Chiral Mixed Phosphorus/Sulfur Ligands for Palladium-Catalyzed Allylic Alkylation and Aminations

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The incorporation of C2 symmetry into chiral ligand design 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 C2 symmetry through the use of electronic effects such as the trans influence. Such effects are a natural consequence of the use of chiral bidentate ligands equipped with strong and weak donor heteroatom pairs (e.g., PR3NR2, or PR3SR2).2 Such electronic effects have the potential to influence both the stability and reactivity of the intervening diastereomeric reaction intermediates in the catalytic cycle. While mixed phosphorus/nitrogen bidentate ligands incorporating this construct have been applied in enantioselective palladium-catalyzed nucelophilic alkylation of allylic esters,3 chiral thioether-containing donor ligands have been less well developed.4 As seen in structure A, thioether complexation creates an S-chiral sulfur center; however, a potential liability associated with these ligands is the relatively low barrier to sulfur inversion (15 kcal/mol) for transition metal-coordinated thioethers.5 In this paper, we report a new class of mixed phosphorus/sulfur ligands 1–3 that incorporates a metal-bound thioether as a chiral control element in asymmetric catalysis. The utility of these ligands is illustrated in the palladium-catalyzed alkylation6 of enol–malonate and amine nucleophiles.

Ligands 1–3 are composed of three subunits that include the ArP, and RS– heteroatom fragments and the interconnecting skeletal backbone. Each of these fragments may be

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Table 1. Allylic Alkylation of 5 with Representative Nucleophiles (Eq 1)‡

<table>
<thead>
<tr>
<th>Ligand</th>
<th>CH2(CO2Me)2, BSAa ee, % (yield 5b, %)</th>
<th>BnNH2a ee, % (yield 5b, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>91 (93)</td>
<td>99 (96)</td>
</tr>
<tr>
<td>1b</td>
<td>98 (97)</td>
<td>95 (97)</td>
</tr>
<tr>
<td>1c</td>
<td>94 (95)</td>
<td>95 (95)</td>
</tr>
<tr>
<td>2a</td>
<td>28 (91)</td>
<td>78 (90)</td>
</tr>
<tr>
<td>2b</td>
<td>30 (94)</td>
<td>66 (95)</td>
</tr>
<tr>
<td>2c</td>
<td>69 (92)</td>
<td>89 (93)</td>
</tr>
</tbody>
</table>

† Reactions were run in CH2Cl2 at −20 °C using 2 mol % Pd and 2.8 mol % L. ‡ Enantioselectivity determined by chiral HPLC analysis (Daicel Chiralcel AD). BSA equiv of malonate and BSA and cat. KOAc were used relative to substrate. *2 equiv of BnNH2 used relative to 4.

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independently varied to generate a large ligand family containing sterically and electronically differentiated analogues. The diarylphosphinite moiety was selected for the P terminus by virtue of its ease of incorporation and its documented utility as a ligand component.7 Diarylphosphinites 1f and 2f were identified as valuable ligands after a survey of both thioether and diarylphosphinite ligand components. For example, in test reactions of the Pd-catalyzed alkylation of 1,3-diphenylpropenyl acetate (4) with dimethyl malonate and bis(trimethylsilyl)acetamide (BSA),8 ligands 1a and 2a afforded product 5a in good yields and enantioselectivities (91 and 98% ee, respectively, Table 1). For the sulfur donor moiety, two trends were noted for the alkylation process with malonate nucleophile. First, increased steric hindrance was found to directly correlate with increased enantioselective with the S-terti-butyl substituent being optimal. Second, alkyl substituents proved to be superior to their aryl counterparts. For the diarylphosphinite moiety, neither electron-withdrawing nor electron-donating substituents proved to be superior to phenyl.9

Ligand 3, readily synthesized in enantiomerically pure form in two steps from cyclohexene oxide and tert-butyldimercaptan using methodology recently reported by Shibasaki,11 was considered as a structural analogue of 2. The corresponding malonate alkylation with ligand 3a afforded product 5a in 94% ee (Table 1). The data in Table 1 also demonstrate that all three ligands promote allylic amination with benzylamine in 95–99% ee. The comparative alkylation reactions of the α-naphthyl ligand series 1b–3b is also

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(8) A range of thioether substituent analogues of ligand 1a were evaluated in reactions between 4 and malonate/BSA. Aryl and alkyl substituents investigated: 3.5-MePh (63% ee), Bn (89% ee), Cy (91% ee), tert-buty1 (91% ee). See the Supporting Information for the ligand synthesis.
(9) A range of thioether substituent analogues of ligand 2a were evaluated in reactions between 4 and malonate/BSA but none were superior to tert-buty1. Aryl and alkyl substituents investigated: 3.5-MePh (85% ee), Bn (75% ee), Cy (81% ee), and tert-buty1 (98% ee). A range of phosphate ary1 substituent analogues of ligand 2 were evaluated but none were superior to toluene. Phosphinite ligands were investigated: 3.5-MePh (80% ee), 3.5-(CF3)2Ph (93% ee), 4-MeOPh (82% ee), 4-FPh (93% ee), 2-MeOPh (29% ee), Cy (47% ee), and α-naphthyl (30% ee). See the Supporting Information for the ligand synthesis.
(10) Trost, B. M.; Murphy, D. J. Organometallics 1985, 4, 1143–1145.
counterpart

1a acetates (2, eqs 2 and 3). From the ligand screen with cycloalkenyl we surveyed these substrates with this ligand family (Table such as 10 phosinate 1b R as the optimal ligand backbone with bis(11). This trend is to be contrasted to the alkylation requirements than their acyclic counterparts.12 Accordingly, active alkylation of cyclic allylic esters have different structural ligand of choice (cf. Table 2).

Evidence that the sulfur is functioning as a coordinating ligand in these reactions is supported by X-ray structures of the [Pd(2a)(π-1,3-diphenylallyl)](SbF₆) complex 1314 and the [Pd(1a)-(cyclohexenyl)](SbF₆) complex 1415 (Figure 1). As predicted, the coordinated thioether ligand in both structures is oriented trans to the isopropyl group to minimize nonbonding interactions. In addition, the adjacent methyl substituent increases the steric demands of the isopropyl moiety by orienting it in the direction of the bound thioether. Noteworthy differences in the two structures may be found in the ring conformations of the bound ligands. While a twist-boat conformation is observed in complex 13, the chelate ring conformation in 14 is more chairlike. These conformational differences appear to be coupled to the conformation of the Ph₂P moiety where the phenyl edgeface relationships are clearly different in the two complexes. The crystal structures also reveal the relative electronic impact of the heteroatom phosphinite and thioether donors. For example, the Pd–C₁ bond trans to the phosphinite is longer than the Pd–C₂ bond trans to the thioether, emphasizing the stronger trans influence of the phosphinite moiety.2 On the basis of the orientation of the π-allyl ligand in the crystal structure, attack of the nucleophile trans to the phosphinite in the illustrated crystal geometries predicts the stereochemistry that is observed for all reactions.13 Further studies in this area are ongoing.

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**Supporting Information Available:** Experimental procedures, spectral data, and enantiomeric purity assays for all compounds.

**Figure 1.** X-ray structures of 13 and 14. SbF₆⁻ counterions from each structure omitted for clarity.

**Table 2. Alkylation of Cyclic Allylic Esters (Eqs 2, 3)**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>CH₂(CO₂Me)₃, BSA² ee</th>
<th>BnNH₂² ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>94 (94) 8a</td>
<td>91 (93) 9a</td>
</tr>
<tr>
<td>7b</td>
<td>94 (91) 8b</td>
<td>91 (97) 9b</td>
</tr>
<tr>
<td>7c</td>
<td>96 (98) 8c</td>
<td>97 (95) 9c</td>
</tr>
<tr>
<td>10</td>
<td>94 (95) 11</td>
<td>94 (99) 12</td>
</tr>
</tbody>
</table>

¹ See Table 1 for footnotes a,b. ² Determined by ¹H NMR chiral shift with Eu(hfc)₃ in C₆D₆. ³ 2 equiv of BnNH₂ was used relative to substrate. ⁴ Determined by achiral HPLC analysis of the corresponding (S)-Mosher amide.

provided. These data establish that the diphenylphosphinyl moiety is superior to its α-naphthyl counterpart for allylic acetate 4. This trend is to be contrasted to the alkylation results for cyclic allylic esters where ligand 1b is the ligand of choice (cf. Table 2).

Chiral ligands that effectively promote the enantioselective alkylation of cyclic allylic esters have different structural requirements than their acyclic counterparts.12 Accordingly, we surveyed these substrates with this ligand family (Table 2, eqs 2 and 3). From the ligand screen with cycloalkenyl acetates 7a–c and malonate, ligand architecture 1 surfaced as the optimal ligand backbone with bis(α-naphthyl)phosphinite 1b being superior (7b → 8b, 94% ee) to its phenyl counterpart 1a (7b → 8b, 90% ee). Heteroatom analogues such as 10 are also effective alkylation substrates (10 → 11, 94% ee). Benzyllamine may also be employed as an effective nucleophile, affording products 9a–c and 12 in equivalent enantioselectivities and yields. As an illustration of the importance of ligand architecture, 2a, while an excellent ligand for 1,3-diphenylpropenyl acetate (4) displacements (95–98% ee, Table 1), affected the 7b → 8b transformation in only 38% ee.

13 Crystals of 13(C₅H₄MeOPSPdSbF₆) were grown from a warm solution of 7 in methanol to yield yellow prisms. The compound crystallizes in the orthorhombic crystal system, space group P2₁2₁2₁; a = 19.597(2) Å, b = 20.706(3) Å, c = 9.794(13) Å, α = β = γ = 90°; V = 3974.4(9) Å³; Z = 4; R = 0.0386, GoF = 0.974. 14 Crystals of 14(C₅H₄MeOPSPdSbF₆) were grown from a warm solution of 13 in methanol to yield yellow prisms. The compound crystallizes in the orthorhombic crystal system, space group P2₁2₁2₁; a = 10.228(5) Å, b = 17.727(8) Å, c = 18.088(7) Å, α = β = γ = 90°; V = 3279 (2) Å³; Z = 4; R = 0.0433, GoF = 1.282. 15 The direction of attack trans to the stronger π-acceptor has been previously documented by others: ref 3. See also: Ward, T. R. Organometallics 1996, 15, 2836–2838.