

# Homogeneous Catalysis: Use of Chiral Titanocene Complexes for Asymmetric Catalytic Diels–Alder Reactions

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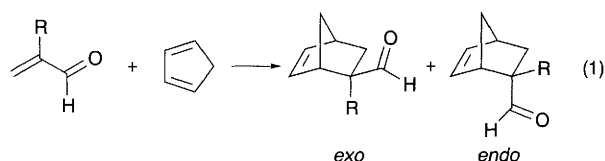
A stable, chiral diaquo titanocene complex is an excellent catalyst for certain Diels–Alder reactions giving good enantioselectivity which indicates that catalysis occurs by metal rather than by proton activation of the dienophile.

The development of structurally defined, air stable and water tolerant transition metal based Lewis acid catalysts is likely to provide a convenient and rational approach to understanding stereochemical transformations promoted by these systems.<sup>1</sup> Such species obviate many of the inherent inconveniences and structural complexities of classical Lewis acids which include water sensitivity and a propensity to oligomerization and to ligand redistribution. We recently reported that the complexes, [Ru(salen)(NO)(H<sub>2</sub>O)]SbF<sub>6</sub><sup>2</sup> and [Ti(η<sup>5</sup>-C<sub>5</sub>Me<sub>5</sub>)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>](OTf)<sub>2</sub><sup>3</sup> (salen = *N,N'*-bis(salicylidene)ethylenediamine, OTf = CF<sub>3</sub>SO<sub>3</sub><sup>-</sup>), were excellent catalysts for certain Diels–Alder reactions. These structurally defined Lewis acids operate at low catalyst loadings (1–2 mol%) and are stable to and function in the presence of water. It was demonstrated for the ruthenium complex that the aquo ligand is readily displaced by the dienophile and similar metal coordination was assumed for the titanium complex. This metal binding is believed to serve in activating the dienophile to reaction. Although arguments<sup>2,3</sup> were presented which supported the exclusion of proton catalysis, it seems necessary to establish the existence of the metal-based path particularly since these titanium aquo complexes are known to be acidic.<sup>4</sup> Perhaps the most unambiguous means of resolving this issue is to demonstrate that aquo complexes of this type can produce high enantioselectivity for the Diels–Alder reaction. Our recent synthesis of the complex, [Ti{(S)-biphenacene}(Cl)<sub>2</sub>]<sup>5</sup> **1** provides such a possibility.

Reaction of **1** in dichloromethane solution with 2 equiv. of AgOTf leads to the formation of the air-stable, green diaquo complex, [Ti{(S)-biphenacene}(H<sub>2</sub>O)<sub>2</sub>](OTf)<sub>2</sub> which was characterized by <sup>1</sup>H and <sup>19</sup>F NMR spectroscopy in dichloromethane solution and by elemental analysis. In dichloromethane solutions the NMR spectrum is complex and varies with temperature. It indicates the existence of rapid equilibration between the diaquo, aquo–triflate and bis-triflate complexes with the first of these species predominating at –78 °C. Thus at 20 °C a broad <sup>19</sup>F NMR signal of OTf ion is observed which at temperatures of and below –10 °C becomes sharp (δ –78.6). The chemical shift of this <sup>19</sup>F NMR resonance is the same as that found for Bu<sub>4</sub>NOTf in dichloromethane.

When dissolved in dichloromethane the [Ti{(S)-biphenacene}(H<sub>2</sub>O)<sub>2</sub>](OTf)<sub>2</sub> complex catalyses Diels–Alder reactions between α,β-unsaturated aldehydes and ketones with a variety of cyclic and acyclic dienes. These reactions occur rapidly and cleanly at 25 °C with 1 mol% of catalyst. The rate of catalysis is retarded when steric hindrance is present in the diene and dienophile and no catalysis occurs with dienophile esters even with intrinsically reactive dienes.

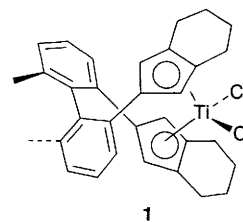
The enantioselectivity of the Diels–Alder reactions depicted in eqn. (1) was investigated. Some of the results obtained are



listed in Table 1. It should be noted that moderate to good e.e.s are observed for these substrates, that the *exo*:*endo* ratio is

improved for the catalysed reaction over that of the thermal reaction and that the rate of catalysis is slowed with increasing steric hindrance. No reaction was observed at –78 °C when R = Pr<sup>i</sup> or Bu<sup>t</sup>. These results clearly suggest that the major, if not the sole, path of catalysis is *via* the metal and is not caused by proton catalysis.

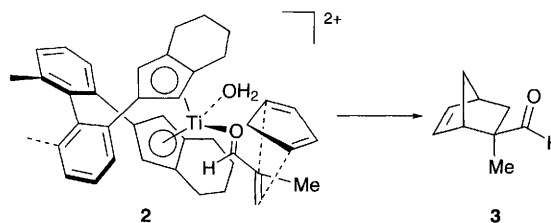
The absolute configuration of the major *exo* product of the reaction with methacrolein was found to be **3<sup>6</sup>** and suggests that the corresponding transition state resembles the structure **2** where the dienophile is in the preferred *s-trans* conformation.



**Table 1** Diels–Alder reactions of cyclopentadiene catalysed by [Ti{(S)-biphenacene}(H<sub>2</sub>O)<sub>2</sub>](OTf)<sub>2</sub> (2 mol%) in dichloromethane at –78 °C<sup>a</sup>

Entry	Dienophile	Time for 90% reaction/h	Isomer ratio <sup>b</sup> ( <i>exo</i> : <i>endo</i> )	% E.e. <sup>c</sup>
1		1	26:74 (20:80)	26
2		0.5	98:2 (86:14)	75
3		24	97:3 (83:17)	74
4		55	96:4 (85:15)	55

<sup>a</sup> All Diels–Alder reactions were run using 0.50 mmol dienophile and 0.75 mmol diene. For example: methacrolein (35 mg) and cyclopentadiene (50 mg) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (396 μl) containing 7.8 mg of catalyst (2 mol%) at –78 °C. Upon completion the solution was run through Florisil and the CH<sub>2</sub>Cl<sub>2</sub> removed under reduced pressure giving the product (>90% yield). <sup>b</sup> Isomer ratios for the thermal reaction are shown in brackets. <sup>c</sup> The e.e.s of the major isomer were determined by chiral shift reagent [(Eu(hfc)<sub>3</sub>] in [2H<sub>6</sub>]benzene by <sup>1</sup>H NMR spectroscopy. The absolute configuration of the product of reaction in entry 2 was determined by the optical rotation ([α]<sub>D</sub><sup>25</sup> = –16.3 (c = 1 g/100 ml, EtOH) which corresponds to the absolute configuration of **3<sup>6</sup>**.



The origin of the enantioselection in this structure is ascribed to the shielding of the lower drawn olefin face by the lower drawn tetrahydroindenyl group. The precise orientation of the metal-methacrolein adduct is not known but it is possible that its conformation could be affected by the nature of the *cis* ligand. Addition of 10 equiv. of Ph<sub>3</sub>PO to a (0.005 mol dm<sup>-3</sup>) solution of [Ti{(S)-biphenacene}(H<sub>2</sub>O)<sub>2</sub>](OTf)<sub>2</sub> caused the colour of the solution to change from green-red to a light orange indicating that Ph<sub>3</sub>PO complexation had occurred. This suggestion is supported by the observation that the Diels-Alder reaction of methacrolein and cyclopentadiene was at least an order of magnitude slower than that with the diaquo complex. Since no catalysis was detected at -78 °C, the reaction was run at 25 °C. The e.e. was similar to that observed at 25 °C with the diaquo complex (*ca.* 10%). This result implies that the *cis* ligand has little effect upon the e.e. and also implies that proton catalysis arising from hydrolysis of the diaquo complex does not occur in the Diels-Alder reaction since the e.e. is the same for the diaquo complex as for the Ph<sub>3</sub>PO adduct. These results serve to illustrate the potential utility of transition metal based Lewis acids.

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