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Modulating electrostatic interactions in ion pair intermediates to alter site-selectivity in C–O deoxygenation of sugars

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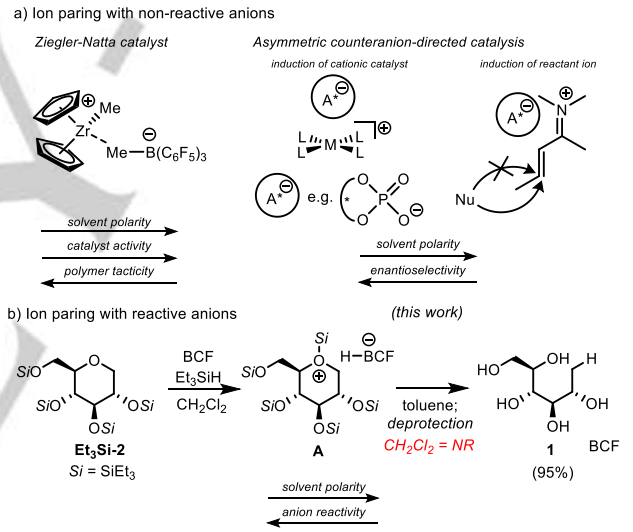
Abstract: Controlling which products one can access from the pre-defined biomass-derived sugars is challenging. Converting from CH_2Cl_2 to a greener alternative, toluene, changes which C–O bonds in a sugar are cleaved using the BCF/$HSiR_3$ catalyst system. This increases the diversity of high-value products that can be obtained through 1-step, high-yielding, catalytic transformations on the base mono-, di-, and oligo-saccharides. Computational methods helped localize this non-intuitive outcome in low dielectric solvents to non-isotropic electrostatic enhancements in the key ion-pair intermediates, which influence the reaction coordinate in the reactivity/selectivity determining step. Molecular-level models for these effects have reaching consequences in stereoselective ion-pair catalysis.

Tris(pentafluorophenyl)borane, BCF, has emerged as a highly effective catalyst for the site-selective deoxygenation of biomass-derived carbohydrates.[1–9] Choice of the sugar's protecting group and reductant (hydrosilane or hydroborane) can tailor which C–O bonds are cleaved to yield high-value chiral products.[7] Since the biorenewables pool is fixed, new approaches to altering site-selectivity diversifies the high-value compounds that can be accessed from it.

Our synthetic and mechanistic experiments on complex sugars are consistent with the Piers mechanism,[1,2,5] wherein BCF activates the silane via an η^1-adduct, and is in turn heterolytically and reversibly cleaved by an oxygenated nucleophile (the sugar) to yield a cationic silyloxonium that is paired to the H–BCF$^-$ anion/reductant.[10–16] According to Sakata and Fujimoto's calculations,[17] these contact ion pairs are dynamic and multiple orientations (local minima) can be sampled prior to rate determining C–O reduction. The rationale for site-selectivity in a sugar necessarily includes which oxygen binds to the silylium along with the barriers of hydride attack (within the ion pair) at each of these positions. Since the key selectivity defining events occur at the point of contact in a dynamic ion pair, they are under Curtin-Hammett control. The added complication of neighboring group participation multiplies the challenge of predicting which site(s) will be reduced in polyols.[2,18–20]

The effect of ion pair structure on catalyst behavior has been investigated in a number of scenarios, including single-site Zeigler-Natta,[21–23] chiral ion-pair intermediates,[24–27] and chiral ion-pair catalysts (organo and transition metal, e.g., Scheme 1a).[28,29] Low polarity solvents enhance the electrostatic interaction between the cation and anion, and where a tighter ion pair is beneficial to stereochemical transfer, e.g., from chiral anion to cation, these solvents enhance enantioselectivity.[30,31]



Scheme 1. a) example of ion pairing in catalysis b) formation of an ion pair involving 1-deoxyglucose.

As part of a broader effort to improve the greenness of site-selective sugar deoxygenations,[6] we discovered that Et_3Si-1-deoxyglucose **Et_3Si-2** (generated in situ from Et_3Si-MeO-glucose)[5] provided an excellent yield of 1-deoxysorbitol **1** when the reaction was carried out in toluene (Scheme 1b). This new product to BCF/$HSiR_3$ catalysis was unexpected as previous attempts to selectively reduce 1-deoxyglucose by BCF/$HSiR_3$ in CH_2Cl_2 failed due to the formation of an unreactive (but spectroscopically characterizable) ion pair [Si-1-deoxyglucose][H–BCF] (**A**, Scheme 1b) that sequestered the catalytic quantities of silylium.[3,5] The heightened reactivity of **A** in toluene was also apparent in pentane and cyclohexane (Scheme 2). A mixture of **1** and **2** was observed for reactions in chloroform, in contrast to *o*-dichlorobenzene and CH_2Cl_2, which do not proceed beyond **2**. Heating the reaction in CH_2Cl_2 to 50°C in a sealed NMR tube

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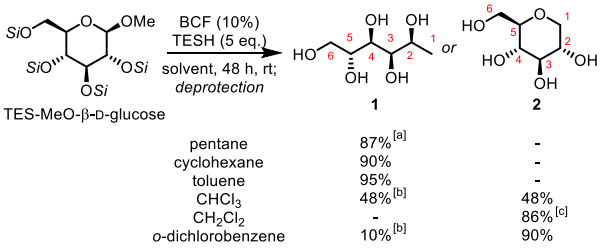
consumed **Et$_3$Si-2**, but non-selective overreduction dominated.

Since low dielectric solvents were expected to slow catalysis by *inhibiting* the formation of ion pairs from neutral precursors, these results prompted an in-depth investigation of mechanism and synthetic utility. The result of these studies not only enhances our understanding of site-selective deoxygenation chemistry, but also ion-pair catalysis more generally.

Scheme 2. Solvent dependence in ring opening of Et$_3$Si-MeO-glucose.



[a]Isolated yields. [b]Isolated as a mixture. [c]Ref. 5.

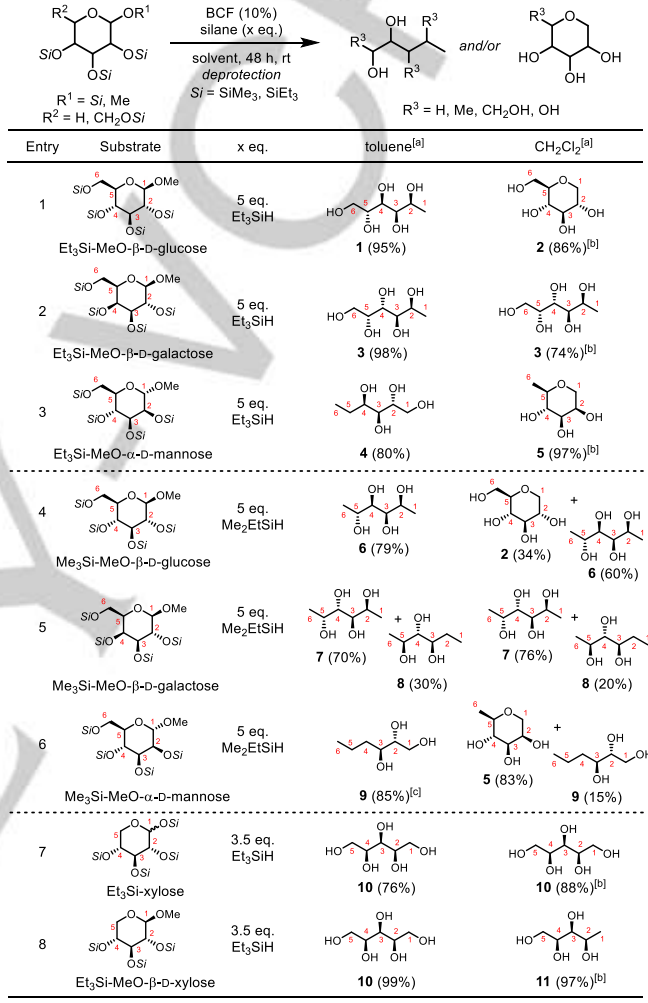
We first sought to determine how broadly this solvent change effected selectivity in monosaccharides. Table 1 compares the reduction selectivity in CH_2Cl_2 and toluene for Et$_3$Si- (Entries 1-3) and Me$_3$Si-protected (Entries 4-6) hexoses and Et$_3$Si-protected pentoses (Entries 7-8). On the whole, toluene provides a different product than does CH_2Cl_2, our originally reported conditions,[5] and Et$_3$Si-protected sugars (using Et$_3$SiH) are less reactive than Me$_3$Si-protected sugars (using Me$_2$EtSiH). For example, in CH_2Cl_2 Et$_3$Si-1-deoxyglucose (Entry 1) is unreactive while Me$_3$Si-1-deoxyglucose gives moderate conversions to **6** (Entry 4).

Although similar outcomes were apparent for CH_2Cl_2 and toluene reductions of protected MeO-galactose, the other hexoses had different selectivity profiles. Controllable differences were achieved based on whether a Et$_3$Si- or Me$_3$Si-protection scheme was employed in each solvent. In this manner, up to 3 unique products could be obtained in high yields and in one synthetic step from a single biofeedstock through choice of solvent and silyl protecting group. Notable cases include accessing 5,6-deoxytetraol **4**[32] (Entry 3) from Et$_3$Si-MeO-α-D-mannose (rather than the more precious 2-deoxyglucose),[5] which required a selective 2°-reduction of **Et$_3$Si-5** (at C5). When Me$_3$Si-protected starting material is used, the tetraol is further reduced (at C4) to **9** in good yields (toluene, Entry 6).

In the pentose series, Et$_3$Si-xylose provided **10** in both solvents (Entry 7), while Et$_3$Si-MeO-xylose (Entry 8) was first de*methoxy*lated in CH_2Cl_2 to produce the ring-opened linear tetraol **11**. This process likely proceeds via an oxocarbenium intermediate (S_N1). In toluene, however, de*methyl*ation of the exocyclic -OMe occurs, which then ring opened to **10**. The in situ observation of methane leads to the conclusion that toluene inhibits oxocarbenium formation relative to CH_2Cl_2 and thereby shifts the selectivity to O–CH$_3$ reduction of the exocyclic silyloxonium.

We have reported that reduction of per-Si-disaccharides with BCF and Me$_2$EtSiH in CH_2Cl_2 provided a 1:1 ratio of the recalcitrant 1-deoxyglucose and products derived from per-Si-glucose (Table 2, Entries 1-3).[3] Switching to toluene nicely converges both primary fragments to **6** in excellent yields, and in the case of Entry 4, at a higher conversion. For the oligo-saccharides in Entries 5-7, toluene more efficiently provided **6** in each case. Overall, these reductions are enhanced in toluene over CH_2Cl_2 and provide the means to converge each sugar unit to a single product.

Table 1. Reduction of sugars in toluene and CH_2Cl_2.



[a]Isolated yields. [b]Ref 5. [c]Isolated as (3:1) mixture with internal triol.

Our synthetic studies demonstrate the profound influence on site-selectivity that a change from CH_2Cl_2 to toluene has for BCF/silane catalysis. Molecular-level insights into the role of solvent were obtained using DFT methods to model the C1-reduction of Me$_3$Si-1-deoxyglucose (see supporting information for full computational details). In practice, this required a full evaluation of the competing chair forms (Figure S1) as C1-reduction of the all-equatorial $^4C_1$ form (**int1**) was prohibitively high (+41.9 kcal/mol vs. starting materials), while the all-axial $^1C_4$ conformer **int2** was more reasonable (+19.4 kcal/mol, Figure 1). Computed barriers for chair flipping Me$_3$Si-1-deoxyglucose from $^4C_1$ to $^1C_4$ were lower than either C–O bond reduction barrier (see supporting information) and lower than that of similarly calculated C–O bond reductions involving BCF/HSiR$_3$.[33] The data suggests that a chair flip to the $^1C_4$ conformer is required to minimize steric clashing between neighboring -OSi groups

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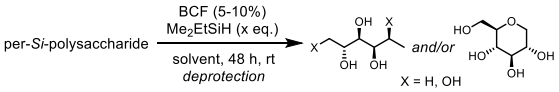
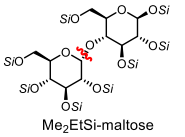
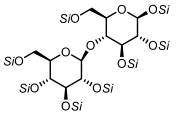
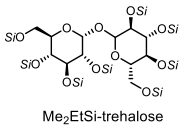
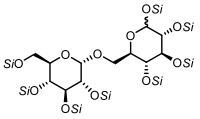
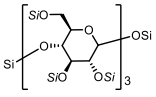
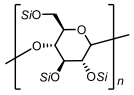
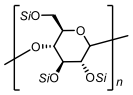
(Figure S2). An analysis of coupling constants ($^3J_{HH}$) showed that Et$_3$Si-1-deoxyglucose and **A** adopt the $^4C_1$ and $^1C_4$ conformers, respectively (Figures S3 and S4), consistent with computed conformer stabilities.

Table 2. Reduction of oligosaccharides in toluene and CH_2Cl_2.



Entry	Substrate	x eq.	toluene[a]	CH_2Cl_2[a]
1	 Me$_2$EtSi-maltose	7 eq.	**6** (96%)	**6** (50%) **2** (48%)[b]
2	 Me$_2$EtSi-cellobiose	7 eq.	**6** (91%)	**6** (50%) **2** (48%)[b]
3	 Me$_2$EtSi-trehalose	7 eq.	**6** (99%)	**6** (50%) **2** (48%)[b]
4	 Me$_2$EtSi-isomaltose	7 eq.	**6** (91%)	**6** (70%)[b]
5	 Me$_2$EtSi-maltotriose	10 eq.	**6** (81%)	**6** (46%) **2** (33%) **1** (16%)
6[c]	 Me$_3$Si-maltodextrin (n = 4-7)	5 eq.	 **12** (8%) **6** (74%)	**6** (59%) **2** (39%)
7[c]	 Me$_3$Si-maltodextrin (n = 16.5-19.5)	5 eq.	**12** (14%) **6** (62%)	**6** (58%) **2** (27%)

[a]Isolated yields. [b]Ref 3. [c]Reaction time 24 h.

Only two of the numerous possible ion pair local minima are included in Figure 1. **int3** is the first local minimum formed upon silane heterolysis and **int4** is that which positions the anion B–H to reduce C1–O. The calculations of Fujimoto, along with our own unpublished work, shows that the barrier for interconverting contact ion pairs is low (<5 kcal/mol).[17] The barrier (**TS1**) for C1 reduction from **int4** is computed to be +19.4 kcal/mol using the CH_2Cl_2 dielectric continuum. The structure of **TS1** is shown in Figure 2 and displays the expected alignment of the B–H nucleophile with the C–OSi$^+$ leaving group. Animation of the single imaginary frequency shows it corresponds to C1–O cleavage.

Repeating calculations of **int4** and **TS1** using dielectric continuums corresponding to other solvents revealed several fascinating observations related to ion pair structure and energetics. As shown in Table 3, ΔG‡ increases with increasing dielectric, consistent with the efficient conversion of the Me$_3$Si-1-deoxyglucose to **6** in toluene and its sluggish conversion in CH_2Cl_2. Metrical parameters for **int4** reveal that the distance in the nascent C1···H bond shortens in progressively lower dielectric solvents (C1–O is largely unchanged). This dielectric shortening of C1···H appears to advance the reaction coordinate towards a fully formed C1–H in the product. Changes in the progression to products are also apparent at the transition state, but in this case the structure is slightly more product like in the high dielectric cases. The sum changes in **int 4** and **TS1** reveal that net movement of hydride in C–H bond formation is reduced in lower dielectric solvents.

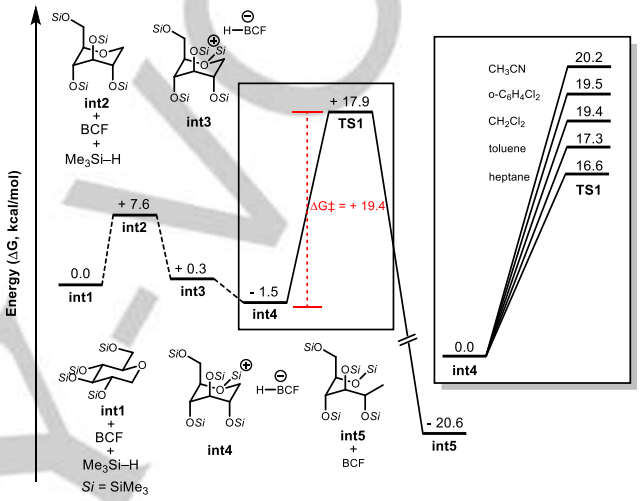


Figure 1. Free energy profiles for C1-reduction of Me$_3$Si-1-deoxyglucose in the $^1C_4$ conformer.

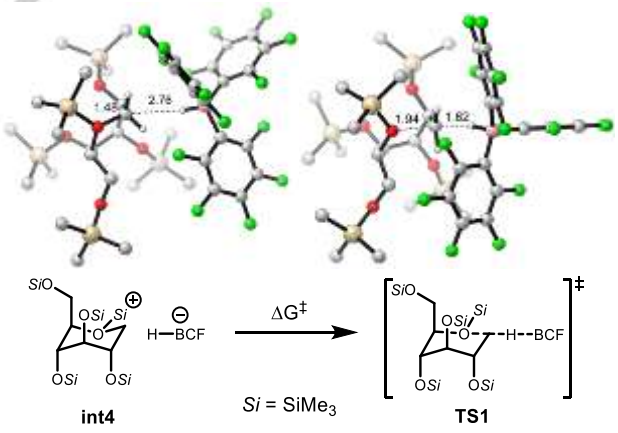


Figure 2. Calculated structures of **int4** and **TS1**.

These data demonstrate how low dielectric solvents create electrostatic compressive forces that can shorten inter-ion bond lengths in a contact ion pair. These strengthened interactions have long been empirically used to enhance stereochemical transfer in chiral ion pair catalysis. More nuanced is the view that an ensemble of discrete but dynamically interconverting ion-pair structures/transition states control the overall selectivity under Curtin-Hammett constraints. In the situation where charge neutralization

occurs in a selectivity determining step, we have demonstrated that such inter-ion forces might also help to pick which structures dominate product output .

Table 3. Computed reduction barriers for Me_3Si-1-deoxyglucose.

Solvent	ε	ΔG‡ (kcal/mol)	int4		TS1		
			d_{C-O}	d_{C-H}	d_{C-O}	d_{C-H}	Δd_{C-H}
heptane	1.9	16.6	1.48 [a]	2.70	1.92	1.63	1.07
toluene	2.4	17.3	1.48	2.71	1.92	1.63	1.08
CH_2Cl_2	8.9	19.4	1.48	2.76	1.94	1.62	1.14
o-$C_6H_4Cl_2$	9.9	19.5	1.47	2.76	1.94	1.62	1.14
CH_3CN	37.5	20.2	1.47	2.77	1.95	1.61	1.16

[a]Bond lengths in Å.

Acknowledgements

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Keywords: ion pairing • sugar • selective deoxygenation • solvent • DFT

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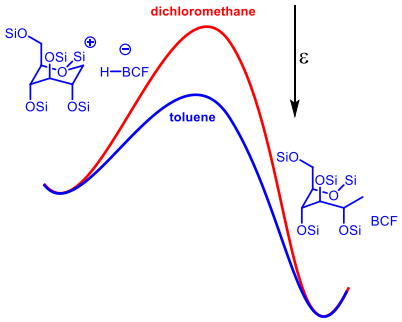

Ion Pairs in Control. Certain ion pair intermediates can be made more reactive when electrostatic forces between a reactive cation and anion can couple to productive C–O bond cleavage processes. Low dielectric media can enhance such forces and speed reactions.