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ASYMMETRIC SYNTHESIS OF 2-AMINO-1-ARYLETHANOLS BY CATALYTIC ASYMMETRIC HYDROGENATION

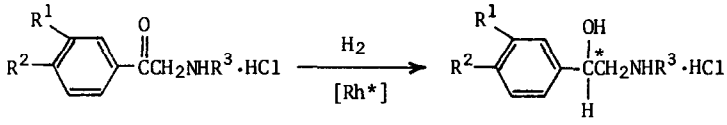
Tamio Hayashi, Akifumi Katsumura, Mitsuo Konishi, and Makoto Kumada*

Department of Synthetic Chemistry, Kyoto University, Yoshida, Kyoto 606, Japan

It is well documented that the *d*- and *l*-isomers of 2-amino-1-arylethanols such as epinephrine show a different biological and pharmacological activity,[1] and the optical isomers have been obtained through the resolution of the racemate[1] or from optically active precursors by chemical transformation.[2] To our knowledge, there has been no example of asymmetric synthesis of 2-amino-1-arylethanols by chemical reduction of prochiral ketones[3] in spite of great current interest in asymmetric synthesis.

In our recent studies on catalytic asymmetric synthesis by chiral phosphine-transition metal complexes,[4] we have developed a chiral (hydroxyalkylferrocenyl)phosphine, (*R*)-α-[(*S*)-1',2-bis-(diphenylphosphino)ferrocenyl]ethyl alcohol ((*R*)-(*S*)-BPPFOH), which brought about an effective asymmetric hydrogenation of prochiral carbonyl compounds when used as a ligand in a rhodium complex.[4d] Now we wish to report that the BPPFOH-rhodium complex catalyzes the hydrogenation of aminomethyl aryl ketones to give the corresponding 2-amino-1-arylethanols in high optical yields (SCHEME).

SCHEME

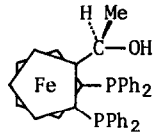


1a, $R^1=R^2=OMe$; $R^3=H$
1b, $R^1=R^2=R^3=H$
1c, $R^1=H$; $R^2=OH$; $R^3=H$
1d, $R^1=R^2=OH$; $R^3=Me$

2a ∿ 2d

[Rh*] = [Rh{(*R*)-(*S*)-BPPFOH}(NBD)]$^+ClO_4^-$ (BPPFOH-Rh$^+$)

(*R*)-(*S*)-BPPFOH + $\frac{1}{2}$[Rh(1,5-hexadiene)Cl]$_2$ (BPPFOH-Rh)



(*R*)-(*S*)-BPPFOH

Hydrogenation of an aminomethyl aryl ketone hydrochloride (1)[5] (1.0 mmol) was carried out in the presence of [Rh{(*R*)-(*S*)-BPPFOH}(NBD)]$^+ClO_4^-$[6] (BPPFOH-Rh$^+$) (0.01 mmol) and triethylamine (0.02 mmol)[7] in 5.0 ml of methanol (2% H_2O) at room temperature and 50 atm initial hydrogen pressure. The hydrogenation was complete in 2-4 days. The reaction mixture was evaporated to dryness, the residue was dissolved in water and the insoluble catalyst was removed by filtration. Evaporation to dryness afforded the product (2) in an almost quantitative yield. The optical purity of 2 obtained was estimated by comparison with the reported optical rotation values for pure enantiomers. 2a and 2b were converted to 2-ethyl-5-aryl-2-oxazolines with ethyl orthopropionate after Meyers' procedure,[8] amd the enantiomeric ratios were established by NMR spectrometry using chiral europium shift reagent Eu(dcm)$_3$.[9,10] The results are summarized in TABLE.

Aminomethyl 3,4-dimethoxyphenyl ketone hydrochloride (1a) was hydrogenated with the BPPFOH-Rh$^+$ catalyst to give (*R*)-O^3,O^4-dimethylnorepinephrine hydrochloride (2a) with an optical purity of 86-90%. An in situ catalyst (BPPFOH-Rh) formed from (*R*)-(*S*)-BPPFOH and [Rh(1,5-hexadiene)Cl]$_2$ showed almost the same degree of enantioselectivity. Use of (-)-DIOP[11] as a ligand of rhodium complex resulted in slow hydrogenation and low optical yield. The BPPFOH-rhodium catalyst was also effective for the hydrogenation of ketones 1b, 1c, and 1d, and the products with *R* configuration were obtained. It is noteworthy that the enantioselectivity of 95% realized in the reduction of 1d to epinephrine hydrochloride (2d) is the highest of all the asymmetric reductions of prochiral carbonyl compounds.[12,13]

Although the precise mechanism of this asymmetric hydrogenation is not clear at present,[13,14] we tentatively assume that the hydrogen bonding possible between the carbonyl group on a substrate and the hydroxy group on BPPFOH ligand can increase conformational rigidity in diastereomeric transition states to cause high enantioselectivity. The high enantioselectivity may also have some connection with the presence of the ammonium function on the ketones. Indeed the asymmetric hydrogenation of simple ketones which lack ammonium group gave different results. Thus, in the hydrogenation of acetophenone and propiophenone with the BPPFOH-Rh$^+$ catalyst, the optical yields were *R* 40% and *R* 31%, respectively.[4d] The steric course of the hydrogenation of 2 is opposite to that of the simple ketones though the configurational designations of the products are the same *R*.

Optically active 2-amino-1-arylethanols obtained here are useful adrenergic drugs or their synthetic intermediates.[1] The present method provides a novel and efficient route to synthesis of optically active 2-amino-1-arylethanols by asymmetric reduction of aminomethyl aryl ketones,

TABLE. Catalytic Asymmetric Hydrogenation of 1.

Ketones	Catalyst[a]	Conv.[b] (%)	$[\alpha]_D$ of 2	Config.	% ee by $[\alpha]_D$[c]	% ee by NMR[d]
1a	BPPFOH-Rh^+	100	-30.8[e]	*R*	86	90
	BPPFOH-Rh	100	-31.7[e]	*R*	89	92
	DIOP-Rh[f]	80[g]	-3.3[e,h]	*R*	12	
1b	BPPFOH-Rh^+	100	-23.2[i]	*R*	52	60
	BPPFOH-Rh[j]	100		*S*		57
	BPPFA-Rh^+[k]	100	-7.4[i]	*R*	17	
1c	BPPFOH-Rh^+	100	-48.1[l,m]	*R*	69	
1d	BPPFOH-Rh^+	100[n]	-50.3[l,o]	*R*	95	

[a] See text. [b] Determined by NMR. In cases of 100% conversion the isolated yields are over 95%. [c] Calculated on the basis of reported values for the optically pure compounds: (*R*)-2a, $[\alpha]_D^{20}$ -35.7° (*c* 1, 50% EtOH), ref 2a; (*S*)-2b (free amine), $[\alpha]_D^{23}$ +44.8° (*c* 2, EtOH), (A, Nabeya, T. Shigemoto, and Y. Iwakura, *J. Org. Chem.*, 40, 3536 (1975)); (*S*)-2c (free amine), $[\alpha]_D$ +86° (1*N* HCl), (J. Van Dijk, V. G. Keizer, J. F. Peelen, and H. D. Moed, *Rec. Trav. Chim. Pays-Bas*, 84, 521 (1965)); (*R*)-2d (free amine), $[\alpha]_D^{22\sim25}$ -53.2° (*c* 1.2, 0.5*N* HCl), (G. G. Lyle, *J. Org. Chem.*, 25, 1779 (1960)). [d] ±5%. [e] (*c* 1, 50% EtOH). [f] Prepared in situ from (-)-DIOP and $[Rh(1,5\text{-hexadiene})Cl]_2$. [g] At 100 atm of H_2 for 10 days. [h] Contaminated with 20% of 1a. [i] Specific ratation of the free amine, (*c* 2, EtOH). [j] (*S*)-(*R*)-BPPFOH was used instead of (*R*)-(*S*)-BPPFOH. [k] $[Rh\{(R)\text{-}(S)\text{-BPPFA}\}(NBD)]^+ClO_4^-$. (*R*)-(*S*)-BPPFA stands for (*R*)-α-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]-ethyldimethylamine, ref 4a. [l] Concentration was corrected to obtain specific rotation of the free amines. [m] (*c* 1, 1*N* HCl). [n] At 40°C for 7 days. [o] (*c* 1, 0.5*N* HCl).

which has been difficult with chiral hydride agents conventionally used for the asymmetric reduction of prochiral carbonyl compounds[12] because of the presence of active hydrogens on the starting ketones and their instability under basic conditions.[15] While catalytic asymmetric hydrogenation of olefins has resulted in great success,[16] little has been achieved in other fields of transition metal complex-catalyzed asymmetric synthesis. The present method also makes a new practical application of catalytic asymmetric synthesis which is the most efficient way to produce optically active compounds[17] if high stereoselectivity is attained.

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