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Highly Enantioselective Conjugate Addition of Malononitrile to 2-Enoylpyridines with Bifunctional Organocatalyst

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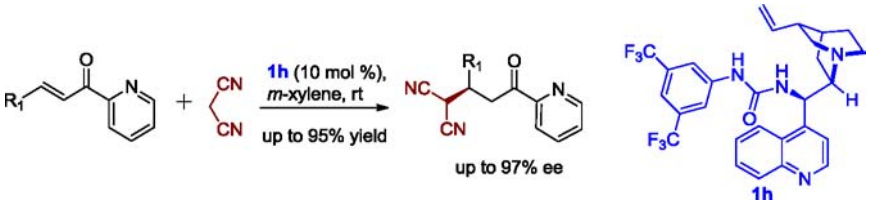
ABSTRACT



An efficient enantioselective conjugate addition of malononitrile to a range of β-substituted 2-enoylpyridines catalyzed by cinchona alkaloid-based bifunctional urea catalysts has been developed. Both enantiomers of the products could be achieved with the same level of enantioselectivity by using pseudoenantiomeric catalysts in up to 97% ee and in excellent yields. One of the enantioenriched products has been transformed to a highly functionalized piperidone derivative.

Asymmetric conjugate addition of nucleophiles to activated olefins is one of the most exploited reactions for the construction of C−C and C−X bonds in organic synthesis.[1] In particular, the enantioselective Michael addition of carbon-based nucleophiles to α,β-unsaturated carbonyls is a convenient route to optically active carbonyls, which are of great synthetic importance.[2] Over the past decade, considerable efforts have been made to develop efficient synthetic methods for such Michael reactions, especially those employing 1,3-dicarbonyl compounds such as malonate ester,[3] keto ester,[4] diketones,[5] and α-nitro and α-cyano esters[6] as nucleophiles. However, there are limited reports on the enantioselective conjugate addition of nitrile derivatives, specifically malononitrile.[7] Moreover, the addition of malononitrile is limited to very few electrophiles like nitroolefins, chalcones, and α,β-unsaturated

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acid derivatives. Since the nitrile group in the malononitrile can easily undergo further transformations to 1,3-dicarbonyls or amines, it serves as an extremely useful substrate in organic synthesis.[8] Therefore, further development of enantioselective catalytic processes involving new electrophilic partners, such as α,β-unsaturated carbonyls attached to a heteroaryl group is highly desirable. The products so obtained could easily be transformed into highly functionalized lactams, which are useful intermediates for the synthesis of heteroaryl-substituted chiral piperidines, natural products, and several pharmaceutically active compounds.[6a,9]

In the past decade, cinchona alkaloid and its derivatives have been increasingly used as efficient organocatalysts for catalyzing several asymmetric organic transformations.[10] Enantioenriched thiourea (urea) catalysts derived from cinchona alkaloid have gained particular importance because of their high level of efficiency in terms of asymmetric induction.[11] Along this path, we envisioned that if the asymmetric Michael addition of malononitrile to α,β-unsaturated carbonyls in the catalytic influence of cinchona alkaloid derived (thio)urea is feasible, it would be easy to access functionalized lactam and pyran derivatives. There are only a few literature reports for the preparation of such valuable scaffolds with high enantiopurity in an organocatalytic fashion.[6a,7d] Therefore, the development of highly enantioselective version of this reaction still remains a worthwhile goal to achieve. Herein, we report a highly enantioselective catalytic conjugate addition of malononitrile to 2-enoylpyridines[12] with cinchona-derived bifunctional urea as organocatalyst.

At the outset, the conjugate addition of malononitrile to 2-enoylpyridine was carried out in the presence of 10 mol % of quinine-derived thiourea **1a** in toluene at room temperature. Interestingly, the corresponding Michael adduct was formed in excellent yield and enantioselectivity (Table 1, entry 1). Encouraged by this initial result, we looked forward to the catalyst screening (Figure 1).

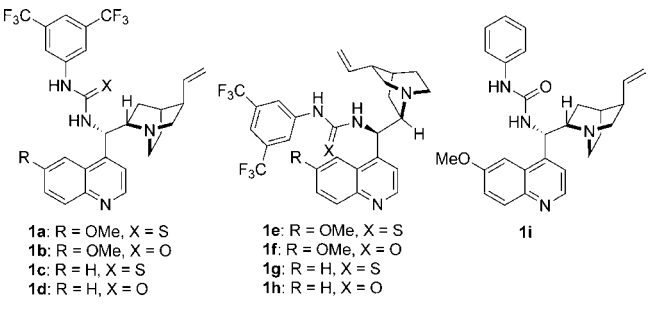

Figure 1. Cinchona alkaloid derived (thio)urea catalysts.

After intensive catalytic screening with catalysts **1a**–**i** (Figure 1), we found that there were two major structural features that were essential for high enantioselection. First, the urea catalysts were superior over corresponding thiourea catalysts, and second, the *N*-3,5-bis(trifluoromethyl)-phenyl group in the aromatic part was essential for achieving high asymmetric induction (Table 1). It is noteworthy that both the enantiomers of the Michael products could be obtained with the same level of enantioselectivity by employing pseudoenantiomeric catalysts. Although, all urea catalysts employed for the reaction gave enantioselectivities in the range of 90%, cinchonine derived urea catalyst **1h** afforded products in 94% ee with 95% yield (Table 1, entry 8). Thus, further optimization of reaction conditions were conducted with urea catalyst **1h**.

Optimization studies with respect to catalyst loading does not make any observable difference on the enantioselectivity (Table 2). It is interesting to note that catalyst loading could be decreased to 2 mol % without any compromise in the optical yield of the reaction (entry 5). Similarly, when the reaction was conducted at lower temperatures, enantioselectivities did not change, but in this case prolonged reaction time was required to achieve appreciable yield (entry 7). Next, the influence of the solvent on the

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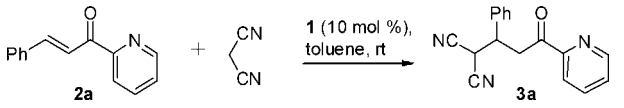
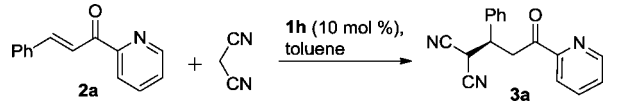
Table 1. Screening of Different Chiral Catalysts[a]



entry	catalyst	yield (%)	ee[b] (%)
1[c]	**1a**	94	92
2[c]	**1b**	94	93
3[c]	**1c**	94	82
4[c]	**1d**	93	94
5	**1e**	94	84
6	**1f**	92	88
7	**1g**	94	93
8	**1h**	95	94
9[c]	**1i**	90	89

[a] Reactions were carried out on 0.1 mmol of **2a** and 0.12 mmol of malononitrile in 1 mL of toluene at rt, unless noted otherwise. [b] Determined by HPLC using chiral column. [c] Opposite enantiomer as major was obtained.

Table 2. Optimization of Reaction Conditions[a]



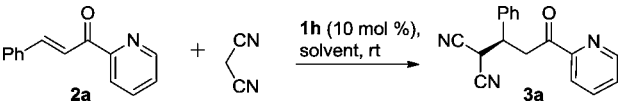
entry	mol %	temp (°C)	time (h)	yield (%)	ee[b] (%)
1	10	rt	11	95	94
2	15	rt	9	95	94
3	20	rt	6	96	93
4	5	rt	24	90	93
5	2	rt	60	80	92
6	10	0	30	90	94
7	10	−20	60	88	93

[a] Reactions were carried out on 0.1 mmol of **2a** and 0.12 mmol of malononitrile in 1 mL of toluene using 10 mol % of catalyst **1h**, unless noted otherwise. [b] Determined by HPLC using chiral column.

enantioselectivity of the reaction was investigated. A series of conventional solvents were screened, and the results are summarized in Table 3. Except for 1,4-dioxane (entry 12) and acetonitrile (entry 13), almost all organic solvents yielded the product **3a** in high enantioselectivity (entries 1−11). A less polar solvent like *m*-xylene was chosen as optimum, and the product was obtained in 96% ee (entries 4 and 14).

With the optimized conditions (Table 3, entry 4), we looked forward to substrate scopes of enantioselective Michael reaction of malononitrile to 2-enoylpyridines, and results are summarized in Table 4. Both aryl- and alkyl-substituted 2-enoylpyridines proved to be good eletrophiles with malononitrile as nucleophilic partner. A maximum of 96% enantioselectivity was obtained for compound **3a**. It is worth noting that the product could be recrystallized to enhance the enantioselctivities up

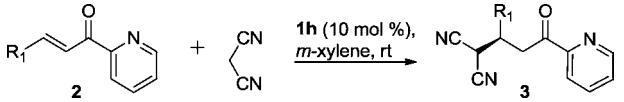
Table 3. Effect of Solvents on Enantioselectivity[a]



entry	solvent	time (h)	yield (%)	ee[b] (%)
1	toluene	11	95	94
2	benzene	11	96	90
3	*o*-xylene	12	95	94
4	*m*-xylene	12	95	96
5	*p*-xylene	12	95	93
6	mesitylene	12	94	96
7	CH_2Cl_2	20	95	93
8	DCE	12	93	92
9	$CHCl_3$	12	95	87
10	Et_2O	11	94	92
11	THF	24	72	80
12	1,4-dioxane	20	70	35
13	CH_3CN	24	84	40
14[c]	*m*-xylene	12	94	95

[a] Reactions were carried out on 0.1 mmol of **2a** and 0.12 mmol of malononitrile in 1 mL of solvent at rt using 10 mol % of catalyst **1h**, unless noted otherwise. [b] Determined by HPLC using chiral column. [c] Catalyst **1d** was used and (*R*) enantiomer was obtained as major.

Table 4. Enantioselective Conjugate Addition of Malononitrile to a Serise of β-Substituted 2-Enoylpyridines[a]

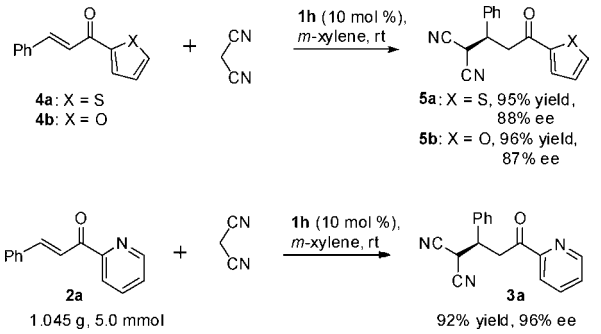


entry	R^1	**3**	time (h)	yield (%)	ee[b] (%)
1[c]	Ph	**3a**	11	95	96 (>99.9)
2	4-MeO-C_6H_4	**3b**	24	85	94
3	4-Me-C_6H_4	**3c**	12	90	94
4	4−Cl-C_6H_4	**3d**	22	92	95
5	3−Cl-C_6H_4	**3e**	9	91	95
6	4−F-C_6H_4	**3f**	11	90	95
7	3-NO_2−C_6H_4	**3g**	24	80	93
8	4-NO_2−C_6H_4	**3h**	10	94	96
9	4-CN-C_6H_4	**3i**	10	93	95
10	4-CF_3−C_6H_4	**3j**	9	79	95
11	2-Cl-6−F-C_6H_3	**3k**	22	82	94
12	3,4-CH_2O_2−C_6H_3	**3l**	29	81	92
13	1-naphthyl	**3m**	18	86	95
14	2-naphthyl	**3n**	18	89	94
15	2-furyl	**3o**	18	80	94
16	(*E*) PhCH=CH	**3p**	29	78	94
17	cyclohexyl	**3q**	28	80	97

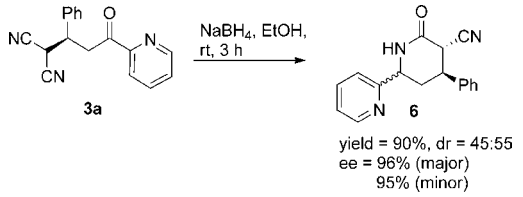
[a] Reactions were carried out on 0.1 mmol of **2** and 0.12 mmol of malononitrile in the presence of 10 mol % of **1h** in 1 mL of *m*-xylene at rt, unless noted otherwise. [b] Determined by HPLC using chiral column. [c] Data in parentheses were obtained after recrystallization, and absolute configuration was determined as (*S*) by X-ray crystallography.

to >99.9% ee (Table 4, entry 1). It was also observed that neither the steric hindrance of the substituents at the

Scheme 1. Substrate Scope and Large-Scale Reaction



Scheme 2. Synthesis of Functionalized Lactam **6**



aromatic rings nor the electronic nature had any effect on the enantioselectivity of the product. Excellent enantioselectivities were obtained in almost all the cases. Michael acceptors having a cyclohexyl group at the β-position also reacted smoothly with malononitrile to yield the corresponding product in high ee (Table 4, entry 17).

The scope of the reaction was further extended to heteroaromatic Michael acceptors such as **4a**−**b**, in which thiophene and furan were attached to the carbonyl carbon. In this case also, the Michael adducts were formed in high enantiopurity with excellent yields under optimized conditions (Scheme 1). In order to check the synthetic viability of our catalytic system, we prepared compound **3a** on a 5.0 mmol scale (Scheme 1) and found that the catalytic system was equally efficient on a gram scale to afford the product **3a** in excellent yield and enantiomeric excess (96% ee).

Finally, we were inclined to check the synthetic utility of the catalytic protocol developed by us. Toward this end, the Michael adduct **3a** was charged with $NaBH_4$ to convert it into highly functionalized piperidone derivative **6** (Scheme 2) in 90% yield with 45:55 of diastereoselectivity. Lactam **6** could serve as an advanced intermediate for further synthetic transformations.

To explain the high stereochemical outcome of the reaction, a plausible transition-state model has been proposed

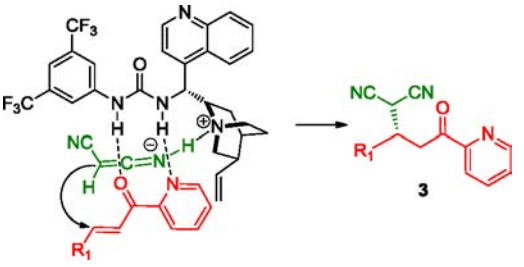


Figure 2. Possible transition-state model.

(figure 2). The bifunctional catalyst simultaneously activates malononitrile and Michael aceptor **2** via double H-bonding as shown in Figure 2. Tertiary amine of **1h** deprotonates malononitrile and the resulting pronucleophile is hydrogen bonded to the protonated quinuclidine nitrogen, while the electrophile **2** is activated through double hydrogen bonding of the urea moiety of the catalyst. Subsequent addition of pronucleophile to the bottom (*Re* face) face of the **2** leads to the formation of required product as major stereoisomer.

In conclusion, we have developed an efficient methodology for the conjugate addition of malononitrile to a range of β-substituted 2-enoylpyridines by using cinchona-based urea catalysts. The Michael products were obtained in excellent enantioselectivities (up to 97% ee) and in higher yields. It has been shown that both enantiomers of products could be achieved with the same level of enantioselectivity. The synthetic utility of the present catalytic asymmetric Michael addition reaction was established by transforming the product to a highly functionalized piperidone derivative **6**. Further studies focusing on enantioselective reactions with cinchona derived (thio)ureas are currently underway in our laboratory.

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Supporting Information Available. Experimental procedures and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org

The authors declare no competing financial interest.