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ASYMMETRIC SYNTHESIS OF N-ACETYL-1-PHENYLETHYLAMINE

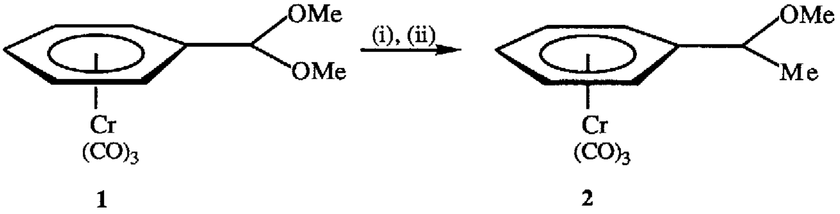
Stephen G. Davies[a]*, Roger F. Newton[b] and Jonathan M.J. Williams[a],

[a]The Dyson Perrins Laboratory, South Parks Road, Oxford, OX1 3QY, UK.
[b]Glaxo Group Research Ltd., Ware, Herts, SG10 0DJ, UK.

Abstract: The chromium tricarbonyl complex of the benzaldehyde acetal derived from RR-butane-2,3-diol undergoes completely stereoselective displacement, with retention of configuration, of the pro-R acetal oxygen on treatment with titanium tetrachloride and trimethyl aluminium: A subsequent Ritter reaction releases the RR-butane-2,3-diol intact and generates stereospecifically after decomplexation R-N-acetyl-1-phenylethylamine.

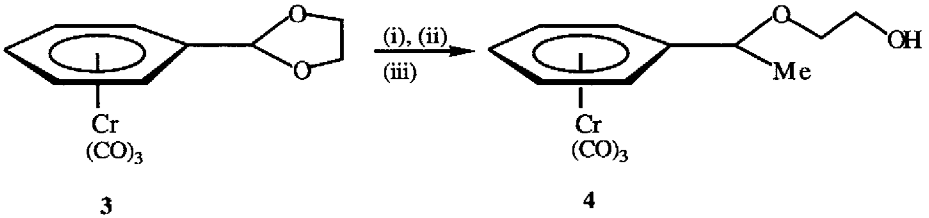
The use of chiral acetal templates for the asymmetric synthesis of secondary alcohols is now well established.[1,2] Treatment of acetals derived from chiral diols with two equivalents of Lewis acid in the presence of nucleophiles results in stereoselective S_N2 displacement with inversion of configuration of one of the diastereotopic benzylic oxygen functions.[1] However, since the primary products are necessarily ethers, destruction of the chiral diol used to prepare the acetal must occur in the step where the product alcohol is released from the auxiliary.[1] The chromium tricarbonyl group in arene chromium tricarbonyl complexes participates in the formation and stabilisation of benzylic carbonium ions.[3] Furthermore, chromium tricarbonyl stabilised carbonium ions are configurationally stable, allowing the solvolysis of benzylic leaving groups to be achieved with retention of configuration.[4] We describe here the combination of chiral acetal template and chromium tricarbonyl methodologies for the asymmetric synthesis of N-acetyl-1-phenylamine.

Thermolysis of chromium hexacarbonyl in the presence of the methanol derived acetal of benzaldehyde generated complex **1**. Treatment of complex **1** with 1-3 equivalents of titanium tetrachloride and trimethyl aluminium in dichloromethane at -78°C gave complex **2** in 80% yield after isolation. Complex **2** was essentially inert to further substitution under the reaction conditions; the formation of cumene chromium tricarbonyl was not observed.



Reagents: (i) $TiCl_4$, (ii) Me_3Al

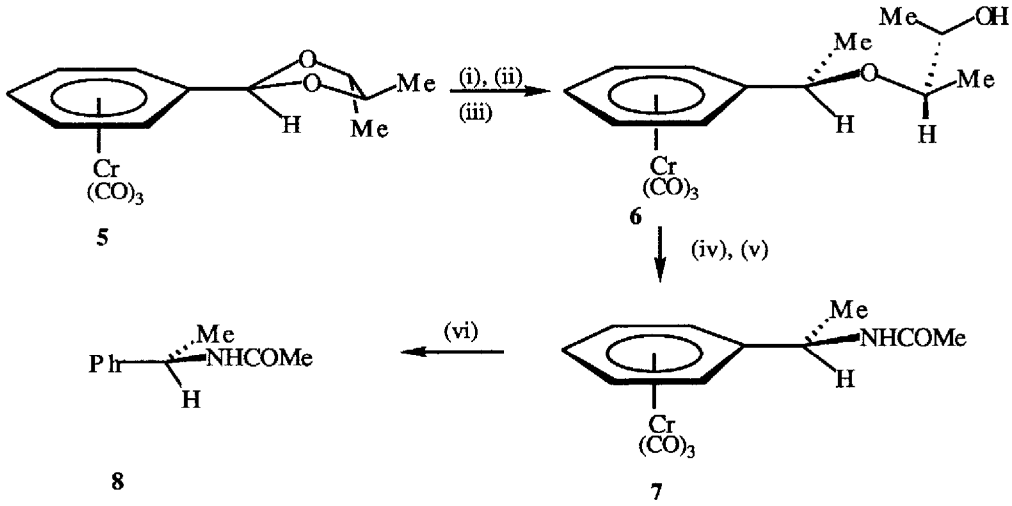
Similar treatment of the chromium tricarbonyl complex of the ethylene glycol derived acetal of benzaldehyde **3** again resulted in substitution of only one of the benzylic oxygen substituents generating **4**.[5] In this case, however, the best yields of product **4**, (73%) were obtained in the presence of just one equivalent of titanium tetrachloride, with starting material being recovered intact in the presence of two or more equivalents.



Reagents: (i) $TiCl_4$, (ii) Me_3Al, (iii) H_3O^+

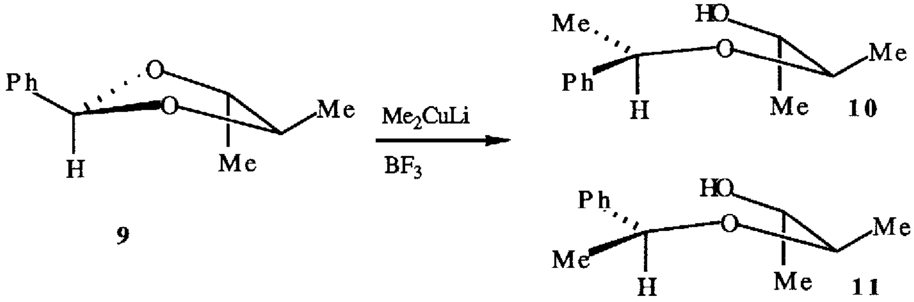
The difference in behaviour between complexes **1** and **3** in the presence of excess Lewis acid is consistent with an S_N1 type mechanism; ionisation being promoted by coordination of titanium tetrachloride to one acetal oxygen and by participation of lone pairs on the chromium and the other acetal oxygen. In complex **1** coordination of one of the acetal oxygens to titanium tetrachloride sterically disfavours complexation of the other acetal oxygen and hence the reaction can proceed even in the presence of excess Lewis acid. In complex **3**, however, coordination of both acetal oxygens is possible with coordination of the second disfavouring formation of the benzylic carbonium ion as well as removing the possibility of oxygen lone pair participation. On the other hand double coordination would favour an S_N2 type mechanism, which operates in the case of uncomplexed acetals.[6]

Treatment of complex **1** with commercial [7] (-)-RR-butane-2,3-diol in the presence of pyridinium tosylate produced complex (-)-**5**. Exposure of complex **5** to one equivalent of titanium tetrachloride and trimethylaluminium generated RRR-**6** stereoselectively in 72% yield. Although complex **6** was diastereoisomerically pure by 300 MHz ^1H nmr spectroscopy, the free ligand, obtained by oxidative decomplexation, contained a trace of the other diastereoisomer (97.5% d.e). The methylation was, however, completely selective at -95°C. Treatment of an acetonitrile solution of pure RRR-**6** with concentrated sulphuric acid gave after work up R-**7** and RR-butane-2,3-diol, the latter being recovered stereochemically intact. Finally oxidative decomplexation of **7** by exposure of an ether solution to air and sunlight liberated (+)-R-N-acetyl-1-phenylethylamine **8** ($[\alpha]_D$ = +137°; lit[8,9] $[\alpha]_D$ = +140° both c=1, $CHCl_3$, 22°C). The ^1H nmr chiral shift reagent, (+)-trifluoroanthracenylethanol gave clean separation of the methyl doublets for the enantiomers of racemic **8**. The amide (+)-R-**8** was assessed as homochiral by this method, confirming the completely stereoselective nature of all of the reactions.

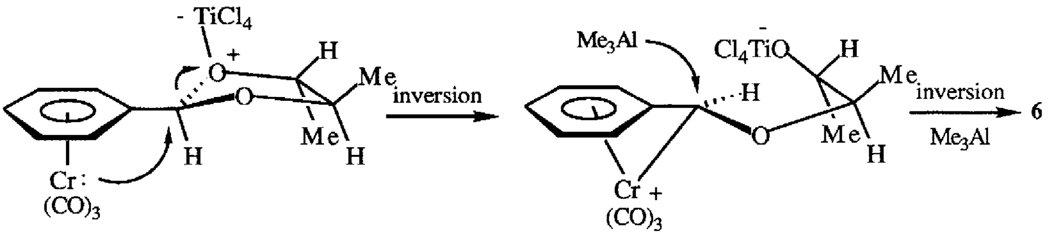


Reagents: (i) $TiCl_4$, (ii) Me_3Al, (iii) H_3O^+, (iv) MeCN, H_2SO_4, (v) H_2O, (vi) O_2, hv, Et_2O

Since the absolute configuration of (+)-**8** is known to be R the configuration of **7** can be assigned as R and that of **6**, assuming by analogy retention of configuration in the Ritter reaction,[9] as RRR. The pro-R acetal oxygen of complex **5** has therefore been displaced with retention of configuration by a methyl group. This procedure is therefore complementary to the uncomplexed case where the pro-R acetal oxygen is replaced with inversion of configuration. Alexakis *et al*[10] have examined a range of boron trifluoride - lithium dialkyl cuprate acetal cleavage reactions with **9** giving the lowest diastereoselectivity.



The reported ratio of **10** to **11** was 16:84, whereas oxidative decomplexation of pure RRR-**6**, and comparison of the ^1H nmr[10] data showed only **10** (>100:1) confirming the retention of configuration . The observed stereoselectivity for the complex is consistent with neighbouring group participation by chromium, in the expected[6b] displacement with inversion of the pro-R acetal oxygen, to generate intermediate **12** : the benzylic carbon to chromium bond thus formed subsequently undergoing displacement, again with inversion, by the trimethylaluminium.



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This procedure yields homochiral R-N-acetyl-1-phenylethylamine and allows for the recovery of the RR-butanediol without loss of stereochemical integrity. The chromium stabilised carbonium ion **12** reacts with nucleophiles other than trimethylaluminium, and the scope of this methodology is currently being investigated.

Acknowledgement: We thank Glaxo Group Research (Ware) for a studentship (to JMJW).

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