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Asymmetric Hydrogenation of Itaconic Acid and Enol Acetate Derivatives with the Rh-TangPhos Catalyst

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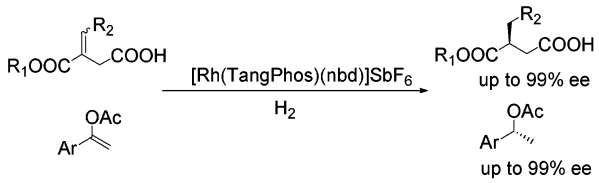
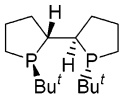
ABSTRACT



The Rh-TangPhos catalyst has been used for asymmetric hydrogenation of itaconic acid and enol acetate derivatives. A variety of chiral 2-substituted succinic acids and chiral acetates have been obtained in excellent ee values (up to 99% ee).

Since Knowles developed the chiral phosphine DIPAMP and realized the first efficient synthesis of chiral α-amino acids via transition metal-catalyzed asymmetric hydrogenation in the 1970s,[1] chemists have taken tremendous efforts in developing efficient chiral phosphine ligands to apply asymmetric hydrogenation for the synthesis of chiral compounds.[2] Today, asymmetric hydrogenation has become one of most efficient methods for the synthesis of chiral α-amino acids, chiral *β*-amino acids, chiral amines, chiral alcohols, and many other important chiral intermediates. However, although a number of efficient chiral ligands and a few successful hydrogenation processes have been developed, the current substrate scope of asymmetric hydrogenation is still far from satisfactory.[2] Developing new efficient chiral ligands and expanding the substrate scope continue to be of great importance. We have recently developed a new chiral bisphospholane ligand-TangPhos (Figure 1), which has been successfully applied in asymmetric hydrogenation of α-(acylamino)acrylic acids,[3a] α-arylenamides,[3a] and *β*-(acylamino)-acrylates.[3b] Herein we report the applications of TangPhos in asymmetric hydrogenation of itaconic acid and enol acetate derivatives. Extremely high enantioselectivities (up to 99% ee) have been obtained in hydrogenation of both alkyl and aryl itaconic acids. Excellent ee values were also achieved in hydrogenation of acyclic enol acetates bearing aromatic substituents.



TangPhos

Figure 1. Structure of TangPhos.

Chiral 2-substituted succinic acids have attracted great interest for their utility as chiral building blocks.[4] One of the simplest methods for their syntheses is the Rh-catalyzed asymmetric hydrogenation of itaconic acids. However,

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(2) For recent reviews of asymmetric hydrogenation, see: (a) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima. I., Ed.; Wiley-VCH: Weinheim, Germany, 2000; p 1. (b) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfalts, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; p 121. (c) Ohkuma, T.; Noyori, R. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfalts, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; p 199. (d) Blaser, H.-U.; Spindler, F. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfalts, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; p 247.

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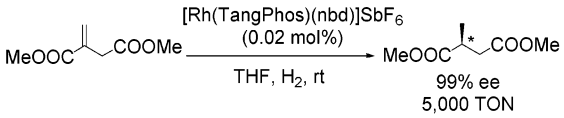
although many chiral ligands have been successfully applied for asymmetric hydrogenation of the parent itaconic acid or its methyl ester,[5] there are only a few successful results for hydrogenation of β-substituted itaconic acid derivatives.[6] The best catalytic system to date is the Rh-Et-DuPhos catalyst, which has shown great ee values for both β-alkyl and β-aryl itaconic acids.[7] We applied TangPhos as the ligand for hydrogenation of dimethyl itaconate (Scheme 1). The initial

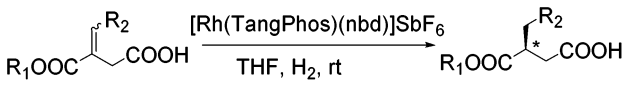
Scheme 1. Asymmetric Hydrogenation of Dimethyl Itaconate



reaction was carried out at room temperature under 20 psi of H_2 pressure with 0.5 mol % of [Rh(TangPhos)nbd]SbF_6 as the catalyst precursor. When methanol was used as the reaction solvent, the hydrogenation product (*S*)-dimethyl 2-methylsuccinate was obtained in 98% ee and in quantitative yield. Further screening of the reaction solvent showed that THF was a better solvent in terms of the enantioselectivity (99% ee in THF). We thus used THF as the solvent to test the catalytic efficiency of the Rh-TangPhos system for this reaction. When 0.02 mol % [Rh(TangPhos)nbd]SbF_6 (2 μmoL) was used as the catalyst precursor, the hydrogenation of dimethyl itaconate (10 mmol) proceeded smoothly to give the product in complete conversion (5000 TON) and in 99% ee (Scheme 1).

We then applied the Rh-TangPhos catalyst to hydrogenation of various β-substituted itaconic acid derivatives (Table 1). The substrates were prepared from dimethyl succinate and aldehydes via Stobbe condensation.[7,8] The obtained *E*/*Z* isomeric mixtures of the substrates were directly used for hydrogenation. The hydrogenations were conducted at room temperature in THF with 0.5 mol % Rh(TangPhos)nbd]SbF_6

Table 1. Asymmetric Hydrogenation of β-Substituted Itaconic Acid Derivatives with the Rh-TangPhos Catalyst



entry[a]	R_1	R_2[b]	ee (%)[c]
1	H	H	99
2	CH_3	$CH(CH_3)_2$	96
3	CH_3	Ph	95
4	CH_3	*p*-MeO−Ph	97
5	CH_3	*p*-Me-Ph	97
6	CH_3	*p*-Cl-Ph	>99
7	CH_3	*m*-Cl-Ph	99
8	CH_3	1-naphthyl	99
9	CH_3	2-naphthyl	99

[a] The hydrogenations were carried out at room temperature in THF under 20 psi of hydrogen pressure with [Rh(TangPhos)(nbd)]SbF_6 (0.5 mol %) as the catalyst precursor. All reactions proceeded completely. The absolute configurations of the products were determined as *S* by comparing the optical rotations with reported values [b]Most substrates (except entry 1) were employed as crude *E*/*Z* mixtures ranging from 2/1 to >10/1.[7] [c] The ee values were determined by chiral HPLC (Chiralcel OD-H) or chiral GC (chiralselect 1000) after conversion of the hydrogenation products into their dimethyl esters.

as the catalyst precursor. As shown in Table 1, a variety of *E*/*Z* isomeric mixtures of β-alkyl and β-aryl itaconic acid derivatives provide excellent ee values with complete conversions. No major electronic effect was observed in hydrogenation of β-aryl itaconic acid derivatives, since all electronic-rich and electronic-poor substrates gave excellent ee values (entries 4−6). Two naphthyl derivatives also provided extremely high ee values (entries 8 and 9). It is noteworthy that these ee values are comparable to those obtained with the Rh-Et-DuPhos system.[7]

Asymmetric hydrogenation of enol acetates may serve as an alternative to direct hydrogenation of ketones since the chiral acetate products can be easily transformed into chiral alcohols. Several efficient chiral Rh[9] or Ru[10] catalysts have been reported for this type of substrate. For example, asymmetric hydrogenation of electron-poor enol actates bearing carboxylic ester[9c] or phosphonate groups[9e] has been successfully realized by the Rh-DuPhos system. High enantioselectivities were also obtained for some acylic enol acetates bearing a vinylic or acetylenic substituent.[9b] Up to 99% ee values have been reported in hydrogenation of cyclic aromatic enol acetates with a Rh-PennPhos catalyst.[9d] However, for acyclic aromatic enol acetates, only modest to good ee values have been reported (Rh-DuPhos: up to 91% ee;[9a] Rh-PennPhos: up to 85% ee:[9d] Ru-−BINAP: 73% ee[10a]). We applied the Rh-TangPhos catalyst for asymmetric

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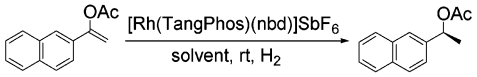
hydrogenation of aromatic enol acetates. 1-(2-Naphthyl)-1-(acetyloxy)ethylene was chosen as the substrate to screen the reaction conditions. As shown in Table 2, a dramatic solvent effect was observed in this hydrogenation reaction. The highest ee (97% ee) value was obtained when EtOAc was used as the solvent. It is noteworthy that this is the best ee reported to date for asymmetric hydrogenation of 1-(2-naphthyl)-1-(acetyloxy)ethylene.

Table 2. Solvent Effect in Asymmetric Hydrogenation of 1-(2-Naphthyl)-1-(acetyloxy)ethylene with the Rh-TangPhos Catalyst

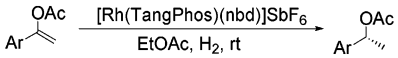


entry[a]	solvent	conversion (%)	ee (%)[b]
1	CH_3OH	100	90
2	THF	100	95
3	toluene	35	94
4	CH_2Cl_2	100	85
5	EtOAc	100	97

[a] The hydrogenations were carried out at room temperature under 20 psi of hydrogen pressure with [Rh(TangPhos)(nbd)]SbF_6 (1 mol %) as the catalyst precursor. The absolute configurations of the products were determined as *R* by comparing the optical rotations with reported data.[b] The ee values were determined by chiral GC (chiralselect 1000).

With EtOAc as the solvent, we thus used the Rh-TangPhos system for asymmetric hydrogenation of various aromatic enol acetate derivatives. The results are shown in Table 3. As can be seen, a diverse set of aromatic enol acetates have been reduced to chiral acetates in excellent ee values. A furyl derivative also gave a high ee (entry 5). To the best of our knowledge, these are among the highest ee values for asymmetric hydrogenation of acyclic aromatic enol acetates.

Table 3. Asymmetric Hydrogenation of Aromatic Enol Acetates with the Rh-TangPhos Catalyst



entry[a]	Ar	ee (%)[b]
1	2-naphthyl	97
2	Ph	96
3	*p*-F-Ph	92
4	*p*-Cl-Ph	97
5	2-furyl	93
6	*p*-NO_2-Ph	99

[a] The hydrogenations were carried out at room temperature in EtOAc under 20 psi of hydrogen pressure with [Rh(TangPhos)(nbd)]SbF_6 (1 mol %) as the catalyst precursor. All reactions proceed completely. The absolute configurations of the products were determined as *R* by comparing the optical rotations with reported data. [b] The ee values were determined by chiral GC (chiral select 1000).

In conclusion, we have applied the Rh-TangPhos catalyst for asymmetric hydrogenation of various substituted itaconic acid and aromatic enol acetate derivatives. High enantioselectivities and reactivities have been observed for both types of substrates. These results demonstrate that the Rh-TangPhos catalyst is a very efficient hydrogenation catalyst for the synthesis of a variety of chiral 2-substituted succinic acids and chiral acetates.

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Supporting Information Available: Procedures for asymmetric hydrogenation and GC or HPLC conditions of chiral products. This material is available free of charge via the Internet at http://pubs.acs.org.

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