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Asymmetric Diels-Alder Reactions of Chiral N-Methacryloylsultams with 1,3-Dienes

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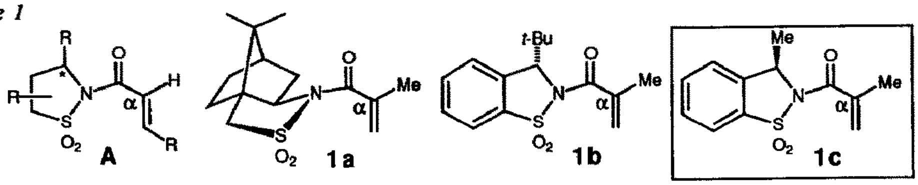
Abstract: R_2AlCl-coordinated *N*-methacryloylsultam **1c** undergoes efficient, *endo*-selective and highly diastereoface controlled [4+2]-additions to cyclopentadiene, isoprene, (*E*)-piperylene and the 2-silyloxydienes **10** and **12**. The resulting crystalline cycloadducts are smoothly reduced with $LiAlH_4$ providing the recovered auxiliary and the corresponding enantiomerically pure alcohols.

Face-selective [4+2]-cycloadditions of C(α)-substituted enoyl dienophiles offer the attractive possibility of constructing a quaternary center of chirality together with up to three more centers in a single step. [1,2]

Encouraged by the efficient and practical use of bornanesultam [3a] and toluenesultam [3b] auxiliaries in asymmetric Diels-Alder reactions of C(α)-non-substituted dienophiles A, we thus explored the additions of C(α)-substituted *N*-enoylsultams to 1,3-dienes.

N-Methacryloylsultams **1a** [4] (m.p. 175-177°C), **1b** [4] (oil) and **1c** [4] (m.p. 75°C) were readily obtained in 79-95% yield by acylation of the corresponding sultams [7] with methacryloyl chloride in the presence of NaH or Et_3N.[3]

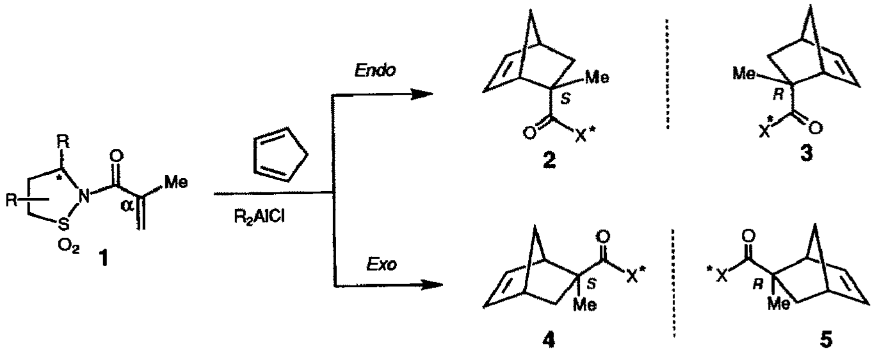
Scheme 1



Dienophiles **1a**, **1b** and **1c** underwent smooth, Et_2AlCl promoted [4+2]-cycloadditions to a range of 1,3-dienes at -90 to -20°C. Our results are summarized in Schemes 2,3 and Table 1. [8]

First, we studied the additions of *N*-methacryloylsultams **1a**, **1b** and **1c** to cyclopentadiene (Scheme 2).

Scheme 2



Successive addition of Et_2AlCl (4 mol-equiv. in hexane) and cyclopentadiene (10 mol-equiv. in CH_2Cl_2) to a stirred solution of bornanesultam derivative **1a**, stirring at -78°C for 20 h, quenching with 1N aq. HCl at -78°C and workup provided, with 27:73-*endo/exo* selectivity, cycloadducts **2a** - **5a** (26 : 1.4 : 32.5 : 40.1) in 74% yield (entry 1). It follows that the π-facial control of this cycloaddition amounts to disappointing 10% in the (favored) *exo-* and to 90% in the *endo*-orientation. Analogous Diels-Alder reaction of *t*-butylsubstituted toluenesultam derivative **1b** at -40°C also proceeded in a moderately *exo*-selective manner but with improved face selection giving *exo*-product **5b** in 76% *d.e. (entry 2).* More satisfactorily, *N*-methacryloyl toluenesultam **1c** reacted with cyclopentadiene at -90°C preferentially in an *endo*-mode (*endo/exo* = 80:20) giving adducts **2c** - **5c** (80 : 0 : 19 : 1) in 82% yield which corresponds to π-facial selections of 100% in the *endo-* and 91% in the *exo*-process (entry 3). Carrying out the reaction of **1c** in toluene/hexane at -78°C gave adducts **2c** - **5c** (78.1 : 0.5 : 18.7 : 2.7) in 97% yield (entry 4).

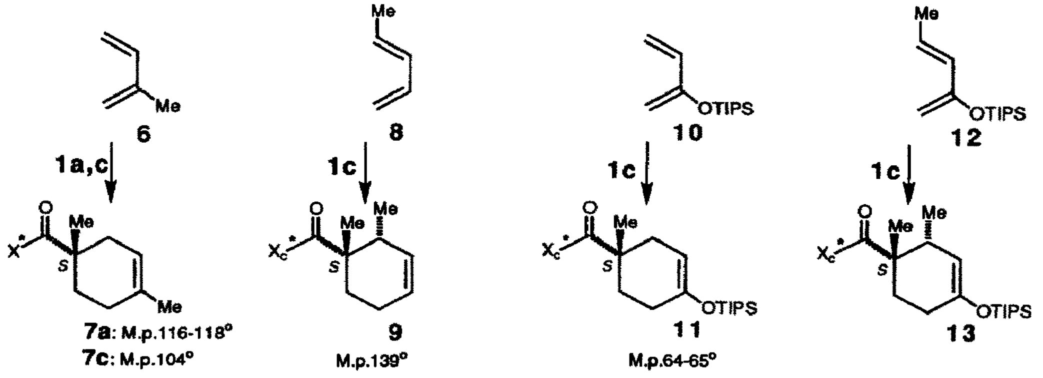
Table 1: Asymmetric Diels-Alder Reactions of Chiral *N*-Methacryloylsultams with 1,3-Dienes (4 equiv. Et_2AlCl in CH_2Cl_2/Hexane)[a])

Entry	Dienophile	Diene	Temp. (°C)	Time (h)	Yield[b]) (%)	*endo/exo* (C=O)	Major Product	*endo* d.e. (%)	*exo* d.e. (%)
1	**1a**	cyclopentadiene	-78	20	74	27 : 73	**5a**	90	10
2	**1b**	cyclopentadiene	-40	20	63	35 : 65	**5b**	83	76
3	**1c**	cyclopentadiene	-90[c])	9	82	80 : 20	**2c**	100	91
4	**1c**	cyclopentadiene	-78[c,d])	15	97	79 : 21	**2c**	99	74
5	**1a**	isoprene	-20	15	63	-	**7a**	91	-
6	**1c**	isoprene	-40	72	94	-	**7c**	97	-
7	**1c**	(*E*)-piperylene	-40	144	83	86 : 14	**9**	80	97
8	**1c**	silyloxydiene **10**	-78	48	67	-	**11**[e])	100	
9	**1c**	silyloxydiene **10**	-30	15	84	-	**11**[e])	95	
10	**1c**	silyloxydiene **12**	-40	15	69	77 : 23	**13**[e])	85	>95

a) Diastereoisomer ratios of crude and purified adducts determined after reductive removal of the auxiliary group ($LiAlH_4$) and analysis of the resulting alcohols i) by GC of their trifluoroacetates using a chiral column (*Lipodex C*): entries 1-7, ii) by *O*-desilylation and GC (*Lipodex C*) of their trifluoroacetates: entry 10, and iii) by ^{19}F-NMR of their 'Mosher esters' derived from (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenacetyl chloride: entry 8, or by direct HPLC comparison of the adducts with a reference mixture of epimers (entries 8,9). b) Yield after FC. c) Me_2AlCl was used instead of Et_2AlCl. d) In toluene/hexane. e) Configurations of adducts **11** and **13** were assigned by analogy with those of adducts **7** and **9**.

We then examined the additions of dienophiles **1** to acyclic dienes (Scheme 3).

Scheme 3



[4+2]-Cycloadditions of methacryloylsultams 1a (at -20°C) and 1c (at -40°C) to isoprene furnished crystalline cyclohexenes 7a 4) and 7c 4) with excellent regiochemical (>98%) and π-facial control of 91% and 97%, respectively (entries 5,6). Thus, reaction of 1c with isoprene (6, entry 6), followed by one recrystallization (MeOH) provided adduct 7c in 85% yield and 99% *d.e.*. X-ray diffraction analysis of 7c proved the depicted regio- and stereochemistry (Figure 1). 9a)

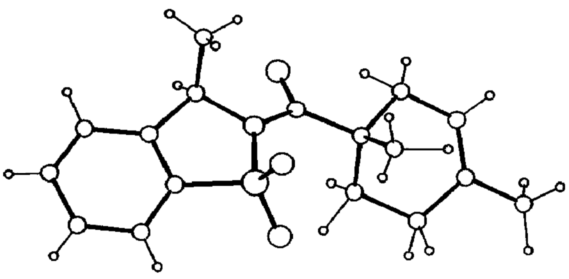


Figure 1: X-ray crystal structure of 7c

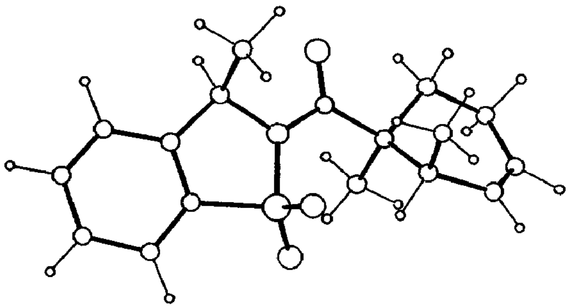


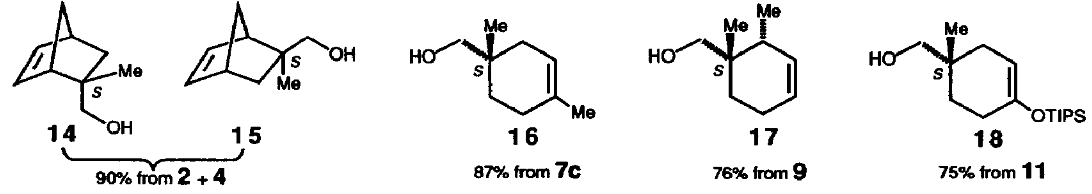
Figure 2: X-ray crystal structure of 9

Addition of toluenesultam dienophile 1c to (*E*)-piperylene proceeded more slowly (6 d at -40°C) with 86:14 *endo*/*exo* preference and with 80% π-face selective formation of *endo*-product 9. 4) After purification (FC, several recrystallizations from hexane/AcOEt then MeOH), the absolute and relative configuration of 9 was unambiguously assigned *via* X-ray diffraction studies (Figure 2). 9b)

Finally, we examined the Et_2AlCl-mediated [4+2]-additions of *N*-methacryloylsultam 1c to triisopropylsilyl (TIPS) protected 2-oxygenated 1,3-dienes 10 and 12. 10) Addition of 1c to 2-silyloxybutadiene 10 at -78°C (48 h) took place with ~100% π-face selection giving, after crystallization (MeOH) pure adduct 11 4) in 62% yield (entry 8). At -30°C, the reaction was complete in 15 h to give adduct 11 in improved yield (84%) with a slightly decreased *d.e.* of 95% (entry 9). Similar cycloaddition of dienophile 1c to 2-silyloxypiperylene 12 (-40°C, 15 h) furnished a 77:23-mixture of *endo*/*exo* adducts (69% yield) with good to excellent π-face discrimination (85% *d.e.* for major *endo*-product 13 and >95% *d.e.* for its *exo*-isomer). These results compare very favorably with previously reported additions of silyloxydienes 10 and 12 to a chiral methacryloyl dienophile. 2a)

Removal of the auxiliary moiety from the [4+2]-adducts by treatment with $LiAlH_4$ gave recovered sultam (87-96%) and enantiomerically pure alcohols 14 - 18 in good yields (Scheme 4). The optical rotations of alcohols 14 and 15 agree with reference values. 4)

Scheme 4



In summary, *N*-methacryloylsultam 1c is a crystalline, readily available α-methylsubstituted dienophile which undergoes highly C(α)-*Re*-face selective [4+2]-cycloadditions to cyclopentadiene as well as acyclic alkyl- or 2-oxygenated dienes. The crystallinity of the products and the efficient recovery of the auxiliary add to its practical value.

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4) All new compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and MS. $[\alpha]_D$ values (20°C, $CHCl_3$ unless otherwise specified, c = g/100 ml)= **1a**: -97.4 (1.02); **1b**: -13.2 (1.03); **1c**: -96.6 (0.93); **7a**: +18.5 (CCl_4, 0.27); **7c**: +32.4 (1.35); **9**: -126.9 (0.59); **11**: +31.1 (CCl_4, 0.9); **14**: -46.9 (95% EtOH, 0.42), -33.5 (0.22), lit. 5) -46.1 (extrapol., 95% EtOH); **ent-14** 6): +33.9 (2.08); **15**: +68.1 (95% EtOH, 0.16); **ent-15** 5): -67.8 (extrapol., 95% EtOH); **16**: -10.3 (1.75); **17**: -147.0 (0.63); **18**:-2.9 (CCl_4, 1.32).

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6) R. K. Boeckman 2a) and private communication.

7) Bornane-10,2-sultam is distributed up to a multi-kg scale by: *NEWPORT Synthesis Ireland Ltd.;* Dublin/Ireland and by *OXFORD ASYMMETRY Ltd*, Abingdon/UK. Preparation of methyl-substituted toluenesultam: W. Oppolzer, M. Wills, C. Starkemann, G. Bernardinelli, *Tetrahedron Lett.* **1990**, *31*, 4117; preparation of *t*-butyl-substituted toluenesultam: W. Oppolzer, A. J. Kingma, S. K. Pillai, *ibid.*, **1991**, *32*, 4893.

8) The following procedures are representative: *Diels-Alder reaction*: A 1 M soln. of Et_2AlCl in hexane (1.56 ml) was added dropwise to a stirred soln. of *N*-methacryloylsultam **1c** (98 mg, 0.39 mmol) in CH_2Cl_2 (1.2 ml) at -78°C. After stirring for 1 h, a soln. of 2-TIPSoxybutadiene **10** (530 mg, 2.34 mmol) in CH_2Cl_2 (0.5 ml) was added over 2 min. by syringe along the cold wall of the reaction flask. Stirring at -78°C for 48 h, addition of sat. aq. $NaHCO_3$ soln. at -78°C, vigorous stirring, workup (CH_2Cl_2), FC (Al_2O_3, act.III, hexane/AcOEt 19:1 → 4:1) furnished adduct **11** (125 mg, 67%; 115 mg, 62% after crystallization from MeOH). *Auxiliary removal*: A soln. of adduct **11** (30 mg, 0.06 mmol) in Et_2O (3 ml) was added to a stirrred suspension of $LiAlH_4$ (3 mg, 0.09 mmol) in Et_2O (1.5 ml). Stirring at r.t. for 1 h, addition of sat. aq. Na_2SO_4 soln. (3 drops), stirring, filtration, drying and evaporation of the filtrate, followed by crystallization of the residue from pentane afforded crystalline sultam auxiliary (10 mg, 87%). Evaporation of the pentane soln. and FC gave pure alcohol **18** (oil, 14 mg, 75%).

9) Crystallographic data for compounds **7c** and **9** have been deposited at the *Cambridge Data Centre*. Structure factors may be obtained from one of us (G.B.). The absolute configuration of both compounds has been determined: G. Bernardinelli, H. D. Flack, *Acta Cryst.* **1985**, *A41*, 500. a) The crystals of cycloadduct **7c** (MeOH, m.p. 104°C) are orthorhombic, $a = 7.087$ (1), $b = 7.544$ (2), $c = 30.379$ (5) Å; $P2_12_12_1$, $Z = 4$; $d_x = 1.31$ g.cm^{-3}; x = 0.17; *F(000)* = 680. $R = 0.049$ ($\omega R = 0.024$; $\omega = 1/\sigma^2(Fo)$) for 1537 observed reflections [$|Fo|>4\sigma(Fo)$]. b) The crystals of cycloadduct **9** (MeOH, m.p. 139°C) are orthorhombic, $a = 7.014$ (1), $b = 9.764$ (2), $c = 24.024$ (8) Å; $P2_12_12_1$, $Z = 4$; $d_x = 1.29$ g.cm^{-3}; x = -0.08; *F(000)* = 680. $R = 0.071$ ($\omega R = 0.026$; $\omega = 1/\sigma^2(Fo)$) for 957 observed reflections [$|Fo|>4\sigma(Fo)$].

10) Silyloxydienes **10** and **12** were prepared by reaction of $(i\text{-}Pr)_3SiOTf/NEt_3$ with methylvinylketone and 3-penten-2-one, respectively, in analogy to the silylation procedure of : E. J. Corey, H. Cho, C. Rücker, D. H. Hua, *Tetrahedron Lett.* **1981**, *22*, 3455.

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