Multicomponent Combinatorial Development of Prolyl Pseudo-Peptide Catalysts: Application in the Direct Asymmetric Michael Addition

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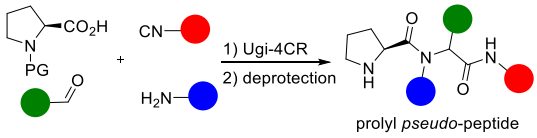
Keywords: Organocatalysis, Michael addition, Multicomponent Reactions

INTRODUCTION

Oligopeptidic scaffolds are an important class of organocatalysts, which have found remarkable applications in a wide range of catalytic asymmetric transformations.[1,2] In this way, MCRs may offer a greater promise in the field of peptide catalysis. The classic Ugi-4CR has been successful applied for the preparation of pseudo-peptidic skeletons, including N-alkylated peptides and a wide variety of peptidomimetic by combinatorial procedures – whereas, each of the four starting materials can be easily altered (Scheme 1).[3] Taking into account that the MCRs have not yet been used for organocatalysts discovery, we focused our attention, ton the implementation of Ugi-4CR as a powerful tool to access new class of prolyl *pseudo*-peptides and therefore, apply them in asymmetric Michael reaction.



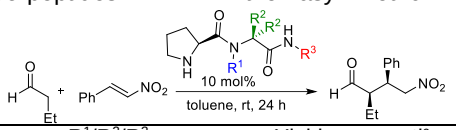
Scheme 1. Synthesis of new class of prolyl *pseudo*-peptides organocatalysts by Ugi-4CR

RESULTS AND DISCUSSION

A small library of Prolyl *pseudo*-peptides was obtained in good to excellent yields (61-93%) by Ugi-4CR protocol. These catalysts were then tested on the directed asymmetric Michael addition (Table 1). Most pseudo-peptides catalyzed the reaction in good to excellent enantio- and diastereoselectivities, where organocatalyst **9** presented the best results in terms of stereocontrol (98% ee, 94:6 dr, entry 9).

Lowest-energy structure of the E-enamine by a theoretical study, shows a significant shielding of the peptidic skeleton to the Re-face (Figure 1, **a**) which explains the high enantioselection provided by catalyst **9** and the syn predomination isomer by a Si-Si attack approach (Figure 1, **b**)

Table 1. Screening of the enamine-catalytic performance of pseudo-peptides 1-12 in the asymmetric Michael addition



Entry	$R^1/R^2/R^3$	Yield (%)[b]	syn:anti[c]	ee (%)[d]
1	Gly-OMe/H/Cy (**1**)	87	96:4	90
2	Val-OMe/H/Cy (**2**)	92	92:8	91
3	Leu-OMe/H/Cy (**3**)	83	97:3	79
4	Ile-OMe/H/Cy (**4**)	89	97:3	90
5	Phe-OMe/H/Cy (**5**)	84	93:7	64
6	^{t}BuGly-OMe/H/Cy (**6**)	94	90:10	82
7	(S)-α-MeBn/H/Cy (**7**)	74	96:4	89
8	Bn/H/Cy (**8**)	91	93:7	92
9	**(S)-α-MeBn/Me/Cy (9)**	**85**	**94:6**	**98**
10	Bn/Me/Cy (**10**)	84	94:6	87
11	(S)-α-MeBn/H/t-Bu (**11**)	93	94:6	91
12	(S)-α-MeBn/H/Gly-OMe (**12**)	77	89:11	85

[a]All reactions were conducted using 3 equiv of the aldehyde. [b]Yield of isolated product as mixture of syn/anti adducts. [c]Determined by ^{1}H-NMR spectroscopy and HPLC analysis. [d]Determined by chiral-phase HPLC analysis on the major diastereomer.

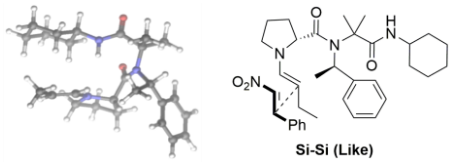


Figure 1. a) Lowest-energy structure of the anti enamine derived from catalyst **9** at M06-2X/6-31+G(d,p)//M06-2X/6-31G(d) [SDM, toluene] level. **b)** Si-Si attack approach of enamine.

CONCLUSION

We have demonstrated the Ugi-4CR-based generation of a new prolyl *pseudo*-peptides combinatorial library and the screening of their catalytic efficacy in the asymmetric conjugate addition of aldehydes to nitroolefins in excellent stereocontrol.

ACKNOWLEDGEMENTS

FAPESP, CNPq and CAPES for financial support.

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