Evidence for the Importance of π - π -Attractive Interactions in Enantioselective Diels-Alder Reactions Chiral Catalysts of Type (RO)₂TiCl₂

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Summary: Reaction of diol 4 with Ti(O i-Pr)4 followed by SiCl4 results in formation of the Ti (IV) complex 5 which is an exceptionally effective catalyst for enantioselective Diels-Alder reactions. The origin of the high enantioselectivities which have been observed (>95:5) probably lies in attractive π - π interaction between an aromatic group and the dienophile as indicated in formula 7.

One of the most interesting of various known catalytic enantioselective Diels-Alder reactions is that reported by Narasaka and colleagues,¹ as exemplified by equation $1.^{2,3}$ The structure of the catalyst (2), which is supported by ¹H NMR data, ^{1a,1b} and the bidentate nature of the dienophile **1** strongly suggest that the catalytic process involves the addition of the diene to an octahedral complex of **1** and **2**. Since there are *ten* possible diastereomeric octahedral complexes between **1** and **2**, and twice as many if both *s*-*cis* and *s*-*trans* conformers of the dienophile are considered, it is quite remarkable that substantial enantioselectivity was observed.⁴ Because of the importance of understanding the mechanistic and structural basis for such enantioselectivity, and our interest in the theory of catalytic enantioselective Diels-Alder processes, ^{3a,3g,3h} the research reported herein was carried out. These studies have provided a much improved catalytic system as well as new insights regarding the origin of enantioselectivity in the Narasaka experiments.

At the outset we considered that the most favorable geometry for an octahedral complex of 1 and 2 might be one in which the α,β -unsaturated carbonyl subunit of 1 and one of the benzhydryl phenyl groups of 2 are in proximity and in parallel planes to allow a π -donor-acceptor interaction and that diene addition might occur from such a structure, or the corresponding ion pair formed by dissociation of a chloride ion. It was therefore decided to study analogs of 2 in which the phenyl groups of the tertiary carbinol subunit are replaced by other aromatic groups with varying π -basicity. In addition, *gem*-diethyl substitution was selected for the ketal moiety of 2 since



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this subunit generates considerable bulk on both faces of the 1,3-dioxolane ring while minimizing the number of possible catalytic complexes. The use of aromatic groups, with para-π-donor groups, such as p-methoxyphenyl, is precluded because of the acid sensitivity of the corresponding benzhydrols and associated difficulties in the formation of analogs of complex 2. Ortho substitution on the benzhydrol subunit is inappropriate for steric reasons. Fortunately, the 3.5-dimethylphenyl analog of 2 could be prepared; it was found to be an exceptionally effective catalyst for enantioselective Diels-Alder reactions.

(R,R)-(+)-Dimethyl tartrate was converted to the 3-pentylidene ketal (3-pentanone, tosic acid, benzene at reflux) which upon treatment with the Grignard reagent from 5-bromo-m-xylene (Aldrich) in THF afforded diol 4 (88%).⁵ Reaction of 4 with 1 equiv of Ti(Oi-Pr)₄ in toluene at 23 °C followed by removal of solvent gave a colorless solid which was identified by ¹H NMR analysis as the complex Ti (4 - 2H) (Oi-Pr)₂. This mixed titanate ester was converted cleanly to 5 by reaction with 1 equiv of SiCl4 in toluene at 23 °C followed by removal of solvent and Cl₂Si(O i-Pr)₂ in vacuo (Method A). The composition of 5 was clear from the 500 MHz ¹H NMR spectrum.⁶ The reaction of cyclopentadiene and 3-(2-propencyl)-2-oxazolidinone (1, R = H) in toluene at -40 °C for 12 h in the presence of 20 mole % of catalyst 5 afforded the Diels-Alder adduct 3, R = H, in 80% yield, with 95:5 endo-exo selectivity and 97:3 enantioselectivity.7 The results of this and other Diels-Alder reactions using catalyst 5 are shown in the Table I. Good enantioselectivity was observed in each case.



Table I. Diels-Alder reactions catalyzed by 5.

BnOCH₂

Н

Н

Н

Η

Me

COOEt

	R1	$N \rightarrow N$ + $N \rightarrow N$	5 20 mole % toluene		
1	R ²	temp, °C; time, h	% yield	endo:exo	% ee (endo)
	Н	-40, 12	80	95:5	94
	BnOCHa	-30 12	83	> 99:1	95

 R^2

99:1

93:7

81:19

93

91

83

92

90

The performance of other catalysts in the Diels-Alder reaction of cyclopentadiene and 1, R = H, was evaluated to determine the effect of changing the aromatic substituents on the 7-membered chelate ring. The results are summarized in Table II.

-30, 12

-10, 8

-30, 8

Table II. Effect of catalyst structure on the Diels-Alder reaction of 1, R = H with cyclopentadiene in toluene.



Catalyst, Ar	temp, °C; time, h	% yield	endo:exo	% ee (endo)
Pha	-50, 12	70	93:7	73
β-Naphth ^a	-50, 36	86	93:7	68
6-MeO-β-Naphth ^a	-50, 40	76	90:10	82
3,5-diMe-Ph ^a	-40, 12	80	95:5	94
3,5-diCF ₃ -Ph ^b	-50, 20	81	92:8	68
3,5-diCl-Ph ^b	-50, 18	75	93:7	44

^aCatalyst prepared by Method A: (1) diol + $Ti(Oi-Pr)_4$; (2) SiCl₄. ^bCatalyst prepared from diol and TiCl₄ in ether, removal of solvent *in vacuo*, addition of toluene and evaporation.

The catalysts 6, Ar = Ph, and 6, Ar = β -Naphth, are comparable with regard to enantioselectivity, but 6, Ar = 6-MeO- β -Naphth, is distinctly better (Table II). On the other hand, replacement of the methyl groups in 6, Ar = 3.5-diMe-Ph, (5) by trifluoromethyl or chlorine substituents degrades enantioselection considerably. These results indicate that π -basicity of the aromatic substituent on the 7-membered chelate ring definitely favors enantioselectivity. There may also be a beneficial effect of meta substituents on the aromatic ring for steric reasons. Well documented instances of attractive π -interactions during Lewis-acid catalyzed Diels-Alder reactions have been observed in this laboratory.^{3h}

We believe that the highly enantioselective Diels-Alder reactions described above for catalyst **5** are most easily understood in terms of the transition state assembly represented by **7**. The dienophile is complexed to the



metal in the *s*-trans geometry such that the α , β -unsaturated carbonyl moiety and the proximate aromatic ring are in parallel planes with a spacing of *ca*. 3 Å, the optimum for π -donor-acceptor interaction. Such an arrangement provides a reasonable explanation both for the preferred formation of one particular octahedral complex and for the absolute stereocourse of the diene addition. Furthermore, it is consistent with our finding of only 14% ee for the adduct from cyclopentadiene, **5** and 3-(2-propenoyl)-4,4-dimethyl-2-oxazolidinone, a dienophile for which the *s*-trans geometry is unlikely.⁸

References and Notes

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- 4. Even if the geminal substituents at C(2) of the 1,3-dioxolane ring are identical, five diastereomeric octahedral complexes are possible.
- 5. (a) Found for the 3-pentylidene ketal of (R,R)-(+)-dimethyl tartrate: $[\alpha]_{D}^{23}$ -16.8° (c = 3.03, CHCl₃). Rf: 0.83 (1:1 AcOEt-hexane); bp 102-104 °C, 0.05 mm Hg; ¹H NMR (270 MHz, CHCl₃): δ 0.90 (t, J = 7.6 Hz, 6H), 1.69 (q, J = 7.6 Hz, 4H), 3.78 (s, 6H), 4.71 (s, 2H); IR (neat): 2977, 2955, 2886, 1751, 1463, 1439, 1379, 1361, 1223, 1204, 1172, 1113 cm⁻¹; FABMS m/e: 247 (M + H)⁺, 269 (M + Na)⁺. (b) Found for 4 (colorless, amorphous solid): $[\alpha]_{D}^{23}$ -87.7° (c = 1.2, CHCl₃); Rf: 0.62 (1:4 AcOEt-hexane); ¹H NMR (500 MHz, C₆D₆): δ 0.84 (t, J = 7.4 Hz, 6H), 1.45 (dq, J = 14.7, 7.4 Hz, 2H), 1.54 (dq, J = 14.7, 7.4 Hz, 2H), 2.02 (s, 12H), 2.15 (s, 12H), 4.10 (s, 2H), 4.91 (s, 2H), 6.66 (s, 2H), 6.75 (s, 2H), 7.36 (s, 4H), 7.53 (s, 4H); ¹³C NMR (125 Hz, C₆D₆): δ 8.58, 21.45, 21.51, 30.20, 78.65, 81.74, 112.60, 126.07, 127.13, 129.20, 129.25, 136.52, 137.41, 143.92, 147.32; IR (neat): 3314, 3307, 3004, 2970, 2940, 2917, 1603, 1459, 1446, 1173, 1073, 1058, 1037 cm⁻¹; FABMS m/e: 629 (M + Na)⁺.
- 6. Preparation of catalyst 5: (all solvents and apparatus must be dry) Ti(O*i*-Pr)₄ (29.8 μl, 100 μmol) was added to a solution of a diol 4 (60.7 mg, 100 μmol) in 1 ml of toluene at 23 °C. After stirring at 23 °C for 1 h, the solvent was removed under reduced pressure with stirring to give a white powder which was dissolved in 1 ml of toluene and treated with SiCl₄ (1M solution in toluene, 100 μl, 100 μmol). The solution was stirred at 23 °C for 1 h and the solvent was removed *in vacuo* to give catalyst 5 as a pale yellow solid. ¹H NMR (500 MHz, C₆D₆): δ 0.68 (t, J = 7.5 Hz, 6H), 1.1 1.4 (m, 4H), 2.04 (s, 12H), 2.09 (s, 12H), 5.67 (s, 2H), 6.71 (s, 2H), 6.72 (s, 2H), 7.15 (s, 4H), 7.55 (s, 4H).
- 7. Synthesis of **3**, **R** = H: A solution of catalyst **5**, prepared as described in footnote 6, in 0.5 ml of toluene at -78 °C was treated with a solution of 3-(2-propenoyl)-2-oxazolidinone (70.6 mg, 500 µmol) in toluene (2 ml) and then with cyclopentadiene (208 µl, 2.5 mmol). The mixture was brought to -40 °C and stirred at -40 °C for 12 h, then poured into brine and extracted with AcOEt. The combined extracts were dried, evaporated and chromatographed on silica gel (AcOEt–hexane 1 : 3) to afford the recovered diol **4** (60 mg) and the Diels-Alder product (83 mg, 401 µmol, 80% yield, *endo* : *exo* ratio 95 : 5); 94% ee as determined by HPLC analysis using a Chiralcel OD column with 5% *i*-PrOH in hexanes for elution (1 ml/min; t^R 24.0 min for 2-*S* enantiomer and 27.7 min for 2-*R* enantiomer). Further chromatography gave the pure *endo* adduct **3**, R = H, [α]²³_D-159.1° (c = 3.26, CHCl₃), mp 68-69 °C. ¹H NMR (270 MHz, CDCl₃): δ 1.44 (m, 3H), 1.95 (m, 1H), 2.94 (s, 1H), 3.30 (s, 1H), 3.97 (m, 3H), 4.40 (t, 2H), 5.85 (dd, J = 2.6, 5.6 Hz, 1H), 6.23 (dd, J = 3.0, 5.6 Hz, 1H). In the *exo* isomer δ 6.16 (m, 2H) was observed for the olefinic protons.
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