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Synthesis of a New Class of Conformationally Rigid Phosphino-oxazolines: Highly Enantioselective Ligands for Ir-Catalyzed Asymmetric Hydrogenation

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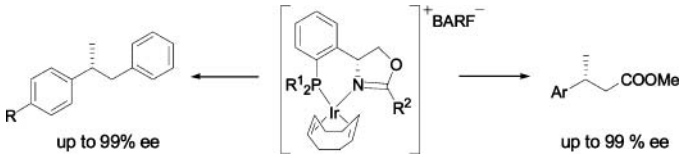
ABSTRACT



A new class of conformationally rigid phosphino-oxazoline ligands were synthesized from readily available enantiopure phenyl glycinol. Ir complexes with these ligands are air-stable and highly enantioselective catalysts for asymmetric hydrogenation of aryl alkenes and α,β-unsaturated esters in up to 99% ee.

Among the most commonly used transition metal catalysts for asymmetric hydrogenation, Ir-based systems are relatively underdeveloped compared to Rh- or Ru-based systems.[1] One well-known Ir complex is the Crabtree catalyst,[2] which is highly efficient for hydrogenation of unfunctionalized polysubstituted olefins, a type of substrate remaining difficult to reduce with Rh or Ru catalysts.[3] The high reactivity of the Crabtree catalyst was attributed to its unique structure containing a phosphorus donor and a nitrogen donor. Pfaltz et al. used optically active phosphino-oxazoline ligands **1** (PHOX) (Figure 1) to mimic a chiral version of the Crabtree catalyst and obtained up to 99% enantiomeric excesses for some functionalized and unfunctionalized olefins.[4] Following this discovery, a number of chiral P,N-containing ligands emerged and were successfully applied to the Ir-catalyzed asymmetric hydrogenation of olefins.[5] Burgess also reported asymmetric hydrogenation of aryl alkenes with novel chiral carbene-oxazoline ligands.[6] However, most of these catalysts suffered from high substrate dependence and relatively low TON (few exceeded 1000). Thus, the development of new efficient chiral ligands for Ir-catalyzed hydrogenation is still needed and challenging. Herein, we report a new class of easily accessible chiral phosphino-oxazoline ligands **2** and

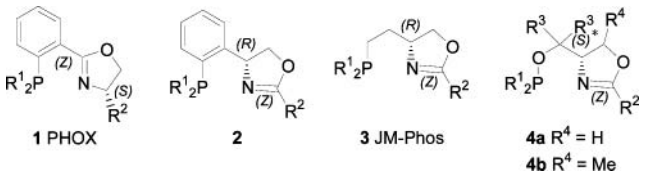


Figure 1. Chiral P,N ligands for asymmetric hydrogenation.

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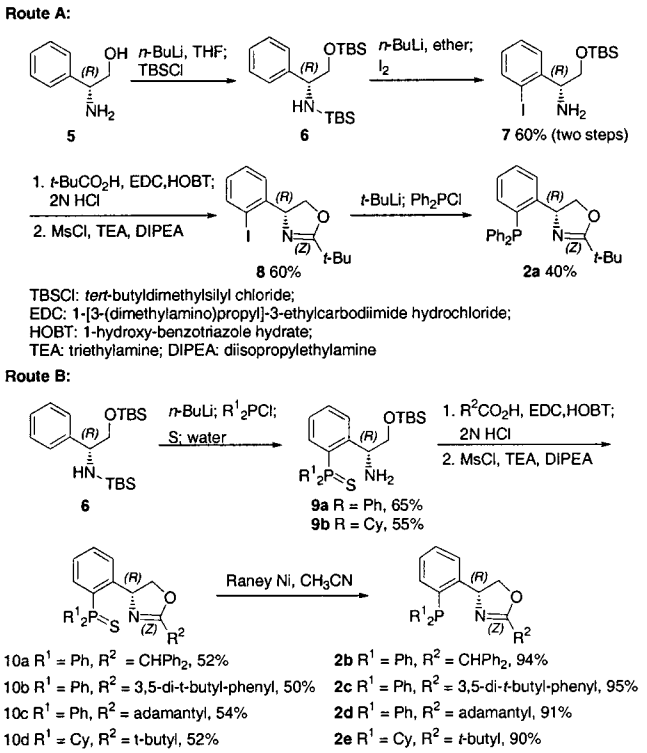
their application to Ir-catalyzed asymmetric hydrogenation. Versatile methods have been developed for making these ligands from the inexpensive phenyl glycinol.

The conformational rigidity of a chiral ligand has been demonstrated to be an important factor for high enantioselectivity in asymmetric catalysis.[7] Bidentate ligands with a more rigid linker between the two coordinating sites can form a more rigid metallocycle with fewer available conformations and thus enhance the enantiofacial differentiation. JM-Phos **3**, reported by Burgess, exhibited very good enantioselectivities in Pd-catalyzed allylic alkylation reactions[8] and Ir-catalyzed hydrogenation of several olefins.[5g] However, the ethylene linker between the phosphine and oxazoline moieties is too flexible to deliver the maximal asymmetric induction from the chiral ligand. In the studies of closely related ligands **4**,[9] Pfaltz found that both diastereomers of **4b** induced significantly higher enantioselectivities than ligands **4a** for a number of hydrogenation substrates. One possible explanation for such an observation is that the additional substituent (R^4 = Me) on the oxazoline ring restricts the conformational flexibility of the five-membered ring and improves the overall enantiofacial differentiation of the chiral catalyst. On the basis of these considerations, we envision that ligands **2** might be superior to JM-Phos due to their more rigid 1,2-phenyl linker. Furthermore, X-ray studies have shown that Ir complexes with **3**[5g] and **4**[9b] have significantly different chiral environments from those in Ir complexes with PHOX **1**. Since ligands **2** are structurally closer to PHOX than **3** and **4**, they would provide a more direct comparison with PHOX in their catalytic behavior.

The inexpensive enantiopure phenyl glycinol is widely used as a building block in chiral ligand synthesis.[5,10] However, ortho-substituted phenyl glycinol derivatives are rarely used due to the lack of efficient synthesis.[11] One of the most direct ways to make ligands **2** would be based on ortho substitution of phenyl glycinol. Thus, developing an efficient method of ortho substitution of phenyl glycinol was needed. Although the α-*N*,*N*-dimethyl amino group is commonly used as an ortho directing group for metalation of aromatic rings,[12] direct use of primary amines for such a purpose was much less explored and not used to construct chiral ligands.[13] Polniaszek et al. prepared (2-chloro- or 2,6-dichlorophenyl)ethylamine from phenylethylamine via ortho lithiation directed by the in situ-generated *N*-lithiosilylamine.[14] After modification of their method, we successfully carried out, for the first time, an ortho lithiation of silyl-protected phenyl glycinol. Subsequent reaction with I_2 or different phosphine chlorides efficiently gave rise to (2-iodo or 2-phosphino)phenyl glycinol derivatives, which are novel and highly modular chiral synthons for ligand synthesis. On the basis of this method, two slightly different routes were developed for making ligands **2** (Scheme 1). In route A, (*R*)-phenyl glycinol **5** was protected with TBSCl to give intermediate **6**, which was directly subjected to ortho lithiation with 3 equiv of *n*-BuLi. Subsequent iodination followed by aqueous workup afforded aryl iodide **7**. Oxazoline formation using literature methods[4] gave the key intermediate **8**. Lithium−halogen exchange of **8** with *t*-BuLi followed by reaction with Ph_2PCl afforded the desired ligand **2a**. Presumably, variation of the phosphine chloride in the

Scheme 1



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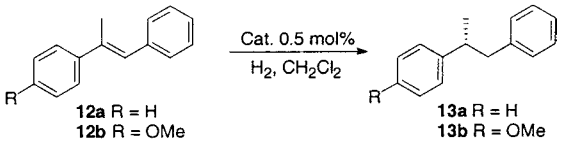
last step would allow a facile tuning of the phosphine site. In route B, a phosphine chloride, instead of I_2, was used as the electrophile after the ortho lithiation step. Subsequent protection of the phosphine with sulfur followed by aqueous workup generated phosphine sulfide **9**, which could be converted into a series of oxazolines **10** with various R^2 substituents by reaction with essentially unlimited carboxylic acids. Reduction of **10** with Raney Ni[15] afforded ligands **2b**−**e**. The combination of both routes provided convenient ways of tuning on either the phosphine site or the oxazoline site from intermediates **8** or **9**. This is useful when building a ligand set to search for the best one for a particular reaction or substrate.

To evaluate the catalytic properties of ligands **2** in asymmetric catalysis, their Ir complexes **11** were prepared according to a literature procedure, in which a weakly coordinating group BARF (tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate) was used as the counterion. These complexes are air-stable and can be stored in air for months without losing their catalytic properties. Methylstilbene **12a**, a typical substrate for Ir-catalyzed asymmetric hydrogenation of unfunctionallized olefins, was initially tested with complexes **11a**−**e** under 50 bar of H_2 pressure at room temperature in CH_2Cl_2. As shown in Table 1, all the catalysts gave excellent

Table 1. Asymmetric Hydrogenation of Methylstilbene Derivatives with **11**[a]



entry	substrate	catalyst	H_2 pressure	temp	conversion [%][b]	ee [%][c]
1	**12a**	**11a**	10 bar	rt	31	98
2	**12a**	**11a**	50 bar	rt	64	98
3	**12a**	**11a**	90 bar	rt	94	97
4	**12a**	**11a**	50 bar	50 °C	98	98
5	**12a**	**11b**	50 bar	rt	77	83
6	**12a**	**11c**	50 bar	rt	68	97
7	**12a**	**11d**	50 bar	rt	98	97
8	**12a**	**11e**	50 bar	rt	>99	99
9	**12a**	**11e**	100 bar	rt	>99	98
10	**12b**	**11a**	100 bar	rt	>99	97
11	**12b**	**11d**	100 bar	rt	>99	97
12	**12b**	**11e**	100 bar	rt	>99	90

[a] See Supporting Information for experimental details. [b] Conversions were determined by GC. [c] Enantiomeric excesses were determined by chiral HPLC (Chiralcel OJ-H), and the absolute configuration was assigned by comparison of the retention times of two enantiomers with reported data.

enantioselectivity (97−99% ee), except for **11b** (83% ee). Although the conversions were not satisfactory with **11a**, **11b**, and **11c**, high conversions were obtained with **11d** and **11e** (entries 7 and 8). Pressure and temperature effects were examined with **11a** on the same substrate (entries 1−4). Increasing the H_2 pressure dramatically improved the conversion, while the enantioselectivity did not change significantly. Performing the reaction at an elevated temperature also resulted in a great increase in conversion. Pfaltz et al. reported that the formation of inactive hydride-bridged Ir trimers during the catalytic cycle might be one of the major reasons for the deactivation of catalyst and isolated a trimeric Ir(PHOX)−hydride complex after treating the corresponding Ir complex with H_2 (Figure 2).[5a] On the basis of this

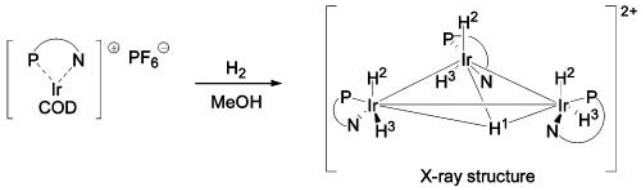
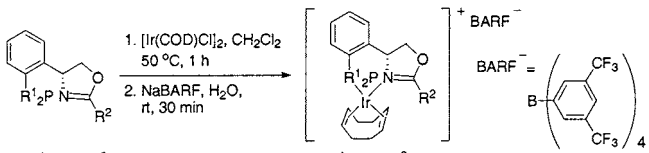


Figure 2. Formation of a hydride-bridged Ir trimer

hypothesis and our observations, we suppose the following: (1) a relatively larger R^2 substituent on the oxazoline ring might be beneficial not only for the enantioselectivity but also for the reactivity; (2) more electron-donating ligands might form more reactive catalyst or more stable catalytic species by preventing the formation of the hydride-bridged Ir trimer, presumably through a trans effect; (3) increasing the H_2 pressure might accelerate the desired catalytic cycle relative to the formation of the Ir trimer; (4) a higher reaction temperature might either accelerate the desired catalytic cycle or possibly decelerate the formation of the Ir trimer. These hypotheses can give us some guidance for further ligand modification and optimization of reaction conditions for a particular substrate, though more experimental data and detailed mechanistic studies are needed. Another methylstilbene derivative **12b** was then examined with a few of the best catalysts (**11a**, **11d**, and **11e**). Complete conversions and very high enantioselectivities were obtained with **11a** and **11d** (entries 10 and 11), while **11e**, the most reactive catalyst, gave a slightly lower selectivity (entry 12). Thus, the overall results for asymmetric hydrogenation of biaryl alkenes with ligands **2** compare favorably with those obtained with JM-Phos **3** (95% ee for **12a** and 93% ee for **12b**).[5g]

Scheme 2



2a R^1 = Ph, R^2 = *t*-butyl
2b R^1 = Ph, R^2 = $CHPh_2$
2c R^1 = Ph, R^2 = 3,5-di-*t*-butyl-phenyl
2d R^1 = Ph, R^2 = Adamantyl
2e R^1 = Cy, R^2 = *t*-butyl

11a R^1 = Ph, R^2 = *t*-butyl, 52%
11b R^1 = Ph, R^2 = $CHPh_2$, 50%
11c R^1 = Ph, R^2 = 3,5-di-*t*-butyl-phenyl, 63%
11d R^1 = Ph, R^2 = Adamantyl, 57%
11e R^1 = Cy, R^2 = *t*-butyl, 58%

Asymmetric hydrogenation of *β*-methyl cinnamic esters, followed by reduction of the ester function, can efficiently

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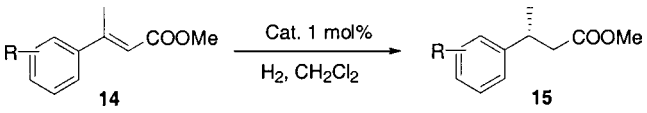
Table 2. Asymmetric Hydrogenation of β-Methylcinnamic Esters with **11**[a]



14 **15**

entry	substrate	catalyst	H_2 pressure	temp	conversion [%][b]	ee [%][c]
1	**14a** R = H	**11a**	100 bar	rt	>99	98
2	**14a** R = H	**11d**	100 bar	rt	>99	99
3	**14a** R = H	**11e**	100 bar	rt	>99	91
4	**14b** R = *p*-F	**11a**	100 bar	rt	32	89
5	**14b** R = *p*-F	**11d**	100 bar	rt	58	91
6	**14b** R = *p*-F	**11e**	100 bar	rt	94	85
7	**14b** R = *p*-F	**11d**	100 bar	50 °C	90	96
8	**14a** R = H	**11d**	100 bar	50 °C	>99	99
9	**14c** R = *p*-Cl	**11d**	100 bar	50 °C	87	98
10	**14d** R = *p*-CH_3	**11d**	100 bar	50 °C	>99	98
11	**14e** R = *m*-CH_3	**11d**	100 bar	50 °C	>99	99
12	**14f** R = *p*-OCH_3	**11d**	100 bar	50 °C	96	94
13	**14g** R = *p*-OCF_3	**11d**	100 bar	50 °C	84	95

[a] See Supporting Information for experimental details. [b] Conversions were determined by GC. [c] Enantiomeric excesses were determined by chiral HPLC (Chiralcel OJ-H) or chiral GC (Chiralselect 1000). Absolute configuration was assigned by comparison of the retention times of two enantiomers with reported data.

form chiral 3-arylbutanols, which are important intermediates for the synthesis of aromatic sesquiterpenes of the bisabolane family.[16] Few systems have been reported to be highly selective for this type of substrate.[5a,e] We were certainly interested in examining these important hydrogenation substrates with the air-stable catalysts **11**. Methyl-(*E*)-β-methyl cinnamate **14a** was initially selected as the substrate to screen ligands and reaction conditions. Complete conversions and extremely high enantioselectivities were observed with complexes **11a** and **11d** under 100 bar at room temperature (entries 1−3). The ee values are significantly higher than with PHOX as a ligand (84% ee). However, when substrate **14b** having a *para*-fluoro substituent on the phenyl ring was subjected to hydrogenation, the conversion was not complete even at elevated temperature. The highest enantioselectivity and conversion for **14b** were obtained with **11d** at 50 °C under 100 bar (entry 7). We therefore used **11d** as a catalyst and these optimized conditions for hydrogenation of several other aryl-(*E*)-β-methylcinnamic esters **14c**−**g**. Excellent ee values (94−99%) were obtained regardless of the substitution pattern on the phenyl ring, which were comparable to the best reported to date.[5a,e] The reactivities seemed quite substrate dependent. However, no obvious trend could be observed.

In conclusion, we have developed a novel and efficient synthesis of ortho-substituted phenyl glycinol, which has led to a new class of conformationally rigid phosphino-oxazoline ligands. Their catalytic potential has been demonstrated in the highly enantioselective Ir-catalyzed hydrogenation of olefins. Further modification of the ligands and more applications of this new class of ligands in asymmetric catalysis are in progress.

Acknowledgment. This work was supported by the National Institutes of Health.

Supporting Information Available: Experimental details and spectroscopic data for all the new compounds and a general hydrogenation procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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