



Recoverable silica-gel supported binam-prolinamides as organocatalysts for the enantioselective solvent-free intra- and intermolecular aldol reaction



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ABSTRACT

Silica-gel supported binam-derived prolinamides are efficient organocatalysts for the direct intramolecular and intermolecular aldol reaction under solvent-free conditions using conventional magnetic stirring. These organocatalysts in combination with benzoic acid showed similar results to those obtained under similar homogeneous reaction conditions using an organocatalyst of related structure. For the intermolecular process, the aldol products were obtained at room temperature and using only 2 equiv of the ketone with high yields, regio-, diastereo- and enantioselectivities. Under these reaction conditions, also the cross aldol reaction between aldehydes is possible. The recovered catalyst can be reused up to nine times providing similar results. More interestingly, these heterogeneous organocatalysts can be used in the intramolecular aldol reaction allowing the synthesis of the Wieland–Miescher and ketone analogues with up to 92% ee, with its reused being possible up to five times without detrimental on the obtained results.

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1. Introduction

The demand of sustainable processes, due to the environmental concerns of our society, has led to the development of greener methods for chemical synthesis.¹ The environmental impact or *E*-factor,² defined as the ratio of the mass of waste per unit of product, in the pharmaceutical industry is bigger than in other industry segments.³ The use of solvents supposes more than 80% of the mass of any pharmaceutical batch processes.⁴ Therefore, the implementation of solvent-free methodologies for the synthesis of drugs are essential, especially if those processes are run with stereochemical control.⁵ One of these processes is the asymmetric aldol reaction,⁶ with the use of organocatalysts,⁷ such as proline or prolinamides derivatives, for this transformation providing excellent results under solvent-free conditions.⁸ Under these reaction conditions, the normally used excess of nucleophile, required to shift the involved equilibrium, can be reduced to a minimum amount and the rate of the reaction is normally increased. Moreover, most of the aldol organocatalyzed reactions⁹ required only mild temperatures and therefore could be considered as an energetic sustainable process. Usually, the use of solvent-free conditions in the aldol reaction¹⁰ is accompanied by the use of ball-milling

techniques,¹¹ in order to allow the efficient mixing of reagents. However, using different binam-prolinamides¹² derivatives **1** (Fig. 1) as organocatalysts for the intermolecular and intramolecular aldol reaction under solvent-free conditions, we have demonstrated that the use of conventional magnetic stirring is enough to allow the reaction to proceed with excellent results.^{10e–h}

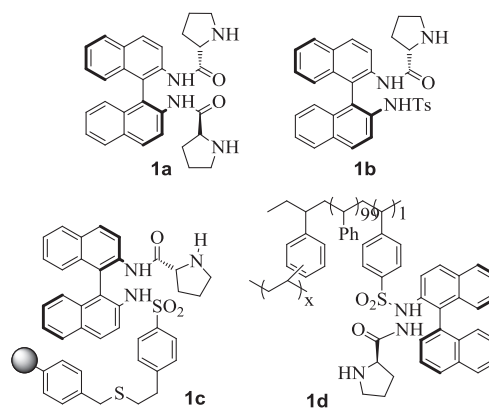


Fig. 1. Binam-prolinamide derivatives used as organocatalyst under solvent-free conditions.

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Thus, when C_2 -symmetrical prolinamide derivative **1a** was used as catalyst under solvent free-conditions, both the amount of catalyst and of nucleophilic ketone were reduced (5 mol % of **1a** and 2 equiv) compared to the required amounts used in solution. The results, in terms of yields and selectivities, were similar to those achieved when the reaction was carried out in solvents, such as DMF, DMF/water mixtures or just water, with the rate of the reaction being increased from days to hours. Furthermore, the best results were obtained using conventional magnetic stirring, both for the intra- and the intermolecular aldol reaction and the catalyst was recovered after the reaction completion by a simple acid-base work-up.^{10f} The use of binam-sulphonamide prolinamide derivative **1b** (5 mol %) under solvent-free conditions, and 1 mol % of benzoic acid as co-catalyst, led also to a similar performance for the intermolecular aldol reaction.^{10g,h} In addition, catalyst **1b** showed to be particularly efficient for the intramolecular aldol reaction, allowing the gram scale synthesis of the Wieland–Miescher ketone and analogues, following a convenient one-pot two-step procedure.^{10g,h,13} Notwithstanding, the recovery of the catalyst was only possible by chromatographic techniques.

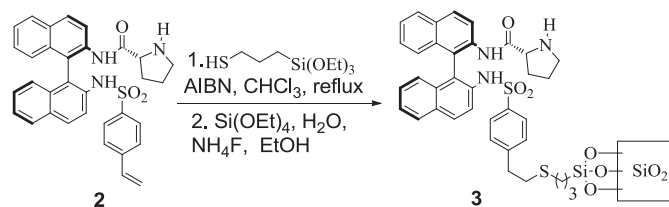
As the use of a supported organocatalyst¹⁴ would allow the recovery of the catalyst, increasing the global efficiency of the process,¹⁵ we have recently synthesized a polymer supported prolinamide system **1c** and a cross-linked supported prolinamide system **1d**, which were very efficient for the intermolecular aldol reaction under solvent-free conditions.¹⁶ However, the application of this supported organocatalyst for the more interesting intramolecular^{10g,h,13} version of this reaction failed, and as far as our knowledge, only unsatisfactory results were achieved by using other supported organocatalysts for this transformation.¹⁷

Therefore, we thought of interest to design a supported binam-prolinamide derivative, which could be used for the general inter- and intramolecular aldol reaction under solvent-free conditions. In order to have a cheap and robust support we decided to anchor our catalytic system to silica-gel.

Here, we report a recoverable silica-gel supported organocatalyst able to catalyze not only the intermolecular but also the intramolecular aldol reaction with high efficiency under mild and solvent-free conditions, which meets all the criteria of a green process.

2. Results and discussion

The immobilization of the binam-prolinamide derivative **2** was carried out by a sol–gel procedure.¹⁸ First, a photoinduced thiolene coupling (TEC)^{16,19} strategy was used to prepare the required silicon precursor (Scheme 1). Hence, the styrylsulfonyl binam-derivative **2** was obtained by reacting commercially available sodium 4-vinylbenzenesulfonate with thionyl chloride to give the expected sulfonyl chloride derivative, which was further reacted with (R_a)-1,1'-binaphthyl-2,2'-diamine. The achieved binam-sulfonyl derivative was subsequently coupled with *N*-Boc-D-pro followed by deprotection with trifluoroacetic acid. A solution of compound **2** was added to 3-(triethoxysilyl)propane-1-thiol and AIBN to afford the required intermediate silicon derivative as a glassy pale yellow solid in 66% yield. This intermediate was



Scheme 1. Synthesis of the silica-gel supported organocatalyst.

reacted with TEOS (tetraethoxysilane) and NH_4F to form a white solid, which after work-up was dried in vacuo for several hours to afford supported catalyst **3** as a white powder. The catalyst loading was determined by elemental analyses being in average 0.32 mmol per gram of silica.

Once the catalyst was immobilized, the reaction conditions parameters, such as catalyst loading, amount of acid added as co-catalyst, amount of nucleophile, addition of water and temperature were evaluated in the model aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde. Initially, the need of the use of benzoic acid (5 mol %) as co-catalyst under solvent-free conditions was explored, finding that was determinant in order to accelerate the reaction and to achieve higher diastereo- and enantioselectivities (Table 1, compare entries 1 and 2). Then, the addition of small amount of water to the reaction mixture was evaluated, with the addition of 12 equiv of water providing the best results in terms of reaction time, diastereo- and enantioselectivities (Table 1, Entries 3–7). Under the presence of 12 equiv of water, the effect of the temperature was studied (Table 1, entries 8 and 9). Decreasing the temperature at 5 °C, led to an increase of the reaction time, with slightly higher diastereo- and enantioselectivity being achieved (Table 1, entry 9). The required catalyst loading was evaluated under solvent-free conditions in the presence of water at 25 °C (Table 1, entries 10 and 11), with 10 mol % of catalyst **3** leading to the best results.

Table 1
Optimization of the intermolecular aldol reaction catalyzed by **3**^a

Entry	Solvent (0.15 mL)	H ₂ O (equiv)	T (°C)	t (h)	Conversion (%) ^b	anti/syn ^c	ee (%) ^d
1 ^e	—	—	25	24	99	70:30	80
2	—	—	25	6	96	93:7	90
3	—	3	25	9	97	92:8	92
4	—	6	25	4	91	94:6	92
5	—	12	25	3	96	93:7	92
6	—	25	25	5	97	93:7	92
7	—	50	25	7	97	88:12	88
8	—	12	10	15	71	97:3	93
9	—	12	5	24	91	94:6	93
10 ^f	—	12	25	6	96	93:7	92
11 ^g	—	12	25	24	91	92:8	92
12	Hexane	—	25	48	80	90:10	88
13	DMF	—	25	72	74	60:40	63
14	CH ₂ Cl ₂	—	25	120	70	86:14	82
15	MeOH	—	25	120	48	65:35	36
16	H ₂ O	—	25	7	97	88:12	88
17	4a	—	25	72	99	75:25	73

^a General reaction conditions: the reaction was carried out using 4-nitrobenzaldehyde (0.15 mmol) cyclohexanone (0.3 mmol), benzoic acid (5 mol %, otherwise stated), H₂O and catalyst **3** (20 mol %, otherwise stated).

^b Conversion based on the amount of the unreacted aldehyde.

^c Determined by ¹H NMR of the crude product.

^d Determined by chiral phase HPLC analysis for the *anti*-**6aa** isomer.

^e The reaction was carried out in the absence of benzoic acid.

^f 10 mol % of catalyst **3** was used.

^g 5 mol % of catalyst **3** was used.

The use of several solvents (0.15 mL), such as hexane, DMF, dichloromethane, methanol, water and cyclohexanone as reaction media was tested (Table 1, entries 12–17), with the best results in being encountered in hexane and pure water (Table 1, entries 12

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