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COMMUNICATION

Highly enantioselective cascade synthesis of spiropyrazolones†‡

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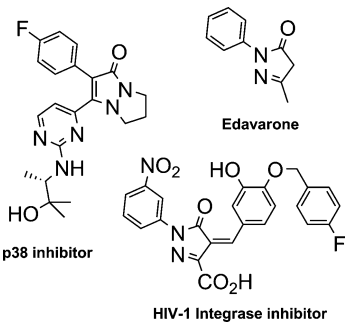
An efficient synthesis of spiropyrazolones based on organocatalysis is described. The reaction between pyrazolones, enolizable aldehydes and enals is catalyzed by secondary amine catalysts and affords the final spiro compounds bearing four contiguous chiral centers in good yields and excellent diastereo- and enantioselectivities.

Pyrazol-3-one derivatives are very important intermediates and products in analytical, dye, biological and pharmaceutical chemistry.[1]

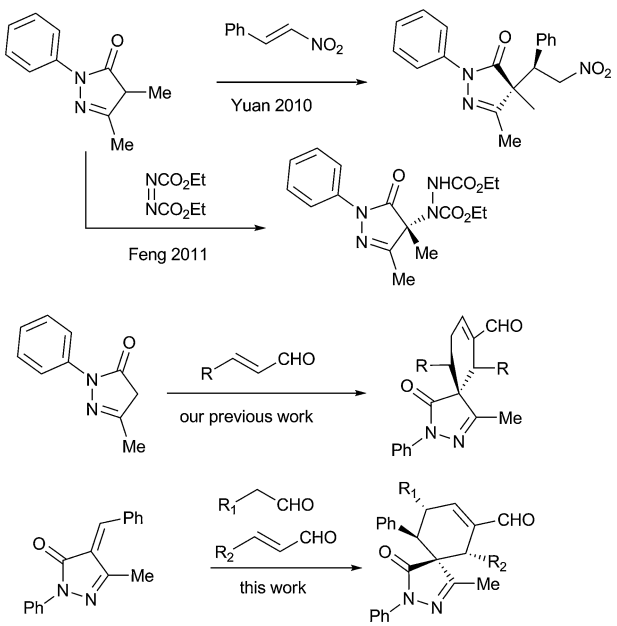
For example, pyrazolone derivatives are used for the extraction and separation of various metal ions and detection and quantification of phenol, cyanides and ammonia. Further pyrazolone-based dyes are widely used as analytical reagents.[2]

In the pharmaceutical industry, pyrazolones have attracted much interest owing to their wide range of biological properties, such as analgesic, antibacterial and antifungal activities,[3] and anti-inflammatory effects,[4] CCR3 antagonist activity,[5] antitumor activity[6] and anti-ischemic effect.[7] Pyrazol-3-ones have been found to act as inhibitors of CD80; moreover they show potent activity in inhibiting the protease-resistant accumulation of prion proteins, cytokines and p38 kinases and have been studied as multidrug resistance modulators (Scheme 1).[8]



Scheme 1 Biologically active pyrazolone derivatives.

Thus the development of asymmetric methodologies to access pyrazolone derivatives with a quaternary stereogenic center at the C-4 position has attracted considerable interest. However, only a few examples have been documented for catalytic asymmetric transformations that yield chiral pyrazolones at C-4. For example, Yuan and co-workers reported a highly enantioselective pyrazolone addition to nitrostyrenes.[9] Very recently, Feng reported the Gd-catalyzed α-amination of pyrazolones with excellent results.[10] Our research group recently carried out a highly stereoselective synthesis of chiral spiropyrazolones *via* a Michael-Michael-aldol reaction (Scheme 2).[11]



Scheme 2 Asymmetric synthesis of pyrazolones.

However, all these methodologies employ pyrazolones as nucleophiles. The use of an unsaturated pyrazolone as an electrophile has been limited to a few non-asymmetric cyloadditions.[12] Encouraged by previous successes in cascade reactions[13] using the oxindole motifs by Melchiorre[14] and others,[15] and by our experience in organocatalysis,[16] we envisioned an easy entry to highly substituted spiropyrazolones *via* a cascade reaction starting with unsaturated pyrazolones.

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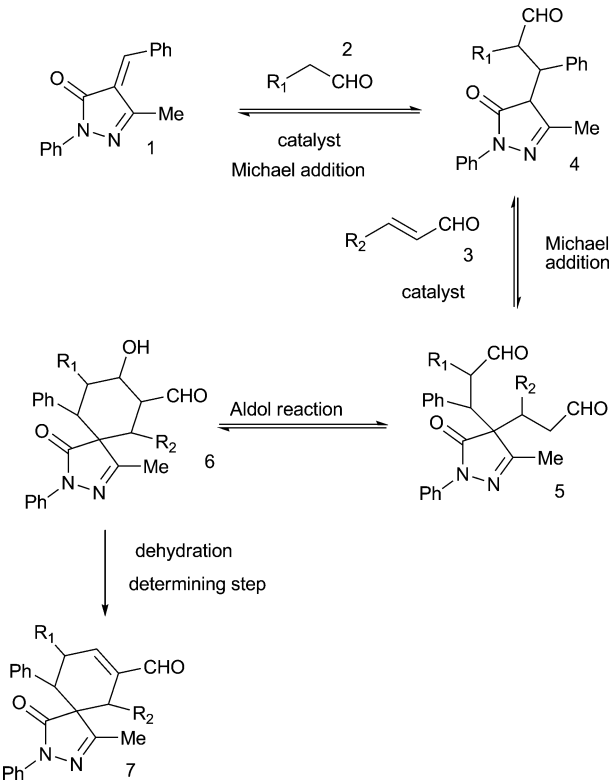
‡ Electronic supplementary information (ESI) available: NMR data and HPLC traces. See DOI: 10.1039/c1ob05753g

Results and discussion

Our strategy first involves a Michael reaction between an enolizable aldehyde and an unsaturated pyrazolone, followed by another Michael reaction between the resulting enolate and an enal. Next, an intramolecular aldol reaction followed by dehydration, which is the determining step of the reaction, is carried out to obtain the final spiropyrazolone (Scheme 3).



Scheme 3 Expected mechanism.

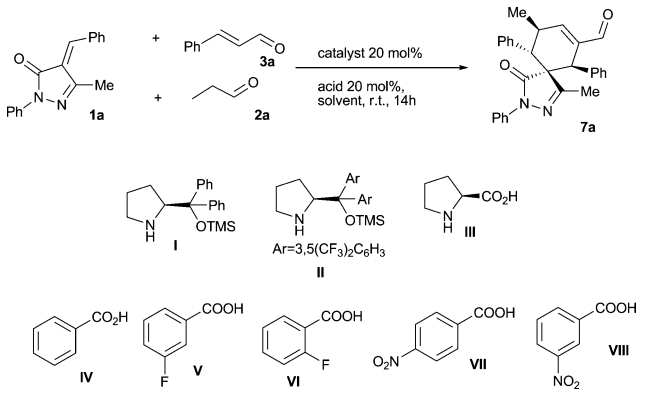
As catalysts for this expected sequence, we considered using secondary amines such as diphenylprolinol derivatives.

To our delight, when enal **3a** was treated in toluene with 2 equiv. of propanal **2a** and 1.5 equiv. of unsaturated pyrazolone **1a** in the presence of 20 mol% of the catalyst and 20 mol% of benzoic acid, the reaction gave the final spirocyclic compound in good yield and excellent stereoselectivity (Table 1; entry 1).

Spurred on by these exceptional results, we decided to optimize the reaction conditions. Remarkably, when no acid was added, the reaction did not proceed (Table 1; entry 3). It should be noted that the use of different benzoic acids did not affect the outcome of the reaction, *i.e.*, all the reactions gave the same result (Table 1; entries 6–9). The use of a highly polar solvent such as DMSO yielded only complex crude mixtures, probably because of aldol side reactions (Table 1; entry 5). The reaction carried out using CH_2Cl_2 gave the final product in low stereoselectivities (Table 1; entry 4). As shown in Table 1, the best results were obtained for the following reaction conditions: toluene as a solvent, 20 mol% of catalyst **I**, and 20 mol% of benzoic acid.

Once we optimized the reaction conditions,§ we decided to explore the scope of the reaction with pyrazolone. As shown in Table 2, the reaction tolerated aromatic and aliphatic substituents

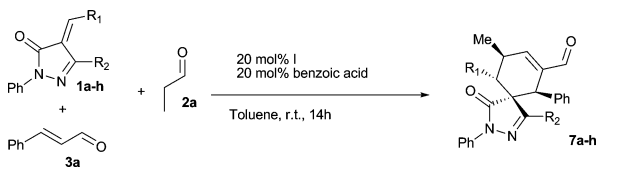
Table 1 Conditions screening[a]



Entry	Catalyst	Acid	Solvent	Conversion[b]	d.r.[c]	ee[d]
1	**I**	**IV**	toluene	100%	>25 : 1	>99%
2	**II**	**IV**	toluene	traces	n.d.	n.d.
3	**III**	—	toluene	n.r.	n.d.	n.d.
4	**I**	**IV**	CH_2Cl_2	100%	1.4 : 1	86%
5	**I**	**IV**	DMSO	traces	n.d.	n.d.
6	**I**	**V**	toluene	100%	>25 : 1	>99%
7	**I**	**VI**	toluene	100%	>25 : 1	>99%
8	**I**	**VII**	toluene	100%	>25 : 1	>99%
9	**I**	**VIII**	toluene	100%	>25 : 1	>99%

[a] 1.0 equiv. of enal **3a**, 1.5 equiv. of pyrazolone **1a** and 2.0 equiv. of aldehyde **2a** in toluene in the presence of 20 mol% of the catalyst and 20 mol% of benzoic acid was stirred overnight at room temperature. [b] Determined by ^{1}H NMR of the crude reaction. [c] Determined by ^{1}H NMR of the crude reaction. [d] Determined by chiral HPLC.

Table 2 Pyrazol-3-one scope[a]

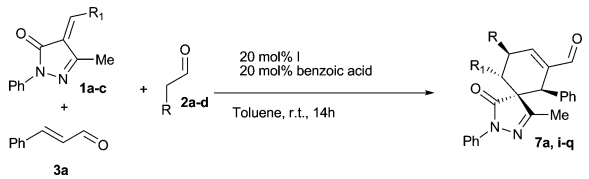


Entry	Pirazolone	7	R^1	R^2	Yield[b]	d.r.[c]	ee[d] (%)
1	**1a**	**7a**	Ph	Me	42%	>25 : 1	>99
2	**1b**	**7b**	*p*Cl-C_6H_4	Me	45%	>25 : 1	>99
3	**1c**	**7c**	*p*CN-C_6H_4	Me	61%	>25 : 1	99
4	**1d**	**7d**	*p*NO_2-C_6H_4	Me	75%	>25 : 1	>99
5	**1e**	**7e**	Et	Me	21%	10 : 1	>99
6[e]	**1f**	**7f**	Ph	Et	29%	10 : 1	>99
7	**1g**	**7g**	Ph	Ph	n.r.	—	—
8	**1h**	**7h**	Ph	*t*-Bu	n.r.	—	—

[a] 1.0 equiv. of enal **3a**, 1.5 equiv. of pyrazolone **1a–h** and 2.0 equiv. of aldehyde **2a** in toluene in the presence of 20 mol% of the catalyst and 20 mol% of benzoic acid was stirred overnight at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude reaction. [d] Determined by chiral HPLC. [e] Reaction run at 60 °C.

at the double bond (Table 2; entries 1 and 5) as well as different functional groups such as NO_2, CN, or Cl (Table 2; entries 2, 3, and 4) in the aromatic rings. However, the reaction with aliphatic unsaturated pyrazolones gave the final compound with low yields owing to the occurrence of side reactions. The only limitation of this methodology is the presence of a highly bulky substituent at C-5. Methyl (42% yield; >25 : 1 d.r.; >99%ee; Table 2; entry 1) and ethyl (29% yield; 10 : 1 d.r.; >99%ee; Table 2; entry 6) derivatives

Table 3 Enolizable aldehyde scope[a]



Entry	Pirazolone	Product	R	Yield[b]	d.r.[c]	ee[d]
1	**1a**	**7a**	Me (**2a**)	42%	>25 : 1	>99%
2[e]	**1a**	**7i**	*i*-Pr (**2b**)	36%	>25 : 1	>99%
3[e]	**1a**	**7j**	Bn (**2c**)	66%	10 : 1	98%
4	**1a**	**7k**	Pr (**2d**)	37%	>25 : 1	98%
5	**1b**	**7m**	Pr (**2d**)	35%	>25 : 1	99%
6[e]	**1b**	**7n**	*i*-Pr (**2b**)	45%	>25 : 1	99%
7	**1c**	**7o**	Pr (**2d**)	47%	7 : 1	>99%
8[e]	**1c**	**7p**	*i*-Pr (**2b**)	52%	7.5 : 1	>99%

[a] 1.0 equiv. of enal **3a**, 1.5 equiv. of pyrazolone **1a–c** and 2.0 equiv. of aldehyde **2a–f** in toluene in the presence of 20 mol% of the catalyst and 20 mol% of benzoic acid was stirred overnight at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude reaction. [d] Determined by chiral HPLC. [e] Reaction run at 60 °C.

gave similar results in terms of selectivity. However, as compared to the methyl derivatives, the ethyl ones required higher reaction temperatures and gave lower yields. Phenyl or *t*-butyl-substituted pyrazolones (Table 2; entries 7 and 8) remained unreacted; this behaviour has been observed in our previous works.[11]

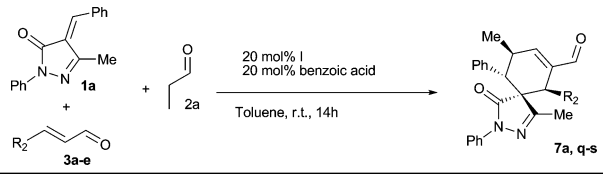
Next, we examined the scope of the reaction with enolizable aldehyde. Table 3 shows that the bulkiness of the aldehyde residue plays an important role in the reaction; the use of a bulky substituent such as *iso*-propyl or benzyl (Table 3; entries 2, 3, 6, and 8) required high reaction temperatures (60 °C). Despite the increase in the temperature, diastereo- and enantioselectivities remained excellent, showing the wide applicability of this methodology with enolizable aldehyde.

Finally, we examined the scope of the reaction with enal. When aromatic enals were used, the final spiro products were obtained in good yields and excellent stereoselectivities. For example, in the case of *p*-Br-cinnamaldehyde or *p*-NO_2-cinnamylaldehyde, the reaction gave the final spirocyclic ring in 45% and 61% yields in diastereo- and enantiopure form, respectively (Table 4; entries 2 and 3). However, when aliphatic enals or the glyoxilate-derived enal were exposed to the reaction conditions, only very complex mixtures were obtained (Table 4; entries 4 and 5).

The relative configuration of the pyrazolone **7a** (Fig. 1) was determined by means of NOE and NOESY NMR experiments (see ESI‡). As it is shown, the relative configuration between the two phenyl groups is, as expected, *trans*, and the relationship between the methyl and the phenyl in position 10 is also *trans*.

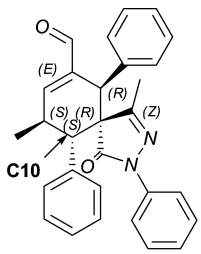
Compound **7a** and the related series miss the heavy atom required for the absolute configuration assignment by the Bijovet method (*i.e.* the anomalous dispersion method).[17] Therefore, the absolute configuration (AC) was assigned by means of chiroptical methods.[18] In the present case, theoretical calculation of ECD spectra was carried out by means of the TD-DFT method, since this technique has been successfully employed several times to predict ECD spectra and to assign the AC of organic molecules.[19] Taking into account the relative configuration obtained by NMR analysis, a conformational search has been carried out using

Table 4 Enal scope[a]



Entry	Product	R^2	Yield[b]	d.r.[c]	ee[d]
1	**7a**	Ph	42%	>25 : 1	>99%
2	**7q**	*p*-Br nC_6H_4	45%	>25 : 1	>99%
3	**7r**	*p*-NO_2 C_6H_4	61%	>25 : 1	99%
4	**7s**	Me	n.r.	—	—
5	**7t**	CO_2Et	n.r.	—	—

[a] 1.0 equiv. of enal **3a–e**, 1.5 equiv. of pyrazolone **1a** and 2.0 equiv. of aldehyde **2a** in toluene in the presence of 20 mol% of the catalyst and 20 mol% of benzoic acid was stirred overnight at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude reaction. [d] Determined by chiral HPLC.



(5*R*,6*R*,9*S*,10*S*)-1,9-dimethyl-4-oxo-3,6,10-triphenyl-2,3-diazaspiro[4.5]deca-1,7-diene-7-carbaldehyde

Fig. 1 Relative configuration of compound **7a**.

Table 5 Calculated relative energies (*E*) and free energies (*G*) of the conformations of **7a** (in kcal mol^{-1}, B3LYP/6-31G(d) level). Populations percentages (*P*) are calculated assuming Boltzmann statistics at $T = 25$ °C

Molecule	Conf	*E*	Pop (ΔE)	$G°$	Pop ($\Delta G°$)
7a	**a**	0.0	98	0.00	96
	b	2.4	2	1.85	4

Monte Carlo searching together with the MMFF94 molecular mechanics force field.[20] All conformations within a 5 kcal mol^{-1} range were then optimized using DFT[21] at the B3LYP/6-31G(d) level,[22] and the harmonic vibrational frequencies of each conformation were calculated at the same level to confirm their stability (no imaginary frequencies were observed), and to evaluate the free energy of each conformation by thermochemistry corrections. After DFT minimization, the MMFF structures clustered in two conformations (**a** and **b**), that are different because of the different disposition of the CHO group (see Fig. 2 and Table 5).

In both conformations, the methyl in position 5 and the phenyl in position 6 occupy the pseudo-equatorial position, whereas the phenyl in position 2 occupies the pseudo-axial position. This relationship is confirmed by the ^{1}H-NMR spectrum where the two CH in positions 5 and 6 exhibit a coupling constant of 10.2 Hz, typical of a *trans*-diaxial relationship.

The energy of the second most stable conformation is remarkably higher (2.0 kcal as total energy, 1.8 kcal mol^{-1}, as free energy difference). This means that the molecule is quite rigid, and this

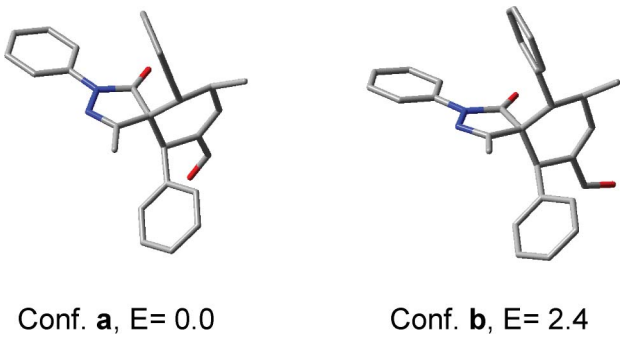


Fig. 2 3D views of the two most stable conformations of compound **7a** (energies in kcal mol^{-1}).

feature enhances greatly the reliability of the method, being the correct evaluation of the relative energy of each conformation its main weakness.

Calculation of the Electronic Circular Dichroism spectra were carried out using the TD-DFT CAM-B3LYP[23]/6-311+G(d,p)//B3LYP/6-31G(d) and TD-DFT BH&HLYP[24]/6-311+G(d,p)//B3LYP/6-31G(d) levels,[25] and assuming 5*R*, 6*R*, 9*S*, 10*S* absolute configuration. Electronic excitation energies and rotational strengths have been calculated for the two conformations, and the rotational strength has been calculated in both the length and velocity representation. The resulting values were very similar, and the errors due to basis set incompleteness should be considered very small.[26] The ECD spectra were then obtained by applying a 0.4 eV Gaussian shaped line width.[27] To cover the 170–400 nm range (see Fig. 3), 75 transitions were calculated for each conformation.

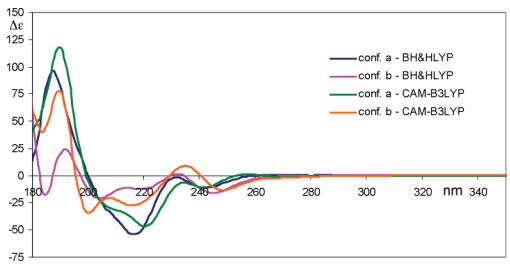


Fig. 3 Calculated ECD spectra for the two conformations of compound **7a**, using the two different models (CAM-B3LYP and BH&HLYP) with the same 6-311+G(d,p) basis set. Vertical scale is Δε, horizontal scale is the wavelength (in nm).

Although the shapes of the spectra calculated for the two conformation **a** and **b** are different, the very small population of the conformation **b** cannot influence the shape of the population weighted spectra at a great extent. The final simulated ECD spectra was obtained taking into account the 96 : 4 population ratios determined starting from the calculated free energies at the B3LYP/6-31G(d) level, and assuming Boltzmann statistics (Fig. 3) The spectra simulated with the two different models are both in good agreement with the experimental one, and the 5*R*, 6*R*, 9*S*, 10*S* configuration can be reliably assigned to compound **7a** when catalyst **I**-(*S*) was used. In addition, the theoretical spectrum obtained by the average of the two simulated spectra simulates even better the experimental trace, by matching the correct wavelength of the two Cotton effects and their intensity ratio (red trace in Fig. 4).

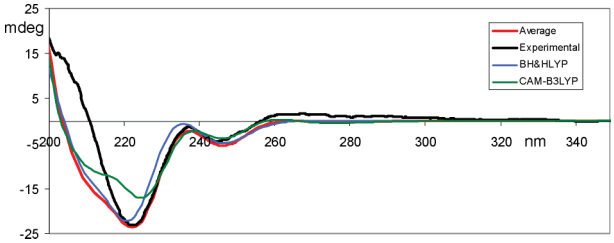


Fig. 4 Experimental ECD spectrum (in black) (using (*S*)-**I** as catalyst) and simulated spectra (blue and green for the BH&HLYP and CAM-B3LYP models, respectively) assuming 5*S*, 6*S*, 9*R*, 10*R* absolute configuration. The red line corresponds to a simulated spectrum obtained by averaging the two simulated spectra. The vertical scale is in mdeg, and the simulated spectra have been scaled accordingly. The simulated spectra have been red-shifted by 6 nm in order to match the experimental trace.

Conclusions

In conclusion, we have developed a new organocatalytic cascade reaction for obtaining spiropyrazolones with four chiral centers in excellent yields and stereoselectivities. Further studies on the application of this reaction to the total synthesis as well as the biological evaluation of the resulting spiropyrazolones are currently in progress in our laboratories.

Acknowledgements

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Notes and references

§ **Typical Experimental Procedure**: In a small flask, pyrazolone **1a** (0.375 mmol, 1.5 equiv.), propanal **2a** (0.5 mmol, 2.0 equiv.) enal **3a** (0.25 mmol, 1 equiv.), catalyst I (0.05 mmol, 0.2 equiv.) and benzoic acid (0.05 mmol, 0.2 equiv.) were added in 1 mL of toluene. The reaction was stirred 14 h at room temperature and it was monitored by ^{1}H NMR. Next, the crude was directly purified by flash chromatography to render 0.046 g of **7a** (42% yield).

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