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Chiral Phosphoric Acid Catalyzed Highly Enantioselective Friedel–Crafts Alkylation Reaction of C3-Substituted Indoles to β,γ-Unsaturated α-Ketimino Esters

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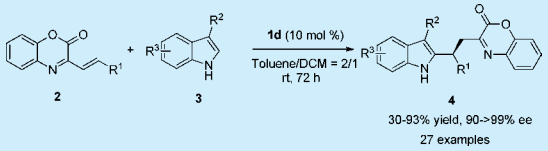
Supporting Information

ABSTRACT: A highly enantioselective C2 Friedel–Crafts alkylation reaction of 3-substituted indoles to β,γ-unsaturated α-ketimino esters has been developed. This reaction was efficiently catalyzed by a chiral phosphoric acid catalyst. The corresponding C2-substituted indole derivatives, bearing an α-ketimino ester motif, were obtained in moderate to high yields (up to 93%) and with high enantioselectivities (up to >99% ee).



The indole skeleton is one of the most important ring systems that can be found in many naturally occurring products and pharmaceuticals.[1,2] Consequently, there has been a strong demand for the development of efficient methods to allow the direct functionalization of indoles. The catalytic asymmetric Friedel–Crafts reaction[3] using chiral metal complexes or chiral organocatalysts is one of the most practical and atom-economical approaches for the synthesis of optically active indole derivatives. Because the electrophilic substitution preferentially occurred at the C3 position of indoles, most of the efforts have been devoted to the functionalization of indole derivatives have focused on the substitution of the C3 position of indoles. Therefore, the direct asymmetric alkylation of the less active C2 position has been less studied.

The Pictet–Spengler reaction[3a,4] of C3-substituted indoles is the most commonly used strategy, but it is confined by the limited scope of substrates. Some indirect protocols have also been reported, which need the preactivation of the indole C2 via the syntheses of intermediates with an active C2 position, for example, the 1,4-conjugate addition of 2-indolyl trifluoroborate salts to enals developed by MacMillan[5] and the Friedel–Crafts alkylation/oxidation of 4,7-dihydroindoles,[6] which are pyrrole derivatives that lead to reaction at the C2 position.

2-Substituted indoles are potential intermediates for many alkaloids and pharmacologically important substances,[3c] and the development of novel and efficiently catalyzed asymmetric syntheses of these compounds appears to be of great importance.[7,8] Recently, Xiao and co-workers realized an efficient asymmetric Friedel–Crafts alkylation/N-hemiacetalization cascade reaction of C3-substituted indoles and β,γ-unsaturated α-ketoesters promoted by a copper(II)–bioxazoline complex.[8a] Feng and co-workers also reported a chiral *N*,*N*′-dioxide–Ni(II) complex catalyzed Friedel–Crafts alkylation of *N*-methylskatole to β,γ-unsaturated α-ketoesters.[8b]

Despite those recent advances, the development of efficient methods allowing the direct asymmetric synthesis of C2-substituted indole derivatives via Friedel–Crafts alkylation under mild condition remains a challenge. Herein, we present our study on the chiral phosphoric acid catalyzed and highly enantioselective Friedel–Crafts reaction of 3-substituted indoles to β,γ-unsaturated α-ketimino esters, generating C2-functionalized indole derivatives.

β,γ-Unsaturated α-ketimino esters are versatile electrophiles that have been used in a wide range of organic transformations,[9] for example, aza-Diels–Alder reaction,[9a,f] 1,4-conjugate addition reaction,[9b,g] asymmetric-transfer hydrogenation reaction,[9c] N-alkylation/vinylogous aldol reaction,[9d] and aza-Morita–Baylis–Hillman reaction.[9e] We expect that those components could also serve as a starting material for Friedel–Crafts alkylation.

In recent years, chiral phosphoric acids have been widely utilized as efficient enantioselective organocatalysts for numerous organic reactions.[10] Among the reactions investigated, the activation of imines by BINOL-based phosphoric acids **1** has proven to be an attractive and efficient method for constructing nitrogen-containing chiral centers.[11] The asymmetric Friedel–Crafts alkylation of electron-rich aromatic compounds to imines using chiral phosphoric acid catalysts has been one of the most extensively studied areas in the past decade.[12] Taking advantage of the highly efficient activation of imines of phosphoric acid, we envisaged that β,γ-unsaturated α-ketimino esters **2** might serve as electrophiles for the asymmetric Friedel–Crafts reaction with 3-substituted indoles, affording C2-functionalized indole derivatives bearing an α-ketimino ester motif to enable many further transformations.

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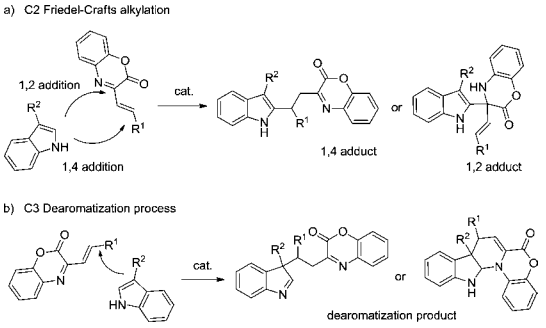
There are many possible pathways in this reaction. One pathway is the C3 nucleophilic addition of 3-substituted indole to β,γ-unsaturated α-ketimino esters to give dearomatization products, which is a known process for indole alkylation chemistry.[13] On the other hand, β,γ-unsaturated α-ketimino esters are ambident electrophiles that undergo 1,2- or 1,4-nucleophilic addition processes by hydrogen-bond activation of the imine motif with an acid catalyst (Scheme 1). It is therefore more challenging to control the regioselectivity, which relies on the nucleophiles and catalytic reagents.[9g] Compared to active β,γ-unsaturated α-ketoesters and β,γ-unsaturated *N*-sulfonylimines, β,γ-unsaturated *N*-phenylcycloimines **2** are less studied because of their low reactivity, which is another challenge that we must face. As a result, there has been no report of β,γ-unsaturated *N*-phenylcycloimines **2** participating in asymmetric Friedel–Crafts alkylation with indoles to date, even though the adducts could be used in the synthesis of unnatural indolyl amino acid derivatives that possess many interesting biological activities.

Scheme 1. Possible Reactions of 3-Substituted Indoles to β,γ-Unsaturated α-Ketimino Esters

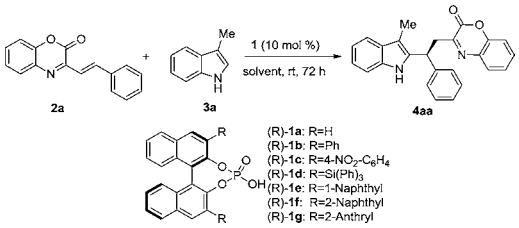


To begin our investigation, the reaction of 3-methylindole (**3a**) and **2a** was chosen as a model reaction. We first examined the catalysis of the Friedel–Crafts reaction with 10 mol % phosphoric acid **1b** in dichloromethane at room temperature. To our delight, the reaction proceeded with only the C2 1,4-conjugate addition process, and the corresponding adduct (**4aa**) was obtained in high yield (92%) but with low enantioselectivity (11% ee, Table 1, entry 2). Different BINOL-based phosphoric acids (**1a–g**) bearing substituents in the 3,3′-position were screened (Table 1). Phosphoric acid **1d** was found to be the best catalyst with respect to enantioselectivity (Table 1, entry 4). The product **4aa** was isolated in 82% yield and 81% ee in 72 h.

Having identified the best catalyst (**1d**), the effect of the reaction solvent was also surveyed to further enhance the enantioselectivity. As shown in Table 1, the reaction medium has a substantial influence on both the reactivity and stereoselectivity. Performing the reaction in toluene resulted in the highest stereoselectivity (97% ee) but low reactivity (32% yield, Table 1, entry 8), while the reaction in dichloromethane led to a better yield and acceptable enantioselectivity (Table, entry 4). Those results suggested that a mixture of dichloromethane and toluene might improve the efficiency of the reaction. Experiments indicated that this was the case, and the best result in terms of yield (64%) and enantioselectivity (97% ee) was obtained using a 2:1 ratio of toluene and dichloromethane (Table 1, entry 13).

With the optimal reaction conditions identified, the Friedel–Crafts alkylation reactions of 3-methylindole to a variety of aromatic β,γ-unsaturated α-ketimino esters (**2**) were surveyed,

Table 1. Optimization of the Reaction Conditions[a]

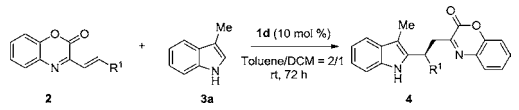


entry	catalyst	solvent	yield[b] (%)	ee[c] (%)
1	**1a**	DCM	25	0
2	**1b**	DCM	92	11
3	**1c**	DCM	69	25
4	**1d**	DCM	82	81
5	**1e**	DCM	80	15
6	**1f**	DCM	63	24
7	**1g**	DCM	78	28
8	**1d**	toluene	32	97
9	**1d**	$ClCH_2CH_2Cl$	65	80
10	**1d**	xylene	35	95
11	**1d**	$CHCl_3$	72	93
12	**1d**	toluene/DCM (1:1)	45	81
13	**1d**	toluene/DCM (2:1)	64	97
14	**1d**	toluene/DCM (4:1)	53	97

[a]Reactions were performed with **2a** (0.1 mmol), **3a** (0.3 mmol), and catalyst (0.01 mmol) in solvent (0.9 mL). [b]Isolated yield. [c]Determined by HPLC analysis using a chiral stationary phase.

and the results are summarized in Table 2. The electronic nature of the substituents on the phenyl ring of β,γ-unsaturated α-ketimino esters have little effect on the stereoselectivity of the

Table 2. Friedel–Crafts Alkylation of 3-Methylindole to Various β,γ-Unsaturated α-Ketimino Esters[a]



entry	R^1	4	yield[b] (%)	ee[c] (%)
1	Ph (**2a**)	**4aa**	64	97
2	4-$NO_2C_6H_4$ (**2b**)	**4ba**	78	99
3	3-$NO_2C_6H_4$ (**2c**)	**4ca**	83	98
4	4-$OCH_3C_6H_4$ (**2d**)	**4da**	44	97
5	3-$OCH_3C_6H_4$ (**2e**)	**4ea**	49	97
6	4-$CH_3C_6H_4$ (**2f**)	**4fa**	46	97
7	2-$CH_3C_6H_4$ (**2g**)	**4ga**	31	97
8	4-BrC_6H_4 (**2h**)	**4ha**	75	97
9	3-BrC_6H_4 (**2i**)	**4ia**	67	98
10	5-Br, 2-FC_6H_3 (**2j**)	**4ja**	30 (41)[d]	96
11	4-ClC_6H_4 (**2k**)	**4ka**	68	98
12	3-ClC_6H_4 (**2l**)	**4la**	67	97
13	4-FC_6H_4 (**2m**)	**4ma**	77	96
14	4-isopropylC_6H_4 (**2n**)	**4na**	70	95
15	1-naphthyl (**2o**)	**4oa**	58	97
16	2-thienyl (**2p**)	**4pa**	70	95
17	2-furyl (**2q**)	**4qa**	65	90
18	4-$CF_3C_6H_4$ (**2r**)	**4ra**	58	97

[a]Reactions were performed with **2** (0.1 mmol), **3a** (0.3 mmol), and **1d** (0.01 mmol) in solvent (0.9 mL). [b]Isolated yield. [c]Determined by HPLC analysis using a chiral stationary phase. [d]Reaction time is 120 h with 45% unreacted **2j** retrieved.

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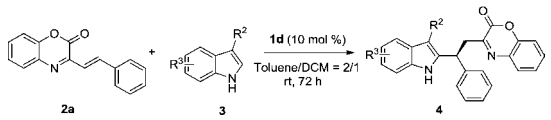
reaction; both the electron-donating and electron-withdrawing groups on the aromatic ring were tolerated, yielding the expected products in high stereoselectivity (90−99% ee, Table 2, entries 1−14 and 18). β,γ-Unsaturated α-ketimino esters (**2**) with electron-donating groups such as methoxyl afforded products with lower yields (Table 2, entries 4−7), while electron-withdrawing groups resulted in high reactivities (Table 2, entries 2 and 3).

The substrate scope of 3-substituted indole for this Friedel−Crafts alkylation reaction was also examined, and the results are presented in Table 3. In general, the reaction proceeded

Table 3. Scope of Substituted Indoles[a]

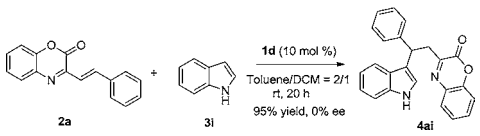


entry	R^2, R^3	4	yield[b] (%)	ee[c] (%)
1	Me, H (**3a**)	**4aa**	64	97
2	Et, H (**3b**)	**4ab**	62	98
3[d]	NHBoc, H (**3c**)	**4ac**	93	92
4	Me, 4-Me (**3d**)	**4ad**	69	97
5	Me, 5-Me (**3e**)	**4ae**	85	97
6	Me, 6-Me (**3f**)	**4af**	84	97
7	Me, 7-Me (**3g**)	**4ag**	71	>99
8	Me, 4-BnO (**3h**)	**4ah**	75	99
9	Me, 5-BnO (**3i**)	**4ai**	75	98
10	Me, 6-BnO (**3j**)	**4aj**	87	>99
11	Me, 5-Cl (**3h**)	**4ah**	<10	

[a]Reactions were performed with **2a** (0.1 mmol), **3** (0.3 mmol), and **1d** (0.01 mmol) in solvent (0.9 mL). [b]Isolated yield. [c]Determined by HPLC analysis using a chiral stationary phase. [d]Used 20 mol % of the catalyst **1d**.

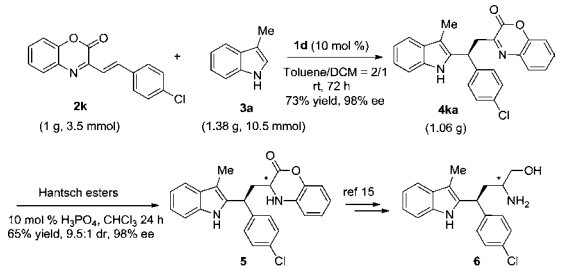
smoothly with substrates bearing electron-donating groups, such as phenoxy and methyl, on the benzene position of 3-methylindole, to afford the products in high yields and stereoselectivities (Table 3, entries 3−10). In contrast, the reaction was suppressed by the introduction of electron-withdrawing groups, and only trace amounts of the corresponding adduct were detected when 5-chloroskatole (**3h**) was used (Table 3, entry 11). The C3 Friedel−Crafts alkylation of **2a** and simple indole (**4i**) was also tested under the optimal reaction conditions, and the C3-functionalized product **4ai** was obtained in high yield but with poor stereoselectivity (Scheme 2, see also Table S1 in the Supporting Information).

Scheme 2. C3 Friedel−Crafts Alkylation of 2a and 3i



To exploit the potential of the Friedel−Crafts alkylation process, the reaction was scaled up to 3.5 mmol of **2k** and 10.5 mmol of 3-methylindole (**3a**). The corresponding product **4ka** could be obtained in 75% yield without a deleterious effect on stereoselectivity (Scheme 3). The absolute configuration of the new chiral center of **4ka** was assigned as *S* by X-ray crystallographic analysis (Figure 1).[14] Compound **4ka** undergoes a Brønsted acid catalyzed transfer hydrogenation reaction by

Scheme 3. Scale Up Reaction and Reduction of 4ka



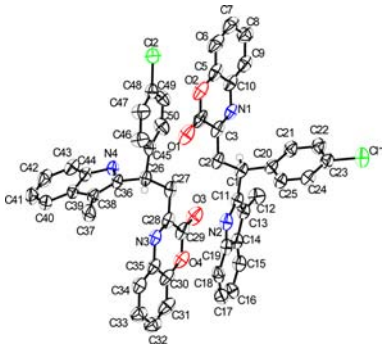


Figure 1. X-ray structure of **4ka**.

employing Hantzsch ester as a hydrogen donor; the resulted α-amino acid derivative **5** was obtained in 65% yield with excellent stereoselectivity (98% ee, 9.5:1 dr, Scheme 2). Compound **5** was an important building intermediate in organic synthesis and could be converted to amino alcohol **6** according to the procedure reported by Maruoka and co-workers.[15]

In conclusion, we have developed a chiral phosphoric acid catalyzed Friedel−Crafts alkylation reaction of 3-substituted indole to β,γ-unsaturated α-ketimino esters. This highly enantioselective protocol gives C2-functionalized indole derivatives bearing a synthetically versatile α-ketimino ester motif. A wide range of β,γ-unsaturated α-ketimino esters react smoothly with 3-substituted indoles to afford the corresponding adducts with moderate to high yields and high stereoselectivities. More importantly, this strategy could be used for the synthesis of a 2-indolyl-α-amino acid skeleton, which is the backbone of many biologically interesting compounds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Typical experimental procedure and characterization for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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