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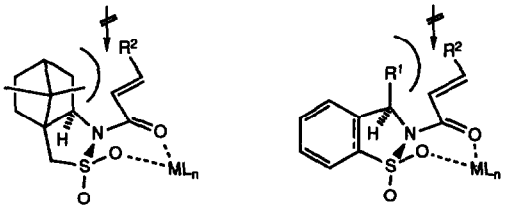
# CHIRAL TOLUENE-2,α-SULTAM AUXILIARIES: ASYMMETRIC DIELS-ALDER REACTIONS OF N-ENOYL DERIVATIVES

Wolfgang Oppolzer*, Martin Wills, Martha J. Kelly, Marcel Signer, Julian Blagg
Département de Chimie Organique, Université de Genève, CH-1211 Genève 4, Switzerland

Abstract: Asymmetric, $R_mAlCl_n$ mediated Diels-Alder reactions of 1,3-dienes to *N*-enoyl derivatives 4 and 9 of (*R*)-methyl-, (*R,S*)-*t*-butyl-, α,α-dimethylbenzyl-, benzyl and (*S*)-methyl-toluene-2,α-sultams 3 as well as to *N*-enoyl derivatives 15 of (*R*)-2,3-dihydro-3-methylisoindolinone 14 are described.

*N*-Enoylbornane-10,2-sultams outperform most chiral dienophiles as to their utility for Lewis-Acid mediated asymmetric Diels-Alder reactions. [1] The postulated involvement of conformationally rigid chelates A has been recently supported by an X-ray diffraction analysis of A ($R^2 = CH_3$, $ML_n = TiCl_4$, Scheme 1). [2]

*Scheme 1*




A B

Extension of this concept to analogous chelates B promised to provide further insight into this type of stereoface direction. To this end we took advantage of the easy access to a range of C(α)-substituted toluene-2,α-sultams 3.

Methyl-substituted sultam 3 ($R^1$ = Me) and its antipode are of particular interest being readily available in enantiomerically pure form *e.g.* by asymmetric hydrogenation of imine 2 ($R^1$ = Me). [3] Acylation with acryloyl chloride afforded chiral dienophiles 4. [4] These underwent smooth [4+2]-cycloadditions to cyclopentadiene, 1,3-butadiene and isoprene. Our results are summarized in Scheme 2 and Table 1. [4]

*Scheme 2*

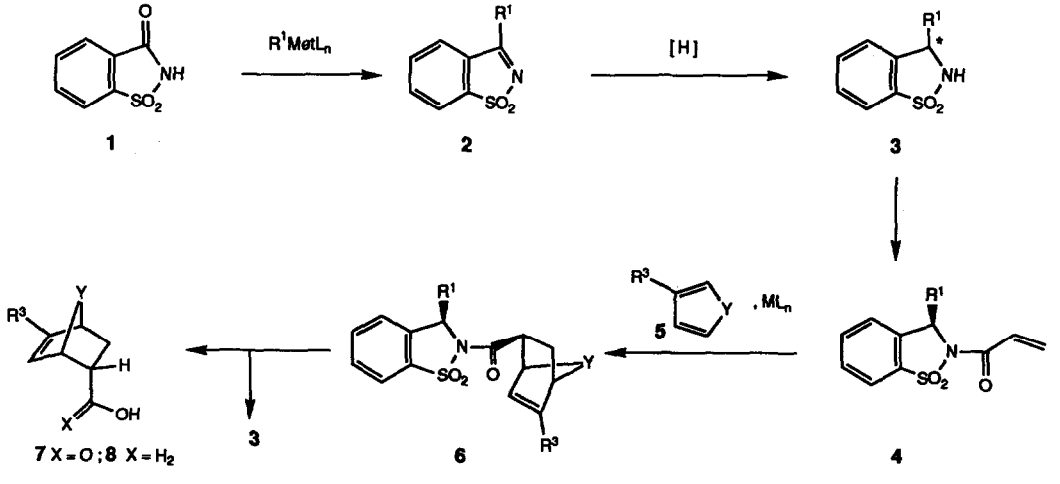


*Table 1* : Asymmetric Diels-Alder Reactions of *N*-Acryloyl-toluene-2,α-sultams 4 + 5 → 6

| Series | Dienophile 4 | | Diene 5 | | Reaction Conditions | | | Product 6 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $R^1$ | Configuration | $R^3$ | Y | $ML_n$ (molequiv) | Temp. [°C] | Time [h] | Yield crude [%] | Ratio endo/ exo | d.e. endo crude [%] | Yield cryst [%] | d.e. cryst. [%] |
| *1* a | Me | *R* | H | $CH_2$ | none | r.t. | | 95 | 96:4 | 62 | | |
| *2* a | Me | *R* | H | $CH_2$ | $BF_3.Et_2O$ (2.0) | -98 | | 30 | 95:5 | 51 | | |
| *3* a | Me | *R* | H | $CH_2$ | $nBu_2BOTf$ (2.0) | -78 | | 44 | >99:1 | 52 | | |
| *4* a | Me | *R* | H | $CH_2$ | $SnCl_4$ (2.0) | -78 | | 91 | >99:1 | 65 | | |
| *5* a | Me | *R* | H | $CH_2$ | $TiCl_4$ (1.0) | -98 | | 25 | 93:7 | 11 | | |
| *6* a | Me | *R* | H | $CH_2$ | $EtAlCl_2$ (2.0) | -78 | | 94 | >99:1 | 91 | | |
| *7* a | Me | *R* | H | $CH_2$ | $Et_2AlCl$ (2.0) | -78 | | 93 | >99:1 | 94 | | |
| *8* a | Me | *R* | H | $CH_2$ | $Me_2AlCl$ (2.0) | -98 | 0.2 | 97 | >99:1 | 93 | 83 | >99 |
| *9* b | *t*Bu | *RS* | H | $CH_2$ | none | r.t. | 24 | 75 | 80:20 | 51 | | |
| *10* b | *t*Bu | *RS* | H | $CH_2$ | $EtAlCl_2$ (1.5) | -78 | 0.2 | - | 95:5 | 77 | | |
| *11* b | *t*Bu | *RS* | H | $CH_2$ | $EtAlCl_2$ (1.5) | -98 | 0.25 | 61 | 96:4 | 90 | | |
| *12* c | $CMe_2Ph$ | *RS* | H | $CH_2$ | $EtAlCl_2$ (1.5) | -98 | 0.25 | 86 | 95:5 | 96 | | |
| *13* d | $CH_2Ph$ | *RS* | H | $CH_2$ | $Me_2AlCl$ (2.0) | -78 | 2 | ~99 | 96:4 | 81 | | |
| *14* d | $CH_2Ph$ | *RS* | H | $CH_2$ | $Me_2AlCl$ (2.0) | -98 | 2 | 85 | 97:3 | 85 | | |
| *15* e | Me | *R* | H | $H_2$ | $EtAlCl_2$ (1.6) | -78 | 18 | 79 | - | 90 | | |
| *16* f | Me | *R* | Me | $H_2$ | $Me_2AlCl$ (1.6) | -78 | 7 | 87 | - | 92 | | |

First we studied the influence of various Lewis acids on the addition of cyclopentadiene to *N*-acryloylsultam 4a ($R^1$ = Me). With (mono-coordinating) boron Lewis acids only modest inductions were observed, approaching those of the non-catalyzed reactions (entries 2,3,1). $SnCl_4$ catalysis, and, even more surprisingly, $TiCl_4$-catalysis furnished adduct 6a in low diastereomeric excesses of 65% and 11% d.e., respectively (entries 4,5). However, on employing 2 molequiv of $EtAlCl_2$, $Et_2AlCl$ or $Me_2AlCl$ at -78° C we obtained cycloaddition product 6a without a trace of its *exo*-isomer in 91 to 94% d.e. (HPLC, entries 6-8). Crystallization (1x hexane/$CH_2Cl_2$) afforded 6a in >99% d.e. (83% yield from 4a). Entry 8 thus shows a chiral efficiency equal to (or slightly better than) those observed with $TiCl_4$- or $AlL_n$-coordinated *N*-acryloylbornane-10,2-sultam A ($R^3$ = H). [1a]

To conveniently explore the influence of other auxiliary substitutents $R^1$, racemic *t*-butyl-, 4b ($R^1$ = *t*-Bu), [4,5] α,α-dimethylbenzyl-, [4,6] 4c ($R^1$ = $CMe_2Ph$) and benzylsultam 4d ($R^1$ = $CH_2Ph$) [4,5] were subjected to similar reaction conditions. *Endo/exo*- and diastereomer ratios [4] of resulting racemates 6b, 6c and 6d show that only the α,α-dimethylbenzyl group in 4c exerts a stereo-directing bias comparable to that of the methyl group (entries 12, 6). In contrast to our expectations, the *t*-butyl- and benzyl derivatives reacted in a less selective manner than their methyl analogue. [7]

Diels-Alder addition of butadiene and isoprene (-78°C, entries 15, 16) to enantiomerically pure (*R*)-*N*-acryloyl-methylsultam 4 ($R^1$ = Me) proceeded again with 90% and 92% diastereoselectivity *i.e.* as high as the bornanesultam standard. [1a]

[4+2]- Cycloadditions of (*E*)-*N*-crotonylsultams 9g, 9h and 9i to cyclopentadiene (Scheme 3, Table 2) proceeded *more* slowly (requiring 0°C with dienophiles 9h and 9i) and were less selective than those of the bornanesultam reference (93% d.e.). [1a] However, crystallization of crude 10g (hexane/$CH_2Cl_2$) raised its diastereomeric purity to >99% d.e. (58% yield from 9g, entry 17).

*Scheme 3*

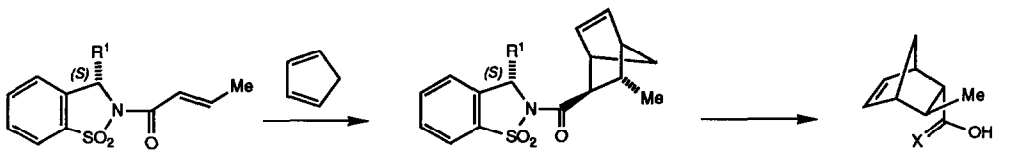


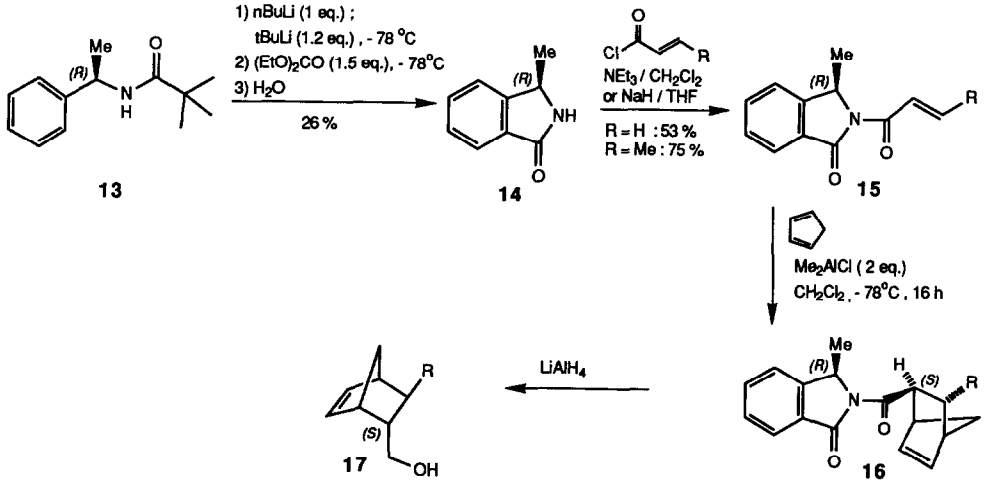

*Table 2* : Asymmetric Diels-Alder Reactions of *N*-Crotonyl-toluene-2,α-sultams 9 → 10

| Series | | Dienophile 9 | | Reaction Conditions | | | Product 10 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $R^1$ | Configuration | $ML_n$ (molequiv) | Temp. [°C] | Time [h] | Yield crude [%] | Ratio endo/ exo | d.e. endo crude[%] | Yield cryst [%] | d.e. cryst. [%] |
| *17* | g | Me | *S* | $Me_2AlCl$ (2.0) | -78 | 24 | 74 | 97:3 | 59 | 58 | >99 |
| *18* | h | *t*Bu | *RS* | $Me_2AlCl$ (2.0) | 0 | 15 | 84 | 85:15 | 74 | | |
| *19* | i | $CH_2Ph$ | *RS* | $Me_2AlCl$ (2.0) | 0 | 15 | 86 | 90:10 | 66 | | |

Removal of the methylsultam moiety from products 6a, 6e, 6f or 10g using $LiOH/H_2O_2$/aq. THF [8] or $LiAlH_4$ [1] furnished smoothly carboxylic acids 7a, [4] 7e [4] and 7f [4] or alcohols 8a [4] and 12g, [4] easily separable from recovered auxiliary 3 ($R^1$ = Me).

Since chelates such as B involving a $SO_2$-Lewis base are relatively unusual [2] we replaced the $SO_2$- by a C=O group and investigated isoindolinone 14 as a potential dienophile auxiliary (Scheme 4). [7]

*Scheme 4*




Successive treatment of (*R*)-*N*-pivaloylamide 13 [3] with *n*-BuLi/*t*-BuLi, [3,9] diethylcarbonate and water afforded (*R*)-isoindolinone 14 [4] in 26% yield. Its *N*-enoyl derivatives 15 [4] were reacted with cyclopentadiene in the presence of $Me_2AlCl$ (2 molequiv, $CH_2Cl_2$, 16 h, -78°C) to give adducts 16 [4] with excellent *endo/exo*-preference but only modest π-face selectivity (crude 16, R = H: 62% yield, *endo/exo*-ratio = 98.8/0.2, 66% d.e.; crude 16, R = Me: 57% yield, *endo/exo*-ratio = 97.4/2.6, 72% d.e.).

We thus conclude that various chiral sultams may serve as advantageous stereoface-directing dienophile auxiliaries in Lewis-acid catalyzed Diels-Alder reactions. Asymmetric alkylations, acylations and aldolizations of toluenesultam-derived "enolates" are described in the following communication.

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2) W. Oppolzer, I. Rodriguez, J. Blagg, G. Bernardinelli, *Helv. Chim. Acta* 1989, *72*, 123.

3) W. Oppolzer, M. Wills, C. Starkemann, G. Bernardinelli, *Tetrahedron Lett.* 1990, *31*, in press.

4) All new compounds were characterized by IR, $^{1H}$-NMR, $^{13C}$-NMR and MS. 6) Melting points(°C)= 4a: 102-104; (±)-4b:121-123; (±)-4c: 100-103; (±)-4d: 142; 6a: 167-169; 9g: 135-136; (±)-9h: 84-85; (±)-9i: 147-149; 10g: 116-117; 15, R=H: 66-68; 15, R=Me: 58-60. $[\alpha]_D$ values, (20° C, solvent, c = g/100 ml) = 4a: -17.8 ($CH_2Cl_2$, 0.27) 4e: +28.9 (EtOH, 0.60); 6a: -187.3 ($CH_2Cl_2$, 0.275); 7a: -68.6 ($CHCl_3$, 0.53); 7f: -68.6 ($CHCl_3$, 0.525); 8a: -82.2 (EtOH, 0.53); 9g: +28.9 (EtOH, 0.60); 10g: +172.6 ($CHCl_3$, 0.475); 12g (from crude 10): +47.5 ($CHCl_3$, 0.23); 15, R=H: -88.0 ($CH_2Cl_2$, 0.23), 15, R=Me: -110.3 (23°C, EtOH, 0.2); 17 (from crude 16, R = H): -60 (EtOH, 0.275); 17 (from crude 16, R = Me): -56 (EtOH, 0.3).

The following procedures are representative: *Enoylsultams*: 3/NaH/enoyl chloride [1] or: Acryloyl chloride (348 mg, 3.85 mmol) was added to a solution of (*R*)-sultam 3a (600 mg, 3.21 mmol) and $NEt_3$ (389 mg, 3.85 mmol) in $CH_2Cl_2$ (20 ml) at 0°C under argon. Stirring at 0°C for 1 h, addition of water (20 ml), extraction of the aq. phase with $CH_2Cl_2$, drying and evaporation of the combined organic phases and crystallization of the residue from hexane/$CH_2Cl_2$ afforded pure 4a (505 mg, 66%). *Diels-Alder reaction*: 1 M $Me_2AlCl$ (3.2 ml in $CH_2Cl_2$) was added over 1 min. to a mixture of acryloylsultam 4a (380 mg, 1.6 mmol) and cyclopentadiene (1.0 g, 15.1 mmol) in $CH_2Cl_2$ (5 ml) at -98°C. Stirring for 10 min. at -98°C, addition of sat. aq. $NH_4Cl$, extraction with $CH_2Cl_2$, drying and evaporation of the organic layer, FC ($SiO_2$, hexane/EtOAc) and crystallization afforded pure 6a (399 mg, 83%). *Saponification*: 6e (17 mg, 0.058 mmol) , 30% aq. $H_2O_2$ (34 µl) and LiOH (2.6 mg) were stirred in THF/$H_2O$ 3:1 (1 ml) at 0°C for 2 h. Addition of sat. aq. $Na_2SO_3$ (0.5 ml), stirring for 10 min, basification to pH = 10 (aq. $NaHCO_3$), evaporation of THF, extraction with $CH_2Cl_2$ and evaporation of extracts gave sultam 3a (9.9 mg, 92%). Acidification of the aq. phase (pH <1), extraction (EtOAc) and evaporation of the extracts yielded acid 7e (6.8 mg, 93%). *Diastereoisomer ratios* of products 6 and 10 were determined by HPLC comparison with reference samples obtained by acylation of sultams 3 with (±)-*endo/exo* mixtures of the corresponding carboxylic acid chloride. GC-analysis of alcohols obtained by reduction ($LiAlH_4$) of crude 6, 10 or 16 confirmed the *endo/exo* ratios. The *absolute configuration(s)* of the induced stereogenic center(s) was (were) determined *via* comparison of $[\alpha]_D$ values (7f, [10] 8a, [1a] 12g [1a]) or the HPLC of (*S*)-1-(1-naphthyl)ethylamides derived from acids 7e and 7f [1a]. The sense of induction obtained with racemic enoylsultams (entries 9-14, 18, 19) is tentatively assigned.

5) 1 → 2b [c.f. [11], *t*BuLi (61%, m.p. 128-130°C)] → 3b [c.f. [12], $NaBH_4$ (91%, m.p. 141.5-142.5°C)]; 1 → 2d [$PhCH_2MgBr$ (24%, m.p. 129-131°C)] → 3d [$NaBH_4$ (75%, m.p. 135-137°C)].

6) Imine 2c (m.p. 189-191°C) was prepared by successive treatment of *N*-*t*-butylbenzenesulfonamide with *n*-BuLi (2.1 molequiv, THF, 0°C, 5 min → r.t., 2 h), α,α-dimethylbenzylnitrile (0°C, 5 min → r.t. 3.5 h) giving an aminosultam (70%) which on heating in polyphosphoric acid (80°C, 0.5 h) gave 2c (70%). Reduction of 2c with $NaBH_4$ provided 3c (94%, m.p. 159-165°C).

7) Asymmetric Diels-Alder additions of 1,3-dienes to chiral *N*-enoyloxazolidinones have been ascribed to involve chelation of two carbonyl groups. An oxazolidinone-benzyl substituent showed a face directing bias superior to a methyl group: D.A. Evans, K.T. Chapman, J. Bisaha. *J. Am. Chem. Soc.* 1988, *110*, 1238.

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