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Diastereoselective construction of *anti*-4,5-disubstituted-1,3-dioxolanes *via* a bismuth-mediated two-component hemiacetal oxa-conjugate addition of γ-hydroxy-α,β-unsaturated ketones with paraformaldehyde†

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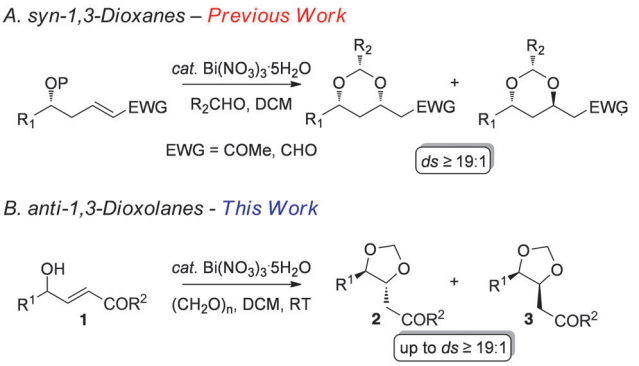
The bismuth-mediated two-component hemiacetal oxa-conjugate addition of γ-hydroxy-α,β-unsaturated ketones with paraformaldehyde affords *anti*-4,5-disubstituted-1,3-dioxolanes in an efficient and stereoselective manner. The reaction provides a practical, inexpensive and atom-economical approach to these types of heterocycles, which represent useful intermediates for target-directed synthesis and precursors to *syn*-1,2-diols.

Chiral 1,2-diols are extremely ubiquitous structural motifs found in a plethora of biologically active natural products, pharmaceuticals,[1] chiral ligands and chiral auxiliaries.[2] As a result, powerful synthetic methodologies for accessing this moiety with high levels of enantio- and diastereocontrol[3] are continually being reported.[4] Furthermore, the direct preparation of semi- and fully-protected 1,2-diols is of great importance since it alleviates the necessity for additional functional group manipulations, which is critical for increasing efficiency in multi-step target-directed synthesis.

In a program directed towards the examination of bismuth-mediated hetero-conjugation reactions,[5–7] we recently reported a highly stereoselective construction of *syn*-1,3-dioxanes *via* a two-component hemiacetal oxa-conjugate addition promoted by bismuth(III) nitrate pentahydrate, which provides a Brønsted acid surrogate (Scheme 1A).[8,9] Although the application of this strategy to γ-hydroxy-α,β-unsaturated ketones would provide the corresponding *1,3-dioxolanes*, the use of alkyl aldehydes as coupling components results in mixtures of diastereoisomers whereas symmetrical ketones are unreactive in this type of process.[10] To this end, we envisioned that paraformaldehyde would circumvent the formation of diastereosiomers and provide the necessary reactivity to afford the requisite 1,3-dioxolane. An additional advantage of this approach over the more classical strategy is the ability to directly prepare the protected 1,2-diol in a single operation from an allylic alcohol derivative, which is particularly attractive given the ubiquity of protected *syn*-1,2-diols in important synthetic intermediates.[1,2]



Scheme 1 Bismuth-mediated two-component hemiacetal oxa-conjugate addition for the construction of *syn*-1,3-dioxanes and *anti*-1,3-dioxolanes.

Herein, we now describe the diastereoselective construction of *anti*-4,5-disubstituted-1,3-dioxolanes **2** *via* the bismuth-mediated hemiacetal oxa-conjugate addition reaction of γ-hydroxy-α,β-unsaturated ketones **1** with paraformaldehyde in a practical, inexpensive and atom-economical manner (Scheme 1B). Furthermore, the dioxolane **2** can be readily reduced and deprotected to afford the corresponding *syn*,*syn*- or *syn*,*anti*-1,2,4-triols in a stereoselective manner, which represent important motifs in an array of biologically active natural products.[11]

Table 1 summarizes the optimization of the bismuth-mediated two-component hemiacetal oxa-conjugate addition reaction of the γ-hydroxy-α,β-unsaturated methyl ketone **1a** with paraformaldehyde to afford the *anti*-4,5-disubstituted-1,3-dioxolane **2a** (Table 1). Preliminary studies focused on the effect of the bismuth salts, which have a dramatic impact on the outcome of this transformation.[7–9] Interestingly, bismuth(III) chloride and bromide promote the desired hemiacetal oxa-conjugate addition to

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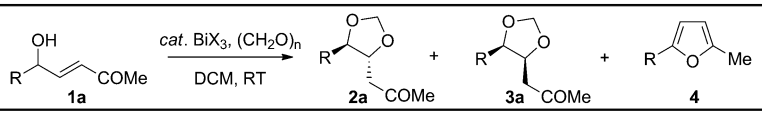
† Electronic supplementary information (ESI) available: Experimental procedures, spectral data and copies of spectra. CCDC 1050168 (**5**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5cc01949d

Table 1 Optimization of the two-component bismuth-mediated hemiacetal oxa-conjugate addition γ-hydroxy-α,β-unsaturated methyl ketone **1a** with paraformaldehyde (R = $Ph(CH_2)_2$)[a]



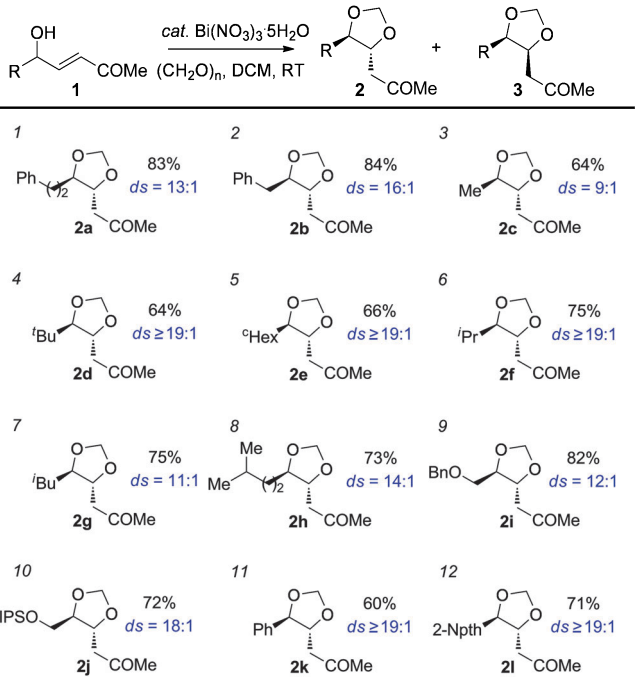
Entry	BiX_3	Mol%	Conc. (M)	Yield[b] (%)	Ratio[c] (**2a**/**3a**) : **4**	*ds*[c] **2a** : **3a**
1	$BiCl_3$	10	0.1	18	1 : 1	6 : 1
2	$BiBr_3$	10	0.1	13	1 : 4	5 : 1
3	BiI_3	10	0.1	—	—	—
4	$Bi(OTf)_3$	10	0.1	16	≥19 : 1	6 : 1
5	$Bi(NO_3)_3{\cdot}5H_2O$	10	0.1	78	≥19 : 1	13 : 1
6	$Bi(NO_3)_3{\cdot}5H_2O$	5	0.1	75	≥19 : 1	13 : 1
7	***$Bi(NO_3)_3{\cdot}5H_2O$***	***10***	***0.25***	***83***	***≥19 : 1***	***13 : 1***

[a] All reaction were carried out on a 0.5 mmol scale using paraformaldehyde (5 equiv.) in reagent grade dichloromethane at room temperature for *ca.* 36 hours. [b] Isolated yield of **2a**/**3a**. [c] The ratio of products and diastereoisomers were determined by 500 MHz ^{1}H NMR on the crude reaction mixtures.

afford **2a** in poor yield and with modest diastereocontrol, in a process that is further complicated by the competitive dehydrative cyclization of **1a** to afford the 2,5-disubstituted furan **4** (entries 1 and 2).[12] In contrast, bismuth(III) iodide is ineffective for either process (entry 3), whereas bismuth(III) triflate favors the chemoselective formation of the 1,3-dioxolanes **2a**/**3a**, albeit with similar efficiency and selectivity (entry 4 *vs.* entries 1 and 2). Further studies demonstrated that bismuth(III) nitrate pentahydrate provides the optimal catalyst for this process, both in terms of the efficiency and selectivity (entry 5). Attempts to reduce the amount of catalyst led to a reduction in the yield, while maintaining similar chemo- and diastereocontrol (entry 6). Finally, increasing the concentration afforded the *anti*-4,5-substituted-1,3-dioxolane **2a** in an improved 83% yield with similar selectivity (entry 7). Overall, this process provides an operationally simple procedure for the diastereoselective preparation of *anti*-4,5-disubstituted-1,3-dioxolanes using environmentally benign reagents in an atom-economical process, which does not require the exclusion of air and moisture. The relative stereochemistry of the 1,3-dioxolane **2a** was unambiguously determined by the X-ray analysis of the dinitrophenylhydrazone derivative **5**, which clearly indicates *anti*-configuration of the alkyl substituents on the five-membered heterocycle (Fig. 1).‡§

Table 2 outlines the application of the optimized reaction conditions (Table 1, entry 7)¶ to an array of γ-hydroxy-α,β-unsaturated methyl ketones **1**. Interestingly, the allylic substituent impacts both the level of stereocontrol and overall efficiency of this process. For example, simple straight chain alkyl groups provide modest selectivity (entries 1–3), whereas α-branched alkyl derivatives afford improved diastereocontrol (entries 4–6). Moreover, β- and γ-branching also provides synthetically useful levels of diastereocontrol (entries 7 and 8). In addition, protected hydroxymethyl groups serve as useful substrates, in which the relative size of the protecting group directly impacts the level of stereocontrol (entry 9 *vs.* 10). The ability to utilize primary silyl ethers as protecting groups is particularly important, given that they have the propensity to undergo protodesilylation. Finally, aryl substituents also proceed with excellent diastereocontrol,

Table 2 Scope of the diastereoselective two-component hemiacetal oxa-conjugate addition of substituted γ-hydroxy-α,β-unsaturated methyl ketones **1** with paraformaldehyde[a,b,c,d]



[a] All reaction were carried out on a 0.5 mmol scale using paraformaldehyde (5 equiv.) in reagent grade dichloromethane at room temperature for *ca.* 36–72 hours. [b] Isolated yield of **2**/**3**. [c] Ratios of diastereoisomers were determined by 500 MHz ^{1}H NMR on the crude reaction mixtures. [d] Trace amounts of the 2,5-disubstituted furan products **4** (5%) were also detected.

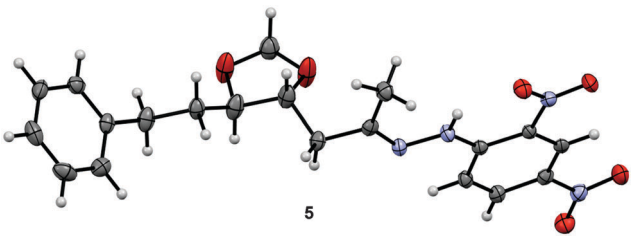


Fig. 1 ORTEP structure of hydrazone **5** derived from the *anti*-4,5-disubstituted 1,3-dioxolane **2a**.

which further serves to demonstrate the scope of this approach (entries 11 and 12). Overall, this method provides a very convenient, inexpensive and atom economical approach to the construction of *anti*-4,5-disubstituted-1,3-dioxolanes with good to excellent levels of stereoinduction.

Fig. 2 details a plausible explanation for the origin of stereocontrol in this type of cyclization reaction. We envision that the addition occurs though the kinetic cyclization[13] of the protonated α,β-unsaturated ketone, which adopts an s-*trans* conformation,[14] to form an allyl type cation[15] **I** that is irreversibly trapped in the *pseudo*-equatorial orientation to afford the favoured diastereoisomer.[16] The minor diastereoisomer can either result from the cyclization of the opposite rotamer **II** or the transition state with the pseudo-axial orientation of the allylic substituent **III**, which are presumably disfavored due to the presence of a 1,3-steric interaction with the allylic substituent (R).

In order to illustrate the utility of this approach, we investigated the divergent reduction of the methyl ketone and removal of the 1,3-dioxolane to provide 1,2,4-triols found in a plethora of natural products (Scheme 2).[11] Treatment of **2j** with lithium aluminum hydride in the presence of lithium iodide in diethyl ether at −100 °C provided the Cram-chelate alcohol **6** in 95% yield with ≥19 : 1 diastereocontrol (Scheme 2A).[17] Alternatively, the samarium diiodide-mediated reduction of **2j** furnished the *anti*-product **7** in 73% yield with modest stereocontrol (*ds* = 7 : 1).[18] To further showcase the benefits of this approach, the 1,3-dioxolane was cleaved to liberate the triol (Scheme 2B). Reduction of the ketone **2a** (*ds* = 13 : 1), followed by acetal cleavage using $BF_3{\cdot}Et_2O$ and 1,3-propanedithiol afforded the triol **8** in 96% overall yield (two steps).[19,20]

In conclusion, we have developed a diastereoselective bismuth-mediated two-component hemiacetal oxa-conjugate addition reaction that provides *anti*-4,5-disubstituted 1,3-dioxolanes using mild and operationally simple conditions. For instance, the transformation can be conducted without exclusion of air and moisture using 10 mol% catalyst loading, with broad substrate scope and functional group compatibility. In addition, the products can be subjected to stereodivergent reduction and deprotected under mild conditions to convert the 1,3-dioxolane to the *syn,syn*- and *syn,anti*-1,2,4-triols. We envision that this approach will find its niche in the area of target-directed synthesis, especially for the construction of complex polyketide natural products.

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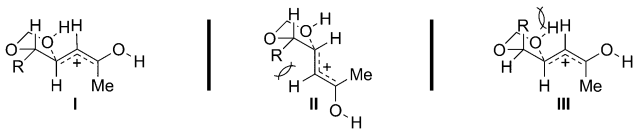
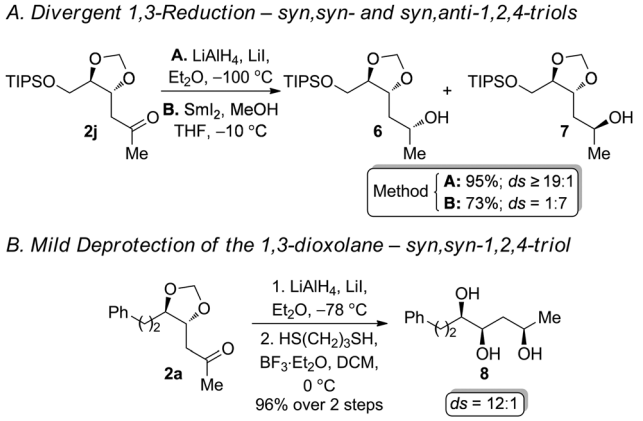


Fig. 2 Origin of stereocontrol in the oxa-conjugate addition reaction.



Scheme 2 Stereodivergent 1,3-reduction and deprotection of 1,3-dioxolanes **2j** and **2a**.

Notes and references

‡ Crystal structure data for **5**: $C_{20}H_{22}N_4O_6$, M = 414.41, colorless needle, 0.5 × 0.07 × 0.03 mm^3, monoclinic, space group $P2_1/n$ (No. 14), a = 18.938(6) Å, b = 5.2580(17) Å, c = 20.517(7) Å, β = 108.760(5)°, V = 1934.4(11) Å^3, Z = 4, T = 100(2) K, D_{calc} = 1.423 g cm^{-3}, MoKα radiation, λ = 0.71073 Å, T = 100(2) K, $2\theta_{max}$ = 50.7°, 9510 reflections collected, 3543 unique (R_{int} = 0.0600). Final GooF = 1.022, R_1 = 0.0510, wR_2 = 0.1117, R indices based on 2158 reflections with $I > 2\sigma(I)$ (refinement on F^2), 272 parameters and 114 restraints.

§ Correspondence regarding the X-ray crystallography should be addressed to: J. Bacsa, Department of Chemistry, Emory University, Atlanta, GA 30322, USA.

¶ Representative experimental procedure for the diastereoselective bismuth-mediated two-component hemiacetal oxa-conjugate addition reaction of γ-hydroxy-α,β-unsaturated ketones with paraformaldehyde: Bismuth(III) nitrate pentahydrate (24 mg, 0.05 mmol, 0.1 equiv.) was added to a stirred solution of the γ-hydroxy-α,β-unsaturated ketone **1a** (102 mg, 0.5 mmol, 1 equiv.) and paraformaldehyde (76 mg, 2.5 mmol, 5 equiv.) in DCM (2 ml) at room temperature. The reaction mixture was then stirred at this temperature for *ca.* 36 hours (t.l.c. control), filtered through a pad of silica gel with diethyl ether and concentrated *in vacuo* to afford the crude product. Purification by flash chromatography (silica gel, 25–30% diethyl ether/petroleum ether gradient) furnished the *dioxolanes* **2a**/**3a** (97.2 mg, 83%) as a colorless oil (*ds* = 13 : 1 by 500 MHz ^{1}H NMR).

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