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Organocatalytic Enantioselective Aza-Friedel–Crafts Reaction of Cyclic Ketimines with Pyrroles using Imidazolinephosphoric Acid Catalysts

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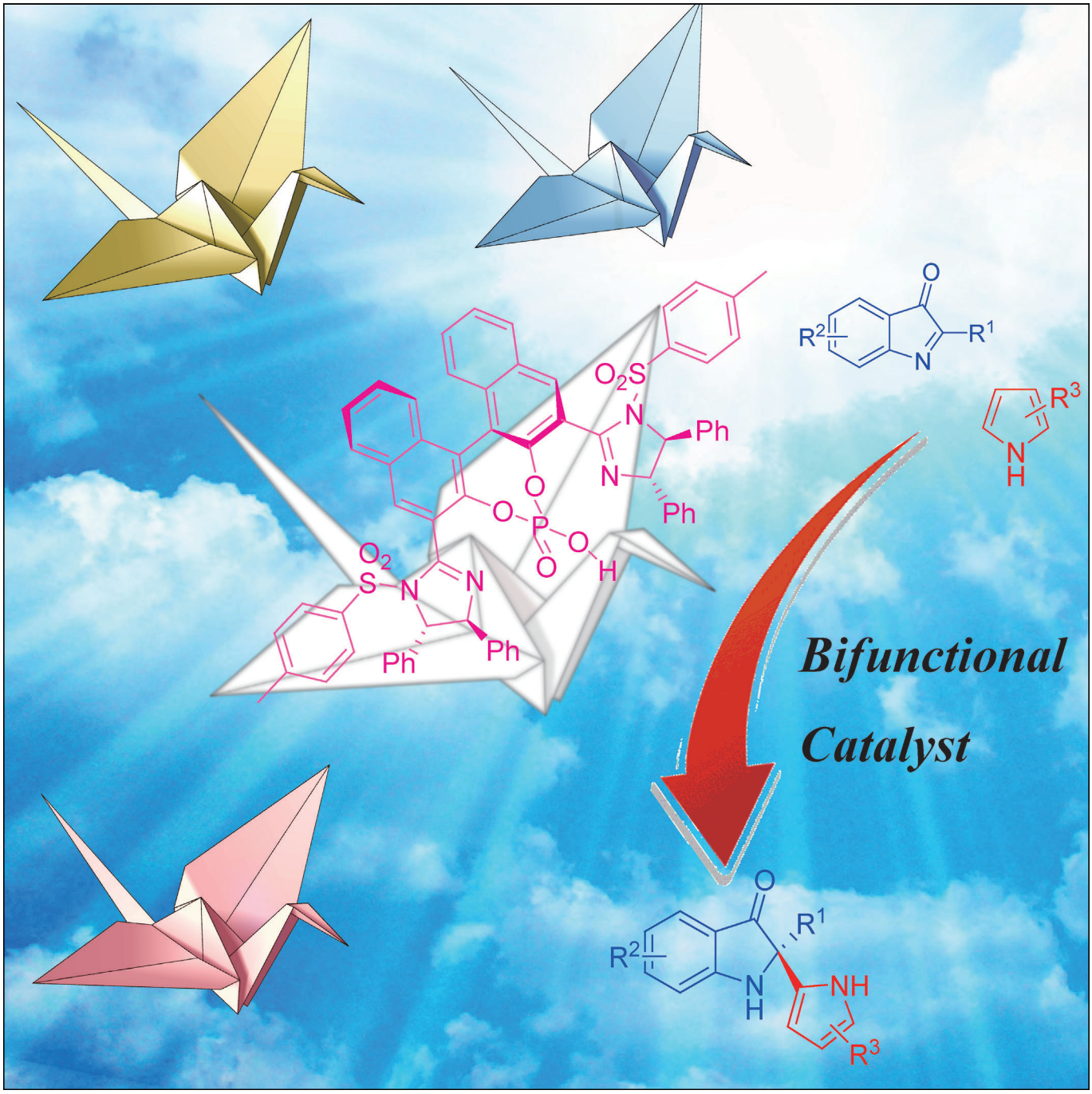

Abstract: Organocatalytic enantioselective aza-Friedel–Crafts reactions of cyclic ketimines with pyrroles or indoles were catalyzed by imidazoline/phosphoric acid catalysts. The reaction was applied to various 3*H*-indol-3-ones to afford products in excellent yields and enantioselectivities. The chiral catalysts can be recovered by a single separation step using column chromatography and are reusable without further purification. Based on the experimental investigations, a possible transition state has been proposed to explain the origin of the asymmetric induction.

Chiral indoline-3-ones with a quaternary chiral carbon center at the 2-position are an important class of synthetic targets, because they are often found in a broad range of biologically active compounds, such as (−)-trigonoliimine C,[1] (+)-isatisine A,[2] (−)-brevianamide B,[3] (+)-aristotelone,[4] (+)-austamide,[5] and other natural compounds (Figure 1).[6] Although many synthetic strategies towards chiral indoline-3-ones have been reported,[7] only a few examples of the catalytic asymmetric synthesis of optically active indoline-3-ones with a quaternary carbon center can be found in literature.[8] One of the simplest ways to construct chiral indoline-3-ones with a quaternary carbon center at the 2-position are reactions of 2-substituted-3*H*-indol-3-one derivatives as cyclic ketimines with nucleophiles. In 2011, Rueping and co-workers reported that the enantioselective reaction of 3*H*-indol-3-ones with indoles using chiral phosphoric acid catalysts gave products with good enantioselectivities (79–91% *ee*).[9] After this pioneering report, several enantioselective reactions of 3*H*-indol-3-ones with different nucleophiles were reported.[10] On the other hand, utilization of the enantioselective aza-Friedel–Crafts reaction as an atom-economical synthetic process for the synthesis of the described compounds is highly desirable. Although there are several reports on the catalytic enantioselective aza-Friedel–Crafts reactions of indoles with various ketimines,[11] only a few challenge the difficulty of the enantioselective Friedel–Crafts reaction of ketimines with pyrroles.[12] We recently reported the highly enantioselective reaction of ketimines with various nucleophiles,[13] and we also developed novel 1,1-bi-2-naphthol (BINOL)-derived phosphoric acid catalysts with chiral imidazoline groups.[14,15] Futhermore, we have reported the first organocatalytic aza-Friedel–Crafts reaction of imines, derived from aldehydes, with non-protected pyrroles.[16] Herein our ongoing interest was extended to the enantioselective aza-Friedel–Crafts reaction of 2-substituted-3*H*-indol-3-ones as ketimines with non-protected pyrroles using our original organocatalysts (Figure 2).

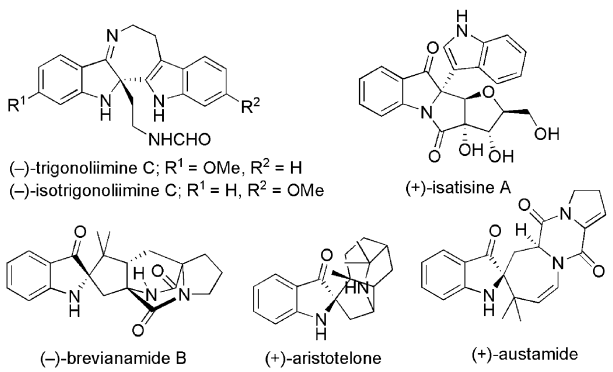

Figure 1. Natural indoline-3-one coumpounds with a quaternary, chiral carbon center.

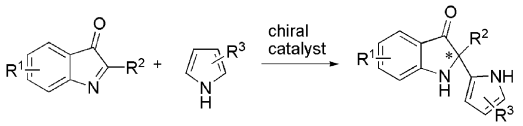

Figure 2. Enantioselective aza-Friedel–Crafts reaction of 2-substituted 3*H*-indol-3-one derivatives with pyrroles.

We first examined the reaction of 2-phenyl-3*H*-indol-3-one (**1a**) with pyrrole (**2a**) (1.2 equiv) in the presence of 5 mol% of the chiral organocatalysts **3a**–**h**. The results are shown in Table 1. To our delight, the reaction of **1a** with **2a** using the chiral imidazolinephosphoric acid catalyst **3a** proceeded efficiently in less than 1 min to afford product **4** in high yield but with low enantioselectivity (Table 1, entry 1). We next investigated the effect of the substituent on the imidazoline catalysts. However, changing the substituent on nitrogen in the imidazoline catalysts from a tosyl to a benzoyl or benzyl group could not improve the enantioselectivity of the product **4** (Table 1, entries 2 and 3). On the other hand, the reaction using the bis(imidazoline)phosphoric acid **3d** afforded product **4** in high yield and enantioselectivity (Table 1, entry 4).[17] The reaction using the bis(imidazoline)phosphoric acid **3e**, which has the opposite stereochemistry on the BINOL backbone, gave product **4** with low enantioselectivity (Table 1, entry 5). We also examined the reactions of the chiral phosphoric acid catalysts **3f,g** bearing triphenylsilyl or 3,5-trifluoromethylphenyl groups, and the 2,2′-diphenyl-[3,3′-biphenanthrene]-4,4′-diol (VAPOL) derived phosphoric acid **3h** that afford **4** with low enantioselectivities (Table 1, entries 6–8). Taken together, **3d** emerged as the most suitable catalyst for this reaction. When the reaction temperature was lowered from room temperature to −40 °C, the enantioselectivity improved (Table 1, entry 9, see Experimental Section for details). The catalyst loading of **3d** was successfully reduced to 2 mol% without the loss of enantioselectivity, although the reactivity and enantioselectivity were reduced in the reaction using 1 mol% of the catalyst **3d** (Table 1, entries 10 and 11). The reaction could be carried out in an

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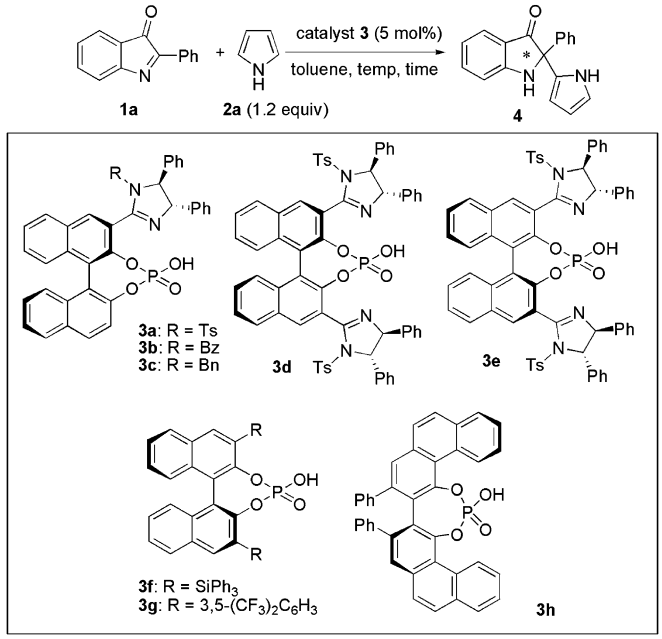
Table 1. Enantioselective aza-Friedel–Crafts reaction of **1a** with **2a** using various organocatalysts **3a–h**.



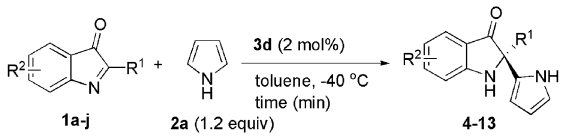
Run	**3a–h**	*T* [°C]	*t* [min]	Yield [%]	*ee*[a,b] [%]
1	**3a**	rt	1	42	9 (*R*)
2	**3b**	rt	30	42	9 (*R*)
3	**3c**	rt	1	26	0
4	**3d**	rt	3	91	96 (*R*)
5	**3e**	rt	1	50	33 (*R*)
6	**3f**	rt	1	31	10 (*S*)
7	**3g**	rt	3	77	41 (*S*)
8	**3h**	rt	1	73	8 (*R*)
9	**3d**	−40	3	99	99 (*R*)
10[c]	**3d**	−40	3	99	99 (R)
11[d]	**3d**	−78	3	97	95 (*R*)
12[c,e]	**3d**	−78	3	99	99 (*R*)

[a] Enantiomeric ratio *ee* was determined by HPLC analysis. [b] The absolute configuration of **4** is provided in parentheses. [c] 2 mol% **3d**. [d] 1 mol% **3d**. [e] The reaction was carried out in an open flask.

open flask to give product **4** without the loss of enantioselectivity (yield 99% with 99% *ee*).

Having established optimized conditions for the reaction of the imine **1a** with **2a**, the reactions of a series of imines **1b–j** with **2a** in the presence of **3d** were examined (Table 2). The reactions of the imines **1b** and **c**, bearing an electron-donating methyl or methoxy group in the *para* position, gave the corresponding products **5** and **6** in high yields with excellent enantioselectivities (Table 2, entries 2 and 3). The electron-deficient imines **1d–h**, with fluoro, chloro, or bromo groups in the *para*, *meta*, or *ortho* position, were tolerated under these reaction conditions to give products **7**–**11** with excellent stereoselectivities (Table 2, entries 4–8). The imine **1i** with a naphthyl group also afforded the product **12** with high enantioselectivity (Table 2, entry 9). The reaction of **2a** with the imine **1j**, with a bromo group, gave rise to the product **13** in excellent yield and enantioselectivity (Table 2, entry 10). Chemical yields and enantioselectivities were excellent in most cases.

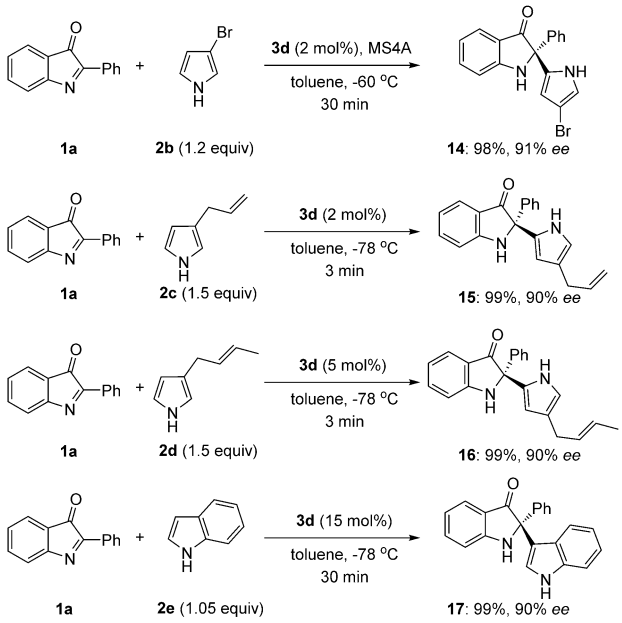
Table 2. Enantioselective aza-Friedel–Crafts reaction of various substituted 3H-indol-3-ones **1a–j** with **2a** using **3d**.



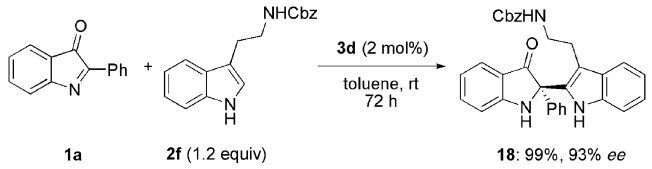
Entry	**1a–j**	R^1	R^2	*t* [min]	Product	Yield [%]	*ee*[a] [%]
1	**1a**	Ph	H	3	**4**	99	99
2	**1b**	4-MeC_6H_4	H	3	**5**	99	96
3	**1c**	4-$MeOC_6H_4$	H	3	**6**	99	96
4	**1d**	4-FC_6H_4	H	3	**7**	99	98
5	**1e**	4-ClC_6H_4	H	3	**8**	99	99
6	**1f**	4-BrC_6H_4	H	3	**9**	99	99
7	**1g**	3-BrC_6H_4	H	3	**10**	99	99
8[b]	**1h**	2-BrC_6H_4	H	40	**11**	99	97
9	**1i**	2-naphthyl	H	3	**12**	80	98
10	**1j**	Ph	6′-Br	3	**13**	99	99

[a] Enantiomeric ratio *ee* was determined by HPLC analysis. [b] At −78 °C.

We also examined the reaction of **1a** with various arene compounds using 2 mol% of the catalyst **3d** at −78 °C. The reaction with 3-bromopyrrole (**2b**), 3-allylpyrrole (**2c**), and 3-crotylpyrrole (**2d**) resulted in the formation of the products **14**–**16** in good yields with high enantioselectivities (Scheme 1).[18] Indole (**2e**) also reacted with **1a** in the presence of **3d** to afford the (*R*)-isomer of the product **17** in excellent yield with good enantioselectivity (Scheme 1). Furthermore, the reaction of **1a** with *N*-Cbz tryptamine (**2f**) using 2 mol% **3d** gave rise to **18** in high yield and enantioselectivity. The obtained 2-substituted indole derivative **18** is an important structural motif analogous to trigonoliimine C (Scheme 2).



Scheme 1. Enantioselective aza-Friedel–Crafts reaction of 2-phenyl-3*H*-indol-3-one (**1a**) with 3-bromopyrrole (**2b**), 3-allylpyrrole (**2c**), 3-crotylpyrrole (**2d**), and indole (**2e**).



Scheme 2. Enantioselective aza-Friedel–Crafts reaction of **1a** with *N*-Cbz-tryptamine (**2f**).

To test the scalability, a gram-scale aza-Friedel–Crafts reaction was performed using 2 mol% of the catalyst **3d** (Scheme 3). The reaction of **2a** (0.4 mL; 1.2 equiv) with **1a** (1.0 g; 1.0 equiv) proceeded to give the product **4** in 99% yield with 99% *ee* within 3 min. It should be noted that most of **3d** was recovered by a single separation step using column chromatography and it was reusable without further purification. The reaction of **1a** with **2a** using the recovered catalyst afforded the product **4** in 99% yield with 97% *ee*.

On the other hand, the enantioselective aza-Friedel–Crafts reaction of the imine **1a** with *N*-methylpyrrole (**2g**) gave the product **19** in good yield, but with moderate enantioselectivity (Scheme 4). Furthermore, the reactivity of **1h** with *N*-deuterated pyrrole ([D]-**2a**, 100% D) was significantly lower due to the isotope effect,[19] and the reaction was only completed after 18 h at −78 °C.

These results imply that hydrogen bonding between pyrrole and the catalyst **3d** plays a key role in the catalytic process. From this consideration, the assumed transition state for the enantioselective aza-Friedel–Crafts reaction using **3d** is shown in Figure 3. Catalyst **3d** could efficiently enhance the nucleophilicity of pyrrole by establishing a hydrogen bond between the oxygen in the phosphoric acid and the imidazoline group. Furthermore, the electrophilicity of 2-phenyl-3*H*-indol-3-one **1a** is also activated through hydrogen-bonding interactions with the phosphoric acid moiety. Therefore, the chiral imidazoline-phosphoric acid **3d** would act as a dual-activating organocatalyst. The reaction of pyrrole with **1a** proceeded in the coordination sphere of the chiral catalyst **3d**, and the *Si*-face of the ketimine reacts with pyrrole to give the (*R*)-isomer of the product with high enantioselectivity. Further studies are required to fully elucidate the mechanistic detail of the aza-Friedel–Crafts reaction of pyrroles with **1a**.

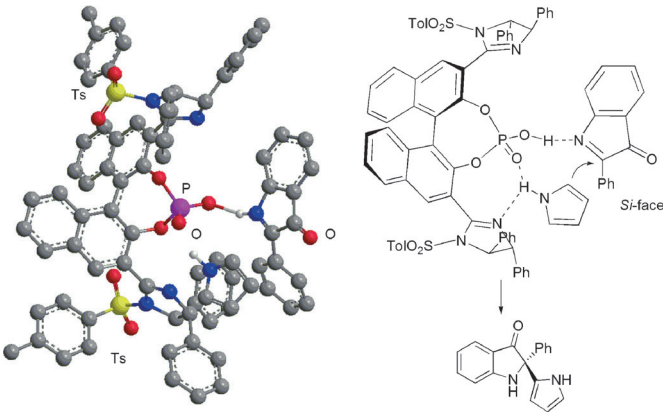
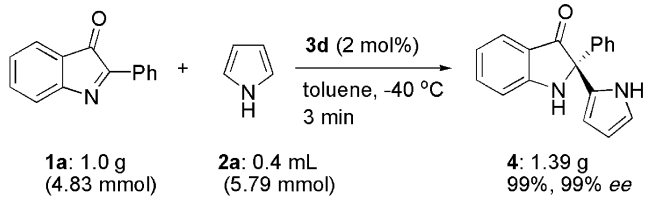
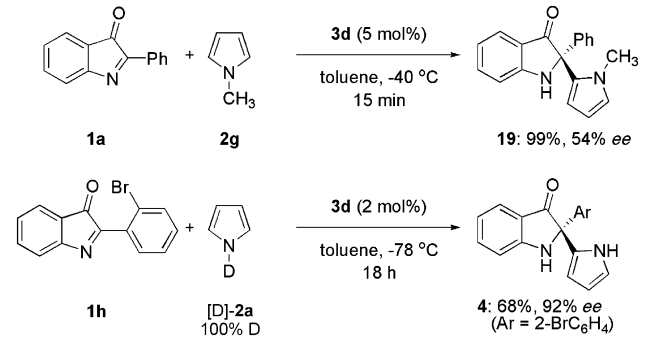


Figure 3. Proposed transition state for the reaction of **1a** with **2a** using the catalyst **3d**.

In conclusion, we developed a highly enantioselective method for the synthesis of quaternary-carbon-center-containing compounds by the aza-Friedel–Crafts reaction of cyclic ketimines with pyrroles or indoles. We identified bis(imidazoline)-phosphoric acid catalysts to be privileged organocatalysts for the described reaction. The catalyst loading was successfully minimized down to 2 mol% without a significant decrease in yield and enantioselectivity. Further studies focusing on the scope of the asymmetric reaction using novel organocatalysts are currently under investigation and will be reported in due course.



Scheme 3. Gram-scale experiment for the enantioselective aza-Friedel–Crafts reaction of **1a** and **2a** using **3d**.



Scheme 4. Enantioselective aza-Friedel–Crafts reaction of 3*H*-indol-3-ones with the *N*-methyl pyrrole (**2g**) or the N-deuterated pyrrole **[D]-2a**.

Experimental Section

A solution of the bis(imidazoline)phosphoric acid catalyst **3d** (0.0042 mmol, 5 mol%) and **1a** (0.0840 mmol) in toluene (1.68 mL) was cooled to −40 °C (Table 1, entry 9). Pyrrole (0.101 mmol) was added and the reaction mixture was stirred at −40 °C. After completion of the reaction monitored by TLC (3 min), the mixture was concentrated and purified by silica-gel column chromatography (hexane/ethyl acetate = 90:10) yielding indoline-3-one **4**. Experimental details for the remaining substrates and catalysts can be found in the Supporting Information.

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Keywords: aza-Friedel–Crafts reaction · enantioselectivity · imidazoline · ketimine · organocatalysis

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[18] The reaction of **1a** and **2b** without MS4A afforded the product **14** in slightly lower yield than that using MS4A.

[19] The reaction mixture was directly purified by silica gel column chromatography but the reaction cannot be stopped completely. Therefore, enantioselectivity of the product was lower than that from the reaction with non-deutarated pyrrole **2a**.

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Organocatalysis

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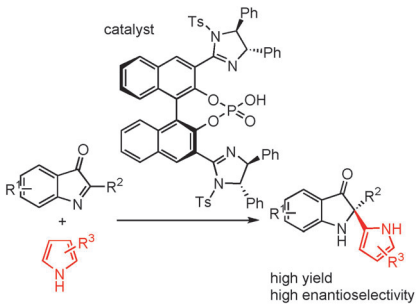
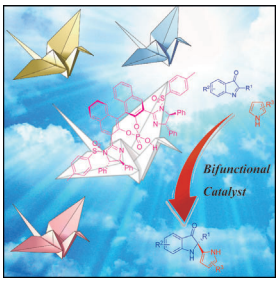
Organocatalytic Enantioselective Aza-Friedel–Crafts Reaction of Cyclic Ketimines with Pyrroles using Imidazolinephosphoric Acid Catalysts



Reusable chiral catalysts: Organocatalytic enantioselective aza-Friedel–Crafts reactions of cyclic ketimines with pyrroles or indoles using imidazoline/phosphoric acid catalysts were developed. The reaction was applied to various 3*H*-indol-3-ones to give products in excellent yields and enantioselectivities. The chiral catalysts can be reusable without further purification.



Chiral Phosphoric Acid Catalysts

Organocatalytic enantioselective aza-Friedel–Crafts reactions of cyclic ketimines with pyrroles or indole were catalyzed by imidazolinephosphoric acid catalysts. The reaction was applied to various 3*H*-indol-3-ones to afford products in excellent yields and enantioselectivities. The graphics shows origami cranes that fly with expanded wings. The bis(imidazoline)/phosphoric acid catalysts also expand their wings like the origami cranes, and form a well-fitting asymmetric space for substrate binding to let the reaction "fly". The full story can be found in the Communication by S. Nakamura and colleagues on page ■■ ff.