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Bifunctional cinchona alkaloid-squaramide-catalyzed highly enantioselective aza-Michael addition of indolines to α,β -unsaturated ketones

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Abstract

An enantioselective aza-Michael addition of indolines to α,β -unsaturated ketones was achieved using a bifunctional cinchona alkaloid-derived chiral squaramide derivative. Various β -indoliny ketone derivatives were obtained in good to excellent yields and with high enantioselectivity. DDQ or MnO_2 oxidation of indoline derivatives provided convenient access to various enantioenriched N-substituted indole derivatives.

Keywords

Aza-Michael reaction; Organocatalysis; Indoline; β -Keto indoline; Cinchona alkaloid; Enantioselective

The indole nucleus is a common structural feature in many bio-active alkaloids.¹ These subunits are also widely utilized in medicinal chemistry. Thus, enantioselective functionalization of indole ring is important. Over the years, a number of methods were developed which involved enantioselective alkylation of indoles at the C-3 position.² Recently, enantioselective alkylation of indoles at the C-2 has been carried out through the Pictet–Spengler reaction or alkylation/oxidation of 4,7-dihydroindoles.³ However, enantioselective derivatization of indoles utilizing indole nitrogen atom has rarely been explored possibly due to its low nucleophilicity.⁴ Interestingly, such N-functionalized indole derivatives are important structural elements of numerous biologically active natural products and synthetic medicinal agents.^{5,6}

Asymmetric Michael addition of nitrogen to α,β -unsaturated carbonyl derivatives represents a straightforward, logical approach. A number of methods have been developed relying upon the use of chiral auxiliaries, chiral starting materials, or stoichiometric amounts of chiral ligands. However, the catalytic enantioselective aza-Michael addition to α,β -unsaturated carbonyl compounds is quite challenging and remained relatively unexplored until recently.⁷ In 2006, MacMillan and co-workers⁸ reported an enantioselective secondary amine-catalyzed intermolecular aza-Michael addition of N-silyloxycarbamates to α,β -unsaturated aldehydes. Subsequently, several other conjugate additions catalyzed by secondary amines were investigated.⁹ The scope of these protocols was extended to α,β -unsaturated aliphatic ketones using primary amines and α,β -unsaturated aromatic ketones

using chiral phosphoric acids as the catalyst.^{10,11} Recently, bifunctional urea derived catalysts were employed for aza-Michael addition, however low enantioselectivity of products and high catalyst loading were some of the drawbacks of these methodologies.¹² Enantioselective aza-Michael addition of indole or indoline has been limited. Recent report of enantioselective aza-Michael addition of indoline to β -nitro styrene only provided 28% ee.¹³ Herein, we describe an enantioselective intermolecular aza-Michael reaction of indolines with α,β -unsaturated aromatic ketones catalyzed by a bifunctional cinchona alkaloid-squaramide catalyst. The resulting indoline derivative can be converted into indole derivative by a mild oxidation protocol. The current methodology provides access to a range of enantioenriched *N*-substituted indoles with good to excellent enantioselectivity.

Our studies were focused on the aza-Michael reaction between chalcone **1a** and indoline **2a** catalyzed by various quinine thiourea derivatives. Initially, we performed all reactions with 20 mol % catalyst in toluene at $-20\text{ }^{\circ}\text{C}$. The results are shown in Table 1. As can be seen, when thiourea catalyst **A**¹⁴ was used, the addition product **3a** showed moderate enantioselectivity (55% ee) and the conversion was excellent (90%, entry 1). We examined various other thiourea catalysts **B-E**.¹⁵ However, these catalysts showed moderate enantioselectivity for the product **3a** (entries 2-5). Subsequently, we investigated squaramide derivatives of quinine **F-J** (entries 6-10).¹⁶ Interestingly, squaramide catalyst **J** showed much improvement in enantioselectivity (78% ee, entry 10), however, conversion (76%) was less satisfactory. In an effort to improve conversion, we examined various solvents for catalyst **J** (entries 10-14). As it turned out, nonpolar solvents were more suitable for optimal conversion and product enantioselectivity. Aza-Michael reaction of **1a** and **2a** catalyzed by squaramide derivative **J** (20 mol %) provided the best result with 83% conversion and 81% ee for the addition product **3a** (entry 14). Raising the reaction temperature to $-10\text{ }^{\circ}\text{C}$ resulted in improvement of conversion (92%) however, enantioselectivity was reduced to 72% ee (entry 15). Also, lowering of reaction temperature to $-30\text{ }^{\circ}\text{C}$ did not improve enantioselectivity and a relatively low conversion (60%) was observed (entry 16). From the above studies, we concluded that squaramide catalyst **J** (20 mol %) in xylene at $-20\text{ }^{\circ}\text{C}$ would be the optimum condition for best enantioinduction and conversion.

We then explored aza-Michael reactions with a variety of α,β -unsaturated ketones **1** and indolines **2** using catalyst **J** in xylene at $-20\text{ }^{\circ}\text{C}$. The results are shown in Table 2. First, we examined various electron-donating and electron-withdrawing substituents on the phenyl and benzoyl rings (**1a-i**).¹⁷ As can be seen, substituents on the benzoyl ring (R^1) have little effect on the enantioselectivity and isolated yields were moderate because of significantly low conversion (entries 2 and 3). Incorporation of an electron-donating group on the phenyl ring (R^2) did not improve conversion (entry 4). Electron-withdrawing substituents on the phenyl ring resulted in both improvement in enantioselectivity and yield of addition products (entries 5-8). Interestingly, *p*-nitrile group on the phenyl ring provided low isolated yield of the product possibly due to hydrogen bonding interaction of a CN-group with the squaramide catalyst (entry 9). Significantly, furyl and methyl β -substituted α,β -unsaturated ketones were also shown to be compatible with the reaction conditions. The corresponding products **3j** and **3k** were isolated in moderate yields but with good enantioselectivity (entries 10 and 11). We have explored substituted indolines containing either an electron-withdrawing group or electron-donating group (5-Br, 5-Cl, 5-Me, and 5-OMe, respectively), for these aza-Michael reactions (entries 12-16). Indolines with electron-donating groups were much more reactive toward conjugate addition and gave Michael adducts in higher yields, and with higher enantioselectivity (entries 14-16). The absolute configuration of products was determined to be *R* as depicted based upon stereochemical outcome of previous 1,4-addition reactions catalyzed by quinine-derived squaramide catalysts.^{16b,18}

We have converted a number of aza-Michael indoline products into the corresponding *N*-substituted indole derivatives by mild oxidation.^{13b} As shown in Table 3, oxidation of various Michael adducts with DDQ (1.05 equiv) in THF at 23 °C for 15 min afforded the *N*-substituted indole derivatives in excellent yields without loss of enantioselectivity (entries 1–4). Similarly, oxidation of Michael adducts with MnO₂ (10 equiv) in CH₂Cl₂ also provided enantioenriched *N*-substituted indole derivatives in excellent yields without any loss of optical purity (entry 5).

In summary, we have developed an enantioselective protocol for aza-Michael additions of indolines to α,β -unsaturated ketones by utilizing bifunctional cinchona alkaloid-squaramide derivatives as catalysts. This asymmetric reaction provided excellent yields and good to excellent enantioselectivity for a variety of substituted chalcones. The indoline derivatives can be oxidized to indoles conveniently without loss of enantioselectivity. The present aza-Michael reaction provides access to highly enantiopure *N*-substituted indole and indoline derivatives. Further applications of this methodology are in progress in our laboratories.

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Table 1
Screening of the reaction conditions^a

Entry	Catalyst	Solvent	Conv ^b (%)	ee ^c (%)
1	A	PhMe	90	55
2	B	PhMe	70	52
3	C	PhMe	34	45
4	D	PhMe	20	25
5	E	PhMe	82	50
6	F	PhMe	56	60
7	G	PhMe	20	40
8	H	PhMe	88	69
9	I	PhMe	25	70
10	J	PhMe	76	78
11	J	CH ₂ Cl ₂	94	70
12	J	Et ₂ O	60	76
13	J	CH ₃ CN	50	45
14	J	Xylene	83	81
15 ^d	J	Xylene	92	72
16 ^e	J	Xylene	60	80

^aUnless otherwise noted, reactions were performed with 0.1 mmol of **1a**, 0.2 mmol of **2a**, and 20 mol % of catalysts in 1 mL solvent at -20 °C for 7 days.

^bDetermined by ¹H NMR analysis.

^cDetermined by HPLC analysis.

^d Reaction was conducted at $-10\text{ }^{\circ}\text{C}$.

^e Reaction was conducted at $-30\text{ }^{\circ}\text{C}$.

Table 2
Asymmetric aza-Michael reaction of indolines and α,β -unsaturated ketones^a

Entry	R ¹ ,R ² ,R ³	Product	Yield ^b (%)	ee ^c (%)
1	H, Ph, H	3a	74 (89)	81
2	CH ₃ , Ph, H	3b	54 (85)	84
3	Br, Ph, H	3c	60 (88)	83
4	H, 4-CH ₃ -Ph, H	3d	55 (83)	86
5	H, 4-CF ₃ -Ph, H	3e	84	95
6	H, 4-Br-Ph, H	3f	86	96
7	H, 4-Cl-Ph, H	3g	83	92
8	H, 3-Cl-Ph, H	3h	84	90
9	H, 4-CN-Ph, H	3i	40 (87)	90
10	H, 2-furyl, H	3j	55 (84)	80
11	H, Me, H	3k	57	84
12	H, 4-Br-Ph, Br	3l	54 (84)	80
13	H, 4-CF ₃ -Ph, Cl	3m	53 (90)	80
14	H, 4-CF ₃ -Ph, Me	3n	93	99
15	H, 4-CF ₃ -Ph, MeO	3o	94	95
16	H, 4-Br-Ph, Me	3p	94	99

^aUnless otherwise noted, reactions were performed with 0.1 mmol of **1**, 0.2 mmol of **2**, and 20 mol % of catalyst **J** in 1 mL xylene at –20 °C for 7 days.

^bYield of isolated product. Yields in parentheses are based upon recovered starting material.

^cDetermined by HPLC analysis.

Table 3
Synthesis of *N*-substituted indoles^a

Entry	Indoline	Product	Yield ^b (%)	ee ^c (%)
1	3a		92	80
2	3f		93	94
3	3h		95	92
4	3l		93	80
5 ^d	3p		94	99

^aUnless otherwise noted, reactions were performed with 0.1 mmol of **3** and 0.105 mmol of DDQ in 1 mL THF at 23 °C for 15 min.

^bYield of isolated product.

^cDetermined by HPLC analysis.

^dUsing MnO₂ (10 equiv) as oxidizing agent.