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A Highly Effective Rhodium Spirocyclic Phosphinite Catalyst for the Asymmetric Hydrogenation of Enamides

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Abstract: A rhodium complex of the phosphinite ligand *spirOP* was found to be an effective catalyst for the asymmetric catalytic hydrogenation of α-substituted enamides with ee values ranging from 85.1% to 97.4%.

Chiral amines and their derivatives are useful pharmaceutical intermediates, resolving agents and chiral auxiliaries.[1] Traditional methods for the synthesis of these valuable compounds include fermentation, optical resolution and the stoichiometric use of chiral auxiliaries.[2] From a practical standpoint, the asymmetric catalytic hydrogenation of enamides is expected to provide a convenient and economical route to chiral amine derivatives.[3] Unfortunately, except for the asymmetric hydrogenation of specific cyclic enamides with Ru(BINAP) catalyst which showed high enantioselectivity,[4] the enantioselective hydrogenation of simple α-substituted enamides has been relatively unsuccessful.[5] For example, in the asymmetric hydrogenation of α-phenylenamide **1a** catalyzed by most of the well known rhodium and ruthenium chiral diphosphine complexes, the ee's of the product were generally quite poor:[5,6] Rh(BINAP), 15.1%; Rh(CHIRAPHOS), 40.7%; Rh(SKEPHOS), 7.1%; Rh(DIOP), 56.6%; Ru(BINAP), 53.7%. This is in great contrast to the highly successful asymmetric hydrogenation of amidoacrylic acids leading to chiral amino acids and derivatives.[7] At present, only two catalyst systems, namely Rh(DuPHOS)[6] and Rh(BDPAB) [including Rh(H_8-BDPAB)][8], are effective in the catalytic asymmetric hydrogenation of simple α-substituted enamides. For the practical and convenient synthesis

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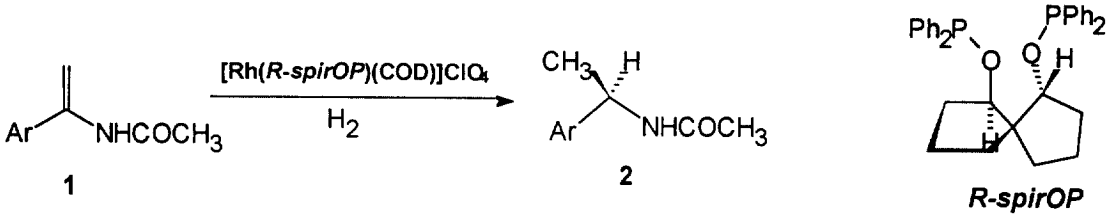
of chiral amines and derivatives, it is highly desirable to develop new catalyst systems which are highly active and enantioselective in the asymmetric hydrogenation of simple α-substituted enamides.

We have recently reported the rhodium phosphinite complexes, [Rh(*R-spirOP*)(COD)]BF_4 and [Rh(*S-spirOP*)(COD)]BF_4, which proved to be highly effective in the asymmetric hydrogenation of amidoacrylic acids.[9] Now we have found that the rhodium-phosphinite complexes are equally effective in the hydrogenation of α-substituted enamides. This communication reports the results of [Rh(*R-spirOP*)]$^+$ catalyzed asymmetric hydrogenation of enamide **1**.



1 **2**

The solvent effect on the hydrogenation of α-phenylenamide **1a** (**1**: Ar = Ph) was examined in a variety of common organic solvents. When the reaction using [Rh(*R-spirOP*)(COD)]BF_4 (1% mol) as the catalyst was carried out at ambient temperature under 100 *psi* H_2 for 10 min, 100% conversion was obtained in all cases and the enantioselectivity was found to be relatively independent of the solvent used: MeOH (83.3% ee), *i*-PrOH (83.5% ee), CH_3COCH_3 (83.1% ee), THF (81.9% ee), CH_2Cl_2(82.5% ee), $C_6H_5CH_3$ (79.3% ee). Similar enantioselectivity was observed in changing the counterion from BF_4^- to ClO_4^-. For example, 85.7% ee was obtained in the hydrogenation of **1a** in isopropanol using [Rh(*R-spirOP*)(COD)]ClO_4 as the catalyst precursor. It was found that the enantioselectivity increased at lower reaction temperature and under lower hydrogen pressure. The best result of [Rh(*R-spirOP*)(COD)]ClO_4 catalyzed hydrogenation of **1a** was achieved in isopropanol at 0°C and under 1 atm of H_2, leading to **2a** in 100% conversion and 89.0% ee.

Under similar conditions, a series of enamides were hydrogenated and the results were summarized in the Table. The best result (97.4% ee) was achieved in the hydrogenation of N-acetyl-α-(2-furanyl) ethenamine (**1g**) (entry 7 of Table). This result is comparable to the best previous literature data obtained from the [*(S,S)*-Me-DuPHOS-Rh(COD)]OTf catalyzed hydrogenation of **1g**, in which 96.1% ee *(S)* of **2g** was obtained.[6]

A remarkable feature of our catalyst is its high catalytic activity. In the [Rh(*R-spirOP*)(COD)]ClO_4 (1% mol) catalyzed hydrogenation of enamides **1a-g**, the reactions were completed within 10 min even under 1 atm of H_2 and at 0°C. The fast hydrogenation rate compares favorably with the Rh-Me-DuPHOS system. For example, 15 hours were required for the complete conversion in the hydrogenation of the enamide substrates

with [*(S,S)*-Me-DuPHOS-Rh(COD)]OTf catalyst (0.2% mol) at 22°C under 60 *psi* of H_2.[6]

Table. Asymmetric Hydrogenation of **1** Catalyzed by [Rh (*R-spirOP*) (COD)]ClO_4.[a]

entry	*Ar*		*e.e.*[b] *(config.)*
1	C_6H_5	**(1a)**	89.0% *(R)*
2	p-CH_3-C_6H_4	**(1b)**	86.5% *(R)*
3	m-CH_3-C_6H_4	**(1c)**	85.6% *(R)*
4	p-Cl-C_6H_4	**(1d)**	86.1% *(R)*
5	p-F-C_6H_4	**(1e)**	87.9% *(R)*
6	p-CF_3-C_6H_4	**(1f)**	90.0% *(R)*
7	2-furanyl	**(1g)**	97.4% *(R)*

[a]The reactions were carried out in isopropanol at 0°C and under 1 atm of H_2 for 10 min using [Rh(*R-spirOP*)(COD)]ClO_4 (1% mol) as catalyst; 100% conversion was observed in all cases. [b]The ee's were determined by GC using a Chropack Chiralsil-L-Val column (25m) as described in ref 6.

In conclusion, we have demonstrated the use of [Rh(*R-spirOP*)(COD)]ClO_4 as a highly effective catalyst for the asymmetric hydrogenation of enamides. The catalytic activity of the complex in the hydrogenation of enamides is comparable to that found in the hydrogenation of amidoacrylic acids. The present study clearly shows the versatility of Rh-*spirOP* catalyst in the hydrogenation of prochiral olefins and offers a convenient path to chiral amine derivatives *via* asymmetric hydrogenation.

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