Highly enantioselective Diels–Alder reaction of Danishefsky-type diene and electron-deficient olefins catalyzed by an Yb(III)/chiral bis-urea complex

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ABSTRACT

The synthesis and utility of the novel axially chiral bis-urea ligand BINUREA are described. A complex of this urea ligand with ytterbium triflate and DBU can be used in the catalytic enantioselective Diels–Alder reaction of Danishefsky-type diene and electron-deficient olefins to give the adducts in good to excellent yield and enantiomeric excess (ee).

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1. Introduction

Urea is a ubiquitous functional group in organic and inorganic chemistries, and has many uses. In the area of synthetic organic chemistry, (thio)ureas can be used as organocatalysts and have fascinated many scientists.[1] Such catalysis features the hydrogen bond-donating ability of the NH moiety to activate electrophiles.[2] This ability to act as hydrogen-bond donors enables (thio)ureas to function as anion-recognizing agents.[3] While these acidic properties of (thio)ureas are quite useful, ureas can also be used as a Lewis base for catalytic reactions.[4] Their coordinative nature shows that they can be very useful as a polar solvent and as an additive to metal catalysis.[5] In addition, thioureas have been shown to be efficient and air-stable ligands of transition metals.[6,7] However, there are few examples of the effective application of chiral ureas as ligands to metal-catalyzed asymmetric reactions.[8]

We recently reported the Yb(III)/BINAMIDE **1** complex, which catalyzed the asymmetric Diels–Alder reaction of electron-deficient olefins and 1-methoxy-3-trialkylsiloxy-1,3-butadienes **2** (Danishefsky-type dienes[9]).[10,11] Due to the instability of the dienes under acidic conditions, the Lewis acid-catalyzed Diels–Alder reaction using Danishefsky-type dienes had been quite difficult.[12] To overcome this problem, the use of lanthanide salts was the key to promoting the desired reaction, as first reported by Inokuchi's group.[13] Based on their results, we developed Yb(III)/BINAMIDE catalyst, which was prepared from Yb(OTf)$_3$, BINAMIDE **1a**, and DBU.[14] While the Diels–Alder reaction of several kinds of alkenes with Danishefsky-type dienes was efficiently facilitated by the catalyst to give the *exo* adduct, the scope of substrates was still unsatisfactory (Scheme 1). Therefore, further optimization of the catalyst was necessary.

Here, we report the synthesis of the new bis-urea ligand BINUREA and its application to the ytterbium(III)-catalyzed enantioselective Diels–Alder reaction of Danishefsky-type dienes with electron-deficient alkenes. We found that the new chiral bis-urea ligand led to good to excellent conversions and enantioselectivities in the Diels–Alder reaction, which were similar to or even higher than those with Yb(III)/BINAMIDE catalyst.

To develop new ligands with a urea functionality, we chose biphenyl and binaphthyl as backbones and chiral sources following the structure of BINAMIDE, and planned to synthesize them from optically active biphenyldiamine **6** and binaphthyldiamine **7** with isocyanates. However, a method for the synthesis of optically active biphenyldiamine **6** has not been established.[15] Thus, we first attached a chiral side-chain on urea expecting to separate each diastereomer after urea formation.

Commercially available chiral isocyanate **8** was stirred with (±)-biphenyldiamine[16] in dichloromethane at room temperature to give the desired bis-urea ligands in good yield. (*R*)-**9** and (*S*)-**9** were
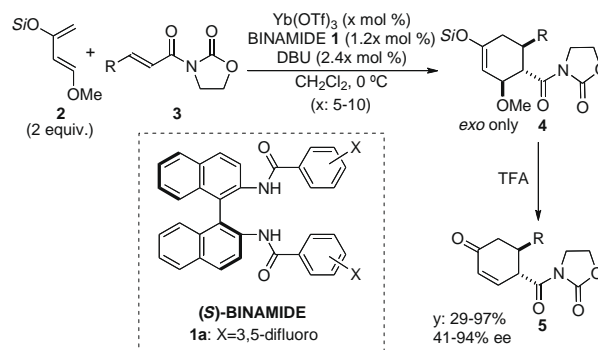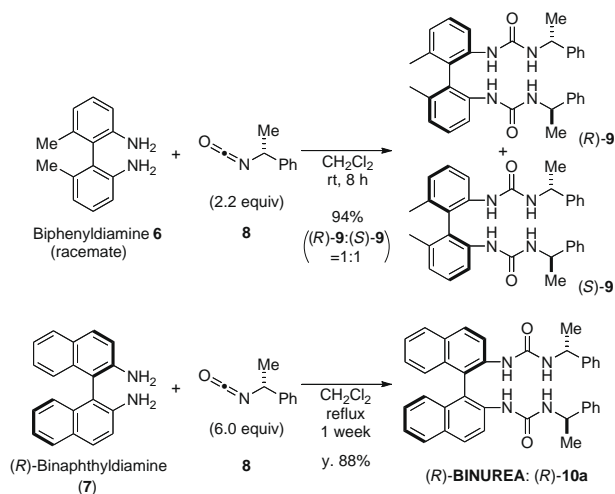

Scheme 1. Asymmetric Diels–Alder reaction of Danishefsky-type dienes catalyzed by Yb(III)/BINAMIDE complex.

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obtained in a 1:1 mixture (total 94% yield), and were easily separated by silica gel column chromatography (Scheme 2).[17] Starting from commercially available chiral (R)-binaphthyldiamine (7), ligand (R)-10a was synthesized. ((S)-10a was also prepared from (S)-diamine following the same procedure.)

We prepared other ligands with different substituents 10b–10e by the condensation of diamine and the corresponding isocyanates to study the effects of their structure on both the catalytic activity and selectivity in the ytterbium-catalyzed Diels–Alder reaction, and also synthesized thiourea derivatives 11a and 11b (Fig. 1).

As an initial screening, synthesized bis-urea ligand was used in the catalytic asymmetric Diels–Alder reaction of Danishefsky-type diene 2a and electron-deficient olefin 3a. The reaction using Yb(OTf)₃, ligand (R)-9, and DBU (1/1.2/2.4: best ratio in the Yb(III)/BINAMIDE/DBU system) proceeded sluggishly to afford the adduct 5a in 2% yield with low enantioselectivity (38% ee). (S)-9 showed a similar reactivity and selectivity (3% yield; 31% ee). For the binaphthyl derivatives (R)- and (S)-10a, matched and mismatched combinations were observed (Table 1, entries 3 and 4), but the results were better than those with their biphenyl derivatives (yields of 18% and 7%, respectively). In these entries, the absolute configuration of the products was regulated by the axial chirality of the ligands. We used the new bis-urea ligand (R)-10a as a tentative ligand, and precisely surveyed the reaction conditions. This catalyst system was quite sensitive to the relative ratio of each reagent, and both the reactivity and selectivity were dramatically affected. After an extensive investigation, the best ratio was found to be Yb(OTf)₃/(R)-10a/DBU = 1/1/2, as shown in entry 5 (99% yield; 98% ee).[18] Notably, Yb(OTf)₃ and each of the ligands were heated at 120 °C under reduced pressure (<0.1 mmHg) before use,[19] and cyclohexene product 4a was obtained as a single diastereomer in each case. The effects of the substituent on urea were

Table 1
Screening conditions

Entry	Ligand (x mol %)	DBU (y mol %)	Time (h)	Yield [a] (%)	% ee
1	(R)-9 (12)	24	4	2	38
2	(S)-9 (12)	24	4	3	−31
3	(R)-10a (12)	24	4	18	96
4	(S)-10a (12)	24	4	7	−91
5	(R)-10a (10)	20	2	99	98
6	(R)-10b (10)	20	3	22	39
7	(R)-10c (10)	20	3	93	94
8	(R)-10d (10)	20	3	20	14
9	(R)-10e (10)	20	3	45	96
10	(R)-11a (10)	20	3	37	27
11	(R)-11b (10)	20	3	46	37

[a] In all entries, cyclohexene adduct 4a was obtained as a single diastereomer.

then evaluated. Aromatic substituents (Ph: 10b) lowered both the reactivity and selectivity (entry 6). Benzyl 10c showed good reactivity and selectivity (entry 7), but did not give better results than α-methylbenzyl 10a. Interestingly, α,α-dimethylbenzyl 10d afforded an almost racemic product, and naphthyl derivative 10e resulted in modest yield. For thiourea analogues, both 11a and 11b resulted in low yields and ees. Among the ligands tested, an α-methylbenzyl side chain proved to be the most active and most selective.[20]

With the optimal reaction conditions in hand, the substrate generality was explored. First, the reaction of a variety of dienophiles with linear alkyl chains 3a–3e was examined. The reactions proceeded smoothly to afford the products in good to excellent yields (Table 2, entries 1–5). The enantioselectivities were all better than those with the Yb(III)/BINAMIDE 1a system. For substrates with a conjugated double bond (3f: entry 6) or chlorine atom (3g: entry 7), however, the reactions did not run to completion. The

Scheme 2. Synthesis of new axially chiral bis-urea ligands.

(R)-10b: R= Ph
(R)-10c: R= benzyl
(R)-10d: R= cumyl
(R)-10e: R= (Me, 1-naphthyl)

(R)-11a: R= Ph
(R)-11b: R= benzyl
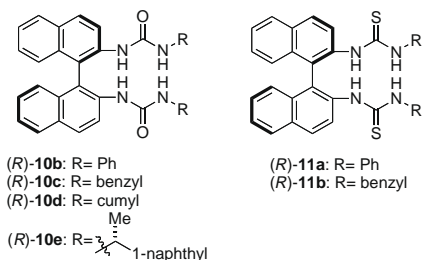
Figure 1. Synthesized BINUREA derivatives and their thiourea analogues.

Table 2
Substrate scope and limitations

Entry	R (substrate)	Product	Concd (M)	Yield [a,b] (%)	% ee [b]
1	Me (3a)	5a	0.2	99 (94)	98 (94)
2	n-Pr (3b)	5b	0.2	94 (93)	99 (97)
3	Ph(CH₂)₂ (3c)	5c	0.2	91 (96)	98 (94)
4	BnOCH₂ (3d)	5d	0.4	73 (97)	98 (89)
5	CH₂=CH(CH₂)₂ (3e)	5e	0.4	63	96
6	CH₃CH=CH (3f)	5f	0.2	8 (29)	98 (70)
7	ClCH₂ (3g)	5g	0.2	50 (79)	39 (88)
8	iPr (3h)	5h	0.6	84 (29)	98 (56)
9	iBu (3i)	5i	0.4	quant. (88)	97 (87)
10	Ph (3j)	5j	0.4	90 (26)	97 (60)
11	CO₂Me [c] (3k)	5k	0.2	93 (93)	79 (92)
12	CO₂Ph [c] (3l)	5l	0.2	88 (quant.)	86 (90)
13	H (3m)	5m	0.2	20 (93)	50 (71)
14	Cl (3n)	5n	0.2	<10 (0)	—

[a] In all entries, the corresponding cyclohexene adduct 4 was obtained as a single diastereomer.
[b] In the parentheses, the optimized data of BINAMIDE are shown.
[c] BF₃·OEt₂ was used in the second step at −78 °C, instead of TFA.

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reaction of dienophiles with branched alkyl chains **3h** and **3i**, and aromatic **3j**, for which the Yb(III)/BINAMIDE **1a** system was not effective (yield 29–88%; 56–87% ee), was dramatically optimized (entries 8–10). Every reaction took place efficiently in good to excellent yields (84%-quantitative yield) with a high level of enantioselectivity (97–98% ee). Concentrated reaction conditions shortened the reaction time without a loss of selectivity. Substrates with methoxy- (**3k**) and phenoxycarbonyl (**3l**) groups could also be used in this catalyst system, although the ees were slightly decreased (entries 11 and 12). In the case of acryloyl-type dienophile **3m**, the desired adduct was obtained in only 20% yield because the dimerization and oligomerization of **3m** were the predominant reactions. The reaction with chlorine-substituted dienophile **3n** also suffered from side reactions, and the reaction mixture turned black as the reaction proceeded.

These reaction products can be readily converted into stereoselectively substituted cyclohexenes or cyclohexenones in high yields according to methods established by our group.[10]

In summary, we have developed axially chiral BINUREA **10** as a new bis-urea ligand, which can be synthesized in a single operation from commercially available compounds. Yb(OTf)$_3$/BINUREA complex catalyzed the asymmetric Diels–Alder reactions of Danishefsky-type diene and electron-deficient olefins to give highly substituted cyclohexenes in optically active form. With BINUREA and BINAMIDE in hand, the Diels–Alder reaction can be applicable to a wide range of substrates. Further studies on this new catalyst system of BINUREA with other metals, and its application to different types of reactions, are now underway.

2. Experimental

2.1. General procedure for the Diels–Alder reaction of Yb(III)/BINUREA complex (2a and 3a to 5a via 4a)

Yb(OTf)$_3$ (18.6 mg, 30.0 μmol) and BINUREA (*R*)-**10a** (17.4 mg, 30.0 μmol) taken in a test tube with a stirring bar were heated at 120 °C under reduced pressure (<0.1 mmHg) for 30 min. After being allowed to cool to room temperature, the test tube was charged with dry argon. Dichloromethane (CH$_2$Cl$_2$) (1.0 mL) and DBU (9.0 μL, 60.0 μmol) were added successively, and the resulting solution was stirred for 2 h at room temperature. The reaction vessel was cooled to 0 °C and a solution of dienophile **3a** (46.6 mg, 0.30 mmol) in CH$_2$Cl$_2$ (0.50 mL) was added, followed by the addition of diene **2a** (150 μL, 0.60 mmol). The mixture was stirred for 3 h at the same temperature, and water (5.0 mL) was then added. Insoluble materials were filtered through a pad of Celite®. The water layer was extracted three times with CH$_2$Cl$_2$, and the combined organic layers were washed with brine and dried over Na$_2$SO$_4$. After the volatile materials were removed under reduced pressure, diastereoselectivity was checked by ^{1}H NMR (a single diastereomer). The crude product could be purified by column chromatography (SiO$_2$, hexane/AcOEt = 5/1) to give **4a** as a colorless oil, which was solidified upon standing.

The resulting crude mixture **4a** was dissolved in CH$_2$Cl$_2$ (3.0 mL), and TFA (0.3 mL) was added at 0 °C. After being stirred for 10 min at room temperature, the reaction was quenched by the addition of aqueous saturated NaHCO$_3$. The mixture was extracted three times with CH$_2$Cl$_2$, and the combined organic layers were washed with brine and dried over Na$_2$SO$_4$. After the volatile materials were removed under reduced pressure, the resulting residue was purified by column chromatography (SiO$_2$, hexane/AcOEt = 1/1) to give **5a** (66.5 mg, yield 99%) as a colorless solid. The enantiomeric excess was determined to be 98% ee by HPLC analysis (Daicel Chiralcel OJ-H, hexane/*i*PrOH = 65/35, f: 1.0 mL/min, 254 nm, 23.9 min (minor), 29.8 min (major)).

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18. For these optimized conditions with (*S*)-**10a** (10 mol %): 7% yield; −76% ee. (*S*)-**10a** was still mismatched ligand.

19. Without this operation, we did not obtain reproducible results. A precise mechanistic investigation is now underway.

20. For the reaction of **2a** and **3a**, (*R*)-**10c** has similar reactivity and selectivity to (*R*)-**10a**. But, for **2a** and **3h**, (*R*)-**10c** gave only 12% yield and 84% ee (0.6 M, 0 °C, 3 h).