Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 2913–2925

TETRAHEDRON: *ASYMMETRY*

Asymmetric Diels–Alder and ene reactions promoted by a Ti(IV) complex bearing a C_2-symmetric tridentate ligand †

G. Manickam and G. Sundararajan *

Department of Chemistry, Indian Institute of Technology, Madras 600 036, India

Received 13 June 1999; accepted 16 July 1999

Abstract

A new Ti(IV) complex obtained from the C_2-symmetric amino diol (1*R*,5*R*)-3-aza-3-benzyl-1,5-diphenyl pentan-1,5-diol, (1*R*,5*R*)-**1**, is used effectively as a Lewis acid promoter in asymmetric Diels–Alder reactions. Using various Evans' oxazolidinones as dienophiles and cyclopentadiene as the diene high yields of the adducts with moderate enantioselectivity, under different reaction conditions are achieved. The effects of solvent, temperature and ligand on the enantioselectivity of the Diels–Alder products are reported. Molecular modelling studies provide an understanding of the diastereofacial selectivity of the Diels–Alder reactions. Asymmetric carbonyl-ene reactions between various glyoxylate esters and α-methyl styrene are also described.

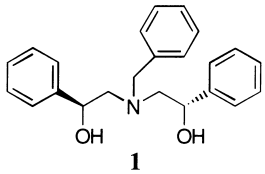
1. Introduction

Pericyclic reactions such as Diels–Alder and ene reactions have found widespread application in organic synthesis, because of their ability to control the relative and more often the absolute stereochemistry during carbon–carbon bond formation.[1] Our objective here is to synthesise a new catalyst system for promoting asymmetric Diels–Alder and glyoxylate-ene reactions that can give high yields and enantioselectivities. Lewis acid catalysts derived from boron,[2] aluminium,[3] titanium,[4] transition metals,[5] magnesium[6] and lanthanides[7] are effectively used as promoters or catalysts in asymmetric Diels–Alder and ene[8] reactions. Although large numbers of catalysts for asymmetric Diels–Alder and ene reactions are known in the literature, greater degrees of asymmetric induction can occur with chiral Lewis acids having chiral C_2-symmetric bidentate diols as ligands[9] and these ligands are mostly derived from the binaphthol or tartaric acid.[10,11]

* Corresponding author. E-mail: gsundar@acer.iitm.ernet.in

† Dedicated to Professor K. K. Balasubramanian on the occasion of his 60th birthday

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00300-6



1

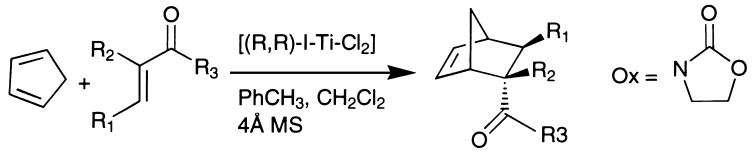
Recently, a wide range of chiral C_2-symmetric tridentate ligands with N and/or O as donor atoms[12] have attracted attention for application in asymmetric catalytic hydrogenation,[13] reduction,[14] epoxidation,[15] cyclopropanation[16] and aldol[17] reactions. For example, the chiral amino diol, (1*R*,5*R*)-3-aza-3-benzyl-1,5-diphenyl pentan-1,5-diol, (1*R*,5*R*)-**1**, has been used as tridentate modifier in asymmetric allylic alkylation,[18] reduction of prochiral ketones,[19] Meerwein–Ponndorf–Verley reduction of aryl methyl ketones,[12a] and in the synthesis of chiral diaza-18-crown-derivatives.[20] More recently, Evans et al. demonstrated that the tridentate py-box copper(II) complexes are very efficient chiral catalysts for asymmetric Diels–Alder reactions.[21] Apart from these references, there is no literature report available for the preparation of titanium(IV) alkoxide complexes derived from this amino diol **1** or their role in promoting asymmetric Diels–Alder and ene reactions.

Recently we reported the synthesis of an aluminium–lithium heterobimetallic complex derived from the amino diol **1** that effectively catalyses the asymmetric Michael addition reaction with high enantioselectivities (up to 94% ee).[22] Also in a preliminary communication, we described the acceleration of the Diels–Alder reaction between cyclopentadiene and symmetrical/unsymmetrical dienophiles by achiral titanium(IV) alkoxide complexes.[23] With our continued interest in the area of asymmetric induction in organic reactions using C_2-symmetric chiral ligands, in this paper, we focus our attention on: (a) asymmetric Diels–Alder reactions of various unsymmetrical dienophiles with cyclopentadiene under different reaction conditions; (b) asymmetric carbonyl-ene reactions of various glyoxylates with α-methyl styrene; and (c) the effects of ligand, solvent and temperature in asymmetric Diels–Alder and carbonyl-ene reactions.

2. Results and discussion

Earlier we detailed the results of our investigation on the Diels–Alder reaction under three different reaction conditions (Scheme 1).[23] In method A, the complex was obtained by mixing $TiCl_4$ and $Ti(O^iPr)_4$ in the ratio of 5:1 followed by the addition of **1** at −78°C. To the complex generated in situ, the dienophile and the diene were added and stirred at −78°C. In method B, the complex was prepared as in method A but the addition of the dienophile and the diene was done at −78°C and the mixture was slowly warmed to room temperature. In method C, the catalyst precursor was prepared in situ by adding $TiCl_4$ to $Ti(O^iPr)_4$ in dichloromethane, 1:1 stoichiometry, at room temperature. To this mixture the amino diol in toluene was added at −78°C, and subsequent solvent removal under reduced pressure gave the required Ti(IV) complex as a white powder. It was noted that depending on the mode of generation, the titanium complexes promoted the Diels–Alder reactions between cyclopentadiene **2** and the dienophiles in varying degrees of efficiency and method C proved to be the most effective for yielding highly *endo*-selective Diels–Alder adducts. With the encouraging observation drawn from the above preliminary work, we decided to study the asymmetric variation of the Diels–Alder reaction using chiral Lewis acids obtained from the reaction of a homochiral amino diol with $Ti(O^iPr)_2Cl_2$. Accordingly, the Diels–Alder reaction was performed under different conditions using Evans' achiral α,β-unsaturated-*N*-acyloxazolidinones[24] as dienophiles and cyclopentadiene as diene with the chiral Ti(IV) complex as catalyst and the results

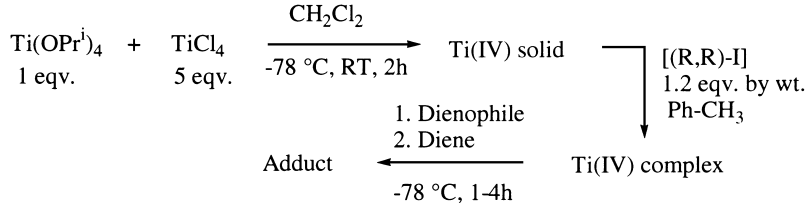
obtained are shown in Table 1 (Eq. 1). In all cases, the amino diol was recovered in good yield from the reaction mixture with same enantiomeric purity and was reused.



2	R_1	R_2	R_3		R_1	R_2	R_3
3	Me	H	Ox	8	Me	H	Ox
4	Ph	H	Ox	9	Ph	H	Ox
5	H	H	Ox	10	H	H	Ox
6	H	CH_2CO_2H	OMe	11	H	CH_2CO_2H	OMe
7	H	Me	Ox	12	H	Me	Ox

(1)

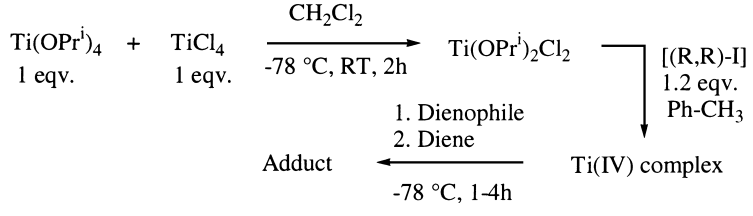
Method A:



Method B:

Dienophile and diene added to the Ti(IV) complex at -78 °C, stirred for 3-4h at RT.

Method C:



Scheme 1. The three methodologies employed for the preparation of the Ti(IV) complex bearing the amino diol **1**

The products were characterised by standard techniques listed in the Experimental. Single crystal X-ray determinations for the adduct **8** and **9** were also obtained.[25] The enantiomeric excesses of the products were calculated from the maximum specific rotation values available in the literature. The enantiomeric excess of adduct **9** obtained by method A was further estimated to be 67% on the basis of HPLC analysis using a Chiracel-OD column (hexane:isopropanol 9:1 mixture as eluent). When we performed the reaction of cyclopentadiene with **3** at −78°C by method C (Table 1, entry 4), there was not much variation in the *endo*:*exo* ratio or enantiomeric excess of the adduct **8**. However, for entry 8 we found an increase in the enantiomeric excess for the adduct **9** (75% on the basis of HPLC and $[\alpha]_D$=−128 (c=1.1, CCl_4)) with no appreciable variation in *endo*:*exo* ratio. Collectively, the experimental results shown in Table 1 suggest that with an increase in temperature there is an increase in the yield, but a decrease in enantiomeric excess. This might suggest that the Lewis acid–dienophile complex is probably more rigid at lower temperatures than at higher temperatures and that the dienophile can rotate freely

Table 1
Diels–Alder reactions between cyclopentadiene, **2**, and unsymmetrical dienophiles (α,β-unsaturated *N*-acyloxazolidinones) promoted by a Ti(IV) complex bearing **1**

No.	Reaction	Method	Time (h)	% Yield	*endo : exo*	% ee[a]
1	**3 to 8**	A	6	35	90:10	57
2	**3 to 8**	B	6	69	90:10	42
3	**3 to 8**	C	6	92	89:11	27
4	**3 to 8**	C[b]	10	38	90:10	29
5	**4 to 9**	A	8	42	87:13	65
6	**4 to 9**	B	8	49	86:14	46
7	**4 to 9**	C	8	60	86:14	20
8	**4 to 9**	C[b]	10	51	85:15	75
9	**5 to 10**	C	12	85	84:16	53
10	**6 to 11**	C	6	86	82:18	nd[c]
11	**7 to 12**	B	8	70	81:19	nd[c]

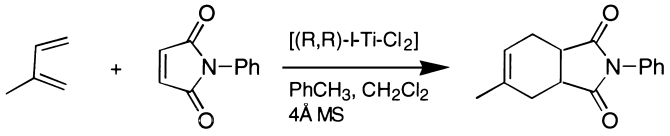
[a] Determined by optical rotation values and/or chiral HPLC analysis,
[b] Reaction temperature –78°C , [c] ee -not determined

Table 2
Effect of the substituent on nitrogen over the asymmetric Diels–Alder reaction between **2** and **4**

No	Ligand (R)	% Yield	endo/exo	% ee
1	Bn	69	88:12	65
2	Cy	62	88:12	62
3	^{i}Pr	63	87:13	59

around the metal centre at higher temperature. As a consequence, the diene approaches the dienophile more rapidly to give a high yield of the adduct at the expense of enantiomeric excess.

Under the same reaction conditions, the diene isoprene **13** with the dienophile *N*-phenylmalimide **14** gave *N*-phenyl-1-methylcyclohexene-3,4-dicarboximide **15** (Eq. 2) in good yield (75%).[26]



(2)

13 **14** **15**

It is known that the regio- and enantioselectivity of the Diels–Alder adduct depends not only on the nature of the substrate and the catalyst used, but also on the nature of substitution on the ligand. Thus to verify this effect, we performed the asymmetric Diels–Alder reaction of **2** with **4**, by varying the substituent on the nitrogen atom of the amino diol **1** and the results obtained are summarised in Table 2.

Table 3
Effect of solvent on asymmetric Diels–Alder reaction between **2** and **3**

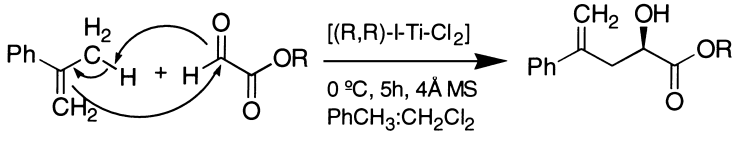
No	Solvents	% Yield	% ee
1	$PhCH_3$	63	30
2	C_6H_6	58	nd*
3	$PhCH_3$:CH_2Cl_2 (1:1)	90	56
4	CH_2Cl_2	48	nd[a]
5	Et_2O	<10	nd[a]
6	THF	40	nd[a]

[a]ee not determined

These results show that by varying the substituent on the nitrogen atom of the amino diol (*R*,*R*)-**1**, there is not much variation in the enantiomeric excess and *endo*:*exo* ratio of the products.

Solvent also plays an important role in achieving a high regio- and enantioselectivity in Diels–Alder products. Hence, the effect of solvent on the regio- and enantioselectivity of the Diels–Alder adducts with the above catalyst was examined. To understand the effect of solvent in asymmetric Diels–Alder reactions, we performed the reaction between **2** and **3** and the results are shown in Table 3. The results reveal that polar coordinating solvents such as THF and diethyl ether decrease the yield of the adduct suggesting a preventive coordination of solvent to the metal centre. But the *endo*:*exo* ratio in all these solvents is approximately 90:10. When benzene or toluene was used as solvent, the yields were not very high, probably because the solubility of the complex is poor in these solvents. The best results (90% yield) were obtained when we used a mixture of solvents (toluene:dichloromethane (1:1)).

The in situ generated chiral Ti(IV) complex was also tested for its ability to promote asymmetric glyoxylate-ene reactions with α-methyl styrene and methyl, ethyl, *n*-butyl or benzyl glyoxylate in the presence of a Ti(IV) complex at 0°C (Eq. 3). The products **21** to **24** were obtained in moderate yields and enantioselectivities. The amino diol **1** and the products were separated from the crude reaction mixture by flash column chromatography and the recovered amino diol **1** was recycled. In all these reactions stoichiometric amounts of Ti(IV) complexes were used as Lewis acid promoters. The observed yields and the enantiomeric excess are summarised in Table 4.



(3)

16

17 R=Me
18 R=Et
19 R= ^{n}Bu
20 R=Bn

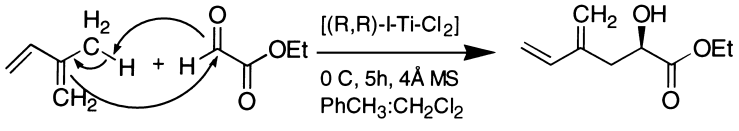
21 R=Me
22 R=Et
23 R=Et
24 R=Bn

Table 4
Asymmetric glyoxylate-ene reaction of α-methyl styrene with various glyoxylate esters

No.	Ene	R	Temp	% Yield	% ee
1	16	Me	-78 °C	40	52
2	,,	Me	0 °C	56	48
3	,,	Me	rt	60	32
4	,,	Et	0 °C	52	nd[a]
5	,,	^{n}Bu	0 °C	48	nd[a]
6	,,	Bn	0 °C	43	nd[a]
7	Isoprene	Et	0 °C	38	52

[a]ee not determined

The spectral data of the resulting α-hydroxy alcohols were in accordance with the literature data. We also performed the reaction of **13** with **18** that gave only the ene product, ethyl-2-hydroxy-4-methylene-5-hexenoate **25**, with moderate yield and enantioselectivity (Eq. 4). We could not detect any Diels–Alder adduct in this reaction.[27]



(4)

13 **18** **25**

The effect of temperature on the enantioselectivity of the ene product was studied for the asymmetric glyoxylate-ene reaction with **16** and **17**. The results showed that an increase in temperature increased the yield, but the enantiomeric excess of the products decreased. This observation is similar to those made in asymmetric Diels–Alder reaction.

Molecular modelling studies were undertaken to provide a better understanding on the diastereofacial selectivity of the Diels–Alder reaction. These studies were performed with the PCMODEL software available from Serena Software, Illinosis, USA. The MMX energy minimised structure for the Ti(IV)dichloro((*R*,*R*)-**1**) complex is shown in Fig. 1(a) and it has a lower total energy of 21.706 kcal/mol. The MMX energy minimised conformation for *trans*-cinnamoyloxazolidinone–Ti(IV) complex was also generated, whose structure is given in Fig. 1(b). This structure has a lower total energy of 53.210 kcal/mol. As illustrated in Fig. 1(b), the approach of the diene towards the bottom side of the *trans*-cinnamoyloxazolidinone–Ti(IV) complex is hindered by the phenyl ring of the ligand and also by the five-membered ring of the oxazolidinone. Consequently the cycloaddition reaction proceeds preferentially via the approach of the diene from the top of the *trans*-cinnamoyloxazolidinone–Ti(IV) complex to give adduct with the expected configuration for the major product. The selected bond parameters are listed in Table 5.

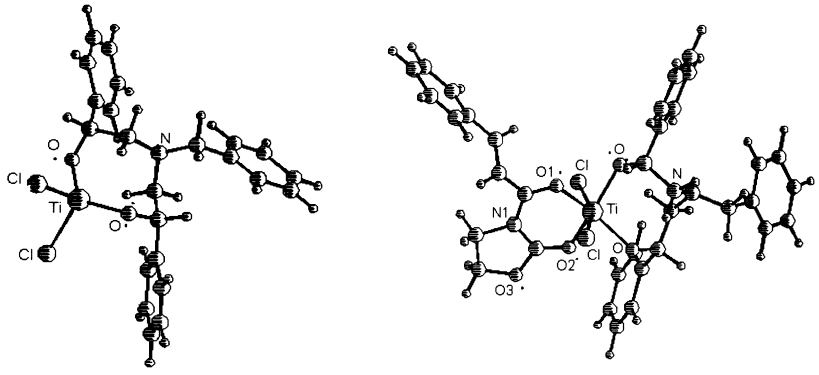


Figure 1. Energy minimised conformation of (a) Ti(IV) complex, (b) cinnamoyloxazolidinone–Ti(IV)–Lewis acid complex

Table 5
Selected parameters for energy minimised conformation of Ti(IV) complex and dienophile–Ti(IV)–Lewis acid complex

Parameters	Free complex (a)	With dienophile (b)
Energy (kcal/mol)	21.708	53.210
Torsion angle	18.983	36.714
Dipole moment	1.310	6.129
Bond distances		
Ti-O	1.99	2.03 (for $=O_1$-Ti, 1.79)
Ti-N	3.33	3.80
Ti-Cl	2.49	2.60
Bond angles		
O-Ti-Cl	106.0	80.2
O-Ti-N	63.0	50.4
O-Ti-O	126.0	104.1 (for $=O_1$-Ti-$O_2=$, 100.4)
Cl-Ti-Cl	106.3	161.9

In conclusion, an asymmetric Diels–Alder reaction was carried out using various Evans' oxazolidinones as dienophiles with cyclopentadiene as the diene in the presence of a Ti(IV) complex bearing a tridentate C_2-symmetric amino diol ligand. The yield and *endo* selectivity were high and enantioselectivity was modest. The catalytic efficiency of the Ti(IV) complex to bring about the asymmetric Diels–Alder reaction was evaluated with respect to temperature, solvent and substituent on the nitrogen atom of the ligand. The ene reaction was carried out between glyoxylate esters and α-methyl styrene using the Ti(IV) complex as a promoter. The resulting ene products were obtained in moderate yield and enantioselectivity. Temperature played an important role in achieving high enantioselectivity and yield of ene products. Energy minimised conformations for free Ti(IV) complex and cinnamoyloxazolidinone–Ti(IV)–Lewis acid complex obtained gave clues to the observed enantioselectivity in the products.

3. Experimental

The dienophile *N*-phenylmalimide,[28] titanium tetraisopropoxide[29] and α,β-unsaturated-*N*-acyloxazolidinones,[30] were synthesised according to literature procedures. Cyclopentadiene was obtained by cracking of dicyclopentadiene (BDH) before use. The glyoxylate esters, lead tetraacetate and α-methyl styrene were prepared as described in the literature.[31] The glyoxylate esters were stored over P_2O_5 in a refrigerator and distilled prior to use. Dimethyl-, diethyl-, di-*n*-butyl- and dibenzyl tartrates were prepared by refluxing the tartaric acid with corresponding alcohol, in the presence of a catalytic amount of *p*-toluenesulfonic acid. The ^1H and ^{13}C NMR were recorded in $CDCl_3$ with a JEOL 400 MHz (model GSX 400) spectrometer. IR spectra were recorded with a Shimadzu (model 470) IR spectrophotometer. Mass spectra were obtained from a Finnigan MAT (model 8230) high resolution mass spectrometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter (with 10 mm cell). Chiral HPLC analyses were performed on a Chiracel OD column with hexane:isopropanol (9:1) as eluent on a Waters HPLC instrument with UV detector.

3.1. General procedure for the asymmetric Diels–Alder reaction

Method A: To a solution of titanium tetraisopropoxide (100 mg, 0.35 mmol) in dichloromethane (2 cm^3), the titanium tetrachloride (333 mg, 1.75 mmol) in hexane (2 cm^3) was added slowly and stirred for 1 h at room temperature. The solvent was removed under reduced pressure to give a titanium(IV) solid as a white powder. To a toluene (2 cm^3) solution of the titanium(IV) solid (252 mg), cooled to −78°C, the diol (302 mg, 0.87 mmol) in toluene (5 cm^3) was added slowly for a period of 30 min, slowly warmed to room temperature and stirred for 2 h. The reaction mixture was then re-cooled to −78°C, the dienophile (1 equiv. w.r.t diol) in dichloromethane (3 cm^3) was added, stirred for 15 min followed by the addition of the diene (excess) and further stirred for 4 h at −78°C. The reaction mixture was quenched by careful addition of an aqueous saturated solution of sodium hydrogen carbonate (1 cm^3), filtered through a sintered crucible over a Celite bed and extracted with dichloromethane. The organic layer was washed twice with saturated sodium chloride solution (2×10 cm^3) and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave a crude resin, which on column chromatography gave the pure adduct.

Method B: The complex was prepared as per method A. Addition of the dienophile and the diene was done at −78°C, the mixture slowly warmed to room temperature and stirred for 4 h at room temperature.

Method C: To a solution of titanium tetraisopropoxide (284 mg, 1 mmol) in dichloromethane (2 cm^3) in the presence of 4 Å MS, the titanium tetrachloride (189 mg, 1 mmol) in hexane (2 cm^3) was added slowly and stirred for 1 h at room temperature. The solvent was removed under reduced pressure to give a titanium dichlorodiisopropoxide as a white powder. To a toluene (2 cm^3) solution of $Ti(O^iPr)_2Cl_2$ (237 mg, 1 mmol), cooled to −78°C, the diol (347 mg, 1 mmol) in toluene (5 cm^3) was added slowly for a period of 30 min, warmed to room temperature and stirred for 1 h. The reaction mixture was then filtered in a Schlenk apparatus under nitrogen and subsequent removal of solvent gave the Ti(IV) complex as a white powder, which was stored at 0–4°C under nitrogen atmosphere. The Diels–Alder reaction was performed under similar conditions as detailed in method A.

3.2. endo-*3-(((1′*S,*2′*S,*3′*R,*4′*R)-*3′-Methylbicyclo[2.2.1]hept-5′-en-2′yl)-carbonyl)-1,3-oxazolidin-2-one* ***8***

Method A: Ti(IV) complex (301 mg, 0.65 mmol), dienophile **3** (101 mg, 0.65 mmol), diene **2** (430 mg, 6.5 mmol), yield (51 mg, 35%); *endo*:*exo* (90:10). B: Ti(IV) complex (260 mg, 0.56 mmol), dienophile **3** (87 mg, 0.56 mmol), diene **2** (370 mg, 5.6 mmol), yield (86 mg, 69%); *endo*:*exo* (90:10). C: Ti(IV) complex (286 mg, 0.62 mmol), dienophile **3** (96 mg, 0.62 mmol), diene **2** (408 mg, 6.2 mmol), yield (126 mg, 92%); *endo*:*exo* (99:11); colourless resin; $\nu_{max}(CCl_4)/cm^{-1}$ 2944, 1788, 1699, 1587 and 1379; δ_H (400 MHz; $CDCl_3$) 1.06 (d, J=6.8, 3H), 1.39 (dd, J=1.9 and 6.8 Hz, 1H), 1.63 (broad d, J=8.3 Hz, 1H), 2.04 (m, 1H), 2.46 (br s, 1H), 3.20 (br s, 1H), 3.46 (t, J=3.9 Hz, 1H), 3.82–3.99 (m, 2H), 4.33 (t, J=7.14 Hz, 2H), 5.70 (dd, J=2.5 and 5.4 Hz, 1H) and 6.29 (dd, J=2.9 and 5.4 Hz, 1H); δ_C (100 MHz; $CDCl_3$) 20.29 (q), 36.34 (d), 42.91 (t), 47.01 (t), 47.34 (d), 49.40 (d), 51.16 (d), 61.79 (t), 130.83 (d), 139.57 (d), 153.37 (s) and 174.28 (s); m/z (EI) 221.1052 (M^+, $C_{12}H_{15}NO_3$ requires 221.1432), 155, 134, 114, 91; $[\alpha]_D^{27}$: A=−118.3 (c 2.6 in CCl_4), ee 57%; B=−87.2 (c 2.3 in CCl_4), ee 42%; C=−56.1 (c 2.5 in CCl_4), ee 27%; [lit.,[30] $[\alpha]_D$=−191 (c 3.6 in CCl_4), ee 92%].

3.3. endo-*3-(((1′*S,*2′*R,*3′*R,*4′*R)-*3′-Phenylbicyclo[2.2.1]hept-5′-en-2′yl)-carbonyl)-1,3-oxazolidin-2-one* ***9***

Method A: Ti(IV) complex (293 mg, 0.63 mmol), dienophile **4** (137 mg, 0.63 mmol), diene **2** (418 mg, 6.3 mmol), yield (75 mg, 42%); *endo*:*exo* (87:13). B: Ti(IV) complex (312 mg, 0.67 mmol), dienophile **4** (146 mg, 0.67 mmol), diene **2** (445 mg, 6.7 mmol), yield (93 mg, 49%); *endo*:*exo* (86:14). C: Ti(IV) complex (278 mg, 0.60 mmol), dienophile **4** (130 mg, 0.60 mmol), diene **2** (396 mg, 6.0 mmol), yield (101 mg, 60%); *endo*:*exo* (86:14); white crystalline solid; mp 118°C (from EtOAc:hexane) (lit.,[8d] 117–118°C); $\nu_{max}(CCl_4)/cm^{-1}$ 3056, 2976, 1789, 1696 and 1376; δ_H (400 MHz; $CDCl_3$) 1.63 (dd, J=1.9 and 8.8 Hz, 1H), 1.99 (d, J=8.8 Hz, 1H), 3.05 (s, 1H), 3.39 (dd, J=1.9 and 5.4 Hz, 1H), 3.51 (s, 1H), 3.97–4.08 (m, 2H), 4.24 (dd, J=3.4 and 4.9 Hz, 1H), 4.39–4.45 (m, 2H), 5.96 (dd, J=7.3 Hz, 1H), 6.57 (dd, J=7.3 Hz, 1H) and 7.31–7.34 (m, 5H); δ_C (100 MHz; $CDCl_3$) 43.3 (t), 47.7 (d), 47.7 (d), 48.4 (d), 50.0 (d), 50.6 (d), 62.2 (t), 126.4, 127.9, 128.7, 132.4, 140.4, 144.0, 153.7 (s) and 174.2 (s); $[\alpha]_D^{27}$: A=−114.7 (c 1.3 in CCl_4), ee 65%; B=−81.7 (c 1.1 in CCl_4), ee 46%; C=−35.3 (c 1.3 in CCl_4), ee 20%; [lit.,[30] $[\alpha]_D$=−143 (c=1.2, CCl_4), ee 81%].

*3.4. 3-((1′*S,*2′*S,*4′*S)-Bicyclo[2.2.1]hept-5′en-2′ylcarbonyl-1,3-oxazolidin-2-one* ***10***

Method C: Ti(IV) complex (240 mg, 0.52 mmol), dienophile **5** (73 mg, 0.52 mmol), diene **2** (342 mg, 5.2 mmol), yield (91 mg, 85%); *endo*:*exo* (84:16); white crystalline solid; mp 67–68°C (from EtOAc:hexane) (lit.,[8d] 68–69°C); $\nu_{max}(CCl_4)/cm^{-1}$ 3056, 2950, 1769, 1690, 1378 and 1340; δ_H (400 MHz; $CDCl_3$) 1.12–2.08 (m, 4H), 3.01 (m, 1H), 3.39 (m, 1H), 3.75–4.51 (m, 5H), 5.91 (dd, J=2.5 and 5.8 Hz, 1H) and 6.25 (dd, J=2.3 and 5.9 Hz, 1H); δ_C (100 MHz; $CDCl_3$) 29.30, 42.08, 43.31 (d), 43.52, 46.42, 50.40 (d), 61.98, 131.62, 138.46, 154.21 and 174.68 (s); $[\alpha]_D^{27}$=−90.6 (c 1.53 in $CHCl_3$), ee 53%; [lit.,[30] $[\alpha]_D$=−65 (c 1.5 in $CHCl_3$), ee 38%].

*3.5. 2-(*endo-*Methylbicyclo[2.2.1]hept-5-ene-2-carboxylate)-acetic acid* ***11***

Method C: Ti(IV) complex (300 mg, 0.65 mmol), dienophile **6** (93 mg, 0.65 mmol), diene **2** (430 mg, 6.5 mmol), yield (120 mg, 86%); *endo*:*exo* (82:18); colourless oil; $\nu_{max}(CCl_4)/cm^{-1}$ 3128, 2960, 1744,

1702, 1635, 1427 and 1331; δ_H (400 MHz; $CDCl_3$) 0.98 (dd, J=2.9 and 12.7 Hz, 1H), 1.45 (m, 1H), 1.73 (d, J=8.8 Hz, 1H), 2.65 (m, 2H), 2.89 (s, 1H), 3.11 (s, 1H), 3.64 (s, 3H), 3.71 (s, 1H), 6.09 (dd, J=2.9 and 5.8 Hz, 1H), 6.28 (dd, J=2.9 and 5.8 Hz, 1H) and 10.04 (bs, 1H); δ_C (100 MHz; $CDCl_3$) 36.52, 42.63, 42.80, 48.11, 50.95, 51.36, 51.89, 134.10 (d), 139.78 (d), 172.64 (s) and 183.43 (s); m/z (EI) 210.08921 (M^+, $C_{11}H_{14}O_4$ requires 210.08735), 164, 144, 113 and 66; $[\alpha]_D^{27}$=−21.2 (c 1.4 in $CHCl_3$).

3.6. 3-((1′S,2′S)-2′-Methyl-bicyclo[2.2.1]hept-5′ en-2′yl-carbonyl-1,3-oxazolidin-2-one ***12***

Method C: Ti(IV) complex (279 mg, 0.60 mmol), dienophile **7** (93 mg, 0.60 mmol), diene **2** (398 mg, 6.0 mmol), yield (93 mg, 70%); *endo*:*exo* (81:19); colourless resin; $\nu_{max}(CCl_4)/cm^{-1}$ 3051, 2961, 1758, 1685, 1372, 1336 and 1133; δ_H (400 MHz; $CDCl_3$) 1.22–1.51 (m, 2H), 1.23 (s, 3H), 1.73 (dd, J=2.4 and 12.7 Hz, 1H), 1.87 (dd, J=3.4 and 12.7 Hz, 1H), 2.13 (dd, J=3.9 and 12.7 Hz, 1H), 2.57 (bs, 1H), 3.87–3.99 (m, 2H), 4.32–4.51 (m, 2H), 6.25 (s, 2H); δ_C (100 MHz; $CDCl_3$) 22.45 (q), 40.61 (t), 44.42 (t), 46.05 (t), 50.74 (d), 51.91 (d), 53.43 (s), 62.23 (t), 133.89 (d), 139.35 (d), 152.44 (s), 178.89 (s); $[\alpha]_D^{27}$=−52.8 (c=1.38 in CCl_4).

3.7. N-*Phenyl-1-methylcyclohexene-3,4-dicarboximide* ***15***

Method C: Ti(IV) complex (310 mg, 0.67 mmol), dienophile **14** (116 mg, 0.67 mmol), diene 13 (456 mg, 6.7 mmol), yield (121 mg, 75%); white crystalline solid, mp 96°C (EtOAc:hexane); $\nu_{max}(CCl_4)/cm^{-1}$ 2982, 1754, 1494 and 1120; δ_H (400 MHz; $CDCl_3$) 1.76 (s, 3H), 2.20–2.34 (m, 2H), 2.57 (dd, J=2.4 and 15.1 Hz, 1H), 2.63 (dddd, J=2.4, 6.8 and 15.4 Hz, 1H), 3.21 (dd, J=2.4 and 5.9 Hz, 1H), 3.20 (dd, J=2.4 and 17 Hz, 1H), 5.60 (m, 1H) and 7.21–7.45 (m, 5H); δ_C (100 MHz; $CDCl_3$) 23.37, 24.40, 28.79, 39.14 (d), 39.57 (d), 120.05 (d), 126.30 (d), 128.41 (d), 128.97 (d), 131.99 (s), 136.46 (s), 179.09 (s) and 179.31 (s); m/z (EI) 241.11028 (M^+, $C_{15}H_{15}NO_2$ requires 241.10874), 174, 121, 94 and 79.

3.8. General procedure for the asymmetric ene reaction

The Ti(IV) complex was prepared by the above mentioned procedure (method C). The complex (1 equiv.) was dissolved in toluene:dichloromethane (1:1) mixture and cooled to 0°C, followed by the addition of glyoxylate ester and α-methyl styrene. The reaction mixture was stirred for a further 5 h at 0°C. A procedure similar to method A was followed for the extraction and isolation of the ene products.

*3.9. (*R*)-(−)-Methyl 2-hydroxy-4-phenyl-4-pentenoate* ***21***

Ti(IV) complex (300 mg, 0.65 mmol), α-methyl styrene (77 mg, 0.65 mmol), methyl glyoxylate (114 mg, 1.3 mmol), yield (75 mg, 56%); colourless oil; $\nu_{max}(CCl_4)/cm^{-1}$ 3455, 2965, 1736, 1443, 1257, 1196, 1110 and 697; δ_H (400 MHz; $CDCl_3$) 2.80 (bs, 1H), 2.85 (dd, J=1.0 and 14.5 Hz, 1H), 3.06 (dd, J=1.0 and 19.0 Hz, 1H), 3.61 (s, 3H), 4.28 (dd, J=4.4 and 7.8 Hz, 1H), 5.20 (d, J=1.4 Hz, 1H), 5.4 (d, J=1.2 Hz, 1H) and 7.21–7.42 (m, 5H); δ_C (100 MHz; $CDCl_3$) 40.42 (t), 52.21 (q), 69.11 (d), 116.27 (t), 126.35 (d), 127.67 (d), 128.30 (d), 140.4, 143.41 (s), 174.72 (s); $[\alpha]_D^{27}$=−15.1 (c 2.8 in $CHCl_3$), ee 48%, [lit.,[32] $[\alpha]_D^{23}$=−30.55 (c 4.83 in $CHCl_3$), ee 97%].

3.10. (R)-(−)-Ethyl 2-hydroxy-4-phenyl-4-pentenoate **22**

Ti(IV) complex (292 mg, 0.63 mmol), α-methyl styrene (74 mg, 0.63 mmol), ethyl glyoxylate (116 mg, 1.13 mmol), yield (68 mg, 52%); colourless oil; $\nu_{max}(CCl_4)/cm^{-1}$ 3496, 3045, 2960, 1738, 1622, 1443, 1255, 1196 and 697; δ_H (400 MHz; $CDCl_3$) 1.02 (t, J=7.3 Hz, 3H), 2.76 (bs, 1H), 2.82–2.85 (m, 1H), 2.98–3.02 (m, 1H), 3.72 (q, J=7.4 Hz, 2H), 4.21 (dd, J=4.2 and 7.3 Hz, 1H), 5.26 (bs, 1H), 5.51 (bs, 1H) and 7.20–7.37 (m, 5H); δ_C (100 MHz; $CDCl_3$) 14.2 (q), 40.1 (t), 53.2 (t), 68.9 (d), 116.3 (t), 125.2 (d), 126.9 (d), 128.0 (d), 140.3 (s), 144.0 (s) and 175.0 (s); $[\alpha]_D^{27}$=−16.5 (c 1.8 in $CHCl_3$).

3.11. (R)-(−)-n-Butyl 2-hydroxy-4-phenyl-4-pentenoate **23**

Ti(IV) complex (261 mg, 0.56 mmol), α-methyl styrene (67 mg, 0.57 mmol), *n*-butyl glyoxylate (147 mg, 1.14 mmol), yield (68 mg, 48%); colourless oil; $\nu_{max}(CCl_4)/cm^{-1}$ 3536, 3040, 2960, 1736, 1620, 1443, 1257, 1196 and 697; δ_H (400 MHz; $CDCl_3$) 0.93 (t, J=7.3 Hz, 3H), 1.31–1.38 (m, 2H), 1.54–1.62 (m, 2H), 2.75 (bs, 1H), 2.83 (dd, J=7.3 and 14.6 Hz, 1H), 3.06 (dd, J=4.4 and 14.6 Hz, 1H), 3.82–4.00 (m, 1H), 4.01–4.09 (m, 1H), 4.27 (dd, J=4.4 and 7.8 Hz, 1H), 5.30 (bs, 1H), 5.42 (bs, 1H), 7.25–7.42 (m, 5H); δ_C (100 MHz; $CDCl_3$) 13.6 (q), 19.0 (t), 30.4 (t), 40.5 (t), 65.5 (t), 69.0 (d), 116.1 (t), 126.4 (d), 127.7 (d), 128.4 (d), 140.3 (s), 143.6 (s), 174.5 (s); $[\alpha]_D^{27}$=−16.2 (c 1.7 in $CHCl_3$).

3.12. (R)-(−)-Benzyl 2-hydroxy-4-phenyl-4-pentenoate **24**

Ti(IV) complex (243 mg, 0.52 mmol), α-methyl styrene (62 mg, 0.52 mmol), benzyl glyoxylate (172 mg, 1.0 mmol), yield (63 mg, 43%); colourless resin; $\nu_{max}(CCl_4)/cm^{-1}$ 3510, 2985, 1738, 1625, 1423 and 1190; δ_H (400 MHz; $CDCl_3$) 2.71 (bs, 1H), 2.79–2.83 (m, 1H), 4.24 (dd, J=4.1 and 7.3 Hz, 1H), 5.21 (s, 2H), 5.30 (bs, 1H), 5.58 (bs, 1H), 7.17–7.41 (m, 10H); δ_C (100 MHz; $CDCl_3$) 40.3 (t), 66.8 (t), 69.3 (d), 116.2 (t), 126.2, 126.3, 127.6, 127.7, 128.4, 128.4, 140.1 (s), 140.1 (s), 143.7 (s), 140.1 (s), 174.5 (s); $[\alpha]_D^{27}$=−22.3 (c 1.6 in $CHCl_3$).

3.13. (+)-Ethyl 2-hydroxy-4-methylene-5-hexenoate **25**

Ti(IV) complex (305 mg, 0.66 mmol), isoprene (250 mg, 3.7 mmol), ethyl glyoxylate (134 mg, 1.3 mmol), yield (84 mg, 38%); colourless resin; $\nu_{max}(CCl_4)/cm^{-1}$ 3495, 2980, 1740, 1618, 1423 and 1189; δ_H (400 MHz; $CDCl_3$) 1.10 (q, J=7.2 Hz, 3H), 2.49–2.62 (m, 1H), 2.73 (bs, 1H), 2.74–2.81 (m, 1H), 4.23–4.31 (m, 2H), 4.43–4.49 (m, 1H), 5.08–5.41 (m, 4H), 6.38 (dd, J=9.8 and 16.9 Hz, 1H); δ_C (100 MHz; $CDCl_3$) 13.8 (q), 40.2 (t), 63.2 (t), 68.3 (d), 115.2 (t), 117.8 (t), 138.4 (d), 141.1 (s), 174.8 (s); $[\alpha]_D^{27}$=+1.1 (c 1.2 in $CHCl_3$), ee 52%, [lit.,[8d] $[\alpha]_D^{20}$=+2 (c 0.9 in $CHCl_3$), ee 91%].

Acknowledgements

We thank the Council of Scientific and Industrial Research, New Delhi for financial assistance. We also thank R.S.I.C. (IITMadras) for high resolution NMR measurements.

References

1. (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876–889. (b) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: New York, 1990; pp. 1–34. (c) Kagan, H. B.; Rlant, O. *Chem. Rev.* **1992**, *92*, 1007–1079. (d) Trost, B. M. *Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency in Modern Organic Chemistry*; Pergamon Press: Oxford, 1991; Vol. 5, pp. 1–27.
2. (a) Kaufman, D.; Bose, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 545–546. (b) Bao, J.; Wulf, W. D. *Tetrahedron Lett.* **1995**, *36*, 3321–3324. (c) Motoyama, Y.; Mikami, K. *J. Chem. Soc., Chem. Commun.* **1994**, 1563–1564.
3. (a) Bao, J.; Wulf, W. D. *J. Am. Chem. Soc.* **1993**, *115*, 3814–3815. (b) Corey, E. J.; Sarshar, S.; Lee, D. H. *J. Am. Chem. Soc.* **1994**, *116*, 12089–12090. (c) Chapuis, C.; Jurczak, J. *Helv. Chim. Acta* **1987**, *70*, 436–440.
4. (a) Maruoka, M.; Murase, N.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 2938–2939. (b) Altava, B.; Burguese, M. I.; Escuder, B.; Luis, S. V.; Salvador, R.; Fraile, J. M.; Royo, A. J. *J. Org. Chem.* **1997**, *62*, 3126–3134. (c) Bosnich, B.; Odenkirk, W. *J. Chem. Soc., Chem. Commun.* **1995**, 1181–1182. (d) Mikami, K.; Matsukawa, S. *Tetrahedron: Asymmetry* **1997**, *8*, 815–816. (e) Posner, G. H.; Eydoux, F.; Lee, J. K.; Bull, D. S. *Tetrahedron Lett.* **1994**, *35*, 7541–7544. (f) Seebach, D.; Beck, A. K.; Imwinkelried, P.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954–972. (g) Mikami, K.; Terada, M.; Motoyama, Y.; Nakai, T. *Tetrahedron: Asymmetry* **1991**, *2*, 643–646. (h) Chapuis, C.; Jurczak, J. *Helv. Chim. Acta* **1987**, *70*, 436–440. (i) Narasaka, K.; Inoue, M.; Okada, N. *Chem. Lett.* **1986**, 1109–1112. (j) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340–5345. (k) Devine, P. N.; Oh, T. *J. Org. Chem.* **1992**, *57*, 396–399. (l) Engler, T. A.; Letavic, M. A.; Lynch, K. O.; Takusagawa, F. *J. Org. Chem.* **1994**, *59*, 1179–1183. (m) Wada, E.; Pei, W.; Kanemasa, S. *Chem. Lett.* **1994**, 2345–2348.
5. (a) Davenport, A. J.; Davies, D. L.; Fawcett, J.; Garratt, S. A.; Lad, L.; Russell, D. R. *J. Chem. Soc., Chem. Commun.* **1997**, 2347–2348. (b) Corey, E. J.; Imai, N.; Zhang, H. Y. *J. Am. Chem. Soc.* **1991**, *113*, 728–729. (c) Evans, D. A.; Shanughnessy, E. H.; Barnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 3193–3194. (d) Takacs, J. M.; Quincy, D. A.; Shay, W.; Jones, B. E.; Ross, C. R. *Tetrahedron: Asymmetry* **1997**, *8*, 3073–3087. (e) Davies, W. I.; Gerena, L.; Catonguay, L.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. V.; Reider, P. J. *J. Chem. Soc., Chem. Commun.* **1996**, 1753–1754.
6. (a) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807–6810. (b) Honda, Y.; Date, T.; Hiramatsu, H.; Yamauchi, M. *J. Chem. Soc., Chem. Commun.* **1997**, 1411–1412.
7. Kobayashi, S.; Ishitani, H.; Hachiya, I.; Arai, M. *Tetrahedron* **1994**, *50*, 11623–11636.
8. (a) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: New York, 1983. (b) Bolm, C.; Berrisford, D. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1717–1719. (c) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949–3954. (d) Jorgensen, K. A.; Johannsen, M. *J. Org. Chem.* **1995**, 60, 5757–5762. Reviews on ene reaction: (e) Trost, B. M. *Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency in Modern Organic Chemistry*; Pergamon Press: Oxford, 1991; Vol. 2, pp. 527–561. (f) Mikami, K.; Shimizu, S. *Chem. Rev.* **1992**, *92*, 1021–1050.
9. Whitesell, J. K. *Chem. Rev*. **1989**, *89*, 1581–1590.
10. Oh, T.; Reilly, M. *Org. Prep. Proced. Int.* **1994**, *26*, 129–158.
11. Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741–761.
12. (a) Evans, D. A.; Nelson, S. C.; Gagne, R.; Muci, A. R. *J. Am. Chem. Soc.* **1993**, *115*, 9800–9801. For more details on chiral catalytic MPV reduction: (b) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051–1069 and references cited therein. (c) Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M.; Hunziger, D. *Helv. Chim. Acta* **1992**, *75*, 2171–2209. (d) Madhusoodan, V. H.; Bhat, T. N.; Kempt, D. J.; Baldwin, E. D.; Liu, B.; Gulnik, S.; Wideburg, N. E.; Norbeck, D. W.; Appelt, K.; Erickson, J. W. *J. Am. Chem. Soc.* **1994**, *116*, 847–855. (e) Kang, S. H.; Do Hyun Ryu. *J. Chem. Soc., Chem. Commun.* **1996**, 355–356.
13. (a) Jiang, Q.; Plew, D. V.; Murtuza, S.; Zhang, X. *Tetrahedron Lett.* **1996**, *37*, 797–800. (b) Jiang, Y.; Jiang, Q.; Zhu, G.; Zhang, X. *Tetrahedron Lett.* **1997**, *38*, 215–218.
14. Dubosis, L.; Fiaud, J. C.; Kagan, H. B. *Tetrahedron: Asymmetry* **1995**, *6*, 1097–1104.
15. (a) Augier, C.; Malara, L.; Lazzeri, V.; Waegell, B. *Tetrahedron Lett.* **1995**, *36*, 8775–8778. (b) Hawkins, J. M.; Sharpless, K. B. *Tetrahedron Lett.* **1987**, *28*, 2825–2828.
16. (a) Nishiyama, H.; Aoki, K.; Itoh, H.; Iwamura, T.; Sakata, N.; Kurihara, O.; Motoyama, Y. *Chem. Lett.* **1996**, 1071–1072. (b) Park, S. B.; Sakata, N.; Nishiyama, H. *Chem. Eur. J.* **1996**, *2*, 303–306. (c) Gupta, A. D.; Bhuniya, D.; Singh, V. K. *Tetrahedron* **1994**, *50*, 13725–13730.
17. Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814–5815.
18. Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327–9347.
19. De Vries, E. F. J.; Brussee, J.; Kruse, C. G.; Van der Gen, A. *Tetrahedron: Asymmetry* **1994**, *5*, 377–386.

20. De Vries, E. F. J.; Steenwinkle, P.; Brussee, J.; Kruse, C. G.; Vander Gen, A. *J. Org. Chem.* **1994**, *58*, 4315–4325.
21. (a) Evans, D. A.; Murry, J. A.; Matt, P. V.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798–800. (b) Evans, D. A.; Kozlowski, M. C.; Tedrow, J. S. *Tetrahedron Lett.* **1996**, *37*, 7481–7484.
22. (a) Manickam, G.; Sundararajan, G. *Tetrahedron* **1999**, *55*, 2721–2736. (b) Manickam, G.; Sundararajan, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2271–2278. (c) Manickam, G.; Sundararajan, G. *Ind. J. Chem., Sect. A and B* **1997**, 36A&B, 516–518.
23. Manickam, G.; Sundararajan, G. *Ind. J. Chem., Sect. B.* **1996**, 35B, 1006–1011.
24. Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256.
25. Manickam, G. Ph.D. Thesis, Indian Institute of Technology, Madras, 1998.
26. Corey, E. J.; Sarshar, S.; Lee, D. H. *J. Am. Chem. Soc.* **1994**, *116*, 12089–12090.
27. Ene preference over Diels–Alder reaction: (a) Mikami, K.; Terada, M. *J. Chem. Soc., Chem. Commun.* **1994**, 833–834. (b) Terada, M.; Matsukawa, S.; Mikami, K. *J. Chem. Soc., Chem. Commun.* **1993**, 327–328. (c) Johannsen, M.; Jørgensen, K. A. *Tetrahedron* **1996**, *52*, 7321–7328 and Ref. 8d.
28. Cava, M. P.; Deana, A. A.; Muth, K.; Mitchell, M. J. *Organic Synthesis Coll. Vol. 5*; Baumgarten, H. E., Ed.; John Wiley & Sons: New York, 1973; p. 944.
29. Bradley, D. C.; Mehrotra, R. C.; Wardalaw, W. *Chem. Soc. J. Part 4* **1952**, 4204–4209.
30. Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340–5345.
31. Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*; Longman Group: UK, 1989; p. 441 and 591.
32. Mikami, K.; Terada, T. *Tetrahedron* **1992**, *48*, 5671–5680.