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Catalytic Asymmetric Synthesis of Diketopiperazines by Intramolecular Tsuji−Trost Allylation

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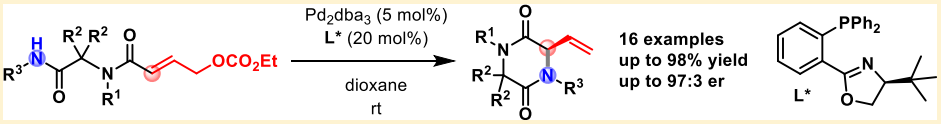
Supporting Information



ABSTRACT: We report the intramolecular Tsuji−Trost reaction of Ugi adducts to give spiro-diketopiperazines in high yield and with high enantioselectivity. This approach allows the catalytic asymmetric construction of a broad range of these medicinally important heterocycles under mild conditions, in two steps from cheap, commercially available starting materials.

INTRODUCTION

Heterocyclic small molecules are of immense importance in drug discovery. In recent years, the focus has shifted from purely aromatic heterocycles to scaffolds with a higher fraction of sp^3-hybridized atoms.[1] Evidently, this is accompanied by a higher number of stereogenic centers. Consequently, new strategies that allow straightforward access to such scaffolds with full stereochemical control are of high and continuous interest. In this context, intramolecular transition metal-catalyzed allylation reactions such as the Tsuji−Trost reaction offer great opportunities, given the high level of stereocontrol and typically mild reaction conditions.[2] While considerable progress has been made in applying this strategy to the synthesis of (hetero)cyclic molecules, we aim to expand the current state of the art to more challenging systems, such as precursors bearing diverse functionalities and/or not naturally predisposed to adopt a favorable conformation for cyclization.

As an example, spiro-2,5-diketopiperazines[3] (DKPs) display diverse biological activities (Figure 1), including neuroprotective properties,[4] anti-inflammatory activity,[5] and antiproliferative effects against drug-resistant human cancer cell lines.[6] Despite these diverse medicinal properties, only few synthetic approaches to spiro-DKPs have been reported. Recent examples include Diels−Alder type reactions,[7] intramolecular aminolysis,[8] and post-Ugi cyclizations[9,10] (Scheme 1A). Importantly, these methods invariably rely on chiral pool starting materials (mostly amino acids) as the source of chirality.[3] Obviously, this leads to limited substituent variation, while the D-configured antipodes are often only available at considerably higher cost. Catalytic asymmetric methods that allow full stereochemical control in a late stage of the synthesis would greatly expand the range of accessible spiro-DKPs and thus their application in drug discovery.

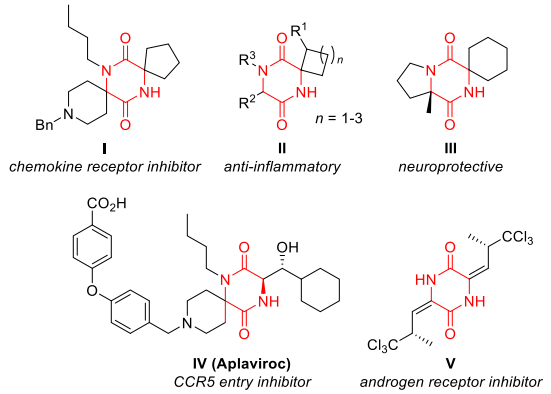


Figure 1. Bioactive compounds and natural products based on DKP scaffold.

However, to the best of our knowledge, no catalytic asymmetric methods to prepare DKPs have been reported to date. In light of our interest in multicomponent reactions, palladium catalysis, and asymmetric synthesis, we envisioned the use of the versatile Ugi reaction to construct compounds **2** as substrates for an enantioselective intramolecular Tsuji−Trost reaction (Scheme 1B). Ugi adducts **2** can be regarded as challenging substrates for Tsuji−Trost cyclization, given their high degree of substitution, potentially unfavorable minimum energy conformation, and electron-deficient allylic system.[11]

On the other hand, strong bases such as LiHMDS, *n*BuLi, or NaH are usually required for the allylation of amides as a result of their low nucleophilicity in their neutral form.[12] However, even a small excess of base could lead to racemization of the newly formed stereocenter (or isomerization of the alkene),

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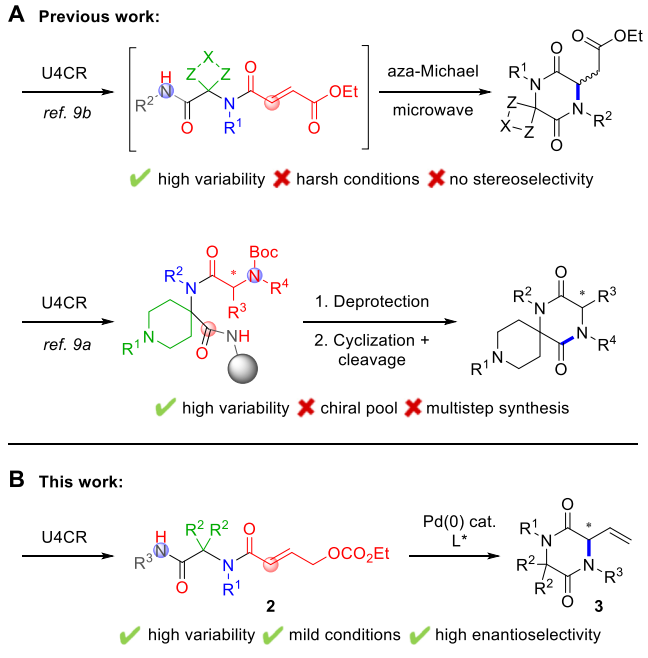
Scheme 1. Synthesis of 2,5 DKPs by Post-Ugi Cyclization

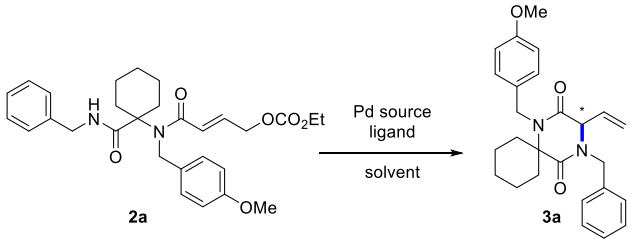


while a substoichiometric amount of base would result in incomplete conversion. Thus, we decided to employ the ethyl carbonate as the leaving group in order to generate the base in situ in precisely stoichiometric amount.

RESULTS AND DISCUSSION

We began our investigation by treating the Ugi adduct **2aa** with Pd_2dba_3 and dppe as the ligand in tetrahydrofuran (THF) at 50 °C. To our delight, the desired product **3a** could be obtained in 86% yield after only 30 min (Table 1, entry 1). After screening various other palladium sources ($Pd(PPh_3)_4$, $Pd(OAc)_2$, and $[PdClallyl]_2$), it became evident that none could match the efficiency of Pd_2dba_3, which was thus selected for the screening of chiral ligands (Figure 2). Interestingly, reaction with the Trost ligand (**L1**) gave no conversion. Ligands **L2**, **L5**, and **L7**–**9** showed poor enantioselectivity, despite the reasonable conversion (in case of **L5** and **L7**–**9**). Higher stereoselectivity was observed with **L3**, **L4**, and **L6**, albeit with modest conversion. Remarkably, the enantioselectivity achieved with **L2** was considerably lower than with **L3** and **L6**, despite their similarity in terms of steric and electronic properties. Ligand **L4**[13] was selected for further optimization, combining the highest enantioselectivity with reasonable conversion. Having selected **L4** as the best ligand, we performed the reaction at room temperature (entry 9), which led to a higher ee, although the reaction needed 24 h to reach completion and the yield dropped slightly. Switching the solvent to CH_2Cl_2 or toluene (entries 12 and 13) led to a decrease in enantioselectivity, whereas no reaction took place in dimethylformamide (DMF) (entry 14). On the other hand, using dioxane as the solvent gave the desired product in slightly better yield and enantioselectivity. Finally, we observed that the concentration plays a crucial role: running the reaction at higher dilution dramatically improved the yield as well as (to a minor degree) the enantioselectivity (entries 15–18), possibly as a result of the increased solubility of the palladium complex.[14] Under the optimized conditions, we screened some additional ligands and conditions in an attempt to further improve the reaction outcome.

Table 1. Optimization of Reaction Conditions



entry[a]	ligand	solvent	T (°C)	yield[b] (%)	er[c]
1	dppe[d]	THF	50	86	
2	**L1**[d]	THF	50		
3	**L2**[d]	THF	50	35	58/42
4	**L3**[d]	THF	50	12	80/20
5	**L4**[e]	THF	50	46	88/12
6	**L5**[d]	THF	50	62	58/42
7	**L6**[d]	THF	50	17	82/18
8	**L7**[d]	THF	50	75	63/27
9	**L8**[d]	THF	50	72	60/40
10	**L9**[d]	THF	50	74	51/49
11	**L4**[e]	THF	rt	31	93/7
12	**L4**[e]	CH_2Cl_2	rt	75	89/11
13	**L4**[e]	PhMe	rt	12	89/11
14	**L4**[e]	DMF	rt		
15	**L4**[e]	Diox	rt	41	94/6
16[f]	**L4**[e]	Diox	rt	53	95/5
17[g]	**L4**[e]	**Diox**	**rt**	**86**	**97/3**
18[h]	**L4**[e]	Diox	rt	58	97/3
19[g]	**L10**[e]	Diox	rt		
20[g]	**L11**[e]	Diox	rt		
21[g]	**L12**[e]	Diox	rt	46	96/4
22[g]	**L13**[e]	Diox	rt	49	71/29
23[g]	**L14**[e]	Diox	rt	81	70/30
24[g]	**L15**[e]	Diox	rt	88	95/5

[a]Reaction conditions: **2aa** (0.20 mmol), $Pd_2(dba)_3$ (0.01 mmol) in the indicated solvent (1 mL). [b]Isolated yield. [c]Determined by chiral HPLC. [d]0.02 mmol ligand. [e]0.04 mmol ligand. [f]0.05 M substrate concentration. [g]0.025 M substrate concentration. [h]0.01 M substrate concentration. Diox = 1,4-dioxane.

Bisoxazole ligands **L10** and **L11** did not promote the reaction. With ligand **L12**, which is highly similar to **L4**, the product was obtained in good stereoselectivity but with only moderate conversion. Ligand **L15** performed similarly as **L4**, but gave slightly lower enantioselectivity. Substitution of the *t*Bu group by an *i*Pr group led to significant erosion of the stereoselectivity (entries 22 and 23). Finally, the use of Me and *t*Bu carbonates proved less efficient, and the addition of commonly used halide additives (LiCl, nBu_4NCl, nBu_4NF) was found to completely inhibit the reaction (for details, see the Supporting Information).

We then examined the scope of the reaction by subjecting various Ugi adducts **2** to the optimized reaction conditions (Scheme 2). We were delighted to observe that the reaction tolerates various spiro ring sizes, affording the desired DKPs smoothly for spiro-fused cyclohexanes and cyclopentanes (**3a**, **3d**, **3g**, **3i**, **3j**, **3l**, **3n**, **3o**, and **3p**) with generally high yield and enantioselectivity. In the case of spiro-cycloheptanes (**3b**–**c**), the yields are generally lower, possibly because of the increased flexibility of the system. To our delight, cyclobutane-containing

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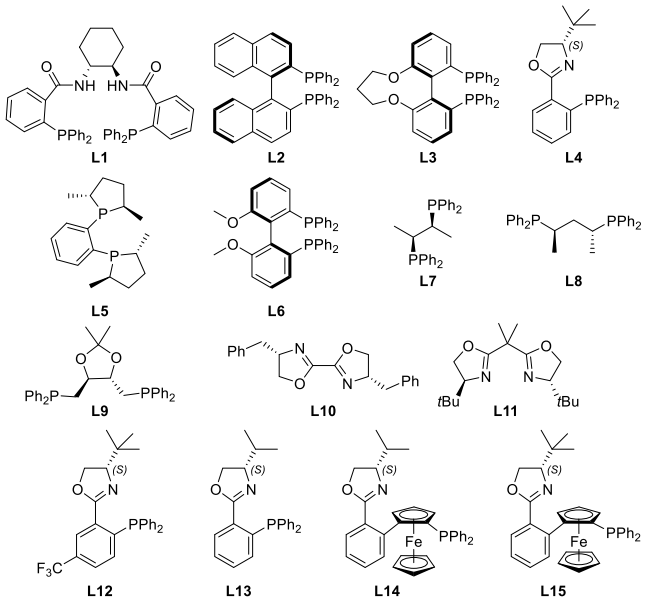
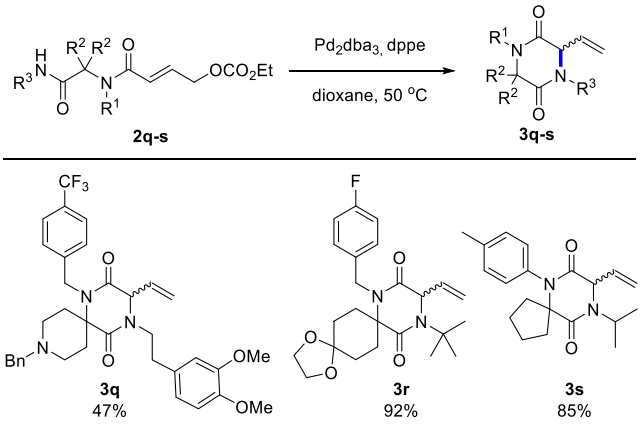


Figure 2. Chiral ligands screened.

substrates gave the corresponding DKP in excellent yield and enantioselectivity with a primary R^3 substituent (**3h**), while the yield dropped with a sterically demanding R^3 substituent (**3k**). The non-spiro products **3e**,**f** were obtained in the lowest yields and selectivity, likely because of the reduced Thorpe−Ingold effect. Substrate **2q** with a basic nitrogen atom in the spiro ring did not undergo the enantioselective cyclization, although the product **3q** could be obtained as a racemate with the achiral catalyst (Scheme 3).

A wide variety of R^3 substituents is tolerated in the reaction. In particular, aromatic and other electron-withdrawing substituents gave the highest yield and enantioselectivity (**3g**, **3h**, **3j**, **3l**, **3m**, **3n**, and **3o**). On the other hand, bulky electron-rich alkyl substituents led to lower yield, probably by increasing

Scheme 3. Scope of the Racemic Tsuji−Trost Cyclization[a]

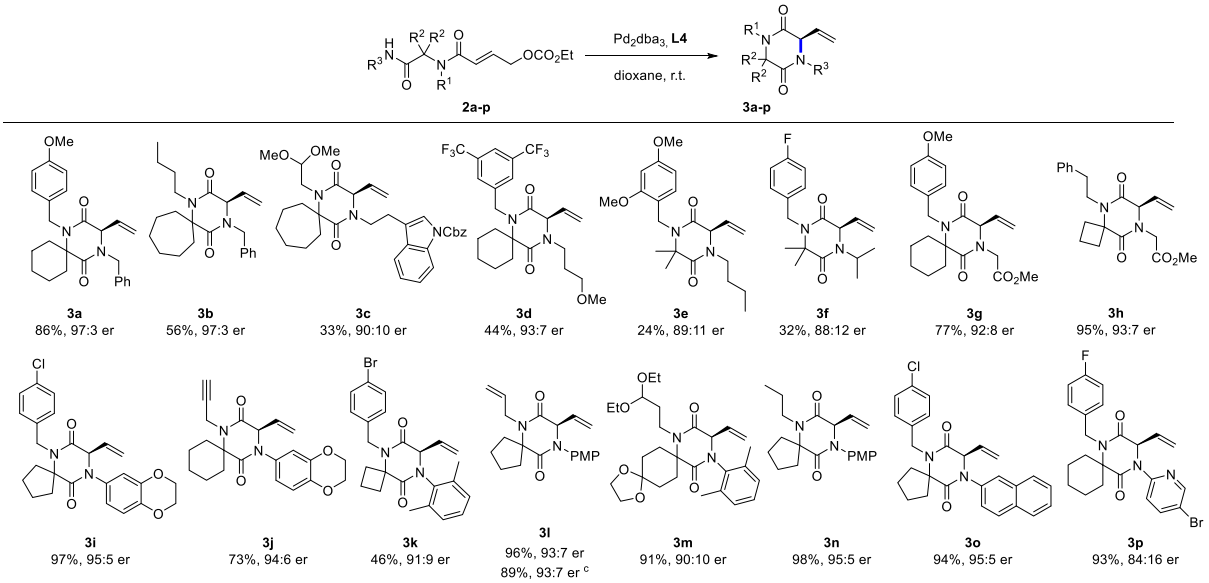


[a]Reaction conditions: **2q−s** (0.20 mmol), $Pd_2(dba)_3$ (0.01 mmol). dppe (0.04 mmol) in THF (2 mL) at 50 °C.

the pK_a of the corresponding amide (**3f**). Primary alkyl substituents present an intermediate scenario, giving the products (**3c**, **3d**, **3e**, and **3f**) in moderate yield. Reaction of *tert*-butyl amide **2r** afforded the product only under the racemic conditions (Scheme 3, **3r**). The lowest enantioselectivity was observed for **3o**, bearing a pyridyl R^3 substituent, probably because of the competing coordination of the Pd complex to the pyridine substituent, (partially) displacing the chiral oxazoline of **L4**. Aromatic R^1 substituents are not tolerated; product **3s** was only formed under the racemic conditions (Scheme 3). On the other hand, a broad range of (primary) aliphatic R^1 substituents containing diverse functionalities (esters, amides, acetals, ethers, alkenes, alkynes, carbamates, and aromatic bromides) were shown to be compatible with the reaction, regardless of their steric and electronic properties.

To further demonstrate the synthetic utility of our method, we isomerized the terminal vinyl group of **3a** to give

Scheme 2. Scope of the Reaction[a,b]



[a]Reaction conditions: **2aa−o** (0.20 mmol), $Pd_2(dba)_3$ (0.01 mmol). **L4** (0.04 mmol) in dioxane (8 mL; 0.025 M) at rt. [b]Determined by chiral SFC analysis. [c]1.0 mmol scale reaction.

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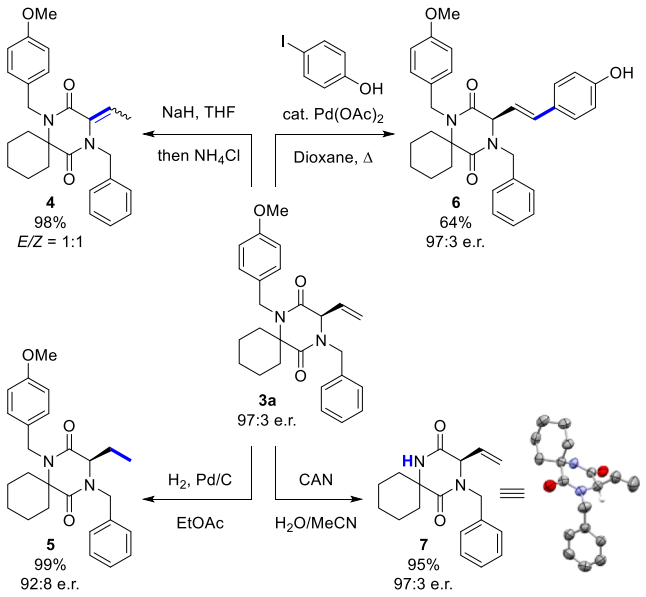
trisubstituted alkene **4** as a 1:1 mixture of *E*/*Z* isomers (Scheme 4). Catalytic hydrogenation of **3a** afforded **5** bearing

Scheme 4. Further Transformations of Spiro-DKP 3a



an ethyl side chain, leaving the two benzylic amides untouched. Furthermore, Heck coupling with the relatively challenging 4-iodophenol under harsh conditions afforded the corresponding alcohol **6** without loss of stereochemical information. Finally, we were able to selectively remove the PMB group of **3a** by treatment with cerium ammonium nitrate (CAN) in H_2O/MeCN to give the secondary amide **7**. X-ray crystallographic analysis of **7** allowed us to unequivocally confirm the absolute configuration of the new stereocenter (*R*).

The mechanism of DKP formation is proposed to proceed via the commonly accepted pathway for the Tsuji−Trost reaction, that is, via a π-allylpalladium intermediate and subsequent cross-coupling with the deprotonated secondary amide. As the pK_a of such amides is considerably lower than the generally accepted cutoff value of 25, C−N bond formation likely proceeds via S_N2-type substitution of the π-allylpalladium intermediate ("soft nucleophile mechanism").[15] The consistent performance of our reaction over various R^3 substituents suggests that all reactions proceed via the same pathway. The regioselectivity is fully governed by the explicit *E*-geometry of the π-allylpalladium intermediate, considering that cyclization can be expected to outcompete allyl isomerization.[15,16]

CONCLUSIONS

In conclusion, we successfully developed the first method for the synthesis of enantioenriched DKPs based on asymmetric catalysis rather than chiral pool starting materials. This two-step method provides access to a wide range of highly functionalized (spiro-)DKPs with good to excellent enantioselectivity. Moreover, the mild reaction conditions tolerate the presence of a wide range of functional groups. Finally, various further transformations to extend the range of accessible products were demonstrated.

EXPERIMENTAL SECTION

General Information. Commercially available reagents were purchased from Sigma-Aldrich, Fischer, Strem Chemicals or Fluorochem and were used as purchased unless mentioned otherwise. Solvents were purchased from VWR Chemicals or Sigma-Aldrich and used without purification, unless stated otherwise. Anhydrous, air-free solvents were obtained from a PureSolv MD 5 solvent purification system. Infrared (IR) spectra were recorded neat using a Shimadzu FTIR-8400s spectrophotometer and wavelengths are reported in cm^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE 600 (150.90 MHz for ^{13}C), Bruker AVANCE 500 (125.78 MHz for ^{13}C), Bruker AVANCE 400 (376.50 MHz for ^{19}F), or Bruker AVANCE 300 using the residual $CHCl_3$ as internal standard (^1H: δ 7.26 ppm, $^{13}C\{^1H\}$: δ 77.16 ppm). Chemical shifts (δ) are given in ppm and coupling constants (J) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), br (broad singlet), and m (multiplet) or combinations thereof. Electrospray ionization (ESI) high-resolution mass spectrometry was carried out using a Bruker micrOTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Flash chromatography was performed on Silicycle Silica-P Flash Silica Gel (particle size 40−63 μm, pore diameter 60 Å) using the indicated eluent. Thin layer chromatography (TLC) was performed using TLC plates from Merck (SiO_2, Kieselgel 60 F254 neutral, on aluminium with fluorescence indicator), and compounds were visualized by UV detection (254 nm) and/or $KMnO_4$ stain. SFC-MS analysis was conducted using a Shimadzu Nexera SFC-MS equipped with a Nexera X2 SIL-30AC autosampler, Nexera UC LC-30AD SF CO_2 pump, Nexera X2 LC-30AD liquid chromatograph, Nexera UC SFC-30A back pressure regulator, prominence SPD-M20A diode array detector, prominence CTO-20AC column oven, and CBM-20A system controller. Enantiomeric excess was determined by SFC-MS analysis using: Lux 3 μm Cellulose-1 column (cellulose tris(3,5-dimethylphenylcarbamate)) (column 1), Lux 3 μm Cellulose-2 column (cellulose tris(3-chloro-4-methylphenylcarbamate)) (column 2), Lux 3 μm Cellulose-3 column (cellulose tris(4-methylbenzoate), 150 × 4.6 mm) (column 3), and Lux 3 μm Cellulose-4 column (cellulose tris(4-chloro-3-methylphenyl-carbamate)) (column 4). A gradient of supercritical CO_2 (A) and methanol (B) was used. Method 1 (column 1): 2% B/98% A to 30% B/70% A over the course of 4 min and was maintained at 30% B/70% A for 2 min (flow: 1.5 mL/min). Method 2 (column 1): 2% B/98% A to 25% B/75% A over the course of 6 min and was maintained at 25% B/75% A for 1 min (flow: 2 mL/min). Method 3 (column 2): 2% B/98% A to 30% B/70% A over the course of 4 min and was maintained at 30% B/70% A for 2 min (flow: 2 mL/min). Method 4 (column 3): 2% B/98% A to 25% B/75% A over the course of 5 min and was maintained at 25% B/75% A for 1 min (flow: 1 mL/min). Method 5 (column 3): 2% B/98% A to 30% B/70% A over the course of 4 min and was maintained at 30% B/70% A for 2 min (flow: 2 mL/min). Method 6 (column 3): 2% B/98% A to 30% B/70% A over the course of 15 min and was maintained at 30% B/70% A for 1 min (flow: 2 mL/min). Method 7 (column 4): 2% B/98% A to 25% B/75% A over the course of 5 min and was maintained at 25% B/75% A for 1 min (flow: 2 mL/min). The sample injection volume was 5 μL. Mass spectrometry analyses were performed using a Shimadzu LCMS-2020 mass spectrometer. The data were acquired in full-scan APCI mode (MS) from m/z 100 to 800 in positive ionization mode. Data were processed using Shimadzu Labsolutions 5.82. Specific rotations were measured with an automatic AA-10 polarimeter.

Procedure A: Synthesis of the Ugi Precursors (GP-A). A solution of the corresponding aldehyde (5 mmol, 1 equiv) and amine (5 mmol, 1 equiv) in MeOH (1 M, 5 mL) was stirred for 30 min, then, the carboxylic acid **1** (871 mg, 5 mmol, 1 equiv) was added and, after 5 min, the corresponding isocyanide (5 mmol, 1 equiv) was added. The reaction mixture was stirred for 24 h, concentrated, and purified by silica gel column chromatography as described in the corresponding synthetic procedure.

Procedure B: Enantioselective Tsuji−Trost Cyclization (GP-B). A solution of $Pd_2(dba)_3$ (9 mg, 0.01 mmol, 0.05 equiv) and **L4** (16 mg, 0.04 mmol, 0.2 equiv) in dioxane (4 mL) was stirred at rt for 30 min, then, a solution of the corresponding Ugi precursor (0.2 mmol, 1 equiv) in dioxane (0.05 M, 4 mL) was added dropwise and

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stirred overnight. The reaction mixture was filtrated, concentrated, and purified by silica gel column chromatography as described in the corresponding synthetic procedure.

Procedure C: Racemic Tsuji–Trost Cyclization (GP-C). A solution of $Pd_2(dba)_3$ (9 mg, 0.01 mmol, 0.05 equiv), dppe (8 mg, 0.02 mmol, 0.1 equiv), and the corresponding Ugi precursor (0.2 mmol, 1 equiv) in dioxane (0.2 M, 2 mL) was stirred at 50 °C in an oil bath until full conversion of the starting material (monitored by TLC). The reaction mixture was filtrated, concentrated, and purified by silica gel column chromatography as described in the corresponding synthetic procedure.

Procedure D: Synthesis of Carboxylic Acid (GP-D). To a solution of the corresponding alcohol (18.303 g, 113.2 mmol, 1.00 equiv) in MeCN (1 M, 113.2 mL) were subsequently added CuBr (812 mg, 5.66 mmol, 0.05 equiv), 2,2′-bipyridine (884 mg, 5.66 mmol, 0.05 equiv), 6-tetramethylpiperidine-1-oxyl (884 mg, 5.66 mmol, 0.05 equiv), and 4-(dimethylamino)pyridine (2.074 g, 16.98 mmol, 0.15 equiv). An O_2-balloon was fit to the flask, then the reaction mixture was degassed under vacuum, and the flask was backfilled with oxygen. This procedure was repeated three times, and the solution was stirred overnight. When the oxidation was complete (checked by TLC), the mixture was cooled to 0 °C and H_2O_2 (35%, 12.170 mL, 1.25 equiv), and a solution of KH_2PO_4 (6.932 g, 50.94 mmol, 0.45 equiv) and $NaClO_2$ (20.476 g, 226.4 mmol, 2.00 equiv) in water (240 mL) was added dropwise. Stirring was continued for 24 h at room temperature.

After complete consumption of the aldehyde (checked by TLC), 1 M HCl was added, and the aqueous phase was extracted with EtOAc (3×). The combined organic phases were dried over Na_2SO_4 and filtered, and the solvent removed under vacuum.

*E-4-((Ethoxycarbonyl)oxy)but-2-enoic Acid (**1a**).* It was prepared according to **GP-D**. Obtained as a pale oil that solidified when cooled to −20 °C (yield: 98%, 19.320 g, 110.936 mmol) and was used without further purification. ^{1}H NMR (600 MHz, $CDCl_3$): δ 12.30–10.95 (br, 1H), 7.04 (dt, J = 15.8, 4.3 Hz, 1H), 6.08 (dd, J = 15.8, 1.9 Hz, 1H), 4.82 (dd, J = 4.3, 1.9 Hz, 2H), 4.23 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 171.1, 154.6, 143.4, 121.4, 65.4, 64.6, 14.2. IR (neat) ν_{max} (cm^{-1}): 3074, 2922, 1745, 1725, 1664, 1366, 1079, 1047. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_7H_{11}O_5$, 175.0601; found, 175.0612.

*E-4-((Methoxycarbonyl)oxy)but-2-enoic Acid (**1b**).* It was prepared according to **GP-D** on 5 mmol scale, obtained as a pale oil (yield: 97%, 777 mg, 4.85 mmol) and was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.29–9.10 (br, 1H), 7.03 (dt, J = 15.8, 4.3 Hz, 1H), 6.06 (d, J = 15.8 Hz, 1H), 4.82 (dd, J = 4.4, 2.0 Hz, 2H), 3.81 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.1, 155.4, 143.4, 121.6, 65.8, 55.3. IR (neat) ν_{max} (cm^{-1}): 2964, 1745, 1682, 1655, 1437, 1252, 1205, 932, 908, 787. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_6H_9O_5$, 161.0444; found, 161.0448.

*E-4-((tert-Butoxycarbonyl)oxy)but-2-enoic Acid (**1c**).* It was prepared according to **GP-D** on 5 mmol scale, obtained as a pale oil that solidified when cooled to −20 °C (yield: 95%, 960 mg, 4.75 mmol), and was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.61–8.43 (br, 1H), 7.04 (dt, J = 15.7, 4.3 Hz, 1H), 6.06 (dt, J = 15.8, 2.0 Hz, 1H), 4.75 (dd, J = 4.4, 2.0 Hz, 2H), 1.49 (s, 9H). ^{13}C NMR{^{1}H} (126 MHz, $CDCl_3$): δ 171.2, 153.0, 143.9, 121.4, 83.1, 64.8, 27.8 (3C). IR (neat) ν_{max} (cm^{-1}): 2982, 1742, 1701, 1369, 1273, 1252, 1155, 1121, 851, 756. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_9H_{15}O_5$, 203.0914; found, 203.0910.

*(E)-4-((1-(Benzylcarbamoyl)cyclohexyl)(4-methoxybenzyl)-amino)-4-oxobut-2-en-1-yl Ethyl Carbonate (**2aa**).* It was prepared according to **GP-A**. Purification of the crude material by silica gel column chromatography (40% EtOAc/cHex) provided the title compound as a pale oil in 82% yield (2.085 g, 4.1 mmol). R_f = 0.31 (50% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35–7.22 (m, 5H), 7.15 (d, J = 8.3 Hz, 2H), 6.86 (dt, J = 15.1, 5.0 Hz, 1H), 6.82 (d, J = 8.3 Hz, 3H), 6.36 (d, J = 15.1 Hz, 1H), 4.71 (d, J = 5.0 Hz, 2H), 4.62 (s, 2H), 4.40 (d, J = 5.5 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.78 (s, 3H), 2.44 (d, J = 12.5 Hz, 2H), 1.71 (td, J = 10.6, 5.4 Hz, 2H), 1.63–1.50 (m, 6H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 173.3, 168.4, 159.0, 154.7, 139.0, 138.7, 130.5, 128.7 (2C), 127.9 (2C), 127.6 (2C), 127.3 (2C), 124.7, 114.4, 66.5, 66.3, 64.4, 55.4, 47.9, 43.9, 33.1, 25.4 (2C), 23.0 (2C), 14.30. IR (neat) ν_{max} (cm^{-1}): 2366, 1745, 1670, 1510, 1355, 978, 704. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{29}H_{36}N_2O_6$, 509.2646; found, 509.2624.

*(E)-4-((1-(Benzylcarbamoyl)cyclohexyl)(4-methoxybenzyl)-amino)-4-oxobut-2-en-1-yl Methyl Carbonate (**2ab**).* It was prepared according to **GP-A**. Purification of the crude material by silica gel column chromatography (40% EtOAc/cHex) provided the title compound as a pale oil in 88% yield (2.176 g, 4.4 mmol). R_f = 0.30 (50% EtOAc/cHex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31–7.28 (m, 2H), 7.27–7.24 (m, 3H), 7.15 (d, J = 8.7 Hz, 2H), 6.86 (dt, J = 15.1, 5.0 Hz, 1H), 6.82 (d, J = 8.6 Hz, 2H), 6.78–6.75 (m, 1H), 6.36 (dt, J = 15.1, 1.8 Hz, 1H), 4.71 (dd, J = 5.0, 1.8 Hz, 2H), 4.62 (s, 2H), 4.40 (d, J = 5.5 Hz, 2H), 3.78 (s, 3H), 3.72 (s, 3H), 2.43 (d, J = 13.2 Hz, 2H), 1.70 (ddd, J = 13.4, 10.7, 3.9 Hz, 2H), 1.64–1.48 (m, 6H). ^{13}C NMR{^{1}H} (126 MHz, $CDCl_3$): δ 173.3, 168.3, 158.9, 155.3, 138.8, 138.6, 130.4, 128.7 (2C), 127.9 (2C), 127.6 (2C), 127.3, 124.7, 114.3 (2C), 66.5 (2C), 55.4, 55.1, 47.8, 43.9, 33.1 (2C), 25.4, 22.9 (2C). IR (neat) ν_{max} (cm^{-1}): 2932, 1749, 1663, 1610, 1512, 1445, 1244, 1173, 1030, 918, 727, 698. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{35}N_2O_6$, 495.2490; found, 495.2486.

*(E)-4-((1-(Benzylcarbamoyl)cyclohexyl)(4-methoxybenzyl)-amino)-4-oxobut-2-en-1-yl tert-Butyl Carbonate (**2ac**).* It was prepared according to **GP-A**. Purification of the crude material by silica gel column chromatography (40% EtOAc/cHex) provided the title compound as a pale oil in 78% yield (2.093 g, 3.9 mmol). R_f = 0.35 (50% EtOAc/cHex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33–7.28 (m, 2H), 7.27–7.24 (m, 3H), 7.15 (d, J = 8.7 Hz, 2H), 6.87 (dt, J = 15.1, 4.9 Hz, 1H), 6.83–6.79 (m, 3H), 6.34 (dt, J = 15.1, 1.8 Hz, 1H), 4.65 (dd, J = 4.9, 1.8 Hz, 2H), 4.61 (s, 2H), 4.39 (d, J = 5.5 Hz, 2H), 3.77 (s, 3H), 2.46–2.40 (m, 2H), 1.74–1.67 (m, 2H), 1.62–1.51 (m, 6H), 1.41 (s, 9H). ^{13}C NMR{^{1}H} (126 MHz, $CDCl_3$): δ 173.3, 168.5, 158.9, 153.0, 139.6, 138.7, 130.4, 128.7 (2C), 127.9 (2C), 127.6 (2C), 127.3, 124.3, 114.3 (2C), 82.7, 66.4, 65.5, 55.3, 47.9, 43.9, 33.1 (2C), 27.7 (3C), 25.4, 23.0 (2C). IR (neat) ν_{max} (cm^{-1}): 2934, 1742, 1661, 1512, 1275, 1246, 1157, 1119, 727, 698. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{31}H_{41}N_2O_6$, 537.2959; found, 537.2961.

*Benzyl (E)-3-(2-(1-(N-(2,2-Dimethoxyethyl)-4-((ethoxy carbonyl)-oxy)but-2-enamido)cycloheptane-1-carboxamido)ethyl)-1H-indole-1-carboxylate (**2b**).* It was prepared according to **GP-A**. Purification of the crude material by silica gel column chromatography (25% EtOAc/cHex) provided the title compound as a pale oil in 74% yield (2.508 g, 3.7 mmol). R_f = 0.33 (50% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.20–8.05 (m, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.50–7.44 (m, 2H), 7.42–7.31 (m, 5H), 7.29 (t, J = 7.8 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 6.76 (dt, J = 15.3, 4.8 Hz, 1H), 6.39 (d, J = 15.3 Hz, 1H), 5.42 (s, 2H), 4.69 (d, J = 4.8 Hz, 2H), 4.62–4.48 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.62–3.54 (m, 2H), 3.51 (q, J = 6.7 Hz, 2H), 3.22 (s, 6H), 2.85 (t, J = 6.9 Hz, 2H), 2.44–2.26 (m, 2H), 1.95–1.79 (m, 2H), 1.73–1.63 (m, 2H), 1.56–1.40 (m, 6H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 154.7, 150.8, 138.2, 136.5, 135.7, 135.2, 130.4, 128.8 (2C), 128.7, 128.5 (2C), 127.3, 124.8, 123.8, 123.0, 122.8, 119.1, 119.0, 115.3, 69.2, 68.7, 66.4, 66.2, 64.4, 55.3 (2C), 46.3 (2C), 39.3, 30.4 (2C), 25.2 (2C), 24.1 (2C), 14.3. IR (neat) ν_{max} (cm^{-1}): 2925, 1736, 1666, 1454, 1396, 1354, 1244, 1180, 1122, 1088, 1049, 1016, 731, 698. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{37}H_{48}N_3O_9$, 678.3385; found, 678.3357.

*(E)-4-((1-(Benzylcarbamoyl)cycloheptyl)(butyl)amino)-4-oxobut-2-en-1-yl Ethyl Carbonate (**2c**).* It was prepared according to **GP-A**. Purification of the crude material by silica gel column chromatography (25% EtOAc/cHex) provided the title compound as a white solid in 78% yield (1.789 g, 3.9 mmol). R_f = 0.27 (50% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41–7.14 (m, 5H), 6.85 (dt, J = 15.1, 4.8 Hz, 1H), 6.44 (dt, J = 15.1, 1.9 Hz, 1H), 6.16 (t, J = 5.6 Hz, 1H), 4.78 (dd, J = 4.8, 1.9 Hz, 2H), 4.43 (d, J = 5.6 Hz, 2H), 4.23 (q, J = 7.1 Hz, 2H), 3.51–3.28 (m, 2H), 2.43 (ddd, J = 15.2, 9.4, 1.6 Hz,

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2H), 2.09−1.89 (m, 2H), 1.76−1.68 (m, 2H), 1.67−1.47 (m, 8H), 1.38−1.25 (m, 5H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$) 175.1, 166.9, 154.8, 138.9, 138.4, 128.6 (2C), 127.9 (2C), 127.3, 123.6, 69.4, 66.3, 64.4, 44.8, 43.9 (2C), 35.7, 34.1, 30.2 (2C), 23.8 (2C), 20.3, 14.4, 13.7. IR (neat) ν_{max} (cm^{-1}): 3321, 2930, 1744, 1670, 1603, 1526, 1423, 1250, 1217, 1188, 997, 957, 793, 716, 644. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{26}H_{38}N_2NaO_5$, 481.2673; found, 481.2660.

*(E)-4-((3,5-Bis(trifluoromethyl)benzyl)(1-((3-methoxy propyl)-carbamoyl)cyclohexyl)amino)-4-oxobut-2-en-1-yl Ethyl Carbonate (**2d**).* It was prepared according to **GP-A**. Purification of the crude material by silica gel column chromatography (50% EtOAc/cHex) provided the title compound as a white solid in 67% yield (2.063 g, 3.8 mmol). R_f = 0.13 (50% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.84 (s, 2H), 7.78 (s, 1H), 6.93 (t, 1H), 6.85 (dt, J = 15.1, 4.8 Hz, 1H), 6.17 (d, J = 15.1 Hz, 1H), 4.80 (s, 2H), 4.66 (d, J = 4.8 Hz, 2H), 4.08 (q, J = 7.1 Hz, 2H), 3.47 (t, J = 5.7 Hz, 2H), 3.41−3.33 (m, 2H), 3.29 (s, 3H), 2.43−2.35 (m, 2H), 1.82−1.73 (m, 2H), 1.62−1.53 (m, 8H), 1.20 (t, J = 7.2 Hz, 3H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 172.8, 168.2, 154.5, 142.0, 139.6, 132.1 (q, J = 33.4 Hz, 2C), 126.6, 123.7 (2C), 123.2 (q, J = 274.8, 2C), 121.4, 72.1, 66.3, 65.9, 64.3, 58.8, 47.7, 38.6, 33.2, 28.8 (2C), 25.3, 22.8 (2C), 14.1. ^{19}F NMR{^{1}H} (376 MHz, $CDCl_3$): δ −62.9. IR (neat) ν_{max} (cm^{-1}): 2932, 1749, 1663, 1653, 1620, 1377, 1348, 1277, 1254, 1169, 1128, 1003, 995, 906, 791, 733, 706, 681, 409. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{27}H_{34}F_6N_2NaO_6$, 619.2213, found, 619.2189.

*(E)-4-((1-(Butylamino)-2-methyl-1-oxopropan-2-yl)(2,4-dimethoxybenzyl)amino)-4-oxobut-2-en-1-yl Ethyl Carbonate (**2e**).* It was prepared according to **GP-A**. Purification of the crude material by silica gel column chromatography (60% EtOAc/cHex) provided the title compound as a white solid in 54% yield (1.254 g, 2.7 mmol). R_f = 0.13 (50% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.50 (d, J = 8.4 Hz, 1H), 6.84 (dt, J = 15.2, 5.2 Hz, 1H), 6.49 (dd, J = 8.4, 2.4 Hz, 1H), 6.42 (d, J = 2.4 Hz, 1H), 6.23 (dt, J = 15.2, 1.7 Hz, 1H), 5.77 (t, J = 5.7 Hz, 1H), 4.64 (dd, J = 5.2, 1.8 Hz, 2H), 4.51 (s, 2H), 4.08 (q, J = 7.1 Hz, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 3.23 (td, J = 7.3, 5.6 Hz, 2H), 1.50−1.42 (m, 2H), 1.39 (s, 6H), 1.33−1.26 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 174.8, 167.0, 160.2, 156.9, 154.6, 138.5, 128.4, 123.8, 118.9, 104.2, 98.4, 66.3, 64.2, 62.5, 55.4, 55.2, 42.5, 39.6, 31.5, 24.1 (2C), 20.2, 14.2, 13.8. IR (neat) ν_{max} (cm^{-1}): 3283, 2962, 2934, 1744, 1643, 1616, 1508, 1412, 1373, 1248, 1209, 1198, 1175, 1159, 1115, 1045, 1036, 1007, 989, 960, 928, 791. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{24}H_{36}N_2NaO_7$, 487.2415; found, 487.2396.

*(E)-Ethyl (4-((4-Fluorobenzyl)(1-(isopropylamino)-2-methyl-1-oxopropan-2-yl)amino)-4-oxobut-2-en-1-yl)carbonate (**2f**).* It was prepared according to **GP-A**. Purification of the crude material by silica gel column chromatography (60% EtOAc/cHex) provided the title compound as a white solid in 47% yield (0.960 g, 2.35 mmol). R_f = 0.10 (50% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44−7.39 (m, 2H), 7.05 (t, J = 8.6 Hz, 2H), 6.88 (dt, J = 15.2 Hz, J = 4.7, 1H), 6.24 (d, J = 15.2 Hz, 1H), 5.49 (d, J = 7.8 Hz, 1H), 4.68 (d, J = 4.7 Hz, 2H), 4.64 (s, 2H), 4.11 (q, J = 7.1 Hz, 2H), 4.05 (m, 1H), 1.42 (s, 6H), 1.23 (t, J = 7.1 Hz, 3H), 1.14 (d, J = 7.8 Hz, 6H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 173.8, 167.6, 167.0, 162.2 (d, J = 245.8 Hz), 154.7, 139.2, 134.4, 128.0, 123.3 (2C), 115.9 (d, J = 21.5 Hz, 2C), 66.2, 64.4, 62.6, 47.0, 41.7 (2C), 22.7 (2C), 14.3. ^{19}F NMR{^{1}H} (376 MHz, $CDCl_3$): δ −115.3. IR (neat) ν_{max} (cm^{-1}): 3323, 2974, 1749, 1651, 1599, 1526, 1508, 1383, 1364, 1252, 1227, 1186, 1173, 1155, 1097, 1057, 1034, 827, 791, 500. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{30}FN_2O_5$, 409.2133; found, 409.2125.

*Methyl (E)-(1-(4-((Ethoxycarbonyl)oxy)-N-(4-methoxybenzyl)but-2-enamido)cyclohexane-1-carbonyl)glycinate (**2g**).* It was prepared according to **GP-A**. Purification of the crude material by silica gel column chromatography (60% EtOAc/cHex) provided the title compound as an orange oil in 79% yield (1.937 g, 3.95 mmol). R_f = 0.11 (50% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.22 (d, J = 8.6 Hz, 2H), 6.95−6.83 (m, 4H), 6.35 (d, J = 15.1 Hz, 1H), 4.70 (dd, J = 4.9, 1.5 Hz, 2H), 4.60 (s, 2H), 4.11 (q, J = 7.1 Hz, 2H), 4.00 (d, J = 5.0 Hz, 2H), 3.79 (s, 3H), 3.73 (s, 3H), 2.43−2.36 (m, 2H), 1.69−1.50 (m, 8H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 173.7, 170.7, 168.4, 159.0, 154.7, 139.1, 130.4 (2C), 127.5, 124.5, 114.4 (2C), 66.3, 66.2, 64.4, 55.4, 52.3, 47.8, 41.6 (2C), 32.9, 25.4, 22.8 (2C), 14.3. IR (neat) ν_{max} (cm^{-1}): 2932, 1744, 1664, 1612, 1512, 1401, 1364, 1244, 1202, 1173, 1028, 1007, 991, 789. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{34}N_2O_8$, 491.2388; found, 491.2390.

*Methyl (E)-(1-(4-((Ethoxycarbonyl)oxy)-N-phenethylbut-2-enamido)cyclobutane-1-carbonyl)glycinate (**2h**).* It was prepared according to **GP-A**. Purification of the crude material by silica gel column chromatography (25% EtOAc/cHex) provided the title compound as a yellow oil in 84% yield (1.875 g, 4.2 mmol). R_f = 0.28 (50% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04 (t, J = 5.8 Hz, 1H), 7.34−7.22 (m, 2H), 7.22−7.16 (m, 1H), 7.14 (d, J = 7.5 Hz, 2H), 6.88 (dt, J = 15.1, 4.7 Hz, 1H), 6.49 (d, J = 15.1 Hz, 1H), 4.78 (dd, J = 4.7, 2.0 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 4.00 (d, J = 5.8 Hz, 2H), 3.68 (s, 3H), 3.45 (t, J = 8.4 Hz, 2H), 2.88−2.63 (m, 4H), 2.28−2.21 (m, 2H), 1.82−1.66 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 174.3, 170.1, 166.7, 154.7, 138.9, 138.0, 128.7 (2C), 128.6 (2C), 126.7, 121.9, 66.0, 65.3, 64.4, 52.1, 47.2, 41.3 (2C), 36.7, 31.8, 14.7, 14.3. IR (neat) ν_{max} (cm^{-1}): 3321, 2930, 1744, 1670, 1655, 1597, 1528, 1508, 1423, 1377, 1252, 1190, 999, 793, 717, 644, 451, 407. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{23}H_{30}N_2NaO_7$, 469.1945; found, 469.1941.

*(E)-4-((4-Chlorobenzyl)(1-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-carbamoyl)cyclopentyl)amino)-4-oxobut-2-en-1-yl Ethyl Carbonate (**2i**).* It was prepared according to **GP-A**. Purification of the crude material by silica gel column chromatography (35% EtOAc/cHex) provided the title compound as a pale oil in 76% yield (2.063 g, 3.8 mmol). R_f = 0.41 (50% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.37 (s, 1H), 7.30 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 8.3 Hz, 2H), 7.10 (d, J = 2.5 Hz, 1H), 6.95 (dt, J = 15.1, 4.7 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 6.75 (d, J = 8.7 Hz, 1H), 6.19 (d, J = 15.0 Hz, 1H), 4.68 (dd, J = 4.7, 1.9 Hz, 2H), 4.62 (s, 2H), 4.20−4.17 (m, 4H), 4.07 (q, J = 7.1 Hz, 2H), 2.81−2.75 (m, 2H), 1.86−1.80 (m, 2H), 1.69−1.62 (m, 4H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 170.8, 169.2, 154.5, 143.4, 140.4, 140.1, 136.7, 133.2, 132.1, 129.1 (2C), 127.3 (2C), 123.0, 117.0, 113.4, 109.5, 74.6, 65.9, 64.4, 64.3, 64.3, 50.5, 36.0 (2C), 22.8 (2C), 14.1. IR (neat) ν_{max} (cm^{-1}): 2328, 1659, 1502, 1414, 1256, 1244, 1203, 1190, 1067, 1014, 982, 812, 783, 608, 482, 451, 411. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{28}H_{31}ClN_2NaO_7$, 565.1712; found, 565.1687.

*(E)-4-((1-((2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)carbamoyl)-cyclohexyl)(prop-2-yn-1-yl)amino)-4-oxobut-2-en-1-yl Ethyl Carbonate (**2j**).* It was prepared according to **GP-A**. Purification of the crude material by silica gel column chromatography (40% EtOAc/cHex) provided the title compound as a pale solid in 77% yield (1.812 g, 3.85 mmol). R_f = 0.51 (50% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.48 (s, 1H), 7.07 (d, J = 2.5 Hz, 1H), 6.91−6.80 (m, 2H), 6.72 (d, J = 8.7 Hz, 1H), 6.55 (d, J = 15.2 Hz, 1H), 4.76 (dd, J = 4.8, 1.9 Hz, 2H), 4.31−4.02 (m, 8H), 2.43 (t, J = 2.4 Hz, 1H), 2.38−2.24 (m, 2H), 2.17−2.06 (m, 2H), 1.74−1.64 (m, 2H), 1.59−1.37 (m, 4H), 1.29 (t, J = 7.2 Hz, 3H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 171.5, 168.5, 154.7, 143.4, 140.2, 139.6, 132.0, 123.6, 117.0, 113.7, 109.8, 80.0, 73.8, 66.9, 66.1, 64.4, 64.4, 64.3, 35.0, 32.9 (2C), 25.3, 22.7 (2C), 14.3. IR (neat) ν_{max} (cm^{-1}): 3288, 2934, 1744, 1664, 1504, 1406, 1379, 1300, 1254, 1240, 1202, 1173, 1067, 885, 802, 791, 737. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{25}H_{30}N_2NaO_7$, 493.1945; found, 493.1935.

*(E)-4-((4-Bromobenzyl)(1-((2,6-dimethylphenyl)carbamoyl)-cyclobutyl)amino)-4-oxobut-2-en-1-yl Ethyl Carbonate (**2k**).* It was prepared according to **GP-A**. Purification of the crude material by silica gel column chromatography (40% EtOAc/cHex) provided the title compound as a white solid in 62% yield (1.685 g, 3.1 mmol). R_f = 0.53 (50% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.94 (s, 1H), 7.47 (d, J = 8.2 Hz, 2H), 7.12 (d, J = 8.2 Hz, 2H), 7.06−6.98 (m, 3H), 6.94 (dt, J = 15.1, 4.5 Hz, 1H), 6.16 (d, J = 15.1 Hz, 1H), 4.66 (d, J = 4.5 Hz, 2H), 4.46 (s, 2H), 4.05 (q, J = 7.1 Hz, 2H), 2.83 (s, 2H), 2.31 (s, 2H), 2.12 (s, 6H), 1.85−1.68 (m, 2H), 1.19 (t, J =

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7.2 Hz, 3H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 170.9, 167.1, 154.2, 140.4, 136.7, 134.7 (2C), 134.0, 131.8 (2C), 127.9 (2C), 127.5 (2C), 126.7, 121.6, 121.2, 66.1, 65.6, 64.1, 48.3, 18.1 (2C), 14.7, 14.0. Two secondary carbons of the cyclobutane are not visible. IR (neat) ν_{max} (cm^{-1}): 2957, 2336, 1745, 1664, 1489, 1462, 1396, 1379, 1248, 11 981, 1009, 787, 770, 480. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{32}BrN_2O_5$, 543.1489; found, 543.1462.

*(E)-4-(Allyl(1-((4-methoxyphenyl)carbamoyl)cyclopentyl)-amino)-4-oxobut-1-en-1-yl Ethyl Carbonate (**2l**).* It was prepared according to **GP-A**. Purification of the crude material by silica gel column chromatography (30% EtOAc/cHex) provided the title compound as a pale solid in 66% yield (1.421 g, 3.3 mmol). R_f = 0.43 (50% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.47 (s, 1H), 7.41 (d, J = 9.0 Hz, 2H), 6.92 (dt, J = 15.1, 4.8 Hz, 1H), 6.83 (d, J = 9.0 Hz, 2H), 6.38 (dt, J = 15.1, 1.8 Hz, 1H), 5.91 (ddt, J = 17.1, 10.4, 4.4 Hz, 1H), 5.29 (d, J = 10.4 Hz, 1H), 5.25 (d, J = 17.1 Hz, 1H), 4.76 (dd, J = 4.8, 1.9 Hz, 2H), 4.20 (q, J = 7.1 Hz, 2H), 4.06−3.96 (m, 2H), 3.77 (s, 3H), 2.94−2.76 (m, 2H), 1.99−1.90 (m, 2H), 1.77−1.65 (m, 4H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 171.3, 169.3, 156.2, 154.8, 139.5, 134.9, 131.8, 123.9, 121.6 (2C), 117.4, 114.2 (2C), 74.6, 66.2, 64.5, 55.6, 50.0, 36.0 (2C), 23.0 (2C), 14.4. IR (neat) ν_{max} (cm^{-1}): 3340, 2957, 1742, 1663, 1624, 1510, 1408, 1396, 1257, 1244, 1227, 1202, 1169, 1034, 993, 976, 959, 920, 829, 789, 523, 419. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{23}H_{30}N_2NaO_6$, 453.1996; found, 453.1989.

*(E)-4-((3,3-Diethoxypropyl)(8-((2,6-dimethylphenyl)carbamoyl)-1,4-dioxaspiro[4.5]decan-8-yl)amino)-4-oxobut-2-en-1-yl Ethyl Carbonate (**2m**).* It was prepared according to **GP-A**. Purification of the crude material by silica gel column chromatography (50% EtOAc/cHex) provided the title compound as a pale solid in 58% yield (1.713 g, 2.9 mmol). R_f = 0.17 (50% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.47 (s, 1H), 7.02−6.84 (m, 3H), 6.77 (dt, J = 15.1, 4.4 Hz, 1H), 6.59 (dt, J = 15.1, 2.2 Hz, 1H), 4.69 (t, J = 4.4, 2.2 Hz, 2H), 4.41 (t, J = 4.7 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.84 (s, 4H), 3.62−3.49 (m, 4H), 3.44−3.30 (m, 2H), 2.52−2.38 (m, 2H), 2.31 (t, J = 11.0 Hz, 2H), 2.09 (s, 6H), 1.96−1.80 (m, 4H), 1.62−1.52 (m, 2H), 1.22 (t, J = 7.1 Hz, 3H), 1.08 (t, J = 7.1 Hz, 6H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 171.4, 168.6, 154.4, 138.4, 134.9 (2C), 134.1, 127.9 (2C), 126.4, 124.0, 107.5, 100.7, 65.9, 65.1, 64.1, 64.0 (2C), 61.9 (2C), 41.1, 35.2 (2C), 31.3 (2C), 30.3, 18.6 (2C), 15.0 (2C), 14.0. IR (neat) ν_{max} (cm^{-1}): 3339, 2976, 2935, 1744, 1684, 1621, 1516, 1366, 1248, 1230, 1198, 1171, 1144, 1109, 1094, 1070, 1038, 991, 959, 947, 926, 899, 889, 866, 852, 793, 775. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{31}H_{46}N_2NaO_9$, 613.3096; found, 613.3074.

*(E)-Ethyl (4-((1-((4-Methoxyphenyl)carbamoyl)cyclopentyl)-(propyl)amino)-4-oxobut-2-en-1-yl)carbonate (**2n**).* It was prepared according to **GP-A**. Purification of the crude material by silica gel column chromatography (30% EtOAc/cHex) provided the title compound as a white solid in 63% yield (1.362 g, 3.15 mmol). R_f = 0.44 (50% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.60 (s, 1H), 7.41 (d, J = 9.0 Hz, 2H), 6.91 (dd, J = 13.5, 4.7 Hz, 1H), 6.83 (d, J = 9.0 Hz, 2H), 6.47 (d, J = 13.5 Hz, 1H), 4.80 (d, J = 4.7 Hz, 2H), 4.23 (q, J = 7.1 Hz, 2H), 3.78 (s, 3H), 3.38 (m, 2H), 2.88−2.75 (m, 2H), 1.95−1.82 (m, 2H), 1.80−1.68 (m, 4H), 1.68−1.55 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H), 0.85 (t, J = 7.4 Hz, 3H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 172.2, 169.2, 156.3, 154.9, 139.0, 132.0, 124.0, 121.7 (2C), 114.3 (2C), 74.2, 66.3, 64.6, 55.7, 49.6, 36.5, 24.4 (2C), 23.0 (2C), 14.5, 11.4. IR (neat) ν_{max} (cm^{-1}): 2935, 1745, 1664, 1620, 1514, 1448, 1418, 1252, 1234, 1198, 1155, 1140, 1026, 789, 700. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{33}N_2O_6$, 433.2333; found, 433.2345.

*(E)-4-((4-Chlorobenzyl)(1-(naphthalen-2-ylcarbamoyl)-cyclopentyl)amino)-4-oxobut-2-en-1-yl Ethyl Carbonate (**2o**).* It was prepared according to **GP-A**. Purification of the crude material by silica gel column chromatography (40% EtOAc/cHex) provided the title compound as an orange solid in 68% yield (1.819 g, 3.4 mmol). R_f = 0.55 (50% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.86 (s, 1H), 8.19 (s, 1H), 7.88−7.72 (m, 3H), 7.48−7.36 (m, 3H), 7.33 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.04 (dt, J = 15.1, 4.7 Hz, 1H), 6.25 (dt, J = 15.1, 1.8 Hz, 1H), 4.73 (dd, J = 4.7, 1.9 Hz, 2H), 4.67 (s, 2H), 4.11 (q, J = 7.1 Hz, 2H), 2.90 (d, J = 13.3 Hz, 2H), 1.97−1.86 (m, 2H), 1.76−1.67 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 171.4, 169.6, 154.6, 140.8, 136.7, 135.9, 134.0, 133.5, 130.6, 129.3 (2C), 128.7, 127.7 (2C), 127.6, 127.5, 126.5, 124.9, 123.2, 120.2, 116.5, 75.0, 66.0, 64.5, 50.8, 36.1 (2C), 22.9 (2C), 14.2. IR (neat) ν_{max} (cm^{-1}): 3244, 2957, 2326, 1744, 1663, 1524, 1491, 1429, 1400, 1354, 1256, 1236, 1215, 1194, 1094, 814, 787, 731, 474. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{30}H_{31}ClN_2NaO_5$, 557.1814; found, 557.1788.

*(E)-4-((1-((5-Bromopyridin-2-yl)carbamoyl)cyclohexyl)(4-fluorobenzyl)amino)-4-oxobut-2-en-1-yl Ethyl Carbonate (**2p**).* It was prepared according to **GP-A**. Purification of the crude material by silica gel column chromatography (30% EtOAc/cHex) provided the title compound as a pale solid in 46% yield (1.294 g, 2.3 mmol). R_f = 0.36 (50% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.96 (s, 1H), 8.26 (d, J = 2.5 Hz, 1H), 8.00 (d, J = 8.9 Hz, 1H), 7.69 (dd, J = 8.8, 2.5 Hz, 1H), 7.24 (dd, J = 8.5, 5.3 Hz, 2H), 6.99 (t, J = 8.6 Hz, 2H), 6.94 (dt, J = 15.1, 4.6 Hz, 1H), 6.37 (dt, J = 15.1, 1.9 Hz, 1H), 4.70 (dd, J = 4.7, 1.9 Hz, 2H), 4.66 (s, 2H), 4.10 (q, J = 7.1 Hz, 2H), 2.43−2.32 (m, 2H), 1.84−1.75 (m, 2H), 1.70−1.51 (m, 6H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 171.7, 168.6, 162.1 (d, J = 246.7 Hz), 154.5, 148.7, 140.4, 140.4, 133.5 (d, J = 3.1 Hz), 128.2 (d, J = 8.0 Hz, 2C), 123.2, 115.9 (d, J = 21.6 Hz, 2C), 115.1, 114.2, 66.7, 66.0, 64.4, 47.8, 32.6 (2C), 25.3, 22.6 (2C), 14.2. ^{19}F NMR{^{1}H} (376 MHz, $CDCl_3$): δ −114.5. IR (neat) ν_{max} (cm^{-1}): 2934, 2330, 1745, 1502, 1452, 1369, 1288, 1256, 1223, 1190, 1157, 1128, 1092, 1001, 824, 791, 737, 631, 515. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{30}BrFN_3O_5$, 562.1347; found, 562.1326.

*(E)-4-((1-Benzyl-4-((3,4-dimethoxyphenethyl)carbamoyl)-piperidin-4-yl)(4-(trifluoromethyl)benzyl)amino)-4-oxobut-2-en-1-yl Ethyl Carbonate (**2q**).* It was prepared according to **GP-A**. Purification of the crude material by silica gel column chromatography (80% EtOAc/cHex) provided the title compound as a pale oil in 49% yield (1.743 g, 2.45 mmol). R_f = 0.10 (90% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.58 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.31−7.16 (m, 5H), 6.87−6.81 (m, 2H), 6.78 (m, 2H), 6.74 (d, J = 7.81 Hz, 1H), 6.10 (d, J = 15.1 Hz, 1H), 4.68 (d, J = 4.7, 2H), 4.58 (s, 2H), 4.04 (q, J = 7.1 Hz, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.56 (q, J = 6.8 Hz, 2H), 3.31 (s, 2H), 2.78 (t, J = 6.8 Hz, 2H), 2.62−2.58 (m, 2H), 2.56−2.50 (m, 2H), 2.06 (t, J = 11.6 Hz, 2H), 1.75 (m, 2H), 1.16 (t, J = 7.1 Hz, 3H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 171.7, 168.7, 154.5, 149.1, 147.7, 142.6, 140.0, 138.0, 131.4, 129.7 (q, J = 32.5 Hz), 129.1 (2C), 128.2 (2C), 127.1, 126.3 (2C), 125.9 (d, J = 3.7 Hz, 2C), 124.0 (d, J = 272.0 Hz), 123.6, 120.8, 111.9, 111.2, 65.9, 64.9, 64.3, 62.7, 55.8, 55.8, 50.3 (2C), 48.3, 40.4, 35.0, 32.8 (2C), 14.1. ^{19}F NMR{^{1}H} (376 MHz, $CDCl_3$): δ −62.4. IR (neat) ν_{max} (cm^{-1}): 2915, 1649, 1323, 1279, 1261, 1238, 1159, 1119, 1067, 1028, 1016, 737, 700. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{38}H_{45}F_3N_3O_7$, 712.3204; found, 712.3232.

*(E)-4-((8-(tert-Butylcarbamoyl)-1,4-dioxaspiro[4.5]decan-8-yl)(4-fluorobenzyl)amino)-4-oxobut-2-en-1-yl Ethyl Carbonate (**2r**).* It was prepared according to **GP-A**. Purification of the crude material by silica gel column chromatography (50% EtOAc/cHex) provided the title compound as a white solid in 74% yield (1.926 g, 3.7 mmol). R_f = 0.25 (50% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.19 (dd, J = 8.1, 5.3 Hz, 2H), 6.96 (t, J = 8.3 Hz, 2H), 6.80 (dt, J = 15.1, 4.7 Hz, 1H), 6.40−6.30 (br, 1H), 6.26 (d, J = 15.1 Hz, 1H), 4.63 (d, J = 4.7 Hz, 2H), 4.55 (s, 2H), 4.04 (q, J = 7.1 Hz, 2H), 3.80 (s, 4H), 2.35−2.24 (m, 2H), 1.96−1.83 (m, 2H), 1.82−1.69 (m, 2H), 1.56−1.46 (m, 2H), 1.19 (s, 9H), 1.14 (t, J = 7.1 Hz, 3H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 171.1, 168.2, 161.7 (d, J = 246.0 Hz), 154.3, 138.9, 134.1, 127.8 (d, J = 7.7 Hz, 2C), 123.9, 115.5 (d, J = 21.5 Hz, 2C), 107.3, 65.7 (2C), 65.6, 64.0, 63.9, 50.7 (2C), 47.3, 31.3 (2C), 30.3, 28.2 (3C), 13.9. ^{19}F NMR{^{1}H} (376 MHz, $CDCl_3$): δ −116.0. IR (neat) ν_{max} (cm^{-1}): 3357, 2296, 1753, 1664, 1616, 1508, 1410, 1367, 1246, 1219, 1190, 1105, 1095, 1040, 951, 895, 862, 814, 791. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{38}FN_2O_7$, 521.2658; found, 521.2641.

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*(E)-Ethyl (4-((1-(Isopropylcarbamoyl)cyclopentyl)(p-tolyl)-amino)-4-oxobut-2-en-1-yl)carbonate (**2s**).* It was prepared according to **GP-A**. Purification of the crude material by silica gel column chromatography (50% EtOAc/cHex) provided the title compound as a pale solid in 67% yield (1.395 g, 3.35 mmol). R_f = 0.27 (50% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.14 (d, J = 8.3 Hz, 2H), 7.07 (d, J = 8.3 Hz, 2H), 6.72 (dt, J = 15.3, 5.1 Hz, 1H), 6.43 (d, J = 7.5 Hz, 1H), 5.68 (d, J = 15.3 Hz, 1H), 4.52 (d, J = 5.1 Hz, 2H), 4.05 (m, 3H), 2.33 (s, 3H), 2.30−2.20 (m, 2H), 1.77−1.66 (m, 2H), 1.58−1.50 (m, 4H), 1.19 (t, J = 7.1 Hz, 3H), 1.13 (d, J = 7.5 Hz, 6H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 173.0, 166.1, 154.5, 138.4, 137.4, 137.1, 129.9 (2C), 129.8 (2C), 124.4, 74.0, 66.1, 64.1, 41.5, 36.8 (2C), 23.2 (2C), 22.3 (2C), 21.1, 14.2. IR (neat) ν_{max} (cm^{-1}): 3346, 2943, 1744, 1655, 1510, 1375, 1244, 1227, 1169, 1036, 966, 829, 791, 685, 525. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{23}H_{33}N_2O_5$, 417.2384; found, 417.2381.

*(R)-4-Benzyl-1-(4-methoxybenzyl)-3-vinyl-1,4-diazaspiro[5.5]-undecane-2,5-dione (**3a**).* It was prepared according to **GP-B** using **2a**. The crude material was purified by silica gel column chromatography (20% EtOAc/cHex) provided the title compound as a colorless oil in 86% yield (71.9 mg, 0.17 mmol). R_f = 0.36 (30% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 (t, J = 7.0 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 7.25−7.21 (m, 2H), 7.10 (d, J = 8.3 Hz, 2H), 6.82 (d, J = 8.3 Hz, 2H), 5.98 (ddd, J = 16.9, 10.3, 5.5 Hz, 1H), 5.50−5.42 (m, 2H), 5.36 (d, J = 16.9 Hz, 1H), 4.94 (d, J = 15.8 Hz, 1H), 4.57 (d, J = 5.6 Hz, 1H), 4.41 (d, J = 15.8 Hz, 1H), 3.84 (d, J = 14.8 Hz, 1H), 3.78 (s, 3H), 2.42 (dddd, J = 17.5, 13.1, 8.7, 4.3 Hz, 1H), 2.05−1.99 (m, 1H), 1.96−1.92 (m, 1H), 1.80 (td, J = 12.9, 5.2 Hz, 1H), 1.74−1.53 (m, 5H), 1.10 (tdd, J = 12.9, 9.0, 3.3 Hz, 1H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 169.7, 167.2, 158.7, 136.1, 133.2, 130.4, 129.0 (2C), 128.2 (2C), 128.0 (3C), 119.0, 114.0 (2C), 63.1, 61.8, 55.4, 47.6, 45.0, 36.0, 33.3, 24.6, 23.5, 22.3. IR (neat) ν_{max} (cm^{-1}): 2926, 2851, 1649, 1512, 1452, 1410, 1354, 1300, 1242, 1175, 1032, 802, 731, 698, 625, 419. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{26}H_{31}N_2O_3$, 419.2329; found, 419.2343. $[\alpha]_D^{20}$ +100.0 (c = 0.2, $CHCl_3$). SFC-MS (method 5) er: 97:3; tret (major) = 3.875 min (96.9%), tret (minor) = 4.067 min (3.1%).

*Benzyl-(R)-3-(2-(1-(2,2-dimethoxyethyl)-2,5-dioxo-3-vinyl-1,4-diazaspiro[5.6]dodecan-4-yl)ethyl)-1H-indole-1-carboxylate (**3b**).* It was prepared according to **GP-B** using **2b**. The crude material was purified by silica gel column chromatography (30% EtOAc/cHex) provided the title compound as a pale oil in 33% yield (37.8 mg, 0.07 mmol). R_f = 0.22 (30% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.47 (d, J = 7.2 Hz, 2H), 7.45−7.36 (m, 4H), 7.32 (t, J = 7.6 Hz, 1H), 7.26 (t, J = 7.2 Hz, 1H), 5.84 (ddd, J = 16.8, 10.2, 6.2 Hz, 1H), 5.42 (s, 2H), 5.35 (d, J = 10.8 Hz, 1H), 5.25 (d, J = 17.1 Hz, 1H), 4.67 (t, J = 5.0 Hz, 1H), 4.41 (d, J = 6.1 Hz, 1H), 4.09 (dt, J = 14.6, 7.4 Hz, 1H), 3.54 (dd, J = 13.9, 4.6 Hz, 1H), 3.42 (s, 3H), 3.40−3.35 (m, 4H), 3.17 (dt, J = 13.5, 7.8 Hz, 1H), 2.98 (t, J = 7.7 Hz, 2H), 2.67 (dd, J = 15.7, 11.1 Hz, 1H), 2.18 (dd, J = 15.9, 7.8 Hz, 1H), 2.05−1.99 (m, 2H), 1.88 (q, J = 7.2 Hz, 1H), 1.74−1.61 (m, 4H), 1.55−1.49 (m, 2H), 1.37−1.31 (m, 1H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$) 169.6, 166.2, 150.8, 135.1, 133.4, 133.3, 130.4, 128.9 (2C), 128.8, 128.6 (2C), 124.9, 123.1, 119.5, 119.1, 118.3, 115.5, 103.0, 76.9, 68.7, 67.9, 63.8, 56.0, 55.9, 47.3, 46.4, 39.7, 36.5, 31.5, 31.3, 25.7, 23.6, 22.9. IR (neat) ν_{max} (cm^{-1}): 2934, 1736, 1666, 1454, 1396, 1354, 1244, 1180, 1122, 1088, 1049, 1016, 731, 698. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{34}H_{42}N_3O_6$, 588.3068; found, 588.3048. $[\alpha]_D^{20}$ +40.0 (c = 0.3, $CHCl_3$). SFC-MS (method 1) er: 90:10; tret (major) = 5.446 min (89.7%), tret (minor) = 6.092 min (10.3%).

*(R)-4-Benzyl-1-butyl-3-vinyl-1,4-diazaspiro[5.6]dodecane-2,5-dione (**3c**).* It was prepared according to **GP-B** using **2c**. The crude material was purified by silica gel column chromatography (30% EtOAc/cHex) provided the title compound as a colorless oil in 56% yield (41.3 mg, 0.11 mmol). R_f = 0.31 (30% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41−7.26 (m, 3H), 7.25−7.11 (m, 2H), 5.89 (ddd, J = 17.1, 10.3, 6.0 Hz, 1H), 5.46 (d, J = 14.7 Hz, 1H), 5.42 (dd, J = 10.2, 1.5 Hz, 1H), 5.33 (dd, J = 17.1, 1.5 Hz, 1H), 4.43 (d, J = 6.0 Hz, 1H), 3.83 (d, J = 14.7 Hz, 1H), 3.51 (ddd, J = 13.5, 11.1, 5.1 Hz, 1H), 3.25 (ddd, J = 13.5, 11.2, 4.9 Hz, 1H), 2.89−2.72 (m, 1H), 2.12 (dd, J = 14.7, 9.0 Hz, 1H), 2.08−1.88 (m, 3H), 1.77 (q, J = 7.6 Hz, 2H), 1.71−1.53 (m, 6H), 1.48−1.23 (m, 3H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 170.0, 165.0, 136.0, 133.3, 128.9 (2C), 128.3 (2C), 127.9, 119.4, 67.6, 61.8, 47.9, 44.2, 40.10, 37.2, 31.6, 31.5, 31.4, 25.9, 23.7, 20.7, 13.8. IR (neat) ν_{max} (cm^{-1}): 2926, 1649, 1452, 1416, 1400, 1393, 1358, 1302, 1250, 1205, 727, 698, 419. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{23}H_{33}N_2O_2$, 369.2537; found, 369.2542. $[\alpha]_D^{20}$ +62.0 (c = 1.0, $CHCl_3$). SFC-MS (method 4) er: 97:3; tret (major) = 2.451 min (96.6%), tret (minor) = 2.586 min (3.4%).

*(R)-1-(3,5-Bis(trifluoromethyl)benzyl)-4-(3-methoxypropyl)-3-vinyl-1,4-diazaspiro[5.5]undecane-2,5-dione (**3d**).* It was prepared according to **GP-B** using **2d**. The crude material was purified by silica gel column chromatography (30% EtOAc/cHex) provided the title compound as a colorless oil in 44% yield (35.3 mg, 0.09 mmol). R_f = 0.39 (40% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.62 (s, 2H), 5.98 (ddd, J = 17.2, 10.4, 4.9 Hz, 1H), 5.41 (dd, J = 10.4, 1.9 Hz, 1H), 5.31 (dd, J = 17.2, 1.9 Hz, 1H), 5.15 (d, J = 16.6 Hz, 1H), 4.75 (dt, J = 5.0, 1.9 Hz, 1H), 4.43 (d, J = 16.6 Hz, 1H), 4.09−3.98 (m, 1H), 3.48−3.37 (m, 2H), 3.30 (s, 3H), 2.93 (dt, J = 13.6, 7.4 Hz, 1H), 2.49−2.32 (m, 1H), 2.06−1.91 (m, 2H), 1.90−1.80 (m, 2H), 1.75−1.66 (m, 2H), 1.64−1.47 (m, 4H), 1.10 (qt, J = 13.8, 4.4 Hz, 1H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 169.0, 167.6, 141.1, 133.6, 132.0 (q, J = 33.3 Hz, 2C), 126.6 (q, J = 3 Hz, 2C), 123.3 (d, J = 272.8 Hz, 2C), 121.3 (h, J = 3.7 Hz) 118.6, 69.9, 63.3, 63.1, 58.7, 45.1, 43.9, 35.3, 33.7, 27.3, 24.5, 23.4, 22.0. ^{19}F NMR{^{1}H} (376 MHz, $CDCl_3$): δ −62.9. IR (neat) ν_{max} (cm^{-1}): 2932, 1745, 1649, 1281, 1240, 1175, 1165, 1121, 1101, 878, 702, 681, 413. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{24}H_{29}F_6N_2O_3$, 507.2077; found, 507.2092. $[\alpha]_D^{20}$ +48.0 (c = 1.0, $CHCl_3$). SFC-MS (method 7) er: 93:7; tret (minor) = 3.926 min (6.9%), tret (major) = 4.063 min (93.1%).

*(R)-1-Butyl-4-(2,4-dimethoxybenzyl)-3,3-dimethyl-6-vinyl Piperazine-2,5-dione (**3e**).* It was prepared according to **GP-B** using **2e**. The crude material was purified by silica gel column chromatography (30% EtOAc/cHex) provided the title compound as a pale solid in 24% yield (18.0 mg, 0.05 mmol). R_f = 0.37 (40% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.00 (d, J = 8.6 Hz, 1H), 6.49−6.35 (m, 2H), 5.97 (ddd, J = 17.2, 10.3, 5.3 Hz, 1H), 5.40 (dd, J = 10.4, 1.7 Hz, 1H), 5.32 (dd, J = 17.2, 1.7 Hz, 1H), 4.69 (d, J = 16.1 Hz, 1H), 4.65 (dt, J = 5.4, 1.8 Hz, 1H), 4.54 (d, J = 16.1 Hz, 1H), 4.02 (ddd, J = 13.5, 8.9, 6.7 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 2.77 (ddd, J = 13.5, 8.7, 5.9 Hz, 1H), 1.61−1.52 (m, 2H), 1.48 (s, 3H), 1.37 (s, 3H), 1.36−1.31 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 170.0, 165.7, 160.0, 157.2, 133.7, 128.4, 118.6, 118.6, 104.4, 98.4, 62.9, 61.9, 55.5, 55.4, 45.3, 39.9, 29.4, 27.1, 25.6, 20.2, 13.9. IR (neat) ν_{max} (cm^{-1}): 2934, 1651, 1612, 1512, 1412, 1244, 1175, 1034, 733, 700. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{31}N_2O_4$, 375.2278; found, 375.2283. $[\alpha]_D^{20}$ +90.0 (c = 0.2, $CHCl_3$). SFC-MS (method 1) er: 12:88; tret (minor) = 5.687 min (11.8%), tret (major) = 6.215 min (88.2%).

*(R)-4-(4-Fluorobenzyl)-1-isopropyl-3,3-dimethyl-6-vinyl Piperazine-2,5-dione (**3f**).* It was prepared according to **GP-B** using **2f**. The crude material was purified by silica gel column chromatography (30% EtOAc/cHex) provided the title compound as a colorless oil in 32% yield (20.4 mg, 0.06 mmol). R_f = 0.22 (30% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.18 (dd, J = 8.6, 5.4 Hz, 2H), 6.95 (t, J = 8.7 Hz, 2H), 5.91 (ddd, J = 17.1, 10.3, 6.1 Hz, 1H), 5.49 (dd, J = 17.1, 1.5 Hz, 1H), 5.38 (dd, J = 10.4, 1.6 Hz, 1H), 4.71 (d, J = 15.6 Hz, 1H), 4.67 (dt, J = 6.1, 1.6 Hz, 1H), 4.51 (d, J = 15.6 Hz, 1H), 4.37 (hept, J = 6.9 Hz, 1H), 1.48 (s, 3H), 1.34 (s, 3H), 1.26 (d, J = 6.9 Hz, 3H), 1.22 (d, J = 6.9 Hz, 3H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 169.2, 166.3, 161.7 (d, J = 245.5 Hz), 135.6, 134.0 (d, J = 3.2 Hz), 128.9 (d, J = 8.1 Hz), 119.5, 115.5 (d, J = 21.5 Hz), 62.0, 60.3, 48.5, 45.3, 27.6, 26.2, 20.4, 20.0. ^{19}F NMR{^{1}H} (376 MHz, $CDCl_3$): δ −115.5. IR (neat) ν_{max} (cm^{-1}): 2926, 2851, 1652, 1508, 1412, 1354, 1221, 1194, 1157, 829, 698, 419. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{24}FN_2O_2$, 319.1816; found, 319.1832.

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$[\alpha]_D^{20}$ +16.0 (c = 0.5, $CHCl_3$). SFC-MS (method 3) er: 88:12; tret (major) = 3.419 min (87.8%), tret (minor) = 3.545 min (12.2%).

*Methyl (R)-2-(1-(4-Methoxybenzyl)-2,5-dioxo-3-vinyl-1,4-diazaspiro[5.5]undecan-4-yl)acetate (**3g**).* It was prepared according to **GP-B** using **2g**. The crude material was purified by silica gel column chromatography (30% EtOAc/cHex) provided the title compound as a pale oil in 77% yield (62.78 mg, 0.15 mmol). R_f = 0.16 (30% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.15 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.02 (m, 1H), 5.43 (d, J = 10.3 Hz, 1H), 5.39 (d, J = 17.1 Hz, 1H), 4.92 (d, J = 15.8 Hz, 1H), 4.69 (d, J = 6.1 Hz, 1H), 4.49 (d, J = 15.8 Hz, 1H), 4.42 (d, J = 17.1 Hz, 1H), 3.78 (s, 3H), 3.77−3.74 (m, 4H), 2.24−2.14 (m, 1H), 1.99−1.92 (m, 2H), 1.76−1.53 (m, 6H), 1.10−1.01 (m, 1H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 170.3, 169.2, 167.1, 158.9, 133.2, 130.6, 128.2 (2), 119.9, 114.3 (2), 64.6, 63.1, 55.6, 52.8, 47.0, 45.3, 36.2, 33.0, 24.8, 23.4, 22.6. IR (neat) ν_{max} (cm^{-1}): 2929, 1747, 1649, 1512, 1427, 1412, 1400, 1263, 1244, 1209, 1176, 1032, 1014, 804. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{29}N_2O_5$, 401.2071; found, 401.2084. $[\alpha]_D^{20}$ +30.0 (c = 1.0, $CHCl_3$). SFC-MS (method 4) er: 92:8; tret (major) = 3.718 min (92.0%), tret (minor) = 3.971 min (8.0%).

*Methyl (R)-2-(6,9-Dioxo-5-phenethyl-7-vinyl-5,8-diazaspiro[3.5]-nonan-8-yl)acetate (**3h**).* It was prepared according to **GP-B** using **2h**. The crude material was purified by silica gel column chromatography (50% EtOAc/cHex) provided the title compound as a pale oil in 95% yield (67.7 mg, 0.19 mmol). R_f = 0.05 (30% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35−7.27 (m, 2H), 7.25−7.19 (m, 3H), 5.82 (ddd, J = 16.9, 10.2, 6.6 Hz, 1H), 5.40−5.25 (m, 2H), 4.58−4.46 (m, 2H), 3.98 (ddd, J = 13.7, 10.4, 5.4 Hz, 1H), 3.82−3.71 (m, 4H), 3.56 (ddd, J = 13.7, 10.2, 5.8 Hz, 1H), 2.97 (ddd, J = 13.2, 10.2, 5.4 Hz, 1H), 2.87−2.75 (m, 2H), 2.52−2.43 (m, 2H), 2.36−2.27 (m, 1H), 2.13−2.00 (m, 1H), 1.89−1.78 (m, 1H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$) 169.4, 168.8, 164.9, 138.5, 132.4, 128.9 (2C), 128.7 (2C), 126.7, 119.9, 64.3, 62.3, 52.5, 46.4, 45.3, 35.6, 34.4, 30.5, 14.5. IR (neat) ν_{max} (cm^{-1}): 2953, 1749, 1655, 1454, 1412, 1402, 1283, 1257, 1207, 1178, 1148, 748, 700, 505. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{25}N_2O_4$, 357.1809; found, 357.1815. $[\alpha]_D^{20}$ +12.0 (c = 1.0, $CHCl_3$). SFC-MS (method 1) er: 88:12; tret (minor) = 5.673 min (12.3%), tret (major) = 6.190 min (87.7%).

*(R)-6-(4-Chlorobenzyl)-9-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-8-vinyl-6,9-diazaspiro[4.5]decane-7,10-dione (**3i**).* It was prepared according to **GP-B** using **2i**. The crude material was purified by silica gel column chromatography (30% EtOAc/cHex) provided the title compound as a brown oil in 97% yield (87.9 mg, 0.19 mmol). R_f = 0.18 (30% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.6 Hz, 1H), 6.82 (d, J = 2.5 Hz, 1H), 6.75 (dd, J = 8.6, 2.5 Hz, 1H), 5.95 (ddd, J = 16.9, 10.3, 6.3 Hz, 1H), 5.42−5.34 (m, 2H), 4.98 (d, J = 16.0 Hz, 1H), 4.92 (dt, J = 6.3, 1.5 Hz, 1H), 4.25 (d, J = 16.0 Hz, 1H), 4.23 (s, 4H), 2.57−2.51 (m, 1H), 2.34 (ddd, J = 12.8, 7.2, 4.7 Hz, 1H), 1.97−1.71 (m, 6H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 170.7, 166.4, 143.7, 143.0, 136.5, 133.3, 132.9 (2C), 128.9 (2C), 127.8 (2C), 120.4, 120.0, 117.6, 116.2, 71.0, 66.3, 64.3, 64.3, 46.5, 41.5, 35.8, 27.0, 26.4. IR (neat) ν_{max} (cm^{-1}): 3292, 2932, 1744, 1664, 1504, 1402, 1302, 1254, 1240, 1202, 1175, 1067, 885, 800, 791, 734, 652, 420. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{25}H_{25}ClN_2NaO_4$, 475.1395; found, 475.1387. $[\alpha]_D^{20}$ +22.0 (c = 1.0, $CHCl_3$). SFC-MS (method 2): er: 95:5; tret (major) = 6.118 min (95.1%), tret (minor) = 6.417 min (4.9%).

It was also prepared according to **GP-B** from 430.5 mg (1.00 mmol) of **2i**, providing the title compound in 89% yield (303.0 mg, 0.89 mmol).

*(R)-4-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-1-(prop-2-yn-1-yl)-3-vinyl-1,4-diazaspiro[5.5]undecane-2,5-dione (**3j**).* It was prepared according to **GP-B** using **2j**. The crude material was purified by silica gel column chromatography (40% EtOAc/cHex), providing the title compound as a pale oil in 73% yield (55.5 mg, 0.15 mmol). R_f = 0.16 (30% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.87 (d, J = 8.5 Hz, 1H), 6.74 (d, J = 2.5 Hz, 1H), 6.69 (dd, J = 8.6, 2.5 Hz, 1H), 5.91 (ddd, J = 16.7, 10.3, 5.9 Hz, 1H), 5.35 (d, J = 17.1 Hz, 1H), 5.32 (dd, J = 10.4, 1.6 Hz, 1H), 4.90 (d, J = 5.9 Hz, 1H), 4.41 (dd, J = 17.6, 2.4 Hz, 1H), 4.30−4.22 (m, 5H), 2.41 (tdd, J = 13.0, 8.8, 4.6 Hz, 1H), 2.26 (t, J = 2.5 Hz, 1H), 2.23−2.19 (m, 1H), 2.14−2.10 (m, 1H), 2.01 (td, J = 12.8, 5.0 Hz, 1H), 1.91 (td, J = 12.9, 4.8 Hz, 1H), 1.76−1.68 (m, 4H), 1.22 (dd, J = 10.6, 6.4 Hz, 1H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 169.0, 166.5, 143.9, 143.1, 133.1, 133.1, 120.5, 120.2, 117.9, 116.7, 80.0, 71.8, 65.9, 64.4, 64.4, 63.1, 35.8, 32.8, 31.5, 24.6, 23.2, 22.3. IR (neat) ν_{max} (cm^{-1}): 2932, 1647, 1504, 1404, 1308, 1292, 1279, 1261, 1242, 1213, 1065, 887, 746, 663, 621, 409. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{25}N_2O_4$, 381.1809; found, 381.1813. $[\alpha]_D^{20}$ +10.0 (c = 1.0, $CHCl_3$). SFC-MS (method 2) er: 94:6; tret (minor) = 4.943 min (5.8%), tret (major) = 5.505 min (94.2%).

*(R)-5-(4-Bromobenzyl)-8-(2,6-dimethylphenyl)-7-vinyl-5,8-diazaspiro[3.5]nonane-6,9-dione (**3k**).* It was prepared according to **GP-B** using **2k**. The crude material was purified by silica gel column chromatography (20% EtOAc/cHex), providing the title compound as a pale oil in 46% yield (41.7 mg, 0.09 mmol). R_f = 0.19 (30% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46 (d, J = 8.4 Hz, 2H), 7.17 (t, J = 7.5 Hz, 1H), 7.14−7.05 (m, 4H), 5.82 (ddd, J = 17.0, 9.9, 8.4 Hz, 1H), 5.32−5.20 (m, 2H), 5.09 (d, J = 16.0 Hz, 1H), 4.74 (d, J = 16.0 Hz, 1H), 4.59 (d, J = 8.4 Hz, 1H), 2.87−2.78 (m, 1H), 2.69 (ddt, J = 12.3, 8.0, 3.7 Hz, 1H), 2.51−2.42 (m, 2H), 2.22 (s, 3H), 2.20 (s, 3H), 2.09−2.00 (m, 1H), 1.85−1.78 (m, 1H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 167.3, 167.1, 137.1, 136.9, 134.9, 132.0 (2C), 131.1, 129.2, 128.8, 128.5 (2C), 128.4, 121.9 (2C), 121.3, 66.3, 63.1, 45.8, 33.9, 30.4, 18.7, 18.1, 14.8. IR (neat) ν_{max} (cm^{-1}): 2957, 1663, 1487, 1398, 1306, 1284, 1221, 1161, 1009, 924, 771, 731, 473. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{26}BrN_2O_2$, 453.1172; found, 453.1162. $[\alpha]_D^{20}$ −38.0 (c = 2.0, $CHCl_3$). SFC-MS (method 2) er: 91:9; tret (major) = 4.955 min (91.1%), tret (minor) = 5.126 min (8.9%).

*(R)-6-Allyl-9-(4-methoxyphenyl)-8-vinyl-6,9-diazaspiro[4.5]-decane-7,10-dione (**3l**).* It was prepared according to **GP-B** using **2l**. The crude material was purified by silica gel column chromatography (30% EtOAc/cHex), providing the title compound as a yellow oil in 96% yield (65.4 mg, 0.19 mmol). R_f = 0.17 (30% EtOAc/cHex). 1 mmol scale: prepared according to **GP-B** using **2l**. The crude material was purified by silica gel column chromatography (30% EtOAc/cHex) providing the title compound as a yellow oil in 89% yield (303.0 mg, 0.89 mmol). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.17 (d, J = 8.9 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 6.02−5.83 (m, 2H), 5.37−5.29 (m, 2H), 5.25−5.09 (m, 2H), 4.83 (d, J = 6.5 Hz, 1H), 4.35−4.24 (m, 1H), 3.79 (s, 3H), 3.77−3.65 (m, 1H), 2.61 (ddd, J = 14.3, 8.4, 7.2 Hz, 1H), 2.36−2.30 (m, 1H), 2.13−2.07 (m, 1H), 2.01−1.95 (m, 1H), 1.94−1.68 (m, 4H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 171.0, 165.4, 158.6, 134.0, 133.6, 132.5, 128.2 (2C), 120.2, 116.6, 114.5 (2C), 70.8, 66.4, 55.5, 46.4, 41.6, 36.0, 27.2, 26.6. IR (neat) ν_{max} (cm^{-1}): 2957, 1655, 1508, 1425, 1404, 1298, 1279, 1238, 1180, 1134, 1030, 926, 827, 532. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{25}N_2O_3$, 341.1860; found, 341.1864. $[\alpha]_D^{20}$ −14.0 (c = 1.0, $CHCl_3$). SFC-MS (method 4) er: 93:7; tret (minor) = 4.244 min (7.3%), tret (major) = 4.479 min (92.7%).

*(R)-9-(3,3-Diethoxypropyl)-12-(2,6-dimethylphenyl)-11-vinyl-1,4-dioxa-9,12-diazadispiro[4.2.58.25]pentadecane-10,13-dione (**3m**).* It was prepared according to **GP-B** using **2m**. The crude material was purified by silica gel column chromatography (50% EtOAc/cHex), providing the title compound as a colorless oil in 91% yield (91.1 mg, 0.18 mmol). R_f = 0.14 (40% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.11 (t, J = 7.5 Hz, 1H), 7.08−6.98 (m, 2H), 5.79 (ddd, J = 16.8, 10.0, 8.3 Hz, 1H), 5.19 (d, J = 9.9 Hz, 1H), 5.11 (d, J = 16.8 Hz, 1H), 4.60 (t, J = 5.6 Hz, 1H), 4.53 (d, J = 8.3 Hz, 1H), 3.93−3.87 (m, 4H), 3.77−3.64 (m, 3H), 3.55−3.48 (m, 2H), 3.42 (ddd, J = 13.8, 10.8, 4.9 Hz, 1H), 2.54 (td, J = 13.2, 4.9 Hz, 1H), 2.33−2.24 (m, 2H), 2.18 (td, J = 13.4, 4.1 Hz, 1H), 2.13 (s, 3H) 2.12 (s, 3H), 2.10−2.04 (m, 3H), 1.88 (dtd, J = 13.2, 6.0, 3.0 Hz, 1H), 1.71−1.65 (m, 2H), 1.20 (q, J = 7.1 Hz, 6H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 167.6, 166.2, 136.6 (2C), 134.3, 129.1, 128.7, 128.3, 121.8, 107.6, 101.0, 65.1, 64.5, 64.2, 61.8, 61.7, 61.1, 39.4, 33.9, 32.7, 31.8, 31.2,

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30.7, 26.9, 18.5, 17.7, 15.3 (2C). IR (neat) ν_{max} (cm^{-1}): 2934, 2874, 1655, 1416, 1371, 1277, 1167, 1121, 1103, 1090, 1051, 1036, 930, 903, 783. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{28}H_{40}N_2NaO_6$, 523.2779; found, 523.2748. $[\alpha]_D^{20}$ −124.0 (c = 1.0, $CHCl_3$). SFC-MS (method 1) er: 90:10; tret (minor) = 5.059 min (9.6%), tret (major) = 6.027 min (90.4%).

*(R)-9-(4-Methoxyphenyl)-6-propyl-8-vinyl-6,9-diazaspiro[4.5]-decane-7,10-dione (**3n**).* It was prepared according to **GP-B** using **2n**. The crude material was purified by silica gel column chromatography (30% EtOAc/cHex), providing the title compound as a colorless oil in 98% yield (67.1 mg, 0.20 mmol). R_f = 0.23 (30% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.17 (d, J = 8.9 Hz, 2H), 6.90 (d, J = 8.9 Hz, 2H), 5.90 (ddd, J = 16.9, 10.3, 6.5 Hz, 1H), 5.38−5.27 (m, 2H), 4.80 (d, J = 6.5 Hz, 1H), 3.80 (s, 3H), 3.53 (ddd, J = 13.4, 11.2, 5.2 Hz, 1H), 3.00 (ddd, J = 13.4, 11.3, 4.9 Hz, 1H), 2.64 (tt, J = 9.8, 4.8 Hz, 1H), 2.35−2.29 (m, 1H), 2.06−1.97 (m, 2H), 1.93−1.77 (m, 5H), 1.67−1.56 (m, 1H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 171.1, 165.6, 158.7, 133.7, 132.6, 128.2 (2C), 120.1, 114.5 (2C), 70.7, 66.5, 55.6, 46.4, 41.6, 36.1, 27.2, 26.5, 22.8, 11.7. IR (neat) ν_{max} (cm^{-1}): 2959, 2934, 1647, 1512, 1420, 1300, 1240, 1034, 928, 831, 808, 563, 527. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{27}N_2O_3$, 343.2016; found, 343.2033. $[\alpha]_D^{20}$ −34.0 (c = 1.0, $CHCl_3$). SFC-MS (method 5) er: 95:5; tret (major) = 3.701 min (95.1%), tret (minor) = 3.945 min (4.9%).

*(R)-6-(4-Chlorobenzyl)-9-(naphthalen-2-yl)-8-vinyl-6,9-diazaspiro[4.5]decane-7,10-dione (**3o**).* It was prepared according to **GP-B** using **2o**. The crude material was purified by silica gel column chromatography (20% EtOAc/cHex), providing the title compound as a pale oil in 94% yield (83.7 mg, 0.19 mmol). R_f = 0.36 (30% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89 (d, J = 8.8 Hz, 1H), 7.86−7.81 (m, 2H), 7.79 (d, J = 2.1 Hz, 1H), 7.54−7.49 (m, 2H), 7.45 (dd, J = 8.7, 2.2 Hz, 1H), 7.33 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 6.07 (ddd, J = 17.1, 10.3, 6.1 Hz, 1H), 5.43 (dd, J = 17.1, 1.5 Hz, 1H), 5.39 (dd, J = 10.3, 1.5 Hz, 1H), 5.18 (dt, J = 6.1, 1.6 Hz, 1H), 5.05 (d, J = 15.8 Hz, 1H), 4.29 (d, J = 15.9 Hz, 1H), 2.66−2.59 (m, 1H), 2.46 (ddd, J = 13.4, 7.3, 4.7 Hz, 1H), 2.06−1.92 (m, 3H), 1.92−1.86 (m, 1H), 1.85−1.76 (m, 2H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 171.0, 166.4, 137.3, 136.5, 133.5, 133.4, 133.0, 132.3, 129.1, 128.9 (2C), 128.0, 127.9 (2C), 127.7, 126.6, 126.6, 125.1, 124.7, 120.4, 71.2, 66.3, 46.6, 41.6, 36.0, 27.1, 26.5. IR (neat) ν_{max} (cm^{-1}): 2957, 1649, 1491, 1398, 1308, 1296, 1273, 1227, 1092, 1014, 808, 793, 748, 733, 476. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{26}ClN_2O_2$, 445.1677; found, 445.1680. $[\alpha]_D^{20}$ +33.0 (c = 2.0, $CHCl_3$). SFC-MS (method 6) er: 95:5; tret (major) = 11.817 min (95.2%), tret (minor) = 13.022 min (4.8%).

*(R)-4-(5-Bromopyridin-2-yl)-1-(4-fluorobenzyl)-3-vinyl-1,4-diazaspiro[5.5]undecane-2,5-dione (**3p**).* It was prepared according to **GP-B** using **2p**. The crude material was purified by silica gel column chromatography (20% EtOAc/cHex), providing the title compound as a pale oil in 93% yield (87.9 mg, 0.19 mmol). R_f = 0.39 (30% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.46 (d, J = 2.4 Hz, 1H), 7.81 (dd, J = 8.8, 2.5 Hz, 1H), 7.77 (d, J = 8.7 Hz, 1H), 7.22 (dd, J = 8.6, 5.4 Hz, 2H), 6.98 (t, J = 8.7 Hz, 2H), 6.23 (dt, J = 4.4, 2.4 Hz, 1H), 6.08 (ddd, J = 17.3, 10.6, 4.2 Hz, 1H), 5.23 (dd, J = 10.6, 2.4 Hz, 1H), 5.15 (dd, J = 17.3, 2.4 Hz, 1H), 5.02 (d, J = 16.0 Hz, 1H), 4.47 (d, J = 16.0 Hz, 1H), 2.41−2.30 (m, 1H), 2.26−2.19 (m, 1H), 1.96−1.91 (m, 1H), 1.77 (dt, J = 13.0, 6.5 Hz, 1H), 1.73−1.49 (m, 5H), 1.13−1.04 (m, 1H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 169.6, 167.5, 161.9 (d, J = 245.4 Hz), 150.2, 148.9, 140.0, 134.1, 134.0 (d, J = 3.2 Hz), 128.6 (d, J = 8.0 Hz, 2C), 121.9, 117.5, 117.1, 115.5 (d, J = 21.5 Hz, 2C), 63.9, 60.4, 44.9, 35.7, 33.0, 24.5, 23.3, 22.2. ^{19}F NMR{^{1}H} (376 MHz, $CDCl_3$): δ −115.5. IR (neat) ν_{max} (cm^{-1}): 2934, 1680, 1643, 1508, 1454, 1394, 1366, 1263, 1221, 1140, 1095, 814, 731, 411. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{24}BrFN_3O_2$, 472.1030; found, 472.1040. $[\alpha]_D^{20}$ +40.0 (c = 2.0, $CHCl_3$). SFC-MS (method 2) er: 84:16; tret (major) = 4.565 min (84.2%), tret (minor) = 4.796 min (15.8%).

*9-Benzyl-4-(3,4-dimethoxyphenethyl)-1-(4-(trifluoromethyl)-benzyl)-3-vinyl-1,4,9-triazaspiro[5.5]undecane-2,5-dione (**3q**).* It was prepared according to **GP-C** using **2q**. The crude material was purified by silica gel column chromatography (80% EtOAc/cHex), providing the title compound as pale solid in 47% yield (58.4 mg, 0.09 mmol). R_f = 0.16 (80% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.57 (d, J = 8.1 Hz, 2H), 7.35−7.17 (m, 7H), 6.83−6.66 (m, 3H), 5.92 (ddd, J = 17.2, 10.3, 5.1 Hz, 1H), 5.39 (dd, J = 10.4, 1.9 Hz, 1H), 5.27 (dd, J = 17.2, 1.8 Hz, 1H), 5.13 (d, J = 16.5 Hz, 1H), 4.52−4.49 (m, 1H), 4.40 (d, J = 16.6 Hz, 1H), 4.31−4.23 (m, 1H), 3.92−3.79 (m, 7H), 3.51 (t, J = 12.2 Hz, 2H), 3.07−2.96 (m, 2H), 2.91−2.85 (m, 2H), 2.74−2.70 (m, 2H), 2.47−2.38 (m, 1H), 2.02−1.91 (m, 2H), 1.65 (d, J = 13.5 Hz, 1H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 169.1, 166.8, 149.2, 148.0, 142.2, 130.5, 133.3, 129.5 (q J = 32.4 Hz), 129.3 (2C) 129.3, 128.4 (2C), 126.7 (2C), 125.7 (q, J = 3.6 Hz 2C), 124.2 (q, J = 272.0 Hz), 120.9, 118.7, 112.2, 111.4, 70.0, 63.0, 62.8, 61.0, 56.0, 56.0, 51.1, 49.0, 47.0, 45.3, 33.0, 29.8; 1 quaternary aromatic C is not visible. ^{19}F NMR{^{1}H} (376 MHz, $CDCl_3$): δ −62.0. IR (neat) ν_{max} (cm^{-1}): 2932, 1649, 1323, 1279, 1261, 1238, 1159, 1119, 1067, 1028, 1016, 737, 700. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{35}H_{39}F_3N_3O_4$, 622.2814; found, 622.2827.

*12-(tert-Butyl)-9-(4-fluorobenzyl)-11-vinyl-1,4-dioxa-9,12-diazadispiro[4.2.58.25]pentadecane-10,13-dione (**3r**).* It was prepared according to **GP-C** using **2r**. The crude material was purified by silica gel column chromatography (30% EtOAc/cHex), providing the title compound as a white solid in 92% yield (72.2 mg, 0.18 mmol). R_f = 0.30 (30% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.17 (dd, J = 8.5, 5.4 Hz, 2H), 6.97 (t, J = 8.7 Hz, 2H), 5.97 (ddd, J = 17.2, 10.4, 5.4 Hz, 1H), 5.49 (dd, J = 17.2, 1.7 Hz, 1H), 5.37 (dd, J = 10.5, 1.8 Hz, 1H), 4.98−4.84 (m, 2H), 4.31 (d, J = 16.0 Hz, 1H), 3.96−3.84 (m, 4H), 2.66 (td, J = 13.1, 5.4 Hz, 1H), 2.09−1.96 (m, 4H), 1.81−1.73 (m, 1H), 1.58 (dq, J = 10.5, 2.7 Hz, 2H), 1.48 (s, 9H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 170.1, 167.7, 161.9 (d, J = 245.0 Hz), 137.2, 134.0 (d, J = 3.1 Hz), 128.3 (d, J = 7.6 Hz, 2C), 118.8, 115.4 (d, J = 21.5 Hz, 2C), 107.9, 64.5, 64.2, 62.3, 60.8, 58.7, 45.3, 32.2, 32.2, 32.0, 30.8, 28.4 (3C). ^{19}F NMR{^{1}H} (376 MHz, $CDCl_3$): δ −116.0. IR (neat) ν_{max} (cm^{-1}): 2939, 1651, 1508, 1400, 1221, 1196, 1178, 1157, 1097, 1034, 928, 808, 486, 465, 413. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{32}FN_2O_4$, 431.2341; found, 431.2341.

*9-Isopropyl-6-(p-tolyl)-8-vinyl-6,9-diazaspiro[4.5]decane-7,10-dione (**3s**).* It was prepared according to **GP-C** using **2s**. The crude material was purified by silica gel column chromatography (20% EtOAc/cHex), providing the title compound as a pale solid in 85% yield (55.52 mg, 0.17 mmol). R_f = 0.25 (30% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.21 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 8.0 Hz, 2H), 6.02 (ddd, J = 17.2, 10.4, 5.6 Hz, 1H), 5.53 (dd, J = 17.2, 1.6 Hz, 1H), 5.39 (dd, J = 10.4, 1.7 Hz, 1H), 4.71 (dt, J = 5.7, 1.8 Hz, 1H), 4.55 (hept, J = 6.9 Hz, 1H), 2.50−2.42 (m, 1H), 2.36 (s, 3H), 2.27 (ddd, J = 14.3, 8.0, 6.6 Hz, 1H), 2.15 (ddd, J = 13.9, 8.2, 6.1 Hz, 1H), 1.76−1.64 (m, 3H), 1.56 (dt, J = 8.6, 6.2 Hz, 1H), 1.29 (d, J = 6.8 Hz, 3H), 1.25 (d, J = 6.9 Hz, 3H), 1.23−1.12 (m, 1H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 170.6, 167.2, 138.4, 135.9, 135.6, 130.2 (4C), 119.2, 71.2, 60.4, 47.8, 42.6, 36.1, 26.4, 26.0, 21.3, 20.6, 20.1. IR (neat) ν_{max} (cm^{-1}): 2942, 1649, 1510, 1393, 1362, 1215, 1188, 949, 802. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{27}N_2O_2$, 327.2067; found, 327.2065.

*Synthesis of (E/Z)-4-Benzyl-3-ethylidene-1-(4-methoxybenzyl)-1,4-diazaspiro[5.5]undecane-2,5-dione (**4a**/**4b**).* To a solution of **3a** (84 mg, 0.2 mmol, 1 equiv) in THF (0.033 M, 6.66 mL) at 0 °C was added NaH (0.22 mmol, 1.1 equiv), which then was allowed to reach rt and stirred for 30 min. The reaction mixture was quenched with a saturated solution of NH_4Cl (2 mL) and extracted with ethyl acetate (2 × 5 mL), the combined organic layers were dried with Na_2SO_4, and the solvent was removed under reduced pressure. The reaction mixture was purified by silica gel column chromatography (25% EtOAc/cHex), affording the product as a colorless solid, as a 1/1 mixture of isomers in 98% yield. The absolute configurations of the two isomers have been assigned with NOESY experiments.

*(E)-4-Benzyl-3-ethylidene-1-(4-methoxybenzyl)-1,4-diaza Spiro-[5.5]undecane-2,5-dione (**4a**).* R_f = 0.45 (30% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 (dd, J = 8.2, 7.0 Hz, 2H), 7.29−7.22 (m, 1H), 7.21−7.13 (m, 4H), 6.83 (d, J = 8.6 Hz, 2H), 5.72 (q, J

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= 7.4 Hz, 1H), 4.91 (s, 2H), 4.76 (s, 2H), 3.79 (s, 3H), 2.21−2.15 (m, 2H), 2.12 (d, J = 7.4 Hz, 3H), 1.81 (qt, J = 11.8, 3.2 Hz, 2H), 1.71−1.50 (m, 5H), 1.11−1.02 (m, 1H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 168.6, 163.5, 158.7, 137.4, 132.8, 130.9, 128.9 (2C), 128.5 (2C), 127.4, 126.3 (2C), 121.0, 114.1 (2C), 62.7, 55.4, 49.4, 43.9, 33.7 (2C), 25.1, 23.3 (2C), 14.1. IR (neat) ν_{max} (cm^{-1}) (1/1 mixture of isomers): 2934, 1672, 1630, 1612, 1387, 1356, 1304, 1242, 810, 727, 700, 407. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{23}N_2O_2$, 299.1754; found, 299.1759.

*(Z)-4-Benzyl-3-ethylidene-1-(4-methoxybenzyl)-1,4-diaza Spiro-[5.5]undecane-2,5-dione (**4b**).* R_f = 0.30 (30% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31 (dd, J = 8.1, 6.7 Hz, 2H), 7.26 (d, J = 3.5 Hz, 1H), 7.21−7.17 (m, 2H), 7.06 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 6.36 (q, J = 7.7 Hz, 1H), 4.88 (s, 2H), 4.71 (s, 2H), 3.78 (s, 3H), 2.18−2.08 (m, 2H), 1.84 (d, J = 7.7 Hz, 3H), 1.81−1.71 (m, 2H), 1.70−1.50 (m, 6H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 170.1, 165.4, 158.7, 137.2, 134.8, 131.0, 128.7 (2C), 128.4 (2C), 127.5, 126.8 (2C), 120.4, 114.0 (2C), 63.1, 55.4, 50.1, 44.1, 33.5 (2C), 25.1, 23.6 (2C), 14.2.

*Synthesis of (R)-4-Benzyl-3-ethyl-1-(4-methoxybenzyl)-1,4-diazaspiro[5.5]undecane-2,5-dione (**5**).* To a solution of **3a** (84 mg, 0.2 mmol, 1 equiv) in EtOAc (4 mL), 10% Pd/C was added (21 mg). The reaction flask was filled with H_2 and then was degassed under vacuum, and the flask was backfilled with H_2. The procedure was repeated three times, and then the reaction mixture was stirred overnight. The crude was filtrated through a Celite pad, and the solvent was removed under reduced pressure, affording the product without further purification as a white solid in 99% yield (83 mg). R_f = 0.36 (30% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39−7.31 (m, 2H), 7.31−7.28 (m, 1H), 7.25−7.20 (m, 2H), 7.12 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 5.39 (d, J = 14.9 Hz, 1H), 4.76 (d, J = 15.7 Hz, 1H), 4.56 (d, J = 15.7 Hz, 1H), 3.97 (d, J = 14.9 Hz, 1H), 3.92 (dd, J = 6.6, 3.5 Hz, 1H), 3.78 (s, 3H), 2.24 (qt, J = 13.0, 4.3 Hz, 1H), 2.12−1.90 (m, 4H), 1.89−1.84 (m, 1H), 1.81−1.72 (m, 3H), 1.69−1.57 (m, 2H), 1.12 (qt, J = 13.2, 4.0 Hz, 1H), 0.97 (t, J = 7.5 Hz, 3H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 169.8, 168.1, 158.6, 136.3, 130.6, 129.0 (2C), 128.0 (2C), 127.9, 127.9 (2C), 114.0 (2C), 62.7, 59.2, 55.4, 46.9, 45.3, 35.2, 34.4, 25.6, 24.5, 23.1, 22.7, 9.9. IR (neat) ν_{max} (cm^{-1}): 2934, 1636, 1614, 1514, 1456, 1427, 1418, 1273, 1250, 1175, 1129, 1040, 797, 739, 702, 600, 492. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{26}H_{33}N_2O_3$, 421.2486; found, 421.2495. $[\alpha]_D^{20}$ +72.0 (c = 1.0, $CHCl_3$). SFC-MS (method 5) er: 91:9; tret (major) = 4.161 min (90.6%), tret (minor) = 4.490 min (9.4%).

*Synthesis of (R,E)-4-Benzyl-3-(4-hydroxystyryl)-1-(4-methoxy benzyl)-1,4-diazaspiro[5.5]undecane-2,5-dione (**6**).* To a solution of **3a** (84 mg, 0.2 mmol, 1.0 equiv), 4-iodophenol (88 mg, 0.4 mmol, 2.0 equiv), palladium(II) acetate (9 mg, 0.04 mmol, 0.2 equiv), and triethyl phosphite (7 μL, 0.04 mmol, 0.20 equiv) in 1,4-dioxane (3.6 mL) was added *N*,*N*-diisopropylethylamine (70 μL, 0.4 mmol, 2.0 equiv) and refluxed overnight. The reaction mixture was diluted with DCM (8 mL), washed with 1 M HCl (4 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (30% EtOAc/cHex), affording the product as a pale solid, in 64% yield (65 mg).

R_f = 0.22 (30% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.52−7.44 (m, 1H), 7.37−7.33 (m, 2H), 7.33−7.28 (m, 1H), 7.27−7.23 (m, 2H), 7.12 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 6.70 (d, J = 8.5 Hz, 2H), 6.46 (d, J = 15.8 Hz, 1H), 5.95 (dd, J = 15.8, 6.7 Hz, 1H), 5.43 (d, J = 14.8 Hz, 1H), 4.97 (d, J = 15.9 Hz, 1H), 4.69 (d, J = 6.7 Hz, 1H), 4.48 (d, J = 15.9 Hz, 1H), 3.96 (d, J = 14.8 Hz, 1H), 3.78 (s, 3H), 2.41 (qt, J = 12.8, 4.2 Hz, 1H), 2.10−2.04 (m, 1H), 2.02−1.95 (m, 1H), 1.87−1.60 (m, 6H), 1.13 (qt, J = 12.4, 3.2 Hz, 1H). ^{13}C NMR{^{1}H} (151 MHz, $CDCl_3$): δ 169.5, 168.1, 158.8, 157.1, 136.1, 134.9, 130.0, 129.1 (2C), 128.3 (2C), 128.2 (2C), 128.0, 127.9 (2C), 127.5, 120.4, 116.0 (2C), 114.2 (2C), 63.3, 61.7, 55.4, 47.6, 45.5, 36.2, 33.4, 24.6, 23.4, 22.4. IR (neat) ν_{max} (cm^{-1}): 2934, 1657, 1632, 1609, 1510, 1414, 1261, 1244, 1171, 908, 802, 725, 698, 519, 444, 434. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{32}H_{35}N_2O_4$, 511.2591; found, 511.2573. $[\alpha]_D^{20}$ +20.0 (c = 0.3, $CHCl_3$). SFC-MS (method 5) er: 96:4; tret (major) = 5.514 min (95.7%), tret (minor) = 5.806 min (4.3%).

*Synthesis of (R)-4-Benzyl-3-vinyl-1,4-diazaspiro[5.5]undecane-2,5-dione (**7**).* To a solution of **3a** (84 mg, 0.2 mmol, 1 equiv) in MeCN (0.2 mL) was added a solution of CAN (329 mg, 0.6 mmol, 3 equiv) in H_2O (0.2 mL), and it was stirred at room temperature for 3 h. The reaction mixture was extracted with DMC (3 × 2 mL), the combined organic layers were dried with Na_2SO_4, and the solvent was removed under reduced pressure. The crude was purified by silica gel column chromatography (40% EtOAc/cHex), affording the product as a white solid, in 95% yield (57 mg).

mp 138.9 °C. R_f = 0.23 (50% EtOAc/cHex). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36−7.27 (m, 3H), 7.21−7.14 (m, 2H), 6.79 (s, 1H), 5.87 (ddd, J = 17.1, 10.2, 6.0 Hz, 1H), 5.51 (d, J = 14.8 Hz, 1H), 5.44 (dd, J = 10.3, 1.5 Hz, 1H), 5.35 (dd, J = 17.1, 1.5 Hz, 1H), 4.36 (d, J = 6.1 Hz, 1H), 3.75 (d, J = 14.8 Hz, 1H), 2.31 (td, J = 13.6, 4.4 Hz, 1H), 1.91 (td, J = 13.1, 3.9 Hz, 1H), 1.83−1.74 (m, 2H), 1.72−1.64 (m, 3H), 1.46−1.30 (m, 3H). ^{13}C NMR {^{1}H} (151 MHz, $CDCl_3$): δ 170.0, 165.9, 135.8, 132.6, 129.0 (2C), 128.3 (2C), 128.1, 119.8, 61.8, 58.3, 47.5, 36.9, 34.5, 24.6, 20.6, 20.6. IR (neat) ν_{max} (cm^{-1}): 2930, 1659, 1649, 1427, 1290, 1269, 1240, 1167, 939, 824, 816, 750, 731, 700, 434. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{23}N_2O_2$, 299.1754; found, 299.1759. $[\alpha]_D^{20}$ +44.0 (c = 0.5, $CHCl_3$). SFC-MS (method 1) er: 96:4; tret (major) = 5.754 min (96.1%), tret (minor) = 6.266 min (3.9%).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b01994.

Additional optimization studies, X-ray crystallography data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

Data for **7** (CIF)

Accession Codes

CCDC 1902629 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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