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Synthesis of a new chiral organocatalyst derived from (*S*)-proline containing a 1,2,4-triazolyl moiety and its application in the asymmetric aldol reaction. Importance of one molecule of water generated *in situ*

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ABSTRACT

A simple and efficient preparation of a novel chiral derivative of (*S*)-proline containing a 1,2,4-triazolyl moiety is described. The high-yielding synthetic protocol includes the use of microwave irradiation to afford new chiral pyrrolidine derivatives in high yield. Our triazolyl-containing heterocycle was evaluated as organocatalyst (10 mol% load, under neat reaction conditions) in the enantioselective aldol reaction between four different types of ketones and a variety of aryl aldehydes. Good results in terms of enantioselectivity and chemical yield were observed under solvent-free reaction conditions and in the absence of any additive. Evidence is provided for the involvement of the water molecule generated upon enamine formation in the transition state of the aldol reaction.

Introduction

The high efficiency exhibited by (*S*)-proline, (*S*)-**1**, in C—C bond-forming reactions [1] has attracted the attention of a significant number of chemists who have demonstrated the enormous potential of organocatalysis in asymmetric synthesis. Nevertheless, the low solubility of (*S*)-proline in most organic solvents is a practical limitation that has led to the incorporation of diverse functional groups aimed to improve proline's solubility while maintaining high stereoselectivity and catalytic efficacy [2].

The asymmetric aldol reaction is a versatile synthetic tool for the construction of C—C bonds with the generation of at least one stereogenic center [3a]. This reaction still proves to be challenging, particularly because it is of great present interest to perform aldol reactions under more sustainable reaction conditions, such as in water [3b–e], in brine [3f], or in the absence of solvent [3g]. Furthermore, several research groups have developed useful aldol methodologies employing supported catalysts or supported organocatalysts [4].

Recently, our group has made several contributions in the area of asymmetric organocatalysis such as in the development of monoterpene-based (*S*)-proline derivatives [5a], the design, synthesis and application of (*S*)-proline-containing chiral phosphoramides for enantiodivergent aldol reactions [5b] and the preparation of diamine derivatives of α,α-diphenyl-(*S*)-prolinol that proved efficient in asymmetric Michael and Mannich reactions [5c]. In addition, several pyrrolidinic camphor- and cinchona-based derivatives have been shown by others groups to be effective in catalyzing various asymmetric transformations [6].

Relevantly, a significant number of privileged bifunctional organocatalysts that exhibit excellent performance incorporate heterocyclic substituents [7]. In a particularly interesting example, Ley et al., Yamamoto et al., and Arvidsson et al. reported that so-called (*S*)-proline-2-tetrazole ((*S*)-**2** in Scheme 1) is rather effective in the organocatalytic aldol reaction as well as in asymmetric Mannich and Michael reactions [8].

The seminar work reported by Yamamoto, Ley and Arvidsson [8] inspired us to develop the synthesis of a novel organocatalytic system derived from (*S*)-proline that incorporates a 1,2,4-triazolyl-5-benzylthio heterocyclic substituent, (*S*)-**3a** (Scheme 1). It is anticipated that the benzylthio group on the triazole substituent will increase its lipophilicity, so that organocatalysis should readily take place both in organic and aqueous media.

The efficiency of our novel organocatalyst was evaluated in asymmetric aldol reactions. It became apparent that the lipophilic heterocyclic ring as well as the benzylthio- substituent do help increase the solubility of (*S*)-proline-derived organocatalyst in organic system because the reaction media were notably

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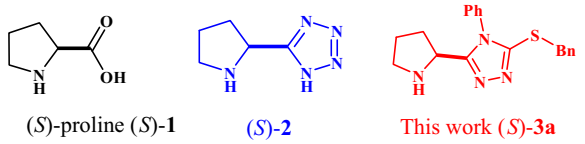


Scheme 1. Emblematic organocatalysts (*S*)-proline, (*S*)-**1**, (*S*)-proline-2-tetrazole, (*S*)-**2**, and novel pyrrolidinic 1,2,4-triazole derivative (*S*)-**3a** described in the present work.

homogenous. Furthermore, theoretical evidence will be provided below that the triazole ring does indeed participate in the stereoinducing transition state via hydrogen bonding interaction with the water molecule that is produced during enamine formation. Such activation by water is in line with the proposal advanced by Nakashima and Yamamoto in their study of (2*S*)-pyrrolidine-tetrazole (*S*)-**2** as organocatalyst in asymmetric aldol reactions [8e].

Results and discussion

*Synthesis of novel organocatalysts (S)-**3a-c***

The synthesis of the novel 2-(1,2,4-triazol-5-thioeter)-(*S*)-proline derivatives (*S*)-**3a-c** was carried out as described in the 'references and notes' section [9]. The structure of the pyrrolidinic 1,2,4-triazol-5-thione (*S*)-**8** precursor was confirmed by single-crystal X-ray diffraction analysis (Fig. S-85, ESI) [11]. Most relevant is the distance between carbon and sulfur, 1.66 Å, that fits well with anticipation for a C=S double bond [12]. In this regard, the length calculated theoretically at the DFT M06 6-311G* level of theory is 1.65 Å (Fig. S-65, ESI, Section 5.1).

In order to obtain the desired alkylthio derivatives (*S*)-**9a-c**, thione (*S*)-**8** was treated with KOH and the resulting thioenolate was treated with the corresponding halide to yield the five-membered heterocycles (*S*)-**9a-c** in good yields (Table 1).

Compound (*S*)-**9a** provided adequate crystals for X-ray diffraction analysis (Fig. 1) [13]. Most salient, it could be corroborated that benzylation is highly regioselective and took place at the sulfur atom. Furthermore, retention of the (*S*) configuration of the proline ring is also confirmed by consideration of the Flack parameter, F = 0.061 (Fig. S-89, ESI).

Finally, compounds (*S*)-**9a-c** were *N*-deprotected under acidic conditions to obtain organocatalysts (*S*)-**3a-c** as hydrochloride salts (Scheme 2).

*Evaluation of organocatalysts (S)-**3a-c.***

The potential efficiency of novel (*S*)-proline derivatives (*S*)-**3a-c** in organocatalysis, either in free form (after treatment with $NaHCO_3$) or as hydrochloride salts, and in presence or absence of water as additive was evaluated in the asymmetric aldol reaction between cyclohexanone and 4-nitrobenzaldehyde. Table 2 summarizes our observations, which indicate that best results in terms of yield and stereoselectivity are obtained with 10 mol% of the catalyst (*S*)-**3a** in its free form, under solvent-free (neat) reaction conditions (entry 1). Quite similar results were obtained with (*S*)-**3b**, anticipated to present similar solubility in organic media (compare entries 1 and 3).

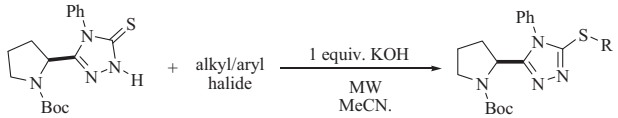
By contrast, with (*S*)-**3c**·HCl the yield and selectivity were rather low, probably as consequence of its diminished solubility (Table 2, entry 4, see also ESI). The use of the protonated form of organocatalysts (*S*)-**3a** and (*S*)-**3b** results in decreased yield and stereoselectivity (entries 2 and 4). On the other hand, while addition of water to the reaction medium was detrimental (entries 5 to 8), thorough water removal with molecular sieves (entry 9) led to a drastic decrease in yield and stereoselectivity. This latter result indicates that water is an essential component for the efficient progress of the aldol reaction [14].

The reaction's scope was then examined with a variety of aldehydes and under the conditions indicated in entry 1 of Table 2 (Table 3).

Organocatalyst (*S*)-**3a** was also evaluated in asymmetric aldol reactions with acetone, cyclopentanone and cycloheptanone, maintaining 4-nitrobenzaldehyde as electrophile. Best results were observed with cyclopentanone (Table 4). As anticipated by the introduction of the lipophilic triazole substituent in proline (see Introduction) miscibility of the organocatalyst with organic partners such as the cyclohexanone, acetone, cyclopentanone and cycloheptanone is remarkably high.

As it was already mentioned, Nakashima and Yamamoto [8e] reported a study on the asymmetric aldol reaction with acetone,

Table 1
Preparation of *N*-Boc-(2*S*)-(5-(thioalkyl)- and *N*-Boc-(2*S*)-(5-(thiobenzyl)-4-phenyl-(1,2,4-triazol)-3-yl)-pyrrolidines (*S*)-**9a-c**.



Product	R-X	Yield (%)
(*S*)-**9a**	benzyl bromide	82
(*S*)-**9b**	2-iodopropane	85
(*S*)-**9c**	1-bromo-2-chloroethane	70

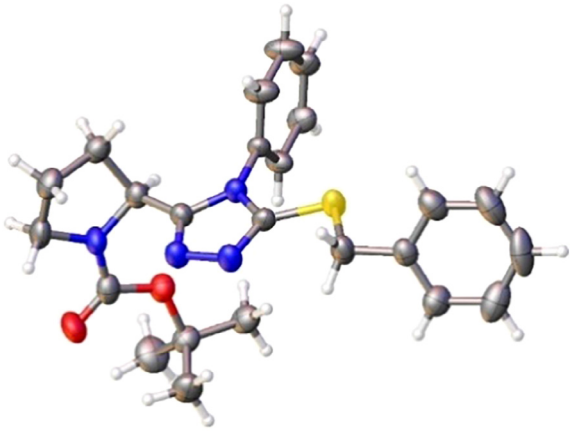
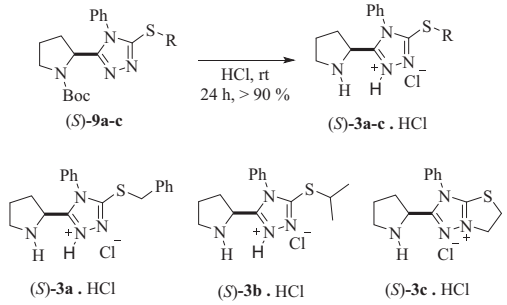
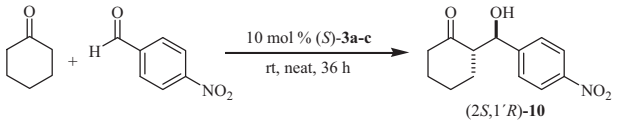


Fig. 1. Single crystal X-ray diffraction analysis of *N*-Boc-(2*S*)-(5-(benzylthio)-4-phenyl-(1,2,4-triazol)-3-yl)-pyrrolidine, (*S*)-**9a**.



Scheme 2. *N*-Deprotection of (*S*)-**9a-c** under acidic conditions to afford the hydrochloride salts (*S*)-**3a-c**·HCl.

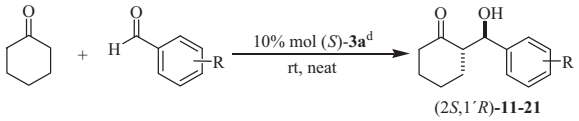
Table 2
Asymmetric aldol reaction between cyclohexanone and 4-nitrobenzaldehyde in the presence of organocatalysts (*S*)-**3a-c**, and in the presence or absence of water.



Entry	Organocatalyst	Additive	Yield (%)[b]	dr (*anti*/*syn*)[c]	er[d]
1	(*S*)-**3a**	None	96	85:15	96:4
2	(*S*)-**3a**·**HCl**	None	85	86:14	84:16
3	(*S*)-**3b**	None	90	80:20	90:10
4	(*S*)-**3c**·**HCl**	None	22	80:20	60:40
5	(*S*)-**3a**	1 mol % H_2O	50	90:10	87:13
6	(*S*)-**3a**	H_2O[a]	42	82:18	89:11
7	(*S*)-**3a**	50 mol % H_2O	35	75:25	80:20
8	(*S*)-**3a**	100 mol % H_2O	24	70:30	55:45
9	(*S*)-**3a**	MS 3Å[e]	18	60:40	60:40

[a] The value corresponds to 10 mol % of additives.
[b] Determined after column purification Hexane-EtOAc, 9:1.
[c] Determined by ^{1}H NMR spectroscopy.
[d] Determined by HPLC analysis with chiral columns (see SI). [e]MS: Molecular Sieves.

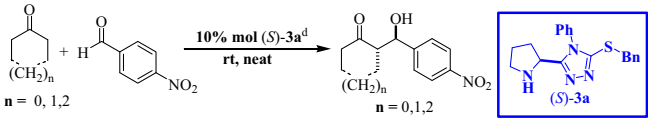
Table 3
Scope of the asymmetric aldol reaction catalyzed with (*S*)-**3a**.



Product	R	Time (h)	Yield (%)[a]	dr (*anti*/*syn*)[b]	er (*anti*)[c]
11	2-nitro	36	94	80:20	90:10
12	3-nitro	36	96	80:20	91:9
13	1-naphth	72	68	70:30	60:40
14	-H	96	63	75:25	70:30
15	2-CF_3	48	92	96:4	60:40
16	4-CN	36	94	80:20	76:24
17	2-Cl	36	93	60:40	65:35
18	4-Cl	36	94	80:20	75:25
19	3-Br	36	92	60:40	60:40
20	4-CF_3	24	92	70:30	70:30
21	4-F	48	90	60:40	65:35

[a] Determined after column purification Hexane-EtOAc, 9:1.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by HPLC analysis. [d]In free form.

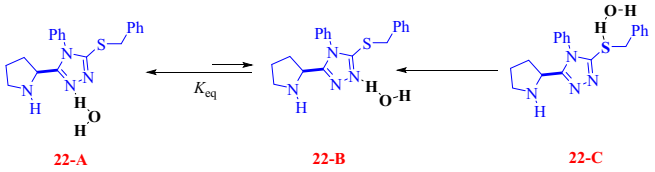
Table 4
Evaluation of the catalyst (*S*)-**3a** with other ketones.



Entry	Ketone	Time (h)	Yield (%)[a]	dr (*anti*/*syn*)[b]	er[c]
1	Acetone	24	96	–	83:17
2	Cyclopentanone	36	92	93:7	92:08
3	Cycloheptanone	36	85	65:35	96:04

[d] In free form.
[a] Determined after column purification hexane-EtOAc, 9:1.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by HPLC analysis.

catalyzed by so-called (*S*)-proline tetrazole (*S*)-**2**. Comparison with our catalytic system, indicates comparable yields and stereoselectivities, although reactions catalyzed by (*S*)-**3a** seem to proceed in shorter times. In this context, Nakashima and Yamamoto have proposed activation by a water molecule of the reaction catalyzed by tetrazole derivative (*S*)-**2** [14]. Suspecting that similar activation is



Scheme 3. Calculated equilibrium geometry (DFT M06 6-31G*) for isomeric species of hydrated (*S*)-**3a**·H_2O.

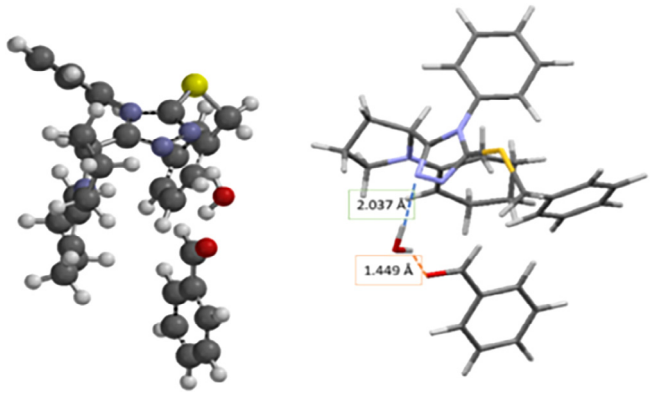


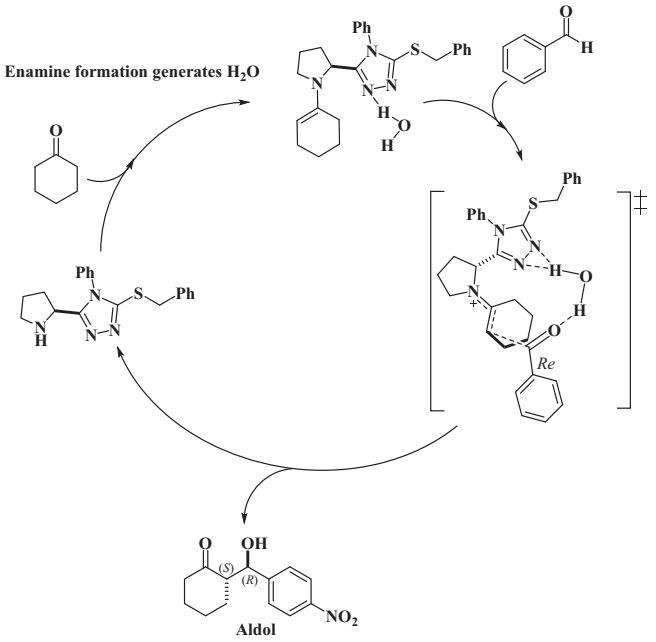
Fig. 2. Modeling of the transition state where organocatalyst (*S*)-**3a** activates the electrophilic aldehyde by hydrogen bonding between the catalyst [N(2) at the triazole ring], water, and the carbonyl substrate.

operative with the triazole analogs (*S*)-**3a** and (*S*)-**3b**, it was deem important to carry out a preliminary computational study of the reaction mechanism involving catalyst (*S*)-**3a**. In a first approximation, the structure of organocatalyst (*S*)-**3a** in the presence of one water molecule was optimized at the Spartan DFT at M06 6-31G* level of theory. Calculations (cf. Scheme 3) suggest that hydrated structure **22-A** with water hydrogen-bonded to N(2) is more stable relative to alternative adducts **22-B** (water coordinated to N(1) or **22-C** (water molecule bound to the exocyclic sulfur).

The above theoretical evidence, together with Yamamoto's proposed activation by hydrogen bonding between water and tetrazolyl nitrogens of electrophilic aldehydes during the aldol reaction catalyzed with (*S*)-**2** [8e] support similar activation of the electrophile by hydrogen bonding between the catalyst (*S*)-**3a** [N(2) at the triazole ring], water, and the carbonyl substrate. Thus, such proposed transition state was modelled using Spartan 16 (DFT-M06-6-31G*) (Fig. 2) [15]. Indeed, calculations converged to the energy minimum and reveal a 2.037 Å distance between atom N(2) of the triazole ring and a hydrogen in the water molecule. The distance between the second hydrogen of the water molecule with the oxygen atom of the aldehyde was estimated as 1.449 Å. These data are in line with the participation of a supramolecular aggregate in the transition state of the asymmetric aldol reaction.

It is then proposed that the equimolar amount of water generated upon enamine formation gets involved in the suggested transition state. A plausible reaction mechanism that is in line with the experimental (*Cf.* Table 2) and theoretical observations (*Cf.* Fig. 2) involves enamine formation in the first step, with the formation of 1 equivalent of water. Such water molecule is then involved in the supramolecular complex that leads to the aldol product and subsequent liberation of the organocatalyst that will enter in a new cycle (Scheme 4).

In conclusion, novel organocatalyst (*S*)-**3a** proved to be effective in asymmetric aldol reactions, offering the desired products in good *enantio*- and diastereoselectivities. Some advantages offered by organocatalyst (*S*)-**3a** include the fact that it does not require the presence of acidic or basic additives. Experimental and theoretical observations suggest that a water molecule is involved in the transition state.



Scheme 4. Plausible reaction mechanism proposed with base on both experimental results and molecular modeling.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151128.

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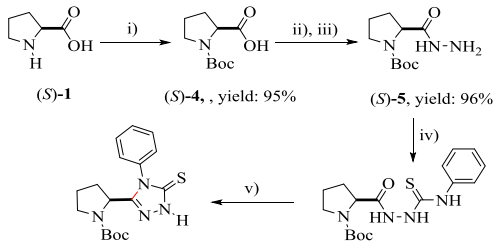
[9] The synthesis of (*S*)-**3a-c** was initiated with *N*-protection of (*S*)-proline (*S*)-**1** with di *t*-butoxycarbonyl anhydride (Boc_2O) to generate *N*-Boc protected (*S*)-**4** in 95% yield. Subsequently, hydrazine was incorporated via the formation of a mixed anhydride with ethyl chloroformate followed by addition of an ethanolic hydrazine hydrate solution [10a,b], affording hydrazide (*S*)-**5** in 96 % yield. The functionalization of compound (*S*)-**5** was carried out by treatment with phenyl isothiocyanate **6** under microwave irradiation in ethanol to afford semi thiocarbazide (*S*)-**7** with high yield [10c]. Intramolecular cyclization of semi thiocarbazide (*S*)-**7** was accomplished by means of dehydration in basic media [10d,e], giving pyrrolidinic 1,2,4-triazol-5-thione derivative (*S*)-**8** as a white solid in 85% yield.



(*S*)-**1** (*S*)-**4,** , yield: 95% (*S*)-**5**, yield: 96%

(*S*)-**8, y**ield: 85% (*S*)-**7, y**ield: 90%

Reaction condition, i) 1.2 equiv. Boc_2O, 2.3 equiv. Na_2CO_3, H_2O/Dioxane, rt, 48h. ii) 1.05 equiv. ClCOOEt, 1.05 equiv. Et_3N, THF, 0°C, 20 min. iii) 1.2 equiv. $N_2H_4.H_2O$, EtOH, 0–rt. 3h. iv) Phenyl isothiocyanate (**6**), EtOH, MW. "crude". v) NaOH (1.25 M), Δ, MW, 20 min.

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