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ARTICLE TYPE

Peptidomimetic Organocatalysts: Efficient Michael Addition of Ketones onto Nitroolefins with Very Low Catalyst Loading†

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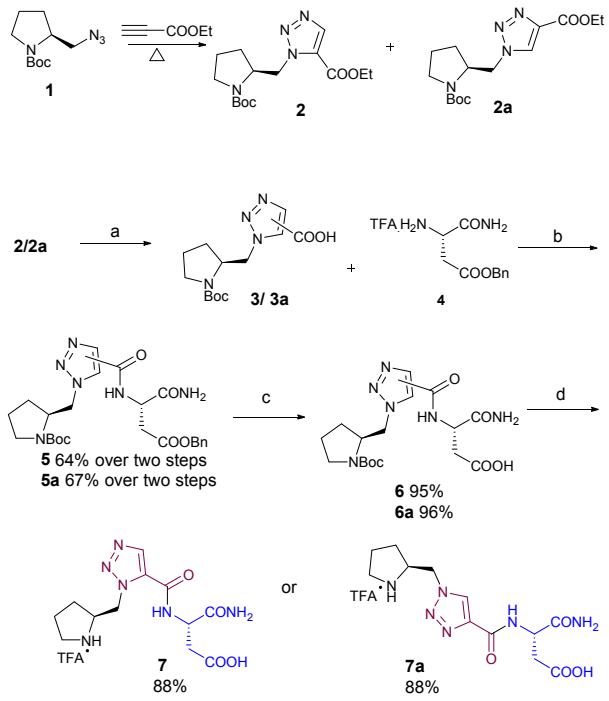
The syntheses of two novel peptidomimetic triazole based organocatalysts that work for the asymmetric conjugate addition of cyclohexanone to nitroolefins are described. The catalysts worked with very low loading (0.5 mol %) in the absence of any additives to provide high diastereo- and enantio-selectivities.

The asymmetric organo-catalyzed aldol and Michael reactions have co-developed in the recent past and paved way for a new era in asymmetric synthesis.[1] Major challenges in organocatalysis still to be addressed are: ease of access to catalyst and its cost, substrate generality and more importantly, catalyst loading. Many of the organocatalysts are substrate/ reaction specific; involve multiple steps for synthesis, incorporate sensitive functionalities and are difficult to recover. Thus, the field is wide open for further innovations. The early examples of organocatalytic asymmetric transformations utilized 20-50 mol % of proline as the catalyst.[2] Recovery of the amino acid was not a criterion for most researchers then. With the exploration of newer synthetic scaffolds as catalysts, which were available in smaller quantities, recovery and recycling of the catalyst became a priority. In addition, experimentation with lower concentrations of catalysts was initiated to mimic reactions in nature. Several groups,[3] including ours,[4] working in the area of organocatalysis have developed catalysts, which are required in ratios of 1 mol % to 10 mol % for a reaction to be fruitful. Recently, small and medium peptides have been established as organocatalysts.[5] Our work on peptidomimetics and turn-inducing properties of the unusual *β*-amino acids[6] inspired us to design and synthesize new scaffolds which could exhibit improved organocatalytic properties. We conceived that the triazole ring, which is an amide bond surrogate,[7] may contribute to form a rigid backbone conformation and thus promote selectivity. We further anticipated that the enhanced number of nitrogen atoms would also have influence on the basicity of the catalysts. An additional amino acid appendage as proposed by Wennemers *et al.*[8], would hopefully provide hydrogen bonding. With this background we initiated the synthesis of pyrrolidine linked triazole having isoaspargine amino acid appendage by following the synthetic strategy as depicted in scheme-1.

Thus, known azidopyrrolidine **1**,[9] was subjected to a thermal Huisgen [3+2] cycloaddition in presence of ethyl propiolate to furnish two regioisomeric triazoles **2** and **2a** in 28:72 ratio, easily separable by chromatography. Both the isomers (1,5- and 1,4-disubstituted triazoles) were independently transformed to corresponding acids **3** or **3a** followed by coupling with isoaspargine **4**, under *N*-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDCI), Hydroxybenzotriazole (HOBt) conditions to realise pyrrolidine-triazoles **5** or **5a**. Hydrogenation of benzyl ester to **6** or **6a** followed by treatment with TFA furnished **7** or **7a**.



a) LiOH.H_2O, THF:H_2O (7:3), 3 h, rt; b) Hydroxybenzotriazole, *N*-Ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride, *N*,*N*-Diisopropylethylamine, 0 °C to rt, 30 h; c) 10% Pd-C/H_2, MeOH, 3 h; d) TFA/CH_2Cl_2 (1:1), 3 h, rt.

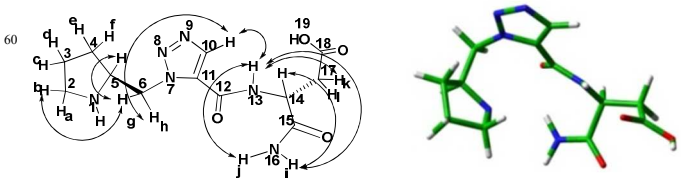
Scheme 1 Synthesis of catalysts **7** and **7a**

Wennemers *et al.*[8] have extensively studied organocatalysts based on turn-inducing *D*-proline-*L*-proline dipeptide[10] and have recently reported a novel high efficiency tripeptide organocatalyst, exhibiting hydrogen bond with isoaspargine.

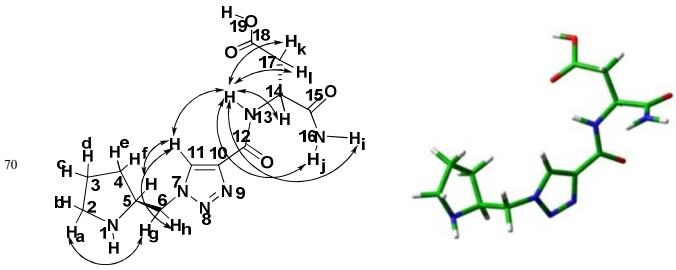
Some of the structural demands for high efficiency have been put forth by the group. These studies suggested that 2° amine at *N*-terminus, the carboxylic acid side chain of the aspartic acid residue and a well-defined turn conformation, are crucial for high catalytic activity and selectivity. Other groups working in the area of organocatalysis have proposed different set of rules for activity, where the turn induction and/or hydrogen bonding are not featured.[11] Thus, based on these studies it can be inferred that organocatalysis works either by turn induction, thereby forming a pocket or in a second instance, without these properties but with hydrogen bonding. The catalyst synthesized by Wennemers *et al.*[8] falls in the first category which works at a low concentration (<1.0 mol %). Computational models have also been put forth to generalise the essential requirements for organocatalytic properties especially for Michael type reactions.[11]

Before embarking on studying the efficiency of the catalysts synthesized, a detailed NMR investigation was taken up for both the compounds to understand the turn pattern and hydrogen bonding properties. Information on the preferred conformation of 1,5-triazole catalyst has been obtained at a concentration of approximately 5 mM in two independent structure supporting solvents: water (90% D_2O+10% H_2O) and CD_3OH, by using 1D and 2D (1H, COSY, TOCSY, and ROESY) NMR spectroscopy techniques. Significant number of intra-residue H-H ROEs is observed for 1,5-triazole catalyst **7**. Specifically, the observed unambiguous ROEs (Figure 1a) for **7** : 10H-13H ; 13H-(16Hi and 16Hj); 13H-17Hk; 14H-16Nhi; 10H-6Hh; 5H-6Hg; and 6Hg-2Hb are helpful in determining the conformation (Figure 1a). In order to delineate low energy structures, ROE-restrained molecular dynamics studies have been carried by using simulated annealing protocol (Insight II). Initially the input structures are rapidly heated from 300K to 900K allowing the structure to remain at 300K, 600K and 900K for 5ps. The velocity scaling temperature controlling method was adopted for heating and the temperature was allowed to vary by an order of 10K. The velocity verlet integration method was used for integration. Further the structures were slowly cooled from 900K to 300K by allowing the structures to remain for 5ps at 800K, 700K, 600K, 500K, 400K and 300K. The cycle of simulated annealing is repeated 250 times and the final structures were stored. Fifteen low energy structures were picked up among the 250 conformations and superimposed. The structures show predominantly single conformation, which is a turn-like compact structure. Similar processor followed for the 1,4-triazole catalyst **7a** also shown in the Figure 1b and the results showed that **7a** adopts an extended conformation, in contrast to **7** (Figure 1).

The detailed NMR investigations followed by ROE-restrained molecular dynamics[10] established that 1,5-disubstituted compound **7** adopts a relatively compact turn-like conformation (Figure 1a) whereas the other isomer (1,4-disubstituted) **7a** exhibited an extended conformation (Figure 1b). Either of these properties is generally required for the asymmetric organocatalytic properties. To have sufficient material on hand, we have conducted experiments with ruthenium and copper catalyst, which gave exclusively 1,5- or 1,4-di-substituted-1,2,3-triazoles.[12-14]



1a



1b

Figure 1 ROE-restrained minimum energy structures for catalyst **7** (1a) and **7a** (1b)

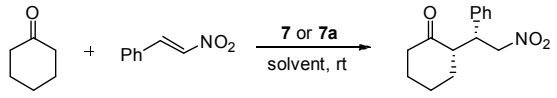
It is anticipated that the observed turn structure of 1,5-triazole catalyst **7** may favour its terminal isoaspargine appendage to participate in hydrogen bonding with the nitro group of nitrostyrene, a stabilizing factor akin to that observed for *D*-Pro-*L*-Pro-Asp-NH_2, for improved catalytic performance of the catalyst.[12] To prove this, a reaction was carried out between cyclohexanone (**8**) and nitrostyrene (**9**) in presence of catalyst **7** (5 mol %) and CH_2Cl_2 as solvent, which resulted in **10** in 55% yield with >99% *er* (Table 1, entry 1). To optimise the reaction conditions, solvents used are water, acetonitrile, isopropanol and methanol (Table 1, entries 3,5,9 and 11). A neat reaction was also carried out with similar results (Table 1, entry 7). Among the solvents tried, methanol was found to give the optimal conditions of yield and selectivity. Therefore all the further reactions were carried out in methanol. As the catalyst performed well at 5 mol % we were interested to see the effect of further reduction in catalyst loading.

At first, catalyst loading was decreased to 2 mol % and after obtaining results similar to 5 mol %, loading of catalyst was further reduced to 1 mol % and then to 0.5 mol % (Table 1, entries 13, 15 and 17). To our surprise even for 0.5 mol % catalyst loading *dr* and *er* were retained but the yield was slightly lower (95% to 80% for 0.5 mol %). These results surprised us as the use of 0.5 mol % of catalysts is rarely reported in literature for aldol reactions and conjugate addition of aldehydes, but not for Michael reaction of ketones to nitroolefins.[15]

A very low loading of the catalyst, the striking feature observed in this study, has prompted us to explore the scope of the catalyst by studying its effect on different substrates for wider application. Thus, substituted aromatic, hetero-aromatic nitroolefins were coupled with cyclohexanone, **8**, using catalyst **7** and it was observed that the outcome of these reactions was similar to the first reaction of nitrostyrene (Table 2, entries 1 to 10). We next changed the ketones to thiopyranone and acetone to get products in good to average yields (Table 2, entries 11 to 14).

Based on these observations one can conclude that both electron donating and withdrawing groups had very little effect on the stereo-selectivity of the reaction. This confirms a wider applicability of the catalyst and non-participation of the substituents or ring structure of the nitroolefin.

Table 1 Study of catalyst loading and solvent effect



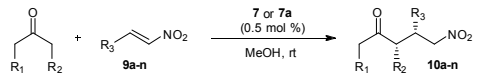
8 **9** **10**

Entry	Catalyst[a] [mol %]	Solvent	Time [h]	Yield[b] [%]	dr[c]	er[d]
1	**7** (5)	CH_2Cl_2	30	55	90:10	>99
2	**7a** (5)	CH_2Cl_2	32	50	93:7	91:9
3	**7** (5)	H_2O	30	72	97:3	99:1
4	**7a** (5)	H_2O	35	70	95:5	99:1
5	**7** (5)	CH_3CN	16	93	92:8	96:4
6	**7a** (5)	CH_3CN	24	90	93:7	95:5
7	**7** (5)	-------	30	92	92:8	97:3
8	**7a** (5)	-------	30	90	94:6	96:4
9	**7** (5)	**MeOH**	**30**	**95**	**96:4**	**97:3**
10	**7a** (5)	MeOH	35	91	94:6	96:4
11	**7** (5)	*i*PrOH	30	96	97:3	97:3
12	**7a** (5)	*i*PrOH	35	94	95:5	96:4
13	**7** (2)	**MeOH**	**35**	**82**	**97:3**	**97:3**
14	**7a** (2)	MeOH	39	79	92:8	91:9
15	**7 (1)**	**MeOH**	**40**	**82**	**97:3**	**97:3**
16	**7a** (1)	MeOH	45	78	91:9	86:14
17	**7 (**0.5)	**MeOH**	**48**	**80**	**96:4**	**98:2**
18	**7a** (0.5)	MeOH	52	78	90:10	96:4

[a]Reactions were performed at rt.
[b]Isolated yield after column chromatography.
[c]Determined by HPLC. [d]Determined by chiral HPLC.

Interestingly, catalyst **7a** having no turn structure was only marginally inferior to **7** (Table 1 and 2). DFT computations at B3LYP/6-31G* level provided more insights into the catalytic activities of **7** and **7a**.[11,12] Standard protocols for observing transition states are followed, by using Gaussian 09 software. Initially, the fully relaxed minimum energy structures of 1,5-triazole catalyst **7**, 1,4-triazole catalyst **7a** and nitrostyrene obtained from simulated annealing are subjected to optimization at B3LYP/6-31* level DFT calculations. The optimization was initially carried out in vacuum and then in MeOD solvent, by adopting PCM (Polarisable Continuum Model). These served as inputs (reactants) for computing transition state structures.

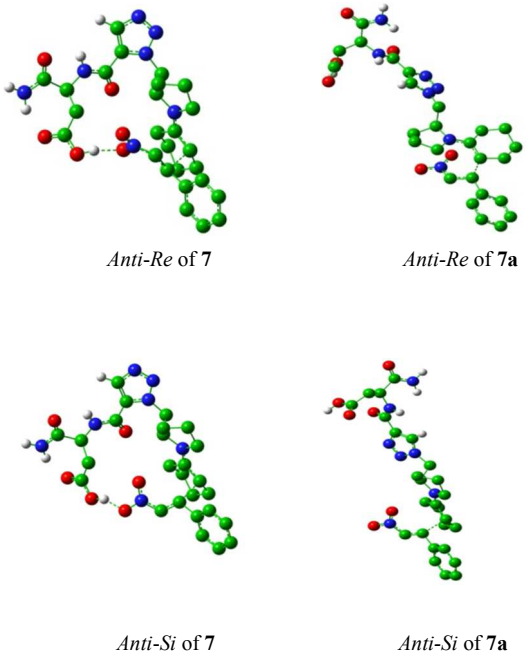
Table 2 Substrate variation for catalysts **7** and **7a**



Entry	Product	Catalyst[a]	Time [h]	Yield [%][b]	dr[c]	er[d]
1	**10a**[f]	**7**	45	52	96:4	94:6
		7a	50	50	95:5	94:6
2	**10b**	**7**	42	72	90:10	93:7
		7a	49	69	88:12	89:11
3	**10c**	**7**	40	72	97:3	87:13
		7a	46	68	93:7	84:16
4	**10d**[f]	**7**	40	68	97:3	79:21
		7a	45	65	94:6	75:25
5	**10e**[f]	**7**	48	64	94:6	96:4
		7a	54	60	93:7	91:9
6	**10f**[f]	**7**	42	65	93:7	96:4
		7a	46	60	95:5	95:5
7	**10g**[f]	**7**	40	71	95:5	91:9
		7a	46	65	94:6	88:12
8	**10h**[f]	**7**	42	70	95:5	99:1
		7a	46	67	93:7	97:3
9	**10i**[f]	**7**	42	66	90:10	82:18
		7a	49	60	81:19	68:32
10	**10j**	**7**	48	73	97:3	95:5
		7a	52	69	94:6	95:5
11[e]	**10k**[f]	**7**	47	70	96:4	93:7
		7a	53	66	95:5	89:11
12[e]	**10l**	**7**	52	50	---	68:32
		7a	57	45	---	65:35
13	**10m**[f]	**7**	50	56	---	68:32
		7a	55	50	---	63:37
14[e]	**10n**	**7**	50	53	---	69:31
		7a	56	50	---	67:33

[a]All reactions were performed at room temperature in MeOH with 0.5 mol% loading of catalyst **7** and **7a**; [b]Isolated yield after column chromatography. [c]Determined by HPLC; [d]Determined by chiral HPLC using chiralpak-IA column 250 x 4.6 mm; [e]Determined by chiral HPLC using chiralpak-IC; [f]The stereochemistry of known compounds was confirmed by comparing optical rotation values with those reported in literature.[16]

The transition states for the addition of *anti* and *syn* enamine to the *si* and *re* faces of nitrostyrene were first located in the gas phase. These transition states are labelled *a-re*, *a-si*, *s-re*, and *s-si*. The noticeable charge separation in the transition state is expected upon addition of enamine to nitrostyrene. To obtain improved estimates of the reaction energetic continuum solvent effects are incorporated by computing the zero-point energies by using the PCM with methanol as the medium. The preferred transition state structures arising from *anti*-enamine for both the catalysts are depicted in Figure 2.



Anti-Re of **7** *Anti-Re* of **7a**

Anti-Si of **7** *Anti-Si* of **7a**

Figure 2 Preferred transition states for **7** and **7a**

On the basis of DFT results a mechanism is proposed to account for the observed stereo-selectivity. The free acid of **7** behaves as a bifunctional catalyst. The proline ring first reacts with cyclohexanone carbonyl group to form an enamine with the help of acidic co-catalyst. Subsequently in the compact turn structure of **7**, the proton of the terminal acid hydroxyl group interacts with the nitro group of nitrostyrene, through hydrogen-bonding. The transition state involving the *re*-face attack on the *anti*-enamine (Figure 2) was lower in energy than other possible transition states (*anti-si, syn-re*, and *syn-si*). Whereas in case of **7a** there is no hydrogen-bond interaction between acid hydroxyl group of catalyst and nitro group of nitrostyrene to provide additional stabilisation factor, so the **7a** transition states are higher in energy than **7** (Table 3).

Table 3 Energies for preferred transition states of **7** and **7a**

Transition State	Transition State Energy (HARTREE)	Transition State Energy (Kcal/Mol)
anti- re (7)	-1844.567544	2.43
anti-si (7)	-1844.565963	3.42
anti- re (7a)	-1844.551983	12.75
anti-si (7a)	-1844. 548347	15.07

Conclusions

In conclusion, we report the syntheses of two compounds which have peptide bond surrogate triazole between a pyrrolidine methylene and isoaspargine, which proved to be excellent catalysts for Michael addition reactions. Low loading of catalyst, a little explored area of organocatalysis, is the highlight of this work. Catalyst **7** seems to be following the mechanism established for tripeptides by a turn-like conformation and thereby an intra-molecular hydrogen bonding, **7a** seems to be in the category of proline and proline-derived catalysts which do not depend on turn-like conformation for activity. These results suggest that catalysts having turn-inducing and hydrogen-bonding property would have slightly superior organocatalytic activity compared to catalysts having either one of the characters. Applications of these catalysts for other reactions are currently being explored.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization, NMR spectra of compounds, HPLC chromatograms, details of NMR and DFT studies. See DOI: 10.1039/b000000x/

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Graphical and Textual Abstract

Peptidomimetic Organocatalysts: Efficient Michael Addition of Ketones onto Nitroolefins with Very Low Catalyst Loading

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The syntheses of two novel peptidomimetic triazole based organocatalysts that work for the asymmetric conjugate addition of cyclohexanone to nitroolefins are described. The catalysts worked with very low loading (0.5 mol %) in the absence of any additives to provide high diastereo- and enantio-selectivities.