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Enantioselective Synthesis of Unsymmetrical Diaryl-Substituted Spirocyclohexanonepyrazolones through a Cascade [4+2] Double Michael Addition

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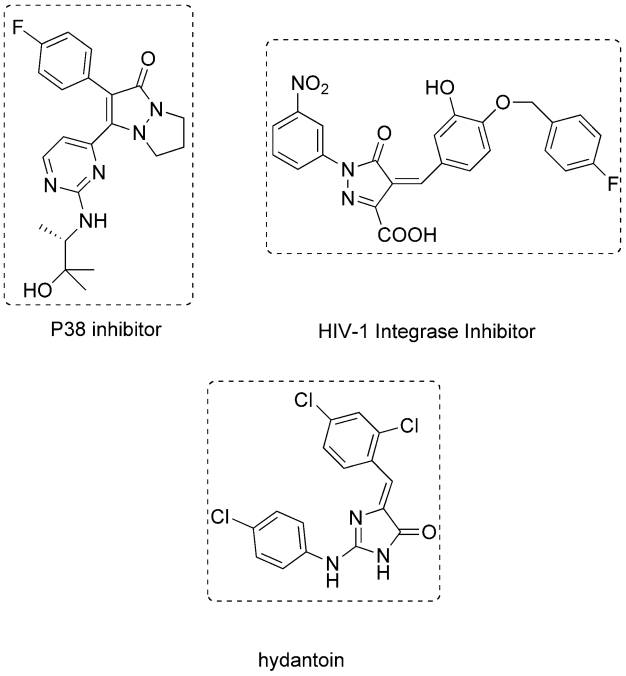
Abstract: The spirocyclic pyrazolones are an important class of molecular structures with significant biological and pharmaceutical activities. Herein, we demonstrate that the combination of a *Cinchona*-based chiral primary amine and an *ortho*-fluorobenzoic acid is an efficient catalyst system for the double Michael addition of arylidenepyrazolones with α,β-unsaturated ketones, providing chiral unsymmetrical 6,10-diaryl-substituted spiro[cyclohexanone-pyrazolone] derivatives in high yields (up to 98%) with good diastereoselectivities and excellent enantioselectivities (up to 88:12 *dr*, 99% *ee*).

Keywords: arylidenepyrazolones; enantioselectivity; Michael addition; organic catalysis

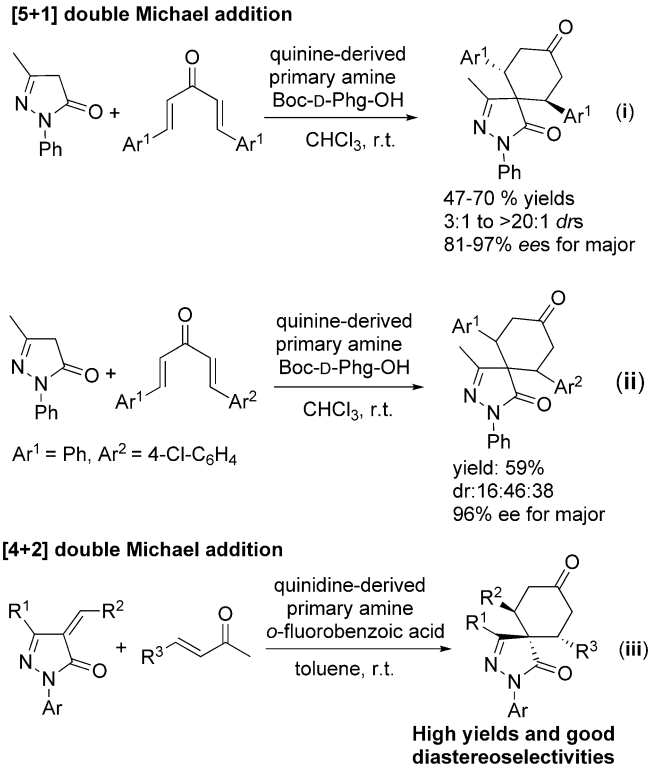
Pyrazolone skeletons are a valuable class of molecular motifs occurring in many natural products and synthetic compounds of pharmaceutical interest.[1] Some examples are shown in Scheme 1, whereby P38 is a very effective inhibitor for the treatment of inflammation,[2] while the HIV-1 integrase inhibitor[2,3] and hydantoin have specific activities against bacteria.[4] In particular, chiral spirocyclic pyrazolones with a quaternary stereogenic center are promising subsets of the spirocyclic family with potential biological and pharmaceutical activities. Thus, the development of catalytic enantioselective synthetic protocols for the efficient preparation of this type of compounds has been of considerable interest for organic chemists.[1d,3,5,6]

It is worthy of note that despite the fact that some useful enantioselective transformations based on mono-Michael addition have been reported for the synthesis of the optically active pyrazolone derivatives,[7] so far only few asymmetric cascade methodologies[8] have been developed for the construction of enantioenriched spirocyclic[9] pyrazolones. In 2011, Rios and co-workers have reported a cascade Michael/Michael/intramolecular aldol reaction sequence, affording the multistereogenic chiral spiro[pyrazolone-cyclohexenecarbaldehyde] compounds in moderate to good yields with excellent enantioselectivities.[10] Very recently, our group has demonstrated that optically active spiro[pyrazolone-cyclohexones] could be efficiently synthesized through a cascade [5+



Scheme 1. Some classic pyrazolone derivatives.

1]double Michael reaction between divinyl ketones and pyrazolones.[11] In that work we have found that in the presence of 20 mol% of quinine-derived primary amine and 40 mol% of Boc-D-Phg-OH, the reactions of symmetrical 1,5-diaryl divinyl ketones with various substituents on phenyl groups, irrespective of their electron-donating or electron-withdrawing nature, proceeded smoothly under the optimized conditions, to give the corresponding spirocyclohexanonepyrazolones in reasonable yields with moderate to good diastereomeric ratios (*dr*) and good to excellent enantioselectivities [Scheme 2, Eq. (i)]. However, the



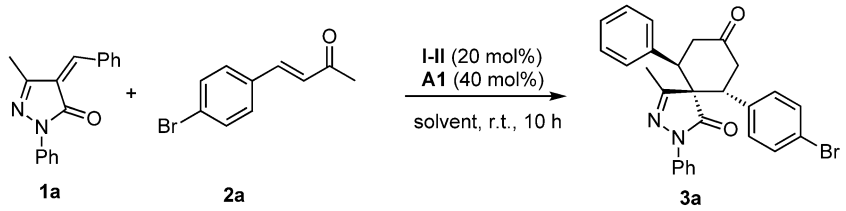
Scheme 2. The construction of multistereogenic symmetrical or non-symmetrical diaryl-substituted spiro[cyclohexanone-pyrazolones] through a cascade [5+1] or [4+2]double Michael addition.

diastereoselectivity declines significantly for the unsymmetrical 1,5-diaryl-substituted divinyl ketones as the Michael acceptors, presumably as a result of the difficulty of the catalyst in differentiating the two enantiofaces of the substrate attacked by the nucleophile during the first Michael addition step. In this case, the corresponding [5+1]double Michael reaction gave an almost equal amount of diastereomers in low yield, albeit with excellent enantioselectivity for two major diastereomers [Scheme 2, Eq. (ii)]. In the present work, we report an alternative organocatalyzed protocol for the asymmetric synthesis of unsymmetrical spiro[cyclohexanone-pyrazolone] derivatives, *via* a cascade [4+2]double Michael addition between arylmethylene pyrazolones and α,β-unsaturated ketones. Under the optimized conditions, a variety of chiral spiro[cyclohexanone-pyrazolones] bearing unsymmetrical diaryl substituents on the cyclohexanone backbone were obtained in high yields with good diastereoselectivities and excellent enantioselectivities [Scheme 2, Eq. (iii).]

We proposed our synthetic approach through a cascade double Michael reaction between arylidenepyrazolones and α,β-unsaturated ketones[12] involving enamine and/or iminium ion intermediates. It is noteworthy that the combination of a *Cinchona* alkaloid-derived primary amine with an organic protonic acid[13] has often been used as a powerful catalyst in many enantioselective enamine and iminium ion-mediated transformations.[14] With this in mind, we started to examine the model reaction between benzylidenepyrazolone **1a** and benzylideneacetone **2a**, using 20 mol% quinidine-derived primary amine[15] **I** or its pseudoenantiomer **II** as catalysts and 40 mol% benzoic acid **A1** as an additive. Initially, several commonly used solvents were screened for the reaction at room temperature. As shown in Table 1, the reaction proceeded smoothly in THF to provide the double Michael adducts in 55% overall yield with three pairs of diastereomers, albeit with over 90% *ee* for two major diastereomers (entry 1). CH_2Cl_2, *n*-hexane, toluene, and PhCl, were further examined as the reaction media, and toluene was found to be optimal, affording the desired product **3a** in 92% yield, 84:16 *dr*, and 99% *ee* for both major and minor diasteroisomers (entry 5 *vs.* entries 2–4). Subsequently, some homologues of toluene were investigated under the catalysis of the amine catalyst **I** and benzoic acid **A1**, but none of them has shown better catalytic results in terms of both reactivity and diastereoselectivity (Table 1, entries 6–9). Finally, quinine-derived primary amine catalyst **II**, a pseudo-enantiomer of **I** has also been also examined in the reaction under otherwise identical conditions. Although the enantioselectivities remain excellent for both diastereomers, some decline in yield and diastereoselectivity of **3a** was observed for this case (entry 10).

In order to explore the influence of the organic protonic acid on reactivity and diastereoselectivity of this transformation, a variety of achiral and/or chiral Brønsted acids was examined in combination with amine catalyst **I**, and the results are shown in Table 2. It was found that for the benzoic acid derivatives (Figure 1) screened in the reaction, **A2** and **A3** bearing an electron-withdrawing group (NO_2 or CF_3) on the phenyl ring led to the product **3a** with higher diastereo- and enantioselectivities, albeit in lower yields (entries 2 and 3 *vs.* 1). In contrast, the use of aromatic acids **A5** or **A6** bearing an electron-donating group

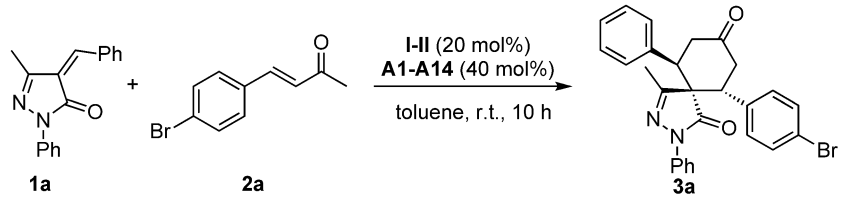
Table 1. Examination of catalysts and solvents.[a]



Entry	Catalyst/Additive	Solvent	Yield [%][b]	*dr* [%][c]	*ee* [%][c]
1	**I/A1**	THF	55	12:35:53	11/98/93
2	**I/A1**	CH_2Cl_2	81	50:50	98/91
3	**I/A1**	*n*-hexane	58	47:53	96/96
4	**I/A1**	PhCl	86	64:36	99/99
5	**I/A1**	toluene	92	84:16	99/99
6	**I/A1**	*o*-xylene	93	75:25	99/99
7	**I/A1**	*m*-xylene	65	89:11	99/96
8	**I/A1**	*p*-xylene	93	72:28	99/98
9	**I/A1**	mesitylene	95	75:25	99/99
10	**II/A1**	toluene	84	69:31	−98/−99

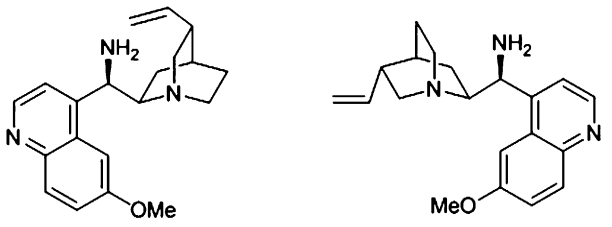
[a] Reactions were performed with **1** (0.2 mmol), **2** (0.4 mmol) and catalyst loading **I** or **II** (20 mol%)/**A1** (40 mol%), in solvents (2.0 mL) at room temperature.
[b] Yield of isolated product.
[c] Determined by chiral HPLC.

Table 2. Screening of achiral and chiral Brønsted acids.[a]



Entry	Catalyst/Additive	Yield [%][b]	*dr* [%][c]	*ee* [%][c]
1	**I/A1**	92	84:16	99/99
2	**I/A2**	60	91:9	98/99
3	**I/A3**	62	92:8	99/99
4	**I/A4**	96	85:15	99/99
5	**I/A5**	94	77:23	99/98
6	**I/A6**	89	71:29	99/99
7	**I/A7**	63	6:83:11	88/98/99
8	**I/A8**	76	87:13	99/99
9	**I/A9**	85	86:14	98/99
10	**I/A10**	trace	nd	nd
11	**I/A11**	54	13:73:14	99/98/99
12	**I/A12**	trace	nd	nd
13	**I/A13**	trace	nd	nd
14	**I/A14**	78	82:18	97/99
15	**II/A14**	60	75:25	−96/−96
16[d]	**I/A4**	60	86:14	99/99

[a] Unless noted otherwise, reactions were performed with **1** (0.2 mmol), **2** (0.4 mmol) and catalyst loading **I** or **II** (20 mol%)/**A1–A14** (40 mol%), in toluene (2.0 mL) at room temperature.
[b] Yield of isolated product.
[c] Determined by chiral HPLC.
[d] At 0 °C.



Additives:

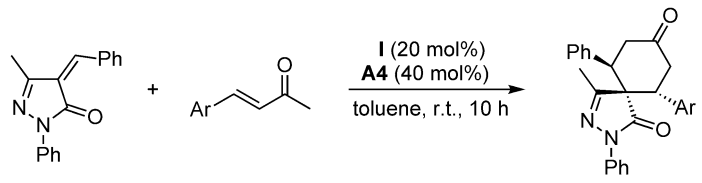
A1: $C_6H_5CO_2H$
A2: 4-NO_2-$C_6H_4CO_2H$
A3: 4-CF_3-$C_6H_4CO_2H$
A4: 2-F-$C_6H_4CO_2H$
A5: 4-CH_3-$C_6H_4CO_2H$
A6: 4-CH_3O-$C_6H_4CO_2H$
A7: CF_3CO_2H
A8: Boc-L-phg-OH
A9: Boc-D-phg-OH
A10: (R)-BINOL-phosphoric acid
A11: (S)-BINOL-phosphoric acid
A12: L-CSA
A13: D-CSA
A14: Naproxen

Figure 1. The catalysts screened in this study.

(Me, OMe) afforded product **3a** in high yields and excellent enantioselectivities but with lower diastereoselectivities (entries 5 and 6 *vs.* 1). When *ortho*-fluorobenzoic acid **A4** was used as the additive, the combination of amine catalyst **I**/**A4** turned out to be optimal in terms of both reactivity and stereoselectivity for this transformation, affording the corresponding product **3a** in 96% yield with good diastereo- and excellent enantioselectivities (entry 4). The stronger acid TFA seemed to have a detrimental effect on both the reactivity and diastereoselectivity, although high enantioselectivities were retained for the three diastereomers (entry 7). Some chiral Brønsted acids **A8**–**A14** were also tested for this reaction. Intriguingly, the combinations of (*R*)-BINOL-derived chiral phosphoric acid **A10**, camphorsulfonic acid **A12** and **A13** with **I**, respectively, were found to be inactive for the catalysis of this transformation, only giving the target product **3a** in trace amounts under otherwise identical conditions (entries 10, 12 and 13). The use of the other amine catalyst/chiral acid additive pairs afforded the desired products in excellent enantioselectivities, but with reduced yields and/or diastereoselectivities (entries 8, 9, 11 and 14). Overall, the combination **I/A4** turned out to be the optimal catalytic system with respect to the double Michael addition of benzylidenepyrazolone **1a** with benzylideneacetone **2a** in toluene at room temperature.

With the optimized reaction conditions in hand, we further examined the scope and limitations of the

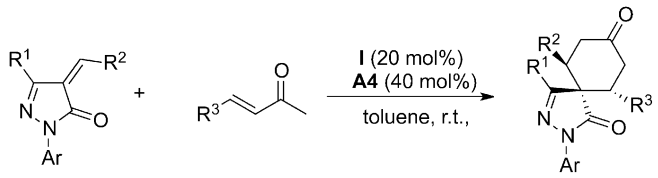
Table 3. Substrate scope of **I/A4**-catalyzed double Michael addition of benzylidenepyrazolone **1a** with α,β-unsaturated ketones **2a–l**.[a]



Entry	Ar	Yield [%][b]	*dr* [%][c]	*ee* [%][c]
1	4-Br-C_6H_4 (**2a**)	**3a**/96	85:15	99/99
2	4-Cl-C_6H_4 (**2b**)	**3b**/95	84:16	97/–
3	3-Cl-C_6H_4 (**2c**)	**3c**/98	88:12	99/99
4	4-F-C_6H_4 (**2d**)	**3d**/95	83:17	99/99
5	2-F-C_6H_4 (**2e**)	**3e**/90	84:16	99/99
6	4-CF_3-C_6H_4 (**2f**)	**3f**/93	82:18	99/95
7	2,4-$(MeO)_2C_6H_3$ (**2g**)	**3g**/77	58:37:5	99/96/94
8	2-MeO-C_6H_4 (**2h**)	**3h**/79	82:18	99/99
9	4-*i*-Pr-C_6H_4 (**2i**)	**3i**/84	85:15	99/83
10	4-Me-C_6H_4 (**2j**)	**3j**/86	88:12	99/99
11	1-naphthyl (**2k**)	**3k**/88	51:49	99/99
12	2-thienyl (**2l**)	**3l**/82	73:27	99/99

[a] Reactions were performed with **1a** (0.2 mmol), **2a–l** (0.4 mmol) and catalyst loading **I** (20 mol%)/**A4** (40 mol%), in toluene (2.0 mL) at room temperature.
[b] Yield of isolated product.
[c] Determined by chiral HPLC.

Table 4. Substrate scope of **I/A4**-catalyzed double Michael addition of α,β-unsaturated pyrazolone derivatives **1b–l** with α,β-unsaturated ketones.[a]



1b–l **2c, 2j, 2m** **3m–y**

Entry	**1** (Ar, R^1, R^2)	R^3	Product/Yield [%][b]	*dr* [%][c]	*ee* [%][c]
1	**1b** (C_6H_5, CH_3, 4-F-C_6H_4)	3-Cl-C_6H_4 (**2c**)	**3m**/93	82:18	99/95
2	**1c** (C_6H_5, CH_3, 3,5-$(MeO)_2C_6H_3$)	3-Cl-C_6H_4 (**2c**)	**3n**/96	88:12	99/99
3	**1d** (C_6H_5, CH_3, 4-ClC_6H_4)	3-Cl-C_6H_4 (**2c**)	**3o**/95	83:17	97/95
4	**1e** (C_6H_5, CH_3, 3-Me-C_6H_4)	3-Cl-C_6H_4 (**2c**)	**3p**/89	86:14	94/99
5	**1b** (C_6H_5, CH_3, 4-F-C_6H_4)	4-Me-C_6H_4 (**2j**)	**3q**/83	72:28	92/99
6	**1c** (C_6H_5, CH_3, 3,5-$(MeO)_2C_6H_3$)	4-Me-C_6H_4 (**2j**)	**3r**/78	80:20	98/96
7	**1d** (C_6H_5, CH_3, 4-Cl-C_6H_4)	4-Me-C_6H_4 (**2j**)	**3s**/88	68:32	94/94
8	**1e** (C_6H_5, CH_3, 3-Me-C_6H_4)	4-Me-C_6H_4 (**2j**)	**3t**/84	78:22	98/–
9	**1f** (C_6H_5, C_6H_5, C_6H_5)	3-Cl-C_6H_4 (**2c**)	**3u**/60	11:43:46	–/99/99
10[d]	**1g** (C_6H_5, CF_3, C_6H_5)	3-Cl-C_6H_4 (**2c**)	<10	–	–
11	**1h** (4-Br-C_6H_4, CH_3, C_6H_5)	3-Cl-C_6H_4 (**2c**)	**3v**/90	74:26	99/99
12	**1i** (3-Cl-C_6H_4, CH_3, C_6H_5)	3-Cl-C_6H_4 (**2c**)	**3w**/90	70:30	98/99
13	**1j** (4-Me-C_6H_4, CH_3, C_6H_5)	3-Cl-C_6H_4 (**2c**)	**3x**/88	84:16	99/99
14	**1k** (4-MeO-C_6H_4, CH_3, C_6H_5)	3-Cl-C_6H_4 (**2c**)	**3y**/93	88:12	91/99
15[d]	**1l** (C_6H_5, CH_3, Cy)	3-Cl-C_6H_4 (**2c**)	<10	–	–
16[d]	**1a** (C_6H_5, CH_3, C_6H_5)	Me (**2m**)	<10	–	–

[a] Unless noted otherwise, reactions were performed with **1** (0.2 mmol), **2** (0.4 mmol) and catalyst loading **I** (20 mol%)/**A4** (40 mol%), in toluene (2.0 mL) at room temperature for 10 h.
[b] Yield of isolated product.
[c] Determined by chiral HPLC.
[d] Reactions were performed for 24 h.

double Michael addition between benzylidenepyrazolone **1a** with α,β-unsaturated ketones **2a–l** under the catalyst loading of 20 mol% quinidine-derived primary amine **I** and 40 mol% *ortho*-fluorobenzoic acid **A4** in toluene at room temperature, and the results are summarized in Table 3. The reactions proceeded smoothly to give the corresponding adducts in good to excellent yields with moderate to good diastereoselectivities and excellent enantioselectivities. While excellent enantioselectivities were retained for all desired products **3a–l**, the steric hindrance and electronic properties of the substituents on the phenyl ring of benzylideneacetone derivatives **2a–l** seem to have some influence on the reactivity and diastereoselectivity of the reactions. Generally, electron-withdrawing substituents on the phenyl ring of benzylideneacetone derivatives **2a–f** showed high reactivity and selectivity to give expected products in 90–98% yields and 82:18 to 88:12 *dr*s (Table 3, entries 1–6), whereas electron-donating substituents on the phenyl ring of benzylideneacetone derivatives **2g–j** provided the corresponding products in lower yields (77–86%) with varying levels of diastereoselectivities (from 58:37:5 to 88:12 *dr*s) (Table 3, entries 7-10). Apparently, α,β-unsaturated ketones **2k** and **2l** containing fused aromatic or heteroaromatic rings were also suitable substrates for this reaction, to provide the desired products **3k** and **3l** in good yields (88% and 82%) with excellent enantioselectivities (99% *ee*s for both diastereomers), respectively, albeit with less satisfactory diastereoselectivities (51:49 and 73:27 *dr*s) (Table 3, entries 11 and 12).

As demonstrated in Table 4, the combination of **I/A4** was also applied in the double Michael addition of α,β-unsaturated ketones **2c** and **2j** with benzylidenepyrazolone derivatives **1b–e** in toluene under the above optimized reaction conditions. The benzylidenepyrazolone derivatives **1b–e** bearing electron-donating or electron-withdrawing substituents on the phenyl rings were amenable to the procedure, and all the reactions proceeded smoothly to give the desired products in good yields (78–96%), moderate to good diastereoselective ratios (68:32 to 88:12 *dr*) and excellent enantioselectivities (92–99% *ee*) (entries 1–8). However, when **1f** was used, changing the methyl group to phenyl group in comparision with **1a**, inferior diastereoselectivity (11:43:46 *dr*) and yield (60%) were obtained, probably due to the effect of the steric

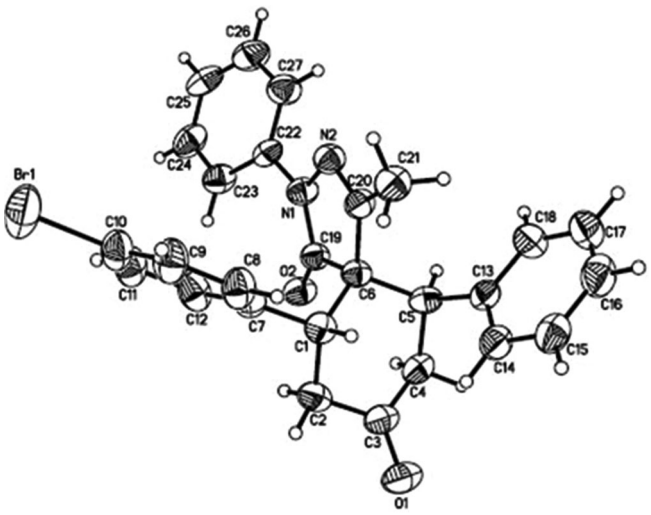


Figure 2. The X-ray crystal structure of **3a**.

hindrance for the first Michael addition (Table 4, entry 9). Trifluoromethyl-substituted benzylidenepyrazolone **1g** was proved to be an ineffective substrate for this transformation (Table 4, entry 10). Subsequently, benzylidenepyrazolones **1h–k** bearing different aryl groups on the nitrogen have also been investigated for the double Michael addition, all the reactions proceeded smoothly to give expected adducts in excellent yields (88–93%) with good diastereoselectivities (70:30 to 88:12 *dr*s) and excellent enantioselectivities (91–99% *ee*s) (Table 4, entries 11–14). In addition, both aliphatic substituted α,β-unsaturated ketones and alkylidenepyrazolones were respectively tested in this reaction, such as **1l** and pent-3-en-2-one **2m**. Unfortunately, under our optimized conditions, catalyst **I**/**A4** was found to be ineffective for the transformation involving these compounds (Table 4, entries 15 and 16). To our delight, the single crystal of compound **3a** was obtained by recrystallization from hexane/acetone, which allowed us to make an unambiguous assignment of the *trans* configuration of C-1 and C-5 stereocenters by X-ray crystallographic analysis, and the newly formed three carbon centers were all designated to be of the *R* configuration. (Figure 2).[16]

In summary, we have developed an efficient protocol for the construction of enantiomerically enriched unsymmetrical diaryl-substituted spirocyclo[hexanone-pyrazolones] *via* a cascade [4+2]double Michael addition reaction between arylideneacetones with arylidenepyrazolones, which is catalyzed by a combination of a *Cinchona*-based chiral primary amine and *ortho*-fluorobenzoic acid. All explored cascade double reactions could provide the spirocyclo-[hexanone-pyrazolone] derivatives in high to good yields with moderate to good diastereoselectivities and excellent enantioselectivities. Studies on the further improvement on diastereoselectivity and expansion of the substrate scope of this catalytic system, as well as biological evaluations of the resulting spirocompounds will be undertaken in the future.

Experimental Section

General Information

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All reactions were carried out in air and using undistilled solvents, without any precautions to exclude moisture unless otherwise mentioned. Organic solutions were concentrated under reduced pressure on a rotary evaporator. Reactions were monitored by thin-layer chromatography (TLC) on silica gel precoated glass plates (0.2 ± 0.03 mm thickness, GF-254, particle size 0.01–0.04 mm). Chromatograms were visualized by fluorescence quenching with UV light at 254 nm. Flash column chromatography was performed using silica gel (particle size 0.04–0.05 mm). ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded in $CDCl_3$ using TMS as the internal reference. Chemical shifts (δ ppm) are relative to the resonance of the deuterated solvent as the internal standard ($CDCl_3$, $\delta = 7.26$ ppm for proton NMR, $\delta =$ 77.00 ppm for carbon NMR). ^{1}H NMR data are reported as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, q = quartet, sep = septet, m = multiplet), coupling constants (J) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). High-resolution mass spectra (HR-MS) for all the compounds were determined on Micromass GCT-TOF mass spertrometer with EI or ESI sources. The enantiomeric excess (*ee*) of the products was determined by HPLC using a Chiralcel OD-H column (0.46 cm × 25 cm), Chiralpak AD-H (0.46 cm × 25 cm), Chiralpak I A (0.46 cm × 25 cm) with 2-propanol/hexane as the eluent. Optical rotation data were examined in $CHCl_3$ solution at 25 °C and $[\alpha]_D^{25}$ values are reported in 10^{-1} dg cm^2 g^{-1}; concentration (c) is reported in g/100 mL.

General Experimental Procedures for the Asymmetric Double Michael Addition Reaction

Pyrazolones derivatives **1** (0.2 mmol), α,β-unsaturated ketones **2** (0.4 mmol), catalyst **I** (20 mol%), *o*-F-PhCOOH (40 mol%) were stirred in toluene (2.0 mL) at room temperature for 10 h in air. Then the reaction mixture was directly subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to afford the corresponding products **3.**

Characterization Data of Michael Addition Products 3

6-(4-Bromophenyl)-4-methyl-2,10-diphenyl-2,3-diazaspiro-[4.5]dec-3-ene-1,8-dione (3a): white solid; yield: 93.5 mg (96%), 85:15 *dr*, 99% ee_{major}, 99% ee_{minor}. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak AD-H with hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL min^{-1}, $\lambda = 254$ nm]: major diastereoisomer $t_{major} =$ 17.425 min, $t_{minor} = 15.072$ min; minor diastereoisomer $t_{major} =$

23.545 min; $[\alpha]_D^{25}$: +42.9 (c 0.42 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.49 (m, 2H), 7.42–7.40 (m, 1H), 7.35–7.28 (m, 5H), 7.20–7.10 (m, 4H), 7.03–6.99 (m, 2H), 3.91–3.79 (m, 2H), 3.64 (dd, J = 14.2, 3.0 Hz, 1H), 3.36 (dd, J = 16.4, 5.2 Hz, 1H), 2.96 (dd, J = 16.4, 9.2 Hz, 1H), 2.61 (dd, J = 16.0, 3.2 Hz, 1H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.0, 174.6, 160.6, 138.3, 136.9, 135.7, 131.8, 129.5, 129.0, 128.9 128.2, 127.7, 125.8, 122.1, 119.9, 61.6, 44.2, 41.8, 41.1, 40.5, 15.7; IR (KBr): ν_{max} = 1707, 1600, 1494, 1401, 758, 693 cm^{-1}; ESI-MS (%): m/z = 487.1 $[M+H]^+$; HR-MS (ESI): m/z = 487.1023 $[M+H]^+$, calcd. for $C_{27}H_{24}BrN_2O_2$: 487.1021.

6-(4-Chlorophenyl)-4-methyl-2,10-diphenyl-2,3-diazaspiro-[4.5]dec-3-ene-1,8-dione (3b): white solid; yield: 84.2 mg (95%), 84:16 *dr*, 97% ee_{major}. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak OD-H with hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL min^{-1}, λ = 254 nm]: major diastereoisomer t_{major} = 19.132 min, t_{minor} = 22.827 min; minor diastereoisomer t = 30.645 min; $[\alpha]_D^{25}$: +45.8 (*c* 0.45 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.41 (m, 2H), 7.35–7.29 (m, 4H), 7.18–7.16 (m, 4H), 7.12–7.01 (m, 4H), 3.92–3.72 (m, 2H), 3.65 (dd, J = 14.4, 2.4 Hz, 1H), 3.37 (dd, J = 16.4, 5.2 Hz, 1H), 2.97 (dd, J = 16.4, 9.2 Hz, 1H), 2.61 (dd, J = 16.0, 2.8 Hz, 1H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.0, 174.6, 160.5, 138.3, 137.0, 135.2, 134.0, 132.7, 129.1, 129.0, 128.8, 128.2, 127.7, 125.8, 119.7, 61.7, 44.2, 41.8, 41.2, 40.5, 15.7; IR (KBr): ν_{max} = 1708, 1597, 1495, 1402, 834, 758, 692 cm^{-1}; ESI-MS (%): m/z = 443.2 $[M+H]^+$; HR-MS (ESI): m/z = 443.1530 $[M+H]^+$, calcd. for $C_{27}H_{24}ClN_2O_2$: 443.1526.

6-(3-Chlorophenyl)-4-methyl-2,10-diphenyl-2,3-diazaspiro-[4.5]dec-3-ene-1,8-dione (3c): white solid; yield: 86.8 mg (98%), 88:12 *dr*, 99% ee_{major}, 99% ee_{minor}. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak OD-H with hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL min^{-1}, λ = 254 nm]: major diastereoisomer t_{major} = 25.862 min; minor diastereoisomer t_{major} = 29.257 min; $[\alpha]_D^{25}$: +46.9 (*c* 0.41 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.50 (m, 2H), 7.40–7.25 (m, 5H), 7.21–7.04 (m, 7H), 3.93–3.78 (m, 2H), 3.64 (d, J = 16.8 Hz, 1H), 3.38 (dd, J = 21.8, 6.2 Hz, 1H), 3.00–2.96 (m, 1H), 2.63 (d, J = 20 Hz, 1H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.8, 174.6, 160.4, 138.6, 138.3, 137.0, 134.4, 132.7, 129.9, 129.0, 128.8, 128.4, 128.2, 128.0, 127.6, 125.8, 119.8, 61.6, 44.1, 42.1, 41.0, 40.5, 15.7; IR (KBr): ν_{max} = 1709, 1591, 1494, 1402, 758, 694 cm^{-1}; ESI-MS (%): m/z = 443.2 $[M+H]^+$; HR-MS (ESI): m/z = 443.1527 $[M+H]^+$, calcd. for $C_{27}H_{24}ClN_2O_2$: 443.1526.

6-(4-Fluorophenyl)-4-methyl-2,10-diphenyl-2,3-diazaspiro-[4.5]dec-3-ene-1,8-dione (3d): white solid; yield: 81.1 mg (95%), 83:17 *dr*, 99% ee_{major}, 99% ee_{minor}. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak OD-H with hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL min^{-1}, λ = 254 nm]: major diastereoisomer t_{major} = 15.365 min; minor diastereoisomer t_{major} = 23.249 min; $[\alpha]_D^{25}$: +54.5 (*c* 0.40 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.42 (m, 2H), 7.34–7.28 (m, 4H), 7.17–7.10 (m, 4H), 6.90–6.86 (m, 2H), 3.94–3.80 (m, 2H), 3.66 (dd, J = 14.2, 2.6 Hz, 1H), 3.33 (dd, J = 16.4, 4.8 Hz, 1H), 2.99 (dd, J = 16.4, 10.0 Hz, 1H), 2.62 (dd, J = 16.0, 2.8 Hz, 1H), 1.69 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.3, 174.9, 163.7, 160.7, 138.5, 137.2, 132.6, 129.7, 129.6, 129.2, 129.0, 128.3, 127.8, 126.0, 119.9, 115.9, 115.6, 62.2, 44.2, 41.8, 41.5, 40.7, 15.9; IR (KBr): ν_{max} = 1709, 1598, 1503, 1401, 1227, 838, 760, 694 cm^{-1}; ESI-MS (%): m/z = 427.2 $[M+H]^+$; HR-MS (ESI): m/z = 427.1823 $[M+H]^+$, calcd. for $C_{27}H_{24}FN_2O_2$: 427.1822.

6-(2-Fluorophenyl)-4-methyl-2,10-diphenyl-2,3-diazaspiro-[4.5]dec-3-ene-1,8-dione (3e): white solid; yield: 76.9 mg (90%), 84:16 *dr*, 99% ee_{major}, 99% ee_{minor}. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak OD-H with hexane/*i*-PrOH (80:20) as the eluent; flow: 1.0 mL min^{-1}, λ = 254 nm]: major diastereoisomer t_{major} = 16.664 min; minor diastereoisomer t_{major} = 26.041 min; $[\alpha]_D^{25}$: +59.0 (*c* 0.41 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.48 (m, 2H), 7.41–7.37 (m, 1H), 7.32–7.25 (m, 5H), 7.16–7.11 (m, 4H), 7.01 (t, J = 7.2 Hz, 1H), 6.94–6.89 (m, 1H), 4.19 (dd, J = 14.2, 3.0 Hz, 1H), 3.97 (dd, J = 10.4, 4.8 Hz, 1H), 3.87–3.79 (m, 1H), 3.29 (dd, J = 16.4, 4.4 Hz, 1H), 3.07 (dd, J = 16.6, 10.6 Hz, 1H), 2.56 (dd, J = 16.6, 3.0 Hz, 1H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.8, 174.9, 161.3, 138.1, 137.2, 129.6, 129.6, 129.2, 129.0, 128.8, 128.1, 127.6, 125.7, 124.6, 123.9, 123.8, 119.8, 115.5, 115.3, 61.6, 43.8, 40.9, 40.5, 33.6, 15.3; IR (KBr): ν_{max} = 1709, 1596, 1496, 1400, 758, 699 cm^{-1}; ESI-MS (%): m/z = 427.2 $[M+H]^+$; HR-MS (ESI): m/z = 427.1803 $[M+H]^+$, calcd. for $C_{27}H_{24}FN_2O_2$: 427.1822.

4-Methyl-2,6-diphenyl-10-[4-(trifluoromethyl)phenyl]-2,3-diazaspiro[4.5]dec-3-ene-1,8-dione (3f): white solid; yield: 88.7 mg (93%), 82:18 *dr*, 99% ee_{major}, 95% ee_{minor}. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak AD-H with hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL min^{-1}, λ = 210 nm]: major diastereoisomer t_{major} = 12.777 min, t_{minor} = 9.827 min; minor diastereoisomer t_{major} = 27.728 min, t_{minor} = 17.306 min; $[\alpha]_D^{25}$: +51.8 (*c* 0.39 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.39 (m, 4H), 7.33–7.25 (m, 6H), 7.20–7.11 (m, 4H), 3.95–3.83 (m, 2H), 3.72 (dd, J = 14.2, 2.6 Hz, 1H), 3.37 (dd, J = 16.4, 5.2 Hz, 1H), 2.99 (dd, J = 16.6, 9.4 Hz, 1H), 2.63 (dd, J = 16.0, 2.4 Hz, 1H), 1.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.5, 174.6, 160.3, 159.8, 140.7, 138.2, 137.0, 130.6, 130.3, 129.1, 128.9, 128.7, 128.3, 128.0, 127.8, 127.7, 126.0, 125.7, 119.8, 61.7, 44.2, 42.2, 41.0, 40.6, 15.8; IR (KBr): ν_{max} = 1710, 1602, 1498, 1326, 1123, 844, 761, 696 cm^{-1}; ESI-MS (%): m/z = 477.2 $[M+H]^+$; HR-MS (ESI): m/z = 477.1765 $[M+H]^+$, calcd. for $C_{28}H_{24}F_3N_2O_2$: 477.1784.

6-(2,4-Dimethoxyphenyl)-4-methyl-2,10-diphenyl-2,3-diazaspiro[4.5]dec-3-ene-1,8-dione (3g): white solid; yield: 72.2 mg (77%), 58:37:5 *dr*, 99% *ee* on the 58% disteroisomer, 96% *ee* on the 37% disteroisomer, 94% *ee* on the 5% disteroisomer. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak AD-H with hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL min^{-1}; λ = 254 nm]: 58% diastereoisomer t_{major} = 22.460 min, t_{minor} = 21.256 min; 37% diastereoisomer t_{major} = 39.709 min, t_{minor} = 11.938 min; 5% diastereoisomer t_{major} = 6.682 min, t_{minor} = 7.354 min; $[\alpha]_D^{25}$: +21.9 (*c* 0.47 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, J = 7.6 Hz, 2H), 7.34–7.28 (m, 3H), 7.12–7.08 (m, 6H), 6.38–6.34 (m, 1H), 6.28 (d, J = 2.0 Hz, 1H), 4.27 (d, J = 14.0 Hz, 1H), 3.97–3.94 (m, 1H), 3.86–3.81 (m, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 3.21 (dd, J = 16.6, 4.2 Hz, 1H), 3.06 (dd, J = 16.6, 11 Hz, 1H), 2.48 (d, J = 16.4 Hz, 1H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.1, 175.4, 162.0, 160.1, 157.2, 138.3, 137.3, 129.4, 128.7, 128.7, 127.5, 125.4, 119.9,

119.1, 117.5, 104.6, 98.0, 62.0, 55.3, 55.0, 43.5, 41.6, 40.4, 33.2, 15.5; IR (KBr): ν_{max} = 1710, 1600, 1500, 1032, 832, 757, 696 cm^{-1}; ESI-MS (%): m/z = 469.2 $[M+H]^+$; HR-MS (ESI): m/z = 469.2129 $[M + H]^+$, calcd. for $C_{29}H_{29}N_2O_4$: 469.2127.

6-(2-Methoxyphenyl)-4-methyl-2,10-diphenyl-2,3-diazaspiro[4.5]dec-3-ene-1,8-dione (3h): white solid; yield: 69.4 mg (79%), 82:18 *dr*, 99% ee_{major}, 99% ee_{minor}. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak AD-H with hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL min^{-1}, λ = 254 nm]: major diastereoisomer t_{major} = 15.772 min; minor diastereoisomer t_{major} = 11.591 min, t_{minor} = 10.905 min; $[\alpha]_D^{25}$: −9.2 (*c* 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.42 (m, 2H), 7.27–7.26 (m, 3H), 7.11–7.12 (m, 6H), 6.84–6.71 (m, 3H), 4.37 (d, *J* = 13.6 Hz, 1H), 3.97 (m, 1H), 3.84–3.76 (m, 1H), 3.69 (s, 3H), 3.25–3.21 (m, 1H), 3.11–3.05 (m, 1H), 2.51 (d, *J* = 16.0 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.0, 175.3, 161.9, 156.3, 138.3, 137.2, 128.9, 128.8, 128.7, 128.0, 127.6, 125.6, 125.1, 120.9, 120.0, 119.1, 110.3, 61.9, 55.1, 43.7, 41.4, 40.5, 33.6, 15.6; IR (KBr): ν_{max} = 1704, 1593, 1493, 1370, 1237, 1023, 759, 695 cm^{-1}; ESI-MS (%): m/z = 439.2 $[M+H]^+$; HR-MS (ESI): m/z = 439.2006 $[M+H]^+$, calcd. for $C_{28}H_{27}N_2O_3$: 439.2022.

6-(4-Isopropylphenyl)-4-methyl-2,10-diphenyl-2,3-diazaspiro[4.5]dec-3-ene-1,8-dione (3i): white solid; yield: 75.8 mg (84%), 85:15 *dr*, 99% ee_{major}, 83% ee_{minor}: The *dr* and *ee* values were determined by HPLC on Daicel Chiralpak AD-H with hexane/*i*-PrOH (80:20) as the eluent; flow: 1.0 mL min^{-1}, λ = 254 nm]: major diastereoisomer t_{major} = 8.126 min, t_{minor} = 9.291 min; minor diastereoisomer t_{major} = 30.943 min, t_{minor} = 16.820 min; $[\alpha]_D^{25}$: +54.7 (*c* 0.59 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.37 (m, 2H), 7.31–7.25 (m, 4H), 7.18–7.12 (m, 4H), 7.05 (m, 4H), 3.95 (dd, *J* = 10.2, 4.8 Hz, 1H), 3.89–3.82 (m, 1H), 3.63 (dd, *J* = 14.2, 3 Hz, 1H), 3.29 (dd, *J* = 16.6, 4.6 Hz, 1H), 3.02 (dd, *J* = 16.8, 10.4 Hz, 1H), 2.76 (sep, *J* = 6.8 Hz, 1H9; 2.65 (dd, *J* = 16.4, 2.8 Hz, 1H), 1.74 (s, 3H), 1.10 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.7, 175.1, 160.8, 148.9, 138.7, 137.3, 133.8, 129.1, 128.9, 128.2, 127.9, 127.7, 126.7, 125.9, 120.3, 62.4, 43.7, 42.3, 41.3, 40.7, 33.9, 24.0, 15.9; IR (KBr): ν_{max} = 1708, 1599, 1500, 1401, 836, 759, 695 cm^{-1}; ESI-MS (%): m/z = 451.2 $[M+H]^+$; HR-MS (ESI): m/z = 451.2379 $[M+H]^+$, calcd. for $C_{30}H_{31}N_2O_2$: 451.2386.

4-Methyl-2,6-diphenyl-10-*p*-tolyl-2,3-diazaspiro[4.5]dec-3-ene-1,8-dione (3j): white solid; yield: 72.8 mg (86%), 88:12 *dr*, 99% ee_{major}, 99% ee_{minor}. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak AD-H with hexane/*i*-PrOH (80:20) as the eluent; flow: 1.0 mL min^{-1}, λ = 254 nm]: major diastereoisomer t_{major} = 10.948 min; minor diastereoisomer t_{major} = 17.781 min; $[\alpha]_D^{25}$: +41.7 (*c* 0.41 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8 Hz, 2H), 7.34–7.29 (m, 4H), 7.17–7.11 (m, 4H), 7.01 (dd, *J* = 18.2, 8.0 Hz, 4H), 3.90–3.83 (m, 2H), 3.65 (dd, *J* = 14, 2.8 Hz, 1H), 3.39 (dd, *J* = 16.0, 5.2 Hz, 1H), 2.95 (dd, *J* = 16.4, 9.2 Hz, 1H), 2.63 (dd, *J* = 16.2, 3 Hz, 1H), 2.19 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 175.0, 160.9, 138.7, 137.8, 137.3, 133.7, 129.3, 129.0, 128.8, 128.1, 127.8, 127.6, 125.6, 119.9, 61.8, 44.4, 42.1, 41.6, 40.7, 21.0, 15.7; IR (KBr): ν_{max} = 1708, 1598, 1499, 1399, 758, 695 cm^{-1}; ESI-MS (%): m/z = 423.2 $[M+H]^+$; HR-MS (ESI): m/z = 423.2053 $[M+H]^+$, calcd. for $C_{28}H_{27}N_2O_2$: 423.2073.

4-Methyl-6-(naphthalen-1-yl)-2,10-diphenyl-2,3-diazaspiro[4.5]dec-3-ene-1,8-dione (3k): white solid; yield: 80.8 mg (88%), 51:49 *dr*, 99% ee_{major}, 99% ee_{minor}. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak AD-H with hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL min^{-1}, λ = 254 nm]: major diastereoisomer t_{major} = 8.131 min, t_{minor} = 12.222 min; minor diastereoisomer t_{major} = 9.309 min, t_{minor} = 11.142 min; $[\alpha]_D^{25}$: −96.8 (*c* 0.41 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.79 (m, 8H), 7.69–7.65 (m, 3H), 7.56–7.37 (m, 14H), 7.25–7.21 (m, 4H), 7.15 (s, 5H), 4.83–4.73 (m, 2H), 3.99–3.81 (m, 6H), 2.93–2.71 (m, 4H), 1.01 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.0, 209.6, 175.6, 175.1, 161.3, 161.2, 139.8, 137.7, 137.5, 135.9, 134.4, 134.1, 133.8, 131.9, 130.7, 129.7, 129.5, 129.3, 129.0, 129.0, 128.9, 128.9, 128.8, 128.6, 128.5, 128.2, 127.7, 127.1, 126.8, 126.3, 126.1, 125.9, 125.7, 125.7, 125.3, 124.4, 122.5, 121.5, 119.9, 119.6, 60.4, 60.3, 47.2, 43.5, 43.2, 42.4, 42.1, 41.3, 39.2, 35.4, 16.0, 15.5; IR (KBr): ν_{max} = 1703, 1595, 1497, 1377, 1011, 771, 696 cm^{-1}; ESI-MS (%): m/z = 459.2 $[M+H]^+$; HR-MS (ESI): m/z = 459.2059 $[M+H]^+$, calcd. for $C_{31}H_{27}N_2O_2$, 459.2067.

4-Methyl-2,6-diphenyl-10-(thiophen-2-yl)-2,3-diazaspiro[4.5]dec-3-ene-1,8-dione (3l): white solid; yield: 68.1 mg (82%), 73:27 *dr*, 99% ee_{major}, 99% ee_{minor}. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak OD-H with hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL min^{-1}, λ = 254 nm]: major diastereoisomer t_{major} = 17.745 min, t_{minor} = 40.106 min; minor diastereoisomer t_{major} = 27.187 min; $[\alpha]_D^{25}$: +23.6 (*c* 0.36 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.62 (d, *J* = 8.0 Hz, 2H), 7.35–7.31 (m, 4H), 7.20–7.10 (m, 5H), 6.85–6.82 (m, 2H), 4.01 (dd, *J* = 13.8, 3 Hz, 1H), 3.85–3.77 (m, 2H), 3.47 (dd, *J* = 16.0, 5.6 Hz, 1H), 2.86 (dd, *J* = 16.0, 7.6 Hz, 1H), 2.78 (dd, *J* = 16.0, 2.8 Hz, 1H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.5, 174.6, 160.9, 139.7, 138.8, 129.2, 128.9, 128.3, 128.0, 127.8, 127.0, 125.7, 125.6, 124.9, 119.7, 61.7, 45.1, 43.1, 40.8, 37.8, 15.7; IR (KBr): ν_{max} = 1708, 1595, 1496, 1398, 756, 690 cm^{-1}; ESI-MS (%): m/z = 415.2 $[M+H]^+$; HR-MS (ESI): m/z = 415.1464 $[M+H]^+$, calcd. for $C_{25}H_{23}N_2O_2S$: 415.1480.

6-(3-Chlorophenyl)-10-(4-fluorophenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.5]dec-3-ene-1,8-dione (3m): white solid; yield: 85.7 mg (93%), 82:18 *dr*, 99% ee_{major}, 95% ee_{minor}. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak AD-H with hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL min^{-1}, λ = 254 nm]: major diastereoisomer t_{major} = 10.143 min, t_{minor} = 13.381 min; minor diastereoisomer t_{major} = 14.660 min, t_{minor} = 11.941 min; $[\alpha]_D^{25}$: +49.0 (*c* 0.35 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.48 (m, 2H), 7.34–7.32 (m, 2H), 7.20–7.10 (m, 6H), 7.03–6.99 (m, 3H), 3.95–3.79 (m, 2H), 3.63–3.59 (m, 1H), 3.33–3.29 (m, 1H), 2.98 (dd, *J* = 15.8, 10.6 Hz, 1H), 2.64 (d, *J* = 16.0 Hz, 1H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.7, 174.6, 160.3, 138.5, 137.0, 134.6, 134.2, 132.9, 130.2, 129.4, 129.32, 129.0, 128.6, 128.2, 126.1, 120.0, 116.3, 116.1, 61.9, 43.4, 42.2, 41.0, 40.7, 15.9; IR (KBr): ν_{max} = 1709, 1597, 1503, 1405, 1226, 838, 760, 692 cm^{-1}; ESI-MS (%): m/z = 461.1 $[M+H]^+$; HR-MS (ESI): m/z = 461.1411 $[M+H]^+$, calcd. for $C_{27}H_{23}ClFN_2O_2$: 461.1432.

6-(3-Chlorophenyl)-10-(3,5-dimethoxyphenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.5]dec-3-ene-1,8-dione (3n): white solid; yield: 96.6 mg (96%), 88:12 *dr*, 99% ee_{major}, 99%

ee_{minor}. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak AD-H with hexane/*i*-PrOH (90:10) as the eluent, flow: 0.6 mL min^{-1}, λ = 254 nm]: major diastereoisomer t_{major} = 25.662 min, t_{minor} = 36.593 min.; minor diastereoisomer t_{major} = 37.498 min, t_{minor} = 59.511 min; $[\alpha]_D^{25}$: +65.3 (*c* 0.50 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8.0 Hz, 2H), 7.35–7.31 (m, 2H), 7.18–7.14 (m, 4H), 7.05–7.04 (m, 1H), 6.36 (s, 1H), 6.23 (s, 2H), 3.89–3.77 (m, 2H), 3.64 (s, 6H), 3.61–3.57 (m, 1H), 3.26 (dd, *J* = 16.8, 4.4 Hz, 1H), 2.97 (dd, *J* = 16.4, 10.4 Hz, 1H), 2.61 (d, *J* = 15.2 Hz, 1H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.8, 174.9, 161.2, 160.6, 140.5, 138.6, 137.2, 136.0, 134.5, 130.1, 129.0, 128.6, 128.3, 126.1, 125.9, 119.8, 105.8, 99.8, 62.0, 55.5, 44.0, 42.4, 41.0, 40.5, 15.9; IR (KBr): ν_{max} = 1712, 1598, 1485, 1154, 1061, 842, 738, 697 cm^{-1}; ESI-MS (%): *m*/*z* = 503.2 $[M+H]^+$; HR-MS (ESI): *m*/*z* = 503.1716 $[M+H]^+$, calcd. for $C_{29}H_{28}ClN_2O_4$: 503.1738.

6-(3-Chlorophenyl)-10-(4-chlorophenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.5]dec-3-ene-1,8-dione (3o): white solid; yield: 90.6 mg (95%), 83:17 *dr*, 97% ee_{major}, 95% ee_{minor}. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak AD-H with hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL min^{-1}, λ = 254 nm]: major diastereoisomer t_{major} = 12.675 min, t_{minor} = 13.712 min; minor diastereoisomer t_{major} = 14.454 min, t_{minor} = 11.559 min; $[\alpha]_D^{25}$: +92.7 (*c* 0.36 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 8 Hz, 2H), 7.36–7.28 (m, 4H), 7.20–7.13 (m, 4H), 7.07–7.05 (m, 3H), 3.95–3.79 (m, 2H), 3.62–3.58 (m, 1H), 3.29 (dd, *J* = 16.4, 4.4 Hz, 1H), 2.98 (dd, *J* = 16.4, 10.4 Hz, 1H), 2.64 (dd, *J* = 16.4, 2.4 Hz, 1H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.5, 174.6, 160.1, 138.4, 137.0, 136.8, 134.6, 134.3, 130.2, 129.4, 129.0, 128.7, 128.2, 126.1, 126.1, 120.2, 120.0, 61.9, 43.4, 42.3, 40.9, 40.5, 16.0; IR (KBr): ν_{max}: 1710, 1597, 1494, 1406, 1094, 834, 759, 692 cm^{-1}; ESI-MS (%): *m*/*z* = 477.1 $[M+H]^+$; HR-MS (ESI): *m*/*z* = 477.1110 $[M+H]^+$, calcd. for $C_{27}H_{23}Cl_2N_2O_2$: 477.1137.

6-(3-Chlorophenyl)-4-methyl-2-phenyl-10-*m*-tolyl-2,3-diazaspiro[4.5]dec-3-ene-1,8-dione (3p): white solid; yield: 81.3 mg (89%), 86:14 *dr*, 94% ee_{major}, 99% ee_{minor}. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak AD-H with hexane/*i*-PrOH (95:5) as the eluent, flow: 0.6 mL min^{-1}, λ = 254 nm]: major diastereoisomer t_{major} = 36.687 min, t_{minor} = 52.714 min; minor diastereoisomer t_{major} = 35.199 min, t_{minor} = 62.777 min; $[\alpha]_D^{25}$: +41.2 (*c* 0.43 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.24–7.06 (m, 7H), 6.94–6.90 (m, 2H), 3.89–3.81 (m, 2H), 3.67–3.62 (m, 1H), 3.38 (dd, *J* = 16.6, 5.0 Hz, 1H), 2.96 (dd, *J* = 16.4, 9.2 Hz, 1H), 2.65 (d, *J* = 16.0 Hz, 1H), 2.29 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.4, 174.9, 160.6, 138.0, 137.1, 135.3, 133.4, 129.7, 129.4, 128.8, 127.6, 125.8, 119.9, 116.1, 115.9, 62.0, 43.5, 42.1, 41.4, 40.7, 21.0, 15.8; IR (KBr): ν_{max} = 1708, 1595, 1495, 1404, 1096, 763, 694 cm^{-1}; ESI-MS (%): *m*/*z* = 457.2 $[M+H]^+$; HR-MS (ESI): *m*/*z* = 457.1655 $[M+H]^+$, calcd. for $C_{28}H_{26}ClN_2O_2$: 457.1683.

6-(4-Fluorophenyl)-4-methyl-2-phenyl-10-*p*-tolyl-2,3-diazaspiro[4.5]dec-3-ene-1,8-dione (3q): white solid; yield: 73.2 mg (83%), 72:28 *dr*, 92% ee_{major}, 99% ee_{minor}. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak AD-H with hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL min^{-1}, λ = 254 nm]: major diastereoisomer t_{major} = 21.591 min, t_{minor} = 17.550 min; minor diastereoisomer t_{major} = 13.992 min; $[\alpha]_D^{25}$: +48.0 (*c* 0.45 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.48 (m, 2H), 7.36–7.32 (m, 2H), 7.18–7.10 (m, 4H), 7.05–6.99 (m, 5H), 3.94–3.83 (m, 2H), 3.62 (dd, *J* = 14.2, 2.6 Hz, 1H), 3.34 (dd, *J* = 16.4, 5.2 Hz, 1H), 2.97 (dd, *J* = 16.2, 9.8 Hz, 1H), 2.64 (dd, *J* = 16.4, 3.2 Hz, 1H), 2.21 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.4, 174.9, 160.6, 138.0, 137.1, 135.3, 133.4, 129.7, 129.4, 128.8, 127.6, 125.8, 119.9, 116.1, 115.9, 62.0, 43.5, 42.1, 41.4, 40.7, 21.0, 15.8; IR (KBr): ν_{max} = 1709, 1600, 1506, 1402, 1228, 833, 757, 690 cm^{-1}; ESI-MS (%): *m*/*z* = 441.2 $[M+H]^+$; HR-MS (ESI): *m*/*z* = 441.1969 $[M+H]^+$, calcd. for $C_{28}H_{26}FN_2O_2$: 441.1978.

6-(3,5-Dimethoxyphenyl)-4-methyl-2-phenyl-10-*p*-tolyl-2,3-diazaspiro[4.5]dec-3-ene-1,8-dione (3r): white solid; yield: 75.3 mg (78%), 80:20 *dr*, 98% ee_{major}, 96% ee_{minor}. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak AD-H with hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL min^{-1}, λ = 254 nm]: major diastereoisomer t_{major} = 8.982 min, t_{minor} = 10.782 min; minor diastereoisomer t_{major} = 13.634 min, t_{minor} = 18.818 min; $[\alpha]_D^{25}$: +57.3 (*c* 0.41 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 8 Hz, 2H), 7.34–7.30 (m, 2H), 7.19–7.13 (m, 2H), 7.05–7.00 (m, 3H), 6.36 (s, 1H), 6.25 (s, 1H), 6.25 (s, 1H), 3.88–3.80 (m, 2H), 3.64 (s, 6H), 3.56–3.50 (m, 1H), 3.27 (dd, *J* = 16.6, 4.6 Hz, 1H), 2.98 (dd, *J* = 16.4, 10.4 Hz, 1H), 2.62 (dd, *J* = 16.4, 2.4 Hz, 1H), 2.21 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.5, 175.1, 161.1, 140.7, 137.9, 137.3, 133.4, 129.3, 128.8, 128.0, 127.7, 125.6, 119.7, 109.9, 105.7, 99.6, 62.1, 55.3, 44.1, 42.3, 41.3, 40.5, 21.0, 15.8; IR (KBr): ν_{max} = 1710, 1600, 1496, 1205, 1152, 1057, 834., 758, 693 cm^{-1}; ESI-MS (%): *m*/*z* = 483.2 $[M+H]^+$; HR-MS (ESI): *m*/*z* = 483.2275 $[M+H]^+$, calcd. for $C_{30}H_{31}N_2O_4$: 483.2284.

6-(4-Chlorophenyl)-4-methyl-2-phenyl-10-*p*-tolyl-2,3-diazaspiro[4.5]dec-3-ene-1,8-dione (3s): white solid; yield: 80.4 mg (88%), 68:32 *dr*, 94% ee_{major}, 94% ee_{minor}. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak AD-H with hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL min^{-1}, λ = 254 nm]: major diastereoisomer t_{major} = 18.058 min, t_{minor} = 14.880 min; minor diastereoisomer t_{major} = 32.081 min, t_{minor} = 13.885 min; $[\alpha]_D^{25}$: +84.4 (*c* 0.44 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 7.9 Hz, 2H), 7.36–7.34 (m, 2H), 7.31–7.29 (m, 2H), 7.20–7.18 (m, 2H), 7.08–7.06 (m, 1H), 7.02 (m, 4H), 3.92–3.82 (m, 2H), 3.60 (d, *J* = 14.4 Hz, 1H), 3.31 (dd, *J* = 16.4, 4.8 Hz, 1H), 2.97 (dd, *J* = 16.6, 10.6 Hz, 1H), 2.64 (d, *J* = 16.4 Hz, 1H), 2.21 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.2, 174.8, 160.4, 138.0, 137.1, 135.4, 134.1, 133.2, 129.4, 129.2, 129.0, 128.8, 127.6, 125.8, 119.9, 62.0, 43.5, 42.2, 41.3, 40.5, 21.0, 15.9; IR (KBr): ν_{max}: 1708, 1598, 1498, 1404, 1103, 1014, 828, 755, 646 cm^{-1}; ESI-MS (%): *m*/*z* = 457.2 $[M+H]^+$; HR-MS (ESI): *m*/*z* = 457.1672 $[M+H]^+$, calcd. for $C_{28}H_{26}ClN_2O_2$: 457.1683.

4-Methyl-2-phenyl-6-*m*-tolyl-10-*p*-tolyl-2,3-diazaspiro-[4.5]dec-3-ene-1,8-dione (3t): white solid; yield: 73.4 mg (84%), 78:22 *dr*, 98% ee_{major}. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak IA with hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL min^{-1}, λ = 254 nm]: major diastereoisomer t_{major} = 12.616 min. t_{minor} = 13.611 min; $[\alpha]_D^{25}$: +45.0 (*c* 0.46 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.51 (m, 2H), 7.37–7.33 (m, 2H), 7.22–7.18 (m, 2H), 7.07–7.00 (m, 5H), 6.98–6.92 (m, 2H), 3.91–3.84 (m,

2H), 3.65 (dd, $J=14.4$, 2.8 Hz, 1H), 3.39 (dd, $J=16.4$, 5.2 Hz, 1H), 2.96 (dd, $J=16.4$, 9.2 Hz, 1H), 2.65 (d, $J=16.0$ Hz, 1H), 2.29 (s, 3H), 2.22 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=209.8$, 175.1, 161.0, 138.7, 138.6, 137.9, 137.3, 136.8, 133.7, 129.4, 128.9, 128.8, 128.6, 127.6, 125.7, 124.6, 120.0, 61.9, 44.4, 42.1, 41.6, 40.7, 21.5, 21.0, 15.8; IR (KBr): $\nu_{max}=1708$, 1599, 1499, 1401, 1118, 829, 757, 696 cm^{-1}; ESI-MS (%): $m/z=437.2$ $[M+H]^+$; HR-MS (ESI): $m/z=437.2207$ $[M+H]^+$, calcd. for $C_{29}H_{29}N_2O_2$: 437.2229.

6-(3-Chlorophenyl)-2,4,10-triphenyl-2,3-diazaspiro-[4.5]dec-3-ene-1,8-dione (3u): white solid; yield: 60.5 mg (60%), 11:43:46 *dr*, 99% *ee* on the 43% diastereoisomer, 99% *ee* on the 46% diastereoisomer. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak AD-H with hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL min^{-1}, $\lambda=254$ nm]: 43% diastereoisomer $t_{major}=14.021$ min; 46% diastereoisomer $t_{major}=18.374$ min; $[\alpha]_D^{25}$: +141.8 (*c* 0.29 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.46$–7.41 (m, 4H), 7.37–7.29 (m, 4H), 7.25–7.14 (m, 10H), 7.06–6.90 (m, 10H), 6.88–6.76 (m, 6H), 6.64–6.50 (m, 4H), 4.19–4.04 (m, 4H), 3.97–3.82 (m, 2H), 3.33–3.21 (m, 2H), 2.92 (dd, $J=17.6$, 3.6 Hz, 1H), 2.82 (dd, $J=17.2$, 3.2 Hz, 1H), 2.56–2.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=209.2$, 175.4, 159.0, 139.4, 137.2, 135.6, 134.4, 132.6, 130.6, 129.7, 129.0, 128.9, 128.5, 128.2, 127.8, 127.6, 127.2, 126.5, 126.3, 125.5, 120.2, 63.4, 43.3, 42.8, 41.1, 39.9; IR (KBr): $\nu_{max}=1717$, 1680, 1597, 1497, 1397, 1331, 1288, 1140, 764., 696, 674 cm^{-1}; ESI-MS (%): $m/z=505.2$ $[M+H]^+$; HR-MS (ESI): $m/z=505.1662$ $[M+H]^+$, calcd. for $C_{32}H_{26}ClN_2O_2$: 505.1677.

2-(4-Bromophenyl)-6-(3-chlorophenyl)-4-methyl-10-phenyl-2,3-diazaspiro[4.5]dec-3-ene-1,8-dione (3v): white solid; yield: 92.9 mg (90%), 74:26 *dr*, 99% ee_{major}, 99% ee_{minor}. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak AD-H with hexane/*i*-PrOH (85:15) as the eluent, flow: 1.0 mL min^{-1}, $\lambda=254$ nm]: major diastereoisomer $t_{major}=15.283$ min. $t_{minor}=19.106$ min; minor diastereoisomer $t_{major}=19.973$ min; $[\alpha]_D^{25}$: +23.9 (*c* 0.36 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.43$–7.34 (m, 5H), 7.17–7.09 (m, 7H), 6.99–6.97 (m, 1H), 3.88–3.73 (m, 2H), 3.62–3.59 (m, 1H), 3.33 (d, $J=14.8$ Hz, 1H), 2.97–2.91 (m, 1H), 2.60 (d, $J=15.6$ Hz, 1H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=208.7$, 174.7, 160.9, 140.4, 138.7, 138.4, 136.3, 135.1, 134.6, 132.0, 130.5, 130.2, 129.3, 128.8, 128.7, 128.5, 128.2, 127.8, 126.0, 121.0, 118.8, 62.0, 44.2, 42.3, 41.1, 40.7, 15.9; IR (KBr): $\nu_{max}=1721$, 1703, 1590, 1490, 1368, 1329, 1008, 826, 702, 656 cm^{-1}; ESI-MS (%): $m/z=523.1$ $[M+H]^+$; HR-MS (ESI): $m/z=523.0571$ $[M+H]^+$, calcd. for $C_{27}H_{23}Br^{81}ClN_2O_2$: 523.0611.

2,6-Bis(3-chlorophenyl)-4-methyl-10-phenyl-2,3-diaza-spiro[4.5]dec-3-ene-1,8-dione (3w): white solid; yield: 85.9 mg (90%), 70:30 *dr*, 98% ee_{major}, 99% ee_{minor}. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak AD-H with hexane/*i*-PrOH (85:15) as the eluent; flow: 1.0 mL min^{-1}, $\lambda=254$ nm]: major diastereoisomer $t_{major}=10.257$ min. $t_{minor}=11.998$ min; minor diastereoisomer $t_{major}=11.041$ min; $[\alpha]_D^{25}$: +34.0 (*c* 0.44 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.59$ (s, 1H), 7.52–7.49 (m, 1H), 7.28–7.20 (m, 4H), 7.10–7.08 (m, 6H), 6.99–6.97 (m, 1H), 3.89–3.74 (m, 2H), 3.63–3.59 (m, 1H), 3.35 (dd, $J=16.4$, 4.8 Hz, 1H), 2.93 (dd, $J=16.0$, 9.6 Hz, 1H), 2.61 (d, $J=14.4$ Hz, 1H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=208.6$, 174.8, 161.0, 140.4, 138.7, 138.4, 136.1, 134.7, 130.2, 130.1, 129.3, 128.9, 128.7, 128.5, 127.8, 126.0, 125.8, 119.5, 117.4, 62.0, 44.3, 42.4, 41.2, 40.7, 15.9; IR (KBr): $\nu_{max}=1721$, 1704, 1594, 1575, 1482, 1368, 1329, 1087, 872, 785, 702, 686 cm^{-1}; ESI-MS (%): $m/z=477.1$ $[M+H]^+$; HR-MS (ESI): $m/z=477.1121$ $[M+H]^+$, calcd. for $C_{27}H_{23}Cl_2N_2O_2$: 477.1131.

6-(3-Chlorophenyl)-4-methyl-10-phenyl-2-p-tolyl-2,3-diazaspiro[4.5]dec-3-ene-1,8-dione (3x): white solid; yield: 80.0 mg (88%), 84:16 *dr*, 99% ee_{major}, 99% ee_{minor}. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak AD-H with hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL min^{-1}, $\lambda=254$ nm]: major diastereoisomer $t_{major}=11.572$ min. $t_{minor}=15.736$ min; minor diastereoisomer $t_{major}=14.209$ min; $[\alpha]_D^{25}$: +41.4 (*c* 0.58 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.34$–7.24 (m, 4H), 7.20–7.02 (m, 9H), 3.88–3.79 (m, 2H), 3.61 (d, $J=12.0$ Hz, 1H), 3.36 (d, $J=13.6$ Hz, 1H), 2.96–2.94 (m, 1H), 2.60 (d, $J=14.8$ Hz, 1H), 2.30 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=209.0$, 174.6, 160.4, 138.9, 138.6, 135.8, 134.7, 134.6, 130.2, 129.6, 129.2, 128.6, 128.4, 128.3, 127.9, 126.1, 120.1, 61.6, 44.4, 42.3, 41.3, 40.7, 21.3, 15.9; IR (KBr): $\nu_{max}=1721$, 1700, 1596, 1573, 1514, 1369, 1330, 1087, 819, 788, 703 cm^{-1}; ESI-MS (%): $m/z=457.2$ $[M+H]^+$; HR-MS (ESI): $m/z=457.1678$ $[M+H]^+$, calcd. for $C_{28}H_{26}ClN_2O_2$: 457.1677.

6-(3-Chlorophenyl)-2-(4-methoxyphenyl)-4-methyl-10-phenyl-2,3-diazaspiro[4.5]dec-3-ene-1,8-dione (3y): white solid; yield: 85.6 mg (93%), 88:12 *dr*, 91% ee_{major}, 99% ee_{minor}. The *dr* and *ee* values were determined by HPLC [Daicel Chiralpak AD-H with hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL min^{-1}, $\lambda=254$ nm]: major diastereoisomer $t_{major}=18.874$ min. $t_{minor}=22.311$ min; minor diastereoisomer $t_{major}=24.189$ min; $[\alpha]_D^{25}$: +42.4 (*c* 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.33$–7.28 (m, 5H), 7.13–7.10 (m, 5H), 7.02–7.00 (m, 1H), 6.84 (d, $J=8.8$ Hz, 2H), 3.89–3.81 (m, 2H), 3.76 (s, 3H), 3.62–3.59 (m, 1H), 3.35 (dd, $J=16.4$, 4.8 Hz, 1H), 2.93 (dd, $J=16.2$, 9.4 Hz, 1H), 2.60 (d, $J=14.6$ Hz, 1H), 1.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=209.1$, 174.5, 160.4, 157.8, 138.9, 138.5, 134.6, 130.3, 130.1, 129.2, 128.6, 128.4, 128.2, 127.9, 126.2, 122.1, 114.2, 61.5, 55.7, 44.3, 42.2, 41.2, 40.7, 15.9; IR (KBr): $\nu_{max}=1721$, 1699, 1596, 1512, 1372, 1298, 1249, 1031, 832, 702, 657 cm^{-1}; ESI-MS (%): $m/z=473.2$ $[M+H]^+$; HR-MS (ESI): $m/z=473.1631$ $[M+H]^+$, calcd. for $C_{28}H_{26}ClN_2O_3$: 473.1626.

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[16] CCDC 875821 [for **8ka**, $C_{27}H_{23}BrN_2O_2$, unit cell parameters: $a=10.8551(13)$, $b=12.9370(16)$, $c=16.384(2)$, space group $P212121$] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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