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8-Azabicyclo[3.2.1]oct-3-en-2-ones via asymmetric 1,3-dipolar cycloaddition of a homochiral 3-oxidopyridinium betaine

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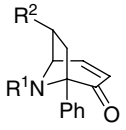
Abstract—8-Azabicyclo[3.2.1]oct-3-en-2-ones were prepared by asymmetric 1,3-dipolar cycloadditions of homochiral pyridinium betaine **4**. Excellent diastereofacial selectivity was achieved for the major 6-*exo* cycloadducts. The absolute stereochemistry of cycloadduct **7** was confirmed by a single-crystal X-ray diffraction study.

We required access to homochiral 8-azabicyclo[3.2.1]-oct-3-en-2-ones, as exemplified by structure **1** or its antipode, to provide intermediates for a program of chemical synthesis.



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The construction of such bicyclic compounds in racemic form utilised efficient 1,3-dipolar cycloaddition of 1-benzyl-2-phenyl-3-oxidopyridinium betaine and a dipolarophile bearing an electron-withdrawing group.[1,2] It was envisaged that an asymmetric synthesis could be accomplished by introducing a chiral controlling element to the dipolar cycloaddition.[3] Two intermolecular approaches for asymmetric synthesis were contemplated, either with a chiral auxilliary on the dipolarophile (Scheme 1, Eq. 1), or on the nitrogen of the betaine (Scheme 1, Eq. 2). Indeed, the feasibility of the former methodology has been demonstrated using (*R*)-*p*-tolyl vinyl sulfoxide **2**[4,5] or an acrylate derived from (*S*)-methyl lactate **3**[6] as the dipolarophile. However, the latter novel approach (Scheme 1, Eq. 2) was attractive to explore due to the versatility offered by potential combination of a homochiral betaine with a variety of dipolarophiles.

An α-methylbenzyl substituent on the pyridinium betaine was chosen as the auxilliary to investigate since this would give a chiral controlling element close to the reacting centres and would be easily removed. Thus, synthesis of homochiral betaine **4** was performed in three steps as outlined in Scheme 2. The key transformations were reductive amination of the hindered ketone **5**, using imine formation with (*S*)-α-methylbenzylamine mediated by titanium(IV) isopropoxide followed by sodium borohydride reduction,[7] and oxidation of the resultant furyl amine **6** (ca. 2:1 mixture of diastereoisomers) with bromine in aqueous tetrahydrofuran.[8]

Dipolar cycloaddition of homochiral betaine **4** with excess *tert*-butyl acrylate was performed in toluene at 95 °C for 4 days to give a 70% overall yield of cycloadducts with complete regioselectivity (Scheme 3). The major 6-*exo* isomer **7** was formed with excellent diastereofacial selectivity (**7**:**8** 96:4). As in the achiral cycloaddition of 1-benzyl-2-phenyl-3-oxidopyridinium betaine with *tert*-butyl acrylate,[2] a significant quantity of 6-*endo* product were also formed (*exo*:*endo* ratio 1.8:1). Interestingly however, the 6-*endo* diastereoselectivity was only moderate (**9**:**10** 67:33). The absolute

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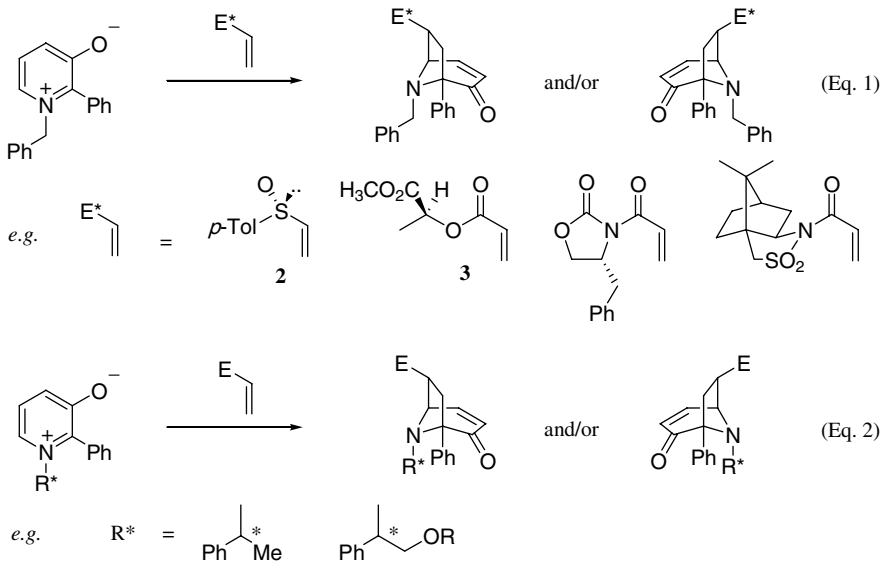
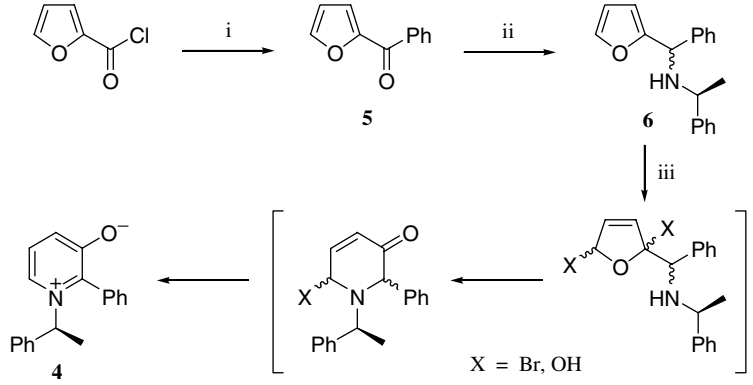
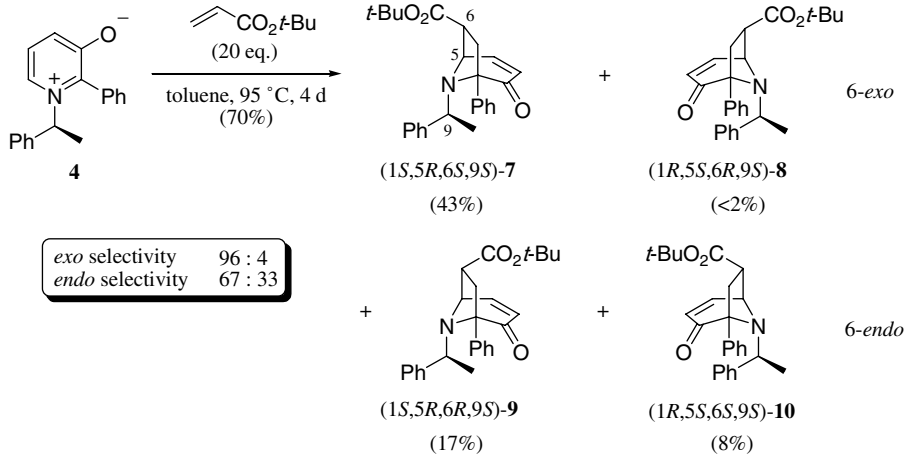


Scheme 1. Potential approaches to asymmetric 1,3-dipolar cycloaddition, either with a chiral auxilliary on the dipolarophile (Eq. 1), or on the nitrogen of the betaine (Eq. 2).



Scheme 2. Reagents and conditions: (i) $NaBPh_4$, $Pd(OAc)_2$, Na_2CO_3, acetone, rt (58%); (ii) (*S*)-(−)-α-methylbenzylamine, $Ti(O\text{-}i\text{-}Pr)_4$, 80 °C then $NaBH_4$, MeOH, rt (95%); (iii) Br_2, THF/H_2O, 0 °C to rt (52%).



Scheme 3. Cycloaddition with *tert*-butyl acrylate.

stereochemistry of cycloadduct **7** was established by a single-crystal X-ray diffraction study, as shown in Figure 1.[9] Structural assignment of cycloadducts **8**–**10** was made on the basis of NMR studies.[10,11]

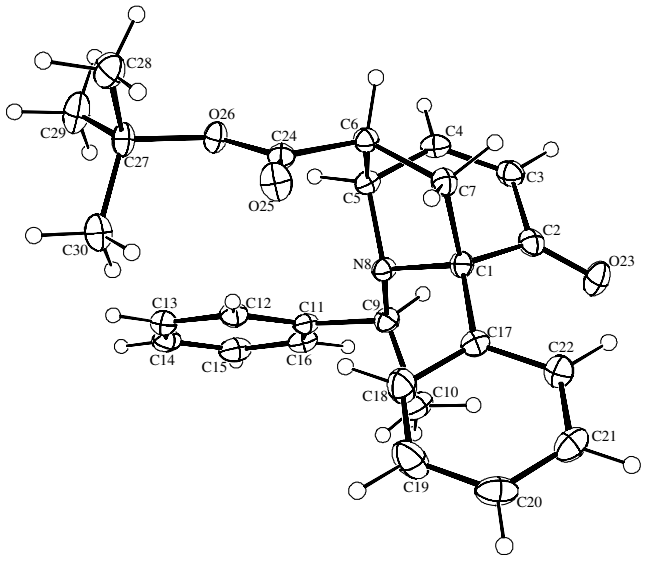


Figure 1. Perspective view of cycloadduct **7** generated by ORTEP3 from the crystallographic coordinates. The ellipsoids for the nonhydrogen atoms are drawn at the 50% level while the H atoms are a fixed size.

Cycloaddition of betaine **4** with phenyl vinyl sulfone was less efficient than previously observed with the corresponding achiral *N*-benzyl betaine.[2] Variation of solvent and reaction temperature suggested that toluene at 90 °C for 4–5 days was the optimum conditions, giving the major 6-*exo* isomer **11** with excellent diastereoselectivity (>95:5) in 31% yield (48% based on recovered SM) together with unreacted betaine **4** (34%) (Scheme 4). Higher reaction temperatures failed to improve the yield of cycloadduct **11**, but instead gave significant amounts of the *O*-α-methylbenzyl compound **12**. The stereochemistry of cycloadduct **11** was assigned on the basis of ^{1}H NMR analysis,[12] supported by the X-ray structure of **7**.

The observed stereocontrol was rationalised by preferential approach of the dipolarophile from the β-face of betaine **4** *anti* to the phenyl moiety of the α-methylbenzyl substituent as illustrated in Figure 2.

The homochiral betaine **4** was efficiently prepared in three steps from 2-furoyl chloride, using (*S*)-α-methylbenzylamine as the source of chirality. 1,3-Dipolar cycloadditions proceeded in moderate to good yields, with excellent diastereofacial selectivity achieved for the major 6-*exo* cycloadducts. The absolute stereochemistry of cycloadduct **7**, the major product from reaction of **4** with *tert*-butyl acrylate (70% overall yield of

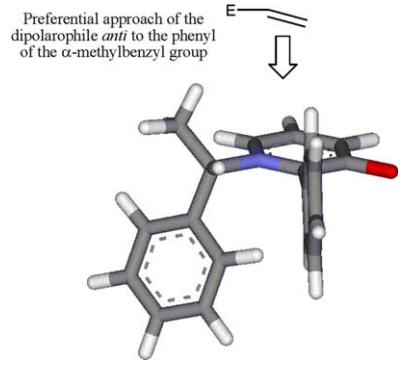


Figure 2. Rationalisation of cycloaddition face selectivity.

cycloadducts), was confirmed by a single-crystal X-ray diffraction study. Asymmetric cycloadditions of homochiral 1,3-dipoles, particularly nitrones and azomethine ylides bearing a chiral substituent on nitrogen, are well established.[3] However, we believe that the work described in this Letter represents the first application of such methodology to cycloaddition of a homochiral 3-oxidopyridium betaine.

Acknowledgements

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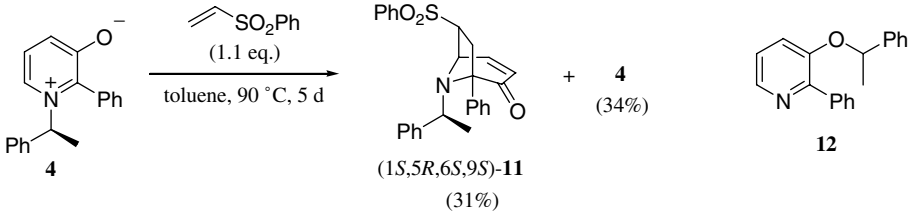

Scheme 4. Cycloaddition with phenyl vinyl sulfone.

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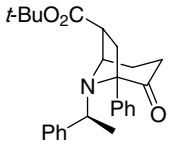
9. Crystallographic data for **7**. $C_{26}H_{29}NO_3$, $M_r = 403.526$, orthorhombic, $P2_12_12_1$, $a = 10.415(2)$, $b = 11.108(3)$, $c = 18.981(4)$ Å, $V = 2196(2)$ Å^3, $Z = 4$, $D_x = 1.220$ g cm^{-3}, monochromatized Mo radiation $\lambda = 0.71073$ Å, $\mu = 0.07$ mm^{-1}, $F(000) = 864$, $T = 100$ K. Data were collected on a Bruker CCD diffractometer to a θ limit of 26.36° which yielded 23,859 reflections. There are 4481 unique reflections with 4057 observed at the two sigma level. The structure was solved by direct methods (SHELXS-97) and refined using full-matrix least-squares on F^2 (SHELXL-97). The final model was refined using 275 parameters and all 4481 data. All nonhydrogen atoms were refined with anisotropic thermal displacements. The final agreement statistics are: $R = 0.029$ (based on 4057 reflections with $I \geqslant 2\sigma(I)$), $wR = 0.069$, $S = 1.02$ with $(\Delta/\sigma)_{max} < 0.01$. The maximum peak height in a final difference Fourier map is 0.129 e Å^{-3} and this peak is without chemical significance. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 287235. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
10. Assignments made by analysis of ^{1}H and COSY spectra of cycloadducts **7**–**10**, supported by ^{1}H, COSY and NOESY spectra of **13** and **14** (derived by hydrogenation of the major 6-*exo* and 6-*endo* cycloadducts, **7** and **9**, respectively). It is known that 6-*exo* cycloadducts show no coupling constant between H-5 and H-6$_{endo}$ so that H-5 appears as a doublet (coupling only to H-4, $J_{4,5}$ typically ca. 5.5 Hz).[1a]



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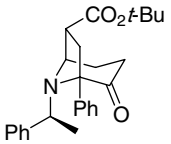

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11. ^{1}H NMR (400 MHz, $CDCl_3$) data for cycloadducts **7**–**10**. Compound **7**: δ 8.18 (2H, d, J 7.7 Hz), 7.37 (2H, t, J 7.7 Hz), 7.30–7.20 (6H, m), 6.74 (1H, dd, J 4.6, 9.7 Hz, H-4), 5.98 (1H, d, J 9.7 Hz, H-3), 4.07 (1H, d, J 4.6 Hz, H-5), 3.95 (1H, q, J 6.9 Hz, C*H*CH$_3$), 2.94 (1H, dd, J 2.0, 14.4 Hz, H-7$_{exo}$), 2.67 (1H, dd, J 1.9, 9.1 Hz, H-6), 2.42 (1H, dd, J 9.0, 14.4 Hz, H-7$_{endo}$), 1.48 (9H, s, C(CH$_3$)$_3$), 0.85 (3H, d, J 6.9 Hz, CHC*H*$_3$). Compound **8** (partial data): δ 6.18 (1H, d, J 9.8 Hz, H-3), 4.31 (1H, d, J 4.7 Hz, H-5), 3.72 (1H, q, J 6.9 Hz, C*H*CH$_3$), 3.26 (1H, dd, J 2.4, 14.5 Hz, H-7$_{exo}$), 2.80 (1H, dd, J 2.4, 9.0 Hz, H-6), 2.22 (1H, dd, J 9.0, 14.5 Hz, H-7$_{endo}$), 1.46 (9H, s, C(CH$_3$)$_3$),1.23 (3H, d, J 6.9 Hz, CHC*H*$_3$). Compound **9**: δ 8.07 (2H, d, J 7.5 Hz), 7.38–7.24 (8H, m), 6.74 (1H, dd, J 4.6, 9.8 Hz, H-4), 6.12 (1H, d, J 9.8 Hz, H-3), 4.00 (1H, q, J 6.9 Hz, C*H*CH$_3$), 3.95 (1H, t, J 5.2 Hz, H-5), 3.52–3.46 (1H, m, H-6), 2.63–2.51 (2H, m, H-7$_{exo}$/H-7$_{endo}$), 1.37 (9H, s, C(CH$_3$)$_3$), 0.85 (3H, d, J 7.0 Hz, CHC*H*$_3$). Compound **10**: δ 7.58 (2H, d, J 7.3 Hz), 7.16–7.02 (7H, m), 6.96 (2H, m), 6.21 (1H, d, J 9.8 Hz, H-3), 4.33 (1H, t, J 5.6 Hz, H-5), 3.79 (1H, q, J 6.9 Hz, C*H*CH$_3$), 3.37–3.31 (1H, m, H-6), 2.71 (1H, dd, J 10.2, 14.2 Hz, H-7$_{exo}$), 2.37 (1H, dd, J 6.8, 14.3 Hz, H-7$_{endo}$), 1.42 (9H, s, C(CH$_3$)$_3$), 1.27 (3H, d, J 6.9 Hz, CHC*H*$_3$).
12. Compound **11**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (2H, d, J 7.5 Hz), 7.82 (2H, m), 7.66 (1H, m), 7.52 (2H, m), 7.39–7.24 (8H, m), 6.61 (1H, dd, J 4.7, 9.7 Hz, H-4), 5.92 (1H, d, J 9.6 Hz, H-3), 4.28 (1H, d, J 4.7 Hz, H-5), 3.91 (1H, q, J 6.9 Hz, C*H*CH$_3$), 3.35 (1H, dd, J 3.5, 9.4 Hz, H-6), 2.90 (1H, dd, J 3.5, 15.2 Hz, H-7$_{exo}$), 2.52 (1H, dd, J 9.5, 15.2 Hz, H-7$_{endo}$), 0.92 (3H, d, J 7.0 Hz, CHC*H*$_3$).