611 (100).

Seco-C_2BI-Indole$_2$ (39). A mixture of crude **28** freshly prepared from **25** (8.0 mg, 21 μmol), EDCI (12 mg, 63 μmol, 3 equiv), and **32**[17] (8.6 mg, 27 μmol, 1.3 equiv) in DMF (0.43 mL) was stirred under Ar at 23 °C for 14 h. Flash chromatography (0.5 × 5 cm SiO_2, 0–100% DMF–EtOAc gradient elution) afforded **39** (8.1 mg, 68%) as a yellow solid: mp >240 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.22 (b s, 1 H, NH), 8.89 (b s, 1 H, NH), 8.73 (b s, 1 H, NH), 7.69 (s, 1 H), 7.59 (d, 1 H, J = 9 Hz, C6-H), 7.44 (d, 1 H, J = 9 Hz, C9-H), 7.26 (s, 1 H), 6.92 (m, 5 H), 6.53 (m, 4 H), 6.37 (t, 1 H, J = 8 Hz), 4.16 (s, 2 H, C2-H_2), 3.80 (d, 2 H, J = 12 Hz, CH_2Cl), 3.70 (d, 2 H, J = 12 Hz, CH_2Cl); IR (solid film) ν_{max} 3242, 2917, 1646, 1644, 1592, 1558, 1542, 1521, 1396, 1313, 1246, 1017, 950, 892 cm^{-1}; FABMS (NBA) m/e (relative intensity) 583 (M + H$^+$, 47), 416 (100); FABHRMS m/e 583.1344 ($C_{32}H_{24}Cl_2N_4O_3$ + H$^+$ requires 583.1304).

C_2BI-Indole$_2$ (40). A suspension of NaH (60%, 0.24 mg, 10 μmol, 3 equiv) in THF (0.25 mL) at 0 °C under Ar was treated with a solution of **39** (2 mg, 3.4 μmol) in DMF (0.25 mL) and stirred for 1 h at 0 °C. The solvent was removed in vacuo, and PCTLC (1 mm × 2 cm SiO_2, 0–100% EtOAc–hexane gradient elution) afforded **40** (0.9 mg, 47%, 47–75%) as a yellow solid: mp >240 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.69 (b s, 1 H, NH), 10.15 (b s, 1 H, NH), 10.05 (b s, 1 H, NH), 8.28 (d, 1 H, J = 8 Hz, C5-H), 8.17 (s, 1 H, C1′-H), 7.79 (t, 1 H, J = 8 Hz, C6-H), 7.66 (m, 2 H), 7.58 (d, 1 H, J = 8 Hz, C3′-H), 7.45 (t, 2 H, J = 8 Hz), 7.36 (d, 1 H, J = 7 Hz), 7.35 (s, 1 H), 7.18 (t, 1 H, J = 8 Hz), 7.05 (t, 1 H, J = 7 Hz), 7.03 (s, 1 H), 6.32 (d, 1 H, J = 9 Hz), 4.18 (d, 1 H, J = 12 Hz, C*H*HCl), 3.89 (m, 3 H, CH*H*Cl and Cl-H_2), 2.33 (d, 1 H, J = 4 Hz, C9-H), 2.25 (d, 1 H, J = 4 Hz, C9-H); IR (solid film) ν_{max} 3268, 2933, 1641, 1621, 1587, 1548, 1410, 1312, 1244, 1145, 1012, 806, 747 cm^{-1}; FABHRMS (NBA) m/e 547.1060 ($C_{32}H_{23}ClN_4O_3$ + H$^+$ requires 547.1537).

Aqueous Solvolytic Reactivity of *N*-BOC-C_2BI (26) and C_2BI (27). *N*-BOC-C_2BI (**26**, 110 μg) was dissolved in CH_3OH (1.5 mL). The CH_3OH solution was mixed with aqueous buffer (pH = 3, 1.5 mL). The buffer contained 4:1:20 (v/v/v) of 0.1 M citric acid, 0.2 M Na_2HPO_4, and H_2O, respectively. After mixing, the solvolysis solutions were stoppered and kept at 22–23 °C in the dark. The UV spectrum of the solution was measured twice in the first day and then every 24 h for 2 months. The UV monitoring was continued until no further change was detectable. The long-wavelength absorption at 314 nm and the short-wavelength absorption at 256 nm were monitored. The solvolysis rates were calculated from the data taken at 256 nm from the least square treatment (r = 1.000) of the slopes of plots of time versus $1 - [(A - A_{initial})/(A_{final} - A_{initial})]$. For **26**, $k = (4.40 \pm 0.08) \times 10^{-7}$ s^{-1} ($t_{1/2}$ = 443 h).

C_2BI (**27**, 50 μg) was dissolved in CH_3OH (1.5 mL) and mixed with buffer (1.5 mL, pH = 3). The buffer contained 4:1:20 (v/v/v) of 0.1 M citric acid, 0.2 M Na_2HPO_4, and H_2O, respectively. No significant change in the UV spectrum was detected when monitored over one week, A = 0.52. Monitoring of the solution every 24 h over 3.5 months and extrapolating to an approximate final 337-nm absorption of 0.183 permitted an estimation of the solvolysis rate for **27**. Least squares treatment (r = 0.99) of the slopes of the plots of time versus $1 - [(A - A_{initial})/(A_{final} - A_{initial})]$ provided an estimate of $k = (8.46 \pm 0.06) \times 10^{-8}$ s^{-1} ($t_{1/2}$ = 2275 h, 95 days).

Treatment of 23 with 3 M HCl–EtOAc. A solution of **23** (2 mg, 5.8 μmol) in 3 M HCl–EtOAc (1 mL) was stirred for 1 h at 0 °C. The reaction mixture was concentrated under a stream of N_2. Flash chromatography (0.5 × 2 cm, 5% EtOAc–hexane) afforded **22** (1.9 mg, 2.2 mg theoretical, 86%) as the only detectable reaction product as a white solid identical in all respects with authentic material. Similar results were obtained when the reaction was conducted at −78 °C.

DNA Alkylation and Cross-Linking Studies. General procedures, the preparation of singly 5′ end-labeled double-stranded DNA, the agent binding studies, gel electrophoresis, and autoradiography were conducted following procedures described in full detail elsewhere.[19b] The cross-linking reactions were conducted under identical conditions with the exception that the thermal cleavage step (30 min, 100 °C) was omitted. Psoralen (10^{-1}, 10^{-2}, and 10^{-3} M) was run as a positive control with cross-linking induced by irradiation at 365 nm for 1 h.

Acknowledgment. This work was assisted through the financial support of the National Institutes of Health (Grants CA41986 and CA55276). We thank Hamideh Zarrinmayeh and Doug Johnson for Figures 3 and 4.

Supplementary Material Available: Experimental details and spectroscopic characterization of **8–13** and a table of representative results of the study of the Wittig reaction of **9** and **17** (5 pages). Ordering information is given on any current masthead page.

A Modular Approach for Ligand Design for Asymmetric Allylic Alkylations via Enantioselective Palladium-Catalyzed Ionizations

Barry M. Trost,* David L. Van Vranken, and Carsten Bingel

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305-5080. *Received January 29, 1992*

Abstract: A new class of ligands for asymmetric transition metal catalysis based on 2-(diphenylphosphino)benzoic acid was used in a mechanistically-defined palladium-catalyzed reaction in which enantiodifferentiation was the result of selective ionization of substrates derived from *cis*-2-cycloalkene-1,4-diols. By making rational, stepwise changes in the ligand structure, the structural requirements for good asymmetric induction were probed. The absolute stereochemistry of the products was found to be related to the chirality of the ligand in a predictable fashion. A mnemonic is given which allows one to predict the mode of ionization (*R* or *S*) solely on the basis of the stereochemistry of the variable chiral linker used to make the ligand.

Transition metal-catalyzed allylations have emerged as extremely versatile and powerful reactions; unfortunately they have been intransigent in succumbing to efforts at making them broadly applicable enantioselective processes.[1-3] The source of the difficulty lies in the spatial relationships of the bond breaking and making of the metal and its attendant ligands. Figure 1 shows the general mechanism for a palladium-catalyzed allylation reaction with a soft nucleophile. The basic catalytic cycle consists of metal–olefin complexation, ionization, alkylation, and decom-

(1) For some elegant exceptions: (a) Mackenzie, P. B.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2046. (b) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033.

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(3) Consiglio, G.; Waymouth, R. *Chem. Rev.* **1989**, *89*, 257.

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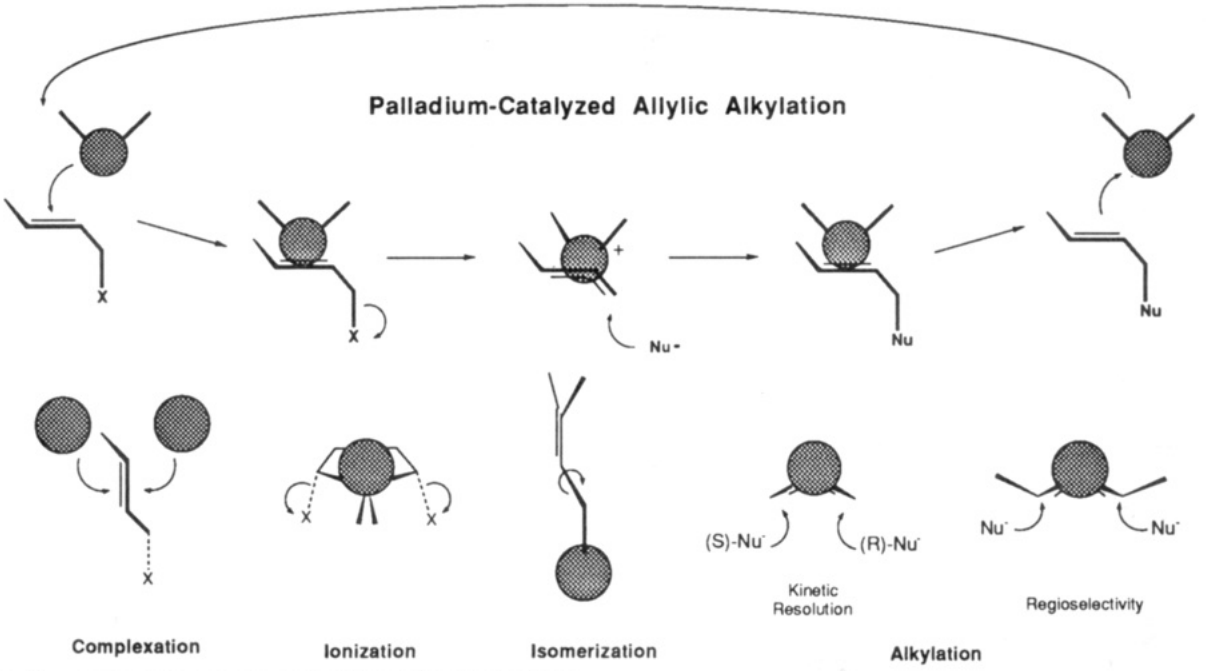
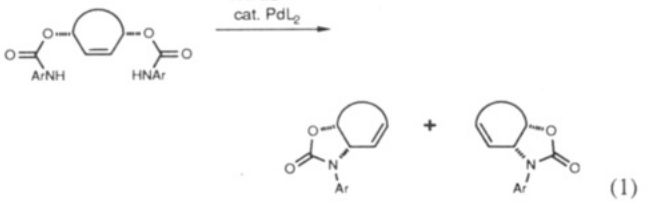


Figure 1. Enantiodiscrimination at various states of the catalytic cycle.

plexation. In order to achieve asymmetric induction, the asymmetric environment of the ligands must be felt on the opposite face of the π-allyl unit where bond breaking and making are occurring. The distal nature of the ligands from the sites of bond changes (see Figure 1) differentiates allylic alkylation from the highly successful asymmetric transfer of oxygen and hydrogen.[4-8] With the exception of decomplexation, each step in the catalytic cycle of allylic alkylation provides the opportunity for enantiodiscrimination (Figure 1). It is often difficult to determine which of these steps makes the greatest contribution to the resulting enantioselectivity and even more difficult to determine the specific interactions which are responsible for selectivity at each step. Although asymmetric palladium catalysis has been the focus of many stochastic investigations, most of these studies have utilized reactions which leave the origin of enantioselection as a matter of speculation at best.[1]

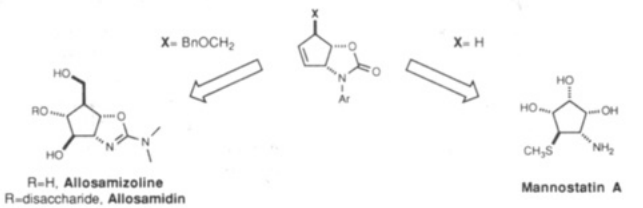
Our development of a highly effective synthesis of oxazolidinones from vinyl epoxides via a palladium-catalyzed reaction provided a new venue for our continued interest in asymmetric transition metal catalysis.[2,9] The extension of this reaction to prochiral substrates (eq 1) provides a convenient system for the



(1)

development and study of asymmetric ligands for transition metal catalysis.[10] Our interest is heightened by our use of this methodology to develop a flexible strategy toward glycosidase inhibitors containing cis hydroxy amino functionality on five-membered rings (Scheme I).[11] Furthermore, since the enantiodiscrimination occurs in the initial ionization, the results should be applicable to a broad range of palladium-catalyzed intermolecular as well as other intramolecular processes.

Scheme I. Oxazolidin-2-ones as Intermediates toward Glycosidase Inhibitors



This reaction of cyclic bis-carbamates is of particular interest not only because of its synthetic potential but also because it is mechanistically defined with respect to the origin of enantioselection (see Scheme II). The enantiodetermining step (ionization) occurs early in the catalytic cycle; once set, the enantiomorphology of the substrate is not changed by subsequent steps.[12] Other features which make this reaction suitable for study of asymmetric palladium catalysis include: (1) only palladium–olefin complexation anti to the leaving groups will lead to product; (2) diastereoface inversion of the metallophosphine moiety (via a change in hapticity) is prevented by the ring; (3) the nucleophile is intramolecular and has a defined trajectory; (4) only one regioisomeric product is possible; (5) the uncatalyzed reaction does not compete with the catalyzed reaction; and (6) there are no competing side reactions.

Such asymmetric induction should not be limited to cyclizations since the enantiodiscriminating step is the ionization of the prochiral leaving groups. Thus, the same ligands should extend to asymmetric induction in allylic alkylations according to Scheme III. In this case, the problem that can be anticipated is double alkylation since the initial product still is a potential substrate for

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(5) Cf. Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063.
(6) Cf. Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1990**, *56*, 4585.
(7) For some reviews, see: Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345. Kagan, H. N. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 1. Koenig, K. E. *Ibid.*, Chapter 3. Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106.
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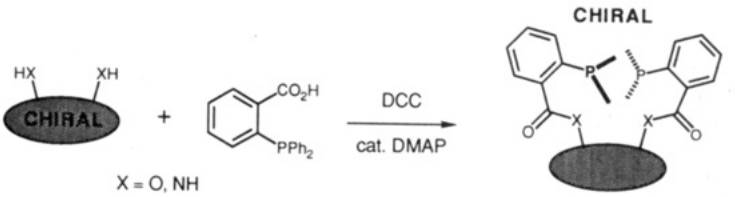
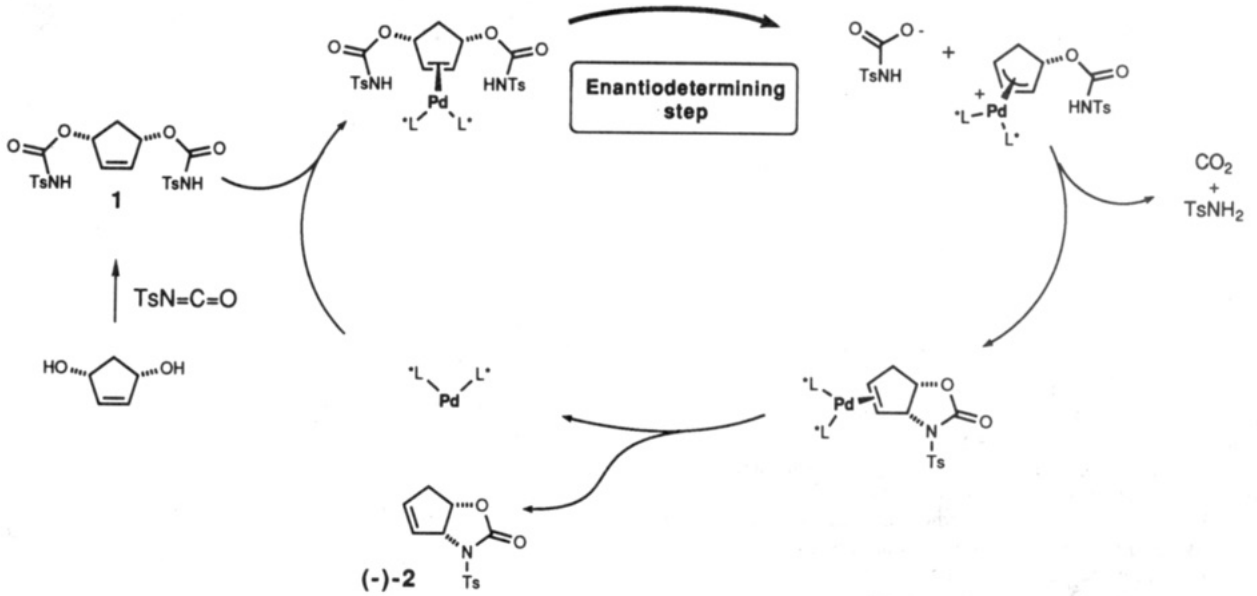
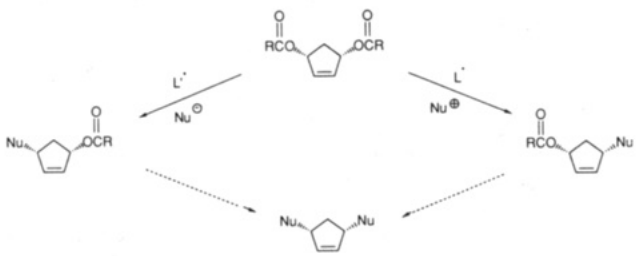


Figure 2. Simple strategy for preparing phosphine ligands from chiral alcohols and amines.

Scheme II. Asymmetric Induction in a Pd-Catalyzed Oxazolidin-2-one Synthesis



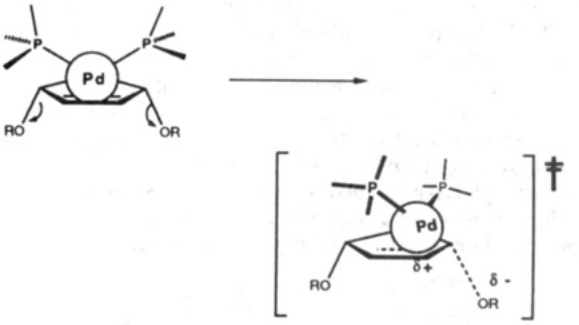
Scheme III. Asymmetric Induction in a Pd-Catalyzed Intermolecular Alkylation



the Pd catalyst. However, such over-reaction should be less of a problem with scalemic ligands that show high ee than with achiral ones since the factors that favor high ee in the initial alkylation should disfavor the required ionization for the second alkylation.

Results

The oxazolidinone-forming reaction was easily carried out by preparing the bis-carbamate substrate in situ. *cis*-Cyclopent-2-ene-1,4-diol in THF was treated with 2.05 equiv of *p*-toluenesulfonyl isocyanate to give the bis-carbamate in an exothermic reaction.[13,14] The bis-carbamate solution was then added to a solution of 5 mol % catalyst, prepared by stirring a mixture of ligand and tris(dibenzylideneacetone)dipalladium–chloroform complex in THF. Only moderate enantiomeric excesses were observed with the commonly used asymmetric ligands BINAPO[2] and the bis(diphenylphosphino)ferrocenylamines[15] (BINAP and DIOP gave no reaction). As pointed out, part of the difficulty encountered in achieving asymmetric induction using chiral ligands in palladium-catalyzed ionizations or alkylations with soft nucleophiles results from the fact that bond breaking/bond formation occurs on the face of the allylic moiety which is opposite that of the chiral metallophosphine moiety (eq 2).[16]



(2)

Chiral Ligands Derived from 2-(Diphenylphosphino)benzoic Acid. 1. Chiral Salt Ligands. To improve the enantioselectivity in the reaction and provide a better understanding of the requirements for good asymmetric induction, we sought a ligand design which would provide simple and flexible preparation—criteria not met by the commonly used chiral phosphine ligands. Factoring the chiral ligand into segments corresponding to a metal

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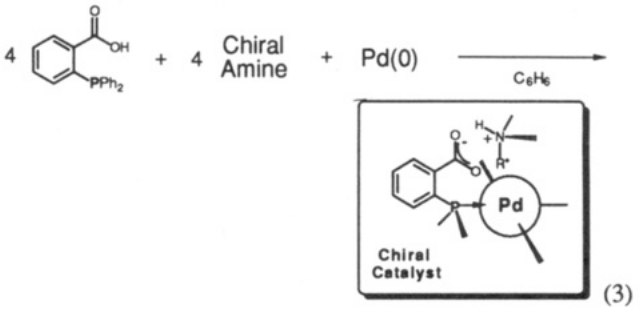
(15) Hayashi, T. Personal communication.

(16) While excellent results have been obtained with 1,3-diarylallyl substrates, such reactions are of only marginal synthetic utility. See ref 2 and (a) Hayashi, T. *Pure Appl. Chem.* **1988**, *60*, 7. (b) Yamaguchi, M.; Shima, T.; Yamagishi, T.; Hida, M. *Tetrahedron: Asymmetry* **1991**, *2*, 663. (c) Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232.
(17) (a) Hoots, J. E.; Rauchfuss, T. B.; Wrobleski, D. A. *Inorg. Synth.* **1982**, *21*, 178. (b) Rauchfuss, T. B. *J. Organomet. Chem.* **1978**, *162*, C19–C22. (c) Jeffrey, J. C.; Rauchfuss, T. B.; Tucker, P. A. *Inorg. Chem.* **1980**, *19*, 3306. (d) Hoots, J. E.; Rauchfuss, T. B.; Schmidt, S. P.; Jeffrey, J. C.; Tucker, P. A. Metal Complexes of Iminophosphine and Iminoarsine Chelating Agents. *Catalytic Aspects of Metal Phosphine Complexes. Adv. Chem. Series, 196*; American Chemical Society: Washington, DC, 1982; Chapter 19, pp 303–311. (e) Rauchfuss, T. B. Functionalized Tertiary Phosphines and Related Ligands in Organometallic Coordination Chemistry and Catalysis. In *Homogeneous Catalysis with Metal Phosphine Complexes*. L. H. Pignolet, Ed.; Plenum Press: NY, 1984; pp 239–256.

binding site and a chiral skeleton or scaffold simplifies the synthesis provided that these two units can be joined by a simple chemical reaction. The ready availability of 2-(diphenylphosphino)benzoic acid (2-DPPBA) as a binding post suggests a strategy for a simple modular design. By examining the effects of stepwise changes in the metallophosphine moiety, we hoped to develop an understanding of the structural requirements of an efficient chiral ligand design for this enantioselective ionization. Our initial approach was to form chiral salt ligands by the addition of chiral amines to 2-DPPBA. Chiral catalysts were prepared in situ by mixing 4 equiv of chiral amine, 4 equiv of 2-DPPBA, and 1 equiv of palladium(0) (as tris(dibenzylideneacetone)dipalladium–chloroform complex) in benzene (eq 3). With chiral amines such as

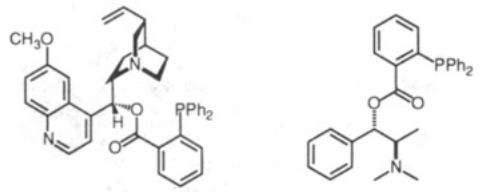


(3)

(−)-nicotine, (+)-sparteine, (+)-Darvon alcohol, and the cinchona alkaloids the enantiomeric excesses in the oxazolidinone-forming reaction (Scheme II) were low (1–8%).[18]

2. Chiral Ester Ligands. The ultimate goal in this and all such systems is to restrict the system to one and only one transition state, thus assuring only a single product (enantiomer). Our means of limiting the number of available transition states in the enantiodetermining step is to restrict the number of degrees of freedom in the phosphine–metal substrate complex. To reduce the number of degrees of freedom in the chiral complexes, we turned from ionic salt linkages to the corresponding covalent ester linkages. We envisioned a modular ligand synthesis based on the preparation of esters (and ultimately amides) with 2-DPPBA (Figure 2).[19] The ready availability of both chiral amines and alcohols makes this approach extremely attractive.

As a simple test of the feasibility of this ligand design we prepared phosphine ligands from chiral alcohols lacking C_2 symmetry and applied them to the palladium-catalyzed reaction in eq 3. (−)-Quinine, (+)-*N*-methylephedrine, and (+)-*threo*-2-amino-1-phenyl-1,3-propanediol were acylated with 2-(diphenylphosphino)benzoic acid using DCC to give the corresponding chiral ligands **3**–**5**. In all cases, enantiomeric excesses



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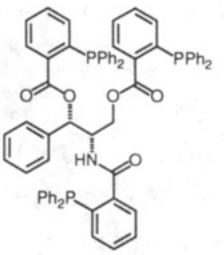

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(18) (−)-Quinine gave (+)-**2** in 8.2% ee. (+)-Quinidine gave (−)-**2** in 8.2% ee.

(19) For a preliminary report of a portion of this work see Trost, B. M.; Van Vranken, D. L. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 228.

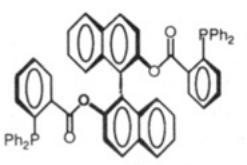
Figure 3. Degree of rotational freedom of mono- and bidentate ligands.

Figure 4. Two possible diastereomeric complexes of bidentate ligand.

Figure 5. Two ways to favor one diastereomeric complex. Left, a ligand with a third binding site. Right, a C_2-symmetrical ligand.

were low. The poor enantioselectivities obtained with ligands **3** and **4** may be attributed to their monodentate nature. The chiral phosphines may rotate freely about the phosphorus–palladium bond without a defined orientation (Figure 3A). The infinite number of rotational states thus allow for an infinite number of competing transition states. To prevent independent ligand rotation, one can connect the two phosphines with a tether (Figure 3B). There is still, however, an additional degree of freedom characteristic of square planar metal–olefin complexes in that two different diastereomeric complexes are possible (Figure 4) which differ only with respect to rotation of the substrate with respect to palladium as in ligand **5**. These may interconvert through either dissociation/reassociation or simple olefin rotation. Two potential solutions to this problem are shown in Figure 5. Placing a third binding group on the ligand may inhibit one of the diastereomeric complexes from forming and reacting. Alternatively, a C_2-symmetrical ligand can form only one complex since a 180° rotation of the metallophosphine moiety is an identity operation.

The importance of C_2 symmetry may be easily tested by preparing ligands from C_2-symmetrical diols. (*S*)-(−)-1,1′-Binaphthol, (−)-1,3:4,6-di-*O*-benzylidene-D-mannitol, and (+)-1,2:5,6-di-*O*-isopropylidene-D-mannitol were acylated with 2-(diphenylphosphino)benzoic acid to give ligands **6**–**8**. The immediate



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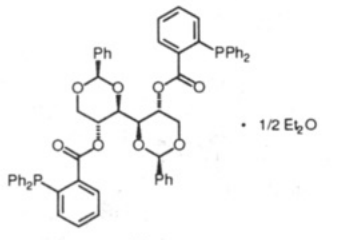

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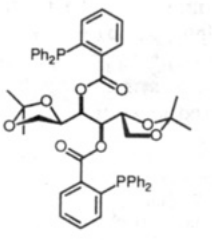

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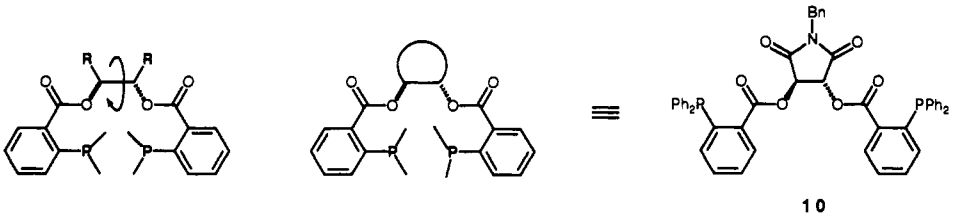
Table I. Catalysis Using Chiral 2-(Diphenylphosphino)benzoate Esters and Amides as Ligands[a]

ligand	mmol substrate	concn (M)	equiv ligand	time (h)	temp (°C)	yield (%)	$[\alpha]_D$ (deg)	c (CH_2Cl_2)	% ee[b]
(+)-**3**	0.220	0.5	0.20	3	−8 to 12	48	−20.8 (±0.1)	3.12	14.8
(+)-**4**	0.150	0.3	0.19	2	−8 to 5	77	−13.7 (±0.3)	3.22	9.7
(−)-**5**	0.174	0.4	0.05	9	−8 to 20	81	−7.3 (±0.2)	3.91	5.2
(+)-**6**	0.168	0.4	0.075	5	rt[d]	87	−56.9 (±0.2)	3.05	40.4
(−)-**7**	0.172	0.6	0.10	8	0 to rt	98	+86.2 (±0.3)	2.40	61.1
(+)-**8**	0.178	0.5	0.075	9	−8 to 20	100	+90.7 (±0.1)	2.49	64.3
(−)-**9**	0.277	0.5	0.075	1	0	100	+83.9 (±0.3)	3.90	59.5
(+)-**10**	0.297	0.4	0.075	2	0 to 5	68	−105.9 (±0.3)	2.82	75.1
(−)-**11**	0.374	0.5	0.075	1	0	97	+112.6 (±0.3)	3.12	79.9
(+)-**11**	0.306	0.5	0.075	0.25	0	91	−111.9 (±0.1)	3.85	79.4
(−)-**11**[c]	1.703	0.5	0.045	0.8	−78	96	+113.6 (±0.3)	2.52	80.6
(+)-**12**	0.374	0.5	0.075	1.5	0 to 5	97	+110.0 (±0.7)	0.99	78.0
(+)-**13**	0.510	0.5	0.094	0.33	0	94	−124.2 (±0.1)	3.41	88.1

[a] Reactions were run with 0.05 equiv of Pd(0) in THF. [b] Enantiomeric excess was determined by comparison with $[\alpha]_D = 141°$ (*c* 2.52, CH_2Cl_2) calculated for the homochiral oxazolidinone **2**. [c] Reaction was run with 0.03 equiv of palladium. [d] Room temperature.

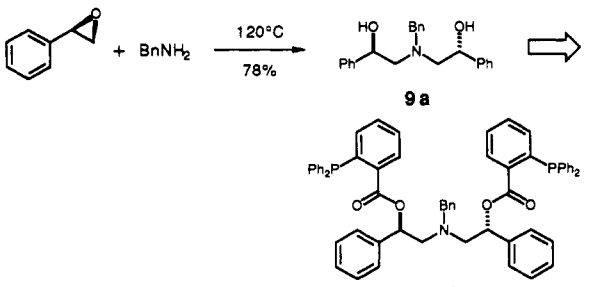


10

Figure 6. Tying the diol into a ring.

improvement in enantioselectivity observed in the reaction in Scheme II with these bidentate ligands (see Table I) is attributable to removing the extra degrees of freedom from the palladium–olefin complex.[20]

As a rudimentary test for the effect of a third binding site, we prepared a diol with an amine in a central location. Benzylamine was reacted with excess (1*R*)-phenyloxirane to afford the C_2-symmetrical amino diol **9a** (eq 4). The diester ligand **9** prepared

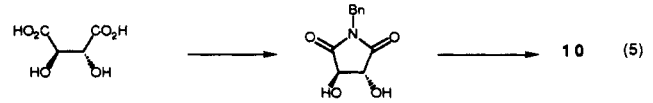


9a

9 (4)

from this diol gave oxazolidinone with an ee of 60%. While we could not test the ability of the nitrogen to chelate to the palladium during the ionization process, the enantioselectivity seems rather high to attribute to a flexible 1,5-diester ligand with no extra chelating properties.

To further improve the enantioselectivity, we next turned to restricting the rotational freedom within the ligand itself. An improvement on the design of ligands **6–9** is to tie the diol into a ring to prevent rotation between the chiral centers (Figure 6). *N*-Benzyltartrimide, easily available in one step by condensation of tartaric acid with benzyl amine, served effectively as the rigid diol for preparation of ligand **10** (eq 5).[21] This change in ligand structure increases the enantiomeric excess to 75%.



10 (5)

3. Chiral Amide Ligands. An additional source of rotational freedom associated with the ester ligand may result from rotation

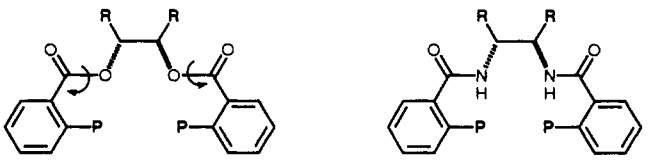
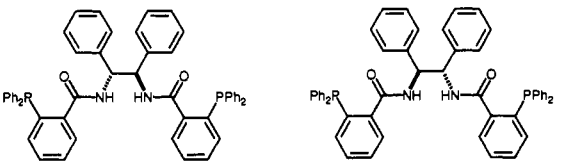
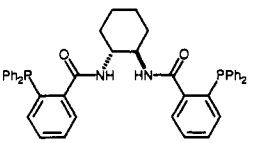


Figure 7. Corresponding amides having restricted rotation.

about the acyl–oxygen bond. We may rigidify this linkage by going to the analogous amide linkage (Figure 7) as in ligands **11** and **12** from the corresponding readily available enantiomerically pure diamines.[22] This change in ligand structure again leads to



(-)-**11** (+)-**11**



12

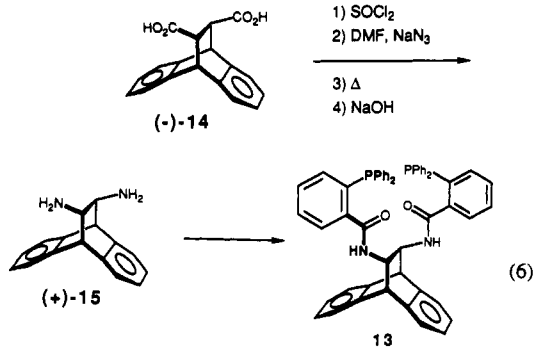
an increase in the enantiomeric excesses achieved in the palladium-catalyzed reaction. The combination of C_2 symmetry and restricted rotation results in enantiomeric excesses of over 80% (see Table I). The enantiopodal ligands derived from 1,2-diphenylethanediamine led to products of equal and opposite rotation.

Our final improvement of the ligand structure was aimed at increasing the dihedral angle of the N–C–C–N linkage (Figure 8). Conceptually, such a change may restrict the number of conformers which allow the phosphines to chelate the metal in

(20) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.
(21) Wong, C. M.; Buccini, J.; TeRaa, J. *Can. J. Chem.* **1968**, *46*, 3091.
(22) (a) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493. (b) Saigo, K.; Kubota, N.; Takebayashi, S.; Hasegawa, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 931.

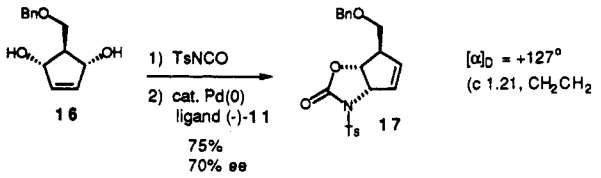
Figure 8. Increasing the dihedral angle.

a bidentate fashion.[23] We obtained the rigid diamine by a Curtius degradation of the known (−)-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid ((−)-**14**) (eq 6).[24] Gratifyingly, the ligand derived from this diamine brought the enantiomeric excess to 88%.

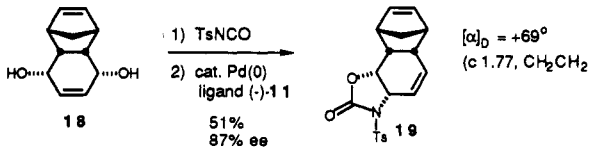


The simple ligand design strategy used here has allowed the facile preparation of a wide range of stable chiral phosphine ligands from readily available chiral alcohols and amines. Table I summarizes the application of these ligands to the reaction of Scheme II. Using this strategy, we have demonstrated the importance of limiting specific degrees of freedom in the chiral catalyst as a means of limiting the number of competing transition states which lead to enantiopodal products—an approach which extends beyond the scope of this study to all reactions involving asymmetric induction.

A brief examination of the applicability of this reaction for the asymmetric synthesis of oxazolidin-2-ones from the other *meso*-2-ene-1,4-diols was pursued. Equation 7 reveals that incorporation



of a substituent on the same face of the olefin to which the palladium must coordinate, as in **16**,[11a,25] causes a slight decrease in the ee of the oxazolidin-2-one **17** (cf. 81% for (−)-**11** in eq 3). On the other hand, use of the conformationally more well-defined six-membered ring system **18**[26] effects a significant enhancement of the ee (eq 8).



Determination of Optical Yields and Absolute Stereochemistry. The optical yields and absolute stereochemistries of the oxazolidinones were determined by diastereomeric derivatization with

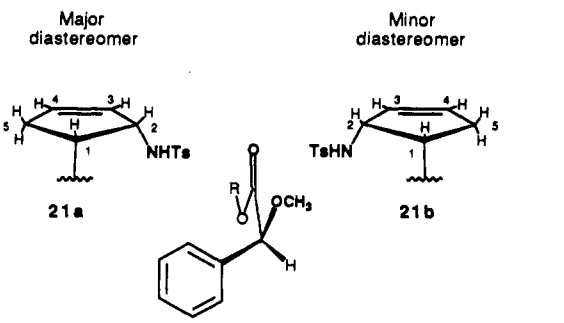
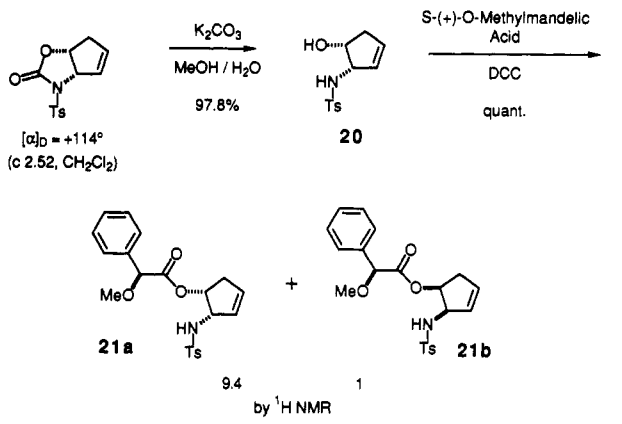


Figure 9. Determination of absolute stereochemistry of oxazolidin-2-one **2**.

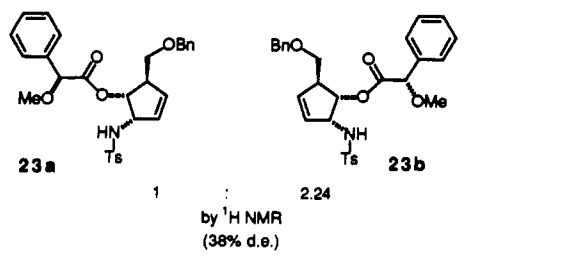
Scheme IV. Determination of Enantiomeric Excess of Oxazolidin-2-one **2**



(*S*)-(+)-α-methoxyphenylacetic acid.[27] Optical purity in subsequent reactions was based upon comparison of the optical rotation with that derived from these studies. Oxazolidinone **2** from the palladium-catalyzed reaction with ligand (−)-**11** was hydrolyzed to give **20** and acylated with (*S*)-(+)-α-methoxyphenylacetic acid to give a mixture of diastereomers **21a** and **21b** (Scheme IV). ^{1}H NMR integration of the signals from H-2, H-3, and H-4 showed a 9.4:1.0 ratio of diastereomers leading to a value of $[\alpha]_D$ = 141° (*c* 2.52, CH_2Cl_2) for the parent oxazolidinone. Enantiomeric excesses were based upon comparison with this value.

The absolute stereochemistry of the major and minor diastereomers were determined from the differential shielding effects of the α-methoxyphenylacetate group observed in the ^{1}H NMR (Figure 9). In isomer **21a**, olefinic protons H-3 (δ 5.68) and H-4 (δ 5.48) are shifted upfield by about 0.1 ppm relative to **21b** (δ 5.78 and 5.57, respectively). In isomer **21b**, proton H-2, α to the sulfonamide (δ 4.38), is shifted upfield by 0.1 ppm relative to **21a** (δ 4.49).

Oxazolidinone **17** was hydrolyzed (K_2CO_3, MeOH, H_2O, 93%) and subjected to acylation using the Stadler esterification[28] procedure to produce a mixture of diastereomers in a 2.24:1 ratio



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(24) (a) Brienne, M.-J.; Jacques, *J. Bull. Soc. Chim. Fr.* **1973**, 190. (b) Hagashita, S.; Kuriyama, K. *Tetrahedron* **1972**, *28*, 1435.

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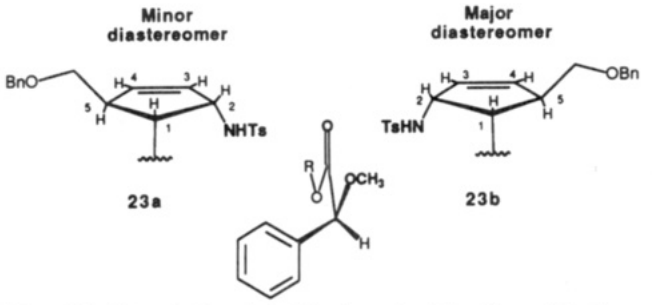


Figure 10. Determination of absolute stereochemistry of oxazolidin-2-one **17**.

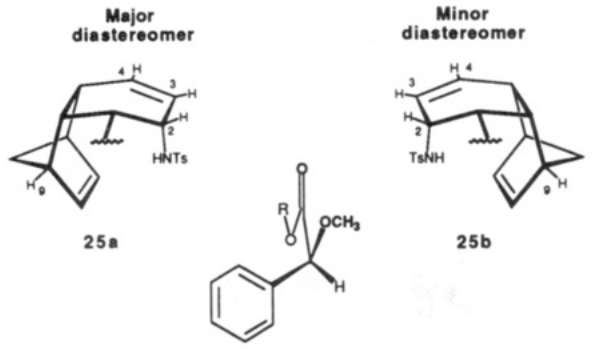
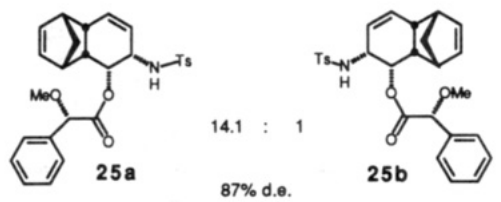


Figure 11. Determination of absolute stereochemistry of oxazolidin-2-one **19**.

(^{1}H NMR). This leads to a value of $[\alpha]_D = 181°$ (c 1.1, CH_2Cl_2) for the homochiral oxazolidinone **17**.

As for **21**, the absolute stereochemistry of the major and minor isomers **23a** and **23b** was determined by the differential shielding effects of the (*S*)-(+)-α-methoxyphenylacetate group (Figure 10). In the minor diastereomer **23a**, H-3 (δ 5.69), H-4 (δ 5.54), and H-5 (δ 2.62) are shifted upfield relative to H-3 (δ 5.74), H-4 (δ 5.63), and H-5 (δ 2.80) in the major diastereomer **23b**. In the major diastereomer **23b**, H-2 (δ 4.45) is shifted upfield relative to H-2 (δ 4.55) in **23a**.

The sequence of hydrolysis (quantitative) and DCC-promoted esterification (quantitative) with (*S*)-*O*-methylmandelic acid similar to that in Scheme IV was carried out with the tetracyclic oxazolidinone **19** (prepared using ligand **13**) to give a mixture of diastereomeric esters **25a** and **25b** in 87% diastereomeric excess



(14.1:1 diastereomer ratio), suggesting an optical purity of 87% for the original scalemic oxazolidinone **19**.

The absolute stereochemistry of oxazolidinones **19** was also determined from the differential shielding effects of (*S*)-(+)-α-methoxyphenylacetate derivatives **25a** and **25b** (Figure 11). In the major diastereomer **25a**, H-9 (δ 2.22) is shifted upfield relative to H-9 (δ 2.97) in the minor diastereomer **25b**. In the minor diastereomer **25b**, H-2 (δ 3.81) and H-3 (δ 4.99) are shifted upfield relative to H-2 (δ 3.89) and H-3 (δ 5.09) in **25a**.

Predicting the Enantioselective Ionization. Once a range of ligands derived from 2-(diphenylphosphino)benzoic acid had been tested, a pattern of enantioselectivity emerged. The ligands may be divided into two groups: ligands which bind palladium without C_2 symmetry and ligands which may bind palladium with C_2 symmetry. For ligand–metal complexes lacking C_2 symmetry, including the salt ligands (eq 3), the enantiomeric excesses were

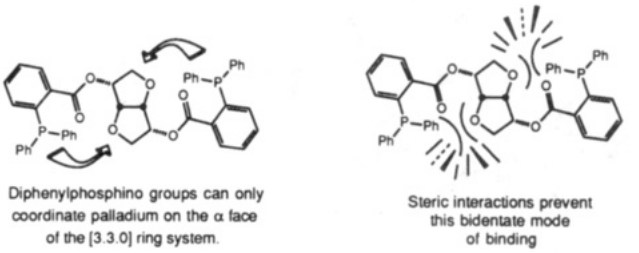
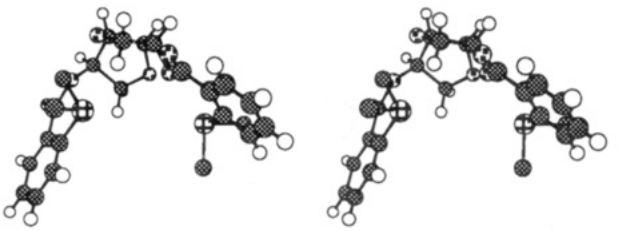


Figure 12. Steric interactions of the isomannide ligand **26**.

uniformly low (≤15%). In contrast, the C_2-symmetrical complexes gave a higher order of enantioselectivity (40–88%) and a predictable enantiomeric preference.

In order to develop a working model to correlate the sense of enantioselective ionization with the absolute configuration of the ligand, we assume that the bis-phosphine ligands function in a bidentate fashion in spite of the fact that such bidentate coordination requires rings ranging from 13 to 16 members. Several observations support this assumption. The experimental stoichiometry of one bidentate ligand for each palladium in a catalytic reaction which was established as optimum by varying the ratio of ligand to palladium indicates that both phosphines are coordinating to palladium. The bidentate ligand from isomannide (**26**, Figure 12) proves to be quite informative. This C_2-symmetric ligand is structurally different from the others in that the cuplike framework creates a steric barrier for bidentate chelation. Forcing



(Phenyl Groups not explicitly shown in Stereoview)

the diphenylphosphino groups to project toward the concave face of the bicyclic ring system, which causes significant steric interaction between the phenyl rings and the bicyclic framework as depicted in Figure 12, destabilizes this conformation required for bidentate coordination to palladium. Thus, while this ligand does have C_2 symmetry, it is probable that it does not act as a bidentate ligand for palladium. Very low ee (7%) is observed when ligand **26** serves as the asymmetric inducing element. These results also disfavor a model invoking an alternative coordinating mode wherein these bisphosphines bridge two palladiums. The isomannide ligand should participate equally well in such a coordination geometry and thereby lead to asymmetric induction comparable to the other ligands, but it does not. While bidentate coordinations involving very large rings are also not common, they are precedented especially in the work of Rauchfuss.[17]

Envisioning the bisphosphine ligands of C_2 symmetry serving as bidentate coordinators, a pattern of enantioselectivity emerged. We noted that in each case the stereochemistry of the chiral linker was directly related to the optical rotation of the product and hence the ionization step (Figure 13). As our study of these chiral ligands progressed, we realized that we could predict which group (*R* or *S*) would preferentially ionize *prior* to preparation of the ligand! Figure 14 provides a simple mnemonic which correlates the ligand stereochemistry with that of the product.

Applying the same model to substrates **16** and **18** leads to the predictions that (−)-**11** should lead to the absolute configurations depicted in formula **17** and **19** (eq 7 and 8). The mandelate analytical method establishes these predicted absolute configurations as the experimentally observed ones.

It is interesting to note that BINAPO follows the mnemonic. Thus, (*S*)-(−)-BINAPO (**26**) complexed to palladium effects

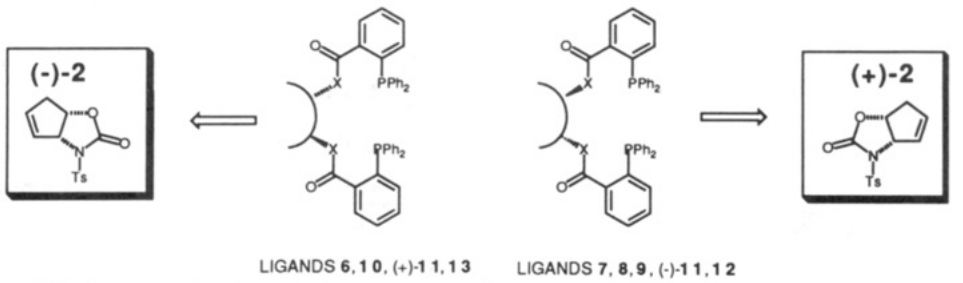


Figure 13. Correlation of absolute stereochemistry of the product with that of the variable chiral linker.

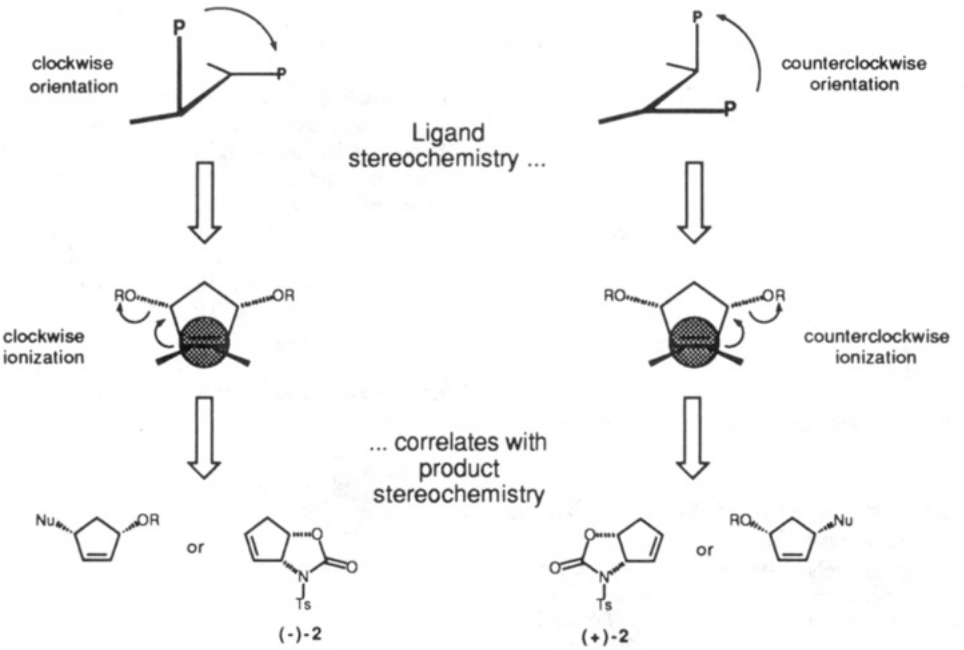
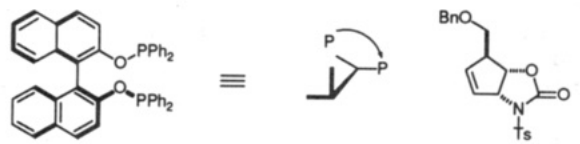


Figure 14. Mnemonic rule for ionization.

cyclization of the bis-urethane intermediates of Scheme II and eq 7 to enantiomers (−)-**2** (30% ee) and **27** (65% ee).



26 **27**

Cautions must be exercised in applying this mnemonic in those cases exhibiting rather low ee. When substrate **16** was tested with ligands **6** and **13**, the product, **17**, was obtained with low ee (18% and 38%, respectively) and the opposite configuration of that predicted by the mnemonic in Figure 14. Unlike *cis*-cyclopent-2-ene-1,4-diol and diol **10**, diol **16** bears a (benzyloxy)methyl group on the *same* face of the cycloalkene as the palladium binds. The impaling of the chiral template by this substituent may change the reacting conformation and thereby the nature of the steric interactions that leads to the chiral recognition. It is interesting to note that an enzymatic hydrolysis of the diacetate derived from *cis*-cyclopent-2-ene-1,4-diol and diol **16** leads to the enantiomerically opposite hydroxy acetates—indicative of a major effect of the benzyloxy substituent here too.[29]

The cartoon shown in Figure 15 provides a working model for the origin of the steric interactions which lead to the observed enantioselectivity. This model suggests that the difference in diastereotopic transition states (ionization of the *pro-S* leaving group versus ionization of the *pro-R* leaving group) is the result

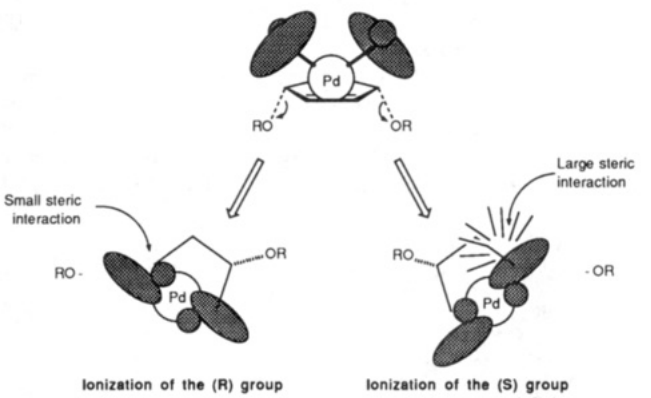


Figure 15. Model for origin of enantioselectivity.

of steric interactions between the chiral ligand and the cycloalkene portion of the substrate. The asymmetric ligand is depicted as having regions that are sterically small (depicted by circle) and sterically large (depicted by elipse) arranged in a C_2-symmetric array. A clockwise twist leading to the ionization of the *pro-R* leaving group allows the sterically small region to move over the face of the ring of the substrate, thereby minimizing unfavorable interactions. On the other hand, a counterclockwise twist that is required to ionize the *pro-S* leaving group forces the sterically demanding region of the ligand over the face of the substrate which should destabilize the transition state for this ionization. Steric interactions between the leaving group and ligand should not have a significant effect on the preference for ionization.

Some important predictions which result from this model are (1) electronic effects (leaving group ability) should have a greater influence than leaving group size;[12] (2) palladium-catalyzed re-

(29) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 5863. However, see: LeGrand, D. M.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1751.

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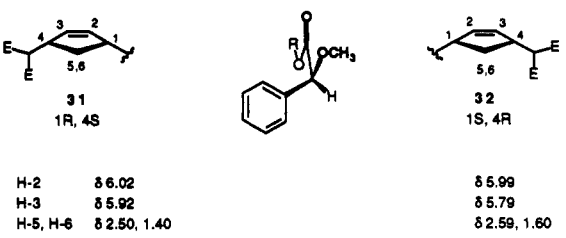
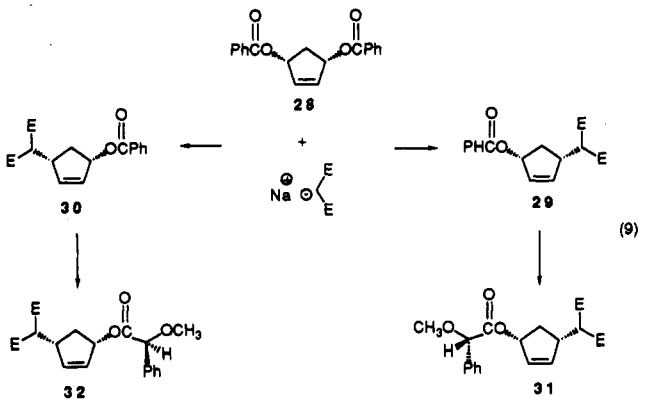


Figure 16. Determination of absolute configuration of a malonate alkylation product.

actions involving substrates similar to **1** will follow the mnemonic shown in Figure 14; and (3) because alkylation is the microscopic reverse of ionization, the ability to predict the difference in transition-state energies for *R*-group and *S*-group ionization should also apply to *pro-R* versus *pro-S* alkylation of cyclic palladium–allyls. The predictions resulting from this model are currently being tested.

Intermolecular Alkylations. Having designed modular ligands capable of effecting high asymmetric induction in a cyclization to form oxazolidin-2-ones, we examined the generality of the concept by considering the feasibility of the intermolecular monoalkylation and its asymmetric induction. We chose the dibenzoate of 2-cyclopentene-1,4-diol (**28**)[13] as our test substrate.



As pointed out in Scheme III, unlike the cyclization examined above, the question of di- vs monoalkylation must be considered. Indeed, early studies with triphenylphosphine as ligand and the diacetate corresponding to **28** revealed the dialkylation product to be the overwhelming one. Fortunately, such a problem can be minimized with the chiral ligands. Our initial effort examined the alkylation of the anion of dimethyl malonate as in eq 9. Analyses of the ee's and the assignment of absolute configuration were performed by conversion to the mandelates **31** and **32** (eq 9) by treatment with magnesium methoxide (CH_3OH, 60 °C) followed by esterification with (*S*)-*O*-methylmandelic acid (DCC, DMAP, CH_2Cl_2, room temperature). As above, differential NMR shifts allowed assignment of configuration (Figure 16). Thus, the absorptions for the vinyl protons appeared at lower field and those for the methylene protons at higher field for the 1*R*,4*S* isomer **31** compared to the 1*S*,4*R* isomer **32**. Integration of the signals at δ 5.92 vs 5.79 allowed determination of ee. Using the same catalytic conditions as for the oxazolidin-2-one synthesis with tartrimide-derived bis-phosphine **10** as the chiral ligand, alkylation as in eq 9 at 0 °C–room temperature provided a 40% yield of monoalkylation product of 64% ee in which enantiomer **30** dominated (18% **29**, 82% **30**). Substantial improvements in both yield and ee occurred upon switching to the amide-derived ligands. Amide ligand (+)-**11** gave a 68% yield of product of 92% ee (4% **29**, 96% **30**), whereas amide ligand **12** gave an 80% yield of alkylated product of 93% ee (96.5% **29**, 3.5% **30**). Note that these two amide ligands which possess enantiomeric scaffolds gave products of opposite chirality. These results contrast to that from using (*S*)-BINAPO[2] which gave only a 38% yield of product of ≤57% ee (21.5% **29**, 78.5% **30**) accompanied by significant dialkylation (32%).

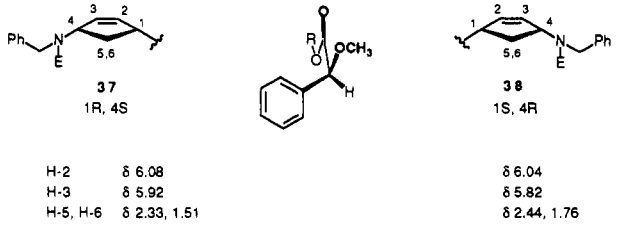
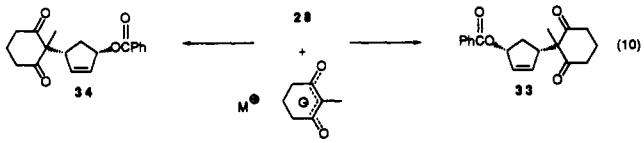


Figure 17. Determination of absolute configuration of amine alkylation products.

To determine the dependence, if any, of the ee on the carbon nucleophile, we explored the reactions of 2-methylcyclohexane-1,3-dione (eq 10). With achiral triphenylphosphine as the ligand,

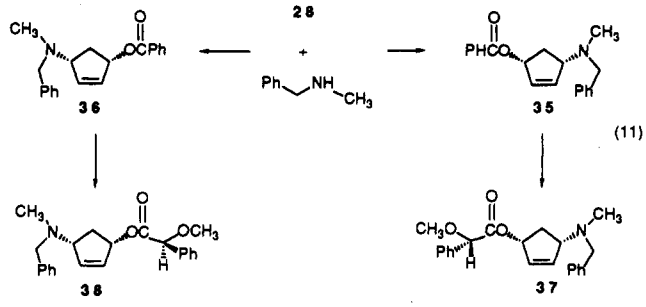


best yields of the monoalkylated product were obtained using DBU as base (80–82%) in contrast to potassium hexamethyldisilamide which gave a 65% yield. Thus, DBU was used for the asymmetric alkylations. Chiral shifts using $Eu(hfc)_3$ in benzene-d_6 caused separation of the absorptions for the vinyl proton for the two enantiomers **33** (lower field) and **34** (higher field) which provided the ee's.

Reaction using our standard catalyst system with diester ligand **10** at 0 °C gave a 51% yield of product of 52% ee (24% **33**, 76% **34**). Expectedly, reaction using the diamide ligand **12** at 0 °C gave a significant enhancement of both yield, to 95%, and ee, to 91% (95.5% **33**, 4.5% **34**). To demonstrate that a counterion had little, if any, effect, alkylation using diamide ligand (+)-**11** was performed with the lithium enolate under otherwise identical conditions and gave an 86% yield of product of 91% ee in which the enantiomer to that obtained from using amide **12** was dominant (4.5% **33**, 95.5% **34**).

Comparing heteroatom to carbanion nucleophiles tests the generality of this asymmetric alkylation. Nitrogen nucleophiles are particularly important and test the limits, since amines have proven to be somewhat schizophrenic in their diastereomeric behavior in allylic alkylations in that they sometimes gave products of both net retention and net inversion of configuration.[31] Conditions for optimizing the alkylation were established using triphenylphosphine as the ligand. To avoid polyalkylation by using large excesses of amine nucleophile, an auxillary tertiary amine base was employed with triethylamine proving to be substantially superior (70% yield) to DBU (16% yield).

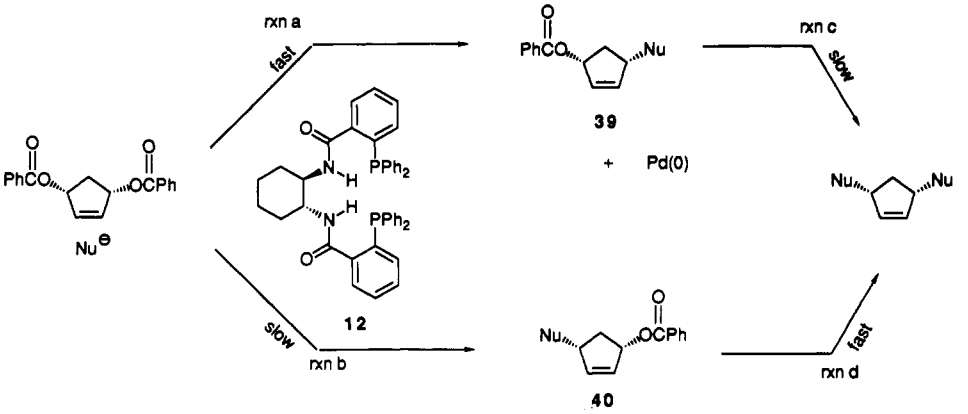
The absolute configuration and ee of the monoalkylation products **35** and **36** were established by conversion to the *O*-methylmandelate esters **37** and **38** (eq 11) by hydrolysis (LiOH,



C_2H_5OH, H_2O, 60 °C) followed by acylation with (*S*)-*O*-methylmandelic acid (DCC, DMAP, CH_2Cl_2, room temperature). Analysis of the NMR spectra allowed assignment of the absolute

(31) Trost, B. M.; Keinan, E. *J. Am. Chem. Soc.* **1978**, *100*, 7779. Also see: Bäckvall, J. E.; Nordberg, R. E.; Zetterberg, K.; Akermark, B. *Organomet.* **1983**, *2*, 1625.

Scheme V. Kinetic Enrichment of Enantioselectivity



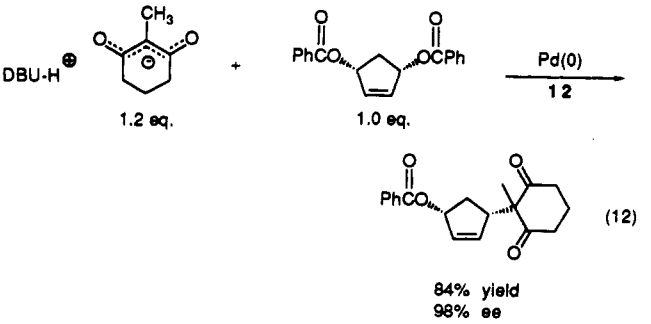
configurations (Figure 17) as well as determination of the ee. As for the malonate alkylation products, the absorptions for the vinyl protons appeared at lower field and those for the methylene protons at higher field for the 1*R*,4*S* isomer **37** compared to the 1*S*,4*R* isomer **38**. Integration of the signals at δ 5.92 vs 5.82 provided a measure of the ee. Surprisingly, alkylation using the standard catalyst system with diester **10** gave a significantly higher ee of 74% (13% **35**, 87% **36**) than with carbon nucleophiles. Another difference between the two types of nucleophiles arose with the amide ligands (+)-**11** and **12** which have shown virtually identical behavior with carbon nucleophiles. In this case, a significantly higher ee was obtained using (+)-**11** (95% ee, 2.5% **35**, 97.5% **36**) compared to using **12** (78% ee, 89% **35**, 11% **36**). As in all the previous examples, ligands **10** and (+)-**11** produce the same major enantiomer, which is the mirror image of that favored by ligand **12**.

Correlation of the absolute configuration of the products with the absolute stereochemistry of the ligands follows the mnemonic outlined in Figure 14. The absolute configurations of the malonate and amine alkylation products were established by the NMR method based upon the *O*-methylmandelate esters[27] as outlined above. The malonate alkylation product also correlated with the same compound recently reported.[30]

Ligands **10** and (+)-**11** correspond to the clockwise orientation of the two binding posts on the chiral scaffold and thus lead to products **30** and **36**. On the other hand, amide ligand **12** corresponds to the counterclockwise orientation of the binding posts with the penultimate result being formation of enantiomers **29** and **35**. In the case of alkylations with 2-methylcyclohexane-1,3-dione, NMR studies with chiral shift reagents show that the major enantiomers from reactions with ligands **10** and (+)-**11** are the same and opposite that from reaction with ligand **12** as observed in all the other cases. By analogy to all of the examples to date, we assign the major enantiomers from reactions with ligands **10** and (+)-**11** to be **34** and that from reaction with ligand **12** to be **33**.

In all the above cases, reactions were performed to minimize any dialkylation since further reactions could distort the enantioselectivity (see Scheme V). Consider the case of amide ligand **10** which favors ionization of the *pro-R* leaving group. Thus, reaction a should be faster than reaction b, leading to an excess of enantiomer **39** over **40**. On the other hand, this same ligand should promote dialkylation via ionization of **40** (rxn d) to a greater extent than via ionization of **39** (rxn c). Thus, to the extent that the ligand makes a mistake in the initial ionization by generating the "wrong" enantiomer, it can become self-correcting by consuming this "wrong" enantiomer more rapidly. A consequence of this behavior is enhancement of ee by kinetic destruction of the "wrong" enantiomer due to its over-reaction. Enzymes exhibit similar behavior,[32] and thus enantioselectivity can be dependent upon extent of reaction or over-reaction—a feature that must be commonly exploited in enzymatic processes to obtain the high ee's desired.

Since dialkylation had been minimized and was not observed in the above reactions, the ee's obtained reflect the true chiral discrimination. On the other hand, this phenomenon offers a simple means of enhancing the ee of this metal-catalyzed reaction simply by allowing the reaction to proceed partially to the dialkylation product. Indeed, performing the alkylation of dibenzoate **28** with a slight excess of the anion of 2-methylcyclohexane-1,3-dione caused the yield to drop to 84%, but the ee was enhanced from 91% to 98% with amide ligand **12** (eq 12).



(12)

General Discussion

A major challenge today involves developing a rational approach to ligand design for asymmetric induction in synthetically useful transition metal-catalyzed reactions. While the processes of oxygen and hydrogen atom transfer are succumbing to efforts to realize this goal, the intransigence of the metal-catalyzed allylic alkylation requires ligands whose availability is not hampered by the complexity of synthesizing the typical chiral phosphines that have been employed in most transition metal-catalyzed reactions.[3-7] The modular design based on derivatives of 2-(diphenylphosphino)-benzoic acid provides easy access by allowing the assembly of the chiral ligand by a simple acylation between the metal binding posts and the chiral linker or template. Using this strategy, stepwise rational changes to remove specific degrees of freedom from the ligand have led to marked improvement in the enantiomeric excesses obtained in a mechanistically defined enantioselective allylic alkylation involving an asymmetric palladium-catalyzed ionization.

Several trends can be noted. Enhancing ligand rigidity enhances ee as evidenced by switching from esters to amides. Within either series, increasing the dihedral angle between the vicinal diol or diamine enhances the ee as evidenced by comparing **8** vs **10** and **11** or **12** vs **13**. Surprisingly, increasing the tether length between the diols has little effect as evidenced by comparing **7** and **8**. One way to understand these effects involves the model depicted in Figure 18 in which the chiral environment created by the conformation of the phenyl rings dictates the chiral recognition in the ionization step.[1,33] Since bond breaking and bond making

(32) Wang, Y.-F.; Chen, C. S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 3695.

(33) Knowles, W. S.; Vineyard, B. D.; Sabacky, M. J.; Stults, B. R. In *Fundamental Research in Homogeneous Catalysis*; Tsutsui, M., Ed.; Plenum Press: New York, 1979, Vol. 3, pp 537-548.

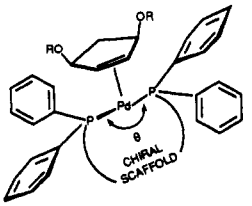
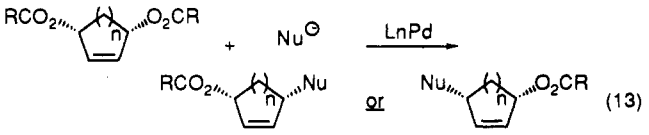


Figure 18. Model for ligand effect.

occur distal to palladium and thus the chiral ligands, forcing the chiral environment to embrace the substrate by opening the "bite angle" θ is necessary for high chiral recognition. Thus, we can envision that the effects of a large chelating C_2-symmetric bisphosphine and increasing the dihedral angle of the vicinal diols and diamines constituting the chiral scaffold increased the bite angle and thus the chiral recognition. Any further discussion is postponed until further experimental support is obtained, but the present findings do constitute a useful working hypothesis.

Since asymmetric induction arises in the ionization step, this approach appears to be generally applicable for allylic alkylations (eq 13) involving inter- as well as intramolecular processes and



(13)

carbon as well as heteroatom nucleophiles. The higher ee's obtained in the intermolecular alkylations (≥91%) compared to the cyclization of the bis-urethane may be attributable to the differences in leaving groups. Since breaking the C–O bond constitutes the enantiodetermining step, the nature of the leaving group is expected to influence the ee. On the other hand, the chiral recognition should be independent of the nucleophile. With the carbon nucleophiles, this expectation is fulfilled. Nevertheless, use of a secondary amine as the nucleophile does affect the ee, the source of which remains undefined. The facts that the amine may hydrogen bond to the leaving group and that the amines behave abnormally in other respects in such palladium-catalyzed reactions may be invoked to help rationalize the effect. Nevertheless, an excellent ee (95%) is obtainable.

Such a metal-catalyzed dissymmetrization of *meso*-2-ene-1,4-diols has a strategic advantage over enzymatic approaches employing lipase-catalyzed acylations[34,35] or esterase-catalyzed hydrolyses.[36,37] With the metal-catalyzed reaction, the asymmetric inducing step can be incorporated as one of the integral bond-forming steps building the final target, whereas the enzymatic approach requires the creation of a chiral compound as a separate operation. Thus, steps in a synthetic sequence can be saved. For example, in an elegant, recently completed allosamizoline synthesis using an enzymatic strategy, eight steps were required from a 2-ene-1,4-diol to a key oxazolidin-2-one intermediate.[29] Using the palladium-catalyzed approach, the same structural elaboration can be accomplished in two steps.[11]

Furthermore, the highest ee reported for the enzymatic preparation of 1(*R*)-acetoxy-4(*S*)-hydroxycyclopentene was 97% with the lipase derived from *Mucor michai* but only at a 48% conversion.[36c] The best result utilizing electric eel cholinesterase reported a 93.6% yield of the 1*R*,4*S* product whose ee was recorded as 96% but after initial crystallization.[36d] For the 1*S*,4*R* enantiomer, transacylation of the diol provided only a 48% yield of product of 95% ee after initial crystallization.[35a] Porcine liver esterase gave an 86% yield of this isomer of 75% ee.[36b] None of these enzymes allowed extension of this strategy to a chiral synthesis of the six-membered ring substrate for which the best result involved a pseudomonas lipase transacylation in which a 51% yield of 1(*S*)-acetoxy-4(*R*)-hydroxycyclohex-2-ene of 95% ee but only when accompanied by 44% of the over-reacted diacetate.[34c]

In contrast to the above, the metal-catalyzed reactions are not so substrate specific—the same ligand permits high ee's with different substrates. Furthermore, our six-membered ring substrate gave higher ee's than our five-membered ring system! In the intermolecular alkylations, all alkylations employing the diamide ligands **11** or **12** gave complete conversion with ≥91% ee, and kinetic enhancement raised the ee to 98% with only a slight diminishment of yield. Combined with the fact that either enantiomer is equally accessible from the enantiomeric ligands in contrast to the biologically based approach, this method should prove generally useful for employing *meso*-2-ene-1,4-diols in asymmetric organic synthesis—a premise already substantiated by the use of the malonate alkylation products **29** and **30** for the synthesis of biologically important cyclopentanoid natural products.[38,39] The prospect of broadening the scope for asymmetric induction in other types of allylic alkylation represents a major thrust. The potential of modular ligands like the ones developed herein for asymmetric induction in other transition metal-catalyzed reactions remains a challenge.

Experimental Section

All reactions were run under an atmosphere of dry nitrogen unless otherwise indicated. Anhydrous solvents were transferred by oven-dried syringe or cannula. Flasks were flame dried under a stream of nitrogen. Acetonitrile, dichloromethane, and pyridine were distilled from calcium hydride. Ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Toluene was distilled from sodium. Dimethylformamide (DMF) was distilled from barium hydroxide at reduced pressure.

Melting points were determined on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. Solvents for chromatography are listed as volume/volume ratios. Optical rotations were determined using a JASCO DIP-360 in 50-mm cells. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrophotometer or a Nicolet 205 spectrophotometer. Elemental analyses were performed by Spang Microlabs, Eagle Harbor, MI; Robertson Laboratories, Madison, NJ; and M-H-W Laboraties, Phoenia, AZ. High resolution mass spectra (HRMS) and low resolution mass spectra (LRMS) were obtained from the Mass Spectrometry Resource, School of Pharmacy, University of California—San Francisco on a Kratos MS9 or through the courtesy of Dr. John Kuo at Shaman Pharmaceuticals, Inc., San Carlos, CA, and are reported as *m/e* (relative intensity). Accurate masses are reported for the molecular ion (M^+) or a suitable fragment ion. Proton and carbon-13 (^1H, ^{13}C) nuclear magnetic resonance spectra were recorded using a Varian XL-400 (400 MHz, 100 MHz) or a Varian Gemini 200 (200 MHz, 50 MHz) or 300 (300 MHz, 75 MHz). Proton NMR spectra used for analytical determinations (e.g., product ratios) were run with an increased delay (0.5–1.0 s) to minimize effects of differential relaxation times.

3-Aza-3-benzyl-1(*R*),5(*R*)-dihydroxy-1,5-diphenylpentane (9a). A neat mixture of benzylamine (92 μL, 90 mg, 0.84 mmol) and (*R*)-(+)-phenyloxirane (0.576 mL, 606 mg, 5.04 mmol, Aldrich) was stirred at room temperature for 5 min and then at 120 °C for 13 h. After cooling to room temperature, the reaction mixture was loaded onto a 2.5 × 13-cm column of silica gel and chromatographed with 40% ethyl acetate/hexanes to afford a mixture of isomeric diols (6:1, ^1H NMR) as an oil (0.318 mg, slightly contaminated with ethyl acetate): minor isomer, R_f 0.55 (50% ethyl acetate/hexanes); major isomer, R_f 0.65 (50%

(34) Cf. (a) Wang, Y. F.; Wong, C. H.; Ngo, J. S.; Kabiak, K. A.; Dygos, J. H. *J. Org. Chem.* **1990**, *55*, 3377. (b) Wong, C. H. *Science* **1989**, *244*, 1145. (c) Harris, K. J.; Gu, Q. M.; Shieh, Y.-E.; Girdaukas, G.; Sih, C. J. *Tetrahedron Lett.* **1991**, *32*, 3941.

(35) (a) Theil, F.; Ballschuh, S.; Schick, H.; Haupt, M.; Häfner, S.; Schwartz, S. *Synthesis* **1988**, 540. (b) Jommi, G.; Orsini, F.; Sisti, M.; Verotta, L. *Gazz. Chim. Ital.* **1988**, *118*, 863.

(36) Cf. (a) Wang, Y.; Chen, C.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 3695. (b) Laumen, K.; Schneider, M. *Tetrahedron Lett.* **1984**, *25*, 5875. (c) *Idem., Chem. Commun.* **1986**, 1298. (d) Deardorff, D. R.; Matthews, A. J.; McMeekin, D. S.; Craney, C. L. *Tetrahedron Lett.* **1986**, *27*, 1255.

(37) Cf. Deardorff, D. R.; Linde, R. G., II; Martin, A. M.; Shulman, M. J. *J. Org. Chem.* **1989**, *54*, 2759. Montforts, F. B.; Gesing-Zibulak, I.; Grammenos, W.; Schneider, M.; Laumen, K. *Helv. Chim. Acta* **1989**, *72*, 1852.

(38) Harre, M.; Raddatz, P.; Walenta, R.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 480. Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847.

(39) See ref 30, 37, and Corey, E. J.; Carbino, P. *Tetrahedron Lett.* **1990**, *31*, 7555.

ethyl acetate/hexanes). The mixture of diols was chromatographed on a 1.6 × 13-cm column of silica gel with 20% ethyl acetate/hexanes to afford the symmetrical diol **9a** as a clear, colorless oil (0.228 g, 78.1%).

Diol 9a: R_f 0.65 (50% ethyl acetate/hexanes); IR (neat film) 3384 (br), 3062, 3029, 2941, 2886, 2835, 1922 (w), 1883 (w), 1812 (w), 1494, 1453, 1405, 1375, 1335, 1253, 1201, 1133, 1090, 1063, 1027, 911 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.32 (m, 15 H), 4.75 (dd, J = 8.8, 4.4 Hz, 2 H), 3.99 (d_{AB}, J = 13.6 Hz), 3.68 (d_{AB}, J = 13.6 Hz, 1 H), 3.32 (br s, 2 H, OH), 2.79 (dd_{ABX}, J = 19.0, 13.4 Hz, 2 H), 2.76 (dd_{ABX}, J = 15.2, 13.5 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 142.37, 138.31, 129.24, 128.60, 128.44, 127.62, 127.49, 126.00, 70.73, 62.42, 59.60, LRMS (m/z): 240 (51), 238 (14), 210 (27), 133 (30), 132 (100), 120 (16), 107 (11), 105 (25), 104 (22). HRMS calcd for $C_{23}H_{25}NO_2$ – C_7H_6O 241.1466, found 241.1412.

(+)-11(*S*),12(*S*)-Diamino-9,10-dihydro-9,10-ethanoanthracene (15). To a stirred slurry of (−)-9,10-dihydro-9,10-ethanoanthracene-11-(*S*),12(*S*)-dicarboxylic acid (2.00 g, 6.80 mmol, $[\alpha]_{405}$ = −35.6 (±0.2)° (*c* 1.96, dioxane)) in anhydrous benzene (16 mL) was added a catalytic amount of anhydrous DMF (1 drop from a Pasteur pipette). The mixture was stirred as a white slurry, and thionyl chloride (1.5 mL, 2.425 g, 2.04 mmol) was then added. The mixture was heated at reflux until evolution of hydrogen chloride gas subsided (3.25 h, tested effluent with wet pH paper). The solution was allowed to cool to room temperature, and solvent and thionyl chloride were removed under reduced pressure (30–60 mmHg). Anhydrous benzene (5 mL) was added, and solvent was again removed under reduced pressure. A final portion of benzene (5 mL) was added, and solvent was removed under reduced pressure to afford the crude bis-acid chloride as a clear beige glass free from thionyl chloride (2.198 g, 97.7%). The crude bis-acid chloride was directly reacted with sodium azide without further purification: IR ($CDCl_3$) 3020, 3000, 1782 (s), 1455, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.37 (m, 4 H), 7.20 (m, 4 H), 4.96 (br s, 2 H), 3.82 (dd, J = 1.6, 1.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.22, 140.35, 138.82, 127.48, 127.43, 125.28, 124.41, 59.19, 46.75.

To the crude bis-acid chloride at 0 °C was added anhydrous DMF (16 mL). The flask was swirled by hand for 35 min (stir bar was fused into the glassy solid) until the substrate had dissolved, and the clear solution was stirred at 0 °C for 1 h. Sodium azide (0.97 g, 15.0 mmol) was added, and the slurry was stirred at 0 °C to room temperature over 3 h. The reaction was poured into ice-cold deionized water (100 mL) and extracted with chilled toluene in four portions (40 mL, 3 × 25 mL). The combined organic layers were dried over sodium sulfate and filtered into a 250-mL round-bottom flask to give a solution of bis-azide. A reflux condenser and extra toluene (20 mL) were added, and the mixture was stirred at room temperature for 3.5 h and then at reflux for 2 h (nitrogen evolution). The solution was allowed to cool to room temperature and then transferred to a 500-mL round-bottom flask. Solvent was removed in vacuo to afford crude bis-isocyanate which was directly hydrolyzed: IR (neat film from $CDCl_3$) 3052, 3042, 3027, 2957, 2250 (s), 1467, 1460, 1356, 1312, 1226, 1168, 1116, 968, 943, 900, 865 cm^{-1}.

To the crude 9,10-dihydro-11(*S*),12(*S*)-diisocyanato-9,10-ethanoanthracene in THF (20 mL) was added 2.5 N aqueous sodium hydroxide (10 mL). The mixture was stirred in an unlighted hood for 2 h. Deionized water (10 mL) and ether (25 mL) were added, and the mixture was acidified to pH <1 (pH paper) by careful addition of concentrated hydrochloric acid. The layers were separated, and the aqueous layer was washed with more ether (25 mL). Sodium hydroxide pellets were added with stirring (one at a time) to the aqueous solution until the solution became milky (pH 14, pH paper). The diamine was extracted with ether (40 mL) and then dichloromethane (2 × 40 mL). The combined organic layers were washed with saturated aqueous sodium chloride and dried over potassium carbonate. Removal of solvent in vacuo afforded the crude diamine as beige crystalline solid **15** (1.55 g, 96.5%). The diamine was recrystallized from benzene to afford fluffy white diamine (0.68 g, 42.3%). The mother liquor contained a large amount of product which was not isolated.

Diamine 15: mp 153–156 °C (benzene); R_f 0.43–0.58 (25% methanol/chloroform); IR (neat film from $CDCl_3$) 3353, 3282, 3174, 3069, 3041, 3021, 2930, 1585, 1465, 1458, 1000, 925, 909 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.32 (m, 4 H), 7.16 (m, 4 H), 4.04 (s, 2 H), 2.67 (s, 2 H), 1.43 (br s, 4 H, NH_2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 142.21, 139.01, 126.50, 126.35, 126.15, 124.13, 62.17, 53.48; $[\alpha]_{577}$ = +21.2 (±0.6)° (*c* 2.275, methanol), $[\alpha]_{405}$ = +81.3 (±0.4)° (*c* 2.275, methanol), $[\alpha]_D$ = +20.5 (±0.2)° (*c* 2.275, methanol). This compound was analyzed as the bis-*N*-acetyl derivative. Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.60; H, 6.26; N, 8.75.

General Procedure A for the Preparation of Ligands with 2-(Diphenylphosphino)benzoic Acid Using DCC. Anhydrous solvent (THF or dichloromethane) was added to the alcohol or amine, excess 2-(diphenylphosphino)benzoic acid, and 5 mol % DMAP and DCC. The resultant yellow, chalky mixture was stirred at room temperature until thin layer chromatography indicated complete reaction. The reaction mixture was filtered through a 2-cm pad of Celite (wetted with dichloromethane), and the filter cake was washed twice with equal volumes of dichloromethane. Solvent was removed in vacuo, and the residue was chromatographed on silica gel.

General Procedure B for the Preparation of Ligands with 2-(Diphenylphosphino)benzoic Acid Using DCC. DCC was added to the alcohol or amine, excess 2-(diphenylphosphino)benzoic acid, and 5 mol % DMAP in anhydrous solvent (THF or dichloromethane). The yellow, chalky mixture was stirred at room temperature until thin layer chromatography indicated complete reaction. The reaction mixture was filtered through a 2-cm pad of Celite (wetted with dichloromethane), and the filter cake was washed twice with equal volumes of dichloromethane. Solvent was removed in vacuo, and the residue was chromatographed on a column of silica gel.

(+)-*N*-Methylephedrine, 2-(Diphenylphosphino)benzoate Ester (4). In a typical procedure (procedure A), anhydrous dichloromethane (4 mL) was added to (+)-*N*-methylephedrine (0.2668 g, 1.488 mmol), 2-(diphenylphosphino)benzoic acid (0.4293 g, 1.402 mmol), DMAP (7.0 mg, 0.057 mmol), and DCC (0.346 g, 1.677 mmol). The mixture was stirred in an unlighted hood for 21 h. The reaction mixture was filtered through Celite to remove dicyclohexylurea, and the filter cake was washed with dichloromethane (10 mL). The filtrate was concentrated in vacuo and chromatographed on silica gel with 80% ethyl acetate/hexanes to afford the ester as a greenish-yellow glass (479.1 mg, 73.1%).

Ligand 4: glass, slowly decomposes with liberation of dimethylamine when stored at room temperature in a sealed flask in the dark; R_f 0.53–0.69 (ethyl acetate); $[\alpha]_D$ = +47.1 (±0.2)° (*c* 3.98, dichloromethane); IR (neat film from $CDCl_3$) 3400 (br), 3068, 3055, 3031, 2976, 2935, 2860, 2825, 2779, 1716 (s), 1462, 1455, 1434, 1290, 1267, 1252, 1140, 1104, 1055, 744, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.20 (m, 1 H), 7.18–7.45 (m, 17 H), 6.92 (m, 1 H), 6.08 (d, J = 5.3 Hz, 1 H), 2.95 (dq, J = 5.4, 6.7 Hz, 1 H), 2.21 (s, 6 H), 1.07 (d, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.50 (d, J = 2.7 Hz), 141.28 (d, J_{CCP} = 28.2 Hz), 139.98, 138.25 (d, J_{CP} = 11.6 Hz), 137.96 (d, J_{CP} = 12.4 Hz), 134.46, 134.21 (d, J_{CCP} = 5.6 Hz), 134.14 (d, J_{CP} = 18.5 Hz), 133.79 (d, J_{CCP} = 5.1 Hz), 132.14, 130.75, 130.71, 128.54 (br, >1 peak), 128.39, 128.29, 128.17, 127.42, 126.56, 75.39, 63.46, 40.96, 9.51; LRMS (m/z) 305 (93), 183 (18), 162 (16), 72 (100); HRMS calcd for $C_{39}H_{37}N_2O_3P$ – $C_{19}H_{14}O_2P$ 162.1283), found 162.1281.

(−)-Tris-*O*¹,*N*²,*O*³-[2-(diphenylphosphino)benzoyl]-L-(+)-*threo*-2-amino-1-phenyl-1,3-propanediol (5). In a typical procedure (procedure B), anhydrous dichloromethane (1.8 mL) followed by DCC (0.276 g, 1.4 mmol) was added to L-(+)-*threo*-2-amino-1-phenyl-1,3-propanediol (60.9 mg, 0.364 mmol, Fluka), 2-(diphenylphosphino)benzoic acid (0.357 g, 1.166 mmol), and DMAP (7.1 mg, 0.058 mL) at room temperature for 14 h. The mixture was filtered through a 2-cm pad of Celite (wetted with dichloromethane), and the filter cake was washed with dichloromethane (2 × 2 mL). After concentration in vacuo, the residue was chromatographed on a 2.5- × 13-cm column of silica gel with 20% ethyl acetate/hexanes to give the triphosphine **5** as a white solid (369.4 mg, 93.3%).

Ligand 5: waxy solid (dichloromethane/hexane): mp 112–116 °C; R_f 0.39 (30% ethyl acetate/hexanes); $[\alpha]_D$ = −21.5 (±0.1)° (*c* 1.78, dichloromethane); IR (neat film from $CDCl_3$) 3400 (br), 3260, 3054, 1717 (s), 1667 (s), 1515, 1478, 1461, 1434, 1269, 1250, 1140, 1106, 1056, 744, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.21 (m, 1 H), 8.12 (ddd, J = 5.5, 3.9, 3.4 Hz, 1 H), 7.0–7.5 (m), 6.90 (m, 3 H), 6.11 (d, J = 8.4 Hz, 1 H), 4.89 (ddd, J = 12.9, 8.2, 3.7 Hz, 1 H), 3.87 (dd_{ABX}, J = 11.6, 4.3 Hz, 1 H), 3.82 (dd_{ABX}, J = 11.6, 3.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.91, 166.48 (d, J = 2.3 Hz), 165.92 (d, J = 2.4 Hz), 140.81 (d, J = 16.6 Hz), 140.30 (d, J = 19.2 Hz), 139.93 (d, J = 25.4 Hz), 75.78, 52.27, 64.40, remaining peaks δ >100 could not be resolved; LRMS (LSIMS) (m/z) 1064 (54, bis-phosphine oxide), 1032 (100), 758 (22), 726 (29).

(+)-Quinine, 2-(Diphenylphosphino)benzoate Ester (3) (Procedure A). The reaction was run with (−)-quinine (474 mg, 1.46 mmol, Merck), 2-(diphenylphosphino)benzoic acid (0.452 g, 1.48 mmol), and DCC (330.3 mg, 1.60 mmol) in dichloromethane (3.1 mL) for 23 h. The residue was chromatographed on a silica gel with 2.5% methanol/chloroform to give an impure product which was loaded onto a column of silica gel and eluted with 50% ethyl acetate/hexanes to remove high R_f impurities, followed by straight ethyl acetate to elute the pure ester **3** (0.532 g, 58.6%).

Ligand 3: glass foam from dichloromethane; R_f 0.75 (20% methanol/chloroform); $[\alpha]_D$ = +45.0 (±0.3)° (*c* 2.49, dichloromethane); IR (neat film from $CDCl_3$) 3070, 2941, 2884, 1716 (s), 1622, 1593, 1509, 1475, 1434, 1250, 1139, 1102, 1055, 1029, 912, 745, 732, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.66 (d, J = 4.6 Hz, 1 H), 8.09 (m, 1 H),

7.98 (d, J = 9.2 Hz, 1 H), 7.45 (d, J = 2.7 Hz, 1 H), 7.12–7.42 (m, 14 H), 6.90 (m, 1 H), 6.65 (d, J = 8.2 Hz), 5.86 (m, 1 H), 6.65 (d, J = 8.2 Hz, 1 H), 5.86 (m, 1 H), 5.04 (dt, J = 5.3, 1.4 Hz, 1 H), 5.005 (d, J = 1.0 Hz, 1 H), 3.89 (s, 3 H), 3.43 (dd, J = 16.9, 8.3 Hz, 1 H), 3.01 (m, 2 H), 2.57 (m, 1 H), 2.25 (m, 1 H), 1.89 (m, 1 H), 1.80 (m, 1 H), 1.66 (m, 1 H), 1.49 (m, 1 H), 1.41 (dd, J = 13.4, 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.80, 157.32, 147.42, 144.762, 143.09, 141.89, 141.28, 140.996, 137.86, 137.75, 137.415, 137.29, 134.40, 134.05, 133.85, 133.81, 133.61, 133.56, 133.38, 132.29, 131.62, 130.60, 128.66, 128.60, 128.48, 128.42, 128.29, 128.22, 128.18, 127.27, 121.78, 119.41, 119.41, 114.38, 101.50, 73.81, 59.07, 56.36, 55.58, 42.16, 39.72, 27.66, 27.48, 24.86, 14.16. (C–P coupling constants not removed); LRMS (m/z) 612 (2), 305 (100), 277 (2), 227 (6), 199 (3), 183 (5), 155 (2), 152 (2), 136 (8); HRMS calcd for $C_{39}H_{37}N_2O_3P$ 612.2544, found 612.2542.

(*S*)-(+)-Bis-*O*-[2-(diphenylphosphino)benzoyl]-1,1′-binaphthol (6) (Procedure B). The reaction was run with (*S*)-(−)-1,1′-binaphthol (96.8 mg, 0.338 mmol), 2-(diphenylphosphino)benzoic acid (226.5 mg, 0.740 mmol), and DCC (0.167 g, 0.809 mmol) in dichloromethane (1.5 mL) for 8 h. The residue was chromatographed on a 2- × 11-cm column of silica gel with 15% ethyl acetate/hexanes to give the diester as a white solid (193.5 mg). The solid was recrystallized from hot dichloromethane/hexanes to give the diester **6** as white needles (160 mg, 54.9%).

Ligand (*S*)-(+)-6: white needles from dichloromethane/hexanes; mp 114–116 °C; R_f 0.55 (30% ethyl acetate/hexanes); $[\alpha]_D$ = +55.44 (±0.55)° (c 1.11, dichloromethane); IR (neat film from $CDCl_3$) 3069, 3056, 3016, 3002, 2932, 2855, 1955 (w), 1901 (w), 1817 (w), 1731 (s), 1585, 1511, 1478, 1463, 1434, 1267, 1245, 1220, 1206, 1137, 1089, 1043, 908, 807, 742, 696, 649 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (d, J = 8.9 Hz, 2 H), 7.85 (d, J = 7.9 Hz, 2 H), 7.38 (td, J = 6.9, 1.2 Hz, 2 H), 7.08–7.30 (m, 28 H), 7.06 (ddd, J = 7.9, 3.7, 1.3 Hz, 2 H), 6.98 (td, J = 7.5, 1.1 Hz, 2 H), 6.75 (ddd, J = 6.9, 4.0, 1.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.31, 146.73, 141.03 (d, J = 27.5 Hz), 137.92 (d, J = 11.2 Hz), 137.62 (d, J = 11.7 Hz), 134.02, 133.88, 133.82, 133.75, 133.68, 133.61, 133.41, 133.16, 132.66, 132.49, 131.91, 131.36, 130.78, 129.24, 128.55, 128.45, 128.37, 128.28, 127.73, 126.79, 125.89, 125.55, 123.41, 121.88; LRMS (m/z) 862 (0.5), 558 (9), 557 (22), 306 (19), 305 (87), 290 (21), 289 (100), 242 (10), 241 (18), 212 (10), 211 (17), 183 (28); HRMS calcd for $C_{58}H_{40}O_4P_2$ 862.2404, found 862.2406. Anal. Calcd for $C_{58}H_{40}O_4P_2$·0.67H_2O: C, 79.62; H, 4.76. Found: C, 79.64; H, 4.85, and C, 79.58; H, 5.08.

(−)-1,3:4,6-Di-*O*-benzylidene-D-mannitol, Bis[2-(diphenylphosphino)-benzoate], Hemietherate Complex (7) (Procedure A). The reaction was run with 1,3:4,6-di-*O*-benzylidene-D-mannitol (272 mg, 0.759 mmol), 2-(diphenylphosphino)benzoic acid (0.5345 g, 1.745 mmol), and DCC (0.396 g, 1.92 mmol) in THF (5.5 mL) for 25 h. The residue was chromatographed on a 2- × 12-cm column of silica gel with 5–10% ether/hexanes to afford impure product. The impure product was mixed with hot ether, and dichloromethane was added with swirling until the mixture became homogeneous. The solution was stored in a refrigerator (7 °C), allowing the formation of diester **7** as clear plates. The crystallization was repeated once more for a total yield of 0.342 g (46.4%) for the two crops. The product holds 0.5 mol ether of crystallization.

Ligand 7: mp 125–127 °C (plates from ether/dichloromethane); R_f 0.59 (30% ethyl acetate/hexanes); $[\alpha]_D$ = −47.83 (±0.39)° (c 1.68, dichloromethane); IR (neat film from $CDCl_3$ solution) 3069, 3056, 2866, 1955 (w), 1890 (w), 1816 (w), 1722 (s), 1585, 1478, 1463, 1435, 1377, 1312, 1266, 1249, 1224, 1140, 1111, 1058, 1027, 998, 909, 745, 731, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.16 (dd, J = 7.7, 3.7 Hz, 2 H), 7.1–7.5 (m, H), 6.92 (dd, J = 7.8, 3.9 Hz, 2 H), 5.49 (ddd, J = 9.8, 9.2, 5.3 Hz, 2 H), 5.24 (s, 2 H), 4.215 (dd, J = 10.4, 5.5 Hz, 2 H), 4.10 (d, J = 9.5 Hz, 2 H), 3.48 (q, J = 7.0 Hz, 2 H, etherate), 3.23 (t, J = 10.4 Hz, 2 H), 1.21 (t, J = 7.0 Hz, 3 H), etherate); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.49 (d, J = 2.6 Hz), 140.51 (d, J = 7.4 Hz), 137.98, 137.88, 137.77, 137.65, 137.28, 134.60, 134.18, 133.90, 133.73, 133.51, 133.34, 132.59, 131.30, 129.02, 128.79, 128.72, 128.65, 128.1–5 (m), 128.02, 126.23, 100.87, 75.62, 67.30, 62.24; LRMS (LSIMS) (m/z) 967 (12, bis-phosphine oxide), 935 (100), 829 (10), 629 (12), 523 (21). Anal. Calcd for $C_{58}H_{48}O_8P_2$: C, 74.51; H, 5.17. Found: C, 74.37; H, 5.55.

(+)-1,2:5,6-Di-*O*-isopropylidene-3,4-bis-*O*-[2′-(diphenylphosphino)-benzoyl]-D-mannitol (8) (Procedure B). The reaction was run with (+)-1,2:5,6-di-*O*-isopropylidene-D-mannitol (0.105 g, 0.400 mmol, Aldrich), 2-(diphenylphosphino)benzoic acid (0.269 g, 0.878 mmol), and DCC (0.206 g, 0.966 mmol) in dichloromethane (1.4 mL) for 11 h. The residue was chromatographed on a 2- × 13-cm column of silica gel with 10% ethyl acetate/hexanes to give the diester **8** as a clear oil (44.3 mg, 13.2%).

Ligand 8: clear oil; R_f 0.83 (60% ethyl acetate/hexanes); $[\alpha]_D$ = +55.45 (±0.15)° (c 4.29, dichloromethane); IR (neat film from $CDCl_3$) 3070, 3055, 2987, 2935, 2890, 1724 (s), 1585, 1478, 1463, 1434, 1381, 1372, 1245 (s), 1139, 1101, 1066, 1054, 909, 850, 745, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.15 (m, 2 H), 7.18–7.42 (m, 24 H), 6.94 (m, 2 H), 5.47 (dt, J = 6.0, 1.1 Hz, 2 H), 4.07 (q, J = 6.1 Hz, 2 H), 3.68 (dd, J = 8.5, 6.1 Hz, 2 H), 3.59 (dd, J = 8.6, 6.5 Hz, 2 H), 1.21 (s, 6 H), 1.20 (s, 6 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.46, 165.40, 141.71 (d, J = 28.8 Hz), 137.97 (d, J = 12.3 Hz), 134.53, 134.18 (d, J = 20.6 Hz), 134.06 (d, J = 21.0 Hz), 133.30 (d, J = 18.1 Hz), 132.50, 131.24, 128.811, 128.69, 128.55, 128.43, 109.30, 74.41, 72.40, 65.82, 26.18, 24.96; LRMS (m/z) 823 (2), 305 (100), 289 (8), 277 (11), 227 (13), 199 (10), 183 (13), 165 (6), 152 (8); HRMS calcd for $C_{50}H_{48}O_8P_2$ + H^+ 839.2905, found 839.2903.

(−)-3-Aza-3-benzyl-1(*R*),5(*R*)-dihydroxy-1,5-bis-*O*-[2′-(diphenylphosphino)benzoyl]-1,5-diphenylpentane (9) (Procedure B). The reaction was run with 3-aza-3-benzyl-1(*R*),5(*R*)-dihydroxy-1,5-diphenylpentane (0.223 g, 0.642 mmol), 2-(diphenylphosphino)benzoic acid (0.413 g, 1.348 mmol), and DCC (0.285 g, 1.38 mmol) in dichloromethane (3 mL) for 36 h. The residue was chromatographed on a 2.5- × 14-cm column of silica gel with 5% ethyl acetate/hexanes and then rechromatographed with 5:20:75 ethyl acetate/chloroform/hexanes to afford ligand **9** as a glassy oil (0.179 g, 30.2%).

Ligand (−)-9: glass oil; R_f 0.60 (30% ethyl acetate/hexanes); $[\alpha]_D$ = −5.04 (±0.4)° (c 1.79, dichloromethane); IR (neat film from $CDCl_3$) 3066, 3031, 2957, 2929, 2830, 1952 (w), 1882 (w), 1813 (w), 1716 (s), 1586, 1495, 1478, 1463, 1455, 1434, 1361, 1310, 1268, 1252, 1141, 1106, 1057, 1027, 1002, 965, 909 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (m, 2 H), 6.85–7.4 (m, 34 H), 5.90 (t, J = 6.6 Hz, 2 H), 3.68 (d, J = 4.0 Hz, 2 H), 3.47 (d, J = 4.0 Hz, 2 H), 2.84 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.98, 140.85, 140.81, 139.23, 138.83, 138.35, 138.18, 138.01, 134.66, 134.44, 134.28, 134.23, 134.01, 133.96, 132.03, 130.98, 128.85, 128.68, 128.59, 128.50, 128.28, 128.17, 128.07, 127.89, 127.79, 127.17, 127.07, 126.73, 74.3, 58.98, 58.52; LRMS (LSIMS) (m/e) 924 (55), 618 (76), 528 (100).

(+)-(2*R*,3*R*)-*N*-Benzyl-2,3-bis-*O*-[2′-(diphenylphosphino)benzoyl]-tartrimide (10) (Procedure A). The reaction was run with (+)-(2*R*,3*R*)-*N*-benzyltartrimide (0.303 g, 1.37 mmol), 2-(diphenylphosphino)benzoic acid (0.922 g, 3.01 mmol), and DCC (0.649 g, 3.45 mmol) in THF (5 mL) for 24 h. The residue was chromatographed on a 2.5- × 13-cm column of silica gel with 10–20% ethyl acetate/hexanes (gradient) to afford ligand **10** as an oil (0.88 g, 70.4%).

Ligand (+)-10: clear oil; R_f 0.36 (1:1 ether/hexanes); $[\alpha]_D$ = +77.5 (±0.3)° (c 1.025, dichloromethane); IR (neat film from $CDCl_3$) 3056, 3070, 2935, 1955 (w), 1888 (w), 1804 (w), 1730 (s), 1586, 1479, 1463, 1435, 1399, 1350, 1332, 1271, 1249, 1171, 1138, 1105, 1069, 1037, 998, 909 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.08 (m, 2 H), 7.13–7.45 (m, 29 H), 6.92 (m, 2 H), 4.73 (d, J = 14.2 Hz, 1 H), 4.58 (d, J = 14.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.94, 165.57, 165.54, 141.63 (d, J = 28.8 Hz), 137.66 (d, J = 11.2 Hz), 137.39 (d, J = 11.6 Hz), 134.72, 134.46, 134.16 (d, J = 20.9 Hz), 134.00 (d, J = 20.7 Hz), 132.96, 132.17 (d, J = 18.6 Hz), 131.75, 131.72, 128.94 (br), 128.81, 128.77, 129.19 (d, J = 4.6 Hz), 128.56, 128.36, 128.23, 73.03, 42.81; LRMS (m/z) 475 (13), 384 (9), 366 (5), 337 (8), 307 (8), 306 (43), 305 (100), 303 (7), 289 (6), 285 (5), 278 (12), 277 (52), 229 (11), 228 (9), 227 (14), 216 (8), 201 (12); HRMS calcd for $C_{49}H_{37}NO_6P_2$ + H^+ 798.2176, found, 798.2174. Anal. Calcd for $C_{49}H_{37}NO_6P_2$: C, 73.77; H, 4.67. Found: C, 73.50; H, 5.01.

(−)-1(*R*),2(*R*)-Bis[2′-(diphenylphosphino)benzamido]-1,2-diphenylethane ((−)-11) (Procedure B). The reaction was run with (+)-1(*R*),2(*R*)-diphenylethanediamine (0.338 g, 1.59 mmol, $[\alpha]_D$ = +103.0 (±0.8)° (c 1.115, methanol)), 2-(diphenylphosphino)benzoic acid (1.024 g, 3.334 mmol), and DCC (0.720 g, 3.493 mmol) in dichloromethane (10 mL) for 4 h. The residue was chromatographed on a 4- × 11-cm column of silica gel with 1:3 ether/hexanes (100 mL) and then 30% ethyl acetate/hexanes (400 mL) followed by 50% ethyl acetate/hexanes (200 mL) to elute the diamide (−)-**11** as a glass (0.798 g, 63.5%).

Ligand (−)-11: white solid precipitated from dichloromethane with hexanes; mp 135–136 °C; R_f 0.61 (60% ethyl acetate/hexanes); $[\alpha]_D$ = −27.5 (±0.5)° (c, 1.63, dichloromethane); IR (neat film from $CDCl_3$) 3410, 3326 (br), 3071, 3046, 2979, 2937, 2873, 1956 (w), 1889 (w), 1818 (w), 1733, 1653 (s), 1586, 1564, 1514 (s), 1459, 1154, 1122, 1091, 1071, 1046, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.64 (m, 2 H), 7.15–7.35 (m, 16 H), 7.05–7.15 (m, 16 H), 6.88–6.93 (m, 6 H), 5.37 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.20, 140.53 (d, J = 24.5 Hz), 138.40, 137.69 (d, J = 12.2 Hz), 137.34 (d, J = 12.0 Hz), 136.77 (d, J = 22.4 Hz), 134.34, 133.87 (d, J = 20.5 Hz), 133.67 (d, J = 21.2 Hz), 130.28, 128.70, 128.48, 128.39, 128.33 (br, >1 signal), 127.91, 127.86, 127.63, 127.49, 59.60; LRMS (m/e) 789 (0.1), 788 (0.2), 787 (0.1), 786 (0.1), 772 (0.1), 771 (0.5), 770 (0.8), 590 (2), 481 (6), 404 (6), 403 (8),

394 (12), 392 (7), 306 (8), 305 (49), 304 (100), 303 (24), 201 (9), 199 (6), 184 (6), 183 (35), 181 (11), 180 (67); HRMS calcd for $C_{52}H_{42}N_2O_2P_2$ 788.2725, found, 788.2722. Anal. Calcd for $C_{52}H_{42}N_2O_2P_2$: C, 79.17; H, 5.37; N, 3.55; P, 7.85. Found: C, 79.17; H, 5.37; N, 3.50; P, 8.24.

(+)-1(*S*),2(*S*)-Bis[2'-(diphenylphosphino)benzamido]-1,2-diphenylethane ((+)-11) (Procedure B). The reaction was run with (-)-1(*S*),2(*S*)-diphenylethanediamine (0.338 g, 1.59 mmol, $[\alpha]_D = -104.0°$ (*c* 1.09, methanol), 2-(diphenylphosphino)benzoic acid (1.024 g, 3.343 mmol), and DCC (0.720 g, 3.493 mmol) in dichloromethane (10 mL) for 6 h. The residue was chromatographed on a 4- × 11-cm column of silica gel with 1:3 ether/hexanes (100 mL) and then 30% ethyl acetate/hexanes (400 mL) followed by 50% ethyl acetate/hexanes (200 mL) to elute the diamide **11** as a glass (0.980 g, 78.0%).

Ligand (+)-11: white solid precipitated from dichloromethane with hexanes; R_f 0.61 (60% ethyl acetate/hexanes); $[\alpha]_D = +27.4$ (±0.6)° (*c* 1.62, dichloromethane).

(+)-1,2-Bis-*N*-[2'-(diphenylphosphino)benzoyl]-1(*R*),2(*R*)-diaminocyclohexane (12) (Procedure A). The reaction was run with (-)-1(*R*),2(*R*)-diaminocyclohexane (0.5349 g, 4.68 mmol), 2-(diphenylphosphino)benzoic acid (3.019 g, 9.83 mmol), DMAP (61.0 mg, 0.500 mmol), and DCC (2.13 g, 10.3 mmol) in dichloromethane (30 mL) for 6 h. The residue was chromatographed on silica gel with 15–30% ethyl acetate/hexanes (gradient) followed by recrystallization from dichloromethane/ether to give the diamide **12** (2.96 g, 89.9%), $[\alpha]_D = +55.1°$ (*c* 2.85, dichloromethane).

Using (-)-1(*R*),2(*R*)-diaminocyclohexane obtained from Aldrich, ligand **12** was obtained as a waxy solid which precipitated from dichloromethane with hexanes, mp 80–120 °C, R_f 0.43 (50% ethyl acetate/hexanes), $[\alpha]_D = 46.7$ (±0.3)° (*c*, 2.366, dichloromethane). This sample was used for the cyclizations to oxazolidin-2-ones which suggests that the ee's obtained may be lower than they should be if the higher rotating diamide were employed; IR (neat film from $CDCl_3$) 3303, 3070, 2935, 2857, 1955 (w), 1887 (w), 1817 (w), 1645 (s), 1538, 1478, 1434, 1328, 1306, 1162, 1091, 909 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.57 (m, 2 H), 7.15–7.26 (m, 24 H), 6.91 (m, 2 H), 6.31 (br d, *J* = 7.7 Hz, 2 H, N–H), 3.77 (m, 2 H), 1.87 (m, 2 H), 1.62 (m, 2 H), 0.9–1.3 (m, 6 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.46, 140.80 (d, *J* = 24.2 Hz), 137.96 (d, *J* = 11.8 Hz), 137.88 (d, *J* = 12.3 Hz), 136.81 (d, *J* = 21.6 Hz), 134.34, 133.97 (d, *J* = 20.3 Hz), 130.23, 128.79, 128.66, 128.57, 128.51, 128.43, 127.63, 127.55, 53.68, 31.71, 24.41; LRMS (FAB) (*m/e*) 722 (25, bis-phosphine oxide), 690 (68), 614 (4), 613 (5), 538 (10), 307 (5), 227 (38). Anal. Calcd for $C_{44}H_{42}N_2O_2P_2$: C, 76.29; H, 6.11; N, 4.04; P, 8.94. Found: C, 76.16; H, 6.28; N, 4.02; P, 8.93.

(+)-11(*S*),12(*S*)-Bis[2'-(diphenylphosphino)benzamido]-9,10-dihydro-9,10-ethanoanthracene (13) (Procedure B). The reaction was run with (+)-11(*S*),12(*S*)-diamino-9,10-dihydro-9,10-ethanoanthracene (0.253 g, 1.071 mmol, $[\alpha]_{405} = +81.3°$ (*c* 2.275, methanol)), 2-(diphenylphosphino)benzoic acid (0.6887 g, 2.248 mmol), and DCC (0.463 g, 2.248 mmol) in dichloromethane (5 mL) for 10 h. The residue was chromatographed on a 4.5- × 11.5-cm column of silica gel with 900 mL of 30% ethyl acetate/hexanes to give diamide **13** as a glass foam (0.860 g, 98.8%).

Ligand (+)-13: glass foam; R_f 0.63 (50% ethyl acetate/hexanes); $[\alpha]_{405} = +211.2$ (±0.3)° (*c* 3.35, 26 °C, dichloromethane); $[\alpha]_{477} = +84.7$ (±0.3)° (*c* 3.35, 25 °C, dichloromethane); IR (neat film from $CDCl_3$) 3418, 3396, 3305 (br), 3070, 3053, 3026, 1955 (w), 1905 (w), 1885 (w), 1818 (w), 1652 (s), 1585, 1505 (s), 1480, 1459, 1327, 1308, 1293, 1250, 1228, 1155, 1124, 1090, 1027, 909 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.0–7.45 (m, 34 H), 6.95 (m, 2 H), 5.72 (br d, *J* = 6.8 Hz, 2 H, N–H), 4.42 (d, *J* = 2.4 Hz, 2 H), 3.94 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.00, 141.17 (d, *J* = 26 Hz), 141.028, 136.76 (d, *J* = 12 Hz), 137.36 (d, *J* = 11.6 Hz), 136.45 (d, *J* = 21.5 Hz), 134.54, 133.95 (d, *J* = 20.3 Hz), 133.79 (d, *J* = 20.2 Hz), 130.36, 128.88, 128.79, 128.74, 128.65, 128.63, 127.60 (d, *J* = 5.1 Hz), 126.75, 126.64, 126.03, 124.83; LRMS (*m/z*) 183 (38), 241 (15), 289 (100), 305 (40), 321 (22), 509 (12), 913 (69); HRMS calcd for $C_{54}H_{42}N_2O_2P_2 + H^+$ 813.2803, found 813.2800. Anal. Calcd for $C_{54}H_{42}N_2O_2P_2$: C, 79.79; H, 5.21; N, 3.45. Found: C, 80.01; H, 5.28; N, 3.36.

General Procedure for Palladium Catalysis with Chiral 2-(Diphenylphosphino)benzoate Esters (See Table I for summary of catalysis using chiral ester and amide ligands derived from 2-DPPBA). **1-(*p*-Tolylsulfonyl)cyclopent-5-eno[4,3-*d*]-(3a*S*,6a*R*)-oxazolidin-2-one (Scalemic) (2).** To a 1 M solution of 1(*R*)*,4(*S*)*-dihydroxycyclopent-2-ene in anhydrous THF was added *p*-toluenesulfonyl isocyanate (205 mol %) dropwise, resulting in an exothermic reaction. The solution was stirred at 50 °C for 1 h.

A dry flask was charged with chiral ligand (15–20 mol % for monodentate and 7.5 mol % for bidentate ligands) and tris(dibenzylideneacetone)dipalladium(0)-chloroform complex (2.5 mol %) under nitrogen, and anhydrous THF was added. The black-purple slurry was stirred at room temperature until a homogeneous solution was obtained and then at 50 °C for 10 min, resulting in a clear, red-orange solution (0.05 M in palladium). The catalyst solution was then cooled to 0 °C, and the bis-carbamate solution was added dropwise. The reaction was stirred at 0 °C until thin layer chromatography (50% ethyl acetate/hexanes) indicated complete consumption of bis-carbamate, and solvent was then removed in vacuo. The resulting brown-orange oil was directly chromatographed on silica gel with 10–20% ethyl acetate/hexanes (gradient) to afford scalemic oxazolidinone **2**.

Oxazolidinone 2: mp 131 °C; R_f 0.59 (50% ethyl acetate/hexanes); IR (neat) 3072, 2983, 2925, 1776 (s), 1596, 1365, 1169, 1144, 1091, 1052, 815, 753, 705, 661, 609 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.95 (d, *J* = 8.4 Hz, 2 H), 7.36 (d, *J* = 8.1 Hz, 2 H), 6.02 (m, 2 H), 5.29 (dd, *J* = 7.4, 1.3 Hz, 1 H), 5.11 (ddd, *J* = 8.3, 5.8, 1.8 Hz, 1 H), 2.83 (m, 1 H), 2.68 (m, 1 H), 2.45 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.35, 145.52, 134.99, 133.86, 129.75, 128.33, 127.97, 76.74, 66.26, 38.95, 21.68; LRMS (*m/z*) 215 (42), 171 (21), 170 (33), 139 (3), 119 (4), 96 (2), 92 (13), 91 (100); HRMS calcd for $C_{13}H_{13}NO_4S - SO_2$ 215.0946, found 215.0945. Anal. Calcd for $C_{13}H_{13}NO_4S$: C, 55.90; H, 4.69; N, 5.01; S, 11.48. Found: C, 55.91; H, 4.57; N, 4.92; S, 11.37.

Palladium Catalysis with Chiral Ligand (+)-13 (Table I, Entry 13). **1-(*p*-Tolylsulfonyl)cyclopent-5-eno[4,3-*d*]-(3a*S*,6a*R*)-oxazolidin-2-one (Scalemic) (2).** In a typical procedure, a 10-mL flask was charged with 1(*R*)*,4(*S*)*-dihydroxycyclopent-2-ene (51.1 mg, 0.51 mmol) under nitrogen. Anhydrous THF (0.50 mL) was added, and the mixture was stirred at room temperature to give a clear, colorless solution. *p*-Toluenesulfonyl isocyanate (0.159 mL, 206 mg, 0.766 mmol) was added dropwise, resulting in an exothermic reaction, and the solution was stirred at 50 °C for 1 h.

To a 10-mL round-bottom flask containing ligand (+)-**13** (39 mg, 48 mmol, $[\alpha]_{405} = +211$ (±0.3)° (*c* 3.35, dichloromethane)) and tris(dibenzylideneacetone)dipalladium(0)chloroform complex (12.8 mg, 12.4 mmol) under nitrogen was added anhydrous THF (0.5 mL). The black-purple slurry was stirred at room temperature until a homogeneous solution was obtained and then at 50 °C for 10 min, resulting in a clear, orange solution. The catalyst solution was then cooled to 0 °C, and the bis-carbamate solution was added dropwise. The reaction was stirred at 0 °C for 20 min, and then solvent was removed in vacuo. The resulting brown-orange oil was directly chromatographed on 1.5- × 13-cm silica gel with 10–20% ethyl acetate/hexanes (gradient) to afford scalemic oxazolidinone **2** (0.1344 g, 94.3%, $[\alpha]_D = -124.2$ (±0.1)° (*c* 3.41, dichloromethane)) (88.1% optical purity, based on (*S*)-α-methoxyphenylacetate-derived value for $[\alpha]_D$).

4(*S*)-Hydroxy-3(*R*)-*p*-toluenesulfonamidocyclopent-1-ene (Scalemic) (20). A 5-mL round-bottom flask equipped with a reflux condenser was charged with scalemic oxazolidinone **2** (33.6 mg, 0.120 mmol, $[\alpha]_D = -41.48$ (±0.10)° (*c* 3.05, dichloromethane)), potassium carbonate (35.6 mg, 0.258 mmol), and a stir bar. Methanol (0.4 mL) and water (40 mL) were added, and the mixture was stirred at 65 °C for 2.5 h.

After the mixture was cooled to room temperature, glacial acetic acid was added until the mixture became homogeneous (about 6 drops). Following removal of solvent in vacuo, the mixture was flushed through a short column of silica gel to remove the potassium acetate. Removal of solvent in vacuo gave an oily residue. The residue was taken up in a very small amount of dichloromethane and precipitated with hexanes. Removal of solvent in vacuo gave 28.3 mg of scalemic hydroxy sulfonamide **20** as a white solid (28.3 mg, 92.8%).

Hydroxy sulfonamide 20: white waxy solid; mp 98–100 °C; R_f 0.36 (50% ethyl acetate/hexanes); IR (neat film evaporated from $CDCl_3$ solution) 3801 (br), 3494 (br), 3278, 3222, 3061, 2940, 1600, 1449, 1327, 1160, 1126, 1093, 1037, 997, 933, 838, 814, 707, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.82 (dt, *J* = 8.4, 2.1 Hz, 2 H), 7.34 (d, *J* = 8.1 Hz, 2 H), 5.83 (m, 1 H, H-3), 5.38 (m, 1 H, H-4), 5.04 (br d, *J* = 7.7 Hz, 1 H, N–H), 4.24 (m, 2 H, H-1, H-2), 2.58 (dtd, *J* = 17.5, 4.85, 2.6 Hz, 1 H, H-1a), 2.45 (s, 3 H, Ar-CH_3), 2.32 (ddt, *J* = 17.5, 4.4, 1.8 Hz, 1 H, H-1b); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 143.81 (Ar-C-1), 137.79 (Ar-C-4), 131.92 (C-3), 129.90 (Ar-C-2), 129.29 (C-4), 127.37 (Ar-C-3), 70.29 (C-2), 61.40 (C-1), 39.97 (C-5), 21.23 (Ar-CH_3); LRMS (*m/z*) 253 (0.9), 210 (5), 198 (4), 197 (35), 172 (3), 157 (5), 156 (4), 155 (37), 139 (13), 133 (21), 132 (4), 124 (3), 108 (5), 107 (7), 98 (100); HRMS calcd for $C_{12}H_{15}NO_3S$ 253.0774, found 253.0762.

(-)-4(*R*)-[(*S*)-α-Methoxyphenylacetoxy]-3(*S*)-*p*-toluenesulfonamidocyclopent-1-ene (21a). To a stirred solution of *S*-(+)-α-methoxyphenylacetic acid (62.4 mg, 0.376 mmol), 4(*S*)-hydroxy-3 (*R*)-*p*-toluenesulfonamidocyclopent-1-ene (**20**) (79.3 mg, 0.313 mmol, prepared from ligand (-)-**11**), and DCC (77.5 mg, 0.376 mmol) in anhydrous dichloromethane (1.2 mL) was added DMAP (1.9 mg, 15.7 mmol). The mixture was stirred at room temperature for 26 h. The reaction slurry was filtered through a 1-cm pad of Celite wetted with dichloromethane.

The filter cake was washed with dichloromethane (3 × 5 mL), and solvent was removed in vacuo. The residue was chromatographed on 2- × 14-cm silica gel with 25% ethyl acetate/hexanes to afford ester products (135.6 mg, 107%). The entire sample was dissolved in dichloromethane, and an aliquot was removed for ^{1}H NMR analysis. Integration of diastereomeric signals showed a 9.4:1 ratio of diastereomers **21a** and **21b**.

An analytical sample of the major diastereomer **21a** was prepared by crystallization from ethyl acetate/hexanes followed by trituration with 30% ethyl acetate/hexanes. **Ester 21a**: mp 98–100 °C (ethyl acetate/hexanes); R_f 0.53 (50% ethyl acetate/hexanes); $[\alpha]_D$ = –9.0 (±0.2)° (*c* 1.56, dichloromethane); IR (neat film evaporated from $CDCl_3$ solution) 3312 (br), 2936, 1746 (s), 1599, 1495, 1331, 1163, 1014, 990, 912, 816 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.63 (br d, *J* = 8.2 Hz, 2 H), 7.39 (m, 5 H), 7.25 (br d, *J* = 8.0 Hz, 2 H), 5.70 (ddd, *J* = 5.9, 4.9, 2.5 Hz, 1 H), 5.50 (m, 1 H), 5.07 (td, *J* = 6.0, 2.0 Hz, 1 H), 4.72 (br d, *J* = 10.6 Hz, 1 H, NH), 4.69 (s, 1 H), 4.48 (m, 1 H), 3.40 (s, 3 H), 2.42 (s, 3 H), 2.55 (dddd, *J* = 18.0, 6.2, 2.3, 1.7 Hz, 1 H), 2.45 (m, 1 H), 2.05 (br d, *J* = 18.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.77, 143.78, 137.68, 135.94, 130.88, 129.88, 129.72, 128.81, 128.72, 127.09, 126.97, 81.92, 72.48, 59.60, 57.15, 37.68, 21.27; LRMS (*m/z*) 252 (17), 235 (8), 186 (5), 172 (6), 171 (7), 148 (10), 122 (70), 121 (55), 118 (7), 105 (18), 92 (12), 91 (100); HRMS calcd for $C_{21}H_{23}NO_5S$ – $C_9H_9O_2$ 252.0694, found 252.0696. Anal. Calcd for $C_{21}H_{23}NO_5S$: C, 62.83; H, 5.77; N, 3.49. Found: C, 62.96; H, 6.04; N, 3.43.

1-(*p*-Tolylsulfonyl)-4(*S*)-[(benzyloxy)methyl]cyclopent-5-eno[4,5-*d*]-(3a*R*,6a*S*)-oxazolidin-2-one (Scalemic) (17). To a stirred solution of diol **16** (83.4 mg, 0.379 mmol) in anhydrous THF (0.38 mL) was added *p*-toluenesulfonyl isocyanate (118 mL, 0.776 mmol). The mixture was stirred at 50 °C for 0.5 h. To a mixture of tris(dibenzylideneacetone)dipalladium(0)–chloroform complex (9.8 mg, 9.5 mmol) and ligand (+)-**13** (23.1 mg, 28.4 mmol) was added anhydrous THF (0.10 mL), and the mixture was stirred till a clear, tan-yellow solution was obtained. The catalyst solution was then cooled to 0 °C, and the bis-carbamate solution was added dropwise. Residual bis-carbamate was transferred with more THF (0.10 mL), and the reaction was stirred at 0 °C to room temperature over 3 h and then at room temperature for 27 h. Solvent was removed in vacuo, and the residue was chromatographed on a 2- × 12-cm column of silica gel with 10–20% ethyl acetate/hexanes to afford the oxazolidinone **17** as a glassy oil (110.4 mg, 73.0%, $[\alpha]_D$ = –69.2 (±0.4)° (*c* 1.10, dichloromethane)).

5(*S*)-(Benzyloxy)methyl-4(*S*)-hydroxy-3(*R*)-*p*-toluenesulfonamidocyclopent-1-ene (Scalemic) (22). A slurry of scalemic oxazolidinone **17** (33.6 mg, 0.120 mmol, $[\alpha]_D$ = –69.2 (±0.4)° (*c* 1.10, dichloromethane)) and potassium carbonate (84 mg, 0.61 mmol) in 10:1 methanol/water (2.2 mL) was stirred at room temperature for 2 h and at 60 °C for 2.5 h. After the mixture was cooled to room temperature, glacial acetic acid was added (6 drops) and solvent was removed in vacuo. Water (10 mL) was added, and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The organic layer was washed with saturated aqueous sodium chloride and dried over magnesium sulfate, and the solvent was removed in vacuo to afford hydroxy sulfonamide **22** as a thick oil (96.2 mg, 93.2%) which was directly acylated with (*S*)-(+)-α-methoxyphenylacetic acid.

Hydroxy sulfonamide 22: mp 82–84 °C; R_f 0.67 (80% EtOAc/Hex); IR (neat) 3500 (br), 3287 (br), 3062, 3030, 2923, 2862, 1597, 1455, 1362, 1329, 1160, 1092, 1027, 930, 815, 737 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, *J* = 8.31, 2 H), 7.26–7.37 (m, 7 H), 5.75 (ddd, *J* = 5.8, 2.1, 2.0 Hz, 1 H), 5.52 (dt, *J* = 5.9, 2.0 Hz, 1 H), 5.00 (br d, *J* = 7.24, 1 H, N–H), 4.49 (s, 2 H, $PhCH_2O$), 4.26 (ddd, *J* = 8.0, 6.2, 1.9 Hz, 1 H), 4.08 (m, 1 H), 3.5 (dd, *J* = 9.1, 5.3 Hz, 1 H, H-6), 3.35 (dd, *J* = 9.91, 7.0 Hz, 1 H, H-6), 2.87 (m, 1 H, H-5), 2.44 (s, 3 H, Ar-CH_3), 2.25 (br d, *J* = 3.7 Hz, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.83, 138.19, 137.44, 13.87, 130.74, 129.92, 128.58, 127.87, 127.73, 127.36, 73.34, 73.16, 70.57, 60.27, 52.94, 21.32; LRMS (*m/z*) 282 (9), 252 (2), 236 (2), 234 (4), 218 (24), 188 (3), 156 (2), 139 (2), 112 (5), 111 (7), 110 (11), 107 (4), 97 (3), 96 (10), 94 (3), 91 (16), 91 (100); HRMS calcd for $C_{20}H_{23}NO_4S$ – C_7H_7 282.0799, found 282.0796.

5(*R*)-[(Benzyloxy)methyl]-4(*S*)-[(*S*)-α-methoxyphenylacetoxy]-3(*R*)-*p*-toluenesulfonamidocyclopent-1-ene (23a) and 5(*S*)-[(benzyloxy)methyl]-4(*R*)-[(*S*)-α-methoxyphenylacetoxy]-3(*S*)-*p*-toluenesulfonamidocyclopent-1-ene (23b). To a stirred solution of DMF (0.10 mL, 1.29 mmol) in anhydrous acetonitrile (0.50 mL) at –15 °C was added dropwise freshly distilled oxalyl chloride (30.8 mL, 0.322 mmol). The mixture was stirred at –15 °C for 15 min, and (*S*)-(+)-α-methoxyphenylacetic acid (53.5 mg, 0.322 mmol) was added to give a clear solution which was stirred at –15 °C for 15 min.

A solution of scalemic hydroxy sulfonamide **22** (96.2 mg, 0.258 mmol) and pyridine (57.3 mL, 0.708 mmol) in anhydrous acetonitrile (0.20 mL) was added dropwise. Residual alcohol/pyridine was transferred with more acetonitrile (0.10 mL), and the solution was stirred at –15 °C to room temperature until thin layer chromatography (50% ethyl acetate/hexanes) indicated consumption of starting material (about 6 h). Dichloromethane (40 mL) was added, and the solution was washed with 0.5 N sodium bisulfate (10 mL), saturated aqueous sodium bicarbonate (10 mL), and saturated aqueous sodium chloride (10 mL). The organic layer was dried over magnesium sulfate, and solvent was removed in vacuo to give a beige oil. The residue was chromatographed on 2- × 13-cm silica gel with 20–30% ethyl acetate/hexanes to afford ester products (120 mg, 89.3%). The entire sample was dissolved in dichloromethane, and an aliquot was removed for ^{1}H NMR analysis. Integration of diastereomeric signals showed a 2.243:1 ratio of diastereomers **23a** and **23b**.

Esters 23a and 23b (major and minor diastereomers): oil; R_f 0.71 (50% ethyl acetate/hexanes) inseparable; IR (neat film evaporated from $CDCl_3$ solution) 3300 (br), 3070, 3040, 2935, 2870, 1755 (s), 1600, 1490, 1455, 1335, 1160, 1090, 920, 815, 730, 695, 660 cm^{-1}; ^{1}H NMR ($CDCl_3$, major diastereomer, 400 MHz) δ 7.2–7.5 (m, 7 H), 7.14 (dm, *J* = 7.9 Hz), 5.74 (dt, *J* = 5.9, 2.7 Hz, 1 H, H-3), 5.63 (dm, *J* = 5.9 Hz, 1 H, H-4), 4.80 (dm, *J* = 4.0 Hz, 1 H, H-1), 4.73 (s, 1 H, a-H), 4.45 (m, 2 H, N–H, H-2), 4.41 (s, 2 H, $PhCH_2$), 3.39 (s, 3 H, OCH_3), 3.48 (dd, *J* = 9.2, 5.2 Hz, 1 H, H-6a), 3.36 (m, 1 H, H-6b), 2.80 (m, 1 H, H-5), 2.39 (s, 3 H, Ar-CH_3); ^{1}H NMR ($CDCl_3$, minor diastereomer, 400 MHz) δ 7.61 (dm, *J* = 8.3 Hz, 2 H), 7.2–7.5 (m, 7 H), 5.70 (dt, *J* = 5.8, 2.1 Hz, 1 H, H-3), 5.55 (dt, *J* = 5.9, 1.9 Hz, 1 H, H-4), 4.97 (dd, *J* = 6.0, 2.7 Hz, 1 H, H-1), 4.71 (s, 1 H, a-H), 4.63 (d, *J* = 10.1 Hz, 1 H, N–H), 4.55 (m, 1 H, H-2), 4.38 (s, 2 H, $PhCH_2$), 3.40 (s, 3 H, OCH_3), 3.36 (m, 2 H, H-6a,b), 2.62 (m, 1 H, H-5), 2.42 (s, 3 H, $ArCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.60, 169.10, 143.44, 143.32, 137.84, 137.47, 137.00, 135.92, 135.87, 133.15, 132.18, 131.99, 130.92, 129.65, 129.50, 129.18, 129.07, 128.68, 128.60, 128.27, 127.52, 127.31, 127.27, 126.96, 126.90, 126.84, 126.78, 82.31, 82.02, 75.36, 74.74, 73.01, 72.96, 69.56, 69.52, 59.36, 59.13, 57.37, 57.23, 51.83, 51.00, 21.44.

Oxazolidinone (Scalemic) 19. To a stirred solution of 1(*R*),4(*S*)-dihydroxy-*endo*-tricyclo[4.2.2.1]undeca-2,8-diene (**18**) (96.1 mg, 0.540 mmol) in anhydrous THF (0.5 mL) at room temperature was added *p*-toluenesulfonyl isocyanate (169 mL, 1.107 mmol). The solution was stirred at 50 °C for 2 h.

Meanwhile, a 10-mL round-bottom flask was charged with tris(dibenzylideneacetone)dipalladium(0)–chloroform complex, $Pd_2(dba)_3$·$CHCl_3$ (14.0 mg, 13.5 mmol), (*R,R*)-DPEDA ligand (–)-**11** (31.9 mg, 40.5 mmol), and a stir bar and fitted with a septum under nitrogen. Anhydrous THF (0.50 mL) was added, and the mixture was stirred at 50 °C for 20 min to give a clear, orange solution. The catalyst solution was then allowed to cool to room temperature, and the bis-carbamate solution was added dropwise. Residual bis-carbamate was transferred with extra THF (0.10 mL). The mixture was stirred at room temperature for 4.5 h and then heated at 50 °C for 1 h, at which time the solution developed a black tinge. Solvent was removed in vacuo, and the mixture was chromatographed on a 2- × 5-cm column of silica gel with 20% ethyl acetate/hexanes to give oxazolidinone **19** as a crystalline white solid (99.0 mg, 51.4%).

Oxazolidinone 19: mp 160–161 °C (ethyl acetate/hexanes); R_f 0.58 (60% ethyl acetate/hexanes); $[\alpha]_D$ = +69.4 (±0.3)° (*c* 1.77, dichloromethane) (scalemic); IR ($CDCl_3$ solution) 3070, 3039, 2975, 2938, 2874, 1781 (s), 1598, 1371, 1340, 1322, 1291, 1178, 1133, 1092, 1064, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.94 (dt, *J* = 8.4, 1.8 Hz, 2 H), 7.35 (dm, *J* = 8.0 Hz, 2 H), 5.94 (dd, *J* = 5.8, 3.4 Hz, 1 H), 5.87 (br s, 1 H), 5.75 (m, 2 H), 4.97 (m, 1 H), 4.79 (m, 1 H), 3.16 (m, 1 H), 2.92 (m, 1 H), 2.71 (m, 1 H), 2.45 (s, 3 H), 1.49 (dt, *J* = 8.4, 1.8 Hz, 1 H), 1.39 (dm, *J* = 8.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 151.68, 145.47, 136.41, 135.63, 134.27, 133.55, 129.78, 128.47, 128.35, 120.98, 73.58, 54.88, 49.89, 46.67, 46.40, 38.90, 38.34, 21.45; LRMS (*m/z*) 357 (4.7), 247 (6), 240 (22), 202 (12), 158 (18), 131 (13), 118 (100), 117 (81), 115 (11), 92 (20), 91 (92); HRMS calcd for $C_{19}H_{19}NO_4S$ 357.1036, found 357.1033.

1(*R*)-Hydroxy-2(*S*)-*p*-toluenesulfonamido-*endo*-tricyclo[4.2.2.1]-undeca-3,8-diene (Scalemic) (24). A slurry of scalemic oxazolidinone **24** (94.1 mg, 0.263 mmol, $[\alpha]_D$ = +69.4 (±0.3)° (*c* 1.77, dichloromethane)) and potassium carbonate (80.0 mg, 0.579 mmol) in 10:1 methanol/water (2.2 mL) was stirred at 60 °C for 6 h. After the mixture was cooled to room temperature, glacial acetic acid was added (3 drops) and solvent was removed in vacuo. Water (10 mL) was added, and the aqueous phase was extracted with chloroform (2 × 40 mL). The organic layer was washed with saturated aqueous sodium chloride and dried over magnesium sulfate. The solvent was removed in vacuo, and the residue was chromatographed on a 1- × 10-cm column of silica gel with 30% ethyl acetate/hexanes to afford hydroxy sulfonamide **24** as a thick oil (94.0 mg, 107%) which was directly acylated with (*S*)-(+)-α-methoxyphenylacetic acid.

Hydroxy sulfonamide 24: oil; R_f 0.57 (60% ethyl acetate/hexanes); $[\alpha]_D$ = +15.2 (±0.2)° (*c* 4.65, dichloromethane) (scalemic); IR ($CDCl_3$ solution) 3545 (b), 3270 (b), 3063, 3030, 2966, 2934, 2869, 1434, 1410, 1333, 1160, 1093, 943, 913, 901, 815 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.77 (d, *J* = 8.3 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 6.29 (dd, *J* = 5.5, 3.0 Hz, 1 H), 6.03 (dd, *J* = 5.6, 3.3 Hz, 1 H), 5.77 (br d, *J* = 9.8 Hz, 1 H, N-H), 5.21 (m, 2 H), 3.79 (m, 2 H), 2.98 (br s, 1 H), 2.88 (br s, 1 H), 2.55 (m, 2 H), 2.44 (s, 3 H), 1.46 (m, 2 H), 1.11 (d, *J* = 11.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.49, 138.50, 138.02, 133.73, 133.35, 129.88, 127.85, 127.02, 69.45, 54.34, 51.23, 45.96, 45.75, 45.54, 39.52, 21.27; LRMS (*m/z*) 327 (6), 331 (3), 265 (0.6) Cp, 234 (9), 213 (16), 177 (12), 176 (100) Ts, 172 (48), 160 (46), 155 (45), 131 (20), 129 (13), 117 (13), 110 (37), 108 (11), 95 (46), 92 (36), 91 (79); HRMS calcd for $C_{18}H_{21}NO_3S$ 331.1243, found 331.1247.

1(*R*)-[(*S*)-α-Methoxyphenylacetoxy]-2(*S*)-*p*-toluenesulfonamido-*endo*-tricyclo[4.2.2.1]undeca-3,8-diene (25a). To a mixture of (*S*)-(+)-α-methoxyphenylacetic acid (51.6 mg, 0.310 mmol), 1(*R*)-hydroxy-2(*S*)-*p*-toluenesulfonamido-*endo*-tricyclo[4.2.2.1]undeca-3,8-diene (**24**) (85.7 mg, 0.259 mmol, $[\alpha]_D$ = +15.2 (±0.2)° (*c* 4.65, dichloromethane)), DCC (64.0 mg, 0.310 mmol), and DMAP (1.6 mg, 12.9 mmol) was added anhydrous dichloromethane (1.5 mL). The mixture was stirred at room temperature for 27 h. The reaction slurry was filtered through a 1.5-cm pad of Celite wetted with dichloromethane. The filter cake was washed with dichloromethane (3 × 2 mL), and solvent was removed in vacuo. The residue was chromatographed on 2- × 14-cm silica gel with 20% ethyl acetate/hexanes to afford ester products (132.3 mg, 107%). The entire sample was dissolved in dichloromethane, and an aliquot was removed for ^1H NMR analysis. Integration of diastereomeric signals showed a 14.1:1 ratio of diastereomers **25a** and **25b** (de 86.5%).

An analytical sample of the major diastereomer was prepared by rechromatographing the product mixture on 2- × 14-cm silica gel with 20% ethyl acetate/hexanes (8-mL fractions, impure fractions discarded) to afford 87.1 mg of pure ester **25a**. **Major diastereomer 25a**: mp 158–160 °C (ethyl acetate/hexanes); R_f 0.34 (50% ethyl acetate/hexanes); $[\alpha]_D$ = +47.5 (±0.8)° (*c* 4.355, dichloromethane); IR (neat film evaporated from $CDCl_3$ solution) 3383, 3110, 3030, 2975, 2937, 2876, 1748 (s), 1456, 1424, 1340, 1270, 1178, 1160, 1117, 1095, 1075 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72 (dt, *J* = 8.4, 1.8 Hz, 2 H), 7.35–7.55 (m, 5 H), 7.30 (br, *J* = 7.9 Hz, 2 H), 5.98 (dd, *J* = 5.5, 3.0 Hz, 1 H), 5.87 (dd, *J* = 5.7, 3.4 Hz, 1 H), 5.16 (dd, *J* = 8.5, 6.0 Hz, 1 H), 5.09 (ddd, *J* = 10.0, 5.2, 1.8 Hz, 1 H), 4.82 (s, 1 H), 4.37 (br, *J* = 9.8 Hz, 1 H), 3.89 (m, 1 H), 3.47 (s, 3 H), 2.84 (m, 1 H), 2.75 (m, 1 H), 2.54 (td, *J* = 8.8, 3.4 Hz, 1 H), 2.43 (s, 3 H), 2.22 (m, 1 H), 1.39 (dt, *J* = 8.5, 1.8 Hz, 1 H), 1.20 (dm, *J* = 8.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.98, 143.26, 138.37, 136.79, 136.67, 134.61, 133.86, 129.69, 128.61, 128.54, 127.36, 126.88, 124.36, 82.08, 69.43, 57.61, 51.33, 48.37, 47.46, 44.15, 40.38, 40.00, 21.52; LRMS (*m/z*) 248 (4), 247 (17), 158 (11), 122 (10), 121 (100, C_8H_9O), 105 (9), 93 (9), 92 (60), 91 (53). Anal. Calcd for $C_{27}H_{29}NO_5S$: C, 67.62; H, 6.10; N, 2.92. Found: C, 67.51; H, 6.39; N, 2.81.

Preparation of Scalemic Dimethyl [1-(Benzoyloxy)cyclopent-2-en-4-yl]malonate (29 and 30). A solution of 4.2 mg (4.05 μmol) of $(dba)_3Pd_2{\cdot}CHCl_3$ and 24.3 μmol of chiral ligand in 0.8 mL of THF at room temperature was stirred for 1–2 h and then cooled to 0 °C. In a separate operation, a solution of 0.162 mmol of dimethyl sodiomalonate, prepared from 42.2 mg (0.32 mmol) of dimethyl malonate and 3.89 mg (0.162 mmol) of sodium hydride in 0.8 mL of THF, was added to 50 mg (0.162 mmol) of 1,4-bis(benzoyloxy)-2-cyclopentene (**28**) at 0 °C. The resulting solution was added to the cold (0 °C) solution of the catalyst and stirred at that temperature for 14 h, at which point it was warmed to room temperature. After the solution was diluted with ether, washed with aqueous 0.5 N hydrochloric acid, water, and brine, dried ($MgSO_4$), and evaporated in vacuo, the residue was purified by chromatography (5:1 hexane/ethyl acetate) to give the product. Using 19.4 mg (24.3 μmol) of ligand **10**, there was obtained 20 mg (40% yield) of scalemic product of 64% ee. Using 10.2 mg (24.3 μmol) of ligand (+)-**11**, there was obtained 35 mg (68% yield) of scalemic product of 92% ee. Using 16.8 mg (24.3 μmol) of ligand **12**, there was obtained 43 mg (83% yield) of scalemic product of 93% ee. The spectral data agree to those previously reported. IR ($CDCl_3$): 1752, 1733, 1714, 1437, 1338, 1315 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.04 (m, 2 H), 7.55 (m, 1 H), 7.45 (m, 2 H), 6.10 (m, 1 H), 5.88 (m, 1 H), 3.76 (s, 3 H), 3.75 (s, 3 H), 3.42 (m, 2 H), 2.74 (m, 1 H), 1.76 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.9, 168.8, 166.5, 137.8, 133.1, 131.7, 130.4, 129.7, 128.5, 79.4, 56.8, 52.45, 52.40, 43.5, 34.5.

Preparation of (*S*)-*O*-Methylmandelate Ester of Dimethyl (1-Hydroxycyclopent-2-en-4-yl)malonate (31 and 32). A solution of approximately 0.10 mmol of the benzoate **29** and/or **30** in 5 mL of methanol containing magnesium methoxide (prepared by dissolving 15 mg (0.625 mg-atom) of magnesium in methanol) was heated 14 h at 60 °C. After being evaporated in vacuo and dissolved in ether, the organic layer was washed with aqueous sodium bisulfate, water, and brine. Drying ($MgSO_4$), evaporating in vacuo, and chromatographing (1:1 hexane/ethyl acetate) gave the product in 46–66% yields. IR ($CDCl_3$): 3609, 3521, 1750, 1733, 1438 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.94 (m, 1 H), 5.85 (m, 1 H), 4.79 (br m, 1 H), 3.76 (s, 3 H), 3.75 (s, 3 H), 3.52 (d, *J* = 7.3 Hz, 1 H), 3.28 (m, 1 H), 2.58 (m, 1 H), 2.26 (br s, 1 H), 1.60 (dt, *J* = 14.3, 4.0 Hz, 1 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 169.5, 169.3, 136.0, 134.4, 76.6, 55.8, 52.5, 52.4, 43.8, 37.1. HRMS: calcd for $C_{10}H_{13}O_5$ 213.0763, found 213.0653.

A solution of approximately 0.06 mmol of the above alcohol in 0.6 mL of methylene chloride was added to a neat mixture of 16.6 mg (0.1 mmol) of (*S*)-*O*-methylmandelic acid, 18.5 mg (0.09 mmol) of DCC, and 0.25 mg (0.002 mmol) of DMAP. After 22 h at room temperature, filtering through Celite to remove the urea, washing the filter cake with ether, washing the ether layer with aqueous sodium bisulfate, aqueous sodium bicarbonate, and brine, drying ($MgSO_4$), and evaporating in vacuo gave the crude ester in 80–90% yield which was directly analyzed to determine the de. Chromatography (2:1 hexane/ethyl acetate) gave analytical samples.

31: IR (neat) 1748, 1739, 1436, 1323 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.33 (m, 5 H), 6.02 (m, 1 H), 5.92 (m, 1 H), 5.67 (m, 1 H), 4.73 (s, 1 H), 3.74 (s, 3 H), 3.70 (s, 3 H), 3.41 (s, 3 H), 3.26 (m, 1 H), 3.19 (d, *J* = 10.0 Hz, 1 H), 2.50 (dt, *J* = 14.6, 7.6 Hz, 1 H), 1.40 (dt, *J* = 14.6, 4.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 168.8, 138.2, 136.3, 131.3, 128.83, 128.78, 127.3, 82.5, 79.6, 57.2, 56.6, 52.4, 43.3, 34.3; HRMS calcd for $C_{10}H_{13}O_4$ (M^+ – $PhCH(OCH_3)CO_2$) 197.0814, found 197.0813.

32: IR (neat) 2954, 1736, 1455, 1436, 1324 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.33 (m, 5 H), 5.99 (m, 1 H), 5.79 (m, 1 H), 5.65 (m, 1 H), 4.74 (s, 1 H), 3.73 (s, 6 H), 3.41 (s, 3 H), 3.29 (br s, 2 H), 2.59 (m, 1 H), 1.60 (m, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.7, 168.87, 168.76, 138.2, 136.3, 131.0, 128.80, 128.75, 127.3, 82.6, 79.7, 57.2, 56.7, 52.49, 52.41, 43.4, 34.5; HRMS calcd for $C_{10}H_{13}O_4$ (M^+ – $PhCH(OCH_3)CO_2$) 197.0814, found 197.0815.

Preparation of Scalemic and Racemic 2-[1′-(Benzoyloxy)cyclopent-2′-en-4′-yl]-2-methyl-1,3-cyclohexanedione (33 and 34). A solution of 4.2 mg (4.05 μmol) of $(dba)_3Pd_2{\cdot}CHCl_3$ and 16–24 μmol of chiral ligand in 0.8 mL of dry THF was stirred 45 min at room temperature, during which time the mixture changed from red-brown to yellow-orange. After being cooled to 0 °C, this catalyst solution was added (followed by rinsing the flask with an additional 0.8 mL of THF) to a suspension of the nucleophile, prepared from 40.8 mg (0.324 mmol) of 2-methyl-1,3-cyclohexanedione and 0.162 mmol of either DBU (24.6 mg) or lithium hexamethyldisilamide (except in case of kinetic enhancement, where 0.194 mmol of DBU was employed), and 50 mg (0.162 mmol) of dibenzoate **28** in 0.8 mL of THF at 0 °C. After the mixture was stirred 1.75 h at 0 °C, ether was added. The organic layer was washed with aqueous sodium bisulfate, aqueous sodium bicarbonate, water, and brine. After drying ($MgSO_4$) and evaporating in vacuo, chromatography (2:1 hexane/ethyl acetate) gave the product. Using 19.4 mg (24.3 μmol) of diester ligand **10**, the reaction produced 26 mg (51% yield) of **34** of 54% ee. Using 19.2 mg (24.3 μmol) of diamide ligand (+)-**11**, there was produced 44 mg (86% yield) of **34** of 91% ee. Using 16.6 mg (24.3 μmol) of diamide ligand **12** and 34.6 mg (0.162 mmol) of DBU, there was produced 48 mg (95% yield) of **33** of 91% ee, whereas using 11.2 mg (16.2 μmol) of diamide ligand **12** and 29.6 mg (0.194 mmol) of DBU, there was produced 42 mg (84%) of **33** of 98% ee.

The same procedure in an achiral experiment using 8.4 mg (8.1 μmol) of $(dba)_3Pd_2{\cdot}CHCl_3$, 25.5 mg (97.2 μmol) of triphenylphosphine, 100 mg (0.324 mmol) of dibenzoate **28**, 81.6 mg (0.648 mmol) of 2-methylcyclohexane-1,3-dione, and 44.7 mg (0.324 mmol) of DBU in 3 mL of THF gave 83 mg (82% yield) of racemic product: IR (neat) 2983, 2947, 1715, 1694, 1452, 1340, 1314 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (m, 2 H), 7.56 (m, 1 H), 7.45 (m, 2 H), 6.04 (m, 1 H), 5.87 (m, 1 H), 5.79 (m, 1 H), 3.43 (m, 1 H), 2.83 (m, 2 H), 2.65 (m, 2 H), 2.45 (dt, *J* = 14.9, 8.2 Hz, 1 H), 2.15 (m, 1 H), 1.80 (m, 1 H), 1.69 (dt, *J* = 15.7, 4.7 Hz, 1 H), 1.56 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.2, 209.0, 166.5, 134.7, 133.2, 132.4, 130.3, 129.8, 128.5, 79.0, 68.6, 49.8, 37.7, 37.6, 31.2, 17.8, 12.0; HRMS calcd for $C_{12}H_{15}O_2$ (M^+ – $PhCO_2$) 191.1072, found 191.1054. Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.85; H, 6.65.

Preparation of Scalemic and Racemic 1-(Benzoyloxy)-4-(*N*-benzyl-*N*-methylamino)cyclopent-2-ene (35 and 36). A solution of 4.2 mg (4.06 μmol) of $(dba)_3Pd_2{\cdot}CHCl_3$ and 16.2 μmol of chiral ligand in 0.8 mL of THF was stirred 45 min at room temperature. After being cooled to 0 °C, this catalyst solution was added (followed by rinsing the flask with an additional 0.4 mL of THF) to a neat mixture of 50 mg (0.162 mmol) of dibenzoate **28**, 41.8 μL (0.324 mmol) of *N*-benzyl-*N*-methylamine, and

0.1 mL (0.7 mmol) of triethylamine at 0 °C. After TLC indicated complete reaction (45–75 min), ether was added. The organic phase was washed with aqueous sodium hydroxide, aqueous sodium bicarbonate, water, and brine. Chromatography (4:1 hexane/ethyl acetate) gave the titled product. Using 12.9 mg (16.2 μmol) of diester ligand **10**, there was produced 31 mg (61% yield) of **36** of 74% ee. Using 12.2 mg (15.5 μmol) of diamide ligand (+)-**11**, there was obtained 35 mg (71% yield) of **36** of 95% ee. Using 11.2 mg (16.2 μmol) of diamide ligand **12**, there were obtained 37 mg (75% yield) of **35** of 73% ee and, in a second run, 42 mg (85% yield) of **35** of 78% ee.

The same procedure in an achiral experiment using 4.2 mg (4.06 μmol) of $(dba)_3Pd_2{\cdot}CHCl_3$, 6.37 mg (24.3 μmol) of triphenylphosphine, 51.1 μL (0.358 mmol) of triethylamine, 50 mg (0.162 mmol) of dibenzoate **28**, and 41.8 μL (0.324 mmol) of *N*-benzyl-*N*-methylamine in 1.6 mL of THF at 0 °C for 27 h gave 35 mg (70% yield) of racemic titled product: IR (neat) 3062, 2943, 1716, 1452, 1335, 1314 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (m, 2 H), 7.59–7.28 (m, 8 H), 6.18 (m, 1 H), 6.07 (m, 1 H), 5.83 (m, 1 H), 3.99 (m, 1 H), 3.64 (d, J = 13.2 Hz, 1 H), 3.50 (d, J = 13.0 Hz, 1 H), 2.57 (m, 1 H), 2.23 (s, 3 H), 1.95 (dt, J = 14.5, 4.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 139.5, 133.1, 131.7, 130.6, 129.8, 129.1, 128.6, 128.52, 128.48, 127.2, 78.4, 67.8, 58.3, 37.8, 30.2; HRMS calcd for $C_{20}H_{21}NO_2$ 307.1572, found 307.1573.

Preparation of (*S*)-*O*-Methylmandelate Esters of 1-Hydroxy-4-(*N*-benzyl-*N*-methylamino)cyclopent-2-ene (37 and 38). A mixture of 19.8 mg (64 μmol) of the above amino benzoate and 8.1 mg (0.193 mmol) of lithium hydroxide monohydrate in 0.4 mL of ethanol and 0.1 mL of water was heated 7 h at 60–65 °C. After evaporation and chromatography (4:1 ether/acetone) of the residue, 12.2 mg (94% yield) of the alcohol was obtained: IR (neat) 3355 (br, OH), 3050, 2937, 2851, 2792, 1453, 1370, 1358 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.25 (m, 5 H), 6.02 (m, 1 H), 5.97 (m, 1 H), 4.73 (m, 1 H), 3.78 (m, 1 H), 3.60 (d, J = 13.1 Hz, 1 H), 3.46 (d, J = 13.1 Hz, 1 H), 2.41 (dt, J = 13.9, 7.6 Hz, 1 H), 2.18 (s, 3 H), 1.91 (br s, OH), 1.67 (dt, J = 13.7, 4.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 135.83, 135.77, 129.1, 128.4, 127.1, 75.5, 68.0, 58.6, 38.06, 34.5; HRMS calcd for $C_{13}H_{17}NO$ 203.1310, found 203.1319.

A solution of 5 mg (24.5 μmol) of the above alcohol in 0.6 mL of methylene chloride cooled to 0 °C was added to a neat mixture of 8 mg (0.05 mmol) of (*S*)-*O*-methylmandelic acid, 8 mg (0.04 mmol) of DCC, and 0.1 mg (0.8 μmol) of DMAP at 0 °C. After stirring 24 h at 0 °C and allowing the reaction to warm to room temperature, ether was added. The organic phase was washed with aqueous sodium hydroxide, aqueous sodium bicarbonate, water, and brine. After drying ($MgSO_4$), evaporating in vacuo, and chromatographing (2:1 hexane/ethel acetate), there was obtained 7.1 mg (82% yield) of the titled ester. NMR analysis before and after chromatography revealed that the diastereomeric ratio was not altered by this purification.

37: IR (neat) 3030, 2940, 2828, 1746, 1455 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.22 (m, 10 H), 6.08 (m, 1 H), 5.92 (m, 1 H), 5.61 (m, 1 H), 4.74 (s, 1 H), 3.85 (m, 1 H), 3.43 (d, J = 13.0 Hz, 1 H), 3.41 (s, 3 H), 3.23 (d, J = 13.3 Hz, 1 H), 2.33 (dt, J = 14.8, 8.0 Hz, 1 H), 2.00 (s, 3 H), 1.51 (dt, J = 14.8, 4.1 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.6, 139.5, 138.6, 136.4, 130.9, 129.0, 128.9, 128.8, 128.4, 127.4, 127.1, 82.5, 78.6, 67.7, 58.0, 57.2, 37.7, 29.8; HRMS calcd for $C_{22}H_{25}NO_3$ 351.1834, found 351.1822.

38: IR (neat) 3030, 2934, 2828, 1745, 1454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44–7.25 (m, 10 H), 6.04 (m, 1 H), 5.82 (m, 1 H), 5.57 (m, 1 H), 4.75 (s, 1 H), 3.88 (m, 1 H), 3.47 (d, J = 13.2 Hz, 1 H), 3.41 (s, 3 H), 3.36 (d, J = 13.2 Hz, 1 H), 2.44 (dt, J = 14.7, 8.0 Hz, 1 H), 2.09 (s, 3 H), 1.76 (dt, J = 14.6, 4.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 139.6, 138.5, 136.4, 130.9, 129.1, 128.8, 128.7, 128.4, 127.3, 127.1, 82.7, 78.8, 67.8, 58.1, 57.3, 37.8, 30.1; HRMS calcd for $C_{22}H_{25}NO_3$ 351.1835, found 351.1841. Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 74.93; H, 7.27; N, 3.77.

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NMR Spectroscopic and Computational Characterization of 1-(*p*-Anisyl)vinyl Cations. Methoxy Group Rotation as a Probe of C_β–Si, C_β–C, and C_β–H Hyperconjugation

Hans-Ullrich Siehl,* Frank-Peter Kaufmann, and Kenzi Hori†

Contribution from the Institut für Organische Chemie, Universität Tübingen, D-7400 Tübingen, Germany, and Department of Chemistry, Faculty of Liberal Arts, Yamaguchi University, Yamaguchi, 753 Japan. *Received June 17, 1992*

Abstract: The 1-(*p*-anisyl)-2-(triisopropylsilyl)vinyl cation **1** and the 1-(*p*-anisyl)vinyl cation **2** were generated in solution and characterized by NMR spectroscopy. Ab initio molecular orbital calculations using the 6-31G basis set were performed for cation **2**, the 1-(*p*-anisyl)-2-methylvinyl cation **3**, and the 1-(*p*-anisyl)-2-silylvinyl cation **4**, serving as a model cation for **1**, to elucidate the importance of α–π aryl stabilization and β–σ bond stabilization in 1-(*p*-anisyl)vinyl cations with various β substituents. For comparison, the *p*-anisylmethyl cation **5** was also calculated. The para carbon chemical shifts, the experimentally determined and calculated torsional barriers around the phenyl–methoxy C–O bond, and the computed geometrical parameters and charges are used to determine the contributions of conjugative and hyperconjugative stabilization effects in 1-(*p*-anisyl)vinyl cations. The ability of β substituents to hyperconjugatively donate electrons to the empty cationic orbital follows the order silyl > methyl > H.

1-Arylvinyl cations, first postulated in 1964,[1] can be regarded as *the* prototype of vinyl cations. They have been generated as transient intermediates in solution in the course of solvolysis reactions, electrophilic addition reactions, and photolysis reactions from various progenitors and have been investigated intensively using mainly indirect techniques like kinetic measurements and product analyses.[2] Gas-phase investigations[3] and several com-

† Yamaguchi University.

(1) Grob, C. A.; Cseh, G. *Helv. Chim. Acta* **1964**, *47*, 194.

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