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Asymmetric Synthesis of Spirocyclic Oxindole-Fused Tetrahydrothiophenes *via N,N′*-Dioxide–Nickel(II) Catalyzed Domino Reaction of 1,4-Dithiane-2,5-diol with 3-Alkenyloxindoles

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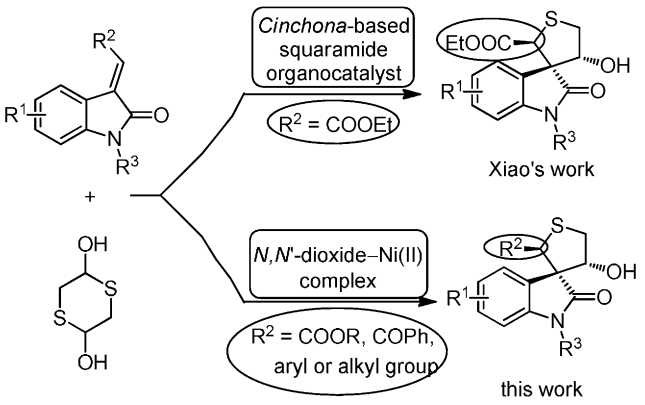
Abstract: A highly efficient chiral *N,N′*-dioxide–nickel(II) complex system has been developed to catalyze the domino thia-Michael/aldol reaction of 1,4-dithiane-2,5-diol with 3-alkenyloxindoles. A series of the desired spirocyclic oxindole-fused tetrahydrothiophenes was obtained in good yields with excellent *ee* and *dr* (up to 97% yield, 98% *ee*, >19:1 *dr*). Besides, based on the X-ray crystal structure of the catalyst as well as the absolute configuration of the product, a catalytic model was proposed to explain the stereocontrol process.

Keywords: asymmetric catalysis; *N,N′*-dioxide–nickel complex; spirooxindoles; tetrahydrothiophenes

Among the various classes of organic sulfur compounds, optically active polysubstituted tetrahydrothiophenes have attracted considerable attention in the past decades, owing to their prevalence in natural products with a large spectrum of biological activities.[1,2] Recently, many strategies have been developed for the synthesis of this structure.[2–4] For the construction of chiral tetrahydrothiophenes, catalytic asymmetric domino[5] thia-Michael/aldol and thia-Michael/Michael reactions between mercaptoacetaldehyde analogues and α,β-unsaturated compounds belong to the most efficient and straightforward processes. The Jørgensen[6] and Wang[7] groups have applied chiral diarylprolinol ethers as organocatalysts to realize these reactions.

A spirocyclic oxindole moiety as the core structure appears in many natural molecules.[8] As a result, enormous efforts were devoted to building this scaffold,[9] especially the chiral 3,3′-spirocyclic oxindoles fused with a heterocycle structure. Several enantioselectively synthetic approaches such as 1,3-dipolar cycloaddition[11a,b] or NHC-catalyzed formal [3+2] annulation,[10d,e,f] have been designed to synthesize spiro oxa[10] and spiro aza[11] heterocycle oxindoles. However, only few asymmetric routes to synthesize the spiro tetrahydrothiophene oxindoles have been disclosed.[12,13] Xiao's group recently reported the first domino thia-Michael/aldol reaction between 1,4-dithiane-2,5-diol and 3-alkenyloxindoles catalyzed by an organo-*Cinchona*-based squaramide, delivering the desired spirocyclic oxindole fused-tetrahydrothiophenes in a good result. However, the substrate scope is limited to the strong electron-deficient ester group



Scheme 1. Catalytic asymmetric thia-domino cyclization of 1,4-dithiane-2,5-diol with 3-alkenyloxindoles.

substituted 3-alkenyloxindoles, and the enantioselectivities (<90% *ee* in most cases)[12] are also need to be further improved (Scheme 1).

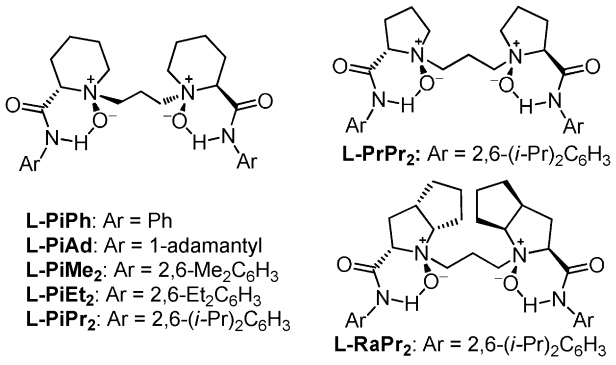
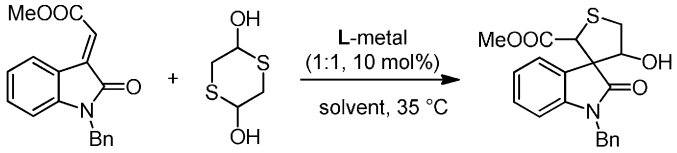


Figure 1. Chiral ligands evaluated in this study.

On the other hand, the asymmetric thia-domino cyclization reactions mentioned above were dominated by organocatalysis and no Lewis acid as catalyst had been reported. The possible reason might be that the strong coordination ability of the sulfur atom to the central metal might poison the catalyst when a Lewis acid is used as catalyst.[14] Therefore, a highly efficient Lewis acid able to catalyze an enantioselective thia-domino cyclization to synthesize the spirocyclic oxindole-fused tetrahydrothiophenes is still desirable and also a challenge. Herein, we have developed a novel Ni(II)-catalyzed asymmetric domino thia-Michael/aldol reaction of 1,4-dithiane-2,5-diol with 3-alkenyloxindoles. In the presence of the chiral *N,N′*-dioxide–Ni(II) complex,[15] a broad spectrum of spirocyclic oxindole-fused tetrahydrothiophene compounds was obtained in excellent results (56–97% yields, 90–98% *ee*, 8:1 to >19:1 *dr*).

In our study, the domino reaction of 3-alkenyloxindole **1a** with 1,4-dithiane-2,5-diol **2** was chosen as the model reaction to probe the optimal reaction conditions. At the beginning, various metal salts coordinated with *N,N′*-dioxide **L-PiPh** derived from (*S*)-pipecolic acid were tested in CH_2Cl_2 at 35 °C (Figure 1).

Table 1. Optimization of the domino thia-Michael/aldol cycloaddition reaction.[a]

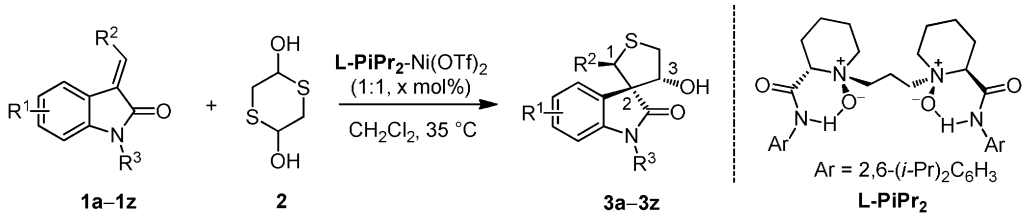


1a 2 3a

Entry	Ligand	Metal	Solvent	Yield [%][b]	*ee* [%][c]	*dr*[d]
1	**L-PiPh**	$Yb(OTf)_3$	CH_2Cl_2	trace	–	–
2	**L-PiPh**	$Sc(OTf)_3$	CH_2Cl_2	46	49	1.5:1
3	**L-PiPh**	$Ni(OTf)_2$	CH_2Cl_2	52	24	4:1
4	**L-PiAd**	$Ni(OTf)_2$	CH_2Cl_2	63	14	>19:1
5	**L-PiMe$_2$**	$Ni(OTf)_2$	CH_2Cl_2	74	30	11.5:1
6	**L-PiEt$_2$**	$Ni(OTf)_2$	CH_2Cl_2	82	83	13.5:1
7[e]	**L-PiPr$_2$**	$Ni(OTf)_2$	CH_2Cl_2	90	93	>19:1
8	**L-PrPr$_2$**	$Ni(OTf)_2$	CH_2Cl_2	71	77	>19:1
9	**L-RaPr$_2$**	$Ni(OTf)_2$	CH_2Cl_2	78	80	16:1
10	**L-PiPr$_2$**	$Ni(OTf)_2$	THF	80	40	9:1
11	**L-PiPr$_2$**	$Ni(OTf)_2$	toluene	79	40	8:1
12[e,f]	**L-PiPr$_2$**	$Ni(OTf)_2$	CH_2Cl_2	90	94	>19:1
13[f,g]	**L-PiPr$_2$**	$Ni(OTf)_2$	CH_2Cl_2	89	94	>19:1
14[h]	**L-PiPr$_2$**	$Ni(OTf)_2$	CH_2Cl_2	13	20	>19:1
15[i]	**L-PiPr$_2$**	$Ni(OTf)_2$	CH_2Cl_2	90	931	>19:1

[a] Unless otherwise noted, all reactions were carried out with **1a** (0.1 mmol), **2** (0.06 mmol) and **L**–metal (1:1, 10 mol%) in solvent (0.5 mL) at 35 °C for 24 h.
[b] Isolated yield of the major diastereoisomer by silica gel column chromatography.
[c] Determined by HPLC analysis for the major diastereoisomer.
[d] Determined by ^{1}H NMR of crude product.
[e] Substrate **1a** consumed completely in 2 h.
[f] Catalyst loading was 5 mol%.
[g] Conducted at 25 °C for 16 h.
[h] Using **L-PiPr$_2$**–$Ni(OTf)_2$ [**L-PiPr$_2$**:$Ni(OTf)_2$ = 1:1.2, 5 mol%] as catalyst.
[i] Catalyst loading was a mol%, substrate **1a** was consumed completely in 8 h.

Table 2. Substrate scope of the domino thia-Michael/aldol cycloaddition reaction.[a]



1a–1z 2 3a–3z L-PiPr$_2$

Entry	R^1	R^2	R^3	x	Time [h]	Yield [%][b]	*ee* [%][c]	*dr*[d]
1	H	COOMe	Bn	5	2	90 (**3a**)	94 (1*S*, 2*R*, 3*R*)	>19:1
2	H	COOEt	Bn	5	2	88 (**3b**)	93 (1*S*, 2*R*, 3*R*)	>19:1
3	H	COO-*i*-Pr	Bn	5	2	92 (**3c**)	93 (1*S*, 2*R*, 3*R*)	>19:1
4	H	COO-*t*-Bu	Bn	5	2	95 (**3d**)	96 (1*S*, 2*R*, 3*R*)	>19:1
5	H	COOPh	Bn	5	2	88 (**3e**)	92 (1*S*, 2*R*, 3*R*)	>19:1
6	H	COOBn	Bn	5	2	87 (**3f**)	94 (1*S*, 2*R*, 3*R*)	>19:1
7	5-Me	COOMe	Bn	5	3	95 (**3g**)	94 (1*S*, 2*R*, 3*R*)	>19:1
8	5-MeO	COOMe	Bn	5	3	97 (**3h**)	93 (1*S*, 2*R*, 3*R*)	>19:1
9	5,7-Me_2	COOMe	Bn	5	3	92 (**3i**)	93 (1*S*, 2*R*, 3*R*)	>19:1
10	5-F	COOMe	Bn	5	2	90 (**3j**)	94 (1*S*, 2*R*, 3*R*)	18:1
11	5-Cl	COOMe	Bn	5	2	90 (**3k**)	94 (1*S*, 2*R*, 3*R*)	12.5:1
12	5-Br	COOMe	Bn	5	2	85 (**3l**)	93 (1*S*, 2*R*, 3*R*)	8.5:1
13	6-Cl	COOMe	Bn	5	2	97 (**3m**)	95 (1*S*, 2*R*, 3*R*)	>19:1
14	7-Br	COOMe	Bn	5	2	86 (**3n**)	90 (1*S*, 2*R*, 3*R*)	13:1
15	7-F_3C	COOMe	Bn	5	2	84 (**3o**)	90 (1*S*, 2*R*, 3*R*)	8:1
16	H	COPh	Bn	5	2	94 (**3p**)	94	>19:1
17[e]	H	Ph	Bn	10	36	80 (**3q**)	95	>19:1
18[e]	H	4-MeC_6H_4	Bn	10	36	56 (**3r**)	91	>19:1
19[e]	H	4-$F_3CC_6H_4$	Bn	10	16	93 (**3s**)	98	>19:1
20[e]	H	4-ClC_6H_4	Bn	10	16	92 (**3t**)	97	>19:1
21[e]	H	2-naphthyl	Bn	10	36	77 (**3u**)	95	>19:1
22[e]	H	3-thienyl	Bn	10	36	50 (**3v**)	91	>19:1
23[e]	H	Me	Bn	10	14	84 (**3w**)	93	11:1
24[e]	H	*t*-Bu	Bn	10	16	85 (**3x**)	95	>19:1
25[e]	H	*n*-decyl	Bn	10	14	80 (**3y**)	82	13:1
26	H	COOEt	Me	5	2	97 (**3z**)	92	>19:1

[a] Unless otherwise noted, all reactions were carried out with **1** (0.1 mmol), **2** (0.06 mmol) and **L-PiPr$_2$**–Ni(OTf)$_2$ (1:1, x mol%) in CH_2Cl_2 (0.5 mL) at 35 °C.
[b] Isolated yield of the major diastereoisomer by silica gel column chromatography; **3i**–**3o** isolated by silica gel column chromatography at 0 °C.
[c] Determined by HPLC analysis for the major diastereoisomer.
[d] Determined by ^{1}H NMR of crude product.
[e] Conducted with 1.0 equiv. of **2**.

As presented in Table 1, when employing **L-PiPh**–Yb(OTf)$_3$ as the chiral catalyst, only a trace amount of product was detected. The **L-PiPh**–Sc(OTf)$_3$ complex delivered the corresponding cycloaddition product **3a** in 46% yield and 49% *ee* but with only 1.5:1 *dr* (Table 1, entry 2). To our delight, the *dr* value could be increased to 4:1 when employing the **L-PiPh**–Ni(OTf)$_2$ complex as the catalyst although with a decrease of enantioselectivity (Table 1, entry 3). To further improve the outcomes, a series of chiral *N,N′*-dioxide ligands containing diverse amines and chiral backbone moieties was synthesized and complexed with Ni(OTf)$_2$ to catalyze the reaction (Table 1, entries 4–9). It was found that the amine substituents had a great influence on the enantioselectivity and diastereoselectivity. The ligand with an aromatic amine substituent was more promising than **L-PiAd** with an alkylamine substituent (Table 1, entry 3 *vs.* entry 4). On increasing the hindrance of the amide from H to Me, Et and *i*-Pr, both the *ee* and *dr* values increased gradually from 24% *ee*, 4:1 *dr* to 93% *ee*, >19:1 *dr* (Table 1, entries 5–7 *vs.* entry 3). The ligands with other chiral backbone moieties had a negative influence on the stereoselectivity (Table 1, entries 8 and 9). Investigation of other solvents did not give rise to better results (Table 1, entries 10 and 11).

Pleasingly, the catalyst loading could be reduced to 5 mol% without loss of yield, enantioselectivity and diastereoselectivity (90% yield, 94% *ee*, >19:1 *dr*; Table 1, entry 12). Decreasing the reaction temperature to 25 °C could give similar results but with longer reaction times (Table 1, entry 13). Notably, when the $Ni(OTf)_2$ was in excess compared to the chiral *N,N′*-dioxide ligand, the reaction was very sluggish. It was speculated that the superfluous $Ni(OTf)_2$ might complex with sulfur atom of mercaptoacetaldehyde which existed in the reaction system in the form of an equilibrium with 1,4-dithiane-2,5-diol,[16] thus the coordinated mercaptoacetadehyde could not take part in the thia-domino cyclization.

Having established the optimal reaction conditions (Table 1, entry 12), we next examined the generality of this domino thia-Michael/aldol reaction (Table 2). The steric hindrance of the ester group showed no obvious influence on the reactivity and stereoselectivity of the reaction, giving the corresponding cyclic adducts in good yields with excellent enantioselectivities and diastereoselectivites (87–95% yields, 92–96% *ee*, >19:1 *dr*; Table 2, entries 1–6). The electronic nature or the position of substituents on the backbone of the oxindole had a slight effect on the diastereoselectivity but no effect on either yield or enantioselectivity (84–97% yields, 90–95% *ee*, 8:1 to >19:1 *dr*; Table 2, entries 7–15).[17] Excellent yield and enantioselectivity were still maintained when the ester group was replaced by a benzoyl group (94% yield, 94% *ee*, >19:1 *dr*; Table 2, entry 16). Significantly, less reactive aryl-substituted 3-alkenyloxindoles including fused- or heteroaromatic substituted ones as well as the alkyl-substituted ones **1w**, **1x**, **1y** could also undergo this reaction smoothly, affording the desired adducts in excellent results (50–93% yields, 82–98% *ee*, 11:1 to >19:1 *dr*; Table 2, entries 17–25). Additionally, the *N*-methyl-protected 3-alkenyloxindole was also well tolerated (97% yield, 92% *ee*, >19:1 *dr*; Table 2, entry 24). Oxindoles without the benzyl protecting group, such as (*E*)-methyl-2-(2-oxoindonlin-3-ylidene)acetate, gave only 26% cycloaddition product with 10% *ee* after 24 h.

The absolute configuration of cyclic adduct **3j** was unambiguously determined by X-ray crystallographic analysis to be (C1*S*, C2*R*, C3*R*).[18] According to the NMR analysis of the products and a comparison with the CD spectra of **3j**, the absolute configurations of other ester group-substituted 3-alkenyloxindole cycloaddition products are also determined as (C1*S*, C2*R*, C3*R*) (Figure 2).

To further evaluate the synthetic utility of the catalytic system, the reaction was conducted on a gram scale. As shown in Scheme 2, by treament of 3 mmol **1a** and 1.8 mmol **2**, the corresponding spirocyclic oxindole-fused tetrahydrothiophene **3a** (1.01 g, 91% yield) was obtained without any loss of diastereo- and enantioselectivity (>19:1 *dr*, 93% *ee*) even using 2 mol% catalyst loading. The enantiopure **3a** could be obtained after one single recrystallization.

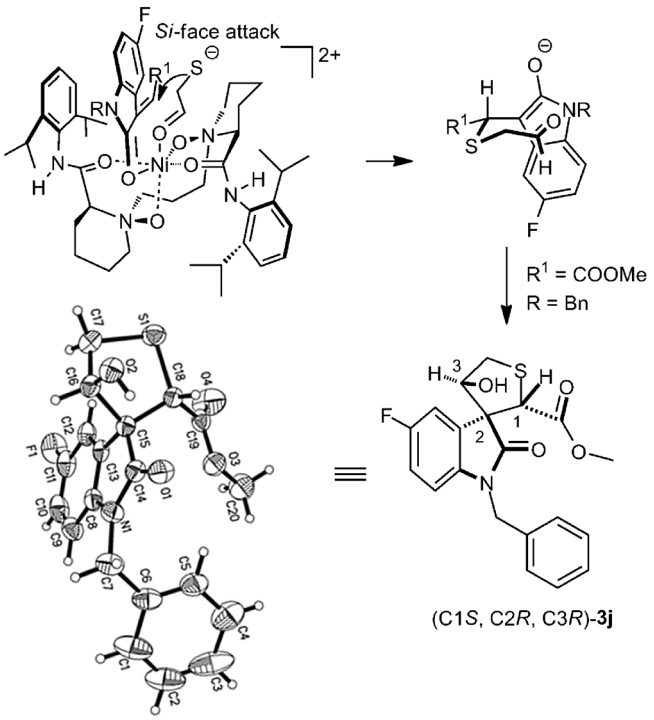
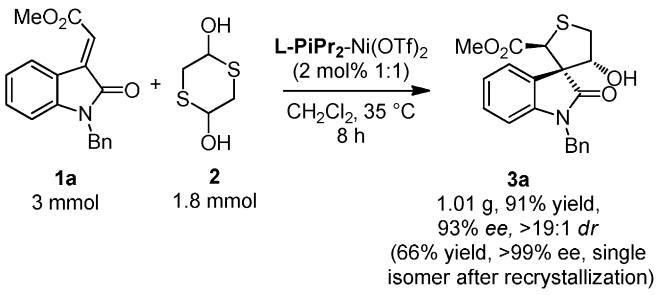


Figure 2. Proposed catalytic model and X-ray single crystal structure of **3j**.



Scheme 2. Scaled-up version of the domino thia-Michael/aldol cycloaddition reaction.

Based on the X-ray crystal structure of the catalyst[19] as well as the absolute configuration of the products, a proposed catalytic model was provided to explain the observed stereocontrol. Both oxygen atoms of the amide and *N*-oxide were complexed with the Ni atom in the complex. The carbonyl oxygen atom of the 3-alkenyloxindole coordinated with the nickel center and was stabilized by the π–π stack interactions between the two aromatic rings. Meanwhile, the strong dipolar ability of *N,N′*-dioxide facilitated the nickel to coordinate with an oxygen atom better than a sulfur atom of the dissociated mercaptoacetadehyde. Due to the fact that the *Re*-face of

oxindole was shielded by the neighboring 2,6-diisopropylphenyl group of the *N,N′*-dioxide, the sulfur atom attacked on the activated olefin at the *Si*-face forming the C1*S* center followed by an intramolecular aldol reaction *via* the chair-like transition state, affording the C1*S*, C2*R*, C3*R* product.

In summary, we have demonstrated an efficient *N,N′*-dioxide–nickel(II) complex-catalyzed asymmetric domino thia-Michael/aldol cycloaddition reaction, which provided a practical access to the enantioenriched spirocyclic oxindole-fused tetrahydrothiophenes. A series of 3-alkenyloxindoles underwent this reaction smoothly, affording the desired products in good yields with excellent enantioselectivities and diastereoselectivities (up to 97% yield, 98% *ee*, >19:1 *dr*). The reaction could be scaled-up to a gram scale without loss of selectivity. Studies on further applications of this catalyst system to other asymmetric reactions are underway.

Experimental Section

Typical Procedure for the Thia-Domino Cyclization of 1,4-Dithiane-2,5-diol with 3-Alkenyloxindoles

An oven-dried test tube was charged with **L-PiPr$_2$** (0.005 mmol, 3.3 mg), Ni(OTf)$_2$ (0.005 mmol, 1.8 mg) and 3-alkenyloxindole **1a** (0.1 mmol, 29.3 mg). The tube was then sealed with a stopper. The vessel was briefly evacuated and backfilled with nitrogen (repeated for three times) before 0.5 mL CH_2Cl_2 was added. After stirring at 35 °C for 10–15 min, 1,4-dithiane-2,5-diol **2** (0.06 mmol, 9.1 mg) was added to the tube. Then the reaction mixture was stirred at the same temperature for 2 h. Finally the residue was purified by flash chromatography on silica gel (eluent: petroleum ether/EtOAc = 3/1) to afford the desired product **3a** as white solid; yield: 90%, 94% *ee*, >19:1 *dr*. The enantiomeric excess (*ee*) was determined by high-performance liquid chromatography (HPLC) with Chiralcel AD-H, Chiralcel IA. The diastereomeric ratio (*dr*) was determined by ^{1}H NMR spectroscopy of crude product. Products **3j–3o** were purified by short silica gel column chromatography at 0 °C (eluent: DCM/EtOAc = 25/1).

Typical Procedure for the Scaled-Up Reaction

An oven-dried 25-mL round-bottom flask was charged with **L-PiPr$_2$** (0.06 mmol, 39.0 mg, 2 mol%), Ni(OTf)$_2$ (0.06 mmol, 21.6 mg, 2 mol%) and model substrate **1a** (3.0 mmol, 879.0 mg). The flask was then sealed with a stopper. The vessel was briefly evacuated and backfilled with nitrogen (repeated for three times) before 10.0 mL CH_2Cl_2 was added. After stirred at 35 °C for 10–15 min, 1,4-dithiane-2,5-diol **2** (1.8 mmol, 274.0 mg) was added. Then the reaction mixture was stirred at the same temperature for another 8 h before it was directly purified by flash chromatography on silica gel (eluent: DCM/EtOAc = 30/1) to afford the desired product **3a**; yield: 91%, 93% *ee*, >19:1 *dr*.

Acknowledgements

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