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Enantiomerically divergent pathways in Tsuji-Trost reactions: exploiting the structural differences between β-acyloxy-*o*-(diphenylphosphino)benzamides and β-amido-*o*-(diphenylphosphino)benzoates

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ABSTRACT

Using a single chiral scaffold, (1*R*,2*S*)-norephedrine, a series of monophosphine ligands have been prepared. The ligands prepared, β-acyloxy-(*o*-diphenylphosphino)amides and β-amido-(*o*-diphenylphosphino)esters, give rise to enantiomerically divergent products in the Tsuji-Trost asymmetric allylic reaction. The phosphinoamides afforded the best enantioselectivities and favored the (*S*)-enantiomer of the product. In contrast the phosphinoesters afforded lower enantioselectivities and favored the (*R*)-enantiomer. A mechanistic rationale for this observation is proposed.

1. Introduction

The Tsuji-Trost asymmetric allylic alkylation reaction has attracted much attention due to its efficiency in the enantioselective synthesis of allylic substrates.[1] Trost ligand **1** has been shown to be highly effective in the allylic alkylation reaction and has represented a high standard in terms of ligand design.[2] In this context, related ligands have been synthesized in the hope of creating ligands of comparable efficacy as chiral ligands for phosphines in the Tsuji-Trost reaction.[3] Since the Trost ligand is derived from a C_2-symmetric chiral diamine, our interest was in exploiting β-aminoalcohols due to the broader diversity and commercial availability of these compounds. Thus, our research group developed a series of bis(phosphine) ligands based on (1*R*,2*S*)-norephedrine **2a**, (1*S*,2*S*)-pseudonorephedrine **2b**,[4] and β-aminoalcohols **3a**–**c**[5] derived from α-amino acids (Fig. 1). These ligand systems proved to be successful in terms of promoting the enantioselective alkylation of *rac*-1,3-diphenyl-1-propenyl acetate with diethylmalonate with enantioselectivities as high as 96% ee. Beyond this success, we were interested in exploring further the chemistry of these compounds as monophosphines. The synthesis of such compounds would allow for a study of the stereochemical consequences of having the key diphenylphosphinobenzoyl (*o*-$Ph_2PC_6H_4CO$–) moiety present as an amide, β-acyloxy-*o*-diphenylphosphinobenzamide **5**, or as an ester, β-amido-*o*-diphenylphosphino benzoate **6** (Fig. 1). Herein, we report on the synthesis of these two ligand families and their application in the Tsuji-Trost reaction. A rationale is proposed for the observed stereoselectivities for the two classes of phosphine ligands.

2. Results and discussion

This investigation began with the synthesis of the β-acyloxy-(*o*-diphenylphosphino)amide ligands **5a**–**d**. (1*R*,2*S*)-Norephedrine was coupled with *o*-(diphenylphosphino)benzoic acid in the presence of EDC and a catalytic amount of DMAP. The amide was then reacted with a variety of acyl chlorides to form the target amide ligands **5a**–**d** (Table 1).

The second group of ligands synthesized employed the same (1*R*,2*S*)-norephedrine template. Norephedrine was reacted with an acyl chloride that had been used in the synthesis of the prior group of ligands. This process yielded four amides, which were then esterified by the addition of *o*-(diphenylphosphino)benzoic acid in the presence of EDC and a catalytic amount of DMAP. This yielded the desired β-amido-(*o*-diphenylphosphino)esters **9a**–**d**.

All of the phosphine ligands **5a**–**d** and **9a**–**d** were fully characterized and evaluated by ^{31}P NMR spectroscopy. The ^{31}P NMR signal for the *o*-diphenylphosphinobenzamido ligands **5a**–**d** appeared between −8.0 and −11 ppm in $CDCl_3$. The ^{31}P NMR signal for the

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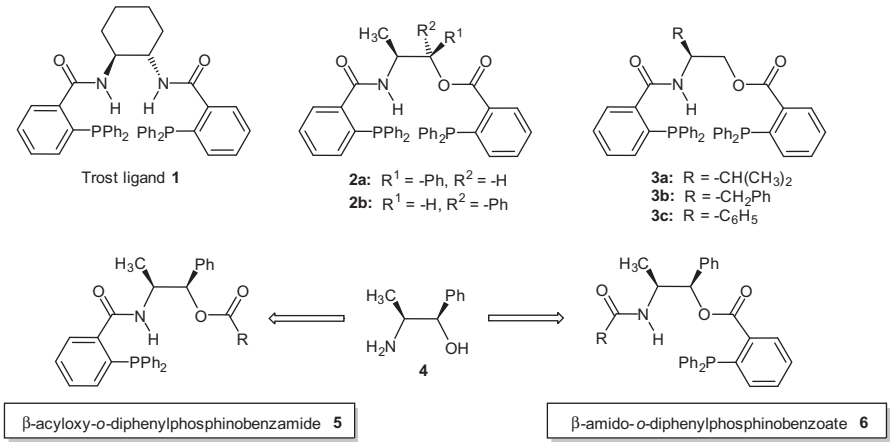
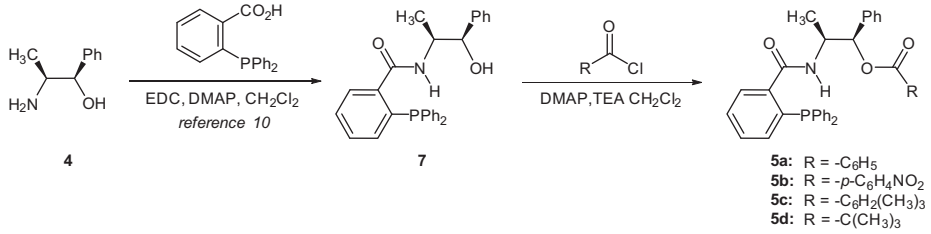


Figure 1. Bis(phosphine) ligands **1**–**3** and proposed monophosphines **5** and **6**.

Table 1
Synthesis of the β-acyloxy-(*o*-diphenylphosphino)amides **5a**–**d**



Entry	R=	Phosphine	Yield[a] (%)
1	$-C_6H_5$	**5a**	88
2	$-p\text{-}C_6H_4NO_2$	**5b**	56
3	$-C_6H_2(CH_3)_3$	**5c**	49
4	$-C(CH_3)_3$	**5d**	61

[a] Isolated yield after purification.

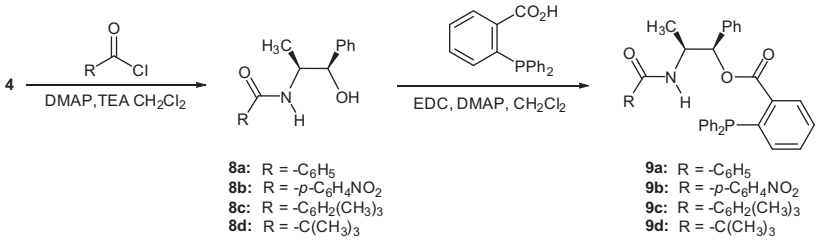
o-diphenylphosphinobenzoate ligands **9a**–**d** appeared between −4.0 and −6.0 ppm in $CDCl_3$. Collectively, these signals appear in nearly the same region as the signal for triphenylphosphine which appears as a singlet at −4.72 ppm in $CDCl_3$. It is worthwhile noting that all but a few of the compounds showed a small singlet (<5%) near 30–37 ppm in the ^{31}P spectrum. We propose that this signal represents the oxidized phosphine of the phosphine being analyzed. An independent sample of triphenylphosphine oxide was analyzed and found to contain a singlet in the same region at 29.7 ppm. The putative phosphine oxides may have originated from the handling of these compounds in the presence of air (Table 2).

The collected ligands **5a**–**d** and **9a**–**d** were then treated with a catalytic amount of the palladium allyl chloride dimer, catalytic potassium acetate, *N*,*O*-bis(trimethylsilyl)acetamide, *rac*-1,3-diphenyl-1-propenyl acetate *rac*-**10**, and diethylmalonate. The observed enantioselectivities from the catalysis indicated that the *o*-diphenylphosphinobenzamide ligands **5a**–**d** afforded high enantioselectivities ranging from 87% to 90% ee while favoring the (*S*)-enantiomer of the product. In contrast, the *o*-diphenylphosphinobenzoate ligands **9a**–**d** afforded low enantioselectivities ranging from 5% to 58% ee while favoring the (*R*)-enantiomer of the product (Table 3).

The enantiodivergence that was observed for these palladium catalyzed reactions can be attributed to the ligand structures and the overall complexing events that occur during the reaction. Using the mechanistic model developed by Burke et al.,[6] it is proposed that the key complexation event that leads to the enantioselective product formation can be represented by complex-**12A** and complex-**12B**. These complexes illustrate a favored pathway for the binding of the palladium with the phosphine and the carbonyl oxygen. In the case of complex-**12A**, the amide component of complex serves as a rigid template and is most likely responsible for ensuring that the enantioselection is high (87.2% to 90% ee through phosphines **5a**–**d**). In this model, the identity of ester component is not critical as it projects away from the point of the introduction of chirality. Thus, the presence of an electron withdrawing nitro group ligand **5b**, the steric volume of the trimethylphenyl group **5c**, and the steric volume of the *tert*-butyl group **5d** did not significantly affect the overall catalysis (Fig. 2).

In contrast, the (*o*-diphenylphosphino)benzoate based complex-**12B** provides a rationale for the lower enantioselectivities that were observed for ligands **9a**–**d**. The mechanistic model that was developed by Burke et al. is invoked again. The conformation that is adopted by the ligand is similar to that in complex-**12A**; however, the positions of the amide and the ester are switched. The stereochemical arrangement of the ligand causes the enantioselection to be reversed compared to complex-**12A**. The compromised enantioselectivity in ligands **9a**–**d** can be attributed to the conformational flexibility of the ester linkage. The ester ligands containing the benzamido group **9a** and the *p*-nitrobenzamido group afforded enantioselectivities of 25.6% ee and 19.3% ee,

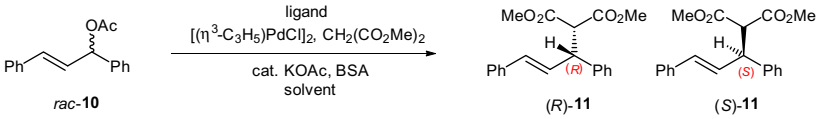
Table 2
Synthesis of the β-amido-(*o*-diphenylphosphino)esters **9a–d**



Entry	Amide	Yield[a] (%)	Phosphine	Yield[a] (%)
1	**8a**	47	**9a**	71
2	**8b**	94	**9b**	62
3	**8c**	83	**9c**	43
4	**8d**	51	**9d**	20

[a] Isolated chemical yield after purification.

Table 3
Asymmetric catalysis with ligands **5a–d** and **9a–d**



Entry	Phosphine	Yield[a] (%)	*R*:*S*	e.e.[b] (%)	Configuration
1	**5a**	64	5.6:94.4	88.8	(*S*)
2	**9a**	69	62.8:37.2	25.6	(*R*)
3	**5b**	79	5.6:94.4	88.8	(*S*)
4	**9b**	91	59.7:40.4	19.3	(*R*)
5	**5c**	83	5.0:95.0	90.0	(*S*)
6	**9c**	67	54.2:45.8	8.4	(*R*)
7	**5d**	40	6.4:93.6	87.2	(*S*)
8	**9d**	58	84.2:15.8	68.4	(*R*)

[a] Isolated chemical yield after purification.
[b] The enantioselectivity of the catalytic reactions was determined by CSP HPLC using a OD-H column, 95:5, hexanes:isopropyl alcohol.

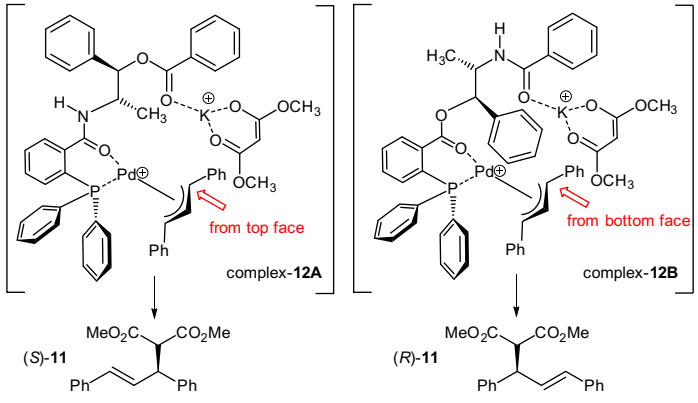


Figure 2. Proposed mechanistic complexation.

respectively. The lower enantioselectivity associated with ligand **9b** versus that of **9a** might be caused by the nitro group causing the carbonyl to be less Lewis basic, resulting in a weaker interaction with the binding phosphine.

The application of the ligand containing the 2,4,6-trimethylbenzamido group **9c** caused the enantioselection to be at its lowest value for this family of ligands with a value of 8.4% ee. This low value is attributed to the steric volume of the benzamido group. This very large volume may distort the complex-**12B** template and may well give rise to alternate conformations that cause the enantioselection to converge to only slightly favor the (*R*)-enantiomer. Finally, the ligand containing the *tert*-butyl ligand **9d** gave the highest level of enantioselectivity. It is proposed that this ligand possesses the optimal balance of an electronic effect and the steric volume of the amido ligand. These features allow for the *o*-diphenylphosphinobenzoate ligand **9d** to have a level of cat-

alytic stereoselectivity comparable to the *o*-diphenylphosphinobenzamide ligand **5d**.

3. Conclusion

In conclusion, we have prepared a series of mono(phosphines) in the class of the *o*-diphenylphosphinobenzamide ligands **5a–d** and the *o*-diphenylphosphinobenzoate ligands **9a–d**. These ligands were employed in the asymmetric allylic alkylation reaction with palladium allyl chloride dimer, *rac*-1,3-diphenyl-1-propenyl acetate, and diethyl malonate. Ligands **5a–d** afforded the highest enantioselectivities due to the rigidity of the diphenylphosphinobenzamide component. Ligands **9a–d** gave lower enantioselectivities due to the conformational flexibility of the ester linkage of the *o*-diphenylphosphinobenzoate component. Ligands **5d** and **9d** gave the most comparable enantioselection.

4. Experimental

4.1. General

Reaction solvents (dichloromethane, tetrahydrofuran) were purchased as an anhydrous reagents and used without further purification. All reactions were run under a nitrogen atmosphere. All ^{1}H and ^{13}C NMR were recorded on a Bruker Avance III 500 MHz NMR spectrometer operating at 500 MHz and 125 MHz, respectively. ^{1}H NMR spectra were referenced to the deuterated chloroform resonance at 7.26 ppm; ^{13}C NMR spectra were referenced to the deuterated chloroform resonance signal centered at 77.00 ppm. All $^{31}P\{^{1}H\}$ NMR spectroscopic data were collected on a Bruker Avance III 400 MHz instrument operating at 400.13 MHz. ^{31}P NMR spectra were externally referenced to 85% H_3PO_4 (0.00 ppm). All spectra were collected at room temperature. Chemical shifts are reported in parts per million (δ scale), and coupling constants (J values) are listed in Hertz (Hz). Infrared spectra are reported in reciprocal centimeters (cm^{-1}) and are measured either as a Nujol mull, a neat liquid, or in $CHCl_3$. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Optical activities were measured using at 589 nm using a digital polarimeter.

4.2. General procedures

4.2.1. Representative reaction for acyl chloride acylation

To a flame-dried, 100 mL round bottom flask under nitrogen were added (1*R*,2*S*)-norephedrine (0.600 g, 3.97 mmol) and 4-(dimethylamino)pyridine (0.121 g, 0.993 mmol). Methylene chloride (12 mL) was added and the mixture was allowed to stir until fully dissolved. Triethylamine (0.76 mL, 6.0 mmol) was then added followed by 2,4,6-trimethylbenzoyl chloride (0.72 mL, 4.4 mmol). The reaction was allowed to stir at room temperature overnight. Methylene chloride (50 mL) was added and the solution was transferred to a separatory funnel and washed with 1 M HCl (50 mL), NH_4Cl (50 mL) and with brine (50 mL). The organic extract was dried over anhydrous $MgSO_4$ and the solvent was removed via rotary evaporation.

4.2.2. Representative reaction for amino acid coupling

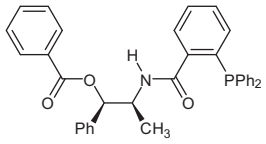
To a flame dried, 100 mL round bottom flask under nitrogen were added (1*R*,2*S*)-norephedrine (0.750 g, 4.96 mmol) and 4-(dimethylamino)pyridine (0.120 g, 0.990 mmol). The mixture was dissolved in methylene chloride (15 mL). To this solution, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1.07 g, 5.20 mmol) and 2-(diphenylphosphino)benzoic acid (1.59 g, 5.20 mmol) were added and the solution was allowed to stir at room temperature overnight. Methylene chloride (50 mL) was added and the solution was transferred to a separatory funnel and washed with 1 M HCl (50 mL), NH_4Cl (50 mL) and with brine (50 mL). The organic extract was dried over anhydrous $MgSO_4$ and the solvent was removed via rotary evaporation.

4.2.3. Representative reaction for the palladium catalyzed Tsuji-Trost asymmetric allylic alkylation using prepared ligands

To a flame dried 100 mL round bottom flask under nitrogen were added **5b** (0.059 g, 0.11 mmol) and $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (0.019 g, 0.054 mmol) and dissolved in THF (4 mL). This solution was allowed to stir for 20 min. Following the induction period, potassium acetate (0.015 g, 0.16 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (2.00 ml, 8.10 mmol) and 1,3-diphenylpropenylacetate (0.733 g, 2.73 mmol) were added. Dimethyl malonate (0.93 mL, 8.1 mmol) was added last and the reaction was allowed to stir at room temperature for 18 hours. The reaction was extracted with diethyl ether (50 mL) and washed with 1 M HCl (50 mL), NH_4Cl (50 mL), and brine (50 mL). The organic extract was collected and dried over $MgSO_4$ and the solvent was removed via rotary evaporation.

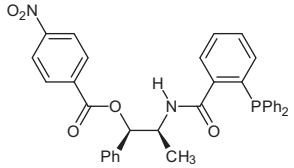
4.3. Ligand syntheses

4.3.1. (1*R*,2*S*)-2-(2-(Diphenylphosphinyl)benzamido)-1-phenylpropyl benzoate 5a



The product was purified by flash column chromatography (80:20, hexanes:EtOAc) to yield 0.382 g (88%) of product as a white solid. $[\alpha]_D^{23} = +31.0$ (*c* 1.11, $CHCl_3$). Mp = 178–179 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.05 (d, J = 7.0 Hz, 3H), 4.59–4.66 (m, 1H), 6.09 (d, J = 3.9 Hz, 1H), 6.19 (d, J = 8.2, 1H), 6.89–6.93 (m, 1H), 7.17–7.37 (m, 18H), 7.45–7.49 (m, 2H), 7.51–7.54 (m, 1H), 7.57–7.61 (m, 1H), 8.10 (dd, J = 8.2, 1.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.70, 49.64, 78.13, 126.26, 127.96, 128.01, 128.06, 128.51, 128.56, 128.62, 128.65, 128.72, 128.83, 128.88, 128.93, 129.87, 130.07, 130.19, 133.29, 133.74, 133.86, 133.93, 134.06, 134.08, 135.51, 135.72, 136.68, 136.79, 136.99, 137.10, 137.42, 141.32, 141.57, 165.58, 168.28. ^{31}P NMR (162 MHz, $CDCl_3$): δ −10.10. IR (Nujol): 1714, 1647, 1274, 745, 711, 702 cm^{-1}. ESI HRMS for $C_{35}H_{30}NO_3P$: calcd (M+H) 544.2042; found 544.2036.

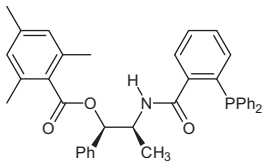
4.3.2. (1*R*,2*S*)-2-(2-(Diphenylphosphinyl)benzamido)-1-phenylpropyl 4-nitrobenzoate 5b



Purified by recrystallization in CH_3Cl/hexanes to yield 0.116 g (56%) of product as a white solid. $[\alpha]_D^{23} = -25.4$ (*c* 0.290, $CHCl_3$).

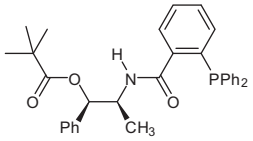
Mp = 177–180 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 (d, J = 6.9 Hz, 3H), 4.54–4.60 (m, 1H), 6.21(d, J = 2.8 Hz, 1H), 6.98–7.00 (m, 1H), 7.12–7.15 (m, 4H), 7.24–7.30 (m, 11H), 7.34–7.43 (m, 3H), 7.90 (d, J = 8.8 Hz, 2H), 7.97–8.00 (m, 1H), 8.11 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.35, 49.01, 79.17, 123.62, 126.53, 127.85, 127.90, 128.43, 128.57, 128.59, 128.63, 128.65, 128.73, 128.87, 128.97, 130.35, 130.99, 133.56, 133.71, 133.76, 133.90, 134.32, 135.38, 135.49, 135.58, 136.24, 136.54, 136.64, 136.71, 136.82, 141.27, 141.53, 150.60, 163.78, 168.40. ^{31}P NMR (162 MHz, $CDCl_3$): δ −10.32. IR ν (cm^{-1}, Nujol mull): 1721, 1644, 1529, 1351, 1276, 862, 745, 720, 700 cm^{-1}. ESI HRMS for $C_{35}H_{29}N_2O_5P$: calcd (M+H$^+$) 589.1892; found 589.1884.

4.3.3. (1*R*,2*S*)-2-(2-(Diphenylphosphinyl)benzamido)-1-phenylpropyl 2,4,6-trimethyl benzoate 5c



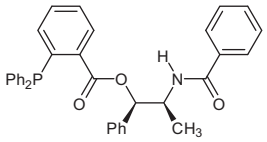
The product was purified by flash column chromatography (80/20, hexanes/EtOAc) followed by recrystallization (EtOAc/hexanes) to yield 0.229 g (49%) of product as a white solid. $[\alpha]_D^{23}$ = +4.4 (c 0.602, $CHCl_3$). Mp = 169–170 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.99 (d, J = 6.7 Hz, 3H), 2.11 (s, 6H), 2.20 (s, 3H), 4.44–4.51 (m, 1H), 6.02 (d, J = 8.2 Hz, 1H), 6.77 (s, 1H), 6.83–6.87 (m, 1H), 7.13–7.30 (m, 19H), 7.38–7.42 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.17, 20.12, 21.18, 49.54, 78.37, 126.93, 127.72, 127.77, 128.21, 128.46, 128.53, 128.55, 128.62, 128.69, 128.76, 128.80, 128.82, 128.98, 130.18, 130.76, 133.77, 133.89, 133.97, 134.05, 134.09, 135.23, 135.68, 135.89, 136.77, 136.89, 137.13, 137.20, 137.24, 139.49, 141.22, 141.48, 168.26, 169.44. ^{31}P NMR (162 MHz, $CDCl_3$): δ −9.86. IR ν (cm^{-1}, Nujol mull): 1715, 1645, 1269, 850, 754, 745, 700. ESI HRMS for $C_{38}H_{36}NO_3P$: calcd (M+H) 586.2511, found 586.2485.

4.3.4. (1*R*,2*S*)-2-(2-(Diphenylphosphinyl)benzamido)-1-phenylpropyl pivalate 5d



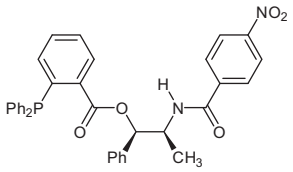
With 0.600 gram of starting material, the product was purified by flash column chromatography (100% hexanes followed by 95/5, hexanes/EtOAc) to yield 0.450 g (61%) of product as a white solid. MP = 195–197 °C. $[\alpha]_D^{23}$ = −12.5 (c 1.03, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (d, J = 7.0 Hz, 3H), 1.12 (s, 9 H), 4.47–4.53 (m, 1H), 5.83 (d, J = 4.1 Hz, 1H), 6.40 (s, 1H), 6.97–7.00 (m, 1H), 7.27–7.38 (m, 14H), 7.43 (td, J = 7.5, 1.2 Hz, 1H), 7.63–7.66 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.98, 26.98, 38.66, 58.14, 78.20, 128.17, 128.24, 128.34, 128.38, 128.41, 128.47, 128.56, 129.93, 129.97, 131.29, 133.15, 133.34, 133.67, 133.85, 135.64, 135.66, 137.45, 137.54, 138.31, 138.41, 140.96, 141.19, 171.04, 176.80. ^{13}P NMR (162 MHz, $CDCl_3$) δ = −9.74. IR ν (cm^{-1}, Nujol mull): 1735, 1648, 1376, 1365, 1148, 751, 720, 702. ESI HRMS for $C_{33}H_{34}NO_3P$: calcd (M+Na) 524.2355, found 524.2355.

4.3.5. (1*R*,2*S*)-2-Benzamido-1-phenylpropyl 2-(diphenylphosphinyl)benzoate 9a



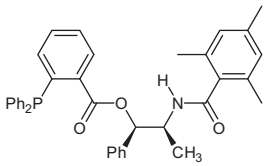
Purified by recrystallization in CH_2Cl_2/hexanes to yield 0.702 g (71%) of product as a white solid. $[\alpha]_D^{23}$ = −5.9 (c 1.04, $CHCl_3$). Mp = 77–81 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (d, J = 7.0 Hz, 3H), 4.64–4.71 (m, 1H), 6.22 (d, J = 2.9 Hz, 1H), 7.03–7.05 (m, 1H), 7.07 (dd, J = 8.8, 2.5 Hz, 1H), 7.20–7.49 (m, 20H), 7.83 (d, J = 8.3 Hz, 2H), 8.08 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.45, 49.63, 79.55, 126.20, 127.28, 127.30, 127.99, 128.48, 128.50, 128.59, 128.66, 128.74, 128.93, 129.00, 130.92, 130.96, 131.38, 132.26, 133.34, 133.53, 133.97, 134.17, 134.63, 134.96, 135.44, 135.67, 137.02, 137.11, 137.15, 137.25, 137.39, 138.57, 138.80, 166.77, 167.03. ^{31}P NMR (162 MHz, $CDCl_3$): δ −5.64. IR ν (cm^{-1}, Nujol mull): 1722, 1627, 1247, 753, 695. ESI HRMS for $C_{35}H_{30}NO_3P$: calcd (M+H) 544.2042; found 544.2042.

4.3.6. (1*R*,2*S*)-2-(4-Nitrobenzamido)-1-phenylpropyl 2-(diphenylphosphinyl)benzoate 9b



Purified by flash column chromatography (50/50, hexanes/EtOAc) to yield 0.300 g (43%) of product as a yellow oil. $[\alpha]_D^{23}$ = −18.9 (c, 1.04 $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (d, J = 7.0 Hz, 3H), 4.61–4.68 (m, 1H), 6.29 (d, J = 2.8 Hz, 1H), 7.06–7.09 (m, 1H), 7.19–7.23 (m, 4H), 7.30–7.38 (m, 11H), 7.43–7.50 (m, 3 H), 7.99 (d, J = 8.8 Hz, 2 H), 8.05–8.08 (m, 1H), 8.18 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.95, 50.41, 79.33, 123.66, 126.10, 128.13, 128.49, 128.52, 128.59, 128.68, 128.75, 128.89, 129.08, 129.17, 130.78, 130.82, 132.42, 133.28, 133.46, 133.76, 133.96, 134.10, 135.11, 135.43, 135.66, 136.75, 136.81, 136.90, 137.15, 138.26, 138.48, 140.25, 149.43, 164.88, 167.33. ^{31}P NMR (162 MHz, $CDCl_3$): δ −5.39. IR ν (cm^{-1}, neat): 3068, 2982, 1717, 1660, 1524, 1346, 1250, 729, 698. ESI HRMS for $C_{35}H_{29}N_2O_5P$: calcd (M+H) 589.1892, found 589.1901.

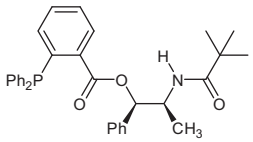
4.3.7. (1*R*,2*S*)-1-Phenyl-2-(2,4,6-trimethylbenzamido)propyl 2-(diphenylphosphinyl)benzoate 9c



Purified by flash column chromatography (80/20, hexanes/EtOAc) to yield 0.481 g (61%) of product as a yellow oil. $[\alpha]_D^{23}$ = +11.7 (c 0.977, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (d,

J = 7.2 Hz, 3H), 2.10 (s, 6H), 2.17 (s, 3H), 4.61–4.68 (m, 1H), 6.05 (m 1H), 6.11 (d, J = 4.0 Hz, 1H), 6.19 (d, J = 4.0 Hz, 1H), 6.20 (m, 1H), 6.71 (s, 2H), 6.90–6.94 (m, 1H), 6.98–7.06 (m, 4H), 7.11–7.27 (m, 8 H), 7.30–7.38 (m, 3H), 7.97–8.00 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.08, 19.01, 21.07, 48.44, 79.16, 125.85, 126.39, 127.97, 128.09, 128.38, 128.45, 128.47, 128.50, 128.57, 128.61, 128.77, 128.85, 130.77, 130.81, 132.09, 133.36, 133.56, 133.85, 134.06, 134.12, 134.70, 135.01, 135.41, 135.64, 136.93, 137.04, 137.41, 138.15, 138.47, 138.71, 165.50, 169.92. ^{31}P NMR (162 MHz, $CDCl_3$): δ −5.67. IR ν (cm^{-1}, neat): 3056, 2978, 1719, 1636, 1378, 1249, 849, 744, 696. ESI HRMS for $C_{38}H_{36}NO_3P$: calcd (M+H) 586.2511, found 586.2502.

4.3.8. (1*R*,2*S*)-1-Phenyl-2-(pivalamido)propyl 2-(diphenylphosphinyl)benzoate 9d



Purified by flash column chromatography (80/20, hexanes/EtOAc) to yield 0.256 g (20%) of product as a yellow oil. $[\alpha]_D^{23}$ = −12.7 (c 0.694, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 (d, J = 6.9 Hz, 3H), 1.04 (s, 9H), 4.35–4.41 (m, 1H), 6.00 (s, 1H), 6.02 (d, J = 3.7 Hz, 1H), 6.90–6.93 (m,1H), 7.14–7.26 (m, 16H), 7.31–7.39 (m, 3H), 8.04–8.07 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.75, 27.58, 38.67, 49.00, 79.18, 126.62, 127.92, 128.38, 128.57, 128.63, 128.68, 128.73, 128.87, 130.90, 130.94, 132.31, 133.47, 133.66, 133.81, 133.96, 134.17, 134.79, 134.89, 135.00, 137.48, 137.58, 137.69, 139.58, 139.84, 166.33, 177.80. ^{31}P NMR (162 MHz, $CDCl_3$): δ −5.24. IR ν (Nujol): 1717, 1652, 1398, 1378, 1251, 746, 697 cm^{-1}. ESI HRMS for $C_{33}H_{34}NO_3P$: calcd ($M+H^+$) 524.2355; found 524.2353.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2016.08.012.

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