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Chiral Hetero- and Carbocyclic Compounds from the Asymmetric Hydrogenation of Cyclic Alkenes

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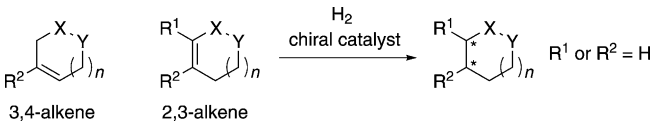
Abstract: Several types of chiral hetero- and carbocyclic compounds have been synthesized by using the asymmetric hydrogenation of cyclic alkenes. N,P-Ligated iridium catalysts reduced six-membered cyclic alkenes with various substituents and heterofunctionality in good to excellent enantioselectivity, whereas the reduction of five-membered cyclic alkenes was generally less selective, giving modest enantiomeric excesses. The stereoselectivity of the hydrogenation depended more strongly on the substrate structure for the five- rather than the six-membered cyclic alkenes. The major enantiomer formed in the reduction of six-membered alkenes could be predicted from a selectivity model and isomeric alkenes had complementary enantioselectivity, giving opposite optical isomers upon hydrogenation. The utility of the reaction was demonstrated by using it as a key step in the preparation of chiral 1,3-*cis*-cyclohexane carboxylates.

Keywords: asymmetric synthesis · heterocyclic compounds · homogeneous catalysis · hydrogenation · iridium

Introduction

Chiral hetero- and carbocycles are used in almost every field of chemistry. They are frequently encountered in, for example, pharmaceuticals,[1] natural products,[2] fragrances,[3] and molecular switches,[4] as well as in catalysts[5] and chiral auxiliaries[6] for organic synthesis. Thus, methods for their enantioselective synthesis are valuable tools for organic chemists. However, the wide range of structural motifs present in chiral hetero- and carbocycles complicates the development of general synthetic methods for their production. The asymmetric hydrogenation by using hydrogen gas and a chiral homogeneous catalyst is a powerful tool in organic synthesis[7] and has potential in the enantioselective synthesis of cyclic molecules, because it is among the most general, atom-efficient, and selective methods for producing chiral compounds.[8] Therefore, asymmetric hydrogenation could give access to a broad spectrum of chiral cyclic building blocks if appropriate catalysts were available (Scheme 1).



Scheme 1. General scheme to access chiral heterocycles through the asymmetric hydrogenation of cyclic alkenes.

Several catalytic systems for the asymmetric hydrogenation of functionalized cyclic alkenes have been reported. For example, the hydrogenation of 1-aza-2-cycloalkene carboxylates with rhodium and ruthenium catalysts has yielded chiral 1- or 2-substituted piperidines and piperazines highly selectively.[9] Zhang and co-workers have reported the asymmetric hydrogenation of β-acetylamino acrylonitriles[10] and the group of Szöllösi has performed enantioselective hydrogenation of carboxylate-substituted 3,4-dehydropiperidines[11] and 5,6-dihydro-2*H*-pyrans.[12] Non- or weakly functionalized cyclic alkenes, however, have been much less explored. N,P-Ligated iridium complexes of the form $[Ir(cod)(N^{\frown}P)]^+[BAr_F]^-$ (cod = 1,5-cyclooctadiene, $[BAr_F]^- = [(3,5\text{-}(F_3C)_2\text{-}C_6H_3)_4B]^-$), originally developed and investigated as asymmetric hydrogenation catalysts by Pfaltz and co-workers,[13] are especially promising for this purpose, because they can selectively and efficiently add dihydrogen to unfunctionalized double bonds[14] without relying on a vicinal metal-coordinating group to direct the stereochemistry.[15] Zhou and co-workers used iridium complexes of spiro phosphoramidite to hydrogenate cyclic *N*-alkyl enamines in high selectivity;[16] however, only five-membered α-substituted

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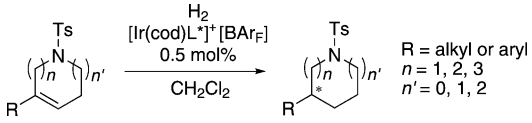
enamides were used. Takaya and co-workers discovered that Ru–BINAP (BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene) reduced 2-methyl-3,4-dihydrofuran in good selectivity while studying the hydrogenation of alkenes bearing adjacent oxygen functionalities.[17]

In an initial study, we reported the iridium-catalyzed asymmetric hydrogenation of cyclic alkenes containing tosyl-protected amines.[18] These were easily obtained from ring-closing metathesis and hydrogenation by using N,P-ligated iridium catalysts and selectively yielded tosyl-protected chiral pyrrolidines, piperidines, and azepanes, typically in greater than 90% *ee* (Scheme 2). Our report was the first on



Scheme 2. The iridium-catalyzed hydrogenation of five-, six-, and seven-membered cyclic alkenes containing an N-Ts heterofunctionality.[18]

the asymmetric hydrogenation of cyclic alkenes of this type and the methodology allowed easy access to azacycles with chiral centers distal to the N atom (Scheme 2).

We have now expanded this study to the asymmetric hydrogenation of a broader range of prochiral cyclic alkenes to better understand which substrates can be hydrogenated to optically active compounds in high selectivity and with which catalysts. We have been striving towards revealing the substrate tolerance, mechanistic considerations, and synthetic utility of the reaction. Several types of prochiral alkenes, of which the majority has not previously been used in asymmetric hydrogenation, including dihydropyrans, cyclic malonate esters, and unsaturated lactones, have been reduced highly selectively. Based on the results of this study and a selectivity model,[19] we also propose a mnemonic device that correctly predicts the absolute configuration of the resulting chiral heteroalkane. The synthesis methodology was also applied in the preparation of 1,3-*cis*-cyclohexane carboxylates.

Results and Discussion

The substrates studied here, which include carbo-, aza-, and oxacycles, possess a range of electronic and steric properties, and we therefore examined an array of iridium-based hydrogenation catalysts (Figure 1). Catalyst class **1** consists of the sterically similar ligands **A**–**D**. Ligands **1A** and **1B**, in which the coordinating N atom is part of a thiazole moiety, have been used for the asymmetric hydrogenation of unfunctionalized olefins, including sterically demanding substrates, such as trisubstituted 1,1-diarylolefins,[20] vinyl phosphonates,[21] and vinyl silanes.[22] In ligands **1C** and **1D**, the coordinating N atom is part of an imidazole ring and thus, is more electron-rich than the thiazole nitrogen, producing more electron-rich, less acidic catalysts that are suitable for acid-sensitive substrates, such as allylic alcohols and vinyl

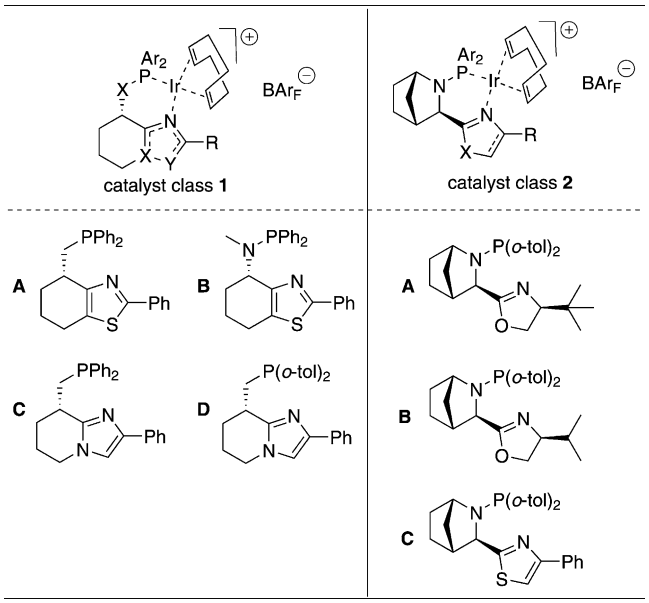
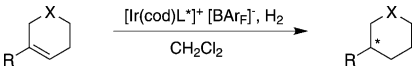


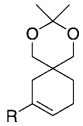
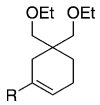
Figure 1. The ligands and the corresponding catalysts used in this study.

fluorides.[23] The ligands in catalyst class **2**, with bicyclic backbones and P(*o*-tol)$_2$ P donors, are more sterically demanding than the ligands of class **1**. These catalysts derive their chirality from amino acids and have been applied to the iridium-catalyzed asymmetric hydrogenations of imines,[24] enamines,[25] and vinyl boronates.[26]

3,4-Unsaturated cyclic alkenes: Our initial study showed that several 3-substituted-3,4-dehydropiperidines could be reduced very effectively and stereoselectively, though the optimal catalyst varied with the alkene substituent (Table 1, entries 1a–g).[18] Alkenes bearing aromatic substituents (entries 1a–d) were most effectively reduced by using the less bulky, open-backbone ligands of class **1**. Notably, the catalyst based on electron-rich ligand **1C** gave better yields and *ee* values than **1A** for the reduction of alkenes with electron-withdrawing aryl substituents, whereas the opposite was true for 3,4-unsaturated azacycles bearing electron-rich aryl groups. Alkenes with non-aryl substituents (Table 1, entries 1e–j) were reduced faster and more selectively by catalysts of which the ligands had bicyclic backbones (class **2**). The same reactivity pattern that was observed for 3-substituted-3,4-dehydropiperidines also applied to 3-substituted 5,6-dihydro-2*H*-pyrans (Table 1, entry 2). The 5,6-dihydro-3-phenyl-2*H*-pyran was hydrogenated in excellent conversion and enantioselectivity by using the catalyst with ligand **1A** (Table 1, entry 2a). Although this catalyst was also effective in the hydrogenation of the 3-benzyl and 3-hydroxymethyl analogues, these substrates were hydrogenated more selectively when the catalyst was based on ligand **2C**. 3,4-Unsaturated carbocycles were also tested in asymmetric hydrogenation. Malonates (entry 3), spirocyclic ketals (entry 4), and ethers (entry 5) were enantioselectively reduced by using catalysts based on ligands **1A** and **1B** (compare entries 1a

Table 1. Iridium-catalyzed asymmetric hydrogenation of 3,4-unsaturated six-membered hetero- and carbocycles.



Entry			R	Ligand	Conv.[a] [%]	*ee*[b] [%]
1[c]		a[d]	Ph	**1A**	>99	>99 (+)
		b[d]	4-MeOC$_6$H$_4$	**1A**	>99	99 (+)
		c[d]	4-ClC$_6$H$_4$	**1C**	94	98 (+)
		d[d]	4-F$_3$CC$_6$H$_4$	**1C**	74	96 (+)
		e[d]	Me	**2A**	99	97 (−) (*S*)
				1B	97	70 (+) (*R*)
		f[d]	Bn	**2A**	97	92 (−) (*R*)
		g[d]	CH$_2$OH	**2A**	>99	97 (−) (*S*)
		h	CH$_2$OAc	**2C**	80	87 (−)
		i	*i*Pr	**2C**	96	66 (−)
		j[e]	OP(O)(OEt)$_2$	**2B**	94	98 (+)
2[c]		a	Ph	**1A**	>99	>99 (+)
		b	CH$_2$OH	**2C**	>99	96 (−) (*R*)
		c	Bn	**2C**	99	92 (+)
3[f,g]		a	Ph	**1A**	48	>99 (−)
		b	Me	**1B**	98	98 (−)
4[f]		a	Ph	**1A**	>99	>99 (+)
		b	Me	**1B**	86	96 (−)
5[f]		a	Ph	**1A**	>99	>99 (+)
		b	Me	**1B**	>99	94 (−)

Reaction conditions: substrate (0.25 M) in CH_2Cl_2, 15 h, RT. [a] Determined by ^{1}H NMR spectroscopy; see the Supporting Information for details. [b] Determined by chiral chromatography; see the Supporting Information for details. [c] Catalyst (0.5 mol%), H_2 (50 bar). [d] See ref. [18] [e] Catalyst (5 mol%), H_2 (50 bar). [f] Catalyst (1 mol%), H_2 (100 bar). [g] E = COOMe.

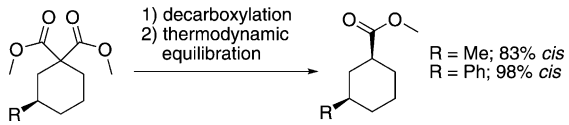
their higher ring strain and lower steric demands. A similar trend of decrease in selectivity when going from six- to five-membered rings has been observed by Pfaltz and co-workers when performing asymmetric hydrogenations of tetrasubstituted cyclic olefins.[28] The excellent selectivities observed for cyclic malonates (Table 2, entries 3a and b), which contain the sterically more demanding carbocycle moiety, suggest that the size of the heterofunctionality significantly affects the selectivity in the asymmetric hydrogenation of five-membered 3,4-unsaturated cyclic compounds.

To further investigate this hypothesis, a dihydropyrrole with a bulky diphenylacetyl protecting group (entry 4) instead of a tosyl group (entry 1b) was prepared. Although no significant improvement was observed when using the catalyst containing ligand **2C**, the one based on ligand **1B** gave the reduced alkene in 80% *ee*, as compared to 21% *ee* for the N-tosyl derivative.

Overall, the nature of the heterofunctionality had little effect on the asymmetric hydrogenation of six-membered cyclic olefins, because excellent enantioselectivities were obtained for most of these substrates. However, the presence of very sterically demanding alkene substituents, such as *i*Pr, decreased selectivity (Table 1, entry 1i). The heterofunctionality had a greater impact on the asymmetric hydrogenation of olefins in five-membered rings; the bulky dimethylmalonate functionality gave the best results. This group likely inhibited inverted substrate coordination, thereby favoring stereoselectivity.

and 1e). Catalysts based on ligands from class **2** were less active for the hydrogenation of these alkenes and generally gave lower selectivity.

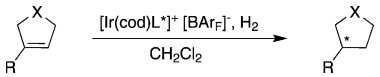
Chiral cyclic 3-substituted malonates give access to 3-substituted cyclohexane esters in high *cis* selectivity after decarboxylation and subsequent thermodynamic equilibration (Scheme 3). Krapcho and Weimaster reported that 3-methylcyclohexane methylcarboxylate could be obtained in 83% *cis* and 17% *trans* form after thermodynamic equilibration with a base.[27] By using their protocol, we obtained 98% of the *cis* diastereomer for the 3-phenyl analogue.

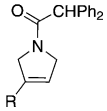


Scheme 3. Preparation of *cis*-3-substituted cyclohexane carboxylates from chiral cyclic malonates.[27]

The asymmetric hydrogenation of five-membered 3,4-unsaturated hetero- and carbocycles was also tested. Generally, these alkenes were reduced faster, but less selectively than their six-membered counterparts (Table 2), likely owing to

Table 2. The iridium-catalyzed hydrogenation of five-membered 3,4-unsaturated hetero- and carbocycles.

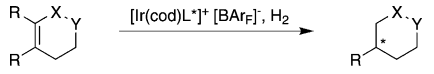


Entry			R	Ligand	Conv.[a] [%]	*ee*[b] [%]
1[c]		a	Ph	**1B**	99	85 (−)
		b	Me	**2C**	>99	44 (+)
		c	Bn	**2C**	>99	54 (+)
2[c]			Ph	**1B**	>99	65 (+)
3[c]		a	Ph	**1B**	99	99 (−)
		b	Me	**1B**	99	93 (−)
4[d]			Me	**2C**	69	47 (−)
				1B	40	80 (+)

Reaction conditions: substrate (0.25 M) in CH_2Cl_2, H_2 (50 bar), 15 h, RT. [a] Determined by ^{1}H NMR spectroscopy; see the Supporting Information for details. [b] Determined by chiral chromatography; see the Supporting Information for details. [c] Catalyst (0.5 mol%). [d] Catalyst (1 mol%).

2,3-Unsaturated cyclic alkenes: Next, we evaluated the hydrogenation of cyclic alkenes with a heteroatom or a substituted carbon atom bound directly to the olefin. These substrates proved more difficult to reduce than their 3,4-unsaturated counterparts and often had to be reduced under harsher conditions. Two phenyl-substituted olefins, *N*-tosyl-3-phenyl-2,3-dehydropiperidine and 5-phenyl-3,4-dihydro-2*H*-pyran (Table 3, entries 1a and 2), were reduced in low enantioselectivity by the catalyst containing ligand **1A**, which had performed well for the phenyl-substituted 3,4-unsaturated hetero- and carbocycles. Better selectivities were obtained by using ligands **2A** and **1B**, although the *ee* values remained modest. The 3-methyl derivative (entry 1b) was reduced in 89% *ee*. We also attempted the hydrogenation of a phosphate enol ether (entry 1c; compare Table 1, entry 1j), but when this leaving group was present on the alkene, *N*-tosylpiperidine was obtained as the only reaction product.

Table 3. The iridium-catalyzed hydrogenation of six-membered, 2,3-unsaturated hetero- and carbocycles.



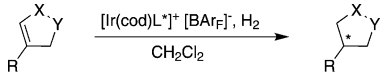
Entry			R	Ligand	Conv.[a] [%]	*ee*[b] [%]
1[c]		a	Ph	**1A**	20	rac.
				2A	21	64 (+)
		b	Me	**2A**	90	89 (+) (*R*)
		c	OP(O)(OEt)$_2$	**2A**	decomposition	
2[c]			Ph	**1A**	39	64 (−)
				1B	29	81 (−)
3[d]			Ph	**1D**	40	66 (−) (*S*)
4		a[e]	Ph	**1D**	>99	94 (−) (*S*)
		b[f]	Me	**1D**	>99	92 (−) (*S*)
		c[f]	Bu	**1D**	47	88 (−) (*S*)
5[g]		a	Ph	**1D**	15	93 (+) (*S*)
		b	Me	**1D**	99	79 (−) (*S*)

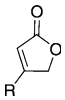
Reaction conditions: substrate (0.25 M) in solvent, RT. [a] Determined by ^{1}H NMR spectroscopy; see the Supporting Information for details. [b] Determined by chiral chromatography; see the Supporting Information for details. [c] CH_2Cl_2, catalyst (0.5 mol%), 15 h, H_2 (50 bar). [d] CH_2Cl_2, catalyst (1 mol%), 15 h, H_2 (50 bar). [e] 2,2,2-trifluoroethanol, catalyst (1 mol%), 24 h, H_2 (100 bar). [f] CH_2Cl_2, catalyst (1 mol%), 24 h, H_2 (50 bar). [g] CH_2Cl_2, catalyst (1 mol%), 24 h, H_2 (100 bar).

The asymmetric hydrogenation of one α-substituted enamide (Table 3, entry 3) was also tested, but the conversion and selectivity of this reaction were as disappointing as those obtained for the β-substituted enamides. The hydrogenations of α,β-unsaturated cyclic ketones and lactones were also performed. Although high enantioselectivities have been obtained in the transfer hydrogenation of this type of alkenes,[29] their direct catalytic hydrogenation is less efficient and the few examples reported to date have shown modest selectivity.[30] Scheuermann née Taylor and Jaekel have developed a rhodium-based system that yields 3-substituted cyclic ketones in moderate to good selectivity,[31] but iridium catalysts have not proven efficient in this reaction. We obtained the targeted 3-substituted ketones and lactones in high selectivity by using catalysts bearing the electron-rich ligand **1D** (Table 3, entries 4 and 5). In the reduction of 3-phenylcyclohex-2-enone, the reaction did not proceed cleanly when performed in CH_2Cl_2. Using simple alcohols (MeOH, EtOH, and *i*PrOH) as solvents gave very low conversion (<10%) of the starting material. However, when the more acidic alcohol 2,2,2-trifluoroethanol was used as solvent, the reaction proceeded satisfactorily, yielding only the desired 3-phenylcyclohex-1-one, fast and in high enantioselectivity (Table 3, entry 4a). For the methyl and butyl derivatives, however, the reaction was slower and less selective when performed in 2,2,2-trifluoroethanol compared to CH_2Cl_2.

Finally, we attempted the hydrogenation of cyclic five-membered 2,3-unsaturated hetero- and carbocycles (Table 4). Good selectivities were obtained for the phenyl-substituted furan (entry 1) and unsaturated lactones (entry 2), although the later were reduced very slowly. Five-membered cyclic enones were essentially inert to these reaction conditions.

Table 4. The iridium-catalyzed hydrogenation of five-membered, 2,3-unsaturated hetero- and carbocycles.



Entry			R	Ligand	Conv.[a] [%]	*ee*[b] [%]
1[c]			Ph	**1C**	>99	90 (−)
2[d]		a	Ph	**2B**	20	92 (−) (*R*)
		b	Me	**2C**	24	85 (−) (*S*)

Conditions: substrate (0.25 M) in CH_2Cl_2, RT. [a] Determined by ^{1}H NMR spectroscopy; see the Supporting Information for details. [b] Determined by chiral chromatography; see the Supporting Information for details. [c] Catalyst (1 mol%), 15 h, H_2 (50 bar). [d] Catalyst (1 mol%), 24 h, H_2 (100 bar).

Origin of enantioselectivity: The reduction of a 3-substituted 3,4-unsaturated six-membered heterocycle gives the opposite enantiomer than the reduction of the isomeric 2,3-unsaturated heterocycle. For instance, the asymmetric hydrogenation of *N*-tosyl-3-methyl-3,4-dehydropiperidine (Table 1, entry 1e) by using the catalyst deriving from ligand **2A** gives the chiral product in the (*S*) configuration, whereas *N*-tosyl-3-methyl-2,3-dehydropiperidine (Table 3, entry 1b) yields the same product, but in the (*R*) configuration. This complementary reaction pattern is especially useful, because the iridium catalyst containing ligand **2A** derives its chirality from *tert*-leucine, therefore, one catalyst enantiomer is considerably cheaper to produce than the other. Thus, it is for-

tunate that both enantiomers of the product can be obtained from the same catalyst by using isomeric alkene substrates. This is likely owing to the substrate coordination modes shown in Figure 2. Several groups have suggested that the catalyst–alkene complex that exists prior to the enantiodetermining migratory insertion has the structure shown in Figure 2a (drawn for simplicity with ethene as the alkene).[19a,32] We have previously used this structure to develop a selectivity model that predicts the absolute configuration of an alkane produced by these hydrogenation catalysts and this model is based on the optimal coordination of a trisubstituted alkene to the catalytic pocket.[19] In the model shown in Figure 2b, the coordination of a trisubstituted alkene is most favorable when the hydrogen of the alkene is positioned in the most encumbered quadrant. In the case of ligand class **1** (Figure 2b, left), quadrant iii is most hindered, because it is occupied by the R group of the ligand heterocycle (see Figure 1). The ligand also contributes some steric bulk to quadrant ii, whereas quadrants i and vi are largely unhindered. The bicyclic ligands present in catalyst class **2** have a different shape and therefore, produce a different chiral environment (Figure 2b, right) than those in catalyst class **1**. Here, quadrant i is occupied by the R group of the heterocycle and consequently most hindered; the $P(o\text{-tol})_2$ group contributes some bulk to quadrant iv. As a result, these two catalysts generate the opposite heterocycloalkane enantiomer upon alkene hydrogenation (Figure 2c). This is clear, for example, from the reductions of *N*-tosyl-3-methyl-3,4-dehydropiperidine (Table 1, entry 1e) and *N*-diphenylacetyl-3-methyl-2,5-dihydropyrrole (Table 2, entry 4). The sign of the quasi-dihedral angle θ between the N–Ir–P plane and the R group of the ligand (measured from the position of the incoming alkene; Figure 2b) can be used to determine the absolute configuration of the reaction product. This has been demonstrated for the hydrogenation of various trisubstituted alkenes by using a large number of N,P-ligated iridium-catalysts.[19a] Hence, the reduction of a 3,4-unsaturated cyclic alkene by a catalyst deriving from ligand **1A** ($\theta<0$) produces one enantiomer of an alkane and the reduction by a catalyst deriving from ligand **2B** ($\theta>0$) gives the other. This model can be used as a mnemonic device to predict the absolute configuration of alkanes produced from the asymmetric hydrogenation of six-membered heterocyclic alkenes (Figure 2c).

Unfortunately, low selectivity and a lack of relevant configuration data in the literature preclude the evaluation of this model in the asymmetric hydrogenation of unsaturated five-membered heterocycles. Nonetheless, it is clear that 3-phenyl-2,5-dihydrofuran (Table 2, entry 2) and 4-phenyl-2,3-dihydrofuran (Table 4, entry 1) give opposite enantiomers upon asymmetric hydrogenation.

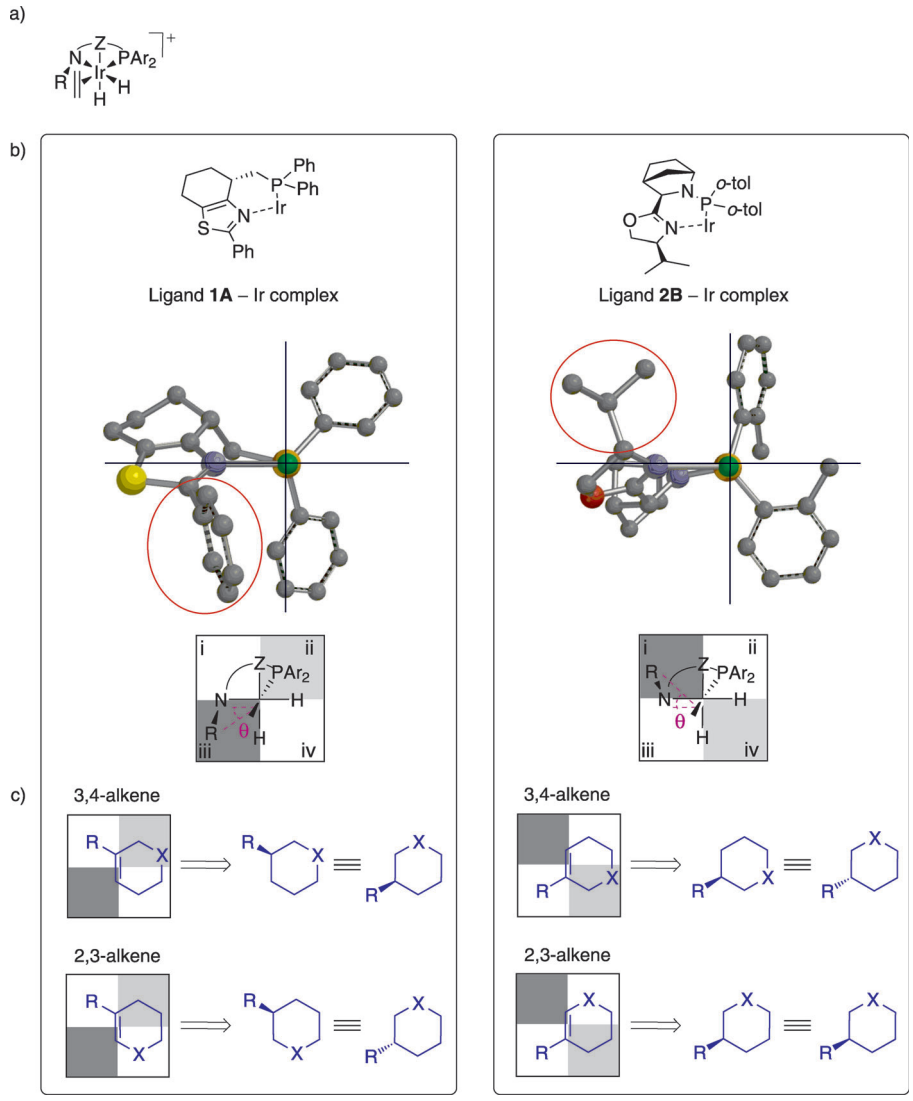


Figure 2. Model explaining the selectivity of the heterocycle hydrogenation. Z = H_2 or solvent. a) Catalyst–alkene complex prior to migratory insertion, b) structure of the open coordination site on the catalyst, as viewed from the perspective of the incoming alkene (some hydrogen atoms have been omitted for clarity), and c) selectivity model for the asymmetric hydrogenation of six-membered heterocyclic alkenes.

Conclusion

Iridium catalysts containing N,P ligands can be used for the highly selective asymmetric hydrogenation of several types of prochiral cyclic alkenes that have not been studied previously. Six-membered 3,4-unsaturated hetero- and carbocycles are reduced with excellent selectivity, mainly regardless of the substituent present on the alkene or the type of cyclic compound. 2,3-Unsaturated cyclic compounds of the same ring size are reduced most selectively when an electron-withdrawing group is adjacent to the alkene. The reduction of an alkene bearing an electron-withdrawing group within or outside the ring is fastest and most selective when the catalyst bears an electron-rich ligand. The reductions of five-membered cyclic alkenes are, with some exceptions, less selective, giving modest enantiomeric excesses. However, the selectivity in the asymmetric hydrogenation of 3,4-unsaturated five-membered heterocycles depends upon the heterofunctionality, therefore, some optimization is possible.

Experimental Section

General procedure for the asymmetric hydrogenation of olefins: A vial was charged with a magnetic stirrer bar, substrate (0.25 M), iridium catalyst, and solvent. The vial was placed in a high-pressure hydrogenation apparatus and the system was purged three times with Ar and then filled to the required pressure with H_2. The reaction was stirred at room temperature for the appropriate time, before the H_2 was released and the solvent was removed in vacuo. The conversion was then determined by ^{1}H NMR spectroscopy. The crude product was filtered through a short plug of silica gel and the *ee* value was determined by using chiral GC or HPLC. See the Supporting Information for detailed procedures regarding preparation, analytical methods, and characterization data.

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Asymmetric Hydrogenation

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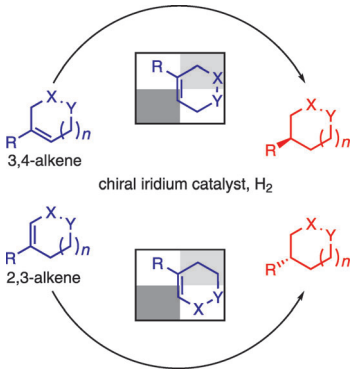
Chiral Hetero- and Carbocyclic Compounds from the Asymmetric Hydrogenation of Cyclic Alkenes



Several types of chiral hetero- and carbocyclic compounds have been synthesized by asymmetric hydrogenation of cyclic alkenes by using N,P-ligated iridium catalysts (see scheme). Six-membered cyclic alkenes were reduced in good to excellent selectivity, whereas the reduction of five-membered cyclic alkenes was generally less selective. The major enantiomer formed could be predicted from a selectivity model and isomeric alkenes gave complementary enantioselectivity.

