Asymmetric Synthesis of α-Substituted *o*-Methoxybenzyl Alcohols *via* Stereoselective Additions to Kinetically Resolved *o*-Anisaldehyde-(tricarbonyl)chromium

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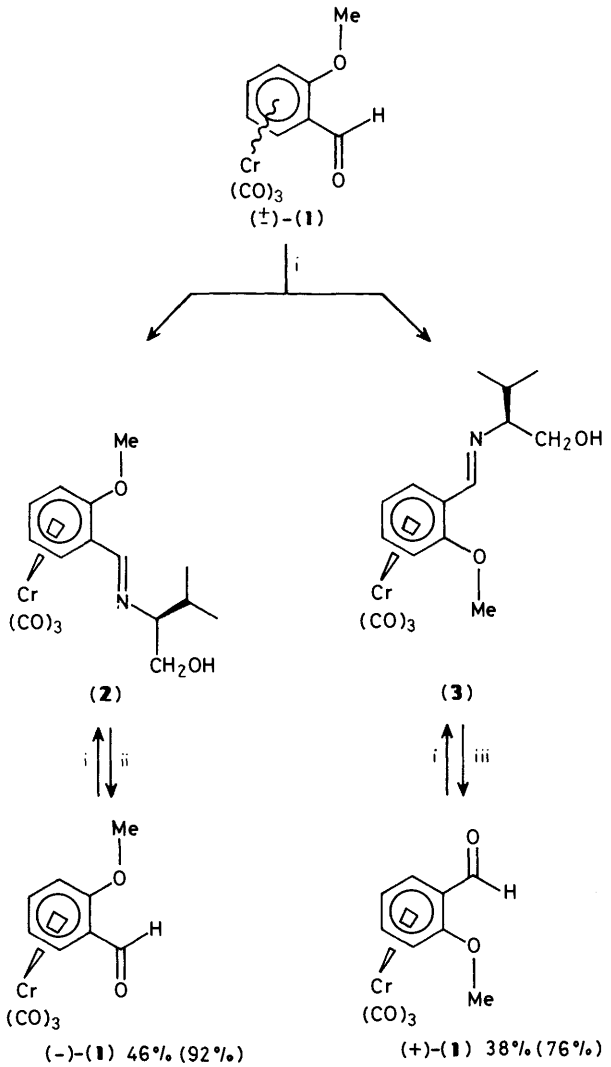
Homochiral (+)-*o*-anisaldehyde(tricarbonyl)chromium, prepared by a kinetic resolution procedure involving selective hydrolysis of the diastereoisomeric L-valinol derived imines, undergoes completely stereoselective addition reactions with methyl- and ethyl-magnesium iodide to give enantiomerically pure (−)-(*S*)-1-(*o*-methoxyphenyl)ethanol and (−)-(*S*)-1-(*o*-methoxyphenyl)propanol.

Stereoselective reactions of chiral *ortho*-substituted benzaldehyde(tricarbonyl)chromium complexes have been reported.[1–3] Although classical resolution procedures have been described for such complexes[4] their application to asymmetric synthesis has been limited by the availability of homochiral material. We describe herein a novel kinetic resolution methodology for the preparation of homochiral *o*-anisaldehyde(tricarbonyl)chromium and the asymmetric synthesis of α-substituted *o*-methoxybenzyl alcohols.

Thermolysis of hexacarbonylchromium with the ethanediol derived acetal of *o*-anisaldehyde, followed by hydrolysis, gave the racemic red complex *o*-anisaldehyde(tricarbonyl)chromium

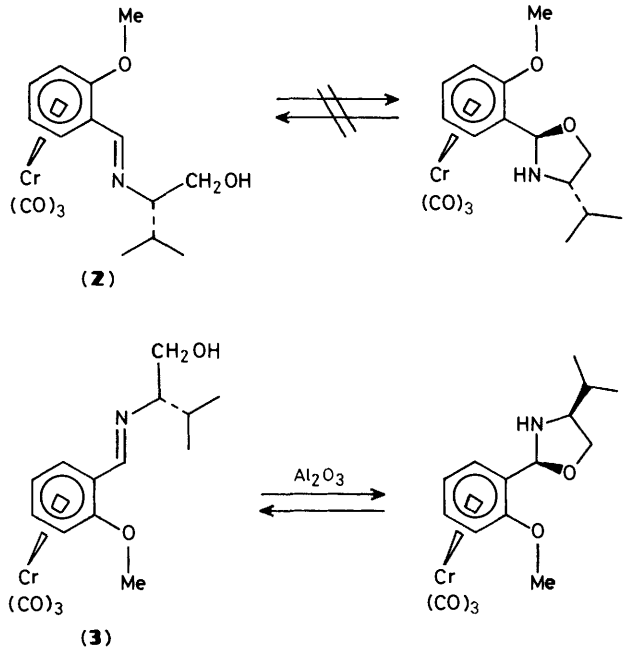
(±)-(**1**).[4] Treatment of (±)-(**1**) in diethyl ether with 1 equiv. of L-valinol (4.5 h, 20 °C) gave an orange solution of the diastereoisomeric imines (**2**) and (**3**). ^{1}H N.m.r. spectroscopy clearly identified (**2**) and (**3**) as imines not oxazolidines. Absorption of the ether solution of the mixture of (**2**) and (**3**) onto deactivated alumina (Grade V) and slow elution with diethyl ether gave a red compound identified as homochiral (−)-(**1**) (46%) $[\alpha]_D = -1\,023°$ (*c* 0.06 $CHCl_3$) {lit.,[4] $[\alpha]_D = +1\,020°$ (*c* 0.06 $CHCl_3$)}. Subsequent elution with dichloromethane–methanol (5:1) gave the orange imine (**3**), which after brief hydrolysis in acidic aqueous tetrahydrofuran gave homochiral red (+)-(**1**) (38%), $[\alpha]_D = +1016°$ (*c* 0.06 $CHCl_3$) {lit.,[4] $[\alpha]_D = +1015°$ (*c* 0.06 $CHCl_3$)}.



Reagents: i, L-valinol, Et_2O, 4.5 h; ii, Al_2O_3; iii, H_3O^+

Addition of L-valinol to a diethyl ether solution of (+)-(**1**) resulted in a colour change from red to orange indicating imine formation. The formation of the imine (**3**) was confirmed by the C=N stretch at 1 633 cm^{-1} in the i.r. spectrum (CH_2Cl_2) and by ^{1}H n.m.r. spectroscopy. Crystallisation (diethyl ether–hexane) gave orange blocks of the imine (**3**), $[\alpha]_D = +512°$ (*c* 0.204 $CHCl_3$). A single crystal *X*-ray structure analysis[5] established the relative configuration within (**3**). Since the absolute configuration of L-valinol is known, the absolute configuration of (+)-(**1**) is as shown and unequivocally confirmed.[6] Acid hydrolysis of (**3**) regenerated homochiral (+)-(**1**) showing that no racemisation occurs on formation or hydrolysis of the imine (**3**). In the case of the L-valinol/(−)-(**1**) adduct crystallisation failed but the product was identified again as the red imine (**2**) on the basis of i.r. and ^{1}H n.m.r. spectroscopy. For both imines (**2**) and (**3**) formed from homochiral (**1**), ^{1}H n.m.r. spectroscopy established their integrity and hence the purity of each complexed aldehyde enantiomer.

The above methodology represents a kinetic resolution procedure for the preparation of homochiral (+)- and (−)-(**1**). The method is based on the completely selective hydrolysis of imine (**2**) by deactivated alumina. Inspection of models derived from the crystal structure of (**3**) suggest that imine (**3**) but not imine (**2**) might be protected from hydrolysis by reversible oxazolidine formation. *cis*-1,3-Disubstituted oxazolidines are more stable and more easily formed than the corresponding *trans* isomers.[7] The conformational restraints and face-directing effects imposed by the arene(tricarbonyl)chromium group favour formation of a *cis*-oxazolidine from (**3**) but not from (**2**).

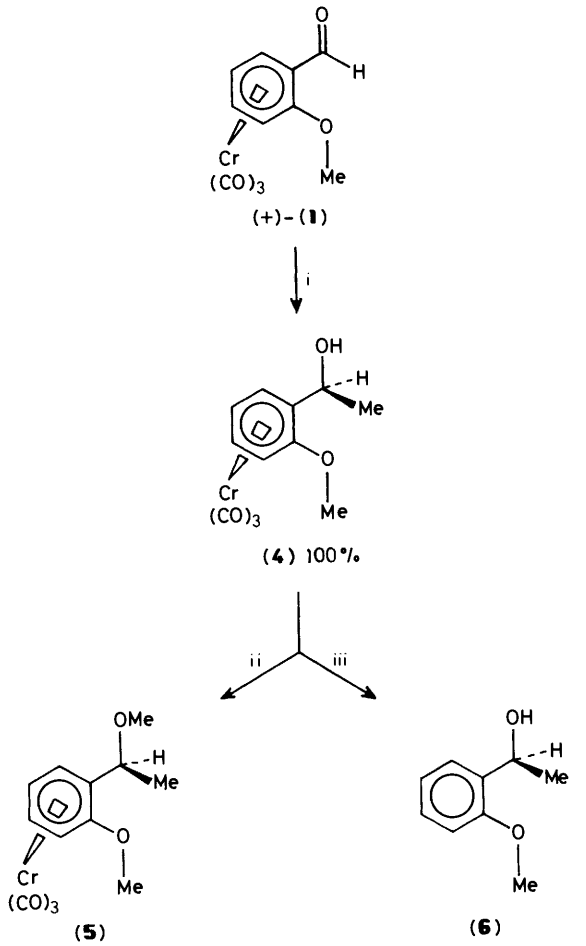


Additions of stabilised carbanions (enolates or perfluoroalkyllithiums), to (**1**) have been observed to proceed with good to complete diastereoselectivities.[2] Addition of methylmagnesium iodide to (±)-(**1**) has been reported to proceed with a diastereoisomeric excess of 90%.[3]

Addition of an excess of methylmagnesium iodide to a THF solution of (+)-(**1**) at −78 °C gave (**4**) as a single diastereoisomer (>100:1). The unambiguous assignment of the relative and hence absolute configurations within (**4**) was achieved by *O*-methylation to give (**5**), which was spectroscopically identical with an authentic sample of racemic (**5**). The relative configuration of racemic (**5**) has been established by an *X*-ray crystal structure determination.[8]

The completely stereoselective formation of (**4**) from (+)-(**1**) is consistent with attack onto the unhindered aldehyde face in the sterically and electrostatically most favoured conformation with the magnesium bound aldehyde oxygen *anti* to the *o*-methoxy group. Chelation control, with the magnesium bound to both the aldehyde and *o*-methoxy oxygens is not operating.

Decomplexation of (**4**) by exposure of a diethyl ether solution to air and sunlight gave (−)-(*S*)-1-(*o*-methoxyphenyl)ethanol (−)-(**6**), $[\alpha]_D = -59°$ (*c* 1.18 toluene). It follows from the

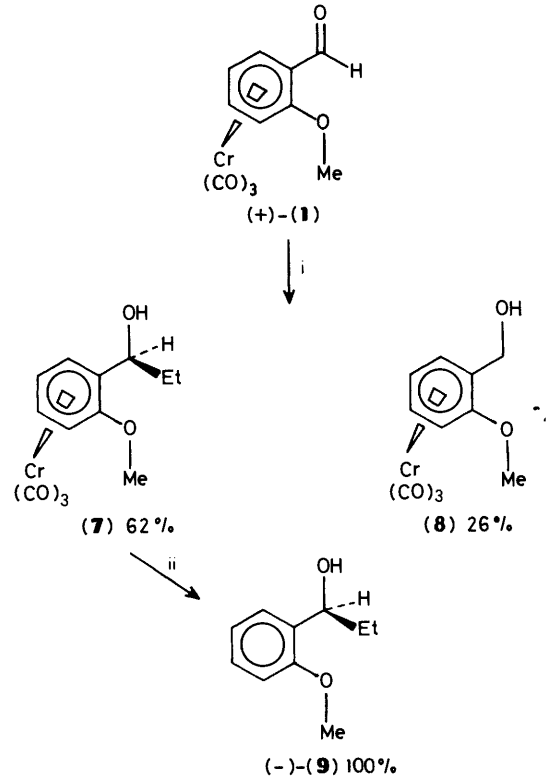


Reagents: i, MeMgI, THF, −78 °C, 2 h; ii, KH, MeI, THF; iii, O_2, sunlight

absolute configuration of (**4**) that the absolute configuration of (−)-(**6**) is *S*, which confirms the previous assignment based on Horeau's method.[9]

Addition of ethylmagnesium iodide to (+)-(**1**) also occurred completely stereoselectively to give (**7**). However, since ethylmagnesium iodide is a reducing Grignard, concomitant reduction of (+)-(**1**) occurred to give as a minor product, the benzyl alcohol complex (**8**). Complexes (**7**) and (**8**) were readily separable by chromatography. Decomplexation of (**7**) gave (−)-(*S*)-1-(*o*-methoxyphenyl)propanol (−)-(**9**), $[\alpha]_D = -57°$ (*c* 1.02 toluene) {lit.,[10] $[\alpha]_D = +47°$ (*c* 1 toluene) for 87% e.e. opposite enantiomer}.

Enantiomeric purities of the free alcohols (−)-(**6**) and (−)-(**9**) were checked by ^{1}H n.m.r. spectroscopic analysis of their (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate esters (Mosher's esters).[11] Authentic racemic alcohols (±)-(**6**) and (±)-(**8**) (prepared from *o*-anisaldehyde and the corresponding alkyllithium reagent), were similarly esterified, to show no kinetic resolution was occurring on esterification, and used as standards. Both alcohols (−)-(**6**) and (−)-(**9**) were enantiomerically pure by this method (>99.5%).



Reagents: i, EtMgI, THF, −78 °C, 2 h; ii, O_2, sunlight

Acknowledgements

We thank the S.E.R.C. for a quota award (C. L. G.).

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Received 12*th August* 1988; *Paper* 8/03298J