## Asymmetric Induction in the Addition of Grignard Reagents to Nitrones

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Grignard reagents add to *N*-(2-phenylpropylidene)cyclohexanamine *N*-oxide with significant asymmetric induction; an *X*-ray structure of one product demonstrates that the addition proceeds according to Cram's rule.

Although 1,3-dipolar cycloaddition reactions of nitrones have been studied extensively,<sup>1</sup> they undergo several other reactions which are far less well known. The addition of Grignard reagents and other nucleophiles to nitrones has been reported,<sup>1-3</sup> but the stereochemical consequences of these



Scheme 1. Reagents: i, RNHOH·HCl, NaOAc, EtOH,  $H_2O$ ; ii, R<sup>1</sup>MgCl, Et<sub>2</sub>O, 0 °C; iii,  $H_2$ , 3% Pd-C, MeOH; iv,  $H_2$ , 3% Pd-C, MeOH, CDCl<sub>3</sub>.

reactions have not been investigated. As part of a synthetic programme we have studied the addition of Grignard reagents to nitrones containing one chiral centre and now report our results.<sup>†</sup> ( $\pm$ )-2-Phenylpropionaldehyde (1) was converted into N-(2-phenylpropylidene)cyclohexanamine N-oxide (2) and N-(2-phenylpropylidene)methanamine N-oxide (3) according to the method of Coates *et al.*<sup>4</sup> The series of Grignard reagents R<sup>1</sup>MgX were then reacted with nitrones (2) and (3) in diethyl ether to afford the hydroxylamines (4a-c) and (5a) as shown in Scheme 1. Table 1 shows the diastereo-isomer ratios obtained in these reactions as determined by 300 MHz <sup>1</sup>H n.m.r. spectroscopy.

Table 1. Addition of Grignard reagents to give (4) and (5).

Nitrone	Grignard	Product	Diastereo- isomer ratio (by n.m.r.)	Yield (%)
$(2), R = C_6 H_{11}$	MeMgCl EtMgCl Pr <sup>i</sup> MgCl	(4a) (4b) (4c)	79:21 83:17 67:33ª	71 68 90
(3), R = Me	MeMgCl	(5a)	72:25	86

<sup>a</sup> Based on <sup>13</sup>C n.m.r.



Figure 1. Crystal structure of the hydrochloride (8).

† All work has been conducted on racemic materials.

N,N-Dialkylhydroxylamines are known to undergo air oxidation to give the corresponding nitroxide radical<sup>5</sup> and indeed all the hydroxylamines (4,5) showed substantial decomposition within days. Hydroxylamine (4c) gave an e.s.r. signal which was consistent with the presence of a nitroxide radical.‡ Attempts to prepare stable hydrochloride salts of the hydroxylamines (4a-c) and (5a) were unsuccessful and accordingly they were hydrogenated to the more stable amine derivatives (6a-c) and (7a). In a different experiment the diastereoisomers of (4a) were separated by flash column chromatography, and then individually hydrogenated to give the amine hydrochloride salts (8) directly owing to the presence of traces of CDCl<sub>3</sub> in the compounds.<sup>6</sup> The major diastereoisomer of (8) was purified by recrystallisation and an X-ray crystal structure determination was carried out§ to determine the relative configuration of the new chiral centre in the amine hydrochloride; the result is shown in Figure 1. From a careful comparison of the 1H and 13C n.m.r. data, we believe that the major product in all the examples in Table 1 has the same relative configuration as (8), and therefore all reactions studied follow one stereochemical course.

The major product as verified by the X-ray results is the distereoisomer predicted by Cram's rule;7 Figure 2 shows the

 $\pm$  E.s.r. data for (4c):  $A_{\parallel} = 33$ ,  $A_{\perp} = 0$  ( $\pm 4$ ) G (G = 10<sup>-4</sup> T); g =2.0024.

§ Crystal data for (8):  $C_{16}H_{25}N \cdot HCl$ , M = 267.9, monoclinic, space group  $P2_1/a$ , a = 12.054(4), b = 5.576(3), c = 23.119(7) Å,  $\beta = 93.18(3)^\circ$ , U = 1552(1) Å<sup>3</sup>, Z = 4,  $\mu = 20.52$  cm<sup>-1</sup>.  $\lambda$ (Mo- $K_{\alpha}$ ) =  $0.7107 \text{ Å}, F(000) = 584.0, D_c = 1.15 \text{ g cm}^{-3}$ . Final residual index R =0.067. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.



Figure 2. Attack of Grignard reagent on the nitrones (4).

attack of the Grignard reagent on the least hindered side of a nitrone conformation predicted by the Felkin-Anh explanation of Cram's rule.8

In conclusion we have shown that Cram's rule can be applied to the addition of Grignard reagents to nitrones containing one chiral centre.

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