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Asymmetric Hydrogenation of Enol Phosphinates by Iridium Catalysts Having N,P Ligands

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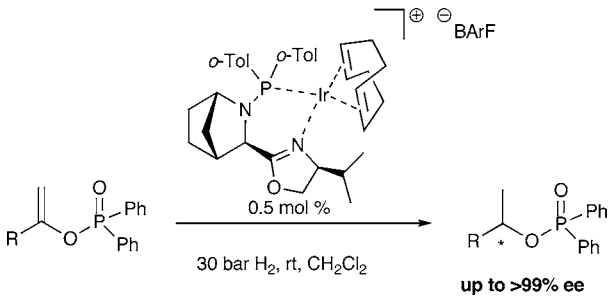
ABSTRACT



Enol phosphinates, which are structural analogues of enol acetates, have for the first time been employed as substrates for Ir-catalyzed asymmetric hydrogenation. A number of enol phosphinates have been synthesized and reduced successfully with up to and above 99% ee.

Asymmetric hydrogenation has become a powerful tool to synthesize various chiral precursors of academic and industrial importance. Particularly, there has been intense interest in asymmetric hydrogenation of prochiral olefins.[1] Since the first reports of Rh-diop[2] and Ru-BINAP[3] catalysts, many phosphine ligands have been developed and evaluated for the hydrogenation of functionalized olefins.[4] Enol esters are of special interest because the products of their asymmetric hydrogenation are chiral esters, which can be easily transformed into chiral alcohols. This reaction is therefore an alternative to the direct hydrogenation of ketones.

However, the hydrogenation of enol esters is generally more difficult than the reduction of their topological analogues, enamides. This may be due to the weaker coordination ability of the enol ester to the metal center. To date, DIPAMP, DuPhos, KetalPhos, and TangPhos complexes of rhodium have been utilized in asymmetric hydrogenations of enol esters, with very good enantioselectivities.[5]

Since the first chiral mimic of Crabtree's complex[6] by Pfaltz and co-workers,[7] and its subsequent successful use in asymmetric hydrogenation of olefins, there have been many reports of chiral N,P ligands and Ir-catalyzed hydrogenations.[8]

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Although Ir-catalyzed asymmetric hydrogenation is well studied for unfunctionalized olefins and excellent results for this reaction have been obtained, there have been very few successful results with olefins bearing weakly coordinating functional groups. This was noted in a recent review, which stated that "more effort has been placed on ligand development for iridium systems, than on investigations of substrate scope".[9]

Chiral phosphine−oxazole ligands developed in our group[10a,b] have been employed in the Ir-catalyzed hydrogenation of allylic alcohols and corresponding acetates, with ee values up to 99%. Pfaltz et al. have reported the hydrogenation of allylic esters[8a] using Ir−phosphinite−oxazoline and Ir−diaminophosphine−oxazoline complexes. Knochel et al.[10c] have demonstrated that amino acid derivatives can be obtained in 96% ee from enamides. However, the substrate scope of functionalized olefins has yet to be fully explored and, to our knowledge, there are very few reports where enol esters or enol ethers have been used as substrates for Ir-catalyzed hydrogenations.[11]

Recently, we have reported on several novel classes of chiral N,P ligands. Their Ir complexes (Figure 1, **1**−**4**) have been employed in asymmetric hydrogenation of aryl imines (up to 92% ee),[12] as well as of di- and trisubstituted unfunctionalized olefins (up to 99% ee).[10a,b] In view of these excellent results, we became interested in applying these complexes to the hydrogenation of enol esters.

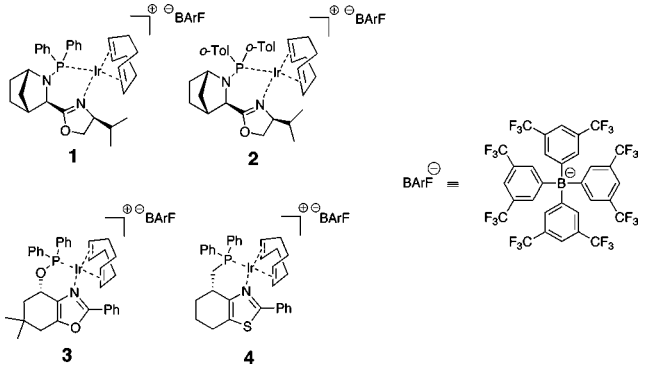
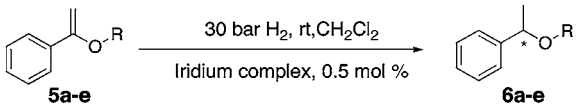


Figure 1. Iridium complexes used in hydrogenation studies.

Table 1. Ligand and Substrate Optimization Studies[a]



R	1	2	3	4
-TMS **5a**	Obtained complex mixture with catalysts 1-4 [b]			
-CH_3 **5b**	Obtained complex mixture with catalysts 1-4 [c]			
5c	Complex mixture[c]	Full conv. Rac	Complex mixture[c]	No conv
5d	Complex mixture[c]	Full conv. 65%ee	Complex mixture[c]	No conv
5e	30%conv 82%ee	**Full conv. 95% ee**	41% conv. 63% ee	No conv

[a] Conversions were determined by ^{1}H NMR spectroscopy; ee values were determined by chiral HPLC. [b] Acetophenone was the major product. [c] Ethyl benzene was the major product.

Initially, we screened these four complexes (Figure 1, **1**−**4**) in the hydrogenation of enol esters and enol ethers to establish reactivity and selectivity. Hydrogenation of enol ethers **5a** and **5b** gave complicated mixtures with all catalysts tried. Complex **4**, which has previously given excellent results with unfunctionalized olefins, was ineffective for all enol esters in this study. Complex **3** showed some conversion but the reactions were generally sluggish and resulted in multiple products. Complex **2** proved to be more efficient than **1** in terms of selectivity and reactivity.

When attempting the reduction of **5c** with **2** we observed a significant amount of ethyl benzene as byproduct, and the alkyl acetate obtained was racemic. This observation may be explained by the formation of Brönsted acids during the reaction, as recently reported by Matsuda et al.[13] These authors found that allylic alcohols behave as good leaving groups in the presence of a catalytic amount of iridium activated by H_2; substitution with external nucleophiles can then occur. They also noted that the replacement of the Ir complex with CF_3SO_3H yielded identical results.

Hydrogenation of **5d** also proceeded to completion, but the hydrogenolysis of the phosphinate group occurred for around 50% of the substrate. Interestingly, enantioselectivity improved to 65% upon the replacement of the C═O group with P═O.

Hydrogenation of enol diphenylphosphinate **5e** with complex **2** resulted in high ee (95%), full conversion, and no detectable loss of phosphityl group. Asymmetric hydrogenation of enol phosphonates and phosphinates was previously observed using Rh-based catalyst, with moderate ee values.[14]

Hydrogenation of **5e** with 0.5 mol % of catalyst **2** under standard conditions but varying H_2 pressures showed 30 bar

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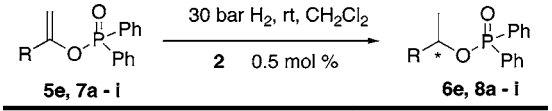
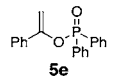
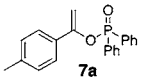
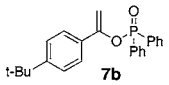
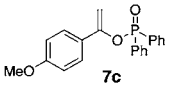
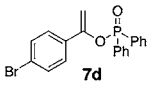
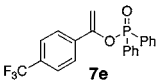
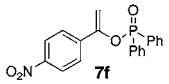
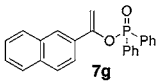
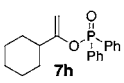
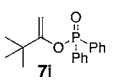
to be optimal. At lower pressures than 30 bar, prolonged reaction times were required, though no significant effect on ee was observed. With use of 30 bar of H_2, **5e** gave the corresponding alkylphosphinate (**6e**) in 95% ee, with almost quantitative conversion in 30 min. The same conditions were applied to the hydrogenation of a range of enol phosphinates **7a**−**i** and the results are illustrated in Table 2.

Substrates bearing an electron-withdrawing group at the para position (entries 5−7) were more reactive (full conversion in 0.5−1 h) than the substrates bearing an electron-donating group (entries 2−4) (full conversion in 3−4 h). This indicates that the electronics of the substrate influence the reactivity but not selectivity. A decrease in ee was noticed with substrate **7f** having a naphthalene moiety.

Table 2. Iridium-Catalyzed Hydrogenation of Substrates[a]



entry	substrate	conv., %[b]	ee, %[c]	abs. config[d]
1	 **5e**	>99	95	(+) R
2	 **7a**	97	96	(+) R
3	 **7b**	93	94	(+) R
4	 **7c**	48[e]	98	(+) R
5	 **7d**	**>99**	**>99**	(+) R
6	 **7e**	**>99**	**99**	(+) R
7	 **7f**	>99	92	(+) R
8	 **7g**	>99	85	(-) R
9	 **7h**	>99	92	(+) R
10	 **7i**	**>99**	**>99**	(-) R

[a] Conditions: 30 bar of H_2, rt, CH_2Cl_2, 0.5 mol % catalyst. [b] Determined by ^1H NMR spectroscopy. [c] Determined by chiral HPLC or chiral GC. [d] Hydrolyzed to the corresponding alcohol and compared with literature data. [e] Reaction performed in the presence of poly(4-vinylpyridine) resin (10 mg) with 50 bar of H_2 and 2 mol % catalyst.

Hydrogenation of **7c** led to decomposition and very little desired product observed (5−10%). This is presumably due to the presence of a strong electron-donating group at the para position, which makes the double bond electron rich. As a result, the phosphinate may become a good leaving group. Formation of diphenylphosphinic acid was confirmed by ^{31}P NMR spectroscopy.

Nevertheless, we were able to improve the yield of the hydrogenation of this substrate to 45−50% via the addition of a proton scavenger (10 mg of poly(4-vinylpyridine) resin). Because the additive also deactivates the catalyst, 2 mol % of catalyst and longer reaction time (overnight) was required. However, the ee of the product obtained was good.

Interestingly, alkyl enol phosphinates (**7h** and **7i**) were also hydrogenated with excellent selectivity, although it was difficult to achive selectivity for alkyl ketones.[4b] For **7h** and **7i** full conversion was accomplished in 3 h, with 92% and 99% ee, respectively.

All alkyl phosphinates were easily transformed to corresponding alcohols without any loss of enantioselectivity by treatment with *n*-BuLi.

As depicted in Figure 2, it is also possible to make chiral phosphane compounds by displacing the phosphityl group with diphenyl phosphine.[15]

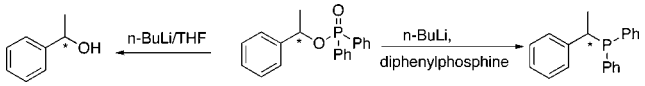


Figure 2. Applications of chiral alkyl phosphinates.

It should be noted that the ee values obtained here are the best ever reported for these substrates, even when compared with reduction of corresponding ketones. In conclusion, we have shown for the first time that Ir complexes of chiral N,P ligands can catalyze the asymmetric hydrogenation of enol esters. Complex **2** has proven to be efficient in hydrogenating a range of enol phosphinate substrates with high selectivity (85−99% ee). Our current effort is focus on further broadening the scope of these catalysts.

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Supporting Information Available: Experimental procedures for the preparation of the substrates, hydrogenation procedures, characterization data, and chiral separation data. This material is available free of charge via the Internet at http://pubs.acs.org.

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