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PRACTICAL ASYMMETRIC SYNTHESIS OF (R)-(-)-PHENYLEPHRINE HYDROCHLORIDE CATALYZED BY (2R,4R)-MCCPM-RHODIUM COMPLEX[1,2]

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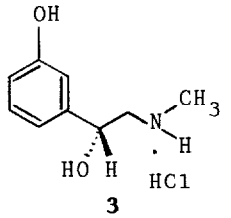
Abstract: The neutral chiral N-substituted CPM-rhodium complexes were found to be efficient catalysts for asymmetric hydrogeantion of 3'-benzyloxy-2-(N-benzyl-N-methyl)aminoacetophenone hydrochloride. A practical asymmetric synthesis of (R)-(-)-phenylephrine hydrochloride catalyzed by newly synthesized (2R,4R)-MCCPM-rhodium complex has been achieved.

(R)-(-)-Phenylephrine hydrochloride (**3**)[3] and β-receptor-stimulating medicines have a chiral benzylic alcohol group. Although several attempts were carried out with asymmetric hydrogenations of the phenacylamine derivatives catalyzed by chiral bisphosphine-rhodium complexes for the syntheses of this chiral functional groups, no practical catalyst has been developed.[4,5,6]

Here we report the asymmetric hydrogenation of 3'-benzyloxy-2-(N-benzyl-N-methyl)aminoacetophenone hydrochloride (**1**)[7] leading to practical synthesis of (R)-(-)-phenylephrine hydrochloride (**3**) catalyzed by neutral chiral N-substituted CPM (**4**)-rhodium complexes which were found to be very efficient chiral catalysts for asymmetric reduction of prochiral carbonyl compounds.[8]

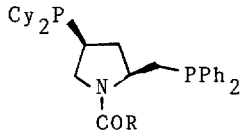
Initially, the asymmetric hydrogenation of 3'-benzyloxy-2-(N-benzyl-N-methyl)aminoacetophenone hydrochloride (**1**) was examined with neutral (2S,4S)-N-substituted CPM (**4a-i**)-rhodium catalysts for the synthesis of dibenzylated phenylephrine hydrochloride (**2**). The N-substituent effects of ligands on the enantioselectivity in the hydrogenation of **1** are summarized in Table 1. The highest enantioselectivity favoring (S)-(+)-**2** (85 %ee) was achieved by using MCPM (**4g**) or MCCPM (**4h**) as a ligand (entries 7 and 8).

Therefore, for catalytic asymmetric synthesis of pharmacologically active (R)-(-)-phenylephrine hydrochloride (**3**) via (R)-(-)-**2**, (2R,4R)-MCCPM



(R)-(-)-Phenylephrine hydrochloride
(Adrenergic Drug, α_1-Receptor
Sympathomimetic Drug)

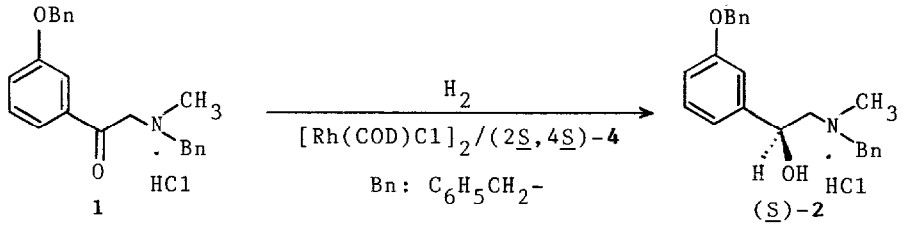
3



(2S,4S)-**4**

4a: BCPM; R=$OC(CH_3)_3$
4b: BCCPM; R=$NHC(CH_3)_3$
4c: PVCPM; R=$C(CH_3)_3$
4d: PCPM; R=OPh
4e: PCCPM; R=NHPh
4f: BZCPM; R=Ph
4g: MCPM; R=OCH_3
4h: MCCPM; R=$NHCH_3$
4i: ACPM; R=CH_3

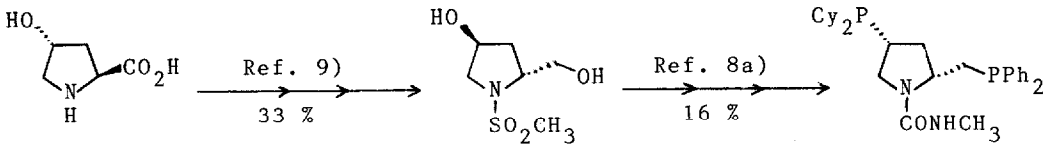
Table 1. Asymmetric Hydrogenation of 3'-Benzyloxy-2-(N-benzyl-N-methyl)-aminoacetophenone Hydrochloride Catalyzed by (2S,4S)-N-Substituted CPM-Rhodium Complexes.[a)]



1 (S)-**2**

entry	ligand (R)	product[b)] $[\alpha]_D^{23}$(c 2.0, H_2O)[c)]	%ee[d)]	confign.
1	**4a** ($OC(CH_3)_3$)	+33.8°	75	S
2	**4b** ($NHC(CH_3)_3$)	+34.5°	76	S
3	**4c** ($C(CH_3)_3$)	+34.1°	75	S
4	**4d** (OPh)	+32.4°	72	S
5	**4e** (NHPh)	+33.6°	74	S
6	**4f** (Ph)	+34.1°	75	S
7	**4g** (OCH_3)	+38.2°	85	S
8	**4h** ($NHCH_3$)	+38.5°	85	S
9	**4i** (CH_3)	+35.5°	79	S

a) All hydrogenations were carried out with substrate (3.0 mmol), triethylamine (0.03 mmol), $[Rh(COD)Cl]_2$ (0.0015 mmol) and ligand (0.0039 mmol) in methanol (10 ml) at 50 °C for 20 h under an initial hydrogen pressure of 20 atm. b) The chemical yields were quantitative. The conversions were 100 %. c) Measured after debenzylation. d) Calculated on the basis of the maximum optical rotation of pure (R)-(-)-phenylephrine hydrochloride; $[\alpha]_D^{23}$= -45.2° (c 2.0, H_2O).



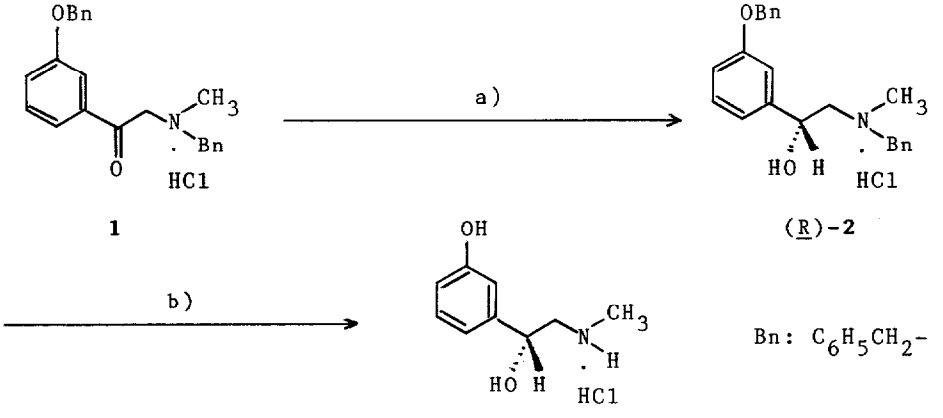
5 6 (2R,4R)-MCCPM

mp 144-146 °C
$[\alpha]_D^{23}$ = +27.1°
(c 0.6, benzene)

Scheme 1

the antipode of **4h**, was synthesized from 4-hydroxy-L-proline (**5**) as shown in Scheme 1. N-(Methylsulfonyl)-4-hydroxy-D-prolinol (**6**) was prepared by the similar method reported previously.[9] By using our method[8a] developed for the syntheses of **4h**, its enantiomer ((2R,4R)-MCCPM) was synthesized in good overall yield.

The asymmetric synthesis of (R)-(-)-phenylephrine hydrochloride (**3**) was carried out with neutral (2R,4R)-MCCPM-rhodium catalyst as shown in Scheme 2. 3'-Benzyloxy-2-(N-benzyl-N-methyl)aminoacetophenone hydrochloride (**1**) (1.15 g, 3.0 mmol) was added to a solution of $[Rh(COD)Cl]_2$ (0.0015 mmol), (2R,4R)-MCCPM (0.0039 mmol) and triethylamine (0.03 mmol) in methanol (10 ml). The asymmetric hydrogenation was carried out at 50 °C for 20 h under the initial hydrogen pressure of 20 atm. After the debenzylation of (R)-(-)-**2**, the reaction mixture was filtered, concentrated and treated with



1 (R)-**2** (R)-**3**

Bn: $C_6H_5CH_2$-

a) chiral rhodium catalyst, triethylamine, H_2, methanol. b) 10 %(w/w) Pd/C, H_2 (10 atm), 3 h, 93 % from **1**.

Scheme 2

active carbon (0.1 g) in water (20 ml). The mixture was filtered and concentrated to give colorless crystals of (R)-(-)-3 (0.57 g, 93 % from **1**); mp 138-141 °C, $[\alpha]_D^{23}$= -38.3° (c 2.0, H_2O)(85 %ee). Optically pure (R)-(-)-3 was obtained by one recrystallization from isopropyl alcohol.

It should be emphasized that this experimental finding offers the practical synthetic method for (R)-(-)-phenylephrine hydrochloride.

References and Notes

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