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Proline dipeptides containing fluorine moieties as oganocatalysts for the asymmetric aldol reaction

Ardiol Ahmetlli, Nikoleta Spiliopoulou, Angeliki Magi-Oikonomopoulou, Dimitrios-Triantaffylos Gerokonstantis, Panagiota Moutevelis-Minakakis**, Christoforos G. Kokotos*

Laboratory of Organic Chemistry, Department of Chemistry, National and Kapodistrian University of Athens, Panepistimiopolis 15771, Athens, Greece

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ABSTRACT

A series of dipeptide analogues consisting of proline, phenylalanine and aniline- or phenol-fluorine derivatives were synthesized. Their catalytic ability was evaluated in the intermolecular asymmetric aldol reaction, both in organic and aqueous media. Aniline-fluorine derivatives proved to be superior and the best results were obtained, when 2-CF_3 aniline was employed. A diverse substrate scope consisting of both aromatic and aliphatic aldehydes, as well as different ketones was demonstrated, where aromatic aldehydes afforded products in high yields (up to 100%) with excellent diastereo- (up to 95:5) and enantioselectivities (up to 97%), whereas the aliphatic aldehydes afforded also excellent selectivities, but relatively low yield. A simple addition of fluorine to a dipeptide analogue affords organocatalysts with new interesting properties that can catalyze the aldol reaction more efficiently.

1. Introduction

Since the beginning of the millennium, small organic molecules have been utilized as organocatalysts to promote asymmetric organic transformations; this new and exciting field of Catalysis is referred as Organocatalysis [1,2]. List, Barbas and Lerner were among the first to reintroduce Organocatalysis, by employing proline as the catalyst in the intermolecular aldol reaction between acetone and 4-nitrobenzaldehyde (Scheme 1, **A**) [3], while MacMillan and his coworkers employed imidazolidinones as catalysts for cycloadditions and in Diels-Alder reaction more precisely (Scheme 1, **B**) [4]. Organocatalysis went blooming and is now considered to be among the traditional tools of Asymmetric Synthesis. One of the most common reactions used in modern Asymmetric Catalysis, in order to form a C–C bond, is the enantioselective aldol reaction (Scheme 1, **C**) [5]. Since Organocatalysis' first days, proline and proline derivatives containing different bioisosteric groups have undoubtedly been the most efficient catalysts in organocatalytic transformations [6]. It is widely accepted that prolinamides that contain functionalities able to act as hydrogen bond donors are among the most effective catalysts employed in the aldol reaction. Different types of organocatalysts have been developed through time, with each and every one of them contributing something different in order to fully understand all the parameters that affect the efficiency of the asymmetric aldol reaction. Representative examples are shown in Fig. 1 (compounds **1**–**9**) [7]. The driving force behind the catalytic potency of these prolinamides is the secondary amine of the five-membered pyrrolidine ring, which can activate carbonyl compounds via enamine formation, as well as the functional groups that allow the formation of hydrogen bonds and enhance the selectivities observed. Among the first examples of prolinamides able to participate in multiple hydrogen bonding networks were compounds **1** and **2**, which required cryogenic conditions to induce high levels of selectivities. Catalyst **4** was an improved version of catalyst **3**, while that study also highlighted the importance of the chiral centers in the diamine moiety for the adopted conformation of the catalyst in the assumed transition state. Peptides have been explored for many years as organocatalysts [8], but the selectivities that were obtained are anything but satisfactory in most cases [9,10]. In addition, the low solubility that peptides display in organic media is a limiting factor, while when aqueous solvents are

* Corresponding author.
** Corresponding author.
E-mail address: ckokotos@chem.uoa.gr (C.G. Kokotos).

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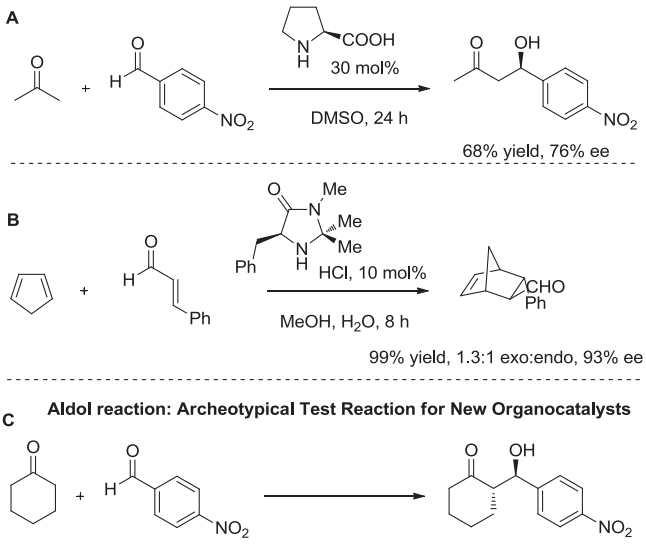

Scheme 1. Rebirth of Organocatalysis.

used, the selectivity drops significantly. Lately, more attention was drawn towards reactions that are conducted in aqueous media, which are considered to be in agreement with the principles of Green Chemistry, as water is a safe, environmentally friendly and abundant medium to carry out reactions. A milestone, for the use of proline [7e,11] and many other aminoacids derivatives [12] in aqueous media as catalysts for the aldol reaction, has been the work from the groups of Hayashi and Barbas [13].

Recently, we have demonstrated that proline dipeptides with *tert*-butyl esters of amino acids can be used as organocatalysts in the aldol reaction [14]. A series of simple dipeptide and tripeptide catalysts was introduced, where catalysts **6** and **7** proved to be the most efficient ones, while providing a green alternative, since the reaction could be performed in aqueous media. Very recently, we have developed prolinamide derivatives bearing 2-pyrrolidinone, like **8** and **9**, which can also catalyze the aldol reaction. Carbon materials in combination with amines have also been used to promote aldol reactions. Taking into account all our previous endeavors in Organocatalysis [15], and in an effort to provide a catalyst that is not only easy and cheap to synthesize, but also may exhibit more interactions with the carbonyl compounds, we questioned whether simple Pro-Phe dipeptides containing fluorine moieties could be employed as organocatalysts in the aldol reaction.

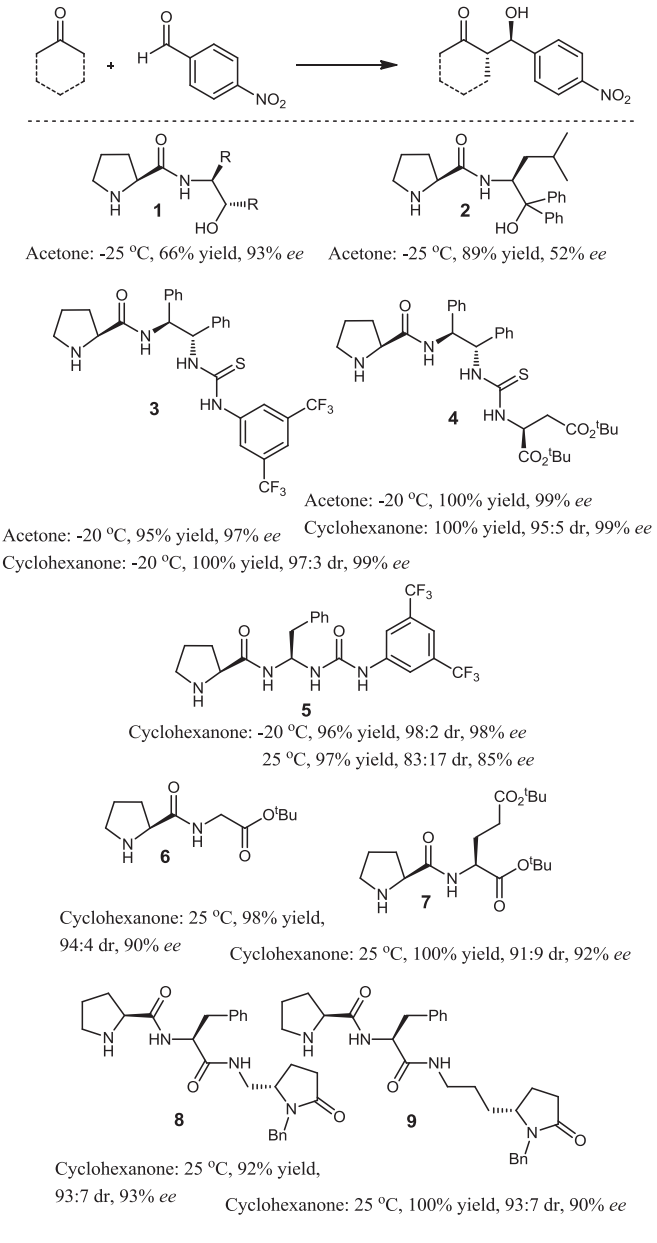

Fig. 1. Known prolinamide organocatalysts.

2. Results and discussion

Proline, although it is a powerful and archeotypical organocatalyst, is mostly insoluble in organic solvents (high catalyst loading) and provides moderate enantioselectivities (<90% *ee*). Also, it cannot be used in aqueous media. Prolinamides, like compounds **1**–**9**, are considered an improvement because they provide multiple recognition sites, via hydrogen bonding interactions, with the electrophile (aldehyde, see Fig. 2, top left). Thus, they provide a more compact transition state, leading from moderate to high enantioselectivities. Our hypothesis was to introduce fluorine moieties on the organocatalyst backbone, in order to create more and better hydrogen bonding interactions on the organocatalyst and/or change the adopted conformation of the catalyst, due to the fluorine, in the transition state (Fig. 2, top right and bottom). This idea would lead to enhanced enantioselectivities, which could also work in aqueous media.

(*S*)-Benzyloxycarbonyl-protected proline (**10**) was coupled with (*S*)-methyl phenylalaninate using *N*-(3-Dimethyl-aminopropyl)-*N*′-ethylcarbodiimide hydro-chloride (WSCI) as the condensing agent, in the presence of 1-hydroxybenzotriazole (HOBt) (Scheme 2). Saponification, under Schotten-Baumann conditions, afforded dipeptide **11**. To the resulting dipeptide, under conventional peptide coupling conditions, aniline or 2-fluoro-aniline were added, leading to peptide analogues **12a** and **12b**. Catalysts **13a** and **13b** were obtained via catalytic hydrogenation (Scheme 2) [16]. Following a similar procedure, but utilizing pentafluorophenol, catalyst **13c** was also prepared (Scheme 3). Unfortunately compounds **12d** and **12e** were not possible to synthesize under those conditions and a different synthetic pathway was followed, using triethyl amine (Et_3N) and ethyl chloroformate via the mixed anhydride intermediate (Scheme 4). Finally, deprotection via catalytic hydrogenation, afforded organocatalysts **13d** and **13e**.

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