Spirooxindoles, containing a spirocyclic system, are unique structural motifs found in a wide range of natural products and bioactive compounds. For instance, Spirotryprostatin B (Fig. 1) was isolated from the fermentation broth of Aspergillus fumigatus and was shown to completely inhibit the G2/M progression of cell division in mammalian tsFT210 cells.† Gelsemium alkaloids (e.g., gelsenicine, gelseidine and gelsedilam) were isolated from the ancient medicine Yakatsu stored in the Shosoin Repository and exhibited a wide range of biological activities, including analgesic, anti-inflammatory, and antitumor effects. Besides, a considerable number of spirooxindoles display anticancer activity. For example, APG-115 and MI77301, which can effectively block the MDM2-p53 protein–protein interaction in cells as MDM2 inhibitors, are under clinical trials as promising anticancer drugs.‡

Consequently, the unique structure of those compounds has attracted much attention from synthetic chemists. Some investigated strategies to access this skeleton include intramolecular reactions via Pictet–Spengler reaction synthesized from tryptamines or tryptophans with isatin (Scheme 1a), oxidative rearrangement of tetrahydro-β-carbolines prepared via Pictet–Spengler reaction (Scheme 1b), metal or small-molecule catalyzed 1,3-dipolar cycloaddition of imino esters with methyleneindolinones (Scheme 1c), Rh-catalyzed [4 + 1] cycloaddition of azocoumpound with vinyl isocyanates (Scheme 1d), chiral iodoarene catalytic oxidative spirocyclization (Scheme 1e), Pd-catalyzed intramolecular addition and domino spirocyclization, intramolecular nucleophilic addition and so on. Despite of several methods developed for the construction of this skeleton, however, less work finished catalytic asymmetric synthesis and preparation of novel chiral spirooxindoles are warmly anticipated. Herein, we report an efficient protocol via an intermolecular condensation/intramolecular Friedel–Crafts reaction to synthesize a new class of 3’4’-dihydro-2’H-spiro[indoline-3,1’-pyrrolo[1,2-a]pyrazin]-2-ones in an asymmetric way.

At the outset of this study, we envisaged that reaction of N-aminoethylpyrroles with isatins, followed by a chiral phosphoric acid-catalyzed asymmetric intramolecular Friedel–Crafts reaction, a new class of valuable chiral 3’,4’-dihydro-2’H-spiro[indoline-3,1’-pyrrolo[1,2-a]pyrazin]-2-ones bearing a quaternary carbon stereocenter were successfully synthesized in good to excellent yields and with moderate to good enantioselectivities under mild reaction conditions.

**Synthesis of six-membered spirooxindoles via a chiral Brønsted acid-catalyzed asymmetric intramolecular Friedel–Crafts reaction†**

Hui-Xuan Chen,† Yaqi Zhang,† Yuyang Zhang,† Xuefeng He,† Zhen-Wei Zhang,† Hao Liang,† Wenhuan He,† Xiaoding Jiang,† Xiangmeng Chen† and Liqin Qiu†

By means of the direct condensation of N-aminoethylpyrroles and isatins, followed by a chiral phosphoric acid-catalyzed asymmetric intramolecular Friedel–Crafts reaction, a new class of valuable chiral 3’,4’-dihydro-2’H-spiro[indoline-3,1’-pyrrolo[1,2-a]pyrazin]-2-ones bearing a quaternary carbon stereocenter were successfully synthesized in good to excellent yields and with moderate to good enantioselectivities under mild reaction conditions.
from BINOL under similar reaction conditions (Table 1). When chiral phosphoric acid PA-4c having a substituent 3,5-
(CH$_3$)$_2$C$_6$H$_3$ at the 3,3$^\prime$-positions was used, the reaction just
only obtained moderate yield and low enantioselectivity (72%
yield and 5% ee). Employment of bulkier catalyst (R)-PA 4e
furnished the product in an excellent yield along with
a moderate improvement in the enantioselection (99% yield
and 21% ee). Catalysis by 2,4,6-triisopropylphenyl
a small protecting group (39% and 68% ee's, respectively,
Table 1, entries 13 and 14). Equivalent ee value was achieved using ether
ether or chloroform (81% and 90% yields; 79% and 78% ee's,
respectively; Table 1, entries 15 and 16). Additionally, reaction
in 1,4-dioxane acquired good yield and ee (Table 1, entry
17; 83% yield and 83% ee). 1,2-Dichloroethane (DCE) gave
similar results as DCM too. Therefore, DCM was selected as
the best solvent. Further studies on nitrogen-protecting
groups revealed that all reactions proceeded smoothly for
different substrates 1 of small or bulky group in this medium.
However, negative influences on the enantioselection were
shown for the substrates without protecting group or with
a small protecting group (39% and 68% ee's, respectively,
Table 1, entries 19 and 20). In spite of bulky N-protecting
group being beneficial to get high yield, the enantioselectivity
decreased a little (97%, 84% and 92% yields; 74%, 74% and
69% ee's, respectively; Table 1, entries 21–23). So, benzyl-
protected substrate is the best choice for the reaction.
Temperature effect was also explored. Conducting the reac-
tion at 0 or 30 °C instead of at room temperature, a noticeable
drop in enantioselectivity was observed (79% and 80% ee's
respectively, entries 24 and 25).

| Entry | Substrate | (R)-PA | Solvent | Temp. [°C] | Yield$^b$ [%] | ee$^c$ [%] |
|-------|-----------|--------|---------|-----------|-------------|-----------|
| 1     | 1a        | 4a     | DCM     | r.t.      | 99          | 5         |
| 2     | 1a        | 4b     | DCM     | r.t.      | 99          | 0         |
| 3     | 1a        | 4c     | DCM     | r.t.      | 72          | 5         |
| 4     | 1a        | 4d     | DCM     | r.t.      | 99          | 0         |
| 5     | 1a        | 4e     | DCM     | r.t.      | 99          | 21        |
| 6     | 1a        | 4f     | DCM     | r.t.      | 99          | 0         |
| 7     | 1a        | 4g     | DCM     | r.t.      | 99          | 0         |
| 8     | 1a        | 4h     | DCM     | r.t.      | 97          | 0         |
| 9     | 1a        | 4i     | DCM     | r.t.      | 96          | 49        |
| 10    | 1a        | 5a     | DCM     | r.t.      | 85          | 88        |
| 11    | 1a        | 5b     | DCM     | r.t.      | 70          | 19        |
| 12    | 1a        | 5a     | THF     | r.t.      | 99          | 80        |
| 13    | 1a        | 5a     | MeCN    | r.t.      | 68          | 62        |
| 14    | 1a        | 5a     | DMF     | r.t.      | 28          | 44        |
| 15    | 1a        | 5a     | Et$_2$O | r.t.      | 81          | 79        |
| 16    | 1a        | 5a     | CH$_3$CN |r.t.  | 90          | 78        |
| 17    | 1a        | 5a     | 1,4-Diox | r.t. | 83          | 83        |
| 18    | 1a        | 5a     | DCE     | r.t.      | 84          | 87        |
| 19    | 1b        | 5a     | DCM     | r.t.      | 89          | 39        |
| 20    | 1c        | 5a     | DCM     | r.t.      | 68          | 68        |
| 21    | 1d        | 5a     | DCM     | r.t.      | 97          | 74        |
| 22    | 1e        | 5a     | DCM     | r.t.      | 84          | 74        |
| 23    | 1f        | 5a     | DCM     | r.t.      | 92          | 69        |
| 24    | 1a        | 5a     | DCM     | 0         | 71          | 79        |
| 25    | 1a        | 5a     | DCM     | 30        | 90          | 80        |

$^a$ Reaction conditions: 1a (0.2 mmol), 2a (1.2 equiv.), (R)-PA (10 mol%), 4 Å MS (30 mg), 2.0 mL of solvent, r.t. − 20 °C, overnight. $^b$ Isolated yield. $^c$ ee was determined by chiral HPLC.
With the set of optimized reaction conditions in hand, we focused our attention on the substrate scope of this catalytic asymmetric intramolecular Friedel–Crafts reaction. At first, substituted isatin derivatives were screened as the substrates in combination with N-aminoethyl pyrrole, affording chiral products in moderate to excellent yields (Table 2). Halogen substitutions at C5 positions of the isatins were tolerated but lower ee values were given for (79%, 90% and 92% yields; 61%, 37% and 32% ee’s respectively). Reaction of isatins bearing an electron-donating group (5-methyl, 3ja and 5-methoxy, 3ia) or an electron-withdrawing group (5-nitro, 3la) achieved relatively lower ee values, which was possibly attributed to two reasons: (1) hydrogen-bonding interactions between the isatin substituents and the catalyst; (2) steric hindrance between the isatin substituents and the catalyst. Obviously, strong hydrogen-bonding interaction led to decrease of the ee value for 3ma (15% ee, 4-fluoro). On the contrary, the ee values for 3na and 3oa increased (61% and 61% ee’s respectively) when the fluorine group was far from the reactive position. In addition, much bulkier 7-isopropyl substituent proved viable and the corresponding product 3pa was obtained with a good ee value (79% ee).

Next, the substrate scope of N-aminoalkylpyrroles was also investigated. As shown in Table 3, 2-methyl substituted pyrrole maintained good reactivity and provided product 3ab in 79% yield with a lower ee of 49%. Introduction of another methyl group at C3 position of the pyrrole ring resulted in lower reactivity and enantioselectivity in comparison to those of the monosubstituted product (3ac, Table 3). In the presence of a Brønsted acid (p-toluenesulfonic acid), racemic 3ad was formed with good regioselectivity (3ad/3ad’ = 5 : 1 determined by 1H NMR), while chiral catalyst (R)-PA 5a gave nearly equal amounts of 3ad and 3ad’ (3ad/3ad’ = 1 : 1.12). Moderate to good enantioselectivities were obtained (46% and 84% ee’s respectively for 3ad and 3ad’, Table 3), albeit with poor regioselectivity. We presumed that the poor regioselectivity might come from the steric hindrance between chiral phosphoric acid PA 5a and the C3-ethyl group of the pyrrole. The cyclization of N-aminoalkylpyrrole with isatin 1a could also furnish the corresponding product 3ae, but both the reactivity and enantioselectivity were poor (9% yield, 12% ee, Table 3). Employing N-aminoethylindole 2f instead of N-aminoalkylpyrroles, the obtained result for product 3f was still satisfactory (73% yield and 80% ee). Similar to di-substituted pyrrole, reaction of 3-methylindole also gained a low ee value (3ac and 3ag, Table 3), which could also be attributed to the increased steric hindrance on chiral phosphoric acid PA 5a introduced in proximity to the reactive position.
Furthermore, a scale up reaction of 1a and 2a was performed, generating product 3aa in 89% yield and 82% ee (Fig. 2). 

Finally, based on the experimental results, together with related studies on CPA-catalyzed reactions,53–55 we proposed a possible reaction pathway to explain the stereochemistry of the formation of spirooxindoles 3 (Scheme 2). Isatins 1 initially participated in a Mannich reaction with N-aminoethylpyrroles 2, affording transient intermediates 6 under the catalysis of Bronsted acid. Through the dual-hydrogen-bond, (R)-CPA 5a interacted with intermediates 6 to realize their catalysis and stereocenter. The enantioenriched spirooxindoles 3 were subsequently yielded via the intramolecular Friedel–Crafts reaction of intermediates 6.

**Conclusions**

In conclusion, we have developed a direct catalytic asymmetric intramolecular Friedel–Crafts reaction of N-aminoethylpyrrole derivatives with isatin derivatives catalyzed by chiral phosphoric acids. This one-pot sequence provides a simple and efficient approach to preparing the new class of 3′,4′-dihydro-2′H-spiro[indoline-3,1′-pyrrolo[1,2-a]pyrazin]-2-ones in good to excellent yields with moderate to good enantioselectivities under mild reaction conditions. Further work with respect to the extension and applications of this methodology is ongoing in our laboratory.

**Conflicts of interest**

There are no conflicts to declare.

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