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

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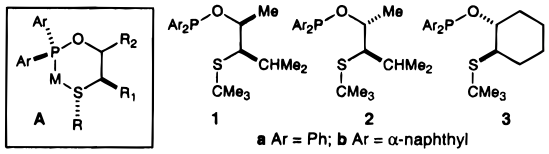
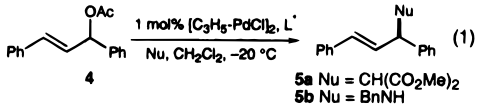
The incorporation of C_2 symmetry into chiral ligand design is a well-recognized strategy for restricting the number of diastereomeric transition states in metal-catalyzed enantioselective processes.[1] Equally powerful stereochemical restrictions may also be realized with chiral ligands lacking C_2 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). 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 nucleophilic 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 (15−20 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 allylic alkylation[6] with enol−malonate and amine nucleophiles.



Ligands **1**−**3** are composed of three subunits that include the Ar_2P- and RS− heteroatom fragments and the interconnecting skeletal backbone. Each of these fragments may be 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 **1**[8] and **2**[9] 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),[10] ligands **1a** and **2a** afforded product **5a** in good yields and enantioselectivities (91 and 98% ee, respectively, eq 1, 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 enantioselection with the S-*tert*-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*-butylmercaptan 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

Table 1. Allylic Alkylation of 5 with Representative Nucleophiles (Eq 1)[a]



L*	$CH_2(CO_2Me)_2$, BSA[b] ee, % (yield **5a**, %)	$BnNH_2$[c] ee, % (yield **5b**, %)
1a	91 (93)	99 (96)
2a	98 (97)	95 (97)
3a	94 (95)	95 (95)
1b	28 (91)	78 (90)
2b	30 (94)	66 (95)
3b	69 (92)	89 (93)

[a] Reactions were run in CH_2Cl_2 at −20 °C using 2 mol % Pd and 2.8 mol % L*. Enantiomeric purity determined by chiral HPLC analysis (Daicel Chiralcel AD). [b] 3 equiv of malonate and BSA and cat. KOAc were used relative to substrate. [c] 2 equiv of $BnNH_2$ used relative to **4**.

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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-Me_2Ph (63% ee), Bn (89% ee), Cy (91% ee), *tert*-butyl (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*-butyl. Aryl and alkyl substituents investigated: 3,5-Me_2Ph (85% ee), Bn (75% ee), Cy (81% ee), and *tert*-butyl (98% ee). A range of phosphinate aryl substituent analogues of ligand **2** were evaluated but none were superior to phenyl. Aryl substituents investigated: 3,5-Me_2Ph (80% ee), 3,5-$(CF_3)_2$Ph (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.

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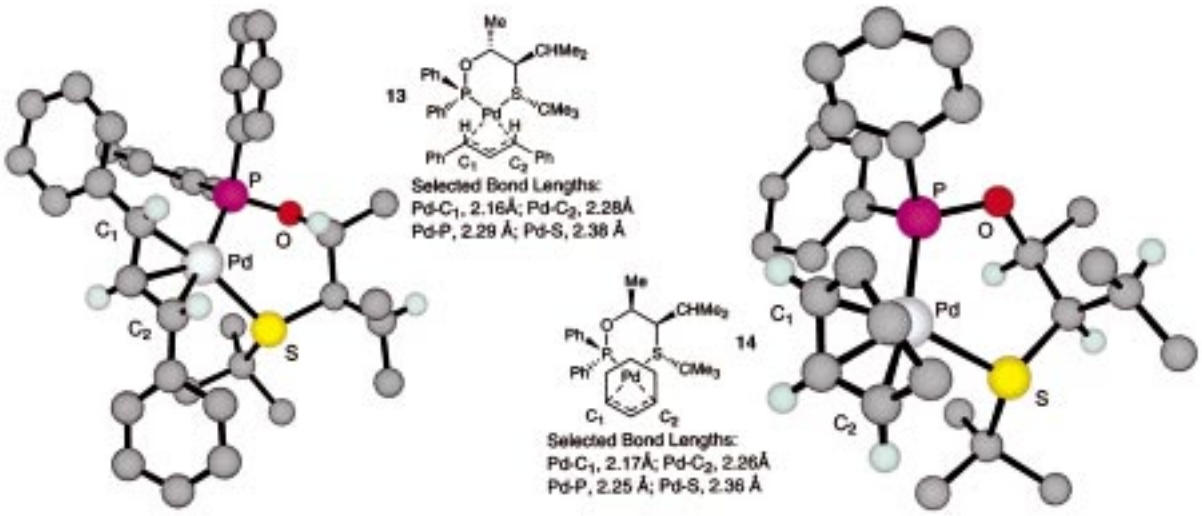
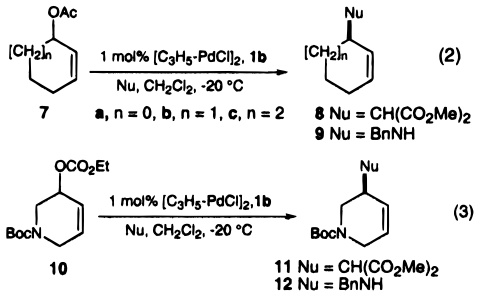


Figure 1. X-ray structures of **13** and **14**. SbF_6^- counterions from each structure omitted for clarity.

Table 2. Alkylation of Cyclic Allylic Esters (Eqs 2, 3)[a]



substrate	$CH_2(CO_2Me)_2$, BSA[b] ee,[c] % (yield, %)	$BnNH_2$[d] ee,[e] % (yield, %)
7a	94 (94) **8a**	91 (93) **9a**
7b	94 (91) **8b**	91 (97) **9b**
7c	96 (98) **8c**	97 (95) **9c**
10	94 (95) **11**	94 (99) **12**

[a] See Table 1 for footnotes a,b. [b] Determined by ^1H NMR chiral shift with $Eu(hfc)_3$ in C_6D_6. [d] 2 equiv of $BnNH_2$ was used relative to substrate. [e] 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 acetates 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). Benzylamine 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.

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)](SbF_6) complex **13**[14] and the [Pd(**1a**)-(cyclohexenyl)](SbF_6) complex **14**[15] (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 Ph_2P moiety where the phenyl edge/face 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−C_1 bond trans to the phosphinite is longer than the Pd−C_2 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.[15] 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.

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(13) Crystals of **13** ($C_{37}H_{44}POSPdSbF_6$) were grown from a warm solution of **7** in methanol to yield yellow prisms. The compound crystallizes in the orthorhombic crystal system, space group *P*212121; a = 19.597(2) Å, b = 20.706(3) Å, c = 9.7944(13) Å, α = β = γ = 90°; V = 3974.4(9) Å^3; Z = 4; R = 0.0386, GoF = 0.974.

(14) Crystals of **14** ($C_{28}H_{40}POSPdSbF_6$) were grown from a warm solution of **13** in methanol to yield yellow prisms. The compound crystallizes in the orthorhombic crystal system, space group *P*212121; a = 10.228(5) Å, b = 17.727(8) Å, c = 18.088(7) Å, α = β = γ = 90°; V = 3279 (2) Å^3; 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.