Effects of Torsional Angles of 2,2'-Biaryldiol Ligands in Asymmetric Diels-Alder Reactions of Acrylates Catalyzed by Their Titanium Complexes

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Abstract In the asymmetric Diels-Alder reaction of acrylates with cyclopentadiene catalyzed by a series of chiral titanium complexes derived from 2,2'-biaryldiols 1-3, ee's of the *endo*-adducts depend on the torsional angles of the ligands and are maximal when 1,1'-bi-2-naphthol 1 or 6,6'-hexylenedioxy-2,2'-biphenyldiol 2 e is used. Copyright © 1996 Published by Elsevier Science Ltd

Complexes of 2,2'-biaryldiols with Lewis acids, in particular those of 1,1'-bi-2-naphthol 1, have been applied as catalysts for a number of useful enantioselective reactions.[1] Recently, attention has been focused on improvement of their performance by modification of a parent structure. Successful results have been reported by increasing the asymmetry around the hydroxy groups via introduction of substituents at the adjacent positions.[2] Although a torsional angle between the arene rings is another important geometric factor that determines the asymmetry associated with the chiral axis, the effects have not been studied systematically.[3]

Recently, we reported a general method for asymmetric synthesis of 6,6'-disubstituted 2,2'-biphenyldiols 2 and 3 whose torsional angles are controlled respectively by the alkylenedioxy bridges and by a size and shape of substituents at the 6 and 6' positions.[4] Reported herein are studies on the Diels-Alder reaction of acrylates catalyzed by chiral titanium complexes derived from a series of 2,2'-biaryldiols 1-3. Although the catalytic asymmetric Diels-Alder reaction using α,β-unsaturated aldehydes and oxazolidinones as dienophiles has been studied extensively, relatively few examples are known for the reactions of α,β-unsaturated esters.[2,5] The results of the present study reveal an effect of the torsional angles on the enantioselectivity of catalytic asymmetric Diels-Alder reactions of acrylates.
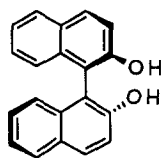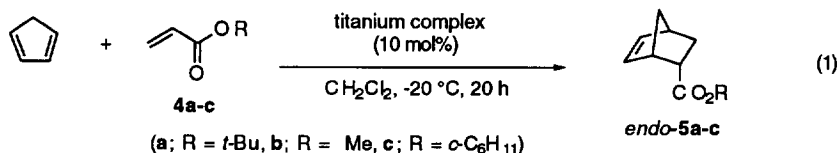

(R)-1
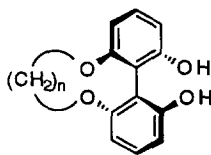
(S)-2a; n = 3
(S)-2b; n = 4
(S)-2c; n = 5
(S)-2d; n = 6
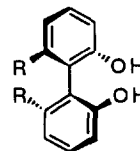
(S)-3a; R = PhO
(S)-3b; R = Me
(S)-3c; R = Et
(S)-3d; R = Octyl
(S)-3e; R = Ph

Titanium complexes were prepared by the reaction of dilithium salts of 2,2'-biaryldiols 1-3 and $TiCl_4$ in CH_2Cl_2. Reactions of acrylates 4a-c and cyclopentadiene (5 equiv) were carried out in CH_2Cl_2 (1.0 M) at -20 °C by using 10 mol% of the titanium complexes as catalysts (Table I). All reactions were performed for 20 h in order to gain information on the catalytic activities of the complexes. The absolute configuration of *endo*-5b was determined by comparison of the specific rotation with a literature reference.[6] The configuration of *endo*-5a and *endo*-5c were determined by reducing ($LiAlH_4$) them to the known *endo*-(5-norbornen-2-yl)methanol.[7]

Of the three dienophiles examined, 4a (R = *t*-Bu) invariably showed higher enantioselectivities while the reactivity was generally lower than that of 4b (R = Me). The sense of the enantioselectivity was constant for all ligands examined; the catalyst derived from (S)- and (R)-ligands gave rise to the preferential formation of (S)- and (R)-*endo*-5a-c, respectively. On the other hand, the degree of the selectivity varied considerably depending on the structures of the ligands. Thus, for a series of ligands 2a-d, ee of *endo*-5a increased with the length of the alkylenedioxy bridges (entries 2-5). For ligands 3a-d, the enantioselectivity decreased with bulkiness of the C-6, 6' substituents (entries 6-10). The highest ee of 77% was obtained when hexylenedioxy bridged ligand 2d was used in the reaction of 4a (entry 5).

A titanium complex prepared by the exchange reaction of (R)-1 and $TiCl_2(iso\text{-}PrO)_2$ in the presence of molecular sieves 4A[8] did not catalyze the reaction of acrylate 4a appreciably under the present reaction conditions. This is probably due to the preferential coordination of *iso*-PrOH liberated in the preparation of the complex. The reaction of 4a using the titanium complex prepared via the dilithium salt of (R)-1 was retarded by the addition of *iso*-PrOH (0.2 equiv), affording (R)-*endo*-5a (48% ee) in 22% yield.

Table I Asymmetric Diels-Alder Reaction of Acrylates and Cyclopentadiene Catalyzed by Titanium Complexes [a]

	dienophile	4a			4b			4c			
entry	ligand	yield[b]	ee[c]	ratio[d]	yield[b]	ee[c]	ratio[d]	yield[b]	ee[c]	ratio[d]	torsional angle ω[e]
1	(R)-1	98	69 (R)	95	96	53 (R)	37	92	38 (R)	32	61.5
2	(S)-2a	39	29 (S)	55	70	32 (S)	22	34	10 (S)	14	55.9
3	(S)-2b	57	65 (S)	41							58.6
4	(S)-2c	55	70 (S)	31	57	43 (S)	24	46	27 (S)	22	57.7
5	(S)-2d	78	77 (S)	40	83	45 (S)	28	100	35 (S)	25	60.2
6	(S)-3a	91	62 (S)	31							61.2
7	(S)-3b	91	47 (S)	37							64.5
8	(S)-3c	90	30 (S)	30	99	26 (S)	21	47	28 (S)	22	66.2
9	(S)-3d	97	28 (S)	31							-
10	(S)-3e	96	32 (S)	38							65.8

[a] Reactions were carried out in CH_2Cl_2 (1.0 M) for 20 h by using 10 mol% of titanium complexes and 5.0 equiv of cyclopentadiene at -20 °C for 20 h. [b] GC yield. [c] Determined by GC analysis by using a CP-Cyclodextrin-B-236-M-19 (25 m) column. [d] The *endo/exo* ratio was determined by a capillary GC analysis. [e] The calculated torsional angle ω (C_2-C_1-C_1'-C_2') of complex 6 in degree.

In order to analyze the observed enantioselectivities in terms of the biaryl torsional angles, we carried out a semiempirical MO (MNDO)[9] calculation for model aluminum complexes 6.[10] The choice of an aluminum as a metal atom is arbitrary and is due mainly to the availability of the reliable parameters for the atom. Although precise structures of the catalyst titanium complexes are uncertain (*vide infra*), the calculation provided us at least qualitative information on their torsional angles. The calculated values of the torsional angles ω (C_2-C_1-$C_{1'}$-$C_{2'}$) increase in the order of 2a, 2c, 2b, and 2d (Table I). The values also increase with the bulkiness of the C-6,6' substituents for ligands 3a-e. A torsional angle of 61.5 deg in the 1-derived complex is slightly larger than that of the 2d-derived complex but is smaller than that of the 3b-derived complex.
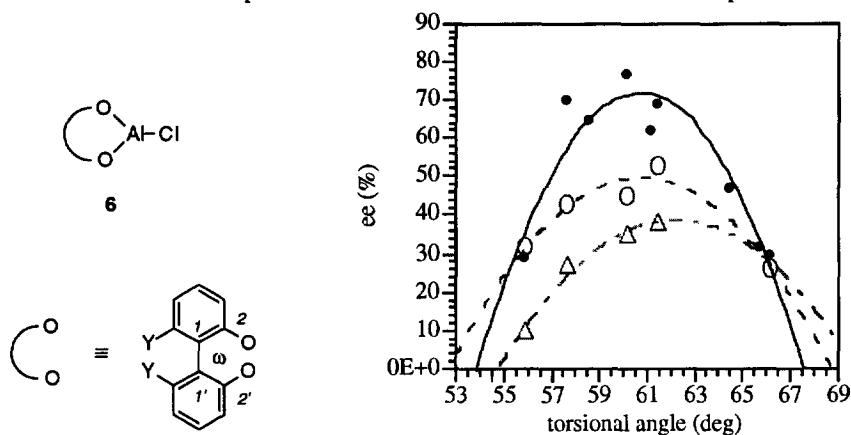

Figure 1. Plot of ee of *endo*-5a-c versus the calculated torsional angle ω of model complex 6; (●) 4a; (O) 4b; (△) 4c.

A characteristic trend in the enantioselectivities emerged from the calculated torsional angles. As the torsional angles increase, the product ee's increase first, reach a maximum when 1 or 2e is used as a ligand, and fall off as the further increase of the torsional angles (Figure 1). The trend was observed not only for 4a but also for 4b and 4c (R = c-C_6H_{11}) while, in these reactions, the enantioselectivity was lower than that of the former.

Recent studies on solid state and solution structures of titanium complexes derived from 2,2'-biaryldiols revealed their structural diversity.[12] Four distinct structural types, mono-nuclear complexes 7, dinuclear complexes 8, 9, and, trinuclear complexes 10, have been characterized. Based on their structural studies, Boyle and his coworkers showed that more sterically demanding ligands, *i.e.*, ligands with bulky substituents adjacent to the hydroxy group, favor the lower nuclearity complexes.[13] An effect of electronegative substituents which favor 14-membered ring-complex 9 has been pointed out by Corey et al..[14] Titanium complexes derived from 2 and 3 most probably exist as their dinuclear species 8 or trinuclear species 10 because these ligands are relatively less sterically demanding and an electronic effect of the alkoxy substituents meta to the hydroxy

X = Cl, *iso*-PrO
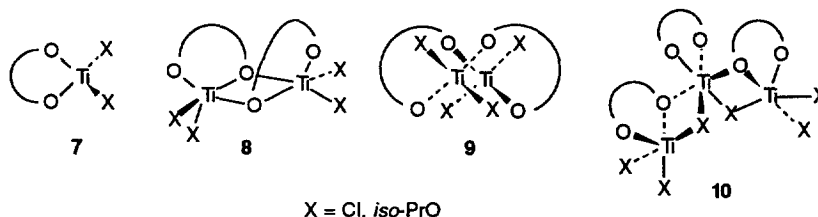
groups in **2** might be negligibly small.[15] Therefore, it is less likely that the observed trend in ee is the result of the change in their aggregation structures. Rather, the trend originates from the variation of asymmetry associated with the chiral axis.

The present study shows that the enantioselectivity of the Diels-Alder reactions is very sensitive to the biaryl torsional angles of the catalyst complexes. Although the degree of the selectivity depends on the structures of acrylates, the ee trend and optimal torsional angles are not affected by their structures. These results provide valuable information on the transition state structure of the acrylate Diels-Alder reaction and molecular design of efficient catalyst complexes.

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