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A highly efficient asymmetric Michael addition of anthrone to nitroalkenes with cinchona organocatalysts

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Abstract—A highly efficient asymmetric Michael addition of anthrone to nitroalkenes catalyzed by cinchona alkaloids was described. Up to 99% ee of the corresponding adduct was obtained.

Cinchona alkaloids have long been known as very useful and robust catalysts for many kinds of organic reactions before the recent explosion of 'organocatalysis'.[1] Although the first example of asymmetric reaction catalyzed by cinchona alkaloids can be dated back to 1912,[2] only after 1960s, with the development of asymmetric phase transfer catalysts (chiral PTC),[3] and asymmetric dihydroxylation by Sharpless,[4] cinchona organocatalysts have drawn much more attention and have been widely used in a variety of asymmetric reactions.

As a unique class of bifunctional cinchona organocatalysts, cupreines and cupreidines have been proved to be powerful chiral catalysts for a wide array of asymmetric transformations[5] only shortly after their first application in the Baylis–Hillman reaction in 1999.[6a] Compared to the previous traditional cinchona catalysts, one of the most noticeable features of cupreines and cupreidines is that they bear a phenolic OH group at C′-6 position, and a free hydroxy moiety at C-9 position, which can be utilized to tune the steric conformation by further functionalization to achieve higher efficiency in asymmetric reactions. Thus far, these dual organocatalysts have been successfully applied in the Baylis–Hillman reaction,[6] conjugate addition,[7] electrophilic amination,[8] and nitroaldol reaction.[9]

Anthrone usually functions as a reactive diene in the presence of base and a variety of dienophiles, furnishing the corresponding Diels–Alder reaction products in good yields rather than the Michael addition adducts.[10] Only in few cases the corresponding Michael adducts were isolated as by-products in Diels–Alder reactions.[11] On the other hand, nitroalkenes, as a reactive Michael acceptor, can be transformed into a variety of functionalities due to the strongly electron-withdrawing nitro group, which is seldom used in the Diels–Alder reaction as a dienophile, although few examples have been reported using nitroalkenes as dienophiles in the Diels–Alder reactions.[12] Therefore, we envisioned that the reaction of anthrone with nitroalkenes, reactive Michael acceptors, could exclusively produce the corresponding Michael addition products in the presence of bifunctional cinchona organocatalysts. In fact, we found that the asymmetric Michael addition of anthrone to nitroalkenes could be achieved in good yields and ee's in the presence of cinchona organocatalysts. To the best of our knowledge, this is the first report on the asymmetric Michael addition of anthrone to nitroalkenes. Herein, we wish to report our preliminary results.

Initial examinations using anthrone **1a** as a substrate and nitroalkene **2a** as a Michael acceptor for the asymmetric Michael addition in the presence of a variety of cinchona organocatalysts were aimed at determining the optimal conditions and the results of these experiments are summarized in Table 1. Using quinine (Q) (10 mol %) as the catalyst in CH_2Cl_2 at 20 °C, the

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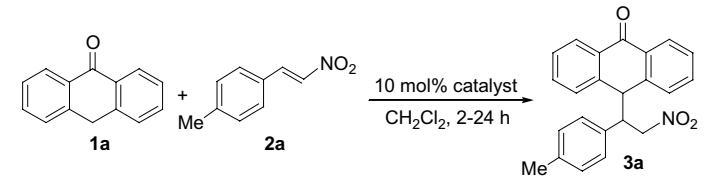
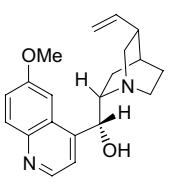
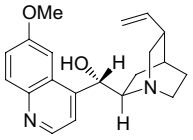
Table 1. Catalysts Screening[a]



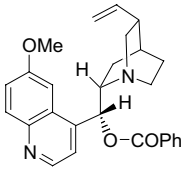
Catalysts:



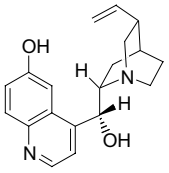
Quinine (Q)



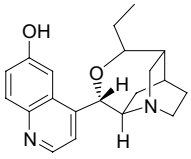
Quinidine (QD)



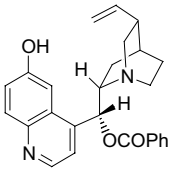
O-Benzoylquinine (BzQ)



Cupreine (CPN)



β-Isocupreidine (β-ICPD)



O-Benzoylcupreine (BzCPN)

Entry	Catalysts	Temperature (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	Q	20	2	97	22 (−)
2	Q	−10	4	99	44 (−)
3	Q	−40	8	99	51 (−)
4	QD	−40	8	99	50 (+)
5	BzQ	−40	24	13	0
6	BzQ	20	8	58	0
7	CPN	−40	8	95	80 (+)
8	β-ICPD	−40	8	99	32 (−)
9	BzCPN	−40	8	97	95 (+)

[a] All reactions were carried out with anthrone **1a** (0.24 mmol), nitroalkene **2a** (0.2 mmol) and cinchona alkaloid (0.02 mmol) in CH_2Cl_2 (3.0 mL) for the specified time.

[b] Yield of isolated product.

[c] The enantiomeric excess (ee) was determined by HPLC on a chiral stationary phase (Chiracel AS-H) and the sign of the optical rotation was shown in the parenthesis.

corresponding adduct **3a** was obtained in 97% yield and 22% ee (Table 1, entry 1). Lowering the reaction temperature to −10 °C and −40 °C improved the ee of **3a** to 44% and 51%, respectively (Table 1, entries 2 and 3). As quinine's pseudo-enantiomer, quinidine (QD) produced **3a** in similar ee but with opposite enantioselectivity under otherwise identical conditions (Table 1, entry 4). Using *O*-benzoylquinine (BzQ), which does not have free hydroxy group, as the catalyst, the reaction became sluggish, affording **3a** in lower yields with no enantioselectivities at 20 °C or −40 °C (Table 1, entries 5 and 6). However, cupreine (CPN) that bears a hydroxy OH group at C-9 position and a phenolic OH group at C′-6 position was found to be a more effective organocatalyst in this reaction, affording **3a** in much higher ee than others (Table 1, entry 7 vs entries 3–6). Encouraged by this result, we further explored cupreine and cupreidine derivatives as catalysts for this reaction. With the cage-like conformationally rigid structure, β-isocupreidine (β-ICPD), as a catalyst, **3a** was formed in only 32% ee (Table 1, entry 8), although it was an effective catalyst for the Baylis–Hillman reactions due to its high nucleophilicity and a phenolic OH group.[6] When using *O*-benzoylcupreine (BzCPN) as the catalyst, the highest ee (95%) was obtained for this Michael addition (Table 1, entry 9).[9c] These results suggest that both the phenolic hydroxy group at C′-6 position and the steric structure around C-9 position played important roles in this asymmetric Michael addition.

Next, we further optimized the reaction conditions with *O*-benzoylcupreine (BzCPN) as the catalyst by examining the solvent effect, the influence of reaction temperature and the catalyst loading. As shown in Table 2, whether in nonpolar or in polar nonprotic solvents, **3a** was produced in high yields (>95%), but in dichloromethane (CH_2Cl_2), **3a** was produced in higher ee (90%) at −10 °C (Table 2, entries 1–4). The lowest yield and ee were obtained by use of ethanol (EtOH) as a solvent presumably due to that the protic solvent disturbed the hydrogen-bonding between the catalyst and the substrates (Table 2, entry 5). Lowering the reaction temper-

Table 2. Optimization of the reaction conditions[a]

Entry	Cat. (mol %)	Solvent	Temperature (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	10	Toluene	−10	8	97	65
2	10	CH_3CN	−10	8	96	84
3	10	THF	−10	8	95	81
4	10	CH_2Cl_2	−10	8	98	90
5	10	EtOH	−10	16	70	5
6	10	CH_2Cl_2	−40	8	97	95
7	5	CH_2Cl_2	−40	12	97	94
8	3	CH_2Cl_2	−40	12	94	91
9	1	CH_2Cl_2	−40	16	80	91

[a] All reactions were carried out with anthrone **1a** (0.24 mmol), nitroalkene **2a** (0.2 mmol), and *O*-benzoylcupreine (0.02–0.002 mmol) in solvent (3.0 mL) for the specified time.
[b] Yield of isolated product.
[c] The enantiomeric excess (ee) was determined by HPLC on a chiral stationary phase (Chiracel AS-H).

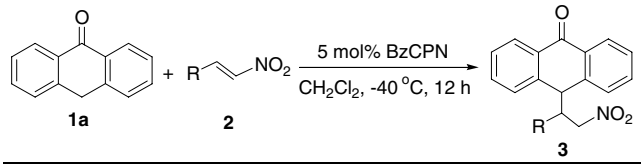
ature to −40 °C can significantly improve the enantioselectivity of **3a** to 95% ee without scarifying the yield (97%) (Table 2, entry 6). Catalyst loading was also examined and it was found that 5 mol % was ideal for this reaction (Table 2, entries 6–9).

With these optimized reaction conditions in hand, the scope and limitations of this interesting asymmetric Michael addition were explored. A variety of nitroalkenes,[13] including those bearing aryl, hetero-aromatic or alkyl substituents, reacted with anthrone **1a** smoothly to afford the corresponding adducts **3** in high yields in the presence of 5 mol % of *O*-BzCPN at −40 °C in CH_2Cl_2 (Table 3). As for aryl nitroalkenes with electron-withdrawing substituents on the benzene ring, slightly higher enantiomeric excesses than those bearing electron-donating ones were observed (Table 3, entries 1–10). 1-Naphthyl, hetero-aromatic and aliphatic group substituted nitroalkenes gave the corresponding adducts **3l–o** in good to high enantioselectivities and high yields as well (Table 3, entries 11–14). The absolute configuration of **3** using *O*-BzCPN as a catalyst was unambiguously determined by an X-ray diffraction of **3i** as *R*-configuration (Fig. 1).[14]

Subsequently, we further investigated the Michael addition of 1,8-disubstituted anthrone **1b** with nitroalkene. The reaction of 1,8-dihydroxyanthrone **1b** with nitroalkene **2f** proceeded smoothly to give the corresponding adduct **3p** in high yield but only with 9% ee (Scheme 1). This control experiment suggests that the phenolic hydroxy groups in 1,8-dihydroxyanthrone might disturb the hydrogen-bonding of catalyst with nitroalkenes resulting in the corresponding adduct **3p** with lower enantioselectivity.

In conclusion, we have developed a highly efficient asymmetric Michael addition of anthrone to nitroalkenes catalyzed by cinchona alkaloid, *O*-benzoylcupreine (BzCPN). Both the free phenolic OH group at C-6′ position and the steric bulkiness and structure at C-9 position in BzCPN are crucial in this reaction to give the corresponding adducts in higher ee than those of catalysts without free phenolic OH group at C-6′ position or with rigid conformation at C-9 position. In this reaction, anthrone functions as a nucleophile rather than an active diene, exclusively affording the corresponding Michael addition products in up to 99% ee and yields. Efforts to elucidate the mechanistic details of this catalytic system and to further extend the scope and limitations of this kind of bifunctional organocatalysts are currently in progress.

Table 3. Asymmetric Michael addition of anthrone **1a** to nitroalkenes **2**[a]



Entry	2	R	3	Yield[b] (%)	ee[c] (%)
1	**2b**	C_6H_5	**3b**	94	96
2	**2c**	4-$MeOC_6H_4$	**3c**	98	91[d]
3	**2d**	4-FC_6H_4	**3d**	99	96
4	**2e**	3-FC_6H_4	**3e**	99	98
5	**2f**	4-ClC_6H_4	**3f**	98	97
6	**2g**	2,4-$Cl_2C_6H_3$	**3g**	99	99
7	**2h**	2-ClC_6H_4	**3h**	99	97
8	**2i**	4-BrC_6H_4	**3i**	99	94[d]
9	**2j**	4-$NO_2C_6H_4$	**3j**	96	99[e]
10	**2k**	3-$NO_2C_6H_4$	**3k**	95	98
11	**2l**	1-Naphthyl	**3l**	94	98
12	**2m**	2-Furyl	**3m**	93	95
13	**2n**	*n*-C_3H_7	**3n**	91	91[e]
14	**2o**	(*E*)-$C_6H_5CH{=}CH$	**3o**	96	80[e]

[a] All reactions were carried out with anthrone **1a** (0.24 mmol), nitroalkenes **2** (0.2 mmol), and *O*-benzoylcupreine (0.01 mmol) in CH_2Cl_2 (3.0 mL) at −40 °C for 12 h.
[b] Yield of isolated product.
[c] Otherwise specified, the enantiomeric excess (ee) was determined by HPLC on a chiral stationary phase (Chiracel AS-H).
[d] The enantiomeric excess (ee) was determined by HPLC on a chiral stationary phase (Chiracel OD-H).
[e] The enantiomeric excess (ee) was determined by HPLC on a chiral stationary phase (Chiracel AD-H).

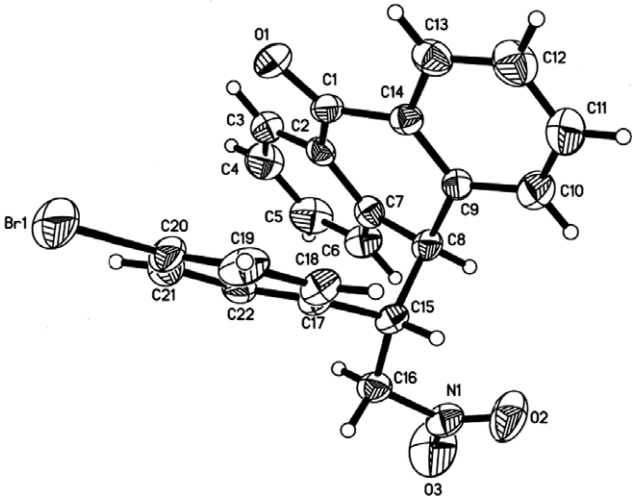
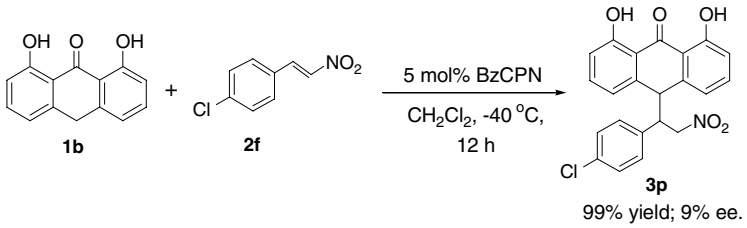


Figure 1. X-ray crystal structure of compound **3i**.



Scheme 1. Michael addition of substituted anthrone **1b** with nitroalkene **2f**.

Acknowledgments

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Supplementary data

Experimental details and characterization data, chiral HPLC, X-ray crystallographic files in CIF format. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.107.

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14. The crystal data of **3i** have been deposited in CCDC with number 631349. Empirical Formula: $C_{22}H_{16}BrNO_3$; formula weight: 422.27; crystal color, habit: colorless, prismatic; crystal system: orthorhombic; lattice type: primitive; lattice parameters: $a = 13.7487(13)$ Å, $b = 12.4288(12)$ Å, $c = 22.033(2)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 3765.0(6)$ Å^3; space group: $P2(1)2(1)2(1)$; $Z = 8$; $D_{calc} = 1.490$ g/cm^3; $F_{000} = 1712$; diffractometer: Rigaku AFC7R; residuals: R; Rw: 0.0427, 0.0929.