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Enantioselective Synthesis of α-Branched α-Hydroxy Ketones via Chiral *N*-Sulfonyl-2-alkyl-2-cyano-1,3-oxazolidines#

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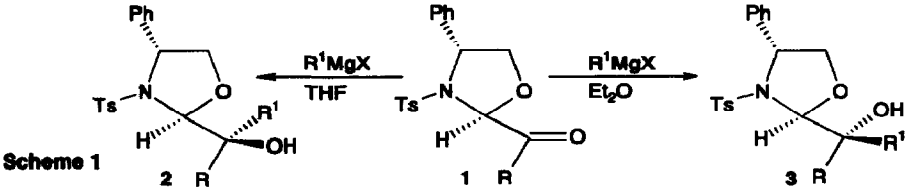
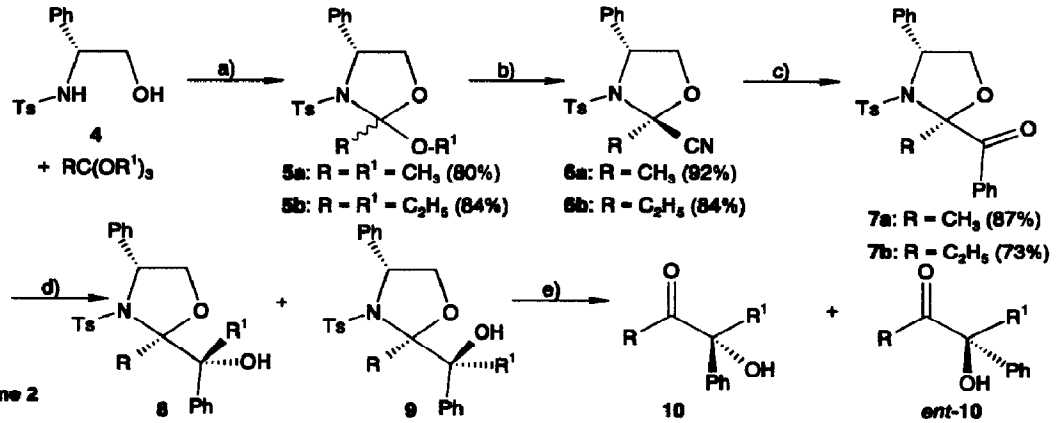
Abstract: The stereochemically homogeneous title compounds **6**, prepared with two steps from orthoesters and *N*-tosyl-phenylglycinol **4**, afford with two sequential Grignard additions predominantly the tertiary alcohols **8**. Electrochemical detosylation, followed by aqueous work up, yields enantiomerically enriched ketones **10**.

Various methods for asymmetric synthesis are based on the utilization of chiral 1,3-oxazolidines.[1] Stereochemically homogeneous 3-arenesulfonyl-1,3-oxazolidines, readily available from enantiomerically pure β-aminoalkanols, are powerful chiral templates for the auxiliary-directed asymmetric synthesis.[2] The 2-acyl derivatives[3] of type **1** are conveniently prepared via the 2-alkoxy derivatives.[4] They add readily nucleophiles to the carbonyl group and the attack can be directed selectively from either of its diastereotopic faces by steric approach or chelate control to give preferentially the protected α-hydroxyalkanals **2** or **3**, respectively[3a] (Scheme 1).



Scheme 1

Similar applications are reported for 2-acyl-3-*tert*-butoxycarbonyl-1,3-oxazolidines.[5] We now present a convenient and flexible method for the synthesis of α-hydroxyalkanones based on this approach. The condensation[4] of (*R*)-*N*-tosyl-phenylglycinol **4** with excess trimethyl orthoacetate or triethyl orthopropionate afforded the 2-alkoxy-1,3-oxazolidines **5a** and **5b**, respectively, with high yield as unseparable 1:1 mixtures of epimers.[6] Trimethylsilyl triflate-catalyzed reaction of **5** with trimethylsilyl cyanide[3a] gave rise to the diastereomerically pure 2-cyano-oxazolidines **6a** or **6b**.[7] Addition of phenylmagnesium bromide to the nitriles **6a,b** yielded the ketones[8] **7a,b** (see Table 1), which were subjected to the reaction with a second Grignard reagent. The preferential attack ocurred from the *si*-face of the carbonyl group leading to the diastereomers of type **8** in excess besides few **9** under optimized reaction conditions[9] (Scheme 2). Single-crystal X-ray structure analysis were obtained from compounds **6b**[10] and **8d**[10] to prove their configuration (Figure 1 and 2). The stereochemical result is in good agreement with the assumption of chelate control. As it was observed in a related reaction,[3a] the diastereomeric ratio is sensitive towards variations of the solvent and the counter ion.[11] The alcohols **8** are crystalline, stable compounds which can be upgraded by recrystallisation or chromatography. For deblocking the oxazolidine-protected ketones **8**, electrochemical reductive detosylation[12,13] turned out to be the method of choice. The intermediate 3-H-substituted oxazolidine (H for Ts in **8**) is readily hydrolyzed during aqueous work up. *ent*-**10d** and its trimethylsilyl ether[14] (Me_3Si for H in *ent*-**10d**), and as well, the *O*-(*N*,*N*-diisopropylcarbamoyl) derivative[15] of *ent*-**10a** are known compounds. An opposite sign of optical rotation was recorded for the derivatives prepared by our method revealing its (*R*)-configuration. The enantiomeric excess of the ketones are collected in Table 1 and were determined by ^{1}H-



Scheme 2

a) 3 eq. $RC(OR^1)_3$, PPTS (25 mole %), toluene, 120°C, 24 h. b) 2 eq. TMSCN, TMSOTf (20 mole %), CH_2Cl_2, 0°C, 24 h. c) 1.3 eq. PhMgBr, Et_2O, rt, 24 h. d) 2 eq. R^1MgX, solvent see Table 1, 0°C, 3-6 h. e) electrolysis: 0.15 M Bu_4NHSO_4-CH_3CN, 0°C, 25-30 min. For **8**, **9**, **10** see Table 1.

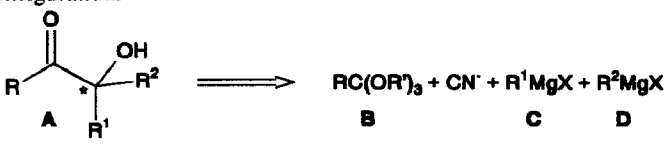
Table 1: Prepared Oxazolidines **5**, **6**, **7**, **8** and Ketones **10**

Educts	Product	R	R^1	yield (%)	ratio	$[\alpha]_D^{20}$ a)	m.p. (°C)e)
5a	**6a**	CH_3	CH_3	92	≥95% ds	-144.8	85
5b	**6b**	CH_2CH_3	CH_2CH_3	84	≥95% ds	-126.1	93
6a, PhMgBr	**7a**	CH_3	C_6H_5	87	≥95% ds	-57.2	137
6b, PhMgBr	**7b**	CH_2CH_3	C_6H_5	73	≥95% ds	-59.6	133
7a, MeMgI[b]	**8a** (+**9a**)	CH_3	CH_3	95	93:7	+2.8	162
7a, BnMgCl[c]	**8b** (+**9b**)	CH_3	$CH_2C_6H_5$	95	94:6	+16.1	142
7a, AllMgBr[c]	**8c** (+**9c**)	CH_3	$CH_2CH{=}CH_2$	81	76:24	-13.4	oil
7b, MeMgI[b]	**8d** (+**9d**)	CH_2CH_3	CH_3	95	98:2	+49.1	176[f]
7b, BnMgCl[c]	**8e** (+**9d**)	CH_2CH_3	$CH_2C_6H_5$	77	85:15	+18.3	146
7b, AllMgBr[c]	**8f** (+**9f**)	CH_2CH_3	$CH_2CH{=}CH_2$	81	85:15	+19.4	143
8a (88% *de*)	**10a**	CH_3	CH_3	59	90% *ee*	-201.9[d]	-
8b (>95% *de*)	**10b**	CH_3	$CH_2C_6H_5$	77	>95% *ee*	-90.3	133
8c (58% *de*)	**10c**	CH_3	$CH_2CH{=}CH_2$	80	58% *ee*	-67.2	-
8d (>95% *de*)	**10d**	CH_2CH_3	CH_3	81	>95% *ee*	-228.3[d]	-
8e (70% *de*)	**10e**	CH_2CH_3	$CH_2C_6H_5$	61	70% *ee*	-49.6	43
8f (70% *de*)	**10f**	CH_2CH_3	$CH_2CH{=}CH_2$	80	72% *ee*	-71.9	-

a) in CH_2Cl_2, c = 0.85-1.3. b) solvent Et_2O/THF, 9:1, c) solvent Et_2O, d) in C_6H_6, e) solvent Et_2O/pentane, f) solvent ethanol

NMR spectroscopic shift experiments in presence of $Eu(hfc)_3$ on the stage of the free hydroxy ketone (for **10b**, **c** and **d**), the trimethylsilyl ethers (**10d**,**e**) or the acetate **10f**. The *ee*-values correspond well with the diastereomeric excess of precursors **8**.

Altogether, the method permits asymmetric assembling of an orthoester **B** with cyanide and two different Grignard reagents **C** and **D** under the influence of chiral aminoalcohols to give α-hydroxy ketones **A** with predictable absolute configuration.



The high stability of the intermediate *N*-sulfonyloxazolidines, which are often crystalline, allows a facile purification and structure elucidation.

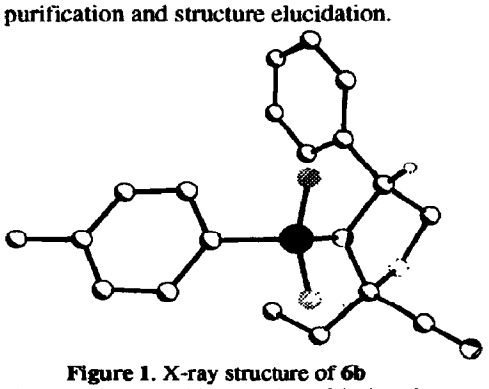


Figure 1. X-ray structure of **6b**

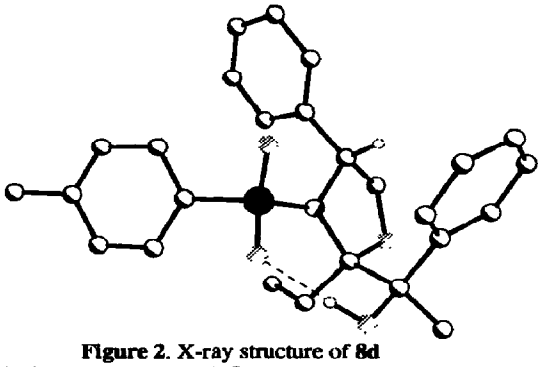


Figure 2. X-ray structure of **8d**

Hydrogen atoms, with exception of hydroxyl protons and tertiary hydrogens, are omitted. Remarkable is the intramolecular hydrogen bond (dashed line).

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References and Footnotes

\# Dedicated to Professor M. Klessinger on the occasion of is his 60th birthday.

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6. Orthoester (150.0 mmol) and pyridinium tosylate (12.5 mmol) were added to a suspension of (*R*)-*N*-tosylphenylglycinol[2c] **4** (50 mmol) in toluene (100 mL) and heated to reflux for 24 h. The mixture was evaporated in vacuo and the product **5a, b** was separated by liquid chromatography on neutral alumina (activity grade II) with ether/pentane. Compounds **5a,b** were obtained analytically pure and characterized by ^{1}H NMR, ^{13}C NMR, IR. **5a**: colourless oil, 300 MHz ^{1}H NMR ($CDCl_3$, δ): 1.96 and 2.03 (s, 3H, 2-CH_3), 2.31 and 2.36 (s, 3H, Tos-CH_3), 3.27 and 3.37 (s, 3H, 2-O-CH_3), 3.77 and 3.94 (dd, J_{gem} = 8.1 Hz and 8.7 Hz, 1H, 5-H), 4.21 and 4.27 (dd, 1H, 5-H), 4.73 and 4.89 (dd, $J_{4,5}$ = 1.9 Hz, $J_{4,5}$ = 7.1 Hz and 7.6 Hz, 1H, 4-H), 7.13-7.68 (m, 9H, 4-Ph- and Tos-H). **5b**: colourless solid, mp 51°C, 300 MHz ^{1}H-NMR ($CDCl_3$, δ): 1.08 and 1.12 (dd, $J_{21,22}$ = 7.2 Hz, 3H, 22-H), 1.19 and 1.24 (dd, $J_{21',22'}$ = 7.2 Hz, 3-H, 22'-H), 2.28 (dq, J_{gem} = 14.7 Hz, 1H, 21-H), 2.38 (s, 3H, Tos-CH_3), 2.46 (dq, 1H, 21-H), 3.473 and 3.63 (dq, J_{gem} = 9.1 Hz, 1-H, 21'-H), 3.61 and 3.79 (dq, 1H, 21'-H), 3.84 (dd, J_{gem} = 7.9 Hz, 1H, 5-H), 4.251 (dd, $J_{4,5}$ = 7.5 Hz, 1H, 5-H), 4.66 (dd, $J_{4,5}$ = 3.4 Hz, 1H, 4-H), 7.08-7.70 (m, 9H, 4-Ph- and Tos-H).

7. Compounds **6a,b** were obtained analytically pure and characterized by ^1H NMR, ^{13}C NMR, IR. **6a**: colourless crystals, $[\alpha]_D^{20}$ = -144.8 (*c* = 1.0, CH_2Cl_2); 300 MHz ^1H NMR ($CDCl_3$, δ): 2.15 (s, 3H, 2-CH_3), 2.35 (s, 3H, Tos-CH_3), 4.07 (dd, J_{gem} = 9.3 Hz, 1H, 5-H), 4.41 (dd, 1H, 5-H), 4.90 (dd, $J_{4,5}$ = 1.7 Hz, $J_{4,5}$ = 7.0 Hz, 1H, 4-H), 7.11-7.51 (m, 9H, 4-Ph- and Tos-H); **6b**: colourless crystals, $[\alpha]_D^{20}$ = -126.1 (*c* = 1.3, CH_2Cl_2); 300 MHz ^1H NMR ($CDCl_3$, δ): 1.19 (dd, $J_{21,22}$ = 7.5 Hz, 3H, 2-H), 2.21 (dq, 1H, 21-H), 2.36 (s, 3H, Tos-CH_3), 2.68 (dq, J_{gem} = 14.3 Hz, 1H, 21-H), 4.10 (dd, J_{gem} = 9.2 Hz, 1H, 5-H), 4.42 (dd, 1H, 5-H), 4.92 (dd, $J_{4,5}$ = 1.9 Hz, $J_{4,5}$ = 7.2 Hz, 1H, 4-H), 7.09-7.50 (m, 9H, 4-Ph- and Tos-H).

8. 2-Cyano-2-alkyl-1,3-oxazolidine **6a** or **6b** (20 mmol) in ether (150 mL) was added to a solution of PhMgBr (26 mmol) in ether (30 mL). After stirring for 12 h at room temperature, the mixture was quenched with 2N HCl and sat. aq. $NaHCO_3$. The product **7a** or **7b** was separated by liquid chromatography on silica gel with ether/pentane.

9. RMgX (2 mmol) in Et_2O (2 mL) or Et_2O/THF (9:1) was slowly added to a solution of ketone **7a** or **7b** (1 mmol) in 25 mL of the same solvent at 0°C. The mixture was stirred for 3-6 h. After work up with sat. aq. NH_4Cl, the products were separated by liquid chromatography on silica gel with ether/pentane.

10. X-ray crystallographic analysis of **6b**: $C_{19}H_{20}N_2O_3S$ (MW = 356.43), orthorhombic, space group $P2_12_12_1$, a = 782.0 (1)pm, b = 1061.0 (1)pm, c = 2193.4 (4)pm, V = 1.82nm^3, Z = 4, ρ_{calc} = 1.301gcm^{-3}, μ(CuKα) = 1.747mm^{-1}. A crystal measuring 0.1*0.2*0.3mm grown from a diethyl ether/pentane solution was used. 2149 intensities were collected with 0° ≤ 2θ ≤ 110° at 293K on an Enraf Nonius CAD4 diffractometer with graphite monochromated CuKα radiation (λ = 154.18pm). After absorption correction using ψ-scans 2017 symmetry independent reflections remained for structure solution and refinement. The structure was solved by extracting the position of the sulfur atom from a sharpend Patterson list and extending the structure with a tangent expansion. The SHELXTL PLUS program system was used for the structure solution and graphical representation, the refinement on F^2 was done with SHELXL-93. Refinement of 229 parameters converged at $wR(F^2)$ = 0.071 and goodness-of-fit = 1.071 (data to parameter ratio = 8.8). The correct absolute configuration was confirmed by the Flack absolute structure parameter (x = 0.00(2)).
X-ray crystallographic analysis of **8d**: $C_{26}H_{29}NO_4S$ (MW = 451.6), monoclinic, space group $P2_1$, a = 821.4 (1)pm, b = 1266.1 (1)pm, c = 1146.3 (2)pm, β = 95.76 (1)°, V = 1.186nm^3, Z = 2, ρ_{calc} = 1.264gcm^{-3}, μ(CuKα) = 1.47mm^{-1}. A crystal measuring 0.1*0.3*0.5mm grown from a diethyl ether/pentane solution was used. 3717 intensities were collected with 2° ≤ 2θ ≤ 110° at 293K on an Enraf Nonius CAD4 diffractometer with graphite monochromated CuKα radiation (λ = 154.18pm). After absorption correction using ψ-scans 2743 symmetry independent reflections remained for structure solution and refinement. The structure was solved by extracting the position of the sulfur atom from a sharpend Patterson list and extending the structure with a tangent expansion. The SHELXTL PLUS program system was used for the structure solution and graphical representation, the refinement on F^2 was done with SHELXL-93. Refinement of 292 parameters converged at $wR(F^2)$ = 0.087 and goodness-of-fit = 1.005 (data to parameter ratio = 9.4). The correct absolute configuration was confirmed by the Flack absolute structure parameter (x = 0.02(2)).
Further details of the crystal structure analysis are available on request from the Fachinformationszentrum Karlsruhe GmbH, D-76344 Eggenstein-Leopoldshafen (Germany), on quoting the deposition number CSD-58367, the names of the authors and journal citation.

11. **7b** → **8d** + **9d** a) MeMgI, Et_2O, 0°C: 85:15 (95%), b) MeMgCl, Et_2O, 0°C: 95:5 (94%), c) MeMgCl, THF, 0°C: 88:12 (94%).

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13. General procedure: Using a divided electrochemical cell with a Hg pool as cathode and Pt foil as anode, a solution of 1,3-oxazolidine **8** (1.0 mmol) and Bu_4NHSO_4 (10.0 mmol) in CH_3CN (75 mL) was added to the cathodic chamber. The electrolysis was carried out with constant current density of 7 mA/cm^2 at 0°C until approximate 234 C were consumed (23-26 min; typically, the potential increased from 18 V to 30 V). The combined solution from the cathodic and anodic chamber was evaporated in vacuo and the residue was dissolved in H_2O (10 mL) and extracted with ether (4x 10 mL). The products **10** and *ent*-**10** were isolated by liquid chromatography on silica gel with ether/pentane.

14. TMS-ether of **10d**: $[\alpha]_D^{20}$ = +125.5 (c = 0.88, CH_2Cl_2). TMS-ether of *ent*-**10d**: $[\alpha]_D^{25}$ = -129.5 (c = 1.29, CH_2Cl_2); Masamune, S., Ali, Sk. A., Snitman, D. L., Garvey, D. S. *Angew. Chem.* **1980**, *92*, 573; *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557.

15. *O*-(*N*,*N*-Diisopropylcarbamoyl) derivative of **10a**: $[\alpha]_D^{20}$ = +110.0 (c = 1.00, CH_2Cl_2). *O*-(*N*,*N*-Diisopropylcarbamoyl) derivative of *ent*-**10a**: $[\alpha]_D^{20}$ = -118.6 (c = 1.03, CH_2Cl_2); Carstens, A. *Dissertation, Univ. Kiel* **1993**.

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