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Immobilized aza-bis(oxazoline) copper catalysts on SAMs: Selectivity dependence on catalytic site embedding

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ABSTRACT

Aza-bis(oxazoline) copper complexes have been immobilized onto alkanethiol self-assembled monolayers with three different surface orientations and tested in the benchmark cyclopropanation reaction of ethyl diazoacetate and styrene. The three surface orientations were the catalyst backbone above, below, and even with the tail groups of the self-assembled monolayer. Enantioselectivity of the product improved to >90% by immobilization of the catalyst at the monolayer surface and was significantly reduced when the catalyst was imbedded in the monolayer. The catalyst presented above the monolayer surface is a solution mimic in terms of selectivity. The catalytic chips proved to be recyclable.

1. Introduction

Cyclopropane derivatives are an important family of chemical compounds with interesting biological properties [1] as well as starting materials and intermediates in organic synthesis [2]. Consequently, extensive work has been devoted to the development of efficient diastereo- and enantioselective methods for the synthesis of cyclopropanes [3–8]. The most versatile method of cyclopropane synthesis is the transition metal-catalyzed cyclopropanation of olefins with diazo-compounds. These homogeneous transition metal catalytic systems have shown high selectivity in the transition metal-catalyzed cyclopropanation reactions with copper [5,7], rhodium [8], and cobalt [4,9]. Bis(oxazoline) [4–6,8] and aza-bis(oxazoline) [7] form superior catalysts for the cyclopropanation reaction.

Recent research efforts have targeted the transition of homogeneous catalyst systems to heterogeneous catalyst systems [10–16]. Heterogeneous catalysis allows for the recycling of transition metals and chiral ligands, thus reducing material cost and waste. While recyclability is an advantage of heterogeneous catalysts, the systematic study of surface-ligand steric interactions inherent in these systems has seen little attention. The ability to control the steric environment of the surface, where the catalyst is bound, may improve catalytic outcome from that of the homogeneous phase. Transition metal catalysts have been immobilized on solid supports, such as organic polymers [10–15], inorganic solids [10–15], and colloids [16]. The latter prompted our group to study heterogeneous catalysts in terms of steric interactions with the monolayer on planar gold.

In this study, self-assembled monolayers (SAMs) of alkanethiols on gold were used because they form predictable structures and allow for simple modification of the environment around the catalyst. As illustrated in Fig. 1, changing the length of the alkanethiol chain changes the steric environment of the catalyst center by moving it to be even with the surface of the monolayer (Fig. 1A), above (Fig. 1B) and below the surface of the monolayer (Fig. 1C).

Allowing the catalyst to be even with the surface of the monolayer (Fig. 1A) may cause the cyclopropanation results to differ, in terms of selectivity, from the homogeneous phase, because one side of catalyst is partially blocked. When the catalytic center is above the monolayer surface (Fig. 1B), results similar to that found in the homogeneous phase should be seen, because the catalyst should not interact with the monolayer. If the catalyst is below the surface of the monolayer (Fig. 1C), the cyclopropanation selectivity should differ from those of the homogeneous phase because of the potential for additional intermolecular interactions around the catalytic center. The objective of this study is to immobilize aza-bis(oxazoline) copper catalysts on SAMs, and to study the effect of environmental changes on the cyclopropanation reaction.

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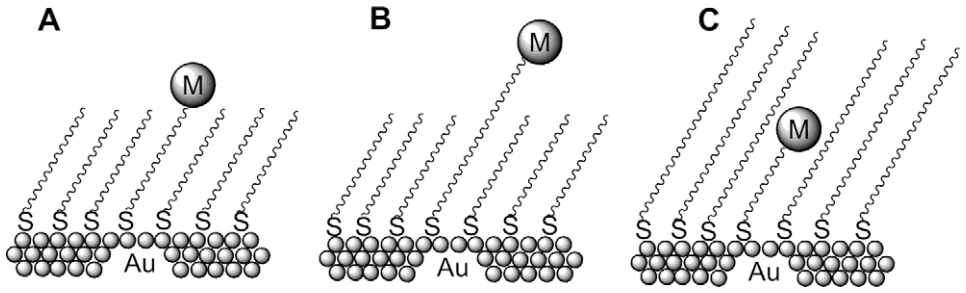


Fig. 1. Schematic representation of metal catalyst attached to thiolate monolayers on gold surfaces. (A) The catalyst is even with the monolayer surface, (B) the catalyst is above the monolayer surface and (C) the catalyst is below the monolayer surface.

2. Experimental

2.1. Materials

All chemicals and solvents were used as received. Thin-layer chromatography (TLC) was preformed with Merck 60 F254 silica gel plates, and compounds were visualized with UV light.

Starting materials for ligand synthesis were as follows: (S)-tert-Leucinol (98% Aldrich), (S)-(+)-2-amino-1-propanol (98% Acros), benzaldehyde (Aldrich), p-toluenesulfonic acid monohydrate (99% Acros) methanol Certified ACS (Fisher).

Starting materials for self-assembled monolayer formation were as follows: 11-mercapto-1-undecanol (97% Aldrich), stearyl mercaptan (97% TCI America), 1-octanethiol (97% Acros), 1-dodecanethiol (98% Alfa Aesar).

Starting materials for gold substrate preparation were as follows: aluminum wire (99.999% Kurt J. Lesker), gold wire (99.99% Kurt J. Lesker), and microscope cover glass (Fisher Scientific).

Starting materials for the Mitsunobu reaction were as follows: diethyl azodicarboxylate (40 wt% solution in toluene Aldrich) and triphenylphosphine (99% Aldrich).

Starting materials for the cyclopropanation reaction were as follows: styrene (99% Acros) ethyl diazoacetate (Aldrich), dichloromethane (99.9% Acros), phenylhydrazine (95% Acros) and $Cu(OTf)_2$ (98% Aldrich).

2.2. Aza-bis(oxazoline) ligand synthesis

Bis[4,5-dihydro-(4S)-(1,1-dimethylethyl)-1,3-oxazole-2-yl]-amine**(1a)** was prepared according to the literature procedure [7]. Bis[4,5-dihydro-(4S)-(methyl)-1,3-oxazole-2-yl]-amine**(1b)** was prepared by slight modification of the literature procedure [7]. The amino alcohol was changed from (S)-tert-leucinol to (S)-(+)-2-amino-1-propanol to generate (**1b)** (bis[4,5-dihydro-(4S)-(methyl)-1,3-oxazole-2-yl]-amine).

2.3. Preparation of heterogeneous catalyst

2.3.1. Gold substrate preparation

Glass microscope slides were cleaned with acetone/deionized-water (50/50 ratio) and allowed to air dry. Aluminum was deposited onto the glass slides by thermal vapor deposition at a pressure of 3×10^{-6} mbar. Gold was deposited onto the aluminum-coated glass slides by thermal vapor deposition at a pressure of 3×10^{-6} mbar.

2.3.2. SAM preparation

Gold chips were immersed in a 2-mM solution of alkanethiols, (ethanol, 4 h) at room temperature (23°C-25°C). Upon removal from solution, the samples were carefully rinsed with CH_2Cl_2.

2.3.3. Mitsunobu reaction

Mixed monolayer chips were placed in a three-necked round bottomed-flask. Aza-bis(oxazoline) ligand (1a or 1b) and triphenylphosphine were added. THF was added and then the reaction flask was placed in an oil bath at 50 °C. Under N_2, diethyl azodicarboxylate was added and the reaction was hand-stirred for 2 h. Hand-stirring the reaction is required because the glass slides break easily if stir bars are used. The procedure of hand-stirring is taking the reaction flask and swirling in a circular motion over the period of the reaction time. The samples were removed from the reaction mixture and rinsed with dichloromethane to remove reagents loosely bound to the surface.

2.4. Surface characterization

2.4.1. DRIFT

The substrates were studied using diffuse reflectance infrared Fourier transform (DRIFT) spectroscopy (Thermo Nicolet-NEXUS 470 FT-IR) to analyze the alkyl chain ordering of the molecules on the surface. The spectra were recorded under nitrogen to eliminate the background signals due to CO_2 and H_2O adsorption bands. Unmodified gold substrates were used as the background spectra. 1024 scans were collected for each sample with a 4-cm^{-1} resolution.

2.4.2. AP MALDI-TOF MS

Atmospheric pressure matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (AP MALDI-TOF MS) was used to analyze the monolayer and to determine if the aza-bis(oxazoline) ligands were attached to the monolayer surface before and after use in the cyclopropanation reaction. A high-resolution AP MALDI (Agilent Tech) with pulsed dynamic focusing was used. MS analysis of the ions was detected in the positive mode using a 337-nm N_2 laser, pulse width of 20 ns, a capillary voltage of 3500 V, fragmentor voltage of 260 V, skimmer voltage of 40 V, and drying temperature of 325 C. External calibration was done using an ES-TOF tuning mix of 10 masses for the range of 100–2300 *m*/*z*. Three to five areas of each sample were characterized using the MALDI-TOF. The spectra were collected by uniformly moving the laser in a circular pattern across the sample for 1 min. The spectra were reproducible within a single sample and using different samples. The matrix, α-cyano-4-hydroxycinnamic acid (CHCA) (Sigma–Aldrich, >99.0% purity), was used without further purification and dissolved in 9/1 ratio of the solvents CH_2Cl_2/EtOH (0.9 ml CH_2Cl_2 and 0.1 ml ethanol for a total volume of 1 ml). The ratio of matrix (CHCA) to solvent was 10 mg/ml. The matrix fragmentation can be observed in each of the spectra.

2.4.2.1. AP MALDI-TOF MS Sample preparation. MALDI preparation was done by dried-drop method where a 1-μl aliquot of the matrix solution was dropped onto each sample and then dried at room

temperature. The matrix solution was added after rinsing of the samples to remove loosely bound material. This method of sample preparation yields a uniform layer of matrix crystals on the samples. The samples were then mounted onto a MALDI sample plate using double-sided tape and loaded onto the MALDI. Analyte ionization was achieved by focusing a laser pulse onto the sample/matrix mixture.

2.5. Cyclopropanation procedures

2.5.1. Homogeneous asymmetric cyclopropanation of styrene and ethyl diazoacetate

The benchmark cyclopropanation reaction was preformed according to the literature procedure [7].

Under nitrogen atmosphere $Cu(OTf)_2$(3.6 mg. 0.01 mmol) and aza-bis(oxazoline) ligand a-b (6.2 mg. 0.022 mol) were dissolved in anhydrous CH_2Cl_2 to produce a light green solution. Phenylhydrazine (22 μl of a 5% solution) was added and the green color disappeared. Styrene (312 mg 3 mmol, 345 μl) was added and then ethyl diazoacetate (EDA) (1 mmol, 1 ml of an 8% solution in CH_2Cl_2 diluted with 7 ml CH_2Cl_2) was added over 4 h. The reaction mixture was allowed to stir for 5 h. The solvent was evaporated in vacuo to give a green oil. The reaction products were purified by p-TLC.

2.5.2. Heterogeneous asymmetric cyclopropanation of styrene and ethyl diazoacetate

The systems 2-4(a-b) (Fig. 1) were added to a three-necked round-bottomed flask and $CH_2Cl_2$was added under nitrogen and the copper pre-catalyst (1 mg) was added to the reaction flask. This was hand-stirred for 10 min and the phenylhydrazine (20 μl of a 5% solution) was added. Styrene (312 mg 3 mmol, 345 μl) was added and then EDA (1 mmol, 1 ml of an 8% solution in CH_2Cl_2 diluted with 7 ml of CH_2Cl_2) was added over 4 h. The reaction was hand-stirred for 5 h. The catalytic chips were removed and the reaction solvent was evaporated and the reaction products were purified by p-TLC.

2.5.3. Recyclability experiment

Catalytic chips were added to a three-necked round-bottomed flask and styrene was added. For the first run copper pre-catalyst (1 mg) was added to activate the catalytic chips. After activation the reaction flask was then placed in a preheated oil bath (70–75 C). Under nitrogen EDA (1 mmol, 1 ml of an 8% solution in CH_2Cl_2 diluted with 7 ml CH_2Cl_2) was added in one portion. The reaction mixture was hand-stirred for 5 hours. The catalytic chips were then removed and the reaction products purified by p-TLC. After use in the cyclopropanation reaction the catalytic chips were rinsed with dichloromethane and dried. The catalytic chips were then re-used in the cyclopropanation reaction using the above procedure with the following exception that the copper pre-catalyst was not added to activate the chips.

2.6. Purification and analysis of cyclopropanation products

2.6.1. Purification and NMR analysis for yield and stereoselectivity

The cyclopropane products were purified using p-TLC. The solvent ratio of 96/4 hexane/diethyl ether was used. CH_2Cl_2 was used to remove the products from the silica gel. The solvent was evaporated under vacuum to yield colorless oil. The oil was then analyzed by ^1H NMR and integration of the cis and trans peaks gave the ratio of cis and trans isomers. The yield of the reaction was determined by first weighing the products before addition of NMR solvent and integration of the cis/trans peaks along with the peak due to side products.

2.6.2. Purification and enantiomeric excess determination

The cis and trans isomers were separated from each other by p-TLC using TLC sheets and the solvent ratio of 96/4 hexane/diethyl ether. CH_2Cl_2 was used to remove the respective isomer products from the silica gel. The solvent was evaporated in vacuo to yield colorless oils for both isomers. The cis and trans isomers were analyzed by ^1H NMR to show separation of the two isomers. After addition of the chiral shift reagent to the NMR samples they were analyzed to give the enantiomeric excess [17–20].

2.7. Statistical analysis

Cyclopropanation reactions for both the homogeneous and heterogeneous phases were preformed six times. Based upon the data obtained from the multiple trials the student *t* test for differences in means was preformed to assess the statistical difference in the enantiomeric excess values obtained between each system.

t (statistic *t*) = ((mean data set 1) − (mean data set 2))/(pooled standard deviation)[square root (((number of data points of 1) + (number of data points of 2))/(((number of data points of 1)(number of data points of 2)))]

The critical value of *t* at the 99.9% confidence level for 10 degrees of freedom is 4.59. If the test statistic *t* which is the value obtained for the student *t* test for differences in means is less than the critical value of *t* then there is no statistical difference between the systems. If the value of *t* is greater than 4.59, the two catalytic systems being compared are considered to be statistically different.

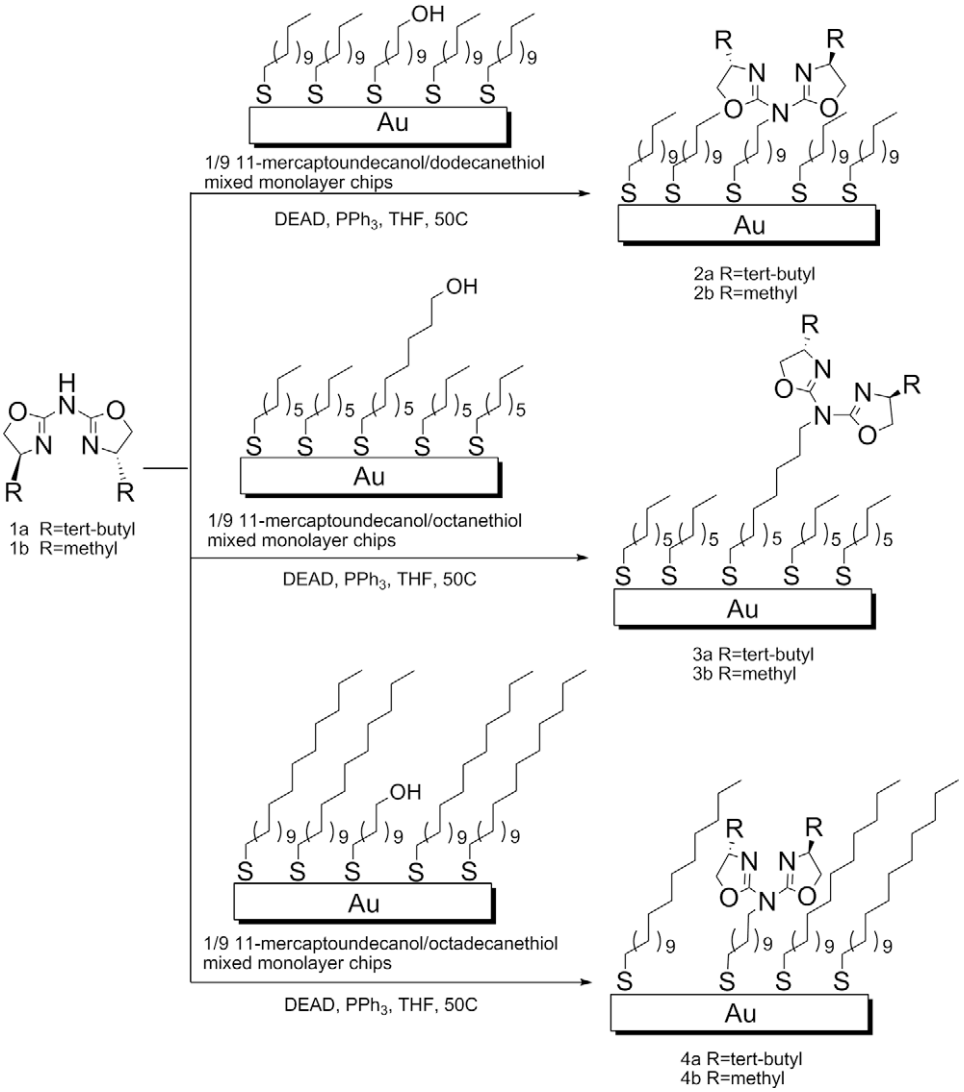
3. Results

3.1. Immobilization

Overall, to explore the three different surface orientations, mixed SAMs on gold in a 1:9 ratio of alkanethiols with hydroxyl and methyl tail groups were prepared. The aza-bis(oxazoline) ligands were then immobilized on the hydroxyl-terminated alkanethiols using a Mitsunobu reaction. The cyclopropanation test reaction for the study is that of ethyl diazo-acetate and styrene. Ethyl diazo-acetate was chosen because of the compound's increased steric bulk compared to methyl diazo-acetate.

All of the mixed monolayer chips were prepared using a 2-mM alkanethiol solution using a 1:9 ratio of hydroxyl and methyl tail group alkanethiols in ethanol. The alkanethiol with the hydroxyl tail group was 11-mercaptoundecanol, which was constant throughout the study. The alkanethiol with the methyl tail group was varied using 1-dodecanethiol (Scheme 1, system 2), 1-octanethiol (Scheme 1, system 3), and octadecanethiol (Scheme 1, system 4) to change the steric environment on the catalytic system. Monolayers were formed by solution deposition method in the alkanethiol solution for 4 hours at room temperature. The samples were rinsed and analyzed by DRIFT IR to confirm SAM formation (Fig. 2a and b).

In the IR spectra (Fig. 2a and b) C-H stretches of the methylene groups of the alkane chains are used as the reference peaks for SAM organization [21–23]. The C–H stretches have two common vibrations seen at ~2850 cm^{-1} (symmetric) and ~2918 cm^{-1} (antisymmetric). These two wavenumber values can shift to higher or lower frequencies depending on the ordering of the alkane chain. A shift to higher frequencies (ν_{CH2} asym >2918 cm^{-1}) corresponds to a disordered monolayer with cis interactions in the alkyl chain [24,25]. A shift to lower frequencies (ν_{CH2} asym < 2918 cm^{-1}) corresponds to an ordered monolayer with all trans interactions in the alkyl chain. In the spectrum of the mixed monolayer systems $\nu_{CH2\ asym}$ = 2917 cm^{-1} and $\nu_{CH2\ sym}$ = 2849 cm^{-1}, indicating that an ordered monolayer is formed (Fig. 2a and b). The small stretch



Scheme 1. Synthesis of immobilization of aza-bis(oxazoline) ligands on the surface of mixed monolayers.

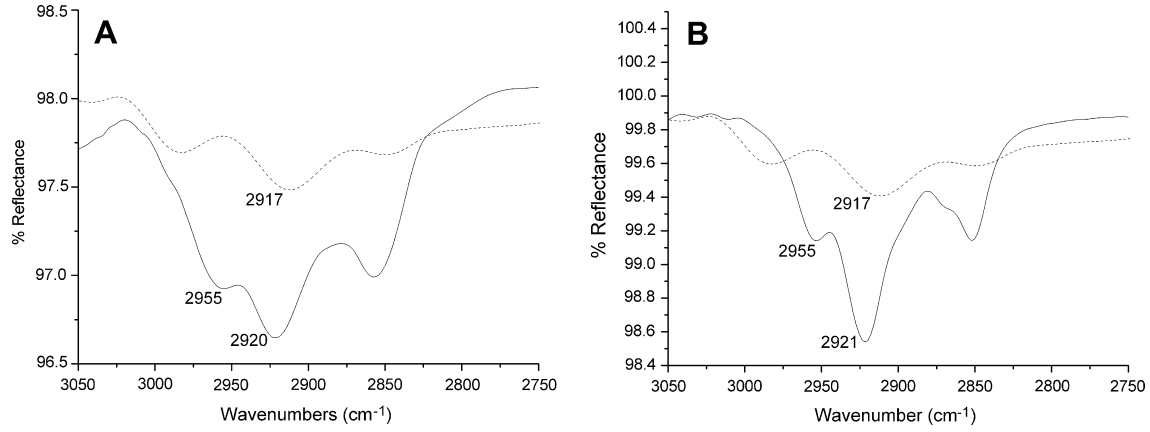


Fig. 2. IR spectrum before and after immobilization of the aza-bis(oxazoline) tert-butyl-substituted ligand. (A) IR spectrum before and after immobilization of the aza-bis(oxazoline) methyl-substituted ligand. (B) The dash line is before immobilization and the solid line is after immobilization of the ligand. The range of the IR spectrum is 3050 to 2750 cm^{-1}.

at 2955 cm^{-1} is due to the C–H stretching of the methyl tail groups (Fig. 2a and b dashed line).

Formation of catalytic systems 2a and 2b (Scheme 1) started with a mixed monolayer of 11-mercaptoundecanol and 1-dodecanethiol. The ligands (bis[4,5-dihydro-(4S)-(1,1-dimethylethyl)-1,3-oxazole-2-yl]-amine (Scheme 1, 1a) and bis[4,5-dihydro-(4S)-(methyl)-1,3-oxazole-2-yl]-amine (Scheme 1, 1b) were attached via a Mitsunobu reaction to hydroxyl tail groups in the mixed

monolayer. Systems 3a and 3b (Scheme 1) were formed using mixed monolayers of 11-mercaptoundecanol and 1-octanethiol, which was then used in the Mitsunobu reaction so as to attach ligands 1a and 1b (Scheme 1) to the tail groups of the monolayer. Systems 4a and 4b (Scheme 1) were formed using mixed monolayer of 11-mercaptoundecanol and octadecanethiol.

In the IR spectra after attachment of the ligand (Fig. 2a and b solid line), the stretch (2955 cm^{-1}) due to C–H of methyl groups has a greater intensity compared to the intensity before attachment of the ligand. This is due to the presence of the ligand and its methyl-containing R groups. The width of the peak is due to overlapping CH stretches from CH groups in the ligand and monolayer. The stretch at 1200 cm^{-1} (Fig. 3) is due to a tertiary amine indicating that the ligand was in fact immobilized to the surface of the monolayer. The stretch at 1125 cm^{-1} is due to the ether group present in the ligand structure [26]. These peaks are not present in the IR spectrum prior to immobilization. The IR spectrum of 3a,b (Scheme 1) and 4a,b (Scheme 1) is similar and can be found in the supplementary section.

3.2. Cyclopropanation reaction

The aza-bis(oxazoline) immobilized monolayer gold chips were then activated with the copper pre-catalyst ($Cu(OTf)_2$) and used in the cyclopropanation reaction of ethyl diazoacetate (EDA) and styrene (Scheme 2). Using phenylhydrazine, the copper(II) species was reduced to the copper(I) species which is the active catalyst. The homogeneous cyclopropanation reaction was performed according to the literature procedure [7]. The amount of pre-catalyst was reduced from 3.6 mg to 1 mg. The reduction in pre-catalyst is because the amount of ligand immobilized is less than the amount used in the homogenous phase.

The ratio of the trans to the cis isomer was determined first by separation of the products from the starting materials by preparatory thin layer chromatography (p-TLC). After purification of the products, the cis/trans ratio of the cyclopropanation products was determined. Based upon the yield of the purified products and ^1H NMR the percent yield of the cyclopropanation products was determined.

In this study the enantiomeric excess of the cyclopropane products was determined by ^1H NMR with the use of the chiral lanthanide shift reagent Europium tris[3-(heptafluoro-propylhydroxymethylene)-(+)-camphorate. Lanthanide shift reagents have seen recent use in enantiomeric excess determinations [17–20].

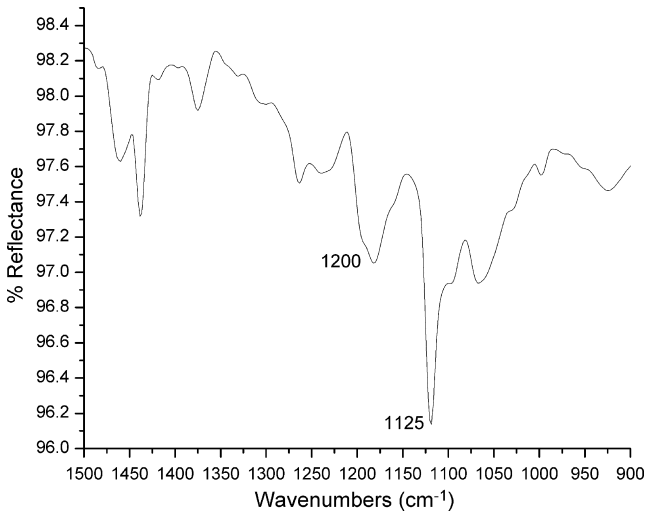


Fig. 3. IR spectrum after immobilization of the aza-bis(oxazoline) tert-butyl-substituted ligand. The range of the IR spectrum is 1500–900 cm^{-1}.

Chiral NMR methods using lanthanide shift reagents offer many advantages, such as easy handling, low cost, and non-destructive analysis [17–20]. Chiral GC and HPLC could also be used to analyze enantiometric excess, but for this study access to GC and HPLC was not convenient. Comparable results for the homogeneous phase to the literature values show that chiral NMR is a viable alterative for enantiomeric excess determinations when access to GC and/or HPLC is not available [17–20]. The diastereomers were separated using p-TLC, analyzed by ^1H NMR to check separation, and then the chiral shift reagent was added to the NMR samples of the two isomers. The NMR samples were analyzed by ^1H NMR after 25 min and again 2 h after addition to verify complete separation of the enantiomers. The homogeneous reaction and a control experiment using only the copper catalyst without ligand were performed and the enantiomeric excess was determined by the use of chiral shift reagent and was comparable to literature values [7].

3.2.1. Bis[4,5-dihydro-(4S)-(1,1-dimethylethyl)-1,3-oxazole-2- yl]-amine copper(I) catalytic systems

The homogenous and heterogeneous Bis[4,5-dihydro-(4S)-(1,1-dimethylethyl)-1,3-oxazole-2-yl]-amine copper(I) catalytic systems were tested in the cyclopropanation reaction and the results are listed in Table 1. In these systems tert-butyl groups are present in the C2 positions.

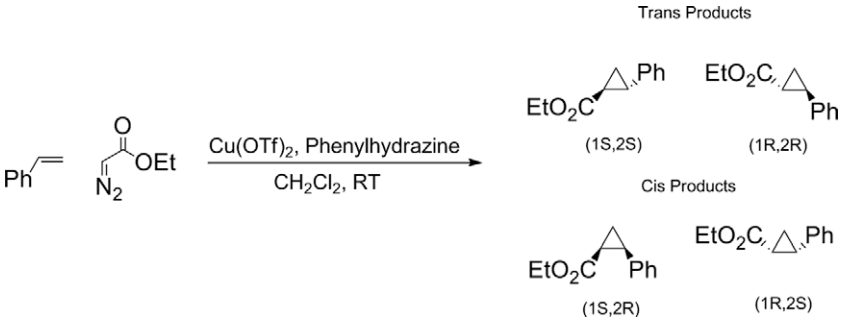
The cis/trans ratio for the homogeneous system (Scheme 1 1a) is 20/80. The enantiomeric excess for the trans isomer is 87% for system 1a (Table 1) and is 80% for the cis isomer (Table 1). In a similar system, Reiser and coworkers [16] used 1a in the cyclopropanation reaction of styrene and methyl-diazoacetate and obtained 33/67 cis/trans ratio which is lower than the results obtained but methyl diazoacetate has less steric bulk than ethyl diazoacetate. The enantioselectivity of system 1a agrees with literature values [16]. In system 2a (Scheme 1) the catalyst is even with the monolayer surface and in this orientation the cis/trans ratio of the cyclopropane products increases from 20/80 (1a Table 1) to 16/84.

The enantiomeric excess of the tert-butyl aza-bis(oxazoline) catalyst even with the monolayer surface is 93% for the trans isomer. The difference in the enantiomeric excess for the trans isomer product from system 1a and system 2a is statistically different based on a 99.9% confidence level. Therefore, when the catalyst is even with the monolayer surface the enantiomeric excess is significantly improved through immobilization.

In system 2a the enantiomeric excess is 82% for the cis isomer. However, in system 2a, enantiomer (1R,2S) is favored over enantiomer (1S,2R) for the cis isomer (Scheme 2). Comparison of the enantiomeric excess for the cis isomer for system 2a and system 1a shows that the difference in enantiomeric excess is not statistically different. Placing the catalyst even with the monolayer surface does not show an improvement in enantiomeric excess for the cis isomer, but there is a reversal in the enantioselectivity of the enantiomer formed.

When the catalyst is above the surface (Scheme 1, 3a), the cis/trans ratio is 23/77 which is similar to the homogeneous phase (Table 1, 1a). Comparison of the enantiomeric excess for the trans isomer for systems 1a (Table 1, 87%) and 3a (Table 1, 85%) shows that the difference in enantiomeric excess of the two systems is not statistically different. The enantiomeric excess of the cis isomer for systems 1a and 3a (81%) is also not statistically different. The statistical treatment of the data indicates that this system (Scheme 1, 3a) may be a good "solution mimic".

When the catalyst is below the monolayer surface, (Scheme 1; 4a), the cis/trans ratio is 28/73, which is lower than the homogeneous phase (Table 1, 1a). In system 4a the enantiomeric excess for the trans isomer is 44% and is 37% for the cis isomer. Comparison of the enantiomeric excess of both the trans and cis isomers



Scheme 2. Benchmark cyclopropanation reaction.

Table 1
Cyclopropanation results of the homogeneous and heterogeneous bis[4,5-dihydro-(4S)-(1,1-dimethylethyl)-1,3-oxazole-2-yl]-amine Copper(I) Catalyst in the benchmark reaction of styrene and ethyl diazoacetate in dichloromethane, room temperature.

Catalytic system	Cis/trans ratio[a]	Trans ee%[b] (1S,2R)	Cis ee%[b] (1S,2R)	Yield[a,c]
1a	20/80	87	80	71
2a	16/84	93	82[d]	74
3a	23/77	85	81	69
4a	28/72	44	37	76

[a] Determined by NMR.
[b] Determined by NMR with chiral shift reagent.
[c] Yield is the yield of the cyclopropanes (cis and trans) compared to the yield of all products (cyclopropane and side products formed).
[d] The (1R,2S) enantiomer is formed over the (1S,2R) enantiomer.

Table 2
Cyclopropanation results of the homogeneous and heterogeneous bis[4,5-dihydro-(4S)-(methyl)-1,3-oxazole-2-yl]-amine Copper(I) Catalyst in the benchmark reaction of styrene and ethyl diazoacetate in dichloromethane, room temperature.

Catalytic system	Cis/trans ratio[a]	Trans ee%[b] (1S,2S)	Cis ee%[b] (1S,2R)	Yield[a,c]
1b	34/66	62	58	71
2b	9/91	86	89[d]	68
3b	29/71	59	68	79
4b	20/80	52	55[d]	62

[a] Determined by NMR.
[b] Determined by NMR with chiral shift reagent.
[c] Yield is the yield of the cyclopropanes (cis and trans) compared to the yield of all products (cyclopropane and side products formed).
[d] The (1R,2S) enantiomer is formed over the (1S,2R) enantiomer.

for systems 1a and 4a shows that the difference between the two systems is statistically different based on a 99.9% confidence level. If the catalyst is below the surface of the monolayer, then there is great reduction in the enantioselectivity of the system for the trans and cis isomers. Steric interactions between the alkane chains and the catalyst may cause the loss in enantioselectivity for the trans and cis isomers.

3.2.2. Bis[4,5-dihydro-(4S)-(methyl)-1,3-oxazole-2-yl]-amine copper(I) catalytic systems

To further probe the effect of surface steric interactions between the monolayer and the catalyst, a less sterically demanding R group at the C2 position a methyl group was utilized. The bis[4,5-dihydro-(4S)-(methyl)-1,3-oxazole-2-yl]-amine copper(I) catalyst was tested in the three different surface orientations (Scheme 1). To prepare the catalytic systems, the copper pre-catalyst was added to the systems 1b–4b in the reaction solvent dichloromethane. The results of the homogeneous and heterogeneous systems are summarized in Table 2.

When the catalytic system 2b (Scheme 1) was tested in the cyclopropanation reaction the cis/trans ratio increased from 34/66 (Table 2, 1b) in the homogeneous phase to 9/91 (Table 2, 2b). Therefore, when the catalyst was immobilized even with the monolayer surface (Scheme 1, 2b) the stereoselectivity greatly improved. The enantiomeric excess for system 2b for the trans isomer is 86% (Table 2, 2b). Comparison of systems 1b and 2b shows that the difference in the enantiomeric excess for the trans isomer is statistically different based on a 99.9% confidence level. Immobilization of the catalyst even with the monolayer surface (Scheme 1, 2b) greatly improves the enantioselectivity for the trans product.

In the case of system 2b the enantiomeric excess for the cis isomer is 89% (Table 2, 2b). Statistical treatment of the enantiomeric excess of the cis isomer for systems 1b and 2b shows that the difference in enantioselectivity is statistically different based on a 99.9% confidence level. Additionally, there is a reversal in the enantiomer produced so that enantiomer (1R,2S) (Scheme 2) is favored over enantiomer (1S,2R) (Scheme 2). The same selectivity reversal was seen in 2a. Therefore, presenting the catalyst at the interface is having a significant effect on the reaction mechanism.

When the catalyst is above the monolayer surface as in the case of 3b (Scheme 1) the cis/trans ratio is 29/71 which is comparable to the homogeneous phase. The enantiomeric excess for the trans isomer for system 3b is 59% (Table 2, 3b). Statistical treatment of the enantiomeric excess for the trans isomer for systems 1b and 3b shows that the difference in enantioselectivity is not statistically different. This proves that when the catalyst is above the monolayer surface the system (3b) behaves like a "solution mimic" in terms of enantioselectivity for the trans isomer.

When the catalyst is below the surface (Scheme 1, 4b) the cis/trans selectivity is 20/80, which is slightly better than 3b, but not as selective as 2b when the catalyst is level with the surface of the monolayer. The enantiomeric excess for trans isomer in system 4b is 52% (Table 2). Statistical treatment of the enantiomeric excess for the trans isomer for systems 1b and 4b shows that the difference in enantioselectivity is a statistically significant reduction. For the cis isomer the enantiomeric excess in system 4b is 55% (Table 2, 4b). Comparison of the enantioselectivity for the cis isomer in systems 1b and 4b shows that they are also statistically different. For system 4b, the cis isomer product formed is a reversal of the usual enantiomer. The enantiomeric excess for both the trans and cis isomers is greater for 3b (Table 2) than for 3a (Table 1) which shows that reduction in the steric bulk at the C2 position of the catalyst allows for greater enantioselectivity when immobilized below the monolayer surface.

3.3. Recycling experiments

One important facet of immobilized catalysts is the ability to easily recycle them. To show that these catalytic chips are recycla-

ble the chips were re-used in the cyclopropanation reaction. A method of converting the copper(II) to copper(I) by heating the reaction mixture to a temperature of roughly 65 °C and changing the reaction solvent from dichloromethane to styrene was utilized [27]. The reaction temperature should not go over 75 °C as polystyrene will be formed as a byproduct and will contaminate the catalytic chips. In all of the reaction the temperature of the reaction was kept at roughly 70–75 °C. This method of copper conversion was chosen over the addition of phenylhydrazine because the latter killed the reaction. In the first run of the reaction the 2a and 2b chips were activated with copper pre-catalyst and then added to the oil bath where ethyl diazoacetate was added to the system. The results for 2a and 2b are summarized in Tables 3 and 4.

Immobilization of the catalyst even with the monolayer surface greatly improved the enantioselectivity of the system compared to the homogenous system in the styrene method. After each use of the catalytic chips in the reaction the chips were rinsed with dichloromethane, dried, and used again in the next run of the cyclopropanation reaction. These catalytic chips can be used up to five times until deformation of the chips occurs. In the first run of the cyclopropanation reaction, the enantiomeric excess for the trans isomer was 92% (Table 3). In the second run of the cyclopropanation reaction, the enantiomeric excess (Table 3) slightly dropped from 92% to 83% and remained stable for the next four runs of the reaction.

The 2b catalytic chips showed the same trends as the 2a chips. The enantioselectivity is significantly better than the homogeneous phase and it drops to a steady level after the first run. After five runs, the gold was delaminating from the glass slide causing the chips to be unusable in further cyclopropanation reactions. Therefore, optimization of the recycling method such as changing the reaction solvent and/or the adhesive layer between the gold and the glass slides is currently underway.

Table 3
Cyclopropanation results of the recycled Bis[4,5-dihydro-(4S)-(1,1-dimethylethyl)-1,3-oxazole-2-yl]-amine copper (I) catalyst level with monolayer surface.

Catalytic system	Run	Cis/trans ratio[a]	Trans ee% (1S,2S)[b]	Yield[a,c]
w/o ligand	–	5/95	7	66
1a	–	5/95	58	65
2a	1	13/87	92	75
2a	2	5/95	83	74
2a	3	5/95	80	75
2a	4	5/95	83	74
2a	5	5/95	85	72

[a] Determined by NMR.
[b] Determined by NMR with chiral shift reagent.
[c] Yield is the yield of the cyclopropanes (cis and trans) compared to the yield of all products (cyclopropane and side products formed).

Table 4
Cyclopropanation results of the recycled bis[4,5-dihydro-(4S)-(methyl)-1,3-oxazole-2-yl]-amine copper(I) catalyst level with the monolayer surface.

Catalytic system	Run	Cis/trans ratio[a]	Trans ee% (1S,2S)[b]	Yield[a,c]
w/o ligand	–	5/95	7	66
1b	–	5/95	62	71
2b	1	17/83	88	73
2b	2	5/95	75	71
2b	3	6/94	79	73
2b	4	5/95	76	74
2b	5	6/94	72	68

[a] Determined by NMR.
[b] Determined by NMR with chiral shift reagent.
[c] Yield is the yield of the cyclopropanes (cis and trans) compared to the yield of all products (cyclopropane and side products formed).

3.4. MALDI analysis of catalytic chips

After the catalysis reaction, the chips were analyzed by atmospheric pressure matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (AP MALDI-TOF MS) to determine whether the SAMs with the aza-bis(oxazoline) copper(II) complexes were still attached to the gold surface. The MALDI spectrum for 2a is shown in Fig. 4. The peak at m/z 516.9364 is due to the aza-bis(oxazoline) copper complex attached to the thiol ($+ H^+$). The peak at m/z 630.0579 is due to the aza-bis(oxazoline) copper complex attached to the 11-mercaptoundecanol (with five sodium atoms). The five sodium atoms could be coordinated to the copper (II) and the ligand's oxygens, or nitrogens or the sulfur of the thiol chain. In Fig. 5, the MALDI spectrum of 2b is shown and the peak at m/z 483.1486 is due to the aza-bis(oxazoline) attached to the 11-mercaptoundeacanol and five sodium atoms. This shows that the ligand was indeed attached to the monolayer surface and was not removed. The MALDI spectra for 3a,b and 4a,b are similar and are in the supplementary material section. Therefore, it can be concluded that the catalysts were indeed immobilized on the SAMs after the catalysis reaction.

4. Discussion

Overall, immobilization of the aza-bis(oxazoline) copper catalyst in the three different orientations with respect to the monolayer surface allowed for the analysis of the effect of surface interactions on the selectivity of the catalytic system.

4.1. Catalyst above monolayer surface

In systems 3a and 3b, when the catalyst is above the monolayer surface, the selectivity of the systems is comparable to the homogeneous phase. This is most likely due to little steric interaction between the monolayer surface and catalytic site therefore, mimicking solution conditions.

4.2. Catalyst level with monolayer surface

The most effective systems in terms of selectivity are 2a and 2b, where the backbone of the catalyst is even with the monolayer surface (Fig. 1 A). The selectivity of system 2a (Scheme 1) is not as great as the 2b system, which could be due to the increased steric bulk of the tert-butyl groups located at the C2 position in 2a. By far the most promising system in terms of selectivity is 2b, where the methyl-substituted aza-bis(oxazoline) copper catalyst is level with respect to the monolayer surface.

In these systems, the trans isomer is favored and the favored enantiomer of the cis product is reversed from that of the other systems. This may be accounted for by a hydrogen-bonding interaction between the bulky ester group on the copper carbene and the hydroxyl groups present at the monolayer surface which may allow one face of the catalytic center to be partially occluded (Fig. 5). This occlusion affects the approach of the phenol group of styrene accounting for the trans product being the major isomer as seen in Fig. 5. In the case of the trans isomer the phenol group on styrene is pointed away from the monolayer surface. In the case of the cis isomer the phenol group of styrene is pointed toward the monolayer surface. Further, for the trans isomer approach B is favored over approach A because of the steric interaction between the ester group on the copper carbene and the R group at the C2 position of the ligand. Approach B forms the predominate trans isomer (1S,2S). For the cis isomer in Fig. 5 pathway B is favored over pathway A thus forming the predominate cis isomer (1R,2S). Finally, for systems 2a and 2b, system 2b has the greater increase in

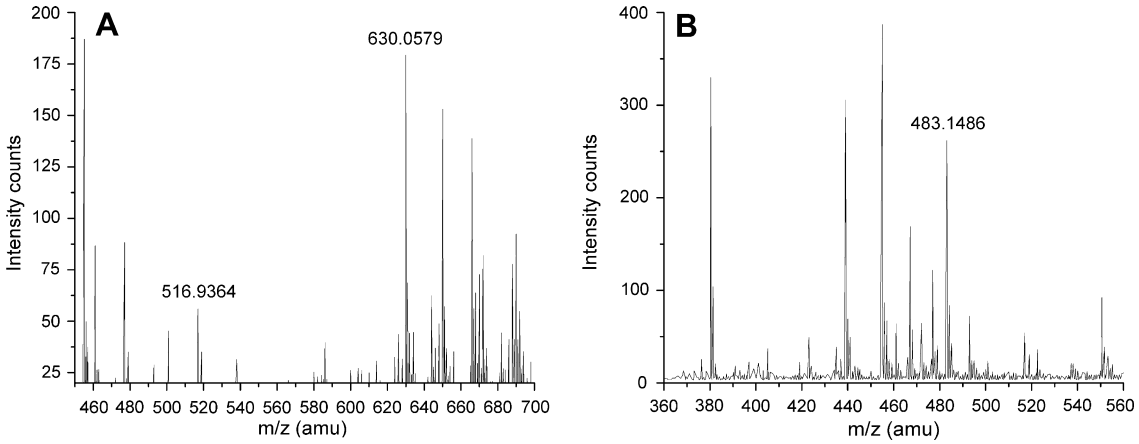


Fig. 4. (A) MALDI spectrum of 2a after use in the cyclopropanation reaction. The peak at m/z 516.9364 is due to the aza-bis(oxazoline) copper complex attached to the thiol and one proton. The peak at m/z 630.0579 is due to the aza-bis(oxazoline) copper complex and five sodium atoms. The other peaks are due to the matrix. (B) MALDI spectrum of 2b after use in the cyclopropanation reaction. The peak at m/z 483.1486 is the aza-bis(oxazoline) ligand attached to the thiol and five sodium atoms. The other peaks in the spectrum are due to the matrix.

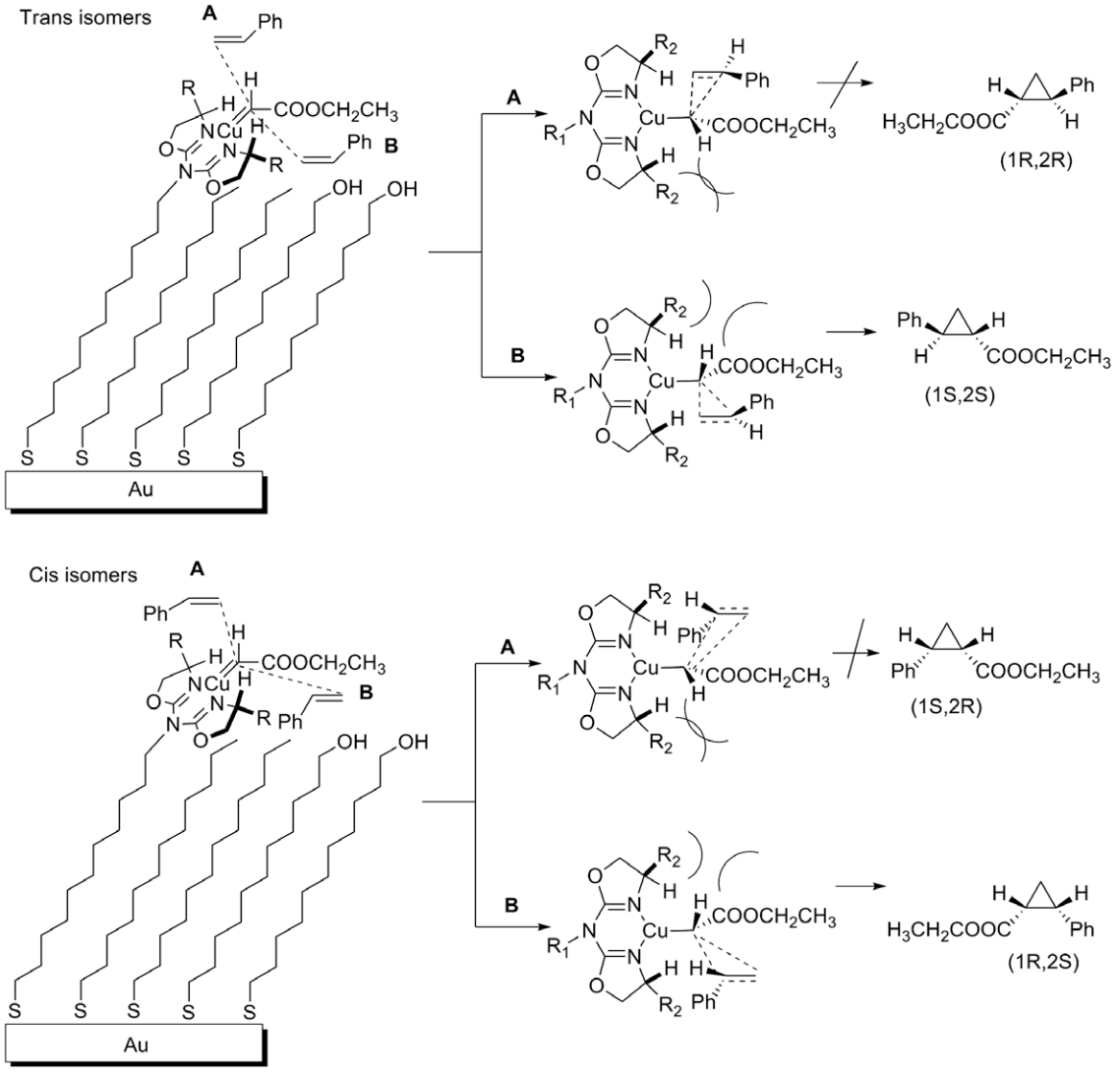


Fig. 5. Possible approach for catalytic systems level with monolayer surface.

selectivity of the two systems because 2b has less steric bulk present at the C2 position of the catalyst and therefore does not interact with the monolayer significantly. While hydrogen-bonding interactions between the ester group of the copper carbene and the hydroxyl groups present at the monolayer surface provide an explanation for the trans isomer selectivity and the reversal of

the enantioselectivity for the cis isomer, further surface characterizations by scanning tunneling microscopy and computations need to be done to probe this hypothesis.

4.3. Catalyst below monolayer surface

Systems 4a and 4b where the catalyst backbone is below the monolayer surface produced diminished selectivity. This is most likely due to steric hindrance and accessibility issues due to the surrounding alkyl chains at the catalytic site.

5. Conclusion

After evaluation of the three different surface orientations of the immobilized aza-bis(oxazoline) catalysts, the following trends can be extracted from the results. When the catalyst is above the monolayer surface the cyclopropanation results were similar to the homogeneous phase. Thus producing a recyclable solution catalyst mimic. When the catalyst is below the monolayer surface the cis/trans ratio is lower than the homogeneous phase and the enantiomeric excess for both the trans and cis isomers decreases. This decrease in selectivity could be due to the steric restriction imposed by the alkane chains causing both faces of the catalytic center to be equally disfavored. The best selectivity is when the catalyst is even with the monolayer surface. In this position, hydrogen bonding between the ester group of the copper carbene and the hydroxyl group present at the monolayer surface obscures one face of the catalyst thus favoring the trans isomer and causing the reversal in enantioselectivity for the cis isomer. The 2b catalytic system shows the greatest effect in terms of selectivity when level with the surface of the monolayer. The enhanced selectivity over 2a is due to less steric bulk at the C2 position of the catalyst. This decrease in steric bulk at the C2 position of the catalyst may allow for the ligand center to come in closer contact with the monolayer surface increasing selectivity. These catalytic systems can be re-used with little decrease in selectivity, but more work needs to be done in developing a more environmentally friendly method of re-use in terms of solvent. Future work on surface analysis on the distribution and position of the catalyst on catalytic chips by STM will be addressed.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jcat.2009.07.016.

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