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Asymmetric Direct Vinylogous Michael Addition to 2-Enoylpyridine *N*-Oxides Catalyzed by Bifunctional Thio-Urea

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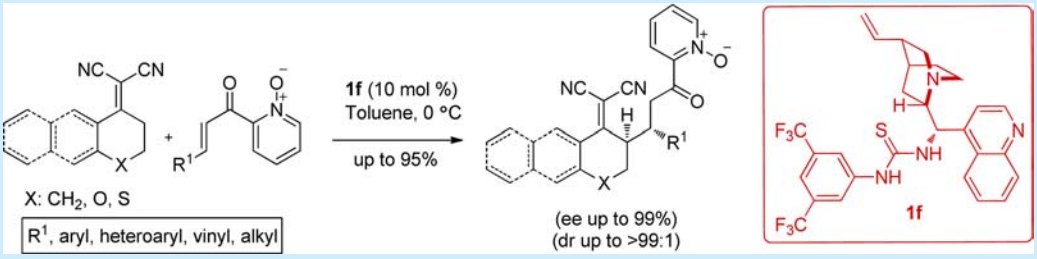
Supporting Information



ABSTRACT: Catalytic enantioselective direct vinylogous Michael addition of α,α-dicyanoalkenes to 2-enoylpyridine *N*-oxides with a bifunctional organocatalyst is described. The methodology offers an efficient way to install an asymmetric carbon−carbon bond at the γ-position of α,α-dicyanoalkenes in excellent regio-, diastereo-, and enantioselectivity. Further, application in desymmetrization of achiral α,α-dicyanoalkene to access highly functionalized enantioenriched cyclohexylidenemalononitrile derivatives has been demonstrated.

Pyridine and their *N*-oxides are ubiquitous structural motifs in a wide range of bioactive natural products with remarkable biological properties.[1] These heterocycles prevail in many pharmaceuticals, agrochemicals, and functional materials[2] and constitute important scaffolds in natural product synthesis.[3] In addition, enantioenriched pyridine *N*-oxides have also gained greater attention in the field of asymmetric catalysis and emerged as an efficient organocatalyst as well as ligand.[4,5] In this context, 2-enoylpyridine *N*-oxide has appeared as an efficient and privileged substrate for various asymmetric transformations.[6] In the past decade, we and others have reported asymmetric Friedel−Crafts, Michael, and Mukaiyama−Michael reactions using 2-enoylpyridine *N*-oxide as a template in the presence of catalytic metal complexes.[7] However, no report has been disclosed utilizing 2-enoylpyridine *N*-oxide as a substrate under asymmetric organocatalysis, to the best of our knowledge.

Asymmetric direct Michael reaction under vinylogous nucleophilicity offers a powerful way to access enantioenriched γ-functionalized α,β-unsaturated carbonyl compounds with the introduction of the concept of vinylogy. The strategy has gained much attention from the atom economy viewpoint as well as green chemistry. Among various synthetic protocols of the asymmetric direct vinylogous Michael reaction, addition of α,α-dicyanoalkenes to different electrophilic partners provides enantioenriched γ-carbon-functionalized exocyclic or acyclic activated alkenes.[8] This has been nicely explored by Deng et al. on α,β-unsaturated ketones[9] and by Chen et al. with *N*-Boc aldimines as electrophilic partners[10] in their pioneering reports.

In the past decade, thio-urea (urea) catalysts with the *cinchona* motif[11] have appreciably influenced many asymmetric transformations highlighting enhanced catalytic ability via activation of both partners in a biomolecular reaction and a high level of stereodifferentiation under mild reaction conditions.[12] Inspired by such catalytic activity, herein, we report the first catalytic asymmetric and direct vinylogous Michael reaction of α,α-dicyanoalkenes to 2-enoylpyridine *N*-oxides with *cinchona* derived bifunctional thio(urea) as an organocatalyst.

At the outset, a model reaction comprising vinylogous donor **2a** and Michael acceptor **3a** was carried out using 5 mol % of quinine derived urea catalyst **1a** in toluene at rt. To our delight, the corresponding vinylogous Michael product was found in exclusive γ-selectivity in high yield with excellent diastereo- and enantioselectivity (Table 1, entry 1). With this result, a variety of *cinchona*-derived bifunctional organocatalysts **1a**−**j**[13] (Figure 1) were then screened. It was found that, in most cases, products were obtained in good to excellent enantioselectivity (Table 1). The best result was achieved in the case of cinchonidine derived thiourea **1f**, in terms of enantioselectivity (Table 1, entry 6). The opposite enantiomer of the Michael product could be accessed by using pseudoenantiomeric catalysts. Complete optimization studies (entries 11−14) revealed that the best result could be achieved in the case of 10 mol % **1f** (Table 1, entry 11).

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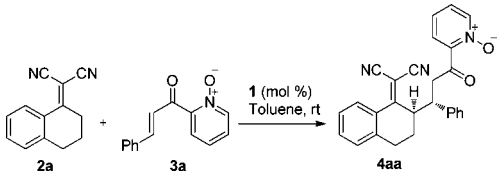
Table 1. Optimization of Direct Vinylogous Michael Reaction[a,b]



entry	cat.	mol %	time (h)	yield[c] (%)	ee[d] (%)
1	**1a**	5	48	95	92
2	**1b**	5	42	88	91
3	**1c**	5	40	90	94
4	**1d**	5	42	89	69
5	**1e**	5	52	85	63
6	**1f**	5	39	90	95
7[e]	**1g**	5	38	90	90
8[e]	**1h**	5	39	90	91
9[e]	**1i**	5	96	70	90
10	**1j**	5	42	89	69
11	**1f**	10	24	95	95
12	**1f**	15	18	95	94
13	**1f**	20	12	94	92
14	**1f**	2	80	92	95

[a]Reactions were carried out on 0.1 mmol of **3a** and 0.13 mmol of **2a** in 1.0 mL of toluene at rt, unless otherwise noted. [b]dr in all cases is found to be >99:1 from ^{1}H NMR analysis. [c]Isolated yield. [d]Determined by HPLC using chiral IA-3 column. [e]Opposite enantiomer as major was obtained.

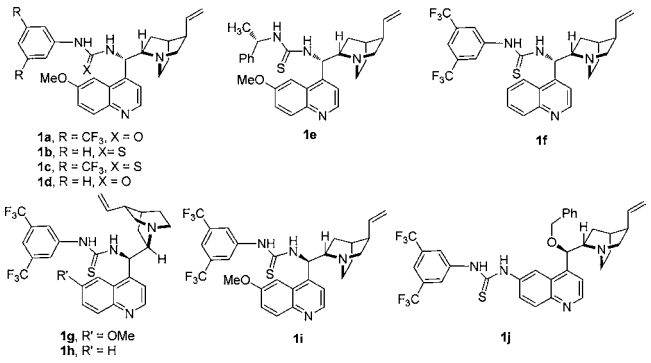
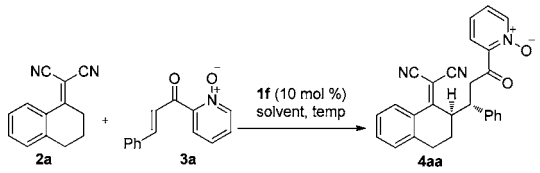


Figure 1. Cinchona alkaloid derived thio-urea (urea) catalysts.

Subsequently, a series of solvents were screened at rt in order to investigate the effect on enantioselectivity in different solvents (Table 2). It was found that most of the solvents worked well for vinylogous Michael addition to offer the product in 90−95% ee (Table 2, entries 1−7). In the case of acetonitrile, the product was found in 94% yield and 78% ee (Table 2, entry 8). It was also observed that both toluene and 1,4-dioxane offered the vinylogous Michael product in 95% ee (Table 2, entries 1 and 7). However, toluene was chosen for further studies from the reaction time standpoint. Further, lowering the reaction temperature from rt to 0 °C, we obtained the product with enhanced enantioselectivity (Table 2, entry 9). No change in enantioselectivity was observed by decreasing the temperature from 0 °C to −25 °C; rather the reaction slowed down (Table 2, entry 10). Thus, we chose 10 mol % catalyst **1f** in toluene at 0 °C for further studies.

Next, the substrate scope for direct vinylogous Michael addition of a variety of *α*,*α*-dicyanoalkenes **2a**−**g** (Figure 2) to a

Table 2. Solvent Study under Different Temperature[a,b]



entry	solvent	temp (°C)	time (h)	yield[c] (%)	ee[d] (%)
1	toluene	rt	24	95	95
2	*p*-xylene	rt	26	91	93
3	CH_2Cl_2	rt	31	88	90
4	DCE	rt	29	88	90
5	$CHCl_3$	rt	31	89	94
6	THF	rt	30	90	94
7	1,4-dioxane	rt	28	91	95
8	CH_3CN	rt	28	94	78
9	toluene	0	30	95	98
10	toluene	−25	60	94	98

[a]Reactions were carried out on 0.1 mmol of **3a** and 0.13 mmol of **2a** in 1.0 mL of solvent at rt, unless otherwise noted. [b]dr in all cases is found to be >99:1 from ^{1}H NMR analysis. [c]Isolated yield. [d]Determined by HPLC using chiral IA-3 column.

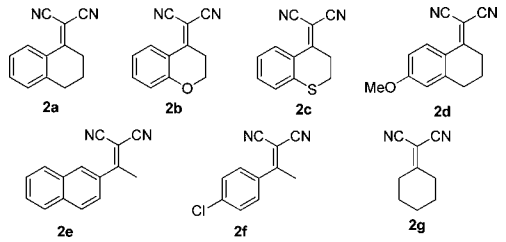


Figure 2. Different *α*,*α*-dicyanoalkenes studied.

variety of 2-enoylpyridine *N*-oxides **3a**−**l** was studied. It is worthwhile to note that the protocol worked well for both aryl- and heteroaryl-substituted 2-enoylpyridine *N*-oxides to achieve corresponding adducts with high enantioselectivity (Table 3, entries 1−9). Later, 2-enoylpyridine *N*-oxide bearing a cinnamyl group **3j** offered the product in 88% ee (Table 3, entry 10). However, ethyl glyoxalate derived 2-enoylpyridine *N*-oxide **3k** yielded the product with a 90% yield and 60% ee (Table 3, entry 11). The *α*,*α*-dicyanoalkenes **2b**−**d** reacted smoothly to afford the products in the range of 90−96% ee (Table 3, entries 12−16).

Later, acyclic *α*,*α*-dicyanoalkenes **2e**−**f** were also employed under optimized conditions and it was found that these compounds also worked well in the asymmetric direct vinylogous Michael addition leading to high enantioselectivities, however, with a longer reaction time as compared to **2a**−**d** (Table 3, entries 17−18). The cyclohexanone derived *α*,*α*-dicyanoalkene also produced the vinylogous product in 84% yield and 90% ee (Table 3, entry 19). It is important to mention that no polymerization of *α*,*α*-dicyanoalkenes **2a**−**g** was observed as an unwanted side reaction under optimized reaction conditions.

The single crystal X-ray analysis of vinylogous product **4ca** confirmed the absolute stereochemistry to be (9*R*, 10*S*) (Figure 3). Eventually, the reaction was carried out in gram scale to highlight the efficiency of the protocol (Scheme 2).

Further, we thought of exploring the scope of our methodology to a desymmetrization strategy using 4-

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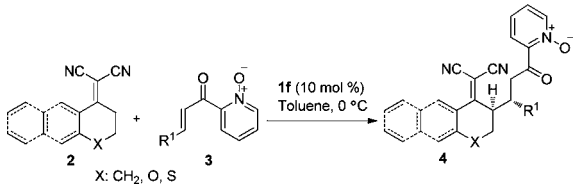
Table 3. Substrate Scope of Direct Vinylogous Michael Reaction[a,b]



entry	2	3, R^1	4	time (h)	yield[c] (%)	ee[d] (%)
1	**2a**	**3a**, C_6H_5	**4aa**	30	95	98
2	**2a**	**3b**, 2-Cl-C_6H_4	**4ab**	32	92	98
3	**2a**	**3c**, 3-Cl-C_6H_4	**4ac**	32	91	97
4	**2a**	**3d**, 4-Cl-C_6H_4	**4ad**	32	89	95
5	**2a**	**3e**, 2-NO_2-C_6H_4	**4ae**	30	88	93
6	**2a**	**3f**, 3-NO_2-C_6H_4	**4af**	30	89	93
7	**2a**	**3g**, 4-F-C_6H_4	**4ag**	31	90	97
8	**2a**	**3h**, 4-Me-C_6H_4	**4ah**	35	93	99
9	**2a**	**3i**, 2-furyl	**4ai**	45	80	91
10	**2a**	**3j**, (*E*)PhCH=CH	**4aj**	65	78	88
11	**2a**	**3k**, CO_2Et	**4ak**	55	90	60
12	**2b**	**3l**, 4-MeO-C_6H_4	**4bl**	40	94	93
13	**2c**	**3l**, 4-MeO-C_6H_4	**4cl**	30	95	90
14	**2b**	**3a**, C_6H_5	**4ba**	32	95	91
15[e]	**2c**	**3a**, C_6H_5	**4ca**	24	95	93
16	**2d**	**3a**, C_6H_5	**4da**	96	74	96
17	**2e**	**3a**, C_6H_5	**4ea**	95	82	98
18	**2f**	**3a**, C_6H_5	**4fa**	94	85	97
19	**2g**	**3h**, 4-Me-C_6H_4	**4gh**	60	84	90

[a]Reactions were carried out on 0.2 mmol of **3** and 0.26 mmol of **2** in 1.5 mL of toluene at 0 °C, unless otherwise noted. [b]dr in all cases is found to be >99:1 from ^{1}H NMR analysis. [c]Isolated yield. [d]Determined by HPLC using chiral column. [e]Enantioselectivity (99.9) was obtained after recrystallization, and absolute stereochemical outcome was determined as (9*R*, 10*S*) by X-ray structural analysis.

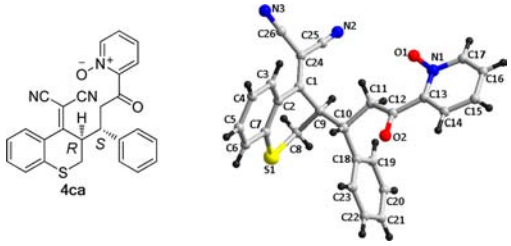
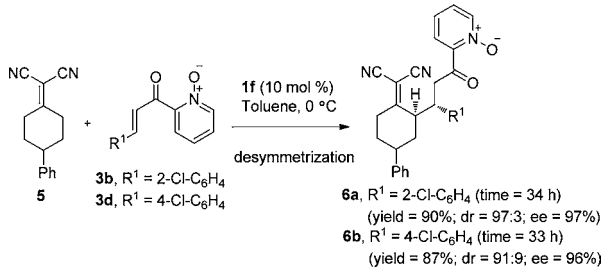


Figure 3. X-ray structure of **4ca**.

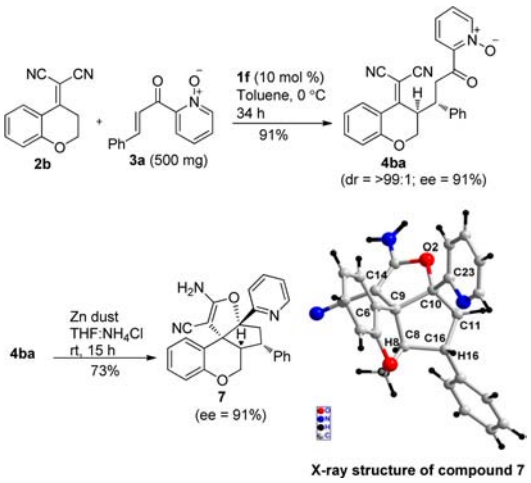
substituted cyclohexanone derived achiral α,α-dicyanoalkene. We envisioned this would produce highly functionalized enantioenriched activated methylenecyclohexane derivatives with three chiral centers (Scheme 1) found as core structures of many natural products.[14] Toward this, 4-phenyl cyclohexanone derived achiral α,α-dicyanoalkene **5** was reacted with 2-enoylpyridine *N*-oxides **3b** and **3d** in the presence of 10 mol % of **1f** (Scheme 1). Gratifyingly, this process enabled us to access highly functionalized cyclohexane derivatives in 96−97% ee with excellent dr.

The synthetic utility of the reaction was shown by reduction of vinylogous Michael adduct **4ba** with Zn dust in THF in the presence of saturated NH_4Cl (Scheme 2). This one-pot process afforded hydrofuran fused hexahydrocyclopenta[*c*]chromane **7** with two contiguous stereogenic quaternary carbons adjacent to

Scheme 1. Desymmetrization of Achiral α,α-Dicyanoalkene 5



Scheme 2. Synthetic Elaboration of Vinylogous Michael Adduct



two contiguous stereogenic tertiary carbons in 73% yield.[15] The structure and absolute stereochemistry of **7** was confirmed unambiguously by X-ray structure analysis.[16] The core of hexahydrocyclopenta[*c*]chromane with multiple chiral centers is found in several natural products.[17]

In conclusion, we disclosed the first asymmetric direct vinylogous Michael addition of α,α-dicyanoalkenes to 2-enoylpyridine *N*-oxides with a bifunctional organocatalyst. This process is operationally simple and afforded a variety of vinylogous Michael products in exclusive γ-selectivity with excellent diastereo- and enantioselectivities. The scope of methodology was further diversified to a desymmetrization strategy to furnish enantioenriched highly functionalized activated methylenecyclohexane derivatives. Further, one of the vinylogous products was transformed to a hydrofuran fused hexahydrocyclopenta[*c*]chromane framework with four contiguous strereogenic carbon centers. Further study on asymmetric organocatalytic strategies under vinylogous nucleophilicity is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This work is dedicated to Professor Ganesh Pandey on the occasion of his 60th birthday.

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