DOI: 10.1002/adsc.200505247

L-Prolinethioamides – Efficient Organocatalysts for the Direct Asymmetric Aldol Reaction

Dorota Gryko,* Radosław Lipiński

Institute of Organic Chemistry, Polish Academy of Science, Kasprzaka 44/52, 01-224 Warsaw, Poland
Fax: (+48)-22-632-6681, e-mail: dgryko@icho.edu.pl

Received: June 16, 2005; Revised: September 8, 2005; Accepted: September 12, 2005

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: A series of novel L-proline derived thioamides has been synthesised. They have been evaluated as organocatalysts in the direct asymmetric aldol reaction for the first time. Thioamides exhibit catalytic ability higher than proline itself and the model aldol reaction of 4-cyanobenzaldehyde with acetone proceeds well in the presence of 5 mol % of catalyst (ee up to 100%). Other aromatic aldehydes gave aldol products with high ees and moderate yields. Small changes in the catalyst's structure [e.g., *N*-Bn versus *N*-CH(CH_3)Ph] as well as the addition of an acid have a profound effect on their activity. The unexpected formation of the catalyst-derived cyclic adducts was observed and their reactivity was established giving valuable insight into the course of the reaction.

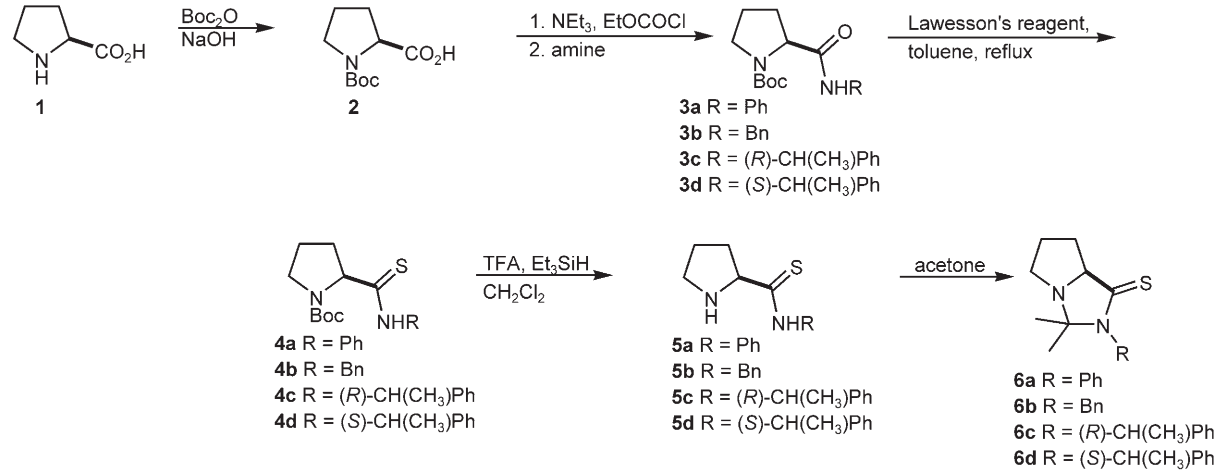
Keywords: asymmetric aldol reaction; C–C bond formation; organic catalysis; proline; thioamides

The aldol reaction is one of the most powerful methods for the formation of complex polyol molecules.[1–5] In recent years many efforts have been spent on developing its catalytic asymmetric versions.[2] One of the most interesting ways involves proline and its derivatives as organocatalysts.[2,6] This approach avoids the use of protecting groups and metals, which can be both expensive and toxic. However, proline itself has some drawbacks too, it is rather poorly soluble in most of organic solvents and a high catalyst loading is required, often up to 30%. Given all the above, the development of an efficient catalyst for the asymmetric catalytic direct aldol reaction is a worthwhile endeavour. Recently Tang et al.[7] has shown that L-prolinamide derivatives are able to efficiently catalyse intermolecular acetone aldolisation with high enantioselectivity. However, the best results were obtained when the catalyst was prepared from L-proline and (1*S*,2*S*)-diphenyl-2-aminoethanol which is very expensive. The use of simple aliphatic or aromatic prolinamides including those derived from chiral 1-phenylethylamine resulted in good yields, albeit with low enantioselectivities. It was observed that the enantioselectivity increased with the increase in the acidity of the amide N–H bond and in the presence of a terminal hydroxy group. Moreover Arvidsson and Hartikka[8] showed that the proline-derived tetrazolic acid was much more effective than proline itself. The increase in the reactivity and selectivity of the catalyst was attributed to the higher acidity of the tetrazolic group in comparison to the carboxylic acid functionality.

With this in mind we set out to design a more reactive catalyst for the direct asymmetric aldol reaction. The presence of the acidic amide N–H bond seemed to be crucial in the catalytic activity of prolinamide-derived catalysts. The replacement of the amide functionality with the thioamide group would increase the acidity of the N–H bond (for example, the pK_a of CH_3CSNH_2 is 18.5 whereas the same value for CH_3CONH_2 is 25.5).[9] Consequently, we expected that the thioamide group would form a stronger hydrogen bond with the acceptor than the amide group and effectively facilitate the required proton transfer.

Here we report a novel class of organic catalysts – (*S*)-pyrrolidine-2-carboxythioamides – that efficiently catalyse the direct aldol reaction of aromatic aldehydes in neat acetone with high enantioselectivity (up to 100%) and in good yields.

Since it has already been established that the acidity of the N–H bond is crucial for the performance of a catalyst, our initial target was a proline-derived thioamide with an aromatic amine. The synthesis of L-prolinethioamide **5a** involved the coupling of *N*-Boc-L-proline[10] (**2**) with aniline[7b] followed by the reaction with the Lawesson's reagent[11] (Scheme 1). After removal of the Boc group[12] the desired catalyst **5a** was obtained in a good yield, but unfortunately it was not optically pure (ee 26%). We found that the racemisation took place during the formation of **4a**. All further attempts to obtain thioamide **5a** in an optically pure form failed.



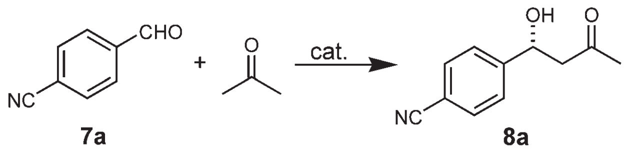
Scheme 1. Synthesis of L-prolinethioamides **5** and their reaction with acetone.

Consequently it was not used as the catalyst in the aldol reaction.

In the light of this result we turned our attention to the less acidic *N*-benzylamine derivative **5b**. An analogous route (Scheme 1) afforded optically pure **5b** in 53% overall yield. Subsequently it was used in a model reaction of 4-cyanobenzaldehyde[7a] with acetone giving the desired aldol **7** in 22% yield and with low enantiomeric excess. The main product formed in this reaction (detected by TLC) decomposed during the column chromatography. Using the ^{1}H NMR technique we found that this compound was the result of the cyclocondensation of the catalyst **5c** with acetone (**6b**, Scheme1). Therefore we thought that if the amine part contained a bulky substituent in the α-position the formation of the cyclic product would be less favourable. Consequently, it would act as a better catalyst for the aldol reaction. With this requirement complied the (*R*)- and (*S*)-phenylethylamines – the simplest analogue of benzylamine. Thus, two diastereoisomeric thioamides **5c** and **5d** derived from L-proline were synthesised (Scheme 1).

We were delighted to find out that the reaction of 4-cyanobenzaldehyde (**7a**) with acetone in the presence of 20% mol **5c** or **5d** at room temperature afforded aldol **8a** with good yield and enantioselectivity (Table 1, entries 1 and 2) and the formation of the analogous bicyclic inidazolidinethione **6c** or **6d** was not detected by TLC. The reaction was completed within 24 hours. When temperature was lowered to +4 °C both the yield as well as the enantioselectivity increased (entry 3). Further de-

Table 1. Aldol reaction of 4-cyanobenzaldehyde (**7a**) with acetone in the presence of **5c** or **5d**.



Entry	Catalyst	Amount of cat. [mol %]	Temperature [°C]	Time [h]	Yield [%][a]	ee [%][b]
1	**5c**	0.20	RT	24	67	72
2	**5d**	0.20	RT	24	62	54
3	**5c**	0.20	+4	72	74	86
4	**5c**	0.20	−18	96	**57**	**93**
5	**5c**	0.30	−18	96	57	93
6	**5c**	0.15	+4	72	71	86
7	**5c**	0.10	+4	72	70	86
8	**5c**	0.05	+4	5d	83	85
9	**5d**	0.20	−18	72	83	80
10	**5d**	0.20	−78	13d	21	**100**

[a] Yields of isolated products.

[b] Determined by HPLC using an ODH column.

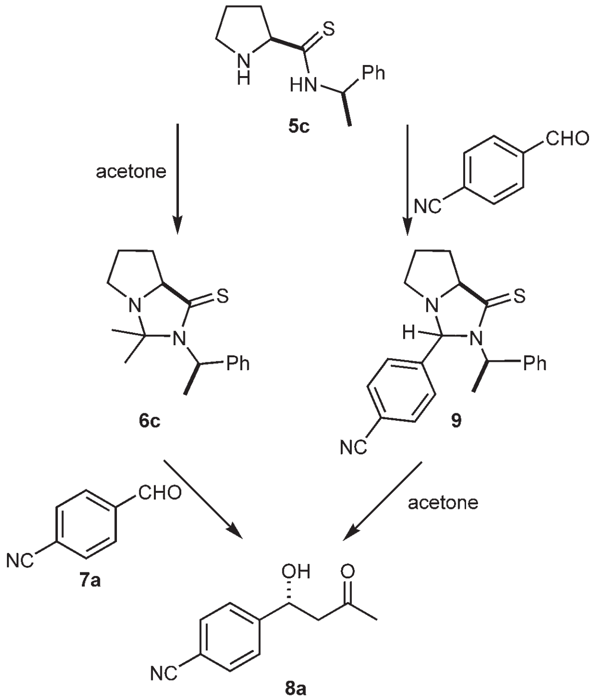
creases in the reaction temperature improved enantioselectivity but at the cost of the yield (entry 4). The use of a larger catalyst loading (30% mol) did not influence the yield (entry 5). Surprisingly the decrease in the catalyst loading improved the yield although leaving the ee at the same level (entries 6–8). Since the catalyst **5d** was more active than **5c** at room temperature we thought that its use would improve the yield. Indeed the reaction catalysed by **5d** at $-18\,^{\circ}$C was faster than those promoted by **5c** although the enantiomeric purity of aldol **8a** was a little bit lower (entry 9). The decrease in the temperature to $-78\,^{\circ}$C afforded optically pure aldol **8a** albeit in low yield (entry 10).

The results indicate that the catalyst **5c** afforded a better level of stereocontrol to its diastereoisomer **5d** which means that the (*R*) configuration at the amine part matched the (*S*)-proline to enhance the enantiocontrol of the aldol reaction. The same situation was observed by Tang's group,[7] but the enantiomeric excess was significantly lower when the respective amide was used instead of thioamide **5c**. This proved the correctness of our hypothesis that the thioamide group would enhance the enantioselectivity of the direct aldol reaction due to the more acidic N–H bond. The use of secondary thioamides with the chiral *N*-alkyl groups gave the same results as the use of the most active amide with the additional OH group (ee 93 versus 88), but the catalyst loading can be lowered considerably (5% mol).

We believe that the level of stereocontrol was influenced by the formation of the imidazolidinethiones **6**. Using the ^{1}H NMR technique we found that, under standard reaction conditions but in the absence of aldehyde, thioamide **5c** did reacted with acetone-d_6 to give analytically pure imidazolidinethione **6c**-d_6 within 80 minutes (Scheme 2).

Compound **6c** was stable even in solution ($CDCl_3$) at room temperature for several days. When isolated imidazolidinethione **6c** was treated with an equimolar amount of 4-cyanobenzaldehyde (**7a**) in acetone the reaction afforded aldol **8a** in 43% yield and 46% ee (Scheme 2). On the other hand when **6c** was used in a catalytic amount in the model reaction, both the yield and the selectivity increased (73%, ee 73%, respectively) reaching the same level of stereocontrol as for the reaction catalysed by thioamide derivative **5c**. Since the above-mentioned reactions gave different results, we assume that the thioamide **5c** had to catalyse the aldol addition before the formation of **6c** which diminished both the yield and the enantioselectivity.

Using a ^{1}H NMR technique List's group[13] was able to detect the formation of oxazolidinones from proline and acetone and to estimate the equilibrium constant. The influence of the oxazolidinone on the course of the aldol reaction was not explained. Furthermore, they proved that in the proline-catalysed reaction of isobutyraldehyde with acetone in DMSO-d_6, proline was initially quantitatively engaged in the formation of oxazolidinone (analogous to **9**), and that the formation of this compound diminished the rate but allowed for turnover. In our case, we did not observe the cyclic compound **9** under the standard reaction conditions (^{1}H NMR). However, when 4-cyanobenzaldehyde was allowed to react with catalyst **5c** in CH_2Cl_2, imidazolidinethione **9** was formed. It was not stable enough for purification and therefore it was used as obtained in the reaction with acetone. After 3 days at room temperature the aldol reaction afforded **8a** in 38% yield and with 43% ee.

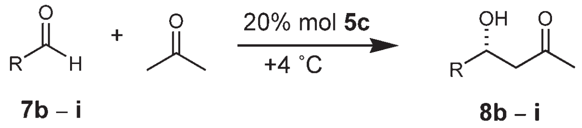


Scheme 2.

Investigations by Blackmond's group[14] have shown that the formation of oxazolidinone-type compounds in the α-aminoxylation reaction enhanced the rate of the process since they were better catalysts of the studied reaction than proline itself. In contrast, we have showed that in the aldol reaction catalysed by thioamide **5c** the unwanted formation of imidazolidinethiones derived both from acetone/**6c** and the aldehyde/**9** diminished the yield and the enantioselectivity.

Encouraged by the above results we performed the direct aldol reaction with a variety of aromatic aldehydes (**7b**–**i**) (Table 2). The prolinethioamide **5c** catalysed these reactions with high ees and moderate yields. We found that in the aldol reaction of the highly reactive pentafluorobenzaldehyde (**7f**) with acetone the desired aldol **8f** was accompanied by a double aldol addition product (i.e., 1,5-dihydroxy-3-ketone). To the best of our knowledge this type of compound was not obtained in the organocatalysed aldol reaction. On the other hand the catalyst **5c** was not suitable for aldol additions employing less reactive aromatic aldehydes or aliphatic al-

Table 2. Prolinethioamide **5c**-catalysed aldol reactions.



Entry	R	Product	Yield [%][a]	ee [%][b]
1	4-$NO_2C_6H_4$	**8b**	62	84
2	4-$NO_2C_6H_4$	**8b**	81[c]	94
3	2-ClC_6H_4	**8c**	70	73
4	4-ClC_6H_4	**8d**	61	87
5	2,6-Cl_2 C_6H_3	**8e**	86	75
6	F_5C_6	**8f**	64[d]	84
7	4-FC_6H_4	**8g**	30	84
8	4-BrC_6H_4	**8h**	20	78
9	β-naphthyl	**8i**	60	82

[a] Yields of isolated products.
[b] Determined by HPLC using ASH or ADH column.
[c] **5c**·TFA was used as the catalyst.
[d] 1,5-Dihydroxy-3-ketone was isolated as a side product.

dehydes. In the reaction of cyclohexanecarboxaldehyde with acetone the catalyst was almost quantitatively transformed into the respective imidazolidinethione (type **9**) thereby preventing the aldol reaction.

We envisaged that the presence of an acid in the commercially available aldehyde samples might influence yields. The reaction of 4-nitrobenzaldehyde (**7b**) (freshly purified) with acetone gave aldol **8b** in only 23% yield while the ee remained at the same level. Subsequently, the same reaction was performed with the use of **5c**·TFA salt and we were delighted to find out that both the yield and the ee increased (to 81% and 94%, respectively) (Table 2, entry 2). It is worthy to mention that the catalyst was added in only 5 mol %. Detailed studies on the influence of the acid are now underway.

In summary, we have demonstrated that the L-proline thioamides **5c** and **5d** are very efficient catalysts for the direct aldol reaction and the catalyst loading has been lowered to 5% mol. The reactivity of the catalyst could be further increased by the change in the amine part as well as the addition of acid and such investigations are in progress.

More importantly, we found that minor changes in the structure of the catalyst could lead to a fundamentally different outcome of the aldol addition. It was shown that the unwanted formation of imidazolidinethione-type compounds **6** diminished both the yield and the ee. Furthermore, our investigations confirmed that the organocatalysed reactions often depend on the essential hydrogen bond stabilisation of the transition state since the thioamides with more acidic N–H protons than the respective amides are more effective catalysts. These results are not only of practical importance but they are also significant from the mechanistic point of view – our observations can eventually lead to a better understanding the aldol addition mediated by proline-type organocatalysts.

Experimental Section

General Procedure for the Aldol Reaction

The catalyst was dissolved in acetone (2 mL) and then 4-cyanobenzaldehyde (1 mmol, 131 mg) was added. The resultant solution was stirred at the temperature indicated in Table 1 until the disappearance of the aldehyde. The reaction was diluted with saturated aqueous NH_4Cl solution and extracted with AcOEt. The organic layers were dried over Na_2SO_4, evaporated and purified by silica-gel column chromatography (hexanes/AcOEt mixtures).

Acknowledgements

We would like to thank Prof. Janusz Jurczak and Dr. Jacek Młynarski for extensive help.

References

[1] B. M. Kim, S. F. Williams, in: *Comprehensive Organic Synthesis*, Vol. 2 (Eds.: B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon, Oxford, **1991**, pp. 229–275.
[2] *Modern Aldol Reactions*, Vols. 1 and 2 (Ed.: R. Marhwald), Wiley-VCH, Weinheim, **2004**.
[3] U. Kazmaier, *Angew. Chem. Int. Ed.* **2005**, *44*, 2186–2188.
[4] A. B. Northrup, D. W. C. MacMillan, *Science* **2004**, *305*, 1752–1754.
[5] A. Córdova, I. Ibrahem, J. Casas, H. Sundén, M. Engqvist, E. Reyes, *Chem. Eur. J.* **2005**, *4772–4784.*
[6] a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; b) B. List, *Tetrahedron* **2002**, *58*, 5573–5590; c) B. List, *Acc. Chem. Res.* **2004**, *37*, 548–557; d) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580–591; e) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175.
[7] a) Z. Tang, F. Jiang, L-T. Yu, X. Cui, L-Z. Gong, A-Q. Mi, Y-Z. Jiang, Y-D. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 5262–5263; b) Z. Tang, F. Jiang, L-T. Yu, X. Cui, L-Z. Gong, A-Q. Mi, Y-Z. Jiang, Y-D. Wu, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5755–5760.
[8] A. Hartikka, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2004**, *15*, 1831–1834.
[9] F. G. Bordwell, G. Z. Ji, *J. Am. Chem. Soc.* **1991**, *113*, 8398–8402.
[10] H. D. Bruce, B. L. Khrishna, J. Madeleine, *Heterocycles* **1986**, *24*, 1045–1060.
[11] S. Scheibe, B. S. Pedersen, S. O. Lawesson, *Bull. Soc. Chim. Belg.* **1978**, *87*, 229–238.
[12] A. Mehta, R. Jaouhari, T. J. Benson, K. T. Douglas, *Tetrahedron Lett.* **1992**, *33*, 5441–5444.

[13] B. List, L. Hoang, H. J. Martin, *Proc. Natl. Acad. Sci.* **2004**, *101*, 5839–5842.

[14] a) H. Iwamura, S. P. Mathew, D. G. Blackmond, *J. Am. Chem. Soc.* **2004**, *126*, 11770–11771; b) H. Iwamura, D. H. Wells, S. P. Mathew, M. Klaussmann, A. Amstrong, D. G. Blackmond, *J. Am. Chem. Soc.* **2004**, *126*, 16312–16313.