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Enantioselective Synthesis of Isoquinoline-1,3(2*H*,4*H*)-dione Derivatives via Chiral Phosphoric Acid Catalyzed aza-Friedel–Crafts Reaction

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A highly enantioselective aza-Friedel–Crafts reaction of structurally new ketimines with indoles and pyrrole is developed by using a chiral phosphoric acid as the catalyst. This protocol enables first enantioselective synthesis of isoquinoline-1,3(2*H*,4*H*)-dione derivatives in good to excellent yields (up to 99% yield) and excellent enantioselectivities (up to >99% ee).

Isoquinoline-1,3(2*H*,4*H*)-dione framework is a class of privileged structural motif because of its prevalence in pharmaceutical and biologically active molecules (Figure 1).[1] For example, compound **I** is an excellent aldose reductase inhibitors and has been proved to be effective for the control of certain diabetic complications; importantly, studies suggested that the (*R*)-enantiomer shows higher enantioselectivity for the aldose reductase binding site than the (*S*)-enantiomer.[1c] As a result, increasing efforts have been devoted to the synthesis of structurally diverse isoquinoline-1,3(2*H*,4*H*)-dione derivatives (Figure 2).[2-6] Noteworthily, in the lighting of literature research, existing reports are all non-asymmetric synthesis. As is well-known, the pharmacological activity, metabolic process and toxicity of the enantiomers of chemical drugs containing chiral factors are significantly different in body. Accordingly, enantioselective synthesis delivering the single enantiomer is significant for pharmaceutical sciences. Given the importance of isoquinoline-1,3(2*H*,4*H*)-dione skeleton and the enantioselective synthesis of these compounds remaining to date elusive, the development of effective method for enantioselective synthesis of which is in high demand.

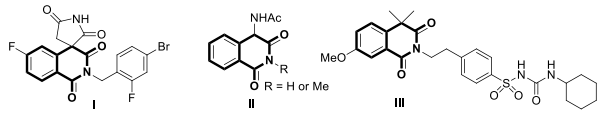

Figure 1. Bioactive isoquinoline-1,3(2*H*,4*H*)-dione-containing molecules.

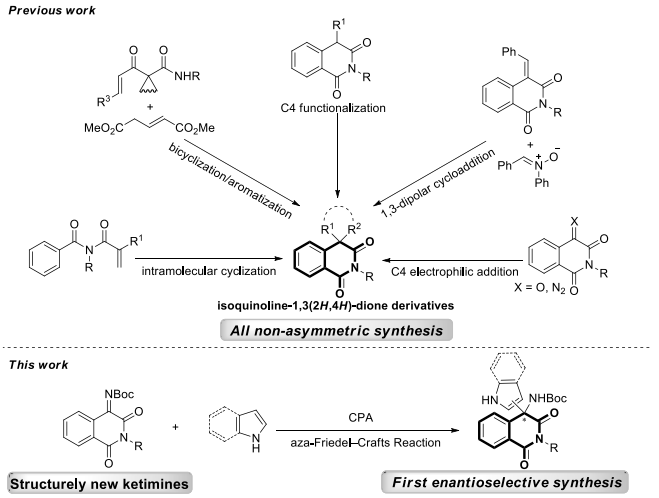

Figure 2. Strategies for synthesis of isoquinoline-1,3(2*H*,4*H*)-dione derivatives.

Imines are an important class of synthon in asymmetric synthesis because of the characters including high-activity, easy to control stereoselectivity and convenience for synthesizing chiral amines and so on. To date, various types of imines such as aldimines, isatin-derived ketimines, cyclic imines are synthesized and used for the asymmetric conversion to construct chiral amines.[7] Among them, especially, asymmetric aza-Friedel–Crafts reaction of imines with indoles is an important reaction[8] because the products of this reaction provide easy access to the synthesis of enantiopure 3-indolyl methanamine derivatives.[9] Based on the importance of imines in synthetic chemistry and isoquinoline-1,3(2*H*,4*H*)-dione skeleton in pharmaceutical chemistry, we intended to prepare new-type isoquinoline-1,3,4(2*H*)-trione ketimines and expected them could engage in asymmetric transformations to access chiral isoquinoline-1,3(2*H*,4*H*)-dione derivatives. Fortunately, the target ketimines were successfully prepared.[10] Therewith, we envisioned that the asymmetric aza-Friedel–Crafts reaction of this ketimines with arenes such as indoles[11] could be achieved with suitable catalytic system (Figure 2). If so, the resulting chiral products combining two privileged structure motifs, isoquinoline-1,3(2*H*,4*H*)-dione and 3-indolyl methanamine, would show great potential in diversity-oriented synthesis and drug discovery. Herein, we

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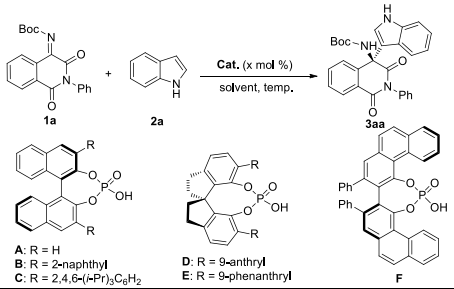
wish to report our research on this subject. Notably, this methodology represents the first example of catalytic asymmetric reaction for the construction of chiral isoquinoline-1,3(2*H*,4*H*)-dione derivatives.

Based on the successful synthesis of ketimines **1**, we started to investigate the aza-Friedel–Crafts reaction of the ketimines with indoles. As shown in Table 1, optimization of the process commenced with using ketimine **1a**, indole **2a**, 10 mol % chiral phosphoric acid (CPA) **A** in DCM at 25 °C. The reaction performed smoothly and the corresponding product **3aa** was obtained with good yield (91 %) but low enantioselectivity (only 4 % ee) after 48 h (entry 1). Magnifying the hindrance of R substituents at the 3,3′-positions of catalyst such as 2-naphthyl and 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$ significantly promoted the enantioselectivity (96% and 93% ee respectively), but shown inconducive for reactivity (entries 2-3). Pleasingly, by employing spirocyclic CPA **D** (R = 9-anthryl) as the catalyst, the reactivity and enantioselectivity could be improved concurrently, obtaining the almost optically pure product **3aa** in excellent yield (entry 4). Furthermore, catalysts **E** and **F** delivered inferior results on reactivity as well as enantioselectivity (entries 5-6). Having identified CPA **D** as the optimal catalyst, the influence of catalyst loading, solvent, substrate concentration, temperature, and the molar ratio of substrates was investigated. Halving the catalyst loading, no differences were observed on reactivity and enantioselectivity (entry 7). Further decreasing to 2 mol %, **3aa** also could be obtained in excellent results, albeit a prolonged reaction time was needed (entry 8). Solvent screening revealed that toluene is the best candidate (entry 10 vs entries 8-9 and 11-12). Increasing the concentration of **1a** to 0.1 M could promote the reactivity but slightly corroded the enantioselectivity (entry 13 vs entry 10). To our delight, raising the temperature to 40 °C could facilitate the reactivity without any erosion on enantioselectivity (entry 14 vs entry 10). Decreasing the molar ratio of **2a**:**1a** from 2:1 to 1.1:1, there were no effects on the results but a longer reaction time was needed (entry 15 vs entry 14), which could be improved by raising the temperature to 60 °C (entry 16). Further rising to 80 °C, no effects were observed on reactivity and enantioselectivity, but the yield was decreased (entry 17). Hence, the optimal reaction conditions were established as shown in table 1, entry 16.

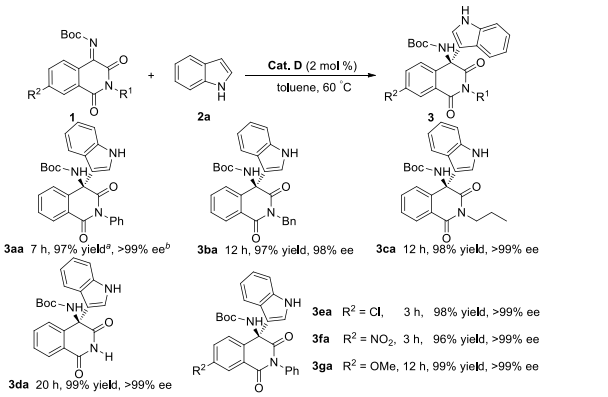
Table 1. Optimization of Reaction Conditions[a]



entry	Cat.	solvent	temp. (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**A**	DCM	25	48	91	4
2	**B**	DCM	25	48	97	96
3	**C**	DCM	25	48	98	93
4	**D**	DCM	25	2	97	>99
5	**E**	DCM	25	48	85	73
6	**F**	DCM	25	48	86	67
7[d]	**D**	DCM	25	3	98	>99
8[e]	**D**	DCM	25	15	93	>99
9[e]	**D**	$CHCl_3$	25	15	86	99
10[e]	**D**	toluene	25	15	98	99
11[e]	**D**	CH_3CN	25	15	trace	ND
12[e]	**D**	THF	25	15	NR	/
13[e,f]	**D**	toluene	25	10	97	98
14[e]	**D**	toluene	40	5	98	99
15[e,g]	**D**	toluene	40	9	97	>99
16[e,g]	**D**	toluene	60	7	97	>99
17[e,g]	**D**	toluene	80	7	86	>99

[a]Unless otherwise noted, the reactions were conducted with **1a** (0.05 mmol), **2a** (0.10 mmol) and 10 mol % catalyst in 1.0 mL of solvent at 25 °C for indicated time. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]5 mol % catalyst was used. [e]2 mol % catalyst was used. [f]0.5 mL toluene was used. [g]1.1 equivalents of **2a** was used. ND = No Detection. NR = No Reaction. DCM = dichloromethane. THF = tetrahydrofuran.

With the optimized conditions in hand, the substrate scope of the reaction was evaluated. We first performed experiments to assess the use of ketimines **1** possessing different substituents on N1 atom or benzene ring in the aza-Friedel–Crafts reaction. As shown in Scheme 1, when substituent on N1 atom was changed from aromatic phenyl to alkyl such as Bn, *n*-Pr, the enantioselectivity was persistent under the optimal conditions but a prolonged reaction time was needed for satisfying yield (**3aa** vs **3ba** and **3ca**). When R^1 was H, the stereoselectivity was not affected and the adduct **3da** could be obtained in 99% yield with >99% ee. In addition, the ketimines with either electron-rich or electron-poor substituents on the phenyl ring were also viable, furnishing the desired products in 96-99% yields with >99% ee values (**3ea**-**3ga**). Understandably, the reactivity of electron-poor ketimines is higher than electron-rich ketimine, which corresponds to the nature of the aza-Friedel–Crafts reaction.



Scheme 1. Substrates scope of ketimines **1**. Reaction condition: the reactions were conducted with **1** (0.05 mmol), **2a** (0.055 mmol) and 2 mol % catalyst **D** in 1.0 mL of toluene at 60 °C for indicated time. [a]Isolated yields. [b]Determined by chiral HPLC analysis.

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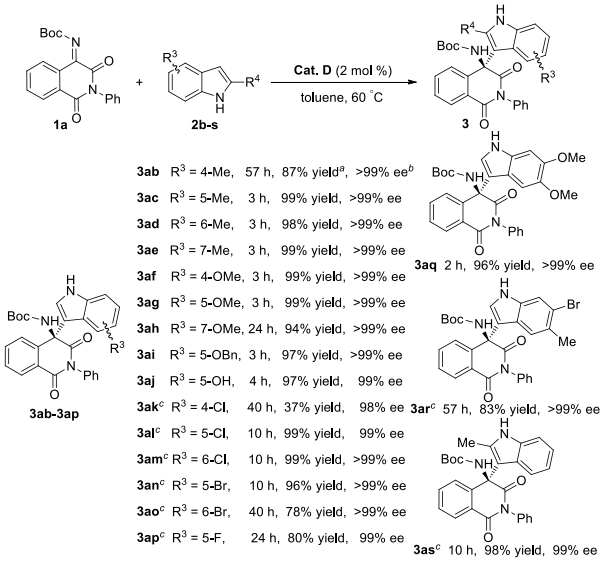
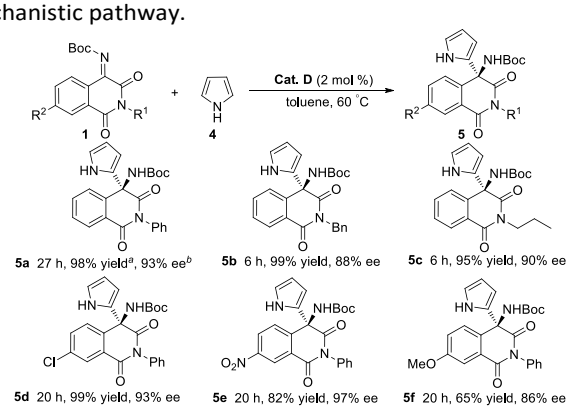
Next, we examined the effect of substituents on the indole **2** reacting with ketimine **1a** (Scheme 2). It was found that the electronic effect of substituents on the benzene ring of indole **2** obviously affects the reactivity. Generally, the reactivity of electron-rich indoles was significantly higher than that of electron-deficient indoles. For example, reaction of ketimine **1a** with electron-donating groups such as Me, OMe, OBn, OH substituted indoles regardless of the position on the benzene ring could proceed smoothly and finished within shorter time under the optimal conditions, giving the desire products in 94-99% yields with ≥99% ee (**3ac**-**3aj** and **3aq**). However, when substituent at 4-position was methyl, the reactivity decreased, which might attribute to the steric hindrance (**3ab**). Replacing electron-donating substituents with electron-withdrawing substituents including Cl, Br, F, regardless of the position, the aza-Friedel–Crafts reaction performed very slowly (data not shown). Nevertheless, by increasing concentration of **1a** to 0.1 M and molar ratio of **2**:**1a** to 2:1, the reaction could be accelerated, delivering the target products **3ak**-**3ap** in 37-99% yields with excellent enantioselectivities within acceptable reaction time. Moreover, disubstituted 6-bromo-5-methyl-1*H*-indole was also suitable for the adjusted reaction conditions and gave the almost optically pure product **3ar** in 83% yield. Particularly, installing methyl, an electron-donating substituent, on 2-position of indole, the reaction still needed to carry out under the adjusted reaction conditions, which might due to the increase of steric hindrance (**3as**).

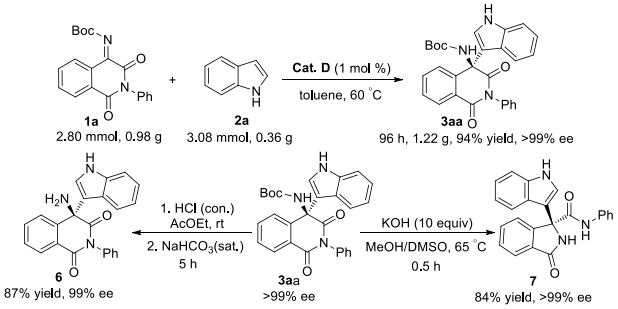


Scheme 2. Substrates scope of indoles **2**. Reaction condition: the reactions were conducted with **1a** (0.05 mmol), **2** (0.055 mmol) and 2 mol % catalyst **D** in 1.0 mL of toluene at 60 °C for indicated time. [a]Isolated yields. [b]Determined by chiral HPLC analysis. [c]The reactions were conducted with **1a** (0.05 mmol), **2** (0.10 mmol) and 2 mol % catalyst **D** in 0.5 mL of toluene at 60 °C for indicated time.

Following these promising results, we attempted to further extend the methodology to the pyrrole for construction of pyrrole-containing isoquinoline-1,3(2*H*,4*H*)-dione derivatives. As shown in Scheme 3, the adjusted reaction conditions enabled the ketimines **1** incorporating various substituents to engage in the aza-Friedel–Crafts reaction smoothly and deliver the corresponding products in moderate to excellent yields with good ee values (65-99% yields, 86-97% ee). Combining alkyl substituents into N1 atom of ketimines showed better reactivity than aryl (**5b** and **5c** vs **5a**). In addition, experimental results suggested that the enantioselectivity of ketimines with electron-withdrawing substituents on benzene ring are liable to be controlled with the established catalytic system (**5d** and **5e** vs **5f**). The absolute (*S*)-configuration of **5c** was determined by X-ray analysis.[12] The configurations of the other products **5** in Scheme 3 were assigned on the assumption of a uniform mechanistic pathway.



Scheme 3. Aza-Friedel–Crafts reaction of pyrrole and ketimines **1**. Reaction condition: the reactions were conducted with **1** (0.05 mmol), **4** (0.10 mmol) and 2 mol % catalyst **D** in 0.5 mL of toluene at 60 °C for indicated time. [a]Isolated yields. [b]Determined by chiral HPLC analysis.



Scheme 4. Gram-scale experiment and transformation of the product **3aa**.

In addition to providing high-value products in near-perfect enantioselectivity, this reaction can be easily performed on gram scale at decreased catalyst loading without impacting yield or selectivity. Using 1 mol % CPA **D**, 2.80 mmol of **1a** reacted with 3.08 mmol of **2a**, which is 56 times larger than the scale of the original reaction shown in Table 1, entry 16, to afford **3aa** in 94% yield and >99% ee. The absolute (*S*)-configuration of **3aa** was determined by X-ray analysis.[12] The configurations of the other products **3** were assigned on the assumption of a uniform mechanistic pathway. Next, the Boc group of **3aa** could be removed easily under acidic conditions to give the primary amine **6** in 87% yield with 99% ee. Furthermore, treatment of **3aa** with KOH in MeOH/DMSO (v/v = 1:1) afforded the compound **7** containing isoindolinone

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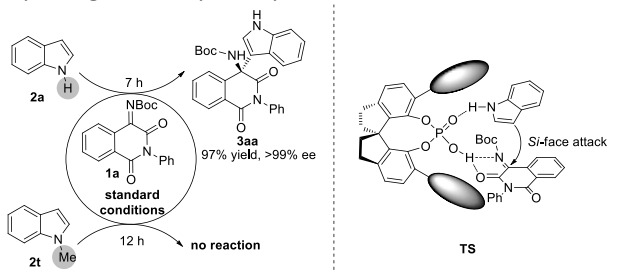
framework[12], a class of important motif frequently found in pharmaceuticals and bioactive natural products,[13] without the loss of enantioselectivity, which provided an effective way to access the isoindolinone derivatives.

A control experiment was conducted to verify the catalytic process. Employing N-methyl indole **2t** to react with **1a** under the standard conditions, the reaction failed to response, which suggests the free N–H of the indole is crucial to ensure reactivity (Scheme 5). Therefore, based on the result, the absolute configuration of **3aa** and previous reports[8d, 8e], a potential transition state can be proposed to account for the observed stereochemical outcome of the aza-Friedel–Crafts reaction. The chiral phosphoric acid simultaneously activates both indole and ketimine through the hydrogen bonding interaction, which create a chiral environment wherein the 3-position of indole preferentially attacks the *Si*-face of the C=N group and gives the specific product.



Scheme 5. Control experiments and the proposed transition state for the aza-Friedel–Crafts reaction of indole with ketimine.

In summary, we have prepared a new class of ketimines and developed an enantioselective aza-Friedel–Crafts reaction using this ketimines with indoles for first enantioselective synthesis of isoquinoline-1,3(2*H*,4*H*)-dione derivatives in moderate to quantitative yields with excellent enantioselectivities. And this reaction was also applicable to pyrrole, yielding the pyrrole-containing products in high yields and enantioselectivities. Moreover, the synthetic utility of this methodology has been demonstrated by gram-scale preparation and converting the product into another important isoindolinone derivative. Further investigations employing this ketimines in catalytic asymmetric reaction are currently being pursued in our laboratories.

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Conflicts of interest

There are no conflicts to declare.

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