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Chiral, non-racemic diols, and α-amino acid-derived β-amino alcohols as templates for chiral catalysts in the Tsuji–Trost reaction

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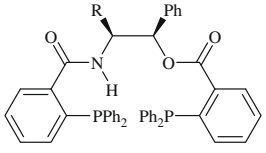
ABSTRACT

A commercially available collection of β-amino alcohols have been converted to their corresponding β-(*o*-diphenylphosphino) benzoyloxy(*o*-diphenylphosphino) benzamides and have been employed in the Tsuji–Trost asymmetric alkylation reaction with 1,3-diphenylpropenyl acetate. The best ligand was derived from L-*tert*-leucinol and when applied to the asymmetric allylic alkylation reaction, yielded the product in an enantiomeric ratio of 99.5:0.5 favoring the (*S*)-enantiomer.

1. Introduction

The development of palladium-catalyzed asymmetric reactions in organic synthesis has experienced much growth over the last two decades.[1] In this context, palladium-catalyzed asymmetric allylic alkylation reactions have proven to be very successful.[2] The pioneering efforts of Tsuji[3] and the refinements led by Trost[4] have given rise to a powerful method for the enantioselective process of carbon–carbon bond formation. Many researchers[2,5] have contributed to this field and there is a continuing effort to create effective chiral, non-racemic ligands for the palladium-catalyzed alkylation reaction. In connection with our ongoing research program concerning the synthesis and application of chiral ligands for asymmetric reactions, we have recently become interested in the development of effective chiral ligands for the alkylation process. Our initial efforts in this field involved a series of norephedrine and pseudonorephedrine-based mono(phosphines) and bis(phosphines) (Fig. 1).[6]



1a: R = -CH_3 (norephedrine)[6]
1b: R = -Ph (1-amino-1,2-diphenylethanol)[7]

Figure 1. *o*-(Diphenylphosphino)benzoyloxy *o*-(diphenylphosphino) benzamides.

This work was followed by a broader study concerning a variety of β-amino alcohols, both cyclic and acyclic, that were used to create phosphine ligands for the asymmetric alkylation reaction.[7] The success of this work prompted us to study further this catalytic process with a different family of ligands. Herein we report the use of chiral, non-racemic diols, and α-amino acid-derived β-amino alcohols as templates for the chiral phosphine ligands, and we report on the results of these efforts.

2. Results and discussion

A series of chiral diols **2a**–**d** were coupled with either one or 2 equiv of *o*-(diphenylphosphino)benzoic acid and the requisite amount of EDC and catalytic DMAP to afford β-hydroxy and β-(*o*-diphenylphosphino) benzyloxy (*o*-diphenylphosphino) benzoates **3**–**8** in yields ranging from 43% to 98% (Scheme 1). With these compounds in hand, the asymmetric allylic alkylation reaction was pursued with a catalytic amount of allylpalladium chloride dimer, 1,3-diphenylpropenyl acetate and dimethyl malonate. Potassium acetate and *N*,*O*-bis(trimethylsilyl) acetamide (BSA) were also employed to facilitate the deprotonation of dimethyl malonate. The collected results of this work are shown in Table 1.

The bisphosphine ligands **4** and **6** were used in the catalytic asymmetric alkylation reaction with the palladium pre-catalyst $\{[(\eta\text{-}C_3H_5)_2PdCl]_2\}$, THF, and the associated reagents to form the target homoallylic malonate **10a** in 77%ee. This was expected as Trost et al.[4] had previously prepared **4** and demonstrated its success in the allylic alkylation process. In contrast, the monophosphines β-hydroxy benzoates **3**, **5**, **7,** and **8** did not serve as suitable ligands for the palladium pre-catalyst system under the reaction conditions and no observable product was detected. This was surprising as the related β-hydroxybenzamides prepared by our group were reactive. The rationale for this lack of reactivity is unclear at this time although the absence of the amido group was speculated to contribute to the deactivation of the palladium catalyst.

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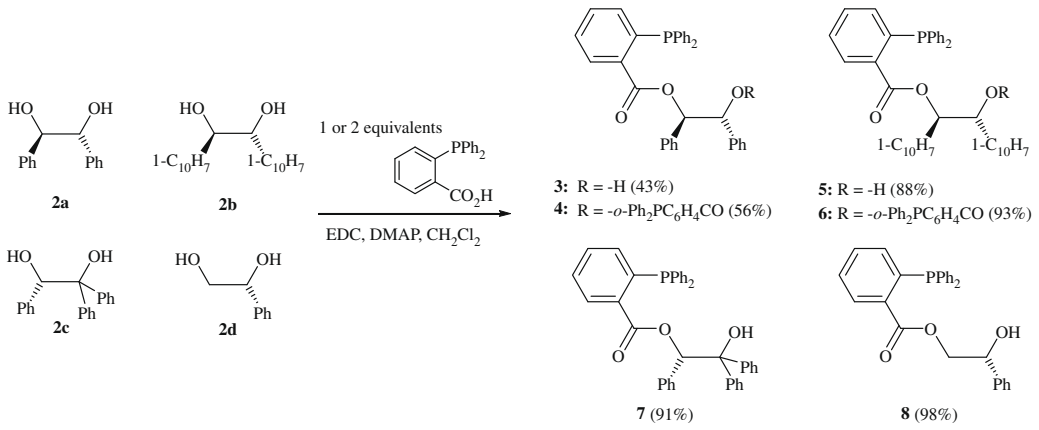
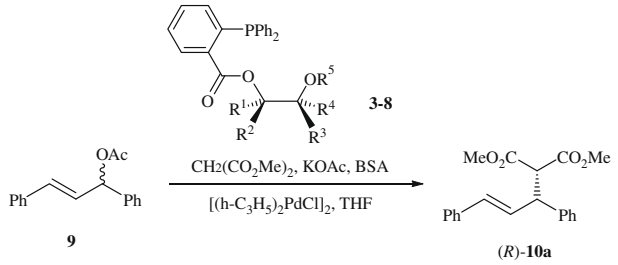


Scheme 1. Synthesis of mono- and bisphosphines **3**–**8**.

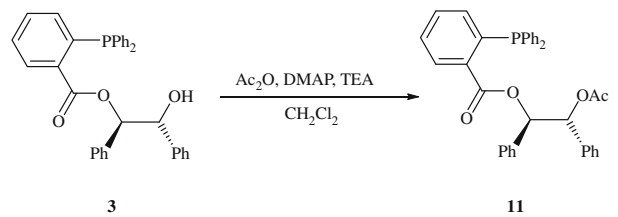
Table 1
Palladium-catalyzed asymmetric alkylation



Entry	Ligand	Time (h)	**9**:ligand:Pd	Yield[a] (%)	er, *R*:*S* (ee)[b,c]
1	**3**	24	25:1:2	nd[d]	nd
2	**3**	48	25:1:2	nd	nd
3	**4**	6	25:1:1	86	88.3:11.7 (77)
5	**5**	24	25:1:2	nd	nd
6	**6**	24	25:1:1	nd	nd
7	**6**	48	25:1:1	80	88.7:11.3 (77)
8	**7**	24	25:1:2	nd	nd
9	**8**	24	25:1:2	nd	nd

[a] Isolated yield after flash chromatography.
[b] Enantiomeric ratios determined by CSP HPLC (Chiralcel AD column).
[c] The identity of the enantiomer was based on elution from the CSP HPLC column.
[d] Not determined.

The failure of the β-hydroxybenzoates to serve as catalysts for the asymmetric alkylation reaction prompted an investigation. The β-hydroxy component was considered to be a potential agent for deactivation of the catalyst. Thus, monophosphine **3** was acylated with acetic anhydride to generate β-acetoxybenzoate **11** (Scheme 2). Using the reaction conditions illustrated in Table 1, it was determined that **11** also did not afford the desired product, suggesting that another factor, other than the presence of a free alcohol was contributing to the failure of the reaction. There is the possibility that ligands **3**, **5**, **7**, **8**, and **11** are coordinating with



Scheme 2. Acetylation of β-hydroxyester **3**.

the palladium pre-catalyst in such a way as to yield catalytically inactive species.[8]

The collected results from the use of diols **2a**–**d** as chiral templates served as the inspiration for pursuing an alternate template family. The previously used β-amino alcohol template from our earlier work[7] proved to be quite successful when converted into bisphosphines. Over the course of this earlier work, it was noted that the two most successful ligands, **12** and **13**, afforded the same absolute stereochemistry of the product of catalysis, even though the two ligands possessed different structural features (Fig. 2).

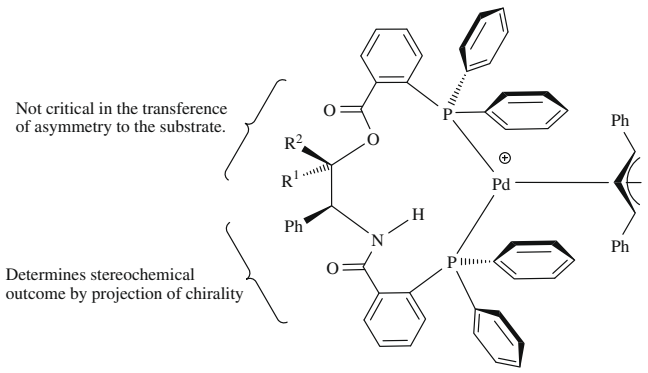
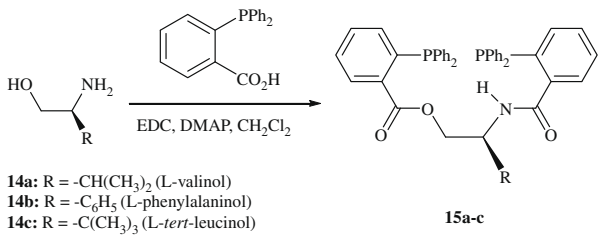


Figure 2. Proposed asymmetric induction.

When the template possessed an *anti*-configuration along the backbone (**12**: R^1 = Ph; R^2 = –H), the observed level of enantioselection in the asymmetric alkylation reaction with dimethyl malonate was 91%ee. When the *syn*-configuration of the β-amino alcohol backbone (**13**: R^1 = H; R^2 = –Ph) was employed, the observed enantiomeric excess was ~96%ee. The collected results suggest that the stereochemical substitution at the carbon bearing the benzoyloxy group does not significantly contribute to the observed asymmetric induction. Indeed, the Lloyd–Jones–Norrby model[9] would suggest that it is the amido group that represents the pocket of reactivity where the transfer of asymmetry is effected. Following this hypothesis, we pursued the synthesis of a series of α-amino acid-derived β-amino alcohol catalysts. These systems would not have substitution at the position bearing the ester group and would serve as investigative tools to test the nature of the transfer of chirality.

To this end, we employed L-*tert*-leucinol, L-phenylglycinol, and L-valinol as templates. These compounds were acylated with

2 equiv of (*o*-diphenylphosphino)benzoic acid with EDC and DMAP to afford the β-(*o*-diphenylphosphino)benzoyl (*o*-diphenylphosphino) benzamides **15a–c** (Scheme 3). With these ligands in hand, the catalytic asymmetric alkylation of 1,3-diphenylpropenyl acetate was again pursued (Table 2). We were able to see that all the ligands performed well under the reaction conditions. The amount of ligand, the palladium precursor, the reaction solvent, and the time duration of reaction were varied for the sake of optimizing the stereochemical outcome.



Scheme 3. Synthesis of β-benzoyloxybenzamides **15a–c**.

The L-valinol-based ligand **15a** performed well, with enantiomeric excesses for the product of catalysis ranging from 84% to 92%ee. The L-phenylglycinol ligand **15b** gave comparable results with enantiomeric excesses ranging from 88 to 98%ee. The best results were obtained when the L-*tert*-leucinol ligand **15c** was employed. The observed enantioselectivity ranged from 94% to 99%ee. The use of sodium acetate as a catalytic base afforded a slightly lower enantiomeric excess as compared to the use of potassium acetate. Ultimately, ligands **15a–c** all proved to be superior catalysts as compared to the chiral diol ligands **3–8**.

The collected results from Table 2 suggest that the carbon bearing the (*o*-diphenylphosphino)benzoyloxy component need not possess any chirality in order for high enantiomeric excesses to be observed. As the Lloyd–Jones–Norrby model would suggest, the region near the amide is of central importance in the transference of asymmetry. Indeed, ligand system **14c** derived from *tert*-L-leucinol provided the highest enantioselectivities, presumably due to the steric volume of the *tert*-butyl group. Mechanistically, this suggests that the amide component is directly responsible for the observed enantioselection and that the ester component is, in effect, a 'coordination space holder' that allows the palladium to maintain an ordered cavity into which the nucleophile might enter and undergo the alkylation process (Fig. 3).

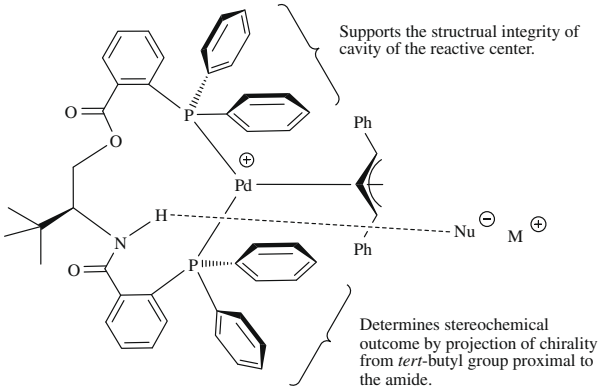
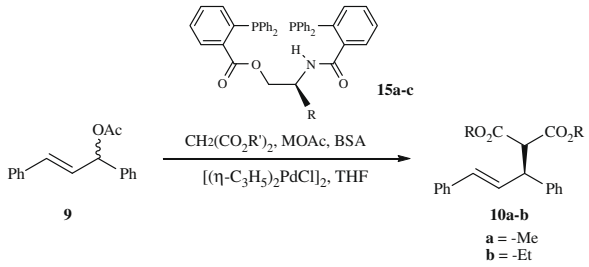


Figure 3. Proposed stereochemical induction.

3. Conclusion

We have developed a series of C_2-symmetric ligands and β-amido-esters derived from L-*tert*-leucinol, L-phenylglycinol, and L-valinol. Mono alcohols derived from C_2-symmetric ligands did not react well. The application of the β-amido-ester derived from L-*tert*-leucinol gave the best enantiomeric excess of 99%ee. Further efforts are currently underway to explore the use of these ligands in other palladium-catalyzed alkylation reactions.

Table 2
Asymmetric allylic alkylation with β-benzoyloxybenzamides **14a–c**



Entry	Ligand	MOAc M =	$CH_2(CO_2R')_2R'$ =	Time (h)	**9**:ligand:Pd	Yield[a] (%)	er, *R*:*S* (ee)[b]	Config.[c]
1	**14a**	K^+	Me-	24	25:1:1	78	7.5:92.5 (85)	(*S*)
2	**14a**	K^+	Me-	6	25:1:1	74	4.0:96.0 (92)	(*S*)
3	**14a**	Na	Me-	24	25:1:1	97	8.0:92.0 (84)	(*S*)
4	**14a**	K^+	Et-	24	25:1:1	76	4.4:95.6 (91)	(*S*)
5	**14b**	K^+	Me-	24	25:1:1	74	3.7:96.3 (93)	(*S*)
6	**14b**	K^+	Me-	6	25:1:1	82	1.0:99.0 (98)	(*S*)
7	**14b**	Na^+	Me-	24	25:1:1	75	4.4:95.6 (91)	(*S*)
8	**14b**	K^+	Et-	24	25:1:1	71	5.8:94.2 (88)	(*S*)
9	**14c**	K^+	Me-	24	25:1:1	87	1.5:98.5 (97)	(*S*)
10	**14c**	K^+	Me-	6	25:1:1	87	0.5:99.5 (99)	(*S*)
11	**14c**	Na^+	Me-	24	25:1:1	65	2.8:97.2 (94)	(*S*)
12	**14c**	K^+	Et-	24	25:1:1	72	1.3:98.7 (97)	(*S*)

[a] Isolated yield after flash chromatography.
[b] Enantiomeric ratios determined by CSP HPLC (Chiralcel AD column).
[c] The identity of the enantiomer was based on elution from the CSP HPLC column.

4. Experimental section

4.1. General remarks

Methylene chloride (CH_2Cl_2), tetrahydrofuran (THF), and toluene were purchased as anhydrous reagents. The allylpalladium chloride dimer {[(η^3-C_3H_5)PdCl]$_2$}, dimethyl malonate, potassium acetate, and *N*,*O*-bis(trimethylsilyl)acetamide (BSA) were purchased and used without further purification or handling.

Unless otherwise stated, all reactions were run under anhydrous conditions and a nitrogen atmosphere. ^{1}H and ^{13}C NMR spectra were recorded using a 500 MHz NMR spectrometer operating at 500 MHz for the recording of ^{1}H NMR spectra and operating at 125 MHz for the recording of ^{13}C NMR spectra. Samples were dissolved in $CDCl_3$ with trimethylsilane (TMS) as the internal standard. Chemical shifts are reported in parts per million (δ scale), and coupling constants (*J* values) are listed in hertz (Hz). ^{1}H NMR spectra were referenced to the deuterated chloroform resonance at 7.26 ppm.

Infrared spectra are reported in reciprocal centimeters (cm^{-1}) and are measured either as a neat liquid or Nujol. Melting points are uncorrected. Flash chromatography was conducted with an automated single pump, fraction-collector chromatograph. Mass spectral analyses were conducted using a quadrupole time of flight mass spectrometer hybrid with MS/MS capability. Enantiomeric ratios were determined using a HPLC with a chiral stationary phase column. Optical activities were measured using at 589 nm using a digital polarimeter purchased with NSF Grant #CHE 644950.

4.2. (1*R*,2*R*)-2-Hydroxy-1,2-diphenyl 2-(diphenylphosphino)benzoate 3

In a 250 mL nitrogen purged round-bottomed flask were added (*R*,*R*)-hydrobenzoin (0.400 g, 1.87 mmol), DMAP (0.046 g, 0.373 mmol), dichloromethane (10 mL), 2-(diphenylphosphino) benzoic acid (0.572 g, 1.87 mmol), and EDC (0.394 g, 2.05 mmol). The reaction mixture was allowed to stir for 24 h and then the reaction was quenched with the addition of 3 M HCl (50 mL × 2). The organic layer was diluted with dichloromethane (100 mL), washed with brine (50 mL), and dried with magnesium sulfate ($MgSO_4$). The solvents were removed via rotary evaporation and the product was isolated by flash column chromatography (hexanes/EtOAc, 6:4). Viscous wax (43%), $[\alpha]_D^{24} = +41.9$ (*c* 0.80, $CHCl_3$). IR (Nujol) (cm^{-1}): 3390, 1715, 1275, 1248, 746, 697. ^{13}C NMR ($CDCl_3$): 76.5, 83.0, 127.1, 127.3, 127.4, 127.6, 127.7, 128.5, 128.55, 128.6, 128.67, 128.70, 128.8, 129.1, 131.9, 132.0, 132.2, 133.1, 133.3, 134.0, 134.2, 134.8, 135.0, 135.2, 136.0, 136.1, 136.2, 136.45, 136.5, 136.6, 136.8, 138.1, 165.9. ESI-HRMS calcd for $C_{33}H_{27}O_3P$ ($M+H^+$): 503.1776. Found: 503.1765.

4.3. (1*R*,2*R*)-1,2-Diphenylethane-1,2-diyl bis(2-(diphenylphosphino)benzoate) 4

In a 250 mL nitrogen purged round-bottomed flask were added (*R*,*R*)-hydrobenzoin (0.300 g, 1.40 mmol), DMAP (0.068 g, 0.560 mmol), dichloromethane (10 mL), 2-(diphenylphosphino)benzoic acid (0.858 g, 2.80 mmol), and EDC (0.537 g, 2.80 mmol). The reaction mixture was allowed to stir for 48 h and then the reaction was quenched with the addition of 3 M HCl (50 mL × 2). The organic layer was diluted with dichloromethane (100 mL), washed with brine (50 mL), and dried with magnesium sulfate ($MgSO_4$). The solvents were removed via rotary evaporation and the product was isolated by flash column chromatography (hexanes/EtOAc, 7:3). Viscous wax (56%), $[\alpha]_D^{23} = +104.4$ (*c* 0.10, $CHCl_3$). IR (Nujol) (cm^{-1}): 1716, 1270, 1248, 744, 696. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.21 (s, 2H), 6.79 (d, *J* = 7.4 Hz, 1H), 6.94–7.30 (m, 36 H), 8.08–8.09 (m, 1H). ^{13}C NMR ($CDCl_3$): 78.1, 127.8, 128.0, 128.2, 128.3, 128.31, 128.4, 128.42, 131.4, 132.0, 133.7, 133.8, 133.9, 134.0, 134.2, 134.4, 134.44, 135.8, 138.06, 138.1, 138.2, 140.5, 140.7, 165.5. ESI-HRMS calcd for $C_{52}H_{40}O_4P_2$ ($M+H^+$): 791.2456. Found: 791.2444.

4.4. (1*R*,2*R*)-2-Hydroxy-1,2-di(naphthalen-1-yl)ethyl 2-(diphenylphosphino)benzoate 5

In a 250 mL nitrogen purged round-bottomed flask was added (*R*,*R*)-1,2-di(1-naphthyl)-1,2-ethanediol (0.087 g, 0.277 mmol), DMAP (0.007 g, 0.055 mmol), dichloromethane (5 mL), 2-(diphenylphosphino)benzoic acid (0.083 g, 0.277 mmol), and EDC (0.058 g, 0.304 mmol). The reaction mixture was allowed to stir for 24 h and then the reaction was quenched with the addition of 3 M HCl (50 mL × 2). The organic layer was diluted with dichloromethane (100 mL), washed with brine (50 mL), and dried with magnesium sulfate ($MgSO_4$). The solvents were removed via rotary evaporation and the product was isolated by flash column chromatography (hexanes/EtOAc, 7:3). Viscous wax (88%), $[\alpha]_D^{24} = +121.5$ (*c* 0.55, $CHCl_3$). IR (Nujol) (cm^{-1}): 3310, 1714, 1289, 1169, 776, 694. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.30 (dd, *J* = 3.2, 13.1 Hz, 1H), 5.71 (d, *J* = 10.6 Hz, 1H), 6.47 (d, *J* = 8.9 Hz, 1H), 6.89–7.61 (m, 27H), 8.05–8.09 (m, 1H). ^{13}C NMR ($CDCl_3$): 74.9, 122.7, 123.6, 124.5, 124.7, 124.9, 124.94, 125.3, 125.5, 125.8, 128.0, 128.2, 128.4, 128.5, 128.7, 128.8, 129.0, 129.1, 129.15, 129.2, 129.4, 130.7, 131.1, 132.3, 132.8, 133.0, 133.5, 133.6, 133.8, 134.0, 134.3, 134.5, 135.3, 135.7, 135.9, 136.3, 136.5, 136.6, 166.7. ESI-HRMS calcd for $C_{41}H_{31}O_3P$ ($M+H^+$): 603.2089. Found: 603.208.

4.5. (1*R*,2*R*)-1,2-Di(naphthalen-1-yl)ethane-1,2-diyl bis(2-(diphenylphosphino)benzoate) 6

In a 250 mL nitrogen purged round-bottomed flask were added (*R*,*R*)-(+)-1,2-di(1-naphthyl)-1,2-ethanediol (0.250 g, 0.795 mmol), DMAP (0.097 g, 0.795 mmol), dichloromethane (10 mL), 2-(diphenylphosphino)benzoic acid (0.487 g, 1.59 mmol), and EDC (0.305 g, 1.59 mmol). The reaction mixture was allowed to stir for 48 h and then the reaction was quenched with the addition of 3 M HCl (50 mL × 2). The organic layer was diluted with dichloromethane (100 mL), washed with brine (50 mL), and dried with magnesium sulfate ($MgSO_4$). The solvents were removed via rotary evaporation and the product was isolated by flash column chromatography (hexanes/EtOAc, 7:3). Viscous wax (93%), $[\alpha]_D^{23} = +276.0$ (*c* 0.21, $CHCl_3$). IR (Nujol) (cm^{-1}): 1711, 1268, 1249, 741, 694. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.85 (m, 2H), 6.97–7.61 (m, 40H), 8.20–8.23 (m, 2H). ^{13}C NMR ($CDCl_3$): 124.6, 125.1, 125.7, 128.1, 128.2, 128.3, 128.4, 128.41, 128.9, 130.8, 131.4, 131.9, 133.2, 133.7, 133.74, 133.8, 133.9, 133.91, 134.0, 134.3, 134.4, 134.5, 137.9, 138.0, 138.1, 138.2, 140.4, 140.6, 165.9. ESI-HRMS calcd for $C_{60}H_{44}O_4P_2$ ($M+H^+$): 891.2793. Found: 891.2762.

4.6. (*S*)-2-Hydroxy-1,2,2-triphenylethyl 2-(diphenylphosphino)-benzoate 7

In a 250 mL nitrogen purged round-bottomed flask were added (*S*)-1,1,2-triphenyl-1,2-ethanediol (0.250 g, 0.861 mmol), DMAP (0.021 g, 0.172 mmol), dichloromethane (5 mL), 2-(diphenylphosphino)benzoic acid (0.264 g, 0.861 mmol), and EDC (0.248 g, 1.29 mmol). The reaction mixture was allowed to stir for 24 h and then the reaction was quenched with the addition of 3 M HCl (50 mL × 2). The organic layer was diluted with dichloromethane (100 mL), washed with brine (50 mL), and dried with magnesium sulfate ($MgSO_4$). The solvents were removed via rotary evaporation and the product was isolated by flash column chromatography (hexanes/EtOAc, 7:3). Viscous wax (91%), $[\alpha]_D^{23} = -131.7$ (*c* 0.44, $CHCl_3$). IR (Nujol) (cm^{-1}): 3550, 1697, 1251, 891, 746. ^{1}H

NMR (500 MHz, $CDCl_3$) δ (ppm): 3.52 (d, J = 3.2 Hz, 1H), 6.87–7.36 (m, 28H), 7.55–7.57 (m, 1H), 7.98–8.01 (m, 1H). ^{13}C NMR ($CDCl_3$): 80.1, 80.4, 126.2, 126.4, 126.7, 127.0, 127.1, 127.6, 128.2, 128.4, 128.5, 128.51, 128.6, 128.63, 128.7, 128.8, 130.0, 131.4, 131.41, 132.2, 133.5, 133.6, 133.7, 133.9, 134.2, 134.3, 134.8, 135.6, 137.0, 137.1, 137.3, 137,4, 139.0, 139.2, 142.7, 145.1, 165.6. ESI-HRMS calcd for $C_{39}H_{31}O_3P$ ($M+H^+$): 579.2089. Found: 579.2099.

4.7. (*R*)-2-Hydroxy-2-phenylethyl 2-(diphenylphosphino)-benzoate 8

In a 250 mL nitrogen purged round-bottomed flask were added (*R*)-1-phenyl-1,2-ethanediol (0.250 g, 1.81 mmol), DMAP (0.221 g, 1.81 mmol), dichloromethane (10 mL), 2-(diphenylphosphino)benzoic acid (1.11 g, 3.62 mmol), and EDC (0.694 g, 3.62 mmol). The reaction mixture was allowed to stir for 24 h and then the reaction was quenched with the addition of 3 M HCl (50 mL × 2). The organic layer was diluted with dichloromethane (100 mL), washed with brine (50 mL), and dried with magnesium sulfate ($MgSO_4$). The solvents were removed via rotary evaporation and the product was isolated by flash column chromatography (hexanes/EtOAc, 7:3). Viscous wax (98%), $[\alpha]_D^{23} = +2.22$ (c 1.68, $CHCl_3$). IR (neat) (cm^{-1}): 3056, 1715, 1217, 745, 668. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.31 (dd, J = 3.6, 12.0 Hz, 1H), 4.46 (dd, J = 8.6, 12.0 Hz, 1H), 6.26 (dd, J = 3.6, 8.6 Hz, 1H), 6.91–6.93 (m, 1H), 7.14–7.36 (m, 17H), 8.07–8.14 (m, 1H). ^{13}C NMR ($CDCl_3$): 66.6, 74.1, 126.7, 128.1, 128.2, 128.22, 128.24, 128.26, 128.3, 128.33, 128.35, 128.4, 128.44, 130.9, 131.0, 131.9, 131.94, 133.4, 133.5, 133.6, 133.62, 133.7, 133.73, 133.8, 133.82, 133.9, 134.1, 134.3, 134.4, 136.0, 137.7, 137.74, 137.8, 137.83, 137.9, 139.9, 140.2, 140.8, 141.0, 165.7, 165.8. ESI-HRMS calcd for $C_{27}H_{23}O_3P$ ($M+H^+$): 425.1307. Found: 425.1310.

4.8. (1*R*,2*R*)-2-Acetoxy-1,2-diphenylethyl 2-(diphenylphosphino) benzoate 11

In a 250 mL nitrogen purged round-bottomed flask were added (1*R*,2*R*)-2-hydroxy-1,2-diphenyl 2-(diphenylphosphino)benzoate (0.266 g, 0.530 mmol), acetic anhydride (0.1 mL, 0.636 mmol), dichloromethane (15 mL), DMAP (0.013 g, 0.106 mmol), and triethyl amine (0.1 mL, 0.795 mmol). The reaction mixture was allowed to stir for 24 h and then the reaction was quenched with the addition of 1 M HCl (50 mL × 2). The organic layer was diluted with dichloromethane (100 mL), washed with brine (50 mL), and dried with magnesium sulfate ($MgSO_4$). The solvents were removed via rotary evaporation and the product was isolated by flash column chromatography (hexanes/EtOAc, 7:3). Viscous wax (64%), $[\alpha]_D^{23} = +19.6$ (c 0.58, $CHCl_3$). IR (Nujol) (cm^{-1}): 3068, 1731, 1251, 757, 667. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 2.02 (s, 3H), 6.11 (d, J = 8.8 Hz, 1H), 6.28 (d, J = 8.8 Hz, 1H), 6.92–7.44 (m, 23H), 8.14–8.16 (m, 1H). ^{13}C NMR ($CDCl_3$): 21.2, 77.4, 77.8, 127.7, 127.72, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.33, 128.35, 128.4, 128.44, 128.5, 130.9, 130.91, 132.1, 133.8, 133.9, 133.91, 134.0, 134.2, 134.6, 135.7, 136.0, 137.8, 137.9, 138.0, 138.1, 140.5, 140.7, 165.2, 170.0. ESI-HRMS calcd for $C_{35}H_{29}O_4P$ ($M+H^+$): 545.1882. Found: 545.1871.

4.9. (*S*)-2-(2-(Diphenylphosphino)benzamido)-3-methylbutyl 2-(diphenylphosphino)benzo- ate 14a

In a 250 mL nitrogen purged round-bottomed flask were added (*S*)-2-amino-3-methyl-1-butanol (0.100 g, 0.969 mmol), DMAP (0.118 g, 0.969 mmol), dichloromethane (5 mL), 2-(diphenylphosphino)benzoic acid (0.594 g, 1.94 mmol), and EDC (0.408 g, 2.13 mmol). The reaction mixture was allowed to stir for 48 h and then the reaction was quenched with the addition of 3 M HCl (50 mL × 2). The organic layer was diluted with dichloromethane (100 mL), washed with brine (50 mL), and dried with magnesium sulfate ($MgSO_4$). The solvents were removed via rotary evaporation and the product was isolated by flash column chromatography (hexanes/EtOAc, 7:3). Viscous wax (56%), $[\alpha]_D^{23} = -8.1$ (c 0.20, $CHCl_3$). IR (neat) (cm^{-1}): 1714, 1652, 1251, 746, 697. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.85 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 1.66–1.76 (m, 1H), 4.11 (dd, J = 3.6, 11.5 Hz, 1H), 4.20–4.25 (m, 1H), 4.34 (dd, J = 5.4, 11.5 Hz, 1H), 6.44 (d, J = 9.5 Hz, 1H), 6.99–7.01 (m, 1H), 7.20–7.47 (m, 25H), 7.67–7.69 (m, 1H), 8.20–8.22 (m, 1H).^{13}C NMR ($CDCl_3$): 18.7, 19.2, 29.3, 53.5, 65.4, 127.9, 127.9, 128.3, 128.4, 128.41, 128.42, 128.46, 128.48, 128.5, 128.6, 128.62, 128.7, 130.0, 131.2, 132.0, 133.5, 133.6, 133.7, 133.8, 134.1, 134.2, 134.3, 134.1, 134.2, 134.3, 135.6, 135.8, 136.9, 137.0, 137.1, 137.2, 137.4, 137.5, 137.54, 137.6, 139.6, 139.8, 141.5, 141.7, 166.7, 168.7. ESI-HRMS calcd for $C_{43}H_{39}NO_3P_2$ ($M+H^+$): 680.2483. Found: 680.2487.

4.10. (*S*)-2-(2-(Diphenylphosphino)benzamido)-2-phenylethyl 2-(diphenylphosphino)benzo-ate 14b

In a 250 mL nitrogen purged round-bottomed flask were added (*S*)-phenylglycinol (0.100 g, 0.729 mmol), DMAP (0.089 g, 0.729 mmol), dichloromethane (5 mL), 2-(diphenylphosphino)benzoic acid (0.447 g, 1.46 mmol), and EDC (0.613 g, 3.21 mmol). The reaction mixture was allowed to stir for 48 h and then the reaction was quenched with the addition of 3 M HCl (50 mL × 2). The organic layer was diluted with dichloromethane (100 mL), washed with brine (50 mL), and dried with magnesium sulfate ($MgSO_4$). The solvents were removed via rotary evaporation and the product was isolated by flash column chromatography (hexanes/EtOAc, 6:4). Viscous wax (71%), $[\alpha]_D^{23} = -6.3$ (c 0.35, $CHCl_3$). IR (Nujol) (cm^{-1}): 1716, 1654, 1217, 751, 697. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.24 (dd, J = 5.6, 14.3 Hz, 1H), 4.46 (dd, J = 8.0, 14.3 Hz, 1H), 5.46–5.50 (m, 1H), 6.90–6.93 (m, 2H), 7.11–7.37 (m, 30H), 7.64–7.67 (m, 1H), 8.02–8.06 (m, 1H). ^{13}C NMR ($CDCl_3$): 52.4, 67.1, 126.8, 127.7, 128.3, 128.32, 128.4, 128.41, 128.45, 128.5, 128.6, 128.64, 128.7, 128.8, 130.2, 131.2, 132.1, 133.6, 133.7, 133.74, 133.9, 133.94, 134.2, 134.3, 135.7, 136.0, 136.7, 136.8, 137.0, 137.1, 137.5, 137.52, 137.6, 137.63, 138.0, 140.1, 140.4, 140.9, 141.2, 166.5, 168.3. ESI-HRMS calcd for $C_{46}H_{37}NO_3P_2$ ($M+H^+$): 714.2327. Found: 714.2335.

4.11. (*S*)-2-(2-(Diphenylphosphino)benzamido)-3,3-dimethylbutyl 2-(diphenylphosphino) benzoate 14c

In a 250 mL nitrogen purged round-bottomed flask were added (*S*)-2-amino-3,3-dimethyl-1-butanol (0.100 g, 0.853 mmol), DMAP (0.104 g, 0.853 mmol), dichloromethane (5 mL), 2-(diphenylphosphino)benzoic acid (0.523 g, 1.71 mmol), and EDC (0.359 g, 1.88 mmol). The reaction mixture was allowed to stir for 48 h and then the reaction was quenched with the addition of 3 M HCl (50 mL × 2). The organic layer was diluted with dichloromethane (100 mL), washed with brine (50 mL), and dried with magnesium sulfate ($MgSO_4$). The solvents were removed via rotary evaporation and the product was isolated by flash column chromatography (hexanes/EtOAc, 7:3). Viscous wax (66%), $[\alpha]_D^{23} = -3.2$ (c 0.40, $CHCl_3$). IR (Nujol) (cm^{-1}): 1714, 1651, 1269, 743, 696. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.86 (s, 9H), 4.16–4.17 (m, 1H), 4.32–4.41 (m, 1H), 6.10 (d, J = 9.9 Hz, 1H), 6.93–7.00 (m, 1H), 7.08–7.43 (m, 26H), 7.63–7.65 (m, 1H), 8.28–8.31 (m, 1H). ^{13}C NMR ($CDCl_3$): 26.6, 33.7, 56.1, 64.6, 128.1, 128.15, 128.19, 128.2, 128.3, 128.4, 128.43, 128.5, 128.6, 128.63, 128.7, 128.8, 130.0, 131.6, 131.8, 132.0, 133.6, 133.61, 133.7, 133.8, 133.9, 133.91, 134.1, 134.3, 134.8, 135.0, 136.7, 136.8, 136.9, 137.0, 137.8,

137.9, 137.91, 138.0, 140.6, 140.8, 142.0, 142.2, 166.5, 169.1. ESI-HRMS calcd for $C_{44}H_{41}NO_3P_2$ ($M+H^+$): 694.2640. Found: 694.2652.

4.12. (*S*)-Dimethyl 2-(1,3-diphenylallyl)malonate (Table 2, entry 10) 10a

In a 50 mL nitrogen purged round-bottomed flask were added ligand (0.048 g, 0.069 mmol), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (0.026 g, 0.070 mmol), KOAc (0.007 g, 0.070 mmol), THF (4 mL), BSA (1.3 mL, 5.3 mmol), 1,3-diphenylpropenyl acetate (0.464 g, 1.73 mmol), and $CH_2(CO_2Me)_2$ (0.6 mL, 5.3 mmol). The reaction mixture was allowed to stir for 6 h at 25 °C and then the reaction was quenched with the addition of 1 M HCl (50 mL) and ammonium chloride (50 mL). The organic layer was diluted with ether (50 mL), washed with brine (50 mL), and dried ($MgSO_4$). The solvents were removed via rotary evaporation and the product was isolated by flash column chromatography (hexanes/EtOAc, 9:1). The products were analyzed by HPLC using an AD column. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.44 (s, 3H), 3.62 (s, 3H), 3.88 (d, J = 10.9 Hz, 1H), 4.19 (dd, J = 8.8, 10.8 Hz, 1H), 6.26 (dd, J = 8.60, 15.8 Hz, 1H), 6.40 (d, J = 15.8 Hz, 1H), 7.10–7.25 (m, 10 H). ^{13}C NMR ($CDCl_3$): 49.2, 52.4, 52.6, 57.6, 126.4, 127.1, 127.5, 127.9, 128.5, 128.7, 129.1, 131.8, 136.8, 140.2, 167.7, 168.2.

4.13. (*S*)-Diethyl 2-(1,3-diphenylallyl)malonate (Table 2, entry 11) 10b

In a 50 mL nitrogen purged round-bottomed flask were added ligand (0.049 g, 0.071 mmol), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (0.026 g, 0.072 mmol), KOAc (0.007 g, 0.072 mmol), THF (4 mL), BSA (1.3 mL, 5.4 mmol), 1,3-diphenylpropenyl acetate (0.476 g, 1.78 mmol), and $CH_2(CO_2Et)_2$ (0.8 mL, 5.4 mmol). The reaction mixture was allowed to stir for 24 h at 25 °C and then the reaction was quenched with the addition of 1 M HCl (50 mL) and ammonium chloride (50 mL). The organic layer was diluted with ether (50 mL), washed with brine (50 mL), and dried ($MgSO_4$). The solvents were removed via rotary evaporation and the product was isolated by flash column chromatography (hexanes/EtOAc, 9:1). The products were analyzed by HPLC using an AD column. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.00 (t, J = 8.8 Hz, 3H), 1.20 (t, J = 8.8 Hz, 3H), 3.92 (d, J = 13.7 Hz, 2H), 3.97 (q, J = 8.8 Hz, 2H), 4.17 (q, J = 8.8 Hz, 2H), 4.26 (dd, J = 10.8, 13.7 Hz, 1H), 6.34 (dd, J = 10.8, 19.7, 1H), 6.5 (d, J = 19.7 Hz, 1H), 7.17–7.30 (m, 10H). ^{13}C NMR ($CDCl_3$): 13.7, 14.1, 49.2, 57.7, 61.3, 61.5, 126.3, 127.0, 127.5, 128.0, 128.4, 128.6, 129.3, 131.6, 136.8, 140.3, 167.4, 167.8.

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