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Bifunctional chiral urea catalyzed highly enantioselective Michael addition of cyclic 1,3-dicarbonyl compounds to 2-enoylpyridines

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ABSTRACT

A highly efficient cinchona alkaloid based bifunctional urea catalyzed enantioselective conjugate addition of cyclic 1,3-dicarbonyl compounds to a range of β-substituted 2-enoylpyridines has been developed. Chiral 2,4-diaryl substituted 1,4-dihydropyridines could easily be accessible from these Michael adducts. Significantly, this asymmetric methodology could afford both enantiomers of the products with the same level of enantioselectivities by using pseudoenantiomeric catalysts with up to 98% ee and in excellent yields.

1,4-Dihydropyridine constitutes a key structural feature present in a vast majority of polyhydroquinolines. These polyhydroquinolines are important Ca^{2+} channel modulators, which are widely used for treatment of hypertension, Parkinson's disease, restless leg syndrome, diabetic, and Alzheimer's diseases. These have now been recognized as vital drugs such as nifedipine, niguldipine, nicardipine, amlodipine and are now available in the market.[1] Hence, the synthesis of enantiomerically pure 1,4-dihydropyridines via catalytic enantioselective process has emerged as an area of active research.[2] Among several polyhydroquinolines, 2,4-diaryl polyhydroquinolines have been found to show important antidiabetic activity via inhibition of PTP-1B, as well as antidyslipidemic activities via significant lipid lowering activity.[3] Although there are a few reports on enantioselective synthesis of 2,4-disubstituted polyhydroquinoline available in the literature, to the best of our knowledge there has been no report on the enantioselective synthesis of 2,4-diaryl polyhydroquinoline published till date. Therefore, the development of highly enantioselective version of this reaction still remains a worthwhile goal to achieve.

In continuation of our ongoing research program in the area of the organocatalytic enantioselective Michael addition[4] reaction of active methylene compounds to various α,β-unsaturated carbonyl compounds, we thought of exploring the enantioselective organocatalytic Michael addition of 1,3-dicarbonyl compounds[5] to various chalcones. The corresponding adducts resulting from this Michael addition reaction could potentially provide chiral intermediates for the synthesis of enantioenriched 2,4-diaryl polyhydroquinolines. However, when we carried out the reaction between dimedone and simple chalcone using thiourea catalyst (**1a**) derived from quinine, longer reaction time (in days) and moderate enantioselectivity were found to be the main limitations in this reaction (Scheme 1). Inspired from our recent success with 2-enoylpyridines as powerful electrophiles in highly enantioselective conjugate addition of malononitrile,[6] we predicted that since the presence of pyridine moiety in 2-enoylpyridines makes them relatively stronger and directional H-bond acceptors in comparison to simple chalcones, it might help to increase the reaction rate as well as enantioselectivity. The products so obtained are very useful in the synthesis of heteroaryl-substituted 1,4-dihydropyridines. Moreover, the importance of nitrogen containing hetero aryl substituted products in organic synthesis makes the reaction highly desirable.

Of late, our group has been involved in cinchona derived thiourea(urea) bifunctional catalyzed several Michael and aldol reactions.[7] These bifunctional catalysts have proven to be highly efficient in synergetic catalysis wherein the catalyst simultaneously activates both the nucleophile as well as the electrophile.

On the basis of our previous report using 2-enoylpyridine as the electrophile in the highly efficient organocatalyzed Michael addition of malononitrile, we hypothesized that chiral urea derived from cinchona alkaloid[8] would catalyze this reaction by forming hydrogen bonds with 2-enoylpyridine effectively to give the enantioenriched Michael adduct.

Our studies commenced with performing a Michael addition reaction of dimedone (**3a**) to chalcone (**2**) in toluene using thiourea

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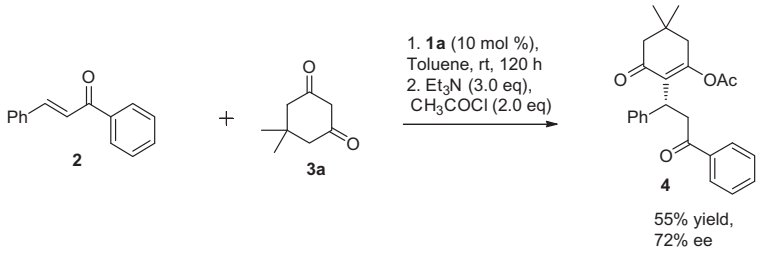
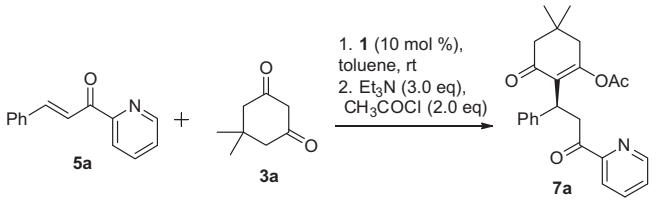


Scheme 1. Enantioselective Michael addition–acetylation.

Table 1
Screening of different chiral catalysts[a]



Entry	Catalyst	Yield (%)	ee[b] (%)
1[c]	**1a**	95	96
2[c]	**1b**	95	96
3[c]	**1c**	93	96
4[c]	**1d**	94	96
5	**1e**	92	94
6	**1f**	95	97
7	**1g**	94	94
8	**1h**	96	97
9[c]	**1i**	93	97

[a] Reactions were carried out on 0.12 mmol of **5a** and 0.1 mmol of **3a** in 1 mL of toluene at rt; after complete conversion of **3a** (ca. 12 h) the acetylation was performed (1 h).
[b] Determined by HPLC using Diacel chiralpak IA-3 column.
[c] Opposite enantiomer as major was obtained.

catalyst derived from quinine (**1a**). Reaction took prolonged time (5 days) and resulted in the Michael adduct with moderate yield (70%). Tautomeric forms of the dimedone make the NMR of Michael adduct complex. Moreover Xia and co-workers,[9] found the unstability of these Michael adducts due to aerobic oxidation. These practical problems prompted us to make the acetyl derivative of the Michael adduct which resulted in stable product with clean NMR. Owing to its high reactivity, 2-enoylpyridine (5**a**) was taken as the electrophile in place of chalcone and conducted the thiourea catalyzed Michael addition. To our delight, the reaction completed in 12 h, affording **7a** with high enantioselectivity (96% ee) and yield (95%) (Table 1, entry 1).

Encouraged by this promising result, several thiourea and urea catalysts (**1a**–**i**, Fig. 1) were examined in the selected reaction, as shown in Table 1. All of them promoted the reaction with higher level of enantioselectivities (Table 1, entries 1–9). We were pleased to find the pseudo enantiomer[10] catalysts such as **1d** and **1h** gave *R* and *S* enantiomers, respectively, with the same level of enantioselectivity (Table 1, entries 4 and 8). Among these catalysts, we chose urea catalyst (**1h**) derived from cinchonine to optimize the reaction conditions and the results are summarized in Table 2.

Optimization studies with respect to catalyst loading revealed that we could successfully decrease the loading of the catalyst without compromising on the enantiopurity (entries 1–3). Subsequently, we investigated the effect of temperature on this reaction. Lowering the temperature had no significant effect on the enantioselectivity of the reaction but affected the rate of the reaction (entries 4 and 5). As shown in Table 3, screening of the various solvents revealed, except acetonitrile, the reaction has shown same level of compatibility in all general solvents and afforded the Michael adduct with higher level of yields and enantioselectivities (Table 3).

With the identification of the optimized conditions, we further proceeded to evaluate the substrate scope of the reaction (Table 4). We were gratified to notice the generality of this highly enantioselective Michael reaction with a wide range of 2-enoylpyridines bearing electron releasing and withdrawing substituents at various positions on the phenyl ring (entries 2–12). We then tested aliphatic substituted 2-enoylpyridines. The reaction of **7p** (β-cinnamyl substituted 2-enoylpyridine) with dimedone also yielded the desired product with good enantioselectivity (86% ee) (entry 16) whereas the Michael acceptor having the cyclohexyl group at β-position gave the corresponding Michael adduct with good yield but moderate ee (entry 17). In addition, we have changed the nucleophile part dimedone to cyclohexane-1,3-dione (**3b**) and the reaction proceeded smoothly to give the Michael adduct with high yield and excellent enantioselectivity (Scheme 2).

Furthermore, we have shown our interest to explore other heteroaromatic Michael acceptors such as **8a**–**b**, in which thiophene and furan were attached to the carbonyl carbon. Albeit, these reactions took prolonged time for completion, the corresponding Michael adducts **9a**–**b** were obtained with good yield and enantioselectivities (Scheme 2).

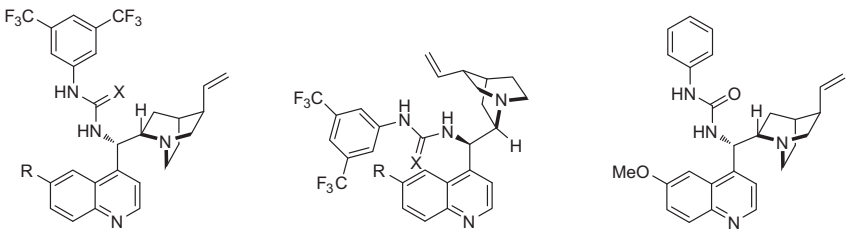
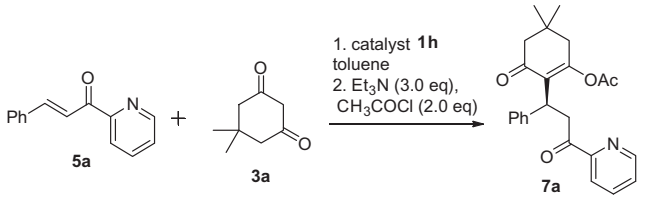


Figure 1. Cinchona alkaloid derived (thio)urea catalysts.

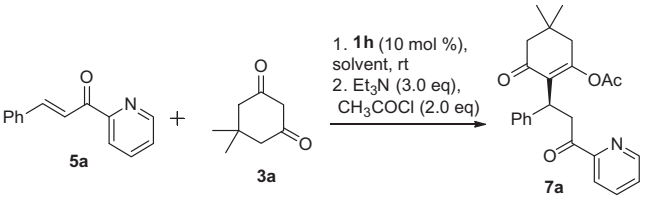
Table 2
Optimization of reaction conditions[a]



Entry	**1h** (mol %)	Temp (°C)	Time (h)	Yield (%)	ee[b] (%)
1	10	rt	12	96	97
2	15	rt	7	96	96
3	5	rt	25	95	96
4	10	0	38	94	95
5	10	−20	76	90	96

[a] Reactions were carried out on 0.12 mmol of **5a** and 0.1 mmol of **3a** in 1 mL of toluene at rt using catalyst **1h**; after complete conversion of **3a** the acetylation was performed (1 h).
[b] Determined by HPLC using Diacel chiralpak IA-3 column.

Table 3
Effect of solvents on enantioselectivity[a]



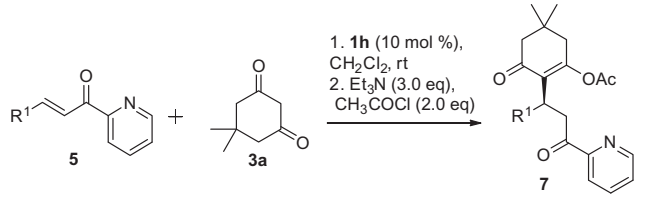
Entry	Solvent	Time (h)	Yield (%)	ee[b] (%)
1	Toluene	12	96	97
2	*m*-Xylene	12	95	97
3	CH_2Cl_2	8	97	98
4	DCE	9	97	97
5	$CHCl_3$	9	97	96
6	THF	24	92	88
7	CH_3CN	12	94	28
8[c]	CH_2Cl_2	8	97	98

[a] Reactions were carried out on 0.12 mmol of **5a** and 0.1 mmol of **3a** in 1 mL of solvent at rt using 10 mol % of catalyst **1h**; after complete conversion of **3a** the acetylation was performed (1 h) unless noted otherwise.
[b] Determined by HPLC using Diacel chiralpak IA-3 column.
[c] Catalyst **1d** was used and (*R*) enantiomer was obtained as major.

The adducts obtained from the Michael addition of dimedone and 2-enoylpyridines are very useful intermediates in organic synthesis. We have demonstrated their synthetic utility by making chiral 1,4-dihydropyridines, which are very easily accessible from these Michael adducts. Treatment of **6** with ammonium acetate in ethanol at 32 °C smoothly furnished the corresponding chiral 1,4-dihydropyridines in good yield with only a slight loss in enantiopurity (Scheme 3). With the help of single crystal X-ray diffraction analysis, we have assigned the absolute configuration of **7k** to be *R* (see Supplementary data).

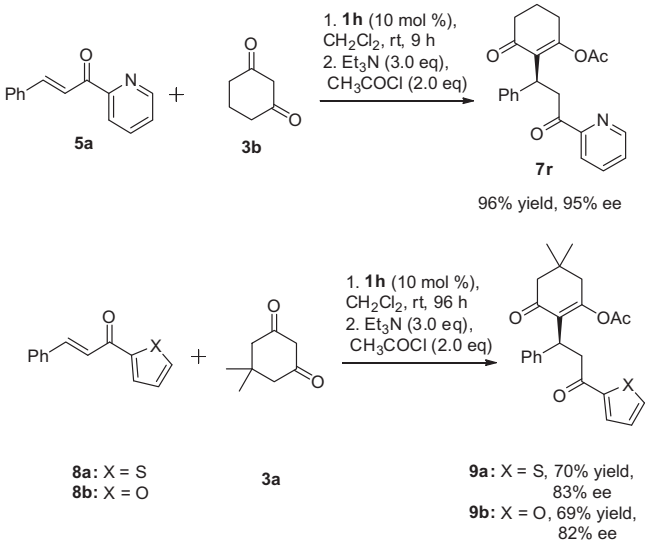
In summary, we have described a highly efficient methodology for the conjugate addition of cyclic 1,3-dicarbonyl compounds to a range of β-substituted 2-enoylpyridines by using cinchona based urea catalysts. The Michael products were obtained in excellent enantioselectivities (up to 98% ee) and in high yields. We have also accomplished both the enantiomers of Michael adduct with the same level of enantioselectivity by using naturally available cinchona derived urea catalysts. Substantially, the synthetic viability of the present catalytic asymmetric Michael addition reaction

Table 4
Substrate scope of the enantioselective conjugate addition of dimedone to β-substituted 2-enoylpyridines[a]



Entry	R^1	**7**	Time (h)	Yield (%)	ee[b] (%)
1	Ph	**7a**	8	97	98
2	4-MeO–C_6H_4	**7b**	10	95	90
3	4-Me–C_6H_4	**7c**	6	96	97
4	4-Cl–C_6H_4	**7d**	12	88	97
5	3-Cl–C_6H_4	**7e**	6	96	97
6	4-F–C_6H_4	**7f**	6	95	97
7	3-NO_2–C_6H_4	**7g**	10	94	97
8	4-NO_2–C_6H_4	**7h**	10	90	98
9	4-CN–C_6H_4	**7i**	10	87	98
10	4-CF_3–C_6H_4	**7j**	6	94	98
11	2-Cl-6-F–C_6H_3	**7k**	12	97	91
12	3,4-CH_2O_2–C_6H_3	**7l**	10	86	92
13	1-Naphthyl	**7m**	17	95	93
14	2-Naphthyl	**7n**	10	96	97
15	2-Furyl	**7o**	13	87	96
16	(*E*) PhCH=CH	**7p**	72	84	86
17	Cyclohexyl	**7q**	72	93	70

[a] Reactions were carried out on 0.1 mmol of **5** and 0.12 mmol of **3a** in the presence of 10 mol % of **1h** in 1 mL of CH_2Cl_2 at rt; after complete conversion of **3a** the acetylation was performed (1 h).
[b] Determined by HPLC using Diacel chiralpak IA-3 column.



Scheme 2. Extended substrate scope of the catalytic system.

was established by transforming the product to a 1,4-dihydropyridine.

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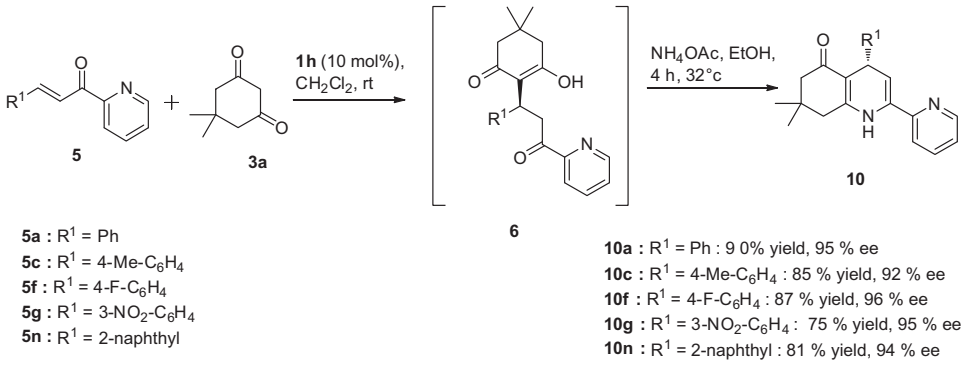

Scheme 3. Synthesis of 2,4-diaryl substituted 1,4-dihydropyridine derivatives.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.003.

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10. See Supplementary data for the substrate scope of the enantioselective conjugate addition of dimedone to β-substituted 2-enoylpyridines using pseudo enantiomer catalyst **1d**.