

Asymmetric Hetero Diels-Alder Reaction of Chiral Imines with Danishefsky's Diene Catalyzed by $\text{Yb}(\text{OTf})_3$

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Reaction of chiral imines with Danishefsky's diene in the presence of a catalytic amount (20 mol%) of ytterbium triflate afforded the corresponding hetero Diels-Alder adducts with a moderate to good diastereoselectivity.

Keywords Hetero Diels-Alder, chiral imines, Danishefsky's diene, ytterbium triflate

Introduction

Piperidine ring is one of the most abundant molecular fragments in both natural products and synthetic compounds with biological activity.¹ For this reason, the development of methods for the asymmetric synthesis of homochiral piperidine building blocks has recently received considerable attentions.² The use of electron-rich butadiene derivatives such as Danishefsky's diene and the use of Lewis acids counteract the low reactivity of common deactivated imines. The diastereoselectivity of this reaction has been investigated with chiral Lewis acids.³ Nevertheless, to the best of our knowledge, there is no example in the literature about the hetero Diels-Alder cycloaddition reactions using lanthanide triflates as the Lewis acids.

On the other hand, lanthanides triflates are one of the strongest Lewis acids because of the electron-withdrawing trifluoromethanesulfonyl group. Moreover, it was stable in water and was easily recovered from aqueous layer after the reaction was completed, and could be reused. We have reported the smooth reaction of glyoxy-

lates with alkenes in the presence of ytterbium triflate,⁴ one pot synthesis of amino phosphonates from aldehydes using ytterbium triflate as the catalyst,⁵ catalytic synthesis of furo[3,2-*c*] and pyrano[3,2-*c*] quinolines by ytterbium triflate⁶ and lanthanide chloride,⁷ lanthanide triflate catalyzed Biginelli reaction, one-pot synthesis of dihydropyrimidiones under solvent-free conditions,⁸ addition of silyl ketene adducts to nitrones and [2+2] cycloaddition reactions of imines with alkynyl-selenides catalyzed by lanthanide triflates,^{9,10} as well as asymmetric hetero-Diels-Alder reaction of glyoxylate esters and Danishefsky's diene catalyzed by chiral bisoxazoline-lanthanide complexes.¹¹ Lanthanide compounds have strong affinity to coordination with imines, which could significantly increase the reactivity of imines with the Danishefsky's diene. Here we would like to report the results of hetero Diels-Alder reaction of chiral imines with Danishefsky's diene catalyzed by $\text{Yb}(\text{OTf})_3$.

Results and discussion

(*S*)- α -Methyl benzylimine (**1a**) can react with Danishefsky's dienes (**2**) in the presence of 20 mol% $\text{Ln}(\text{OTf})_3$ (Scheme 1). In all cases, the reaction proceeds smoothly to afford the desired products, which contain two isomers (**3** and **4**). Among the lanthanide triflate screened, $\text{La}(\text{OTf})_3$ and $\text{Sm}(\text{OTf})_3$ gave the best yields after 20 h at -78°C . However, $\text{Yb}(\text{OTf})_3$ exhibited a superior diastereoselectivity, although the yield of

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Scheme 1

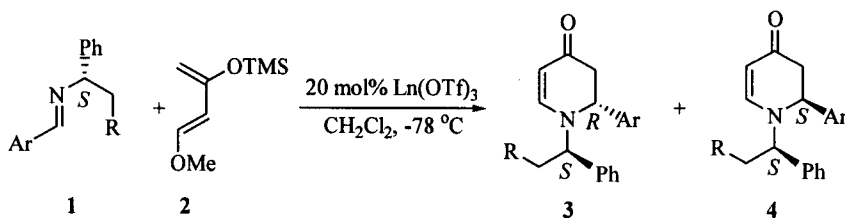


Table 1 Effect of catalyst, temperature and solvents on the hetero Diels-Alder reaction of chiral imines **1a** with Danishefsky's diene **2** in the presence of 20 mol% catalyst

Entry	Ln(OTf) ₃	Solvent	Temp. (°C)	Time (h)	3:4 ^a	Yield ^b (%)
1	La(OTf) ₃	CH ₂ Cl ₂	-78	20	79:21	90
2	Sm(OTf) ₃	CH ₂ Cl ₂	-78	20	79:21	90
3	Sc(OTf) ₃	CH ₂ Cl ₂	-78	20	76:24	58
4	Yb(OTf) ₃	CH ₂ Cl ₂	-78	8	89:11	50
5	Yb(OTf) ₃	CH ₂ Cl ₂	-45	8	87:13	56
6	Yb(OTf) ₃	CH ₂ Cl ₂	-23	8	77:23	70
7	Yb(OTf) ₃	CH ₂ Cl ₂	0	8	76:24	80
8	Yb(OTf) ₃	CH ₂ Cl ₂	rt	8	74:26	82
9	Yb(OTf) ₃	CH ₃ CN	-78	20	83:17	39
10	Yb(OTf) ₃	C ₆ H ₅ CH ₃	-78	20	80:20	34
11	Yb(OTf) ₃	THF	-78	20	87:13	39
12	Yb(OTf) ₃	Et ₂ O	-78	20	86:14	44

^aThe diastereomeric ratios were determined by ¹H-NMR; ^b The isolated yield.

adduct was lower than that of other lanthanide triflates (Table 1, entries 1, 2, 3, 4). Therefore, we selected Yb(OTf)₃ as the efficient catalyst for this reaction.

To optimize the catalytic hetero Diels-Alder reactions of chiral imines **1a** with Danishefsky's diene **2** using Yb(OTf)₃ as the catalyst, the influence of temperature and solvent was examined. Using dichloromethane as the solvent, a 89/11 diastereomeric mixture of the desired hetero Diels-Alder adducts **3** and **4** was obtained in about 50% isolated yield at -78 °C after 8 h (entry 4). The diastereoselectivity decreased with the raise of the reaction temperature, though the isolated yield was increased (entries 5–8). The effect of the solvent was also investigated (entries 9–12). When the reaction was carried out in acetonitrile, toluene or tetrahydrofuran, the yield and the diastereoselectivity were lower than those of in dichloromethane.

The diastereomeric ratios were determined directly from the product by ¹H NMR. The structure of **3** is known,^{3b} which was determined by X-ray analysis. Moreover, the diastereomeric isomers of **3** could be distinguished in the 300 MHz ¹H NMR spectra. The ¹H

NMR spectra of the main components of the adduct of (*S*)- α -methylbenzylimine and Danishefsky's diene catalyzed by Ln(OTf)₃ are the same as those of reported in the literature.^{3b} The plausible working model depicted in Fig. 1: (*S*)- α -methylbenzylimine has three kinds of possible conformations, among them, **a** is the most stable conformation. Danishefsky's diene attacked the imine from the *Re* face, therefore, the absolute configuration of the newly formed stereogenic carbon was ascertained to be (*R*).

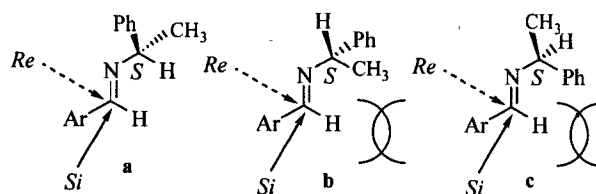


Fig. 1 Plausible working model.

Several chiral imines were examined and the results are summarized in Table 2. In all cases, the reaction proceeded smoothly in the dichloromethane at -78 °C to give the corresponding adducts with high diastereoselectivity and moderate isolated yields.

Experimental

¹H NMR spectra were recorded as CDCl₃ solutions on a VXL-300 instrument. Infrared spectra were recorded on a Perkin-Elmer 983 FT-IR spectrometer as liquid films on potassium bromide plates unless otherwise noted. Mass spectra were recorded on a HP5989A spectrometer and Elemental analysis was carried out on a MOD-1106 elemental analyzer.

A typical procedure for hetero Diels-Alder reactions of chiral imines and Danishefsky's diene catalyzed by Yb(OTf)₃

Yb(OTf)₃ (82 mg, 0.13 mmol) and imine **2** (138 mg, 0.66 mmol) were added into 2 mL of CH₂Cl₂ and

Table 2 Hetero Diels-Alder reactions of chiral imines **1a–f** with Danishefsky's diene **2** catalyzed by Yb(OTf)₃ (20 mol%)

Entry	Imines (Ar, R)	Time (h)	Adduct (3:4) ^a	Yield (%) ^b
1	1a (Ph, H)	8	3a, 4a (89:11)	50
2	1b (<i>p</i> -MeOC ₆ H ₄ , H)	20	3b, 4b (86:14)	52
3	1c (<i>o</i> -MeOC ₆ H ₄ , H)	20	3c, 4c (78:22)	73
4	1d (<i>p</i> -ClC ₆ H ₄ , H)	20	3d, 4d (85:15)	54
5	1e (PhCH=CH, H)	20	3e, 4e (84:16)	36
6	1f (<i>p</i> -ClC ₆ H ₄ , OCH ₃)	20	3f, 4e (93:7)	36

^aDiastereomeric ratios were determined by ¹H NMR; ^b isolated yield; at -78°C.

stirred for 30 min. After cooling the mixture to -78°C, Danishefsky's diene **1a** (136 mg, 0.79 mmol) was added. After stirring for 8 h at -78°C, the mixture of THF-water was added to quench the reaction, then 10 mL of EtOAc and 1 mL of water were added, the organic layer was separated, washed with saturated brine, dried with anhydrous sodium sulfate. Analytical pure products were then obtained (91 mg, overall yield 50%) by column chromatography. *de* values (78%) were determined by the ¹H NMR spectrum.

3a ¹H NMR (CDCl₃, 300 MHz) δ: 7.40—7.26 (m, 10H), 7.05 (d, *J* = 7.76 Hz, 1H), 5.04 (d, *J* = 7.76 Hz, 1H), 4.69 (dd, *J* = 6.62, 8.77 Hz, 1H), 4.47—4.40 (m, 1H), 2.82 (dd, *J* = 6.61, 16.36 Hz, 1H), 2.70 (dd, *J* = 8.79, 16.39 Hz, 1H), 1.46 (d, *J* = 6.87 Hz, 3H); IR (neat) ν: 3027, 2974, 1635, 1576, 1492, 1449, 1396, 1357, 1296, 1226, 1208, 1153, 1032, 765, 704 cm⁻¹; MS (70 eV) *m/z* (%): 277 (M⁺, 26.45), 262 (11.6), 249 (5.52), 173 (16.45), 105 (100); HRMS calcd. for C₁₉H₁₉NO 277.1468, found 277.1467.

4a ¹H NMR (CDCl₃, 300 MHz) δ: 7.61 (d, *J* = 7.78 Hz, 1H), 7.40—7.26 (m, 10H), 5.14 (d, *J* = 7.78 Hz, 1H), 4.47—4.40 (m, 1H), 4.29 (q, *J* = 7.02 Hz, 1H), 2.83 (dd, *J* = 7.28, 16.46 Hz, 1H), 2.61 (dd, *J* = 6.93, 16.46 Hz, 1H), 1.57 (d, *J* = 7.05 Hz, 3H); HRMS calcd. for C₁₉H₁₉NO 277.1468, found 277.1467.

3b ¹H NMR (CDCl₃, 300 MHz) δ: 7.56—7.22 (m, 7 H), 6.99 (d, *J* = 7.74 Hz, 1H), 6.89—6.86 (m, 2H), 5.00 (d, *J* = 7.74 Hz, 1H), 4.62 (dd, *J* = 6.73, 8.98 Hz, 1H), 4.40 (q, *J* = 6.86 Hz, 1H), 3.77 (s, 3H), 2.79—2.63 (m, 2H), 1.43 (d, *J* = 6.86 Hz, 3H); IR (neat) ν: 3058, 3029, 2970, 2835, 1635, 1576, 1508, 1449, 1300, 1251, 1209, 1182, 1153, 1035, 836, 703

cm⁻¹; MS (70 eV) *m/z* (%): 308 (M⁺ + 1, 16.97), 307 (45.71), 279 (9.35), 202 (14.53), 134 (37.13), 105 (100); HRMS calcd. for C₂₀H₂₁NO₂ 307.1572, found 307.1579.

3c ¹H NMR (CDCl₃, 300 MHz) δ: 7.37—7.15 (m, 7H), 7.09 (d, *J* = 7.63 Hz, 1H), 6.94—6.82 (m, 2H), 5.18 (t, *J* = 6.86 Hz, 1H), 4.95 (d, *J* = 7.63 Hz, 1H), 4.44 (q, *J* = 6.87 Hz, 1H), 3.80 (s, 3H), 2.79 (dd, *J* = 7.11, 16.45 Hz, 1H), 1.45 (d, *J* = 6.87 Hz, 3H); IR (neat) ν: 3029, 2972, 2837, 1635, 1576, 1489, 1458, 1390, 1292, 1246, 1109, 1054, 760, 704 cm⁻¹; MS (70 eV) *m/z* (%): 308 (M⁺ + 1, 15.31), 307 (M⁺, 34.59), 202 (20.04), 105 (100); HRMS calcd. for C₂₀H₂₁NO₂ 307.1572, found 307.1580.

3d ¹H NMR (CDCl₃, 300 MHz) δ: 7.40—7.24 (m, 9H), 7.09 (d, *J* = 7.73 Hz, 1H), 5.03 (d, *J* = 7.73 Hz, 1 H), 4.65 (m, 1H), 4.44 (q, *J* = 6.89 Hz, 1H), 2.82 (dd, *J* = 6.72, 16.37 Hz, 1H), 2.59 (dd, *J* = 7.50, 16.37 Hz, 1H), 1.46 (d, *J* = 6.89 Hz, 3H); IR (neat) ν: 3048, 2966, 1626, 1576, 1490, 1449, 1377, 1155, 1088, 1032, 908, 860, 783, 732, 700 cm⁻¹; MS (70 eV) *m/z* (%): 311 (M⁺, 13.25), 207 (7.16), 105 (100); HRMS calcd. for C₁₉H₁₈ClNO 311.1077, found 311.1083.

3e ¹H NMR (CDCl₃, 300 MHz) δ: 7.39—7.25 (m, 10H), 7.01 (d, *J* = 7.66 Hz, 1H), 6.56 (d, *J* = 15.86 Hz, 1H), 6.32 (dd, *J* = 8.10, 15.86 Hz, 1H), 4.99 (d, *J* = 7.66 Hz, 1H), 4.67 (q, *J* = 6.87 Hz, 1H), 4.27 (q, *J* = 6.34 Hz, 1H), 2.77 (dd, *J* = 6.34, 16.34 Hz, 1H), 2.47 (dd, *J* = 6.34, 16.34 Hz, 1H), 1.62 (d, *J* = 6.87 Hz, 1H); IR (neat) ν: 3025, 2973, 1634, 1576, 1495, 1449, 1390, 1278, 1249, 1224, 1154, 1031, 972, 755, 700 cm⁻¹; MS (70 eV) *m/z* (%): 303 (M⁺, 8.11), 275 (30.66), 198 (6.11), 105 (100); HRMS calcd. for C₂₁H₂₁NO 303.1623, found 303.1624.

3f ^1H NMR (CDCl_3 , 300 MHz) δ : 7.34—7.09 (m, 10H), 4.97 (d, $J = 7.72$ Hz, 1H), 4.75 (d, $J = 6.78$ Hz, 1H), 4.42 (dd, $J = 4.69$, 7.61 Hz, 1H), 3.71—3.65 (m, 2H), 3.24 (s, 3H), 2.83 (dd, $J = 7.15$, 16.30 Hz, 1H), 2.48 (dd, $J = 6.52$, 16.30 Hz, 1H); IR (neat) ν : 2894, 1637, 1583, 1489, 1410, 1299, 1231, 1105, 1017, 830, 735, 701 cm^{-1} ; MS (70 eV) m/z (%): 342 ($\text{M}^+ + 1$, 18.6), 341 (M^+ , 7.15), 298 (20.48), 296 (56.66), 158 (100), 134 (10.50), 103 (28.97).

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