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Novel Sulfinyl Imine Ligands for Asymmetric Catalysis

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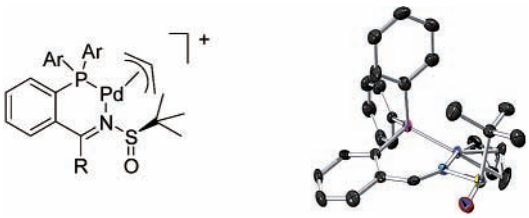
ABSTRACT



A novel class of *P*,*N*-sulfinyl imine ligands has been prepared that incorporates chirality solely at sulfur. The Pd complex of ligand 14 catalyzes the allylic alkylation reaction with high enantioselectivity (94%), and the first crystal structure of a Pd-bound sulfinyl imine provides insight into binding mode and origins of stereoselectivity.

Over the past several years, many useful chiral ligand classes have been developed due to the increasing importance of asymmetric catalysis in organic synthesis.[1] The vast majority of these ligands incorporate chirality at a carbon center, and very few ligands that rely solely on heteroatom chirality have provided promising levels of asymmetric induction.[2] Recently, we reported on the synthesis and utility of bis(sulfinyl)imidoamidine (SIAM) ligands, whose Cu(II) complexes provide extremely high levels of enantio- and diastereoselectivity in the Diels−Alder reaction.[3] Chirality in these ligands is derived solely from the chiral sulfur center of *tert*-butanesulfinamide, a commercially available compound that can readily be transformed into sulfinyl imines through condensation with aldehydes and ketones.[4] Sulfinyl imines are attractive as a versatile ligand class due to their ease of synthesis, which enables straightforward modification of their steric and electronic properties. Furthermore, there is potential for metal coordination proximal to the chiral center through the N, O, or S atoms.[3,5] Herein, we report on the utility of a new class of sulfinyl imine ligands **1** (Figure 1), which provides high levels of enantioselectivity in palladium-catalyzed allylic alkylation. In addition, we report the first X-ray crystal structure of a Pd-bound sulfinyl imine ligand, which provides insight into the binding mode and origins of selectivity.

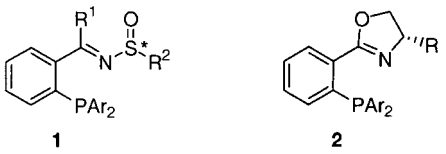


Figure 1. Sulfinyl imine and phosphinooxazoline ligand scaffolds.

In designing chiral, sulfinamide-based ligands for palladium catalysis, we focused on the phosphinooxazoline

(1) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed; Wiley-VCH: New York, 2000.

(2) For leading references: (a) Hiroi, K.; Suzuki, Y.; Kawagishi, R. *Tetrahedron Lett.* **1999**, *40*, 715. (b) Bolm, C.; Simić, O. *J. Am. Chem. Soc.* **2001**, *123*, 3820. (c) Harmata, M.; Ghosh, S. *Org. Lett.* **2001**, *3*, 3321. (d) Hiroi, K.; Watanabe, K.; Abe, I.; Koseki, M. *Tetrahedron Lett.* **2001**, *42*, 7617. (e) Bolm, C.; Simić, O.; Martin, M. *Synlett.* **2001**, *12*, 1878.

(3) Owens, T.; Hollander, F.; Oliver, A.; Ellman, J. *J. Am. Chem. Soc.* **2001**, *123*, 1539.

(4) Liu, G.; Cogan, D.; Owens, T.; Tang, T.; Ellman, J. *J. Org. Chem.* **1999**, *64*, 1278.

(5) Souers, A.; Owens, T.; Oliver, A.; Hollander, F.; Ellman, J. *Inorg. Chem.* **2001**, *40*, 5299.

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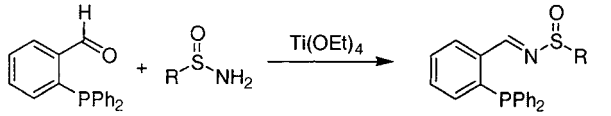
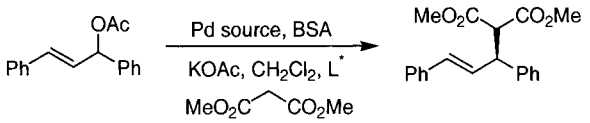
ligand class **2** (Figure 1) due to the success of these and other related *P*,*N* ligands in palladium-catalyzed transformations.[6] The sulfinyl imine scaffold was thus designed to incorporate a chelating phosphine and sp^2 nitrogen in positions relative to the chiral center that are analogous to those in the phosphinooxazoline scaffold. Ligand **3** was selected for initial optimization of the allylic alkylation conditions. Preparation of **3** was completed in a single step via Ti-mediated condensation of *tert*-butanesulfinamide with commercially available 2-(diphenylphosphino)benzaldehyde (Scheme 1). A range of solvents and Pd reagents was then

Scheme 1. One-Step Synthesis of Sulfinyl Imine Ligands



explored in the allylic alkylation of 1,3-diphenylpropenyl acetate using ligand **3** (Table 1). While moderate enantioselectivities were observed in coordinating solvents (entries 1−3), a significant improvement in selectivity occurred upon switching to benzene (entries 4 and 5). We were pleased to find that in methylene chloride (entry 6), the Pd complex of **3** generated from $[Pd(allyl)Cl]_2$ catalyzed the allylic alkylation reaction with 93% ee and in high conversion. Surprisingly, an excess of palladium relative to ligand was required for high enantioselectivity (entry 7). This interesting result when an excess of ligand is present could potentially be due to displacement of the chiral sulfinyl imine moiety from palladium by the phosphine of another ligand molecule to give a less stereoselective catalyst.

Table 1. Optimization of the Allylic Alkylation[a]

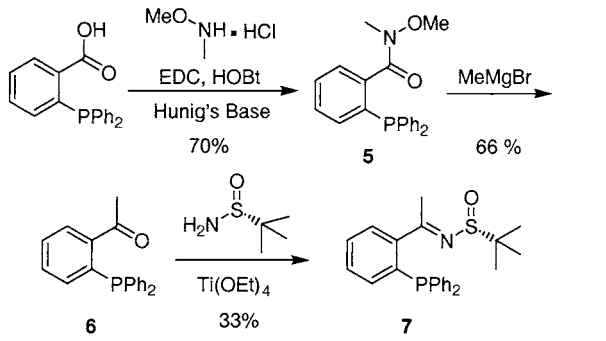


entry	L*	solvent[b]	Pd source	time[c] (h)	% ee[d]
1	**3**	CH_3CN	$[Pd(allyl)Cl]_2$	6	43
2	**3**	CH_3CN	$Pd_2dba_3{\cdot}CHCl_3$	1	53
3	**3**	THF	$Pd_2dba_3{\cdot}CHCl_3$	5	67
4	**3**	C_6H_6	$[Pd(allyl)Cl]_2$	26	86
5	**3**	C_6H_6	$Pd_2dba_3{\cdot}CHCl_3$	>33[e]	88
6	**3**	CH_2Cl_2	$[Pd(allyl)Cl]_2$	8.5	93
7	**3**	CH_2Cl_2	$[Pd(allyl)Cl]_2$	20	41[f]
8	**4**	CH_2Cl_2	$[Pd(allyl)Cl]_2$	>25[e]	0
9	**7**	CH_2Cl_2	$[Pd(allyl)Cl]_2$	5	56

[a] Reactions run with 30 mol % L* and 1:1.3 L*/Pd. [b] Reactions run at [0.07] in substrate. [c] Time required for disappearance of starting material by TLC analysis. [d] Determined by chiral HPLC (Chiralpak AD). [e] Reaction was not complete in time indicated. [f] Reaction run with 20 mol % **3** and 2:1 **3**/Pd.

Having identified optimal reaction conditions for **3**, the effects of varying both R^1 and R^2 of the ligand structure (Figure 1) were investigated. With **4**, the reaction proceeded slowly and the product formed was racemic (Table 1, entry 8), suggesting that either the greater steric bulk or the increased electron-donating ability of the *tert*-butyl group relative to the *p*-tolyl group is required for catalytic activity and stereoselectivity. Ketimine ligand **7** (Scheme 2) was next prepared in three steps from 2-(diphenylphosphino)benzoic acid via the Weinreb amide intermediate **5**. Under the optimized conditions for the allylic alkylation reaction, **7** provided a modest increase in reaction rate but with a significant reduction in stereoselectivity (Table 1, entry 9).

Scheme 2. Synthesis of Ketimine Ligand **7**



To elucidate the way in which **3** imparts stereoselectivity, an X-ray crystal structure was obtained of the π-allyl Pd(II) complex of **3**, which corresponds to the Pd(II) intermediate in the catalytic cycle (Figure 2). This structure confirms that ligand **3** binds palladium through phosphorus and nitrogen to form a six-membered ring chelate. Similar to previously reported π-allyl Pd crystal structures, the palladium in complex **8** has a slightly distorted square-planar geometry,[7] and the disorder of the allyl unit reflects a known $\eta^3-\eta^1-\eta^3$ isomerization.[8]

Notably, the bond lengths between palladium and the carbons of the allyl unit exhibit a trans influence similar to that reported for other *P*,*N* ligands (Table 2).[9] It has been shown that mixed chelate ligands can electronically induce asymmetry due to the lengthening, and thus increased reactivity, of the Pd−allyl carbon bond trans to the better π-acceptor. Nucleophilic attack is known to occur prefer-

(6) (a) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. (b) Hou, D.-R.; Reibenspies, J.; Burgess, K. *J. Org. Chem.* **2001**, *66*, 206. (c) Gilbertson, S.; Xie, D.; Fu, Z. *J. Org. Chem.* **2001**, *66*, 7240. (d) Saitoh, A.; Morimoto, T.; Achiwa, K. *Tetrahedron*: *Asymmetry*, **1997**, *8*, 3567.

(7) (a) Sprinz, J.; Kiefer, M.; Helmchen, G. *Tetrahedron Lett.* **1994**, *35*, 1523. (b) Albinati, A.; Kunz, R.; Amman, C.; Pregosin, P. *Organometallics* **1991**, *10*, 1800 and references therein.

(8) Von Matt, P.; Lloyd-Jones, G.; Minidis, A.; Pfaltz, A.; Macko, L.; Neuburger, M.; Zehnder, M.; Ruegger, H.; Pregosin, P. *Helv. Chim. Acta* **1995**, *78*, 265.

(9) Frost, C.; Howarth, J.; Williams, J. *Tetrahdron*: *Asymmetry*, **1992**, *3*, 1089.

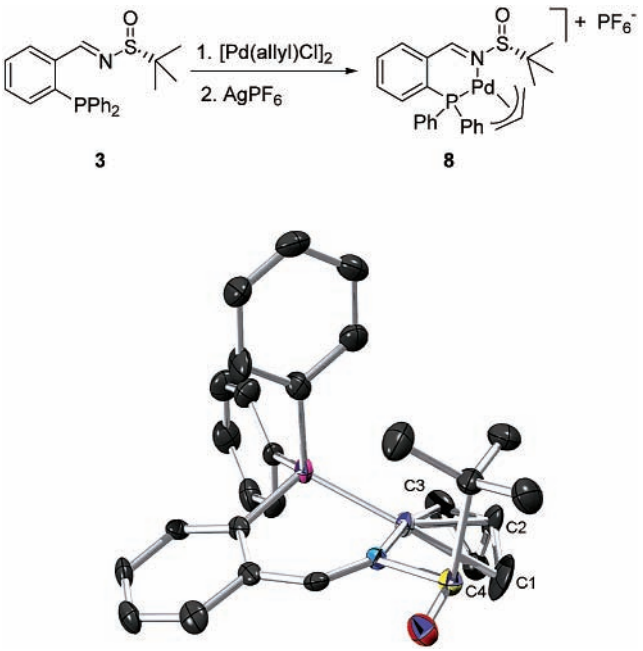


Figure 2. X-ray crystal structure of π-allyl Pd-bound **3**. Hydrogens and the counterion have been omitted for clarity.

entially at the allyl carbon trans to the phosphorus atom in related systems.[9]

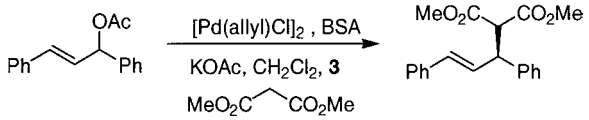
Table 2. Selected Bond Distances and Angles in Complex 8

bond	distance (Å)	angle	deg
Pd−N	2.10	N−Pd−P	88.4
Pd−P	2.27	P−Pd−C1	100.1
Pd−C1	2.21	C1−Pd−C3	68.1
Pd−C2	2.14	C3−Pd−N	103.1
Pd−C3	2.12		
Pd−C4	2.21		

While ligand **3** performed well in the Pd-catalyzed allylic alkylation at 30 mol % catalyst loading (Table 1), attempts to reduce the catalyst loading to 5 mol % were disappointing. Under the optimized conditions, the reaction rate was drastically reduced (Table 3, entry 1). Furthermore, the stereoselectivity showed a profound concentration dependence, with higher concentrations resulting in a dramatic reduction in enantioselectivity (entries 2−4). At low concentration (entry 5), the rate of reaction was unacceptably slow.

Having already investigated changes in the ligand scaffold at both the chiral sulfur center and the imine carbon, we chose to evaluate ligands with substituents on phosphorus with different steric and electronic properties in order to improve the performance of the catalyst system. The dicyclohexylphosphine **13** would allow evaluation of a dialkylphosphine ligand, while the di(*o*-tolyl)phosphine **14** was selected

Table 3. Allylic Alkylation with **3** at 5 Mol % Catalyst Loading[a]

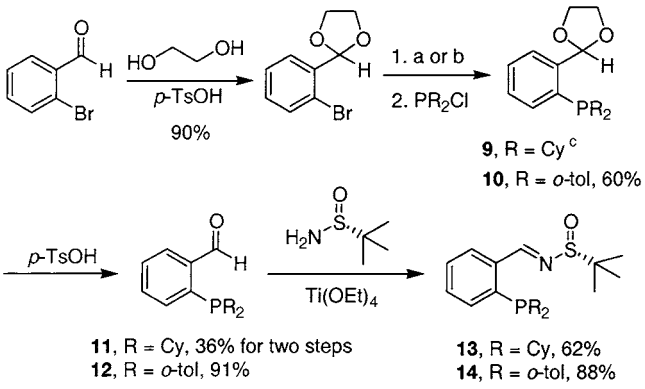


entry	concentration (M)	time[b] (h)	% ee[c]
1	0.07	>30	86
2	0.10	>30	86
3	0.20	>30	71
4	0.40	>30	19
5	0.03	>168	92

[a] Reactions run with 5 mol % **3** and 1:1.3 **3**/Pd ratio. [b] Reaction was not complete in time indicated. [c] Determined by chiral HPLC.

to significantly increase steric hindrance about the phosphorus. Preparation of these second-generation ligands began with formation of the acetal of 2-bromobenzaldehde (Scheme 3). Treatment with magnesium or *t*-BuLi, followed by

Scheme 3. Preparation of Ligands **13** and **14**[a]

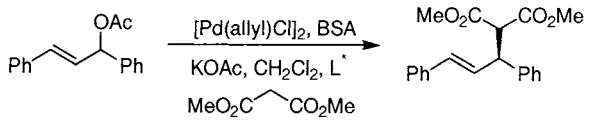


[a] R = Cy, *t*-BuLi. [b]R = *o*-tol, Mg. [c]Crude material was carried on to the next step without purification.

addition to the diaryl- or dialkylphosphine chloride, provided compounds **9** and **10**. The acetals were deprotected to give aldehydes **11** and **12**, which were subsequently condensed with *tert*-butanesulfinamide to provide the desired ligands **13** and **14** in good yields.

Table 4 summarizes the activity of **13** and **14** in the allylic alkylation reaction. At 30 mol % catalyst loading, the Pd complex of **13** was inferior in both rate and enantioselectivity (entry 1) when compared with ligand **3** (entry 6, Table 1). In contrast, at 30 mol % catalyst loading the Pd complex of **14** was both more active and stereoselective (entry 2). Notably, additional experiments demonstrated that both high catalytic activity and stereoselectivity were maintained at various ligand/Pd ratios (entries 3 and 4) and at high and low concentrations (entries 5−7). Furthermore, low catalyst loading gave complete conversion in 6 h to provide the allylic alkylation product in 95% isolated yield and 94% ee (entry

Table 4. Evaluation of **13** and **14** in the Allylic Alkylation



entry	L*	mol % L*	L*:Pd	concentration[a] (M)	time[b] (h)	% ee[c]
1	**13**	30	1:1.3	0.10	24	49
2	**14**	30	1:1.3	0.07	2	96
3	**14**	30	1.5:1	0.07	1	96
4	**14**	30	1:1	0.07	1	96
5	**14**	5	1:1	0.07	6	94
6	**14**	5	1:1	0.10	4	93
7	**14**	5	1:1	0.20	4	93

[a] Substrate concentration. [b] Time required for disappearance of starting material by TLC analysis. [c] Determined by chiral HPLC.

5). The observed selectivity approaches that of the most selective of the phosphinooxazoline catalysts (99% ee),[10] and we anticipate that further optimization of the phosphine sulfinyl imine ligand scaffold will result in improved selectivity.

(10) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 2, *4*, 566.

In conclusion, a new sulfinyl imine ligand class has been developed with the design and synthesis of phosphine-containing scaffolds. The Pd complex of ligand **14** catalyzes the allylic alkylation of 1,3-diphenylpropenyl acetate with high levels of enantioselectivity at low catalyst loading. The first X-ray crystal structure of a π-allyl Pd-bound sulfinyl imine confirms that these are *P*,*N* ligands and suggests that high enantioselectivity is achieved via a trans influence. The application of this new ligand class to additonal Pd- and other transition metal-catalyzed reactions is forthcoming.

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Supporting Information Available: Crystallographic data, full experimental details, and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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