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Asymmetric Synthesis of Pyrazolone Fused Spirocyclohexeneimines via a Vinylogous Michael Reaction/Cyclization Cascade

Sara Meninno,[a] Andrea Mazzanti,[b] and Alessandra Lattanzi[a]*

[a] Dipartimento di Chimica e Biologia "A. Zambelli", Università di Salerno, Via Giovanni Paolo II 132, I-84084, Fisciano, Italy
[Fax: (+39)-089-969603; phone: (+39)-089-969563
E-mail: lattanzi@unisa.it
[b] Dipartimento di Chimica Industriale "Toso Montanari", Università di Bologna, V. Risorgimento 4, I-40136 Bologna, Italy

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Abstract. Diastereoisomeric pyrazolone-fused spirocyclohexenimines, bearing contiguous all-carbon quaternary and tertiary stereocenters, are readily synthesized for the first time in good to excellent yield (up to 98%) and high enantioselectivity (up to 97% ee) via vinylogous Michael reaction/cyclization cascade of α-arylidene pyrazolones and α,α-dicyanoalkylidenes. The formal [4+2] atom-economical annulation proceeds with commercially available Takemoto's catalyst under mild reaction conditions. Easy scale-up and hydrolytic post-transformation were also demonstrated.

Keywords: asymmetric synthesis; organocatalysis; spirocyclic compounds; dicyanoalkenes; cascade reactions

The interest of chemists toward the asymmetric synthesis of spirocyclic compounds constantly increased in the last decade.[1] This is a highly challenging goal in organic synthesis as the quaternary stereocenter links two cyclic compounds, often decorated with additional tertiary or quaternary stereocenters, whose stereochemistry has to be controlled. Most of these studies were inspired by natural and synthetic bioactive compounds, bearing heterocyclic and carbocyclic units, with the idea to create new hybrid spirocylic compounds of potentially widespread biological activities. Among the classes of spirocyclic compounds, those bearing the pyrazolone unit and the carbocyclic cyclohexane,[2] cyclohexanone,[3] cyclohexenone[4] and cyclohexadiene rings,[5] have attracted considerable interest due to their relevance in medicinal chemistry (Figure 1).[6] Some selected examples, illustrated in Figure 1, showed that these compounds display diverse and valuable biological activities as phosphodiesterase inhibitor,[2b] antimicrobial,[3a] anticancer[4] and anti-inflammatory agents.[7]

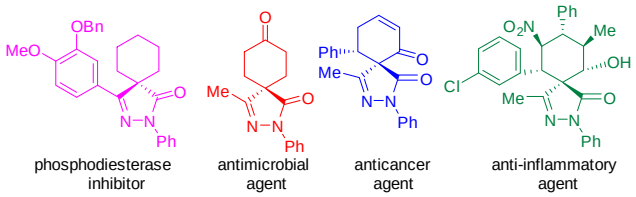
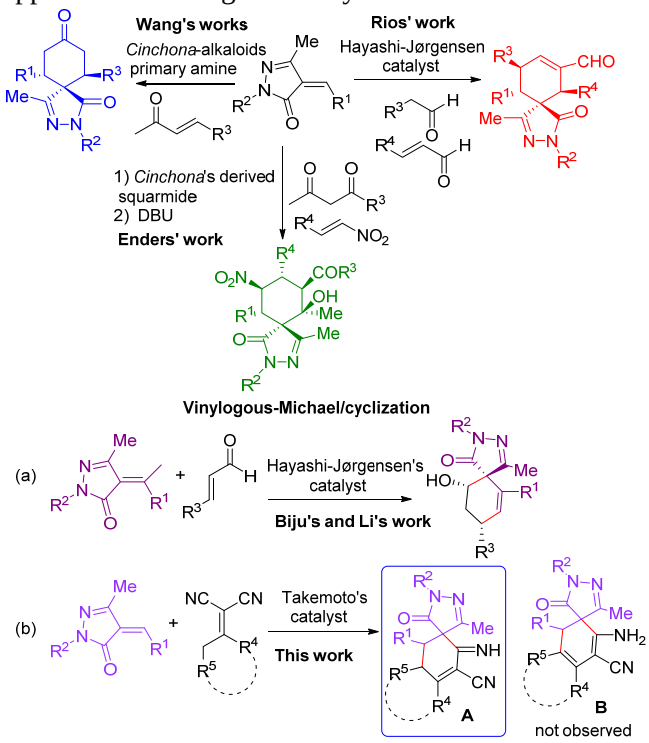


Figure 1. Representative examples of bioactive spiropyrazolones containing six-membered rings.

From a synthetic point of view, the methodologies designed to prepare these compounds essentially relied on organocatalytic cascade double Michael reaction or double Michael reaction followed by aldol reaction.[8] These practical approaches successfully guaranteed mild and environment friendly conditions as well as high control of the stereoselectivity. In this context, α-alkylidene pyrazolinones have been used as Michael acceptors to obtain a few complex spirocyclic cyclohexane derivatives, bearing quaternary and tertiary stereocenters, as demonstrated by the groups of Rios,[9] Wang[3c,10] and Enders[11] (Scheme 1). The organocatalytic approaches were successfully developed using popular Hayashi-Jørgensen's catalyst and *Cinchona* alkaloids derived primary or tertiary amines. Very recently, Biju[12] and Li[13] applied a less investigated approach based on vinylogous Michael/aldol cascade using the α-alkylidene pyrazolinones as vinylogous enolates and α,β-unsaturated aldehydes as acceptors, using the Hayashi-Jørgensen catalyst to give the pyrazolone-fused spirocyclohexenols in good yields and high stereocontrol (Scheme 1a).

α,α-Dicyanoalkylidenes have been used as versatile nucleophiles in vinylogous Michael/cyclization/tautomerization (Thorpe/-Ziegler cyclization) cascade reactions to obtain racemic spirocyclic compounds incorporating indole,[14] barbituric acid,[15] 1,3-indandione,[15] thioheterocycles.[16]

However, only rare reports illustrated enantioselective variants.[17] In all these approaches, the isolated products were of type **B**, tautomers of the firstly formed imines of type **A** (Scheme 1b). To the best of our knowledge, racemic mixtures of diastereoisomeric spirocyclic imines have been described in a DBU-catalysed cascade reaction of 3-methyleneoxindoles with 2-(3,4-dihydronaphthalen-1(2H)-ylidene) malononitrile.[18] Interestingly, indole fused spirocyclohexanimines showed to have potent antitubercular activity.[19] The stereoselective construction of structurally diverse spiropyrazolones represents still a significant challenge and no example of pyrazolone fused spirocyclohexenimines has been reported. Hence, new methods which account for their formation are of synthetic interest in view of applications in drug discovery.



Scheme 1. Organocatalytic strategies for the asymmetric synthesis of spiroyrazolone-cyclohexane derivatives.

As part of a research program focused on the stereoselective synthesis of spiropyrazolone fused heterocycles,[20] we devised a complementary pathway to new spiropyrazolones incorporating six-membered ring architectures, via an organocatalyzed strategy based on vinylogous Michael/cyclization cascade of α,α-dicyanoalkylidenes with α-alkylidene pyrazolinones (Scheme 1b). Herein, we report a first enantioselective synthesis of pyrazolone fused spirocyclohexenimines, which effectively proceeds at room temperature with high enantioselectivity, using commercially available Takemoto's catalyst.

The process was initially studied by reacting α-alkylidene pyrazolinone **1a** and 2-(3,4-dihydronaphthalen-1(2H)-ylidene) malononitrile **2a** in toluene at room temperature using 10 mol% of bifunctional organocatalysts (Table 1).

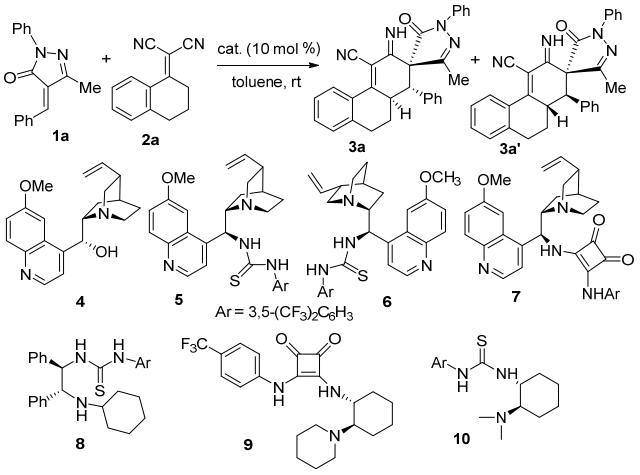


Table 1. Catalyst screening.[a]

Entry	Cat.	t [h]	Yield [%][b]	**3a**/**3a'**[c]	ee **3a**/**3a'** [%][d]
1[e]	**4**	42	85	20/1	4/nd
2	**5**	5	54	35/65	-80/-55
3	**6**	5	55	60/40	68/62
4	**7**	41	<5	nd	nd
5	**(DHQD)$_2$PYR**	24	20	60/40	nd
6	**8**	24	15	40/60	nd
7	**9**	24	18	50/50	nd
8	**10**	4.5	90	55/45	91/92

[a] Reactions were performed at 0.08 mmol scale of **1a** (*C* 0.2 M) and **2a** (1.5 equiv).
[b] Yield of both isolated diastereoisomers.
[c] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[d] Determined by chiral HPLC analysis. Negative sign indicates enantiomeric excess for the opposite enantiomer.
[e] 20 mol % of catalyst was used.

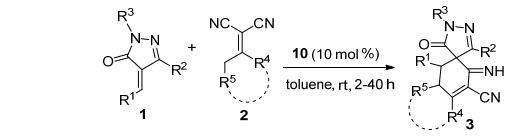
Quinine **4**, used at 20 mol%, provided the pyrazolone fused spirocyclohexenimine **3a** with high diastereoselectivity in almost racemic form, without observing tautomeric isomers of type **B** (entry 1). *Cinchona* alkaloids derived thiourea **5** afforded, in a more efficient manner, a diastereoisomeric mixture of compounds **3a** and **3a'** in 54% yield and with 80% and 55% ee values, respectively (entry 2). The pseudoentiomeric promoter **6** behaved in a comparable manner in terms of diastereoselectivity and enantioselectivity (entry 3). Surprisingly, the

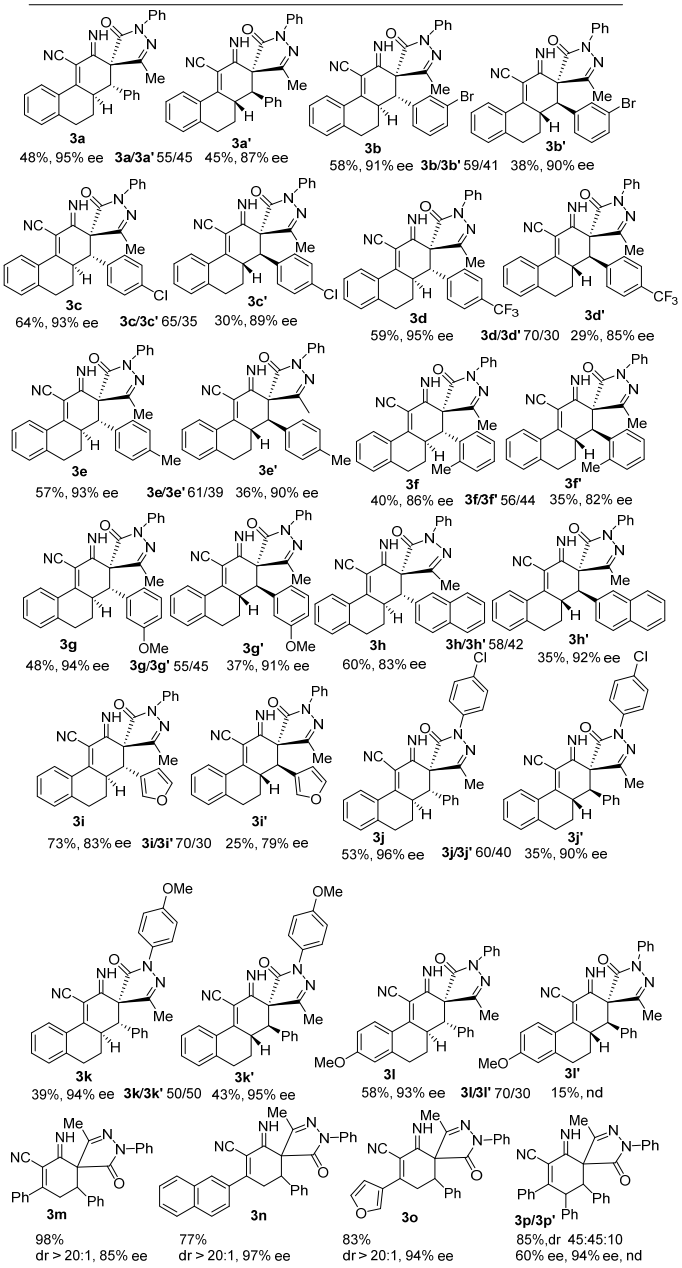
corresponding squaramide **7** was completely ineffective (entry 4). Dimeric hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether **(DHQD)$_2$PYR**, poorly promoted the process (entry 5). Amine-thiourea **8**, previously employed as a valuable organocatalyst by our group in tandem reactions,[21] did not work (entry 6). Commercially available 1,2-cyclohexanediamine derived squaramide **9** and Takemoto's thiourea **10** were then checked. Squaramide **9** likewise **7** showed to be a poor promoter (entry 7). To our delight, the process was efficiently catalyzed by Takemoto's thiourea **10**, providing in a short reaction time, both diastereoisomers **3a**/**3a'** in similar ratio, 90% overall yield and high enantioselectivity (entry 8). This promising result prompted us to conduct further studies on this process employing catalyst **10**. Solvent and other parameters were optimized on reaction of compounds **1a** and **2a,** enabling the determination of the best reaction conditions to access the compounds in enantioenriched form.[22]

The scope of the cascade reaction was assessed reacting α-alkylidene pyrazolinones **1** and α,α-dicyanoalkylidenes **2** with catalyst **10** at 10 mol% loading in toluene at room temperature (Table 2). Various α-alkylidene pyrazolinones, bearing electron-withdrawing and electron-releasing groups at different position in the phenyl ring, reacted smoothly with 2-(3,4-dihydronaphthalen-1(2H)-ylidene) malononitrile **2a** to give diastereoisomers **3a-g/3a'-g'** in generally comparable amounts, high overall yields and enantioselectivity. Interestingly, the *ortho*-substituted alkene **1** yielded both diastereoisomers **3f**/**3f'** with good ee values. The cascade process was compatible with β-naphthyl and β-heteroaryl substituted α-alkylidene pyrazolinones **1**, whose products **3h**,**i**/**3h'**,**i'** were isolated in high overall yields and good to high ee values. Aryl substitution at nitrogen of the unsaturated pyrazolinones or in the 2-(3,4-dihydronaphthalen-1(2H)-ylidene) malononitrile was tolerated, observing high conversion and excellent ee values for compounds **3j**,**k**,**l**,/**3j'**,**k'**,**l'**.[23] Unfortunately, the reaction was incompatible with α-alkylidene pyrazolinones, bearing an alkyl group (R^1) or more sterically demanding group (R^2) at position 3 of the pyrazolone moiety, which showed to be unreactive. However, other α,α-dicyanoalkylidenes derived from acyclic aromatic and heteroaromatic methyl ketones proved to be useful reagents for the process. In this case, the corresponding pyrazolone fused spirocyclohexenimines **3m-o** were isolated with excellent diastereocontrol, high yields and ee values, ranging from 85% to 97%. Finally, the α,α-dicyanoalkylidene derived from 1,2-diphenylethan-1-one, when reacted with alkene **1a**, afforded essentially two diastereoisomers **3p**/**3p'**in equal ratio, showing 60% ee and 94% ee, respectively.

The relative configuration of diastereoisomers **3c** and **3c'** was determined by NOE-NMR and simulation of the NMR coupling constants of the aliphatic region.

Table 2. Substrate scope and limitations.[a]





[a] Reactions were performed at 0.1 mmol scale of **1** (*C* 0.2 M) and **2** (1.5 equiv).
[b] Yield of isolated single diastereoisomer.
[c] Dr ratio determined by ^{1}H NMR analysis of the crude reaction mixture.
[d] Determined by chiral HPLC analysis.

The absolute configurations of **3c** (1*S*,2*R*,10a*R*) and **3c'** (1*R*,2*R*,10a*S*) were determined by TD-DFT simulation of the electronic circular dichroism (ECD) spectra (Figure 2).[22] According to these data, a plausible mechanism for the enantioselective formation of diastereisomers of type **3a** and **3a'** is proposed in Figure 3.

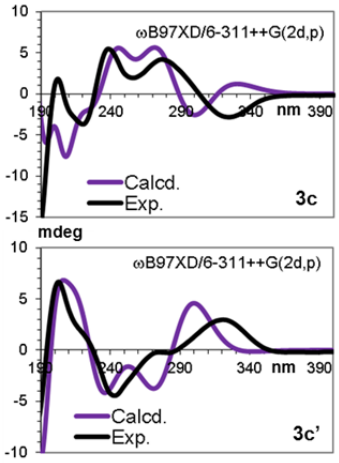


Figure 2. Experimental and calculated ECD spectra for compounds **3c** and **3c'**.

The bifunctional catalyst **10** is able to deprotonate the α,α-dicyanoalkylidene at γ-position to give a carbanion, whereas the thiourea group is engaged via H-bonding with the α-arylidene pyrazolone. Two plausible transition states are likely involved in pathways (a) and (b), leading to adducts **I** and **II**, respectively. Thorpe-Ziegler cyclization of adducts onto the cyano groups would give products **3a** and **3a'**.[24]

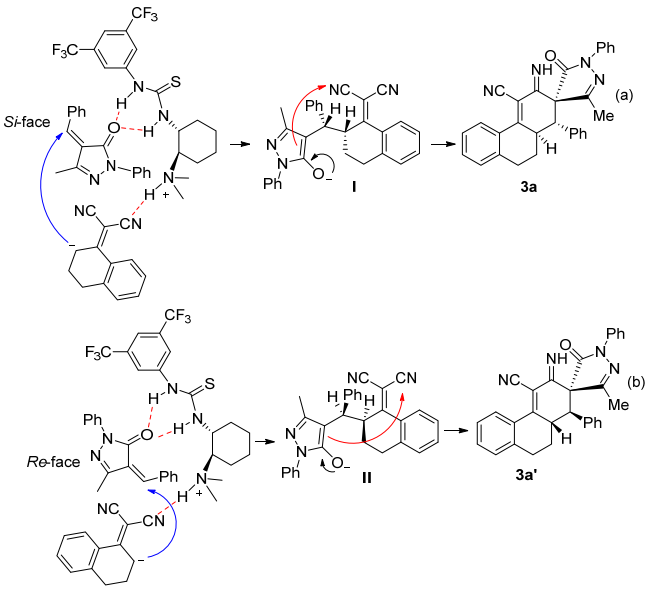
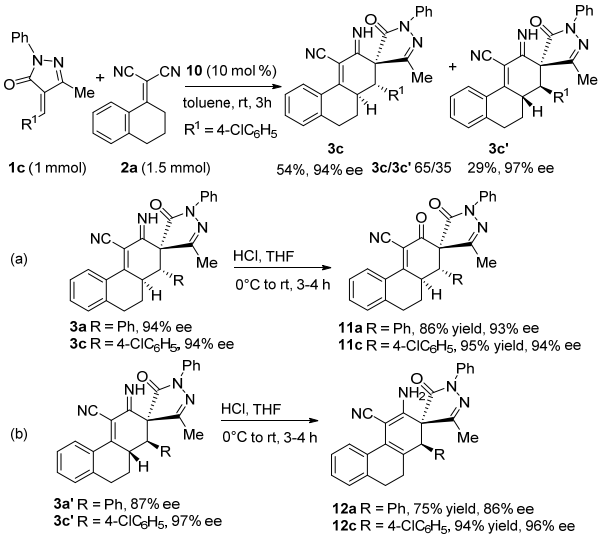


Figure 3. Proposed pathway of the cascade process.

The versatility of the methodology was demonstrated by scaling up the reaction of alkene **1c** and 2-(3,4-dihydronaphthalen-1(2H)-ylidene) malononitrile **2a** to 1 mmol, under standard conditions (Scheme 2). The reaction proceeded well, affording the spirocyclic imines **3c**/**3c'** in 83% overall yield, 65/35 ratio and improved enantioselectivity, respectively 94% and 97% ee.

Acid hydrolysis of compounds **3a**,**c**/**3a'**,**c'** was next studied. Compounds **3a**,**c** selectively led to the unsaturated α-cyano ketones **11a**,**c** in high yields, without erosion of the enantioselectivity (Scheme 2a). Cyclic β-oxoalkenenitriles are useful electrophilic intermediates[25] and polycyclic β-oxoalkenenitriles showed to be potent inhibitors of the enzyme 5α-reductase.[26] In contrast, diastereoisomers **3a'**,**c'**, treated under the same conditions, underwent tautomerization to compounds **12a**,**c** maintaining the level of enantioselectivity (Scheme 2b). Although further investigation on the kinetics is needed, calculations of the reaction free energies suggest that formation of the enamine **12c** from compound **3c'** is energetically favored with respect to the ketone.[22]



Scheme 2. Scale-up process and hydrolytic elaboration.

The opposite trend has been determined when starting from compound **3c**, in agreement with the experimental results.[22]

In conclusion, we developed a catalytic, atom-economical formal [4+2] annulation of readily available α-arylidene pyrazolones and α,α-dicyanoalkylidenes, which selectively led to diastereoisomeric pyrazolone-fused spirocyclohexenimines in high yields and enantioselectivity. To the best of our knowledge this is the first example of a catalytic enantioselective access to spirocyclic cyclohexenimines, expanding the arena of pyrazolinone based spirocyclohexane derivatives potentially useful in medicinal chemistry.[27] Mild reaction conditions, commercial availability of the organocatalyst and feasibility of scale-up are other attractive features of the process.

Experimental Section

A screw cap glass vial equipped with a magnetic stirring bar was charged with unsaturated pyrazolone **1** (0.10 mmol), olefin **2** (0.15 mmol), catalyst **10** (4.1 mg, 0.01 mmol) and dry toluene (0.5 mL). The resulting mixture was stirred at room temperature and the reaction completion checked by TLC (PE/EtOAc 8/2). The

diastereoisomeric ratio was determined by ^{1}H-NMR analysis of the crude reaction mixture. The crude reaction mixture was then directly loaded into the column and purified by flash chromatography (hexane/EtOAc 98/2 to 80/20) to afford chiral compounds **3**.

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