Origins of Enantioselectivity with Nitrogen−Sulfur Chelate Ligands in Palladium-Catalyzed Allylic Substitution

Harry Adams,[†] James C. Anderson,*[,†] Rachel Cubbon,[†] Daniel S. James,[†] and John P. Mathias[‡]

Department of Chemistry, University of Sheffield, Sheffield, S3 7HF U.K., and Pfizer Central Research, Sandwich, Kent, CT13 9NJ U.K.

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The reaction of 1,3-diphenyl-2-propenyl acetate (**9**) with dimethylmalonate to give the substitution product **10** is effectively catalyzed by Pd complexes containing chiral imine−sulfide chelate ligands derived from amino acids. The ligand of choice, (*S*)-*N*-2′-chlorobenzylidene-2-amino-3-methyl-1-thiophenylbutane (**6e**), prepared in only two steps from (*S*)-valinol, gave an ee of 94%. Because the explanation of selectivity with the majority of other nitrogen−sulfur chelate ligands in this reaction assumes the selectivity to be controlled by an electronic bias, which contradicts our results, we characterized the Pd−allyl intermediate **14** by X-ray diffraction and solution NMR. The possible mechanism of chirality transfer is discussed. The site of nucleophilic attack on the allyl ligand is not *trans* to the perceived better π-acceptor ligand (sulfur), which would be analogous to chiral nitrogen−phosphorus systems. This reaction occurs *trans* to the imine donor, and the enantioselectivity is ultimately controlled by the subtle steric environment of the chiral imine−sulfur chelate ligand, which predisposes the allyl unit of the reaction intermediate to a preferred reaction trajectory. In light of results that emphasize the power of electronic desymmetrization for chiral recognition, these results suggest that electronically dissimilar ligands may not give rise to chiral recognition through electronic dissimilarity.

Since the first example of an enantioselective palladium-catalyzed allylic substitution reaction with a stabilized nucleophile,[1] there have been numerous reports of the design and synthesis of chiral bidentate ligands to affect such a process.[2] The reaction is characterized by bond breaking and bond making on the face of the π-allyl unit opposite palladium and its requisite chiral environment, provided by judiciously chosen ligands. The development of effective chiral ligands for this process has been arduous, as the stereochemical information inherent to the chiral ligand has to be transmitted across the plane of the allyl fragment to the bond-forming/-breaking event that is responsible for enantiodiscrimination. Homobidentate C_2-symmetric ligands have been extensively investigated and transition-state models proposed.[3−8] More recently, heterobidentate nitrogen−phosphorus chiral ligands have been reported which capitalize upon the difference in electronic character of the two donor atoms to exert a stereoelectronic bias upon intermediate π-allyl complexes.[8] Stereoelectronically, the palladium−allyl terminus bond opposite the more powerful acceptor atom (phosphorus) will be longer and hence more susceptible to cleavage as a result of nucleophilic attack.[9] Such physical attributes have been verified by NMR and X-ray studies and are claimed to control enantioselection.[8f,10] Heterobidentate nitrogen−sulfur ligands can also control the enantioselection of this process,[11−15] but many researchers rationalize results by

[†] University of Sheffield.

[‡] Pfizer Central Research.

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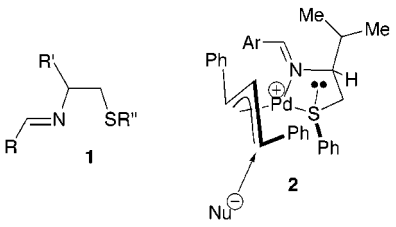
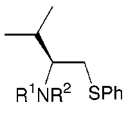
analogy to nitrogen−phosphorus chelating systems.[10a,11d,13a,14] As part of an ongoing research program, we have developed a new series of heterodentate chelate ligands, derived from amino acids, where the chirality inherent to the backbone of the amino acid can be transmitted closer to the reaction center due to the correct choice of donor groups and substituents.[16] The emphasis of this work is on understanding the origins of chirality induction in our ligand systems to aid the design of simpler, more efficient chiral ligands for asymmetric catalysis. Recently we reported that the sulfur−imine mixed donor chiral ligand **1** (R = 2-ClC_6H_4, R′ = ^{i}Pr, R″ = Ph), derived from (*S*)-valinol, gave 94% enantiomeric excess in the palladium-catalyzed allylic substitution reaction between dimethyl malonate and (±)-(*E*)-diphenyl-2-propenyl acetate.[17] We proposed a transition-state model, **2**, based upon our results and the accepted notion that nucleophilic attack of the π-allyl complex occurs *trans* to the better π-acceptor end of the chelate ligand from the most stable Pd−allyl intermediate.[8f,10,18] In the absence of any data, we argued that in our ligand the imine group is the better π-acceptor, as thioethers are considered poor π-acceptors.[19]



Our explanation contradicts those offered in the literature to account for the sense of enantioselection of other chiral nitrogen−sulfur ligands.[10a,11d,13a,14] Aside from one report dealing with a NMR analysis of the mechanism of enantioselection,[15] there is scant structural evidence reported for these types of ligands in this reaction. We have investigated the steric and electronic factors which account for the high enantioselection of this ligand system using a combination of single-crystal X-ray crystallography and NMR.

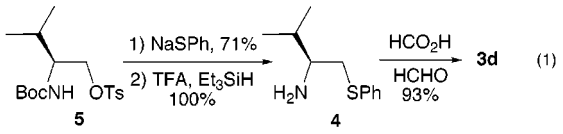
Results

Synthesis of Ligands. Amine ligands **3a,b** were synthesized according to our previously reported route.[16b] Ligand **3c** was synthesized by subjection of (*S*)-*N*-methyl-



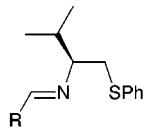
3	R^1	R^2
a	Ph	H
b	Ts	H
c	Ph	Me
d	Me	Me

N-phenyl-2-amino-3-methylbutan-1-ol[16b] to the Hata protocol[20] in a sealed tube for 3 days (96%). Ligand **3d** was derived from (*S*)-valinol via the intermediate sulfide **4**. This key compound can be synthesized by exchange of the hydroxyl group for the phenylsulfide in a moderate yield (58%) up to a 1 mmol scale using the Hata protocol, but problems arose with the separation of **4** from the excess of reagents and byproducts when the reaction was scaled up. An alternative series of straightforward reactions, starting from known **5**,[21] provided a similar overall yield and was amenable to larger scale synthesis. Eschweiler−Clarke *N*,*N*-dimethylation[22] furnished **3d** in 93% yield (eq 1).

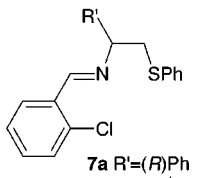


(1)

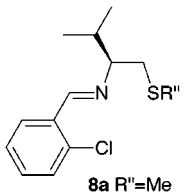
Imines **6a**−**h** were synthesized from **4** by condensation with the requisite aromatic aldehyde in the presence of magnesium sulfate. Imine **6i** was synthesized by stirring



6	R
a	Ph
b	4-$O_2NC_6H_4$
c	4-$MeOC_6H_4$
d	1,2,6-$Me_3C_6H_2$
e	2-ClC_6H_4
f	4-ClC_6H_4
g	2,6-$Cl_2C_6H_3$
h	2-BrC_6H_4
i	Me



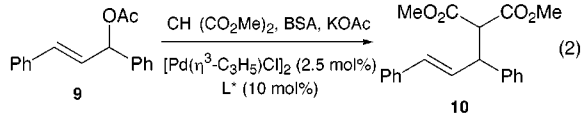
7a R′=(*R*)Ph
7b R′=(*S*)^{t}Bu



8a R″=Me
8b R″=2,6-$Me_2C_6H_3$

amine **4** with freshly distilled acetaldehyde in the presence of basic alumina. The imines were judged >95% pure by ^{1}H NMR and, as they were unstable to chromatography, were used crude. Ligands **7a,b** were most quickly prepared from (*S*)-*tert*-leucinol and (*R*)-phenylglycinol using the Hata protocol (37% and 46% respectively), followed by standard quantitative imine formation. Ligands **8a,b** were synthesized in good yield according to eq 1 using the appropriate sodium thiolate.

Asymmetric Alkylation. Our studies used the popular test reaction involving the substitution of 1,3-diphenyl-2-propenyl acetate **9** with the nucleophile derived from the reaction of dimethylmalonate and *N*,*O*-bis(trimethylsilyl)acetamide (BSA) using potassium acetate as catalyst (eq 2).[23] This test reaction was chosen as the



(2)

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Table 1. Asymmetric Alkylation of 9 Catalyzed by Palladium−1 Complexes

ligand	R	R^1	R^2	yield[a] **10** (%)	ee[b] **10** (%) (abs conf)
6a	Ph	^{i}Pr	Ph	86	89 (*R*)
6b	4-$O_2NC_6H_4$	^{i}Pr	Ph	77	82 (*R*)
6c	4-$MeOC_6H_4$	^{i}Pr	Ph	85	88 (*R*)
6d	1,2,6-$Me_3C_6H_2$	^{i}Pr	Ph	90	84 (*R*)
6e	2-ClC_6H_4	^{i}Pr	Ph	87	94 (*R*)
6f	4-ClC_6H_4	^{i}Pr	Ph	78	89 (*R*)
6g	2,6-$Cl_2C_6H_3$	^{i}Pr	Ph	19	90 (*R*)
6h	2-BrC_6H_4	^{i}Pr	Ph	27	94 (*R*)
6i	Me[c]	^{i}Pr	Ph	88	84 (*R*)
7a	2-ClC_6H_4	(*R*)-Ph	Ph	30	65 (*S*)
7b	2-ClC_6H_4	(*S*)-^{t}Bu	Ph	35	78 (*R*)
8a	2-ClC_6H_4	^{i}Pr	Me	86	90 (*R*)
8b	2-ClC_6H_4	^{i}Pr	2,6-$Me_2C_6H_3$	88	96 (*R*)

[a] Isolated yield. [b] Determined by ^{1}H NMR using the chiral shift reagent Eu(hfc)$_3$. [c] Ligand contained ∼2% of the *syn* isomer by ^{1}H NMR.

mechanism is fairly well understood and we could quickly decipher the efficiency of our ligand system. Using ligands **3a** or **3b**, no appreciable reaction was observed after 5 days, so it was decided to modify **3a** to contain an *N*-methyl substituent (**3c**) in an attempt to make the lone pair a stronger donor. In the test reaction, **3c** gave a poor yield (9%) of the product methyl-2-carbomethoxy-3,5-diphenylpent-4-enoate (**10**) in essentially racemic form after 5 days. The *N*,*N*-dimethyl derivative **3d**, the sulfur analogue of valphos,[24] gave product (*R*)-**10** in 93% yield and 43% ee in only 1 day.

These disappointing results led us to speculate that the lone pair of nitrogen needed to be as sterically unencumbered as possible and "softer" for good coordination to the central metal atom of the reaction. It was decided to transform the amine into an imine, **1**. The nitrogen atom of ligand **1** now resembled that present in the very successful oxazoline-containing heterobidentate ligands of Helmchen,[8a] Pfaltz,[8b] and Williams.[8c]

We began our investigation by screening a series of ligands which possessed different imine substituents **6** (Table 1). We found that it was unnecessary to preform the Pd−L* complex and that simply stirring the ligand and Pd dimer in dichloromethane for 15 min at room temperature prior to the addition of the remaining reagents was sufficient. Additionally, degassing the reaction mixture in three freeze−evacuate−thaw cycles once all the reagents had been added was found to increase the yields, as did a nonaqueous workup. Each ligand **6a**−**i** gave the (*R*)-isomer of **10**, and overall the results demonstrated that the choice of imine substituent did not significantly affect the enantioselectivity. The ligand system did not appear to be sensitive to electronic effects. Steric bulk in the ortho position only had mild effects. Substitution at both ortho positions reduced the ee (**6d** and **g**), but mono *o*-chloro gave an enhanced ee (**6e**, 94%) in good yield (87%). The corresponding bromo substituent (**6h**) gave an identical ee (94%) but a much reduced yield (27%). Replacement of the aromatic imine with a less sterically demanding methyl imine still resulted in ee's comparable to those of some aromatic substitutents

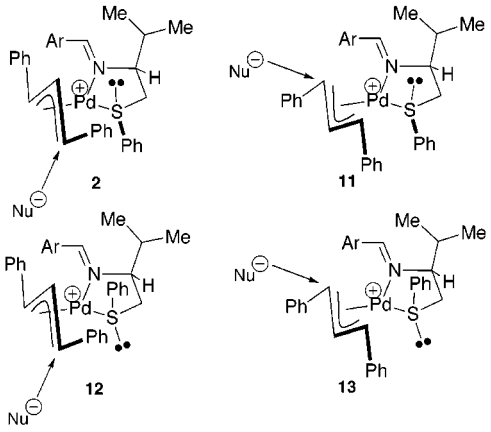

Figure 1. Possible transition-state models leading to (*R*)-**10**.

(compare ligand **6i** with **6b** and **6d**). The increase in steric bulk of the backbone chiral center was investigated by preparation of the analogous ligands **7a** and **7b** from (*R*)-phenylglycinol and (*S*)-*tert*-leucinol (entries 11 and 12). The ee's with these ligand systems were significantly smaller (65% and 78%) and the chemical yields dramatically diminished (30% and 35%). Finally, the steric bulk of the thiol ether was investigated by substituting the phenyl group for methyl (**8a**) and 2,6-dimethylphenyl (**8b**). It can be seen that the smaller substituent only slightly reduced the ee (compare **6e** with **8a**) and that the larger group gave our highest ee (**8b**, 96%).

Discussion

The most influential part of this ligand system, to ensure high enantiodiscrimination, appears to be the size of the chiral backbone substituent. The transmission of stereochemical information from this point to the reaction sphere dominates the reaction and can be enhanced by the correct choice of substituents on the mixed donor atoms of the chelate system. There is a subtle balance between sterics and electronics which effects the efficiency of this ligand system in this particular reaction. We were interested in a transition-state model which could explain the sense of enantioselection in this system.

In our original hypothesis, we considered all four possible chiral ligand−Pd−π-allyl intermediates of this reaction that could lead to the observed enantiomer of the product (Figure 1). We assumed that the intermediates have a rapid mechanism of isomerization, and only the *syn*,*syn* conformers of the allyl group were populated to any significant extent. Although the importance of *syn*,*anti* conformers has been recently highlighted in other ligand systems,[7b] we have found no evidence of this conformation in our system. Additionally, as the reaction is exothermic, we assumed that the energy difference in the ground state is reflected in the corresponding diastereomeric transition states.[25] Thus, as a starting point, we may assume the major diastereoisomer of the intermediate π-allyl complex leads to the major enantiomer observed for the product.[17] Based upon conformational analysis and our original premise that the N=C π^* orbital may be a better π-acceptor than sulfur,[19] we arrived at transition state structure **2** (Figure 1), which has the π-allyl group arranged in a "W" orientation of

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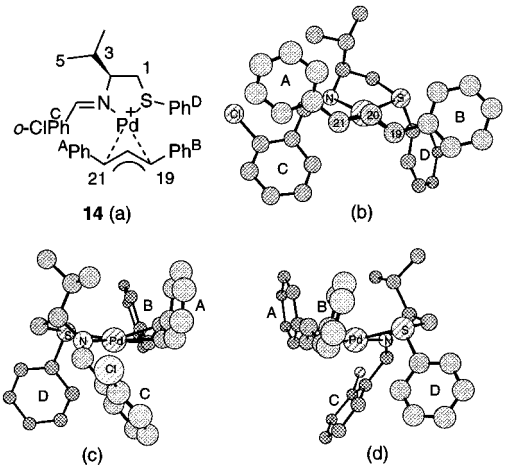

Figure 2. (a) Schematic representation of X-ray structure. (b) Front view. (c) Left-hand-side view. (d) Right-hand-side view.

the π-allyl group. Transition-state structure **2** is preferred over **12**, as the latter possesses a destabilizing 1,3-interaction between the sulfide phenyl substituent and the isopropyl group on the backbone of the chelate ligand.[17] Other reports of nitrogen−sulfur chiral chelate ligands used in this reaction have assumed that the sulfur atom is the better π-acceptor,[10a,11d,13a,14] which would mean transition-state models **11** and **13**, having the "M" orientation of the π-allyl unit, had to be considered. Initially, we could not categorically rule out **11** and **13**, but they both contain destabilizing interactions with respect to **2**. Specifically, **11** has an unfavorable interaction between the allyl phenyl group and the sulfide phenyl group, while **13** possesses destabilizing interactions similar to those described for **12**. To provide firm evidence for our transition-state model and to help us understand the mechanism of chirality transfer for the chiral ligand−Pd−π-allyl intermediate of this reaction, we decided to obtain structural data in the solid state by X-ray diffraction and in solution by NMR spectroscopy.

A high-quality crystal of the complex formed from the *trans*-1,3-diphenylpropenyl palladium chloride dimer[26] and ligand **6e** in the presence of silver perchlorate was obtained by slow evaporation from dichloromethane. The crystal structure was found to be the π-allyl intermediate **14** drawn as part of transition-state structure **2** (Figure 2). The sulfur phenyl group is oriented *trans* to the isopropyl group, thus avoiding an unfavorable 1,3-interaction. The configuration of the imine is *trans* and is accompanied by a twisting of the *o*-chlorophenyl ring out of conjugation with the C=N bond by 40.9°. The plane of the allyl ligand is tilted 15.5° from the perpendicular to the Pd−N−S plane. In line with the structural evidence for nitrogen−phosphorus ligands, we expected that the two palladium-terminal allyl carbon bond distances would be different, with the bond trans to nitrogen longer than the bond trans to sulfur.[10,8f] The actual bond distances are 215.4 and 217.7 pm, respectively (Figure 3a), almost equal within experimental error (2.3 pm, ~1% difference). However, the N−Pd−C bond angle of 107.5° is larger than the S−Pd−C bond angle of 101.8° (Figure 3b), suggesting some interaction between the ligand and

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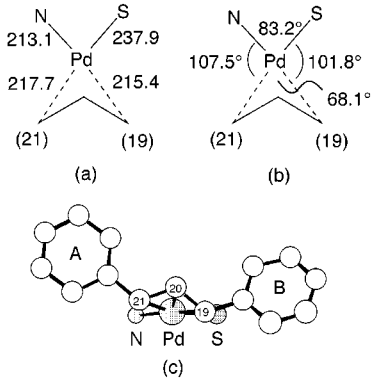

Figure 3. (a) Bond lengths to Pd (pm). (b) Bond angles around Pd. (c) Projection of the allyl ligand along the N−Pd−S plane.

the C(21) allylic terminus. As expected, there is a significant difference in the bond length between N−Pd (213.1 pm) and S−Pd (237.9 pm, Figure 3a). The allyl ligand does not lie in an idealized orientation to the Pd−N−S plane; it is rotated clockwise about the Pd−allyl axis as shown (part structure) in Figure 3c. The idealized geometry should possess two identical interplanar angles defined by the Pd−N−S plane with the Pd−C(20)−C(21) and Pd−C(19)−C(20) planes, respectively.[10c] Instead, we note angles of 24.7° and 41.5°, respectively. This means that the C(21)−C(20) (trans to nitrogen) is already predisposed toward planarity with the Pd−N−S plane.

We elucidated the solution structure in CD_2Cl_2 (to reflect the reaction medium) to help ascertain if this structure was the same as the major intermediate in the reaction mixture. We also conducted the identical catalytic experiment (eq 2) but with 5 mol % of complex **14** as the source of chiral catalyst. This gave the substitution product in a slightly lower yield of 73%, but with an identical ee of 94%. This experiment verified that the catalytically active species does not contain a chloride substituent, that a 1:1 complex of Pd:chiral ligand gives the same high ee and suggests that, although N,S-ligands are, in genral, considered weakly coordinating when compared to their phosphorus counterparts, this particular ligand system forms a catalytically active palladium chelate complex. The ^{1}H NMR spectrum of the complex at the same temperature of the reaction (25 °C) showed essentially one structure present (>95%), and its conformation was assigned through a combination of COSY, ^{13}C−^{1}H correlation, and selected one-dimensional NOE experiments. The ^{1}H NMR showed only the *syn*,*syn* arrangement of the allyl unit, as evidenced by the coupling constants between the allyl protons H(19), H(20), and H(21) of around 12 Hz. Key NOE enhancements (Figure 4) suggest the complex is in the same "W" conformation in solution as in solid-state **14** (Figure 2). Irradiation of the signal at δ 8.39 (1H, dd, J = 7.6, 1.8 Hz) induced an enhancement of 6.8% at δ 7.83 (1H, td, J = 7.8, 1.6 Hz) and 5.1% at δ 4.54 (1H, d, J = 11.3 Hz). The former lower field signals are single proton resonances, coupled to each other as evidenced by the COSY spectrum, and originate from the unsymmetrical aromatic ring C of the benzylidene. Taking into account the position and electronic effects of the substituents, the signals at δ 8.39 and δ 7.83 can be assigned to H(12) and H(11), respectively. By virtue of its multiplicity, the magnitude of the coupling constant, and its NOE enhancement upon irradiation of H(12), the single proton

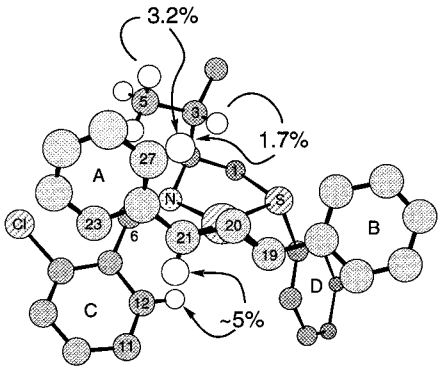

Figure 4. View of X-ray structure with selected protons to show key NOE enhancements.

resonance at δ 4.54 can be assigned to H(21). This indicates that H(12) and H(21) are on the same face of the palladium complex. Irradiation of H(21) gave a corresponding enhancement of 5.0% at H(12), 10.8% at the other allylic hydrogen H(19), and 6.3% at δ 6.77 (2H, dd, J = 8.2, 0.9 Hz). This latter signal (δ 6.77) we assign to the ortho protons of aromatic ring A, H(23) and H(27).[27] Irradiation of the isopropyl proton H(3) at δ 2.03−2.17 (1H, m) induced an enhancement of 1.7% at H(27). Irradiation of one of the methyl signal at δ 0.98 (3H, d, J = 6.7) induced an enhancement at H(6) δ 8.73 (1H, s), while irradiation of the other methyl signal at δ 0.84 (3H, d, J = 6.4 Hz) gave an enhancement of 7.4% at H(1β) δ 3.71 (1H, dd, J = 12.5, 1.1 Hz). The methyl signal at δ 0.98 is assigned to the C(5) methyl, and irradiation of this signal also gave a 3.2% enhancement of H(27). These NOE contacts indicate that the isopropyl group and aromatic ring A were on the same face of the complex in solution.[28] From the $^{13}C-^{1}H$ correlation spectrum, the chemical shifts for C(19) and C(21) (83.0 and 86.0 ppm, respectively) indicate little difference between the electronic environments of these atoms in solution, which is in agreement with the crystal structure and much smaller than the difference observed for oxazoline−thioglucose ligands.[15]

Mechanistic Implications. The NMR experiments verified that the intermediate in a solution of CD_2Cl_2 at room temperature had the same orientation of the allyl unit as in the solid state. This structure was the only one clearly visible (≥95%) by NMR. and as all our reactions were performed in CH_2Cl_2 at room temperature, we believe the X-ray structure **14** depicts the palladium intermediate from which the major (*R*)-enantiomer of **10** is formed. This requires the nucleophile to attack the allyl group *trans* to the imine function at C(19). This occurs despite the possible electronic preference for attack *trans* to sulfur, as suggested by the slightly longer Pd−C(21) bond and lower field ^{13}C chemical shift. To account for the preferred trajectory, we believe that the steric influence of the chiral ligand predisposes the allyl group toward nucleophilic attack at C(19). This is manifested in the X-ray structure, where the C(20)−C(21) bond is tending toward coplanarity with the N−Pd−S plane. This type of distortion has been noted[10c] in a crystal structure

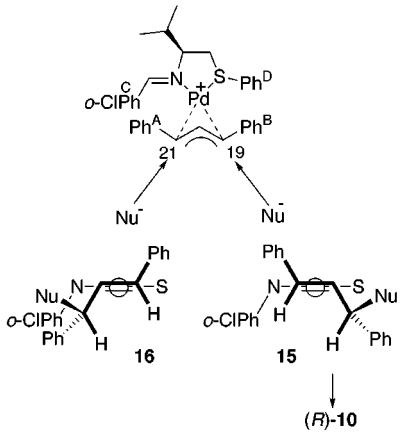

Figure 5. Front view of two possible Pd^0(olefin) complexes resulting from nucleophilic attack of the most stable Pd^+(allyl) intermediate.

of a nitrogen−phosphorus chiral ligand and is evident in others[8f,10a] but has always served to reinforce the electronic preference set up by the trans effect of the heterodentate ligand.[29] In our case, this distortion is of paramount importance, as reaction of the nucleophile with the (η^3-allyl)Pd complex to form the primary (η^2-olefin)Pd^0 complex must be accompanied by rotation. This concept was first advanced by Trost[6a] for ionization and then for nucleophilic attack by the microscopic reverse. The involvement of preferential rotation[7] to help explain enantioselection in asymmetric palladium-catalyzed allylic substituion reactions has been promoted by Brown[8f] and others.[7,10c,15] In our case, the primary product resulting from nucleophilic attack at C(19) gives the thermodynamically more stable (η^2-olefin)Pd^0 complex **15** (Figure 5). Formation of complex **16** from nucleophilic attack at C(21) would involve a more strenuous rearrangement in the transition state, causing unfavorable steric interactions between the aromatic A ring and the benzylidene aromatic ring C. We believe that this steric interaction, as described by the NOE contacts, is dominant. The desired and lowest energy pathway (**2**, Figure 1) obeys the principle of least motion[30] and gives the thermodynamically most stable primary product **15**, which upon decomplexation gives the observed major enantiomer of the product (*R*)-**10**.

Conclusion

We can conclude that the catalyst provides a unique chiral environment which orientates the allyl fragment into a predisposed conformation around the Pd−allyl axis and dictates reaction at one end of the allyl fragment. In our particular system, sterics account for the nucleophile approaching trans to the imine donor. This is contrary to expectation from previously studied nitrogen−sulfur ligands. This work serves to illustrate the principle that the correct choice of substituents can reinforce the stereoinducing power of the chirality inherent to a ligand system. It would appear as so much emphasis has been placed on the power of electronic desymmetrization for chiral recognition that, in the absence of physical data

(27) For other NOE enhancements, see table in Supporting Information.

(28) The existence of this NOE contact suggests that, when the steric bulk of the backbone substituent was increased to Ph (**7a**) or *t*-Bu (**7b**), which resulted in decreased yield and enantioselectivity, the formation of π-allyl intermediates similar to **14** is less favourable.

(29) For theoretical treatments, see: (a) Ward, T. R. *Organometallics* **1996**, *15*, 2836−8. (b) Blöchl, P. E.; Togni, A. *Organometallics* **1996**, *15*, 4125−32.

(30) For a review, see: Hine, J. *Adv. Phys. Org. Chem.* **1977**, *15*, 1−61.

for most other nitrogen−sulfur chelate ligand systems,[31] it has been assumed that the trans effect dominates enantioselection. We propose that the trans effect in many of these systems is minimal and that enantioselection arises through the predisposition of the allyl fragment through the asymmetric steric influence of the ligand system. The explanation for enantioselectivity which we have structurally detailed is similar to explanations promoted by Brown[8f] and others[7,10c,15] to account for the enantioselection of other ligand systems. These effects may have important implications in the design criteria of similar N,S-ligand systems, where attention needs to be paid to both steric and electronic interactions.

Experimental Section

General Methods. Our general experimental details have been reported elsewhere.[32] Syntheses of compounds **3c,d**, **7a,b**, and **8a,b** and spectroscopic data for **6a**−**i** are contained in the Supporting Information.

(*S*)-2-Amino-3-methyl-1-thiophenylbutane (4). Thiophenol (1.67 mL, 16.3 mmol, 1.05 equiv) was added dropwise to prewashed (hexane, 3 × 10 mL) NaH (0.65 g, 80% dispersion in mineral oil, 16.3 mmol, 1.05 equiv) in DMF (30 mL) at 0 °C. After 15 min, a solution of (*S*)-*N*-*tert*-butoxycarbonyl-2-amino-3-methyl-1-butyl-*p*-toluenesulfonate[21] (5.53 g, 15.5 mmol) in DMF (20 mL) was added, the mixture was stirred for 1 h at 0 °C and 2 h at room temperature, and then aqueous NaOH (1 M, 200 mL) was added. The mixture was extracted with Et_2O, and the combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification by column chromatography (15% ethyl acetate/light petroleum) gave the protected amine (*S*)-*N*-*tert*-butoxycarbonyl-2-amino-3-methyl-1-thiophenylbutane as a white solid (1.17 g, 71%): mp 74−75 °C; $[\alpha]^{21}_D = +31.0°$ (*c* 1.00, CH_2Cl_2); IR (thin film) 3441, 2968, 2933, 2875, 1708, 1584, 1500, 1368, 1167 cm^{-1}; ^1H NMR δ 0.90 (6H, t, $J = 6.4$ Hz), 1.41 (9H, s), 1.85−1.98 (1H, m), 3.07 (2H, d, $J = 5.5$ Hz), 3.62−3.68 (1H, m), 4.56 (1H, d, $J = 8.2$ Hz), 7.14−7.39 (5H, m); ^{13}C NMR δ 17.9, 19.5, 28.4, 30.8, 37.6, 55.2, 83.9, 129.0, 129.7, 133.2, 155.4; MS (EI^+) 295 (M^+). Anal. Calcd for $C_{16}H_{25}NO_2S$: C, 65.05; H, 8.53; N, 4.74; S, 10.83. Found: C, 65.12; H, 8.76; N, 4.74; S, 11.05.

The protected amine (1.30 g, 4.40 mmol) was stirred with trifluoroacetic acid (4.41 mL, 57.3 mmol, 13 equiv) and Et_3SiH (1.76 mL, 11.0 mmol, 2.5 equiv) in CH_2Cl_2 (15 mL) for 1 h at room temperature. Aqueous NaOH (1 M, 100 mL) was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give **4** as a light brown oil (0.86 g, 100%): $[\alpha]^{21}_D = +79.8°$ (*c* 0.99, CH_2Cl_2); IR (thin film) 3372, 3059, 2958, 1584, 1480, 1367 cm^{-1}; ^1H NMR δ 0.91 (3H, d, $J = 5.2$ Hz), 0.94 (3H, d, $J = 5.2$ Hz), 1.38 (2H, br s), 1.65−1.78 (1H, m), 2.66−2.76 (2H, m), 3.12−3.22 (1H, m), 7.14−7.37 (5H, m); ^{13}C NMR δ 17.6, 19.3, 33.0, 41.0, 55.4, 126.1, 128.9, 129.4, 136.3; MS (EI^+) 195 (M^+). Anal. Calcd for $C_{11}H_{17}NS$: C, 67.58; H, 8.86; N, 7.03; S, 16.65. Found: C, 67.58; H, 8.86; N, 7.03; S, 16.65.

General Procedure for the Formation of Imine Ligands 6a−h. An equimolar mixture of **4** and the requisite aromatic aldehyde with $MgSO_4$ (0.54 g/mmol) was stirred in CH_2Cl_2 (2.5 mL/mmol) for 24 h. Filtration and concentration in vacuo gave ligands **6a**−**i** as oils which were unstable to chromatography but judged to be >95% pure by ^1H NMR.

General Procedure for Palladium-Catalyzed Allylic Substitution. A solution of the acetate **9** (252 mg, 1.0 mmol), allylpalladium chloride dimer (9.1 mg, 0.025 mmol), and ligand (0.1 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 15 min before a solution of dimethyl malonate (396 mg, 3.0 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (0.74 mL, 3.0 mmol) in CH_2Cl_2 (1 mL) was added dropwise, followed by potassium acetate (2.5 mg, 0.03 mmol). The reaction mixture was degassed in three freeze−evacuate−thaw cycles and stirred at room temperature for 24−96 h. Evaporation of the volatile components and purification by column chromatography (8% ethyl acetate/light petroleum) gave **10** as a clear oil.[11d]

{[(*S*)-*N*-2′-Chlorobenzylidene-2-amino-3-methyl-1-thiophenylbutane]-(η^3-*trans*-1,3-diphenylallyl)palladium Perchlorate. To a stirred solution of 1,3-diphenylpalladium chloride dimer[26] (460 mg, 0.7 mmol) in $MeOH/CH_2Cl_2$ (1:1, 10 mL) was added $AgClO_4$ (285 mg, 1.4 mmol) at room temperature in the absence of light. After 45 min, the reaction mixture was filtered through a 2-cm plug of Celite and washed with $MeOH/CH_2Cl_2$ (1:1, 5 mL). A solution of ligand **6e** (436 mg, 1.4 mmol) in 50% methanol/dichloromethane (5 mL) was added to the clear yellow filtrate, which was stirred for a further 45 min. Concentration in vacuo gave an orange powder, which was recrystallized from CH_2Cl_2/hexane to give the title compound as orange crystals (927 mg, 94%): mp > 250 °C; $[\alpha]^{21}_D = +25.9°$ (*c* 0.19, CH_2Cl_2); IR (KBr) 2966, 1627 cm^{-1}; ^1H NMR δ 0.84 (3H, d, $J = 6.4$ Hz, C^4H_3), 0.98 (3H, d, $J = 6.7$ Hz, C^5H_3), 2.03−2.17 (1H, m, C^3H), 3.05 (1H, dd, $J = 12.8$, 4.3 Hz, $C^1H\alpha H\beta$), 3.48−3.57 (1H, m, C^2H), 3.71 (1H, dd, $J = 12.5$, 1.1 Hz, $C^1H\alpha H\beta$), 4.54 (1H, d, $J = 11.3$ Hz, $C^{21}H$), 5.18 (1H, d, $J = 12.2$ Hz, $C^{19}H$), 6.48 (1H, t, $J = 12.1$ Hz, $C^{20}H$), 6.77 (2H, dd, $J = 8.2$, 0.9 Hz, $C^{23}H + C^{27}H$), 7.09 (2H, t, $J = 7.8$ Hz, $C^{24}H + C^{26}H$), 7.18 (2H, t, $J = 7.5$ Hz, $C^{30}H + C^{32}H$), 7.25−7.48 (9H, m, Ar*H*), 7.35 (1H, dd, $J = 7.0$, 1.5 Hz, C^9H), 7.72 (1H, td, $J = 7.8$, 1.6 Hz, $C^{10}H$), 7.83 (1H, dd, $J = 7.6$, 0.9 Hz, $C^{11}H$), 8.39 (1H, dd, $J = 7.6$, 1.8 Hz, $C^{12}H$), 8.73 (1H, s, C^6H); ^{13}C NMR δ 18.7 (C^4), 20.0 (C^5), 32.1 (C^3), 44.2 (C^1), 81.0 (C^2), 83.0 (C^{19}), 86.0 (C^{21}), 107.2 (C^{20}), 127.2 ($C^{23} + C^{27}$), 127.8 (Ar), 128.3 (C^{11}), 128.7 (Ar), 129.2 ($C^{24} + C^{26}$), 129.4 (Ar), 129.6 ($C^{30} + C^{32}$), 130.1 (Ar), 130.5 (Ar), 130.9 (Ar), 131.0 (C^{12}), 133.1 (Ar), 133.5 (Ar), 134.9 (C^{10}), 136.1 (Ar), 136.5 (Ar), 136.7 (Ar), 168.3 (C^6); MS (FAB^+) 617 (MH^+). Anal. Calcd for $C_{33}H_{33}NO_4S_2Cl_2Pd$: C, 55.28; H, 4.64; N, 1.95; S, 4.47; Cl, 9.89. Found: C, 55.56; H, 4.42; N, 1.85; S, 4.52; Cl, 9.96.

X-ray Crystallographic Structure Determination of 14. Crystallographic and data collection parameters are provided as Supporting Information. Crystal data for $C_{33}H_{33}Cl_2NO_4PdS$: $M = 716.96$; crystallizes from dichloromethane as orange blocks, crystal dimensions 0.66 × 0.34 × 0.34 mm; monoclinic, $a = 9.347(4)$, $b = 18.920(8)$, and $c = 9.648(5)$ Å, $\beta = 108.71(2)°$, $U = 1616.0(13)$ Å^3, $Z = 2$, $D_c = 1.473$ Mg/m^3, space group $P2_1$ (C_2^2 No.4), Mo Kα radiation ($\bar{\lambda} = 0.710\ 73$ Å), μ(Mo Kα) = 0.841 mm^{-1}, $F(000) = 732$. Three-dimensional, room-temperature X-ray data were collected in the range $3.5 < 2\theta < 50°$ on a Siemens P4 diffractometer by the ω scan method. Of the 3648 reflections measured, all of which were corrected for Lorentz and polarization effects and for absorption by semiempirical methods based on symmetry-equivalent and repeated reflections (minimum and maximum transmission coefficients 0.6067 and 0.7630), 2540 independent reflections exceeded the significance level $|F|/\sigma(|F|) > 4.0$. The structure was solved by direct methods and refined by full-matrix least-squares on F^2. Hydrogen atoms were included in calculated positions and refined in riding mode. Refinement converged at a final $R = 0.0510$ ($wR_2 = 0.1842$, for all 3087 data, 398 parameters, mean and maximum δ/σ 0.000, 0.000) with allowance for the thermal anisotropy of all non-hydrogen atoms. Minimum and maximum final electron density were −1.790 and 0.828 e Å^{-3}. A weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0648P)^2 + 0.6799P]$, where $P = (F_o^2 + 2F_c^2)/3$ was used in the latter stages of refinement. Complex scattering factors were taken from the program package SHELXL97[33] as implemented on the Viglen Pentium computer.

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(31) See ref 15 for NMR mechanistic study.

(32) Anderson, J. C.; Siddons, D. C.; Smith, S. C.; Swarbrick, M. E. *J. Org. Chem.* **1996**, *61*, 4820−3.

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Supporting Information Available: Syntheses of compounds **3c,d**, **7a,b**, and **8a,b** and spectroscopic data for **6a**−**i**; an ORTEP plot for **14**; tables of crystal data, structure solution and refinement, atomic coordinates, bond lengths and angles, anisotropic thermal parameters; table of NOE data and pertinent NOE, COSY, and $^{13}C-^{1}H$ correlation spectra for **14**; and 250-MHz ^{1}H NMR spectra of compounds **3c,d**, **6a**−**i**, **7a,b**, **8a,b**, and **14**. An X-ray crystallographic file, in CIF format, for **14** is also available. This material is available free of charge via the Internet at http://pubs.acs.org.

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