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The asymmetric hetero-Diels–Alder reaction of enamide aldehydes with Danishefsky's diene and an efficient synthesis of chiral binaphthyl ligands

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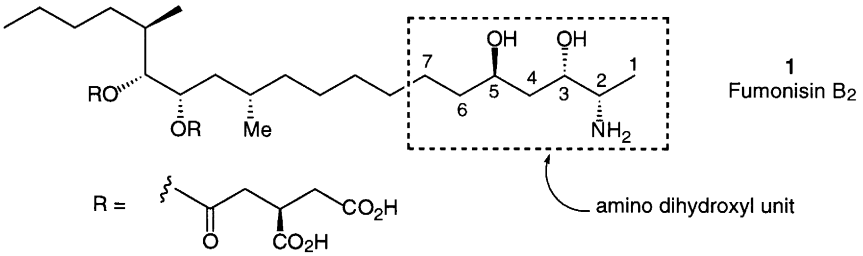
Abstract

By varying the substituents on the nitrogen of enamide aldehydes, their reaction mode with Danishefsky's diene in the presence of Lewis acid catalysts can be controlled and the desired formal hetero-Diels–Alder products obtained. A new and efficient method to synthesize chiral binaphthyl ligands containing sterically bulky 3,3′-substituents has been developed. Lewis acid complexes prepared from these binaphthyl ligands and $AlMe_3$ are used to catalyze the hetero-Diels–Alder reaction of an enamide aldehyde with Danishefsky's diene with up to 78% *ee*. This catalytic asymmetric reaction may allow for the efficient synthesis of biologically interesting molecules such as fumonisins.

Keywords: hetero-Diels–Alder reactions; asymmetric; catalysis; binaphthyl.



1
Fumonisin B_2

Fumonisins, such as Fumonisin B_2 (**1**), are mycotoxins found in sorghum, corn and other grains.[1] This class of molecules has shown a wide variety of biological activities.[1,2] For example, they have been linked with human esophageal cancer resulting from the consumption of contaminated corn in certain countries. A significant number of studies on these compounds has been carried out in the past decade.[1–3] In 1997, Kishi and co-workers accomplished the first total synthesis of Fumonisin B_2 (**1**).[3a] As shown in

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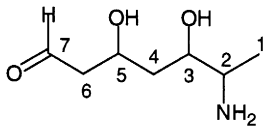
the structure of **1**, all fumonisins contain a chiral amino dihydroxyl unit. We have initiated a project to enantioselectively synthesize a chiral amino dihydroxyl molecule **2** as a precursor to fumonisins by the asymmetric hetero-Diels–Alder reaction of Danishefsky's diene **3**[4] with enamide aldehydes **4** followed by asymmetric hydrogenation and hydrolysis. Herein, we report our study on this asymmetric hetero-Diels–Alder reaction catalyzed by chiral Lewis acid complexes as well as a new and efficient synthesis of chiral binaphthyl ligands.



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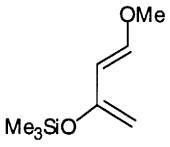

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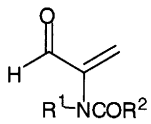
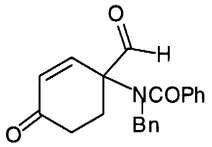


4

4a: R^1 = Bn, R^2 = Ph
4b: R^1 = H, R^2 = Me
4c: R^1 = H, R^2 = Ph

Enamide aldehyde **4a** was readily synthesized from serinol (2-amino-1,3-propandiol).[5] We reacted **4a** with **3** by using $ZnCl_2$ as the Lewis acid catalyst. This, however, did not lead to the desired hetero-Diels–Alder reaction product. Instead, a normal Diels–Alder reaction occurred between **3** and the alkene double bond of **4a** to generate **5** as the major product in 30% isolated yield after treatment with trifluoroacetic acid.[6] We then studied the effect of the nitrogen substituents R^1 and R^2 on this reaction. We found that compounds **4b** and **4c**, where the benzyl group of **4a** was removed, underwent a 'formal' hetero-Diels–Alder reaction with **3** to give compounds **6a** and **6b** in 50–60% isolated yields after treatment with trifluoroacetic acid. This reaction was found to proceed via a Mukaiyama aldol condensation followed by cyclization.[7c,d,8] Therefore, by simply varying the nitrogen substituents of the enamide aldehydes, the reaction pathway of these molecules is dramatically altered. In order to conduct a catalytic enantioselective synthesis, we then explored the use of chiral Lewis acid catalysts for the reaction of **4b** with **3**.



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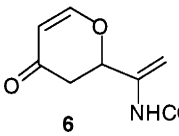
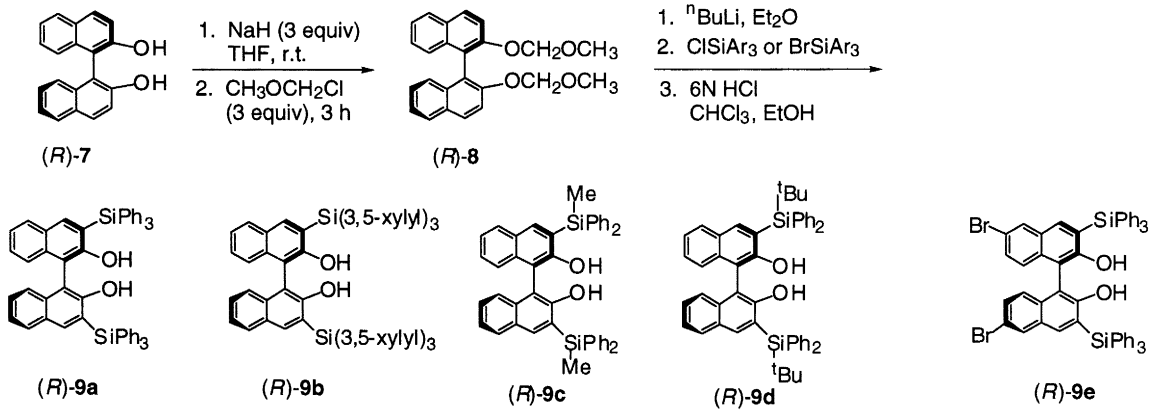


6

6a: R' = Me
6b: R' = Ph

In 1988, Yamamoto and co-workers[9a,b] discovered that optically active binaphthyl ligands **9** with bulky 3,3′-substituents in combination with $AlMe_3$ are highly enantioselective catalysts for the hetero-Diels–Alder reaction of unfunctionalized aldehydes with Danishefsky's dienes.[7,9] These ligands were synthesized by a five-step reaction sequence starting from (*R*)-1,1′-bi-2-naphthol [(*R*)-BINOL, (*R*)-**7**].[10] In order to test the applicability of these chiral ligands to the asymmetric hetero-Diels–Alder reaction of the enamide aldehydes with **3**, we have developed a new and concise three-step synthesis of (*R*)-**9a**–**d** that contains various bulky 3,3′-substituents by using Snieckus' ortho-aromatic metalation strategy[11] (Scheme 1). A typical procedure for the conversion of a methoxymethyl protected BINOL (*R*)-**8** to (*R*)-**9a** is described here. To a solution of (*R*)-**8** (1.87 g, 5.0 mmol) in Et_2O (dried, 40 mL) under nitrogen was added *n*-BuLi (2.5 M, 6.0 mL, 15.0 mmol) dropwise via syringe at room temperature. After stirring for 4 h, a THF (20 mL) solution of triphenylsilylchloride (6.16 g, 20.9 mmol) and HMPA (2.6 mL, 15.0 mmol), respectively, were added. After stirring for another 4 h, the reaction mixture was quenched with saturated NH_4Cl solution, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was mixed with HCl (6N, 20 mL) and $CHCl_3$ (30 mL). EtOH (ca. 40 mL) was added to generate a homogeneous solution which was heated at reflux for 48 h. The organic solvents were then removed

by roto-evaporation, and the aqueous suspension was extracted with EtOAc. The combined organic solution was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was recrystallized from CH_2Cl_2/hexane to yield (*R*)-**9a** (3.20 g, 80%) as a white crystal. (*R*)-**9a** was also converted to (*R*)-**9e** in 70% yield by treatment with bromine in acetic acid and methylene chloride at −20°C. Introduction of the electron-withdrawing 6,6′-bromine atoms in (*R*)-**9e** was to electronically modify the binaphthyl ligand.



Scheme 1. Synthesis of chiral binaphthyl ligands containing bulky 3,3′-substituents

The chiral Lewis acid complexes made from ligands (*R*)-**9a**–**e** and $AlMe_3$ were used to catalyze the asymmetric hetero-Diels–Alder reaction of **3** with **4b**. The results are summarized in Table 1. All of these reactions were carried out at −40°C in the presence of 20 mol% of $AlMe_3$ and 22 mol% of chiral ligand for 36 h unless indicated otherwise. After hydrolysis and work-up, compound **6a** was obtained and characterized.[12] As shown in Table 1, these reactions were strongly influenced by solvents. In solvents containing coordinating oxygen atoms, such as THF and Et_2O, no reaction was observed. A polar solvent like CH_2Cl_2 was found to be more favorable than a less polar toluene. The more sterically bulky ligand (*R*)-**9b** showed much higher enantioselectivity than (*R*)-**9a**. Up to 78% *ee* of **6a** was obtained when the reaction was catalyzed by 10 mol% of (*R*)-**9b**+$AlMe_3$. Introduction of the 6,6′-bromine atoms in (*R*)-**9e** should increase the acidity of the hydroxyl groups, but showed no improvement on the enantioselectivity. Other chiral Lewis acids that were successfully used in different asymmetric hetero-Diels–Alder reactions, such as BINOL-Ti(O^iPr)$_2$,[7c] and BINAP-Cu(OTf)$_2$,[7j] could not catalyze this reaction.

In summary, we have demonstrated that the reaction mode of an enamide aldehyde with a conjugated diene can be dramatically altered by simply changing the substituents on the nitrogen atom. In the presence of chiral Lewis acid catalysts, we have achieved the formal asymmetric hetero-Diels–Alder reaction of enamide aldehydes with Danishefsky's diene with encouraging enantioselectivity. This strategy, when coupled with the well-developed asymmetric hydrogenation of enamides,[13] could facilitate the synthesis of biologically interesting molecules such as fumonisins. We have also developed a very efficient method to prepare optically active BINOL ligands containing bulky 3,3′-substituents. These ligands are very useful for a number of asymmetric organic transformations including a Claisen rearrangement,[14a,b] an ene reaction[14c] and a radical substitution,[14d] in addition to the hetero-Diels–Alder reaction.

Table 1
The asymmetric hetero-Diels–Alder reaction of **3** and **4b** to form **6a** catalyzed by the complexes of (*R*)-**9a–e** and $AlMe_3$

Entry	Ligand	Solvent	Yield (%)	ee (%)[a]
1	(*R*)-**9a**	Et_2O	0	
2	(*R*)-**9a**	THF	0	
3	(*R*)-**9a**	Toluene	40	42
4	(*R*)-**9a**	CH_2Cl_2	50	45
5	(*R*)-**9b**	Toluene	40	46
6	(*R*)-**9b**	CH_2Cl_2	45	73
7	(*R*)-**9b**	CH_2Cl_2	20	78[b]
8	(*R*)-**9c**	CH_2Cl_2	35	46
9	(*R*)-**9d**	CH_2Cl_2	30	25
10	(*R*)-**9e**	CH_2Cl_2	60	44

a. The ee was determined on HPLC with a Chiracel OD column.[12] b. Catalyzed by 10 mol% of $AlMe_3$ + 11 mol% of (*R*)-**9b**.

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6. (a) Compound **5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (s, 1H), 7.29–7.54 (m, 10 H), 6.78 (d, J=10.2 Hz, 1H), 6.15 (d, J=10.2 Hz, 1H), 4.80 (d, J=17.4 Hz, 1H), 4.63 (d, J=17.4 Hz, 1H), 2.31–2.71 (m, 4H). (b) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807–7808.
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8. Following are the NMR data of a Mukaiyama aldol condensation product involved as an intermediate in the reaction of **3** with **4b**: ^{1}H NMR (300 Hz, $CDCl_3$) δ 7.60 (d, *J*=12.8 Hz, 1H), 7.30 (br s, 1H), 5.72 (br s, 1H), 5.57 (d, *J*=12.8 Hz, 1H), 4.62–4.68 (m, 2H), 3.71 (s, 3H), 2.58–2.85 (m, 2H), 2.08 (s, 3H), 0.13 (s, 9H).

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12. Characterization of **6a**: $[\alpha]_D$=−80.2 (*c*=0.5, THF). Enantiomeric excess: 73%, determined by HPLC (Chiralcel OD column. Eluent: hexane:isopropanol=75:25. Flow rate: 0.5 mL/min. Retention time: t^1_{major}=17.07 min, t^2_{minor}=19.9 min). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (d, 1H, *J*=6.2 Hz), 6.88 (br s, 1H), 5.90 (br s, 1H), 5.49 (d, 1H, *J*=6.2 Hz), 4.93 (dd, *J*=13.5, 3.6 Hz, 1H), 4.86 (br s, 1H), 2.58–2.85 (m, 2H), 2.13 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.4, 169.0, 161.8, 136.7, 107.9, 102.4, 79.6, 40.2, 24.5. MS (CI) m/e 182 ([M+1], 100), 164, 140, 123. The absolute configuration of **6a** is tentatively assigned to be *R* on the basis of Yamamoto's study.[9a,b]
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