Catalytic, Enantioselective Hetero-Diels–Alder Reaction with Novel, Chiral Bis-Titanium(IV) Catalyst

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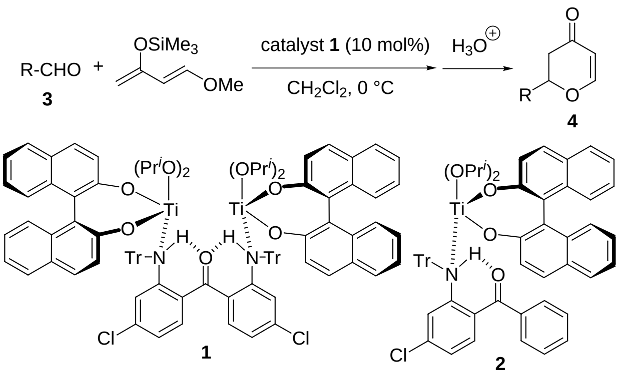
Abstract: Our recently designed chiral bis-titanium(IV) catalyst can be successfully utilized for the catalytic enantioselective hetero-Diels–Alder reaction of aldehyde and Danishefsky's diene. The high asymmetric induction is achievable in the case of sterically less hindered aldehydes.

Key words: hetero-Diels–Alder, asymmetric synthesis, catalyst, titanium(IV) complex

Our recent publication on the practical, catalytic enantioselective allylation of aldehydes with allyltributyltin in the presence of bis-titanium(IV) catalyst **1** prompted us to examine the possibility of its application to other catalytic enantioselective reactions.[1] Among several asymmetric reactions, our attention has been focused on a catalytic asymmetric cycloaddition. Herein, we wish to disclose the catalytic enantioselective hetero-Diels–Alder reaction of aldehyde and Danishefsky's diene by the aid of our recently designed chiral bis-titanium(IV) catalyst **1** as shown in Scheme 1.[2]

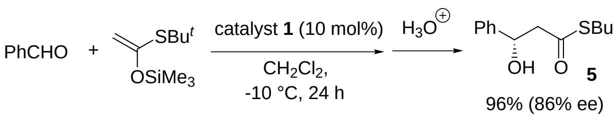


Scheme 1

The chiral bis-titanium(IV) catalyst **1** is prepared as described previously by simply mixing of 2,2′-bis(tritylamino)-4,4′-dichlorobenzophenone with Ti(*i*-PrO)$_4$ (2 equiv) in CH$_2$Cl$_2$ and subsequent treatment with (*S*)-binaphthol (2 equiv).[1a] Reaction of phenylpropargyl aldehyde **3** (R = C≡CPh) with Danishefsky's diene (1.2 equiv) under the influence of in situ generated chiral bis-Ti(IV) catalyst **1** (10 mol%) in CH$_2$Cl$_2$ proceeds smoothly at 0 °C for 5 h to furnish, after acidic hydrolysis, 2-(2-phenylethynyl)-2,3-dihydro-4*H*-pyran-4-one **4** (R = C≡CPh) in 78% yield with 98% ee.[3] It should be noted that the enantioselectivity of the hetero-Diels–Alder reaction is lowered (e.g., 83% ee for phenylpropargyl aldehyde **3** (R = C≡CPh)) under similar reaction condition with a chiral mono-Ti(IV) complex **2** derived from Ti(*i*-PrO)$_4$, (*S*)-binaphthol, and 4-chloro-2-(tritylamino)benzophenone as monodentate ligand (each 10 mol%).[4]

Other selected examples are listed in Table. Several characteristic features of the present hetero-Diels–Alder reaction are as follows: (1) In general, sterically less hindered aldehydes give rise to higher enantioselectivity compared to benzaldehyde and valeraldehyde (entries 5 and 6). (2) Both the reactivity and enantioselectivity of the hetero-Diels–Alder reaction are lowered under similar reaction condition with a chiral mono-Ti(IV) complex **2** [e.g., 29% and 60% ee for benzaldehyde **3** (R = Ph)]. (3) The steric hindrance of diene parts is not influential to the asymmetric induction. For example, switching of methoxy group of Danishefsky's diene to isopropoxy and *t*-butoxy groups gives similar enantioselectivity in the asymmetric hetero-Diels–Alder reaction of benzaldehyde: 43%, 76% ee; 50%, 71% ee, respectively.

The chiral bis-titanium(IV) catalyst **1** is also applicable to the asymmetric aldol reaction of aldehydes with ketene silyl thioacetal with fairly high enantioselectivity (Scheme 2).[5,6]



Scheme 2

Typical experimental procedure for the preparation of chiral bis-Ti(IV) catalyst 1 and the hetero-Diels–Alder reaction of aldehyde and Danishefsky's diene with chiral bis-Ti(IV) catalyst 1 is as follows:

A solution of 2,2′-bis(tritylamino)-4,4′-dichlorobenzophenone (76.6 mg, 0.1 mmol) in CD$_2$Cl$_2$ (2 mL) was carefully degassed and then treated with Ti(*i*-PrO)$_4$ (59 μL, 0.2 mmol) at room temperature under argon. After 1 h, (*S*)-binaphthol (57.3 mg, 0.2 mmol) was added at r.t., and the mixture was stirred there for 15 h. The solution was transferred by cannula to a 5-mm NMR tube, and the NMR spectra were taken at room temperature. This catalyst **1** contains in situ generated *i*-PrOH. ^{1}H NMR (CD$_2$Cl$_2$) δ 9.09 (2 H, s, NH), 7.96

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Table Asymmetric Hetero-Diels–Alder Reaction of Aldehydes and Danishefsky's Diene Catalyzed by Chiral Bis-Ti(IV) Complex **1**[a]

Entry	Aldehyde (R-CHO)	Condition (°C, h)	%Yield[b]	%ee[c] (Config.)
1	$PhCH_2CH_2CHO$	0, 3	77	97
2	$CH_3(CH_2)_4CHO$	0, 5	57	95 (*S*)[e]
3	$CH_3(CH_2)_6CHO$	0, 5	79	92
4	PhC≡CCHO	0, 3	78[d]	98
5	$CH_3(CH_2)_3C{\equiv}CCHO$	0, 7	45[d]	95
6	Ph-CHO	0, 3	64	71 (*S*)[e]
7	$(CH_3)_2CHCHO$	0, 5	60	64
8	$CH_3(CH_2)_3CH{=}CHCHO$	0, 5	58	69

[a] The hetero-Diels–Alder reaction of aldehyde and Danishefsky's diene (2 equiv) was carried out in the presence of chiral bis-Ti(IV) catalyst **1** (10 mol%) in CH_2Cl_2 under the given reaction conditions.
[b] Isolated yield.
[c] Determined by capillary GLC analysis using GL SCIENCE CP-CHIRASIL-DEX CB.
[d] Use of 1.2 equiv of Danishefsky's diene.
[e] See ref.[7]

(4 H, d, J = 8.1 Hz, binaphthyl-H), 7.60 (4 H, d, J = 8.7 Hz, binaphthyl-H), 6.89 (4 H, br s, binaphthyl-H), 6.51 (2 H, dd, J = 2.1, 8.4 Hz, benzophenone 5,5′-CH), 6.29 (2 H, d, J = 2.1 Hz, benzophenone 3,3′-CH), 4.51 [4 H, br s, $TiOCH(CH_3)_2$], 4.07 [4 H, br s, $HOCH(CH_3)_2$], 1.88 (4 H, s, *i*-PrOH), 1.19 [36 H, br d, J = 6.0 Hz, $TiOCHCH_3$ and $HOCH(CH_3)_2$], 1.17 (12 H, br d, J = 6.0 Hz, $TiOCHCH_3$); ^{13}C NMR (CD_2Cl_2) δ 199.46 (C=O), 158.79 (binaphthoxy C-O), 149.26 (benzophenone 2,2′-CN), 144.49, 138.00, 134.36, 132.90, 129.89, 128.70, 128.00, 126.94, 126.40, 125.29, 123.18, 121.02, 120.20, 118.18, 116.39, 114.92, 80.70 [Ti-$OCH(CH_3)_2$], 71.30 (CPh_3), 64.20 [$HOCH(CH_3)_2$], 24.86 [$CH(CH_3)_2$], 24.78 [$CH(CH_3)_2$]; IR (CH_2Cl_2) 3609, 3356, 2972, 1614, 1591, 1560, 1504, 1464, 1427, 1366, 1237, 1225, 1163, 1130, 1022, 1001, 951, 887, 818, 772 cm^{-1}.

A solution of 2,2′-bis(tritylamino)-4,4′-dichlorobenzophenone (38.3 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) was carefully degassed and then treated with Ti(*i*-PrO)$_4$ (30 μL, 0.1 mmol) at room temperature under argon. After 1 h, (*S*)-binaphthol (28.6 mg, 0.1 mmol) was added at room temperature, and the mixture was stirred there for 15 h. The solution was cooled to –15 °C, and treated sequentially with phenylpropargyl aldehyde (61 μL, 0.5 mmol) and Danishefsky's diene (117 μL, 0.6 mmol) at –15 °C. The whole mixture was allowed to warm to 0 °C and stirred there for 5 h. The reaction mixture was quenched by saturated $NaHCO_3$, extracted with CH_2Cl_2, and the organic extracts were dried over Na_2SO_4. After evaporation of solvents, the residual oil was diluted with THF (5 mL) and treated with aqueous 1 N HCl (1 mL) at 0 °C for 30 min. With usual work-up, the crude products were extracted with ether and the organic extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel (diethyl ether–hexane = 1:2) gave 2-(2-phenylethynyl)-2,3-dihydro-4*H*-pyran-4-one **4** (R = C≡CPh) as a colorless oil (77 mg, 78% yield). The enantiomeric purity of the product was determined to be 98% ee by capillary GLC analysis [GL SCIENCE CP-CHIRASIL-DEX CB, 80 kPa, column temp = 150 °C, t_R = 52.54 min, t_R = 54.63 min] in comparison with the racemic sample.

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(4) The hetero-Diels–Alder reaction of phenylpropargyl aldehyde **3** (R = C≡ CPh) proceeded smoothly with a chiral mono-Ti(IV) complex **2** (10 mol%) to give adduct **4** (R = C≡ CPh) in 47% yield. In contrast, however, the reactivity of the hetero-Diels–Alder reaction of benzaldehyde **3** (R = Ph) are lowered (e.g., 29% yield) under similar reaction condition with a chiral mono-Ti(IV) **2** (10 mol%).

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