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EFFICIENT ASYMMETRIC HYDROGENATION OF α-AMINOACETOPHENONE DERIVATIVES LEADING TO PRACTICAL SYNTHESIS OF (S)-(-)-LEVAMISOLE[1,2)]

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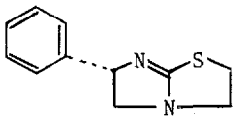
Abstract: The neutral (2S,4S)-MCCPM-rhodium complex was found to be an efficient catalyst for asymmetric hydrogenation of α-aminoacetophenone derivatives. A practical asymmetric synthesis of (S)-(-)-levamisole was realized by using this hydrogenation as a key reaction.

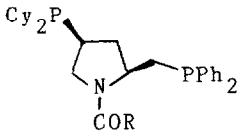
Optically active β-amino-α-phenylethanol derivatives are important chiral building blocks for the syntheses of useful biologically active compounds. Most syntheses of these compounds have relied mainly on the classical optical resolution method.[3)] Although several attempts were made to achieve homogeneous asymmetric hydrogenation of α-aminoacetophenone derivatives with chiral bisphosphine-rhodium catalysts for the synthesis of optically active β-amino-α-phenylethanols, β-reseptor-stimulating medicines and the related compounds, no practical catalyst has been developed.[4,5,6)]

Here we report the asymmetric hydrogenation of α-aminoacetophenone derivatives (**1**) with high stereoselectivity and high catalytic activity leading to (S)-(-)-levamisole (**3**)[7,8)] catalyzed by neutral (2S,4S)-N-substituted CPM (**5**)-rhodium complexes which were developed on our new concept[9)] for design of efficient chiral catalysts for asymmetric hydrogenations.[10)]

The initial results from the asymmetric hydrogenation of α-aminoacetophenone derivatives (**1**) are summarized in Table 1. All asymmetric hydrogenations of **1a-e** (5.0 mmol) proceeded smoothly in the presence of 0.1-0.001 mol% of a neutral rhodium catalyst prepared *in situ* by mixing $[Rh(COD)Cl]_2$ and a chiral ligand (**5**) in a ratio of 1 : 2.6 and 0.025 mmol of triethylamine in methanol (10 ml) at 50 °C for 20 h under the initial hydrogen pressure of 20 atm. The (2S,4S)-BCPM (**5a**)- and MCCPM (**5b**)-rhodium complexes were found to give β-amino-α-phenylethanol derivatives (**2a-e**) with high stereoselectivities (87-97 %ee) as well as high catalytic activities



(S)-(-)-Levamisole (3)

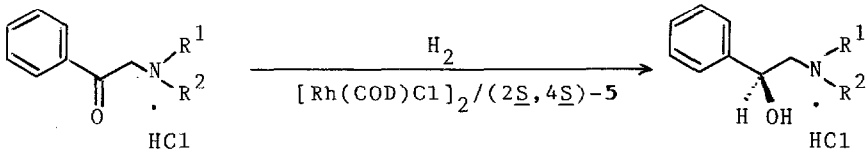


(2S,4S)-**5a, b**

5a: BCPM; R=OC(CH$_3$)$_3$

5b: MCCPM; R=NHCH$_3$

Table 1. Asymmetric Hydrogenations of α-Aminoacetophenone Hydrochloride Derivatives Catalyzed by Neutral Rhodium Complexes of (2S,4S)-N-Substituted CPM[a)]



1a-e **2a-e**

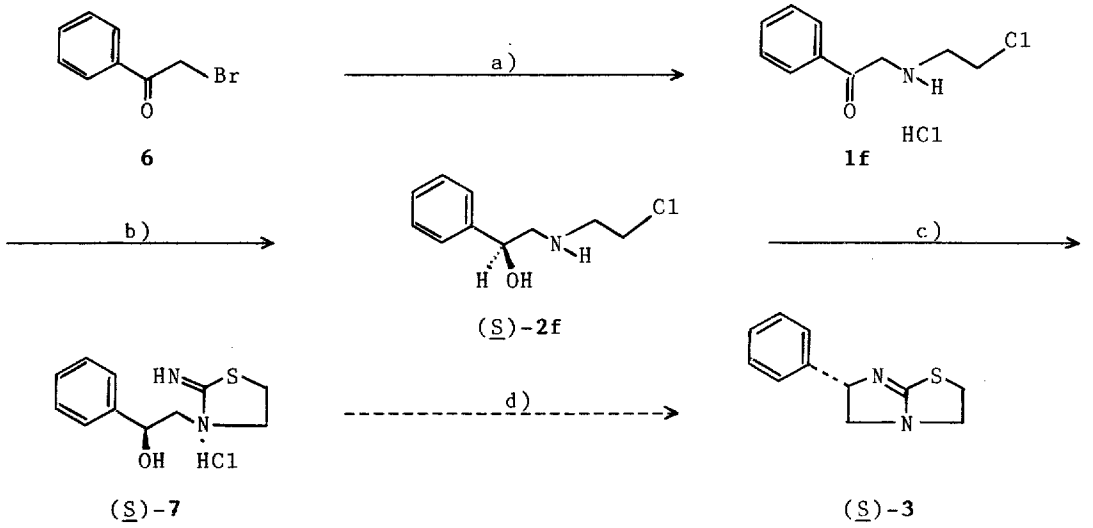
entry	substrate			ligand	conditions[a)]		product[b)]		
		R^1	R^2		subst./cat.	H_2(atm)		$[\alpha]_D^{23}$	%ee[c)] (confign.)
1	**1a**	H	H	**5a**	1000	20	**2a**	+35.5°	81 (S)
2	**1b**	Me	H	**5a**	1000	20	**2b**	+42.7°	81 (S)
3	**1c**	Me	Bn	**5a**	1000	20	**2c**	+50.9°	85 (S)
4	**1c**	Me	Bn	**5b**	1000	20	**2c**	+54.2°	90 (S)
5	**1c**	Me	Bn	**5b**	1000	5	**2c**	+54.8°	91 (S)
6	**1c**	Me	Bn	**5b**	10000	20	**2c**	+53.0°	88 (S)
7	**1d**	H	Bn	**5a**	1000	20	**2d**	+24.1°	87 (S)
8	**1d**	H	Bn	**5b**	1000	20	**2d**	+25.9°	93 (S)
9	**1d**	H	Bn	**5b**	10000	20	**2d**	+25.2°	91 (S)
10	**1e**	Et	Et	**5a**	1000	20	**2e**	+60.2°	93 (S)
11	**1e**	Et	Et	**5b**	1000	20	**2e**	+62.5°	97 (S)
12	**1e**	Et	Et	**5b**	100000	20	**2e**	+61.8°	96 (S)

Bn: $C_6H_5CH_2$-

a) All hydrogenations were carried out with substrate (5.0 mmol) and triethylamine (0.025 mmol) in methanol (10 ml) at 50 °C for 20 h. b) The chemical yields were quantitative. The conversions were 100 %, which were determined by TLC analysis. c) Calculated on the basis of the maximum optical rotations of pure enantiomers (S)-(+)-**2a-e**; [R^1, R^2, $[\alpha]_D^{23}$ (c 5.0, H_2O): H, H, +43.7°; Me, H, +52.7°; H. Bn, +27.8°; Me, Bn, +60.1°; Et, Et, +64.6°].

([Subst.]/[Rh]=1000-100000) in hydrogenation of **1a-e**.

The present asymmetric hydrogenation also finds an application in the asymmetric synthesis of biologically active compound such as (S)-(-)-levamisole (**3**) as shown in Scheme 1.



6 **1f** (S)-**2f** (S)-**7** (S)-**3**

a) 2-chloroethylamine hydrochloride, sodium hydroxide, benzenen 20 °C, 22 h, 43 %. b) chiral rhodium catalyst, triethylamine, H_2, methanol, 96 %. c) potassium thiocyanate, ethanol, H_2O, reflux, 30 h, 90 %. d) ref. 7a.

Scheme 1

2-Bromoacetophenone (**6**) was converted to 2-[N-(2-chloroethyl)]amino-acetophenone hydrochloride (**1f**)[11] with 2-chloroethylamine. The aminoacetophenone hydrochloride (**1f**) (4.68 g, 20 mmol) was added to a solution of $[Rh(COD)Cl]_2$ (0.01 mmol), (2S,4S)-MCCPM (**5b**) (0.024 mmol) and triethylamine (0.048 mmol) in methanol (30 ml). The solution was stirred at 50 °C for 20 h under an initial hydrogen pressure of 20 atm. Usual work-up gave colorless crystals of **2f**[12] (4.52 g, 96 %); mp 145-147 °C, $[\alpha]_D^{23}$= +37.2° (c 1.0, H_2O). The amino-alcohol hydrochloride (**2f**) was allowed to react with potassium thiocyanate, yielding 3-(2-hydroxyphenyl)-2-iminothiazolidine hydrochloride ((S)-(+)-**7**) in 90 %ee; mp 198-200 °C, $[\alpha]_D^{23}$= +68.2° (c 1.0, methanol), $[\alpha]_D^{23}$= +47.8° (c 2.0, H_2O)(lit.[7a] $[\alpha]_D^{25}$= +70.3° (c 1.0, methanol), 93 %ee). Thus, a formal synthesis (S)-(-)-levamisole (**3**) has been achieved by using (S)-(+)-**7** as the key intermediate.[7a]

The MCCPM-rhodium complex was found to be a very efficient catalyst for the asymmetric hydrogenation of α-aminoacetophenone derivatives and a practical synthesis of (S)-(-)-levamisole have been achieved. These

experimental findings offer practical synthetic access to optically active β-amino-α-phenylethanol derivatives which are the key intermediates for the synthesis of biologically active compounds.

References and Notes

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11) **1f**: mp 187-189 °C (decomp.). ^{1}H-NMR (DMSO-d_6) δ 3.45 (t, 2H), 4.02 (t, 2H), 4.68 (s, 2H), 7.05-8.20 (m, 5H), 9.80 (br, 1H).
12) **2f**: ^{1}H-NMR (DMSO-d_6) δ 3.12 (dd, 2H), 3.41 (t, 2H), 3.97 (t, 2H), 5.05 (dd, 1H), 6.23 (br, 1H), 7.38 (s, 5H), 9.46 (br, 1H).

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