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ASYMMETRIC SYNTHESIS OF CIS-2-SUBSTITUTED CYCLOHEXANAMINES WITH HIGH OPTICAL PURITY

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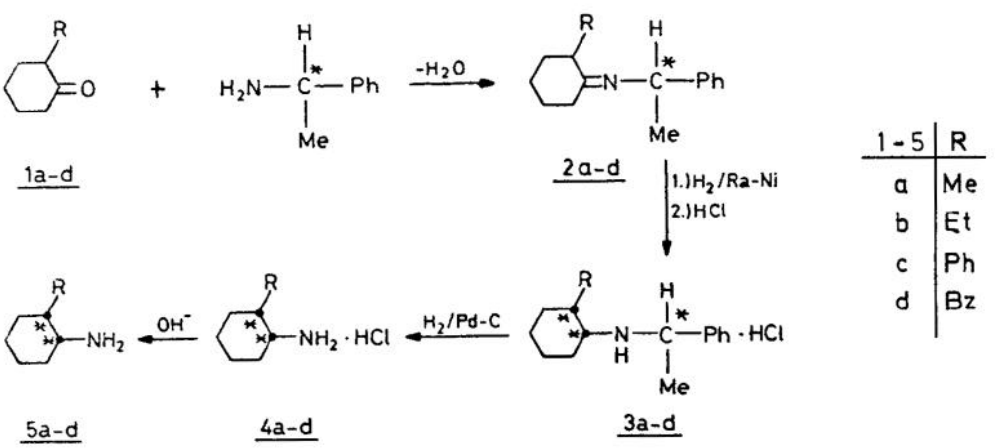
Abstract: Asymmetric reductive amination of racemic 2-substituted cyclohexanones (R= methyl, ethyl, phenyl, benzyl) using optically active 1-phenylethylamines yields optically active cis-cyclohexanamines.

The nonenzymatic asymmetric synthesis of open-chain amines and amino acids from the corresponding ketones or keto acids is well documented [1-5]. Hiskey [6] and later on Harada [7] were the first who synthesized optically active amino acids from keto acids by hydrogenolytic asymmetric transamination in good optical yield. Barfknecht [8] and Standridge [9] showed the general applicability of this reaction in the synthesis of psychotomimetic phenyl-isopropylamines and analogues of mescaline (optical purities between 95 and 100%).

We report now the high-yield asymmetric synthesis of optically active cis-2-substituted cyclohexanamines 5a-d from racemic 2-substituted ketones 1a-d (Scheme 1), which is, by our knowledge, the first asymmetric synthesis of carbocyclic amines from corresponding cyclanones.

Scheme 1



1-5	R
a	Me
b	Et
c	Ph
d	Bz

It is remarkable, that the hydrogenation leads to optically pure cis-products (enantiomeric excess > 92%), thus running under both highly diastereoselective and enantioselective control.

Reaction of racemic cyclohexanones 1a-d with either R-(+)- or S-(-)-1-phenylethylamine in a Dean-Stark-apparatus yields azomethines 2a-d, which are immediately hydrogenated over Raney-nickel in a Parr-shaker at 5 bar. The resulting secondary amines are isolated as hydrochlorides 3a-d in good chemical yield (Table 1).

TABLE 1: PROPERTIES OF SECONDARY AMINE-HYDROCHLORIDES 3a-d [a]

Compound	Starting amine	Yield [b] [%]	m.p. [°C]	$[\alpha]_D^{23}$ (c=1.2/EtOH)
3a	+	88	279-80	+ 52.8
	-		280-81	- 52.9
3b	+	90	245-47	+ 52.9
	-		245-47	- 53.3
3c	+	49 [c]	--- [d]	---
	-		--- [d]	---
3d	+	80	256-59	+ 85.7
	-		257-59	- 83.7

[a] spectroscopical data and microanalyses are in agreement with structures proposed; [b] based on starting ketones; [c] yield of N-(2'-phenylcyclohexan)-1-phenylethylamine-hydrochlorid 3c is significantly lower than that of the other amines because of partly isomerisation of azomethine 2c to the corresponding enamine, which is not hydrogenated under the reaction conditions; [d] liquid.

Without further purification 3a-d are hydrogenolized with palladium-on-charcoal catalyst (5%) at 5 bar and 45°C in a Parr-shaker to yield optically active 2-substituted cyclohexanamine-hydrochlorides 4a-d in good chemical and optical yield (Table 2). Hydrochlorides are liberated to free bases 5a-d by aqueous sodium hydroxidequantitatively for spectroscopical purposes only (fast carbonisation occurs!).

TABLE 2: PROPERTIES OF PRIMARY AMINE-HYDROCHLORIDES 4a-d [a]

Compound	Starting amine	Yield [b] [%]	m.p. [°C]	$[\alpha]_D^{23}$ (c=1.3/EtOH)	enantiomeric excess [%]
4a	+	78	234-35	+ 8.0	96
	-		234-35	- 8.1	97
4b	+	79	193-95	- 0.5	92
	-		193-94	+ 0.6	94
4c	+	42	248	- 106.6	94
	-		247-48	+ 104.4	92
4d	+	68	272-74	+ 14.3	99
	-		272-74	- 14.0	98

[a] spectroscopical data and microanalyses are in agreement with structures proposed and literature data [21-23]; [b] overall yield

The purity of the secondary and primary amines was checked by chromatographical and spectroscopical methods. Neither TLC and HPLC nor ^{1}H- and ^{13}C-NMR showed any traces of the trans-amines. The optical purity of the corresponding enantiomeres was checked by HPLC. For this purpose 4a-d were acylated by the method of Dale [10] with optical pure (+)-2-methoxy-2-trifluormethyl-phenylacetic acid chloride (MTPA-Cl) to the diastereomeric amides. In all cases the enantiomeric excess was higher than 92%.

Under above conditions only the thermodynamically less stable cis-compounds are isolated. This is consistent with Barton's rule [11], although it is known, that under more vigorous hydrogenation conditions (i.e. 80 bar, 100°C) always the thermodynamically more stable products dominate in comparable cases [12,13].

With exception of compound 4c, cis configurated compounds 3a-d and 4a-d are synthesized for the first time in its enantiomeric forms [14]. Although racemic and optically active trans-2-methyl-cyclohexanamines are well known [15-17], from the corresponding cis-compounds only the racemic modification is documented [18-20].

The absolute configuration of the synthesized compounds is not yet established. CD- and X-ray-analyses are in progress and will be published later.

In forth-coming publications we shall show the result of our investigations, which deal with cyclanones of different ring sizes and R-groups in changing positions.

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