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# The Importance of Hydrogen Bonding for the Catalysis of the Enantioselective Aldol Reaction by Tripeptide-like Prolinamide Thioureas

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The majority of the organocatalysts developed up to now for asymmetric organic transformations employ more than one functionalities in the catalytic mechanism that act through either covalent or non-covalent interactions. For example, proline employs the pyrrolidine nitrogen and the carboxylic acid group, while chiral thioureas combine the thiourea functionality with a tertiary or a primary amino group. We have recently shown that an amide of proline with a diamine carrying a thiourea group is a very good catalyst for the enantioselective aldol reaction.<sup>1</sup> Trying to improve the activity, we have found that a tripeptide-like thiourea having as building blocks (S)-proline, (1S,2S)-diphenylethylenediamine and (S)-di-tert-butyl aspartate provides the products of the reaction between ketones and aromatic aldehydes in high to quantitative yields and high stereoselectivities (up to 99:1 dr and 99% ee). A number of structural modifications of the catalyst were undertaken in order to understand the role of the hydrogen bond donors of the catalyst, i.e. the prolinamide hydrogen and the two hydrogen atoms of the thiourea group. We have come to the conclusion that the importance of the hydrogen bond donors of the catalyst follows the order: thiourea hydrogen originated from aspartate > amide hydrogen > thiourea hydrogen originated from diphenylethylenediamine.

## Acknowledgments

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1. S. Fotaras, C. G. Kokotos, G. Kokotos, *Eur. J. Org. Chem.*, **2011**, 1310-1317.



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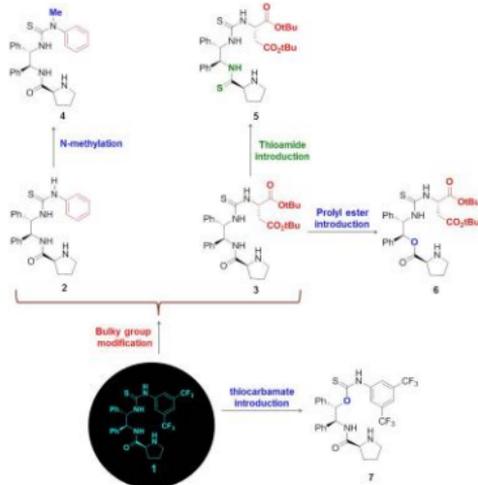
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## INTRODUCTION

The majority of the organocatalysts developed up to now for asymmetric organic transformations employ more than one functionalities in the catalytic mechanism that act through either covalent or non-covalent interactions. For example, proline employs the pyrrolidine nitrogen and the carboxylic acid group, while chiral thioureas combine the thiourea functionality with a tertiary or a primary amino group.<sup>1</sup> We have recently shown that an amide of proline with a diamine carrying a thiourea group is a very good catalyst for the enantioselective aldol reaction.<sup>2</sup> Trying to improve the activity, we have found that a tripeptide-like thiourea having as building blocks (S)-proline, (1S,2S)-diphenylethylenediamine and (S)-di-tert-butyl aspartate provides the products of the reaction between ketones and aromatic aldehydes in high to quantitative yields and high stereoselectivities (up to 99:1 dr and 99% ee).<sup>3</sup> A number of structural modifications of the catalyst were undertaken in order to understand the role of the hydrogen bond donors of the catalyst, i.e. the prolinamide hydrogen and the two hydrogen atoms of the thiourea group.<sup>3</sup>

## RESULTS AND DISCUSSION

Prolinamides **2** and **3** derived from our previously reported 3,5-bis(trifluoromethyl) catalyst **1**,<sup>2</sup> were modified further somewhat that the thiourea nitrogen of the aniline derivative **2** originated from the bulky group was methylated (**4**), while the prolinamide group of the (S)-di-tert-butyl aspartate derivative **3** was replaced by a prolinethioamide (Scheme 1).<sup>3</sup> Additional information about the potential significance of the prolinamide unit could be taken, by the introduction of an ester linkage between the prolyl unit and the spacer of the thiourea catalyst **3**, so as to obtain derivative **6**.<sup>3</sup> Finally, a thiocarbamate-based prolinamide derivative of our initial thiourea catalyst **1** was synthesized (**7**), in order to highlight the potential role of the thiourea hydrogen originated from the diamine spacer.<sup>3</sup>



Scheme 1. Modifications of the catalyst, in order to highlight the importance of hydrogen bonding in reactivity.<sup>3</sup>

Table 1. Direct asymmetric aldol reaction between acetone and 4-nitro-benzaldehyde using various catalysts.<sup>2,3</sup>

Entry	Catalyst	Yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	1	95	97
2 <sup>c</sup>	2	100	98
3	3	100	99
4 <sup>d</sup>	4	98	29
5	5	100	97
6 <sup>e</sup>	6	92	48
7 <sup>c</sup>	7	79	70

<sup>a</sup> Isolated yield. <sup>b</sup> The enantiomeric excess (ee) was determined by chiral HPLC. <sup>c</sup> Reaction time: 48 h. 4-NBA: 4-nitro-benzoic acid.



The reaction of acetone with 4-nitro-benzaldehyde is a usual model reaction to study the efficacy of new organocatalysts. The catalytic activity of all catalysts that were synthesized was evaluated under our previous optimized reaction conditions utilizing toluene as a solvent at  $-20\text{ }^{\circ}\text{C}$  for 24 hours (Table 1).<sup>2,3</sup> When the NH of the thiourea was replaced by NMe, a dramatic loss of the enantioselectivity was observed (entry 2 vs 4, Table 1). The low ee (29%) highlights the importance of that NH for the outcome of the reaction. The use of thioamide led to similar results as those obtained with catalyst **3** (entry 3 vs 5, Table 1). Thus subtle changes in the hydrogen bonding power of the prolinamide unit provide alterations in the catalytic activity, showing that this amide bond is most likely taking part in influencing the outcome of the reaction as well. Derivative **6** provided the product in high yield and moderate ee compared to prolinamide catalyst **3**, clearly demonstrating the involvement of the amide hydrogen in the transition state (entry 3 vs 6, Table 1). Finally the replacement of the NH by O in derivative **7**, led to mediocre enantioselectivity (entry 1 vs 7, Table 1). Taken together, the importance of the hydrogen bond donors of the catalyst follows the order: thiourea hydrogen originated from the bulky group > amide hydrogen > thiourea hydrogen originated from the diamine.

## ACKNOWLEDGMENTS

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