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TETRAHEDRON: *ASYMMETRY*

Asymmetric electrophilic amination of enolates by a chiral *N*-alkoxycarbonyloxaziridine

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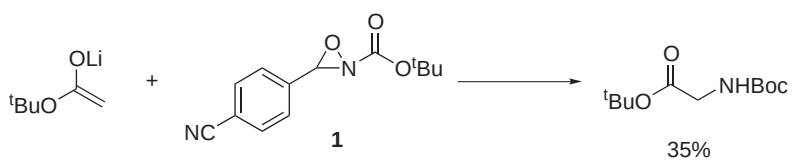
Abstract—A new chiral 3-aryl-*N*-alkoxycarbonyloxaziridine, derived from menthol, has been prepared and tested as a reagent for asymmetric electrophilic amination of enolates. The aminated products were obtained in low diastereoselectivities of up to 21% d.e.

1. Introduction

Electrophilic amination provides a powerful method for the introduction of nitrogen into organic molecules.[1] An asymmetric variant of this methodology would be especially useful.[2] Work to date has largely involved the use of chiral enolate derivatives with achiral aminating agents, but the development of chiral sources of electrophilic nitrogen would offer greater synthetic flexibility. We have been attracted[3] to the pioneering work of Vidal and Collet,[4–8] who showed that *N*-alkoxycarbonyloxaziridines (e.g. **1)** transfer nitrogen rather than oxygen to a number of nucleophiles. When the amination of ester enolates is considered, this methodology provides a conceptually simple synthesis of α-amino acids (Scheme 1). In this paper, we report the first examples of the use of chiral, non-racemic oxaziridines in this process, leading to asymmetric electrophilic amination.

2. Results and discussion

The first class of chiral, non-racemic oxaziridines we investigated are analogues of the Vidal and Collet compounds **1** where the ^{t}Bu-carbamate is replaced by one derived from a chiral alcohol, specifically **4**, derived from (–)-menthol. The preparation of **4** is shown in Scheme 2. Aza–Wittig reaction[9] of *p*-cyanobenzaldehyde with the iminophosphorane[10] derived from menthyl chloroformate **2**[11] gave the imine **3**; this sensitive intermediate was used in the next step without purification since analysis of the crude ^{1}H NMR spectrum showed a very clean conversion (>95%) from the starting aldehyde. Oxidation to the oxaziridine was then performed using *m*-CPBA/BuLi.[12] Since the ring carbon and nitrogen in **4** are both stereocentres, this oxidation step could potentially lead to the formation of four diastereoisomers, two pairs of which could undergo interconversion by inversion at nitrogen. We



Scheme 1.

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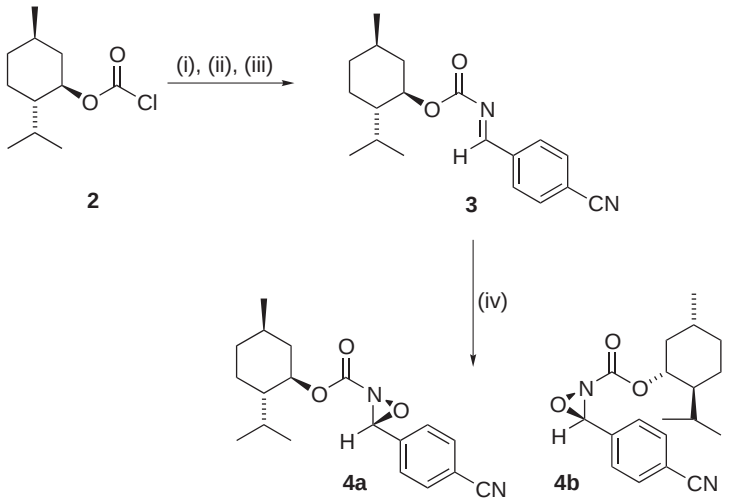


Scheme 2. *Reagents*: (i) NaN_3, Bu_4NBr, CH_2Cl_2, H_2O; (ii) PPh_3, CH_2Cl_2, 81% for two steps; (iii) (*p*-CN)C_6H_4CHO, PhMe, reflux, 48 h; (iv) *m*-CPBA, *n*-BuLi, CH_2Cl_2, −78°C to rt, 61% for two steps.

had originally assumed that facial selectivity on nucleophilic addition to the imine would be low, leading to a mixture of diastereomers at the ring carbon. Providing these were separable, testing of the individual isomers in the amination reaction would then provide valuable information on the mechanism of asymmetric induction in the amination process. Interestingly, however, the oxidation product was shown by HPLC analysis under several sets of conditions to be a single isomer. The ^{1}H NMR spectrum of **4** indicated the presence of two compounds in a ca. 9:1 ratio. Variable temperature studies showed coalescence of the two sets of resonances over a temperature range of 70–80°C. This suggests that they are (*E*)- and (*Z*)-isomers **4a** and **4b**, interrelated by inversion at nitrogen with a barrier of ca. 16–17 kcal/mol.[13] However, we were unable to detect other diastereomers by ^{1}H or ^{13}C NMR, suggesting that the compounds were single diastereomers at the ring carbon. Thus, the oxidation appears to have proceeded highly diastereoselectively with respect to facial attack on the imine carbon. It is not clear at this time whether this phenomenon represents kinetic or thermodynamic control, since nucleophilic addition to the imine is potentially reversible. An X-ray crystal structure[14] of **4** (Fig. 1) allowed assignment of configuration to the ring carbon. Compound **4** therefore appears to represent a rare example of a chiral, non-racemic *N*-alkoxycarbonyloxaziridine.[15]

With the synthesis of the desired non-racemic oxaziridine accomplished, attention was then turned to its use in the amination of enolates derived from achiral

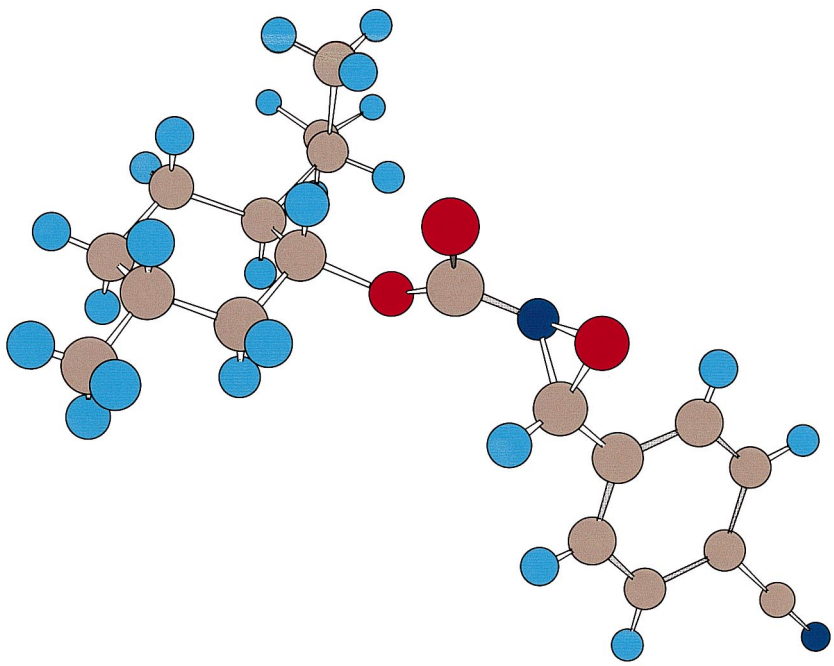
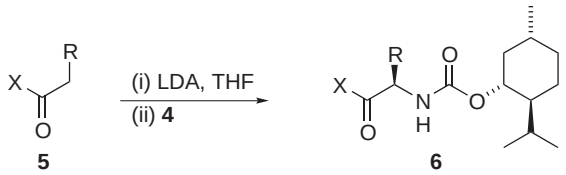


Figure 1. X-Ray structure of oxaziridine **4a**.

Table 1. Enolate amination with oxaziridine **4**[a]



5 **6**

Entry	R	X	Yield (%)[c]	D.e. (%)[d]
1	H	O^{t}Bu	60	–
2	H	Ph	59	–
3	H	NMe_2	56	–
4	Me	OMe	57	5
5	Me	OEt	52	8
6	Me	O^{t}Bu	51	7
7	Me	Ph	62	5[e]
8	^{i}Pr	OEt	49	17
9[b]	^{i}Pr	OEt	51	21

[a] Using 1 equiv. of oxaziridine with respect to enolate (see Ref. 16).
[b] 1 Equiv. $Ti(O^iPr)_4$ added to the lithium enolate prior to the addition of oxaziridine.
[c] Isolated yields of pure products.
[d] Determined by GC. Configuration assigned by comparison to authentic samples prepared from enantiomerically pure amino acid esters and (–)-menthyl chloroformate. Major isomer as depicted.
[e] Relative configuration not determined.

ketones and esters **5** (Table 1). In a typical amination reaction,[16] a THF solution of the oxaziridine was added to the lithium enolate of the substrate in THF at −78°C; reaction was completed by allowing it to warm to room temperature after 2–3 h. Diastereoselectivity was measured where appropriate by GC analysis, and configuration assigned by comparison to authentic samples of the diastereomerically pure products prepared by reaction of the commercially available enantiomerically pure amino acid esters with (–)-menthyl chloroformate. To confirm the reactivity of **4**, a number of investigations were performed initially using simple terminal enolates derived from esters, ketones and amides (entries 1–3). In all cases the amination reaction proceeded to afford α-amino compounds **6** in good yield. Amination of a range of lithium enolates of propionates (entries 4–7) revealed that there was low but reproducible diastereoselectivity in the nitrogen transfer process with 5–8% d.e. values, with the same relative configuration being obtained at the new stereocentre in each case.

Importantly, it was established that the products were not undergoing epimerisation under the reaction conditions by submitting diastereomerically pure samples to the basic reaction conditions; these were recovered unchanged. The low degree of stereoselectivity in the amination process could be related either to low facial selectivity in the approach of the oxaziridine to the enolate, or to the presence of a mixture of (*E*)- and (*Z*)-enolates. Precedent for highly stereoselective enolate formation under these conditions[17] suggests that the former explanation is more likely.

Since the nature of the ester substituent appeared to have little effect on the diastereoselectivity (compare entries 4–6), we next investigated an alternative R group in **5**. Using an *iso*-valerate (entry 8), an improved diastereoselectivity, with product of 17% d.e., was observed (entry 8). While the low levels of diastereoselectivity observed make construction of a working TS-model premature, it is conceivable that coordination between the enolate and the oxaziridine might lead to a more highly organised TS. In a preliminary study along these lines, we found that the addition of $Ti(O^iPr)_4$ to the lithium enolate of ethyl *iso*-valerate (entry 9) afforded a further small increase in amination diastereoselectivity to give a d.e. of 21%.

3. Conclusion

In conclusion, we have prepared the novel chiral, non-racemic oxaziridine **4** and demonstrated for the first time that such compounds can be used to effect the asymmetric electrophilic amination of enolates, albeit with low diastereoselectivity. Having demonstrated that the concept is feasible, future studies will be aimed at improving the diastereoselectivity, both by optimisation of the reaction conditions and in particular by the design and preparation of further structurally varied novel chiral oxaziridines that provide a better defined chiral environment.

Acknowledgements

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References

1. Reviews: (a) Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947–1980; (b) Greck, C.; Genet, J. P. *Synlett* **1997**, 741–748; (c) Mulzer, J.; Altenbach, H.-J. In *Organic Synthesis Highlights*; VCH: Weinheim, 1991; pp. 45–53; (d) Dembach, P.; Seconi, G.; Ricci, A. *Chem. Eur. J.* **2000**, *6*, 1281; (e) *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2000.
2. Recent examples: (a) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595–598; (b) Harris, J. M.; McDonald, R.; Vederas, J. C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2669–2674; (c) Svenstrup, N.; Bøgevig, A.; Hazell, R. G.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1559–1565; (d) Oppolzer, W.; Tamuira, O.; Sunarababu, G.; Signer, M. *J. Am. Chem. Soc.* **1992**, *114*, 5900.
3. Armstrong, A.; Atkin, M. A.; Swallow, S. *Tetrahedron Lett.* **2000**, *41*, 2247–2251.
4. Vidal, J.; Drouin, J.; Collet, A. *J. Chem. Soc., Chem. Commun.* **1991**, 435–437.
5. Vidal, J.; Guy, L.; Sterin, S.; Collet, A. *J. Org. Chem.* **1993**, *58*, 4791–4793.

6. Vidal, J.; Damestoy, S.; Collet, A. *Tetrahedron. Lett.* **1995**, *36*, 1439–1442.
7. Vidal, J.; Damestoy, S.; Guy, L.; Hannachi, J.; Aubry, A.; Collet, A. *Chem. Eur. J.* **1997**, *3*, 1691–1709.
8. Vidal, J.; Hannachi, J.-C.; Hourdin, G.; Mulatier, J.-C.; Collet, A. *Tetrahedron Lett.* **1998**, *39*, 8845–8848.
9. Golobokov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353.
10. **CAUTION**: to avoid the risk of explosion in large scale preparations, it is advised **NOT** to concentrate the CH_2Cl_2 solution of the intermediate azidoformate. On a small scale, the azidoformate was concentrated in vacuo to yield the crude product as an off-white solid, which could be recrystallised from ethanol.
11. Purchased from Aldrich, or prepared from (–)-menthol according to: Goren, Z.; Heeg, M. J.; Mobashery, S. *J. Org. Chem.* **1991**, *56*, 7186–7188.
12. The procedure of Ref. 3 was employed using anhydrous *m*-CPBA (1.6 equiv.) and *n*-BuLi (1.5 equiv.), except that after addition of the imine, the reaction was stirred at −78°C for 3 h, then brought to rt over 90 min before quenching and work-up. Data for **4**: formed as a white solid (61% from aldehyde): $[\alpha]_D^{20}$ +39.5 (c 1.0, $CHCl_3$); mp 55°C; ν_{max} ($CHCl_3$ solution)/cm^{-1} 2960, 2931, 2872, 2233, 1772, 1754, 1494, 1387, 1319, 1081, 981; δ_H (400 MHz, $CDCl_3$), equilibrium mixture of *trans* and *cis* isomers in 90:10 ratio at 300 K: 7.73 (2H, d, *J* 8.1 Hz), 7.60 (2H, d, *J* 8.1 Hz), 5.39 (1H, s, *trans*), 5.09 (1H, s, *cis*), 4.73 (1H, td, *J* 10.9 and 4.5 Hz, *trans*), 4.40 (1H, td, *J* 10.9 and 4.5 Hz, *cis*), 2.07 (1H, m), 1.94 (1H, m), 1.72 (2H, m), 1.52 (1H, m), 1.09 (2H, m), 0.94 (3H, d, *J* 6.6 Hz), 0.91 (3H, d, *J* 7.0 Hz), 0.86 (2H, m), 0.81 (3H, d, *J* 7.0); δ_C (67 MHz, $CDCl_3$) 159.9 (C), 137.7 (C), 132.5 (2×CH), 128.7 (2×CH), 128.0 (C), 118.5 (C), 79.9 (CH), 77.2 (CH), 46.9 (CH), 40.4 (CH_2), 33.9 (CH_2), 31.4 (CH), 26.1 (CH), 23.3 (CH_2), 21.9 (CH_3), 20.6 (CH_3), 16.2 (CH_3); MS (FAB) *m*/*z* 329 (M+H, 21%), 189 (M−menthyl, 85%); HRMS observed 329.1870, $C_{19}H_{25}N_2O_3$ requires 329.1865. Calcd for $C_{19}H_{25}N_2O_3$: C, 69.47; H, 7.37; N, 8.53. Found: C, 69.31; H, 7.36; N, 8.49%.
13. This barrier to ring inversion is consistent with those reported previously (see Ref. 7).
14. We are grateful to Dr. A. J. Blake (School of Chemistry, University of Nottingham) for this structure determination. Full details will be provided in a separate account of this work.
15. The first example of a chiral, non-racemic *N*-alkoxycarbonyloxaziridine was reported recently: Page, P. C. B.; Murrell, V. L.; Limousin, C.; Laffan, D. D. P.; Bethell, D.; Slawin, A. M. Z.; Smith, T. A. D. *J. Org. Chem.* **2000**, *65*, 4204–4207.
16. Typical procedure for enolate aminations: as in Ref. 3.
17. Ireland, R. E.; Wipf, P.; Armstrong, III, J. D. *J. Org. Chem.* **1991**, *56*, 650–657.