Journal of Organometallic Chemistry, 406 (1991) C15–C19
Elsevier Sequoia S.A., Lausanne
JOM 21680PC

Preliminary communication

Chiral arene-chromium-tricarbonyl complexes: a 2-step synthesis of halostachin analogues

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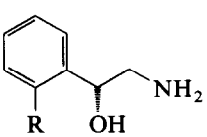
(Received November 12th, 1990)

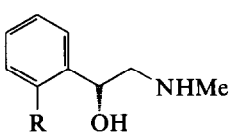
Abstract

High diastereoselectivity ($\geq 98/2$) was obtained upon addition of the anion of t-butylformamidine (**4**) to chiral arene-chromium-tricarbonyl complexes **3a–c**. After saponification and decomplexation (one-pot reaction) analogues of halostachin were obtained in high yield.

During work on asymmetric synthesis of bioactive substances [1–3], we developed a 3-step synthesis [1] of optically pure aminoalcohols **1a–d**. However two more steps were still necessary to reach the *N*-methylated target-compounds **2a–d**, which are analogues of natural (*R*) or unnatural (*S*) halostachin (**2**) [4].



(**1a**, R = OMe
1b, R = Me
1c, R = F
1d, R = CF_3)



(**2**, R = H: *R*(−)-halostachin
2a, R = OMe
2b, R = Me
2c, R = F
2d, R = CF_3)

We report here our initial results on a 2-step synthesis of the aminoalcohols **2a–c** shown in Scheme 1.

We recently found that upon addition of benzaldehyde to formamidine carbanion very high yields (90–95%) could be obtained [5]; in spite of the different reactivity expected after $Cr(CO)_3$-complexation of the aromatic ring, chiral complexed aldehydes **3a–3c** underwent addition of the formamidine carbanion **4** with satisfactory yields. The result are shown in Table 1.

* Reference number with asterisk indicates a note in the list of references.

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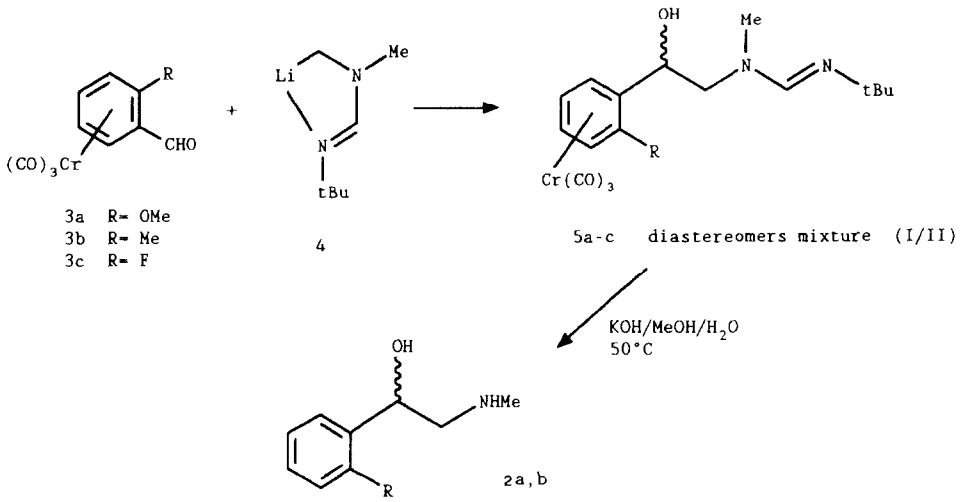
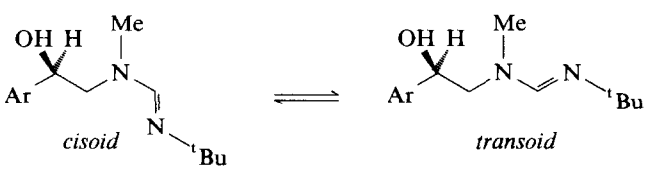
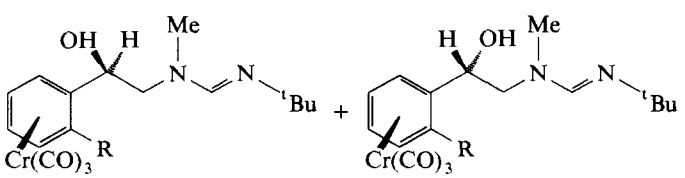


Scheme 1.

Products **5a–5c** were analysed by 200 MHz ^{1}H NMR and 50 MHz ^{13}C NMR spectroscopy before and after purification [6*,7*]. Complete diastereoselectivity was observed in addition of anion **4** to compound **3a**, which is consistent with previous reports on nucleophilic additions to *ortho*-substituted complexes [1,8–10]. It was found, however, that addition of anion **4** to complex **3b** gave a mixture of two isomers. Those two isomers could, of course, be the *cisoid* and *transoid* forms of the formamidine group (eq. 1) or the two possible diastereomers of the *cisoid* or of the *transoid* formamidine-forms (eq. 2). Because none of the non-equivalent proton signals (N–CH_3, N–CH_2, aromatic CH, –CH–) coalesce when the temperature is increased to 50 °C in $CDCl_3$ or to 80 °C in DMSO-d_6 (Fig. 1) we judged that they might be the two possible diastereomers of one of the formamidine forms (eq. 2).



(1)



(2)

1*RS* 1*RR*

To confirm this suggestion the ^{1}H NMR spectrum of compound **5a**, which showed only one type of signal, was recorded at various temperatures (Fig. 2). It was found that on lowering of the temperature the signals broadened and then some of them split, which must be attributed to a *cisoid/transoid* equilibrium. It would be difficult to explain why the *cisoid/transoid* forms would not exchange at +80 °C in

Table 1

Addition of anion **4** to complexes **3a–c**

Starting material	Solvent	t °C (reaction time)	Added salt	Compound **5a–c**	
				Yield	I/II
3a	ether/THF	−50° (2 h)		70%	≈100/0
3a	ether/THF	−25° (2 h)		75%	≈100/0
3b	ether/THF	−50° (2 h)		75%	70/30
3b	ether/THF	−130° (1 h)		85%	80/20
3b	THF	−50° (2 h)	$MgBr_2$	80%	≈100/0
3b	THF	−78° (3, 5 h)		90%	80/20
3c	THF	−50° (4, 5 h)	$MgBr_2$	55%	≈100/0

compound **5b** but exchange at −20 °C in compound **5a** and so it is reasonable to conclude that the two **5b** isomers are the two possible diastereomers.

Such a poor diastereoselectivity (80/20–70/30) was not observed in the reactions of the *ortho*-substituted complexes, except in the case of the KF-induced nitromethane addition [11]. Fortunately replacing Li^+ by Mg^{2+} led to an increase in the diastereoselectivity to 98/2 (the other isomer was not detected in the 200 MHz ^1H NMR spectra).

Saponification of the formamidine group and decomplexation can be carried out quantitatived in one step. Because of the high diastereoselectivity obtained under

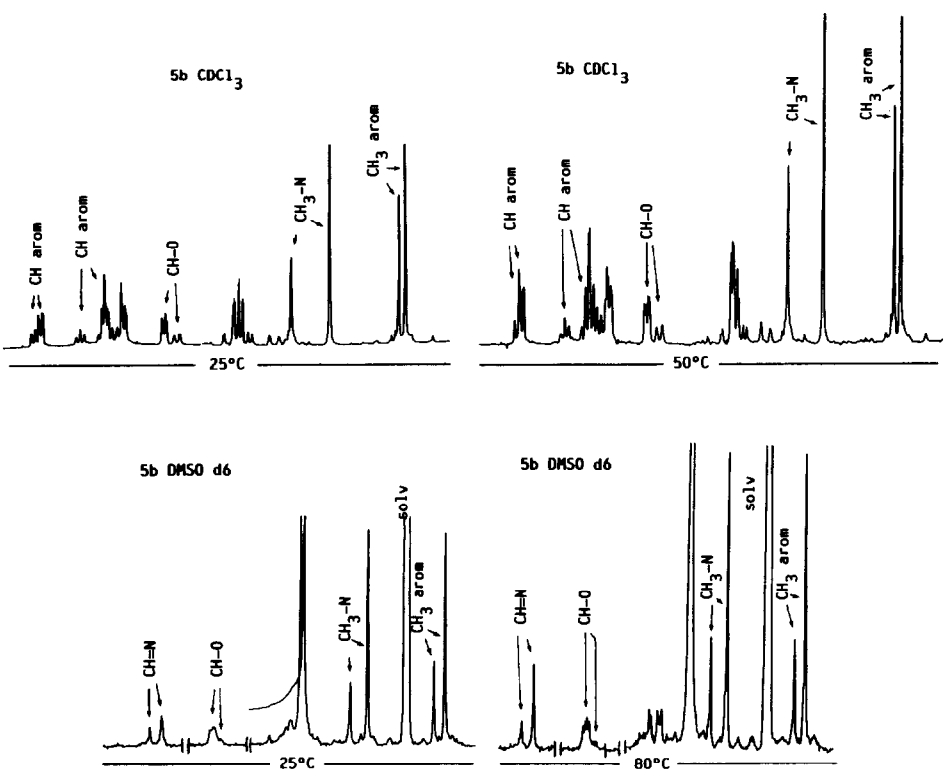


Fig. 1. Effect of increasing the temperature on the ^1H NMR spectrum of mixture **5b**.

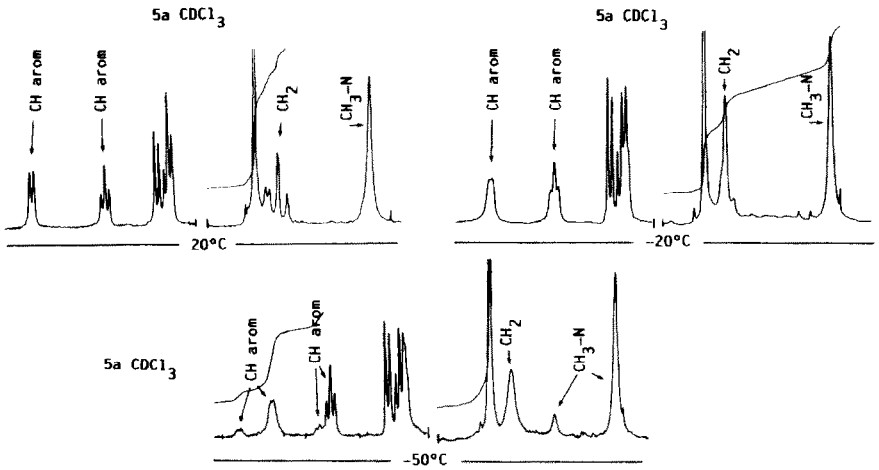


Fig. 2. Effect of lowering the temperature on the ^{1}H NMR spectrum of **5a**.

suitable conditions it is evident that, when optically pure complexes are used [12] this method will provide optically pure amino alcohols of type **5** in only two steps. From our model of the approach of the reagents [13] it can also be expected that the 1*S* complexes will afford the desired *R* aminoalchols.

References and notes

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5 A. Solladié-Cavallo and M. Bencheqroun, Tetrahedron Lett., 31 (1990) 2157.
6 *Compound 5a*: ^{1}H-NMR, 200 MHz ($CDCl_3$/TMS); only one type of signal is observed at the probe temperature (21°C), below that splitting occurs: δ 1.25 (s, 9H, ^{t}Bu); 2.85 (bs, 3H, N–CH_3); 3.55 (AB part of an ABX, 2H, CH_2, $\Delta\nu = 25$ Hz, $J_{AB} = 14$ Hz, $J_{AX} = 0$ Hz, $J_{BX} = 6$ Hz); 3.70 (s, 3H, OCH_3); 4.90 (d, 1H, X part of an ABX, CH(OH)); 4.92 (t, 1H, H arom); 5.0 (d, 1H, H arom); 5.40 (t, 1H, H arom) 5.96 (d, 1H, H arom); 7.4 (bs, 1H, CH=N). ^{13}C-NMR, 50 MHz ($CDCl_3$/TMS): δ 31.1 (^{t}Bu), 40.18 (N–CH_3); 52.93 (quat. ^{t}Bu); 55.82 (O–CH_3 + N–CH_2); 68.70, 73.94, 85.67, 93.18 (CH arom.) 73.94 (CH–O); 103.66, 139.92 (quat. arom.); 152.30 (CH=N); 233.32 (C≡O). Anal. Calc. for $C_{18}H_{24}N_2O_5Cr$: C, 53.99; H, 6.04; N, 7.99. Found C, 53.84; H, 6.35; N, 5.88%.
Compound 5b: ^{1}H-NMR, 200 MHz ($CDCl_3$/TMS); two types of signal are observed at the probe temperature (21°C) in $CDCl_3$ and in DMSO-d_6 there is no coalescence when the temperature increases. *Isomer 1*, δ 1.20 (s, 9H, ^{t}Bu); 2.2 (s, 3H, CH_3 arom.); 2.8 (s, 3H, NCH_3); 3.5 (AB part of an ABX, 2H, CH_2, $\Delta\nu = 20$ Hz, $J_{AB} = 14$ Hz, $J_{AX} = 5$ Hz, $J_{BX} = 2$ Hz); 4.81 (dd, 1H, X part of an ABX, CH–O); 5.12 (dd, 1H arom.); 5.27 (2td, 2H arom.); 5.78 (dd, 1H arom.); 7.35 (bs, 1H, CH=N). *Isomer 2*, δ 1.25 (s, 9H, ^{t}Bu); 2.28 (s, 3H, CH_3 arom.); 3.15 (s, 3H, N–CH_3) 3.25 (d, 1H, CH_2, $J = 14$ Hz), ≈ 3.5 (1H, CH_2 overlapping with the AB part of isomer 1); 4.7 (d, 1H, CH–O); 5.1 and 5.25 (2H arom. overlapping with isomer 1); 5.47 (t, 1H, H arom.); 5.85 (d, 1H, H arom.); 7.45 (bs, 1H, CH=N). ^{13}C-NMR 50 MHz ($CDCl_3$/TMS). *Isomer 1*, δ 18.5 (CH_3); 31.0 (^{t}Bu); 40.3 (N–CH_3); 53.35 (quat. ^{t}Bu); 56.8 (N–CH_2); 70.0 (CH–O); 90.84, 91.44, 94.14, 94.58 (CH arom.); 105.13, 113.16 (quat. arom.); 152.40 (CH=N); 233.50 (C≡O).
Compound 5c: ^{1}H-NMR, 200 MHz ($CDCl_3$/TMS); only one type of signal is observed at the probe temperature (21°C); however they are broad and multiplicity is not clear indicating that exchange is occurring at that temperature: δ 1.2 (bs, 9H, ^{t}Bu); 2.85 (bs, 3H, NCH_3); 3.57 (bs, 2H, CH_2); 4.95

(bm, 2H, 1H arom. + CH–O); 5.4 (bm, 2H, H arom.); 5.75 (bt, 1H, H arom.); 7.35 (bs, 1H, CH=N). ^{13}C-NMR, 50 MHz ($CDCl_3$/TMS): δ 30.9 (^{t}Bu); 40.44 (N–CH_3); 53.16 (quat. ^{t}Bu); 56.90 (CH_2N); 68.29 (CH–O); 78.6 (d, $J = 20$ Hz, C arom.); 86.34 (C arom.); 91.5 (2d, $J \simeq 30$ Hz, 2C arom.); 101.4 (d, $J = 13$ Hz, C arom.); 143.8 (d, $J = 261$ Hz, C arom.); 152.3 (CH=N), 231.7 (C=O).

Compound ***2a***: ^{1}H-NMR, 200 MHz ($CDCl_3$/TMS): δ 2.5 (s, 3H, NCH_3); 2.82 (AB part of an ABX, 2H, CH_2, $\Delta\nu \simeq 30$ Hz, $J_{AB} = 13$ Hz, $J_{AX} \simeq 3$ Hz, $J_{BX} = 8$ Hz); 5.1 (dd, X part of an ABX, 1H, CH); 6.85 (d, 1H, H arom.); 7.0 (t, 1H, H arom.); 7.3 (td, 1H, H arom.); 7.48 (dd, 1H, H arom.).

Compound ***2b***: ^{1}H-NMR, 200 MHz ($CDCl_3$/TMS): δ 2.35 (s, 3H, NCH_3); 2.5 (s, 3H, N–CH_3); 2.75 (AB part of an ABX, 2H, CH_2, broad); 5.0 (broad dd, X part of an ABX, 1H, CH); 7.1 (m, 3H, H arom.); 7.5 (broad d, 1H, H arom.).

7 Flash chromatography on silicagel using as eluent NEt_3/Et_2O/hexane 10/45/45 for compound **3a** and NEt_3/AcOEt 10/90 for compounds **3b** and **3c**.

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12 For resolution of the complexes see: (a) A. Solladié-Cavallo, G. Solladié and E. Tsamo, J. Org. Chem., 44 (1979) 4189; (b) S.G. Davies and C.L. Goodfellow, J. Chem. Soc., Perkin Trans. I, (1989) 192.

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