Asymmetric Catalysis

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Proline-Based P,O Ligand/Iridium Complexes as Highly Selective Catalysts: Asymmetric Hydrogenation of Trisubstituted Alkenes**

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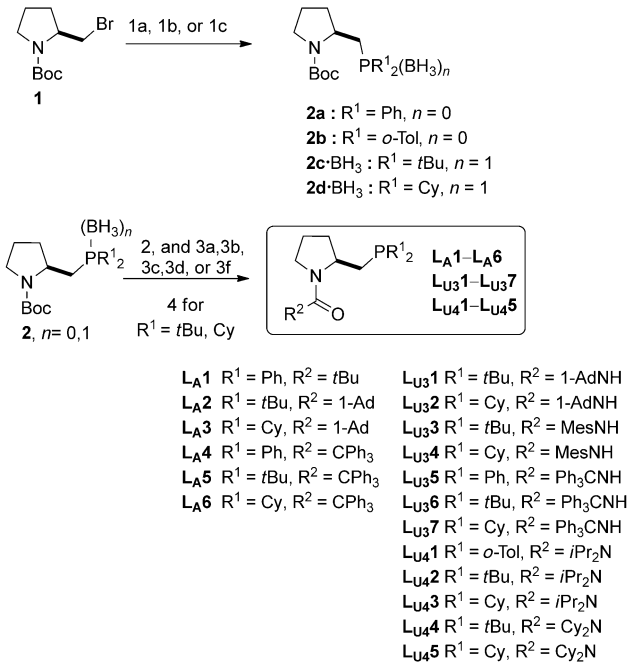
Heteroatom-based bidentate ligands are ubiquitous in the field of asymmetric catalysis. However, only a few ligands that coordinate to a transition metal through a carbonyl oxygen atom have been reported. Tomioka and co-workers have extensively studied the chiral amidophosphine $\mathbf{L_A1}$ (see Scheme 1 for structure) in combination with rhodium or copper in the asymmetric Michael addition of a variety of organometallic reagents to α,β-unsaturated carbonyl compounds with moderate to excellent enantioselectivities.[1–4] In the coordination to rhodium(I), this P,O ligand was shown to behave as a hemilabile ligand, in which the amide carbonyl group is weakly bound to the transition metal.[1] More recently Reek et al. have published on a rhodium-based phosphine urea P,O-ligand system which gives moderate enantioselectivity in asymmetric hydrogenation.[5,6]

Iridium complexes with chiral N,P ligands have emerged as highly efficient catalysts for the asymmetric hydrogenation of olefins.[7–24] In contrast to rhodium and ruthenium diphosphine catalysts, they do not require a coordinating group near the C=C bond and, therefore, can be applied to a wide range of functionalized and unfunctionalized olefins. However, there are still important substrate classes that give unsatisfactory results with known catalysts. Therefore, the search for new ligands that could fill these methodological gaps continues.

In a broad automated screening of various metal/ligand combinations, an iridium complex formed in situ from the ligand $\mathbf{L_A1}$ and $[Ir(cod)]_2BAr_F$ (cod = 1,5-cyclooctadiene; BAr_F = tetrakis[bis-3,5-(trifluoromethyl)phenyl]borate) gave promising enantioselectivities of up to 68% *ee* in the hydrogenation of (*E*)-1,2-diphenylprop-1-ene. This result was unexpected considering the assumed lability of the Ir–O bond. The ready accessibility and the modular nature of the ligand $\mathbf{L_A1}$ prompted us to synthesize a diverse library of proline-derived P,O ligands by systematic variation of the substituents on the P and N atoms to evaluate their potential in the iridium-catalyzed asymmetric hydrogenation (Scheme 1).

As described by Tomioka and co-workers, a linear approach was used to synthesize these P,O ligands with introduction of the phosphine moiety prior to the substituents at the N atom (Scheme 1).[4a–d] Starting from (*S*)-*tert*-butyl-2-(bromomethyl)pyrrolidine-1-carboxylate (**1**) precursors **2** were obtained by nucleophilic substitution with various metallated phosphines.[25] After removal of the N-Boc protecting group, the free amine was reacted with acetyl chlorides, isocyanates, or carbamoyl chlorides, allowing access to a variety of P,O ligands. The introduction of the N substituents generally proceeded in high yield for both, amides (43–98%) and ureas (61–93%). Oxygen-sensitive compounds such as di-*tert*-butyl- or dicyclohexylphosphines were protected as borane adducts to avoid oxidation.



Scheme 1. Synthesis of the L-proline-based P,O ligands. 1a) $KPPh_2$, THF for R^1 = Ph, n = 0; 1b) *o*-Tol_2PCl, Na, THF for R^1 = *o*-Tol, n = 0; 1c) $R^1{}_2PH{\cdot}BH_3$, *n*BuLi, THF for R^1 = *t*Bu, Cy, n = 1. 2) HCl, 1,4-dioxane. 3a) R^2COCl, NEt_3, CH_2Cl_2 for R^1 = Ph and R^2 = *t*Bu, CPh_3; 3b) R^2COCl, K_2CO_3, CH_2Cl_2 for R^1 = *t*Bu, Cy, and R^2 = 1-Ad, CPh_3; 3c) Ph_3CNCO, NEt_3, CH_2Cl_2 for R^1 = Ph and R^2 = CPh_3; 3d) R^2NCO, K_2CO_3, CH_2Cl_2 for R^1 = *t*Bu, Cy and R^2 = 1-AdNH, MesNH, Ph_3CNH; 3e) iPr_2NCOCl, NEt_3 for R^1 = *o*-Tol and R^2 = iPr_2N; 3f) $R^2{}_2NCOCl$, K_2CO_3, CH_2Cl_2 for R^1 = *t*Bu, Cy and R^2 = iPr_2N, Cy_2N. 4) Et_2NH. Ad = adamantyl, Boc = *tert*-butoxycarbonyl, Cy = cyclohexyl, Mes = 2,4,6-trimethylphenyl, THF = tetrahydrofuran.

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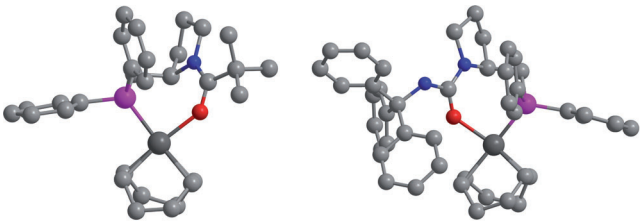
Crystals suitable for X-ray diffraction analysis of the iridium/amidophosphine $\mathbf{L_A1}$ and iridium/ureaphosphine $\mathbf{L_{U3}5}$ complexes were obtained to determine the coordination mode of this new ligand class (Figure 1).[26] The solid-state structures clearly indicate coordination of the P,O ligands in a bidentate fashion to the metal center with both donors bonding in a σ fashion, which is consistent with the rhodium amidophosphine complex reported previously.[1]

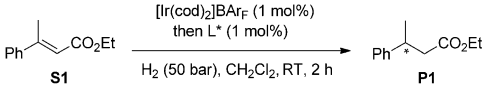


[(*R*) – (**L$_A$1**) Ir(cod)] BAr_F [(*S*) – (**L$_{U3}$5**) Ir(cod)] PF_6

Figure 1. Crystal structures of complex [(*R*)-(**L$_A$1**)Ir(cod)]BAr_F and [(*S*)-(**L$_{U3}$5**)Ir(cod)]PF_6; the counterions have been omitted for clarity. Red O, blue N, magenta P, dark gray Ir, light gray C.

The library of P,O ligands was evaluated in the iridium-catalyzed asymmetric hydrogenation of various prochiral trisubstituted unfunctionalized and functionalized alkenes by an in situ protocol for a rapid assessment of the selectivity/reactivity profile. The precatalyst was generated through complexation of $[Ir(cod)_2]BAr_F$ and the respective P,O ligand in dichloromethane with subsequent addition of the stock solution to the substrate. Preliminary investigations were conducted with **S1** as an initial screen (Table 1 and Table 2). We were pleased to find that these P,O ligands showed high activity and selectivity in the test reactions. Excellent conversions and enantiomeric excesses of up to 98% were obtained when amidophosphines were employed (Table 1, entries 1–6). We observed that very sterically demanding substituents attached to the carbonyl group led to significantly higher selectivities in combination with the stronger electron-donating dialkyl phosphines. Carbamates **2a–d** gave only low to moderate enantioselectivities (Table 1, entries 7–10).

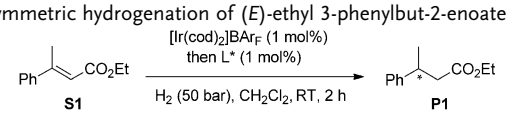
Table 1: Screening of the amide- and carbamate-based ligands $\mathbf{L_A1}$–$\mathbf{L_A6}$ and **2a–d** in the asymmetric hydrogenation of (*E*)-ethyl 3-phenylbut-2-enoate (**S1**).[a]



Entry	L*	R^1	R^2	Yield [%][b]	*ee* [%][c]
1	(*S*)-$\mathbf{L_A1}$	Ph	*t*Bu	65	33 (*R*)
2	(*S*)-$\mathbf{L_A2}$	*t*Bu	1-Ad	>99	50 (*R*)
3	(*S*)-$\mathbf{L_A3}$	Cy	1-Ad	98	26 (*R*)
4	(*S*)-$\mathbf{L_A4}$	Ph	CPh_3	88	89 (*R*)
5	(*S*)-$\mathbf{L_A5}$	*t*Bu	CPh_3	>99	98 (*R*)
6	(*S*)-$\mathbf{L_A6}$	Cy	CPh_3	>99	94 (*R*)
7	(*S*)-**2a**	Ph	O*t*Bu	74	42 (*R*)
8	(*S*)-**2b**	*o*-Tol	O*t*Bu	99	9 (*R*)
9	(*S*)-**2c**	*t*Bu	O*t*Bu	80	78 (*R*)
10	(*S*)-**2d**	Cy	O*t*Bu	99	75 (*R*)

[a] Reaction conditions: $[Ir(cod)_2BAr_F]$ (2.50 μmol), ligand (2.50 μmol), CH_2Cl_2 (0.5 mL), substrate (250 μmol). [b] Yields were determined by GC analysis. [c] Enantioselectivities were determined by GC analysis using a chiral stationary phase.

Table 2: Screening of the urea-based ligands $\mathbf{L_{U3}1}$–$\mathbf{L_{U3}7}$ and $\mathbf{L_{U4}1}$–$\mathbf{L_{U4}5}$ in the asymmetric hydrogenation of (*E*)-ethyl 3-phenylbut-2-enoate (**S1**).[a]



Entry	L*	R^1	R^2	Yield [%][b]	*ee* [%][c]
1	(*S*)-$\mathbf{L_{U3}1}$	*t*Bu	1-AdNH	>99	92 (*R*)
2	(*S*)-$\mathbf{L_{U3}2}$	Cy	1-AdNH	>99	93 (*R*)
3	(*S*)-$\mathbf{L_{U3}3}$	*t*Bu	MesNH	>99	88 (*R*)
4	(*S*)-$\mathbf{L_{U3}4}$	Cy	MesNH	>99	90 (*R*)
5	(*S*)-$\mathbf{L_{U3}5}$	Ph	Ph_3CNH	99	92 (*R*)
6	(*S*)-$\mathbf{L_{U3}6}$	*t*Bu	Ph_3CNH	98	94 (*R*)
7	(*S*)-$\mathbf{L_{U3}7}$	Cy	Ph_3CNH	>99	98 (*R*)
8	(*S*)-$\mathbf{L_{U4}1}$	*o*-Tol	iPr_2N	>99	44 (*R*)
9	(*S*)-$\mathbf{L_{U4}2}$	*t*Bu	iPr_2N	>99	97 (*R*)
10	(*S*)-$\mathbf{L_{U4}3}$	Cy	iPr_2N	>99	90 (*R*)
11	(*S*)-$\mathbf{L_{U4}4}$	*t*Bu	Cy_2N	>99	99 (*R*)
12	(*S*)-$\mathbf{L_{U4}5}$	Cy	Cy_2N	>99	97 (*R*)

[a] Reaction conditions: See Table 1.

The urea-based P,O ligands also gave high enantioselectivities of up to 99% *ee* (Table 2, entry 11) under identical screening conditions. Again, very bulky substituents attached to the carbonyl function were essential for obtaining high levels of enantioselectivity. Electron-rich alkyl-substituted phosphines consistently demonstrated higher enantioselectivities than the corresponding diarylphosphines. In some cases dicyclohexylphosphines were superior to di-*tert*-butylphosphine analogues, possibly as a result of steric overcrowding at the metal center (Table 2, entries 1–4, 6,7). *Ortho*-tolyl-substituted phosphines generally induced drastically lower enantioselectivities (Table 2, entry 8).

To compare our P,O ligand complexes with the state-of-the-art iridium catalysts, we carried out a broad screening including some demanding substrates for which efficient catalysts are still lacking (Figure 2; for a comprehensive compilation of the results, see the Supporting Information). Alkenes bearing carbonyl or hydroxy groups seemed of special interest, because Lewis basic substituents of this type could severely affect the performance of the catalyst by replacing the coordinating carbonyl group of the P,O ligand.

The proline-based P,O catalysts gave excellent selectivities with the much studied (*E*)-α-methylstillbene (**S2**), with many of the better ligands giving results equal to the best N,P systems. However, the more strongly coordinating allylic alcohol **S2** was reduced with much lower selectivity with these catalysts in general, albeit with full conversion.

Conjugate reduction of α,β-unsaturated ketones and esters appears to be a particularly well-suited area of application for these catalysts with both classes of alkenes giving high *ee* values. Substrates **S4a**, **S4b**, and **S6** were recently reduced in record levels of selectivity in this

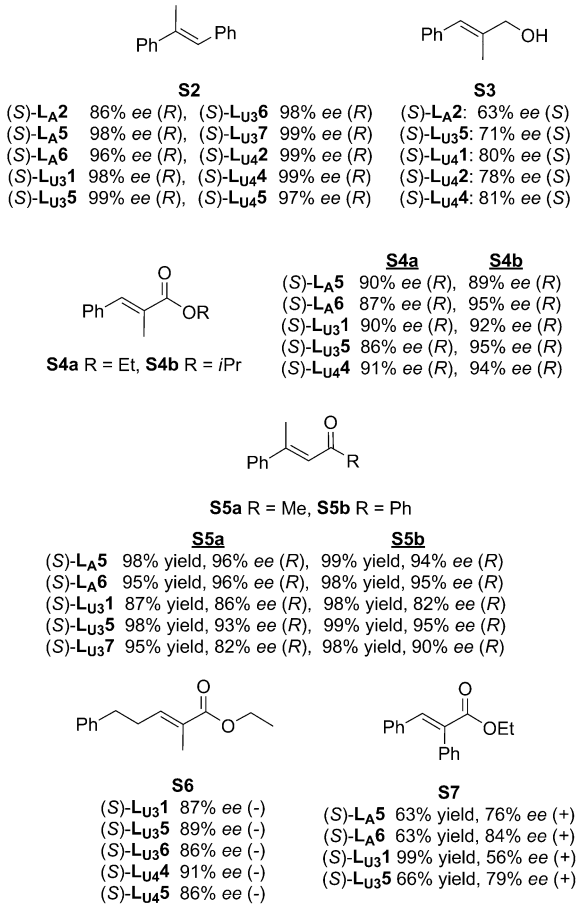


Figure 2. Selected hydrogenation results; see the Supporting Information for reaction conditions.

laboratory with pyridyl phosphinite based catalysts.[13] The easily prepared proline-based P,O ligands give comparable results to these systems but with the added advantage of using inexpensive starting materials from the chiral pool for the ligand syntheses. The very challenging α-aryl ester **S7** was reduced in moderate yield and good selectivity. Perhaps more impressive is the level of enantioselectivity obtained with methyl ketone **S5a**, which was reduced by using several catalysts, with selectivities much higher than previously reported for the N,P based systems.[20c] Conversion in the hydrogenation of **S5a** was always complete, but sometimes accompanied, as reported, by the reduction to the saturated alcohol in variable and uncontrolled amounts.[20c] To overcome this issue, the reaction was carried out with a catalyst that was isolated instead of using the in situ complexation method (see the Supporting Information). By using this procedure essentially no overreduction was observed. The corresponding phenyl ketone **S5b** gave similar results to that of the methyl ketone **S5a**.

Although experimental structural information about the catalytic cycle is still lacking, computational studies of Ir/N,P ligand and Ir/C,N ligand catalysts suggest that the enantiodiscrimination occurs during the migratory insertion step.[7,19a–c,21–24] In an Ir/phox complex the olefin is proposed to coordinate trans to the P atom as shown in Figure 3. The

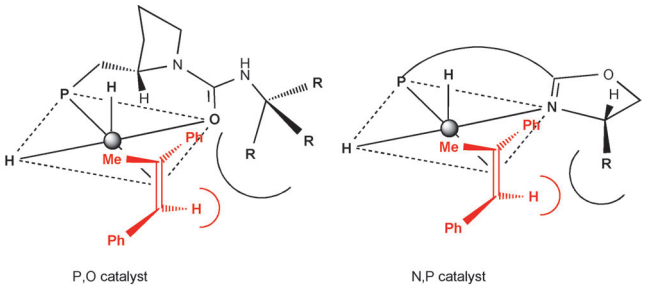


Figure 3. Qualitative model rationalizing the enantioselectivity of Ir/N,P ligand and Ir/P,O ligand catalysts.

major enantiomer is formed via an intermediate in which the small H atom is pointing toward the large substituent at the stereogenic center of the oxazoline ring, thus minimizing the steric repulsion between the chiral ligand and the substrate. Assuming an analogous coordination mode for P,O complexes, a sterically similar situation results if we infer a ligand conformation based on the crystal structures shown in Figure 1. The large substituents of the amide or urea group occupy the same region in space as the substituent in the oxazoline ring of a phox ligand. This qualitative model explains why rather bulky amide or urea groups are necessary for high enantioselectivity and rationalizes the sense of asymmetric induction.

Our results show that proline-derived phosphines bearing bulky amide or urea groups at the pyrrolidine N atom form efficient Ir catalysts for the asymmetric hydrogenation of olefins. These new P,O ligands give high enantioselectivities with several classes of alkenes, most notably with α,β-unsaturated carboxylic esters and ketones, where they match or even surpass the *ee* values reported for the best N,P and C,N ligands. The ligands are readily prepared in enantiomerically pure form starting from inexpensive chiral precursors. Their modular nature easily allows structural tuning by variation of the coordinating P and O units. We are currently exploring further applications of these ligands including other metal-catalyzed reactions.

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