

Chiral titanium complexes for enantioselective catalysis

KOICHI MIKAMI and MASAHIRO TERADA

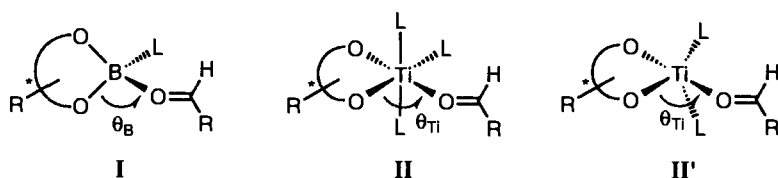
1. Introduction

Enantioselective catalysis is an economical and environmentally benign process, since it achieves 'multiplication of chirality'¹ thereby affording a large amount of the enantio-enriched product, while producing a small amount of waste material, due to the very small amount of chiral catalyst used. Thus, the development of enantioselective catalysts is a most challenging and formidable endeavour for synthetic organic chemists.^{2,3} Highly promising candidates for such enantioselective catalysts are metal complexes bearing chiral organic ligands. Thus, the choice of the central metal and the molecular design of the chiral organic ligand are most crucial for the development of enantioselective catalysts. The degree of enantioselectivity should be critically influenced by metal–ligand bond lengths, particularly metal–oxygen and –nitrogen bond lengths in case of metal alkoxide and amide complexes (Table 6.1),^{4,5} as well as the steric demand of the organic ligands. The shorter the bond length, in principle, the higher the enantioselectivity, because the asymmetric environment constructed by the chiral ligand is closer to the reaction centre. Therefore, boron and aluminium are the main group elements of choice, and

Table 6.1 Metal-oxygen (M-O) and metal-nitrogen (M-N) bond length

Metal	M-O bond length (Å)	M-N bond length (Å)
Li	1.92–2.00	2.12
Mg	2.01–2.13	2.22
Zn	1.92–2.16	2.16
Sn	2.70	2.25
Al	1.92	1.95
B	1.36–1.47	1.40
Ti	1.62–1.73	2.30
Zr	2.15	2.30

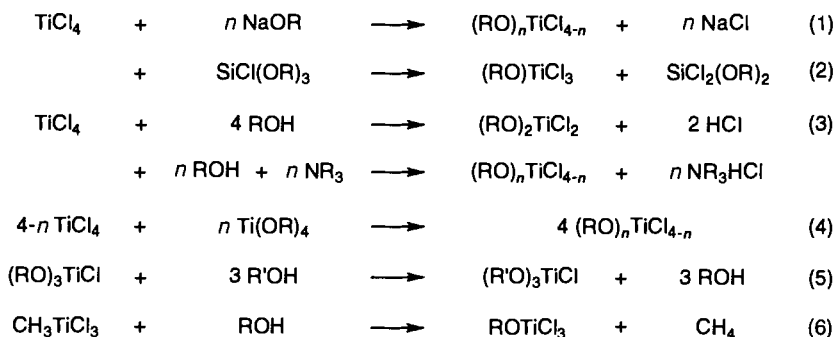
titanium is one of the best early transition metals with hexa- and penta-co-ordination (Scheme 6.1).



Scheme 6.1

The Lewis acidity of metal complexes is generally proportional to the value of (charge density) \times (ionic radius)^{-3.6}. Electron donating and sterically demanding ligands decrease the Lewis acidity but increase the configurational stability of titanium complexes in the order: Cp (cyclopentadienyl) > NR₂ > OR > X (halides).^{4,7,8} Therefore, the Lewis acidity of titanium complexes decreases on going from titanium halides to titanium alkoxides to titanium amides. The Lewis acidity can be fine-tuned by mixing ligands such as in alkoxytitaniumhalide complexes. By contrast, bond strengths with titanium decrease in the order: M–O > M–Cl > M–N > M–C.⁴ The M–C bond strengths in Ti(IV) compounds are comparable with those of other metal–carbon bonds. However, the Ti–O bond is exceptionally strong.

General preparative procedures for chiral titanium complexes are classified in Scheme 6.2.^{9–13} (1) A halide can be replaced with metalated ligands by transmetalation (eq. 1). (2) A halide can be replaced by metathesis of a silylated ligand with accompanying generation of silylhalide (eq. 2). (3) HCl is evolved with protic ligands, and hence must be evaporated or neutralized with a base (eq. 3). (4) Ligand redistribution results in disproportionation (eq. 4) (Protocol 1). (5) A chiral titanate ester is prepared using an alkoxy exchange reaction (*trans*-esterification) with a free chiral alcohol (eq. 5). The equilibrium is shifted towards the chiral titanium complex by azeotropic removal of



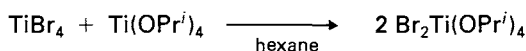
Scheme 6.2

the volatile achiral alcohol. (6) Alkyl (methyl, in particular) titanium complexes can be used for deprotonation of the chiral ligands along with generation of alkane (methane) (eq. 6). Chiral titanium alkoxide complexes thus obtained usually form bridged dimers, or trimers in extreme cases. Such aggregates are the favoured form even in solution. As shown above, there are many ways to prepare chiral titanium complexes for the enantioselective catalysis of carbon–carbon bond forming reactions or asymmetric functional group transformations. However, reactions of the latter type such as the Sharpless oxidation^{14–17} or reduction^{18–23} are beyond the scope of this manuscript due to limited space.

Protocol 1.

Preparation of di-isopropoxytitanium(IV) dibromide *via* ligand redistribution^{24,25}

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- A pre-dried, pre-weighed, two-necked, round-bottomed flask (50 mL) equipped with a three-way stopcock, a magnetic stirring bar, and a septum cap. The three way stopcock is connected to a vacuum/argon source
- Dry gas-tight syringe
- Thermometer for low temperatures

Materials

- | | |
|--|---|
| • Titanium(IV) bromide (FW 367.5), 7.35 g, 20 mmol | corrosive, lachrymator, moisture sensitive |
| • Titanium(IV) isopropoxide (FW 284.3), 5.94 mL, 20 mmol | flammable liquid, irritant, moisture sensitive |
| • Dry hexane, total 40 mL | flammable liquid, irritant |
| • Dry toluene, 87.6 mL | flammable liquid, toxic |

1. Flame dry reaction vessel and accessories under dry argon. After cooling to room temperature, add the titanium (IV) bromide (7.35 g, 20 mmol) to the pre-weighed, two-necked, round-bottomed flask under a flow of argon.
2. Introduce 20 mL of hexane to this flask to form a red–brown suspension and then add the titanium(IV) isopropoxide (5.94 mL, 20 mmol) carefully over ~7 min at ambient temperature with the syringe. The addition of titanium (IV) isopropoxide causes the mixture to warm to about 40°C.
3. Stir for 10 min at that temperature to give a yellow solution. Then allow to stand for 6 h at room temperature. Isolate the pale-yellow precipitate that has formed by removal of the supernatant solvent with a syringe.

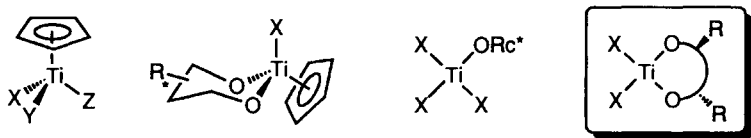
Protocol 1. Continued

4. Wash with hexane (5 mL \times 2) and recrystallize from hexane (10 mL). The recrystallization is carried out in the same flask by heating to reflux and then leaving the solution at room temperature overnight.
5. Remove the supernatant solvent again with the syringe. Vacuum dry the pale-yellow crystalline solid to give di-isopropoxytitanium(IV) dibromide (5.71 g, 44%), a highly moisture sensitive product.
6. Dissolve the crystalline in dry toluene (87.6 mL) to give a 0.2 M solution. Store the solution in a refrigerator.

Additionally, the crystalline solid may be stored at 0 \sim -20°C .

2. Carbonyl addition reaction

Alkyltitanium complexes can be obtained from alkaline metal carbanions via titanation. Introduction of chirality at the titanium centre or on the ligand (or a combination of both) (Scheme 6.3) allows for the possibility of asymmetric induction in the carbonyl addition reaction.



Scheme 6.3

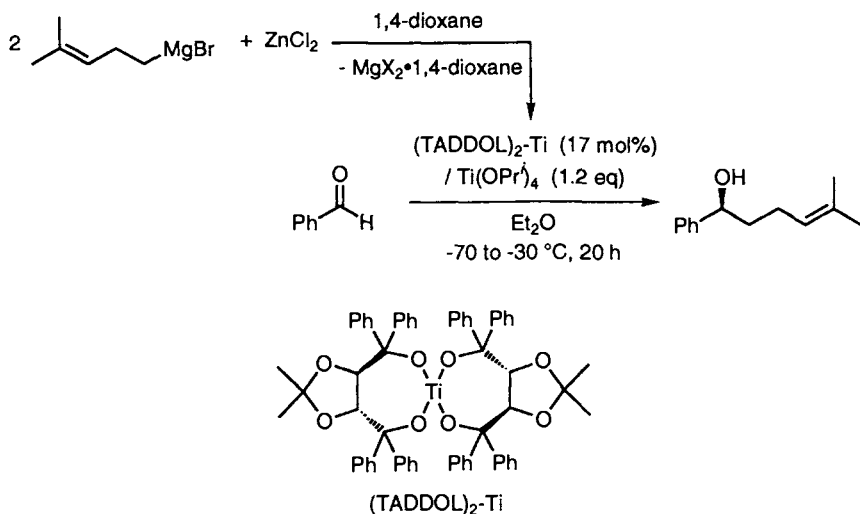
However, the use of complexes which are chiral at the titanium centre, which is the closest to the reacting carbonyl group, generally affords only low enantioselectivity, because of the configurational lability of chiral titanium centre.²⁶ The use of a C_2 symmetric 1,1'-bi-2-naphthol (BINOL)²⁷ derived titanium complex has been unsuccessful so far in allylation or methylation reactions.⁴ In an exceptional case, high enantioselectivity was obtained with a BINOL-modified phenyltitanium reagent. In that reaction, chiral titanium 'ate' complexes formed from BINOL-Ti(OPr)ⁱ₂²⁸ and arylmagnesium halides could also be used.^{29,30} Allylation of aromatic and aliphatic aldehydes by (4*R*,5*R*)- $\alpha,\alpha,\alpha',\alpha'$ -tetra-aryl-1,3-dioxolane-4,5-dimethanol (TADDOL)^{31–34}-derived cyclopentadienyltitanium complexes was found to give homoallyl alcohols with high enantioselectivity.³⁵ Exploitation of the Schlenk equilibrium of a mixture of a Grignard reagent, RMgX and 0.5 equiv. of ZnCl₂ with dioxane allowed the *in situ* generation of a functionalized alkyl zinc reagent along with MgX₂-dioxane complex (Protocol 2).^{36,37} Such R₂Zn can be used as nucleophile for (TADDOL)₂-Ti complex-catalysed carbonyl addition reaction with

high enantioselectivity. Chiral titanium bis-sulfonylamine complexes have also been used to accelerate the addition reaction of dialkylzinc.^{38–43}

Protocol 2.

TADDOL–Ti complex-catalysed asymmetric carbonyl addition reaction with functionalized dialkylzinc compounds, generated *in situ* from Grignard reagents^{36,37} (Scheme 6.4)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 6.4

Equipment

- A pre-dried, three-necked round-bottomed flask (100 mL) equipped with a condenser, a three-way stopcock, a magnetic stirring bar, and a septum cap. The three-way stopcock is connected to a vacuum/argon source
- A pre-dried, three-necked, round-bottomed flask (100 mL) equipped with a magnetic stirring bar, a glass filter, a three-way stopcock, and a septum cap. The three-way stopcock is connected to a vacuum/argon source
- A pre-dried, two-necked, round-bottomed flask (100 mL) equipped with a three-way stopcock, a magnetic stirring bar, and a septum cap. The three-way stopcock is connected to a vacuum/argon source
- Dry gas-tight syringe
- Thermometers for low temperature

Materials

- (4*R*,5*R*)-2,2-dimethyl- $\alpha,\alpha,\alpha',\alpha'$ -tetraphenyl-1,3-dioxolane-4,5-dimethanol (FW 466.6), 9.33 g, 20 mmol
- Distilled titanium(IV) ethoxide (FW 228.2), 2.3 mL, 11 mmol
- Dry toluene, 20 mL

flammable liquid, moisture sensitive
flammable liquid, toxic

Protocol 2. Continued

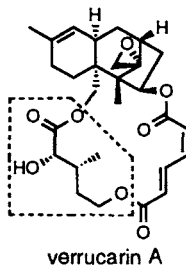
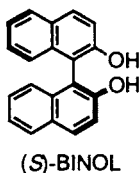
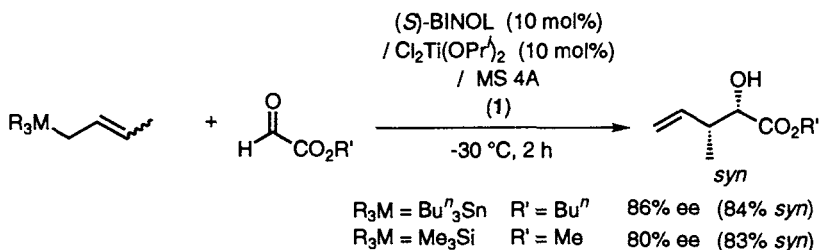
- Titanium(IV) isopropoxide (FW 284.3), 1.80 mL, 6 mmol **flammable liquid, irritant, moisture sensitive**
 - 1.0 M solution of zinc chloride in ether, 10 mL, 10 mmol **flammable liquid, moisture sensitive**
 - 1.05 M solution of 4-methyl-3-penten-1-ylmagnesium bromide in ether, 19 mL, 20 mmol **flammable liquid, moisture sensitive**
 - Dry ether **flammable liquid, toxic**
 - Dry 1,4-dioxane (FW 88.1), 6 mL, 70 mmol **cancer suspect agent, flammable liquid**
 - Benzaldehyde (FW 106.1) 0.51 mL, 5 mmol **highly toxic, cancer suspect agent**
1. Add the (4*R*,5*R*)-2,2-dimethyl- $\alpha,\alpha,\alpha',\alpha'$ -tetraphenyl-1,3-dioxolane-4,5-dimethanol (9.33 g, 20 mmol) to the pre-dried three-necked round-bottomed flask with condenser, and purge with argon.
 2. Add the dry toluene (20 mL) and the distilled titanium(IV) ethoxide (2.3 mL, 11 mmol), giving to rise a slightly yellow suspension.
 3. Stir for 12 h at 40°C. Heat the resulting clear solution to reflux temperature for an additional 5 h.
 4. Slowly evaporate the solvent *in vacuo*. Control the speed of the distillation by regulation of the vacuum.
 5. Dry the resulting yellow, waxy solid *in vacuo* to obtain the (TADDOL)₂-Ti complex in quantitative yield. The (TADDOL)₂-Ti complex should be stored under argon.
 6. Add the (TADDOL)₂-Ti complex (0.856 g, 0.85 mmol) to the other pre-dried three-necked round-bottomed flask fitted with a glass filter. Dissolve the (TADDOL)₂-Ti complex with ether (12 mL) and introduce the titanium(IV) isopropoxide (1.8 mL, 6 mmol) by the syringe.
 7. Introduce the 1.0 M ether solution of zinc chloride (10 mL, 10 mmol) into the pre-dried two-necked round bottomed flask with a syringe and dilute with ether (5 mL).
 8. Add 1.05 M Grignard reagents (19 mL, 20 mmol), 4-methyl-3-penten-1-ylmagnesium bromide,^a and stir at room temperature for 2 h.
 9. Add 1,4-dioxane (6 mL, 70 mmol) to the suspension and stir for an additional 45 min. To obtain a clear solution of the dialkyl zinc reagent, filter under an argon atmosphere. Add the filtrate directly to the TADDOL-Ti solution, obtained above, at -78°C.
 10. After stirring at -78°C for 1 h, add benzaldehyde (0.51 mL, 5 mmol) and then raise the reaction temperature to -30°C.
 11. Stir at -30°C for 20 h and then quench with saturated NH₄Cl solution (10 mL) and add ether (25 mL) at -30°C. Filter through a pad of Celite and rinse the filter cake with ether. Wash the organic phase with H₂O and brine, dry over Na₂SO₄, filter the solution, and concentrate *in vacuo*.
 12. To crystallize and separate from the TADDOL ligand, add pentane to the

resulting crude product. Again concentrate the supernatant solution and isolate by bulb to bulb distillation to collect 0.847 g (89%) of 1-phenyl-5-methylhex-4-en-1-ol.

13. The enantiomeric purity is determined by the capillary GC analysis using a heptakis(2,3,6-tri-*O*-ethyl)- β -cyclodextrin in OV 1701 as a chiral stationary phase column (96% ee).

^a Prepared as usual from 5-bromo-2-methylpent-2-ene and magnesium turnings and titrated shortly before use.

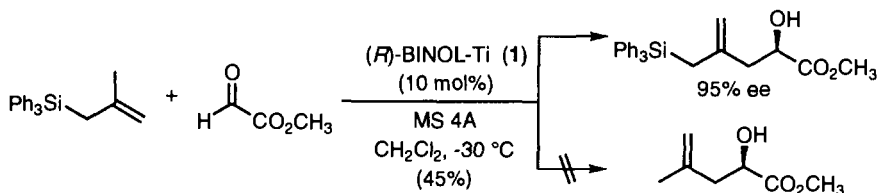
Further pursuing our research project on the asymmetric catalysis of the carbonyl-ene reaction, we have found that the BINOL-Ti complexes (**1**),⁴⁴ which are prepared *in situ* in the presence of MS 4A from di-isopropoxy-titanium dihalides ($X_2Ti(OPr^i)_2$; $X = Br$ or Cl) and optically pure BINOL (see below), catalyse rather than promote stoichiometrically the carbonyl addition reaction of allylic silanes and stannanes.⁴⁵ The addition reactions to glyoxylate of (*E*)-2-butenylsilane and -stannane proceed smoothly to afford the *syn*-product in high enantiomeric excess (Scheme 6.5). The *syn*-product thus obtained could readily be converted into the lactone portion of verrucarline A.^{46,47}



Scheme 6.5

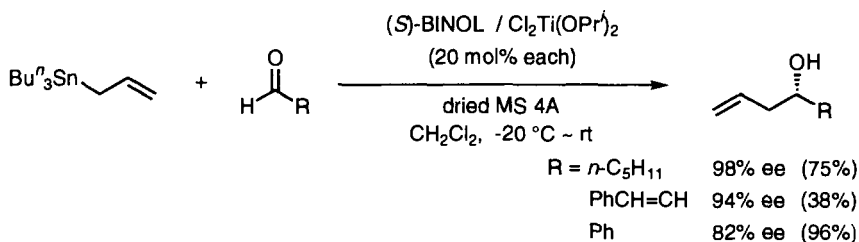
We have further found the BINOL-Ti (**1**) catalysis for the Sakurai-Hosomi reaction of methallylsilanes with glyoxylates (Scheme 6.6).⁴⁸ Surprisingly,

however, the products were obtained in the allylic silane (ene product) form (see below), with high enantioselectivity.

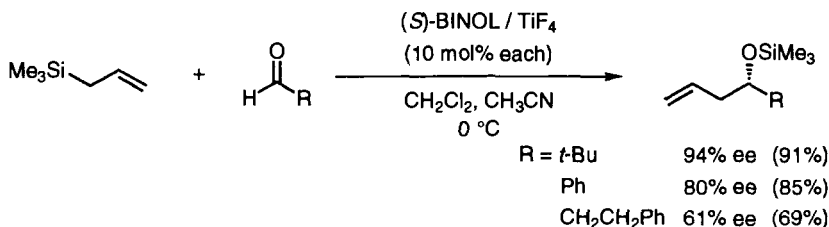


Scheme 6.6

Asymmetric catalysis by BINOL-Ti complexes of the reaction of aliphatic and aromatic aldehydes with an allylstannane has been reported independently by Tagliavini, Umami-Ronchi, and Keck.^{49–52} In Tagliavini's case,⁴⁹ a new complex generated by reaction of the BINOL-Ti complex with allylstannane has been suggested to be the catalytic species which provides the remarkably high enantioselectivity (Scheme 6.7). Interestingly enough, no reaction occurs if MS 4A is not present during the preparation stage of the chiral catalyst, and MS 4A affects the subsequent allylation reaction. MS 4A dried for 12 h at 250 °C and 0.1 Torr was recommended. Keck reported that addition of CF₃CO₂H or CF₃SO₃H strongly accelerates the reactions catalysed by BINOL-Ti(OPr^{*i*})₂ complex (2).⁵⁰



Scheme 6.7



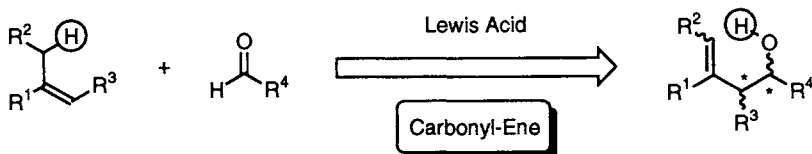
Scheme 6.8

The BINOL-Ti complex-catalysed allylsilane addition to aliphatic and aromatic aldehydes has been reported by Carreira.⁵³ The catalyst is prepared

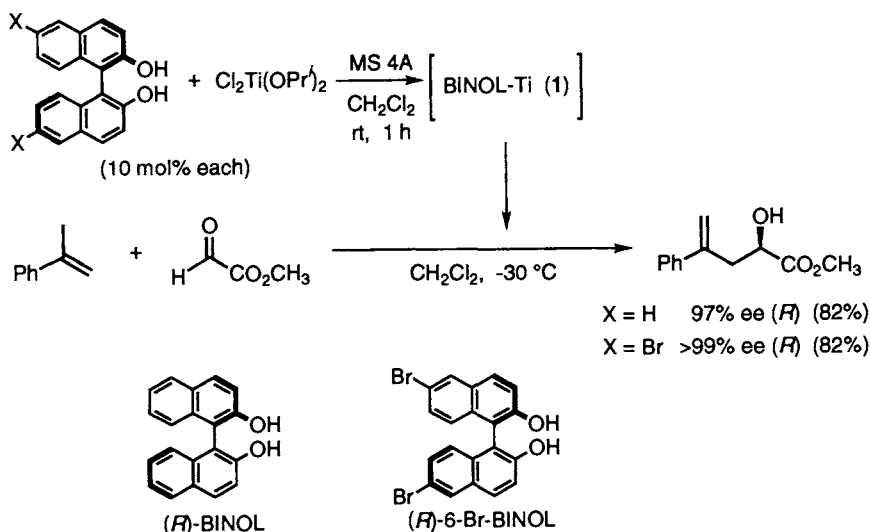
from BINOL and polymeric TiF_4 (Scheme 6.8). The presence of a small amount of CH_3CN is crucial to attain not only high catalytic activity but also high enantioselectivity.

3. Carbonyl-ene reaction

The class of ene reactions which involves a carbonyl compound as the enophile, which we refer to as the 'carbonyl-ene reaction',^{54–57} constitutes a useful synthetic method for the construction of carbon skeleton (Scheme 6.9).



We have been investigating the possibility of stereocontrol in carbonyl-ene reactions promoted by a stoichiometric or catalytic amount of various Lewis acids.^{58–60} In particular, we have developed a chiral titanium catalyst for the glyoxylate-ene reaction which provides the α -hydroxy esters of biological and synthetic importance^{61–64} in an enantioselective fashion (Scheme 6.10).^{65–70} Various chiral titanium catalysts were screened.⁷¹ The best result was obtained with the titanium catalyst (1) prepared *in situ* in the presence of MS



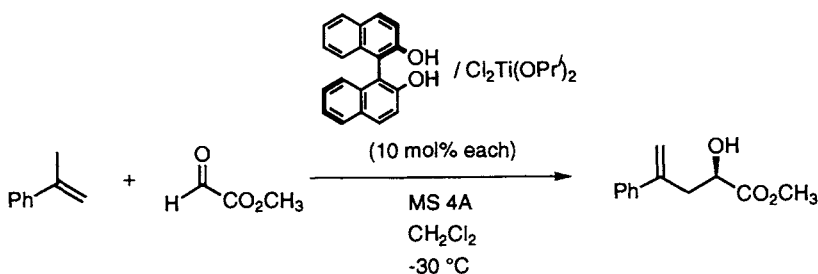
X = H 97% ee (*R*) (82%)
X = Br >99% ee (*R*) (82%)

4A from di-isopropoxytitanium dihalides ($X_2Ti(OPr^i)_2$: $X = Br^{24}$ or Cl^{25}) and optically pure BINOL or 6-Br-BINOL^{72–74} (Protocol 3) (These two ligands are now commercially available in (*R*)- and (*S*)-forms.) The remarkable levels of enantioselectivity and rate acceleration observed with these BINOL–Ti catalysts (**1**) stem from the favourable influence of the inherent C_2 symmetry and the higher acidity of BINOLs compared to those of aliphatic diols. The reaction is applicable to a variety of 1,1-disubstituted olefins to provide the ene products in extremely high enantiomeric excess (ee) (Table 6.2). In the reactions with mono- and 1,2-disubstituted olefins, however, no ene product was obtained.

Protocol 3.

Asymmetric carbonyl-ene reaction catalysed by BINOL-derived titanium complex. Catalytic asymmetric synthesis of α -hydroxyester^{24,68,69} (Scheme 6.11)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 6.11

Equipment

- A pre-dried, three-necked, round-bottomed flask (100 mL) equipped with a magnetic stirring bar, a dropping funnel, a three-way stopcock and a septum cap. The three-way stopcock is connected to a vacuum/argon source
- Dry gas-tight syringe
- Thermometers for low temperature

Materials

- Molecular sieves 4A,^a powder, <5 mm, activated, 2.0 g
- (*R*)-(+)- or (*S*)-(–)-1,1'-bi-2-naphthol (FW 286.3), 100 mg, 0.35 mmol
- 0.2 M solution of di-isopropoxytitanium(IV) dibromide in toluene, 1.75 mL, 0.35 mmol
- α -Methylstyrene (FW 118.2), 14.0 mL, 108 mmol
- Freshly distilled methyl glyoxylate^b (FW 88.1), 6.16 g, 70 mmol
- Dry dichloromethane, 45 mL

irritant, hygroscopic

irritant

moisture sensitive, irritant

corrosive, lachrymator

lachrymator, irritant

toxic, irritant

6: Chiral titanium complexes for enantioselective catalysis

1. Add the powder molecular sieves 4A (2.0 g) and (*R*)-(+)-1,1'-bi-2-naphthol (100 mg, 0.35 mmol) to the three-necked flask, purge with argon, and suspend with CH_2Cl_2 (20 mL). Stir for 15 min at room temperature.
2. Add a 0.2 M toluene solution of di-isopropoxytitanium dibromide (0.33 mL, 0.10 mmol) (prepared as described in Protocol 1) by syringe at room temperature.
3. After stirring for 1 h at room temperature, cool to -30°C . Add the α -methylstyrene (14.0 mL, 108 mmol) in CH_2Cl_2 (5 mL) by syringe. Add the methyl glyoxylate (6.16 g, 70 mmol) dissolved in CH_2Cl_2 (20 mL) dropwise over 30 min.
4. Stir for 6 h at -30°C . The reaction temperature must be kept in the range of -35°C to -30°C . The progress of the reaction is monitored by TLC.
5. Pour the CH_2Cl_2 solution into a beaker containing 10 mL of saturated NaHCO_3 and 50 mL of ether. Filter off molecular sieves 4A through a pad of Celite and rinse the filter cake three times with ethyl acetate. Separate the phases and extract the aqueous phase three times with 80 mL of ethyl acetate. Wash the combined organic phases twice with 50 mL of brine, dry over magnesium sulfate, and filter the solution.
6. Concentrate the crude product under vacuum and distil the residue at 0.2 mmHg to collect 12.1 g (84%) of methyl 2-hydroxy-4-phenyl-4-pentenoate boiling at $105\text{--}106^\circ\text{C}$. The product displays the appropriate spectral characteristics and high resolution mass spectral data.
7. The enantiomeric purity is determined by the HPLC analysis using a CHIRALPAK AS as a chiral stationary phase column with 25% *i*-PrOH/hexane as a mobile phase (94% ee).


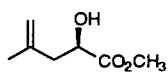

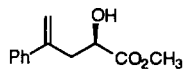

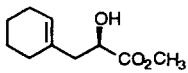

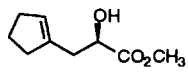
^a Purchased from Aldrich Chemical Company, Inc. and used without activation.

^b Immediately prior use, the methyl glyoxylate is depolymerized by vacuum distillation from phosphorus pentoxide (10% weight) b.p. $62^\circ\text{C}/60\text{ mmHg}$, bath temperature $120\text{--}140^\circ\text{C}$.

This limitation has been overcome by the use of vinylic sulfides and selenides instead of mono- and 1,2-disubstituted olefins. With these substrates, the ene products are formed with virtually complete enantioselectivity and high diastereoselectivity.⁷⁵ The synthetic utility of the vinylic sulfide and selenide approach is exemplified by the synthesis of enantiopure (*R*)-(-)-ipsdienol, an insect aggregation pheromone (Scheme 6.12).^{76–78}

The synthetic potential of the asymmetric catalytic carbonyl-ene reaction depends greatly on the functionality which is possible in the carbonyl enophile. However, the types of enophile that can be used in the asymmetric catalytic ene reaction have previously been limited to aldehydes such as glyoxylate^{68,69} and chloral.⁷⁰ Thus, it is highly desirable to develop other types of carbonyl enophiles to provide enantio-enriched molecules with a wider range

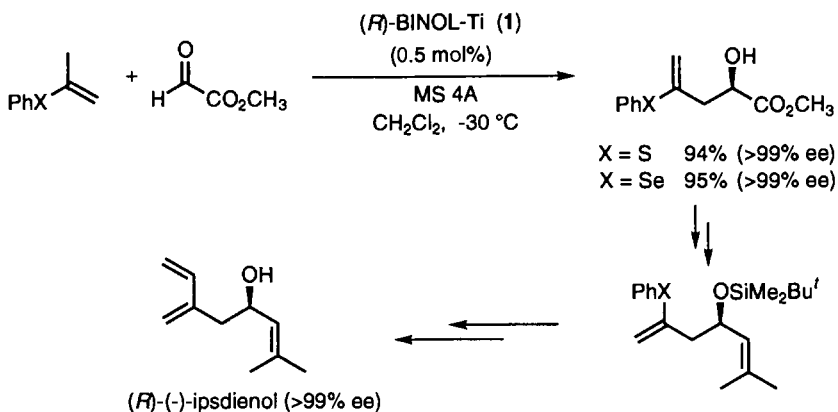
Table 6.2 Asymmetric catalytic glyoxylate-ene reactions with various olefins^a

Run	olefin	X ₂ Ti(OPr ^{<i>i</i>}) ₂ (X)	catalyst (mol%)	time (h)	products	%yield	%ee ^b
A		Cl	10	8		72	95 <i>R</i>
		Cl	10	8		68	95 <i>S</i> ^c
		Cl	1.0	8		78	93 <i>R</i>
		Br	10	3		87	94 <i>R</i>
B		Cl	1.0	8		97	97 (<i>R</i>)
		Br	1.0	3		98	95 (<i>R</i>)
C		Cl	10	8		82	97 (<i>R</i>)
		Br	5	3		89	98 (<i>R</i>)
D		Cl	10	8		87	88 (<i>R</i>)
		Br	5	3		92	89 (<i>R</i>)

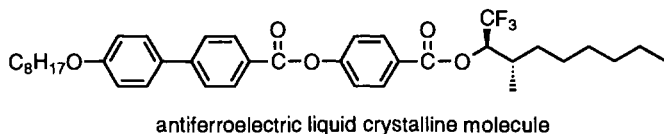
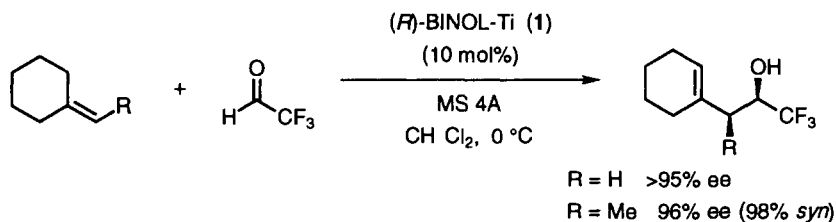
^a All reactions were carried out using 1.0 mmol of methyl glyoxylate, 2.0 mmol of olefin, and indicated amount of BINOL-Ti complex at -30 °C.

^b Determined by LIS-NMR analysis after conversion to the corresponding α-methoxy esters. The configuration in parentheses could be assigned by the similarity in shift pattern seen in the LIS-NMR spectra using (+)-Eu(dppm)₃ as a chiral shift reagent.

^c (S)-BINOL was used instead of the (*R*)-counterpart.

**Scheme 6.12**

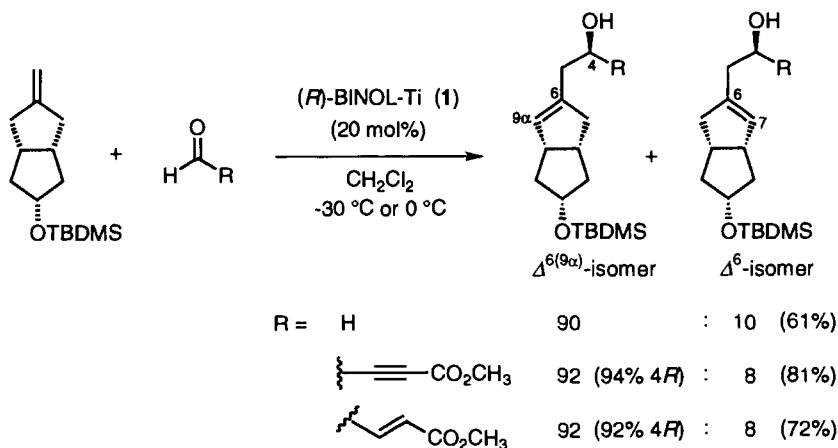
of functionalities. We have developed an asymmetric catalytic fluoral-ene reaction,^{79–81} which provides an efficient approach for the asymmetric synthesis of some fluorine-containing compounds of biological and synthetic importance.⁸² The reaction of fluoral with 1,1-disubstituted and trisubstituted olefins proceeds quite smoothly under the catalysis by the BINOL-Ti complex (**1**) to provide the corresponding homoallylic alcohol with extremely high enantioselectivity (>95% ee) and *syn*-diastereoselectivity (>90%) (Scheme 6.13).



Scheme 6.13

The sense of asymmetric induction in the fluoral-ene reaction is exactly the same as observed for the glyoxylate-ene reaction; (*R*)-BINOL-Ti (**1**) provides the (*R*)- α -CF₃ alcohol. The *syn*-diastereomers of α -trifluoromethyl- β -methyl-substituted compounds thus synthesized with *two stereogenic centres* show anti-ferroelectric properties preferentially to the *anti*-diastereomers.^{83–86}

The BINOL-Ti catalysis can also be used for the carbonyl-ene reaction with formaldehyde or vinyl and alkynyl analogues of glyoxylates in an asymmetric catalytic desymmetrization (see below) approach to the asymmetric synthesis of isocarbacycline analogues (Scheme 6.14).^{87,88}

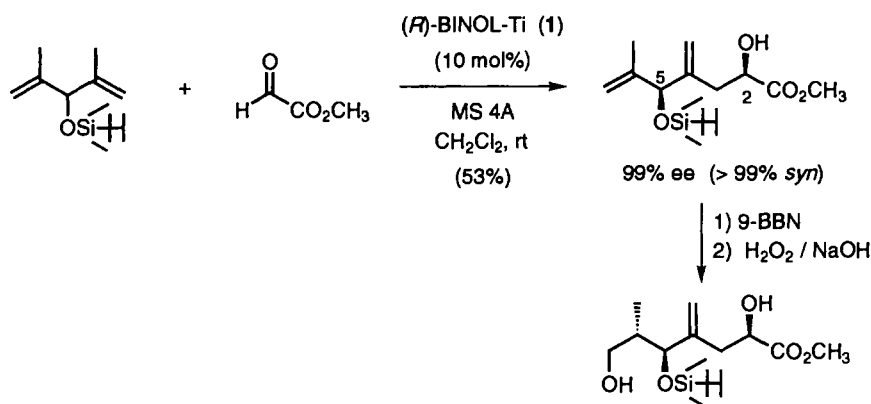


Scheme 6.14

4. Asymmetric catalytic desymmetrization

Desymmetrization of an achiral, symmetrical molecule through a catalytic process is a potentially powerful but relatively unexplored concept for

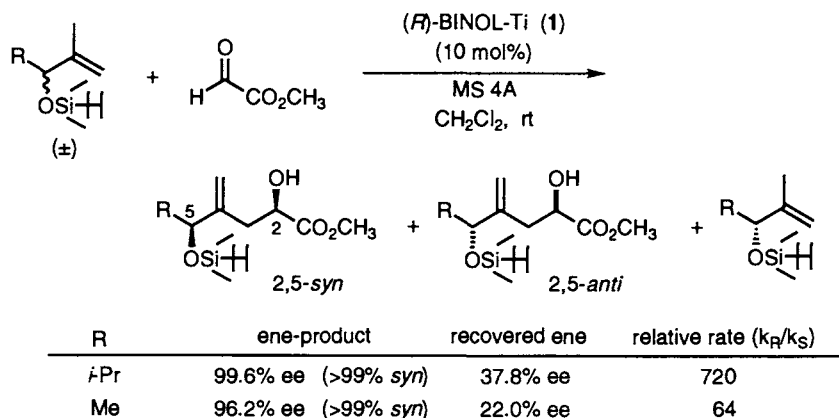
asymmetric synthesis. Although the ability of enzymes to differentiate between enantiotopic functional groups is well known,⁸⁹ little has been explored on a similar ability of non-enzymatic catalysts, particularly for carbon–carbon bond-forming processes. The desymmetrization by the catalytic glyoxylate–ene reaction of prochiral ene substrates with the planar symmetry provides an efficient access to remote⁹⁰ and internal⁹¹ asymmetric induction which is otherwise difficult to attain (Scheme 6.15).⁹² The (2*R*,5*S*)-*syn*-product is obtained in >99% ee along with more than 99% diastereoselectivity. The diene thus obtained can be transformed to a more functionalized compound in a regioselective and diastereoselective manner.



Scheme 6.15

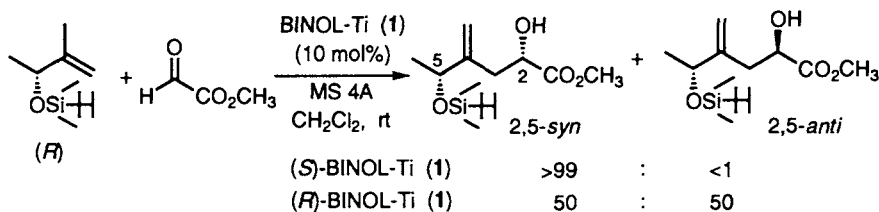
5. Kinetic optical resolution

On the basis of desymmetrization concept, the kinetic optical resolution of a racemic substrate^{93,94} might be recognized as an intermolecular version of desymmetrization. The kinetic resolution of a racemic allylic ether by the glyoxylate–ene reaction also provides an efficient access to remote but relative⁹¹ asymmetric induction. The reaction of allylic ethers catalysed by the (*R*)-BINOL-derived complex (1) provides the 2*R*,5*S*-*syn*-products with >99% diastereoselectivity along with more than 95% ee (Scheme 6.16). The high diastereoselectivity, coupled with the high ee, strongly suggests that the catalyst/glyoxylate complex efficiently discriminates between the two enantiomeric substrates to accomplish the effective kinetic resolution. In fact, the relative rates between the reactions of the either enantiomers, calculated by the equation $\{ \ln[(1-c)(1-ee_{\text{recov}})] \} \times \{ \ln[(1-c)(1+ee_{\text{recov}})] \}^{-1}$, $c = (ee_{\text{recov}}) \times (ee_{\text{recov}} + ee_{\text{prod}})^{-1}$, $0 < c$, $ee < 1$ where c is the fraction of consumption), were approx. 700 for $R = i\text{-Pr}$ and 65 for $R = \text{Me}$. As expected, the double asymmetric induction^{95,96} in the reaction of (*R*)-ene component using the



Scheme 6.16

catalyst (*S*)-1 ('matched' catalytic system) leads to the complete (>99%) 2,5-syn-diastereoselectivity in high chemical yield, whereas the reaction of (*R*)-ene using (*R*)-1 ('mis-matched' catalytic system) produces a diastereomeric mixture in quite low yield (Scheme 6.17).

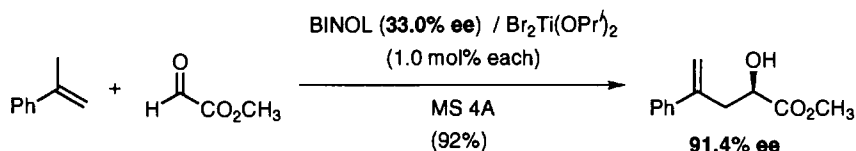


Scheme 6.17

6. Positive non-linear effect of non-racemic catalysts

Deviation from the linear relationship, namely 'non-linear effect' (NLE) is sometimes observed between the enantiomeric purity of chiral catalysts and the optical yields of the products. Among, the convex deviation, which Kagan^{97,98} and Mikami^{99,100} independently refer to as positive non-linear effect (abbreviated as (+)-NLE (asymmetric amplification¹⁰¹)) has attracted current attention to achieve higher level of asymmetric induction than the enantio-purity of the non-racemic (partially resolved) catalysts.^{97,98,101-103} In turn, (-)-NLE stands for the opposite phenomenon of concave deviation, namely negative non-linear effect.

We have observed a remarkable level of (+)-NLE in the catalytic ene reaction. For instance, in the glyoxylate-ene reaction, the use of a catalyst prepared from BINOL of 33.0% ee provides the ene product with 91.4% ee in 92% chemical yield (Scheme 6.18).^{99,100} The ee thus obtained is not only much



Scheme 6.18

higher than the ee of the BINOL employed, but also very close to the value (94.6% ee) obtained using enantiomerically pure BINOL (Fig. 6.1).

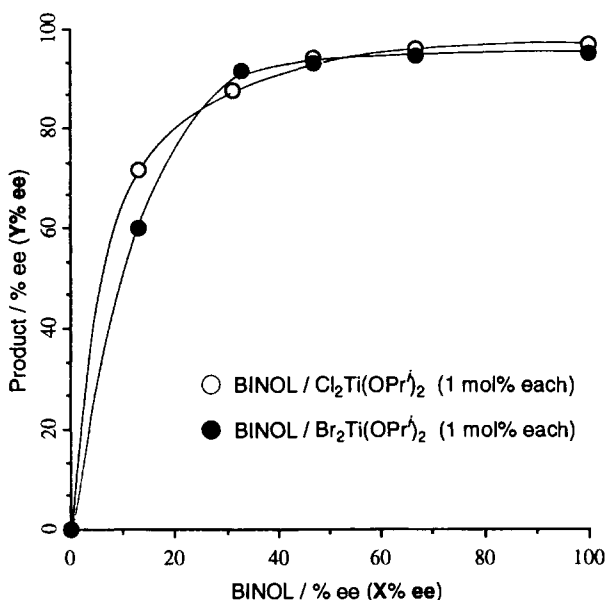


Fig. 6.1. (+)-NLE in asymmetric glyoxylate-ene reaction catalysed by BINOL-Ti complex (2).

7. Enantiomer-selective activation of racemic catalysts

Whereas non-racemic catalysts can generate non-racemic products with or without NLE, racemic catalysts inherently produce only racemic products. A strategy whereby a racemic catalyst is enantiomer-selectively de-activated by a chiral molecule has been shown to yield non-racemic products.^{104,105} However, the level of asymmetric induction does not exceed the level attained by the enantiopure catalyst (Fig. 6.2a). Recently, ‘chiral poisoning’¹⁰⁶ has been named for such a *de-activating* strategy. In contrast, we have reported an alternative but conceptually opposite strategy to asymmetric catalysis by

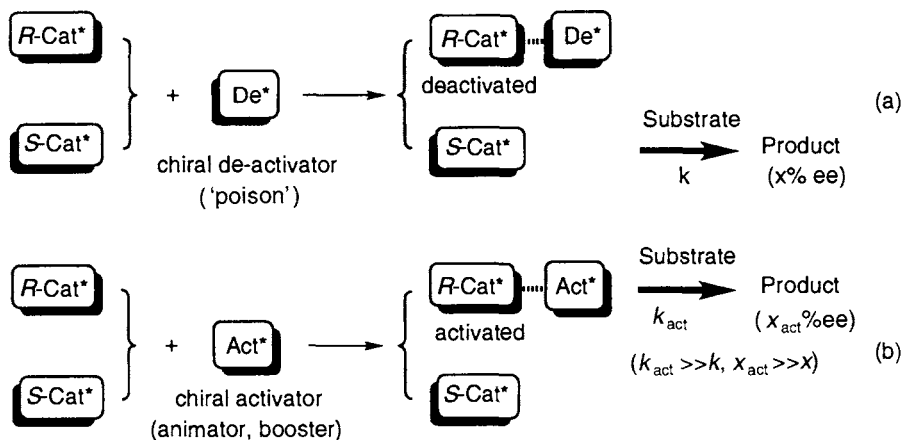
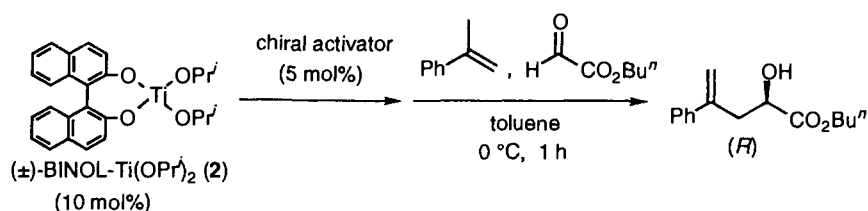


Fig. 6.2. Asymmetric de-activation (a) and asymmetric activation (b) of racemic catalysts.

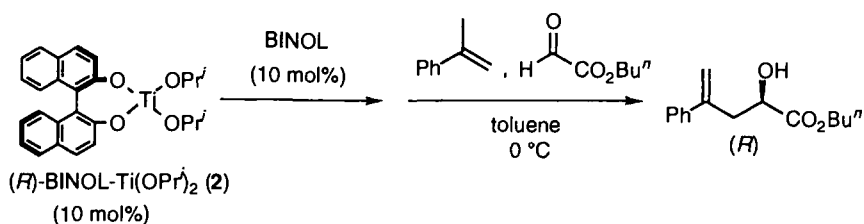
racemic catalysts. A *chiral activator* selectively activates one enantiomer of a racemic chiral catalyst. Higher enantioselectivity might be attained than that achieved by an enantio-pure catalyst ($\% \text{ ee}_{\text{act}} \gg \% \text{ ee}_{\text{enantio-pure}}$), in addition to a higher level of catalytic efficiency ($k_{\text{act}} \gg k_{\text{enantio-pure}}$) (Fig. 6.2b). However, this still remains to be examined.

Catalysis with racemic $\text{BINOL-Ti(OPr}^i)_2$ (**2**) achieves extremely high enantioselectivity by adding another diol for the enantiomer-selective activation (Table 6.3).^{107–110} Significantly, a remarkably high enantioselectivity (90% ee, *R*) was achieved using just a half-molar amount (5 mol%) of (*R*)-BINOL activator added to a *racemic* (\pm)-BINOL- $\text{Ti(OPr}^i)_2$ complex (**2**) (10 mol%).

The activation of the enantiopure (*R*)-BINOL- $\text{Ti(OPr}^i)_2$ catalyst (**2**) was investigated by further addition of (*R*)-BINOL (Table 6.4). The reaction proceeded quite smoothly to provide the carbonyl-ene product in higher chemical yield (82%) and enantioselectivity (97% ee) than without additional BINOL (95% ee, 20%). Comparing the results of enantiomer-selective activation of the racemic catalyst (90% ee, *R*) with those of the enantiopure catalyst (with (97% ee, *R*) or without activator (95% ee, *S*)), the reaction catalysed by the (*R*)-BINOL- $\text{Ti(OPr}^i)_2$ /(*R*)-BINOL complex (**2'**) is calculated to be 26.3 times as fast as that catalysed by the (*S*)-BINOL- $\text{Ti(OPr}^i)_2$ (**2**) in the racemic case (Fig. 6.3). Indeed, kinetic studies according to a rapid-quench GC analysis show that the reaction catalysed by the (*R*)-BINOL- $\text{Ti(OPr}^i)_2$ /(*R*)-BINOL complex (**2'**) is 25.6 times as fast as that catalysed by the (*R*)-BINOL- $\text{Ti(OPr}^i)_2$ (**2**). These results imply that the racemic (\pm)-BINOL- $\text{Ti(OPr}^i)_2$ (**2**) and half-molar amount of (*R*)-BINOL assemble preferentially into the (*R*)-BINOL- $\text{Ti(OPr}^i)_2$ /(*R*)-BINOL complex (**2'**) and unchanged (*S*)-BINOL- $\text{Ti(OPr}^i)_2$ (**2**). In contrast, the enantiomeric

Table 6.3 Enantiomer selective activation of racemic BINOL-Ti(OPr^{*i*})₂ (2)

Run	Chiral activator	%yield	% ee
1	none	1.6	0
2		20	0
3		38	81
4		52	90
5 ^a		35	80

^a 2.5 mol% of (*R*)-BINOL was used as a chiral activator.**Table 6.4** Asymmetric activation of enantiopure (*R*)-BINOL-Ti(OPr^{*i*})₂ (2)

Run	BINOL	Time (min)	%yield	% ee
1	none	60	20	95
2		1	1.6	95
3	(<i>R</i>)-BINOL	60	82	97
4		1	41	97
5		0.5	24	97
6	(<i>S</i>)-BINOL	60	48	86
7		0.5	2.6	86
8	(±)-BINOL	60	69	96

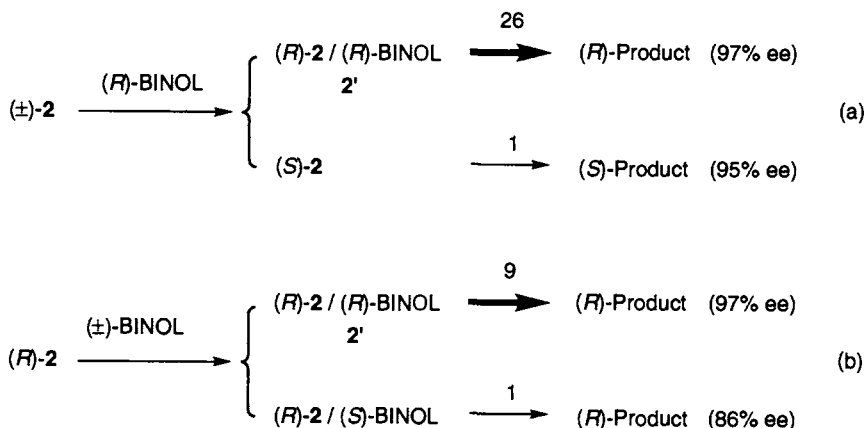


Fig. 6.3. Kinetic features of asymmetric activation of BINOL-Ti(OPrⁱ)₂ (3).

form of the additional chiral ligand ((*S*)-BINOL) activates the (*R*)-BINOL-Ti(OPrⁱ)₂ (2) to a smaller degree, thus providing the carbonyl-ene product in lower optical (86% ee, *R*) and chemical (48%) yields than (*R*)-BINOL does.

The great advantage of asymmetric activation of the racemic BINOL-Ti(OPrⁱ)₂ complex (2) is highlighted in a catalytic version (Table 6.3, Run 5). High enantioselectivity (80.0% ee) is obtained by adding less than the stoichiometric amount (0.25 molar amount) of additional (*R*)-BINOL. A similar phenomenon on enantiomer-selective activation has been observed in aldol and (hetero) Diels-Alder reactions catalyzed by a racemic BINOL-Ti(OPrⁱ)₂ catalyst (2) (see below).

Another possibility was explored using racemic BINOL as an activator. Racemic BINOL was added to the (*R*)-BINOL-Ti(OPrⁱ)₂ (2), giving higher yield and enantioselectivity (96% ee, 69%) than those obtained by the original catalyst (*R*)-BINOL-Ti(OPrⁱ)₂ (2) without additional BINOL (95% ee, 20%). Comparing the results (96% ee, *R*) by the racemic activator with those of enantiopure catalyst, (*R*)-BINOL-Ti(OPrⁱ)₂/*(R)*-BINOL (2') (97% ee, *R*) or (*R*)-BINOL-Ti(OPrⁱ)₂/*(S)*-BINOL (86% ee, *R*), the reaction catalysed by the (*R*)-BINOL-Ti(OPrⁱ)₂ catalyst/*(R)*-BINOL complex (2') is calculated to be 8.8 times as fast as that catalysed by the (*R*)-BINOL-Ti(OPrⁱ)₂/*(S)*-BINOL (Fig. 6.3). A rapid-quench GC analysis revealed the reaction catalysed by the (*R*)-BINOL-Ti(OPrⁱ)₂/*(R)*-BINOL complex (2') to be 9.2 times as fast as that catalysed by the (*R*)-BINOL-Ti(OPrⁱ)₂/*(S)*-BINOL.

8. Ene cyclization

Conceptually, intramolecular ene reactions¹¹¹⁻¹¹⁴ (ene cyclizations) can be classified into six different modes (Fig. 6.4).^{54,115} In the ene cyclizations, the

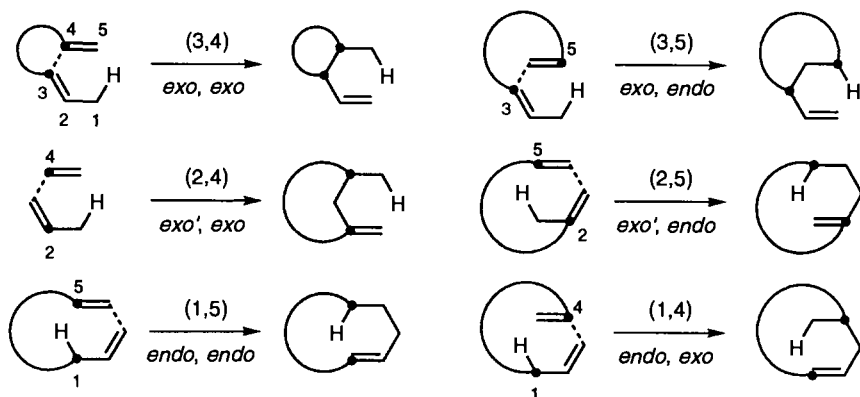
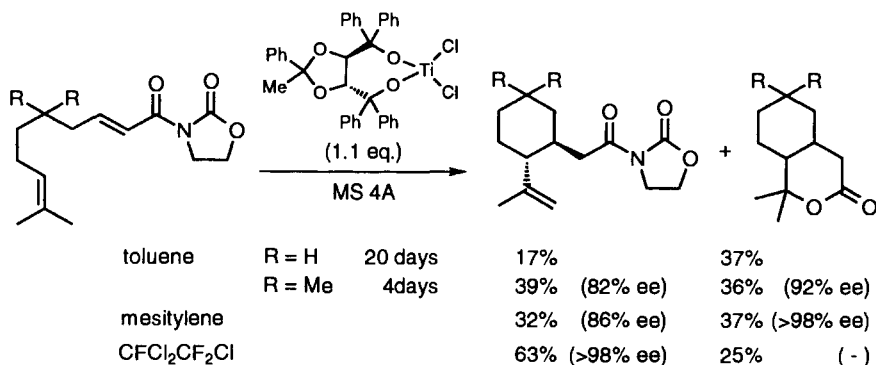


Fig. 6.4. Classification of ene cyclizations.

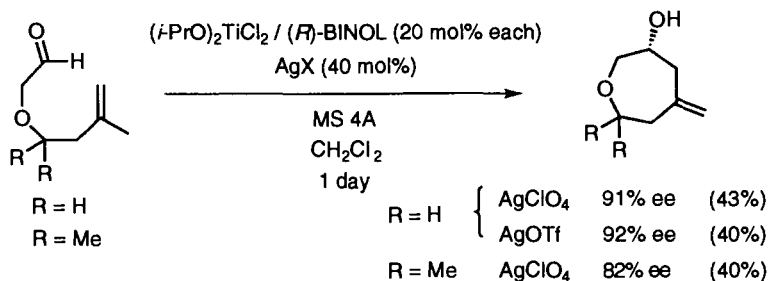
carbon numbers where the tether connects the [1,5]-hydrogen shift system, are expressed in (m,n) type. A numerical prefix stands for the forming ring size.

Asymmetric catalysis of ene reactions was initially explored in the intramolecular cases, since the intramolecular versions are much more facile than their intermolecular counterparts. The first example of an enantioselective 6-(3,4) carbonyl-ene cyclization was reported using a BINOL-derived zinc reagent.^{116,117} However, this was successful only when using an excess of the zinc reagent (at least 3 equivalents). Recently, an enantioselective 6-(3,4) olefin-ene cyclization has been developed using a stoichiometric amount of a TADDOL-derived chiral titanium complex (Scheme 6.19).¹¹⁸ In this ene reaction, a hetero Diels–Alder product was also obtained, the ratio depending critically on the solvent system employed. In both cases, geminal disubstitution is required in order to obtain high ee's values. However, neither reaction constitutes an example of a truly catalytic asymmetric ene cyclization.

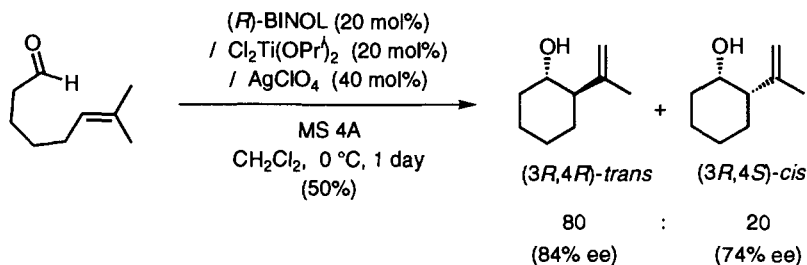


Scheme 6.19

We reported the first examples of asymmetric catalysis of intramolecular carbonyl-ene reactions of types (3,4) and (2,4), using the BINOL-derived titanium complex (**1**).^{115,119} The catalytic 7-(2,4) carbonyl-ene cyclization gives the oxepane with high ee, and gem-dimethyl groups are not required (Scheme 6.20). In a similar catalytic 6-(3,4) ene cyclization, the *trans*-tetrahydropyran is preferentially obtained with high ee (Scheme 6.21). The sense of asymmetric induction is exactly the same as observed for the glyoxylate-ene reaction: the (*R*)-BINOL-Ti catalyst provides the (*R*)-cyclic alcohol. Therefore, the chiral BINOL-Ti catalyst works efficiently for both the chiral recognition of the enantioface of the aldehyde and the discrimination of the diastereotopic protons of the ene component in a truly catalytic fashion.



Scheme 6.20



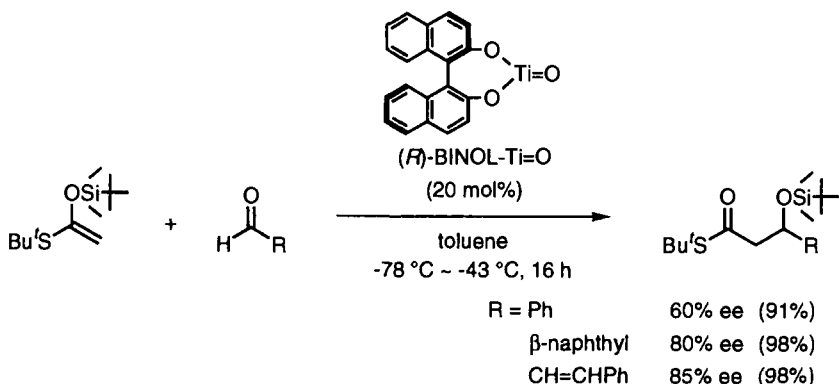
Scheme 6.21

9. Aldol reaction

The aldol reaction constitutes one of the most fundamental bond construction processes in organic synthesis.^{120,121} Therefore, much attention has been focused on the development of asymmetric catalysts for aldol reactions using silyl enol ethers of ketones or esters as storable enolate components (the Mukaiyama aldol condensation).

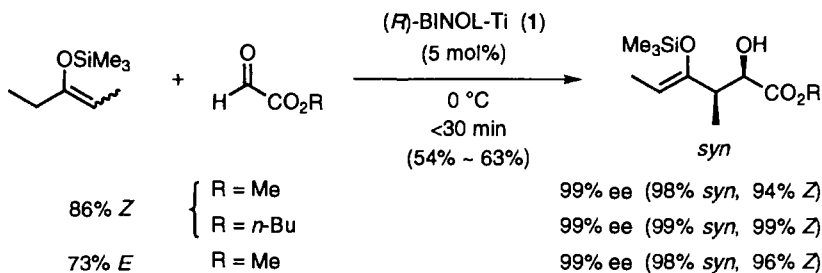
Reetz reported the catalysis by BINOL-TiCl₂ of aldol reactions with aliphatic aldehydes.¹²² In his case, BINOL-TiCl₂ was prepared by treatment of the lithium salt of BINOL with TiCl₄ in ether. After removal of the ether, the

residue was treated with dry benzene and the solid was separated under nitrogen. Removal of the solvent provided the red-brown complex, which was used as the catalyst for the aldol reaction to give 8% ee. Later, Mukaiyama reported the use of BINOL-Ti oxide prepared from $(i\text{-PrO})_2\text{Ti}=\text{O}$ and BINOL, giving moderate to high levels of enantioselectivity (Scheme 6.22).^{123,124}



Scheme 6.22

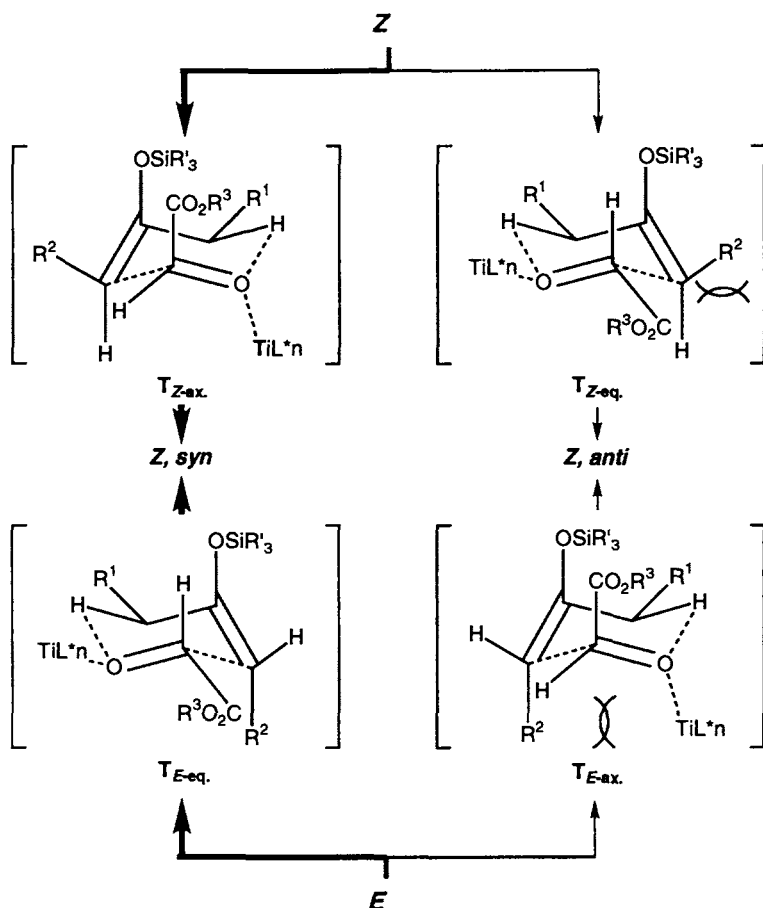
We have found that the BINOL-derived titanium complex serves as an efficient catalyst for the Mukaiyama-type aldol reaction of ketone silyl enol ethers with good control of both absolute and relative stereochemistry (Scheme 6.23).¹²⁵ Surprisingly, however, the aldol products were obtained in the silyl enol ether (ene product) form, with high *syn*-diastereoselectivity from either geometrical isomer of the starting silyl enol ethers.



Scheme 6.23

It appears likely that the reaction proceeds through an ene reaction pathway. Such an ene reaction pathway has not been previously recognized as a possible mechanism in the Mukaiyama aldol condensation. Usually an acyclic antiperiplanar transition state model has been used to explain the formation of the *syn*-diastereomer from either (*E*)- or (*Z*)-silyl enol ethers.^{126,127} How-

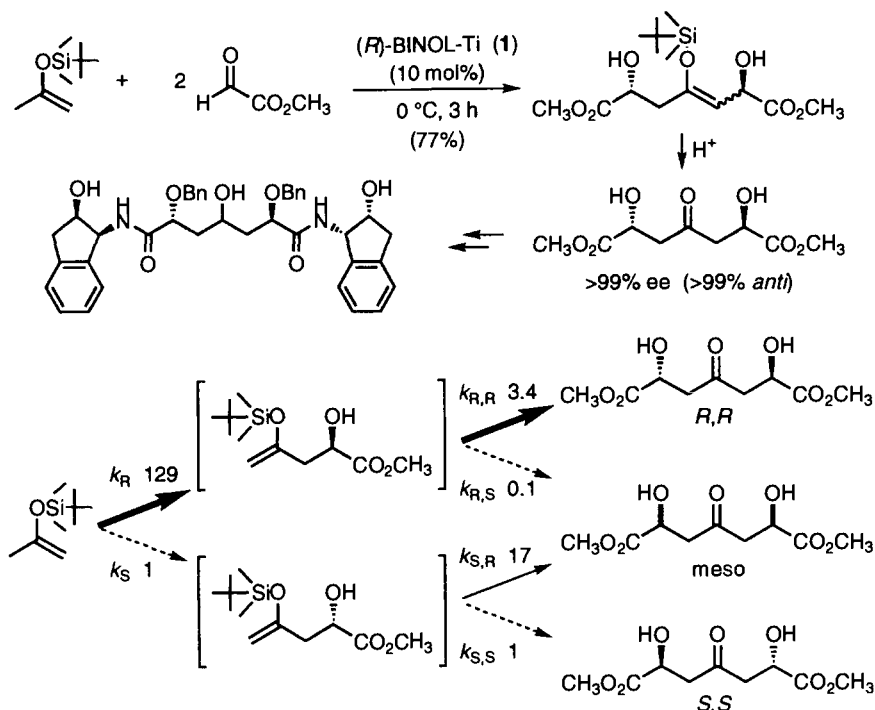
ever, the cyclic ene mechanism now provides another rationale for the *syn*-diastereoselection irrespective of the enol silyl ether geometry (Scheme 6.24).



Scheme 6.24

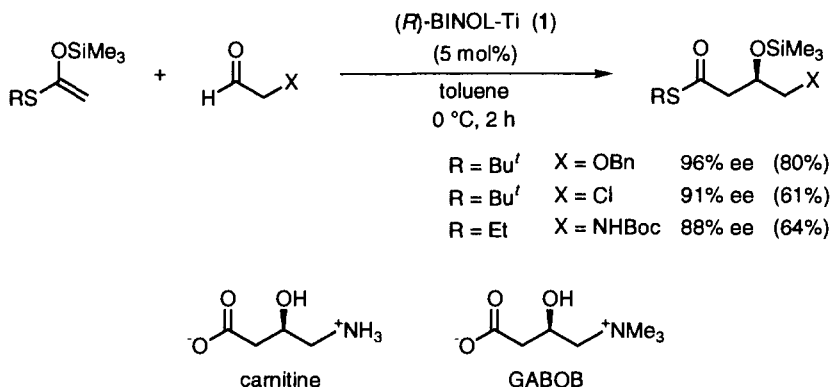
The aldol reaction of a silyl enol ether proceeds in double and two-directional fashion, upon addition of an excess amount of an aldehyde, to give the silyl enol ether in 77% isolated yield and in more than 99% ee and 99% de (Scheme 6.25).¹²⁸ The present asymmetric catalytic aldol reaction is characterized by a kinetic amplification phenomenon of the product chirality on going from the one-directional aldol intermediate to the two-directional product. Further transformation of the *pseudo* C_2 symmetric product whilst still being protected as the silyl enol ether leads to a potent analogue of an HIV protease inhibitor.

The silatropic ene pathway, that is direct silyl transfer from an enol silyl ether to an aldehyde, may be involved as a possible mechanism in the



Scheme 6.25

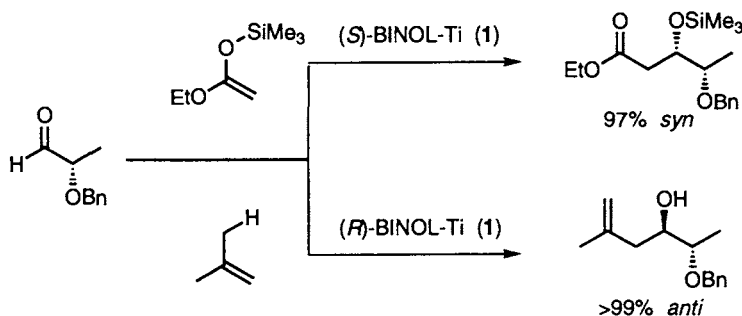
Mukaiyama aldol-type reaction. Indeed, *ab initio* calculations show the silatropic ene pathway involving the cyclic (boat and chair) transition states for the BH_3 -promoted aldol reaction of the trihydrosilyl enol ether derived from acetaldehyde with formaldehyde to be favoured.¹²⁹ Recently, we have reported the possible intervention of a silatropic ene pathway in the asymmetric



Scheme 6.26

catalytic aldol-type reaction of silyl enol ethers of thioesters.¹³⁰ Chloro and amino compounds thus obtained are useful intermediates for the synthesis of carnitine and GABOB (Scheme 6.26).^{131,132}

There is a dichotomy in the sense of *syn*- vs. *anti*-diastereofacial preference, dictated by the bulkiness of the migrating group.¹²⁹ The sterically demanding silyl group shows *syn*-diastereofacial preference but the less demanding proton leads to *anti*-preference (Scheme 6.27). The *anti*-diastereoselectivity in carbonyl-ene reactions can be explained by the Felkin–Anh-like cyclic transition state model (**T₁**) (Fig. 6.5). In the aldol reaction, by contrast, the inside-crowded transition state (**T₁'**) is less favourable than **T₂'**, because of the steric repulsion between the trimethylsilyl group and the inside methyl group of aldehyde (**T₁'**). Therefore, the *syn*-diastereofacial selectivity is visualized by the anti-Felkin–Anh-like cyclic transition state model (**T₂'**).



Scheme 6.27

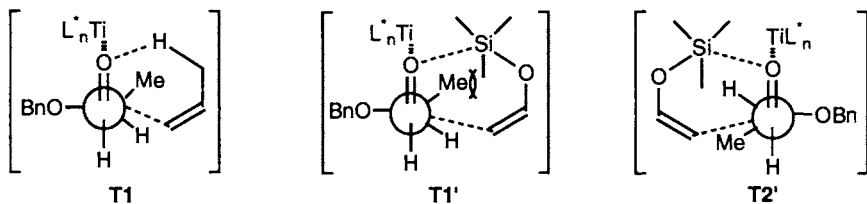
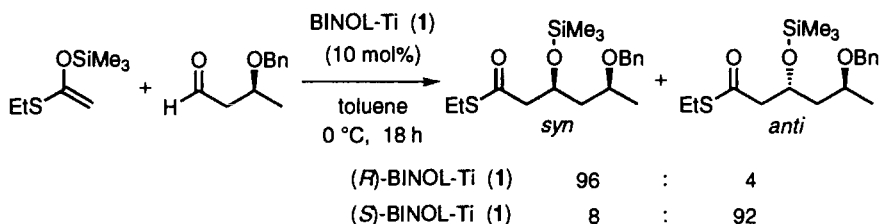


Fig. 6.5. Cyclic transition state models of ene and silatropic ene pathway.

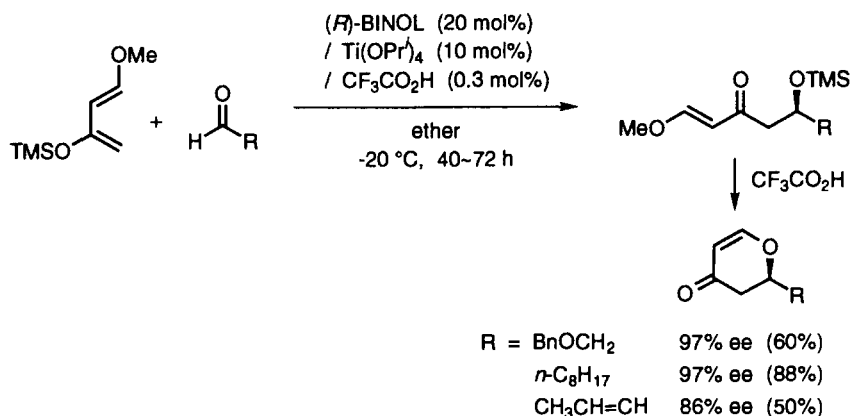
An aldol reaction with chiral β -benzyloxy aldehyde provides a method for the stereodivergent synthesis of both *syn*- and *anti*-diastereomers^{133–136} with high levels of diastereoselectivity dictated primarily by the chirality of a BINOL-Ti catalyst (**1**) rather than a β -benzyloxy aldehyde (Scheme 6.28).^{137–139} The aldol products can be used as useful key intermediates for β -lactone synthesis.¹⁴⁰

Keck¹⁴¹ and Carreira^{142,143} have independently reported catalytic asymmetric Mukaiyama aldol reactions. Keck *et al.* also reported an aldol reaction of α -benzyloxy aldehyde with Danishefsky's diene. The aldol product was trans-



Scheme 6.28

formed to the hetero Diels–Alder type product through acid-catalysed cyclization. In their method, the catalyst is prepared using 1:1 and 2:1 stoichiometry of BINOL and $\text{Ti}(\text{OPr}^i)_4$ (Scheme 6.29).¹⁴⁴ In their cases, oven dried MS 4A is used to generate the catalyst, which they reported to be of BINOL- $\text{Ti}(\text{OPr}^i)_2$ structure, under refluxing conditions.

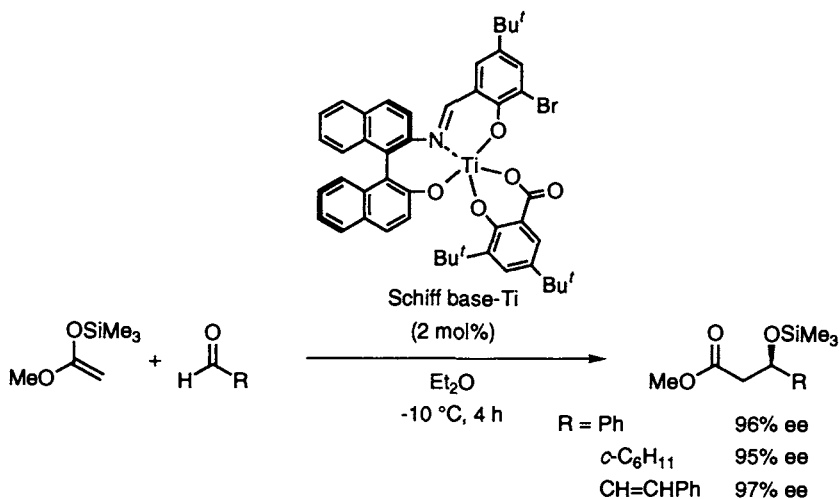


Scheme 6.29

Carreira employed a chiral BINOL-derived Schiff base–titanium complex as a catalyst for aldol reactions with acetate-derived ketene silyl acetals (Scheme 6.30).^{142,143} The catalyst was prepared in toluene in the presence of salicylic acid, which was reported to be crucial to attain a high enantioselectivity.

10. (Hetero) Diels–Alder reaction

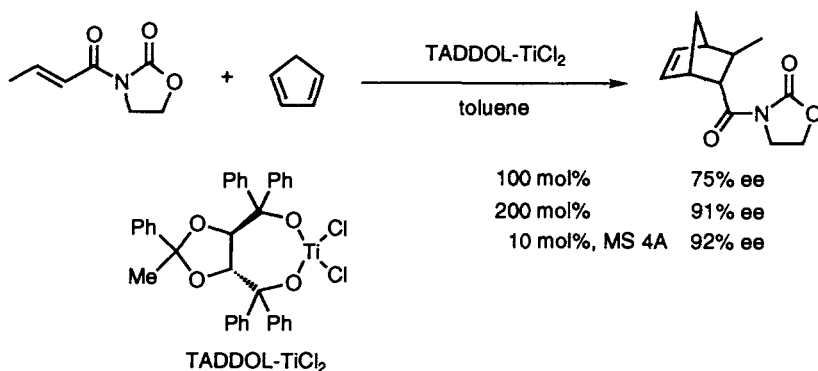
The (hetero) Diels–Alder (D–A) reaction also constitutes one of the most efficient carbon–carbon bond forming processes in the construction of six-membered rings by virtue of its high level of regioselectivity and the high



Scheme 6.30

potential for control of the absolute stereochemistry of the up to four newly created chiral centres.^{145,146}

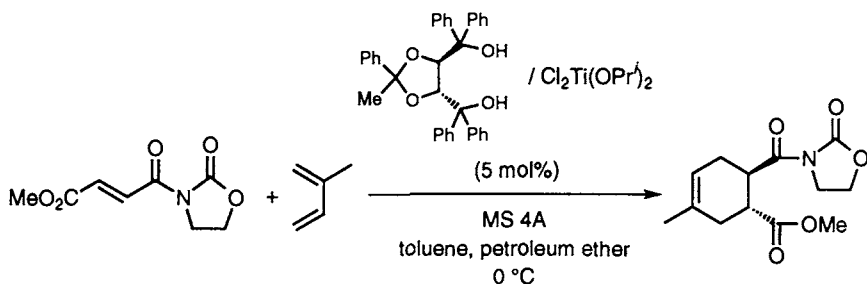
Narasaka has reported that a TADDOL–Ti dichloride—in the presence of MS 4A, acts as a good catalyst for the asymmetric catalytic D–A reactions with oxazolidinone derivatives of acrylates, giving extremely high enantioselectivities (Scheme 6.31) (Protocol 4).^{147–153}



Scheme 6.31

Protocol 4.**Asymmetric Diels–Alder reaction catalysed by TADDOL-derived titanium complex^{147,148} (Scheme 6.32)**

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.

**Scheme 6.32****Equipment**

- A pre-dried, two-necked, round-bottomed flask (30 mL) equipped with a magnetic stirring bar, a three-way stopcock, and a septum cap. The three-way stopcock is connected to a vacuum/argon source
- Dry gas-tight syringe
- A pre-dried, two-necked, round-bottomed flask (500 mL) equipped with a three-way stopcock, a magnetic stirring bar, and a septum cap. The three-way stopcock is connected to a vacuum/argon source
- Double-ended cannula

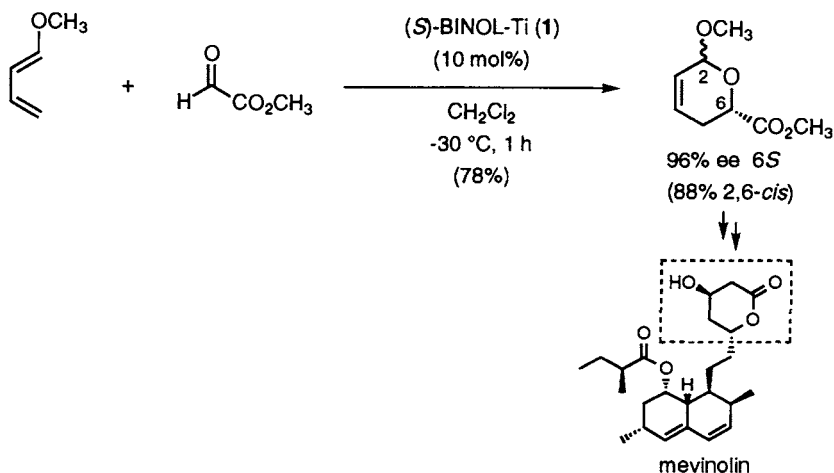
Materials

- Molecular sieves 4A, powder, <5 μm , activated, 3.74 g irritant, hygroscopic
- (2*R*,3*R*)-2,3-*O*-(1-phenylethylidene)-1,1,4,4-tetraphenylbutane-1,2,3,4-tetraol (FW 528.6), 1.32 g, 2.5 mmol
- Di-isopropoxytitanium(IV) dichloride (FW 237.0), 540 mg, 2.3 mmol moisture sensitive, irritant
- 3-((*E*)-3-(Methoxycarbonyl)propenyl)-1,3-oxazolidin-2-one (FW 199.0), 9.10 g, 46 mmol irritant
- Isoprene (FW 68.1), 50 mL cancer suspect agent, flammable liquid
- Dry toluene (distilled from P_2O_5 and from CaH_2 and stored over MS 4A) flammable liquid, toxic
- Dry petroleum ether, 150 mL flammable liquid, toxic

1. Add the di-isopropoxytitanium dichloride (540 mg, 2.3 mmol) (prepared in a similar manner as described in protocol 1) to the two-necked flask (30 mL) under argon flow, then dissolve in toluene (5 mL).
2. Add (2*R*,3*R*)-2,3-*O*-(1-phenylethylidene)-1,1,4,4-tetraphenylbutane-1,2,3,4-tetraol (1.32 g, 2.5 mmol) in toluene (5 mL) by syringe, then stir for 1 h at room temperature.
3. In the separate flask (500 mL), add toluene (175 mL) to the powdered molecular sieves 4A (3.74 g) to give a suspension.

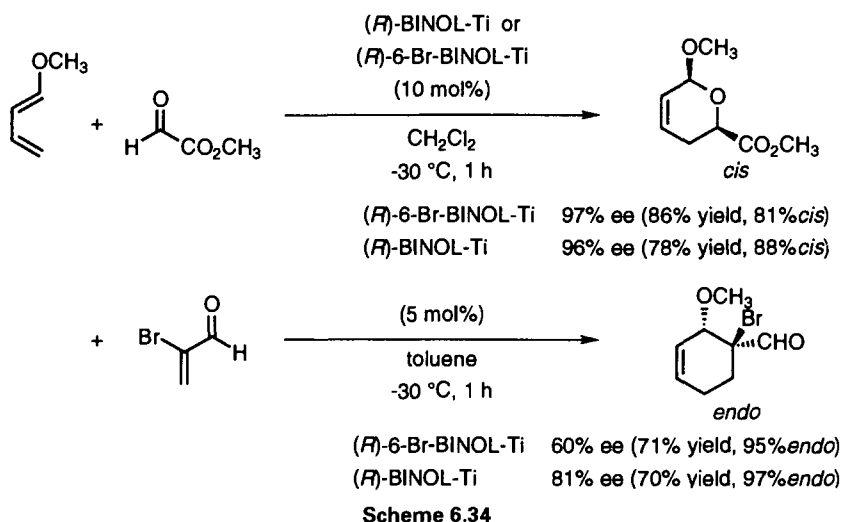
4. Add, *via* the double-ended cannula, the titanium catalyst solution to the suspension of molecular sieves 4A at room temperature.
5. Cool to 0 °C, then add 3-((*E*)-3-(methoxycarbonyl)propenoyl)-1,3-oxazolidin-2-one (9.10 g, 46 mmol), petroleum ether (150 mL), and isoprene (50 mL) in this order.
6. After stirring overnight at 0 °C, add pH 7 phosphate buffer. Filter off molecular sieves 4A through a pad of celite and rinse the filter cake with ethyl acetate. Separate the phases and extract the aqueous phase three times with ethyl acetate. Dry over Na₂SO₄, and filter the solution.
7. Concentrate the crude product under vacuum and purify the crude product by silica-gel column chromatography with hexane-ethyl acetate (4:1) as eluent to obtain 3-(((4'*R*,5'*R*)-1'-methyl-5'-(methoxycarbonyl)cyclohexen-4'-yl)-carbonyl)-1,3-oxazolidin-2-one (11.6 g, 94% yield, 93% ee). The product displays the appropriate spectral characteristics and elemental analysis. The enantiomeric purity is determined by NMR analysis with a chiral NMR shift reagent, Eu(hfc)₃ (MeO signal separated).
8. Recrystallize from hexane-ethyl acetate to give the optically pure product in 64% yield.

We have also reported that the hetero D–A reactions of glyoxylates with 1-methoxy-1,3-butadienes proceed smoothly under catalysis by BINOL–Ti complex to give the *cis*-product with high ee (Scheme 6.33).¹⁵⁴ The hetero D–A products thus obtained can be transformed into monosaccharides.^{155,156} Furthermore, the hetero D–A product can readily be converted into the lactone portion of HMG-Co A inhibitors such as mevinolin or compactin¹⁵⁷ in few steps.

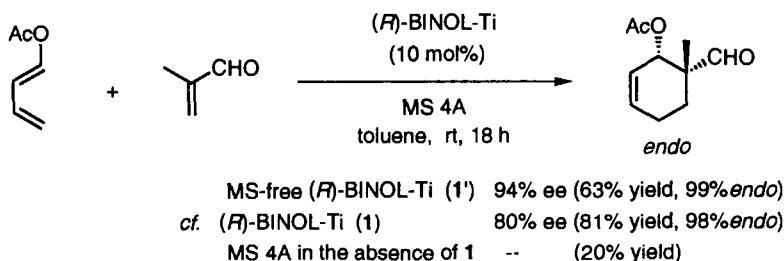


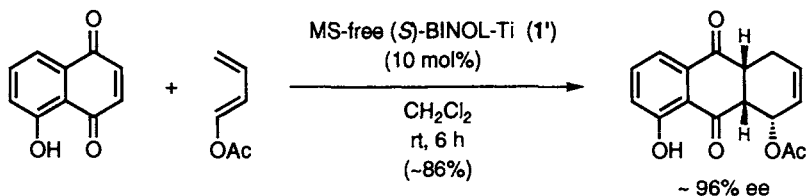
Scheme 6.32

The chiral titanium complex derived from 6-Br-BINOL affords higher enantioselectivity and catalytic activity than the parent BINOL-Ti catalyst in the hetero D-A reactions of 1-methoxydienes with glyoxylate, but not with bromoacrolein (Scheme 6.34).¹⁵⁸



The D-A reaction of methacrolein with 1,3-dienol derivatives can also be catalysed by the BINOL-derived titanium complex. However, the catalyst must be freed from MS to give the *endo*-adduct with high enantioselectivity (Scheme 6.35) (Protocol 5).^{159,160} Because MS works as an achiral catalyst for the D-A reaction. The asymmetric D-A reaction catalysed by the MS-free (MS-(–)) BINOL-Ti complex (**1'**) can be applied to naphthoquinone derivatives as the dienophile to provide an entry to the asymmetric synthesis of tetra- and anthracyclinone^{161–163} aglycones (Scheme 6.36). The sense of asymmetric induction is exactly the same as observed for the asymmetric catalytic reactions described above in the presence of MS.



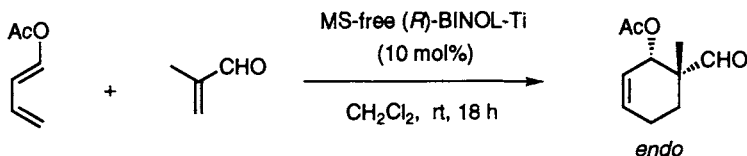


Scheme 6.36

Protocol 5.

Asymmetric Diels–Alder reaction catalyzed by MS-free BINOL-derived titanium complex^{159,160} (Scheme 6.37)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 6.37

Equipment

- A pre-dried, two-necked, round-bottomed flask (100 mL) equipped with a magnetic stirring bar, a three-way stopcock, and a septum cap. The three-way stopcock is connected to an argon source
- A pre-dried, two-necked, round-bottomed flask (100 mL) equipped with a magnetic stirring bar, a three-way stopcock, and a septum cap. The three-way stopcock is connected to a vacuum/argon source
- A pre-dried distillation apparatus
- Two pre-dried centrifuge tubes (40 mL) equipped with a septum cap
- A pre-dried, two-necked, round-bottomed flask (20 mL) equipped with a magnetic stirring bar, a three-way stopcock, and a septum cap. The three-way stopcock is connected to an argon source
- Dry gas-tight syringe
- Double-ended cannula
- Thermometers for low temperature

Materials

- Molecular sieves 4A,^a powder, <5 μm , activated, 10 g
- (*R*)-(+)- or (*S*)-(–)-1,1'-bi-2-naphthol (FW 286.3), 0.573 g, 2.0 mmol
- Di-isopropoxytitanium(IV) dibromide (FW 325.9), 0.652 g, 2.0 mmol
- 1-Acetoxy-1,3-butadiene (mixture of *trans/cis*, 6:4) (FW 112.1), 198 mL, 1.67 mmol (*trans* isomer 1.0 mmol)
- Freshly distilled methacrolein (FW 70.1), 82.8 mL, 1.0 mmol
- Dry dichloromethane
- Dry toluene
- Triethylamine (FW 101.2), 70 mL, 0.5 mmol

irritant, hygroscopic
irritant
moisture sensitive, irritant

flammable liquid, toxic
flammable liquid, corrosive
toxic, irritant
flammable liquid, toxic
flammable liquid, corrosive

1. Add the powdered molecular sieves 4A (10 g) and (*R*)-(+)-1,1'-bi-2-naphthol (0.573 g, 2.00 mmol) to the pre-dried two-necked flask, purge with argon, and add the dry CH_2Cl_2 (60 mL). Stir for 15 min at room temperature.

Protocol 5. Continued

2. Add di-isopropoxytitanium dibromide (0.652 g, 2.0 mmol) (prepared as described in protocol 1) to the suspension in one portion under a flow of argon. At this point the reaction mixture will turn into a red-brown suspension.
3. After stirring for 1 h at room temperature, transfer the suspension with the double-ended cannula to two pre-dried centrifuge tubes capped with a septum by pressurizing with argon.
4. Sediment the molecular sieves 4A by centrifugation at 4000 r.p.m. for 20 min. Transfer the resulting supernatant solvent with the double-ended cannula into the pre-dried two-necked round-bottomed flask. Exchange the septum cap with a distillation apparatus under a flow of argon.
5. Slowly evaporate the solvent *in vacuo* at 0°C. Control the speed of the distillation by regulation of the vacuum.
6. Dry the resulting dark-red solid *in vacuo* and obtain 0.58–0.62 g of the BINOL–Ti complex.^b The MS-free BINOL–Ti complex may be stored under argon in refrigerator.
7. Add the MS-free BINOL–Ti complex (43 mg, 0.1 mmol^b) to the pre-dried two-necked round-bottomed flask. Dissolve the BINOL–Ti complex with toluene (3 mL).
8. Add freshly distilled methacrolein (82.8 mL, 1 mmol) and a solution of 1-acetoxy-1,3-butadiene (198 mL, 1.67 mmol) in toluene (1 mL) at room temperature.
9. After stirring for 18 h at room temperature, dilute the resulting solution with ether (5 mL) and quench with a solution of triethylamine (70 mL, 0.5 mmol) in hexane (10 mL). At this point, a yellow precipitate will form.
10. Filter off the precipitate through a pad of Celite and florisil, and rinse the filter cake three times with ether.
11. Concentrate the crude product *in vacuo* and purify the residue by silica gel chromatography to collect 115 mg (63%) of 2-acetoxy-1-methylcyclohex-3-enecarbaldehyde. The product displays the appropriate spectral characteristics and high resolution mass spectral data.
12. The enantiomeric purity is determined by the capillary GC analysis using a CP-cyclodextrin- β -2,3,6-M-19 as a chiral stationary phase column (94% ee).

^a Purchased from Aldrich Chemical Company, Inc. and used without activation.

^b Exact molecular weight of the MS-free BINOL–Ti complex has not been determined yet. However, on the basis of elemental analysis of the BINOL–Ti complex, there exists almost any bromine (<0.1%) and the content of titanium is ranging from 10.8% to 11.2%. The catalyst mol% is therefore calculated by its titanium content (averaged value 11.0%) wherein 434 mg of the BINOL–Ti complex equal 1 mmol of titanium.

Table 6.5 NLE in asymmetric D–A reaction of 1-acetoxy-1,3-butadiene and methacrolein catalyzed by MS-free BINOL-Ti (**1'**)

Run	MS-free BINOL-Ti (1') (% ee)	%yield	%endo	%ee
1 ^a	52	41	98	76
2 ^b	50	50	99	74
3 ^c	50	62	99	40
4 ^d	50	67	99	60
5 ^e	50	62	95	29
6 ^f	–	20	–	–
7 ^g	50	52	99	53

^a Prepared from partially resolved BINOL (52% ee) and Cl₂Ti(OPrⁱ)₂.^b MS-free (*R*)-**1'** and MS-free (±)-**1'** (1:1).^c MS-free (*R*)-**1'** and MS-free (*S*)-**1'** (3:1).^d Prepared from MS-free (*R*)-**1'** and MS-free (*S*)-**1'** (3:1) in the presence of MS which was filtered prior to the reaction.^e MS-free (*R*)-**1'** and MS-free (±)-**1'** (1:1) in the presence of MS 4A.^f No MS-free catalyst (**1'**) in the presence of MS 4A.^g MS-free (*R*)-**1'** and MS-free (*S*)-**1'** (3:1) in CH₂Cl₂.

The mode of preparation of the MS-free BINOL-Ti catalyst (**1'**) determines the presence or the absence of a non-linear effect (NLE) (Table 6.5, Fig. 6.6). When the MS-free catalyst (**1'**) was prepared from partially resolved BINOL, a (+)-NLE was observed (Run 1). The combined use of an enantiopure (*R*)-**1'** and (±)-**1'** catalysts in a ratio of 1:1 results in a similar (+)-NLE (Run 2). By contrast, mixing enantiopure (*R*)- and (*S*)-**1'** catalysts in a ratio of 3:1 leads to a linearity (no NLE) (Run 3). However, a MS-free catalyst obtained by mixing (*R*)- and (*S*)-**1'** catalysts in the same ratio of 3:1 *in the presence of MS*, which was filtered off prior to the reaction, showed a (+)-NLE (Run 4). These experimental facts can be explained if the complex consists of oligomers which do not interconvert *in the absence of MS* in toluene but do interconvert in dichloromethane (see Run 7 for the 9(+)-NLE in CH₂Cl₂). When the reaction was carried out *in the presence of MS*, however, a (–)-NLE was observed (Run 5), because MS acts as an achiral catalyst for the D–A reaction (Run 6). Moreover, in dichloromethane, the combined use of (*R*)- and (*S*)-**1'** catalysts (3:1), even without prior treatment with MS, exhibited a (+)-NLE (Run 7).

Asymmetric activation of the BINOL-Ti(OPrⁱ)₂ (**2**) by (6-Br)-BINOLs is essential to provide higher levels of enantioselectivity than those attained by the enantiopure BINOL-Ti catalyst (5% ee) in the D–A reaction of glyoxylates with the Danishefsky diene (Scheme 6.38) (Protocol 6)¹¹⁰

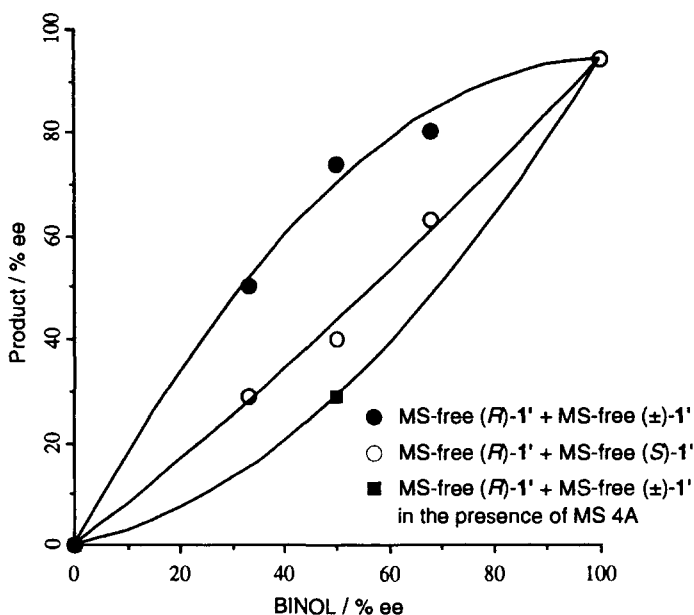
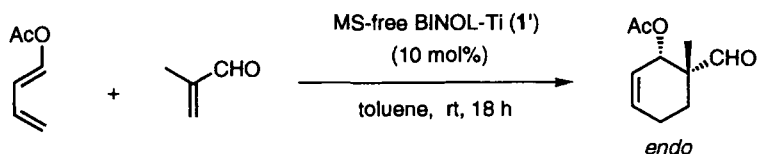
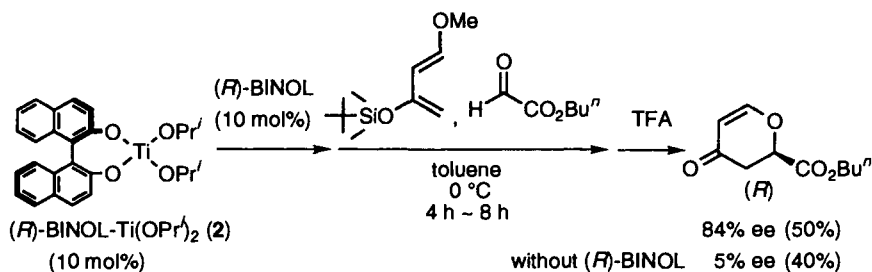


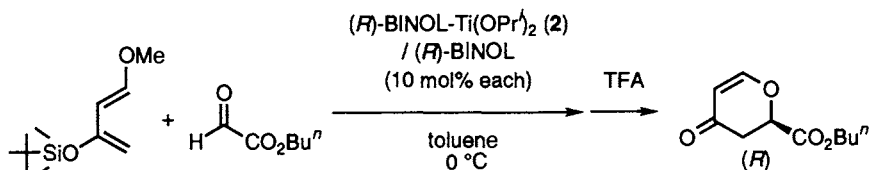
Fig. 6.6. (+)-, (-)-NLE, and linear relationships depending on the catalyst preparation.



Scheme 6.38

Protocol 6.**Asymmetric hetero Diels–Alder reaction catalysed by (*R*)-BINOL-Ti(OPr^{*i*})₂/*(R)*-BINOL complex: Asymmetric activation of (*R*)-BINOL-Ti(OPr^{*i*})₂ by additional (*R*)-BINOL¹¹⁰ (Scheme 6.39)**

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.

**Scheme 6.39****Equipment**

- A pre-dried, two-necked, round-bottomed flask (100 mL) equipped with a magnetic stirring bar, a three-way stopcock, and a septum cap. The three-way stopcock is connected to an argon source
- Dry gas-tight syringe
- Thermometers for low temperature

Materials

- (*R*)-(+)-1,1'-bi-2-naphthol (FW 286.3), 28.6 mg, 0.1 mmol × 2
- Titanium(IV) isopropoxide (FW 284.3), 0.297 mL, 0.1 mmol
- (*E*)-1-Methoxy-3-((*tert*-butyldimethylsilyl)oxy)-1,3-butadiene (FW 214.4), 257 mg, 1.2 mmol
- Freshly distilled *n*-butyl glyoxylate^a (FW 130.1), 130.1 mg, 1.0 mmol
- Dry toluene
- Trifluoroacetic acid (FW 114.0), 0.1 mL, 1.3 mmol

irritant
moisture sensitive, irritant

flammable liquid, toxic
lachrymator, irritant
flammable liquid, toxic
corrosive, toxic

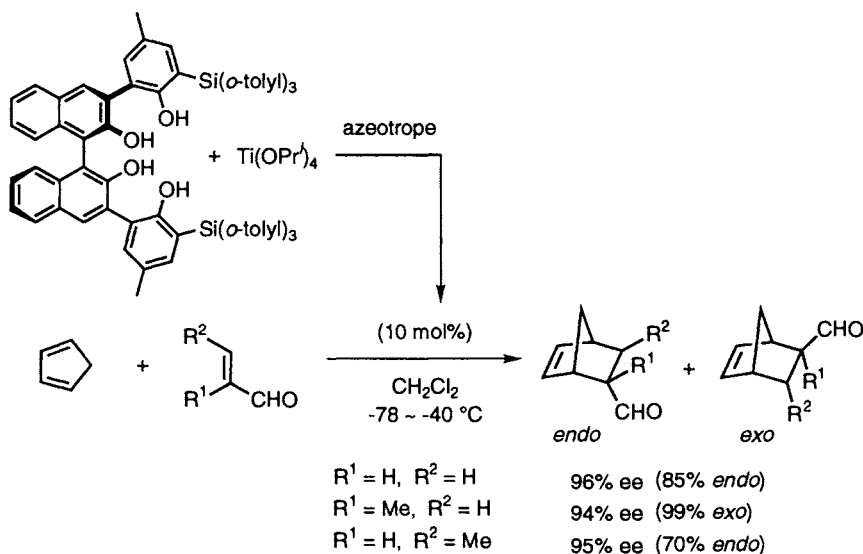
1. Add (*R*)-(+)-1,1'-bi-2-naphthol (28.6 mg, 0.1 mmol) to the pre-dried two-necked flask, purge with argon, and add the dry toluene (2 mL) and the titanium(IV) isopropoxide (0.297 mL, 0.1 mmol) in this order. Stir for at room temperature 20 min. At this point the mixture will turn into a yellow–orange solution.
2. Add additional amount of (*R*)-(+)-1,1'-bi-2-naphthol (28.6 mg, 0.1 mmol) to the solution in one portion under a flow of argon. The mixture will turn immediately into a red–brown solution.
3. After stirring at room temperature for 20 min, cool the catalyst solution to 0 °C. Add the (*E*)-1-methoxy-3-((*tert*-butyldimethylsilyl)oxy)-1,3-butadiene (257 mg, 1.2 mmol) and the freshly distilled *n*-butyl glyoxylate (130.1 mg, 1.0 mmol) in this order to the catalyst solution.
4. After stirring at 0 °C for 2 h, add the trifluoroacetic acid (0.1 mL, 1.3 mmol) to the reaction mixture at that temperature.

Protocol 6. Continued

5. Stir for an additional 5 min at 0°C and then add saturated NaHCO₃ (10 mL) at that temperature. Filter the resulting yellowish suspension through a pad of Celite and rinse the filter cake with ether.
6. Separate the phases of the filtrate and extract the aqueous phase three times with ether (15 mL). Wash the combined organic phases twice with brine, dry over magnesium sulfate, and filter the solution.
7. Concentrate the crude product under vacuum and purify the crude product by silica-gel column chromatography with hexane–ethyl acetate (10:1) as eluent to obtain butyl 3,4-dihydro-4-oxo-2*H*-pyran-2-carboxylate (99.1 mg, 50% yield).
8. The product displays the appropriate spectral characteristics. The enantiomeric purity is determined by the HPLC analysis using a CHIRALPAK AS as a chiral stationary phase column with 10% *i*-PrOH/hexane as a mobile phase (84 %ee).

^a Immediately prior use, the *n*-butyl glyoxylate is depolymerized by vacuum distillation from phosphorus pentoxide (10% weight) bp. 80°C/35 mmHg, bath temperature 120–140°C.

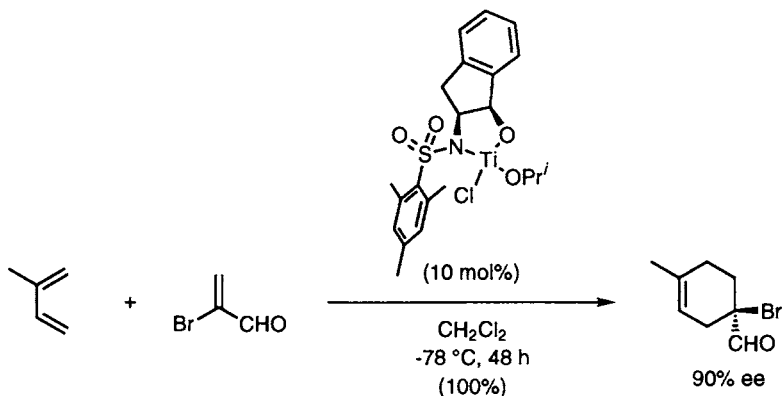
As shown above, asymmetric catalysis of the D–A reactions have been attained using chiral titanium complexes bearing chiral diol ligands.^{164–166} Whereas Yamamoto has reported a chiral helical titanium complex derived from Ti(OPr^{*i*})₄ and a BINOL-derived tetraol ligand (Scheme 6.40).¹⁶⁷ The

**Scheme 6.39**

6: Chiral titanium complexes for enantioselective catalysis

D–A products are obtained with uniformly high enantioselectivity, irrespective of the substituent pattern of α,β -unsaturated aldehydes.

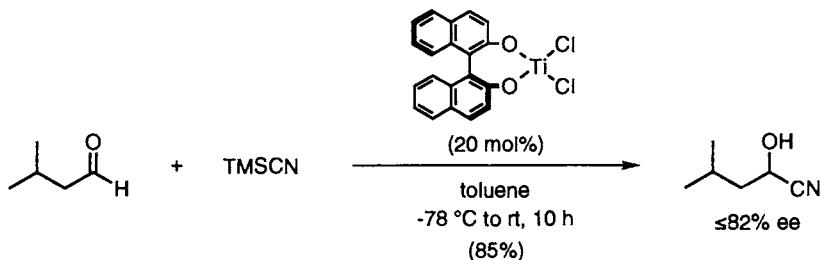
Corey has also reported a new type of chiral titanium complex, which is derived from an amino alcohol ligand¹⁶⁸ (Scheme 6.41). The chiral titanium complex serves as an efficient asymmetric catalyst for the reaction of 2-bromoacrolein to yield the D–A product in high enantioselectivity.



Scheme 6.41

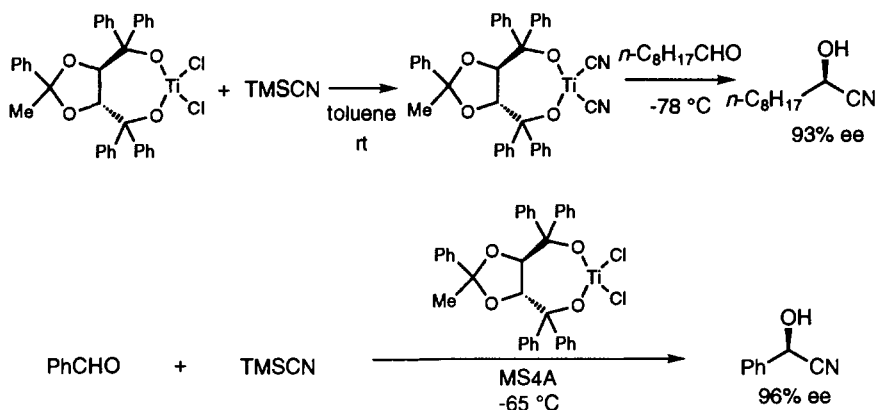
11. Cyanohydrine formation

In the addition reaction of cyanotrimethylsilane¹⁶⁹ to aliphatic aldehydes, another synthetic application of a BINOL-Ti catalyst was reported by Reetz.¹²² In his case, however, BINOL- TiCl_2 was reported to be prepared by treatment of the lithium salt of BINOL with TiCl_4 in ether (see above). The BINOL- TiCl_2 thus obtained was used as a catalyst for the cyanosilylation reaction to give the cyanohydrins in $<82\%$ ee (Scheme 6.42).



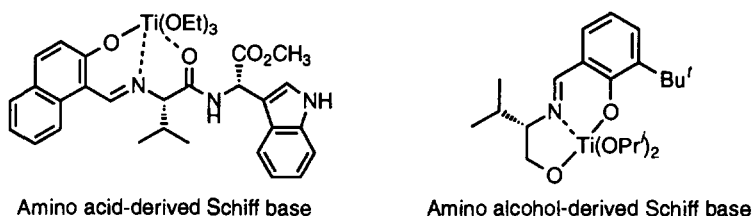
Scheme 6.42

Narasaka has also reported that TADDOL-Ti dichloride acts as a good catalyst for the asymmetric addition of trimethylsilylcyanide to aromatic and aliphatic aldehydes (Scheme 6.43).¹⁷⁰ The reactions proceeded only in the



Scheme 6.43

presence of MS 4A. In the reaction with aromatic aldehydes, a chiral cyanotitanium species, which is obtained by mixing of the TADDOL-Ti dichloride and trimethylsilylcyanide prior to addition of the aldehydes, acts as a better chiral cyanating agent to afford higher enantiomeric excesses. Chiral titanium complexes obtained after addition of a salicylaldehyde-type Schiff bases have been reported to catalyse the asymmetric addition of hydrogen cyanide¹⁷¹ or trimethylsilylcyanide^{172–174} to aromatic and aliphatic aldehydes with high enantioselectivity (Scheme 6.44).



Scheme 6.44

12. Miscellaneous reactions

Chiral titanium complexes are also used as effective asymmetric catalysts for other carbon–carbon bond forming reactions, such as inverse electron-demand Diels–Alder reactions,^{175–177} [2+2] additions,^{178,179} [2+3] additions,¹⁸⁰ Michael additions,^{181,182} and others^{183–187}. From a practical point of view, the development of more active and efficient catalysts is important, for the molecular design of asymmetric catalysts is the key to the basis of the structure–catalytic activity relationship. Although structure determination of active titanium species has been quite limited so far,^{188–194} any progress along this line is highly promising and worth the effort.

Acknowledgements

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