



Seebach's oxazolidinone is a good catalyst for aldol reactions

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ABSTRACT

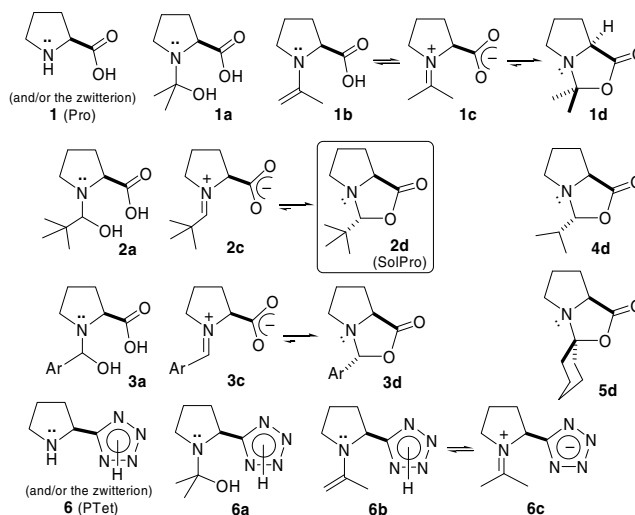
Seebach's proline-derived oxazolidinone **2d** overcomes (*S*)-proline and is at least as efficient as (*S*)-5-(pyrrolidin-2-yl)tetrazole in several organocatalytic aldol reactions examined. A quick exchange takes place between **2d** and carbonyl compounds that gives new bicyclic oxazolidinones, in equilibrium with the very minor active species (enamines). Maximum yields of the aldols (β -hydroxy ketones) were achieved after 1–4 h when, with proline, they are attained after 30–48 h.

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Organocatalysis is a subject of widespread interest.¹ Although great advances have been made,² many organocatalytic reactions, especially proline-catalyzed aldol-like reactions, are very slow. This is due to the existence of pre-equilibria before the key reaction of the enamine (of one carbonyl compound) with the second carbonyl compound takes place. Indeed, in these aldol reactions several species may coexist such as the hemiaminal from *L*-proline (Pro, **1**) and acetone (see **1a**, Scheme 1) and its dehydration products, enamine **1b**, zwitterion **1c** and bicyclic aminal **1d**.¹ Even when one of the CO groups has no α -H, that is, when its enamine(s) cannot be formed, the overall number of species in the reaction medium is still high (see, e.g., **2a/2c/2d**, from **1** and ^tBuCHO, and **3a/3c/3d**, from **1** and ArCHO). Any 'trick' for the rapid appearance in the equilibria of the active forms (e.g., of the appropriate conformer of enamine **1b**) would be welcome.

In this context, Blackmond et al. reported that **4d** (the aminal from **1** and ^tPrCHO) accelerated the reactions of EtCHO with PhN = O and of EtCHO with DEAD, but not aldol reactions,³ whilst Seebach et al. showed that **5d** (the aminal from **1** and cyclohexanone) reacted with electrophiles affording **5d** derivatives.⁴ In agreement with these exciting results and going farther, we report here that the aminal from **1** and ^tBuCHO, Seebach's bicyclic oxazolidinone **2d**,⁵ which in sharp contrast to **1** is very soluble in all solvents—we call it SolPro—⁶ is a good catalyst or pre-catalyst for aldol reactions. This was quite surprising bearing in mind the relative stability of this *cis,exo*-bicyclic oxazolidinone.

Since (*S*)-2-(5-tetrazolyl)pyrrolidine, or (*S*)-5-(pyrrolidin-2-yl)-tetrazole (PTet, **6**, see Scheme 1 for a simplified representation),



Scheme 1.

is also very soluble in DMSO and can be advantageously used in many reactions,⁷ we compared **1** and **6** in some experiments. As above, several species may be formed in the aldol reactions of acetone in the presence of **6**, namely, hemiaminal **6a**, the tautomers and conformers represented by **6b**, zwitterion **6c** and the tricyclic compound (not drawn, which is not expected to be the major species^{7e} in the corresponding equilibria, by contrast to **1d–5d**). In principle, the practical advantage of **2d** with regard to **6** is that the preparation of stock solutions of **2d** in DMSO, DMSO-*d*₆, CDCl₃ or CH₂Cl₂ is quite easy,⁸ whereas **6** requires five synthetic steps to

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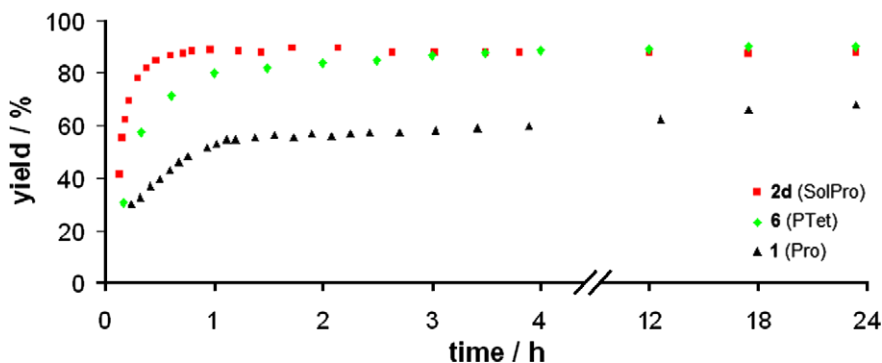


Figure 1. Appearance of **7** (% vs time) in the presence of 0.3 equiv of **2d**, **6** or **1**, in DMSO- d_6 .

be obtained from **1**.⁹ In this regard, Gong et al. have just shown that some prolinamide derivatives may perform fantastically even in water,¹⁰ but a few steps are necessary to prepare these catalysts (with several stereocentres). We did not plan to compete with sophisticated prolinamide derivatives (in many cases much better than **1**,² and even perhaps than **2d**) or to argue in favour of one or the other catalyst depending on each reaction, but planned to show that a cheap and practical proline derivative permits to reach the equilibria very rapidly.

The first reaction examined by us was a standard, that of 4-nitrobenzaldehyde with 20 equiv of acetone (propan-2-one),¹ in the presence of 0.3 equiv of SolPro (**2d**), 0.3 equiv of Pro (**1**) or

0.3 equiv of PTet (**6**), under identical conditions. The appearance of the hydroxy ketone (**7**) in DMSO- d_6 (Fig. 1) was followed by ¹H NMR spectroscopy. With **2d**, after 30 min the percentage of **7** was already over 80% (twice that one with **1**). After 1 h, no further appearance of **7** was noted (the equilibrium position had been reached).

Compound **6** turned out to be 'less quick' than **2d** (Fig. 1); within 2 h, 'only' 80% of **7** was formed. However, after 12 h, the reaction catalyzed by **6** attained the same conversion as that by **2b**. After 24 h, **6** slightly overcame **2d**.

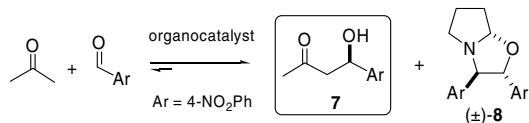
The main products were isolated (Table 1): scalemic aldol (β -hydroxy ketone **7**), its dehydration product (the enone, not indicated to save space, below 4% in all cases) and the decarboxyl-cycloaddition product **8**.¹¹

That the reaction catalyzed by **2d** could be more rapid because of its solubility was envisaged, but to our delight also the yield of **7** increased. Eventually (see Table 1, entry 1), the isolated yield of **7**, with **2d** for 1 h, was 88%. This is ca. 20% above that with **1** for 24 h or for 30 h (maximum yield reached under our conditions). On the other hand, with **2d**, the amount of **8** decreased. Thus, the rate increase showed an additional advantage, unexpected at first sight: the probability of the formation of by-products arising from the concomitant reaction of Pro with ArCHO (Ar = 4-nitrophenyl) diminished.^{11d} Since the decarboxylation cannot take place, obviously, with **6**, it is understandable that with this catalyst the yield of **7** in DMSO still grew after several hours. This is not the case with **1** (it stops within 30 h under our conditions) and **2d** (it stops within 1 h), as part of ArCHO disappeared by its direct reaction with **1** followed by decomposition and by reaction with **2d** (by a process explained below).

Either standard DMSO with 1–2% of water (as detected by ¹H NMR at δ 3.30) or anhydrous DMSO gave rise to the same outcome (Table 1, entry 1). Thus, **2d** is efficient with any source of commercially available DMSO, which is very practical.

Table 1

Comparison of the effect of **2d**, **1** and **6**, under identical conditions (0.3 equiv of catalyst, rt, identical concentrations),^a on the yield of **7** and **8**



Entry	Solvent	Yield (ee) of 7 , in %, ^b time (h)			Yield of 8		
		With 2d	With 1	With 6	2d	1	6
1	DMSO	88 (73), 1	69 (73), 30	80 (78), 2	4	14	0
2	Me ₂ CO	83 (62), 2	71 (63), 48		3	12	
3	CH ₂ Cl ₂	55 (45), ^c 4	32 (45), 48		3	12	

^a From 0.60 mmol of 4-nitrobenzaldehyde in 3.7 mL of solvent, plus 20 equiv of acetone (880 μ L). Anhydrous **1** was added as a finely powdered solid. SolPro (**2d**, 300 μ L, 0.6 M in DMSO) was added with a syringe. Pyrrolidinyltetrazole **6** (25 mg, 0.18 mmol, in 300 μ L of DMSO) was added via syringe. Results in DMF (slightly lower yields and ee values of **7** than in DMSO) are not included to save space.

^b Yields and enantioexcesses, \pm 2%, as mean values of 2–3 experiments.

^c In this case **2d** was added from a stock solution in CH₂Cl₂ (not in DMSO). Results in CH₂Cl₂–hexane are worst than in CH₂Cl₂.

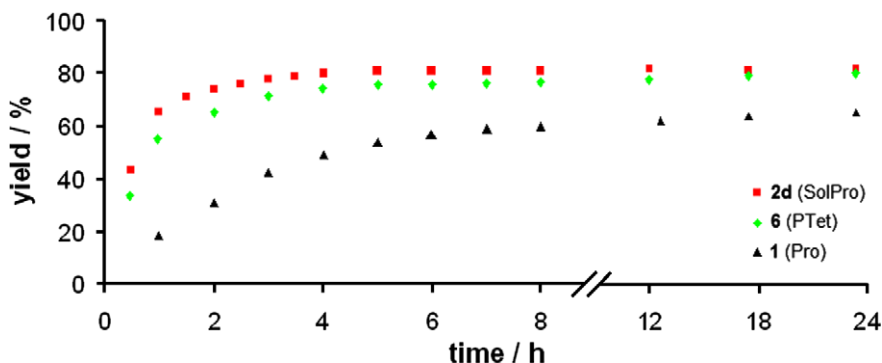
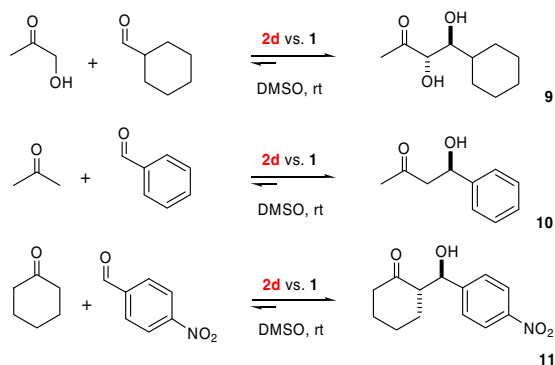


Figure 2. Formation of **9** (% vs time) in the presence of 0.3 equiv of **2c**, **6** or **1**, in DMSO- d_6 .

Table 2
Comparison of the effect of **2d** and **1** on the yields of **9–11**^a



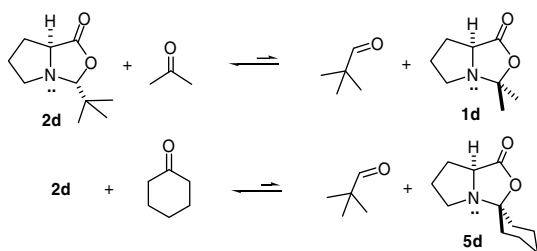
Entry	Catalyst (equiv)	Time (h)	Yield% ^b (ee%) of 9	Yield% (ee%) of 10	Yield% ^c (ee%) of 11
1	2d (0.3)	4	72 (>99)	72 (66)	80 (88)
2	2d (1.0)	2	72 (>99)	73 (67)	82 (89)
3	1 (0.3)	48	61 (>99)	60 (67)	65 (89)

^a Aldehydes (1.0 mmol) and ketones (20 mmol) in DMSO (5 mL) at rt.

^b Only the *anti* isomer was detected.

^c 2:1 *anti/syn* ratio; ee of the *anti* isomer.

In other solvents (see entries 2 and 3 of Table 1 and footnotes), known to be less favourable than DMSO,¹ all the reactions were



Scheme 2. Exchanges examined by ¹H NMR.

slower, but yields of **7** with **2d** after 2–4 h were also 12–23% higher than with **1** after 48 h.

The ee values of **7** were the expected ones. In fact, we did not envisage any increase or loss of the er, since the key C–C bond formation step must be identical with **1** or **2d**. The er values depend on the relative arrangement of the conformers of enamine **1b** and ArCHO in the transition state.¹

Three additional reactions, not so rapid as the preceding one, leading to aldols **9–11**,¹² were reexamined by us in the best solvent. We monitored the effect of **2d**, **1** and **6** in DMSO-*d*₆ under the same conditions of concentration, temperature and ketone/aldehyde/catalyst ratio (20:1.0:0.3). Again, it was noted by NMR that the reactions with **2d** were slightly more rapid than with **6** and much more rapid than with **1**. See Figure 2 for a representative example.

Repetition of the experiments at a large scale, comparing **2d** (the maximum yields were reached in 4 h) and **1** (in ca. 48 h), gave the outcome shown in Table 2.

When stoichiometric amounts of **2d** were employed,¹³ the reactions could be quenched within 2 h (see entry 2 of Table 2) to afford the same results as in entry 1. Again, as the reactions were more rapid, less by-products were formed. The yields of **9–11** were improved by 11–17% (although, as already mentioned, it was not our goal).

Two main questions remained: (i) are the higher reaction rates with **2d** only a consequence of its larger solubility?; (ii) how are enamines (e.g., **1b**) formed from **2d**? Solubility is important always, but there is another factor in the case of **2d**. We examined by ¹H NMR whether **2d** reacted with ketones or not.¹⁴ To our surprise, exchanges between **2d** and acetone and between **2d** and cyclohexanone did occur *without any additive* (Scheme 2). They occurred in standard DMSO-*d*₆ (water detected), in anhydrous DMSO-*d*₆ (no water detected) and even in the presence of activated 4-Å MS in the NMR tube, *quite rapidly in all cases*. Spectra of the two exchanges of Scheme 2 are given in Figures 3 and 4.

Saturation of the DMSO-*d*₆ solutions with **1** (Pro) did not enhance the exchange rates and did not modify the equilibrium positions either. These exchanges also took place in CDCl₃, despite the fact that free **1** cannot be detected in our solutions of **2d** in

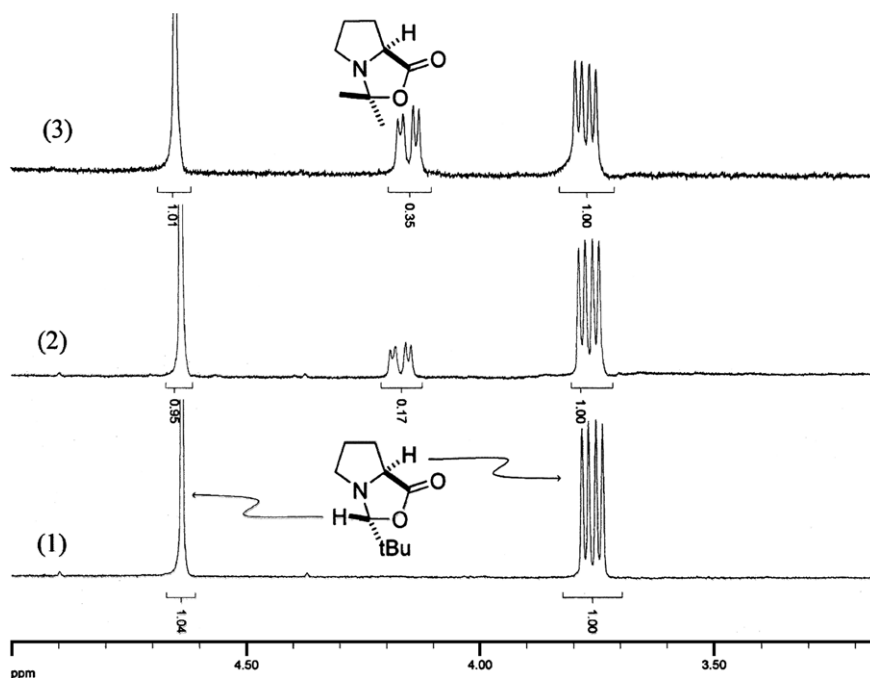


Figure 3. ¹H NMR spectra of relevant methine protons in DMSO-*d*₆: (1) **2d**; (2) **2d** + 20 equiv of acetone,¹⁵ after 30 min; (3) **2d** + 40 equiv of acetone, after 30 min.

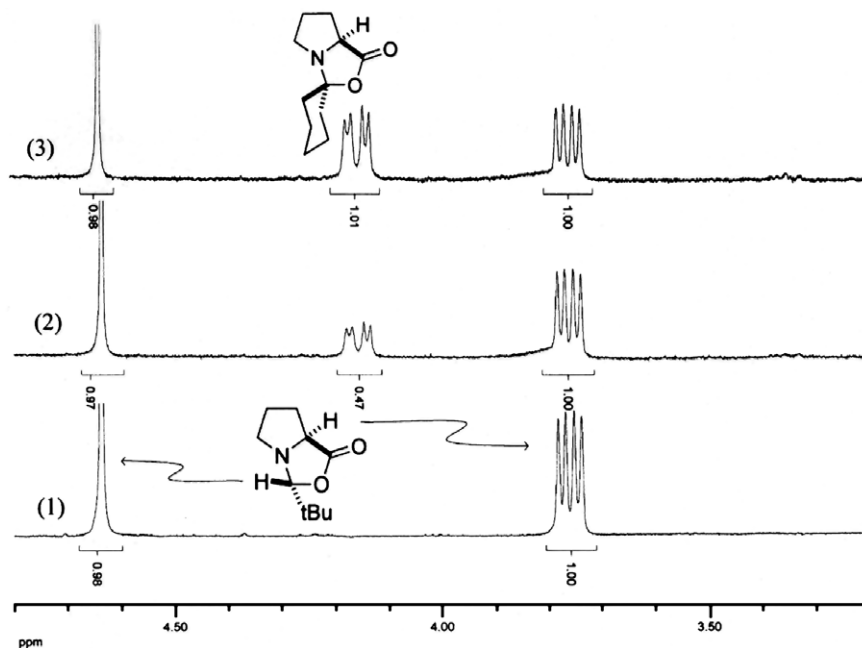
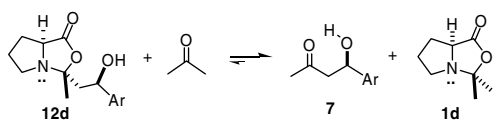


Figure 4. ^1H NMR spectra of relevant methine protons in $\text{DMSO-}d_6$: (1) **2d**; (2) **2d** + 20 equiv of cyclohexanone, after 30 min; (3) **2d** + 40 equiv of cyclohexanone, after 30 min.



Scheme 3. Plausible equilibrium between **12d** and acetone.

CDCl_3 (too much insoluble, as expected). In short, free **1** may not be involved in these direct exchanges.

Similar exchanges took place between **2d** and $i\text{PrCHO}$ (fully shifted to the right but giving secondary reactions) as well as between **2d** and ArCHO (accompanied by the already mentioned formation of **8**).

These quick exchanges explain why we did not observe bicyclic adducts (e.g., adduct **12d**)¹⁶ when the aldol reactions of Figures 1 and 2 were monitored by ^1H NMR in $\text{DMSO-}d_6$. The excess of acetone likely shifts the '**12d** + acetone = **7** + **1d**' equilibrium fully to the right (Scheme 3) as soon as the reaction progresses;¹⁷ **1d** (and obviously **1b**, in equilibrium with it) enters again into the catalytic cycle.

In summary, **2d** is an efficient catalyst for aldol reactions, the most efficient amongst those of the bicyclic oxazolidinone type to date.^{6,18} It affects pre-equilibria, owing to its large solubility (as **6**) and its ready exchange with the other CO groups present in the medium. The active but very minor species (enamines) seem to appear much more quickly than using **1** and slightly more quickly than using **6**. Thus, the use of **2d** shortens largely the overall reaction times (and, as far as the various equilibria and secondary reactions permit, increase the yields). Development of other simple and soluble catalysts or pre-catalysts is under way.

Acknowledgements

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Supplementary data

Supplementary data associated with this article (DFT calculations of Scheme 2 and related equilibria as well as a mechanistic proposal for the exchanges) can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.028.

References and notes

- Most recent reviews: (a) Xu, L.-W.; Lu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2047–2053; (b) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037–2046; (c) Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2008**, *47*, 42–47; (d) Kotsuki, H.; Ikishima, H.; Okuyama, A. *Heterocycles* **2008**, *75*, 493–529; (e) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743; (f) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569; (g) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416–5470; (h) Guillena, G.; Nájera, C.; Ramón, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249–2293; (i) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, 2065–2092; (j) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267–9331; (k) Sulzer-Mosse, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123–3135; (l) Enders, D.; Grondal, C.; Hüttel, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581; (m) Guillena, G.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693–700; (n) Longbottom, D. A.; Franckevicius, V.; Ley, S. V. *Chimia* **2007**, *61*, 247–256; Proline-catalyzed intermolecular aldol reaction 'primer' (o) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
- These include reactions 'in the presence of water', in ionic liquids, and under other unconventional conditions, which have been reviewed (Ref. 1f). For the effect of the presence of water, see: (a) Blackmond, D. G.; Armstrong, A.; Coombe, V.; Wells, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3798–3800. and references cited therein; (b) Zotova, N.; Franzke, A.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 15100–15101. For very recent works, see: (c) Ramasastry, S. S. V.; Albertshofer, K.; Utsumi, N.; Barbas, C. F., III. *Org. Lett.* **2008**, *10*, 1621–1624 and references cited therein; (d) Siyutkin, D. E.; Kucherenko, A. S.; Struchkova, M. I.; Zlotin, S. G. *Tetrahedron Lett.* **2008**, *49*, 1212–1216; (e) Luo, S.; Zhang, L.; Mi, X.; Qiao, Y.; Cheng, J.-P. *J. Org. Chem.* **2007**, *72*, 9350–9352; (f) Pihko, P. M.; Laurikainen, K. M.; Usano, A.; Nybrg, A. I.; Kaavi, J. A. *Tetrahedron* **2006**, *62*, 317–328; (g) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Tabake, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 734–735; (h) Huang, J.; Zhang, X.; Armstrong, D. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 9073–9077. For a review of asymmetric catalysis in ionic liquids, see: (i) Durand, J.; Teuma, E.; Gómez, M. *C.R. Chimie* **2007**, *10*, 152–177.
- (a) Iwamura, H.; Mathew, S. P.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 11770–11771; (b) Iwamura, H.; Wells, D. H.; Mathew, S. P.; Klussmann, M.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 16312–16313. For the formation of bicyclic analogs from thioamides, see: (c) Gryko, D.; Lipinski, R. *Adv. Synth. Catal.* **2005**, *347*, 1948–1952.
- Seebach, D.; Beck, A. K.; Badine, D. M.; Limbach, M.; Eschenmoser, A.; Treasurywala, A. M.; Hobi, R.; Prikozovich, W.; Linder, B. *Helv. Chim. Acta* **2007**, *90*, 425–471.

- Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390–5398.
- (a) (2*R*,5*S*)-1-Aza-2-*tert*-butyl-3-oxabicyclo[3.3.0]octan-4-one, **2d**, is nowadays commercially available. We chose **2d** because it cannot give obviously an enamine and because of its intermediate stability between the CCl_3 analogue (too stable, no catalytic power) and less bulky alkyl derivatives (aldol reactions occurring during their preparation in DMSO and/or inappropriate for exchange reactions with ketones—see below). Moreover, $^t\text{BuCHO}$ present in the medium was supposed to be less reactive than most RCHO and many ArCHO . Isart, C. Universitat de Barcelona, Master Thesis, 2005, and DEA Thesis, 2007; (b) Previous studies in our group on derivatives of **1**: Rodríguez-Escrich, C. Universitat de Barcelona, Master Thesis, 2003.
- (a) Cobb, A. J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558–560; (b) Torii, H.; Nakadaï, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983–1986; (c) Hartikka, A.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2004**, *15*, 1831–1834 (the solubility of **6** and the higher acidity of the tetrazole ring in DMSO with regard to a COOH group may play a role); For an excellent, very recent review, see: (d) Longbottom, D. A.; Franckevicius, V.; Kumarn, S.; Oelke, A. J.; Wascholowski, V.; Ley, S. V. *Aldrichim. Acta* **2008**, *41*, 3–11. Also see (e) Hartikka, A.; Arvidsson, P. I. *Eur. J. Org. Chem.* **2005**, 4287–4295 (where it was demonstrated that no tricyclic amination from **6** and $^t\text{BuCHO}$ is detected by ^1H NMR on mixing both compounds in $\text{DMSO}-d_6$, in sharp contrast to what happens on mixing **1** and $^t\text{BuCHO}$).
- Preparation of stock solutions of 2d (SolPro)**: Finely powdered L-proline (**1**, 1.40 g, 12.2 mmol), dried overnight in an oven over P_2O_5 at 40 °C and 0.1 Torr, was added to anhydrous DMSO (10 mL), freshly distilled $^t\text{BuCHO}$ (1.12 mL, or 860 mg, 10 mmol), and crushed and activated 4-Å MS (6 g), under Ar. After a vigorous stirring for 12–24 h, the excess of **1** as well as the MS was filtered under Ar pressure. The solution was stored over MS in a dried flask capped with a septum. The concentration of **2d** was evaluated by NMR, with an internal standard of PhCOPh , to be 0.60 ± 0.05 M. No signals of water (δ 3.30) were detected, even increasing the sensitivity to a maximum. Only 'impurity' signals due to $^t\text{BuCHO}$ (2–10 mol %) and, sometimes, a trace of remaining **1** (<2 mol %) were noted. No decomposition or hydrolysis was observed. Similarly but at a smaller scale, solutions of **2d** in $\text{DMSO}-d_6$ were prepared. Stock solutions of **2d** in CH_2Cl_2 and in CDCl_3 were prepared analogously. The concentrations attained were ca. 0.45 M, which can be increased by a simple removal of solvent. Evaporation to dryness in a vacuum line afforded **2d** only impurified with $^t\text{BuCHO}$.
- Pyrrolidinyltetrazole **6** is now commercially available (though expensive).
- Even with very low catalyst loadings, the yields, dr and er are often excellent. See: Zhao, J.-F.; He, L.; Jiang, J.; Tang, Z.; Cun, L.-F.; Gong, L.-Z. *Tetrahedron Lett.* **2008**, *49*, 3372–3375. Nevertheless, for the most standard reaction examined (acetone plus 4-nitrobenzaldehyde, see Table 1 below), yields of 85% (71% ee) were only achieved.
- (a) Orsini, F.; Pelizzoni, F.; Forte, M.; Destro, R.; Gariboldi, P. *Tetrahedron* **1988**, *44*, 519–541; (b) Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3055–3057; (c) we confirmed by chiral HPLC that **8** was racemic (with Chiralpak AD-H, 90:10 hexane/ $^i\text{PrOH}$, flow rate 1 mL/min, λ 254 nm, t_R 19.0 and 44.1 min); (d) we corroborated that at rt, without additives, Pro and aromatic aldehydes (4- $\text{NO}_2\text{C}_6\text{H}_4\text{CHO}$ more quickly than PhCHO , 4-MeOC $_6\text{H}_4\text{CHO}$ and 2-MeOC $_6\text{H}_4\text{CHO}$) gave products of type **8**. See Ref. 2b for related experiments.
- (a) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387; (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267. For very recent improvements on these reactions, see: (c) Luo, S.; Li, J.; Xu, H.; Zhang, L.; Cheng, J.-P. *Org. Lett.* **2007**, *9*, 3675–3678; (d) Xu, X.-Y.; Wang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2007**, *9*, 4247–4249; (e) Luo, S.; Xu, H.; Zhang, L.; Li, J.; Cheng, J.-P. *Org. Lett.* **2008**, *10*, 653–656.
- Compound **2d** is so soluble that it can be used even in a larger excess, if it was needed.
- Blackmond et al. (Ref. 3b) demonstrated an exchange between **4d** and propanal, in CD_2Cl_2 .
- To note the equilibria, 20–40 mol of the corresponding ketones per mol of **2d** had to be added (e.g., with acetone, $K_{\text{eq}} = 0.004$, $\Delta G^\circ = 3.3 \pm 0.4$ kcal/mol), cf: List, B.; Hoang, L.; Martin, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5839–5842. However, we could not detect the analogous exchanges between **4d** and a large excess of acetone or cyclohexanone by ^1H NMR (the probable equilibrium is too shifted to the left). This explains why **4d** does not catalyse aldol reactions.
- We have depicted **12d** (in Scheme 3) as a representative of the four bicyclic stereoisomers (with different conformers) that can be formed as adducts.
- Any aldehyde remaining in the reaction flask will do the same (see Supplementary data).
- In the reactions of Table 1, the use of **2d** means that species **1b/1c/1d**, **2c/2d**, **3c/3d** and **b/c/d**-like derivatives of the reaction products (see, e.g., **12d** in Scheme 3) can be all present in the equilibrium mixture. In spite of that, ca. 90% of **7** is formed (after 30–60 min!).