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# Enantioselective Aza-Friedel-Crafts Reaction of Cyclic Ketimines with Indoles Using Chiral Imidazoline-Phosphoric Acid Catalysts

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**The enantioselective aza-Friedel Crafts reaction of cyclic 4-aryl-3-oxo-1,2,5-thiadiazol-1,1-oxides as cyclic ketimines with indoles was developed. High enantioselectivities were observed for the reaction of various cyclic ketimines and indoles using chiral imidazoline-phosphoric acid catalysts. The obtained products can be converted to chiral α-amino amide and hydantoin.**

The aza-Friedel-Crafts reaction of ketimines with arene compounds is recognized as one of the most powerful and an atom-economical synthetic methods for chiral amines having a tetra-substituted chiral carbon centre. Especially, the enantioselective aza-Friedel-Crafts reaction of α-iminoesters with arene compounds gives optically active α,α-diaryl-α-amino acids, therefore the development of this type of reaction is highly desired. However, the enantioselective aza-Friedel-Crafts reaction of α-iminoesters with arene compounds is rare. The first report for this type of reaction was reported by Bolm and co-workers where, the enantioselective aza-Friedel-Crafts reaction of a ketimine derived from trifluoropyruvate with various indoles gave products in high yield with high enantioselectivities.[1] Piersanti and co-workers examined the reaction using enamines derived from α-ketoesters with indoles to give products with moderate enantioselectivities (up to 66% ee).[2] Furthermore, enantioselective aza-Friedel-Crafts reaction using ketimines derived from isatins,[3] cyclic α-ketoacid derivatives,[4] or other ketimines,[5] as well as an intramolecular aza-Friedel-Crafts reaction,[6] have been reported. However, these methods have some problems related to substrate limitation and difficulty in converting simple α-amino acid derivatives. On the other hand, the enantioselective reaction of 4-aryl-3-oxo-1,2,5-thiadiazol-1,1-oxides as cyclic ketimines is an attractive synthetic method for chiral simple α-amino acid derivatives, because the reaction affords sulfahydantoin compounds, which can be easily converted to α-amino acids having tetra-substituted stereogenic carbon centre. Furthermore, sulfahydantoins are also important structures for biologically active compounds.[7] However, there are only two reports on the enantioselective C-C bond formation reaction of 4-aryl-3-oxo-1,2,5-thiadiazol-1,1-oxides.[8] Nishimura and Hayashi reported a pioneering result for the enantioselective reaction of 4-aryl-3-oxo-1,2,5-thiadiazol-1,1-oxides with *p*-tolylboroxine using chiral rhodium/diene catalyst to give a product with good enantioselectivity (79% ee).[9] More recently, Xu and co-workers reported the highly enantioselective arylation of 4-aryl-3-oxo-1,2,5-thiadiazol 1,1-oxides using rhodium/phosphite-olefin catalysts.[10] On the other hand, we recently reported the highly enantioselective aza-Friedel-Crafts reaction of 2-substituted-3H-indol-3-one derivatives with pyrroles using novel chiral imidazoline-phosphoric acid catalysts[11,12,13] and enantioselective reactions of ketimines with various nucleophiles.[14] Herein our ongoing interest was extended to the catalytic aza-Friedel-Crafts reaction of 4-aryl-3-oxo-1,2,5-thiadiazol-1,1-oxides with indoles (Fig.1 ).

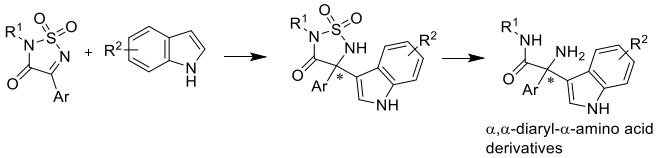
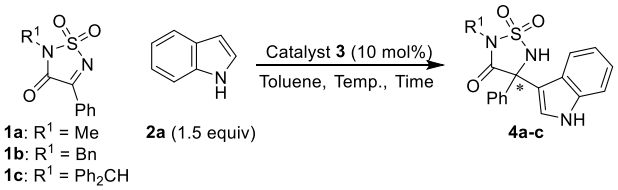


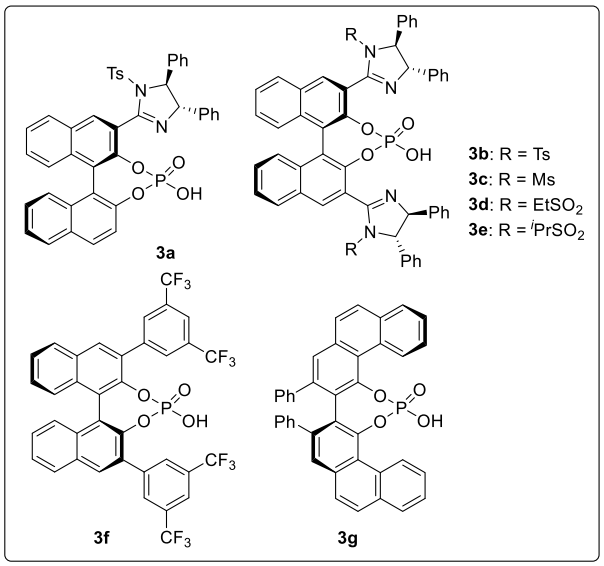

**Fig. 1** Enantioselective aza-Friedel-Crafts reaction of 4-aryl-3-oxo-1,2,5-thiadiazol 1,1-oxides with indoles.

First, we examined the reaction of *N*-alkyl-4-aryl-3-oxo-1,2,5-thiadiazol 1,1-oxides **1a-c** (1.0 equiv.) with indole **2a** using 10 mol% of various chiral imidazoline-phosphoric acid catalysts **3a-g** in toluene (Table 1). The reaction of *N*-methyl and *N*-benzyl ketimines **1a**,**b** with indole **2a** using catalyst **3a** afforded products **4a**,**b** in good yield but with low enantioselectivities (entries 1 and 2). On the other hand, the reaction of *N*-diphenylmethyl ketimine **1c** gave product **4c** with moderate enantioselectivity (entry 3). Encouraged by these results, we next examined the reaction of **1c** with **2a** using various chiral imidazoline-phosphoric acid catalysts **3b-g** (entries 4-9). Although the reaction using chiral bis(imidazoline)-phosphoric acid catalyst **3b** having a *p*-toluenesulfonyl group on imidazoline nitrogen showed low enantioselectivity, the reaction using **3c-e** having alkanesulfonyl groups gave product **4c** in high yield with high enantioselectivities (entries 4-7). The best enantioselectivity was obtained in the reaction using **3e** to give product **4c** in 99% yield with 90% ee (entry 7). On the other hand, 3,5-trifluoromethylphenyl-substituted chiral phosphoric acid catalyst **3f** and VAPOL-phosphoric acid **3g** afforded product **4c** with lower enantioselectivity than that from the reaction using catalyst **3e** (entries 8 and 9). When the reaction was carried out at a lower temperature (−10 °C), enantioselectivity improved (entry 10). Good enantioselectivity (97% ee) was still observed, even when catalyst loading of **3e** was reduced to 5 or 2 mol% (entries 11 and 12). After the reaction, most of catalyst **3e** could be recovered by column

chromatography, and reused in the reaction of **1c** and **2a** giving **4c** in 97% yield with 99% ee.

**Table 1** Enantioselective aza-Friedel-Crafts reaction of **1** with indole **2** using various organocatalysts **3a-g**.[a]



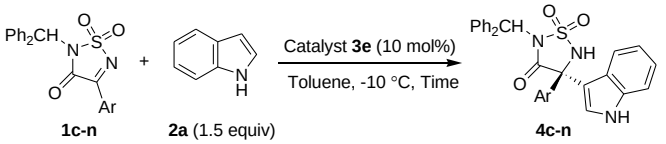




| Entry | 1 | 3 | Temp. (°C) | Time (h) | Yield (%) | Ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **1a** | **3a** | rt | 72 | 76 | 5 |
| 2 | **1b** | **3a** | rt | 72 | 71 | 5 |
| 3 | **1c** | **3a** | rt | 72 | 64 | 53[c] |
| 4 | **1c** | **3b** | rt | 72 | 86 | 2 |
| 5 | **1c** | **3c** | rt | 18 | 96 | 78 |
| 6 | **1c** | **3d** | rt | 18 | 97 | 86 |
| 7 | **1c** | **3e** | rt | 18 | 99 | 90 |
| 8 | **1c** | **3f** | rt | 72 | 68 | 23[c] |
| 9 | **1c** | **3g** | rt | 72 | 61 | 16 |
| 10 | **1c** | **3e** | −10 | 40 | 98 | 99 |
| 11[d] | **1c** | **3e** | −10 | 72 | 97 | 97 |
| 12[e] | **1c** | **3e** | −10 | 168 | 85 | 97 |

[a]Reaction conditions: **1** (0.05 mmol), **2** (1.5 equiv.), and **3** (10 mol%) in toluene (0.2 M). [b]Enantiomeric excess was determined by HPLC analysis using a chiral column. [c]Opposite enantiomer was obtained. [d]5 mol% of **3e** was used. [e]2 mol% of **3e** was used.

With optimized reaction conditions for the reaction of imine **1c** with indole **2a**, we next examined the scope of imines for this reaction (Table 2). The reaction of electron-rich imine **1d-f** having a methyl or methoxy group in the para or meta position using catalyst **3e** gave corresponding products **4d-f** in high yield with high enantioselectivities (entries 2-4). The reaction of imine **1g-l** bearing electron-withdrawing groups, such as a fluoro, chloro, bromo or trifluoromethyl group, was also acceptable, to afford products **4g-l** in good yield with good enantioselectivities (entries 5-10). 2-Naphthyl imine **1m** reacted with **2a** to give product **4m** in good yield with high enantioselectivity (77%, 91% ee, entry 11). The reaction of 3-thienyl imine **1n** also afforded product **4n** in 91% yield with 97% ee (entry 12). The X-ray crystallographic analysis product **4f** clearly showed their absolute configuration as (*R*), and the configuration of other products was tentatively assumed by analogy.

**Table 2 Enantioselective aza-Friedel-Crafts reaction of various substituted ketimines 1c-n with indole 2a using 3e.[a]**




| Entry | 1 | Ar | 4 | Time (h) | Yield (%) | Ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **1c** | Ph | **4c** | 40 | 98 | 99 |
| 2 | **1d** | 4-$CH_3C_6H_4$ | **4d** | 72 | 93 | 98 |
| 3 | **1e** | 3-$CH_3C_6H_4$ | **4e** | 120 | 97 | 95 |
| 4 | **1f** | 4-$CH_3OC_6H_4$ | **4f** | 96 | 87 | 98 |
| 5 | **1g** | 4-$FC_6H_4$ | **4g** | 72 | 95 | 96 |
| 6 | **1h** | 3-$FC_6H_4$ | **4h** | 96 | 98 | 91 |
| 7 | **1i** | 4-$ClC_6H_4$ | **4i** | 72 | 95 | 95 |
| 8 | **1j** | 3-$ClC_6H_4$ | **4j** | 120 | 85 | 92 |
| 9 | **1k** | 4-$BrC_6H_4$ | **4k** | 72 | 94 | 96 |
| 10 | **1l** | 4-$CF_3C_6H_4$ | **4l** | 40 | 98 | 96 |
| 11[c,d] | **1m** | 2-Naphthyl | **4m** | 120 | 77 | 91 |
| 12[e] | **1n** | 3-Thienyl | **4n** | 120 | 91 | 97 |

[a]Reaction conditions: The reaction was carried out using **1** (0.05 mmol), **2a** (1.5 equiv.), and **3e** (10 mol%) in toluene (0.2 M) at –10 °C. [b]Enantiomeric excess was determined by HPLC analysis. [c]At rt. [d]20 mol% of **3e** was used. [e]At 0 °C.

We next examined the enantioselective reaction of **1c** with various substituted indoles **2b-i** using catalyst **3e** (Table 3). The reaction of indoles **2b-e** having electron-donating groups such as a methyl or methoxy group in the 5-, 6- or 7-position gave corresponding products **5-8** in high yield with high enantioselectivities (entries 1-4, 97-99% yield, 93-98% ee). The reaction of indoles **2f-h** bearing electron-withdrawing groups such as a fluoro, chloro, or bromo group also afforded products **9-11** in high yield with high enantioselectivities (entries 5-7, 80-90% yield, 93-95% ee). On the other hand, the reaction of **1c** with *N*-methylindole **2i** did not give any product **12** (entry 8).

The gram-scale synthesis of sulfahydantoin **4c** via the reaction of 1.0 g of **1c** with **2a** using 5 mol% of catalyst **3e** successively proceeded to give 1.29 g of product **4c** (Scheme 1).

We next examined the transformation of product **4c** obtained (Scheme 2). Removal of the sulfonyl group in **4c** using $LiAlH_4$ in THF gave α-amino amide **13** in 89% yield without the loss of enantiopurity. Furthermore, the reaction of **13** with triphosgene afforded **14**, and the removal of diphenylmethyl group in **14** using 1 atm of $H_2$ in the presence of 20 wt% of Pd/C in THF/methanol gave hydantoin **15** (Scheme 2a). In addition, the reaction of **4c** with $H_2$ and Pd/C in THF/methanol proceeded to

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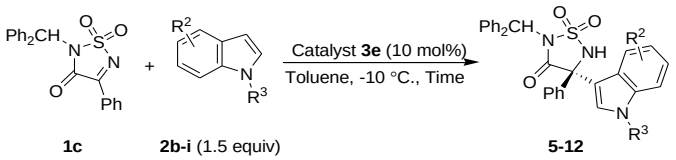
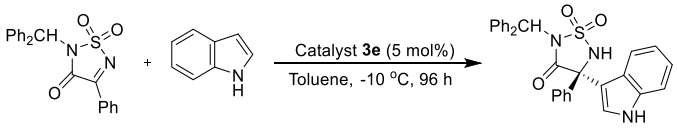
remove the diphenylmethyl group on nitrogen in **4c** (Scheme 2b).[15]

**Table 3** Enantioselective aza-Friedel-Crafts reaction of **1c** with various substituted indoles **2b-i** using **3e**.[a,b]

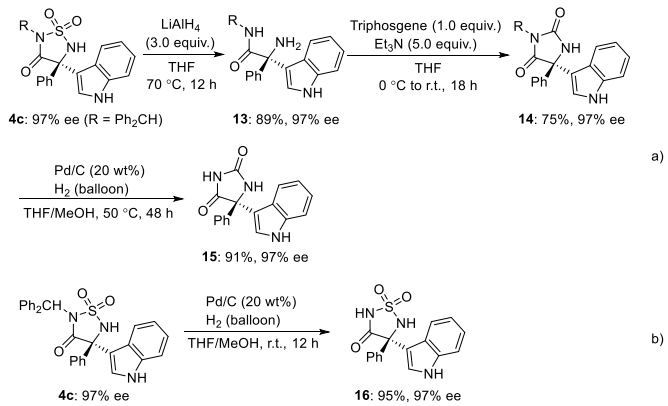



| Entry | 2 | $R^2$ | $R^3$ | Product | Time (h) | Yield (%) | Ee (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | **2b** | 5'-Me | H | **5** | 96 | 99 | 96 |
| 2 | **2c** | 6'-Me | H | **6** | 96 | 98 | 93 |
| 3 | **2d** | 7'-Me | H | **7** | 96 | 97 | 97 |
| 4[c] | **2e** | 5'-MeO | H | **8** | 48 | 99 | 98 |
| 5[d] | **2f** | 5'-F | H | **9** | 168 | 90 | 95 |
| 6[d,e] | **2g** | 5'-Cl | H | **10** | 168 | 86 | 93 |
| 7[d,e] | **2h** | 5'-Br | H | **11** | 168 | 80 | 94 |
| 8 | **2i** | H | Me | **12** | 96 | trace | - |

[a]Reaction conditions: The reaction was carried out using **1c** (0.05 mmol), **2** (1.5 equiv.), and **3e** (10 mol%) in toluene (0.2 M) at –10 °C. [b]Enantiomeric excess was determined by HPLC analysis. [c]At –20 °C. [d]At 0 °C. [e]Indole (2.0 equiv.) was used.




**Scheme 1** Gram-scale synthesis of sulfahydantoin **4c** by the reaction of **1c** with **2a** using catalyst **3e**.




**Scheme 2** Transformation of **4c** to chiral α-amino amide **13** and sulfahydantoin **14**.

The reaction of *N*-methylindole drastically decreased the reactivity in comparison with the reaction of the unprotected indole (Table 2, entry 1 vs. Table 3, entry 8). These results suggest that hydrogen bonding between N-H in indole and the imidazoline nitrogen or phosphonyl oxygen plays an important role in enhancing reactivity. Therefore, the assumed catalytic cycle for the reaction of **2a** with **1c** using catalyst **3** is shown in Figure 2. First, the phosphoric acid moiety in catalyst **3** activates the cyclic ketimine **1c** to form complex **A**. Then, the imidazoline group in catalyst **3** enhances the reactivity of indole by hydrogen bonding (complex **B**), and the nucleophilic reaction between indole **2a** and activated ketimine **1c** gives a product.

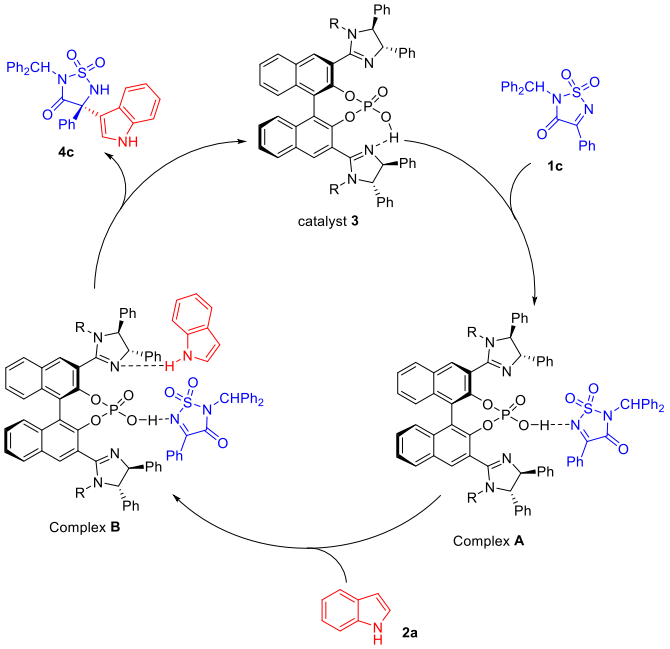



**Fig. 2** Assumed reaction cycle for the reaction of indole **2a** with ketimine **1c** using catalyst **3**.

The assumed transition state for the enantioselective reaction of ketimine **1c** with indole **2a** using catalyst **3e** is shown in Figure 3. Catalyst **3e** could enhance the electrophilicity of ketimine **1a** and nucleophilicity of indole by hydrogen bonding. Namely, chiral imidazoline-phosphoric acid **3e** acts as a dual activating organocatalyst. Indole **2a** approaches from the *Re*-face of ketimine avoiding steric repulsion between the phenyl group on imidazoline to afford the (*R*)-isomer of the product with high enantioselectivity.

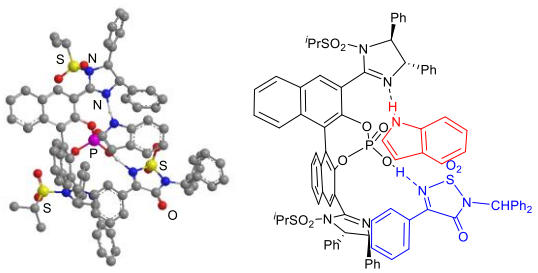


**Fig. 3** Assumed transition state for the reaction of **1c** with **2a** using catalyst **3e**. H atoms have been omitted for clarity.

In conclusion, we developed efficient access to a series of optically active sulfahydantoin derivatives having a tetra-substituted stereogenic centre by the aza-Friedel-Crafts reaction of cyclic *N*-sulfonylketimines using chiral imidazoline-phosphoric acid catalysts. The reaction was applicable to various cyclic ketimines and indoles. The obtained products can be converted to chiral α-amino amide and hydantoin without the loss of enantiopurity.

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## Notes and references

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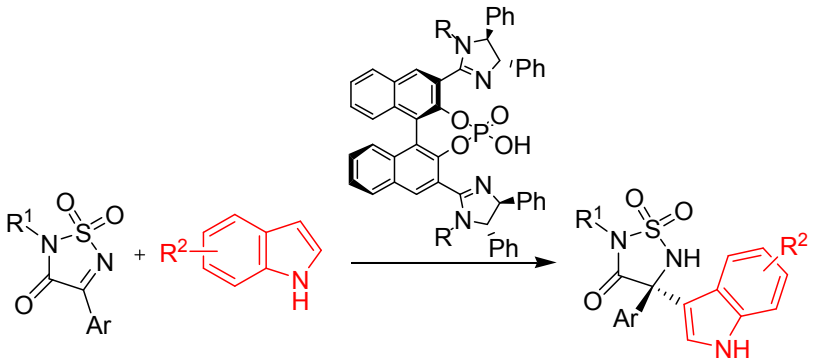


The highly enantioselective aza-Friedel Crafts reaction of cyclic 4-aryl-3-oxo-1,2,5-thiadiazol-1,1-oxides as cyclic ketimines with indoles was developed.