Asymmetric syntheses of benzaldehyde and *o*-anisaldehyde methyl isopropyl acetals

Stephen G. Davies* and Luís M. A. R. B. Correia

The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford, UK OX1 3QY

Asymmetric syntheses of (+)-(αR)-benzaldehyde and (+)-(αR)-*o*-anisaldehyde methyl isopropyl acetals in 93 and >95% ee respectively using methodology based on the stereoselective reactions of enantiopure (*ortho*-substituted benzaldehyde) chromium tricarbonyl complexes are described.

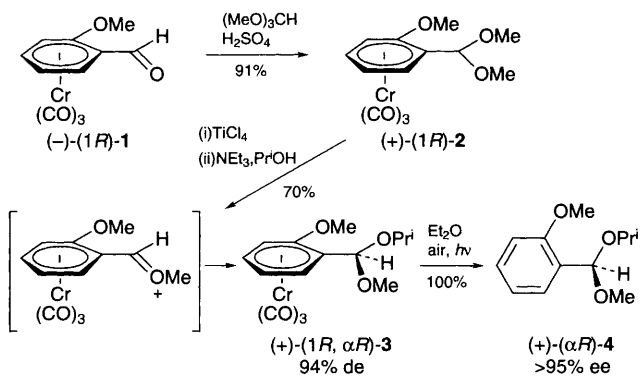
The Lewis acid-promoted reaction of acetals with a nucleophile is a synthetic method with a wide range of applications.[1] These include aldol reactions,[2] alkylations,[3] allylations,[4] intramolecular cyclisations[5] and cyanations.[6] The application of this method in asymmetric synthesis has relied mainly on the use of homochiral, cyclic acetals, which are derived from enantiopure diols and the corresponding aldehyde.[7] Stereoselective cleavages of acyclic acetals derived from aldehydes possessing α- or β-stereogenic centres have also been reported.[8] The asymmetric induction in the reactions of both cyclic and acyclic acetals is provided by stereogenic centres placed away from the acetal carbon, which is the actual reaction centre. The generality of the Lewis acid promoted reaction of acetals with a nucleophile has prompted extensive investigations into the mechanism of this process with efforts in particular being focussed on the dichotomy of S_N1 *vs.* S_N2 substitutions at the acetal carbon.[9] These mechanistic investigations have been hampered by the inaccessibility of enantiopure acetals in which the acetal carbon is the only stereogenic centre, *i.e.* where the oxocarbenium ion intermediate in a purely S_N1 process would be achiral and hence unbiased towards approach of nucleophiles.

We describe here the first methodology applicable to the asymmetric synthesis of an acetal in which the acetal carbon is the only stereogenic centre. The methodology is based on the stereoselective reactions of readily available enantiopure (*o*-substituted benzaldehyde)chromium tricarbonyl complexes,[10,11] and gives access to (+)-(α*R*)-benzaldehyde and (+)-(α*R*)-*o*-anisaldehyde methyl isopropyl acetals.

The starting material (−)-(1*R*)-(*o*-anisaldehyde)chromium tricarbonyl (−)-(1*R*)-**1** was readily obtained *via* our previously reported kinetic resolution involving the diastereoisomeric imines formed by reaction of the racemate with L-valinol.[10] Treatment of enantiopure aldehyde (−)-(1*R*)-**1** with trimethylorthoformate and sulfuric acid afforded the dimethyl acetal (+)-(1*R*)-**2** in 91% yield, {$[\alpha]_D^{25}$ +204 (*c* 0.48, $CHCl_3$)}. Treatment of acetal (+)-(1*R*)-**2** with titanium tetrachloride at −78 °C followed by quenching with triethylamine and isopropanol afforded the methyl isopropyl acetal (+)-(1*R*,αR)-**3** with 94% de in 70% yield, {$[\alpha]_D^{25}$ +227 (*c* 2.29, $CHCl_3$)}, Scheme 1. The relative configurations within **3** were assigned from an X-ray crystal structure analysis[12] of racemic (1*RS*,α*RS*)-**3** with the absolute configuration following from that previously established for (−)-(1*R*)-**1**.[10] The stereoselective formation of **3** is consistent with ionisation of the dimethylacetal to give a chromium-stabilised oxocarbenium ion in a conformation where the oxocarbenium ion lies *anti* to the bulky *ortho*-substituent in order to minimise non-bonded interactions. The nucleophile then attacks from the *exo* face, away from the large chromium tricarbonyl unit to generate (+)-(1*R*,αR)-**3** stereoselectively.[13]

Decomplexation of (+)-(1*R*,α*R*)-**3** was achieved by dissolution in diethyl ether and exposure to air and sunlight. This afforded (+)-(α*R*)-*o*-anisaldehyde methyl isopropyl acetal (+)-(α*R*)-**4** in quantitative yield {$[\alpha]_D^{25}$ +20.9 (*c* 1.15, $CHCl_3$)}. The sample was shown to be enantiopure (>95% ee) by ^1H NMR spectroscopic analysis upon comparison with authentic racemic (α*RS*)-**4** using (+)-(1*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol as the chiral shift reagent.

We were also interested in obtaining the parent benzaldehyde methyl isopropyl acetal in non-racemic form and approached this synthesis using homochiral (*o*-trimethylsilylbenzaldehyde)-chromium tricarbonyl as the enantiopure benzaldehyde equivalent.[11] The starting (−)-(1*R*)-(*o*-trimethylsilylbenzaldehyde) chromium tricarbonyl (−)-(1*R*)-**5** was obtained by chromatographic separation of the diastereoisomeric imines formed by reaction of racemic (1*RS*)-**5** with L-valinol.[11] Treatment of (−)-(1*R*)-**5** with trimethylorthoformate and sulfuric acid afforded the dimethyl acetal (+)-(1*R*)-**6** in 96% yield {$[\alpha]_D^{21}$ +36.2 (*c* 0.78, $CHCl_3$)}. Reaction with titanium tetrachloride at −78 °C followed by quenching with triethylamine and isopropanol was not very stereoselective affording the epimeric methyl isopropyl acetals (−)-(1*R*,α*S*)-**7** and (+)-(1*R*,α*R*)-**8** in the ratio 1:2, Scheme 2. The decrease in selectivity relative to the *o*-anisaldehyde series is a consequence of the greater steric bulk of the trimethylsilyl group.[11] The epimers (−)-(1*R*,α*S*)-**7** and (+)-(1*R*,α*R*)-**8** were separable by column chromatography on alumina grade V, (eluent light petroleum–Et_2O, 20:1). The absolute configuration of the major epimer (+)-(1*R*,α*R*)-**8** {$[\alpha]_D^{24}$ +19.8 (*c* 0.40, $CHCl_3$)} was established from an X-ray crystal structure analysis.[14] This also unambigously established the absolute configuration of (−)-(1*R*)-**5**.[11] The absolute configuration of (−)-(1*R*,α*S*)-**7** {$[\alpha]_D^{24}$ −4.1 (*c* 0.75, $CHCl_3$)} follows from that of (+)-(1*R*,α*R*)-**8**. Treatment of acetal (+)-(1*R*,α*R*)-**8** with hydrated tetrabutylammonium fluoride followed by decomplexation afforded (+)-(α*R*)-benzaldehyde methyl isopropyl acetal (+)-(α*R*)-**9** {$[\alpha]_D^{25}$ +19.2 (*c* 0.78, $CHCl_3$)}. The sample was shown to have an ee of 93% by ^1H NMR spectroscopic analysis upon



Scheme 1

comparison with authentic racemic (αRS)-**9** using (+)-(1*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol as the chiral shift reagent.

In summary, the first asymmetric syntheses of acetals in which the acetal carbon is the only stereogenic centre have been achieved *via* methodology based on stereoselective reactions of readily available enantiopure (*o*-substituted benzaldehyde)-chromium tricarbonyl complexes and gives access to (+)-(α*R*)-benzaldehyde and (+)-(α*R*)-*o*-anisaldehyde methyl isopropyl acetals in 93 and >95% ee respectively.

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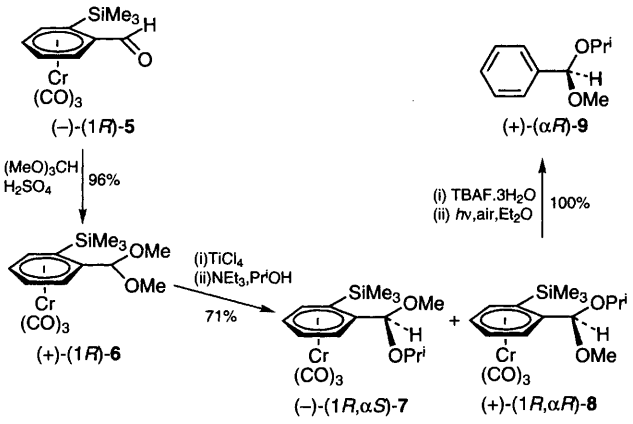

Scheme 2

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