Diastereoselective Formation of Cyclopropanols by a Chromium(II)-mediated Cross-coupling Reaction

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Various 2-(α-hydroxyalkyl)cyclopropanols were generated by chromium(II)-mediated cross-coupling of acroleins and aldehydes with high diastereoselectivities up to 95 %. The unstable diols were converted selectively to the stable monosilyl ethers by treatment with TBDMS-Cl in the presence of the second secondary alcohol.

Key words: Chromium, Aldehydes, C-C Coupling, Cross-coupling, Diastereoselectivity

Introduction

The formation of cyclopropanes is of high interest in synthetic organic chemistry due to their pharmaceutical profile. Up to now, a variety of cyclopropanes [1] was successfully examined regarding their antibacterial, antibiotic and herbicidal activities. The well known ciprofloxacin is a member of a group of antibacterial agents containing a cyclopropane ring [2]. Many others are currently under investigation. Particularly interesting is the diastereoselective formation of cyclopropanols [3] because of their unique reactivity which might be useful in pharmaceuticals. Takai *et al.* [4] reported on cyclopropanol formations using aldehydes and vinylketones as reactants. The corresponding products were obtained with moderate diastereoselectivities using $CrCl_2$ in DMF as reagent.

Results and Discussion

In this communication, we wish to present a method for the synthesis of cyclopropanols bearing one quaternary carbon within the three-membered ring (Fig. 1).

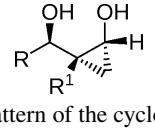
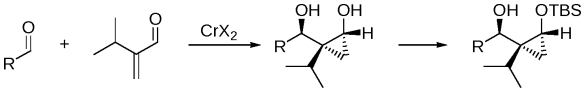


Fig. 1. Substitution pattern of the cyclopropanols prepared.

The ring strain, which is already high in cyclopropanols, is increased by repulsion of two bulky substituents at the same carbon atom. The products of the coupling reactions of isopropylacrolein and various aldehydes are summarized in Table 1. Due to the instability of the cyclopropanes they had to be protected prior to isolation. Best results were obtained with linear aldehydes (entries 1 – 3, 5). If only one substituent in β-position of the aldehyde is present, the coupling proceeds with good yields and high diastereoselectivities. In the case of α,β-disubstituted aldehydes slightly lower yields and a decrease in diastereoselectivity (from $>$ 90 to 80 %) are observed (entry 4).

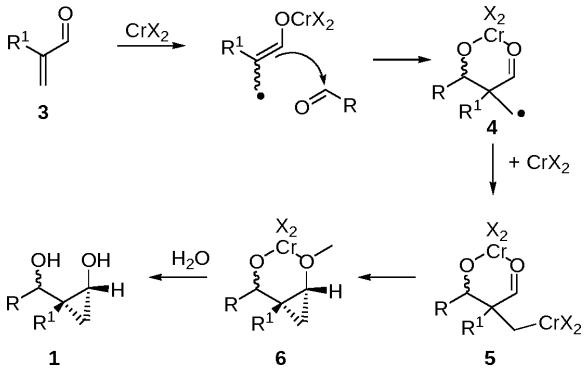
Table 1. Coupling products of aldehydes with isopropylacrolein.



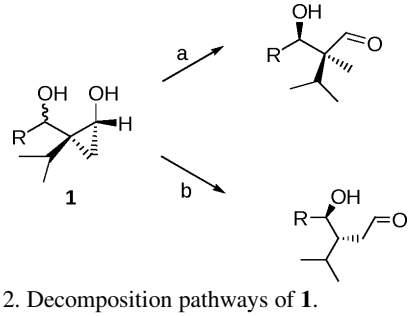
1 2

Entry	No.	Aldehyde with R =	Yield over 2 steps (%)	d. e. (%)
1	**2a**	$PhCH_2CH_2-$	57	95
2	**2b**	$PhCH_2-$	55	92
3	**2c**	$C_5H_{11}-$ (*n*-pentyl)	54	95
4	**2d**	$CH(CH_3)_2CH_2-$	43	80
5	**2e**	$C_7H_{15}-$	56	90

Similar couplings were performed with methacrolein, which yielded the methylcyclopropanols in moderate yields. According to a proposed mechanism (Scheme 1) the first step of the cyclopropanation is a single electron transfer (SET) from the chromium(II) species to the acrolein **3** yielding a chromium(III) enolate radical. The latter attacks the carbonyl functionality of the aldehyde resulting in the chromium aldol species **4**.



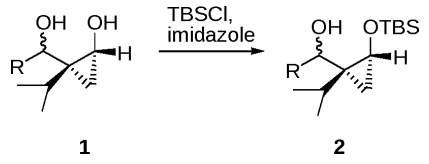
Scheme 1. Mechanism of the coupling reaction.



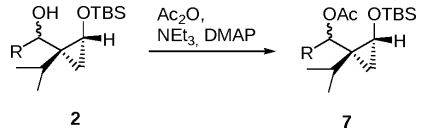
Scheme 2. Decomposition pathways of **1**.

Intermediate **5** is formed by another single-electron transfer from chromium(II) to the alkyl radical **4**. Subsequent intramolecular addition to the carbonyl results in the formation of cyclopropanol **6**. Because of the moderate reducing power of chromium, the first one-electron transfer to the acrolein proceeds selectively, while the aldehyde is not attacked. The configuration of cyclopropanol **1** is determined by the coordination of the chromium(III) center to both the carbonyl and the alkoxy groups. Therefore R and the alcohol group of the cyclopropane are found to be *cis*. The first one-electron transfer is likely to be promoted by the Lewis acidity of the chromium salt.

In order to perform the coupling reaction, a solution of $CrCl_2$ in DMF was stirred at 0 °C, and a solution of acrolein and aldehyde was added simultanously by a syringe pump. After stirring for 3 h at 0 °C and aqueous work-up the desired cyclopropanols **1** were obtained. The cyclopropanes were found to be highly unstable at r. t. As there are two sterically demanding substituents on the same edge of the three-membered ring, the stability of the latter is considerably decreased. After several hours at 40 °C, cyclopropanol **5** (R = Bn) is decomposed by 80 %, forming a mixture of several aldehydes. The two major compounds are shown in Scheme 2.



Scheme 3. Selective protection of the cyclopropane alcohol.



Scheme 4. Acylation of monosilylated cyclopropanols.

Due to this fast decomposition, a method for the selective protection of the cyclopropanol had to be found. By treating the free cyclopropanols with TBDMS-Cl, a selective silylation of the sterically less hindered cyclopropanol was achieved (Scheme 3).

Although both hydroxy groups are secondary ones, only the one directly bound to the cyclopropanol undergoes the reaction with TBDMS-Cl. As the binding angle within the three-membered ring is less than the usual 109.6° at a substituted aliphatic carbon atom, the hydroxy group is exposed in a manner similar to primary alcohols. The relative configuration was determined as described before *via* the acetonides [5]. After protection of the hydroxy group attached to the cyclopropane ring, we tried to functionalize the external hydroxy group. Acylation in the presence of 4-(dimethylamino)pyridine (DMAP) proved to be successful (Scheme 4).

Conclusion

A simple method for the diastereoselective formation of cyclopropanols starting from aldehydes and aroleins has been established. The highly functionalized products might serve as synthons in pharmaceutical research because both hydroxy functions can be further functionalized selectively.

Experimental Section

Procedures for coupling reactions

Note: All coupling reactions were performed under nitrogen atmosphere. The coupling products were stored at −25 °C.

Step 1: coupling reactions

Representative procedure for Table 1, entry 1: $CrCl_2$ (0.98 g, 8 mmol) was dissolved in dry, oxygen-free DMF

(8 mL) and the mixture vigorously stirred at 0 °C. A solution of acrolein (2 mmol) and aldehyde (1 mmol) in DMF (5 mL) was added dropwise, while the blue-green color of the $CrCl_3$ solution turned to brown-green. Stirring was continued at 0 °C for at least 3 h, and the reaction mixture was subsequently poured into water. The aqueous layer was extracted 4 times with diethyl ether. After being dried over $MgSO_4$ the combined organic extracts were evaporated, and the products were obtained as free diols. Due to the instability of the free diols, purification was conducted only after the following step.

Step 2: silylation with TBDMS-Cl

The residue of step 1 was dissolved in dry DMF (8 mL) and the solution stirred at 0 °C. Imidazole (5 mmol, 385 mg) in DMF (2 mL) was added dropwise, followed by the addition of a 50 % solution of TBDMS-Cl in toluene (1.5 mL, 4 mmol). Stirring was continued until no starting material could be found (TLC, 2 – 4 h). A saturated aqueous solution of NH_4Cl (20 mL) was added, and the mixture was extracted 4 times with diethyl ether. The organic extracts were dried over $MgSO_4$ and evaporated *in vacuo*. Purification by column chromatography on silica gel (35 : 1 pentane : ethyl acetate) provided the desired product in 57 % yield (197 mg).

Step 3: acylation of the product from step 2

The product obtained in step 2 was dissolved in dichloromethane (2 mL), and acetic acid anhydride (135 μL), triethylamine (180 μL) and DMAP (10 mg) were added. The mixture was stirred for 4 h at r. t. and afterwards poured into water. Extraction of the aqueous layer with diethyl ether and evaporation of the solvent after drying supplied the acylated cyclopropanols in yields of 60 – 65 %.

*1-(2-(tert-Butyldimethylsilyl)oxy-1-isopropylcyclopropyl)-3-phenylpropan-1-ol (**2a**)*

According to the general procedure, phenylpropanal and isopropylacrolein were coupled with $CrCl_2$. The monosilylated diol was obtained in 55 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (m, 5 H, 1 – 3), 3.57 (dd, J = 4.0 and 9.5 Hz, 1 H, 7-CH), 3.35 (dd, J = 3.3 and 6.4 Hz, 1 H, 10-CH), 2.90 (2m, 2 H, 5-CH_2), 2.67 (bs, 1 H, 7-OH), 2.00 (m, 1 H, 11-CH) 1.90 (m, 2 H, 6-CH_2), 0.88 and 0.73 (2d, J = 7.0 and 7.0 Hz, 6 H, 12-CH_3 and 12′-CH_3), 0.88 (s, 9 H, 15 CH_3), 0.57 and 0.50 (2m, 2 H, 10-CH_2), 0.12 and 0.07 (2s, 6 H, 13 CH_3). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.6 (C-4), 128.6 and 128.5 (C-2 and C-3), 125.6 (C-1), 75.3 (C-7), 54.4 (C-10), 35.3 (C-6), 33.0 (C-8), 32.3 (C-5), 26.5 (C-11), 25.7 (C-15), 20.6 and 20.3 (C-12 and C-12′), 17.8 (C-14), 16.7 (C-9), −5.0 and −5.2 (C-13). – TLC: R_f = 0.45 (PE/EE 20 : 1). – MS (GC/MS): *m/z* (%) = 315 (2), 273 (3), 239 (8), 161 (18), 145 (15), 115 (33), 97 (45). – IR (thin layer): ν = 3524, 2956, 2858, 1472, 1361, 1257, 1162, 1056, 881, 837, 778, 699 cm^{-1}. – Elemental analysis: calcd. C 72.35, H 10.41; found C 71.7, H 10.43.

*1-(2-(tert-Butyldimethylsilyl)oxy-1-isopropylcyclopropyl)-2-phenylethanol (**2b**)*

According to the general procedure, phenylethanal and isopropylacrolein were coupled with $CrCl_2$. The monosilylated diol was obtained in 55 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (m, 5 H, 1 – 3), 3.86 (dd, J = 3.8 and 8.9 Hz, 1 H, 6-CH), 3.39 (dd, J = 3.8 and 6.2 Hz, 1 H, 9-CH), 2.95 (m, 2 H, 5-CH_2), 2.31 (bs, 1 H, 6-OH), 2.07 (m, 1 H, 10-CH), 0.93 and 0.78 (2d, J = 6.9 and 6.9 Hz, 6 H, 11-CH_3 and 11′-CH_3), 0.88 (s, 9 H, 14-CH_3), 0.59 (m, 2 H, 8-CH_2), 0.12 and 0.09 (2s, 6 H, 12-CH_3). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.3 (C-4), 129.0 and 128.2 (C-3 and C-2), 125.8 (C-1), 76.8 (C-6), 54.5 (C-9), 40.2 (C-5), 32.5 (C-7), 26.8 (C-10), 26.4 (C-14), 20.6 and 20.3 (C-11 and C-11′), 17.9 (C-13), 16.5 (C-8), -4.9 and −5.2 (C-12). – TLC: R_f = 0.38 (PE/EE 20 : 1). – MS (GC/MS): *m/z* (%) = 316 (7), 273 (5), 259 (8), 161 (25), 131 (80), 91 (60). – HRMS: *m/z* = 317.2295186, (calcd. 317.23007 for $C_{20}H_{33}O_1Si_1$, $[M–OH]^+$).

*1-(2-(tert-Butyldimethylsilyl)oxy-1-isopropylcyclopropyl)-2-phenylethanoylacetate (**7b**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (m, 5 H, 1 – 3), 5.13 (dd, J = 6.4 and 7.8 Hz, 1 H, 6-CH), 3.23 (dd, J = 3.7 and 6.6 Hz, 1 H, 9-CH), 3.16 and 3.01 (2m, 2 H, 5-CH_2), 1.93 (m, 1 H, 10-OH), 1.92 (s, 3 H, 16-CH_3), 1.00 and 0.80 (2d, J = 6.8 and 7.1 Hz, 6 H, 11-CH_3 and 11′-CH_3), 0.88 (s, 9 H, 14-CH_3), 0.50 and 0.13 (2m, 2 H, 8-CH_2), 0.07 and 0.05 (m, 6 H, 12-CH_3). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4 (C-15), 138.9 (C-4), 129.4 and 128.1 (C-3 and C-2), 126.1 (C-1), 76.7 (C-6), 53.4 (C-9), 38.5 (C-5), 30.2 (C-7), 27.9 (C-10), 25.7 (C-14), 21.2 (C-16), 20.6 and 20.4 (C-11 and C-11′), 18.0 (C-13), 17.5 (C-8), −4.9 and −5.2 (C-12). – TLC: R_f = 0.38 (PE/EE 20 : 1). – MS (GC/MS): *m/z* (%) = 316 (13), 273 (12), 259 (39), 161 (89), 117 (100), 91 (59), 73 (91). – IR (thin layer): ν = 2450, 2960, 2857, 1739, 1498, 1471, 1373, 1259, 1167, 1028, 802 cm^{-1}. – HRMS: *m/z* = 317.2295186, (calcd. 317.23007 for $C_{20}H_{33}O_1Si_1$, $[M–OAc]^+$).

*1-(2-(tert-Butyldimethylsilyl)oxy-1-isopropylcyclopropyl) hexan-1-ol (**2c**)*

According to the general procedure, hexanal and isopropylacrolein were coupled with $CrCl_2$. The monosilylated diol was obtained in 54 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.54 (dd, J = 5.5 and 8.1 Hz, 1 H, 6-CH), 3.33 (dd, J = 3.4 and 6.4 Hz, 1 H, 9-CH), 2.25 (bs, 1 H, 6-OH), 1.89 (m, 1 H, 10-CH), 1.63 (m, 2 H, 5-CH_2), 1.29 (m, 6 H, 2,3,4-CH_2), 0.95 (m 3 H, 1-CH_3), 0.88 and 0.71 (2d, J = 7.0 and 7.0 Hz, 6 H, 11-CH_3 and 11′-CH_3), 0.88 (s, 9 H, 14-CH_3), 0.58 and 0.53 (2m, 2 H, 8-CH_2), 0.12 and 0.09 (2s, 6 H, 12-CH_3). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 76.4 (C-6), 54.2 (C-9), 33.4 (C-5), 32.2 (C-7), 32.0 (C-3), 26.5 (C-4), 26.2 (C-10), 25.7 (C-14), 22.6 (C-2), 20.7 and 20.2 (C-11 and C-11′), 17.8 (C-13), 17.0 (C-8), 14.1 (C-1), −4.9 and −5.3 (C-12). – TLC: R_f = 0.72 (PE/EE 15 : 1). – MS (GC/MS): *m/z* (%) = 283 (2), 239 (3), 213 (6), 161 (25), 115 (55), 73 (100). – IR (thin layer): ν = 3537, 2957, 2859, 1464, 1362, 1254, 1154, 1056, 886, 837, 778 cm^{-1}. – Elemental analysis: calcd. C 68.72, H 12.18, O 10.17, Si 8.93; found C 68.7, H 10.8.

*1-(2-(tert-Butyldimethylsilyl)oxy-1-isopropylcyclopropyl)-3-methylbutan-1-ol (**2d**)*

According to the general procedure, 3-methylbutanal and isopropylacrolein were coupled with $CrCl_2$. The monosilylated diol was obtained in 43 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.64 (dd, J = 3.8 and 9.7 Hz, 1 H, 7-CH), 3.34 (dd, J = 3.4 and 6.4 Hz, 1 H, 4-CH), 2.27 (bs, 1 H, 4-OH), 1.90 (m, 1 H, 8-CH), 1.81 (m, 1 H, 2-CH), 1.62 and 1.35 (2m, 2 H, 3-CH_2), 0.93 (d, 6 H, 1-CH_3), 0.87 and 0.72 (2d, J = 6.7 and 6.9 Hz, 6 H, 9-CH_3 and 9′-CH_3), 0.88 (s, 9 H, 12-CH_3), 0.55 (m, 2 H, 6-CH_2), 0.12 and 0.10 (2s, 6 H, 10-CH_3). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 73.7 (C-4), 54.5 (C-7), 42.6 (C-3), 32.3 (C-5), 26.3 (C-8), 25.7 (C-12), 24.8 (C-2), 23.8 (C-1), 21.5 (C-1′), 20.6 and 20.3 (C-9 and C-9′), 17.8 (C-11), 16.5 (C-6), −4.9 and −5.2 (C-10). – TLC: R_f = 0.72 (PE/EE 15 : 1). – MS (GC/MS): *m/z* (%) = 296 (3), 253 (5), 213 (7), 154 (25), 115 (55), 73 (100). – IR (thin layer): ν = 3421, 2956, 2930, 2858, 1463, 1388, 1255, 1154, 1056, 883, 837, 778 cm^{-1}. – Elemental analysis: calcd. C 67.9, H 12.0, O 10.7; found C 67.9, H 11.4.

*1-(2-(tert-Butyldimethylsilyl)oxy-1-isopropylcyclopropyl) octan-1-ol (**2e**)*

According to the general procedure, octanal and isopropylacrolein were coupled with $CrCl_2$. The monosilylated diol was obtained in 56 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.55 (dd, J = 5.5 and 8.1 Hz, 1 H, 8-CH), 3.33 (dd, J = 3.3 and 6.4 Hz, 1 H, 11-CH), 2.15 (bs, 1 H, 8-OH), 1.89 (m, 1 H, 12-CH), 1.63 (m, 2 H, 7-CH_2), 1.48 (m, 2 H, 6-CH_2), 1.27 (m, 8 H, 2,3,4,5-CH_2), 0.96 (m, 3 H, 1-CH_3), 0.89 and 0.72 (2d, J = 7.0 and 6.9 Hz, 6 H, 13-CH_3 and 13′-CH_3), 0.88 (s, 9 H, 16-CH_3), 0.59 and 0.53 (2m, 2 H, 10-CH_2), 0.12 and 0.10 (2s, 6 H, 14-CH_3). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 76.4 (C-8), 54.1 (C-11), 33.2 (C-7), 31.9 (C-9), 31.6 (C-5), 29.5 (C-4), 29.0 (C-3), 26.5 (C-6), 25.9 (C-12), 25.4 (C-16), 22.3 (C-2), 20.3 and 19.9 (C-13 and C-13′), 17.5 (C-15), 16.7 (C-10), 13.7 (C-1), −5.5 and −5.8 (C-14). – TLC: R_f = 0.78 (PE/EE 20 : 1). – MS (GC/MS): *m/z* (%) = 324 (4), 281 (10), 213 (5), 161 (23), 115 (38), 73 (100). – HRMS: *m/z* = 325.2921189 (calcd. 325.29267 for $C_{20}H_{41}O_1Si_1$, [M–OH]$^+$).

*1-(2-(tert-Butyldimethylsilyl)oxy-1-isopropylcyclopropyl) octan-1-oylacetate (**7e**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.55 (dd, J = 5.5 and 8.1 Hz, 1 H, 8-CH), 3.33 (dd, J = 3.3 and 6.4 Hz, 1 H, 11-CH), 1.89 (m, 1 H, 12-CH), 1.63 (m, 2 H, 7-CH_2), 1.48 (m, 2 H, 6-CH_2), 1.27 (m, 8 H, 2,3,4,5-CH_2), 0.96 (m 3 H, 1-CH_3), 0.89 and 0.72 (2d, J = 7.0 and 6.9 Hz, 6 H, 13-CH_3 and 13′-CH_3), 0.88 (s, 9 H, 16-CH_3), 0.59 and 0.53 (2m, 2 H, 10-CH_2), 0.12 and 0.10 (2s, 6 H, 14-CH_3). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4 (C-17), 76.8 (C-8), 53.5 (C-11), 32.4 (C-7), 31.5 (C-5), 30.6 (C-9), 29.5 (C-4), 28.9 (C-3), 27.3 (C-12), 26.1 (C-6), 25.4 (C-16), 22.3 (C-2), 21.1 (C-18), 20.4 and 20.1 (C-13 and C-13′), 17.7 (C-15), 17.4 (C-10), 13.7 (C-1), −5.5 and −5.7 (C-14). – TLC: R_f = 0.83 (PE/EE 20 : 1). – MS (GC/MS): *m/z* (%) = 324 (31), 281 (100), 267 (8), 239 (23), 191 (20), 73 (90). – IR (thin layer): ν = 3581, 2957, 1739, 1471, 1370, 1245, 1167, 1056, 911, 837, 777 cm^{-1}. – HRMS: *m/z* = 325.2921189 (calcd. 325.29267 for $C_{20}H_{41}O_1Si_1$, [M–OAc]$^+$).

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