

An Efficient Synthesis of Chiral Diamines with Rigid Backbones: Application in Enantioselective Michael Addition of Malonates to Nitroalkenes

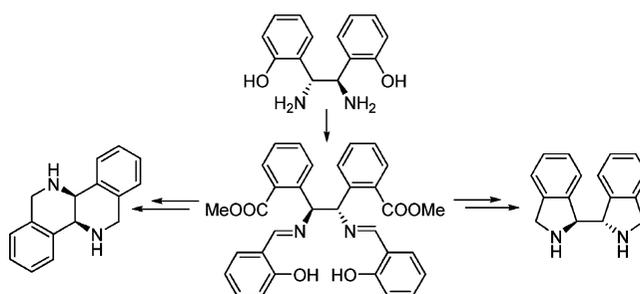
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ABSTRACT



A new and efficient route for synthesis of enantiomerically pure bisindoline and its isomer based on the diaza-Cope rearrangement reaction with chiral 1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane as starting material has been developed. The newly prepared bisindoline was employed as a chiral ligand in the Ni(II)-catalyzed enantioselective Michael addition of malonates to conjugated nitroalkenes, and good to excellent enantioselectivities were obtained.

The design and synthesis of new chiral amines have attracted a great deal of attention from both academia and industry since they are building blocks not only for stereoselective catalysts¹ but also for a variety of therapeutic agents.² For many years, a number of chiral 1,2-diamines have been extensively explored as chiral ligands in asymmetric catalysis due to their easy modifiability and relative air stability compared to phosphorus ligands.¹ Among them, the most frequently used chiral diamines were 1,2-diaminocyclohexane

(DACH) and 1,2-diphenylethylenediamine (DPEN). By contrast, the DPEN-derived catalysts were less efficient than DACH-derived catalysts in terms of reactivity and enantioselectivity. This might be ascribed to the conformational flexibility of DPEN, which arose from the free rotation of the phenyl group on the backbone (Figure 1). To overcome this problem, by the conformational analysis of the structure of DPEN, we here propose that if two methylene groups can be introduced onto the scaffold to bridge the phenyl group

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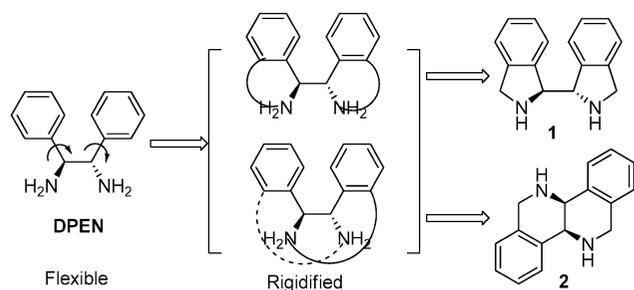
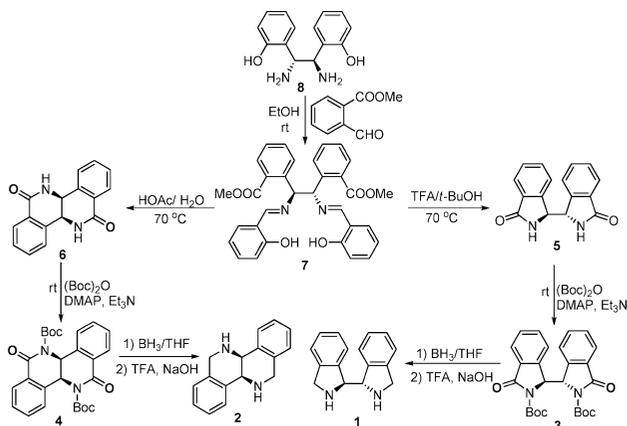


Figure 1. Design of the rigid chiral amines **1** and **2**.

and $-\text{NH}_2$, two kinds of cyclic diamines would be constructed, namely biisoindoline **1** and hexahydrodibenzo[*c,h*]-[1,5]naphthyridine **2** (Figure 1). The two additional cyclic rings in their backbones might improve the conformational rigidity by restraining the free rotation of the phenyl group. The chiral amines **1** and **2**, possessing bipyrolidine³ and diaza-*cis*-decalin⁴ backbones, respectively, are expected to be more conformationally rigid due to the fused benzene rings on their scaffolds. The conformational rigidity of a chiral ligand has been demonstrated to be an important factor for high enantioselectivity in asymmetric catalysis.⁵ In addition, the chiral amine **1** containing the isoindoline backbone, could be regarded as biisoindoline. The isoindoline backbone is a common structure in various natural products and pharmaceuticals.⁶ In this context, these two chiral amines are expected to be key platform molecules not only for synthesis of chiral ligands but also for chiral drugs. Herein we report the design and synthesis of the novel optically pure biisoindoline **1** and its isomer **2** as well as their applications as chiral ligands in metal-catalyzed asymmetric reactions.

As shown in Scheme 1, the synthesis of the chiral amines **1** and **2** was quite straightforward, the basic strategy of which

Scheme 1. Synthesis of the Rigid Chiral Amines **1** and **2**



involved the stereoselective diaza-Cope rearrangement procedure.⁷ As the first step, simple condensation of (1*R*,2*R*)-

1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane **8** with methyl 2-formylbenzoate at room temperature in EtOH and via enantioselective diaza-Cope rearrangement reaction gave the corresponding key diimine **7** in 86% yield with completely inversion of stereochemistry to give the (*S,S*)-enantiomer. The key ester-containing diimine **7** was then treated with water in the presence of Brønsted acid leading to intramolecular hydrolysis cyclization, which afforded the lactams **5** and **6**. As indicated in Table 1, the regioselectivity of

Table 1. Reactions of **7** under Various Conditions^a

entry	conditions	5 (%)	6 (%)
1	H ₂ O, 70 °C, 24 h	0	0
2	TFA (2 equiv), H ₂ O, 70 °C, 2 h	84.5	0
3	TFA (2 equiv), <i>t</i> -BuOH/H ₂ O, 70 °C, 2 h	92.8	0
4	H ₂ O (30 equiv), TFA, 70 °C, 24 h	66.2	0
5	AcOH (2 equiv), H ₂ O, 70 °C, 24 h	33.2	5.7
6	AcOH (2 equiv), <i>t</i> -BuOH/H ₂ O, 70 °C, 2 h	64.3	19.2
7	H ₂ O (30 equiv), AcOH, 70 °C, 2 h	58.2	25.7

^a All reactions were performed on a 0.5 mmol scale, and the yield shown is the isolated yield.

cyclization was strongly dependent on the Brønsted acid and reaction conditions. The ester-containing diimine **7** was stable and remained intact after heating 24 h in H₂O (entry 1), but in the presence of acetic acid or trifluoroacetic acid (TFA), **7** underwent hydrolysis cyclization to form products **5** and **6**. In the presence of TFA, only the five-membered lactam **5** could be observed (entries 2–4). Remarkably, heating of **7** in *t*-BuOH and water in the presence of TFA led to the exclusive formation of the biisoindolinone **5** in excellent yield (entry 3). On the other hand, with AcOH as promoter, both the five-membered and six-membered lactams could be formed, and the five-membered biisoindolinone **5** was always the major product regardless of changing the reaction

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conditions. The structures of lactam **5** and **6** were established on the basis of spectroscopic data (see the Supporting Information). To further confirm the stereochemistry of products beyond doubt, the structures of the lactams **5** and **6** were determined unambiguously by X-ray crystallography (Figure 2).⁸

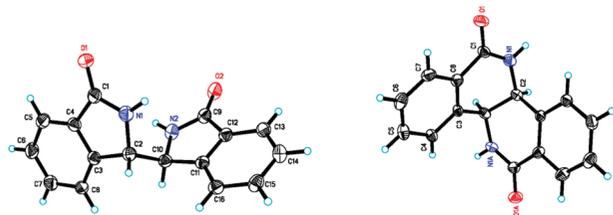


Figure 2. X-ray crystal structure of **5** (left) and **6** (right).

The lactams were then protected with (Boc)₂O in the presence of Et₃N and DMAP to generate the corresponding **3** and **4** in 92–96% yield, which were reduced with BH₃·THF in refluxing THF, and then the protection group was removed with TFA to furnish the desired amines in 54–62% yield. The enantiomeric excess of the two newly prepared chiral amines **1** and **2** determined by chiral HPLC (see the Supporting Information) was found to be >99% ee in each case.

The (*S,S*)-configuration of the (+)-enantiomer **1** was determined by the X-ray analysis of the corresponding diastereomer (*S,S,S*)-disulfonamide **9** derived from (1*S*)-camphor-10-sulfonyl chloride (Figure 3).⁸ Similarly, the

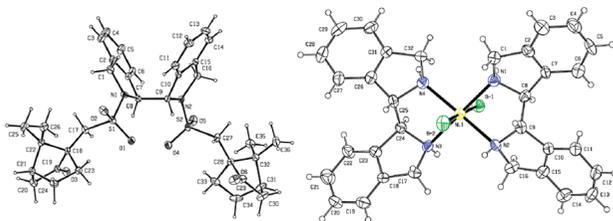


Figure 3. X-ray crystal structure of **9** (left) and **10** (right).

absolute configuration of (+)-enantiomer **2** should also be assigned as (*S,S*) by analogy. With the (*S,S*)-biisoindoline in hand, we successfully prepared the corresponding complex

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with NiBr₂ in CH₃CN. Complex **10** was crystallized from CH₃CN to obtain a single crystal suitable for analysis. As can be seen from the X-ray structure of **10**, the biisoindoline framework adopts a stairlike conformation, which consists of that of the Zn complex prepared from 2,2-bipyrridine.^{3c} The two biisoindoline ligands coordinate to nickel in a *trans* geometry while two bromides occupy the apical positions.⁸

The potential of the amines **1** and **2** as chiral ligands in asymmetric catalysis was studied on the Ni-catalyzed enantioselective Michael addition of malonates to conjugated nitroalkenes.⁹ Commercially available nitrostyrene and diethyl malonate were initially chosen to screen the reaction conditions. Some representative results are shown in Table 2. The first attempt, following Evans' procedure^{9d} using the

Table 2. Ni-Catalyzed Michael Addition of Diethyl Malonate to Nitrostyrene^a

entry	L/NiBr ₂	additive	yield ^b (%)	ee ^c (%)
1	2:1		50	80 (<i>S</i>)
2	2:1	NMM (1 equiv)	99	10 (<i>S</i>)
3	1:1	NMM (1 equiv)	99	76 (<i>S</i>)
4	1:1	NMM (10%)	75	78 (<i>S</i>)
5	1:1	PMP (10%)	99	74 (<i>S</i>)
6	1:1	PMP (5%)	99	80 (<i>S</i>)
7	1:1	PMP (2%)	80	78 (<i>S</i>)
8 ^d	1:1	PMP (5%)	78	9 (<i>R</i>)

^a Unless otherwise stated, reactions were performed on a 0.5 mmol scale using 2 equiv of the 1,3-dicarbonyl compound at 80 °C for 9 h with 2 mol % of catalyst. ^b Isolated yield. ^c Determined by chiral HPLC, the absolute configuration was determined by comparison of the optical rotation with reported data. ^d Chiral amine **2** was used as ligand.

complex **10** as catalyst, afforded the desired product in only 50% yield with 80% ee. On addition of *N*-methylmorpholine (NMM) as an additive, the reaction proceeded smoothly with full conversion to give the desired product in quantitative yield, while the enantioselectivity was dramatically decreased (entry 1 vs entry 2). Interestingly, while used the catalyst which was prepared with the 1:1 ratio of NiBr₂ and **1** as

(8) CCDC 737040 contains the crystallographic data for **5**, CCDC 737041 contains the data for **6**, CCDC 737042 contains the data for **9**, and CCDC 737043 contains the data for **10**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/conts/retrieving.html.

(9) For metal-catalyzed enantioselective Michael additions of 1,3-dicarbonyl compounds to nitroalkenes, see: (a) Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999**, *121*, 10215. (b) Barnes, D. A.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097. (c) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958. (d) Evans, D. A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*, 11583. (e) MacCulloch, A. C.; Yolka, S.; Jackson, R. F. W. *Synlett* **2002**, 1700. (f) Sibi, M. P.; Gorikunti, U.; Liu, M. *Tetrahedron* **2002**, *58*, 8357. (g) Palomo, C.; Pazos, R.; Oiarbide, M.; Garcia, J. M. *Adv. Synth. Catal.* **2006**, *348*, 1161. (h) Nichols, P. J.; DeMattei, J. A.; Barnet, B. R.; LeFur, N. A.; Chuang, T.-H.; Piscopio, A. D.; Koch, K. *Org. Lett.* **2006**, *8*, 1495.

well as with *N*-methylmorpholine (1 equiv) as an additive, the ee was significantly increased from 10% to 76% with 99% yield. Further optimization of the reaction conditions by screening of various bases as additives has shown that the most sterically hindered base PMP (1,2,2,6,6-pentamethylpiperidine) afforded the best results in terms of reactivity and selectivity when the amount of additive was reduced to 5 mol % (entry 6). The amine **2** has proved to be unsuitable for this reaction (entry 8). Screening of the solvents and temperature with 1:1 ratio of NiBr₂ and **1** as catalyst and PMP as additive has shown that the highest yield and enantioselectivity were obtained when the reaction was performed at 80 °C and MTBE was used as solvent (see the Supporting Information).

Having succeeded in developing an efficient enantioselective catalyst, we next probed the generality of this enantioselective conjugate reaction catalyzed by the catalyst. The results are summarized in Table 3. The reactivity and enantioselectivity were dependent on the steric demands of the malonates. When the alkyl ester group was changed from methyl to *tert*-butyl the required reaction time for was increased to 24 h (entries 1–4), with the enantioselectivity increased to 87%. The reaction of di-*tert*-butyl malonate with a number of electron-rich and electron-poor aromatic nitroalkenes provided the desired product in excellent yield with 79–90% ee. The absolute configurations of the adduct products were assigned as (*S*) which were determined by comparison of the optical rotation with reported data.⁹

In conclusion, we have designed two kinds of new chiral diamines bisindoline **1** and hexahydrodibenzo[*c,h*][1,5]-naphthyridine **2** with rigid backbones. They were prepared through a rapid and reliable procedure based on the diaza-Cope rearrangement reaction with chiral 1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane as starting material for the first time, which diversifies the families of chiral diamines and isoindolines. The present procedure will permit efficient access to a variety of interesting chiral cyclic amines not only for asymmetric catalysis but also for pharmaceutical chemistry. The effectiveness of bisindoline as a chiral ligand was demonstrated by Ni(II)-catalyzed enantioselective Michael addition of malonates to conjugated nitroalkenes. Further applications of the newly developed chiral amines

Table 3. Ni-Catalyzed Michael Addition of Malonates to Nitroalkenes^a

entry	R ¹	R ²	product (%) ^b	ee (%) ^c
1	Ph, 11a	Et, 12a	13aa (99)	80
2	Ph, 11a	Me, 12b	13ab (97)	78
3	Ph, 11a	Bn, 12c	13ac (99)	72
4	Ph, 11a	<i>t</i> -Bu, 12d	13ad (96)	87
5	2-BrPh, 11b	<i>t</i> -Bu, 12d	13bd (98)	87
6	4-BrPh, 11c	<i>t</i> -Bu, 12d	13cd (93)	85
7	4-ClPh, 11d	<i>t</i> -Bu, 12d	13dd (97)	85
8	4-MePh, 11e	<i>t</i> -Bu, 12d	13ed (99)	87
9	4-MeOPh, 11f	<i>t</i> -Bu, 12d	13fd (93)	87
10	2-MeOPh, 11g	<i>t</i> -Bu, 12d	13gd (98)	90
11	3,4-(MeO)Ph, 11h	<i>t</i> -Bu, 12d	13hd (98)	87
12	2,3-(MeO)Ph, 11i	<i>t</i> -Bu, 12d	13id (87)	87
13	1-naphthyl, 11j	<i>t</i> -Bu, 12d	13jd (98)	79
14	(<i>Z</i>)-PhCH=CH-, 11k	<i>t</i> -Bu, 12d	13kd (72)	85
15	2-furyl, 11l	<i>t</i> -Bu, 12d	13ld (99)	88

^a Unless otherwise stated, reactions were performed at 80 °C for 9–36 h on a 0.5 mmol scale using 2 equiv of Malonate with 2 mol % of catalyst (NiBr₂:**1** = 1:1) and 5 mol % of PMP. ^b Isolated yield. ^c Determined by chiral HPLC.

in asymmetric catalysis are in progress and will be reported in due course.

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

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