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N,N′-Dioxide–nickel(II) complex catalyzed asymmetric Michael addition of cyclic 1,3-dicarbonyl compounds to β,γ-unsaturated α-ketoesters

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ABSTRACT

A direct asymmetric Michael addition of cyclic 1,3-dicarbonyl compounds to β,γ-unsaturated α-ketoesters could be efficiently catalyzed by an *N,N′*-dioxide–nickel(II) complex. A series of chiral warfarin derivatives were obtained in excellent yields (up to 99%) with high enantioselectivities (up to 90% ee) under mild conditions within shorter reaction time.

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Coumarin derivatives are probably one of the most common skeletons found in natural products.[1] Due to their extensive array of biological activities and pharmacological properties, the synthesis of this kind of compounds has been long-standing challenge in organic chemistry. Among the coumarin family members, 4-hydroxycoumarin core, such as warfarin, bromadiolone and phenproocoumon are especially important.[2] Warfarin has been used as an anticoagulant for more than half a century. Since different pharmacological effects of two enantiomers, the synthesis of chiral warfarin and analogues are of great interest.[3]

Several methodologies have been made for the synthesis of diversely structured chiral warfarin.[4] Among them, the asymmetric Michael addition of 4-hydroxycoumarin to α,β-unsaturated system has become a very attractive methodology in recent years, since chiral warfarin can be obtained simply and quickly via such method.[5] Compared with α,β-unsaturated ketone which can conduce chiral warfarin directly, the reaction using β,γ-unsaturated α-ketoester as Michael accepter was also significant which can be obtained as a warfarin analogue.[6,7] Initially, Jørgensen and co-workers developed a bisoxazoline–copper(II) complex catalyzed Michael addition of cyclic 1,3-dicarbonyl compound to β,γ-unsaturated α-ketoester which can be obtained as a warfarin analogue.[7a] Last year, Xu group,[7b] Zhao group,[7c] and Wang group[7d] reported organocatalyst squaramides and thioureas catalyzed enantioselective Michael reaction of 4-hydroxycoumarin and β,γ-unsaturated α-ketoester, respectively. Recently, our group reported an *N,N′*-dioxide–copper(II) complex catalyzed Michael addition of cyclic diketones to β,γ-unsaturated α-ketoester producing a chromene derivative. On the other hand, chiral *N,N′*-dioxide metal complexes have shown powerful catalytic capability in various reactions with a tunable electronic and steric chiral scaffolds.[8,9] Herein, we describe a readily available chiral *N,N′*-dioxide–nickel(II) complex for the enantioselective synthesis of warfarin derivatives via a direct Michael addition of cyclic 1,3-dicarbonyl compounds to β,γ-unsaturated α-ketoester. Excellent yields and high enantioselectivities were obtained for a wide range of substrates using 5 mol % catalyst loading.

At the outset of this study, *N,N′*-dioxide **L1** derived from (*S*)-proline was coordinated with various metal salts and used to catalyze the direct Michael reaction of 4-hydroxycoumarin **2a** and β,γ-unsaturated α-ketoester **1a** in CH_2Cl_2 at room temperature. As shown in Table 1, the rare-metal complexes promoted the reaction smoothly in 12 h, but the enantioselectivities were very poor (Table 1, entries 1–3). Considering the excellent ability of *N,N′*-dioxide-copper system for the asymmetry Michael addition of cyclic diketones to β,γ-unsaturated α-ketoester, we test various transition metal complexes including Cu(II), Fe(II), Co(II) and Ni(II) (Table 1, entries 4–7). To our delight, the $Ni(acac)_2$–**L1** complex could promote the reaction very quickly. Excellent yield and promising enantioselectivity could be obtained in 10 min (99% yield, 29% *ee*; Table 1, entry 7). To improve the enantioselectivity, various *N,N′*-dioxide ligands with different chiral backbone moieties and amines were investigated (Fig. 1). It was found that the chiral backbone moiety of the *N,N′*-dioxides had a significant effect on the enantioselectivity (Table 1, entries 7–9). (*S*)-Pipecolic acid derived *N,N′*-dioxide **L3**

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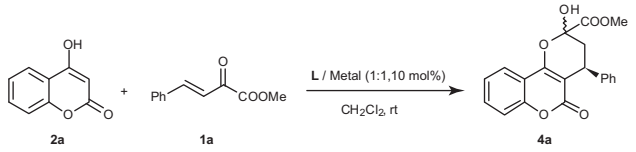
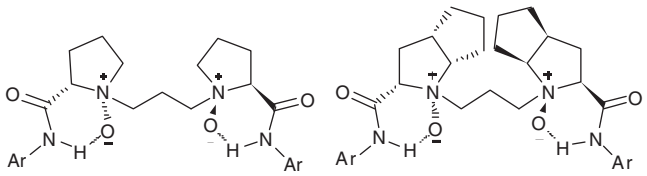
Table 1
Screening of ligands and metals for the Michael reaction[a]



Entry	Ligand	Metal	Time	Yield[b] (%)	*ee*[c] (%)
1	**L1**	$Sc(OTf)_3$	12 h	63	0
2	**L1**	$La(OTf)_3$	12 h	81	0
3	**L1**	$Yb(OTf)_3$	12 h	86	9
4	**L1**	$Cu(OTf)_2$	12 h	95	17
5	**L1**	$Fe(acac)_2$	12 h	78	0
6	**L1**	$Co(acac)_2$	12 h	81	10
7	**L1**	$Ni(acac)_2$	10 min	99	29
8	**L2**	$Ni(acac)_2$	10 min	99	17
9	**L3**	$Ni(acac)_2$	10 min	99	55
10	**L4**	$Ni(acac)_2$	10 min	99	59
11	**L5**	$Ni(acac)_2$	10 min	99	70 (*S*)[d]
12	**L6**	$Ni(acac)_2$	10 min	99	43
13	**L7**	$Ni(acac)_2$	10 min	99	69
14	**L8**	$Ni(acac)_2$	10 min	99	35
15	**L9**	$Ni(acac)_2$	10 min	99	5

[a] Unless otherwise noted, the reactions were performed with **2a** (0.10 mmol), **1a** (0.11 mmol), *N*,*N*′-dioxide (0.01 mmol), metal (0.01 mmol) in 1 mL CH_2Cl_2 at room temperature for required time.
[b] Yield of isolated product.
[c] Determined by HPLC analysis.
[d] The absolute configuration was determined by comparing with literature.[7c]



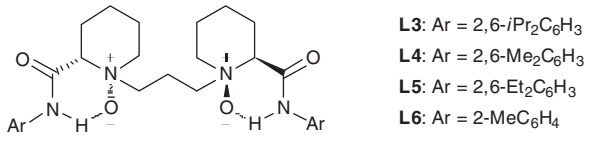
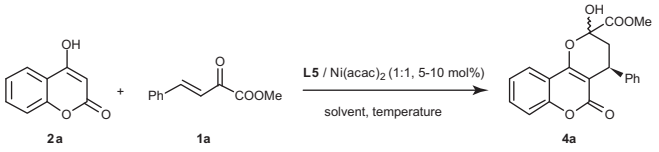


Figure 1. *N*,*N*′-Dioxide ligands evaluated for this reaction.

was superior to both **L1** (derived from (*S*)-proline) and **L2** (derived from (*S*)-ramipril acid) with excellent yield and moderate *ee* value (Table 1, entry 9). In addition, the amide moiety of the *N*,*N*′-dioxide played an important role on the enantioselectivity. Ligands with a bulkier electron-donating group at the *ortho* position of the aniline gave higher enantioselectivity (Table 1, entries 10–13 vs entry 14). The best result was obtained with 99% yield and 70% *ee* value when the ligand **L5**, having an appropriate ethyl group at the *ortho* position of the aniline, was used (Table 1, entry 11).

The effect of solvent, additive, reaction temperature, and catalyst loading were also investigated. The screening of solvent re-

Table 2
Optimization of the reaction conditions[a]



Entry	Solvent	Time	Yield[b] (%)	*ee*[c] (%)
1	THF	3 h	96	17
2	$PhCH_3$	3 h	95	29
3	Et_2O	3 h	97	13
4	MeOH	3 h	96	3
5	$CHCl_3$	30 min	96	45
6	$Cl_2CHCHCl_2$	30 min	99	71
7	$ClCH_2CH_2Cl$	20 min	99	73
8[d]	$ClCH_2CH_2Cl$	40 min	99	79
9[d,e]	$ClCH_2CH_2Cl$	40 min	99	83
10[d,e,f]	$ClCH_2CH_2Cl$	4 h	99	89

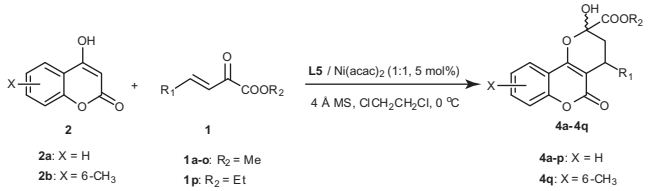
[a] Unless otherwise noted, the reactions were performed with **2a** (0.10 mmol), **1a** (0.11 mmol), *N*,*N*′-dioxide (0.01 mmol), metal (0.01 mmol) in 1 mL solvent at room temperature for required time.
[b] Yield of isolated product.
[c] Determined by HPLC analysis.
[d] 5 mol % catalyst loading was used.
[e] 10 mg 4 Å MS was added.
[f] Reaction was carried out at 0 °C.

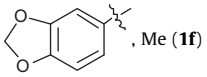
vealed that except chlorinated alkanes, other solvents all had greatly deleterious effects on the activity and enantioselectivity (Table 2, entries 1–4). Minor improvement of the enantioselectivity was obtained when CH_2Cl_2 was changed to $ClCH_2CH_2Cl$ (Table 2, entry 7). Up to 79% *ee* value was attained when the catalyst loading was decreased to 5 mol % with a little extension of reaction time (Table 2, entry 8). When 10 mg 4 Å MS was used, the enantioselectivity was increased to 83% *ee* (Table 2, entry 9). Decreasing the reaction temperature to 0 °C improved the *ee* value to 89% with a longer reaction time (4 h, 99% yield; Table 2, entry 10). Furthermore, this reaction could tolerate air and moisture. It was unnecessary to prepare the catalyst beforehand, herein the experimental procedure could become very simple.

Under the optimal reaction conditions, the asymmetric Michael addition of various cyclic 1,3-dicarbonyl compounds to a series of β,γ-unsaturated α-ketoesters were examined. As shown in Table 3, for nearly all of the substrates, this reaction could proceed quickly to afford warfarin analogues in nearly complete yields with high enantioselectivities. Neither the steric hindrance nor the electronic nature of the aromatic ring (R_1) had any obvious effect on the enantioselectivities (87–90% *ee* value; Table 3, entries 1–12). It is worth noting that the substrates with condensed-ring, heteroaromatic and cinnamyl group performed well, giving the corresponding products in excellent yields and high enantioselectivities (Table 3, entries 13–15). Moreover, α-keto ester **1p** with ethyl substrate also gave excellent yield and high enantioselectivity (Table 3, entry 16). 4-Hydroxycoumarin **2b**, containing 6-methyl group, also afforded excellent yield and high enantioselectivity (Table 3, entry 17). To our delight, the catalyst system could be extended to the Michael addition of 4-hydroxy-6-methyl-2-pyrone **3** to the β,γ-unsaturated α-ketoester **1a**. Pyranone analogue could be obtained with excellent yield and good enantioselectivity (Scheme 1).

To explain the reaction process, a possible transition state was proposed based on the absolute configuration of the product (Fig. 2). We speculated that *N*,*N*′-dioxide **L5** and β,γ-unsaturated α-ketoester **1a** coordinated with $Ni(acac)_2$ to form a complex. Then

Table 3
Substrate scope for catalytic asymmetric Michael addition[a]



Entry	2 X	1 R_1, R_2	Time (h)	Yield[b] (%)	*ee*[c] (%)
1	H	Ph, Me (**1a**)	4	99	89 (*S*)[d]
2	H	3-MeC_6H_4, Me (**1b**)	4	99	89
3	H	4-MeC_6H_4, Me (**1c**)	4	99	89 (*S*)
4	H	3-$MeOC_6H_4$, Me (**1d**)	4	99	87
5	H	4-$MeOC_6H_4$, Me (**1e**)	4	99	88
6	H	 , Me (**1f**)	5	98	89
7	H	4-PhC_6H_4, Me (**1g**)	4	98	87
8	H	3-ClC_6H_4, Me (**1h**)	10	78	89
9	H	4-ClC_6H_4, Me (**1i**)	4	99	87 (*S*)
10	H	3-BrC_6H_4, Me (**1j**)	5	89	87
11	H	4-BrC_6H_4, Me (**1k**)	4	99	89 (*S*)
12	H	4-FC_6H_4, Me (**1l**)	4	99	90 (*S*)
13	H	2-Naphthyl, Me (**1m**)	4	97	89
14	H	2-Thienyl, Me (**1n**)	6	98	87
15	H	PhCH=CH, Me (**1o**)	10	96	89
16	H	Ph, Et (**1p**)	9	98	85 (*S*)
17	6-CH_3	Ph, Me (**1a**)	4	98	87

[a] Unless otherwise noted, the reactions were performed with **2** (0.10 mmol), **1** (0.11 mmol), *N,N′*-dioxide **L5** (0.005 mmol), Ni(acac)$_2$ (0.005 mmol), 4 Å MS 10 mg in 1 mL $ClCH_2CH_2Cl$ at 0 °C for required time.
[b] Yield of isolated product.
[c] Determined by HPLC analysis.
[d] The absolute configuration was determined by comparing with literature.[7c]

4-hydroxycoumarin **2a** could only attack the *Re* face of the doube bond for which the *Si* face of the doube bond was hindered by the sterically bulky group. The corresponding product **4a** was afforded with the *S* configuration.

In summary, we have developed a highly enantioselective Michael addition of cyclic 1,3-dicarbonyl compound to β,γ-unsaturated α-ketoester catalyzed by *N,N′*-dioxide–Ni(acac)$_2$ complex. The reaction performed well for a range of substituted β,γ-unsaturated α-ketoester and cyclic 1,3-dicarbonyl compounds, giving the desired warfarin analogues in excellent yields (up to 99%) with high enantioselectivities (up to 90% *ee*). Based on experimental results, a possible transition state has been proposed. Further application of the methodology is ongoing.

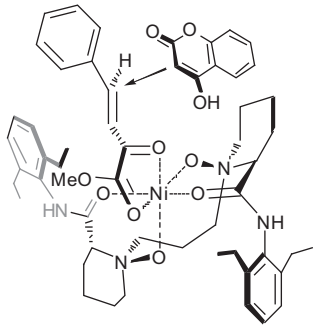


Figure 2. The proposed transition state.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.04.089.

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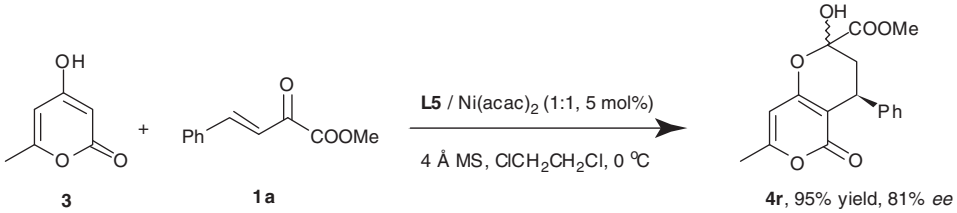

Scheme 1. 4-Hydroxy-6-methyl-2-pyrone was used as nucleophilic reagent.

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