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Copper-Catalyzed Enantioselective Friedel–Crafts Alkylation of Pyrrole with Isatins

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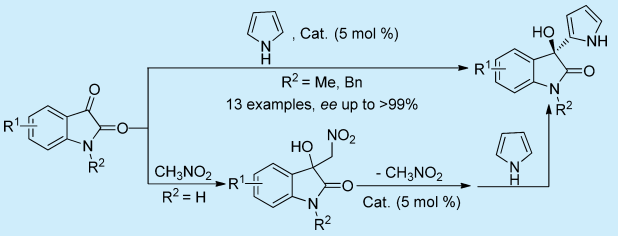
Supporting Information

ABSTRACT: The highly enantioselective Friedel–Crafts alkylation of pyrrole with isatins catalyzed by the tridentate Schiff base/Cu catalyst was developed. Hexafluoroisopropanol (HFIP) was used as a crucial additive to improve the enantioselectivity. In the case of *N*-unprotected isatins, an innovative substrate slow-releasing strategy was applied by virtue of a Henry/retro-Henry reaction.



Optically active 3-substituted 3-hydroxy-2-oxindole is an important structural unit which exists in a vast array of natural products and drug candidates, such as Dioxibrassinine, Maremycin B, and SM-130686 (Figure 1).[1] A number of

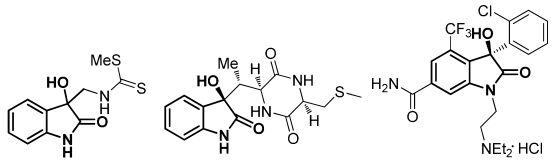


Figure 1. 3-hydroxy-2-oxindole structural motif in natural products and drug candidates.

elegant synthetic strategies have been reported for the construction of these useful structures,[2] of which catalytic asymmetric addition of isatins with various nucleophiles has emerged as one of the most attractive methods since isatins are readily available substrates in organic synthesis.[3] Recent publications indicated that asymmetric Friedel–Crafts alkylation of isatins with electron-rich aromatic compounds could give biologically interesting chiral 3-aryl-3-hydroxy-2-oxindoles efficiently with high *ee* values. However, successful catalysts are limited to chiral metal–pybox complexes and cinchona alkaloid derivatives, and the results were not always satisfactory.[4] As far as we know, only one successful example of asymmetric Friedel–Crafts alkylation of isatins with pyrroles has been reported by the Franz group.[4d] As a result, developing new catalytic systems with a broad substrate scope and simple manipulations is still highly required.

In our previous studies, we found that chiral tridentate Schiff base/metal complexes could successfully catalyze the Friedel–Crafts alkylation of indoles or pyrroles with nitroalkenes.[5] To further explore the catalytic potential of these complexes and achieve the construction of chiral 3-substituted 3-hydroxy-2-oxindoles, chiral tridentate Schiff base/metal complex catalyzed Friedel–Crafts alkylation of pyrrole with isatins was investigated in our laboratory.

Initially, *N*-methylisatin **1a** and pyrrole **2a** were chosen as reaction substrates (Table 1), with our previously established Schiff base/Zn complex (catalyst **A**)[5a] or Schiff base/Cu complex (catalyst **B**)[5b] as chiral catalysts. Different solvent systems were tested for this reaction (Table 1, entries 1–5). When catalyst **A** was used, THF was the best solvent to afford product **3a** in 90% yield with 70% *ee*, while, in the case of catalyst **B**, dichloromethane was the best choice with a yield of 96% and an enantiomer excess of 77% respectively. To further improve the enantioselectivity of this reaction, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was selected as an additive for this reaction (Table 1, entries 6–8).[6] When 20 μL of HFIP were added to the reaction mixture and catalyst **B** was employed, the *ee* value could be significantly enhanced to 99% (Table 1, entry 6). Notably, this reaction proceeded at the C2-position of pyrrole exclusively to give the corresponding optically active 3-substituted 3-hydroxy-2-oxindoles.

With the optimal conditions in hand, the scope of this reaction was investigated (Table 2). *N*-Methylisatins with different substituents at the 5-, 6-, or 7-positions could react with pyrrole smoothly to give the corresponding products in over 90% *ee*'s with almost quantitative yields (Table 2, entries 1–9). In a previous report, shifting the substituent group to the 4-position of *N*-methyl isatin had an unfavorable effect on the reactivity, even to the extent no reaction occurred.[4d] Now under our catalytic system, **3k** could be isolated in 94% yield with 82% *ee* after 24 h (Table 2, entry 11). When *N*-benzyl isatin was used instead of *N*-methyl isatin, it reacted readily

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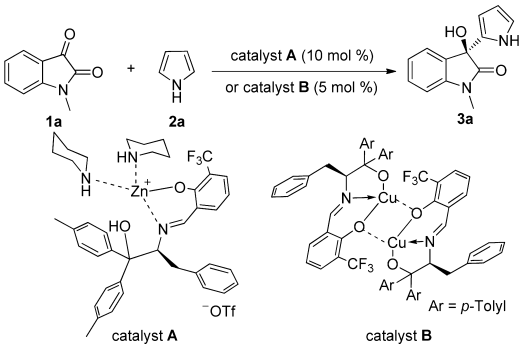
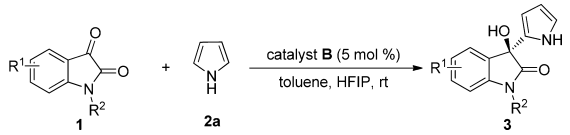
Table 1. Optimization of Reaction Conditions for the Friedel–Crafts Alkylation of Pyrrole with *N*-Methylisatin[a]



		catalyst A[b]		catalyst B[c]	
entry	solvent	yield (%)[d]	*ee* (%)[e]	yield (%)[d]	*ee* (%)[e]
1	toluene	80	56	85	60
2	CH_2Cl_2	93	34	96	77
3	THF	90	70	90	25
4	CH_3CN	98	39	97	58
5	*i*-PrOH	96	60	98	−7
6[f]	toluene	99	18	96	99
7[f]	CH_2Cl_2	97	5	99	78
8[f]	THF	98	10	99	33

[a]The reactions were carried out with **1a** (0.3 mmol) and **2a** (0.45 mmol) in 1.0 mL of solvent at room temperature for 12 h. [b]Catalyst **A**: *in situ* generated from $Zn(OTf)_2$ (0.03 mmol), ligand (0.03 mmol), and piperidine (0.09 mmol). [c]Catalyst **B**: preformed catalyst from $CuBr_2$ (0.015 mmol), ligand (0.015 mmol), and piperidine (0.03 mmol). [d]Isolated yield. [e]Detected by chiral HPLC analysis on chiral stationary phase. [f]Performed with HFIP (20 μL).

Table 2. Reaction Scope of the Enantioselective Friedel–Crafts Alkylation of Isatins with Pyrrole[a]



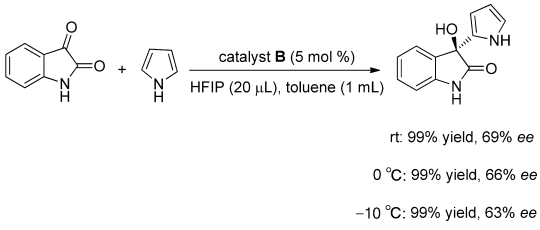
entry	R^1	R^2	product	yield (%)[b]	*ee* (%)[c]
1	H	CH_3	**3a**	96	99
2	5-F	CH_3	**3b**	97	98
3	5-Cl	CH_3	**3c**	99	99
4	5-Br	CH_3	**3d**	95	98
5	5-I	CH_3	**3e**	97	91
6	5-NO_2	CH_3	**3f**	98	94
7	5-CH_3	CH_3	**3g**	98	99
8	6-Br	CH_3	**3h**	97	99
9	7-Br	CH_3	**3i**	96	99
10	7-CF_3	CH_3	**3j**	96	88
11[d]	4,7-dichloro	CH_3	**3k**	94	82
12[e]	H	Bn	**3l**	97	95
13[f]	H	H	**3m**	99	69
14[f]	5-CH_3	H	**3n**	91	63
15[f]	5-Br	H	**3o**	95	56

[a]The reactions were carried out with **1** (0.3 mmol), **2a** (0.45 mmol), HFIP (20 μL) in 1.0 mL of toluene at room temperature for 12 h. [b]Isolated yield. [c]Detected by HPLC analysis on chiral stationary phase. [d]The reaction time is 24 h. [e]The reaction time is 1 h. [f]The reaction time is 3 h.

with pyrrole to give the product **3l** in excellent yield with excellent enantioselectivity (Table 2, entry 12).

However, when unprotected isatins were used as substrates under the optimal reaction conditions, the reactions were completed within 3 h, only giving moderate enantioselectivity (Table 2, entries 13–15). The poor enantioselectivity was probably due to the severe background reactions with unprotected isatins.[7] The conventional strategy of lowering the temperature led to a diminished enantioselectivity under our catalytic system (Scheme 1). This is perhaps due to the lower temperature making the dimer catalyst more difficult to dissociate into an active monomeric catalyst. To avoid the racemic background reaction, we decided to employ a substrate slow-releasing strategy, in which isatin can first react with a reagent to afford an intermediate, and then the intermediate can release isatin slowly to give a low concentration of isatin. How to realize this strategy and control the concentration of isatin in situ? With this question in mind, the Henry reaction entered into our consideration.[8] Under acidic or basic conditions, aldehydes or ketones can react with nitromethane to form the corresponding nitroalcohols. On the other hand, several studies disclosed that this process was reversible under appropriate conditions. As a result, aldehydes or ketones could also be released from the corresponding nitroalcohols.[6d]

Scheme 1. Asymmetric Friedel–Crafts Alkylation of Isatin with Pyrrole at Different Temperatures[a]



[a]The reactions were carried out with isatin (0.3 mmol), pyrrole (0.45 mmol), catalyst **B** (5 mol %), and HFIP (20 μL) in 1.0 mL of toluene at room temperature for 12 h. The yields were isolated yields, and the *ee* values were detected by HPLC analysis on chiral stationary phase.

By virtue of this Henry/retro-Henry process, we elaborated a retro-Henry reaction to modulate the concentration of the isatin in the reaction. In our experiment, we added a catalytic amount of diethylamine to a solution of isatin in nitromethane. The corresponding nitroalcohol was obtained in a quantitative yield in less than 5 min. Diethylamine and excess nitromethane were removed under reduced pressure. The nitroalcohol was further dissolved in toluene, and then catalyst **B**, HFIP, and pyrrole were added into the nitroalcohol solution subsequently. As expected, a retro-Henry reaction proceeded smoothly to release isatin slowly, which was used as the substrate for the consequent enantioselective Friedel–Crafts alkylation with pyrrole. To our delight, by using this strategy, the *ee* values of **3m**–**3o** could be enhanced to 93%–99% after 36 h (Scheme 2). It was worth mentioning that these processes were carried out in one pot starting from isatins.

To further investigate the substrate scope and the reaction mechanism, a few other electron-rich heteroaryls were tested (Scheme 3). The reaction of *N*-methylisatin with indole could gave the adduct **3p** in 96% yield with 45% *ee*. 3,4-Disubstituted pyrrole **2q** was also an applicable substrate for this enantioselective alkylation, which could give 5-alkylated

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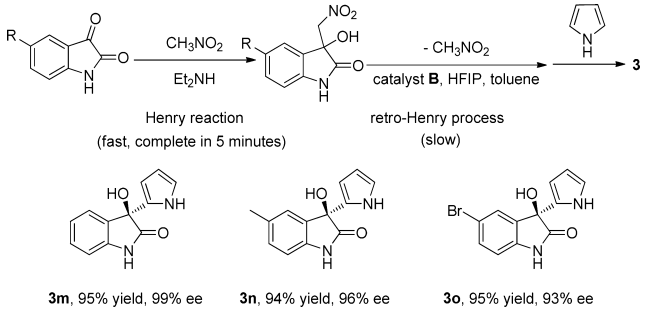
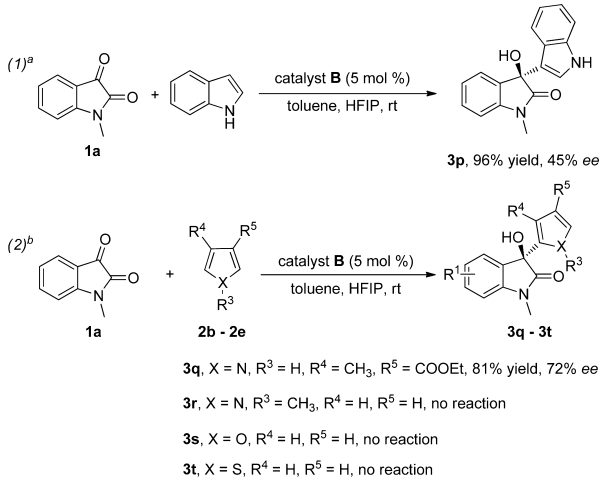
Scheme 2. Slow Release of Isatin by Using Henry/retro-Henry Strategy[a]



[a]The reactions were carried out with 5-substituted isatins (0.3 mmol), diethylamine (25 μL) in nitromethane (3 mL) for 5 min. Then the reactions were performed with the corresponding nitroalcohols, catalyst **B** (5 mol %), and HFIP (20 μL) in 1.0 mL of toluene at room temperature for 36 h.

Scheme 3. Scope of the Asymmetric Friedel–Crafts Alkylation of *N*-Methylisatin with Other Heteroaryls



[a]The reaction was carried out with **1a** (0.3 mmol), indole (0.45 mmol), catalyst **B** (5 mol %), and HFIP (20 μL) in 1.0 mL of toluene at room temperature for 8 h. The yield was isolated yield, and the *ee* value was detected by HPLC analysis on chiral stationary phase. [b] The reactions were carried out with **1a** (0.3 mmol), **2b** or **2c** (0.45 mmol), catalyst **B** (5 mol %), and HFIP (20 μL) in 1.0 mL of toluene at room temperature for 8 h. The yields were isolated yields, and the *ee* values were detected by HPLC analysis on chiral stationary phase.

product exclusively with 72% *ee* and 81% yield. It should be noted that the heteroaryls without the NH group, such as furan and thiophene, did not work in the reaction. This meant that the NH group perhaps formed a hydrogen bond with the catalyst **B**. The addition of HFIP favored this reaction. Perhaps HFIP can favor the hydrogen bond of NH of isatin with the catalyst **B** because of the weak Brønsted acidity of HFIP.[6c] Also, the influence of HFIP on the reaction was investigated in detail.[9] Based on these results and our previous mechanism study,[5] a hypothetical bifunctional mode of action in the transition state was proposed (Figure 2). The isatin was activated by chelating with a metal center in the catalyst complex, while the NH in pyrrole served as a hydrogen bond donating group to direct the alkylation at the *Si* face of isatin.

In summary, we developed a mild and highly efficient catalytic system for the asymmetric Friedel–Crafts alkylation of

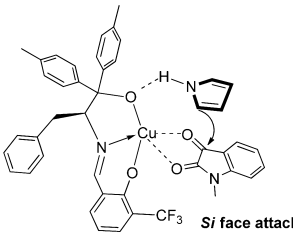


Figure 2. A hypothetical action mode of the transition state of the asymmetric Friedel–Crafts alkylation of *N*-methylisatin with pyrrole.

pyrrole with isatins. A variety of 3-substituted 3-hydroxy-2-oxindoles were synthesized in high yields and excellent enantioselectivities under mild conditions. For *N*-unprotected isatins, a novel and efficient substrate slow-releasing strategy was employed to achieve high enantioselectivities. Applications of this catalytic system as well as the substrate slow-releasing strategy to other asymmetric reactions are ongoing in our group.

■ ASSOCIATED CONTENT

Supporting Information

Details of experimental procedures, spectroscopic data, and physical properties of new compounds can be found in this material. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(9) For details about the role of HFIP in this reaction, see section 1.8 in the Supporting Information.