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TRIPEPTIDE-LIKE PROLINAMIDE CATALYSTS FOR THE ALDOL REACTION

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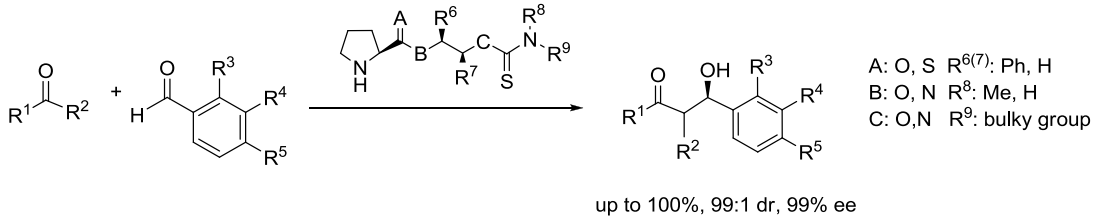
Enzymes are the foundation upon which the majority of organocatalysts bearing more than one catalytic functionalities and act either by covalent or non-covalent interactions, has been developed. The proline and its derivatives containing bio-isosteric groups as replacements of the carboxylic group, constitute a good example of catalysts that bring out transformations as the aldol and Michael reaction succesfully, via bifunctional catalysis.[1] Important improvement has been the development of catalysts combining a proline or proline derivative unit with additional functionalities able to act as hydrogen bond donors. Amide catalysts based on (S)-proline and (1S,2S)-1,2-diphenylethylenediamine or (1S,2S)-1,2-diphenyl-2-aminoethanol are representative examples featuring amine or hydroxyl group respectively, as the terminal donor group.[2] These analogues provide the opportunity of introducing chiral substituents between donor groups and/or to the terminal heteroatom, thus enhancing the efficacy of the resulting catalyst. Furthemore, combination of additional chiral units, together with even more hydrogen bond donors, would mimic much better a “miniature active site”, providing therefore multifunctional organocatalysts. We have shown that prolinamide catalyst based on (1S,2S)-1,2-diphenylethylenediamine and bears a double hydrogen bond donor thiourea group linked to a substituted aromatic ring, efficiently catalyze the aldol reaction between ketones and aromatic aldehydes in high to quantitative yields and with high stereoselectivities.[3] Herein, we report a structure activity relationship study undertaken to identify the functional groups of the catalyst responsible for the activity resembling structure activity relationship studies to identify the pharmacophores of a lead bioactive compound. A tripeptide-like prolinamide-thiourea catalyst having as building blocks (S)-proline (1S,2S)-1,2-diphenylenediamine and (S)-di-tert-butyl aspartate provides the products of the aldol reaction in high to quantitative yields and in high stereoselectivities (up to 99:1 dr and 99% ee).



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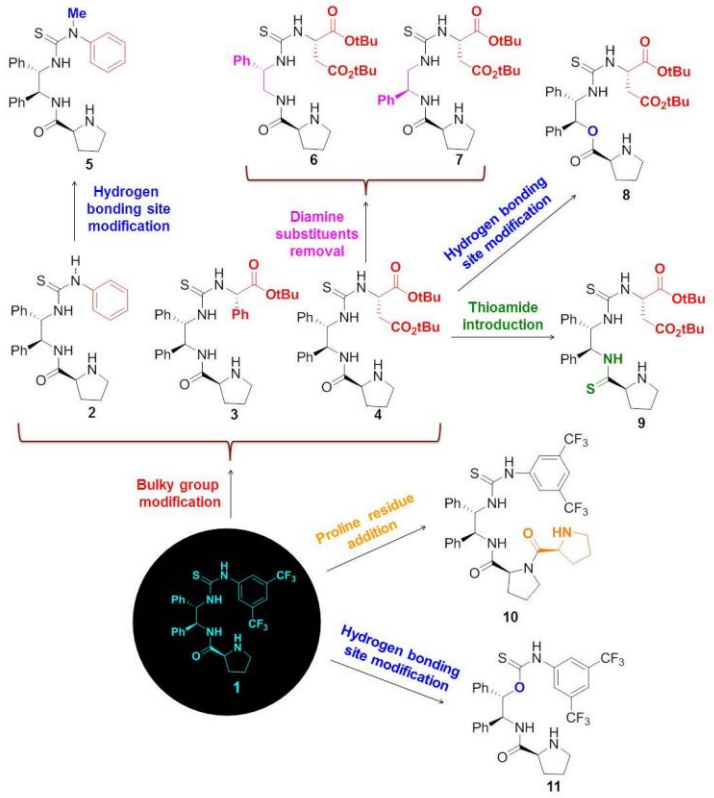
INTRODUCTION

Organocatalysis is a powerful methodology for the synthesis of chiral bioactive compounds. Proline and its derivatives containing bio-isosteric groups as replacements of the carboxylic group constitute a good example of catalysts that bring out asymmetric transformations as the aldol and Michael reaction successfully, via bifunctional catalysis.[1] Furthermore, combination of additional chiral units, together with even more hydrogen bond donors, would mimic much better a "miniature enzyme active site", providing therefore multifunctional organocatalysts. We have shown that a prolinamide catalyst based on (1*S*,2*S*)-1,2-diphenylethylenediamine bearing a double hydrogen bond donor thiourea group linked to a substituted aromatic ring, efficiently catalyzes the aldol reaction between ketones and aromatic aldehydes in high to quantitative yields and with high stereoselectivities.[2] Herein, we report a structure activity relationship study undertaken to identify the structural requirements of the catalyst in order to achieve optimum reactivity.[3]

RESULTS AND DISCUSSION

Our previously reported prolinamide **1** bearing a thiourea group, was designed based on the assumption that the pyrrolidine group would activate the nucleophile, while both the amide group and the thiourea functionality would activate the electrophile through hydrogen bonding.[2,3] The stereochemistry of the diamine substitutents should play a crucial role on the conformation adopted by the catalyst. In an optimum scenario, these moieties should bring the thiourea moiety in close proximity to the area where the electrophile is placed in the transition intermediate. At the same time, the terminal bulky group would lock the conformation adopted by the electrophile, thus determining the face of the electrophile attack. Simultaneously, it would efficiently block the back face of the transition intermediate.



Scheme 1. *Modifications of the prolinamide catalyst **1** in order to achieve optimum efficacy.* [3]

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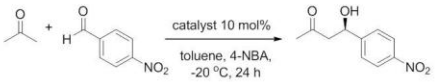
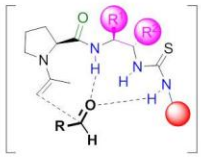
Additionally, there is no experimental evidence about which of the amide hydrogen or the thiourea hydrogens is really involved in the formation of hydrogen bonds. A series of prolinamide analogues were synthesized in order to scrutinize the above stuctural requirements, clarifying specifically the importance of the presence of: (a) a new chiral center in the amine of the thiourea (**2**, **3**, **4**, Scheme 1), (b) the stereogenic centers of the diamine unit (**6**, **7**, Scheme 1), (c) a thioamide instead of an amide bond (**9**, Scheme 1), (d) an additional proline residue (**10**, Scheme 1) and (e) the hydrogen bond donors of the catalyst (amide hydrogen and hydrogen atoms of the thiourea group) (**5**, **8**, **11**, Scheme 1).

Table 1. Direct asymmetric aldol reaction between acetone and 4-nitro-bezaldehyde using various catalysts.[3]



Entry	Catalyst	Yield (%)[a]	ee (%)[b]
1	**1**	95	97
2[c]	**2**	100	98
3	**3**	96	96
4	**4**	100	99
5[c]	**5**	98	29
6	**6**	97	58
7	**7**	70	4
8[c]	**8**	92	48
9	**9**	100	97
10	**10**	53	5
11[c]	**11**	79	70



[a] Isolated yield. [b] The enantiomeric excess (*ee*) was determined by chiral HPLC. [c] 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. At the beginning, the catalytic activity of all catalysts that were synthesized was evaluated under our previous optimized reaction conditions utilizing toluene as a solvent at –20 °C for 24 hours (Table 1). From the new organocatalysts, the one based on *tert*-butyl phenylglycinate (**3**) led to similar results, while the one based on di-*tert*-butyl aspartate provided the product in quantitative yield and excellent enantioselectivity (99% *ee*) (entries 3 and 4 Table1). The bulkiness provides additional blocking of the back face and also controls the face of the attack of the electrophile by pushing the aryl moiety away from it. As shown in entries 6 and 7 of Table 1, both chiral centers bearing a phenyl group is required otherwise the enantioselectivity is considerably lower. When one of the chiral centers and the phenyl moiety is missing a different conformation may be adopted which leads to diminished catalytic activity. The use of thioamide **9** led to similar results as those obtained with catalyst **4** (entry 9, Table 1). Peptide-like catalyst **10** led to far inferior results, thus leading to the conclusion that adding a prolyl unit in the catalyst do not lead in adopting the appropriate conformation for high reactivity (entry 10, Table 1). We assume that taking further apart the pyrrolidine nitrogen and the hydrogen bonding sites of the catalyst (changing the optimum distance), as well as the lack of the α-amide in relation to the free pyrrolidine nitrogen are the key reasons for this deterioration in both reactivity and selectivity. Both thiourea hydrogen originated from the chiral bulky group and the amide hydrogen, play a predominant role for the hydrogen bonding (entry 2,5,8 and 11, Table 1). 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.

These studies led to the tripeptide-like catalyst **4** which effectively catalyzes the aldol reaction. This improved organocatalyst catalyzes the reaction between various cyclic ketones and 4-nitro-benzaldehyde in high to quantitative yields and in high stereoselectivities (up to 99:1 dr and 99% ee).[3]

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