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Organocatalytic Asymmetric Biginelli-like Reaction Involving Isatin

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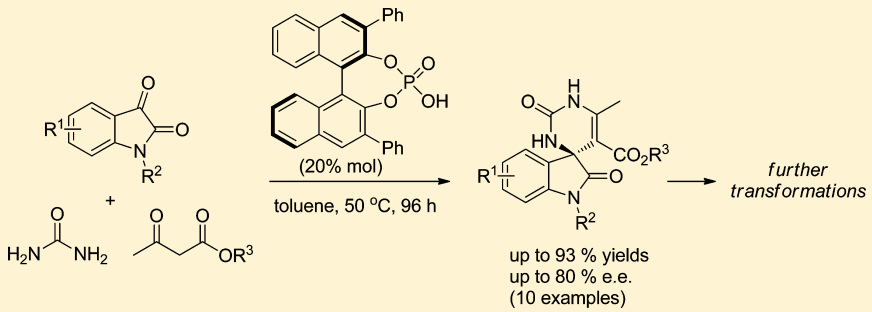
Supporting Information



ABSTRACT: The first asymmetric, Brønsted acid catalyzed Biginelli-like reaction of a ketone has been developed, employing *N*-substituted isatins as carbonyl substrates, and urea and alkyl acetoacetates as further components. BINOL-derived phosphoric acid catalysts have been used to achieve the synthesis of a small library of chiral, enantioenriched spiro(indoline-pyrimidine)-diones derivatives. The absolute configuration of the new spiro stereocenter was assessed on diastereoisomeric derivatives through computer-assisted NMR spectroscopy. X-ray diffractometry allowed the disclosure of the overall molecular conformation in the solid state and the characterization of the crystal packing of a Br-substituted Biginelli-like derivative, while computational studies on the reaction transition state allowed us to rationalize the stereochemical outcome.

INTRODUCTION

2-Oxindoles, especially those 3,3-disubstituted or spiro-fused to other cyclic frameworks, continue to be recognized as valuable compounds for drug discovery. They feature in a large number of natural and unnatural compounds with important biological activities and serve as key intermediates for the synthesis of many kinds of drug candidates.[1]

In particular, spirooxindoles, having cyclic structures fused at the C3 carbon, move away from the flat heterocycles encountered in many drug discovery programs. For this reason, they are of special interest, being able to potentially provide improved physicochemical properties in their interaction with biological systems.[2]

As more examples of the enantiospecific biological activity are identified, efficient and reliable asymmetric synthesis of such compounds becomes ever more valuable. In particular, the improvement of practical and versatile multicomponent approaches has attracted considerable interest owing to their synthetic efficiency and extensive diversity-generating ability.[3] Multicomponent reactions (MCRs) are very efficient tools to quickly prepare pharmacological compounds. However, their combination with asymmetric catalysis, in particular organocatalysis, remains a largely unmined area of research, although the results reported until now show the possibilities and versatility of this type of strategy, which allows elevated levels of atom efficiency and enantioselectivity to be reached at the same time.[4] In the field of oxindole chemistry, to date, only a few organocatalyzed multicomponent methods have been reported toward the asymmetric generation of the structurally rigid architecture of 3,3-disubstituted or spiro-fused oxindoles.[5] Noteworthy among them is the cinchona alkaloid derived amine-catalyzed Michael-type addition developed in highly efficient three-component versions using readily available malononitrile, isatins, and ketones.[6,7] Quite recently, isatin-derived 3-indolylmethanols have emerged as useful substrates for phosphoric acid catalyzed three-component cascade Michael/Pictet-Spengler reactions.[8] On the other hand, intense effort have been devoted to develop organocatalytic MCRs to form spiro[pyrrolidin-3,2′-oxindoles] and spirooxindole pyran derivatives by means of 1,3-dipolar cycloadditions[9] or cascade [3 + 2][10] or [2 + 2 + 2] cycloadditions.[11]

As part of our interest in the asymmetric synthesis of 3,3-disubstituted oxindole derivatives and related spiro-compounds,[12] we turned our attention to the MCRs field, in order to explore the *single reactant replacement* (SRR)

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Scheme 1. Strategy Used for the Asymmetric Construction of the Spiro(indoline-pyrimidine)-dione Scaffold

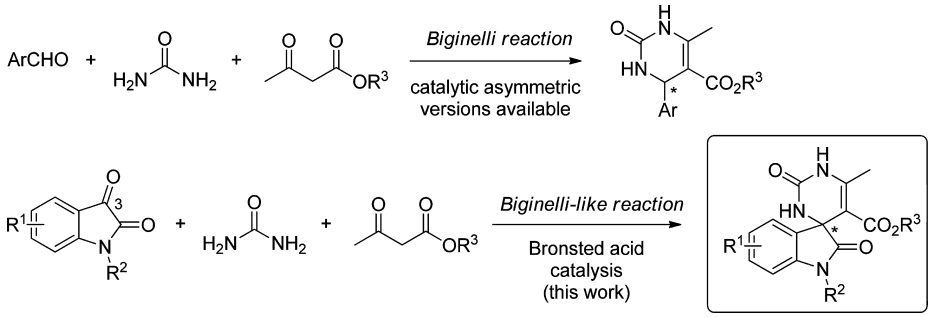
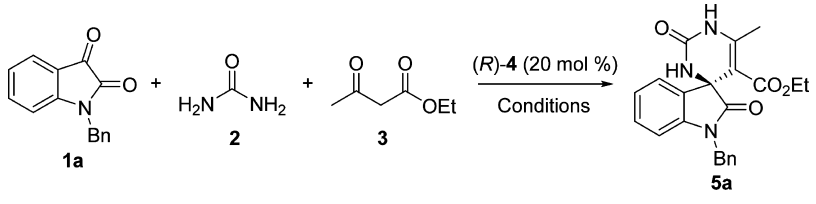
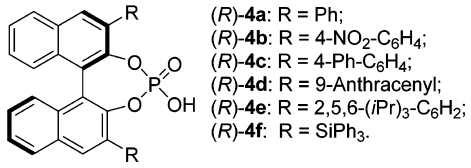
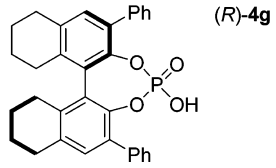


Table 1. Optimization of the Asymmetric Biginelli-like Reaction[a]







entry	catalyst	solvent	conc. [mol/L]	temp. [°C], time [h]	yield[b] [%]	ee[c] [%]
1	**4a**	CH_2Cl_2	0.2	rt, 96	trace	
2	**4a**	toluene	0.2	rt, 96	trace	
3	**4a**	CH_2Cl_2	0.2	50, 48	32	75
4	**4a**	toluene	0.2	50, 48	51	80
5	**4b**	toluene	0.2	50, 48	trace	
6	**4c**	toluene	0.2	50, 48	30	79
7	**4d**	toluene	0.2	50, 48	31	81
8	**4e**	toluene	0.2	50, 48	trace	
9	**4f**	toluene	0.2	50, 48	trace	
10	**4g**	toluene	0.2	50, 48	26	79
11	**4a**	toluene	0.2	50, 96	60	80
12	**4a**	toluene	0.2	50, 240	66	77
13	**4a**	toluene	0.2	70, 96	65	48
14	**4a**	toluene	0.4	50, 96	62	66

[a]Reactions were performed on a 0.16 mmol scale with **1**/**2**/**3** in a 1/1.2/3 ratio, in the presence of 20 mol % (*R*)-**4** (0.032 mmol). [b]Isolated yield. [c]Determined by chiral HPLC analysis.

approach.[13] By this strategy, starting from a well-known MCR, new applications can be found just replacing a single component with a different input, which was able to display the key chemical reactivity necessary for that MCR to occur. In this context, we focused on the Biginelli reaction, one of the well-established MCRs, mainly employed for the synthesis of 3,4-dihydropyrimidine-2(1*H*)-ones (DHPMs). Such heterocyclic scaffolds have found increasing applications in medicinal chemistry, because of their important pharmacological and biological properties.[14] Only few examples are reported on enantioselective organocatalytic Biginelli reactions, all involving aromatic aldehydes as carbonyl components.[15] The milestone was placed by Gong,[16−18] who disclosed the first highly enantioselective protocol, based on BINOL-derived chiral phosphoric acids as organocatalysts. Also, dual-activation routes have been developed, by using combined catalysts consisting of a Brønsted acid and a chiral secondary amine[19,20] or, alternatively, a chiral bifunctional primary amine-thiourea.[21]

To the best of our knowledge, only two examples of the multicomponent preparation of racemic DHPMs derivatives starting from isatin are reported.[22,23] In general, application of organocatalysis to the Biginelli-like reaction, employing a ketone as the carbonyl component, is even now quite unexplored. Herein, we report the Brønsted acid catalyzed asymmetric synthesis of spiro(indoline-pyrimidine)-diones derivatives via a Biginelli-like reaction, consisting of a three-component cyclocondensation of alkyl acetoacetates, urea, and isatin derivatives instead of aldehydes (Scheme 1).

RESULTS AND DISCUSSION

Our initial studies were performed taking into account the Brønsted acid catalytic enantioselective protocol reported by

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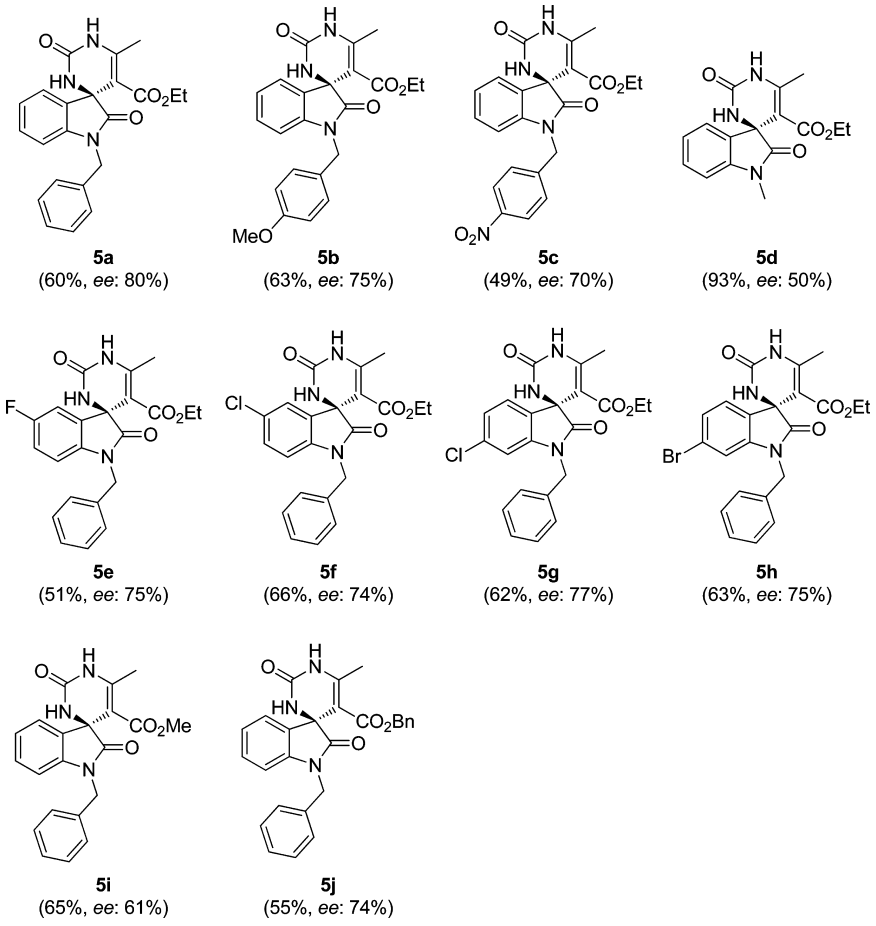

Figure 1. Substrate scope of the Biginelli-like reaction catalyzed by (*R*)-**4a**.

Gong for the true, aldehyde-involving, Biginelli reaction. Isatin **1a**, urea **2**, ethyl acetoacetate **3**, and (*R*)-BINOL-derived phosphoric acid **4a** were chosen for preliminary experiments (Table 1).

At room temperature, the reaction proceeds with difficulty both in CH_2Cl_2 and in toluene (entries 1 and 2), and after 96 h, only trace amounts of the desired compound **5a** could be detected by ^{1}H NMR of the crude reaction mixture. The lower reactivity of the C-3 carbonyl group of isatin compared to aldehydes, along with its higher steric demand, appears to be the key factor hindering the reaction from successfully proceeding at room temperature.

To our delight, increasing the temperature to 50 °C (entries 3 and 4) entailed a significant effect on the chemical conversion. Toluene proved to be the solvent of choice, affording product **5a** in acceptable yield and with a good level of enantioselectivity. Screening of more hindered catalysts **4b**–**f**, aimed to evaluate the impact of the 3,3′-substitution, and of octahydro-BINOL-based **4g**, was performed (entries 5–10). Increasing the size of the 3,3′-substituents on the phosphoric acid proved detrimental for the chemical conversion, with only catalysts **4c** and **4d** able to afford product **5a**, with maintenance of the same level of enantioselectivity as **4a**, but in definitely decreased yields. After that, we established **4a** as the catalyst of choice, and further screening of the reaction conditions was performed. Some yield improvement without sacrificing the stereoselectivity could be achieved by prolonging the reaction time until 96 h (entry 11). More prolonged times are not convenient for the balance among yield and *ee* (entry 12). Increasing the reaction temperature deeply eroded the enantioselectivity, albeit with better yield (entry 13). The same happened when the reaction was conducted in more concentrated conditions (entry 14). Lowering the reactant concentration or the catalyst loading led to a significant decrease in yield.

After establishing the optimal conditions, the Biginelli-like reaction of a isatins series was examined, using (*R*)-**4a** as catalyst, in toluene at 50 °C for 96 h (Figure 1).

The substrate scope was surveyed, by evaluating differently *N*-substituted isatins and the presence of substituents at the 5- or 6-position of the isatin nucleus. In general, all isatins readily undergo this reaction, to afford the desired products **5a**–**h** in moderate to high yields, with a good degree of enantioselectivity. Only the sterically demanding *N*-trityl isatin failed to participate in the reaction, and the corresponding Biginelli-like adduct could not be detected. The *N*-Me isatin gave a better result than the corresponding *N*-benzyl, *N*-*p*-nitrobenzyl, and *N*-*p*-methoxybenzyl ones in terms of yield (93% in comparison to up to 63%), but suffering a drop in *ee* (50% in comparison to up to 80%).

The presence of various halogen substituents at the aryl ring has almost no effect on both yield and *ee*. Variations at the ester moiety of the *β*-ketoester component were also evaluated. Methyl and benzyl acetoacetates participated at the reaction efficiently to provide adducts **5i**–**j** in good yields and moderate *ee*'s.

In this kind of reaction, surprisingly, neither thiourea in place of urea nor various linear or cyclic *β*-diketones in place of alkyl

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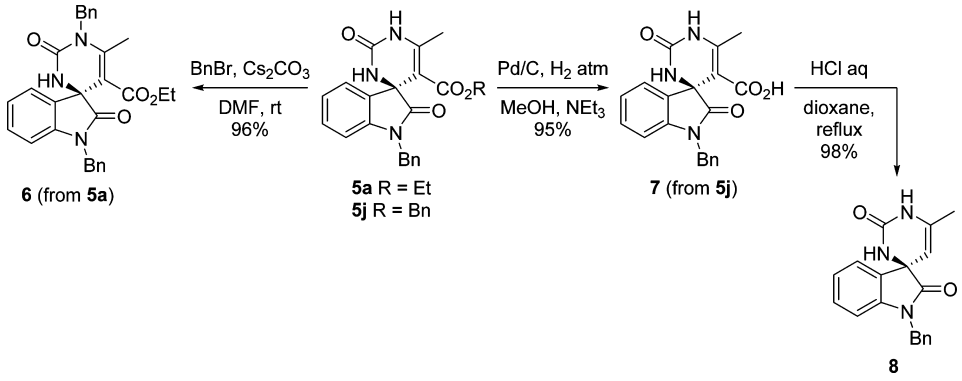
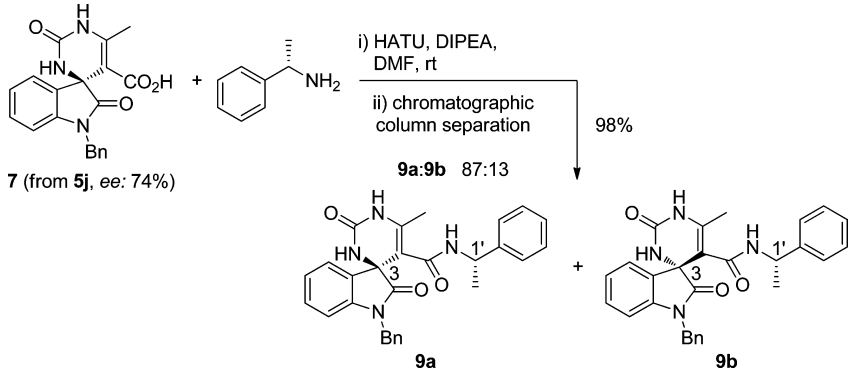
Scheme 2. Synthetic Transformations of Compounds 5a and 5j



Scheme 3. Synthesis of Diastereoisomeric Compounds 9a and 9b, Starting from Acid 7



acetoacetates showed to be suitable, together with *N*-benzylisatin. With thiourea, no reaction occurred, whereas, with *β*-diketones, a complex mixture of products could be detected.

Then, we examined some product transformations, first of all, the facile regioselective mono-*N*-alkylation of the dihydropyrimidin-2-one ring. Starting from the Biginelli-like compound **5a**, the corresponding *N*-benzyl derivative **6** was achieved in high yield and regioselectivity, by reaction with benzyl bromide and cesium carbonate, in DMF at room temperature (Scheme 2).

Further, catalytic hydrogenolysis of the benzyl ester moiety of compound **5j** allowed us to easily obtain the carboxylic acid derivative **7**, which can be regarded as a useful key intermediate toward the synthesis of peptidomimetic compounds. The carboxylic acid functional group of **7** can also be quantitatively removed to give **8**, by heating in acidic conditions.

In order to demonstrate the reactivity of acid **7** and aiming at the same time to gain information on the absolute configuration of the major enantiomer **5j** (*vide infra*), obtained in the (*R*)-**4a**-catalyzed Biginelli-like reaction, we pursued the transformation depicted in Scheme 3.

By reaction with (*S*)-1-phenylethanamine in the presence of the condensing agent HATU, acid **7** was cleanly converted into diastereoisomeric amides **9a** and **9b**, which could be efficiently separated by flash chromatography, establishing the possible application of **7** in peptidomimetic chemistry.

Confiding at first on X-ray diffractometry in order to determine the C3 absolute configuration of compounds **5**, we planned to perform the crystallographic analysis on **5h**. This molecule was selected as a suitable derivative, due to the presence of the bromine atom as anomalous dispersor. Initially, **5h** disclosed a recalcitrant crystallization behavior in yielding single crystals and, only after many attempts, well diffracting crystals were obtained. The X-ray data revealed that the 12:88 molar mixture of enantiomers crystallized in a centrosymmetric space group, showing the more favored crystallization of the racemate instead of the major enantiomer. In the solid state, the overall molecular conformation is determined by the spiro-(indoline-pyrimidine)-dione system, with the dihydropyrimidin-2-one ring, having an almost planar conformation, perpendicularly oriented with respect to oxindole (Figure 2a). The conformation of the benzyl group shows the phenyl ring pointing in the same direction of the dihydropyrimidin-2-one carbonyl moiety (see the Supporting Information). The crystal packing is characterized by strong centrosymmetric N–H···O

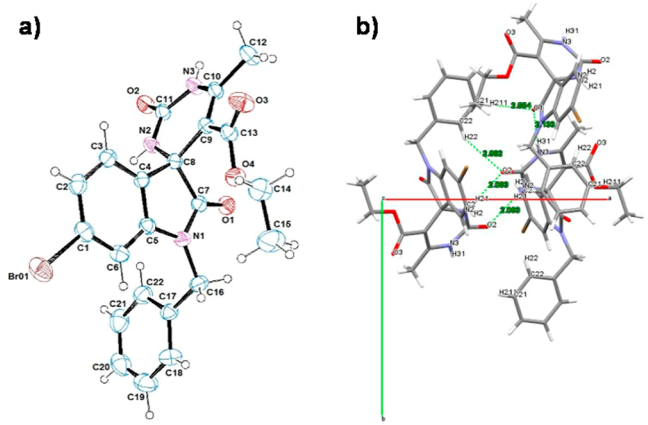


Figure 2. (a) ORTEP[25] drawing of **5h**, showing the arbitrary atomic numbering (displacement ellipsoids at 40% probability). (b) Intermolecular interactions viewed along the *c* axis.

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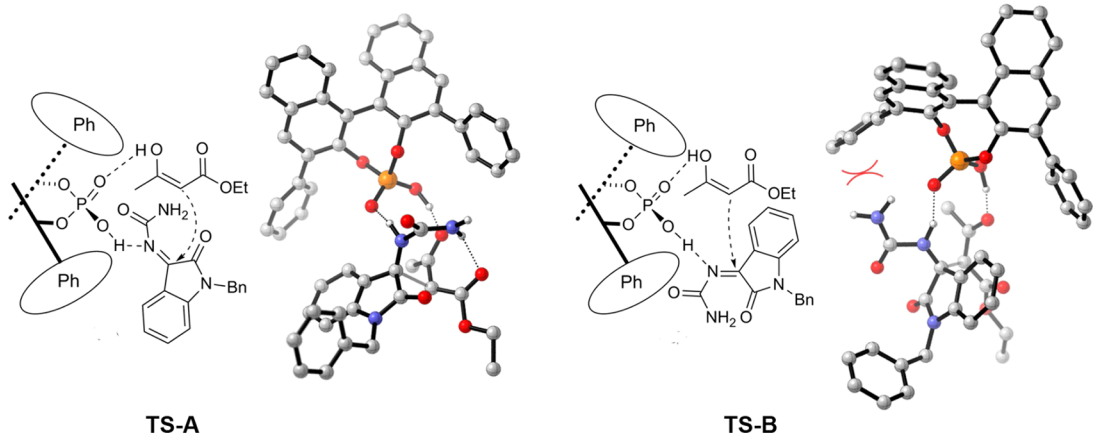

Figure 3. Proposed transition states **TS-A** and **TS-B** (and the corresponding 3D structures) of the BINOL-derived phosphoric acid catalyzed Biginelli-like reaction to give **5a**. In 3D, **TS-B** red lines highlight the steric hindrance between one phenyl substituent of (*R*)-**4a** and the ureidic residue.

hydrogen bonds, leading to the formation of dimers, that are in turn stabilized by Cπ−H···O contacts, as depicted in Figure 2b. This interaction pattern can be employed for rationalizing the preferential crystallization of the racemate, which is indeed consistent with the close packing found in the crystal environment, dominated by unique characteristics of hydrogen bonds involved in dimer formation. This easier racemate crystallization is in agreement with previous literature data,[24] showing the tendency for several racemic crystals to be more stable and denser than their chiral counterparts.

Although it was not possible to obtain suitable crystals for X-ray-based determination of the prevailing enantiomer **5h**, we were able to determine the C3 stereochemistry through *ab initio* calculation of NMR shifts, a technique pioneered by Bifulco.[26] We considered the differences in both ^{1}H and ^{13}C NMR spectra for compounds **9a** and **9b** and then performed a theoretical conformational search on both (3*S*,1′*S*) and (3*R*,1′*S*) possible diastereoisomers, employing the Monte Carlo algorithm and molecular mechanics (MMFF force field). After DFT optimization, we calculated ^{1}H and ^{13}C NMR chemical shifts, by subjecting the shielding constants to Boltzmann averaging over the conformers, followed by linear regression, as reported by Pierens.[27] From comparison of experimental and calculated data, the (3*S*,1′*S*) absolute configuration could be confidently assigned to the major diastereoisomer **9a** and, consequently, the (3*R*,1′*S*) one to the minor **9b**. To make this assignment safe beyond any doubt, we also calculated the comparison parameter (CP3), especially designed[28] for the computer-assisted assignment of the stereochemistry of diastereoisomer pairs, in which only the configuration of one stereocenter is unknown. By this way, our stereochemical assignment could be made quite secure also from a quantitative point of view (see the Supporting Information).

These results allowed us to disclose the C3-*S* favoring enantioselectivity of the described organocatalyzed reaction and prompted us to perform theoretical calculations on the stereogenic center forming step. The mechanism of the Biginelli reaction has been previously investigated by means of computational tools,[29] also in the presence of tartaric acid as catalyst.[30] Results indicated the iminium path as the most favorable, in accordance with a previously proposed mechanism.[31] Therefore, we decided to investigate the initial addition of the enol form of ethyl acetoacetate on the imine formed between isatin **1a** and urea **2**, in the presence of (*R*)-**4a**, since, in this step, the final configuration of **5a** is determined. DFT study at the B3LYP/6-31G(d,p) level of theory was performed taking into account the two possible spatial arrangements of the more stable *Z*-imine in the reagents−catalyst complex,[32] leading to the diastereoisomeric transition state models **TS-A** and **TS-B** (Figure 3). All the calculations were performed with the Spartan ’08[33] suite (see the Supporting Information). The energy profiles clearly indicate a strong preference for **TS-A**, with a $\Delta\Delta G^{\ddagger}$ = 1.47 kcal/mol with respect to **TS-B**, at T = 323 K, from which an expected 85% *ee* could be calculated. These results are in satisfactory agreement with the experimental observed *ee*’s, and once again support the previously predicted *S* configuration for major diastereoisomer **9a**.

Looking at the transition state 3D structures, the steric hindrance between one phenyl substituent of (*R*)-**4a** and the ureidic residue could explain the higher activation energy of **TS-B** and the resulting favored nucleophilic attack on the *si*-face of the imine (**TS-A**). Moreover, in **TS-A**, a hydrogen bond between the ureidic NH of the imine and the carbonyl oxygen of the acetoacetate ester is established, thus further stabilizing this structure.

■ CONCLUSION

In conclusion, we developed the first enantioselective organocatalyzed Biginelli-like reaction applied to a ketone, namely, isatin, with good yields and enantioselectivity. By employing BINOL-based phosphoric acids as catalysts and different isatins and alkyl acetoacetates as substrates, together with urea, a small library of enantioenriched spiro[indoline-pyrimidine]-dione derivatives could be obtained. Postcondensation reactions have been performed, increasing the number of potentially useful compounds.

The solid state conformation of a Br-containing Biginelli-like compound was investigated, putting in evidence its crystallization behavior leading to the more favored racemate, instead of the major enantiomer. The absolute configuration at the oxindole C3 quaternary stereocenter was assessed to be *S* for the major enantiomer, by means of quantum mechanical methods and NMR spectroscopy on diastereoisomeric derivatives. Computational studies on the reaction transition

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state (TS) allowed us to explain the experimentally observed enantioselectivity and stereochemical outcome.

EXPERIMENTAL SECTION

General Information. All commercial materials were used without further purification. All solvents were of reagent grade or HPLC grade. All reactions were carried out under a nitrogen atmosphere unless otherwise noted. All reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel 60 F254; spots were visualized with UV light or by treatment with a 1% aqueous $KMnO_4$ solution. Products were purified by flash chromatography on silica gel 60 (230−400 mesh). ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on 300 and 400 MHz spectrometers. Chemical shifts are reported in parts per million relative to the residual solvent. ^{13}C NMR spectra have been recorded using the APT pulse sequence. Multiplicities in ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, br s = broad singlet. High-resolution MS spectra were recorded with a Q-TOF mass spectrometer, equipped with an ESI source. Chiral HPLC analysis was performed with a UV detector and binary HPLC pump at 254 nm. A Chiralcel OD column was used. Specific optical rotation $[\alpha]_D^T$ was measured with a cell of 1 dm path length and 1 mL capacity. The light used has a wavelength of 589 nm (sodium D line). *N*-Substituted isatins[34] and BINOL-phosphoric acids[35] were synthesized according to the reported literature.

General Procedure for the Asymmetric Organocatalyzed Synthesis of Compounds 5a−j. Substituted isatin **1** (0.16 mmol, 1 equiv), urea **2** (0.19 mmol, 1.2 equiv), alkyl acetoacetate **3** (0.48 mmol, 3 equiv), and (*R*)-**4a** catalyst (0.03 mmol, 0.2 equiv) were dissolved in toluene (0.800 mL, 0.2 M). The reaction was stirred at 50 °C for 96 h. The resulting mixture was then concentrated under reduced pressure, to give a residue which was purified by flash chromatography (FC) as indicated below.

(S)-Ethyl 1-Benzyl-6′-methyl-2,2′-dioxo-2′,3′-dihydro-1′H-spiro-[indoline-3,4′-pyrimidine]-5′-carboxylate ***5a***. Prepared according to the general procedure starting from *N*-benzyl isatin and ethyl acetoacetate; FC:dichloromethane:methanol, 97.5:2.5; yield: 60%; white solid; mp 223−224 °C; $[\alpha]_D^{20}$ − 45.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (br s, 1H), 7.42 (d, *J* = 7.4 Hz, 2H), 7.38−7.24 (m, 4H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 5.69 (br s, 1H), 4.99 (d, *J* = 15.5 Hz, 1H), 4.80 (d, *J* = 15.5 Hz, 1H), 3.99−3.86 (m, 1H), 3.70−3.55 (m, 1H), 2.38 (s, 3H), 0.71 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 165.2, 151.9, 149.9, 143.2, 136.3, 132.9, 130.5, 129.5 (2C), 128.5 (3C), 124.6, 124.0, 109.9, 99.4, 64.2, 60.6, 45.0, 20.1, 14.1; HRMS (ESI) calcd for $C_{22}H_{21}N_3NaO_4^+$ $[MNa]^+$ 414.1434, found 414.1442; enantiomeric excess: 80%, determined by chiral HPLC (*n*-hexane:isopropanol = 80:20, flow rate 1.0 mL/min): t_R = 14.98 min (major), t_R = 33.78 min (minor).

(S)-Ethyl 1-(4-Methoxybenzyl)-6′-methyl-2,2′-dioxo-2′,3′-dihydro-1′H-spiro[indoline-3,4′-pyrimidine]-5′-carboxylate ***5b***. Prepared according to the general procedure starting from *N*-(4-methoxybenzyl) isatin and ethyl acetoacetate; FC:dichloromethane:methanol, 97.5:2.5; yield: 63%; white solid; mp 193−194 °C; $[\alpha]_D^{20}$ + 4.5 (*c* 0.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of conformers 6:1) δ 8.87 (br s, 0.15H), 8.74 (br s, 0.85H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.17 (t, *J* = 7.7 Hz, 1H), 6.98 (t, *J* = 7.3 Hz, 1H), 6.88−6.70 (m, 3H), 6.01 (br s, 0.86H), 5.81 (br s, 0.14H), 4.85 (d, *J* = 15.3 Hz, 1H), 4.71 (d, *J* = 15.3 Hz, 1H), 3.96−3.78 (m, 1H), 3.74 (s, 0.43H), 3.71 (s, 2.57H), 3.64−3.43 (m, 1H), 2.33 (s, 0.44H), 2.27 (s, 2.56H), 0.64 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of conformers 6:1) δ 175.9, 164.6, 159.1, 152.1, 149.5, 142.6, 132.5, 129.7, 129.2 (2C), 127.8, 123.9, 123.2, 114.1 (2C), 109.2, 98.5, 63.4, 59.8, 55.2, 43.7, 19.1, 13.5; HRMS (ESI) calcd for $C_{23}H_{23}N_3NaO_5^+$ $[MNa]^+$ 444.1530, found 444.1519; enantiomeric excess: 75%, determined by chiral HPLC (*n*-hexane:isopropanol = 65:35, flow rate 1.0 mL/min): t_R = 9.85 min (major), t_R = 27.96 min (minor).

(S)-Ethyl 6′-Methyl-1-(4-nitrobenzyl)-2,2′-dioxo-2′,3′-dihydro-1′H-spiro[indoline-3,4′-pyrimidine]-5′-carboxylate ***5c***. Prepared according to the general procedure starting from *N*-(4-nitrobenzyl) isatin and ethyl acetoacetate; FC:dichloromethane:methanol, 97.5:2.5; yield: 49%; white solid; mp 201−202 °C; $[\alpha]_D^{20}$ − 8.2 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of conformers 5:1) δ 8.48 (br s, 0.17H), 8.40 (br s, 0.83H), 8.21−8.08 (m, 2H), 7.65−7.54 (m, 2H), 7.30 (d, *J* = 7.3 Hz, 1H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.62 (d, *J* = 7.6 Hz, 1H), 6.28 (br s, 0.84H), 6.12 (br s, 0.16H), 5.09−4.87 (m, 2H), 4.07−3.89 (m, 1H), 3.86−3.68 (m, 1H), 2.34 (s, 0.5H), 2.30 (s, 2.5H), 0.88 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of conformers 5:1) δ 176.0, 164.6, 151.8, 149.0, 147.5, 143.0, 141.9, 132.2, 130.0, 128.4 (2C), 124.1, 124.0 (2C), 123.8, 109.0, 98.9, 63.51, 60.3, 43.7, 19.5, 13.8; HRMS (ESI) calcd for $C_{22}H_{20}N_4NaO_6^+$ $[MNa]^+$ 459.1275, found 459.1268; enantiomeric excess: 70%, determined by chiral HPLC (*n*-hexane:isopropanol = 50:50, flow rate 1.0 mL/min): t_R = 10.05 min (major), t_R = 45.50 min (minor).

(S)-Ethyl 1,6′-Dimethyl-2,2′-dioxo-2′,3′-dihydro-1′H-spiro-[indoline-3,4′-pyrimidine]-5′-carboxylate ***5d***. Prepared according to the general procedure starting from *N*-methyl isatin and ethyl acetoacetate; FC:dichloromethane:methanol, 95:5; yield: 93%; white solid; mp 228−229 °C; $[\alpha]_D^{20}$ − 1.6 (*c* 0.35, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.45 (br s, 1H), 7.75 (br s, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 7.3 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 3.68 (q, *J* = 7.1 Hz, 2H), 3.10 (s, 3H), 2.26 (s, 3H), 0.75 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.2, 164.8, 150.9 (2C), 144.0, 134.0, 129.6, 123.4, 122.8, 108.7, 97.1, 63.1, 59.5, 26.6, 18.7, 13.8; HRMS (ESI) calcd for $C_{16}H_{17}N_3NaO_4^+$ $[MNa]^+$ 338.1111, found 338.1123; enantiomeric excess: 50%, determined by chiral HPLC (*n*-hexane:isopropanol = 65:35, flow rate 1.0 mL/min): t_R = 7.25 min (major), t_R = 38.20 min (minor).

(S)-Ethyl 1-Benzyl-5-fluoro-6′-methyl-2,2′-dioxo-2′,3′-dihydro-1′H-spiro[indoline-3,4′-pyrimidine]-5′-carboxylate ***5e***. Prepared according to the general procedure starting from 5-fluoro-*N*-benzyl isatin and ethyl acetoacetate; FC:dichloromethane:methanol, 97.5:2.5; yield: 51%; white solid; mp 135−136 °C; $[\alpha]_D^{20}$ + 3.8 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of conformers 5:1) δ 8.76−8.49 (br, m, 1H), 7.38 (d, *J* = 7.2 Hz, 2H), 7.34−7.16 (m, 3H), 7.03 (dd, *J* = 7.3, 2.5 Hz, 1H), 6.88 (td, *J* = 8.8, 2.4 Hz, 1H), 6.67 (dd, *J* = 8.5, 3.8 Hz, 1H), 6.13−5.88 (br, m, 1H), 4.92 (d, *J* = 15.5 Hz, 1H), 4.76 (d, *J* = 15.5 Hz, 1H), 4.04−3.83 (m, 1H), 3.74−3.52 (m, 1H), 2.35 (s, 0.5H), 2.30 (s, 2.5H), 0.83−0.68 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of conformers 5:1) δ 175.7, 164.4, 161.1, 157.9, 151.80, 149.75, 138.42, 135.34, 128.77 (2C), 127.81, 127.74 (2C), 116.17 and 115.86 (1C), 112.19 and 111.9 (1C), 110.0 and 109.9 (1C), 98.2, 63.6, 60.1, 44.4, 19.3, 13.6; HRMS (ESI) calcd for $C_{22}H_{20}FN_3NaO_4^+$ $[MNa]^+$ 432.1330, found 432.1326; enantiomeric excess: 75%, determined by chiral HPLC (*n*-hexane:isopropanol = 70:30, flow rate 1.0 mL/min): t_R = 8.15 min (major), t_R = 16.35 min (minor).

(S)-Ethyl 1-Benzyl-5-chloro-6′-methyl-2,2′-dioxo-2′,3′-dihydro-1′H-spiro[indoline-3,4′-pyrimidine]-5′-carboxylate ***5f***. Prepared according to the general procedure starting from 5-chloro-*N*-benzyl isatin and ethyl acetoacetate; FC:dichloromethane:methanol, 97.5:2.5; yield: 66%; white solid; mp 126−127 °C; $[\alpha]_D^{20}$ + 33.6 (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of conformers 5:1) δ 8.76 (br s, 0.16H), 8.69 (br s, 0.84H), 7.37 (d, *J* = 7.1 Hz, 2H), 7.33−7.18 (m, 4H), 7.14 (d, *J* = 8.3, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 6.24 (br s, 0.83H), 6.18 (br s, 0.17H), 4.90 (d, *J* = 15.6 Hz, 1H), 4.77 (d, *J* = 15.7 Hz, 1H), 4.01−3.84 (m, 1H), 3.75−3.56 (m, 1H), 2.34 (s, 0.5H), 2.29 (s, 2.5H), 0.83−0.68 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 164.4, 151.9, 149.8, 141.1, 135.2, 134.0, 129.7, 128.8 (2C), 128.5, 127.8, 127.7 (2C), 124.3, 110.3, 98.1, 63.4, 60.1, 44.4, 19.3, 13.6; HRMS (ESI) calcd for $C_{22}H_{20}ClN_3NaO_4^+$ $[MNa]^+$ 448.1035, found 448.1049; enantiomeric excess: 74%, determined by chiral HPLC (*n*-hexane:isopropanol = 70:30, flow rate 1.0 mL/min): t_R = 9.05 min (major), t_R = 16.45 min (minor).

(S)-Ethyl 1-Benzyl-6-chloro-6′-methyl-2,2′-dioxo-2′,3′-dihydro-1′H-spiro[indoline-3,4′-pyrimidine]-5′-carboxylate ***5g***. Prepared according to the general procedure starting from 6-chloro-*N*-benzyl isatin and ethyl acetoacetate; FC:dichloromethane:methanol, 97.5:2.5; yield: 62%; white solid; mp 213-214 °C; $[\alpha]_D^{20}$ − 1.0 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (br s, 1H), 7.39 (d, *J* = 7.0 Hz, 2H), 7.35−7.22 (m, 3H), 7.19 (d, *J* = 7.7 Hz, 1H), 6.98 (d, *J* = 7.6 Hz,

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1H), 6.79 (s, 1H), 6.14 (br s, 1H), 4.90 (d, J = 15.5 Hz, 1H), 4.75 (d, J = 15.5 Hz, 1H), 3.90 (m, 1H), 3.60 (m, 1H), 2.29 (s, 3H), 0.74 (t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 164.4, 151.9, 149.4, 143.9, 135.6, 135.1, 130.7, 128.8 (2C), 127.9, 127.8 (2C), 124.8, 123.1, 109.9, 98.4, 63.0, 60.1, 44.4, 19.2, 13.6; HRMS (ESI) calcd for $C_{22}H_{20}ClN_3NaO_4^+$ $[MNa]^+$ 448.1035, found 448.1039; enantiomeric excess: 77%, determined by chiral HPLC (n-hexane:isopropanol = 65:35, flow rate 1.0 mL/min): t_R = 8.65 min (major), t_R = 15.35 min (minor).

(S)-Ethyl 1-Benzyl-6-bromo-6′-methyl-2,2′-dioxo-2′,3′-dihydro-1′H-spiro[indoline-3,4′-pyrimidine]-5′-carboxylate ***5h***. Prepared according to the general procedure starting from 6-bromo-*N*-benzyl isatin and ethyl acetoacetate; FC:dichloromethane:methanol, 97.5:2.5; yield: 63%; white solid; mp 221−222 °C; $[\alpha]_D^{20}$ + 7.6 (c 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (br s, 1H), 7.39 (d, J = 7.3 Hz, 2H), 7.26 (m, 3H), 7.18−7.06 (m, 2H), 6.95 (s, 1H), 6.22 (br s, 1H), 4.87 (d, J = 15.6 Hz, 1H), 4.75 (d, J = 15.6 Hz, 1H), 4.00−3.77 (m, 1H), 3.70−3.49 (m, 1H), 2.27 (s, 3H), 0.72 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 164.4, 152.0, 149.5, 144.0, 135.1, 131.3, 128.8 (2C), 127.9, 127.8 (2C), 126.1, 125.2, 123.4, 112.6, 98.3, 63.1, 60.1, 44.1, 19.2, 13.6; HRMS (ESI) calcd for $C_{22}H_{20}BrN_3NaO_4^+$ $[MNa]^+$ 492.0529, found 492.0518; enantiomeric excess: 75%, determined by chiral HPLC (n-hexane:isopropanol = 70:30, flow rate 1.0 mL/min): t_R = 9.35 min (major), t_R = 16.50 min (minor).

(S)-Methyl 1-Benzyl-6′-methyl-2,2′-dioxo-2′,3′-dihydro-1′H-spiro[indoline-3,4′-pyrimidine]-5′-carboxylate ***5i***. Prepared according to the general procedure starting from *N*-benzyl isatin and methyl acetoacetate; FC:dichloromethane:methanol, 97.5:2.5; yield: 65%; white solid; mp 143−144 °C; $[\alpha]_D^{20}$ − 6.8 (c 0.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (br s, 1H), 7.40 (d, J = 7.7 Hz, 2H), 7.36−7.23 (m, 4H), 7.20 (td, J = 7.8, 1.2 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 7.7 Hz, 1H), 5.29 (br s, 1H), 4.94 (d, J = 15.5 Hz, 1H), 4.83 (d, J = 15.4 Hz, 1H), 3.20 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 165.0, 151.3, 149.2, 142.3, 135.6, 132.1, 129.9, 128.8 (2C), 127.9 (2C), 127.8, 123.8, 123.3, 109.2, 98.7, 63.5, 51.0, 44.3, 19.4; HRMS (ESI) calcd for $C_{21}H_{19}N_3NaO_4^+$ $[MNa]^+$ 400.1268, found 400.1257; enantiomeric excess: 61%, determined by chiral HPLC (n-hexane:isopropanol = 70:30, flow rate 1.0 mL/min): t_R = 9.15 min (major), t_R = 18.30 min (minor).

(S)-Benzyl 1-Benzyl-6′-methyl-2,2′-dioxo-2′,3′-dihydro-1′H-spiro[indoline-3,4′-pyrimidine]-5′-carboxylate ***5j***. Prepared according to the general procedure starting from *N*-benzyl isatin and benzyl acetoacetate; FC:dichloromethane:methanol, 97.5:2.5; yield: 55%; white solid; mp 147−148 °C; $[\alpha]_D^{20}$ + 17.2 (c 0.5, dioxane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (br s, 1H), 7.41−7.17 (m, 10H), 7.18−7.09 (m, 1H), 6.98 (t, J = 7.5 Hz, 1H), 6.85 (d, J = 6.5 Hz, 1H), 6.44 (d, J = 7.8 Hz, 1H), 5.39 (br s, 1H), 4.85−4.70 (m, 2H), 4.63 (d, J = 12.0 Hz, 1H), 3.81 (d, J = 15.6 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 164.4, 162.2, 150.2, 142.3, 135.8, 132.2, 129.9, 128.9 (4C), 128.6 (2C), 128.3, 127.8, 127.7 (2C), 124.0, 123.4, 109.8, 66.5, 43.8, 19.6 (3 quaternary carbons are missed); HRMS (ESI) calcd for $C_{27}H_{23}N_3NaO_4^+$ $[MNa]^+$ 476.1581, found 476.1589; enantiomeric excess: 74%, determined by chiral HPLC (n-hexane:isopropanol = 80:20, flow rate 1.0 mL/min): t_R = 13.50 min (major), t_R = 28.20 min (minor).

Procedure for the Synthesis of Ethyl (*S*)-1,1′-Dibenzyl-6′-methyl-2,2′-dioxo-2′,3′-dihydro-1′*H*-spiro[indoline-3,4′-pyrimidine]-5′-carboxylate (6). To a solution of compound **5a** (0.25 mmol, 1 equiv) in anhydrous dimethylformamide (0.830 mL, 0.3 M) was added $CsCO_3$ (0.33 mmol, 1.3 equiv); then, the mixture was stirred for 1 h at room temperature. Benzyl bromide (0.38 mmol, 1.5 equiv) was slowly added, and the mixture was stirred overnight. After the completion of reaction (monitored by TLC), saturated aq. NaCl (1 mL) was added. The reaction mixture was extracted with ethyl acetate (3 × 2 mL). The combined organic layer was washed with water (2 × 6 mL), followed by brine (2 × 6 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the crude product, which was purified by FC (n-hexane:ethyl acetate, 7:3), affording the desired product **6** (115 mg, 96%) as a white solid; mp 91−92 °C; $[\alpha]_D^{20}$ − 32.4 (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51−7.24 (m, 11H), 7.21 (d, J = 7.7 Hz, 1H), 7.02 (t, J = 7.4 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 5.32 (d, J = 17.0 Hz, 1H), 5.16 (br s, 1H), 5.00−4.78 (m, 3H), 3.91−3.73 (m, 1H), 3.57−3.42 (m, 1H), 2.40 (s, 3H), 0.52 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 165.1, 152.2, 150.7, 142.9, 137.7, 135.6, 131.7, 129.8, 128.9 (2C), 128.7 (2C), 127.8 (3C), 127.1, 126.0 (2C), 123.9, 123.2, 109.1, 101.9, 62.3, 60.0, 46.0, 44.2, 16.8, 13.2; HRMS (ESI) calcd for $C_{29}H_{27}N_3NaO_4^+$ $[MNa]^+$ 504.1894, found 504.1898.

Procedure for the Synthesis of (*S*)-1-Benzyl-6′-methyl-2,2′-dioxo-2′,3′-dihydro-1′*H*-spiro[indoline-3,4′-pyrimidine]-5′-carboxylic Acid (7). Palladium (10 wt % on carbon, 0.025 mmol, 0.05 equiv) was added to a solution of Biginelli-adduct **5j** (0.50 mmol, 1 equiv) and Et_3N (0.50 mmol, 1 equiv) in 7.5 mL of dioxane/methanol (2:1). The reaction mixture was degassed *in vacuo*, placed under an atmosphere of H_2 (g), and stirred in the dark at rt for 3h. The mixture was filtered through a pad of Celite eluting with methanol (10 mL), and the combined organic layers were concentrated *in vacuo* to give the crude carboxylic acid derivative **7** (173 mg, 95%) as a white solid, sufficiently pure to be directly used in the next step; mp not measured (decomposition); $[\alpha]_D^{20}$ − 19.2 (c 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.97 (br s, 1H), 9.39 (br s, 1H), 7.89 (br s, 1H), 7.47 (d, J = 6.7 Hz, 2H), 7.39−7.25 (m, 3H), 7.23 (d, J = 7.2 Hz, 1H), 7.16 (t, J = 7.7 Hz, 1H), 6.98 (t, J = 7.4 Hz, 1H), 6.62 (d, J = 7.7 Hz, 1H), 4.96 (d, J = 16.3 Hz, 1H), 4.70 (d, J = 16.3 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 176.1, 166.4, 150.7, 149.4, 142.7, 136.3, 133.9, 128.8, 128.3 (2C), 127.1 (2C), 127.0, 123.0, 122.3, 108.9, 97.8, 63.0, 43.4, 18.5; HRMS (ESI) calcd for $C_{20}H_{17}N_3NaO_4^+$ $[MNa]^+$ 386.1111, found 386.1121.

Procedure for the Synthesis of (*R*)-1-Benzyl-6′-methyl-1′*H*-spiro[indoline-3,4′-pyrimidine]-2,2′(3′H)-dione (8). To a solution of the carboxylic acid derivative **7** (0.1 mmol, 1 equiv) in 1 mL of dioxane/methanol (1:1) was added hydrochloric acid in dioxane (4 M, 0.4 mmol, 4 equiv), and the reaction was stirred at 90 °C for 0.5 h. The solvent was removed under reduced pressure to afford compound **8** (31 mg, 98%) in high purity as a white solid, with no need for further purifications; mp 95−96 °C; $[\alpha]_D^{20}$ − 25.6 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (br s, 1H), 7.40 (d, J = 7.3 Hz, 1H), 7.37−7.23 (m, 5H), 7.18 (t, J = 7.7 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.71 (d, J = 7.8 Hz, 1H), 5.72 (br s, 1H), 4.93 (d, J = 15.6 Hz, 1H), 4.79 (d, J = 15.6 Hz, 1H), 4.24 (s, 1H), 1.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 154.4, 142.0, 136.4, 136.1, 132.6, 130.5, 129.5 (2C), 128.4, 128.0 (2C), 125.7, 124.2, 110.2, 95.4, 64.3, 44.7, 19.4; HRMS (ESI) calcd for $C_{19}H_{17}N_3NaO_2^+$ $[MNa]^+$ 342.1213, found 342.1206.

Procedure for the Synthesis of Diastereoisomers (*S*)-1-Benzyl-6′-methyl-2,2′-dioxo-*N*-((*S*)-1-phenylethyl)-2′,3′-dihydro-1′*H*-spiro[indoline-3,4′-pyrimidine]-5′-carboxamide (9a) and (*R*)-1-Benzyl-6′-methyl-2,2′-dioxo-*N*-((*S*)-1-phenylethyl)-2′,3′-dihydro-1′*H*-spiro[indoline-3,4′-pyrimidine]-5′-carboxamide (9b). To a solution of carboxylic acid derivative **8** (0.9 mmol, 1 equiv) and DIPEA (1.8 mmol, 2 equiv) in 9.4 mL of anhydrous dimethylformamide was added HATU (1.4 mmol, 1.5 equiv). After 5 min, (*S*)-(−)-α-methylbenzylamine (0.9 mmol, 1 equiv) and DIPEA (1.8 mmol, 2 equiv) were added, and the reaction was stirred at room temperature for 24 h. The resulting mixture was partitioned between ethyl acetate (20 mL) and water (20 mL). The organic phase was washed with brine (6 × 10 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford the crude diastereoisomeric mixture **9**, which was purified by flash chromatography (ethyl acetate:*n*-hexane, 95:5), obtaining the two isolated stereoisomers **9a** (358 mg, 86%) and **9b** (54 mg, 12%).

9a. White solid; mp 149−150 °C; $[\alpha]_D^{20}$ + 16.5 (c 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (br s, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.62 (br s, 1H), 7.46 (d, J = 7.3 Hz, 2H), 7.33 (d, J = 7.4 Hz, 1H), 7.32−7.22 (m, 7H), 7.18 (q, J = 8.4, 7.8 Hz, 2H), 7.00 (t, J = 7.5 Hz, 1H), 6.63 (d, J = 7.8 Hz, 1H), 4.78 (s, 2H), 4.71−4.59 (m, 1H), 1.91 (s, 3H), 1.04 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.4, 165.6, 153.2, 145.3, 144.4, 138.0, 137.3, 132.4, 130.2, 129.4 (2C), 129.3 (2C), 128.3 (2C), 128.1, 127.6, 127.2 (2C), 125.3, 123.0, 109.9, 105.1, 64.3, 48.6, 44.2, 23.0, 18.3. HRMS (ESI) calcd for $C_{28}H_{26}N_4NaO_3^+$ $[MNa]^+$ 489.1897, found 489.1905.

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9b. White solid; mp 138−139 °C; $[\alpha]_D^{20}$ − 89.5 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 8.81 (br s, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 7.62 (br s, 1H), 7.42 (d, *J* = 6.4 Hz, 2H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.29−7.19 (m, 3H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.11 (m, 3H), 7.00 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 7.4 Hz, 2H), 6.57 (d, *J* = 7.8 Hz, 1H), 4.88−4.67 (m, 3H), 2.01 (s, 3H), 1.32 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.4, 165.6, 153.0, 144.9, 144.32, 138.3, 137.3, 132.7, 130.1, 129.4 (2C), 128.9 (2C), 128.2 (2C), 128.07, 127.1, 126.8 (2C), 125.3, 123.2, 110.0, 105.12, 64.4, 48.1, 44.2, 22.5, 18.4. HRMS (ESI) calcd for $C_{28}H_{26}N_4NaO_3^+$ $[MNa]^+$ 489.1897, found 489.1909.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02680.

^1H and ^{13}C NMR spectra of all novel compounds, HPLC chromatograms (compounds **5a−j**), experimental for X-ray analysis, and computational data (PDF)

Crystallographic data for compound **5h** (CIF)

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Notes

The authors declare no competing financial interest.

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