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Highly Stereoselective Synthesis of Spiropyrazolones

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Dedicated to Carmen Nájera on the occasion of her 60th birthday

Keywords: Diastereoselectivity / Enantioselectivity / Michael addition / Organocatalysis / Spiro compounds

The synthesis of spiro compounds through a Michael–Michael–aldol reaction is reported. The reaction affords spiropyrazolone derivatives in good yields, in almost diastereo- and enantiopure form, and is catalyzed by diphenylprolinol derivatives. The reaction showed strong nonlinear effects. Remarkably, when a catalyst with 70 % *ee* is used, the reaction still affords the final spiro compound in almost diastereo- and enantiopure form.

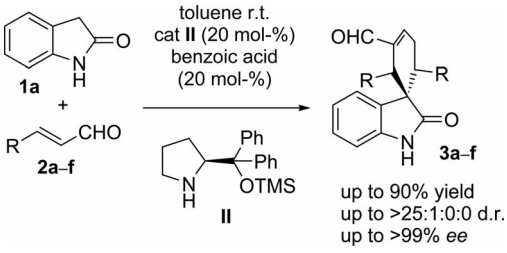
Introduction

The synthesis of natural products with very complex scaffolds and well-defined three-dimensional structure is currently one of the goals of organic chemists.[1] This complexity is generally correlated with stereospecificity in the biological properties. Finding cost-effective, atom-economic and sustainable methodologies that can be used to build complex structures in a stereocontrolled fashion, if possible in a catalytic way, is thus crucial for the chemical community.

In this context, organocatalysis and, in particular, organocascade reactions, have emerged as powerful tools for these complex syntheses.[2] For example, in 2007, Jørgensen and co-workers reported a powerful triple domino asymmetric reaction between malononitrile and unsaturated aldehydes that relied on a Michael–Michael–aldol reaction to construct cyclohexene in excellent yields and enantioselectivities, but only in moderate to good diastereoselectivities.[3] In 2009, Enders and co-workers employed the same concept starting from nitromethane and unsaturated aldehydes, with similar results.[4]

One of the most difficult examples of the synthesis of complex structures is the asymmetric construction of spiro motifs. In the last year, several research groups have reported asymmetric organocatalytic methodologies for the synthesis of spiro compounds based in the unique structure of oxindoles. For example, Melchiorre reported in 2009 the synthesis of spirooxindoles starting from methylene oxindoles by using an organocatalytic cascade reaction promoted by primary or secondary amines.[5] Subsequently, similar structural motifs have been built in an enantioselective fashion through [4+2] cycloaddition,[6] [3+2] cycloaddition, Knoevenagel/Michael cyclization,[7] [2+2+2] cyclization,[8] and a quadruple domino reaction.[9]

Very recently, fascinated by the synthesis of spiro compounds, our research group has developed a multicomponent cascade reaction between oxindoles and enals that affords the corresponding cyclohexenes in excellent yields and stereoselectivities (Scheme 1).[10] We have shown that this methodology can be applied to different heterocycles, such as benzofuranones,[11] oxazolines, or pyrazolones.



Scheme 1. Synthesis of spirooxindoles reported by our group.[10]

Pyrazolones are constituents of several useful intermediates for medicinal drugs,[12] and have a wide range of approved biological and pharmaceutical activities, such as analgesic and antipyretic properties,[13] antiischemic effects,[14] antiinflammatory,[13a] antiviral,[15] antitumor,[16] antibacte-

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rial[17] and other useful properties (Figure 1).[18] Numerous pyrazolone derivatives are also used in the dye industry[19] and as anticorrosives.[20]

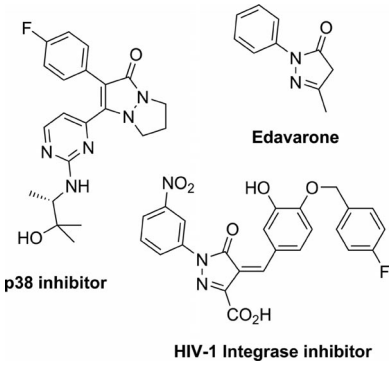
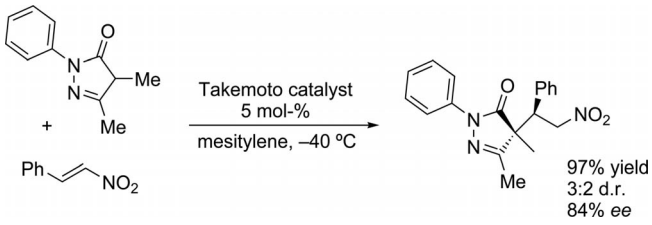


Figure 1. Biologically active pyrazolone derivatives.

However, despite their wide use in pharmaceutical chemistry, there are few reports on the synthesis of chiral pyrazolones. Only very recently, Yuan and co-workers developed an elegant asymmetric organocatalytic pyrazolone addition to nitroalkenes catalyzed by bifunctional thiourea catalysts (Scheme 2).[21]

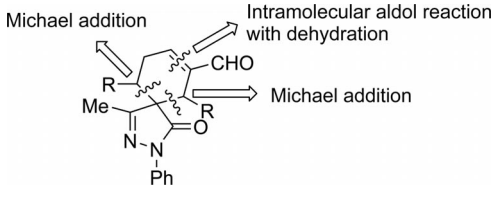


Scheme 2. Organocatalytic pyrazolone addition to nitroalkenes reported by Yuan.[21]

Based on these previous reports and on our experience in organocatalysis,[22] we envisioned an easy entry to chiral spiropyrazolones through a double Michael addition followed by an aldol-dehydration process.

Results and Discussion

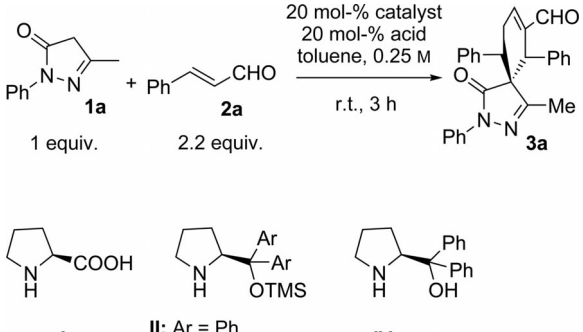
We disclosed that pyrazolones could react with unsaturated aldehydes through a Michael–Michael–aldol condensation to furnish the desired spirocyclic compounds (Scheme 3).



Scheme 3. Proposed reaction.

To our delight, when pyrazolone **1a** was treated with cinnamaldehyde (**2a**) in the presence of catalyst **II** (20%) and benzoic acid (20%) in toluene, the reaction rendered only one product, in diastereo- and enantiopure form. It should be noted that the use of benzoic acid is crucial for the formation of these spiro compounds; without the addition of acid, the reaction does not work, probably because of retro-Michael reactions previously reported. We then screened several catalysts and acids; the best catalyst was catalyst **II** (Table 1, entry 2). Proline did not catalyze the reaction, probably due to its poor solubility in toluene (Table 1, entry 1). Catalyst **III**, which is commonly used in similar methodologies, and catalyst **IV** both resulted in very slow reactions, affording only trace amounts of product after 14 h (Table 1, entries 3 and 4). Remarkably, the use of different acids did not result in any difference in the reaction; *o*-fluorobenzoic acid, *o*-nitrobenzoic acid, and *p*-nitrobenzoic acid (Table 1, entries 4, 5, and 6) all gave the same results: full conversion after 14 h and total diastereo- and enantioselectivity.

Table 1. Catalyst screening.[a]



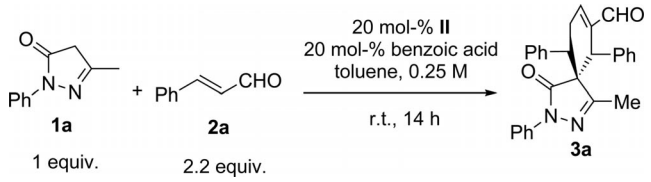
Entry	Cat.	Acid	Conv. [%][b]	*dr*[b]	*ee* [%][c]
1	**I**	$C_6H_5CO_2H$	0	–	–
2	**II**	$C_6H_5CO_2H$	100	>25:1	>99
3	**III**	$C_6H_5CO_2H$	<10	n.d.	n.d.
4	**IV**	$C_6H_5CO_2H$	<10	n.d.	n.d.
5	**II**	*o*-$FC_6H_4CO_2H$	100	>25:1	>99
6	**II**	*o*-$NO_2C_6H_4CO_2H$	100	>25:1	>99
7	**II**	*p*-$NO_2C_6H_4CO_2H$	100	>25:1	>99

[a] Reagents and conditions: **1a** (0.25 mmol, 1.0 equiv.), **2a** (0.60 mmol, 1.2 equiv.), catalyst **I**–**IV** (0.05 mmol, 0.2 equiv.), acid (0.05 mmol, 0.2 equiv.), toluene (1 mL), 14 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC analysis.

With this catalytic system in hand, we tested the reaction in different solvents. The reaction worked in other solvents, such as ethyl acetate (EtOAc) and chloroform ($CHCl_3$), albeit with lower conversions and diastereoselectivities (Table 2, entries 2 and 5).

Having thus identified the optimal catalyst and solvent, we then studied the scope of the reaction with a variety of α,β-unsaturated aldehydes, and found that the reaction worked with both aliphatic and aromatic unsaturated aldehydes with excellent yields (Table 3, entries 1, 2, and 3). Aromatic enals rendered the final spiro compounds with excellent diastereo- and enantioselectivities. On the other hand, aliphatic enals gave lower diastereoselectivities. The reaction tolerated several functional groups, such as CN, NO_2, or halogens (Table 3, entries 4, 5, and 6) without any loss of diastereo- or enantioselectivity.

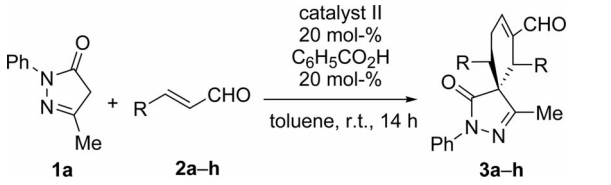
Table 2. Solvent screening.[a]



Entry	Solvent	Conv. [%][b]	*dr*[b]	*ee* [%][c]
1	toluene	100	>25:1	>99
2	EtOAc	100	5:1	>99
3	MeOH	<10	n.d.	n.d.
4	DMSO	<10	n.d.	n.d.
5	$CHCl_3$	100	13:1	>99
6	Et_2O	100	11:1	>99

[a] Reagents and conditions: **1a** (0.25 mmol, 1.0 equiv.), **2a** (0.60 mmol, 1.2 equiv.), catalyst **II** (0.05 mmol, 0.2 equiv.), benzoic acid (0.05 mmol, 0.2 equiv.), solvent (1 mL), 14 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC analysis.

Table 3. Enal scope.[a]

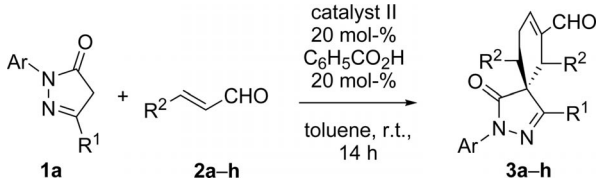


Entry	R	3	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	Ph	**3a**	55	>25:1:0:0	>99
2	*p*-CNC_6H_4	**3b**	80	>25:1:0:0	99
3	*p*-BrC_6H_4	**3c**	63	>25:1:0:0	>99
4	*p*-ClC_6H_4	**3d**	52	>25:1:0:0	99
5	CO_2Et	**3e**	48	>25:1:0:0	99
6	Me	**3f**	68	7:1:0:0	96
7	Et	**3g**	73	4.5:1:0:0	94
8[e]	Et	**3g**	60	7:1:0:0	>99
9	Bu	**3h**	51	7:1:0:0	>99

[a] Reagents and conditions: **1a** (0.25 mmol, 1.0 equiv.), **2a**–**h** (0.60 mmol, 1.2 equiv.), catalyst **II** (0.05 mmol, 0.2 equiv.), acid (0.05 mmol, 0.2 equiv.), toluene (1 mL), 14 h. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude mixture. [d] Determined by chiral HPLC analysis. [e] Reaction run at 4 °C.

When the reaction was conducted with different pyrazolones, to our delight, the final spiropyrazolones were afforded in diastereo- and enantiopure form when small aliphatic residues, such as ethyl groups, occupied position 3 of the pyrazolone ring (Table 4, entries 2–6). Remarkably, substitution of the phenylic ring of the pyrazolone by a *p*-(trifluoromethyl)phenyl group gave the final spiro compounds in good yields and excellent diastereo- and enantioselectivities (Table 4, entries 11–14). However, when bulky substituents, such as phenyl or *tert*-butyl (Table 4, entries 7 and 8), or highly electron-withdrawing groups, such as trifluoromethyl, occupied position 3 (Table 4, entries 9 and 10), no reaction was observed.

Table 4. Pyrazolone scope.[a]



Entry	Ar	3	R^1	R^2	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	Ph	**3a**	Me	Ph	55	>25:1:0:0	>99
2	Ph	**3i**	Et	*p*-CNC_6H_4	72	7:1:0:0	99
3	Ph	**3j**	Et	*p*-BrC_6H_4	51	20:1:0:0	>99
4	Ph	**3k**	Et	CO_2Et	58	20:1:0:0	99
5	Ph	**3l**	Et	Ph	74	>25:1:0:0	97
6	Ph	**3m**	Et	Me	64	6.5:1:0:0	93
7	Ph	**3n**	*t*Bu	Ph	n.r.[e]	–	–
8	Ph	**3o**	Ph	Ph	n.r.[e]	–	–
9	Ph	**3p**	CF_3	Ph	n.r.[e]	–	–
10	Ph	**3q**	CF_3	Me	n.r.[e]	–	–
11	*p*-$CF_3C_6H_4$	**3r**	Me	Ph	68	>25:1:0:0	>99
12	*p*-$CF_3C_6H_4$	**3s**	Me	CO_2Et	42	5:1:0:0	>99
13	*p*-$CF_3C_6H_4$	**3t**	Me	*p*-CNC_6H_4	84	>25:1:0:0	>99
14	*p*-$CF_3C_6H_4$	**3u**	Me	Me	58	7:1:0:0	92

[a] Reagents and conditions: **1a**–**f** (0.25 mmol, 1.0 equiv.), **2a**–**e** (0.60 mmol, 1.2 equiv.), catalyst **II** (0.05 mmol, 0.2 equiv.), benzoic acid (0.05 mmol, 0.2 equiv.), toluene (1 mL), 14 h. [b] After column chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by chiral HPLC analysis. [e] n.r. (no reaction).

The relative configuration of the spiropyrazolone **3a** was determined by means of NOE and NOESY NMR experiments, as well as by X-ray diffraction analysis of a monocrystal (Figure 2). As can be seen, the relative configuration between the two phenyl groups is, as expected, *trans*.

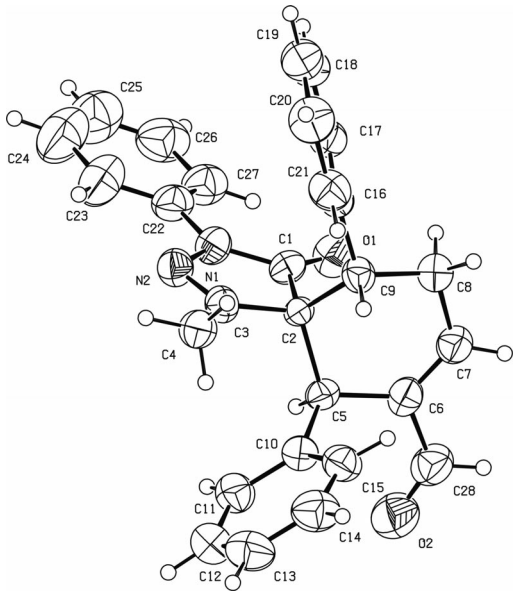


Figure 2. Crystal structure of **3a**.

Unfortunately, compound **3a** lacks the heavy atom required to confirm the absolute configuration assignment by the Bijvoet method (the anomalous dispersion method). Therefore, the absolute configuration (AC) was assigned by

means of chiroptical methods.[23] In the present case, a theoretical calculation of the electronic circular dichroism (ECD) spectra was carried out by means of the TD-DFT method, because this technique has been successfully employed several times previously to predict ECD spectra and to assign the AC of organic molecules.[24] Starting from the relative configuration obtained by NMR analysis and X-ray diffraction, a conformational search was carried out using Monte Carlo searching together with the MMFF94 molecular mechanics force field (as implemented in Titan 1.0.5, Wavefunction Inc.). All conformations within a 5 kcal/mol window were then optimized using DFT at the B3LYP/6-31G(d) level,[25] and the harmonic vibrational frequencies of each conformation were calculated at the same level to confirm their stability (no imaginary frequencies observed), and to evaluate the free energy of each conformation by zero point energy (ZPE) correction. After DFT minimization, the MMFF structures clustered in two conformations (**a** and **b**), which differed in the disposition of the CHO group (see Figure 3 and Table 5). The most stable structure (**a**) corresponded to the conformation observed in the solid state, and the energy of the second most stable conformation (**b**) was remarkably higher (2.0 kcal/mol). This means that the molecule is quite rigid, which is a feature that greatly enhances the reliability of the method, because the correct evaluation of the relative energy of each conformation it generally the main weakness of this approach.

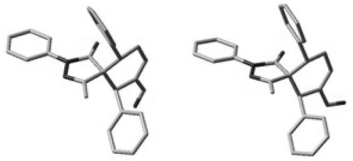


Figure 3. 3D view of the two most stable conformations of compound **3a** (energies in kcal/mol).

Table 5. Calculated relative energies (*E*) and free energies (*G*) of the conformations of **3a** [in kcal/mol, B3LYP/6-31G(d) level]. Populations percentages (P) were calculated assuming Boltzmann statistics at $T = 25$ °C.

	Conf.	*E*	*G*	Pop. (ΔG)
3a	**a**	0.0	0.00	96
	b	2.4	2.0	4

Calculation of the ECD spectra of both conformations were carried out using the TD-DFT-BH&HLYP/6-311+G(d,p)//B3LYP/6-31G(d) and TD-DFT-B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) levels,[26] assuming 5*S*,6*S*,10*R* absolute configuration (Figure 4).[27] Rotational strengths were calculated in both length and velocity representation. Because the resulting values were very similar, the errors due to basis set incompleteness were very small.[28] Electronic excitation energies and rotational strengths were calculated for the two conformations, and the ECD spectra were obtained by applying a 0.4 eV Gaussian-shaped line width.[29] In order to cover the 170–400 nm range, 70 transition were calculated for each conformation.

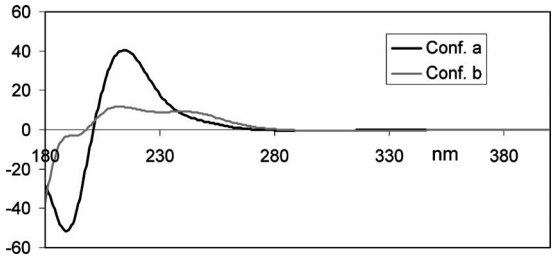


Figure 4. Calculated ECD spectra for the two conformations of compound **3a**. Vertical scale in $\Delta\varepsilon$, horizontal scale in nm.

Although the shapes of the two spectra are different, in both cases the cotton effects below 250 nm are positive, indicating that the resulting weighted ECD spectrum is not strongly influenced by the relative population of the conformations. The final simulated ECD spectra was obtained by 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 (Figure 5). The simulated spectrum was in good agreement with the experimental data, and the 5*S*,6*S*,10*R* configuration could thus be reliably assigned to compound **3a** [when (*R*)-**II** catalyst was used].

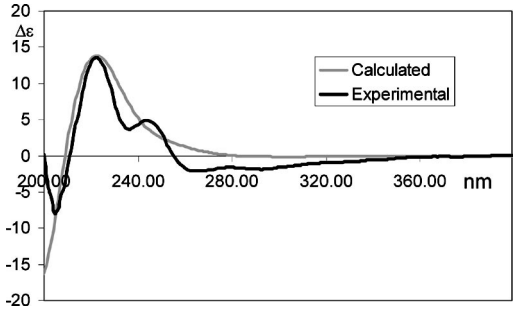
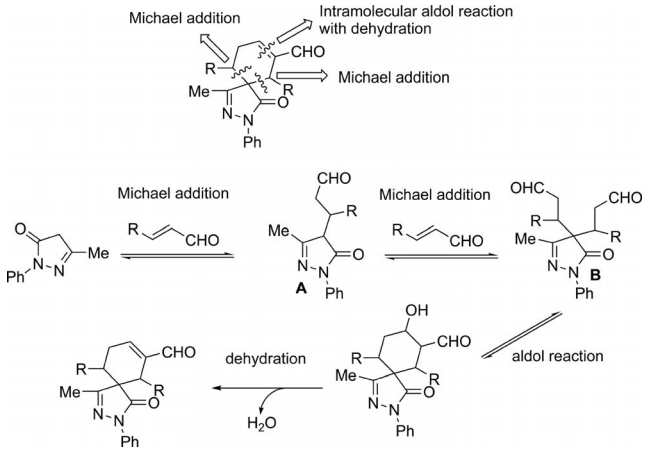


Figure 5. Experimental ECD spectrum (in black) [using (*R*)-**II** as catalyst] and simulated spectrum (in gray) assuming 5*S*,6*S*,10*R* absolute configuration. The vertical scale is in mdeg, and the simulated spectrum has been scaled accordingly. The simulated spectrum has been red-shifted by 8 nm in order to match the experimental trace.

Both relative and absolute configurations were in agreement with related aminocatalytic conjugate additions promoted by catalyst **II**.[10,11]

Once the relative and the absolute configuration of the obtained spiropyrazolone was determined, we turned out our attention to the mechanism of the reaction. We assumed that the reaction proceeds through a double Michael addition–aldol condensation pathway, as shown in Scheme 4. We propose that the two Michael addition reactions are reversible and that these additions proceed with good enantioselectivities but probably with poor diastereoselectivities in the first step. However, the quaternary carbon formed in compound B is a pro-stereogenic center

when the two pendant chains have the same absolute configuration, and this compound would be desymmetrized by the last irreversible aldol reaction (Scheme 4). On the other hand, cyclization of the remaining diastereomers of B, leading to *cis*-isomers of the spiropyrazolone, is probably more difficult, which explains the high diastereo- and enantioselectivity of the process.



Scheme 4. Possible mechanism.

To obtain experimental support for this proposed pathway, the presence of nonlinear effects in this reaction were studied (Figure 6 and Table 6). As illustrated in Figure 6, the enantiomeric excess of the major product exhibits a strong nonlinear dependence on the enantiomeric purity of the catalyst. When catalyst **II** with 20% enantiomeric excess (*ee*) was used, the reaction afforded, remarkably, the final compound with a 2:1:1:0 diastereomeric ratio and with 78% *ee* for the major diastereomer. These data seem to support the proposed equilibria in the Michael additions steps and in the aldol step. Moreover, the reaction renders the final compound in almost enantiopure form (98% *ee*) and with high diastereoselectivity (8:1:1:0 *dr*) using a catalyst with only 50% *ee*.

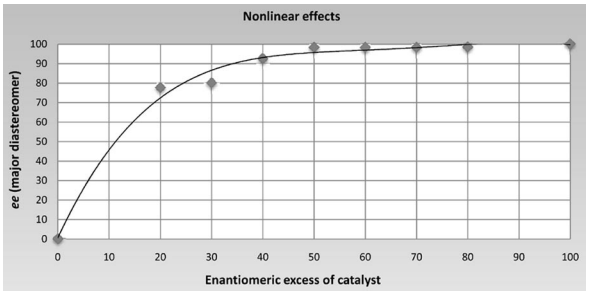


Figure 6. Nonlinear plot.

Table 6. Nonlinear effects.[a]

ee (cat.) [%]	Conv. [%][b]	*dr*[b]	*er*[c]	Yield [%][d]
100	100	>25:1:0:0	>99.9:0.1	55
80	100	>25:1:0:0	99.2:0.8	52
70	100	21:3:1:0	99.1:0.9	56
60	100	11:1:1:0	99.1:0.9	48
50	100	8:1:1:0	99.1:0.9	43
40	100	7:1:1:0	96.3:3.7	61
30	100	6:2:1:0	90.0:10.0	54
20	100	4:1:1:0	88.8:11.2	59
0	100	2:1:1:0	n.d.	49

[a] Reagents and conditions: **1a** (0.25 mmol, 1.0 equiv.), **2a** (0.60 mmol, 1.2 equiv.), catalyst **II** (0.05 mmol, 0.2 equiv.), benzoic acid (0.05 mmol, 0.2 equiv.), toluene (1 mL), 14 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC analysis of the major diastereomer. [d] After column chromatography.

Conclusions

We have developed a new methodology for the construction of spiropyrazolones based on organocatalysis. The final products are obtained in good to excellent yields and in a totally stereocontrolled fashion in several instances. Moreover, we studied the nonlinear effects of the reaction, which displayed amazing asymmetric amplification. Further studies on the application of this reaction to total synthesis, as well as biological evaluations of the resulting spiropyrazolones, are ongoing in our laboratories.

Experimental Section

General: Chemicals and solvents were either purchased from commercial suppliers (P.A. grade) or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F_{254} were used; compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2{\cdot}H_2O$ (10 g) followed by heating. Flash chromatography was performed with silica gel Merck 60 (particle size 0.063–0.200 mm). ^{1}H and ^{13}C NMR spectra were recorded with Varian UNITY INOVA-300 or Varian MERCURY-400 spectrometers. Chemical shifts for protons are given in δ units relative to tetramethylsilane (TMS) and are referenced to residual protons in the NMR solvent ($CDCl_3$: δ = 7.26 ppm). Chemical shifts for carbon are given in δ units relative to TMS and are referenced to the carbon resonances in the solvent ($CDCl_3$: δ = 77.0 ppm). Coupling constants (J) are given in Hz. Chiral HPLC was carried out with a LCP 5020 Ignos liquid chromatography pump with an LCD 5000 spectrophotometric detector.

General Procedure for the Synthesis of Spiropyrazolones: In a small flask, pyrazolone **1a**–**e** (0.25 mmol, 1.0 equiv.), enal **2a**–**h** (0.60 mmol, 1.2 equiv.), catalyst **II** (0.05 mmol, 0.2 equiv.), and benzoic acid (0.05 mmol, 0.2 equiv.) in toluene (1 mL), were stirred over 14 h. The crude material was purified by column chromatography to afford **3a**–**u**.

Compound 3a: Yield 58 mg (55%); white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.51 (s, 1 H, CHO), 7.80–7.66 (m, 2 H, ArH), 7.42–7.30 (m, 8 H, ArH), 7.23–7.09 (m, 6 H, ArH, CH), 4.20 (s, 1 H, CH), 3.57 (dd, J = 5.6, 11.5 Hz, 1 H, CH), 3.45–3.35 (m, 1 H, CH_2), 2.96–2.87 (m, 1 H, CH_2), 0.95 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.1, 150.3, 139.3, 138.5, 131.7, 131.6, 129.3, 128.9, 128.8, 128.5, 128.2, 127.9, 127.6, 127.6, 125.3, 45.3, 39.6, 31.5, 15.6 ppm. HRMS (ESI): calcd. for $C_{28}H_{25}N_2O_2$ [M + H]$^+$ 421.1911; found 421.1912. HPLC (Chiralpak IB; *n*-hexane/*i*PrOH, 95:5; λ = 254 nm; 1.0 mL/min): t_R = 13.3, 27.0 min. IR: $\tilde{\nu}_{max}$ = 703, 758, 1123, 1159, 1288, 135, 1454, 1595, 1651, 1687. $[\alpha]_D^{25}$ = +69.8 [c = 0.7, $CHCl_3$, *ee* >99%, (*R*)-cat.].

Compound 3b: Yield 94 mg (80%); yellow scum. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (s, 3 H, CH_3), 2.99–2.89 (dt, J = 19.8,

4.8 Hz, 1 H, CH_2), 3.46–3.35 (m, 1 H, CH_2), 3.56–3.50 (dd, J = 11.4, 5.4 Hz, 1 H, CH), 4.24 (s, 1 H, CH), 7.22–7.76 (m, 14 H, ArH, CH), 9.51 (s, 1 H, CHO) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 16.1, 30.9, 40.0, 45.1, 58.8, 112.6, 112.7, 118.2, 118.3, 119.3, 126.0, 128.7, 129.2, 132.7, 132.8, 133.0, 133.1, 137.4, 137.8, 143.8, 144.2, 150.3, 159.7, 173.1, 191.7 ppm. HRMS (ESI): calcd. for $C_{30}H_{22}N_4NaO_2$ [M + Na]$^+$ 493.1634; found 493.1635. HPLC (Chiralpak IB; *n*-hexane/*i*PrOH, 90:10; λ = 254 nm; 1.0 mL/min): t_R = 18.2, 20.6 min; $[\alpha]_D^{25}$ = +51.7 [c = 0.7, $CHCl_3$, *ee* 99%, (*R*)-cat.].

Compound 3c: Yield 91 mg (63%); yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (s, 3 H, CH_3), 2.94–2.84 (dt, J = 4.8, 19.5 Hz, 1 H, CH_2), 3.40–3.29 (m, 1 H, CH_2), 3.49–3.44 (dd, J = 11.4, 5.4 Hz, 1 H, CH), 4.14 (s, 1 H, CH), 6.96–6.99 (d, J = 8.7 Hz, 2 H, ArH), 7.60–7.19 (m, 9 H, ArH, CH), 7.77–7.75 (d, J = 7.5 Hz, 2 H, ArH), 8.11–8.08 (d, J = 7.2 Hz, 1 H, ArH), 9.49 (s, 1 H, CHO) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 16.1, 31.4, 39.3, 44.8, 59.0, 119.3, 122.2, 122.6, 125.7, 128.7, 129.1, 129.3, 129.5, 130.4, 132.0, 132.3, 132.6, 133.4, 133.9, 137.5, 137.6, 138.2, 138.3, 150.4, 160.9, 171.4, 173.7, 192.0 ppm. HRMS (ESI): calcd. for $C_{28}H_{23}Br_2N_2O_2$ [M + H]$^+$ 577.0123; found 577.0121. HPLC (Chiralpak IB; *n*-hexane/*i*PrOH, 90:10; λ = 254 nm; 1.0 mL/min): t_R = 13.8, 16.4 min; $[\alpha]_D^{25}$ = +89.5 [c = 0.3, $CHCl_3$, *ee* > 99%, (*R*)-cat.].

Compound 3d: Yield 64 mg (53%); white scum. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (s, 3 H, CH_3), 2.93–2.86 (dt, J = 20.0, 5.2 Hz, 1 H, CH_2), 3.39–3.31 (m, 1 H, CH_2), 3.50–3.46 (dd, J = 11.6, 5.6 Hz, 1 H, CH), 4.16 (s, 1 H, CH), 7.05–7.03 (d, J = 8.4 Hz, 2 H, ArH), 7.62–7.15 (m, 9 H, ArH, CH), 7.78–7.76 (d, J = 8.0 Hz, 2 H, ArH), 8.11–8.10 (d, J = 7.2 Hz, 1 H, ArH), 9.50 (s, 1 H, CHO) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 16.1, 31.4, 39.2, 44.7, 59.2, 119.4, 125.7, 128.7, 129.1, 129.7, 130.4, 133.1, 133.9, 134.1, 134.5, 137.0, 137.7, 138.4, 150.5, 160.9, 173.7, 192.1 ppm. HRMS (ESI): calcd. for $C_{28}H_{23}Cl_2N_2O_2$ [M + H]$^+$ 489.1133; found 489.1131. HPLC (Chiralpak IB; *n*-hexane/*i*PrOH, 90:10; λ = 254 nm; 1.0 mL/min): t_R = 12.0, 14.6 min; $[\alpha]_D^{25}$ = +46.5 [c = 0.4, $CHCl_3$, *ee* 99%, (*R*)-cat.].

Compound 3e: Yield 49 mg (53%); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.75 (s, 1 H, CHO), 8.08–8.05 (m, 2 H, ArH), 7.66–7.60 (m, 2 H, ArH), 7.49–7.40 (m, 2 H, ArH, CH), 4.56–4.30 (m, 4 H, $COOCH_2$), 3.92 (s, 1 H, CH), 3.88 (dd, J = 6.1, 10.8 Hz, 1 H, CH), 3.56–3.46 (m, 1 H, CH_2), 3.25–3.15 (m, 1 H, CH_2), 2.25 (s, 3 H, CH_3), 1.56 (t, J = 7.1 Hz, 3 H, CH_3), 1.39 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.6, 172.0, 171.0, 170.1, 158.2, 150.6, 137.7, 136.6, 128.8, 125.3, 119.1, 62.2, 61.7, 52.4, 42.8, 39.7, 26.0, 14.6, 13.9, 13.9 ppm. HRMS (ESI): calcd. for $C_{44}H_{48}N_4NaO_{12}$ [2M + Na]$^+$ 847.3161; found 847.3158. HPLC (Chiralpak IC; *n*-hexane/*i*PrOH, 90:10; λ = 254 nm; 1.0 mL/min): t_R = 20.0, 25.3 min; $[\alpha]_D^{25}$ = +107.7 [c = 1.25, $CHCl_3$, *ee* = 99%, (*R*)-cat.].

Compound 3f: Yield 50 mg (68%); colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.46 (s, 1 H, CHO), 7.86–7.81 (m, 2 H, ArH), 7.40–7.33 (m, 2 H, ArH), 7.19–7.12 (m, 1 H, ArH), 6.95–6.91 (m, 1 H, CH), 3.01 (q, J = 7.0 Hz, 1 H, CH), 2.68–2.60 (m, 2 H, CH_2), 2.43–2.32 (m, 1 H, CH), 2.22 (s, 3 H, CH_3), 1.24 (d, J = 7.0 Hz, 3 H, CH_3), 0.90 (d, J = 6.7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.9, 173.6, 161.2, 150.4, 128.7, 125.0, 118.8, 58.6, 32.4, 31.3, 26.8, 18.1, 16.5 ppm. HRMS (ESI): calcd. for $C_{18}H_{21}N_2O_2$ [M + H]$^+$ 297.1599; found 297.1599. HPLC (Chiralpak IB; *n*-hexane/*i*PrOH, 98.5:1.5; λ = 254 nm; 1.0 mL/min): t_R = 21.9, 23.1 min; $[\alpha]_D^{25}$ = –23.0 [c = 0.85, $CHCl_3$, *ee* = 96%, (*R*)-cat.].

Compound 3g: Yield 59 mg (73%); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97–0.91 (m, 6 H, 2×CH_3), 1.57–1.46 (m, 2 H, CH_2), 1.89–1.82 (m, 2 H, CH_2), 2.25 (s, 3 H, CH_3), 2.60 (m, 1 H, CH_2), 2.75–2.72 (dd, J = 6.8, 4.4 Hz, 1 H, CH_2), 2.80–2.78 (dd, J = 6.8, 4.4 Hz, 1 H, CH), 2.89–2.86 (t, J = 5.6 Hz, 1 H, CH), 7.02–7.00 (t, J = 3.6 Hz, 1 H, CH), 7.52–7.15 (m, 3 H, ArH), 7.82–7.81 (d, J = 7.6 Hz, 2 H, ArH), 9.51 (s, 1 H, CHO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.7, 13.3, 17.5, 24.9, 25.9, 28.9, 34.4, 39.1, 59.0, 119.0, 125.1, 128.9, 130.4, 133.9, 138.1, 140.3, 150.9, 161.6, 174.0, 193.3 ppm. HRMS (ESI): calcd. for $C_{40}H_{48}N_4NaO_4$ [2M + Na]$^+$ 671.3578; found 671.3568. HPLC (Chiralpak IB; *n*-hexane/*i*PrOH, 99.5:0.5; λ = 254 nm; 1.0 mL/min): t_R = 30.0, 35.6 min; $[\alpha]_D^{25}$ = –13.1 [c = 0.4, $CHCl_3$, *ee* = 94%, (*R*)-cat.].

Compound 3h: Yield 49 mg (51%); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.49 (s, 1 H, CHO), 7.84–7.81 (m, 2 H, ArH), 7.39–7.33 (m, 2 H, ArH), 7.18–7.12 (m, 1 H, ArH), 6.98–6.95 (m, 1 H, CH), 2.87 (dd, J_1 = J_2 = 5.6 Hz, 1 H, CH), 2.74 (ddd, J = 4.4, 6.6, 20.5 Hz, 1 H, CH), 2.61–2.50 (m, 1 H, CH_2), 2.30–2.21 (m, 1 H, CH_2), 2.23 (s, 3 H, CH_3), 1.78–1.67 (m, 1 H), 1.60–1.00 (m, 11 H), 0.90–0.85 (m, 6 H, 2×CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.9, 173.8, 161.4, 150.3, 140.5, 137.9, 128.7, 124.9, 118.7, 59.6, 37.9, 32.7, 32.3, 31.4, 30.9, 29.1, 23.0, 22.6, 17.2, 14–0, 13.9 ppm. HRMS (ESI): calcd. for $C_{24}H_{32}N_2NaO_2$ [M + Na]$^+$ 403.2356; found 403.2357. HPLC (Chiralpak IB, *n*-hexane/*i*PrOH = 99:1, λ = 254 nm, 1.0 mL/min): t_R = 8.8, 10.0 min; $[\alpha]_D^{25}$ = –5.3 [c = 0.4, $CHCl_3$, *ee* > 99%, (*R*)-cat.].

Compound 3i: Yield 87 mg (72%); colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.49 (s, 1 H, CHO), 7.82–7.77 (m, 2 H, ArH), 7.62–7.64 (m, 2 H, ArH), 7.53–7.33 (m, 8 H, ArH, CH), 7.27–7.20 (m, 2 H, ArH), 4.21 (s, 1 H, CH), 3.55 (dd, J = 5.5, 11.3 Hz, 1 H, CH), 3.45–3.32 (m, 1 H, CH_2), 3.00–2.88 (m, 1 H, CH_2), 1.40–1.10 (m, 2 H, CH_2), 0.64 (t, J = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.5, 173.1, 163.4, 150.1, 144.1, 143.7, 137.7, 137.4, 132.8, 132.7, 132.5, 132.3, 129.0, 128.8, 128.4, 125.7, 119.0, 118.1, 118.0, 112.4, 58.6, 50.0, 39.9, 30.9, 22.8 ppm. HRMS (ESI): calcd. for $C_{31}H_{25}N_4O_2$ [M + H]$^+$ 485.1972; found 485.1979. HPLC (Chiralpak IB; *n*-hexane/*i*PrOH, 90:10; λ = 254 nm; 1.0 mL/min): t_R = 64.8, 69.0 min; $[\alpha]_D^{25}$ = –117.4 [c = 1.3, $CHCl_3$, *ee* = 99%, (*S*)-cat.].

Compound 3j: Yield 75 mg (51%); colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.47 (s, 1 H, CHO), 7.84–7.79 (m, 2 H, ArH), 7.54–7.37 (m, 5 H, ArH), 7.35–7.15 (m, 5 H, ArH, CH), 7.00–6.93 (m, 2 H, ArH), 4.12 (s, 1 H, CH), 3.48 (dd, J = 5.5, 11.4 Hz, 1 H, CH), 3.39–3.26 (m, 1 H, CH_2), 2.94–2.83 (m, 1 H, CH_2), 1.43–1.20 (m, 2 H, CH_2), 0.67 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.1, 175.0, 165.9, 151.5, 139.5, 139.5, 138.8, 135.0, 134.4, 133.5, 133.4, 133.1, 1315, 130.5, 130.4, 130.2, 129.8, 126.7, 123.6, 123.2, 120.4, 60.2, 46.0, 40.5, 32.8, 24.0, 10.5 ppm. HRMS (ESI): calcd. for $C_{29}H_{25}Br_2N_2O_2$ [M + H]$^+$ 591.0277; found 591.0284. HPLC (Chiralpak IB; *n*-hexane/*i*PrOH, 95:5; λ = 254 nm; 1.0 mL/min): t_R = 14.6, 19.2 min; $[\alpha]_D^{25}$ = +117.2 [c = 1.0, $CHCl_3$, *ee* >99%, (*R*)-cat.].

Compound 3k: Yield 62 mg (58%); yellow oil. ^{1}H NMR (300 MHz. $CDCl_3$): δ = 9.49 (s, 1 H, CHO), 7.86 (d, J = 7.8 Hz, 2 H, ArH), 7.40–7.30 (m, 2 H, ArH), 7.20–7.10 (m, 2 H, ArH, CH), 4.30–4.00 (m, 4 H, 2×CH_2), 3.65–3.55 (m, 2 H, 2×CH), 3.30–3.20 (m, 1 H, CH_2), 3.05–2.95 (m, 1 H, CH_2), 2.19 (q, J = 7.2 Hz, 2 H, CH_2), 1.33–1.25 (m, 6 H, 2×CH_3), 1.13 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz. $CDCl_3$): δ = 193.1, 172.6, 171.7, 163.8, 152.0, 147.4, 141.6, 138.7, 130.2, 126.7, 120.5, 65.6, 63.2, 44.4, 41.1, 27.7, 23.1, 15.4, 15.3, 11.1 ppm. HRMS: calcd. for $C_{23}H_{27}N_2O_6^+$ [M + H]$^+$ 427.1864; found 427.1868. HPLC (Chiralpak IA; hexane/IPA, 95:5; λ = 254 nm^{-1}; 1 mL/min): t_R = 17.9, 57.0 min; $[\alpha]_D^{25}$ = +98.7 [c = 0.95, $CHCl_3$, (*R*)-cat.].

Compound 3l: Yield 80 mg (74%); pale-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.51 (s, 1 H, CHO), 7.85 (dd, J = 8.8, 2.2 Hz, 2 H, ArH), 7.42–7.31 (m, 8 H, ArH), 7.23–7.09 (m, 6 H, ArH, CH), 4.19 (s, 1 H, CH), 3.59 (dd, J = 5.7, 11.4 Hz, 1 H, CH), 3.44–3.35 (m, 1 H, CH_2), 2.95–2.88 (m, 1 H, CH_2), 1.39–1.29 (m, 2 H, CH_2), 0.60 (t, J = 7.1 Hz, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.1, 174.2, 165.3, 150.4, 139.4, 138.5, 137.9, 133.6, 131.5, 130.1, 129.0, 128.9, 128.7, 128.4, 128.1, 127.8, 127.5, 125.1, 119.2, 59.3, 45.4, 39.7, 31.7, 22.4, 9.1 ppm. HRMS (ESI): calcd. for $C_{29}H_{27}N_2O_2$ $[M + H]^+$ 435.2067; found 435.2070. HPLC (Chiralpak IB; *n*-hexane/*i*PrOH, 90:10; λ = 254 nm; 1.0 mL/min): t_R = 8.1, 13.9 min; $[a]_D^{25}$ = –66.80 [c = 1.0, $CHCl_3$, *ee* = 97.5%, (*S*)-cat.].

Compound 3m: Yield 50 mg (64%); yellow oil. ^{1}H NMR (300 MHz. $CDCl_3$): δ = 9.46 (s, 1 H, CHO), 7.87 (d, J = 8.0 Hz, 2 H, ArH), 7.40–7.35 (m, 2 H, ArH), 7.20–7.10 (m, 1 H, ArH), 6.95–6.90 (m, 1 H, CH), 2.99 (q, J = 6.8 Hz, 2 H, 2×CH), 2.65–2.45 (m, 2 H, CH_2), 2.40–2.30 (m, 2 H, CH_2), 1.38 (t, J = 6.8 Hz, 3 H, CH_3), 1.22 (d, J = 6.8 Hz, 3 H, CH_3), 0.87 (d, J = 6.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz. $CDCl_3$): δ = 194.2, 166.5, 151.7, 149.6, 142.9, 139.3, 130.0, 126.1, 120.0, 60.1, 33.7, 32.7, 28.2, 25.2, 19.5, 18.0, 11.5 ppm. HRMS: calcd. for $C_{19}H_{23}N_2O_2^+$ $[M + H]^+$ 311.1754; found 311.1751. HPLC (Chiralpak IA; hexane/IPA, 97:3; λ = 254 nm^{-1}; 1 mL/min): t_R = 10.4, 14.2 min; $[a]_D^{25}$ = +18.9 [c = 0.95, $CHCl_3$, (*S*)-cat.].

Compound 3r: Yield 83 mg (68%); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (s, 3 H, CH_3), 2.98–2.90 (dt, J = 20.4, 5.6 Hz, 1 H, CH_2), 3.42–3.33 (m, 1 H, CH_2), 3.60–3.56 (dd, J = 11.6, 6.0 Hz, 1 H, CH), 4.19 (s, 1 H, CH), 7.96–7.06 (m, 11 H, ArH, CH), 7.98–7.96 (d, J = 8.8 Hz, 2 H, ArH), 8.12–8.10 (d, J = 8.0 Hz, 2 H, ArH), 9.51 (s, 1 H, CHO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9, 31.6, 39.9, 45.5, 59.7, 118.7, 126.2, 126.3, 127.7, 127.8, 128.3, 128.5, 128.7, 128.8, 129.2, 129.5, 130.4, 131.8, 133.9, 138.3, 138.6, 139.2, 140.7, 150.4, 162.5, 171.5, 174.6, 192.2 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –65.2 (s, 3 F) ppm. HRMS (ESI): calcd. for $C_{29}H_{24}F_3N_2O_2$ $[M + H]^+$ 489.1785; found 489.1784. HPLC (Chiralpak IB; *n*-hexane/*i*PrOH, 90:10; λ = 254 nm; 1.0 mL/min): t_R = 10.8, 19.2 min; $[a]_D^{25}$ = –88.9 [c = 0.75, $CHCl_3$, *ee* >99%, (*S*)-cat.].

Compound 3s: Yield 50 mg (42%); pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (s, 1 H, CHO), 8.26 (d, J = 8.8 Hz, 2 H, ArH), 7.88 (d, J = 8.8 Hz, 2 H, ArH), 7.51–7.47 (m, 1 H, CH), 4.60–4.30 (m, 4 H, 2×CH_2), 3.94–3.87 (m, 2 H, 2×CH), 3.55–3.42 (m, 1 H, CH_2), 3.29–3.17 (m, 1 H, CH_2), 2.26 (s, 3 H, CH_3), 1.56 (t, J = 7.2 Hz, 3 H, CH_3), 1.39 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –62.2 (s, 3 F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.5, 172.3, 171.0, 169.9, 159.0, 150.4, 134.5, 129.7, 129.2, 128.3, 127.7, 126.1, 126.0, 118.3, 62.3, 61.8, 46.4, 42.7, 39.7, 26.1, 14.6, 13.9, 13.9 ppm. HRMS (ESI): calcd. for $C_{23}H_{24}F_3N_2O_6$ $[M + H]^+$ 481.1581; found 481.1588. HPLC (Chiralpak IB; *n*-hexane/*i*PrOH, 90:10; λ = 254 nm; 1.0 mL/min): t_R = 7.3, 8.2 min; $[a]_D^{25}$ = +75.8 [c = 1.0, $CHCl_3$, *ee* >99%, (*R*)-cat.].

Compound 3t: Yield 113 mg (84%); pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (s, 3 H, CH_3), 3.01–2.93 (dt, J = 20.4, 5.2 Hz, 1 H, CH_2), 3.43–3.35 (m, 1 H, CH_2), 3.56–3.52 (dd, J = 11.2, 5.6 Hz, 1 H, CH), 4.24 (s, 1 H, CH), 7.21–7.19 (d, J = 8.4 Hz, 2 H, ArH), 7.71–7.33 (m, 9 H, ArH, CH), 7.96–7.94 (d, J = 8.8 Hz, 2 H), 9.51 (s, 1 H, CHO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.1, 29.9, 30.8, 39.9, 45.0, 59.0, 112.7, 112.8, 118.0, 118.6, 126.4, 126.5, 128.5, 133.1, 137.7, 140.1, 143.4, 143.9, 150.1, 160.4, 173.4, 191.5 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –61.8 (s, 3 F) ppm. HRMS (ESI): calcd. for $C_{31}H_{22}F_3N_4O_2$ $[M + H]^+$ 539.1691; found 539.1689. HPLC (Chiralpak IB; *n*-hexane/*i*PrOH, 80:20; λ = 254 nm; 1.0 mL/min): t_R = 26.0, 36.4 min; $[a]_D^{25}$ = –68.9 [c = 0.4, $CHCl_3$, *ee* >99%, (*R*)-cat.].

Compound 3u: Yield 53 mg (58%); pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89–0.91 (d, J = 6.8 Hz, 3 H, CH_3), 1.26–1.24 (d, J = 7.2 Hz, 3 H, CH_3), 1.46–1.44 (dd, J = 6.4, 3.2 Hz, 1 H, CH), 2.24 (s, 3 H, CH_3), 2.43–2.37 (m, 1 H, CH_2), 2.66–2.63 (m, 1 H, CH_2), 3.05–2.99 (q, J = 7.2 Hz, 1 H, CH), 7.50–7.46 (t, J = 8.0 Hz, 1 H, CH), 7.63–7.61 (d, J = 8.8 Hz, 2 H, ArH), 8.03–8.01 (d, J = 8.4 Hz, 2 H, ArH), 9.47 (s, 1 H, CHO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.8, 17.4, 18.3, 27.1, 31.4, 32.7, 59.1, 118.3, 126.2, 128.6, 130.3, 133.8, 140.7, 141.6, 150.4, 162.2, 174.1, 193.0 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –59.3 (s, 3 F) ppm. HRMS (ESI): calcd. for $C_{19}H_{20}F_3N_2O_2$ $[M + H]^+$ 365.1464; found 365.1471. HPLC (Chiralpak IB; *n*-hexane/*i*PrOH, 95:5; λ = 254 nm; 1.0 mL/min): t_R = 9.5, 10.1 min; $[a]_D^{25}$ = +12.1 [c = 0.46, $CHCl_3$, *ee* 92%, (*S*)-cat.].

CCDC-808508 (for **3a**) 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.

Supporting Information (see footnote on the first page of this article): X-ray crystal structure determination data, NMR and HPLC spectra.

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