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Chiral *N,N*'-Dioxide/Co(II)-Promoted Asymmetric 1,3-Dipolar Cycloaddition of Nitrones with Methyleneindolinones †

Dong Zhang, Chengkai Yin, Yuhang Zhou, Yali Xu, Lili Lin,* Xiaohua Liu and Xiaoming Feng*^a

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A chiral N,N'-dioxide/Co(BF₄)₂·6H₂O complex catalytic system has been developed to efficiently catalyze the asymmetric 1,3-dipolar cycloaddition of nitrones with methyleneindolinones. The corresponding chiral multisubsitituted spiroisoxazolidines with three contiguous quaternary-tertiary stereocenters were obtained in moderate to high yields with excellent dr and ee values (up to 97% yield, >19:1 dr and 98% ee).

Five-membered heterocyclic isoxazolidines are important synthetic intermediates in organic chemistry.¹ Undoubtedly, one of the most convergent ways to synthesize isoxazolidines is the 1,3-dipolar cycloaddition (1,3-DC) of nitrones with alkenes.² Numerous chiral metal complexes³ and organocatalysts⁴ have been developed to catalyze the reaction, offering optically active isoxazolidines in high efficiency. On the other hand, spirooxindole scaffold is found in a large family of natural alkaloids and has been identified as one of the privileged scaffolds for drug discovery.⁵

The asymmetric 1,3-DC of nitrones with methyleneindolinones or their analogues can afford enantioenriched spiro-[isoxazolidine-3,3'-oxindole] derivatives, which possess both the meaningful isoxazolidine and spirooxindole moieties. In 2013, Cheng applied a bisthiourea to realize the asymmtetric 1,3-DC of nitrones with methyleneindolinones. $^{\rm 6}$ The catalyst with two thiourea functional groups activated the two reactants in a concerted way through multiple-hydrogen-bonds (Scheme 1). In our previous work, it was found that the chiral N,N'-dioxide/metal complexes can also well induce the reactions about methyleneindolinones by coordinating in a bidentate manner.⁷ We conceived that this strategy may help the competitive coordination of methyleneindolinones to the N,N'dioxide/metal catalyst in the presence of Lewis basic nitrones and promote the reaction more efficiently. Herein, we report our efforts in developing a N, N'-dioxide/Co(BF₄)₂·6H₂O complex system for the asymmetric 1,3-DC between nitrones and methyleneindolinones,

Scheme 1 Reactions of nitrones and methyleneindolinones



affording more type of products with both spirooxindole and isoxazolidine structures and contiguous quaternary-tertiary stereocenters in higher efficiency under milder reaction conditions.

Initially, the cycloaddition of tert-butyl (E)-3-(2-(tert-butoxy)-2oxoethylidene)-2-oxoindoline-1-carboxylate (1a) and nitrone (2a) was selected as the model reaction to optimize the reaction conditions. The representative results are summarized in Table 1. Firstly, various metal salts were investigated by complexing with the chiral N,N'-dioxide ligand L-PrPr₂ in toluene at 30 °C for 24 h. The complex of Ni(OTf)₂ afforded the desired cycloaddition product 3a good yield and diastereoselectivity, but moderate in enantioselectivity (87% yield, 85:15 dr, 46% ee, Table 1, entry 1). When the reaction was catalyzed by L-PrPr₂/Sc(OTf)₃ or L-PrPr₂/Mg(OTf)₂, the diastereoselectivity was low albeit with high enantioselectivity (Table 1, entries 2 and 3). Comparatively, L- $PrPr_2/Co(ClO_4)_2 \cdot 6H_2O$ complex offered higher activity and better enantioselectivity (Table 1, entry 4, 90% yield, 68:32 dr, 83% ee). When the counter ion of Co(II) was examined, the L- $PrPr_2/Co(BF_4)_2 \cdot 6H_2O$ complex improved the ee value from 83% to 91% (Table 1, entry 5). Next, various ligands were evaluated. Upon changing the amide moiety of the N,N'-dioxide ligands from 2,6diisopropyl to 2,4,6-triisopropyl group, the ee value was decreased from 91% to 79% (Table 1, entry 5 vs 6). Decreasing the steric hindrance from 2,6-diisopropyl to phenyl group, the ee value was decreased sharply from 91% to 63% (Table 1, entry 5 vs 7). When the backbone of the ligand was investigated, it was found that Lproline derived L-PrPr₂ was superior to both L-pipecolic acid derived L-PiPr₂ and L-ramipril derived L-RaPr₂ (Table 1, entry 5 vs entries 8

^{a.} Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, People's Republic of China.

Fax: (+)86 28 85418249 E-mail: <u>lillin@scu.edu.cn</u>; xmfeng@scu.edu.cn † Footnotes relating to the title and/or authors should appear here. Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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of the reaction conditions **Table 2** Substrate scope of methyleneindolinones **1**^a

R		R				
Entry ^a	Ligand	Metal salt	Solvent	Yield ^b (%)	dr ^c	ee ^d (%)
1	L-PrPr ₂	Ni(OTf) ₂	Toluene	87	85:15	46
2	L-PrPr ₂	Sc(OTf) ₃	Toluene	70	70:30	70
3	L-PrPr ₂	Mg(OTf) ₂	Toluene	78	50:50	79
4	L-PrPr ₂	$Co(ClO_4)_2 \cdot 6H_2O$	Toluene	90	68:32	83
5	L-PrPr ₂	$Co(BF_4)_2 \cdot 6H_2O$	Toluene	88	66:34	91
6	L-PrPr ₃	$Co(BF_4)_2 \cdot 6H_2O$	Toluene	91	64:36	79
7	L-PrPh	$Co(BF_4)_2 \cdot 6H_2O$	Toluene	86	80:20	63
8	L-PiPr ₂	$Co(BF_4)_2 \cdot 6H_2O$	Toluene	90	67:33	87
9	$L-RaPr_2$	$Co(BF_4)_2 \cdot 6H_2O$	Toluene	80	50:50	77
10	$L-PrPr_2$	$Co(BF_4)_2 \cdot 6H_2O$	THF	56	70:30	67
11	$L-PrPr_2$	$Co(BF_4)_2 \cdot 6H_2O$	CH_2CI_2	70	60:40	79
12	$L-PrPr_2$	$Co(BF_4)_2 \cdot 6H_2O$	EtOAc	84	90:10	94
13 ^e	$L-PrPr_2$	$Co(BF_4)_2 \cdot 6H_2O$	EtOAc	97	96:4	98
14 ^e	ent- L-PrPr₂	Co(BF ₄) ₂ ·6H ₂ O	EtOAc	96	97:3	-96

^{*a*} Unless otherwise noted, all reactions were carried out with **1a** (0.1 mmol), **2a** (0.11 mmol), ligand/metal salt (1:1, 10 mol%) in indicated solvent (1.0 mL) under N₂ at 30 °C for 24 h. ^{*b*} Isolated yield. ^{*c*} The diastereoselectivities were determined by HPLC analysis. ^{*d*} Determined by chiral HPLC analysis. ^{*e*} The reaction was performed at 0 °C for 72 h.

and 9). Subsequently, the solvent effect was examined. No positive effect was found when THF or CH_2Cl_2 was used as the solvent (Table 1, entries 10 and 11). Fortunately, when the reaction was performed in EtOAc, the diastereoselectivity increased to 90:10 (Table 1, entry 12). By lowering the reaction temperature to 0 °C and prolonging the reaction time to 72 h, the product was obtained in 97% yield with 96:4 dr and 98% ee (Table 1, entry 13). Besides, the *ent*-**L**-**PrPr_2/**Co(BF₄)₂·6H₂O complex could also promote the reaction efficiently, affording a similar good result. (Table 1, entry 13 vs 14). Therefore, the optimal reaction conditions were estabilished as **L**-**PrPr_2**/Co(BF₄)₂·6H₂O (1:1, 10 mol%) in EtOAc at 0 °C for 72 h.

With the optimized conditions in hand, the substrate scope was then evaluated. As shown in Table 2, methyleneindolinones with either electron withdrawing or electron donating substituent (R^1) on the phenyl ring of the oxindole could be smoothly converted to the corresponding cycloaddition products in good yields with excellent ee values (Table 2, **3b-3i**). When the steric hindrance of ester group was decreased from *tert*-butyl group to methyl or isopropyl group, the corresponding products could also be obtained in good to excellent yields with excellent dr and good ee values



^{*a*} Unless otherwise noted, all reactions were carried out with **1** (0.1 mmol), **2a** (0.11 mmol), **L-PrPr**₂/Co(BF₄)₂·6H₂O (1:1, 10 mol%) in EtOAc (1.0 mL) under N₂ at 0 °C. ^{*b*} Isolated yield. ^{*c*} The diastereoselectivities were determined by ¹H NMR spectra. ^{*d*} Determined by chiral HPLC analysis.

(Table 2, 3j-3k).

Subsequently, the scope of nitrones was investigated. Electron withdrawing or electron donating subsitituent (R³) on the phenyl ring had no obvious effect on the diastereo- and enantioselectivity. The corresponding products **3I-3v** were obtained in 73-95% yields, 12:1 to >19:1 dr, 91-99% ee (Table 3, entries 1-11). Significantly, heterofuryl-substituted nitrone 2w was proved a suitable candidate in our case, the corresponding desired product 3w was obtained in 72% yield, >19:1 dr and 95% ee (Table 3, entry 12), to our knowledge, heteroaryl-substituted nitrones have never been applied in the metal Lewis acid catalyzed 1,3-dipolar cycloaddition of electron-deficient olefins before. It is worth to mention that the aliphatic nitrone substrate 2x was also well tolerated in this catalytic system, delivering the desire product 3x in 98% yield, 90:10 dr and 92% ee (Table 3, entry 13). On the other hand, various substituents (R⁴) were also examined, the electronic character and the position of the substituents on the phenyl ring had a slight effect on the reaction. Electron-deficient subsitituents showed better reactivities and selectivities than that of electron donating subsitituents (Table 3, entries 14-17). In addition, N-methyl nitrone

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Table 3 Substrate scope of nitrone 2

^t -BuO ₂	C,		t-p		N ⁻ R ⁴
~		L-PrPr ₂ /Co(E	3F ₄) ₂ .6H ₂ O	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	J.,,3
\int	>=0 + PN. C	(1:1, 10	mol%)		=0
	`N	EtOAc	, 0 ºC	Ň	
1a	Boc 2			3 ^{Bo}	DC .
Entry	D ³	P ⁴	Yield ^b	d u ^C	ee ^d
а	к	к	(%)	ar	(%)
1	$4-FC_6H_4$	C_6H_5	95 (3I)	>19:1	97
2	4-CIC ₆ H ₄	C_6H_5	83 (3m)	>19:1	98
3	$3-BrC_6H_4$	C_6H_5	76 (3n)	>19:1	99
4	$4-IC_6H_4$	C_6H_5	73 (3o)	12:1	93
5	4-NCC ₆ H ₄	C_6H_5	75 (3p)	>19:1	95
6	$4-F_3CC_6H_4$	C_6H_5	78 (3q)	>19:1	91
7	2,3-Cl ₂ C ₆ H ₃	C_6H_5	82 (3r)	>19:1	96
8	4-MeC ₆ H ₄	C_6H_5	88 (3s)	>19:1	99
9	4-MeOC ₆ H ₄	C_6H_5	74 (3t)	>19:1	94
10	2-Naphthyl	C_6H_5	90 (3u)	>19:1	98
11		C_6H_5	87 (3v)	>19:1	99
12	2-furyl	C_6H_5	72 (3w)	>19:1	95
13 ^e	Cyclohexyl	C_6H_5	98 (3x)	9:1	92
14	C_6H_5	$4-FC_6H_4$	75 (3y)	>19:1	97
15	C_6H_5	3-CIC ₆ H ₄	96 (3z)	>19:1	99
16	C_6H_5	$4-CIC_6H_4$	95 (3aa)	>19:1	91
17	C_6H_5	$4-MeC_6H_4$	85 (3ab)	9:1	91
18 ^f	C_6H_5	Me	45 (3ac)	16:1	95

^{*a*} Unless otherwise noted, all reactions were carried out with **1a** (0.1 mmol), **2** (0.11 mmol), **L-PrPr₂**/Co(BF₄)₂·6H₂O (1:1, 10 mol%) in EtOAc (1.0 mL) under N₂ at 0 °C for 72 h. ^{*b*} Isolated yield. ^{*c*} The diastereoselectivities were determined by ¹H NMR spectra. ^{*d*} Determined by chiral HPLC analysis. ^{*e*} Reaction time 88 h. ^{*f*} Reaction time 5 days.

2ac was also tested. The reactivity was moderate, but the diastereo- and enatioselectivity were excellent (45% yield, 16:1 dr, 95% ee, Table 3, entry 18). The absolute configuration of product **3a** was determined to be (3R, 3'R, 5'R) by X-ray crystallography analysis⁸ and others were assigned to be the same by comparing the Cotton effect of the CD spectra with that of **3a**.

To evaluate the synthetic potential of the catalytic system, a gram-scale synthesis of **3a** was carried out. As shown in Scheme 2, catalyzed by 10 mol% **L-PrPr₂**/Co(BF₄)₂·6H₂O complex, 4.0 mmol **1a** and 4.4 mmol **2a** transformed smoothly to **3a** in 91% yield (1.97 g) with >19:1 dr and 98% ee.

Scheme 2 Gram-scaled version of the reaction



To gain some insight into the reaction mechanism, operando IR experiments and control experiments were performed. Firstly, the reaction between **1a** and **2a** was monitored by the operando IR spectrometer (Fig. 1). It can be seen clearly from the figure that the amount of product increased with the consuming of starting materials and no intermediates were observed in the process. Hence, we speculated that the reaction might proceed in a

Fig. 1 The operando IR experiments



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Table 4 Control experiments⁴

	R ¹ N Pg	Ph ⁺ N∖- Ph 2a	L-PrPr ₂ /Co (1:1, EtOA	o(BF₄)₂·6H₂C 10 mol%) ∧c, 0 °C		`N´ ^{Ph} ↓★ Ph)⇒O
Entry	R^1	Pg	1	Yield ^b	dr ^c	ee ^c
1	C-H-	Boc	1ad	(/0) N R		(70)
2		Boc	1ae	N R		
3	Bz	Boc	1af	12	N.D.	N.D.
4	CO ₂ ^{t-} Bu	Me	1ag	30	N.D.	0
5	CO2 ^{t-} Bu	Bn	1ah	26	N.D.	0
6	CO ₂ ^{t-} Bu	н	1ai	18	N.D.	0
7	CO ₂ ^{t-} Bu	Ac	1aj	74	70:30	40
8	CO2 ^{t-} Bu	Cbz	1ak	72	64:36	65
9	CO2 ^{t-} Bu	Boc	1al	97	96:4	98

 a Unless otherwise noted, all reactions were carried out with 1 (0.1 mmol), 2a (0.11 mmol), L-PrPr_2/Co(BF_4)_2·6H_2O (1:1, 10 mol%) in EtOAc (1.0 mL) under N_2 at 0 °C for 72 h. b Isolated yield. c Determined by chiral HPLC analysis.

concerted way.

Next, the control experiments were carried out under the standard reaction condition. As exhibited in Table 4, when the substituent R¹ was electron donating phenyl group or tert-butyl group, the reaction did not occur (Table 4, entries 1 and 2). When the substituent R¹ was electron-deficient benzoyl group, the reaction occurred in a low activity (Table 4, entry 3). These results suggested that the electron property of R¹ influenced the reaction reactivity a lot. On the other hand, the coordination effect of the protecting group was investigated, when the substrates 1ag, 1ah and 1ai which have no metal coordination site on respective protecting group were carried out in the reaction, almost all of them afforded the desire products in low activities without any enantioselectivities (Table 4, entries 4 - 6). In contrast, N-acetyl protected 1aj and N-benzoxycarbonyl protected 1ak gave the desire products in moderate yields, dr and ee values (Table 4, entries 7 and 8). Changing the protecting group with tert-butyloxycarbonyl, the reactivity, diastereoselectivity and enatioselectivity sharply improved, affording the corresponding product in 97% yield with >19:1 dr and 98% ee (Table 4, entry 9). It indicated that the protecting group on the nitrogen atom of the substrates which has a coordination ester site and large steric hindrance was crucial for both the activation and stereo control.

On the basis of the experimental results, our previous work⁹ and the absolute configuration of the products, a possible transitionstate model was proposed. As illustrated in Scheme 3, the four

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Scheme 3 Crystal structure of 3a and the proposed transition-state model



oxygens in the ligand and the oxygen atoms of both amide and the *N*-Boc in the methyleneindolinone coordinated with the Co (II) to form an octahedral complex. The *Si* face of the methyleneindolinone was shielded by the 2,6-diisopropylphenyl group of the ligand. Therefore, the nitrone would attack from the *Re* face to afford the product with (3*R*, 3'*R*, 5'*R*) configuration, which was coincident with the X-ray crystallographic analysis.

In summary, we have developed an efficient chiral N,N'-dioxide/Co(BF₄)₂·6H₂O complex catalytic system for the asymmetric 1,3-DC between nitrones and methyleneindolinones. A range of optically active products bearing both spirooxindole and isoxazolidine structures with three contiguous stereocenters were obtained in good yields with excellent diastereo- and enantioselectivity. The synthetic potential of this methodology was demonstrated by a gram-scale synthesis. Furthermore, a possible transition-state model was proposed to explain the stereochemistry. Further applications of the catalysts are underway in our laboratory.

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