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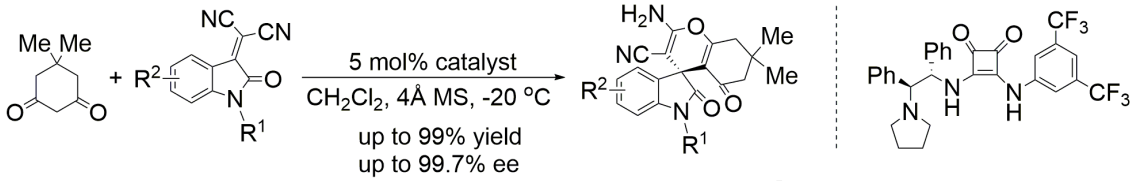
Key Laboratory for Advanced Materials and Institute of Fine Chemicals, School of Chemistry & Molecular Engineering, East China University of Science and Technology, Shanghai 200237, P. R. China



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ABSTRACT

A highly enantioselective Michael/cyclization tandem reaction between dimedone and isatylidene malononitriles has been developed. With 5 mol% of bifunctional organocatalyst **C15**, chiral spiro[2-amino-4*H*-pyran-oxindole] derivatives were obtained in excellent yields (97-99%) with excellent enantioselectivities (up to > 99% ee).

1. Introduction

The chiral spirooxindole scaffold is widely found in natural products and bioactive compounds.[1] In the past decade, great efforts have been made towards the asymmetric synthesis of chiral spirooxindoles owing to their excellent biological activities.[1c,1f,2] Both asymmetric cycloadditions and formal cycloaddition reactions (i.e. actual tandem reactions for the latter) with 3-alkenyl-2-oxindoles are common strategies to produce chiral spirooxindoles. These strategies have received much attention because of their high efficiency and the atom-economy.[2d,2g,3] 4*H*-Pyrans are important heterocycles with a variety of bioactivities including anti-tumor, antimicrobial and kinase inhibitory activities.[4] However, the asymmetric construction of chiral spirooxindoles incorporating a 4*H*-pyran motif has been barely descried. Traditionally isatylidene malononitriles derived from isatins have been applied as 1,3-bis-electrophiles in the enantioselective formal [3+3] cycloaddition reaction to construct chiral spirooxidoles incorporating a 2-amino-4*H*-pyran scaffold. Over the past few years, several efficient strategies have been developed for this enantioselective process.[5] In the previous reports, the 1,3-bis-nucleophiles used include dicarbonyl compounds[5a,5b], phenols[5b], β-hydroxyl-α,β-unsaturated carbonyl compounds[5b,5c], pyrazolones[5d] and α-cyano ketones[5e]. The introduction of an amino group to the 4*H*-pyrans motif has been proven to be useful for some synthetic transformations.[5b,5d,6]

Dimedone is a cyclic 1,3-dicarbonyl compound with an outstanding reactivity, which can be used as a 1O,3C-bis-nucleophile.[7] Among the asymmetric synthetic protocols developed for 2-amino-4*H*-pyran scaffolds with dimedone, the enantioselectivity had hardly exceeded 77% ee.[5a,8] Furthermore, the enantioselective tandem reaction with dimedone to construct chiral spiro[2-amino-4*H*-pyran-oxindoles] has been barely documented. A rare example is the three-component tandem reaction among dimedone, isatins and malononitrile, catalyzed by cupreine, affording spiro[2-amino-4*H*-pyran-oxindoles] with only 7% *ee*, however.[5a] With continuing interest in the asymmetric synthesis of chiral spirooxindoles,[5d,5e,9] herein we report a highly enantioselective tandem reaction between dimedone and isatylidene malononitriles.

2. Results and discussion

Initially, the Michael/cyclization tandem reaction between dimedone (**1**) and *N*-benzyl isatylidene malononitrile (**2a**) was selected as a model reaction to screen the chiral organocatalysts (Fig. 1). The reactions were performed with 5 mol% of chiral organocatalysts in dichloromethane at -20 °C (Table 1). All chiral oraganocatalysts screened could promote the tandem reaction efficiently, providing 99% chemical yield with different enantioselectivities. Cinchona alkaloid-derived bifunctional organocatalysts **C3**-**C7** with sulfamide, thiourea or squaramide as H-bonding donator provided better enantioselectivities than

* Corresponding author. E-mail addresses: xinyanwu@ecust.edu.cn (X.-Y. Wu).

quinine (**C1**) and cinchonideine (**C2**) (entries 3-7 vs entries 1 and 2). Among them, thiourea **C5** resulted in the best enantioselectivity (72% ee, entry 5). In the presence of $(DHQD)_2PYR$ (**C8**), only 10% ee was obtained (entry 8). These results indicated that the hydrogen-bonding effect of the organocatalysts played an important role in controlling the stereoselectivity. To improve the enantioselectivity of the model reaction, tertiary amine organocatalysts based on chiral 1,2-diaminocyclohexane or 1,2-diphenylethanediamine backbone were investigated (entries 9-16). To our delight, the squaramide **C15** could achieve chiral spirooxindole **3a** in 76% ee (entry 15). Based on the above results, chiral squaramide **C15** was selected as catalyst for further studies.

Next, the effect of solvents was investigated (Table 2). In toluene, halogenated solvents and ethers, the tandem reactions achieved excellent yields but with only 52%-76% ee (entries 1-6). Chloroform and 1,2-dichloroethane were examined because the highest enantioselectivity (76% ee) was obtained in dichloromethane (entries 2-4). The reaction was completed in ether in 48 hours, probably due to the poor solubility of dimedone in ether (entry 5). In the polar aprotic solvents used such as ethyl acetate, acetonitrile, and DMF, the enantioselectivity of the tandem reaction was poor (entries 7-9). In a protic polar solvent, ethanol, the catalytic reaction took 18 hours, and the enantioselectivity was poor (entry 10). This is probably due to the presence of hydroxyl group-containing solvent that compromises the hydrogen-bonding effect of the chiral organocatalyst. As a result, dichloromethane was selected as the solvent for further reaction optimization.

To further enhance the enantioselectivity of the tandem reaction, other reaction conditions including the reaction temperature, the ratio of dimedone to substrate **2a**, the substrate concentration, the catalyst loading and additives were investigated (Table 3). The results indicated that a lower reaction

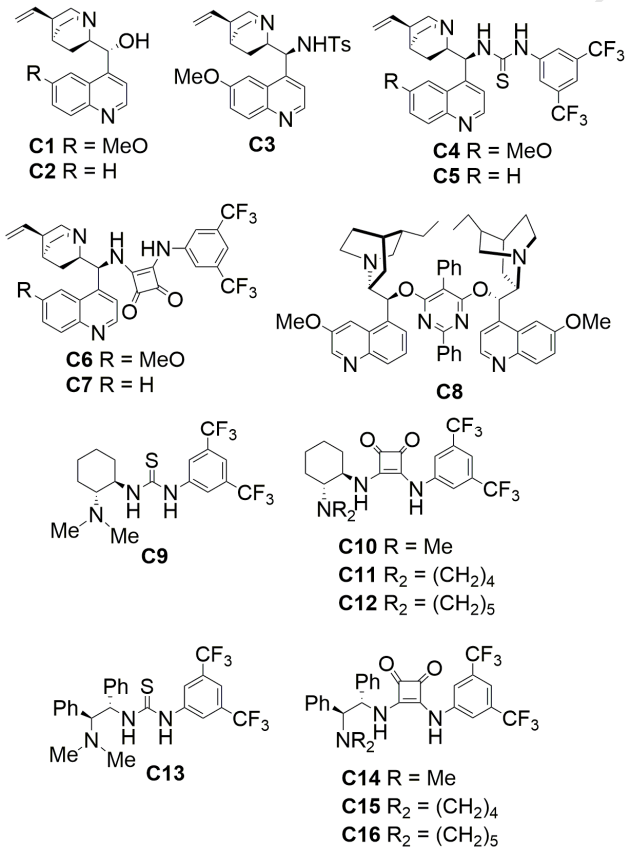
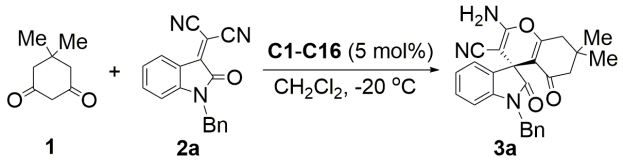


Fig. 1 Structures of the chiral organocatalysts screened.

Table 1 Screening of the chiral organocatalysts for the tandem reaction[a]



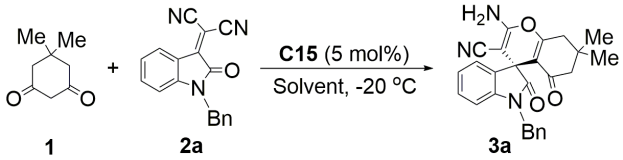
Entry	Catalyst	Time (min)	Yield (%)[b]	Ee (%)[c]
1	**C1**	10	99	-4
2	**C2**	10	99	0
3	**C3**	20	99	40
4	**C4**	20	99	42
5	**C5**	20	99	72
6	**C6**	30	99	30
7	**C7**	45	99	66
8	**C8**	30	99	10
9	**C9**	50	99	26
10	**C10**	50	99	54
11	**C11**	20	99	64
12	**C12**	40	99	6
13	**C13**	100	99	22
14	**C14**	120	99	66
15	**C15**	30	99	76
16	**C16**	100	99	52

[a] All reactions were performed with dimedone (0.12 mmol), substrate **2a** (0.10 mmol) and chiral organocatalyst (5 mol%) in CH_2Cl_2 (1 mL) at -20 °C.

[b] Isolated yields.

[c] Determined by HPLC analysis.

Table 2 The effect of solvent on the Michael/cyclization tandem reaction[a]



Entry	Solvent	Time	Yield (%)[b]	Ee (%)[c]
1	Toluene	3 h	99	68
2	CH_2Cl_2	30 min	99	76
3	$CHCl_3$	20 min	99	76
4	$ClCH_2CH_2Cl$	2 h	99	68
5	Et_2O	48 h	99	58
6	THF	50 min	99	52
7	EtOAc	35 min	99	28
8	CH_3CN	35 min	92	4
9	DMF	20 min	99	0
10	EtOH	18 h	99	6

[a] All reactions were performed with dimedone (0.12 mmol), substrate **2a** (0.10 mmol) and organocatalyst **C15** (5 mol%) in solvent (1 mL) at -20 °C.

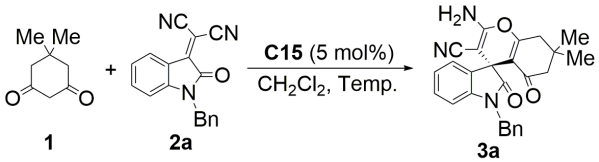
[b] Isolated yields.

[c] Determined by HPLC analysis.

[b] Isolated yields.

temperature could lead to a slightly higher enantioselectivity but with a longer reaction time, and a temperature of -20 °C gave the best result (entries 1-4). The ratio of substrates affected the enantioselectivity rather than yields (69%-76% ee, entries 5-8 and 2). When the substrate concentration was increased to 0.2 M, the spirooxindole **3a** was obtained in 72% ee (entry 10). The enantioselectivity of the tandem reaction was reduced to 74% ee when 2 mol% chiral organocatalyst **C15** was used (entry 11 vs entry 2). Then, we chose molecular sieves as an additive to improve the enantioselectivity (entries 12-17). The results showed that adding 4Å molecular sieves to the reaction system could improve the enantioselectivity. The improvement of enantioselectivity was related to the quantity of molecular sieves added and their pore size. Adding 50 mg of 4Å molecular sieves to a 0.1 mmol reaction system increased the enantioselectivity to 83% ee (entry 14). However, the addition of 3Å molecular sieves or 5Å molecular sieves did not improve the reaction (entries 16 and 17 vs entry 14). In order to understand the role of molecular sieves in the catalytic reaction, we added 1 equivanlent amount

Table 3 Further optimization of reaction conditions[a]



Entry	1:2a	Temp. (°C)	Additives	Time	Yield (%)[b]	Ee (%)[c]
1	1.2:1	0	-	20 min	99	66
2	1.2:1	-20	-	30 min	99	76
3	1.2:1	-50	-	18 h	99	76
4	1.2:1	-78	-	72 h	99	78
5	2:1	-20	-	30 min	99	72
6	1:1	-20	-	30 min	99	74
7	1:1.2	-20	-	35 min	99	70
8	1:2	-20	-	35 min	99	69
9[d]	1.2:1	-20	-	40 min	98	76
10[e]	1.2:1	-20	-	30 min	99	72
11[f]	1.2:1	-20	-	50 min	99	74
12	1.2:1	-20	4 Å MS (10 mg)	30 min	99	78
13	1.2:1	-20	4 Å MS (25 mg)	40 min	99	80
14	1.2:1	-20	4 Å MS (50 mg)	40 min	99	83
15	1.2:1	-20	4 Å MS (75 mg)	40 min	99	78
16	1.2:1	-20	3 Å MS (50 mg)	40 min	99	80
17	1.2:1	-20	5 Å MS (50 mg)	40 min	99	78
18	1.2:1	-20	H_2O (1.8 μL)	30 min	99	74
19	1.2:1	-20	4 Å MS (50 mg), H_2O (1.8 μL)	45 min	99	77
20	1.2:1	-20	4 Å MS (50 mg), H_2O (9.0 μL)	45 min	79	70

[a] Unless stated otherwise, the reactions were performed with dimedone (0.12 mmol), substrate **2a** (0.10 mmol) and chiral organocatalyst **C15** (5 mol%) in CH_2Cl_2 (1 mL) at -20 °C.

[c] Determined by chiral HPLC analysis.

[d] In 2 mL CH_2Cl_2.

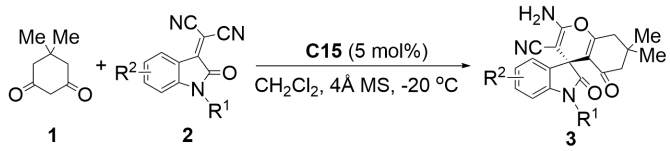
[e] In 0.5 mL CH_2Cl_2.

[f] With 2 mol% of catalyst **C15**.

of deionized water to the reaction system. The enantioselectivity was reduced when compared with that in the absence of deionized water, and the yield was unchanged (entry 18 vs entry 2 and entry 19 vs entry 14). When 5 equiv. water was added to the system with 50 mg of 4Å molecular sieves, the chemical yield and enantioselectivity were decreased obviously (entry 20 vs entries 14 and 19). We postulate that the molecular sieves functioned mainly by water absorption. Considering these results, the optimal reaction conditions were determined to be 0.1 M isatylidene malononitrile in dichloromethane with 1.2 equiv. of dimedone, 5 mol% of the chiral organocatalyst **C15** and 4Å molecular sieves (50 mg/0.1 mmol isatylidene malononitrile) at -20 °C.

Under the optimized reaction conditions, the substrate scope of the tandem reaction was investigated (Table 4). In all cases, excellent chemical yields were achieved. The results indicated that the substituents on the nitrogen atom of isatylidene malononitriles significantly influenced the enantioselectivity (entries 1-6), and the *N*-trityl substrate yielded the best result (98% ee, entry 6). The different *N*-trityl isatylidene malononitriles were tolerated to the tandem reaction, providing 97-99% yields with 94-99.7% ee values (entries 6-18). Notably, 4-substituted (such as 4-Cl) isatylidene malononitrile could undergo the tandem reaction, although a longer reaction time was required to improve the conversion (entry 7).

Table 4 Substrate scope of the enantioselective Michael/cyclization tandem reaction[a]



Entry	R^1	R^2	Time	Yield (%)[b]	Ee (%)[c]
1	Bn	H	40 min	**3a**, 99	83
2	Ph	H	1 h	**3b**, 99	58
3	Me	H	40 min	**3c**, 99	68
4	H	H	1 h	**3d**, 99	6
5	$CHPh_2$	H	1 h	**3e**, 99	79
6	CPh_3	H	30 min	**3f**, 99	98
7	CPh_3	4-Cl	36 h	**3g**, 99	94
8	CPh_3	5-MeO	20 min	**3h**, 99	99
9	CPh_3	5-Me	40 min	**3i**, 99	98
10	CPh_3	5-F	15 min	**3j**, 98	98
11	CPh_3	5-Cl	35 min	**3k**, 99	98
12	CPh_3	5-Br	30 min	**3l**, 97	99.2
13	CPh_3	6-MeO	24 h	**3m**, 99	99.2
14	CPh_3	6-Me	2 h	**3n**, 99	99.6
15	CPh_3	6-F	1 h	**3o**, 99	99.1
16	CPh_3	6-Cl	1 h	**3p**, 99	99

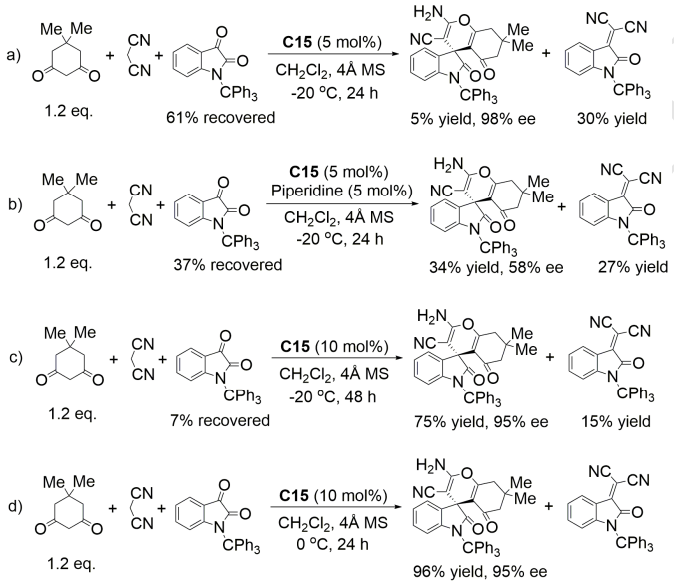
17	CPh_3	6-Br	1 h	**3q**, 99	99.7
18	CPh_3	7-F	3 h	**3r**, 99	99

[a] All reactions were performed with dimedone (0.12 mmol), **2** (0.10 mmol), 4 Å MS (50 mg) and **C15** (5 mol%) in CH_2Cl_2 (1 mL) at -20 °C.

[b] Isolated yields.

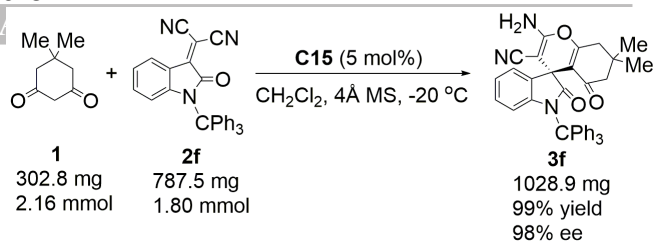
[c] Determined by chiral HPLC analysis.

Moreover, we attempted the one-pot three component reaction of dimedone, malononitrile and *N*-trityl isatin under the optimal conditions. However, the corresponding chiral spiro product **3f** was obtained only in 5% yield with 98% ee for 24 hours. *N*-trityl isatin was recovered with 61% yield, and *N*-trityl isatylidene malononitrile was obtained in 30% yield (Scheme 1a). To improve the one-pot reaction, 5 mol% piperidine was added. The yield of product **3f** was increased to 34% with an obvious decrement of enantioselectivity, and there were 37% *N*-trityl protected isatin and 27% *N*-trityl isatylidene malononitrile remaining (Scheme 1b). We suspected that piperidine could promote both the knoevenagel condensation and the subsequent Michael/cyclization reaction, and our suspect has been proved by examining the corresponding two-component reaction under the same reaction condition. Therefore, 10 mol% of chiral catalyst **C15** was used to catalyze the one-pot reaction rather than adding achiral base. To our delight, the yield of product **3f** was increased to 75% with 95% ee after 48 hours (Scheme 1c). While 15% yield of *N*-trityl isatylidene malononitrile was isolated, the reaction temperature was increased to 0 °C in order to improve the conversion. As predicted, the one-pot three component reaction was achieved in 96% yield and 95% ee (Scheme 1d).

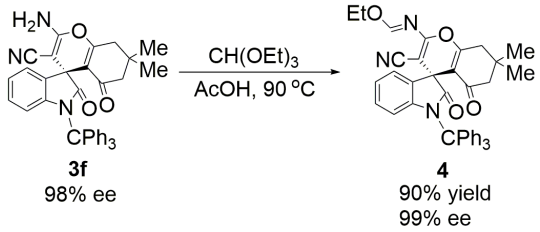


Scheme 1 Attempt of one-pot three component reaction

To demonstrate the synthetic utility of this work, gram-scale construction of spiro compound **3f** was performed under the optimized reaction conditions. The tandem reaction was achieved in 99% yield with 98% ee (Scheme 2).



Scheme 2 Gram-scale construction of spiro compound **3f**



Scheme 3 The transformation of spiro compound **3f**

As shown in Scheme 3, the transformation of the amino group of the spiro 2-amino-4*H*-pyran was achieved by this reaction.[5b,5d] Treatment of chiral product **3f** with triethyl orthoformate in the presence of acetic acid at 90 °C afforded imine **4** in 90% yield with 99% ee.

The absolute configuration of spirooxindole **3h** was addressed to be *R* by X-ray crystallography (Fig. 2, CCDC1856973). The configurations of the other spiro[2-amino-4*H*-pyran-oxindole] derivatives **3** were assigned by analogy.

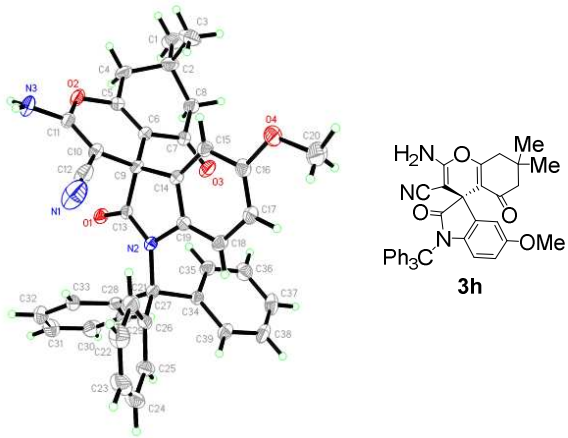


Fig. 2 X-ray structure of product **3h**.

3. Conclusions

In conclusion, a highly enantioselective Michael addition/cyclization tandem reaction of dimedone to isatylidene malononitriles was developed. In the presence of 5 mol% chiral tertiary amine-squaramide organocatalyst **C15**, *N*-trityl multicyclic spirooxindoles were achieved with high yields (97-99%) with excellent enantioselectivities (94->99% ee). This methodology represents an efficient approach to the synthesis of novel chiral spiro[2-amino-4*H*-pyran-oxindole] compounds.

4. Experimental section

4.1. General methods

Melting points were taken without correction. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 400 spectrometer. ^{1}H NMR spectra were referenced to tetramethylsilane (δ 0.00 ppm) using $CDCl_3$ or DMSO-d_6 as solvent. ^{13}C NMR spectra were referenced to solvent carbons (δ 77.0 ppm for $CDCl_3$ or δ 39.52 ppm for DMSO-d_6). IR spectra were recorded on IR Prestige-21 spectrometer. High resolution mass spectra (HRMS) were performed on electron spray ionization time-of-flight (EI-TOF) mass spectrometer and electron spray ionization time-of-flight (ESI-TOF) mass spectrometer. Optical rotations were measured with a WZZ-2S polarimeter. Enantiomeric excesses were determined by chiral HPLC analysis using Waters 510 liquid chromatograph instrument and Waters 2487 dual absorbance detector with Daicel Chiralcel OD-H column, Chiralpak AD-H column and Chiralpak AS-H column. Thin-layer chromatography (TLC) was performed on 10-40 μm silica gel plates. Column chromatography was performed on silica gel (300-400 mesh) eluted with ethyl acetate and CH_2Cl_2.

All solvents were purified by conventional methods and distilled before use. Commercially available reagents and chiral organocatalysts such as quinine (**C1**), cinchonidine (**C2**) and $(DHQD)_2PYR$ (**C8**) were used without further purification.

Organocatalysts **C3-C7**, **C9-C16**[10] and isatylidene malononitriles **2a-2r**[5d,11] were prepared according to literature procedures.

*4.2. General procedure for the asymmetric tandem reaction and characterization of the products **3a-3r***

To a solution of isatylidene malononitrile **2** (0.10 mmol, 1.0 eq.), chiral catalyst **C15** (5 mol%) and 4Å molecular sieves (50 mg) in 1 mL of dichloromethane was added dimedone (0.12 mmol, 1.2 eq.) at -20 °C, and the resulting mixture was stirred at this temperature until the starting materials disappeared (monitored by TLC). The residue was directly purified by flash column chromatography (4:1-20:1 CH_2Cl_2/EtOAc) to give the desired spiro product **3**.

*4.2.1. (R)-2-amino-1'-benzyl-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (**3a**)*

White solid, 99% yield, 83% ee, mp 291.1-291.3 °C, $[\alpha]_D^{20}$ +62.1 (*c* 0.71, CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 7.54 (d, *J* = 6.8 Hz, 2H), 7.40 (s, 2H), 7.38-7.28 (m, 3H), 7.20-7.13 (m, 2H), 7.01 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 4.99 (d, *J* = 16.4 Hz, 1H), 4.93 (d, *J* = 16.0 Hz, 1H), 2.68 (d, *J* = 17.6 Hz, 1H), 2.62 (d, *J* = 17.2 Hz, 1H), 2.27 (d, *J* = 15.6 Hz, 1H), 2.17 (d, *J* = 16.0 Hz, 1H), 1.10 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 195.1, 176.7, 164.5, 159.0, 142.6, 136.2, 133.6, 128.4, 128.3, 127.2, 127.1, 123.0, 122.6, 117.4, 110.7, 108.9, 57.2, 49.9, 46.6, 43.3, 32.0, 27.6, 27.0; IR (KBr, cm^{-1}): *v* 3389, 3331, 3202, 2958, 2199, 1717, 1679, 1659, 1601, 1479, 1466, 1421, 1344, 1293, 1215, 1170, 1048, 984, 894, 753, 701; HRMS (ESI) calcd for $C_{26}H_{22}N_3O_3$ ($[M-H]^+$): 424.1661, found: 424.1646; HPLC analysis (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-PrOH = 80/20, flow rate: 0.9 mL/min): t_R = 23.28 min (minor), 34.44 min (major).

*4.2.2. (R)-2-amino-7,7-dimethyl-2',5-dioxo-1'-phenyl-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (**3b**)*

White solid, 99% yield, 58% ee, mp 295.9-296.8 °C, $[\alpha]_D^{20}$ +117.3 (*c* 0.82, CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 7.61 (t, *J* = 7.6 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.42 (s, 2H), 7.38 (d, *J* = 7.6 Hz, 2H), 7.18 (q, J_1 = 7.6 Hz, J_2 = 15.6 Hz, 2H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 2.64 (d, *J* = 17.6 Hz, 1H), 2.53 (d, *J* = 17.6 Hz, 1H), 2.23 (d, *J* = 16.0 Hz, 1H), 2.15 (d, *J* = 16.4 Hz, 1H), 1.05 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 195.3, 176.2, 164.5, 158.9, 143.3, 134.8, 133.3, 129.7, 128.5, 128.1, 126.6, 123.5, 123.1, 117.3, 110.9, 108.6, 57.1, 49.8, 46.6, 32.1, 27.7, 27.0; IR (KBr, cm^{-1}): *v* 3440, 3312, 3157, 2951, 2193, 1717, 1684, 1659, 1627, 1601, 1498, 1473, 1357, 1318, 1293, 1254, 1221, 1164, 1054, 759, 701; HRMS (ESI) calcd for $C_{25}H_{22}N_3O_3$ ($[M+H]^+$): 412.1658, found: 412.1661; HPLC analysis (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-PrOH = 80/20, flow rate: 0.9 mL/min): t_R = 20.56 min (minor), 26.92 min (major).

*4.2.3. (R)-2-amino-1',7,7-trimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (**3c**)*

White solid, 99% yield, 68% ee, mp 254.5-254.6 °C, $[\alpha]_D^{20}$ +57.4 (*c* 0.50, CH_2Cl_2) ; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 7.37 (s, 2H), 7.31 (td, J_1 = 1.2 Hz, J_2 = 7.6 Hz, 1H), 7.12-7.10 (m, 1H), 7.07-7.02 (m, 2H), 3.19 (s, 3H), 2.63 (d, *J* = 3.6 Hz, 2H), 2.21 (d, *J* = 16.0 Hz, 1H), 2.14 (d, *J* = 15.6 Hz, 1H), 1.09 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 194.9, 176.6, 164.3, 158.9, 143.6, 133.6, 128.4, 122.8, 122.4, 117.2, 110.7, 108.2, 57.0, 49.9, 46.5, 32.0, 27.5, 27.1, 26.4; IR (KBr, cm^{-1}): *v* 3382, 3157, 2958, 2199, 1704, 1665, 1607, 1498, 1465, 1351, 1318, 1215, 1164, 1126, 1087, 1048, 900, 746; HRMS (ESI) calcd for $C_{20}H_{19}NaN_3O_3$ ($[M+Na]^+$): 372.1324, found: 372.1319; HPLC analysis (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-PrOH = 70/30, flow rate: 0.9 mL/min): t_R = 20.53 min (major), 40.42 min (minor).

*4.2.4. (R)-2-amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indo-line]-3-carbonitrile (**3d**)*[12]

White solid, 99% yield, 6% ee, mp 290.0-290.8 °C, $[\alpha]_D^{20}$ +25.9 (*c* 0.48, CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 10.41 (s, 1H), 7.24 (s, 2H), 7.13 (d, *J* = 6.4 Hz, 1H), 6.98 (d, *J* = 6.4 Hz, 1H), 6.90 (d, *J* = 6.4 Hz, 1H), 6.78 (d, *J* = 6.8 Hz, 1H), 2.56 (s, 2H), 2.17 (d, *J* = 16.0 Hz, 1H), 2.09 (d, *J* = 15.6 Hz, 1H), 1.03 (s, 3H), 1.00 (s, 3H); HPLC analysis (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-PrOH = 70/30, flow rate: 0.9 mL/min): t_R = 15.87 min (major), 35.63 min (minor).

*4.2.5. (R)-2-amino-1'-benzhydryl-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (**3e**)*

White solid, 99% yield, 79% ee, mp 277.8-278.8 °C, $[\alpha]_D^{20}$ +116.6 (*c* 0.25, CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 7.47 (d, *J* = 7.2 Hz, 2H), 7.42-7.38 (m, 6H), 7.37-7.34 (m, 4H), 7.15-7.13 (m, 1H), 7.00-6.93 (m, 2H), 6.91 (s, 1H), 6.28 (dd, J_1 = 1.6 Hz, J_2 = 6.4 Hz, 1H), 2.68 (d, *J* = 17.6 Hz , 1H), 2.62 (d, *J* = 18.0 Hz , 1H), 2.27 (d, *J* = 16.0 Hz , 1H), 2.19 (d, *J* = 16.4 Hz , 1H), 1.09 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 195.1, 176.9, 164.6, 159.0, 142.3, 137.8, 137.7, 133.9, 128.5, 128.4, 128.3, 127.7, 127.6, 127.5, 123.1, 122.3, 117.6, 111.0, 110.7, 58.0, 57.3, 49.9, 46.2, 32.0, 27.6, 27.1; IR (KBr, cm^{-1}): *v* 3370, 3176, 2964, 2186, 1698, 1685, 1659, 1601, 1466, 1415, 1351, 1312, 1228, 1164, 1054, 907, 798, 753, 733, 695; HRMS (ESI) calcd for $C_{26}H_{28}N_3O_3$ ($[M+H]^+$): 502.2137, found: 502.2131; HPLC analysis (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-PrOH = 80/20, flow rate: 0.9 mL/min): t_R = 10.79 min (minor), 25.87 min (major).

*4.2.6. (R)-2-amino-7,7-dimethyl-2',5-dioxo-1'-trityl-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (**3f**)*

White solid, 99% yield, 98% ee, mp 268.8-270.6 °C, $[\alpha]_D^{20}$ -10.6 (*c* 2.31, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.58 (d, *J* = 7.6 Hz, 6H), 7.28-7.24 (m, 6H), 7.19 (t, *J* = 6.8 Hz, 3H),

6.93-6.91 (m, 1H), 6.86-6.84 (m, 2H), 6.40-6.37 (m, 1H), 4.58 (s, 2H), 2.44 (d, *J* = 17.2 Hz, 1H), 2.36 (d, *J* = 17.6 Hz, 1H), 2.17 (d, *J* = 15.6 Hz, 1H), 2.10 (d, *J* = 16.0 Hz, 1H), 1.06 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): *δ* 194.3, 177.2, 163.6, 158.3, 143.1, 141.7, 133.0, 129.8, 127.4, 127.1, 126.7, 122.5, 122.4, 117.5, 116.0, 111.7, 74.8, 61.9, 50.4, 47.2, 40.8, 32.0, 28.6, 27.4; IR (KBr, cm^{-1}): *ν* 3376, 3189, 2951, 2193, 1717, 1672, 1595, 1460, 1415, 1351, 1318, 1273, 1215, 1170, 1048, 733, 694; HRMS (ESI) calcd for $C_{38}H_{30}N_3O_3$ ([M-H]$^+$): 576.2287, found: 576.2286; HPLC analysis (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-PrOH = 95/5, flow rate: 0.9 mL/min): t_R = 31.33 min (minor), 39.66 min (major).

*4.2.7. (R)-2-amino-4'-chloro-7,7-dimethyl-2',5-dioxo-1'-trityl-5,6,7,8-tetrahydrospiro-[chromene-4,3'-indoline]-3-carbonitrile (**3g**)*

White solid, 99% yield, 94% ee, mp 255.7-260.0 °C, $[\alpha]_D^{20}$ -21.0 (*c* 1.36, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): *δ* 7.56 (d, *J* = 7.6 Hz, 6H), 7.27 (t, *J* = 7.2 Hz, 6H), 7.20 (t, *J* = 7.2 Hz, 3H), 6.80 (d, *J* = 4.4 Hz, 2H), 6.34 (t, *J* = 9.2 Hz, 1H), 4.71(s, 2H), 2.45 (d, *J* = 17.6 Hz, 1H), 2.35 (d, *J* = 17.2 Hz, 1H), 2.21 (d, *J* = 15.6 Hz, 1H), 2.14 (d, *J* = 16.0 Hz, 1H), 1.08 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): *δ* 194.6, 176.4, 164.4, 159.3, 145.0, 141.4, 129.8, 129.5, 128.3, 127.8, 127.5, 126.9, 123.3, 117.3, 114.6, 110.7, 75.2, 59.8, 50.3, 47.6, 40.8, 32.0, 29.0, 27.4; IR (KBr, cm^{-1}): *ν* 3453, 3363, 3202, 3054, 2964, 2193, 1730, 1672, 1595, 1492, 1447, 1344, 1267, 1215, 1170, 1138, 1048, 977, 887, 772, 726, 701; HRMS (ESI) calcd for $C_{38}H_{30}ClNaN_3O_3$ ([M+Na]$^+$): 634.1873, found: 634.1345; HPLC analysis (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-PrOH = 95/5, flow rate: 0.9 mL/min): t_R = 24.37 min (minor), 35.49 min (major).

*4.2.8. (R)-2-amino-5'-methoxy-7,7-dimethyl-2',5-dioxo-1'-trityl-5,6,7,8-tetrahydrospiro-[chromene-4,3'-indoline]-3-carbonitrile (**3h**)*

White solid, 99% yield, 99% ee, mp 259.9-260.2 °C, $[\alpha]_D^{20}$ -25.5 (*c* 2.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): *δ* 7.57 (d, *J* = 7.6 Hz, 6H), 7.28-7.25 (m, 6H), 7.19 (t, *J* = 7.2 Hz, 3H), 6.50 (d, *J* = 2.0 Hz, 1H), 6.38 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 6.27 (d, *J* = 8.8 Hz, 1H), 4.65 (s, 2H), 3.62 (s, 3H), 2.45 (d, *J* = 17.6 Hz, 1H), 2.37 (d, *J* = 17.6 Hz, 1H), 2.18 (d, *J* = 16.4 Hz, 1H), 2.10 (d, *J* = 16.4 Hz, 1H), 1.07 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): *δ* 194.2, 177.0, 163.6, 158.2, 155.5, 141.8, 136.5, 134.3, 129.8, 127.4, 126.7, 117.4, 116.4, 111.8, 111.4, 109.7, 74.8, 62.4, 55.3, 50.4, 47.6, 40.8, 32.1, 28.7, 27.5; IR (KBr, cm^{-1}): *ν* 3389, 3196, 2958, 2193, 1710, 1672, 1601, 1485, 1447, 1344, 1318, 1280, 1215, 1170, 1054, 798, 740, 695; HRMS (ESI) calcd for $C_{39}H_{33}NaN_3O_4$ ([M+Na]$^+$): 630.2369, found: 630.2439; HPLC analysis (AS-H column, λ = 254 nm, eluent: *n*-hexane/EtOH = 90/10, flow rate: 0.9 mL/min): t_R = 11.65 min (minor), 15.45 min (major).

*4.2.9. (R)-2-amino-5'-methyl-7,7-trimethyl-2',5-dioxo-1'-trityl-5,6,7,8-tetrahydrospiro-[chromene-4,3'-indoline]-3-carbonitrile (**3i**)*

White solid, 99% yield, 98% ee, mp 268.2-268.8 °C, $[\alpha]_D^{20}$ -32.5 (*c* 1.97, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): *δ* 7.58 (d, *J* = 7.6 Hz, 6H), 7.26 (t, *J* = 7.6 Hz, 6H), 7.18 (t, *J* = 7.2 Hz, 3H), 6.72 (s, 1H), 6.64 (d, *J* = 8.2 Hz, 1H), 6.25 (d, *J* = 8.0 Hz, 1H), 4.62 (s, 2H), 2.44 (d, *J* = 17.2 Hz, 1H), 2.37 (d, *J* = 18.0 Hz, 1H), 2.17 (d, *J* = 17.2 Hz, 1H), 2.15 (s, 3H), 2.10 (d, *J* = 16.4 Hz, 1H), 1.06 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): *δ* 194.2, 177.2, 163.5, 158.2, 141.9, 140.7, 132.9, 131.9, 129.8, 127.8, 127.4, 126.7, 123.2, 117.5, 115.7, 111.9, 74.8, 62.4, 50.4, 47.3, 40.9, 32.1, 28.6, 27.6, 20.9; IR (KBr, cm^{-1}): *ν* 3395, 3196, 2958, 2186, 1710, 1672, 1595, 1492, 1447, 1351, 1324, 1267, 1215, 1048, 1010, 804, 726, 695; HRMS (ESI) calcd for $C_{39}H_{33}NaN_3O_3$ ([M+Na]$^+$): 614.2420, found: 614.1722; HPLC analysis (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-PrOH = 95/5, flow rate: 0.9 mL/min): t_R = 26.69 min (minor), 34.66 min (major).

*4.2.10. (R)-2-amino-5'-fluoro-7,7-dimethyl-2',5-dioxo-1'-trityl-5,6,7,8-tetrahydrospiro-[chromene-4,3'-indoline]-3-carbonitrile (**3j**)*

White solid, 98% yield, 98% ee, mp 267.3-267.8 °C, $[\alpha]_D^{20}$ -13.3 (*c* 1.48, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): *δ* 7.56 (d, *J* = 8.0 Hz, 6H), 7.27 (t, *J* = 7.6 Hz, 6H), 7.20 (t, *J* = 7.2 Hz, 3H), 6.67 (dd, J_1 = 2.4 Hz, J_2 = 7.2 Hz, 1H), 6.56 (td, J_1 = 2.8 Hz, J_2 = 9.2 Hz, 1H), 6.32 (dd, J_1 = 4.4 Hz, J_2 = 8.8 Hz, 1H), 4.70 (s, 2H), 2.44 (d, *J* = 17.6 Hz, 1H), 2.37 (d, *J* = 17.6 Hz, 1H), 2.18 (d, *J* = 16.4 Hz, 1H), 2.11 (d, *J* = 16.4 Hz, 1H), 1.06 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): *δ* 194.3, 177.0, 163.9, 160.1, 158.3, 157.7, 141.5, 139.1 (d, J_{C-F} = 1.5 Hz), 134.5 (d, J_{C-F} = 7.3 Hz), 129.8, 127.5, 126.8, 117.2, 116.7 (d, J_{C-F} = 8.0 Hz), 113.7 (d, J_{C-F} = 22.6 Hz), 111.5, 110.1 (d, J_{C-F} = 24.3 Hz), 74.9, 61.7, 50.4, 47.5, 40.8, 32.1, 28.6, 27.5; IR (KBr, cm^{-1}): *ν* 3453, 3356, 2951, 2193, 1717, 1679, 1595, 1479, 1447, 1351, 1324, 1273, 1221, 1157, 1048, 1016, 958, 900, 811, 746, 733, 701; HRMS (ESI) calcd for $C_{38}H_{30}FNaN_3O_3$ ([M+Na]$^+$): 618.2169, found: 618.2164; HPLC analysis (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-PrOH = 95/5, flow rate: 0.9 mL/min): t_R = 29.55 min (minor), 34.51 min (major).

*4.2.11. (R)-2-amino-5'-chloro-7,7-dimethyl-2',5-dioxo-1'-trityl-5,6,7,8-tetrahydrospiro-[chromene-4,3'-indoline]-3-carbonitrile (**3k**)*

White solid, 99% yield, 98% ee, mp 265.5-266.0 °C, $[\alpha]_D^{20}$ -43.4 (*c* 1.22, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): *δ* 7.55 (d, *J* = 7.6 Hz, 6H), 7.29-7.24 (m, 6H), 7.20 (t, *J* = 7.2 Hz, 3H), 6.90 (d, *J* = 2.4 Hz, 1H), 6.82 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.31 (d, *J* = 8.4 Hz, 1H), 4.70 (s, 2H), 2.43 (d, *J* = 17.6 Hz, 1H), 2.38 (d, *J* = 17.6 Hz, 1H), 2.18 (d, *J* = 16.4 Hz, 1H), 2.11 (d, *J* = 16.4 Hz, 1H), 1.06 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): *δ* 194.3, 176.8, 163.9, 158.3, 141.9, 141.4, 134.7, 129.7, 128.0, 127.5, 127.3, 126.9, 122.8, 117.2, 116.9, 111.4, 75.0, 61.5, 50.3, 47.3, 40.8, 32.1, 28.4, 27.7; IR (KBr, cm^{-1}): *ν* 3395, 3318, 2958, 2186, 1717, 1672, 1595, 1473, 1447, 1351, 1318, 1286, 1254, 1221, 1164, 1106, 1054, 1003, 894, 811, 746, 701; HRMS (ESI) calcd for $C_{38}H_{30}ClNaN_3O_3$ ([M+Na]$^+$): 634.1873, found: 634.1873; HPLC analysis (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-PrOH = 95/5, flow rate: 0.9 mL/min): t_R = 29.26 min (minor), 36.01 min (major).

*4.2.12. (R)-2-amino-5'-bromo-7,7-dimethyl-2',5-dioxo-1'-trityl-5,6,7,8-tetrahydrospiro-[chromene-4,3'-indoline]-3-carbonitrile (**3l**)*

White solid, 97% yield, 99.2% ee, mp 261.2-262.1 °C, $[\alpha]_D^{20}$ -40.2 (*c* 2.17, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): *δ* 7.55 (d, *J* = 7.6 Hz, 6H), 7.27 (t, *J* = 7.2 Hz, 6H), 7.20 (t, *J* = 7.2 Hz, 3H), 7.04 (d, *J* = 2.0 Hz, 1H), 6.96 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 6.27 (d, *J* = 8.4 Hz, 1H), 4.72 (s, 2H), 2.43 (d, *J* = 18.0 Hz, 1H), 2.38 (d, *J* = 18.0 Hz, 1H), 2.18 (d, *J* = 16.0 Hz, 1H), 2.11 (d, *J* = 16.4 Hz, 1H), 1.05 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): *δ* 194.3, 176.6, 163.9, 158.4, 142.4, 141.4, 135.0, 130.1, 129.7, 127.5, 126.9, 125.6, 117.3, 115.5, 111.4, 75.0, 61.3, 50.3, 47.2, 40.8, 32.1, 28.4, 27.7; IR (KBr, cm^{-1}): *ν* 3401, 3312, 2958, 2186, 1724, 1679, 1633, 1601, 1473, 1440, 1415, 1344, 1312, 1280, 1221, 1157, 1054, 900, 804, 733, 701; HRMS (EI) calcd for $C_{19}H_{15}BrN_3O_3$ ([M-CPh$_3$]$^+$): 412.0297, found: 412.0294; HPLC analysis (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-PrOH = 95/5, flow rate: 0.9 mL/min): t_R = 25.84 min (minor), 34.32 min (major).

*4.2.13. (R)-2-amino-6'-methoxy-7,7-dimethyl-2',5-dioxo-1'-trityl-5,6,7,8-tetrahydrospiro-[chromene-4,3'-indoline]-3-carbonitrile (**3m**)*

White solid, 99% yield, 99.2% ee, mp 260.1-260.3 °C, $[\alpha]_D^{20}$ -21.0 (*c* 2.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.58 (d, *J* = 8.0 Hz, 6H), 7.28-7.23 (m, 6H), 7.19 (t, *J* = 7.2 Hz, 3H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.38 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 5.97 (d, *J* = 2.0 Hz, 1H), 4.59 (s, 2H), 3.42 (s, 3H), 2.42 (d, *J* = 17.6 Hz, 1H), 2.34 (d, *J* = 17.2 Hz, 1H), 2.16 (d, *J* = 16.0 Hz, 1H), 2.09 (d, *J* = 16.4 Hz, 1H), 1.04 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 194.4, 177.7, 163.4, 158.6, 158.1, 144.3, 141.7, 129.8, 127.4, 126.7, 125.2, 122.7, 117.5, 111.9, 107.2, 103.8, 74.8, 62.3, 55.0, 50.4, 46.8, 40.8, 32.0, 28.6, 27.5; IR (KBr, cm^{-1}): *v* 3440, 3389, 2958, 2186, 1724, 1679, 1621, 1601, 1498, 1447, 1351, 1318, 1215, 1151, 1106, 1054, 1016, 753, 733,701; HRMS (ESI) calcd for $C_{39}H_{32}N_3O_4$ ([M-H]$^+$): 606.2393, found: 606.2393; HPLC analysis (OD-H column, λ = 254 nm, eluent: *n*-hexane/EtOH = 95/5, flow rate: 0.9 mL/min): t_R = 20.70 min (minor), 26.36 min (major).

*4.2.14. (R)-2-amino-6'-methyl-7,7-dimethyl-2',5-dioxo-1'-trityl-5,6,7,8-tetrahydrospiro-[chromene-4,3'-indoline]-3-carbonitrile (**3n**)*

White solid, 99% yield, 99.6% ee, mp 272.3-272.4 °C, $[\alpha]_D^{20}$ -20.4 (*c* 1.97, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.57 (d, *J* = 8.0 Hz, 6H), 7.28-7.24 (m, 6H), 7.19 (t, *J* = 7.2 Hz, 3H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.67 (d, *J* = 7.2 Hz, 1H), 6.16 (s, 1H), 4.56 (s, 2H), 2.43 (d, *J* = 17.6 Hz, 1H), 2.35 (d, *J* = 17.2 Hz, 1H), 2.16 (d, *J* = 16.0 Hz, 1H), 2.09 (d, *J* = 16.0 Hz, 1H), 2.00 (s, 3H), 1.05 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 194.3, 177.5, 163.4, 158.1, 143.3, 141.9, 137.0, 130.1, 130.0, 127.3, 126.7, 123.2, 122.1, 117.4, 117.0, 112.0, 74.8, 62.7, 50.5, 47.0, 40.9, 32.1, 28.7, 27.5, 21.9; IR (KBr, cm^{-1}): *v* 3453, 3376, 2964, 2919, 2199, 1717, 1672, 1595, 1492, 1447, 1415, 1351, 1318, 1293, 1260, 1215, 1164, 1100, 1048, 939, 907, 804, 746, 733, 708; HRMS (ESI) calcd for $C_{39}H_{32}N_3O_3$ ([M-H]$^+$): 590.2444, found: 590.2446; HPLC analysis (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-PrOH = 95/5, flow rate: 0.9 mL/min): t_R = 27.31 min (minor), 35.71 min (major).

*4.2.15. (R)-2-amino-6'-fluoro-7,7-dimethyl-2',5-dioxo-1'-trityl-5,6,7,8-tetrahydrospiro-[chromene-4,3'-indoline]-3-carbonitrile (**3o**)*

White solid, 99% yield, 99.1% ee, mp 261.1-261.3 °C, $[\alpha]_D^{20}$ -16.8 (*c* 1.98, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.56 (d, *J* = 6.0 Hz, 6H), 7.27 (d, *J* = 6.4 Hz, 6H), 7.21 (d, *J* = 5.6 Hz, 3H), 6.86 (s, 1H), 6.56 (s, 1H), 6.13 (d, *J* = 10.4 Hz, 1H), 4.66 (s, 2H), 2.44 (d, *J* = 17.6 Hz, 1H), 2.38 (d, *J* = 17.6 Hz, 1H), 2.17 (d, *J* = 14.8 Hz, 1H), 2.11 (d, *J* = 16.0 Hz, 1H), 1.06 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 194.3, 177.4, 163.7, 162.8, 160.4, 158.2, 144.7 (d, $J_{C\text{-}F}$ = 11.7 Hz), 141.5, 141.4, 129.8, 129.7, 128.4 (d, $J_{C\text{-}F}$ = 2.9 Hz), 127.5, 127.4, 126.9, 123.1 (d, $J_{C\text{-}F}$ = 9.5 Hz), 117.2, 111.7, 109.1, 108.9, 104.9, 104.6, 75.1, 62.3, 50.4, 46.8, 40.9, 32.1, 28.5, 27.6; IR (KBr, cm^{-1}): *v* 3446, 3382, 2958, 2193, 1724, 1679, 1601, 1492, 1447, 1351, 1318, 1293, 1215, 1151, 1087, 1048, 945, 847, 746, 726, 701; HRMS (ESI) calcd for $C_{38}H_{29}FN_3O_3$ ([M-H]$^+$): 594.2193, found: 594.2192; HPLC analysis (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-PrOH = 95/5, flow rate: 0.9 mL/min): t_R = 34.95 min (minor), 44.32 min (major).

*4.2.16. (R)-2-amino-6'-chloro-7,7-dimethyl-2',5-dioxo-1'-trityl-5,6,7,8-tetrahydrospiro-[chromene-4,3'-indoline]-3-carbonitrile (**3p**)*

White solid, 99% yield, 99% ee, mp 257.6-258.1 °C, $[\alpha]_D^{20}$ -32.8 (*c* 2.03, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.55 (d, *J* = 7.2 Hz, 6H), 7.28 (t, *J* = 7.2 Hz, 6H), 7.21 (t, *J* = 7.2 Hz, 3H), 6.84 (d, *J* = 0.8 Hz, 1H), 6.35 (s, 1H), 4.64 (s, 2H), 2.43 (d, *J* = 17.6 Hz, 1H), 2.37 (d, *J* = 17.6 Hz, 1H), 2.16 (d, *J* = 16.4 Hz, 1H), 2.10 (d, *J* = 16.4 Hz, 1H), 1.05 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 194.4, 177.1, 163.9, 158.3, 144.3, 141.3, 132.8, 131.4, 129.7, 127.5, 126.9, 123.1, 122.6, 117.2, 116.3, 111.4, 75.1, 61.5, 50.4, 46.9, 40.8, 32.1, 28.5, 27.6; IR (KBr, cm^{-1}): *v* 3465, 3376, 2958, 2193, 1717, 1672, 1601, 1479, 1447, 1415, 1351, 1318, 1260, 1215, 1164, 1081, 1048, 1016, 932, 887, 740, 695; HRMS (ESI) calcd for $C_{38}H_{29}ClN_3O_3$ ([M-H]$^+$): 610.1897, found: 610.1904; HPLC analysis (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-PrOH = 95/5, flow rate: 0.9 mL/min): t_R = 30.78 min (minor), 39.39 min (major).

*4.2.17. (R)-2-amino-6'-bromo-7,7-dimethyl-2',5-dioxo-1'-trityl-5,6,7,8-tetrahydrospiro-[chromene-4,3'-indoline]-3-carbonitrile (**3q**)*

White solid, 99% yield, 99.7% ee, mp 254.8-255.2 °C, $[\alpha]_D^{20}$ -44.9 (*c* 2.17, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.55 (d, *J* = 8.0 Hz, 6H), 7.28 (t, *J* = 7.2 Hz, 6H), 7.21 (t, *J* = 7.2 Hz, 3H), 7.00 (dd, J_1 = 1.6 Hz, J_2 = 7.6 Hz , 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.48 (d, *J* = 1.6 Hz, 1H), 4.66 (s, 2H), 2.43 (d, *J* = 17.6 Hz, 1H), 2.37 (d, *J* = 17.6 Hz, 1H), 2.16 (d, *J* = 16.4 Hz, 1H), 2.10 (d, *J* = 16.4 Hz, 1H), 1.05 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 194.4, 176.9, 163.9, 158.3, 144.5, 141.3, 131.9, 129.7, 127.5, 126.9, 125.4, 123.5, 120.8, 119.0, 117.2, 111.4, 75.1, 61.4, 50.3, 46.9, 40.8, 32.1, 28.5, 27.6; IR (KBr, cm^{-1}): *v* 3370, 3196, 2958, 2193, 1717, 1672, 1601, 1473, 1454, 1415, 1351, 1318, 1260, 1215, 1170, 1054, 1015, 887, 798, 733, 701; HRMS (ESI) calcd for $C_{38}H_{29}BrN_3O_3$ ([M-H]$^+$): 654.1409, found: 654.1392; HPLC analysis (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-PrOH = 95/5, flow rate: 0.9 mL/min): t_R = 34.38 min (minor), 42.30 min (major).

*4.2.18. (R)-2-amino-7'-fluoro-7,7-dimethyl-2',5-dioxo-1'-trityl-5,6,7,8-tetrahydrospiro-[chromene-4,3'-indoline]-3-carbonitrile (**3r**)*

White solid, 99% yield, 99% ee, mp 231.7-232.4 °C, $[\alpha]_D^{20}$ -18.7 (*c* 1.97, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.55 (d, *J* = 7.6 Hz, 6H), 7.26 (t, *J* = 6.8 Hz, 6H), 7.19 (d, *J* = 7.2 Hz, 3H), 6.89 (td, J_1 = 3.6 Hz, J_2 = 7.6 Hz, 1H), 6.79 (dd, J_1 = 0.8 Hz, J_2 = 7.2 Hz ,1H), 6.68-6.63 (m, 1H), 4.68 (s, 2H), 2.45 (d, *J* = 17.6 Hz, 1H), 2.37 (d, *J* = 17.6 Hz, 1H), 2.21 (d, *J* = 16.4 Hz, 1H), 2.14 (d, *J* = 16.4 Hz, 1H), 1.07 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 194.4, 176.8, 163.7, 158.3, 147.9, 145.5, 143.4, 135.8 (d, $J_{C\text{-}F}$ = 2.2 Hz), 130.4 (d, $J_{C\text{-}F}$ = 8.0 Hz), 129.3, 127.2 126.5, 124.4 (d, $J_{C\text{-}F}$ = 7.3 Hz), 118.7 (d, $J_{C\text{-}F}$ = 2.9 Hz), 118.0, 117.8, 117.4, 111.8, 75.5, 61.8, 50.4, 47.4, 40.8, 32.1, 28.7, 27.4; IR (KBr, cm^{-1}): *v* 3446, 3195, 2958, 2193, 1723, 1672, 1601, 1485, 1454, 1351, 1318, 1235, 1221, 1157, 1054, 907, 868, 733, 708; HRMS (ESI) calcd for $C_{38}H_{29}FN_3O_3$ ([M-H]$^+$): 594.2193, found: 594.2178; HPLC analysis (OD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-PrOH = 95/5, flow rate: 0.9 mL/min): t_R = 36.64 min (minor), 41.68 min (major).

4.3.** General procedure for the preparation of the racemic products **3a**-**3r

To a solution of isatylidene malononitrile **2** (0.10 mmol, 1.0 eq.), 1-(3,5-bis(trifluoromethyl)phenyl)-3-(2-dimethylamino) ethyl)thiourea (5 mol%) in dichloromethane (1 mL) was added dimedone (0.12 mmol, 1.2 eq.) at 25 °C, and the resulting mixture was stirred at this temperature until the starting materials disappeared (monitored by TLC). The residue was directly purified by flash column chromatography (4:1-20:1 CH_2Cl_2/EtOAc) to give the corresponding racemic product **3**.

4.4. General procedure for the one-pot three component reaction

Scheme 1d: To a solution of malononitrile (0.10 mmol, 1.0 eq.), *N*-trityl isatin (0.10 mmol, 1.0 eq.), chiral catalyst **C15** (10 mol%), 4Å molecular sieves (50 mg) in 1 mL of dichloromethane was added dimedone (0.12 mmol, 1.2 eq.) at 0 ^{o}C. Then the resulting mixture continued to stirred at this temperature for 24 hours (monitored by TLC). The residue was directly purified by flash column chromatography (20:1 CH_2Cl_2/EtOAc) to give the desired spiro product **3f**, Knoevenagel condensation product **2f** and recovered *N*-trityl isatin.

*4.5. General procedure for the transformation of product **3f** and characterization of compound **4***

A mixture of the product **3f** (346.6 mg, 0.6 mmol), 3 mL triethyl orthoformate, and 1 mL acetic acid was stirred at 90 ^{o}C until the reaction was completed (monitored by TLC). The resulting mixture was cooled to room temperature and added water (10 mL), then extracted with CH_2Cl_2 (10 mL*3). The organic phase was washed with water and then dried over anhydrous Na_2SO_4. After concentrated under vacuum, the residue was purified by column chromatography (2:1 petroleum ether/EtOAc) and recrystallization to give the desired product **4**.

*(R,E)-Ethyl-N-(3-cyano-7,7-dimethyl-2',5-dioxo-1'-trityl-5,6,7,8-tetrahydrospiro[chromene-4,3'-indolin]-2-yl)formimidate (**4**)*

White solid, 90% yield, 99% ee, mp 250.5-250.8 ^{o}C, $[\alpha]_D^{20}$ +14.4 (*c* 1.17, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.22 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 6H), 7.28-7.24 (m, 6H), 7.19 (t, *J* = 6.8 Hz, 3H), 6.97-6.94 (m, 1H), 6.90-6.86 (m, 2H), 6.43-6.41 (m, 1H), 4.45-4.36 (m, 2H), 2.50 (d, *J* = 17.2 Hz, 1H), 2.43 (d, *J* = 17.6 Hz, 1H), 2.19 (d, *J* = 16.4 Hz, 1H), 2.12 (d, *J* = 16.4 Hz, 1H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.09 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 194.2, 176.4, 164.0, 159.7, 156.9, 143.5, 141.7, 132.2, 129.9, 127.6, 127.4, 126.7, 122.6, 116.1, 115.7, 111.4, 82.6, 75.1, 64.6, 50.5, 49.3, 41.0, 32.1, 28.7, 27.5, 13.8; IR (KBr, cm^{-1}): *v* 3448, 3058, 2961, 2213, 1732, 1673, 1615, 1466, 1362, 1304, 1251, 1186, 1089, 1043, 757, 725, 698; HRMS (EI) calcd for $C_{41}H_{35}N_3O_4$ ([M-CPh_3]$^+$): 390.1454, found: 390.1444 ; HPLC analysis (AD-H column, λ = 254 nm, eluent: *n*-hexane/*i*-PrOH = 30/1, flow rate: 0.9 mL/min): t_R = 12.99 min (minor), 14.79 min (major).

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