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Iridium-Catalyzed Asymmetric Hydrogenation of Vinyl Ethers

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Dedicated to Professor Andreas Pfaltz's 60th birthday.

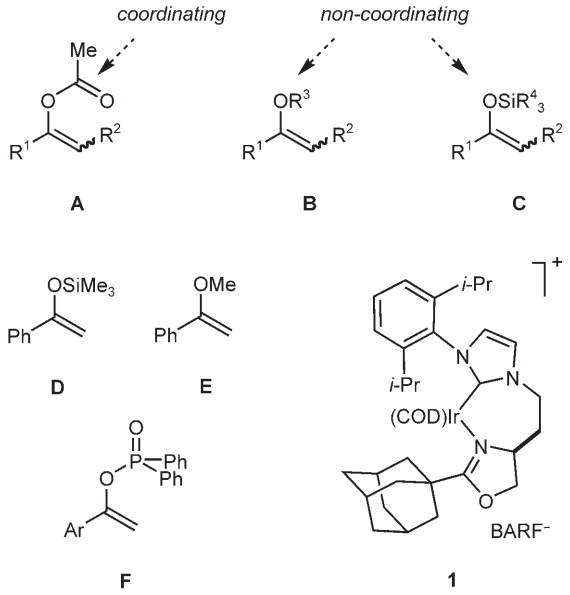
Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: A carbene-oxazoline catalyst **1** proved to be an effective catalyst for reduction of an enol ether that the literature suggested could not be hydrogenated effectively by *P,N*-Ir catalysts. Thus, a series of ester and alcohol substrates were hydrogenated using catalyst **1**. Good to excellent enantioselectivities and high conversions were obtained.

Keywords: alkenes; asymmetric catalysis; enol ethers; N-heterocyclic carbenes; hydrogenation; iridium

In our view, alkenes for asymmetric hydrogenations can be divided into three categories.[1] At one extreme, there are "coordinatively-functionalized alkenes", that have proximal directing groups that are likely to bind transition metals in a catalytic cycle. Alkenes with only alkyl substitutents are at the other extreme; they are completely unfunctionalized. Intermediate between these extremes are "non-coordinatively functionalized alkenes". These have a proximal functional group that does *not* coordinate to transition metal catalysts and direct stereofacial modifications. There are more non-coordinative functional groups than coordinative ones, so this intermediate category is the *largest*. It also contains an abundance of precursors to useful chirons for organic syntheses.

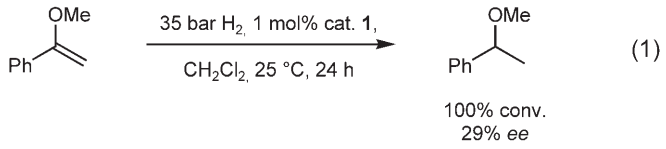
Asymmetric hydrogenations of enol ethers illustrate the viewpoint outlined above. Enol acetates **A** have a coordinative functional group, the carbonyl of the acetate, that can transiently bind to a metal center. Consequently, the literature contains many examples of asymmetric hydrogenations of enol acetates, and most of them are quite successful.[2–13] Conversely, alkylated, and silylated enol ethers, **B** and **C** are, by our definition, non-coordinatively functionalized. There are relatively few reports of asymmetric hydrogenations of these, and the enantioselectivities observed have not reached levels that are practical for general application in organic syntheses (alkylated enol ethers,[14–16] silylated enol ethers,[17] furans[16,18]).



Pfaltz's realization[19] that phosphine-oxazoline ligands could be used to form chiral analogues of Crabtree's catalyst[20] has inspired many researchers. Following his lead, Andersson and co-workers investigated chiral *N,P*-ligated iridium complexes in asymmetric hydrogenations of the silyl and methyl enol ethers **D** and **E**, but complex mixtures were obtained using four different catalysts. Subsequently, their study evolved into an investigation of the successful hydrogenations of the enol phosphinates **F**.[21] Our group was also studying enol ethers as substrates at the time this research was published. Our data are now reported here.

The reaction of Eq. (1) shows the first hydrogenation of an enol ether studied in our laboratories. 1-Methoxy-1-phenylethene (**E**) was reduced *efficiently*

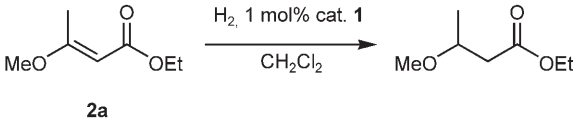
to product using the carbene-oxazoline catalyst **1**. The low enantioselectivity observed for this particular substrate was not a concern because there are many routes to chiral aryl-(1-hydroxyethyl) compounds. On the other hand, the high conversion to one single product obtained with the carbene-oxazoline catalyst **1** contrasted with the poor results reported for similar *N,P*-ligands, and provided motivation to investigate the substrate scope.



(1)

The enol ether **2a**, available from the corresponding keto ester and trimethyl orthoformate, was selected as a substrate for further studies and optimization of the reaction conditions (Table 1). Hydrogen pressures

Table 1. Optimization of hydrogenation conditions for substrate **2a**.



2a

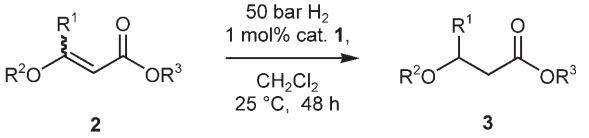
Entry	Temp. [°C]	Pressure [bar]	Time [h]	Conversion[a] [%]	*ee*[b] [%]
1	25	5	24	<5	5
2	25	50	24	81	78
3	25	100	24	82	79
4	25	50	48	>99	78
5	50	50	12	95	73
6	−20	50	12	30	83
7	25	50	12	95	77[c]
8	25	50	12	68	83[d]

[a] Determined by ^{1}H NMR.
[b] Determined via chiral GC.
[c] Catalyst loading, 5 mol%.
[d] Catalyst loading, 0.2 mol%.

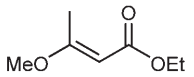
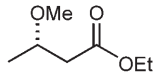
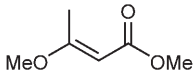
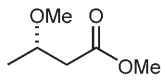
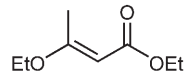
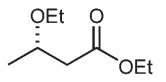
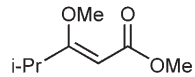
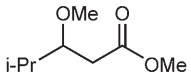
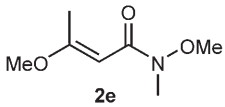
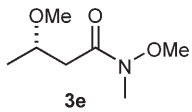
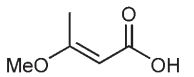
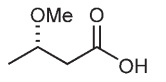
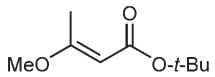
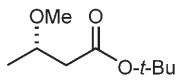
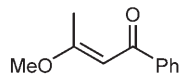
greater than 5 bar were shown to be necessary, but increasing from 50 to 100 bar had no productive effect (entries 1–3). Complete conversion was observed when the reaction time was extended from 24 to 48 h (entry 4). At 50 °C the reaction proceeded faster but the enantioselectivity decreased (entry 5). Conversely, a slightly higher enantioselectivity was observed at −20 °C but the conversion was poor (entry 6). Entries 7 and 8 show that a slightly higher enantioselectivity was observed at a lower catalyst loading, but the conversion was less reflecting a slower reaction rate. On the basis of these observations, the conditions used in entry 4 were selected for application to different substrates.

Table 2 shows hydrogenations of similar substrates **2a**–**h** at 48 h reaction time. High conversions could be

Table 2. Asymmetric hydrogenation of vinyl ether esters.



2 **3**

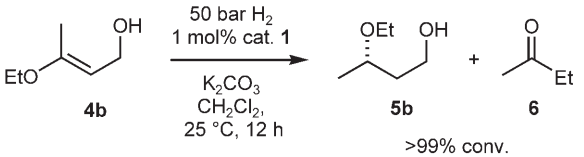
2	Conversion [%][a]	*ee* [%][b]	**3**[c]
 **2a**	>99	78	 **3a**
 **2b**	85	60	 **3b**
 **2c**	>99	66	 **3c**
 **2d**	15	n.d.[d]	 **3d**
 **2e**	90	90	 **3e**
 **2f**	99	63	 **3f**
 **2g**	>99	88	 **3g**
 **2h**	<5	n.d.[e]	

[a] Determined by ^{1}H NMR.
[b] Determined *via* analysis on a chiral GC column.
[c] Stereochemical assignments *via* reduction of the hydrogenation products to primary alcohol then comparison with authentic samples.
[d] Assignment of the absolute configuration of the product was not made.
[e] *E/Z* isomerization occurs during the reaction and most of the starting material remains.

achieved for esters **2a**–**c** where the substituents are not large, but the isopropyl-substituted enol ether **2d** gave only 15% conversion in the first 48 h of the reaction. The *N*-methoxy amide **2e** was a good substrate for this reaction; it gave a high conversion and the best enantiomeric excess in the series. However, the enantioselectivity for the corresponding acid **2f** was significantly diminished. When the size of the ester group in this series was increased to *tert*-butyl as in substrate **2g**, the enantiomeric excess increased significantly. Finally, the phenyl ketone **2h** did not hydrogenate quickly under these conditions and *E/Z*-isomerization of the alkene was observed.

DIBAL reduction of the ester **2c** gave the allylic alcohol **4b**. However, when this was hydrogenated under the conditions specified in Table 2 (and Table 3, entry 1) then the ketone **6** was formed in preference to the desired ether **5b**. One explanation for this is protonation of the hydroxy group, elimination to an enone, then hydrogenation. Indeed, entries 2–4 in Table 3 show that progressively higher amounts of anhydrous potassium carbonate enhance the chemoselectivity of the reaction in favor of the hydrogenation product **5b**, and the *ee* values throughout were excellent. It was also observed that when 4 Å molecular sieves were used (and *no* potassium carbonate) then **5b** could also be the major product (data not shown).

Table 3. Optimization of the hydrogenation conditions to avoid ketone formation.

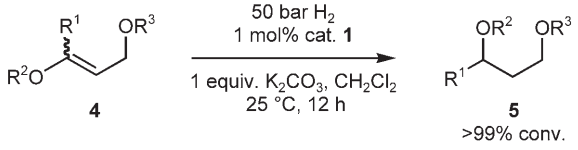


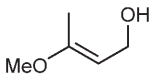
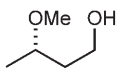
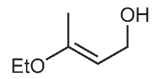
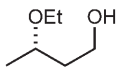
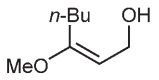
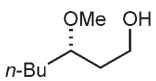
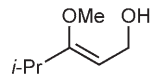
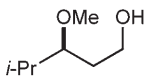
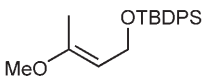
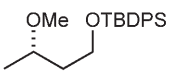
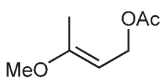
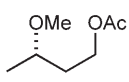
Entry	K_2CO_3 [mol%]	**5b**:**6**[a]
1	0	30:70
2	20	67:33
3	30	83:17
4	50	>99:1.0

[a] Determined by ^{1}H NMR.

The observations outlined above led us to broaden the substrate scope to include those shown in Table 4. Substrates **4a** and **b** have methyl-to-ethyl relationships, and this change did not significantly alter the enantioselectivities observed. The enantioselectivity reduced only very slightly when the alkene methyl-substituent was replaced with an *n*-butyl as in substrate **4c**. Substrate **4d** has a *Z*-stereochemistry and a more bulky substituent (*i*-Pr). For this compound the enantioselectivity observed was also high, and the catalyst approached the alkene from the same face effectively giving an inverted stereochemistry because the alkene geometry was reversed. Hydrogenation of substrate **4e** compared with the corresponding alcohol **4a** indicates that the catalyst approaches the alkene from the *same* direction for the silylated substraste, and high enantiomeric selectivity is maintained. Similarly the acetate **4f** was hydrogenated with good enantioselectivity and from the same face. Potassium carbonate was *not* required to obtain high conversions with the protected alcohols **4e** and **f**. Conversions were very high throughout this series and the reaction was faster than for the corresponding esters shown in Table 2.

Table 4. Asymmetric hydrogenation of vinyl ether alcohols.



4	*ee* [%][a]	**5**[b]
 **4a**	96	 **5a**
 **4b**	98	 **5b**
 **4c**	93	 **5c**
 **4d**	91	 **5d**
 **4e**	89[c]	 **5e**
 **4f**	92[c]	 **5f**

[a] Determined by ^{1}H NMR.[a] Determined *via* analysis on a chiral GC column.
[b] Stereochemical assignments were made via comparison with authentic samples.
[c] K_2CO_3 was not required in this case.

Finally, the reaction of Eq. (2) was performed on a slightly larger scale than those shown in Table 4. The

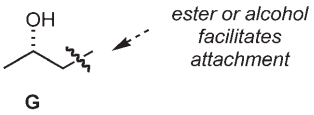
product of this reaction **5a** was isolated in high yield *via* column chromatography.

(2)

The data presented in this paper raise some interesting questions. Firstly, why did these transformations succeed when similar ones featuring *N,P*-iridium complexes did not, at least in the case of the reaction of Eq. (1)?[21] We hypothesize that this difference might be related to the Ir-electron densities in the catalyst. Assuming that Ir(5+) complexes are involved,[22–24] superior acceptor-backbonding to phosphine ligands relative to imidazolinidine ligands stabilizes *lower* oxidation states. Lower oxidation states result from deprotonation of the metal center. Thus we predict that Ir(5+) intermediates are more acidic for phosphine complexes compared to the corresponding carbene ones (Figure 1). If so, this acidity may be detrimental in hydrogenations of acid-sensitive substrates like enol ethers.

Previous studies from our laboratory had highlighted greater degrees of double bond migration in Ir-mediated hydrogenations based on *N,P*-catalysts, relative to *N,carbene*-systems.[25] Enhanced acidities for the phosphine catalysts may play a role in this situation.

Hydrogenation of substrates **2** and **4** both provide access to the terminal fragment **G** in more complex molecules. That small motif is common in natural products and their analogues; consequently, hydrogenation of these substrates, particularly **4**, can be regarded as a route to this privileged chiron.



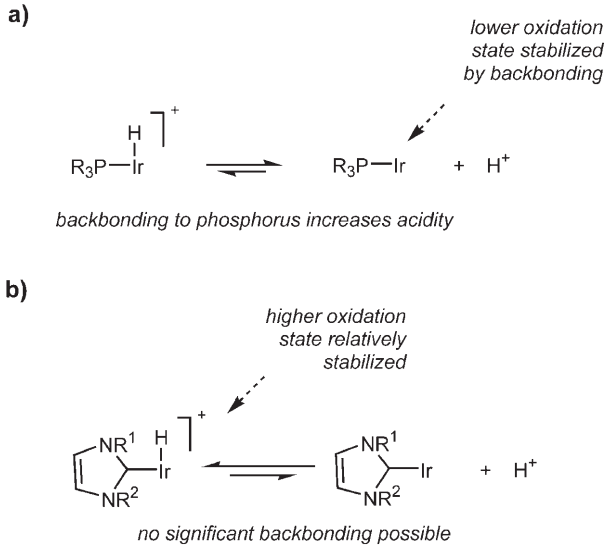


Figure 1. Postulated increased acidity for phosphine Ir(5+) complexes relative to the corresponding carbenes.

Experimental Section

Typical Hydrogenation Procedure

The alkene was dissolved in CH_2Cl_2 (0.5 M) and the iridium catalyst **1** (1 mol%) was then added. The resulting solution was degassed by three cycles of freeze-pump-thaw and then transferred to a Parr bomb. The bomb was flushed with hydrogen for 1 min without stirring. The mixture was then stirred at 700 rpm under 50 bars of H_2. After 48 h (for esters and its derivatives) or 12 h (for alcohols and its derivatives), the bomb was vented and the solvent evaporated. The conversion was measured by ^{1}H NMR. The crude product was passed through a silica plug (EtOAc/hexanes = 3:7) to obtain the purified material. Enantiomeric ratios were measured through chiral capillary GC analysis using a β- or a γ-CD column (carrier gas: helium; column pressure: 18.21 psi; gas flow rate: 1.6 mL min^{-1}; gradient temperature: 5 °C min^{-1}: 60 °C hold time: 10 min, 120 °C, 15 min).[27]

Acknowledgements

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