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Organocatalytic and direct asymmetric vinylogous Michael addition of 3-cyano-4-methylcoumarins to α,β-unsaturated ketones

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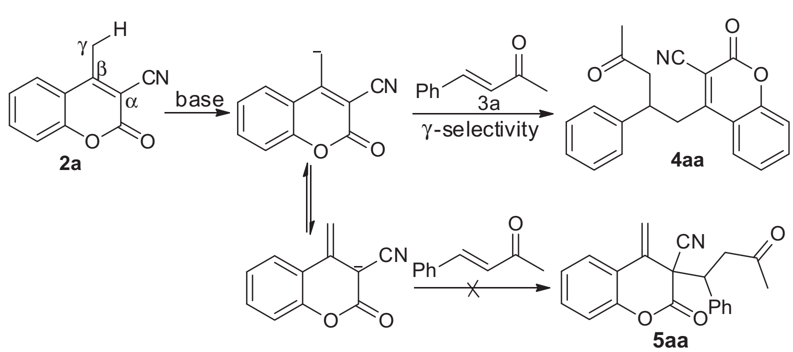
ABSTRACT

The first highly regio-, chemo-, and enantio-selective direct vinylogous Michael addition of 3-cyano-4-methylcoumarin derivatives to α,β-unsaturated ketones is described, employing readily available 9-amino-9-deoxy-epiquinine as the iminium organocatalyst.

Development of novel synthetic methods for the construction of new and optically active analogs of bioactive heterocyclic compounds represents a major challenge in synthetic organic and medicinal chemistry. The Michael reactions have been employed as one of the most powerful synthetic tools to afford optically active compounds from simple and easily available starting materials and catalysts.[1] Moreover, the Michael addition of nucleophiles to α,β-unsaturated ketones is a challenging benchmark for such a development owing to its potential for the construction of C–C, C–N, C–O, C–S bonds with simultaneous generation of up to three adjacent stereogenic centers and because of the pivotal importance of the carbonyl group as a precursor to many functionalities.[2–4] Therefore, the development of enantioselective catalytic protocols for this reaction has been the subject of intensive research.[2–4]

Coumarins are important heterocycles, widely present in natural products exhibiting a broad range of biological and therapeutic activities, which have been the subject of intensive research.[5–7] During our ongoing studies of 3-cyano-4-methylcoumarin **2a**, we envisaged that the acidity of γ-C–H might be greatly enhanced when strong electron withdrawing groups are attached to C=C bond, which allows the easy generation of nucleophilic species by in situ deprotonation under mild conditions. Thus, as illustrated in Scheme 1, facile deprotonation of **2a** could occur to generate the vinylogous carbanion under mild basic conditions. It is interesting that high regioselectivity was observed when the reaction was carried out between 3-cyano-4-methylcoumarin **2a** and benzylideneacetone **3a** in the presence of catalytic $BnNH_2$ and DIPEA. The vinylogous Michael addition proceeded smoothly to afford the product **4aa** and no product **5aa** was observed. Moreover, organocatalytic direct vinylogous Michael reactions have attracted increasing attention over the past five years.[8,9] Herein we present such an advance and its direct application in an atom-economic synthesis of optically active coumarins derivatives based on the development of a new organocatalytic enantioselective vinylogous Michael addition of 3-cyano-4- methylcoumarins to α,β-unsaturated ketones.



Scheme 1. Regioselectivity in the C–C bond formation reaction of 3-cyano-4-methylcoumarin under mild basic conditions.

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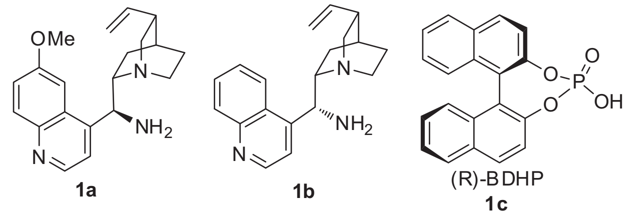
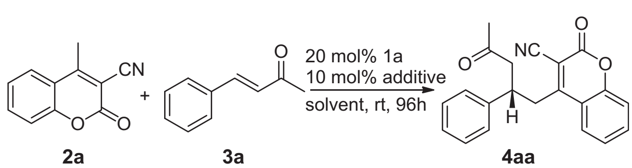


Figure 1. The structure of amine catalysts and **1c**.

Recently, amines and amino acids were investigated and established as effective organocatalysts in asymmetric catalysis[10] and many exciting discoveries have been made in the amine/amino acid-catalyzed multi-catalysis reactions, such as multi-component,[11] organo-click reactions,[12] and domino reactions.[13] Moreover, we have reported the Michael addition of some nucleophiles to α,β-unsaturated ketones by employing primary aminocatalyst **1a**[14] (Fig. 1) and the primary amine **1a** has been used successfully in the asymmetric Michael reactions by many groups.[15,16] Inspired by the recent reports on iminium activation of α,β-unsaturated ketones by chiral primary aminocatalyst **1a**, we envisioned that the organocatalyst **1a** would be an efficient catalyst for the Michael reaction of 3-cyano-4-methylcoumarins to α,β-unsaturated ketones. Table 1 shows some screening results for the reaction of **2a** with **3a**. In the course of our screening studies of organocatalytic vinylogous Michael addition of 3-cyano-4-methylcoumarin **2a** to benzylideneacetone **3a**, the effects of acidic additives were very evident. The 9-amino-9-deoxy-epiquinine **1a** (Fig. 1, 20 mol %) in combination with TFA (40 mol %) that has been successfully used in the asymmetric Michael reactions,[14–16] was inert in the reaction of 3-cyano-4-methylcoumarin **2a** to benzylideneacetone **3a** (Table 1, entry 1). The ee and yield were dramatically increased when the TFA was reduced to 10 mol %. To our surprise, 9-amino-9-deoxy-epiquinine **1a** exhibited excellent catalytic activity when no acidic additives were added, and high

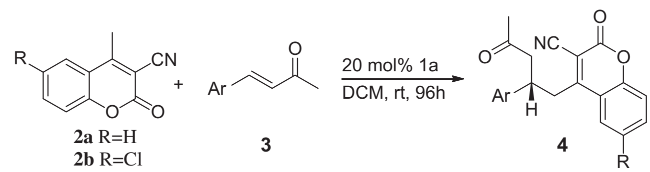
Table 1
Screening studies of organocatalytic vinylogous Michael addition of 3-cyano-4-methylcoumarin **2a** to benzylideneacetone **3a**.[a]



Entry	solvent	additive	Yield[b] (%)	ee[c] (%)
1[d]	DCM	TFA	0	–
2[e]	DCM	TFA	Trace	–
3	DCM	TFA	33	91
4	DCM	–	82	91
5[f]	DCM	(*R*)-**1c**	60	91
6	DCM	HCl	43	88
7	MeOH	–	45	63
8	Toluene	–	53	71
9	DMF	–	77	69
10	THF	–	70	78
11[g]	DCM	–	81	−91

[a] Otherwise noted, reactions performed with 0.1 mmol of **2a**, 0.15 mmol of **3a**, 20 mol % catalyst **1a**, 10 mol % additive, in 1 mL solvent at room temperature for 96 h.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] 40 mol % TFA was added.
[e] 20 mol % TFA was added.
[f] 10 mol % additive was added.
[g] Catalyzed by **1b**.

Table 2
Asymmetric vinylogous Michael addition of 3-cyano-4- methylcoumarins **2** to α,β-unsaturated ketones **3**.[a]



Entry	2	Ar (3)	Yield of 4[b] (%)	ee[c](%)
1	**2a**	Ph (**3a**)	82 (**4aa**)	91
2	**2a**	*p*-Me-Ph (**3b**)	61 (**4ab**)	91
3	**2a**	*p*-MeO-Ph (**3c**)	51 (**4ac**)	91
4	**2a**	*p*-Cl-Ph (**3d**)	86 (**4ad**)	95
5	**2a**	*p*-Br-Ph (**3e**)	76 (**4ae**)	93
6	**2a**	2-furanyl (**3f**)	75 (**4af**)	92
7	**2b**	Ph (**3a**)	91 (**4ba**)	91
8	**2b**	*p*-Me-Ph (**3b**)	88 (**4bb**)	91
9	**2b**	*p*-MeO-Ph (**3c**)	75 (**4bc**)	85
10	**2b**	*p*-Cl-Ph (**3d**)	82 (**4bd**)	93
11	**2b**	*p*-Br-Ph (**3e**)	87 (**4be**)	92
12	**2b**	2-furanyl (**3f**)	73 (**4bf**)	92

[a] All the reactions were performed with 0.1 mmol of **2**, 0.15 mmol of **3**, 20 mol% of **1a** in 1 mL DCM at room temperature for 96 h.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis

enantioselectivity (91% ee) and good yield (82% yield) were obtained (entry 4). Subsequently we investigated the effects of other acidic additives and solvents with **1a**. The same enantioselectivity was obtained while the yield was decreased in the presence of other acidic additives (entries 5 and 6). Good yields were obtained in THF and DMF but the ees were reduced (entries 9 and 10). Both reactivity and enantioselectivity were decreased in toluene or methanol (entries 7 and 8). It is worthy of note that 9-Amino-9-deoxyepicinchonine **1b** gave the same enantioselectivity while the adduct with opposite configuration was obtained (entry 11).

With the optimal reaction conditions in hand, we then examined a variety of α,β-unsaturated ketones and 3-cyano-4-methylcoumarin derivatives to establish the general utility of the catalytic transformation.[17] The vinylogous Michael reaction was generally conducted with 20 mol % of **1a** at 25 °C for 96 h. As illustrated in Table 2, the electronic effect of **3** was very marginal and remarkable enantioselectivity was achieved (entries 2–6). High enantioselectivities were achieved in the reaction of **2a** with various α,β-unsaturated ketones **3b**–**3f** having an electron-rich, electron-deficient aromatic group or heteroaromatic group (entries 2–6). Up to 95% ee was obtained in the reaction of **2a** with 4-chlorobenzylideneacetone **3d**. On the other hand, an electron-withdrawing substituent on aryl ring of 3-cyano-4-methylcoumarin **2b** has little effect on the asymmetric vinylogous Michael

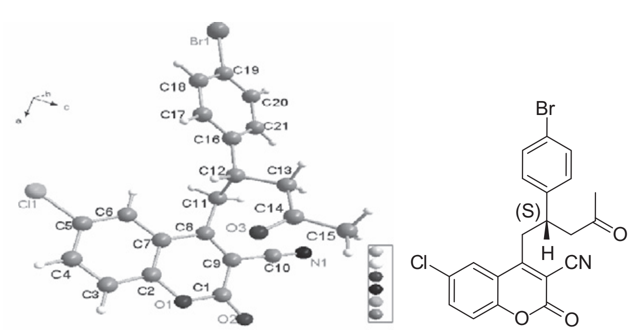


Figure 2. Molecular structure of enantiopure **4be** (ellipsoids with 30% probability).

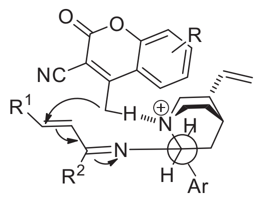


Figure 3. Proposed mechanism for the vinylogous Michael reaction.

reactions. Similarly, excellent enantioselectivities were also achieved in the reaction of **2b** with various α,β-unsaturated ketones **3b**–**3f** bearing an electron-rich, electron-deficient aromatic group or heteroaromatic group.

To determine the absolute configuration of the vinylogous Michael addition products, single crystal suitable for X-ray crystallographic analysis was fortunately obtained from enantiopure **4be** that bears a bromine atom. As shown in Figure 2, it composes of (*C12S*) configuration.[18]

The stereochemical outcome in the Michael addition reaction can be rationalized by the following plausible mechanism (Fig. 3). According to the previous literature,[14–16] chiral primary amine **1a** is an effective catalyst for the formation of iminium with 2-hydroxy-benzalacetone **3,** while the 3-cyano-4-methylcoumarin **2** would be deprotonated by the amino group of **1a**, furnishing the corresponding vinylogous carbanion, then a subsequent Michael addition reaction affords the desired product **4**.

In conclusion, we have successfully demonstrated the first asymmetric direct vinylogous Michael addition reaction of electron-deficient 3-cyano-4-methylcoumarin**s** to α,β-unsaturated ketones with excellent enantioselectivity, employing readily available 9-amino-9-deoxy-epiquinine as the iminium organocatalyst. This methodology provides facile access to various enantioenriched multifunctional compounds that, to date, have not been reported in the literature. The novel and chiral coumarins derivatives might have important biological and pharmaceutical activities in the future. Current studies are actively and well underway to expand the synthetic utility of this new reaction, as well as of this catalytic system in other asymmetric transformations.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.055.

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17. Typical experimental procedure for asymmetric vinylogous Michael addition of 3-cyano-4-methylcoumarins **2** to α,β-unsaturated ketones **3.** 3-cyano-4-methylcoumarin **2a** (0.1 mmol)**,** α,β–unsaturated ketone (0.15 mmol), primary amine **1a** 6.5 mg (0.02 mol) were stirred in DCM (1.5 mL) at room temperature for 96 h, then flash column chromatography on silica gel was performed (monitored by TLC, 10% ethyl acetate/petroleum ether as eluent) gave **4aa** as a pale yellow solid (82% yield). Mp 120–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.32 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 7.2 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.36 (d, J = 8.3 Hz, 1H), 7.27–7.22 (m, 3H), 7.05 (d, J = 8.0 Hz, 2H), 3.65–3.59 (m, 2H), 3.25–3.10 (m, 2H), 3.04–2.98 (m, 1H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 207.2, 163.9, 156.5, 153.4, 140.4, 135.0, 128.9, 127.8, 127.4, 127.0, 125.7, 117.7, 117.4, 113.4, 102.8, 49.4, 41.1, 39.0, 30.5; IR (KBr) cm^{-1} 3069, 2956, 2223, 1723, 1700, 1601, 1543, 1268, 809, 716; ESI-HRMS: calcd for $C_{21}H_{17}NO_3$+Na 354.11061, found 354.11006; $[\alpha]_D^{25}$ −45.0 (c 0.7, ethyl acetate), 91% ee; The enantiomeric ratio was determined by HPLC on Chiralpak AS column (30% 2-propanol/hexane, flow rate 1 mL/min, λ = 254 nm), t_{major} = 12.867 min, t_{minor} = 17.596 min.
18. Crystal data for **4be** $C_{21}H_{15}BrClNO_3$ (444.70), orthorhombic, space group $P2(1)2(1)2(1)$, a = 8.93930(10), b = 11.8849(2), c = 18.7529(3) Å, U = 1992.36(5) Å^3, Z = 4, specimen 0.554 × 0.304 × 0.053 mm^3, T = 296(2) K, SIEMENS P4 diffractometer, absorption coefficient 2.218 mm^{-1}, reflections collected 31275, independent reflections 4598 [R(int) = 0.0431], refinement by full- matrix least-squares on F^2, data/restraints/parameters 4598/0/244, goodness-of-fit on F^2 = 1.011, final R indices [$I > 2s\sigma(I)$] R_1 = 0.0317, wR_2 = 0.0664, R indices (all data) R_1 = 0.0518, wR_2 = 0.0718, largest diff. peak and hole 0.297 and −0.284 e Å^{-3}.