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SYNTHESIS AND DEPROTONATION OF 1-(*p*-TOLUENESULFONYL)-2-ALKENYL CARBAMATES. DICHOTOMOUS ACHIRAL d^1 AND CHIRAL d^3 REAGENTS FOR CARBONYL ADDITION DIRECTED BY METAL EXCHANGE

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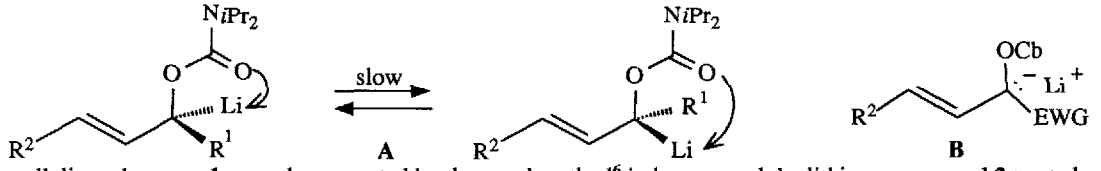
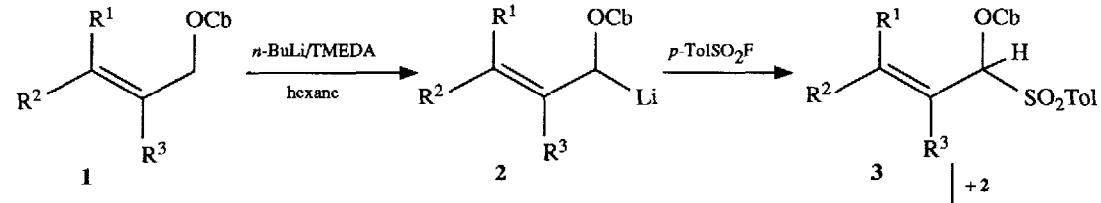
Summary: The title compounds **3** were prepared by electrophilic sulfonylation of allylic carbamates **1**. The achiral lithium anions **4** add to carbonyl compounds with the α-position, thus permitting nucleophilic alkenoylation, whereas the chiral titanium derivates **8** undergo completely regioselective γ-addition, representing a new class of homoenolate reagents.

Chiral, α-lithiated 2-alkenyl carbamates of type **A**, R^1 = alkyl or H, exhibit considerable configurational stability[1,2,3] and have been used for homoenolate reagents in enantioselective homoaldol reactions.[4] The addition of **A** to aldehydes takes place with a high degree of reagent-controlled chirality transfer.[1] This quality is detrimental when an asymmetric induction on newly formed stereocenters *by the chiral reaction partner*, e.g. a chiral aldehyde, is required. In order to create an achiral allylic anion **B** with planar or rapidly inverting α-carbon atom, we introduced as electron withdrawing group (EWG) *p*-toluenesulfonyl.[5]



The allylic carbamates **1** were deprotonated by the usual method[6] in hexane and the lithium compound **2** treated with *p*-toluenesulfonyl fluoride (TosF)[7,8] to give the desired sulfones **3**; Table 1. With the exception of the γ-unsubstituted compounds **2a** and **2b**, which gave rise to some γ-adduct **5**, the substitution reaction proceeds with high α-regioselectivity (Table 1). Owing to a rapid proton transfer from the more acidic sulfones[9] **3** onto **2**, the maximum yield is 50%, based on **1** (Method A). The yields are improved by sequential addition of *n*-butyllithium and TosF in portions to the solution of **1** (Method B).



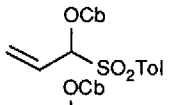
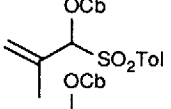
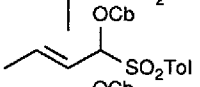
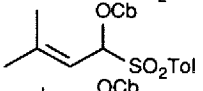
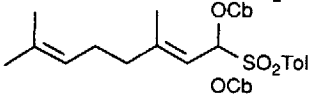
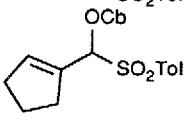
1-5	R^1	R^2	R^3
a	H	H	H
b	H	H	CH_3
c	H	CH_3	H
d	CH_3	CH_3	H
e	CH_3	C_6H_{11}	H
f	H	$CH_2CH_2CH_2$	

Cb = $CNiPr_2$ (O)

Tol = 4-CH_3-C_6H_4

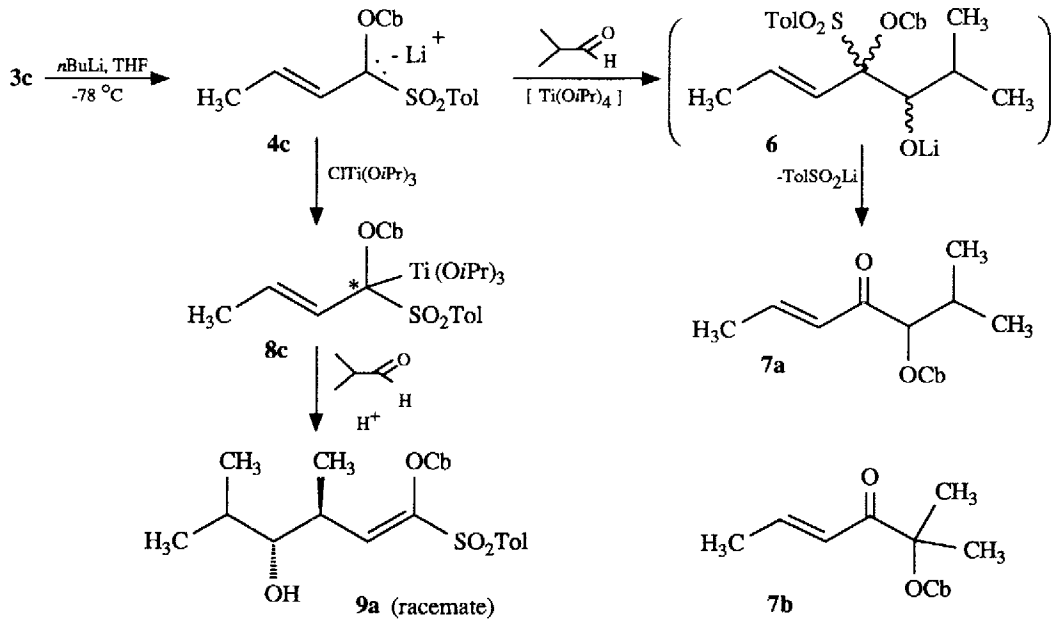
C_6H_{11} = $(CH_3)_2C{=}CH\text{-}CH_2\text{-}CH_2$

Table 1: 1-(*p*-Toluenesulfonyl)-2-alkenyl Carbamates **3** Prepared

Compound **3**[a]		Yield[b] (%) Method B	A	mp[c] °C
3a		-	24 [d]	107
3b		54 [e]	38	70 - 72
3c		70	46	71
3d		48	35	108
3e		39	35	63 - 64
3f		79	-	93 - 95

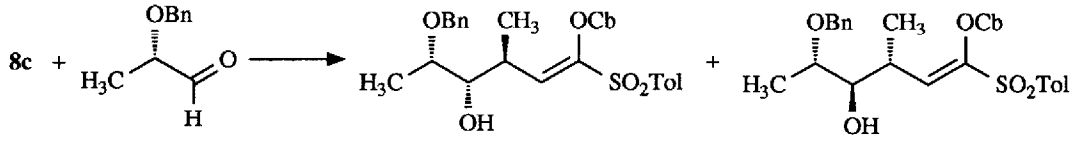
[a] All compounds **3** have been characterized by correct microanalyses C±0.2, H±0.2. [b] Yields based on carbamate **1**. [c] mp after recrystallisation from ether/pentane. [d] In addition 17% of **5a**. [e] In addition 25 % of **5b**.

After deprotonation of **3c** (*n*-BuLi, THF, -78 °C) and addition of 2-methylpropanal, LC separation afforded the enone **7a**[10] with 55% yield besides some starting material **3c**. Similarly, acetone gave the enone **7b** with 45% yield. Enones **7** are formed via the α-adducts of type **6**, followed by formal migration of the Cb group and loss of lithium *p*-toluenesulfinate. The addition of 1-2 equiv. tetra(isopropoxy)titanium (TIPT)[11] to the solution of **4c** does not change the reaction course, but gives slightly increased yields.[12]



In contrast, when chloro-tri(isopropoxy)titanium[11] (1.1 equiv.) was used, solely the γ-adduct **9**[13] as a single *E-anti*-diastereoisomer is formed with 85% yield. From both the high γ-regioselectivity and 3,4-*anti*-diastereoselectivity one must conclude that a titanium intermediate **8c** is involved; it adds onto the aldehyde in a pericyclic process with complete allylic inversion. Surprisingly, it is not formed by means of TIPT.

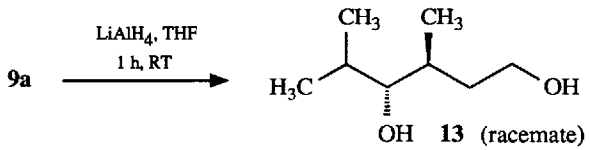
8c is a chiral, but racemic compound which is capable of addition with concominant chirality transfer. This was shown by a procedure, outlined earlier.[1b,3] With (*S*)-2-benzyloxypropanal[14] [(*S*)-**10**] both possible diastereoisomers[15] **11** and **12** result in equal amounts, whereas with *rac*-**10** the ratio *rac*-**11** / *rac*-**12** is 31 : 69. Here by mutual kinetic resolution, the formation of **12** via the matched pairs (*S*)-**10** / (*R*)-**8c** and (*R*)-**10** / (*S*)-**8c** is favoured.[3] Contrarily, as expected, the lithium compounds **4** serve as achiral reagents, this was applied for asymmetric nucleophilic alkenoylation, see subsequent Letter.[12]



(*S*)-**10** **11** (33%) **12** (33%)

rac-**10** *rac*-**11** (23%) *rac*-**12** (51%)

Owing to the capto-dative stabilization, the double bond in 1-sulfonyl-1-alkenyl carbamates **9-11** is inert to most of the common nucleophilic or electrophilic reagents. However, by reduction of **9a** with excess lithium aluminium hydride the 1,4-diol[16] **13** was obtained with 80% yield.



13 (racemate)

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8. Typical Procedures: To a stirred solution of carbamate[6] **1** (20 mmol) and TMEDA (22 mmol) in hexane (20 mL), kept below -70 °C under argon, 1.6N *n*-butyllithium in hexane (20 mmol) and after 1 h stirring below -70 °C, *p*-toluenesulfonyl fluoride[7] (TosF) (13 mmol) in hexane was added dropwise. After each an additional 1 h, the procedure was repeated twice with *n*-BuLi (11 mmol) and TosF (5 mmol); and secondly, *n*-BuLi (5 mmol) and TosF (2 mmol) (Method B). For Method A *n*-BuLi (22 mmol) and TosF (11 mmol) are added sequentially. After the reaction mixture was allowed to warm to 0 °C and pored to ether, water and 2N hydrochloric acid (100 mL each). The usual work-up, followed by LC on silica gel with ether/pentane (1:4) afforded **3**.

9. **3c**: IR: 1710 (C=O), 1335, 1155 cm^{-1} (O=S=O). 300 MHz ^1H NMR (δ, $CDCl_3$): 0.8 - 1.3 (m, NCHCH_3); 1.75 (ddd 4-H_3); 2.36 (s, aryl-CH_3); 3.55 and 3.90 (NCH); 5.60 (ddq, 2-H); 5.99 (dqd, 3-H); 6.15 (ddq, 1-H); 7.24 and 7.71 (m, aryl-H). $J_{1,2}$= 7.4 Hz, $J_{1,3}$ = 1.1 Hz, $J_{1,4}$ = 0.8 Hz, $J_{2,3}$ =15.4 Hz, $J_{2,4}$ = 1.7 Hz, $J_{3,4}$ = 6.6 Hz. 75 MHz ^{13}C NMR (δ, $CDCl_3$): 18.18 (C-4), 20.26 and 20.95 (NCHCH_3), 21.54 (aryl-CH_3), 46.39 (NCH), 86.97 (C-1), 119.25 (C-3), 129.39, 129.59, 133.51, 144.92 (aryl-C), 136.69 (C-2), 151.40 (C=O).

10. **7a**: mp. 96 °C, 300 MHz ^1H NMR (δ, $CDCl_3$): 0.96 (d, 7-H_3); 1.05 (d, 6-CH_3); 1.1 - 1.4 (m, NCHCH_3); 1.90 (dd, 1-H_3); 2.21 (qqd, 6-H); 3.82 and 4.06 (m, NCH); 4.99 (d,5-H); 6.27 (dq, 3-H); 6.99 (dq, 2-H). $J_{1,2}$ = 6.9 Hz, $J_{1,3}$ = 1.7 Hz, $J_{2,3}$ = 15.5 Hz, $J_{6,7}$ = 6.9 Hz. 75 MHz ^{13}C NMR (δ, $CDCl_3$): 17.36 (C-7), 18.21 (C-1), 19.37 (6-CH_3), 20 - 21 (NCHCH_3), 29.71 (C-6), 45 - 46 (NCH), 81.91 (C-5), 127.71 (C-3), 143.06 (C-2), 154.86 (NC=O), 196.39 (C-4).

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13. For the preparation of homoaldol adducts **9a**, **11** and **12** to the solution of lithium compound **4c** in ether[8] (1.0 mmol) chloro-tris(isopropoxy)titanium (1.1 mmol) in hexane was added. The reaction mixture was allowed to warm to -22 °C (30 min) and, again below - 70 °C, the aldehyde was added, the cooling bath removed and stirring was continued at 20 °C for 16 h. Work-up was accomplished as described in ref.8. **9**: Oil; 300 MHz ^1H NMR (δ, $C_6D_6/CDCl_3$ = 1:2): 0.72 (d, 6-H_3); 0.83, 0.97, 1.03 and 1.06 (d, NCHCH_3); 0.88 (d, 3-CH_3); 0.98 (d, 5-CH_3); 1.64 (qqd, 5-H); 2.13 (s, aryl-CH_3); 2.42 (ddq, 3-H); 3.19 (ddd, 4-H); 3.27 (d, OH); 3.38 and 3.94 (qq, NCH); 6.86 (d. 2-H); 7.06 and 7.79 (m, aryl-*H*). $J_{2,3}$ = 11.1 Hz, $J_{3,4}$ = 8.6 Hz, $J_{3,3\text{-}CH3}$ = 6.7 Hz, $J_{4,5}$ = 2.9 Hz, $J_{5,5\text{-}CH3}$ = 6.8 Hz, $J_{5,6}$ = 6.7 Hz.

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15. **11**:Oil; $[\alpha]_D^{20}$ = +14.7 (c = 4.59, CH_3OH); 300 MHz ^1H NMR (δ, $CDCl_3$): 1.01, 1.05, 1.184 and 1.20 (d, NCHCH_3); 1.04 (d, 3-CH_3); 1.182 (d, 6-H_3); 2.39 (s, aryl-CH_3); 2.62 (ddq, 3-H); 3.25 (br., OH); 3.34 (dd, 4-H); 3.47 (qd, 5-H); 3.61 and 3.99 (qq, NCH); 4.382, 4.604 (AB, aryl-CH_2); 6.86 (d, 2-H); 7.2 - 7.4 and 7.75 (m, aryl-*H*). $J_{2,3}$ = 11.0 Hz, $J_{3,4}$ = 5.9 Hz, $J_{3,3\text{-}CH3}$ = 6.9 Hz, $J_{4,5}$ = 5.1 Hz, $J_{5,6}$ = 6.2 Hz, J_{AB} = 11.8 Hz.

12: Oil; $[\alpha]_D^{20}$ = -11.2 (c = 0.86, CH_3OH), 300 MHz ^1H NMR ($CDCl_3$): 1.01, 1.071, 1.132 and 1.18 (d, NCHCH_3); 1.074 (d, 3-CH_3); 1.15 (d, 6-H_3); 2.39 (s, aryl-CH_3); 2.52 (ddq, 3-H); 3.18 (br., OH); 3.50 (dq, 5-H); 3.59 and 4.00 (qq, NCH); 3.624 (dd, 4-H); 4.48 and 4.58 (AB, aryl-CH_2); 6.83 (d, 2-H), 7.2 - 7.4 and 7.75 (m, aryl-*H*).

16. **13**: Oil; 300 MHz ^1H NMR ($CDCl_3$): 0.91 (d, 3-CH_3); 0.936 (d, 6-H_3 and 5-CH_3); 1.59 (m, 3-H); 1.73 (m, 3-H); 1.73 (m, 2-H_2); 1.83 (qqd, 5 H), 3.05 (br., 2 OH); 3.10 (dd, 4-H); 3.61, 3.76 (AB, 1-H_2). J_{AB} = 10.7 Hz, $J_{A,2}$ = 6.7 Hz, $J_{B,2}$ = 4.8 Hz, $J_{3,8}$ = 6.9 Hz, $J_{3,4}$ = 6.6 Hz, $J_{4,5}$ = 5.1 Hz, $J_{5,6}$ = $J_{5,5\text{-}CH3}$ = 6.8 Hz.

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