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# The stereospecific addition of hydroxylamines to α,β-unsaturated sulfones, nitriles and nitro compounds

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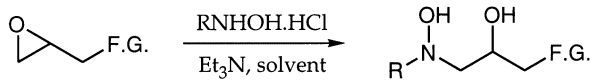
**Abstract**—*N*-Alkyl hydroxylamines have been shown to undergo a highly stereospecific *cis* addition to α,β-unsaturated sulfones, nitriles and nitro compounds. © 2001 Published by Elsevier Science Ltd.

As part of our studies on the use of the reverse-Cope cyclisation in the synthesis of nitrogen heterocycles we have shown that functionalised hydroxylamines can be readily prepared by the ring opening of epoxides with simple *N*-alkylhydroxylamines (Scheme 1). The reaction is regioselective and gives access to the desired substrates for the subsequent reverse-Cope cyclisations.[1]

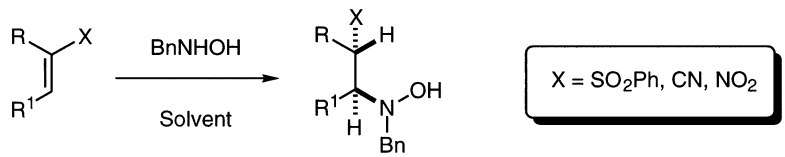
In order to extend the methodology, we wished to prepare a range of hydroxylamines, which possessed an electron-withdrawing group β to the hydroxylamine nitrogen so that further functionalisation was possible. The conjugate addition of *N*-alkylhydroxylamines to α,β-unsaturated ketones, lactones and esters is well documented in the literature,[2] however the analogous addition to other Michael acceptors such as α,β-unsaturated sulfones, nitriles and nitro compounds has not been previously investigated in any detail.[3] We wish to disclose that these reactions proceed smoothly giving the addition products in high yield and with very high diastereoselectivity (Scheme 2).




**Scheme 1.**

The substrates were prepared according to standard literature methods. We initially examined the addition of *N*-benzylhydroxylamine to simple activated *trans* β-substituted styrenes.

As expected, the hydroxylamine underwent rapid addition to the nitrostyrene, the reaction being complete in five minutes. Addition to the α,β-unsaturated sulfone was complete in 12 h, however it took 7 days for addition to the α,β-unsaturated nitrile.




**Scheme 2.**

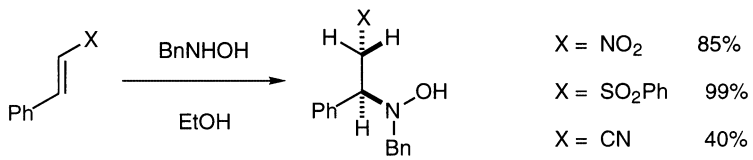



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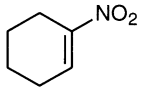
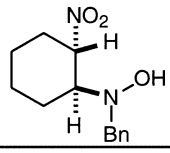
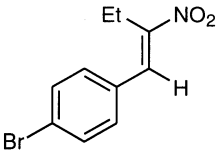
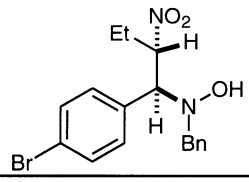
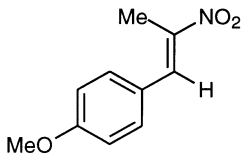
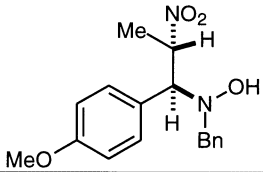
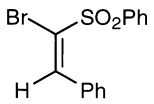
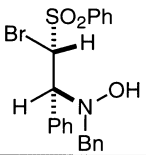
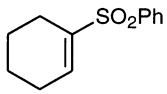
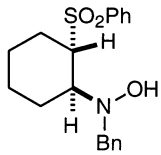
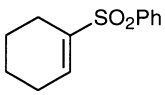
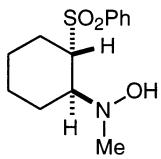
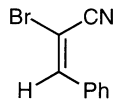
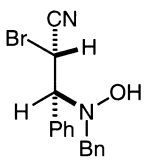
**Table 1.** Addition of *N*-alkylhydroxylamines to Michael acceptors

| Entry | Substrate | Conditions | Product | % Yield |
|---|---|---|---|---|
| 1 |  | BnNHOH. HCl, $Et_3N$, EtOH, r.t., 1h |  | 93 |
| 2 |  | BnNHOH. HCl, $Et_3N$, EtOH, r.t., 1h |  | 88 |
| 3 |  | BnNHOH. HCl, $Et_3N$, EtOH, r.t., 1h |  | 82 |
| 4 |  | BnNHOH. HCl, $Et_3N$, EtOH, r.t., 12h |  | 83 |
| 5 |  | BnNHOH. HCl, $Et_3N$, EtOH, Δ, 7 days |  | 5 |
| 6 |  | MeNHOH. HCl, $Et_3N$, MeOH, Δ, 1 day |  | 65 |
| 7 |  | BnNHOH. HCl, $Et_3N$, MeOH, r.t., 72hrs |  | 45 |

Zhao and others have[2] recently shown that the addition of hydroxylamines to α,β-unsaturated esters and lactones proceeds with high stereospecificity. In order to ascertain if such high selectivity was observed with our substrates we prepared a number of geometrically defined trisubstitued nitroalkenes,[4] two α,β-unsaturated sulfones[5] and an α,β-unsaturated nitrile.[6] The results are shown in Table 1. Addition of *N*-benzylhydroxylamine to the four trisubstituted nitroalkenes was high yielding, rapid and complete within 1 h. In all cases a single diastereoisomer was formed as indicated by $^1H$ NMR analysis, which indicated that addition had occurred in a stereospecific *syn* fashion. The structures of two of these derivatives were confirmed by X-ray analysis (Fig. 1) and both showed that the *N*-benzylhydroxylamine had added in a *syn* stereospecific fashion to the nitroalkene.

Addition to two α,β-unsaturated sulfones was examined. The bromosulfone (entry 5) underwent clean and

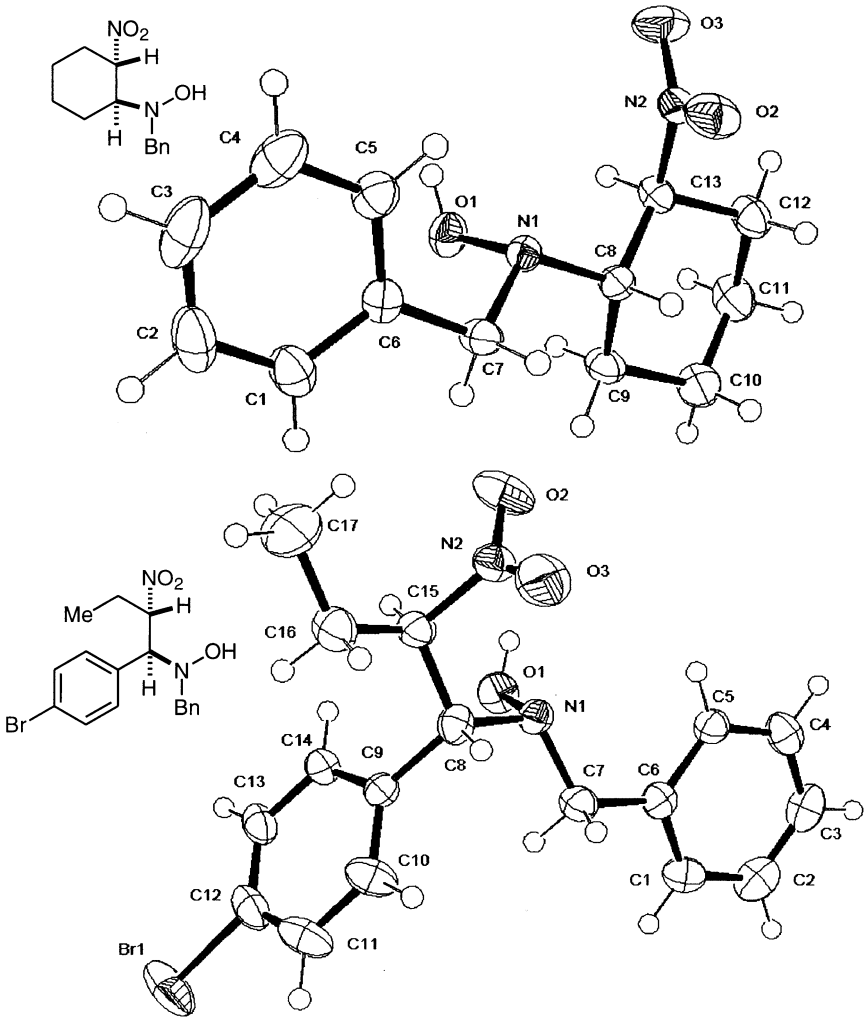
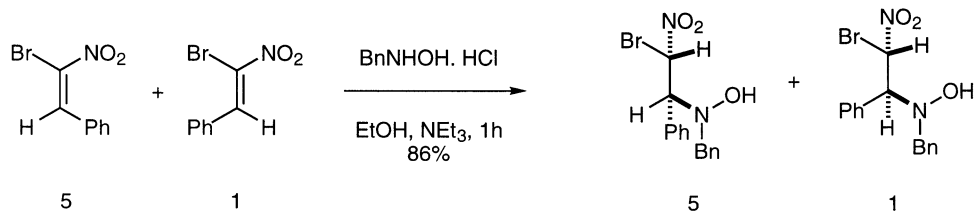


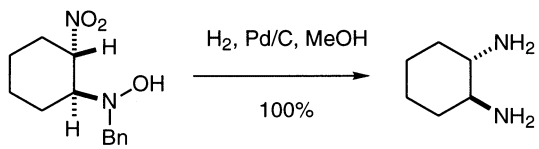

**Figure 1.** ORTEP view of the molecular structure of the hydroxylamine (Table 1, entry 1) and the hydroxylamine (Table 1, entry 2).



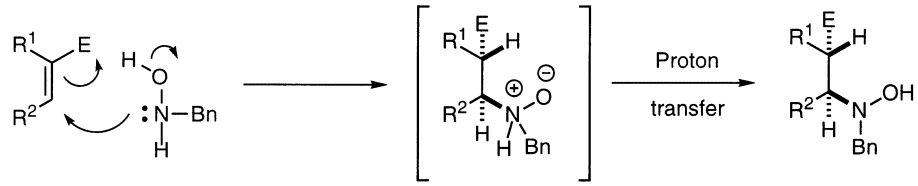

**Scheme 3.**

rapid addition to give a single diasteroisomeric hydroxylamine, again consistent with a stereospecific *syn* addition. The reaction of cyclohexene sulfone (entries 5 and 6) with two hydroxylamines was investigated. Addition with the *N*-benzylhydroxylamine was found to be very sluggish and gave only 5% of the desired product, as a single diastereoisomer after 7 days at reflux. However, use of *N*-methylhydroxylamine gave the addition product again as a single diastereoisomer in 65% after 1 day.

Finally, addition to the bromonitrile (entry 7) gave a modest yield of the product as a single diastereoisomer. The stereospecificity of the addition was also illustrated by subjecting a 5:1 mixture of the nitroalkenes shown in Scheme 3 to the addition reaction. The two diastereoisomeric products were formed in a matching 5:1 ratio.




**Scheme 4.**




**Scheme 5.**

The potential utility of this diastereoselective addition reaction is shown in Scheme 4. Hydrogenation of the β-nitro hydroxylamine gave racemic *trans*-cyclohexane-1,2-diamine in quantitative yield, highlighting the synthetic potential of this addition reaction. We are currently examining asymmetric examples of this stereospecific reaction, which will be reported in due course.

The stereospecific addition of hydroxylamines to these α,β-unsaturated systems are consistent with a concerted mechansim and the reaction could be viewed as an intermolecular reverse-Cope cyclisation (Scheme 5).

## Acknowledgements

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## References

1. (a) O'Neil, I. A.; Southern, J. M. *Tetrahedron Lett*. **1998**, *39*, 9089–9092; (b) O'Neil, I. A.; Cleator, E.; Southern, J. M.; Hone, N.; Tapolczay, D. J. *Synlett*. **2000**, 695–697; (c) O'Neil, I. A.; Cleator, E.; Southern, J. M.; Hone, N.; Tapolczay, D. J. *Synlett*. **2000**, 1408–1410.
2. (a) Niu, D.; Zhao, K. *J. Am. Chem. Soc*. **1999**, *121*, 2456–2459; (b) Pan, S.; Wang, J.; Zhao, K. *J. Org. Chem*. **1999**, *64*, 4–5; (c) Sibi, M. P.; Liu, M. *Org. Lett*. **2000**, *2*, 3393–3396; (d) Reetz, M. T.; Röhrig, D.; Harms, K.; Frenking, G. *Tetrahedron Lett*. **1994**, *35*, 8765–8768.
3. Kliegel, W.; Lubkowitz, G.; Rettig, S. J.; Trotter, J. *Can. J. Chem*. **1992**, *70*, 2027–2032.
4. Sas, W. *Chem. Commun*. **1984**, 862–863.
5. (a) Gairaud, C. B.; Lappin, G. R. *J. Org. Chem*. **1953**, *18*, 1–3; (b) Carlier, P.; Gelas-Mialhe, Y.; Vessiere, R. *Can. J. Chem*. **1977**, *55*, 3190–3201.
6. Karmarkar, S. N.; Kelkar, S. L.; Wad, M. S. *Synthesis* **1985**, 510–512.