# cis-Diastereoselective Synthesis of Spirooxindolo-β-Lactams by Staudinger Cycloaddition with TsCl as Activating Co-reagent

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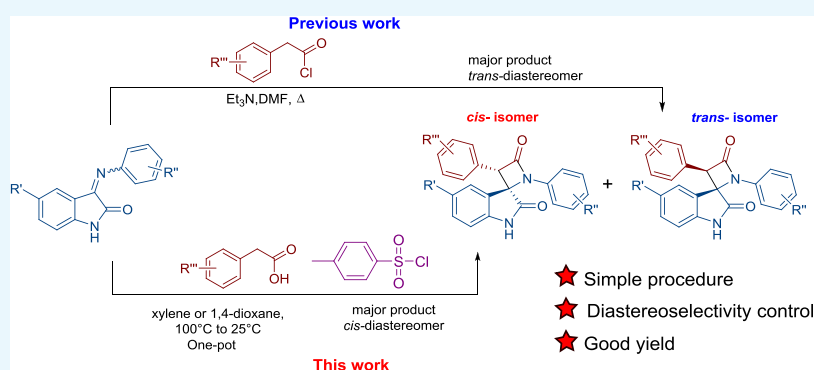
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**ABSTRACT:** A convenient and versatile one-pot method for synthesis of 1,3-bis-aryl spirooxindolo-β-lactams from isatin Schiff bases and substituted phenylacetic acids using ketene−imine cycloaddition reaction with TsCl for a ketene generation has been developed. The reaction procedure does not require absolute solvents and unstable starting reagents. The studied reactions lead to cis-diastereoselective β-lactam formation for all tested phenylacetic acids except $4\text{-MeOC}_6\text{H}_4\text{CH}_2\text{COOH}$. An increase of trans-diastereomers yields with increasing temperature and solvent polarity was demonstrated.

## INTRODUCTION

The research of small-molecule inhibitors (SMIs) for targeted therapy, despite being carried out for several decades, is a hot topic of organic and medicinal chemistry.[1,2] Drugs based on SMIs using different means of delivery or specific mechanisms of action cause less or no harm to ordinary healthy cells compared to conventional chemotherapy.[3,4] These agents are usually more potent since targeting specific protein targets critical for tumor survival is much more efficient than chemotherapy based on regular cytotoxic agents. In addition, this field of study is greatly expanded by a vast diversity of potential targets.[5,6]

Among a great variety of targets, the MDM2 protein for over a decade has kept the attention of researchers engaged in design and synthesis of SMIs.[7−9] This protein, being an endogenous inhibitor of the "genome guardian" cellular protein p53, regulates SMI levels, keeping it at moderate and thus preventing early cell aging. On the other hand, in cancer cells, the MDM2 protein can be overexpressed. This leads to a complete elimination of p53, which in turn leads to further breach of the cell cycle and provides a suitable environment for cancer proliferation.[10,11] Consequently, blocking of p53−MDM2 interaction by inhibition of the MDM2 active site is considered a favorable therapeutic strategy. A released p53 is

expected to restore the cell cycle or initiate an apoptotic sequence in cancer cells.[12,13]

The most popular approach for design of MDM2 inhibitors is imitation of the structural fragment of the p52 protein responsible for complementary binding to MDM2.[14] This fragment (Trp23) has led to the development of multiple classes of spirooxindoles since indoline-2-one has a good compatibility with the active site of MDM2, and spiroconjugation provides the capacity for further functionalization and conformational stability.[13,15] For more than a decade, a large number of reports have been published presenting many novel classes of spirooxindoles derived through diverse synthesis pathways, including the reactions of 1,3-dipolar cycloaddition.[15−18] However, there are only some cases of successful advances through clinical trials. For instance, the phase I study of spirooxindole SAR405838 (Figure 1a) developed by Sanofi in patients with solid tumours was recently reported by de
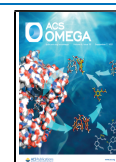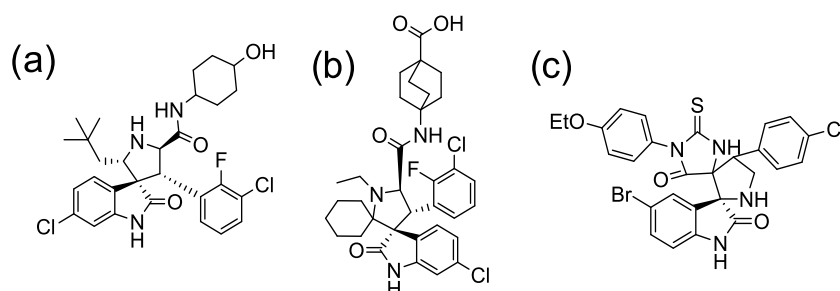
**Figure 1.** Spirooxindoles SAR405838[17] (a) and APG-115[21] (b) on clinical trials; spirooxindole KM-140[15,22] successfully passing the preclinical trials (c). The structures are depicted by the authors of this article based on the results presented in relevant publications.

**Scheme 1. Previously Reported Methods for Synthesis of 1,3-Diaryl-spiro[azetidine-2,3-indoline]-2,4-diones**
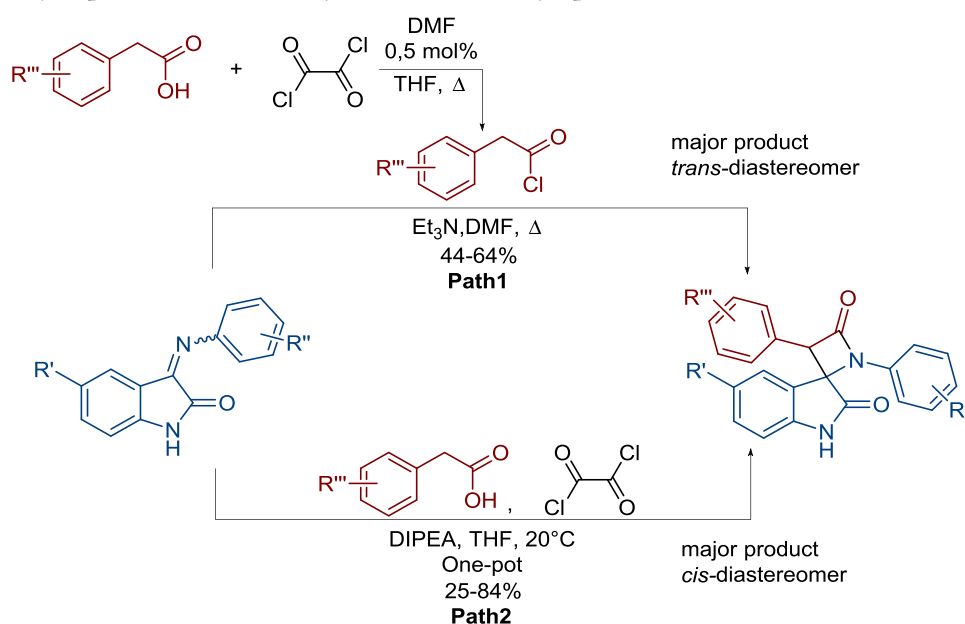


**Scheme 2. Synthesis of 1,3-Diaryl-spiro[azetidine-2,3-indoline]-2,4-diones Using TsCl**
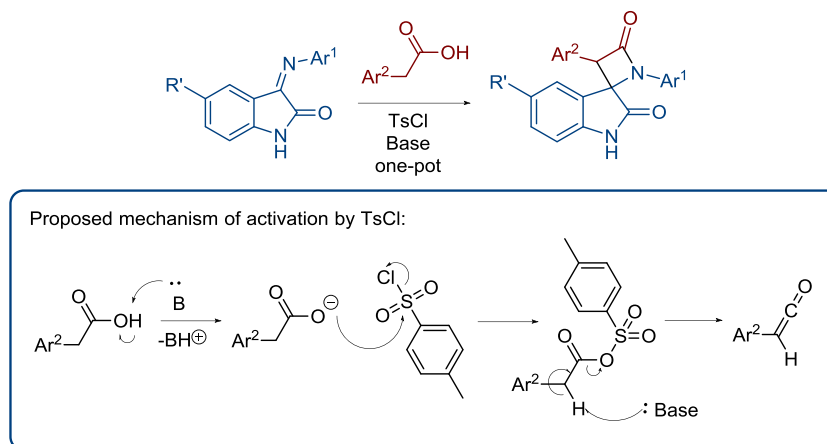


Weger and co-workers.[19] As another example of dispirooxindoles, APG-115 (Figure 1b) antitumor activity in patients with unresectable or metastatic melanomas and advanced solid tumors has been reported.[20]

Recently we have developed a new structure class of 1,3-diaryl-spiro[azetidine-2,3-indoline]-2,4-diones displaying a great potential as inhibitors of MDM2 in molecular docking studies. It was demonstrated that only *cis*-diastereomer shows a considerable affinity to the binding site of MDM2. We have also reported several synthesis methods for creation of the desired spiroconjugation including a novel one-pot reaction of imines with substituted phenylacetic acids activated by oxalyl chloride[23] (Scheme 1). The conventional approach of imine's reaction with ketene formed in situ from acylchloride has provided a series of designed spirooxindoles (Scheme 1, Path 1). Yet, the diastereoselectivity was inclined heavily towards
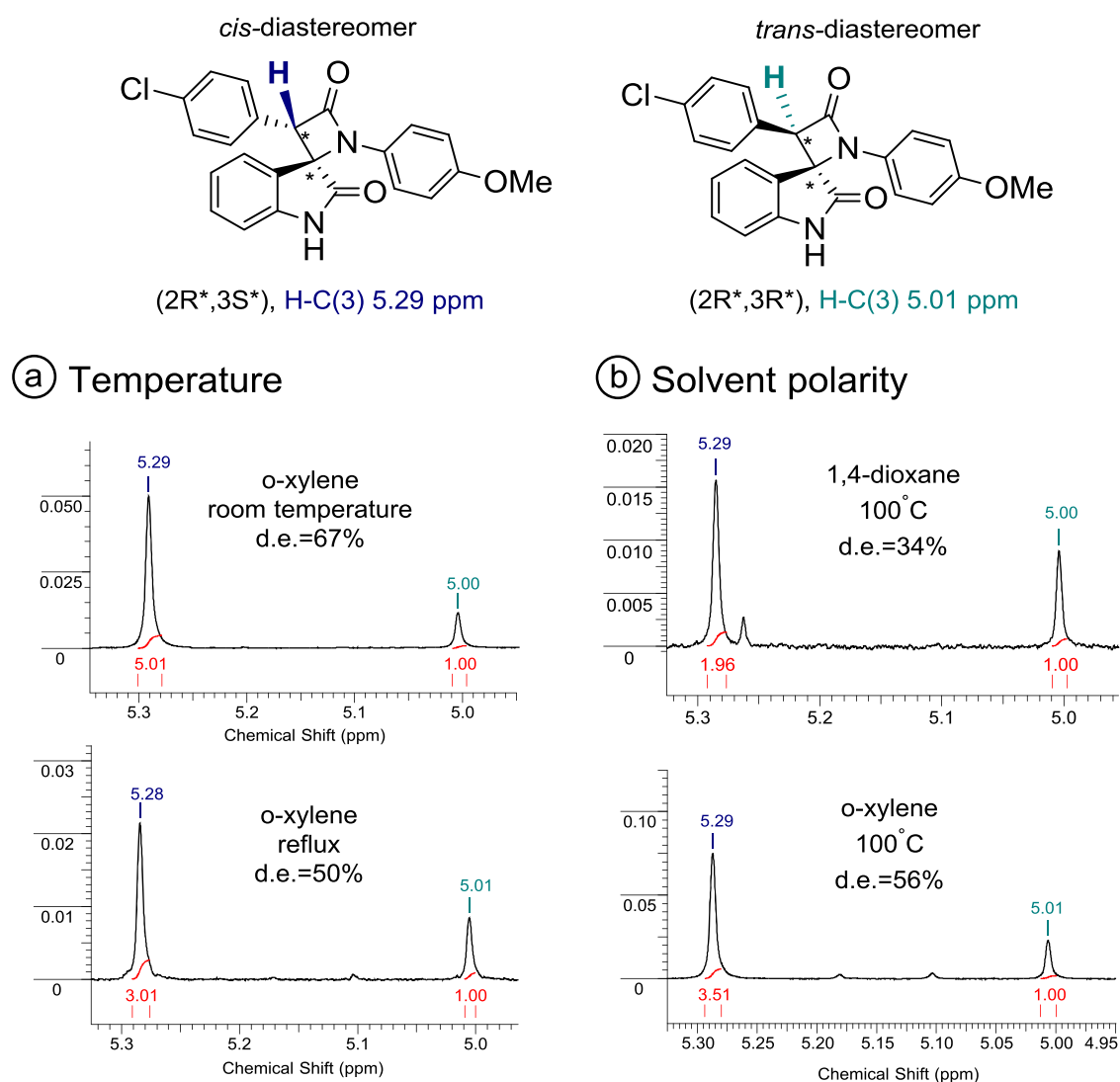
**Figure 2.** Characteristic signals of H-C(3) of the azetidin ring displaying diastereomer ratio with (a) change of temperature and (b) change of solvent polarity.

the *trans*-diastereomer, which was less desirable according to molecular modeling. The one-pot approach (Scheme 1, Path 2) provided a favorable diastereoselectivity, but due to the high reactivity of oxalyl chloride, the applicability of these reactions was severely restricted.
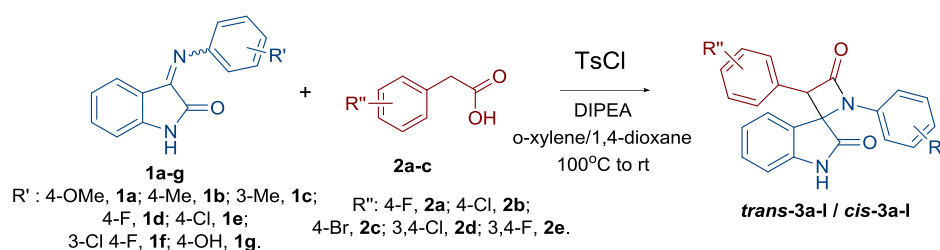
### ■ RESULTS AND DISCUSSION

In our current study, we implemented TsCl as a substitute for oxalyl chloride. Since mixed anhydrides of 4-toluene sulfonic acid and carboxylic acids are known to be relatively stable,[24−27] the formation of ketene is expected to proceed more slowly, providing a more simple procedure. TsCl is known as an activation co-reagent in β-lactam ring formation reactions.[28−32]

Our study commenced with application of the methodology previously used for reactions with oxalyl chloride.[23] To derive a desired spirooxindol-β-lactam, we stirred a mixture of 4-chlorophenyl isatinimine, 4-chlorophenylacetic acid, TsCl, and diisopropyl ethyl amine in tetrahydrofuran (THF) at room temperature for 24 h (Scheme 2). Alternatively, we carried out the same procedure at reflux. It was found out that the reactions either proceed at a very slow rate or give a very low yield, or both. Thus, we carried out the preliminary formation

of a mixed anhydride from 4-chlorophenylacetic acid and tosyl chloride in the presence of tertiary amine as a base at 120 °C, followed by cooling and addition of imine with another equivalent of base at room temperature. Thus, we were able to obtain the desired spiro-β-lactams **3i**, although the reaction still proceeded with the formation of both *cis*- and *trans*-diastereomers.

To optimize the reaction in terms of better yield and diastereoselectivity, we carried out a series of reactions of 4-methoxyphenyl isatinimine with TsCl and 4-chlorophenyl-acetic acid in *o*-xylene at room temperature, at 110 °C and reflux. Each reaction yielded a mixture of diastereomers; yet, according to the NMR spectra of the reaction mixtures, depending on the temperature the isomer ratio shifted notably. At room temperature, the *cis*-isomer prevails over the *trans*-isomer. But at temperatures above 100 °C, the content of *trans*-isomers increases significantly. This could be easily traced by the change of intensities of the characteristic signals of amide protons of the isatin fragment, and the more distinct H-C(3)-protons of the azetidin ring in the corresponding NMR spectra (Figure 2). Additionally, we found that at the same temperature, the reaction carried out in more polar solvents,

**Scheme 3. Diastereoselective One-Pot Synthesis of *cis*-1,3-Diaryl-spiro[azetidine-2,3-indoline]-2,4-diones from Isatin Schiff Bases 1a–g, Substituted Phenylacetic Acids, and TsCl**



**1a–g**
R' : 4-OMe, **1a**; 4-Me, **1b**; 3-Me, **1c**; 4-F, **1d**; 4-Cl, **1e**; 3-Cl 4-F, **1f**; 4-OH, **1g**.

**2a–c**
R'': 4-F, **2a**; 4-Cl, **2b**; 4-Br, **2c**; 3,4-Cl, **2d**; 3,4-F, **2e**.

TsCl
DIPEA
o-xylene/1,4-dioxane
100 °C to rt

***trans*-3a-l / *cis*-3a-l**

| | R' | R'' | ratio* trans-/cis-trans | yield, % trans | yield, % cis | | R' | R'' | ratio* trans-/cis-trans | yield, % trans | yield, % cis |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 3a | 4-OMe | 4-F | 1/2.7 | – | 69 | 3g | 4-Me | 3,4-F | 1/5.3 | – | 37 |
| 3b | 4-OMe | 4-Cl | 1/2.2 | 20 | 67 | 3h | 3-Me | 4-Cl | 1/1.7 | – | 22 |
| 3c | 4-OMe | 4-Br | 1/5.4 | 12 | 67 | 3i | 4-Cl | 4-Cl | 1/2.9 | – | 42 |
| 3d | 4-OMe | 3,4-Cl | 1/16 | – | 59 | 3j | 4-Cl | 4-Br | 1/1.9 | – | 20 |
| 3e | 4-Me | 4-Cl | 1/1.5 | – | 34 | 3k | 3-Cl-4-F | 4-Br | 1/1.9 | 3 | 21 |
| 3f | 4-Me | 4-Br | 1/4 | – | 65 | 3l | 4-OH | 4-Cl | 1/5.3 | 5 | 24 |

such as 1,4-dioxane, yields a higher content of *trans*-isomers than observed in the less polar *o*-xylene. This tendency was observed for reactions in DCM, THF, and MeCN, though the low solubility of imine leads to slow kinetics and a high content of side products hinders quantitative NMR analysis of the reaction media.

A correlation between the structure of the isomers and NMR signals was confirmed by X-ray analysis of the compounds ***cis*-3f**, ***cis*-3k**, and ***trans*-3i** crystals (see the Supporting Information). Thus, further reactions for preferential formation of *cis*-spiro-β-lactams were carried out in *o*-xylene at room temperature.

For the synthesis of 1,3-diaryl-spiro[azetidine-2,3-indoline]-2,4-diones, we carried out reactions of different isatin Schiff bases **1a–g** and substituted phenylacetic acids **2a–c**. Schiff bases **1a–g** as *E/Z* isomer mixtures were prepared according to previously published methods[18,33–36] (Scheme 3).

For 4-hydroxyphenyl isatinimine, due to its bad solubility in xylenes, the reactions were carried out in 1,4-dioxane. In all cases, the mixtures of *cis/trans*-isomers of the desired spiro-β-lactams were obtained, with predominant or exclusive preparative release of *cis*-isomers from the reaction mixtures by column chromatography. The yields of the target spiro-β-lactams **3a–l** varied from moderate for imines with more electron-withdrawing substitutes to good for imines with electron-donating substitutes.

To explain the formation of both diastereomers and the correlations between the isomer ratio and the reaction conditions, an analysis of the reaction mechanism may be considered (Scheme 4). The principles of Staudinger β-lactam synthesis have been recently thoroughly studied by Cossio and co-workers.[37] First, the formation of both diastereomers is possible due to the existence of both isomers of the initial Schiff base and significantly depends on the *Z/E*-ratio of the starting imines. However, the *cis/trans*-ratio of the reaction products never directly correlated with the *Z/E*-ratio of the starting imines, meaning other factors were involved. For instance, a decrease of *cis*-diastereomer content with increase of temperature can be explained by the *EZ*-zwitterionic intermediate gaining enough energy to proceed with cyclization into *trans*-β-lactam instead of isomerization into the *ZZ*-zwitterion cyclizing into *cis*-β-lactam. The solvent polarity dependence can be explained by the assumption that a more polar solvent better stabilizes zwitterionic intermediates, restricting the *ZZ*-zwitterion from spontaneous cyclization and thus enabling it to isomerize into *EZ*-zwitterion, which in turn can cyclize into *trans*-spiro-β-lactam. In addition, according to quantum calculations carried out in our previous work[23] and the current experimental data, *cis*-diastereomer should be considered a kinetic product of *E*-imine. Meanwhile, for *Z*-imine, the kinetic product is the *trans*-diastereomer of spirooxindolo-β-lactam. An important point is that thermodynamic control is hardly applicable since the calculated difference between the free energies of *cis/trans*-diastereomers is less than 0.5 kcal/mol.

Note especially the results obtained for the reaction of 4-methoxyphenylacetic acid with the series of isatinimines, where the diastereoselectivity was inverse to that observed for reactions of other phenylacetic acids (Scheme 5). The obtaining of ketene–imine cycloaddition products for 4-

**Scheme 4. Possible Mechanism of Spirooxindolo-$\beta$-Lactam Formation**
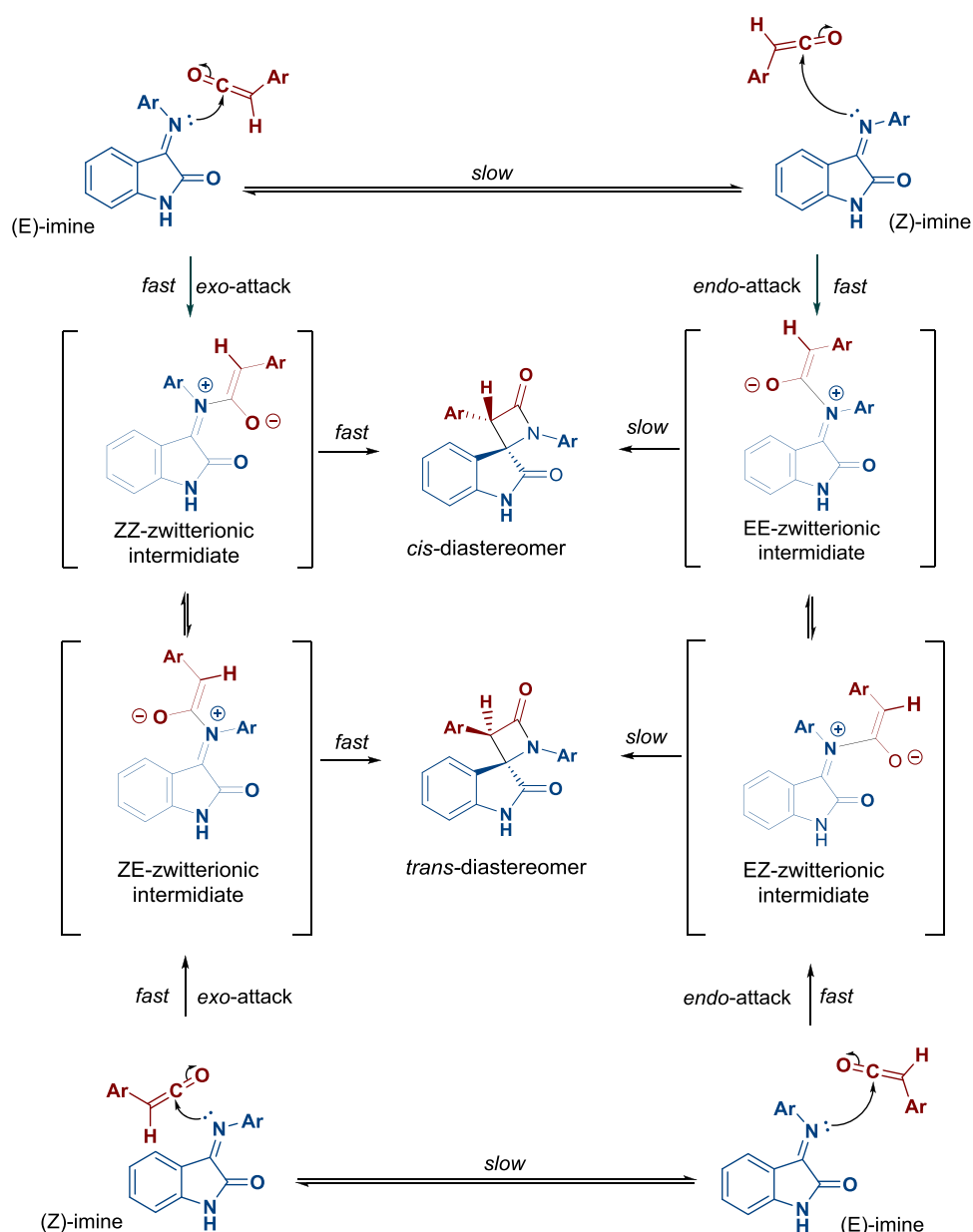


methoxyphenylacetic acid was a good result in itself since Staudinger synthesis of $\beta$-lactams involving 4-methoxyphenyl ketene previously required the use of $\alpha$-diazoketone[37,38] or included an additional step of acyl halide formation,[39] or in the case of isatinimines, required a protective group on the amide nitrogen.[40] Still more important is the fact that the diastereoselectivity of the reactions surprisingly became completely the opposite of what we have observed for any other substituted phenylacetic acid since the *trans*-diaster-eomer was a major product even at room temperature. However, a tendency of increase of *trans*-isomer content with increase of temperature and solvent polarity still existed, similar to the pattern observed for other substituted phenyl-acetic acids.
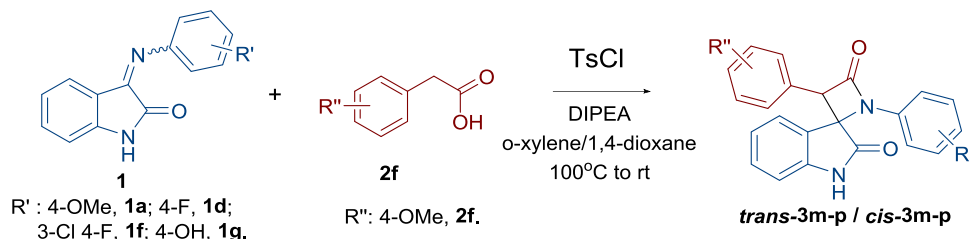
## ■ CONCLUSIONS

Summing up, we developed an easy and convenient method for bis-aryl spirooxindolo-$\beta$-lactam synthesis suitable for

starting izatines and phenylacetic acids with different substitutes. The proposed technique provides the target products with reasonable *cis*-diastereoselectivity for the most tested phenylacetic acids. A phenylacetic acid with electron-donating substituent (4-MeOC$_6$H$_4$CH$_2$COOH) was first employed in a one-pot Staudinger synthesis with $\beta$-lactam ring formation, and in this case, *trans*-spirooxindolo-$\beta$-lactams were obtained as the main products. The main advantages of the proposed synthesis technique include (1) the first proposed use of tosyl chloride instead of oxalyl chloride for the ketene generation in Staudinger reaction in the synthesis of spiro-$\beta$-lactams; (2) the course of this reaction with the predominant obtaining of 1,3-diaryl-spiro[azetidine-2,3-indo-line]-2,4-diones with *cis*-configuration.

The developed technique may be useful as a method of diastereoselective synthesis of *cis*-spiro-$\beta$-lactams, complement-ing the previously known method of using *trans*-diastereose-lective materials for such reactions.

**Scheme 5. Diastereoselective Synthesis of *trans*-Spiro-β-lactams from 4-Methoxyphenylacetic Acid and Isatinimines**



R' : 4-OMe, **1a**; 4-F, **1d**;
3-Cl 4-F, **1f**; 4-OH, **1g**.

R'': 4-OMe, **2f**.

*trans*-**3m-p** / *cis*-**3m-p**

| | R' | R'' | ratio* trans-/cis- | yield, % trans | cis |
|---|---|---|---|---|---|
| **3m** | —OMe | —OMe | 2/1 | 26 | 22 |
| **3n** | —F | —OMe | 2.6/1 | 51 | - |
| **3o** | Cl, F | —OMe | 4.2/1 | 20 | 21 |
| **3p** | —OH | —OMe | 4/1 | 11 | - |

## ■ EXPERIMENTAL SECTION

**General Information.** All solvents used were purified and dehydrated using the methods described in ref 41. All starting reagents were purchased from Sigma-Aldrich. Microwave-heated reactions were performed using a Monowave 300—Anton Paar reactor in sealed glass vessels with external temperature control. The reactions were analyzed by TLC analysis using silica plates with a fluorescent indicator (254 nm) and visualized with a UV lamp. $^1$H and $^{13}$C NMR spectra were recorded using a Bruker Avance spectrometer (400 MHz for $^1$H, 100 MHz for $^{13}$C) in DMSO-$d_6$. Chemical shifts are reported in parts per million relative to TMS. Electrospray ionization high-resolution mass spectra were recorded in positive ion mode using a TripleTOF 5600+ quadrupole time-of-flight mass spectrometer (ABSciex, Concord, Canada) equipped with a DuoSpray ion source. The following MS parameters were applied: capillary voltage 5.5 kV; nebulizing and curtain gas pressure 15 and 25 psi, respectively; ion source temperature—ambient; declustering potential 20 V; m/z range 100−1200. Elemental compositions of the detected ions were determined based on accurate masses and isotopic distributions using Formula Finder software (ABSciex, Concord, Canada). The maximum allowed deviation of the experimental molecular mass from the calculated one was 5 ppm.

The data of *cis*-**3f**, *cis*-**3k**, and *trans*-**3i** were collected at room temperature using an STOE diffractometer Pilatus100K detector, focusing on mirror collimation Cu Kα (1.54086 Å) radiation, in rotation method mode. STOE X-AREA software was used for cell refinement and data reduction. Data collection and image processing were performed with X-Area 1.67 (STOE & Cie GmbH, Darmstadt, Germany, 2013). Intensity data were scaled with LANA (part of X-Area) in order to minimize the differences in intensities of symmetry-equivalent reflections (multiscan method).

Structures were Solved with SHELXT and Refined with SHELX (14a). The non-hydrogen atoms (for both substances) were refined using the anisotropic full-matrix least-squares procedure. All hydrogen atoms were placed in the calculated positions and allowed to ride on their parent atoms [C−H 0.93−0.98; Uiso 1.2 Ueq (parent atom)].

CCDC-2084190 (*cis*-**3f**), 2084191 (*cis*-**3k**), and 2084193 (*trans*-**3i**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. website.

**Synthesis Procedures.** General procedure for synthesis of isatinimines.

*General Procedure A.*[36] Aromatic amine (11 mmol) was added into a boiling solution of isatin (10 mmol) in 25 mL of absolute ethanol containing a few drops of glacial acetic acid. The reaction mixture was refluxed for 3 h. The completion was checked by TLC. After the cooling of the reaction mixture to room temperature, it was filtered under reduced pressure. The precipitate was washed with cold EtOH (5 mL), then dried.

*General Procedure B.*[35] A suspension of aromatic amine (11 mmol) and isatin (10 mmol) in 15 mL of absolute MeOH containing a few drops of glacial acetic acid was stirred under microwave irradiation for 15 min at 70 °C (the power is adjusted automatically). The reaction completion was checked by TLC. After the cooling of the reaction mixture to room temperature, it was filtered under reduced pressure. The precipitate was washed twice with cold Et$_2$O (5 mL), then dried.

*3-((4-Methoxyphenyl)imino)indolin-2-one (1a).*[18] A reaction between 4-methoxyaniline (1355 mg, 11 mmol) and isatin (1471 mg, 10 mmol) yields 3-((4-methoxyphenyl)imino)-indolin-2-one as an orange solid (2346 mg, 93%, E/Z = 5.23/1).

(E) ^{1}H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.96 (s, 1H), 7.34 (td, J = 7.70, 1.22 Hz, 1H), 7.04 (d, J = 8.99 Hz, 2H), 6.98 (d, J = 8.99 Hz, 2H), 6.89 (d, J = 7.76 Hz, 1H), 6.75 (td, J = 7.63, 0.89 Hz, 1H), 6.65 (d, J = 7.64 Hz, 1H), 3.80 (s, 3H).

(Z) ^{1}H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.85 (s, 1H), 7.55 (d, J = 7.40 Hz, 1H), 7.41 (td, J = 7.70, 1.22 Hz, 1H), 7.18 (d, J = 8.86 Hz, 2H), 6.96−7.06 (m, 1H), 6.88−6.91 (m, 2H), 6.84 (d, J = 7.76 Hz, 1H), 3.77 (s, 3H).

*3-(p-Tolylimino)indolin-2-one (1b).*[42] A reaction between p-toluidine (1178 mg, 11 mmol) and isatin (1471 mg, 10 mmol) yields 3-(p-tolylimino)indolin-2-one as an orange solid (2055 mg, 87%, E/Z = 6.25/1).

(E) ^{1}H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.94 (br. s., 1H), 7.33 (t, J = 7.73 Hz, 1H), 7.27 (d, J = 8.07 Hz, 2H), 6.88 (d, J = 8.13 Hz, 3H), 6.73 (t, J = 7.64 Hz, 1H), 6.47 (d, J = 7.70 Hz, 1H), 2.35 (s, 3H).

(Z) ^{1}H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.94 (br. s., 1H), 7.55−7.59 (m, 1H), 7.43 (t, J = 7.70 Hz, 1H), 7.11 (d, J = 8.13 Hz, 2H), 7.05 (t, J = 7.55 Hz, 1H), 6.95 (d, J = 8.07 Hz, 2H), 6.84 (s, 1H), 2.30 (s, 2H).

*3-(m-Tolylimino)indolin-2-one (1c).*[43] A reaction between m-toluidine (1178 mg, 11 mmol) and isatin (1471 mg, 10 mmol) yields 3-(m-tolylimino)indolin-2-one as a yellow solid (1914 mg, 81%, E/Z = 7.5/1).

(E) ^{1}H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.98 (s, 1H), 7.29−7.38 (m, 2H), 7.06 (d, J = 7.46 Hz, 1H), 6.89 (d, J = 7.82 Hz, 1H), 6.69−6.81 (m, 3H), 6.38 (d, J = 7.64 Hz, 1H), 2.33 (s, 3H).

(Z) ^{1}H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.86 (s, 1H), 7.57 (d, J = 7.46 Hz, 1H), 7.44 (td, J = 7.73, 1.10 Hz, 1H), 7.18 (t, J = 7.64 Hz, 1H), 7.01−7.09 (m, 1H), 6.84−6.94 (m, 2H), 6.68−6.81 (m, 2H), 2.28 (s, 3H).

*3-((4-Fluorophenyl)imino)indolin-2-one (1d).*[18] A reaction between 4-fluoroaniline (1222 mg, 11 mmol) and isatin (1471 mg, 10 mmol) yields 3-((4-fluorophenyl)imino)indolin-2-one as a yellow solid (2066 mg, 86%, E/Z = 4.5/1).

(E) ^{1}H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.99 (s, 1H), 7.27−7.38 (m, 3H), 7.01−7.07 (m, 2H), 6.90 (d, J = 7.82 Hz, 1H), 6.76 (t, J = 7.70 Hz, 1H), 6.43 (d, J = 7.70 Hz, 1H).

(Z) ^{1}H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.87 (s, 1H), 7.58 (d, J = 7.34 Hz, 1H), 7.45 (td, J = 7.70, 1.10 Hz, 1H), 7.27−7.38 (m, 1H), 7.07−7.17 (m, 3H), 6.86 (d, J = 7.82 Hz, 1H).

*3-((4-Chlorophenyl)imino)indolin-2-one (1e).*[33] A reaction between 4-chloroaniline (1403 mg, 11 mmol) and isatin (1471 mg, 10 mmol) yields 3-((4-chlorophenyl)imino)indolin-2-one as an orange solid (2258 mg, 88%, E/Z = 4/1).

(E) ^{1}H NMR (400 MHz, DMSO-$d_6$) δ ppm 11.00 (s, 1H), 7.52 (d, J = 8.56 Hz, 2H), 7.33−7.39 (m, 1H), 7.01−7.10 (m, 2H), 6.90 (d, J = 7.76 Hz, 1H), 6.77 (t, J = 7.64 Hz, 1H), 6.43 (d, J = 7.70 Hz, 1H).

(Z) ^{1}H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.90 (s, 1H), 7.59 (d, J = 7.46 Hz, 1H), 7.46 (t, J = 7.67 Hz, 1H), 7.33−7.39 (m, 2H), 7.01−7.09 (m, 3H), 6.87 (d, J = 7.95 Hz, 1H).

*3-((3-Chloro-4-fluorophenyl)imino)indolin-2-one (1f).*[44] A reaction between 3-chloro-4-fluoroaniline (1601 mg, 11 mmol) and isatin (1471 mg, 10 mmol) yields 3-((3-chloro-4-fluorophenyl)imino)indolin-2-one as a bright orange solid (2500mg, 91%, E/Z = 2.4/1).

(E) ^{1}H NMR (400 MHz, DMSO-$d_6$) δ ppm 11.01 (s, 1H), 7.51 (t, J = 8.99 Hz, 1H), 7.26−7.39 (m, 2H), 7.00−7.08 (m, 1H), 6.90 (d, J = 7.82 Hz, 1H), 6.78 (t, J = 7.64 Hz, 1H), 6.46 (d, J = 7.64 Hz, 1H).

(Z) ^{1}H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.90 (s, 1H), 7.57 (d, J = 7.46 Hz, 1H), 7.45 (t, J = 7.76 Hz, 1H), 7.26−7.39 (m, 2H), 7.00−7.08 (m, 2H), 6.86 (d, J = 7.82 Hz, 1H).

*3-((4-Hydroxyphenyl)imino)indolin-2-one (1g).*[45] A reaction between 4-aminophenol (1200 mg, 11 mmol) and isatin (1471 mg, 10 mmol) yields 3-((4-hydroxyphenyl)imino)-indolin-2-one as a red solid (2239 mg, 94%, E/Z = 4.8/1).

(E) ^{1}H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.92 (br. s., 1H), 9.55 (br. s., 1H), 7.30−7.36 (m, 1H), 6.81−6.90 (m, 5H), 6.70−6.80 (m, 2H).

(Z) ^{1}H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.82 (br. s., 1H), 9.55 (br. s., 1H), 7.53 (d, J = 7.34 Hz, 1H), 7.39 (t, J = 7.70 Hz, 1H), 7.17 (d, J = 8.68 Hz, 2H), 7.03 (t, J = 7.52 Hz, 1H), 6.82−6.91 (m, 1H), 6.70−6.79 (m, 2H).

*General Procedure for Synthesis of Spirooxindolo-β-lactams 3a−p.* A solution of phenylacetic acid (1.5 mmol) and DIPEA (1.5 mmol) in 15 mL of dry o-xylene powdered TsCl (2 mmol) was stirred at room temperature. The resultant mixture was heated to 100 °C, stirred for 1.5 h at 100 °C, and then cooled down to room temperature. An additional DIPEA (1.5 mmol) was added, the mixture was stirred for 5 minutes, and then isatinimine 1 (1 mmol) was added. The reaction mixture was stirred at room temperature until the reaction completion by TLC. The solvent was evaporated under reduced pressure to afford a viscous oily residue, which was then purified by column chromatography on silica gel using a hexane−ethyl acetate mixture (4:1) as an eluent (in all cases, the cis-isomer has a higher chromatographic mobility). The eluent was evaporated under reduced pressure, and fractions corresponding to cis- and trans-diastereomers of 3 were recrystallized from diethyl ether, resulting in white solids.

In the cases of the reactions with 4-hydroxyphenyl isatinimine 1g, 1,4-dioxane was used as a solvent instead of o-xylene and the column chromatography was carried using hexane−ethyl acetate mixture (2:1) as an eluent.

When only one product is given in the description of the experimental results, the minor isomer was not isolated and its formation and content in the reaction solution were determined from the NMR data of the reaction mixtures (see the main text of the article).

*(2R\*,3S\*)-3-(4-Fluorophenyl)-1-(4-methoxyphenyl)spiro-[azetidine-2,3′-indoline]-2′,4-dione (cis-3a).* A reaction of 2-(4-fluorophenyl)acetic acid (231 mg, 1.5 mmol), 4-toluene-sulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-((4-methoxyphenyl)imino)-indolin-2-one (252 mg, 1 mmol) yields 268 mg (69%) of spiro-b-lactam as a white solid.

^{1}H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.82 (s, 1H), 7.64 (d, J = 7.46 Hz, 1H), 7.37 (t, J = 7.73 Hz, 1H), 7.07−7.23 (m, 5H), 6.98 (d, J = 7.95 Hz, 3H), 6.87−6.91 (m, 2H), 5.26 (s, 1H), 3.66 (d, J = 0.79 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-$d_6$) δ ppm 172.75, 163.85, 162.99, 160.56, 160.34, 156.02, 141.88, 130.72, 130.63, 130.54, 129.87, 127.69, 127.66, 124.56, 124.42, 122.66, 117.86, 115.27, 115.06, 114.75, 110.78, 66.23, 64.57, 55.26.

HRMS (ESI) calcd for $C_{23}H_{18}FN_2O_3^+$ [M + H$^+$]: 389.1296; found, 389.1303.

*(2R\*,3S\*)-3-(4-Chlorophenyl)-1-(4-methoxyphenyl)spiro-[azetidine-2,3′-indoline]-2′,4-dione (cis-3b).* A reaction of 2-(4-chlorophenyl)acetic acid (256 mg, 1.5 mmol), 4-toluene-sulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-((4-methoxyphenyl)imino)-

indolin-2-one (252 mg, 1 mmol) yields 271 mg (67%) of spiro-*b*-lactam as a white solid.

$^1$H NMR (400 MHz, CHLOROFORM-d) δ ppm 10.84 (s, 1H), 7.64 (d, *J* = 7.34 Hz, 1H), 7.36−7.41 (m, 3H), 7.17 (d, *J* = 8.44 Hz, 2H), 7.11 (t, *J* = 7.52 Hz, 1H), 6.95−7.00 (m, 3H), 6.87−6.91 (m, 2H), 5.29 (s, 1H), 3.66 (s, 3H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ ppm 172.69, 163.57, 156.05, 141.89, 132.67, 130.79, 130.55, 130.18, 129.83, 128.34, 124.62, 124.33, 122.69, 117.87, 114.76, 110.84, 66.13, 64.36, 55.27.

HRMS (ESI) calcd for $C_{23}H_{18}ClN_2O_3^+$ [M + H$_+$]: 405.1000; found, 405.0999.

*(2R\*,3R\*)-3-(4-Chlorophenyl)-1-(4-methoxyphenyl)spiro[azetidine-2,3′-indoline]-2′,4-dione (trans-3b).* A reaction of 2-(4-chlorophenyl)acetic acid (256 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-((4-methoxyphenyl)imino)indolin-2-one (252 mg, 1 mmol) yields 81 mg (20%) of spiro-*b*-lactam as a white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 11.09 (s, 5H) 7.34 (d, *J* = 8.44 Hz, 12H) 7.18−7.25 (m, 18H) 6.86−7.00 (m, 30H) 6.68−6.74 (m, 12H) 5.01 (s, 6H), 3.66 (s, 18H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ ppm 174.90, 163.31, 156.18, 142.48, 132.65, 130.90, 130.65, 129.80, 128.57, 125.35, 121.83, 121.31, 117.94, 114.77, 110.78, 65.39, 63.32, 55.28.

HRMS (ESI) calcd for $C_{23}H_{18}ClN_2O_3^+$ [M + H$^+$]: 405.1000; found, 405.0998.

*(2R\*,3S\*)-3-(4-Bromophenyl)-1-(4-methoxyphenyl)spiro[azetidine-2,3′-indoline]-2′,4-dione (cis-3c).* A reaction of 2-(4-bromophenyl)acetic acid (323 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-((4-methoxyphenyl)imino)indolin-2-one (252 mg, 1 mmol) yields 301 mg (67%) of spiro-*b*-lactam as a white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.84 (s, 1H), 7.64 (d, *J* = 7.34 Hz, 1H), 7.52 (d, *J* = 8.38 Hz, 2H), 7.38 (td, *J* = 7.72, 1.07 Hz, 1H), 7.07−7.14 (m, 3H), 6.94−7.01 (m, 3H), 6.85−6.92 (m, 2H), 5.27 (s, 1H), 3.66 (s, 3H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ ppm 172.68, 163.50, 156.05, 141.89, 131.26, 130.97, 130.79, 130.46, 129.82, 124.62, 124.32, 122.69, 121.28, 117.87, 114.76, 110.84, 66.06, 64.39, 55.27.

HRMS (ESI) calcd for $C_{23}H_{18}BrN_2O_3^+$ [M + H$^+$]: 449.0495; found, 449.0499.

*(2R\*,3R\*)-3-(4-Bromophenyl)-1-(4-methoxyphenyl)spiro[azetidine-2,3′-indoline]-2′,4-dione (trans-3c).* A reaction of 2-(4-bromophenyl)acetic acid (323 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-((4-methoxyphenyl)imino)indolin-2-one (252 mg, 1 mmol) yields 54 mg (12%) of spiro-*b*-lactam as a white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 11.10 (s, 1H), 7.47 (d, *J* = 8.44 Hz, 2H), 7.13−7.24 (m, 3H), 6.96−7.00 (m, 2H), 6.94 (d, *J* = 7.76 Hz, 1H), 6.86−6.91 (m, 2H), 6.68−6.74 (m, 2H), 5.00 (s, 1H), 3.66 (s, 3H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ ppm 174.90, 163.26, 156.18, 142.49, 131.48, 131.29, 130.95, 130.67, 129.80, 125.37, 121.85, 121.31, 121.29, 117.94, 114.77, 110.79, 65.32, 63.39, 55.28.

HRMS (ESI) calcd for $C_{23}H_{18}BrN_2O_3^+$ [M + H$^+$]: 449.0495; found, 449.0492.

*(2R\*,3S\*)-3-(3,4-Dichlorophenyl)-1-(4-methoxyphenyl)-spiro[azetidine-2,3′-indoline]-2′,4-dione (cis-3d).* A reaction

of 2-(3,4-dichlorophenyl)acetic acid (308 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-((4-methoxyphenyl)imino)indolin-2-one (252 mg, 1 mmol) yields 259 mg (59%) of spiro-*b*-lactam as a white solid.

$^1$H NMR (400 MHz, CHLOROFORM-d) δ ppm 10.89−10.93 (m, 1H), 7.65 (d, *J* = 7.34 Hz, 1H), 7.60 (d, *J* = 8.31 Hz, 1H), 7.37−7.42 (m, 2H), 6.96−7.02 (m, 3H), 6.87−6.92 (m, 2H), 5.34 (s, 1H), 3.67 (s, 3H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ ppm 174.67, 162.81, 156.28, 142.58, 132.99, 131.16, 130.83, 130.10, 129.70, 129.64, 129.14, 125.43, 121.91, 121.12, 118.12, 118.01, 114.76, 110.89, 65.33, 62.60, 55.29.

HRMS (ESI) calcd for $C_{23}H_{17}Cl_2N_2O_3^+$ [M + H$^+$]: 439.0611; found, 439.0607.

*(2R\*,3S\*)-3-(4-Chlorophenyl)-1-(p-tolyl)spiro[azetidine-2,3′-indoline]-2′,4-dione (cis-3e).* A reaction of 2-(4-chlorophenyl)acetic acid (256 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-(p-tolylimino)indolin-2-one (236 mg, 1 mmol) yields 132 mg (34%) of spiro-*b*-lactam as a white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.87 (s, 1H), 7.64 (d, *J* = 7.27 Hz, 1H), 7.36−7.42 (m, 3H), 7.07−7.20 (m, 5H), 7.01 (d, *J* = 7.76 Hz, 1H), 6.90 (d, *J* = 7.58 Hz, 1H), 6.59 (d, *J* = 8.50 Hz, 1H), 5.32 (s, 1H), 2.21 (s, 3H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ ppm 172.61, 163.84, 141.83, 134.14, 133.65, 132.70, 130.79, 130.46, 130.17, 129.86, 128.36, 124.60, 124.31, 122.69, 116.12, 110.86, 65.96, 64.31, 20.42.

HRMS (ESI) calcd for $C_{23}H_{18}ClN_2O_2^+$ [M + H$^+$]: 389.1051; found, 389.1051.

*(2R\*,3S\*)-3-(4-Bromophenyl)-1-(p-tolyl)spiro[azetidine-2,3′-indoline]-2′,4-dione (cis-3f).* A reaction of 2-(4-bromophenyl)acetic acid (323 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-(p-tolylimino)indolin-2-one (236 mg, 1 mmol) yields 282 mg (65%) of spiro-*b*-lactam as a white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.85 (s, 1H), 7.63 (d, *J* = 7.46 Hz, 1H), 7.52 (d, *J* = 8.38 Hz, 2H), 7.38 (td, *J* = 7.73, 1.16 Hz, 1H), 7.06−7.13 (m, 5H), 7.00 (d, *J* = 7.76 Hz, 1H), 6.92 (d, *J* = 8.38 Hz, 2H), 5.29 (s, 1H), 2.19 (s, 3H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ ppm 172.61, 163.78, 141.83, 134.14, 133.66, 131.28, 130.88, 130.80, 130.44, 129.86, 124.60, 124.31, 122.70, 121.31, 116.13, 110.87, 65.89, 64.35, 20.43.

HRMS (ESI) calcd for $C_{23}H_{17}BrN_2O_2^+$ [M + H$^+$]: 433.0546; found, 433.0541.

*(2R\*,3S\*)-3-(3,4-difluorophenyl)-1-(p-tolyl)spiro[azetidine-2,3′-indoline]-2′,4-dione (cis-3g).* A reaction of 2-(3,4-difluorophenyl)acetic acid (258 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-(p-tolylimino)-indolin-2-one (236 mg, 1 mmol) yields 144 mg (37%) of spiro-*b*-lactam as a white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.90 (s, 1H), 7.63 (d, *J* = 7.40 Hz, 1H), 7.35−7.44 (m, 2H), 7.19 (ddd, *J* = 11.31, 7.95, 1.65 Hz, 1H), 7.07−7.13 (m, 3H), 7.00 (d, *J* = 7.76 Hz, 2H), 6.92 (d, *J* = 8.38 Hz, 2H), 5.32 (s, 1H), 2.19 (s, 3H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ ppm 172.59, 163.58, 141.83, 134.03, 133.78, 130.87, 129.88, 125.78, 125.74, 125.70,

125.69, 124.67, 124.13, 122.75, 117.63, 117.55, 117.46, 117.37, 116.20, 110.91, 65.98, 63.83, 20.42.

HRMS (ESI) calcd for $C_{23}H_{17}F_2N_2O_2^+$ [M + H$^+$]: 391.1253; found, 391.1254.

*(2R\*,3S\*)-3-(4-Chlorophenyl)-1-(m-tolyl)spiro[azetidine-2,3′-indoline]-2′,4-dione (cis-3h).* A reaction of 2-(4-chlorophenyl)acetic acid (256 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-(m-tolylimino)indolin-2-one (236 mg, 1 mmol) yields 86 mg (22%) of spiro-b-lactam as a white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.87 (s, 1H), 7.64 (d, J = 7.27 Hz, 1H), 7.36−7.42 (m, 3H), 7.07−7.20 (m, 5H), 7.01 (d, J = 7.76 Hz, 1H), 6.90 (d, J = 7.58 Hz, 1H), 6.59 (d, J = 8.50 Hz, 1H), 5.32 (s, 1H), 2.21 (s, 3H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ ppm 172.56, 164.10, 141.79, 138.98, 136.58, 132.73, 130.83, 130.38, 130.17, 129.35, 128.37, 125.13, 124.61, 124.33, 122.73, 117.06, 112.75, 110.84, 65.98, 64.27, 21.13.

HRMS (ESI) calcd for $C_{23}H_{18}ClN_2O_2^+$ [M + H$^+$]: 389.1051; found, 389,1043.

*(2R\*,3S\*)-1,3-bis(4-Chlorophenyl)spiro[azetidine-2,3′-indoline]-2′,4-dione (cis-3i).* A reaction of 2-(4-chlorophenyl)-acetic acid (256 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-((4-chlorophenyl)imino)indolin-2-one (257 mg, 1 mmol) yields 172 mg (42%) of spiro-b-lactam as a white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.91 (s, 1H), 7.68 (d, J = 7.34 Hz, 1H), 7.36−7.44 (m, 5H), 7.17 (d, J = 8.38 Hz, 2H), 7.12 (t, J = 7.58 Hz, 1H), 6.98−7.06 (m, 3H), 5.38 (s, 1H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ ppm 172.27, 164.14, 141.83, 135.27, 132.80, 130.95, 130.10, 129.59, 128.38, 128.18, 124.70, 123.81, 122.78, 117.68, 110.98, 66.13, 64.62.

HRMS (ESI) calcd for $C_{22}H_{15}Cl_2N_2O_2^+$ [M + H$^+$]: 409.0505; found, 409,0494.

*(2R\*,3S\*)-3-(4-Bromophenyl)-1-(4-chlorophenyl)spiro-[azetidine-2,3′-indoline]-2′,4-dione (cis-3j).* A reaction of 2-(4-bromophenyl)acetic acid (323 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-((4-chlorophenyl)imino)-indolin-2-one (257 mg, 1 mmol) yields 91 mg (20%) of spiro-b-lactam as a white solid.

$^1$H NMR (400 MHz, CHLOROFORM-d) δ ppm 10.92 (s, 1H), 7.68 (d, J = 7.34 Hz, 1H), 7.53 (d, J = 8.44 Hz, 2H), 7.38−7.43 (m, 3H), 7.08−7.14 (m, 3H), 6.99−7.04 (m, 3H), 5.36 (s, 1H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ ppm 172.30, 164.11, 141.84, 135.29, 131.34, 131.00, 130.58, 130.40, 129.63, 128.20, 124.75, 123.81, 122.82, 121.43, 117.69, 111.02, 66.08, 64.65.

HRMS (ESI) calcd for $C_{22}H_{15}BrClN_2O_2^+$ [M + H$^+$]: 453.0000; found, 452.9997.

*(2R\*,3S\*)-3-(4-Bromophenyl)-1-(3-chloro-4-fluorophenyl) spiro[azetidine-2,3′-indoline]-2′,4-dione (cis-3k).* A reaction of 2-(4-bromophenyl)acetic acid (323 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), diisopropylethyl-amine (520 μL, 388 mg, 3 mmol), and 3-((3-chloro-4-fluorophenyl)imino)indolin-2-one (275 mg, 1 mmol) yields 99 mg (21%) of spiro-b-lactam as a white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.95 (s, 1H), 7.71 (d, J = 7.40 Hz, 1H), 7.53 (d, J = 8.44 Hz, 2H), 7.36−7.44 (m, 3H), 7.08−7.16 (m, 3H), 7.02 (d, J = 7.82 Hz, 1H), 6.71−6.76 (m, 1H), 5.41 (s, 1H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ ppm 172.13, 164.22, 141.88, 133.50, 133.47, 131.36, 131.17, 130.38, 124.91, 123.45, 122.91, 121.48, 120.45, 120.26, 118.31, 118.21, 116.05, 115.98, 111.04, 66.30, 64.79.

HRMS (ESI) calcd for $C_{22}H_{14}BrClFN_2O_2^+$ [M + H$^+$]: 470.9906; found, 470.9896.

*(2R\*,3R\*)-3-(4-Bromophenyl)-1-(3-chloro-4-fluorophenyl) spiro[azetidine-2,3′-indoline]-2′,4-dione (trans-3k).* A reaction of 2-(4-bromophenyl)acetic acid (323 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), diisopropylethyl-amine (520 μL, 388 mg, 3 mmol), and 3-((3-chloro-4-fluorophenyl)imino)indolin-2-one (275 mg, 1 mmol) yields 14 mg (3%) of spiro-b-lactam as a white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 11.20 (s, 1H), 7.48 (d, J = 8.44 Hz, 2H), 7.38−7.44 (m, 2H), 7.24 (td, J = 7.58, 1.41 Hz, 1H), 7.19 (d, J = 8.44 Hz, 2H), 6.97 (d, J = 7.76 Hz, 1H), 6.69−6.80 (m, 3H), 5.12 (s, 1H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ ppm 174.30, 163.96, 142.48, 140.36, 131.52, 131.03, 130.75, 125.59, 122.03, 121.50, 120.46, 120.27, 118.46, 118.30, 116.11, 116.03, 110.96, 65.55, 63.92,

HRMS (ESI) calcd for $C_{22}H_{14}BrClFN_2O_2^+$ [M + H$^+$]: 470.9906; found, 470.9901.

*(2R\*,3S\*)-3-(4-Chlorophenyl)-1-(4-hydroxyphenyl)spiro-[azetidine-2,3′-indoline]-2′,4-dione (cis-3l).* A reaction of 2-(4-chlorophenyl)acetic acid (256 mg, 1.5 mmol), 4-toluene-sulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-((4-hydroxyphenyl)imino)-indolin-2-one (238 mg, 1 mmol) yields 94 mg (24%) of spiro-b-lactam as a white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.79 (s, 1H), 9.44 (s, 1H), 7.63 (d, J = 7.29 Hz, 1H), 7.32−7.43 (m, 3H), 7.17 (d, J = 8.39 Hz, 2H), 7.10 (t, J = 7.56 Hz, 1H), 6.97 (d, J = 7.73 Hz, 1H), 6.88 (d, J = 8.82 Hz, 2H), 6.68 (d, J = 8.88 Hz, 2H), 5.24 (s, 1H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ ppm 172.77, 163.39, 154.38, 141.86, 132.62, 130.69, 130.65, 130.18, 128.46, 128.30, 124.55, 124.49, 122.64, 118.24, 115.84, 110.78, 66.17, 64.33.

HRMS (ESI) calcd for $C_{22}H_{16}ClN_2O_3^+$ [M + H$^+$]:391,0844; found, 391,0846.

*(2R\*,3R\*)-3-(4-Chlorophenyl)-1-(4-hydroxyphenyl)spiro-[azetidine-2,3′-indoline]-2′,4-dione (trans-3l).* A reaction of 2-(4-chlorophenyl)acetic acid (256 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), diisopropylethyl-amine (520 μL, 388 mg, 3 mmol), and 3-((4-hydroxyphenyl)-imino)indolin-2-one (238 mg, 1 mmol) yields 20 mg (5%) of spiro-b-lactam as a white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 11.05 (s, 1H), 9.46 (s, 1H), 7.33 (d, J = 8.44 Hz, 2H), 7.14−7.25 (m, 3H), 6.83−6.96 (m, 3H), 6.63−6.75 (m, 4H), 4.97 (s, 1H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ ppm 175.03, 163.17, 154.54, 142.46, 132.63, 131.02, 130.65, 128.56, 128.46, 125.34, 121.80, 121.48, 118.30, 115.86, 110.75, 65.44, 63.27.

HRMS (ESI) calcd for $C_{22}H_{16}ClN_2O_3^+$ [M + H$^+$]: 391,0844; found, 391,0844.

*(2R\*,3S\*)-1,3-bis(4-Methoxyphenyl)spiro[azetidine-2,3′-indoline] -2′,4-dione (cis-3m).* A reaction of 2-(4-methoxyphenyl)acetic acid (249 mg, 1.5 mmol), 4-toluene-sulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-((4-methoxyphenyl)imino)-

indolin-2-one (252 mg, 1 mmol) yields 88 mg (22%) of spiro-*b*-lactam as a white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.73 (s, 1H), 7.61 (d, *J* = 7.34 Hz, 1H), 7.36 (td, *J* = 7.73, 1.08 Hz, 1H), 7.06–7.11 (m, 3H), 6.95–7.00 (m, 3H), 6.84–6.91 (m, 4H), 5.16 (s, 1H), 3.72 (s, 3H), 3.67 (s, 3H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ ppm 175.23, 164.08, 158.83, 156.07, 142.43, 130.42, 130.14, 130.00, 125.43, 123.57, 121.76, 121.69, 117.85, 114.73, 113.90, 110.64, 65.72, 64.04, 55.26, 55.01.

HRMS (ESI) calcd for $C_{24}H_{21}N_2O_4^+$ [M + H$^+$]: 401.1496; found, 401.1490.

*(2R\*,3R\*)-1,3-bis(4-Methoxyphenyl)spiro[azetidine-2,3′-indoline]-2′,4-dione (trans-3m).* A reaction of 2-(4-methoxyphenyl)acetic acid (249 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-((4-methoxyphenyl)imino)-indolin-2-one (252 mg, 1 mmol) yields 104 mg (26%) of spiro-*b*-lactam as a white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 11.05 (s, 1H), 7.19 (td, *J* = 7.54, 0.82 Hz, 1H), 7.13 (d, *J* = 8.55 Hz, 2H), 6.98 (d, *J* = 8.99 Hz, 2H), 6.93 (d, *J* = 7.73 Hz, 1H), 6.88 (d, *J* = 9.04 Hz, 2H), 6.82 (d, *J* = 8.61 Hz, 2H), 6.76 (d, *J* = 7.13 Hz, 1H), 6.70 (t, *J* = 7.37 Hz, 1H), 4.90 (s, 1H), 3.68 (s, 3H), 3.66 (s, 3H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ ppm 175.23, 164.08, 158.83, 156.07, 142.43, 130.42, 130.14, 130.00, 125.43, 123.57, 121.76, 121.69, 117.85, 114.73, 113.90, 110.64, 65.72, 64.04, 55.26, 55.01.

HRMS (ESI) calcd for $C_{24}H_{21}N_2O_4^+$ [M + H$^+$]: 401.1496; found, 401.1491.

*(2R\*,3R\*)-1-(4-Fluorophenyl)-3-(4-methoxyphenyl)spiro[azetidine-2,3′-indoline]-2′,4-dione (trans-3n).* A reaction of 2-(4-methoxyphenyl)acetic acid (249 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-((4-fluorophenyl)-imino)indolin-2-one (240 mg, 1 mmol) yields 198 mg (51%) of spiro-*b*-lactam as a white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 11.10 (s, 1H), 7.11–7.23 (m, 5H), 7.02–7.08 (m, 2H), 6.94 (d, *J* = 7.76 Hz, 1H), 6.77–6.85 (m, 3H), 6.71 (t, *J* = 7.55 Hz, 1H), 4.96 (s, 1H), 3.68 (s, 3H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ ppm 174.92, 164.49, 158.89, 142.41, 130.58, 130.18, 125.49, 123.29, 121.85, 121.28, 118.01, 117.93, 116.57, 116.34, 113.92, 110.76, 65.79, 64.30, 55.04.

HRMS (ESI) calcd for $C_{23}H_{18}FN_2O_3^+$ [M + H$^+$]: 389.1296; found, 389.1294.

*(2R\*,3S\*)-1-(3-Chloro-4-fluorophenyl)-3-(4-methoxyphenyl) spiro[azetidine-2,3′-indoline]-2′,4-dione (cis-3o).* A reaction of 2-(4-methoxyphenyl)acetic acid (249 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-((3-chloro-4-fluorophenyl)imino)indolin-2-one (275 mg, 1 mmol) yields 89 mg (21%) of spiro-*b*-lactam as a white solid.

$^1$H NMR (400 MHz, CHLOROFORM-d) δ ppm 10.83 (s, 1H), 7.69 (d, *J* = 7.34 Hz, 1H), 7.36–7.43 (m, 3H), 7.12 (t, 1H), 7.08 (d, *J* = 8.56 Hz, 2H), 6.99 (d, *J* = 7.76 Hz, 1H), 6.87 (d, *J* = 8.80 Hz, 2H), 6.70–6.75 (m, 1H), 5.29 (s, 1H), 3.72 (s, 3H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ ppm 174.66, 164.84, 159.00, 142.45, 130.83, 130.27, 129.96, 125.67, 123.03, 121.99, 120.85, 118.37, 118.05, 116.06, 113.97, 113.74, 110.86, 66.00, 64.63, 55.06.

HRMS (ESI) calcd for $C_{23}H_{17}ClFN_2O_3^+$ [M + H$^+$]: 423.0906; found, 423.0919.

*(2R\*,3R\*)-1-(3-Chloro-4-fluorophenyl)-3-(4-methoxy-phenyl) spiro[azetidine-2,3′-indoline]-2′,4-dione (trans-3o).* A reaction of 2-(4-methoxyphenyl)acetic acid (249 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-((3-chloro-4-fluorophenyl)imino)indolin-2-one (275 mg, 1 mmol) yields 85 mg (20%) of spiro-*b*-lactam as a white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 11.16 (s, 1H), 7.36–7.43 (m, 2H), 7.22 (t, *J* = 7.70 Hz, 1H), 7.16 (d, *J* = 8.68 Hz, 2H), 6.95 (d, *J* = 7.76 Hz, 1H), 6.80–6.85 (m, 3H), 6.70–6.75 (m, 2H), 5.02 (s, 1H), 3.68 (s, 3H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ ppm 174.62, 164.81, 158.96, 152.61, 142.44, 133.64, 130.79, 130.25, 125.65, 123.02, 121.95, 120.83, 120.43, 120.25, 118.35, 118.25, 118.03, 116.02, 115.94, 113.93, 110.83, 65.96, 64.59, 55.03.

HRMS (ESI) calcd for $C_{23}H_{17}ClFN_2O_3^+$ [M + H$^+$]: 423.0906; found, 423.0909.

*(2R\*,3R\*)-1-(4-Hydroxyphenyl)-3-(4-methoxyphenyl)-spiro[azetidine-2,3′-indoline]-2′,4-dione (trans-3p).* A reaction of 2-(4-methoxyphenyl)acetic acid (249 mg, 1.5 mmol), 4-toluenesulfonyl chloride (381 mg, 2 mmol), diisopropylethylamine (520 μL, 388 mg, 3 mmol), and 3-((4-hydroxyphenyl)imino)indolin-2-one (238 mg, 1 mmol) yields 43 mg (11%) of spiro-*b*-lactam as a white solid.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 11.01 (s, 1H), 9.44 (s, 1H), 7.18 (t, *J* = 7.58 Hz, 1H), 7.12 (d, *J* = 8.56 Hz, 2H), 6.85–6.93 (m, 3H), 6.82 (d, *J* = 8.74 Hz, 2H), 6.65–6.76 (m, 4H), 4.86 (s, 5H), 3.68 (s, 3H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ ppm 175.33, 163.92, 158.80, 154.41, 142.41, 130.34, 130.12, 128.65, 125.40, 123.69, 121.84, 121.70, 118.19, 115.82, 113.88, 110.59, 65.76, 63.96, 55.01.

HRMS (ESI) calcd for $C_{23}H_{19}N_2O_4^+$ [M + H$^+$]: 387.1339; found, 387.1336.

## ■ ASSOCIATED CONTENT

### ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c03063.

> Experimental procedure, optimization study, NMR spectra ($^1$H and $^{13}$C), crystal data, and HRMS spectra of the products (PDF)

### Accession Codes

CCDCs 2084190, 2084191, 2084193 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; Fax: +44 1223 336033.

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## Notes

The authors declare no competing financial interest.

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