Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 1867–1870

TETRAHEDRON: *ASYMMETRY*

# Enantiospecific nucleophilic substitution of the dimethylamino group in (*R*)-tricarbonyl[-{(1-dimethylamino)ethyl}-$\eta^6$-benzene]chromium

Ulli Englert, Albrecht Salzer * and Daniela Vasen

*Institut für Anorganische Chemie, RWTH Aachen, D 52056 Aachen, Germany*

Received 5 May 1998; accepted 13 May 1998

**Abstract**

Treatment of (*R*)-tricarbonyl[-{(1-dimethylamino)ethyl}-$\eta^6$-benzene]chromium **1** with esters of chloroformic acid leads to enantiospecific substitution of the dimethylamino group for a chloro substituent. The chloro group in turn can enantiospecifically be replaced for a diphenylphosphino group. Both reactions proceed with retention.


There has been great interest in the synthesis of optically active phosphines as ligands for asymmetric synthesis. Particular attention has recently been paid to phosphines having an organometallic backbone. Chiral ferrocenyl phosphines have found a number of important industrial applications.[1] A major reason for this is that a very efficient methology has been developed for the separation of enantiopure {1-(dimethylamino)ethyl}ferrocene from racemic precursors and its enantioselective transformation into a variety of chelating phosphine ligands.[2]

Similar use of (arene)chromium complexes as chiral ligands is still rare, with a few notable examples published by Uemura et al.[3,4] The synthesis of (*R*)-tricarbonyl[-{(1-dimethylamino)ethyl}-$\eta^6$-benzene]chromium **1** is in fact quite simple, starting from commercially available (*R*)-phenylethylamine.[5,6] However, no method has been established for the enantioselective substitution of the dimethylamino group, although it is possible to introduce planar chirality by enantioselective metallation and electrophilic substitution in the *ortho* position of the arene ring.[5]

The substitution of the dimethylamino or other leaving groups in the α-position of the ferrocene moiety is favoured by the stabilization of α-ferrocenyl carbocations[7,8] while a similar stabilization in the α-position of (arene)chromium tricarbonyl complexes is less pronounced, possibly due to the electron-withdrawing nature of the $Cr(CO)_3$ moiety. Enantiospecific substitution therefore occurs only under special conditions.[9,10]

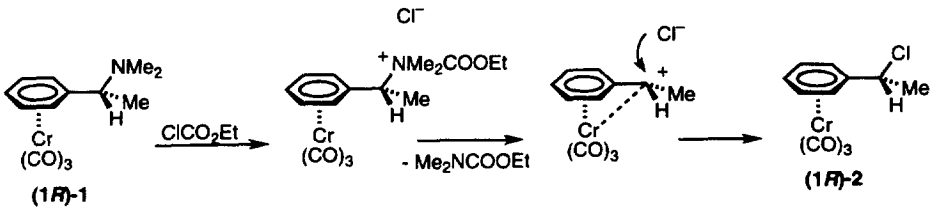
* Corresponding author. E-mail: albrecht.salzer@ac.rwth-aachen.de

0957-4166/98/$19.00 
*PII:* S0957-4166(98)00192-X

We have found that treatment of **1** with either ethyl chloroformate or chloroethyl chloroformate leads to clean substitution of the dimethylamino group and formation of tricarbonyl[-{(1-chloro)ethyl}-$\eta^6$-benzene]chromium **2** in 93% yield.[11]

This method is quite established for the conversion of tertiary amines into secondary amines, benzyl being the best leaving group.[12] Interestingly enough, the fate of the leaving group has never been fully established and it is not known whether this reaction proceeds enantiospecifically in organic compounds. We have performed a similar reaction on uncomplexed (*R*)-phenylethylamine and have isolated as the major aromatic product styrene, but only a minimum amount of phenylethylchloride, whose enantiomeric purity we have not been able to determine.

Compound **2** was found to be 96% enantiomerically pure by HPLC.[13] As the enantiomeric excess of the starting (*R*)-phenylethylamine was also 96%, the reaction is completely enantiospecific. A possible mechanism for the conversion is shown in Scheme 1.




Scheme 1.

The absolute configuration of **2** was established by X-ray crystal structure analysis[14,15,22–24] and was found to be (*R*)[16], so that the reaction had proceeded via retention (Fig. 1).

A chloride substituent, in contrast to the dimethylamino group, should be easily replaceable via nucleophilic substitution. We have therefore treated **2** with lithium diphenylphosphide (Scheme 2). This generates tricarbonyl[-{(1-diphenylphosphino)ethyl}-$\eta^6$-benzene]chromium **3** in 62% yield.[17] Enantiomeric excess after recrystallization was determined by NMR via complexation to [chloro{(*R*)-(dimethylamino-*kN*)phenyl-*kC*$^1$}palladium]$_2$[18] and was found to be >99%. The absolute configuration was also determined by X-ray crystal structure analysis[19,20,23,24] and was also found to be have an (*R*) configuration (Fig. 1).[21,25]

This result is somewhat surprising, as nucleophilic substitution in such a reaction would normally be expected to proceed via inversion and not retention. It is not yet clear, which factors govern the

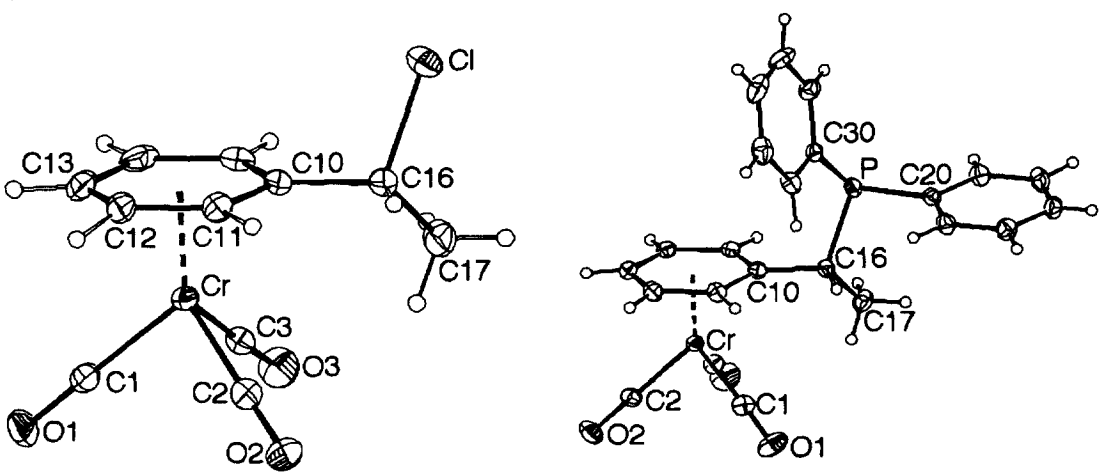
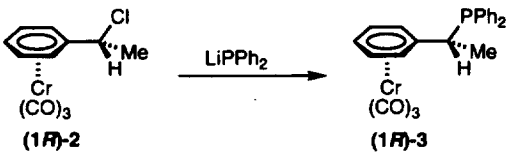



Fig. 1. X-Ray structures of **2** (left) and **3** (right) (ORTEP)




(1*R*)-2 (1*R*)-3

Scheme 2.

stereochemistry of this reaction, as it seems unlikely that under the reaction conditions a metal-stabilized carbocation is formed.

We are currently examining the reactivity of other nucleophiles with **2**. The method outlined in this paper should open the route into a large variety of optically active arenes starting from readily available **1**.

## Acknowledgements

The authors gratefully acknowledge financial support by the Deutsche Forschungsgemeinschaft DFG within the Collaborative Research Center (SFB) 380: 'Asymmetric Syntheses with Chemical and Biological Means' and by the Fonds der Chemischen Industrie. We thank Arne Gerlach from Prof. Bolm's group for performing the HPLC measurements.

## References

1. Togni, A. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1475–1477.
2. Hayashi, T. In *Ferrocenes*, Togni, A.; Hayashi, T. Eds. VCH: Weinheim, 1995; pp. 105–142.
3. Uemura, M.; Miyake, R.; Nishimura, H. *Tetrahedron: Asymmetry* **1992**, *3*, 213–216.
4. Hayashi, Y.; Sakai, H.; Kaneta, M.; Uemura, M. *J. Organomet. Chem.* **1995**, *503*, 143–148.
5. Davies, S. G.; Blagg, J.; Goodfellow, C. L.; Sutton, K. H. *J. Chem. Soc., Perkin Trans. 1* **1987**, *35*, 1805–1811.
6. Heppert, J. A.; Aubé, J.; Thomas-Miller, M. E.; Milligan, M. L.; Takusagawa, F. *Organometallics* **1990**, *9*, 727–739.
7. Richards, J. H.; Hill, E. A. *J. Am. Cem Soc.* **1959**, *81*, 3484–3485.
8. Turbitt, T. D.; Watts, W. E. *J. Chem. Soc., Perkin Trans. 2* **1974**, 177–184.
9. Davies, S. G.; Donohoe, T. J. *Synlett* **1993**, 323–332.
10. Top, S.; Jaouen, G.; McGlinchey, *J. Chem. Soc., Chem Commun.* **1980**, 1110.
11. Preparation of **1**: A stirred solution of (+)-(*R*)-($\eta^6$-α-N,N-dimethylaminoethylbenzene)tricarbonylchromium(0) (5.00 g, 17.5 mmol) in $Et_2O$ was treated dropwise with chloroethylformiate (2.17 g, 20.0 mmol) at −40°C. The solution was stirred overnight without cooling, filtered, and then evaporated. The residue was recrystallised from mesitylene/hexane at −30°C to give **1** as yellow needles (4.52 g, 16.3 mmol, 93%). M.p. 49–50°C, [α] −41.2 (*c* 1.49, $CHCl_3$); (found: C, 47.65; H, 3.22. $C_{11}H_9ClCrO_3$ requires: C, 47.76; H, 3.28%); $\nu_{max}$ 1969 and 1894 (CO) $cm^{-1}$; $^1$H-NMR ($C_6D_6$, 200 MHz) δ 4.59 (dm, 1H, *ortho* H), 4.51 (dm, 1H, *ortho* H), 4.33–4.23 (m, 3H, *meta* and *para* H), 4.11 (q, 1H, J=6.77 Hz, *CH*ClCH$_3$), 1.31 (d, 3H, J=6.77 Hz, CHClC*H*$_3$); $^{13}$C-NMR ($C_6D_6$, 50 MHz) δ 232.72 (*CO*), 110.98 (*ipso* C), 93.63, 92.40, 91.33 90.98, 90.07 (*ortho*, *meta* and *para* C) 56.73 (*C*HClCH$_3$), 23.71 (CHCl*C*H$_3$).
12. For a review see: Cooley, J. H.; Evain, E. J. *Synthesis* **1989**, 1–7.
13. Column: CHIRALCEL OD; eluent: hexane:*i*-propanol (9:1).
14. Intensity data were collected at −70°C on a CAD4 diffractometer with the ω/2θ mode using graphite monochromated CuKα radiation, λ=1.54184 Å. Further details on the structure determination are available from the Cambridge Crystallographic Data Center, CSD-xxxxxx.
15. Crystal data of **2**: formula $C_{11}H_9ClCrO_3$, $M_r$=276.64; orthorhombic $P2_12_12_1$ (No. 19); *a*=9.311(3), *b*=9.316(2), *c*=12.838(7) Å, *U*=1113.6(7) Å$^3$, *Z*=4. There were 3465 reflections in the range 5.0<θ<70.0, numerical absorption correction,[22] 1950 independent observed intensities with *I*>1.0 σ(*I*). Structure solution with direct methods.[23] Refinement on structure factors[24] of 145 variables with anisotropic displacement parameters for non-hydrogen atoms and riding hydrogen atoms resulted in *R*=0.043, $R_w$=0.050, GOF=1.100.

16. A tentative refinement of the alternative enantiomorph resulted in $R_w$=0.099.
17. Preparation of **2**: Diphenylphosphine (0.67 g, 3.61 mmol) in dry THF (90 ml) was treated dropwise with *n*-BuLi (1.6 M in hexane, 2.26 ml, 3.61 mmol) at −78°C. After stirring at −78°C for 1 h, a solution of (−)-(*R*)-($\eta^6$-α-chloroethylbenzene)tricarbonylchromium(0) (1.00 g, 3.61 mmol) in dry THF (5 ml) was added dropwise. The reaction mixture was warmed overnight and the solvent was removed. The residue was dissolved in $Et_2O$ and filtered. The solution was evaporated and the residue chromatographed on silica gel [elution with ethylacetate]. Crystallisation from ethylacetate/hexane at −30°C furnished the pure product as yellow needles (0.94 g, 2.20 mmol, 61%). M.p. 150°C; [α] −17.8 (*c* 1.51, $CHCl_3$); (found: C, 64.83; H, 4.49. $C_{23}H_{19}CrO_3P$ requires: C, 64.79; H, 4.49%); $\nu_{max}$ 1961 and 1887 (CO) $cm^{-1}$; UV 317 $nm^{-1}$; $^1$H-NMR ($C_6D_6$, 500 MHz) δ 7.36–6.87 (m, 10H, P*Ph*$_2$), 4.65 (brd, 1H, *ortho* H), 4.38 (trd, 1H, J=6.41 Hz, J=1.22 Hz, *meta* H), 4.32 (trtr, 1H, J=6.26 *para* H), 4.21 (brd, 1H, *ortho* H), 4.11 (trd 1H, J=6.26 Hz, J=1.22 Hz, *meta* H) 2.96 (dq, 1H, $J_{HH}$=7.02 Hz, $J_{PH}$=3.66 Hz, C*H*(PPh$_2$)CH$_3$), 1.30 (dd, 3H, $J_{PH}$=13.73 Hz, $J_{HH}$=7.02 Hz, CH(PPh$_2$)C*H*$_3$); $^{13}$C-NMR ($C_6D_6$, 150 MHz) δ 233.78 (*C*O), 115.34 (d, $J_{CP}$=14.7 Hz, *ipso* C), 95.83, 92.13, 91.88, 91.77 (d, $J_{CP}$=5.5 Hz) 90.86 (*ortho*, *meta* and *para* C), 37.34 (d, $J_{CP}$=17.7 Hz, *C*H(PPh$_2$)CH$_3$), 17.38 (d, $J_{CP}$=18.9 Hz, CH(PPh$_2$)*C*H$_3$); $^{31}$P-NMR ($C_6D_6$, 202 MHz) δ +10.39.
18. Otsuka, S.; Nakamura, A.; Kano, T.; Tani, K. *J. Am. Chem. Soc.* **1971**, *93*, 4301–4303. $^{31}$P-NMR data of the (*R*,*R*)-diastereomer: +49.44 ppm. $^{31}$P-NMR data of the (*R*,*S*)-diastereomer: +50.16 ppm.
19. Intensity data were collected at −70°C on a CAD4 diffractometer with the ω mode using graphite monochromated MoKα radiation, λ=0.71073 Å. Further details on the structure determination are available from the Cambridge Crystallographic Data Center, CSD-xxxxxx.
20. Crystal data of **3**: formula $C_{23}H_{19}CrPO_3$, $M_r$=426.38; orthorhombic $P2_12_12_1$ (No. 19); *a*=10.657(3), *b*=11.883(4), *c*=16.036(6) Å, *U*=2031(1) Å$^3$, *Z*=4. There were 10232 reflections in the range 2.0<θ<28.0 and 4417 independent observed intensities with *I*>1.0 σ(*I*). Structure solution with direct methods.[23] Refinement on structure factors[24] of 329 variables with anisotropic displacement parameters for non-hydrogen atoms and isotropically refined hydrogen atoms resulted in *R*=0.032, $R_w$=0.031, GOF=0.801.
21. The Flack enantiomorph polarity parameter[25] obtained was 0.006(16).
22. Coppens, P.; Leiserowitz, L.; Rabinovich, D. *Acta Crystallogr.* **1965**, *18*, 1035–1038.
23. Sheldrick, G. M. *SHELXS86, Program for Structure Solution*, **1986**, University of Göttingen, Germany.
24. ENRAF-Nonius, *SDP Version 5.0*, **1989**, Delft, The Netherlands.
25. Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881.