Diastereoselective Tandem Michael−Intramolecular Wittig Reactions of a Cyclic Phosphonium Ylide with 8-Phenylmenthyl Enoates

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The diastereoselective tandem Michael−intramolecular Wittig reactions of a five-membered cyclic phosphonium ylide **2** using 8-phenylmenthyl enoates were examined. The reaction of the phosphonium ylide with 8-phenylmenthyl cinnamate followed by the hydrolysis of the resulting enol ether **4a** afforded (3*R*,4*S*)-4-(diphenylphosphinyl)-3-phenylcycloheptanone (3*R*,4*S*)-**5a** as the major isomer. The diastereoselectivity of the initial tandem reactions was estimated to be 94:6 from the ^{31}P NMR of a mixture of the diastereomeric ketal derivatives **6a** and **6′a** which were obtained by the reaction of **5a** with (2*R*,3*R*)-2,3-butanediol, and the absolute configuration of the major isomer was determined by the single-crystal X-ray analysis. Similar reactions using some 8-phenylmenthyl alkenoates were attempted. As a result, it was clarified that the corresponding *trans*-ketones **5b**−**d** were obtained and that the diastereomer ratios of their ketal derivatives were 60:40−73:27.

Introduction

Tandem, domino, or cascade reactions are a powerful methodology for efficiently synthesizing complex molecules. The formation of multiple carbon−carbon or carbon−heteroatom bonds can be accomplished in one pot without isolating the intermediates, and these reactions often proceed stereoselectively.[1] In particular, they are useful for the stereoselective synthesis of multifunctionalized cyclic or fused cyclic compounds.[2] We have previously reported that the tandem Michael−intramolecular Wittig reactions of a five-membered cyclic phosphonium ylide with α,β-unsaturated ketones, esters, or thioesters afford a single stereoisomer of the corresponding multifunctionalized cycloheptene derivatives.[3] The high level of stereoselectivity was thought to be attained during the intramolecular Wittig reaction in their tandem reactions because the reaction was considered to proceed via a rigid phosphabicyclic intermediate containing a chair-form phosphacyclohexane in which the configuration of the substituents was strictly controlled. Therefore, if the diastereotopic faces of the enoates attacked by the ylide are distinguished using a chiral auxiliary, a chiral synthesis of *trans* enol ether is expected.

In this work, we attempted the diastereoselective tandem Michael−intramolecular Wittig reactions with chiral enoates derived from (−)-8-phenylmenthol[4] and the stereoselectivity for the reactions was evaluated.

Results and Discussion

In a preliminary experiment, the reactions of the ylide **2** generated from a phosphonium salt **1** with (−)-menthyl or (−)-8-phenylmenthyl cinnamate were attempted under various reaction conditions, and the approximate diastereoselectivity of the corresponding enol ether derivatives was estimated by HPLC analysis. It was found that the enol ether hydrolyzed to some extent during the purification steps. Therefore, the enol ether **4a** obtained by the reaction of **2** with 8-phenylmenthyl cinnamate was hydrolyzed without purification and the diastereoselectivity evaluation for the tandem reactions was attempted by the ^{31}P NMR spectrum of the diastereomeric ketal derivatives derived from the resulting ketone **5a**.

The reaction of the ylide **2** generated from **1** using *t*-BuOK with the enoate **3a** in refluxing ether for 42 h followed by hydrolysis afforded the desired ketone **5a** in 66% yield (Scheme 1). The ^{31} P and ^{13} C NMR spectra of **5a** indicated that **5a** was a single geometric isomer.

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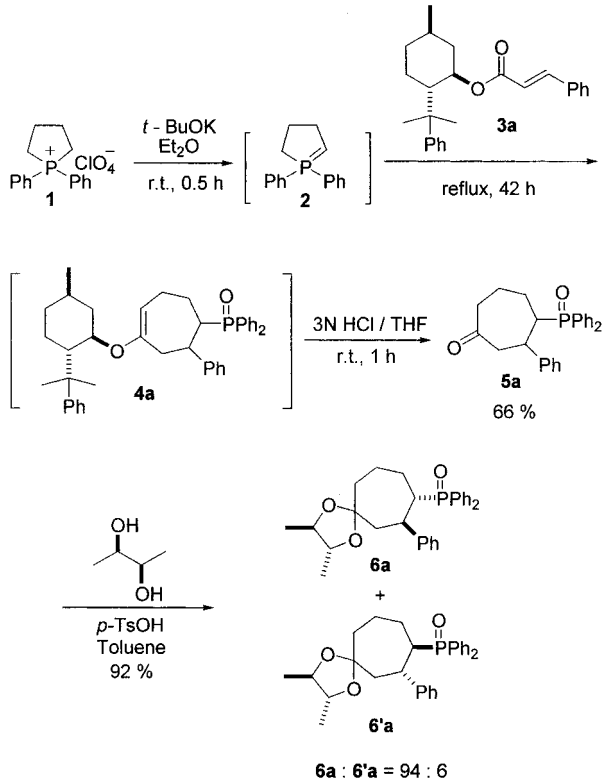
Scheme 1



6a : **6'a** = 94 : 6

Therefore, even though the enoates have a bulky alkoxy group such as the 8-phenylmenthyl group, it indicated that the reaction proceeded via a rigid phosphabicyclic intermediate (Table 1). The diastereoselectivity during the initial tandem reactions was determined by the ^{31}P NMR of a mixture of the ketal derivatives **6a** and **6′a** obtained from **5a** and (2*R*,3*R*)-2,3-butanediol in the presence of catalytic *p*-toluenesulfonic acid. Only two signals were observed in the ^{31} P NMR spectrum of the crude products and it was determined from their peak areas that the ratio of the diastereomers was 94:6. The ^{31} P NMR spectrum of the ketal derivatives obtained from the racemic ketones, which were synthesized by similar reactions using ethyl cinnamate, showed that the two signals ascribed to each diastereomer appeared at similar positions with 1:1 peak areas.

The absolute configuration of the major isomer **6a** was elucidated by X-ray analysis. As a result, it was confirmed that a phenyl group attached to the cycloheptanone ring was *trans* to the diphenylphosphinyl group. Moreover, the neighboring asymmetric centers substituted by their substituents were determined to have a 3*R* and 4*S* configuration, respectively, based on the configuration of the two methyl groups in the ketal ring. Accordingly, the major isomer of the enol ether formed during the initial tandem reactions was deduced to be the (1*S*,2*R*)-(2-phenyl- 4-cyclohepten-1-yl)diphenylphosphine oxide derivative **4a**.

The reason the (1*S*,2*R*) adduct was preferentially formed could be explained by considering the phosphabicyclic intermediates from the four possible intermediates **A**−**D** (Scheme 2). Intermediates **A**−**D** were generated via addition of the ylide **2** to the diastereotopic face opposite to the side blocked by the benzene ring of the 8-phenylmenthyl group in the *s-cis* conformer or the *s-trans* conformer of the enoate. For the intramolecular Wittig reaction from their intermediates **A**−**D**, attack of the regenerated ylide on the ester carbonyl carbon atom from the front face (*Si* face) was favored due to shielding by the benzene ring of the 8-phenylmenthyl group. Between the intermediates **A** and **B** from the *s-cis* conformer of the enoate, **B** could not form the product because the reaction should proceed via an unfavorable phosphabicycle where phenyl groups and the 8-phenylmenthyloxy group occupied the axial positions. On the other hand, the intermediates **C** from the *s-trans* conformer of the enoate also do not lead to suitable intermediates for the subsequent intramolecular Wittig reaction. The attack of the ylide carbon needed to occur from the hindered face of the carbonyl group (for **D**) in order to form the appropriate phosphabicyclic intermediate. In this intermediate both the 8-phenylmenthyloxy group and phenyl group occupied equatorial positions. The enantiomer (1*R*,2*S*) adduct could be obtained for the reaction course. Consequently, the (1*S*,2*R*) adduct was considered to form via intermediate **A** from the *s-cis* conformer of the enoate which would easily lead to the most favorable phosphabicycle. The high stereoselective formation of the (1*S*,2*R*) adduct despite high reaction temperature was considered to be due to the effective stereocontrol during the intramolecular Wittig reaction among the consecutive reactions.

Subsequently, reactions of some acrylate derivatives having a proton or an alkyl group at the β-carbon atom of the enoate with a phosphonium ylide were attempted under the same reaction conditions (Table 1). The resulting enol ethers were hydrolyzed to the corresponding ketones **5b**−**d** and the diastereoselectivity was estimated by the ^{31}P NMR spectra of a mixture of the diastereomeric ketal derivatives **6b**−**d** and **6′b**−**d**. Although the desired ketones were obtained from all enoates in 48−86% yields, the stereoselectivity was disappointingly reduced compared to the reaction using the cinnamate derivative. The reason for the low diastereoselectivity in the reactions of the alkenoate derivatives **3b**−**d** remains to be elucidated.

In conclusion, it was elucidated that the tandem reactions of the cyclic phosphonium ylide with 8-phenylmenthyl cinnamate proceeds with high diastereoselectivity and the reaction mechanism was proposed from the structure of the product. The present method will serve as a novel stereoselective synthesis procedure for multifunctionalized cycloheptane derivatives, and more suitable chiral auxiliaries for the diastereoselective reaction of acrylate derivatives are under investigation.

Experimental Section

Reactions were run in dried glassware under a nitrogen atmosphere. Et_2O was distilled from sodium benzophenone ketyl. Flash column chromatography was carried out on silica gel 60 (Cica-MERCK). The 8-phenylmenthol was synthesized according to the reported procedure.[5] The 8-phenylmenthyl enoates were prepared from the reaction of the corresponding acid chlorides or acids activated by DCC with 8-phenylmenthol. 1,1-Diphenylphospholanium perchlorate **1** was prepared by the anion exchange reaction of the corresponding bromide salt which was synthesized by the modified conventional method.[6] ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a 400 MHz spectrometer using $CDCl_3$ as the solvent. Chemical

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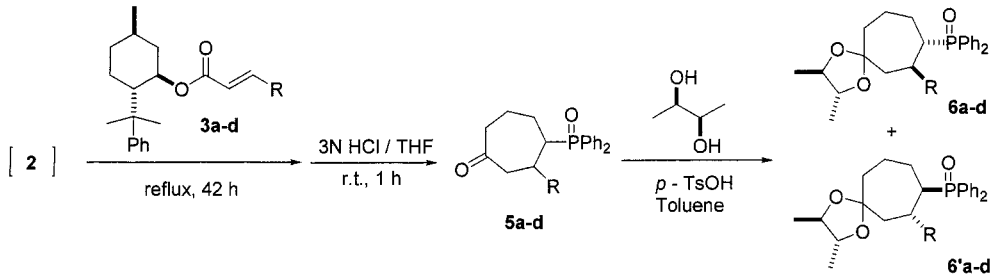
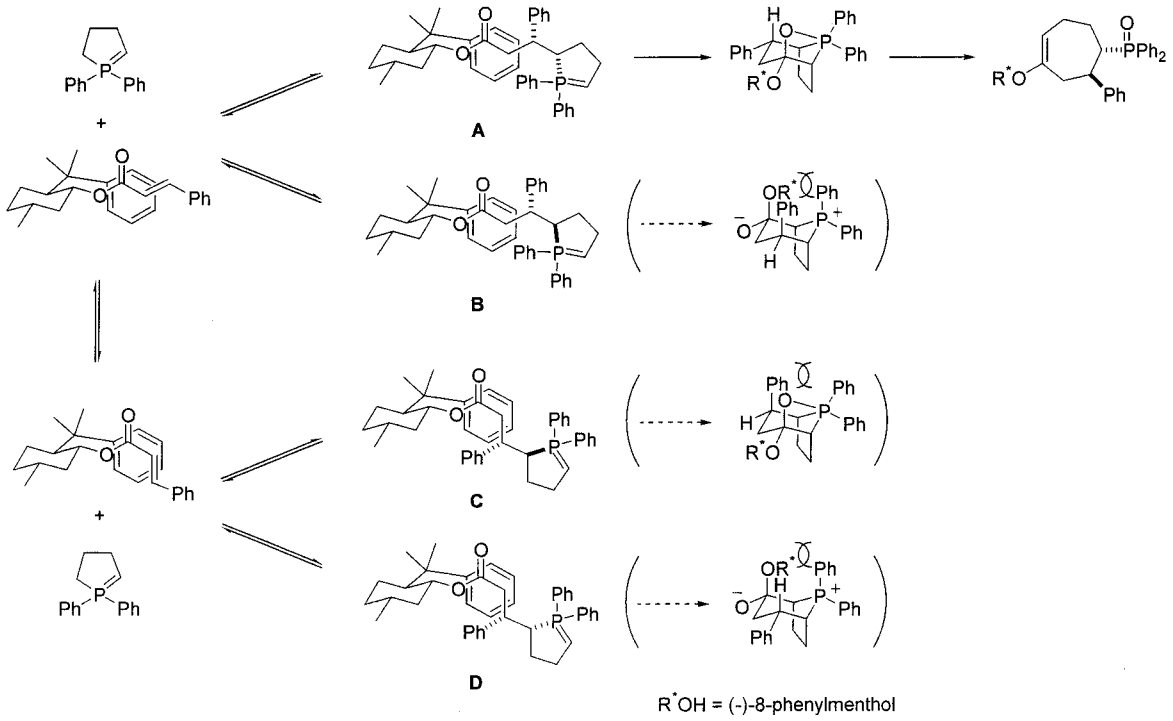
Table 1. Synthesis of Ketones 5a−d and Their Diastereomeric Ketals 6a−d and 6′a−d via the Diastereoselective Reaction of the Phosphonium Ylide 2 with 8-Phenylmenthyl Enoates 3a−d



		ketone			ketal			
entry	R	compd	yield[a] (%)	^{31}P NMR[b] (ppm)	compd	yield[a] (%)	^{31}P NMR[b] (ppm)	ratio (**6**:**6′**)[c]
1	Ph	**5a**	66	35.27	**6a**, **6′a**	92	35.14, 36.10	94:6
2	Me	**5b**	62	37.47	**6b**, **6′b**	88	36.98, 37.61	73:27
3	*i*-Pr	**5c**	86	37.61	**6c**, **6′c**	94	36.45, 37.56	65:35
4	*n*-Pent	**5d**	48	37.52	**6d**, **6′d**	96	36.96, 37.47	60:40

[a] Isolated yield. [b] ^{31}P chemical shifts using 85% phosphoric acid as an external standard. [c] Determined by ^{31}P NMR analysis.

Scheme 2



shifts are reported in δ from TMS as the internal standard for the ^{1}H and ^{13}C NMR spectra. ^{31}P chemical shifts were recorded relative to the signal for 85% phosphoric acid which was used as the external reference. Mass spectra and HRMS were obtained by EI at 70 eV or FAB. Melting points are uncorrected.

General Procedure for the Reaction of Cyclic Phosphonium Ylide 2 with Enoates 3a−d. A suspension of the phosphonium salt (1.64 g, 4.8 mmol) and *t*-BuOK (0.57 g, 5.04 mmol) in dry Et_2O (100 mL) was stirred at room temperature for 0.5 h. A solution of the 8-phenylmenthyl enoate (4.8 mmol) in dry Et_2O (30 mL) was added dropwise to the mixture, and the resulting solution was refluxed for 42 h. After being cooled to room temperature, the mixture was quenched with water and extracted with CH_2Cl_2. The combined organic layer was washed with water and concentrated under reduced pressure. After the residue was treated with aqueous 3 N HCl (17 mL) in THF (85 mL) at room temperature for 1 h, the mixture was made basic by aqueous saturated $NaHCO_3$ and then extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using AcOEt as the eluent.

***trans*-4-(Diphenylphosphinyl)-3-phenylcycloheptanone (5a).** The reaction of the phosphonium salt (1.02 g, 3.00 mmol), *t*-BuOK (0.35 g, 3.15 mmol), and enoate (1.09 g, 3.00 mmol) in dry Et_2O (84 mL) and the hydrolysis by 3 N HCl (10.7 mL) in THF (54 mL) were performed according to the general procedure to give **5a** (0.76 g, 66%) as a white solid: mp 224.5−228 °C; ^{1}H NMR δ 1.66−1.74 (m, 1H), 1.92−2.15 (m, 2H), 2.28−2.44 (m, 2H), 2.83−2.91 (m, 2H), 3.00−3.06 (m, 2H), 3.72−3.78 (m, 1H), 6.92−7.04 (m, 5H), 7.16−7.30 (m, 3H), 7.42−7.54 (m, 5H), 7.77−7.83 (m, 2H); ^{13}C NMR δ 21.38 (C_6, $^3J_{PC}$ = 6.9 Hz), 25.95 (C_5), 39.60 (C_3), 42.80 (C_4, $^1J_{PC}$ = 69.0 Hz), 42.85 (C_7), 49.18 (C_2, $^3J_{PC}$ = 7.7 Hz), 126.54−143.73 (aromatic carbons), 212.08 (C_1); IR (KBr) 1690 cm^{-1} (C=O), 1170 cm^{-1} (P=O); $[\alpha]^{28}_D$ +20.35 (c = 1.01, $CHCl_3$); MS (EI) m/z 388 (M^+); HRMS (EI) calcd for $C_{25}H_{25}O_2P$, M, 388.1593, found, M^+, 388.1595.

***trans*-4-(Diphenylphosphinyl)-3-methylcycloheptanone (5b).** The reaction was performed according to the general procedure to give **5b** (0.97 g, 62%) as a white solid:

mp 145.5−147.5 °C; ^{1}H NMR δ 0.99 (d, J = 7 Hz, 3H), 1.55−1.64 (m, 1H), 1.78−1.93 (m, 1H), 1.97−2.06 (m, 1H), 2.23−2.60 (m, 6H), 3.65 (dd, J = 13 Hz, 3 Hz, 1H), 7.48−7.55 (m, 6H), 7.82−7.88 (m, 4H); ^{13}C NMR δ 20.55 (C_6, $^3J_{PC}$ = 6.1 Hz), 20.93 (CH_3, $^3J_{PC}$ = 12.3 Hz), 24.95 (C_5), 28.05 (C_3), 41.95 (C_4, $^1J_{PC}$ = 69.8 Hz), 44.26 (C_7), 47.38 (C_2, $^3J_{PC}$ = 2.3 Hz), 128.72−133.30 (aromatic carbons), 213.73 (C_1); IR (KBr) 1690 cm^{-1} (C=O), 1175 cm^{-1} (P=O); $[\alpha]^{29}_D$ −0.017 (c = 1.00, $CHCl_3$); MS (FAB) m/z 327 (M^+ + 1).

***trans*-4-(Diphenylphosphinyl)-3-isopropylcycloheptanone (5c).** The reaction was performed according to the general procedure to give **5c** (1.46 g, 86%) as a white solid: mp 164.5−167.5 °C; ^{1}H NMR δ 0.88 (d, J = 7 Hz, 6H), 1.56−1.62 (m, 1H), 1.70−1.86 (m, 2H), 2.03−2.11 (m, 1H), 2.20−2.29 (m, 1H), 2.53−2.70 (m, 3H), 2.73−2.80 (m, 1H), 3.89 (dd, J = 14 Hz, 2 Hz, 1H), 7.44−7.55 (m, 6H), 7.82−7.88 (m, 4H); ^{13}C NMR δ 20.00 (C_6), 20.34, 21.22 (CH_3), 25.39 (C_5), 29.60 (CH, $^3J_{PC}$ = 12.3 Hz), 37.27 (C_4, $^1J_{PC}$ = 70.5 Hz), 40.35 (C_3), 43.95 (C_2), 44.33 (C_7), 128.74−131.66 (aromatic carbons), 214.33 (C_1); IR (KBr) 1685 cm^{-1} (C=O), 1175 cm^{-1} (P=O); $[\alpha]^{27}_D$ −25.60 (c = 1.02, $CHCl_3$); MS (FAB) m/z 355 (M^+ + 1); HRMS calcd for $C_{22}H_{28}O_2P$, M + 1, 355.1827, found, M^+ + 1, 355.1836.

***trans*-4-(Diphenylphosphinyl)-3-pentylcycloheptanone (5d).** The reaction was performed according to the general procedure to give **5d** (0.88 g, 48%) as a white solid: mp 117.5−119.5 °C; ^{1}H NMR δ 0.81 (t, J = 7 Hz, 3H), 1.03−1.09 (m, 2H), 1.14−1.27 (m, 5H), 1.35−1.40 (m, 1H), 1.55−1.60 (m, 1H), 1.73−1.88 (m, 1H), 2.02−2.11 (m, 1H), 2.15−2.39 (m, 3H), 2.46−2.64 (m, 3H), 3.78 (dd, J = 13 Hz, 3 Hz, 1H), 7.46−7.52 (m, 6H), 7.82−7.88 (m, 4H); ^{13}C NMR δ 13.97 (CH_3), 20.17 (C_6, $^3J_{PC}$ = 5.4 Hz), 22.42, 26.61, 31.28 (CH_2), 24.97 (C_5), 32.76 (C_3), 33.86 (CH_2, $^3J_{PC}$ = 11.5 Hz), 39.71 (C_4, $^1J_{PC}$ = 69.8 Hz), 44.37 (C_7), 45.44 (C_2), 128.72−133.21 (aromatic carbons), 213.91 (C_1); IR (KBr) 1685 cm^{-1} (C=O), 1170 cm^{-1} (P=O); $[\alpha]^{27}_D$ −9.60 (c = 1.02, $CHCl_3$); MS (FAB) m/s 383 (M^+ + 1); HRMS calcd for $C_{24}H_{32}O_2P$, M + 1, 383.2140, found, M^+ + 1, 383.2158.

General Procedure for the Reaction of the Ketones 5a−d with (*R*,*R*)-(−)-2, 3-Butanediol. A solution of (*R*,*R*)-(−)-2,3-butanediol (14 mg, 0.16 mmol), a catalytic amount of *p*-toluenesulfonic acid monohydrate, and the ketone (0.08 mmol) in dry toluene (3 mL) was refluxed for 16 h using the Dean−Stark apparatus. After being cooled to room temperature, the mixture was poured into an aqueous 10% NaOH solution and the resulting solution was extracted with CH_2Cl_2. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. After the measurement of ^{31}P NMR, the crude product was purified by flash column chromatography on silica gel using AcOEt as the eluent.

[(2*R*,3*R*,7*R*,8*S*)- and (2*R*,3*R*,7*S*,8*R*)-2,3-Dimethyl-7-phenyl-1,4-dioxaspiro[4.6]undec-8-yl]diphenylphosphine Oxide (6a, 6′a). A mixture of **6a** and **6′a** was obtained in 92% yield as a white solid: ^{1}H NMR δ 1.09 (d, J = 6 Hz, 3H), 1.21 (d, J = 6 Hz, 3H), 1.54−1.62 (m, 1H), 1.70−1.79 (m, 1H), 1.89−2.12 (m, 5H), 2.43 (dd, J = 15 Hz, 10 Hz, 1H), 2.90−2.98 (m, 1H), 3.42−3.57 (m, 2H), 3.66−3.74 (m, 1H), 6.82−6.92 (m, 5H), 6.98−7.04 (m, 2H), 7.11−7.17 (m, 1H), 7.33−7.41 (m, 5H), 7.71−7.76 (m, 2H); MS (EI) m/z 460 (M^+); HRMS (EI) calcd for $C_{29}H_{33}O_3P$, M, 460.2167, found, M^+, 460.2161.

[(2*R*,3*R*,7*S*,8*S*)- and (2*R*,3*R*,7*R*,8*R*)-2,3,7-Trimethyl-1,4-dioxaspiro[4.6]undec-8-yl]diphenylphosphine Oxide (6b, 6′b). A mixture of **6b** and **6′b** was obtained in 88% yield as a white solid: ^{1}H NMR δ 0.80−0.93 (m, 3H), 1.12−1.27 (m, 6H), 1.40−1.50 (m, 1H), 1.69−1.87 (m, 6H), 1.92 (brd, 1H), 2.28−2.50 (m, 2H), 3.51−3.58 (m, 2H), 7.40−7.51 (m, 6H), 7.77−7.82 (m, 4H); MS (FAB) m/z 399 (M^+ + 1); HRMS calcd for $C_{24}H_{32}O_3P$, M + 1, 399.2089, found, M^+ + 1, 399.2085.

[(2*R*,3*R*,7*R*,8*S*)- and (2*R*,3*R*,7*S*,8*R*)-7-Isopropyl-2,3-dimethyl-1,4-dioxaspiro [4.6]undec-8-yl]diphenylphosphine Oxide (6c, 6′c). A mixture of **6c** and **6′c** was obtained in 94% yield as a white solid: ^{1}H NMR δ 0.59 (d, J = 7 Hz), 0.62 (d, J = 7 Hz), 0.67 (d, J = 7 Hz), 0.69 (d, J = 7 Hz) (total 6H), 1.19−1.27 (m, 6H), 1.32−1.95 (m, 8H), 1.99−2.10 (m, 1H), 2.34−2.65 (m, 2H), 3.50−3.63 (m, 2H), 7.40−7.55 (m, 6H), 7.78−7.90 (m, 4H); MS (FAB) m/z 427 (M^+ + 1); HRMS calcd for $C_{26}H_{36}O_3P$, M + 1, 427.2402, found, M^+ + 1, 427.2421.

[(2*R*,3*R*,7*S*,8*S*)- and (2*R*,3*R*,7*R*,8*R*)-2,3-Dimethyl-7-pentyl-1,4-dioxaspiro[4.6]undec-8-yl]diphenylphosphine Oxide (6d, 6′d). A mixture of **6d** and **6′d** was obtained in 96% yield as a white solid: ^{1}H NMR δ 0.74−1.46 (m, 17H), 1.70−1.97 (m, 8H), 2.20−2.38 (m, 2H), 3.48−3.56 (m, 2H), 7.42−7.48 (m, 6H), 7.77−7.84 (m, 4H); MS (FAB) m/z 455 (M^+ + 1); HRMS calcd for $C_{28}H_{40}O_3P$, M + 1, 455.2715, found, M^+ + 1, 455.2739.

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Supporting Information Available: A modified procedure for synthesis of phosphonium salt **1**, ^{1}H, ^{13}C, and ^{31}P NMR spectra for compounds **5a**−**d**, ^{1}H and ^{31}P NMR spectra for a mixture of diastereomers **6a**−**d** and **6′a**−**d**, and X-ray crystallographic data for **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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