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Ferrocenylphosphine-amide ligands for palladium-catalyzed asymmetric allylation

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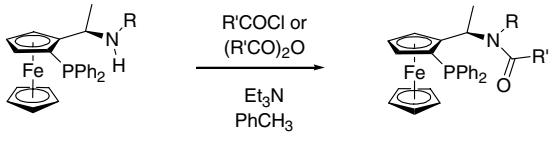
Abstract—A new series of phosphine-amide ligands has been prepared on a ferrocenylethyl backbone. These species are effective for enantioselective palladium-catalyzed substitution reactions of allylic acetates. The modular nature of the ligand design has allowed ready optimization to afford products of up to 98.8% ee.

The asymmetric alkylation of allylic electrophiles catalyzed by palladium complexes has been extensively investigated due to the synthetic potential of the products of these types of reactions. A wide variety of ligands have been found to be effective for these transformations.[1] One particular class of ligands that has received little attention has been the phosphine-amide ligands.[2,3] This is likely because the enantioselectivities achieved using these species are generally below 90% ee. This is perhaps not surprising, as many of the species prepared to date have been derived from phosphinobenzoic acid, with the chirality remote from the reaction center, residing on the conformationally labile amino portion of the amide. We reasoned that if the chirality was placed on the backbone of the molecule the transfer of stereochemical information might be more efficient. Our interest was augmented by our ready access to chiral amino-phosphine precursors, ferrocenyl species **2**, which are the final intermediates in the synthesis of a variety of recently introduced ferrocenyl phosphine-aminophosphine ligands for asymmetric hydrogenation.[4] The amides **1** derived from phosphine-amines **2** seemed ideal species to investigate, as these molecules possess two modes of chirality (planar and side chain) that are both held in fairly rigid conformations. In addition, the binding of the previously prepared phosphine-amides to palladium has been shown to occur through the phosphine and amide oxygen to afford a six-membered chelate.[2] We were interested in examining the effect of a potentially larger chelate ring size (eight membered).

Conversion of ferrocenyl phosphine-amines **2** to ferrocenyl phosphine-amides **1** occurred in a straightforward manner by reaction with either an acid chloride or anhydride. These materials were generally readily isolable crystalline solids that often precipitated from the acylation reaction mixture.[5] As shown in Scheme 1, a variety of species with variation of both the R and R′ groups was prepared.



2 **1**

a: R = H, R' = CH_3
b: R = H, R' = Et
c: R = H, R' = *t*-Bu
d: R = H, R' = Ph
e: R = H, R' = O*t*-Bu
f: R = R' = CH_3
g: R = CH_3, R' = Et
h: R = Ph, R' = Et
i: R = CH_2Ph, R' = CH_3
j: R = CH_2Ph, R' = Et

Scheme 1. Synthesis of BoPhoz™ phosphine-amide ligands **1**.

The reaction characteristics of the palladium complexes of these ligands were explored using acetamide **1a** and propionamide **1b** as ligands for the reaction of 1,3-diphenylpropenyl acetate **3** with dimethyl malonate, the standard test reaction for asymmetric allylation chemistry. The initial conditions utilized THF as solvent and potassium acetate as base in the presence of

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N,*O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA). This latter reagent was used for convenience, and subsequent reactions indicated identical results with the more commonly used *N*,*O*-bis(trimethylsilyl)acetamide (BSA). Initial results were promising, with the propionamide **1b** affording slightly higher enantioselectivity compared to the acetamide **1a**.

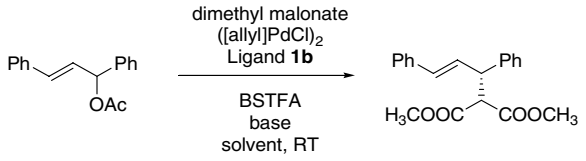
The effects of the reaction conditions were examined using the palladium complex of the *N*-propionyl species **1b**.[6] These results are shown in Table 1, and indicate that both the solvent and the base employed can have an effect on the course of the reaction. An initial screen indicated that TBME (*tert*-butyl methyl ether) was the best solvent for this reaction, although good results were also obtained with THF and toluene. Poor reactivity was observed with dichloromethane, diethoxymethane (DEM), and tetrachloroethylene (TCE). Lithium carbonate, potassium acetate, and sodium acetate all afforded good enantioselectivity while lithium acetate afforded decidedly poorer results. Sodium carbonate and potassium carbonate afforded high enantioselectivities but a reduced reaction rate. The rationale behind these results is unclear, and illustrates the subtleties inherent in this complex multi-component reaction.

The ligand **1** affords ample opportunity for tuning the reactivity and selectivity of the catalyst by variation of both the R substituent and the R′ of the acyl group on the nitrogen. We initially investigated the variation of the acyl group of the primary amide. The results shown in Table 2 indicate that the *N*-propionyl group is decidedly superior for this transformation, affording under the optimum conditions (TBME, Li_2CO_3, BSTFA) 100% conversion with 98.8% ee for the *S* enantiomer of **4** (entry 3). Larger groups afforded significantly poorer results. The *N*-pivaloyl species **1c** afforded very poor enantioselectivity (entry 4) while the *N*-benzoyl species **1d** showed poor reactivity, although affording high enantioselectivity (entry 6). The Boc carbamate **1e** afforded no reaction.

Previously reported asymmetric hydrogenation work using phosphine-aminophosphine ligands based on structure **1** indicated a limited influence of the R groups on the reaction characteristics of the ligand.[4] That was not the case for allylic alkylation, as variation of the R group had a profound effect upon the reaction and perhaps afforded some insight into the nature of the catalysts based on ligands **1**. As indicated in Table 3, adding steric bulk around the nitrogen resulted in extremely slow reactions, affording poor conversion even after extended reaction times with high catalyst loadings. The enantioselectivities of these reactions were also generally poor. It is quite intriguing that most of these *N*-alkyl compounds afforded the product **4** with the opposite *R* configuration in contrast to the *N*–H ligands. The lone exception was ligand **1f**, which showed a curious change in selectivity with reaction duration. At short reaction times the *S* enantiomer of **4** predominated, albeit with low enantioselectivity (entries 1 and 2). However, at longer reaction times the *R* enantiomer became the major product (see entries 2 and 3, which were the same run at differing reaction times), suggesting that there may be more than one active catalyst species present.

The generality of the palladium-catalyzed allylic alkylation reactions utilizing ligand **1b** was investigated by examining the reaction of dimethyl malonate with cyclohex-2-enyl acetate. This substrate has decidedly different steric demands compared to **3**, and afforded a more moderate 83% ee under the best conditions (2 mol% catalyst, Li_2CO_3, TBME).

Table 1. Optimization using ligand **1b**[a]

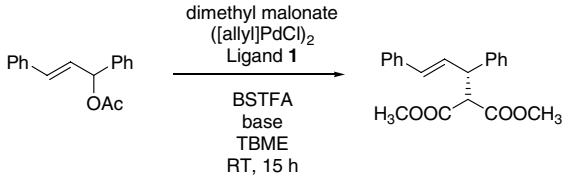


3 **S-4**

Entry	Solvent	Base	Time (h)	Conversion (%)	Ee (%)[b]	Yield (%)[c]
1	TBME	Li_2CO_3	15	100	98.8	88
2	THF	Li_2CO_3	18	99.5	97.2	88
3	Toluene	Li_2CO_3	18	99.3	94.4	94
4	CH_2Cl_2	Li_2CO_3	18	54.2	97.4	nd
5	DEM	Li_2CO_3	18	3.0	nd	nd
6	TCE	Li_2CO_3	18	2.5	nd	nd
7	TBME	KOAc	15	>99	95.4	nd
8	TBME	LiOAc	15	>99	73.2	87
9	TBME	NaOAc	15	90.7	96.2	86
10	TBME	Na_2CO_3	40	100	96.6	84
11	TBME	K_2CO_3	40	100	95.8	81

[a] Reactions run with 2 mol% catalyst for the time indicated.
[b] Enantiomeric excess of **4** was determined by chiral HPLC using a 250×4.6 mm Chiralcel OD-H column (Chiral Technologies), mobile phase 98:2 hexane–isopropanol, flow rate 1 mL/min, $\lambda = 254$ nm.
[c] Yield of isolated product after flash chromatography (SiO_2, 9:1 heptane–ethyl acetate).

Table 2. Variation of acyl R′ of ligand **1**[a]

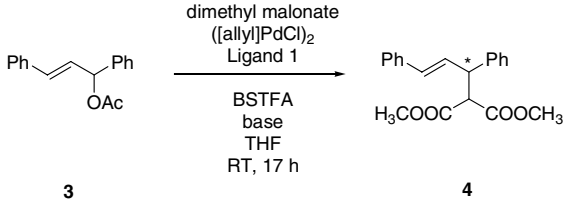


3 **S-4**

Entry	Ligand	R′	Base	Conversion (%)	Ee (%)
1	**1a**	CH_3	KOAc	99.1	96.6
2	**1b**	Et	KOAc	>99	95.4
3	**1b**	Et	Li_2CO_3	100	98.8
4	**1c**	*t*-Bu	KOAc	97.4	4.8
5[b]	**1d**	Ph	KOAc	26.9	24.8
6[c]	**1d**	Ph	Li_2CO_3	95.8	93.1
7[d]	**1e**	O′Bu	Li_2CO_3	0	Nd

[a] Reaction run with 2 mol% catalyst for 15 h except where indicated.
[b] Reaction run for 38 h.
[c] Reaction run with 10 mol% catalyst in THF for 41 h.
[d] Reaction run with 10 mol% catalyst for 17 h.

Table 3. Variation of R group of ligand **1**[a]



3 **4**

Entry	Ligand	R	R′	Base	Conversion (%)	Ee (%)
1[b]	**1f**	CH_3	CH_3	KOAc	16.7	10.8 *S*
2	**1f**	CH_3	CH_3	Li_2CO_3	3.8	17.3 *S*
3[c]	**1f**	CH_3	CH_3	Li_2CO_3	9.6	16.1 *R*
4	**1g**	CH_3	Et	Li_2CO_3	12.3	38.4 *R*
5	**1h**	Ph	Et	Li_2CO_3	1.8	52.7 *R*
6	**1i**	CH_2Ph	CH_3	Li_2CO_3	0	nd
7	**1j**	CH_2Ph	Et	Li_2CO_3	0	nd

[a] Reactions run with 10 mol% catalyst for 17 h except where indicated.
[b] Reaction run with 2 mol% catalyst in CH_2Cl_2 for 36 h.
[c] Reaction run for 41 h.

Previous work has indicated that phosphine-amide species ligate to the palladium through the phosphorus and the amide oxygen.[2,3] The ligands used in those investigations, however, are structurally disposed to afford a six-membered palladacycle. It is yet unknown how ligands **1** interact with the palladium, whether via a phosphorus–nitrogen six-membered palladacycle or a phosphorus–oxygen eight-membered palladacycle. Absolute determination of the binding mode could best be answered by X-ray crystallographic analysis. Unfortunately, most of the complexes investigated exhibited poor crystallization behavior. The sole exception was the combination of ligand **1b** and allylpalladium chloride dimer, which afforded suitable crystals from THF solution. Unfortunately, the crystal structure indicated that this material was a monodentate phosphorus-ligated palladium(II) chloride species, which at best can be considered a pre-catalytic complex and is not particularly relevant to understanding the reactivity and enantioselectivity of these catalysts. In contrast, the results of the allylation reactions provide indirect evidence for the preferred binding mode of ligands **1**. The high enantioselectivity and reactivity of the *N*–H ligands coupled with the poor reactivity and inverse selectivity of the *N*-alkyl amides (which are more sterically hindered around the nitrogen), implies a nitrogen–phosphorus binding mode. In addition, the selectivity inversion at extended reaction times observed for ligand **1f**, the least sterically encumbered of the *N*-alkyl species, suggests that a slow interconversion between two catalytically active species, perhaps a phosphorus–nitrogen ligated species converting to a phosphorus–oxygen ligated species, may be occurring during the course of the reaction. The monodentate nature of the crystallized precatalyst also implies that the amide is a weak binding donor, which could facilitate the interconversion of *N*-ligated and *O*-ligated complexes. Additional support for the phosphorus–nitrogen ligation for ligands **1a**–**1d** includes the fact that the palladium complex of unsubstituted amine **2** (R = H) shows good reactivity (100% conversion) and fairly high enantioselectivity (89% ee *S*) for the reaction of **3** with dimethyl malonate.

Thus we have demonstrated that a new class of phosphine-amide ligands based on a diphenylphosphinoferrocenylethylamine backbone can afford exceedingly high enantioselectivities for palladium-catalyzed allylic alkylation reactions. The nature of the ligation is not yet proven, but the evidence suggests that productive binding occurs through the phosphorus and the nitrogen of the amide, at variance with other phosphine-amides, which involve phosphorus–amide oxygen ligation.

Acknowledgements

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References and notes

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5. A typical procedure for the preparation of ligand **1b** is as follows: Amine **2** (R = H) (480 mg, 1.16 mmol) was dissolved in 5 mL of toluene, cooled in ice-water, and purged with argon for 15 min. Triethylamine (240 mL, 1.74 mmol, 1.5 equiv) was added followed by propionic anhydride (178 mL, 1.39 mmol, 1.2 equiv). Solid was noted after 15 min. The reaction mixture was allowed to warm to ambient temperature overnight at which point TLC analysis indicated no **2** present (1:2 heptane–ethyl acetate). Water (5 mL) and heptane (10 mL) were added and the mixture was stirred for 10 min at ambient temperature. The precipitate was collected by filtration, washed with water and heptane, and dried to afford 0.40 g (73%) of **1b**, mp 157–158 °C. ^{1}H NMR ($CDCl_3$) δ 7.54–7.48 (m, 2H); 7.38–7.35 (m, 3H); 7.26–7.16 (m, 5H); 5.887 (br s, 1H); 5.178 (m(5), 1H, $J = 6.87$ Hz); 4.462 (br s, 1H); 4.296 (t, 1H, $J = 2.47$ Hz); 4.015 (s, 5H); 3.787 (m, 1H); 1.79–1.52 (m, 2H); 1.371 (d, 3H, $J = 6.87$ Hz); 0.903 (t, 3H, $J = 7.69$ Hz). ^{13}C NMR ($CDCl_3$) δ 171.7 (s); 139.9 (d, $J_{C-P} = 9$ Hz); 137.0 (d, $J_{C-P} = 8$ Hz); 135.1 (d, $J_{C-P} = 21$ Hz); 132.6 (d, $J_{C-P} = 18$ Hz); 129.4 (s); 128.3 (d, $J_{C-P} = 9$ Hz); 128.3 (s); 128.2 (s); 95.5 (d, $J_{C-P} = 23$ Hz); 74.7 (d, $J_{C-P} = 11$ Hz); 72.2 (s); 70.5 (d, $J_{C-P} = 4$ Hz); 70.0 (s); 69.3 (s); 44.8 (d, $J_{C-P} = 5$ Hz); 29.3 (s); 21.9 (s); 9.7 (s). FDMS: m/z 469 (M^+). HRMS calcd for $C_{27}H_{29}FeNOP$ $(M+H)^+$: 470.1336, found: 470.1345. Anal. Calcd for $C_{27}H_{28}FeNOP$: C, 69.10; H, 6.01; N, 2.98. Found: C, 69.04; H, 6.08; N, 2.97. $[\alpha]_D^{23} = -308$ (c 1.05, methanol).
6. A typical allylation procedure is as follows: Allylpalladium chloride dimer (3.7 mg, 0.01 mmol, 0.01 equiv), ligand **1b** (11.3 mg, 0.024 mmol, 0.024 equiv), 1,3-diphenylpropenyl acetate **3** (252 mg, 1.0 equiv), and lithium carbonate (2 mg, 0.027 mmol, 0.027 equiv) were combined and 6 mL of TBME was added. The mixture was stirred at ambient temperature for 15 min. Dimethyl malonate (0.34 mL, 3.0 mmol, 3.0 equiv) and BSTFA (0.74 mmol, 3.0 mmol, 3.0 equiv) were added and the reaction mixture was stirred at ambient temperature for 15 h, at which point chiral HPLC analysis indicated 100% conversion and 98.8% ee for *S*-**4**. The volatiles were stripped and the residue was flash-chromatographed on silica gel and eluted with 1:9 ethyl acetate–heptane to afford 285 mg of (*S*)-**4** (88%). ^{1}H NMR ($CDCl_3$) δ 7.34–7.19 (m, 5H); 6.478 (d, 1H, $J = 15.93$ Hz); 6.304 (dd, 1H, $J = 8.52$, 15.66 Hz); 4.257 (dd, 1H, $J = 8.52$, 10.99 Hz); 3.950 (d, 1H, $J = 10.99$ Hz); 3.699 (s, 3H); 3.514 (s, 3H). Chiral HPLC (Chiralcel OD-H column [Chiral Technologies], mobile phase 98:2 hexane–isopropanol, 1 mL/min, $\lambda = 254$ nm): t_R 13.0, 13.6 min (**3**); t_R 15.2 min [(*R*)-**4**]; t_R 16.2 min [(*S*)-**4**]. $[\alpha]_D^{23} = -17.6$ (c 1.68, ethanol), indicating (*S*)-enantiomer for **4**.[2b]