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Asymmetric Hydrogenation of α,β-Unsaturated Ester-Phosphonates

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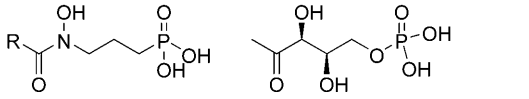
Abstract: The rhodium-catalyzed asymmetric hydrogenation of readily available α,β-unsaturated ester-phosphonates affords the corresponding α-chiral phosphonates in excellent yield and *ee*. The resulting products are useful multifunctional building blocks applied in the synthesis of physiologically active compounds.

Keywords: asymmetric hydrogenation; homogeneous catalysis; phosphonates; rhodium

Introduction

Compounds containing phosphonic acids and alkyl phosphonates are frequently encountered in the field of medicinal chemistry.[1] As phosphonic acids and phosphonates act as isosteres of carboxylic acids and esters, respectively, these functional groups are employed to improve the activity or availability of physiologically active compounds. In addition, phosphonic acids act as non-hydrolyzable phosphate mimics.[2]

Phosphonate analogues of glutamic acid are being studied in the treatment of diseases of the central nervous system such as Huntington's disease and Parkinson's disease because of their enhanced selectivity for glutamate receptors.[3] In addition, phosphonates are excellent chelators of calcium and magnesium, and as such they find application in the treatment of osteoporosis, bone cancer and calcium metabolism.[4]



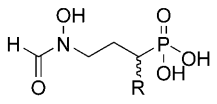
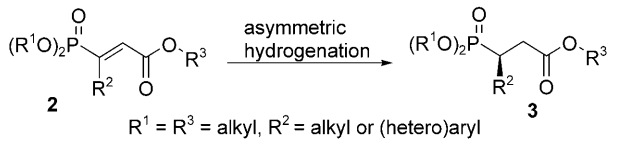


Figure 1. The natural substrate of 1-deoxy-D-xylulose 5-phosphate reducto-isomerase and its corresponding phosphonate inhibitors.

Fosmidomycin (Figure 1) is an effective inhibitor of 1-deoxy-D-xylulose 5-phosphate reducto-isomerase.[5] A derivative of fosmidomycin, FR900098, is currently on the market as a drug against malaria. It has been shown recently, however, that fosmidomycin analogues substituted next to the phosphonic acid moiety are more active than fosmidomycin itself.[6] As these derivatives were tested as racemates, it would be very interesting to study their single enantiomers.

Whereas the asymmetric synthesis of α-amino- and α-hydroxy-phosphonates has been thoroughly studied because of their structural resemblance to amino acids and hydroxy acids, the asymmetric synthesis of other chiral phosphonates, especially those with a stereogenic center next to phosphorus, has received much less attention. To address the deficit in asymmetric methods to prepare this important class of molecules, we initiated a study of the asymmetric hydrogenation of functionalized phosphonates **2** to provide compounds of type **3** (Scheme 1). These compounds are multifunctional building blocks containing a stereogenic center next to phosphorus and an ester group amendable for further manipulation at the β-position. Nevertheless, compounds like **2** are not trivial extensions of known substrates for asymmetric rho-



Scheme 1. Asymmetric hydrogenation of unsaturated ester phosphonates.

dium-catalyzed hydrogenation as their structure differs considerably from the dehydro amino acids, itaconic acids, and cinnamic acids, established substrates for asymmetric hydrogenation.[7]

Only a few studies have been devoted to the asymmetric synthesis of **3**. Conjugate addition of chiral enantiopure phosphites to Knoevenagel adducts has been reported by Enders et al.,[8] whereas Wyatt et al. reported a single example of a diastereoselective alkylation of an enantiopure benzyldiazaphosphine oxide with *tert*-butyl bromoacetate, which upon hydrolysis afforded the corresponding phosphonic acid.[9] In a recent and extensive study, Jørgensen et al. reported the asymmetric organocatalytic phosphonylation of α,β-unsaturated aldehydes.[10] Although this approach turned out to be effective, the *ee*s did not pass the 90% mark, and an excess of aldehyde had to be used.

To the best of our knowledge, only one report has appeared studying the asymmetric hydrogenation of **2**. Bargon et al. used Rh/BPPM in the hydrogenation of **2a** (Scheme 2) and found a 42% *ee*.[11] A somewhat related asymmetric hydrogenation of β-substituted unsaturated phosphonates was very recently reported by the group of Zheng.[12] Excellent *ee*s were obtained using a ferrocene-based phosphoramidite ligand.

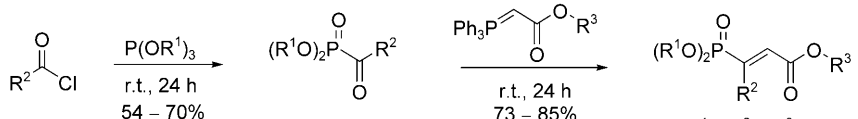
Results and Discussion

We started our study by developing an efficient two-step procedure for the synthesis of **2** (Scheme 2). An arbuzov reaction of trimethyl or triethyl phosphite with a series of aliphatic and aromatic acid chlorides afforded the corresponding α-oxo-phosphonates **1** in moderate to good yields.[13] It became clear that subsequent treatment of the products with methyl or *tert*-butyl (triphenylphosphoranylidene)acetate in a Wittig reaction afforded the substrates **2** selectively in the *E*-stereochemistry[14] in good to high yields. This route is very flexible as it allows the variation of all reaction partners, the alkyl phosphites, the acid chlorides and the Wittig reagent.

An initial study on the hydrogenation of **2** focused on substrate **2b**. Using $Rh(COD)_2BF_4$ as the rhodium precursor and MonoPhos[15] (**L12**, Figure 2) as the ligand, dichloromethane was found to be a suitable solvent – using 40 bar of H_2 (gas) at room temperature, **3b** was obtained in 53% *ee* at full conversion. Increasing the pressure of the H_2 (gas) did not lead to a higher *ee*. To increase the enantioselectivity, the hydrogenation was studied using a series of catalysts based on the chiral ligands depicted in Figure 2 (Table 1). In the monodentate phosphoramidite series the highest enantioselectivity was found using PipPhos (**L11**). Shifting to bidentate phosphines did not show much improvement, as both TolBINAP[16] **L1** and JosiPhos-type[17] ligand **L4** afforded 33% *ee* (full conversion). A marked increase in enantioselectivity was found using **L5** and especially **L3**, **L8** and **L10**.

We were pleased to see, however, that the hydrogenation of **2c** using a catalyst containing **L6**, a ligand of the JosiPhos family, gave **3c** in an excellent 95% *ee* with full conversion. The increase in enantioselectivity observed upon changing from **L3** to **L6** is noteworthy and most probably caused by the steric bulk of the *tert*-butyl groups.

As we wondered whether the use of a bidentate ligand was essential to achieve a high enantioselectivity in the asymmetric hydrogenation of this novel substrate class, we continued studying monodentate phosphoramidite ligands and finally were rewarded when **L7** was used. The catalyst containing this ligand showed excellent enantioselectivity (95%) in the hydrogenation of **2c**, and gave full conversion.



1a: $R^1 = R^2 = Me$
1b: $R^1 = Et$, $R^2 = Me$
1c: $R^1 = Et$, $R^2 = Ph$
1d: $R^1 = Me$, $R^2 = Ph$
1e: $R^1 = Me$, $R^2 = p$-Cl-C_6H_4
1f: $R^1 = Me$, $R^2 = p$-MeOC_6H_4
1g: $R^1 = Et$, R^2 = thiophene
1h: $R^1 = Et$, $R^2 = n$-propyl

2a: $R^1 = R^2 = R^3 = Me$
2b: $R^1 = Et$, $R^2 = R^3 = Me$
2c: $R^1 = Et$, $R^2 = Ph$, $R^3 = Me$
2d: $R^1 = R^3 = Me$, $R^2 = Ph$
2e: $R^1 = R^3 = Me$, $R^2 = p$-Cl-C_6H_4
2f: $R^1 = R^3 = Me$, $R^2 = p$-MeOC_6H_4
2g: $R^1 = Et$, R^2 = thiophene, $R^3 = Me$
2h: $R^1 = Et$, $R^2 = n$-propyl, $R^3 = Me$
2i : $R^1 = Et$, $R^2 = Ph$, $R^3 = t$-Bu

Scheme 2. Synthesis of compounds **1** and **2**.

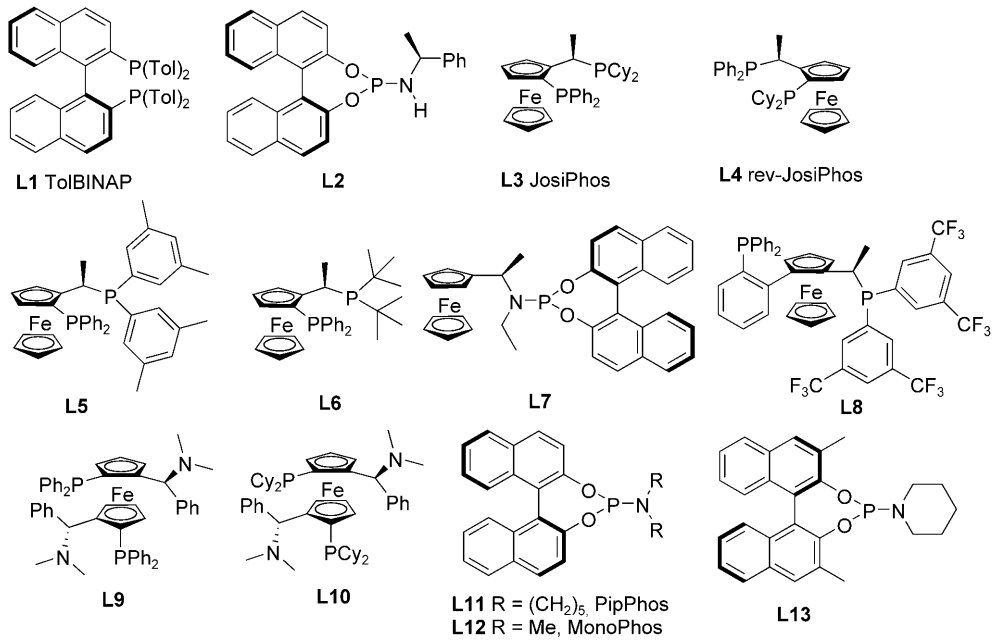
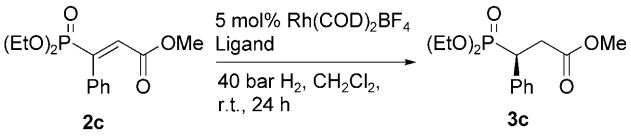


Figure 2. Ligands used in the rhodium catalyzed hydrogenation of **2**.

Table 1. Asymmetric hydrogenation of **2c**.[a]



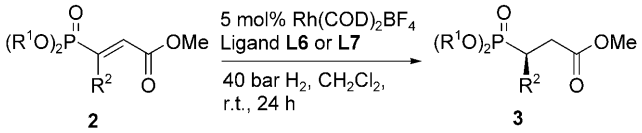
Entry	Ligand	Conv.[%][b]	*ee* [%][c]
1	**L1**	100	33
2	**L2**	0	–
3	**L3**	100	85
4	**L4**	100	33
5	**L5**	100	65
6	**L6**	100	95
7	**L7**	100	95
8	**L8**	100	79
9	**L9**	100	19
10	**L10**	100	83
11[d]	**L11**	100	60
12[e]	**L12**	100	53
13[d]	**L13**	100	-43

[a] Reactions were performed on a 0.2-mmol scale.
[b] Conversions were determined by ^{1}H NMR.
[c] The *ee* was determined by chiral HPLC, see Supporting Information.
[d] 25 bar H_2 pressure was used and **2b** was the substrate.
[e] **2b** was the substrate.

With two highly selective catalysts in hand, we commenced studying the generality of the high enantioselectivity. A series of substrates was hydrogenated using catalysts derived from **L6** and **L7** and, at least with **L6**, enantioselectivities were mostly above 90% with complete conversion (Table 2).

Upon changing from methyl to ethyl phosphonate esters, the enantioselectivity of the hydrogenation seemed to increase slightly using **L6** as the ligand, (91% versus 94%, entries 1 and 3), however, when R^2 was a phenyl moiety there was no difference (both 95%). When R^2=Ph, the shift from R^3=Me to a bulky *tert*-butyl ester decreased the *ee* to 86% (entry 18). Using **L6** as the ligand, catalyst loadings could be decreased to 2 mol% maintaining full conversion and a similar *ee* (entries 5 and 6), whereas further reductions in the catalyst loading led to incomplete conversions (entry 7). The high enantioselectivity found amongst the range of derivatives we tested with a variety of groups at the α-position of the phosphonate (R^2) suggests that this selectivity is quite general. Especially using **L6** as the ligand, high to excellent enantioselectivities were obtained with both aliphatic and aromatic substitutents. Changing the substituent adjacent to the phosphonate from a methyl to a propyl led to only a small reduction in the *ee* (93%, entry 16). Both electron withdrawing (Cl) and electron donating (OMe) substituents on the phenyl ring did not influence the enantioselectivity (94–95%, entries 10 and 12). The thienyl containing substrate showed a small decrease in *ee* to 89%. High isolated yields were obtained consistently for all these reactions. The enantioselectivities of the hydrogenation using the catalyst based on phosphoramidite **L7** were clearly less consistent with regard to substrate variation; excellent enantioselectivities were only obtained in the hydrogenation of **2c** and the thienyl-substituted substrate **2g**.

Table 2. Hydrogenation of **2** with ligand **L6** and **L7**.



2 3

Entry	Subst.[a]	Ligand	R^1	R^2	Conversion [%][b]	*ee* [%][c,h]
1	**2a**	**L6**	Me	Me	100 (73)	91 (−)
2	**2a**	**L7**	Me	Me	100	63
3	**2b**	**L6**	Et	Me	100 (85)	94 (−)
4	**2c**	**L6**	Et	Phenyl	100 (95)	95 (−)
5	**2c**	**L6**[d]	Et	Phenyl	100 (90)	95
6	**2c**	**L6**[e]	Et	Phenyl	100	93
7	**2c**	**L6**[f]	Et	Phenyl	77	93
8	**2c**	**L7**	Et	Phenyl	100	95 (+)
9	**2d**	**L6**	Me	Phenyl	100 (96)	95 (−)
10	**2e**	**L6**	Me	4-Cl-C_6H_4	100 (94)	95 (−)
11	**2e**	**L7**	Me	4-Cl-C_6H_4	100	40
12	**2f**	**L6**	Me	4-MeO-C_6H_4	100 (95)	94 (−)
13	**2f**	**L7**	Me	4-MeO-C_6H_4	100	65
14	**2g**	**L6**	Et	Thienyl	100 (90)	89 (−)
15	**2g**	**L7**	Et	Thienyl	100	89 (+)
16	**2h**	**L6**	Et	*n*-Propyl	100 (87)	93 (+)
17	**2h**	**L7**	Et	*n*-Propyl	100	71
18[g]	**2i**	**L6**	Et	Phenyl	100	86 (−)

[a] Reactions were performed on a 0.2-mmol scale.
[b] Conversions were determined by ^{1}H NMR spectroscopy; numbers in parenthesis are isolated yields.
[c] The *ee* was determined by chiral HPLC.
[d] 3 mol% of catalyst was used.
[e] 2 mol% of catalyst was used.
[f] 1 mol% of catalyst was used.
[g] R^3 is *tert*-butyl.
[h] The absolute configuration of the products is not known, the sign of the determined optical rotation is given in brackets.

Conclusions

In summary, we have developed the first highly enantioselective catalytic preparation of α-chiral phosphonate esters of type **3** by the asymmetric hydrogenation of readily available vinyl phosphonate precursors (two steps). Using a rhodium/bisphosphine catalyst, very high enantioselectivities and yields are obtained with a range of substituents adjacent to phosphonate. The resulting products are useful multifunctional building blocks for application in the synthesis of physiologically active compounds including enantiopure analogues of fosmidomycin.

Experimental Section

General Experimental Details

Starting materials were purchased from Aldrich, Alfa Aesar or Acros and used as received unless stated otherwise. All solvents were reagent grade and, if necessary, dried and distilled prior to use. Column chromatography was performed on silica gel (Aldrich 60, 230–400 mesh). TLC was performed on silica gel 60/Kieselguhr F_{254}. ^{1}H and ^{13}C NMR spectra were recorded on a Varian AMX 400 [399.93 MHz for ^{1}H, 100.59 MHz for ^{13}C and 161.9 MHz (^{1}H-decoupled) for ^{31}P] spectrometer in $CDCl_3$ unless stated otherwise. Carbon assignments are based on APT ^{13}C experiments. Mass spectra (HR-MS) were performed on a Jeol JMS-600 H. HPLC analysis was performed on a Shimadzu HPLC system equipped with two LC-10AD solvent delivery systems, a DGU-14 A degasser, a SIL-10AD *vp* auto injector, an SPD-M10 A *vp* diode array detector, a CTO-10 A *vp* column oven, and an SCL-10 A *vp* system controller using the columns indicated for each compound separately. Optical rotations were measured on a *Schmidt+Haensch* polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g/100 mL). Ligand **L7** was prepared according to the literature procedure.[21,22]

General Procedure for the Synthesis of Compounds 1a–1h

The compounds **1a–1h** were synthesized *via* an Arbuzov reaction.[12] The corresponding acyl chloride (24 mmol) was added to trimethyl or triethyl phosphite (20 mmol) at 0 °C under a nitrogen atmosphere. The mixture was stirred for

24 h at room temperature. Unreacted phosphite was removed under vacuum, and further purification by column chromatography (SiO_2, 4/1, heptane/EtOAc) gave the corresponding products in 54–70% yield.

Dimethyl acetylphosphonate (1a):[13] Pale yellow liquid; yield: 60%; ^{1}H NMR ($CDCl_3$): $\delta = 3.61$ (d, $^3J_{P,H} = 10.8$ Hz, 6H), 2.23 (d, $^3J_{P,H} = 5.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta =$ 208.1 (d, $J_{P,C} = 169.8$ Hz), 54.0 (d, $^2J_{P,C} = 7.2$ Hz, 2C), 20.9 (d, $^2J_{P,C} = 36.0$ Hz); ^{31}P NMR ($CDCl_3$): $\delta = -0.35$ (s).

Diethyl acetylphosphonate (1b):[13] Pale yellow liquid; yield: 63%; ^{1}H NMR ($CDCl_3$): $\delta = 3.95$–4.03 (m, 4H), 2.24 (d, $^3J_{P,H} = 5.1$ Hz, 3H), 1.14 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR ($CDCl_3$): $\delta = 208.8$ (d, $J_{P,C} = 171$ Hz), 63.7 (d, $^2J_{P,C} = 7.3$ Hz, 2C), 30.6 (d, $^2J_{P,C} = 59.4$ Hz), 16.4 (d, $^3J_{P,C} = 5.5$ Hz, 2C); ^{31}P NMR ($CDCl_3$): $\delta = -2.1$ (s).

Diethyl benzoylphosphonate (1c):[18] Green liquid; yield: 65%; ^{1}H NMR ($CDCl_3$): $\delta = 8.24$ (AA′BB′C, $J_{app} = 7.8$ Hz, 2H), 7.61 (AA′BB′C, $J_{app} = 7.4$ Hz, 1H), 7.48 (AA′BB′C, $J_{app} = 7.4$ Hz, 2H), 4.22–4.29 (m, 4H), 1.36 (t, $J = 7.0$ Hz, 6H); ^{13}C NMR ($CDCl_3$): $\delta = 199.2$ (d, $J_{P,C} = 175$ Hz), 135.8 (d, $^2J_{P,C} = 63.4$ Hz), 135.0, 130.1, 129.1, 64.2 (d, $^2J_{P,C} = 7.3$ Hz, 2C), 16.6 (d, $^3J_{P,C} = 5.9$ Hz, 2C); ^{31}P NMR ($CDCl_3$): $\delta = -0.2$ (s).

Dimethyl benzoylphosphonate (1d):[13] Green liquid; yield: 64%; ^{1}H NMR ($CDCl_3$): $\delta = 8.04$ (AA′BB′C, $J_{app} =$ 6.5 Hz, 2H), 7.40 (AA′BB′C, $J_{app} = 7.0$ Hz, 1H), 7.28 (AA′BB′C, $J_{app} = 7.8$ Hz, 2H), 3.71 (d, $^3J_{P,H} = 10.9$ Hz, 6H); ^{13}C NMR ($CDCl_3$): $\delta = 198.0$ (d, $J_{P,C} = 175.1$ Hz), 135.4 (d, $^2J_{P,C} = 63.4$ Hz), 135.1, 129.8, 129.1, 54.3 (d, $^2J_{P,C} =$ 7.4 Hz,2C); ^{31}P NMR ($CDCl_3$): $\delta = 1.6$ (s).

Dimethyl 4-chlorobenzoylphosphonate (1e):[19] Green liquid; yield: 54%; ^{1}H NMR ($CDCl_3$): $\delta = 7.82$ (AA′BB′, $J_{app} = 8.6$ Hz, 2H), 7.10 (AA′BB′, $J_{app} = 8.6$ Hz, 2H), 3.56 (d, $^3J_{P,H} = 10.9$ Hz, 6H); ^{13}C NMR ($CDCl_3$): $\delta = 197.1$ (d, $J_{P,C} =$ 177.2 Hz), 141.3, 133.78 (d, $^2J_{P,C} = 64.8$ Hz), 131.1, 129.2, 64.1 (d, $^2J_{P,C} = 6.5$ Hz, 2C); ^{31}P NMR ($CDCl_3$): $\delta = 1.0$ (s).

Dimethyl 4-methoxybenzoylphosphonate (1f):[19] Green liquid; yield: 70%; ^{1}H NMR ($CDCl_3$): $\delta = 7.92$ (AA′BB′, $J_{app} = 8.7$ Hz, 2H), 6.65 (AA′BB′, $J_{app} = 8.6$ Hz, 2H), 3.59 (d, $^3J_{P,H} = 10.9$ Hz, 6H), 3.54 (s, 3H); ^{13}C NMR ($CDCl_3$): $\delta =$ 195.6 (d, $J_{P,C} = 173.6$ Hz), 165.1, 132.3 (d, $^3J_{P,C} = 1.4$ Hz), 128.7 (d, $^2J_{P,C} = 65.7$ Hz), 114.2, 55.6, 54.0 (d, $^2J_{P,C} = 7.3$ Hz, 2C); ^{31}P NMR ($CDCl_3$): $\delta = 2.2$ (s).

Diethyl thiophene-3-carbonylphosphonate (1g): Green liquid; yield: 59%; ^{1}H NMR ($CDCl_3$): $\delta = 8.36$- 8.38 (m, 1H), 7.76- 7.79 (m, 1H), 7.14- 7.17 (m, 1H), 4.17- 4.25 (m, 4H), 1.31 (t, $J = 7.0$ Hz, 6H); ^{13}C NMR ($CDCl_3$): $\delta = 190.6$ (d, $J_{P,C} = 183.3$ Hz), 143.4 (d, $^2J_{P,C} = 80.8$ Hz), 138.2, 137.3, 129.2 (d, $^3J_{P,C} = 1.1$ Hz), 64.4 (d, $^2J_{P,C} = 7.1$ Hz, 2C), 16.5 (d, $^3J_{P,C} = 5.8$ Hz, 2C); ^{31}P NMR ($CDCl_3$): $\delta = -1.40$ (s); HR-MS (EI+): $m/z = 249.0344$, calcd. for $C_9H_{14}O_4P^{32}S$: 249.0345.

Diethyl butyrylphosphonate (1h):[20] Pale yellow liquid; yield: 64%; ^{1}H NMR ($CDCl_3$): $\delta = 3.90$–3.97 (m, 4H), 2.53 (dt, $J = 1.5$ Hz, 7.1 Hz, 2H), 1.32–1.40 (m, 2H), 1.09 (t, $J =$ 7.1 Hz, 6H), 0.65 (t, $J = 7.4$ Hz, 3H); ^{31}P NMR ($CDCl_3$): $\delta =$ −2.06 (s).

General Procedure for the Synthesis of the Compounds 2a–i *via* a Wittig reaction

Methoxycarbonylmethyltriphenylphosphonium or *tert*-butoxycarbonylmethyltriphenylphosphonium bromide (5 mmol) in benzene (40 mL) was treated with sodium amide (10 mmol) at room temperature for 24 h. The sodium bromide formed and the unreacted sodium amide were filtered off under a nitrogen flow. Compound **1** (5 mmol) was then added dropwise to the solution of the phosphorane at 0 °C and the mixture was allowed to react at room temperature for 24 h. Benzene was removed under vacuum and the residue was purified by crystallization of the triphenylphosphine oxide from heptane/toluene and its removal by filtration. Further purification by column chromatography (SiO_2, 1/1, heptane/EtOAc) gave the corresponding products **2**; yield: 73–85%.

(*E*)-Methyl 3-(dimethoxyphosphoryl)but-2-enoate (2a):[11] Pale yellow liquid; yield: 73%; ^{1}H NMR ($CDCl_3$): $\delta = 6.64$ [dq, $J = 1.7$, 24.3 ($^3J_{P,H}$) Hz, 1H], 3.77 (d, $^3J_{P,H} = 10.8$ Hz, 6H), 3.75 (s, 3H), 2.26 [dd, $J = 1.7$, 15.5 ($^3J_{P,H}$) Hz, 3H); ^{31}P NMR ($CDCl_3$): $\delta = 21.7$ (s).

(*E*)-Methyl 3-(diethoxyphosphoryl)but-2-enoate (2b):[11] Pale yellow liquid; yield: 77%; ^{1}H NMR ($CDCl_3$): $\delta = 6.56$ [dq, $J = 1.7$, 24.3($^3J_{P,H}$) Hz, 1H], 3.98–4.08 (m, 4H), 3.68 (s, 3H), 2.19 [dd, $J = 1.7$, 15.5($^3J_{P,H}$) Hz, 3H], 1.26 (t, $J = 7.1$ Hz, 6H); ^{31}P NMR ($CDCl_3$): $\delta = 18.7$ (s).

(*E*)-Methyl 3-(diethoxyphosphoryl)-3-phenylacrylate (2c): Green liquid; yield: 83%; ^{1}H NMR ($CDCl_3$): $\delta = 7.18$–7.28 (m, 5H), 6.81 (d, $^3J_{P,H} = 23.0$ Hz, 1H), 3.95–4.05 (m, 4H), 3.49 (s, 3H), 1.18 (t, $J = 7.0$ Hz, 6H); ^{13}C NMR ($CDCl_3$): $\delta =$ 165.1 (d, $^3J_{P,C} = 28.8$ Hz), 145.3 (d, $J_{P,C} = 172.9$ Hz), 134.2 (d, $^2J_{P,C} = 6.8$ Hz), 132.0 (d, $^2J_{P,C} = 11.3$ Hz), 128.5 (d, $^3J_{P,C} =$ 2.1 Hz), 128.2, 128.2, 63.1 (d, $^2J_{P,C} = 6.1$ Hz, 2C), 51.9, 16.4 (d, $^3J_{P,C} = 6.2$ Hz, 2C); ^{31}P NMR ($CDCl_3$): $\delta = 15.0$ (s); HR-MS (EI+): $m/z = 299.1044$, calcd. for $C_{14}H_{20}O_5P$: 299.1043.

(*E*)-Methyl 3-(dimethoxyphosphoryl)-3-phenylacrylate (2d): Green liquid; yield: 81%; ^{1}H NMR ($CDCl_3$): $\delta = 7.19$–7.30 (m, 5H), 6.84 (d, $^3J_{P,H} = 23.2$ Hz, 1H), 3.65 (d, $^3J_{P,H} =$ 11.1 Hz, 6H), 3.51 (s, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 165$ (d, $^3J_{P,C} = 29.0$ Hz), 144.0 (d, $J_{P,C} = 173.3$ Hz), 134.0 (d, $^2J_{P,C} =$ 6.8 Hz), 132.8 (d, $^2J_{P,C} = 11.1$ Hz), 128.7, 128.3, 128.1 (d, $^3J_{P,C} = 5.4$ Hz), 53.4 (d, $^2J_{P,C} = 6.1$ Hz, 2C), 52.0; ^{31}P NMR ($CDCl_3$): $\delta = 17.8$ (s); HR-MS (EI+): $m/z = 271.0729$, calcd. for $C_{12}H_{16}O_5P$: 271.0730,.

(*E*)-Methyl 3-(4-chlorophenyl)-3-(dimethoxyphosphoryl)-acrylate (2e): Green liquid; yield: 85%; ^{1}H NMR ($CDCl_3$): $\delta = 7.28$ (AA′BB′, $J_{app} = 8.1$ Hz, 2H), 7.15 (AA′BB′, $J_{app} =$ 8.4 Hz, 2H), 6.83 (d, $^3J_{P,H} = 23.1$ Hz, 1H), 3.66 (d, $^3J_{P,H} =$ 11.0 Hz, 6H), 3.54 (s, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 164.7$ (d, $^3J_{P,C} = 28.7$ Hz), 143.1 (d, $J_{P,C} = 174.7$ Hz), 134.8, 133.1 (d, $^2J_{P,C} = 11.3$ Hz), 132.4, 129.7 (d, $^2J_{P,C} = 5.4$ Hz), 128.6, 53.5 (d, $^2J_{P,C} = 6.1$ Hz, 2C), 52.1; ^{31}P NMR ($CDCl_3$): $\delta = 17.3$ (s); HR-MS (EI+): $m/z = 305.0339$, calcd. for $C_{12}H_{15}O_5P^{35}Cl$: 305.0340.

(*E*)-Methyl 3-(dimethoxyphosphoryl)-3-(4-methoxyphenyl)acrylate (2f): Green liquid; yield: 77%; ^{1}H NMR ($CDCl_3$): $\delta = 7.18$ (AA′BB′, $J_{app} = 8.7$ Hz, 2H), 6.84 (AA′BB′, $J_{app} = 8.9$ Hz, 2H), 6.80 (d, $^3J_{P,H} = 23.2$ Hz, 1H), 3.75 (s, 3H), 3.67 (d, $^3J_{P,H} = 11.0$ Hz, 6H), 3.56 (s, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 165.2$ (d, $^3J_{P,C} = 29.0$ Hz), 160.1, 143.2 (d, $J_{P,C} = 173.2$ Hz), 132.2 (d, $^2J_{P,C} = 11.9$ Hz), 129.7 (d, $^3J_{P,C} =$ 5.6 Hz), 125.8 (d, $^2J_{P,C} = 7.2$ Hz), 113.9, 55.4, 53.4 (d, $^2J_{P,C} =$ 6.1 Hz, 2C), 52.0; ^{31}P NMR ($CDCl_3$): $\delta = 18.4$ (s); HR-MS (EI+): $m/z = 301.0836$, calcd. for $C_{13}H_{18}O_6P$: 301.0836.

(*E*)-Methyl 3-(diethoxyphosphoryl)-3-(thiophen-3-yl)acrylate (2g): Green liquid; yield: 81%; ^{1}H NMR ($CDCl_3$): $\delta =$

7.40 (d, $J=5.1$ Hz, 1H), 7.30 (m, 1H), 7.03 (dd, $J=4.0$ Hz, 4.7 Hz, 1H), 6.90 (d, $^3J_{P,H}=22.96$ Hz, 1H), 4.04–4.19 (m, 4H), 3.70 (s, 3H), 1.29 (t, $J=7.1$ Hz, 6H); ^{13}C NMR ($CDCl_3$): $\delta=165.5$ (d, $^3J_{P,C}=27.5$ Hz), 135.7 (d, $J_{P,C}=175.9$ Hz), 133.6 (d, $^2J_{P,C}=9.5$ Hz), 131.9 (d, $^2J_{P,C}=10.8$ Hz), 129.9 (d, $^3J_{P,C}=6.3$ Hz), 128.4, 127.1, 63.1 (d, $^2J_{P,C}=5.8$ Hz, 2C), 52.1, 16.3 (d, $^3J_{P,C}=6.1$ Hz, 2C); ^{31}P NMR ($CDCl_3$): $\delta=14.9$ (s); HR-MS (EI+): $m/z=305.0607$, calcd. for $C_{12}H_{18}O_5P^{32}S$: 305.0607.

(*E*)-Methyl 3-(diethoxyphosphoryl)hex-2-enoate (2h): Pale yellow liquid; yield: 77%; ^{1}H NMR ($CDCl_3$): $\delta=6.55$ (d, $^3J_{P,H}=24.3$ Hz, 1H), 4.0–4.10 (m, 4H), 3.68 (s, 3H), 2.60 [dt, $J=7.8$ Hz, 20.7 ($^3J_{P,H}$) Hz, 2H], 1.47–1.55 (m, 2H), 1.27 (t, $J=7.0$ Hz, 6H), 0.90 (t, $J=7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta=165.3$ (d, $^3J_{P,C}=32.1$ Hz), 148.8 (d, $J_{P,C}=167.2$ Hz), 130.2 (d, $^2J_{P,C}=12.5$ Hz), 62.5 (d, $^2J_{P,C}=5.9$ Hz, 2C), 51.7, 30.9 (d, $^2J_{P,C}=6.7$ Hz), 22.8, 16.4 (d, $^3J_{P,C}=6.2$ Hz, 2C), 14.4; ^{31}P NMR ($CDCl_3$): $\delta=19.1$ (s); HR-MS (EI+): $m/z=265.1197$, calcd. for $C_{11}H_{22}O_5P$: 265.1199.

(*E*)-*tert*-Butyl 3-(diethoxyphosphoryl)-3-phenylacrylate (2i): Green liquid; yield: 79%; ^{1}H NMR ($CDCl_3$): $\delta=7.17$–7.27 (m, 5H), 6.72 (d, $^3J_{P,H}=23.2$ Hz, 1H), 3.95–4.05 (m, 4H), 1.18 (t, $J=7.0$ Hz, 6H), 1.14 (s, 9H); ^{13}C NMR ($CDCl_3$): $\delta=164.2$ (d, $^3J_{P,C}=27.5$ Hz), 142.2 (d, $J_{P,C}=173.5$ Hz), 134.9 (d, $^2J_{P,C}=6.6$ Hz), 134.6 (d, $^2J_{P,C}=6.9$ Hz), 128.4, 128.2, 128.1, 81.8, 62.8 (d, $^2J_{P,C}=6.1$ Hz, 2C), 27.7 (d, $^3J_{P,C}=8.6$ Hz, 2C), 16.4 (3C); ^{31}P NMR ($CDCl_3$): $\delta=15.8$ (s); HR-MS (EI+): $m/z=341.1514$, calcd. for $C_{17}H_{26}O_5P$: 341.1512.

General Procedure for the Hydrogenation

The standard operating procedure for hydrogenation using an autoclave was as follows: To a glass reaction vessel was added 0.20 mmol of substrate, bidentate ligand (0.010 mmol) or monodentate ligand (0.020 mmol), $Rh(COD)_2BF_4$ (0.010 mmol) and 4.0 mL of solvent. The reaction vessel was placed in the autoclave and purged 4 times with nitrogen followed by purging with hydrogen, and finally pressurized to 40 bar of hydrogen. The sample was stirred at 700 rpm for 24 h. The reaction mixture was filtered over a silica plug (1/1, EtOAc/heptane) after which the conversion and *ee* were determined by ^{1}H NMR spectroscopy and chiral HPLC, respectively.

Methyl 3-(dimethoxyphosphoryl)butanoate (3a):[11] Colourless oil; ^{1}H NMR ($CDCl_3$): $\delta=3.69$ (d, $^3J_{P,H}=10.6$ Hz, 6H), 3.63 (s, 3H), 2.64–2.76 (m, 1H), 2.30–2.44 (m, 1H), 2.20–2.30 (m, 1H), 1.15 [dd, $J=7.1$, 18.2 ($^3J_{P-H}$) Hz, 3H]; ^{31}P NMR ($CDCl_3$): $\delta=36.05$ (s); $[\alpha]_D$: −4 (*c* 0.35, $CHCl_3$, 91% *ee*); Chiral HPLC (Chiralpak AD-H, 40 °C, heptane/IPA 97:3, 0.5 mL min^{-1}): $t_r=34.7$ min (major **3a**), 38.8 min (minor **3a**).

Methyl 3-(diethoxyphosphoryl)butanoate (3b):[11] Colourless oil; ^{1}H NMR ($CDCl_3$): $\delta=4.04$–4.07 (m, 4H), 3.65 (s, 3H), 2.64–2.80 (m, 1H), 2.20–2.41 (m, 2H), 1.27 (t, $J=7.0$ Hz, 6H), 1.13 [dd, $J=7.0$, 18.3 ($^3J_{P,H}$) Hz, 3H]; ^{31}P NMR ($CDCl_3$): $\delta=33.52$ (s); $[\alpha]_D$: −2.75 (*c* 0.8, $CHCl_3$, 94% *ee*); chiral HPLC (Chiralpak AD-H, 40 °C, heptane/IPA 97:3, 0.5 mL min^{-1}): $t_r=31.9$ min (major **3b**), 35.5 min (minor **3b**).

Methyl 3-(diethoxyphosphoryl)-3-phenylpropanoate (3c): Colourless oil; ^{1}H NMR ($CDCl_3$): $\delta=7.37$–7.23 (m, 5H), 3.98–4.08 (m, 2H), 3.86–3.93 (m, 1H), 3.70–3.80 (m, 1H), 3.63 [ddd, $J=22.5$ ($^2J_{P,H}$), 10.3, 4.8 Hz, 1H], 3.57 (s, 3H), 3.05–3.13 (m, 1H), 2.91–3.00 (m, 1H), 1.27 (t, $J=7.0$ Hz, 3H), 1.11 (t, $J=7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta=171.6$ (d, $^3J_{P,C}=19.1$ Hz), 135.4 (d, $^2J_{P,C}=6.9$ Hz), 129.2 (d, $^3J_{P,C}=6.5$ Hz), 128.7 (d, $^5J_{P,C}=2.3$ Hz), 127.6 (d, $^4J_{P,C}=3.0$ Hz), 63.0 (d, $^2J_{P,C}=6.96$ Hz), 62.3 (d, $^2J_{P,C}=7.3$ Hz), 52.1, 40.1 (d, $J_{P,C}=140.4$ Hz), 35.2, 16.6 (d, $^3J_{P,C}=6.0$ Hz), 16.4 (d, $^3J_{P,C}=5.9$ Hz); ^{31}P NMR ($CDCl_3$): $\delta=28.2$ (s); $[\alpha]_D$: −4.2 (*c* 0.7, $CHCl_3$, 95% *ee*); HR-MS (EI+): $m/z=301.1199$, calcd. for $C_{14}H_{22}O_5P$: 301.1199; chiral HPLC (Chiralpak AD-H, 40 °C, heptane/IPA 95:5, 0.5 mL min^{-1}): $t_r=34.4$ min (minor **3c**), 37.7 min (major **3c**).

Methyl 3-(dimethoxyphosphoryl)-3-phenylpropanoate (3d):[9] Colourless oil; ^{1}H NMR ($CDCl_3$): $\delta=7.20$–7.33 (m, 5H), 3.64 (d, $^3J_{P,H}=10.7$ Hz, 3H), 3.59–3.68 (m, 1H), 3.52 (s, 3H), 3.45 (d, $^3J_{P,H}=10.6$ Hz, 3H), 2.99–3.07 (m, 1H), 2.86–2.96 (m, 1H); ^{13}C NMR ($CDCl_3$): $\delta=171.5$ (d, $^3J_{P,C}=18.8$ Hz), 135.1 (d, $^2J_{P,C}=7.2$ Hz), 129.2 (d, $^3J_{P,C}=6.6$ Hz), 128.8 (d, $^5J_{P,C}=2.4$ Hz), 127.8 (d, $^4J_{P,C}=3.1$ Hz), 53.8 (d, $^2J_{P,C}=7.0$ Hz), 53.1 (d, $^2J_{P,C}=7.2$ Hz), 52.1, 40.1 (d, $J_{P,C}=140.4$ Hz), 35.1; ^{31}P NMR ($CDCl_3$): $\delta=30.6$ (s); $[\alpha]_D$: −10.4 (*c* 0.5, $CHCl_3$, 95% *ee*); HR-MS (EI+): $m/z=273.0889$, calcd. for $C_{12}H_{18}O_5P$: 273.0886; chiral HPLC (Chiralpak AS-H, 40 °C, heptane/IPA 95:5, 0.5 mL min^{-1}): $t_r=25.4$ min (major **3d**), 30.0 min (minor **3d**).

Methyl 3-(4-chlorophenyl)-3-(dimethoxyphosphoryl)propanoate (3e): Colourless oil; ^{1}H NMR ($CDCl_3$): $\delta=7.27$ (s, 4H), 3.68 (d, $^3J_{P,H}=10.6$ Hz, 3H), 3.56–3.65 (m, 1H), 3.55 (s, 3H), 3.52 (d, $^3J_{P,H}=10.6$ Hz, 3H), 2.99–3.08 (m, 1H), 2.84–2.92 (m, 1H); ^{13}C NMR ($CDCl_3$): $\delta=171.3$ (d, $^3J_{P,C}=19.1$ Hz), 133.8 (d, $^2J_{P,C}=7.1$ Hz), 133.7, 130.5 (d, $^3J_{P,C}=6.4$ Hz), 129.1 (d, $^4J_{P,C}=2.5$ Hz), 53.9 (d, $^2J_{P,C}=7.0$ Hz), 53.2 (d, $^2J_{P,C}=7.4$ Hz), 52.2, 39.57 (d, $J_{P,C}=141.0$ Hz), 35.0; ^{31}P NMR ($CDCl_3$): $\delta=30.0$ (s); $[\alpha]_D$: −8.8 (*c* 0.5, $CHCl_3$, 95% *ee*); HR-MS (EI+): m/z=307.0497, calcd. for $C_{12}H_{17}O_5P^{35}Cl$: 307.0497; chiral HPLC (Chiralpak AS-H, 40 °C, heptane/IPA 95:5, 0.5 mL min^{-1}): $t_r=27.6$ min (major **3e**), 30.0 min (minor **3e**).

Methyl 3-(dimethoxyphosphoryl)-3-(4-methoxyphenyl)-propanoate (3f): Colourless oil; ^{1}H NMR ($CDCl_3$): $\delta=7.25$ (AA′BB′, $J_{app}=8.4$ Hz, 2H), 6.84 (AA′BB′, $J_{app}=8.1$ Hz, 2H), 3.76 (s, 3H), 3.67 (d, $^3J_{P,H}=10.7$ Hz, 3H), 3.58–3.63 (m, 1H), 3.55 (s, 3H), 3.49 (d, $^3J_{P,H}=10.5$ Hz, 3H), 2.98–3.06 (m, 1H), 2.84–2.93 (m, 1H); ^{13}C NMR ($CDCl_3$): $\delta=171.6$ (d, $^3J_{P,C}=19.6$ Hz), 159.2 (d, $^5J_{P,C}=3.1$ Hz), 130.2 (d, $^3J_{P,C}=6.3$ Hz), 126.9 (d, $^2J_{P,C}=7.4$ Hz), 114.3 (d, $^4J_{P,C}=2.3$ Hz), 55.4, 53.8 (d, $^2J_{P,C}=6.9$ Hz), 53.1 (d, $^2J_{P,C}=7.4$ Hz), 52.1, 39.3 (d, $J_{P,C}=141.4$ Hz), 35.3; ^{31}P NMR ($CDCl_3$): $\delta=30.9$ (s); $[\alpha]_D$: −8 (*c* 0.25, $CHCl_3$, 94% *ee*); HR-MS (EI+): $m/z=303.0991$, calcd. for $C_{13}H_{20}O_6P$: 303.0992; chiral HPLC (Chiralpak AD-H, 40 °C, heptane/IPA 90:10, 0.5 mL min^{-1}): $t_r=28.3$ min (minor **3f**), 30.0 min (major **3f**).

Methyl 3-(diethoxyphosphoryl)-3-(thiophen-3-yl)propanoate (3g): Colourless oil; ^{1}H NMR ($CDCl_3$): $\delta=7.19$ (d, $J=5.1$ Hz, 1H), 7.03 (t, $J=3.4$ Hz, 1H), 6.94 (t, $J=4.2$ Hz, 1H), 4.01- 4.09 (m, 2H), 3.85–4.01 (m, 3H), 3.61 (s, 3H), 3.05–3.13 (m, 1H), 2.85- 2.94 (m, 1H), 1.28 (t, $J=7.1$ Hz, 3H), 1.18 (t, $J=7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta=171.3$ (d, $^3J_{P,C}=17.9$ Hz), 137.4 (d, $^2J_{P,C}=8.2$ Hz), 127.1 (d, $^4J_{P,C}=3.3$ Hz), 127.0 (d, $^3J_{P,C}=7.8$ Hz), 125.1 (d, $^3J_{P,C}=3.8$ Hz), 63.3 (d, $^2J_{P,C}=6.9$ Hz), 62.7 (d, $^2J_{P,C}=7.1$ Hz), 52.2, 36.6, 36.0 (d, $J_{P,C}=145.6$ Hz), 16.6 (d, $^3J_{P,C}=6.1$ Hz), 16.5 (d, $^3J_{P,C}=$

6.1 Hz); ^{31}P NMR ($CDCl_3$): $\delta = 26.1$ (s); $[\alpha]_D$: −41 (*c* 0.7, $CHCl_3$, 89% *ee*); HR-MS (EI+): m/z = 307.0764, calcd. for $C_{12}H_{20}O_5P^{32}S$: 307.0764; chiral HPLC (Chiralpak OJ-H, 40 °C, heptane/IPA 95:5, 0.5 mL min^{-1}): $t_r = 29.0$ min (major **3g**), 52.4 min (minor **3g**).

Methyl 3-(diethoxyphosphoryl)hexanoate (3h): Colourless oil; ^{1}H NMR ($CDCl_3$): $\delta = 4.01$–4.08 (m, 4H), 3.64 (s, 3H), 2.58–2.70 (m, 1H), 2.29–2.40 (m, 2H), 1.61–1.75 (m, 2H), 1.32–1.44 (m, 2H), 1.26 (t, $J = 7.0$ Hz, 6H), 0.86 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 172.7$ (d, $^3J_{P,C} = 14.1$ Hz), 61.98 (d, $^2J_{P,C} = 6.7$ Hz), 61.9 (d, $^2J_{P,C} = 6.9$ Hz), 52.0, 33.9 (d, $^2J_{P,C} = 2.3$ Hz), 32.7 (d, $J_{P,C} = 142.3$ Hz), 31.3 (d, $^2J_{P,C} = 3.6$ Hz), 20.8 (d, $^3J_{P,C} = 9.9$ Hz), 16.60 (d, $^3J_{P,C} = 5.9$ Hz, 2C), 14.2; ^{31}P NMR ($CDCl_3$): $\delta = 33.5$ (s); $[\alpha]_D$: +4.4 (*c* 0.9, $CHCl_3$, 93% *ee*); HR-MS (EI+): *m/z* = 267.1354, calcd. for $C_{11}H_{24}O_5P$: 267.1356; chiral HPLC (Chiralpak AD-H, 40 °C, heptane/IPA 97:3, 0.5 mL min^{-1}): $t_r = 29.2$ min (major **3h**), 31.6 min (minor **3h**).

***tert*-Butyl 3-(diethoxyphosphoryl)-3-phenylpropanoate (3i):** Colourless oil; ^{1}H NMR ($CDCl_3$): $\delta = 7.22$–7.34 (m, 5H), 3.98–4.06 (m, 2H), 3.86–3.95 (m, 1H), 3.71–3.81 (m, 1H), 3.56 [ddd, $J = 22.5$ ($^2J_{P,H}$), 10.99, 4.7 Hz, 1H], 2.94–3.01 (m, 1H), 2.81–2.91 (m, 1H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.23 (s, 9H), 1.10 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 170.3$ (d, $^3J_{P,C} = 20.0$ Hz), 135.5 (d, $^2J_{P,C} = 6.95$ Hz), 129.4 (d, $^3J_{P,C} = 6.3$ Hz), 128.6 (d, $^5J_{P,C} = 2.6$ Hz), 127.5 (d, $^4J_{P,C} = 3.3$ Hz), 81.1, 62.9 (d, $^2J_{P,C} = 6.95$ Hz), 62.3 (d, $^2J_{P,C} = 7.3$ Hz), 41.0 (d, $J_{P,C} = 139.6$ Hz), 36.4, 28.0 (3C), 16.6 (d, $^3J_{P,C} = 5.9$ Hz), 16.5 (d, $^3J_{P,C} = 5.7$ Hz); ^{31}P NMR ($CDCl_3$): $\delta = 28.5$ (s); $[\alpha]_D$: −9 (*c* 1.4, $CHCl_3$, 86% *ee*); HR-MS (EI+): *m/z* = 343.1670, calcd. for $C_{17}H_{28}O_5P$: 343.1669; chiral HPLC (Chiralpak AS-H, 40 °C , heptane/IPA 95:5, 0.5 mL min^{-1}): $t_r = 8.7$ min (major **3i**), 10.0 min (minor **3i**).

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