Asymmetric epoxidation of *N*-enoylsultams with urea-hydrogen peroxide/trifluoroacetic anhydride

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Diastereomeric isomers of epoxides **15–28** are obtained in high yield and moderate to high optical purity when *N*-enoylsultams **1–14** incorporating a variety of chiral sultams as the chiral induction elements are treated with urea-hydrogen peroxide/trifluoroacetic anhydride.

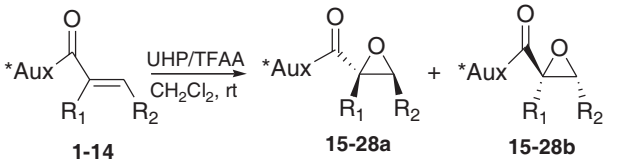
Keywords: asymmetric epoxidation, auxiliary, synthesis, chiral sultam, urea hydrogen peroxide

Chiral epoxides are very important building blocks in organic synthesis.[1] Subsequent stereoselective ring opening of the epoxide by various nucleophiles provides easy access to a large number of target molecules.[2] Thus, the development of efficient methodologies for the stereochemical control of epoxidation is of considerable interest. Most applications in auxiliary-controlled epoxidation are of oxazolidine or oxazolidinone auxiliaries.[3] Oppolzer's sultam, from natural camphor, had been applied as a versatile chiral auxiliary in asymmetric synthesis for the last two decades.[4] Synthetic chiral sultams developed as new auxiliaries by chemical design have been recently demonstrated by us and others.[5] To date, however, reports on asymmetric epoxidation controlled by Oppolzer's sultam or other synthetic chiral sultams have been scarce.

The most popular oxidants for the epoxidations of alkenes are dioxiranes[3,6] and peracids.[3,7] Although the diastereoselective epoxidation of electron-rich alkenes by these two oxidants is well documented,[8] the reaction of electron-poor substrates remains a synthetic challenge.[9] Urea-hydrogen peroxide (UHP) is both cheap and safe, yielding an innocuous by-product in oxidation reactions. It has the advantages of being relatively stable and more convenient in use than aqueous hydrogen peroxide.[10] To extend our study of the exploitation of sultams in asymmetric synthesis,[5] we have synthesised several chiral sultams and explored the behaviours of them as chiral controlling auxiliaries in asymmetric epoxidation with UHP and trifluoroacetic anhydride (TFAA) as oxidants.

Optically active *N*-enoylsultams **1–14** were prepared in good yields from the corresponding chiral sultams by standard published procedures. *N*-Enoylsultam **1** was chosen to explore the optimum epoxidation condition. The extent of conversion and diastereoselectivities of the reaction were determined by ^{1}H NMR. We screened the solvent, temperature, reaction time and propartion of reagents and finally, the optimum epoxidation conditions were obtained, *i.e.* with UHP (10 eq)/TFAA (10 eq) as oxidant and at room temperature in dichloromethane (Scheme 1). The epoxidations of *N*-enoylsultams **2–14** were carried out under the same conditions and the experimental results are listed in Table 1.

Careful examination of the results in Table 1 shows that the diastereoselectivities of the reactions are highly dependent on the exact structure of the auxiliaries. Furthermore, substrates possessing a tricyclic sultam moiety exhibited higher diastereoselectivity than their bicyclic and monocyclic counterparts (Substrates **1**, **9**, **12**, **13** versus **6**, **14**). In particular, substrate **12** was epoxidised to give products with the highest dr (15:85). Remarkably, minor structural variation of the chiral



Scheme 1

auxiliary may exert great impact on the dr of the reaction as exemplified by substrates **9** and **12**. It becomes apparent that, by proper molecular design of the auxiliary, synthetic chemists should achieve high control in creating new stereogenic centre(s) in these diastereoselective transformations. On the other hand, the major epoxide obtained is also dependent on the structure of the auxiliary. For example the major isomer obtained from **1** is **15a** whereas that from **9** is **23b**. This may be rationalised in terms of the energy difference between the transition state structures for these oxygen-transfer processes. According to reports,[11] the UHP complex in the TFAA can generate trifluoroperacetic acid (TFPAA), which may be the key oxidant in the epoxidation. TFPAA has the ability to form the strong hydrogen bonding with the substrate and transition state structures of T1$^{\#}$ for **1** and T2$^{\#}$ for **9** can be obtained. For *N*-enoylsultams, the favourable conformation is with *s-trans* and the C=O group oriented away from the SO_2 unit (Fig. 1). It has been well documented that hydrogen bonding plays an important role in peracids epoxidation.[12] Due to the presumed hydrogen bonding interactions between TFPAA and sulphonyl groups of the enoylsultams **1** and **9**, transition state structures T1$^{\#}$ and T2$^{\#}$ were favoured. An attack by the epoxidant from the less hindered C_α *re* face would afford the desired major diastereomers **15a** and **23b,** respectively.

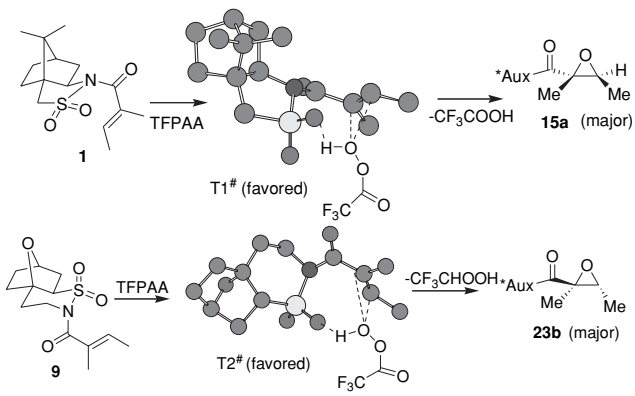


Fig. 1 Proposed transition state structures of **1** and **9** with oxidants. All hydrogen atoms are omitted for the sake of clarity.

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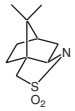
Table 1 Epoxidation results of *N*-Enoylsultams **1–14** with UHP/TFAA

Aux*	Substrate	R_1	R_2	Epoxide	Time /h	Yield /%[a]	dr[b] **a:b**
	**1**	Me	Me	**15**	0.5	95	72:28
	2	H	Me	**16**	2	88	58:42
	3	H	Pr	**17**	2	72	63:37
	4	Me	H	**18**	5	70	62:38
	**5**	H	Me	**19**	1	57	60:40
	6	Me	Me	**20**	1	86	68:32
	7	H	H	**21**	36	<5	
	**8**	H	Me	**22**	2	70	55:45
	**9**	Me	Me	**23**	1	72	27:73
	10	Me	H	**24**	2	68	31:69
	11	H	Pr	**25**	7	77	33:67
	**12**	Me	Me	**26**	1	75	15:85
	**13**	**Me**	**Me**	**27**	**1**	**30**	**83:17**
	**14**	Me	Me	**28**	1	93	66:34

[a]Isolated yields. [b]Determined by ^{1}H NMR spectroscopy.

Experiments

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian INOVA Unity (400MHz for ^{1}H, and 100.6MHz for ^{13}C) or on a JOEL JNM-EX 270 (270 MHz for ^{1}H, and 67.8 MHz for ^{13}C) spectrometer. Chemical shifts were recorded in *ppm* (δ) relative to TMS. High-resolution mass spectra (HRMS *m/z*) were recorded on a QSTAR Pulsar/LC/MS/MS system.

General procedure for the epoxidation of enoylsultams **1–14**: To a solution of enoylsultams **1**–**14** (1.0 equiv) in dichloromethane (10 ml), was added UHP (10 equiv) at room temperature. Trifluoroacetic anhydride (10 equiv) was dissolved in dichloromethane (10 ml) and dropped slowly into the mixture. The reaction mixture was stirred at room temperature and reaction progress was monitored by TLC. After the reaction was completed, the reaction mixture was poured into saturated sodium bicarbonate solution, and extracted with dichloromethane (3 × 25 ml). The combined organic layer was dried over anhydrous sodium sulfate and evaporated in a vacuum. The residue was purified by flash column chromatography on silica gel (EA/PE) to give the pure epoxide product **15–28** in 95%–57% yield, respectively. Unfortunately, some of the epoxide mixtures cannot be separated cleanly by column chromatography. The following are the spectra data of some new compounds.

Spectra data of some major epoxide products

15a: ^{1}H NMR ($CDCl_3$, 270MHz) δ 3.91 (dd, *J*=7.6, 5.1 Hz, 1H), 3.48 (d, *J*=13.2 Hz, 1H), 3.40 (d, *J*=13.2 Hz, 1H), 3.34 (q, *J*=5.4 Hz, 1H), 2.13–1.89 (m, 5H), 1.58 (s, 3H), 1.47–1.31 (m, 2H), 1.38 (d, *J*=2.4 Hz, 3H), 1.16 (s, 3H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 170.6, 65.1, 60.8, 58.2, 53.1, 48.8, 47.9, 44.6, 38.1, 32.9, 26.5, 20.8, 19.9, 14.9, 13.1; HRMS calcd for $C_{15}H_{23}NO_4NaS$ 336.1245, found 336.1264.

17a: ^{1}H NMR ($CDCl_3$, 270MHz) δ 3.89 (dd, *J*=8.0, 5.4 Hz, 1H), 3.82 (d, *J*=1.9 Hz, 1H), 3.54 (d, *J*=13.8 Hz, 1H), 3.44 (d, *J*=13.8 Hz, 1H), 3.12 (m, 1H), 2.13 (m, 2H), 1.91 (m, 3H), 1.57–1.35 (m, 6H), 1.94 (s, 3H), 0.99 (s, 3H), 0.97 (t, *J*=2.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 167.4, 65.0, 59.9, 53.3, 52.9, 49.2, 47.8, 44.5, 38.1, 33.5, 32.8, 26.4, 20.8, 19.8, 18.7, 13.8; HRMS calcd for $C_{16}H_{25}NO_4NaS$ 350.1402, found 350.1403.

20a: ^{1}H NMR ($CDCl_3$, 270MHz) δ 6.89 (dd, *J*=7.0, 2.7 Hz, 1H), 6.54 (dd, *J*=7.0, 1.9 Hz, 1H), 5.11 (m, 1H), 3.20 (q, *J*=5.4Hz, 1H), 2.20 (m, 1H), 1.42 (d, *J*=5.4 Hz, 3H), 1.03 (d, *J*=7.0 Hz, 3H), 0.88 (d, *J*=4.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 171.4, 135.4 126.9, 64.8, 61.0, 58.5, 31.14, 18.6, 17.0, 14.1, 13.2; HRMS cacld for $C_{11}H_{17}NO_4NaS$ 282.0775, found 282.0771.

22a: ^{1}H NMR ($CDCl_3$, 270MHz) δ 4.68 (m, 1H), 3.81 (d, *J*=1.9 Hz, 1H), 3.31 (m, 1H), 3.16–3.07 (m, 2H), 2.53–2.39 (m, 2H), 2.09 (m, 2H), 1.68 (m, 1H), 1.45 (d, *J*=5.13 Hz, 3H), 0.98 (d, *J*=7.0 Hz, 3H), 0.93 (d, *J*=6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 169.5, 62.7, 57.7, 56.1, 53.3, 28.2, 24.9, 20.5, 20.1, 19.6, 17.6; HRMS cacld for $C_{11}H_{19}NO_4NaS$ 284.0932, found 284.0950.

23b: ^{1}H NMR ($CDCl_3$, 400MHz) δ 4.795 (t, *J*=5.6 Hz, 1H),4.42 (m, 1H), 3.80 (m, 1H), 3.26 (dd, *J*=8.4, 3.6 Hz, 1H), 3.15 (q, *J*=5.6 Hz, 1H), 2.57 (m, 1H), 2.15 (m, 2H), 2.01 (dd, *J*=13.2, 8.8 Hz, 1H), 1.89 (m, 1H), 1.65 (m, 3H), 1.61 (s, 3H), 1.37 (d, *J*=5.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 171.0, 86.4, 76.6, 67.0, 62.2, 59.2, 42.8, 35.8, 32.8, 31.0, 28.3, 16.1, 13.4; HRMS cacld for $C_{13}H_{19}NO_5NaS$ 324.0881, found 324.0913.

25b: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 4.79 (t, *J*=5.1 Hz, 1H), 4.61 (m, 1H) 4.16 (d, *J*=1.6 Hz, 1H) 3.87 (m, 1H), 3.49 (dd, *J*=8.6, 3.8 Hz, 1H), 3.14 (m, 1H), 2.54 (m, 1H), 2.19 (m, 2H), 2.04 (dd, *J*=13.8, 8.4 Hz, 1H), 1.92 (m, 1H), 1.77–1.46 (m, 6H), 0.97 (t, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 167.5 86.5, 76.4, 66.7, 59.8, 54.7, 42.0, 35.7, 33.4, 32.8, 30.9, 28.5, 18.8, 13.8; HRMS cacld for $C_{14}H_{21}NO_5NaS$ 338.1038, found 338.1006.

28a: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.73 (m, 2H), 7.48 (m, 3H), 5.57 (dd, *J*=8.9, 2.7 Hz, 1H), 5.21 (d, *J*=8.9 Hz, 1H), 5.01 (d, *J*=13.8 Hz, 1H), 3.83 (dd, *J*=13.8, 3.5 Hz, 1H), 3.12 (q, *J*=5.4 Hz, 1H), 1.53 (s, 3H), 1.27 (d, *J*=7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 169.5, 151.8, 131.2, 129.0, 127.2, 81.5, 76.5, 71.6, 61.0, 58.4, 45.5, 31.0, 27.1, 14.2, 13.8; HRMS cacld for $C_{15}H_{16}N_2O_5NaS$ 359.0677, found 359.0695.

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