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Organocatalytic enantioselective construction of multi-functionalized spiro oxindole dienes†

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A diastereo- and enantio-selective domino Michael-cyclization–tautomerization reaction of isatylidene malononitriles with α,α-dicyanoalkenes catalyzed by a cinchona alkaloid-derived bifunctional thiourea catalyst has been developed. A series of multi-functionalized spiro oxindole diene derivatives have been obtained in good to excellent yields (up to 97%) with good to excellent enantioselectivities (up to 96%) as well as good diastereoselectivities (up to 7.9 : 1). In addition, an anomalous temperature effect on the enantioselectivity has also been studied for this transformation.

Introduction

Spirocyclic oxindole scaffolds bearing a spirocyclic quaternary stereocenter at the C-3 position are privileged structural motifs, which are prevalent in numerous natural products and biologically active molecules.[1] Recently, a large number of chiral spirocyclic oxindoles have been reported as important molecular probes for studying biological activities toward different cellular processes.[2] As a result of their importance, various synthetic protocols catalyzed by either chiral transition-metal complexes or chiral organocatalysts have been developed to achieve optically active spirocyclic oxindole compounds.[3] Among these procedures, one-pot domino transformation is especially attractive, as it permits the stereoselective formation of several bonds catalyzed by a single catalyst in a single operation without the necessity to isolate the intermediates.[4] In 2009, Melchiorre and co-workers reported enantioselective synthesis of multistereogenic spiro oxindole hexanones *via* [4 + 2] domino double Michael additions.[5] Since then, more intriguing spirocyclic oxindole skeletons have been constructed by asymmetric organocatalytic domino reactions.[6] Our group has also synthesized a series of spirocyclic oxindoles through organocatalyzed domino [4 + 2] type[7] or [5 + 1] type[8] double Michael addition, Michael/reduction/cyclization[9] and Michael-aldol[10] additions. However, to the best of our knowledge, efficient catalytic stereoselective methods to access multifunctionalized spiro oxindoles with diene moieties remain less explored. Therefore, the development of efficient catalytic systems is in high demand.

Although prepared more than a century ago,[11] α,α-dicyanoalkenes were first applied as successful vinylogous donors in asymmetric synthetic chemistry in 2005.[12,13] Shortly afterwards, a series of highly enantioselective Michael addition reactions of α,α-dicyanoalkenes and α,β-unsaturated compounds were disclosed.[14] A non-asymmetric version of functionalized spirocyclic oxindoles by one-pot tandem reactions of alkylidene malononitriles with isatylidene malononitriles was reported by Perumal's group[15] in 2010. Based on these literature reports, we envisioned that α,α-dicyanoolefins could be used as a versatile building block for the construction of chiral spiro oxindole compounds. Herein, we present our study on an organocatalyzed asymmetric Michael-cyclization–tautomerization process between isatylidene malononitriles and α,α-dicyanoalkenes at relatively high temperature, which furnished a series of multi-functionalized spiro oxindole dienes in good to excellent yields with good diastereoselectivities as well as good to excellent enantioselectivities.

Results and discussion

In a preliminary study, the model reaction of isatylidene malononitrile **1a** and 2-cyclohexylidene malononitrile **2** catalyzed by different organic catalysts **3a–m** was carried out in toluene at room temperature, and the results are summarized in Table 1. When cinchona alkaloid derivatives **3a–3c** were employed as the catalysts, only 17–26% ees were observed (entries 1–3). Bifunctional thiourea catalysts **3d–3g** with different stereogenic structures were also investigated (entries 4–7), and the results

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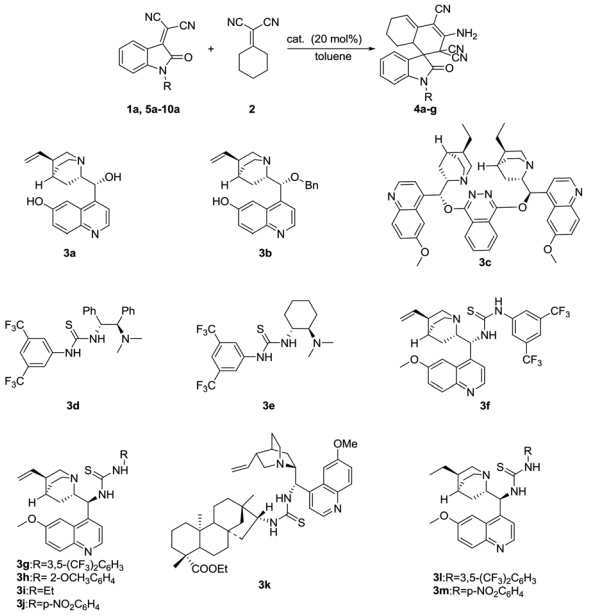
Table 1 Evaluation of model substrates and catalysts of the asymmetric cascade Michael-cyclization–tautomerization between **1a**, **5a–10a** and **2**[a]



Entry	Cat.	Substrate	Time (h)	Product	Yield[b] (%)	ee[c] (%)	dr[d]
1	**3a**	R = H/**1a**	1	**4a**	95	17	2.7 : 1
2	**3b**	R = H/**1a**	1.75	**4a**	93	17	4.0 : 1
3	**3c**	R = H/**1a**	1.75	**4a**	92	26	1.6 : 1
4	**3d**	R = H/**1a**	24	**4a**	94	−30	3.5 : 1
5	**3e**	R = H/**1a**	6	**4a**	95	9	4.9 : 1
6	**3f**	R = H/**1a**	4	**4a**	96	−24	3.6 : 1
7	**3g**	R = H/**1a**	4	**4a**	97	52	2.1 : 1
8	**3h**	R = H/**1a**	1.5	**4a**	94	22	4.0 : 1
9	**3i**	R = H/**1a**	0.5	**4a**	97	35	2.4 : 1
10	**3j**	R = H/**1a**	3	**4a**	94	54	1.9 : 1
11	**3k**	R = H/**1a**	12	**4a**	95	30	4.9 : 1
12	**3l**	R = H/**1a**	2	**4a**	97	70	1.2 : 1
13	**3m**	R = H/**1a**	2.5	**4a**	96	72	2.1 : 1
14	**3m**	R = Me/**5a**	2	**4b**	89	65	2.1 : 1
15	**3m**	R = Bn/**6a**	2	**4c**	95	62	2.1 : 1
16	**3m**	R = Allyl/**7a**	1.5	**4d**	89	63	2.1 : 1
17	**3m**	R = Bz/**8a**	2	**4e**	91	77	3.6 : 1
18	**3m**	R = MOM/**9a**	2.5	**4f**	98	76	2.4 : 1
19	**3m**	R = Ac/**10a**	3.5	**4g**	93	72	5.7 : 1

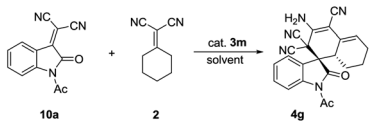
[a] Unless noted otherwise, reactions were carried out with **1a**, **5a–10a** (0.1 mmol), **2** (0.12 mmol), and **3** (20 mol%), in toluene (1.0 mL) at room temperature. [b] Isolated yield. [c,d] Determined by chiral HPLC, the ee of the major diastereomer.

revealed that quinine-based bifunctional thiourea catalyst **3g** performed better and the desired product **4a** was isolated in 97% yield with 2.1 : 1 dr and 52% ee (entry 7). Subsequently, more cinchona alkaloid based bifunctional catalysts **3h–3k** were tested in this reaction (entries 8–11), among which **3g** and **3j** proved to be the best performers in terms of enantioselectivities (entries 7, 10 *vs.* 8, 9, 11). This may be attributed to the increase in acidity of the thiourea due to the presence of electron-withdrawing 1,3-bis(trifluoromethyl)phenyl and *p*-nitrophenyl groups, respectively. Inspired by these findings, hydroquinine-derived thioureas **3l** and **3m** were synthesized and examined for this transformation. To our delight, the desired product **4a** was obtained in 97% and 96% yields with 1.2 : 1 and 2.1 : 1 drs, 70% and 72% ees, respectively (entries 12, 13 *vs.* 7, 10). In terms of both reactivity and stereoselectivity, **3m** proved to be the best catalyst (entries 12 *vs.* 13).

Having identified the optimal catalyst, we proceeded to study the influence of different N-protecting groups of the oxindole moiety (entries 14–19). When substrates **5a–10a** bearing different substituents such as –methyl, –benzyl, –allyl, –Bz, –MOM and –Ac groups were tested, the desired products **4e–4g** were furnished in excellent yields with slightly higher enantioselectivities and diastereoselectivities than those of **4b–4d** (entries 17–19 *vs.* entries 14–16). Generally, taking into account stereoselectivity, the reaction with the substrate **10a** bearing a –Ac protecting group was demonstrated to be a suitable model for further optimization of the reaction conditions.

With the optimal model substrate and catalyst in hand, other parameters were further optimized, including the reaction solvent, additive, concentration, temperature and catalyst loading. The results are summarized in Table 2. Although the reaction between **10a** and **2** proceeded smoothly in a wide range of solvents, the enantioselectivities were found to vary dramatically (entries 1–15). The desired product **4g** was furnished in 93% yield with 5.3 : 1 dr, 48% ee in acetonitrile (entry 4), whereas no desired product was detected in DMF and ethanol (entries 2 and 3). Thus relatively polar solvents are not favorable for this transformation. However, the reaction proceeded smoothly in less polar solvents, such as DCM, $CHCl_3$, THF, Et_2O, and MTBE, which produced the desired product **4g** in 49–93% yields with 4.6 : 1–10.1 : 1 drs and 32–70% ees (entries 5–9). Subsequently, aromatic hydrocarbon solvents were tested, such as ethylbenzene, xylene, *o*-xylene, *p*-xylene, *m*-xylene, and mesitylene (entries 10–15). Overall, *m*-xylene was found to be the optimal solvent, which gave rise to **4g** in 93% yield, 86% ee and 6.1 : 1 dr (entry 14). The examination of reactant concentration revealed that the reaction did not work better in either more concentrated or dilute mixtures in comparison with 0.1 M of substrate **10a** (entries 14, 16, 17). The enantioselectivity was slightly improved in anhydrous *m*-xylene without sacrificing the yield and stereoselectivity (entry 18, 96% yield, 90% ee, 5.7 : 1 dr). Encouraged by these results, additives were tested in this reaction, including 3 Å, 4 Å, 5 Å and 13× molecular sieves, which gave rise to better results including excellent yields (90–95%), good diastereoselective ratios (5.7 : 1 to 6.1 : 1) and excellent enantioselectivities (92–93%) (entries 19–22). Overall, the 3 Å molecular sieve was proved to be the optimal additive, as the desired product **4g** was obtained in 94% yield, 93% ee and 5.7 : 1 dr (entry 19). A study on the effect of reaction temperature (entries 23–29) revealed that when it was decreased to −5 °C, only a trace amount of **4g** was detected even after the reaction time was prolonged to 48 h (entry 23). Interestingly, **4g** was obtained in high yield (97%) with a slightly increased enantioselectivity (94% ee) at 50 °C within 0.7 h (entry 26 *vs.* entries 19, 24 and 25).

Table 2 Optimization of the reaction conditions for the asymmetric cascade Michael-cyclization–tautomerization between **10** and **2**[a]



Entry	Solvent	Additive	Temp. (°C)	Time (h)	Yield[b] (%)	ee[c] (%)	dr[d]
1	Toluene	—	25	3.5	93	72	5.7 : 1
2	DMF	—	25	4.0	<5	nd	nd
3	EtOH	—	25	0.5	<5	nd	nd
4	CH_3CN	—	25	5.0	93	48	5.3 : 1
5	DCM	—	25	5.0	76	32	10.1 : 1
6	$CHCl_3$	—	25	5.0	49	47	5.7 : 1
7	THF	—	25	3.5	91	69	5.3 : 1
8	Et_2O	—	25	3.0	95	69	4.6 : 1
9	MTBE	—	25	3.5	92	70	4.6 : 1
10	Ethylbenzene	—	25	20	87	27	7.3 : 1
11	Xylene	—	25	3.0	91	80	6.7 : 1
12	*o*-Xylene	—	25	3.0	92	71	6.1 : 1
13	*p*-Xylene	—	25	3.0	95	78	6.7 : 1
14	*m*-Xylene	—	25	3.0	93	86	6.1 : 1
15	Mesitylene	—	25	20	94	67	5.7 : 1
16[e]	*m*-Xylene	—	25	12	87	76	5.7 : 1
17[f]	*m*-Xylene	—	25	2.0	92	77	5.3 : 1
18[g]	*m*-Xylene	—	25	3.0	96	90	5.7 : 1
19[g]	*m*-Xylene	3 Å	25	2.0	94	93	5.7 : 1
20[g]	*m*-Xylene	4 Å	25	2.0	90	93	5.7 : 1
21[g]	*m*-Xylene	5 Å	25	5.0	95	92	5.7 : 1
22[g]	*m*-Xylene	13X	25	5.0	93	92	6.1 : 1
23[g]	*m*-Xylene	3 Å	−5	48	<10	nd	nd
24[g]	*m*-Xylene	3 Å	10	22	87	87	6.7 : 1
25[g]	*m*-Xylene	3 Å	40	1.3	95	93	5.7 : 1
26[g]	*m*-Xylene	3 Å	50	0.7	97	94	5.7 : 1
27[g]	*m*-Xylene	3 Å	60	0.7	96	92	5.3 : 1
28[g]	*m*-Xylene	3 Å	80	0.5	95	90	4.9 : 1
29[g]	*m*-Xylene	3 Å	100	1.0	88	75	4 : 1
30[g,h]	*m*-Xylene	3 Å	50	1.5	97	94	6.7 : 1
31[g,i]	*m*-Xylene	3 Å	50	3.5	95	90	5.7 : 1

[a] Unless noted otherwise, reactions were carried out with **10a** (0.1 mmol), **2** (0.12 mmol), and **3m** (20 mol%), in the corresponding solvent (1.0 mL) at room temperature. [b] Isolated yield. [c,d] Determined by chiral HPLC, the ee of the major diastereomer. [e] [**10a**] = 0.05 M. [f] [**10a**] = 0.2 M. [g] Anhydrous solvent was used. [h] 10 mol% **3m** was used. [i] 5 mol% **3m** was used.

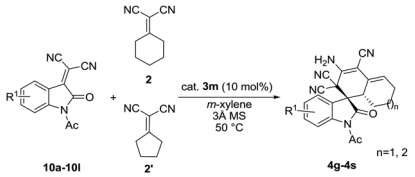
When the temperature was further elevated, the ee and dr values slightly dropped (entries 27–29). Thus, 50 °C was selected as the optimal reaction temperature.

Finally, the feasibility to reduce the catalyst loading was also studied (entries 30 and 31). When the reaction was conducted in the presence of 10 mol% **3m**, **4g** was isolated in 97% yield, 94% ee and 6.7 : 1 dr after the reaction time was prolonged to 1.5 h. In addition, when the catalyst loading was further decreased to 5 mol%, the reaction evidently became sluggish and the values of enantio- and diastereo-selectivities also somewhat dropped (entry 31). Thus, the optimal reaction conditions for the Michael-cyclization–tautomerization reaction between **10** and **2** were finally established as the reaction being performed at 50 °C, with a substrate concentration of 0.1 M in the presence of 10 mol% catalyst **3m** and 3 Å molecular sieves as additives.

Having established the optimal reaction conditions, we further explored the substrate scope of the **3m** catalyzed cascade Michael-cyclization–tautomerization sequence between isatylidene malononitriles **10a–10l** and 2-cyclohexylidene malononitrile **2**, and the results are summarized in Table 3. The cascade approach was applicable to isatylidene malononitriles bearing various substituents, and the desired products were isolated in moderate to excellent yields (53–97%), moderate to good diastereoselectivities (3.2 : 1 to 7.9 : 1) and good to excellent enantioselectivities (80–96%) (entries 1–12). The steric hindrance and electronic properties of the substituents on the phenyl rings of the oxindole backbones seemed to have somewhat influenced the reactivities and diastereoselectivities of the reactions. Notably, substrates **10b** and **10c** with substituents (–Cl or –Br) at the 4-position of oxindole backbones led to the isolation of the desired products **4h** and **4i** in distinctively different yields (92 and 53%) with excellent enantioselectivities (93 and 86%) and moderate diastereoselectivities (3.2 : 1 and 4.2 : 1), respectively (entries 2 and 3). In comparison, all reactions involving substrates **10d–10l** bearing substituents (–F, –Cl, –Br, $–NO_2$, –Me, –OMe) at 5- or 6-positions of oxindole backbones completed in less than 2 h, which furnished the desired products **4j–4r** in 66–95% yields with 5.7 : 1 to 7.9 : 1 drs and 91–96% ees (entries 4–12). For the substrate **10g** bearing a strong electron-withdrawing $–NO_2$ group, the corresponding reaction gave the desired product **4m** in good dr (6.4 : 1) and excellent ee (94%), although the yield dropped to 66% (entries 7 *vs.* 4–6 and 8–12). Furthermore, 2-cyclopentylidene malononitrile **2′** was also tested for this transformation, and the reaction proceeded very fast (within 0.3 h) and produced the expected product **4s** in 70% ee and 1.9 : 1 dr (entry 13). A better result of 75% ee and 2 : 1 dr was obtained when catalyzed by **3l** (entry 14). This finding suggests that the substrate **2** bearing a six-membered ring is more favorable for this transformation (entry 1 *vs.* entries 13 and 14).

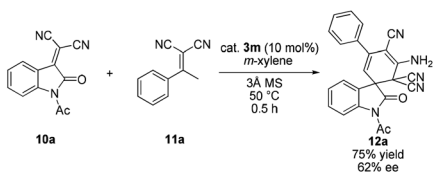
In order to further explore the substrate scope, the cascade reaction between **10a** and 2-(1-phenylethylidene)malononitrile **11a** was investigated under otherwise identical reaction conditions, and the desired product **12a** was isolated in 75% yield

Table 3 Substrate scope for the reaction of the asymmetric cascade Michael-cyclization–tautomerization[a]



Entry	Substrate	Time (h)	Product	Yield[b] (%)	ee[c] (%)	dr[d]
1	R^1 = H/**10a**	1.5	**4g**	97	94	6.7 : 1
2	R^1 = 4-Cl/**10b**	1.2	**4h**	92	93	3.2 : 1
3	R^1 = 4-Br/**10c**	1.3	**4i**	53	86	4.2 : 1
4	R^1 = 5-F/**10d**	1	**4j**	92	96	6.7 : 1
5	R^1 = 5-Cl/**10e**	1.5	**4k**	94	91	5.7 : 1
6	R^1 = 5-Br/**10f**	1.5	**4l**	93	94	6.1 : 1
7	R^1 = 5-NO_2/**10g**	1.5	**4m**	66	94	6.4 : 1
8	R^1 = 5-CH_3/**10h**	1.5	**4n**	92	91	6.1 : 1
9	R^1 = 5-OCH_3/**10i**	1.5	**4o**	96	94	7.1 : 1
10	R^1 = 6-Cl/**10j**	1.5	**4p**	94	92	7.2 : 1
11	R^1 = 6-Br/**10k**	1.5	**4q**	95	91	6.2 : 1
12	R^1 = 5,6-F_2/**10l**	1.2	**4r**	91	80	7.9 : 1
13[e]	R^1 = H/**10a**	0.3	**4s**	88	70	1.9 : 1
14[e,f]	R^1 = H/**10a**	0.3	**4s**	93	75	2.0 : 1

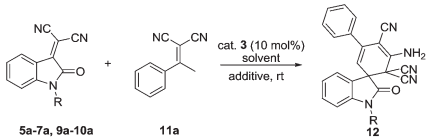
[a] Reactions were performed with **10** (0.2 mmol), **2** (0.24 mmol), 40 mg 3 Å MS and 10 mol% catalyst **3m** in 2.0 mL *m*-xylene at 50 °C. [b] Isolated yield. [c] Determined by HPLC analysis, the ee of the major diastereomer. [d] Determined by ^{1}H NMR of crude products. [e] **2′** was used as a reactant. [f] Catalyst **3l** was used as a catalyst.



Scheme 1 The asymmetric cascade Michael-cyclization–tautomerization between **10a** and **11a**.

with 62% ee (Scheme 1). Apparently, the above established reaction conditions were not suitable for this transformation. In order to improve both reactivity and enantioselectivity, the reaction parameters were then further optimized, including various N-protecting groups of substrates, catalysts, solvents and additives, and the results are summarized in Table 4. When substrates **10a** and **5a–7a**, **9a** bearing different N-protecting groups such as –Ac, –Me, –Bn, –allyl, and –MOM reacted with **11a** in the presence of catalyst **3m** in toluene, the corresponding products **12a–12e** were obtained in excellent yields (93–98%) with low to moderate enantioselectivities (13–69% ee, entries 1–5). Based on these results, the *N*-methyl group turned out to be the optimal protecting group of the substrate **5a**, and the reaction furnished the desired product **12b** in 93% yield with 69% ee after 3 h of reaction (entry 2). After the screening of different catalysts (entries 6–8), solvents (entries 9–13), and additives (entries 14 and 15), the best result (91% yield, 70% ee) was obtained in the presence of 10 mol% cata-

Table 4 Optimization of reaction conditions for the asymmetric cascade Michael-cyclization–tautomerization between **5a–7a**, **9a–10a** and **11a**[a]



Entry	Substrate	Cat.	Solvent	Product	Time (h)	Yield[b] (%)	ee[c] (%)
1	R = Ac/**10a**	**3m**	Toluene	**12a**	3	93	47
2	R = Me/**5a**	**3m**	Toluene	**12b**	0.7	93	69
3	R = Bn/**6a**	**3m**	Toluene	**12c**	1.2	95	46
4	R = Allyl/**7a**	**3m**	Toluene	**12d**	1.2	96	44
5	R = MOM/**9a**	**3m**	Toluene	**12e**	1	98	13
6	R = Me/**5a**	**3f**	Toluene	**12b**	4	89	−22
7	R = Me/**5a**	**3g**	Toluene	**12b**	1.3	92	37
8	R = Me/**5a**	**3l**	Toluene	**12b**	0.7	91	63
9	R = Me/**5a**	**3m**	Xylene	**12b**	1.2	95	67
10	R = Me/**5a**	**3m**	*o*-Xylene	**12b**	1.2	92	48
11	R = Me/**5a**	**3m**	*p*-Xylene	**12b**	2	94	24
12	R = Me/**5a**	**3m**	*m*-Xylene	**12b**	1.2	91	63
13	R = Me/**5a**	**3m**	Mesitylene	**12b**	1.2	89	66
14[d]	R = Me/**5a**	**3m**	Toluene	**12b**	0.5	94	63
15[e]	R = Me/**5a**	**3m**	Toluene	**12b**	0.5	91	70

[a] Unless noted otherwise, reactions were carried out with **5a–7a**, **9a–10a** (0.1 mmol), **11a** (0.12 mmol), cat. **3** (10 mol%), and in the corresponding solvent (1.0 mL) at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC. [d] 20 mg 3 Å MS was used as an additive. [e] 20 mg 4 Å MS was used as an additive.

lyst **3m** with 20 mg of 4 Å MS after 0.5 h of reaction at room temperature in toluene (Table 1, entry 15).

Intriguingly, it was found that the reaction temperature largely influenced the enantioselectivity of this transformation (Fig. 1). When the reaction was performed at −20 and −40 °C, respectively, the product was obtained in racemic form. However, when the temperature was elevated from 0 °C to 100 °C, the ee values increased from 34% to 95% (Fig. 1). It is generally accepted that lowered temperature will be preferred for achieving higher enantioselectivity, whereas elevated temperature will significantly reduce the enantioselectivity for organocatalysis.[16] Only recently, some publications have reported such an abnormal phenomenon in the field of organocatalysis.[17] However, to the best of our knowledge, no study has reported that the desired product was obtained in racemic form at relatively low temperature, whereas higher enantioselectivity can be obtained at higher temperature. In this instance, we also observed that when the reaction temperature was further elevated to over 70 °C, the enantioselectivity of the desired product was still moved up, albeit the yield dramatically decreased, which may be due to the decomposition of the product at relatively high temperature.[18] In terms of both the isolated yield and the enantioselectivity of the desired product, 70 °C was selected as the appropriate reaction temperature for this transformation. The product **12b** was obtained in 87% yield with 89% ee under the optimal reaction conditions.

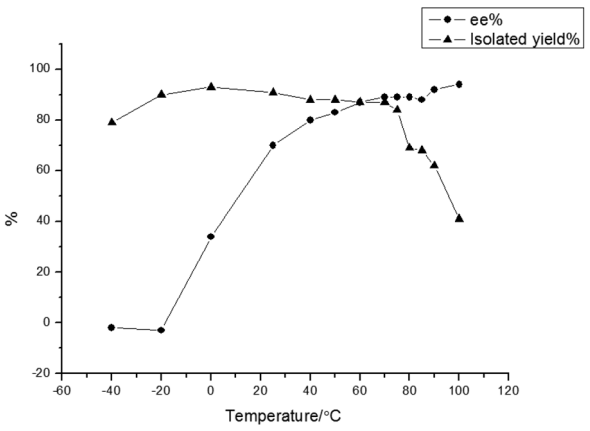
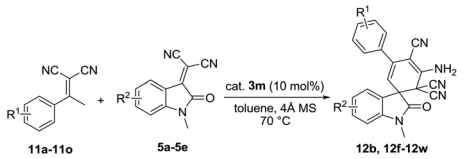


Fig. 1 The influence of temperature on the domino reaction of **5a** and **11a**. Unless noted otherwise, reactions were carried out with **5a** (0.1 mmol), **11a** (0.12 mmol), cat. **3m** (10 mol%), 20 mg 4 Å MS and in toluene (1.0 mL) for 0.5 h. −40 °C for 24 h; −20 °C for 10 h; 0 °C for 2 h.

The substrate scope was further explored for the enantioselective domino Michael-cyclization–tautomerization reaction between **5** and **11**. As shown in Table 5, for substrates **11** bearing either electron-donating or electron-withdrawing groups at *o*-, *m*-, or *p*-positions of the phenyl ring, the corresponding products **12f–12s** were obtained in 57–93% yields with 79–95% ees (entries 2–15). Both the electronic and steric properties of the substituents on phenyl rings of substrates **11** influence the catalytic outcomes of this transformation. For substrates **11b–11e** bearing halogen substituents (–F, –Cl, –Br or –I) at the 4-positions of the phenyl rings, the enantioselectivities of the desired products **12f–12i** decreased from 95% to 81% following the sequence –F, –Cl, –Br and –I, while their yields decreased from 91% to 72% (entries 2–5). When the –F substituent was installed at *p*-, *m*-, and *o*-positions of the phenyl rings, respectively, the ee values of the corresponding products dropped from 95% to 83% (entries 2 *vs.* 8

Table 5 Substrate scope in the reaction of the asymmetric cascade Michael-cyclization–tautomerization between **5** and **11**[a]

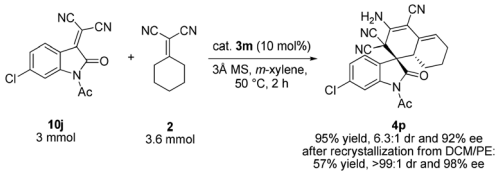


Entry	Substrate **11**	Substrate **5**	Product	Yield[b] (%)	ee[c] (%)
1	R^1 = H/**11a**	R^2 = H/**5a**	**12b**	87	89
2	R^1 = 4-F/**11b**	R^2 = H/**5a**	**12f**	91	95
3	R^1 = 4-Cl/**11c**	R^2 = H/**5a**	**12g**	81	85
4	R^1 = 4-Br/**11d**	R^2 = H/**5a**	**12h**	79	82
5	R^1 = 4-I/**11e**	R^2 = H/**5a**	**12i**	72	81
6	R^1 = 4-NO_2/**11f**	R^2 = H/**5a**	**12j**	93	84
7	R^1 = 4-CF_3/**11g**	R^2 = H/**5a**	**12k**	87	80
8	R^1 = 3-F/**11h**	R^2 = H/**5a**	**12l**	93	89
9	R^1 = 3-Cl/**11i**	R^2 = H/**5a**	**12m**	73	86
10	R^1 = 2-F/**11j**	R^2 = H/**5a**	**12n**	92	83
11	R^1 = 3,4-F_2/**11k**	R^2 = H/**5a**	**12o**	92	95
12	R^1 = 4-CH_3/**11l**	R^2 = H/**5a**	**12p**	72	83
13	R^1 = 4-OCH_3/**11m**	R^2 = H/**5a**	**12q**	74	88
14	R^1 = 4-Ph/**11n**	R^2 = H/**5a**	**12r**	61	79
15	R^1 = 2-furan/**11o**	R^2 = H/**5a**	**12s**	57	93
16	R^1 = 4-F/**11b**	R^2 = 5-F/**5b**	**12t**	90	92
17	R^1 = 4-F/**11b**	R^2 = 5-OCH_3/**5c**	**12u**	72	74
18	R^1 = 4-F/**11b**	R^2 = 6-Cl/**5d**	**12v**	76	78
19	R^1 = 4-F/**11b**	R^2 = 7-F/**5e**	**12w**	72	76

[a] Reactions were performed with **11** (0.2 mmol), **5** (0.24 mmol), 40 mg 4 Å MS and 10 mol% catalyst **3m** in 2.0 mL toluene at 70 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

vs. 10). Notably, the reactions with substrates bearing strong electron-withdrawing groups (–F, $–NO_2$ and $–CF_3$) proceeded smoothly within 0.5 h and furnished desired products in more than 90% yields with good to excellent enantioselectivities (80–95% ees, entries 2, 6–11). In contrast, reactions of substrates **11l–11n** bearing –Me, –OMe and –Ph groups afforded the desired products **12p–12r** in lower yields of 61–74% yields with decreased ees of 79–88% (entries 12–14). In addition, heteroatoms are tolerated in this catalytic system, as **11o** bearing a furyl group was transformed to the corresponding product **12s** in 57% yield with 93% ee (entry 15). Isatylidene malononitriles **5b–5e** were also investigated for this transformation under otherwise identical reaction conditions, which afforded the desired products **12t–12w** in 72–90% yields with 74–92% ee (entries 16–19). The catalytic outcomes implied that the substituents on the oxindole backbones played important roles in predominating the reactivity and enantioselectivity.

A gram-scale synthesis of **4p** was performed in the presence of 10 mol% of catalyst **3m**, and led to 1.19 g of the desired product in 95% yield with 6.3 : 1 dr and 92% ee (Scheme 2). After recrystallization from dichloromethane and petroleum ether, optically active **4p** (98% ee, >99 : 1 dr) was obtained, 0.72 g in 57% yield. Single crystals of **4p** were obtained from dichloromethane and isopropanol, and the configuration of the two contiguous stereo centers was unambiguously determined by X-ray diffraction analysis (Fig. 2).[19]



Scheme 2 Gram-scale asymmetric synthesis of **4p**.

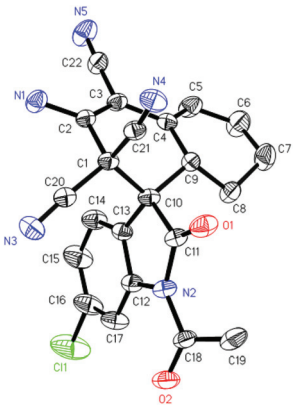
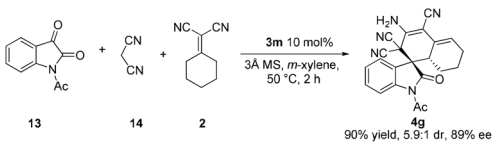


Fig. 2 X-ray crystal structure of the chiral compound **4p**.



Scheme 3 A one-pot, three-component reaction for synthesis of **4g**.

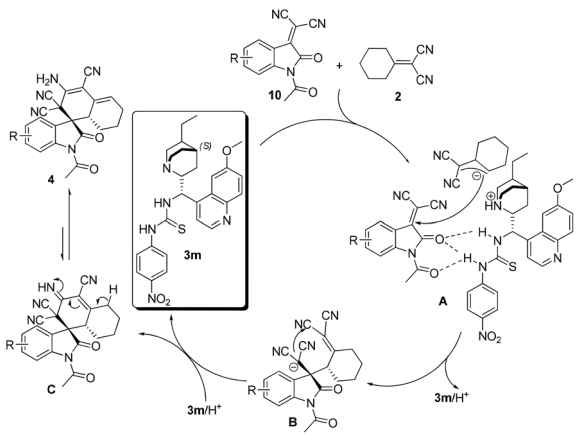


Fig. 3 Proposed reaction mechanism.

A one-pot, three-component approach involving isatin derivative **13**, malononitrile **14**, and **2** was investigated, which proceeded smoothly under optimal reaction conditions, and produced the desired product **4g** in 90% yield with 5.9 : 1 dr and 89% ee (Scheme 3).

A plausible mechanism is proposed as shown in Fig. 3. The deprotonation of 2-cyclohexylidene malononitrile **2** by bifunc-

tional organocatalyst **3m** generates the nucleophilic anion, which may form an ion pair with protonated **3m**. At the same time, isatylidene malononitriles **10** would be concertedly activated by mono- or bis-hydrogen bonding(s) between the thiourea moieties and carbonyl groups of oxindole backbones. Michael addition, subsequently, takes place from the *Re*-face attack of **10**. The resulting intermediate **B** undergoes an intramolecular nucleophilic addition on the –CN group to form an imine **C**, which upon isomerization generates the corresponding spirocyclic oxindole dienes **4** in a one-pot fashion.

Conclusions

In summary, we have developed an asymmetric domino Michael-cyclization–tautomerization reaction between isatylidene malononitriles with α,α-dicyanoalkenes catalyzed by a cinchona alkaloid-derived bifunctional thiourea at a relatively high reaction temperature. A series of multi-functionalized spiro oxindole dienes were synthesized in good to excellent yields (up to 97%) with good diastereoselectivities (up to 7.9 : 1) and good to excellent enantioselectivities (up to 96%). In addition, the temperature effect on the reaction outcomes has also been investigated, which revealed that the desired product was obtained in racemic form at relatively low temperature, whereas high enantioselectivity was observed at relatively high temperature. Further interpretation of the temperature effect, expansion of the reaction system, as well as biological evaluations of the resulting spiro compounds are ongoing in our laboratory.

Experimental section

General information

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. Toluene and *m*-xylene were freshly distilled from sodium. Column chromatography purifications were performed using 300–400 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova-400 spectrometer. The solvent for NMR is $CDCl_3$ or DMSO-d_6, unless otherwise noted. Chemical shifts are reported in delta (δ) units in parts per million (ppm) relative to the singlet (0 ppm) for tetramethylsilane (TMS). Data are reported as follows: chemical shift, multiplicity (s = single, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on 100 MHz or 75 MHz. Chemical shifts are reported in parts per million relative to the central line of the multiplet at 77.0 ppm for $CDCl_3$, 39.5 ppm for DMSO. Mass spectra were carried out using an Agilent 6120 Quadrupole LC/MS system with an ESI resource. High-resolution mass spectra (HRMS) for all the compounds were determined on a Micromass GCT-TOF mass spectrometer with an ESI resource. High performance liquid chromatography (HPLC) was performed on an Agilent 1200 Series chromatograph using a chiral column with 2-propanol–hexane as the eluent. Infrared spectra were obtained on a Varian-1000 FT-IR spectrometer. Optical rotations were measured at 589 nm (Na D line) on an Autopol IV automatic polarimeter. X-ray data were recorded on a Rigaku Mercury CCD/AFC diffractometer. Optical rotations are reported as follows: $[\alpha]_D^{rt}$ (*c* in g per 100 mL, solvent).

General procedure for the preparation of 4g–4s. 20 mg of activated 3 Å molecular sieve powders (3 Å MS) was added to a solution of **10** (0.2 mmol), **2** or **2′** (0.24 mmol), and organocatalyst **3m** (10 mol%) in anhydrous *m*-xylene (2 mL). The reaction mixture was stirred at 50 °C for a suitable reaction time until complete consumption of **10** (monitored by TLC). The solvent was evaporated, and the residue was purified by flash column silica gel chromatography (DCM–EA = 20/1–10/1) to provide the corresponding products **4g–4s**. Yields and spectral and analytical data for compounds **4g–4s** are as follows:

1-Acetyl-3′-amino-2-oxo-6′,7′-dihydro-2′*H*-spiro[indoline-3,1′-naphthalene]-2′,2′,4′(8′*H*,8a′*H*)-tricarbonitrile (4g): white solid, 97% yield, 6.7 : 1 dr, 94.0% ee; the enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (90 : 10) as the eluent. Flow: 1.0 mL min^{-1}; λ = 254 nm: t_{major} = 15.196 min; t_{minor} = 13.407 min (major). t_{major} = 14.213 min; t_{minor} = 18.1517 min (minor). $[\alpha]_D^{25}$: +26.0 (*c* 0.50 in CH_3COCH_3). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.24 (d, *J* = 8.1 Hz, 1H), 7.67 (s, 2H), 7.55 (t, *J* = 8.1 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 9.3 Hz, 1H), 5.98 (s, 1H, major), 5.86 (s, 1H, minor), 3.05 (d, *J* = 9.3 Hz, 1H), 2.70 (s, 3H, major), 2.55 (s, 3H, minor), 2.19–2.13 (m, 1H), 1.98–1.87 (m, 1H), 1.68–1.61 (m, 2H), 1.51–1.47 (m, 1H), 0.44 (q, *J* = 11.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.37, 170.15, 141.65, 140.58, 131.30, 126.38, 124.74, 124.56, 121.33, 116.21, 115.37, 110.39, 109.83, 81.67, 55.27, 42.44, 38.06, 26.72, 24.51, 23.44, 20.09; IR (film) ν_{max}: 3551.2, 3410.0, 3337.3, 3225.1, 2940.6, 2215.5, 1753.8, 1732.2, 1655.9, 1639.8, 1600.9, 1465.8, 1370.5, 1336.1, 1269.9, 1180.4, 1018.0, 881.7, 754.2, 594.6 cm^{-1}; ESI-MS: $[M + Na]^+$ *m*/*z* = 406.1; HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{17}N_5NaO_2$: 406.1274; found: 406.1265.

1-Acetyl-3′-amino-4-chloro-2-oxo-6′,7′-dihydro-2′*H*-spiro[indoline-3,1′-naphthalene]-2′,2′,4′(8′*H*,8a′*H*)-tricarbonitrile (4h): white solid, 93% yield, 3.2 : 1 dr, 93.0% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak IA with hexane–i-PrOH (90 : 10) as the eluent. Flow: 1.0 mL min^{-1}; λ = 254 nm: t_{major} = 13.080 min; t_{minor} = 10.221 min (major). t_{major} = 14.324 min; t_{minor} = 16.994 min (minor). $[\alpha]_D^{25}$: +190.8 (*c* 0.50 in CH_3COCH_3). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.28 (d, *J* = 8.4 Hz, 1H, minor), 8.23 (d, *J* = 8.4 Hz, 1H, major), 7.63 (t, *J* = 8.1 Hz, 1H), 7.51 (s, 1H), 7.46 (s, 2H), 5.86 (s, 1H), 3.86 (d, *J* = 10.2 Hz, 1H), 2.70 (s, 3H, minor), 2.55 (s, 3H, major), 2.24–2.16 (m, 1H), 2.11–2.01 (m, 1H), 1.76–1.73 (m, 1H) 1.51–1.40 (m, 2H), 1.02 (q, *J* = 12.0 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.27, 169.12, 142.22, 139.10, 132.51, 130.69, 127.74, 124.98, 121.64, 118.40, 115.20, 114.68, 110.70, 109.96, 82.29, 57.47, 41.90, 33.37, 26.08, 24.25, 23.91, 20.53; IR (film) ν_{max}: 3555.9, 3471.8, 3414.9, 3230.5, 2953.3, 2217.5, 1767.6, 1721.3, 1638.5, 1615.9, 1439.5, 1369.7, 1271.8, 1255.6, 1168.5, 1177.5, 1033.4, 790.5, 619.6, 598.3 cm^{-1}; ESI-MS:

$[M + Na]^+$ m/z = 440.1; HRMS: m/z $[M + Na]^+$ calcd for $C_{22}H_{16}ClN_5NaO_2$: 440.0885; found: 440.0866.

1-Acetyl-3′-amino-4-bromo-2-oxo-6′,7′-dihydro-2′*H*-spiro-[indoline-3,1′-naphthalene]-2′,2′,4′(8′*H*,8a′*H*)-tricarbonitrile (4i): white solid, 53% yield, 4.2 : 1 dr, 86% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak IA with hexane–i-PrOH (90 : 10) as the eluent. Flow: 1.0 mL min^{-1}; λ = 254 nm: t_{major} = 14.314 min; t_{minor} = 11.090 min (major). t_{major} = 15.972 min; t_{minor} = 17.647 min (minor). $[\alpha]_D^{25}$: +170.2 (c 0.50 in CH_3COCH_3). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.32 (m, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.42 (s, 2H), 5.82 (s, 1H), 3.98–3.94 (m, 1H), 2.67 (s, 3H, minor), 2.49 (s, 3H, major), 2.23–1.91 (m, 2H), 1.77–1.40 (m, 3H), 0.98 (q, J = 12.3 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.29, 169.23, 142.60, 139.10, 132.53, 131.47, 124.91, 121.53, 119.77, 119.07, 115.18, 115.12, 110.80, 109.99, 82.28, 57.35, 41.97, 33.17, 26.15, 24.26, 23.93, 20.58; IR (film) ν_{max}: 3559.9, 3461.3, 3417.9, 3210.5, 2207.5, 1777.6, 1731.6, 1639.7, 1625.1, 1432.5, 1359.2, 1261.8, 1245.4, 1162.3, 1174.9, 1032.4, 779.5, 612.6 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 484.0; HRMS: m/z $[M + Na]^+$ calcd for $C_{22}H_{16}BrN_5NaO_2$: 484.0380; found: 484.0375.

1-Acetyl-3′-amino-5-fluoro-2-oxo-6′,7′-dihydro-2′*H*-spiro-[indoline-3,1′-naphthalene]-2′,2′,4′(8′*H*,8a′*H*)-tricarbonitrile (4j): white solid, 92% yield, 6.7 : 1 dr, 96.0% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralcel OD-H with hexane–i-PrOH (90 : 10) as the eluent. Flow: 1.0 mL min^{-1}; λ = 254 nm: t_{major} = 18.765 min; t_{minor} = 9.889 min (major). t_{major} = 13.112 min; t_{minor} = 10.731 min (minor). $[\alpha]_D^{25}$: +29.2 (c 0.50 in CH_3COCH_3). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.29 (q, J = 5.2 Hz, 1H), 7.73 (s, 2H), 7.48–7.42 (m, 1H), 6.74 (dd, J = 8.4, 2.4 Hz, 1H), 6.01 (s, 1H, major), 5.86 (s, 1H, minor), 3.06 (d, J = 4.2 Hz, 1H), 2.70 (s, 3H, major), 2.55 (s, 3H, minor), 2.20–2.13 (m, 1H), 1.99–1.92 (m, 1H), 1.70–1.62 (m, 2H), 1.57–1.48 (m, 1H), 0.46 (q, J = 12.0 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.26, 169.40, 158.81 (d, $^1J_{C,F}$ = 242 Hz), 140.81, 136.51, 124.80, 123.60, 122.56 (d, $^3J_{C,F}$ = 8 Hz), 117.64, 117.43 (d, $^2J_{C,F}$ = 12 Hz), 114.61, 111.25 (d, $^2J_{C,F}$ = 26 Hz), 109.47, 109.08, 80.93, 54.61, 41.63, 37.37, 26.03, 23.89, 22.79, 19.44; IR (film) ν_{max}: 3424.7, 3349.5, 3226.7, 2939.5, 2216.2, 1760.7, 1722.3, 1642.3, 1479.0, 1372.6, 1291.1, 1256.3, 1174.3, 1021.3, 837.9, 587.3 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 424.1; HRMS: m/z $[M + H]^+$ calcd for $C_{22}H_{17}FN_5O_2$: 402.1366; found: 402.1358.

1-Acetyl-3′-amino-5-chloro-2-oxo-6′,7′-dihydro-2′*H*-spiro-[indoline-3,1′-naphthalene]-2′,2′,4′(8′*H*,8a′*H*)-tricarbonitrile (4k): white solid, 94% yield, 5.7 : 1 dr, 91% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (90 : 10) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 11.493 min; t_{minor} = 13.122 min (major). t_{major} = 12.114 min; t_{minor} = 10.608 min (minor). $[\alpha]_D^{25}$: −4.8 (c 0.50 in CH_3COCH_3). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.29 (d, J = 8.7 Hz, 1H), 7.76 (s, 2H), 7.68 (d, J = 8.4 Hz, 1H), 6.91 (s, 1H), 6.02 (s, 1H, major), 5.80 (s, 1H, minor), 3.06 (d, J = 8.1 Hz, 1H), 2.70 (s, 3H, major), 2.53 (s, 3H, minor), 2.20–1.98 (m, 2H), 1.71–1.51 (m, 3H), 0.45 (q, J = 11.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.98, 169.46, 140.82, 139.00, 130.86, 129.48, 124.81, 123.63, 123.50, 122.74, 117.44, 114.55, 109.40, 109.09, 80.89, 54.52, 41.64, 37.38, 26.08, 23.89, 22.79, 19.43; IR (film) ν_{max}: 3550.4, 3423.9, 3361.5, 2939.6, 2215.2, 1762.7, 1728.6, 1639.6, 1600.9, 1470.3, 1372.5, 1321.6, 1293.6, 1200.5, 1176.7, 1020.6, 834.5, 613.1 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 440.1; HRMS: m/z $[M + Na]^+$ calcd for $C_{22}H_{16}ClN_5NaO_2$: 440.0885; found: 440.0873.

1-Acetyl-3′-amino-5-bromo-2-oxo-6′,7′-dihydro-2′*H*-spiro-[indoline-3,1′-naphthalene]-2′,2′,4′(8′*H*,8a′*H*)-tricarbonitrile (4l): white solid, 93% yield, 6.1 : 1 dr, 94% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (95 : 5) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 29.007 min; t_{minor} = 35.805 min (major). t_{major} = 30.981 min; t_{minor} = 26.179 min (minor). $[\alpha]_D^{25}$: −10.8 (c 0.50 in CH_3COCH_3). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.13 (d, J = 8.7 Hz, 1H), 7.72 (d, J = 9.3 Hz, 1H), 7.68 (s, 2H), 6.96 (s, 1H), 5.94 (s, 1H, major), 5.78 (s, 1H, minor), 2.98 (d, J = 8.1 Hz, 1H), 2.62 (s, 3H, major), 2.46 (s, 3H, minor), 2.12–2.06 (m, 1H), 1.99–1.80 (m, 1H), 1.59–1.54 (m, 2H), 1.42 (s, 1H), 0.40 (q, J = 11.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.27, 169.84, 141.21, 139.78, 134.12, 126.71, 125.15, 124.03, 123.39, 118.12, 117.88, 114.90, 109.77, 109.47, 81.26, 54.82, 42.05, 37.78, 26.47, 24.28, 23.17, 19.81; IR (film) ν_{max}: 3550.9, 3416.1, 3229.6, 2938.7, 2213.7, 1760.6, 1728.9, 1638.4, 1617.8, 1467.3, 1371.7, 1294.4, 1258.5, 1175.8, 1020.2, 827.5, 607.9 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 484.0; HRMS: m/z $[M + Na]^+$ calcd for $C_{22}H_{16}BrN_5NaO_2$: 484.0366; found: 484.0380.

(1-Acetyl-3′-amino-5-nitro-2-oxo-6′,7′-dihydro-2′*H*-spiro-[indoline-3,1′-naphthalene]-2′,2′,4′(8′*H*,8a′*H*)-tricarbonitrile (4m): white solid, 66% yield, 6.4 : 1 dr, 94% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (90 : 10) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 17.141 min; t_{minor} = 23.685 min (major). t_{major} = 31.506 min; t_{minor} = 21.701 min (minor). $[\alpha]_D^{25}$: −4.6 (c 0.25 in CH_3COCH_3). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.51 (d, J = 2.1 Hz, 1H), 8.48 (s, 1H), 7.81 (s, 2H), 7.77 (d, J = 2.1 Hz, 1H), 6.06 (s, 1H, major), 5.89 (s, 1H, minor), 3.12 (d, J = 10.5 Hz, 1H), 2.74 (s, 3H, major), 2.58 (s, 3H, minor), 2.24–2.13 (m, 1H), 1.98–1.90 (m, 1H), 1.73–1.49 (m, 3H), 0.47 (q, J = 11.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.02, 169.61, 145.07, 144.18, 140.66, 127.23, 125.32, 123.38, 121.83, 119.15, 116.41, 114.46, 109.23, 109.00, 80.84, 54.33, 41.54, 37.44, 26.19, 23.86, 22.71, 19.39; IR (film) ν_{max}: 3557.5, 3467.4, 3414.2, 3222.6, 2939.6, 2214.9, 1765.9, 1737.7, 1651.0, 1617.4, 1531.5, 1470.4, 1344.1, 1288.8, 1171.9, 1020.8, 849.6, 758.2, 613.5 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 451.1; HRMS: m/z $[M + Na]^+$ calcd for $C_{22}H_{16}N_6NaO_4$: 451.1125; found: 451.1111.

1-Acetyl-3′-amino-5-methyl-2-oxo-6′,7′-dihydro-2′*H*-spiro-[indoline-3,1′-naphthalene]-2′,2′,4′(8′*H*,8a′*H*)-tricarbonitrile (4n): white solid, 92% yield, 6.1 : 1 dr, 91% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (90 : 10) as the eluent. Flow: 0.8 mL min^{-1}; λ = 254 nm: t_{major} = 14.045 min; t_{minor} = 16.056 min (major). t_{major} = 14.782 min; t_{minor} = 13.431 min (minor). $[\alpha]_D^{25}$: +49.8 (c 0.5 in CH_3COCH_3). ^{1}H NMR (300 MHz, DMSO-d_6)

δ 8.15 (d, J = 8.4 Hz, 1H), 7.66 (s, 2H), 7.38 (d, J = 8.1 Hz, 1H), 6.79 (s, 1H), 5.99 (s, 1H, major), 5.86 (s, 1H, minor), 3.04 (d, J = 9.0 Hz, 1H), 2.69 (s, 3H, major), 2.65 (s, 3H, minor), 2.41 (s, 3H, minor), 2.30 (s, 3H, major), 2.20–2.14 (m, 1H), 1.99–1.92 (m, 1H), 1.67–1.54 (m, 2H), 1.56–1.51 (m, 1H), 0.47 (q, J = 11.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ 172.82, 169.38, 141.04, 137.77, 134.79, 131.11, 124.14, 124.06, 120.78, 115.47, 114.76, 109.81, 109.26, 81.08, 54.69, 41.86, 37.46, 26.04, 23.88, 22.81, 20.50, 19.50; IR (film) ν_{max}: 3550.9, 3431.3, 3358.9, 2937.0, 2213.0, 1759.9, 1718.5, 1640.8, 1597.6, 1485.2, 1372.8, 1325.8, 1308.3, 1266.2, 1194.4, 1020.3, 828.4, 631.1, 586.3 cm^{-1}; ESI-MS: [M + Na]$^+$ m/z = 420.1; HRMS: m/z [M + Na]$^+$ calcd for $C_{23}H_{19}N_5NaO_2$: 420.1431; found: 420.1421.

1-Acetyl-3′-amino-5-methoxy-2-oxo-6′,7′-dihydro-2′*H*-spiro-[indoline-3,1′-naphthalene]-2′,2′,4′(8′*H*,8a′*H*)-tricarbonitrile (4o): white solid, 96% yield, 7.1 : 1 dr, 94% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (85 : 15) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 9.484 min; t_{minor} = 11.625 min (major). t_{major} = 12.416 min; t_{minor} = 10.249 min (minor). $[\alpha]_D^{25}$: −7.8 (c 0.5 in CH_3COCH_3). ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 8.18 (d, J = 8.7 Hz, 1H), 7.68 (s, 2H), 7.13 (d, J = 8.1 Hz, 1H), 6.50 (s, 1H), 5.97 (s, 1H, major), 5.84 (s, 1H, minor), 3.81 (s, 3H, minor), 3.72 (s, 3H, major), 3.03 (d, J = 7.8 Hz, 1H), 2.66 (s, 3H), 2.17–2.11 (m, 1H), 1.96 (s, 1H), 1.62–1.46 (m, 3H), 0.46 (q, J = 11.1 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ 172.65, 169.20, 156.30, 141.07, 133.24, 124.27, 124.05, 122.00, 116.73, 114.64, 113.81, 111.03, 109.70, 109.20, 80.92, 54.78, 54.66, 41.82, 37.43, 25.94, 23.91, 22.82, 19.49; IR (film) ν_{max}: 3430.1, 2937.9, 2213.8, 1760.5, 1703.6, 1639.9, 1595.4, 1486.3, 1373.6, 1295.1, 1271.9, 1183.8, 1015.6, 834.9, 603.9 cm^{-1}; ESI-MS: [M + Na]$^+$ m/z = 436.1; HRMS: m/z [M + Na]$^+$ calcd for $C_{23}H_{19}N_5NaO_3$: 436.1380; found: 436.1369.

1-Acetyl-3′-amino-6-chloro-2-oxo-6′,7′-dihydro-2′*H*-spiro-[indoline-3,1′-naphthalene]-2′,2′,4′(8′*H*,8a′*H*)-tricarbonitrile (4p): white solid, 94% yield, 7.2 : 1 dr, 92% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (85 : 15) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 6.969 min; t_{minor} = 6.026 min (major). t_{major} = 9.379 min; t_{minor} = 15.758 min (minor). $[\alpha]_D^{25}$: +25.6 (c 0.5 in CH_3COCH_3). ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 8.26 (s, 1H), 7.71 (s, 2H), 7.49 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 7.5 Hz, 1H), 6.00 (s, 1H, major), 5.88 (s, 1H, minor), 3.06 (d, J = 7.2 Hz, 1H), 2.71 (s, 3H, major), 2.56 (s, 3H, minor), 2.20–2.14 (m, 1H), 1.99–1.95 (m, 1H), 1.67–1.51 (m, 3H), 0.46 (q, J = 11.1 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ 172.35, 169.73, 141.10, 140.91, 135.10, 125.86, 125.69, 124.65, 123.88, 119.80, 115.77, 114.79, 109.63, 109.25, 81.13, 54.64, 41.75, 37.47, 26.17, 24.00, 22.92, 19.55; IR (film) ν_{max}: 3424.6, 3359.2, 3223.7, 2939.1, 2214.1, 1761.3, 1728.9, 1640.7, 1600.6, 1472.2, 1423.0, 1372.1, 1333.9, 1295.5, 1282.2, 1258.2, 1177.9, 934.9, 880.5, 615.7 cm^{-1}; ESI-MS: [M + Na]$^+$ m/z = 440.1; HRMS: m/z [M + Na]$^+$ calcd for $C_{22}H_{16}ClN_5NaO_2$: 440.0885; found: 440.0865.

1-Acetyl-3′-amino-6-bromo-2-oxo-6′,7′-dihydro-2′*H*-spiro-[indoline-3,1′-naphthalene]-2′,2′,4′(8′*H*,8a′*H*)-tricarbonitrile (4q): white solid, 95% yield, 6.2 : 1 dr, 91% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (90 : 10) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 10.897 min; t_{minor} = 9.276 min (major). t_{major} = 15.524 min; t_{minor} = 28.433 min (minor). $[\alpha]_D^{25}$: +45.6 (c 0.25 in CH_3COCH_3). ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 8.39 (s, 1H), 7.70 (s, 2H), 7.62 (d, J = 7.2 Hz, 1H), 6.97 (d, J = 8.1 Hz, 1H), 6.00 (s, 1H, major), 5.86 (s, 1H, minor), 3.05 (d, J = 9.0 Hz, 1H), 2.70 (s, 3H, major), 2.54 (s, 3H, minor), 2.19–2.08 (m, 1H), 1.98–1.94 (m, 1H), 1.69–1.61 (m, 2H), 1.54–1.47 (m, 1H), 0.46 (q, J = 11.7 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ 172.17, 169.63, 141.05, 140.80, 128.67, 125.83, 124.55, 123.77, 123.56, 120.10, 118.40, 114.69, 109.51, 109.15, 81.02, 54.58, 41.55, 37.32, 26.07, 23.89, 22.81, 19.44; IR (film) ν_{max}: 3555.7, 3416.8, 3228.7, 2937.7, 2214.5, 1762.2, 1730.2, 1638.4, 1596.5, 1470.9, 1417.4, 1371.5, 1332.9, 1295.9, 1282.0, 1255.8, 1197.7, 1178.2, 1024.9, 929.0, 879.3, 760.9, 610.5 cm^{-1}; ESI-MS: [M + Na]$^+$ m/z = 484.0; HRMS: m/z [M + Na]$^+$ calcd for $C_{22}H_{16}BrN_5NaO_2$: 484.0380; found: 484.0371.

1-Acetyl-3′-amino-5,6-difluoro-2-oxo-6′,7′-dihydro-2′*H*-spiro-[indoline-3,1′-naphthalene]-2′,2′,4′(8′*H*,8a′*H*)-tricarbonitrile (4r): white solid, 91% yield, 7.9 : 1 dr, 80% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak IA with hexane–i-PrOH (95 : 5) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 12.455 min; t_{minor} = 13.528 min (major). t_{major} = 15.896 min; t_{minor} = 14.696 min (minor). $[\alpha]_D^{25}$: +18.8 (c 0.5 in CH_3COCH_3). ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 8.24–8.18 (m, 1H), 7.67 (s, 2H, major), 7.43 (s, 2H, minor), 6.92 (t, J = 9.3 Hz, 1H), 5.98 (s, 1H, major), 5.82 (s, 1H, minor), 3.01 (d, J = 8.7 Hz, 1H), 2.65 (s, 3H, major), 2.45 (s, 3H, minor), 2.15–2.09 (m, 1H), 1.93–1.87 (m, 1H), 1.61–1.57 (m, 2H), 1.45 (s, 1H), 0.46 (q, J = 11.7 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ 171.85, 169.37, 151.54, 148.27, 148.07, 145.01, 144.84, 140.56, 138.88, 136.80, 136.69, 125.08, 124.76, 123.34, 117.18, 114.58, 113.57, 113.29, 109.35, 109.02, 106.42, 106.09, 80.96, 54.45, 41.58, 37.32, 25.94, 23.88, 22.70, 19.40. IR (film) ν_{max}: 3556.8, 3476.9, 3415.9, 3353.3, 3230.6, 2938.0, 2217.9, 1760.8, 1728.0, 1638.1, 1619.7, 1494.8, 1446.5, 1376.6, 1275.6, 1220.1, 1167.2, 1012.1, 877.0, 792.6, 623.2 cm^{-1}; ESI-MS: [M + Na]$^+$ m/z = 442.1; HRMS: m/z [M + Na]$^+$ calcd for $C_{22}H_{15}F_2N_5NaO_2$: 442.1086; found: 442.1093.

1′-Acetyl-6-amino-2′-oxo-3,3a-dihydrospiro[indene-4,3′-indoline]-5,5,7(2*H*)-tricarbonitrile (4s): white solid, 90% yield, 2.0 : 1 dr, 75% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak IA with hexane–i-PrOH (90 : 10) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 12.268 min; t_{minor} = 11.104 min (major). t_{major} = 15.394 min; t_{minor} = 13.979 min (minor). $[\alpha]_D^{25}$: −37.6 (c 0.5 in CH_3COCH_3). ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 8.22 (t, J = 8.1 Hz, 1H), 7.96 (s, 2H, major), 7.76 (s, 2H, minor), 7.62–7.44 (m, 1H), 7.34 (t, J = 7.5 Hz, 1H), 6.99 (d, J = 7.8 Hz, 1H) 5.70 (s, 1H, major), 5.58 (s, 1H, minor), 3.70–3.52 (m, 1H), 2.67 (s, 3H, major), 2.54 (s, 3H, minor), 2.34–2.12 (m, 2H), 1.96–1.87 (m, 1H, major), 1.61–1.58 (m, 1H, minor), 1.21–1.11 (m, 1H, minor), 0.69–0.62 (m, 1H, major). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ 172.45, 170.76, 169.61, 169.44, 143.52, 142.49, 140.07, 139.52, 131.69, 130.75, 130.66,

125.78, 125.49, 124.08, 123.97, 123.29, 122.76, 120.97, 120.37, 115.64, 115.10, 114.61, 110.46, 109.86, 109.65, 109.25, 77.45, 76.60, 54.37, 53.87, 45.98, 43.02, 42.37, 30.53, 30.03, 26.03, 25.90, 24.63; IR (film) ν_{max}: 3543.4, 3472.1, 3418.1, 3221.4, 2938.4, 2848.4, 2215.2, 1756.2, 1725.6, 1644.6, 1586.9, 1465.9, 1371.2, 1312.0, 1268.6, 1178.8, 1018.1, 755.7, 593.7 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 392.1; HRMS: m/z $[M + Na]^+$ calcd for $C_{21}H_{15}N_5NaO_2$: 392.1118; found: 392.1119.

General procedure for the preparation of 12b, 12f–12w. 20 mg of activated 4 Å molecular sieve powders (4 Å MS) was added to a solution of **5** (0.2 mmol), **11** (0.24 mmol), and the organocatalyst **3m** (10 mol%) in anhydrous toluene (2 mL). The reaction mixture was stirred at 70 °C for 30 min. The solvent was evaporated, and the residue was purified by flash column silica gel chromatography (DCM–EA = 20/1–10/1) to provide the corresponding products **12b**, **12f–12w**. Yields and spectral and analytical data for compounds **12b**, **12f–12w** are as follows:

5-Amino-1′-methyl-2′-oxo-3-phenylspiro[cyclohexa[2,4]diene-1,3′-indoline]-4,6,6-tricarbonitrile (12b): brown solid, 87% yield, 89% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (70 : 30) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 10.019 min; t_{minor} = 14.573 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.30 (s, 2H), 7.53 (t, J = 7.8 Hz, 1H), 7.47–7.36 (m, 6H), 7.25–7.17 (m, 2H), 5.54 (s, 1H), 3.24 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.62, 148.47, 144.05, 139.47, 137.02, 131.81, 129.42, 128.94, 127.70, 124.73, 124.27, 116.86, 111.81, 110.89, 110.43, 77.09, 54.27, 44.04, 27.23; IR (film) ν_{max}: 3551.5, 3481.0, 3432.7, 3303.5, 3220.9, 2204.6, 1709.8, 1638.6, 1615.9, 1564.5, 1470.5, 1375.7, 1351.7, 756.6, 690.9, 623.9, 541.4 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 400.1; HRMS: m/z $[M + H]^+$ calcd for $C_{23}H_{16}N_5O$: 378.1349; found: 378.1340.

5-Amino-3-(4-fluorophenyl)-1′-methyl-2′-oxospiro[cyclohexa-[2,4]diene-1,3′-indoline]-4,6,6-tricarbonitrile (12f): brown solid, 91% yield, 95% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (70 : 30) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 11.517 min; t_{minor} = 15.334 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.33 (s, 2H), 7.53 (t, J = 7.5 Hz, 1H), 7.47–7.40 (m, 3H), 7.28–7.17 (m, 4H), 5.55 (s, 1H), 3.24 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ 171.56, 162.83 (d, $^1J_{C,F}$ = 259 Hz), 148.49, 144.04, 138.45, 133.46, 131.83, 129.97 (d, $^3J_{C,F}$ = 8 Hz), 128.63, 124.68, 124.30, 116.82, 115.90 (d, $^2J_{C,F}$ = 20 Hz), 111.86, 110.85, 110.43, 76.91, 54.25, 44.00, 27.23; IR (film) ν_{max}: 3481.4, 3431.7, 3412.5, 3303.8, 3216.2, 2204.6, 1712.3, 1642.9, 1618.9, 1609.7, 1565.0, 1511.9, 1470.7, 1375.9, 1351.4, 1239.9, 1155.7, 893.0, 841.7, 790.5, 756.3, 684.5, 633.6, 496.2 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 418.1; HRMS: m/z $[M + Na]^+$ calcd for $C_{23}H_{14}FN_5NaO$: 418.1075; found: 418.1059.

5-Amino-3-(4-chlorophenyl)-1′-methyl-2′-oxospiro[cyclohexa-[2,4]diene-1,3′-indoline]-4,6,6-tricarbonitrile (12g): brown solid, 81% yield, 85% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (70 : 30) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 13.614 min; t_{minor} = 17.267 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.33 (s, 2H), 7.55–7.43 (m, 4H), 7.39 (d, J = 8.4 Hz, 2H), 7.25–7.17 (m, 2H), 5.58 (s, 1H), 3.24 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.48, 148.56, 144.06, 138.36, 135.87, 134.07, 131.86, 129.62, 129.00, 124.61, 124.44, 124.30, 116.73, 112.31, 110.81, 110.45, 76.67, 54.26, 43.97, 27.23; IR (film) ν_{max}: 3477.5, 3433.9, 3311.4, 3222.4, 3203.0, 2205.1, 1713.8, 1645.9, 1609.1, 1571.9, 1489.5, 1470.1, 1374.9, 1349.4, 1095.5, 1014.8, 921.5, 892.6, 835.5, 792.8, 753.7, 626.2 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 434.1; HRMS: m/z $[M + Na]^+$ calcd for $C_{23}H_{14}ClN_5NaO$: 434.0779; found: 434.0769.

5-Amino-3-(4-bromophenyl)-1′-methyl-2′-oxospiro[cyclohexa-[2,4]diene-1,3′-indoline]-4,6,6-tricarbonitrile (12h): brown solid, 79% yield, 82% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (70 : 30) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 14.490 min; t_{minor} = 18.062 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.34 (s, 2H), 7.61 (d, J = 8.1 Hz, 2H), 7.55–7.45 (m, 2H), 7.32 (d, J = 7.8 Hz, 2H), 7.24–7.17 (m, 2H), 5.58 (s, 1H), 3.29 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.46, 148.58, 144.05, 138.47, 136.24, 131.92, 129.87, 124.60, 124.30, 122.72, 116.74, 112.25, 110.81, 110.42, 76.63, 54.28, 43.97, 27.24; IR (film) ν_{max}: 3557.1, 3480.8, 3414.6, 3312.1, 3223.2, 3203.8, 2205.4, 1714.0, 1645.6, 1610.5, 1573.0, 1488.6, 1470.4, 1373.6, 1348.6, 1074.7, 1011.1, 921.2, 833.6, 792.7, 754.0, 621.9 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 478.0; HRMS: m/z $[M + Na]^+$ calcd for $C_{23}H_{14}BrN_5NaO$: 478.0274; found: 478.0276.

5-Amino-3-(4-iodophenyl)-1′-methyl-2′-oxospiro[cyclohexa-[2,4]diene-1,3′-indoline]-4,6,6-tricarbonitrile (12i): brown solid, 72% yield, 81% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (70 : 30) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 15.617 min; t_{minor} = 20.182 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.32 (s, 2H), 7.76 (d, J = 8.1 Hz, 2H), 7.52–7.42 (m, 2H), 7.22–7.14 (m, 4H), 5.54 (s, 1H), 3.22 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.46, 148.58, 144.04, 138.68, 137.76, 136.56, 131.85, 129.84, 124.60, 124.30, 116.75, 112.12, 110.82, 110.42, 95.90, 76.60, 54.28, 43.97, 27.25; IR (film) ν_{max}: 3557.2, 3480.7, 3411.9, 3233.1, 2205.1, 1722.2, 1638.2, 1616.4, 1573.7, 1487.6, 1471.0, 1372.9, 1349.8, 1259.6, 1091.9, 1005.9, 927.0, 824.0, 751.5, 616.1 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 526.0; HRMS: m/z $[M + Na]^+$ calcd for $C_{23}H_{14}IN_5NaO$: 526.0135; found: 526.0115.

5-Amino-1′-methyl-3-(4-nitrophenyl)-2′-oxospiro[cyclohexa-[2,4]diene-1,3′-indoline]-4,6,6-tricarbonitrile (12j): brown solid, 93% yield, 84% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (70 : 30) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 26.216 min; t_{minor} = 36.952 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.48 (s, 2H), 8.27 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.7 Hz, 2H), 7.56–7.47 (m, 2H), 7.26–7.13 (m, 2H), 5.77 (s, 1H), 3.25 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.29, 148.85, 147.97, 144.10, 143.39, 137.90, 131.98, 129.32, 129.21, 128.62, 125.73, 124.36, 124.18, 116.58, 114.24, 110.70, 110.50, 76.02, 54.31, 43.89, 27.27; IR (film) ν_{max}: 3480.6, 3413.5, 3236.9, 2205.1, 1722.9, 1639.7, 1615.4, 1573.5, 1519.6, 1471.0, 1372.5, 1346.9, 1260.5, 1092.3, 894.6, 851.8, 753.2, 697.5, 618.6 cm^{-1}; ESI-MS:

$[M + Na]^+$ m/z = 445.1; HRMS: m/z $[M + Na]^+$ calcd for $C_{23}H_{14}N_6O_3$: 445.1020; found: 445.1030.

5-Amino-1′-methyl-2′-oxo-3-(4-(trifluoromethyl)phenyl)-spiro-[cyclohexa[2,4]diene-1,3′-indoline]-4,6,6-tricarbonitrile (12k): brown solid, 87% yield, 80% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (70 : 30) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 11.832 min; t_{minor} = 16.842 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (s, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 7.6 Hz, 1H), 7.27–7.19 (m, 2H), 7.03–6.94 (m, 1H), 5.69 (s, 1H), 3.25 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.39, 148.74, 144.09, 141.05, 138.33, 131.93, 129.44, 129.33, 128.71, 128.63, 125.96, 125.90, 125.73, 124.49, 124.33, 116.69, 113.43, 110.76, 110.47, 107.92, 76.32, 54.28, 43.95, 27.25. IR (film) ν_{max}: 3556.9, 3480.5, 3413.9, 3235.3, 2206.8, 1722.5, 1638.5, 1616.5, 1573.9, 1492.6, 1471.6, 1325.1, 1169.9, 1126.5, 1067.6, 1017.2, 852.1, 753.2, 620.4 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 468.1; HRMS: m/z $[M + Na]^+$ calcd for $C_{24}H_{14}F_3N_5NaO$: 468.1043; found: 468.1030.

5-Amino-3-(3-fluorophenyl)-1′-methyl-2′-oxospiro[cyclohexa-[2,4]diene-1,3′-indoline]-4,6,6-tricarbonitrile (12l): brown solid, 93% yield, 89% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (70 : 30) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 8.777 min; t_{minor} = 19.323 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.34 (s, 2H), 7.53–7.44 (m, 3H), 7.26–7.18 (m, 5H), 5.64 (s, 1H), 3.24 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.46, 162.37 (d, $^1J_{C,F}$ = 243 Hz), 148.63, 144.07, 139.26 (d, $^3J_{C,F}$ = 8 Hz), 138.26, 131.88, 131.02 (d, $^3J_{C,F}$ = 8 Hz), 124.58, 124.34, 123.97, 116.75, 116.27 (d, $^2J_{C,F}$ = 20 Hz), 114.64 (d, $^2J_{C,F}$ = 22 Hz), 112.77, 110.80, 110.44, 76.57, 54.24, 43.97, 27.24; IR (film) ν_{max}: 3479.7, 3434.3, 3414.1, 3304.8, 3221.8, 2205.3, 1711.0, 1638.2, 1616.4, 1565.2, 1488.2, 1470.7, 1444.2, 1346.7, 1351.2, 1265.3, 1086.7, 899.1, 781.9, 755.5, 694.1, 630.6 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 418.1; HRMS: m/z $[M + Na]^+$ calcd for $C_{23}H_{14}FN_5NaO$: 418.1075; found: 418.1086.

5-Amino-3-(3-chlorophenyl)-1′-methyl-2′-oxospiro[cyclohexa-[2,4]diene-1,3′-indoline]-4,6,6-tricarbonitrile (12m): brown solid, 73% yield, 86% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (70 : 30) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 8.383 min; t_{minor} = 19.869 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.38 (s, 2H), 7.56–7.42 (m, 5H), 7.35 (d, J = 6.0 Hz, 1H), 7.26–7.18 (m, 2H), 5.66 (s, 1H), 3.25 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.43, 148.63, 144.07, 139.02, 138.01, 133.65, 131.86, 130.85, 129.30, 127.52, 126.50, 124.56, 124.31, 116.71, 112.93, 110.79, 110.42, 76.45, 54.24, 43.93, 27.25; IR (film) ν_{max}: 3557.2, 3480.6, 3412.9, 3232.6, 2208.2, 1714.9, 1636.9, 1614.8, 1557.9, 1548.8, 1489.2, 1470.9, 1378.0, 1344.8, 1260.0, 1125.9, 1095.4, 1039.9, 788.2, 750.3, 692.3, 617.3 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 434.1; HRMS: m/z $[M + Na]^+$ calcd for $C_{23}H_{14}ClN_5NaO$: 434.0779; found: 434.0765.

5-Amino-3-(2-fluorophenyl)-1′-methyl-2′-oxospiro[cyclohexa-[2,4]diene-1,3′-indoline]-4,6,6-tricarbonitrile (12n): brown solid, 92% yield, 83% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (80 : 20) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 19.460 min; t_{minor} = 26.822 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.24 (s, 2H), 7.53 (t, J = 5.7 Hz, 1H), 7.46 (d, J = 5.1 Hz, 2H), 7.31–7.21 (m, 5H), 5.55 (s, 1H), 3.24 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.44, 159.53 (d, $^1J_{C,F}$ = 245 Hz), 146.98, 144.07, 134.69, 131.90, 131.66 (d, $^3J_{C,F}$ = 8 Hz), 130.89, 125.22, 125.08 (d, $^2J_{C,F}$ = 15 Hz), 124.40 (d, $^2J_{C,F}$ = 17 Hz), 124.33, 116.42 (d, $^3J_{C,F}$ = 8 Hz), 116.08, 113.77, 110.78, 110.47, 77.99, 54.17, 43.85, 27.27. IR (film) ν_{max}: 3478.2, 3434.2, 3308.0, 3224.0, 2207.3, 1711.7, 1640.2, 1615.1, 1568.1, 1488.4, 1470.2, 1376.7, 1352.0, 1221.5, 1086.0, 893.6, 753.8, 686.2, 620.5 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 418.1; HRMS: m/z $[M + Na]^+$ calcd for $C_{23}H_{14}FN_5NaO$: 418.1075; found: 418.1085.

5-Amino-3-(3,4-difluorophenyl)-1′-methyl-2′-oxospiro[cyclohexa[2,4]diene-1,3′-indoline]-4,6,6-tricarbonitrile (12o): brown solid, 92% yield, 95% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (70 : 30) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 10.206 min; t_{minor} = 18.180 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 2H), 7.55–7.44 (m, 4H), 7.25–7.18 (m, 3H), 5.62 (s, 1H), 3.23 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.41, 148.65, 144.06, 137.54, 134.42, 131.87, 129.31, 128.61, 124.94, 124.57, 124.39, 124.31, 118.19, 117.98, 117.26, 117.04, 116.74, 112.73, 110.74, 110.41, 76.44, 54.07, 43.94, 27.06. IR (film) ν_{max}: 3480.7, 3433.9, 3304.1, 3218.9, 2205.6, 1713.7, 1641.9, 1610.5, 1565.7, 1520.2, 1470.9, 1433.9, 1376.3, 1350.9, 1303.2, 1276.4, 1087.3, 900.0, 830.1, 770.1, 756.7, 685.9, 639.5 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 436.1; HRMS: m/z $[M + Na]^+$ calcd for $C_{23}H_{13}F_2N_5NaO$: 436.0980; found: 436.0985.

5-Amino-1′-methyl-2′-oxo-3-*p*-tolylspiro[cyclohexa[2,4]diene-1,3′-indoline]-4,6,6-tricarbonitrile (12p): brown solid, 72% yield, 83% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (70 : 30) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 12.556 min; t_{minor} = 20.131 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.26 (s, 2H), 7.52–7.43 (m, 2H), 7.30–7.10 (m, 6H), 5.48 (s, 1H), 3.24 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.66, 148.39, 144.04, 139.37, 138.95, 134.20, 131.78, 129.47, 127.60, 124.83, 124.25, 116.92, 111.13, 110.93, 110.41, 77.24, 54.25, 44.04, 27.22, 21.23; IR (film) ν_{max}: 3557.2, 3480.7, 3413.9, 3311.5, 3204.5, 2206.7, 1714.3, 1645.1, 1609.1, 1572.6, 1488.8, 1470.1, 1373.1, 1349.9, 1084.8, 892.7, 825.5, 789.7, 756.4, 684.1, 625.7 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 414.1; HRMS: m/z $[M + Na]^+$ calcd for $C_{24}H_{17}N_5NaO$: 414.1325; found: 14.1325.

5-Amino-3-(4-methoxyphenyl)-1′-methyl-2′-oxospiro[cyclohexa[2,4]diene-1,3′-indoline]-4,6,6-tricarbonitrile (12q): brown solid, 74% yield, 88% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (70 : 30) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 17.709 min; t_{minor} = 21.768 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.24 (s, 2H), 7.52 (t, J = 7.8 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.24–7.17 (m, 2H), 6.97 (d, J = 8.4 Hz, 2H), 5.45 (s, 1H), 3.77 (s, 3H), 2.24 (s, 3H). ^{13}C NMR

(75 MHz, DMSO-d_6) δ 171.72, 160.24, 148.37, 144.02, 139.01, 131.75, 129.29, 129.07, 124.90, 124.25, 117.00, 114.28, 110.95, 110.41, 77.32, 55.65, 54.25, 44.08, 27.20; IR (film) ν_{max}: 3551.3, 3485.7, 3413.2, 3306.6, 3197.7, 2206.7, 1713.6, 1645.1, 1614.8, 1567.8, 1515.9, 1469.9, 1375.5, 1349.9, 1259.8, 1035.9, 892.6, 791.1, 772.7, 685.3, 623.3 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 430.1; HRMS: m/z $[M + Na]^+$ calcd for $C_{24}H_{17}N_5NaO_2$: 430.1274; found: 430.1267.

5-Amino-3-(biphenyl-4-yl)-1′-methyl-2′-oxospiro[cyclo-hexa-[2,4]diene-1,3′-indoline]-4,6,6-tricarbonitrile (12r): brown solid, 61% yield, 79% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (70 : 30) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 17.870 min; t_{minor} = 29.426 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.33 (s, 2H), 7.71 (t, J = 8.4 Hz, 4H), 7.56–7.35 (m, 7H), 7.26–7.18 (m, 2H), 5.59 (s, 1H), 3.26 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.61, 148.59, 144.09, 141.07, 139.70, 139.11, 136.07, 131.82, 129.44, 128.33, 127.07, 124.78, 124.31, 116.95, 111.84, 110.92, 110.42, 107.91, 77.02, 54.33, 44.10, 27.24; IR (film) ν_{max}: 3415.1, 3230.9, 2204.6, 1722.3, 1639.0, 1613.5, 1573.3, 1488.5, 1470.9, 1372.3, 1348.9, 1259.3, 1091.9, 1006.9, 848.4, 758.4, 697.6, 616.8 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 476.1; HRMS: m/z $[M + Na]^+$ calcd for $C_{29}H_{19}N_5NaO$: 476.1482; found: 476.1466.

5-Amino-3-(furan-2-yl)-1′-methyl-2′-oxospiro[cyclohexa-[2,4]-diene-1,3′-indoline]-4,6,6-tricarbonitrile (12s): brown solid, 57% yield, 93% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (70 : 30) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 13.131 min; t_{minor} = 20.500 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.33 (s, 2H), 7.76 (s, 1H), 7.53 (t, J = 5.4 Hz, 1H), 7.41 (d, J = 5.4 Hz, 1H), 7.25–7.17 (m, 2H), 6.91 (s, 1H), 6.61 (s, 1H), 5.79 (s, 1H), 3.23 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.47, 148.95, 148.84, 144.47, 144.06, 131.87, 127.86, 124.66, 124.29, 117.01, 112.42, 110.69, 110.48, 110.35, 108.65, 73.75, 53.85, 43.86, 27.28; IR (film) ν_{max}: 3485.9, 3431.3, 3304.9, 3227.1, 2208.3, 1709.3, 1637.9, 1611.7, 1573.4, 1558.5, 1487.5, 1470.7, 1376.7, 1351.8, 1264.8, 1162.5, 1015.5, 898.9, 750.9, 665.7, 618.4 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 390.1; HRMS: m/z $[M + Na]^+$ calcd for $C_{21}H_{13}N_5NaO_2$: 390.0961; found: 390.0973.

5-Amino-5′-fluoro-3-(4-fluorophenyl)-1′-methyl-2′-oxospiro-[cyclohexa[2,4]diene-1,3′-indoline]-4,6,6-tricarbonitrile (12t): brown solid, 90% yield, 92% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (70 : 30) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 9.558 min; t_{minor} = 16.551 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.31 (s, 2H), 7.41–7.37 (m, 3H), 7.24–7.18 (m, 4H), 5.50 (s, 1H), 3.20 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.28, 162.88 (d, $^1J_{C,F}$ = 244 Hz), 159.02 (d, $^1J_{C,F}$ = 238 Hz), 148.20, 140.51, 138.85, 133.38, 130.05 (d, $^3J_{C,F}$ = 8 Hz), 126.00 (d, $^3J_{C,F}$ = 9 Hz), 118.33 (d, $^2J_{C,F}$ = 23 Hz), 116.70, 115.89 (d, $^2J_{C,F}$ = 20 Hz), 112.29 (d, $^2J_{C,F}$ = 26 Hz), 111.62 (d, $^3J_{C,F}$ = 8 Hz), 111.16, 110.72, 110.61, 77.07, 54.44, 43.84, 27.41; IR (film) ν_{max}: 3556.8, 3471.9, 3440.7, 3414.3, 3308.4, 3223.8, 2205.3, 1714.1, 1644.3, 1618.5, 1571.5, 1491.5, 1364.2, 1269.0, 1242.0, 1157.7, 841.9, 818.9, 687.0, 623.5 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 436.1; HRMS: m/z $[M + Na]^+$ calcd for $C_{23}H_{13}F_2N_5NaO$: 436.0980; found: 436.0993.

5-Amino-3-(4-fluorophenyl)-5′-methoxy-1′-methyl-2′-oxo-spiro[cyclohexa[2,4]diene-1,3′-indoline]-4,6,6-tricarbonitrile (12u): brown solid, 72% yield, 74% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (70 : 30) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 11.702 min; t_{minor} = 19.917 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.32 (s, 2H), 7.45–7.41 (m, 2H), 7.25 (t, J = 8.7 Hz, 2H), 7.19–7.10 (m, 2H), 7.02 (s, 1H), 5.54 (s, 1H), 3.74 (s, 3H), 3.21 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.09, 162.90 (d, $^1J_{C,F}$ = 245 Hz), 156.38, 148.33, 138.61, 137.34, 133.42, 129.99 (d, $^3J_{C,F}$ = 8 Hz), 125.80, 116.78, 115.86 (d, $^2J_{C,F}$ = 22 Hz), 115.62, 111.85, 111.70, 110.97, 110.88, 110.79, 76.92, 55.99, 54.47, 44.00, 27.26; IR (film) ν_{max}: 3564.7, 3414.7, 3230.9, 2207.8, 1715.0, 1639.5, 1619.3, 1601.4, 1506.7, 1495.5, 1384.4, 1367.2, 1289.9, 1232.8, 1161.9, 1032.2, 841.1, 808.1, 625.9 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 448.1; HRMS: m/z $[M + Na]^+$ calcd for $C_{24}H_{16}FN_5NaO_2$: 448.1180; found: 448.1197.

5-Amino-6′-chloro-3-(4-fluorophenyl)-1′-methyl-2′-oxo-spiro-[cyclohexa[2,4]diene-1,3′-indoline]-4,6,6-tricarbonitrile (12v): brown solid, 76% yield, 78% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (70 : 30) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 13.826 min; t_{minor} = 26.548 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.33 (s, 2H), 7.45–7.39 (m, 4H), 7.25 (t, J = 8.4 Hz, 3H), 5.54 (s, 1H), 3.25 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.63, 146.90 (d, $^1J_{C,F}$ = 196 Hz), 138.63, 136.46, 133.35, 129.99 (d, $^3J_{C,F}$ = 8 Hz), 125.75, 123.98, 123.45, 116.68, 115.90 (d, $^2J_{C,F}$ = 22 Hz), 111.33, 111.00, 110.71, 110.63, 76.99, 54.02, 43.83, 27.47; IR (film) ν_{max}: 3467.9, 3419.3, 2209.9, 1722.8, 1639.8, 1608.1, 1506.9, 1374.7, 1237.6, 1161.4, 1106.1, 1072.4, 902.8, 842.3, 815.8, 613.4 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 452.1; HRMS: m/z $[M + Na]^+$ calcd for $C_{23}H_{13}ClFN_5NaO$: 452.0685; found: 452.0692.

5-Amino-7′-fluoro-3-(4-fluorophenyl)-1′-methyl-2′-oxo-spiro-[cyclohexa[2,4]diene-1,3′-indoline]-4,6,6-tricarbonitrile (12w): brown solid, 72% yield, 76% ee. The enantiomeric excess was determined by HPLC on a Daicel Chiralpak AD-H with hexane–i-PrOH (70 : 30) as the eluent. Flow: 1 mL min^{-1}; λ = 254 nm: t_{major} = 12.393 min; t_{minor} = 23.977 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.33 (s, 2H), 7.44–7.39 (m, 3H), 7.33–7.20 (m, 4H), 5.55 (s, 1H), 3.40 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.31, 148.24, 138.63, 133.37, 130.66, 130.04, 129.93, 127.49, 125.48, 120.68, 119.62, 116.67, 116.05, 115.76, 111.35, 110.67, 76.96, 54.41, 43.99, 29.52; IR (film) ν_{max}: 3479.9, 3432.5, 3303.4, 3219.1, 2205.4, 1714.5, 1641.4, 1564.4, 1510.9, 1489.3, 1475.3, 1369.7, 1261.3, 1239.6, 1131.3, 1059.0, 859.9, 840.5, 784.3, 731.7, 634.9 cm^{-1}; ESI-MS: $[M + Na]^+$ m/z = 436.1; HRMS: m/z $[M + Na]^+$ calcd for $C_{23}H_{13}F_2N_5NaO$: 436.0980; found: 436.0997.

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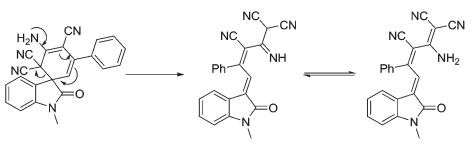
18 The compound **12b** was decomposed under high temperature as follows:



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19 CCDC 951552 (for **4p**) contains the supplementary crystallographic data for this paper. See the ESI† for details.