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# Enantioselective synthesis of 1,2,4-triazolines catalyzed by a cinchona alkaloid-derived organocatalyst†

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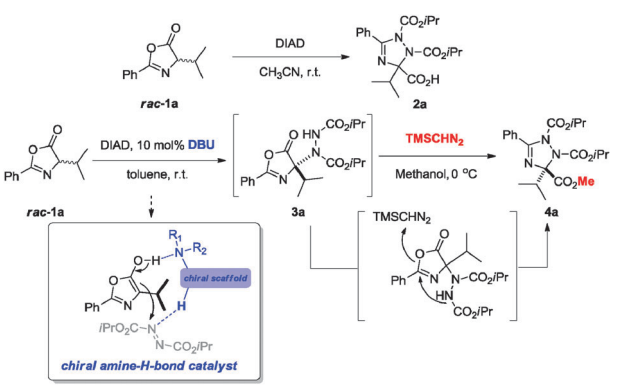
**An enantioselective organocatalytic process for the one-step synthesis of poly-substituted 1,2,4-triazolines is reported. The heterocycle formation is believed to go through a step-wise mechanism of nucleophilic addition of an azlactone to an azodicarboxylate in the presence of an organic base catalyst, followed by a $TMSCHN_2$ mediated heterocyclization. Both theoretical calculations and experimental evidence suggest the pre-organization of the transition state for the chirality determining step *via* a unique 7-membered intramolecular hydrogen bonding.**

Nitrogen-containing heterocycles are vital structures for natural products and drug candidates.[1] Development of highly efficient methods for the synthesis of nitrogen-containing heterocycles, especially the small, rigid rings bearing stereogenic centers, has been a major focus for enantioselective organocatalysis.[2] 1,2,4-Triazolines are a class of heterocycles that exist in a wide range of bioactive molecules that have antiviral, anticancer, anti-inflammatory, and anticonvulsant properties.[3] However, this heterocyclic motif has been underexplored regarding its use in medicinal chemistry due, in part, to the lack of efficient asymmetric synthetic methods. The 1,2,4-triazoline-3,3-alkylcarboxylic acids are a family of rigid, *gem*-diamino acids that could be potentially incorporated into peptides and affect their overall conformation and physical properties. There are adequate reports on the racemic synthesis of 1,2,4-triazolines with a quaternary C-3 carbon bearing a carboxylic functional group, most of which involved a Mitsunobu reaction of α-amino acids,[4] cycloaddition to oxazoles,[5] addition of imidazopyridine to azodicarboxylates,[6] and reactions of azodicarboxylates with *N*-[(trimethylsilyl) methyl] iminiumtriflates.[7] In 2010, Tepe *et al.* reported a convenient method for the racemic synthesis of such heterocycles through direct addition of azlactones to azodicarboxylates.[8] Jørgensen[9] and Wang[10] recently reported the synthesis of 1,2,4-triazolines *via* reactions of azodicarboxylate with α-isocyano esters/amides or 2-azidoacrylates, respectively. However, literature on the enantioselective synthesis remains rare. Jørgensen *et al.* in the aforementioned triazoline synthesis disclosed preliminary data using a phase-transfer catalyst in an effort to accomplish the enantioselective synthesis.[9] Very recently, highly enantioselective synthesis using similar substrates was also reported.[11] Both methods only enabled access to analogues lacking substitution at the 5-carbon of the heterocycle. Herein we report a general enantioselective approach to synthesize poly-substituted 1,2,4-triazolines catalyzed by a *cinchona* alkaloid-derived organocatalyst (Scheme 1).

Following Tepe's protocol,[8] we confirmed that the cycloaddition between racemic 4-isopropyl-2-phenyloxazol-5(4*H*)-one ***rac*-1a** and diisopropyl azodicarboxylate (DIAD) in acetonitrile occurred smoothly at room temperature in the absence of a catalyst to yield the desired 1,2,4-triazoline carboxylic acid ***rac*-2a** in high yield. This cycloaddition reaction slowed down drastically when less polar solvents were employed. Only trace amount of a primary nucleophilic addition product ***rac*-3a** was observed




**Scheme 1** Mechanistic insights and reaction design.

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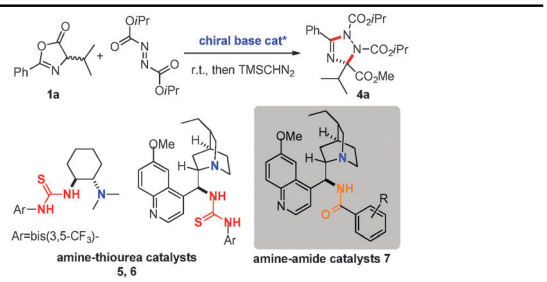
in toluene, DCM and ethereal solvents after several days, rendering these reaction conditions ideal for the development of the enantioselective process. We subsequently found that this nucleophilic addition step could be accelerated by an organic base catalyst (Scheme 1). It was discovered that **3a** underwent subsequent ring closure to generate the corresponding 1,2,4-triazoline **4a** upon treatment of the reaction mixture with $TMSCHN_2$ (Scheme 1). We envisioned that a double substrate conformational locking, base/hydrogen-bonding dual functional organocatalyst would serve as a good candidate for an enantioselective variant of this transformation.[12] Considering that the stereogenic center is created in the first step, a basic tertiary amine catalyst would activate the azlactone through enol stabilization, while an appending H-bond donor would impose additional rotation restriction on the catalyst–substrate complex through hydrogen bonding (Scheme 1).

The investigation of the catalyst was carried out using azlactone **1a** and DIAD as model substrates. Upon complete consumption of starting material **1a**, the reaction mixture was treated with $TMSCHN_2$ in methanol, and the desired 1,2,4-triazoline methyl ester **4a** was isolated and analyzed for optical purity. The most commonly used bifunctional catalysts were able to catalyze this reaction with decent efficiency. To our surprise, the privileged cyclohexane diamine **5** and quinine **6** derived thioureas, two of the most widely used dual functional organocatalysts for nucleophilic addition reactions, yielded a nearly racemic product (Table 1, entries 1 and 2). Various steric and electronic modifications of both scaffolds failed to improve the selectivity.

In-depth studies suggested that the selectivity of this reaction was quite sensitive to both the hydrogen-bond strength and the steric topology surrounding the H-bond donors. Single point H-bond donors were superior compared to the double H-bonded thioureas, possibly due to their dynamic rotational

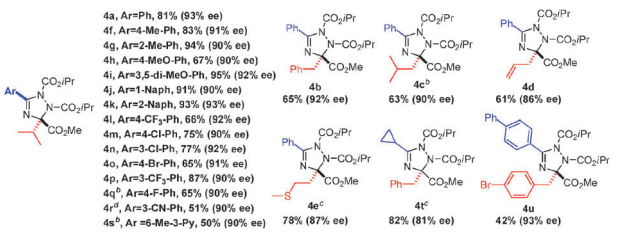
**Table 1** Catalyst screening and reaction optimization[a]




| Entry | Catalyst | R | Yield (%) | ee[b] (%) |
|---|---|---|---|---|
| 1 | **5** | — | 42 | 8 |
| 2 | **6** | — | 43 | 7 |
| 3 | **7a** | H | 70 | 65 |
| 4 | **7b** | *p*-MeO | 70 | 64 |
| 5 | **7c** | *p*-$CF_3$ | 68 | 76 |
| 6 | **7d** | bis(3,5-$CF_3$) | 64 | 84 |
| 7[c] | **7d** | bis(3,5-$CF_3$) | 81 | 93 |
| 8[d] | **7d** | bis(3,5-$CF_3$) | 52 | 90 |

[a] Unless otherwise noted, reactions were conducted using **1a** (0.1 mmol), DIAD (0.1 mmol), and a catalyst (0.01 mmol, 10 mol%) in MTBE (1 mL) at 25 °C for 12 hours. Isolated yield. [b] Determined by chiral HPLC analysis. [c] The reaction was carried out in diethyl ether using 5 mol% catalyst for 6 hours. [d] The reaction was carried out in diethyl ether using 1 mol% catalyst for 48 hours.

**Table 2** The substrate scope of azlactones for enantioselective synthesis of 1,2,4-triazolines[a]



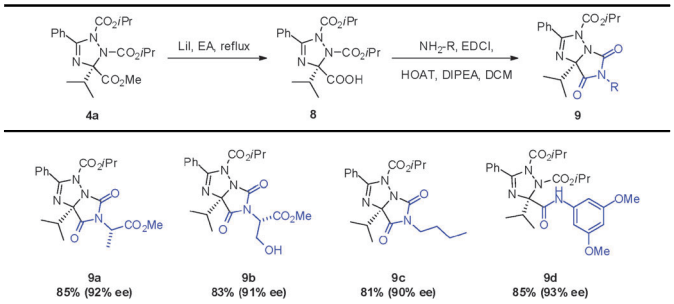

[a] Unless specified, the standard conditions were: 5 mol% **7d** on a 1 mmol scale; 1:1 substrate ratio in diethyl ether (0.1 M); r.t. for 6 hours. [b] Molecular sieves (5 Å, 100 mg) were used. [c] The reaction was carried out in diisopropyl ether. [d] The reaction was carried out in toluene.

flexibility that enables better substrate alignment in the transition state. Both thioamides and amides enjoyed noticeable selectivity improvement.[13] The amide H-bond functionality was essential since the corresponding imide led to a very slow reaction and a racemic product. Although amides of cinchona alkaloids have been used for organocatalysis previously,[14] we have not seen examples with such discrepancy in selectivity when compared to the corresponding thiourea catalysts. The bulky bis(3,5-trifluoromethyl) benzamide, **7d**, catalyzed this reaction with 64% yield and 84% ee using MTBE as a solvent (Table 1, entry 6). Solvent and catalyst loading survey led to further enhancement of both the yield and ee. The catalyst loading could be further decreased to 1 mol% without compromising selectivity (Table 1, entry 8).

The scope of azlactones was explored and results are summarized in Table 2. Racemic azlactone starting materials **1** were prepared from the corresponding *rac*-*N*-acyl amino acids, using trifluoroacetic anhydride as the dehydrating agent.[9] Various di-substituted azlactones were well tolerated. Both yields and enantioselectivities were uniformly satisfactory. Azlactones substituted by electron-rich aryl groups generally displayed higher reactivities than their electron-deficient counterparts. In most cases, near or above 90% ee's were obtained regardless of the electronic pattern. However, strong electron-withdrawing aryl groups or severe sterically bulky alkyl groups diminished the reactivity. No desired product was obtained for substrates with a 3,5-di-$NO_2$-Ph or *t*-Bu group. Both heteroaryl and cyclopropyl groups were tolerated. The most commercially available azodicarboxylates were tolerated for this reaction. Moderately reactive azodicarboxylates led to the best yields and enantioselectivities.[13,15] Constraint of the azodicarboxylate also led to a significant diminution of enantioselectivity.[13]

The triazolines prepared herein were readily converted into their corresponding bicyclic or cyclic compounds through simple amide coupling protocols. The corresponding methyl esters were hydrolyzed under lithium iodide/ethyl acetate refluxing conditions. Standard amide coupling with alkyl amines and amino esters triggered a concurrent cyclization to generate [5,5] hetero bicyclic products, while anilines led to normal amide products. During these chemical manipulations, the seemingly sensitive heterocyclic aminal remained untouched and no racemization of the stereogenic center was observed (Table 3).

**Table 3** Derivatization of 1,2,4-triazolines[a]




[a] The standard conditions were **4a** and 3 equiv. LiI in EA (0.2 M) refluxed overnight (step 1); **8**, 1.5 equiv. amine, 2 equiv. EDCI, 2 equiv. HOAT and 8 equiv. DIPEA in DCM at r.t. (step 2).

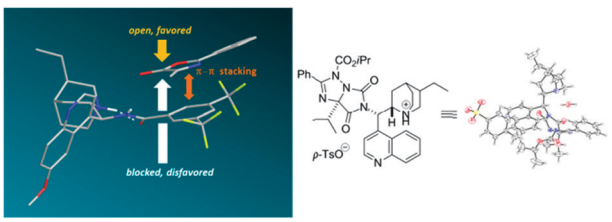



**Fig. 1** Optimized geometry of the catalyst–substrate complex and the proposed transition state showing the top face of the azlactone enolate being open and the lower face blocked by the catalyst. Absolute stereochemistry is determined by X-ray analysis. Maestro software (V. 9.0, Schrodinger Inc., New York, NY, USA) was used. i-Pr is omitted in the transition state for clarity.

To understand the mechanism of the enantioselectivity of the reaction, theoretical investigations were performed. The lowest energy conformer was minimized along with the deprotonated azlactone substrate. Fig. 1 shows the optimized geometry of the catalyst and the substrate complex. In this geometry, the protonated basic nitrogen of the quinuclidine forms an intramolecular hydrogen bond with the oxygen atom of the amide carbonyl group of the catalyst. The deprotonated azlactone sits on top of the 3,5-bis-trifluoromethylphenyl group of the catalyst, forming a π–π-stacking interaction. This complex is further stabilized by a hydrogen bond between the NH group of the catalyst and the deprotonated oxygen atom on the azlactone core. The addition of DIAD is preferred from the top face, which leads to *S* enantiomer products. As predicted, the absolute stereochemistry of the product was determined to be *S* by X-ray analysis of a benzamide derivative (CCDC 955229, Fig. 1).[13]

In summary, we have established a straightforward, highly enantioselective protocol to access poly-substituted 1,2,4-triazolines that are structurally complementary to existing protocols, from azlactones and azodicarboxylates using a chiral organocatalyst. While the popular cinchona–thiourea catalysts failed to deliver a decent facial discrimination, a single H-bond amide variant was designed and synthesized to accomplish high enantioselectivity. The reactions were believed to proceed through an addition–ring-closure mechanism where $TMSCHN_2$ was discovered to promote the triazoline ring formation step.

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