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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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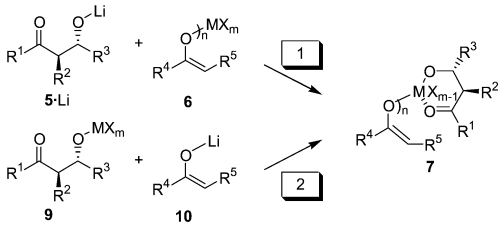
Received (in Cambridge, UK) 1st October 2002, Accepted 6th November 2002
First published as an Advance Article on the web 12th December 2002

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.



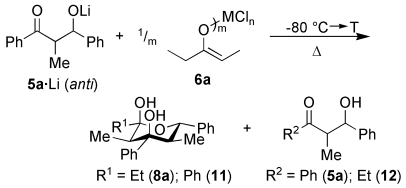
Scheme 2

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.

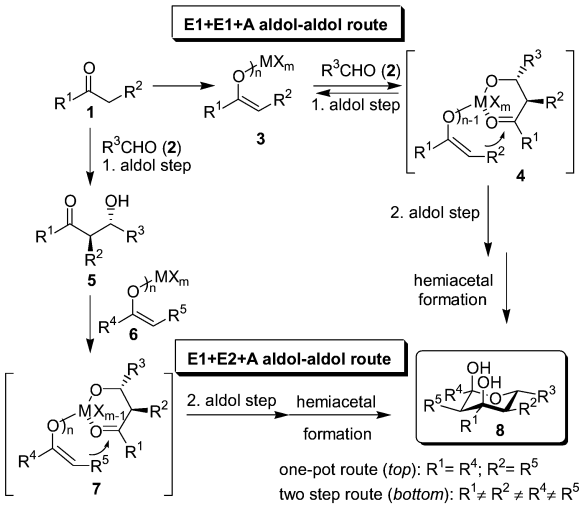
Most importantly, however, no retro-aldol cleavage of **5a** was observed with $SnCl_4$, whereas use of $ZrCl_4$, $InCl_3$, and $ZnCl_2$ led additionally to tetrahydropyran-2,4-diol **11**, propiophenone and β-hydroxyketone **12**, in particular at higher temperatures. The formation of the latter compounds 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



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).

† 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/

DOI: 10.1039/b209536j

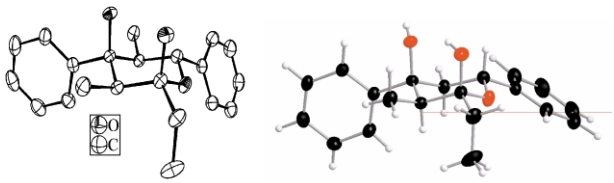


Fig. 1 X-ray structure of **8a**.‡§ Enantiomorphous crystals of **8a** were received from EtOH (conglomerate). The ellipsoids (left) represent a probability factor of 50%; stick and ball representation (right).

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.

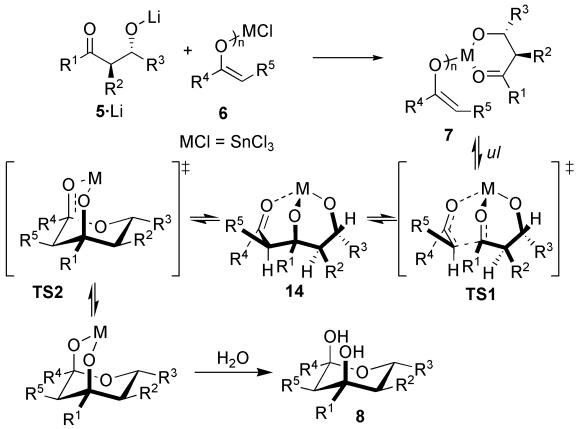
Table 1 Preparation of tetrahydropyran-2,4-diols **8** from **5** and **6** (−80 °C → 40 °C, 4 h) in the presence of $SnCl_4$

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**.

This work was supported by the Deutsche Forschungsgemeinschaft and by the Fonds der Chemischen Industrie.

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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