Organocatalytic one-pot 1,4-/1,6-/1,2-addition sequence for the stereocontrolled formation of six consecutive stereocenters†

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An unprecedented stereoselective organocatalytic one-pot 1,4-/1,6-/1,2-addition sequence between β-dicarbonyl compounds, β-nitroalkenes and 4-nitro-5-styrylisoxazoles sequentially catalyzed by low loading of a squaramide catalyst and an achiral base has been developed. The protocol opens an efficient entry to isoxazole bearing cyclohexanes with six consecutive stereogenic centers including one tetrasubstituted carbon in good yields and excellent diastereo- and enantioselectivities.

Over the last ten years, asymmetric organocatalytic cascade reactions have emerged as a powerful strategy for the synthesis of complex molecules bearing multiple stereogenic centers in a highly stereocontrolled fashion.1 These one-pot organocatalytic reactions were successfully employed for the creation of cyclohexane ring systems bearing up to six stereocenters.2 Most of these triple cascade reactions are governed by more common 1,4-/1,4-/1,2 addition sequences. Another important class of addition reactions involving the enantioselective 1,6-addition to control the formation of a remote stereocenter is more challenging and less explored in comparison to the other addition variants.3 Moreover, organocatalytic cascade reactions using all possible types of addition reactions, i.e. 1,4-/1,6-/1,2-addition reactions, are not known so far. Hence we took the challenge to develop a new stereoselective one-pot organocascade sequence using 1,4-/1,6-/1,2-additions (Scheme 1).

In addition, the isoxazole core is present in various important naturally occurring and synthetic bioactive molecules (Fig. 1). For example, compounds A–D are β-lactamase-resistant antibiotics,4 while an isoxazole containing natural product E is a powerful neurotoxin, which is used as a brain-lesioning agent.5 A synthetic androgenic steroid danazol D bearing an isoxazole ring suppresses the production of gonadotrophins and also has some weak androgenic effects.6 Moreover, isoxazoles serve as precursors for the synthesis of various synthetically useful organic compounds.7 Thus, the development of efficient asymmetric methods for the synthesis of isoxazole ring containing molecules can provide a new series of potentially bioactive molecules.

Recently, organo- and metal-catalyzed 1,6-additions to 4-nitro-5-styrylisoxazoles emerged as an efficient method to generate enantiopure isoxazole derivatives bearing one or two stereocenters.8,9 However, the 4-nitro-5-styrylisoxazoles remained less explored substrates in stereoselective cascade reactions.9d Very recently, Jørgensen’s group utilized 4-nitro-5-styrylisoxazoles in trienamine-mediated asymmetric [4+2] cycloaddition reactions to afford cyclohexene products bearing three vicinal stereocenters.10 Herein we report a novel cascade reaction involving a 1,4-/1,6-/vinylogous 1,2-addition sequence to access enantio- pure cyclohexane rings bearing as many as six contiguous

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stereogenic centers, sequentially catalyzed by low loading of a cinchona derived squaramide and an achiral base.

Initially, we started our investigation with a squaramide I (1 mol%) catalyzed one-pot three component reaction between ethyl acetacetate (1a), β-nitrostyrene (2a) and 4-nitro-5-styrylisoxazole (3a) (Table 1, entry 1). However our attempt to obtain the desired cyclohexane ring failed completely, and only the formation of the Michael adduct was observed. We envisaged that the squaramide catalyst was not enough active to generate a nitronate anion in the corresponding Michael adduct to initiate a cascade sequence to provide the desired product.

Once equipped with optimized reaction conditions, we evaluated the substrate scope at a 0.5 mmol scale of the squaramide II (Table 2). It showed that 30 mol% of DBU in CH2Cl2 provides a maximum yield of 62% and excellent stereoselectivity (98% ee and >20:1 dr). Further optimization of the reaction conditions by screening different solvents (entries 3–5) and bases (entries 6–11) showed that 30 mol% of DBU in CH2Cl2 provides a maximum yield of 62% and excellent stereoselectivity (entry 6). The use of a quinidine derived squaramide catalyst II led to the opposite enantiomer of the cyclohexane ent-4a with a similar yield, ee and dr (entry 12).

| Entry | Base (x mol%) | Solvent | Time (h) | Yield (%) | ee (%) |
|-------|---------------|---------|----------|-----------|--------|
| 1*    | —             | CH2Cl2  | 24       | —         | —      |
| 2     | DBU (20)      | CH2Cl2  | 24 + 24  | 46        | 98     |
| 3     | DBU (20)      | CHCl3   | 24 + 24  | 35        | 98     |
| 4     | DBU (20)      | Toluene | 24 + 24  | 44        | 98     |
| 5     | DBU (30)      | THF     | 24 + 24  | 36        | 98     |
| 6a    | DBU (30)      | CH2Cl2  | 24 + 48  | 62        | 99     |
| 7a    | DBU (30)      | CH2Cl2  | 24 + 48  | 62        | 99     |
| 8a    | DBU (30)      | CH2Cl2  | 24 + 48  | 36        | 97     |
| 9a    | DBU (30)      | CH2Cl2  | 24 + 48  | 29        | 98     |
| 10a   | DBU (30)      | CH2Cl2  | 24 + 48  | 36        | 97     |
| 11a   | DBU (30)      | CH2Cl2  | 24 + 48  | 36        | 97     |
| 12a   | DBU (30)      | CH2Cl2  | 24 + 48  | 58        | 96     |

* Reaction conditions: 0.2 mmol of 1a, 0.2 mmol of 2a, 1 mol% of I, 0.24 mmol of 3a and x mol% of base (0.1 M in solvent). | Time in hours for both reaction steps. | Enantiomeric excess of the major diastereomer (>20:1 dr) determined by HPLC analysis on a chiral stationary phase. | Yield of isolated 4a after column chromatography. | Enantiomeric excess of the major diastereomer determined by HPLC analysis on a chiral stationary phase.

| 4/ent-4 | R1 | R2 | R3 | Yield (%) | ee (%) |
|---------|----|----|----|-----------|--------|
| 4a      | OEt| Ph | Ph | 61        | 98     |
| 4b      | OEt| 4-FC6H4 | Ph | 64        | 99     |
| 4c      | OEt| 4-ClC6H4 | Ph | 55        | 99     |
| 4d      | OEt| 4-MeC6H4 | Ph | 63        | 93     |
| 4e      | OEt| 4-OMeC6H4 | Ph | 67        | 97     |
| 4f      | OEt| 2-Thienyl | Ph | 61        | 91     |
| 4g      | OEt| Ph | 4-FC6H4 | 60        | 98     |
| 4h      | OEt| Ph | 4-ClC6H4 | 61        | 97     |
| 4i      | OEt| Ph | 3-ClC6H4 | 69        | 97     |
| 4j      | OEt| Ph | 4-MeC6H4 | 73        | 99     |
| 4k      | OEt| Ph | 2-MeC6H4 | 49        | 95     |
| 4l      | OEt| Ph | 4-OMeC6H4 | 39        | 96     |
| 4m      | OMe| Ph | 2-Thienyl | 50        | 97     |
| 4n      | OMe| Ph | 64        | 98     |
| 4o      | Me | Ph | Ph | 50        | 96     |
| 4p      | OEt| Ph | Ph | 69        | 96     |
| 4q      | OEt| 4-FC6H4 | Ph | 63        | 97     |
| 4r      | OEt| 4-ClC6H4 | Ph | 51        | 95     |
| 4s      | OEt| 4-MeC6H4 | Ph | 64        | 98     |
| 4t      | OEt| 4-OMeC6H4 | Ph | 66        | 95     |
| 4u      | OEt| 2-Thienyl | Ph | 59        | 96     |
| 4v      | OEt| Ph | 4-ClC6H4 | 60        | 97     |
| 4w      | OEt| Ph | 2-MeC6H4 | 50        | 96     |

* Reaction conditions: 0.5 mmol of 1, 0.5 mmol of 2 and 0.5% of I (entry 1-17) or II, 1.0 mmol of 3 and 30 mol% of DBU (0.1 M in CH2Cl2). Yield of isolated product after column chromatography.

| 4                  | R1       | R2       | Yield (%) | ee (%) |
|--------------------|----------|----------|-----------|--------|
| 0.15 mmol of 1a, 0.3 mmol of 2a, 0.5% of I (entry 1-17) or II, 1.0 mmol of 3 and 30 mol% of DBU (0.1 M in CH2Cl2). | 4a        | OEt      | Ph       | 61        | 98     |
| 4b                  | OEt      | 4-FC6H4  | Ph       | 64        | 99     |
| 4c                  | OEt      | 4-ClC6H4 | Ph       | 55        | 99     |
| 4d                  | OEt      | 4-MeC6H4 | Ph       | 63        | 93     |
| 4e                  | OEt      | 4-OMeC6H4 | Ph    | 67        | 97     |
| 4f                  | OEt      | 2-Thienyl | Ph     | 61        | 91     |
| 4g                  | OEt      | Ph       | 4-FC6H4  | 60        | 98     |
| 4h                  | OEt      | Ph       | 4-ClC6H4 | 61        | 97     |
| 4i                  | OEt      | Ph       | 3-ClC6H4 | 69        | 97     |
| 4j                  | OEt      | Ph       | 4-MeC6H4 | 73        | 99     |
| 4k                  | OEt      | Ph       | 2-MeC6H4 | 49        | 95     |
| 4l                  | OEt      | Ph       | 4-OMeC6H4 | 39        | 96     |
| 4m                  | OMe      | Ph       | 2-Thienyl | 50        | 97     |
| 4n                  | OMe      | Ph       | 64        | 98     |
| 4o                  | Me       | Ph       | Ph       | 50        | 96     |
| 4p                  | OEt      | Ph       | Ph       | 69        | 96     |
| 4q                  | OEt      | 4-FC6H4  | Ph       | 63        | 97     |
| 4r                  | OEt      | 4-ClC6H4 | Ph       | 51        | 95     |
| 4s                  | OEt      | 4-MeC6H4 | Ph       | 64        | 98     |
| 4t                  | OEt      | 4-OMeC6H4 | Ph    | 66        | 95     |
| 4u                  | OEt      | 2-Thienyl | Ph     | 59        | 96     |
| 4v                  | OEt      | Ph       | 4-ClC6H4 | 60        | 97     |
| 4w                  | OEt      | Ph       | 2-MeC6H4 | 50        | 96     |
The enantiomeric purity could be enriched to >99% ee after a single crystallization of the product. In conclusion, we have developed a novel 1,4-/1,6-/1,2-addition cascade sequence catalyzed sequentially by low loading of a cinchona-derived squaramide and a commercially available achiral base to afford a series of highly substituted cyclohexane derivatives bearing six consecutive stereogenic centers in good yields and excellent stereoselectivities. The enantiomeric cyclohexanes are also easily synthesized on a same level of asymmetric catalysis, with a single crystallization of the product.

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Notes and references

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