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Discrimination of carbonyl groups of *meso*-α-diketones with Horner–Wadsworth–Emmons reagent of chiral binaphthyl esters

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Abstract—Asymmetric Horner–Wadsworth–Emmons reactions of selected *meso*-α-dicarbonyl compounds with chiral phosphonate reagents, which possessed axially dissymmetric 1,1′-bi-2- or 8-naphthol at the carboxylate moiety as a chiral auxiliary, were examined. The reactions proceeded smoothly with good chemical yields as well as with high diastereoselectivities. *Z*-olefins were preferentially formed, and it was found that the free hydroxy group at the 2′- or 8′-position on the naphthalene ring plays a crucial role in the high diastereoselectivity, probably due to a complex-induced proximity effect. Mechanistic considerations are also described.

1. Introduction

Wittig and related reactions such as the Horner–Wadsworth–Emmons (HWE)[1] reaction have become versatile synthetic transformation involving carbon–carbon bond formation. Their mechanisms and stereochemical courses as well as the refined reaction conditions have been extensively investigated.[2,3] These types of reactions are often used as crucial connective steps in natural product synthesis. Although reactions to carbonyl compounds play key roles in synthetic transformations, including asymmetric synthesis, the olefins themselves are generally not chiral. Hence, progress toward developing direct asymmetric reactions using Wittig-style olefinations had been rather slow before the last two decade.[3] Meanwhile, substantial progress has been made toward directly and effectively preparing non-racemic olefins from different types of ketonic precursors.[4,5] Because the asymmetric synthesis of optically active organic compounds from *meso*-precursors has attracted much attention from the standpoint of asymmetric desymmetrization, various biological[6] and chemical methods[7] have been reported with respect to this categorical approach. However, compared to transformations by biocatalysts, only scattered examples involving carbon–carbon bond formation based on desymmetrization of *meso*-compounds have appeared in the literature.[8] Wittig-type reactions have also been scarcely applied for such asymmetric desymmetrization.[9] We have reported a marked degree of intermolecular differentiation between enantiotopic ketones of *meso*-α-dicarbonyl compounds using chiral phosphonate reagent (*S*)-**1**, which yielded an optically active enone with 98% ee,[10] while the anion of (*S*)-**2** exhibited an excellent discrimination ability between the π-faces of enones (Fig. 1).[11,12]

With these successful results in hand, we then considered an alternative type of reagent, which does not possess a chiral auxiliary at the phosphonate moiety, but can maintain the ability of asymmetric induction with the same type of *meso*-α-diketones. Thus, two optically active phosphonate reagents, (*R*)-**3** and (*S*)-**5**, were selected based on the following reasons.

First, it is already known that axially chiral binaphthol derivatives, including 8,8′-binols, are effective for asymmetric induction,[13] and the equivalency of the 2- and 2′- or 8- and 8′-hydroxy groups due to C_2 symmetry causes no formation of diastereomers in their derivatization. Second, both enantiomers of the reagent are easily prepared, and the chiral auxiliary is easily recovered after the reaction. Third,

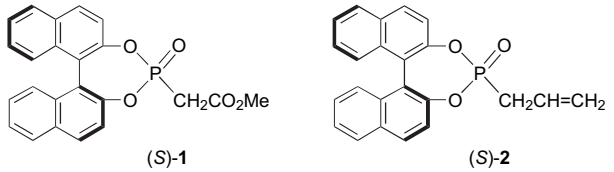

Figure 1.

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✠ This paper is dedicated to the late Professor Kiyoshi Tanaka, who passed away on December 8, 2004.

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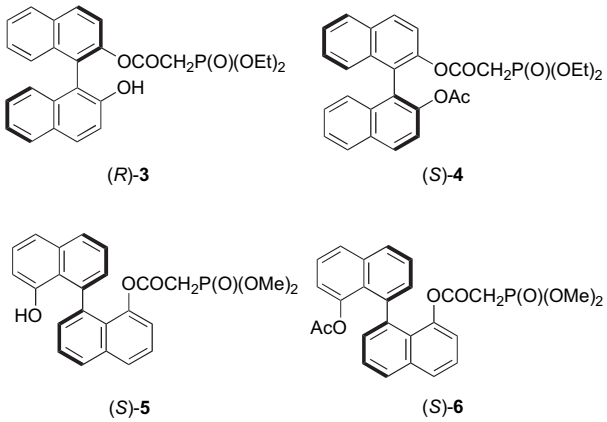
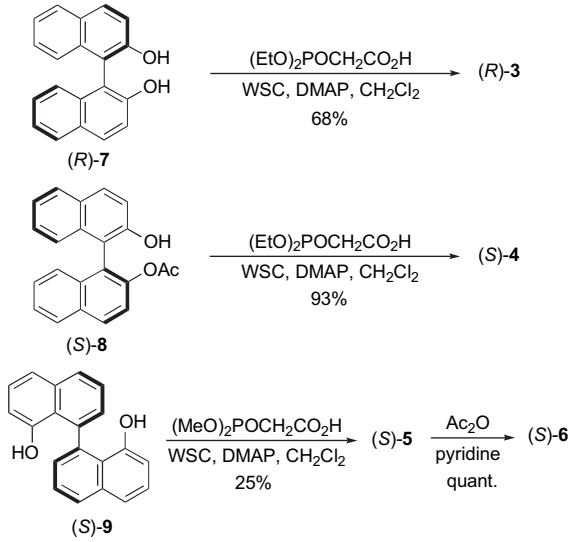


Figure 2.

separation and purification of the adducts by chromatographic methods are possible without employing chiral stationary phases. Finally, in addition to the asymmetric induction brought about by an effective chiral environment due to the axial chirality of the binaphthyl, the intramolecular hydroxy group of these reagents may lead to a complex-induced proximity effect (CIPE).[14] Herein, we report our results of the diastereoselective differentiation of the *meso*-α-diketones using readily available optically active phosphonate reagents (*R*)-**3**, (*S*)-**5**, and related reagents (Fig. 2).

2. Results and discussion

Chiral phosphonate reagents (*R*)-**3** and (*S*)-**5** were prepared by condensation of the corresponding optically active 1,1′-bi-2-naphthol (*R*)-**7** or 1,1′-bi-8-naphthol (*S*)-**9** with diethyl- or dimethylphosphonoacetic acid, respectively. The optical purity of these reagents was verified by HPLC analysis on a chiral column. In order to compare the diastereoselectivity observed in the HWE reactions, the corresponding acetates (*S*)-**4** and (*S*)-**6** were also prepared in a similar manner from the monoacetate[15] of (*S*)-1,1′-bi-2-naphthol (*S*)-**8** and acetylation of (*S*)-**5**, respectively (Scheme 1).



Scheme 1.

The HWE reaction of *meso*-α-diketone **10**, which was derived from commercially available 5-norbornene-2,3-dicarboxylic anhydride, with (*R*)-**3**, was initially examined using the same reaction conditions as previously described,[10] except the 2.5 equiv of NaH used (Table 1). The reactions proceeded smoothly with a good chemical yield to give four possible diastereomers **11a**, **12a**, **13a**, and **14a** in a ratio of 89.5:1.5:1.2:7.8, respectively (Table 1, entry 1). Thus, this reaction produced a significantly high diastereoselectivity, and the observed diastereomeric excesses for the *Z*- and *E*-adducts were 97% and 73%, respectively. Interestingly, the *Z*/*E* ratio of the adducts, which was determined by careful inspection of the ^{1}H NMR spectra as well as HPLC analysis, was 91:9, which suggests a kinetically controlled reaction.[2g]

In contrast, the diastereoselectivity (19% de for *Z*-adduct) of the reaction with (*S*)-**4** was considerably decreased compared to the HWE reaction with (*R*)-**3** under the same reaction conditions (Table 1, entry 2). The reaction with (*S*)-**4** gave a mixture of four diastereomers **11b**, **12b**, **13b**, and **14b** in a ratio of 48.1:32.7:6.7:12.5, respectively, but a comparable *Z*/*E* ratio (81:19) was again observed. These results strongly suggest that the prominent role of the 2′-hydroxy group[14] is for the high degree of induction of the diastereoselectivity.

The *E*/*Z* stereochemistry of the products was mainly deduced by comparing the chemical shift of the olefinic protons in their ^{1}H NMR spectra[10] and by comparing the chemical transformation to the known compound.

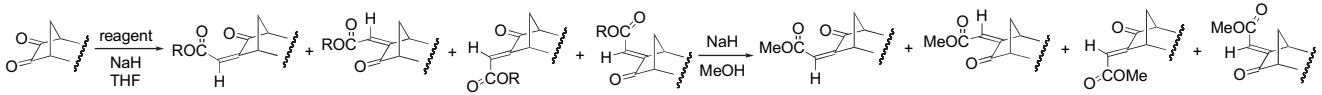
Thus, the stereostructure of the major *Z*-diastereomer **11a** obtained in the reaction with (*R*)-**3** was confirmed by a chemical transformation through an ester exchange reaction to the methyl ester **15**,[16] whose absolute structure has already been established,[10] and identified using HPLC analysis in the chiral stationary phase. Additionally, the stereostructure of major *E*-diastereomer **14a** obtained in the same reaction with (*R*)-**3** was determined by a similar ester exchange reaction (Table 1, entry 1). The stereostructures of the adducts obtained in the reaction with (*S*)-**4** were also elucidated in a similar way to that described above (Table 1, entry 2).

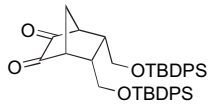
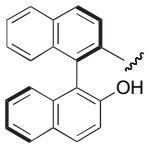
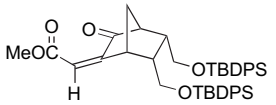
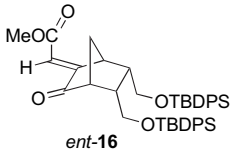
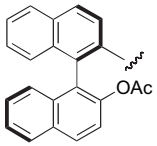
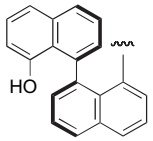
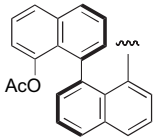
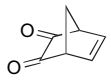
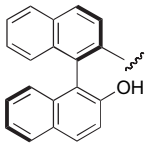
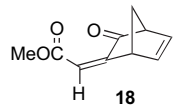
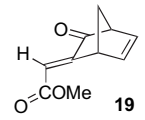
By these stereochemical outcomes of the products, it has been clearly shown that reagent (*R*)-**3** preferentially discriminates the opposite carbonyls of substrate **10**, which leads to *Z*- and *E*-adducts, **11a** and **14a**, respectively.[17]

Another aspect of this symmetric HWE reaction worth noting is that the anions of (*S*)-**1**[10] and (*R*)-**3**, which have opposite chiralities, both afford major products with identical absolute structures in the bicyclo systems. This indicates that the same sense of chiral auxiliary could be used to produce opposite enantiomers by altering the structure of the reagents.

Next, the asymmetric HWE reaction of **10** with the anions of (*S*)-**5** and (*S*)-**6** was carried out. In the reaction with the anion of (*S*)-**5**, *Z*-diastereomer **11c** was obtained as the major product (Table 1, entry 3). This also indicates that the reaction with (*S*)-**5** is also kinetically controlled. The ee value of **15**, which was derived from the ester exchange reaction of

Table 1. Asymmetric HWE reaction with chiral phosphonate reagents



Entry	Substrate	Reagent	R	Product ratio (**11**:**12**:**13**:**14**)	*Z*/*E* ratio	de (%)		Combined yield of isomers (%)	Methyl ester (ee%)	
						Z	*E*		*Z*	*E*
1	 **10**	(*R*)-**3**		**11a**:**12a**:**13a**:**14a** (89.5:1.5:1.2:7.8)	91/9	97	73	88	 **15** 80% ee	 *ent*-**16** 51% ee
2	**10**	(*S*)-**4**		**11b**:**12b**:**13b**:**14b** (48.1:32.7:6.7:12.5)	81/19	19	30	69	**15** 14% ee	*ent*-**16** 15% ee
3	**10**	(*S*)-**5**		**11c**:**12c**:**13c**:**14c**[a] (85.8:8.7:4.5:1.0)	—	>90[c]	—	70	**15** 90% ee	—
4	**10**	(*S*)-**6**		**11d**—**14d**[b]	—	>64[c]	>66[c]	86	**15** 64% ee	*ent*-**16** 66% ee
5	 **17**	(*R*)-**3**		**11e**:**12e**:**13e**:**14e** (24.8:9.2:45.2:20.8)	34/66	46	37	69	 **18** 46% ee	 **19** 37% ee

[a] The detailed correlation of each isomers (8.7:4.5:1.0) to **12c**–**14c** has yet to be assigned, except for the major product **11c** that corresponds to 85.8.
[b] The product ratio has yet to be determined.
[c] Evaluated from the ee values of **15** and *ent*-**16**.

a mixture of the products, was 90% ee. On the other hand, the same reaction with the anion of (*S*)-**6** resulted in the formation of both *Z*- and *E*-olefins with moderate diastereoselectivity (Table 1, entry 4). The direct ester exchange reaction of the reaction mixture afforded **15** and *ent*-**16** in 64% ee and 66% ee, respectively. These results also indicate the important role of the 8′-hydroxy group[14] for a high degree of stereoselectivity.

The HWE reaction of an alternate α-diketone **17**[18] with reagent (*R*)-**3** gave the mixture of **11e**–**14e** in 69% yield with lower *Z*/*E* ratio and diastereoselectivity than those of **10** (Table 1, entry 5). Thus, the *Z*/*E* ratio was 34:66 and the diastereoselectivity for *Z*- and *E*-adducts was 46% de and 37% de, respectively. In order to elucidate the stereochemical relationship among these adducts **11e**–**14e**, the transformation to methyl esters **18** and **19** and the following HPLC analyses using the chiral stationary phase were carried out. Consequently, it was found that preferentially formed methyl ester **18** from major *Z*-adduct **11e** is identical to that[17] obtained from the asymmetric HWE reaction of **17** with (*S*)-**1**. Unlike the reaction of **10**, the anion of (*R*)-**3** discriminated the same carbonyl groups of **17** to give **18** and **19** as the two major diastereomers (Table 1, entry 5).

It is likely that the HWE reaction described above is governed by kinetically controlled factors; thus, the stereochemical outcomes of the reactions can be explained by considering a transition state (TS) involving a chelated reagent. The presence of a hydroxy group attached to the additional naphthalene ring renders a more rigid chelate formation due to the tridentate type complex with a metal cation, while the axially dissymmetric binaphthyl topology dictates the orientation of the approach to the electrophile from the less hindered side, *si*-face of the anion of (*R*)-**3** (Fig. 3a). It is reasonable that the preferential direction of approach of a nucleophile occurs from the *exo*-direction when **10** is employed as the substrate (Fig. 3b). Assuming these factors, two TSs, TS-A and TS-B in which a ketonic carbonyl coordination to a metal cation is considered, are conceptualized, the former leads to **11a** and the latter to **14a** through simultaneous eliminations. Inspection of the stereomodels indicates that TS-B suffers from an unfavorable steric interaction between the substrate and one of the OEt groups of the reagent. Thus, the observed *E*/*Z* ratio can be explained by virtue of this interaction in the TS.

The formation of minor adducts **12a** and **13a** could result from an unfavorable *endo*-attack by a reagent. The following two factors, nucleophilic attack of an *E*-enolate and/or reaction from *re*-face of a reagent, could also be considered to explain the formation of **12a** and **13a**.

In contrast to the reaction with a type **3** reagent, the reaction of a type **4** reagent seems to differ. Here, for simplification, the mechanistic explanation using reagent (*R*)-**4** in lieu of

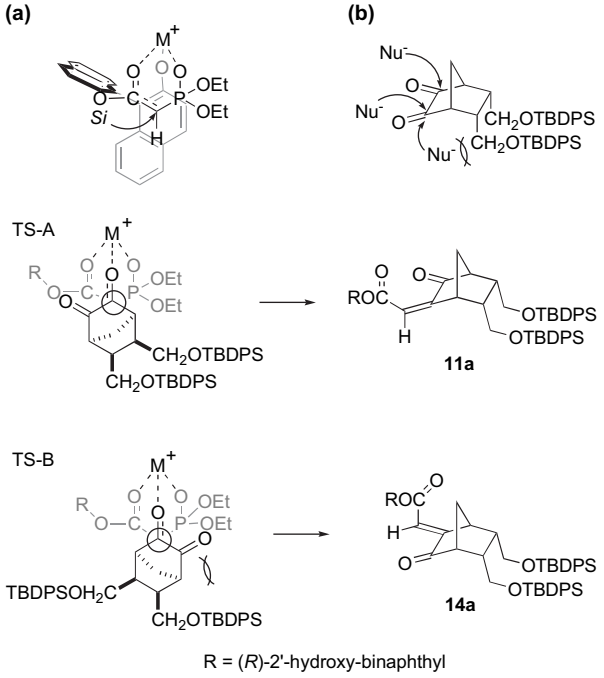


Figure 3.

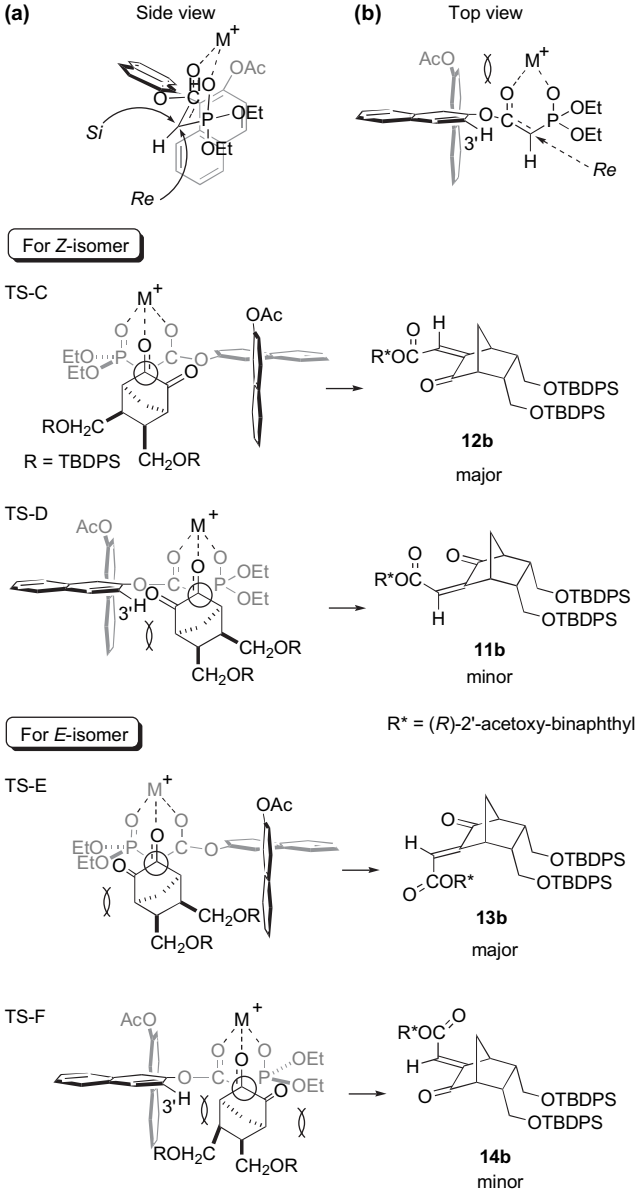


Figure 4.

(*S*)-**4** is tentatively considered. Thus, tridentate chelation is impossible for acetate **4**. Hence, deviation from the rigid form causes comparative space for the *re*-face approach to the electrophile (Fig. 4a and b). Consequently, two TSs based on an *exo*-attack of the reagents, TS-C and TS-D, might be considered for the formation of the *Z*-olefin (Fig. 4). Comparison of these TS models suggests that the repulsive interaction between the substrate and 3′-H of the reagent in TS-D dictates that *Z*-**11b** is the minor product. As for *E*-adducts, the same type of steric interaction for aforementioned TS-B exists in both TS-E and TS-F, and this might be why *E*-adducts are minor products. Furthermore, the additional repulsive interaction depicted in TS-F makes *E*-**14b** a less favorable. We now return to the reaction with (*S*)-**4** (Table 1, entry 2). The proportion of the products, **11b**, **12b**, **13b**, and **14b** (48.1:32.7:6.7:12.5), can be explained in agreement with these considerations.

It is plausible that the moderate *Z*/*E* selectivity as well as diastereoselectivity observed in the asymmetric HWE reaction of **17** with (*R*)-**3** might be attributable to the structural feature of the α-diketone, where bulky *endo*-substituents do not exist. Consequently, a considerable degree of *endo*-approach of the nucleophile would be realized.

3. Conclusions

In conclusion, the present study indicates that the optically active phosphonate reagents of **3** or **5** type with C_2-symmetrical element are not only versatile but also complementary to the HWE reagent of the **1** type and asymmetric desymmetrization of α-diketones with σ-symmetry. The reactions in this study provide a fascinating methodology to create optically active molecules. The optically active binaphthol molecules function as efficient chiral inducers by their axial chirality as well as neighboring-group participation of the free hydroxy group in these diastereoselective HWE reactions. Because both enantiomers of **3** or **5** are easily prepared in optically pure form and the auxiliary can be recovered by hydrolytic cleavage or ester exchange reactions of the adducts, the diastereoselective HWE reaction outlined above may be exploited immediately for the practical synthesis of a wide range of interesting non-racemic compounds, such as intermediates of natural products.[19]

4. Experimental

4.1. General

Melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were taken at 200 MHz in $CDCl_3$ with chemical shifts being reported as δ ppm from tetramethylsilane as an internal standard and couplings are expressed in hertz. Infra-red (IR) spectra were measured in $CHCl_3$ solution. THF was distilled from benzophenone ketyl and dichloromethane was from calcium hydride. Unless otherwise noted, all reactions were run under an argon atmosphere. All extractive organic solutions were dried over anhydrous $MgSO_4$. Flash column chromatography was carried out with Silica Gel 60 (spherical, 150–325 mesh), and Silica Gel 60 F_{254} plates (Merck) were used for preparative TLC (prep. TLC).

4.2. HPLC analysis of derivatives 3, 4, 11a–14e, 15, 16, 18, and 19

HPLC analyses were performed using a solvent system of hexane/2-PrOH at the flow rates indicated below, and each peak was detected at 254 nm. Either silica or chiral column with the following solvent ratio for 2-PrOH in hexane was used. Chiralpak AD, 20%, 1.0 mL/min for (*R*)-**3** and (*S*)-**4**; Shim-pack PREP SIL(H), 1.0%, 0.5 mL/min for **11a**–**14a**, **11b**–**14b**, and **11e**–**14e**; Chemco ORB, 1.0%, 1.0 mL/min for **11c**–**14c**; Backbond DNBPG (covalent) chiral, 1.0%, 1.0 mL/min for **15**; Chiralpak AS (Daicel Chemical Ind. LTD) 0.5%, 0.5 mL/min for **16**; Chiralpak AS, 3.0%, 1.0 mL/min for **18**; Chiralcel OJ (Daicel Chemical Ind. LTD) 1.0%, 0.5 mL/min for **19**.

4.3. 2′-Hydroxy-1,1′-binaphthyl diethoxyphosphonoacetate ((*R*)-3), 2′-acetoxy-1,1′-binaphthyl diethoxyphosphonoacetate ((*S*)-4), and 8′-hydroxy-1,1′-binaphthyl dimethoxyphosphonoacetate ((*S*)-5)

Preparation of 2′-hydroxy binaphthyl diethoxyphosphonoacetate reagents (*R*)-**3** is typical. Diethyl phosphonoacetic acid (1.9 mL, 9.8 mmol), DMAP (120 mg, 1.0 mmol, 10 mol %), and WSC (2.8 g, 14.7 mmol, 1.5 equiv) at 0 °C were added, dropwise, to a stirred solution of (*R*)-bi-2-naphthol (3.1 g, 10.8 mmol, 1.1 equiv) in CH_2Cl_2 (20 mL). The mixture was stirred for 12 h at room temperature. The reaction mixture was poured into a cold saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated to give a residue, which was purified by flash column chromatography with EtOAc/hexane (4:1) to afford (*R*)-(+)-2′-hydroxy-1,1′-binaphthyl diethoxyphosphonoacetate (**3**) in 68% yield. (*S*)-(+)-2′-Acetoxy-1,1′-binaphthyl diethoxyphosphonoacetate (**4**) and (*S*)-(+)-8′-hydroxy-1,1′-binaphthyl dimethoxyphosphonoacetate (**5**) were similarly prepared in 93% and 25% yields, respectively.

4.3.1. Compound (*R*)-3. Mp 146–147 °C; colorless powder (from hexane/EtOAc); $[\alpha]_D^{20}$ +46.4 (*c* 1.08, $CHCl_3$, >99% ee); ^{1}H NMR δ 1.17 (t, 3H, *J*=7.0), 1.24 (t, 3H, *J*=7.0), 2.83 (d, 2H, *J*=21.4), 3.91 (q, 2H, *J*=7.0), 4.01 (q, 2H, *J*=7.0), 7.02 (d, 1H, *J*=8.1), 7.19–7.54 (m, 7H), 7.83–8.09 (m, 4H); ^{13}C NMR δ 15.9, 16.0, 32.5, 34.9, 62.7, 62.8, 62.9, 113.9, 118.6, 121.5, 123.5, 123.6, 124.7, 126.0, 126.4, 126.7, 127.4, 128.0, 128.3, 129.0, 130.3, 130.6, 132.4, 133.6, 133.7, 147.7, 152.2, 165.3, 165.4; ^{31}P NMR δ 18.89 (from 85% H_3PO_4); IR ($CHCl_3$) 1760, 1620, 1600, 1260, 1220 cm^{-1}; MS (*m*/*z*) 464 (M^+); HRMS (*m*/*z*) calcd for $C_{26}H_{25}O_6P$ (M^+): 464.1389; found: 464.1402. Anal. Calcd for $C_{26}H_{25}O_6P$: C, 67.24; H, 5.43. Found: C, 67.45; H, 5.40.

4.3.2. Compound (*S*)-4. Colorless oil; $[\alpha]_D^{20}$ +4.6 (*c* 1.32, $CHCl_3$, >99% ee); ^{1}H NMR δ 1.19 (t, 3H, *J*=7.0), 1.21 (t, 3H, *J*=7.0), 1.84 (s, 3H), 2.77 (q, 1H, *J*=14.5), 2.88 (q, 1H, *J*=14.5), 3.90–4.12 (m, 4H), 7.13–7.50 (m, 8H), 7.91–8.02 (m, 4H); ^{13}C NMR δ 15.6, 15.7, 20.0, 31.9, 34.5, 62.2, 62.3, 62.4, 77.0, 121.1, 121.7, 122.8, 123.0, 125.5, 125.6, 125.9, 126.5, 126.6, 127.8, 129.4, 129.5, 131.3, 131.4, 133.0, 133.1, 146.3, 146.6, 164.2, 164.3, 169.4; ^{31}P NMR δ 19.45 (from 85% H_3PO_4); IR ($CHCl_3$) 1760, 1260, 1200,

1100 cm^{-1}; MS (*m/z*) 506 (M^+); HRMS (*m/z*) calcd for $C_{28}H_{27}O_7P$ (M^+): 506.1494; found: 506.1476. Anal. Calcd for $C_{28}H_{27}O_7P$: C, 66.40; H, 5.37. Found: C, 65.95; H, 5.44.

4.3.3. Compound (*S*)-5. Yellow powder; $[\alpha]_D^{22}$ +171.4 (*c* 0.50, $CHCl_3$, >99% ee); ^1H NMR δ 1.43 (dd, 1H, *J*=14.2, 33.7), 1.85 (dd, 1H, *J*=14.2, 33.7), 3.57 (q, 6H, *J*=11.2), 6.81–8.04 (m, 12H); IR ($CHCl_3$) 1755, 1265, 1225, 1209, 1105, 1057, 1038 cm^{-1}; FABMS (*m/z*) 437 $(M+H)^+$. Anal. Calcd for $C_{24}H_{21}O_6P\cdot 1/4H_2O$: C, 65.38; H, 4.81. Found: C, 65.34; H, 4.95.

4.4. 8′-Acetoxy-1,1′-binaphthyl dimethoxyphosphonoacetate ((*S*)-6)

Pyridine (17 mg, 0.22 mmol, 1.0 equiv), acetyl chloride (18.8 μL, 0.26 mmol, 1.2 equiv) at 0 °C were added, dropwise, to a stirred solution of (*S*)-**5** (100 mg, 0.22 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL). The mixture was stirred for 2 h at room temperature. The reaction mixture was poured into a cold saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated to give a residue, which was purified by flash chromatography with EtOAc/hexane (2:3) to afford (*S*)-(+)-8′-acetoxy-1,1′-binaphthyl dimethoxyphosphonoacetate (**6**) (107 mg) in quantitative yield.

4.4.1. Compound (*S*)-6. Yellow powder; $[\alpha]_D^{22}$ +228.7 (*c* 0.60, $CHCl_3$, >99% ee); ^1H NMR δ 0.90 (s, 3H), 1.35 (dd, 1H, *J*=6.9, 14.2), 1.75 (dd, 1H, *J*=6.9, 14.2), 3.58 (q, 6H, *J*=11.2), 7.05–7.93 (m, 12H); IR (CH_3Cl) 1757, 1368, 1265, 1225, 1202, 1103, 1057, 1037, 775, 737 cm^{-1}; FABMS (*m/z*) 479 $(M+H)^+$.

4.5. HWE reaction of 10 with the anion of chiral phosphonate reagent. General procedure

The HWE reaction of α-diketone **10** with the anion of (*R*)-**3** is typical. Compound (*R*)-**3** (49 mg, 0.11 mmol, 1.0 equiv) at −78 °C was added, dropwise, to a stirred solution of NaH (10 mg, 0.26 mmol, 2.5 equiv) in THF (3 mL). After stirring for 10 min at 0 °C, the reaction mixture was cooled to −78 °C. A solution of α-diketone **10** (28 mg, 0.04 mmol) in THF (1 mL) was added, and the mixture was stirred for 2 h at the same temperature. The reaction mixture was poured into a cold saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated to give a residue, which was subjected to flash column chromatography with EtOAc/hexane (1:5) to afford a mixture of diastereomers **11a–14a** (90 mg, 88% yield) in a ratio of 89.5:1.5:1.2:7.8. Prep. TLC of the mixture gave pure samples.

4.5.1. Compound 11a. Colorless oil; ^1H NMR δ 0.88 (s, 9H), 0.95 (s, 9H), 1.77 (br s, 2H), 2.36–2.61 (m, 2H), 2.72 (br s, 1H), 3.16 (br s, 1H), 3.39 (d, 2H, *J*=7.0), 3.41 (dd, 1H, *J*=7.0, 10.2), 3.93 (dd, 1H, *J*=5.0, 10.2), 5.27 (br s, 1H), 5.45 (s, 1H), 7.01–8.15 (m, 32H); ^{13}C NMR δ 18.7, 18.9, 26.5, 26.6, 35.6, 41.7, 42.7, 43.0, 45.7, 52.3, 52.9, 61.7, 61.9, 62.0, 114.0, 118.4, 119.9, 122.1, 123.0, 123.5, 124.8, 125.9, 126.3, 126.7, 127.3, 127.6, 127.7, 127.8, 127.9, 128.0, 128.4, 129.0, 129.7, 130.3, 130.9, 132.4, 132.9, 133.2, 133.4, 133.6, 133.7, 135.3, 135.5, 135.6, 146.0, 147.9, 152.0, 165.4, 202.3; IR ($CHCl_3$) 1760, 1740, 1660, 1620, 1220, 1110 cm^{-1}; MS (*m/z*) 971 (M^+). Anal. Calcd for $C_{63}H_{62}O_6Si_2\cdot 1/2H_2O$: C, 77.19; H, 6.48. Found: C, 76.99; H, 6.61.

4.5.2. Compound 12a. Colorless oil; ^1H NMR δ 0.79 (s, 9H), 0.87 (s, 9H), 1.80 (br s, 2H), 2.39–2.62 (m, 2H), 2.75 (br s, 1H), 3.19 (m, 1H), 3.34 (m, 3H), 3.87 (dd, 1H, *J*=4.9, 10.3), 5.32 (br s, 1H), 5.51 (s, 1H), 7.05–8.15 (m, 32H); IR ($CHCl_3$) 1740, 1660, 1620, 1600, 1110, 1060 cm^{-1}; MS (*m/z*) 971 (M^+).

4.5.3. Compound 13a. Colorless oil; ^1H NMR δ 0.79 (s, 9H), 1.02 (s, 9H), 1.08 (d, 1H, *J*=11.0), 1.38 (d, 1H, *J*=11.0), 2.07 (m, 1H), 2.50 (m, 1H), 2.56 (br d, 1H, *J*=3.5), 3.14 (t, 1H, *J*=10.8), 3.32 (t, 1H, *J*=10.8), 3.56 (dd, 1H, *J*=4.1, 10.7), 4.18 (dd, 1H, *J*=4.9, 10.6), 4.95 (br s, 1H), 6.13 (s, 1H), 6.72–8.00 (m, 32H); IR ($CHCl_3$) 1735, 1625, 1600, 1115, 1055 cm^{-1}; MS (*m/z*) 971 (M^+).

4.5.4. Compound 14a. Colorless oil; ^1H NMR δ 0.81 (s, 9H), 0.99 (s, 9H), 1.44 (d, 1H, *J*=10.6), 1.76 (d, 1H, *J*=10.6), 2.41–2.62 (m, 2H), 3.02 (br d, 1H, *J*=2.2), 3.29 (t, 1H, *J*=7.4), 3.30 (t, 1H, *J*=9.2), 3.53 (br d, 1H, *J*=2.2), 3.59 (dd, 1H, *J*=5.5, 10.9), 4.06 (dd, 1H, *J*=4.1, 10.9), 4.89 (br s, 1H), 6.13 (s, 1H), 6.96–7.98 (m, 32H); IR ($CHCl_3$) 1735, 1620, 1600, 1115, 1080 cm^{-1}; MS (*m/z*) 971 (M^+).

4.5.5. Compound 11b. Colorless oil; ^1H NMR δ 0.87 (s, 3H), 0.97 (s, 3H), 1.70 (d, 1H, *J*=13.0), 1.77 (d, 1H, *J*=13.0), 1.80 (s, 3H), 2.40–2.59 (m, 2H), 2.68 (br s, 1H), 3.20 (br s, 1H), 3.45 (d, 1H, *J*=7.3), 3.49 (d, 1H, *J*=10.2), 3.55 (d, 1H, *J*=10.2), 3.95 (dd, 1H, *J*=4.9, 11.2), 5.77 (s, 1H), 7.17 (d, 1H, *J*=7.8), 7.23–7.61 (m, 26H), 7.86 (d, 1H, *J*=9.1), 7.89 (d, 1H, *J*=8.1), 7.93 (d, 1H, *J*=8.8), 7.95 (d, 1H, *J*=8.1), 8.05 (d, 1H, *J*=9.1); ^{13}C NMR δ 18.8, 19.0, 20.4, 26.3, 26.5, 26.7, 33.8, 35.7, 41.9, 42.6, 45.9, 53.0, 62.0, 62.1, 120.7, 122.0, 122.3, 123.0, 123.5, 125.7, 126.2, 126.3, 126.5, 126.7, 126.8, 127.7, 127.8, 127.9, 128.0, 128.2, 128.4, 129.6, 129.7, 131.6, 131.7, 133.4, 133.5, 133.6, 133.9, 135.5, 135.6, 135.7, 141.7, 145.9, 146.9, 147.0, 164.5, 169.9, 202.3; IR ($CHCl_3$) 1750, 1730, 1650, 1590, 1190, 1110 cm^{-1}. Anal. Calcd for $C_{65}H_{64}O_7Si_2$: C, 77.04; H, 6.37. Found: C, 76.60; H, 6.53.

4.5.6. Compound 12b. Colorless oil; ^1H NMR δ 0.78 (s, 9H), 0.84 (s, 9H), 1.77 (d, 1H), 1.83 (s, 3H), 1.90 (d, 1H), 2.38–2.56 (m, 2H), 2.71 (br s, 1H), 3.22 (br s, 1H), 3.33 (dd, 1H, *J*=6.7, 11.1), 3.36 (br d, 2H, *J*=6.7), 3.83 (dd, 1H, *J*=4.9, 10.2), 5.63 (s, 1H), 7.10–7.54 (m, 27H), 7.84 (d, 1H, *J*=8.9), 7.86 (d, 1H, *J*=8.1), 7.93 (d, 1H, *J*=8.8), 7.97 (d, 1H, *J*=7.6), 8.06 (d, 1H, *J*=9.2); ^{13}C NMR δ 18.7, 20.5, 26.5, 35.6, 41.9, 42.5, 46.2, 53.1, 61.8, 62.1, 120.6, 122.0, 122.3, 123.1, 123.4, 125.8, 126.3, 126.4, 126.6, 126.7, 126.8, 127.7, 128.1, 128.2, 129.7, 131.6, 131.8, 133.3, 133.4, 133.5, 133.8, 135.4, 135.5, 135.6, 146.4, 146.9, 164.1, 169.8, 202.1; IR ($CHCl_3$) 1750, 1735, 1655, 1590, 1190, 1105, 1080 cm^{-1}; MS (*m/z*) 1013 (M^+). Anal. Calcd for $C_{65}H_{64}O_7Si_2$: C, 77.04; H, 6.37. Found: C, 76.57; H, 6.47.

4.5.7. Compound 14b. Colorless oil; ^1H NMR δ 0.75 (s, 9H), 1.01 (s, 1H), 1.30 (d, 1H, *J*=9.4), 1.40 (d, 1H,

J=9.4), 1.99 (m, 1H), 2.53 (m, 1H), 2.60 (br d, 1H, J=3.8), 3.01 (br d, 1H, J=3.8), 3.13 (t, 1H, J=9.5), 3.32 (t, 1H, J=9.5), 3.38 (m, 1H), 4.09 (m, 1H), 6.18 (s, 1H), 6.83–7.52 (m, 26H), 7.57–7.64 (m, 3H), 7.82–7.95 (m, 3H).

4.5.8. Compound 11c. Yellow oil; ^{1}H NMR δ 0.95 (s, 9H), 1.07 (s, 9H), 1.25–1.55 (m, 1H), 2.04 (s, 1H), 2.23–2.55 (m, 1H), 2.58 (br s, 1H), 2.85 (br s, 1H), 3.31 (m, 2H), 3.83 (m, 1H), 4.17 (m, 1H), 4.77 (s, 1H), 5.25 (s, 1H), 6.75–7.65 (m, 32H); IR ($CHCl_3$) 2961, 2932, 2859, 1732, 1427, 1373, 1265, 1250, 1233, 1217, 1211, 1190, 1111 cm^{-1}.

4.6. HWE reaction of 17 with the anion of (*R*)-3

Compound (*R*)-**3** (254 mg, 0.55 mmol, 1.0 equiv) at −78 °C was added, dropwise, to a stirred solution of NaH (55 mg, 1.38 mmol, 2.5 equiv) in THF (15 mL). After stirring for 10 min at 0 °C, the reaction mixture was cooled to −78 °C. A solution of α-diketone **17** (67 mg, 0.55 mmol) in THF (2 mL) was added, and the mixture was stirred for 2 h at the same temperature. The reaction mixture was added to H_2O and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution, brine, dried, and evaporated to give a residue, which was subjected to flash column chromatography with EtOAc/hexane (1:3) to afford a mixture of diastereomers **11e**–**14e** (163.2 mg, 69% yield). The integration of ^{1}H NMR indicated the *Z*/*E* ratio of these products in a ratio of 34:66. Further purification of these adduct was performed by prep. TLC to give *Z*- (**11e**, **12e**) and *E*-isomers (**13e**, **14e**) in 65 mg (27%) and 95 mg (40%), respectively. According to the general procedure (see Section 4.7), both *Z*- and *E*-isomers converted to the corresponding methyl esters **18** and **19**, respectively. The ee values of **18** and **19** were measured by HPLC analysis on chiral stationary phase to give 46% ee and 37% ee, respectively. Because no *Z*- to *E*-isomerization occurred on **18**, these ee values are equal to the de values of *Z*- (**11e**, **12e**) and *E*-adducts (**13e**, **14e**). By using both the de values and *Z*/*E* ratio of the adducts, the product ratio of **11e**, **12e**, **13e**, and **14e** was calculated to give 24.8:9.2:45.2:20.8 as shown in Table 1.

4.6.1. Compound 11e. Orange oil; ^{1}H NMR δ 2.08 (d, 1H, J=9.5), 2.34 (dt, 1H, J=1.8, 9.5), 3.18 (br s, 1H), 3.35 (br s, 1H), 5.35 (br s, 1H), 5.62 (s, 1H), 6.27 (dd, 1H, J=2.9, 5.4), 6.50 (q, 1H, J=2.9), 7.06 (dd, 1H, J=1.1, 8.3), 7.19–7.38 (m, 6H), 7.51 (dt, 1H, J=1.1, 8.1), 7.85 (dd, 1H, J=8.9, 20.4), 7.86 (d, 1H, J=8.9), 7.99 (d, 1H, J=8.1), 8.12 (d, 1H, J=8.9); ^{13}C NMR δ 47.4, 49.1, 54.9, 112.3, 114.0, 116.7, 118.4, 122.0, 123.0, 123.5, 124.8, 125.8, 126.3, 126.7, 127.3, 127.9, 128.0, 128.4, 129.0, 130.3, 130.9, 132.4, 133.5, 133.7, 134.2, 141.7, 144.8, 147.9, 148.2, 152.0, 165.3, 200.7; IR ($CHCl_3$) 1760, 1740, 1665, 1620, 1600, 1510, 1200, 1170, 1150 cm^{-1}; MS (*m*/*z*) 432 (M^+); HRMS (*m*/*z*) calcd for $C_{29}H_{20}O_4$ (M^+): 432.1362; found: 432.1373. Anal. Calcd for $C_{29}H_{20}O_4$: C, 80.54; H, 4.66. Found: C, 80.02; H, 4.70.

4.6.2. Compound 13e. Orange oil; ^{1}H NMR δ 1.81 (d, 1H, J=9.9), 2.21 (dt, 1H, J=1.8, 9.9), 3.09 (br s, 1H), 3.98 (br s, 1H), 5.27 (s, 1H), 5.74 (dd, 1H, J=3.0, 5.5), 6.11 (s, 1H), 6.12 (m, 1H), 7.09 (br d, 1H, J=7.3), 7.23–7.61 (m, 8H), 7.85 (d, 1H, J=8.1), 7.90 (d, 1H, J=9.5), 8.00 (d, 1H, J=8.1), 8.12 (d, 1H, J=8.8); ^{13}C NMR δ 44.5, 47.8, 53.2, 113.0, 114.0, 118.2, 118.3, 121.7, 123.1, 123.8, 124.5, 125.8, 126.5, 126.9, 127.6, 128.1, 128.4, 129.1, 130.5, 130.9, 132.4, 133.6, 134.7, 134.8, 141.6, 147.9, 151.9, 152.1, 152.2, 165.3, 202.4; IR ($CHCl_3$) 1750, 1730, 1620, 1600, 1515, 1510, 1170, 1150 cm^{-1}; MS (*m*/*z*) 432 (M^+); HRMS (*m*/*z*) calcd for $C_{29}H_{20}O_4$ (M^+): 432.1362; found: 432.1363. Anal. Calcd for $C_{29}H_{20}O_4$: C, 80.54; H, 4.66. Found: C, 80.28; H, 4.77.

4.7. General procedure for ester exchange of the HWE adducts to methyl esters

The ester exchange reaction of Wittig adduct **13e** to the methyl ester **19** is typical. Wittig adduct **13e** (321 mg, 0.74 mmol) in MeOH (2 mL) at room temperature was added to a solution of NaH (60 mg, 1.50 mmol, 2.0 equiv) in MeOH (12 mL). After stirring for 1 h, the reaction mixture was poured into a cold saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated to give a residue, which was purified by flash column chromatography with EtOAc/hexane (1:5) to afford **19** (59 mg) in 47% yield.

4.7.1. Compound 18. Colorless oil; $[\alpha]_D^{20}$ −142.5 (*c* 0.87, $CHCl_3$, 46% ee); ^{1}H NMR δ 2.17 (d, 1H, J=9.5), 2.39 (dt, 1H, J=9.5, 1.8), 3.21 (br s, 1H), 3.50 (br s, 1H), 3.81 (s, 3H), 5.94 (s, 1H), 6.31 (dd, 1H, J=3.3, 5.4), 6.60 (dd, 1H, J=2.9, 5.4); IR ($CHCl_3$) 1740, 1735, 1720, 1700, 1680, 1670, 1655 cm^{-1}; MS (*m*/*z*) 178 (M^+); HRMS (*m*/*z*) calcd for $C_{10}H_{10}O_3$ (M^+): 178.0630; found: 178.0631. Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.51; H, 5.73.

4.7.2. Compound 19. Colorless oil; $[\alpha]_D^{20}$ −14.1 (*c* 0.52, $CHCl_3$, 37% ee); ^{1}H NMR δ 2.05 (d, 1H, J=9.8), 2.43 (dt, 1H, J=1.8, 9.8), 3.22 (br s, 1H), 3.78 (s, 3H), 4.59 (br s, 1H), 6.29 (dd, 1H, J=3.0, 6.4), 6.33 (s, 1H), 6.57 (dd, 1H, J=3.0, 5.5); IR ($CHCl_3$) 1745, 1720, 1340, 1200 cm^{-1}; MS (*m*/*z*) 178 (M^+); HRMS (*m*/*z*) calcd for $C_{10}H_{10}O_3$ (M^+): 178.0630; found: 178.0650. Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.50; H, 5.69.

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