Pergamon

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# New chiral sultam auxiliaries: preparation and their application in asymmetric Diels–Alder reactions

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***Abstract:*** Enantiomerically pure sultams (+)-**4** and (−)-**4** were synthesized from tricyclic sultone **1** *via* a four-step reaction sequence. Their uses as new chiral auxiliaries in asymmetric Diels–Alder reactions with diastereoselectivity up to 94:6 are presented. © 1997 Elsevier Science Ltd

Development of chiral auxiliaries has been continuously a challenging topic which interests many research groups.[1] Intensive investigations over the last twenty years culminated in the evolution of several versatile chiral auxiliaries of wide applicabilities. Oppolzer's chiral sultams accessible from (+) and (−)-camphorsulfonic acid are noteworthy examples, which have been successfully used as chiral auxiliaries in asymmetric Diels–Alder, alkylation, acylation, and aldolization reactions.[2] A closer examination revealed that minor variations in the structure of an auxiliary may sometimes have great influence on the effectiveness of the asymmetric induction in a chemical transformation.[3] Although natural products are convenient sources for the design and development of new chiral auxiliaries, the effectiveness of chiral auxiliaries of this type is relatively difficult to optimize *via* systematic structural modifications. In contrast, chiral auxiliaries based on rational chemical design provide greater flexibility for improvement through structural variations. This paper describes our efforts in developing a general route for the synthesis of chiral sultams and their subsequent use in the asymmetric Diels–Alder reactions.[4]

Recently, we reported the synthesis of tricyclic sultones using prop-1-ene-1,3-sultone as a dienophile in Diels–Alder reactions with various dienes.[5] For instance, sultone **1** was obtained in quantitative yield by reacting cyclopentadiene and prop-1-ene-1,3-sultone. The preparation of optically pure tricyclic chiral sultams was achieved in four simple steps as shown in Scheme 1. Facile nucleophilic ring opening of racemic sultone **1** by (*S*)-(−)-α-methylbenzylamine at 70°C led to the formation of a 1:1 diastereomeric mixture of internal salts **2**. After cooling to room temperature, **2b** precipitated out from the solution. Recrystallization of the crude precipitate once with ethanol furnished enantiomeric pure **2b** (*vide infra*) in 20% isolated yield from **1**. Alternatively, treatment with excess phosphorus oxychloride in THF, the mixture **2a** and **2b** underwent cyclization to afford **3a** and **3b** which can be separated by column chromatography. X-ray cystallographic analysis on one of the diastereomers (i.e. **3a**) established unambiguously the absolute configuration of both diastereomers as depicted. Debenzylation of **3a** and **3b** by treatment with formic acid followed by base hydrolysis afforded enantiomerically pure chiral sultams (+)-**4** and (−)-**4** in 73% overall yield, respectively.[6]

The efficiency of sultam **4** as a chiral auxiliary was assessed in asymmetric Diels–Alder reactions. The required chiral dienophiles **5** and **6** were prepared in a straightforward manner. Thus, *N*-acylation of **4** by successive treatment with NaH and the corresponding acyl chloride gave the *N*-acryloyl and *N*-crotonyl sultams **5** and **6** in 40% and 80% yield, respectively. With these chiral dienophiles in hand, their reactions with cyclopentadiene under various conditions were carried out (Table 1).

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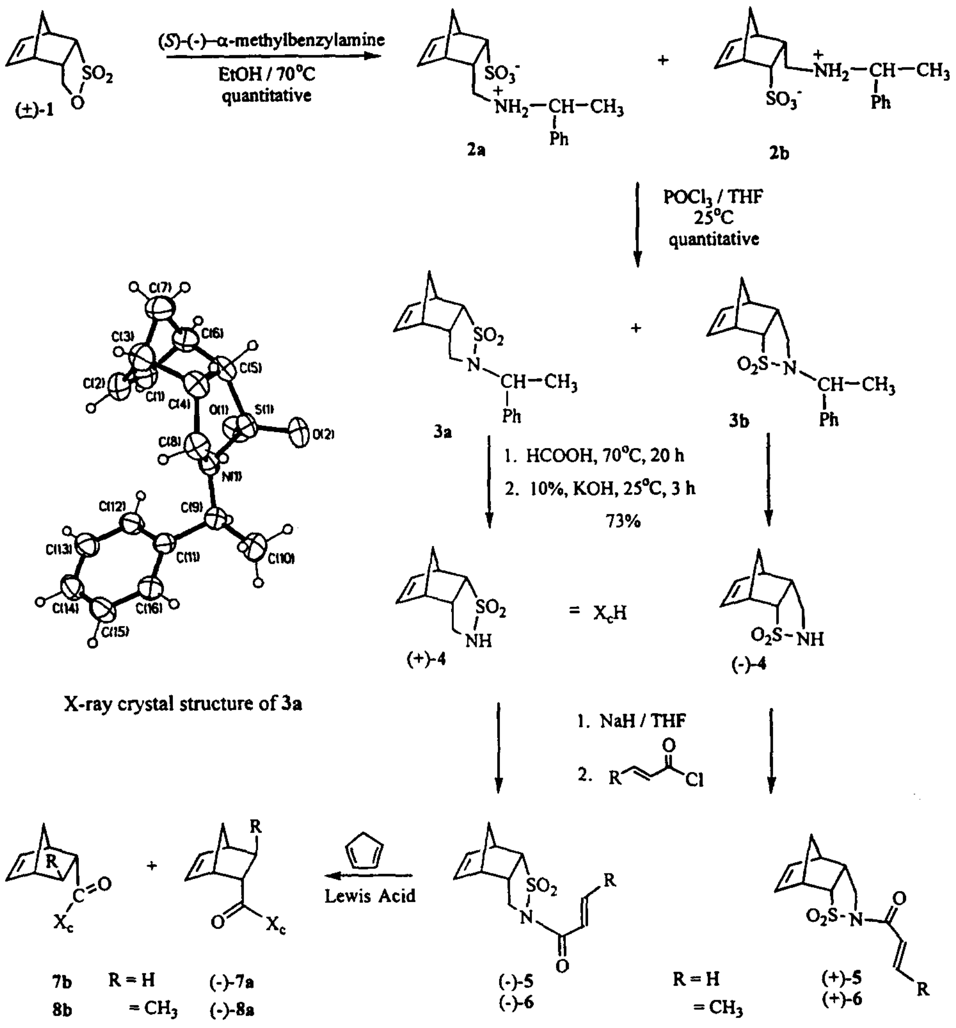
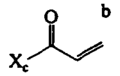
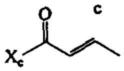


Scheme 1.

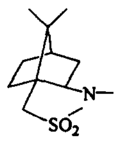
For steric reasons, **5** exhibited a higher reactivity than that of **6**. Even in the absence of Lewis acids, **5** reacted with cyclopentadiene at −20°C to afford a 1:1 diastereomeric mixture of **7a** and **7b** (Entry 1). On the other hand, the asymmetric Diels–Alder reaction of **5** with cyclopentadiene catalyzed by $SnCl_4$ or $TiCl_4$ proceeded well at −78°C, both showing high diastereoselectivity (Entries 2 and 3). For the less reactive dienophile **6**, $SnCl_4$ was ineffective to promote the Diels–Alder reaction at low temperature. Prolonged reaction at −78°C with cyclopentadiene led only to the formation of polymeric materials. The rate enhancement and diastereoselection promoted by $ZnBr_2$ was only marginally observed (Entry 5). $TiCl_4$ emerged as the best Lewis acid for activating the asymmetric Diels–Alder reaction of **6** with cyclopentadiene with 94:6 diastereoselectivity (Entry 6). In all cases, the endo/exo selectivity in the Diels–Alder reactions was found to be excellent. Hydrolysis of both **7a** and **8a** by LiOH (8 eq., 24 h, 25°C) in aqueous THF solution regenerated the pure chiral auxiliary in over 85% recovery yield together with the formation of the corresponding optically active acids in 81% and 85% yield, respectively.[7]

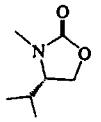
In conclusion, we have developed an efficient method for the preparation of both enantiomerically pure sultams (+)-**4** and (−)-**4**. Their uses as chiral auxiliaries in asymmetric Diels–Alder reactions

**Table 1**. Results for the Diels-Alder reactions of dienophiles 5, 6 and some known dienophiles with cyclopentadiene

| Entry | Dienophile | Lewis Acid (Equiv.) | Temp. [°C] (time, h) | Adduct | Yield [%] | endo[a] [%] | **7a** : **7b**[a] or **8a** : **8b**[a] |
|---|---|---|---|---|---|---|---|
| 1 | (-)-**5** | - | -20 (14) | **7** | 80 | >90 | 1 : 1 |
| 2 | (-)-**5** | $SnCl_4$ (0.5) | -78 (5) | **7** | 87 | 98 | 94 : 6 |
| 3 | (+)-**5** | $TiCl_4$ (1.5) | -78 (2) | **7** | 73 | 96 | 14 : 86 |
| 4 |  [b] | $Et_2AlCl$ (1.4) | -100 (0.1) | **7** | 81 | 99 | 7 : 93 |
| 5 | (-)-**6** | $ZnBr_2$ (10) | 20 (6) | **8** | 88 | 91 | 62 : 38 |
| 6 | (-)-**6** | $TiCl_4$ (0.8) | -78 (21) | **8** | 90 | 97 | 94 : 6 |
| 7 |  [c] | $TiCl_4$ (0.5) | -78 (1) | **8** | 98 | 99 | 96 : 4 |

[a] The endo : exo ratio and diastereoselectivity of the new reaction was determined by $^1$H NMR (270 MHz).

[b] Chiral auxiliary $X_c$ =  .

[c] Chiral auxiliary $X_c$ =  .

have been demonstrated. High diastereoselectivities comparable to many other widely used chiral auxiliaries[8] (Entry 4 and 7) with the corresponding acryl and crotonyl dienophile in Diels–Alder reactions with cyclopentadiene were achieved.

## Acknowledgements

Financial support from the Faculty Research Committee of the Hong Kong Baptist University (FRG/95-96/II-75) and the Research Grant Council (HKBU 136/94P) is gratefully acknowledged.

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6. (−)-**4**: mp 208–210°C; $[\alpha]_D^{22} = -3.8$ (C=0.9, $CHCl_3$); $^1$H NMR ($CDCl_3$, 270 MHz) δ 1.45 (d, 1 H, $J$=8.90 Hz), 1.63 (d, 1 H, $J$=8.90 Hz), 2.94 (m, 1 H), 3.10 (br. s, 1 H), 3.21–3.31 (m, 2 H), 3.39

(br. s, 1 H), 3.79 (dd, 1 H, $J$=7.60, 4.20 Hz), 3.87 (br. s, 1 H), 6.38 (dd, 1 H, $J$=6.80, 2.80 Hz), 6.45 (dd, 1 H, J=6.80, 2.80); $^{13}$C NMR ($CDCl_3$, 67.8 MHz) $\delta$ 43.8, 46.2, 46.8, 46.9, 51.5, 62.9, 134.0, 136.4; IR (KBr) $\nu$/cm$^{-1}$ 3263 (N–H); Analysis for $C_8H_{11}NO_2S$, found: C, 52.03%, H, 6.10%, N, 7.55% calculated C, 51.87%, H, 5.99%, H, 7.56%. All new compounds were characterized by spectroscopic methods (IR, $^1$H, $^{13}$C, NMR, HRMS and/or elemental analysis).

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