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Asymmetric Synthesis of 2-Aryl-Tetrahydropyrans *via* Arene Chromium Tricarbonyl Methodology 1: *cis*-2-Aryl-4-Chloro-Tetrahydropyrans

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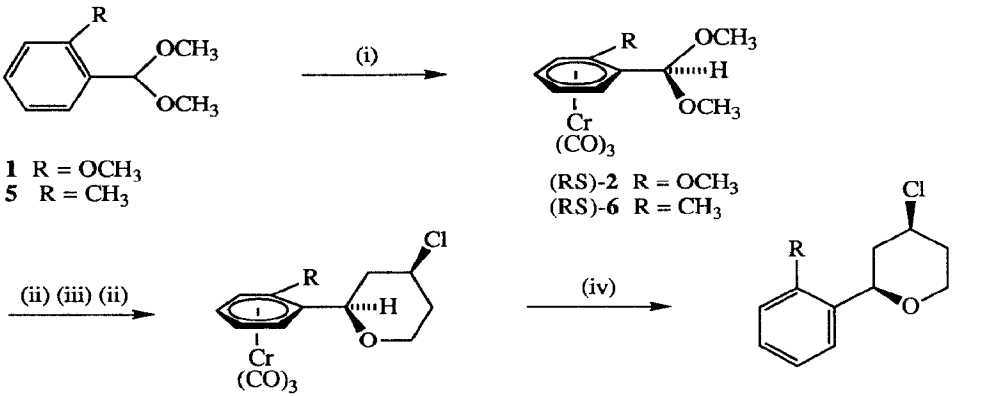
Abstract: Treatment of acetals derived from *ortho* substituted benzaldehyde chromium tricarbonyl complexes and methanol with homoallylic alcohol and titanium tetrachloride produces the corresponding (RS,RS,SR,RS)-*cis*-2-aryl-4-chloro-tetrahydropyran complexes completely diastereoselectively. Thus, by this method, homochiral (R)-(-)-*o*-anisaldehyde chromium tricarbonyl is converted, after decomplexation, to homochiral (R,S)-(+)-*cis*-2-*o*-anisyl-4-chloro-tetrahydropyran.

The stereoselective synthesis of racemic *all-cis*-2-phenyl-4-halo-6-alkyl-tetrahydropyrans *via* intramolecular Lewis acid promoted cyclisations of hemiacetals derived *in situ* from homoallylic alcohols and benzaldehyde has been reported by Taddei *et al.*[1] We describe herein a general approach to the asymmetric synthesis of homochiral 2-aryl-4-chloro-tetrahydropyrans based on arene chromium tricarbonyl methodology. The chromium tricarbonyl complexes of unsymmetrical *ortho* disubstituted arenes are chiral and this has been exploited for the asymmetric synthesis of, for example, α-substituted benzyl alcohols *via* highly stereoselective nucleophilic additions to homochiral *ortho* substituted benzaldehyde chromium tricarbonyl complexes.[2] Complexation of an arene to chromium tricarbonyl greatly increases the ease of formation and stability of benzylic carbonium ions.[3] It was expected,[4] therefore, that the chromium tricarbonyl moiety would promote the formation of oxonium ions from complexed benzaldehyde acetals and furthermore that the presence of an *ortho* substituent should render the reactions of such oxonium ions stereoselective.

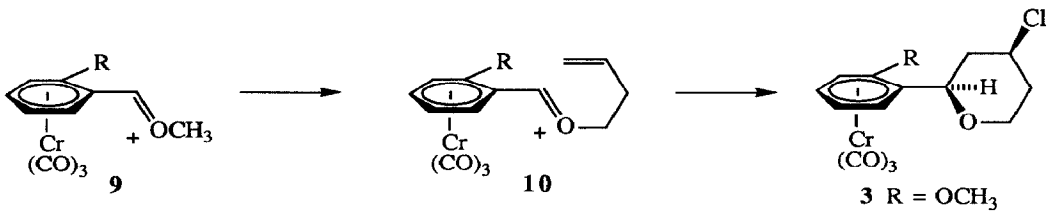
Thermolysis of chromium hexacarbonyl in the presence of the acetal **1**, derived from *o*-anisaldehyde and methanol, generated the racemic complex (RS)-**2** (75%). Sequential treatment of (RS)-**2** at -78°C with titanium tetrachloride (0.5 equivalent), but-3-en-1-ol (3 equivalents) and titanium tetrachloride (1.5 equivalents) generated, after 36h, the racemic tetrahydropyran complex (RS,RS,SR)-**3** (Scheme 1).[5] ^{1}H Nmr spectroscopic analysis of the crude product confirmed complete reaction and demonstrated that only a single product diastereoisomer had been formed. Work-up gave pure **3** in 85% yield. Oxidative decomplexation of **3** gave, in essentially quantitative yield, racemic *cis*-2-*o*-anisyl-4-chloro-tetrahydropyran (RS,SR)-**4** in 83% overall yield from **2**. Analysis of the ^{1}H nmr coupling constant data for **3** established that the C2-H and C4-H were axial, hence the 2- and 4-substituents must be equatorial and, therefore, *cis*.[6] The assignment of the configuration of the *o*-anisyl chromium tricarbonyl moiety in complex **3** relative to the configurations at C2 and C4 was made on mechanistic grounds (*vide infra*).



Scheme 1: Reagents: (i) $Cr(CO)_6$; (ii) $TiCl_4$, -78°C; (iii) CH_2=$CHCH_2CH_2OH$; (iv) O_2, Et_2O, hv.

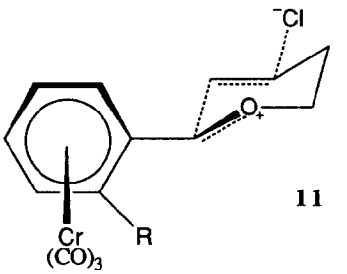
In an analogous sequence of reactions, the acetal **5**, derived from *o*-tolualdehyde and methanol, gave on complexation racemic (RS)-**6** (71%), then on cyclisation complex (RS,RS,SR)-**7** and after decomplexation *cis*-2-*o*-tolyl-4-chloro-tetrahydropyran, (RS,SR)-**8**. The conversion of **6** to **8** occurred in 90% overall yield with the cyclisation again being completely stereoselective by ^{1}H nmr spectroscopic analysis, which also revealed the *cis* relationship of the tetrahydropyranyl substituents.[7]

The completely stereoselective formation of complexes **3** and **7** is consistent with the following mechanism: The first portion of titanium tetrachloride induces formation of the oxonium ion **9**, which is trapped by the homoallylic alcohol. The second portion of titanium tetrachloride forms the oxonium ion **10** which adopts the most favourable conformation with the benzylic hydrogen *syn* to the *ortho* substituent. This oxonium ion is then trapped intramolecularly by the olefin which approaches the least hindered face, away from the bulky chromium tricarbonyl, thus setting the relative stereochemistry between the arene chromium tricarbonyl moiety and C2 (Scheme 2).[8]



Scheme 2

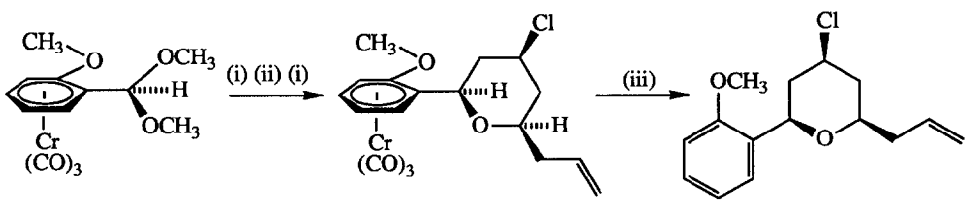
The relative stereochemistry between C2 and C4 suggests the chair transition state **11** with the aryl chromium tricarbonyl adopting an equatorial position and with antiperiplanar addition of the oxonium and chloride ions across the double bond.



11

Although the mechanism outlined above explains the formation of (SR,RS,SR)-**3** and (RS,RS,SR)-**7**, the involvement of an S_N2[9] cylisation of the acetal or non simultaneous carbon - chlorine bond formation[10] are not excluded.

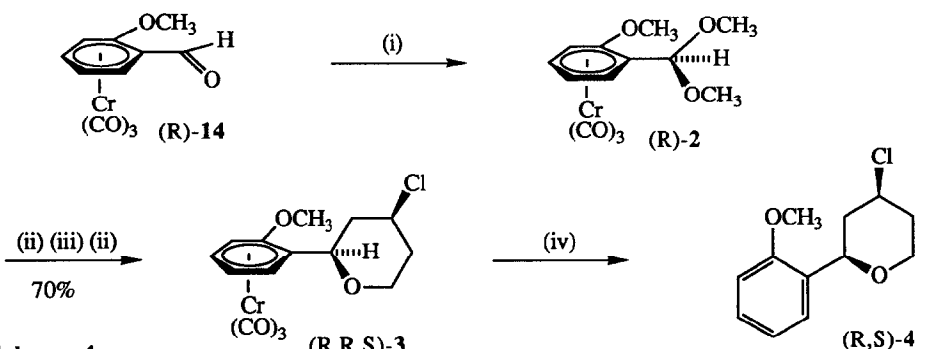
Treatment of the acetal complex **2** sequentially with titanium tetrachloride, hepta-1,6-dien-4-ol and titanium tetrachloride gave the complex (RS,RS,SR,RS)-**12**, and, after decomplexation, *all-cis*-2-*o*-anisyl-4-chloro-6-allyl-tetrahydropyran, (RS,SR,RS)-**13** (Scheme 3). The relative stereochemistry within **13** was established by ^1H nmr spectroscopy:[11] Coupling constant data established axial hydrogens on C2, C4 and C6, which was confirmed by nOe experiments.



(RS)-**2** (RS,RS,SR,RS)-**12** (80%) (RS,SR,RS)-**13** (96%)

Scheme 3: Reagents: (i) $TiCl_4$, -78°C; (ii) $(CH_2{=}CHCH_2)_2CHOH$ (iii) O_2, Et_2O, hv.

Homochiral *o*-anisaldehyde chromium tricarbonyl **14** is readily available *via* kinetic resolution with L-valinol.[12] The acetal, derived from (R)-(-)-**14** on treatment with methyl orthoformate and acid, (R)-(+)-**2**,



(R)-**14** (R)-**2** (R,R,S)-**3** (R,S)-**4**

Scheme 4:

Reagents: (i) H_2SO_4, $(CH_3O)_3CH$; (ii) $TiCl_4$, -78°C; (iii) $CH_2{=}CHCH_2CH_2OH$; (iv) O_2, Et_2O, hv.

gave, on treatment with titanium tetrachloride and but-3-en-1-ol as above, the cyclised complex (R,R,S)-(+)-**3** as a single diastereoisomer by ^{1}H nmr spectroscopy (de >96%), $[\alpha]_D^{22}$ +197.5 (c = 0.08, $CHCl_3$) (Scheme 4). Decomplexation of (R,R,S)-(+)-**3** gave (R,S)-(+)-*cis*-2-*o*-anisyl-4-chloro-tetrahydropyran (R,S)-(+)-**4** which was judged to be diastereomerically pure and homochiral (>98% ee), $[\alpha]_D^{22}$ +93.7 (c = 0.34, $CHCl_3$) by ^{1}H nmr spectroscopic analysis in the presence of the chiral shift agent (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol and in comparison with a racemic sample of **4**.

In conclusion we have demonstrated the potential of arene chromium tricarbonyl methodology for the asymmetric synthesis of *cis*-2-aryl-4-chloro-tetrahydropyrans.

Acknowledgement: We thank ICI Pharmaceuticals and the SERC for a CASE award (to T.J.D.).

References and notes:

1. L. Coppi, A. Ricci and M. Taddei, *J. Org. Chem.*, 1988, **53**, 911, and references therein.

2. L. A. Bromley, S. G. Davies and C. L. Goodfellow, *Tetrahedron: Asymmetry*, 1991, **2**, 139. See also ref 12.

3. J. D. Holmes, D. A. K. Jones, and R. Pettit, *J. Organometal. Chem.*, 1965, **4**, 324.

4. S. G. Davies, R. F. Newton and J. M. J. Williams, *Tetrahedron Lett.*, 1989, **22**, 2967.

5. For a description of the application of the Cahn-Ingold-Prelog notation of absolute stereochemistry within molecules possessing planar chirality, such as arene chromium tricarbonyl complexes, see K. Schlogl, *Topics in Stereochem.*, 1967, **1**, 39. For the purposes of this paper, the aldehyde, acetal or tetrahydropyranyl substituent is assumed to be attached to the 1-position of the arene. The absolute stereochemistry of the arene chromium tricarbonyl fragment is specified at this centre regardless of the other ring substituent. In all cases the configuration of the arene chromium tricarbonyl moiety is specified first followed by the others in the usual way.

6. All new compounds have been fully characterised. Selected ^{1}H-nmr for **3**, δ 4.37 (dd, 1H, J= 11.8, 1.8, ArC**H**OCH_2), 4.18-4.05 (tt, 1H, J= 11.7, 4.4, C**H**Cl).

7. Selected ^{1}H nmr data for **7**, δ 4.16 (dd, 1H, J= 11.6, 2.0, ArC**H**OCH_2), 4.10 (tt, 1H, J= 11.8, 4.4, C**H**Cl).

8. This assignment of relative stereochemistry between the arene chromium tricarbonyl unit and C2 has been unambiguously confirmed by X-ray crystal structure analysis on a more complex example; see the following paper.

9. I. Mori, K. Ishihara, L. A. Flippin, K. Nozaki, H. Yammamoto, P. A. Bartlett and C. H. Heathcock, *J. Org. Chem.*, 1990, **55**, 6107; S. E. Denmark and T. M. Wilson, *J. Am. Chem. Soc.*, 1989, **111**, 3475.

10. S. D. Elakovich and J. D. Traynham, *J. Org. Chem.*, 1973, **38**, 873.

11. Selected ^{1}H nmr data for **12**, δ 4.40 (dd, 1H, J= 11.1, 1.9, ArC**H**OCH_2), 4.11 (tt, 1H, J= 11.8, 4.4, C**H**Cl). **13**, δ 4.67 (dd, 1H, J= 11.0, 1.8, ArC**H**OCH_2), 3.76 (tt, 1H, J= 11.8, 4.4, C**H**Cl). NOE studies, irradiation of C2-H gave the following enhancements: C4-H- 6.2%; C6-H-9.3%, irradiation of C4-H gave: C2-H-5.0%; C6-H-4.3%, irradiation of C6-H gave: C2-H-11.0%; C4-H-6.0%.

12. S. G. Davies and C. L. Goodfellow, *J. Chem. Soc., Perkin Trans. I*, 1989, 192.