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Organocatalytic enantioselective tandem aldol-cyclization reaction of α-isothiocyanato imides and activated carbonyl compounds

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ABSTRACT

The organocatalytic enantioselective tandem aldol-cyclization reactions of α-isothiocyanato imides and activated carbonyl compounds, such as isatins, an α-ketolactone and a 1,2-dione, have been studied with cinchona alkaloid-derived thiourea-catalysts. This methodology provided an easy way to access enantiomerically enriched spirobicyclic thiocarbamates with high yields and good to excellent stereoselectivity, which have been demonstrated to be useful precursors for the synthesis of biologically active molecules.

1. Introduction

Cyclic thiocarbamates are a very useful class of compounds in modern organic synthesis.[1] Moreover, many compounds containing this structural motif show interesting biological and pharmacological activities.[2] Due to their importance, there has been a lot of interest in developing an asymmetric synthesis of these heterocycles and their derivatives in recent years.[3] These interesting heterocyclic compounds can be synthesized by the direct condensation of carbon disulfide and β-aminoalcohols.[4] Nevertheless, this method cannot be made enantioselective. Since tandem reactions are a powerful tool for assembling complex organic structures from relatively simple starting materials,[5] a better way to assemble these heterocycles utilizes the tandem aldol[6]-cyclization reaction between isothiocyanatoalkanes and aldehydes or ketones.[7] Asymmetric versions of the latter strategy have already been reported.[3a–e] For example, Willis et al. reported the first enantioselective synthesis of cyclic thiocarbamates using Mg-PYBOX as the catalyst.[3a] Recently, Shibasaki and co-workers developed a highly enantioselective synthesis of these derivatives using Mg–Schiff base complexes as catalysts.[3b] On the other hand, Seidel and co-workers reported the first organocatalyzed tandem aldol-cyclization reaction between α-isothiocyanato imides and aldehydes for the enantioselective synthesis of cyclic thiocarbamates, which may be used for the synthesis of enantiomerically enriched α-hydroxy-β-amino acids.[3c] Most recently, the tandem aldol-cyclization reaction of α-isothiocyanato imides and α-ketoesters were also independently reported by Wang and co-workers and Seidel and co-workers.[3d,e]

Our group is interested in using activated carbonyl compounds as enamine or enol acceptors in novel organocatalyzed aldol reactions for the asymmetric synthesis of molecules of biological significance.[8] In this regard, we have recently reported the first quinine thiourea-catalyzed cross aldol reaction of isatins and unactivated ketones via an enolate mechanism, in which isatin was demonstrated to be an excellent enolate acceptor in cross aldol reactions.[8d] Inspired by the work of Siedel and co-workers and Wang and co-workers on the reaction of α-isothiocyanato imides and α-ketoesters,[3d,e] we envisioned that an organocatalyzed tandem aldol-cyclization reaction of α-isothiocyanato imides and activated carbonyl compounds, such as isatins, should lead to the enantioselective synthesis of cyclic thiocarbamates with a spiro indolinone substituent, a unique structural feature that may have interesting biological relevance.[9,10] Herein we report a cinchonidine thiourea-catalyzed[11] tandem aldol-cyclization reaction for the highly stereoselective synthesis of 2′-thioxospiro[indoline-3,5′-oxazolidin]-2-one derivatives. It should be mentioned that, while our work was still under progress, Wang and co-workers reported a rosin-derived thiourea-catalyzed synthesis of similar derivatives.[10]

2. Results and discussion

Amine thioureas, especially those derived from cinchona alkaloids, have been proven to be powerful catalysts in a wide range of asymmetric transformations involving enolate intermediates.[11,12] These bifunctional catalysts are able to activate both nucleophiles and electrophiles. Moreover, the thiourea moiety can also help improve stereoselectivities by directing the approach of the substrates with hydrogen bonding. We envisioned that these thioureas should also be good catalysts for the present reaction. Thus, several amine thioureas, mainly those derived from cinchona alkaloids **6a–d**, **6h**, and **6i**, (Fig. 1) were selected as catalysts for the preliminary screening. For the sake of comparison, some cinchona alkaloids **6e–g** without the thiourea moiety were also screened (Fig. 1).

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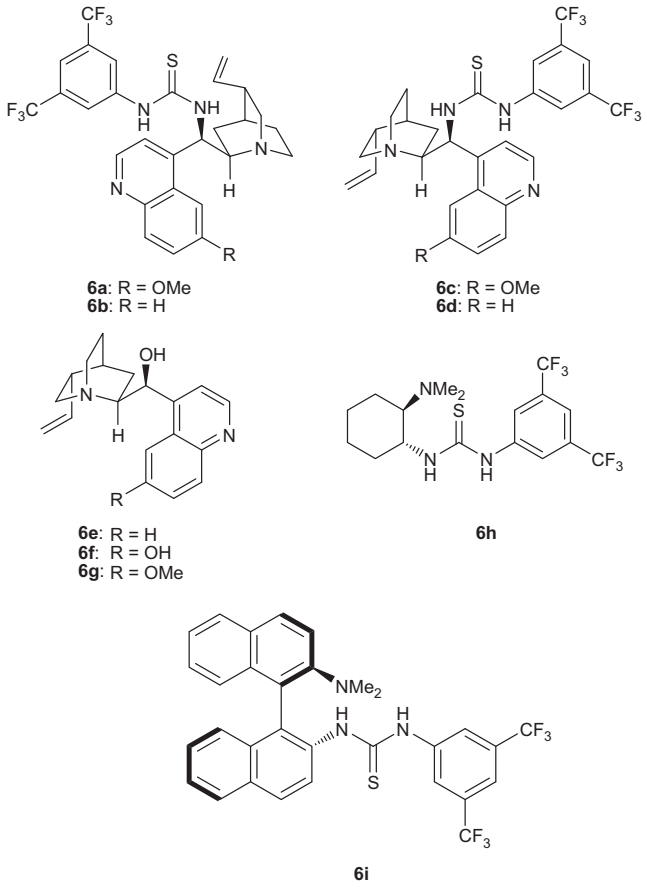


Figure 1. Catalysts screened for the tandem aldol-cyclization reaction of isatin **1a** and α-isothiocyanatoacetate derivatives **2**.

With isatin **1a** as the substrate and quinidine thiourea **6a** as the catalyst, we first screened several α-isothiocyanatoacetate derivatives **2a–c**. The results of this screen are collected in Table 1. As shown in Table 1, under the catalysis of **6a**, the reaction between isatin **1a** and methyl α-isothiocyanatoacetate **2a** in toluene at rt for 24 h afforded the desired product **3** in 65% yield with a low dr ratio of 56:44 and poor ee value of 35% (entry 1). Replacing the methoxy group in **2a** with an oxazolidinone group **2b**[13] led to a dramatic improvement of the reactivity (entry 2); the reaction time was reduced to 3 h and the yield for **4** was improved to 90%. Moreover, although the dr was not much improved, the ee value of the product improved to 75% (entry 2). Higher diastereoselectivity (78:22) was achieved when two methyl groups were introduced onto the oxazolidinone moiety at the C4 position (**2c**, entry 3). The ee value of product **5a** was also improved to 88% (entry 3). Thus, among the three α-isothiocyanatoacetate derivatives, isothiocyanato imide **2c** provided the best stereocontrol in this reaction. A similar trend was also observed by Siedel and co-workers.[3c] Since **2c** yielded the best results, it was chosen as the model substrate in our further screening (Table 1).

Next, the other amine thiourea catalysts were screened. Cinchonine-derived thiourea **6b** gave very similar results to **6a** (entry 4). Quinine thiourea **6c**, the pseudo enantiomer of **6a**, gave almost exactly the same results as **6a**, with the exception that the major enantiomer obtained was the opposite to that obtained with **6a** (entry 5). Among these cinchona alkaloid thiourea congeners, cinchonidine thiourea **6d** was found to be superior to the other catalysts in terms of both the diastereoselectivity and enantioselectivity obtained for the product: **5a** was obtained in a dr ratio of 81:19 with 95% ee for the major diastereomer (entry 6). In contrast, cinchona alkaloid catalysts **6e–g** that did not carry a thiourea moiety all led to poor enantioselectivities (Table 1, entries 7–9), although the desired product was also obtained in high yields and with similar diastereoselectivities. Takemoto's thiourea **6h** was also screened in this reaction and good results were obtained (entry 10); nonetheless, the ee value obtained for the major diastereomer was slightly inferior to that with catalyst **6d**. In contrast, the less basic 1,1′-binaphthyl-2,2′-diamine-derived thiourea catalyst **6i** gave only trace amounts of the product (entry 11). These results indicate that the thiourea moiety is crucial for maintaining high enantioselectivity in this reaction. However, the diastereoselectivity of this reaction is largely independent of the catalyst structure (e.g., catalyst **6i** gives a similar dr as those cinchona alkaloid catalysts). With the best catalyst in hand, the solvent used in this reaction was optimized further. We found that the solvent did not have major influence on the enantioselectivity of the reaction (entries 12–18), but it did show some influence on the diastereoselectivity and the reaction rate. Among the common solvents screened, diethyl ether appeared to be the best, in which the highest dr, ee, and the reaction rate were obtained (entry 13). Conducting the reaction at a lower temperature (5 °C) under the optimized conditions proved to be counterproductive, since lower diastereoselectivity, enantioselectivity, and reaction rates were observed (entry 19)

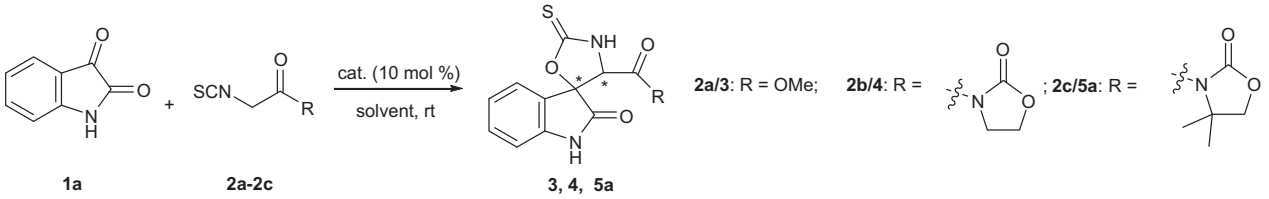
The reaction of **2c** with various isatin derivatives was then evaluated under optimized reaction conditions, and the results are summarized in Table 2. As shown by the results in Table 2, besides isatin **1a**, a number of substituted isatins bearing either an electron-withdrawing or an electron-donating group all gave high ee values of the desired products (⩾94% ee, entries 1–4; 6–9), with the exception of 5-bromoisatin, which produced a slightly lower ee value of 88% (entry 5). Furthermore, the product yields were almost quantitative in most cases. Although the substituents on the isatin aromatic ring did show some influence on the diastereoselectivity, the variation in diastereoselectivity is quite small. According to the data, both the substituent position on the phenyl ring and its electronic nature can exert some influence on the diastereoselectivity. For example, 4-bromoisatin **1c** (entry 3) gave a slightly higher dr than 5-bromoisatin **1e** (entry 5) and 6-bromoisatin **1g** (entry 7). As an example of the electronic effects, 5-methoxyisatin **1f** (entry 6) leads to a higher dr value of the product than 5-bromoisatin **1e** (entry 5) or 5-fluoroisatin **1d** (entry 4). Lower diastereoselectivity was obtained for the *N*-benzyl protected isatin **1i** (entry 9), which might be due to the steric effects.

In addition to isatins, some other activated carbonyl compounds were also studied (Scheme 1). The reaction of 4,4-dimethyldihydrofuran-2,3-dione **7** and **2c** under the optimized reaction conditions led to a high yield (91%) of the desired product **8**. The stereoselectivity of this reaction was also excellent (92:8 dr, 94% ee, Scheme 1, top equation). 1,2-Cyclohexanedione **9** is also an activated electrophile for enolate.[14] Its reaction with **2c** has also been studied.[15] Although the desired product **10** was obtained in a lower yield (51%) and mediocre diastereoselectivity (65:35), the ee value of the major enantiomer was excellent (90%, Scheme 1, lower equation).

The absolute configuration of the major enantiomer of compound **5a** obtained in the reactions between isatin **1a** and α-isothiocyanato imide **2c** was determined to be (3*R*,4′*S*) by X-ray crystallography analysis (Fig. 2).[17] The stereochemistry of the other products was assigned on the basis of the reaction mechanism.

On the basis of the stereochemistry of the major stereoisomer obtained herein and the previously reported mechanisms[10,16] for these bifunctional cinchona alkaloid-derived thioureas, a plausible mechanism of this reaction was proposed. As shown in Scheme 2, the tertiary amine in the cinchonidine-thiourea catalyst backbone first deprotonates one of the acidic α-protons from the imide **2c**. After deprotonation, **2c** closely associates with the catalyst through

Table 1
Catalyst screening and optimization of the reaction conditions[a]

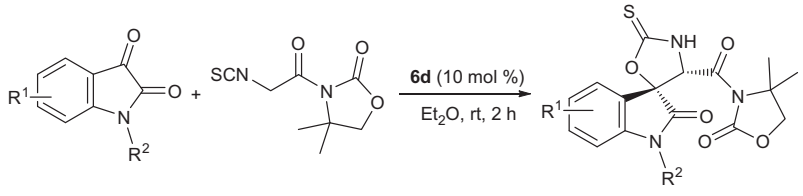


1a 2a-2c 3, 4, 5a

Entry	α-Isothiocyanato derivative	Catalyst	Solvent	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)	Configuration[e]
1	**2a**	**6a**	Toluene	24	65	56:44	35	nd[f]
2	**2b**	**6a**	Toluene	3	90	64:36	75	(3*S*,4′*R*)[g]
3	**2c**	**6a**	Toluene	3	98	78:22	88	(3*S*,4′*R*)
4	**2c**	**6b**	Toluene	3	99	76:24	86	(3*S*,4′*R*)
5	**2c**	**6c**	Toluene	3	99	77:23	88	(3*R*,4′*S*)
6	**2c**	**6d**	Toluene	3	99	81:19	95	(3*R*,4′*S*)
7	**2c**	**6e**	Toluene	5	90	74:26	43	(3*R*,4′*S*)
8	**2c**	**6f**	Toluene	5	98	83:17	52	(3*R*,4′*S*)
9	**2c**	**6g**	Toluene	5	99	73:27	51	(3*R*,4′*S*)
10	**2c**	**6h**	Toluene	2	99	80:20	90	(3*S*,4′*R*)
11	**2c**	**6i**	Toluene	24	0[h]	—	—	—
12	**2c**	**6d**	Xylene	6	97	75:25	93	(3*R*,4′*S*)
13	**2c**	**6d**	Et_2O	2	99	85:15	95	(3*R*,4′*S*)
14	**2c**	**6d**	Benzene	2	99	83:17	94	(3*R*,4′*S*)
15	**2c**	**6d**	CH_2Cl_2	2	99	70:30	95	(3*R*,4′*S*)
16	**2c**	**6d**	DME	5	97	85:15	95	(3*R*,4′*S*)
17	**2c**	**6d**	THF	3	98	81:19	89	(3*R*,4′*S*)
18	**2c**	**6d**	1,4-Dioxane	5	99	84:16	95	(3*R*,4′*S*)
19[i]	**2c**	**6d**	Et_2O	24	98	79:21	91	(3*R*,4′*S*)

[a] Unless otherwise specified, all reactions were performed with **2** (0.050 mmol), **1** (0.060 mmol, 1.2 equiv), and the catalyst (10 mol %) in the specified solvent (1.0 mL) at rt.
[b] Combined yield of both diastereomers after column chromatography.
[c] Determined by ^{1}H NMR analysis of the crude product.
[d] Determined by HPLC analysis using a ChiralCel OD-H column.
[e] Unless otherwise indicated, the absolute configuration of the product was determined by X-ray crystallography.
[f] Not determined.
[g] The absolute configuration of this product was assigned based on the reaction mechanism.
[h] Only trace amounts of the product were detected.
[i] The reaction was carried out at 5 °C.

Table 2
Reaction of isatin derivatives and **2c** as catalyzed by **6d**[a]

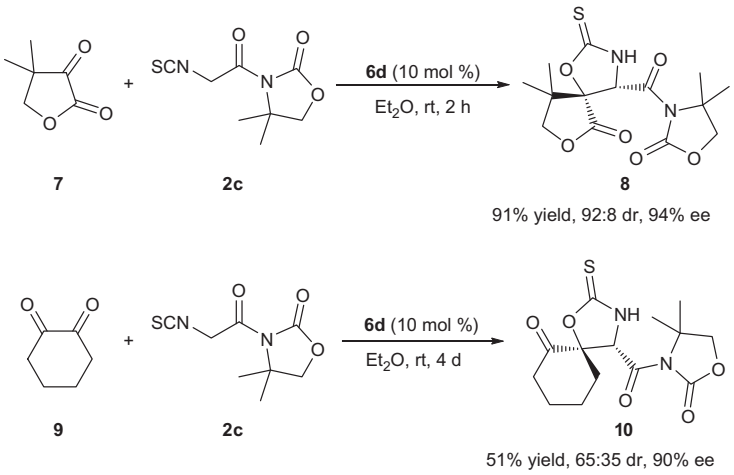


1 2c 5

Entry	R^1	R^2	1/5	Yield[b] (%)	dr[c]	ee[d]
1	H	H	**a**	98	85:15	95
2	4-Cl	H	**b**	95	78:22	98
3	4-Br	H	**c**	99	85:15	95
4	5-F	H	**d**	98	78:22	95
5	5-Br	H	**e**	90	81:19	88
6[e]	5-OMe	H	**f**	90	86:14	97
7	6-Br	H	**g**	98	80:20	95
8	4,7-diCl	H	**h**	96	85:15	96
9	H	Bn	**i**	99	70:30	94

[a] All reactions were conducted with **2** (0.050 mmol), **1** (0.060 mmol, 1.2 equiv), and catalyst **6d** (10 mol %) in Et_2O (1.0 mL) at rt.
[b] Combined yield of both diastereomers after column chromatography.
[c] Determined by ^{1}H NMR analysis of the crude product.
[d] Determined by HPLC analysis on a ChiralCel OD-H column.
[e] Reaction was carried out with 2 equiv of **1f**.

ionic interactions between the imide moiety and the ammonium. Simultaneously, two hydrogen bonds are formed between the two carbonyl groups of isatin and the thiourea moiety of the catalyst. In addition to activating the ketone group toward enolate attack, these hydrogen bonds also direct the orientation of isatin. Amongst the two possible orientations, the *si* face orientation is fa-



Scheme 1. Tandem aldol-cyclization reaction of activated carbonyl compounds with **2c** catalyzed by **6d**.

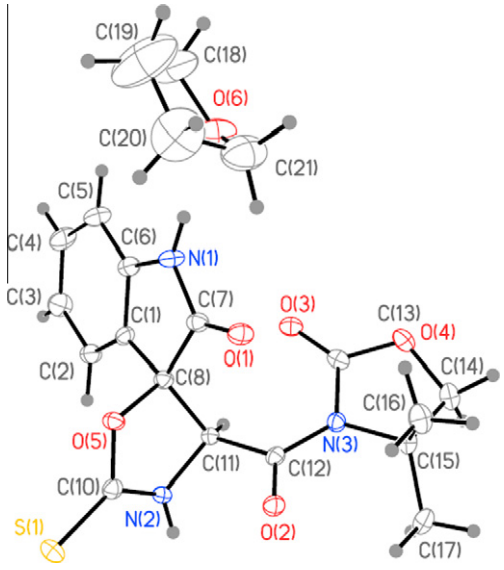


Figure 2. ORTEP drawing of compound **5a** (THF solvate).

vored (Scheme 2, top left) since unfavorable interactions between the isatin benzene ring and the oxazolidinone moiety of **2c** is avoided. The attack of the α-isothiocyanato imide from the back onto the *re* face of the isatin produces the product with the observed configuration (3*R*,4′*S*). In contrast, the *re* face orientation of the isatin (Scheme 1, bottom left) is disfavored due to the steric interactions. An intramolecular reaction between the hydroxy group of the resulting aldol intermediate and the isothiocyanate group affords the observed spirocyclic product **5a**. The observed improvement in the ee values of the products when the α-isothiocyanato imide is introduced with two methyl groups at the 4-position of the five-membered ring (Table 1, entries 2 and 3) may be rationalized with these proposed transition states, since an increase of the steric bulk at the oxazolidinone moiety further disfavors the *si* face attack.

3. Conclusion

In conclusion, we have demonstrated that the cinchonidine thiourea-catalyzed tandem aldol-cyclization reaction between 3-(2-isothiocyanatoacetyl)-4,4-dimethyloxazolidin-2-one **2c** and various activated carbonyl compounds is a facile method for the enantioselective synthesis of spirobicyclic thiocarbamates, which may be used for the synthesis of biologically active spiroindoline phytoalexin analogues.[10] The desired products can be obtained in high yields, excellent enantioselectivities, and with good diastereoselectivities.

4. Experimental

4.1. General

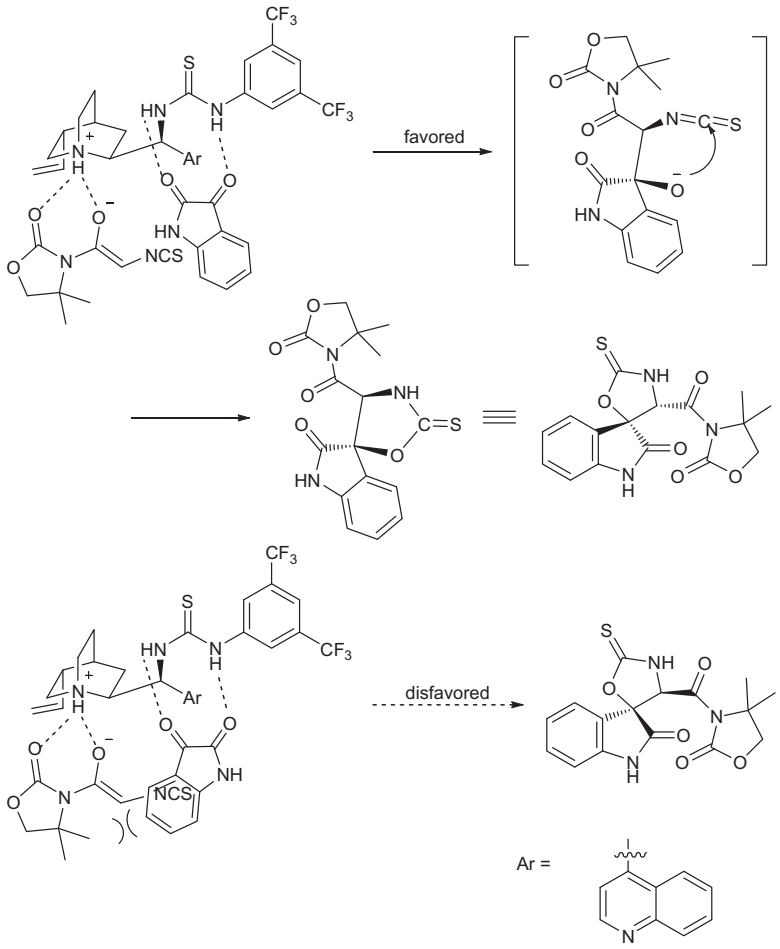
Unless otherwise noted, ^{1}H, and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer (75 MHz for ^{13}C). Melting points were recorded in open capillaries and are uncorrected. TLC was performed with silica gel GF_{254} precoated on plastic plates and spots were visualized with UV. Flash column chromatography was performed on silica gel. HPLC analysis was performed on a Shimadzu HPLC instrument equipped with a UV–Vis detector. ChiralCel and ChiralPak HPLC columns were purchased from Daicel Chemical Industry, Ltd Microanalyses were conducted by Atlantic Microlab, Inc (6180 Atlantic Blvd. Suite M, Norcross, Georgia 30071, USA). Compounds used herein were purchased from Aldrich, Alfa-Aesar, or TCI and were used as received. Catalysts **6a**–**d**,[18] **h**,[19] **i**[20] and isothiocyanate **2b**,[3c] **c**[3c] were prepared according to the literature procedures.

4.2. Representative procedure for the enantioselective tandem aldol-cyclization reaction of α-isothiocyanato imide 2c with isatins 1 using cinchonidine thiourea 6d as the catalyst

α-Isothiocyanato imide **2c** (10.7 mg, 0.050 mmol) and catalyst **6d** (2.8 mg, 0.005 mmol, 10 mol %) were dissolved in diethyl ether (1.0 mL) in a glass vial while stirring. Isatin **1a** (8.8 mg, 0.060 mmol) was added and the mixture was further stirred at room temperature for 2 h. The reaction progress was monitored by TLC analysis. Upon completion, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography on silica gel (1:1 hexane/ethyl acetate) to give the desired product.

4.2.1. (3R,4′S)-Ethyl 2-oxo-2′-thioxospiro[indoline-3,5′-oxazolidine]-4′-carboxylate 3

White solid; yield: 9.0 mg (65%); mp 108–111 °C; Mixture of two diastereomers: ^{1}H (300 MHz, acetone-d_6): δ = 3.41 and 3.56 (s, 3H), 5.08 and 5.29 (s, 1H), 7.01–7.69 (m, 4H), 9.61, 9.79 and



Scheme 2. Proposed transition states of the tandem aldol-cyclization reaction between isatin and **2c**.

9.94 (br, 2H); mixture of two diastereomers: ^{13}C (75 MHz, acetone-d_6): δ = 52.5 and 52.6, 64.3 and 64.5, 85.8 and 86.4, 111.2 and 111.4, 123.3 and 123.6, 125.4 and 125.8, 126.0, 132.5 and 132.6, 143.0 and 143.3, 167.2, 171.8 and 172.3, 188.2 and 188.7; ν_{max}: 1103, 1169, 1470, 1618, 1728, 1756, 3234 cm^{-1}. $[\alpha]_D^{25} = -34.7$ (*c* 0.27, MeOH), 35% ee. Anal. calcd for $C_{12}H_{10}N_2O_4S$: C, 51.79; H, 3.62; N, 10.07. Found: C, 52.01; H, 3.72; N, 9.87.

4.2.2. (3R,4′S)-4′-(2-Oxooxazolidine-3-carbonyl)-2′-thioxospiro[indoline-3,5′-oxazolidin]-2-one 4

White solid; yield: 15.1 mg (90%); mp 203–205 °C; ^{1}H (300 MHz, DMSO-d_6): δ = 3.79–4.03 (m, 2H), 4.37–4.52 (m, 2H), 5.48 (s, 1H), 6.88–7.39 (m, 4H), 10.88 (br, 2H); ^{13}C = (75 MHz, DMSO-d_6): δ = 42.38, 63.4, 63.9, 86.2, 110.6, 122.7, 123.0, 127.3, 131.4, 141.9, 154.1, 165.8, 169.3, 187.8; $[\alpha]_D^{25} = +129.1$ (*c* 0.18, MeOH), 75% ee. ν_{max}: 1033, 1173, 1241, 1398, 1470, 1538, 1734, 1762, 3216 cm^{-1}. HRMS calcd for $C_{14}H_{12}N_3O_5S$: 334.0498 (M+H); found: 334.0490.

4.2.3. (3R,4′S)-4′-(4,4-Dimethyl-2-oxooxazolidine-3-carbonyl)-2′-thioxospiro[indoline-3,5′-oxazolidin]-2-one 5a

White solid; yield: 17.8 mg (98%); m.p.167–169 °C; ^{1}H (300 MHz, acetone-d_6): δ = 1.60 (d, *J* = 6.3 Hz, 6H), 4.15 (d, *J* = 8.7 Hz, 1H), 4.20 (d, *J* = 8.7 Hz, 1H), 5.49 (s, 1H), 6.95–7.48 (m, 4H), 9.42 (s, 1H), 9.70 (s, 1H); ^{13}C (75 MHz, acetone-d_6): δ = 23.7, 24.0, 61.1, 65.1, 76.4, 87.3, 110.8, 123.1, 123.4, 128.3, 131.6, 142.5, 155.2, 166.9, 169.6, 189.7; ν_{max}: 1025, 1095, 1254, 1304, 1511, 1622, 1735, 1770, 3255 cm^{-1}. $[\alpha]_D^{25} = +89.0$ (*c* 0.87, THF) 95% ee. Enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using ChiralCel OD-H (hexanes: *i*-PrOH 90:10 at 1.0 mL/min), major isomer: t_R = 47.0 min, minor isomer: t_R = 97.5 min. HRMS calcd. for $C_{16}H_{15}N_3O_5S$: 362.0811 (M+1); found: 362.0807.

4.2.4. (3R,4′S)-4-Chloro-4′-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2′-thioxospiro[indoline-3,5′-oxazolidin]-2-one 5b

White solid; yield: 18.8 mg (95%); mp 188–190 °C; ^{1}H (300 MHz, acetone-d_6): δ = 1.58 (d, *J* = 6.3 Hz, 6H), 4.16 (s, 2H), 5.67 (s, 1H), 6.91–7.39 (m, 3H), 9.42 (s, 1H), 9.96 (s, 1H); ^{13}C (75 MHz, acetone-d_6): δ = 23.7, 23.9, 61.1, 64.0, 76.4, 87.5, 109.7, 123.7, 125.5, 130.7, 132.8, 144.8, 154.9, 166.6, 169.4, 188.3; ν_{max}: 1096, 1174, 1240, 1308, 1515, 1621, 1730, 1764, 3291 cm^{-1}. $[\alpha]_D^{25} = +63.1$ (*c* 1.04, THF), 98% ee. Enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using ChiralCel OD-H (hexanes/*i*-PrOH 90:10 at 1.0 mL/min), major isomer: t_R = 50.4 min, minor isomer: t_R = 84.8 min. HRMS calcd for $C_{16}H_{15}ClN_3O_5S$: 396.0421 (M+H); found: 396.0372.

4.2.5. (3R,4′S)-4-Bromo-4′-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2′-thioxospiro[indoline-3,5′-oxazolidin]-2-one 5c

White solid; yield: 21.8 mg (99%); mp 208–210 °C; ^{1}H (300 MHz, acetone-d_6): δ = 1.58 (d, *J* = 8.1 Hz, 6H), 4.16 (dd, *J* = 10.5, 8.7 Hz, 2H), 5.72 (s, 1H), 6.94–7.31 (m, 3H), 9.41 (s, 1H), 9.95 (s, 1H); ^{13}C (75 MHz, acetone-d_6): δ = 24.2, 24.5, 61.7, 64.6, 76.9, 88.6, 110.7, 119.3, 127.5, 127.8, 133.4, 145.6, 155.3, 167.1, 170.0, 188.8; ν_{max}: 1105, 1174, 1251, 1446, 1536, 1716, 1774,

3150 cm^{-1}. $[\alpha]_D^{25} = +73.7$ (*c* 0.99, MeOH), 95% ee. Enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using ChiralCel OD-H (hexanes/*i*-PrOH 90:10 at 1.0 mL/min), major isomer: t_R = 58.9 min, minor isomer: t_R = 95.1 min. Anal. calcd for $C_{16}H_{14}BrN_3O_5S$: C, 43.65; H, 3.21; N, 9.54. Found: C, 43.41; H, 3.03; N, 9.35.

4.2.6. (3R,4′S)-4′-(4,4-Dimethyl-2-oxooxazolidine-3-carbonyl)-5-fluoro-2′-thioxospiro[indoline-3,5′-oxazolidin]-2-one 5d

White solid; yield: 18.6 mg (98%); mp 194–196 °C; ^{1}H (300 MHz, DMSO-d_6): δ = 1.51 (d, *J* = 9.0 Hz, 6H), 4.15 (dd, *J* = 19.5, 9.0 Hz, 2H), 5.39 (s, 1H), 6.87–7.21 (m, 3H), 10.79 (b, 1H), 10.83 (s, 1H); ^{13}C (75 MHz, DMSO-d_6): δ = 23.6, 23.7, 60.5, 64.0, 75.7, 86.2, 110.7, 111.1, 111.5, 111.6, 117.6, 117.9, 128.5. 128.6, 138.4, 154.4, 166.1, 169.3, 187.6; ν_{max}: 1047, 1097, 1165, 1253, 1486, 1510, 1731, 1768, 3224 cm^{-1}. $[\alpha]_D^{25} = +95.2$ (*c* 0.45, THF), 95% ee. Enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using ChiralCel OD-H (hexanes/*i*-PrOH 92:8 at 1.0 mL/min), major isomer: t_R = 60.0 min, minor isomer: t_R = 92.4 min. Anal. calcd for $C_{16}H_{14}FN_3O_5S{\cdot}CH_3OH$: C, 49.63; H, 4.31; N, 10.31. Found: C, 49.44; H, 3.93; N, 10.67.

4.2.7. (3R,4′S)-5-Bromo-4′-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2′-thioxospiro[indoline-3,5′-oxazolidin]-2-one 5e

White solid; yield: 19.8 mg (90%); mp 209–211 °C; ^{1}H (300 MHz, acetone-d_6): δ = 1.59 (d, *J* = 2.7 Hz, 6H), 4.16 (dd, *J* = 15.0, 8.7 Hz), 5.55 (s, 1H), 6.95–7.62 (m, 3H), 9.34 (s, 1H), 9.87 (s, 1H); ^{13}C (75 MHz, acetone-d_6): δ = 24.3, 24.5, 61.7, 65.5, 77.0, 87.3, 113.4, 115.3, 127.0, 130.9, 135.0, 142.4, 155.8, 167.2, 169.8, 189.8; ν_{max}: 1025, 1183, 1254, 1472, 1508, 1731, 1765, 3229 cm^{-1}. $[\alpha]_D^{25} = +58.7$ (*c* 0.78, THF), 88% ee. Enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using ChiralCel OD-H (hexanes/*i*-PrOH 90:10 at 1.0 mL/min), major isomer: t_R = 35.5 min, minor isomer: t_R = 54.5 min. Anal. calcd for $C_{16}H_{14}BrN_3O_5S$: C, 43.65; H, 3.21; N, 9.54. Found: C, 43.41; H, 3.03; N, 9.28.

4.2.8. (3R,4′S)-4′-(4,4-Dimethyl-2-oxooxazolidine-3-carbonyl)-5-methoxy-2′-thioxospiro[indoline-3,5′-oxazolidin]-2-one 5f

White solid; yield: 17.6 mg (90%); mp 209–211 °C; ^{1}H (300 MHz, acetone-d_6): δ 1.59 (d, *J* = 5.1 Hz, 6H), 3.78 (s, 3H), 4.15 (dd, *J* = 13.5, 8.7 Hz, 2H), 5.51 (s, 1H), 6.86–7.07 (m, 3H), 9.22 (s, 1H), 9.53 (s, 1H); ^{13}C (75 MHz, acetone-d_6): δ = 24.3, 24.6, 56.2, 61.6, 65.6, 77.0, 88.2, 110.9, 112.0, 116.7, 129.8, 136.2, 155.7 156.9, 167.5, 170.1, 190.2; ν_{max}: 1186, 1254, 1397, 1509, 1700, 1770, 3256 cm^{-1}. $[\alpha]_D^{25} = +95.8$ (*c* 0.51, THF), 97% ee. Enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using ChiralCel OD-H (hexanes/*i*-PrOH 85:15 at 1.0 mL/min), major isomer: t_R = 24.4 min, minor isomer: t_R = 39.0 min. Anal. calcd for $C_{17}H_{17}N_3O_6S$: C, 52.07; H, 4.38; N, 10.74. Found: C, 51.66; H, 4.46; N, 10.35.

4.2.9. (3R,4′S)-6-Bromo-4′-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2′-thioxospiro[indoline-3,5′-oxazolidin]-2-one 5g

White solid; yield: 21.6 mg (98%); mp 211–212 °C; ^{1}H (300 MHz, acetone-d_6): δ = 1.62 (d, *J* = 2.7 Hz, 6H), 4.16 (dd, *J* = 15.6, 8.4 Hz, 2H), 5.51 (s, 1H), 7.16–7.43 (m, 3H), 9.34 (s, 1H), 9.93 (s, 1H); ^{13}C (75 MHz, acetone-d_6): δ = 24.3, 24.5, 61.6, 65.5, 77.0, 87.2, 114.6, 125.2, 125.7, 126.5, 128.1, 144.6, 155.8, 167.2, 170.0, 190.0; ν_{max}: 1100, 1188, 1246.48, 1499, 1610, 1732, 1779, 3143 cm^{-1}. $[\alpha]_D^{25} = +117.4$ (*c* 0.45, THF), 97% ee. Enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using ChiralCel OD-H (hexanes/*i*-PrOH 90:10 at 1.0 mL/min), major isomer: t_R = 48.8 min, minor isomer: t_R = 81.5 min. Anal. calcd for $C_{16}H_{14}BrN_3O_5S$: C, 43.65; H, 3.21; N, 9.54. Found: C, 43.40; H, 3.05; N, 9.45.

4.2.10. (3R,4′S)-4,7-Dichloro-4′-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2′-thioxospiro[indoline-3,5′-oxazolidin]-2-one 5h

White solid; yield: 20.5 mg (96%); mp 214–216 °C; ^{1}H (300 MHz, acetone-d_6): δ = 1.58 (d, *J* = 9.0 Hz, 6H), 4.18 (s, 2H), 5.68 (s, 1H), 7.14–7.47 (m, 2H), 9.50 (s, 1H), 10.33 (s, 1H); ^{13}C (75 MHz, DMSO-d_6): δ = 23.7, 23.8, 60.6, 63.5, 75.8, 86.7, 113.8, 124.3, 124.8, 126.1, 128.2, 142.2, 154.5, 165.8, 169.3, 186.6; ν_{max}: 1107, 1163, 1249, 1317, 1507, 1613, 1772, 3241 cm^{-1}. $[\alpha]_D^{25} = +78.3$ (*c* 0.54, THF), 96% ee. Enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using ChiralCel OD-H (hexanes/*i*-PrOH 92:8 at 1.0 mL/min), major isomer: t_R = 69.5 min, minor isomer: t_R = 107.6 min. HRMS calcd for $C_{16}H_{14}C_{l2}N_3O_5S$: 430.0031 (M+H); found: 430.0026.

4.2.11. (3R,4′S)-1-Benzyl-4′-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2′-thioxospiro[indoline-3,5′-oxazolidin]-2-one 5i

White solid; yield: 22.3 mg (99%); mp 124–125 °C; ^{1}H (300 MHz, acetone-d_6): δ = 1.62 (d, *J* = 8.7 Hz, 6H), 4.18 (dd, *J* = 12.9, 8.7 Hz, 2H), 4.96 (dd, *J* = 27.3, 15.9 Hz, 2H), 5.57 (s, 1H), 6.91–7.53 (m, 9H), 9.33 (s, 1H), ^{13}C (75 MHz, acetone-d_6): δ = 25.0, 25.2, 45.3, 62.3, 66.1, 66.2, 77.7, 88.2, 111.6, 124.5, 125.0, 128.9, 129.0, 130.1, 132.8, 137.0, 144.7, 155.4, 168.1, 169.9, 190.8; ν_{max}: 1030, 1154, 1245, 1611, 17034, 1766, 3240 cm^{-1}. $[\alpha]_D^{25} = +87.0$ (*c* 0.87, THF), 94% ee. Enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using ChiralCel OD-H (hexanes/*i*-PrOH 85:15 at 1.0 mL/min), major isomer: t_R = 31.0 min, minor isomer: t_R = 50.5 min. Anal. calcd for $C_{23}H_{21}N_3O_5S$: C, 61.18; H, 4.69; N, 9.31. Found: C, 60.96; H, 4.66; N, 9.20.

4.2.12. (4S,5R)-4-(4,4-Dimethyl-2-oxooxazolidine-3-carbonyl)-8,8-dimethyl-2-thioxo-1,7-dioxa-3-aza-spiro[4.4]nonan-6-one 8

White solid; yield: 15.6 mg (91%); mp 208–210 °C; ^{1}H (300 MHz, acetone-d_6): δ = 1.24 (s, 3H), 1.39 (s, 3H), 1.57 (s, 6H), 4.22 (m, 4H), 5.76 (s, 1H), 9.05 (s, 1H); ^{13}C (75 MHz, acetone-d_6): δ = 21.7, 21.8, 24.0, 24.5, 44.5, 61.9, 62.1, 76.8, 77.7, 92.9, 155.4, 168.1, 170.3, 190.1; ν_{max}: 1009, 1091, 1156, 1240, 1348.16, 1499, 1705, 1787, 3201 cm^{-1}. $[\alpha]_D^{25} = +62.3$ (*c* 0.90, THF), 94% ee. Enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using ChiralCel OD-H (hexanes/*i*-PrOH 92:8 at 1.0 mL/min), major isomer: t_R = 65.4 min, minor isomer: t_R = 56.8 min. Anal. calcd for $C_{14}H_{18}N_2O_6S$: C, 49.11; H, 5.30; N, 8.18. Found: C, 49.14; H, 5.29; N, 8.07.

4.2.13. (4S,5R)-4-(4,4-Dimethyl-2-oxooxazolidine-3-carbonyl)-8,8-dimethyl-2-thioxo-1,7-dioxa-3-aza-spiro[4.4]nonan-6-one 10

Foam; yield: 8.5 mg (52%); ^{1}H (300 MHz, $CDCl_3$): δ = 0.88–2.78 (m, 14H), 4.10 (dd, *J* = 17.4, 8.3 Hz, 1H), 4.93 (s, 1H), 7.81 (s, 1H); ^{13}C (75 MHz, $CDCl_3$): δ = 20.8, 23.8, 25.0, 26.2, 38.8, 39.8, 61.5, 64.3, 76.4, 95.7, 154.8, 169.9, 187.8, 201.0; ν_{max}: 1030, 1180, 1240, 1377, 1497, 1707, 1767 cm^{-1}. $[\alpha]_D^{25} = +47.9$ (*c* 1.04, THF), 90% ee. Enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using ChiralCel OD-H (hexanes/*i*-PrOH 90:10 at 1.0 mL/min), major isomer: t_R = 26.3 min, minor isomer: t_R = 56.1 min. HRMS calcd for $C_{14}H_{19}N_2O_5S$: 327.1015 (M+H); found: 327.1009.

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