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Stereoelectronic effects in the DIBAL reduction of aryl-1,2-ethanediol benzylidene acetals

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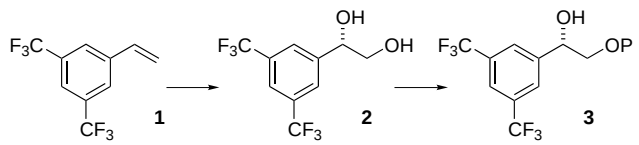
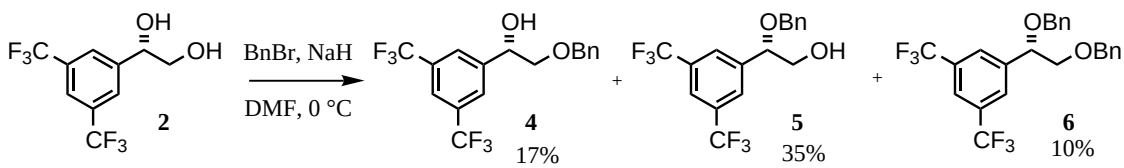
Abstract—Reduction of benzylidene acetal **8** with DIBAL-H selectively gave **4** in 89% yield. 1-Aryl-1,2-diol benzylidene acetals display unusual regioselectivity with electron withdrawing groups on the aryl group.

As part of our NK-1 receptor antagonist program, we required primary protected (*S*)-1-(3,5-bis(trifluoromethyl)phenyl)-1,2-ethanediol **3** (Eq. (1)). In this communication, a synthesis of crystalline (*S*)-1-(3,5-bis(trifluoromethyl)phenyl)-2-(4-bromobenzyloxy)-1-ethanol (**13**) from **2** and a study on the stereoelectronic influence of benzylidene acetal reduction are described. A plausible mechanistic rational to explain the unusual regioselectivity of the benzylidene acetal reduction is proposed.



(1)

(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-1,2-ethanediol (**2**, 99% ee) was prepared via Sharpless asymmetric dihydroxylation of 3,5-bis(trifluoromethyl)phenyl styrene.[1] *t*-Butyldimethylsilyl protection (**3**, P=TBS) was achieved under standard conditions (TBS-Cl, imidazole, DMF, 95%), however, a crystalline intermediate was desired. Several approaches to benzyl protected **3** were explored. Unfortunately, standard benzylation conditions (NaH, BnBr, DMF or Bn-trichloroacetimidate, TMSOTf, THF) did not yield the desired secondary alcohol **4** with satisfactory yield or regioselectivity (Eq. (2)). Epoxide opening of 3,5-bis(trifluoromethyl)phenyl styrene oxide (**7**) with BnOH afforded a respectable yield and ratio of the desired product (88%, 10:1, **4**/**5**, Eq. (3)). However, asymmetric epoxidation[2] of 3,5-bis(trifluoromethyl)phenyl styrene gave (*S*)-**7** in only 80% ee.[3] The benzylidene acetal **8** (1:1 *cis*/*trans* mixture), prepared in 90% yield from (*S*)-diol **2**, $PhCH(OMe)_2$ and cat. *p*TsOH in toluene, was reduced with DIBAL-H[4] (2.5 equiv., 0°C) to provide a favorable 17:1 ratio (**4**/**5**) of alcohol products (Eq. (4)).[5] Desired regioisomer (*S*)-**4** was isolated by chromatography in 89% yield as a low melting solid (mp 5–7°C).[6] In expectation of preparing a higher melting crystalline analogue, we prepared *p*-methoxybenzyl and 4-bromobenzyl protected alcohols **11** and **13** via the respective benzylidene intermediates **9** and **10** (Eq. (5)). The DIBAL-H reduction was faster with **9** (0.5 h) and slower with **10** (3 h) compared to unsubstituted benzylidene **8**, however, the regioselective outcome was unperturbed. To our satisfaction, the bromobenzyl-protected diol **13** was isolated as a crystalline solid,[7] thus providing a means to eliminate chromatographic purification.



(2)

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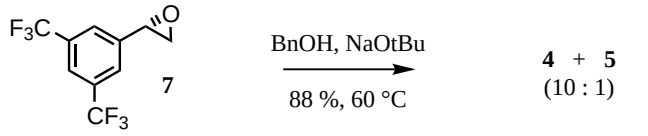
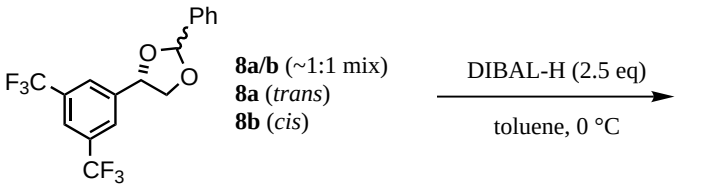


(3)

The reduction of benzylidene acetals to give mono benzyl protected diols is a valu-able reaction for the selective functionalization of organic intermediates.[8] Benzylidene acetals are generally reduced at the less sterically hindered oxygen, yielding the more hindered alcohol protected as the benzyl ether.[9] The unusual



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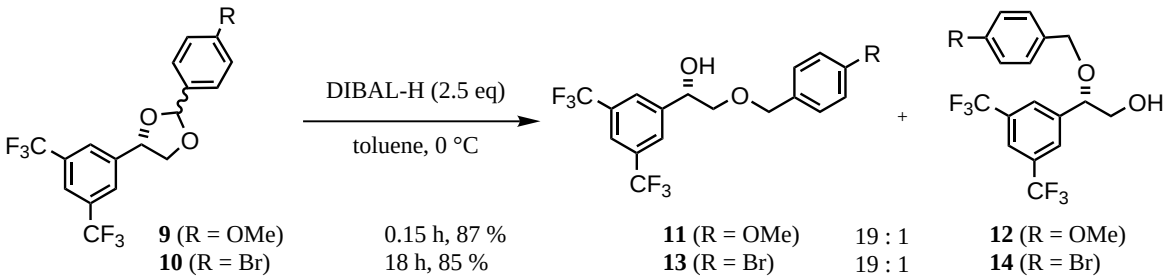
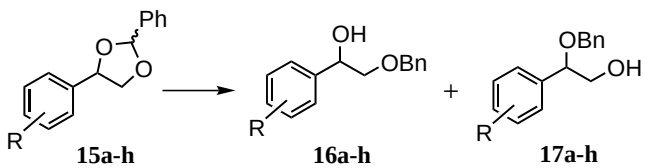


(5)

Table 1. DIBAL-H (2.5 equiv.) reduction of acetals **15a–h** in toluene at 0°C

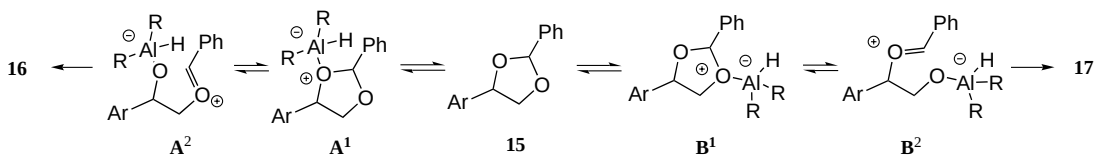


Entry	15[a]	R	Ratio 16:17[b]	Yield (%)[c]
1	**a**	Perfluoro	8.2:1	70
2	**b**	3-CF_3	3.9:1	95
3	**c**	4-F	2.0:1	87
4	**d**	4-Cl	2.6:1	78
5	**e**	4-Br	2.5:1	83
6	**f**	H	1.3:1	90
7	**g**	3-Me	1:1.1	78
8	**h**	4-MeO	1:3	83

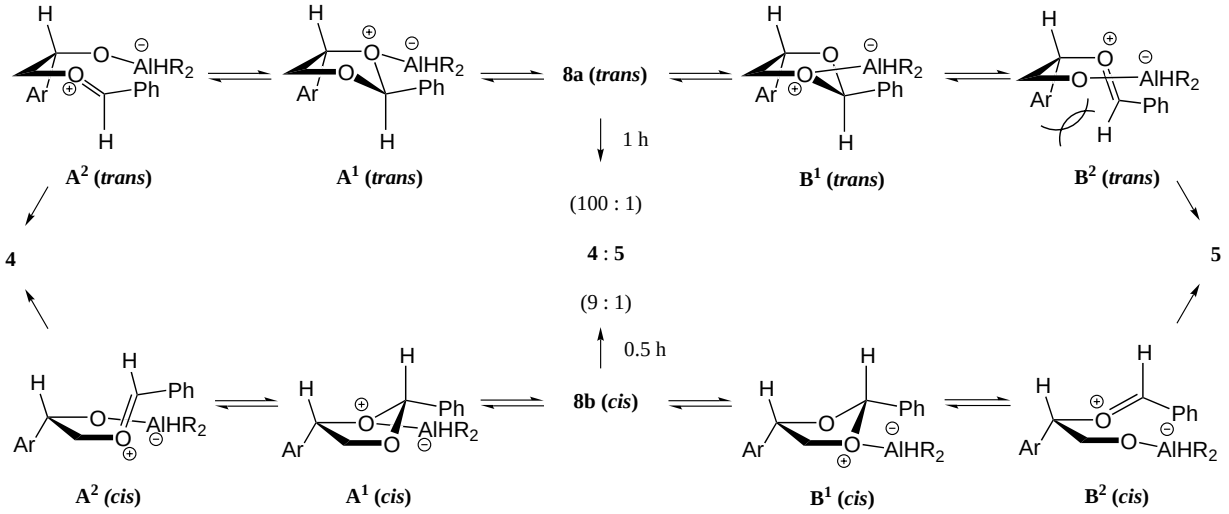
[a] The purified acetals were isolated as a ~1:1 mixture of diastereomers.
[b] Ratios were determined by ^{1}H NMR of the crude reaction mixtures.
[c] Combined unoptimized yield of **16** and **17** after chromatography.

regioselectivity in the reduction of **8**, **9** and **10** with the secondary alcohol being the major product, prompted us to explore the electronic effects of aryl group substitution in this reaction.[10] A series of 1-aryl-1,2-ethanediols[11] was converted to the benzylidene acetals **15a–h** ($PhCH(OMe)_2$, *p*TsOH in toluene, 23°C) and then reduced with DIBAL-H at 0°C (Table 1).[12] A trend is observed as selectivity for **16** diminishes with attenuated electron withdrawing capacity of the aryl substituent. Electron donating groups (**15g** and **15h**, entries 7 and 8, Table 1) affected only slight preference for **17**, the anticipated product based upon sterics.

Lewis acid-mediated nucleophilic additions to acetals have been the focus of significant research effort and several mechanistic investigations have been recently conducted.[13] A plausible mechanistic rational for the regioselectivity in **8** is outlined in Scheme 1. Lewis acid complex $\mathbf{A^1}$ may be considered higher in energy than $\mathbf{B^1}$ with an electron withdrawing aryl group (Ar). DIBAL is associated with the less hindered oxygen in complex $\mathbf{B^1}$. Thus, the $\mathbf{A^1}/\mathbf{B^1}$ equilibrium should favor $\mathbf{B^1}$ both kinetically and thermodynamically. However, the $\mathbf{A^1}/\mathbf{B^1}$



Scheme 1.



Scheme 2.

ratio appears to be less important in determining the product outcome.[14] Oxocarbenium ion **B²** is destablized with electron withdrawing groups compared with **A²**. Thus, the product-determining factor in the reaction pathway depends on the relative stabilities of oxocarbenium ions **A²**/**B²**.[15]

The *cis* and *trans* benzylidene acetals **8a** and **8b** (Eq. (4)) were separated by column chromatography, assigned by ^{1}H NMR difference NOE, and subsequently each isomer was reduced. Interestingly, the *trans* diastereomer was reduced slower (1 h versus 0.5 h) and with enhanced regioselectivity (100:1 versus 9:1).[16] A model is illustrated in Scheme 2 to explain the difference in rate and selectivity. Isomers **8a**/**8b** proceed through diastereomeric Lewis acid complexes **A¹** (*trans*)/**A¹** (*cis*) and **B¹** (*trans*)/**B¹** (*cis*), respectively. These Lewis acid complexes generate the *E*-oxocarbenium ion pairs **A²** (*trans*)/**A²** (*cis*) and **B²** (*trans*)/**B²** (*cis*), which ultimately yield products **4** and **5**, respectively. The slower reduction rate observed for **8a** can be attributed to the increased steric demand of the coordinated DIBAL. The *trans* Ar and Ph groups dictate a more congested psuedo-axial/equatorial relationship in complexes **A¹** (*trans*) and **B¹** (*trans*). The enhanced regioselectivity observed for **8a** may be due to the non-bonded interactions that impede the C–O bond shortening[17] of the incipient *E*-oxocarbenium ion **B²** (*trans*). These non-bonded interactions are absent in the formation of other *E*-oxocarbenium ions.

We have developed a two-step chromatography-free procedure to make (*S*)-1-(3,5-bis(trifluoromethyl)-phenyl)-2-(4-bromobenzyloxy)-1-ethanol (**13**) from (*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-1,2-ethanediol (**2**) via reduction of benzylidene acetal **10**. In this work, we report that the electronic nature of aryl-1,2-ethanediols affects the selectivity of the reduction in that opposite regioselectivities dominate with electron withdrawing aryl groups.

Acknowledgements

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5. Solvent effects were briefly explored. The reaction was much slower in THF and faster in DCM, but gave no significant change in the **4**:**5** ratio.
6. Compound (*S*)-**4** (99% ee) was isolated by column chromatography as a low melting solid (mp 5–7°C); ^{1}H NMR ($CDCl_3$): δ 7.87 (s, 2H), 7.83 (s, 1H), 7.36 (m, 5H), 5.02 (ddd, J=8.2, 3.6, 3.1 Hz, 1H), 4.62 (s, 2H), 3.71 (dd, J=9.6, 3.6 Hz, 1H), 3.52 (dd, J=9.6, 8.2 Hz, 1H), 3.13 (d, J=3.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 143.1, 137.2, (CF_3: 132.1, 131.7, 131.4, 131.1), 128.5, 128.1, 127.8, 126.4, 124.7, ($CF_3\underline{C}$: 122.0, 121.6), 74.9, 73.6, 71.6. The % ee was determined by SFC chromatography using a Chiracel OJ column with a 4–40% MeOH gradient.
7. Compound (*S*)-**13** (99% ee) was prepared as follows: A suspension of (*S*)-diol **2** (2.74 g, 10.0 mmol), 4-bromobenzaldehyde dimethyl acetal (2.77 g, 12.0 mmol) and *p*TsOH (0.10 g, 0.5 mmol) in toluene (30 mL) was aged for 1 h at 60°C. The solution was concentrated in vacuo (40°C, 50 mmHg) and flushed with one volume of tolu-

ene. The resulting solution was washed with 10% aq. $NaHSO_3$ (3×30 mL) and saturated brine (15 mL). The solution was azeotropically dried by flushing with one volume of toluene. The solution of **10** (ca. 1:1 mixture of acetal diastereomers) was cooled to 0°C and added 1.0 M DIBAL-H in toluene (25 mL, 25.0 mmol). The solution was aged 18 h at 0°C. The reaction was washed with 10% NaOH (25 mL) and saturated brine (15 mL). The solution was concentrated to a solid. (*S*)-**13** was recrystallized from hexanes (10 mL/g) yielding 3.10 g (70%) of a white solid (mp = 74–75°C). ^{1}H NMR ($CDCl_3$): δ 7.83 (s, 2H), 7.80 (s, 1H), 7.47 (d, J = 2.1 Hz, 2H), 7.16 (d, J = 2.1 Hz, 2H), 5.00 (m, 1H), 4.53 (s, 2H), 3.67 (dd, J = 2.4, 0.9 Hz, 1H), 3.48 (t, J = 2.2 Hz, 1H), 2.94 (d, J = 0.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 142.9, 136.2, (CF_3: 131.9, 131.7, 131.5), 129.4, 126.4, 124.6, ($CF_3\underline{C}$: 122.0, 121.9, 121.8), 74.9, 72.8, 71.7.

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9. The product outcome can be directed with a vicinal functional group via Lewis acid chelation. For example, see: (a) Mikami, T.; Asano, H.; Mitsunobu, O. *Chem. Lett*. **1987**, 2033; (b) Pasto, M.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron: Asymmetry* **1995**, *6*, 2329–2342; (c) Takano, S.; Kurotaki, A.; Sekiguchi, Y.; Satoh, S.; Hirama, M.; Ogasawara, K. *Synthesis* **1986**, 811–817; (d) Flasche, M.; Scharf, H.-D. *Tetrahedron: Asymmetry* **1995**, *6*, 1543–1546.
10. For examples of reagent controlled regioselection in the reduction of benzylidene protected carbohydrates, see: (a) Garegg, P. J. *Pure Appl. Chem*. **1984**, *56*, 845–858; (b) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Chem. Commun*. **1984**, 201–202; (c) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371–2374.
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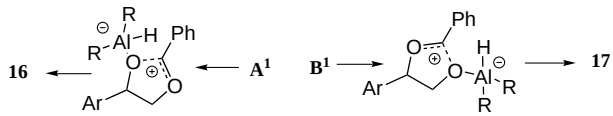
15. Reduction may also occur through intimate ion pairs precluding the formation of solvent separated oxocarbenium ions $\mathbf{A^2}$/$\mathbf{B^2}$ (see Ref. 13). However, the overall electronic consequence is analogous.



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