Synthesis and Application of Chiral Phosphino-Imidazoline Ligands: Ir-Catalyzed Enantioselective Hydrogenation

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ABSTRACT



A series of chiral phosphino-imidazolines (PHIM ligands) 1a–j with different substituents at the stereogenic center, the nitrogen atom of the imidazoline ring, and at the phosphorus atom were synthesized. Iridium complexes derived from these ligands have been evaluated as catalysts for the enantioselective hydrogenation of unfunctionalized olefins. In several cases, higher enantiomeric excesses were observed than with analogous phosphino-oxazoline ligands.

Phosphino-oxazolines **2** (PHOX ligands) are versatile chiral ligands that have found a wide range of applications in asymmetric catalysis.¹ Cationic iridium complexes derived from these ligands have proven to be highly effective catalysts for the enantioselective hydrogenation of imines and olefins, including unfunctionalized alkenes.² The modular nature of the ligand structure made it possible to vary the backbone, the oxazoline part, and the phosphorus substituents extensively. This led us to several related ligand classes such as the pyrrolyl-derived phosphino-oxazolines 3^3 and the phosphinite-oxazolines 4,⁴ which have considerably expanded the scope of Ir-catalyzed hydrogenation.^{5,6}

Analogous imidazoline-derived P,N-ligands such as **5** have not received attention so far, although they can be easily prepared from readily available chiral precursors such as diamines or amino alcohols.⁷ This is surprising, because the additional nitrogen atom provides a handle for tuning the

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⁽⁷⁾ We have found only one publication on imidazoline-phosphine ligands: Bussaca, C. (Boehringer Ingelheim Pharmaceuticals), US Patent Application, US6316620, 2001. Ligands of this type are also under investigation in the laboratory of Dr. Mike Casey, University College Dublin (Casey, M. Personal communication).

electronic and conformational properties of the ligand by proper choice of the \mathbb{R}^3 group. Moreover, this group could also serve as a linker for attaching the ligand to a solid support. Therefore, we felt that phosphino-imidazolines could be a valuable addition to the known phosphino-oxazolines and decided to synthesize a series of imidazoline derivatives $5\mathbf{a}-\mathbf{j}$ in order to evaluate their scope as ligands in the Ircatalyzed enantioselective hydrogenation.



Starting from easily accessible β -hydroxyamides **6**, the 2-phenylimidazolines **7** were conveniently prepared, using an efficient method recently reported by Casey et al. (Scheme 1).⁸ Subsequent ortho-lithiation, followed by reaction with



^{*a*} Reaction conditions: (a) SOCl₂, 85 °C, 4 h, then TEA, R³NH₂, Et₂O, 3 h, rt, 38–86%; (b) *sec*BuLi, TMEDA, pentane, from -78 °C to room temperature, then ClPR²₂, 12 h at room temperature, 9–79%; (c) [Ir(COD)Cl]₂, CH₂Cl₂, 2 h, 40 °C, then NaBAr_F, H₂O, rt (71–94%).

different diaryl-chlorophosphines led to phosphino-imidazolines $5\mathbf{a}-\mathbf{j}$ (R¹, R², R³, see Table 1). The yields in this step varied from 9 (**5h**) to 79% (**5e**).

The corresponding iridium complexes 1a-j, having different substituents at the stereogenic center and the phophorus and nitrogen atoms, were obtained in high yields using the standard protocol developed for Ir-PHOX complexes.^{2b}

Table 1.	Hydrogenation of <i>trans</i> -α-Methylstilbene					
	Ph Ph		1 mol% 1a-j 50 bar H ₂ , 25 °	$\begin{array}{c} \bullet \\ C \end{array} Ph R Ph$		
	8		CH ₂ Cl ₂ , 2 h			
catalyst	\mathbb{R}^1	\mathbb{R}^2	\mathbb{R}^3	conversion ^a (%)	ee ^b (%)	
1a	<i>i</i> Pr	Ph	<i>i</i> Pr	>99	63	
1b	<i>i</i> Pr	Ph	Су	>99	65	
1c	<i>i</i> Pr	Ph	Bn	>99	60	
1d	<i>i</i> Pr	Ph	Ph	>99	74	
1e	<i>t</i> Bu	Ph	Ph	>99	76	
1f	<i>t</i> Bu	Ph	<i>p</i> MeO-C ₆ H ₄	98	69	
1g	<i>t</i> Bu	Ph	pCF ₃ -C ₆ H ₄	>99	73	
1h	<i>t</i> Bu	Ph	pTol	92	74	
1i	<i>t</i> Bu	<i>o</i> Tol	Ph	>99	94	
1j	<i>t</i> Bu	<i>o</i> Tol	Bn	96	85	
Ir-2 ^c	<i>t</i> Bu	<i>o</i> Tol	_	>99	97	

 a Determined by GC. b Determined by HPLC (see ref 2b). c Entry taken from ref 2b.

Crystalline BAr_F (tetrakis[3,5-bis(trifluormethyl)phenyl]borate) salts are air and moisture stable and could be purified by chromatography on silica gel without special precautions.

Crystal structures of PHIM complex **1i** and the corresponding PHOX complex **Ir-2**, bearing the same substituents at the phosphorus atom (*o*-Tol) and the stereogenic center (*t*Bu), closely resemble each other (Figure 1). However, the



Figure 1. Structure of PHIM complex 1ⁱ⁹ in the solid state and an analogous PHOX complex (**Ir-2**).¹⁰ Anions and cyclooctadienes have been omitted.

torsion angles (τ) between the central phenyl ring and the five-membered heterocycle differ by 20° (C–C–C–O angle = -11° vs C–C–C–N angle = -31°). The Ir–P distances (2.3009(12) in **1i** vs 2.3055(17) Å in **Ir-2**) and the Ir–N distances (2.080(5) vs 2.106 (3) Å) are almost identical, indicating that the electron densities on the coordinating nitrogen atoms are similar.

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⁽⁹⁾ Single crystals of **1i** obtained with PF_6^- instead of BAr_F^- gave better results in the refinement. Crystallographic data has been deposited under CCDC 197021. Further details can be found in Supporting Information.

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Table 2. Hydrogenation of (E)-2-(4-Methoxyphenyl))-2-buten
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MeO		9	1 mol% 1a-j 50 bar H ₂ , 25 ° CH ₂ Cl ₂ , 2 h	► C MeO	R
catalyst	\mathbb{R}^1	\mathbb{R}^2	R ³	conversion ^a (%)	ee ^b (%)
1a	<i>i</i> Pr	Ph	<i>i</i> Pr	>99	45
1b	<i>i</i> Pr	Ph	Су	>99	45
1c	<i>i</i> Pr	Ph	Bn	>99	46
1d	<i>i</i> Pr	Ph	Ph	>99	69
1e	<i>t</i> Bu	Ph	Ph	>99	82
1f	<i>t</i> Bu	Ph	pMeO-C ₆ H ₄	>99	81
1g	<i>t</i> Bu	Ph	pCF ₃ -C ₆ H ₄	>99	78
1h	<i>t</i> Bu	Ph	<i>p</i> Tol	>99	80
1i	<i>t</i> Bu	<i>o</i> Tol	Ph	>99	81
1j	<i>t</i> Bu	<i>o</i> Tol	Bn	>99	90
Ir-2 ^c	<i>t</i> Bu	oTol	-	>99	81

 a Determined by GC. b Determined by HPLC (see ref 2b). c Entry taken from ref 5.

In the hydrogenation of $trans-\alpha$ -methylstilbene (8), different catalysts $1\mathbf{a}-\mathbf{j}$ gave ee values between 60 and 94% (Table 1). The results show that the substituents at the imidazoline nitrogen atom have a distinct influence on the enantioselectivity, with *N*-aryl groups ($1\mathbf{d}-\mathbf{i}$) being superior to analogous *N*-alkyl groups ($1\mathbf{a}-\mathbf{c}$, $1\mathbf{j}$). The effect of a π -donor or π -acceptor substituent in the para position of the *N*-aryl group is small ($1\mathbf{e}-\mathbf{h}$). Complex 1**i** proved to be almost as selective as the coresponding Ir-PHOX complex I**r**-2 (94 vs 97% ee).

Similar trends were observed for the hydrogenation of (E)-2-(4-methoxyphenyl)-2-butene (9) within the series 1a-d and 1e-h (Table 2). However, with catalysts 1i and 1j, the selectivity order between *N*-phenyl and *N*-benzyl observed with alkene 8 and other substrates (Tables 3 and 4) was

Table 3. Hydrogenation of (Z)-2-(4-Methoxyphenyl)-2-butene						
MeO		0	1 mol% 1a-j 50 bar H ₂ , 25 ° CH ₂ Cl ₂ , 2 h	MeO MeO	$\frac{1}{s}$	
catalyst	\mathbb{R}^1	\mathbb{R}^2	\mathbb{R}^3	conversion ^a (%)	ee ^b (%)	
1a	<i>i</i> Pr	Ph	<i>i</i> Pr	>99	16	
1b	<i>i</i> Pr	Ph	Су	>99	13	
1c	<i>i</i> Pr	Ph	Bn	>99	12	
1d	<i>i</i> Pr	Ph	Ph	>99	58	
1e	<i>t</i> Bu	Ph	Ph	97	86	
1f	<i>t</i> Bu	Ph	<i>p</i> MeO-C ₆ H ₄	98	82	
1g	<i>t</i> Bu	Ph	pCF ₃ -C ₆ H ₄	>99	87	
1h	<i>t</i> Bu	Ph	<i>p</i> Tol	92	84	
1i	<i>t</i> Bu	<i>o</i> Tol	Ph	>99	88	
1j	<i>t</i> Bu	<i>o</i> Tol	Bn	>99	83	
Ir-2 ^c	<i>t</i> Bu	<i>o</i> Tol	-	>99	63	

 a Determined by GC. b Determined by HPLC (see ref 2b). c Entry taken from ref 5.

Table 4.	Hydrogenation of
6-Methoxy	y-1-methyl-3,4-dihydronaphthalene

5-Methoxy-1-methyl-5,4-diffydronaphthalene						
MeO			1 mol% 1a 50 bar H ₂ , 25 CH ₂ Cl ₂ , 2	-j j °C h MeO	s S	
catalyst	\mathbb{R}^1	\mathbb{R}^2	R ³	conversion ^a (%)	ee^{b} (%)	
1a 1b 1c 1d 1e 1f 1g 1h 1i 1j	<i>i</i> Pr <i>i</i> Pr <i>i</i> Pr <i>t</i> Bu <i>t</i> Bu <i>t</i> Bu <i>t</i> Bu <i>t</i> Bu <i>t</i> Bu	Ph Ph Ph Ph Ph Ph Ph oTol oTol	<i>i</i> Pr Cy Bn Ph Ph <i>p</i> MeO-C ₆ H ₄ <i>p</i> CF ₃ -C ₆ H ₄ <i>p</i> Tol Ph Bn	> 99 > 99 82 > 99 > 99 > 99 > 99 97 > 99 87	5 rac 52 76 72 75 73 91 67	
Ir-2 ^c	<i>t</i> Bu	<i>o</i> Tol	-	>99	72	

 a Determined by GC. b Determined by HPLC (see ref 2b). c Entry taken from ref 2b.

reversed ($R^3 = Bn$, 90% ee; $R^3 = Ph$, 81% ee). With this substrate, the PHOX complex **Ir-2** was less selective than the best imidazoline-derived catalyst **1j** (81 vs 90% ee).

In the hydrogenation of the (*Z*)-alkene **10**, catalyst **1i** with a *N*-phenyl-substituted ligand produced the highest enantiomeric excess (88%), whereas the *N*-benzyl analogue gave a somewhat lower selectivity of 83% ee (Table 3). The PHOX-derived catalyst **Ir-2** was significantly less selective in this case.

Essentially the same selectivity order between catalysts **1a**-**j** was observed for the hydrogenation of dihydronaphthalene derivative **11** (Table 4).

Again, PHIM complex **1i** was the most selective catalyst, outperforming the Ir–PHOX complex **Ir-2** (91 vs 72% ee).

Table 5. Hydrogenation of 2-(4-Methoxyphenyl)-1-butene							
$MeO \begin{array}{c} 1 \text{ mol\% 1a-j} \\ 1 \text{ bar H}_2 \\ CH_2CI_2, 30 \text{ min} \end{array} \begin{array}{c} MeO \end{array} \begin{array}{c} MeO \end{array}$						5	
catalyst	\mathbb{R}^1	\mathbb{R}^2	\mathbb{R}^3	$T(^{\circ}C)$	conversion ^a (%)	ee ^b (%)	
1e	<i>t</i> Bu	Ph	Ph	25	>99	50	
1e	<i>t</i> Bu	Ph	Ph	0	48	47	
1f	<i>t</i> Bu	Ph	pMeO-C ₆ H ₄	25	>99	52	
1f	<i>t</i> Bu	Ph	pMeO-C ₆ H ₄	0	65	50	
1g	<i>t</i> Bu	Ph	pCF ₃ -C ₆ H ₄	25	>99	54	
1g	<i>t</i> Bu	Ph	$pCF_3-C_6H_4$	0	>99	44	
1h	<i>t</i> Bu	Ph	pTol	25	>99	53	
1i	<i>t</i> Bu	<i>o</i> Tol	Ph	25	42	54	
1i	<i>t</i> Bu	<i>o</i> Tol	Ph	0	4	18	
1j	<i>t</i> Bu	<i>o</i> Tol	Bn	25	74	52	
1j	<i>t</i> Bu	<i>o</i> Tol	Bn	0	13	24	
Ir-2 ^c	<i>t</i> Bu	<i>o</i> Tol	_	25	>99	60	

 a Determined by GC. b Determined by HPLC (see ref 2b). c Entry taken from ref 5.

As previously observed⁴ in the hydrogenation of the terminal alkene **12**, the best enantioselectivities were obtained at ambient pressure (Table 5). In this case, the ee values were somewhat lower than with the Ir-PHOX catalyst **Ir-2**. Lowering the temperature to 0 °C resulted in slower reaction rates and inferior enantioselectivities, especially in the case of catalysts **1i** and **1j**.

The results obtained with phosphino-imidazoline ligands **5** are encouraging. In several cases, the enantioselectivities were higher than with phosphino-oxazolines **2**. As iridium complexes of phosphinite-oxazolines **4** have often proven to be superior to PHOX-derived catalysts,⁴ we plan to synthesize analogous phosphinite-imidazolines and evaluate the corresponding iridium complexes as catalysts. Moreover, in view of the wide range of applications found for PHOX

ligands 2,¹ further studies of phosphino-imidazoline ligands 5 seem to be worthwhile.

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Supporting Information Available: Experimental procedures, analytical data for all new compounds, and X-ray data for **1i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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