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Enantioselective Synthesis of Nitrogen Derivatives by Allyl Grignard Addition on Optically Active Nitroalkanes

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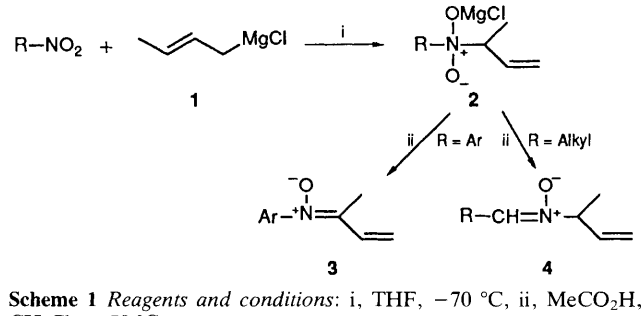
Reaction of optically active nitroalkanes with allyl Grignard reagents affords *E–Z* mixtures of nitrones which can be reduced to chiral hydroxylamines and amines.

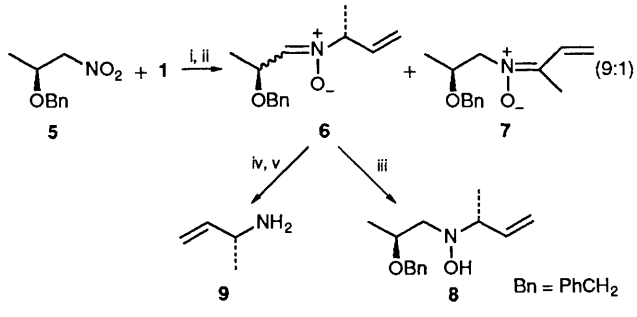
Nitrogen containing molecules having optical activity occupy a dominant position in the field of biologically active substances.[1] This provides a great incentive for developing new methods to control the stereochemical outcome of chemical transformations involving this class of compounds. Recently we have reported a very efficient synthesis of nitrones starting from aromatic and aliphatic nitrocompounds and 2-butenylmagnesium chloride **1**[2] (Scheme 1).

Interestingly when simple nitroalkanes are used as substrates in this reaction, the non-conjugate nitrone **4** is preferentially formed over the apparently more stable regioisomer.[3] Since nitrones represent a versatile class of compounds in organic synthesis[4] we decided to check the degree of enantioselection for our reaction using as substrate some nitroalkanes bearing a chiral centre in the proximity of the nitro-group. For this we chose (*S*)-(2-benzyloxy)-1-nitropropane **5** easily obtained from the corresponding iodide[5] by nucleophilic displacement with nitrite anion in dimethyl sulphoxide.†

Reaction of **5** with **1** in tetrahydrofuran (THF) at −70 °C gave the nitrones **6** in 86% yield as equimolar mixture of *E–Z* stereoisomers, as well as the conjugated isomer **7** in 10% yield. Product **6** is easily separable from **7** by column chromatography and its reduction with $NaBH_4$ in MeOH afforded hydroxylamine **8** in 92% yield with the new chiral centre of *R* configuration‡ (Scheme 2). No detectable amount of the *S* isomer has been found in this reaction.



Scheme 1 *Reagents and conditions*: i, THF, −70 °C, ii, $MeCO_2H$, CH_2Cl_2, −70 °C to room temp.

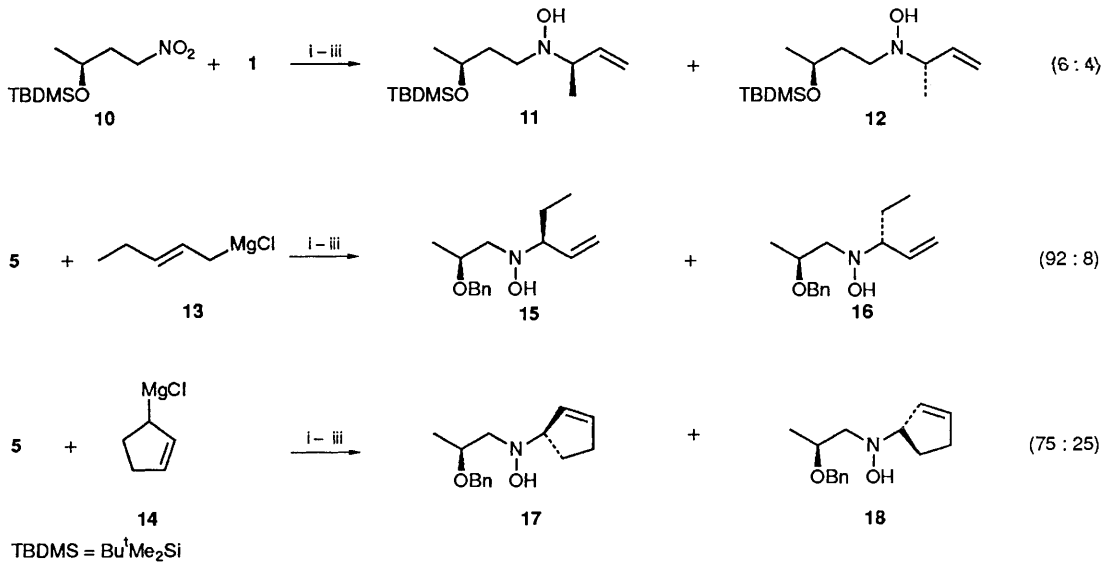


Scheme 2 *Reagents and conditions*: i and ii as for Scheme 1; iii, $NaBH_4$, MeOH, 0 °C, 92%; iv, HCl (0.5 mol dm^{-3}), $CHCl_3$, 12 h, room temp.; v, $LiAlH_4$, THF, 0 °C

† *Selected spectroscopic data* for **5**: m.p. 51 °C; $[\alpha]^{20}_D$ +11.9° (*c* 2.03, EtOH); ^1H NMR (300 MHz) δ 1.30 (d, 3H, *J* 6.0 Hz), 4.25–4.35 (m, 1H), 4.38 (d, 1H, *J* 3.8 Hz), 4.51 (d, 1H, *J* 3.8 Hz), 4.70 (d, 1H, *J* 11.3 Hz), 4.80 (d, 1H, *J* 11.3 Hz) and 7.22–7.45 (m, 5H).

‡ A typical experimental procedure is as follows: **5** (0.02 mol, 3.9 g) is dissolved in dry THF (50 ml) and cooled to −70 °C. Grignard reagent **1** (0.22 mol) is then added dropwise and after 20 min the reaction mixture is quenched by addition of acetic acid (0.03 mol, 1.75 ml) in CH_2Cl_2 (25 ml) at −70 °C. The temperature is allowed to rise to room temp. and usual work-up gives the crude product which is purified by column chromatography (hexane–ethyl acetate–ethanol 6:3:1), 3.96 g, 86% yield). The mixture of nitrones **6** dissolved in MeOH (50 ml), is cooled at 0 °C, $NaBH_4$ (0.0186 mol, 0.7 g) is then added and stirring continued at this temperature for 25 min. Usual work-up affords crude compound **8** which can be purified by column chromatography (hexane–ethyl acetate 7:3) (3.67 g, 92% yield).

Spectroscopic data for **8**: m.p. 63 °C, $[\alpha]^{20}_D$ + 5.61° (*c* 4.65, EtOH); IR ν_{max}/cm^{-1}, 3400 (OH); ^1H NMR (300 MHz) δ 1.20 (d, 3H, *J* 6.5 Hz), 1.25 (*d*, 3H, *J* 6.8 Hz), 2.80 (d, 2H, *J* 6.5 Hz) 3.20–3.35 (m, 1H), 3.80–3.90 (m, 1H), 4.50–4.65 (m, 2H), 5.10–5.20 (m, 2H), 5.45 (bs, 1H), 5.80–5.95 (m, 1H) and 7.20–7.40 (m, 5H).



Scheme 3 *Reagents and conditions*: as for Scheme 2

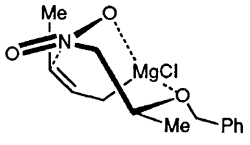


Fig. 1 Transition state for formation of **6**

The absolute stereochemistry has been assigned by hydrolysis of the nitrones to the parent hydroxylamine which upon reduction with $LiAlH_4$ afforded amine **9** of known configuration. {*N*-2,4-Dinitrophenyl derivative $[\alpha]^{22}_D$ −145.6° (*c* 1, EtOH); Lit.[6] $[\alpha]^{22}_D$ −146° (*c* 1, EtOH)}. Lower enantioselectivity is obtained if the chiral centre is shifted one carbon atom away from the nitro-group. Nitroalkane **10**[7] gave a mixture of nitrones which after reduction produced two diastereoisomeric hydrolyamines **11** and **12** in a 6 : 4 ratio.

Some allyl Grignard reagents other than **1** have been used for this reaction and the relative amount of hydroxylamines obtained after reduction of the corresponding nitrone derivative are reported in Scheme 3.

The all-equatorial substituents conformation for the proposed transition state chelation model (Fig. 1) seems to be the most probable pathway for our reaction.[8] Since allylmagnesium reagents undergo fast *E*–*Z* isomerisation[9] the most plausible assumption is that only one of the two possible configuration reacts preferentially with the nitro-group with consequent formation of a single stereoisomer. We are currently looking for some experimental data to confirm this suggestive hypothesis. No selectivity in the subsequent formation of the nitrone from the intermediate **2** has been shown.

It is also evident that any change of the six member ring geometry of the transition state as occurs with compound **10** will result in a decrease of the enantioselectivity of the reaction. A similar effect could be caused by an increase of the steric hindrance of the Grignard reagent as in **13** and **14**. Mechanistic studies and synthetic developments of these reactions are currently in progress in our laboratory.

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