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

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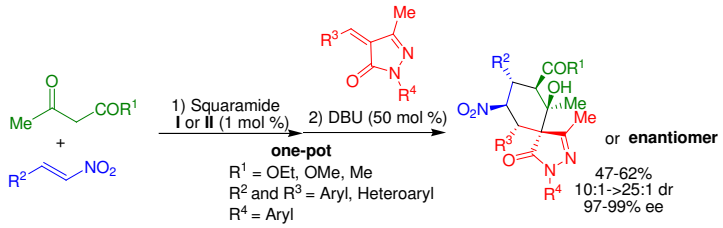
Supporting Information Placeholder



ABSTRACT: A highly stereoselective one-pot procedure for the synthesis of spiropyrazolone 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 spiropyrazolones are obtained in good yields (47-62%) and excellent stereoselectivities (up to >25:1 dr and 98-99% ee). The opposite enantiomers of the spiropyrazolones 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.[11]

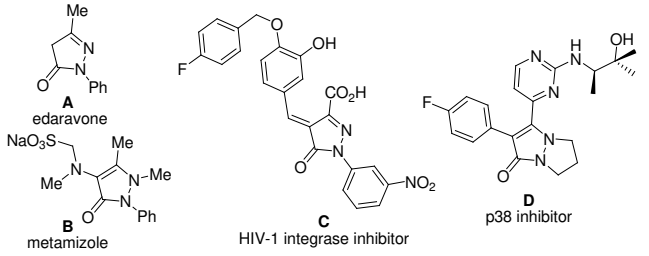


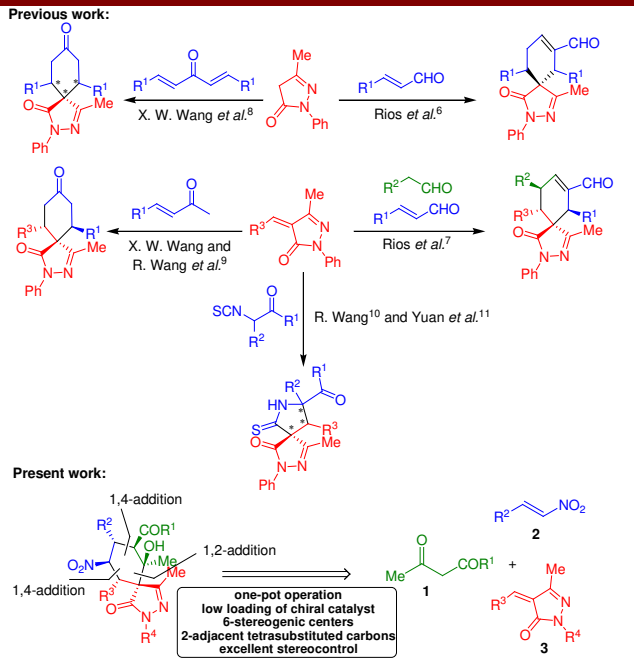
Figure 1. Biologically active pyrazolone derivatives.

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 spiropyrazolones is less explored.

The Rios group reported the asymmetric synthesis of spiropyrazolones bearing three contagious 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 spiropyrazolones 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 pyrazolones[8] and the unsaturated pyrazolones[9] to afford the spirocyclohexanonepyrazolones with three consecutive stereogenic centers. Recently, spiropyrazolones bearing a *N*-heterocyclic ring with three adjacent stereogenic centers were synthesized by amino-thioureas[10] and quinine[11] catalyzed domino Michael/cyclization reactions.

To the best of our knowledge, the asymmetric synthesis of spirocyclohexanepyrazolones 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 spiropyrazolones 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 organocatalysis[12] using a chiral bifunctional organocatalyst[13] and an achiral base could afford such highly functionalized spiropyrazolones (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**)



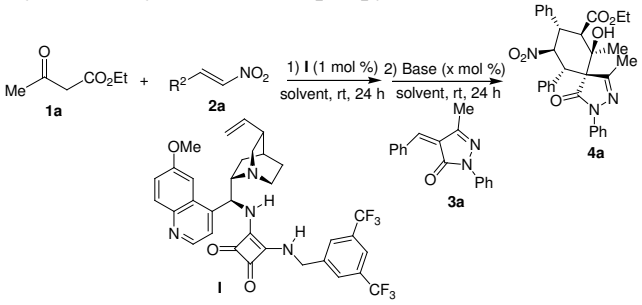
Scheme 1. Catalytic enantioselective strategies for the synthesis of spiropyrazolone derivatives.

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 organocascade 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]

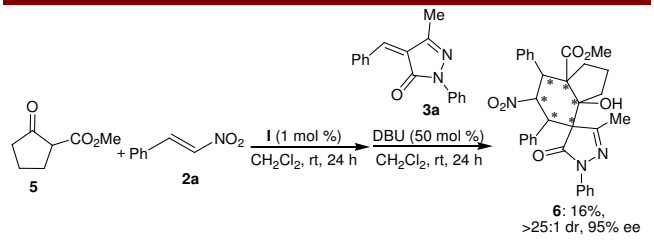


entry	base (x mol%)	solvent	yield (%)[b]	ee (%)[c]
1	**TBD** (20)	CH_2Cl_2	41	99
2	**DBU** (20)	CH_2Cl_2	44	99
3	**DBN** (20)	CH_2Cl_2	43	99
4	**DABCO** (20)	CH_2Cl_2	12	99
5[d]	**Piperidine** (20)	CH_2Cl_2	14	98
6[d]	**Pyrrolidine** (20)	CH_2Cl_2	12	98
7	**DBU** (20)	$CHCl_3$	35	99
8	**DBU** (20)	Toluene	34	99
9	**DBU** (20)	THF	35	99
10	**DBU** (30)	CH_2Cl_2	46	99
11	**DBU** (50)	CH_2Cl_2	52	99
12[e]	**DBU** (100)	CH_2Cl_2	36	99
13[f]	**DBU** (30)	CH_2Cl_2	57	99
14[f]	**DBU** (50)	CH_2Cl_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.

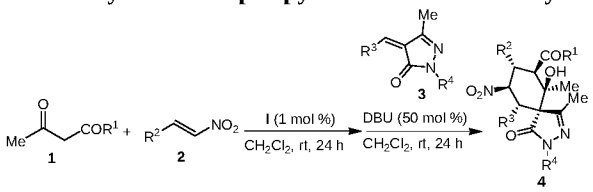
such as methyl acetoacetate and acetylacetone, which efficiently reacted under this one-pot protocol to afford the adducts **4r** and **4s** in 57% and 53% yield and 99% ee (entries 18-19).

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_6H_4	Ph	**4b**	58	99
3	OEt	Ph	4-BrC_6H_4	Ph	**4c**	62	99
4	OEt	Ph	4-$CF_3C_6H_4$	Ph	**4d**	61	99
5	OEt	Ph	3-ClC_6H_4	Ph	**4e**	60	99
6	OEt	Ph	4-MeC_6H_4	Ph	**4f**	52	99
7	OEt	Ph	4-$MeOC_6H_4$	Ph	**4g**	57	99
8	OEt	Ph	2-MeC_6H_4	Ph	**4h**	55	99
9	OEt	Ph	3-$MeOC_6H_4$	Ph	**4i**	57	99
10	OEt	Ph	2-Thienyl	Ph	**4j**	55	99
11	OEt	Ph	Ph	2-ClC_6H_4	**4k**	47	99
12	OEt	4-FC_6H_4	Ph	Ph	**4l**	57	99
13	OEt	4-ClC_6H_4	Ph	Ph	**4m**	58	99
14	OEt	4-MeC_6H_4	Ph	Ph	**4n**	56	98
15	OEt	4-$MeOC_6H_4$	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 CH_2Cl_2). [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]

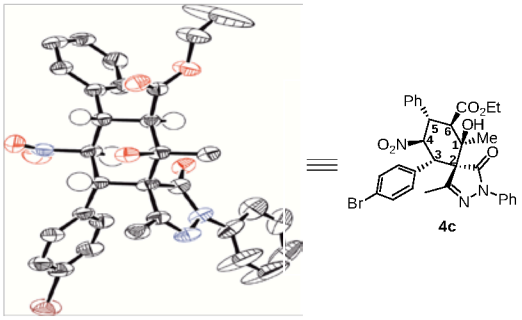


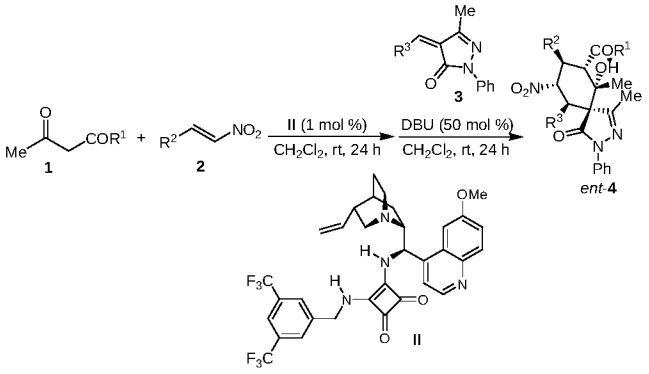
Figure 1. X-ray structure of **4c**.

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.

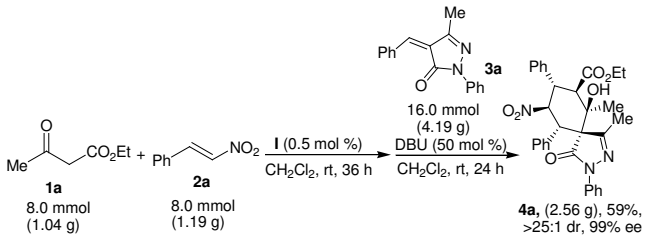
In conclusion, we have disclosed a one-pot procedure for the synthesis of a new series of potentially biologically important spiropyrazolone derivatives. A variety of spirocyclo

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



entry	R^1	R^2	R^3	*ent*-**4**	yield (%)[b]	ee (%)[c]
1	OEt	Ph	Ph	*ent*-**4a**	61	99
2	OEt	Ph	4-ClC_6H_4	*ent*-**4b**	57	97
3	OEt	Ph	3-ClC_6H_4	*ent*-**4e**	60	98
4	OEt	Ph	4-MeC_6H_4	*ent*-**4f**	50	98
5	OEt	Ph	3-$MeOC_6H_4$	*ent*-**4i**	57	98
6	OEt	4-FC_6H_4	Ph	*ent*-**4l**	60	97
7	OEt	4-ClC_6H_4	Ph	*ent*-**4m**	57	98
8	OEt	4-MeC_6H_4	Ph	*ent*-**4n**	56	97
9[d]	OEt	2-Thienyl	Ph	*ent*-**4q**	61	98
10	OMe	Ph	Ph	*ent*-**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 CH_2Cl_2). [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 spiropyrazolone **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 spiropyrazolones 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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Streocontrolled Construction of Six Vicinal Stereogenic Centers on Spiropyrazolones *via* Organocascade Michael/Michael/1,2-Addition Reactions

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