Stereocontrolled Construction of Six Vicinal Stereogenic Centers on Spiropyrazolones *via* Organocascade Michael/Michael/1,2-Addition Reactions

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Supporting Information Placeholder

ABSTRACT: A highly stereoselective one-pot procedure for the synthesis of spiro-pyrazolone derivatives bearing six contiguous stereogenic centers including two tetrasubstituted carbons has been developed. Under sequential catalysis by two organocatalysts, a cinchona-derived amino squaramide and DBU, a series of diversely functionalized spiro-pyrazolones are obtained in good yields (47-62%) and excellent stereoselectivities (up to >25:1 dr and 98-99% ee). The opposite enantiomers of the spiro-pyrazolones are also accessible by employing a pseudo-enantiomeric amino-squaramide catalyst.

The synthesis of pyrazolone derivatives has attracted considerable attention in recent years due to the wide spectrum of applications in dye, analytical and pharmaceutical chemistry.^{1,2} Edaravone (**A**) - a neuroprotective agent, and metamizole (**B**) - an effective analgesic and antipyretic agent are two important pharmaceutically valuable pyrazolones (Figure 1).^{1c-f} In addition to these the pyrazolone derivatives such as **C** exhibit HIV inhibition activity.^{1g} Recently the pyrazolones were found to be inhibitors of the CD80 protein, and also possessing potent activity in inhibiting protease-resistant prion protein accumulation, cytokines, and p38 kinases.^{1h-k} Pyrazol-3-one derivatives have also been studied as multidrug resistance modulators.^{1l}

Figure 1. Biologically active pyrazolone derivatives.

On the other hand, spirocyclic frameworks frequently found in many synthetic bioactive compounds and natural products fascinated many researchers to develop synthetic strategies for their construction. Due to their complex three-dimensional structure the stereoselective synthesis of spirocyclic molecules from simple precursors in an atom-economic fashion is considered as a tough challenge.³ Recently, the organocatalytic cascade/domino reactions emerged as an efficient strategy, which provide such complex structures in an

operationally simple one-pot procedure,⁴ and we have witnessed a tremendous growth in the asymmetric synthesis of spirocyclic oxindole derivatives especially employing organocascade sequences.⁵ Despite of the many important applications of the pyrazolone moiety, the catalytic asymmetric synthesis of spiro-pyrazolones is less explored.

The Rios group reported the asymmetric synthesis of spiro-pyrazolones bearing three contiguous stereogenic centers *via* a secondary amine catalyzed domino reaction (Scheme 1).⁶ Rios and co-workers were also able to construct four stereocenters on a spiro-pyrazolones in a three component domino reaction.⁷ The cinchona-derived primary amines were found to catalyze the domino Michael/Michael reaction of the enones with the pyrazolones⁸ and the unsaturated pyrazolones⁹ to afford the spirocyclohexanonepyrazolones with three consecutive stereogenic centers. Recently, spiro-pyrazolones bearing a *N*-heterocyclic ring with three adjacent stereogenic centers were synthesized by amino-thioureas¹⁰ and quinine¹¹ catalyzed domino Michael/cyclization reactions.

To the best of our knowledge, the asymmetric synthesis of spirocyclohexanonepyrazolones bearing more than four stereocenters are not known. We took up this challenge and developed a one-pot protocol for the asymmetric synthesis of the spiro-pyrazolones bearing as many as six stereogenic centers including two adjacent tetrasubstituted ones. It was envisaged that an organocascade sequence involving a stereoselective Michael/Michael/1-2-addition reaction between β-dicarbonyl compounds **1**, nitroalkenes **2** and unsaturated pyrazolones **3** mediated by sequential organocatalysis¹² using a chiral bifunctional organocatalyst¹³ and an achiral base could afford such highly functionalized spiro-pyrazolones (Scheme 1).

To attain our objective at the onset, we performed a one-pot reaction which involved a quinine derived squaramide (1 mol %) catalyzed Michael addition of ethyl acetoacetate (**1a**)

Scheme 1. Catalytic enantioselective strategies for the synthesis of spiropyrazolone derivatives.

to (*E*)- β -nitrostyrene (**2a**) in dichloromethane. After 24 hours, the unsaturated pyrazolone **3a** and a guanidine base TBD (20 mol%) in dichloromethane were added sequentially. To our delight the desired spiropyrazolone bearing four tertiary and two tetrasubstituted stereogenic centers were obtained in good yield of 41% and excellent enantio- (99% ee) and diastereoselectivity (>25:1 dr) (Table 1, entry 1). The screening of other achiral bases (entries 2–6) showed that the DBU provides the best yield as well as excellent stereoselectivity (entry 2). The screening of solvents such as chloroform, toluene and THF did not result in any improvement in the product yield (entries 7–9). Further efforts for optimizing the yield of **4a** by increasing the catalyst loading of DBU revealed that with 50 mol% DBU a better yield was observed, however further increase in the amount of DBU did not show any improvement in the product yield. Using 2 equivalents of **3** the spiropyrazolone **4** was isolated in maximum yield of 60% with excellent stereoselectivity (entries 13, 14).

Once armed with optimized conditions, we further evaluated the substrate scope on a 0.5 mmol scale (Table 2). Various pyrazolone derived olefins bearing electron withdrawing and electron releasing substituents at the different aromatic position reacted efficiently under the standard reaction condition to afford desired spiropyrazolones **4b–i** in good yields and excellent enantio- and diastereoselectivities (entries 2–9). The heteroaromatic pyrazolone derivative also tolerated under this one-pot organocatalytic procedure, thus resulting in the desired spiropyrazolone **4j** in 55% yield with excellent ee (entry 10). **The unsaturated pyrazolone bearing an ortho-chloro phenyl group gives 47% yield of product 4k with 99% ee (entry 11)**

Different aromatic nitroalkenes bearing electron withdrawing as well as electron donating substituents also allowed an efficient access to the spiropyrazolones **4l–o** in good yield and excellent ee of 98–99% (entries 12–15). The nitroalkenes bearing heteroaromatic groups also provide the desired adducts **4p** and **4q** in good yields and excellent stereoselectivities (entries 16–17). We also tried other dicarbonyl compounds

Table 1. Optimization of the reaction conditions for the asymmetric synthesis of the spiropyrazolone **4a**.^a

entry	base (x mol %)	solvent	yield (%) ^b	ee (%) ^c
1	TBD (20)	CH ₂ Cl ₂	41	99
2	DBU (20)	CH ₂ Cl ₂	44	99
3	DBN (20)	CH ₂ Cl ₂	43	99
4	DABCO (20)	CH ₂ Cl ₂	12	99
5 ^d	Piperidine (20)	CH ₂ Cl ₂	14	98
6 ^d	Pyrrolidine (20)	CH ₂ Cl ₂	12	98
7	DBU (20)	CHCl ₃	35	99
8	DBU (20)	Toluene	34	99
9	DBU (20)	THF	35	99
10	DBU (30)	CH ₂ Cl ₂	46	99
11	DBU (50)	CH ₂ Cl ₂	52	99
12 ^e	DBU (100)	CH ₂ Cl ₂	36	99
13 ^f	DBU (30)	CH ₂ Cl ₂	57	99
14 ^f	DBU (50)	CH ₂ Cl ₂	60	99

^a 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). ^b Yield of isolated **4a** after flash column chromatography. ^c Enantiomeric excess of the major diastereomer (>25:1 dr) determined by HPLC analysis on a chiral stationary phase. ^d The reaction was run for 96 hours in the second step. ^e The reaction was run for 0.5 hours in the second step. ^f 0.40 mmol of **3a** was used.

such as methyl acetoacetate and acetylacetone, which efficiently reacted under this one-pot protocol to afford the adducts **4r** and **4s** in 57% and 53% yield and 99% ee (entries 18–19).

After generating two tetrasubstituted adjacent carbon atoms on the spiropyrazolone, we tried to create three consecutive tetrasubstituted carbons by employing a trisubstituted β -ketoester. A one-pot organocatalytic sequence promoted by **I** and DBU between the β -ketoester **5**, (*E*)- β -nitrostyrene (**2a**) and pyrazolone **3a** provided the spiropyrazolone **6** bearing three contiguous tertiary and three tetrasubstituted stereogenic centers in excellent stereoselectivity (>25:1 dr and 95% ee) albeit a low yield of 16% (Scheme 2).

Scheme 2. Asymmetric synthesis of spiropyrazolone with three contiguous tetrasubstituted stereocenters.

Table 2. Substrate scope of the asymmetric synthesis of spiropyrazolones 4 with catalyst I.^a

entry	R ¹	R ²	R ³	R ⁴	4	yield (%) ^b	ee (%) ^c
1	OEt	Ph	Ph	Ph	4a	62	99
2	OEt	Ph	4-ClC ₆ H ₄	Ph	4b	58	99
3	OEt	Ph	4-BrC ₆ H ₄	Ph	4c	62	99
4	OEt	Ph	4-CF ₃ C ₆ H ₄	Ph	4d	61	99
5	OEt	Ph	3-ClC ₆ H ₄	Ph	4e	60	99
6	OEt	Ph	4-MeC ₆ H ₄	Ph	4f	52	99
7	OEt	Ph	4-MeOC ₆ H ₄	Ph	4g	57	99
8	OEt	Ph	2-MeC ₆ H ₄	Ph	4h	55	99
9	OEt	Ph	3-MeOC ₆ H ₄	Ph	4i	57	99
10	OEt	Ph	2-Thienyl	Ph	4j	55	99
11	OEt	Ph	Ph	2-ClC ₆ H ₄	4k	47	99
12	OEt	4-FC ₆ H ₄	Ph	Ph	4l	57	99
13	OEt	4-ClC ₆ H ₄	Ph	Ph	4m	58	99
14	OEt	4-MeC ₆ H ₄	Ph	Ph	4n	56	98
15	OEt	4-MeOC ₆ H ₄	Ph	Ph	4o	56	99
16 ^d	OEt	2-Furanyl	Ph	Ph	4p	55	99
17	OEt	2-Thienyl	Ph	Ph	4q	59	99
18	OMe	Ph	Ph	Ph	4r	57	99
19	Me	Ph	Ph	Ph	4s	53	99

^a Reaction conditions: 0.5 mmol of **1**, 0.5 mmol of **2**, 1 mol % of **I**, 1.0 mmol of **3** and 50 mol % of DBU (0.1 M in CH₂Cl₂). ^b Yield of the isolated product after flash column chromatography. ^c Enantiomeric excess of the major diastereomer (>25:1 dr). ^d 12:1 dr.

The absolute configuration of the spiropyrazolones **4a-s** could be assigned as (1*R*), (2*S*), (3*S*), (4*S*), (5*S*) and (6*R*) based on the X-ray structure of **4c** (Figure 2).¹⁴

Figure 1. X-ray structure of **4c**.

We have also tested the catalytic potential of amino-squaramide catalyst **II** derived from quinidine in place of catalyst **I** to generate the opposite enantiomer of the corresponding product. With catalyst **II** various spiropyrazolone derivatives were accessible in good yields, excellent enantio- and diastereoselectivities (Table 3).

In order to demonstrate the practical utility of this one-pot protocol, we have performed a gram scale cascade Michael/Michael/1,2-addition reaction between **1a**, **2a** and **3a** using a lower loading (0.5 mol%) of catalyst **I** (Scheme 3). The desired spiropyrazolone **4a** was obtained in 59% yield without deteriorating the stereochemical outcome of the reaction.

In conclusion, we have disclosed a one-pot procedure for the synthesis of a new series of potentially biologically important spiropyrazolone derivatives. A variety of spirocyclo

Table 3. Substrate scope of the asymmetric synthesis of spiropyrazolones *ent*-4 with catalyst II.^a

entry	R ¹	R ²	R ³	<i>ent</i> -4	yield (%) ^b	ee (%) ^c
1	OEt	Ph	Ph	<i>ent</i> - 4a	61	99
2	OEt	Ph	4-ClC ₆ H ₄	<i>ent</i> - 4b	57	97
3	OEt	Ph	3-ClC ₆ H ₄	<i>ent</i> - 4e	60	98
4	OEt	Ph	4-MeC ₆ H ₄	<i>ent</i> - 4f	50	98
5	OEt	Ph	3-MeOC ₆ H ₄	<i>ent</i> - 4i	57	98
6	OEt	4-FC ₆ H ₄	Ph	<i>ent</i> - 4l	60	97
7	OEt	4-ClC ₆ H ₄	Ph	<i>ent</i> - 4m	57	98
8	OEt	4-MeC ₆ H ₄	Ph	<i>ent</i> - 4n	56	97
9 ^d	OEt	2-Thienyl	Ph	<i>ent</i> - 4q	61	98
10	OMe	Ph	Ph	<i>ent</i> - 4r	59	98

^a Reaction conditions: 0.5 mmol of **1**, 0.5 mmol of **2**, 1 mol % of **II**, 1.0 mmol of **3** and 50 mol % of DBU (0.1 M in CH₂Cl₂). ^b Yield of the isolated product after flash column chromatography. ^c Enantiomeric excess of the major diastereomer (>25:1 dr). ^d 10:1 dr.

Scheme 3. Gram-scale one-pot stereoselective synthesis of spiro-pyrazolone **4a**.

hexanepyrazolone derivatives bearing six stereocenters including two vicinal tetrasubstituted carbons were obtained in good yields and excellent stereoselectivities *via* sequential organocatalytic Michael/Michael/1,2-addition reactions facilitated by a low loading of a cinchona-derived amino squaramide and a readily available achiral base. This one-pot cascade sequence can be scaled up without losing the reaction efficiency in terms of product yield and stereoselectivity. The opposite enantiomer of the spiro-pyrazolones can be also synthesized in good yield and excellent stereoselectivity by employing a pseudo-enantiomeric catalyst.

SUPPORTING INFORMATION

Experimental details and full spectroscopic data for all new-compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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NOTES

The authors declare no competing financial interest

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- CCDC 997149 (for **4c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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