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PAPER

Organocatalytic enantioselective pyrazol-3-one addition to maleimides: Reactivity and stereochemical course†

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The enantioselective synthesis of pyrazol-3-ones has not been extensively studied in organic synthesis. Here in we report the first asymmetric addition of pyrazolones to maleimides catalyzed by bifunctional thiourea catalysts.

Introduction

Pyrazolones[1] are important structural motifs in several biologically active compounds: antibacterials,[2] antifungals,[3] anti-inflammatories,[4] CCR3 antagonists,[5] and antitumor[6] and anti-ischemic[7] drugs. Pyrazol-3-ones have been found to inhibit CD80; strongly inhibit protease-resistant prion protein accumulation, cytokines, and p38 kinases; and even exhibit multidrug resistance modulation (Scheme 1).[8] Despite their importance, however, only few asymmetric methodologies have been developed for the synthesis of chiral pyrazolones. Similar heterocycles have attracted more interest for organic chemists, such as oxindoles,[9] benzofuranones,[10] and oxazolones;[11] however, very recently, there has been growing activity in the development of new asymmetric methodologies for the synthesis of chiral pyrazol-2-ones.

For example, in 2010, Yuan and co-workers reported a highly diastereo- and enantioselective pyrazol-3-one addition to nitroalkenes using bifunctional thioureas as catalysts.[12] Our research group has developed different methodologies for the synthesis of spiropyrazol-3-ones, *via* a Michael–Michael–aldol cascade reaction, with excellent results (Scheme 2).[13]

In 2011, Feng and co-workers developed a scheme for amination of pyrazol-3-ones *via* nucleophilic attack of diazodicarboxylates catalyzed by Gd salts. The final compounds were obtained in excellent yields and enantioselectivity.[14]

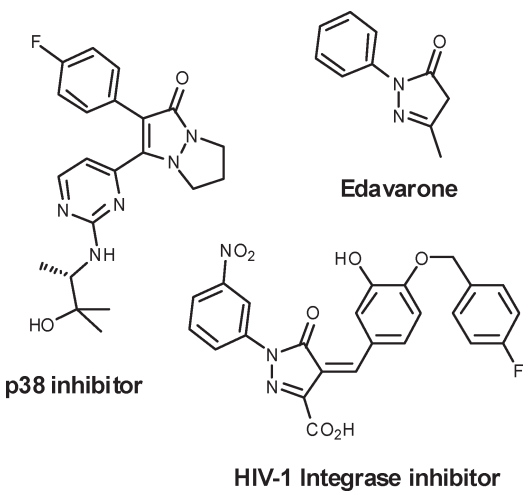
Maleimides have been extensively used in organocatalysis as Michael acceptors. Since the first report on the addition of 1,3-dicarbonyl compounds to maleimides by Bartoli and Melchiorre and up to the most recently reported schemes for oxazolone or benzofuranone addition to maleimides, maleimides have shown a great utility in the synthesis of complex and highly functionalized structures.[15]

On the basis of these previous reports and our experience in organocatalysis,[16] we envisioned achieving easy access to highly functionalized chiral pyrazolones *via* an unprecedented Michael[17] reaction between 4-alkyl-pyrazol-3-ones and maleimides.

Results and discussion

To our delight, when pyrazol-3-one **1a** was treated with maleimide **2a** in toluene at room temperature in the presence of catalyst **III**, the desired addition product was obtained in good yields and high diastereoselectivity.

Next, we decided to optimize the reaction conditions to obtain an enantioselective version of the reaction. As shown in Table I,



Scheme 1 Biologically active pyrazolone derivatives.

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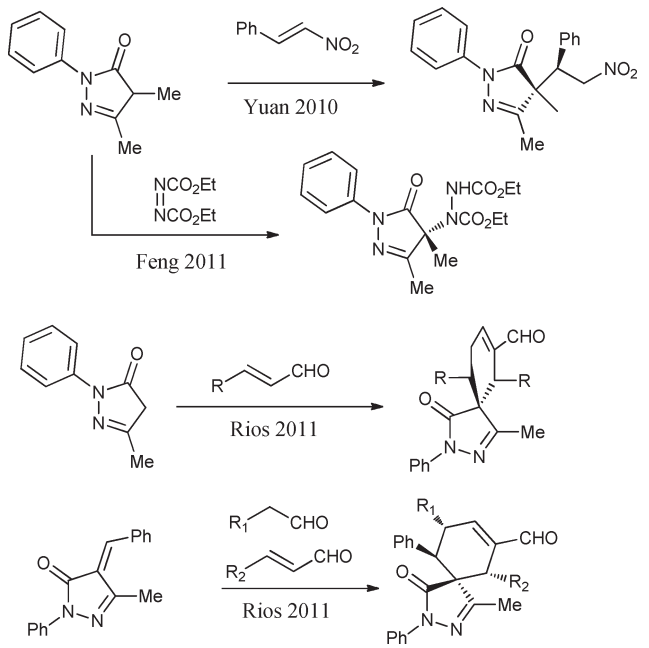


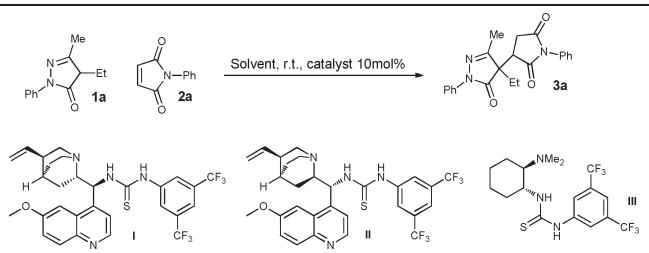
Scheme 2 Enantioselective reactions with pyrazol-3-ones.

enantioselectivity decreased (entries 2, 3, and 6); and when DMSO or DMF was used as the solvent, only traces of the final product were obtained. However, in all the examples, the diastereoselectivity was excellent, although the enantioselectivity was highly dependent on the nature of the catalyst: the best enantioselectivity was obtained with Takemoto thiourea[18] (entry 1, Table 1); chiral bases such as quinine, quinidine, and Sharpless' ligand can catalyze the reaction, albeit with low enantioselectivity (entries 7–14; Table 1). Surprisingly, decreases in temperature did not increase the enantioselectivity or greatly increase the reaction time (entry 15; Table 1).

After the optimized reaction conditions had been identified, we shifted our focus to the scope of the reaction. First, we performed the reaction with different maleimides.

As shown in Table 2, the substituent at the N position in the maleimide has great influence on stereoselectivity. In all the examples, the final adducts were obtained in excellent yields. However, when *N*-aliphatic maleimides were used, the stereoselectivity decreased dramatically (entries 7, 8; Table 2). In addition, *N*-(4-substituted-aryl) maleimides afforded the final products in excellent diastereoselectivity and moderate-to-good enantioselectivity (entries 1–6, 9; Table 2). Finally, *N*-(2-substituted-aryl) maleimides achieved high enantioselectivity (entries 10 and 11; Table 2, but with low diastereoselectivity. This suggests a strong π-interaction between the aryl group of the maleimide and the bistrifluoromethyl benzene ring of the catalyst.

Table 1 Screening conditions[a]



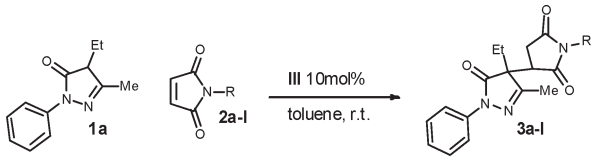
Entry	Solvent	Catalyst	Conversion[b]	d.r.[c]	e.e.[d]
1	toluene	**III**	100%	>10 : 1	80%
2	$CHCl_3$	**III**	100%	>10 : 1	52%
3	AcOEt	**III**	100%	>10 : 1	30%
4	DMSO	**III**	traces	>10 : 1	0%
5	DMF	**III**	traces	>10 : 1	2%
6	THF	**III**	100%	>10 : 1	28%
7	toluene	**I**	100%	>10 : 1	46%
8	toluene	**II**	100%	>10 : 1	12%
9	toluene	quinine (**IV**)	100%	>10 : 1	−52%
10	toluene	quinine (**IV**)	100%	>10 : 1	52%
11	toluene	$(DHQ)_2PYR$ (**VI**)	100%	>10 : 1	15%
12	toluene	$(DHQD)_2PHAL$(**VII**)	100%	>10 : 1	2%
13	toluene	$(DHQD)_2AQN$(**VIII**)	100%	>10 : 1	0%
14	toluene	$(DHQ)_2PYR$ (**IX**)	100%	>10 : 1	−17%
15[e]	toluene	**III**	100%	>10 : 1	65%

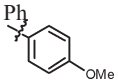
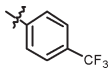
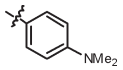
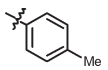
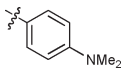
[a] 1.0 equiv. of pyrazol-3-one **1a**, 1.5 equiv of maleimide **2a** in 1 mL of toluene in presence of 10 mol% catalyst were stirred at room temperature for 14 h. [b] Determined by ^{1}HNMR of the crude reaction. [c] Determined by ^{1}HNMR of the crude reaction. [d] Determined by chiral HPLC [e] Reaction run at −20 °C, 96 h.

the reaction was performed in different solvents with chiral bases and bifunctional thiourea as catalysts.

The reaction is efficiently catalyzed by bases or bifunctional catalysts, reaching full conversion to the final compounds in 14 h. When $CHCl_3$, AcOEt, or THF was used, the

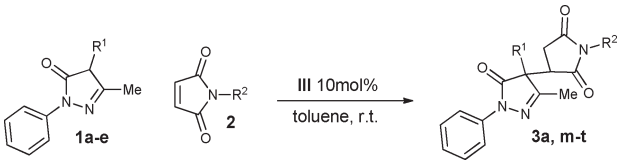
Table 2 Maleimide scope[a]



Entry	R	Product	Yield (%)[b]	d.r.[c]	e.e.[d]
1	Ph	**3a**	84	>10 : 1	80%
2		**3b**	83	7 : 1	60%
3		**3c**	78	10 : 1	50%
4		**3d**	88	10 : 1	40%
5		**3e**	92	10 : 1	84%
6		**3f**	79	10 : 1	38%
7		**3g**	93	3 : 1	18%/74%
8		**3h**	92	1 : 1	42%/80%
9		**3i**	88	10 : 1	50%
10		**3j**	83	2.5 : 1	90%/n.d.
11		**3l**	87	1.5 : 1	87%/n.d.

[a] 1.0 equiv. of pyrazol-3-one **1a**, 1.5 equiv of maleimide **2a–l** in 1 mL of toluene in presence of 10 mol% catalyst **III** were stirred at room temperature for 14 h. [b] Isolated yield. [c] Determined by ^{1}HNMR of the crude reaction. [d] Determined by chiral HPLC.

Table 3 Pyrazol-3-one scope[a]



Entry	R^1	R^2	Product	Yield (%)[b]	d.r.[c]	e.e.[d]
1	Et		**3a**	84	>10 : 1	80%
2	Me		**3m**	82	>10 : 1	64%
3	Me		**3n**	86	>10 : 1	79%
4	Me		**3o**	74	1.5 : 1	86%/n.d
5	Bn		**3p**	85	1.6 : 1	53%/n.d
6	Bn		**3q**	88	10 : 1	n.d.
7	iPr		**3r**	85	>10 : 1	55%
8	iPr		**3s**	90	>10 : 1	66%
9	Ph		**3t**	89	>10 : 1	37%

[a] 1.0 equiv. of pyrazol-3-one **1a–e**, 1.5 equiv of maleimide **2a**, **e**, **j**, **k** in 1 mL of toluene in presence of 10 mol% catalyst **III** were stirred at room temperature for 14 h. [b] Isolated yield. [c] Determined by ^{1}HNMR of the crude reaction. [d] Determined by chiral HPLC

Next, we decided to explore the scope of the reaction in terms of the pyrazolone moiety. As shown in Table 3, the reaction affords the final products in good yields in all the examples. However, the stereoselectivity of the reaction seems to be very dependent of the bulkiness at the C-5 position of the pyrazolone. In fact, increasing the steric hindrance of the pyrazolone ring decreases the enantioselectivity of the reaction dramatically (entries 1, 2, 5, 7, 9; Table 3). As observed previously, substitution of groups of the maleimide has considerable influence on the stereoselectivity of the reaction: when 2-substituents were placed on the aryl ring of the maleimide, the diastereoselectivity decreased and the enantioselectivity increased.

The relative configuration of compound **3c** was determined by means of X-ray crystallography. Unfortunately, it crystallizes in the centrosymmetric *C*2/*c* space group and any attempt to crystallize a single enantiomer from the enantioenriched mixture gave good crystals containing the racemate. For this reason the X-ray data yield the relative stereochemistry of the two chiral carbons and suitable information about the molecular conformation whereas the assignment of the absolute configuration by the anomalous dispersion method[19] is precluded. The relative configuration derived from X-ray analysis is 3*R**,4*S**(C8 and C13 respectively).

For this reason, the absolute configuration (AC) was assigned by means of chiroptical methods.[20] In the present case, theoretical calculations of Electronic Circular Dichroism (ECD) and Vibrational Circular Dichroism (VCD) spectra were carried out by means of the TD-DFT and DFT methods. These techniques have been successfully employed many times to assign the AC of organic molecules.[14,21] Compound **3a** was selected instead of **3c**, because it misses the heavy bromine atom that would lengthen the calculation times. Taking into account the relative configuration and the conformation observed in the X-Ray structure of **3c**, a conformational search was carried out using the Monte Carlo approach and the MMFF94 molecular mechanics force field.[22] All conformations within a 5 kcal mol^{-1} windows were then optimized using DFT[23] at the B3LYP/6-31G(d) level.[24] For each stationary point the harmonic vibrational frequencies 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 nine conformations (**a–i**) (Table 4). due to the relative disposition of the two rings (C8–C13 bond) and to the position of the ethyl group. (C8–C10 bond, see Fig. 1).

These corresponded to the possible orientation of the pyrazolone ring with respect to the maleimide ring (C16–C13–C8–C7 dihedral angle, see Fig. 1) integrated with the three dispositions of the ethyl group (C13–C8–C10–C11 dihedral). Each conformation is labelled with respect to these dihedral angles in Table 4.

Comfortably, the conformation corresponding to that observed in the solid state of **3c** is calculated to be the most stable if the ZPE uncorrected energy is taken into account, and the second most stable in the ZPE-corrected free energy scale, with a small difference with the best structure (Fig. 2).

Table 4 Calculated ZPE-uncorrected internal energies (E) and ZPE-corrected free energies ($G°$) of the conformations of **3a** (in kcal mol^{-1}, B3LYP/6-31G(d) level). Populations percentages (Pop, %) are calculated assuming Boltzmann statistics at T = 25 °C

Conf.	Descriptors[a]	E	$G°$	Pop (%)
a	a, a	0.076	0.000	55 (34[b])
b	−g, a	0.000	0.287	33 (49[b])
c	a, +g	0.605	0.975	10 (14[b])
d	−g,−g	1.766	2.097	2 (3[b])
e	−g,+g	2.413	3.065	—
f	a,−g	5.173	5.199	—
g	+g, a	7.278	7.586	—
h	+g,+g	9.559	9.899	—
i	+g, −g	10.439	10.722	—

[a] *Anti* (a) and *gauche* (±g) conformations are labelled with respect to the C16–C13–C8–C7 and C13–C8–C10–C11 dihedral angles (first and second descriptor, respectively). [b] Based on total energy.

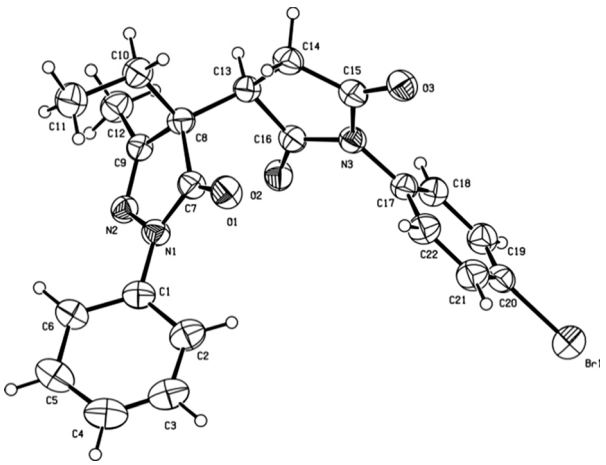


Fig. 1 X-Ray structure of compound **3c**.

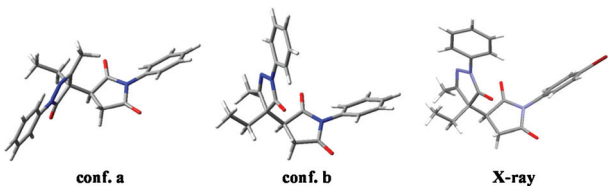


Fig. 2 3D views of the two most stable conformations of compound **3a**. The X-ray structure of **3c** is also reported (right).

The good agreement of the calculated with the experimental structure shows that the theoretical approach can reliably tackle the conformational analysis of these compounds. Assuming a 2 kcal mol^{-1} limit,[25] the DFT optimization suggest that only four conformations should be populated, whereas the energies of the remaining five are too high. Therefore, despite the apparent flexibility, these molecules should be considered quite rigid, with well-defined conformational preferences. This finding greatly enhances the reliability of the chirooptical methods, being the correct scan of the potential energy surface and the evaluation of the relative energies of the conformations their main weakness.[26]

The experimental ECD spectrum of **3a** was obtained on an enantioenriched sample (80% e.e. by HPLC) and the

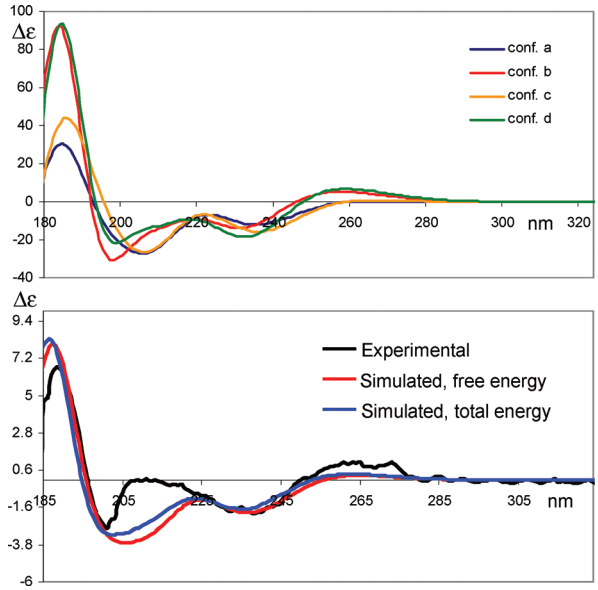


Fig. 3 Top: Calculated ECD spectra for the four conformations of compound **3a**, using CAM-B3LYP/6-311+G(d,p). Vertical scale is $\Delta\varepsilon$, horizontal scale is the wavelength (in nm). Bottom: experimental ECD spectrum of **3a** (in black, using (*R*,*R*)-TUC **III**) and simulated spectra (blue and red for the total energy and free energy ratios, respectively) assuming 3*S*,4*R* absolute configuration. The vertical scale is in $\Delta\varepsilon$ (L mol^{-1} cm^{-1}). The simulated spectra were red-shifted by 3 nm and vertically scaled to match the experimental trace.

experimental $\Delta\varepsilon$ has been accordingly scaled to obtain the spectrum of the enantiopure compound. Because of the distance between the phenyl chromophores and to the presence of the carbonyl moieties, the intensity of the spectrum is rather limited, and shifted to the low wavelengths region of the UV spectrum, where the absorbance of the solvents become very strong. For this reason the sample was prepared using far-UV HPLC grade acetonitrile, and the spectrum could be reliably recorded down to 190 nm. Calculation of the Electronic Circular Dichroism spectra were carried out using the TD-DFT CAM-B3LYP[27]/6-311+G(d,p) //B3LYP/6-31G(d) and assuming 3*S*,4*R*, absolute configuration. Electronic excitation energies and rotational strengths have been calculated for the four populated conformations of **3a** (Table 4), and the rotational strength were calculated in both the length and velocity representation. The resulting values were very similar, thus the errors due to basis set incompleteness should be considered very small.[28] To cover the 170–400 nm range (see Fig. 3), 65 transitions were calculated for each conformation The ECD spectra were then obtained by applying a 0.5 eV Gaussian shaped line width.[29]

The shapes of the calculated spectra for the four conformation **a**–**d** are very similar, albeit with different relative intensities of the Cotton effects. This feature limits the effects due to any error in the determination of the relative population, that could modify the intensity of the spectrum, but it should not heavily influence the pattern of the weighted spectra. The weighted ECD spectra were obtained taking into account the 54 : 33 : 10 : 2 and the 34 : 49 : 14 : 3 population ratio determined starting from the calculated free energies or from the uncorrected total energies at the B3LYP/6-31G(d) level, and assuming Boltzmann statistics at

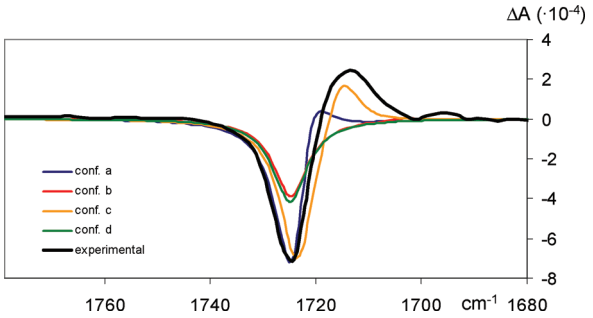


Fig. 4 comparison of the calculated VCD spectra for the **a**–**d** conformations (coloured traces) and experimental VCD spectrum (black line) of the carbonyl stretching region. Calculations at the CAM-B3LYP/6-311+G(d,p) level. The experimental spectrum was recorded in CCl_4.

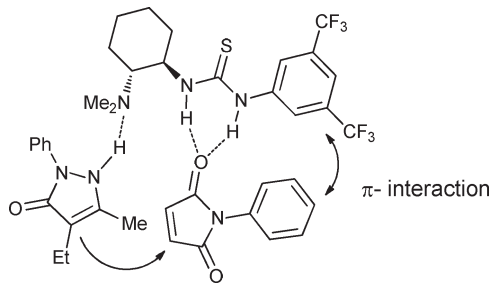


Fig. 5 Proposed transition state.

+25 °C (Fig. 3). Both the simulated spectra with the two different population ratio are in good agreement with the experimental one, and the sequence and relative intensities of the Cotton effects are correctly reproduced. The 3*S*,4*R*, configuration should be therefore assigned to compound **3a**.

However, the intensity of the ECD spectrum is rather weak, and a cross-check of the assignment by an independent approach is strongly advisable.[30] Compound **3a** bears three carbonyl moiety that exhibit strong IR bands. For this reason the Vibrational Circular Dichroism spectrum (VCD) of **3a** was acquired in CCl_4 solution (4 cm^{-1} spectral resolution, 10 000 scans). The most intense bands of the VCD spectrum are indeed the carbonyl stretching bands, that show two signals with opposite phase. Calculations of the Vibrational Circular Dichroism spectra were carried out using the same CAM-B3LYP[31]/6-311+G(d,p) level employed in the simulation of the ECD spectrum, within the harmonic approximation[32] and assuming the same 3*S*,4*R* absolute configuration. The simulations of the four spectra of conformers **a**–**d** in the carbonyl region are shown in Fig. 4, together with the experimental trace (in black). All the calculations correctly simulate the negative band, and the simulations obtained for conformations **a** and **c** simulate also the positive band at lower wavenumbers. Taking into account that both the chiroptical approaches (ECD and VCD) yield the same results, the 3*S*,4*R* absolute configuration can be reliably assigned to compound **3a** when (*R*,*R*)-TUC III was used as catalyst.

The stereochemical course of the pyrazolone-maleimide Michael reaction catalyzed by the bifunctional thiourea (*R*,*R*)-**I** can be easily accounted for within the working mechanistic hypothesis schematized by the transition state depicted in Fig. 5. The low enantioselectivity and diastereoseelctivities obtained with *N*-alkyl-substituted maleimides suggest that π-stacking interactions between the *N*-arylmaleimide substituent and the (3,5-bistrifluoromethyl)phenyl moiety of the catalyst play a key role in determining the preferred orientation of the maleimide.

Conclusions

In summary, we have been developed the first enantioselective addition of pyrazolones to maleimides. The reaction is efficiently catalyzed by bifunctional thiourea catalysts and affords the final compounds in excellent yields, moderate-to-excellent diastereoselectivity, and good enantioselectivity. Moreover we ascertained the absolute configurations of adducts **3** by chiroptical techniques (ECD and VCD) coupled with DFT calculations.

Experimental Section

General Procedure: In a small vial, pyrazolone **1a** (50 mg, 0.25 mmol, 1 equiv.), maleimide **2a** (65 mg, 0.375 mmol, 1.5 equiv) and catalyst **III** (12 mg, 10 mol%) in 1 mL of toluene were stirred at room temperature overnight. The crude mixture was monitored by ^{1}H NMR and after completion the crude was purifies by column chromatography, affording 79 mg of compound **3a** (84% yield).

3a: White scum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.86 (d, J = 7.7 Hz, 2H), 7.45–7.35 (m, 5H), 7.25–7.15 (m, 3H), 3.37 (dd, J = 5.7 Hz, J' = 9.6 Hz, 1H), 3.23 (dd, J = 5.7 Hz, J' = 18.3 Hz, 1H), 2.96 (dd, J = 9.6 Hz, J' = 18.3 Hz, 1H), 2.21 (s, 3H), 2.11 (q, J = 7.4 Hz, 2H), 0.83 (t, J = 7.4 Hz, 3H). ^{13}C NMR (CDC_3, 100 MHz) δ (ppm): 175.8, 175.1, 174.3, 161.8, 138.7, 132.7, 130.5, 130.3, 130.2, 127.6, 126.9, 120.5, 60.0, 44.6, 31.6, 28.2, 15.8, 9.4. HRMS (ESI): calcd. for $[M+H]^+$ ($C_{22}H_{22}N_3O_3$) requires 376.1656, found 376.1659. HPLC (Chiralpak IA, n-hexane: *i*-PrOH = 80 : 20, λ = 220 nm, 1.0 mL min^{-1}): t_R = 13.1, 17.5 min. $[\alpha]_D^{25}$ −40.3 (c 0.8, $CHCl_3$, e.e. = 80%).

3b: White scum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.85, (d, J = 7.7 Hz, 2H), 7.42–7.38 (n, 2H), 7.24–7.18 (m, 1H), 7.08, (d, J = 8.7 Hz, 2H), 6.91, (d, J = 8.9 Hz, 2H), 3.79 (s, 3H), 3.34 (dd, J = 5.6 Hz, J' = 9.3 Hz, 1H), 3.30–3.15 (m, 1H), 2.93 (dd, J = 9.3 Hz, J' = 18.0 Hz, 1H), 2.19 (s, 3H), 2.15–2.05 (m, 2H), 0.82 (t, J = 7.3 Hz, 3H). ^{13}C NMR (CDC_3, 100 MHz) δ (ppm): 176.1, 175.5, 174.4, 161.9, 161.0, 138.8, 130.3, 129.3, 129.0, 128.9, 126.9, 120.5, 116.0, 115.9, 115.9, 60.0, 56.9, 44.6, 31.5, 28.2, 15.9, 9.5. HRMS (ESI): calcd. for $[M+H]^+$ ($C_{23}H_{24}N_3O_4$) requires 406.1761, found 406.1769. HPLC (Chiralpak IB, n-hexane: *i*-PrOH = 80 : 20, λ = 254 nm, 1.0 mL min^{-1}): t_R = 21.9, 31.4 min.

3c: White solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.85, (d, J = 8.6 Hz, 2H), 7.53, (d, J = 8.7 Hz, 2H), 7.43–7.37 (m, 2H), 7.25–7.18 (m, 1H), 7.07, (d, J = 8.7 Hz, 2H), 3.40–3.20 (m, 2H), 2.96 (dd, J = 9.0 Hz, J' = 17.7 Hz, 1H), 2.20 (s, 3H), 2.13–2.00 (m, 2H), 0.83 (t, J = 7.4 Hz, 3H). ^{13}C NMR (CDC_3, 100 MHz) δ (ppm): 138.8, 133.8, 130.4, 129.2, 127.0, 120.5, 59.8, 44.8, 31.5, 28.3, 15.8, 9.4. HRMS (ESI): calcd. for $[M+H]^+$ ($C_{22}H_{21}BrN_3O_3$) requires 454.0761, found 454.0766. HPLC (Chiralpak IB, n-hexane: *i*-PrOH = 80 : 20, λ = 254 nm, 1.0 mL min^{-1}): t_R = 13.1, 18.4 min.

3d: White scum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.95, (d, J = 8.5 Hz, 2H), 7.84, (d, J = 8.6 Hz, 2H), 7.37–7.23 (m, 4H), 7.23–7.17 (m, 1H), 3.43–3.33 (m, 2H), 2.99 (dd, J = 10.5 Hz, J' = 19.2 Hz, 1H), 2.21 (s, 3H), 2.13–2.00 (m, 2H), 0.83 (t, J = 7.4 Hz, 3H). ^{13}C NMR (CDC_3, 100 MHz) δ (ppm): 175.3, 174.7, 174.2, 161.9, 138.5, 135.6, 130.2, 130.1, 128.3, 127.8, 127.6 (m, CF3), 126.9, 120.3, 59.5, 44.7, 31.3, 28.2, 15.6, 9.4. HRMS (ESI): calcd. for $[M+H]^+$ ($C_{23}H_{21}F_3N_3O_3$) requires 444.1530, found 444.1523. HPLC (Chiralpak IA, n-hexane: i-PrOH = 80 : 20, λ = 254 nm, 1.0 mL min^{-1}): t_R = 12.0, 16.0 min.

3e: White scum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.85 (d, J = 7.7 Hz, 2H), 7.40 (t, J = 7.7 Hz, 2H), 7.23–7.18 (m, 1H), 7.00 (d, J = 9.1 Hz, 2H), 3.33 (dd, J = 5.6 Hz, J' = 9.3 Hz, 1H), 3.11–3.01 (m, 1H), 3.00–2.85 (m, 1H), 2.93 (s, 6H), 2.18 (s, 3H), 2.17–2.00 (m, 2H), 0.81 (t, J = 7.4 Hz, 3H). ^{13}C NMR (CDC_3, 100 MHz) δ (ppm): 176.4, 175.9, 174.5, 161.9, 151.9, 138.8, 130.3, 128.3, 126.9, 120.6, 113.8, 60.4, 44.5, 41.8, 31.6, 28.2, 16.0, 9.5. HRMS (ESI): calcd. for $[M+H]^+$ ($C_{26}H_{33}N_4O_3$) requires 449.2547 found 449.2558. HPLC (Chiralpak IA, n-hexane: i-PrOH = 85 : 15, λ = 254 nm, 1.0 mL min^{-1}): t_R = 44.4, 63.7 min.

3f: White scum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.86 (d, J = 7.8 Hz, 2H), 7.42–7.36 (m, 2H), 7.22–7.18 (m, 2H), 7.04, (d, J = 8.1 Hz, 2H), , 3.34 (dd, J = 5.5 Hz, J' = 9.4 Hz, 1H), 3.22–3.12 (m, 1H), 2.93 (dd, J = 9.4 Hz, J' = 18.1 Hz, 1H), 2.33 (s, 3H), 2.18 (s, 3H), 2.12–2.08 (m, 2H), 0.81 (t, J = 7.5 Hz, 3H). ^{13}C NMR (CDC_3, 100 MHz) δ (ppm): 176.0, 175.4, 174.4, 162.0, 140.3, 138.8, 131.3, 131.2, 130.3, 127.9, 127.5, 127.5, 126.9, 120.5, 60.0, 44.7, 31.6, 28.2, 22.6, 15.9, 9.5. HRMS (ESI): calcd. for $[M+H]^+$ ($C_{23}H_{24}N_3O_3$) requires 390.1812 found 390.1817. HPLC (Chiralpak IA, n-hexane: i-PrOH = 80 : 20, λ = 254 nm, 1.0 mL min^{-1}): t_R = 14.0, 19.5 min.

3g: White scum (mixture of diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.90–7.80 (m, 4H), 7.45–7.10, (m, 2H), 7.00–6.95 (m, 2H), 3.40–3.30 (m, 1H), 3.25–3.20 (m, 1H), 2.90–2.75 (m, 2H), 2.00 (s, 3H), 2.00–1.95 (m, 1H), 1.95 (s, 3H), 1.92–1.70 (m, 2H), 0.80–0.75 (m, 6H). ^{13}C NMR (CDC_3, 100 MHz) δ (ppm): 176.2, 176.0, 175.4, 174.5, 174.3, 162.4, 160.3, 139.0, 138.6, 130.3,1130.3, 130.2, 130.0, 129.9, 129.9, 129.7, 129.6, 129.4, 129.3, 129.0, 126.9, 126.0, 61.4, 60.4, 60.0, 59.6, 44.5, 44.1, 32.4, 31.1, 28.5, 27.3, 16.1 15.6, 9.6, 9.5. HRMS (ESI): calcd. for $[M+H]^+$ ($C_{23}H_{24}N_3O_3$) requires 390.1812 found 390.1807. HPLC (Chiralpak IB, n-hexane: i-PrOH = 85 : 15, λ = 254 nm, 1.0 mL min^{-1}): t_R = 14.0.5, 17.0, 21.4, 28.4 min.

3h: White scum (mixture of diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.90–7.80 (m, 4H), 7.44–7.16, (m, 22H), 7.13–7.06 (m, 2H), 7.01–6.94 (m, 2H), 6.54 (s, 1H), 6.47 (s, 1H), 3.42–3.10 (m, 3H), 2.87–2.76 (m, 2H), 2.42–2.35 (m, 1H), 2.04 (s, 3H), 1.95 (s, 3H), 3.25–3.20 (m, 1H), 2.90–2.75 (m, 2H), 2.00 (s, 3H), 2.10–1.90 (m, 4H), 2.00–1.95 (m, 1H), 1.95 (s, 3H), 0.77 (m, 6H). ^{13}C NMR (CDC_3, 100 MHz) δ (ppm): 176.2, 176.0, 175.4, 174.6, 174.3, 162.4, 160.3, 138.7, 138.6, 138.2, 130.4, 130.3, 130.0, 129.9, 129.8, 129.7, 129.7, 129.6, 129.4, 129.2, 129.0, 126.9, 126.8, 120.5, 120.2, 61.4, 60.4, 60.0, 59.6, 44.5, 44.1, 32.4, 31.1, 28.5, 27.3, 16.1, 15.7, 9.6, 9.5. HRMS (ESI): calcd. for $[M+H]^+$ ($C_{23}H_{24}N_3O_3$) requires

3i: White scum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.85 (d, J = 7.7 Hz, 2H), 7.45–7.35 (m, 3H), 7.23–7.18 (m,2H), 7.13 (d, J = 8.6 Hz, 2H), 3.39–3.24 (m, 2H), 2.96 (dd, J = 9.1 Hz, J' = 18.3 Hz, 1H), 2.20 (s, 3H), 2.18–2.04 (m, 2H), 0.83 (m, 3H). ^{13}C NMR (CDC_3, 100 MHz) δ (ppm): 175.6, 174.9, 174.3, 161.9, 147.6, 144.7, 138.7, 137.8, 136.0, 130.8, 130.7, 130.4, 130.3, 128.9, 127.0, 59.8, 44.8, 32.3, 31.5, 28.3, 15.8, 9.5. HRMS (ESI): calcd. for $[M+H]^+$ ($C_{22}H_{21}ClN_3O_3$) requires 410.1266 found 410.1275. HPLC (Chiralpak IB, n-hexane: i-PrOH = 90 : 10, λ = 254 nm, 1.0 mL min^{-1}): t_R = 24.6, 39.3 min.

3j: White scum (mixture of diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.90–7.85 (m, 4H), 7.45–7.35, (m, 4H), 7.30–7.15 (m, 8H), 7.02–6.96 (m, 1H), 6.88–6.84 (m, 1H), 3.75 (dd, J = 5.4 Hz, J' = 18.0 Hz, 1H), 3.43–3.34 (m, 2H), 3.25–3.16 (m, 1H), 3.05–2.93 (m, 2H), 2.24 (s, 3H), 2.21 (s, 3H), 2.15–2.05 (m, 1H), 2.11 (s, 3H), 1.95–1.85 (m, 1H), 1.77 (s, 3H). ^{13}C NMR (CDC_3, 100 MHz) δ (ppm): 175.8, 175.6, 175.5, 175.2, 174.4, 174.3, 162.6, 161.9, 139.0, 137.3, 132.6, 132.5, 131.9, 131.1, 131.0, 130.3, 130.2, 129.2, 129.0, 128.5, 128.2, 127.0, 126.7, 120.5, 120.3, 60.2, 59.0, 45.4, 44.8, 31.9, 31.1, 28.8, 28.3, 19.1, 18.9, 16.0, 15.6, 9.5, 9.4. HRMS (ESI): calcd. for $[M+H]^+$ ($C_{23}H_{24}N_3O_3$) requires 390.1812 found 390.1801. HPLC (Chiralpak IB, n-hexane: i-PrOH = 90 : 10, λ = 254 nm, 1.0 mL min^{-1}): 24.3, 38.1 min.

3l: White scum (mixture of diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.90–7.85 (m, 4H), 7.42–7.35, (m, 4H), 7.25–7.00 (m, 8H), 3.62 (dd, J = 5.6 Hz, J' = 18.5 Hz, 1H), 3.50–3.30 (m, 3H), 3.07–2.90 (m, 3H), 2.64 (dd, J = 6.5 Hz, J' = 18.5 Hz, 1H), 2.50–2.40 (m, 1H), 2.24 (s, 3H), 2.20 (s, 3H), 2.19 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 2.00–1.85 (m, 1H), 1.84 (s, 3H). ^{13}C NMR (CDC_3, 100 MHz) δ (ppm): 175.4, 175.3, 175.1, 174.7, 174.5 174.3, 162.6, 160.2, 139.0, 137.6, 137.4, 136.7, 136.7, 131.3, 131.2, 130.9, 130.4, 130.2, 130.2, 130.0, 129.9, 129.9, 129.7, 126.9, 126.7, 120.5, 120.3, 61.2, 58.9, 45.4, 44.9, 32.7, 31.1, 28.9, 27.3, 22.0, 19.4, 19.2, 19.1, 19.0, 16.4, 15.6, 9.6, 9.4. HRMS (ESI): calcd. for $[M+H]^+$ ($C_{25}H_{28}N_3O_3$) requires 418.2125 found 418.2121. HPLC (Chiralpak IB, n-hexane: i-PrOH = 90 : 10, λ = 254 nm, 1.0 mL min^{-1}): 16.8, 21.6 min.

3m: White scum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.83 (d, J = 7.6 Hz, 2H), 7.45–7.35 (m, 5H), 7.25–7.15 (m, 3H), 3.35 (dd, J = 5.8 Hz, J' = 9.7 Hz, 1H), 3.23–3.18 (m, 1H), 2.96 (dd, J = 9.7 Hz, J' = 18.1 Hz, 1H), 2.23 (s, 3H), 1.56 (s, 3H). ^{13}C NMR (CDC_3, 100 MHz) δ (ppm): 175.6, 174.8, 174.7, 163.0, 138.6, 132.4, 130.2, 130.0, 129.9, 127.3, 126.5, 120.0, 54.4, 44.5, 31.3, 20.7, 15.3. HRMS (ESI): calcd. for $[M+H]^+$ ($C_{21}H_{20}N_3O_3$) requires 362.1499, found 362.1489. HPLC (Chiralpak IB, n-hexane: i-PrOH = 80 : 20, λ = 254 nm, 1.0 mL min^{-1}): t_R = 16.9, 19.3 min.

3n: White scum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.86 (d, J = 8.7 Hz, 2H), 7.42–7.36 (m, 2H), 7.22–7.17 (m, 1H), 7.01 (d, J = 8.9 Hz, 2H), 6.69 (d, J = 8.9 Hz, 2H), 3.31 (dd, J = 5.7 Hz, J' = 9.2 Hz, 1H), 3.08–2.08 (m, 2H), 2.94 (s, 6H), 2.20 (s, 3H),1.61 (s, 3H). ^{13}C NMR (CDC_3, 100 MHz) δ (ppm): 176.5, 175.8, 175.2, 163.3, 152.0, 139.0, 130.3, 128.7, 128.3, 126.7,

121.1, 120.5, 113.9, 113.8, 55.1, 44.6, 41.9, 31.7, 21.0, 15.8. HRMS (ESI): calcd. for $[M+H]^+$ ($C_{23}H_{25}N_4O_3$) requires 405.1921 found 405.1919. HPLC (Chiralpak IB, n-hexane: *i*-PrOH = 85 : 15, λ = 254 nm, 1.0 mL min^{-1}): t_R = 60.9, 65.8 min.

3o: White scum (mixture of diastereomers). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.90–7.80 (m, 4H), 7.45–7.15, (m, 12H), 7.01–6.99 (m, 1H), 6.89–6.86 (m, 1H), 3.73 (dd, J = 5.2 Hz, J' = 18.1 Hz, 1H), 3.40–3.30 (m, 2H), 3.22–3.12 (m, 1H), 3.05–2.95 (m, 2H), 2.27 (s, 3H), 2.24 (s, 3H), 2.12 (s, 3H), 1.90 (s, 3H), 1.63 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (CDC_3, 100 MHz) δ (ppm): 176.7, 175.4, 175.1, 164.0, 139.2, 137.4, 136.8, 132.7, 132.6, 131.9, 131.1, 131.0, 130.5, 130.4, 130.2, 129.3, 129.0, 128.5, 128.2, 126.9, 126.7, 120.5, 120.3, 53.7, 46.6, 44.9, 31.9, 31.2, 21.6, 21.1, 19,1, 18.9, 15.7, 15.3. HRMS (ESI): calcd. for $[M+H]^+$ ($C_{22}H_{22}N_3O_3$) requires 376.1656 found 376.1661. HPLC (Chiralpak IB, n-hexane: *i*-PrOH = 80 : 20, λ = 254 nm, 1.0 mL min^{-1}): 21.4, 28.0 min.

3p: White scum (mixture of diastereomers). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.61–7.53 (m, 4H), 7.45–7.30, (m, 6H), 7.20–7.10 (m, 14H), 7.06–6.96 (m, 4H), 3.80 (s, 3H), 3.75–3.70 (m, 1H), 3.64 (s, 3H), 3.60–3.50 (m, 3H), 3.42–3.35 (m, 2H), 3.06–2.96 (m, 3H), 2.85–2.75 (m,1H), 2.29 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (CDC_3, 100 MHz) δ (ppm): 176.2, 176.0, 174.9, 174.8, 174.2, 174.1, 161.0, 156.0, 138.5, 135.2, 135.0, 132.5, 132.5, 130.7, 130.6, 130.5, 130.4, 130.2, 129.9, 129.9, 129.1, 129.0, 127.1, 127.0, 122.4, 121.5, 121.1, 121.0, 62.1, 61.5, 57.3, 56.9, 44.4, 44.1, 41.0, 40.8, 32.4, 32.3, 16.8, 16.6. HRMS (ESI): calcd. for $[M+H]^+$ ($C_{28}H_{26}N_3O_4$) requires 468.1918 found 468.1921. HPLC (Chiralpak IB, n-hexane: *i*-PrOH = 80 : 20, λ = 254 nm, 1.0 mL min^{-1}): 23.2, 27.8 min.

3q: White scum. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.53 (d, J = 8.7 Hz, 2H), 7.36–7.28 (m, 2H), 7.21–7.00 (m, 8H), 6.72 (d, J = 9.0 Hz, 2H), 3.58 (d, J = 13.1 Hz, 1H), 3.53–3.48 (m, 1H), 3.38 (d, J = 13.1 Hz, 1H), 3.05–2.91 (m, 2H), 2.96 (s, 6H), 2.23 (s, 3H). ^{13}C NMR (CDC_3, 100 MHz) δ (ppm): 176.7, 175.7, 174.3, 161.0, 152.1, 128.5, 135.1, 130.7, 130.3, 130.0, 129.2, 128.4, 127.2, 121.2, 113.9, 61.7, 44.2, 41.9, 41.0, 32.1, 16.9. HRMS (ESI): calcd. for $[M+H]^+$ ($C_{29}H_{29}N_4O_3$) requires 481.2234 found 481.2228.

3r: White scum. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.84 (d, J = 7.6 Hz, 2H), 7.50–7.30 (m, 5H), 7.20–7.14 (m, 3H), 3.62 (dd, J = 7.5 Hz, J' = 7.5 Hz, 1H), 3.00–2.90 (m, 2H) 2.64–2.54 (m, 1H), 2.20 (s, 3H), 1.14 (d, J = 6.5 Hz, 3H), 1.04 (d, J = 7.3 Hz, 3H). ^{13}C NMR (CDC_3, 100 MHz) δ (ppm): 176.3, 175.4, 174.6, 161.7, 138.9, 133.0,130.8, 130.5, 130.4, 127.8, 127.1, 120.7, 62.9, 42.2, 32.9, 31.9, 19.1, 17.8, 17.5. HRMS (ESI): calcd. for $[M+H]^+$ ($C_{23}H_{24}N_3O_3$) requires 390.1812 found 390.1819. HPLC (Chiralpak IA, n-hexane: *i*-PrOH = 90 : 10, λ = 254 nm, 1.0 mL min^{-1}): t_R = 15.6, 29.3 min.

3s: White scum. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.84 (d, J = 8.8 Hz, 2H), 7.42–7.36 (m, 2H), 7.22–7.17 (m, 1H), 7.01 (**d**, J = 8.8 Hz, 2H), 6.69 (d, J = 8.9 Hz, 2H), 3.60 (dd, J = 6.9 Hz, J' = 8.5 Hz, 1H), 2.98–2.80 (m, 2H), 2.94 (s, 6H), 2.66–2.56 (m, 1H), 2.17 (s, 3H), 1.17 (d, J = 6.3 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H). ^{13}C NMR (CDC_3, 100 MHz) δ (ppm): 176.8, 176.0, 174.6, 161.8, 152.1, 138.9, 130.5, 130.4, 128.5, 127.1, 121.3, 120.7, 114.0, 113.9, 63.1, 42.0, 41.9, 32.7, 31.9, 19.2, 17.8, 17.4. HRMS (ESI): calcd. for $[M+H]^+$ ($C_{25}H_{29}N_4O_3$) requires 433.2234 found 433.2240. HPLC (Chiralpak IA, n-hexane: *i*-PrOH = 90 : 10, λ = 254 nm, 1.0 mL min^{-1}): t_R = 28.8, 62.6 min.

3t: White scum. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.93 (d, J = 7.7 Hz, 2H), 7.48–7.10 (m, 13H), 3.99 (dd, J = 4.7 Hz, J' = 9.5 Hz, 1H), 3.36 (dd, J = 4.7 Hz, J' = 18.5 Hz, 1H), 2.92 (dd, J = 9.5 Hz, J' = 18.5 Hz, 1H), 2.20 (s, 3H). ^{13}C NMR (CDC_3, 100 MHz) δ (ppm): 175.9, 175.4, 174.2, 162.7, 138.9, 135.6, 132.9, 131.3, 131.2 130.7, 130.6, 130.5, 130.4, 130.4, 130.2, 128.3, 127.9, 127.8, 127.7, 127.1, 120.8, 63.5, 44.2, 32.9, 15.8. HRMS (ESI): calcd. for $[M+H]^+$ ($C_{29}H_{29}N_4O_3$) requires 481.2234 found 481.2228. HPLC (Chiralpak IB, n-hexane: *i*-PrOH = 90 : 10, λ = 254 nm, 1.0 mL min^{-1}): t_R = 47.6, 65.4 min.

Standard UV absorption spectra were recorded at 25 °C in acetonitrile. ECD spectra of **3a** were recorded at 24 °C on a JASCO J-810 spectrapolarimeter in far-UV HPLC grade acetonitrile solutions (1×10^{-4} M), using a path length of 0.2 cm. Spectra were recorded in the range 190-400 nm; reported $\Delta\varepsilon$ values are expressed as L mol^{-1} cm^{-1}.

VCD spectra of **3a** were recorded on a single-PEM BioTools CHIRAL-IR2X spectrometer using a 4 cm^{-1} resolution. Spectra were recorded in CCl_4 solution (6 mg in 0.3 mL, 0.053 M) in a BaF_2 cell with a pathlenght of 100 µm. 10000 scans were collected (3.5 h). The spectra were calibrated using the internal calibration files, based on the spectra of α-pinene. Baseline artefacts were corrected by subtracting the VCD spectrum of the pure CCl_4 solvent in the same 100 µm cell to the spectrum of the compound.

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Notes and references

1 For an excellent book about the chemistry of pyrazol-3-ones, see:Pyrazol-3-ones. Part IV: Synthesis and Applications, G. Varvounis, in *Adv. Heterocyclic Chem.*, A. R. Katritzky (Ed.); Academic Press Inc, 2009, Vol. 98, p. 143.
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