Mechanisms of nucleophilic substitutions of acetals

Steven D. Bull, Luís M. A. R. B. Correia and Stephen G. Davies *

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

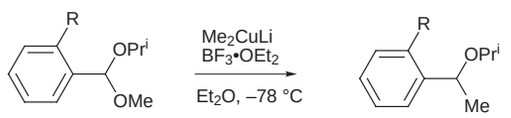
1 PERKIN COMMUNICATION

The nucleophilic substitution of (+)-(*R*)-benzaldehyde methyl isopropyl acetal (α*R*)-1 (93% ee) and (+)-(*R*)-*o*-anisaldehyde methyl isopropyl acetal (α*R*)-2 (homochiral) with Me_2CuLi–BF_3·OEt_2 occurs completely chemoselectively to afford (+)-(α*R*)-α-methyl(benzyl) isopropyl ether (+)-(α*R*)-3 (40% ee) and (+)-(α*R*)-α-methyl(*o*-methoxybenzyl) isopropyl ether (+)-(α*R*)-4 (34% ee) respectively, demonstrating that the mechanism of the former reaction involves a free oxonium ion to the extent of 56% and the latter to the extent of 66%.

The use of homochiral, cyclic acetals, generally derived from butane-2,3-diol or pentane-2,4-diol, in asymmetric synthesis is now well established.[1,2] Of particular relevance is the highly stereoselective nucleophilic cleavage promoted by Lewis acids.[3,4] This has been applied as the key step in the syntheses of various natural products.[5] Initial attempts to explain the high selectivity of the nucleophilic substitution [3] were followed by more rigorous mechanistic studies. These included studies on the influence of reaction parameters (*e.g.* nucleophile, Lewis acid and solvent) on the selectivity,[6,7] spectroscopic identification of intermediates [8] and use of model [7] and labelled [9] compounds. Three mechanisms may be envisaged for this process, an S_N2 mechanism with inversion of configuration and an S_N1 mechanism involving either trapping of the initially formed ion pair leading to inversion of configuration or nucleophilic attack on a solvated oxonium ion intermediate leading to both inversion and retention of configuration. It has been recognised that an important problem associated with the mechanistic studies using cyclic acetals in this area is that the intermediate solvated oxonium ion in the third mechanism is chiral and therefore will possess an inherent facial bias towards nucleophilic addition. This makes it impossible to distinguish between the possible mechanisms on the basis of the stereospecificity.

Our simple approach to a study of the mechanisms of nucleophilic substitutions of acetals was to investigate the stereospecificity of the reactions of acetals in *which the acetal carbon is the only stereogenic centre*. In this case any free solvated oxonium ion formed would be unbiased towards nucleophilic addition and the amount of racemisation would provide a meaningful measure of the importance of the third mechanism. This would still however be a minimum measure of the importance of the S_N1 mechanism since any excess inversion could arise from either an S_N2 mechanism or, *via* trapping of the initial ion pair, from an S_N1 mechanism.

We have previously described the asymmetric synthesis of (+)-(α*R*)-benzaldehyde and (+)-(α*R*)-*o*-anisaldehyde methyl isopropyl acetals (+)-(α*R*)-**1** and (+)-(α*R*)-**2**,[10] and herein we describe the stereospecificity of their nucleophilic substitution reactions with Me_2CuLi–BF_3·OEt_2. Initial experiments involved racemic acetals (α*RS*)-**1** and (α*RS*)-**2** in order to establish the chemoselectivity of the substitution of one of the alkoxy groups (Scheme 1). In both cases, it was found that Me_2CuLi–BF_3·OEt_2 displaced exclusively the methoxy group with a methyl group. This is consistent with the preferential coordination of the Lewis acid to the least hindered oxygen as is also observed for cyclic acetals.[8] The observed complete chemoselectivity justified our choice of the methyl isopropyl acetals since the secondary isopropyl group provides a good comparison for the secondary alkyl groups also present in the acetals from butane-2,3-diol or pentane-2,4-diol.



(α*RS*)-**1** R = H (α*RS*)-**3**

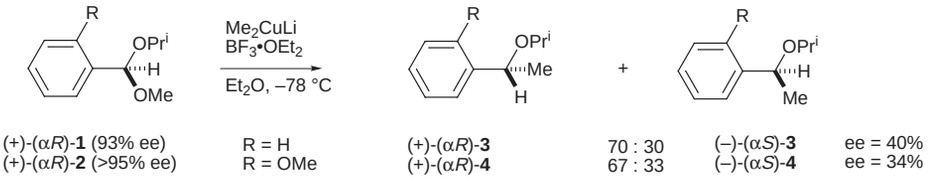
(α*RS*)-**2** R = OMe (α*RS*)-**4**

Scheme 1

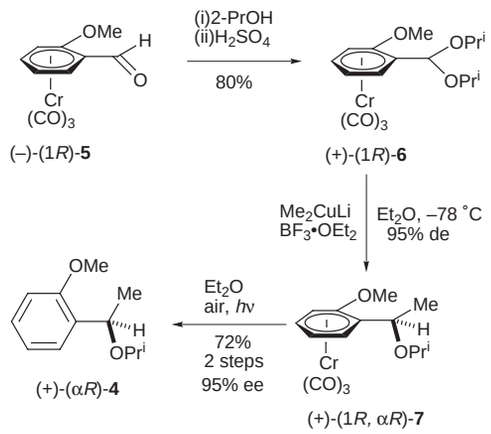
The stereospecificities of the reactions of the acetals (α*R*)-**1** (93% ee) and (α*R*)-**2** (homochiral) with Me_2CuLi–BF_3·OEt_2 are shown in Scheme 2. The enantiomeric excesses of the products **3** and **4** were assessed by ^{1}H NMR spectroscopic analysis using (+)-(1*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol as the chiral shift reagent. While it is reasonable to assume that the major product enantiomer was in each case the result of inversion of configuration, this was unambiguously established in the *o*-anisyl series by an independent synthesis of (+)-(*R*)-**4**—*vide infra*. In order to ensure the configurational stability of both **2** and **4** under these reaction conditions, important control reactions were carried out to ensure that neither reactants nor products had been inadvertently racemised. The enantiomeric excess of a sample of (α*R*)-**2** (homochiral) reisolated from a Me_2CuLi–BF_3·OEt_2 reaction mixture, which had proceeded to 73% conversion, was unchanged, while scalemic (α*R*)-**2** (33% ee) treated with two equivalents of BF_3·OEt_2 in Et_2O at −78 °C was the only material recovered in 75% yield (33% ee). Similarly a sample of (+)-(*R*)-**4** (homochiral) exposed to Me_2CuLi–BF_3·OEt_2 in Et_2O at −78 °C was also reisolated in homochiral form.

These results indicate that the formation of **3** from **1** and of **4** from **2** proceed *via* a free oxonium ion mechanism to the extent of 56% (corrected for ee of starting material) and 66% respectively. The greater preference for this mechanism in the *o*-anisyl series is consistent with the electron donating *ortho* methoxy group promoting ionisation and breakdown of the initial ion pair by stabilisation of the oxonium ion relative to that from the phenyl series.

The independent synthesis of (+)-(α*R*)-α-methyl(*o*-methoxybenzyl) isopropyl ether (+)-(α*R*)-**4** is shown in Scheme 3. The readily available (−)-(*R*)-(*o*-anisaldehyde) chromium tricarbonyl **5** [11] was converted to the novel (+)-(1*R*)-(*o*-anisaldehyde diisopropyl acetal) chromium tricarbonyl **6** by stirring in propan-2-ol with a catalytic amount of H_2SO_4 (98%) at 20 °C {$[a]_D^{25}$ +217 (*c* 0.66, $CHCl_3$)}. Treatment of (+)-(1*R*)-**6** with Me_2CuLi–BF_3·OEt_2 at −78 °C afforded (+)-(1*R*,α*R*)-[α-methyl-(*o*-methoxybenzyl) isopropyl ether] chromium tricarbonyl **7** as a single diastereomer by ^{1}H NMR spectroscopy after work-up and crystallisation {$[a]_D^{25}$ +226 (*c* 0.48, $CHCl_3$)}. The relative configuration within (+)-(*R*,*R*)-**7** was assigned by comparison of its ^{1}H NMR spectrum with those from (*RS*,*RS*)- and



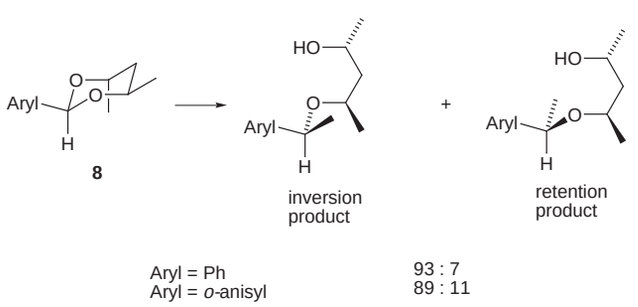
Scheme 2



Scheme 3

(*RS*,*SR*)-[(α-methyl *o*-methoxybenzyl) methyl ether] chromium tricarbonyl complexes of known relative configuration.[12] Finally, the desired ether (+)-(α*R*)-**4** was obtained by exposing an ether solution of (+)-(1*R*,α*R*)-**7** to air and sunlight {$[a]_D^{25}$ +115 (*c* 0.37, $CHCl_3$)}.

It is interesting to compare the results obtained for the substitution reaction of acyclic acetals with the same reaction of the corresponding cyclic acetals, since the latter have been shown to occur with high diastereoselectivity. Alexakis and co-workers have reported the reaction of the acetal **8** (Aryl = phenyl) derived from benzaldehyde and pentane-2,4-diol with Me_2CuLi–BF_3·OEt_2 and observed 95% inversion of configuration.[4a] We have repeated this under our conditions for a direct comparison and also investigated the *o*-anisaldehyde derived acetal. We observe 93% and 89% inversion of configuration respectively (Scheme 4).



Scheme 4

In summary the nucleophilic substitutions of the cyclic acetals **8** with Me_2CuLi–BF_3·OEt_2 are highly stereoselective in favour of the product resulting from inversion of configuration. These results however do not elucidate the relative importances of the S_N2, ion pair and S_N1 mechanisms because the intermediate oxonium ion in the S_N1 mechanism is chiral. For the reactions of acetals **1** and **2** with the only stereogenic centre being the acetal carbon, the major pathway has been shown to involve an S_N1 mechanism and the amount of product deriving from a free oxonium ion has been quantified. Further efforts will be necessary to decide the relative importance of the S_N2 and ion pair mechanisms.

Experimental

General procedure for methylation of acetals 1, 2 and 8

Methyllithium (1.2 ml, 1.7 mmol) was slowly added (10 min) to a suspension of cuprous iodide (160 mg, 0.84 mmol) in ether (5 ml) at −30 °C, and the solution cooled to −78 °C. A solution of acetal (0.29 mmol) in ether at −78 °C was then added, followed by the dropwise addition of BF_3·OEt_2 (0.1 ml, 0.81 mmol). The reaction mixture was stirred at −78 °C for 2 hours, and allowed to warm to −30 °C over a period of 3 hours. The reaction mixture was quenched with NH_4Cl(aq), extracted with ether (3 × 10 ml), the organic layer dried (sodium sulfate), and the solvent removed under vacuum to afford the desired ether. Enantiomeric excesses were determined by recording ^{1}H NMR spectra in $CDCl_3$ in the presence of 5 equivalents of (+)-(*S*)-trifluoroanthrylethanol {(+)-(*S*)-TFAE}.

(+)-(α*R*)-α-Methyl(*o*-methoxybenzyl) isopropyl ether 4 (34% ee)

Treatment of (+)-(*R*)-*o*-anisaldehyde methyl isopropyl acetal **2** (homochiral) according to the general protocol afforded the title compound in 93% yield (Calculated for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.16; H, 9.36%); $[a]_D^{25}$ +19.3 (*c* 0.76, $CHCl_3$); δ_H($CDCl_3$) 1.14 (3H, d, *J* 6.0), 1.18 (3H, d, *J* 6.0), 1.36 (3H, d, *J* 7.4), 3.45–3.50 (1H, m), 3.84 (3H, s), 4.95–5.00 (1H, q, *J* 7.4), 6.86 (1H, d, *J* 7.0), 6.99 (1H, t, *J* 7.0), 7.23 (1H, t, *J* 7.0), 7.47 (1H, d, *J* 7.0); 5 equivalents of (+)-(*S*)-TFAE split the doublet at δ 1.36 in a ratio of 2 : 1.

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