Accepted Manuscript

Further insights into the organocatalytic reaction of 2,2-dimethyl-1,3-dioxan-5-one with α-silyloxy aldehydes

Dani Sánchez, Héctor Carneros, Alejandro Castro-Alvarez, Enric Llàcer, Ferran Planas, Jaume Vilarrasa

Please cite this article as: Sánchez, D., Carneros, H., Castro-Alvarez, A., Llàcer, E., Planas, F., Vilarrasa, J., Further insights into the organocatalytic reaction of 2,2-dimethyl-1,3-dioxan-5-one with α-silyloxy aldehydes, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.10.042

Further insights into the organocatalytic reaction of 2,2-dimethyl-1,3-dioxan-5-one with α-silyloxy aldehydes

Dani Sánchez, Héctor Carneros, Alejandro Castro-Alvarez, Enric Llàcer, Ferran Planas, Jaume Vilarrasa[*]

Organic Chemistry Section, Facultat de Química, Universitat de Barcelona, Av. Diagonal 645, 08028 Barcelona, Catalonia, Spain

ARTICLE INFO

ABSTRACT

Proline-catalysed reactions of dihydroxyacetone isopropylidene acetal, **1,** with enantiopure α-silyloxy aldehydes **2/4/6/8** afford 90–95% yields of cross-aldol products (only one stereoisomer in each case), provided that 15 ± 10 equiv of H_2O are present in the medium. Individual reaction steps have been monitored by NMR spectroscopy to gain insight into the cause of these remarkable results. It is confirmed that proline 'protects' **2** as oxazolidinone **2-ox**, but it means that proline—the catalyst—is trapped by **2**; several equiv of H_2O are required to avoid it. Moreover, H_2O mediates prolyl group exchanges and goes against the dehydration of aldols. For the first time, we detected by NMR one 'wanted' intermediate (an enamine of the adduct).

The proline-catalysed reaction of the natural product dihydroxyacetone and its derivatives, especially of 2,2-dimethyl-1,3-dioxan-5-one (dihydroxyacetone isopropylidene acetal, **1**), with various aldehydes has been often used for the preparation of polyols and monosaccharides;[1,2] the pioneers were the groups of Barbas, MacMillan, Enders and Cordova.[1] It is a remarkable direct cross-aldol-like reaction (formation of β-hydroxy ketones or ketols), as the enamine of a ketone (**1**) reacts with an aldehyde, whereas self-aldol products are minor. The challenge is that both carbonyl compounds have α-hydrogens. Most of these reactions have been performed with achiral aldehydes or D-glyceraldehyde derivatives, affording acceptable or good yields and stereoselectivities.[1,2] More recently, Hanessian[3] and Enders groups[4] have reported two outstanding examples with chiral α-silyloxy aldehydes (Scheme 1).

We were interested in going further: to widen the scope of aldehydes and reaction conditions reported by Enders et al.;[4] to gain insight into the features of α-OR aldehydes and dihydroxyacetone derivatives; and to apply the improved conditions to the preparation of pentitol analogues (instead of hexitols[1]) that may give natural aminosaccharide antibiotics by standard replacement of appropriate OH groups for azide ion.
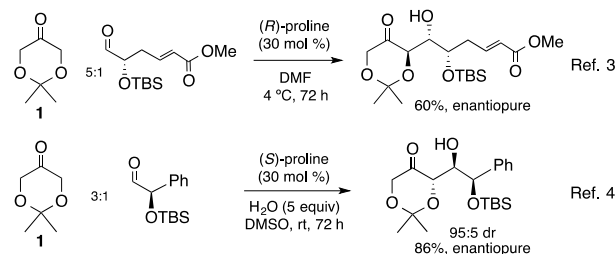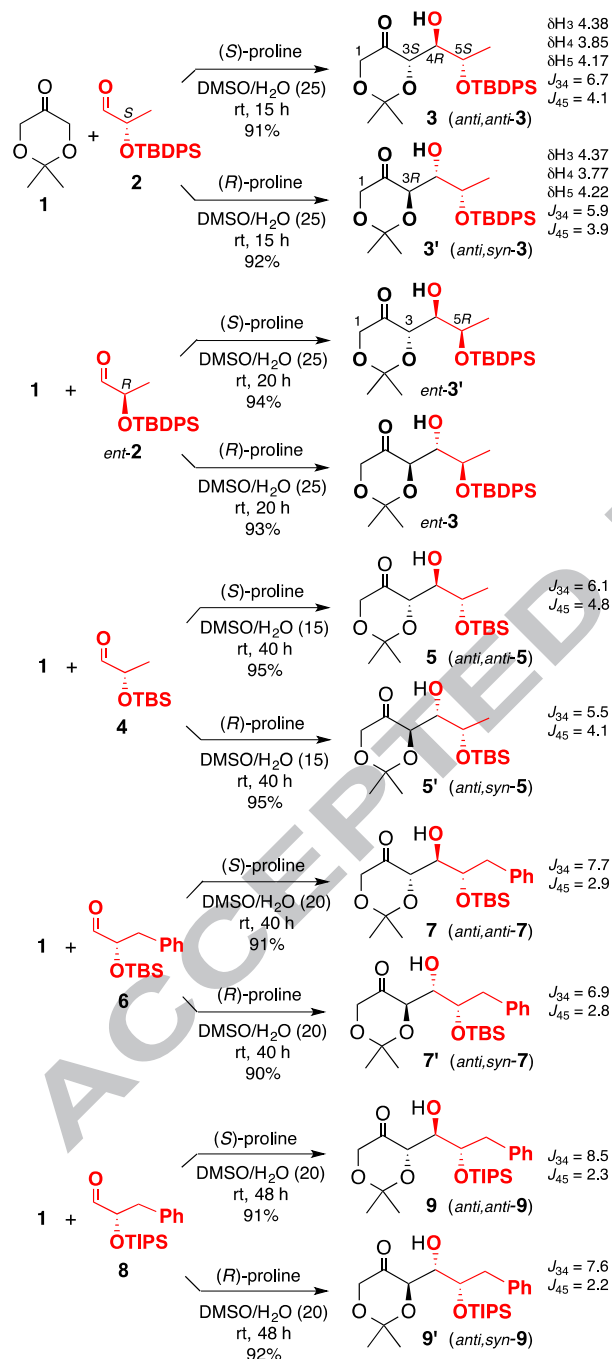

Scheme 1. Reaction of **1** with α-silyloxy aldehydes. Precedents.

To our delight, in a preliminary experiment with **1**, *tert*-butyldiphenylsilyloxy propanal **2** and (*S*)-proline (Pro), hydroxyketone **3** was formed more rapidly than in the examples of Scheme 1, in 10:1 v/v DMSO/H_2O. In fact, the conversion of **2** into **3** was complete within 15 h.[5] Only one stereoisomer was observed (that shown in Scheme 2, top); the isolated yield was 91%.[5] In the experiment we had used 25 equiv of H_2O! Although the beneficial effect of several equiv of H_2O on Pro-mediated aldol reactions is well known,[6] such a large excess of H_2O should be very detrimental for the formation of any enamine and/or iminium salt. We soon found that the addition of 5 to 25 equiv of H_2O was ideal in this particular case.[7,8]

———
* Corresponding author. Tel.: +34 934021258, fax: +34 933397878.
  E-mail address: jvilarrasa@ub.edu

Tetrahedron Letters

With 15 mol % of Pro (**1/2**/Pro/H$_2$O in 3 : 1 : 0.15 : 15 ratio), for 48 h, the reaction was also complete. Thus, it is not necessary to use 30 mol % of Pro. As expected, the lower the amount of catalyst the lower the reaction rate, but nothing else. With only 1.2 equiv of **1** and 10 mol % of Pro (1.2 : 1 : 0.10 : 10) the reaction was slower (66% of conversion within two days, ca. 100% after one week), as also expected, but the stereoselectivity was maintained.
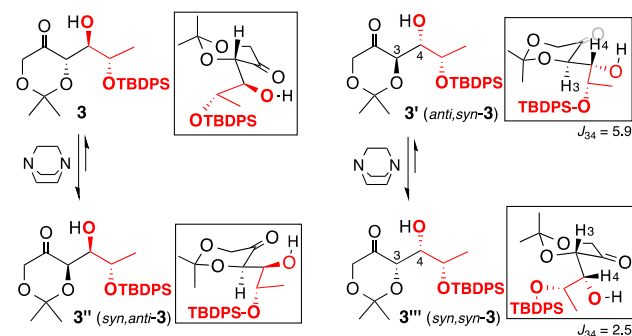
Using (*R*)-proline, the diastereomer of **3** drawn in Scheme 2 (1,3,4,5-tetrahydroxypentan-2-one derivative **3'**) was exclusively formed. The OH/OR groups are in a 3,4-*anti*-4,5-*syn* relationship, according to their NMR spectra (which agree with those reported[1–4] for related compounds). Moreover, the enantiomers of **3** and **3'** were readily prepared by using the enantiomer of **2**. Chiral HPLC (see Supplementary Data) confirmed the stereopurity of the products.

We examined the scope of the reaction using other α-silyloxy aldehydes (**4**, **6** and **8**). Complete conversions to stereopure *anti* adducts (see Scheme 2) were also obtained, with various silyl groups,[9] although the reaction times had to be lengthened in some cases.

To discard that some stereoisomers formed in minute amounts were not detected by NMR or HPLC, we prepared the stereoisomers of **3** shown in Scheme 3 by equilibration at room temperature via the enolate, in the presence of a weakly basic tertiary amine such as 1,4-diazabicyclo[2.2.2]-octane (DABCO, 20 mol %), to prevent retro-aldol reactions. Thus, **3** was converted into **3''** (1:3 ratio, after 48 h in DMSO-d_6, 1:1.5 after 7 days in CDCl$_3$). We separated the mixture and confirmed by NMR and HRMS the structure of **3''**. Similarly, **3'** was converted into **3'''** (1:2.8 ratio after 7 days in CDCl$_3$). The J_{34} values of **3''** and **3'''** were much lower than those of their respective precursors. Calculations to understand why these equilibria are shifted toward the *syn* isomers, as well as to explain the differences between the coupling constants, are given as Supplementary Data. In summary, the 3,4-*anti* isomers (consequence of the aldol reaction) can be partially isomerised to their 3,4-*syn* analogues. These *syn* isomers were absent from the aldol reactions.

Scheme 2. Direct cross-aldol reaction between **1** and **2/4/6/8** in DMSO-d_6 with 15–25 equiv of H$_2$O (indicated in parentheses) and 0.3 equiv of Pro. Reaction times for complete conversion are given for a 3:1 ratio of **1** to the aldehydes. Relevant ^{1}H NMR spectral data in CDCl$_3$ are included.

Scheme 3. Isomerisation of *anti*-aldols **3** and **3'** to their *syn*-aldols.

Such a stereopurity is astonishing. A partial racemisation of **2**/**4**/**6**/**8** in such polar media may be expected (as well as self-aldol adducts from partially racemised aldehydes via their enamines).[10] However, we demonstrated that α-OR aliphatic aldehydes gave rise to oxazolidinone tautomers rather than enamine tautomers when they are treated with equimolar amounts of Pro.[11] We have now determined $K_{eq} \approx 200 \pm 20$ for the equilibrium of Scheme 4. Moreover, we confirmed that α-silyloxy aldehydes and 0.3 equiv of Pro did not racemise at all in DMSO-d_6 or in DMSO-d_6 with 25 equiv of D$_2$O, for 24 h.

The fact is that the reaction of **2/4/6/8** with Pro to form bicyclic *exo*-oxazolidinones (e.g. **2-ox**) is so favoured that the solid (Pro) is solved rapidly in anhydrous DMSO (stored over MS) and also in DMF, despite the fact that only up to 0.3 equiv of H_2O can be generated, as only 0.3 equiv of Pro is used. In our case, Pro was stored in a desiccator over P_4O_{10} to ensure that no additional moisture was introduced. In other words, the added water is not necessary to solubilise Pro. *Addition of several equiv of H_2O is required to avoid that the catalyst (Pro) almost completely disappears from the medium by reaction with α-silyloxy aldehydes*, which, obviously, are in excess with regard to the catalyst.[12]
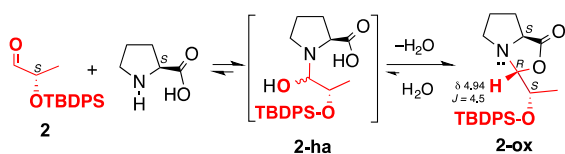
Scheme 4. Reaction of **2** with (*S*)-proline. Tautomers of **2-ox** such as enamines and zwitterions were not detected by ^{1}H NMR.

α-Silyloxy aldehydes are special indeed. α-Alkoxy aldehydes do not behave identically. 4-Methoxybenzyloxy derivative **10**, chosen as representative, was also fully converted into the aldol adducts, within 40 h, but in this case the formation of C5-epimers as impurities was observed,[13] more in the presence of Pro than of (*R*)-Pro (Scheme 5). An explanation is that the multiple equilibria[12] involved in the formation of the oxazolidinones are not so shifted to oxazolidinone **10-ox** as in the parallel equilibria involving **2/4/6/8**. A scheme is given as Supplementary Data.
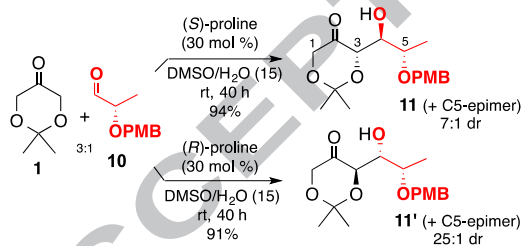

Scheme 5. Reaction of **1** with **10** in the presence of proline.

Nevertheless, the question is to know which species predominate(s) when 15±10 equiv of H_2O is added to the DMSO solutions of the oxazolidinones **2-ox/4-ox/6-ox/8-ox**. To a solution of **2-ox** in DMSO-d_6 (prepared by mixing equimolar amounts of **2** and Pro, in the presence of crushed 4 Å MS and filtering under Ar) we added 10 equiv of D_2O. This gave rise to the appearance of a small aldehyde signal (**2**), that is, to the reversal of Scheme 4, as expected. No other intermediates, such as hemiaminals (**2-ha**) or any enamine tautomer or conformer (**2-en**), were detected. With 25 equiv of D_2O, similar molar amounts of **2-ox**, **2** (δH_1 9.50, $^3J = 0.8$) and the hydrate of **2** (δH_1 4.67, $^3J = 4.5$) were noted. In other words, it is necessary to add > 10 equiv of H_2O to observe a

significant amount of free **2**. With 50 equiv of D_2O, the hydrate of **2** became the major compound (and nothing else was detected, that is, **2-ox** and **2** disappeared).[14] Thus, it is confirmed that *without adding ≥ 10 equiv of H_2O the catalyst (Pro) is mostly trapped by α-OSiR$_3$ aldehydes, so the enamine of **1** can hardly be formed. It is also noted that the formation of hydrates, which may have a negative effect, is not significant under the reaction conditions*.

Not all the merit belongs to Pro. Part of the success has to be attributed to the special features of **1**. In fact, the parallel reaction performed with cyclohexanone (instead of **1**) and **2**, plus 0.3 equiv of Pro and 25 equiv of H_2O for 15 h, gave the corresponding aldol(s) with a conversion of only 38%. With 10 equiv of cyclohexanone and with 10 equiv of H_2O, after 48 h of reaction the outcome was only 51%; this fact can be explained by the low concentration of cyclohexanone enamine in the medium rather than by a low reactivity.

We examined the reaction of ketone **1** with Pro alone (Scheme 6). After mixing them one-to-one in anhydrous DMSO-d_6, enamine **1-en** was the only new product observed in the ^{1}H and HSQC NMR spectra. Oxazolidinone **1-ox** was not detected by ^{1}H NMR even after overnight accumulation. The K_{eq} for **1** + Pro = **1-en** + H_2O, determined from the integration of appropriate signals, is 2.5 (2.5 ± 0.5). By contrast, cyclohexanone (and most ketones) do not form enamines in the same ratio; for example, we estimate $K_{eq(en)} \approx 0.006$ for the formation of the enamine from cyclohexanone and Pro. It may explain why ketone **1** (but not standard ketones) is efficient in the cross-aldol reactions here examined: at least there is a detectable concentration of enamine **1-en** in the medium.
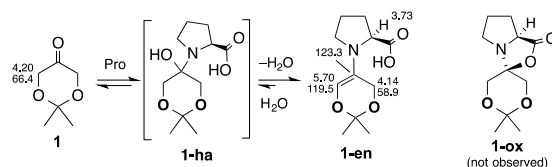
**Scheme 6.** Dioxanone **1** and Pro give enamine **1-en** rather than oxazolidinone **1-ox**.

Mixing **1** and **2-ox** may give rise to the **1** + **2-ox** = **1-en** + **2** equilibrium, an exchange of the 'prolyl group' between an enamine and an oxazolidinone (Scheme 7, top). This equation is the subtraction of the formation equilibrium of **2-ox** and that of **1-en**. The K value would be ≈ 2.5 ± 0.5 / 200 ± 20 ≈ 0.013 ± 0.002.[15] In practice, this equilibrium cannot be established as **1-en** and **2** shall react from the very beginning. We have performed such an experiment. We prepared **2-ox** in DMSO-d_6 (in the presence of MS) and added 3 equiv of **1**, without water. Nothing happened. However, when this reaction was repeated with 10 equiv of H_2O, aldol **3** appeared quickly; it was the major species noted by ^{1}H NMR after few hours and the predominant product after 15 h (as in Scheme 2). Thus, *the role of water may be viewed as a mediator or initiator of the exchange of the prolyl group between **1** and **2-ox***.

The presence of several equiv of H_2O is not necessary to cause the hydrolysis of the intermediates within brackets of Scheme 7 (where other possible tautomers are not included to save space). In DMSO, the last hydrolysis is so shifted toward the final product that moisture and/or part of the 0.3 equiv of H_2O produced from the reactions of Pro with **1** and **2** are sufficient for the turnover of Pro. These intermediates behave as dehydrating agents. Exchange reactions may also participate in the hydrolysis of these intermediates.[16]
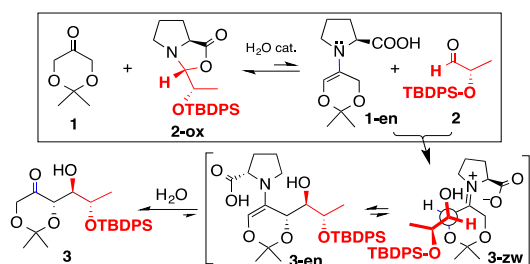
Scheme 7. Transfer of the prolyl group between **1** and bicyclic oxazolidinone **2-ox**, followed by the reaction of **1-en** with **2**.

It was hard to detect by NMR any of the intermediates within brackets of Scheme 7.[17] However, *when we treated 1 and 2 with 120 mol % of Pro under very anhydrous conditions* (DMSO-d_6, 4 Å MS, CaH_2), *two enamines were clearly observed* by ^{1}H NMR, HSQC and HMBC, viz. **1-en** and **3-en** (Figure 1). Other tautomers of **3-en** (the regio-isomeric enamine, oxazolidinones and zwitterion **3-zw**) were not detected. Mixing **1** and Pro (1:1) *under these dehydrating conditions,* to first form sufficient amounts of **1-en**, followed by addition of **2**, provided identical spectra, *but the appearance of dehydrated dimer of 1 (self-condensation) and dehydrated aldol as by-products was often observed by NMR.*
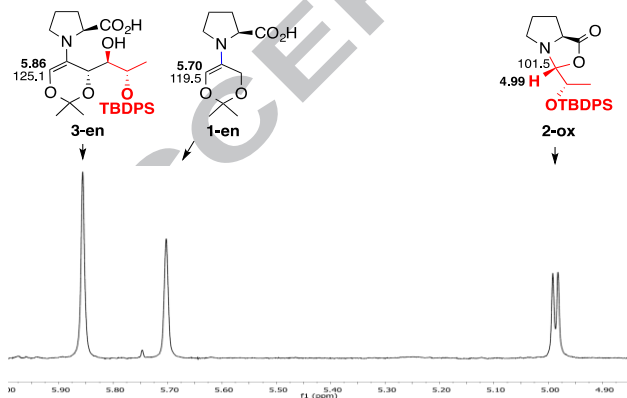

Figure 1. Reaction of **1**, **2** and Pro in the presence of dehydrating agents (^{1}H NMR spectrum, from 5.90 to 4.90 ppm)

By addition of 10 equiv of D_2O to the NMR tube (of Figure 1) hydrolysis of **3-en** took place, as expected, whereas the product (deuterated **3**) appeared. The NMR signals of **1-en** and **2-ox** also disappeared, although not so irreversibly and/or rapidly as the signals of **3-en**. See Supple-

mentary Data. Moreover, in another experiment we added **1** to a DMSO-d_6 solution such as that of Figure 1. Nothing significant occurred. However, *it was sufficient to pour 0.5 equiv of D_2O into the NMR tube to observe a prolyl exchange: decrease of 3-en, rise of 1-en and 3 (1 + 3-en = 1-en + 3).* If drops of D_2O were added all the intermediates were hydrolysed, as expected. The direct hydrolysis and the exchange reaction mediated by H_2O are two faces of the same coin, but may be viewed as independent.

In summary, fully stereoselective cross-aldol reactions between ketone **1** (via its enamine **1-en**) and enantiopure aldehydes **2/4/6/8** are reported, expanding the reactivity of **1** already known. Besides, different stereoisomers of aldol **3**, a representative member of the series, have been prepared and characterised for the first time. As aldehydes **2/4/6/8** fully trap the catalyst (Pro) to give the corresponding bicyclic *exo*-oxazolidinones, 15±10 equiv of H_2O must be added to shift the equilibrium position of Scheme 4 to the left otherwise there is no sufficient catalyst available for the formation of enamine **1-en** (which is obviously not favoured by the presence of H_2O); this has been assumed by several authors, but it is now shown by NMR. Such a huge excess of H_2O is not necessary for the last step, i.e. for the hydrolysis of the intermediate detected here for the first time, **3-en**, since it is very prone *per se* to hydrolysis. Trace amounts of H_2O favour the exchanges of the prolyl group and some amounts of H_2O militate against aldol condensations (dehydration of the aldol). In short, *the excellent yields are owing to four favourable effects of H_2O counter-acting two unfavourable effects.* Final corollary: trace amounts or much lower amounts of H_2O (and/or of Pro) would be required if the equilibrium of Scheme 8 was more shifted to the right, viz. using analogues of **1** with a higher tendency to give enamines and using aldehydes with a slightly lower tendency to give oxazolidinones than the silyloxy derivatives examined here, as we hope to demonstrate in due course.
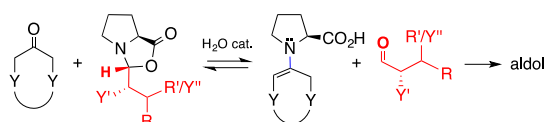
Scheme 8. Plausible equilibria between analogues of **1** and Pro-protected aldehydes (bicyclic oxazolidinones) other than **2/4/6/8**.

Supplementary data

Supplementary data associated with this article (experimental details, NMR spectra, complementary schemes and DFT calculations at different levels) can be found, in the online version, at http://dx.doi.org/ 10.1016/j._tetlett.2015...

References and notes

1. For reviews, see: (a) Mlynarski, J.; Gut, B. *Chem. Soc. Rev.* **2012**, *41*, 587–596: (b) Enders, D.; Narine, A. A. *J. Org. Chem.* **2008**, *73*, 7857–7870, and refs. 9 and 18 therein; (c) Markert, M.; Mahrwald, R. *Chem. Eur. J.* **2008**, *14*, 40–48.

2. For very recent papers, see: (a) Enders, D.; Terteryan, V.; Palecek, J. *Synthesis* **2010**, 2979–2984; (b) Albrecht, L.; Jiang, H.; Dickmeiss, G.; Gschwend, B.; Hansen, S. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 9188–9196; (c) Yang, H.; Mahapatra, S.; Cheong, P. H.-Y.; Carter, R. G. *J. Org. Chem.* **2010**, *75*, 7279–7290; (d) Pearson, A. J.; Panda, S. *Tetrahedron* **2011**, *67*, 3969–3975; (e) Doyagüez, E. G.; Corrales, G.; Garrido, L.; Rodríguez-Hernández, J.; Gallardo, A.; Fernández-Mayoralas, A. *Macromolecules* **2011**, *44*, 6268–6276; (f) Pearson, A. J.; Panda, S. *Org. Lett.* **2011**, *13*, 5548–5551; (g) Ma, G.; Bartoszewicz, A.; Ibrahem, I.; Cordova, A. *Adv. Synth. Catal.* **2011**, *353*, 3114–3122; (h) Fanton, J.; Camps, F.; Castillo, J. A.; Guérard-Hélaine, C.; Lemaire, M.; Charmantray, F.; Hecquet, L. *Eur. J. Org. Chem.* **2012**, 203–210; (i) Palyam, N.; Niewczas, I.; Majewski, M. *Synlett* **2012**, *23*, 2367–2370, and preceding articles; (j) Cieplak, M.; Ceborska, M.; Cmoch, P.; Jarosz, S. *Tetrahedron: Asymmetry* **2012**, *23*, 1213–1217; (k) Enders, D.; David, S.; Deckers, K.; Greb, A.; Raabe, G. *Synthesis* **2012**, *44*, 3483–3488; (l) Doyaguez, E. G.; Fernández-Mayoralas, A. *Tetrahedron* **2012**, *68*, 7345–7354; (m) Halperin, S. D.; Britton, R. *Org. Biomol. Chem.* **2013**, *11*, 1702–1705; (n) Miura, D.; Fujimoto, T.; Tsutsui, A.; Machinami, T. *Synlett* **2013**, *24*, 1501–1504; (o) Dibello, E.; Brovetto, M.; Seoane, G.; Gamenara, D. *Tetrahedron Lett.* **2013**, *54*, 5895–5897; (p) Leczycka, K.; Chaciak, B.; Cieplak, M.; Cmoch, P.; Jarosz, S. *Carbohydr. Res.* **2015**, *403*, 98–103; (q) Miura, D.; Machinami, T. *Modern Res. Catal.* **2015**, *4*, 20–27; (r) for an application to the synthesis of palmerolide C, see: Florence, G. J.; Wlochal, J. *Chem. Eur. J.* **2012**, *18*, 14250–14254.

3. Hanessian, S.; Mi, X. *Synlett* **2010**, 761–764.

4. Enders, D.; David, S.; Deckers, K.; Greb, A.; Raabe, G. *Synthesis* **2012**, *44*, 3483–3488.

5. The reactions of **1** (0.6 M) with **2** (0.2 M, concentrations in DMSO/H_2O, 10:1 v/v, that is, around 25 equiv of H_2O), were complete after stirring overnight and gave exclusively (TLC, HPLC, ^{1}H NMR) the indicated stereoisomer, starting from chiral methyl lactate ($\geq$ 98% ee). Apart from the excess of **1**, the only impurity in the final reaction mixture was its dimer (15%), see: Enders, D.; Grondal, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1210–1212.

6. For the beneficial effect of several equiv of H_2O on Pro-mediated reactions, see: (a) Nyberg, A.; Usano, A.; Pihko, P. M. *Synlett* **2004**, 1891–1896 (a case with 10 equiv, the highest yield but poor ee); (b) Pihko, P.; Pihko, P. M.; Laurikainen, K. M.; Usano, A.; Nyberg, A. I.; Kaavi, J. A. *Tetrahedron* **2006**, *62*, 317–328; (c) See Ref. 2d and ref. 14 therein; (d) see Ref. 2b (**1**, 5 equiv of H_2O, 68–90% yields); (e) Hayashi, Y.; Aratake, S.; Itoh, T.; Okano, T.; Sumiya, T.; Shoji, M. *Chem. Commun.* **2007**, 957–959 (best conditions: 3 equiv of H_2O); (f) also see: Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983–1986; for a dual role of H_2O, see: (g) Zotova, N.; Franzke, A.; Armstrong, A.;

Blackmond, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 15100–15101; for excellent, representative reviews, see: (h) Gruttadauria, M.; Giacalone, F.; Noto, R. *Adv. Synth. Catal.* **2009**, *351*, 33–57; (i) Rah, M.; Singh, V. K. *Chem. Commun.* **2009**, 6687–6703; (j) Mase, N.; Barbas, C. F. *Org. Biomol. Chem.* **2010**, *8*, 4043–4050; (k) Bhowmick, S., Mondal, A.; Ghosh, A.; Bhowmick, K. C. *Tetrahedron: Asymmetry* **2015**, *26*, 1215–1244.

7. When we performed the reaction of **1** and **2** without adding H_2O, after 15 h at rt the conversion was 40%. With 3 equiv of H_2O (with regard to **2**) the conversion reached 85%. With 5, 15, and 25 equiv of H_2O, 100%. With 30 equiv, 85%. With 35 equiv, 75%. With 50 equiv, 40%. Thus, in this case there is a plateau between 5 and 25 equiv of H_2O. Using 5 equiv and 15 equiv of H_2O, the initial reaction rates were similar (48% conversions after 4 h).

8. We only consider here homogeneous solutions, in which the concentration of H_2O can affect some steps. We do not deem biphasic systems ("on water" or "under water", where the enamine is found in the organic layer formed by non-polar solvents and/or large excesses of carbonyl compounds floating on the water phase), catalysts with long hydrophobic chains that may trap enamines, etc. For excellent essays, see: (a) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 8100–8102; (b) Hayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8103–8104; (c) Blackmond, D. G.; Armstrong, A.; Coombe, V.; Wells, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3798–3800.

9. Organocatalytic reactions of **1** with **2/4/6/8** have not been reported (exhaustive SciFinder search). Reactions of **1** with BnOCH$_2$CHO are known, however: (a) Cordova, A.; Zou, W.; Dziedzic, P.; Ibrahem, I.; Reyes, E.; Xu, Y. *Chem. Eur. J.* **2006**, *12*, 5383–5397; (b) Ibrahem, I.; Zou, W.; Xu, Y.; Cordova, A. *Adv. Synth. Catal.* **2006**, *348*, 211–222; (c) Grondal, C.; Enders, D. *Tetrahedron* **2006**, *62*, 329–337; (d) Ibrahem, I.; Cordova, A. *Tetrahedron Lett.* **2005**, *46*, 3363–3367: (e) Ref. 5.

10. That Pro may racemise chiral α-substituted aldehydes is not a surprise. See, e.g., the first article of the three famous papers of R. B. Woodward et al. on the synthesis of erythromycin (*J. Am. Chem. Soc.* **1981**, *103*, 3210–3213).

11. Sánchez, D.; Castro-Alvarez, A.; Vilarrasa, J. *Tetrahedron Lett.* **2013**, *54*, 6381–6384.

12. Many authors explained that H_2O suppresses the formation of unproductive species (oxazolidinones). Some pointed out that H_2O increases the catalyst concentration. See Refs. 6h–j. In the present case, it is compulsory to add H_2O.

13. In contrast to **2/4/6/8**, aldehyde **10** racemises in the presence of Pro, in DMSO at room temperature. The epimer of **11** turned out to be the enantiomer of **11'**. The epimer of **11'** was *ent*-**11**.

14. This hydrate was not observed in DMSO-d_6 by addition of only 15 equiv of D_2O, unless the medium was more ionic: only when we added 5 equiv of anhydrous LiBr, the percentage of hydrate in relation to aldehyde was 1:15.

15. The result was 0.023 when measured indirectly by exchange reactions (see Supplementary Data). By contrast, for standard ketones such as cyclohexanone, we estimate that the corresponding exchange equilibria have $K < 3 \cdot 10^{-5}$.

16. The exchange of the prolyl group between these intermediates and the carbonyl compounds yet present in the medium, mediated by trace amounts of H_2O, is very shifted to the right. See: Isart, C.; Burés, J.; Vilarrasa, J. *Tetrahedron Lett.* **2008**, *49*, 5414–5418. Also see the main text below.

17. This is general for α-substituted ketones. For aldehydes and cyclic ketones, all these types of intermediates have been characterised in different solvents. (a) Seebach, D.; Beck, A. K.; Badine, D. M.; Limbach, M.; Eschenmoser, A.; Treasurywala, A. M.; Hobi, R.; Prikoszovich, W.; Linder, B. *Helv. Chim. Acta* **2007**, *90*, 425–471. (b) Haindl, M. H.; Hioe, J.; Gschwind, R. M. *J. Am. Chem. Soc.* **2015**, *137*, 12835–12842, and refs. cited therein.

Graphical abstract

Further insights into the organocatalytic reaction of 2,2-dimethyl-1,3-dioxan-5-one with α-silyloxy aldehydes

Dani Sánchez, Héctor Carneros, Alejandro Castro-Alvarez, Enric Llàcer, Ferran Planas, Jaume Vilarrasa∗

Tetrahedron Letters
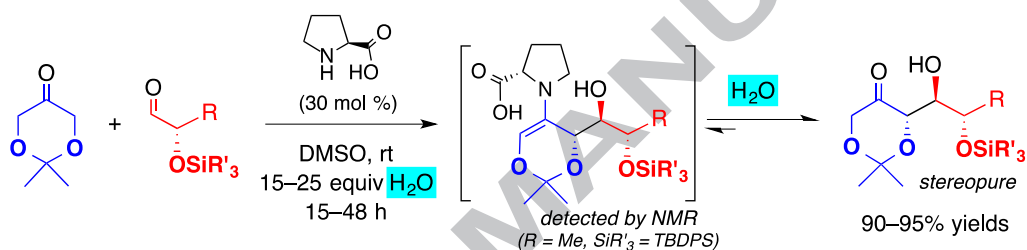
Highlights

Further insights into the organocatalytic reaction of 2,2-dimethyl-1,3-dioxan-5-one with α-silyloxy aldehydes

Dani Sánchez et al., TL 2106

_____
_____
_____

· Excellent yield and selectivity of proline-catalysed reactions with α-OSiR$_3$ aldehydes

· Several aldols (pentitol derivatives) were characterised for the first time

· H$_2$O has many roles, not only the hydrolysis of protected aldehydes (oxazolidinones)

· Possible negative (2) and positive (4) effects of D$_2$O, in DMSO-d_6, have been examined

· A 'wanted' reaction intermediate, an enamine of the aldol, has been detected by NMR