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Enantioselective Mukaiyama–Michael Reaction of Silyl Enol Ethers to 2-Enoylpyridine *N*-Oxides Catalyzed by Copper-Bis(oxazoline) Complex

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This paper is dedicated to Dr. J. S.Yadav on the occasion of his birthday.

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Abstract: A catalytic enantioselective Mukaiyama–Michael reaction of 2-enoylpyridine *N*-oxides has been developed using a simple bis(oxazoline)-copper complex. A variety of silyl enol ethers undergo smooth Michael addition with 2-enoylpyridine *N*-oxides to furnish the corresponding Michael adducts in high yields with high enantioselectivities (up to 97% *ee*).

Keywords: asymmetric catalysis; bis(oxazoline) ligands; copper complexes; Michael reaction; silyl enol ethers

The Mukaiyama–Michael addition is one of the most simple C–C bond forming reactions to generate the 1,5-dicarbonyl compounds, which are important building blocks for the synthesis of various biologically active molecules.[1] Therefore, the Michael reaction has emerged as a powerful synthetic route for constructing various molecules.[2] Consequently, a large number of organocatalysts has been developed for this transformation.[3] In most cases, an unmodified ketone has been used as substrate. Among several Michael acceptors, nitrostyrenes,[4] alkylidene malonates,[5] vinyl phosphonates,[6] vinyl sulfones[7] vinyl ketones,[8] and α,β-unsaturated thiol esters are the most widely used substrates.[9] Although several catalysts are known for the direct Michael reaction, only few catalysts are reported for the Mukaiyama–Michael reaction of silyl enol ethers with enones.[10,11] In particular, the silyl enol ethers derived from acetophenone are less explored for the conjugate addition reactions.[12] This is due to the low nucleophilicity of the silyl enol ethers derived from acetophenones.[13] Therefore, the development of an efficient catalytic system for the enantioselective Mukaiyama–Michael reaction still remains as a challenging task. Recently, Pedro et al. have explored 2-enoylpyridine *N*-oxides as efficient bidentate substrates for various enantioselective transformations[14] including the Friedel–Crafts reaction and Michael addition reactions of dialkylmalonates.[15] More recently, Faita et al. have developed an elegant approach for the addition of cyclic enol silyl ethers to 2-alkenoylpyridine *N*-oxides using Cu(II)-bis(oxazoline) complexes.[16]

Because of the electron-withdrawing nature of the pyridine *N*-oxide moiety, it is reactive and effective in conjugate addition reactions. Inspired by the inherent properties of enoylpyridine *N*-oxides, we were interested to explore these substrates for the Mukaiyama–Michael reaction with less reactive silyl enol ethers. Furthermore, pyridine *N*-oxides can easily be cleaved into the corresponding carboxylic acids under mild conditions.[17]

Following our interest in asymmetric synthesis using bis-oxazoline ligands,[18] we herein report a catalytic enantioselective Mukaiyama–Michael reaction of 2-enoylpyridine *N*-oxides. Initially, we attempted the Michael addition of the silyl enol ether derived from acetophenone **5a** with 2-enoylpyridine *N*-oxide **4a** using the bis(oxazoline)-$Cu(OTf)_2$ complex. To optimize the reaction, a set of chiral bis(oxazoline) ligands was tested (Figure 1). Most of the bis(oxazoline)-$Cu(OTf)_2$ complexes were found to catalyze the reaction at room temperature in excellent yields but with low to moderate enantiomeric excess. Among them, the ligands **1a** and **1b** in combination with $Cu(OTf)_2$ gave the product in good yields but with low *ee* values of 47% and 54%, respectively (Table 1, entries 1 and 2). Similarly, the **1c**-$Cu(OTf)_2$ complex afforded the product with a low *ee* value of 22% (Table 1, entry 3). Notably, **1d**-$Cu(OTf)_2$ complex gave the product **6a** with relatively with good enantio-

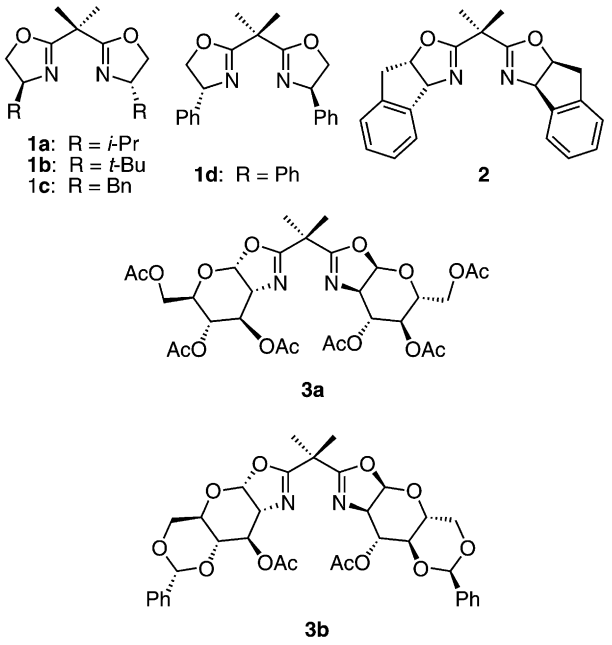
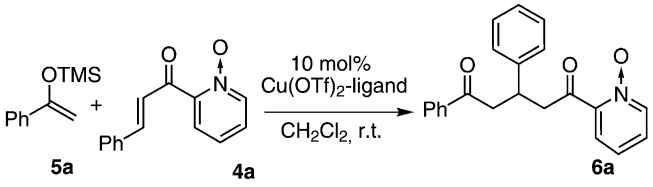


Figure 1. Bisoxazoline ligands.

Table 1. Screening of various bis(oxazoline) ligands in Mukaiyama–Michael reaction between silyl enol ether **5a** and enoylpyridine *N*-oxide **4a**.[a]

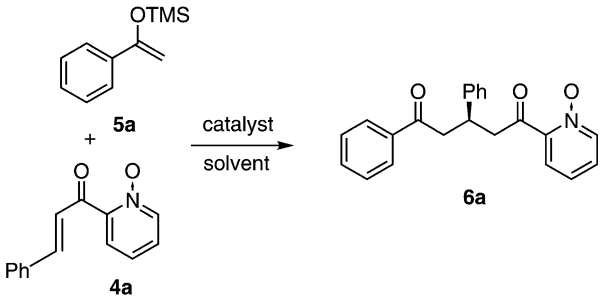


Entry	Ligand	Time [h]	Yield[b] [%]	*ee*[c] [%]
1	**1a**	3	92	47
2	**1b**	3	91	54
3	**1c**	3	88	22
4	**1d**	3	92	70
5	**2**	3	90	13
6	**3a**	5	88	45
7	**3b**	5	78	54

[a] All the reactions were carried out using 1.0 mmol of **4a** and 2.0 mmol of **5a** in the presence of 10 mol% of the catalyst in 2 mL of dichloromethane at room temperature.
[b] Yield after purification.
[c] The *ee*s were determined by HPLC analysis.

selectivity (70% *ee*, Table 1, entry 4). To our surprise, aminoindanol-derived ligand **2** and $Cu(OTf)_2$ complex gave the product with very low *ee* (Table 1, entry 5). Similarly, sugar-derived *gluco*BOX ligands (**3a** and **3b**) also gave the product with low *ee* values (Table 1, entries 6 and 7).

Table 2. Screening of various parameters in the enantioselective Mukaiyama–Michael reaction of **4a** with silyl enol ether **5a**.[a]



Entry	Solvent	Temp. [°C]	Time [h]	Yield[b] [%]	*ee*[c] [%]
1	CH_2Cl_2	0	3	93	80
2	CH_2Cl_2	–30	3	93	95
3	CH_2Cl_2	–50	6	93	96
4	$CHCl_3$	–50	10	90	82
5	THF	–50	6	94	87
6	Et_2O	–50	12	75	82
7	CH_3OH	–50	24	15	7
8	CH_3CN	–50	12	40	25
9	toluene	–50	12	90	87
10[d]	CH_2Cl_2	–50	6	93	96
11[e]	CH_2Cl_2	–50	20	85	90

[a] All the reactions were carried out using 1.0 mmol **4a** and 2.0 mmol of **5a** in the presence of 10 mol% **1d**-$Cu(OTf)_2$ in 2.0 mL solvent.
[b] Yield after purification.
[c] The *ee*s were determined by HPLC analysis
[d] 5 mol% of the catalyst was used.
[e] 2 mol% of the catalyst was used.

To improve the *ee*, various reaction parameters were screened and the results are presented in Table 2. Initially, we have examined the effect of reaction temperature on enantioselectivity. By lowering the reaction temperature from 0 °C and –50 °C, a considerable enhancement in enantiomeric excess was observed from 80 to 96% *ee* (Table 2, entry 3). No improvement in enantiomeric excess was observed by further lowering the reaction temperature. Among various metal sources[19] tested, $Cu(OTf)_2$ was found to be the best choice for the Mukaiyama–Michael reaction to obtain good yields and enantioselectivity.

Among various solvents (chloroform, tetrahydrofuran, diethyl ether and toluene) tested, dichloromethane gave the best results in terms of yields and enantioselectivity (Table 2, entry 3 *vs.* entries 4–9). As shown in Table 2, 5 mol% of the catalyst is optimal to provide the best results (Table 2, entry 10).

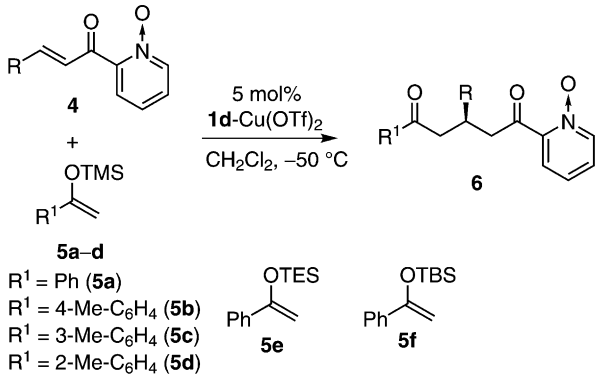
After optimizing the reaction conditions, we extended this method to various enoylpyridine *N*-oxides and silyl enol ethers (Table 3). Accordingly, we attempted to study the effect of substituents on the aromatic ring of the enoylpyridine *N*-oxides. Interestingly, all the *p*-substituted arylidenoylpyridine *N*-oxides reacted effectively with silyl enol ether **5a** to afford the corresponding products in good yields with high enantioselectivities (Table 3, entries 2–6). Among *p*-substituted enoylpyridine *N*-oxides, the best *ee* value of 96% was obtained with the substrate **4d** (Table 3, entry 4). However, *o*-substituted enoylpyridine *N*-oxides **4g** and **4h** gave the corresponding products with lower enantioselectivities than the *para* counterpart (Table 3, entries 7 and 8, 84% and 82%, respectively).

Next an attempt was made to examine the reactivity of *meta*-substituted arylidenoylpyridine *N*-oxides. In the case of *meta*-substituted substrates, the *ee* was slightly higher than with *para*-substituted benzene derivatives. The substrates **4i** and **4j** reacted effectively with enol ether **5a** and the corresponding products **6i** and **6j** were obtained with high *ee* values of 97% each (Table 3, entries 9 and 10). However, the reaction of 2-furyl-substituted enoylpyridine *N*-oxide **4k** with **5a** gave the product **6k** in relatively low yield and enantiomeric excess (80% yield with 83% *ee*, Table 3, entry 11). Notably, a sterically bulky substrate, i.e., 2-naphthyl-substituted *N*-oxide **4l** gave the Michael adduct **6l** with excellent *ee* (93%, Table 3, entry 12).

Furthermore, we examined the scope of the Mukaiyama–Michael reaction of alkylidenoyl pyridine *N*-oxides. The reaction of *tert*-butyl substituted enoyl *N*-oxide **4m** with the silyl enol ether **5a** gave the product in 88% yield with 91% *ee* (Table 3, entry 13). To our surprise, the reaction of cyclohexyl-substituted *N*-oxide **4n** with enol ether **5a** was found to be sluggish and only a trace amount of the product was obtained after a long reaction time (Table 3, entry 14). Furthermore, 1,4-addition of enol ether **5a** with enoylpyridine *N*-oxide **4o** gave the product **6o** in 80% yield with 72% *ee* (Table 3, entry 15). It is noteworthy to mention that the conjugated substrate **4o** underwent a smooth 1,4-addition exclusively rather than 1,6-addition under the present reaction conditions.

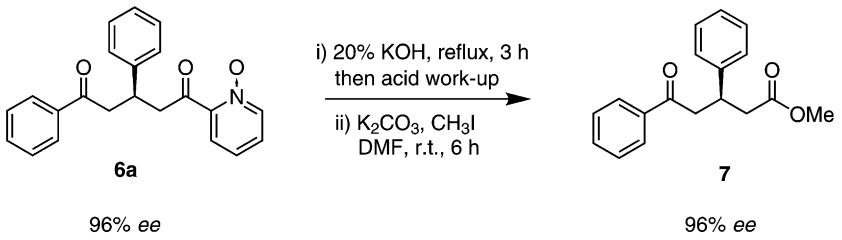
Subsequently, we examined the scope of various silyl enol ethers in the Mukaiyama–Michael reaction with **4a**. It was clearly observed that the silyl enol ethers derived from electron-rich acetophenones only participated in this enantioselective Mukaiyama–Michael reaction. For example, silyl enol ethers such as

Table 3. Scope of various 2-enoylpyridine *N*-oxides and silyl enol ethers in the enantioselective Mukaiyama–Michael reaction.[a]



Entry	R	Enolsilane	6	Time [h]	Yield[b] [%]	*ee*[c] [%]
1	Ph (**4a**)	**5a**	**6a**	6	93	96
2	4-Cl-C_6H_4 (**4b**)	**5a**	**6b**	6	90	92
3	4-Br-C_6H_4 (**4c**)	**5a**	**6c**	6	91	95
4	4-NO_2-C_6H_4 (**4d**)	**5a**	**6d**	4	92	96
5	4-F-C_6H_4 (**4e**)	**5a**	**6e**	4	88	90
6	4-Me-C_6H_4 (**4f**)	**5a**	**6f**	8	82	92
7	2-NO_2-C_6H_4 (**4g**)	**5a**	**6g**	6	91	84
8	2-F-C_6H_4 (**4h**)	**5a**	**6h**	6	85	82
9	3-NO_2-C_6H_4 (**4i**)	**5a**	**6i**	6	92	97
10	3-F-C_6H_4 (**4j**)	**5a**	**6j**	4	90	97
11	2-furyl (**4k**)	**5a**	**6k**	6	80	83
12	2-naphthyl (**4l**)	**5a**	**6l**	10	86	93
13	*tert*-Butyl (**4m**)	**5a**	**6m**	24	88	91
14	cyclohexyl (**4n**)	**5a**	**6n**	100	trace	nd[d]
15	PhCH=CH (**4o**)	**5a**	**6o**	24	80	72
16	Ph (**4a**)	**5b**	**6p**	24	90	82
17	Ph (**4a**)	**5c**	**6q**	24	88	75
18	Ph (**4a**)	**5d**	**6r**	24	75	80
19	Ph (**4a**)	**5e**	**6a**	80	86	91
20	Ph (**4a**)	**5f**	**6a**	12	35	85

[a] All the reactions were carried out on a 1.0-mmol scale in 2.0 mL solvent using 5 mol% of the catalyst with 2.0 equiv. of silyl enol ether.
[b] After purification.
[e] Determined by HPLC analysis
[d] nd = not determined.



Scheme 1. Determination of absolute stereochemistry of compound **6a**.

5b, **5c** and **5d** reacted well with **4a** to afford the corresponding products **6p**, **6q** and **6r** in good yields with *ee* values of 82, 80 and 75%, respectively (Table 3, entries 16, 17 and 18).

Furthermore, triethylsilyl enol ether **5e** and *tert*-butyldimethylsilyl enol ether **5f** also reacted with enoylpyridine *N*-oxide **4a** under similar reaction conditions. But the reactions were slow in comparison with those of trimethylsilyl enol ethers. For instance, the reaction of **5e** with **4a** gave the product **6a** in good yield with 91% *ee* (Table 3, entry 19). However, TBS enol ether **5f** was found to be less reactive under the optimized conditions and the product **6a** was obtained in low yield 35% with 85% *ee* (Table 3, entry 20). It is noteworthy to mention that the reactivity of various silyl enol ethers is in the order of TMS > TES > TBS.

Subsequently, we focused on the determination of the absolute stereochemistry of the Mukaiyama–Michael products. Accordingly, we converted the product **6a** to a known ester **7**. The cleavage of the pyridine *N*-oxide moiety of product **6a** with KOH gave the acid which was then esterified with methyl iodide to furnish the methyl ester **7** (Scheme 1). The optical rotation of the methyl ester **7** was then compared with that of a known ester reported in the literature.[20]

Next an attempt was made to formulate a transition state model to explain the stereochemical outcome of the enantioselective Mukaiyama–Michael reaction (Figure 2). From the stereochemical outcome, it is clear that the product was obtained as an (*R*)-isomer. As per Jørgensen et al.'s observation, the Ph-BOX-copper complex is not exactly square planar but rather shows a static equilibrium between square planar and tetrahedral geometry.[21] The flexibility of the Cu(II)-Ph-BOX complex from a square-planar to a tetrahedral intermediate plays a crucial role in determining the stereochemistry of the product. Thus, we assume that the Cu(II)-Ph-BOX complex co-ordinated to the substrate is not in a square planar but rather in almost tetrahedral geometry (Figure 2a). In the case of tetrahedral geometry, the silyl enol ether attacks from the top face which leads to the formation of a product with (*R*)-configuration. If the substrate co-ordinates with Cu(II)-Ph-BOX in a square-planar geometry, the silyl enol ether still attacks from the top face but the product forms predominately as an (*S*)-isomer (Figure 2b). The stereochemical outcome of the reaction clearly indicates that the reaction proceeds through a tetrahedral transition state as depicted in Figure 2a. Conversely, the Cu(II)-BOX-catalyzed enantioselective Mukaiyama–Michael reaction of enol silanes also proceeds through a cyclic transition state which would transform into the product as shown in Figure 2a.

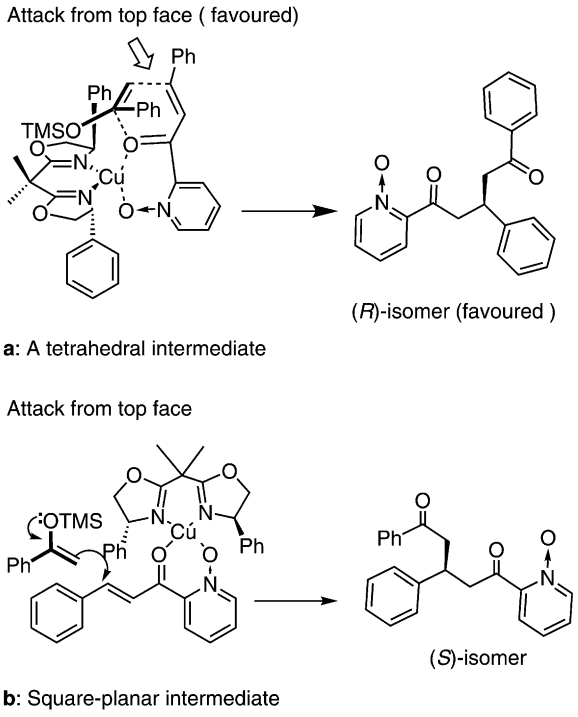


Figure 2. Plausible transition state models

In conclusion, we have developed a catalytic enantioselective Mukaiyama–Michael reaction of silyl enol ethers with 2-enoylpyridine *N*-oxides using the Cu-$(OTf)_2$-bis(oxazoline) complex. The reaction was successful with a large number of enoylpyridine *N*-oxides and silyl enol ethers. Further applications of bis(oxazoline) ligands for asymmetric synthesis are being studied in our laboratory.

Experimental Section

Typical Procedure for Enantioselective Mukaiyama–Michael Reaction

A solution of a ligand **1d** (17 mg, 0.050 mmol) and $Cu(OTf)_2$ (18 mg, 0.050 mmol) in dry dichloromethane (2.0 mL) was stirred at room temperature for 1 h under a nitrogen atmosphere. To this solution, 2-enoylpyridine *N*-oxide **4a** (1.0 mmol) was added. The resulting mixture was stirred at room temperature for 10 min and then cooled to −50 °C. To this mixture, a solution of silyl enol ether **5a** (2.0 mmol) in 0.5 mL dichloromethane was added slowly and then allowed to stir at −50 °C until completion of the reaction (as judged by TLC analysis). After completion of the reaction, TBAF (1.0 mmol) was added slowly to the reaction mixture at the same temperature and then the mixture was stirred for another 30 min at the same temperature. The mixture was then allowed to warm to room temperature. The solvent was removed and the resulting mixture was purified by column chromatography on silica gel using hexane:ethyl acetate mixture as eluent to afford the pure product **6a** as a solid; yield: 93%; 96% *ee*; mp 102-104 °C; $[\alpha]_D^{25}$: +49.2 (*c* 0.4, $CHCl_3$). The optical purity was determined by chiral HPLC (Daicel Chiralpak OD-H column, hexane/*i*-PrOH = 70:30, flow rate 1.0 mL min^{-1}, 254 nm): t_R = 20.29 min (*R*) and 22.96 min (*S*); ^{1}H NMR (500 MHz; $CDCl_3$): δ = 3.34 (dd, *J* = 6.6, 17.0 Hz. 1H), 3.40 (dd, *J* = 6.6, 17.0 Hz, 1H), 3.62 (dd, *J* = 6.6, 10.5 Hz, 1H), 3.70 (dd, *J* = 6.6, 10.5 Hz, 1H), 4.20 (t, *J* = 5.2 Hz, 1H), 7.10 (dd ~t, *J* = 6.6, 10.5 Hz, 1H), 7.18 (dd ~ t, *J* = 6.6, 10.5 Hz, 3H), 7.26 (dd, *J* = 7.8, 5.2 Hz, 3H), 7.38 (t, *J* = 7.9 Hz, 4H), 7.50 (dd, *J* = 6.6, 7.9 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (75 MHz; $CDCl_3$): δ = 36.8, 44.9, 48.7, 126.5, 127.4, 128.4, 132.9, 136.7, 140.3, 143.5, 146.5, 146.9, 196.1, 198.1; IR (neat): υ = 3448.4, 2924.5, 1683.6, 1429.5, 1258.6, 1158.0, 1032.1, 995.5, 760.02 cm^{-1}; HR-MS (ESI): *m/z* = 368.1259, calcd. for $C_{22}H_{19}NO_3Na$: 368.1263.

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