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Substrate-Dependent Nonlinear Effects in Proline–Thiourea-Catalyzed Aldol Reactions: Unraveling the Role of the Thiourea Co-Catalyst

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Dedicated to Prof. Santiago Olivella on occasion of his 65th birthday

The venerable aldol reaction[1] is enjoying a second youth, since the re-discovery of its catalysis by proline at the beginning of the century, and the subsequent explosive development of enantioselective organocatalysis.[2–5] Even if proline is an exceptionally good catalyst for this reaction in terms of its structural simplicity and easy availability, it exhibits two main drawbacks: a low solubility in nonpolar solvents and a relatively low reactivity, that requires its use in large amounts (typically 20–30 mol%) and that leads to the formation of parasitic reaction products especially in the case of aldol reactions with aromatic aldehydes.[6] It is therefore not surprising that in the past few years considerable effort has been devoted to the chemical modification of proline (or of 4-hydroxyproline) in order to obtain catalytic systems both with better solubility in common organic media and/or with higher acidity of the directing acid proton.[3,6b,7] A conceptually attractive alternative strategy to this goal, due to its simplicity, would be based in the in situ preparation of a catalytically competent supramolecular assembly from unmodified proline and a simple hydrogen-bond-donor co-catalyst, taking advantage of the well-known ability of carboxylic acids to participate in hydrogen-bonding networks.[8] While some precedent for this approach can be found in the work of Zhou,[9] Zhao,[10] and Clarke,[11] these authors either use chiral co-catalysts[9,10] or perform extensive chemical modification of proline.[11,12] In 2006, Miller and co-workers[13] described that the addition of *N*-methylimidazole to L-proline enhanced the rate of the Morita–Baylis–Hillman reaction between methyl vinyl ketone and aromatic aldehydes, although the resulting adducts were obtained with very low enantiomeric purity. At the beginning of the present year, Reis et al.[4] reported that the addition of equimolar quantities of Schreiner's thiourea **1**[14] to proline in nonpolar solvents resulted in the formation of a supramolecular catalyst that gave excellent conversions and stereoselectivities in the aldol reaction of cyclohexanone with various aromatic aldehydes. In a closely related approach, we have subsequently demonstrated[5] that the combination of proline with several kinds of achiral hydrogen-bond donors (*o*-phenylene dicarbamates, 2-(arylamino)benzimidazoles, *N,N′*-diarylthioureas), using toluene as a solvent, provides a simple solution to the direct aldol desymmetrization of 4-substituted cyclohexanones, a challenging reaction that is not efficiently catalyzed by proline itself.

To explain their results, Reis et al. proposed the initial formation of a proline–thiourea complex, much more soluble than proline itself in apolar organic solvents (Figure 1, left), and suggested that this supramolecular assembly was carried out to the List–Barbas–Houk transition state,[2b,c,15] improving the stereoselectivity of the aldol reaction by enhancing the directing effect of the carboxylic acid group of proline (Figure 1, right).[4]

While we have demonstrated the formation of stable 1:1 complexes between proline and *N,N′*-diaryl thioureas (including Schreiner's thiourea, **1**) in chloroform by UV and fluorescence spectroscopic techniques;[5] the high dilution conditions in which these experiments are performed bear no direct relationship with the concentration of the catalyst in the actual aldol reactions, which on the other hand are

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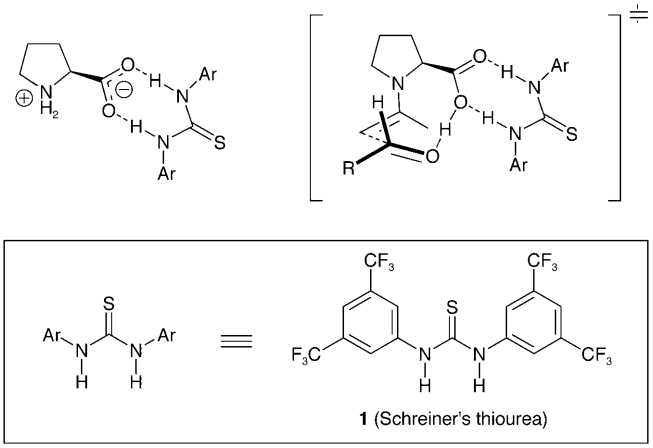


Figure 1. Left: Proposed structure of the proline–thiourea complex. Right: Proposed transition state for the proline-thiourea catalyzed aldol reaction.

run in less polar hydrocarbon solvents such as toluene and hexane. Most recently, McQuade and co-workers[16] have disclosed the results of a study on the effect of bifunctional urea co-catalysts in the asymmetric α-aminoxylation of aldehydes under proline catalysis.

This reaction gives excellent levels of enantioselectivity, and the authors centered their attention on the reaction rate, which turns out to be substantially increased upon addition of the urea co-catalyst. Interestingly enough, simple NMR experiments showed that the solubility of proline in the reaction medium (ethyl acetate) was not appreciably enhanced by the presence of the urea, and the authors, building upon previous kinetic studies of Blackmond,[17] proposed that observed rate enhancement might be due to the interaction between Seebach's oxazolidinone intermediate[6] and the urea, that would increase the rate of enamine formation (Figure 2).[16]

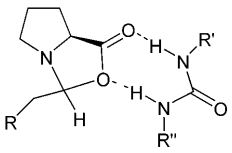


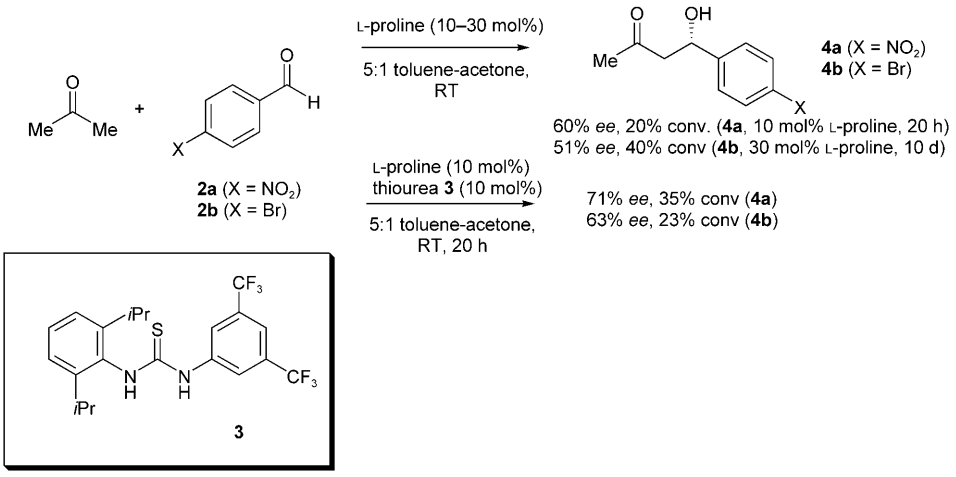
Figure 2. Possible interaction by hydrogen bonding between a Seebach oxazolidinone and a urea (adapted from reference [16]).

These findings cast serious doubts upon the extent and relevance of proline solubilization by the thiourea co-catalyst in the aldol reactions explored by Reis et al.[4] and by us,[5] and we felt that this important issue deserved more detailed consideration. We envisaged that the comparative study of nonlinear effects[18] in the heterogeneous proline-catalyzed aldol reaction, both in the absence and in the presence of a thiourea co-catalyst, could shed some light on this problem. As demonstrated in the pioneering contributions of Hayashi[19] and Blackmond,[20] the higher solubility of enantiopure proline with respect to the racemic gives rise to characteristic nonlinear effects (positive for low *ee*'s and negative for high *ee*'s of the solid proline catalyst, joined by a plateau reflecting the formation of an eutectic for intermediate *ee*'s of proline) that give a direct and clear-cut indication of the presence of solid proline as a catalyst source in the reaction medium.[21] We report now on our initial results in this subject, which have revealed a hitherto unprecedented substrate dependence of the nonlinear effects and strongly suggest that the role of the hydrogen-bond-donor co-catalyst is much more complex than previously assumed by Reis et al.[4]

We selected as benchmark reactions the heterogeneous proline-catalyzed aldol additions of acetone to 4-nitrobenzaldehyde (**2a**) and to 4-bromobenzaldehyde (**2b**) (as representative highly reactive and less reactive aromatic aldehydes, respectively) in a 5:1 toluene–acetone mixture (in which the catalyst is only sparingly soluble) as the solvent. The chosen co-catalyst was the *N*-(3,5-bis (trifluoromethyl)-phenyl)-*N*′-(2,6-diisopropylphenyl) thiourea (**3**), a compound that had given excellent results in the aldol desymmetrizations studied by us.[5] The reactions with 4-nitrobenzaldehyde were performed at ambient temperature with a 10 mol% of proline, and with a 0.25 M concentration of aldehyde. In the case of 4-bromobenzaldehyde, the reaction rate was very low with a 10 mol% amount of proline, and the study was performed with a 30 mol% of the catalyst. After stirring for 2 h a suspension of the proline catalyst in the toluene/acetone mixture (to ensure the full establishment of solubility equilibria and therefore avoiding the presence of disturbing "kinetic conglomerate" effects[22]), the aldehyde (either **2a** or **2b**) was added in one portion. The conversion of the reaction was monitored by ^{1}H NMR spectroscopy, and the enantiomeric purities of the aldol adducts **4a** and **4b** were determined by HPLC.[23] The reactions with the proline–thiourea catalytic assembly were run in a similar way (10 mol% proline + 10 mol% thiourea **3**). The results obtained with enantiopure L-proline are summarized in Scheme 1.

The presence of thiourea **3** substantially increased the rate of these reactions. Thus, the aldol addition of 4-bromobenzaldehyde (**2b**) required four days to achieve a 40% conversion with 0.3 equiv of L-proline as the sole catalyst, while a similar conversion was reached after only 24 h when 0.1 equivalents of L-proline and 0.1 equivalents of thiourea **3** were used. A similar effect, albeit less pronounced, was observed for the more reactive 4-nitrobenzaldehyde (**2a**); thus, a 15% conversion was achieved after 20 h with 0.1 equivalents of L-proline, and a 35% conversion was measured after the same time with 10 mol% of the L-proline–thiourea catalytic system. As can be seen in Scheme 1, the proline–thiourea catalytic combination also afforded sizable increases in the enantiomeric purities of the aldol products (from 60–71% *ee* in the case of **4a**, and from 51–63% *ee* in the case of **4b**).

We then proceeded to the study of nonlinear effects, by running the reactions in the same conditions described above, but using freshly prepared, carefully dried solid pro-



Scheme 1. Aldol reactions of acetone with benzaldehyde derivatives **2a** and **2b** catalyzed by L-proline and by a proline–thiourea complex.

line samples of different enantiomeric purities. The results of this study are summarized in Figures 3 (for aldehyde **2a**) and 4 (for aldehyde **2b**), in which we show the usual plots

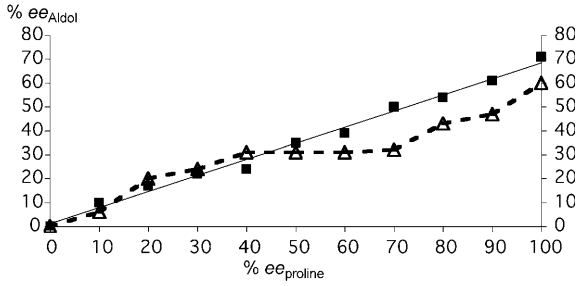


Figure 3. Influence of the thiourea co-catalyst (10 mol%) in the nonlinear effects in the proline-catalyzed (10 mol% of proline) aldol reaction between acetone and 4-nitrobenzaldehyde (**2a**) (△ without urea, ■ with urea).

of catalyst % *ee* versus product % *ee*, both in the absence and in the presence of thiourea **3**. The points in each graphic are the mean values of at least two duplicate experiments.

The results obtained for 4-nitrobenzaldehyde **2a** were clear-cut, and seemed to support a complete solubilization of proline by the thiourea **3** in the reaction medium. In effect, in its absence a characteristic nonlinear graph was obtained (i.e., the enantiomeric purity of the aldol remained essentially constant at 30% *ee* between 40 and 70% *ee* of the catalyst), indicating that the enantiomeric purity of the proline in solution was mainly governed by the formation of a eutectic mixture. On the other hand, the use of the preformed 1:1 proline–thiourea complex as the catalyst led to a linear graph, pointing towards the complete solubilization of proline (Figure 3). We were utterly surprised to find, however, that completely different results were obtained for 4-bromobenzaldehyde **2b** (Figure 4). In this case, the addition of the thiourea co-catalyst only marginally changed the shape of the graph, showing that a eutectic mixture of proline was still present in the reaction medium. The nonlinear effects are therefore dependent on the structure of the substrate, a phenomenon that has been rarely observed in homogeneous catalytic asymmetric reactions[24] and that, to the best of our knowledge, is totally unprecedented for partially soluble catalysts.

In the light of these findings, we reexamined the solubility behavior of proline in [D_8]toluene and in 5:1 [D_8]toluene/[D_6]acetone in the

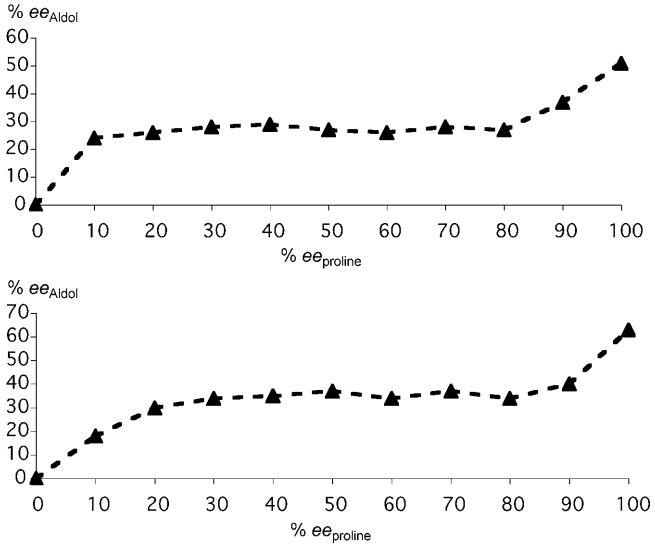


Figure 4. Influence of the thiourea co-catalyst (10 mol%) on the nonlinear effects in the proline-catalyzed (10 mol%) aldol reaction between acetone and 4-bromo benzaldehyde **2b** with (bottom) and without (top) thiourea. The experiments without thiourea were performed with a 30 mol% of proline.

presence of Schreiner's thiourea **1** (or of thiourea **3**) by means of ^{1}H NMR spectroscopy, at the concentrations used in the actual aldol reactions. In the absence of acetone, and starting from a 1:1 thiourea/proline mixture, no signals corresponding to proline could be observed in the solution.[25] On the other hand, in the toluene/acetone mixture two proline-derived species could be observed, in an approximate 3:1 ratio (Figure 5, top). The minor compound was identified as the oxazolidinone **5**, and the major compound as the open zwitterionic iminium species **6**, by comparison of their spectral data (chemical shift and multiplicities of the C_2- and C_5-proline protons) with those reported by Seebach for the corresponding cyclohexanone-derived species in

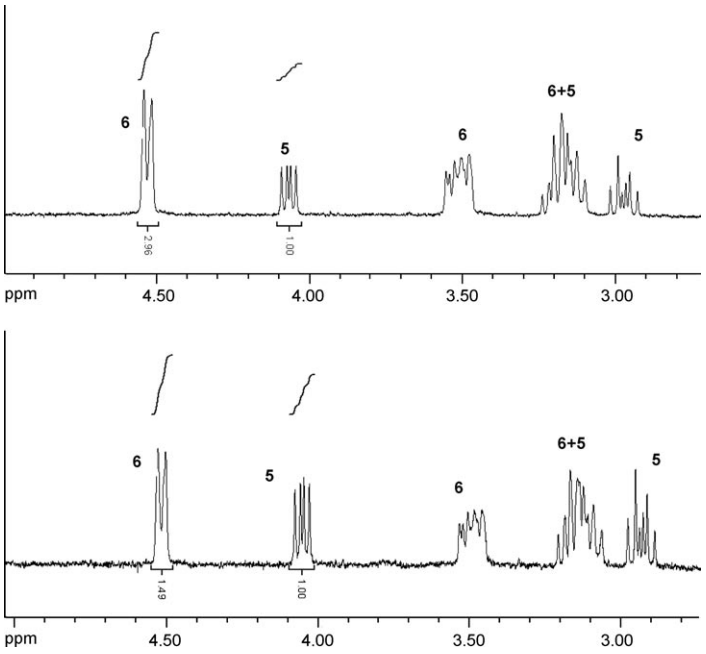


Figure 5. Top: ^{1}H NMR spectrum (300 MHz) of a solution of L-proline (0.025 mmol mL^{-1}) and of thiourea **1** (0.025 mmol mL^{-1}) in 5:1 [D_8]toluene/[D_6]acetone, after 2 h of stirring at room temperature. Bottom: ^{1}H NMR spectrum (300 MHz) of a solution of L-proline (0.025 mmol mL^{-1}) and of thiourea **1** (0.012 mmol mL^{-1}) in 5:1 [D_8]toluene/[D_6]acetone, after 2 h of stirring at room temperature. See Scheme 2 for the structures of compounds **5** and **6**.

[D_6]benzene.[6a,26] We assume that both compounds are complexed with the thiourea, the NH protons of which exhibited a low-field shift indicative of hydrogen-bonding.[4,8] The estimated solubilization percentage of proline was 65%, according to the thiourea/(**5**+**6**) ratio calculated from the integrated ^{1}H NMR spectrum. Further support for this structural identification was provided by an ESI-MS spectrum of a 1:1 proline–thiourea mixture in 5:1 toluene–acetone; in the positive mode a signal (*m/z* 156) for **5**+H (or **6**+H) was observed. In the negative ESI mode, signals (*m/z* 499, *m/z* 999) for the dissociated thiourea **1** and for its dimer with another molecule of thiourea could be identified.[27] On the other hand, no peaks ascribable to free proline or to a proline–thiourea complex could be found in the ESI-MS spectra. It is also interesting to observe that when the thiourea/proline ratio was decreased to 1:2, the total proline solubilization percentage diminished only slightly to 57%, but the iminium/oxazolidinone ratio dropped from about 3:1 to about 1.5:1 (Figure 5, bottom). It is therefore clear that the amount of iminium zwitterionic species **6** increases with the amount of thiourea present in the medium. This is in complete accordance with the results obtained by Seebach, who observed that the presence of acids of decreasing pK_a generated increasing amounts of iminium derivative from the oxazolidinone.[6a]

Next, aldehydes **2a** and **2b** (one molar equivalent with respect to proline) were added to the 1:1 proline–thiourea solution, and ^{1}H NMR spectra were recorded after a few minutes. In the case of **2a**, some new species were clearly seen, albeit in minor quantities, and, more interestingly, the total amount of proline solubilization was higher than 87% (Figure 6, top). If we assume that the new signals also correspond to proline-derived compounds (see below), a practically complete solubilization of the initial proline has taken place.

The new species appearing in Figure 6 (top) was identified as the diastereomeric pair (*cis*/*trans*) of the well-known "parasitic" bicyclic compound **7** arising from the 1,3-dipolar cycloaddition between the azomethine ylide species derived from the proline–aldehyde iminium adduct and free aldehyde.[5,6b] This identification is also supported by the corresponding ESI-MS spectrum (in nondeuterated solvents), which exhibits in the positive mode an enhanced intensity for the peak at *m/z* 156 and a new peak at *m/z* 356 corresponding to **7**+H.[28] No traces of the oxazolidinone precursor derived from proline and **2a**,[6b] or of the corresponding iminium species, were present in the NMR spectrum, although a relatively weak peak at *m/z* 205, corresponding to the protonated azomethyne ylide intermediate (**8**+H$^+$; see Scheme 2), was present in the ESI-MS spectrum (positive mode). Contrary to this, in the case of **2b**, no new signals were apparent and the solubilization percentage of proline remained essentially constant (60%, Figure 6, bottom).

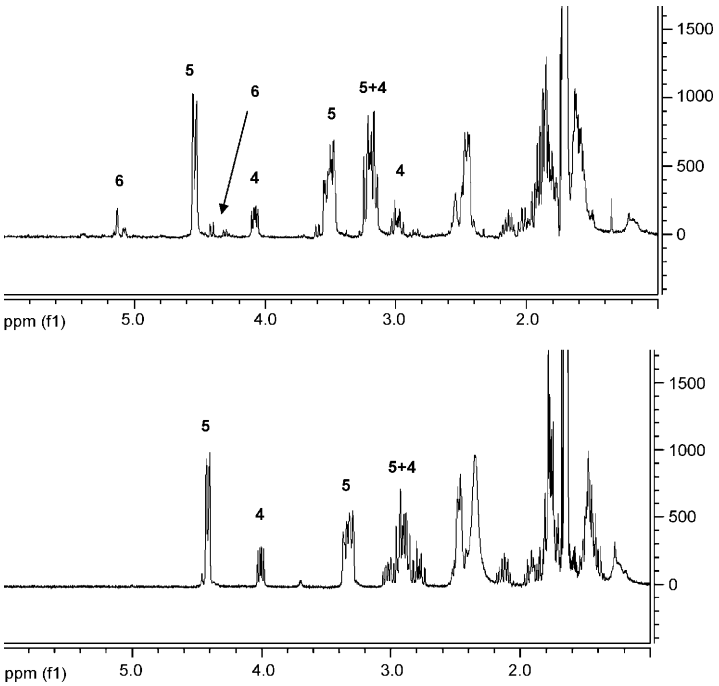
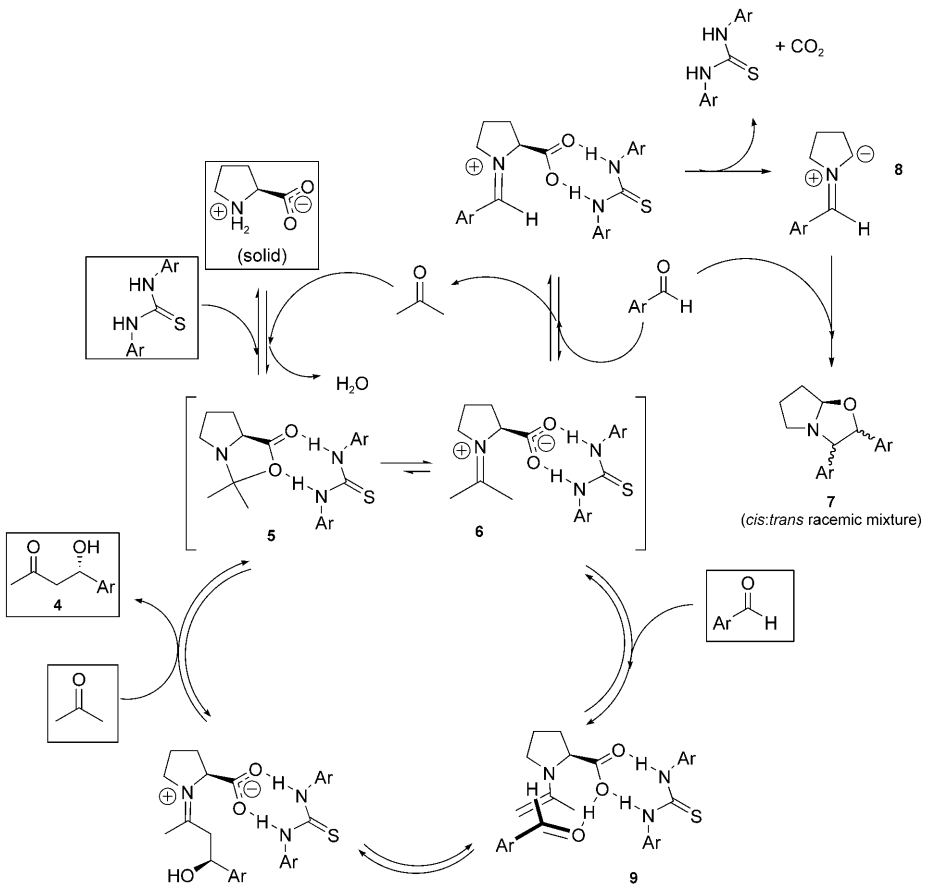


Figure 6. Top: ^{1}H NMR spectrum (300 MHz) of a solution of L-proline (0.025 mmol mL^{-1}) and of thiourea **1** (0.025 mmol mL^{-1}) in 5:1 [D_8]toluene/[D_6]acetone, after 2 h of stirring at room temperature, and addition of aldehyde **2a** (1 equivalent with respect to proline). Bottom: ^{1}H NMR spectrum (300 MHz) of a solution of L-proline (0.025 mmol mL^{-1}) and of thiourea **1** (0.025 mmol mL^{-1}) in 5:1 [D_8]toluene/[D_6]acetone, after 2 h of stirring at room temperature, and addition of aldehyde **2b** (1 equiv with respect to proline). See Scheme 2 for the structures of compounds **5**, **6**, and **7**.



Scheme 2. Proposed mechanism for the generation and fate of proline-derived soluble species in the proline–thiourea-catalyzed intermolecular aldol reaction in hydrocarbon solvents.

These simple NMR and ESI-MS experiments are therefore completely consistent with the results of the study of nonlinear effects. Although more work is clearly needed at this point, we suggest, on the basis of the data presented above, a possible explanation of the role of thiourea in the proline-catalyzed aldol reactions studied by Reis et al.[4] and by us[5] that can be summarized as follows (Scheme 2).

The addition of one molar equivalent of thiourea to a suspension of proline in toluene (or hexane), in the presence of excess ketone, leads to the partial solubilization of proline as an approximate 1:3 mixture of the bicyclic oxazolidinone **5** and its open zwitterionic counterpart **6**. The equilibrium between solid proline and these soluble proline-derived species can be further shifted to the right upon addition of the aldehyde, especially in the case of strongly electron-deficient aldehydes, such as 4-nitrobenzaldehyde (**2a**), leading to the formation of the bicyclic 1-oxapyrrolizidine **7** by a multistep process that involves conversion into the aldehyde-derived oxazolidinone,[29] decarboxylation of the corresponding zwitterionic monocyclic species, and 1,3-dipolar cycloaddition of the resulting azomethyne ylide **8** with another molecule of aldehyde **2a**. Although this process reduces the amount of proline, the concentration of the zwitterionic species **6** is increased (see Supporting Information). A non-negligeable part of the "catalytic" effect of the thiourea in the aldol reaction can therefore be ascribed to the formation of the acetone-derived species **5**+**6**, which are the direct precursors of the key enamine–aldehyde intermediate **9**[16] in solution. On the other hand, the present experiments do not rule out the possibility of a hydrogen-bonding stabilization of the transition state by the thiourea co-catalyst (see Figure 1, right), as previously proposed by Reis et al.[4] and by us.[5]

In summary, we have disclosed, from a study of nonlinear effects in the proline–thiourea-catalyzed aldol reaction between acetone and 4-substituted benzaldehydes in dry toluene, an unprecedented dependence of these effects on the nature of the aromatic aldehyde. These results strongly suggest that the main role of the thiourea co-catalyst (at least in hydrocarbon solvents) is not that of generating a soluble proline–thiourea hydrogen-bonded species, a conclusion that is supported both by simple ^{1}H NMR and ESI-MS experiments. In fact, the hydrogen-bonded interaction between proline and thiourea appears to be operative only in the presence of the ketone reagent, promoting both the formation of the ketone–oxazolidinone intermediate **5** and its equilibration with the "open" zwitterionic structure **6**. These species, after conversion to the proline–ketone enamine, could in fact be the true catalysts of the aldol reaction in a mechanistic cycle similar to that proposed by Seebach[6a] and Vilarrasa,[6c] that runs in the absence of water. The nature of the aromatic aldehyde is also very relevant for the extent of proline solubilization, through its partial conversion to the "parasitic" 1-oxapyrrolizidine species. Further experimental and theoretical work on these issues is currently underway in our laboratory.

Experimental Section

Experimental procedure for the study of nonlinear effects

1) In the absence of thiourea: An ordinary vial equipped with a magnetic stirring bar was charged with dry proline (6 mg, 0.05 mmol for **2a**; 17 mg, 0.15 mmol for **2b**) and 5:1 toluene-acetone (2 mL), and stirred for 2 h at room temperature. Then, the aldehyde **2a/b** (0.50 mmol) was added in one portion. After 20 h (**2a**) or 10 days (**2b**), the conversion was measured by NMR spectroscopy of an aliquot of the reaction mixture and

the enantiomeric purity of the aldol **4a/b** was determined by chiral HPLC.[23]

b) In the presence of thiourea: An ordinary vial equipped with a magnetic stirring bar was charged with dry proline (6 mg, 0.05 mmol), thiourea **3** (22 mg, 0.05 mmol), and 5:1 toluene–acetone (2 mL), and stirred for 2 h at room temperature. Then, the aldehyde **2a/b** (0.50 mmol) was added in one portion. After 20 h, the conversion was measured by NMR spectroscopy of an aliquot of the reaction mixture and the enantiomeric purity of the aldol **4a/b** was determined by chiral HPLC.[23]

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Keywords: aldol reaction · nonlinear effects · organocatalysis · proline · thiourea

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[26] Substitution of [D_6]acetone by acetone led to a 1:3.8 mixture of the nondeuterated species **5** and **6**. On the other hand, the ^{1}H NMR spectrum of a 1:1 proline/thiourea **1** solution (0.025 M) in 5:1 [D_8]toluene/pivalaldehyde showed a completely different set of signals, corresponding to the formation of the expected bicyclic oxazolidinone (SolPro)[6c] as the sole soluble proline-derived species. Finally, a solution of oxazolidinone [D_6]**5** was independently generated by exchange from SolPro (obtained from L-proline and pivalaldehyde in benzene by adaptation of the procedure described by Vilarrasa et al.[6c]) with [D_6]acetone; upon addition of thiourea **1** to this solution, equilibration of **5** with the zwitterionic species **6** was observed (see the Supporting Information).

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[29] The ready interconversion between aldehyde- and ketone-derived proline oxazolidinones has been nicely demonstrated by Vilarrasa and co-workers; see reference [6c].

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