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Chiral Titanium Complex-Catalyzed Diels-Alder Reaction: A Practical Route to Anthracycline Intermediates

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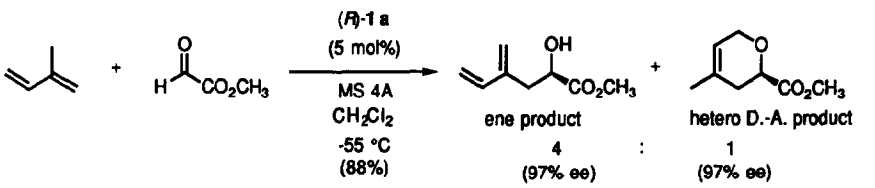
Abstract: Asymmetric Diels-Alder reactions of methacrolein and 1,4-naphthoquinone with 1,3-dienol derivatives catalyzed by the chiral binaphthol (BINOL)-derived titanium complex **1** are shown to provide the corresponding *endo*-adducts in high enantiomeric purity. The naphthoquinone adduct can serve as a synthetic intermediate of tetracycline antibiotics.

The development of asymmetric catalysis, particularly for carbon-carbon bond formations, is one of the most challenging and formidable endeavors in organic synthesis.[1] Recently we have reported the enantioselective carbonyl-ene reaction[2] and hetero-Diels-Alder reaction[3] with methyl glyoxylate catalyzed by the chiral titanium complex of type (*R*)-**1** prepared *in situ* from $(i\text{-PrO})_2TiX_2$ and optically pure binaphthol (BINOL) in the presence of molecular sieves (MS 4A) (eq 1).[4,5] Herein we report that the chiral BINOL-derived titanium catalyst **1** is also effective for the enantioselective Diels-Alder reaction.



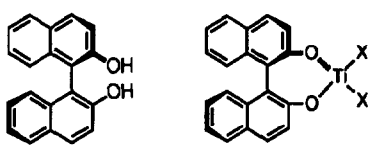


Table 1 summarizes the results of the Diels-Alder reaction of methacrolein (**3**) with 1,3-dienol derivatives (**2a-c**). The BINOL-derived titanium complex **1** was prepared as previously reported for the glyoxylate-ene reactions.[4a] To a solution of (*R*)-**1a** (0.1 mmol) in CH_2Cl_2 (3 mL) in the presence of MS 4A was added methacrolein (**3**) (2.0 mmol) and butadienyl carbamate (**2a**)[6] (1.0 mmol) at 0 °C. After stirring for 58 h at that

temperature, the solution was poured into sat. $NaHCO_3$. The molecular sieves were filtered off through Celite and usual work up followed by silica gel chromatography gave the adduct **4a** in 82% yield (86% ee, 99.6% *endo*). Thus, the chiral titanium complex **1a** was found to be an efficient asymmetric catalyst for the Diels-Alder reaction to afford exclusively the *endo*-adduct **4a**[7] with high enantioselectivity (entry 2). The absolute configuration of the *endo*-adduct **4a** was determined to be 1*S*,2*R* after reduction ($LiAlH_4$, Et_2O, 0 °C, 69%; then H_2, 5% Pd/C, EtOH, room temperature, 99%) to the known diol **6**: $[\alpha]_D^{23}$ +14.8 (c 2.95, $CHCl_3$); lit.[8] (1*S*, 2*S*)-**6**: $[\alpha]_D^{20}$ +3 (c 1, CH_2Cl_2) (20% ee). Thus, the sense of asymmetric induction (2*R*) by (*R*)-**1** is exactly the same as observed for the glyoxylate-ene[4] and hetero-Diels-Alder reaction.[5] The use of methyl ether **2b**, in spite of its higher reactivity, led to the lower chemical yield due to the unstability of **2b** under the acidic conditions (entry 3). The acetate **2c** provides the comparably high levels of *endo*- and enantioselectivity (entries 1 vs. 4). There is little solvent effect observed in the present reaction with both dienes (**2a** and **2c**) (entries 5-7), in sharp contrast to the dramatic solvent effect in the reaction of α,β-unsaturated acyloxazolidinones catalyzed by a chiral tartrate-derived titanium complex.[3c] The dibromo catalyst **1b** affords a slightly lower *endo*- and enantioselectivity (entry 8). A notable feature of the present catalytic process is that a simple α,β-enal can be used as a dienophile to give high *endo*- and enantioselectivities.

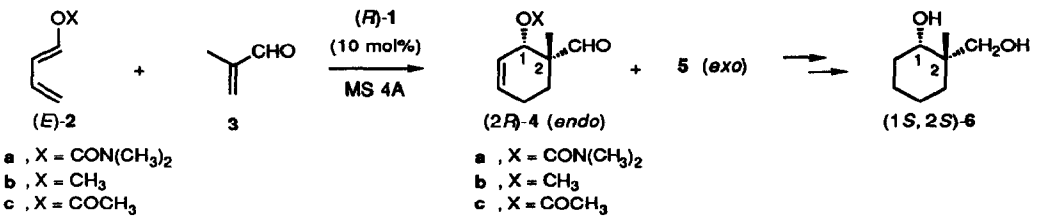


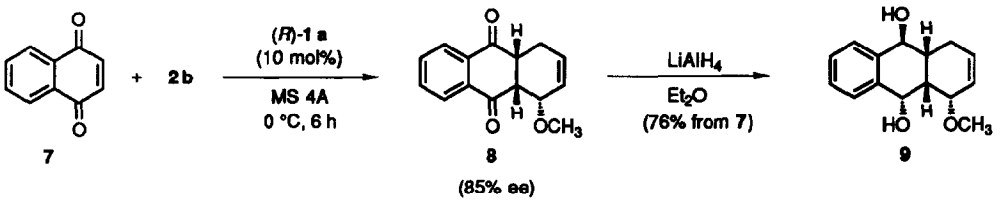
Table 1. Asymmetric Diels-Alder reaction catalyzed by the chiral titanium complex (1).

entry	catalyst	2	solvent	condition	yield (%)	*endo* / *exo*[a]	% ee[b]
1	1a	2a	CH_2Cl_2	r.t., 13 h	71	99 / 1	82
2	1a	2a	CH_2Cl_2	0 °C, 58 h	82	99.6 / 0.4	86
3	1a	2b	CH_2Cl_2	-30 °C, 5 h	43	87 / 13	71
4	1a	2c	CH_2Cl_2	r.t., 18 h	69	97 / 3	78
5	1a	2c	toluene	r.t., 18 h	81	98 / 2	80
6	1a	2a	toluene	0 °C, 48 h	80	99.4 / 0.6	85
7	1a	2a	CH_2Cl_2 - $CF_2ClCFCl_2$ (1 : 1)	0 °C, 48 h	67	99.5 / 0.5	85
8	1b	2a	CH_2Cl_2	0 °C, 58 h	80	99 / 1	80

[a] The *endo* / *exo* ratio was determined by ^1H NMR analysis (see: ref. 7). [b] Determined by LIS-NMR analysis using Eu(hfc)$_3$ as a chiral shift reagent.

The observed sense of enantioselection provides a mechanistic insight into the state of complexation between the chiral titanium catalyst (*R*)-**1** and the enal **3**. Since the enal **3** possesses the *transoid* conformation[9] and the titanium catalyst **1** should be complexed in an *anti* fashion,[9b] the reaction could occur on the *transoid-anti* complex of **1** and **3**, just like the carbonyl-ene[4] and hetero-D.-A. reaction[5] with glyoxylate. Thus, these observations reveal that the BINOL-derived titanium catalyst **1** is effective for the π-facial selection not only over the complexed formyl group of glyoxylate but also over the olefinic group attached to the complexed formyl group of enal.

Asymmetric catalytic Diels-Alder reaction of naphthoquinone derivatives as the dienophile is one of the most efficient entry to the asymmetric synthesis of anthracyclinone aglycones.[10,11] The reaction of naphthoquinone **7** with **2b** catalyzed by (*R*)-**1a** was found to provide the chiral adduct **8** with complete *endo*-selectivity.[12] The adduct was transformed stereoselectively to the more stable derivative **9** with $LiAlH_4$ in Et_2O. The optical purity of the adduct **8** was determined to be 85% ee by 500-MHz ^1H NMR analysis of the (*S*)-MTPA diester of **9**. Thus, the present catalytic process provides a potential entry to the asymmetric synthesis of anthracycline antibiotics.



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