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β-Hydroxy and β-(*o*-diphosphino)benzoyloxy(*o*-diphosphino) benzamides as ligands for asymmetric allylic alkylation

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ABSTRACT

Diphenylphosphinobenzoic acid was treated with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC), DMAP, and with either one of two equivalents of (1*R*,2*S*)-norephedrine and (1*S*,2*S*)-pseudonorephedrine. This process yielded a series of β-hydroxy and β-(diphosphino) benzoyloxy(diphosphino)benzamides that were employed in the Tsuji–Trost asymmetric allylic alkylation process. It was determined that the diastereomeric geometry of the norephedrine series was superior to that of the pseudonorephedrine-based ligands. In addition, it was determined that the norephedrine-based β-(*o*-diphosphino)benzoyloxy(*o*-diphosphino)benzamide afforded the best enantiomeric ratio (94:6) favoring the (*S*)-enantiomer.

1. Introduction

The Tsuji–Trost asymmetric allylic alkylation process[1–3] has been quite successful and has inspired many to pursue the development of chiral, non-racemic ligands as templates for conducting asymmetric syntheses. Among the ligands that have been widely studied and applied is the Trost bis(diphenylphosphinobenzamide) **1** (Fig. 1).[4] The successful application of the Trost ligand has spurred the development of new ligands with key differences that are meant to enhance their applicability.[5] Mino et al.[6] developed a β-methoxy(diphosphino benzamide) **2** derived from L-phenylalaninol which gave very good enantioselectivities. This work was followed by the design and application of β-hydroxy(diphosphinobenzamides) **3** and **4** by Burke et al.[7] Burke et al. sought to exploit the presence of the free alcohol as a coordination site for the palladium, potentially leading to an augmented enantiomeric ratio. The observed enantioselectivities ranged from moderate to good. The authors speculated that the hydroxyl group served as an additional binding site but was led to the dual problems of deactivation of the palladium and allylic isomerization ($\eta^3 \rightarrow \eta^1 \rightarrow \eta^3$) that diminish the transfer of asymmetry from the ligand to the substrate. The source of asymmetric induction in the ligands developed independently by Mino et al. and Burke et al. was a single stereogenic center bound to the nitrogen. We considered the possibility of employing β-aminoalcohols containing two stereocenters that might suppress the proposed allylic isomerization and thereby enhance the asymmetric induction of the allylic alkylation process. The potential issue of moderating the deactivation of the catalyst by the hydroxyl group in the new ligand application was also of interest. Thus, in connection with our ongoing research program involving the use of *Ephedra* alkaloids, we became interested in employing (1*R*,2*S*)-norephedrine and (1*S*,2*S*)-pseudonorephedrine[8] as chiral, non-racemic templates for the construction of ligands that might be suitable for usage. In addition to using these β-aminoalcohols in an attempt to obtain better enantioselectivities, we were also interested in the idea of using the alcohol as a tool for introducing a second coordinating phosphine ligand. Herein, we report on the synthesis of four ligands based on these *Ephedra* alkaloids and their application in the Tsuji–Trost reaction.

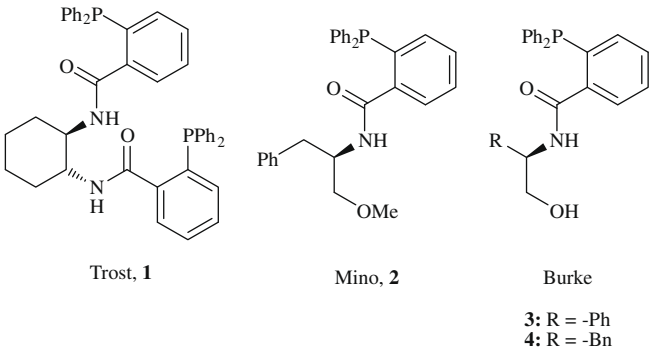

Figure 1. Phosphine ligands research and development.

2. Results and discussion

(1*R*,2*S*)-Norephedrine and (1*S*,2*S*)-pseudonorephedrine were treated with *o*-diphenyl phosphinobenzoic acid and 1-ethyl-3-(3-

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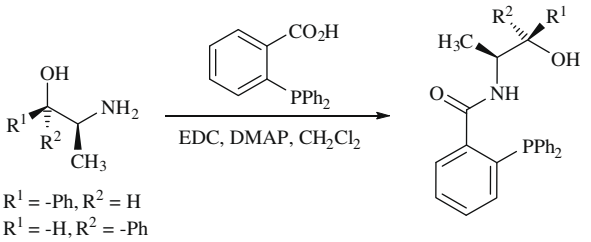
dimethylaminopropyl)carbodiimide (EDC) and a catalytic amount of DMAP to give β-hydroxy(diphenylphosphino)benzamides **7** and **8**, in 71% and 54%, respectively (Scheme 1). With the *Ephedra*-based phosphine ligands in hand, we applied these compounds in the asymmetric allylic alkylation reaction with 1,3-diphenylpropenyl acetate, dimethylmalonate, and $[\eta^3\text{-}(C_3H_5)PdCl]_2$. Initial experimentation focused on the relative amounts of the substrate, benzamide **7**, and the palladium (0) source (Table 1, entries 1–3). Of these entries, entry 1 afforded the best combination, although the highest enantioselectivity was a modest 56% ee. This suggested that the addition of more of the palladium source and phosphine ligand **7** relative to the allylic acetate substrate was detrimental in optimizing the enantioselection of the reaction. Reducing the temperature to 0 °C from 25 °C did not improve the enantiomeric ratio of the product (cf. Table 1, entries 1 and 4). Furthermore, increasing the amount of ligand to the palladium (0) source at the lower temperature only led to diminished enantioselectivities. In contrast, progressively increasing the amount of the palladium (0) source from a ratio of 1:1 to 1:2 to 1:3 revealed that the optimal ligand/Pd ratio was 1:2 with an enantiomeric ratio of 87.5:12.5 (75). We were gratified to learn that we were able to obtain a good level of enantioselectivity, moreso than that obtained with the related L-phenylalaninol and L-phenylglycinol benzamide ligands developed by Burke et al.[7] The use of dichloromethane as the reaction solvent in place of THF gave comparable results with differing ratios of ligand to the palladium pre-catalyst (see Table 1, entries 9 and 10). We became interested in the use of the (1*S*,2*S*)-pseudonorephedrine-derived benzamide ligand and applied it to the asymmetric allylic alkylation process. An enantiomeric ratio 76.5:23.5 favoring the (*R*)-enantiomer was obtained using this ligand. Thus, the diastereomeric ligands **7** and **8** yielded the same absolute stereochemistry in the product. It is proposed that the two ligands **7** and **8** form palladium complexes **7A**, **7B**, **8A,** and **8B**, respectively (Fig. 2). These intermediates are similar to those proposed by Burke et al.[7] Based on the fact that the absolute stereochemistry of the product from the asymmetric alkylation is the same when either ligand **7** or **8** is employed, it is proposed that the dominant control element of the asymmetric induction is the stereocenter that is proximal to the benzamide nitrogen (i.e., conformations **7A** and **8A**). In contrast, complexes **7B** and **8B**, wherein there is coordination with the hydroxyl group would appear to be of lesser importance, as the conformations of these complexes place the benzylic position closes to the reacting center. As these complexes have opposing stereochemical features near the reactive palladium center, it is unlikely that this conformational mode is responsible for the observed enantioselection.



5: R^1 = -Ph, R^2 = H
6: R^1 = -H, R^2 = -Ph

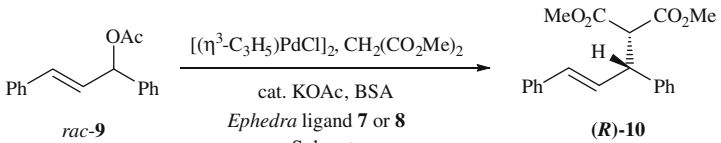
7: R^1 = -Ph, R^2 = H
8: R^1 = -H, R^2 = -Ph

Scheme 1. Synthesis of β-hydroxybenzoyloxy(diphosphino)benzamides.

The successful application of **7** and **8** prompted the synthesis of the bis(phosphine) ligands **11** and **12** (see Scheme 2). Thus, *Ephdra* alkaloids **5** and **6** were coupled with 2 equiv of *o*-(diphenylphosphino)benzoic acid, EDC, and DMAP to afford β-(*o*-diphosphino)benzoyloxy(*o*-diphosphino)benzamides **11** and **12** in 44% and 54%, respectively. These compounds were employed in the asymmetric allylic alkylation reaction. It was determined that these ligands afforded enantioselectivities of 94:6 for **11** and 81.5:18.5 for **12** favoring the formation of the (*S*)-enantiomer of the product. These observations were contrary to earlier findings that the *o*-(diphosphino)benzamides **7** and **8** predominantly favored the formation of the (*R*)-enantiomer. In addition to this, it was determined that the level of enantioselection of the alkylation reaction using **11** did not vary when the relative amount of the palladium pre-catalyst was changed (Table 2, cf. entries 1 and 2).

To gain a better understanding of the difference and similarity between **7**, **8**, **11**, and **12**, ^{31}P NMR spectra were collected (Fig. 3). In the proton decoupled ^{31}P NMR spectra collected for the ligands, monophoshines **7** and **8** contain a single resonance at −10.40 and −10.32 ppm, respectively. The bis(phosphines) ligands **11** and **12** had two resonances each appearing at −9.32 and −5.54 ppm, and

Table 1
Tsuji–Trost reaction of **9** and **10** with *rac*-1,3-diphenylpropenyl acetate



rac-**9** (***R***)-**10**

Entry	Ligand	Solvent	Temp (°C)	**9**:Ligand:Pd	Yield[a] (%)	er (|*R*–*S*|)[b,c]	Enant.[c]
1	**7**	THF	25	50:2:1	62	78.0:22.0 (56)	(*R*)
2	**7**	THF	25	25:2:1	87	74.0:26.0 (48)	(*R*)
3	**7**	THF	25	16.7:2:1	47	68.0:32.0 (36)	(*R*)
4	**7**	THF	0	50:2:1	49	76.0:24.0 (52)	(*R*)
5	**7**	THF	0	100:4:1	56	68.0:32.0 (36)	(*R*)
6	**7**	THF	25	25:1:1	62	81.5:18.5 (63)	(*R*)
7	**7**	THF	25	25:1:2	68	87.5:12.5 (75)	(*R*)
8	**7**	THF	25	25:1:3	43	75.5:24.5 (51)	(*R*)
9	**7**	CH_2Cl_2	25	50:2.5:1	47	85.5:14.5 (71)	(*R*)
10	**7**	CH_2Cl_2	25	25:1:2	42	86.5:13.5 (73)	(*R*)
11	**8**	CH_2Cl_2	25	25:1:2	47	76.5:23.5 (53)	(*R*)

[a] Isolated yield after flash chromatography.
[b] Enantiomeric ratios determined by CSP HPLC (Chiralcel AD column).
[c] The identification of the enantiomers was based on the order of elution from the CSP HPLC AD column. The correlation between the elution and the absolute stereochemistry of the products has been established.[12]

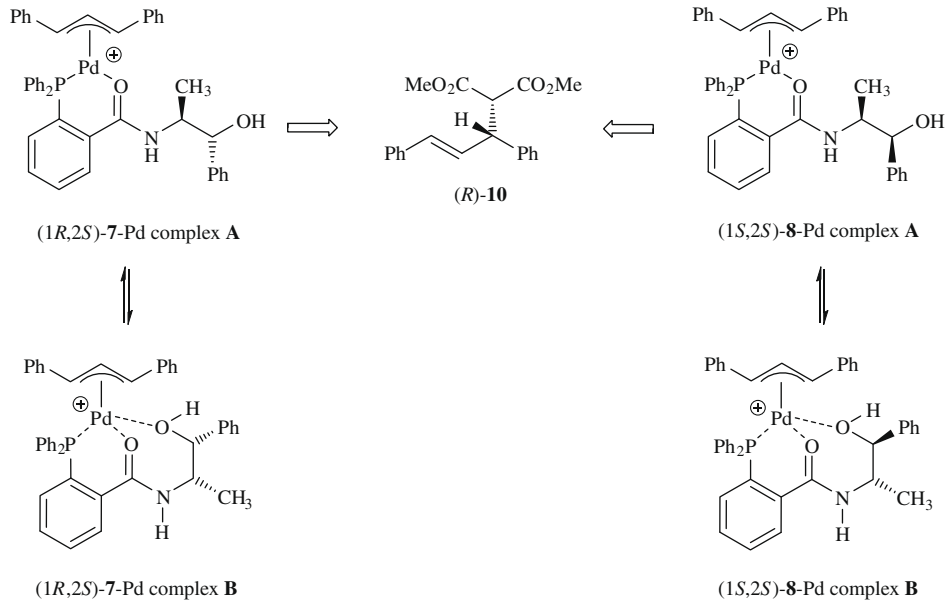
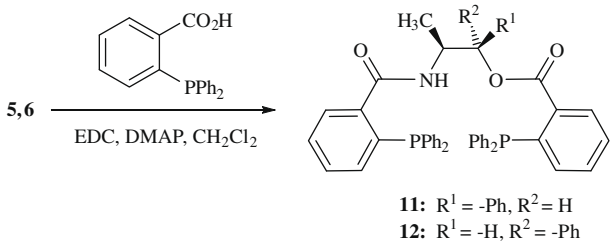
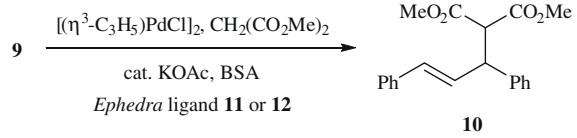


Figure 2. Putative intermediates in the asymmetric allylic alkylation with **7** and **8**.



Scheme 2. Synthesis of β-(diphosphino)benzoyloxy(diphosphino)benzamides **11** and **12**.

Table 2
Asymmetric alkylation reaction of **11** and **12** with *rac*-1,3-diphenylpropenyl acetate



Entry[a]	Ligand	**9**:Ligand:Pd	Yield[b] (%)	er (|*R*–*S*|)[c]	Enantiomer[d]
1	**11**	25:1:2	59	94.0:6.0 (88)	(*S*)
2	**11**	25:1:1	51	94.0:6.0 (88)	(*S*)
3	**12**	25:1:1	65	81.5:18.5 (63)	(*R*)

[a] All reactions were conducted in THF at 25 °C.
[b] Isolated yield after flash chromatography.
[c] Enantiomeric ratios determined by CSP HPLC (Chiralcel AD column).
[d] The identity of the enantiomer was based on elution from the CSP HPLC column.

at −9.44 and −4.69 ppm, respectively. The phosphine bound to the aryl ester appeared at an averaged frequency of −5.12 ppm; the phosphorus bound to the aryl amide appeared at an averaged frequency of −9.38 ppm. The collected data support the fact that the two phosphorus atoms in **11** and **12** are similar but unique. The chemical shifts for all of the phosphorus atoms appear in the same region as the resonance signal of triphenylphosphine (Ph_3P) collected under similar conditions (singlet at −4.72 ppm). For the sake of comparison, data were also collected on triphenylphosphine oxide (singlet at 29.68 ppm) to ensure that the ligands were not themselves oxidized during the course of their use in these studies. Notably, no resonancesignals were observed in the positive region of the ^{31}P NMR spectra, indicating that the newly prepared compounds were free of phosphine oxides. Ultimately, the similarity between the chemical shifts of triphenylphosphine and the ligands suggested that the phosphines all shared nearly the same electronic environment.

A rationale for the formation of the (*S*)-enantiomer as the dominant enantiomer for the bis(phosphine) ligand **11** is only putative at this time but it may be possible that bis(phosphine) **11** may be involved in complex equilibria involving the palladium propenyl cationic complexes **13A**–**D** (Scheme 3). Related putative intermediates have been isolated and proposed in independent investigative studies by Lloyd–Jones,[9] Amatore,[10] and Dahan (nickel allyl complexes).[11] Palladium complex **13A** is viable but would not be the key intermediate as the stereochemical result would be the same as the mono(phosphine) ligands **7** and **8**. Complex **13B** does not seem plausible as the dominant catalytic entity either as there is no participation from the phosphorus bound the amide portion of the molecule, which is in stark contrast to known activity observed in **7** and **8**. The bis(palladium)–bis(phosphine) complex **13C** is not believed to be the dominant pathway as there would be two stereochemical pathways opposing each other leading to a compromised enantioselection. Based on these rationalizations, it is believed that **13D**, or some derivative thereof, is the species most responsible for the observed enantiomeric ratios, although there may be other catalytic species that have not been considered.

Interestingly, the (1*S*,2*S*)-pseudonorephedrine ligand **12** yielded the opposite stereochemistry (*S*)-enantiomer of the product as the dominant product. This is in contrast to the case of ligand **8** of the same stereochemical family. Based on this result, it can be postulated that the mode of asymmetric induction for the mono(phosphine) ligand is significantly different from that of the bis(phosphine) ligands.

3. Conclusion

A series of *Epedra*-based β-hydroxy and β-(*o*-diphosphino)benzoyloxy(*o*-diphosphino) benzamides have been successfully applied in the asymmetric allylic alkylation reaction. The use of the

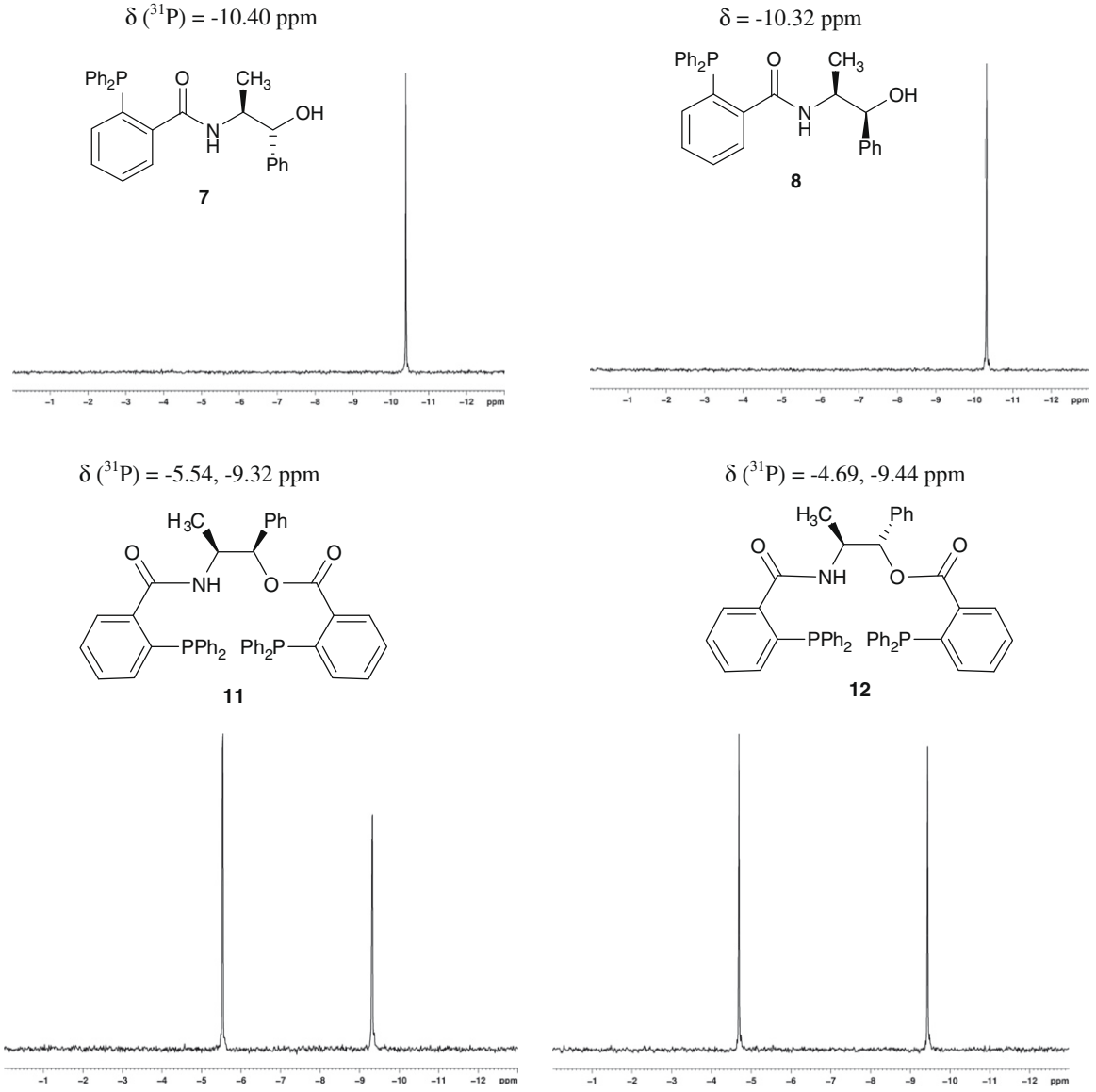


Figure 3. ^{31}P NMR spectroscopic data for ligands **7**, **8**, **11**, and **12**.

four ligands have revealed interesting aspects about the catalysis process based on the mixed phosphine ligand system employed. Efforts are underway to investigate the further use of the norephedrine-based ligand and related systems (e.g., 2-amino-1,2-diphenyl-1-ethanol) in asymmetric allylation reactions to further pursue the use of dissymmetrical bis(phosphines).

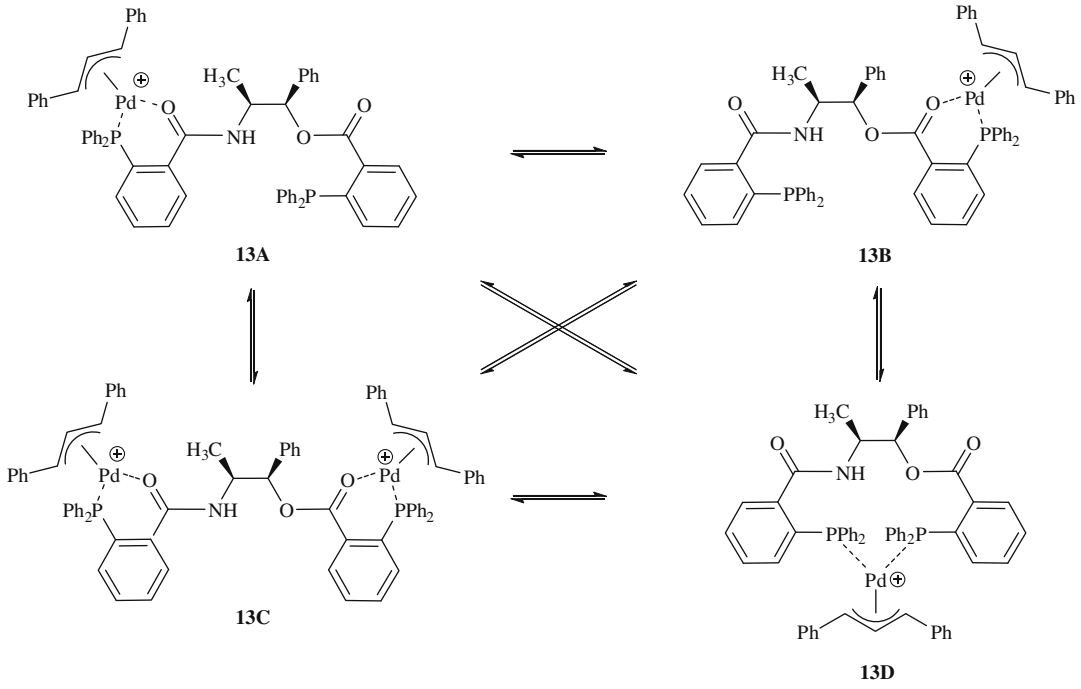
4. Experimental

4.1. General remarks

Methylene chloride (CH_2Cl_2) was purchased as an anhydrous reagent. Unless otherwise stated, all reactions were run under anhydrous conditions and a nitrogen atmosphere. ^{1}H and ^{13}C NMR spectra were recorded either on a Varian spectrometer in $CDCl_3$ operating at 500 MHz and 125 MHz. Chemical shifts are reported in parts per million (δ scale), and coupling constants (J values) are listed in hertz (Hz). All ^{1}H and ^{31}P{^{1}H} NMR spectral data were collected on a Bruker Avance III 500 MHz instrument operating at 500.13 MHz and 202.45 MHz, respectively. ^{1}H NMR spectra were referenced to the deuterated chloroform resonance at 7.26 ppm while ^{31}P NMR spectra were externally referenced to 85% H_3PO_4 (0.00 ppm). All spectra were collected at 300 K. Infrared spectra are reported in reciprocal centimeters (cm^{-1}) and are measured either as a neat liquid or as a KBr window. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Flash chromatography was conducted with an Analogix chromatograph. Mass spectroscopic analyses were conducted by the mass spectrometry analytical laboratories of the University of Illinois at Urbana-Champaign using a quadrapole time of flight mass spectrometer hybrid with MS/MS capability. Enantiomeric ratios were determined using a Shimadzu HPLC with either Chiral Stationary Phase Chiralcel AD column. Optical activities were measured at 589 nm using a digital polarimeter purchased with NSF grant #CHE 644950.

4.2. *o*-(Diphenylphosphino)-*N*-(1*R*,2*S*)-1-hydroxy-1-phenyl-2-propyl)benzamide 7

In a 250 mL nitrogen purged round-bottomed flask were added (1*R*,2*S*)-norephedrine (0.740 g, 4.90 mmol), DMAP (0.119 g,



Scheme 3. Proposed intermediates for the asymmetric allylation reaction.

0.979 mmol), dichloromethane (13 mL), 2-(diphenylphosphino) benzoic acid (1.50 g, 4.89 mmol), and EDC (1.03 g, 5.39 mmol). The reaction mixture was allowed to stir for 24 h and 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 ($MgSO_4$). The solvents were removed via rotary evaporation and the product was isolated by recrystallization from chloroform and hexanes (1:2). White solid (71%), $[\alpha]_D^{23} = -15.6$ (*c* 0.10, $CHCl_3$). Mp = 168–171 °C. IR (nujol) (cm^{-1}): 3373, 3325, 1623, 1581, 1008. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.85 (d, *J* = 6.6 Hz, 3H), 3.26 (s, 1H), 4.29 (pd, *J* = 7.3, 1H), 6.03 (d, *J* = 7.3, 1H), 6.95–6.98 (m, 1H), 7.32–7.34 (m, 17H), 7.59–7.62 (m, 1H). ^{13}C NMR ($CDCl_3$, extra peaks were observed due to the coupling interaction between ^{13}C and ^{31}P nuclei): 13.3, 51.8, 75.2, 126.1, 127.2, 128.1, 128.6, 128.6, 128.71, 128.7, 128.8, 128.94, 128.9, 129.0, 130.2, 133.8, 133.8, 133.9, 133.9, 134.0, 135.0, 135.2, 136.3, 136.4, 136.5, 136.6, 140.8, 141.5, 141.7, 169.3. $^{31}P\{^1H\}$ NMR ($CDCl_3$): −10.40 ppm. ESI-HRMS calcd for $C_{28}H_{26}NO_2P$ ($M+H^+$): 440.1779. Found: 440.1774.

4.3. *o*-(Diphenylphosphino)-*N*-(1*S*,2*S*)-1-hydroxy-1-hydroxy-1-phenyl-2-propyl)benzamide 8

In a 250-mL nitrogen purged round-bottomed flask were added (1*S*,2*S*)-norephedrine (0.494 g, 3.27 mmol), DMAP (0.079 g, 0.653 mmol), dichloromethane (13 mL), *o*-(diphenylphosphino) benzoic acid (1.000 g, 3.265 mmol), and EDC (0.689 g, 3.592 mmol). The reaction mixture was allowed to stir for 24 h and then 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 $MgSO_4$. The solvents were removed via rotary evaporation and the product was isolated by flash column chromatography (hexanes/EtOAc, 1:1). Viscous wax (54%), $[\alpha]_D^{24} = +11.3$ (*c* 0.10, $CHCl_3$). IR (NaCl) (cm^{-1}): 3372, 3325, 1626, 1522, 1006. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.90 (d, *J* = 6.8 Hz, *3H*), 3.67 (s, 1H), 4.20 (sextet, *J* = 6.8 Hz), 4.45–4.47 (m, 1H), 6.05 (d, *J* = 8.0 Hz), 6.94–6.97 (m, 1H), 7.25–7.35 (m, 17H), 7.50–7.53 (m, 1H). ^{13}C NMR ($CDCl_3$, extra peaks were observed due to the coupling interaction between ^{13}C and ^{31}P nuclei) 16.9, 52.1, 77.2, 126.5, 127.5, 127.7, 127.7, 128.1, 128.5, 128.5, 128.7, 128.7, 130.0, 133.6, 133.6, 133.8, 133.8, 133.9, 135.3, 135.5, 136.6, 136.7, 136.8, 141.1, 141.4, 169.5 $^{31}P\{^1H\}$ NMR ($CDCl_3$): −10.32 ppm. ESI-HRMS calcd for $C_{28}H_{26}NO_2P$ ($M+H^+$): 440.1779. Found: 440.1773.

4.4. (1*R*,2*S*)-2-(*o*-Diphenylphosphino)benzamido)-1-phenyl-2-propyl(*o*-diphenyl phosphino)benzoate 11

In a 250-mL nitrogen purged round-bottomed flask were added (1*R*,2*S*)-norephedrine (0.420 g, 2.78 mmol), DMAP (0.271 g, 2.22 mmol), dichloromethane (15 mL), *o*-(diphenylphosphino)benzoic acid (1.70 g, 5.55 mmol), and EDC (1.06 g, 5.55 mmol). The reaction mixture was allowed to stir for 24 h and 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 over $MgSO_4$. The solvents were removed via rotary evaporation and the product was isolated by flash column chromatography (hexanes/EtOAc, 75:25). Yellow oil (44%), $[\alpha]_D^{23} = +7.8$ (*c* 0.10, $CHCl_3$). IR (NaCl) (cm^{-1}): 3303, 1716, 1652, 1586, 1250. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.81 (d, *J* = 6.9 Hz, 3H), 4.50–4.55 (m, 1H), 6.07(d, *J* = 3.4 Hz, 1H), 6.70 (d, *J* = 8.3 Hz, 1H), 6.92–6.94 (m, 1H), 7.00–7.03 (m, 1H), 7.11–7.31 (m, 1H), 7.39–7.47 (m, 1H), 7.54–7.57 (m, 1H), 8.10–8.13 (m,1H). ^{13}C NMR ($CDCl_3$, extra peaks were observed due to the coupling interaction between ^{13}C and ^{31}P nuclei): 14.3, 49.1, 78.9, 126.0, 127.7, 127.7, 127.7, 128.2, 128.3, 128.4, 128.4, 128.5, 128.5, 128.6, 128.7, 128.7, 129.8, 130.8, 130.8, 131.9, 133.3, 133.4, 133.6, 133.8, 133.8, 133.8, 133.9, 134.6, 135.2, 135.4, 136.1, 136.3, 137.0, 137.1, 137.1, 137.2, 137.2, 137.3, 138.7, 138.9, 141.1, 141.3, 166.3, 167.9. $^{31}P\{^1H\}$ NMR ($CDCl_3$): −5.54, −9.32 ppm. ESI-HRMS calcd for $C_{47}H_{40}NO_3P_2$ ($M+H^+$): 728.2483. Found: 728.2466.

4.5. (1*S*,2*S*)-2-(*o*-Diphenylphosphino)benzamido)-1-phenyl-2-propyl(*o*-diphenylphosphino) benzoate 12

In a 250-mL nitrogen purged round-bottomed flask were added (1*S*,2*S*)-norephedrine (0.420 g, 2.78 mmol), DMAP (0.271 g, 2.22 mmol), dichloromethane (15 mL), *o*-(diphenylphosphino)benzoic acid (1.70 g, 5.55 mmol), and EDC (1.06 g, 5.55 mmol). The reac-

tion mixture was allowed to stir for 24 h and then 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 over $MgSO_4$. The solvents were removed via rotary evaporation and the product was isolated by flash column chromatography (hexanes/EtOAc, 75:25). Yellow oil (54%). $[\alpha]_D^{23} = -16.9$ (c 0.10, $CHCl_3$). IR (NaCl) (cm^{-1}): 3350, 1714, 1652, 1585, 1251. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.88 (d, J = 6.7, 3H), 4.59–4.65 (m, 1H), 5.89 (d, J = 7.3, 1H), 6.36 (d, J = 8.8, 1H), 6.89–6.94 (m,1H), 7.11–7.17 (m, 1H), 7.21–7.29 (m, 28H), 7.36–7.49 (m, 1H), 8.20–8.23 (m, 1H). ^{13}C NMR ($CDCl_3$), extra peaks were observed due to the coupling interaction between ^{13}C and ^{31}P nuclei): 17.4, 49.6, 78.9, 127.2, 127.6, 128.2, 128.3, 128.4, 128.4, 128.5, 128.5, 128.5, 128.6, 129.9, 131.4, 131.4, 132.2, 133.5, 133.6, 133.6, 133.7, 133.7, 133.8, 133.8, 133.9, 133.9, 133.9, 134.1, 134.5, 135.9, 136.1, 137.0, 137.2, 137.4, 137.5, 137.6, 137.6, 137.6, 137.7, 139.9, 140.1, 141.2, 141.4, 166.1, 168.3. $^{31}P\{^1H\}$ NMR ($CDCl_3$): −4.69, −9.44 ppm. ESI-HRMS calcd for $C_{47}H_{40}NO_3P_2$ ($M + H^+$): 728.2483. Found: 728.2466.

4.6. General procedure for the catalytic asymmetric allylic alkylation reactions (Table 1, entry 1)

In a 50-mL nitrogen purged round-bottomed flask were added ligand (0.048 g, 0.109 mmol), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (0.019 g, 0.054 mmol), KOAc (0.005 g, 0.054 mmol), THF (4 ml), BSA (1.65 g, 8.10 mmol), 1,3-diphenylpropenyl acetate (0.733 g, 2.73 mmol), $CH_2(CO_2Me)_2$ (1.07 g, 8.10 mmol). The reaction mixture was allowed to stir for 24 h at 25 °C and 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 Shimadzu HPLC using an AD column.

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