Asymmetric Synthesis of (*R*)-α-Phenylalkylamines *via* Alkylation of Chiral Hydrazones by Grignard Reagents

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Summary Chiral hydrazones, obtained by the condensation of (−)-*N*-aminoephedrine with aryl aldehydes, reacted with Grignard reagents to give chiral hydrazines in almost 100% diastereomeric excess, which were hydrogenolysed to give (*R*)-α-phenylalkylamines and ephedrine hydrochloride in extremely high enantiomeric excess.

We here report an asymmetric synthesis of (*R*)-α-phenylalkylamines using *N*-aminoephedrine, easily obtained from commercially available ephedrine hydrochloride, which

Table 1. Reaction of chiral hydrazones (**2a**—**d**) with RMgX in tetrahydrofuran

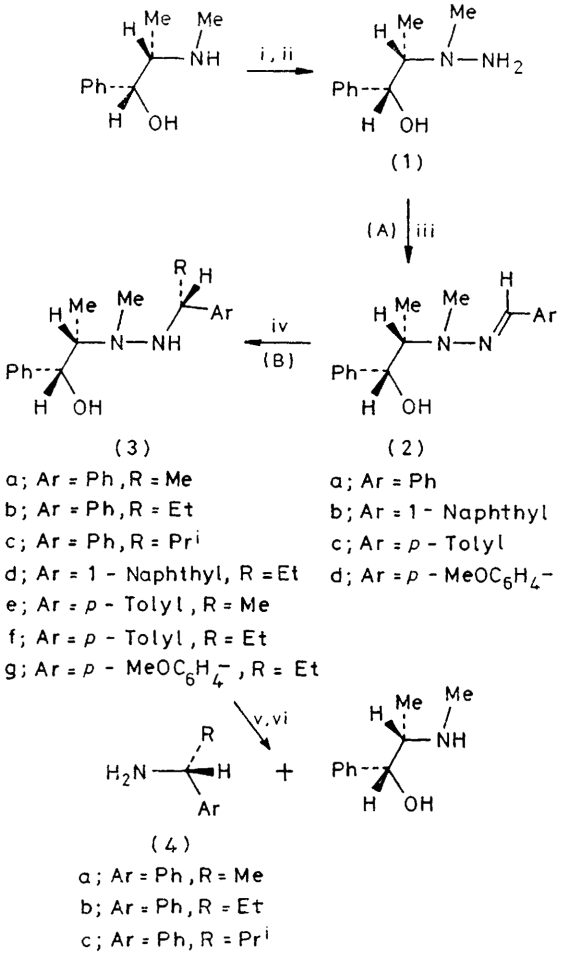
Starting material	Grignard reagents		Reaction conditions		Product	Chemical yield/%	Diastereomeric[a] excess/%
	R	X	Temp/°C	Time/h			
(**2a**)	Me	Br	40 20	6[b] 37	(**3a**)	79	>96
(**2a**)	Et	Cl	45	3	(**3b**)	>95	>98
(**2a**)	Pr^i	Br	25	46	(**3c**)	80	>96
(**2b**)	Et	Cl	40	3	(**3d**)	>95	>96
(**2c**)	Me	Br	40 20	6[b] 20	(**3e**)	80	>98
(**2c**)	Et	Cl	40	3	(**3f**)	>95	>98
(**2d**)	Et	Cl	40	3	(**3g**)	>95	>98

[a] N.m.r. spectra of the crude products (**3a**—**g**) showed only one diastereomer within experimental error. [b] Reaction was at 40 °C for 6 h, in addition to 20 °C for 37 (or 20 h).

Table 2. Hydrogenolysis of chiral hydrazines (**3a**—**c**) in HCl–EtOH

	Reaction conditions			Chemical yield %			Chiral data (**4a**—**c**)		
Starting material	Pressure /kg cm^{-2}	Temp/°C	Time/h	(**4a**—**c**)	Ephedrine hydrochloride	Starting material	Optical purity %	Configuration	Ephedrine[b] hydrochloride $[\alpha]_D^{20}$
(**3a**)	6	50—60	15	72	68	10	>96	*R*	−33·5°
(**3b**)	6	50—60	8	89	67	3	>96	*R*	−33·5°
(**3c**)	50	40—50	8	32	60	20	76	*R*	−30·0°

[a] The chiral data of the *N*-salicylideneamines were determined by c.d. absorption maxima at 405, 315, and 275 nm. [b] The specific rotation of the original ephedrine hydrochloride used was −34·0°.



Scheme. i, HNO_2; ii, Zn–AcOH; iii, ArCHO; iv, RMgX; v, Pd–C, H_2; vi, HCl.

proceeds in extremely high enantiomeric excess (e.e.), and allows for the recovery of the chiral auxiliary reagents. Condensation of *N*-aminoephedrine[1] (**1**) with various aryl aldehydes in stirred benzene solution at ambient temperature gave the chiral hydrazones (**2a**—**d**), in almost quantitative yield, each showing only one t.l.c. spot. Treatment of the hydrazones (**2a**—**d**) with Grignard reagents in tetrahydrofuran under nitrogen afforded the pale yellow oily hydrazines (**3a**—**g**). Two diastereomeric forms of each compound could be formed owing to the newly created chiral centre, but n.m.r., t.l.c., and g.l.c. comparisons[2] established that these products contained only one isomer. The results obtained using various Grignard reagents are summarized in Table 1.

Hydrogenolysis of the hydrazines (**3a**—**c**) using a Pd–carbon catalyst under hydrogen in HCl–EtOH produced the α-phenylalkylamines (**4a**—**c**) and ephedrine hydrochloride. Compounds (**4a**—**c**) were converted into *N*-salicylidene-α-phenylalkylamines, whose optical purities and configurations were determined by comparison with data reported by Smith *et al.*[3] These results indicated that the chiral amines had an *R* configuration with extremely high optical purity.† The specific rotation of ephedrine hydrochloride which was used as the chiral auxiliary reagent was unchanged during the reaction sequence. The results are summarized in Table 2.

It seems that this asymmetric reaction sequence includes two important stereoselective steps, *i.e.*: (i) condensation of *N*-aminoephedrine with aryl aldehydes leads to the conformationally locked hydrazones (**2a**—**d**) which possess, virtually completely, *E*-stereochemistry at the C=N bond (Scheme, step A); (ii) the rigid structure formed by complexation of the chiral hydrazones (**2a**—**d**) with the magnesium of the Grignard reagent leads to a highly stereoselective attack of the alkyl group originating from the Grignard reagent (Scheme, step B).

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† It is assumed that (*R*)-α-phenylneopentylamine underwent partial racemization owing to the high pressure hydrogenolysis conditions.

[1] H. Takahashi, H. Noguchi, K. Tomita, and H. Otomasu, *Yakugaku Zasshi*, 1978, **98**, 618.
[2] H. Takahashi, K. Tomita, H. Noguchi, and H. Otomasu, unpublished data.
[3] H. E. Smith and R. Records, *Tetrahedron*, 1966, **22**, 813; M. E. Warren, Jr. and H. E. Smith, *J. Amer. Chem. Soc.*, 1965, **89**, 1757.