Highly stereoselective indium trichloride-catalysed asymmetric aldol reaction of formaldehyde and a glucose-derived silyl enol ether in water

Teck-Peng Loh,*† Guan-Leong Chua, Jagadese J. Vittal and Meng-Wah Wong

Department of Chemistry, National University of Singapore, 10 Kent Ridge Crescent, Singapore 119260

The yield and stereochemical outcome of the reaction between D-glucose-derived silyl enol ether 1 (*Z* and *E* isomers) and commercial formaldehyde in water catalysed by indium(III) choride was studied.

The many possible advantages of performing carbon–carbon bond formation in aqueous media has resulted in studies by several groups. This relatively unfamiliar territory, especially reactions that are done without organic solvents, lends itself to exploration in terms of reaction characteristics and stereochemical behaviour.[1]

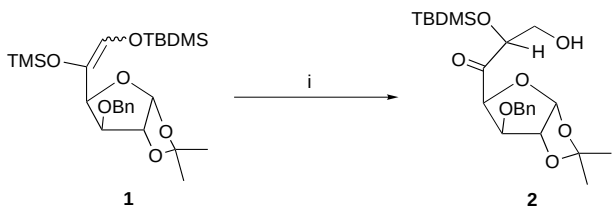
Here we report an efficient and highly stereoselective aldol reaction between commercially available aqueous formaldehyde (37% in water) and silyl enol ether **1**, which can be easily obtained using glucose as starting material (Scheme 1). The reaction conditions chosen have allowed for formaldehyde to be used without prior dissolution or *in situ* generation in highly basic or acidic conditions from paraformaldehyde, as compared to reactions in organic solvents.

The use of **1** has allowed for the study of asymmetric induction *via* the chiral centers and steric bulk of the various groups. In addition, we aim to provide a stereoselective one-carbon extension of glucose under mild conditions employing readily available starting materials, in contrast to existing methodologies.[2] Previously reported use of commercial formaldehyde solution for Mukaiyama aldol reactions using lanthanide triflates was unable to be carried out efficiently in the absence of organic solvents.[3] Our aim in completely excluding organic solvents had led us to our choice of $InCl_3$ as a water-stable Lewis acid from our earlier work.[4] We had also studied the characteristics of the unexplored $In(OTf)_3$ and did a comparative study with the lanthanide triflate $Yb(OTf)_3$. Our study demonstrated the superiority of $InCl_3$ in terms of yield and selectivity.

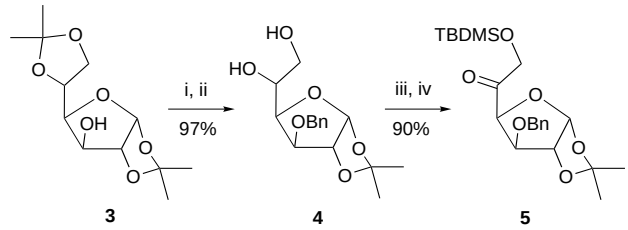
Ketone **5**, precursor of silyl enol ether **1**, was derived from diacetone D-glucose in two steps (Scheme 2). Deprotonation of C-6 using LDA and subsequent trapping of the enolate with trimethylsilyl chloride gave (*Z*)-**1** and (*E*)-**1** in an approximate ratio of 80 : 20 [Scheme 3, reaction conditions (i)]. The ratio of the isomers was determined *via* ^{1}H NMR spectroscopy, through integration of the α-vinylic proton resonances, with the *Z*-isomer at a lower field than the *E*-isomer.[5]‡

The aqueous Mukaiyama aldol-type reaction was performed by first activating the formaldehyde (commercial solution, 37% in water, 2 equiv.) using Lewis acid (0.4 equiv. $InCl_3$, 0.02 equiv. $In(OTf)_3$ or 0.4 equiv. $Yb(OTf)_3$) and then adding this solution to the silyl enol ether. The reaction mixture was then stirred vigorously§ at room temperature and monitored by TLC for complete consumption of **1**. Aqueous workup followed by flash chromatography gave the desired products. The results are shown in Table 1 (entries 1 to 3). The low yield observed for the reaction catalysed by triflates was due to the significant conversion of **1** to the ketone, particularly with 0.4 equiv. of $In(OTf)_3$, and deprotection of C-6 hydroxy group from the product **2**. Diastereoselectivities obtained were good, with catalysis by $InCl_3$ proceeding with excellent selectivity.¶ The stereochemistry about C-6 of product (*R*)-**2** was determined by X-ray crystallographic analysis of (*R*)-6 obtained from deprotection of the C-6 hydroxy group (Scheme 4).‖

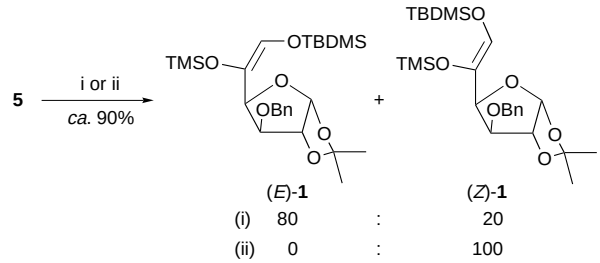
The lack of correlation between the isomer ratio of **1** and the diastereoselectivities of the products suggests that both isomers gave the same major product *via* conformational preference



Scheme 1 *Reagents and conditions*: i, CH_2O (37% in H_2O), Lewis acid, room temp.



Scheme 2 *Reagents and conditions*: i, NaH, BnBr, Bu_4NI, THF, room temp., 48 h; ii, 0.06 M HCl, MeOH, room temp., 3 days; iii, TBDMSCl, Et_3N, DMAP, CH_2Cl_2, room temp., 18 h; iv, DMSO, $(COCl)_2$

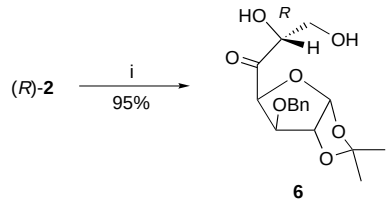


Scheme 3 *Reagents and conditions*: i, LDA, $SiMe_3Cl$, THF, −78 °C to room temp.; ii, Et_3N, $SiMe_3Cl$, DMF, 70 °C, 2 days

Table 1 Yields and diastereoselectivities for reactions described in Scheme 1

Entry	*E* : *Z*	Lewis acid (equiv.)	*t*	Yield[a] (%)	*R* : *S*
1	80 : 20	$InCl_3$ (0.4)	4–7 d	73	96 : 4
2	80 : 20	$In(OTf)_3$ (0.4)	30 min	0[b]	—
3	80 : 20	$In(OTf)_3$ (0.02)	0.5–1 d	38	93 : 7
4	80 : 20	$Yb(OTf)_3$ (0.4)	2–3 d	40	88 : 12
5	0 : 100	$InCl_3$ (0.4)	4–7 d	68	82 : 18
6	0 : 100	$In(OTf)_3$ (0.02)	0.5–1 d	37	70 : 30
7	0 : 100	$Yb(OTf)_3$ (0.4)	2–3 d	35	54 : 46

[a] Purified yield. [b] Extensive decomposition occurs.



Scheme 4 *Reagents and conditions*: i, TBAF, THF, 0 °C, 1 h

governed by thermodynamic factors. To further investigate this, we managed to obtain exclusively (Z)-**1** by use of Et_3N as base instead of LDA [Scheme 3, reaction conditions (ii)].[6] Reaction of (Z)-**1** with formaldehyde using $InCl_3$ as catalyst results in a (*R*)-**2** : (S)-**2** ratio of 82 : 18 (Table 1, entry 5), a lower diastereoselection from that previously obtained. Similar trends were also observed with the triflates as Lewis acids (Table 1, entries 6 and 7).

To rationalise our results, we propose the existence of a preferred path of approach of the formaldehyde nucleophile owing to the steric requirements imposed by the rigid silyl enol ether. Hence, diastereofacial selection would depend on the favoured conformation of the silyl enol ether. Standard *ab initio*[7,8] studies carried out for the four possible conformers of silyl enol ether **4** are in good accord with the experimental finding that the *R*-isomer is the preferred observed product (Fig. 1).

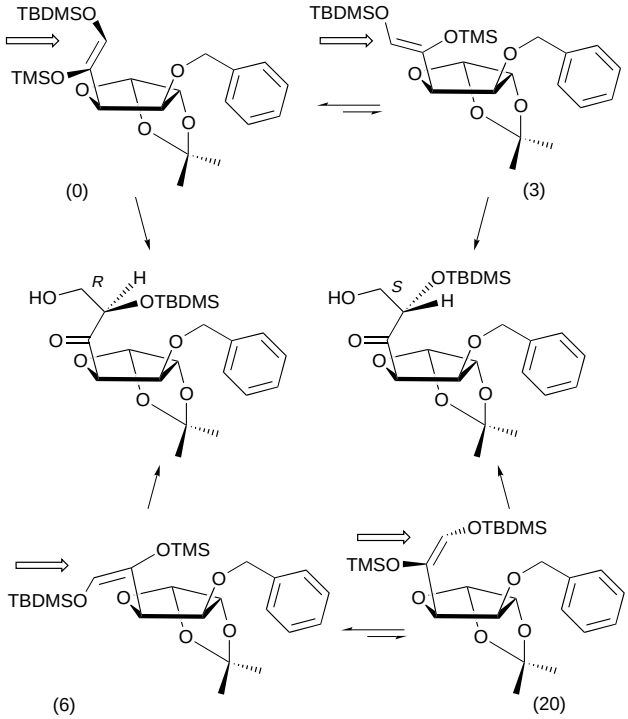


Fig. 1 Numbers in parentheses denote the calculated relative energies in kJ mol^{-1}

In effect, this methodology exploits the structure provided by the glucose derivative to achieve a highly stereoselective means of one carbon extension under mild and readily accessible reaction conditions. This, together with the well-established chemistry of the carbohydrates, would provide for its adaptation to natural product syntheses.

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Notes and References

† E-mail: chmlohtp@nus.edu.sg

‡ Chemical shifts of α-vinylic protons: (*Z*)-**1** (s, 1 H, δ 6.21); (*E*)-**1** (s, 1 H, δ 6.08).

§ The heterogeneous nature of the mixture demands good continuous mixing.

¶ Selectivities were determined from ^{13}C NMR analysis of the purified product through comparison of the signal intensities due to the carbonyl carbon at δ 205 for (*R*)-**2** and δ 206 for (*S*)-**2**.

‖ The assignment of the stereochemistry *via* X-ray crystallography is based on the known and unchanged stereochemistry of the four chiral centres in the furanose ring. *Crystal data* for (*R*)-**6**: $C_{17}H_{22}O_7$, M = 338.35, T = 296(2) K, orthorhombic, space group $P2_12_12_1$, a = 6.0536(1), b = 13.5051(1), c = 21.8795(5) Å, U = 1788.75(5) Å^3, Z = 4, D_c = 1.256 Mg m^{-3}, μ(Mo-Kα radiation, λ = 0.71073 Å) = 0.098 mm^{-1}, $2\theta_{max}$ = 58.76°, F(000) = 720. Absorption correction: SADABS (Sheldrick, 1996), independent reflections = 4327, final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0566, $wR2$ = 0.1413, R indices (all data): $R1$ = 0.0899, $wR2$ = 0.1596, GOF on F^2 = 1.051.

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