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Catalytic, Asymmetric *trans*-Selective Hetero Diels–Alder Reactions Using a Chiral Zirconium Complex

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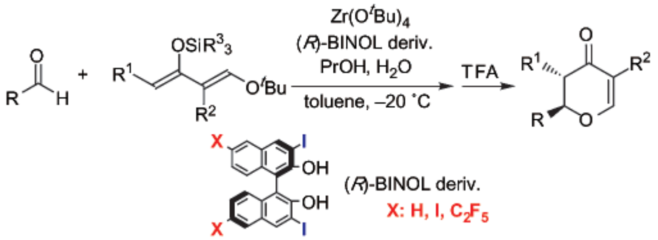
ABSTRACT



The first catalytic, asymmetric 2,3-*trans*-selective hetero Diels–Alder reaction has been developed. The reactions of aldehydes with Danishefsky's dienes proceeded smoothly to afford the pyranone derivatives in high yields with high *trans*-selectivities and enantioselectivities in the presence of a chiral zirconium complex, which was prepared from zirconium *tert*-butoxide and (*R*)-3,3′-diiodobinaphthol or its derivatives, primary alcohol, and a small amount of water. This reaction was applied to the concise synthesis of (+)-prelactone C.

Hetero Diels−Alder (HDA) reactions of aldehydes with 1-alkoxy-3-trialkylsilyloxy-1,3-butadiene (Danishefsky's diene) mediated by a chiral Lewis acid provide one of the most powerful synthetic tools to construct chiral 2,3-dihydro-4*H*-pyranone derivatives.[1] Recently, some effective chiral catalysts for HDA reactions have been developed and applied to the total synthesis of natural products.[2] However, the main products of the HDA reactions are 3-unsubstituted or 2,3-*cis*-disubstituted pyranone derivatives in most cases, and no catalyst system to afford *trans*-2,3-disubstituted products has been reported.[3] In this Letter, we report the first catalytic, asymmetric *trans*-selective HDA reactions of aldehydes using a chiral zirconium catalyst.

We have recently shown that several chiral zirconium complexes having 1,1′-bi-2-naphthol (BINOL) moieties are effective catalysts for asymmetric carbon−carbon bond-forming reactions such as Mannich reactions,[4] aza Diels−Alder reactions,[5] Strecker reactions,[6] allylation reactions,[7]

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[1] Reviews: (a) Danishefsky, S. J. *Chemtracts: Org. Chem.* **1989**, 273. (b) Danishefsky, S. J. *Aldrichimica Acta* **1986**, *19*, 59. (c) Boger, D. L. In *Comprehensive Organic Synthesis*; Trost B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 451. (d) Waldmann H. *Synthesis* **1994**, 535. (e) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558.

[2] For catalytic asymmetric HDA reactions of aldehydes involving Danishefsky's diene and its analogues, see: (a) Bednarski, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 3716. (b) Bednarski, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1986**, *108*, 7060. (c) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310. (d) Togni, A. *Organometallics* **1990**, *9*, 3106. (e) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907. (f) Gao, Q.; Ishihara, K.; Maruyama, T.; Mouri, M.; Yamamoto, H. *Tetrahedron*. **1994**, *50*, 979. (g) Keck, G. E.; Li, X.-Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998. (h) Matsukawa, S.; Mikami, K. *Tetrahedron: Asymmetry*. **1997**, *8*, 815. (i) Hanamoto, T.; Furuno, H.; Sugimoto, Y.; Inanaga, J. *Synlett* **1997**, 79. (j) Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403. (k) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398. (l) Simonsen, K. B.; Svenstrup, N.; Roberson, M.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 123. (m) Aikawa, K.; Irie, R.; Katsuki, T. *Tetrahedron* **2001**, *57*, 845. (n) Kezuka, S.; Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1333.

[3] *trans*-Selective HDA reactions of aldehydes mediated by achiral Lewis acids have been reported. (a) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246. (b) Mujica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *Tetrahedron* **1996**, *52*, 2167. *trans*-Selective catalytic asymmetric aza Diels−Alder reactions have been reported. (c) Yao, S.; Johannsen, M.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 3121.

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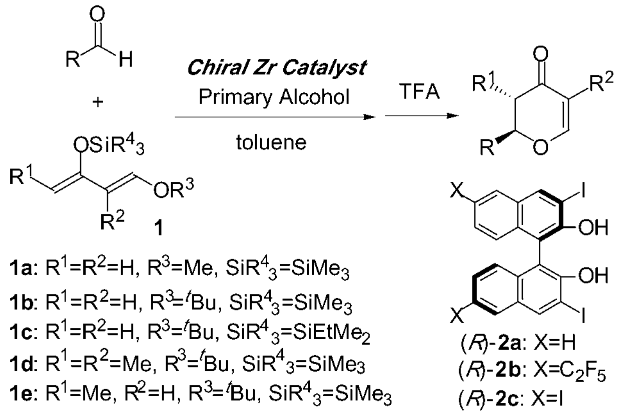
Mukaiyama aldol reactions,[8] etc. These reactions proceed in high yields with high selectivities, which are strongly dependent on the unique characteristics of the zirconium catalysts. We envisioned that these chiral zirconium catalysts were also effective for HDA reactions (Scheme 1).

Scheme 1



In an initial investigation, we employed a chiral zirconium catalyst prepared from Zr(O^{t}Bu)$_4$, (*R*)-3,3′-diiodo-1,1′-bi-2-naphthol ((*R*)-3,3′-I$_2$BINOL), *n*-propanol (PrOH), and water in a model HDA reaction of benzaldehyde with 1-methoxy-3-trimethylsiloxy-1,3-butadiene (**1a**) (Table 1). When the reaction was performed in toluene at 0 °C, the yield and enantioselectivity of the desired product were low (39% yield, 22% ee (Table 1, entry 1)). It was thought at this stage that methanol produced during the reaction might decompose the diene and also interact with the zirconium catalyst to decrease the yield and enantioselectivity. We then decided to use 1-*tert*-butoxy-3-trimethylsiloxy-1,3-butadiene (**1b**) instead of **1a**. It turned out that the yield and enantioselectivity were much improved and that the desired pyranone adduct was obtained in 50% yield with 91% ee (entry 2). When the reaction was carried out using 80 mol % of PrOH in toluene at −20 °C, the yield and enantioselectivity were further improved to 70% yield with 97% ee (entry 5). Further, when the more stable diene **1c** having an ethyldimethylsiloxy group was employed, the desired product was obtained in 80% yield with 97% ee (entry 7). We then tested other substrates of aldehydes and dienes under these conditions, and the results are summarized in Table 2, entries 1−5.

Table 1. Catalytic Asymmetric Hetero Diels−Alder Reactions of Benzaldehyde with Danishefsky's Dienes (**1**) Using a Chiral Zirconium Catalyst[a]

entry	diene	PrOH (mol %)	temp (°C)	yield (%)[b]	ee (%)
1	**1a**	50	0	39	22
2	**1b**	50	0	50	91
3	**1b**	80	0	65	94
4	**1b**	120	0	44	94
5	**1b**	80	−20	70	97
6	**1b**	80	−45	trace	
7	**1c**	80	−20	80	97

[a] All reactions were performed in the presence of 10 mol % of Zr catalyst. The catalyst was prepared from Zr(O^{t}Bu)$_4$ (10 mol %), (*R*)-3,3′-I$_2$BINOL (12 mol %), PrOH, and H$_2$O (20 mol %). The concentration of the reactions was 0.2 M. After the reaction, the crude products were treated with TFA to afford the desired adduct. [b] Isolated yield.

Table 2. Effect of Substrates[a]

entry	aldehyde	diene	BINOL	yield (%)[b]	*cis*/*trans*	ee (%)
1	PhCHO	**1c**	**2a**	80		97
2	4′-MeC$_6$H$_4$CHO	**1b**	**2a**	58		93
3	4′-ClC$_6$H$_4$CHO	**1b**	**2a**	65		84
4	PhCH$_2$CH$_2$CHO	**1c**	**2a**	84		90
5	CH$_3$(CH$_2$)$_4$CHO	**1c**	**2a**	69		91
6	PhCHO	**1d**	**2a**	trace		-
7	PhCHO	**1d**	**2b**	quant.	1/12	98[c]
8	4′-MeC$_6$H$_4$CHO	**1d**	**2b**	93	1/7	90[c]
9	4′ClC$_6$H$_4$CHO	**1d**	**2b**	99	1/9	97[c]
10[d]	(*E*)-PhCH═CHCHO	**1d**	**2b**	78	1/7	87[c]
11[e]	PhCH$_2$CH$_2$CHO	**1d**	**2c**	68	1/9	87[c]

[a] All reactions were performed in the presence of 10 mol % of catalyst at −20 °C for 18 h, unless otherwise noted. The concentration of the reactions was 0.2 M. [b] Isolated yield. [c] *trans*-Product. [d] −10 °C. [e] The reaction was performed for 48 h using PrOH (120 mol %) in higher concentration (0.5 M).

Aromatic as well as aliphatic aldehydes reacted with Danishefsky's dienes to afford the desired HDA adducts in good to high yields with high enantioselectivities. It is noted that a high level of stereocontrol was achieved even in the reactions of aliphatic aldehydes.

Next, we investigated the HDA reactions of 4-methyl-substituted Danishefsky's diene. 1-*tert*-Butoxy-2-methyl-3-trimethylsiloxy-1,3-pentadiene (**1d**) was prepared and subjected to reaction with benzaldehyde using the chiral zirconium catalyst having a (*R*)-3,3′-I$_2$BINOL moiety. Unfortunately, the reaction did not proceed in toluene at −20 °C. This result indicated that 4-substituted diene **1d** was less reactive than 4-unsubstituted dienes **1a**−**c**. We then focused on increasing the Lewis acidity of the zirconium catalyst and

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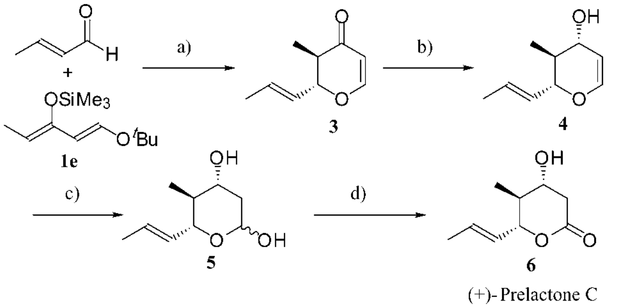
decided to introduce electron-withdrawing groups at the 6,6′ positions of BINOL derivatives. (*R*)-3,3′-Diiodo-6,6′-bispentafluoroethyl-1,1′-bi-2-naphthol ((*R*)-3,3′-I_2-6,6′-$(C_2F_5)_2$-BINOL) was chosen as a chiral ligand, and a chiral zirconium catalyst was prepared from $Zr(O^tBu)_4$, (*R*)-3,3′-I_2-6,6′-$(C_2F_5)_2$-BINOL, *n*-propanol (PrOH), and water. It was found that in the presence of a catalytic amount of this chiral zirconium catalyst, the reaction of benzaldehyde with **1d** proceeded smoothly to afford the desired HDA adduct quantitatively in toluene at −20 °C. Furthermore, the desired *trans*-adduct was obtained preferentially, and the enantiomeric excess of the *trans*-adduct was proven to be 98%. We examined reactions of other aldehydes including aromatic, α,β-unsaturated, and aliphatic aldehydes using this chiral zirconium catalyst. In all cases, the reactions proceeded smoothly to give the desired pyranone derivatives in high yields with high *trans*-selectivities, and the enantiomeric excesses of the *trans*-adducts were also high. It is noted that this is the first example of the catalytic asymmetric *trans*-selective HDA reaction of aldehydes.

Finally, to demonstrate the utility of this catalytic, asymmetric *trans*-selective HDA reaction, we performed the asymmetric synthesis of prelactone C[9,10] (Scheme 2). A key HDA reaction of crotonaldehyde with 1-*tert*-butoxy-3-trimethylsiloxy-1,3-pentadiene (**1e**) was performed under standard conditions using the chiral zirconium catalyst, to afford the desired pyranone derivative in 81% yield with good *trans*-selectivity (*trans*/*cis* = 6/1). The enantiomeric excess of the *trans*-adduct was 90% determined by HPLC analysis. After separation of the diastereomers, the *trans*-pyranone derivative was reduced using sodium borohydride in the presence of cerium chloride to give allylic alcohol **3** in excellent yield and diastereoselectivity.[11] The allylic alcohol (**3**) was then hydrated using acidic resins in the presence of water to produce lactol **4**,[12] which was oxidized selectively using the Fetizon reagent[13] to afford prelactone C in excellent yield. All physical data of the synthetic sample were consistent with those of the literature.[9,10]

Scheme 2. Short Synthesis of (+)-Prelactone C[a]



[a] Reaction conditions: (a) $Zr(O^tBu)_4$ (10 mol %), (*S*)-**2c** (15 mol %), PrOH (120 mol %), H_2O (20 mol %), toluene, −20 °C, 48 h, then $Sc(OTf)_3$ (10 mol %), CH_2Cl_2, r.t., 81% yield, *trans*/*cis* = 6/1, 90% ee (*trans*); (b) $NaBH_4$-$CeCl_3$, EtOH-CH_2Cl_2, −78 °C, 90%, ds = 96/4; (c) Dowex® 50W-X2, LiBr, H_2O, THF, 0 °C, 79%; (d) Ag_2CO_3-Celite®, benzene, reflux, 96%.

In summary, we have developed the first catalytic, asymmetric *trans*-selective HDA reaction of aldehydes. The highly stereoselective reaction was successfully applied to the concise synthesis of (+)-prelactone C. Further investigation to clarify a mechanistic aspect of this reaction is now in progress.

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Supporting Information Available: Experimental details and ^1H and ^{13}C NMR spectral data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Asymmetric total syntheses of (+)-prelactone C have already been reported. However, in every case, many reaction steps were required. (a) Esumi, T.; Fukuyama, H.; Oribe, R.; Kawazoe, K.; Iwabuchi, Y.; Irie, H.; Hatakeyama, S. *Tetrahedron Lett.* **1997**, *38*, 4823. (b) Chakraborty, T. K.; Tapadar, S. *Tetrahedron Lett.* **2001**, *42*, 1375.

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