Imidazolidinone intermediates in prolinamide-catalyzed aldol reactions†

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The reaction between acetone and 4-nitrobenzaldehyde catalyzed by aniline prolinamide **1** was studied in depth. Working in different solvents with equimolar amounts of reagents and monitoring the reaction by ^{1}H NMR, we detected and identified several imidazolidinones, such as those of the acetone **4**, the aldol products **5a** and **5b**, and aldehydes **10a** and **10b**. According to our results, these compounds could influence the reaction rate and diminish product enantioselectivity. Furthermore, acetone imidazolidinone **4** was seen to react with 4-nitrobenzaldehyde to furnish the aldol product **3**. This reaction can be catalyzed by different nucleophiles and acids. In fact, strong acids such as camphorsulfonic or trifluoroacetic acid, convert imidazolidinones into iminium salts and afford more enantioselective aldol reactions when different aromatic prolinamides are used. Enantiomeric excesses of *ca.* 82% are reached.

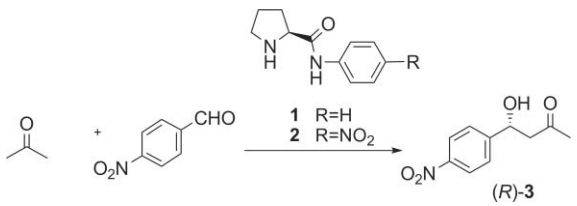
Introduction

In recent years aldol reactions catalyzed by prolinamides have attracted a great deal of interest owing to the possibility of achieving high enantiomeric ratio inductions.[1] Moreover, prolinamides are assumed to overcome some of the drawbacks of proline, such as:

1. limited solubility in apolar organic solvents;
2. the low concentration of the basic amine necessary to generate the enamine intermediate (in solution, most of the proline is present in the zwitterionic form);
3. the geometric requirements for the protonation of the reactive intermediate from the *syn* carboxylic acid, while *anti* carboxylic acids are more stable.

Custom-made catalysts, based on prolinamides, can be readily synthesized using different amines. This explains the interest in the use of prolinamides as organocatalysts.[2] Although in many cases the yields and enantiomeric excesses obtained are impressive,[3] different results have been reported for the same aldol reaction catalyzed by the same prolinamide. As an illustrative example, the aldol reaction between acetone and 4-nitrobenzaldehyde catalyzed by the prolinamides **1**[4] and **2**,[3a] yielded disparate results as shown in Table 1.

Table 1 Reported results for the aldol reaction of 4-nitrobenzaldehyde with acetone catalyzed by prolinamides **1** and **2** (20 mol% of the catalyst)



Entry	Catalyst	Yield (%)	ee (%)
1[a]	**1**	88	8
2[b]	**1**	87	15
3[c]	**1**	88	37
4[d]	**1**	68	71
5[c]	**2**	80	39
6[a]	**2**	80	54
7[d]	**2**	76	72

[a] The reaction of aldehyde (0.3 mmol, 1 equiv) with acetone (6.0 mmol, 20 equiv) was run in HMPA/H_2O in the presence of catalyst (0.06 mmol, 0.2 equiv).[5] [b] 4-Nitrobenzaldehyde (2 mmol, 1 equiv), acetone (40 mmol, 20 equiv) in H_2O using **1**·HBr (0.4 mmol, 0.2 equiv).[6] [c] 4-Nitrobenzaldehyde (0.5 mmol, 0.5 M) in neat acetone and catalyst (0.1 mmol, 0.1 M).[3a] [d] The reaction was run in DMF with 4-nitrobenzaldehyde (0.66 mmol, 1 equiv), catalyst (0.13 mmol, 0.2 equiv), acetone (13.2 mmol, 20 equiv) and TFA (0.066 mmol, 0.1 equiv).[7]

The mechanism of these reactions is assumed to be similar to that proposed by Houk for proline catalysis,[8] in which a Zimmerman–Traxler intermediate generates the enantioselectivity. Nevertheless, the details of the process are not fully known.[9] One of the main points of discussion is the role of oxazolidinones (in proline catalysis)[10] or imidazolidinones (when prolinamides are used)[2k–m] in these reactions.

Prolinamides have proven to be satisfactory catalysts in intramolecular aldol additions,[11] and recently we have found imidazolidinones as intermediates in these processes.[12] In this paper, we study the possible relevance of imidazolidinones in intermolecular aldol reactions. We start with the model aldol reaction[13] between

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† Electronic supplementary information (ESI) available: Experimental procedures, ^{1}H and ^{13}C NMR spectra of the catalyzed reaction mixtures at different times, spectroscopic NMR data for the new compounds, graphic for competitive titration and CIF files of imidazolidinones **4**, **10a** and **10b**. CCDC reference numbers 741181–741183. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b926284a

acetone and 4-nitrobenzaldehyde catalyzed by the readily available aniline prolinamide **1** in neat acetone where the large excess of acetone favored the aldol addition product. As has been shown in the literature, this reaction is very sensitive to solvent changes; so we turn our attention to other solvents as chloroform and methanol and finally we evaluate the role of imidazolidinones in enantioselectivity.

Results and discussion

Deuteroacetone as solvent

As a starting point for this study, the concentrations of aldehyde and prolinamide were set to the same value, 1.0 M.

Five minutes after dissolving 4-nitrobenzaldehyde and prolinamide **1** in neat deuteroacetone, a new compound was detected in the ^{1}H NMR spectrum. Its signals (methyl groups at 1.31 and 1.45 ppm) could be assigned to the acetone imidazolidinone **4** (yield > 95%) similar to the thioimidazolidinones previously reported.[2k–m]

The structure of this compound was confirmed by an X-ray diffraction study (Fig. 1).[14] As prolinamide **1** has been synthesized starting from enantiopure L-proline (*S* en C2), the absolute stereochemistry of imidazolidinone **4** could be established. The most interesting feature is the almost 90° dihedral angle which the phenyl aniline ring forms with the proline carbonyl group, showing that this is a strained compound with a large loss of conjugation energy. The same characteristic can be observed in solution, as revealed by the ^{1}H NMR chemical shifts, since the aniline *ortho* protons are strongly shielded with respect to the same protons in the prolinamide (from 7.69 ppm in prolinamide **1** to 7.12 ppm in the imidazolidinone **4**, ESI†).

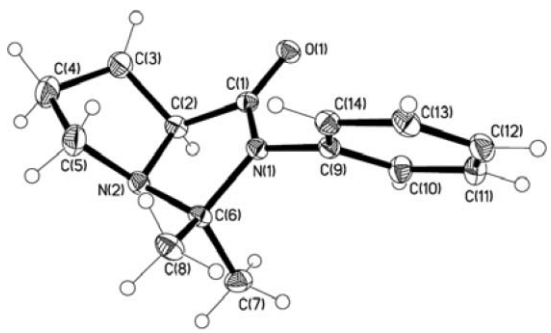
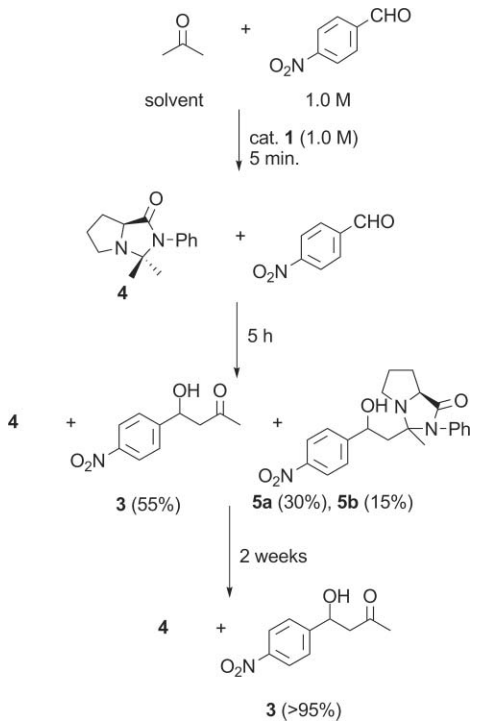


Fig. 1 ORTEP diagram of the acetone imidazolidinone **4**. Thermal ellipsoids are drawn at the 50% probability level.

After 5 h, the reaction in acetone was almost complete, since only a very small amount of the aldehyde was detected in the ^{1}H NMR spectrum (see the ESI†). The other reaction products were the expected aldol **3** (55% yield respect to the initial aldehyde), the acetone imidazolidinone **4**, and two new imidazolidinones, **5a** and **5b** (at a proportion of 2 : 1, 30% and 15% yield respectively, according to ^{1}H NMR integration), which corresponded to two different stereoisomers of the aldol imidazolidinones (Scheme 1).

A study of the evolution of the reaction over time revealed that the minor aldol imidazolidinone **5b** was transcarbonylated faster than the major **5a** (see the ESI†). After two weeks, these two imidazolidinones **5a** and **5b** had disappeared from the solution,



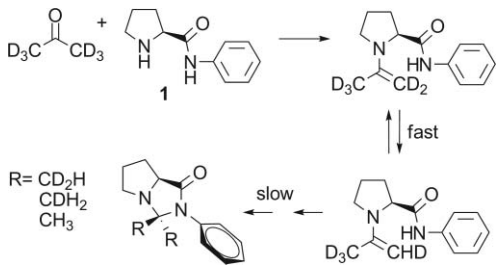
Scheme 1 Evolution of the reaction between acetone (solvent) and 4-nitrobenzaldehyde catalyzed by prolinamide **1**.

and only the mixture of aldol **3** (yield > 95%) and acetone imidazolidinone **4** was detected in the spectrum.

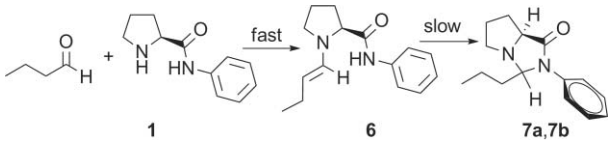
The structure of imidazolidinones **5a** and **5b** was established from their NMR spectra and a tentative assignation of all their signals was accomplished (see the ESI†). Both compounds showed the aminal carbons at 82.1 and 82.8 ppm. Comparison of the ^{13}C chemical shifts of the methyl groups of **5a** (19.7 ppm) and **5b** (22.1 ppm) with those of imidazolidinone **4** (*endo* methyl group at 23.7 ppm; *exo* methyl group at 28.4 ppm) unambiguously assigned through bidimensional correlations, showed that only the *exo* methyl group supported aldol addition.

Since the acetone imidazolidinone was the first reaction product in neat acetone, it was thought to be of interest to study this compound. The generation of imidazolidinone **4** in deuteroacetone (deuteration degree 99.8%) should yield a compound with a high degree of deuteration in the methyl groups; however, at the beginning of the reaction the deuteriums of the imidazolidinone methyl groups were replaced by the protons originally standing in the prolinamide NH groups. After 45 min, it was possible to estimate a 1.3–1.4 average degree of exchange (almost the statistical amount between 2 CH_3 groups and H_2O). This was reduced to 0.2 after two weeks. From the shape of the methyl signals in the ^{1}H NMR spectrum (see the ESI†) it was possible to deduce a total proton scramble in both methyl groups. This is consistent with a mechanism in which enamines would be generated, as shown in Scheme 2.

The above-formulated hypothesis was also supported by the results concerning the reaction of butyraldehyde and prolinamide **1** in $CDCl_3$. The initial product observed in the ^{1}H NMR was the enamine **6** (Scheme 3). Cyclization to the imidazolidinones **7a** and **7b** was the slowest process (see the ESI†). Nevertheless, these were the most stable compounds and they accumulated in the reaction



Scheme 2 Formation of imidazolidinones **4** (with different degrees of deuteration) in deuteroacetone.



Scheme 3 Reaction of the prolinamide **1** (0.1 M) with n-butyraldehyde (0.1 M) in deuterochloroform.

mixture. Only the most stable imidazolidinone **7b**, with the propyl group in the *exo* position, was isolated after equilibration in hot acetic acid.

Gryko and Lipinski[2l,m] reported that the use of thioimidazolidinone as catalyst instead of prolinethioamide affords slower reactions and lower enantioselectivities. In our hands, this was also the case. The purified imidazolidinone **4** reacted very slowly with 4-nitrobenzaldehyde, as shown in Fig. 2.

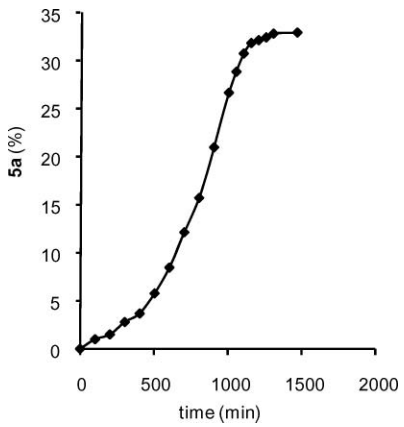


Fig. 2 Generation of aldol **5a** in the reaction of the imidazolidinone **4** (1.0 M) with 4-nitrobenzaldehyde (1.0 M) in CD_3COCD_3 at 20 °C.

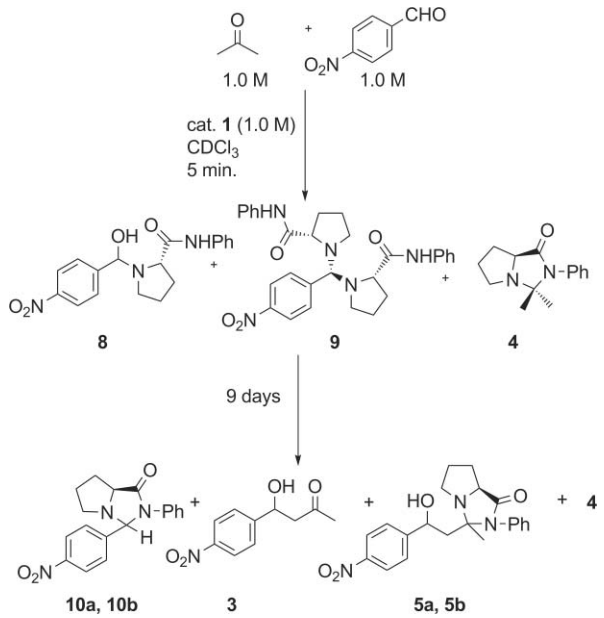
Scrutiny of the kinetics suggested that, as in other similar processes,[10e,15] the reaction is autocatalytic, and a good reason for this could be the presence of a hydroxyl group in the aldol. Indeed, water was also able to catalyze the aldol reaction of the imidazolidinone **4** with 4-nitrobenzaldehyde, and this might explain the previous observations of Gryko and Saletra.[2n] Other nucleophiles such as dodecanethiol, imidazole or methanol also showed catalytic activity (Table 2).[16] Acids such as phenol (entry 6) or 4-nitrophenol (entry 2) catalyzed the aldol reaction in deuteroacetone too.

Table 2 Exploration of several catalysts (0.5 M) for the aldol reaction between acetone imidazolidinone **4** (1.0 M) and 4-nitrobenzaldehyde (1.0 M) in deuteroacetone

Entry	Catalyst	$t_{1/2}$/min
1	None	700
2	4-Nitrophenol	2
3	Decanoic acid	8
4	Imidazole	28
5	Dodecanethiol	31
6	Phenol	46
7	H_2O	260

Deuterochloroform as solvent

When the aldol reaction was run in deuterochloroform with equimolar concentrations of 4-nitrobenzaldehyde, acetone and prolinamide (1.0 M), ^{1}H NMR analysis revealed the presence of several compounds, some of them different from the intermediates previously detected for the reaction in neat acetone. (Scheme 4).



Scheme 4 Evolution of the reaction between acetone and 4-nitrobenzaldehyde in $CDCl_3$ catalyzed by aniline prolinamide **1**.

After five minutes, together with the absorptions from the aldehyde, acetone and prolinamide, the ^{1}H NMR spectrum (see the ESI†) displayed signals that suggested the presence of the following compounds: the addition product **8** of the prolinamide to the aldehyde (singlets at 5.42 and 5.44 ppm, corresponding to both stereoisomers), the 4-nitrobenzaldehyde aminal **9** (singlet at 4.52 ppm) and the acetone imidazolidinone **4** (methyl groups at 1.23 and 1.40 ppm). After nine days, the recorded spectrum no longer showed the initial aldehyde adducts (**8** and **9**); instead, the aldehyde imidazolidinones (56%) **10a** and **10b** (6.34 ppm and 5.72 ppm, respectively) and the acetone imidazolidinone **4** (4.05 ppm, 30%) were the main products as established by integration of the NMR signals.

Other signals in the ^{1}H NMR spectrum (14%) could be assigned to the expected aldol products (**3**, 5.1 ppm) and to a structure that might correspond to the imidazolidinones of these

aldols (**5a**, 4.87 ppm; **5b**, 5.13 ppm). Acetone and traces of 4-nitrobenzaldehyde were also present (Scheme 4).

While aldehyde adducts **8** and **9** were difficult to isolate owing to their instability, it was possible to obtain the aldehyde imidazolidinones **10a** and **10b**. These compounds could be prepared from 4-nitrobenzaldehyde and prolinamide **1** in deuterochloroform as solvent. However, this reaction was sluggish (as already shown). Finally, after nine days a mixture of imidazolidinones (5 : 1 according to the ^{1}H NMR integration signals of singlets at 6.34 ppm and 5.72 ppm respectively) was obtained. It was possible to purify the major compound **10a** by crystallization (CH_2Cl_2–hexane). X-Ray diffraction[17] revealed a structure with the nitrophenyl group in the *endo* position. The absolute stereochemistry at C2 (*S*) and C6 (*S*) could be unambiguously assigned as configuration at C2 is already known from the synthesis. Its ^{1}H NMR spectrum (see the ESI†) showed a strong shielding in the proline 5-H protons (0.6 ppm upfield), consistent with a structure in which the nitrophenyl ring occupies an *endo* position, as shown in Fig. 3.

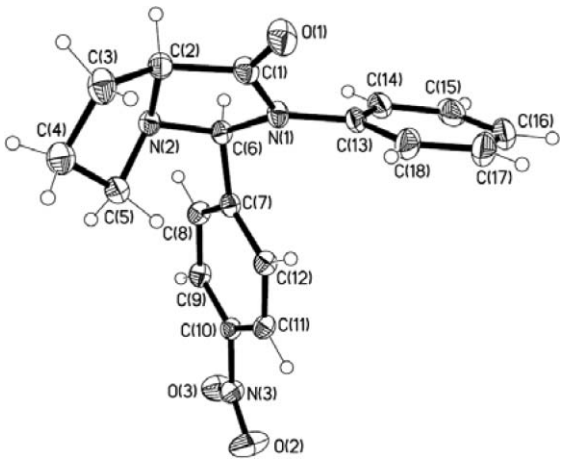


Fig. 3 ORTEP diagram of the imidazolidinone **10a**. Thermal ellipsoids are drawn at the 50% probability level.

Since the isomer with the nitrophenyl ring in the *exo* position should be more stable, equilibration of the isomers was carried out in hot acetic acid, to yield essentially compound **10b**. X-Ray diffraction indeed revealed an *exo* nitrophenyl group in this structure (Fig. 4).[18] As in the case of compound **10a**, absolute configurations at C2 (*S*) and C6 (*R*) could be inequivocally established.

An explanation of the formation of the initial kinetic aldehyde imidazolidinone is shown in Scheme 5; cyclization from the most stable iminium salt yielded the most hindered imidazolidinone **10a**. Harsher conditions were needed to obtain imidazolidinone **10b** since it is produced from a less stable iminium salt.

Deuteromethanol as solvent

Since alcohols are good catalysts for imidazolidinone aldol additions, the reaction was also tested in deuteromethanol. Two observations regarding this process were of interest. The first was that the reaction with the aldehyde led to an equilibrium, as shown in Scheme 6.

Indeed, when the aldol **3** (1.0 M) was reacted with prolinamide **1** (1.0 M) in deuterochloroform a similar mixture of products was

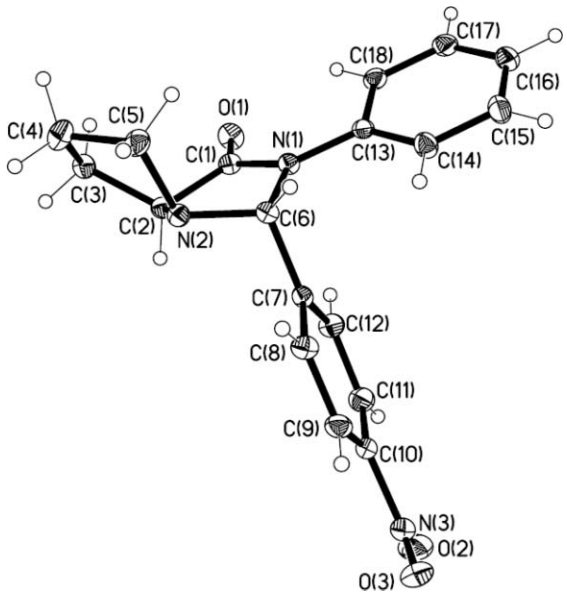
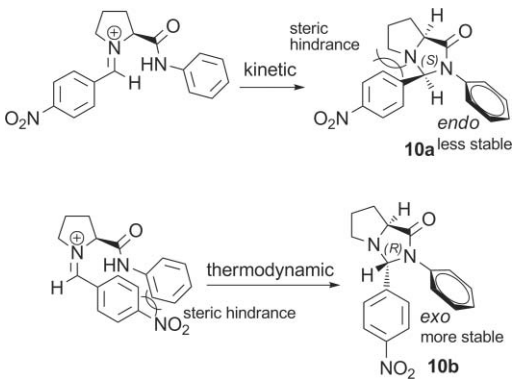
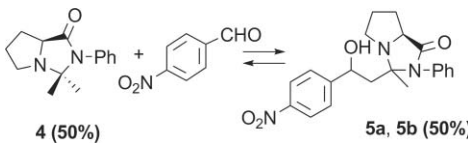


Fig. 4 ORTEP diagram of the imidazolidinone **10b**. Thermal ellipsoids are drawn at the 50% probability level.



Scheme 5 Possible explanation for the formation of aldehyde imidazolidinones **10a** and **10b**.

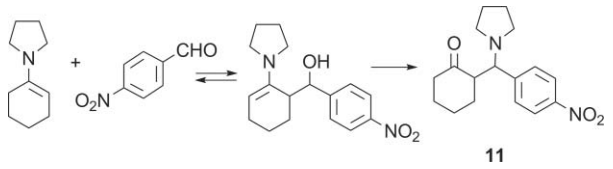


Scheme 6 Reaction between acetone imidazolidinone **4** (0.5 M) and 4-nitrobenzaldehyde (0.5 M) in deuteromethanol after 14 h.

obtained, because of the occurrence of a retroaldol reaction. The acetone imidazolidinone **4**, aldehyde imidazolidinones **10a** and **10b**, the aldol imidazolidinone **5a** and even 4-nitrobenzaldehyde and acetone were detected (see the ESI†).

Taking into account the small driving force of aldol reactions, this result is not surprising. In fact, when cyclohexanone enamine was reacted with 4-nitrobenzaldehyde after initial addition the reaction stopped. Other processes took over; in our hands, the final product was the Mannich compound **11** (see Scheme 7 and the ESI†).

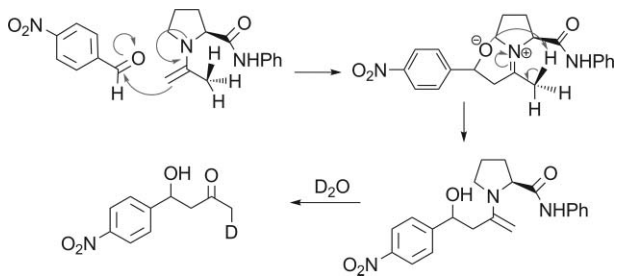
This lack of driving force, even with a very reactive compound such as 4-nitrobenzaldehyde, explains the limited use of these reactions until recently; for example, in the enamine reviews



Scheme 7 Reaction of the pyrrolidine cyclohexanone enamine (0.16 M) and 4-nitrobenzaldehyde (0.16 M) in deuterochloroform.

from Hickmott[19] there are no references to reactions of enamines with aldehydes. The current successful results reported in the literature[2,3] correspond to catalytic amounts of prolinamides in which the enamines are always hydrolyzed or undergo transcarbonylation after the aldol addition to the corresponding carbonyl compounds.

The other interesting feature of the reaction of the imidazolidinone **4** (0.5 M) and 4-nitrobenzaldehyde (0.5 M) in deuteromethanol was the deuteration exchange. A large amount of deuteration exchange arose in the imidazolidinone methyl group after the aldol addition, as judged from the shape and integral of its NMR signal, while a small degree of deuteration was observed in the methylene group. This suggests that the reaction yields the enamine in the α′-carbon, as shown in Scheme 8, which might indicate a concerted ene-like mechanism. In this mechanism, the role of the prolinamide NH is limited to setting a strong H-bond with the aldehyde carbonyl group, which stabilizes the transition state.



Scheme 8 A possible ene-like mechanism for aldol reaction catalyzed by prolinamides.

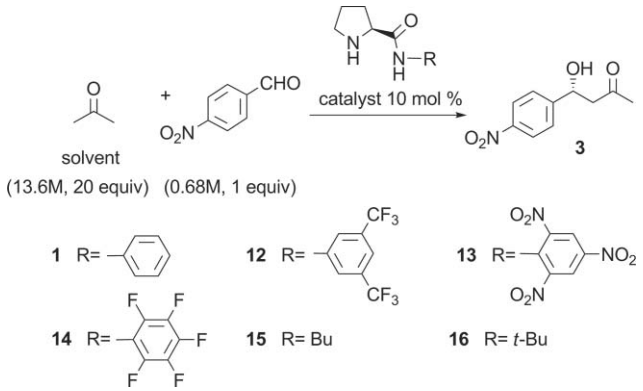
Influence of imidazolidinones in enantioselectivity

As shown in the introduction, the reaction of acetone with 4-nitrobenzaldehyde catalyzed by aniline prolinamide **1** has been reported to yield very different enantiomeric excesses. (Table 1, entries 1–4).

In our hands, the enantioselectivity could be even lower (Table 3, entry 1). When the aldol reaction was conducted in neat deuteroacetone with aldehyde (0.68 M) and 10 mol% of catalyst **1**, an enantiomeric excess as low as 10% was obtained. The formation of the aldol imidazolidinones **5a** and **5b** as reaction intermediates could explain these poor results. Their presence in the solution, as revealed in the ^{1}H NMR spectra, shows a rate-limiting transcarbonylation of the compounds. Hence the initial aldol addition products, which should be generated with good chiral assistance, can revert back to reagents. Therefore, part of the enantioselectivity of the products being lost (Scheme 9).

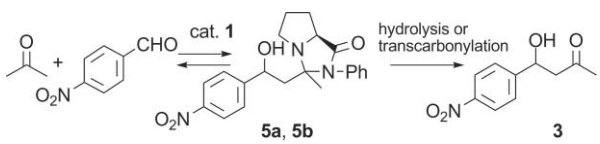
We have observed that the addition of trifluoroacetic acid (TFA) can overcome this drawback, since with TFA as an additive

Table 3 Enantiomeric excesses for the aldol reaction catalyzed by prolinamides either in neutral form or as their trifluoroacetate salts



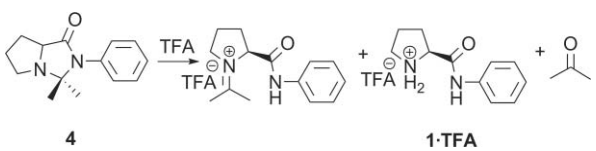
Entry	Catalyst	Time/h	Yield (%)	ee (%)[a]
1	**1**[b]	70	21	10
2	**1**·**TFA**	5	21	61
3	**12**[c]	12	31	2
4	**12**·**TFA**	11	35	65
5	**13**[d]	2	>99	60
6	**13**·**TFA**	7	72	82
7	**14**[e]	67	95	13
8	**14**·**TFA**	43	66	80
9	**15**[f]	5	93	32
10	**15**·**TFA**	126	24	16
11	**16**[g]	3	86	28
12	**16**·**TFA**	47	18	2

[a] Enantiomeric excesses were determined by chiral HPLC. [b] For reported results for the same catalyst see ref. 3*a* and 6. [c] For reported results for the same catalyst see ref. 12 [d] For reported results for the same catalyst see ref. 5. [e] For reported results for the same catalyst see ref. 7. [f] For reported results for the same catalyst see ref. 13*f*. [g] For reported results for the same catalyst see ref. 3*a*.



Scheme 9 Aldol imidazolidinones as intermediates in the reaction between acetone and 4-nitrobenzaldehyde catalyzed by prolinamide **1**.

imidazolidinones were not accumulated. Instead, the protonated prolinamides and iminium salts are identified in the NMR spectra, as shown by Gryko *et al.*[2k] (Scheme 10).



Scheme 10 Iminium salt and protonated prolinamide generated from imidazolidinone **4** in the presence of TFA.

We suggest that the explanation for the lack of imidazolidinones under acidic conditions is their surprisingly low pK_a. After the addition of camphorsulfonic acid to a mixture of prolinamide **1** and its acetone imidazolidinone **4** in deuterochloroform we observed protonation only in the prolinamide **1** nitrogen. After

this compound had been completely protonated, the subsequent protonation of the imidazolidinone **4** took place (see the ESI†).

Other ^{1}H NMR competitive titrations between the imidazolidinone and pyridine afforded similar pK_a values (p$K_{a\,\text{pyridine}}$/p$K_{a\,\text{imidazolidinone}\ 4}$ = 1.34), while in chloroform the prolinamide had almost the same pK_a as imidazole.

When the prolinamide was used as its trifluoroacetate salt (**1**·**TFA**), the enantiomeric excess was increased up to ee = 61% (Table 3, entry 2), in agreement with the absence of imidazolidinones as the rate-limiting step. Other aromatic prolinamides (**12**, **13** and **14**) showed a similar behaviour (Table 3, entries 3–8).

Bis(trifluoromethylaniline)prolinamide **12** behaved like prolinamide **1**, while trinitroanilineprolinamide **13** afforded up to 82% enantiomeric excess (Table 3, entry 6). Pentafluoroanilineprolinamide **14** yielded the most remarkable effect, changing from only 13% ee for the neutral prolinamide to 80% ee in the presence of TFA (Table 3, entries 7 and 8). However, when non-aromatic prolinamides were used the situation was more complex. The presence of TFA was detrimental to both the enantioselectivity and conversion (Table 3, entries 9–12) affording nearly racemic aldol **3** when the reaction was catalyzed for prolinamide **16** as its trifluoracetate salt. (Table 3, entry 12).

Conclusions

In summary, we have shown that imidazolidinones can be formed from aniline prolinamide **1** and all the carbonyl compounds present in the reaction medium during the aldol addition. Aldol imidazolidinones influence the reaction enantioselectivity explaining the different results reported in the literature. Under neutral conditions, imidazolidinone hydrolysis is at least partially rate-limiting, and the enantiomeric excesses are reduced. In contrast, under acidic conditions the low basicity of imidazolidinones prevents their formation and enantioselectivity is enhanced.

Acetone imidazolidinone and both aldehyde imidazolidinones have been isolated and their X-ray structures have been obtained.

Experimental

(*S*)-3,3-Dimethyl-2-phenyl-hexahydropyrrolo[1,2-*e*]imidazol-1-one (4)

Prolinamide **1** (1.27 g, 6.68 mmol) was dissolved in acetone (10 cm^3) and either anhydrous Na_2SO_4 or K_2CO_3 (1 g) was added. The mixture was stirred for 12 h at room temperature and then filtered to remove the salts. Then, the acetone was evaporated to afford the crude product which was purified by recrystallization from acetone (1.13 g, 73.5%), mp 89–92 °C; $[\alpha]_D^{25}$ +46 (*c* 0.98 in $CHCl_3$). (Found: C, 73.10; H, 7.75; N, 11.98. $C_{14}H_{18}N_2O$ requires C, 73.01; H, 7.88; N, 12.16); ν_{max}(film cm^{-1}) 3059, 1690, 1378 and 717; δ_H(400 MHz, CD_3COCD_3) 1.72 (3H, s), 1.86 (3H, s), 2.13 (1H, m), 2.24 (1H, m), 2.33 (1H, m), 2.48 (1H, m), 3.05 (1H, m), 3.35 (1H, t, *J* 7.6), 4.36 (1H, dd, *J* 4.6 and 9.6), 7.60 (2H, d, *J* 8), 7.72 (1H, t, *J* 8), 7.82 (2H, t, *J* 8); δ_C(100 MHz, CD_3COCD_3) 23.7, 25.9, 26.5, 28.4, 49.1, 63.9, 81.1, 127.9, 138.2 and 176.1; HRMS calcd for $C_{14}H_{18}N_2O$ + Na requires 253.1311, found 253.1316.

(3*S*,7a*S*)-3-(4-Nitrophenyl)-2-phenylhexahydropyrrolo[1,2-*e*]imidazol-1-one (10a)

4-Nitrobenzaldehyde (72 mg, 0.48 mmol) and aniline prolinamide **1** (94.7 mg, 0.50 mmol) were dissolved in $CDCl_3$ (0.5 cm^3). The reaction was monitored by ^{1}H NMR. After nine days, the solvent was evaporated off under reduced pressure and the crude product was recrystallized from CH_2Cl_2/undecane, mp 71–72 °C; $[\alpha]_D^{25}$ +16.9 (*c* 0.95 in $CHCl_3$); (Found: C, 55.64; H, 4.68; N, 10.30. $C_{18}H_{17}N_3O_3{\cdot}CH_2Cl_2$ requires C, 55.89; H, 4.69; N, 10.29); ν_{max}(film cm^{-1}) 1703, 1599, 1346 and 729; δ_H(200 MHz, $CDCl_3$) 1.79 (2H, m), 2.29 (3H, m), 2.40 (1H, m), 4.03 (1H, dd, *J* 3.4 and 8.4), 6.45 (1H, s), 7.09 (1H, m), 7.28 (4H, m), 7.45 (2H, d, *J* 8.8), 8.14 (2H, d, *J* 8.8); δ_C(50 MHz, $CDCl_3$) 25.1, 27.2, 49.2, 65.9, 78.2, 122.2, 124.0, 125.7, 129.2, 129.6, 137.2, 141.9, 148.3 and 176.7; HRMS calcd for $C_{18}H_{17}N_3O_3$ + Na requires 346.1168, found 346.1146.

(3*R*,7a*S*)-3-(4-Nitrophenyl)-2-phenylhexahydropyrrolo[1,2-*e*]imidazol-1-one (10b)

4-Nitrobenzaldehyde (0.42 g, 2.78 mmol) and aniline prolinamide **1** (0.52 g, 2.74 mmol) were dissolved in glacial acetic acid (1 cm^3) and heated at 75–80 °C for three hours. The reaction mixture was then treated with an aqueous solution of sodium carbonate (4%) and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated off to yield a crude compound that was purified by recrystallization (CH_2Cl_2/undecane) to afford compound **10b** as a white solid (0.84 g, 95%), mp 159–161 °C; $[\alpha]_D^{25}$ −19.2 (*c* 1.2 in $CHCl_3$); (Found C, 66.57; H, 5.33; N, 12.96. $C_{18}H_{17}N_3O_3$ requires C, 66.86; H, 5.30; N, 13.00); ν_{max}(film cm^{-1}) 3072, 1696, 1339, 827 and 762; δ_H(200 MHz, $CDCl_3$) 1.92 (2H, m), 2.22 (2H, m), 2.92 (1H, m), 3.44 (1H, m), 3.99 (1H, t, *J* 6.8), 5.77 (1H, s), 7.13 (1H, t, *J* 6.6), 7.29 (2H, t, *J* 6.6), 7.44 (2H, t, *J* 6.6), 7.47 (2H, d, *J* 14.6), 8.18 (2H, d, *J* 14.6); δ_C(50 MHz, $CDCl_3$) 25.1, 27.9, 56.5, 64.7, 82.9, 121.5, 124.5, 125.9, 127.5, 129.5, 137.3, 146.8, 148.1 and 174.8; HRMS calcd for $C_{18}H_{17}N_3O_3$ + Na requires 346.1168, found 346.1146.

(7a*S*)-2-Phenyl-3-propyl-hexahydropyrrolo[1,2-*e*]imidazol-1-one (7b)

Aniline prolinamide **1** (0.14 g, 0.74 mmol) and butyraldehyde (0.28 cm^3, 3.10 mmol) were dissolved in glacial acetic acid (0.14 cm^3) and heated at 70–80 °C for ten minutes. Then, the solution was quenched with a saturated solution of sodium carbonate and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated off under reduced pressure. Purification by column chromatography on silica gel (eluent, CH_2Cl_2–ethyl acetate) afforded the imidazolidinone **7b** as a pale yellow oil (0.14 g, 80%); $[\alpha]_D^{25}$ −31.4 (*c* 2.5 in $CHCl_3$); (Found C, 73.54; H, 8.39; N, 11.33. $C_{15}H_{20}N_2O$ requires C, 73.74; H, 8.25; N, 11.47); ν_{max}(film cm^{-1}) 3059, 1696, 1488 and 786; δ_H(200 MHz, $CDCl_3$) 0.87 (3H, t, *J* 7.4), 1.51 (3H, m), 1.83 (2H, m), 2.10 (3H, m), 2.70 (1H, m), 3.25 (1H, m), 3.98 (1H, dd, *J* 4.7 and 8.8), 4.71 (1H, dd, *J* 3.4 and 7.3), 7.17 (1H, t, *J* 8), 7.37 (2H, t, *J* 8), 7.48 (2H, d, *J* 8); δ_C(50 MHz, $CDCl_3$) 14.0, 18.4, 25.2, 27.9, 36.8, 56.7, 65.3, 82.7, 122.7, 125.8, 129.4, 137.3 and 174.3; MS (ESI) (*m*/*z*) 267.1 (M +Na)$^+$, 245.1 (M+H)$^+$.

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