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# A Catalytic Asymmetric Isatin-Involved Povarov Reaction: Diastereo- and Enantioselective Construction of Spiro[indolin-3,2′-quinoline] Scaffold

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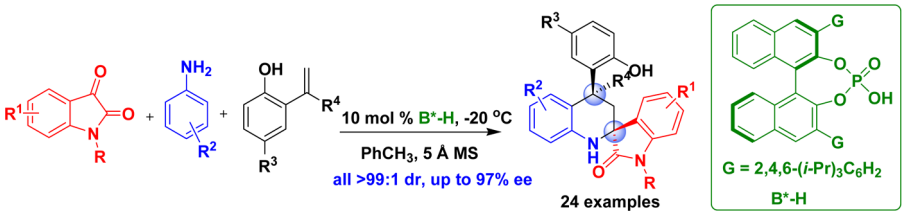
## ABSTRACT




**The first catalytic asymmetric isatin-involved Povarov reaction has been established. This method provides an unprecedented approach to access the enantioenriched spiro[indolin-3,2′-quinoline] scaffold with concomitant creation of two quaternary stereogenic centers in high yields and excellent stereoselectivities (all >99:1 *dr*'s, up to 97% *ee*).**

The Povarov reaction[1] has exhibited its great significance in organic synthesis, which represents an inverse electron-demand aza-Diels–Alder reaction (IEDDA reaction) between 2-azadienes and electronically rich olefins. In particular, the catalytic asymmetric Povarov reaction is a powerful protocol to obtain enantioselective tetrahydroquinoline skeletons, which exist in a variety of natural products and synthetic compounds with relevant pharmaceutical properties.[2] As a result, the catalytic enantioselective Povarov reactions of aldehyde-derived 2-azadienes with electron-rich olefins have been extensively investigated and well-developed in the past decades (eq 1).[3] However, in sharp contrast, *ketone-derived 2-azadienes have not yet been employed as* reaction *components* to participate in the catalytic enantioselective Povarov reactions (eq 2). Only a few nonenantioselective Povarov reactions of ketimines with olefins were sporadically documented,[4] presumably due to the low reactivity inherent in both ketones and its

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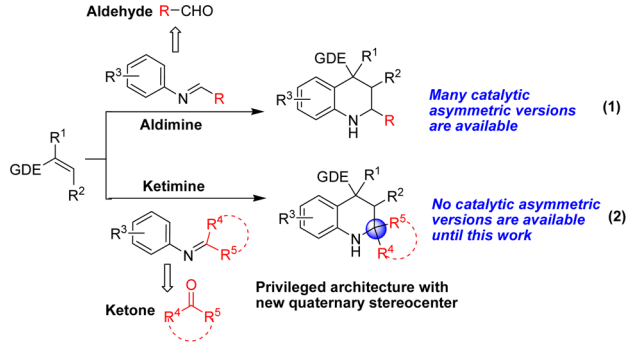
2-azadiene derivatives. Therefore, the development of ketone-involved Povarov reactions, especially the catalytic asymmetric transformations, has become an urgent need in the organic community.



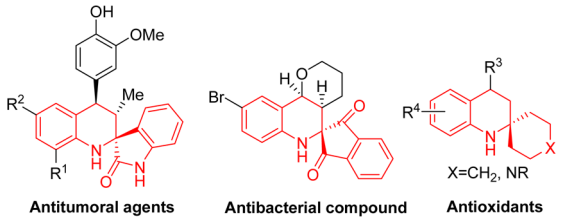




**Figure 1.** Bioactive spiro-tetrahydroquinolines.

More importantly, the asymmetric Povarov reaction with ketones, in particular with unsymmetrical cyclic ketones, would directly furnish enantioenriched spiro-tetrahydroquinolines with a new quaternary stereogenic center (eq 2), which defines the characteristic structural core of a large family of heterocycles with pronounced and diverse bioactivities (Figure 1).[4b,5] Of particular concern is that isatins, a type of unsymmetrical cyclic ketones with high activity, have emerged as privileged building blocks in the synthesis of spiro-fused heterocycles with potential bioactivities.[6] In this context, the asymmetric Povarov reaction of isatin-derived 2-azadiene with electron-rich olefins would allow for the construction of an optically pure spiro[indolin-3,2′-quinoline] scaffold, which constitutes the core structural element of antitumoral molecules[4b] (in Figure 1) and hence holds great synthetic importance.

We recently described a number of chiral phosphoric acid[7] catalyzed multicomponent reactions for the synthesis of enantioenriched heterocycles with biological relevance.[3m,8] Inspired by the above success and the fact that there has not been a report on an enantioselective ketone-involved Povarov reaction for the synthesis of important spiro-[indolin-3,2′-quinoline] scaffolds, we considered utilizing isatin in the asymmetric Povarov reaction, wherein the isatin-derived ketimine should be activated by the chiral phosphoric acid. In this work, we present the first enantioselective ketone-involved Povarov reaction, which directly assembles isatins, anilines, and styrenes into biologically important spiro[indolin-3,2′-quinolines] with two quaternary stereogenic centers in high yields and excellent stereoselectivities (all >99:1 *dr*'s, up to 97% *ee*).

Our study commenced with a three-component reaction of 1-benzylisatin **1a**, 4-methoxyaniline **2a**, and α-methyl *o*-hydroxystyrene **3a** in the presence of 10 mol % of chiral phosphoric acids **5** in toluene at 50 °C (Table 1). All the chiral phosphoric acids **5** enabled the reaction to proceed smoothly to afford a single diastereomer of spiro[indolin-3,2′-quinoline] **4aaa** in high yields but with various levels of enantioselectivity (entries 1−6). The results revealed that 2,4,6-triisopropylphenyl-substituted phosphoric acid (Trip-PA) **5f** was far more superior to other analogues with regard to enantioselectivity (entry 6 vs 1−5). The subsequent screening of the solvents at 25 °C disclosed that toluene was the most suitable reaction media, affording the desired product in 92% yield and 81% *ee* (entry 7 vs 8−10). Lowering the reaction temperature from 25 to −20 °C led to a substantial increase in the enantioselectivity with maintained reactivity (entries 7, 11−12), but lowering the temperature further to −30 °C resulted in a moderate yield albeit with an excellent enantiomeric excess (entry 13). Finally, increasing the stoichiometry of **3a** rendered the reaction to proceed at −20 °C in a quantitative yield of 99% with a maintained enantioselectivity of 94% *ee* (entry 14 vs 12).

With the optimal conditions in hand, we then carried out the investigation on the substrate scope of isatins **1** (Table 2). At first, isatins bearing different types of *N*-substituents were utilized as substrates (entries 1−5), which demonstrated that this approach was applicable to various isatins with *N*-benzyl, alkyl, or phenyl substituents, affording spiro[indolin-3,2′-quinolines] in excellent diastereoselectivities (all >99:1 *dr*s) and with a high level of enantiomeric excesses (up to 97% *ee*). Generally speaking, isatins with *N*-benzyl groups were superior to those with *N*-alkyl or *N*-phenyl groups in terms of yield and enantioselectivity (entries 1−3 vs 4−5). As for *N*-benzyl substituted isatins, changing the substituents on the benzyl group had some delicate effect on the enantioselectivity (entries 1−3). Notably, the perfluorinated *N*-benzylisatin **1c** exhibited the highest capability of affording the corresponding product in 99% yield and 97% *ee* (entry 3). Basically, the reactivity of *N*-alkyl and *N*-phenyl substituted isatins was lower than that of *N*-benzylisatins; therefore the reaction temperature was increased to 50 °C to render a cleaner reaction (entries 4−5). Moreover, the use of $CCl_4$ as

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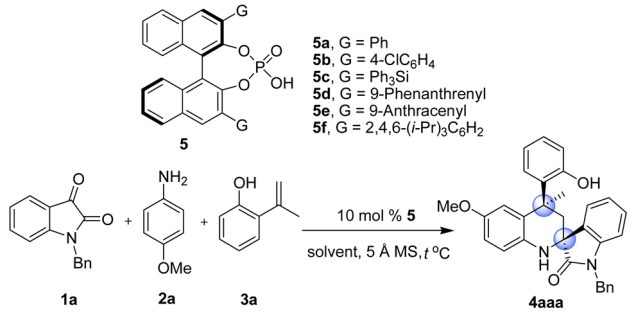
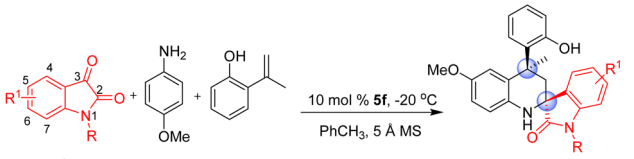
**Table 1.** Optimization of Reaction Conditions[a]




| entry | 5 | solvent | $t$ (°C) | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | **5a** | $PhCH_3$ | 50 | 81 | 36 |
| 2 | **5b** | $PhCH_3$ | 50 | 97 | 14 |
| 3 | **5c** | $PhCH_3$ | 50 | 99 | 10 |
| 4 | **5d** | $PhCH_3$ | 50 | 99 | 43 |
| 5 | **5e** | $PhCH_3$ | 50 | 99 | 44 |
| 6 | **5f** | $PhCH_3$ | 50 | 99 | 76 |
| 7 | **5f** | $PhCH_3$ | 25 | 92 | 81 |
| 8 | **5f** | $CH_2Cl_2$ | 25 | 12 | 73 |
| 9 | **5f** | $CHCl_3$ | 25 | 19 | 69 |
| 10 | **5f** | $CCl_4$ | 25 | 99 | 78 |
| 11 | **5f** | $PhCH_3$ | 0 | 99 | 88 |
| 12[d] | **5f** | $PhCH_3$ | −20 | 90 | 93 |
| 13[d] | **5f** | $PhCH_3$ | −30 | 58 | 95 |
| 14[d,e] | **5f** | $PhCH_3$ | −20 | 99 | 94 |

[a] Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in solvent (1 mL) with 5 Å MS (150 mg) for 48 h, and the ratio of **1a**/**2a**/**3a** was 1.2/1/2.4. [b] Isolated yield and a single diastereomer was observed unless indicated otherwise. [c] Determined by HPLC. [d] The reaction time was 84 h. [e] The ratio of **1a**/**2a**/**3a** was 1.2/1/3.6.

**Table 2.** Substrate Scope of Isatins[a]




| entry | 4 | $R^1$/R (1) | yield (%)[b] | dr (%)[c] | ee (%)[d] |
|---|---|---|---|---|---|
| 1 | **4aaa** | H/Bn (**1a**) | 99 | >99:1 | 94 |
| 2 | **4baa** | H/*p*-*t*Bu$C_6H_4CH_2$ (**1b**) | 90 | >99:1 | 93 |
| 3 | **4caa** | H/$C_6F_5CH_2$ (**1c**) | 99 | >99:1 | 97 |
| 4 | **4daa** | H/*i*Pr (**1d**) | 41[e] (79[f]) | >99:1[e] (>99:1[f]) | 88[e] (84[f]) |
| 5 | **4eaa** | H/Ph (**1e**) | 31[e] (56[g]) | >99:1[e] (>99:1[g]) | 90[e] (82[g]) |
| 6[e] | **4faa** | 5-Cl/Bn (**1f**) | 65 | >99:1 | 81 |
| 7 | **4gaa** | 6-F/Bn (**1g**) | 76 | >99:1 | 96 |
| 8 | **4haa** | 6-Cl/Bn (**1h**) | 95 | >99:1 | 97 |
| 9 | **4iaa** | 6-Br/Bn (**1i**) | 99 | >99:1 | 93 |
| 10 | **4jaa** | 6-$CH_3$/Bn (**1j**) | 99 | >99:1 | 96 |
| 11 | **4kaa** | 7-F/Bn (**1k**) | 99 | >99:1 | 92 |
| 12 | **4laa** | 7-Br/Bn (**1l**) | 99 | >99:1 | 93 |
| 13 | **4maa** | 7-$CF_3$/Bn (**1m**) | 89 | >99:1 | 94 |
| 14 | **4naa** | 7-$CH_3$/Bn (**1n**) | 60 | >99:1 | 94 |
| 15 | **4oaa** | 5,6-$F_2$/Bn (**1o**) | 87 | >99:1 | 93 |
| 16 | **4paa** | 7-Br/*p*-*t*Bu$C_6H_4CH_2$ (**1p**) | 63 | >99:1 | 95 |

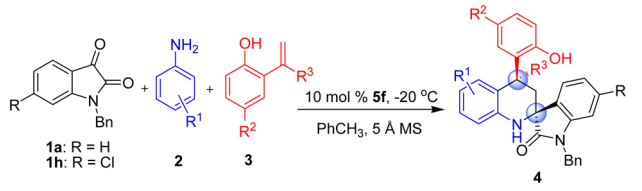
[a] Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in toluene (1 mL) with 5 Å MS (150 mg) at −20 °C for 84 h, and the ratio of **1**/**2a**/**3a** was 1.2/1/3.6. [b] Isolated yield. [c] Determined by $^1$H NMR. [d] Determined by HPLC. [e] Performed at 50 °C. [f] In the presence of 15 mol % **5f** with 4 Å MS at 50 °C in $CCl_4$. [g] Performed at 50 °C in $CCl_4$ with 4 Å MS.

solvent greatly improved the yield but with a slightly decreased enantioselectivity (entries 4−5, in parentheses). Then, the influence of various substituents at different positions of the phenyl moiety of isatins on the reaction was investigated. As shown in entries 6−16, this protocol is amenable to a wide range of electronically different substituents at the C5, C6, or C7 position of isatins, delivering structurally diverse spiro[indolin-3,2′-quinolines] in high yields (60−99%) and good stereoselectivities (all >99:1 *dr*'s, 81−97% *ee*'s). The position of the substituent seemingly exerts some influence on the enantioselectivity and reactivity. For instance, the C5-substituted isatin exemplified by **1f** showed lower reactivity and enantioselectivity than C6- or C7-substituted analogues; thus the reaction was conducted at 50 °C (entry 6). The C6- or C7-substituted isatins regardless of the electronic feature of the substituents were able to deliver high yields and excellent enantioselectivities (92−97% *ee*s), and no remarkable difference in the stereoselectivity was observed between the C6- and C7-substituted isatins (entries 7−14 and 16). Moreover, C5,C6-disubstituted isatin **1o** also smoothly participated in the reaction with 93% *ee* and 87% yield (entry 15).

Next, the substrate scope with respect to anilines **2** was explored by the reaction with isatin **1a** or **1h** and α-methyl *o*-hydroxystyrene **3a** (Table 3, entries 1−6). The results disclosed that the anilines substituted with electron-donating groups served as appropriate substrates, providing the corresponding products in good yields (70−99%) and excellent stereoselectivities (all >99:1 *dr*'s, 91−97% *ee*'s, entries 1−5). In addition, the anilines with electron-withdrawing groups such as **2d** could also be employed to react with excellent diastereoselectivity and reasonable enantioselectivity (>99:1 *dr*, 78% *ee*, entry 6). The generality for α-alkyl *o*-hydroxystyrenes **3** was also examined by the reaction with isatin **1h** and 4-methoxyaniline **2a**. Several α-alkyl *o*-hydroxystyrenes bearing different substituents on their benzene rings or with different α-alkyl groups were accommodated in the reaction, leading to the generation of desired products in high yields (86−99%) and good stereoselectivities (all >99:1 *dr*s, 89−97% *ee*s, entries 1 and 7−9). Significantly, the use of α-alkyl *o*-hydroxystyrenes as dienophiles to react with isatin-derived ketimine provides an easy access to optically pure spiro[indolin-3,2′-quinolines] with two quaternary stereogenic centers, one of which is an all-carbon quaternary chiral center.

The absolute configuration of compound **4had** (>99% *ee* after recrystallization) was unambiguously determined to be

**Table 3.** Substrate Scope of Anilines and α-Alkyl *o*-Hydroxystyrenes[a]




| entry | 4 | 1 | $R^1$ (2) | $R^2/R^3$ (3) | yield (%)[b] | dr (%)[c] | ee (%)[d] |
|---|---|---|---|---|---|---|---|
| 1 | **4haa** | **1h** | 4-OMe (**2a**) | H/Me (**3a**) | 95 | >99:1 | 97 |
| 2 | **4aba** | **1a** | 4-OEt (**2b**) | H/Me (**3a**) | 70 | >99:1 | 94 |
| 3 | **4hba** | **1h** | 4-OEt (**2b**) | H/Me (**3a**) | 99 | >99:1 | 97 |
| 4 | **4aca** | **1a** | 4-OPh (**2c**) | H/Me (**3a**) | 99 | >99:1 | 91 |
| 5 | **4hca** | **1h** | 4-OPh (**2c**) | H/Me (**3a**) | 99 | >99:1 | 95 |
| 6[e] | **4ada** | **1a** | 4-F (**2d**) | H/Me (**3a**) | 44 | >99:1 | 78 |
| 7 | **4hab** | **1h** | 4-OMe (**2a**) | Me/Me (**3b**) | 99 | >99:1 | 90 |
| 8 | **4hac** | **1h** | 4-OMe (**2a**) | OMe/Me (**3c**) | 86 | >99:1 | 90 |
| 9 | **4had** | **1h** | 4-OMe (**2a**) | H/Et (**3d**) | 87 | >99:1 | 89 |

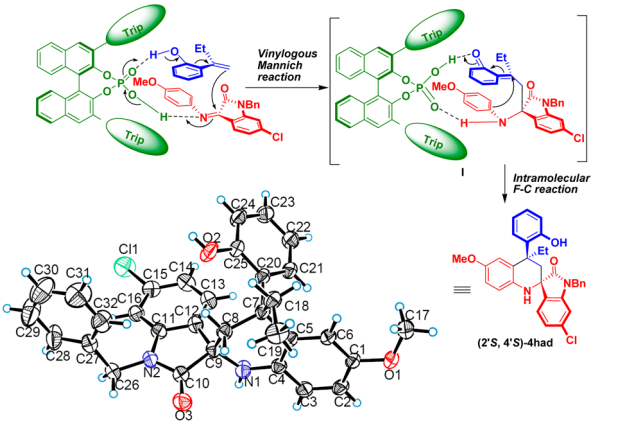
[a] Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in toluene (1 mL) with 5 Å MS (150 mg) at −20 °C for 84 h, and the ratio of **1**/**2**/**3** was 1.2/1/3.6. [b] Isolated yield. [c] Determined by $^1$H NMR. [d] Determined by HPLC. [e] Performed at 50 °C.

(2′*S*,4′*S*) by single-crystal X-ray diffraction analysis (in Scheme 1).[9] The configurations of other spiro[indolin-3,2′-quinolines] were assigned by analogy.

Based on our experimental results and recent related studies on the reaction mechanism,[3m] we proposed a plausible reaction pathway to explain the stereochemistry of the isatin-involved Povarov reaction (Scheme 1). As exemplified by the formation of **4had**, α-ethyl *o*-hydroxystyrene **3d** initially participated in the vinylogous Mannich reaction with the ketimine generated from isatin **1h** and aniline **2a** under

(9) CCDC 910489. See the Supporting Information for details.

**Scheme 1.** Proposed Reaction Mechanism




the catalysis of chiral phosphoric acid **5f** via a hydrogen-bonding interaction, generating a transient intermediate **I**, which subsequently underwent an intramolecular Friedel–Crafts reaction facilitated by the same phosphoric acid **5f**, to afford the enantioenriched spiro[indolin-3,2′-quinoline] (2′*S*,4′*S*)-**4had**.

In conclusion, we have realized the first enantioselective isatin-involved Povarov reaction, which is applicable to a variety of reaction components, delivering new spiro-[indolin-3,2′-quinolines] with concomitant creation of two quaternary stereogenic centers in high yields and excellent stereoselectivities (all >99:1 *dr*'s, up to 99% yield and 97% *ee*). This transformation has provided the first example of a ketone-involved asymmetric Povarov reaction and also has offered an efficient method to obtain enantioenriched spiro[indolin-3,2′-quinoline] scaffolds with medicinal relevance.

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**Supporting Information Available.** Experimental details, characterization of new compounds, and crystal data of **4had**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.