Asymmetric Induction in the Addition of Grignard Reagents to Nitrones

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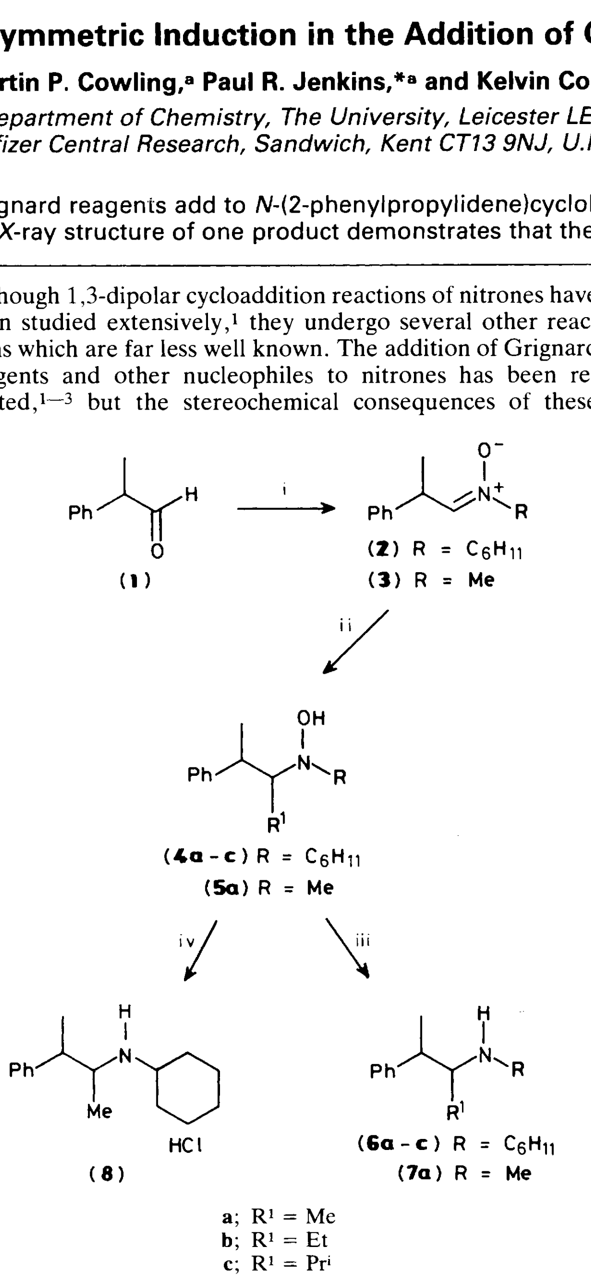
Grignard reagents add to *N*-(2-phenylpropylidene)cyclohexanamine *N*-oxide with significant asymmetric induction; an *X*-ray structure of one product demonstrates that the addition proceeds according to Cram's rule.

Although 1,3-dipolar cycloaddition reactions of nitrones have been studied extensively,[1] they undergo several other reactions which are far less well known. The addition of Grignard reagents and other nucleophiles to nitrones has been reported,[1—3] but the stereochemical consequences of these 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.† (±)-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.*[4] The series of Grignard reagents R^1MgX 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 diastereoisomer ratios obtained in these reactions as determined by 300 MHz ^1H n.m.r. spectroscopy.



Scheme 1. *Reagents*: i, RNHOH·HCl, NaOAc, EtOH, H_2O; ii, R^1MgCl, Et_2O, 0 °C; iii, H_2, 3% Pd–C, MeOH; iv, H_2, 3% Pd–C, MeOH, $CDCl_3$.

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_6H_{11}	MeMgCl	(**4a**)	79 : 21	71
	EtMgCl	(**4b**)	83 : 17	68
	Pr^iMgCl	(**4c**)	67 : 33[a]	90
(**3**), R = Me	MeMgCl	(**5a**)	72 : 25	86

[a] Based on ^{13}C n.m.r.

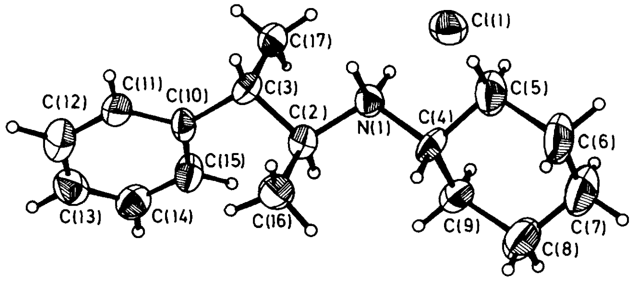


Figure 1. Crystal structure of the hydrochloride (**8**).

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† All work has been conducted on racemic materials.

N,*N*-Dialkylhydroxylamines are known to undergo air oxidation to give the corresponding nitroxide radical[5] 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 $CDCl_3$ in the compounds.[6] 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 ^{13}C 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 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]

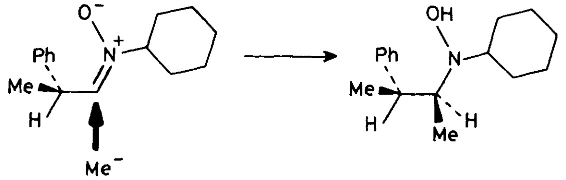

Figure 2. Attack of Grignard reagent on the nitrones (**4**).

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

§ *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, $\beta = 93.18(3)°$, $U = 1552(1)$ Å^3, $Z = 4$, $\mu = 20.52\,cm^{-1}$. $\lambda(Mo\text{-}K_\alpha) = 0.7107$ Å, $F(000) = 584.0$, $D_c = 1.15\,g\,cm^{-3}$. 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.