

Article

One-Pot Two-Step Organocatalytic Asymmetric Synthesis of Spirocyclic Piperidones via Wolff Rearrangement–Amidation–Michael–Hemiaminalization Sequence

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Abstract: A highly enantioselective organocatalytic Wolff rearrangement–amidation–Michael–hemiaminalization stepwise reaction is described involving a cyclic 2-diazo-1,3-diketone, primary amine and α,β -unsaturated aldehyde. Product stereocontrol can be achieved by adjusting the sequence of steps in this one-pot multicomponent reaction. This approach was used to synthesize various optically active spirocyclic piperidones with three stereogenic centers and multiple functional groups in good yields up to 76%, moderate diastereoselectivities of up to 80:20 and high enantioselectivities up to 97%.

Keywords: organocatalysis; asymmetric synthesis; one-pot reaction; multicomponent reaction; aminocatalysis; spirocyclic piperidone

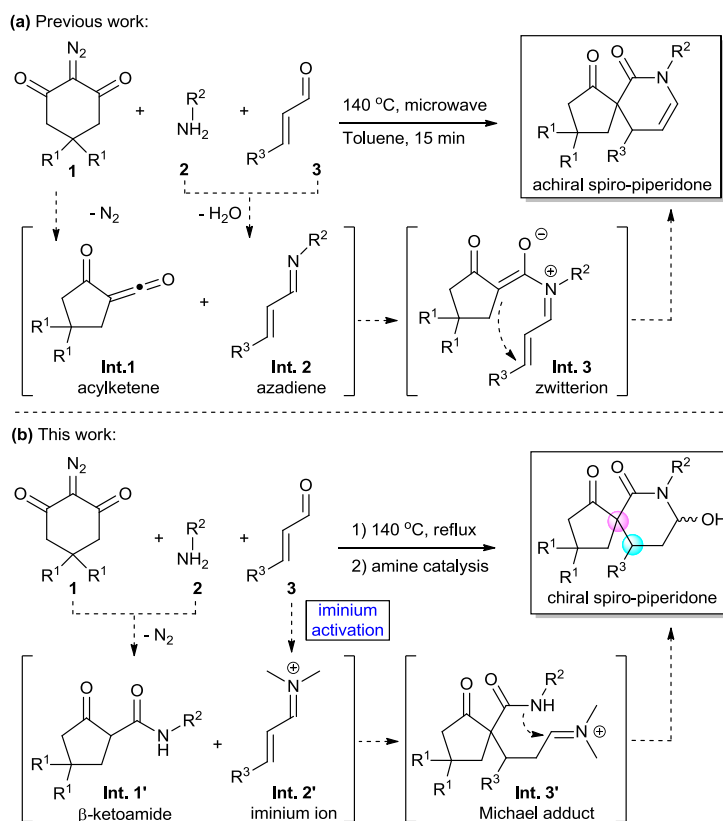
1. Introduction

Chiral piperidine frameworks exist widely in biologically active natural products and pharmaceuticals and are highly desirable targets in organic synthesis [1]. Over the past decade, asymmetric organic catalysis [2–17], quite powerful for synthesizing various heterocyclic molecules, has formed the basis of several elegant approaches to construct chiral single-heterocycle piperidine skeletons with high efficiency and low toxicity under environmentally friendly conditions [18–39]. In contrast, relatively few organocatalytic methods have been described to stereo-selectively form spirocyclic piperidine derivatives [30–36], particularly ones with a quaternary stereocenter [37–39].

In 2010, Chen's group used formal [2 + 2 + 2] annulation to develop a one-pot tandem reaction to synthesize diverse spirocyclic oxindoles incorporating a piperidine motif [40]. In 2012, Wang and co-workers used organocatalytic inverse-electron-demand Diels–Alder reactions to efficiently construct spiro-piperidine skeletons [41]. In addition, Rodriguez and co-workers developed a different approach for asymmetric synthesis of spiro-piperidines, in which α -branched β -ketoamide-based [3 + 3] cycloaddition is catalyzed by bifunctional thiourea-tertiary amine [42]. Despite these advances,

additional efficient organo-catalytic methods for asymmetric synthesis of spiro-piperidine scaffolds are still in high demand.

Recently, the groups of Rodriguez and Coquerel generated various spirocyclic piperidones using a microwave-assisted three-component system [43] in which the reaction of primary amine with α,β -unsaturated aldehyde generates 1-azadiene in situ, which then undergoes formal [4 + 2] cycloaddition with acylketene, previously generated via Wolff rearrangement of the cyclic 2-diazo-1,3-diketone (Scheme 1a). Although this approach can provide spirocyclic piperidine backbones in high yield and excellent diastereoselectivity, it has not been adapted to asymmetric synthesis.



Scheme 1. Synthesis of spirocyclic piperidones. (a) Previous method from Rodriguez and Coquerel; (b) Our synthetic strategy.

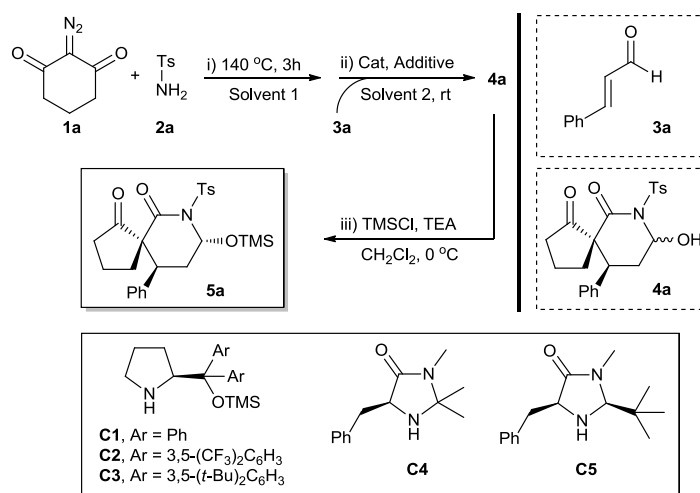
As part of our ongoing research program on organocatalytic synthesis of various drug-like spirocyclic scaffolds [44–47], we wondered whether we could synthesize chiral spirocyclic piperidones via asymmetric catalysis if we adjusted the sequence of reaction steps in this one-pot stepwise reaction. We hypothesized that we could begin with heat-assisted Wolff rearrangement–amidation of the cyclic 2-diazo-1,3-diketone with primary amine. The resulting cyclic β -ketoamide would directly participate in the secondary amine-catalytic cycle by serving as a donor in an asymmetric Michael reaction involving enal under iminium activation. Subsequent hydrolysis and hemiaminalization would provide the desired spiro-hemiaminal (Scheme 1b). Here, we present the results of experiments to verify whether this Wolff rearrangement–amidation–Michael–hemiaminalization tandem reaction can efficiently furnish chiral spiro-piperidine derivatives.

2. Results and Discussion

We began with the Wolff rearrangement–amidation of cyclic 2-diazo-1,3-diketone **1a** and *p*-toluenesulfonamide **2a**. After both substrates were nearly consumed, cinnamyl aldehyde **3a**,

Hayashi–Jørgensen catalyst **C1** and acid additive were added to the reaction mixture. We were delighted to find that the reaction afforded the expected hemiaminalization product **4a**. Direct protection of the hydroxyl with trimethylchlorosilane gave the more stable corresponding product **5a** in 43% total yield with moderate enantioselectivity but poor diastereoselectivity (Table 1, entry 1). Various catalysts were screened in order to enhance stereoselectivity (entries 2–5). MacMillan’s imidazolidinone catalyst **C5** in the presence of 20 mol % trifluoroacetic acid was found to be the most promising catalyst for the conversion (entry 5). Screening of acidic additives allowed us to improve the enantioselectivity (entries 6–8): adding benzoic acid generated product **5a** with 90% ee. Screening solvents allowed us to improve diastereoselectivity (entries 9–13): conducting the reaction in a mixture of dichloromethane and toluene (2:1, *v/v*) enhanced the diastereomeric ratio (*dr*) to 75:25 (entry 12).

Table 1. Optimization of reaction conditions ^a.



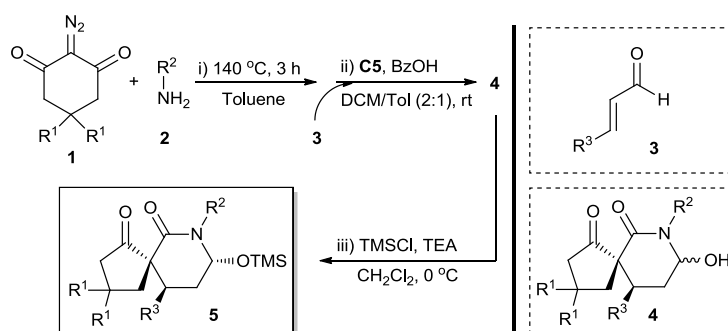
Entry	Catalyst	Additive	Solvent 1	Solvent 2	Yield (%) ^b	<i>dr</i> ^c	ee (%) ^d
1	C1	BzOH	Tol	Tol	43	55:45	42
2	C2	BzOH	Tol	Tol	45	58:42	48
3	C3	BzOH	Tol	Tol	41	58:42	46
4	C4	TFA	Tol	Tol	66	60:40	70
5	C5	TFA	Tol	Tol	68	62:38	76
6	C5	TsOH	Tol	Tol	65	60:40	74
7	C5	AcOH	Tol	Tol	64	62:38	82
8	C5	BzOH	Tol	Tol	64	65:35	84
9	C5	BzOH	Tol	MeCN	73	62:38	80
10	C5	BzOH	Tol	THF	70	60:40	78
11	C5	BzOH	Tol	DCM	68	70:30	86
12 ^e	C5	BzOH	Tol	DCM	72	75:25	90
13 ^f	C5	BzOH	Tol	DCM	70	73:27	88

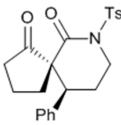
^a Unless noted otherwise, reactions were performed with 0.1 mmol of **1a**, 0.1 mmol of **2a** in 1 mL of solvent 1 at 140 °C, after which 0.12 mmol of **3a**, 0.02 mmol of catalyst and 0.02 mmol of acidic additive were added in 1 mL of solvent 2 at r.t.; ^b Yield of isolated major isomer **5a** over two steps; ^c Calculated based on ¹H-NMR analysis of the crude reaction mixture; ^d Determined by chiral HPLC analysis of the major diastereoisomer; ^e 2 mL of solvent 2 was used; ^f 3 mL of solvent 2 was used.

Using these optimized conditions (Table 1, entry 12), we explored the scope and limitations of this method using α,β -unsaturated aldehyde **3**, cyclic 2-diazo-1,3-diketone **1** and primary amine **2** (Table 2). Generally, the reaction was flexible in affording the desired spirocyclic piperidones. Halogen substitutions such as -F, -Cl, and -Br at the *meta* or *para* positions of aryl groups in enal **3** (entries 2–5) gave better yields and stereoselectivities than such substitutions at the *ortho* position (entries 6 and 7). Strong electron-withdrawing aryl groups on enal **3** (entries 8 and 9) gave slightly higher yields and stereoselectivities than electron-donating aryl groups (entries 10–12). The heteroaromatic group

furan led to the desired product **5m** with high ee and good dr value (entry 13). The crotonaldehyde delivered the alkyl-functionalized product **5n** in 53% yield with poor diastereoselectivity, probably due to the polymerization tendency of the crotonaldehyde (entry 14). Introducing a methyl moiety in cyclic 2-diazo-1,3-diketone **1** gave the corresponding products with two quaternary carbon centers in good yields with 70%–73% ee and 72:28–75:25 dr (entries 15–17). Using benzenesulfonyl- and methylsulfonyl-substituted primary amines provided the expected spiro-products **5r** and **5s** (entries 18 and 19). In terms of the alkyl primary amine, benzyl was also compatible with this reaction system, generating the products **5t** in good results (entry 20). Importantly, the benzyl group can be deprotected by hydrogenation more easily than the sulfonyl group. When using BocNH₂ or AcNH₂ as material, the carbonyl protecting groups were not stable enough in the reaction condition of high temperature, and the desired spiro-piperidones could not be obtained directly. Chemoselective reduction of hemiaminal using Et₃SiH and BF₃·Et₂O at –10 °C provided the dehydroxylation spiro-product **5s** (entry 21). The absolute configuration of **5m** was determined by X-ray crystallography to be 5*R*,8*R*,10*S* (Figure 1) [48]. The absolute configurations of other spiro-piperidone derivatives **5** were assigned by analogy.

Table 2. Investigation of the scope of the tandem reaction using the optimized conditions ^a.



Entry	R ¹	R ²	R ³	Yield (5) (%) ^b	dr ^c	ee (%) ^d
1	H	Ts	Ph	72 (5a)	75:25	90
2	H	Ts	3-FC ₆ H ₄	72 (5b)	72:28	93
3	H	Ts	4-FC ₆ H ₄	74 (5c)	75:25	94
4	H	Ts	4-ClC ₆ H ₄	74 (5d)	73:27	95
5	H	Ts	4-BrC ₆ H ₄	73 (5e)	75:25	96
6	H	Ts	2-FC ₆ H ₄	69 (5f)	70:30	94
7	H	Ts	2-ClC ₆ H ₄	68 (5g)	70:30	91
8	H	Ts	2-NO ₂ C ₆ H ₄	70 (5h)	72:28	93
9	H	Ts	4-NO ₂ C ₆ H ₄	76 (5i)	78:22	97
10	H	Ts	2-MeOC ₆ H ₄	64 (5j)	70:30	91
11	H	Ts	4-MeC ₆ H ₄	66 (5k)	72:28	91
12	H	Ts	4-(Me) ₂ NC ₆ H ₄	62 (5l)	68:32	90
13	H	Ts	2-furyl	75 (5m)	80:20	96
14	H	Ts	Me	53 (5n)	64:36	50
15	Me	Ts	Ph	70 (5o)	72:28	91
16	Me	Ts	4-BrC ₆ H ₄	71 (5p)	74:26	91
17	Me	Ts	2-furyl	73 (5q)	78:22	95
18	H	PhSO ₂	Ph	76 (5r)	76:24	94
19	H	MeSO ₂	Ph	75 (5s)	80:20	95
20	H	Bn	Ph	70 (5t)	73:27	90
				70 (5u)		
21 ^e	H	Ts	Ph		74:26	95

^a See entry 12 and footnote ^a in Table 1; ^b Yield of isolated major isomer **5** over two steps; ^c Calculated based on ¹H-NMR analysis of the crude reaction mixture; ^d Determined by chiral HPLC analysis of the major diastereoisomer; ^e Reduction in the hydroxy group of hemiaminal intermediate.

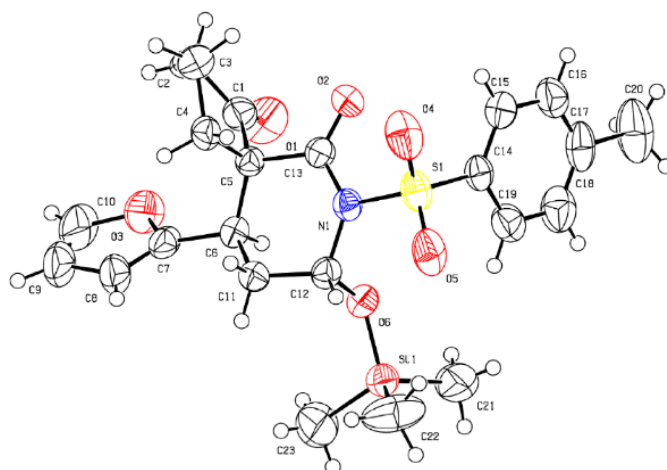


Figure 1. Oak Ridge Thermal Ellipsoid Plot (ORTEP) drawing of compound **5m**.

To explain the observed stereochemistry of our asymmetric organocatalytic relay tandem reaction, we propose a possible reaction transition state based on the MacMillan group's model of the iminium intermediate (Figure 2) [49,50]. In terms of the enantioselectivity of the α,β -unsaturated aldehyde's stereocenter, the steric hindrance of the benzyl group and tertiary butyl group on the catalyst framework blocks one face (up face), so the nucleophilic enol attacks from the *Si* face of the iminium intermediate (bottom face). Thus, the selectivity of the α,β -unsaturated aldehyde stereocenter can be explained. In terms of the control of the stereocenter of the ketoamide substrate, the cyclopentanone moiety with folded structure possesses more steric hindrance than the benzenesulfonyl moiety with planar structure. So, if carbon-carbon bond formation takes place from the *Re* face of the enol (Figure 2, left), the steric repulsion between the bulky cyclopentenol moiety of the β -ketoamide and the β -substituent of the unsaturated aldehyde could be avoided. The major isomer can be obtained with (*R,S*)-configuration, which is observed in the isolated product. Otherwise, when carbon-carbon bond formation takes place from the *Si* face of the enol (Figure 2, right), the steric repulsion between the bulky cyclopentenol moiety of the β -ketoamide and the β -substituent of the unsaturated aldehyde is obvious, which is unfavored.

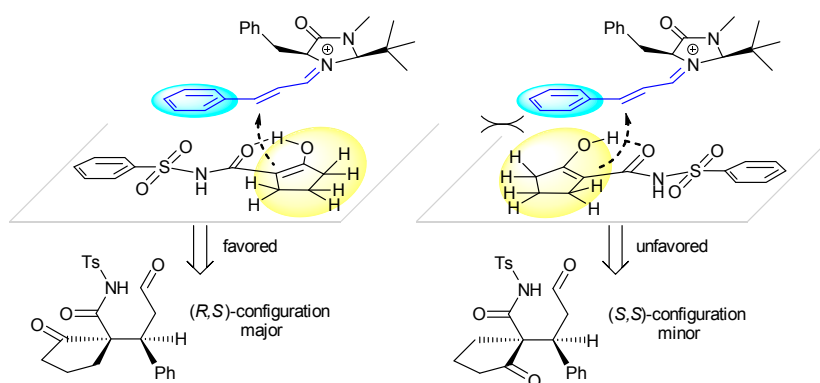


Figure 2. Proposed catalytic models to explain stereochemistry.

3. Materials and Methods

3.1. General Information

NMR data were obtained for ^1H at 400 MHz, and for ^{13}C at 100 MHz (Varian, Palo Alto, CA, USA). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance in

CDCl_3 solution as the internal standard. ESI-HRMS (Electrospray Ionization, High Resolution Mass Spectrum) was performed on a SYNAPT G2-Si (Waters, Milford, MA, USA). Enantiomeric ratios were determined by comparing HPLC analyses of products (Figures S2–S22) on chiral columns with results obtained using authentic racemates. The following Daicel Chiralpak columns and Kromasil columns were used: AD-H (250 mm \times 4.6 mm), OD-H (250 mm \times 4.6 mm), IC (250 mm \times 4.6 mm) or AmyCoat (250 mm \times 4.6 mm). UV detection was performed at 210, 220 or 254 nm. Optical rotation values were measured with MCP (Modular Compact Polarimeter) 200 (Anton Parar GmbH, Shanghai, China) operating at $\lambda = 589$ nm, corresponding to the sodium D line at 20 °C. Column chromatography was performed on silica gel (200–300 mesh) using an eluent of ethyl acetate and petroleum ether. Thin Layer Chromatography (TLC) was performed on glass-backed silica plates; products were visualized using UV light and I_2 . Melting points were determined on a Mel-Temp apparatus (Electrothermal, Staffordshire, UK) and were not corrected. All chemicals were used from Adamas-beta (Adamas, Shanghai, China) without purification unless otherwise noted.

3.2. General Procedure for the Synthesis of Chiral Spirocyclic Piperidones 5

A mixture of cyclic 2-diazo-1,3-diketone **1** [51] (0.1 mmol) and primary amine **2** (0.1 mmol) was refluxed at 140 °C in toluene (1.0 mL) for 3 hours until both of the substrates were nearly consumed (monitored by TLC, petroleum ether/ethyl acetate = 3:1). After the reaction was cooled to room temperature, α,β -unsaturated aldehyde **3** (0.12 mmol), amine catalyst **C5** (0.02 mmol) and benzoic acid (0.04 mmol) were added in CH_2Cl_2 (2.0 mL). The reaction mixture was stirred until the reaction was completed (monitored by TLC, petroleum ether/ethyl acetate = 2:1). Then, the reaction mixture was concentrated and the residue was purified by elaborative chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) to give the hemiaminal **4**.

To a solution of hemiaminal **4** in CH_2Cl_2 (1.0 mL) was added Triethylamine (TEA) (0.3 mmol in 0.5 mL CH_2Cl_2) at ice bath, after which Trimethyl Chlorosilane (TMSCl) (0.2 mmol in 0.5 mL CH_2Cl_2) was added. The reaction mixture was stirred until the reaction was completed (monitored by TLC). Then, the reaction was quenched with aqueous NaHCO_3 , extracted with CH_2Cl_2 . The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 8:1) to give the spirocyclic piperidine **5** (Figure S1) which was dried under vacuum and further analyzed by $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, HRMS (High Resolution Mass Spectrometer), chiral HPLC analysis, etc.

(5*R*,8*R*,10*S*)-10-Phenyl-7-tosyl-8-((trimethylsilyl)oxy)-7-azaspiro[4.5]decane-1,6-dione (**5a**): white solid, 35.0 mg, 72% yield, dr 75:25, ee 90%, $[\alpha]_{\text{D}}^{20} = -13.6$ (CH_2Cl_2 , $c = 1.06$); mp 193–194 °C; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ (ppm): 7.93 (d, $J = 8.4$ Hz, 2H), 7.31–7.28 (m, 5H), 7.11 (d, $J = 7.2$ Hz, 2H), 6.18 (br s, 1H), 4.19 (d, $J = 13.6$ Hz, 1H), 2.50 (t, $J = 13.6$ Hz, 1H), 2.43 (s, 3H), 2.34–2.56 (m, 1H), 2.17–2.08 (m, 3H), 1.85–1.64 (m, 2H), 1.05–0.95 (m, 1H), 0.22 (s, 9H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ (ppm): 216.1, 172.5, 144.5, 137.9, 136.2, 129.2, 128.6, 128.6, 128.5, 127.6, 77.9, 77.3, 77.2, 77.0, 76.7, 63.0, 39.9, 36.5, 34.3, 30.8, 21.6, 19.2, 0.2; HRMS (ESI): m/z calculated for $\text{C}_{25}\text{H}_{31}\text{NO}_5\text{SSiNa}^+$: 508.1590, found: 508.1588.

(5*R*,8*R*,10*S*)-10-(3-Fluorophenyl)-7-tosyl-8-((trimethylsilyl)oxy)-7-azaspiro[4.5]decane-1,6-dione (**5b**): white solid, 36.3 mg, 72% yield, dr 72:28, ee 93%, $[\alpha]_{\text{D}}^{20} = -19.5$ (CH_2Cl_2 , $c = 1.05$); mp 190–192 °C; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ (ppm): 7.92 (d, $J = 8.4$ Hz, 2H), 7.31–7.21 (m, 3H), 6.96 (td, $J = 8.4, 2.4$ Hz, 1H), 6.90–6.82 (m, 2H), 6.17 (t, $J = 2.8$ Hz, 1H), 4.20 (dd, $J = 13.2, 1.6$ Hz, 1H), 2.47 (dd, $J = 13.6, 2.4$ Hz, 1H), 2.43 (s, 3H), 2.38–2.20 (m, 1H), 2.19–2.04 (m, 3H), 1.90–1.68 (m, 2H), 1.14–1.04 (m, 1H), 0.22 (s, 9H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ (ppm): 215.7, 172.2, 162.9 (d, $J_{\text{CF}} = 245.6$ Hz), 144.6, 140.7 (d, $J_{\text{CF}} = 6.8$ Hz), 136.3, 130.3 (d, $J_{\text{CF}} = 8.1$ Hz), 129.3, 128.6, 124.5 (d, $J_{\text{CF}} = 2.9$ Hz), 115.7 (d, $J_{\text{CF}} = 21.5$ Hz), 114.7 (d, $J_{\text{CF}} = 20.8$ Hz), 77.8, 62.9, 39.9, 36.4, 34.4, 30.9, 21.7, 19.3, 0.3; HRMS (ESI): m/z calculated for $\text{C}_{25}\text{H}_{30}\text{FNO}_5\text{SSiNa}^+$: 526.1496, found: 526.1496.

(5*R*,8*R*,10*S*)-10-(4-Fluorophenyl)-7-tosyl-8-((trimethylsilyl)oxy)-7-azaspiro[4.5]decane-1,6-dione (**5c**): white solid, 37.3 mg, 74% yield, dr 75:25, ee 94%, $[\alpha]_{\text{D}}^{20} = -9.9$. (CH_2Cl_2 , $c = 1.00$); mp 174–175 °C; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ (ppm): 7.92 (d, $J = 8.4$ Hz, 2H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.10–7.06 (m,

2H), 6.99 (t, $J = 8.4$ Hz, 2H), 6.17 (t, $J = 2.8$ Hz, 1H), 4.18 (dd, $J = 13.6, 2.0$ Hz, 1H), 2.47 (dd, $J = 13.6, 2.8$ Hz, 1H), 2.43 (s, 3H), 2.37–2.28 (m, 1H), 2.19–2.03 (m, 3H), 1.90–1.78 (m, 1H), 1.73–1.65 (m, 1H), 1.13–1.03 (m, 1H), 0.22 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm): 215.9, 172.6, 162.2 (d, $J_{\text{CF}} = 245.5$ Hz), 144.6, 136.3, 133.8 (d, $J_{\text{CF}} = 3.3$ Hz), 130.3 (d, $J_{\text{CF}} = 7.8$ Hz), 129.3, 128.6, 115.7 (d, $J_{\text{CF}} = 21.1$ Hz), 77.9, 63.0, 39.9, 35.9, 34.6, 30.7, 21.7, 19.3, 0.3; HRMS (ESI): m/z calculated for $\text{C}_{25}\text{H}_{30}\text{FNO}_5\text{SSiNa}^+$: 526.1496, found: 526.1498.

(5*R*,8*R*,10*S*)-10-(4-Chlorophenyl)-7-tosyl-8-((trimethylsilyl)oxy)-7-azaspiro[4.5]decane-1,6-dione (**5d**): white solid, 38.5 mg, 74% yield, dr 73:27, ee 95%, $[\alpha]_{\text{D}}^{20} = -11.2$ (CH_2Cl_2 , $c = 1.07$); mp 189–190 °C; ^1H -NMR (400 MHz, CDCl_3) δ (ppm): 7.89 (d, $J = 6.8$ Hz, 2H), 7.27–7.24 (m, 4H), 7.02 (d, $J = 6.8$ Hz, 2H), 6.14 (br s, 1H), 4.14 (d, $J = 13.6$ Hz, 1H), 2.46–2.43 (m, 1H), 2.39 (s, 3H), 2.32–2.24 (m, 1H), 2.11–2.04 (m, 3H), 1.87–1.76 (m, 1H), 1.71–1.63 (m, 1H), 1.10–1.08 (m, 1H), 0.18 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm): 215.8, 172.2, 144.7, 136.6, 136.3, 133.7, 130.1, 129.3, 129.0, 128.6, 77.9, 63.0, 39.9, 36.1, 34.5, 30.7, 21.8, 19.3, 0.3; HRMS (ESI): m/z calculated for $\text{C}_{25}\text{H}_{30}\text{ClNO}_5\text{SSiNa}^+$: 542.1200, found: 542.1202.

(5*R*,8*R*,10*S*)-10-(4-Bromophenyl)-7-tosyl-8-((trimethylsilyl)oxy)-7-azaspiro[4.5]decane-1,6-dione (**5e**): white solid, 41.2 mg, 73% yield, dr 75:25, ee 96%, $[\alpha]_{\text{D}}^{20} = -9.2$ (CH_2Cl_2 , $c = 1.09$); mp 182–183 °C; ^1H -NMR (400 MHz, CDCl_3) δ (ppm): 7.92 (d, $J = 8.0$ Hz, 2H), 7.43 (d, $J = 8.0$ Hz, 2H), 7.29 (d, $J = 8.4$ Hz, 2H), 6.98 (d, $J = 8.4$ Hz, 2H), 6.17 (t, $J = 2.4$ Hz, 1H), 4.16 (d, $J = 12.4$ Hz, 1H), 2.47 (dd, $J = 13.6, 2.4$ Hz, 1H), 2.42 (s, 3H), 2.37–2.29 (m, 1H), 2.17–2.00 (m, 3H), 1.91–1.79 (m, 1H), 1.70 (dt, $J = 18.0, 8.0$ Hz, 1H), 1.18–1.08 (m, 1H), 0.21 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm): 215.8, 172.2, 144.7, 137.1, 136.3, 131.9, 130.5, 129.3, 128.6, 121.8, 77.8, 62.9, 39.9, 36.1, 34.4, 30.7, 21.8, 19.3, 0.3; HRMS (ESI): m/z calculated for $\text{C}_{25}\text{H}_{30}\text{BrNO}_5\text{SSiNa}^+$: 586.0695, found: 586.0692.

(5*R*,8*R*,10*S*)-10-(2-Fluorophenyl)-7-tosyl-8-((trimethylsilyl)oxy)-7-azaspiro[4.5]decane-1,6-dione (**5f**): white solid, 34.8 mg, 69% yield, dr 70:30, ee 94%, $[\alpha]_{\text{D}}^{20} = -14.4$ (CH_2Cl_2 , $c = 1.01$); mp 151–152 °C; ^1H -NMR (400 MHz, CDCl_3) δ (ppm): 7.92 (d, $J = 8.0$ Hz, 2H), 7.30 (d, $J = 8.4$ Hz, 2H), 7.26–7.23 (m, 1H), 7.15–7.05 (m, 3H), 6.27 (t, $J = 2.8$ Hz, 1H), 4.17 (dd, $J = 13.6, 2.4$ Hz, 1H), 3.31 (td, $J = 14.0, 1.2$ Hz, 1H), 2.74–2.66 (m, 1H), 2.43 (s, 3H), 2.14–1.98 (m, 2H), 1.85–1.75 (m, 2H), 1.68–1.62 (m, 1H), 1.14–1.03 (m, 1H), 0.24 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm): 215.8, 170.2, 160.8 (d, $J_{\text{CF}} = 244.0$ Hz), 144.5, 136.5, 129.4 (d, $J_{\text{CF}} = 9.2$ Hz), 129.3 (d, $J_{\text{CF}} = 3.4$ Hz), 129.3, 128.7, 126.2 (d, $J_{\text{CF}} = 13.7$ Hz), 124.9 (d, $J_{\text{CF}} = 3.6$ Hz), 115.9 (d, $J_{\text{CF}} = 23.3$ Hz), 78.4, 62.1, 39.9, 34.1, 32.9, 32.6, 21.8, 20.0, 0.3; HRMS (ESI): m/z calculated for $\text{C}_{25}\text{H}_{30}\text{FNO}_5\text{SSiNa}^+$: 526.1496, found: 526.1493.

(5*R*,8*R*,10*S*)-10-(2-Chlorophenyl)-7-tosyl-8-((trimethylsilyl)oxy)-7-azaspiro[4.5]decane-1,6-dione (**5g**): white solid, 35.4 mg, 68% yield, dr 70:30, ee 91%, $[\alpha]_{\text{D}}^{20} = -11.9$ (CH_2Cl_2 , $c = 1.09$); mp 139–140 °C; ^1H -NMR (400 MHz, CDCl_3) δ (ppm): 7.92 (d, $J = 8.0$ Hz, 2H), 7.42–7.40 (m, 1H), 7.31 (d, $J = 8.0$ Hz, 2H), 7.22–7.14 (m, 3H), 6.25 (br s, 1H), 4.49 (d, $J = 12.8$ Hz, 1H), 3.26 (t, $J = 13.2$ Hz, 1H), 2.70–2.63 (m, 1H), 2.43 (s, 3H), 2.15–2.07 (m, 2H), 1.85–1.64 (m, 3H), 1.10–1.00 (m, 1H), 0.25 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm): 216.1, 170.0, 144.3, 136.9, 136.4, 134.8, 130.2, 129.1, 129.1, 128.9, 128.6, 127.5, 78.3, 62.5, 39.9, 36.2, 34.7, 32.3, 21.7, 19.9, 0.2; HRMS (ESI): m/z calculated for $\text{C}_{25}\text{H}_{30}\text{ClNO}_5\text{SSiNa}^+$: 542.1200, found: 542.1199.

(5*R*,8*R*,10*S*)-10-(2-Nitrophenyl)-7-tosyl-8-((trimethylsilyl)oxy)-7-azaspiro[4.5]decane-1,6-dione (**5h**): white solid, 37.2 mg, 70% yield, dr 72:28, ee 93%, $[\alpha]_{\text{D}}^{20} = +8.2$ (CH_2Cl_2 , $c = 0.95$); mp 196–197 °C; ^1H -NMR (400 MHz, CDCl_3) δ (ppm): 7.90 (d, $J = 8.4$ Hz, 2H), 7.68 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.51 (dt, $J = 7.6, 1.2$ Hz, 1H), 7.43 (dt, $J = 7.6, 1.2$ Hz, 1H), 7.35 (dd, $J = 7.6, 0.8$ Hz, 1H), 7.30 (d, $J = 8.4$ Hz, 2H), 6.26 (t, $J = 2.8$ Hz, 1H), 4.35 (dd, $J = 13.2, 2.4$ Hz, 1H), 3.34 (td, $J = 13.2, 2.4$ Hz, 1H), 2.69–2.62 (m, 1H), 2.43 (s, 3H), 2.15 (dt, $J = 18.4, 7.6$ Hz, 1H), 1.91 (dt, $J = 13.6, 2.8$ Hz, 1H), 1.87–1.65 (m, 3H), 1.06–0.97 (m, 1H), 0.27 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm): 215.9, 169.4, 151.6, 144.5, 136.3, 132.4, 132.4, 129.4, 129.2, 128.7, 128.6, 124.2, 78.0, 62.0, 39.9, 34.7, 34.6, 33.1, 21.7, 19.8, 1.0, 0.2; HRMS (ESI): m/z calculated for $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_7\text{SSiNa}^+$: 553.1441, found: 553.1444.

(5*R*,8*R*,10*S*)-10-(4-Nitrophenyl)-7-tosyl-8-((trimethylsilyl)oxy)-7-azaspiro[4.5]decane-1,6-dione (**5i**): white solid, 40.3 mg, 76% yield, dr 78:22, ee 97%, $[\alpha]_{\text{D}}^{20} = +9.4$ (CH_2Cl_2 , $c = 1.00$); mp 199–200 °C; ^1H -NMR (400 MHz, CDCl_3) δ (ppm): 8.17 (d, $J = 8.4$ Hz, 2H), 7.92 (d, $J = 8.4$ Hz, 2H), 7.30 (d, $J = 8.4$ Hz,

4H), 6.20 (t, $J = 2.8$ Hz, 1H), 4.34–4.30 (m, 1H), 2.53 (td, $J = 13.6, 2.8$ Hz, 1H), 2.43 (s, 3H), 2.40–2.34 (m, 1H), 2.24–2.18 (m, 1H), 2.13 (dt, $J = 13.6, 2.8$ Hz, 1H), 2.01–1.85 (m, 2H), 1.70 (dt, $J = 18.4, 8.0$ Hz, 1H), 1.19–1.09 (m, 1H), 0.22 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm): 215.1, 171.5, 147.4, 145.6, 144.7, 136.0, 129.8, 129.3, 128.6, 123.8, 77.6, 62.7, 39.6, 36.5, 34.3, 30.5, 21.7, 19.2, 0.2; HRMS (ESI): m/z calculated for $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_7\text{SSiNa}^+$: 553.1441, found: 553.1444.

(5*R*,8*R*,10*S*)-10-(2-Methoxyphenyl)-7-tosyl-8-((trimethylsilyl)oxy)-7-azaspiro[4.5]decane-1,6-dione (**5j**): white solid, 33.0 mg, 64% yield, dr 70:30, ee 91%, $[\alpha]_{\text{D}}^{20} = +11.9$ (CH_2Cl_2 , $c = 0.97$); mp 191–192 °C; ^1H -NMR (400 MHz, CDCl_3) δ (ppm): 7.93 (d, $J = 8.4$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 7.23 (td, $J = 8.0, 1.6$ Hz, 1H), 7.05 (dd, $J = 8.0, 1.2$ Hz, 1H), 6.89 (d, $J = 8.0$ Hz, 2H), 6.24 (t, $J = 2.8$ Hz, 1H), 4.38 (d, $J = 12.0$ Hz, 1H), 3.82 (s, 3H), 3.26 (td, $J = 13.6, 2.4$ Hz, 1H), 2.66–2.59 (m, 1H), 2.42 (s, 3H), 2.10–2.01 (m, 2H), 1.75–1.61 (m, 3H), 1.06–0.96 (m, 1H), 0.22 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm): 216.4, 170.7, 157.4, 144.3, 136.7, 129.2, 128.7, 128.7, 127.8, 121.1, 111.6, 78.8, 62.6, 55.6, 39.9, 34.4, 32.5, 21.8, 19.9, 0.3; HRMS (ESI): m/z calculated for $\text{C}_{26}\text{H}_{33}\text{NO}_6\text{SSiNa}^+$: 538.1696, found: 538.1694.

(5*R*,8*R*,10*S*)-10-(*p*-tolyl)-7-tosyl-8-((trimethylsilyl)oxy)-7-azaspiro[4.5]decane-1,6-dione (**5k**): white solid, 33.0 mg, 66% yield, dr 72:28, ee 91%, $[\alpha]_{\text{D}}^{20} = -22.9$ (CH_2Cl_2 , $c = 0.91$); mp 150–151 °C; ^1H -NMR (400 MHz, CDCl_3) δ (ppm): 7.93 (d, $J = 8.4$ Hz, 2H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.09 (d, $J = 8.0$ Hz, 2H), 6.98 (d, $J = 8.0$ Hz, 2H), 6.17 (t, $J = 2.8$ Hz, 1H), 4.15 (dd, $J = 13.6, 2.0$ Hz, 1H), 2.48 (dd, $J = 13.6, 2.8$ Hz, 1H), 2.42 (s, 3H), 2.31 (s, 3H), 2.30–2.25 (m, 1H), 2.14–2.08 (m, 3H), 1.85–1.64 (m, 2H), 1.09–0.99 (m, 1H), 0.21 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm): 216.1, 172.6, 144.4, 137.3, 136.4, 134.9, 129.3, 129.2, 128.5, 77.9, 63.1, 39.9, 36.2, 34.4, 30.9, 29.7, 21.7, 21.0, 19.3, 1.0, 0.2; HRMS (ESI): m/z calculated for $\text{C}_{26}\text{H}_{33}\text{NO}_5\text{SSiNa}^+$: 522.1746, found: 522.1744.

(5*R*,8*R*,10*S*)-10-(4-(Dimethylamino)phenyl)-7-tosyl-8-((trimethylsilyl)oxy)-7-azaspiro[4.5]decane-1,6-dione (**5l**): white solid, 32.8 mg, 62% yield, dr 68:32, ee 90%, $[\alpha]_{\text{D}}^{20} = -63.5$ (CH_2Cl_2 , $c = 1.02$); mp 186–187 °C; ^1H -NMR (400 MHz, CDCl_3) δ (ppm): 7.93 (d, $J = 8.4$ Hz, 2H), 7.28 (d, $J = 8.4$ Hz, 2H), 6.96 (d, $J = 8.8$ Hz, 2H), 6.63 (d, $J = 8.8$ Hz, 2H), 6.15 (t, $J = 2.4$ Hz, 1H), 4.09 (dd, $J = 13.6, 2.0$ Hz, 1H), 2.92 (s, 6H), 2.45 (dd, $J = 13.8, 2.4$ Hz, 1H), 2.41 (s, 3H), 2.32–2.24 (m, 1H), 2.16–2.06 (m, 3H), 1.83–1.66 (m, 2H), 1.12–1.06 (m, 1H), 0.20 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm): 216.5, 172.9, 149.7, 144.3, 136.5, 129.3, 129.2, 128.5, 125.3, 112.3, 78.1, 63.3, 40.4, 39.9, 35.8, 34.6, 30.9, 21.6, 19.7, 0.3; HRMS (ESI): m/z calculated for $\text{C}_{27}\text{H}_{36}\text{N}_2\text{O}_5\text{SSiNa}^+$: 551.2012, found: 551.2011.

(5*R*,8*R*,10*S*)-10-(Furan-2-yl)-7-tosyl-8-((trimethylsilyl)oxy)-7-azaspiro[4.5]decane-1,6-dione (**5m**): white solid, 35.7 mg, 75% yield, dr 80:20, ee 96%, $[\alpha]_{\text{D}}^{20} = -62.3$ (CH_2Cl_2 , $c = 1.09$); mp 140–141 °C; ^1H -NMR (400 MHz, CDCl_3) δ (ppm): 7.90 (d, $J = 8.4$ Hz, 2H), 7.29 (m, 3H), 6.29 (dd, $J = 3.2, 1.6$ Hz, 1H), 6.15 (t, $J = 2.8$ Hz, 1H), 6.04 (d, $J = 3.2$ Hz, 1H), 4.20 (dd, $J = 13.2, 2.0$ Hz, 1H), 2.42 (s, 3H), 2.34 (dd, $J = 13.6, 2.4$ Hz, 1H), 2.23–1.85 (m, 6H), 1.30–1.20 (m, 1H), 0.24 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm): 215.1, 171.8, 152.6, 144.5, 142.1, 136.3, 129.2, 128.5, 110.4, 107.5, 77.8, 61.7, 39.3, 32.7, 32.2, 31.8, 21.6, 19.0, 0.2; HRMS (ESI): m/z calculated for $\text{C}_{23}\text{H}_{29}\text{NO}_6\text{SSiNa}^+$: 498.1383, found: 498.1381.

(5*R*,8*R*,10*S*)-10-Methyl-7-tosyl-8-((trimethylsilyl)oxy)-7-azaspiro[4.5]decane-1,6-dione (**5n**): white solid, 22.5 mg, 53% yield, dr 64:36, ee 50%, $[\alpha]_{\text{D}}^{20} = -16.9$ (CH_2Cl_2 , $c = 1.10$); mp 146–147 °C; ^1H -NMR (400 MHz, CDCl_3) δ (ppm): 7.89 (d, $J = 8.4$ Hz, 2H), 7.26 (d, $J = 7.2$ Hz, 2H), 6.00 (t, $J = 2.8$ Hz, 1H), 2.98–2.90 (m, 1H), 2.56–2.47 (m, 1H), 2.40 (s, 3H), 2.18–2.04 (m, 4H), 1.89–1.80 (m, 3H), 0.82 (d, $J = 6.8$ Hz, 3H), 0.23 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm): 215.8, 172.6, 144.4, 136.5, 129.1, 128.6, 78.5, 62.1, 39.8, 37.1, 29.4, 26.2, 21.6, 19.3, 15.7, 0.2; HRMS (ESI): m/z calculated for $\text{C}_{20}\text{H}_{29}\text{NO}_5\text{SSiNa}^+$: 446.1433, found: 446.1430.

(5*R*,8*R*,10*S*)-3,3-Dimethyl-10-phenyl-7-tosyl-8-((trimethylsilyl)oxy)-7-azaspiro[4.5]decane-1,6-dione (**5o**): white solid, 36.0 mg, 70% yield, dr 72:28, ee 91%, $[\alpha]_{\text{D}}^{20} = -33.9$ (CH_2Cl_2 , $c = 1.14$); mp > 210 °C; ^1H -NMR (400 MHz, CDCl_3) δ (ppm): 7.94 (d, $J = 8.4$ Hz, 2H), 7.32–7.27 (m, 5H), 7.13–7.11 (m, 2H), 6.14 (t, $J = 2.4$ Hz, 1H), 4.18 (dd, $J = 13.2, 2.0$ Hz, 1H), 2.45–2.40 (m, 4H), 2.38–2.32 (m, 1H), 2.14–2.05 (m, 2H), 1.96 (d, $J = 14.4$ Hz, 1H), 1.51 (d, $J = 18.4$ Hz, 1H), 1.02 (s, 3H), 0.23 (s, 3H), 0.19 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ (ppm): 215.0, 172.9, 144.4, 138.3, 136.3, 129.3, 129.2, 128.7, 128.6, 127.8, 77.9, 65.4,

55.0, 43.5, 37.1, 34.5, 32.9, 30.5, 29.7, 21.6, 0.2; HRMS (ESI): m/z calculated for $C_{27}H_{35}NO_5SSiNa^+$: 536.1903, found: 536.1907.

(5*R*,8*R*,10*S*)-10-(4-Bromophenyl)-3,3-dimethyl-7-tosyl-8-((trimethylsilyl)oxy)-7-azaspiro[4.5]decane-1,6-dione (**5p**): white solid, 42.1 mg, 71% yield, dr 74:26, ee 91%, $[\alpha]_D^{20} = -17.9$ (CH_2Cl_2 , $c = 1.04$); mp 206–207 °C; 1H -NMR (400 MHz, $CDCl_3$) δ (ppm): 7.93 (d, $J = 8.4$ Hz, 2H), 7.44 (d, $J = 8.4$ Hz, 2H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.01 (d, $J = 8.4$ Hz, 2H), 6.13 (t, $J = 2.8$ Hz, 1H), 4.14 (dd, $J = 13.6, 2.0$ Hz, 1H), 2.44–2.39 (m, 4H), 2.40–2.33 (m, 1H), 2.05–2.00 (m, 3H), 1.04 (s, 3H), 0.90–0.82 (m, 1H), 0.28 (s, 3H), 0.19 (s, 9H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ (ppm): 214.6, 172.6, 144.5, 137.5, 136.2, 131.7, 131.0, 129.2, 128.7, 121.9, 77.8, 65.4, 55.0, 43.5, 36.4, 34.5, 32.9, 30.4, 29.9, 21.7, 0.2; HRMS (ESI): m/z calculated for $C_{27}H_{34}BrNO_5SSiNa^+$: 614.1008, found: 614.1005.

(5*R*,8*R*,10*S*)-10-(Furan-2-yl)-3,3-dimethyl-7-tosyl-8-((trimethylsilyl)oxy)-7-azaspiro[4.5]decane-1,6-dione (**5q**): white solid, 36.8 mg, 73% yield, dr 78:22, ee 95%, $[\alpha]_D^{20} = -13.4$ (CH_2Cl_2 , $c = 0.97$); mp 108–109 °C; 1H -NMR (400 MHz, $CDCl_3$) δ (ppm): 7.91 (d, $J = 8.0$ Hz, 2H), 7.32–7.26 (m, 3H), 6.29 (dd, $J = 2.8, 2.0$ Hz, 1H), 6.11 (t, $J = 2.4$ Hz, 1H), 6.08 (d, $J = 2.8$ Hz, 1H), 4.21 (dd, $J = 13.2, 2.4$ Hz, 1H), 2.50 (d, $J = 18.0$ Hz, 1H), 2.41 (s, 3H), 2.33 (td, $J = 14.0, 2.8$ Hz, 1H), 2.14–2.10 (m, 2H), 2.00–1.89 (m, 2H), 1.07 (s, 3H), 0.48 (s, 3H), 0.21 (s, 9H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ (ppm): 214.1, 172.3, 152.6, 144.5, 142.1, 136.3, 129.1, 128.6, 110.6, 108.5, 77.8, 64.0, 54.4, 44.8, 33.2, 33.0, 32.6, 30.6, 30.1, 21.6, 0.2; HRMS (ESI): m/z calculated for $C_{25}H_{33}NO_6SSiNa^+$: 526.1696, found: 526.1698.

(5*R*,8*R*,10*S*)-10-Phenyl-7-(phenylsulfonyl)-8-((trimethylsilyl)oxy)-7-azaspiro[4.5]decane-1,6-dione (**5r**): white solid, 35.8 mg, 76% yield, dr 76:24, ee 94%, $[\alpha]_D^{20} = -13.5$ (CH_2Cl_2 , $c = 0.99$); mp 193–194 °C; 1H -NMR (400 MHz, $CDCl_3$) δ (ppm): 8.08–8.04 (m, 2H), 7.62–7.58 (m, 1H), 7.53–7.48 (m, 2H), 7.31–7.27 (m, 3H), 7.12–7.10 (m, 2H), 6.19 (t, $J = 2.8$ Hz, 1H), 4.12 (dd, $J = 13.6, 2.0$ Hz, 1H), 2.51 (td, $J = 13.6, 2.4$ Hz, 1H), 2.29 (ddd, $J = 18.0, 8.4, 6.8$ Hz, 1H), 2.16–2.10 (m, 3H), 1.84–1.64 (m, 2H), 1.06–0.96 (m, 1H), 0.22 (s, 9H). ^{13}C -NMR (100 MHz, $CDCl_3$) δ (ppm): 215.9, 172.6, 139.3, 137.9, 133.5, 128.7, 128.7, 128.6, 128.4, 127.6, 78.0, 63.1, 39.8, 36.6, 34.4, 30.9, 19.3, 0.2; HRMS (ESI): m/z calculated for $C_{24}H_{29}NO_5SSiNa^+$: 494.1433, found: 494.1433.

(5*R*,8*R*,10*S*)-7-(Methylsulfonyl)-10-phenyl-8-((trimethylsilyl)oxy)-7-azaspiro[4.5]decane-1,6-dione (**5s**): white solid, 30.7 mg, 75% yield, dr 80:20, ee 95%, $[\alpha]_D^{20} = -32.75$ (CH_2Cl_2 , $c = 0.97$); mp 165–166 °C; 1H -NMR (400 MHz, $CDCl_3$) δ (ppm): 7.34–7.28 (m, 3H), 7.14 (dd, $J = 8.4, 2.0$ Hz, 2H), 5.99 (t, $J = 2.4$ Hz, 1H), 4.24 (dd, $J = 14.0, 2.4$ Hz, 1H), 3.31 (s, 3H), 2.49 (td, $J = 13.6, 2.4$ Hz, 1H), 2.43–2.35 (m, 1H), 2.23–2.13 (m, 2H), 2.05 (dt, $J = 14.0, 2.8$ Hz, 1H), 1.92–1.70 (m, 2H), 1.20–1.10 (m, 1H), 0.18 (s, 9H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ (ppm): 216.3, 174.5, 138.0, 129.1, 129.0, 128.0, 79.1, 77.6, 77.3, 77.0, 63.4, 42.9, 40.1, 37.0, 34.3, 30.8, 19.5, 0.3; HRMS (ESI): m/z calculated for $C_{19}H_{27}NO_5SSiNa^+$: 432.1277, found: 432.1277.

(5*R*,8*R*,10*S*)-7-Benzyl-10-phenyl-8-((trimethylsilyl)oxy)-7-azaspiro[4.5]decane-1,6-dione (**5t**): white solid, 29.5 mg, 70% yield, dr 73:27, ee 90%, $[\alpha]_D^{20} = -20.1$ ($c = 1.08$ in CH_2Cl_2); mp 164–165 °C; 1H -NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37–7.23 (m, 8H), 7.16–7.14 (m, 2H), 5.16 (d, $J = 15.2$ Hz, 1H), 5.01 (dd, $J = 7.6, 6.8$ Hz, 1H), 4.30 (d, $J = 14.4$ Hz, 1H), 3.65–3.58 (m, 1H), 2.51–2.42 (m, 1H), 2.39–2.30 (m, 1H), 2.28–2.21 (m, 2H), 2.19–2.13 (m, 1H), 1.94–1.80 (m, 2H), 0.91–0.84 (m, 1H), 0.08 (s, 9H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ (ppm): 217.7, 171.9, 138.2, 136.3, 128.0, 128.1, 127.9, 127.1, 126.9, 126.6, 79.0, 60.6, 44.0, 39.5, 38.8, 34.6, 30.1, 19.3, -0.3 ; HRMS (ESI): m/z calculated for $C_{25}H_{31}NO_3SiNa^+$: 444.1971, found: 444.1974.

(5*R*,10*S*)-10-Phenyl-7-tosyl-7-azaspiro[4.5]decane-1,6-dione (**5u**): white solid, 27.8 mg, 70% yield, dr 74:26, ee 95%, $[\alpha]_D^{20} = +32.7$ (CH_2Cl_2 , $c = 0.99$); mp 140–141 °C; 1H -NMR (400 MHz, $CDCl_3$) δ (ppm): 7.89 (d, $J = 8.0$ Hz, 2H), 7.32 (d, $J = 8.0$ Hz, 2H), 7.30–7.27 (m, 3H), 7.14–7.12 (m, 2H), 4.46 (ddd, $J = 12.0, 5.2, 2.0$ Hz, 1H), 3.78 (td, $J = 12.0, 4.4$ Hz, 1H), 3.19–3.08 (m, 1H), 2.99 (dd, $J = 13.6, 2.8$ Hz, 1H), 2.74 (dt, $J = 15.6, 8.0$ Hz, 1H), 2.43 (s, 3H), 2.10–1.95 (m, 3H), 1.80–1.70 (m, 1H), 1.66–1.57 (m, 1H), 1.00–0.86 (m, 1H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ (ppm): 216.1, 170.4, 144.7, 139.1, 135.9, 129.4, 128.9, 128.5, 128.4, 127.9, 62.1, 48.9, 46.2, 40.0, 33.6, 25.5, 21.7, 19.7; HRMS (ESI): m/z calculated for $C_{22}H_{23}NO_4SNa^+$: 420.1245, found: 420.1246.

4. Conclusions

In summary, we have developed an organocatalytic stepwise reaction to achieve the asymmetric assembly of cyclic 2-diazo-1,3-diketones, primary amines and α,β -unsaturated aldehydes into chiral spirocyclic piperidone architectures bearing up to three stereogenic centers and multiple functional groups in good yields with moderate diastereoselectivities and high enantioselectivities. The reaction proceeds via sequential Wolff rearrangement–amidation–Michael–hemiaminalization. Product stereocontrol can be achieved by adjusting the sequence of steps in this one-pot multicomponent reaction. We are now investigating the application of these pharmacologically interesting chiral spiro-piperidine derivatives to the discovery of lead compounds, and the results will be reported in due course.

Supplementary Materials: The supplementary materials are available online at www.mdpi.com/2073-4344/7/2/46/s1. Figure S1, Structure of compounds **5a–5u**; Figures S2–S22, HPLC chromatograms and NMR spectra.

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