

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

Michael Schmittel,*^a Andreas Haeuseler,^a Tom Nilges^b and Arno Pfitzner^b

^a FB 8 – OC1 (Chemie-Biologie), Universität Siegen, Adolf-Reichwein-Str, D-57068 Siegen, Germany.

E-mail: schmittel@chemie.uni-siegen.de; Fax: (+49) 271 740 3270; Tel: (+49) 271 740 4356

^b Institut für Anorganische Chemie, Universität Regensburg, Universitätsstr. 31, D-93040 Regensburg, Germany

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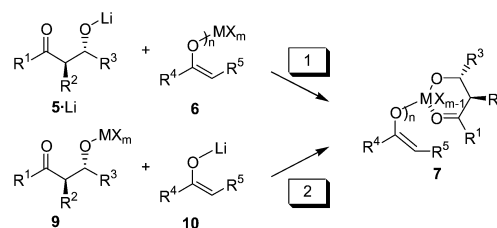
Three different carbonyl components are assembled to tetrahydropyran-2,4-diols by two successive diastereoselective aldol reactions.

Contrary to the ample usage of the aldol reaction in domino/tandem¹ processes,^{2,3} its use in two consecutive aldol–aldol reactions is rare⁴ 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, R¹ = R⁴; R² = R⁵)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.



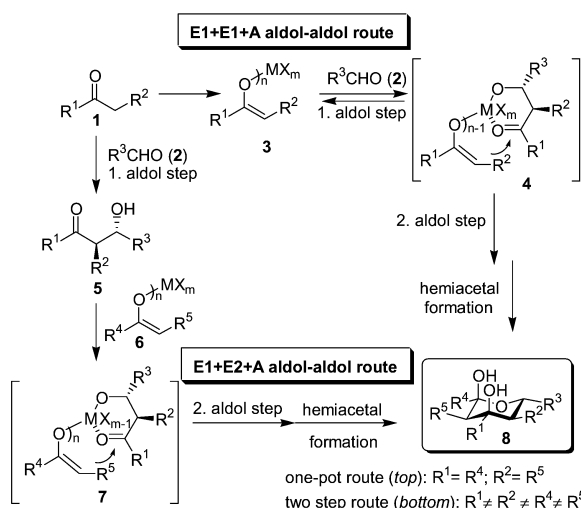
Scheme 2

Following our earlier results,⁶ the influence of various metal fragments (MX_{m+n} = TiCl₄, TiCl₄–Bu₃N, Ti(OiPr)₂Cl₂, ZrCl₄, SnCl₄, InCl₃, AlCl₃, and ZnCl₂) in the reaction of metal enolate **6a** (R⁴ = Et, R⁵ = Me) with *anti* **5a**·Li⁷ (R¹ = Ph, R² = Me, R³ = Ph; d.e. = 75%) to afford **8a** as the **E1** + **E2** + **A** product was explored (Scheme 3). From the metal fragments, only ZrCl₄ (19%), SnCl₄ (28%), InCl₃ (7%) and ZnCl₂ (14%) afforded **8a** in some detectable yield.

Most importantly, however, no retro-aldol cleavage of **5a** was observed with SnCl₄, whereas use of ZrCl₄, InCl₃, and ZnCl₂ 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 SnCl₄ varying the temperature, reaction time and stoichiometry. Finally, **8a** was furnished in 63% at 40 °C, 4 h using SnCl₄: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 SnCl₄: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.

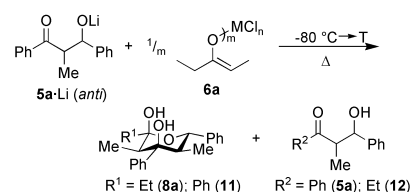
The **E1** + **E2** + **A** product **8a** *via* ¹H-NMR and X-ray structure analysis (Fig. 1) shows all alkyl and aryl substituents in the equatorial positions and both hydroxy groups axially. Typically, as already known from **E1** + **E1** + **A** products, the two methyl groups in **8a** appear at 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 R¹, R² and R³, see Table 1) changing the *syn*:*anti* ratio of the latter. Indeed, as predicted



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/>



Scheme 3

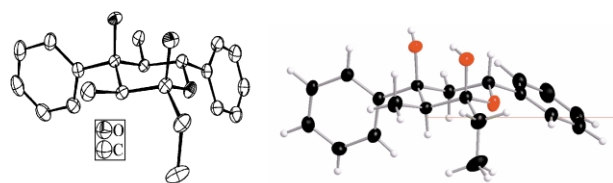


Fig. 1 X-ray structure of **8a**.[‡] Enantiomorphous crystals of **8a** were received from EtOH (conglomerate). The ellipsoids (left) represent a probability factor of 50%; stick and ball representation (right).

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 of 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 reaction 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 R¹–R⁵ 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 laborato-

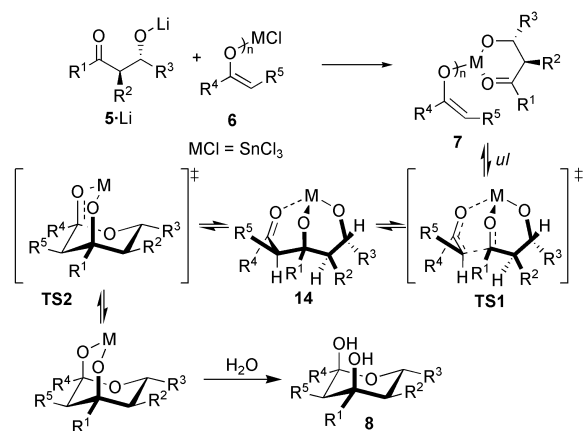
Table 1 Preparation of tetrahydropyran-2,4-diols **8** from **5** and **6** (–80 °C → 40 °C, 4 h) in the presence of SnCl₄

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>i</i> Pr	Et	Me	8b	56
3	Ph	Me	Ph	Ph	H	8c	53
4	Ph	Me	<i>i</i> Pr	Ph	H	8d	45
5	Et	Me	Ph	Ph	Me	8e	43
6	Et	Me	<i>i</i> Pr	Ph	Me	8f	56
7	Et	Me	Ph	Ph	H	8g	41
8	Et	Me	<i>i</i> Pr	Ph	H	8h	48
9	Ph	H	Ph	Et	Me	8i	48 ^b
10	Ph	H	<i>i</i> Pr	Et	Me	8k	22 ^b
11	Ph	H	Ph	Ph	Me	8l	—
12	Ph	H	<i>i</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**–SnCl₄

Entry	Aldolate	<i>syn</i> : <i>anti</i>	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**.

ries aim to use the diversified tetrahydropyran-2,4-diol structures as bidentate ligands in metal catalysed reactions.

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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 *Pna*2₁ (No. 33), *a* = 10.9177(9), *b* = 17.2334(10), *c* = 9.4999(5) Å, *V* = 1787.4(2) Å³, *Z* = 4, *ρ*_{calc} = 1.213 g cm^{–3}, data collection: STOE IPDS, 27347 reflections, 4247 independent reflections, *R*_{int} = 0.0409, *T* = 173 K, Mo-*K*α radiation (*λ* = 0.71069 Å), 2 θ _{max} = 56.22°, –14 ≤ *h* ≤ 14, –22 ≤ *k* ≤ 22, –12 ≤ *l* ≤ 12, crystal size 0.45 × 0.4 × 0.3 mm, no absorption correction, structure solution by direct methods, refinement against *F*² (SHELX-97⁹). The refinement of 322 parameters converged at *R* = 0.0292 and *wR* = 0.0732 (*I* > 2 σ (*I*)) and *R* = 0.0324 and *wR* = 0.0746 (all reflections). Flack¹⁰ parameter 0.8(6). The absolute configuration could not be determined from X-ray. CCDC 163263. See <http://www.rsc.org/suppdata/cc/b2/b209536/> for crystallographic data in CIF or other electronic format.

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