KIMIKA Volume 22, Number 1, pp.33-42 (2006)

ISSN 0115-2130

Design and Synthesis of Chiral Lewis Acid Catalysts for Aqueous Diels-Alder and Barbier Reactions

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We report here the successful synthesis of two 3, 3'-difluorenyl binaphthols. In the divergent strategy employed in the synthesis, the 3,3' and 2,2'-positionsof (S)-(-)-1,1'-binaphthol were brominated and methylated, respectively, leading to the formation of a product that can be converted to a Grignard reagent. A Grignard addition to 9-fluorenone followed by deprotection afforded the target compounds. We also present here the method of testing their utility as ligands in chiral Lewis acid-catalyzed aqueous Barbier and Diels-Alder methodologies. The chiral Lewis acid complexes (CLAC) were generated *in situ* by mixing lanthanide triflates and 3,3'-binaphthol derivatives. Among the six lanthanide triflates tested, only the $Yb(OTf)_3$ –3,3'-binaphtol derivative complex showed promising results for both model reactions.

Keywords: Lewis acids, chiral, enantioselectivity, stereoselectivity, binaphthol, aqueous media, Diels-Alder, Barbier, lanthanide

INTRODUCTION

Many carbon to carbon bond-forming reactions employed in organic synthesis are subject to Lewis-acid-promoted rate acceleration [1]. Examples of these are cycloadditions, conjugate additions, and Aldol additions. When the Lewis acid is chiral, the absolute stereochemical course of these catalyzed processes may be strongly influenced; hence, chiral Lewis acid catalysis has become one of the most important techniques being employed in organic synthesis to produce an enantiomerically enriched target product. Chiral Lewis acids used as catalysts in organic syntheses are either organometallic or metal coordination complexes of chiral ligands. The metal centers of these complexes act as Lewis acids while the chiral ligands impart the chirality to the complex. Of the latter type, the C_2-symmetric complexes of binaphthol and its derivatives have received much attention [2, 3].

Ligands with the binaphthol backbone for chiral Lewis acid catalysis have proven to be excellent in promoting enantiofacial discrimination and their metal complexes are reputed to have very wide utility [4]. Its chirality is derived from the hindered rotation about the sigma bond that joins the two-naphthyl moieties. Such chiral molecules are called atropisomers [5].

The factors that make the binaphthol complexes good catalysts for promoting asymmetry of reactions are electronic effects, torsion angle, and

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steric effects. The first two are largely dependent on the nature of the coordinating metals. Steric effects are fundamental properties necessary for efficient asymmetric induction. The chiral recognition property of chiral complexes is a manifestation, not only of their inherent chirality, but also of the bulky groups present as substituents in the chiral ligand. Functionalizing the various substitution positions in the binaphthyl backbone is the usual method of altering the steric factors. Various research groups have focused on the 3, 3'- position by substituting aromatic, alkyl and groups that would act as Brønsted bases [6, 7].

The development of chiral catalysts for asymmetric synthesis has recently become an important and fast-growing area of research [8]. One major application is in the preparation of optically pure drugs and natural products. Of particular interest among the more recent chiral catalysts that have been prepared are coordination complexes of lanthanide metals [6].

In recent years, it was discovered that Diels-Alder and Barbier reactions can be carried out even in aqueous media [9]. The use of aqueous conditions for both of these reaction types proved to be more advantageous in terms of yield, rate, and "greenness" [10]. However, the asymmetric synthesis under aqueous conditions is usually hampered by the inherent instability of transition metal complex catalysts in water [11].

It was reported that chiral Lewis acid catalysts with lanthanide metal centers were able to catalyze asymmetric and symmetric Diels-Alder reactions [10] and aza-Diels-Alder reactions [12] in organic media. The reactions can be carried out even in aqueous media, since the lanthanide metals as catalytic centers were stable in water [10, 12].

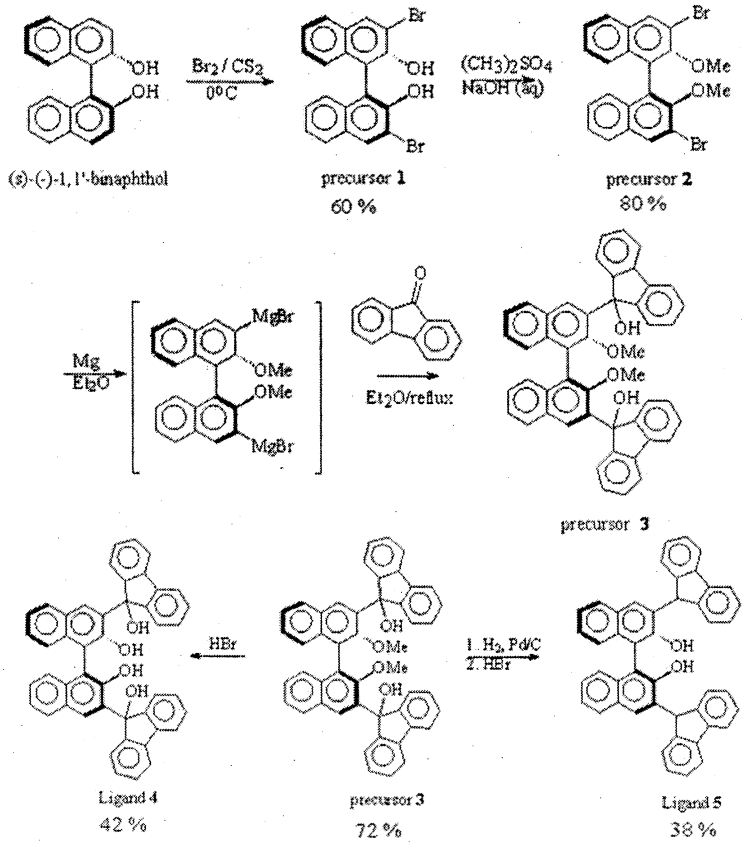
The asymmetric synthesis of Barbier reactions with chiral Lewis acid catalysts with tin metal centers in aqueous media has been performed with moderate yield and stereoselectivity [13].

In connection with these developments, we pursued our own research in the field of asymmetric synthesis in aqueous media. We present here the synthesis of two 3, 3'-difluorenyl derivatives and their utility as ligands for the *in situ* preparation of water tolerant chiral Lewis acid catalysts for two model aqueous reaction systems: aqueous Diels-Alder and Barbier reactions. This study could be best described by considering the outlined schemes (see schemes 1 and 2). Scheme 1 shows the overall synthetic strategy for the preparation of the target compounds. Ligands **4** and **5** were prepared from (S)-(-)-1, 1'-binaphthol (also known as binol) by a series of functional group transformations. The 3, 3' and 2, 2'-positions of the starting material were brominated and protected, respectively, such that the resulting product can be converted to a Grignard reagent. Grignard addition to the 9-fluorenone followed by deprotection afforded compounds **4** and **5**. Scheme 2 outlines the utility of the prepared catalysts for their ability to promote asymmetry in Diels-Alder and Barbier reactions.

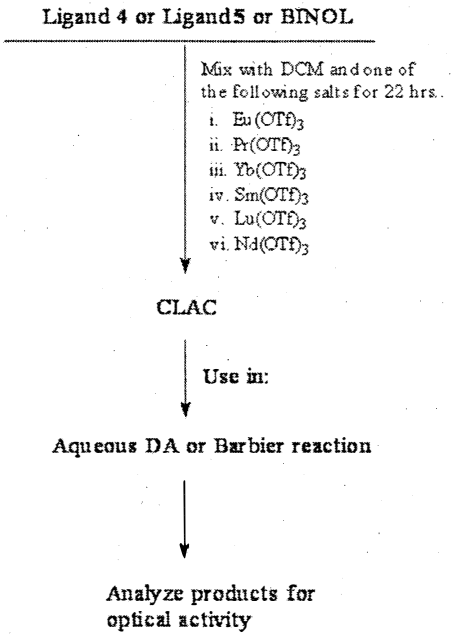
METHODOLOGY

General Procedure

Infrared (IR) spectra were recorded on a Bio-Rad FTS Fourier Transform Spectrophotometer using KBr as reference. Ultraviolet-visible (UV-vis) spectra were recorded on a Shimadzu UV/Vis spectrophotometer. Nuclear Magnetic Resonance (NMR) spectra were recorded using JEOL Lambda 400 NMR spectrometer. Chemical shifts are in ppm relative to tetramethylsilane (TMS) standard. Mass spectra (MS) were obtained using LCQ Finnigan MAT LC-Mass Spectrophotometer. Optical activities were determined using JASCO CD-ORD J-715 Spectrometer and Atago Polarimeter. Reactions were monitored visually or by thin layer chromatography (TLC) using either UV illumination (λ = 254 nm) or by immersion in 10 % H_2SO_4 in EtOH and warming on a hot plate. Uncorrected melting points were determined using Fischer Johns Melting Point apparatus. The solvents used were either AR or HPLC grade. Deionized distilled water was used for the reactions. All reagents were obtained from Sigma-Aldrich except for S-(-)-binaphthol (Tokyo Kasei), carbon disulfide (Fluka), dicyclopentadiene (Fluka), bromine (Fluka), and 3-methyl-2-butenal (Tokyo Kasei). Pyridyl-2-crotonate was recrystallized from ligroin. Magnesium turnings were acid washed (3 % HCl) before use.



Scheme 1. Preparation of Ligands



Scheme 2. Assay of enantioselective ability of CLACs

Synthesis of Ligands

(S)-3,3'-dibromo-2, 2'-dihydroxy-1, 1'-dinaphthyl (1). A stirred solution of binaphthol (1000 mg, 3.5 mmol) in carbon disulfide (75 mL) was cooled to 0°C. Bromine (0.35 mL, 7.00 mmol) in carbon disulfide (25 mL) was added dropwise for a period of 1 hour. The mixture was then stirred for 72 hours at 0°C after which the resulting solution was quenched with saturated solution of $NaHSO_3$ (10 mL) and subsequently neutralized with saturated $NaHCO_3$ (5 g/ 100 mL) solution. The layers were then separated and the organic phase was dried over Na_2SO_4, and then concentrated by evaporation. The crude pale yellow crystals were collected, washed with water (3 x 10 mL) and then dried. Purification of the precipitate by silica gel chromatography using hexane-EtOAc (4:1) yielded 932 mg (60 %) of the pure product as white powder: m.p. = 82-84°C; $[\alpha]_D^{27.5}$ -95° (c = 0.21, CH_3OH); IR (KBr) cm^{-1}: 3400, 3095, 1450,

1365, 1125; ^{1}H NMR ($CDCl_3$) δ 5.53 (s, 2H), 7.05 (d, 7.6 Hz, 2H), 7.23-7.46 (m, 4H), 7.76 (d, 7.6 Hz, 2H), 8.16 (s, 2H); ^{13}C NMR δ 116.65, 119.26, 128.24, 128.44, 130.94, 133.40, 136.47, 136.84, 152.78; *m/e* M^+ 444.15 (^{79}Br).

(S)-3,3'-dibromo-2, 2'-dimethoxy-1, 1'-dinaphthyl (2). Dimethyl sulfate (5.5 mL, 3.68 mmol) was added to a cooled mixture of (S)-3,3'-dibromo-2, 2'-dihydroxy-1, 1'-dinaphthyl (**1**) (500 mg, 1.13 mmol) and 0.5 M aqueous sodium hydroxide (70 mL). The resulting mixture was stirred for 3 hours; water (50 mL) was then added. The mixture was then extracted with ether (3 x 20 mL). Subsequently, the ethereal extract was evaporated to give a white solid residue. Purification of the collected solids by silica gel chromatography using hexane-CH_2Cl_2-EtOAc (50:2:1) yielded 430 mg (80 %) of pure product as white powder: m.p. = 176-177 °C; $[\alpha]_D^{27.5}$ –19° (c = 0.20, $CHCl_3$); IR (KBr) cm^{-1}: 3045, 2950, 2865, 1230, 1155, 1035; ^{1}H NMR δ 3.57 (s, 6H), 7.37 (m, 6H), 7.86 (m, 2H), 8.31 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 55.87, 114.12, 116.32, 124.37, 126.33, 127.85, 129.07, 130.55, 135.63, 158.70; *m/e* M^+ 472.12 (^{79}Br).

(S)-3,3'-di-(9-hydroxy-9H-fluoren-9-yl)-2,2'-dimethoxy-1, 1'-dinaphthyl (3). A continuously nitrogen flushed 3-necked round bottom flask equipped with magnetic stirring bar and reflux condenser with drying tube was charged with dry diethyl ether (15 mL), magnesium turnings (60 mg, 2.54 mmol) and a crystal of iodine. A solution of (S)-3,3'-dibromo-2, 2'-dimethoxy-1, 1'-dinaphthyl (**2**) (150 mg, 0.31 mmol in 10 mL ether) was then added dropwise via cannula. After the formation of the gray-brown Grignard reagent, a solution of 9-fluorenone (300 mg, 0.635 mmol) in dry diethyl ether (10 mL) was slowly added via cannula. The resulting mixture was refluxed for 3 hours. The mixture was then cooled to room temperature and hydrolyzed with 3 M HCl (3 x 1 mL) until the aqueous phase is acidic, as indicated by litmus paper. The organic layer was separated and the aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined ether extracts were dried over Na_2SO_4. The solvent was then evaporated to give a pale yellow solid. The crude extract was purified by column chromatography using hexane-CH_2Cl_2-EtOAc (50:2:1) yielding 155 mg (72 %) of pale yellow crystals: m.p. = 122-124°C; $[\alpha]_D^{27.5}$ –47° (c = 0.20, $CHCl_3$); IR (KBr) cm^{-1}: 3388, 3055, 2945, 2875, 1436, 1226, 1038; ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 6H), 5.31 (s, 2H), 7.22-7.29 (m, 6H), 7.31 (m, 4H), 7.41 (m, 4H), 7.57 (m, 4H), 7.63 (m, 4H), 8.02 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 57.65, 77.32, 113.11, 124.95, 126.03, 127.15, 127.92, 128.06, 128.68, 130.44, 130.79, 132.16, 137.21, 140.84, 160.52; *m/e* M^+ 674.83, 222.

(S)-2,2'-dihydroxy-3, 3'-di-(9-hydroxy-9H-fluoren-9-yl) -1, 1'-dinaphthyl (4). Precursor **3** (20 mg, 0.03 mmol) and HBr (0.5 ml, 48 %) was stirred vigorously for 2 hours. Water (3 mL) was added followed by solid Na_2CO_3 (50 mg). The mixture was stirred for 15 minutes and the resulting mixture was extracted with ether (2 x 1 mL). The organic layer was discarded and the aqueous layer was acidified with HCl. The resulting mixture was then extracted with ether (3 x 10 mL). The solvent was evaporated to yield a white solid (8 mg, 42 %). m.p. = 161-163°C; $[\alpha]_D^{27.5}$ –116° (*c* = 0.21, CH_3OH); IR (KBr) cm^{-1}: 3370, 3075, 1456, 1415, 1367, 1345, 1260; ^{1}H NMR ($CDCl_3$) δ 1.6 (s, 2H), 3.7 (s, 2H), 6.9 (s, 2H), 7.27 (m, 12H), 7. 5 (m, 4H), 7.82 (m, 4H), 8.1 (m, 4H); *m/e* M^+ 646.77, 633.

(S)-3,3'-di-(9H-fluoren-9-yl)-2, 2'-dihydroxy-1, 1'-dinaphthyl (5). Precursor **3** (20 mg, 0.03 mmol) was dissolved in xylene (5 mL). Palladium in charcoal (5 mg) was added and the resulting mixture was bubbled with hydrogen gas for 3 hours. The mixture was filtered and the filtrate was evaporated to afford a white residue. The white residue was then subjected to the same procedure as described in the preparation of ligand **4**. White solids were obtained (7 mg, 38 %, over two steps). m.p. = 145-147°C; $[\alpha]_D^{27.5}$ –167° (*c* = 0.21, CH_3OH); IR (KBr) cm^{-1}: 3380, 3075, 2955, 2890, 1410, 1325, 1255; ^{1}H NMR ($CDCl_3$) δ 3.3 (s, 2H), 4.7 (s, 2H), 6.98 (s, 2H), 7.25 (m, 6H), 7. 35 (m, 4H), 7.12 (m, 4H), 7.28 (m, 4H), 7.54 (m, 4H); *m/e* M^+ 614.35, 393.35, 222.

Assay of CLACS

Diels Alder Reaction: Uncatalyzed. Pyridyl-2-crotonate (30 mg), cyclopentadiene (0.5 mL), and water (2 mL) were placed in a 10 mL round

bottom flask fitted with a magnetic bar. The mixture was stirred for four hours at room temperature. The excess cyclopentadiene was evaporated and the mixture was then filtered by gravity. The residue was washed with ethanol (2 x 3mL) to afford the adduct as white solids (42 mg, 99 %). m.p. = 133-135 °C; IR (KBr) cm^{-1}: 3265, 3083, 2927, 2863, 1704, 1613, 1543, 1362, 1053; *m/e* M^+ 229.3.

Diels-Alder Reaction: Catalyzed. The same procedure above was applied with the addition of 5 mole percent CLAC prepared by stirring a mixture of ligand **4** or ligand **5** and lanthanide triflates in DCM (10 mL) for 22 hours. Yield of the adduct for all the complexes averaged 90 %.

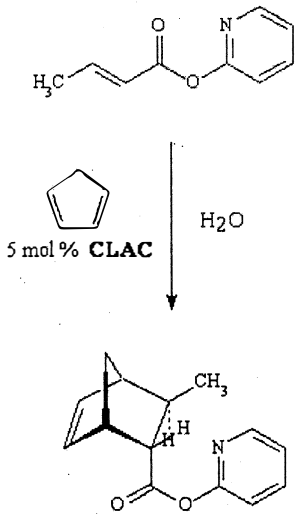


Fig. 1. *Chiral Lewis Acid-catalyzed Aqueous Diels-Alder Reaction*

Barbier reaction: Uncatalyzed. A mixture of water (3.0 mL), tin powder (1.0 g), prenyl bromide (1.0 mL), and 3-methyl-2-butenal (1.0 mL) was thoroughly stirred in a reaction vial for 4 hours at room temperature. The resulting grayish white mixture was then extracted with diethyl ether (2 x 10 mL). The organic layer was washed with water (2 x 10 ml), then with brine (2 x 5 mL) and dried over $MgSO_4$. After evaporation, the oily residue was purified using column chromatography over silica gel affording artemisia alcohol (yield = 656 mg, 77 %). IR (film) cm^{-1}: 3467, 3045, 2985, 1452, 1212, 987 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 5.64 - 4.29 (m, 3H), 4.1 (s, 1H), 3.55 (s, 1H), 2.66 (s, 1H), 1.55 (s, 6H) (s, 3H), 0.98 (s, 3H).

Barbier reaction: Catalyzed. The same procedure above was applied with the addition of 5 mole percent CLAC prepared by stirring a mixture of ligand **4** or ligand **5** and lanthanide triflates in DCM (3.0 mL) for 22 hours. Yield of artemisia alcohol for all the complexes averaged 70 %.

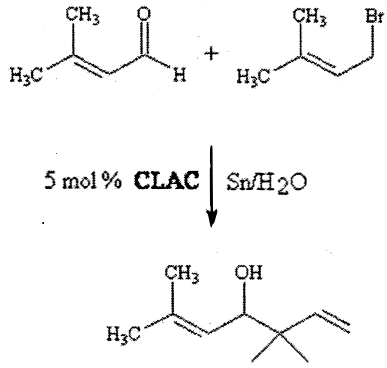


Fig. 2. *Chiral Lewis Acid-catalyzed Barbier Reaction*

DISCUSSION OF RESULTS

Synthesis of Ligands

The preparation of ligands **4** and **5** comprised 4 and 6 steps, respectively. This involved the 3, 3' - functionalization of the binaphthol backbone as the central feature. S-(-)-1,1'-binaphthol was first regioselectively brominated at the 3, 3' position by electrophilic bromination with the use of carbon disulfide (CS_2) as solvent at 0°C. This procedure is a great departure from standard literature bromination protocols of dibrominating the binaphthol 3,3' position since almost all brominations are conducted at low temperatures (-78 °C) in a nucleophilic fashion. [14].

Literature procedures use n-butyl lithium as the base in nucleophilic bromination. In either case, regioselectivity is achieved in good yields due to the higher reactivity of the binaphthol 3, 3'-protons with respect to the other protons in the backbone [14]. Obviously, our bromination protocol can be regarded as a more advantageous alternative to the more expensive nucleophilic bromination protocols. Chemical throughput is viable with an average yield of 60 % for three runs (not shown) conducted. Spectral analysis of the dibromo product confirmed its structure and therefore its successful synthesis. Its ^1H NMR and

^{13}C NMR shifts matched literature values [14]. The disappearance of one proton signal compared to the expected NMR peaks suggests substitution. The mass spectrum of **1** showed the prominent isotope peaks of $^{79}Br^{+}$. The IR spectrum showed =C-Br stretching frequencies at 1125 cm^{-1}. Polarimetry experiments have shown that the dibromo product is optically active with a specific rotation of –95°C.

The second step involved the methylation of the 1, 1' hydroxyl moiety of the dibromo derivative, precursor **1**. The protection was necessary in the synthetic strategy since Grignard reaction was involved in the incorporation of the fluorenyl moiety in the succeeding step. Methylation was carried out by use of dimethyl sulfate ($(CH_3)_2SO_4$) under aqueous basic conditions. The melting point range of the methylated dibromo product, precursor **2** matches that of literature value [14]. Likewise, its ^{13}C NMR and ^{1}H NMR shifts match literature values. The disappearance of the broad -OH stretching frequency in the 3000-3500 cm^{-1} region of its IR spectrum suggests complete methylation of the hydroxyl groups. Also, the stretching peaks at 1155 cm^{-1} manifest the C-O-C bond formation, which is very characteristic of ethers. Recorded specific optical rotation is -19° that conforms to literature [14] value. Since the optical rotation matches the literature value, it can be inferred that full optical activity was retained and no racemization occurred in the dibromination step.

Precursor **3** was prepared via Grignard cross coupling of the fluorenone and the Grignard reagent. The reaction proceeded smoothly to give 72% yield of the desired product. The successful coupling of the fluorenyl moiety to the 3, 3'-position was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy. The appearance of a small broad peak at the aliphatic region in the ^{1}H NMR spectrum is an indication that an alcoholic proton is present. Overall, the ^{1}H NMR spectrum was more complex in comparison to precursor **2**. The peaks due to the coupled fluorenyl moieties contributed to this complexity. The ^{13}C NMR spectrum was likewise complicated. Fifteen carbon signals were manifested compared to ten in precursor **2**. One signal was added to the aliphatic carbon peak relative to precursor **2**, which accounts for the 9-C position of the fluorenyl group. Four ^{1}H NMR signals due to the aromatic protons of the fluorenyl group were also manifested. Mass spectral data further confirms the synthesis of **3**. The observed peak with a charge-to-mass ratio m/e of 674.83 corresponds to the molecular ion. Fluorenyl ion fragments are manifested with the observation of peaks with m/e of 222.

Deprotection of precursor **3** yielded ligand **4**. Deprotection was accomplished by hydrobromic acid mediated hydrolysis. Again, this adopted method is not in consonance with the existing methods wherein BBr_3 is used as a demethylating reagent [15]. Hydrobromic acid was used to prevent or minimize substitution of the hydroxyl groups present in the 9-C and 9'-C of the fluorenyl moieties. As can be noted, these are tertiary carbons and the fact that these carbons are adjacent to aromatic groups would entail that the radical or carbocation that will be formed in radical or electrophilic substitutions would have very high stability. This is attributed to the resonance stabilizing effects of the aromatic groups [16]. This is actually very similar to the property manifested by the trityl radical or carbocation [17].

The ^{1}H NMR spectrum of ligand **4** shows two proton peaks that correspond to hydroxyl groups. One has a δ value of 3.7 ppm and the other has a δ value of 1.6 ppm. In addition, the spectrum does not show any manifestation of proton exchangeability (presence of a broad proton peak), which is expected to be shown by the fluorenyl alkyl OH. This is not very surprising since, as what have been mentioned and implied earlier, the 9-C fluorenyl position would rather loose the OH than give up H since the resulting alkoxy anion is not very stable. By this reasoning, it is proposed that proton exchangeability is hampered. The mass spectrum also adds further proof of synthesis of **4**. Aside from realizing that the molecular weight is 646.77 g/mole, the fragmentation pattern of the molecular ion confirms the presence of a trityl-like moiety. This is evidenced by the ion fragment with m/e of 633, which corresponds to the M+1-17. This indicates that water has been removed from the molecular ion, as manifested by an alkyl OH.

Reduction of the 9-C position of the flourenyl proceeded readily via hydrogenolysis. Subsequent

deprotection of the methyl groups provided Ligand **5**. The ^{1}H NMR spectrum shows only one proton peak for a hydroxyl proton. The ^{1}H NMR spectrum of **5** is very similar with that of the spectrum of **4**. The mass spectrum shows the molecular ion peak at m/e = 614.35, which is an indication that **5** was synthesized. Further support of this is seen at M+1-222 and a fragment with m/e = 222, an indication of the fluorenyl fragment.

Assay of CLACS

The synthesized ligands (compounds **4** and **5**) were used to prepare the chiral Lewis acid catalysts (CLACs) (Scheme 2). The catalysts were prepared *in situ* and used in the succeeding model reactions without further purification. The two model reactions were used to test the chiral inducting efficiency of the CLACs: they are aqueous Diels-Alder and Barbier reactions. For the Diels-Alder reaction, pyridyl-2-crotonate and cyclopentadiene were used as the diene-dienophile system. For the Barbier reation, prenyl bromide and 3-methyl-2-butenal were used as the reactant system in the presence of tin, to produce artemisia alcohol, a naturally occurring monoterpene.

These two reaction systems were chosen for this study for two reasons: a) because both reactions are known to proceed in water in water and b) to test the generality of the prepared CLACs. Confirmation of optical purity of the assay products was done by CD spectroscopy.

Results of the assay for both Diels-Alder and Barbier reactions are presented in Figures 3 and 4, respectively. Various lanthanide metals were used in the reaction, such as Eu, Pr, Yb, Sm, Lu, and Nd. Ytterbium seems to be the most promising metal for coordination with the synthesized ligands. This is shown in the CD spectra of the products obtained (Figures 3 and 4).

We have considered first using chiral HPLC to separate the enantiomers of the DA adduct, but since we did not have a compatible column suited for separation, we resorted instead to CD spectroscopy, which gave us only an indication of asymmetric catalysis.

We would like to point out that we are not certain that the inclusion of the CLACs to the reaction mixtures affected the rates of the reactions. However, the results of various workers who had made contributions in water-mediated reaction chemistry [10, 12, 13] indicate that the rates of reactions were basically dependent on the medium and not on the catalyst. At any rate, our study shows that chiral Lewis acid catalysis in aqueous medium is possible. For the Diels-Alder reaction, catalysis is postulated to occur via at least one of the accepted modes. One such mode is chelation.

In attempting to design general chiral Lewis acidic metal complexes, we have presumed that good levels of stereocontrol were feasible. The general design plan illustrated in Figure 5 highlights the unifying feature of this study (for the Diels-Alder reaction). We propose in Figure 5 the transition state of the model Diels-Alder reaction. The transition state shows that the diene coordinates with the catalyst via a distorted octahedron. This idea of coordination is based on the notion that substrates undergoing activation must be capable of chelating to the chiral Lewis acidic lanthanide (III) complex. Rigidification of the reacting entity bearing chiral information is frequently achieved through hydrogen bonding, π stacking, or chelation [1]. Both chelation control and π stacking interactions have been identified as control elements in this process. From a structural point of view, compounds **4** and **5** both posses bulky groups that we thought would help in promoting asymmetry when we make chiral lanthanide complexes out of them for catalysis. However, the similar CD spectral profiles of the products for both model reactions described herein suggest that derivatization of the binaphthol backbone have no effect in promoting asymmetry (Figures 3 and 4).

For the Barbier reaction, we postulate π stacking as the influencing factor but we do not know yet whether chiral Lewis acid catalysis by CLACs of **4** and **5** did, indeed, occur. However, it seems that it was more likely to have happened, since the results of the experiments indicate enantiomeric enrichment of products.

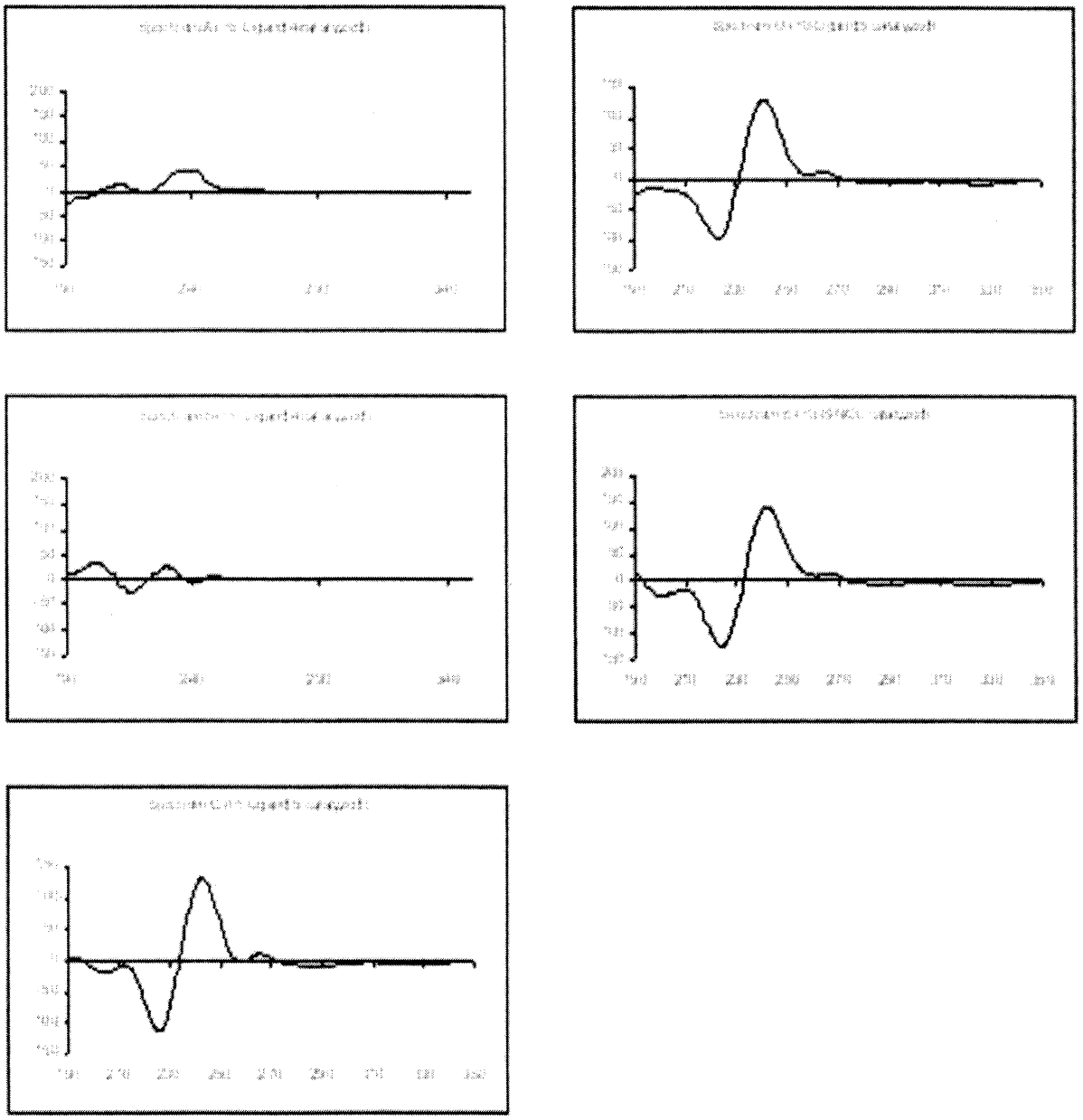


Fig. 3. The CD spectra of isolated Diels-Alder adduct obtained by the reaction of cyclopentadiene and pyridyl-2-crotonate. Spectra A and B represent Diels-Alder products of the reactions that were catalyzed by (Yb-Ligand 4) and (Pr-Ligand 4), respectively. Note that Spectrum A shows more enrichment of the (+) enantiomer compared to Spectrum B. Spectra C and D represent Diels-Alder adducts of the reactions that were catalyzed by (Pr-Ligand 5) and (Yb-Ligand 5), respectively. As can be seen, spectrum D shows more enrichment of the (+) isomer of the endo product. Spectrum E shows the CD profile of Yb-BINOL catalyzed Diels-Alder reaction. From spectra A to D relative to spectrum E, it can be seen that enantiomeric enrichment of the reaction depends on the metal center and the type of ligand.

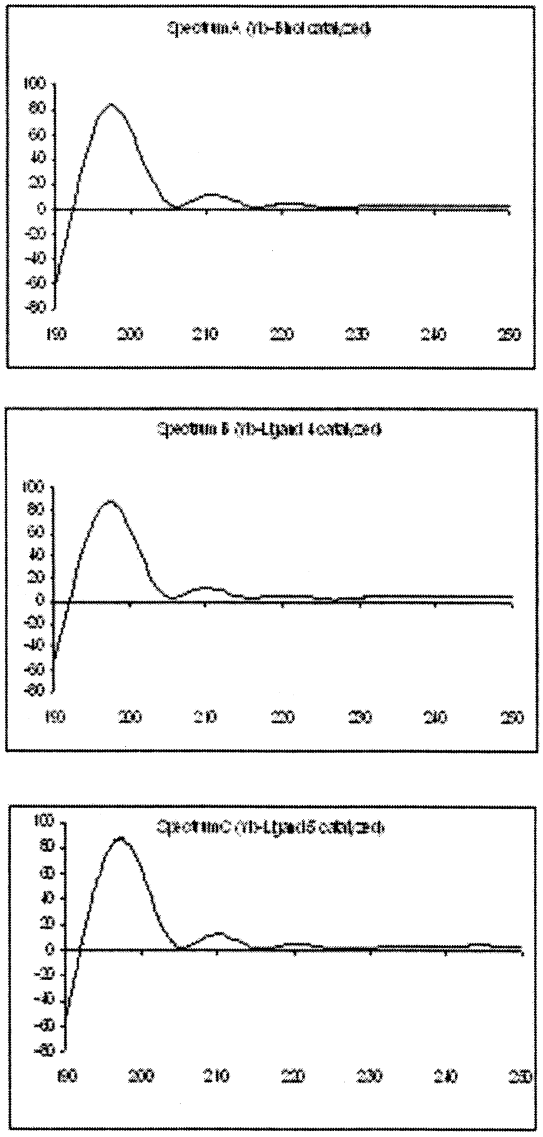


*Fig. 4. The CD spectra of isolated artemisia alcohol obtained by the reaction of 3-methlyl-2-butenal with prenyl bromide. Spectrum A represents a product that was catalyzed by (Yb-BINOL). Spectra B and C were catalyzed by (Yb-Ligand **4**) and (Yb-Ligand **5**), respectively. Note their very similar CD profiles suggest that derivatization of the binaphthol backbone have no effect on promoting asymmetry of products for Barbier reaction. The spectra also show that the catalysts favor the formation of (+)-artemisia alcohol.*

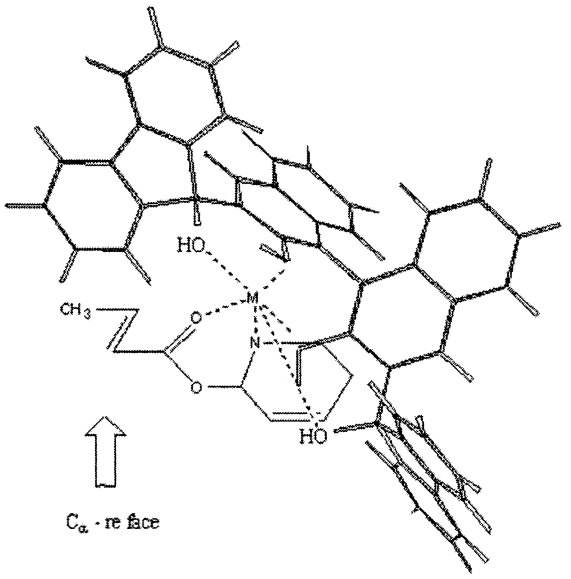


Fig. 5. Proposed transition state of DA reaction showing selective facial attack due to steric hindrance

SUMMARY AND CONCLUSIONS

Results of our experiments indicate that chiral Lewis acid catalysis in aqueous medium is feasible; the CD curves of the products clearly show that asymmetric induction has been achieved (Figures 4 and 5). Furthermore, Lewis acidity does not play a major role per se in the reaction, but the electronic interactions of the catalyst with the forming transition state do. It is postulated that π stacking and chelation are the factors that influence asymmetry for Barbier and Diels-Alder reactions. Out of the six tested lanthanide metal triflates, only $Yb(OTf)_3$ showed the most promising results.

ACKNOWLEDGEMENTS

We thank the Natural Sciences Research Institute (NSRI) of the University of the Philippines, Diliman for funding this research project. Dr. Seiji Mori of Ibaraki University is also acknowledged for providing us the NMR spectra of our ligands. We also would like to thank Mr. Marte Villena and Mang Nick for their technical assistance.

REFERENCES

1. Johnson, J.S. and Evans, D.A., *Acc. Chem. Res.* 33, 325-335 (2000).

2. Willis, M.C., Johnson, J.N., and Evans, D.A., *J. Am. Chem. Soc.* 121, 1994-1995 (1999).

3. Narasaka, K., Iwasawa, N., Yamada T., and Nakashima, M., *J. Am. Chem. Soc.* 11, 5340-5345 (1989).

4. Johnson, J.S. and Evans, D.A., *Org. Lett.* 1, 595-598 (1999).

5. Eliel, J.R., *Principles of Stereochemistry* 2nd Ed, (Academic Press, New York, 1982).

6. Chapman, K.T., Bihasa, J., and Evans, D.A.,. *J. Am. Chem. Soc.* 110, 1238-1256 (1988).

7. Shibasaki, M., and Hamashima, Y., *J. Am. Chem. Soc.* 121, 2641-2642 (1999).

8. Kim, S., and Kim, S.H., *Tetrahedron Lett.* 36, 3723-3724 (1995).

9. Chao, J.L., *Chem. Rev.* 93, 2023-2035 (1993).

10. Kobayashi, S., Ishitani, H., Hachiya, I., and Araki, M., *Tetrahedron* 50, 11623-11636 (1994).

11. Lingenfelter, D.S., Helgeson, R.C., and Cram, D.J., *J. Org. Chem.* 46, 393-406 (1981).

12. Yu, L., Chen, D., and Wang, P.G.. *Tetrahedron Letters* 37 (13), 2169-2172 (1996).

13. Kobayashi, S. and Horibe, M., *Tetrahedron Asymmetry* 6 (10), 2565-2569 (1995).

14. Lingenfelter, D.S., Helgeson, R.C., and Cram, D.J., *J. Org. Chem.* 46, 406-412 (1981).

15. Miranda, J. T., and Arco, S.D., *Proceedings of the 19th Philippine Chemistry Congress* 262-264 (2004).

16. Carey, F. and Sandberg, J., . *Advanced Organic Chemistry Part two.* 3rd Ed. (Plenum Press, New York, 1992).

17. Morisson, F. and Boyd, R., *Organic Chemistry.* 5th Ed., (Prentice Hall, New York, 1985).