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Preparation of Chiral Multifunctional Thiourea–Phosphanes and Synthesis of Chiral Allylic Phosphites and Phosphane Oxides through Asymmetric Allylic Substitution Reactions of Morita–Baylis–Hillman Carbonates

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Keywords: Organocatalysis / Asymmetric catalysis / Allylic compounds / Amines

We developed a synthetic method to prepare chiral multifunctional thiourea–phosphane catalysts for the asymmetric allylic substitution reaction of Morita–Baylis–Hillman carbonates with diphenyl phosphite or diphenylphosphane oxide to give allylic phosphites and allylic phosphane oxides in high yields with excellent enantioselectivity.

Introduction

Chiral multifunctional phosphane organocatalysts, which contain Lewis basic and Brønsted acidic sites within one molecule, have received considerable attention because they are highly active catalysts for enantioselective Morita–Baylis–Hillman (MBH) reactions, aza-Morita–Baylis–Hillman (aza-MBH) reactions, cycloaddition reactions of allenoates with electron-deficient olefins, and other related reactions.[1] To date, the synthesis of chiral multifunctional phosphane catalysts has focused on the following three classes of compounds: hydroxy–phosphanes, amide–phosphanes and thiourea–phosphanes. For example, our group, Sasai, and Liu have developed a series of chiral multifunctional hydroxy–phosphane organocatalysts derived from an axially chiral binaphthyl scaffold that could effectively catalyze MBH and aza-MBH reactions.[2] Moreover, our group and Lu and co-workers have synthesized a series of chiral multifunctional amide–phosphanes that are very efficient catalysts for asymmetric aza-MBH reactions and asymmetric allylic substitution reactions of MBH acetates, affording the corresponding products in good yields with high enantioselectivities under mild conditions.[3] The groups of Miller, Zhao, and Lu have also recently reported the synthesis of chiral multifunctional amide–phosphanes from α-amino acids. These compounds catalyzed asymmetric [3+2] cycloadditions of allenoates and electron-deficient olefins, giving the corresponding cyclopentene derivatives in excellent yields with excellent diastereo- and enantioselectivities.[4] Furthermore, in 2008, Jacobson and co-workers developed a series of thiourea–phosphane catalysts synthesized from chiral *trans*-2-amino-1-(diphenylphosphanyl)cyclohexane that catalyzed imine–allenate [3+2] cycloaddition reactions with high enantioselectivity.[5] Meanwhile, Wu and co-workers used these chiral multifunctional thiourea–phosphanes as catalysts in a variety of inter- and intramolecular asymmetric MBH reactions and intramolecular asymmetric Rauhut–Currier reactions, giving the corresponding products in good yields with high enantiomeric excess (*ee*) values.[6] More recently, Lu synthesized chiral multifunctional thiourea–phosphanes from α-amino acids and used them to catalyze asymmetric [3+2] annulations of MBH carbonates and isatylidene malononitriles to give the corresponding spirocyclopenteneoxindoles in excellent yields with excellent diastereo- and enantioselectivities.[7]

Very recently, we have been working on the synthesis of chiral multifunctional thiourea–phosphane catalysts from axially chiral binaphthyl scaffolds that are highly active and enantioselective catalysts in both the asymmetric aza-MBH reaction and asymmetric allylic substitution reactions of MBH adducts.[8] These catalysts were synthesized by heating precatalyst **I** with the corresponding isothiocyanate in tetrahydrofuran (THF) at 60 °C for 3–5 d. For example, TP-**I** was prepared by heating compound **I** with phenyl isothiocyanate in THF at 60 °C for 153 h and was isolated in 70% yield after purification [Scheme 1, Equation (1)]. Interestingly, if the reaction was heated to reflux in THF, within 2 d isothiocyanate–phosphane compound **II** was obtained in 54% yield along with TP-**I** in 20% yield [Scheme 1, Equation (2)]. A mechanism for the formation of compound **II** is proposed in the Supporting Information. The structure of compound **II** was determined by X-ray diffraction studies (Figure 1).[9] Compound **II** is a very useful intermediate precatalyst in the preparation of chiral multifunctional thiourea–phosphanes because readily available amines can be used as starting reagents rather than isothiocyanates, which are much more difficult to prepare. There-

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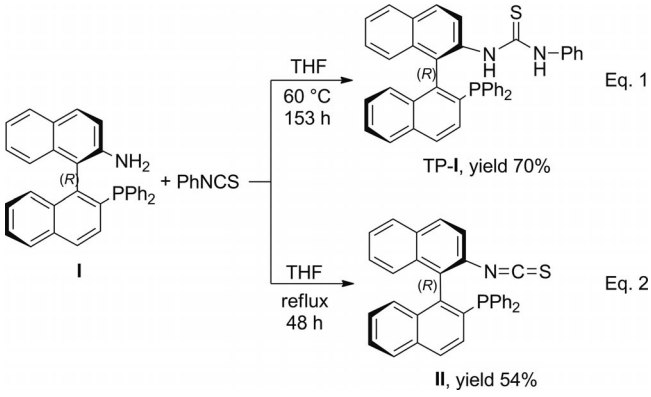
fore, we synthesized a series of multifunctional thiourea–phosphane catalysts TP**1**–TP**10** by using various anilines, benzylamines, (*1S*,*2R*)-(–)-*cis*-1-amino-2-indanol, and Betti bases in 61–89% yield in dichloromethane (CH_2Cl_2) within 12 h at room temperature (Scheme 2).[10] A further advantage of this method is that the synthesis is carried out at room temperature.



Scheme 1. Synthesis of chiral multifunctional thiourea–phosphane catalysts.

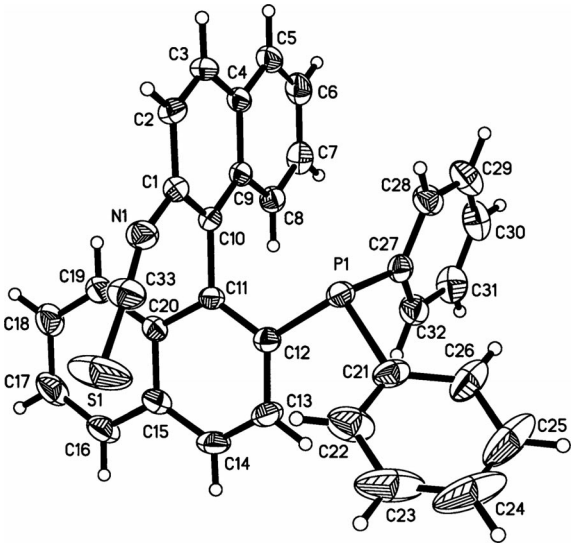
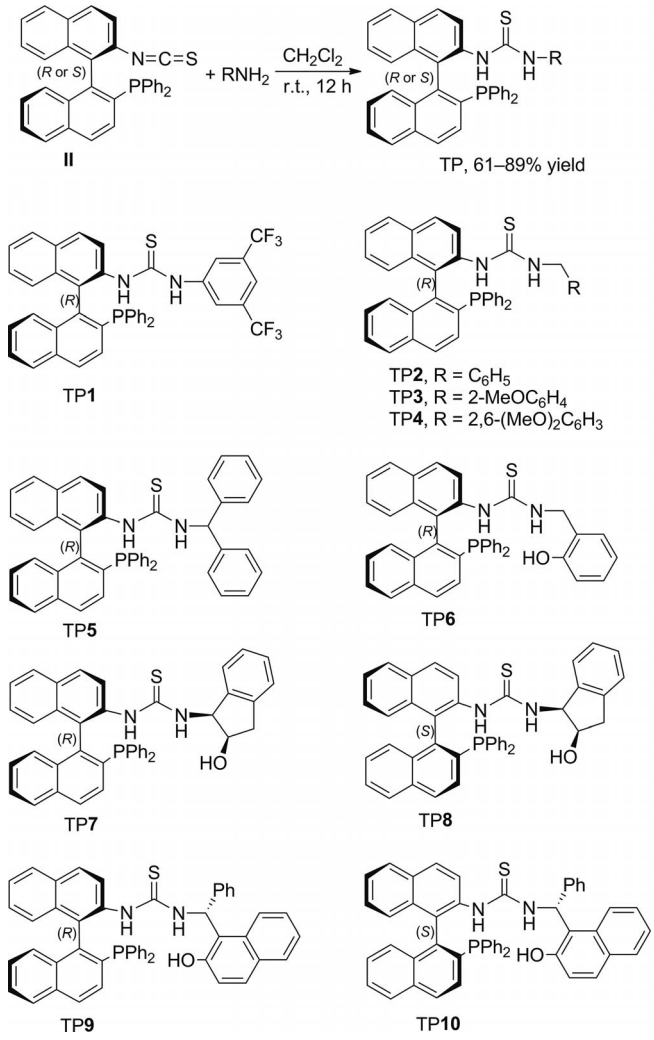


Figure 1. ORTEP representation of the molecular structure of compound **II**.

Recently, chiral phosphorus compounds have attracted much attention because of their application in metal-catalyzed or organocatalyst-catalyzed asymmetric reactions as well as the promising biological properties of chiral aminophosphonic acids and their derivatives.[1,11,12] Although numerous methods for the enantioselective construction of C–P bonds have been reported, few have been used in the preparation of chiral allylic phosphites and phosphane oxides.[13] In 2010, Wang reported the use of cinchona alkaloids as catalysts to synthesize chiral allylic phosphane oxides through asymmetric substitution of MBH carbonates with phosphane oxide under mild conditions in excellent yields and with high enantioselectivities.[8b,8c,14b,14c,15] Later, Swamy demonstrated hydrophosphonylation of activated



Scheme 2. Preparation of chiral multifunctional thiourea–phosphane catalysts TP**1**–TP**10**.

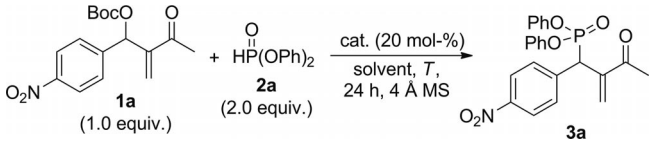
alkenes and alkynes by fluoride ion activation in an ionic liquid medium.[16] In 2004, Krische[17] reported chiral phosphane-catalyzed asymmetric substitution reactions of MBH acetates with phthalimide and its derivatives to give the corresponding products in good yields with moderate *ee* values. Herein, we report new chiral multifunctional thiourea–phosphane catalysts for asymmetric allylic substitution reactions of MBH carbonates with diphenyl phosphite or diphenylphosphane oxide to efficiently synthesize allylic phosphites and phosphane oxides in good yields and with high *ee* values under mild conditions.

Results and Discussion

Initially, we examined multifunctional thiourea–phosphanes catalysts TP**1**–TP**10** (Scheme 2) in the asymmetric allylic substitution reaction of MBH carbonate **1a** with diphenyl phosphite (**2a**). The results are summarized in

Table 1. We tested catalysts TP**1**–TP**5** in reactions of **1a** with **2a** in the presence of 4 Å molecular sieves (MS) in CH_2Cl_2 at room temperature and found that TP**1**, which was an excellent catalyst for the asymmetric aza-MBH reaction,[8a] did not catalyze this reaction (Table 1, Entry 1). However, TP**2**–TP**5** were fairly effective catalysts in this reaction. TP**5** performed best, affording product **3a** in 96% yield and 73%*ee* at room temperature (Table 1, Entries 2–5). Next, we examined the effect of solvent and temperature by using TP**5** as the catalyst and found that CH_2Cl_2, 1,2-dichloroethane (DCE), and PhCN were better solvents, giving **3a** in excellent yield and 73, 72, and 76%*ee*, respectively, at room temperature (Table 1, Entries 5, 9, and 11). The use of THF, CH_3CN, or CCl_4 as solvent afforded **3a** in lower yields at room temperature (Table 1, Entries 7, 8, and 10). The use of toluene or $PhCH_2CN$ as the solvent gave poorer enantioselectivity (Table 1, Entries 6 and 12). Lowering the reaction temperature to 0 °C produced **3a** in 80% yield with 80%*ee* in PhCN (Table 1, Entry 13). Decreasing the reaction temperature to –20 °C gave **3a** in 85% yield with 83%*ee* in CH_2Cl_2 (Table 1, Entry 14), but further reduction of the reaction temperature to –78 °C gave a lower yield with lower enantioselectivity (Table 1, Entry 15). In CH_2Cl_2 at –20 °C, we tested catalysts TP**6**–TP**10** and found that TP**10** was the most efficient, resulting in **3a** in 57% yield with 97%*ee* (Table 1, Entries 16–20). The optimum conditions for the reaction were found to be a temperature of 0 °C, affording **3a** in 82% yield and 90%*ee* (Table 1, Entry 21).

Table 1. Optimization of the reaction conditions for the asymmetric allylic substitution reaction of MBH carbonate **1a** with diphenyl phosphite (**2a**).[a]

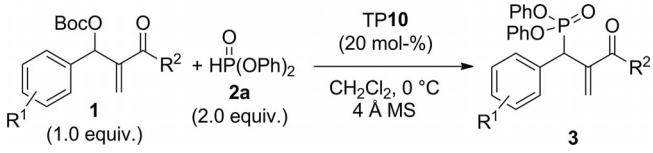


Entry	Catalyst	Solvent	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	TP**1**	CH_2Cl_2	r.t.	–	–
2	TP**2**	CH_2Cl_2	r.t.	94	70 (–)
3	TP**3**	CH_2Cl_2	r.t.	91	66 (–)
4	TP**4**	CH_2Cl_2	r.t.	87	71 (–)
5	TP**5**	CH_2Cl_2	r.t.	96	73 (–)
6	TP**5**	toluene	r.t.	87	42 (–)
7	TP**5**	CH_3CN	r.t.	25	81 (–)
8	TP**5**	THF	r.t.	16	31 (–)
9	TP**5**	DCE	r.t.	91	72 (–)
10	TP**5**	CCl_4	r.t.	43	48 (–)
11	TP**5**	PhCN	r.t.	89	76 (–)
12	TP**5**	$PhCH_2CN$	r.t.	85	63 (–)
13	TP**5**	PhCN	0	80	80 (–)
14	TP**5**	CH_2Cl_2	–20	85	83 (–)
15	TP**5**	CH_2Cl_2	–78	48	73 (–)
16	TP**6**	CH_2Cl_2	–20	91	64 (–)
17[d]	TP**7**	CH_2Cl_2	–20	85	89 (–)
18[d]	TP**8**	CH_2Cl_2	–20	80	80 (–)
19[d]	TP**9**	CH_2Cl_2	–20	53	91 (–)
20[d]	TP**10**	CH_2Cl_2	–20	57	97 (–)
21	TP**10**	CH_2Cl_2	0	82	90 (–)

[a] All reactions were carried out with **1a** (0.1 mmol) and **2a** (0.2 mmol) in the presence of catalyst and 4 Å MS (50 mg) in solvent (1.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC. [d] Reactions were performed for 48 h.

Under these optimal conditions, we investigated the scope of this reaction with various MBH carbonates **1b**–**m**. The results are summarized in Table 2. All of the reactions proceeded smoothly, providing desired products **3a**–**m** in good yields (70–87%) with excellent enantioselectivity (94–97%*ee*) regardless of whether they had electron-withdrawing or electron-donating substituents on their aromatic rings (Table 2, Entries 1–11). Introducing more than one substituent on the aromatic ring gave the corresponding product **3l** in 72% yield with 95%*ee* (Table 2, Entry 12). MBH carbonate **1m**, derived from ethyl vinyl ketone, also gave a good result, affording **3m** in 75% yield with 96%*ee* (Table 2, Entry 13).

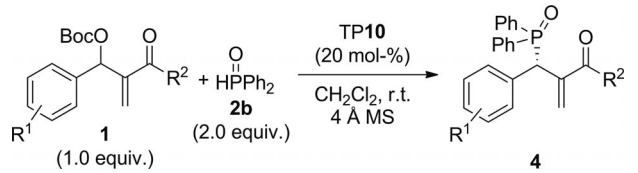
Table 2. Substrate scope for the asymmetric allylic substitution reaction of MBH carbonates **1** with diphenyl phosphite (**2a**).[a]



Entry	R^1	R^2	Yield [%][b]	*ee* [%][c]
1	**1a**, 4-NO_2	Me	**3a**, 82	90 (+)
2	**1b**, 3-NO_2	Me	**3b**, 87	96 (+)
3	**1c**, 4-CF_3	Me	**3c**, 78	96 (+)
4	**1d**, 4-CN	Me	**3d**, 79	95 (+)
5	**1e**, 4-Br	Me	**3e**, 81	96 (+)
6	**1f**, 4-$MeSO_2$	Me	**3f**, 83	94 (+)
7	**1g**, 4-Cl	Me	**3g**, 70	97 (+)
8	**1h**, 3-Cl	Me	**3h**, 87	95 (+)
9	**1i**, 2-Cl	Me	**3i**, 75	97 (+)
10	**1j**, H	Me	**3j**, 71	96 (+)
11	**1k**, 4-Me	Me	**3k**, 81	96 (+)
12	**1l**, 3,4-Cl_2	Me	**3l**, 72	95 (+)
13	**1m**, 4-NO_2	Et	**3m**, 75	96 (+)

[a] All reactions were carried out with **1** (0.1 mmol), **2a** (0.2 mmol) and 4 Å MS (50 mg) in CH_2Cl_2 (1.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC.

Table 3. Substrate scope for the asymmetric allylic substitution reaction of MBH carbonates **1** with diphenylphosphane oxide (**2b**).[a]



Entry	R^1	R^2	Yield [%][b]	*ee* [%][c]
1	**1a**, 4-NO_2	Me	**4a**, 99	97 (*S*)
2	**1e**, 4-Br	Me	**4b**, 96	96 (*S*)
3	**1g**, 4-Cl	Me	**4c**, 86	97 (*S*)
4	**1j**, H	Me	**4d**, 94	97 (*S*)
5	**1k**, 4-Me	Me	**4e**, 99	96 (*S*)

[a] All reactions were carried out with **1** (0.1 mmol), **2b** (0.2 mmol), and 4 Å MS (50 mg) in CH_2Cl_2 (1.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC.

Finally, we examined the scope of the asymmetric allylic substitution reactions of the MBH carbonates with diphenylphosphane oxide (**2b**) under the optimal conditions described above. The results are summarized in Table 3. Once again, regardless of whether there was an electron-withdrawing or electron-donating substituent on the aromatic ring, all of the reactions proceeded smoothly to afford desired products **4a**–**e** in excellent yields (86–99%) with excellent enantioselectivities (96–97%*ee*; Table 3, Entries 1–5). The absolute configuration of **4a**–**e** was determined to be *S* by X-ray diffraction of **4b** bearing a bromine atom on the benzene ring (Figure 2).[9]

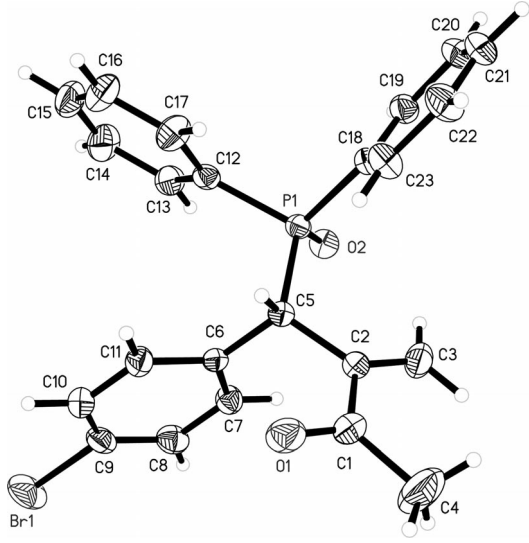


Figure 2. ORTEP representation of the molecular structure of **4b**.

Conclusions

In summary, we have developed a new method to synthesize various chiral multifunctional thiourea–phosphane catalysts from readily available amines. The advantage of this method is that a wide range of catalysts can be prepared without the need for functionalized isothiocyanate compounds that tend to be difficult to prepare. Furthermore, catalyst TP**10**, derived from precatalyst **II** and Betti base, can efficiently catalyze the asymmetric allylic substitution reactions of MBH carbonates with diphenyl phosphite or diphenylphosphane oxide, affording the corresponding allylic phosphites in 71–87% yield with 90–97%*ee* and allylic phosphane oxides in 86–99% yields with 96–97%*ee*. Currently, we are studying the use of the thiourea–phosphane catalysts in other asymmetric reactions.

Experimental Section

General Remarks: Melting points were determined with a digital melting point apparatus. Optical rotations were determined at 589 nm (sodium D line) by using a Perkin–Elmer-341 MC digital polarimeter. ^{1}H NMR spectra were recorded with a Bruker AM-300 and AM-400 spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were recorded with a Bruker AM-300 and AM-400 spectrophotometers (75 or 100 MHz) with complete proton decoupling spectrometers ($CDCl_3$: 77.0 ppm).) ^{31}P NMR spectra were recorded with a Bruker AM-400 spectrophotometer (161.94 MHz) with 85% H_3PO_4 as an internal standard. Infrared spectra were recorded with a Perkin–Elmer PE-983 spectrometer. Flash column chromatography was performed by using 300–400 mesh silica gel. For thin-layer chromatography (TLC), silica gel plates (Huanghai GF254) were used. Chiral HPLC was performed with a Shimadzu SPD-10A vp series with Chiralpak AD-H, OD-H, and IC-H columns 4.6 × 250 mm, (Daicel Chemical Ind., Ltd.) and Phenomenex Lux 5μ Amylose-2 column 4.6 × 250 mm [PA-2, (Phenomenex Ind., Ltd.)] chiral columns. Mass spectra were recorded by EI, ESI, and MALDI techniques and HRMS were measured with a HP-5989 instrument.

General Procedure for the Preparation of Catalysts: A mixture of compound **II** (1.0 equiv.) and amine (2.0 equiv.) in CH_2Cl_2 (1.0 mL) was stirred at room temperature under an argon atmosphere. After compound **II** was consumed, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc).

1-[(*S*)-2′-(Diphenylphosphanyl)-(1,1′-binaphthalen)-2-yl]-3-[(*R*)-(2-hydroxynaphthalen-1-yl)(phenyl)methyl]thiourea (TP10): Following the general procedure a mixture of compound **II** (99 mg, 0.2 mmol) and amine (100 mg, 0.4 mmol) in CH_2Cl_2 (1.0 mL) provided TP**10** as a syrupy oil (123 mg, 83%). $[\alpha]_D^{20}$ = –75.8 (*c* = 1.0, $CHCl_3$). IR (CH_2Cl_2): $\tilde{\nu}$ = 3372, 3057, 2926, 1626, 1583, 1519, 1487, 1434, 1330, 1264, 1216, 1064, 1028, 950, 849, 816, 762, 696, 668 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 6.62 (d, *J* = 8.4 Hz, 1 H), 6.83–6.92 (m, 5 H), 6.97–7.12 (m, 8 H), 7.17–7.23 (m, 3 H), 7.27–7.33 (m, 5 H), 7.35–7.40 (m, 5 H), 7.51 (dd, *J* = 3.2, 8.4 Hz, 1 H), 7.63–7.65 (m, 2 H), 7.75–7.83 (m, 3 H), 7.85–7.88 (m, 2 H), 7.92 (d, *J* = 8.4 Hz, 1 H), 8.01 (br., 1 H) ppm. ^{31}P NMR (161.94 MHz, $CDCl_3$): δ = –13.37 ppm. MS (MALDI): *m*/*z* (%) = 745.4 (100) [M + 1]$^+$. HRMS: calcd. for $C_{50}H_{38}N_2OPS^+$ [M + 1]$^+$ 745.2437; found 745.2440.

General Procedure for the Asymmetric Allylic Substitution Reaction of Morita–Baylis–Hillman Carbonates by Diphenyl Phosphite: A mixture of **1** (0.1 mmol), **2a** (0.2 mmol, 29 mg), TP**10** (0.02 mmol, 15 mg), and 4 Å molecular sieves (50 mg) in CH_2Cl_2 (1 mL) was stirred at 0 °C under an argon atmosphere. After compound **1** was completely consumed, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc) to provide compound **3**.

Diphenyl [2-Methylene-1-(4-nitrophenyl)-3-oxobutyl]phosphonate (3a): Following the general procedure provided **3a** as a white solid (36 mg, 82%). $[\alpha]_D^{20}$ = +96.1 (*c* = 1.0, $CHCl_3$). M.p. 135–142 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 3056, 2929, 1681, 1596, 1523, 1490, 1455, 1422, 1348, 1266, 1211, 1187, 1162, 1109, 1072, 1025, 1007, 940, 902, 857, 737, 703, 653, 633, 614 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, CH_3), 5.33 (d, $J_{H,P}$ = 24.0 Hz, 1 H, CH), 6.52 (d, $J_{H,P}$ = 3.6 Hz, 1 H, CH), 6.80 (d, *J* = 8.4 Hz, 2 H, ArH), 6.96 (d, $J_{H,P}$ = 2.8 Hz, 1 H, CH), 7.07–7.11 (m, 3 H, ArH), 7.16–7.20 (m, 3 H, ArH), 7.29–7.33 (m, 2 H, ArH), 7.72 (dd, *J* = 2.0, 8.8 Hz, 2 H, ArH), 8.16 (d, *J* = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.2, 42.0 (d, $J_{C,P}$ = 143.1 Hz), 120.1 (d, $J_{C,P}$ = 4.3 Hz), 120.3 (d, $J_{C,P}$ = 4.3 Hz), 123.8, 125.3, 125.4, 129.6, 129.8, 129.8, 130.7 (d, $J_{C,P}$ = 8.0 Hz), 141.9 (d, $J_{C,P}$ = 6.0 Hz), 142.8 (d, $J_{C,P}$ = 1.8 Hz), 143.7 (d, $J_{C,P}$ = 2.6 Hz), 150.0 (d, $J_{C,P}$ = 9.7 Hz), 150.3 (d, $J_{C,P}$ = 9.1 Hz), 196.8 (d, $J_{C,P}$ = 10.8 Hz) ppm. ^{31}P NMR (161.93 MHz, $CDCl_3$): δ = 16.26 ppm. MS (ESI): *m*/*z* (%) = 460.1 (100) [M + Na]$^+$. HRMS (ESI): calcd. for $C_{23}H_{20}NNaO_6P^+$ [M +

Na]$^+$ 460.0920; found 460.0934. Enantiomeric excess was determined by HPLC (Chiralcel OD-H column, λ = 214 nm, hexane/isopropanol = 70:30, flow rate = 0.7 mL min^{-1}): t_R = 17.06 (minor), 20.56 (major) min; *ee* = 90%.

Supporting Information (see footnote on the first page of this article): Spectroscopic data of all new compounds, detailed descriptions of the experimental procedures, spectroscopic data, chiral HPLC traces, and X-ray data for compounds **II** and **4b**.

Acknowledgments

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