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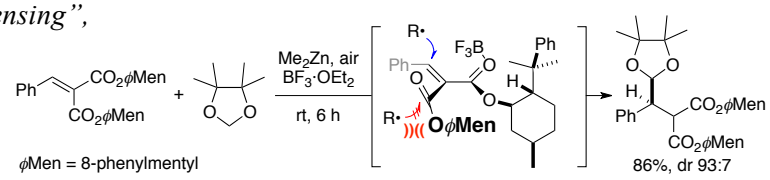

φMen = 8-phenylmentyl

Tetrahedron
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The Rationale for Stereoinduction in Conjugate Addition to Alkylidenemalonates Bearing a Menthol-derived Chiral Auxiliary.

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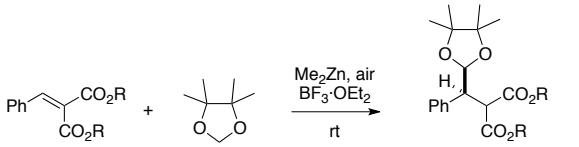
ABSTRACT

Density-functional theory (DFT) calculations provided a new model to rationalize the stereoselectivity in the asymmetric addition to alkylidenemalonate bearing 8-phenylmentyl groups as a chiral auxiliary. The diastereoselectivity in the addition reactions of a tetramethyldioxolanyl radical with various alkyl 8-phenylmentyl benzylidenemalonates strongly supports the proposed model.

1. Introduction

Understanding the origin of the stereoselectivity of chiral auxiliaries is important to gain insights into the design of a new auxiliary. We have been engaged in the development of radical reactions using dimethylzinc.[1,2,3] In the course of the study, we developed benzylidenemalonate bearing 8-phenylmentyl (*ϕ*Men) chiral auxiliaries[4] (**1a**) as useful radical acceptors, to realize high stereoselectivity in radical conjugate addition (Scheme 1).[5,6] A C-centered radical was formed from acetal **2** through C–H bond cleavage by the action of dimethylzinc–air and underwent addition to the benzylidenemalonate with a high diastereomer ratio (dr) of 93:7. Recently, Maruoka and coworkers also utilized this radical acceptor and achieved excellent results.[7] Although the origin of its stereoinduction was unclear, the phenyl groups of the auxiliaries must play an important role for the high selectivity because the corresponding reaction with di-*l*-mentyl (Men) benzylidenemalonate (**1b**) provided a significantly lower dr of 60:40.[5b,7a]



1a: R = *ϕ*Men
1b: R = Men
2
3a: 6 h, 86%, dr 93:7
3b: 5 h, 79%, dr 60:40

Scheme 1. The Asymmetric Radical Addition of **1** and **2** Producing **3**.[5b]

The stereoselectivity in reactions of *ϕ*Men alkenoates was explained as shown in Figure 1 (left).[8] The attraction of the π–π interaction locates the phenyl group of the chiral auxiliary to shield a face of the conjugated C=C bond with s-*trans* conformation so that a reaction occurs on the other face of the double bond. This leads to the expectation that one of the two chiral auxiliaries of the benzylidenemalonate (CO_2R in Figure 1, middle) could be unimportant and omittable. Moreover, the second auxiliary might decrease the selectivity by shielding the face opposite to that the other auxiliary shields (Figure 1, middle vs right). Recently, we developed the *E*/*Z*-selective synthesis of alkylidenemalonates and related compounds.[9] We planned to use this methodology to clarify the roles of the each chiral auxiliary. Here, we report the experimental and computational approaches to propose a new model to explain the stereochemical outcomes of the reaction.

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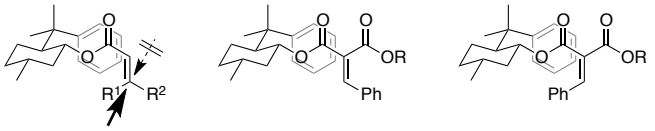
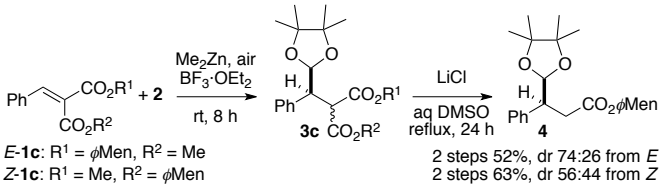


Figure 1. The π–π Interaction Model to Rationalize the Stereoselectivity in 8-Phenylmentyl Alkenoates (left) and the Analogy to Benzylidenemalonate (middle and right).

2. Results and Discussion

2.1. The Conjugate Addition Reaction of the Acetal Radical to Benzylidenemalonates Bearing One Chiral Auxiliary

The two isomeric methyl φMen benzylidenemalonates *E*- and *Z*-**1c** were selectively prepared by our method[9] and tested in a radical conjugate addition (Scheme 2). To a mixture of *E*-**1c** and acetal **2** (250 equiv), $BF_3 \cdot OEt_2$ (2 equiv) and a hexane solution of Me_2Zn (6 equiv) were added. After 8 h, **3c** was obtained as a diastereomixture. The diastereoselectivity was determined at the stage of **4** after removal of the CO_2Me groups by Krapcho decarboxylation with LiCl in refluxing aqueous DMSO. Against our expectation, the selectivity drastically decreased, and the *E*-isomer produced **4** with low diastereoselectivity (dr 74:26). The configuration of the newly created stereogenic center was determined to be *S*, the same as **3a** that obtained from the reaction involving **1a**, by converting **3c** to β-phenyl-γ-butyrolactone and comparing the specific rotation to the reported value (see Experimental Section for detail). Although the other diastereomer of **4** was expected to be produced from the analogy shown in Figure 1 (middle and right), *Z*-**1c** produced the same diastereomer with slight preference (dr 56:44). The rigidity of the olefinic geometry during the reaction was confirmed by leaving *Z*-**1c** and **2** at room temperature (rt) for 8 h in the presence of $BF_3 \cdot OEt_2$ to only recover *Z*-**1c**. After obtaining these puzzling results, we conducted density-functional theory (DFT) calculations to obtain insight into the stereo-determining factors.



Scheme 2. The Asymmetric Radical Addition of *E*- and *Z*-**1c** and **2** Followed by Demethoxycarbonylation to Produce **4**.

2.2. DFT Calculations of the Transition State Structures

Initially, the transition state geometry search was conducted for the addition reaction of the 4,4,5,5-tetramethyl-1,3-dioxan-2-yl radical to dimethyl benzylidenemalonate coordinated to BF_3. Popular functionals, such as B3LYP, B3LYP-D3, M06-2X, and ωB97X-D, with the 6-31G* basis set failed to locate the transition state geometry, which was finally found by using BHandHLYP, previously reported as a suitable functional for radical reactions.[10] The obtained geometry was utilized as a basis for the transition state geometry search for the reaction with methyl φMen ester *E*-**1c**. A conformational search followed by the geometry optimization of the conformers at the BHandHLYP/6-31G* theoretical level provided two transition state structures, TS_{minor} and TS_{major}, leading to the minor and major diastereomers, respectively, with the lowest energies (Figure 2). The ΔG of the transition states was 1.73 kcal/mol at the BHandHLYP/6-31+G*//BHandHLYP/6-31G* theoretical level, corresponding to 95:5 selectivity at 27 °C, and thus the energy difference was overestimated by ca. 1 kcal/mol according to the experimental result (dr 76:24, Scheme 2).

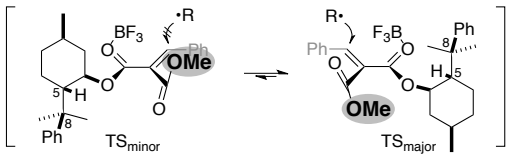


Figure 2. Calculated Transition States for the Radical Addition to **1c**.

In both transition states, the esters in a *cis*-relationship to the vinylic hydrogen take the s-*cis* conformation, and the other ester groups are out of the conjugation.[11] The phenyl groups of the chiral auxiliary are directed toward the outside of the molecules and thus have no π–π interaction probably to avoid unfavorable steric and/or electronic interaction with the ester groups out of the conjugation. The methoxy and carbonyl oxygen atoms in TS_{minor} and TS_{major}, respectively, are directed toward the hydrogen atom at the C-radical center of the approaching acetal radical, likely enjoying favorable electrostatic interaction. The methyl groups of the esters are located on the opposite side of the bulky 5-substituents of the chiral auxiliaries to most likely avoid steric repulsion, causing axial chirality in the C–C bonds between the (*E*)-cinnamate moieties and the ester groups out of conjugation. As a result, the carbonyl oxygen pointed toward the approaching radical in the major transition state TS_{major}, where the axial chirality is R_a, as also observable in the methoxy group in the minor transition state TS_{minor}, where the axial chirality is S_a. This leads to the following speculation: the chiral auxiliary of the s-*cis* ester should differentiate the π-faces of the C=C bond to locate the methyl group of the other ester on the opposite side of the bulky substituent of the auxiliary. Thus, the minor transition state would be destabilized by the steric repulsion between the approaching radical and the methyl group.

The observed low diastereoselectivity with **1b** could also be rationalized according to the above model. When the phenyl group of the auxiliary is replaced with a hydrogen atom (Figure 3), the other ester mentyl group could more easily locate to the same side of the 5-substituent of the chiral auxiliary because the steric repulsion can be relieved in the conformation where the hydrogen atom is pointed toward the ester moiety ($TS^{Men}_{minor}2$). In this conformation, where the axial chirality is R_a, approach of the radical from the same direction must be much easier without the steric repulsion of the ester alkyl group that exists in TS_{minor} (Figure 2) and $TS^{Men}_{minor}1$ (Figure 3). Thus, it would be the role of the phenyl group to prohibit the conformation where the ester alkyl group locates on the same side as the 5-substituent of the auxiliary.

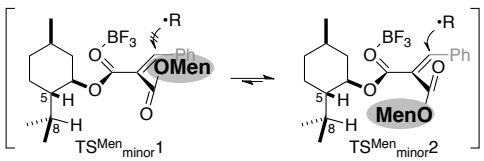


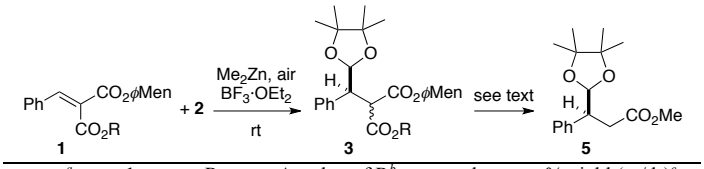
Figure 3. Possible Transition States $TS^{Men}_{minor}1$ and $TS^{Men}_{minor}2$ to Give *epi*-**3b** in the Asymmetric Radical Addition of **2** to **1b**.

2.3. The Steric Effect of the Leaning Ester Group

To verify the above hypothesis, mono φMen benzylidenemalonates, bearing alkyl groups of a different size, were prepared and compared in a reaction (Table 1). To simplify the analysis, the stereoselectivity in the radical addition was determined after removing the stereogenic centers—other than

the newly created one via hydrolysis—with KOH in refluxing aqueous DMSO, followed by decarboxylation and methyl esterification with $TMSCHN_2$ to give **5**. The enantiomer ratio (er) of **5**, as derived from **3c**, was 74:26, which was compatible with the result observed in Scheme 2. In the same manner, the radical addition with isopropyl ester **1d** gave a diastereomeric mixture of **3d**, which was then converted to **5**. As expected, **1d** (A-value of *i*-Pr: 2.21[12]) yielded **5** with a better er of 80:20 (entry 2) than methyl ester *E*-**1c** (A-value of Me: 1.74;[12] entry 1). A mixture of **3e**, obtained from the reaction with *tert*-butyl ester **1e**, could also be converted into **5** analogously to the aforementioned steps. Although not as high as 8-phenylmentyl ester **1a** (A-value of ϕMen: 6.1;[13] entry 4), **1e** (A-value of *t*-Bu: 4.9[14]) realized a good selectivity of 86:14 (entry 3). The observed relationship between the selectivity and the A values of the alkyl groups strongly supports our hypothesis.

Table 1. Asymmetric Radical Addition[a] of **2** with Alkyl 8-Phenylmentyl Benzylidenemalonates **1a**–**d** Followed by Dealkoxycarbonylation.



1 3 5

entry[a]	1	R	A-value of R[b]	product	% yield (er/dr)[c]
1	*E*-**1c**	Me	1.74	**5**	24 (er 74:26)
2	**1d**	*i*-Pr	2.21	**5**	33 (er 80:20)
3	**1e**	*t*-Bu	4.9	**5**	33 (er 86:14)
4[d]	**1a**	ϕMen	6.1	**3a**	86 (dr 93: 7)

[a] The radical reactions were conducted for 9, 3, 3, and 6 h, respectively. [b] Refs 12–14. [c] Er and dr were determined by chiral HPLC analysis after conversion to β-phenyl-γ-butyrolactone and ^{1}H NMR, respectively. [d] Data from ref 5b for comparison.

3. Conclusion

A model to rationalize the stereoselectivity in the asymmetric radical addition to alkylidenemalonate bearing 8-phenylmentyl groups as chiral auxiliaries was proposed. The experimental and computational results indicate that only one of the chiral esters, bearing a *cis*-relationship to the vinylic hydrogen, differentiates the π-faces of the C=C bond to locate the alkyl group of the other ester in the opposite side to the bulky moiety of the chiral auxiliary, and the role of the ester, *trans* to the hydrogen, is just of steric hindrance. This is an example of chirality transfer, where the chirality of the former ester far from the reacting site is transferred to the much closer axial chirality in the C=C–CO_2R moiety of the latter ester.[15] The proposed model is probably applicable to other type of reactions with alkylidenemalonates, and the provided insight must be beneficial toward the design of new chiral auxiliaries.

4. Experimental section

4.1. General

All melting points are uncorrected. Silica gel was used for column chromatography. NMR (400 and 100 MHz for ^{1}H and ^{13}C, respectively) was measured in $CDCl_3$. Chemical shifts (δ) and coupling constants (*J*) are presented in parts per million relative to tetramethylsilane (0 ppm for ^{1}H) or $CDCl_3$ (77.0 ppm for ^{13}C), and hertz, respectively. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; sept, septet; m, multiplet; br, broad. The wave numbers of maximum absorption peaks of IR spectroscopy are presented in cm^{-1}. TOF mass spectrometers were used for ESIMS. Commercially available solvents and reagents were purchased and used without purification.

4.2. Starting Materials

Benzylidenemalonates *E*- and *Z*-**1c**[9], and dioxolane **2**[16] were prepared as reported, and **1d** and **1e** were prepared according to the reported procedure[9] from isopropyl and *tert*-butyl phenylpropiolate,[17] respectively, as follows.

*4.2.1. (E)-Isopropyl (1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Benzylidenemalonate (**1d**)*

A solution of isopropyl phenylpropiolate (1.18 g, 6.27 mmol) in THF (10 mL) were added $Pd(OAc)_2$ (28.2 mg, 12.6 μmol), PPh_3 (82.2 mg, 31.3 μmol) and Bu_3SnH (2.02 mL, 7.51 mmol) at 0 ºC and stirred at the same temperature for 6 h. Then, the reaction mixture was evaporated in vacuo and passed through silica gel column (hexane to hexane/Et_2O 40:1) to provide a crude mixture (1.51 g) which contains isopropyl (*E*)-3-phenyl-2-(tributylstannyl)acrylate and isopropyl (*E*)-3-phenyl-3-(tributylstannyl)acrylate in the ratio of 73:27. The mixture (500 mg), $[Pd_2(dba)_3]\cdot CHCl_3$ (26.9 mg, 26.0 μmol), PPh_3 (34.1 mg, 130 μmol), and $ClCO_2\phi$Men[18] (409 mg, 1.39 mmol) were dissolved in DME (10 mL) in a dry 100-mL round-bottomed flask under argon atmosphere, and the resulting solution was stirred at 80 °C for 12 h. After the addition of H_2O, the mixture was cooled to room temperature and extracted with EtOAc twice. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (10% K_2CO_3 in silica gel,[19] hexane/Et_2O, 25:1 to 15:1) to give **1d** (206 mg, 22% over 2 steps) as a colorless oil with $[\alpha]^{21}_D$ +8.0 (*c* 1.21, $CHCl_3$): ^{1}H NMR: 7.39–7.33 (m, 5H), 7.29 (d, *J* = 7.0, 2H), 7.23 (t, *J* = 7.0, 2H), 7.12 (s, 1H), 7.00 (t, *J* = 7.0, 1H), 5.21 (sept, *J* = 6.5, 1H), 5.00 (td, *J* = 11.0, 4.5, 1H), 2.09–1.95 (m, 2H), 1.65–1.55 (m, 2H), 1.47 (m, 1H), 1.35 (s, 3H), 1.29 (d, *J* = 6.5, 3H), 1.27 (s, 3H), 1.26 (d, *J* = 6.5, 3H), 1.13–1.01 (m, 2H), 0.87 (d, *J* = 6.5, 3H), 0.84 (m, 1H). ^{13}C NMR: 165.9 (C), 163.3 (C), 150.9 (C), 141.1 (CH), 133.1 (C), 130.1(CH), 129.4 (CH), 128.5 (CH), 128.0 (CH), 127.0 (C), 125.5 (CH), 125.2 (CH), 75.8 (CH), 69.2 (CH), 50.7 (CH), 41.7 (CH_2), 39.9 (C), 34.5 (CH_2), 31.3 (CH), 27.1 (CH_3), 26.9 (CH_2), 26.3 (CH_3), 21.7 (CH_3), 21.6 (CH_3), 21.4 (CH_3). IR (neat): 2968, 2870, 1730, 1627, 1450, 1360, 1250, 1100, 950, 750. ESIMS *m*/*z*: 471 (M + Na, 100). HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{29}H_{36}NaO_4$, 471.2511; found, 471.2496.

*4.2.2. (Z)-tert-Butyl (1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Benzylidenemalonate (**1e**)*

A similar procedure to that for **1d** using *tert*-butyl phenylpropiolate (2.00 g, 9.89 mmol) instead of isopropyl phenylpropiolate, THF (20 mL), $Pd(OAc)_2$ (45.4 mg, 20.2 μmol), PPh_3 (141 mg, 53.7 μmol), and Bu_3SnH (2.93 mL, 10.9 mmol); and $[Pd_2(dba)_3]\cdot CHCl_3$ (26.4 mg, 25.5 μmol), PPh_3 (33.4 mg, 12.7 μmol), $ClCO_2\phi$Men (401 mg, 1.36 mmol), and DME (10 mL) gave **1e** (248 mg, 42% over 2 steps) as a colorless oil with $[\alpha]^{21}_D$ +3.1 (*c* 1.46, $CHCl_3$): ^{1}H NMR: 7.45–7.41 (m, 2H), 7.37–7.33 (m, 3H), 7.28 (d, *J* = 7.0, 2H), 7.23 (t, *J* = 7.0, 2H), 7.01 (s, 1H), 7.00 (t, *J* = 7.0, 1H), 5.02 (td, *J* = 11.0, 4.5, 1H), 2.07–1.97 (m, 2H), 1.65–1.43 (m, 3H), 1.54 (s, 9H), 1.35 (s, 3H), 1.27 (s, 3H), 1.12–1.00 (m, 2H), 0.87 (d, *J* = 6.5, 3H), 0.83 (m, 1H). ^{13}C NMR: 165.6 (C), 163.5 (C), 150.9 (C), 140.0 (CH), 133.2 (C), 130.0 (CH), 129.5 (CH), 128.4 (CH), 128.0 (CH), 127.9 (CH), 125.5 (CH), 125.2 (CH), 82.4 (C), 75.6 (CH), 50.7 (CH), 41.8

(CH_2), 39.9 (C), 34.5 (CH_3), 31.3 (CH), 27.9 (CH_3), 27.2 (CH_2), 26.9 (CH_2), 26.2 (CH_3), 21.7 (CH_3). IR (neat): 2960, 2920, 1710, 1620, 1460, 1370, 1250, 1150, 1080, 740. ESIMS *m*/*z*: 485 (M + Na, 100). HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{30}H_{38}NaO_4$, 485.2668; found, 485.2663.

*4.3. Asymmetric Radical Addition of E- and Z-**1c** (Scheme 2): (1R,2S,5R)-5-Methyl-2-(2-methyl-phenylethyl)cyclohexyl (S)- and (R)-3-Phenyl-3-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)propanoate (**4** and epi-**4**)*

*4.3.1. The Reaction with E-**1c***

To a solution of *E*-**1c** (89.4 mg, 0.213 mmol) and $BF_3 \cdot OEt_2$ (53 μL, 0.43 mmol) in **2** (7.4 mL, 50 mmol), was added a 0.96 M hexane solution of Me_2Zn (1.33 mL, 1.3 mmol). The mixture was stirred for 8 h at rt under ordinary atmosphere, and sat. aq. NH_4Cl was added. The whole was extracted with EtOAc twice, and the organic layers were washed with brine, dried over Na_2SO_4, concentrated in vacuo, and passed through a short silica pad (hexane/EtOAc 3:1). The residue was dissolved in DMSO (2 mL), and LiCl (45.2 mg, 1.07 mmol) and H_2O (29 μL, 1.6 mmol) were added to the solution. The mixture was stirred at 130 °C for 24 h and diluted with water, and the whole was extracted with Et_2O twice. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 50:1 to 10:1) to give a 74:26 mixture of **4** and *epi*-**4** (54.2 mg, 52%) as a colorless oil with $[\alpha]^{21}_D$ +1.1 (*c* 1.07, $CHCl_3$). ^{1}H NMR: 7.33–7.08 (m, 10H), 5.04 (d, *J* = 4.0, 0.74H), 5.00 (d, *J* = 4.0, 0.26H), 4.68 (td, *J* = 8.5, 3.5, 0.74H), 4.64 (td, *J* = 8.5, 3.5, 0.26H), 3.17 (td, *J* = 4.5, 4.0, 0.74H), 3.08 (td, *J* = 4.5, 4.0, 0.26H), 2.42 (dd, *J* = 12.0, 4.5, 0.74H), 2.42 (dd, *J* = 12.0, 4.5, 0.26H), 2.28 (dd, *J* = 12.0, 4.5, 0.26H), 2.16 (dd, *J* = 12.0, 4.5, 0.74H), 1.94–1.85 (m, 1H), 1.63–1.52 (m, 3H), 1.43–1.37 (m, 1H), 1.28 (s, 2.22H), 1.25 (s, 0.78H), 1.19 (s, 0.78H), 1.18 (s, 2.22H), 1.15 (s, 2.22H), 1.14–1.08 (m, 1H), 1.13 (s, 2.22H), 1.12 (s, 0.78H), 1.11 (s, 0.78H), 1.10 (s, 2.22H), 1.09 (s, 0.78H), 1.06 (s, 0.78H), 1.05 (s, 2.22H), 1.02–0.95 (m, 1H), 0.77 (d, *J* = 5.5, 0.78H), 0.74 (d, *J* = 5.5, 2.22H). ^{13}C NMR **4**: 171.6 (C), 151.5 (C), 139.4 (C), 129.1 (CH), 127.9 (CH), 127.8 (CH), 126.7 (CH), 125.4 (CH), 125.1 (CH), 102.1 (CH), 82.0 (C), 81.9 (C), 74.2 (CH), 50.3 (CH), 47.0 (CH), 41.2 (CH_2), 39.7 (C), 35.7 (CH_2), 34.5 (CH_2), 31.1 (CH), 27.2 (CH_3), 26.6 (CH_3), 25.6 (CH_3), 24.1 (CH_3), 22.3 (CH_3), 22.2 (CH_3), 21.6 (CH_3). ^{13}C NMR *epi*-**4**: 171.4 (C), 151.3 (C), 139.6 (C), 129.1 (CH), 128.0 (CH), 127.8 (CH), 127.3 (CH), 125.5 (CH), 125.1 (CH), 102.3 (CH), 82.0 (C), 81.9 (C), 74.3 (CH), 50.2 (CH), 46.8 (CH), 41.2 (CH_2), 39.7 (C), 36.0 (CH_2), 34.5 (CH_2), 31.1 (CH), 26.9 (CH_3), 26.6 (CH_3), 25.8 (CH_3), 24.1 (CH_3), 22.2 (CH_3), 22.1 (CH_3), 21.7 (CH_3). IR (neat): 2970, 2920, 1740, 1440, 1360, 1260, 1150, 1125, 760, 700. ESIMS *m*/*z*: 515 (M + Na, 100). HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{30}H_{38}NaO_4$, 515.3137; found, 515.3115.

*4.3.2. The Reaction with Z-**1c***

The same procedure as *E*-**1c** using *Z*-**1c** (86.2 mg, 0.205 mmol) gave a 56:44 mixture of **4** and *epi*-**4** (60.7 mg, 62%) as a yellow oil.

*4.4. Asymmetric Radical Addition of **1c–e** (Table 1): (S)-3-Phenyl-3-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)propanoate (**5**) and (S)-β-Phenyl-γ-butyrolactone*

*4.4.1. The Reaction with E-**1c***

To a solution of *E*-**1c** (108 mg, 0.257 mmol) and $BF_3 \cdot OEt_2$ (65 μL, 0.53 mmol) in **2** (9.2 mL, 62 mmol), was added a 0.96 M hexane solution of Me_2Zn (1.61 mL, 1.5 mmol). The mixture was stirred for 9 h at rt under ordinary atmosphere, and sat. aq. NH_4Cl was added. The whole was extracted with EtOAc twice, and the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated in vacuo, and passed through short silica pad (hexane/EtOAc 3:1). The residue was dissolved in DMSO (4 mL), and 4 M KOH (0.7 mL, 2 mmol) was added. After stirred at 140 °C for 4 h, the mixture was partitioned between ice–water and Et_2O (2 mL each). The separated aqueous layer was washed with Et_2O and acidified by the addition of 10% HCl (2 mL) at 0 °C. The aqueous layer was extracted with Et_2O twice, and the combined organic layer were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was dissolved in benzene (3.5 mL) and MeOH (0.5 mL), and a 1 M hexane solution of $TMSCHN_2$ (1.0 mL, 1 mmol) was added to the solution at rt. The mixture was stirred until gas evolution ceased, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc 9:1) to give **5** (18.3 mg, 24%) as a colorless oil with $[\alpha]^{20}_D$ +1.5 (*c* 0.59, EtOH): ^{1}H NMR: 7.32–7.19 (m, 5H), 5.12 (d, *J* = 5.5, 1H), 3.57 (s, 3H), 3.35 (ddd, *J* = 9.0, 6.0, 5.5, 1H), 2.93 (dd, *J* = 15.5, 6.0, 1H), 2.66 (dd, *J* = 15.5, 9.0, 1H), 1.16 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H), 1.09 (s, 3H). The NMR data was identical to that reported.[5b]

A mixture of the above obtained **5** (10.0 mg, 34.2 μmol) and Et_3SiH (55 μL, 0.34 mmol) in TFA (1 mL) was stirred at 90 °C for 4 h. The mixture was cooled to rt, concentrated in vacuo, and purified by silica gel column chromatography (hexane/EtOAc 5:1) to give (*S*)-β-phenyl-γ-butyrolactone (6.3 mg, quant) with a 74:26 er as a colorless oil with $[\alpha]^{21}_D$ +12 (*c* 0.62, $CHCl_3$) {lit:[5b] $[\alpha]^{25}_D$ +39 (*c* 1.1, $CHCl_3$) for 85% ee}: ^{1}H NMR: 7.37 (t, *J* = 7.0, 2H), 7.31 (t, *J* = 7.0, 1H), 7.24 (d, *J* = 7.0, 2H), 4.68 (dd, *J* = 9.0, 8.0, 1H), 4.38 (dd, *J* = 9.0, 8.0, 1H), 3.80 (ddt, *J* = 9.5, 8.5, 8.0, 1H), 2.93 (dd, *J* = 17.5 8.5, 1H), 2.68 (dd, *J* = 17.5, 9.5, 1H). The NMR data was identical to that reported.[5b] The er was determined by chiral HPLC (Daicel Chiralcel AD-H; hexane/*i*-PrOH 98:2; 1.0 mL/min; 220 nm; *S* 20.9 min, *R* 22.6 min).

*4.4.2. The Reaction with **1d***

The same procedure as *E*-**1c** using **1d** (90.8 mg, 0.202 mmol) gave **5** (19.5 mg, 33%) with $[\alpha]^{20}_D$ +7.8 (*c* 0.76, EtOH), 10.0 mg of which was then converted to (*S*)-β-phenyl-γ-butyrolactone (7.0 mg, quant) with an 80:20 er: $[\alpha]^{18}_D$ +21 (*c* 0.43, $CHCl_3$).

*4.4.3. The Reaction with **1e***

The same procedure as *E*-**1c** using **1e** (90.9 mg, 0.196 mmol) gave **5** (19.1 mg, 33%) with $[\alpha]^{20}_D$ +13 (*c* 0.33, EtOH), 10.0 mg of which was then converted to (*S*)-β-phenyl-γ-butyrolactone (7.1 mg, quant) with an 86:14 er: $[\alpha]^{18}_D$ +30 (*c* 0.59, $CHCl_3$).

4.5. DFT Calculations

The bond length of the forming C–C bond at the transition state was calculated for the addition reaction of the 4,4,5,5-tetramethyl-1,3-dioxolan-2-yl radical to dimethyl benzylidenemalonate in the presence of BF_3 at the BHandHLYP/6-31G(d) theoretical level using the Gaussian 09W program.[20] The forming C–C distance was restricted to that calculated (2.479 Å) during conformational search for the transition state geometry with methyl *ϕ*Men ester *E*-**1c**, which was conducted with a Merck Molecular Force Field using the Spartan 16 program,[21] followed by the geometry optimization at the BHandHLYP/6-31G(d) theoretical level using the Gaussian 09W. The transition state search was performed at the BHandHLYP/6-31G(d) theoretical level using the obtained geometries as initial geometries provided TS_{minor} and TS_{major} leading to the minor and major diastereomers, respectively, as those with the lowest energies. The geometries were verified by the frequency analysis.

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Supplementary Material

Supplementary data (copies of NMR spectra, chiral HPLC charts, and detail of the DFT calculations) to this article can be found online.

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