A Novel Chiral H′$_4$-NOBIN Schiff Base for Hetero-Diels–Alder Reaction of Danishefsky's Diene with Aldehydes

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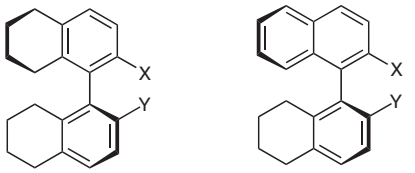
Abstract: Novel chiral H′$_4$-NOBIN was synthesized in 66% yield through partial hydrogenation of 2-amino-2′-hydroxy-1,1′-binaphthyl, and the structure was proved via X-ray analysis of its salicylaldehyde Schiff base, which was tested in the enantioselective titanium-catalyzed hetero-Diels–Alder reaction of Danishefsky's diene with aldehydes. The reaction provided dihydropyranone in moderate to high yield (up to 99%) and enantioselectivities (up to 84.5% ee).

Key words: asymmetric catalysis, Schiff bases, Diels–Alder reactions, heterocycles, titanium



1 X = Y = OH
2 X = Y = NH_2
3 X = OH, Y = NH_2

4 X = Y = OH
5 X = NH_2, Y = OH
6 X = OH, Y = NH_2

Figure 1

Optically active 1,1′-bi-2-naphthol (BINOL), 1,1′-bi-2-naphthylamine (BINAM), 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN), and their derivatives have been successfully developed as chiral ligands for many asymmetric reactions.[1] Some results showed that the catalysts derived from partially saturated 1,1′-binaphthyl exhibit higher efficiency and enantioselectivity for some asymmetric reactions than those obtained from their parent ligands, due to the steric and electronic modulations on the binaphthyl backbone.[2] The procedure of preparing chiral H_8-BINOL (**1**), H_8-BINAM (**2**), H_8-NOBIN (**3**) and H_4-BINOL (**4**, Figure 1) has been developed by using different catalysts and conditions, such as PtO_2 (15 mol%) at 25 °C for 7 days (Cram et al.) and 10% Pd/C (10 mol%) at room temperature for 2 days (Sigimura et al.) for **1**,[3] Ni/Al alloy in dilute H_2O–*i*-PrOH alkaline solution for **1**–**4** (Ding et al.),[4] 5% Pd/C (7 mol%) at 80 °C under 50–60 bar pressure for several hours for **1** and **2** (Börner et al.).[5] Among these methods, the procedure of Börner provided a practical way for synthesis of **1** and **2**, but preparation of **3** using of Börner's method was not reported. Our study needs multigram scale of **3**. The hydrogenation of (*S*)-NOBIN were carried out according Börner's procedure, but the method provided (*S*)-5′,6′,7′,8′-tetrahydro-2-amino-2′-hydroxy-1,1′-binaphthyl (H′$_4$-NOBIN, **5**) in 66% yield and **3** in 19% yield. To the best of our knowledge, this is the first report on the synthesis of **5**.[6] In the present work, we wish to report the details on the synthesis of **5** and its Schiff base–titanium complex used as catalyst for the enantioselective hetero-Diels–Alder reaction (HDA) between Danishefsky's diene and aldehydes.

The NOBIN was found to be an excellent chiral ligand for asymmetric reactions and its synthesis has been well developed.[7,8] The two naphthalene rings of NOBIN, unlike the C_2-symmetric BINOL and BINAM, have slightly difference in terms of electron density due to the difference of hydroxyl and amino groups. The difference of the electronic properties makes the selective hydrogenation possible. The hydrogenation of (*S*)-NOBIN was carried out with 5% Pd/C (5 mol%) as catalyst at 80 °C under 80 bar of hydrogen pressure in ethanol (Scheme 1 and Table 1).[9] Shorter reaction time gave a mixture of NOBIN, **3** and **5** (Table 1, entries 1 and 2). Higher catalyst loading improved the yield of **3** (Table 1, entry 4). The complete conversion of starting material needed 10 hours (Table 1, entry 3). The hydrogenation product was isolated in 66% yield after purification with column chromatography. The ^{1}H NMR spectrum of the product showed that the ratio of aromatic protons to alkyl protons is 1:1 rather than the expected value of 1:4 for octahydrobinaphthyl derivatives, and the ^{13}C NMR spectrum showed only four carbon at-

Table 1 Catalytic Hydrogenation of (*S*)-NOBIN[a]

Entry	Time (h)	Ratio of **3**/**5**/NOBIN[b]	Yield of **3** (%)[c]	Yield of **5** (%)[c]
1	5	9:58:33	–	41
2	7	15:70:15	7	62
3	10	26:74:0	18	66
4[d]	10	45:55:0	33	48

[a] Reaction conditions: 0.57 g NOBIN, 0.2 g 5% Pd/C, 80 bar of H_2 pressure, 80 °C, 15 mL EtOH.
[b] Determined by GC.
[c] Isolated yield. The ee >99.5% was determined by chiral HPLC using Chiralcel AD-H or OJ-H column.
[d] The amount of 0.4 g 5% Pd/C was used.

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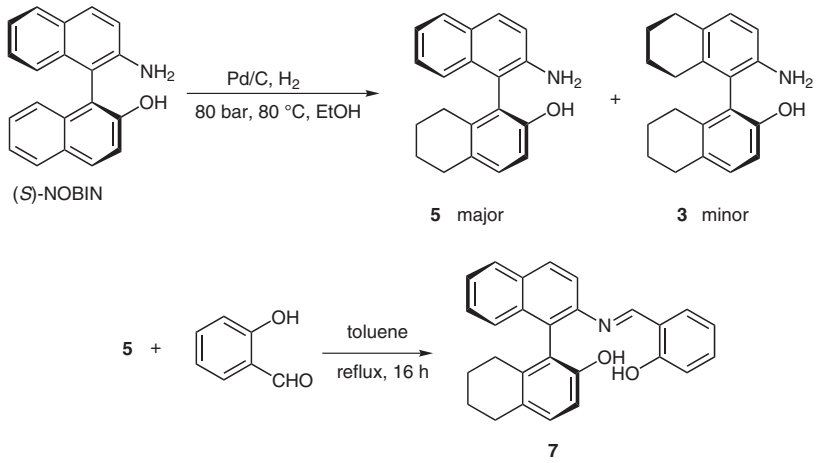


Scheme 1 Synthesis of (*S*)-**5** and ligand (*S*)-**7**.

oms at the high field region. The result indicated that four hydrogen atoms were added on the non-C_2-symmetric NOBIN. Thus, two different compounds were at least formed: 5′,6′,7′,8′-tetrahydro-2-amino-2′-hydroxy-1,1′-binaphthyl (**5**, H′$_4$-NOBIN) and 5,6,7,8-tetrahydro-2-amino-2′-hydroxy-1,1′-binaphthyl (**6**, H_4-NOBIN). The final determination that the molecular structure was **5** and not **6** was ascertained by characterization of its salicylaldehyde Schiff base using X-ray crystallographic analysis.

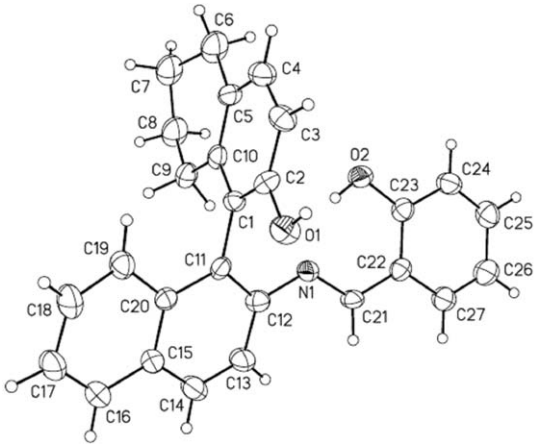


Figure 2 Molecular structure of (*R*)-**7**.

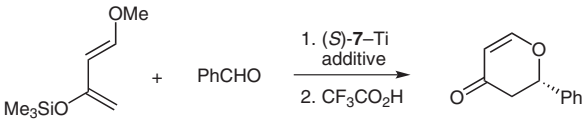
The Schiff base (*R*)-**7** was synthesized by condensation of (*R*)-**5** with salicylaldehyde in refluxing toluene (Scheme 1).[10] The structure of (*R*)-**5** was confirmed by the analysis of X-ray crystal structure of (*R*)-**7**.[11] As shown in Figure 2, the C–C bond lengths of C5−C6, C6−C7, C7−C8, and C9−C10 are between 1.49−1.52 Å. The dihedral angle of the two binaphthyl rings (99.01°) is larger than its parent Schiff base (75.61°), and the dihedral angle of imino naphthyl ring and salicylidene phenyl ring (0.72°) is smaller than its parent Schiff base (23.51°).[7b] The short distance of N1−H(O2) (1.78 Å) suggested that the imino nitrogen atom formed a strong intramolecular hydrogen bond with the hydroxy group of salicylidene moiety rather than that of naphthyl unit.

The HAD reaction between dienes and carbonyl derivatives provides one of the most direct methods for the construction of substituted 2,3-dihydro-4*H*-pyran-4-ones, which have extensively applied in synthesis of natural or unnatural products.[12] Recently, the chiral NOBIN-derived Schiff base–titanium complexes were reported to be effective catalysts for the enantioselective HDA reaction of Danishefsky's diene and aldehydes by Ding et al.[7b] With the novel ligand **7** in hand, we tested its asymmetric induction in the HDA reaction. Naproxen was not the choice of additive due to a change of configuration of the ligand. Thus, a number of acids were screened (Table 2). The results showed that the additive could remarkably improve the yields and ee, and the additive 2-naphthoic acid was found to be the best.

The HDA reaction of Danishefsky's diene and a variety of aldehydes, including aromatic, α,β-unsaturated and aliphatic aldehydes, was carried out with 2-naphthoic acid as additive in the presence of the Ti−(*S*)-**7** complex (Table 3).[13] The results showed that aromatic aldehydes provided higher yield and enantiomeric excess than aliphatic aldehydes. The electronic effect of substituents of aromatic ring on reactivity was obvious. The presence of either electron-withdrawing groups such as Br, Cl, CF_3, to NO_2 (Table 3, entries 2−5), or electron-donating capability from 3-MeO to 3-Me (Table 3, entries 6 and 7), resulted in lower enantioselectivities. Furfural and *trans*-cinnamaldehyde afforded the corresponding dihydropyrones with moderate enantioselectivity and high yield (Table 3, entries 8 and 9). The HDA reaction of cyclohexanecarboxaldehyde and diene provided dihydropyrone in modest enantioselectivity and yield (Table 3, entry 10). The results obtained showed that the enantioselectivities were inferior to its parent catalyst.

In summary, novel chiral (*S*)-H′$_4$-NOBIN was prepared by partial hydrogenation of (*S*)-NOBIN, and the structure was determined by X-ray crystal structure analysis. The (*S*)-H′$_4$-NOBIN-derived Schiff base was tested in the enantioselective titanium-catalyzed HDA reaction of Danishefsky's diene and aldehydes. The reaction provid-

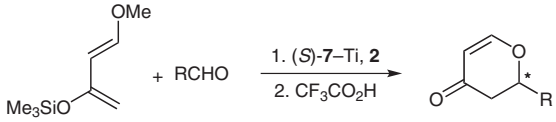
Table 2 Effect of Various Carboxylic Acid Additives on the Enantioselectivity of the Reaction[a]



Entry	Additive	Yield (%)[b]	ee (%)[c]
1[d]	–	43	41.8 (*S*)
2	Naproxen	97	63.8 (*S*)
3	2-Naphthoic acid	99	69.2 (*S*)
4	Benzoic acid	82	64.4 (*S*)
5	*o*-Chlorobenzoic acid	76	44.6 (*S*)
6	*m*-Chlorobenzoic acid	83	53.2 (*S*)
7	*p*-Chlorobenzoic acid	75	63.9 (*S*)
8	*p*-Bromobenzoic acid	76	44.3 (*S*)
9	*p*-Fluorobenzoic acid	80	65.7 (*S*)
10	*p*-Trifluoromethylbenzoic acid	81	52.4 (*S*)
11	(*S*)-2-Methoxy-2-phenylacetic acid	95	54.0 (*S*)
12	1-Adamantanecarboxylic acid	93	62.3 (*S*)

[a] All of the reactions were carried out with (*S*)-**7**/Ti(O*i*-Pr)$_4$/additive/substrate = 0.2:0.1:0.05:1 in toluene in the presence of 4 Å MS at r.t. for 12 h.
[b] Isolated yields.
[c] The ee values were determined by HPLC on Chiralcel OD-H. Absolute configurations were determined by comparison of specific rotations with literature data.
[d] An additive was not used.

Table 3 Asymmetric HDA Reaction of Danishefsky's Diene with Aldehydes in the Presence of (*S*)-**7**[a]



Entry	R	Yield (%)[b]	Ee (%)[c]
1	Ph	98	66.4 (*S*)
2	4-BrC_6H_4	99	84.5
3	4-ClC_6H_4	99	79.2
4	4-$CF_3C_6H_4$	99	72.8
5	4-$O_2NC_6H_4$	96	60.9
6	3-MeC_6H_4	80	45.1
7	3-MeOC_6H_4	89	70.3
8	Fur-2-yl	88	38.4
9	*trans*-Cinnamyl	91	61.78
10	Cyclohexyl	59	11.0 (*R*)

[a] All of the reactions were carried out with (*S*)-**7**/Ti(O*i*-Pr)$_4$/**2**/substrate = 0.2:0.1:0.05:1 in toluene in the presence of 4 Å MS at r.t. for 12 h.
[b] Isolated yields.
[c] The ee were determined by HPLC on Chiralcel OD-H. Absolute configurations were determined by comparison of specific rotations with literature data.

ed dihydropyranone in moderate to high yields and up to 84.5% ee. Further studies of the derivatives of (*S*)-H′$_4$-NOBIN as a ligand in asymmetric synthesis are currently under investigation.

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(9) **Synthesis of (*S*)-5′,6′,7′,8′-tetrahydro-2-amino-2′-hydroxy-1,1′-binaphthyl (*S*)-5**

(*S*)-NOBIN (0.57 g, 2 mmol), 5% Pd/C (0.21 g), and EtOH (15 mL) were placed into a 100 mL autoclave and stirred under 80 bar hydrogen pressure at 80 °C for 10 h. The reaction mixture was cooled to r.t., the catalyst was filtered off, and washed with THF (2 × 10 mL). The combined filtrates were concentrated in vacuum to give a mixture of **3** and **5**, which was submitted to column chromatographic separation on silica gel with hexane–EtOAc (9:1) as eluent to afford (*S*)-**5** (382 mg, 66% yield) as a foam solid with >99.5% ee [HPLC on an AD-H column with hexane–*i*-PrOH (90:10) as eluent, 1 mL min^{-1}, t_R = 13.88 (*R*) min, t_R = 22.73 min (*S*)]; mp 113–115 °C; $[\alpha]_D^{20}$ –59 (*c* 1, THF). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.60–1.63 (m, 2 H), 1.70−1.74 (m, 2 H), 2.13−2.18 (m, 1 H), 2.21−2.26 (m, 1 H), 2.77−2.80 (m, 2 H), 3.76 (s, 2 H), 4.59 (s, 1 H), 6.80 (d, 1 H, *J* = 8.4 Hz), 7.09−7.17 (m, 3 H), 7.26−7.30 (m, 2 H), 7.74 (d, 2 H, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.0, 23.1, 26.8, 29.3, 110.3, 112.8, 117.9, 120.5, 122.6, 127.2, 128.2, 128.3, 129.8, 130.1, 130.4, 133.5, 137.7, 142.7, 151.4. IR (KBr): 3447, 3376, 3052, 2926, 1619, 1471 cm^{-1}. Anal. Calcd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 82.94; H, 6.68; N, 4.80.

(10) **Synthesis of Ligand (*S*)-7**

Compound (*S*)-**5** (285 mg, 0.1 mmol) and salicylaldehyde (122 mg, 0.12 mmol) were stirred in toluene (20 mL) and the mixture was heated to reflux for 16 h. The solvent was removed in vacuo and the product was isolated by flash chromatography on silica gel (316 mg, 80.3% yield); mp 166−168 °C, $[\alpha]_D^{20}$ −118 (*c* 0.2, THF). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.54−1.58 (m, 2 H), 1.67−1.70 (m, 2 H), 1.99−2.10 (m, 1 H), 2.14−2.17 (m, 1 H), 2.76−2.81 (m, 2 H), 4.27 (s, 1 H), 6.84−6.89 (m, 3 H), 7.11−7.13 (m, 1 H), 7.27−7.32 (m, 3 H), 7.48−7.52 (m, 2 H), 7.59−7.61 (m, 1 H), 8.01−8.03 (m, 1 H), 8.51−8.53 (m, 1 H), 8.73 (s, 1 H), 12.3 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.9, 23.0, 23.1, 27.4, 29.3, 112.7, 117.2, 117.4, 118.8, 119.3, 122.1, 125.7, 126.3, 127.2, 127.5, 128.2, 129.7, 130.2, 130.3, 132.3, 132.7, 132.9, 133.1, 136.4, 143.9, 150.6, 161.3, 162.1. IR (KBr): 3381, 3053, 2928, 1610, 1569 cm^{-1}. Anal. Calcd for $C_{27}H_{23}NO_2$: C, 82.42; H, 5.89; N, 3.56. Found: C, 82.39; H, 5.88; N, 3.58.

(11) Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 658558 [(*R*)-**7**]. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk.].

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(13) **General Procedure for Catalytic Enantioselctive Hetero-Diels–Alder Reaction**

A mixture of (*S*)-Schiff Base (19.7 mg, 0.05 mmol), Ti(O*i*-Pr)$_4$ in toluene (0.25 M, 0.1 mL, 0.025 mmol) and activated powdered 4 Å MS (40 mg) in toluene (1 mL) was stirred for 2 h at 50 °C. The red solution was cooled to r.t. and naproxen (5.8 mg, 0.025 mmol), aldehyde (0.25 mmol), and Danishefsky's diene (60 μL, 0.3 mmol) were added sequentially. The mixture was stirred for 12 h at r.t. before quenched with TFA (0.2 mL). After stirring for additional 30 min, the mixture was neutralized with sat. $NaHCO_3$ (3 mL). After filtration through a plug of Celite, the organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhyd Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc−hexane, 1:4) to give the products for ^1H NMR and HPLC analysis.