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Asymmetric Additions to Dichlorophenyldioxane, A New Chiral Acetal

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abstract: 4-(2,6-Dichlorophenyl)-1,3-dioxanes have been reacted with weak nucleophiles and $TiCl_4$ to give benzyl ethers with high selectivity. The major products are consistent with an S_N2-like mechanism. The benzyl ether is removed in one step using Li/NH_3 to give non-racemic secondary alcohols.

Chiral acetals efficiently mediate the asymmetric addition[1] of weak carbon nucleophiles,[2] reductions,[3] and cation-olefin reactions.[4] Mechanistically, the origin of asymmetric induction remains unclear.[5] While most evidence supports an S_N2-type inversion process via a tight ion pair, recent studies indicate that the conformation of the oxocarbenium ion may be the controlling factor via an S_N1-type process.[5a] The new acetal, dichlorophenyldioxane now reported, provides for highly selective addition reactions and allows for one step removal of the ether functionality (Fig. 1).[6] The two-step oxidation-elimination sequence required with the established 4,6-dimethyldioxane acetal to remove the hydroxy-ether functionality after addition is now avoided. The new acetal provides for a mechanistic distinction between the S_N2-inversion tight ion pair process and the S_N1-oxocarbenium routes. In contrast to the common Johnson 4,6-dimethyldioxane acetal where the two routes lead to the same isomeric product, the phenylacetal partitions to the two diastereomeric product depending on the route followed (Fig. 2).[7]

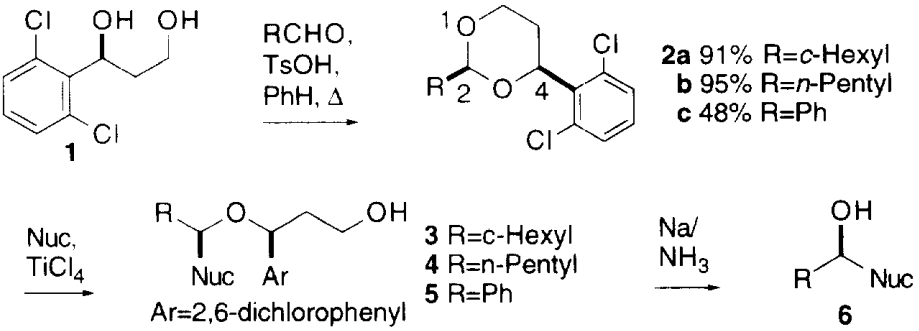


Figure 1. Acetals **2** are formed from **1** and reacted to give **3**, **4**, and **5**.

Initial additions using 2-alkyl-4-phenyldioxanes (Ar=phenyl, Fig. 1) with trimethyl-allylsilane and titanium tetrachloride at low temperature under standard conditions were disappointing. Cleavage of the O_3-C_4 bond occurred giving significant amounts (15-20%) of product arising from allyl addition to free aldehyde together with material derived from addition to the benzylic carbenium ion. Changing the Lewis acid and reactions conditions did not lead to improvements. To prevent this unwanted ionization pathway, a chloride

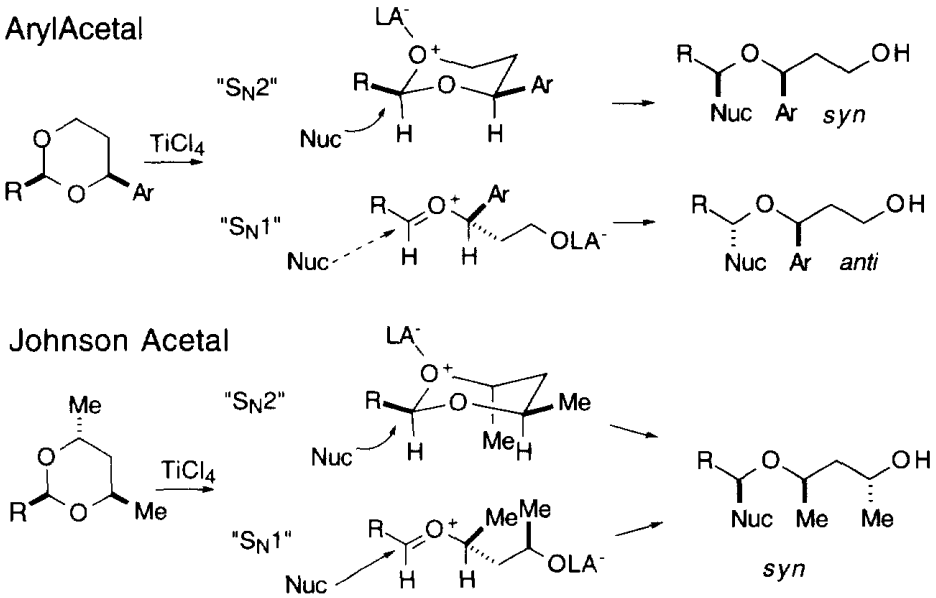


Figure 2. S_N2 and S_N1 pathways of the Aryl and Johnson Acetals

substituent was incorporated to inductively deactivate the phenyl group, disfavor cleavage of the O_3-C_4 bond, and indirectly promote O_1-C_2 cleavage. Side by side comparisons were made with additions to phenyl, *o*-chlorophenyl, and dichlorophenylacetals. Dichlorophenyldioxane proved superior by cleanly providing the desired benzyl ether product.

Acetals **2a-c** were produced from non-racemic *(S)*-1-(2,6-dichlorophenyl)propane-1,3-diol **1** that was obtained from asymmetric allylborane addition to 2,6-dichlorobenzaldehyde (Fig. 3).[8] Ozonolysis in methylene chloride-methanol (1:1) at -78 °C followed by reductive work up with $NaBH_4$ and gave diol **1**. The enantiomeric excess was judged to be >98% after recrystallization from ethyl acetate and hexanes.[9] Dioxanes **2a-c** were then formed by reacting the aldehydes with diol **1** under Dean-Stark conditions producing the *cis*-diequatorial isomers exclusively (Fig. 1).

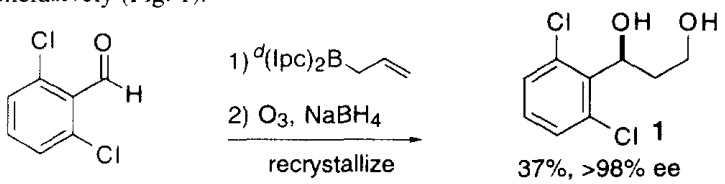
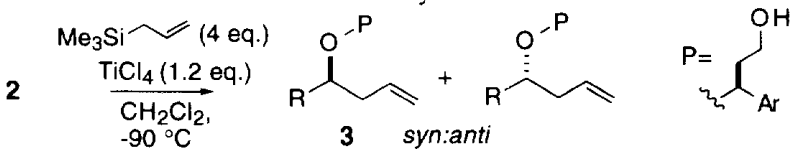


Figure 3. Synthesis of diol **1**.

Nucleophiles were added to the acetals **2a-c** using titanium tetrachloride at low temperature in methylene chloride. Allylsilane added with variable yields and high selectivities ranging from 53:1 for **2a** to 6:1 for **2c** (Table 1).[2a] These reactions were performed by adding $TiCl_4$ dropwise to a methylene chloride (0.2 M) solution containing trimethylallylsilane and acetal **2** at -90 °C. After five minutes, the reactions were quenched with saturated $NaHCO_3$ and the products were isolated using radial chromatography. The major product from acetal **2a** was confirmed to be the *syn*-*(S,S)*-isomer as depicted. Treatment of the product **3a** with Na/NH_3 in THF-ethanol at -78 °C gave the known *(S)*-)-homoallylic alcohol **6** (R=*c*-hexyl, Nuc=allyl) in 78% yield (Fig. 1).[10] Similar results were observed with pinacolone silylenol ether (Table 2).[2b] High *syn*-

Table 1. Addition of allylsilane to acetals **2**.



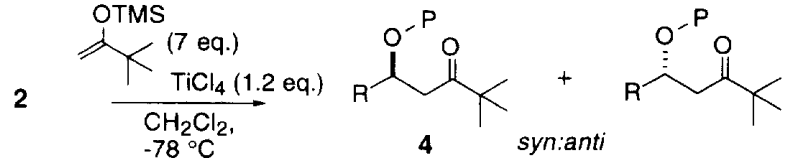
Substrate (R)	Yield % **3**	*syn:anti*
2a, *c*-hexyl	98	53:1[a]
2b, *n*-pentyl	73	19:1[b]
2c, phenyl	56	6:1[b]

[a]HPLC ratio, [b]^{13}C NMR

selectivities were obtained with **2a** and **2b** while **2c** again gave a lower ratio (6:1).

With diethylzinc the results were different (Table 3).[11] Immediately upon addition of titanium tetrachloride, a dark brown solution resulted indicating that a transmetallation process was operative. In addition, the selectivities switched over to give a slight preference for the *anti*-isomers.[12] The major *anti*-isomer for diethylzinc addition was confirmed (R=*n*-hexyl) by separation of the resultant

Table 2. Addition of enolsilane to acetals **2**.

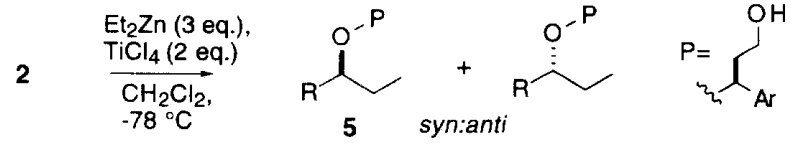


Substrate (R)	Yield % **4**	*syn:anti*
2a, *c*-hexyl	84	20:1[a]
2b, *n*-pentyl	84	10:1[b]
2c, phenyl	85	6:1[a]

[a]^{13}C NMR, [b]HPLC ratio

diastereomers followed by Na/NH_3 treatment of the major isomer to give the known *(R)*-nonan-3-ol[13] in 72% yield. The observed *anti*-selectivity in this case is consistent with internal delivery of the nucleophile from the Lewis acid (LA=$EtTiCl_3$, Fig. 2) to the *re*-face of the oxocarbenium ion. The lower 2:3 *syn:anti* selectivity for **2c** can be attributed to the stabilizing effect of the phenyl moiety on the oxocarbenium ion.

Table 3. Addition of diethylzinc to acetals **2**.



Substrate (R)	Yield % **5**	*syn:anti*
2a, *c*-hexyl	56	1:3.5[a]
2b, *n*-pentyl	64	1:4
2c, phenyl	85	2:3[b]

[a]HPLC ratio, [b]^{13}C NMR

The allyl and enolsilane reactions favoring production of the *syn*-isomer are consistent with the S_N2-type pathway with inversion at the acetal carbon (Fig. 2). The stability imparted by the phenyl group in **2c** allows for increased production of the minor *anti*-isomer presumably through the S_N1 pathway. If the free oxocarbenium ion pathway were operative, the nucleophile would attack the *re*-face away from the larger aryl group approaching next to the methylene and generate the *anti*-product (Fig. 2).[14] However, the *syn*-isomer is the major product, indicating that the conformation of a free oxocarbenium ion intermediate does not govern the stereocontrol in this case. This result stands in contrast to the Johnson acetal,[5a] where the free oxocarbenium ion S_N1 route is implied by the observation that the deuterated axial methyl group is scrambled in the products. Also, in contrast to the phenyldioxane, the S_N2 and S_N1 routes with the Johnson acetal lead to the same *syn*-isomer as the major product. Now with the dichlorophenyl-dioxane acetal, the free S_N1 oxocarbenium route is clearly disfavored as seen by the observed stereochemistry of the products indicating an S_N2 tight ion pair mechanism where the selectivity is dependent on the structure of the acetal and the nature of the nucleophile. In addition, the new acetal allows for the liberation of the non-racemic secondary alcohol products in one step using lithium-ammonia. Applications to other asymmetric transformations are currently under investigation.

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