Application of Chiral Mixed Phosphorus/Sulfur Ligands to Palladium-Catalyzed Allylic Substitutions

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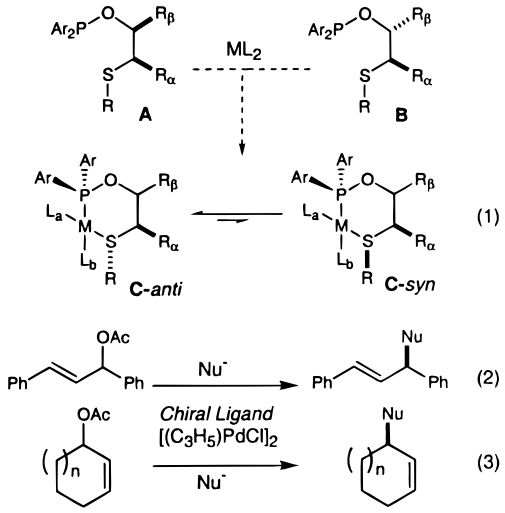
Abstract: A modular approach to the synthesis of a class of mixed phosphorus/sulfur ligands was designed to identify important ligand structural features for enantioselective palladium-catalyzed allylic subsitutions of acyclic and cyclic ayllic esters. After a systematic variation of the ligand substituents at sulfur, phosphorus, and the ligand backbone, ligand **11k** was found to be optimal in the palladium-catalyzed allylic substitution of 1,3-diphenylpropenyl acetate with dimethyl malonate or benzylamine in high yield and excellent enantioselectivity (95−98% ee). A similar optimization of the mixed phosphorus/sulfur ligand for the palladium-catalyzed allylic substitution of cycloalkenyl acetates showed that **49g** afforded the highest enantioselectivities (91−97% ee). Application of this methodology to heterocyclic substrates was developed as an efficient approach to the enantioselective synthesis of 3-substituted piperidines and dihydrothiopyrans. Models for asymmetric induction are discussed based on the absolute stereochemistry of the products, X-ray crystallographic data, and NMR spectroscopic data for relevant π-allyl complexes.

Introduction

The use of C_2 symmetry as a chiral ligand design element is a well-recognized strategy for restricting the number of diastereomeric transition states in metal-catalyzed enantioselective processes.[1] Equally powerful stereochemical restrictions may also be realized with chiral ligands lacking C_2 symmetry through the use of electronic effects such as the trans influence.[2] Such effects are a natural consequence of the use of chiral bidentate ligands equipped with strong and weak donor heteroatom pairs (e.g. PR_3/NR_3 or PR_3/SR_2) and have the capacity to influence both the stability and reactivity of the intervening diastereomeric reaction intermediates in the catalytic cycle. An added feature of the P/S ligand family (e.g. **A** and **B**) is the incorporation of an *S*-chiral sulfur center that is created upon complexation as illustrated in diastereomeric complexes **C**-*anti* and **C**-*syn* (eq 1). Combination of these two ligand attributes positions the labile ligand L_b trans to the stronger phosphorus donor and adjacent to the chiral sulfur center (eq 1).

The purpose of this investigation has been to determine the utility of the illustrated mixed P/S ligands **A** and **B** whose derived metal complexes employ both sulfur-based chirality and the trans influence as control elements in asymmetric catalysis.[3] While these ligands have been evaluated in the palladium-catalyzed allylic alkylation with enolmalonate and amine nucleophiles (eqs 2 and 3),[4] we are optimistic that the scope of these ligands might be extended to other metal-catalyzed processes as well.



P/N and N/S Ligands. Pioneering studies in the allylic substitution of 1,3-diphenylpropenyl acetate have relied heavily on chiral ligands containing C_2 symmetry to reduce the number of diastereomeric intermediates in the reaction pathway.[5] Nevertheless, chiral non-C_2 symmetric ligands have also proven to afford excellent stereochemical control in these processes. For example, the phosphino-oxazoline **D**, pairing a strong phosphorus donor with a weaker nitrogen donor, is a highly

(1) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581−1590.

(2) (a) Appleton, T. G.; Clark, H. C.; Manzer, L. E. *Coord. Chem. Rev.* **1973**, *10*, 335−422. (b) Murray, S.; Hartley, F. *Chem. Rev.* **1981**, *81*, 365−414. The general trend for the trans influences of ligand donors is: PR3 > SR2 > C5H5N > R2NH ≫ OR2.

(3) For a preliminary account of this work see: Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Org. Chem.* **1999**, *64*, 2994−2995.

(4) For a general review of the asymmetric transition metal-catalyzed allylic alkylation, see: Trost, B. M; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422 and references therein.

(5) (a) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932−7934. (b) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143−1145. (c) Pfaltz, A. *Acc. Chem Res.* **1993**, *26*, 339−345. (d) Seebach, D.; Devaquet, E.; Ernst, A.; Hayakawa, M.; Kuhnle, F. N. M.; Schweizer, W. B.; Weber, B. *Helv. Chem. Acta* **1995**, *78*, 1636−1650.

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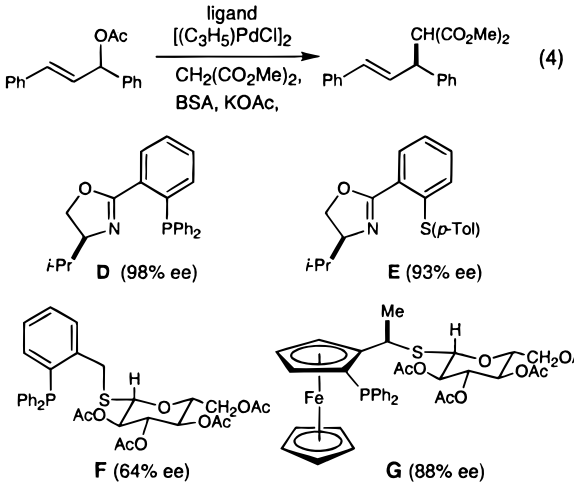
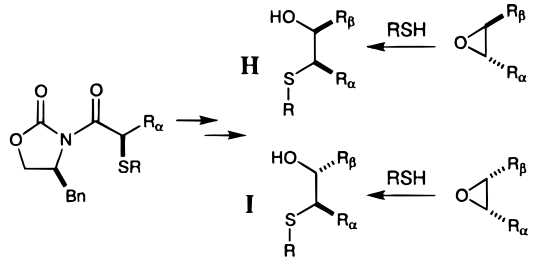
effective chiral ligand in this reaction (eq 4).[6] In a complementary study, Williams reported the performance of the complementary N/S ligand **E**, in the same reaction.[7] While both of these studies demonstrate the utility of the trans influence on this alkylation process, the stereochemistry of the bound sulfur ligand in the latter process is undetermined.

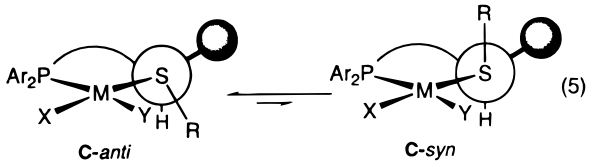


Few mixed thioether-containing ligands have been applied to enantioselective allylic alkylations.[8] While the coordinating ability of thioether donors in late transition metal complexes is well precedented,[2b] the stereogenic center formed at sulfur upon coordination may be compromised by its low inversion barrier (15−20 kcal/mol).[9] Any attempt to incorporate a thioether donor into a chiral ligand must consider potential erosion of enantioselectivities as a result of sulfur inversion. During the course of this investigation, Pregosin reported that ligand **F** afforded modest enantioselectivities (eq 4) in the allylic alkylation of 1,3-diphenylpropenyl acetate.[10] He attributed the erosion of reaction enantioselectivity to sulfur inversion which was detected by ^{1}H NMR spectroscopy on the complex [Pd(C_3H_5)(**F**)](OTf). This group also evaluated the performance of ligand **G** which contains more structural rigidity. While the enantioselectivities in the allylic alkylation were improved, this study was unable to distinguish sulfur inversion from allyl isomerization in the ^{1}H NMR spectroscopic analysis of [Pd(C_3H_5)(**G**)](OTf).[11] By inspection, no obvious stereochemical bias exists at sulfur in ligand **F**, while the adjacent stereocenter in the backbone of ligand **G** may not be large enough to effectively control the sulfur stereochemistry.

Scheme 1



The premise of this study rests on the proposition that if sulfur inversion can be controlled, bidentate ligands containing a stereogenic metal-bound sulfur ligand might lead to better induction than that observed for ligands containing asymmetry further removed from the metal center.[12,13] Sulfur inversion might be effectively controlled if the equilibrium between diastereomeric complexes **C**-*anti* and **C**-*syn* strongly favors the anti diastereomer. This stereochemical bias may be achieved through the incorporation of sterically demanding substituents both on the sulfur (R) and on the stereocenter bearing the thioether in the chelate backbone (eq 5). In this generic ligand, the stronger trans influence of the phosphinite (vs the thioether) should place the more labile site (Y) of the metal complex in proximity to the stereogenic sulfur center.



With the aforementioned criteria in mind, a conformationally rigid six-membered chelate was chosen as the optimal size to prevent sulfur inversion due to conformational flexibility.[14] Additionally, a modular approach to the ligand synthesis was desired such that the substituents at phosphorus (Ar), at sulfur (R), and on the backbone (R_α, R_β) might be varied independently. Generic ligands **A** and **B** fit these criteria, and were readily derived from β-hydroxysulfides **H** and **I** respectively which can be obtained via regioselective thiolate openings of acyclic and cyclic epoxides[15] or via α-sulfenylation of carbonyl compounds followed by reduction (Scheme 1).

In the following sections, the synthesis of a set of structurally diverse P/S ligands is reported. These ligands, as their derived Pd complexes, are evaluated in the allylic alkylation of cyclic and acyclic allylic substrates. Finally, X-ray structures and NMR

(6) (a) Pfaltz, A. *Acta Chim. Scand.* **1996**, *50*, 189−194 and references therein. (b) Kudis, S.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3047−3050. (c) Dawson, G. J.; Frost, G.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 3149−3150.

(7) (a) Morimoto, T.; Tachibana, K.; Achiwa, K. *Synlett* **1997**, 783−785. (b) Anderson, J. C.; James, D. S.; Mathias, J. P. *Tetrahedron: Asymmetry* **1998**, *9*, 753−756. (c) Sprinz, J.; Keifer, M.; Helmchen, G.; Regglein, M.; Huttner, G.; Walter, O.; Zsolanai, L. *Tetrahedron Lett.* **1994**, *10*, 1523−1526. (d) Allen, J.; Bower, J.; Williams, J. *Tetrahedron: Asymmetry* **1994**, *5*, 1895−1898. (e) Boog-Wick, K.; Pregosin, P.; Trabesinger, G. *Organometallics* **1998**, *17*, 3254−3264.

(8) (a) Togni, A.; Hausel, R. *Synlett* **1990**, 633−635. (b) Gladiali, S.; Dore, A.; Fabbri, D. *Tetrahedron: Asymmetry* **1994**, *5*, 1143−1146. (c) Hiraoka, M.; Nishikawa, A.; Morimoto, T.; Achiwa, K. *Chem. Pharm. Bull.* **1998**, *46*, 704−706. (d) Hiroi, K.; Suzuki, Y. *Tetrahedron Lett.* **1998**, 39, 6499−6502. (e) Hauptman, E.; Shapiro, R.; Marshall, W. *Organometallics* **1998**, *17*, 4976−4982. (f) Hiraoka, M.; Nishikawa, A.; Morimoto, T.; Achiwa, K. *Chem. Pharm. Bull.* **1998**, *46*, 704−707. (g) Enders, D.; Peters, R.; Runsink, J.; Bats, J. W. *Org. Lett.* **1999**, *1*, 1863−1866.

(9) (a) Abel, E.; Bhargava, S. K.; Orrell, K. G. *Prog. Inorg. Chem.* **1984**, *32*, 1−118. (b) Abel, E.; Dormer, J.; Ellis, D.; Orrell, K. G.; Sik, V.; Hursthouse, M. B.; Mazid, M. A. *J. Chem. Soc., Dalton Trans.* **1992**, 1073−1080.

(10) Albinati, A.; Pregosin, P.; Wick, K. *Organometallics* **1996**, *15*, 2419−2421 and references therein.

(11) Albinati, A.; Eckert, J.; Pregosin, P.; Ruegger, H.; Salzmann, R.; Stossel, C. *Organometallics* **1997**, *16*, 579−590 and references therein.

(12) Enhanced enantioselectivities were observed with increased chelate size using chiral diphosphines, reflective of a greater penetration of the (*P*)-phenyl rings into the space occupied by the π-allyl moiety. Reference 5b.

(13) *P*-chiral diphosphines also have stereogenicity close to the metal center. For examples of the application of the *P*-chiral diphosphine DIPAMP in asymmetric catalysis see: (a) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 2567−2568. (b) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946−5952.

(14) It has been noted by Pregosin and co-workers that conformationally flexible mixed phosphorus/sulfur ligand chelates suffered from sulfur inversion at ambient temperature. Albinati, A.; Eckert, J.; Pregosin, P.; Ruegger, H.; Salzmann, R.; Stossel, C. *Organometallics* **1997**, *16*, 579−590 and references therein.

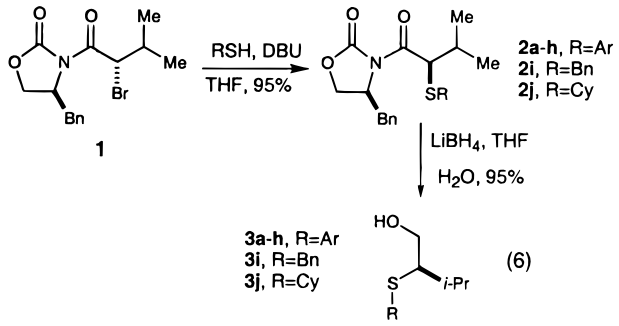
(15) Walford, C.; Jackson, R. F. W.; Rees, N. H.; Clegg, W.; Heath, S. *J. Chem. Soc., Chem. Commun.* **1997**, 1855−1856 and references therein.

characterization of the intermediate π-allyl complexes are provided to reinforce the proposed stereochemical models.

Results and Discussion

Ligand Syntheses. While thiolate opening of epoxides affords diastereomerically pure β-hydroxysulfides, alkylmetal additions to α-sulfenylated aldehydes is precedented to afford mixtures of both β-hydroxysulfide diastereomers.[16] Access to both diastereomeric β-hydroxysulfides was desirable to evaluate the effect of the relative backbone stereochemistry on reaction enantioselectivities. Accordingly, the α-sulfenylation route was incorporated into the design of ligands **A** and **B**. The ligand synthesis satisfied the requirement of a modular installation of sulfur, backbone, and phosphorus components and the incorporation of a bulky substituent at the stereogenic center adjacent to the thioether (R_1 = *i*-Pr).

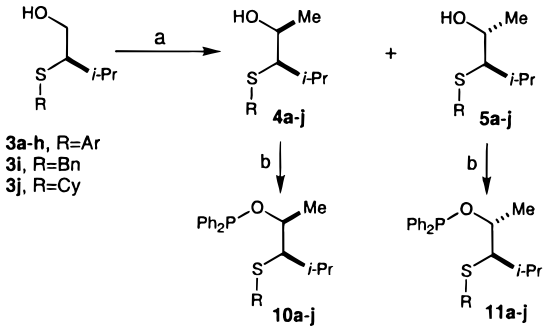
Thiolate displacement on the known α-bromoimide **1**[17] was readily accomplished with a variety of thiols to yield thioethers **2**(**a**−**h**, R = Ar; **i**, R = Bn; **j**, R = Cy) in good yield with no observable epimerization (eq 6). Reductive cleavage of the auxiliary proceeded at the exocyclic carbonyl, yielding the parent β-hydroxysulfides **3a**−**j**,[18] which served as a template for further functionalization.



A second stereogenic center was desired in the ligand backbone to orient the isopropyl substituent in the direction of the coordinated thioether in the ligand−metal complex. It was believed that a β-methyl substituent would be sufficient to effect this conformational bias. Incorporation of this second stereocenter in the ligand backbone was achieved by oxidation of **3a**−**j** under standard Swern conditions, followed by in situ quench of the resulting aldehyde with methylmagnesium bromide. The ratio of diastereomers was 2.5:1, favoring the product derived from Felkin-controlled addition to the aldehyde (i.e. **4a**−**j**).[19,20,21]

The diarylphosphinite moiety was selected for the P terminus by virtue of its ease of incorporation at the end of the synthetic route (Scheme 2), and its documented utility as a ligand component.[22] The β-hydroxysulfides **4a**−**j** and **5a**−**j** were deprotonated with *n*-butyllithium at 0 °C, then treated with chlorodiphenylphosphine, affording the desired ligands **10a**−**j** and **11a**−**j**, which could be separated from the lithium chloride byproduct by direct concentration of the unpurified reaction mixture and trituration with hexane. Although the resulting ligands are acid-labile, they can be purified by rapid flash chromatography on silica gel, with product yields in the vicinity of 85%.

Scheme 2[a]



[a] Key: (a) i. Swern, −50 °C; ii. MeMgBr, THF, −78 °C, 85−92%; (b) *n*-BuLi, Ph_2PCl, 85%.

The synthetic scheme described above proved to be effective for ligands containing *S*-aryl **10a**−**h**, **11a**−**h**, *S*-benzyl **10i**, **11i**, and *S*-cyclohexyl **10j**, **11j** substituents. The route was not amenable to the incorporation of an *S*-*tert*-butyl group **10k**, **11k** because *tert*-butylthiolate displacement on α-bromoimide **1** could not be accomplished. An alternative synthesis of the desired *S*-*tert*-butyl β-hydroxysulfide was developed based on the method of Kagan for the synthesis of enantiomerically pure, chiral sulfoxides. (*R*)-*tert*-Butyl isobutylsulfoxide (**17**) was synthesized in good yield and >99% ee in two steps from the readily prepared cyclic sulfite (eq 7).[23]

Casey and co-workers have reported that *tert*-butyl sulfoxides may be deprotonated and trapped with electrophiles to afford diastereomerically pure sulfoxides with excellent 1,2-induction but low 1,3-induction.[24] The Casey conditions were employed with **17** to afford β-hydroxysulfoxides **18k** and **19k** in a 1:1 ratio (Scheme 2),[25] which were separated using medium-pressure liquid chromatography (MPLC). Reduction of the sulfoxides **18k** and **19k** to the thioethers **4k** and **5k**, respectively, was readily accomplished with BH_3−THF, and phosphinylation afforded the desired *S*-*tert*-butyl analogues **10k**−**15k**.

Allylic Alkylation of Acyclic Substrates.[26] Ligand architectures **10** and **11** were evaluated in the palladium-catalyzed allylic alkylation of 1,3-diphenylpropenyl acetate with dimethyl malonate, using *N*,*O*-bis(trimethylsilyl)acetamide (BSA) as the base (Table 1, eq 8). The reactions were complete in 3 h at 0

(16) (a) Enders, D.; Schäfer, T.; Piva, O.; Zamponi, A. *Tetrahedron* **1994**, *50*, 3349−3362. (b) Enders, D.; Piva, O.; Burkamp, F. *Tetrahedron* **1996**, *52*, 2893−2908 and references therein.

(17) (a) Evans, D. A; Ellman, J. A.; Dorow, R. L. *Tetrahedron Lett.* **1987**, *28*, 1123−1126. (b) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011−4030.

(18) When the reductive cleavage was attempted on the α-arylthioimide derived from 3,3-dimethylbutanoic acid, reaction was only observed at the endocyclic carbonyl.

(19) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61−70.

(20) For β-hydroxy sulfides containing an *S*-benzyl substituent, the product derived from *anti*-Felkin-controlled addition was the major diastereomer.

(21) The relative stereochemistry was determined by analysis of the *O*-methylmandelate esters according to the method of: Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370−2374.

(22) (a) Reference 5b. (b) Nomura, N.; Mermet-Bouvier, Y. C.; Rajan-Babu, T. V. *Synlett* **1996**, 745−746 and references therein. (c) Seebach, D.; Devaquet, E.; Ernst, A.; Hayakawa, M.; Kuhnle, F.; Schweizer, W. B.; Weber, B. *Helv. Chim. Acta* **1995**, *78*, 1636−1650.

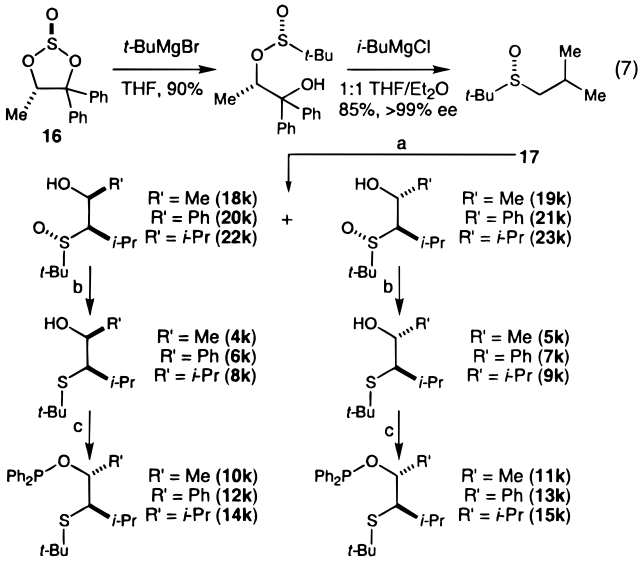
(23) Rebeiere, F.; Samuel, O.; Ricard, L.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 5991−5999.

(24) Casey, M.; Mukherjee, I.; Trabsa, H. *Tetrahedron Lett.* **1992**, *33*, 127−130.

(25) A similar ratio was obtained when benzaldehyde was used (**20k**:**21k** = 1:1), but some selectivity was observed when isobutyraldehyde was employed (**22k**:**23k** = 1:3).

(26) (a) Steinhagen, H.; Reggelin, M.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2108−2110. (b) Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, *35*, 1523−1526. (c) Togni, A.; Burckhardt, U.; Gramlich, V.; Pregosin, P. S.; Salzmann, R. *J. Am. Chem. Soc.* **1996**, *118*, 1031−1037. (d) Boog-Wick, K.; Pregosin, P. S.; Trabesinger, G. *Magn. Reson. Chem.* **1998**, *36*, S189−S194 and references therein.

Scheme 3[a]



(7)

[a] Key: (a) i. LDA, THF, −78 °C; ii. R′CHO, 90%; (b) BH_3-THF, room temperature; (c) *n*-BuLi, Ph_2PCl, 0 °C, 85%.

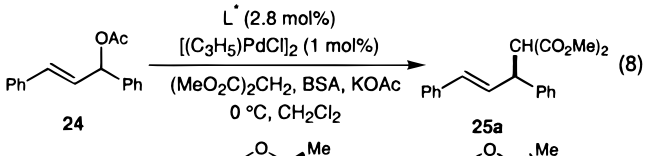
°C, using only 2 mol % of Pd and 2.8 mol % of ligand, to afford the desired alkylated product **25a** in 90−99% yield.

Variation of Sulfur Substituents. The enantiomeric excesses in the allylic alkylation of 1,3-diphenylpropenyl acetate with dimethyl malonate showed a strong dependence on the nature of the sulfur substituent in the ligand (Table 1). While the parent *S*-phenyl ligand **11a** afforded moderate enantioselectivities, incorporation of electron-donating groups (**11b**) or electron-withdrawing groups (**11c**) resulted in significantly lower enantioselectivities. Bulkier *S*-phenyl substituents which incorporated ortho (**11g**), meta (**11e**), or para (**11d**) alkyl substitution raised the enantioselectivity as compared to the parent *S*-phenyl ligand **11a**, while methyl substitution at the meta positions (**11e**) afforded the best results among *S*-aryl substituents, providing **25a** in 85% ee. In comparison to their *S*-aryl counterparts, an increase in reaction rate was observed with the *S*-alkyl ligands **10i**−**k**, **11i**−**k**, affecting complete conversion at 0 °C with 2 mol % of catalyst in 90 min. The reactions were optimally run at −20 °C, affording alkylated product **25a** in 3 h.[27] Along with an increase in reaction rate, an enhanced enantioselectivity was observed for ligands **10i**−**k** and **11i**−**k** (Table 1), affording **25a** in 98% ee and 93% yield when ligand **11k** was used. From the data in Table 1, it is evident that (A) the sense of induction is always dominated by the stereogenic center attached to the thioether substituent (R_α) with the β-stereocenter playing a subordinate role and (B) the enantioselectivities increase with bulkier sulfur substituents. These results suggest that the *S*-chiral center may an important stereocontrolling element in the ligand design, and that sulfur inversion may be more effectively controlled as the size of the sulfur substituent is increased.

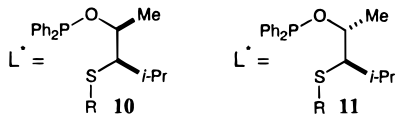
Variation of Backbone Substituents. Ligand class **11** possessing the anti diastereochemical relationship almost always afforded higher enantioselectivities than ligand class **10** for the illustrated set of sulfur and phosphorus substituents (Table 1). It is possible that variation of the relative stereochemistry on the backbone alters the preferred chelate geometry and, as a result, the inductive effect of the ligand (Figure 1). In particular,

(27) Lowering of the temperature below −20 °C caused the reactions to stall at 75% conversion and no increase in the enantioselectivity.

Table 1. Effect of Sulfur Substituent on Enantioselectivity (Eq 8)[a,e]



(8)



R	% ee[b, c]	% ee[b, c]
Ph	**10a,** 42	**11a,** 70
4-MeOPh	**10b,** 44	**11b,** 58
2,3,5,6-F_4Ph	**10c,** 18	**11c,** 22
4-*t*-BuPh	**10d,** 70	**11d,** 77
3,5-Me_2Ph	**10e,** 63	**11e,** 85
3,5-*t*-Bu_2Ph	**10f,** 33	**11f,** 51
1-Nap	**10g,** 60	**11g,** 74
2-Nap	**10h,** 56	**11h,** 76
Bn	**10i,** 89[d]	**11i,** 75[d]
Cy	**10j,** 91[d]	**11j,** 81[d]
t-Bu	**10k,** 91[d]	**11k,** 98[d]

[a] Reactions were carried out in CH_2Cl_2 (0.36 M in substrate) and proceeded to completion. [b] Determined by chiral HPLC. [c] Absolute stereochemistry was determined to be (*S*) by comparison of specific rotation to literature values. [d] The reactions were run at −20 °C. [e] Yields were >90% after isolation by chromatography.

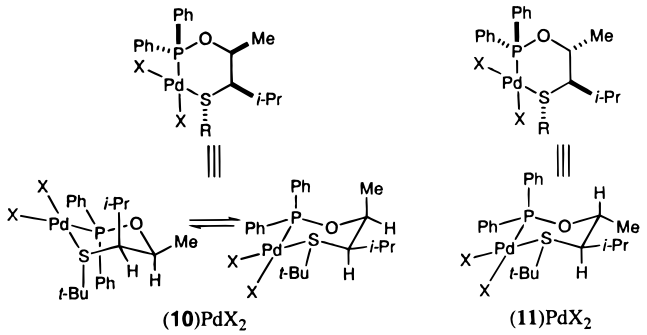


Figure 1. Possible conformations of (**10**)PdX_2 and (**11**)PdX_2.

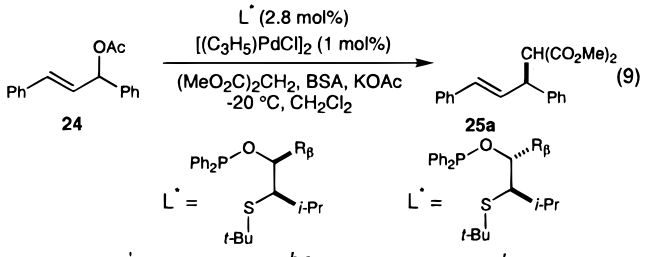
(**10**)PdX_2 could well exist in either of the two illustrated chair conformations as well as a twist boat conformer that is induced by one of the axial substituents. In subsequent studies (vide infra) we have determined that (**10**)$PdCl_2$ exists in that half-chair conformation orienting the isopropyl group in a pseudo-axial conformation.

The influence of the β-substituent, R_β, in ligands **10k**−**15k** was also evaluated (Table 2, eq 9). As the size of the β-substituent was increased, the enantioselectivities dropped significantly (Table 2). Presumably, bulkier alkyl groups at R_β disrupt the preferred chelate geometry of the complex when R_β = Me, resulting in lower enantioselectivities.

Ligands containing no β-substituent, **29**, or two β-substituents, **32**, were attractive due to the absence of diastereomeric mixtures in the synthesis (Scheme 4). The enantioselectivities obtained using ligands containing monosubstitution at the β-position, **10k** and **11k**, were superior to both **29** and **32** (Table 3, eq 10). The enantioselectivity observed for **29** was particularly low (67% ee), possibly reflective of more chelate conformational flexibility.

Variation of Phosphorus Substituents. The electronically differentiated phosphinites **33a**−**g** were readily prepared from β-hydroxysulfide **5k** under the standard phosphinylation con-

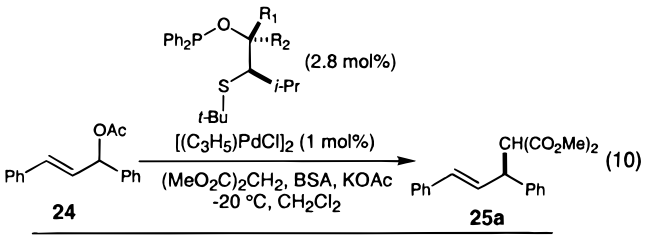
Table 2. Effect of β-Substituent on Enantioselectivity (Eq 9)[a,c]



R	L* =	% ee[b,c]	L* =	% ee[b]
Me		**10k**, 91		**11k**, 98
Ph		**12k**, 75		**13k**, 91
i-Pr		**14k**, 75		**15k**, 69

[a] Reactions were carried out in CH_2Cl_2 (0.36 M in substrate) and proceeded to completion. [b] Determined by chiral HPLC. [c] Yields were >94% after isolation by chromatography.

Table 3. Effect of β-Substituent on Enantioselectivity (Eq 10)[a,c]

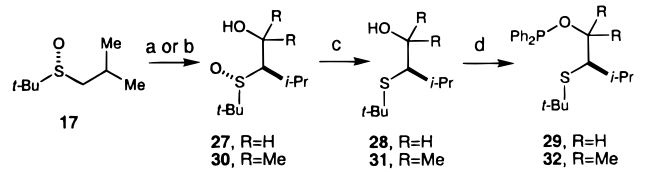


Ligand	R_1	R_2	% ee[b]
29	H	H	67
10k	Me	H	91
11k	H	Me	98
32	Me	Me	85

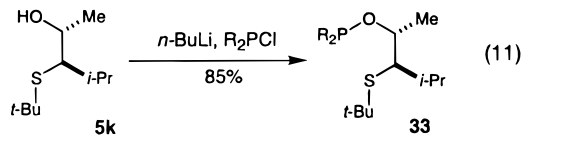
[a] Reactions were carried out in CH_2Cl_2 (0.36 M in substrate) and proceeded to complete conversion. [b] Determined by chiral HPLC. [c] Yields were >94% after isolation by chromatography.

ditions with a variety of diaryl- and dialkylchlorophosphines (eq 11).

Scheme 4[a]

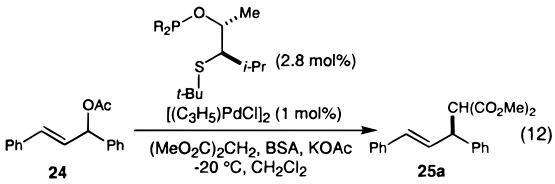


[a] Key: (a, R = H) i. LDA, THF, −78 °C; ii. BOM-Cl, iii. H_2, 10% Pd/C 33%; (b, R = Me) i. LDA, THF, −78 °C; ii. $CH_3C(O)CH_3$, 85%; (c) BH_3-THF, room temperature; (d) *n*-BuLi, Ph_2PCl, 0 °C, 85%.



Incorporation of electron-donating *P*-aryl substituents into the phosphinite moiety **33a**,**b** severely decreased the enantioselectivity of the alkylated adduct **25a** compared to the parent ligand **11k** (Table 4, eq 12). In contrast, ligands containing electron-withdrawing *P*-aryl substituents **33c**,**d** showed only a small decrease in enantioselectivity compared to parent ligand **11k**. More sterically demanding aryl substituents (**33b,d**−**g**) also afforded significantly lower enantioselectivities than **11k**, reflective of the intolerance of the reaction to a more sterically congested environment.

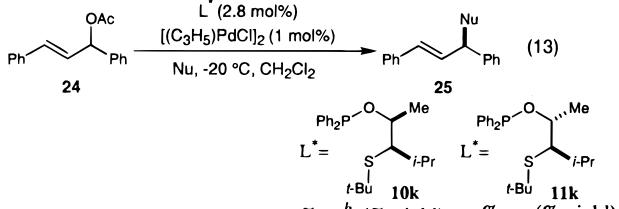
Table 4. Effect of R_2P Group on Enantioselectivity (Eq 12)[a,c]



R	Ligand	% ee[b]
Ph	**11k**	98
4-MeOPh	**33a**	82
2-MeOPh	**33b**	29
4-FPh	**33c**	93
3,5-$(CF_3)_2$Ph	**33d**	92
3,5-Me_2Ph	**33e**	80
α-Nap	**33f**	30
Cy	**33g**	47

[a] Reactions were carried out in CH_2Cl_2 (0.36 M in substrate) and proceeded to completion. [b] Determined by chiral HPLC. [c] Yields were >94% after isolation by chromatography.

Table 5. Effect of Nucleophile on Enantioselectivity (Eq 13)[a,f]



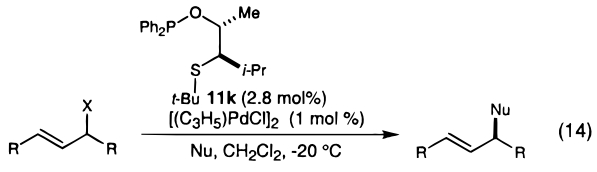
Nu	Product	% ee[b] (% yield)	% ee (% yield)
$(MeO_2C)_2CH_2$, BSA	**25a**	91[d] (93)	98[d] (97)
$(MeO_2C)_2C(H)Me$, BSA	**25b**	95[e] (95)	98[e] (98)
$(t\text{-}BuO_2C)_2CH_2$, BSA	**25c**	94[d] (92)	97[d] (95)
$(t\text{-}BuO_2C)_2NH$, BSA[c]	**25d**	81[d] (90)	71[d] (91)
$BnNH_2$	**25e**	99[d] (96)	95[d] (97)

[a] Reactions carried out in CH_2Cl_2 (0.36 M in substrate) and proceeded to completion. [b] Absolute stereochemistry was determined by comparison of specific rotation to literature values. [c] Reaction was run at 0 °C. [d] Determined by chiral HPLC. [e] Determined by ^1H NMR chiral shift using $Eu(hfc)_3$. [f] Yields determined after isolation by chromatography.

Other Nucleophiles. Ligands **10k** and **11k** were determined to be the most effective in the allylic alkylation of 1,3-diphenylpropenyl acetate with dimethyl malonate, affording **25a** in 91% and 98% ee, respectively. These ligands were evaluated with other nucleophiles in the allylic substitution process. When either ligand **10k** or **11k** was used, the reaction was insensitive to the steric demands of both the ester components and alkyl substitution on the malonate, and only slightly dependent on temperature (Table 5).

A nitrogen nucleophile which was isosteric with di-*tert*-butyl malonate was expected to give similarly high enantioselectivities. Surprisingly, the enantiomeric excess of the adduct derived from di-(*tert*-butoxycarbonyl)amine **25d** was significantly lower than that derived from di-*tert*-butyl malonate **25c** under the same conditions (Table 5). In contrast, benzylamine delivered the desired aminated adduct **25e** in very high enantioselectivity. In fact, while ligand **11k** was optimal for alkylations with dimethyl malonate, ligand **10k** proved to be superior for aminations with benzylamine, affording the adduct **25e** in 99% ee. Although a suitable amine nucleophile was applied to the allylic substitution of 1,3-diphenylpropenyl acetate, a variety of other carbon and heteroatom nucleophiles afforded low yields and enantioselectivities. The nucleophiles investigated were *p*-$TolSO_2Na$ (65% ee, 63% yield), *t*-BuSH (<5% yield), *t*-$BuSSiMe_3$ (<5% yield),

Table 6. Allylic Substitution of 1,3-Dialkylpropenyl Substrates with Dimethyl Malonate and Benzylamine (Eq 14)[a,f]



(14)

R	Substrate, X	Nu = $(MeO_2C)_2CH_2$, BSA % ee[b] (% yield)	Nu = $BnNH_2$ % ee[b] (% yield)
Me	**34a**, OAc	**35a**, 65[c] (87)	**35b**, 68[d] (87)
n-Pr	**34b**, OCO_2Me	**36a**, 78[c] (92)	**36b**, 80[d] (92)
i-Pr	**34c**, OCO_2Me	**37a**, 90[c] (50)	**37b**, 92[d] (40)
Cy	**34d**, OCO_2Me	NR[e]	NR[e]

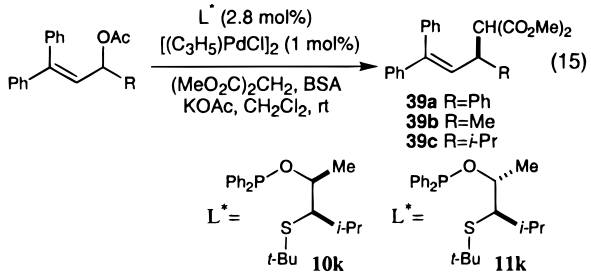
[a] Reactions were carried out in CH_2Cl_2 (0.36 M in substrate) and proceeded to complete conversion. [b] Absolute stereochemistry was determined to be (*R*) by comparison of specific rotation to literature values. [c] Determined by ^1H NMR chiral shift assay using Eu(hfc)$_3$. [d] Determined by chiral capillary GC. [e] No reaction was observed after 24 h. [f] Yields determined after chromatography.

p-$MeOC_6H_4OH$ (0% ee, 89% yield), PhC(OTMS)=CH_2 (no reaction), and *t*-BuSC(OTMS)=CH_2 (7% ee, 44% yield).

Other Acyclic Substrates. The enantioselectivities and reaction rates for the allylic substitution of 1,3-dialkylpropenyl substrates **34a**−**d**[28] using ligand **11k** were very dependent on the size of the alkyl substituent on the substrate (Table 6, eq 14). Alkylation and amination of **34a**, containing relatively small methyl substituents, afforded products **35a**,**b** in only 65% and 68% ee, respectively, at −20 °C over a period of 14 h.[29] In contrast, alkylation and amination of **34c**, containing isopropyl substituents, proceeded in 90% and 92% ee, respectively; however, the overall conversion suffered, requiring the allylic carbonate instead of the allylic acetate to afford only 50% yield of substituted products **37a**,**b** at −20 °C over 2 days. No product was observed when the even bulkier, 1,3-dicyclohexylpropenyl carbonate (**34d**) was used as the substrate.

Regioselective Allylic Alkylations. The regioselective allylic alkylation of trisubstituted π-allyl precursors **38a**−**c**[30] was attempted with ligands **10k** and **11k**. At room temperature, complete conversion of **38a**,**b** was observed over a period of 4 h using one full equivalent of KOAc to prevent the reaction from stalling.[31] For substrates **38a**,**b**, ligand **10k** proved optimal, affording adducts **39a**,**b** in high yield and good enantioselectivity (Table 7, eq 15).[32] Interestingly, ligand **11k**, which proved to be the most effective for most of the previously described reactions, afforded adducts **39a**,**b** in much lower enantioselectivities. Only dimethyl malonate was an effective nucleophile for these reactions; nitrogen nucleophiles afforded no detectable substituted product.

Table 7. Regioselective Allylic Alkylations (Eq 15)[a,e]

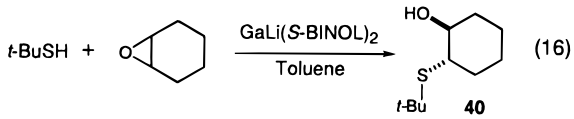


(15)

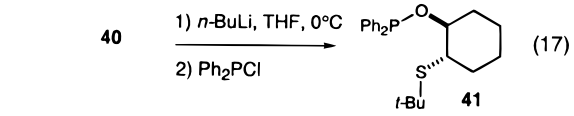
R	% ee[b] (% yield)	% ee[b] (% yield)
Ph (**38a**)	94[c] (94)	41[c] (92)
Me (**38b**)	76[c] (94)	23[c] (95)
i-Pr (**38c**)	NR[d]	NR[d]

[a] Reactions were carried out in CH_2Cl_2 (0.36 M in substrate) and proceeded to completion. [b] Absolute stereochemistry determined by comparison of specific rotation to literature values. [c] Determined by chiral HPLC. [d] No reaction was observed after 48 h at 40 °C. [f] Yields determined after chromatography.

Practical Synthesis of a Mixed P/S Ligand. Ligand **41** served as a readily constructed, structural analogue of **11k** in which the ligand backbone is constrained in a ring. Ligand precursor **40** was obtained from the enantioselective desymmetrization of cyclohexene oxide with *tert*-butyl mercaptan according to the method of Shibasaki (eq 16).[33] The adduct of this reaction **40** was converted to ligand **41** (eq 17).



(16)



(17)

Ligand **41** was highly effective in the palladium-catalyzed allylic substitution of 1,3-diphenylpropenyl acetate with both dimethyl malonate and benzylamine as nucleophiles, affording products in nearly equivalent enantioselectivities and yields as observed for **11k** (Table 8).

Mechanistic Considerations. Insight into the chelate geometry of mixed phosphorus/sulfur ligands, the control of stereochemistry at coordinated sulfur, and the application of the trans influence to enantioselective palladium-catalyzed allylic substitutions was derived from X-ray crystallographic and NMR spectroscopic analysis of ligand−metal complexes. X-ray quality crystals of (**11k**)$PdCl_2$ (**42**) were obtained from CH_2Cl_2/Et_2O and its structure was determined (Figure 2).[34] Complex **42** adopts a twist-boat geometry, accommodating both backbone substituents in equatorial positions. Additionally, the β-methyl substituent orients the isopropyl group in the direction of the coordinated thioether as predicted. In accord with the ligand

(28) (a) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl*. **1993**, *32*, 566−568. (b) Wiese, B.; Helmchen, G. *Tetrahedron Lett.* **1998**, *39*, 5727−5730 and references therein. (c) Trost, B. M.; Krueger, A. C.; Bunt, R.; Zambrano, J. *J. Am. Chem. Soc*. **1996**, *118*, 6520−6521. For analogous allylic aminations see: (d) Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 191−193.

(29) It was believed that a more sterically demanding chiral pocket would increase the enantiomeric excess observed in the alkylation of 1,3-dimethylpropenyl acetate; however, using ligands containing bulkier phosphine substituents (**33f** and **33g**) resulted in significantly lower enantioselectivities, 14% ee and 49% ee, respectively.

(30) These substrates were reported to afford exclusive alkylation at the less substituted terminus. (a) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033−2046. (b) Dawson, G. J.; Williams, J. M. J.; Coote, S. J. *Tetrahedron: Asymmetry* **1995**, *6*, 2535−2546 and references therein.

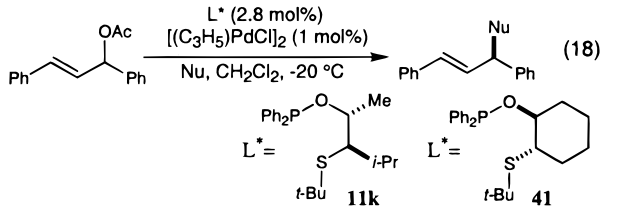
(31) In contrast to most of the previously described allylic alkylations, these reactions showed no conversion at temperatures lower than room temperature.

(32) No product was observed in the allylic alkylation of **34d**.

(33) Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc*. **1997**, *119*, 4783−4784. Separation of enantiomers on the corresponding benzoate ester by HPLC analysis (Daicel Chiralcel AD) determined the enantiomeric excess to be >99%.

(34) Crystals of **42** ($C_{22}H_{31}POSPdCl_2$) were grown by slow diffusion of Et_2O into a solution of **42** in CH_2Cl_2 to yield amber prisms. The compound crystallizes in the tetragonal crystal system, space group $P4_1$; a = 12.4686 (4) Å, b = 12.4686 (4) Å, c = 15.3591 (6) Å, $\alpha = \beta = \gamma = 90°$; V = 2387.82 (4) Å^3; Z = 4; R = 0.0627, GoF = 1.019.

Table 8. Comparison of Ligands **11k** and **41** (Eq 18)[a,e]



Nu	% ee[b] (% yield)	% ee[b,c] (% yield)
$(MeO_2C)_2CH_2$, BSA	98 (97)	94 (95)
$BnNH_2$	95 (97)	95 (95)

[a] Reactions were carried out in CH_2Cl_2 (0.36 M in substrate) and proceeded to complete conversion. [b] Determined by chiral HPLC. [c] Absolute stereochemistry of products obtained using **41** were enantiomeric to those observed for **11k**. [d] Yields determined after chromatographic purifcation.

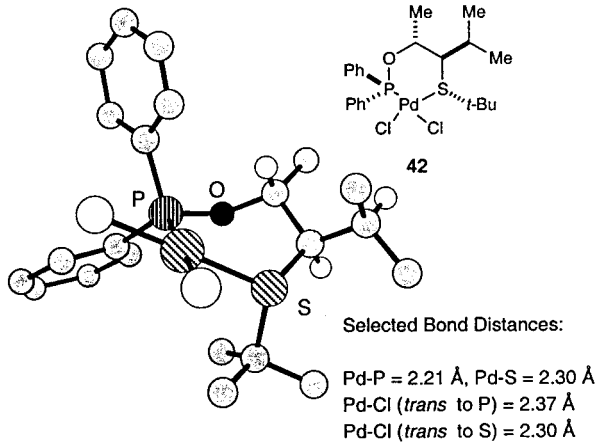


Figure 2. X-ray crystal structure of (**11k**)$PdCl_2$.

design, the *tert*-butyl substituent on sulfur and the adjacent isopropyl group were oriented anti to each other in the chelate. The stronger trans influence of the phosphinite (vs the thioether) was reflected in the difference in Pd−Cl bond lengths trans to phosphorus (2.37 Å) and trans to sulfur (2.30 Å).

While the crystal structure of **42** shows only one diastereomeric complex at sulfur, the solution dynamics of **42** were also probed to confirm that the stereogenic sulfur center was effectively controlled.[35] ^{1}H NMR and ^{31}P NMR spectroscopic studies on **42** in CD_2Cl_2 showed only one diastereomeric complex from −80 to +40 °C, indicative of the strong steric bias imposed upon the sulfur substituent by the adjacent gearing substituent. Similar variable-temperature ^{1}H NMR and ^{31}P NMR spectroscopic analysis on (**10k**)$PdCl_2$ also showed a preference for a single diastereomeric complex from −80 to +40 °C.

Structure of Pd-π-Allyl Complexes. The X-ray structure of **42** coupled with a variable-temperature NMR study confirmed that the ligand architecture effectively controls the stereochemistry at the coordinated thioether. As a result, palladium π-allyl complexes with **10k** may be analyzed with a good degree of certainty that any observed diastereomeric complexes were a result of π-allyl isomerization rather than sulfur inversion.[36] Before the solution dynamics of the π-allyl complex were

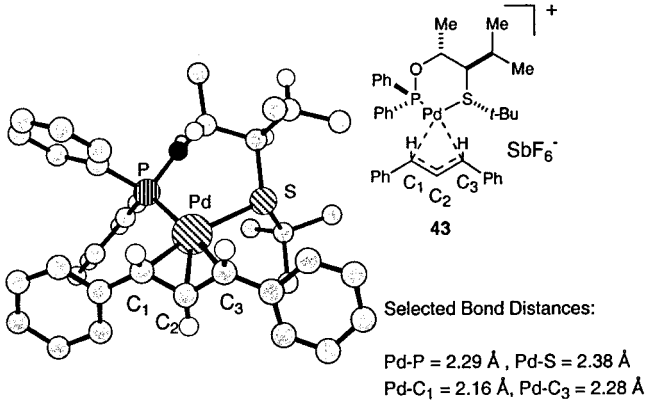
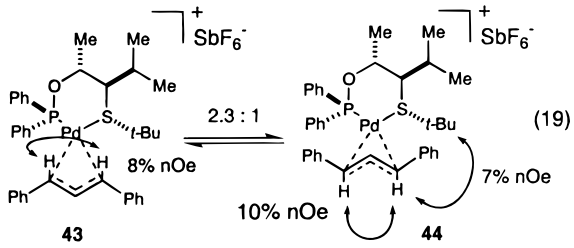


Figure 3. X-ray structure of [Pd(**11k**)(1,3-diphenylpropenyl)](SbF_6) (counterion omitted for clarity).

investigated, an X-ray crystal structure of [Pd(**11k**)(1,3-diphenylpropenyl)](SbF_6) (**43**) was obtained (Figure 3).[37] The overall conformation of the ligand complex **43** closely resembled that observed in **42**. Additionally, the longer Pd−C bond trans to phosphorus (Pd−C_3 = 2.28 Å) compared to the Pd−C bond trans to sulfur (Pd−C_1 = 2.16 Å) reflected the stronger trans influence of the phosphinite ligand and a more electrophilic π-allyl terminus at C_3.[11] While the π-allyl moiety was not significantly twisted out of the P−Pd−S plane,[38] the bond lengths were not entirely symmetrical.[39] Based on the orientation of the π-allyl moiety in the crystal structure, the observed stereochemical outcome of the reaction may be rationalized by invoking nucleophilic addition trans to the phosphinite ligand. Although the X-ray structure of **43** showed only one diastereomeric π-allyl complex, it is well precedented that palladium π-allyl isomerization is a facile process in solution.[36] ^{1}H NMR and ^{31}P NMR studies of **43** in CD_2Cl_2 showed a 2.3:1 mixture of diastereomeric complexes in rapid equilibrium. The major isomer exhibited nOe data consistent with the structure of **43** while the minor isomer correlated to **44** (eq 19).



The NMR data for **43** also supported the different trans influences of the heteroatom donors and their effect on the electrophilicity of the π-allyl termini. In accord with the data reported by Vitagliano, the chemical shift of the proton on the π-allyl terminus trans to phosphorus in the major isomer **43** was 5.91 ppm, while that trans to sulfur was 5.30 ppm, indicative

(35) For an example of an X-ray crystal structuce of a single diastereomeric complex showing two diastereomers in solution by NMR, see: Berger, H.; Nesper, R.; Pregosin, P. S.; Rüegger, H.; Wörle, M. *Helv. Chim. Acta* **1993**, *76*, 1520−1538.

(36) For an excellent reveiew on the structure and dynamics of chiral allyl complexes of Pd(II) see: Pregosin, P. S.; Salzmann, R. *Coord. Chem. Rev.* **1996**, *96*, 35−68.

(37) Crystals of **43** ($C_{37}H_{44}POSPdSbF_6$) were grown from a warm solution of **43** in methanol to yield yellow prisms. The compound crystallizes in the orthorhombic crystal system, space group $P2_12_12_1$; a = 19.597 (2) Å, b = 20.706 (3) Å, c = 9.7944 (13) Å, $\alpha = \beta = \gamma = 90°$; V = 3974.4 (9) Å^3; Z = 4; R = 0.0386, GoF = 0.974.

(38) Strongly rotated allyl moieties have been reported in crystal structures of various mixed donor ligand−palladium π-allyl complexes. (a) Albinati, A.; Pregosin, P. S.; Wick, K. *Organometallics* **1996**, *15*, 2419−21. (b) Togni, A.; Burckhardt, U.; Gramlich, V.; Pregosin, P. S.; Salzmann, R. *J. Am. Chem. Soc.* **1996**, *118*, 1031−1037. (c) Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, *35*, 1523−6.

(39) The C1−C2 bond distance is 1.45 Å, while the C2−C3 bond distance is 1.38 Å. These differences are consistent with the greater σ-bond character of the Pd−C1 bond and an η^2 bond between Pd and C2−C3.

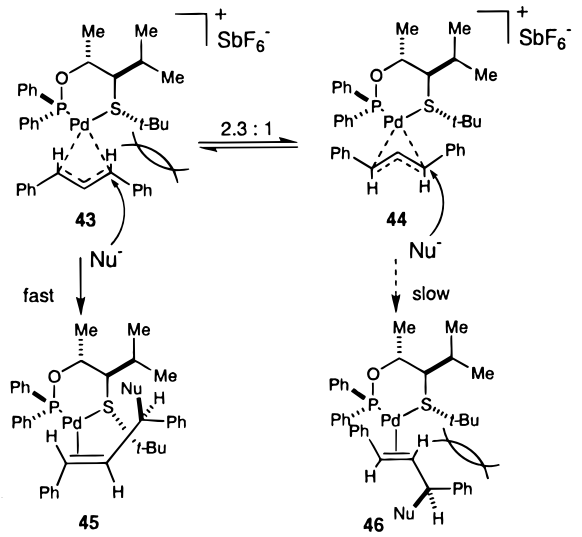


Figure 4. Proposed model for acyclic substrates.

of the greater π-accepting ability of the phosphinite as compared to the thioether.[40] These data complement the X-ray crystal structure data for **43** and support nucleophilic substitution trans to the phosphorus.

The X-ray structure coupled with the NMR spectroscopic data suggest that the high enantioselectivity observed for the reaction is the result of a Curtin−Hammett condition in which nucleophilic addition trans to phosphorus occurs faster in the major diastereomeric π-allyl complex **43**, while allyl isomerization is fast (Figure 4).[41] In π-allyl complex **43**, there are nonbonding interactions between the *S-tert*-butyl substituent on the ligand and the proximal phenyl substituent on the π-allyl moiety. Upon nucleophilic addition, this strain is released, affording the palladium−olefin complex **45**. In the minor diastereomeric complex **44**, the π-allyl moiety is arranged such that the phenyl substituent and the *tert*-butyl substituent in the ligand are staggered, avoiding the steric strain that is present in **43**. In fact, one can envision that steric strain is developed upon nucleophilic addition to π-allyl complex **44** to form the olefin complex **46**.

The results obtained regarding the allylic substitution of acyclic substrates support a more reactive major diastereomeric π-allyl complex. These results are in contrast to the observations made in the allylic alkylations of cyclic substrates, in which the minor diastereomeric π-allyl complex is more reactive (vide infra).

Allylic Substitutions of Cyclic Substrates. Although investigations of the palladium-catalyzed asymmetric allylic substitution of acyclic substrates have spanned a variety of ligands, the corresponding substitutions on cycloalkenyl acetates have been a formidable challenge.[42] Often ligands that afford almost enantiomerically pure material in the allylic alkylation of 1,3-diphenylpropenyl acetate afford very low enantioselectivities in the alkylation of cycloalkenyl acetates.[43] Presumably this lack of generality is derived from a different ligand structural requirement for the successful alkylation of cyclic substrates

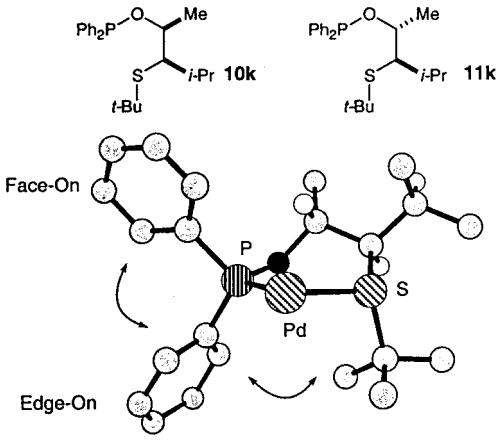


Figure 5. Gearing of *P*-phenyl groups in the X-ray structure of [Pd(**11k**)(1,3-diphenylpropenyl)](SbF_6) (counterion and π-allyl ligand omitted for clarity).

compared to their acyclic counterparts.[44] In the X-ray crystal structures of both (**11k**)$PdCl_2$ and [Pd(**11k**)(1,3-diphenylpropenyl)](SbF_6), the proximity of the stereogenic sulfur center to the metal effectively gears the *P*-phenyl substituents (Figure 5). The *P*-phenyl group proximal to the *S-tert*-butyl substituent is geared in an edge-on orientation, while the other *P*-phenyl substituent is organized in a face-on orientation due to its proximity to the open quadrant created by the stereogenic sulfur center.

Through gearing, the *P*-phenyl substituent syn to the *S-tert*-butyl group is oriented in an edge-on conformation (Figure 5). This interaction positions both sterically demanding groups in the same lower hemisphere of the metal−ligand complex defined by the P−Pd−S plane. This ligand conformation should induce a high preference for π-allyl complex **47** in which the cycloalkenyl moiety is oriented away from the bulky lower hemisphere, while the diastereomeric complex **48** should be disfavored due to multiple nonbonding interactions between the π-allyl moiety and the ligand (Figure 6). Consequently, nucleophilic substitution trans to phosphorus in **47** predicts that adduct **55** should be observed experimentally in preference to (*ent*)-**55**.

Mixed phosphorus/sulfur ligands **10** and **11** were tested in the palladium-catalyzed allylic alkylation of cyclohexenyl acetate with dimethyl malonate. Under the same reaction conditions as in the acyclic cases, the alkylations proceeded to completion within 12 h at −20 °C.

Variation of Sulfur Substituents. As the size of the sulfur substituent R increases, the enantioselectivity of the alkylation increases. It is interesting to note that ligands containing sufficiently small sulfur substituents (i.e. **10e**, **11e**) afford the opposite sense of induction to those ligands with bulkier sulfur substituents (**10i**−**k**, **11i**−**k**). The optimal ligand for the allylic

(40) A similar chemical shift difference was observed in the minor diastereomeric complex. δ H_{allyl}(trans to P) = 6.83 ppm; δ H_{allyl}(trans to S) = 5.48 ppm.

(41) Mackenzie, P. B.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2046−2054. For a review on Curtin−Hammett kinetics with numerous examples, see: Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83−134.

(42) Although the enantioselective allylic alkylation is difficult to accomplish, the substrate synthesis is quite facile by allylic oxidation of the desired cycloalkene. Hansson, S.; Heumann, A.; Rein, T.; Akermark, B. *J. Org. Chem.* **1990**, *55*, 975−984.

(43) While Pd−sparteine complexes catalyze the allylic alkylation of 1,3-diphenylpropenyl acetate in 75% ee, the corresponding alkylation on cyclohexenyl acetate proceeds in only 50% ee. (a) Togni, A. *Tetrahedron: Asymmetry* **1991**, *2*, 683−690. Similarly, chiral phenanthroline complexes were found to catalyze the allylic alkylation of 1,3-diphenylpropenyl acetate in 92% ee, but the alkylation of cyclohexenyl acetate proceeds in only 16% ee. (b) Pena-Cabrera, E.; Norrby, P.; Sjögren, M.; Vitagliano, A.; de Felice, V.; Oslob, J.; Ishii, S.; O'Neill, D.; Akermark, B.; Helquist, P. *J. Am. Chem. Soc.* **1996**, *118*, 4299−4313.

(44) The ligands developed by Trost are effective for the allylic alkylation of both cyclic and acyclic substrates; however, only acyclic substrates containing sterically small substituents gave high enantiomeric excesses. (a) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089−4090. (b) Knuehl, G.; Sennhenn, P.; Helmchen, G. *J. Chem. Soc., Chem. Commun.* **1995**, 1845−1846 and references therein. (c) Kudis, S.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3047−3050.

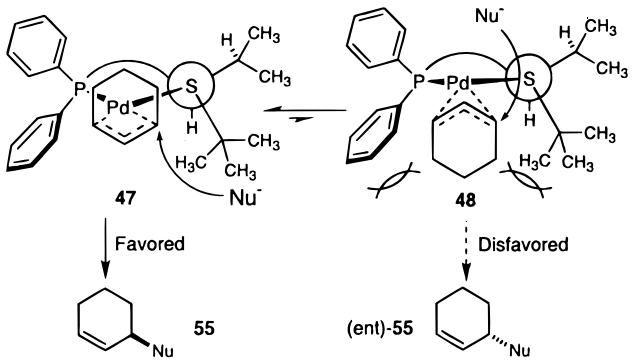
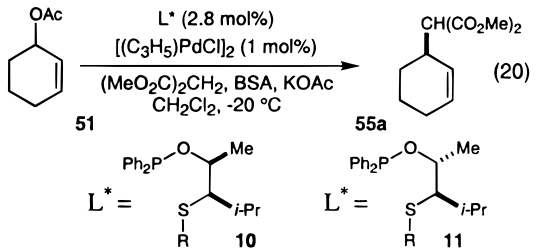


Figure 6. Proposed mechanism of induction in the allylic substitution of cycloalkenyl acetates.

Table 9. Effect of *S*-Substituent on Enantioselectivity (Eq 20)[a,d]



R	% ee[b]	% ee[b]
3,5-Me_2Ph	**10e**, -35	**11e**, -48
Bn	**10i**, 51[c]	**11i**, 1[c]
Cy	**10j**, 71[c]	**11j**, 28[c]
t-Bu	**10k**, 90[c]	**11k**, 38[c]

[a] Reactions were carried out in CH_2Cl_2 (0.36 M in substrate) and proceeded to completion. [b] Determined by ^{1}H NMR chiral shift assay using Eu(hfc)$_3$. [c] Absolute stereochemistry of the product was determined to be (*R*) by comparison of the specific rotation to literature values. [d] Reaction was run at 0 °C. [e] Yields >90% after isolation by chromatography.

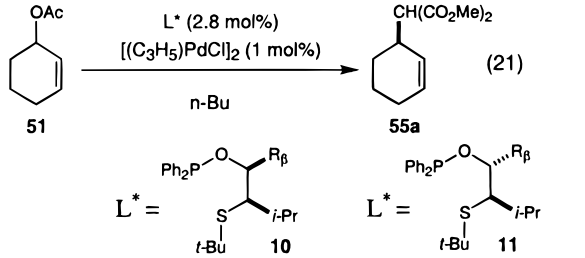
alkylation of cyclohexenyl acetate is **10k**, which affords alkylated product **55a** in 90% ee,[45] favoring the enantiomer predicted by our model (Figure 6). Surprisingly, when ligand **11k** was used under the same conditions, alkylated adduct **55a** was obtained in only 38% ee. This drastic dependence of enantioselectivity on the relative stereochemistry of the ligand backbone substituents, favoring the syn vicinal alkyl groups, held for the illustrated set of sulfur and phosphorus substituents (Table 9).

Variation of Backbone Substituents. Regardless of the nature of the β-substituent R_β, ligands containing backbone substituents which were syn-disposed in the ligand chelate, **10k**, **12k**, and **14k**, gave uniformly higher enantioselectivities than their anti counterparts **11k**, **13k**, and **15k** (Table 10, eq 21). In accord with the alkylations of acyclic substrates, as the size of the β-substituent was increased, the enantioselectivity decreased.

In an effort to further elucidate the importance of the β-substituent on the reaction enantioselectivities, ligands **29** and **32** were evaluated in the allylic alkylation of cyclohexenyl acetate with dimethyl malonate (Table 11). In the absence of any β-substituent, ligand **29** delivered **55a** in 77% ee, more closely resembling the results obtained with **10k**. In contrast, ligand **32**, which contains dimethyl substitution at the β-position, afforded **55a** in only 25% ee, similar to the enantioselectivity observed using **11k**.

(45) Using **10k** as the ligand and $NaCH(CO_2Me)_2$ or $KCH(CO_2Me)_2$ as the nucleophile in THF afforded good yields of **55a** in 58% and 89% ee, respectively.

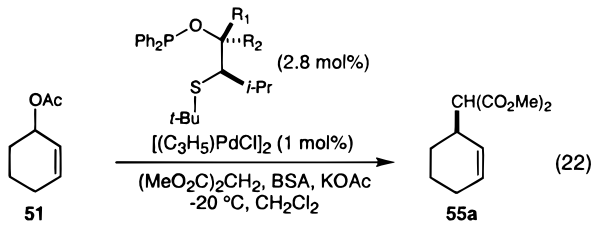
Table 10. Effect of β-Substituent on Enantioselectivity (Eq 21)[a,c]



R	% ee[b]	% ee[b]
Me	**10k**, 90	**11k**, 38
Ph	**12k**, 89	**13k**, 37
i-Pr	**14k**, 70	**15k**, 30

[a] Reactions were carried out in CH_2Cl_2 (0.36 M in substrate) and proceeded to completion. [b] Determined by ^{1}H NMR chiral shift assay using Eu(hfc)$_3$. [c] Yields >90% after isolation by chromatography.

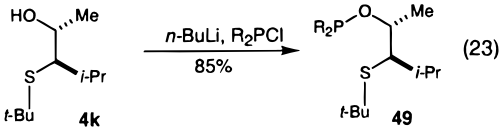
Table 11. Effect of β-Substituent on Enantioselectivity (Eq 22)[a,c]



Ligand	R_1	R_2	% ee[b]
29	H	H	77
10k	Me	H	90
11k	H	Me	38
32	Me	Me	25

[a] Reactions were carried out in CH_2Cl_2 (0.36 M in substrate) and proceeded to complete conversion. [b] Determined by ^{1}H NMR chiral shift assay using Eu(hfc)$_3$. [c] Yields >94% after isolation by chromatography.

Variation of Phosphorus Substituents. A variety of *P*-substituted phosphinites were readily prepared from β-hydroxysulfide (**4k**) to afford ligands **49a**−**g** (eq 23), which were subsequently tested in the allylic alkylation of cyclohexenyl acetate (Table 12).



Incorporation of either electron-withdrawing (**49a**, **49e**) or electron-donating (**49b**, **49c**) substituents on the *P*-phenyl moiety resulted in lower enantioselectivities (Table 12). Even incorporation of the electronically and sterically different cyclohexyl substituents at phosphorus (**49f**) resulted in significantly lower enantioselectivities compared to those observed with **10k**. We speculated that bulkier aryl substituents at phosphorus would more effectively discriminate between diastereomeric π-allyl complexes **47a** and **48a**, leading to higher enantioselectivities (Figure 7). In accord with this postulate, incorporation of bis-(α-naphthyl) substituents at phosphorus (**49g**) resulted in improved enantioselectivity in the alkylation of cyclohexenyl acetate affording the desired alkylated product **55a** in 94% ee and 91% yield.

Other Substrates and Nucleophiles. Ligand **49g** proved to be optimal for the allylic alkylation of 5-, 6-, and 7-membered

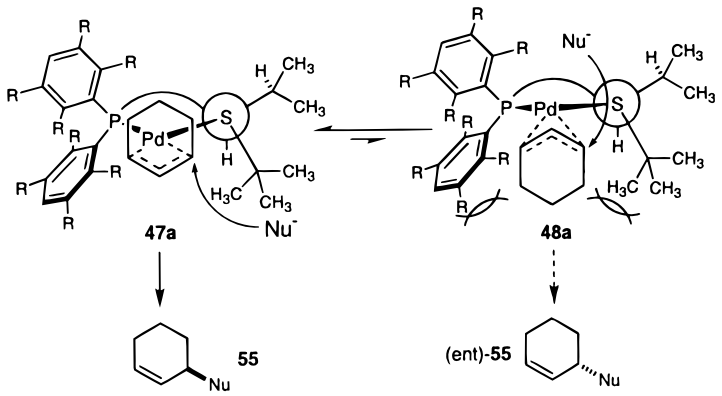
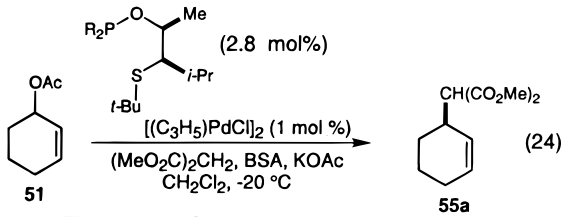


Figure 7. Increased π-allyl selectivity through incorporation of bulky *P*-aryl substituents.

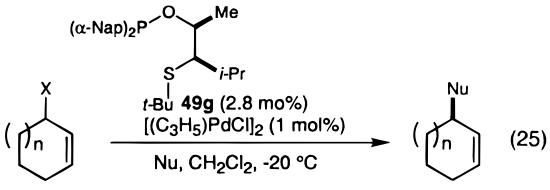
Table 12. Effect of *P*-Substituent on Enantioselectivity (Eq 24)[a,e]



R	Ligand	% ee[b]
Ph	**10k**	90
4-FPh	**49a**	85
4-MeOPh	**49b**	87
2-MeOPh	**49c**	55
3,5-$(CH_3)_2$Ph	**49d**	85
3,5-$(CF_3)_2$Ph	**49e**	58
Cy	**49f**	75
α-Nap	**49g**	94

[a] Reactions were carried out in CH_2Cl_2 (0.36 M in substrate) and proceeded to completion. [b] Determined by ^{1}H NMR chiral shift assay using Eu(hfc)$_3$. [c] Yields were >90% after isolation by chromatography.

Table 13. Allyl Substitution of Cycloalkenyl Acetates (Eq 25)[a,e]

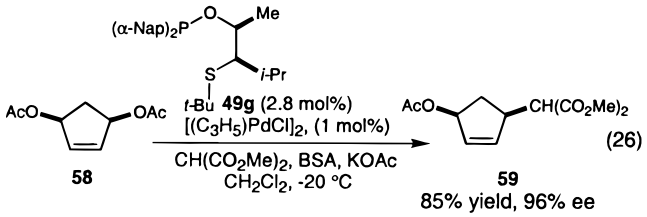


n	X	Nu = $(MeO_2C)_2CH_2$, BSA % ee,[b,c] (% yield)	Nu = $BnNH_2$ % ee,[d] (% yield)
0	OAc (**50**)	**54a**, 94 (94)	**54b**, 91 (93)
1	OAc (**51**)	**55a**, 94 (91)	**55b**, 91 (97)
2	OAc (**52**)	**56a**, 96 (98)	**56b**, 97 (95)
3	OCO_2Et (**53**)	**57a**, 79 (95)	NR[e]

[a] All reactions were carried out in CH_2Cl_2 (0.36 M in substrate) and proceeded to completion conversion. [b] Determined by ^{1}H NMR chiral shift assay using Eu(hfc)$_3$. [c] Determined chiral HPLC. [d] No reaction was observed after 24 h. [e] All yields were determined after isolation by chromatography.

cycloalkenyl acetates **50**−**52** with dimethyl malonate, affording adducts **54a**−**56a** in good yields and ≥94% ee (Table 13). Although *cis*-cyclooctenyl acetate was unreactive under the reaction conditions, the allylic carbonate **53** was alkylated to give **57a** in 79% ee exclusively as the cis olefin isomer. This process was also amenable to the allylic amination of 5-, 6-, and 7-membered substrates **50**−**52** with benzylamine, to afford **54b**−**56b** in >91% ee.

Alkylation of 1,4-Diacetoxycycloalkenes. It has been previously demonstrated that ligands which are successful in the alkylation of cycloalkenyl acetates also afford high enantioselectivities in allylic alkylations of 1,4-diacetoxycyclopentene (**58**).[46] The allylic alkylation of this difunctional allylic substrate was investigated, and the optimal ligand was **49g**, affording the monoalkylated adduct **59** in 85% yield and 96% ee (eq 26).[47]



Alkylation of Heterocyclic Substrates. Although success in the enantioselective allylic substitution of cycloalkenyl acetates has been reported, extension to heterocyclic analogues has been almost unexplored,[48] presumably due to a lack of a straightforward synthesis of these substrates. Practical syntheses of the six-membered heterocyclic substrates **62** and **67** were developed which utilize recent developments in catalytic ring-closing metathesis.[49]

Synthesis of the nitrogen-containing heterocycle **62** began with a highly regioselective opening of butadiene monoxide with allylamine[50] followed by protection of the secondary amine to afford the metathesis precursor **60** (Scheme 5). Grubbs' catalyst[51] could be used directly on **60** to afford the ring-closing metathesis product **61** in 85% yield. Conversion of the allylic alcohol to the carbonate afforded substrate **62** in good yield.

A similar synthesis of the thiine **67** was attempted in analogy to **62** (Scheme 5). Addition of butadiene monoxide to a neat solution of DBU and allyl mercaptan gave the desired regioisomer **63** in 60% yield. Synthesis of the acetate **64** proceeded cleanly in quantitative yield, and ring-closing metathesis with

(46) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327−9343.

(47) When ligands **10k** and **11k** were used in the allylic alkylation of 1,4-diacetoxycyclopentene, the monoalkylated adduct was obtained in 91% and 62% ee, respectively.

(48) The most notable exception is the asymmetric palladium-catalyzed allylic substitution of *cis*-2,5-diacyloxy-2,5-dihydrofuran toward the synthesis of nucleosides. Trost, B. M.; Shi, Z. *J. Am. Chem. Soc.* **1996**, *118*, 3037−3038,

(49) Hoveyda, A. *Top. Organomet. Chem.* **1998**, *1*, 106−132 and references therein.

(50) Bottini, A. T.; Dev, V. *J. Org. Chem.* **1962**, *27*, 968−973.

(51) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887−3897 and references cited therein.

Scheme 5[a]

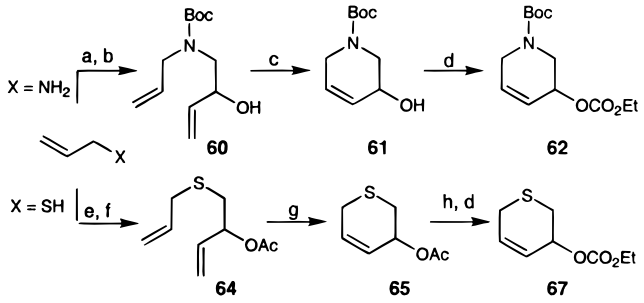
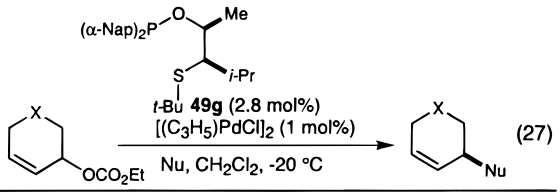


Table 14. Alkylation of Heterocyclic Substrates (Eq 27)[a,e]



X	Nu	% ee[b] (% yield)
N-Boc (**62**)	$CH(CO_2Me)_2$, BSA	**68a**, 94(94)[b]
	$BnNH_2$	**68b**, 94(95)[c]
S (**67**)	$CH(CO_2Me)_2$, BSA	**69a**, 50(60)[c,d]
	$BnNH_2$	**69b**, 92(62)[c]

[a] Reactions carried out in CH_2Cl_2 (0.36 M in substrate) and proceeded to complete conversion. [b] Determined by chiral shift assay using $Eu(hfc)_3$. [c] Determined by chiral HPLC. [d] 5 mol % $[(C_3H_5)PdCl]_2$ and 12 mol % **49g** was used. [e] Yields determined after isolation by chromatography.

the Schrock catalyst[52] afforded **65** cleanly in 85% yield. The acetate **65** proved to be unreactive in allylic substitutions, so the carbonate **67** was synthesized by hydrolysis of **65** followed by treatment with ethyl chloroformate and triethylamine.

The nitrogen-containing heterocycle **62** underwent allylic alkylation and amination using ligand **49g** to afford **68a**,**b** in 94% ee and >93% yield (Table 14). The alkylation of the sulfur-containing heterocycle **67** did not proceed at the standard loading of 2 mol % of Pd, but at 10 mol % of catalyst loading a 60% yield of **69a** was obtained in only 50% ee. In contrast, the allylic amination of **67** with benzylamine proceeded with only 2 mol % of Pd to afford **69b** in 62% yield and 92% ee.

Mechanistic Considerations. Much of the insight into the optimal catalyst design for these cyclic substrates was obtained from structural analysis of [Pd(**10k**)(cyclohexenyl)](SbF_6) (**70**)[53] by single-crystal X-ray diffraction and NMR spectroscopy (Figure 8). The gearing effects in **70** were similar to those observed in [Pd(**11k**)(1,3-diphenylpropenyl)](SbF_6) (Figure 3). The π-allyl moiety is bound in such a manner that the ring is oriented away from the bulky hemisphere containing the *S*-*tert*-butyl substituent and the edge-on *P*-phenyl group. The larger trans influence of the phosphinite was reflected in the longer Pd−C bond trans to phosphorus (Pd−C_1 = 2.26 Å) compared to sulfur (Pd−C_2 = 2.17 Å). As with π-allyl complex **43**, the asymmetry of the π-allyl moiety supports σ-bond character in

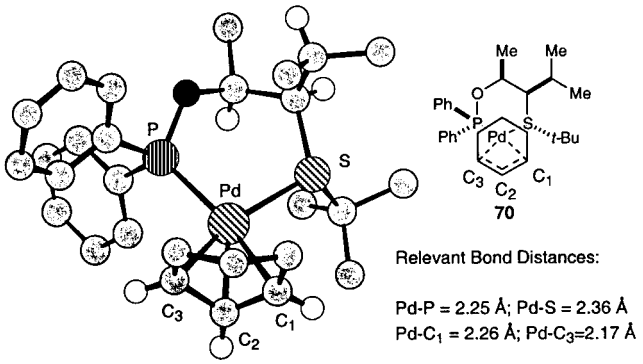


Figure 8. X-ray crystal structure of [Pd(**10k**)(cyclohexenyl)](SbF_6) (counterion omitted for clarity).

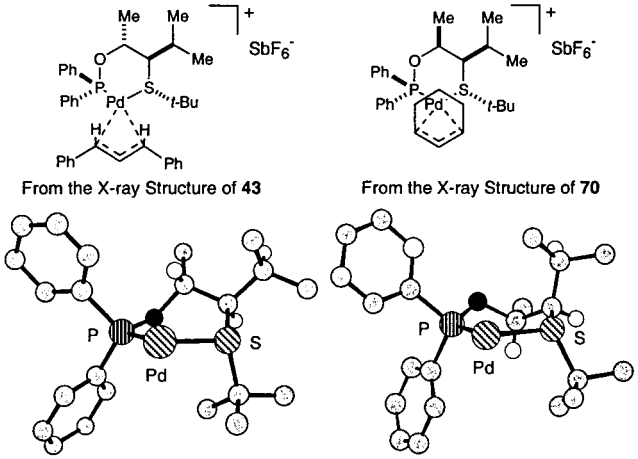


Figure 9. A comparison of the chelate geometries in **43** and **70**.

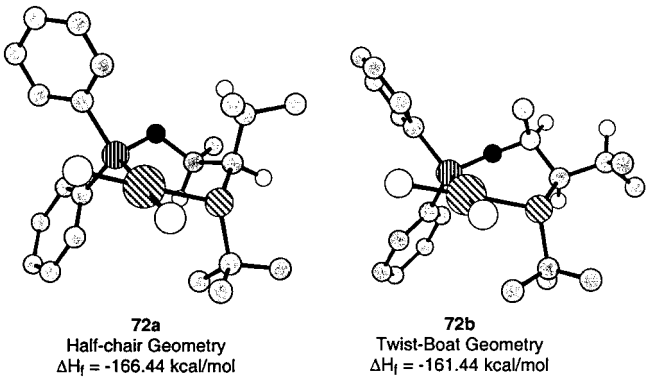


Figure 10. PM3 minimized structures of (**10k**)$PdCl_2$.

Pd−C_3 and more olefin character in C_1−C_2.[54] In accord with the acyclic substrates, the experimentally observed stereochemistry could be rationalized by invoking nucleophilic substitution trans to phosphorus.

It is interesting to note that [Pd(**10k**)(cyclohexenyl)](SbF_6) exists in a half-chair chelate geometry, which differs from the twist-boat geometry observed for complexes with ligand **11k** (Figure 9). Molecular modeling supports a strong dependence of the chelate geometry on the stereochemistry of the β-substituent. Geometry optimization of (**10k**)$PdCl_2$ shows a preference for the half-chair geometry **72a** over the twist-boat geometry **72b** by 5.0 kcal/mol (Figure 10). In contrast, modeling of (**11k**)$PdCl_2$ complexes reveals that the twist-boat geometry **73b** is 1.0 kcal/mol lower in energy than the chair geometry **73a** (Figure 11).[55,56]

(52) 2,6-Diisopropylphenylimidoneophylidenemolybdenum(VI) bis(hexafluoro-*tert*-butoxide). Schrock, R. R. *Pure Appl. Chem.* **1994**, *66*, 1447−1454 and references therein.

(53) Crystals of **70** ($C_{28}H_{40}POSPdSbF_6$) were grown from a warm solution of **70** in methanol to yield yellow prisms. The compound crystallizes in the orthorhombic crystal system, space group $P2_12_12_1$; a = 10.228 (5) Å, b = 17.727 (8) Å, c = 18.088 (7) Å, $\alpha = \beta = \gamma = 90°$; V = 3279 (2) Å^3; Z = 4; R = 0.0433, GoF = 1.282.

(54) C1−C2 is shorter (1.36 Å) than C2−C3 (1.44 Å).

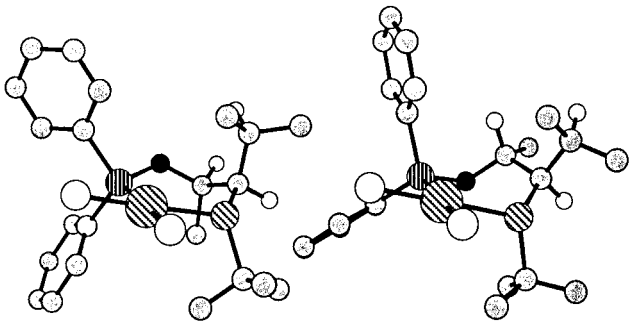


Figure 11. PM3 minimized structures of (**11k**)$PdCl_2$.

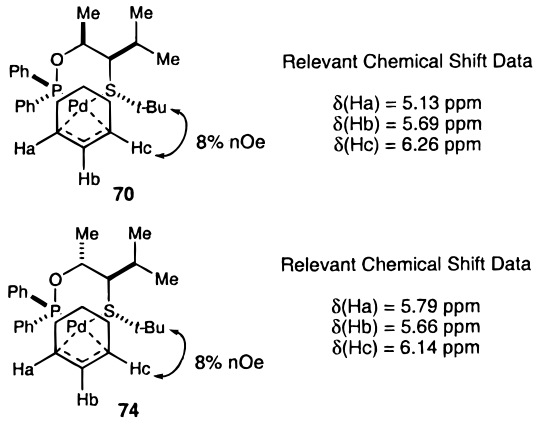
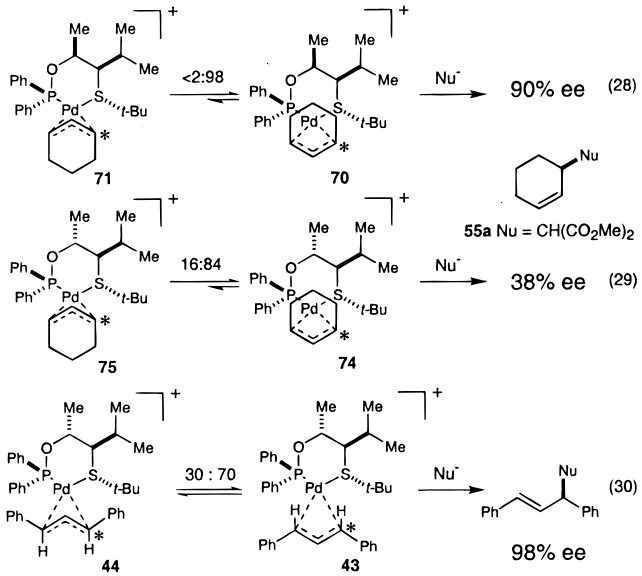


Figure 12. NMR data for π-allyl complexes **70** and **74**.

^1H NMR and ^{31}P NMR spectroscopic analysis of [Pd(**10k**)-(cyclohexenyl)](SbF_6) (**70**) in CD_2Cl_2 revealed only one diastereomeric π-allyl complex (>98:2), consistent with the X-ray structure of **70** (Figure 12). The chemical shift of the allyl proton H_c trans to phosphorus is over 1 ppm further downfield than H_c which is trans to sulfur (6.26 ppm versus 5.13 ppm). These data, coupled with the bond lengths observed in the X-ray structure of **70**, strongly support a model in which nucleophilic substitution occurs trans to phosphorus.

Although the absolute stereochemistry of the alkylated product **55a** is derived from nucleophilic substitution trans to phosphorus in complex **70**, the observed enantioselectivity (90% ee) is lower than expected for a complex that is diastereomerically pure in solution. The erosion of enantioselectivity could be the result of an undetectable, more reactive minor diastereomeric π-allyl complex **71** which is below the detection limit of ^1H NMR (eq 28).[57] Evidence supporting this assertion was obtained from the NMR spectroscopic analysis of [Pd(**11k**)-(cyclohexenyl)](SbF_6) in which both the major and minor π-allyl diastereomeric complexes **74** and **75**, respectively, could be detected (eq 29). As before, the absolute stereochemistry of the alkylated product **55a** is derived from alkylation trans to phosphorus in the major π-allyl diastereomer **74**; however, a comparison of the diastereomeric ratio (84:16) to the experimentally observed enantioselectivity (38% ee) suggests that the minor π-allyl diastereomer **75** is more reactive. This evidence is to be contrasted with the observations made in the alkylation of acyclic substrates; the absolute stereochemistry of the alkylated product is derived from the major π-allyl diastereomer **43**, and a comparison of the diastereomeric ratio (70:30) to the experimentally observed enantioselectivity (98% ee) suggests that the major π-allyl diastereomer is more reactive (eq 30).



These results emphasize the influence of the substrate structure on the relative reactivity of diastereomeric complexes and highlight the difficulties in the design of an enantioselective catalyst for the allylic substitution of cyclic substrates, where even undetectable quantities of the minor diastereomer will significantly erode the enantioselectivity.

Conclusion

A class of mixed phosphorus/sulfur ligands has been developed which addresses the issue of sulfur inversion in coordinated thioether complexes by the incorporation of a bulky substituent at the adjacent stereocenter in the ligand backbone. With the appropriate set of ligand components, high enantiomeric excesses (90−98% ee) may be realized in the allylic substitution of 1,3-diphenylpropenyl acetate and cycloalkenyl acetates with dimethyl malonate or benzylamine as nucleophiles. What differentiates this study from other published ligand systems is the modular design of the ligand synthesis which allowed a correlation between ligand−metal structure and reaction enantioselectivity to be drawn. Identification of important structural features in the ligand−metal chelate provided the necessary information to develop ligands which are readily prepared (such as **40**) and afford enantioselectivities which are competitive with the best published alternatives. More recently, these ligands were tested in the rhodium-catalyzed hydrogenation of olefins (eq 31)[58] and the rhodium-catalyzed hydrosilylation of ketones (eq

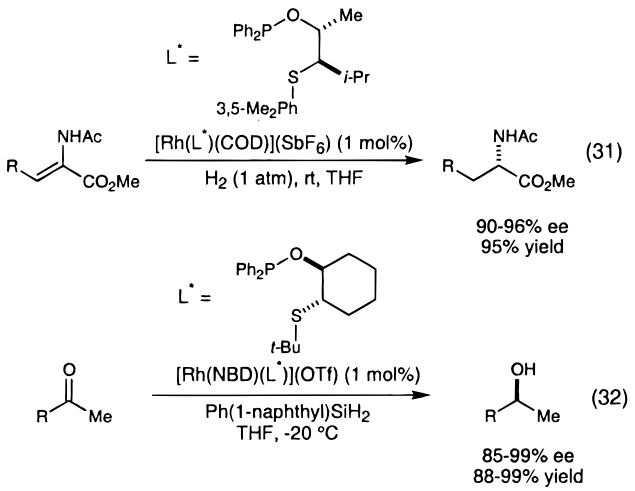
(55) Geometry optimizations were performed at the PM3(tm) level using the Spartan Semiempirical Program 5.0 (Wavefunction Inc., Irvine, CA 92715) on a Silicon Graphics Impact 10000 (195 MHz, 128 M RAM) running IRIX 6.2. Calculations ere performed without counterions or solvent using these parameters: optcycle = 2000, maxcycle = 2000, charge = 0, multiplicity = 0. Calculations converged (energy difference between cycles <0.0005 kcal/mol) in ≤4 h CPU time.

(56) Interestingly, the preference for a specific conformation in both (**29**)-$PdCl_2$ and (**32**)$PdCl_2$ is small (<1.0 kcal/mol), making it difficult to determine the nature of the drastic difference in the observed enantioselectivities in the allylic substitution of both acyclic and cyclic substrates.

(57) The most notable example of a minor diastereomeric complex reacting faster than the major was reported by Halpern in the rhodium-catalyzed hydrogenation of (*Z*)-acetamidocinnamates. (a) Halpern, J. *Science* **1982**, 217, 401−407. (b) Halpern, J.; Landis, C. R. *J. Am. Chem. Soc.* **1987**, *109*, 1746−1754 and references therein.

(58) Evans, D. A.; Michael, F. M.; Tedrow, J. S.; Campos, K. R. *Org. Lett.* **1999**, manuscript in preparation.

32)[59] with excellent results. We believe that this modular ligand



design could be tailored to any metal-catalyzed transformation of interest and deliver valuable information about the relationship between ligand architecture and reaction enantioselectivity.

Experimental Section

General Procedure for Thiolate Displacements on (4*S*)-3-((2*S*)-2-Bromo-3-methylbutanoyl)-4-benzyl-1,3-oxazolidin-2-one (1): 3-[(2*R*)-2-Phenylthio-3-methylbutanoyl]-(4*S*)-4-benzyl-1,3-oxazolidin-2-one (2a). To a cooled (0 °C) solution of **1** (1.02 g, 3.0 mmol) and thiophenol (0.397 g, 3.6 mmol) in THF (0.3 M) was added DBU dropwise (0.45 mL, 7.2 mmol). After allowing the cloudy white solution to be stirred at ambient temperature for 1 h, the organic solution was diluted with 10 mL of 1:1 hexane−ethyl acetate and washed successively with water and brine. After drying over $MgSO_4$, the organic solution was concentrated in vacuo, and the product was purified by flash chromatography (90% hexane, 10% ethyl acetate) to yield **2a** as a white solid (0.96 g, 87% yield). $[\alpha]_d^{23}$ +149° (*c* 1.22, CH_2Cl_2); IR (film) 2964, 1777, 1965, 1583, 1472, 1387, 1360, 1310, 1197, 1098, 1051, 1025, 998, 746, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52−7.47 (m, 2H), 7.35−7.24 (m, 6H), 7.22−7.19 (m, 2H), 5.09 (d, 1H, *J* = 9.2 Hz), 4.48 (dddd, 1H, *J* = 10.0, 7.7, 3.3, 2.2 Hz), 4.05 (dd, 1H, *J* = 9.0, 2.0 Hz), 3.86 (t, 1H, *J* = 8.3 Hz), 3.29 (dd, 1H, *J* = 13.3, 3.2 Hz), 2.68 (dd, 1H, *J* = 13.2, 10.0 Hz), 2.27 (dsept, 1H, *J* = 9.3, 6.7 Hz), 1.22 (d, 3H, *J* = 6.7 Hz), 1.08 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 153.0, 135.3, 133.9, 132.8, 129.4, 129.0, 128.9, 128.3, 127.4, 66.0, 55.8, 54.7, 38.0, 30.5, 20.9, 19.9; TLC R_f 0.30 (85% hexane, 15% ethyl acetate); exact mass calcd for $C_{21}H_{23}N_1O_3S_1$ requires *m*/*z* 369.1399, found *m*/*z* 369.1404 (EI).

General Procedure for Reductive Cleavage of the Chiral Imide Auxiliary: **(2*R*)-2-Phenylthio-3-methylbutan-1-ol (3a)**. To a cooled (0 °C) solution of α-thioimide (**2a**) (937 mg, 2.54 mmol) in THF (0.25 M) was added deionized water (91 μL, 5.1 mmol) followed by $LiBH_4$ (2.54 mL, 2.0 M in THF, 5.1 mmol). After being stirred at 0 °C for 3 h, the solution was quenched by adding 1 M $HCl_{(aq)}$ dropwise. Once clear, the solution was diluted with EtOAc and washed with 1 M $HCl_{(aq)}$ and brine. The organic solution was dried over $MgSO_4$ and concentrated in vacuo, and the product was purified by flash chromatography (90% hexane, 10% ethyl acetate) to yield **3a** as a colorless oil (0.47 g, 94% yield). $[\alpha]_d^{23}$ +3.9° (*c* 0.78, CH_2Cl_2); IR (film) 3376, 2960, 2872, 1584, 1479, 1438, 1384, 1366, 1062, 1025, 802, 740, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47−7.43 (m, 2H), 7.32−7.21 (m, 3H), 3.75 (ddd, 1H, *J* = 11.6, 7.4, 5.1 Hz), 3.62 (ddd, 1H, *J* = 11.5, 7.1, 5.0 Hz), 3.06 (ddd, 1H, *J* = 7.2, 5.7, 5.3 Hz), 2.21 (t, 1H, *J* = 5.0 Hz), 2.01 (dsept, 1H, *J* = 6.7, 6.2 Hz), 1.08 (d, 3H, *J* = 6.7 Hz), 1.06 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.2, 132.1, 129.1,-127.1, 62.6, 60.8, 29.8, 20.4, 19.9; TLC R_f 0.25 (85% hexane, 15% ethyl acetate); exact mass calcd for $C_{11}H_{16}O_1S_1$ requires *m*/*z* 196.0922, found *m*/*z* 196.0919 (CI−NH_3).

General Procedure for Alcohol Oxidation/Alkylation. (a) (2*S*,3*R*)-3-Phenylthio-4-methylpentan-2-ol (4a). To a cooled (−78 °C) solution of oxalyl chloride (241 μL, 2.8 mmol) in CH_2Cl_2 (0.28 M) was added DMSO dropwise (392 μL, 5.52 mmol). After gas evolution ceased (5 min), a solution of alcohol **3a** (0.45 g, 2.3 mmol) in CH_2Cl_2 (2.3 M) was added via cannula (1 mL wash). After the solution was stirred for another 10 min, DIPEA (1.60 mL, 9.2 mmol) was added via syringe and the now clear solution was allowed to stir at −50 °C for 1 h. This solution was cooled to −78 °C and transferred via cannula to a precooled (−78 °C) solution of MeMgBr (5.37 mL, 3.0 M in Et_2O, 16.1 mmol) in an equal volume of CH_2Cl_2. The reaction was quenched after 0.5 h by the addition of saturated $NH_4Cl_{(aq)}$ and allowed to warm to room temperature. The solution was then diluted with Et_2O, separated from the aqueous solution, and washed successively with 1 M $HCl_{(aq)}$ and brine. After the organic solution was dried with $MgSO_4$ and concentrated in vacuo, the resulting mixture of diastereomers was purified by flash chromatography (90% pentane, 10% diethyl ether) to yield **4a** as a colorless oil (370 mg, 71% yield). $[\alpha]_d^{23}$ +2.8° (*c* 0.69, CH_2Cl_2); IR (film) 3412, 3058, 2962, 2871, 1583, 1479, 1438, 1383, 1062, 1025, 978, 916, 822, 736, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, 2H, *J* = 7.1 Hz), 7.27 (t, 2H, *J* = 7.4 Hz), 7.19 (t, 1H, *J* = 7.3 Hz), 4.04 (br t, 1H, *J* = 5.5 Hz), 3.01 (dd, 1H, *J* = 6.7, 5.3 Hz), 2.56 (br s, 1H), 2.09 (oct, 1H, *J* = 6.7 Hz), 1.26 (d, 3H, *J* = 6.3 Hz), 1.08 (d, 3H, *J* = 6.7 Hz), 1.07 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 131.1, 128.9, 126.5, 68.0, 66.6, 30.7, 21.4, 20.1, 19.8; TLC R_f 0.30 (90% pentane, 10% diethyl ether); exact mass calcd for $C_{12}H_{18}O_1S_1$ requires *m*/*z* 210.1078, found *m*/*z* 210.1075 (EI).

(b) (2*R*,3*R*)-3-Phenylthio-4-methylpentan-2-ol (5a). From the reaction described above, separation of diastereomers by flash chromatography yielded **5a** as a colorless oil (109 mg, 21% yield). $[\alpha]_d^{23}$ −39.6° (*c* 0.71, CH_2Cl_2); IR (film) 3448, 2962, 1584, 1480, 14348, 1382, 1366, 1264, 1088, 1048, 1024, 930, 831, 736, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, 2H, *J* = 7.1 Hz), 7.27 (t, 2H, *J* = 7.4 Hz), 7.19 (t, 1H, *J* = 7.3 Hz), 3.87 (br quint, 1H, *J* = 6.2 Hz), 2.92 (dd, 1H, *J* = 7.5, 4.0 Hz), 2.81 (br s, 1H), 2.12 (dsept, 1H, *J* = 6.7, 4.0 Hz), 1.29 (d, 3H, *J* = 6.2 Hz), 1.08 (d, 3H, *J* = 6.7 Hz), 0.98 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 131.0, 129.0, 126.5, 68.6, 68.3, 30.5, 21.9, 20.9, 17.8; TLC R_f 0.35 (90% pentane, 15% diethyl ether); exact mass calcd for $C_{12}H_{18}O_1S_1$ requires *m*/*z* 210.1078, found *m*/*z* 210.1081 (EI).

General Procedure for Phosphinite Incorporation: (a) [(2*S*,3*R*)-3-Phenylthio-4-methylpent-2-oxy]diphenylphosphine (10a). To a Schlenck flask containing β-hydroxysulfide 4a (57.0 mg, 0.275 mmol) in THF (0.28 M) at 0 °C was added *n*-BuLi (2.50 M in hexanes, 110 μL, 0.275 mmol). The reaction was warmed to room temperature and stirred for 1 h. The reaction was then cooled to 0 °C and chlorodiphenylphosphine (49 μL, 0.275 mmol) was added via syringe. The reaction was allowed to warm to room temperature and stirred for 3 h. The solvent was removed in vacuo, and the reaction was diluted with 95:5 hexane−ethyl acetate (0.5 mL, dried over sieves and degassed with argon). The resulting slurry was loaded onto a plug of silica and purified by flash chromatography (1 × 3 cm, 95% hexane, 5% ethyl acetate) to yield 10a as an oil (101 mg, 93% yield). $[\alpha]_d^{23}$ +27.1° (*c* 0.28 CH_2Cl_2); IR (CH_2Cl_2) 2965, 1480, 1436, 1046, 978, 882 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.62−7.57 (m, 4H), 7.40 (d, 2H, *J* = 7.2 Hz), 7.13−7.08 (m, 4H), 7.07−7.01 (m, 2H), 6.98−6.95 (m, 2H), 6.90 (t, 1H, *J* = 7.1 Hz), 4.33 (qdd, 1H, *J* = 8.2, 7.5, 6.3 Hz), 3.17 (dd, 1H, *J* = 7.5, 4.3 Hz), 2.28 (dsept, 1H, *J* = 6.7, 4.3 Hz), 1.40 (d, 3H, *J* = 6.2 Hz), 0.99 (d, 3H, *J* = 6.8 Hz), 0.97 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 143.8 (d, *J* = 18 Hz), 143.0 (d, *J* = 17 Hz), 138.5, 131.4, 131.3, 131.2, 130.7, 130.4, 129.5, 129.3, 129.2, 129.1, 128.5, 128.4, 126.3, 79.2 (d, *J* = 21 Hz), 64.7 (d, *J* = 6 Hz), 29.1, 21.7, 20.7 (d, *J* = 5 Hz), 18.3; ^{31}P NMR (202 MHz, C_6D_6) δ 109.6 (s); TLC R_f 0.6 (95% hexane, 5% ethyl acetate); exact mass calcd for $C_{24}H_{28}O_1P_1S_1$−H requires *m*/*z* 395.1599, found *m*/*z* 395.1590 (CI−NH_3).

(b) [(2*R*,3*R*)-3-Phenylthio-4-methylpent-2-oxy]diphenylphosphine (11a). The following reagents were combined in the amounts indicated according to the general procedure for phosphinite incorporation: **5a** (43.8 mg, 0.21 mmol), *n*-BuLi (2.50 M in hexanes, 83 μL, 0.21 mmol),

(59) Evans, D. A.; Tedrow, J. S.; Michael, F. M.; Campos, K. R. *Org. Lett.* **1999**, manuscript in preparation.

and chlorodiphenylphosphine (37 μL, 0.21 mmol). The resulting slurry was loaded onto a plug of silica and purified by flash chromatography (1 × 3 cm, 95% hexane, 5% ethyl acetate) to yield **11a** as an oil (77 mg, 94% yield). $[\alpha]_d^{23}$ +22.3° (*c* 0.26, CH_2Cl_2); IR (CH_2Cl_2) 2965, 1480, 1436, 1024, 934, 882 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.64 (q, 4H, J = 7.4 Hz), 7.38 (d, 2H, J = 7.5 Hz), 7.12 (t, 2H, J = 7.4 Hz), 7.09−6.96 (m, 6H), 6.90 (t, 1H, J = 7.4 Hz), 4.42 (qdd, 1H, J = 7.8, 6.3, 3.5 Hz), 2.93 (dd, 1H, J = 6.4, 3.5 Hz), 2.09 (oct, 1H, J = 6.7 Hz), 1.40 (d, 3H, J = 6.3 Hz), 1.01 (d, 3H, J = 6.7 Hz), 0.95 (d, 3H, J = 6.7 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 143.9 (d, J = 18 Hz), 143.0 (d, J = 17 Hz), 138.7, 131.3, 131.0, 130.6, 130.4, 129.5, 129.3, 129.2, 129.0, 128.5, 128.4, 126.0, 78.3 (d, J = 21 Hz), 63.7 (d, J = 6 Hz), 30.8, 21.7, 20.7, 20.4 (d, J = 5 Hz); ^{31}P NMR (202 MHz, C_6D_6) δ 108.8 (s); TLC R_f 0.6 (95% hexane, 5% ethyl acetate); exact mass calcd for $C_{24}H_{27}O_1P_1S_1-H$ requires *m*/*z* 395.1599, found *m*/*z* 395.1590 (CI−NH_3).

General Procedure for Addition of *tert*-Butyl Isobutylsulfoxide to Aldehydes: (a) (R_S,2*S*,3*R*)-3-*tert*-Butylsulfinyl-4-methyl-2-pentanol (18k). To a cooled (−78 ° C) solution of diisopropylamine (1.16 mL, 8.3 mmol) in THF (0.27 M) was added *n*-BuLi (1.59 M in hexanes, 5.2 mL, 8.3 mmol). The reaction was warmed to 0 °C and stirred for 30 min. The reaction was cooled to −78 °C, and a solution of **17** (1.25 g, 7.7 mmol) in THF (0.63 M) at −78 °C was added via cannula to the reaction and stirred for 1 h. Acetaldehyde (522 μL, 8.3 mmol) was added to the reaction mixture dropwise via syringe at −78 °C, and the reaction was stirred for 30 min. The reaction was quenched with saturated $NH_4Cl_{(aq)}$, diluted with Et_2O, and washed twice with saturated $NH_4Cl_{(aq)}$ and once with brine. The combined aqueous solutions were extracted with CH_2Cl_2, and the combined organic solutions were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude reaction mixture shows a 1:1 mixture of diastereomers at C_2. Separation of diastereomers by MPLC (Michel-Miller column size D, 80% hexane, 20% acetone) followed by recrystallization from cyclohexane yielded **18k** as a white solid (750 mg, 47% yield): mp 88.4−88.7 °C; $[\alpha]_d^{23}$ +131° (*c* 1.02, CH_2Cl_2); IR (film) 3420, 2960, 2872, 2361, 1844, 1792, 1653, 1636, 1559, 1540, 1507, 1465, 1436, 1386, 1365, 1267, 1209, 1178, 1126, 1056, 1030, 984, 913, 856, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.66 (br q, 1H, J = 6.6 Hz), 2.49 (m, 2H), 1.38 (d, 3H, J = 6.6 Hz), 1.32 (d, 3H, J = 6.5 Hz), 1.29 (s, 9H), 1.03 (d, 3H, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 67.1, 62.7, 54.6, 25.9, 23.4, 23.3, 20.5, 20.1; TLC R_f 0.18 (80% hexane, 20% acetone); exact mass calcd for $C_{10}H_{23}S_1O_2$ requires *m*/*z* 207.1419, found *m*/*z* 207.1428 (CI−NH_3).

(b) (R_S,2*R*,3*R*)-3-*tert*-Butylsulfinyl-4-methyl-2-pentanol (19k). From the reaction described above, separation of diastereomers by MPLC followed by recrystallization from cyclohexane yielded **19k** as a white solid (645 mg, 40% yield): mp 72.8−73.1 °C; $[\alpha]_d^{23}$ −74.0° (*c* 1.00, CH_2Cl_2); IR (film) 3442, 2980, 2361, 2090, 1652, 1559, 1541, 1521, 1506, 1465, 1456, 1436, 1395, 1368, 1333, 1298, 1257, 1206, 1168, 1104, 1074, 1002, 958, 915 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.31 (dq, 1H, J = 9.2, 6.3 Hz), 2.70 (dd, 1H, J = 10.5, 2.1 Hz), 1.88 (dquint, 1H, J = 7.0, 2.1 Hz), 1.33 (d, 3H, J = 6.3 Hz), 1.31 (s, 9H), 1.00 (d, 3H, J = 7.2 Hz), 0.91 (d, 3H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 66.1, 65.2, 55.3, 28.9, 23.7, 22.0, 19.5, 18.6; TLC R_f 0.20 (80% hexane, 20% acetone); exact mass calcd for $C_{15}H_{24}S_1O_2$ requires *m*/*z* 207.1419, found *m*/*z* 207.1408 (CI−NH_3).

General Procedure for the Reduction of β-Hydroxysulfoxides: (a) (2*S*,3*R*)-3-*tert*-Butylthio-4-methyl-2-pentanol (4k). To a solution of β-hydroxysulfoxide **18k** (703 mg, 3.6 mmol) in THF (0.1 M) was added BH_3−THF (12 mL, 1.0 M in THF, 12.0 mmol) and the reaction was stirred at room temperature for 12 h. The reaction mixture was then cooled to 0 °C and saturated $NH_4Cl_{(aq)}$ was slowly added. The reaction mixture was diluted with Et_2O, washed with saturated $NH_4Cl_{(aq)}$, saturated $NaHCO_{3(aq)}$, and brine. The combined aqueous solutions were extracted with CH_2Cl_2. The combined organic solutions were dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by flash chromatography (4 × 6 cm, 90% hexane, 10% ethyl acetate) to yield **4k** as an oil (650 mg, 95% yield): $[\alpha]_d^{23}$ +0.99° (*c* 0.49, CH_2Cl_2); IR (film) 3446, 2962, 2903, 2872, 1460, 1365, 1328, 1261, 1211, 1162, 1110, 1074, 1049, 1029, 970, 930, 861, 818, 821, 747, 731 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 3.98 (dq, 1H, J = 6.3, 1.5 Hz), 2.44 (dd, 1H, J = 6.4, 4.8 Hz), 2.37 (d, 1H, J = 7.8 Hz), 1.88 (sext, 1H, J = 6.7 Hz), 1.21 (d, 3H, J = 6.3 Hz), 1.20 (s, 9H), 1.13 (d, 3H, J = 6.8 Hz), 0.94 (d, 3H, J = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 68.4, 57.9, 42.6, 32.1, 30.0, 21.5, 20.8, 20.0; TLC R_f 0.50 (90% hexane, 10% ethyl acetate); exact mass calcd for $C_{10}H_{22}S_1O_1-NH_4$ requires *m*/*z* 208.1735, found *m*/*z* 208.1742 (CI−NH_3).

(b) (2*R*,3*R*)-3-*tert*-Butylthio-4-methyl-2-pentanol (5k). The following reagents were combined in the amounts indicated according to the general procedure for the reduction of β-hydroxysulfoxides: **19k** (703 mg, 3.6 mmol) and BH_3−THF (12 mL, 1.0 M in THF, 12.0 mmol). The product was purified by flash chromatography (4 × 6 cm, 90% hexane, 10% ethyl acetate) to yield **5k** as an oil (635 mg, 92% yield): $[\alpha]_d^{23}$ −49.2° (*c* 0.45, CH_2Cl_2); IR (film) 3474, 2963, 2872, 1456, 1436, 1421, 1384, 1365, 1324, 1267, 1211, 1160, 1127, 1076, 1042, 967, 931, 830, 816, 739 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 3.60 (m, 1H), 2.89 (br d, 1H, J = 2.2 Hz), 2.40 (dd, 1H, J = 7.5, 2.6 Hz), 1.81 (dquint, 1H, J = 6.8, 3.0 Hz), 1.21 (d, 3H, J = 6.1 Hz), 1.14 (s, 9H), 0.99 (d, 3H, J = 6.7 Hz), 0.81 (d, 3H, J = 6.7 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 67.6, 59.9, 42.5, 32.2, 30.0, 22.2, 21.1, 17.8; TLC R_f 0.50 (90% hexane, 10% ethyl acetate); exact mass calcd for $C_{10}H_{22}S_1O_1-NH_4$ requires *m*/*z* 208.1735, found *m*/*z* 208.1733 (CI−NH_3).

(c) [(2*S*,3*R*)-3-*tert*-Butylthio-4-methylpent-2-oxy]diphenylphosphine (10k). The following reagents were combined in the amounts indicated according to the general procedure for phosphinite incorporation: **4k** (607 mg, 3.2 mmol), *n*-BuLi (1.41 M in hexanes, 2.3 mL, 3.2 mmol), and chlorodiphenylphosphine (574 μL, 3.2 mmol). The resulting slurry was loaded onto a plug of silica and purified by flash chromatography (3 × 3 cm, 95% hexane, 5% ethyl acetate) to yield **10k** as an oil (1.0 g, 83% yield). $[\alpha]_d^{23}$ +25.3° (*c* 0.56, CH_2Cl_2); IR (CH_2Cl_2) 3073, 3045, 2964, 2871, 1959, 1890, 1733, 1480, 1461, 1435, 1374, 1318, 1246, 1160, 1129, 1096, 1071, 1046, 971, 930, 800, 825, 787 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.68 (q, 4H, J = 7.5 Hz), 7.14 (m, 4H), 7.05 (m, 2H), 4.30 (dq, 1H, J = 14.9, 6.3 Hz), 2.60 (dd, 1H, J = 6.8, 3.3 Hz), 2.32 (dquint, 1H, J = 6.8, 3.3 Hz), 1.50 (d, 3H, J = 6.3 Hz), 1.18 (s, 9H), 1.00 (d, 6H, J = 6.8 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 144.1 (d, J = 19 Hz), 143.2 (d, J = 18 Hz), 131.6, 131.5, 130.8, 129.5, 129.2, 128.5, 128.4, 128.3, 127.9, 80.5 (d, J = 20 Hz), 55.9, 46.6, 42.6, 32.2, 29.0, 22.0, 21.5 (d, J = 5 Hz), 18.4; ^{31}P NMR (202 MHz, C_6D_6) δ 109.9 (s); TLC R_f 0.6 (95% hexane, 5% ethyl acetate); exact mass calcd for $C_{22}H_{31}O_1P_1S_1-H$ requires *m*/*z* 375.1912, found *m*/*z* 375.1900 (CI−NH_3).

(d) [(2*R*,3*R*)-3-*tert*-Butylthio-4-methylpent-2-oxy]diphenyl-phosphine (11k). The following reagents were combined in the amounts indicated according to the general procedure for phosphinite incorporation: **5k** (614 mg, 3.2 mmol), *n*-BuLi (1.41 M in hexanes, 2.3 mL, 3.2 mmol), and chlorodiphenylphosphine (574 μL, 3.2 mmol). The resulting slurry was loaded onto a plug of silica and purified by flash chromatography (3 × 3 cm, 95% hexane, 5% ethyl acetate) to yield **11k** as an oil (1.1 g, 91% yield). $[\alpha]_d^{23}$ −12.6° (*c* 0.63, CH_2Cl_2); IR (CH_2Cl_2) 3073, 3047, 2962, 2901, 2869, 1960, 1591, 1480, 1461, 1436, 1380, 1366, 1329, 1221, 1161, 1130, 1097, 1058, 1034, 970, 953, 932, 870, 828 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.68 (t, 2H, J = 7.7 Hz), 7.63 (t, 2H, J = 7.2 Hz), 7.10 (m, 4H), 7.02 (m, 2H), 4.50 (m, 1H), 2.67 (t, 1H, J = 3.8 Hz), 2.23 (dsext, 1H, J = 6.8, 4.3 Hz), 1.46 (d, 3H, J = 6.5 Hz), 1.21 (s, 9H), 1.06 (d, 3H, J = 6.7 Hz), 0.99 (d, 3H, J = 6.7 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 143.8 (d, J = 20 Hz), 143.6 (d, J = 18 Hz), 131.5, 131.3, 130.3, 130.2, 129.6, 129.1, 128.5, 128.3, 128.1, 127.9, 81.7 (d, J = 21 Hz), 54.1 (J = 5 Hz), 42.6, 31.8, 28.1, 22.8, 20.9, 18.7 (d, J = 5 Hz); ^{31}P NMR (202 MHz, C_6D_6) δ 109.0 (s); TLC R_f 0.6 (95% hexane, 5% ethyl acetate); exact mass calcd for $C_{22}H_{31}O_1P_1S_1-H$ requires *m*/*z* 375.1912, found *m*/*z* 375.1916 (CI−NH_3).

(e) [(2*S*,3*R*)-3-*tert*-Butylthio-4-methylpent-2-oxy]bis(α-naphthyl)-phosphine (49 g). The following reagents were combined in the amounts indicated according to the general procedure for phosphinite incorporation: **4k** (221 mg, 1.16 mmol), *n*-BuLi (1.41 M in hexanes, 820 μL, 1.16 mmol), and chlorobis(α-naphthyl)phosphine (373 mg, 1.16 mmol). The resulting slurry was loaded onto a plug of silica and purified by flash chromatography (2 × 3 cm, 5% ethyl acetate, 95% hexane) to yield **49g** as a solid (0.5 g, 91% yield). $[\alpha]_d^{23}$ −11.4° (*c* 0.38, CH_2Cl_2); IR (CH_2Cl_2) 3077. 3041, 2997, 2963, 2932, 2895, 2874, 1726, 1589, 1504, 1461, 1382, 1365, 1331, 1161, 1044, 1022, 971,

930, 879, 791 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 9.00 (m, 1H), 8.60 (m, 1H), 8.29 (m, 1H), 7.92 (m, 1H), 7.72 (dd, 1H, J = 8.0, 4.0 Hz), 7.62−7.49 (m, 4H), 7.40−7.30 (m, 3H), 7.20−7.08 (m, 2H), 4.48 (dquint, 1H, J = 8.4, 6.3 Hz), 2.63 (dd, 1H, J = 6.3, 3.8 Hz), 2.16 (dquint, 1H, J = 6.8, 3.8 Hz), 1.54 (d, 3H, J = 6.3 Hz), 1.10 (s, 9H), 0.92 (d, 3H, J = 6.7 Hz), 0.90 (d, 3H, J = 6.7 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 144.1, 143.2, 138.3, 132.5, 130.9, 130.5, 130.0, 129.1, 128.2, 128.0, 127.9, 127.8, 127.6, 126.5, 126.4, 126.0, 125.9, 125.8, 125.7, 125.6, 124.6, 81.0 (d, J = 20 Hz), 56.1, 42.5, 32.1, 29.6, 21.8, 21.1, 18.8; ^{31}P NMR (202 MHz, C_6D_6) δ 95.4 (s); TLC R_f 0.6 (95% hexane, 5% ethyl acetate); exact mass calcd for $C_{30}H_{35}O_1P_1S_1-Na$ requires *m*/*z* 497.2044, found *m*/*z* 497.2041 (FAB with NaI and *p*-nitrobenzyl alcohol added).

(f) (1*S*,2*S*)-2-*tert*-Butylthiocyclohexanol (57). To a 100 mL Schlenck flask was added (*S*)-Gallium lithium bis((*S*)-Binolate) ((*S*)-GaLB)[60] (15 mL, 0.048 M in THF, 0.612 mmol) and 4 Å mol sieves (122 mg, dried at 50 mTorr at 180 °C for 18 h prior to use). The slurry was stirred under argon atmosphere for 30 min, then the solvent was removed in vacuo. Toluene (12 mL) was added followed by cyclohexene oxide (613 μL, 6.12 mmol). *tert*-Butylthiol (825 μL, 7.34 mmol) was added and the reaction was stirred at ambient temperature for 24 h. The mixture was diluted with Et_2O (200 mL) and filtered over a Celite pad. The filtrate was washed successively with 5% citric $acid_{(aq)}$ (100 mL), saturated $NaHCO_{3(aq)}$ (100 mL), and brine (100 mL) and dried over $MgSO_4$. The organic solution was concentrated in vacuo and the residue was purified by flash chromatography (5 × 5 cm, 10% acetone, 90% hexanes) to afford a crystalline white solid (1.05 g, 91% yield). This was then recrystallized from methanol and water to afford **40** (850 mg, 2 crops, 73% yield). $[\alpha]_d^{23}$ +107.7° (*c* 0.18, CH_2Cl_2); IR (film) 3431, 2975, 2928, 2845, 1461, 1447, 1365, 1350, 1327, 1212, 1161, 1074 $cm^{-1;}$ ^1H NMR (400 MHz, C_6D_6) δ 3.17−3.12 (m, 1H), 3.14 (br s, 1H), 2.32 (ddd, 1H, J = 11.4, 9.98, 4.1 Hz), 2.20−2.16 (m, 1H), 2.00−1.95 (m, 1H), 1.50−1.46 (m, 1H), 1.41−1.29 (m, 3H), 1.15 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 72.4, 43.2, 36.1, 34.1, 31.6, 26.7, 24.6; exact mass calcd for $C_{10}H_{20}O_1S_1-NH_4$ requires *m*/*z* 206.1579, found *m*/*z* 206.1578 (CI−NH_3). Separation of enantiomers on the corresponding benzoate ester by HPLC analysis (Daicel Chiralcel AD, flow rate 0.5 mL/min, 99% hexane, 1% *i*-PrOH, T_r (*S*,*S*) isomer 9.1 min, (*R*,*R*) isomer 11.1 min) determined the enantiomeric excess to be >99%.

(g) [(1*S*,2*S*)-2-*tert*-Butylthiocyclohexyloxy]diphenylphosphine (41). The following reagents were combined in the amounts indicated according to the general procedure for phosphinite incorporation: **40** (290 mg, 1.54 mmol), *n*-BuLi (1.50 M in hexanes, 1.02 mL, 1.54 mmol), and chlorodiphenylphosphine (303 μL, 1.7 mmol). The resulting slurry was loaded onto a plug of silica and purified by flash chromatography (3 × 3 cm, 95% hexane, 5% ethyl acetate degassed with argon) to yield **41** as a white solid (514 mg, 90% yield). $[\alpha]_d^{23}$ +35.5° (*c* 0.42, CH_2Cl_2); IR (CH_2Cl_2) 2937, 2861, 1436, 1364, 1155, 1034, 964, 843, 777 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.72 (app. t, 2H, J = 7.2 Hz), 7.63 (app t, 2H, J = 7.2 Hz), 7.15−7.11 (m, 4H), 7.07−7.05 (m, 2H), 4.16−4.14 (m, 1H), 2.98−2.96 (m, 1H), 2.25−2.22 (m, 1H), 2.21−2.00 (m, 1H), 1.99−1.54 (m, 4H), 1.33−1.30 (m, 1H), 1.23−1.21 (m, 1H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 143.9, 143.7, 143.5, 131.4, 131.1, 130.6, 130.4, 129.4, 129.2, 128.5, 128.5, 128.4, 81.8, 80.9, 44.5, 43.3, 31.3, 30.3, 23.1, 21.5; ^{31}P NMR (202 MHz, C_6D_6) δ 107.5 (s); TLC R_f 0.5 (95% hexane, 5% ethyl acetate); exact mass calcd for $C_{22}H_{29}O_1P_1S_1-H$ requires *m*/*z* 373.1755, found *m*/*z* 373.1761 (CI−NH_3).

General Procedure for the Allylic Alkylations with Dimethyl Malonate: (a) (*S*,*E*)-Methyl 2-Carbomethoxy-3,5-diphenylpent-4-enoate (25a). To a Schlenck flask containing ligand **11k** (5.9 mg, 0.016 mmol) was added CH_2Cl_2 (0.016 M) followed by $[(C_3H_5)-PdCl]_2$ (2.1 mg, 0.011 mmol Pd). The mixture was stirred at room temperature for 1 h. Allylic acetate **24** (70 μL, 0.37 mmol) was added to the reaction via syringe, and the mixture was cooled to −20 °C. Dimethylmalonate (141 μL, 1.12 mmol) was added to the reaction at −20 °C followed by *N*,*O*-bis(trimethylsilyl)acetamide (280 μL, 1.12 mmol) and potassium acetate (0.5 mg, 0.005 mmol). After 24 h, the reaction was diluted with Et_2O, washed with saturated $NH_4Cl_{(aq)}$, saturated $NaHCO_{3(aq)}$, and brine. The combined aqueous solutions were extracted with CH_2Cl_2. The combined organic solutions were dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by flash chromatography (3 × 7 cm, 85% hexane, 15% ethyl acetate) to yield **25a** as an oil (110 mg, 93% yield): ^1H NMR ($CDCl_3$, 500 MHz) δ 7.4−7.1 (m, 10H), 6.48 (d, 1H, J = 15.9 Hz), 6.33 (dd, 1H, J = 15.9, 8.5 Hz), 4.27 (dd, 1H, J = 10.9, 8.6 Hz), 3.95 (d, 1H, J = 10.9 Hz), 3.70 (s, 3H) 3.52 (s, 3H). Separation of enantiomers by HPLC analysis (Daicel Chiralcel AD, flow rate 1.0 mL/min, 95% hexane, 5% *i*-PrOH, T_r 12.3, 17.4 min) determined the ee to be 98%. Absolute stereochemistry of the product was determined by comparison of the optical rotation to literature values. $[\alpha]_D^{25}$ −22.0 (*c* 1.13, $CHCl_3$); $[\alpha]_D^{25}$ −22.4 (*c* 1.8, $CHCl_3$) for optically pure **25a**.[61]

(b) (*R*)-Dimethyl 3-Cycloheptenylmalonate (56a). Treating cycloheptenyl acetate (**52**) (75 μL, 0.69 mmol) under the representative procedure for the allylic alkylations with dimethyl malonate yielded **56a** (88 mg, 80% yield). ^1H NMR ($CDCl_3$, 500 MHz) δ 5.85 (dddd, 1H, J = 11.0, 8.5, 6.6, 2.0 Hz), 5.60 (dd, 1H, J = 11.1, 4.4 Hz), 3.75 (s, 3H), 3.74 (s, 3H), 3.50 (d, 1H, J = 8.5 Hz), 3.05 (m, 1H), 2.17 (m, 1H), 1.95 (m, 3H), 1.33 (m, 2H). Separation of enantiomers was accomplished by ^1H NMR chiral shift using $Eu(hfc)_3$ in C_6D_6. To a solution of product (4.0 mg) in 400 μL of C_6D_6 was added 100 μL of a saturated solution of $Eu(hfc)_3$ in C_6D_6. Integration of OMe peaks showed enantiomeric excess to be 96%. Absolute stereochemistry of the product was determined by comparison of the optical rotation to literature values. $[\alpha]_D^{25}$ +8.0 (*c* 1.70Cl_2); $[\alpha]_D^{25}$ −7.75 (*c* 4.52Cl_2) for enantiomerically enriched (93% ee) **56a**.[54]

General Procedure of the Allylic Aminations with Benzylamine: (a) (*S*,*E*)-*N*-Benzyl-(1,3-diphenyl-2-propenyl)amine (25e). To a Schlenck flask containing ligand **10k** (5.9 mg, 0.016 mmol) was added CH_2Cl_2 (0.016 M) followed by $[(C_3H_5)PdCl]_2$ (2.1 mg, 0.011 mmol Pd). The mixture was stirred at room temperature for 1 h. Allylic acetate **24** (70 μL, 0.38 mmol) was added via syringe to the reaction solution, and the mixture was cooled to −20 °C. Benzylamine (115 μL, 1.12 mmol) was added to the reaction at −20 °C. After 24 h, the reaction was diluted with Et_2O, washed with saturated $NH_4Cl_{(aq)}$, saturated $NaHCO_{3(aq)}$, and brine. The combined aqueous solutions were extracted with CH_2Cl_2. The combined organic solutions were dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by flash chromatography (3 × 7 cm, 85% hexane, 15% ethyl acetate) to yield **25e** as an oil (110 mg, 96% yield): ^1H NMR ($CDCl_3$, 500 MHz) δ 7.4−7.1 (m, 10H), 6.58 (d, 1H, J = 15.8 Hz), 6.33 (dd, 1H, J = 15.8, 7.4 Hz), 4.41 (d, 1H, J = 7.4 Hz), 3.80 (d, 1H, J = 13.3 Hz), 3.77 (d, 1H, J = 13.4 Hz), Separation of enantiomers by HPLC analysis (Daicel Chiralcel OJ, flow rate 1.0 mL/min, 98% hexane, 2% EtOH, T_r 17.0, 22.5 min) determined the enantiomeric excess to be 99%. The absolute stereochemistry of the product was determined by comparison of the optical rotation to literature values. $[\alpha]_D^{25}$ −24.0 (*c* 1.38, $CHCl_3$); $[\alpha]_D^{25}$ −24.8 for enantiomerically enriched (97% ee) **25e**.[62]

(b) (*R*)-*N*-Benzyl(cyclohept-2-enyl)amine (56b). Treating **52** (75 μL, 0.49 mmol) under the representative procedure of the allylic aminations with benzylamine yielded **56b** (94 mg, 95% yield). $[\alpha]_d^{23}$ +25.9° (*c* 1.0Cl_2); IR (film) 3315, 3085, 3062, 3024, 2922, 2850, 2802, 1944, 1869, 1809, 1734, 1652, 1605, 1495, 1453, 1394, 1351, 1310, 1267, 1200, 1123, 1074, 1028, 974, 906, 820, 788, 733, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 4H), 7.25 (m, 1H), 5.83 (m, 1H), 5.73 (m, 1H), 3.83 (d, 1H, J = 13.0 Hz), 3.77 (d, 1H, J = 13.0 Hz), 3.39 (m, 1H), 2.17 (m, 1H), 2.07 (m, 1H), 1.97 (m, 1H), 1.78 (m, 1H), 1.66 (m, 1H), 1.58 (m, 1H), 1.50 (m, 1H), 1.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.6, 137.6, 131.0, 128.4, 128.2, 126.8, 64.8, 58.2, 51.6, 46.1, 34.0, 29.0, 28.5, 26.6; TLC R_f 0.2 (60% ethyl acetate, 40% hexane); exact mass calcd for $C_{14}H_{19}N_1$ requires *m*/*z* 201.1517, found *m*/*z* 201.1525 (EI). Separation of enantiomers was accomplished by HPLC analysis of the diastereomeric (*R*)-Mosher amides to show

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an enantiomeric excess of 97% (see Supporting Information). The absolute stereochemistry of the product was assigned by analogy to **78a**.

(c) [(2*R*,3*R*)-3-*tert*-Butylthio-4-methylpent-2-oxy]diphenylphosphine Palladium(1,3-diphenylpropenyl) Hexafluoroantimonate (43, 44). To a Schlenck flask containing **11k** (48.7 mg, 0.13 mmol) in CH_2Cl_2 (1.0 mL) was added $[(1,3\text{-diphenylpropenyl})PdCl]_2$ (43.6 mg, 0.065 mmol), and the reaction was allowed to stir for 1 h. The solution was transferred by cannula into a flask containing $AgSbF_6$ (45.0 mg, 0.13 mmol) in CH_2Cl_2 (1.0 mL) and stirred for 1 h in the absence of light. The reaction was cannula filtered into a Schlenck flask and concentrated in vacuo to yield a 2.3:1 mixture of diastereomeric π-allyl complexes **43**, **44** (100 mg, 85% yield). ^{1}H NMR (500 MHz, CD_2Cl_2) δ (**43**) 7.80−6.90 (m, 18H), 6.90−6.80 (m, 1H), 6.63 (dd, 2H, J = 11.8, 7.2 Hz), 5.91 (dd, 1H, J = 13.5, 11.4 Hz), 5.30 (dd, 1H, J = 13.4, 2.1 Hz), 4.01 (dsext, 1H, J = 10.1, 6.2 Hz), 2.76 (dd, 1H, J = 10.1, 7.8 Hz), 2.13 (dquint, 1H, J = 6.7, 1.9 Hz), 1.26 (d, 3H, J = 6.3 Hz), 1.13 (d, 3H, J = 6.7 Hz), 1.05 (d, 3H, J = 6.7 Hz), 0.86 (s, 9H); ^{31}P NMR (202 MHz, CD_2Cl_2) δ 129.8 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ (**44**) 7.80−6.90 (m, 18H), 6.90−6.80 (m, 3H), 5.48 (br d, 1H, J = 12.4 Hz), 5.31 (t, 1H, J = 12.8 Hz), 3.73 (dsext, 1H, J = 10.2, 6.2 Hz), 2.65 (dd, 1H, J = 10.3, 1.8 Hz), 1.87 (dquint, 1H, J = 5.5, 1.0 Hz), 1.25 (s, 9H), 1.20 (d, 3H, J = 6.1 Hz), 0.79 (d, 3H, J = 6.7 Hz), 0.58 (d, 3H, J = 6.7 Hz); ^{31}P NMR (202 MHz, CD_2Cl_2) δ 136.7 (s); exact mass calcd for $C_{37}H_{44}P_1O_1S_1Pd_1$ requires m/z 673.1885, found m/z 673.1880 (FAB with NaI and *p*-nitrobenzyl alcohol added). X-ray quality crystals were grown by dissolving **43**, **44** (100 mg) in MeOH (1 mL). The suspension was warmed to 40 °C at which point the solution became clear, then the solution was allowed to cool to room temperature, and then the solution was cooled to −20 °C overnight. Orange crystals were observed the next day. A suitable crystal was selected for X-ray crystal structure analysis (0.4 × 0.3 × 0.2 mm); see Appendix 2 (Supporting Information).

General Procedure for the Synthesis of [Pd(L*)(cyclohexenyl)](SbF$_6$) Complexes: (a) [(2*S*,3*R*)-3-*tert*-Butylthio-4-methylpent-2-oxy]diphenylphosphine Palladium(cyclohexenyl) Hexafluoroantimonate (70). To a Schlenck flask containing ligand **10k** (17.5 mg, 0.047 mmol) in CH_2Cl_2 (0.04 M) was added $[(\text{cyclohexenyl})PdCl]_2$ (10.2 mg, 0.024 mmol) and the reaction was allowed to stir for 1 h. The solution was transferred via cannula into a flask containing $AgSbF_6$ (1.0 equiv) in CH_2Cl_2 (0.12 M) and stirred for 1 h in the absence of light. The reaction was cannula filtered into a Schlenck flask and concentrated in vacuo to yield **70** (43 mg, 90% yield) as a single diastereomeric π-allyl complex by ^{1}H NMR. mp >175 °C; $[\alpha]_d^{23}$ −24.7° (*c* 0.66, CH_2Cl_2); IR (CH_2Cl_2) 3067, 2966, 2934, 2872, 1732, 1462, 1438, 1370, 1246, 1158, 1136, 1104, 1078, 1046, 1013, 977, 938 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.00−7.20 (m, 10H), 6.26 (m, 1H), 5.69 (t, 1H, J = 7.1 H), 5.13 (m, 1H), 4.23 (m, 1H), 2.66 (m, 1H), 2.56 (dquint, 1H, J = 6.7, 2.7 Hz), 2.27 (m, 1H), 2.09 (m, 1H), 1.8 (m, 2H), 1.41 (d, 3H, J = 6.5 Hz), 1.41 (s, 9H), 1.22 (t, 6H, J = 5.9 Hz); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 134.2, 134.0, 133.8, 131.9, 130.1, 130.0, 129.9, 129.6, 129.5, 111.6, 111.5, 102.4, 79.4, 76.8, 52.5, 50.4, 31.7, 27.2, 26.7, 23.3, 22.2, 20.5, 19.7; ^{31}P NMR (202 MHz, CD_2Cl_2) δ 139.8; exact mass calcd for $C_{28}H_{40}P_1O_1S_1Pd_1$ requires m/z 561.1572, found m/z 562.1580 (FAB with NaI and *p*-nitrobenzyl alcohol added). X-ray quality crystals were grown by dissolving **70** (40 mg) in MeOH (0.5 mL). The suspension was warmed to 40 °C at which point the solution became clear, then the solution was allowed to cool to room temperature, and then the solution was cooled to −20 °C overnight. Orange crystals were observed the next day. A suitable crystal was selected for X-ray diffraction (0.2 × 0.1 × 0.08 mm); see Appendix 3 (Supporting Information).

(b) [(2*R*,3*R*)-3-*tert*-Butylthio-4-methylpent-2-oxy]diphenylphosphine Palladium(cyclohexenyl) Hexafluoroantimonate (74, 75). Treating **11k** (25.9 mg, 0.069 mmol) under the representative procedure for the synthesis of [(L*)Pd(cyclohexenyl)](SbF$_6$) complexes yielded a 5.4:1 mixture of diastereomeric π-allyl complexes **74**, **75** by ^{1}H NMR (80 mg, 80% yield). ^{1}H NMR (500 MHz, CD_2Cl_2) δ (**74**) 7.70−7.30 (m, 10H), 6.14 (m, 1H), 5.79 (m, 1H), 5.66 (t, 1H, J = 7.1 Hz), 3.97 (m, 1H), 2.82 (dd, 1H, J = 9.9, 2.2 Hz), 2.41 (dquint, 1H, J = 12.7, 5.5 Hz), 2.16 (m, 2H), 1.92 (m, 1H), 1.80 (m, 2H), 1.54 (d, 3H, J = 6.1 Hz), 1.23 (s, 9H), 1.18 (d, 3H, J = 6.8 Hz), 0.90 (d, 3H, J = 6.8 Hz); ^{31}P NMR (202 MHz, CD_2Cl_2) δ 134.8; ^{1}H NMR (500 MHz, CD_2Cl_2) δ (**75**) 7.80−7.20 (m, 10H), 6.30 (m, 1H), 5.94 (t, 1H, J = 5.4 Hz), 5.50 (m, 1H), 3.60 (m, 1H), 2.83 (dd, 1H, J = 10.0, 2.0 Hz), 2.18 (m, 1H), 2.18 (m, 2H), 1.92 (m, 1H), 1.80 (m, 1H), 1.69 (m, 1H), 1.42 (s, 9H), 1.27 (d, 3H, J = 6.1 Hz), 1.13 (d, 3H, J = 6.7 Hz), 0.78 (d, 3H, J = 6.8 Hz); ^{31}P NMR (202 MHz, CD_2Cl_2) δ 131.8; exact mass calcd for $C_{28}H_{40}P_1O_1S_1Pd_1$ requires m/z 561.1572, found m/z 561.1589 (FAB with NaI and *p*-nitrobenzyl alcohol added).

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Supporting Information Available: Complete experimental procedures and characterization of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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