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An Efficient Enantioselective Method for Asymmetric Friedel–Crafts Alkylation of Indoles with α,β-Unsaturated Aldehydes

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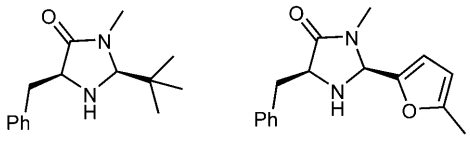
Abstract: The Lewis base-Lewis base bifunctional catalytic system has been developed and successfully applied to the asymmetric Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes. The reactions are promoted by chiral diphenylprolinol trimethylsilyl ether in the presence of triethylamine. By this protocol, optically active 3-substituted indoles can be obtained in an organocatalytic process that is free of Lewis or protic acid in high yields with up to 98% *ee*. Besides, this reaction could be carried out on a gram scale without any loss in the enantioselectivity.

Keywords: Friedel–Crafts reaction; indoles; Michael addition; organic catalysis; α,β-unsaturated aldehydes

Introduction

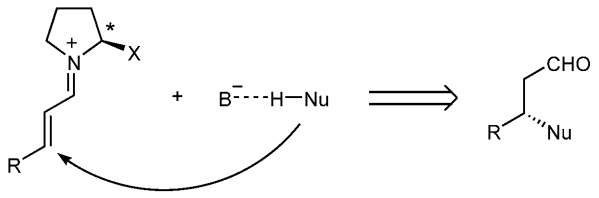
The Lewis acid or protic acid-promoted Friedel–Crafts alkylation is a powerful carbon-carbon bond forming process in organic chemistry.[1] Recently, with the development of organocatalysis,[2] it is now also possible to perform enantioselective Friedel–Crafts alkylation[3] in the presence of a chiral amine, in particular, and protic acid as co-catalyst. However, many of these procedures frequently require large quantities of Lewis or protic acid 'catalysts' that are destroyed during work-up and cause corrosion problems. Thus, the development of an enantioselective, acid-free Friedel–Crafts alkylation appeared to be of great significance.[4]

3-Substituted indole structures are abundant in natural products that possess a broad array of biological activities.[5] Accordingly, a number of synthetic strategies has been reported for the construction of these "privileged" structural motifs.[3] In spite of considerable effort, most of the successful examples of such process are limited to use of bidentate chelating carbonyl substrates, including β,γ-unsaturated-α-keto esters,[6a–b] acyl phosphonates,[6c] alkylidenemalonates,[6d–f] α-hydroxy enones,[6g] 2-acyl imidazoles,[6h] and nitroalkenes.[6i–l] The use of simple non-chelating α,β-unsaturated carbonyl compounds as electrophiles represents a considerable synthetic challenge. Recently several catalytic systems based on metal catalysis[7] or organocatalysis[8] have been developed and successfully applied to the asymmetric alkylation of indoles with α,β-unsaturated ketones. In sharp contrast, the use of simple non-chelating α,β-unsaturated aldehydes[9] as electrophiles represents a considerable synthetic challenge and has been less studied. Only three contributions based on MacMillan's LUMO-lowering activation using the imidazolidinone catalysts **1** (Figure 1) have been reported. MacMillan[9b] was the first to report the asymmetric Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes by the use of imidazolidinone **1a**. King[9e] later showed that α-branched α,β-unsaturated aldehydes were competent electrophiles in the presence of imidazolidinone



1a **1b**

Figure 1. Developed catalysts **1** for Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes.



Scheme 1. Lewis Base-Lewis base bifunctional catalysis by LUMO-lowering activation of α,β-unsaturated aldehyde and HOMO-raising activation of nucleophilic reagent.

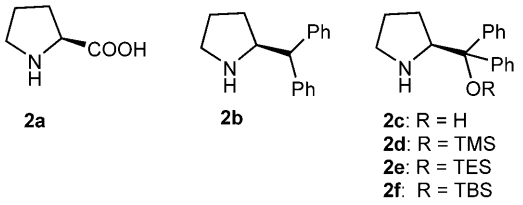
1b. Recently Xiao[9f] reported the intermolecular Friedel–Crafts alkylation promoted by **1a**.

We wondered if there was a possibility to improve catalytic reactivity without adding any acids, and envisioned that Lewis base-Lewis base bifunctional catalysis combining both LUMO-lowering and HOMO-raising mechanisms could be a new tool for the asymmetric Friedel–Crafts alkylation (Scheme 1).[12n] In this bifunctional catalysis, a Lewis base such as a chiral amine catalyst was used to activate the α,β-unsaturated aldehyde and induce the chirality of the reaction by the iminium mechanism[10] and a Lewis base such as triethylamine was used to activate the nucleophilic reagent by deprotonation or hydrogen-bond interaction.[11] Thus, it was expected that this kind of bifunctional catalysis could enhance the efficiency and practicability.

Results and Discussion

Diphenylprolinol silyl ether **2d** (Figure 2),[12] independently developed by Jørgensen's and Hayashi's groups, has been revealed as an efficient organocatalyst for many asymmetric reactions, particularly for the enantioselective transformation of carbonyl compounds. However, there are no date available concerning its use as a chiral catalyst in the Friedel–Crafts reaction. We considered that **2d** could be a reasonable candidate to evaluate the above assumption.

To test our hypothesis, our experiments began with the addition of indole **4a** to crotonaldehyde **3a** by the readily available diphenylprolinol TMS ether **2d**. Reaction optimization involved variation of additive, catalyst, solvent, and temperature.



2a **2b** **2c**: R = H **2d**: R = TMS **2e**: R = TES **2f**: R = TBS

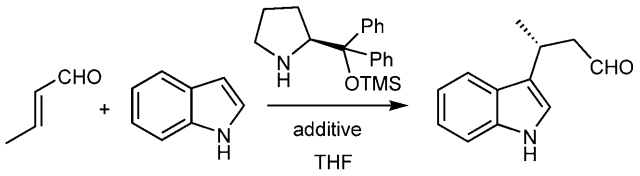
Figure 2. Proposed catalysts **2** for Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes.

Effect of Additive

The effects of the additive including acids and bases were investigated first and representative results are shown in Table 1.[13]

The addition of indole **4a** to crotonaldehyde **3a** proceeded with different results using different kinds of additive. The reaction gave poor results under ordinary iminium catalytic conditions using 20 mol% of **2d** as the organocatalyst, even with a Brønsted acid as a cocatalyst which could promote the formation of iminium (entry 2).[14] Because of the decomposition of the catalyst, there was barely any product when CF_3COOH was used (entry 3). Interestingly, a remarkable enhancement was achieved when triethylamine[15] was introduced to the reaction system, which supposedly enhances the nucleophilicity by deprotonation or hydrogen-bond interaction of the N–H of the indole (entry 4). The significant acceleration by triethylamine encouraged us to perform a screen of different organic bases for their ability to improve the reaction. It was found that *i*-Pr_2EtN was also suitable for obtaining satisfactory conversion and enantioselectivity, and gave a similar result to that with triethyl-

Table 1. Effect of additive.[a]



3a **4a** **5aa**

Entry	Additive (mol%)	Yield [%][b]	*ee* [%][c]
1	none	51	52
2	PhCOOH (20)	38	30
3	CF_3COOH (20)	<10	n.d.[d]
4	Et_3N (20)	71	75
5	*i*-Pr_2EtN (20)	67	75
6	NMM (20)	48	54
7	2,6-lutidine (20)	50	56
8	KO-*t*-Bu (20)	<10	n.d.[d]
9	NaOAc (20)	52	53
10	Et_3N·HCl (20)	47	52
11	Et_3N (40)	70	76
12	Et_3N (50)	70	78
13	Et_3N (60)	69	78
14	Et_3N (80)	68	77
15	Et_3N (100)	65	76

[a] Unless otherwise noted, all reactions were performed with 0.36 mmol of **4a**, 0.3 mmol of **3a**, 0.06 mmol of **2** in 0.7 mL THF at room temperature for 12 h.
[b] Isolated yield of product after column chromatography.
[c] Determined by chiral HPLC on a Chiralpak OD-H column after $NaBH_4$ reduction.
[d] Not determined.

amine (entry 5). But some other organic bases such as *N*-methylmorpholine or 2,6-lutidine gave poor results (entries 6 and 7). The addition of KO-*t*-Bu barely gave any product due to the background reaction (entry 8). The results in Table 1 also indicated that the use of NaOAc[16] or $Et_3N{\cdot}HCl$ could not efficiently improve the outcome of the reaction (entries 9 and 10).

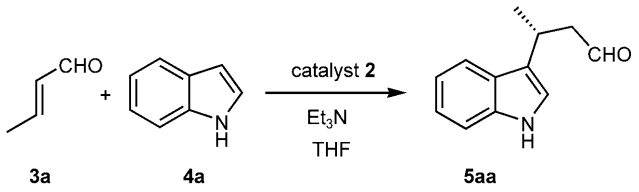
The effect of the loading of the additive base, triethylamine, on the reaction was evaluated next. In general, the loading of triethylamine had little effect on the reactivity and enantioselectivity in the range from 20 to 100 mol% (entries 11–15). And the best result was obtained when 50 mol% triethylamine was used. In this instance, 3-substituted indole **5aa** was obtained in high yield and enantioselectivity (entry 12).

Although this reaction could take place with ordinary iminium catalysis using **2d** solely as the organocatalyst, the reaction in the Lewis base-Lewis base bifunctional catalysis conditions was much more efficient. In fact, the existence of additive base was essential to obtain a high yield and enantioselectivity. Thus, Lewis base-Lewis base bifunctional catalysis might provide a practical and efficient method for the enantioselective Friedel–Crafts alkylation.

Catalyst Screen

We started our investigation directed at the identification of the most efficient amine catalyst for the enantioselective Friedel–Crafts alkylation. The results are shown in Table 2.

Table 2. Effect of catalyst.[a]



3a 4a 5aa

Entry	Catalyst	Yield [%][b]	*ee* [%][c]
1	**2a**	<10	n.d.[d]
2	**2b**	60	63
3	**2c**	38	27
4	**2d**	70	78
5	**2e**	33	rac
6	**2f**	56	79

[a] Unless otherwise noted, all reactions were performed with 0.36 mmol of **4a**, 0.3 mmol of **3a**, 0.06 mmol of **2d** in 0.7 mL THF at room temperature for 12 h.
[b] Isolated yield of product after column chromatography.
[c] Determined by chiral HPLC on a Chiralpak OD-H column after $NaBH_4$ reduction.
[d] Not determined.

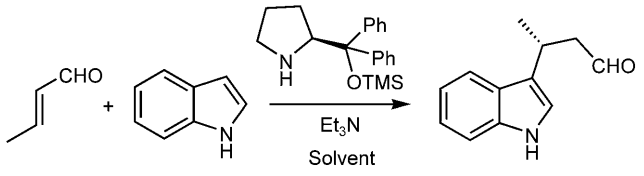
Preliminary experiments identified diphenylprolinol TMS ether **2d** as a suitable catalyst (entry 4). The outcomes varied dramatically when changing the trimethylsilyl group into either a *tert*-butyldimethylsilyl group or a triethylsilyl group. The TBS derivative **2f** catalyzed the reaction to afford **5aa** with similar enantioselectivity to that with **2d**, but with a lower yield (entry 6). Surprisingly, the TES derivative **2e** was not active in the present reaction probably due to the bulk hindrance (entry 5). As expected, proline **2a** and prolinol **2c** gave the product in low yields and led to the formation of significant amounts of by-products (entries 1 and 3). Furthermore, the pyrrolidine catalyst **2b** catalyzed the reaction with moderate yield and enantioselectivity (entry 2).

On the basis of the outcomes obtained from the above investigation, we chose diphenylprolinol TMS ether **2d** as the catalyst used in further studies aimed at optimizing reaction conditions by focusing on surveying the reaction medium and the reaction temperature.

Solvent Screen

Solvents play an important role in governing the rates and enantioselectivities of a reaction. Therefore, we probed the effects of reaction medium on the **2d**-promoted Friedel–Crafts alkylation process (Table 3).

Table 3. Effect of solvent.[a]



3a 4a 5aa

Entry	Solvent	Yield [%][b]	*ee* [%][c]
1	THF	70	78
2	ether	69	72
3	dioxane	53	79
4	MTBE	85	83
5	DME	58	80
6	toluene	90	33
7	CH_3CN	n.r.[d]	–
8	DMF	n.r.[d]	–
9	CH_3OH	45	34
10	CH_2Cl_2	50	41

[a] Unless otherwise noted, all reactions were performed with 0.36 mmol of **4a**, 0.3 mmol of **3a**, 0.06 mmol of **2d** in 0.7 mL solvents at room temperature for 12 h.
[b] Isolated yield of product after column chromatography.
[c] Determined by chiral HPLC on a Chiralpak OD-H column after $NaBH_4$ reduction.
[d] No reaction.

Reactions performed in ethereal solvents such as THF, ether, dioxane, MTBE and DME (entries 1–5) generally afforded better results in terms of reaction yield and enantioselectivity. And the highest enantioselectivity was obtained when the reaction was conducted in MTBE. Interestingly, the reaction in toluene gave the best yield, but the *ee* dropped dramatically (entry 6). The outcomes varied dramatically with the utilization of polar solvents. No reaction occurred in DMF or CH_3CN (entries 7 and 8), whereas the processes took place in MeOH in spite of the low yield and *ee* (entry 9). A less promising result was also obtained in a non-polar solvent such as CH_2Cl_2 (entry 10).

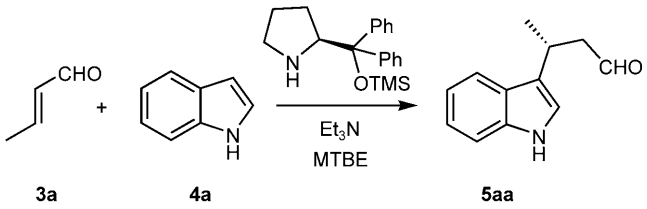
Effect of Temperature

The reaction temperature also plays an important effect on the enantioselectivity (Table 4).

In general, lowering the temperature results a slight decrease of the reaction rate but a slight increase of the enantioselectivity. In the presence of 20 mol% of **2d**, 83 yield, 87% *ee* of **5aa** was obtained at room temperature and 0 °C (entries 1 and 2). When the reaction was run at −20 °C, the enantioselectivity increased to 92% *ee* without remarkably decreasing the yield, although the reaction time must be lengthened to 36 h (entry 3). Further decreasing the temperature to −40 °C also gave the product in 94% *ee* but with a lower yield (entry 4). Considering the practical usage, we gave up this condition.

Thus, after investigating the effects of a series of factors, the optimal conditions had been established. That is using 20 mol% of amine catalyst **2d**, 50 mol% of TEA in 0.7 mL MTBE at −20 °C for 36 h. Under these optimal conditions, the Friedel–Crafts alkylation product **5aa** was obtained in high yield and enantioselectivity.

Table 4. Effect of temperature.[a]



Entry	Temperature [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	r.t.	12	85	83
2	0	24	74	87
3	−20	36	69	92
4	−40	48	53	94

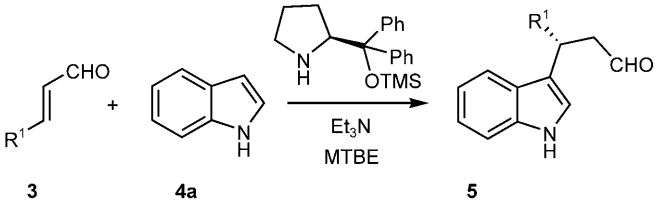
[a] Unless otherwise noted, all reactions were performed with 0.36 mmol of **4a**, 0.3 mmol of **3a**, 0.06 mmol of **2d** in 0.7 mL MTBE at different temperature for different time.
[b] Isolated yield of product after column chromatography.
[c] Determined by chiral HPLC on a Chiralpak OD-H column after $NaBH_4$ reduction.

Addition of Indole to Representative α,β-Unsaturated Aldehydes

Having established the optimal conditions for the reaction, the generality of the reaction was then examined in detail. The addition of indole to representative α,β-unsaturated aldehydes was investigated first and the results are presented in Table 5.

The reaction proceeded well for various α,β-unsaturated aldehydes and significant structural variation of α,β-unsaturated aldehydes can be tolerated. The electronic nature of the aromatic rings of α,β-unsaturated aldehydes had limited influence on the stereochemical outcome. It demonstrated that the electron-withdraw-

Table 5. Organocatalyzed alkylation of indole with representative α,β-unsaturated aldehydes.[a]



Entry	R^1	Product	Yield [%][b]	*ee* [%][c]
1	methyl (**3a**)	**5aa**	69	92
2	ethyl (**3b**)	**5ab**	74	94
3	propyl (**3c**)	**5ac**	71	96
4	isopropyl (**3d**)	**5ad**	67	97
5	phenyl (**3e**)	**5ae**	78	96
6	2-ClC_6H_4 (**3f**)	**5af**	92	98
7[d]	2-ClC_6H_4 (**3f**)	**5af**	83	94
8	3-ClC_6H_4 (**3g**)	**5ag**	81	96
9	4-FC_6H_4 (**3h**)	**5ah**	80	95
10	4-ClC_6H_4 (**3i**)	**5ai**	80	97
11	2-$MeOC_6H_4$ (**3j**)	**5aj**	88	95
12	3-$MeOC_6H_4$ (**3k**)	**5ak**	76	96
13	4-MeC_6H_4 (**3l**)	**5al**	75	96
14	4-$MeOC_6H_4$ (**3m**)	**5am**	75	96
15	2-furyl (**3n**)	**5an**	73	95
16[e]	2-ClC_6H_4 (**3f**)	**5af**	95	98

[a] Unless otherwise noted, all reactions were performed with 0.36 mmol of **4a**, 0.3 mmol of **3**, 0.06 mmol of **2d** in 0.7 mL MTBE at −20 °C for 36 h.
[b] Isolated yield of product after column chromatography.
[c] For analysis of the *ee* values of the products, see the Supporting Information.
[d] 5 mol% catalyst was used.
[e] The reaction was performed on a gram scale (20 mmol) at −20 °C for 60 h.

ing (entries 6–10), electron-donating (entries 11–14) and neutral (entry 5) systems can participate in the reactions. A similar trend was observed for the steric effect as well (entries 9, 10, 13 and 14). In the case of heteroaromatic systems, excellent enantioselectivity was obtained (entry 15). Also significant was that the process tolerated the less reactive alkyl α,β-unsaturated aldehydes. Both good yields and excellent enantioselectivities were seen (entries 1–4). It should be noted that, when the loading of the catalyst was reduced to 5 mol%, the enantioselectivity of the reaction still remained high (entry 7).

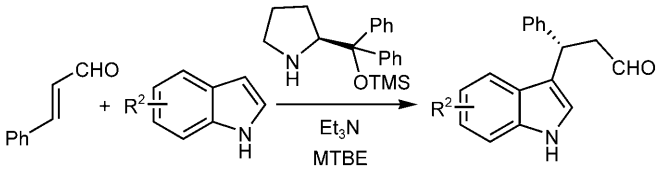
Importantly, this reaction could be carried out on a gram scale (20 mmol) to demonstrate the synthetic utility of the present system. When the reaction was performed with 20 mmol of **4a** at −20 °C for 60 h, the corresponding adduct **5af** was obtained in high chemical yield without any loss in the enantioselectivity (entry 16).

Addition of Representative Indoles to Cinnamaldehyde

The effect of indole derivatives was next evaluated under similar conditions (Table 6).

Indole derivatives with either electron-withdrawing or electron-donating substituents at C-5 were competent substrates (entries 4 and 5). While a C-2 or C-7 alkyl substituent lowered the conversion, a good level of enantioselectivity was still observed (entries 3 and 6). However, as a limitation of the approach, the substitution on the indolic nitrogen had a detrimental effect on the reactivity (entry 2). The failure of the reaction of *N*-methylindole with cinnamaldehyde was consistent with the fact that a base such as triethylamine was used to activate indole by deprotonation, because the *N*-methylindole cannot be deprotoned by a base.[7a,b]

Table 6. Organocatalyzed alkylation of representative indoles with cinnamaldehyde.[a]



3a 4 5

Entry	R^2	Product	Yield [%][b]	*ee* [%][c]
1	H (**4a**)	**5ab**	78	96
2	1-Me (**4b**)	**5bb**	<5	n.d.[d]
3	2-Me (**4c**)	**5cb**	70	94
4	5-MeO (**4d**)	**5db**	77	97
5	5-Br (**4e**)	**5eb**	81	96
6	7-Me (**4f**)	**5fb**	66	98

[a] Unless otherwise noted, all reactions were performed with 0.36 mmol of **4**, 0.3 mmol of **3a**, 0.06 mmol of **2d** in 0.7 mL MTBE at −20 °C for 36 h.
[b] Isolated yield of product after column chromatography.
[c] For analysis of the *ee* values of the products, see the Supporting Information.
[d] Not determined.

Conclusions

In summary, we have developed a new Lewis base-Lewis base bifunctional catalysis for the asymmetric Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes with high efficiency and enantioselectivity. This method offers substantial advantages over the traditional approaches, not only by avoiding the use of any acids, but also in terms of the yield and selectivity of the process. Furthermore, the enantioselective reactions introduced here demonstrate that it is possible to carry out Friedel–Crafts alkylation reactions without a traditional Lewis or protic acid only by the use of chiral diphenylprolinol TMS ether as a promoter in the presence of triethylamine. Moreover, the non-covalent activation of unsaturated aldehydes allows further transformations with diverse nucleophiles to be carried out, which is the subject of current studies. Further studies to extend the reaction scope are currently underway in our laboratory.

Experimental Section

General Information

Commercial reagents were purified prior to use. Catalysts **2** were synthesized according to refs.[12d,17] Column chromatography were carried out on silica gel. ^{1}H NMR spectra were recorded at 400 MHz in $CDCl_3$ and ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ using TMS as internal standard. IR spectra were recorded on an FT-IR spectrometer and only major peaks are reported in cm^{-1}. High-resolution mass spectra (HR-MS) were obtained by use of ESI ionization sources. Mass spectra were recorded on an API 200 LC/MS system. Elemental analyses were preformed on a Vario EL III elementary analysis instrument. The *ee* value determination was carried out using chiral HPLC with a Daicel Chiracel OD-H or an AD column on Waters with a 996 UV-detector.

General Procedure for Friedel–Crafts Alkylation of Indoles with α,β-Unsaturated Aldehydes

To a *tert*-butyl methyl ether solution (0.7 mL) of catalyst **2d** (0.06 mmol, 20 mol%) and α,β-unsaturated aldehyde **3** (0.3 mmol) were added triethylamine (0.15 mmol, 50 mol%) and indole **4** (0.36 mmol) at −20 °C. The resulting suspension was stirred at −20 °C for 36 h. The resulting mixture

was quenched with saturated aqueous NH_4Cl. The organic materials were extracted with AcOEt and dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **5**. The enantioselectivity was determined by subjecting approximately 10 mg of the title compound to an excess of $NaBH_4$ and 1 mL of methanol. After 30 min, the solution was treated with saturated aqueous $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The organic layer was separated, filtered through a silica gel plug and subjected to chiral HPLC analysis (conditions noted). The absolute configuration of adducts was assigned by comparison to the literature data.[9b]

Acknowledgements

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