or disubstituted systems, 1,3-allylic strain tends to prevent any substituent from lying perpendicular to the double bond, hence orbital effects are less important than sterics. Consequently, in the latter case the size of the OR′ group and the R substituent becomes important. However, the diastereoselectivity difference among alkyl-, vinyl-, and allylcopper reagents cannot be explained by the reviewer's mechanism.

(22) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett.* **1991**, *32*, 6939 and references cited therein.

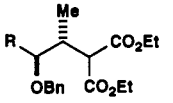
(23) We also carried out the reaction of **3a** with 3 equiv of the copper reagents and confirmed that the diastereoselectivity did not depend upon the amount of reagents.

4a (entries 4–7). The transition-state geometry **14** suffers from a severe steric repulsion if the steric demand of the R′ group increases, leading **15** to be more favorable. Accordingly, the syn-selectivity of **4b** is enhanced in comparison with that of **4a**. The syn-selectivity of **5b** was similar to that of **5a**. This is reasonable, since the influence of the steric bulk of the outside OR′ upon the stability of the transition state **13** is negligible, compard with the influence upon **12** and **14**.

Next we changed the R group from Me to the sterically more bulky groups such as Ph and *t*-Bu in order to know how the variation exerts an influence upon the diastereoselectivity. The results are summarized in Table VI. The syn-selectivity of **20**

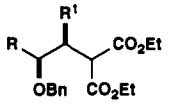


20; R = Ph
21; R = t-Bu



antl

22 a; R = Ph
b; R = t-Bu



syn

23 a; R = Ph, R^1 = Me
b; R = t-Bu, R^1 = Me
c; R=t-Bu, R^1 = nBu

was enhanced in comparison with that of **5a** (entries 1–6). Most of the methylcopper reagents produced the syn isomer **23a** with stereoselectivities greater than 90%. This is reasonable because the transition-state geometry **13a** becomes more favorable with the increase of the steric bulk of the anti R group. An impressive diastereoselectivity was produced in **21** (entries 7–12). The syn isomer **23b** was obtained as a single stereoisomer in high chemical yields (entries 7–12). The exclusive formation of **23b** is quite rational from the model **13a**.[24]

Conclusion. We are now in a position to understand reasonably the previous apparent discrepancies between the diastereoselectivities observed by Nicolaou, Roush, Ziegler, and ourselves. Each previous result was reproducible, and the diastereoselectivity relationship between the substrate and the reagent is summarized in Table IV. Transition-state models **12**, **13**, **15** (or **19**), and **16** are proposed to interpret these diastereoselectivities. A balance of the following factors determines the most stable transition geometry: (1) either an ordinary nucleophilic attack mechanism or a π-complex mechanism, which depends upon the oxidation potential of $RCuL_n$ and/or the reduction potential of Michael acceptors; (2) 1,3-allylic strain between the substituent at the γ-chiral center and the cis substituent of the double bond;[25] (3) steric repulsion between the incoming nucleophile and the substituent at the γ-chiral center; (4) stereoelectronic effect of the substituent on the anti position. The validity of these models was tested with the Ph- and *t*-Bu-substituted diesters (**20** and **21**)[24] and with the TBDMS-protected series (**3b–5b**). The diastereoselectivities in these cases are in good agreement with those predicted by the new models. Interestingly, the new models **12** and **19** are inconsistent with Morokuma's models obtained from the ab initio calculations for a trans and cis enoate, respectively. Finally, a synthetically useful level of stereoselectivity was produced by increasing the steric bulk of the R group at the γ-position.

Experimental Section

General information concerning instrumentation and materials was described previously.[14] The *E* isomer **3a** was prepared in 82% yield by the reaction of easily available 2-(benzyloxy)propanol[26] with triethyl phosphonoacetate according to the general procedure:[27] ^{1}H NMR (CCl_4) δ 1.29 (t, J = 7 Hz, 3 H), 1.30 (d, J = 7 Hz, 3 H), 4.00 (ddq, J = 1, 6, and 7 Hz, 1 H), 4.13 (q, J = 7 Hz, 2 H), 4.36 (d, J = 12 Hz, 1 H), 4.50 (d, J = 12 Hz, 1 H), 5.86 (dd, J = 1 and 16 Hz, 1 H), 6.70 (dd, J = 6 and 16 Hz, 1 H), 7.17 (m, 5 H); IR (neat) 700, 740, 980, 1030, 1090, 1180, 1270, 1300, 1350, 1370, 1450, 1500, 1660, 1720, 2870, 2950 cm^{-1}; HRMS calcd for $C_{14}H_{18}O_3$ m/z 234.1256, found m/z 234.1264. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.97; H, 7.50. The *Z* isomer **4a** was prepared as follows. To a solution of 6 mmol of $Ph_3PBrCH_2CO_2Et$[28] (2.58 g) dissolved in 15 mL of distilled EtOH was added 6 mmol of EtONa in EtOH under nitrogen at 0 °C. The mixture was stirred for 1 h at room temperature and then cooled to 0 °C. 2-(Benzyloxy)propanal (3 mmol, 0.45 mL) dissolved in 3 mL of EtOH was added. The resulting mixture was allowed to warm to room temperature and was stirred overnight. Ether (20 mL) was added, and the reaction was quenched with a saturated NH_4Cl solution. The usual workup gave a 9:1 mixture of **4a** and **3a**. Both isomers were separated by column chromatography on silica gel (hexane:ether (20:1) as eluant). Pure **4a** was obtained in 71% yield: ^{1}H NMR (CCl_4) δ 1.24 (t, J = 7 Hz, 3 H), 1.25 (d, J = 7 Hz, 3 H), 4.09 (q, J = 7 Hz, 2 H), 4.40 (s, 2 H), 5.06 (dq, J = 6 and 8 Hz, 1 H), 5.71 (d, J = 12 Hz, 1 H), 6.09 (dd, J = 8 and 12 Hz, 1 H), 7.19 (m, 5 H); IR (neat) 700, 740, 830, 1030, 1080, 1110, 1200, 1390, 1410, 1450, 1640, 1720, 2940, 2980 cm^{-1}; HRMS calcd for $C_{14}H_{18}O_3$ m/z 234.1256, found m/z 234.1292. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.90; H, 7.47. The diester **5a** was prepared by the reaction of 2-(benzyloxy)propanal with diethyl malonate according to the literature procedure:[29] ^{1}H NMR (CCl_4) δ 1.20 (t, J = 7 Hz, 3 H), 1.28 (t, J = 7 Hz, 3 H), 1.30 (d, J = 7 Hz, 3 H), 4.16 (q, J = 7 Hz, 2 H), 4.23 (q, J = 7 Hz, 4.34 (d, J = 11 Hz, 1 H), 4.50 (d, J = 11 Hz, 1 H), 6.74 (d, J = 8 Hz, 1 H), 7.20 (m, 5 H); IR (neat) 700, 740, 860, 1050, 1090, 1150, 1215, 1250, 1370, 1450, 1730, 2990 cm^{-1}; MS m/z 306 (M^+). Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.94; H, 7.01.

Ethyl *trans*-4-((*tert*-Butyldimethylsilyl)oxy)-2-pentenoate (3b). To a CH_2Cl_2 solution (200 mL) of ethyl lactate (22.7 g, 200 mmol) at 0 °C were added imidazole (27.2 g, 400 mmol) and (TBDMS)Cl (30.1 g, 200 mmol) under an N_2 atmosphere. The mixture was stirred overnight at room temperature and then refluxed for 10 h. Addition of water, repeated extraction with ether, rapid washing of the ther extract with 1 N HCl solution, subsequent washing with saturated $NaHCO_3$ aqueous solution and brine, drying with anhydrous Na_2SO_4, and concentration under vacuum gave the desired TBDMS-protected ethyl lactate in essentially quantitative yield. To a dry ether (10 mL) solution of this lactate (10 g, 43 mmol) cooled at −78 °C was added, dropwise 1 N Dibal in hexane (60 mL, 60 mmol). The mixture was stirred at −78 °C for 30 min, and then 1 N HCl was added. The mixture was allowed to warm to room temperature and was extracted three times with ether. The ether solution was washed with saturated NaCl aqueous solution, dried with anhydrous $MgSO_4$, and concentrated under vacuum. Purification by silica-gel column chromatography (SiO_2, 100 g) using *n*-hexane–AcOEt (25:1) as eluant gave 4.7 g (25 mmol) of the corresponding aldehyde (58.3% yield). In a 200-mL flask under Ar was placed 60% NaH (0.85 g, 21.1 mmol), and the mineral oil was washed several times with dry hexane. The hexane was removed, and THF (100 mL) was added. Triethyl phosphonoacetate (4.2 mL, 21.1 mmol) was added dropwise at 0 °C, and the stirring was continued for 10 min until evolution of H_2 ceased. The aldehyde (2.84 g, 15.1 mmol) was added dropwise, and the mixture was stirred for 30 min at room temperature. Addition of water, repeated extraction with ether, washing the ether extract with saturated NaCl aqueous solution, drying with anhydrous $MgSO_4$, concentration under vacuum, and purification by silica-gel column chromatography (SiO_2, 120 g) using *n*-hexane–AcOEt (30:1) as an eluent gave crude **3b**. Further purification (SiO_2, 120 g, *n*-hexane–AcOEt 60:1) produced pure **3b** (1.8 g, 6.9 mmol) in 45.7% yield: ^{1}H NMR ($CDCl_3$) δ 0.066 (s, 3 H), 0.072 (s, 3 H), 0.913 (s, 9 H), 1.261 (d, J = 6.5 Hz, 3 H), 1.296 (t, J = 7.2 Hz, 3 H), 4.196 (q, J = 7.2 Hz, 2 H), 4.458 (ddq, J = 2.0, 3.8, and 6.5 Hz, 1 H), 5.984 (dd, J = 2.0 and 15.0 Hz, 1 H), 6.928 (dd, J = 3.8 and 15.0 Hz, 1 H); HRMS calcd for $C_{13}H_{26}O_3Si$ 258.1651, found 258.1652.

Ethyl *cis*-4-((*tert*-Butyldimethylsilyl)oxy)-2-pentenoate (4b). The general procedure mentioned above for the preparation of cis esters could not be applied to **4b** presumably because of the steric bulkiness of the TBDMS group. To a THF (30 mL) solution of diisopropylamine (3.5 mL, 25 mmol) cooled at 0 °C under Ar was added slowly a hexane solution of *n*-BuLi (15.2 mL × 1.64 M, 24.9 mmol), and the mixture was stirred at 0 °C for 30 min and then cooled to −78 °C. Ethyl propiolate (2.5 mL, 24.7 mmol) was slowly added, and the mixture was stirred for 30 min at −78 °C. To this yellow solution was slowly added acetaldehyde (1.4 mL, 23.0 mmol), and the mixture was stirred for 1.5 h at −78 °C. TBDMSOTf ((*tert*-butyldimethylsilyl)triflate) (4.8 mL, 25.1 mmol) was added, and the mixture was allowed to warm to room temperature. Ether extraction, washing with saturated $NaHCO_3$ aqueous solution and with brine, drying with anhydrous $MgSO_4$, concentration under vacuum, and

(24) The reactions of the Ph- and *t*-Bu-substituted monoesters should be examined for comparison purpose, but the reactivities of those substrates was quite low in comparison with those of **3** and **4**.

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purification by silica-gel column chromatography (SiO_2, 150 g, *n*-hexane:AcOEt = 100:1 to 50:1) gave ethyl 4-((*tert*-butyldimethylsilyl)oxy)-2-pentynoate (1.99 g, 7.8 mmol) in 31.5% yield. When (TBDMS)Cl was used instead of TBDMSOTf, the yield of the product was diminished. Reduction of the triple bond was carried out with Lindlar catalyst (0.21 g) in EtOH (6 mL). Removal of the catalyst with a short column of silica gel followed by purification with column chromatography (SiO_2, 150 g, *n*-hexane:AcOEt = 100:1) gave **4b** (1.08 g, 4.18 mmol) in 53.8% yield: ^{1}H NMR ($CDCl_3$) δ 0.034 (s, 3 H), 0.052 (s, 3 H), 0.877 (s, 9 H), 1.252 (d, J = 6.5 Hz, 3 H), 1.288 (t, J = 7.0 Hz, 3 H), 4.170 (q, J = 7.0 Hz, 2 H), 5.440 (ddq, J = 1.0, 6.5, and 8.0 Hz, 1 H), 5.645 (dd, J = 1.0 and 11.5 Hz, 1 H), 6.202 (dd, J = 8.0 and 11.5 Hz, 1 H); HRMS calcd for $C_{13}H_{26}O_3Si$ 258.1651, found 258.1638. Anal. Calcd for $C_{13}H_{26}O_3Si$: C, 60.41; H, 10.14. Found: C, 60.18; H, 10.04.

Ethyl 4-((*tert*-Butyldimethylsilyl)oxy)-2-(ethoxycarbonyl)-2-pentenoate (5b). Dry THF (100 mL) was placed in a 300-mL flask kept at 0 °C under Ar, and $TiCl_4$ (3.8 mL, 34.4 mmol) was added with a syringe to give a yellow suspension. Diethyl malonate (2.63 mL, 17.3 mmol) and then 2-((*tert*-butyldimethylsilyl)oxy)propanal (3.24 g, 17.2 mmol) were added. The color of the solution changed from yellow to brown. Addition of pyridine (5.6 mL, 69 mmol) gave a deep red-brown solution. The mixture was stirred for 2 days at room temperature. Addition of saturated NH_4Cl aqueous solution, extraction three times with ether, washing the organic layer with saturated NaCl aqueous solution, drying with anhydrous $MgSO_4$, concentration under vacuum, and purification by silica-gel column chromatography (SiO_2, 150 g, *n*-hexane:AcOEt = 10:1) gave **5b** (3.46 g, 7.6 mmol) in 43% yield: ^{1}H NMR ($CDCl_3$) δ 0.038 (s, 3 H), 0.047 (s, 3 H), 0.874 (s, 9 H), 1.277 (d, J = 8.2 Hz, 3 H), 1.302 (t, J = 9.2 Hz, 3 H), 1.328 (t, J = 9.2 Hz, 3 H), 4.205–4.353 (m, 4 H), 4.678 (dq, J = 11.0 and 8.2 Hz, 1 H), 6.884 (d, J = 11.0 Hz, 1 H). Anal. Calcd for $C_{16}H_{30}O_5Si$: C, 58.14; H, 915. Found: C, 57.84; H, 9.15.

Ethyl 4-(Benzyloxy)-2-(ethoxycarbonyl)-4-phenyl-2-butenoate (20). In a 300-mL flask under Ar were placed Li wire (3.7 g, 0.53 mol) and ether (50 mL). An ether (100 mL) solution of bromobenzene (28.0 mL, 0.266 mol) was added at a rate sufficiently slow to keep a gentle reflux. After the addition was complete, reflux was continued for 2 h. An ether solution of phenyllithium thus obtained was cooled to −78 °C. An ether (50 mL) solution of 3-methyl-2-butenal (20 mL, 0.207 mol) was added dropwise, and the mixture was allowed to warm to room temperature. Stirring was continued for 12 h. Addition of saturated NH_4Cl aqueous solution, washing with brine, drying with anhydrous $MgSO_4$, concentration under vacuum, and purification by column chromatography (SiO_2, 150 g, *n*-hexane:AcOEt = 10:1) gave 3-methyl-1-phenyl-2-buten-1-ol (21.4 g, 132 mmol) in 63.7% yield: ^{1}H NMR ($CDCl_3$) δ 1.746 (s, 1 H), 1.755 (d, J = 1.0 Hz, 3 H), 1.812 (d, J = 1.0 Hz, 3 H), 5.39–5.50 (m, 2 H), 7.26–7.42 (m, 5 H).

In a 300-mL flask kept under Ar was placed 60% NaH (5.8 g, 145 mmol), and the mineral oil was removed by washing several times with hexane. THF (100 mL) was added as a solvent, and the alcohol obtained above was added. Stirring was continued until hydrogen evolution ceased. After 1 h, benzyl bromide (15.7 mL, 132 mmol) was added at room temperature. Stirring was continued for 2 days to give a white suspension. Addition of saturated NH_4Cl aqueous solution, extraction with ether three times, washing the ether extract with brine, drying with anhydrous $MgSO_4$, and concentration under vacuum gave the corresponding benzyl ether: ^{1}H NMR ($CDCl_3$) δ 1.713 (d, J = 1.0 Hz, 3 H), 1.750 (d, J = 1.0 Hz, 3 H), 4.473 (d, J = 12.0 Hz, 1 H), 4.487 (d, J = 12.0 Hz, 1 H), 5.37–5.41 (m, 1 H), 5.083 (d, J = 9.0 Hz, 1 H). Without further purification, the double bond of the benzyl ether was oxidized with ozone. In a 200-mL flask were placed the benzyl ether and CH_2Cl_2 (30 mL), and the mixture was cooled to −78 °C. O_3 was passed through the solution until the typical color of ozonide appeared. Oxygen was passed through the solution for 10 min, and dimethyl sulfide (20 mL) was added. The mixture was allowed to warm to room temperature, and the solvent was removed by aspirator. Purification by column chromatography (SiO_2, 250 g, *n*-hexane:AcOEt = 10:1) gave 2-(benzyloxy)-2-phenylethanal (8.38 g, 37.5 mmol) in 28.4% yield: ^{1}H NMR ($CDCl_3$) δ 4.55 (d, J = 11.5 Hz, 1 H), 4.69 (d, J = 11.5 Hz, 1 H), 4.81 (d, J = 1.8 Hz, 1 H), 7.29–7.44 (m, 10 H), 9.63 (d, J = 1.8 Hz, 1 H). The reaction of the aldehyde with diethyl malonate was carried out as described above. Purification of the product by column chromatography (SiO_2, 100 g, *n*-hexane:AcOEt = 25:1 to 10:1) gave **20** (1.72 g, 4.7 mmol) in 52.8% yield: ^{1}H NMR ($CDCl$)$_3$ δ 1.25 (t, J = 7.0 Hz, 3 H), 1.273 (t, J = 7.0 Hz, 3 H), 4.50 (s, 2 H), 5.260 (d, J = 8.0 Hz, 1 H), 7.27–7.46 (m, 10 H); HRMS calcd for $C_{22}H_{24}O_5$ 368.1624, found 368.1592.

Ethyl 4-(Benzyloxy)-5,5-dimethyl-2-(ethoxycarbonyl)-2-hexenoate (21). In a 100-mL flask kept under Ar were placed trityl chloride (27.9 g, 100 mmol), DMAP (0.5 g, 4.1 mmol), DMF (20 mL), 3,3-dimethyl-1,2-butanediol (11.8 g, 100 mmol), and Et_3N (21 mL). The mixture was stirred for 2 days at room temperature. Addition of water, extracting three times with CH_2Cl_2, drying with anhydrous Na_2SO_4, and concentration under vacuum gave the corresponding trityl ether; selective protection of the primary alcohol was accomplished. In a 500-mL flask kept under Ar was placed 60% NaH (4.4 g, 100 mmol), which was washed several times with hexane. THF (100 mL) was added, and then the trityl ether dissolved in 50 mL of THF was added dropwise at room temperature. The mixture was stirred for 24 h. Benzyl bromide (11.9 mL, 100 mmol) was added, and the mixture was stirred for 2 days. Addition of saturated NH_4Cl aqueous solution, extraction with ether and then with CH_2Cl_2, washing the organic layer with brine, drying with anhydrous $MgSO_4$, and concentration under vacuum gave the corresponding benzyl ether. Selective deprotection of the trityl group was carried out as follows. A mixture of the benzyl ether, methanol, and small amounts of TsOH was heated at 80 °C for 8 h. Extraction with ether, washing with saturated $NaHCO_3$ aqueous solution and with brine, drying with anhydrous $MgSO_4$, concentration, and purification (SiO_2, 300 g, *n*-hexane:AcOEt = 10.1 to 5:1) gave 2-(benzyloxy)-3,3-dimethylbutan-1-ol (8.35 g, 40.1 mmol) in 40.1% yield: ^{1}H NMR ($CDCl_3$) δ 0.975 (s, 9 H), 1.749 (dd, J = 4.8 and 7.7 Hz, 1 H), 3.191 (s, J = 3.3 and 7.3 Hz, 1 H), 3.633 (ddd, J = 4.8, 7.3, and 11.3 Hz, 1 H), 3.774 (ddd, J = 3.3, 7.7, and 11.3 Hz, 1 H), 4.681 (d, J = 11.7 Hz, 1 H), 4.707 (d, J = 11.7 Hz, 1 H), 7.28–7.40 (m, 5 H). In a 300-mL flask under Ar was placed CH_2Cl_2 (100 mL) at −78 °C. Oxalyl chloride (4.1 mL, 48.1 mmol) and then DMSO (7.8 mL, 120.3 mmol) were added. After the reaction mixture was stirred for 10 min, the benzyloxy alcohol (8.25 g, 40.1 mmol) obtained above, dissolved in CH_2Cl_2 (30 mL), was added slowly and the mixture was stirred at −78 °C for 45 min. Addition of Et_3N (50 mL) at 0 °C, stirring overnight, and the usual workup and purification (SiO_2, 200 g, *n*-hexane: AcOEt = 20:1) gave 2-(benzyloxy)-3,3-dimethyl-1-butanal (6.75 g, 32.7 mmol) in 81.6% yield: ^{1}H NMR ($CDCl_3$) δ 1.560 (s, 9 H), 3.290 (d, J = 3.6 Hz, 1 H), 4.441 (d, J = 11.7 Hz, 1 H), 4.658 (d, J = 11.7 Hz, 1 H), 7.36–7.29 (m, 5 H), 9.734 (d, J = 3.6 Hz, 1 H).

The reaction of the aldehyde (4.9 g, 23.7 mmol) with diethyl malonate (3.6 mL, 23.7 mmol) was carried out as described above. Purification (SiO_2, 300 g, *n*-hexane:AcOEt = 20:1 to 10:1) gave **21** (7.28 g, 20.9 mmol) in 88.1% yield: ^{1}H NMR ($CDCl_3$) δ 0.946 (s, 9 H), 1.271 (t, J = 7.0 Hz, 3 H), 1.313 (t, J = 7.0 Hz, 3 H), 3.790 (d, J = 9.8 Hz, 1 H), 4.238 (q, J = 7.0 Hz, 2 H), 4.266 (q, J = 7.0 Hz, 2 H), 4.313 (d, J = 12.0 Hz, 1 H), 4.578 (d, J = 12.0 Hz, 1 H), 6.905 (d, J = 9.5 Hz, 1 H), 7.27–7.33 (m, 5 H); HRMS calcd for $C_{20}H_{28}O_5$ 348.1937, found 349.2018. Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.62; H, 8.04.

Reaction of Vinylcopper Reagents. In a 50-mL flask kept under Ar was placed 3 equiv of the copper reagent. An ether (2 mL) solution of the substrates (0.3 mmol) was added dropwise at −35 °C, and the resulting mixture was stirred at this temperature for 4 h. The reaction was quenched by adding a 1:1 mixture (5 mL) of saturated NH_4Cl aqueous solution and aqueous ammonium solution. The usual workup gave the conjugate addition product, which was analyzed by capillary GLC (SE-30, Shimazu).

Vinyllithium was synthesized by the reported procedure,[30] and the concentration was determined by the usual titration. Vinylcopper reagents were prepared as follows. (Vinyl)Cu: Vinyllithium (0.9 mmol) was added to an ether (2 mL) suspension of CuI (171.4 mg, 0.9 mmol) cooled at −35 °C, and the resulting black suspension was stirred for 10 min. $(Vinyl)_2CuLi$: Vinyllithium (1.8 mmol) was added to an ether (2 mL) suspension of CuI (0.9 mmol) at −35 °C, and the resulting black suspension was stirred for 10 min. (Vinyl)Cu(CN)Li: Vinyllithium (0.9 mmol) was added to an ether (2 mL) solution of CuCN (80.6 mg, 0.9 mmol) at −78 °C, and the mixture was stirred for 10 min. $(Vinyl)_2Cu(CN)Li_2$: Vinyllithium (1.8 mmol) was slowly added to an ether (2 mL) solution of CuCN (80.6 mg, 0.9 mmol) at −78 °C, and the mixture was again cooled to −78 °C. $(Vinyl)CuL_n{\cdot}BF_3$: Vinylcopper reagents prepared as shown above were cooled to −78 °C; then $BF_3{\cdot}OEt_2$ (0.11 mL, 0.9 mmol) was added and the mixture was stirred for 5 min at this temperature.

Reaction of Alkylcopper Reagents. To an ether solution of 3 equiv of the copper reagents, cooled at −78 °C, was slowly added an ether (2 mL) solution of substrates (0.3 mmol); the mixture was allowed to warm to −30 °C, and stirring was continued for 2 h at this temperature. The usual workup gave the products, whose diastereomer ratios were determined by capillary GLC in the case of the Me adducts and by ^{1}H NMR in the case of the Bu adduct. Alkylcopper reagents were prepared as follows.

(30) Wakefield, B. J. *Organolithium Methods*; Academic Press: London, 1988; p 46.

MeCu: An ether solution of MeLi·LiBr (0.86 M × 1.05 mL, 0.9 mmol) was slowly added to a precooled ether (2 mL) suspension of CuI (171.4 mg, 0.9 mmol) at 0 °C, stirring was continued for 10 min at this temperature, and then the mixture was cooled to −78 °C. Me_2CuLi: A procedure similar to that above, except for the use of 2 equiv of MeLI·LiBr, was used. Me_3CuLi_2: MeLi·LiBr (3 equiv) was used, and the rest of the procedure was the same as above. MeCu(CN)Li: An ether solution of MeLi·LiBr (0.86 M × 1.05 mL, 0.9 mmol) was added slowly to a precooled ether (2 mL) suspension of CuCN (80.6 mg, 0.9 mmol) at −78 °C. The mixture was allowed to warm to 0 °C, and a homogeneous solution was obtained. After 10 min, the solution was cooled to −78 °C. $Me_2Cu(CN)Li_2$: A procedure similar to that above, except for the use of 2 equiv of MeLi·LiBr, was used. $MeCuL_n{\cdot}BF_3$: $BF_3{\cdot}OEt_2$ (0.11 mL, 0.9 mmol) was added to each $MeCuL_n$ at −78 °C, and the mixture was stirred for 5 min. $BuCuL_n$: A procedure similar to that above, except for the use of BuLi–hexane solution instead of MeLi·LiBr and for the use of −50 °C instead of 0 °C, was used.

Reaction of Methallylcopper Reagents. To an ether solution of 3 equiv of the copper reagents, cooled at −78 °C, was added an ether (2 mL) solution of substrates (0.3 mmol), and the mixture was stirred for 3 h at −40 °C. In the case of the $BF_3{\cdot}OEt_2$-complexed reagent, stirring was carried out at −78 °C for 3 h. The usual workup followed by a short silica-gel column chromatography (hexane as an eluent) to remove tributyltin residues gave the products, which were analyzed by capillary GLC. Methallyllithium was prepared from methallyltributyltin and *n*-BuLi according to the literature procedure.[31] Methallylcopper reagents were prepared as follows. (Methallyl)Cu: Methallyllithium (0.9 mmol) was slowly added to an ether (2 mL) suspension of CuI (171.4 mg, 0.9 mmol) at −40 °C, and the mixture was stirred for 10 min. $(Methallyl)_2CuLi$: Two equivalents of methallyllithium were used at −40 °C. (Methallyl)Cu(CN)LI: Methallyllithium (0.9 mmol) was slowly added to an ether (2 mL) solution of CuCN (80.6 mg, 0.9 mmol), cooled at −78 °C, and the mixture was stirred for 10 min at this temperature. $(Methallyl)_2Cu(CN)Li_2$: A procedure similar to that above, except for the use of 2 equiv of methallyllithium, was used. $(Methallyl)CuL_n{\cdot}BF_3$: $BF_3{\cdot}OEt_2$ (0.11 mL, 0.9 mmol) was added at −78 °C to each copper reagent, and stirring was continued for 5 min at this temperature.

Ethyl *anti*-3-(1-(Benzyloxy)ethyl)-4-pentenoate (6a): ^{1}H NMR ($CDCl_3$) δ 1.14 (d, *J* = 6.2 Hz, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 2.39 (dd, *J* = 9.0 and 14.8 Hz, 1 H), 2.58 (dd, *J* = 5.4 and 14.8 Hz, 1 H), 2.74–2.86 (m, 1 H), 3.59 (dq, *J* = 3.8 and 6.2 Hz, 1 H), 4.09 (q, *J* = 7.1 Hz, 2 H), 4.45 (d, *J* = 11.8 Hz, 1 H), 4.57 (d, *J* = 11.8 Hz, 1 H), 5.09 (dd, *J* = 2.0 and 16.5 Hz, 1 H), 5.10 (dd, *J* = 2.0 and 11.3 Hz, 1 H), 5.76 (ddd, *J* = 8.5, 11.3, and 16.5 Hz, 1 H), 7.32–7.37 (m, 5 H); IR (CCl_4) 2983, 1726, 1640, 1446, 1369, 1332, 1263, 1175, 1093, 1025, 920, 692 cm^{-1}; HRMS calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1559.

Ethyl *syn*-3-(1-(Benzyloxy)ethyl)-4-pentenoate (7a): ^{1}H NMR ($CDCl_3$) δ 1.18 (d, *J* = 6.0 Hz, 3 H), 1.21 (t, *J* = 7.0 Hz, 3 H), 2.32 (dd, *J* = 9.0 and 15.0 Hz, 1 H), 2.64 (dd, *J* = 5.0 and 15.0 Hz, 1 H), 2.68–2.81 (m, 1 H), 3.44 (dq, *J* = 6.0 and 6.0 Hz, 1 H), 4.07 (q, *J* = 7.0 Hz, 2 H), 4.44 (d, *J* = 11.5 Hz, 1 H), 4.60 (d, *J* = 11.5 Hz, 1 H), 5.08 (dd, *J* = 2.0 and 10.0 Hz, 1 H), 5.11 (dd, *J* = 2.0, 2.0, and 17.0 Hz, 1 H), 5.73 (ddd, *J* = 8.5, 10.0, and 17.0 Hz, 1 H), 7.32–7.37 (m, 5 H); IR (CCl_4) 2983, 1727, 1640, 1450, 1371, 1260, 1179, 1092, 1029, 923, 694 cm^{-1}; HRMS calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1567.

Ethyl *anti*-3-(1-(Benzyloxy)ethyl)-2-(ethoxycarbonyl)-4-pentenoate (8a): ^{1}H NMR ($CDCl_3$) δ 1.20 (d, *J* = 6.0 Hz, 3 H), 1.20 (t, *J* = 7.0 Hz, 3 H), 1.22 (t, *J* = 7.0 Hz, 3 H), 2.92 (ddd, *J* = 6.8, 8.8, and 10.0 Hz, 1 H), 3.63 (dq, *J* = 6.0 and 8.8 Hz, 1 H), 3.84 (d, *J* = 6.8 Hz, 1 H), 4.00–4.20 (m, 4 H), 4.36 (d, *J* = 11.0 Hz, 1 H), 4.57 (d, *J* = 11.0 Hz, 1 H), 5.14 (dd, *J* = 2.0 and 10.0 Hz, 1 H), 5.16 (dd, *J* = 2.0 and 17.0 Hz, 1 H), 5.89 (ddd, *J* = 10.0, 10.0, and 17.0 Hz, 1 H), 7.31–7.35 (m, 5 H); IR (CCl_4) 2983, 1729, 1450, 1367, 1129, 1025, 925, 692 cm^{-1}; HRMS calcd for $C_{19}H_{26}O_5$ 334.1781, found 334.1780.

Ethyl *syn*-3-(1-(Benzyloxy)ethyl)-2-(ethoxycarbonyl)-4-pentenoate (9a): ^{1}H NMR ($CDCl_3$) δ 1.17 (d, *J* = 6.0 Hz, 3 H), 1.21 (t, *J* = 7.0 Hz, 3 H), 1.22 (t, *J* = 7.0 Hz, 3 H), 2.86 (ddd, *J* = 2.5, 10.5, and 10.5 Hz, 1 H), 3.70 (dq, *J* = 2.5 and 7.0 Hz, 1 H), 3.75 (d, *J* = 10.5 Hz, 1 H), 4.00–4.21 (m, 4 H), 4.30 (d, *J* = 11.5 Hz, 1 H), 4.56 (d, *J* = 11.5 Hz, 1 H), 5.12 (dd, *J* = 2.0 and 17.0 Hz, 1 H), 5.16 (dd, *J* = 2.0 and 10.5 Hz, 1 H), 5.79 (ddd, *J* = 10.5, 10.5, and 17.0 Hz, 1 H), 7.31–7.38 (m, 5 H); IR (CCl_4) 2983, 1733, 1444, 1258, 1150, 1029, 925, 695 cm^{-1}; HRMS calcd for $C_{19}H_{26}O_5$ 334.1781, found 334.1782.

Ethyl 4-(Benzyloxy)-3-methylpentanoate (6b and 7b): **6b** ^{1}H NMR ($CDCl_3$) δ 0.96 (d, *J* = 6.4 Hz, 3 H), 1.16 (d, *J* = 6.1 Hz, 3 H), 1.22 (t, *J* = 7.0 Hz, 3 H), 2.11–2.27 (m, 2 H), 2.48–2.54 (m, 1 H), 3.35 (m, 1 H), 4.08 (q, *J* = 7.0 Hz, 2 H), 4.42 (d, *J* = 11.6 Hz, 1 H), 4.57 (d, *J* = 11.6 Hz, 1 H), 7.24–7.33 (m, 5 H); **7b** ^{1}H NMR δ 0.95 (d, *J* = 6.7 Hz, 3 H), 1.13 (d, *J* = 6.4 Hz, 3 H), 1.23 (t, *J* = 7.0 Hz, 3 H), 2.11–2.27 (m, 2 H), 2.48–2.54 (m, 1 H), 3.48 (m, 1 H), 4.08 (q, *J* = 7.0 Hz, 2 H), 4.45 (d, *J* = 11.9 Hz, 1 H), 4.54 (d, *J* = 11.9 Hz, 1 H), 7.24–7.33 (m, 5 H); IR (CCl_4) 700, 720, 1120, 1180, 1280, 1380, 1450, 1730, 2950 cm^{-1}; HRMS calcd for $C_{15}H_{22}O_3$ *m/z* 250.1507, found *m/z* 250.1567.

Ethyl 4-(Benzyloxy)-3-butylpentanoate (6c and 7c): **6c** ^{1}H NMR ($CDCl_3$) δ 0.87–0.93 (m, 3 H), 1.10–1.55 (6 H), 1.17 (d, *J* = 6.1 Hz, 3 H), 1.21 (t, *J* = 7.0 Hz, 3 H), 2.05 (m, 1 H), 2.30 (dd, *J* = 6.7 and 15.3 Hz, 1 H), 2.38 (dd, *J* = 6.7 and 15.3 Hz, 1 H), 3.50 (m, 1 H), 4.07 (q, *J* = 7.0 Hz, 2 H), 4.42 (d, *J* = 11.6 Hz, 1 H), 4.57 (d, *J* = 11.6 Hz, 1 H), 7.25–7.33 (m, 5 H); **7c** ^{1}H NMR δ 0.87–0.93 (m, 3 H), 1.18–1.51 (6 H), 1.11 (d, *J* = 6.4 Hz, 3 H), 1.22 (t, *J* = 7.0 Hz, 3 H), 2.15 (dd, *J* = 7.3 and 15.0 Hz, 1 H), 2.25 (m, 1 H), 2.52 (dd, *J* = 5.8 and 15.0 Hz, 5 H), 3.59 (m, 1 H), 4.08 (q, *J* = 7.0 Hz, 2 H), 4.48 (d, *J* = 11.9 Hz, 1 H), 4.50 (d, *J* = 11.9 Hz, 1 H), 7.23–7.34 (m, 5 H); IR (neat) 720, 1040, 1080, 1120, 1180, 1280, 1380, 1460, 1730, 1790, 2880, 2950, 2980 cm^{-1}; HRMS calcd for $C_{18}H_{28}O_3$ *m/z* 292.2039, found *m/z* 292.1996.

4-(Benzyloxy)-2-(ethoxycarbonyl)-3-methylpentanoate (8b and 9b): **9b** ^{1}H NMR ($CDCl_3$) δ 0.99 (d, *J* = 7.0 Hz, 3 H), 1.20 (t, *J* = 7.0 Hz, 3 H), 1.21 (d, *J* = 6.4 Hz, 3 H), 1.26 (t, *J* = 7.0 Hz, 3 H), 2.44 (ddq, *J* = 3.0, 7.0, and 9.5 Hz, 1 H), 3.53 (d, *J* = 9.5 Hz, 1 H), 3.61 (dq, *J* = 3.0 and 6.4 Hz, 1 H), 4.17 (q, *J* = 7.0 Hz, 4 H), 4.34 (d, *J* = 11.6 Hz, 1 H), 4.52 (d, *J* = 11.6 Hz, 1 H), 7.25–7.32 (m, 5 H); IR (neat) 700, 740, 1040, 1160, 1180, 1200, 1280, 1310, 1380, 1460, 1740, 1760, 3000 cm^{-1}; HRMS calcd for $C_{18}H_{26}O_5$ *m/z* 322.1781, found *m/z* 322.1783. The anti isomer **8b** could not be isolated in a pure form but was obtained as a mixture with **9b**. The mixture was decarboxylated, and a mixture of the monoesters **6b** and **7b** was obtained. The product identification was carried out at this stage.

4-(Benzyloxy)-3-butyl-2-(ethoxycarbonyl)pentanoate (8c and 9c): **8c** ^{1}H NMR ($CDCl_3$) δ 0.86–0.90 (m, 3 H), 1.16–1.44 (15 H), 2.32 (m, 1 H), 3.61 (m, 1 H), 3.64 (d, *J* = 6.1 Hz, 1 H), 4.01 (q, *J* = 7.0 Hz, 2 H), 4.18 (q, *J* = 7.0 Hz, 2 H), 4.40 (d, *J* = 11.3 Hz, 1 H), 4.53 (d, *J* = 11.3 Hz, 1 H), 7.23–7.36 (m, 5 H); ^{1}H NMR ($CDCl_3$) δ 0.86–0.90 (m, 3 H), 1.16–1.44 (15 H), 2.47 (m, 1 H), 3.57 (d, *J* = 8.2 Hz, 1 H), 3.71 (m, 1 H), 4.01 (q, *J* = 7.0 Hz, 2 H), 4.18 (q, *J* = 7.0 Hz, 2 H), 4.39 (d, *J* = 11.6 Hz, 1 H), 4.47 (d, *J* = 11.6 Hz, 1 H), 7.23–7.36 (m, 5 H); IR (neat) 700, 740, 1040, 1150, 1250, 1270, 1380, 1460, 1730, 1750, 2880, 2980 cm^{-1}; HRMS calcd for $C_{12}H_{32}O_5$ *m/z* 364.2250, found *m/z* 364.2250.

Ethyl *anti*-3-(1-(Benzyloxy)ethyl)-5-methyl-5-hexenoate (6d): ^{1}H NMR ($CDCl_3$) δ 1.17 (d, *J* = 6.3 Hz, 3 H), 1.21 (t, *J* = 7.0 Hz, 3 H), 1.88–2.00 (m, 1 H), 2.21–2.36 (m, 4 H), 3.55 (dq, *J* = 3.6 and 6.3 Hz, 1 H), 4.07 (q, *J* = 7.0 Hz, 2 H), 4.42 (d, *J* = 11.6 Hz, 1 H), 4.57 (d, *J* = 11.6 Hz, 1 H), 4.65–4.80 (br d, 2 H), 7.32–7.36 (m, 5 H); IR (CCl_4) 2990, 1733, 1450, 1380, 1200, 1160, 1096, 1032, 895, 732, 700 cm^{-1}; HRMS calcd $C_{18}H_{26}O_3$ 290.1882, found 290.1880.

Ethyl *syn*-3-(1-(Benzyloxy)ethyl)-5-methyl-5-hexenoate (7d): ^{1}H NMR ($CDCl_3$) δ 1.14 (d, *J* = 6.3 Hz, 3 H), 1.22 (t, *J* = 7.0 Hz, 3 H), 1.72 (br s, 3 H), 1.94–2.54 (m, 5 H), 3.57 (dq, *J* = 3.9 and 6.3 Hz, 1 H), 4.07 (q, *J* = 7.0 Hz, 2 H), 4.46 (d, *J* = 11.5 Hz, 2 H), 4.53 (d, *J* = 11.5 Hz, 1 H), 4.68–4.79 (br d, 2 H), 7.32–7.37 (m, 5 H); IR (CCl_4) 2975, 1727, 1442, 1371, 1196, 1154, 1092, 1125, 892, 720, 692 cm^{-1}; HRMS calcd for $C_{18}H_{26}O_3$ 290.1882, found 290.1888.

Ethyl *syn*-3-(1-(Benzyloxy)ethyl)-2-(ethoxycarbonyl)-5-methyl-5-hexenoate (9d): ^{1}H NMR ($CDCl_3$) δ 1.15 (t, *J* = 7.1 Hz, 3 H), 1.23 (d, *J* = 6.2 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.73 (br s, 3 H), 2.19 (dd, *J* = 7.0 and 14.0 Hz, 1 H), 2.25 (dd, *J* = 7.0 and 14.0 Hz, 1 H), 2.69 (ddt, *J* = 3.0, 7.0, and 7.0 Hz, 1 H), 3.55 (d, *J* = 7.0 Hz, 1 H), 3.76 (dq, *J* = 3.0 and 6.2 Hz, 1 H), 4.37 (d, *J* = 12.3 Hz, 1 H), 4.47 (d, *J* = 12.3 Hz, 1 H), 4.73–4.81 (br s, 2 H), 7.30–7.34 (m, 5 H); IR (CCl_4) 2990, 1733, 1644, 1454, 1446, 1378, 1258, 1217, 1154, 1096, 1033, 897, 729, 686 cm^{-1}; HRMS calcd for $C_{21}H_{30}O_5$ 362.2094, found 362.2093.

Preparation of 10 and 11. The benzyl protective group was easily removed by the usual catalytic hydrogenation using 5% Pd on carbon in EtOH. In the case of **6a,d** and **7a,d**, the double bond was reduced simultaneously. The deprotections of **6** and **7** under H_2 at room temperature for 12 h produced the lactones **10** and **11**, respectively, in an essentially quantitative yield.

Ethyl *anti*-4-((*tert*-Butyldimethylsilyl)oxy)-3-methylpentanoate: ^{1}H NMR ($CDCl_3$) δ 0.037 (s, 3 H), 0.043 (s, 3 H), 0.882 (s, 9 H), 0.920 (d, *J* = 6.2 Hz, 3 H), 1.089 (d, *J* = 6.2 Hz, 3 H), 1.260 (t, *J* = 7.0 Hz, 3 H), 1.90–2.52 (m, 3 H), 3.662 (dq, *J* = 4.9 and 6.2 Hz, 1 H), 4.128 (q, *J* = 7.0 Hz, 2 H); HRMS calcd for $C_{14}H_{30}O_3Si$ 274.1964, found 259.1729 ($M^+ - CH_3$).

Ethyl *syn*-((4-*tert*-Butyldimethylsilyl)oxy)-3-methylpentanoate: ^{1}H NMR ($CDCl_3$) δ 0.030 (s, 3 H), 0.038 (s, 3 H), 0.882 (s, 9 H), 0.886 (d, *J* = 6.5 Hz, 3 H); 1.064 (d, *J* = 6.3 Hz, 3 H), 1.254 (t, *J* = 7.0 Hz,

(31) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079.

3 H), 1.93-2.51 (m, 3 H), 3.776 (dq, J = 6.3 and 3.4 Hz, 1 H), 4.126 (q, J = 7.0 Hz, 2 H); HRMS calcd for $C_{14}H_{30}O_3Si$ 274.1964, found 259.1723 ($M^+ - CH_3$).

Ethyl *anti*-4-((*tert*-Butyldimethylsilyl)oxy)-2-(ethoxycarbonyl)-3-methylpentanoate: ^1H NMR ($CDCl_3$) δ 0.046 (s, 3 H), 0.052 (s, 3 H), 0.879 (2, 9 H), 0.968 (d, J = 7.0 Hz, 3 H), 1.095 (d, J = 6.0 Hz, 3 H), 1.265 (t, J = 7.0 Hz, 6 H), 2.262 (ddq, J = 6.0, 7.0, and 7.0 Hz, 1 H), 3.568 (d, J = 7.0 Hz, 1 H), 3.788 (dq, J = 6.0 and 6.0 Hz, 1 H), 4.12-4.23 (m, 4 H); HRMS calcd for $C_{17}H_{34}O_5Si$ 346.2176, found 346.2170.

Ethyl *syn*-4-((*tert*-Butyldimethylsilyl)oxy)-2-(ethoxycarbonyl)-3-methylpentanoate: ^1H NMR ($CDCl_3$) δ 0.00 (s, 3 H), 0.024 (s, 3 H), 0.884 (s, 9 H), 0.898 (d, J = 6.8 Hz, 3 H), 1.136 (d, J = 6.2 Hz, 3 H), 1.258 (t, J = 7.0 Hz, 3 H), 1.269 (t, J = 7.0 Hz, 3 H), 2.254 (ddq, J = 2.8, 6.8, and 10.1 Hz, 1 H), 3.432 (d, J = 10.1 Hz, 1 H), 3.904 (dq, J = 2.8 and 6.4 Hz, 1 H), 4.12-4.14 (m, 4 H); HRMS calcd for $C_{17}H_{34}O_5Si$ 346.2176, found 346.2174.

Ethyl *syn*-4-(Benzyloxy)-2-(ethoxycarbonyl)-5,5-dimethyl-3-methylhexanoate (23b): ^1H NMR ($CDCl_3$) δ 0.987 (s, 9 H), 1.032 (d, J = 6.8 Hz, 3 H), 1.268 (t, J = 7.2 Hz, 3 H), 1.282 (t, J = 7.2 Hz, 3 H), 2.668 (ddq, J = 1.0, 6.8, and 10.5 Hz, 1 H), 3.045 (d, J = 1.0 Hz, 1 H), 3.396 (d, J = 10.5 Hz, 1 H), 4.15-4.30 (m, 4 H), 4.562 (d, J = 11.0 Hz, 1 H), 4.646 (d, J = 11.0 Hz, 1 H), 7.33-7.40 (m, 5 H); HRMS calcd for $C_{21}H_{32}O_5$ 364.2250, found 364.2248.

Ethyl *syn*-3-(1-(Benzyloxy)-2,2-dimethylpropyl)-2-(ethoxycarbonyl)-heptanoate (23c): ^1H NMR ($CDCl_3$) δ 0.84 (t, J = 6.8 Hz, 3 H), 0.98 (s, 9 H), 1.257 (t, J = 7.0 Hz, 3 H), 1.283 (t, J = 7.0 Hz, 3 H), 0.9-1.6 (m, 5 H), 1.66-1.85 (m, 1 H), 2.38-2.48 (m, 1 H), 3.112 (d, J = 2.5 Hz, 1 H), 3.48 (d, J = 8.0 Hz, 1 H), 4.165 (q, J = 7.0 Hz, 2 H), 4.192 (q, J = 7.0 Hz, 2 H), 4.538 (d, J = 11.4 Hz, 1 H), 4.651 (d, J = 11.4 Hz, 1 H), 7.32-7.37 (m, 5 H); HRMS calcd for $C_{24}H_{38}O_5$ 406.2720, found 406.2716.

Supplementary Material Available: ^1H NMR spectra for **3-9** and **20-23** (21 pages). Ordering information is given an any current masthead page.

A Novel 1,8-Photoaddition of Dimethyl 1,4-Naphthalenedicarboxylate to Alkenes

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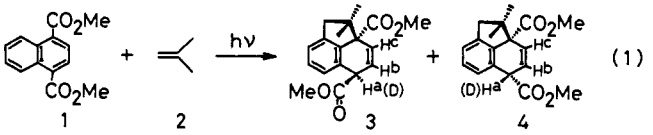
Abstract: Irradiation of dimethyl 1,4-naphthalenedicarboxylate (**1**) with various alkenes **2**, and **10a-d** is found to give novel 1,8-adducts **3**, **11a-d**, **12a,b,d**, and **13b,d**. The 1,8-photoaddition proceeds with retention of the stereochemistry of the alkenes in the reactions with *trans*- and *cis*-2-butene (**5** and **7**). Because there is no evidence for a preformed ground-state complex between **1** and the alkenes, the 1,8-addition proceeds from the singlet excited state of **1**. Fluorescence of **1** is inefficiently but significantly quenched by alkenes, and an exciplex emission is observed on quenching by **10c**. A possible mechanism for the 1,8-photoaddition, involving exciplex formation and an almost synchronous two-bond formation in the exciplex to give a zwitterionic intermediate **15** followed by suprafacial proton transfer, is proposed.

Introduction

Photoadditions of aromatic compounds to alkenes have been extensively investigated for the elucidation of the role of exciplexes and for the exploitation of the synthetic potentials, but considerable interest is still evident.[1] For benzene derivatives, 1,2- (ortho), 1,3- (meta), and 1,4-photoadditions (para) to alkenes have been reported.[1,2] The 1,2- and 1,3-additions are the most common, and the latter is currently receiving considerable attention.[3] On the other hand, for naphthalene derivatives, a number of instances of 1,2- and 1,4-photoaddition have been noted, but 1,3-additions have been seldom observed.[1] We here report a novel 1,8-photoaddition of dimethyl 1,4-naphthalenedicarboxylate (**1**) to alkenes, a formal [3 + 2] photoaddition, which proceeds stereospecifically possibly via a unique zwitterionic intermediate.

Results and Discussion

Irradiation of **1** (4 mM) in the presence of isobutene (**2**) (1 M) in ether leads to the efficient (77%) production of 1,8-adduct **3** (eq 1). The 1,8-photoaddition also proceeds in benzene (47%)



(1)

and in acetonitrile (54%, 1-h irradiation, conversion 25%). However, the secondary isomerization from **3** to the stereoisomer **4** to give an equilibrium mixture of **3** and **4** (**3**:**4** = 3:7) is observed only in acetonitrile with prolonged irradiation time (4 h). The facile isomerization from **3** to **4** is observed upon irradiation of **1** (4 mM), **3** (4 mM), and 1-hexene (**10a**) (800 mM) in acetonitrile with concomitant formation of adducts of **1** and **10a** (vide infra), while the product **3** is photostable in acetonitrile as well as in ether and in benzene.[4] Thus, the secondary isomerization from **3** to **4** observed in acetonitrile may occur through the conjugated base of **3** and **4** that is caused by a base formed during the course of the photoreaction.

The structures and stereochemistry of **3** and **4** are determined from the ^1H and ^{13}C NMR spectra. A smaller vicinal H^a-H^b coupling constant (2.0 or 2.9 Hz) in **3** compared with that (5.5 Hz) in **4** is consistent with a larger dihedral angle (H^a-C-C-H^b) of 95° in **3** compared with that of 30° in **4**, as predicted by the molecular models.

The photoreaction of **1** with **2** in 10% CH_3OD-benzene leads to **3** with a single deuterium incorporated α to the ester carbonyl (D content, 88%). The D contents in **3** and **4** for the reaction in 10% CH_3OD-acetonitrile are 75% and 100%, respectively. The D contents in **3** and **4** are maintained almost constant during the course of the photoreaction, even at low conversion, both in 10% CH_3OD-benzene and in 10% CH_3OD-acetonitrile.

Interestingly, the 1,8-photoaddition proceeds with retention of the stereochemistry of the alkenes. Thus, irradiation of **1** (4 mM) with *trans*-2-butene (**5**) (1 M) in ether gives **6** (85%), and that

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(2) (a) Mattay, J. J. *Photochem.* **1987**, *37*, 167 and references therein. (b) Hamrock, S. J.; Sheridan, R. S. *J. Am. Chem. Soc.* **1989**, *111*, 9247.
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(4) Isomerization from **3** to **4** is also observed upon irradiation of **1** (4 mM) and **3** (4 mM) at a slower rate (~1/10) than that observed in the presence of **10a**.

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