

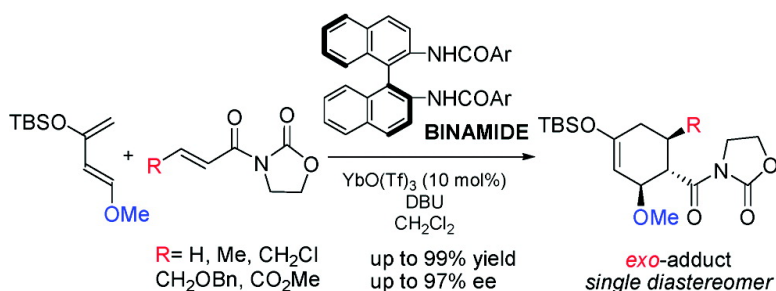
Communication

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Highly Enantioselective Diels–Alder Reactions of Danishefsky Type Dienes with Electron-Deficient Alkenes Catalyzed by Yb(III)-BINAMIDE Complexes

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1-Methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) **1a** was first introduced to organic synthesis by Danishefsky and Kitahara in 1974¹ and is recognized as a synthetically useful diene due to its high reactivity in the Diels–Alder (DA) reaction with electron-deficient alkenes to give oxygen-functionalized cyclohexenes.² Upon treatment with acids, the cycloadducts can be converted to substituted cyclohexenones, which are important building blocks for the total synthesis of natural products.^{3,4} However, the development of catalytic enantioselective versions of DA reactions through the use of Danishefsky type dienes with electron-deficient alkenes has been difficult because of the instability of the dienes under Lewis acidic conditions.^{5–7} Inokuchi et al. recently reported that lanthanide salts were effective catalysts for the DA reaction with Danishefsky's dienes.⁸ Based on their results, we surmised that chiral Yb(III)-BINAMIDE complexes, which are prepared from Yb(OTf)₃, BINAMIDE, and amines,⁹ may be effective catalysts for enantioselective DA reactions (Figure 1). We report here the highly diastereo- and enantioselective DA reaction of Danishefsky type dienes with electron-deficient alkenes in the presence of an Yb(III)-BINAMIDE complex.

We first investigated the asymmetric DA reaction of TBSoxydiene **1b** with dienophile **2a** (Scheme 1). In the presence of 10 mol% of the Yb(III)-BINAMIDE complex, prepared from Yb(OTf)₃, BINAMIDE **3b**, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a mixture of dienophile **2a** and diene **1b** (3 equiv) was stirred at 0 °C for 4 h to give cycloadduct **4a** as a single diastereomer quantitatively. The product was assigned to be an *exo* adduct based on the results of an extensive NMR study and X-ray analysis after chemical conversion.^{10,11} This diastereoselectivity is in sharp contrast to the original reaction with acrylate and also to Rawal's asymmetric DA reaction using 1-amino-3-siloxybutadienes catalyzed by Cr(III)-salen complexes, in which *endo* adducts are exclusively obtained.⁷ Acid treatment of **4a** gave substituted cyclohexenone **5a** quantitatively. The enantiomeric excess of **5a** was determined to be 91% ee by HPLC analysis.¹²

The effects of ligand modification on the DA reaction are summarized in Table 1. 4-Bromobenzoyl ligand **3b** showed higher reactivity and selectivity than unsubstituted benzoyl-type ligand **3a** (entry 1 vs 2). Ligands with electron-withdrawing groups at the 3-positions of the benzoyl moiety (**3c–e**) gave better results, and the enantiomeric excess was improved to 89% ee (entries 3–5). On the other hand, 2-bromobenzoyl ligand **3f** gave an almost racemic product (entry 6). Among the ligands tested, BINAMIDE ligands possessing two electron-withdrawing groups at the 3- and 5-positions of the benzene ring (**3g** and **3h**) gave excellent selectivities (up to 94% ee), even with a smaller amount of the diene (entries 7 and 8). Furthermore, in the case of 3,5-difluorobenzoyl ligand **3g**, both the reactivity and selectivity were maintained even when catalyst loading was decreased to 5 mol% (entry 9).

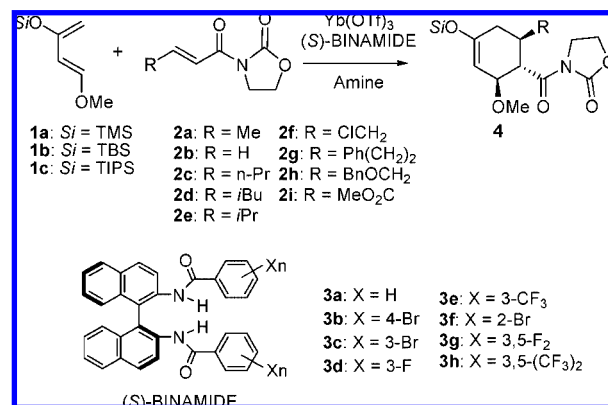
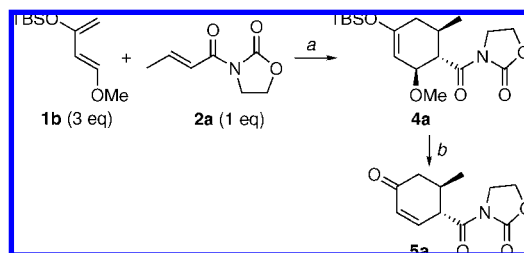


Figure 1. Asymmetric Diels–Alder reaction of Danishefsky type dienes catalyzed by an Yb(III)-BINAMIDE complex.

Scheme 1^{a, b}



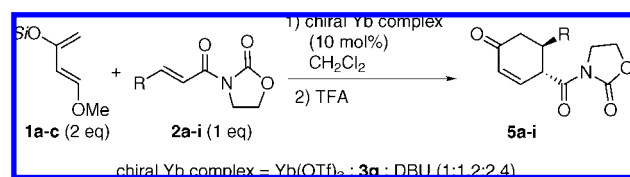
^a Chiral Yb complex [Yb(OTf)₃/**3b**/DBU = 1:1.2:2.4], 10 mol%, CH₂Cl₂, 0 °C, 4 h (98%). ^b TFA/ClCH₂CH₂Cl (1:50), 60 °C, 0.5 h (quant, 91% ee).

Table 1. Ligand Effect on Asymmetric Diels–Alder Reaction of Danishefsky Type Diene

entry	ligand	catalyst (mol%)	1b (equiv)	time (h)	5a ^a (%)	ee ^b (%)
1	3a	10	3	24	84	63
2	3b	10	3	4	98	91
3	3c	10	3	4	90	84
4	3d	10	3	4	quant	87
5	3e	10	3	4	quant	89
6	3f	10	3	24	48	2
7	3g	10	2	4	93	92
8	3h	10	2	4	quant	94
9	3g	5	2	5	94	94
10	3h	5	2	24	89	85

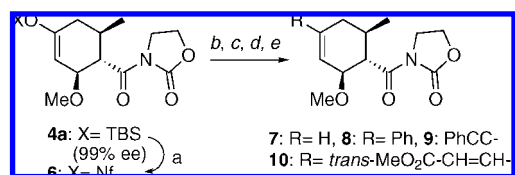
^a Yields of products after purification. ^b Determined by HPLC analysis.

Under these optimized conditions, asymmetric DA reactions by a combination of dienophiles **2a–i** with Danishefsky type dienes **1a–c** were tested. The results are summarized in Table 2. We first examined the effect of the size of the substituents R on the dienophiles (entries 2–8). In the reaction of acryloyl imide (R = H), enantioselectivity was lowered and diene **1c**, which has a large

Table 2. Scope and Limitations of Asymmetric Diels–Alder Reaction Using Danishefsky Type Diene

entry	dienophile	diene (Si)	temp (°C)	time (h)	product ^a (%)	ee ^b (%)
1 ^c	2a (R = Me)	1b (TBS)	0	5	5a (94)	94
2	2b (R = H)	1b (TBS)	0	4	5b (91)	45
3	2b (R = H)	1a (TMS)	0	3	5b (89)	41
4	2b (R = H)	1c (TIPS)	-20	3	5b (93)	71
5	2c (R = <i>n</i> -Pr)	1b (TBS)	rt	6	5c (93)	97
6	2d (R = <i>i</i> Bu)	1b (TBS)	rt	26	5d (43)	56
7	2d (R = <i>i</i> Bu)	1a (TMS)	rt	5	5d (88)	87
8	2e (R = <i>i</i> Pr)	1a (TMS)	rt	27	5e (29)	56
9	2f (R = ClCH ₂)	1b (TBS)	0	24	5f (79)	88
10	2g (R = Ph(CH ₂) ₂)	1b (TBS)	rt	4	5g (96)	94
11	2h (R = BnOCH ₂)	1b (TBS)	0	24	5h (97)	89
12 ^d	2i (R = MeO ₂ C)	1a (TMS)	0	2	5i (93)	92

^a Yields of products after purification. ^b Determined by HPLC analysis. ^c 5 mol% of the catalyst was used. ^d The elimination step was promoted by BF₃–OEt₂.

Scheme 2. a, b, c, d, e

^a F₃C(F₂C)₃SO₂F, *n*-Bu₄NSiPh₃F₂, CH₂Cl₂, 0 °C (83%). ^b Pd(PPh₃)₂Cl₂ (5 mol%), PPh₃ (5 mol%), formic acid, Et₃N, DMF, 65 °C (**7**: 88%). ^c Pd(PPh₃)₄ (2.5 mol%), PhB(OH)₂, aq. Na₂CO₃, DME, reflux (**8**: 86%). ^d Pd(PPh₃)₂Cl₂ (5 mol%), CuI (5 mol%), Et₃N, phenylacetylene, DMF, rt (**9**: 99%). ^e Pd(PPh₃)₂Cl₂ (5 mol%), methyl acrylate, Et₃N, DMF, 70 °C (**10**: 71%).

TIPS group, gave the best result (entry 4). In contrast, when the substituent was large (R = *i*Bu), diene **1a** which has a small TMS group, gave the best result (entry 7). The steric interactions between the substituent of the dienophile and the silyloxy group of the diene might be the reason for these results. However, sterically hindered isopropyl-substituted dienophile **2e** gave a poor result even when diene **1a** was used (entry 8). A variety of functional groups on the dienophiles **2f–g** (halogen, aromatic ring, ether, and ester) were tolerable and gave the desired cyclohexenones with good to excellent enantiomeric excesses (88–94% ee, entries 9–12).

The enantiomeric excess of cycloadduct **4a** was enriched from 91% ee to 99% ee by single recrystallization from *n*-hexane. Next, we turned our attention to the conversion of **4a** to the nonafluorobutanesulfonylation (nonaflate) **6**, which is a useful intermediate for various coupling reactions (Scheme 2). The fluorine-catalyzed nonafluorobutanesulfonylation¹³ of **4a** produced the corresponding nonaflate **6** in 83% yield. We then used **6** for various Pd-catalyzed couplings (Suzuki coupling, Sonogashira coupling, and Mizoroki–Heck reaction) and obtained desired products **8–10** in yields of 71–99%. Moreover, the nonaflate **6** could be reduced to alkene **7** by Pd-catalyzed hydrogenolysis.

In summary, we have developed a highly diastereo- and enantioselective DA reaction of Danishefsky type dienes with electron-deficient alkenes catalyzed by Yb(III)-BINAMIDE complexes. The reaction gives a variety of chiral cyclohexenes and cyclohexenones. Apparent (+)-nonlinear effects between asymmetric induction and the enantiomeric composition of BINAMIDE **3g** may suggest the possible formation of a reservoir of nonreactive aggregates.¹⁴ Further studies to elucidate the precise catalyst structure and to apply this reaction to the synthesis of biologically active compounds are in progress.¹⁵

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Supporting Information Available: Experimental details and ¹H and ¹³C NMR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (10) Determined by X-ray analysis of compound **7**. See Supporting Information.
- (11) When the reaction was carried out in the presence of 25 mol% of an achiral Yb(OTf)₃·iPr₂NEt complex, the *exo* adduct **4a** was obtained exclusively in 63% yield. Thus, the *exo* selectivity should originate from substrate control. Even when the reaction was carried out at 100 °C without any catalyst, a mixture of diastereoisomers was obtained (*exolendo* = 3:2). The presence of an oxazolidinone unit in the structure of dienophiles is essential for high enantiomeric induction. Results obtained using other chiral ligands with Yb(OTf)₃ are shown in the Supporting Information.
- (12) The absolute stereochemistry of **5b** was determined to be *4S* by comparison of the specific rotation of (*S*)-4-(hydroxymethyl)cyclohex-2-enone (**11**) with the reported value (ref 7). The absolute stereochemistries of **5a** and **5c–i** were estimated to be *4S* by analogy to **5b**. See Supporting Information for details.
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