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# An asymmetric Brønsted acid-catalyzed Friedel–Crafts reaction of indoles with cyclic *N*-sulfimines†

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A highly enantioselective organocatalytic Friedel–Crafts reaction of indoles with cyclic *N*-sulfimines using a chiral phosphoric acid as an organocatalyst has been developed. This organocatalytic reaction provides for the first time 3-indolyl sulfamidate derivatives in good yields and with high enantioselectivities (up to 97% ee) with a broad range of functional groups and substitution patterns.

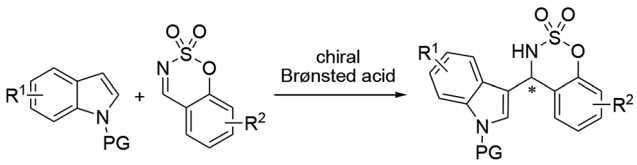


The indole skeleton is the most universal heterocycle structure in nature and is well established as a privileged scaffold; it is commonly encountered in many biologically active natural products and pharmaceutical compounds. Owing to the great structural diversity of biologically active indoles, indole units are of great importance in medicinal chemistry and are widely used in the pharmaceutical industry for the design of compounds with pharmacological properties.[1] In particular, indoles bearing a nitrogen atom at the α-position are widely present as the structural core of many natural products and pharmaceuticals that exhibit a broad range of biological activities and have been the focus of extensive synthetic efforts for a long time.[2] Because of their immense significance, numerous methods for the synthesis of chiral 3-indolyl methanamine structural scaffolds with careful stereochemical control have been developed. The asymmetric catalytic Friedel–Crafts reaction is one of the most powerful, straightforward and convenient methods for the preparation of these useful indole structures.[3] To promote these transformations, significant progress has been made by employing both a chiral metal and an organocatalyst in the reaction of indoles with imines.[4] However, to the best of our knowledge, an asymmetric Friedel–Crafts reaction with cyclic *N*-sulfimines that could enable the development of new strategies for the asymmetric synthesis of chiral indole derivatives has not yet been reported.[5]

Cyclic *N*-sulfimines have attracted much attention and have been proven to be powerful building blocks in the syntheses of functionalized benzosulfamidate heterocycles.[6] These sulfamidate compounds exhibit important biological activities such as antibiotic, antiviral, anticancer, anticonvulsant, antiobesity, antiarthritis, and antiosteoporosis activities.[7] Therefore, several reactions using cyclic *N*-sulfimines for the synthesis of sulfamidate derivatives have been reported, including allylation, annulation, cycloaddition, and the Mannich reaction.[8] Herein, we report the first highly enantioselective Friedel–Crafts reaction of indoles with cyclic *N*-sulfimines catalyzed by a chiral Brønsted phosphoric acid (Scheme 1).[9,10]

In our initial investigation, we began our studies on the Friedel–Crafts reaction between *N*-methylindole (**1a**) and benzoxathiazine 2,2-dioxide (**2a**) as the model substrates in the presence of a chiral BINOL-derived phosphoric acid catalyst **3** in toluene at room temperature (Table 1). The reaction proceeded smoothly to afford the desired product **4a** in good yield (78%), but with 20% ee when phosphoric acid **3a** (10 mol%) was used as the catalyst (Table 1, entry 1). Encouraged by this result, we investigated catalysts with various substitution patterns at the 3,3′-position of the binaphthyl scaffold (Table 1, entries 2–6), and chiral phosphoric acid **3b** bearing two phenyl groups at the 3,3′-position of the binaphthyl scaffold proved to be the optimal catalyst, affording product **4a** in 89% yield with 73% ee (Table 1, entry 2).

We further optimized the reaction conditions by using chiral phosphoric acid **3b** as the catalyst. The results are summarized in Table 2. First, we screened a variety of solvents. Unfortunately, inferior results were generally observed (Table 2, entries 2–8). Then, the effect of the reaction temperature was investigated for this Friedel–Crafts reaction. The temperature was found to have a significant effect on the reaction. In general, lowering the temperature resulted in an increase of the enantioselectivity (73 to 91% ee, from room temperature to −40 °C, Table 2, entries 1, 9–11). Lower catalyst loadings were examined, and the use of 5 mol% of phosphoric acid **3b** also led to the




Scheme 1 Enantioselective Friedel–Crafts reaction of indole with cyclic *N*-sulfimine.

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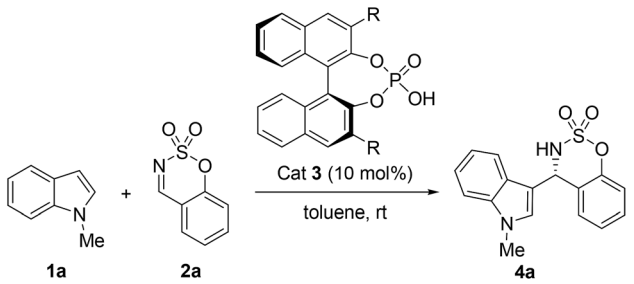
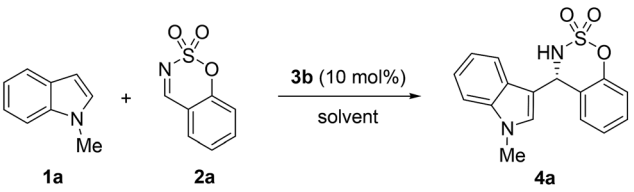
Table 1 Screening of chiral phosphoric acids in enantioselective Friedel–Crafts reaction of *N*-methylin dole with cyclic *N*-sulfimine[a]




| Entry | 3, R | Time (h) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | **3a**, H | 72 | 78 | 20 |
| 2 | **3b**, Pheny1 | 18 | 89 | 73 |
| 3 | **3c**, 4-Bipheny1 | 60 | 52 | 8 |
| 4 | **3d**, 1-Naphthy1 | 48 | 43 | 7 |
| 5 | **3e**, 2-Naphthy1 | 60 | 28 | 20 |
| 6 | **3f**, 4-$NO_2$-$C_6H_4$ | 48 | 36 | 3 |

[a] The reactions were carried out in toluene (0.2 M) with **1a** (0.15 mmol) and **2a** (0.1 mmol) in the presence of 10 mol% catalyst at room temperature. [b] Isolated yield after chromatographic purification. [c] Determined by chiral-phase HPLC analysis.

Table 2 Optimization of the reaction conditions[a]




| Entry | Solvent | *T* (C) | Time (h) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1 | Toluene | rt | 18 | 89 | 73 |
| 2 | $CH_2Cl$ | rt | 24 | 88 | 41 |
| 3 | $ClCH_2CH_2Cl$ | rt | 24 | 73 | 57 |
| 4 | $CHCl_3$ | rt | 24 | 95 | 55 |
| 5 | *o*-Xylene | rt | 18 | 87 | 71 |
| 6 | $CH_3CN$ | rt | 48 | 81 | 33 |
| 7 | THF | rt | 48 | 95 | 51 |
| 8 | MeOH | rt | 24 | 98 | 5 |
| 9 | Toluene | 0 | 24 | 93 | 78 |
| 10 | Toluene | −20 | 24 | 98 | 88 |
| 11 | Toluene | −40 | 24 | 93 | 91 |
| 12[d] | Toluene | −40 | 72 | 87 | 90 |

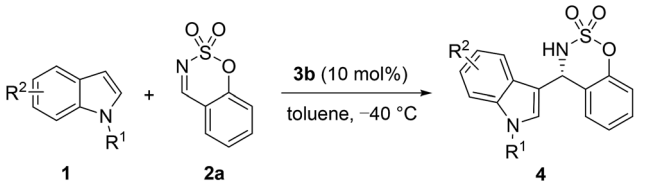
[a] The reactions were carried out in toluene (0.2 M) with **1a** (0.15 mmol) and **2a** (0.1 mmol) in the presence of 10 mol% catalyst at the indicated temperature. [b] Isolated yield after chromatographic purification. [c] Determined by chiral-phase HPLC analysis. [d] Reaction using 5 mol% catalyst **3b**.

desired product in high yield and enantioselectivity, but a longer reaction time was required (Table 2, entry 12).

With the optimized reaction conditions in hand (1.5 equiv. of **1**, 1 equiv. of **2**, 10 mol% of catalyst **3b**, in toluene at −40 °C), the substrate scope and generality of the reaction were investigated. First, we tested a variety of indole substrates **1** to examine the generality of the Friedel–Crafts reaction to yield 3-indolyl sulfamidate derivatives (Table 3).[11] It appeared that N-protecting groups on the indole (such as Me, Bn, and allyl groups) were tolerated and the desired products were obtained in good yields (76–93%) with excellent enantioselectivities (90–92% ee, Table 3, entries 1–3). Both electron-donating and electron-withdrawing substituents on the indole ring were well tolerated, mostly leading to the desired products with good to excellent enantioselectivities. Electron-donating groups generally led to higher reaction activities and enantioselectivities than electron-withdrawing groups did (**4d**, **4e** *vs.* **4f**; **4g–4h** *vs.* **4i–4l**). Moreover, the position of the substituent on the indole ring was found to have a minimal impact on the reaction efficiency as well as the enantioselectivity, although the reaction with 6-chloroindole provided a moderate yield (Table 3, entries 13–15).

Encouraged by the excellent results obtained with various indoles, we then investigated the Friedel–Crafts reaction with respect to the cyclic *N*-sulfimines. As shown in Table 4, the 3-indolyl sulfamidate products were obtained in good yields with high enantioselectivities regardless of the electronic nature, bulkiness, and position of the substituent on the phenyl ring of the *N*-sulfimines. The cyclic *N*-sulfimines with electron-donating groups in the 6-position led to slightly higher enantioselectivities compare to those with electron-withdrawing

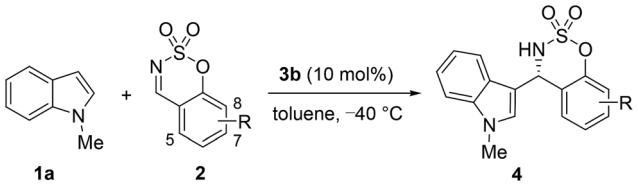
Table 3 Variation of the indole substrate[a]




| Entry | $R^1$ | $R^2$ | Time (h) | Product | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | Me | H | 24 | **4a** | 93 | 91 |
| 2 | Bn | H | 48 | **4b** | 76 | 90 |
| 3 | Allyl | H | 68 | **4c** | 85 | 92 |
| 4 | Bn | 5-OMe | 72 | **4d** | 95 | 94 |
| 5 | Bn | 5-OBn | 72 | **4e** | 73 | 97 |
| 6[d] | Bn | 5-Br | 48 | **4f** | 74 | 88 |
| 7 | Me | 5-OMe | 24 | **4g** | 98 | 89 |
| 8 | Me | 5-OBn | 24 | **4h** | 99 | 89 |
| 9[d] | Me | 5-Br | 48 | **4i** | 87 | 68 |
| 10[d] | Me | 5-CN | 36 | **4j** | 45 | 84 |
| 11[d] | Me | 5-$CO_2$Me | 24 | **4k** | 85 | 87 |
| 12[e] | Me | 5-$NO_2$ | 168 | **4l** | 88 | 78 |
| 13 | Me | 6-Cl | 72 | **4m** | 48 | 78 |
| 14 | Me | 6-F | 72 | **4n** | 88 | 85 |
| 15 | Me | 7-Me | 18 | **4o** | 79 | 88 |

[a] Unless otherwise noted, the reactions were carried out in toluene (0.2 M) with **1** (0.15 mmol) and **2a** (0.1 mmol) in the presence of 10 mol% catalyst **3b** at −40 °C. [b] Isolated yield after chromatographic purification. [c] Determined by chiral-phase HPLC analysis. [d] Reaction at 0 °C. [e] Reaction at RT.

Table 4 Variation of the cyclic *N*-sulfimine substrate[a]




| Entry | R | Time (h) | Product | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1 | 6-Me | 72 | **4p** | 95 | 91 |
| 2 | 6-OMe | 72 | **4q** | 99 | 93 |
| 3 | 6-F | 72 | **4r** | 96 | 84 |
| 4 | 6-Cl | 72 | **4s** | 99 | 84 |
| 5 | 6-Br | 72 | **4t** | 92 | 83 |
| 6 | 7-Me | 72 | **4u** | 93 | 89 |
| 7 | 7-OMe | 72 | **4v** | 45 | 80 |
| 8 | 6,8-Cl | 72 | **4w** | 91 | 81 |
| 9 | 6,8-Br | 72 | **4x** | 94 | 84 |
| 10 | 8-OMe | 72 | **4y** | 96 | 85 |

[a] The reactions were carried out in toluene (0.2 M) with **1a** (0.15 mmol) and **2** (0.1 mmol) in the presence of 10 mol% catalyst **3b** at −40 °C. [b] Isolated yield after chromatographic purification. [c] Determined by chiral-phase HPLC analysis.

groups (**4p**, **4q** *vs.* **4r**–**4t**). In addition, cyclic *N*-sulfimines bearing functional groups in the 8-position were also tolerated as substrates (Table 4, entries 8, 9 and 10).

The absolute configuration was unambiguously determined by X-ray crystallographic analysis of 3-indolyl sulfamidate compound **4n** and found to be *S* (Fig. 1a).[12] The absolute configurations of the other products were assigned by analogy. On the basis of our experimental results and the transition state model of BINOL-phosphoric acids,[13] we have proposed a simplistic plausible transition state to account for the observed stereoselectivity of the reaction (Fig. 1b). The cyclic *N*-sulfimine is activated by the phosphoric acid proton and then *N*-methylindole attacks the *N*-sulfimine from the *Si*-face preferentially, leading to an *S*-configuration adduct. Finally, an asymmetric catalytic Friedel–Crafts reaction of cyclic *N*-sulfimine with other nucleophiles have been developing. For example, the 2-pyrrolyl sulfamidate compound **6** was obtained in moderate yield and enantioselectivity (57% yield and 74% ee) when the catalytic Friedel–Crafts reaction between *N*-benzylpyrrole (**5**) and benzoxathiazine 2,2-dioxide (**2a**) in the presence of catalyst **3d** in toluene at −20 °C (Scheme 2).

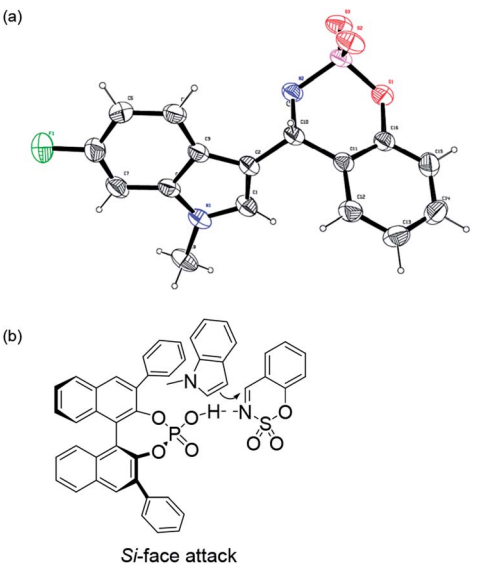
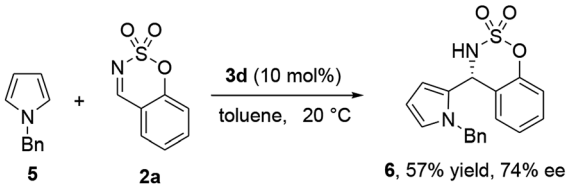



Fig. 1 X-ray structure of **4n** (a) with thermal ellipsoids at the 50% probability level and the proposed transition state model (b).




Scheme 2 Enantioselective Friedel–Crafts reaction of *N*-benzylpyrrole **5** with cyclic *N*-sulfimine **2a**.

## Conclusions

In summary, we have developed a highly enantioselective Friedel–Crafts reaction of indoles with cyclic *N*-sulfimines catalyzed by a chiral phosphoric acid. This method represents the first aza-Friedel–Crafts reaction with cyclic *N*-sulfimines as electrophiles and provides the corresponding optically active 3-indolyl sulfamidate derivatives in good yields and with high enantioselectivities (up to 97% ee) with a broad range of functional groups and substitution patterns. Current work is focused on expanding the substrate scope of this asymmetric catalytic reaction. Studies on the biological activity of these 3-indolyl sulfamidate derivatives against diabetic peripheral neuropathy, in particular, are currently underway, and the results will be presented in due course.

## Acknowledgements

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