JOC Article

A New Class of Chiral *P,N*-Ligands and Their Application in Palladium-Catalyzed Asymmetric Allylic Substitution Reactions

Michael P. A. Lyle, Arun A. Narine, and Peter D. Wilson*

Department of Chemistry, Simon Fraser University, 8888 University Drive,
Burnaby, British Columbia, Canada V5A 1S6

pwilson@sfu.ca

Received April 6, 2004

An efficient and modular synthesis of a series of chiral nonracemic *P,N*-ligands is reported. The *P,N*-ligands were prepared from 2-chloro-4-methyl-6,7-dihydro-5*H*-[1]pyrindine-7-one and a series of substituted chiral C_2-symmetric 1,2-ethanediols (R = Me, *i*-Pr, and Ph). The ligands were evaluated for use in catalytic asymmetric synthesis in the palladium-catalyzed allylic substitution reactions of a racemic allylic acetate and dimethyl malonate. In the case of the *P,N*-ligand (R = Ph), the reaction was found to be highly stereoselective (90% ee).

Introduction

We have recently designed, synthesized, and evaluated a series of 7-hydroxyindan-1-one-derived chiral auxiliaries **1** (Figure 1).[1] These structurally rigid chiral auxiliaries were synthesized in a modular and convergent manner from readily available 7-hydroxyindan-1-one **2** and a series of chiral nonracemic C_2-symmetric 1,2-diols **3**. Of note, the use of C_2-symmetric diols ensured that only a single diastereoisomer of these acetals was formed and that one of the substituents of the orthogonally fused acetal moiety blocked one of the diastereotopic faces of these molecules. In the case of the acrylate derivative **4** of the 7-hydroxyindan-1-one-derived chiral auxiliary **1** (R = *i*-Pr), a high degree of stereochemical induction was observed in a diethylaluminum chloride-promoted Diels−Alder reaction with cyclopentadiene (91:9 dr). This demonstrated that these chiral acetals could serve as effective chiral directors in asymmetric substrate-directed reactions.

In this article, we describe an extension of the design concept employed in the synthesis of these novel chiral auxiliaries and report an efficient and modular synthesis of a series of chiral nonracemic *P,N*-ligands.[2] In addition, the evaluation of these ligands in palladium(II)-catalyzed asymmetric allylic substitution reactions is described in which excellent levels of asymmetric stereochemical induction were achieved.[3] Of the many different types of chiral ligands that have been studied in catalytic asymmetric reactions, chiral *P,N*-ligands have received considerable recent attention.[2] This type of unsymmetrical chiral ligand is of interest because of the different electronic properties of the phosphorus and nitrogen atoms and the effect that this has on the reactivity of transition metal complexes in catalytic asymmetric processes. This effect is absent in the well-studied and electronically symmetrical *N,N*-bidentate ligands, such as the 2,2′-bipyridine and bis(oxazoline) ligands, that have been employed in many asymmetric transformations.[4,5]

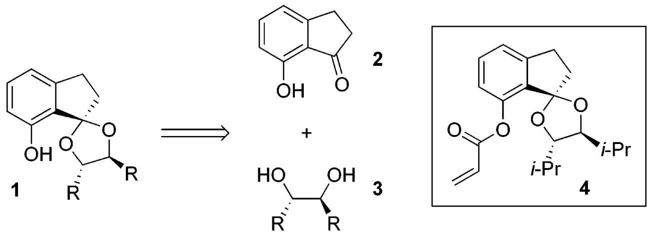


FIGURE 1. 7-Hydroxyindan-1-one-derived chiral auxiliaries **1**.

The retrosynthetic analysis of a series of novel chiral nonracemic 2-(phosphinoaryl)pyridine ligands (*P,N*-ligands) **5a**−**c** (R = Me, *i*-Pr, and Ph) is illustrated below (Figure 2). Condensation of the chloroketone **6** with a series of chiral nonracemic C_2-symmetric 1,2-diols **3a**−**c** (R = Me, *i*-Pr, and Ph) should afford the corresponding acetals. Subsequent elaboration of the 2-chloropyridine moiety of these acetals, to install the phosphinoaryl substituent, would complete the synthesis of the target *P,N*-ligands. For these investigations, we selected three C_2-symmetric 1,2-diols [(2*R*,3*R*)-2,3-butanediol (**3a**: R = Me), (1*S*,2*S*)-1,2-diisopropyl-1,2-ethanediol (**3b**: R = *i*-Pr), and (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediol (**3c**: R =

---

[1] Narine, A. A.; Wilson, P. D. *Synthesis and Evaluation of 7-Hydroxyindan-1-one-Derived Chiral Auxiliaries.* Submitted for publication.

[2] For recent reviews on chiral nonracemic *P,N*-ligands; see: (a) Chelucci, G.; Orrù, G.; Pinna, G. A. *Tetrahedron* **2003**, *59*, 9471. (b) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336.

[3] For reviews on transition metal-catalyzed asymmetric allylic substitution reactions, see: (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (c) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 8E.

[4] For recent reviews on chiral 2,2′-bipyridyl ligands; see: (a) Malkov, A. V.; Kocovsky, P. *Curr. Org. Chem.* **2003**, *7*, 1737. (b) Chelucci, G.; Thummel, R. P. *Chem. Rev.* **2002**, *102*, 3129. (c) Fletcher, N. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1831.

[5] For a recent review on chiral bis(oxazoline) ligands; see, for example: Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

10.1021/jo0494275 CCC: $27.50

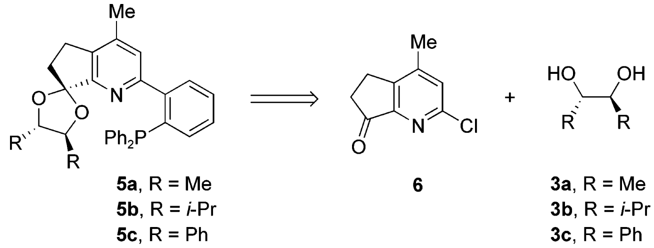
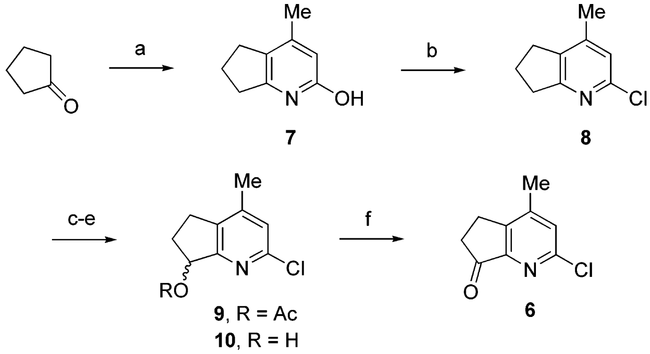


FIGURE 2. Retrosynthetic analysis of chiral *P,N*-ligands **5a**−**c** (R = Me, *i*-Pr, and Ph). For R = Me, the compound used in the following study was the enantiomer of that indicated in the figure.

SCHEME 1. Synthesis of Chloroketone 6[a]



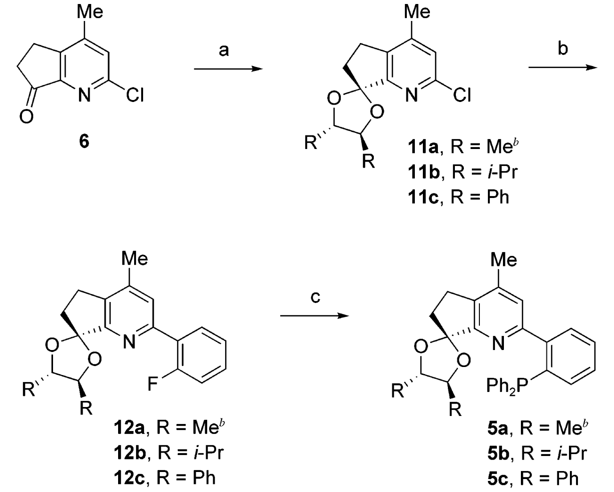
[a] Reagents and conditions: (a) ethyl acetoacetate, NH_4OAc (ref 6); (b) $PhP(O)Cl_2$, 160 °C, 16 h, 83%; (c) H_2O_2, H_2O, AcOH, 80 °C, 16 h; (d) Ac_2O, room temperature, 1 h then 100 °C, 4 h, 60% (over two steps); (e) LiOH, THF, H_2O, room temperature, 16 h, 94%; (f) $(COCl)_2$, DMSO, CH_2Cl_2; NEt_3, −78 °C to room temperature, 90%.

Ph)] in order to vary the steric environment around the complexation site of the chiral *P,N*-ligands.

Results and Discussion

The chloroketone **6** was synthesized in six steps from the 2-hydroxypyridine **7** that can be prepared on a multigram scale from cyclopentanone and ethyl acetoacetate (Scheme 1).[6] The latter compound was then converted to the 2-chloropyridine **8** on heating with phenylphosphonic dichloride.[7] Subsequent oxidation with hydrogen peroxide afforded the corresponding pyridine *N*-oxide that was converted to the known acetate **9** on heating with acetic anhydride.[8,9] Hydrolysis of the acetate **9** with lithium hydroxide afforded the corresponding alcohol **10** and subsequent Swern oxidation afforded the desired chloroketone **6**.[10]

SCHEME 2. Synthesis of *P,N*-Ligands 5a−c (R = Me, *i*-Pr, and Ph)[a]



[a] Reagents and conditions: (a) 1,2-diols **3a**−**c** (R = Me, *i*-Pr, and Ph), *p*-TsOH (cat.), benzene, reflux, 16 h, 85% (**11a**), 89% (**11b**), 79% (**11c**); (b) *o*-fluorophenylboronic acid, 5 mol % of Pd_2dba_3, 10 mol % of $P(t\text{-}Bu)_3$, Cs_2CO_3, THF, reflux, 16 h, 93% (**12a**), 81%, (**12b**), 88% (**12c**); (c) Ph_2PH, KO*t*-Bu, 18-crown-6, THF, room temperature, 24 h, 72% (**5a**), 66% (**5b**), 63% (**5c**). [b] The compound used in this study was the enantiomer of that indicated in the reaction scheme.

The chiral *P,N*-ligands **5a**−**c** (R = Me, *i*-Pr, and Ph) were synthesized in three steps from the chloroketone **6** (Scheme 2). The chiral acetals **11a**−**c** were prepared in good yield on condensation of the chloroketone **6** with the corresponding chiral nonracemic C_2-symmetric 1,2-diols **3a**−**c** (R = Me, *i*-Pr, and Ph) on heating at reflux in benzene with a catalytic amount of *p*-toluenesulfonic acid.[11] The acetals **11a**−**c** were then subjected to a Suzuki coupling reaction with *o*-fluorophenylboronic acid.[12] It was found that the 2-chloropyridine moiety of these acetals reacted exceedingly slowly with this boronic acid under standard reaction conditions.[13] However, the reactions proceeded smoothly on employment of the conditions recently reported by Fu and co-workers and afforded the desired reaction products, the aromatic fluorides **12a**−**c** (R = Me, *i*-Pr, and Ph), in good yield.[14] These reaction conditions involved heating a mixture of the acetals **11a**−**c**, the boronic acid, and anhydrous cesium carbonate at reflux in tetrahydrofuran with catalytic amounts of tris(dibenzylideneacetone)dipalladium(II) and tri-*tert*-butylphosphine. The products of the latter reactions were then converted efficiently to the target compounds, the *P,N*-ligands **5a**−**c**, on reaction with the potassium salt of diphenylphosphine in the presence of 18-crown-6.[15] Of note, this modular and efficient synthetic route is amendable to the preparation of multigram quantities of these *P,N*-ligands.[16]

With a series of structurally diverse chiral *P,N*-ligands **5a**−**c** (R = Me, *i*-Pr and Ph) in hand, we undertook the

---

(6) Sakurai, A.; Midorikawa, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 165.

(7) Robison, M. M. *J. Am. Chem. Soc.* **1958**, *80*, 6254.

(8) Detailed synthetic procedures for the preparation of the acetate **9** have been described elsewhere; see: Lyle, M. P. A.; Wilson, P. D. *Org. Lett.* **2004**, *6*, 855 (Supporting Information). In this instance, the acetate **9** was used to prepare a nonrelated chiral bipyridyl ligand that was used in the asymmetric copper(I)-catalyzed cyclopropanation reactions of a series of alkenes and diazoesters.

(9) The synthesis of the acetate **9** by similar methods has been communicated by Fu and co-workers; see: Rios, R.; Liang, J.; Lo, M. M.-C.; Fu, G. C. *Chem. Commun.* **2000**, 377.

(10) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(11) The noncommercially available chiral nonracemic diol **3b** (R = *i*-Pr) was prepared from L-diethyl tartrate according to literature procedures; see: (a) Wang, X.; Erickson, S. D.; Iimori, T.; Still, W. C. *J. Am. Chem. Soc.* **1992**, *114*, 4128. (b) Matteson, D. S.; Beedle, E. C.; Kandil, A. A. *J. Org. Chem.* **1987**, *52*, 5034.

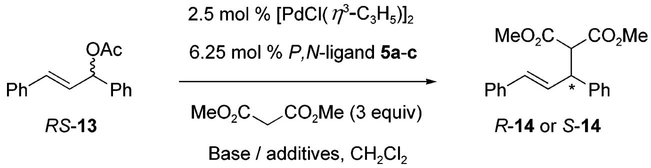
(12) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(13) Tetrakis(triphenylphosphine)palladium(0) [$(Pd(PPh_3)_4$] was employed as a catalyst for this reaction in the first instance. The reactions were performed at reflux in benzene or toluene with potassium carbonate as the base.

(14) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

(15) Kündig, E. P.; Meier, P. *Helv. Chim. Acta* **1999**, *82*, 1360.

TABLE 1. Palladium-Catalyzed Asymmetric Allylic Substitution Reactions



entry	*P,N*-ligand	base/additives	temp	yield (%)[a]	ee (%)[b]	conf[c]
1	**5a**	BSA, KOAc (cat.)	rt	97	65	*S*
2	**5a**	K_2CO_3, 18-crown-6	rt	97	60	*S*
3	**5a**	Cs_2CO_3	rt	97	60	*S*
4	**5b**	BSA, KOAc (cat.)	rt	92	43	*R*
5	**5b**	K_2CO_3, 18-crown-6	rt	93	54	*R*
6	**5b**	Cs_2CO_3	rt	97	60	*R*
7	**5c**	BSA, KOAc, (cat.)	rt	71	58	*R*
8	**5c**	K_2CO_3, 18-crown-6	rt	97	62	*R*
9	**5c**	Cs_2CO_3	rt	97	86	*R*
10	**5c**	Cs_2CO_3	12 °C	97	88	*R*
11	**5c**	Cs_2CO_3	0 °C	91	90	*R*
12	**5c**	Cs_2CO_3	−12 °C	83	90	*R*

[a] Isolated yield of the reaction product *R*-**14** and *S*-**14** after purification by flash chromatography. [b] Determined by analytical chiral HPLC (Daicel Chiracel OD column). [c] The absolute stereochemistry of the reaction product was determined by comparison of the optical rotation with literature values (ref 18).

evaluation of these ligands in the palladium(II)-catalyzed asymmetric allylic substitution reaction of racemic 3-acetoxy-1,3-diphenyl-1-propene *RS*-**13** with dimethyl malonate (Table 1). In the series of asymmetric allylic substitution reactions that were performed, the active asymmetric palladium(II) catalyst was generated by the reaction of 6.25 mol % of the chiral *P,N*-ligand **5a**−**c** with 2.5 mol % of allylpalladium(II) chloride dimer in dichloromethane at room temperature.[17] On subsequent addition of racemic 3-acetoxy-1,3-diphenyl-1-propene *RS*-**13** (1 equiv) and dimethyl malonate (3 equiv), a range of bases and associated reagents were then added. The bases and associated reagents employed in these reactions were the following: (1) *N,O*-bis(trimethylsilyl)-acetamide (BSA, 3 equiv) and a catalytic amount of potassium acetate;[3b] (2) anhydrous potassium carbonate (3 equiv) and 18-crown-6 (3 equiv);[3b] and (3) anhydrous cesium carbonate (3 equiv).[3a]

In all cases, these catalytic systems proved to be reactive and afforded the expected product, (1,3-diphenylallyl)-malonic acid dimethyl ester **14**, in good yield (up to 97%). However, the enantioselectivities of these reactions varied substantially depending on the *P,N*-ligand and reaction conditions that were employed. The use of the *P,N*-ligand **5a** (R = Me), derived from (2*R*,3*R*)-2,3-butanediol (**3a**: R = Me), afforded the product *S*-**14** in moderate enantiomeric excess (60−65%) with the three individual sets of reaction conditions.[18] These results were encouraging when one considers that this asymmetric reaction is directed by the steric influence of a methyl group. The use of the *pseudo*-enantiomeric *P,N*-ligand **5b** (R = *i*-Pr), derived from (1*S*,2*S*)-1,2-diisopropyl-1,2-ethanediol (**3b**: R = *i*-Pr), afforded the enantiomeric product *R*-**14** in similar enantiomeric excess (43−60%). It was somewhat surprising that the use of ligand **5b** (R = *i*-Pr) showed, in general, slightly lower enantioselectivity. The superior result (60% ee) was obtained when cesium carbonate was employed as the base. The use of the *P,N*-ligand **5c** (R = Ph), derived from (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediol (**3c**: R = Ph), again afforded the product *R*-**14** in similar enantiomeric excess (58−62%) when BSA and a catalytic amount of potassium acetate or potassium carbonate and 18-crown-6 were employed as reagents. However, and to our delight, the product *R*-**14** was formed in high enantiomeric excess (86%) and in excellent yield (97%) when cesium carbonate was employed as the base in this room temperature reaction. On decreasing the temperature to 12 °C a further improvement in the enantioselectivity of the reaction was observed (88% ee). The optimal reaction conditions involved performing this catalytic asymmetric reaction with cesium carbonate at 0 °C for 4 h. This afforded the product *R*-**14** in high enantiomeric excess (90%). A further decrease in the reaction temperature to −12 °C did not result in any further improvement of the enantioselectivity and the yield of this reaction was compromised.

To postulate a plausible mechanism for this highly enantioselective reaction (90% ee), a ^{31}P NMR study was undertaken. The corresponding cationic π-allyl palladium complex was prepared in deuterated dichloromethane by the reaction of (1,3-diphenylpropenyl)palladium(II) chloride dimer and the *P,N*-ligand **5c** (R = Ph) in the presence of silver tetrafluoroborate.[19,20] Examination of the ^{31}P NMR spectrum of this reaction mixture indicated the formation of two isomeric complexes in a ~2:1 ratio. These isomeric π-allyl intermediates were assigned as the *W*- and *M*-isomers (*W*-**5c** and *M*-**5c**), respectively (Figure 3).[21] Assuming that these intermediates are involved in the reaction of racemic 3-acetoxy-1,3-diphenyl-1-propene *RS*-**13** with the *P,N*-ligand **5c** (R = Ph) and allylpalladium(II) chloride dimer, the reaction pathway can be described by a Curtin−Hammett scheme.[22] Thus, the interconversion of these π-allyl intermediates must be rapid with respect to nucleophilic attack of the anion of dimethyl malonate.

It would be expected that nucleophilic attack of the anion of dimethyl malonate on these isomeric π-allyl intermediates *W*-**5c** and *M*-**5c** would be regioselective and

---

(16) A typical catalyst loading was employed in these asymmetric reactions; see refs 2 and 3b.

(17) Analytical chiral HPLC (Daicel Chiracel OD column) indicated that the enantiomeric purity of the *P,N*-ligands **5a**−**c** was greater than 99% ee. For a related class of chiral nonracemic *P,N*-ligands, see: Ito, K.; Kashiwagi, R.; Iwasaki, K.; Katsuki, T. *Synlett* **1999**, 1563.

(18) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905.

(19) (1,3-Diphenylpropenyl)palladium(II) chloride dimer was prepared from the corresponding propenyl chloride according to a literature procedure; see: Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301.

(20) Gilbertson, S. R.; Lan, P. *Org. Lett.* **2001**, *3*, 2237.

(21) This assignment was made on the basis of careful inspection of molecular models of the *M*- and *W*-isomers of the π-allyl intermediate. It was observed that the isomer *M*-**5c** was more sterically encumbered (and presumably less stable) than the corresponding isomer *W*-**5c**. This is due to the close proximity of the 1,3-diphenylallyl moiety and one of the phenyl rings on the acetal as indicated by the double-headed arrow (see Figure 3). It was not possible to make this assignment with ^1H NMR techniques. Of note, other isomers of π-allyl complexes are possible. However, *M*- and *W*-isomers are assumed to be the mechanistically relevant π-allyl intermediates; for discussion, see ref 3b.

(22) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

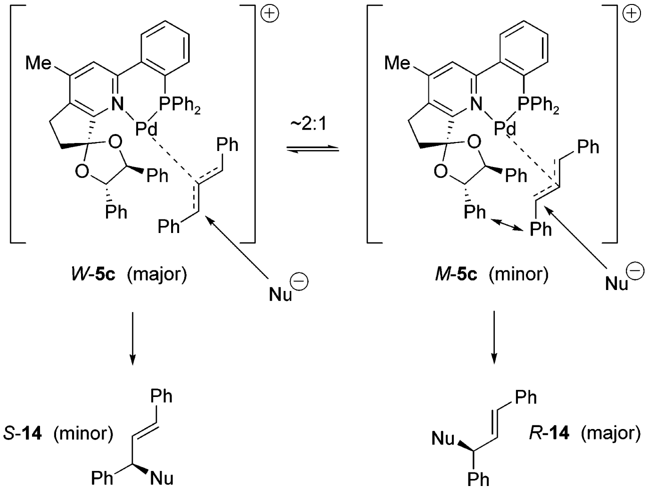


FIGURE 3. Isomeric *π*-allyl intermediates *W*-**5c** and *M*-**5c** and stereochemical rationale [Nu = $CH(CO_2Me)_2$].

occur trans to the phosphine moiety.[23] It also would be expected that the nucleophile would attack these *π*-allyl intermediates from the top face of the complex as indicated. This would be influenced by one of the phenyl substituents of the acetal moieties, which is positioned beneath the palladium *π*-allyl complexes. Thus, to account for the observed absolute stereochemistry of the major reaction product, (1*R*)-(1,3-diphenylallyl)malonic acid dimethyl ester *R*-**14**, we conclude that the *π*-allyl intermediate *M*-**5c** reacts at a faster rate with the anion of dimethyl malonate.[24] A related stereochemical interpretation has also been described recently by Helmchen and Pfaltz for a chiral *P*,*N*-ligand.[2b]

Conclusion

An efficient and modular synthesis of a series of chiral nonracemic *P*,*N*-ligands **5a**–**c** (R = Me, *i*-Pr, and Ph) has been achieved. These novel acetals were prepared from 2-chloro-4-methyl-6,7-dihydro-5*H*-[1]pyridine-7-one **6** and a series of chiral C_2-symmetric 1,2-diols **3**. The palladium-catalyzed asymmetric allylic substitution reaction of racemic 3-acetoxy-1,3-diphenyl-1-propene *RS*-**13** with dimethyl malonate was investigated. The *P*,*N*-ligand **5c** (R = Ph), derived from (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediol (**3c**: R = Ph), proved to be the most effective ligand and afforded the product (1*R*)-(1,3-diphenylallyl)malonic acid dimethyl ester **14** in high enantiomeric excess (up to 90%) and in good yield up to (97%). The optimal reaction conditions involved the use of 6.25 mol % of the chiral *P*,*N*-ligand, 2.5 mol % of allylpalladium(II) chloride dimer, and cesium carbonate (3 equiv) in dichloromethane at 0 °C. Current investigations are focused on the use of the *P*,*N*-ligands **5a**–**c** in other catalytic asymmetric processes.

Experimental Section

(7*RS*)-2-Chloro-4-methyl-6,7-dihydro-5*H*-[1]pyridine-7-ol (10). To a stirred solution of the acetate **9**[8,9] (2.00 g, 8.88 mmol) in tetrahydrofuran:water (3:1, 20 mL) was added lithium hydroxide monohydrate (1.49 g, 35.6 mmol) and the resultant solution was stirred at room temperature for 16 h. The reaction mixture was then diluted with water (15 mL) and extracted with chloroform (3 × 25 mL). The combined organic extracts were washed with brine (15 mL) and water (15 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford the crude product. Flash chromatography with hexanes:ether (1:1) as the eluant afforded the title compound **10** (1.37 g, 94%) as a white crystalline solid. Mp 100–102 °C, hexanes/ether; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99–2.16 (1H, m), 2.24 (3H, s), 2.47–2.57 (1H, m), 2.62–2.72 (1H, m), 2.92 (1H, ddd, J = 4.0, 8.9, 13.1 Hz), 3.82 (1H, broad s), 5.19 (1H, dd, J = 5.8, 7.3 Hz), 6.99 (1H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 18.8, 25.9, 32.5, 74.7, 124.0, 135.0, 147.6, 150.4, 164.8; IR (KBr) 3283 (broad), 1594, 1567, 1445, 1374, 1298, 1191, 1094, 1064, 1019, 965, 925, 888, 861 cm^{-1}; MS (CI) *m/z* (rel intensity) 184 (M + H, 100), 166 (20). Anal. Calcd for $C_9H_{10}ClNO$: C, 58.86; H, 5.49; N, 7.63. Found: C, 58.62; H, 5.62; N, 7.46.

2-Chloro-4-methyl-6,7-dihydro-5*H*-[1]pyridine-7-one (6). To a stirred solution of oxalyl chloride (57 μL, 0.65 mmol) in dichloromethane (6 mL) at −78 °C was added dimethyl sulfoxide (150 μL, 2.18 mmol) and the resultant solution was stirred for 10 min. A solution of the alcohol **10** (100 mg, 0.540 mmol) in dichloromethane (5 mL) was then added via a cannula over the course of 5 min. The reaction mixture was stirred for an additional 10 min and triethylamine (380 μL, 2.73 mmol) was then added and the reaction mixture was allowed to warm slowly to room temperature. The reaction mixture was then diluted with ether (30 mL) and washed with brine (3 × 5 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo to afford the crude product. Flash chromatography with hexanes:ether (1:1) as the eluant afforded the title compound **6** (89 mg, 90%) as a white crystalline solid. Mp 149–152 °C, hexanes/ether; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (3H, s), 2.69–2.78 (2H, m), 2.96–3.06 (2H, m), 7.26 (1H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 17.9, 22.1, 35.1, 128.7, 148.9, 149.6, 153.3, 153.8, 204.0; IR (KBr) 1714, 1587, 1439, 1421, 1285, 1256, 1203, 1112, 871, 570 cm^{-1}; MS (CI) *m/z* (rel intensity) 182 (M + H, 100). Anal. Calcd for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71. Found: C, 59.44; H, 4.44; N, 7.67.

2-Chloro-4-methyl-6,7-dihydro-5*H*-[1]pyridine-7-one (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediol Acetal (11c): Representative Procedure for the Preparation of Acetals (11a and 11b). To a stirred solution of the chloroketone **6** (100 mg, 0.550 mmol) in benzene (3 mL) was added (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediol **3c** (152 mg, 0.719 mmol) and *p*-toluenesulfonic acid monohydrate (16 mg, 0.083 mmol). The resultant solution was heated at reflux in a Dean–Stark apparatus for 16 h. The reaction mixture was then allowed to cool to room temperature and potassium carbonate (100 mg) was added. After an additional 10 min, the reaction mixture was filtered and the filter-cake was washed with ether (10 mL). The combined filtrates were concentrated in vacuo to afford the crude product. Flash chromatography with hexanes:ether (4:1) as the eluant afforded the title compound **11c** (163 mg, 79%) as a white foam/solid. Mp 44–46 °C; $[\alpha]^{20}_{D}$ −108 (*c* 0.38, chloroform); ^{1}H NMR (400 MHz, C_6D_6) δ 1.54 (3H, s), 2.26–2.32 (2H, m), 2.51–2.65 (2H, m), 4.99 (1H, d, J = 8.9 Hz), 5.99 (1H, d, J = 8.9 Hz), 6.68 (1H, s), 7.07–7.15 (4H, m), 7.18–7.29 (4H, m), 7.74–7.79 (2H, m); ^{13}C NMR (101 MHz, C_6D_6) δ 18.0, 24.1, 36.9, 87.1, 87.9, 115.7, 125.4, 127.8, 129.1, 129.2, 135.4, 137.5, 138.1, 147.7, 152.1, 162.9; IR (KBr) 2914, 2362, 2336, 1594, 1570, 1496, 1453, 1443, 1384, 1320, 1298, 1267, 1229, 1201, 1160, 1113, 1059, 1021, 939, 925, 879, 759, 699 cm^{-1}; MS (CI) *m/z* (rel intensity) 378 (M + H, 41), 271 (27), 182 (100). Anal. Calcd for $C_{23}H_{20}ClNO_2$: C, 73.11; H, 5.33; N, 3.71. Found: C, 72.96; H, 5.39; N, 3.78.

2-(2-Fluorophenyl)-4-methyl-6,7-dihydro-5*H*-[1]pyridine-7-one (1*S*,2*S*)-1,2-Diphenyl-1,2-ethanediol Acetal (12c): Representative Procedure for the Preparation of

---

[23] The strong trans-effect of the phosphine donor relative to the pyridine donor is well-established in related *P*,*N*-ligands; see ref 2.

[24] This stereochemical assumption was based on inspection of molecular models of the *M*- and *W*-isomer of the *π*-allyl intermediate as discussed earlier; see also footnote 21.

Aromatic Fluorides (12a and 12b). To a stirred solution of the acetal **11c** (351 mg, 0.926 mmol) and *o*-fluorophenylboronic acid (195 mg, 1.39 mmol) in degassed tetrahydrofuran (20 mL) was added tris(dibenzylideneacetone)dipalladium(II) (41.1 mg, 0.0463 mmol), tri-*tert*-butylphosphine (925 μL of a 0.10 M solution in tetrahydrofuran, 0.0925 mmol), and anhydrous cesium carbonate (1.51 g, 4.63 mmol). The resultant suspension was heated at reflux for 16 h. The reaction mixture was then allowed to cool to room temperature and was diluted with ethyl acetate (15 mL). The resultant solution was washed with brine (10 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford the crude product. Flash chromatography with hexanes:ether (8:1) as the eluant afforded the title compound **12c** (356 mg, 88%) as a white foam/solid. Mp 46−48 °C; $[\alpha]^{20}_{D}$ +119.1 (*c* 0.56, chloroform); ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.36 (3H, s), 2.64−2.79 (2H, m), 2.94−3.02 (2H, m), 4.87 (1H, d, $J = 8.6$ Hz), 5.72 (1H, d, $J = 8.6$ Hz), 7.14−7.21 (1H, m), 7.27−7.34 (9H, m), 7.35−7.42 (1H, m), 7.62−7.69 (3H, m), 8.12−8.17 (1H, m); ^{13}C NMR (101 MHz, CDCl$_3$) δ 41.8, 52.2, 55.4, 61.6, 75.8, 110.6, 120.9, 123.6, 127.9, 128.59, 128.62, 128.8, 128.9, 129.5, 129.9, 131.2, 134.3, 157.2, 157.9, 167.3; IR (KBr) 3061, 2904, 1654, 1598, 1541, 1455, 1377, 1347, 1320, 1275, 1241, 1211, 1176, 1154, 1099, 1060, 1019, 936, 884, 867, 818, 761 cm^{-1}; MS (CI) m/z (rel intensity) 438 (M + H, 25), 331 (6), 242 (100), 197 (19), 169 (11), 146 (8), 113 (22), 81 (59). Anal. Calcd for C$_{29}$H$_{24}$FNO$_2$: C, 79.61; H, 5.53; N, 3.20. Found: C, 79.90; H, 5.52; N, 3.41.

2-(2-Diphenylphosphanylphenyl)-4-methyl-6,7-dihydro-5*H*-[1]pyrindine-7-one (1*S*,2*S*)-1,2-Diphenyl-1,2-ethanediol Acetal (5c): Representative Procedure for the Preparation of *P*,*N*-Ligands (5a and 5b). To a stirred solution of potassium *tert*-butoxide (177 mg, 1.58 mmol) and 18-crown-6 (502 mg, 1.90 mmol) in tetrahydrofuran (12 mL) at 0 °C was added diphenylphosphine (294 mg, 1.58 mmol) and the resultant red solution was stirred for 1 h. A solution of the aromatic fluoride **12c** (346 mg, 0.790 mmol) in tetrahydrofuran (5 mL) was then added via a cannula and the resultant mixture was stirred at room temperature for 24 h. The reaction was quenched by the addition of methanol (5 mL) and concentrated in vacuo to afford the crude product. Flash chromatography with hexanes:ether (8:1) as the eluant afforded the title compound **5c** (302 mg, 63%) as a white crystalline solid. Mp 79−80 °C, hexanes:ether; $[\alpha]^{20}_{D}$ −129 (*c* 0.55, chloroform); ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.16 (3H, s), 2.55−2.75 (2H, m), 2.83−2.97 (2H, m), 4.75 (1H, d, $J = 8.7$ Hz), 5.38 (1H, d, $J = 8.7$ Hz), 7.04−7.06 (1H, m), 7.12−7.35 (20H, m), 7.47 (1H, m), 7.56−7.62 (2H, m), 7.73 (1H, ddd, $J = 1.1, 4.4, 7.6$ Hz); ^{13}C NMR (101 MHz, CDCl$_3$) δ 18.4, 24.3, 36.5, 85.5, 86.5, 115.7, 126.5, 126.6, 126.9, 128.2, 128.3, 128.49, 128.53, 128.6, 128.7, 128.9, 130.6, 130.7, 134.1, 134.2, 134.3, 134.4, 134.6, 135.0, 136.2, 136.4, 137.2, 137.3, 138.5, 138.65, 138.69, 138.8, 143.6, 147.4, 147.6, 159.2, 160.7; IR (KBr) 3452, 3052, 2923, 1655, 1600, 1585, 1495, 1477, 1453, 1376, 1346, 1319, 1277, 1177, 1156, 1102, 1073, 1059, 1021, 937, 923, 760, 746, 698 cm^{-1}; MS (MALDI-TOF) 605 (M + H). Anal. Calcd for C$_{41}$H$_{34}$NO$_2$P: C, 81.57; H, 5.68; N, 2.32. Found: C, 81.63; H, 5.72; N, 2.33.

General Procedures for Palladium(II)-Catalyzed Asymmetric Allylic Substitution Reactions: Asymmetric Synthesis of (1*R*)-(1,3-Diphenylallyl)malonic Acid Dimethyl Ester (*R*-14) and (1*S*)-(1,3-Diphenylallyl)malonic Acid Dimethyl Ester (*S*-14). A solution of allylpalladium(II) chloride dimer (3.7 mg, 0.010 mmol) and the chiral *P*,*N*-ligand **5a**−**c** (0.025 mmol) in dichloromethane (1.5 mL) was stirred at room temperature for 1 h. A solution of (3*RS*)-3-acetoxy-1,3-diphenyl-1-propene *RS*-**13** (100 mg, 0.400 mmol) and dimethyl malonate (208 mg, 1.20 mmol) in dichloromethane (1.5 mL) was then added via a cannula followed by one of three bases and associated reagents [(1) BSA (295 μL, 1.20 mmol) and a catalytic amount of potassium acetate (3.0 mg); (2) potassium carbonate (166 mg, 1.20 mmol) and 18-crown-6 (296 mg, 1.20 mmol); (3) anhydrous cesium carbonate (391 mg, 1.20 mmol)]. The reaction mixture was then stirred at the temperature specified (see Table 1) and was monitored by thin-layer chromatography until the starting material had been consumed (the reaction times varied from 2 to 24 h depending on the ligand and reagents employed). The reaction mixture was then diluted with ether (25 mL) and washed with a saturated aqueous solution of ammonium chloride (5 mL) and water (5 mL) before being dried over anhydrous magnesium sulfate and concentrated in vacuo to afford the crude product. Flash chromatography with hexanes:ether (3:1) as the eluant afforded the title compounds *R*-**14** or *S*-**14** as colorless oils. The enantiomeric purity of the reaction products was determined by analytical chiral HPLC, using a Daicel Chiracel OD column [hexanes:2-propanol (97:3), flow rate at 0.5 mL/min, detection at $\lambda = 245$ nm; $t_1 = 19.4$ min, $t_2 = 20.5$ min]. The absolute configuration of the reaction product was determined by comparing the sign of the optical rotation to literature values.[18] ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.53 (3H, s), 3.71 (3H, s), 3.96 (1H, d, $J = 10.7$ Hz), 4.27 (1H, dd, $J = 8.6, 11.0$ Hz), 6.33 (1H, dd, $J = 8.6, 15.9$ Hz), 6.48 (1H, d, $J = 15.9$ Hz), 7.17−7.35 (10H, m); ^{13}C NMR (101 MHz, CDCl$_3$) δ 49.2, 52.4, 52.6, 57.6, 126.4, 127.2, 127.6, 127.9, 128.5, 128.7, 129.1, 131.8, 136.8, 140.2, 167.8, 168.2; IR (KBr) 1759, 1733, 1600, 1494, 1433, 1321, 1261, 1141, 1020, 968, 921, 803, 766, 745, 700 cm^{-1}; MS (CI) m/z (rel intensity) 324 (M + H, 3), 235 (10), 193 (100).

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC) and Simon Fraser University (SFU) for financial support. In addition, the authors wish to acknowledge the Canadian Foundation for Innovation (CFI) for support of our research program. M.P.A.L. thanks SFU for graduate research fellowships and an entrance scholarship. A.A.N. also thanks SFU for graduate research fellowships. We are grateful to Mrs. Marcy Tracey for assistance with the ^{31}P NMR studies.

Supporting Information Available: Detailed experimental procedures and complete product characterization data for all of the additional new compounds synthesized (**5a**, **5b**, **11a**, **11b**, **12a,** and **12b**), as well as ^{1}H and ^{13}C NMR spectra for compounds **5a**−**c**, **6**, **10**, **11a**−**c**, and **12a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0494275