Combining prolinamides with 2-pyrrolidinone: Novel organocatalysts for the asymmetric aldol reaction

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ABSTRACT

Peptides and especially prolinamides have been identified as excellent organocatalysts for the aldol reaction. The combination of prolinamides with derivatives bearing the 2-pyrrolidinone scaffold, deriving from pyroglutamic acid, led to the identification of novel organocatalysts for the intermolecular asymmetric aldol reaction. The new hybrids were tested both in organic and aqueous media. Among the compounds tested, **22** afforded the best results in petroleum ether, while **25** afforded the products in brine in high yields and selectivities. Then, various ketones and aldehydes were utilized and the products of the aldol reaction were obtained in high yields (up to 100%) with excellent diastereo- (up to 97:3 *dr*) and enantioselectivities (up to 99% *ee*).

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1. Introduction

Since 2000, the year of its rebirth, asymmetric Organocatalysis, the use of small organic molecules as catalysts for the promotion of asymmetric organic transformations, has provided elegant solutions to previously under-developed reactions, complementary reactivities to transition-metal catalysis and biocatalysis and new ways of thinking and solving chemical problems.[1,2] It is often acknowledged that the work of List, Lerner and Barbas on the use of proline as the catalyst for the intermolecular aldol reaction[3] and the work by Macmillan on the use of imidazolidinones as catalysts for cycloadditions[4] had set the first stones on building the field of Organocatalysis, that nowadays is considered a common practice. The enantioselective aldol reaction is among the most commonly employed C–C bond forming reactions in modern asymmetric catalysis, and today is considered a test reaction for novel organocatalysts.[5] Since Organocatalysis' first days, it was evident that proline and proline derivatives have a prime role as catalysts in organocatalytic transformations.[6] Even today, research on the identification of novel organocatalysts is vibrant and it is well accepted that prolinamides containing functionalities able to act as

hydrogen bond donors are the most successful class of organocatalysts. Representative examples are shown in Fig. 1 (compounds **1**–**7**).[7] It is well accepted that the catalytic power of these compounds derives from the secondary amine of the pyrrolidine ring, which can activate carbonyl compounds via enamine formation, while the additional hydrogen bonding interaction moieties on the molecules are responsible for the enhanced selectivities observed. For many years, peptides have been explored as potential organocatalysts,[8] unfortunately, low or moderate selectivities have been observed in most cases.[9,10] A very powerful step forward would be the use of water as the solvent, since it will coincide with the principles of Green Chemistry, since water is an abundant, safe and environmentally friendly medium to carry out reactions. Unfortunately, proline and most peptides fail to deliver high selectivities, until the pioneering work of Hayashi and Barbas on the aldol reaction.[11] Then, a number of amino acid derivatives[12] and proline derivatives[7e,13] have been successfully developed for aldol reactions being performed in aqueous media.

Recently, we have demonstrated that tripeptides of Pro-Phe with a *tert*-butyl ester from an amino acid are excellent organocatalysts for the aldol reaction,[14] while the use of dipeptides can also be successful.[7i,7j] We have also attempted to use carbon materials in combination with amines, in order to promote aldol reactions.[15] Having in mind our previous endeavours in Organocatalysis,[16] herein, we describe our efforts to combine the

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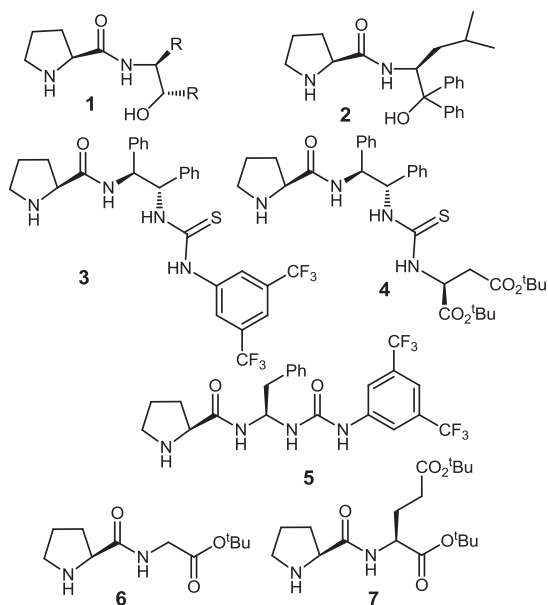
Fig. 1. Known prolinamide organocatalysts.

prolinamide efficiency with the 2-pyrrolidinone scaffold.

2. Results and discussion

(S)-Benzyloxycarbonyl protected proline (**8**) was coupled with either (S)-methyl phenylalaninate (**9**) or (R)-methyl phenyl-alaninate (**10**) using dicyclohexylcarbodiimide (DCC) as the coupling reagent, in the presence of 1-hydroxybenzotriazole (HOBt).[17] Saponification afforded the, N-protected diastereomeric dipeptides, **11** and **12**, respectively. To the resulting dipeptides, a series of amines (**13**−**16**), derived from either (S)- or (R)- pyroglu-tamic acid, were added under conventional peptide coupling con-ditions, affording the protected amides **17**−**21**. We have previously shown that no epimerization is occurring at this step.[14] Finally, deprotection via catalytic hydrogenation, afforded organocatalysts **22**−**27** (Scheme 1).

For the synthesis of 2-pyrrolidinone amines **13**−**16**, 2-pyroglutamic acid was employed (Schemes 2−4). Starting from alcohols **28**-(S) and **29**-(R),[18] a convenient method that avoids epimerization[19] was selected for the synthesis of the corresponding amines [**13**-(S) and **14**-(R)]. This synthetic approach combines mesyl ester activation, substitution from an azide and Staudinger reaction (Scheme 2). In order to study the efficiency of the addi-tional hydrogen bonding, deriving from the 2-pyrrolidinone moi-ety, 2-pyrrolidinone amine **15**, having an extended alkyl chain between the 2-pyrrolidinone and the amine, was synthesized from **28** (Scheme 3). Wittig reaction was followed by hydrogenation and reduction in order to lead to alcohol **34**. Following the same route as before, alcohol **15** was obtained (Scheme 3). Finally, starting from **36**,[20] benzylation afforded compound **37**. Deprotection under acidic conditions led to alcohol **38**. As above, this was selectively trans-formed to amine **16**.

The synthesized organocatalysts were then evaluated in the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde both in organic and aqueous medium (Table 1). Initially, peptide **22**, based on Pro-Phe and 2-pyrrolidinone was tested, leading to high yields in both reaction conditions (organic solvent of aqueous conditions) with good diastereoselectivity and enantioselectivity (entries 1 and 2, Table 1). Comparing the catalytic activity of **22** with the corresponding dipeptide Pro-Phe or H-Pro-Phe-ᵗBu,[7i]
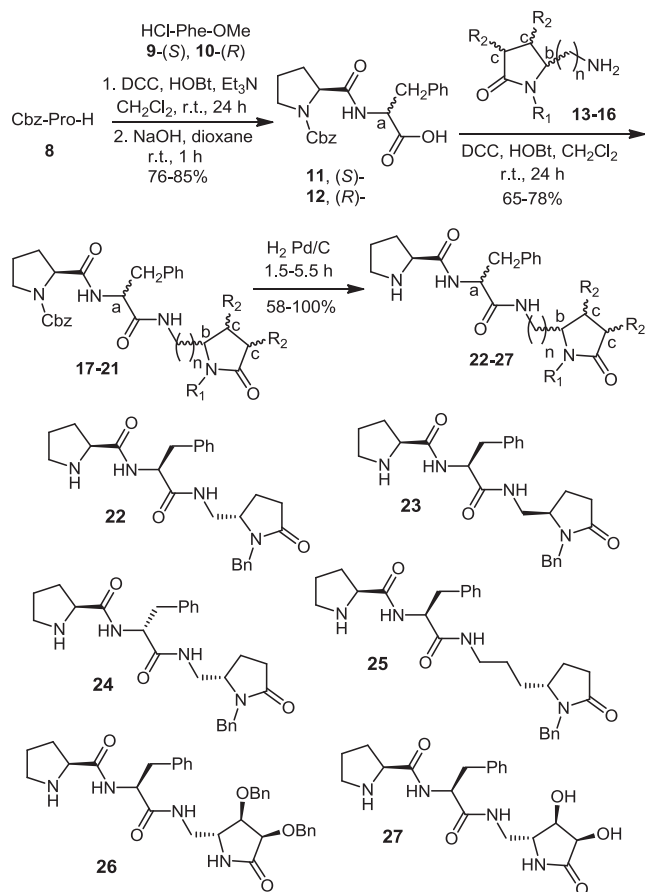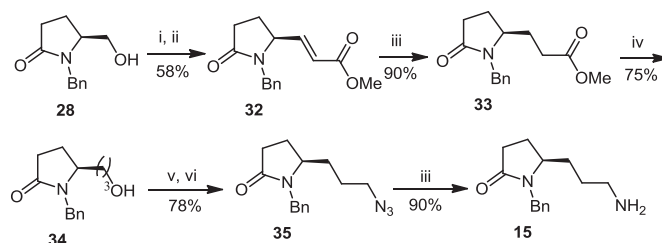

Scheme 1. Synthesis of the organocatalysts **22**−**27**.
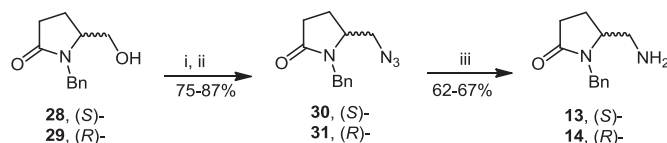
i: MeSO₂Cl, Et₃N in CH₂Cl₂; ii: NaN₃, in dry DMF at 55 °C; iii: H₂, Pd/C, r.t., 2-4 h.

Scheme 2. Synthesis of 2-pyrrolidinone amines **13** and **14**.

i: Moffatt oxidation: EDC.HCl, Pyridine, TFA drops in dry toluene, dry DMSO, under Ar. ii: PPh₃=CHCOOCH₃ in dry THF, 1 h reflux under Ar. iii: H₂, 10% Pd/C in MeOH, r.t.. iv: LiBH₄ in dry THF. v: MeSO₂Cl, Et₃N in CH₂Cl₂. vi: NaN₃, in dry DMF at 55 °C.

Scheme 3. Synthesis of 2-pyrrolidinone amine **15**.

there is a significant increase on the catalytic activity that can be attributed to the additional 2-pyrrolidinone ring. When the development of a chiral catalyst requires the presence of more than one chiral centers, matched and mis-matched effects might be