

Enantioselective Michael Addition of Malonates to 2-Enoylpyridine *N*-Oxides Catalyzed by Chiral Bisoxazoline–Zn(II) Complex

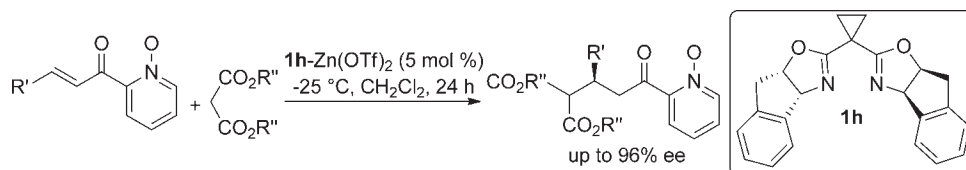
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ABSTRACT



An enantioselective Michael addition of malonates to 2-enoylpyridine *N*-oxides catalyzed by a chiral bisoxazoline–Zn(II) complex has been developed. The corresponding Michael adducts have been obtained in high yields with up to 96% ee. A plausible transition-state model has been proposed to explain the stereochemical outcome of the reaction.

The Michael reaction is one of the most fascinating and powerful C–C bond forming reactions and has wide utility in organic synthesis.¹ The asymmetric version of this reaction can afford various chiral functionalized adducts from numerous Michael acceptors and donors.² Among them, the enantioselective addition of malonates to α,β -unsaturated carbonyls is an atom economical route to optically active tricarboxyl Michael adducts, which are key intermediates in synthesis.³ Due to their synthetic

versatility, considerable effort has been devoted to the development of efficient synthetic methods for such Michael reactions. As a result, several efficient methods involving organocatalysis⁴ as well as organometallic catalysis⁵ have been developed. Most of the reported methods have a limited substrate scope. Thus, there is still a need to develop catalyst systems for the Michael reaction of α,β -unsaturated carbonyls, which can show substrate generality.

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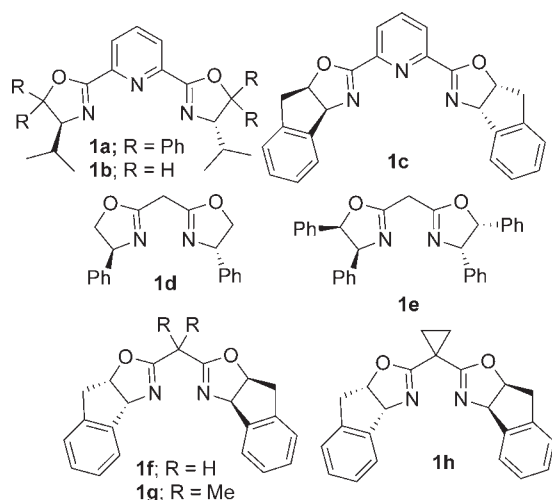


Figure 1. Chiral bisoxazoline ligands used in enantioselective Michael reaction.

Recently, Pedro and co-workers introduced 2-enoylpyridine *N*-oxides as excellent prochiral chelating substrates for chiral metal complex catalyzed Diels–Alder reactions.⁶ Later, the use of 2-enoylpyridine *N*-oxides was extended in a hetero Diels–Alder reaction⁷ and nitron cycloaddition reaction.⁸ We have also used these substrates in an enantioselective Friedel–Crafts alkylation reaction of indoles⁹ and pyrroles¹⁰ furnishing products in high yields and enantioselectivities (up to >99% *ee*). Apart from the higher reactivity and enantioselectivity associated with this template in comparison to 2-enoylpyridine, an additional attractive feature with 2-enoylpyridine *N*-oxide is that the pyridine *N*-oxide ring can be cleaved to give the corresponding acid, allowing further transformations. Furthermore, the characteristic chemistry of pyridine *N*-oxides can be used to perform several attractive transformations.¹¹ Inspired by our previous studies, it was thought that an active methylene group could be added to 2-enoylpyridine

N-oxides in place of indole and pyrrole in a Michael fashion, expanding the scope and versatility of the template. In this communication, we report the Michael addition of malonates to 2-enoylpyridine *N*-oxides catalyzed by bisoxazoline–Zn(II) complexes (Figure 1).

Table 1. Screening of Various Ligands for Enantioselective Michael Reaction^a

entry	ligand	time	yield (%) ^b	ee (%) ^c
1 ^d	1a	3 d	nr ^e	nd ^f
2	1a	36 h	75	0
3	1b	4 d	40	0
4	1c	48 h	53	0
5	1d	24 h	76	16
6	1e	72 h	50	0
7	1f	24 h	90	57
8	1g	24 h	90	0
9	1h	20 h	92	76
10 ^g	–	24 h	nr ^e	nd ^f

^a All reactions were run on a 0.2 mmol scale in 1.0 mL of solvent, 10 mol % **1**–Zn(OTf)₂ complex, and 10 mol % Et₃N. ^b Isolated yield. ^c Determined by HPLC using Chiralpak IA3 column. ^d Reaction was carried out without Et₃N. ^e nr = no reaction. ^f nd = not determined. ^g Reaction was carried out only with 10 mol % Et₃N.

Since **1a**¹² was an efficient ligand in an enantioselective Friedel–Crafts alkylation reaction,^{9,10} it was worthwhile to try it, in the first instance, for the enantioselective Michael reaction. The catalyst **1a**–Zn(OTf)₂ failed to catalyze the Michael addition of dimethyl malonate to benzylidene-2-acetylpyridine-*N*-oxide **2a** (Table 1, entry 1). So, a catalytic amount of base such as Et₃N was added for the activation of dimethyl malonate. Thus, the electrophile as well as nucleophile both were activated toward the Michael reaction under dual acid/base catalysis. Under this condition, the reaction did proceed, but there was no enantioselectivity (Table 1, entry 2). Two other pybox ligands, **1b** and **1c**, also gave disappointing results as the product was obtained as a racemic mixture (Table 1, entries 3 and 4). Next, various bidentate bisoxazoline ligands were examined. Ligands **1d** and **1e** gave 16% *ee* and no *ee*, respectively (Table 1, entries 5 and 6). Because, in our earlier study, we had successfully used the ligand **1f** in carbonyl ene reactions,¹³ we investigated its use in an enantioselective Michael reaction. The catalyst **1f**–Zn(II) complex furnished the desired product in 90% yield and with 57% *ee* (Table 1, entry 7). Encouraged by this result, the effect of

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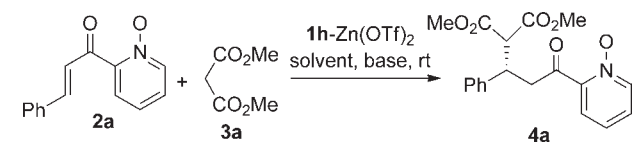
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Table 2. Effect of Solvent and Basic Additives on Enantioselective Michael Reaction^a

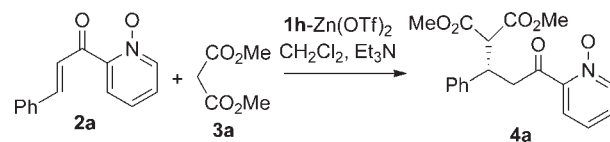
entry	solvent	base	time (h)	yield (%) ^b	ee (%) ^c
1	CH ₂ Cl ₂	Et ₃ N	20	92	76
2 ^d	CH ₂ Cl ₂	Et ₃ N	40	80	25
3	CHCl ₃	Et ₃ N	24	85	63
4	DMF	Et ₃ N	48	60	70
5	DMSO	Et ₃ N	72	82	68
6	Toluene	Et ₃ N	30	84	70
7	Benzene	Et ₃ N	30	80	72
8	THF	Et ₃ N	16	95	68
9	CH ₃ CN	Et ₃ N	60	70	78
10	CH ₂ Cl ₂	^t Pr ₂ NEt	30	90	55
11	CH ₂ Cl ₂	DBU	48	88	0
12	CH ₂ Cl ₂	NMM	24	80	65
13	CH ₂ Cl ₂	K ₂ CO ₃	35	90	37
14	CH ₂ Cl ₂	1-Me-Im	30	56	15
15	CH ₂ Cl ₂	Pyridine	24	79	50
16	CH ₂ Cl ₂	DMAP	20	85	38

^a All reactions were run on a 0.2 mmol scale in 1.0 mL solvent, 10 mol % **1h**-Zn(OTf)₂ complex and 10 mol % base. ^b Isolated yield. ^c Determined by HPLC using chiralpak IA3 column. ^d 4 A MS were used.

substitution was tested on the bridging carbon of the bisoxazoline ring. To our surprise, the ligand **1g** with *gem*-dimethyl substitution at the bridging carbon gave the racemic product (Table 1, entry 8). However, spirobis-(oxazoline) ligand **1h** having a cyclopropyl ring at the bridging carbon gave the product in good yield and 76% *ee* (Table 1, entry 9). A control experiment showed that Et₃N alone, in the absence of **1h**-Zn(OTf)₂, did not catalyze the reaction (Table 1, entry 10).¹⁴ Subsequently, the effect of solvent and basic additives was investigated. Among various solvents used, a good yield (95%) was obtained in THF, but the enantioselectivity was only 68% (Table 2, entry 8). Acetonitrile gave 78% enantioselectivity, but the lower yield and prolonged reaction time discouraged us from using this solvent (Table 2, entry 9). Considering both the chemical yield and the enantioselectivity, dichloromethane gave the best results, and it was chosen as a solvent of choice for further studies. Since the addition of base is essential for the reaction to proceed, various bases were screened in the reaction (Table 2, entries 10–16). It was found that triethylamine was superior to all other screened basic additives for the reaction.

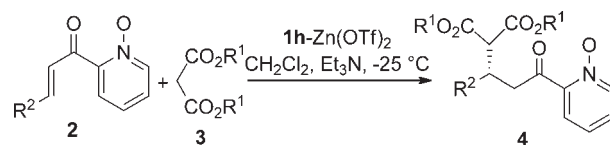
To improve the enantioselectivity further, the effects of the catalyst loading and reaction temperature were investigated (Table 3). It was found that the catalyst was equally efficient at the 5 mol % catalyst loading, producing **4a** in 92% yield and 78% *ee* (Table 3, entry 3). Further, lowering

(14) In order to demonstrate the role of an additive, a control experiment was performed according to a reviewer's comment. We thank the reviewer for his valuable suggestion.

Table 3. Effect of Temperature and Catalyst Loading on Enantioselective Michael Reaction^a

entry	catalyst	temp	time (h)	yield (%) ^b	ee (%) ^c
1	10 mol %	rt	20	92	76
2	15 mol %	rt	16	90	73
3	5 mol %	rt	24	92	78
4	2 mol %	rt	30	86	75
5	5 mol %	-5 °C	24	93	87
6	5 mol %	-25 °C	30	96	92
7	5 mol %	-35 °C	48	90	89

^a All reactions were run on a 0.2 mmol scale in 1.0 mL of solvent and 10 mol % Et₃N. ^b Isolated yield. ^c Determined by HPLC using Chiralpak IA3 column.

Table 4. Substrate Scope of Enantioselective Michael Reaction^a

entry	R ¹	R ²	4	t (h)	yield (%) ^b	ee (%) ^c
1	Me	Ph (2a)	4a	30	96	92
2	Et	Ph (2a)	4b	36	90	85 ^d
3	^t Pr	Ph (2a)	4c	12	86	79
4	Bn	Ph (2a)	4d	24	84	74
5	^t Bu	Ph (2a)	4e	24	60	16
6	Me	4-FC ₆ H ₄ (2b)	4f	30	95	90
7	Me	4-MeOC ₆ H ₄ (2c)	4g	48	87	88
8	Me	3-NO ₂ C ₆ H ₄ (2d)	4h	36	92	88
9	Me	4-ClC ₆ H ₄ (2e)	4i	30	97	91
10	Me	3-ClC ₆ H ₄ (2f)	4j	48	96	87
11	Me	2-ClC ₆ H ₄ (2g)	4k	30	95	96
12	Me	1-naphthyl (2h)	4l	48	83	96
13	Me	2-furyl (2i)	4m	36	96	94
14	Me	(<i>E</i>)PhCH=CH (2j)	4n	72	75	86
15	Me	cyclohexyl (2k)	4o	96	70	92
16	Me	^t Bu (2l)		100	nr ^e	nd ^f

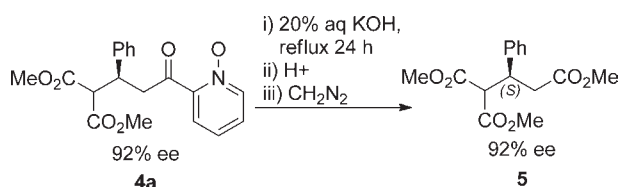
^a All reactions were run on a 0.2 mmol scale in 1.0 mL of solvent, 5 mol % **1h**-Zn(OTf)₂ complex, and 10 mol % Et₃N. ^b Isolated yield. ^c Determined by HPLC using chiral columns. ^d *ee* was determined after *N*-deoxygenation of the product. ^e nr = no reaction. ^f nd = not determined.

the catalyst loading to 2 mol % causes a slight loss in enantioselectivity of the corresponding product. So, with optimization of 5 mol % catalyst, the effect of temperature was studied. Lowering of the temperature to -25 °C improved the enantioselectivity to 92% *ee* (Table 3, entry 6). After optimizing the reaction conditions, the substrate scope of the catalyst system was investigated. First, the effect of various nucleophiles was studied (Table 4, entries 1–5).

It was observed that the enantioselectivity of the product was dependent on the ester group. Sterically hindered malonates gave poor enantioselectivities. Dimethyl malonate gave the best results (Table 4, entry 1).

The reaction was then extended to different β -substituted 2-enoylpyridine *N*-oxides (Table 4, entries 6–16). A maximum of 96% ee was obtained in the reaction. The catalyst works well with heteroaromatic and aliphatic substrates (Table 4, entries 13–15). The substrate with the cinnamyl group at the β -position also underwent a Michael reaction and gave the corresponding product with 86% ee. However, the reaction did not proceed with sterically hindered substrate **2l**, and no product was observed even after 100 h.

Scheme 1. Determination of the Absolute Configuration of **4a**



The absolute stereochemistry of the product was determined by converting the product to a literature known compound. The product **4a** was transformed to a triester **5** via cleavage of a pyridine *N*-oxide ring followed by esterification of acid with diazomethane, without any loss in enantioselectivity. The comparison of optical rotation of triester **5** with literature, elucidated the absolute configuration of the product to be (*S*) (Scheme 1).⁵¹

The stereochemical outcome in the above Michael reaction has been rationalized by a proposed transition state. It is proposed that the ligand **1h** and 2-enoylpyridine *N*-oxide coordinate to Zn(II) giving a tetrahedral complex as shown

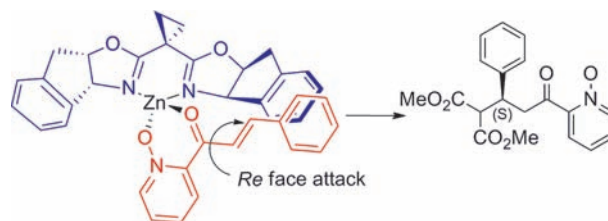


Figure 2. Plausible transition state.

in Figure 2. The addition of malonate takes place from the sterically less demanding *Re* face as the *Si* face is hindered by the aryl ring of the ligand, giving the (*S*)-isomer of the product.

In conclusion, 2-enoylpyridine *N*-oxides have been successively used in an enantioselective Michael reaction with malonate. The reaction was catalyzed by a highly efficient bisoxazoline–Zn(II) complex with a 5 mol % catalyst loading. A possible transition state has been proposed based on the stereochemical outcome of the product. Further investigation to explore the 2-enoylpyridine *N*-oxides template in an asymmetric Michael reaction with other nucleophiles is in progress in our laboratory.

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Supporting Information Available. General experimental procedures and full characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.