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Application of *P,N*-Sulfinyl Imine Ligands to Iridium-Catalyzed Asymmetric Hydrogenation of Olefins

Laurie B. Schenkel and Jonathan A. Ellman*

Center for New Directions in Organic Synthesis, Department of Chemistry, University of California, Berkeley, California 94720

jellman@uclink.berkeley.edu

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The utility of a novel class of *P,N*-ligands incorporating a chiral sulfinyl imine moiety is demonstrated in the iridium-catalyzed hydrogenation of both functionalized and unfunctionalized olefins, in which enantioselectivities of up to 94% are achieved. The modularity of the *P,N*-sulfinyl ligand class is highlighted by the facile preparation of a variety of sterically and electronically different ligands. Interesting structure−activity data for both the phosphine and sulfinamide components is provided by this expanded ligand set.

Introduction

The importance of asymmetric catalysis in organic synthesis has led to the development of a number of versatile chiral ligand classes.[1] A ligand class that is easily prepared and modified and which can provide products with high enantioselectivity in a variety of different reactions is ideal. Recently, we reported on the synthesis and utility of several novel ligands incorporating a chiral *tert*-butanesulfinyl imine moiety (Figure 1).[2] The Cu(II) complexes of the bis(sulfinyl)imidoamidine (SIAM) ligands provide extremely high levels of enantio- and diastereoselectivity in the Diels−Alder reaction,[2a,b] while the *P,N*-sulfinyl imine ligands provide enantioselectivities of up to 94% in the Pd-catalyzed allylic alkylation reaction.[2c] With the vast majority of successful chiral ligands relying on chirality about a carbon center, these are among a small number of ligands incorporating only heteroatom chirality for which high levels of enantioselectivity have been achieved.[3]

The asymmetry induced by sulfinyl imine-metal complexes is due to the chirality of the sulfur center of the sulfinamide component. *tert*-Butanesulfinamide is a commercially available compound that can readily be transformed into sulfinyl imines in high yields through condensation with aldehydes and ketones.[4] The ease with which sulfinyl imines can be prepared allows for facile modification of their steric and electronic properties, rendering them attractive as a versatile ligand class. Previous application of the *P,N*-sulfinyl imines to the Pd-catalyzed allylic alkylation reaction demonstrated the dramatic effect of the phosphine component on reaction rate and asymmetric induction; however, only ligands derived from *tert*-butanesulfinamide and *p*-toluenesulfinamide were explored.[2c] Recent reports on the preparation of a variety of sulfinamides with distinct steric and electronic properties[5] prompted us to investigate the effects of their incorporation into the *P,N*-sulfinyl imine scaffold. Here, we report the synthesis of *P,N*-sulfinyl imine ligands having diverse substitution on the sulfinamide moiety, and their application to the Ir-catalyzed asymmetric hydrogenation of both functionalized and unfunctionalized olefins.[6] This work further highlights the modularity of the *P,N*-sulfinyl imine scaffold by providing interesting structure−activity data for both the

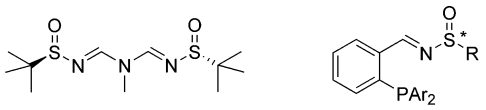

FIGURE 1. Bis(sulfinyl)imidoamidine (SIAM) and *P,N*-sulfinyl imine ligands.

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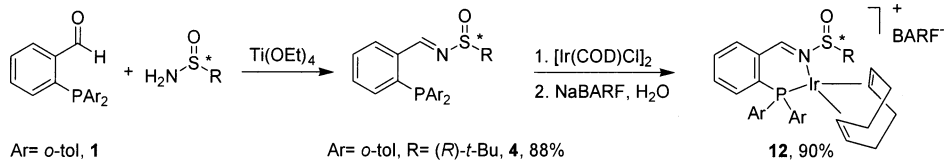
SCHEME 1. Preparation of *P,N*-Sulfinyl Imine Ligands and Their Iridium Complexes

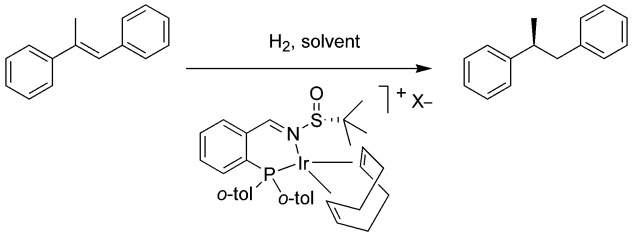


Ar= *o*-tol, **1**
Ar= 3,5-dimethylphenyl, **2**
Ar= Ph, **3**

Ar= *o*-tol, R= (*R*)-*t*-Bu, **4**, 88%
Ar= *o*-tol, R= (*S*)-1-adamantane, **5**, 94%
Ar= *o*-tol, R= (*S*)-3-ethylpentane, **6**, 90%
Ar= *o*-tol, R= (*S*)-*p*-toluene, **7**, 75%
Ar= *o*-tol, R= (*S*)-mesitylene, **8**, 80%
Ar= 3,5-dimethylphenyl, R= (*R*)-*t*-Bu, **9**, 95%
Ar= Ph, R= (*R*)-*t*-Bu, **10**, 77%
Ar= *o*-tol, R= (*S*)-2,4,6-triisopropylbenzene, **11**, 97%

12, 90%
13, 94%
14, 90%
15, 95%
16, 93%
17, 95%
18, 90%
-

TABLE 1. Optimization of the Asymmetric Hydrogenation of α-Methylstilbene[a]



entry	solvent	pressure (bar)	X⁻	conv[b] (%)	% ee[c]
1	THF	50	BARF	0	
2	toluene	50	BARF	0	
3	dichloroethane	50	BARF	50	69
4	chlorobenzene	50	BARF	94	74
5	$CHCl_3$	50	BARF	65	87
6	CH_2Cl_2	50	BARF	>99	94
7[d]	CH_2Cl_2	50	BARF	>99	94
8[e,f]	CH_2Cl_2	50	Cl	0	
9	CH_2Cl_2	100	BARF	>99	92
10	CH_2Cl_2	25	BARF	>99	91
11	CH_2Cl_2	1	BARF	70	3

[a] Reactions were run at room temperature for 1 h with 5 mol % catalyst loading. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC. [d] Experiment was run with crude catalyst. [e] Experiment run with 10 mol % catalyst for 18 h. [f] See the Supporting Information for preparation of the chloride complex.

sulfinamide and phosphine components. Furthermore, enantioselectivities of up to 94% in the Ir-catalyzed hydrogenation reaction establish the versatility of this novel ligand class.

Results and Discussion

Application of the *P,N*-sulfinyl imine ligands to the asymmetric hydrogenation of unfunctionalized olefins began with ligand **4**, which is prepared via Ti-mediated condensation with aldehyde **1** (Scheme 1). Previous use of **4** in the Pd-catalyzed allylic alkylation reaction had shown that it provides a highly selective and robust catalyst;[2c] thus, we were optimistic that its iridium complex would perform well. Preparation of the iridium complex **12** was carried out in a two-step, one-pot process in 90% yield (Scheme 1). When **12** was utilized in the hydrogenation of α-methylstilbene, a dramatic effect on both rate of reaction and enantioselectivity was observed when the solvent, pressure, and counterion were varied (Table 1). Similar to the iridium catalysts reported by both Crabtree[7] and Pfaltz,[8] *P,N*-sulfinyl imine−Ir complexes require chlorinated solvents for turnover. In both THF and toluene (entries 1−2) no product was observed, while in dichloroethane, chlorobenzene, and chloroform product was obtained in good to high yields (entries 3−5), and in chloroform with good selectivity (entry 5). Methylene chloride proved to be the most effective solvent with complete conversion occurring within 1 h at 50 bar H_2 and with 94% ee (entry 6). Furthermore, the use of crude catalyst (entry 7) did not result in a reduction of either the conversion or enantioselectivity, eliminating the need for purification of the complexes.

The counterion for the iridium complex of **12** played a critical role in catalyst performance. In analogy with related *P,N*-ligand iridium catalyst systems, the noncoordinating tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BARF) counterion was required for efficient catalyst turnover and high selectivity.[6] When the coordinating chloride counterion was employed, no product was observed, even with higher catalyst loading and extended reaction times (entry 8). An examination of pressure effects revealed that between 25 and 100 bar H_2 there was little impact on reaction rate or selectivity (entries 9−10); however, at atmospheric pressure (entry 11) there was a dramatic decrease in both reaction rate and selectivity.

Having identified optimal reaction conditions for the asymmetric hydrogenation of α-methylstilbene with **12**, we next investigated the effects that modification of the sulfinamide component would have on catalyst turnover and enantioselectivity. A diverse set of sulfinyl imine ligands and their iridium complexes were prepared (Scheme 1) from a collection of sulfinamides with a wide range of steric and electronic properties (Figure 2). Notably, the iridium complex of **11** (Scheme 1) could not be prepared, most likely due to the extremely hindered environment caused by the *o*-isopropyl groups.

Table 2 summarizes the results of the enantioselective hydrogenation of α-methylstilbene using the Ir complexes **12**−**18**. We were optimistic that increasing the steric bulk of the sulfinamide component by the incorporation of 1-adamantanesulfinamide **20** and 3-ethylpentanesulfinamide **21** would further improve the enantioselectivity. Unfortunately, complexes **13** and **14** (entries 2 and 3) were inferior to complex **12** (entry 1) in terms of both reaction rate and selectivity. These results could potentially be attributed to an unfavorable geometry about the

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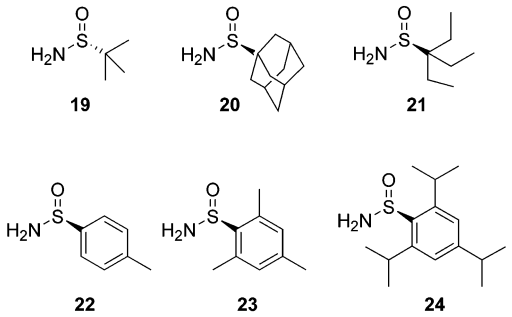
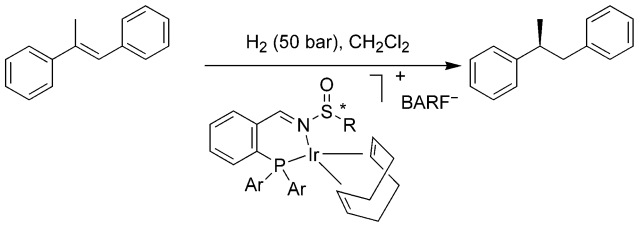


FIGURE 2. Sulfinamides selected for incorporation into *P,N*-sulfinyl imine scaffold.

TABLE 2. Sulfinyl Imine Complexes 12−18 in the Hydrogenation of α-Methylstilbene[a]



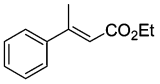
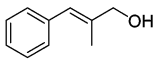
entry	R	Ar	complex	conv[b] (%)	% ee[c]
1	(*R*)-*t*-Bu	*o*-tol	**12**	>99	94
2	(*S*)-1-adamantyl	*o*-tol	**13**	58	84
3	(*S*)-3-ethylpentane	*o*-tol	**14**	75	84
4	(*S*)-*p*-tolyl	*o*-tol	**15**	>99	5
5	(*S*)-mesitylene	*o*-tol	**16**	52	7
6	(*R*)-*t*-Bu	3,5-dimethyl-phenyl	**17**	53	57
7	(*R*)-*t*-Bu	Ph	**18**	20	55

[a] Reactions were run at room temperature for 2 h with 5 mol % crude catalyst. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC.

metal center, enforced by the increased steric bulk of the sulfinamide substituent. Comparison of the data for complexes **12-14** (entries 1−3) versus that for complexes **15** and **16** (entries 4 and 5) clearly indicates the negative impact that the arenesulfinyl imines have on the enantioselectivity of the reaction. While the *p*-toluenesulfinyl imine complex **15** was competitive with the *tert*-butanesulfinyl imine in terms of catalytic turnover, very little selectivity was observed. This result is consistent with the low selectivities that we have seen in previous studies with ligands derived from *p*-toluenesulfinyl imines.[2b,c] Although we had hoped that the complex incorporating the mesitylenesulfinyl imine ligand **8** would provide improved selectivity over the complex incorporating the *p*-toluenesulfinyl imine ligand **7**, only very poor enantioselectivity and inefficient catalysis were observed (entry 5). A limited survey of complexes **17** and **18** bearing different aryl phosphine components (entries 6 and 7) illustrates that, in analogy with our *P,N*-sulfinyl imine ligands in the allylic alkylation reaction[2c] and Pfaltz' *P,N*-oxazoline ligands in hydrogenation reactions,[8e] the *o*-tolyl substitution is required for both high turnover and enantioselectivity.

Encouraged by the performance of complex **12** in the asymmetric hydrogenation of an unfunctionalized olefin, we were interested in examining the substrate scope of

TABLE 3. Sulfinyl Imine Complexes in the Hydrogenation of Functionalized Olefins[a]

Entry	Alkene	Complex	Conv (%)[b]	% ee[c]
1	 **25**	**12**	>99	65
2		**13**	>99	35
3		**14**	66	59
4		**15**	>99	0
5		**16**	>99	0
6	 **26**	**12**	>99	70
7		**13**	>99	31
8		**14**	93	68
9		**15**	>99	0
10		**16**	>99	0

[a] Reactions run with 5 mol % catalyst at 50 bar H_2 in CH_2Cl_2 at room temperature for 2 h. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC.

the *P,N*-sulfinyl imine−Ir complexes. Two functionalized olefins were selected, and our expanded set of catalyst precursors was tested under the previously optimized conditions. When utilized in the asymmetric hydrogenation of α,β-unsaturated ester **25**, the *P,N*-sulfinyl imines were efficient catalysts; however, the enantioselectivities did not exceed 65% (Table 3, entries 1−5). Similar results were observed for hydrogenation of the allylic alcohol **26** (entries 6−10), with complex **12** again providing the highest enantioselectivity (entry 6).

In summary, the work presented here serves to significantly expand the scope of the *P,N*-sulfinyl imine-based catalysts. The ease with which a variety of sterically and electronically distinct ligands could be prepared allowed us to gain valuable structure−activity information for these ligands in the Ir-catalyzed enantioselective hydrogenation of olefins. Notably, enantioselectivities of up to 94% are observed for the hydrogenation of a challenging unfunctionalized olefin substrate. The *N*-sulfinyl imine-based *P,N*-ligand class is easily prepared and has now been successfully applied with high enantioselectivity to two different transition-metal-catalyzed reactions.

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

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