



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.

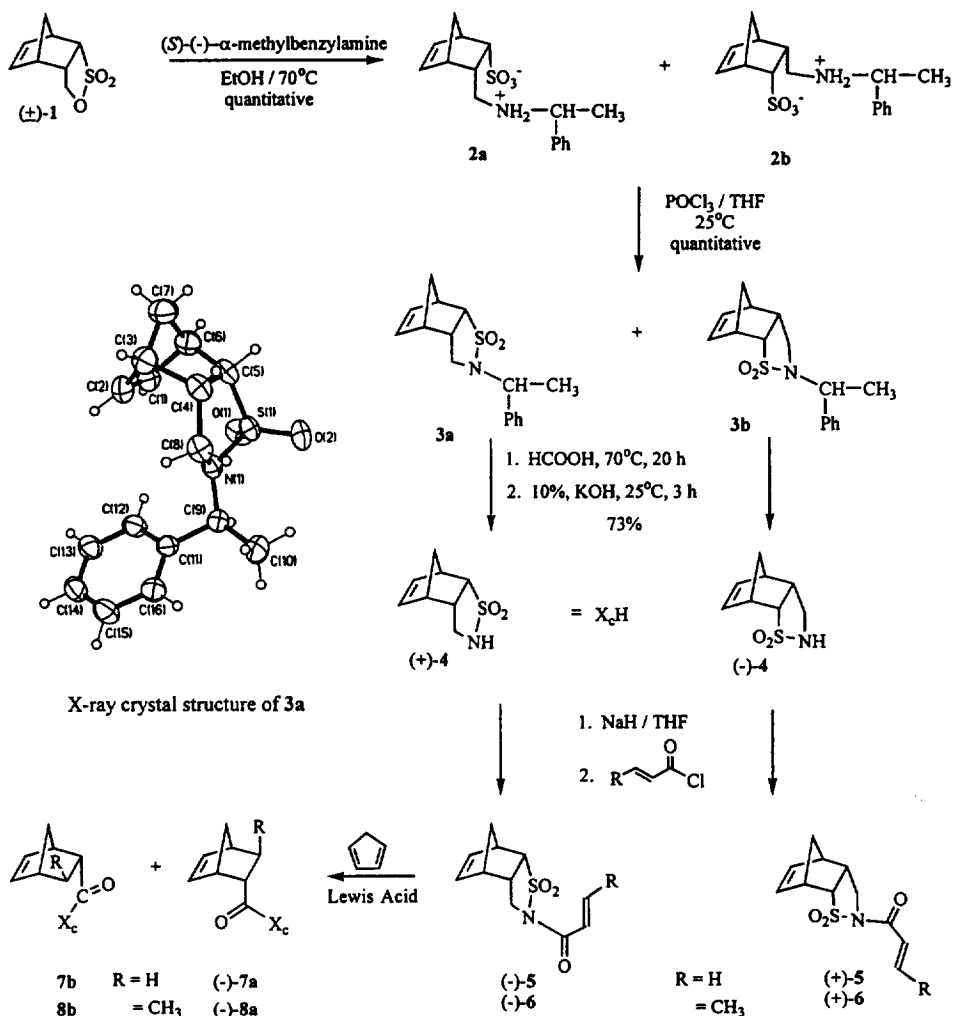
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Development of chiral auxiliaries has been continuously a challenging topic which interests many research groups.¹ Intensive investigations over the last twenty years culminated in the evolution of several versatile chiral auxiliaries of wide applicabilities. 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 enantiomerically 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 crystallographic 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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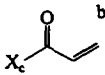
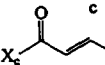


Scheme 1.

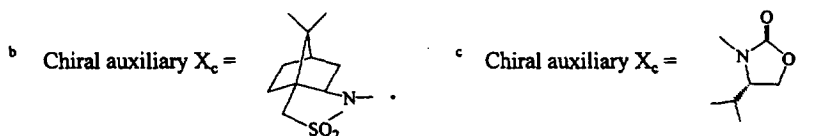
For steric reasons, **5** exhibited a higher reactivity than that of **6**. Even in the absence of Lewis acids, **5** reacted with cyclopentadiene at -20°C to afford a 1:1 diastereomeric mixture of **7a** and **7b** (Entry 1). On the other hand, the asymmetric Diels–Alder reaction of **5** with cyclopentadiene 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		Et ₂ AlCl (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		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 ¹H NMR (270 MHz).



have been demonstrated. High diastereoselectivities comparable to many other widely used chiral auxiliaries⁸ (Entry 4 and 7) with the corresponding acryl and crotonyl dienophile in Diels-Alder reactions with cyclopentadiene were achieved.

Acknowledgements

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References

1. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Seyden Penne, J., Eds.; John Wiley & Sons, Inc.: New York, 1995.
2. Oppolzer W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.*, **1990**, *112*, 2767–2772 and references therein.
3. (a) Oppolzer, W.; Kingma, A. J.; Pillai, S. K. *Tetrahedron Lett.*, **1991**, *32*, 4893–4896. (b) Poll, T.; Hady, A. F. A.; Karge, R.; Linz, G.; Weetman, J.; Helmchen, G. *Tetrahedron Lett.*, **1989**, *30*, 5595–5598.
4. For reviews on the Asymmetric Diels-Alder reactions see: (a) Oppolzer, W. *Angew. Chem. Int. Ed. Engl.*, **1984**, *23*, 876–889. (b) Helmchen, G.; Karge, R.; Weetman, J. In *Modern Synthetic Methods*; Schveffold, R. Ed.; Springer: Berlin, 1986; Vol. 4, pp. 262–306. (c) Taschner, M. In *Organic Synthesis Theory and Applications*; Hudlicky, T. Ed.; JAI: Greenwich, CT, 1989; Vol. 1, pp. 91–101.
5. Lee, A. W. M.; Chan, W. H.; Jiang, L. S.; Poon, K. W. *J. Chem. So. Chem. Commun*, **1997**, 611–612.
6. (-)-**4**: mp 208–210°C; [α]_D²² = -3.8 (C=0.9, CHCl₃); ¹H NMR (CDCl₃, 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) δ 43.8, 46.2, 46.8, 46.9, 51.5, 62.9, 134.0, 136.4; IR (KBr) ν/cm^{-1} 3263 (N-H); Analysis for $\text{C}_8\text{H}_{11}\text{NO}_2\text{S}$, found: C, 52.03%, H, 6.10%, N, 7.55% calculated C, 51.87%, H, 5.99%, N, 7.56%. All new compounds were characterized by spectroscopic methods (IR, ^1H , ^{13}C , NMR, HRMS and/or elemental analysis).

7. Krotz, A.; Helmchen, G. *Tetrahedron: Asymm.*, **1990**, *1*, 537.

8. Gawley, R. E.; Aube, J. *Principles of Asymmetric Synthesis*; Pergamon: New York; 1996, p. 267.

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