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CHIRAL TOLUENE-2,α-SULTAM AUXILIARIES: ASYMMETRIC ALKYLATIONS, ACYLATIONS AND ALDOLIZATIONS OF N-ACYL DERIVATIVES

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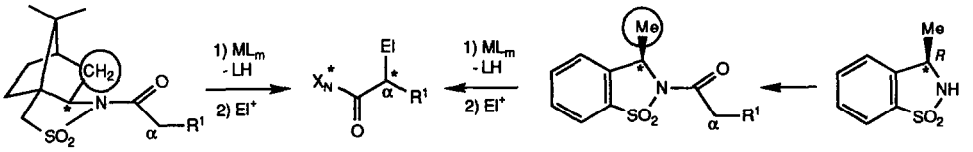
Abstract: Successive treatment of (*R*)-*N*-acylsultams 4 with NHDMS/alkyl halides or NHDMS/acyl chlorides provides alkylated or acylated products 6 or 7. Diastereoselective reductions of 7 with $Zn(BH_4)_2$ or $NaHB(sBu)_3$ gives "*syn*"- or "*anti*"-aldols 8 or 9. Reaction of 4 with BEt_3/TfOH/EtN(*i*Pr)$_2$ followed by addition of aromatic or aliphatic aldehydes affords diastereomerically pure "*syn*"-aldols 10. Non-destructive removal of auxiliary 3 from 6, 8, 9 and 10 yields enantiomerically pure products 12 to 16.

N-Acylbornane-10,2-sultams 1 provide stereochemically pure, crystalline α-substituted products 2 *via* metalation and subsequent reaction with a variety of electrophiles El$^+$ (e.g., alkyl halides, [1a,b] aldehydes, [1c] 1-chloro-1-nitrosocyclohexane, [1d] NBS, [1e] etc., Scheme 1).

Scheme 1



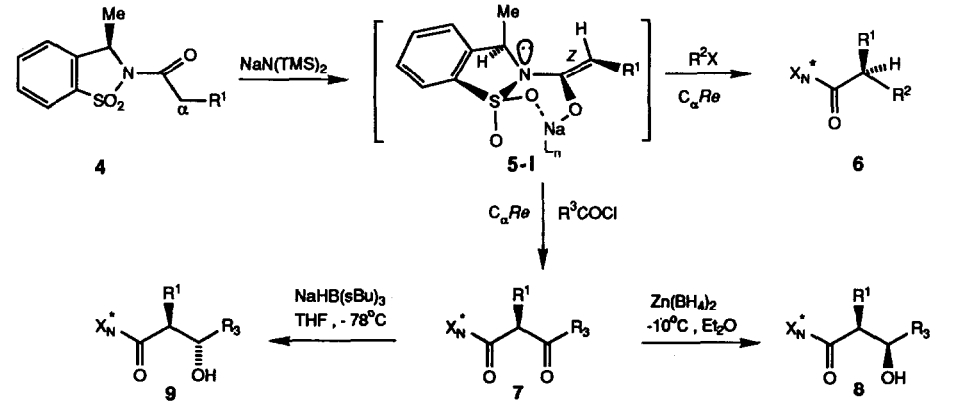
1 2 4 3

Exploring the potential of the related saccharin-derived sultam 3 (and its readily available antipode) as a chiral auxiliary, [2] we focus here on asymmetric carbon/carbon bond forming reactions. Sultam 3 was smoothly transformed into acyl derivatives 4 following protocols for the preparation of 1. [1]

Alkylations (Scheme 2, Table 1): [3]

Deprotonation of 4 with sodium hexamethyldisilazide (NHMDS) followed by treatment with benzyl- or allyl iodide, flash chromatography (FC) and crystallization (MeOH) furnished stereochemically pure alkylation products 6a, 6c or 6f (entries 1,3,6). Alkylations with less reactive methyl iodide or *t*-butyl α-bromoacetate were carried out in the presence of HMPA or Bu_4NI (entries 2,4 or 5) whereas ethyliodide failed to give the corresponding product 6.

Scheme 2



4 5-I 6

9 7 8

Table 1 : Asymmetric Alkylations 4 → 6

	R^1	R^2X	Additive	Time [h]	Product	Purification	m.p.[°C]	d.e.[%]	yield [%]
1	Me	$PhCH_2I$	--	2.5	6a	FC/cryst.	73-74	> 99	81
2	$PhCH_2$	MeI	HMPA	6.5	6b	FC/cryst.	79-80	> 99	71
3	Me	CH_2=CH-CH_2I	--	3.5	6c	FC/cryst.	38-39	> 97[a]	75
4	CH_2=CH-CH_2	MeI	HMPA	5.5	6d	FC	oil	90[a]	91
5	Me	$tBuO_2C$-CH_2Br	Bu_4NI	6.0	6e	FC	oil	> 99	76
6	N=CPh_2	$PhCH_2I$	--	8.0	6f	FC/cryst.	156-157	> 99	71

a) ^{1}H-NMR (360 MHz).

The topicity of the transformations 4 → 6 are consistent with a predominant attack of the electrophile to the C(α)-*Re* face of the chelated *(Z)*-"enolate" 5-I.

Acylations/Reductions (Scheme 2, Table 2): [3]

Table 2 : Asymmetric Acylation 4 → 7

	R^1	R^3	d.e.[%] crude	Product	Purification	m.p.[°C]	d.e.[%]	yield [%]
7	Me	Ph	99.4	7a	FC/cryst.	120-121	> 99	89
8	Me	Me	86[a]	7b	FC/cryst.	104-105	99.2	62
9	Me	Et	91	7c	FC/cryst.	113-114	> 99	71
10	Me	$CHMe_2$	92.8	7d	FC/cryst.	64-65	> 97	76
11	Me	CH_2CHMe_2	> 97[b]	7e	FC	oil	> 97[b]	81
12	Et	Ph	> 99	7f	FC/cryst.	108-109	> 99	71
13	Et	Me	97.6	7g	FC	oil	97.6	70

a) GC; b) ^{1}H-NMR (360 MHz): only 1 isomer visible.

The same topicity was displayed by the C-acylation reactions 4 → 7. [4] Successive treatment of acylsultams 4 with NHDMS and a carboxylic acid chloride afforded 1,3-dicarbonyl products 7. Those epimerized only slowly with 1 M NEt_3 (25 molequiv in CH_2Cl_2, r.t., 12 h: *(S)*-7a → *(S)*-7a + *(R)*-7a 1:1), analogous to *N*-(3-oxoacyl)oxazolidinones. [4a] The lowest diastereoselectivity was observed on acylation of 4, R^1 = Me with (the sterically least demanding) acetyl chloride (entry 8). However, resulting 7b (d.e. = 86%) was conveniently purified (d.e. = 99.2%) by FC/crystallization, as were most other C-acylation products 7.

Table 3 : *Syn*- or *Anti*- Aldols 8 or 9 by Diastereoselective Reductions of *N*-(3-Oxoacyl)sultams 7

	R^1	R^3	Hydride	Ratio 8/9	Purification	Major Product	m.p.[°C]	purity[%]	yield [%]
14	Me	Ph	$Zn(BH_4)_2$	99.1 : 0.9	cryst.	8a	126-127	> 99	82
15	Me	Me	$Zn(BH_4)_2$	91.3 : 8.7	FC	8b	oil	> 99	81
16	Me	$CHMe_2$	$Zn(BH_4)_2$	98.8 : 1.2	cryst.	8d	108-109	> 99	72
17	Me	Ph	$NaHB(sBu)_3$	0.7 : 99.3	FC	9a	146-147	> 99	82
18	Me	Me	$NaHB(sBu)_3$	0.2 : 99.8	FC	9b	oil	> 99	80
19	Me	CH_2CHMe_2	$NaHB(sBu)_3$[b]	2.1 : 97.9	FC	9e	oil	> 99	53
20	Et	Me	$NaHB(sBu)_3$	--	FC	9g	oil	> 97[a]	80

a) ^{1}H-NMR (200 MHz) : only 1 isomer visible; b) at -50°C.

Chelate-controlled reduction of *N*-(3-oxoacyl)sultams 7 with zinc borohydride [4a, 5a] proceeded without epimerization and afforded selectively "*syn*"-aldols 8 (Scheme 2, Table 3, entries 14 to 16).

"*Anti*"-aldols 9 were obtained almost exclusively when reducing the keto group of 7 with sodium tri-*s*-butylborohydride (entries 17 to 20). [5] The purity of aldols 8 and 9 was increased to >99% by crystallization or FC.

Aldolizations (Scheme 3, Table 4): [3]

More directly, "*syn*"-aldols 10 were produced by successive treatment of acylsultam 4 (R^1 = Me) with a dialkylboryl triflate/EtN(*i*Pr)$_2$ and an aldehyde (Scheme 3, Table 4).

Scheme 3

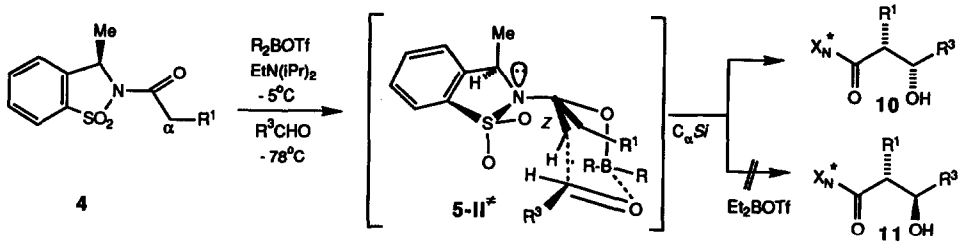


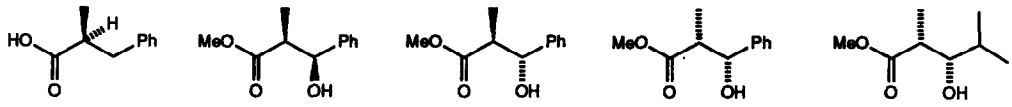
Table 4 : Asymmetric Aldolizations 4 → 10

	R^1	Aldehyde R^3	Boryltriflate R	(molequiv)	Enolate formation [°C]	Conversion of 4	Product Ratio 10/8/11/9	Product	Yield cryst [%]	M.p.[°C]	Purity [%]
21	Me	Ph	Bu	(1.4)	-10 to -5	94	97.8/ 0 / 2.2 / 0	10a	58	117-118	> 99
22	Me	Ph	Bu	(2.0)	-10 to -5	62	7.5/41.4/27.7/23.4	--	--	--	--
23	Me	*i*Bu	Bu	(0.7)	-5	56	98 / 2 / 0 / 0	--	--	--	--
24	Me	*i*Bu	Bu	(1.2)	-5	61	21 /43 /36 / 0	--	--	--	--
25	Me	*i*Pr	Bu	(1.6)	-5	90	93.7/ 1.5/ 1.8/ 3	10d	50	112-114	98.5
26	Me	Ph	Et	(2.0)[a]	-5	100	>99 / 0 / 0 / 0	10a	84	118-119	> 99
27	Me	Me	Et	(2.0)[a]	-5	100	>99 / 0 / 0 / 0	10b	71	104-106	> 99
28	Me	*i*Pr	Et	(2.0)[a]	-5	99	>99 / 0 / 0 / 0	10d	95[b]	oil	> 99
29	Me	*i*Bu	Et	(2.0)[a]	-5	92	>99 / 0 / 0 / 0	10e	78	113-114	> 99

a) Prepared *in situ* from BEt_3 and CF_3SO_3H; b) Purified by FC.

Employing freshly prepared dibutylboryl triflate led to incomplete conversions and an excess of $Bu_2BOTf/EtN(iPr)_2$ resulted in lower stereoselectivities (cf., entries 21/22, 23/24). More conveniently, more efficiently and more selectively, aldols 10 were obtained by using *in situ* prepared diethylboryl triflate/EtN(*i*Pr)$_2$ (2 molequiv, entries 26 to 29). [1c] Under these conditions a variety of aldehydes furnished without exception pure aldols 10 in high yields. As expected, [1c] aldolizations 4 → 10 reflect an electrophilic attack to the opposite "enolate" π-face (C(α)-*Si*) than observed with alkylations 4 → 6 and acylations 4 → 7. We ascribe this dichotomy to the transition state 5-II* again involving a (*Z*)-"enolate". However, with the boron atom being fully coordinated (and, thus, incapable of chelation with a SO_2 oxygen atom) the "enolate" adopts an (electrostatically favored) N-SO_2/C-OML_n *s-trans* conformation.

Hydrolyses, Absolute Configurations (Scheme 4): [3]



81 % from 6a — 88 % from 8a — 94 % from 9a — 94 % from 10a — 71 % from 10d

12 — 13 — 14 — 15 — 16

Hydroperoxide-assisted saponification (6a → 12), combined with esterification (8a → 13, 9a → 14, 10a → 15 and 10d → 16) provided enantiomerically pure α-branched carboxylic acid 12 or methoxycarbonyl aldols 13 to 16 in good yields with 92 to 94% recovery of auxiliary sultam 3. The absolute configurations of 12, 13, 15 and 16 were determined by comparing their optical rotations with published reference values. This correlation allowed to assign the sense of induction in alkylations 4 → 6, acylations 4 → 7 and 4 → 10 as depicted in the Schemes 2, 3 and 4.

Conclusion:

The topicities of the alkylations, acylations and aldolizations described here parallel those observed with *N*-acylbornane-10,2-sultams 1. [1] An advantageous application of a related toluene-2,α-sultam auxiliary will be reported in due course.

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REFERENCES AND NOTES

1) a) W. Oppolzer, R. Moretti, S. Thomi, *Tetrahedron Lett.* 1989, *30*, 5603; b) *idem, ibid.*, 1989, *30*, 6009; c) W. Oppolzer, J. Blagg, I. Rodriguez, E. Walther, *J. Am. Chem. Soc.* 1990, *112*, 2767; d) W. Oppolzer, O Tamura, *Tetrahedron Lett.* 1990, *31*, 991; e) W. Oppolzer, *Pure & Appl. Chem.* 1990, *62*, in press.

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

3) All new compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and MS. D.e. values were determined by direct HPLC analyses, unless otherwise stated. Aldol-stereoisomer ratios 10/8/11/9 were determined by comparison (HPLC of crude products or GC of TBDMS derivatives) with authentic mixtures. The ^{1}H-NMR spectra showed typical coupling constants $J(2,3)$ = 3-4.5 Hz for "*syn*"-aldols (8, 10, 13, 15, 16) and $J(2,3)$ = 7-8.5 Hz for "*anti*"-aldols (9, 14). Melting point: 4, R^1 = Me: 94.5-95°C. $[\alpha]_D$ values, (20° C, $CHCl_3$, g/100 ml): 4, R^1 = Me: -19.5° (1.2); 12: +28.3°(0.85), Lit [1a]: +29.3° (1.15); 13: -23.6° (1.66), Lit [1c] antipode: +23.5° (3.2); 14: +58.9° (1.88); 15: +26.1°, Lit [1c] : +23.5° (3.2); 16: +9.4° (0.83), Lit [1c] : -7.14° (1.19).
The following procedures are representative: *Acylation of Sultam* 3: Propionyl chloride (2.28 ml, 26 mmol) in CH_2Cl_2 (10 ml) was added to a mixture of sultam 3 (4.0 g, 22 mmol), NEt_3 (34 ml, 24 mmol) and CH_2Cl_2 (22 ml) at 0°C. Stirring for 3 h , workup and crystallization (hexane/Et_2O) gave 4, R^1 = Me (4.48 g, 85%). Acylsultam 4, R^1 = N=CPh_2 was prepared from 3, $MeO_2CCH_2N{=}CPh_2/Me_3Al$ c.f. ref [1b]. *Alkylation*: Sultam 4, R^1 = Me (250 mg, 1.04 mmol) in THF (3 ml) was added to 1 M NHDMS (THF, 1.14 mmol) over 0.5 h at -78°C. Stirring for 0.5 h, addition of benzyl iodide (270 μl, 2.14 mmol), stirring at -78°C for 2.5 h, quenching with sat. aq. NH_4Cl, workup, FC (hexane/EtOAc 9:1) and crystallization (MeOH) gave product 6a (277 mg, 81%). *Acylation*: 1 M NHDMS (2.46 ml in THF) was added to sultam 4, R^1 = Me (535 mg, 2.24 mmol) in THF (10 ml) at -78°. Stirring for 0.5 h , addition of benzoyl chloride (0.68 ml, 3.3 mmol) at -78°C, continued stirring for 0.5 to 1h, quenching with aq. phosphate buffer (pH = 7), work up and crystallization (EtOH) provided *N*-(3oxoacyl)sultam 7a (668 mg, 89%). (Acylation of 4 R^1 = Me with acetyl- and *n*-propionyl chlorides, entries 8,9 were carried out in the presence of HMPA (1 molequiv)). *Reductions of Oxoacylsultam*: a) 0.16 M $Zn(BH_4)_2$ (Et_2O, 2 ml) was added to 7a (100 mg, 0.29 mmol) in Et_2O (10 ml) at -10°. Stirring at -10°C for 0.5 h, addition of 3N aq. HCl, workup and crystallization (hexane/ether) gave "*syn*"-aldol 8a (82 mg, 82%). b) 1 M Sodium selectride (THF, 1 ml) was added dropwise to 7a (250 mg, 0.73 mmol) in THF (4 ml) at -78°C. Stirring for 0.5 h, quenching with phosphate buffer, work up and FC (SiO_2, hexane/EtOAc 4:1) yielded "*anti*"-aldol 9a (205 mg, 82%). *Aldolization*: CF_3SO_3H (73.8 μl, 0.84 mmol) was added to 1M BEt_3 (hexane, 0.84 mmol) at r.t.. Stirring at 40°C until the gas evolution had ceased (~5 min), cooling to -5°C, addition of 4, R^1 = Me (100 mg, 0.42 mmol) in CH_2Cl_2 (1.4 ml) and of 1 M $NEt(iPr)_2$ (CH_2Cl_2, 0.9 ml), stirring at -5°C for 0.5 h, addition of benzaldehyde (85μl, 0.84 mmol) at -78°C, stirring at -78°C for 20 min, addition of aq. phosphate buffer (2 ml), extraction with Et_2O, washing of the extracts with sat. aq. NH_4Cl, drying ($MgSO_4$), evaporation, FC (SiO_2, hexane/EtOAc 2:1) and crystallization (MeOH) afforded aldol 10a (122mg, 84%). *Saponification/Esterification*: Aq. (30%) H_2O_2 (74 μl, 0.72 mmol) and $LiOH.H_2O$ (15.2 mg, 0.36 mmol) were added at 0°C to 10a (100 mg, 0.29 mmol) in THF/H_2O (3:1, 2 ml). Stirring at 0°C for 2 h, addition of sat. aq. Na_2SO_3 (1 ml), basification to pH = 11 (NH_4OH), extraction (CH_2Cl_2), drying and evaporation of the extracts and crystallization of the residue gave sultam 3 (49 mg, 92%). Acidification of the aq. phase to pH = 1 (HCl), extraction (Et_2O), drying of the extracts, addition of CH_2N_2 (excess), evaporation and FC (hexane/EtOAc 3:1) furnished hydroxyester 15 (53 mg, 94%).

4) Previously published asymmetric acylations of chiral "enolates": a) D.A. Evans, M.D. Ennis, T. Le, N. Mandel, G. Mandel *J. Am. Chem. Soc.* 1984, *106*, 1154; b) Y. Ito, T. Katsuki, M. Yamaguchi, *Tetrahedron Lett.* 1984, *25*, 6015.

5) Previously published reductions of 3-oxoamide derivatives a) with $Zn(BH_4)_2$ giving "*syn*"-aldols [4]; b) with $KBEt_3H$ giving "*anti*"-aldols: Y. Ito T. Katsuki, M. Yamaguchi, *Tetrahedron Lett.* 1985, *26*, 4643.

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