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Asymmetric Hydrogenation of Allylic Alcohols Using Ir–N,P-Complexes

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S Supporting Information

ABSTRACT: In this study, a series of γ,γ -disubstituted and β,γ -disubstituted allylic alcohols were prepared and successfully hydrogenated using suitable N,P-based Ir complexes. High yields and excellent enantioselectivities were obtained for most of the substrates studied. This investigation also revealed the effect of the acidity of the N,P–Ir-complexes on the acid-sensitive allylic alcohols. DFT $\Delta\rho K_a$ calculations were used to explain the effect of the N,P-ligand on the acidity of the corresponding Ir-complex. The selectivity model of the reaction was used to accurately predict the absolute configuration of the hydrogenated alcohols.

KEYWORDS: asymmetric synthesis, γ,γ -disubstituted allylic alcohols, β,γ -disubstituted allylic alcohols, DFT, iridium, hydrogenation

INTRODUCTION

Enantioenriched alcohols provide a valuable feedstock for the synthesis of bioactive natural products¹ and pharmaceuticals² because the hydroxyl group can be readily transformed to other functional groups, most often in a high stereospecific manner.³ Furthermore, derivatives of alcohols bearing stereogenic centers on the β - and/or γ -carbon also exist widely in natural products,⁴ pharmaceuticals,⁵ agrochemicals,⁶ and fragrances.⁷ Transition-metal-catalyzed asymmetric hydrogenation has emerged as one of the most powerful tools for the preparation of chiral compounds in both academic research and industrial production. Some attractive features of this transformation include high enantioselectivity, low catalyst loadings, high yields, mild reaction conditions, and near-perfect atom economy.⁸

The enantioselective reduction of allylic alcohols constitutes a useful and practical route affording the corresponding optically active alcohols in a single step.⁹ Originally, Rh- and Ru-diphosphine complexes were utilized, and high enantioselectivities have been obtained. Rh-complexes generally result in high ee's for the asymmetric hydrogenation of allylic alcohols bearing at least one aryl group on the γ -carbon.¹⁰ When Rh complexes are employed as catalysts, high catalyst loading and often long reaction times are required.¹¹ Despite the high enantioselectivities achieved using Ru catalysts, the scope of the reaction, especially considering substrates bearing aliphatic substituents is quite limited.¹² Highly diastereoselective hydrogenations of allylic alcohols have also been achieved using N-heterocyclic carbenes (NHCs), N-based Ir-complexes.¹³ For asymmetric hydrogenation using Ir-complexes, only a few

catalysts have been shown to give high enantioselectivities,¹⁴ and the reduction often resulted in complex mixtures.¹⁵ Notably, the isomerization of C=C is often observed as a competitive process when using Rh, Ru, and Ir-complexes in the hydrogenation, especially at low pressure.¹⁶ Overall, allylic alcohols remain challenging substrates in transition-metal-catalyzed asymmetric hydrogenation.

The N,P-ligated Ir-complexes have recently proved to be effective catalysts for the asymmetric hydrogenation of alkenes having little or no functionality.^{8a,17} It has been shown that alkenes bearing Lewis basic substituents can coordinate to Ir, and this effect may influence the performance of catalysts in the hydrogenation process.¹⁸ It is well-known that Crabtree's iridium catalyst often shows a high tendency to coordinate to alcohol groups in the substrate resulting in highly diastereoselective hydrogenations. This was studied by Stork and co-workers where it was discovered that there was coordination to Ir in the hydrogenation of both homoallylic and allylic alcohols using Crabtree's catalyst $[(\text{PCy})_3(\text{Pyridine})\text{Ir}(\text{COD})]^+[\text{PF}_6]^-$,¹⁹ in which COD is 1,5-cyclooctadiene. However, there exists no clear evidence for this coordination in asymmetric iridium-catalyzed hydrogenations, where the monodentate phosphine and pyridine ligands have been replaced by a bulky, bidentate chiral N,P-ligand. In a computational study carried out by Burgess and co-workers, it was found that a 2-substituted allylic alcohol (2-methylbut-2-

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76 en-1-ol) did not coordinate to Ir during the hydrogenation.²⁰
 77 Also, recent studies by Pfaltz did not provide any evidence for
 78 strong coordination between the hydroxyl group and Ir.^{14d,21}

79 Successful examples of asymmetric hydrogenations of allylic
 80 alcohols with Ir-complexes do exist.^{14,17b,22} There are
 81 numerous derivatives of (*E*)-cinnamyl alcohols that have been
 82 hydrogenated with high enantioselectivity, but the (*Z*)-
 83 cinnamyl alcohols usually gave lower reactivities and
 84 selectivities.^{14d} Dialkylsubstituted allylic alcohols were also
 85 difficult to hydrogenate in high enantioselectivities.²³ In fact, it
 86 has been shown in the Ir-catalyzed asymmetric hydrogenation,
 87 that high enantioselectivities are easy to obtain for alkenes
 88 bearing at least one aryl substituent on the prochiral carbon.
 89 This is partially attributed to π - π interaction between the aryl
 90 ring and the catalyst.²⁴ Pure alkyl-substituted alkenes usually
 91 result in low ee's in this transformation. This is possibly due to
 92 the similar size of the substituents and the lack of interaction
 93 between the substrate and catalyst resulting in the difficulty to
 94 distinguish the *Re* and *Si* faces in the hydrogenation process.^{10b}

95 Overall, the substrate scope in the Ir-catalyzed asymmetric
 96 hydrogenation of allylic alcohols is still limited. Moreover,
 97 dialkyl and (*Z*)-allylic alcohols remain difficult substrates in
 98 transition-metal-catalyzed asymmetric hydrogenation. Thus,
 99 there is still room to explore new complexes for the efficient
 100 hydrogenation of diverse allylic alcohols.

101 We have previously shown the highly enantioselective
 102 hydrogenation of functionalized olefins using Ir-N,P cata-
 103 lysts.²⁵ As an extension of our study, we now report the
 104 asymmetric hydrogenation of a wide range of disubstituted
 105 allylic alcohols with the intention to study the substrate scope
 106 in the Ir-catalyzed asymmetric hydrogenation.

107 ■ RESULTS AND DISCUSSION

108 The asymmetric hydrogenation of γ -substituted cinnamyl
 109 alcohol was chosen for the initial study (Table 1). In the
 110 hydrogenation of (*E*)-allylic alcohol **1**, catalyst **A** (Figure 1)
 111 gave an excellent ee of 98%, and a high isolated product yield
 112 was also obtained. No isomerization product, 3-phenylbutanal,
 113 was detected by ¹H NMR under the reaction conditions used.
 114 The impact of steric and electronic effects on the
 115 enantioselectivity is often a problem in the Ir-catalyzed
 116 asymmetric reaction,²⁷ and we were pleased to see that
 117 significant structure variation in the substituents on C=C was
 118 tolerated without affecting the ee in this hydrogenation.

119 Electron-donating or -withdrawing groups at the *para* position
 120 of the aryl ring only affected the hydrogenation slightly
 121 (substrates **2** and **3**). The resulting chiral saturated alcohols
 122 were obtained with excellent yields and enantioselectivities.
 123 Sterically bulkier substituents (ethyl, isopropyl, and cyclohexyl)
 124 had no significant influence on enantioselectivities and yields.
 125 Substrates **4–6** gave excellent ee's and over 95% isolated yields.

126 Chiral diarylmethine compounds are present in numerous
 127 natural products and bioactive compounds.²⁸ The diaryl-
 128 substituted allylic alcohol **7**²⁹ was employed in the hydro-
 129 genation and produced excellent results: 96% yield and 95% ee.
 130 When compared to a similar study of the hydrogenation of
 131 diaryl-substituted allylic alcohols using an imidazole catalyst,
 132 this hydrogenation does not need a special solvent, α,α,α -
 133 trifluorotoluene, and was carried out at 50 bar H₂ instead of 100
 134 bar H₂.^{14a} Recently, Ding and co-workers reported a Rh-
 135 catalyzed asymmetric hydrogenation of β,β -diarylpropionic
 136 acids prepared from the hydroxylation of 3,3-diaryl acrylates.
 137 Similar enantioselectivities (up to 96% ee) were achieved;

Table 1. Asymmetric Hydrogenation of γ -Substituted Cinnamyl Alcohols^a

$\begin{array}{c} \text{R}^1 \\ \\ \text{R}^2-\text{C}=\text{C}-\text{CH}_2\text{OH} \end{array} \xrightarrow[50 \text{ bar H}_2, \text{CH}_2\text{Cl}_2, 17 \text{ h, r.t.}]{1.0 \text{ mol\% catalyst}} \begin{array}{c} \text{R}^1 \\ \\ \text{R}^2-\text{CH}_2-\text{CH}_2-\text{OH} \end{array}$					
Entry	Substrate	Catalyst	Product	Yield ^b (%)	ee ^c (%)
1		A		98	98 (<i>R</i>) ^[31]
2		A		99	95 (<i>R</i>) ^[32]
3		A		98	94 (<i>R</i>) ^[6]
4		A		95	98 (<i>R</i>) ^[33]
5		A		98	99 (<i>S</i>) ^[33]
6		A		96	99 (<i>S</i>) ^[33b, 34]
7		A		96	95 (<i>S</i>) ^[35]
8		C		96	95 (<i>S</i>) ^[31]
9		C		95	86 (<i>S</i>) ^[33]
10		E		95	93 (<i>R</i>) ^[36]
11		D		92	85 (<i>R</i>) ^[33]
12		D		98	98 (<i>R</i>) ^[33b, 34]
13		K		60	72 (<i>R</i>) ^{[37][9]}

^aReaction conditions: 0.25 mmol of substrate, 1.0 mol % catalyst, 2 mL of CH₂Cl₂, 50 bar H₂, 17 h, r.t. See refs 31–37, as noted in the table. ^bIsolated product yields. ^cDetermined by chiral GC or HPLC analysis, see Supporting Information for details. ^dAssignment of absolute configuration is based on literature reference. ^eAbsolute configuration of the hydrogenated product was tentatively assigned on the basis of elution order. ^fReaction carried out under 100 bar H₂. ^gConversion determined by ¹H NMR.

however, in that case, a mixed-ligand approach had to be used
 in order to obtain enough activity, and morpholine had to be
 used as base.³⁰

Figure 1. Catalysts used in this study.²⁶

The influence of the stereochemistry of the C=C on both reactivity and enantioselectivities are frequently observed in hydrogenation reactions. In contrast to (*E*)-configured alkenes, the corresponding (*Z*)-alkenes are usually more difficult to hydrogenate and generally result in lower enantioselectivities in the Ir-catalyzed asymmetric hydrogenation.²¹ However, substituted (*Z*)-configured cinnamyl alcohols were also successfully hydrogenated. Higher catalyst loading, H₂ pressure, or longer reaction time were not required to achieve full conversion when using the same substrate concentration and temperature as (*E*)-olefins. Instead, enantioselectivities were found to be sensitive to the steric bulk of the substituent close to the C=C. In the hydrogenation of (*Z*)-allylic alcohols **8** and **9**, complex **C** was

found to be the most selective catalyst. The methyl-substituted substrate **8** gave an excellent ee of 95%, whereas only 86% ee was obtained for the ethyl derivative **9**. An excellent ee of 93% was obtained in the hydrogenation of *n*-Bu-substituted allylic alcohol **10**. Complex **D** was the most selective catalyst for the hydrogenation of sterically more demanding substrates (substrates **11** and **12**). Perfect selectivity (98% ee) was obtained for the hydrogenation of cyclohexyl-substituted substrate **12**. The reduction of (*Z*)-configured substrates **8**–**12** was very clean with excellent isolated product yields of between 92 and 98% being attained. No double bond isomerization products, aldehydes, or (*E*)-configured allylic alcohols were detected under the reaction conditions used. Diol **13** was also successfully hydrogenated. As the synthetic equivalent of 2-substituted succinic acid derivatives, the hydrogenation product can function as valuable and important building blocks in the syntheses of biologically active compounds and natural products.³⁸

With a few exceptions, high enantioselectivities have previously only been reported for alkenes bearing aryl groups on C=C. Pure alkyl-substituted alkenes are still considered challenging substrates in the asymmetric hydrogenation using Ir–N,P-complexes.^{8a,17} High enantioselectivities and diastereoselectivities have been achieved in the hydrogenation of allylic alcohols bearing two or more C=C bonds^{8a} (e.g., farnesol and with a stereogenic center adjacent to the C=C bond).¹³ However, the diversity of substrates was quite limited. In a previous study on the hydrogenation of γ,γ -dialkylsubstituted allylic alcohols, (*E*)- and (*Z*)-3-methyl-5-phenylpent-2-en-1-ol, gave only moderate enantioselectivities (64% ee for (*E*)-configured isomer and 69% ee for the (*Z*)-isomer) using Ir-PHOX complex.²³ In the asymmetric hydrogenation of (*E*)-3-methyl-5-phenylpent-2-en-1-ol **14**, catalyst **B** proved to be the best catalyst in the catalyst screening. Substrates **14**–**16**, bearing 3-phenylpropyl, benzyl, and neopentyl on C=C, gave good to excellent enantioselectivities (78–91% ee's). A more sterically demanding cyclohexyl group as the substituent

Figure 2. Quadrant model for predicting the absolute configuration in the asymmetric hydrogenation of trisubstituted alkenes using Ir–N,P-complexes: (a) steric environment around Ir; (b) 3-D model for asymmetric hydrogenation of allylic alcohols **10** and **12**.

Table 2. Asymmetric Hydrogenation of Dialkyl Substituted Allylic Alcohols^{a–e,k}

Entry	Substrate	Catalyst	Product	Yield ^b (%)	ee ^{c,d} (%)
1		B		97	78 (S) ^{38f}
2		B		98	82 (S) ^{6f}
3		B		93	91 (S) ^{40g}
4		B		97	49 (R) ^{21f}
5		C		92	91 (R) ^{41h}
6		C		98	90 (R) ^{39f}
7		C		96	92 (R) ^{6f}
8		C		94	36 (R) ^{40g}
9		C		96	92 (S) ^{21f}
10		F		98	98 (S) ^{42g}
11		A		93	93 (R) ^{43g}
12		D		95	95 (R) ^{6f}
13		D		99	93 (R) ^{44f,g,h,i}
14		F		96	58 (S) ^{45g,h,i}
15		J		99	87 (S) ^{46h}
16		C		99	82 (R) ^{47h}

^{a–e}See the corresponding footnotes in Table 1. ^fAbsolute configuration of the hydrogenated product was tentatively assigned based on specific optical rotation. ^gAbsolute configuration of the hydrogenated product was tentatively assigned on the basis of elution order and specific optical rotation. ^hReaction carried out with 1.5 mol % catalyst under 100 bar H₂. ⁱReaction carried out under 100 bar H₂. ^jConversion determined by ¹H NMR. ^kSee refs 21, 39–47, as noted in the table

Transition-metal-hydride complexes can be considered as potential Lewis acids or Brønsted acids.⁵⁴ There are a number of transformations catalyzed by metal-hydrides based on their

Table 3. Correlation of Observed and Predicted Absolute Configurations^a

Entry	R ¹	R ²	Catalyst	Orientation of ligand bulk toward N-Ir-P plane	Observed absolute configuration	Predicted absolute configuration	Ref.
1	Me	Ph	A	above	R	R	[31]
2	Me	<i>p</i> -MeO-Ph	A	above	R	R	[32]
3	Et	Ph	A	above	R	R	[33]
4	IPr	Ph	A	above	S	S	[33]
5	Cy	Ph	A	above	S	S	[33b, 34]
6	Ph	<i>m</i> -Me-Ph	A	above	S	S	[35]
7	Ph	<i>n</i> Bu	E	below	R	R	[36]
8	Me	PhCH ₂ CH ₂	B	above	S	S	[38]
9	Me	<i>t</i> BuCH ₂	B	above	S	S	[40]
10	Me	Cy	B	above	R	R	[21]
11			D	above	R	R	[44]
12			F	below	S	S	[45]

^aSee refs 21, 31–35, 38–40, 44, 45, as noted in the table.

used in the asymmetric hydrogenation of olefins with or without coordinating functional groups. In our previous study^{27a} of the asymmetric hydrogenation of some sensitive enol ethers using N,P based Ir-complexes, base had to be added in the hydrogenation to avoid side reactions that may be caused by proton generation by the Ir catalyst. Base was also required using NHCs-based Ir-complexes.⁵⁷ Recently, Burgess and co-workers showed that NHCs-based Ir-complexes are less acidic than N,P based Ir-complexes. This difference in acidity can be explained by the electronic features of the NHCs and the phosphine ligands. NHCs are superior σ -donors and inferior π -acceptors, and this results in a more electron-rich complex from which protons are more difficult to dissociate from Ir.⁵⁸

In this work, a number of different N-heterocyclic ligand donors have been studied, which includes imidazoles (complex F, G), thiazoles (complex A, D, E), and oxazoles (complex I). A combination of DFT energy calculations and experimental studies indicates that the basicity of the N-heterocycles has a significant contribution on the relative acidity of the corresponding N,P-based Ir-complexes.

The pK_aH of the parent 5-membered protonated heterocycles is as follows: imidazole has a pK_aH of 7.0 and is classified as a medium strong base; thiazole is less basic with a pK_aH of 2.5; and oxazole has a pK_aH of 0.8 (Figure 3a). The experimental pK_aH were measured in dimethyl sulfoxide.⁵⁹

The ΔG values for the metal hydrides in the deprotonation reactions as depicted in the acid–base relationship (Figure 3a) was calculated and used to generate the ΔpK_a values. Because one pK_a unit corresponds to 1.37 kcal·mol^{−1} difference in free

acidity.⁵⁵ Moreover, reactivities of these complexes and the results of reactions they catalyze, are directly related to their acidities which are presented as pK_a values.⁵⁶ The N,P and NHCs, N-based Ir-complexes are the two major types of catalysts that are chiral mimics of Crabtree's catalyst and are

Figure 3. (a) Acid–base relationship of metal hydrides. (b) pK_aH of the protonated heterocycles and trend depicting the decrease of ΔpK_a values in dichloromethane as the N donors varied.

energy,⁶⁰ ΔpK_a values were calculated for the Ir-complexes (Figure 3b) in dimethyl sulfoxide and dichloromethane. A similar trend for the ΔpK_a values was observed in both solvents. (Calculation details and XYZ coordinates with energies are available in the Supporting Information.) The oxazole complex **I** was calculated to have the lowest energy. The energy differences were then measured relative to complex **I**, which was set to zero.

Allylic alcohols can be considered as relatively acid sensitive compounds. Protonation of the hydroxyl group and subsequent elimination of water, results in the generation of an allyl carbocation. It was assumed that the reason for the complex mixture of reaction products that was observed in some of the hydrogenations was due to the formation of carbocation intermediates. Several allylic alcohols that can generate different types of carbocations were tested in the hydrogenation using a set of catalysts based on different heterocycles.

In the hydrogenation of primary allylic alcohol **30**, excellent yields (over 99%) were obtained with all catalysts. This is possibly due to the difficulty in the formation of the primary carbocation. When the secondary allylic alcohol **31**, bearing a methyl group on the allylic position, was applied in the hydrogenation the amount of desired hydrogenation products follow the order $F > G > E > H > I$, which is consistent with the decreasing basicity of the heterocycle in the ligand (Figure 4).

Figure 4. Performance of Ir-complexes in hydrogenation of acid-sensitive compounds.

The same trend was observed for the hydrogenation of the phenyl substituted secondary allylic alcohol **32** and resulted in a lower yield of hydrogenated product because the generation of the carbocation is easier when the phenyl group is in the allylic position. Furthermore, when the diphenyl-substituted tertiary allylic alcohol **33** was used as substrate, an intramolecular Friedel–Crafts reaction took place instead of hydrogenation (Scheme 1).

Racemic **36** (determined by chiral HPLC analysis) was obtained as the sole product, and the C=C hydrogenation product **38** could not be detected by ¹H NMR. The Friedel–Crafts product **36** is a tetrasubstituted olefin which is usually difficult to hydrogenate using Ir–N,P catalysts.⁶¹ The cyclization of allylic alcohol **33** has earlier been reported to take place using strongly acidic conditions (Brønsted acid, e.g., FSO₃H–SO₂⁶² and Lewis acid, e.g., FeCl₃·6H₂O⁶³) as depicted in Scheme 1. The hydrogenation of the acid sensitive enol acetate was also attempted. When **39** with an alkyl substituent

Scheme 1. Intramolecular Friedel–Crafts Alkylation Catalyzed by Ir-Complexes under H₂

was used as substrate, only the imidazole complex **F** gave full conversion and excellent yield. No conversions were observed using catalyst **G**, **E**, **H**, and **I**. The hydrogenation of the phenyl substituent enol acetate **40** resulted in complex mixtures with all catalysts.

CONCLUSION

High yields and excellent enantioselectivities were obtained for most of the substrates studied using various Ir–N,P-complexes. The ΔpK_a values that have been calculated for the Ir-complexes using DFT indicate that there is a trend in the decrease of the acidity of the metal hydrides with increasing basicity of the heterocyclic ligand. The selectivity model was successfully used to confirm the observed and predicted absolute configuration of the products of hydrogenation.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b02456.

Experimental procedures, spectroscopic and computational data (PDF)

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Notes

The authors declare no competing financial interest.

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374 ■ ABBREVIATIONS

375 COD 1,5-cyclooctadiene; DFT Density Functional Theory;
376 GC/MS Gas Chromatography Mass Spectroscopy; HPLC high
377 performance liquid chromatography

378 ■ REFERENCES

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