

Asymmetric Hydrogenation of Trisubstituted Olefins with Iridium–Phosphine Thiazole Complexes: A Further Investigation of the Ligand Structure

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Abstract: New chiral bidentate phoshine thiazoles have been prepared and successfully applied as ligands in the homogeneous iridium-catalyzed asymmetric hydrogenation of aryl alkenes and aryl alkene esters. The ligands are designed to be highly modular and have one common chiral intermediate, from which diversity can be introduced at a late stage in the synthetic pathway. It was found that a six-member-ring backbone of the rigid ligand structure was preferred over seven- or five-member rings. In this study it is shown that the substituent pattern of the ligands has a major influence on the stereochemical outcome of the products. By applying the selectivity model proposed in this study, it is possible to match different substrates against different catalysts. In this way, good to excellent enantioselectivity can be obtained for typically difficult substrates. Geometrically different derivatives of α - and β -methyl cinnamic acid ethyl esters were hydrogenated, to demonstrate the validity of the selectivity model and to verify the importance of steric and electronic matching of the catalyst and the substrate.

Introduction

Enantioselective hydrogenation is one of the most powerful methods in asymmetric catalysis.1 While ruthenium- and rhodium-catalyzed asymmetric hydrogenations of chelating olefins have a long history,² unfunctionalized olefins still represent a challenging class of substrates. Early work in this field has mainly focused on chiral metallocene complexes.^{3a-e} During the past few years, Pfaltz and co-workers have successfully developed and used phoshine and phosphinite oxazoline Ir complexes for the asymmetric hydrogenation of weakly coordinating olefins⁴ and imines,⁵ subsequently followed by others.^{6a-j} Recently there have been more structural variations in ligand design such as the oxazoline carbene ligand structure of Burgess and co-workers and the use of a non-carbon chiral sulfoxide phosphine ligand reported by Ellman.^{7,8} However,

iridium-catalyzed asymmetric hydrogenation is still highly substrate dependent and the development of efficient chiral ligands that tolerate a broader range of substrates remains a challenge. Pfaltz has developed his original ligand structure to obtain better enantioselectiveties with a broader range of substrates.9a-i

In this publication, we report a new class of iridium phosphine thiazole complexes, which are highly enantioselective for a wide range of substrates. Recently, a number of papers have appeared in the literature dealing with the mechanism of the Ir-catalyzed asymmetric hydrogenation of aryl alkenes.^{10–12} Since little is known about the mechanism or the enantioselectivity determin-

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Figure 1. Calculated complex structures, from left (a) oxazole complex and then thiazole complexes with (b) five-, (c) six-, and (d) seven-membered cyclic backbones.15

ing factors of asymmetric iridium-catalyzed hydrogenations, our group recently undertook a computational and kinetic study of the hydrogenation of (E)-1,2-diphenyl-1-propene with Pfaltz iridium-PHOX complex.12 Encouraged by the results from our previous studies, we became interested in further investigating the structure selectivity relationship of these systems. We therefore decided to develop a new set of ligands that relies on the same ligand principle that we previously have reported.¹³ These new ligands are highly modular and allow for the late stage diversity of the ligand. The variations in the ligands can be used to study how structural changes influences the enantioselectivity of the hydrogenation. Moreover the selectivity model derived in this study can be used to rationalize the results. The preparation of thiazoles is much more expedient than oxazoles, and introduction of a halogen at the 2-position allows for more structural variation in the ligand structure.¹⁴ It was

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Scheme 1. Going from Oxazole to Thiazole Increasing both Ligand Stability and Late Stage Diversification of the Structure



also desirable to change the labile P-O bond into the more stable P-CH₂ bond and thereby gain a more stable ligand structure compared to the previously reported oxazole ligand structure (Scheme 1).¹³

Results and Discussion

To systematically vary the critical selectivity governing factors of the ligand structure, we started to evaluate the importance of the cyclic backbone by calculating the distance between the *ipso*-carbon of the substituent in the 2-position on the heterocycle and the chelated Ir atom. This was done for five-, six-, and seven-membered cyclic backbones of the ligand structure and the previously reported oxazole structure (Figure 1).¹³ The calculated structures showed a large difference between

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Table 1. Comparison between Catalysts 1-3 and the Corresponding Oxazole Complex 413



^{*a*} Conditions: P = 10 bar (entry 1) and 50 bar (entries 2–6); all reactions performed at room temperature overnight; catalyst loading 0.5 mol % in all entries. All reactions were performed in freshly distilled (CaH₂, ethanol free) CH₂Cl₂ as 0.25 M solutions. ^b Reaction time 2 h.

the five- and six-membered ring size and a smaller difference between the six- and seven-membered rings suggesting that altering the ring size of the backbone may have a major impact on the stereochemical outcome. It is also favorable to change the oxygen atom to a sulfur atom in the heterocyclic backbone since this results in a shorter distance between the *ipso*-carbon and the Ir atom, resulting in a more congested complex.

To investigate any differences among the five-, six-, and seven-membered cyclic backbones, the ligands were synthesized and the corresponding Ir complexes evaluated in the hydrogenation of olefins.

Reterosynthetic analysis suggested that bromination in the least substituted position of cyclic β -keto esters, followed by Hantzsch condensation with thiobenzamide, should result in the desired thiazoles.¹⁶ Reduction of the ester functionality followed by preparative chiral chromatography should give chiral alcohols, suitable for conversion into phosphinothiazoles (Scheme 2).

Synthesis of the five- (1), six- (2), and seven- (3) membered cyclic backbone complexes (Scheme 2) starts with treatment of 5a-c with Br₂, under previously established conditions,¹⁷ followed by a Hantzsch condensation with PhC(S)NH₂ to give the corresponding thiazole esters 6-8. Reduction of 6-8 with LiAlH₄ gave the corresponding racemic alcohols 9-11 in good yields, followed by resolution of racemates 9-11 into their enantiomers by preparative chiral HPLC (Chiracel OD). The resolved alcohols were then converted to their corresponding tosylates 12-14, followed by substitution with Ph₂P(BH₃)Li, and deprotection with Et₂NH gave the free phosphines 18-20, which were subsequently transformed into their corresponding Ir complexes 1-3 according to the standard procedure.⁴

Initial hydrogenation results revealed a difference in selectivities among complexes 1-3, with complex 2 as the overall most Scheme 2. Synthesis of Complexes 1-3^a



^{*a*} Reagents and conditions: (i) Br₂, Et₂O, 0 °C, 3 h; (ii) PhC(S)NH₂, MeOH (**5c**) or EtOH (**5a,b**), 1 h rt, then reflux over night, and then aqueous K₂CO₃; (iii) LiAlH₄, THF, 0 °C to rt, yielding alcohols **9–11**; (iv) preparative HPLC, Chiracel OD; (v) TsCl, pyridine, CH₂Cl₂, 0 °C to rt; (vi) Ph₂P(BH₃)H, BuLi, THF, DMF, -78 °C to rt over 16 h, yielding **15– 17**; (vii) Et₂NH (large excess), 18 h, rt; (viii) [IrCl(COD)]₂, CH₂Cl₂, reflux 30 min and then H₂O, NaBArF·3H₂O, rt, 1 h.

selective catalyst (Table 1). For substrate **21** (entry 1, Table 1) a slight effect on enantioselectivity could be detected at 10 bar, in favor of catalyst **2** over **1** and **3**. However, at 50 bar (entry 2, Table 1) the structural differences between the catalysts do not affect the enantioselectivity for substrate **21**; this was also the case for substrate **22** (entry 3, Table 1). For substrate **23** (entry 4, Table 1), catalyst **2** is superior to **1** and slightly better than **3**. Substrate **24** gave, as expected, close to racemic material and low conversions (entry 5, Table 1), in agreement with the proposed selectivity model (Figure 5).

The results in Table 1 show that a six-membered cyclic backbone is preferable and also the thiazole moiety proved to be much better than the oxazole; therefore, an improved synthetic protocol for the enantiomerically pure six-membered cyclic backbone was developed (Scheme 3).

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^{*a*} Reagents and conditions: (i) Br₂, Et₂O, 0 °C, 3 h, 95%; (ii) thiourea, absolute EtOH, rt (room temperature), 18 h, 94%; (iii) 10% aqueous K₂CO₃, warm (40 °C) CHCl₃, yielding rac-25, quantitative; (iv) (L)-DBTA·H₂O, 80:20 MeCN/H₂O, 37% over two recrystallizations, +99.5% ee of (*S*)-25·DBTA; (v) 10% aqueous K₂CO₃, warm (40 °C) CHCl₃, quantitative; (vi) HBr, CuBr₂, *t*-BuONO, MeCN, 0 °C, 2 h, 78%, +99.5% ee; (vii) 2.2 equiv of DIBAL, THF, -40 °C, 1.5 h, 85%, +99.5% ee; (ix) PhB(OH)₂, DPPF·PdCl₂ (5 mol %), K₂CO₃, toluene/H₂O, 80 °C, 3 h, 87%, +99.5% ee; (xi) CHCl₂, DPPF·PdCl₂ (5 mol %), K₂CO₃, toluene/H₂O, 80 °C, 3 h, 87%, +99.5% ee; (xii) THF, DMF, -78 °C to rt, 16 h, yielding **16** and **30**-**32**; (xii) Et2NH (large excess), 18 h, rt; (xiii) [IrCl(COD)]₂, CH₂Cl₂, reflux 30 min and then H₂O, NaBArF·3H₂O, rt, 1 h.

With the encouraging results from this initial study, the synthesis of second generation ligands is outlined in the following way: bromination of ketoester 5a with Br₂ in Et₂O at 0 °C gave the corresponding 3-bromo derivative in almost quantitative yield. Treatment with thiourea in absolute ethanol at room temperature gave the aminothiazole hydrobromide (rac-25·HBr) in excellent yield.¹⁸ The free base (rac-25) was then resolved as its (L)-dibenzoyltartrate salt, formed by addition of (L)-DBTA·H₂O to rac-25 in a carefully controlled volume of hot 80% aqueous MeCN. The resolution step was optimized in terms of mass yield and enantioselectivity. The reaction conditions yielding 37% of (S)-25-DBTA proved to be the best compromise, producing a crystal crop of 95-98% enantiomeric excess, directly from the racemic mixture. One single recrystallization yielded material of more than 99% enantiomeric excess. The unwanted enantiomer (R)-25, isolated from the mother liquids, can be recycled by racemization employing a catalytic amount of sodium ethoxide in refluxing absolute ethanol. This is according to our knowledge the first example of an optical resolution of a chemical compound by salt formation on a remote aminothiazole moiety. Treatment of (S)- **25**•DBTA with aqueous potassium carbonate gave the enantiopure free base (*S*)-**25**. Converting (*S*)-**25** in situ to its hydrogen bromide salt, followed by diazotation under anhydrous conditions employing *t*-BuONO in acetonitrile with CuBr₂, as halogen source, gave **26** in good yield.¹⁹

Intermediate 26 could then be converted either into bromothiazole alcohol 27 by treatment with 2 equiv of DIBAL at -40 °C or into the debrominated 2-*H*-thiazole derivative **28** by the action of an excess of DIBAL at 0 °C. Compound 27 smoothly underwent Suzuki coupling with PhB(OH)₂ according to a standard protocol, which gave 10 in high yield.²⁰ No racemization of (S)-10, 26, 27, or 28 could be detected by chiral HPLC during the synthetic sequence, by comparison of retention times of previously synthesized racemic material. Alcohols 10 and 28 were then converted into their corresponding tosylates 13 and 29 in good yields. Treatment of tosylates 13 and 29 with Ar₂P(BH₃)Li at 0 °C in THF, followed by stirring at room temperature overnight, in DMF, yielded the P-borane-protected phosphines 16 and 30 to 32 in high yields. At this point the borane adducts are stable to hydrolysis and oxidation, compared to the unstable first generation phosphinite ligands. Removal of the borane-protecting group by stirring in neat Et₂NH gave the deprotected phosphines 19 and 33-35. Complex formation was performed according to the previously employed protocol, and complexes 2 and 36-38 were isolated in high yields (Scheme 3).

All attempts to obtain crystals suitable for single-crystal X-ray analysis from the aminothiazole-(L)-DBTA salt ((S)-**25**-DBTA) failed; a crystalline bis-tosylated derivative of **25** was synthesized instead.²¹ The absolute configuration of this material was established by X-ray crystallography and was found to be (S).²² Comparison of the HPLC elution order and optical rotation of the five-, six-, and seven-membered structures established the (S) configuration of the five- and seven-membered structures.²³

The complexes 2 and 36-38 proved to be highly efficient in the asymmetric hydrogenation of a wide variety of trisubstituted olefins (Table 2). As expected, the steric bulk of the heteroaromatic substituent is important for achieving high enantioselectivity, clearly seen in substrate 21 where a dramatic drop in enantioselectivity is observed for complexes 37 and 38, lacking the phenyl group. Also the size of the phosphine substituents, occupying the semihindered quadrant, is of importance for substrates such as 22 and 39 (entries 2, 3, Table 2), where changing from 2 (phenyl) to 36 (o-tolyl) leads to a dramatic loss of enantioselectivity in both cases. All complexes showed a dramatic difference in enantioselectivity between substrates 40 (entry 4, Table 2) and 41 (entry 5, Table 2), caused by the presence of an electron-donating methoxy group in 40. Allylic alcohol 43 (entry 7, Table 2) worked exceptionally well for all complexes 2 and 36–38. Ethyl α -methyl trans-cinnamate 44 (entry 8, Table 2) gave good enantioselectivities only with the

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⁽²²⁾ Crystallographic data for the bis-tosylate have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 286224 by Professor Lars Kristian Hansen (University of Tromsø). Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax +44-(0)1223-336033 or e-mail deposit@ccdc.cam.ac.uk).

⁽²³⁾ On the basis of comparison of HPLC (Chiracel OD-H) elution order among 9-11 with elution order of 10, synthesized from the route in Scheme 3. Also the products from hydrogenations had the same absolute configuration as products from 2.

Table 2. Results of Hydrogenation with Complexes 2 and 36-38ª

entry	ntry substrate		2 conv. <i>ee</i> (%)		conv	36 conv. <i>ee</i> (%)		37 conv. <i>ee</i> (%)		38 conv. <i>ee</i> (%)	
1	Me Ph Ph	21	>99	>99 (<i>S</i>)	>99	>99 (<i>S</i>)	>99	77 (<i>S</i>)	>99	48 (<i>S</i>)	
2	p-MeO-C ₆ H₄	22	>99	99 (<i>S</i>)	>99	58 (<i>S</i>)	>99	98(<i>S</i>)	>99	30 (<i>S</i>)	
3	Ph Me	39	>99	99 (<i>S</i>)	99	60 (<i>S</i>)	35	16 (<i>S</i>)	30	rac.	
4	Meo	40	>99	93 (<i>R</i>)	99	31 (<i>R</i>)	>99	78 (<i>R</i>)	>99	40 (<i>R</i>)	
5	Me	41	99	55 (<i>R</i>)	99	19 (<i>S</i>)	74	50 (<i>R</i>)	90	15 (<i>R</i>)	
6	Me	42	99	98 (<i>S</i>)	99	75 (<i>S</i>)	99	26 (<i>S</i>)	99	rac.	
7	Ph	43	>99	99 (<i>S</i>)	>99	99 (<i>S</i>)	>99	99 (<i>S</i>)	>99	99 (<i>S</i>)	
8	Ph CO ₂ Et Me	44	>99	40 (<i>S</i>)	>99	80 (<i>S</i>)	50	40 (<i>S</i>)	95	80 (<i>S</i>)	
9	Me Ph	23	>99	98 (<i>S</i>)	>99	98 (<i>S</i>)	91	87 (<i>S</i>)	99	69 (<i>S</i>)	
10	Ph CO ₂ Et	24	85	rac.	99	72 (<i>R</i>)	99	95 (<i>R</i>)	99	95 (<i>R</i>)	

^{*a*} Absolute configurations of products given in parentheses after the ee-value. Conditions: P = 50 bar in all entries; all reactions performed at room temperature for 2 h, except entries 7 and 10 were reactions run overnight instead; catalyst loading 0.5 mol % in all entries, except 7, where 1 mol % was used. All reactions were performed in freshly distilled (CaH₂, ethanol free) CH₂Cl₂ as 0.25 M solutions.

Figure 2. Schematic representation of electronically neutral trisubstituted olefin coordination to the catalyst.

o-tolyl-complexes **36** and **38**. For substrate **24**, (entry 10, Table 2), the 2-*H*-thiazole complexes **37** and **38** prove to be superior, giving high conversions and excellent enantioselectivities for the previous very unreactive substrate. Conversely, substrate **23** (entry 9, Table 2) gave excellent conversions and enantio-selectivities with complexes **2** and **36**.

Computational Details. Geometries of all substrates were calculated with the Jaguar program²⁴ using the B3LYP hybrid density functional,²⁵ together with the LACVP** ECP and basis set. Normal-mode analysis revealed one imaginary frequency for each transition state. LACVP in Jaguar defines a combination of the LANL2DZ basis set²⁶ for iridium and the 6-31G basis set for other atoms. LACVP implies the use of an effective core

potential for 60 core electrons of iridium and a (5s,6p,3d) primitive basis contracted to [3s,3p,2d]. Final energies were retrieved from single point calculations at B3LYP/LACV3p+**. LACV3p+** differs from LACVP** by using the 6-311+G** basis set in place of 6-31G**.

Selectivity Model. To establish a model for the enantiodetermining step, calculations were performed on the full-sized catalyst **2**, with **39** as the substrate. By addition of a quadrant scheme over the catalyst with the olefin coordination site centered over the origin in front of the iridium atom, with the phosphine ligand to the right and the thiazole amine to the left, the steric bulk will be oriented into the lower left quadrant. This schematic description of the catalytic system is depicted in Figure 2. The bulky substituent in the 2 position of the heterocycle on the ligand creates an almost perfect pocket; especially well adapted to host trisubstituted olefins. In case of trisubstituted olefins the least sterically demanding substituent,

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A (0.0 kcal)

B (12.7 kcal)

Figure 3. Calculated enantiodetermining migratory-insertion TS of methyl *trans-\beta*-methyl cinnamate: (left) sterically and electronically favored β -addition; (right) sterically and electronically unfavored α -addition.

Figure 4. Calculated enantiodetermining migratory-insertion TS of *trans*- α -methyl cinnamate: (left) sterically favored, electronically unfavored α -addition; (right) sterically unfavored, electronically favored β -addition.

i.e., the proton, will face the steric bulk of the ligand. The catalyst then offers two open sites, located in a trans position to each other, and a fourth site facing one of the aryl groups of the phosphine. This fourth site could accommodate smaller olefin substituents.

Coordination of a trisubstituted olefin into the empty quadrant model reveals that the olefin will preferentally coordinate to the catalyst from the Re side, as the opposite coordination mode will result in unfavorable interactions between one of the large trans-substituents with the steric bulk of the ligand. This determines the stereochemical outcome of the reaction and sets the facial recognition of an electronically neutral trisubstituted olefin.

Substrates possessing a polarized double bond, such as α,β unsaturated esters, add a complicating electronic effect. DFT calculations with methyl *trans-* β -methyl cinnamate show a strong preference for β -addition of the hydride in the migratory insertion step (13 kcal mol⁻¹).

The migration of the substrate into the Ir-H bond leads to a tilt of the C-C double bond toward the hydride. For steric reasons, this means that migratory insertions into an axial hydride pointing up will be preferred over insertion into an axial

hydride pointing down, since the former leads to a less congested transition state where the substrate is moving away from the close proximity of the phenyl ring on the thiazole. For substrate 23 this results in a TS A that is both sterically and electronically favored over TS B. As seen in Figure 3, β -addition is much more favored over α -addition, resulting in a lower energy of the TS due to minimized steric repulsions and a match electronic polarization of the substrate. In the case of methyl trans- α methyl cinnamate, 44, a β -addition of the hydride will require a migratory insertion step in a iridium-hydride bond pointing in the same direction as the steric bulk of the thiazole moiety (Figure 4, right). Thus, there will be a substantial steric interaction between substrate and catalyst. For this substrate the steric and electronic effects will be mismatched and result in a reduced reaction rate and a deterioration of the enantioselectivity. Competitive experiments between the two substrates revealed that 23 is indeed hydrogenated 6.7 times faster than 44.

This gives another tool for predicting enantioselectivity and reactivity of substrates toward asymmetric hydrogenation by Ir-(P,N) systems. For successful reaction, a steric and electronic match between substrate and catalyst is necessary. This fact can be rationalized by the addition of a *direction* to the enantiode-

Figure 5. Preferred coordination of a polarized substrate (top) and possible facial coordination of substrates 23 and 44 (bottom).

terminating migratory insertion step, in the quadrant selectivity model.¹² A substrate possessing a conjugated electron-withdrawing group (EWG) will show a strong β -preference for the initial hydride addition (Figure 5).¹³ Substrate **44** orients into a sterically matched but electronically *mis*matched orientation, hence the lower selectivities obtained with this substrate compared to **23**. Substrate **23** however possesses perfect overlap for catalysts **2** and **36** (Figure 5) resulting in exceptionally high selectivity for those catalysts.

Conclusions

In conclusion, we have developed a new type of heterocyclic (P,N) ligand for the asymmetric Ir-catalyzed hydrogenation of olefins. The results, in terms of enantioselectivites for typically difficult substrates, are among the best so far reported. The results obtained for the second-generation thiazole ligands have allowed a more detailed selectivity model to be derived, revealing the relation between steric and electronic effects and their importance for activity and enantioselectivity. The effect

of the substituent on the thiazole ring, which is situated in the blocked quadrant, was also studied, and it was found that its presence is important for the stereoselectivity of the catalysts. Decreasing the bulk of this substituent generally results in decreased ee of the products with the exception of cis-substrates, which are better accommodated in catalysts having a small substituent on the thiazole ring.

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Supporting Information Available: Experimental procedures for the preparations of the ligands and complexes, hydrogenation procedures, characterization data, chiral separation data, computational details, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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