5.1. Introduction

The cyclopropane subunit has always been fascinated organic chemists as it is a basic structural element found in a wide range of naturally occurring compounds. [1] The cyclopropane ring is a highly strained entity, found in naturally occurring compounds like terpenes, pheromones, fatty acid metabolites and unusual amino acids. Many natural products of primary and secondary metabolism consists cyclopropane subunits. Cyclopropanes have been used as versatile synthetic intermediates in the synthesis of more functionalized cycloalkanes. The enantioselective synthesis of cyclopropanes are very significant though challenging task as the cyclopropanes with simple or complex functionalities are containing a broad spectrum of biological properties including antimicrobial, antibiotic, antibacterial, antitumor and antiviral, enzyme inhibition and insecticidal, antifungal, herbicidal activities.[2]

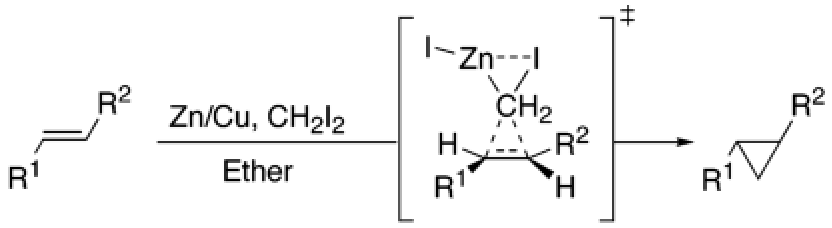
5.1.1. Brief History

The asymmetric cyclopropanation reaction is mainly classified into three types

a) Simmons – Smith cyclopropanation
b) Michael – initiated ring closure
c) Transition–metal–catalyzed decomposition of diazoalkanes

a) Simmons–Smith cyclopropanation

Simmons and Smith discovered that the reaction of alkenes with diiodomethane in the presence of activated zinc afforded cyclopropanes in high yield.[3]

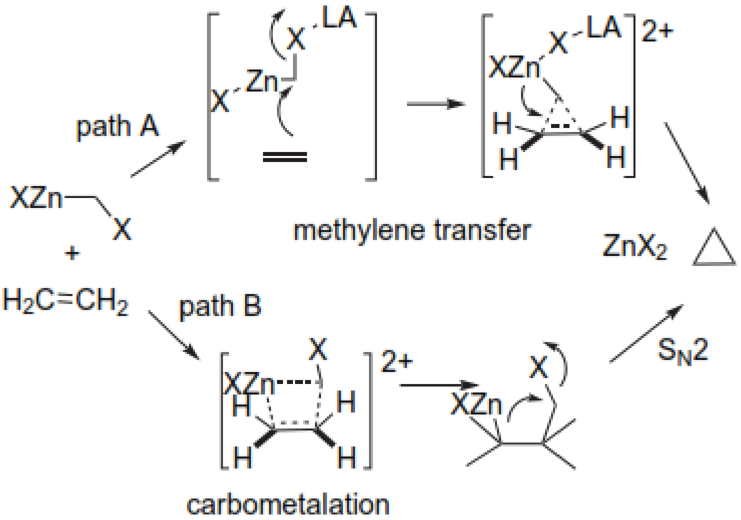


Scheme 5.1 Simmons–Smith cyclopropanation

The reactive intermediate in this process is $RZnCH_2I$ species. The Simmons–Smith reaction with an allylic alcohol has distinct advantages over the reaction with a simple olefin in relation to the reaction rate and stereocontrol. There are two methodologies by which the Simmons–Smith reaction can be carried out, one is without any chiral catalyst, in which the starting chiral material plays the role of chiral auxiliary. The second is using chiral catalyst for the asymmetric cyclopropanation reaction.

The mechanistic pathway for the asymmetric cyclopropanation by Simmons–Smith process remained unclear till 2003, earlier there was a controversy regarding the mechanism pathway as scientist had proposed two pathways 1) methylene–transfer and 2) carbometalation (Scheme 5.2).

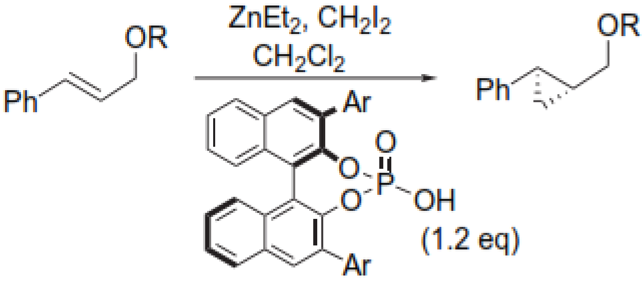
In 2003 Nakamura et al. [4] studied the reaction pathways of cyclopropanation using the Simmons–Smith reagent by means of the B3LYP hybrid density functional method, confirming that the methylene transfer pathway was the favored reaction course.



Scheme 5.2 Reaction pathways of Simmons–Smith reaction

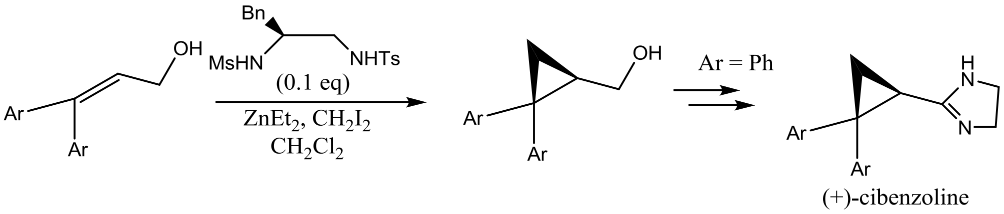
Various chiral auxiliaries have been developed in the past few years for the reaction with Simmons–Smith reagents, such as chiral allylic ethers, allylic amines, allylic alcohols, ketals, α,β-unsaturated carbonyl derivatives, enamines, enol ethers, and also unfunctionalised olefins.

Several catalytic systems have been reported for the enantioselective Simmons–Smith cyclopropanation reaction among them only few could be used in catalytic amounts. Charette et al. [5] have successfully employed a chiral phosphoric acid derivative derived from 3,3'-disubstituted Binol to design a novel chiral zinc phosphate reagent for the enantioselective cyclopropanation of protected allylic alcohols (Scheme 5.3).



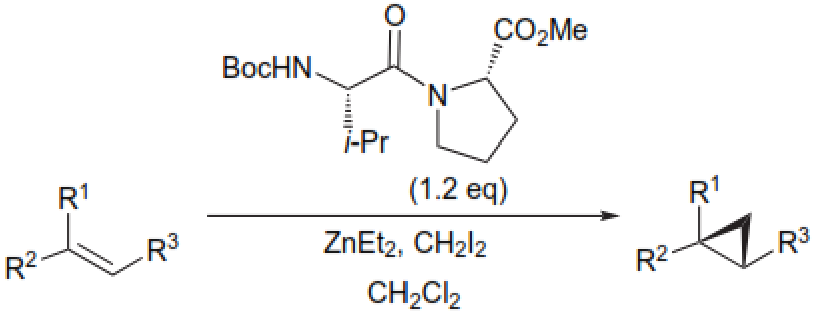
Scheme 5.3 Asymmetric cyclopropanation in presence of BINOL-derived phosphoric acid

In 2006, Imai et al. [6] have reported the syntheses of (+)-cibenzoline, an antiarrythmic agent, and its analogous via catalytic enantioselective cyclopropanation using simple chiral disulfonamides derived from α-amino acids such as (S)-phenylalanine derived disulfonamides (Scheme 5.4).



Scheme 5.4 Asymmetric cyclopropanation in presence of (S)-phenylalanine derived disulfonamide

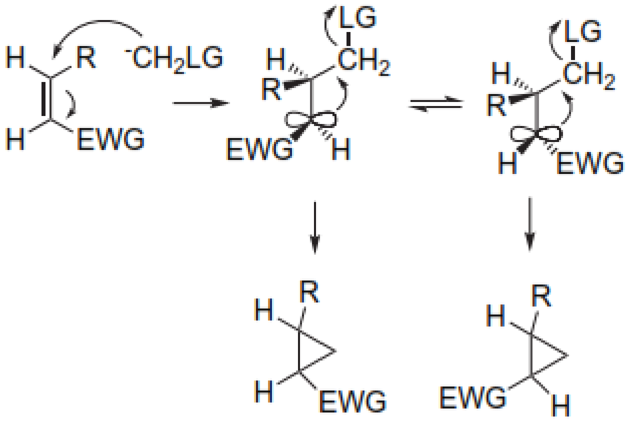
Shi et al. [7] have found that the background reaction between dipeptide and $Zn(CH_2I)_2$ is reduced in the presence of EMA, enhancing the enantioselectivity in the cyclopropane product (Scheme 5.5).



Scheme 5.5 Asymmetric cyclopropanation of unfunctionalised olefins in presence of dipeptide

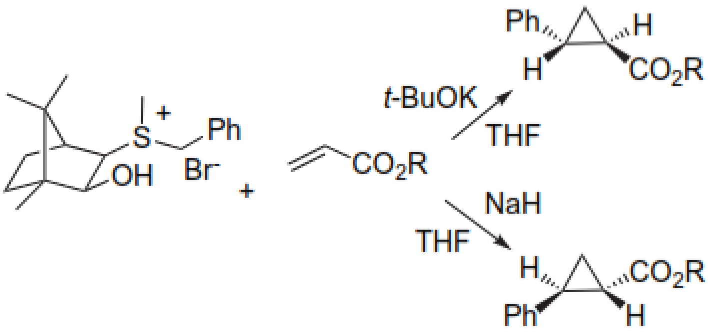
b) Michael-initiated ring closure

Cyclopropanation reactions involving a conjugate addition to an electrophilic alkene to produce an enolate, which then subsequently undergoes an intramolecular ring closure, are defined as Michael-initiated ring closure (MIRC) reactions. Stereospecific cyclopropanation reactions using the MIRC reaction are observed only when the ring closure process is faster than the rotation around the single bond in the first intermediate formation. (Scheme 5.6)



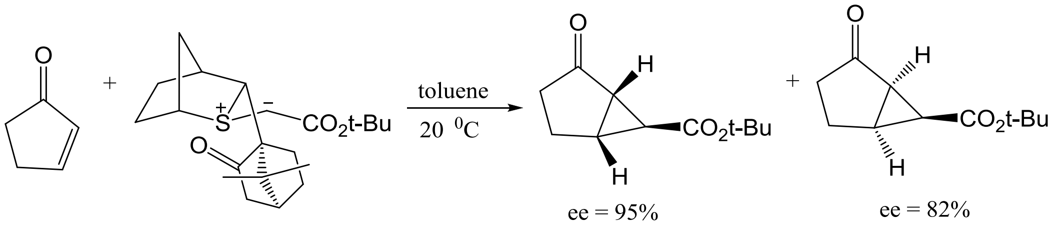
Scheme 5.6 Michael initiated ring closure cyclopropanation reaction

Huang et al. [8] have developed camphor derived sulfonium ylide as the chiral auxiliary nucleophile for the enantioselective synthesis of 2-phenyl-1-cyclopropane carboxylates via MIRC processes (Scheme 5.7).



Scheme 5.7 Asymmetric cyclopropanation via camphor derived sulfonium ylide

In 2006, Aggarwal et al. [9] have used chiral ester stabilized sulfonium ylides for the cyclopropanation of cyclopentenone (Scheme 5.8).



Scheme 5.8 Asymmetric sulfonium ylide mediated cyclopropanation

Most of the MIRC reactions have been catalyzed by sulfur derived ylides; there are relatively few examples in the literature that employ nitrogen derived ylides. Kojima et al. have demonstrated that chiral pyridinium ylides could be applicable for cyclopropanation [10]

Other examples of ylides used as chiral auxiliary for asymmetric cyclopropanation of olefins are summarized by Pellissier. [11]

c) Transition–metal–catalyzed decomposition of diazoalkanes

The cyclopropanation of olefins using the transition–metal–catalyzed decomposition of diazoalkanes is one of the most extensively studied reactions in the organic chemist’s arsenal. [12]

Cyclopropanation by transition metal mediated carbene transfer from aliphatic diazo compounds to carbon-carbon double bond is a major and best developed method available for synthetic organic chemist. [13]

The metal catalyzed carbenoid cyclopropanation reactions are classified as *Intermolecular cyclopropanation* and *Intramolecular cyclopropanation* reactions.

5.1.1.1. Intermolecular cyclopropanation reactions

The first example of intermolecular asymmetric cyclopropanation of styrene using structurally well defined chiral transition metal complex is chiral Schiff base Cu(II) complex (Fig. 5.1) developed in the year of 1966 in Prof. H. Nozaki's laboratory.

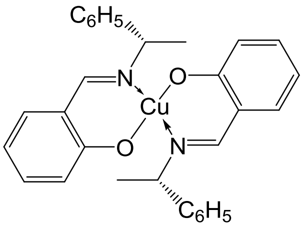


Figure 5.1 Chiral Schiff base Cu(II) complex

Later T. Aratani [14,15] invented an excellent chiral copper catalyst (Fig. 5.2) for asymmetric cyclopropanation. The catalyst was used for the industrial synthesis of chrysanthemates (efficient insecticides) and (*S*)-2,2-cyclopropanecarboxylic acid. The later compound is a building block of cilastatin, an in vivo stabilizer of the carbapenem antibiotic, imipenem.

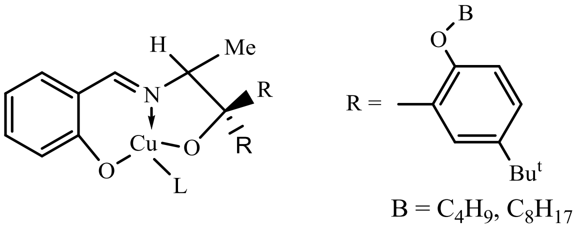
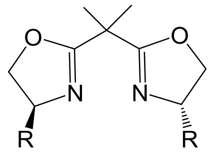


Figure 5.2 Aratani's copper catalyst used in the commercial manufacture of *cilastatin*

Several ligand systems for the asymmetric cyclopropanation reaction had been developed, out of which chiral C_2–symmetric bidentate bisoxazoline [16] ligands

(Figure 5.3) are widely used in copper catalyzed asymmetric cyclopropanation reaction.



R = *i*-Pr; *t*-Bu; Ph:

Bisoxazoline ligand

Figure 5.3 Chiral C_2-symmetric bisoxazoline ligand

In 1986 Pfaltz et al. [17] have developed an efficient C_2–symmetric ligand called semicorrins from pyroglutamic acid (Fig. 5.4). The wide range of structural variations and the rigid ligand scaffold with stereogenic center in close proximity to the metal center makes the ligand more effective and efficient.

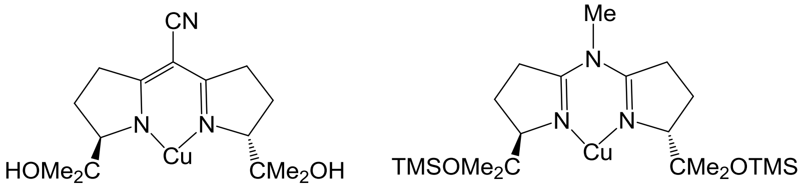


Figure 5.4 First semicorrin type ligand

Later Masamune et al. and Evans et al. [18] developed bisoxazoline (Fig. 5.5) ligand system and reported their copper complexes as an efficient catalyst for the asymmetric cyclopropanation of olefins.

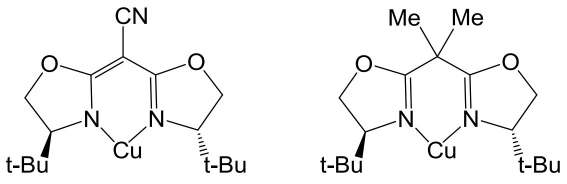
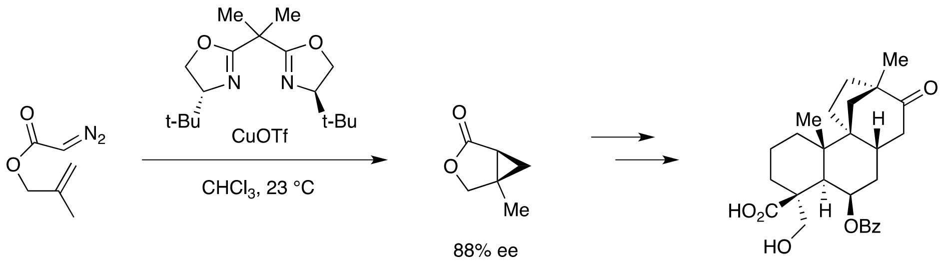


Figure 5.5 Masamune and Evans’ catalysts

5.1.1.2. Intramolecular cyclopropanation reactions

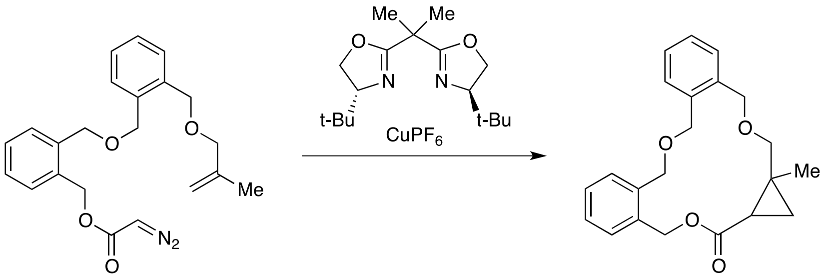
Overman et al. [20] have used Evan’s bisoxazoline Cu(I) catalyst for the synthesis of natural product via intramolecular cyclopropanation reaction.



(–)-scopadulcic acid A

Scheme 5.9 Synthesis of (–)scopadulcic acid A

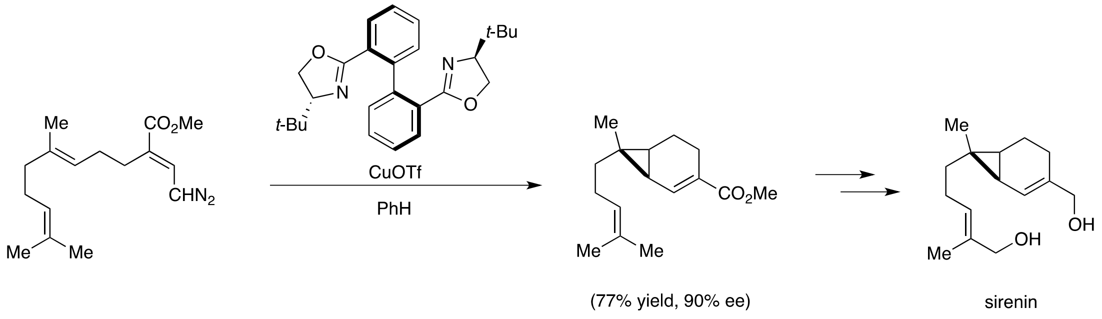
Doyle et al. [21] have used the Evan’s Cu(I) bisoxazoline catalyst for macrocyclic cyclization via intramolecular cyclopropanation reaction.



cis:*trans* 69:31
trans: 85% *ee*

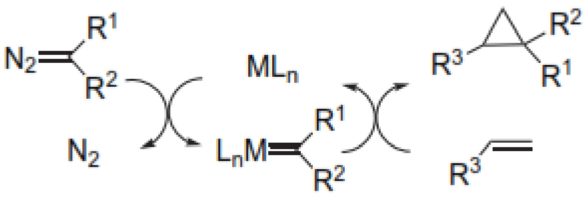
Scheme 5.10 Macrocyclic cyclization via intramolecular cyclopropanation

Corey et al. [22] have synthesized sirenin using a non–traditional bisoxazoline ligand scaffold for an enantioselective cyclopropanation reaction.



Scheme 5.11 Synthesis of sirenin via intramolecular cyclopropanation reaction

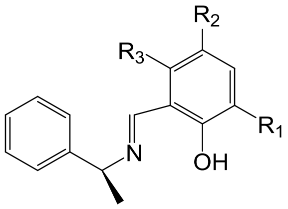
The enantioselectivity of intermolecular cyclopropanation reaction is controlled by the particular olefin/diazo compound combination. In transition metal catalyzed cyclopropanation reaction, the diazoalkanes decomposes to form carbene with concomitant release of nitrogen. The carbene forms metallocarbene complex intermediate (Scheme 5.12), which then transfers carbene to the substrate. The chiral ligand surrounding the metal center may control the enantioselectivity in the carbene transfer step. The cyclopropanation of styrene with ethyl diazoacetate (EDA) serves as the bench-mark reaction for the evaluation of any new catalyst system.



Scheme 5.12 Catalytic cycle of metal–catalyzed carbenoid cyclopropanation reactions with diazo compounds

It is known that very small structural changes in the ligand sometimes have drastic and unpredictable effects on the enantioselectivity.

Somanathan and Hake et al. [23] had used a series of chiral Schiff base copper (II) complexes as cyclopropanation catalysts. The Schiff base used for their study is shown in the Figure 5.6.



a) R_1= R_2= R_3= H
b) R_1= *tert*-Butyl; R_2= R_3= H
c) R_1= R_2= *tert*-Butyl; R_3= H
d) R_1= H; R_2,R_3= Naphthyl

Figure 5.6 Schiff base used by Somanathan and Hake

The foremost difference between the Betti base and the Schiff base shown above is the position of chiral carbon. The Schiff bases used by Somanathan and Hake have similar structure as that of the Schiff base used by Prof. H. Nozaki. The single crystal X-ray structures of the **Cu1**and Schiff base are shown in the Figure 5.7 (a) & (b).

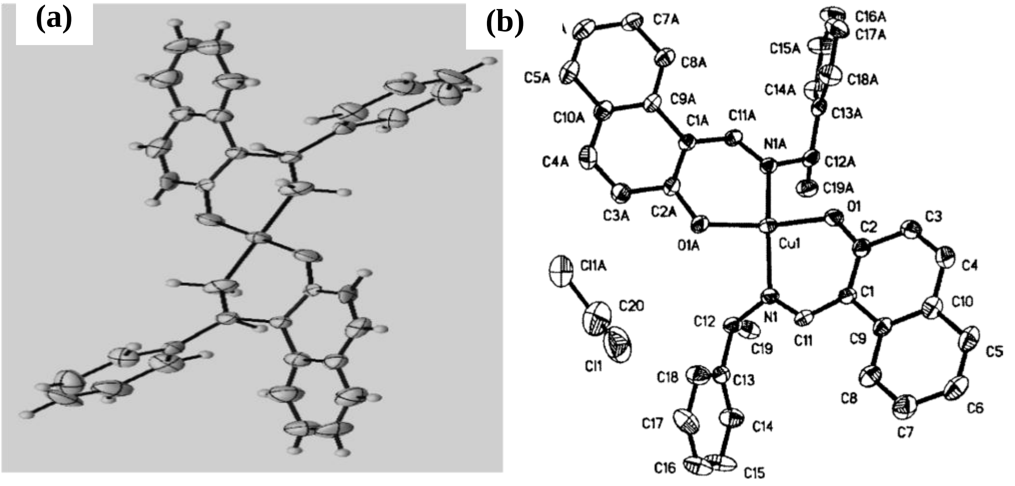


Figure 5.7 (a) Cu(II) Betti base complex (b) Cu(II) Schiff base complex

The similarity in structures prompted us to check the feasibility of the copper (II) complexes with Betti base and its derivative as catalyst for cyclopropanation.

The copper(II) complexes with rigid chelate rings are found to be poor catalyst towards such reaction due to inability of copper center to form bond with carbene. Under such condition, the enantioselectivity of the product is merely controlled by the distorted conformer of the metal complex which is generated by the reduction of Cu(II) to Cu(I) during catalysis. The redox active ligand can cooperatively participate in the reduction process of the metal ion. It can also help in the bond formation of carbene with metal ion through its participation in the process.

So in the present study the asymmetric cyclopropanation of styrene by Cu(II) Betti base complexes were carried out to investigate the effect of redox active behavior of Betti bases over intermolecular carbene insertion to terminal olefin i.e. styrene.

5.2. Experimental

5.2.1. Materials

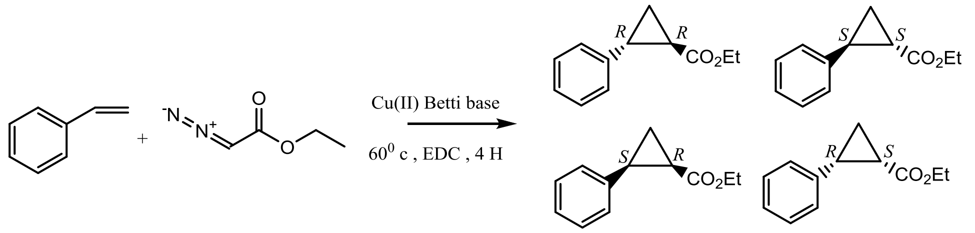
Styrene, Ethyl diazoacetate (EDA) were purchased from Aldrich. Styrene was passed through a pad of neutral alumina before use. The Cu(II) complexes with racemic and optically pure Betti bases were synthesized as described in chapter 3. Freshly distilled solvents were employed for all synthetic purposes. Spectroscopic grade solvents were employed for spectral work. All other chemicals were of AR grade.

5.2.2. Catalytic reactions

A mixture of a Cu(II) Betti base complex (0.01mmol) and styrene (0.4 mmol) in dichloroethane (DCE, 2 mL) was placed in a 25-mL round-bottom flask under N_2 in a glove box. The solution was heated to 60°C. A DCE (2 mL) solution of EDA (1.0 mmol) was slowly added via dropping funnel over a period of 3-4 hours under N_2. After the addition was complete the reaction mixture was stirred for 2 h at room temperature. The solution was then pressure filtered through silica gel to remove catalyst. The crude samples were then analyzed by gas chromatography (GC), using Perkin Elmer Clarus 500 chromatograph equipped with a chiral column Rt-βDEXsm (30 m long, 0.25 µm df, 0.32 mm ID.) and a flame ionization detector (FID). Ultrapure N_2 was used as a carrier gas (rate 0.5 mL/min) with the injection port temperature set at 210˚C. The column temperature was programmed in the range of 60–200˚C.via Chiral GC (Rt-βDEXsm)

5.3. Results and Discussion

The results for the asymmetric cyclopropanation are tabulated in the Table 5.1.



Sr. No.	Catalyst	% conversion of EDA	trans:cis [a]	% ee [a]	
				trans	**cis**
1	Cu1	100.0	24:76	trace (S,S)	40.0 (S,R)
2	Cu2	100.0	96:04	11.5 (R,R)	15.0 (S,R)
3	Cu3	100.0	94:06	10.3 (R,R)	14.0 (S,R)
4	Cu4	100.0	100:00	1.5 (S,S)	----
5	Cu5	100.0	65:35	trace (S,S)	15.4 (S,R)
6	Cu6	100.0	63:37	1.8 (S,S)	14.5 (S,R)
7	Cu7	100.0	80:20	trace	15.4 (S,R)
8	Cu8	100.0	40:60	1.5 (S,S)	30.0 (S,R)
9	Cu9	100.0	73:27	1.4 (S,S)	12.0 (S,R)
10	$Cu(OTf)_2 + L_1$	99.2	92:08	32.4 (S,S)	39.2 (R,S)
11	$Cu(OTf)_2 + L_2$	99.8	94:06	32.0 (S,S)	34.0 (R,S)

Table 5.1 Reaction conditions : EDA (1.0 mmol), styrene (2.0 mmol), catalyst (0.01 mmol), DCE , 4 h at 60^0 C, 2 h at RT.

[a] The conversion of EDA and enantioselectivity was determined by Chiral GC (Rt-βDEXsm)

As can be seen from the Table 5.1, the catalyst **Cu1** and **Cu8** are stereoselective towards cis product, while all other catalysts are selectively produce trans product.

The catalyst **Cu1** (copper complex with racemic ligand **L_1**) is perfectly square planar whereas all other catalysts persist distorted geometry; the distortion in the geometry was confirmed by EPR spectral analysis (chapter 3).

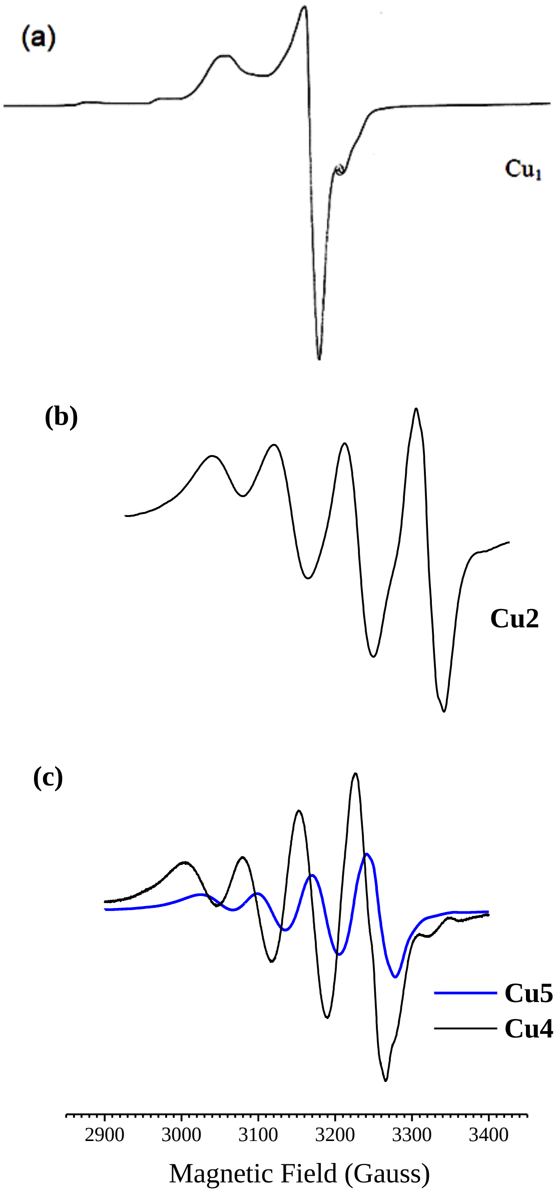


Figure 5.8 EPR spectra of Cu(II) complexes (10 mM in DCM). Spectra were collected at room temperature, ν_0 = 9.1 GHz. (a) **Cu1** (b) **Cu2** (c) **Cu5** & **Cu6**

The catalyst **Cu1** yielded 24:76, trans:cis isomers with 40% ee for (S,R) enantiomer of cis isomer. Whereas the catalysts **Cu2** & **Cu3** (copper complex with enantiopure ligands, **L**$_2$ & **L**$_3$) yielded 96% trans isomer with 15% ee for (S,R) cis isomer and 11% ee for (R,R) trans isomer. The catalyst **Cu4** (complex with racemic ligand, **L**$_4$) was found to be stereospecific towards trans isomer, with negligible ee (1.5%) for (S,S) trans isomer. The catalysts **Cu5** & **Cu6** (complexes with enantiopure ligands, **L**$_5$ & **L**$_6$) were stereoselective towards trans isomer yielded 65:35, trans:cis isomers with 15% ee for (S,R) cis isomer. On the basis of the results obtained for the asymmetric cyclopropanation of styrene (Table 5.1) it can be concluded that the catalysts (**Cu1** &

Cu8) with square planar geometry are stereoselective towards cis isomer of the product, where as the catalysts with more distorted structure are selectively produce trans isomer of the cyclopropane product.

Many scientists had worked to understand the mechanistic pathways of the carbene approach towards metal center. The bond formation between carbene and the metal center would make an adduct more electrophilic, facilitating the attack of electron rich substrates. In the year of 2002, Norrby et al. [25] had proposed two approaches for the attack of carbene towards copper center namely 'Open' and 'Cyclic' (Figure 5.9). The open approach corresponds to a concerted but very asynchronous addition, whereas the cyclic path leads to initial formation of a metallacyclobutane, in analogy with known metathesis catalysts. [26]

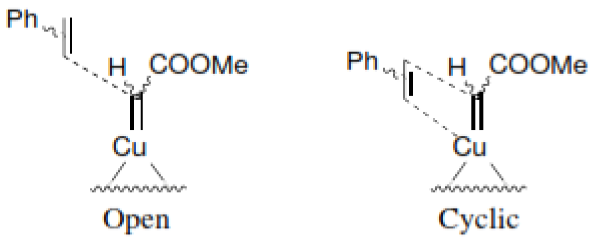


Figure 5.9 Two addition mechanisms for cyclopropanation reaction

A close look at the open mechanism reveals that, the alkene will orient to avoid eclipsing the carbene substituents, where as the cyclic mechanism can only be realized when the two reacting bonds are parallel. The face selectivity of the carbene and the alkene approach, both affects the final configuration of the carbene carbon.

We have previously observed the noninnocent behavior of **Cu1** complex during epoxidation of styrene. The redox active nature of the Betti base facilitates the intramolecular electron transfer in **Cu1**. Due to actor behavior of the coordinated ligand, a reasonably strong bond formation between carbene and metal center is expected. The parallel approach of styrene is possible due to square planar geometry of **Cu1.** On the other hand, such approach of styrene is difficult for the metal complexes with distorted geometry. Hence a cyclic mechanism is proposed in case of **Cu1** in which 40% ee for cis product is obtained, where as catalysts other than **Cu1** would follow the more asynchronous open mechanism, ultimately yielding product with low enantiomeric excess.

The probable mechanism is shown in the Figure 5.10

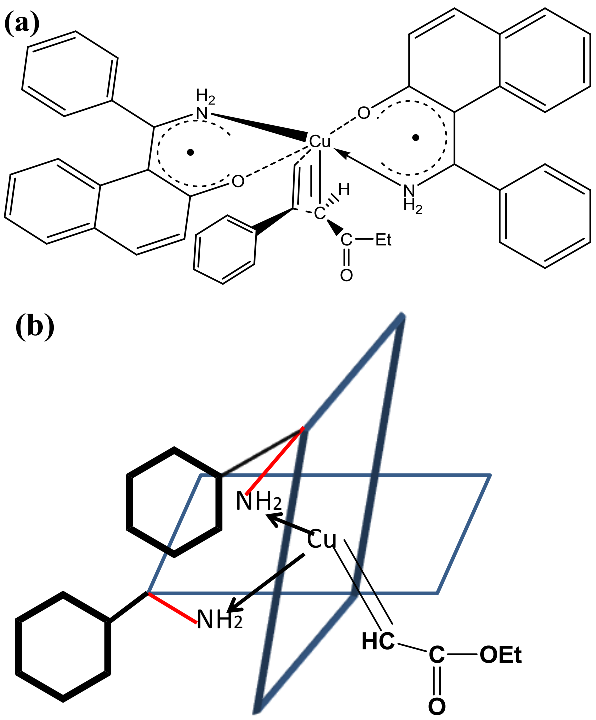


Figure 5.10 Probable pathway for the formation of metal-carbene adduct

In case of **Cu1**, the *Re* face attack of styrene with exo approach is proposed [Figure 5.10(a)], in which the stereoselectivity of the carbene carbon is controlled by the steric hindrance of the ligand. The distorted geometry of the other complexes would lead to trans product.

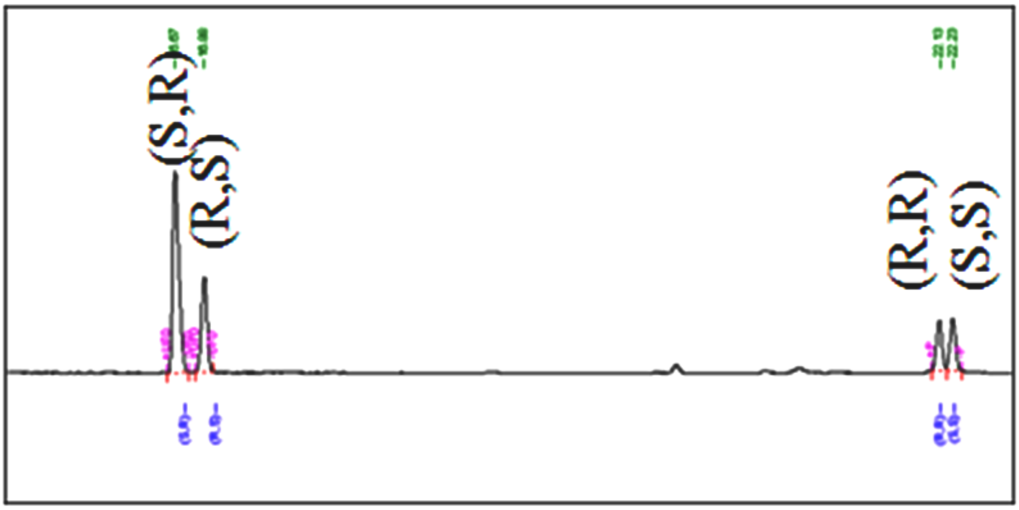
5.4. Conclusion

In the present study, the effect of distorted geometry of metal complexes towards asymmetric cyclopropanation of styrene has been carried out. The square planar geometry of the complexes **Cu1** and **Cu8** would facilitate styrene to approach parallel to the metal carbene adduct, a favorable condition for the cyclic mechanism ultimately produce 40% cis product due to steric hindrance of the coordinated ligand. On the other hand complexes with distorted geometry exerts steric hindrance for the parallel approach of styrene towards the adduct, resulted in asynchronous open mechanism for asymmetric cyclopropanation reaction which ultimately yielded trans product with negligible enantioselectivity.

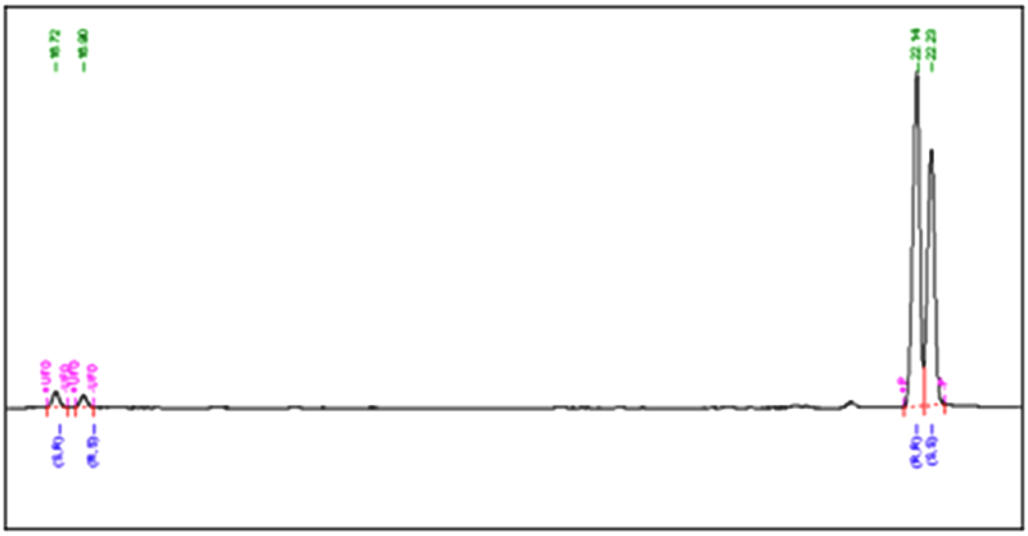
5.5. Supporting information

Traces of GC/GCMS Chromatograms

(a) Cu1 catalyzed cyclopropantion reaction



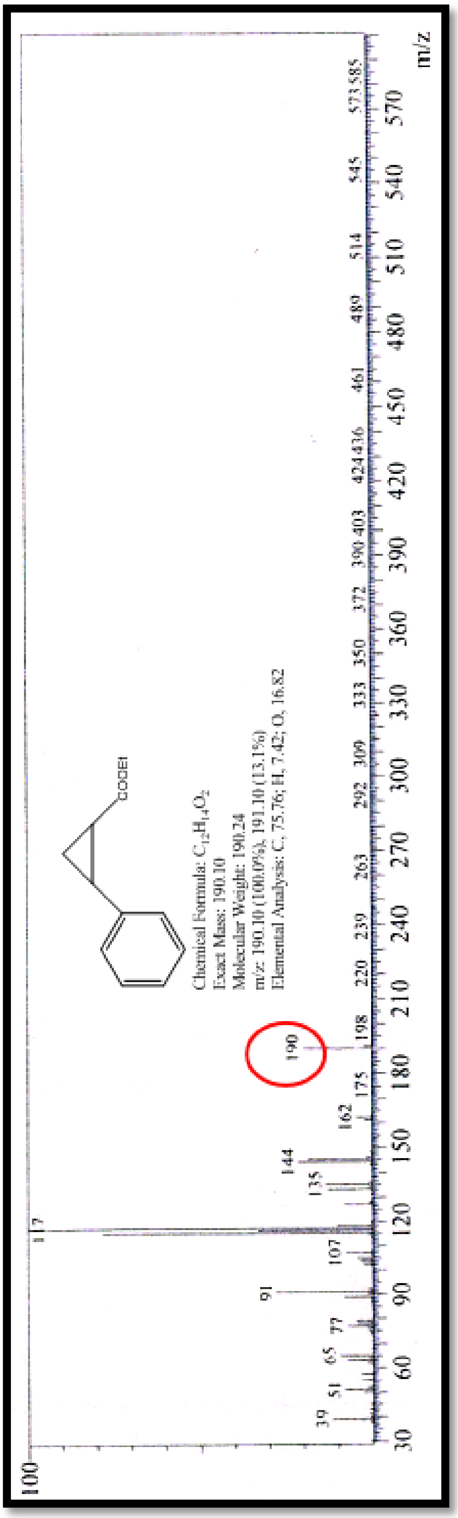
(b) Cu2 catalyzed cyclopropanation reaction



(c) Cu4 catalyzed cyclopropanation reaction

(d) Cu5 catalyzed cyclopropanation reaction

(e) GC Mass spectral analysis



GC-MS spectra for the cyclopropanation reaction of styrene

5.6. References

[1] a) C. Djerassi, G.A. Doss, *New J. Chem.* **1990**, *14*, 713–719; e) R. Faust, *Angew. Chem., Int. Ed.* **2001**, *40*, 2251–2253.

[2] a) D. Arlt, M. Jautelat, R. Lantzsch, *Angew. Chem., Int. Ed.* **1981**, *20*, 703–722.

[3] a) H.E. Simmons, R.D. Smith, *J. Am. Chem. Soc.* **1958**, 80, 5323–5324; b) H.E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1959**, 81, 4256–4264.

[4] M. Nakamura, A. Hirai, E. Nakamura, *J. Am. Chem. Soc.* **2003**, 125, 2341–2350.

[5] J.F. Fournier, S. Mathieu, A.B. Charette, *J. Am. Chem. Soc.* **2005**, 127, 13140–13141.

[6] T. Miura, Y. Murakami, N. Imai, *Tetrahedron: Asymmetry* **2006**, 17, 3067–3069.

[7] J.C. Lorenz, J. Long, Z. Yang, S. Xue, Y. Xie, Y. Shi, *J. Org. Chem.* **2004**, 69,327–334.

[8] K. Huang; Z.Z. Huang, *Synlett* **2005**, 1621–1623.

[9] V.K. Aggarwal, E. Grange, *Chem. Eur. J.* **2006**, 12, 568–575.

[10] S. Kojima, K. Hiroike, K. Ohkata, *Tetrahedron Lett.* **2004**, 45, 3565–3568.

[11] H. Pellissier, *Tetrahedron* **2008**, 64, 7041–7095.

[12] a) H.M.L. Davies, E. Antoulinakis, *Org. React.* **2001**, 57, 1–326; (b) T. Rovis, D.A. Evans, *Prog. Inorg. Chem.* **2001**, 50, 1–150; c) H. Nishiyama, *Enantiomer* **1999**, 4, 569–574; d) V.K. Singh, A. DattaGupta, G. Sekar, *Synthesis* **1997**, 137–149.

[13] a) G. Boche, J.C.W. Lohrenz, *Chem. Rev.* **2001**, 101, 697–756; b) M.P. Doyle, M.A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley and Sons: New York, NY, 1998; c) M.P. Doyle, D.C. Forbes, *Chem. Rev.* **1998**, 98, 911–936.

[14] T. Aratani, Y. Yoneyoshi, T. Nagase, *Tetrahedron Lett.* **1977**, *18*, 2599–2602.

[15] T. Aratani, *Pure Appl. Chem.* **1985**, *57*, 1839–1844.

[16] G. Desimoni, G. Faita, K.A. Jorgensen, *Chem. Rev.* **2006**, 106, 3561–3651.

[17] a) H. Fritschi, U. Leutenegger, A. Pfaltz, *Angew. Chem., Int. Ed.* **1986**, *25*, 1005–1006. b) U. Leutenegger, G. Umbricht, C. Fahrni, P. von Matt, A. Pfaltz, *Tetrahedron* **1992**, *48*, 2143–2156.

[18] a) R.E. Lowenthal, A. Abiko, S. Masamune, *Tetrahedron Let.* **1990**, *31*, 6005–6008; b) D.A. Evans, K.A. Woerpel, M.M. Hinman, M.M. Faul, *J. Am. Chem. Soc.* **1991**, *113*, 726–728.

[19] a) M. Schinnerl, C. Bohm, M. Seitz, O. Reiser, *Tetrahedron: Asymm.* **2003**, *14*, 765–771; b) R.B. Chhor, B. Nosse, S. Sorgel, C. Bohm, M. Seitz, O. Reiser, *Chem. Eur. J.* **2003**, *9*, 260–270; c) B. Nosse, R.B. Chhor, W.B. Jeong, C. Bohm, O.Reiser, *Org. Lett.* **2003**, *5*, 941–944.

[20] M.E. Fox, L. Chi, J.P. Marino, L.E. Overman, *J. Am. Chem. Soc.* **1999**, 121, 5467–5480.

[21] M.P. Doyle, W. Hu, B. Chapman, A.B. Marnett, C.S. Peterson, J.P. Vitale, S.A. Stanley, *J. Am. Chem. Soc.* **2000**, *122*, 5718–5728.

[22] T.G. Gant, M.C. Noe, E.J. Corey *Tetrahedron Lett.* **1995**, *36*, 8745–8748.

[23] A.L. Iglesias, G. Aguirre, R. Somanathan, M.P. Hake, Polyhedron **2004**, 23, 3051–3062.

[24] S. Bhatt, B. Trivedi, Polyhedron **2012**, 35, 15–22.

[25] T. Rasmussen, J.F. Jensen, N. Ostergaard, D. Tanner, T. Ziegler, P.O. Norrby, *Chem. Eur. J.* **2002**, 8, 177–184.

[26] a) M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, 1998; b) A. Pfaltz, *Transition Metals for Organic Synthesis* (Eds. : M. Beller, C. Bolm), Wiley-VCH, Weinheim, 1998, pp. 100 – 113; c) A. Pfaltz, *Comprehensive Asymmetric Catalysis*, Vol . II, Springer, Berlin, 1999, pp. 513 – 538.