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Enantioselective Construction of Tetrahydroquinolin-5-one-Based Spirooxindole Scaffold via an Organocatalytic Asymmetric Multicomponent [3 + 3] Cyclization

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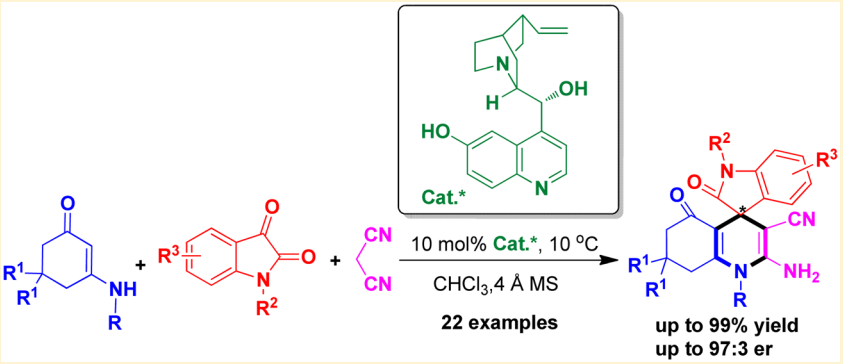
Supporting Information



ABSTRACT: The first catalytic enantioselective construction of biologically important tetrahydroquinolin-5-one-based spirooxindole has been developed via a chiral cinchona alkaloid catalyzed asymmetric three-component [3 + 3] cyclization of cyclic enaminone, isatin, and malononitrile, which afforded a series of tetrahydroquinolin-5-one-based spirooxindoles in high yields and with excellent enantioselectivities (up to 99% yield, 97:3 er). This reaction could be applicable to large-scale synthesis of enantioenriched tetrahydroquinolin-5-one-based spirooxindoles. This synthetic methodology will not only provide a unique approach for the construction of chiral tetrahydroquinolin-5-one-based spirooxindole scaffolds but also increase our understanding of catalytic enantioselective multicomponent reactions.

INTRODUCTION

Spirooxindole represents one of the most important heterocyclic frameworks, which constitutes the core structures of many natural alkaloids and pharmaceuticals.[1,2] Among the large family of spirooxindoles, tetrahydroquinolin-5-one-based spirooxindoles exhibit a wide spectrum of bioactivities such as antimicrobial,[3a] cytotoxicity to MCF-7,[3a] lifespan-altering,[3b] antioxidant,[4a] and inhibition of alanyl aminopeptidase[4b] (Figure 1). Consequently, the construction of such spiro frameworks has received much attention from chemists. However, all established methods focus on the synthesis of racemic tetrahydroquinolin-5-one-based spirooxindoles.[5] *In sharp contrast, no catalytic asymmetric approaches are available for synthesizing such biologically important chiral spirooxindoles.* Nevertheless, the enantioselective construction of bioactive molecules is important because the enantiomers may have different or better bioactivities compared with the racemates.[6] Thus, it is important to develop catalytic enantioselective approaches for the construction of chiral tetrahydroquinolin-5-one-based spirooxindole scaffolds.

In recent years, due to the significance of chiral spirooxindoles in medicinal chemistry, numerous catalytic asymmetric reactions have been developed rapidly for the enantioselective construction of a wide range of structurally diversified spirooxindole skeletons (Scheme 1, eq 1).[7,8] *Despite these recent advances in this research field, the catalytic*

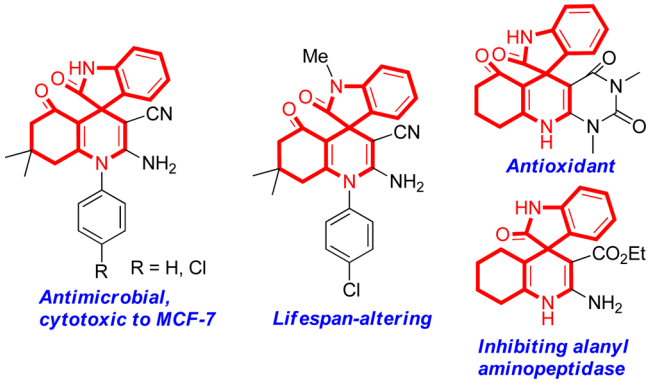


Figure 1. Selected bioactive tetrahydroquinolin-5-one-based spirooxindoles.

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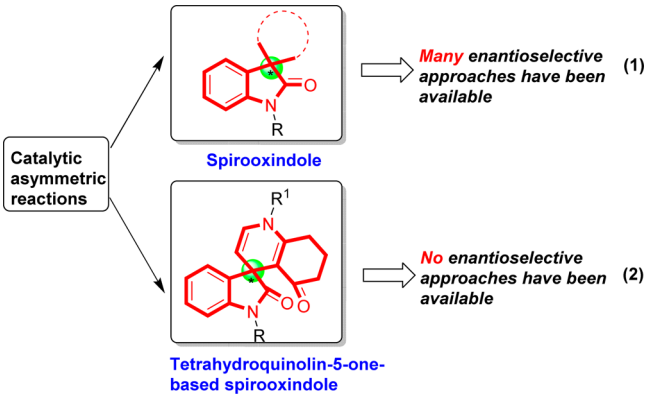
Scheme 1. Profile of Catalytic Enantioselective Construction of Spirooxindole Skeletons



enantioselective construction of the tetrahydroquinolin-5-one-based spirooxindole scaffold remains underdeveloped (eq 2). This may be associated with challenges in enantioselectively constructing this framework, such as the design of the enantioselective reaction, the selection of chiral catalysts based on the reaction mechanism, and the activation mode. Therefore, it is important to design catalytic enantioselective reactions and identify suitable catalytic systems to construct a spirooxindole framework.

Organocatalytic asymmetric transformations,[9,10] especially multicomponent reactions, are considered robust methods for the enantioselective construction of frameworks with medicinal relevance, which can avoid transition-metal contamination of the products.[11] In addition, catalytic enantioselective [3 + 3] cyclizations, especially organocatalytic enantioselective multicomponent [3 + 3] cyclizations, have proven to be efficient strategies for constructing chiral six-membered rings in a single step.[12] To construct a tetrahydroquinolin-5-one-based spirooxindole scaffold in an enantioselective fashion, and due to our continuous interest in organocatalytic enantioselective transformations,[13] we designed an organocatalytic enantioselective multicomponent [3 + 3] cyclization (Scheme 2). In this design, we envisioned the three-component reaction of cyclic enaminone **1**, isatin **2**, and malononitrile **3** could be catalyzed by a tertiary amine based bifunctional catalyst, which could form multiple hydrogen bonds with enaminone **1** and intermediate **A** to facilitate an enantioselective Michael addition and subsequent intramolecular nucleophilic addition of the intermediate **B**, thus constructing the desired tetrahydroquinolin-5-one-based spirooxindole scaffold in an enantioselective fashion.

Herein, we report the first catalytic asymmetric construction of a chiral tetrahydroquinolin-5-one-based spirooxindole scaffold (up to 99% yield, 97:3 er) that takes advantage of the three-component [3 + 3] cyclization of enaminone, isatin, and malononitrile in the presence of a chiral bifunctional organocatalyst. This reaction also represents the first catalytic enantioselective version of this type of three-component [3 + 3] cyclization.

RESULTS AND DISCUSSION

To test the feasibility of our hypothesis, the reaction of dimedone-derived enaminone **1a**, *N*-benzyl-substituted isatin **2a**, and malononitrile **3** was used as a model reaction in the presence of chiral cinchona alkaloid catalyst **5a**, which smoothly afforded the desired tetrahydroquinolin-5-one-based spirooxindole **4aa** but in a moderate yield and with low enantioselectivity (Table 1, entry 1). A series of bifunctional catalysts, **5b–i**, derived from various cinchona alkaloids[14] were screened (entries 2–9). Although the yields were still unsatisfactory, cinchona alkaloid derivatives **5b** and **5d** bearing two hydroxyl groups were superior to others in controlling the enantioselectivity (entries 2 and 4 vs entries 1, 3 and 5–9), which may be attributed to the action of the two hydroxyl groups in forming multiple hydrogen bonds with enaminone **1** and intermediate **A**. In particular, catalyst **5d** afforded the product with the highest level of enantioselectivity (entry 4 vs

Scheme 2. Design of the Catalytic Asymmetric Reaction for the Construction of an Enantioenriched Tetrahydroquinolin-5-one-Based Spirooxindole Scaffold

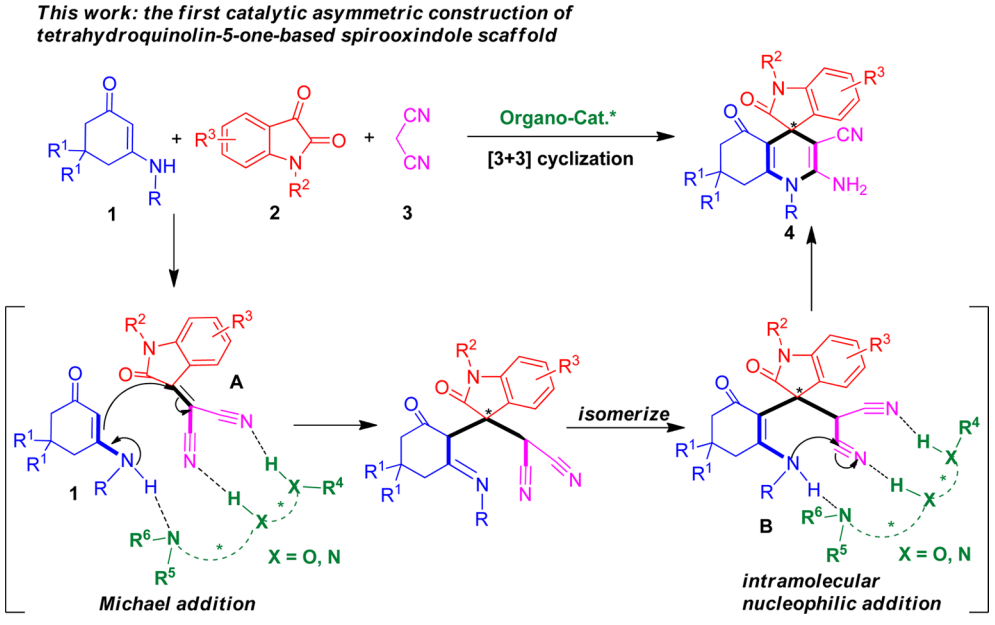


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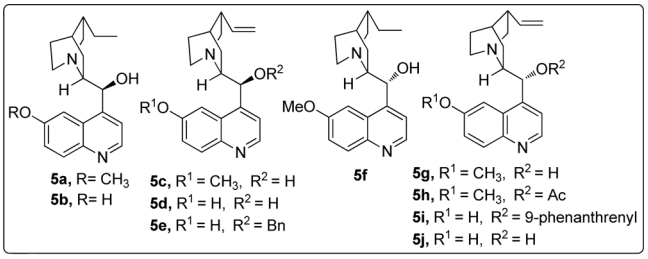
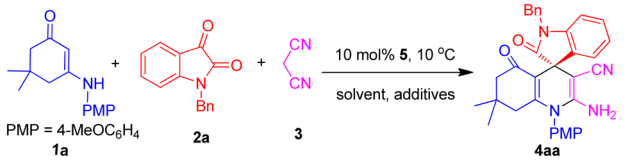
Table 1. Screening of Catalysts and Optimization of Reaction Conditions[a]





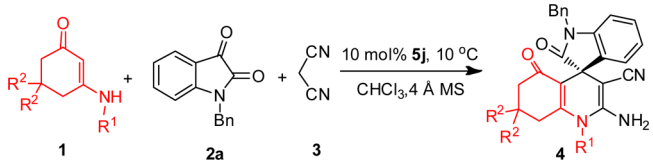
entry	5	solvent	additives	yield[b] (%)	er[c]
1	5a	$CHCl_3$	5 Å MS	22	53:47
2	5b	$CHCl_3$	5 Å MS	69	70:30
3	5c	$CHCl_3$	5 Å MS	39	52:48
4	5d	$CHCl_3$	5 Å MS	46	79:21
5	5e	$CHCl_3$	5 Å MS	61	44:56
6	5f	$CHCl_3$	5 Å MS	54	57:43
7	5g	$CHCl_3$	5 Å MS	99	52:48
8	5h	$CHCl_3$	5 Å MS	17	50:50
9	5i	$CHCl_3$	5 Å MS	20	49:51
10	5d	toluene	5 Å MS	22	77:23
11	5d	THF	5 Å MS	trace	
12	5d	CH_3CN	5 Å MS	38	52:48
13	5d	EtOAc	5 Å MS	trace	
14	5d	acetone	5 Å MS	trace	
15	5j	$CHCl_3$	5 Å MS	50	88:12
16	5j	$CHCl_3$	3 Å MS	62	82:18
17	5j	$CHCl_3$	4 Å MS	81	88:12
18	5j	$CHCl_3$	$MgSO_4$	47	81:19
19[d]	5j	$CHCl_3$	4 Å MS	80	90:10
20[e]	5j	$CHCl_3$	4 Å MS	54	94:6
21[e,f]	5j	$CHCl_3$	4 Å MS	75	94:6
22[g,f]	5j	$CHCl_3$	4 Å MS	45	95:5
23[e,f,h]	5j	$CHCl_3$	4 Å MS	43	94:6
24[e,f,i]	5j	$CHCl_3$	4 Å MS	80	94:6
25[e,i,j]	5j	$CHCl_3$	4 Å MS	91	96:4

[a]Unless otherwise indicated, the reaction was performed at the 0.05 mmol scale and catalyzed by 10 mol % of **5** in solvent (0.5 mL) with additives (100 mg) at 10 °C for 2 days, and the molar ratio of **1a**:**2a**:**3** was 1.2:1:1. [b]Isolated yield. [c]The er value was determined by high-performance liquid chromatography (HPLC). [d]The volume of solvent was 1 mL. [e]The volume of solvent was 2 mL. [f]The molar ratio of **1a**:**2a**:**3** was 1:1.5:1.5. [g]The volume of solvent was 3 mL. [h]Performed at 0 °C. [i]The reaction time was 4 days. [j]The molar ratio of **1a**:**2a**:**3** was 1:4:4.

entry 2). Subsequently, screening the solvents showed that chloroform remained the best solvent, which delivered the reaction with the highest enantioselectivity of 79:21 er with a moderate yield of 46% (entry 4 vs entries 10−14). Under these conditions, the replacement of catalyst **5d** by **5j** resulted in further improved enantioselectivity of 88:12 er, but with no obvious enhancement in yield (entry 15 vs entry 4). In addition, several chiral thiourea−tertiary amine and squaramide−tertiary amine catalysts **5k**−**u** were applied to the model reaction, but all showed lower catalytic activity than **5j** in terms of enantioselective control (see the Supporting Information for details). Thus, catalyst **5j** was selected as the optimal catalyst. To further improve the enantioselectivity and yield, different additives were evaluated in the presence of catalyst **5j** (entries 15−18), which revealed that $MgSO_4$ was inferior to other additives with regard to the enantioselective control and yield (entry 18 vs entries 15−17). Among these additives, 4 Å molecular sieves (MS) were the most suitable, which could improve the yield to 81% with a retained enantioselectivity of 88:12 er (entry 17 vs entries 15−16 and 18). When we increased the volume of the solvent from 0.5 to 2 mL, the enantioselectivity increased to 94:6 er albeit with a decreased yield (entry 20 vs entries 18−19). Fortunately, when the molar ratio of reagents was changed to 1:1.5:1.5, the yield could be increased to 75% with a retained enantioselectivity (entry 21 vs entry 20). However, when we further increased the volume of the solvent or lowered the reaction temperature, the yields decreased sharply with no improvement in enantioselectivity (entry 21 vs entries 22 and 23). Finally, the best enantioselectivity of 96:4 er and the highest yield of 91% were obtained by modulating the molar ratio to 1:4:4 with a prolonged reaction time (entry 24).

After the optimal reaction conditions were established, we investigated the substrate scope of this organocatalytic enantioselectivity multicomponent reaction. First, we examined the generality of enaminones **1** by the reaction with *N*-benzyl-substituted isatin **2a** and malononitrile **3**. As shown in Table 2,

Table 2. Substrate Scope of Enaminones 1[a]



entry	4	R^1/R^2	yield[b] (%)	er[c]
1	4aa	4-$OMeC_6H_4$/Me (1a)	91	96:4
2	4ba	4-MeC_6H_4/Me (1b)	99	93:7
3	4ca	4-FC_6H_4/Me (1c)	99	93:7
4	4da	4-ClC_6H_4/Me (1d)	99	94:6
5[d]	4ea	3-$OMeC_6H_4$/Me (1e)	78	90:10
6	4fa	3-FC_6H_4/Me (1f)	85	91:9
7	4ga	C_6H_5/Me (1g)	79	92:8
8	4ha	2-naphthyl/Me (1h)	85	92:8
9[e]	4ia	Bn/Me (1i)	43	93:7
10[e]	4ja	*n*-C_3H_7/Me (1j)	71	90:10
11[f]	4ka	4-$OMeC_6H_4$/H (1k)	45	93:7

[a]Unless otherwise indicated, the reaction was performed at the 0.1 mmol scale and catalyzed by 10 mol % of **5j** in chloroform (4 mL) at 10 °C for 4 days, and the molar ratio of **1**:**2a**:**3** was 1:4:4. [b]Isolated yields. [c]The er value was determined by HPLC. [d]Performed at 0 °C for 4 days. [e]Performed at 70 °C for 7 days. [f]Performed at 50 °C for 4 days.

this approach was applicable to a wide range of substrates **1** bearing different R^1/R^2 groups, which afforded structurally diverse tetrahydroquinolin-5-one-based spirooxindoles **4** at generally high yields and excellent enantioselectivities (90:10 to 96:4 er). In detail, the electronic nature of the aniline moieties had no obvious effect on the enantioselectivity (entries 1−6). For example, in the cases of *meta*-substituted aniline-derived enaminones, both electron-donating groups such as

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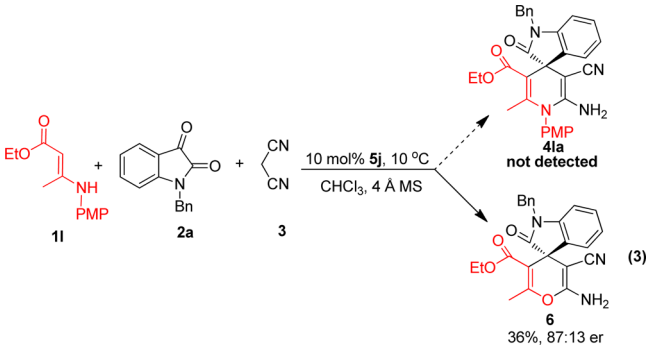
methoxy (OMe) and electron-withdrawing groups such as fluorine (F) proved to be suitable substituents for enaminone substrates, which delivered the reaction in nearly identical enantioselectivities (entries 5 and 6). However, the position of the substituents in the aniline moieties seemed to have effects on both the reactivity and enantioselectivity because *para*-substituted aniline-derived enaminones **1a**–**d** showed higher reactivity and capability in enantioselective control than their *meta*-substituted counterparts **1e**,**f** (entries 1–4 vs entries 5–6). Substrate **1h** bearing a 2-naphthyl group could be utilized in this reaction at a high yield of 85% and a good enantioselectivity of 92:8 er (entry 8). Alkylamine-derived enaminones **1i** and **1j** successfully participated in this reaction to generate the corresponding [3 + 3] cyclization products with good enantioselectivities (entries 9 and 10). These results increase the applicability of this reaction. Apart from dimedone-derived enaminones, cyclohexanedione-derived enaminone **1k** could play a role in the reaction with a good enantioselectivity of 93:7 er (entry 11).

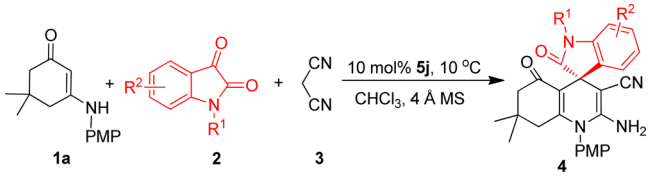
Furthermore, in place of cyclic enaminones, ethyl acetoacetate-derived enaminone **1l** was tentatively used as a substrate for this [3 + 3] cyclization under optimal conditions (eq 3);



however, no desired spirooxindole **4la** was generated. Instead, pyran-based spirooxindole **6** was obtained in an acceptable enantioselectivity of 87:13 er, albeit with a low yield of 36%. The generation of product **6** may be ascribed to the instability of enaminone **1l**, which easily decomposed into ethyl acetoacetate to undergo [3 + 3] cyclization.

Next, the substrate scope of isatins **2** was studied on the basis of the reaction with enaminone **1a** and malononitrile **3**. As summarized in Table 3, this protocol was amenable to a series of isatins **2**, which generated structurally diversified spirooxindoles **4** at overall high yields (60% to 91%) and with excellent enantioselectivities (90:10 to 96:4 er). We first investigated the effect of *N*-substituents of isatins **2** in the reaction (entries 1–5). Generally, *N*-benzyl-substituted isatins **2a**–**c** showed similar capability in enantioselective control with *N*-alkyl-substituted and *N*-allyl-substituted isatins **2d** and **2e** (entries 1–3 vs entries 4 and 5). *N*-Unprotected isatin **2f** could play a role in this [3 + 3] reaction with a good enantioselectivity of 90:10 er and a high yield of 86% (entry 6). Next, a wide scope of isatins **2** bearing electronically different substituents at various positions of the phenyl moiety were applied to the [3 + 3] reactions (entries 7–12), which revealed that the position of the substituents influenced the enantioselectivity. For example, C5-substituted isatins were inferior to C7-substituted isatins in terms of enantioselective control (entries 10 and 11 vs entries 7–9). Moreover, apart from monosubstituted substrates, disubstituted

Table 3. Substrate Scope of Isatins 2[a]



entry	4	R^1/R^2	yield[b] (%)	er[c]
1	**4aa**	Bn/H (**2a**)	91	96:4
2	**4ab**	*o*-$FC_6H_4CH_2$/H (**2b**)	87	93:7
3[d]	**4ac**	$C_6F_5CH_2$/H (**2c**)	63	90:10
4	**4ad**	Allyl/H (**2d**)	60	93:7
5[d]	**4ae**	Me/H (**2e**)	72	96:4
6	**4af**	H/H (**2f**)	86	90:10
7	**4ag**	Bn/5-OMe (**2g**)	84	90:10
8	**4ah**	Bn/5-Me (**2h**)	74	94:6
9[d]	**4ai**	Bn/5-Br (**2i**)	82	90:10
10	**4aj**	Bn/7-OMe (**2j**)	77	96:4
11	**4ak**	Bn/7-Me (**2k**)	72	95:5
12	**4al**	Bn/5,7-Me_2 (**2l**)	66	97:3

[a]Unless indicated otherwise, the reaction was performed at the 0.1 mmol scale and catalyzed by 10 mol % of **5j** in chloroform (4 mL) at 10 °C for 4 days, and the molar ratio of **1a**:**2**:**3** was 1:4:4. [b]Isolated yields. [c]The er value was determined by HPLC. [d]Performed at 0 °C for 4 days.

isatin **2l** could smoothly undergo the [3 + 3] cyclization in the highest enantioselectivity of 97:3 er (entry 12).

The absolute configuration of product **4aa** (>99:1 er after recrystallization) was determined to be *R* on the basis of single-crystal X-ray diffraction analysis (see the Supporting Information for details).[15] Thus, the absolute configurations of other tetrahydroquinolin-5-one-based spirooxindoles **4** were assigned by analogy.

Based on the experimental results, we suggested a possible reaction pathway and activation mode to explain the stereochemistry of this three-component reaction. As exemplified by the formation of product **4aa** (Scheme 3), the Knoevenagel condensation of isatin **2a** with malononitrile **3** in the presence of catalyst **5j** afforded an intermediate **A**.[16] The intermediate **A** and dimedone-derived enaminone **1a** were simultaneously activated by chiral cinchona alkaloid **5j** through multiple hydrogen-bonding activation mode. This activation mode and the fixed orientation between the substrates and catalyst **5j** promoted an enantioselective Michael addition of dimedone-derived enaminone **1a** to the intermediate **A**, leading to the generation of another intermediate **B** with a fixed configuration. Subsequently, activated again by multiple hydrogen bonds between the catalyst **5j** and the intermediate **B**, this intermediate immediately underwent an intramolecular nucleophilic addition of the amino group to the cyano group, which resulted in the formation of the final product **4aa** with (*R*)-configuration.

To verify our suggested reaction pathway, we performed a control experiment (Scheme 4). We monitored the reaction mixture, which revealed that the intermediate **A** (isatylidene malononitrile **A**) was rapidly generated within a short reaction time of 5 min. We then used isatylidene malononitrile **A** as the starting material to perform [3 + 3] cyclization with enaminone **1a** under standard conditions. As expected, this two-component reaction gave rise to the desired product **4aa** in the same enantioselectivity of 96:4 er with that of the three-component

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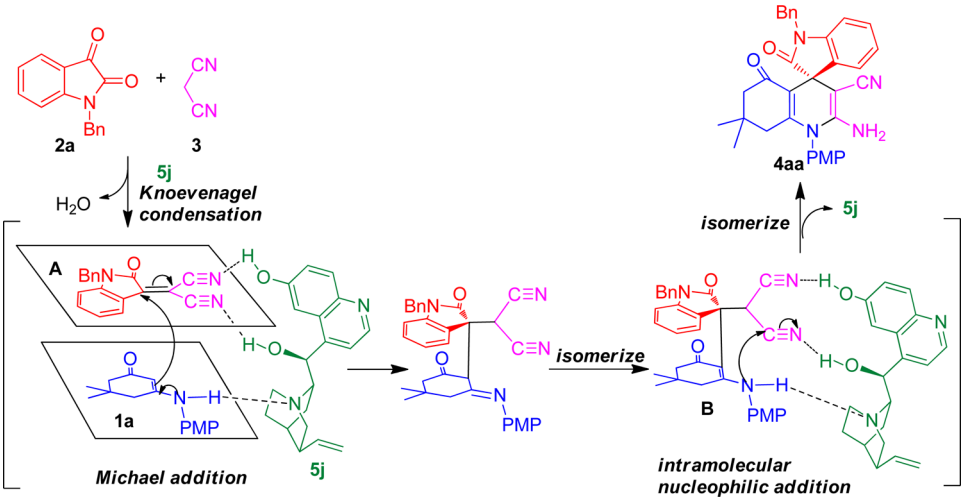
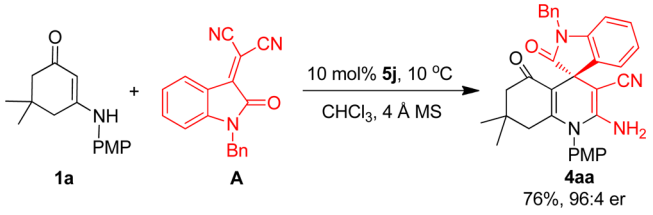
Scheme 3. Suggested Transition State and Activation Mode

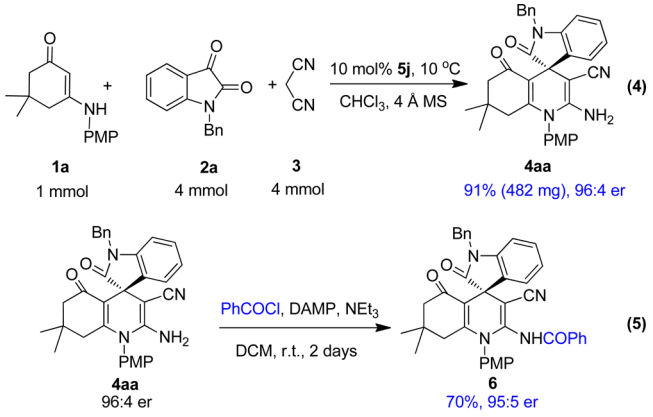


Scheme 4. Control Experiment



reaction. This outcome demonstrated that the Knoevenagel condensation of isatins **2** with malononitrile **3** was indeed the first step of this one-pot, three-component reaction.

Finally, to explore the potential of this approach, the model reaction was performed at a 1 mmol scale under standard conditions. As shown in eq 4, compared with the small-scale



reaction (Table 2, entry 1), the desired product **4aa** was obtained at a high yield of 91% and an excellent enantioselectivity of 96:4 er. This outcome indicated that this approach could be applicable for a large-scale synthesis of enantioenriched tetrahydroquinolin-5-one-based spirooxindoles. In addition, product **4aa** could be easily acylated by benzoyl chloride to generate compound **7** at a good yield of 92% and an almost retained enantioselectivity of 95:5 er (eq 5).

CONCLUSIONS

Overall, we established the first catalytic enantioselective construction of a biologically important tetrahydroquinolin-5-one-based spirooxindole scaffold in high yields and with excellent enantioselectivities (up to 99% yield, 97:3 er) that takes advantage of chiral cinchona alkaloid catalyzed enantioselective three-component reactions. Moreover, this reaction combined the merits of the multicomponent reaction and asymmetric organocatalysis, which realized the first catalytic enantioselective three-component [3 + 3] cyclization of cyclic enaminone, isatin, and malononitrile. Additionally, this reaction can be applied to large-scale synthesis of tetrahydroquinolin-5-one-based spirooxindoles in an enantioselective fashion. This synthetic methodology will not only provide an efficient approach for the construction of chiral tetrahydroquinolin-5-one-based spirooxindole scaffolds with biological importance but also increase our understanding of catalytic enantioselective three-component [3 + 3] cyclizations.

EXPERIMENTAL SECTION

^{1}H and ^{13}C NMR spectra were measured at 400 and 100 MHz, respectively. The solvents used for NMR spectroscopy were $CDCl_3$, acetone-d_6, and DMSO-d_6, using tetramethylsilane as the internal reference. HRMS (ESI) was determined by a HRMS/MS instrument. Enantiomeric ratios (er) were determined by chiral high-performance liquid chromatography (chiral HPLC). The chiral columns used for the determination of enantiomeric ratios by chiral HPLC were Chiralpak AS-H, OD-H, AD-H, and IA columns. Optical rotation values were measured with instruments operating at λ = 589 nm, corresponding to the sodium D line at the temperatures indicated. The X-ray source used for the single-crystal X-ray diffraction analysis of compound **4aa** was CuKα (λ = 1.54178). Analytical grade solvents for the column chromatography were used after distillation. All starting materials commercially available were used directly.

Typical Experimental Procedure for the Synthesis of Products 4 and 6. To the mixture of enaminones **1** (0.1 mmol), isatins **2** (0.4 mmol), malononitrile **3** (0.4 mmol), chiral catalyst **5j** (0.01 mmol), and 4 Å MS (100 mg) was added chloroform (4 mL). After being stirred at 10 °C for 4 days, the reaction mixture was filtered to remove the molecular sieves, and the solid powder was washed with ethyl acetate. The resultant solution was concentrated under reduced pressure to give the residue, which was purified through flash column chromatography on silica gel to afford pure products **4** or **6**.

*(R)-2′-Amino-1-benzyl-1′-(4-methoxyphenyl)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4aa**).* Flash column chromatography eluent, dichloromethane/ethyl acetate = 4/1; reaction time = 4 d; yield 91% (48.4 mg); white solid; mp 189−190 °C; $[\alpha]_D^{20}$ = +14.1 (*c* 0.7, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.6 Hz, 2H), 7.38−7.30 (m,

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2H), 7.30−7.27 (m, 1H), 7.25−7.19 (m, 2H), 7.13 (d, J = 7.2 Hz, 1H), 7.10−6.93 (m, 4H), 6.58 (d, J = 7.6 Hz, 1H), 5.11 (d, J = 16.0 Hz, 1H), 4.95 (d, J = 16.0 Hz, 1H), 4.29 (s, 2H), 3.85 (s, 3H), 2.20 (d, J = 16.0 Hz, 1H), 2.15−2.03 (m, 2H), 1.91 (d, J = 17.2 Hz, 1H), 0.97 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 178.7, 160.7, 152.2, 151.1, 142.2, 136.1, 135.4, 131.0, 130.6, 128.7, 128.4, 127.8, 127.3, 127.2, 122.8, 122.7, 118.7, 116.0, 115.5, 111.1, 109.4, 62.7, 55.7, 49.7, 48.6, 44.5, 42.1, 32.5, 29.3, 27.0; IR (KBr) 3468, 2959, 2929, 2184, 1716, 1649, 1509, 1362, 1253, 758, 696; ESI FTMS exact mass calcd for $(C_{33}H_{30}N_4O_3 + H)^+$ requires m/z 531.2396, found m/z 531.2405. The enantiomeric ratio (er) value, 96:4, determined by HPLC (Daicel Chiralpak AS-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 5.860 (major), t_R = 8.613 (minor).

*(R)-2′-Amino-1-benzyl-7′,7′-dimethyl-2,5′-dioxo-1′-(p-tolyl)-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4ba**).* Flash column chromatography eluent, dichloromethane/ethyl acetate = 4/1; reaction time = 4 d; yield: 99% (51.0 mg); white solid; mp 209−211 °C; $[\alpha]_D^{20}$ = +12.6 (c 0.8, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.2 Hz, 2H), 7.45−7.33 (m, 4H), 7.33−7.29 (m, 1H), 7.28−7.20 (m, 2H), 7.20−7.07 (m, 2H), 7.05−6.95 (m, 1H), 6.62 (d, J = 7.6 Hz, 1H), 5.14 (d, J = 16.0 Hz, 1H), 5.00 (d, J = 16.0 Hz, 1H), 4.19 (s, 2H), 2.49 (s, 3H), 2.29−2.18 (m, 1H), 2.18−2.07 (m, 2H), 1.93 (d, J = 17.2 Hz, 1H), 1.00 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 178.6, 151.8, 150.7, 142.3, 141.0, 136.0, 135.3, 133.0, 131.4, 131.3, 129.5, 129.2, 128.7, 128.4, 127.3, 127.2, 122.8, 122.7, 118.5, 111.2, 109.4, 63.2, 49.8, 48.6, 44.6, 42.1, 32.5, 29.2, 27.0, 21.3; IR (KBr) 3445, 2958, 2355, 2335, 2182, 1716, 1645, 1362, 1185, 1152, 750, 694; ESI FTMS exact mass calcd for $(C_{33}H_{30}N_4O_2 + H)^+$ requires m/z 515.2447, found m/z 515.2439. The enantiomeric ratio (er) value, 93:7, determined by HPLC (Daicel Chiralpak AS-H, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 7.330 (major), t_R = 11.077 (minor).

*(R)-2′-Amino-1-benzyl-1′-(4-fluorophenyl)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4ca**).* Flash column chromatography eluent, dichloromethane/ethyl acetate = 4/1; reaction time = 4 d; yield: 99% (51.2 mg); white solid; mp 320−321 °C; $[\alpha]_D^{20}$ = +9.0 (c 0.8, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 7.6 Hz, 2H), 7.44−7.29 (m, 5H), 7.26−7.18 (m, 2H), 7.15−7.05 (m, 2H), 7.03−6.93 (m, 1H), 6.60 (d, J = 8.0 Hz, 1H), 5.10 (d, J = 16.0 Hz, 1H), 4.95 (d, J = 16.0 Hz, 1H), 4.21 (s, 2H), 2.25−2.16 (m, 1H), 2.14−2.04 (m, 2H), 1.86 (d, J = 17.2 Hz, 1H), 0.97 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 178.5, 163.2 (J = 251.2 Hz), 151.5, 150.7, 142.3, 135.9, 135.2, 132.0 (J = 8.6 Hz), 131.6, 131.6, 131.5, 128.7, 128.5, 127.3, 127.2, 122.8, 118.4, 117.9 (J = 26.8 Hz), 111.5, 109.5, 63.4, 49.7, 48.6, 44.6, 42.2, 32.5, 29.2, 27.0; IR (KBr) 3447, 3365, 2960, 2359, 2181, 1701, 1650, 1364, 1154, 1252, 758, 694; ESI FTMS exact mass calcd for $(C_{32}H_{27}FN_4O_2 + H)^+$ requires m/z 519.2196, found m/z 519.2208. The enantiomeric ratio (er) value, 93:7, determined by HPLC (Daicel Chiralpak AS-H, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 8.363 (major), t_R = 16.387 (minor).

*(R)-2′-amino-1-benzyl-1′-(4-chlorophenyl)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4da**).* Flash column chromatography eluent, dichloromethane/ethyl acetate =4/1; Reaction time =4 d; yield: 99% (53.2 mg); white solid; mp 278−280 °C; $[\alpha]_D^{20}$ = +19.3 (c 0.7, Acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.48 (m, 4H), 7.39−7.31 (m, 3H), 7.26−7.21 (m, 1H), 7.15−7.05 (m, 3H), 7.01−6.95 (m, 1H), 6.61 (d, J = 7.6 Hz, 1H), 5.10 (d, J = 16.0 Hz, 1H), 4.96 (d, J = 16.0 Hz, 1H), 4.20 (s, 2H), 2.21 (d, J = 16.0 Hz, 1H), 2.14−2.05 (m, 2H), 1.87 (d, J = 17.2 Hz, 1H), 0.98 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 178.5, 151.2, 150.4, 142.3, 136.8, 135.9, 135.1, 134.2, 128.7, 128.5, 128.3, 127.3, 127.2, 127.0, 122.8, 122.8, 120.7, 118.3, 111.6, 109.5, 63.7, 49.7, 48.6, 44.6, 42.2, 32.6, 29.2, 27.0; IR (KBr) 3056, 2957, 2358, 2185, 1716, 1649, 1360, 1091, 1015, 754, 696; ESI FTMS exact mass calcd for $(C_{32}H_{27}ClN_4O_2 + H)^+$ requires m/z 535.1901, found m/z 535.1923. The enantiomeric ratio (er) value, 94:6, determined by HPLC (Daicel Chiralpak AS-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 5.510 (major), t_R = 8.027 (minor).

*(R)-2′-Amino-1-benzyl-1′-(3-methoxyphenyl)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4ea**).* Flash column chromatography eluent, dichloromethane/ethyl acetate = 4/1; reaction time = 4 d; yield 78% (41.3 mg); white solid; mp 158−160 °C; $[\alpha]_D^{20}$ = +11.1 (c 0.6, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59−7.43 (m, 3H), 7.39−7.29 (m, 2H), 7.25−7.20 (m, 1H), 7.17−7.05 (m, 3H), 7.02−6.76 (m, 3H), 6.60 (d, J = 7.6 Hz, 1H), 5.11 (d, J = 16.0 Hz, 1H), 4.97 (d, J = 16.0 Hz, 1H), 4.23 (s, 2H), 3.87 (d, J = 9.6 Hz, 3H), 2.28−2.12 (m, 2H), 2.09 (d, J = 16.4 Hz, 1H), 1.96 (d, J = 17.2 Hz, 1H), 0.98 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 178.6, 161.2, 151.5, 150.5, 142.3, 136.7, 136.0, 135.3, 131.5, 131.3, 128.7, 128.4, 127.2, 122.8, 121.8, 121.4, 118.5, 116.5, 115.7, 115.5, 115.2, 109.4, 63.1, 55.8, 49.8, 48.6, 44.6, 41.9, 32.6, 29.2, 27.0, 26.9; IR (KBr) 3441, 2961, 2186, 1716, 1645, 1362, 1259, 1021, 734; ESI FTMS exact mass calcd for $(C_{33}H_{30}N_4O_3 + H)^+$ requires m/z 531.2396, found m/z 531.2401. The enantiomeric ratio (er) value, 90:10, determined by HPLC (Daicel Chiralpak AS-H, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 10.333 (major), t_R = 16.723 (minor).

*(R)-2′-Amino-1-benzyl-1′-(3-fluorophenyl)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4fa**).* Flash column chromatography eluent, dichloromethane/ethyl acetate = 4/1; reaction time = 4 d; yield 85% (44.2 mg); white solid; mp 178−180 °C; $[\alpha]_D^{20}$ = +10.9 (c 0.7, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.49 (m, 3H), 7.39−7.27 (m, 3H), 7.26−7.17 (m, 2H), 7.16−7.02 (m, 3H), 7.01−6.94 (m, 1H), 6.60 (d, J = 7.6 Hz, 1H), 5.10 (d, J = 16.0 Hz, 1H), 4.96 (d, J = 16.0 Hz, 1H), 4.22 (s, 2H), 2.25−2.11 (m, 2H), 2.07 (s, 1H), 1.89 (d, J = 17.2 Hz, 1H), 0.98 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 178.4, 163.2 (J = 251.4 Hz), 151.2, 151.1, 150.3, 142.3, 137.1 (J = 9.3 Hz), 135.9, 135.1, 132.0, 128.7, 128.5, 127.3, 122.8, 118.3, 118.1 (J = 20.6 Hz), 111.6, 109.5, 63.7, 49.8, 48.6, 44.6, 42.0, 32.6, 29.1, 27.0; IR (KBr) 3648, 3586, 3326, 2957, 2359, 2189, 1705, 1652, 1362, 1175, 797, 660; ESI FTMS exact mass calcd for $(C_{32}H_{27}FN_4O_2 + H)^+$ requires m/z 519.2196, found m/z 519.2194. The enantiomeric ratio (er) value, 91:9, determined by HPLC (Daicel Chiralpak AS-H, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 8.177 (major), t_R = 13.227 (minor).

*(R)-2′-Amino-1-benzyl-7′,7′-dimethyl-2,5′-dioxo-1′-phenyl-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4ga**).* Flash column chromatography eluent, dichloromethane/ethyl acetate = 4/1; reaction time = 4 d; yield 79% (39.5 mg); white solid; mp 279−280 °C; $[\alpha]_D^{20}$ = +10.8 (c 0.6, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.51 (m, 5H), 7.40−7.30 (m, 4H), 7.24 (d, J = 7.2 Hz, 1H), 7.17−7.13 (m, 1H), 7.12−7.06 (m, 1H), 7.03−6.94 (m, 1H), 6.60 (d, J = 7.6 Hz, 1H), 5.12 (d, J = 16.0 Hz, 1H), 4.97 (d, J = 16.0 Hz, 1H), 4.18 (s, 2H), 2.27−2.10 (m, 2H), 2.09−2.03 (m, 1H), 1.94−1.81 (m, 1H), 0.96 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 178.6, 151.6, 150.6, 142.3, 136.0, 135.8, 135.3, 130.8, 130.6, 129.9, 129.6, 128.7, 128.5, 128.4, 127.3, 127.2, 122.8, 118.5, 111.3, 109.5, 63.3, 49.8, 48.6, 44.6, 42.1, 32.5, 29.2, 27.0; IR (KBr) 3471, 3310, 2958, 2360, 2196, 1640, 1363, 1153, 1048, 745, 699; ESI FTMS exact mass calcd for $(C_{32}H_{28}N_4O_2 + H)^+$ requires m/z 501.2290, found m/z 501.2308. The enantiomeric ratio (er) value, 92:8, determined by HPLC (Daicel Chiralpak AS-H, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 9.740 (major), t_R = 16.327 (minor).

*(R)-2′-Amino-1-benzyl-7′,7′-dimethyl-1′-(naphthalen-1-yl)-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4ha**).* Flash column chromatography eluent, dichloromethane/ethyl acetate = 4/1; reaction time = 4 d; yield: 85% (46.5 mg); white solid; mp 264−265 °C; $[\alpha]_D^{20}$ = +12.9 (c 0.7, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13−8.03 (m, 1H), 8.03−7.83 (m, 3H), 7.75−7.60 (m, 2H), 7.53 (d, J = 7.6 Hz, 2H), 7.48−7.37 (m, 1H), 7.37−7.30 (m, 2H), 7.25−7.17 (m, 2H), 7.14−7.06 (m, 1H), 7.05−6.97 (m, 1H), 6.60 (d, J = 7.6 Hz, 1H), 5.15−5.05 (m, 1H), 4.95 (d, J = 16.0 Hz, 1H), 4.23 (d, J = 7.2 Hz, 2H), 2.28−2.06 (m, 3H), 2.03−1.86 (m, 1H), 0.98−0.86 (m, 6H); ^{13}C NMR (100 MHz, acetone-d_6)

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δ 193.8, 178.2, 142.8, 136.9, 136.3, 133.7, 133.6, 130.6, 129.9, 128.4, 128.0, 127.7, 127.3, 127.3, 126.9, 123.2, 122.1, 118.5, 108.6, 68.8, 62.2, 54.6, 49.6, 48.8, 43.8, 41.8, 32.2, 31.1; IR (KBr) 3648, 3310, 2958, 2359, 2183, 1716, 1646, 1361, 1260, 1173, 1101; ESI FTMS exact mass calcd for $(C_{36}H_{30}N_4O_2 + H)^+$ requires m/z 551.2447, found m/z 551.2462. The enantiomeric ratio (er) value, 92:8, determined by HPLC (Daicel Chiralpak AS-H, hexane/2-propanol = 90/10, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 30.020 (major), t_R = 47.763 (minor).

*(R)-2′-Amino-1,1′-dibenzyl-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4ia**).* Flash column chromatography eluent, dichloromethane/ethyl acetate = 4/1; reaction time = 7 d; yield 43% (22.1 mg); white solid; mp 269−271 °C; $[\alpha]_D^{20}$ = +13.3 (*c* 0.4, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.45 (m, 4H), 7.41−7.33 (m, 3H), 7.30−7.27 (m, 3H), 7.13−7.04 (m, 2H), 7.02−6.96 (m, 1H), 6.62 (d, J = 7.6 Hz, 1H), 5.11 (d, J = 16.0 Hz, 1H), 5.05−4.82 (m, 3H), 4.48 (s, 2H), 2.59−2.36 (m, 2H), 2.26−2.02 (m, 2H), 1.07 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 178.8, 152.4, 151.9, 142.2, 135.9, 135.6, 135.2, 129.7, 128.7, 127.2, 125.2, 122.9, 118.6, 112.4, 109.5, 65.9, 49.4, 49.0, 48.3, 44.6, 40.7, 32.6, 28.7, 27.4; IR (KBr) 3438, 2963, 2360, 2184, 1652, 1363, 1261, 800, 668; ESI FTMS exact mass calcd for $(C_{33}H_{30}N_4O_2 + H)^+$ requires m/z 515.2447, found m/z 515.2455. The enantiomeric ratio (er) value, 93:7, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 16.653 (minor), t_R = 19.590 (major).

*(R)-2′-Amino-1-benzyl-7′,7′-dimethyl-2,5′-dioxo-1′-propyl-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4ja**).* Flash column chromatography eluent, dichloromethane/ethyl acetate = 4/1; reaction time = 7 d; yield: 71% (32.9 mg); white solid; mp 250−251 °C; $[\alpha]_D^{20}$ = +28.0 (*c* 0.6, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64−7.49 (m, 2H), 7.45−7.35 (m, 2H), 7.33−7.26 (m, 1H), 7.16−7.05 (m, 1H), 7.04−6.94 (m, 2H), 6.62 (d, J = 7.6 Hz, 1H), 5.12 (d, J = 16.4 Hz, 1H), 4.98 (d, J = 16.4 Hz, 1H), 4.92 (s, 2H), 3.82−3.50 (m, 2H), 2.76−2.39 (m, 2H), 2.28−2.10 (m, 2H), 1.89−1.62 (m, 2H), 1.17 (s, 3H), 1.08 (s, 3H), 1.05−0.96 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 179.3, 152.4, 152.1, 142.0, 135.9, 135.2, 128.8, 128.7, 128.4, 127.3, 127.2, 122.9, 122.8, 119.3, 112.3, 109.4, 64.9, 49.5, 48.9, 46.5, 44.6, 40.7, 32.5, 28.9, 27.7, 23.1, 11.0; IR (KBr) 3189, 2961, 2359, 2181, 1651, 1380, 1029, 734, 693; ESI FTMS exact mass calcd for $(C_{29}H_{30}N_4O_2 + H)^+$ requires m/z 467.2447, found m/z 467.2457. The enantiomeric ratio (er) value, 90:10, determined by HPLC (Daicel Chiralpak OD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 9.727 (minor), t_R = 34.767 (major).

*(R)-2′-Amino-1-benzyl-1′-(4-methoxyphenyl)-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4ka**).* Flash column chromatography eluent, dichloromethane/ethyl acetate = 4/1; reaction time = 4 d; yield 45% (22.8 mg); white solid; mp 181−182 °C; $[\alpha]_D^{20}$ = +34.5 (*c* 0.2, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.2 Hz, 2H), 7.40−7.31 (m, 3H), 7.30−7.27 (m, 1H), 7.26−7.21 (m, 1H), 7.17−7.12 (m, 1H), 7.12−7.03 (m, 3H), 7.02−6.95 (m, 1H), 6.59 (d, J = 7.6 Hz, 1H), 5.12 (d, J = 16.0 Hz, 1H), 4.99 (d, J = 16.0 Hz, 1H), 4.17 (s, 2H), 3.88 (s, 3H), 2.42−2.25 (m, 2H), 2.24−2.09 (m, 2H), 2.00−1.88 (m, 1H), 1.88−1.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 178.7, 160.8, 153.9, 150.7, 142.3, 136.0, 135.4, 130.9, 130.6, 128.7, 128.4, 127.8, 127.2, 127.2, 122.9, 122.7, 118.5, 115.9, 115.5, 112.5, 109.4, 63.2, 55.7, 48.7, 44.6, 36.3, 28.6, 21.2; IR (KBr) 3361, 2963, 2359, 2178, 1705, 1635, 1261, 1022, 801, 694; ESI FTMS exact mass calcd for $(C_{31}H_{26}N_4O_3 + H)^+$ requires m/z 503.2083, found m/z 503.2098. The enantiomeric ratio (er) value, 93:7, determined by HPLC (Daicel Chiralpak AS-H, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 15.467 (major), t_R = 23.407 (minor).

*(R)-2′-Amino-1-(2-fluorobenzyl)-1′-(4-methoxyphenyl)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4ab**).* Flash column chromatography eluent, dichloromethane/ethyl acetate = 4/1; reaction time = 4 d; yield 87% (47.8 mg); white solid; mp 256−258 °C; $[\alpha]_D^{20}$ = +18.5 (*c* 0.8, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.58 (m, 1H), 7.35−7.26 (m, 1H), 7.25−7.18 (m, 2H), 7.16−6.95 (m, 7H), 6.65 (d, J = 7.6 Hz, 1H), 5.17−4.95 (m, 2H), 4.24 (s, 2H), 3.87 (s, 3H), 2.27−2.09 (m, 2H), 2.09−2.03 (m, 1H), 1.97−1.87 (m, 1H), 0.97 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 178.8, 160.7, 160.5 (J = 243.6 Hz), 152.2, 151.0, 142.0, 135.3, 130.9, 130.6, 129.6 (J = 3.6 Hz), 128.8 (J = 8 Hz), 128.5, 127.8, 124.6, 123.1, 122.9, 118.6, 115.8 (J = 47.2 Hz), 115.0, 114.8, 111.1, 108.9, 62.8, 55.7, 49.7, 48.7, 42.1, 37.7, 32.5, 29.2, 27.0; IR (KBr) 3472, 2957, 2328, 2148, 1716, 1649, 1609, 1511, 1362, 1252, 1028, 909, 758, 690; ESI FTMS exact mass calcd for $(C_{33}H_{29}FN_4O_3 + H)^+$ requires m/z 549.2302, found m/z 549.2307. The enantiomeric ratio (er) value, 93:7, determined by HPLC (Daicel Chiralpak AS-H, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 8.940 (major), t_R = 14.810 (minor).

*(R)-2′-Amino-1′-(4-methoxyphenyl)-7′,7′-dimethyl-2,5′-dioxo-1-((perfluorophenyl)methyl)-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4ac**).* Flash column chromatography eluent, dichloromethane/ethyl acetate = 4/1; reaction time = 4 d; yield 63% (39.0 mg); white solid; mp 220−221 °C; $[\alpha]_D^{20}$ = +11.0 (*c* 0.6, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.18 (m, 3H), 7.15−7.09 (m, 1H), 7.08−6.98 (m, 3H), 6.93 (d, J = 7.6 Hz, 1H), 5.23 (d, J = 15.2 Hz, 1H), 4.83 (d, J = 15.2 Hz, 1H), 4.20 (s, 2H), 3.89 (s, 3H), 2.22−2.04 (m, 2H), 2.04−1.97 (m, 1H), 1.90 (d, J = 17.2 Hz, 1H), 0.96 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 177.9, 160.7, 151.5 (J = 130.9 Hz), 138.4, 130.8 (J = 30.4 Hz), 128.6, 127.7, 123.1, 123.1, 117.9, 115.7 (J = 34.4 Hz), 110.9, 107.9, 62.5, 55.7, 49.6, 48.2, 42.0, 32.5, 32.0, 28.9, 27.1; IR (KBr) 3475, 3333, 2959, 2187, 1724, 1645, 1363, 1254, 1047, 954, 606; ESI FTMS exact mass calcd for $(C_{33}H_{25}F_5N_4O_3 + H)^+$ requires m/z 621.1925, found m/z 621.1952. The enantiomeric ratio (er) value, 90:10, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 14.587 (minor), t_R = 17.857 (major).

*(R)-1-Allyl-2′-amino-1′-(4-methoxyphenyl)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4ad**).* Flash column chromatography eluent, dichloromethane/ethyl acetate = 4/1; reaction time = 4 d; yield 60% (28.8 mg); white solid; mp 197−198 °C; $[\alpha]_D^{20}$ = +7.7 (*c* 0.6, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.27 (m, 1H), 7.25−7.17 (m, 2H), 7.14−7.09 (m, 1H), 7.09−7.04 (m, 2H), 7.03−6.97 (m, 1H), 6.83 (d, J = 7.6 Hz, 1H), 6.03−5.84 (m, 1H), 5.56−5.41 (m, 1H), 5.32−5.15 (m, 1H), 4.50−4.35 (m, 2H), 4.17 (s, 2H), 3.90 (s, 3H), 2.24−1.99 (m, 3H), 1.96−1.83 (m, 1H), 0.95 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 178.1, 160.7, 152.0, 150.9, 142.3, 135.3, 131.7, 130.9, 130.6, 128.4, 127.8, 122.8, 122.6, 118.4, 117.5, 116.0, 115.5, 111.2, 109.2, 63.0, 55.7, 49.7, 48.5, 42.9, 42.1, 32.5, 29.2, 27.0; IR (KBr) 3315, 3213, 2958, 2924, 2185, 1719, 1650, 1509, 1363, 1252, 848, 605; ESI FTMS exact mass calcd for $(C_{29}H_{28}N_4O_3 + H)^+$ requires m/z 481.2239, found m/z 481.2254. The enantiomeric ratio (er) value, 93:7, determined by HPLC (Daicel Chiralpak AS-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 5.773 (major), t_R = 8.960 (minor).

*(R)-2′-Amino-1′-(4-methoxyphenyl)-1,7′,7′-trimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4ae**).* Flash column chromatography eluent, dichloromethane/ethyl acetate = 4/1; reaction time = 4 d; yield 72% (32.7 mg); white solid; mp 144−145 °C; $[\alpha]_D^{20}$ = +1.6 (*c* 0.6, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.27 (m, 1H), 7.27−7.18 (m, 2H), 7.11 (d, J = 7.2 Hz, 1H), 7.09−7.03 (m, 2H), 7.04−6.97 (m, 1H), 6.84 (d, J = 7.6 Hz, 1H), 4.16 (s, 2H), 3.90 (s, 3H), 3.30 (s, 3H), 2.15 (d, J = 16.0 Hz, 1H), 2.10−2.00 (m, 2H), 1.89 (d, J = 17.2 Hz, 1H), 0.95 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 178.5, 160.7, 151.9, 150.9, 143.2, 135.3, 130.9, 130.6, 128.6, 127.8, 122.7, 122.6, 118.4, 116.0, 115.5, 111.3, 108.1, 62.9, 55.7, 49.7, 48.5, 42.1, 32.5, 29.1, 27.0, 26.7; IR (KBr) 3674, 3445, 2962, 2923, 2359, 2184, 1715, 1645, 1260, 801, 668; ESI FTMS exact mass calcd for $(C_{27}H_{26}N_4O_3 + H)^+$requires m/z 455.2083, found m/z 455.2096. The enantiomeric ratio (er) value, 96:4, determined by HPLC (Daicel Chiralpak AS-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 7.297 (major), t_R = 12.977 (minor).

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*(R)-2′-Amino-1′-(4-methoxyphenyl)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4af**).* Flash column chromatography eluent, dichloromethane/ethyl acetate = 4/1; reaction time = 4 d; yield: 86% (38.0 mg); white solid; mp 269−271 °C; $[\alpha]_D^{20}$ = +6.6 (*c* 0.2, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H), 7.43 (d, *J* = 7.2 Hz, 1H), 7.35 (d, *J* = 7.2 Hz, 1H), 7.24−7.07 (m, 4H), 7.00−6.86 (m, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 5.37 (s, 2H), 3.85 (s, 3H), 2.19−2.06 (m, 2H), 1.97−1.81 (m, 2H), 0.89 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 194.3, 180.0, 160.3, 152.8, 151.9, 141.9, 137.2, 131.7, 131.4, 128.6, 128.1, 123.6, 121.8, 119.5, 116.0, 115.6, 110.7, 109.3, 61.0, 56.0, 49.8, 48.9, 41.8, 32.5, 28.8, 27.1; IR (KBr) 3675, 3385, 2971, 2900, 2359, 1647, 1508, 1260, 1048, 880, 669; ESI FTMS exact mass calcd for $(C_{26}H_{24}N_4O_3+ Na)^+$ requires *m*/*z* 463.1746, found *m*/*z* 463.1731. The enantiomeric ratio (er) value, 90:10, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm) t_R = 21.313 (minor), t_R = 28.627 (major).

*(R)-2′-Amino-1-benzyl-5-methoxy-1′-(4-methoxyphenyl)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4ag**).* Flash column chromatography eluent, dichloromethane/ethyl acetate = 4/1; reaction time = 4 d; yield 84% (46.8 mg); white solid; mp 199−200 °C; $[\alpha]_D^{20}$ = −13.4 (*c* 0.9, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.2 Hz, 2H), 7.37−7.27 (m, 3H), 7.25−7.17 (m, 2H), 7.08−6.94 (m, 2H), 6.78−6.67 (m, 1H), 6.63−6.54 (m, 1H), 6.47 (d, *J* = 8.4 Hz, 1H), 5.13−4.83 (m, 2H), 4.25 (s, 2H), 3.85 (s, 3H), 3.69 (s, 3H), 2.21 (d, *J* = 16.4 Hz, 1H), 2.15−2.02 (m, 2H), 1.95−1.85 (m, 1H), 0.97 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 178.3, 160.7, 156.0, 152.2, 151.0, 136.9, 136.1, 135.9, 130.9, 130.6, 128.6, 127.8, 127.3, 127.2, 118.6, 116.0, 115.5, 111.6, 111.3, 111.1, 109.6, 63.0, 55.7, 55.6, 49.7, 49.0, 44.6, 42.1, 32.5, 29.2, 27.1; IR (KBr) 3462, 3336, 2956, 2836, 2360, 1713, 1648, 1510, 1252, 804, 606, 563; ESI FTMS exact mass calcd for $(C_{34}H_{32}N_4O_4 + H)^+$ requires *m*/*z* 561.2502, found *m*/*z* 561.2515. The enantiomeric ratio (er) value, 90:10, determined by HPLC (Daicel Chiralpak AS-H, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm) t_R = 13.013 (major), t_R = 25.820 (minor).

*(R)-2′-Amino-1-benzyl-1′-(4-methoxyphenyl)-5,7′,7′-trimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4ah**).* Flash column chromatography eluent, dichloromethane/ethyl acetate = 4/1; reaction time = 4 d; yield 74% (40.0 mg); white solid; mp 279−280 °C; $[\alpha]_D^{20}$ = +3.1 (*c* 0.7, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.2 Hz, 2H), 7.38−7.28 (m, 3H), 7.25−7.19 (m, 2H), 7.11−7.00 (m, 2H), 6.95−6.77 (m, 2H), 6.47 (d, *J* = 8.0 Hz, 1H), 5.16−4.85 (m, 2H), 4.21 (s, 2H), 3.88 (s, 3H), 2.26 (s, 3H), 2.23−2.11 (m, 2H), 2.07 (s, 1H), 1.93 (d, *J* = 17.2 Hz, 1H), 0.98 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ194.7, 178.6, 160.7, 152.0, 150.9, 139.9, 136.1, 135.4, 132.0, 131.0, 130.7, 128.8, 128.6, 127.9, 127.2, 127.1, 123.6, 118.7, 116.0, 115.5, 111.3, 109.1, 63.2, 55.7, 49.8, 48.7, 44.5, 42.1, 32.5, 29.1, 27.2, 21.3; IR (KBr) 3445, 2956, 2358, 2180, 1715, 1644, 1362, 1256, 1148, 1029, 806, 701; ESI FTMS exact mass calcd for $(C_{34}H_{32}N_4O_3 + H)^+$ requires *m*/*z* 545.2552, found *m*/*z* 545.2581. The enantiomeric ratio (er) value, 94:6, determined by HPLC (Daicel Chiralpak AS-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm) t_R = 4.960 (major), t_R = 7.477 (minor).

*(R)-2′-Amino-1-benzyl-5-bromo-1′-(4-methoxyphenyl)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4ai**).* Flash column chromatography eluent, dichloromethane/ethyl acetate = 4/1; reaction time = 4 d; yield 82% (49.6 mg); white solid; mp 280−282 °C; $[\alpha]_D^{20}$ = −17.3 (*c* 1.0, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.2 Hz, 2H), 7.39−7.27 (m, 4H), 7.26−7.23 (m, 1H), 7.23−7.14 (m, 2H), 7.14−7.00 (m, 2H), 6.52−6.41 (m, 1H), 5.12−4.92 (m, 2H), 4.23 (s, 2H), 3.90 (s, 3H), 2.28−2.10 (m, 2H), 2.10−2.02 (m, 1H), 1.95 (d, *J* = 17.2 Hz, 1H), 0.99 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 178.1, 160.8, 152.4, 151.0, 141.5, 137.3, 135.5, 131.2, 130.9, 130.6, 128.8, 127.5, 127.4, 127.2, 126.1, 118.3, 116.0, 115.7, 115.4, 110.9, 110.7, 62.5, 55.8, 49.7, 48.8, 44.6, 42.1, 32.5, 28.9, 27.4; IR (KBr) 3451, 3312, 3211, 2956, 2603, 2359, 2186, 1720, 1640, 1362, 1028, 808, 698; ESI FTMS exact mass calcd for $(C_{33}H_{29}BrN_4O_3 + H)^+$ requires *m*/*z* 609.1501, found *m*/*z* 609.1511. The enantiomeric ratio (er) value, 90:10, determined by HPLC (Daicel Chiralpak AS-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm) t_R = 5.853 (major), t_R = 11.587 (minor).

*(R)-2′-Amino-1-benzyl-7-methoxy-1′-(4-methoxyphenyl)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4aj**).* Flash column chromatography eluent, dichloromethane/ethyl acetate = 4/1; reaction time = 4 d; yield 77% (42.9 mg); white solid; mp 209−211 °C; $[\alpha]_D^{20}$ = +24.9 (*c* 0.8, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.2 Hz, 2H), 7.35−7.27 (m, 3H), 7.24−7.14 (m, 2H), 7.10−6.99 (m, 2H), 6.98−6.90 (m, 1H), 6.82−6.69 (m, 2H), 5.31−5.14 (m, 2H), 4.18 (s, 2H), 3.87 (s, 3H), 3.53 (s, 3H), 2.26−2.09 (m, 2H), 2.06 (d, *J* = 6.4 Hz, 1H), 1.96−1.85 (m, 1H), 0.97 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 178.9, 160.7, 152.0, 150.9, 144.9, 139.0, 136.9, 131.0, 130.6, 130.5, 128.1, 128.0, 127.0, 126.3, 123.3, 118.6, 116.0, 115.7, 115.5, 112.9, 111.3, 63.3, 55.8, 55.7, 49.8, 48.7, 46.4, 42.1, 32.5, 29.2, 27.0; IR (KBr) 3442, 3273, 2955, 2836, 2359, 2183, 1655, 1254, 1029, 736, 633; ESI FTMS exact mass calcd for $(C_{34}H_{32}N_4O_4 + H)^+$ requires *m*/*z* 561.2502, found *m*/*z* 561.2510. The enantiomeric ratio (er) value, 96:4, determined by HPLC (Daicel Chiralpak AS-H, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm) t_R = 9.143 (major), t_R = 16.177 (minor).

*(R)-2′-Amino-1-benzyl-1′-(4-methoxyphenyl)-7,7′,7′-trimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4ak**).* Flash column chromatography eluent, dichloromethane/ethyl acetate = 4/1; reaction time = 4 d; yield 72% (39.0 mg); white solid; mp 270−271 °C; $[\alpha]_D^{20}$ = +31.7 (*c* 0.4, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.6 Hz, 2H), 7.43−7.35 (m, 2H), 7.34−7.30 (m, 1H), 7.28−7.17 (m, 2H), 7.13−7.00 (m, 3H), 6.99−6.86 (m, 2H), 5.42−5.20 (m, 2H), 4.19 (s, 2H), 3.91 (s, 3H), 2.32−2.18 (m, 4H), 2.17−2.06 (m, 2H), 1.94 (d, *J* = 17.2 Hz, 1H), 1.00 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 179.6, 160.7, 151.9, 150.8, 140.5, 138.5, 136.3, 132.5, 130.9, 130.6, 128.7, 127.9, 126.7, 126.1, 122.8, 121.0, 119.7, 118.7, 116.0, 115.5, 111.6, 63.7, 55.7, 49.8, 48.1, 45.9, 42.1, 32.5, 29.3, 26.9, 18.7; IR (KBr) 3565, 2931, 2327, 2180, 1690, 1641, 1512, 1363, 1256, 849, 736; ESI FTMS exact mass calcd for $(C_{34}H_{32}N_4O_3 + H)^+$ requires *m*/*z* 545.2552, found *m*/*z* 545.2559. The enantiomeric ratio (er) value, 95:5, determined by HPLC (Daicel Chiralpak AS-H, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm) t_R = 7.850 (major), t_R = 13.960 (minor).

*(R)-2′-Amino-1-benzyl-1′-(4-methoxyphenyl)-5,7,7′,7′-tetramethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4al**).* Flash column chromatography eluent, dichloromethane/ethyl acetate = 4/1; reaction time = 4 d; yield 66% (36.7 mg); white solid; mp 272−273 °C; $[\alpha]_D^{20}$ = +26.9 (*c* 0.7, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.6 Hz, 2H), 7.37−7.27 (m, 3H), 7.25−7.17 (m, 2H), 7.11−6.97 (m, 2H), 6.78 (s, 1H), 6.71 (s, 1H), 5.23 (s, 2H), 4.18 (s, 2H), 3.88 (s, 3H), 2.24 (s, 3H), 2.21−2.16 (m, 3H), 2.15−2.10 (m, 2H), 2.09−2.04 (m, 1H), 1.93 (d, *J* = 17.2 Hz, 1H), 0.97 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 179.6, 160.7, 151.9, 150.7, 138.5, 138.0, 136.5, 133.1, 132.0, 131.0, 130.7, 128.7, 127.9, 126.7, 126.1, 121.8, 119.3, 118.8, 116.0, 115.5, 111.6, 63.8, 55.7, 49.8, 48.2, 45.9, 42.1, 32.5, 29.1, 27.1, 21.0, 18.6; IR (KBr) 3627, 2954, 2359, 2181, 1699, 1643, 1557, 1363, 1253, 1029, 930, 752, 668; ESI FTMS exact mass calcd for $(C_{35}H_{34}N_4O_3 + H)^+$ requires *m*/*z* 559.2709, found *m*/*z* 559.2720. The enantiomeric ratio (er) value, 97:3, determined by HPLC (Daicel Chiralpak AS-H, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm) t_R = 6.527 (major), t_R = 11.353 (minor).

*(R)-Ethyl 2′-amino-1-benzyl-3′-cyano-6′-methyl-2-oxospiro-[indoline-3,4′-pyran]-5′-carboxylate (**6**).* Flash column chromatography eluent, dichloromethane/ethyl acetate = 4/1; reaction time = 4 d; yield 36% (14.9 mg); white solid; mp 209−211 °C; $[\alpha]_D^{20}$ = +14.9 (*c* 0.4, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.2 Hz, 2H), 7.40−7.33 (m, 2H), 7.31 (s, 1H), 7.24−7.11 (m, 2H), 7.08−6.99 (m, 1H), 6.77−6.71 (m, 1H), 5.12 (d, *J* = 15.6 Hz, 1H), 4.85 (d, *J* = 14.8 Hz, 1H), 4.79 (s, 2H), 3.98−3.85 (m, 1H), 3.68−3.53 (m, 1H),

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2.43 (s, 3H), 0.77−0.57 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 164.6, 159.5, 158.5, 142.8, 135.5, 133.2, 129.1, 128.7, 127.7, 123.6, 123.2, 116.7, 109.3, 105.2, 61.0, 60.7, 44.6, 19.1, 13.3; IR (KBr) 3391, 2922, 2359, 2192, 1715, 1362, 1082, 794, 668; ESI FTMS exact mass calcd for $(C_{24}H_{21}N_3O_4 + H)^+$ requires m/z 416.1610, found m/z 416.1600. The enantiomeric ratio (er) value, 87:13, determined by HPLC (Daicel Chiralpak AS-H, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 8.320 (major), t_R = 10.080 (minor).

Procedure for the Synthesis of Intermediate A. To the mixture of *N*-benzyl-substituted isatin **2a** (3 mmol), malononitrile **3** (3 mmol), and $MgSO_4$ (1 g) was added dichloromethane (20 mL). After being stirred at rt for 1 h, the reaction mixture was filtered to remove the $MgSO_4$. The resultant solution was concentrated under reduced pressure to give the residue, which was purified through flash column chromatography on silica gel to afford pure product **A**.

2-(1-Benzyl-2-oxoindolin-3-ylidene)malononitrile (Intermediate A). Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 1 h; yield 86% (735.2 mg); purple solid; mp 200−202 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 7.8 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.41−7.28 (m, 5H), 7.11 (t, J = 7.6 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 4.91 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 149.2, 146.2, 137.6, 134.2, 129.1, 128.4, 127.5, 126.9, 123.9, 118.3, 112.3, 110.6, 82.9, 44.2; IR (KBr) 3492, 2228, 1719, 1612, 1593, 1470, 1348, 1110, 1084, 789, 629; ESI FTMS exact mass calcd for $(C_{18}H_{11}N_3O + H)^+$ requires m/z 286.0980, found m/z 286.0982.

Procedure for the Synthesis of Compound 7. Freshly distilled dichloromethane (1 mL) was added to the mixture of compound **4aa** (0.2 mmol) and DMAP (0.05 mol) in a dried reaction bottle. After Et_3N (0.8 mmol) was added, the reaction mixture was stirred at room temperature for 15 min. Then, benzoyl chloride (0.3 mmol) and distilled dichloromethane (1 mL) were added to the reaction mixture, which was stirred at room temperature for 2 days. After completion of the reaction as indicated by TLC, 1 M HCl was added to the reaction mixture, which was further extracted by dichloromethane and dried by anhydrous Na_2SO_4. The resultant organic layer was concentrated under reduced pressure to give the residue, which was purified through flash column chromatography on silica gel to afford pure product **7**.

(R)-N-(1-Benzyl-3′-isocyano-1′-(4-methoxyphenyl)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro[indoline-3,4′-quinolin]-2′-yl)benzamide (7). Flash column chromatography eluent, petroleum ether/ethyl acetate = 1/1; reaction time = 2 d; yield 70% (89.0 mg); white solid; mp 175−176 °C; $[\alpha]_D^{20}$ = −11.5 (*c* 0.2, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.3 Hz, 2H), 7.43 (d, *J* = 6.8 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.24−7.21 (m, 1H), 7.18−7.11 (m, 4H), 7.09−7.04 (m, 1H), 7.04−6.96 (m, 4H), 6.95−6.89 (m, 1H), 6.81−6.74 (m, 1H), 6.59 (d, *J* = 7.6 Hz, 1H), 5.19 (d, *J* = 16.0 Hz, 1H), 4.95 (d, *J* = 16.0 Hz, 1H), 3.75 (s, 3H), 2.30 (d, *J* = 16.0 Hz, 1H), 2.18 (d, *J* = 17.2 Hz, 1H), 2.12 (d, *J* = 16.0 Hz, 1H), 1.90 (d, *J* = 17.2 Hz, 1H), 0.99 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 176.9, 169.7, 160.8, 152.5, 146.1, 142.0, 135.9, 134.0, 133.9, 132.6, 132.6, 131.3, 130.6, 129.3, 128.6, 128.0, 127.9, 127.3, 127.2, 115.4, 114.8, 111.1, 109.5, 91.6, 55.7, 50.9, 49.8, 44.8, 41.9, 32.5, 29.5, 26.6; IR (KBr) 3543, 3120, 2707, 2292, 1867, 1449, 1025, 612; ESI FTMS exact mass calcd for $(C_{40}H_{34}N_4O_4 + H)^+$ requires m/z 635.2658, found m/z 635.2660. The enantiomeric ratio (er) value, 95:5, determined by HPLC (Daicel Chiralpak OD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 7.510 (major), t_R = 15.377 (minor).

■ ASSOCIATED CONTENT

Supporting Information

Screening of catalysts and optimization of reaction conditions, characterization data (including ^{1}H, ^{13}C NMR and HPLC spectra) of products **4**, **6** and **7**, single crystal data of product **4aa**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01598.

Screening of catalysts and optimization of reaction conditions; characterization data (including ^{1}H, ^{13}C NMR and HPLC spectra) of products **4**, **6**, and **7**; single-crystal data of product **4aa** (PDF)

X-ray data for compound **4aa** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For some selected examples, see: (a) Jossang, A.; Jossang, P.; Hadi, H. A.; Sevenet, T.; Bodo, B. *J. Org. Chem.* **1991**, *56*, 6527. (b) Cui, C. B.; Kakeya, H.; Osada, H. *Tetrahedron* **1996**, *52*, 12651. (c) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (d) Murugan, R.; Anbazhagan, S.; Sriman Narayanan, S. *Eur. J. Med. Chem.* **2009**, *44*, 3272. (e) Kumari, G.; Nutan; Modi, M.; Gupta, S. K.; Singh, R. K. *Eur. J. Med. Chem.* **2011**, *46*, 1181. (f) Cao, Z.-Y.; Wang, X.; Tan, C.; Zhao, X.-L.; Zhou, J.; Ding, K. *J. Am. Chem. Soc.* **2013**, *135*, 8197. (g) Yin, X.-P.; Zeng, X.-P.; Liu, Y.-L.; Liao, F.-M.; Yu, J.-S.; Zhou, F.; Zhou, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 13740.

(2) For a recent review, see: (f) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104.

(3) (a) Ghozlan, S. A. S.; Mohamed, M. F.; Ahmed, A. G.; Shouman, S. A.; Attia, Y. M.; Abdelhamid, I. A. *Arch. Pharm.* **2015**, *348*, 113. (b) Goldfarb, D. S. U.S. Pat. Appl. Publ. US 20090163545 A1 20090625, 2009.

(4) (a) Baharfar, R.; Azimi, R. *J. Chem. Sci.* **2015**, *127*, 1389. (b) Ansorge, S.; Bank, U.; Nordhoff, K.; Tager, M.; Striggow, F. *PCT Int. Appl.* WO 2005037257 A2 20050428, 2005.

(5) For some selected examples, see: (a) Chen, H.; Shi, D.-Q. *J. Comb. Chem.* **2010**, *12*, 571. (b) Quiroga, J.; Portillo, S.; Perez, A.; Galvez, J.; Abonia, R.; Insuasty, B. *Tetrahedron Lett.* **2011**, *52*, 2664. (c) Hao, W.-J.; Wang, S.-Y.; Ji, S.-J. *ACS Catal.* **2013**, *3*, 2501. (d) Khalafi-Nezhad, A.; Mohammadi, S. *ACS Comb. Sci.* **2013**, *15*, 512. (e) Kang, S. R.; Lee, Y. R. *Synthesis* **2013**, *45*, 2593. (f) Mondal, A.; Mukhopadhyay, C. *ACS Comb. Sci.* **2015**, *17*, 404. (g) De, K.; Bhaumik, A.; Banerjee, B.; Mukhopadhyay, C. *Tetrahedron Lett.* **2015**, *56*, 1614.

(6) (a) Yeung, B. K. S.; Zou, B.; Rottmann, M.; Lakshminarayana, S. B.; Ang, S. H.; Leong, S. Y.; Tan, J.; Wong, J.; Keller-Maerki, S.; Fischli, C.; Goh, A.; Schmitt, E. K.; Krastel, P.; Francotte, E.; Kuhen, K.; Plouffe, D.; Henson, K.; Wagner, T.; Winzeler, E. A.; Petersen, F. R.; Brun; Dartois, V.; Diagana, T. T.; Keller, T. H. *J. Med. Chem.* **2010**, *53*, 5155. (b) Chinigo, G. M.; Paige, M.; Grindrod, S.; Hamel, E.; Dakshanamurthy, S.; Chruszcz, M.; Minor, W.; Brown, M. L. *J. Med. Chem.* **2008**, *51*, 4620.

(7) For some reviews, see: (a) Shen, K.; Liu, X.; Lin, L.; Feng, X. *Chem. Sci.* **2012**, *3*, 327. (b) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381. (c) Klein, J. E. M. N.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2011**, *2011*, 6821. (d) Dou, X. W.; Lu, Y. X. *Chem. - Eur. J.* **2012**, *18*, 8315. (e) Rios, R. *Chem. Soc. Rev.* **2012**, *41*, 1060. (f) Hong, L.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 1023. (g) Cheng, D.; Ishihara, Y.; Tan, B.; Barbas, C. F., III *ACS Catal.* **2014**, *4*, 743.

(8) For representative examples on the catalytic enantioselective synthesis of spirooxindoles using 3-isothiocyanato oxindoles, see:

DOI: 10.1021/acs.joc.6b01598
J. Org. Chem. 2016, 81, 7898−7907

(a) Chen, W.-B.; Wu, Z.-J.; Hu, J.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2011**, *13*, 2472. (b) Kato, S.; Yoshino, T.; Shibasaki, M.; Kanai, M.; Matsunaga, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 7007. (c) Wu, H.; Zhang, L.-L.; Tian, Z.-Q.; Huang, Y.-D.; Wang, Y.-M. *Chem. - Eur. J.* **2013**, *19*, 1747. (d) Tan, F.; Lu, L.-Q.; Yang, Q.-Q.; Guo, W.; Bian, Q.; Chen, J.-R.; Xiao, W.-J. *Chem. - Eur. J.* **2014**, *20*, 3415. (e) Kayal, S.; Mukherjee, S. *Eur. J. Org. Chem.* **2014**, *2014*, 6696. (f) Zhao, J.-Q.; Zhou, M.-Q.; Wu, Z.-J.; Wang, Z.-H.; Yue, D.-F.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2015**, *17*, 2238. (g) Kayal, S.; Mukherjee, S. *Org. Lett.* **2015**, *17*, 5508.

(9) For selected reviews on organocatalytic asymmetric reactions, see: (a) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (b) Zhou, J. *Chem. - Asian J.* **2010**, *5*, 422. (c) Li, J.-L.; Liu, T.-Y.; Chen, Y.-C. *Acc. Chem. Res.* **2012**, *45*, 1491. (d) Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9748. (e) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 253. (f) Wang, Y.; Lu, H.; Xu, P.-F. *Acc. Chem. Res.* **2015**, *48*, 1832. (g) Zhang, L.; Fu, N.; Luo, S. *Acc. Chem. Res.* **2015**, *48*, 986. (h) Wang, T.; Han, X.; Zhong, F.; Yao, W.; Lu, Y. *Acc. Chem. Res.* **2016**, *49*, 1369.

(10) For selected recent examples, see: (a) Liu, Y.-L.; Wang, X.; Zhao, Y.-L.; Zhu, F.; Zeng, X.-P.; Chen, L.; Wang, C.-H.; Zhao, X.-L.; Zhou, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 13735. (b) Manna, M. S.; Mukherjee, S. *Chem. Sci.* **2014**, *5*, 1627. (c) Manna, M. S.; Mukherjee, S. *J. Am. Chem. Soc.* **2015**, *137*, 130. (d) Yu, J.-S.; Liao, F.-M.; Gao, W.-M.; Liao, K.; Zuo, R.-L.; Zhou, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 7381. (e) Ni, Q.; Xiong, J.; Song, X.; Raabe, G.; Enders, D. *Chem. Commun.* **2015**, *51*, 14628. (f) Zou, L.-H.; Philipps, A. R.; Raabe, G.; Enders, D. *Chem. - Eur. J.* **2015**, *21*, 1004. (g) Yao, W.; Dou, X.; Lu, Y. *J. Am. Chem. Soc.* **2015**, *137*, 54. (h) Wang, T.; Yu, Z.; Hoon, D. L.; Phee, C. Y.; Lan, Y.; Lu, Y. *J. Am. Chem. Soc.* **2016**, *138*, 265.

(11) For some reviews, see: (a) de Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969. (b) Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 237.

(12) For selected recent examples, see: (a) Tong, M.-C.; Chen, X.; Tao, H.-Y.; Wang, C.-J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12377. (b) Guo, H.; Liu, H.; Zhu, F.-L.; Na, R.; Jiang, H.; Wu, Y.; Zhang, L.; Li, Z.; Yu, H.; Wang, B.; Xiao, Y.; Hu, X.-P.; Wang, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 12641. (c) Huang, J.; Luo, S.; Gong, L. *Huaxue Xuebao* **2013**, *71*, 879. (d) Dai, W.; Lu, H.; Li, X.; Shi, F.; Tu, S.-J. *Chem. - Eur. J.* **2014**, *20*, 11382. (e) Chen, X.; Qi, Z.-H.; Zhang, S.-Y.; Kong, L.-P.; Wang, Y.; Wang, X.-W. *Org. Lett.* **2015**, *17*, 42. (f) Chen, X.; Zhang, J.-Q.; Yin, S.-J.; Li, H.-Y.; Zhou, W.-Q.; Wang, X.-W. *Org. Lett.* **2015**, *17*, 4188.

(13) (a) Zhang, Y.-C.; Zhao, J.-J.; Jiang, F.; Sun, S.-B.; Shi, F. *Angew. Chem., Int. Ed.* **2014**, *53*, 13912. (b) Zhao, J.-J.; Sun, S.-B.; He, S.-H.; Wu, Q.; Shi, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 5460. (c) Zhang, Y.-C.; Zhu, Q.-N.; Yang, X.; Zhou, L.-J.; Shi, F. *J. Org. Chem.* **2016**, *81*, 1681.

(14) For a review, see: (a) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7496. For some selected examples, see: (b) Chen, W.-B.; Wu, Z.-J.; Pei, Q.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2010**, *12*, 3132. (c) Guo, W.; Wang, X.; Zhang, B.; Shen, S.; Zhou, X.; Wang, P.; Liu, Y.; Li, C. *Chem. - Eur. J.* **2014**, *20*, 8545. (d) Madhusudhan Reddy, G.; Ko, C.-T.; Hsieh, K.-H.; Lee, C.-J.; Das, U.; Lin, W. *J. Org. Chem.* **2016**, *81*, 2420.

(15) CCDC 1483323 for compound **4aa**. See the Supporting Information for details.

(16) For selected examples on isatylidene malononitrile **A**-involved enantioselective reactions, see: (a) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 7837. (b) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Chem. Sci.* **2012**, *3*, 1231. (c) Han, X.; Chan, W.-L.; Yao, W.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2016**, *55*, 6492.

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J. Org. Chem. 2016, 81, 7898−7907