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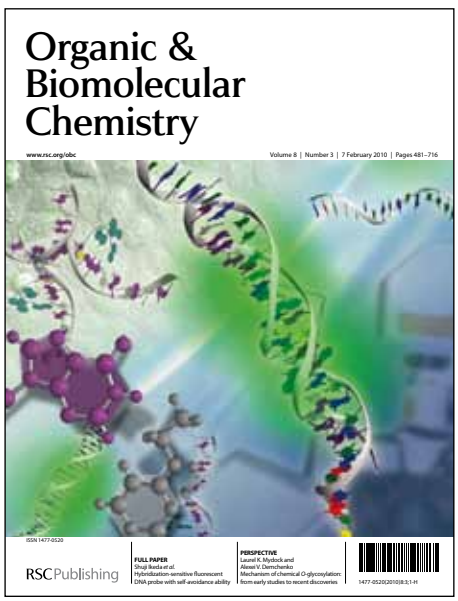

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Communication

An Organocatalytic Asymmetric Double Michael Cascade Reaction of Unsaturated Ketones and Unsaturated Pyrazolones: Highly Efficient Synthesis of Spiropyrazolones Derivatives†

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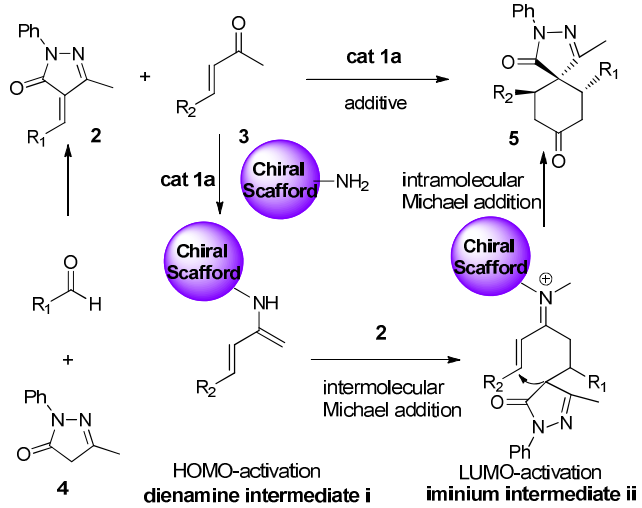
The first organocatalytic double Michael cascade reaction between unsaturated ketones and unsaturated pyrazolones has been developed which provides spiropyrazolones core structures containing two interval or three consecutive stereogenic centers with excellent diastereo- (>20:1) and enantioselectivities (up to 99% ee). Moreover, a pair of enantiomers 5a and 5a' can be achieved via different catalyst.

The heteroatom-containing spirocyclic subunits are featured in a number of naturally occurring products as well as biologically, pharmaceutically, and medically active molecules. As a consequence, finding simple and effective synthetic methods to realize functional diversity, architectural complexity, and stereochemical unicity of the core draws increasing attention of organic chemists and a number of excellent achievements have been reported during the past decades especially based on the flourishing development of asymmetric organocatalysis.[1] To date, many efforts are concentrated on the synthesis of chiral spirooxindoles[2] while other spiroheterocyclic motifs are rarely involved.[3]

Pyrazol-3-one derivatives, because of their approved antiinflammatory, antiviral, antitumor, and antibacterial properties, exist widely in clinical and listed drugs.[4] For example, the very common structure of compound **4**, which is known as edavarone, is used in the treatment of blood brain barrier injury. Although various synthetic protocols have been achieved on the construction of 4-substitute pyrazolones, there are few reports concerning on the synthesis of chiral pyrazolones with quaternary stereogenic center at the C-4 position and intriguing spiropyrazolones combining of multistereogenic cyclohexanone and pyrozolone motifs. In 2010, Yuan and co-workers reported an enantioselective pyrazolone Michael addition to nitrostyrenes by organocatalysis.[5] In 2011, Feng's group disclosed a highly enantioselective reaction of pyrazolones and azodicarboxylates by metal catalysis.[6] Shortly after, Rios reported the first example of Michael-Michael-aldol condensation of pyrazolone **4** and unsaturated aldehydes for the preparation of chiral spiropyrazolones.[7] In 2012, Wang's group reported a double Michael reaction between pyrazolones and divinyl ketones that gave spiropyrazolones with excellent yields and enantioselectivities.[8]

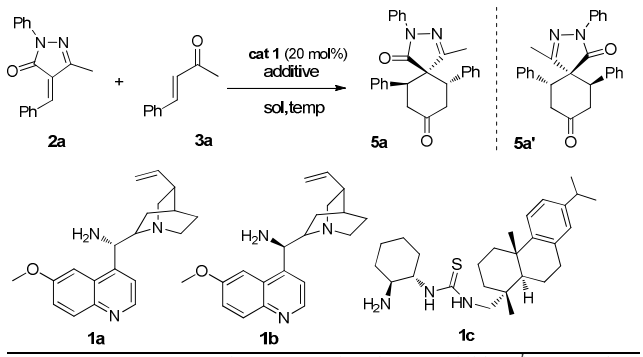
Recently, Rios and co-workers disclosed an organocatalytic enantioselective pyrazol-3-one addition to maleimides catalyzed by bifunctional thiourea catalysts.[9] All of the above methodologies employ pyrazolones as nucleophiles. Considering the similar electronic and structural properties between pyrazolone and oxindole and the successful application of unsaturated oxindole, the use of an unsaturated pyrazolone as an electrophile is also promising. However, so far only a single asymmetric catalytic entry currently available to spiropyrazolones was described by Rios and co-workers, consisting of a domino cyclization reaction among aldehyde, unsaturated aldehyde and unsaturated pyrazolone.[10] No results have been reported in the literature for constructing chiral spiropyrazolones using unsaturated ketones and unsaturated pyrazolones. As part of our ongoing research program toward the exploitation of organocatalytic cascade reaction and our interests in seeking enantioselective approach toward the construction of spirocyclic motif,[11] we will in this context present the first asymmetric organocatalytic double Michael cascade cycloaddition reaction of unsaturated ketones and unsaturated pyrazolones, providing spiropyrazolones derivatives in moderate yields and excellent diastereo- and enantioselectivities.



Scheme 1. General strategy for the construction of chiral spiropyrazolones

As early as in 2002, Barbas's group firstly introduced dienamine activation mode of unsaturated ketones with reactive hydrogen at C-terminal.[12] They used secondary amines derived from proline to catalyze the DA reaction of unsaturated ketones and nitro olefins with excellent yields and no asymmetric catalysis was referred to. Chen and Melchiorre's group independently[13]developed this concept and proved that quinine or quinidine alkaloid-derived primary amine can act as powerful catalyst to activate these ketones to complete chiral induction. Inspired by these experimental results, we envisaged the following reaction mechanism: Unsaturated ketone **3** should first intercept the primary amine catalyst via HOMO-activation concept to generate the activated dienamine ion intermediate **i**. The resulting prochiral carbon nucleophile **i** should be reactive enough to initiate an intermolecular Michael addition to unsaturated pyrazolones **2**, and the LUMO-active intermediate **ii** adduct would further undergo an intramolecular conjugate addition, thus affording the desired spiropyrazolone **5** in a one-pot fashion (Scheme 1).

Table 1. Screening of the Catalysts, Solvents, and Reaction Conditions for the Reactions[a]

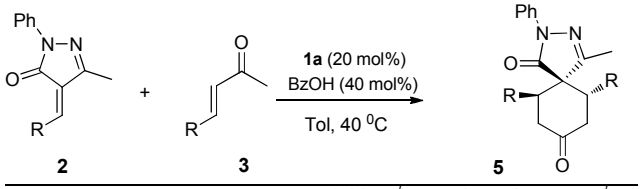


entry	Cat	solvent	Time[h]	yield[%][b]	ee[c]
1	**1a**	Toluene	120	-	-
2[d]	**1a**	Toluene	72	87	>99
3[d,f]	**1b**	Toluene	72	81	>99
4[d]	**1c**	Toluene	120	76	93
6[d]	**1a**	MTBE	72	59	96
7[d]	**1a**	THF	72	55	86
8[d]	**1a**	CH_2Cl_2	72	79	93
9[d]	**1a**	MeCN	72	46	84
10[d,e]	**1a**	Toluene	3.5	85	>99
11[d,e,f]	**1b**	Toluene	3.5	80	>99

[a] Unless noted, the reaction was performed on 0.1 mmol scale with **2a** (1.0 equiv), **3a** (2.0 equiv) and catalyst **1a** (20 mol%) at rt (17 ° C) for displayed time. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] BzOH (40 mol%) was used as cocatalyst. [e] The reaction was performed at 40 °C. [f] The enantiomers **5'** of compound **5** was obtained using the same steps while catalyst 1b was employed during the reaction process.

To identify the validation of our strategy, we began the investigation by testing the model reaction between **2a** and **3a** catalyzed by primary amine **1a** in toluene at rt. However, no product was observed after 120h (Table 1, entry 1). Under the same condition, the using of protic acid BzOH as cocatalyst to the reactive system triggered the reaction and provided the desired product **5a** in 87% yield and >99% ee value after 72h (entry 2). Encouraged by this outcome, we further explored **1b** and **1c** as catalysts for this reaction, and the results were shown in Table 1. Using catalyst **1b**, we were delighted to obtain spirocyclic product **5a'** with comparable ee value, yield and reversed configuration (entry 3). Although an acceptable ee value (93%) was obtained with catalyst **1c**, the reaction needed longer time and afforded the product in lower yield (entry 4). Considering the enantioselectivity as well as yield, catalyst **1a** and **1b** both delivered ideal results and a pair of enantiomers **5a** and **5a'** can be achieved via different catalysis. However, in these two cases the reaction was found to be somewhat sluggish, which demanded 72h to completion. Therefore, taking primary amine **1a** as catalyst, the reaction conditions were further optimized. Toluene was selected as the optimal solvent in terms of both yield and enantioselectivity (entries 2 and 6-9). The temperature had a pronounced effect on the reaction rate and would shorten the reaction time from 72h to 3.5h without sacrificing of either yield or enantioselectivity (entries 2 and 10) through the elevation of temperature from rt to 40 °C.

Table 2. Substrate Scope of Cat **1a**/ BzOH-Catalyzed Double Michael Addition of Unsaturated Pyrazolones **2a-j** and Unsaturated Ketones **3a-j** with Same Substituents[a]



entry	5	R	yield[%][b]	dr [%][c]	ee[d]
1	**5a**	Ph	87	>20:1	>99
2	**5b**	4-$CH_3C_6H_4$	75	>20:1	>99
3	**5c**	4-FC_6H_4	81	>20:1	>99
4	**5d**	4-ClC_6H_4	88	>20:1	>99
5	**5e**	4-BrC_6H_4	84	>20:1	>99
6	**5f**	4-$MeOC_6H_4$	68	>20:1	>99
7	**5g**	3-ClC_6H_4	83	>20:1	>99
8	**5h**	3-$MeOC_6H_4$	71	>20:1	>99
9	**5i**	2-naphthyl	64	>20:1	>99
10	**5j**	2-furyl	55	>20:1	nd[e]

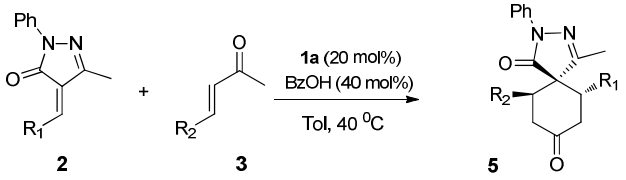
[a] Unless noted, the reaction was performed on 0.1 mmol scale with **2a** (1.0 equiv), **3a** (2.0 equiv), BzOH (40 mol%) and catalyst **1a** (20 mol%) at 40 °C for 3-12 h. The control comparative experiments details, see the Supporting Information. [b] Yield of isolated product. [c] Measured by ^{1}H NMR spectroscopic analysis. [d] Determined by HPLC analysis on a chiral stationary phase. [e] The ee value can not be determined by HPLC analysis.

Having established the optimal reaction conditions (Table 1, entry 10), we next examined the scope and limitations of the above system with variants of reactants **2** and **3**. Considering the product **5** with two interval (same substituent on reactants **2** and **3**) or three consecutive stereocenters (different substituent on reactants **2** and **3**), we will describe them separately. We first tested reactions of compound **2** and **3** with same substituent and the results were summarized in Table 2. Unsaturated pyrazolones **2** and unsaturated ketones **3** with same substituents in meta- and para- positions could be tolerated and underwent smooth cyclization reactions, providing spiropyrazolones **5b-5h** in good yields and with excellent diastereo- and enantioselectivities (entries 2-8). The electronic properties of the substituents seemed to have no influence on the enantioselectivity, although the reaction yields were a little lower for reactants possessing

electron-rich substituents (entries 6 and 8). Conjugated aromatic (entry 9) and heteroaromatic (entry 10) substrates could also be applied to the present process, despite the ee value of product **5j** could not be detected using HPLC.

Next, we were concentrated on constructing spiropyralones **5** with three consecutive stereocenters. Under optimized conditions, we choosed reactants **2** and **3** with different substituent optionally to manipulate the reaction, the results were somehow complicated mainly displaying of poor dr value (1:1) and difficult separation on HPLC (Table 3, entry 14). When an ortho-substituented unsaturated pyrazolone or unsaturated ketone was used, the diastereoselectivity was improved greatly and the results were described in Table 3. When 2-Cl-benzalacetone was utilized, electron-neutral (entry 2), electron-withdrawing (entries 3-4), electron-donating (entries 5-6), and double-substituted (entry 7) unsaturated pyrazolones **2** on the aryl ring were well tolerated and provided reaction products in moderate yields and excellent enantio- and diastereoselectivities; moreover, fused aromatic unsaturated pyrazolone was also suitable substrate for this reaction (entry 8). When 2-Cl-substituted unsaturated pyrazolone was employed, a wide range of unsaturated ketones were also tested. In most cases, the reactions were completed with excellent ee's (>99%) and dr's (>20:1) (entries 9-12) except in the occasion of alkyl-substituted unsaturated ketone with a 2:1 dr value (entry 13). The absolute configuration of the products was determined by X-ray crystallography analysis of compound **5s** (see Supporting Information).[14]

Table 3. Substrate Scope of Cat **1a**/ BzOH-Catalyzed Double Michael Addition of Unsaturated Pyrazolones **2** and Unsaturated Ketones **3** with Different Substituents[a]



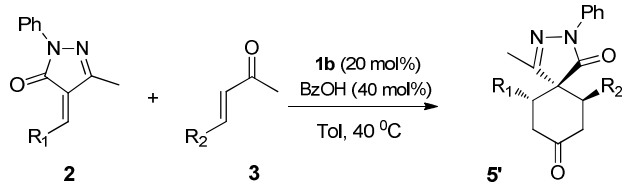
2 **3** **5**

entry	R_1	R_2	**5**	yield [%][b]	ee [%][c]	dr[d]
1	Ph	2-ClPh	**5k**	67	>99	>20:1
2	4-CH_3Ph	2-ClPh	**5l**	63	>99	>20:1
3	4-ClPh	2-ClPh	**5m**	65	>99	>20:1
4	3-ClPh	2-ClPh	**5n**	64	>99	>20:1
5	4-MeOPh	2-ClPh	**5o**	48	>99	>20:1
6	3-MeOPh	2-ClPh	**5p**	52	>99	>20:1
7	3,4-$(CH_3)_2$Ph	2-ClPh	**5q**	54	>99	>20:1
8	2-naphthyl	2-ClPh	**5r**	52	>99	>20:1
9	2-ClPh	4-BrPh	**5s**	69	>99	>20:1
10	2-ClPh	4-MeOPh	**5t**	52	>99	>20:1
11	2-ClPh	Ph	**5u**	68	>99	>20:1
12	2-ClPh	2-furyl	**5v**	50	>99	>20:1
13	2-ClPh	i-Bu	**5w**	67	98	2:1
14	Ph	4-CH_3Ph	**5x**	82	>99	1:1

[a] Unless noted, the reaction was performed on 0.1 mmol scale with **2a** (1.0 equiv), **3a** (2.0 equiv), BzOH (40 mol%) and catalyst **1a** (20 mol%) at 40 °C for 3-12 h. The control comparative experiments details, see the Supporting Information. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Measured by ^{1}H NMR spectroscopic analysis. [d] Determined by HPLC analysis on a chiral stationary phase.

In the initial screening of catalysts, we found that catalyst **1b** also resulted in spiropyrazolones **5'** with comparable yield, enantio- and diastereoselectivity and inversed configuration, so we also tested the generality of the catalytic system and the results were depicted in Table 4. The desired spirocyclic products **5g'-5h', 5l', 5r'-5x'** were obtained in 42-64% yields with 1:1->20:1 dr's and 98- >99% ee's (Table 4, entries 1-10).

Table 4. Substrate Scope of Cat **1b**/ BzOH-Catalyzed Double Michael Addition of Unsaturated Pyrazolones **2** and Unsaturated Ketones **3**[a]



2 **3** **5'**

entry	R_1	R_2	**5'**	yield [%][b]	ee [%][c]	dr[d]
1	3-ClPh	3-ClPh	**5g'**	57	>99	>20:1
2	3-MeOPh	3-MeOPh	**5h'**	63	>99	>20:1
3	4-CH_3Ph	2-$ClPh_4$	**5l'**	61	>99	>20:1
4	2-naphthyl	2-ClPh	**5r'**	50	>99	>20:1
5	2-ClPh	4-BrPh	**5s'**	55	>99	>20:1
6	2-ClPh	4-MeOPh	**5t'**	64	>99	>20:1
7	2-ClPh	Ph	**5u'**	48	>99	>20:1
8	2-ClPh	2-furyl	**5v'**	52	>99	>20:1
9	2-ClPh	i-Bu	**5w'**	54	98	2:1
10	Ph	4-CH_3Ph	**5x'**	42	>99	1:1

[a] Unless noted, the reaction was performed on 0.1 mmol scale with **2a** (1.0 equiv), **3a** (2.0 equiv), BzOH (40 mol%) and catalyst **1a** (20 mol%) at 40 °C for 3-12 h. The control comparative experiments details, see the Supporting Information. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Measured by ^{1}H NMR spectroscopic analysis.

Conclusions

In summary, we have developed the first organocatalytic double Michael cascade reaction of unsaturated ketones and unsaturated pyrazolones that provides spiropyrazolones core structures with two interval or three consecutive stereogenic centers, including a spiro quaternary center with excellent diastereo- (>20:1) and enantioselectivities (up to 99% ee). Moreover, a pair of enantiomers **5a** and **5a'** can be achieved via different catalysit. This simple and effective reaction provides rapid entry to stereochemically complex spiropyrazolones derivatives.

Acknowledgment

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†Electronic Supplementary Information (ESI) available: Experimental procedure,characterization dataand NMR spectraof the products. See DOI: 10.1039/b000000x

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14 CCDC 907183 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.

Table 1.

entry	Cat	solvent	Time[h]	yield[%][b]	ee[c]
1	**1a**	Toluene	120	-	-
2[d]	**1a**	Toluene	72	87	>99
3[d,f]	**1b**	Toluene	72	81	>99
4[d]	**1c**	Toluene	120	76	93
6[d]	**1a**	MTBE	72	59	96
7[d]	**1a**	THF	72	55	86
8[d]	**1a**	CH_2Cl_2	72	79	93
9[d]	**1a**	MeCN	72	46	84
10[d,e]	**1a**	Toluene	3.5	85	>99
11[d,e,f]	**1b**	Toluene	3.5	80	>99

Table 2.

entry	**5**	R	yield[%][b]	dr [%][c]	ee[d]
1	**5a**	Ph	87	>20:1	>99
2	**5b**	4-$CH_3C_6H_4$	75	>20:1	>99
3	**5c**	4-FC_6H_4	81	>20:1	>99
4	**5d**	4-ClC_6H_4	88	>20:1	>99
5	**5e**	4-BrC_6H_4	84	>20:1	>99
6	**5f**	4-$MeOC_6H_4$	68	>20:1	>99
7	**5g**	3-ClC_6H_4	83	>20:1	>99
8	**5h**	3-$MeOC_6H_4$	71	>20:1	>99
9	**5i**	2-naphthyl	64	>20:1	>99
10	**5j**	2-furyl	55	>20:1	nd[e]

Table 3.

entry	R_1	R_2	**5**	yield [%][b]	ee [%][c]	dr[d]
1	Ph	2-ClPh	**5k**	67	>99	>20:1
2	4-CH_3Ph	2-ClPh	**5l**	63	>99	>20:1
3	4-ClPh	2-ClPh	**5m**	65	>99	>20:1
4	3-ClPh	2-ClPh	**5n**	64	>99	>20:1
5	4-MeOPh	2-ClPh	**5o**	48	>99	>20:1
6	3-MeOPh	2-ClPh	**5p**	52	>99	>20:1
7	3,4-$(CH_3)_2$Ph	2-ClPh	**5q**	54	>99	>20:1
8	2-naphthyl	2-ClPh	**5r**	52	>99	>20:1
9	2-ClPh	4-BrPh	**5s**	69	>99	>20:1
10	2-ClPh	4-MeOPh	**5t**	52	>99	>20:1
11	2-ClPh	Ph	**5u**	68	>99	>20:1
12	2-ClPh	2-furyl	**5v**	50	>99	>20:1
13	2-ClPh	i-Bu	**5w**	67	98	2:1
14	Ph	4-CH_3Ph	**5x**	82	>99	1:1

Table 4.

entry	R_1	R_2	**5'**	yield [%][b]	ee [%][c]	dr[d]
1	3-ClPh	3-ClPh	**5g'**	57	>99	>20:1
2	3-MeOPh	3-MeOPh	**5h'**	63	>99	>20:1
3	4-CH_3Ph	2-$ClPh_4$	**5l'**	61	>99	>20:1
4	2-naphthyl	2-ClPh	**5r'**	50	>99	>20:1
5	2-ClPh	4-BrPh	**5s'**	55	>99	>20:1
6	2-ClPh	4-MeOPh	**5t'**	64	>99	>20:1
7	2-ClPh	Ph	**5u'**	48	>99	>20:1
8	2-ClPh	2-furyl	**5v'**	52	>99	>20:1
9	2-ClPh	i-Bu	**5w'**	54	98	2:1
10	Ph	4-CH_3Ph	**5x'**	42	>99	1:1