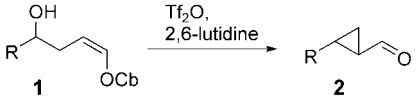
Cyclizations

Synthesis of Stereohomogeneous Cyclopropanecarbaldehydes and Cyclopropyl Ketones by Cycloalkylation of 4-Hydroxy-1-alkenyl Carbamates**

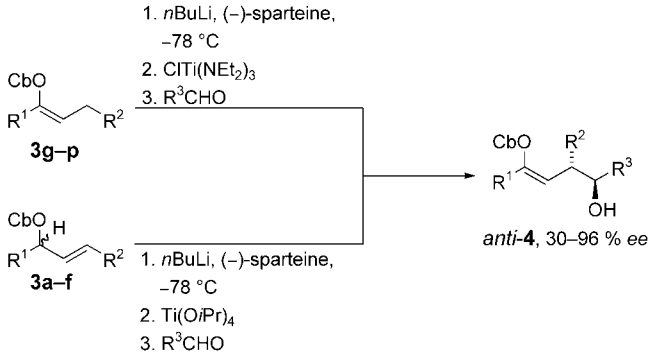
*Rainer Kalkofen, Sven Brandau, Birgit Wibbeling, and Dieter Hoppe**

Only a few methods are known for the synthesis of optically active cyclopropanecarbaldehydes and cyclopropyl ketones by ring-forming reactions.[1–3] Taylor et al.[4] very recently described the synthesis of several racemic, disubstituted cyclopropanecarbaldehydes by intramolecular cycloalkylation of (*Z*)-4-hydroxy-2-alkenyl *N*,*N*-diisopropylcarbamates **1** by activation of the hydroxy group with trifluoromethanesulfonic anhydride (Tf_2O; Scheme 1).



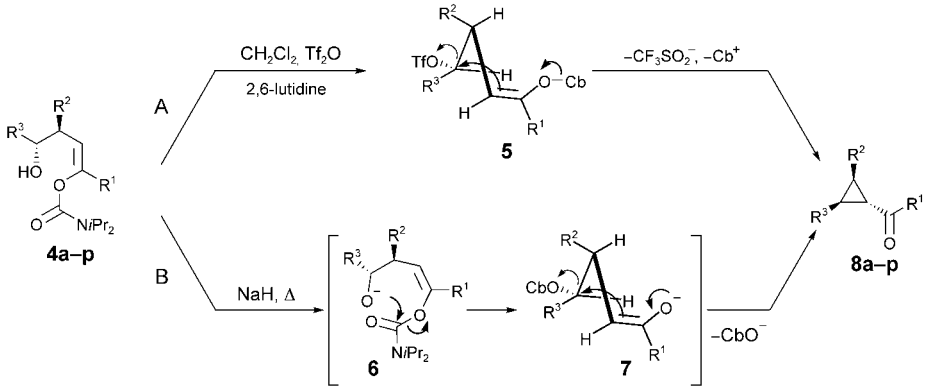
Scheme 1. Cyclopropane formation according to Taylor et al. Cb = $CONiPr_2$, Tf = triflate.[4]

We found in our initial studies that this method can be extended to the synthesis of optically active, trisubstituted cyclopropanecarbaldehydes and cyclopropyl ketones **8** starting from compounds **4**, which in turn are readily obtained by enantioselective homoaldol reaction in the presence of (−)-sparteine[5–7] (Scheme 2). According to Taylor et al., the (*Z*)-*anti* homoallylic alcohols **4** are converted into the corresponding triflates **5**, which undergo immediate intramolecular attack by the weakly nucleophilic enol carbamate moiety.[8] The substitution step (Scheme 3, Method A) proceeds with complete stereoinversion, leading to a *cis* arrangement of R^2 and R^3 and placing the acyl residue into the *trans* position to both of them via transition state **5**.



Scheme 2. Enantioselective synthesis of 4-hydroxy-1-alkenyl carbamates **4**. **4g–p**: R^1 = Ph, **4a–f**: R^1 = H, R^2, and R^3 in Table 1.

During the course of our work we made a surprising observation: simply treating the homoaldol adducts **4** with sodium hydride furnished the cyclopropanes **8** with excellent diastereoselectivity and complete chirality transfer (Method B, Scheme 3, Table 1). When alcohols **4** and sodium hydride were heated in THF or DMF for several hours, the cyclopropanes **8a–p** formed smoothly with the same efficiency as that observed for Method A. Apparently the *N*,*N*-diisopropylcarbamoyl group in alkoxide **6** migrates to the O4 atom,[9] forming the (*Z*)-enolate **7**, which undergoes cycloalkylation by nucleophilic substitution of the carbamate group with strict stereoinversion. The enolate moiety occupies an *anti* position in transition state **7** in order to avoid steric repulsion with R^2 and R^3. Method B also works well



Scheme 3. Synthesis of highly enantioenriched disubstituted cyclopropanes.

even when a formyl group is generated (Table 1, entries 3 and 5).

The relative configuration of **8h** was confirmed by a single-crystal X-ray analysis.[10] The absolute configuration of the precursor **4** is retained at C3, and the *ee* values of the products **8** correspond to those of the starting compounds **4** (Table 1). The combination of the cycloalkylation with the (−)-sparteine-mediated homoaldol reaction results in a two-step stereoselective route to cyclopropyl ketones.[11] The *N*,*N*-diisopropylcarbamoyl group is required for the activation in the deprotonation step of the homoaldol reaction. Moreover,

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Table 1:

Entry	Route	Solv.	Substr. (% *ee*)	Prod. (% *ee*)	R^1	R^2	R^3	Yield [%]	d.r.	$[\alpha]_D^{20}$[a]
1	A	CH_2Cl_2	**4a** (30)[b]	**8a** (30)[c]	H	$(CH_2)_2CH_3$	$(CH_2)_2Ph$	70	98:2	+2
2	A	CH_2Cl_2	**4b** (71)[b]	**8b** (71)[c]	H	CH_3	Ph	>99	95:5	+110
3	B	DMF	**4b** (71)[b]	**8b** (71)[b]	H	CH_3	Ph	71	95:5	+110
4	A	CH_2Cl_2	**4c** (87)[b]	**8c** (87)[c]	H	CH_3	$(CH_2)_2Ph$	48	95:5	+3
5	B	DMF	**4c** (87)[b]	**8c** (87)[b]	H	CH_3	$(CH_2)_2Ph$	58	98:2	+3
6	A	CH_2Cl_2	**4d** (82)[c]	**8d** (82)[c]	H	CH_3	$CH(CH_3)_2$	>99	98:2	−4
7	A	CH_2Cl_2	**4e** (83)[c]	**8e** (83)[c]	H	CH_3	cyclopropyl	39	88:12	–[d]
8	A	CH_2Cl_2	**4f** (86)[c]	**8f** (>80)[c]	H	CH_3	$(CH_2)_4CH_3$	61	98:2	+1
9	A	CH_2Cl_2	**4g** (96)[b]	**8g** (96)[b]	Ph	CH_3	Ph	80	98:2	+153
10	B	THF	**4g** (92)[b]	**8g** (91)[b]	Ph	CH_3	Ph	98	98:2	+142
11	A	CH_2Cl_2	**4h** (93)[b]	**8h** (93)[b]	Ph	CH_3	$C(CH_3)_3$	83	98:2	−17
12	B	DMF	**4h** (95)[b]	**8h** (94)[b]	Ph	CH_3	$C(CH_3)_3$	64	98:2	−17
13	A	CH_2Cl_2	**4i** (91)[b]	**8i** (91)[b]	Ph	CH_3	*p*-BrC_6H_4	41	92:8	+148
14	B	THF	**4i** (93)[b]	**8i** (93)[b]	Ph	CH_3	*p*-BrC_6H_4	91	98:2	+151
15	B	DMF	**4f** (86)[b]	**8f** (>80)[b]	H	CH_3	$(CH_2)_4CH_3$	62	98:2	+1
16	B	THF	**4j** (94)[b]	**8j** (92)[b]	Ph	CH_3	naphthyl	84	98:2	+206
17	B	THF	**4k** (92)[e]	**8k** (92)[e]	Ph	CH_3	furyl	98	98:2	+177
18	B	THF	**4l** (91)[b]	**8l**[f]	Ph	CH_3	CH_3	84	98:2	–
19	B	THF	**4m** (95)[b]	**8m**[g]	Ph	CH_3	CH_2CH_3	96	98:2	−85
20	B	DMF	**4n** (96)[b]	**8n** (96)[b]	Ph	CH_3	$CH(CH_3)_2$	62	98:2	−19
21	B	THF	**4o** (95)[b]	**8o** (95)[b]	Ph	CH_3	cyclopropyl	74	98:2	−50
22	B	THF	**4p** (95)[b]	**8p** (95)[c]	Ph	CH_3	cyclohexyl	78	98:2	−9

[a] $c = 0.15$–0.92, $CHCl_3$. [b] Determined by HPLC, column: Chira Grom-2. [c] Determined by chiral GC, column: β-Dex 120. [d] Due to the volatility of the compound it was not possible to determine the specific optical rotation. [e] Determined by HPLC, column: Chira Grom-1, solvent: *n*-hexane/isopropyl alcohol. [f] Achiral. [g] Not determined.

through the carbamoyl migration both the nucleophilic and the electrophilic properties of the stable precursors **4** are activated. These features fulfill in an exemplarily manner one demand of modern organic synthesis, namely minimizing the number of steps in a synthetic sequence.[12]

Experimental Section

Synthesis of cyclopropanecarbaldehydes and cyclopropyl ketones:

Method A: A flame-dried flask was charged with **4b** (199 mg, 0.3 mmol, 1 equiv) in 10 mL CH_2Cl_2 under an argon atmosphere. 2,6-Lutidine (140 mg, 1.3 mmol, 4 equiv) was added by syringe, the solution was cooled to −78 °C, and then freshly distilled triflic anhydride (314 mg, 1.1 mmol, 3 equiv) was injected. The reaction mixture was stirred for 1 h, quenched with 1 mL water, and allowed to warm to room temperature. The mixture was diluted with 25 mL CH_2Cl_2, the aqueous phase was separated, and the organic layer was washed with saturated $NaHCO_3$ solution (1 × 10 mL). The organic phase was dried over $MgSO_4$ and the solvent evaporated in vacuum. The crude product was purified by flash chromatography on silica gel (diethyl ether/*n*-pentane 1:10).

Method B: To the *anti*-homoaldol adduct **4i** (169 mg, 0.37 mmol, 1 equiv) was added sodium hydride (60% in mineral oil; 20 mg, 0.5 mmol, 1.35 equiv). The flask was placed under argon, THF (2 mL) was injected, and the resulting solution was heated for 14 h at 60 °C. When DMF was used as the solvent the solution was stirred 1 h at room temperature and then heated for 2–12 h at 60 °C (tlc control). For workup 10 mL saturated sodium chloride solution was added. The aqueous phase was separated and extracted with diethyl ether (3 × 25 mL). The combined organic extracts were dried over $MgSO_4$ and the solvents evaporated in vacuum. The crude product **8i** was purified by flash chromatography on silica gel (diethyl ether/*n*-pentane 1:5). For yields and enantiomeric excesses see Table 1.

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[10] X-ray crystal structure analysis of **8h**: $C_{15}H_{20}O$, $M_w = 216.31$, colorless crystal $0.50 \times 0.15 \times 0.10$ mm, $a = 5.975(1)$, $b = 10.359(1)$, $c = 11.161(1)$ Å, $\beta = 103.30(1)°$, $V = 672.3(1)$ Å^3, $\rho_{calcd} = 1.069$ g cm^{-3}, $\mu = 4.96$ cm^{-1}, empirical absorption correction ($0.790 \le T \le 0.952$), $Z = 2$, monoclinic, space group $P2_1$ (No. 4), $\lambda = 1.54178$ Å, $T = 223$ K, ω and ϕ scans, 3002 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.59$ Å^{-1}, 1640 independent ($R_{int} = 0.036$) and 1590 observed reflections [$I \ge 2\sigma(I)$], 149 refined parameters, $R = 0.039$, $wR^2 = 0.111$, Flack parameter 0.1(4), max. residual electron density 0.09 (-0.12) e Å^{-3}, hydrogens calculated and refined as riding atoms. Data set was collected with a Nonius KappaCCD diffractometer. Programs used: data collection COLLECT (Nonius B. V., **1998**), data reduction Denzo-SMN (Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307–326), absorption correction SORTAV (R. H. Blessing, *Acta Crystallogr. Sect. A* **1995**, *51*, 33–37; R. H. Blessing, *J. Appl. Crystallogr.* **1997**, *30*, 421–426), structure solution SHELXS-97 (G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467–473), structure refinement SHELXL-97 (G. M. Sheldrick, Universität Göttingen, **1997**), graphics SCHAKAL (E. Keller, **1997**). CCDC-240544 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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