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Diarylprolinol Silyl Ether Catalyzed Asymmetric Friedel–Crafts Alkylation of Indoles with α,β-Unsaturated Aldehydes: Enhanced Enantioselectivity and Mechanistic Investigations

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A highly enantioselective Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes with excellent enantioselectivities (up to >99 %*ee*) has been developed, and this improved method offers substantial advantages over traditional approaches, not only by avoiding the use of acids or bases, but also in terms of the higher level of stereoselectivity. In addition, we have demonstrated through a plausible mechanism that the role of silicon in the diarylprolinol silyl ethers (Jørgensen–Hayashi organocatalyst) not only serves as a bulky group to induce steric repulsion but also serves as a Lewis acidic promoter to accelerate the reaction between the secondary amine and the substrate (α,β-unsaturated aldehyde).

Introduction

Since 2000,[1] the organocatalytic creation of structurally diverse molecules from readily available and simple starting materials has drawn much attention.[2] Although enormous asymmetric organocatalytic reactions have been reported in the past decade, the design of efficient organocatalysts, especially in a predictable manner, remains elusive.[3] Recently, the role that silicon-containing bulky groups might play in asymmetric catalysis has been well recognized.[4] Among the known organocatalysts with bulky silyl groups, diarylprolinol silyl ethers are arguably the most famous and powerful.[5] Since it was first introduced by Jørgensen and Hayashi independently in 2005,[6] the past few years have witnessed an explosive growth in the applications of diarylprolinol silyl ethers in asymmetric organocatalytic reactions. Prolinol silyl ethers have been applied to various organic transformations, including aldol reactions, Mannich reactions, oxidations and reductions, α- and γ-hetereofunctionalizations, cycloadditions, and domino reactions, via either enamine or iminium intermediates.[4,5]

3-Substituted indoles are important motifs in natural products and they are biologically significant molecules; their synthesis through the iminium-based organocatalytic Friedel–Crafts alkylation of α,β-unsaturated aldehydes has been studied.[7,8] The diarylprolinol silyl ether catalyzed asymmetric Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes has recently been reported by the groups of Bao[9] and Wang[10] independently. Excellent enantiomeric excess of the Friedel–Crafts adducts (up to 98 %*ee*) was attainable in the reported reactions; however, large amounts of a tertiary amine as additive (Et_3N, 50–100 mol-%) and an expensive solvent (methyl *tert*-butyl ether, MTBE) were required for these reactions. Herein, we report an improved protocol for the Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes; a modified diarylprolinol silyl ether containing tertiary amine moiety was used as the highly enantioselective organocatalyst, which resulted in the formation of 3-alkylated products with 98→99 %*ee*. Moreover, mechanistic insights will also be presented in this report.

Results and Discussion

Initially, we prepared interesting and fine-tuned diarylprolinol ethers **5** and **6** containing imidazole and tertiary amine moieties that showed excellent catalytic activities in aqueous Michael reactions of aldehydes to nitroolefins.[11] To achieve the highly enantioselective Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes, we relied on diarylprolinol ethers **4**–**6** for the model Friedel–Crafts addition of indole (**1a**) to *trans*-cinnamaldehyde (**2a**) under

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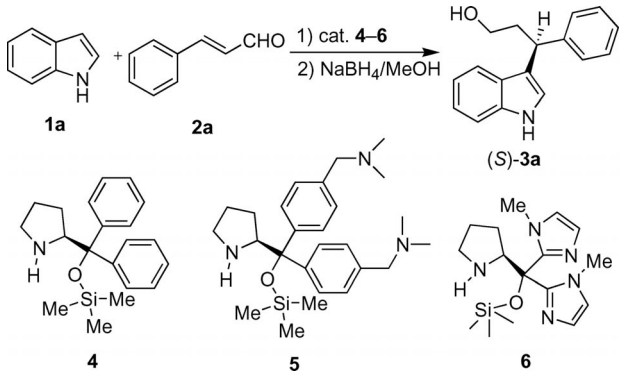
standard conditions (Scheme 1 and Table 1). Preliminary experiments on the reaction of **1a** to **2a** using catalysts **4**–**6** revealed that catalyst **5** provided the best results (Table 1, Entries 1–3), which may be due to the existence of the tertiary amine moiety at the aromatic ring of diarylprolinol silyl ether **5**. This is in accordance with the previous report that the addition of a tertiary amine is important for the enhancement in the enantioselectivities.[10] Indeed, catalyst **5**, which is easily prepared from L-proline and (4-bromophenyl)-*N*,*N*-dimethylmethanamine, had a very positive effect on asymmetric induction in comparison to that of catalyst **4** under different conditions. For example, catalyst **4** bearing no additional group gave the product with only moderated enantioselectivities (49–73%*ee*) in most of solvents, which are lower than those obtained with catalyst **5** (76–92%*ee*) under almost the same conditions (Table 1; Entry 5 vs. 4, entry 7 vs. 6, entry 9 vs. 8, and entry 11 vs. 10). In particular, when the reaction was performed in acetonitrile without any additive, the best enantioselectivity obtained was 92%*ee* with good isolated yields of this two-step transformation at room temperature (Table 1, Entry 6). Correspondingly, catalyst **4** resulted in only moderate enantioselectivity in acetonitrile (72%*ee*). Interestingly and unexpectedly, it is should be noted that we found that catalyst **6** containing an imidazole moiety was inactive in this reaction. Furthermore, the addition of a large amount of tertiary amine to this reaction did not result in any improvement. Although subsequent experiments showed acidic additives could improve the catalytic activity of **6** in this reaction, the yields were still poor; for example, the addition of *p*-ClPhCOOH (40 mol-%) as additive resulted in only 29% yield and 43%*ee*.



Scheme 1.

With catalyst **5** in hand and on the basis of these preliminary results, a beneficial effect on the asymmetric induction was found by lowering the temperature (Table 1, Entries 16 and 17), whereas lowering the temperature to –40 °C led to a further improvement in the enantioselectivity (99%*ee*, 51% yield; Table 1, Entry 17). When the reaction was performed at –20 °C the enantioselectivity was also found to be excellent (98%*ee*, 65% yield; Table 1, Entry 16). On the basis of other reports[9,10] and the present findings, we determined that catalyst **5** gives better enantioselectivity than those reported for other organocatalysts in previous methods[7–10] under the same conditions.

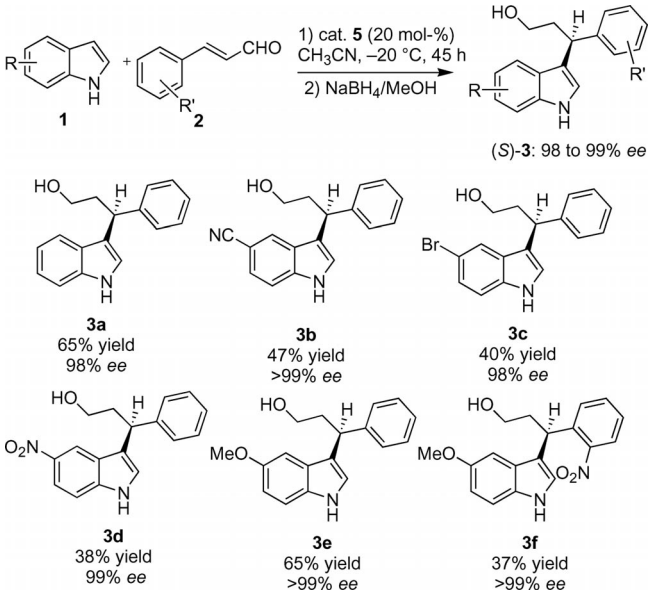
Table 1. Optimization of reaction conditions: representative results.[a]

Entry	Cat.	Solvent	Time [h]	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**4**	MeOH	36	r.t.	65	73[d]
2	**5**	MeOH	45	r.t.	84	76
3	**6**	MeOH	72	r.t.	trace	–
4	**5**	THF	45	r.t.	48	87
5	**4**	THF	36	r.t.	33	63[d]
6	**5**	CH_3CN	45	r.t.	80	92
7	**4**	CH_3CN	36	r.t.	46	72[d]
8	**5**	CH_2Cl_2	45	r.t.	86	85
9	**4**	CH_2Cl_2	36	r.t.	42	60[d]
10	**5**	EtOH	45	r.t.	96	77
11	**4**	EtOH	36	r.t.	42	49[d]
12	**5**	toluene	45	r.t.	75	79
13	**5**	HMDSO[e]	45	r.t.	29	76
14	**5**	CH_3CN/H_2O	45	r.t.	59	90
15	**4**	MTBE/Et_3N	36	–20	78	96[f]
16	**5**	CH_3CN	45	–20	65	98
17	**5**	CH_3CN	45	–40	51	99

[a] Reaction conditions: cinnamaldehyde (**2a**; 0.5 mmol, 1 equiv.), indole (**1a**; 0.6 mmol, 1.2 equiv.), catalyst **4**–**6** (20 mol-%), and solvent (0.5 mL). [b] Total isolated yield for two-step operation. [c] Determined by chiral HPLC analysis. [d] From ref.[9]: cinnamaldehyde (0.5 mmol, 1 equiv.), indole (1.0 mmol, 2 equiv.), catalyst **4** (15 mol-%), and solvent (1.0 mL). [e] HMDSO = hexamethyl disiloxane ($Me_3SiOSiMe_3$). [f] Ref.[10]

With these conditions in hand, the scope of the asymmetric Friedel–Crafts alkylation of indoles was subsequently explored by using **5** as the organocatalyst and acetonitrile as the solvent (Scheme 2). Several indoles containing electron-neutral, electron-deficient, and electron-rich substituents proceeded equally well with α,β-unsaturated aldehydes to give the corresponding products with good results with promising enantioselectivities. To the best of our knowledge, these examples of organocatalyst-promoted Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes showed the highest enantioselectivities reported (98→99%*ee*). Notably, although a simple increase in the reaction time was sufficient to obtain the Friedel–Crafts adducts in good yield, these reactions were carried out for 45 h to differentiate the reactivities of the substrates. In addition, these results showed that the use of fine-tuned diarylprolinol ether **5** containing a tertiary amine moiety as the catalyst in the Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes resulted in a higher level of enantioselectivity in comparison to those obtained with the use of catalyst **4** reported by Bao et al.[9] and Wang et al.[10] in 2009.

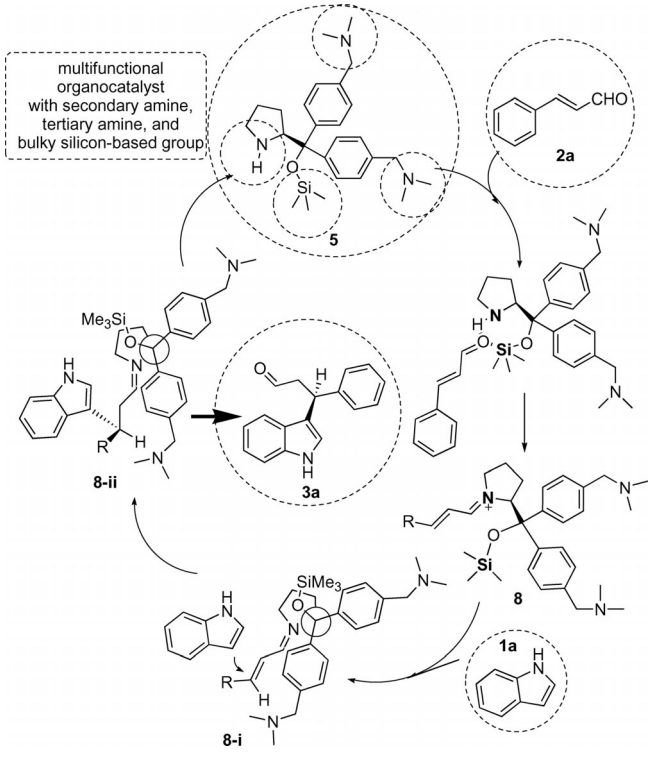
Why do diarylprolinol silyl ethers **4**–**6** show different catalytic activity in the asymmetric Friedel–Crafts alkylation of indoles? Some reasons could be concluded from the iminium mechanism, in which selective attack is affected by the 2-substituent (diaryl and silicon-based bulky group) on the pyrrolidine ring.[12] In previous discussions of possible mechanisms involving the iminium intermediate of di-



Scheme 2. Catalytic asymmetric Friedel–Crafts alkylation of indoles.

arylprolinol silyl ethers,[12c,12e] the contribution of silicon was only limited to a shielding effect as a result of the steric repulsion caused by the bulky group. However, other effects of silicon were completely overlooked in previous mechanistic studies. In fact, silicon has an energetically accessible *d* orbital, so it can act as a Lewis acid.[13,14] Therefore, it is interesting to consider the functionality of the silicon atom in this amino organocatalyst. Herein, in light of previous mechanistic studies of diarylprolinol silyl ether catalyzed transformations[12] and the aforementioned asymmetric Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes, we report the preliminary investigation of the mechanism, with an emphasis on the role of silicon, by comparing the differences in enantioselectivity of catalysts **4**–**6** with the aid of ^{29}Si NMR spectroscopy.

On the basis of experimental results and ^{29}Si NMR analysis (Supporting Information), the mechanism of diarylprolinol silyl ether catalyzed Friedel–Crafts alkylation of indoles was proposed (Scheme 3). It is speculated that the silicon atom in the diarylprolinol silyl ethers not only serves as a bulky group to strengthen steric repulsion, but it also serves as a promoter/activator to accelerate the initial step of the reaction between the secondary amine and the substrate (α,β-unsaturated aldehyde). In this hypothesis, the possible activated silicon species is able to facilitate the interaction between the secondary amine and the α,β-unsaturated aldehyde, which provides iminium intermediate **8** efficiently and quickly.[15] In addition, in the catalytic cycle, the bulky silicon group at C-2 on the pyrrolidine is essential for high enantioselectivity.[12]



Scheme 3. Proposed mechanism for the **5**-catalyzed Friedel–Crafts alkylation of indole with α,β-unsaturated aldehyde.

Conclusions

In summary, we have developed a highly enantioselective Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes with excellent enantioselectivities (up to >99% *ee*). This improved method offers substantial advantages over the traditional approaches, not only by avoiding the use of any acids or bases but also in terms of the high level of stereoselectivity. In addition, on the basis of experimental results and ^{29}Si NMR spectroscopic analysis, we have demonstrated a possible mechanism in which the role of the silicon atom in diarylprolinol silyl ethers (Jørgensen–Hayashi catalyst) not only serves as a bulky group to induce steric repulsion but also serves as a Lewis acidic promoter to facilitate the crucial step involving the formation of the iminium intermediate derived from the secondary amine and the substrate (α,β-unsaturated aldehyde). Furthermore, this work shows that modification of the Jørgensen–Hayashi catalyst with the introduction of an amino group on the diarylprolinol silyl ether increases the stereoselectivity in certain asymmetric transformations and sets the basis for further development.

Experimental Section

General Remarks: All reagents and solvents were used directly without purification. Flash column chromatography was performed over silica (200–300 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, with an Advance (Bruker) 400 MHz spectrometer and were referenced to the internal solvent signals. Thin-layer chromatography was performed by using

silica gel F254 TLC plates and visualized with ultraviolet light. HPLC was carried out with a Waters 2695 Millennium system equipped with a photodiode array detector. EI and CI mass spectra were performed with a Trace DSQ GC–MS spectrometer. Friedel–Crafts reaction products were known and confirmed by GC–MS and usual spectral methods (^{1}H NMR, ^{13}C NMR). ESI MS analysis of the samples were performed with an LCQ advantage mass spectrometer (ThermoFisher Company, USA) equipped with an ESI ion source in the positive ionization mode; data acquisitioning was performed with Xcalibur software (Version 1.4). Diarylprolinol silyl ethers **4**–**6** were synthesized according to reported procedures.[6,11]

Typical Procedure for the Asymmetric Friedel–Crafts Alkylation of Indoles with α,β-Unsaturated Aldehydes: To a solution of catalyst (*S*)-**5** (32 mg, 0.10 mmol, 20 mol-%) dissolved in CH_3CN (1 mL) in a 12-mL vial at room temperature was added cinnamaldehyde (66 mg, 0.5 mmol). The mixture was stirred for 30 min, and indole (70 mg, 0.6 mmol) was added to the mixture. The vial was capped, and the mixture was stirred at –20 °C for 45 h. An excess amount of $NaBH_4$ (57 mg, 1.5 mmol) was added, followed by the addition of MeOH (1 mL). Then, the –20 °C cooling bath was replaced by an ice bath, and the mixture was stirred for a further 20 min. The mixture was slowly added to sat. NH_4Cl (5 mL) at 0 °C and extracted with Et_2O (10 × 3 mL). The organic layer was collected, washed with H_2O (5 mL) and brine (5 mL), then dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:1) to afford **3a** (98%ee). This is a known compound with spectroscopic properties in accordance with those reported.[7,9,10] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (br. s, 1 H), 7.45 (d, J = 8.0 Hz, 1 H), 7.25–7.34 (m, 5 H), 7.16 (dd, J = 7.2, 15.4 Hz, 2 H), 7.07 (s, 1 H), 7.03 (t, J = 7.2 Hz, 1 H), 4.42 (t, J = 8.0 Hz, 1 H), 3.63–3.73 (m, 2 H), 2.44–2.52 (m, 1 H), 2.24–2.33 (m, 1 H) ppm. HPLC (Daicel Chiralpak OD-H, hexane/2-propanol = 80:20, flow rate = 1.0 mL/min): t_r = 15.34, 18.40 min.

Supporting Information (see footnote on the first page of this article): General remarks, spectroscopic data, and HPLC diagrams for the Friedel–Crafts adducts; ^{29}Si NMR spectra of diarylprolinol silyl ethers **4**–**6** and their enamine and iminium intermediates; circular dichroism and UV/Vis absorption spectra of catalysts **4**–**6** in CH_3CN.

Acknowledgments

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[15] Except for catalyst **6**, which showed poor activity in this reaction, we found that the catalytic activity of pyrrolidine without a functional group was very low in the Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes. The use of triethylamine or an organic acid as additive improved the reactivity but the yield was still low (<30% yield) along with long reaction time (96 h).

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