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The elusive aldol reaction of enolates with aldolates—a highly stereoselective process using three different carbonyl components†

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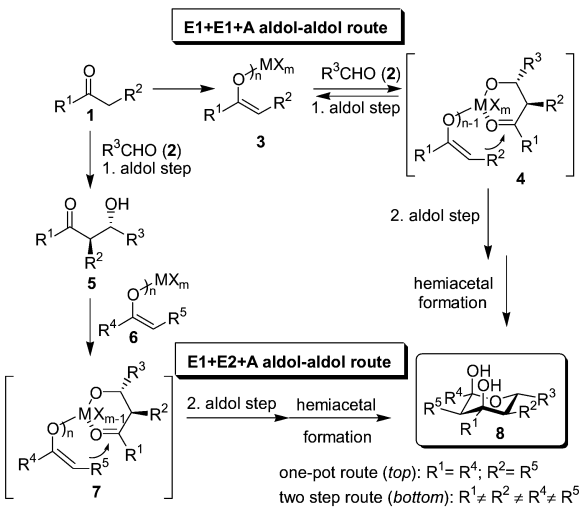
Three different carbonyl components are assembled to tetrahydropyran-2,4-diols by two successive diastereoselective aldol reactions.

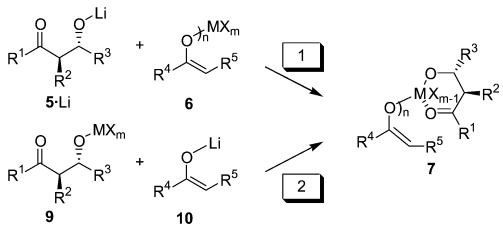
Contrary to the ample usage of the aldol reaction in domino/tandem[1] processes.[2,3] its use in two consecutive aldol–aldol reactions is rare[4] and often limited to trimerisation protocols.[5] We have recently outlined the first examples of a highly diastereoselective and widely applicable one-pot domino–aldol–aldol–hemiacetal strategy using metal bisenolates (or polyenolates) **3** and various aldehydes **2** (Scheme 1, top route, $R^1 = R^4$; $R^2 = R^5$)[6] yielding tetrahydropyran-2,4-diols **8** along the **E1** + **E1** + **A** route (using only one enol **E1** and one aldehyde **A**). We now wish to report the first case of an **E1** + **E2** + **A** aldol–aldol protocol to yield structurally diversified tetrahydropyran-2,4-diols with up to 5 different groups R in a highly stereoselective manner.

As **4** is a plausible intermediate (the metal center coordinates both to the aldolate‡ and enolate) in the **E1** + **E1** + **A** reaction,[6] we contemplated realising the elusive **E1** + **E2** + **A** aldol–aldol reaction *via* its structural analogue **7**. In such an approach, however, one has to worry that rapid retro-aldol reaction, as observed in the **E1** + **E1** + **A** route (**4** → **3** + **2**), leads to a disastrous scrambling of the enol components, most likely the reason why any **E1** + **E2** + **A** reaction has been intangible so far.

Realistically, the **E1** + **E2** + **A** aldol–aldol reaction can only be orchestrated when (i) an adequate way to assemble the desired intermediate **7** is found, and (ii) a metal is met that renders the 2. aldol step (Scheme 1) more rapid than retro-aldol reaction. **7** may originate from the reaction of mono-aldolate **5**·Li with metal enolate **6**. (pathway 1, Scheme 2; X = leaving group) or alternatively from lithium enolate **10** and metal aldolate **9** (pathway 2). Independent of the pathway the aldolate must have the correct relative *anti* configuration as in the tetrahydropyran-2,4-diol.



Scheme 1 General concept for the synthesis of tetrahydropyran-2,4-diols by two successive aldol reaction steps (**E1** and **E2** denote the nucleophilic enolates, **A** the aldehyde component).



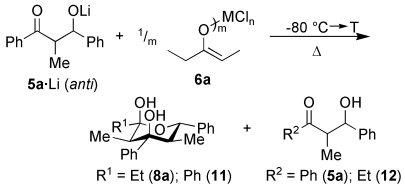
Scheme 2

Following our earlier results,[6] the influence of various metal fragments (MX_{m+n} = $TiCl_4$, $TiCl_4$–Bu_3N, $Ti(OiPr)_2Cl_2$, $ZrCl_4$, $SnCl_4$, $InCl_3$, $AlCl_3$, and $ZnCl_2$) in the reaction of metal enolate **6a** (R^4 = Et, R^5 = Me) with *anti* **5a**·Li[7] (R^1 = Ph, R^2 = Me, R^3 = Ph; d.e. = 75%) to afford **8a** as the **E1** + **E2** + **A** product was explored (Scheme 3). From the metal fragments, only $ZrCl_4$ (19%), $SnCl_4$ (28%), $InCl_3$ (7%) and $ZnCl_2$ (14%) afforded **8a** in some detectable yield.

Most importantly, however, no retro-aldol cleavage of **5a** was observed with $SnCl_4$, whereas use of $ZrCl_4$, $InCl_3$, and $ZnCl_2$ led additionally to tetrahydropyran-2,4-diol **11**, propiophenone and β-hydroxyketone **12**, in particular at higher temperatures. The formation of the latter compounds unequivocally indicates occurrence of the unwanted retro-aldol reaction. Thus, the reaction was optimized with $SnCl_4$ varying the temperature, reaction time and stoichiometry. Finally, **8a** was furnished in 63% at 40 °C, 4 h using $SnCl_4$: enolate : monoaldolate = 1 : 2 : 2 attesting that two molecules of **8a** form in the coordination sphere of one tin(IV) center. Further decrease of the $SnCl_4$: enolate ratio to 1 : 5 failed to provide **8a**, which precludes a catalytic route. Notably, all efforts to achieve the **E1** + **E2** + **A** reaction *via* pathway 2 (Scheme 2) proved far less successful.

The **E1** + **E2** + **A** product **8a** *via* ^{1}H-NMR and X-ray structure analysis (Fig. 1) shows all alkyl and aryl substituents in the equatorial positions and both hydroxy groups axially. Typically, as already known from **E1** + **E1** + **A** products, the two methyl groups in **8a** appear at high field (δ = 0.36 and 0.77 ppm).

With a successful approach to **8a** at hand, we now studied the reaction of **6a** with aldolates **5a,b** (for R^1, R^2 and R^3, see Table 1) changing the *syn* : *anti* ratio of the latter. Indeed, as predicted



Scheme 3

† Electronic supplementary information (ESI) available: synthesis and spectroscopic data for **8a**. Crystallography for **8a**. Fig. S1: crystal structure of **8a**; Fig. S2: hydrogen bonding in **8a**. See http://www.rsc.org/suppdata/cc/b2/b209536j/

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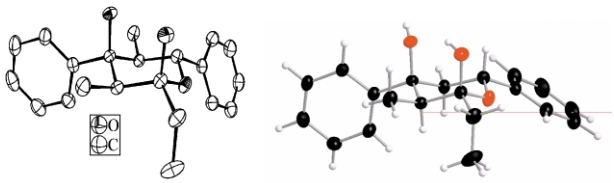


Fig. 1 X-ray structure of **8a**.‡§ Enantiomorphous crystals of **8a** were received from EtOH (conglomerate). The ellipsoids (left) represent a probability factor of 50%; stick and ball representation (right).

above, rather low yields of **8a**, **b**, were received starting from *syn* enriched monoaldolates **5a,b** while yields amounted to >50% with *anti*-aldolates as starting material (Table 2). Formation of **8b** from *syn*-**5b** (entry d) is explained by partial *syn* → *anti* isomerisation of the β-hydroxyketone *via* a retro-aldol process, especially at elevated temperatures.[7]

The general applicability of the concept was further explored by varying the enolates and aldehydes. Rewardingly, Table 1 documents that 10 out 12 desired **E1** + **E2** + **A** products could be prepared in a highly stereoselective manner. In no case were other diastereomeric tetrahydropyrandiols detected.

Some problems arise with β-hydroxyketones containing the acetophenone subunit as they easily dehydrate under the reacton conditions to afford α,β-unsaturated ketones. Dehydration could be minimized for entries 9 and 10 by reducing the reaction temperature to 0 °C. However, no formation of **8l,m** was detected even at low temperatures (Table 1, entries 11 and 12).

A mechanistic rationale (Scheme 4) for these results has to acknowledge the *anti* configuration of the starting aldolate. Thus, to minimize steric interactions in the transition state for the 2. aldol step (**TS1**) a chair-twistboat conformation allows the bulky groups to assume a pseudo equatorial position. Similarly, **14** should be most stable in chair-boat conformation. Formation of the final hemiacetal *via* **TS2** should therefore be accompanied by a release of strain as all R[1]–R[5] substituents move into equatorial positions.

In summary, a novel methodology is described for the highly stereoselective synthesis of tetrahydropyran-2,4-diols starting from simple carbonyl compounds in two sequential aldol reactions. The utility of the concept has been demonstrated preparing a variety of products from different alkyl and aryl ketones and aldehydes. Current investigations in our laboratories aim to use the diversified tetrahydropyran-2,4-diol structures as bisdentate ligands in metal catalysed reactions.

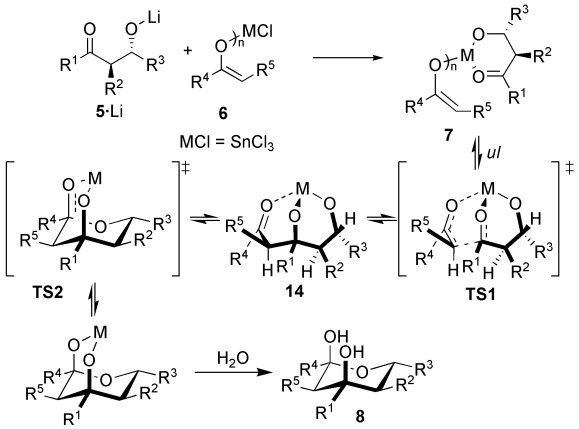
Table 1 Preparation of tetrahydropyran-2,4-diols **8** from **5** and **6** (−80 °C → 40 °C, 4 h) in the presence of $SnCl_4$

Entry	R[1]	R[2]	R[3]	R[4]	R[5]	Product	Yield[a] (%)
1	Ph	Me	Ph	Et	Me	**8a**	63
2	Ph	Me	*i*Pr	Et	Me	**8b**	56
3	Ph	Me	Ph	Ph	H	**8c**	53
4	Ph	Me	*i*Pr	Ph	H	**8d**	45
5	Et	Me	Ph	Ph	Me	**8e**	43
6	Et	Me	*i*Pr	Ph	Me	**8f**	56
7	Et	Me	Ph	Ph	H	**8g**	41
8	Et	Me	*i*Pr	Ph	H	**8h**	48
9	Ph	H	Ph	Et	Me	**8i**	48[b]
10	Ph	H	*i*Pr	Et	Me	**8k**	22[b]
11	Ph	H	Ph	Ph	Me	**8l**	—
12	Ph	H	*i*Pr	Ph	Me	**8m**	—

[a] Isolated yields. [b] Reaction temperature = 0 °C.

Table 2 Dependence of the yields of **8** on the diastereomeric ratio of the starting aldolate **5** (−80 °C → 40 °C, 4 h) in the presence of **6a**–$SnCl_4$

Entry	Aldolate	*syn*:*anti*	Yield (%)
a	**5a**[7]	15:85	**8a**/63
b	**5a**[8]	95:5	**8a**/7
c	**5b**[7]	<1:>99	**8b**/54
d	**5b**[8]	>99:<1	**8b**/9



Scheme 4 Mechanistic proposal for the formation of **8**.

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Notes and references

‡ We use the expression aldolate also for a ketolate (= β-hydroxyketone).

§ Crystal data for **8a**: orthorhombic, space group $Pna2_1$ (No. 33), a = 10.9177(9), b = 17.2334(10), c = 9.4999(5) Å, V = 1787.4(2) Å^3, Z = 4, ρ_{calc} = 1.213 g cm^{-1}, data collection: STOE IPDS, 27347 reflections, 4247 independent reflections, R_{int} = 0.0409, T = 173 K, Mo-Kα radiation (λ = 0.71069 Å), $2\theta_{max}$ = 56.22°, $-14 \leqslant h \leqslant 14$, $-22 \leqslant k \leqslant 22$, $-12 \leqslant l \leqslant 12$, crystal size 0.45 × 0.4 × 0.3 mm, no absorption correction, structure solution by direct methods, refinement against F^2 (SHELX-97[9]). The refinement of 322 parameters converged at R = 0.0292 and wR = 0.0732 ($I > 2\sigma(I)$) and R = 0.0324 and wR = 0.0746 (all reflections). Flack[10] parameter 0.8(6). The absolute configuration could not be determined from X-ray. CCDC 163263. See http://www.rsc.org/suppdata/cc/b2/b209536j/ for crystallographic data in CIF or other electronic format.

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