Journal of Catalysis 275 (2010) 149–157

Contents lists available at ScienceDirect

Journal of Catalysis

journal homepage: www.elsevier.com/locate/jcat

Immobilized aza-bis(oxazoline) copper catalysts on alkanethiol self-assembled monolayers on gold: Selectivity dependence on surface electronic environments

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ARTICLE INFO

Article history:
Received 10 June 2010
Revised 27 July 2010
Accepted 28 July 2010

Keywords:
Asymmetric cyclopropanation
Aza-bis(oxazolines) copper
Immobilization
Nitrogen ligand
Chiral shift reagents
Self-assembled monolayers
Heterogeneous catalysis

ABSTRACT

Aza-bis(oxazoline) copper complexes have been immobilized onto alkanethiol self-assembled monolayers on gold utilizing five background tail groups with different electronic characteristics. The catalyst was tested in the standard cyclopropanation reaction of ethyl diazoacetate and styrene. The five different tail groups were hydroxyl, bromine, carboxylic acid, ester, and nitrile. Enantioselectivity improved to 95% when the surrounding tail groups were hydroxyl- and bromine-terminated surfaces. The carboxylic acid and ester tail groups reduced the enantioselectivity compared to the homogeneous phase. Additionally, the homogeneous cyclopropanation reaction was performed in methanol, acetonitrile, ethyl acetate, and acetic acid to determine whether similar trends in selectivity could be obtained by varying the homogenous electronic environment. However, the cyclopropanation reaction in these solvents gave greatly reduced selectivity and yield of the cyclopropane products demonstrating the positive aspects of immobilization of self-assembled monolayer supports.

1. Introduction

Cyclopropane derivatives are important chemical compounds with interesting biological properties [1] as well as utility in organic synthesis [2]. Consequently, extensive work has been devoted to the development of efficient diastereo- and enantio-selective methods for the synthesis of cyclopropanes [3–8]. One versatile method of cyclopropane synthesis is the transition metal-catalyzed cyclopropanation of olefins with diazo compounds. In the literature, many homogeneous transition metal catalytic systems have been developed, which show high selectivity in the transition metal-catalyzed cyclopropanation reactions with copper [5–7], rhodium [8], and cobalt [4,9]. Nitrogen ligands with C2 symmetry such as bis(oxazoline) [4–6,8] and aza-bis(oxazoline) [7] form superior catalysts for the cyclopropanation reaction. Traditional transition metal catalysts have been immobilized on solid supports, such as organic polymers [10–15], inorganic solids [10–15], and colloids [16]. Immobilization of transition metal catalysts allows for further modification of the ligand systems, which may produce selectivity enhancements and cost reduction through the ability to recycle the catalyst multiple times.

In a previous study conducted by our group, the aza-bis(oxazoline) copper complexes were immobilized onto self-assembled monolayers with three different surface orientations: even, above, and below monolayer surface [17]. In the previous study orientating the catalyst even with the monolayer surface obtained the greatest selectivity in the cyclopropanation reaction. This enhanced selectivity may be the result of hydrogen bonding between the copper carbene and the surface hydroxyl groups [17]. The enhanced selectivity obtained by immobilizing the catalyst even with the monolayer surface prompted our group to study the influence of changing the electronic properties of the tail group molecules in the monolayer surrounding the catalyst.

The generally accepted catalytic pathway for the copper catalyzed cyclopropanation reaction of ethyl diazoacetate and styrene is shown in Fig. 1 [18,19]. There are two proposed mechanisms that account for this reaction pathway, the concerted and stepwise [20]. There are opinions and data to support both mechanisms. However, this work will not focus on this ongoing discussion. However, one interesting interaction called the "secondary effect" will be touched upon in this paper. Initially proposed by Doyle [21], the nucleophilic oxygen of the polar carbene substituent can stabilize the developing electropositive center of the reacting alkene as shown in Fig. 2. This "secondary" effect is similar to the one that controls endo selectivity in the Diels–Alder reaction. In the literature, modification of the polar group of the metal carbene has allowed for effective diastereocontrol [20–25]. Modification of the polar group of the metal carbene requires synthesis of multiple diazo compounds.

Another way of controlling the electronic influences in the cyclopropanation reaction without modification of the polar substituent of the metal carbene may be the addition of solid supports with electron withdrawing and donating groups present near the

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doi:10.1016/j.jcat.2010.07.027

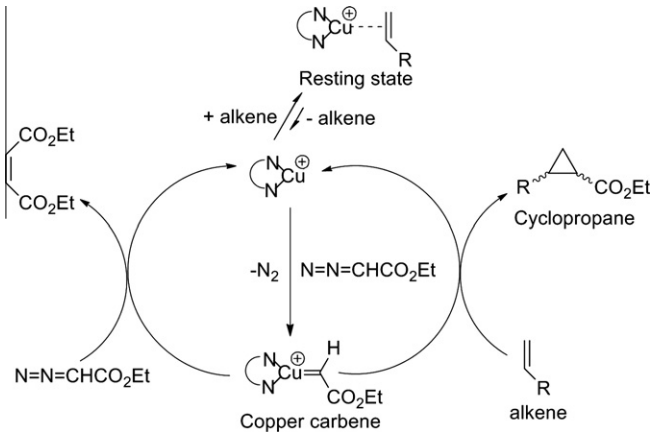


Fig. 1. The catalytic cycle for the copper catalyzed cyclopropanation reaction of ethyl diazoacetate and styrene.

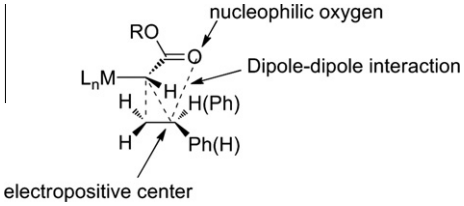


Fig. 2. The secondary effect of the oxygen of the polar copper carbene stabilizing the developing electropositive center of the reacting alkene. The orientation of the phenol or hydrogen depends on the steric influence of the catalyst.

catalytic site. These electron withdrawing and donating groups can interact with the catalytic site through hydrogen bonding and dipole–dipole intermolecular interactions. Based on the secondary effect, the presence of surface carbonyl groups will have a profound influence on the selectivity of the system. The surface carbonyl groups near the catalytic site will reduce selectivity of the system because they can stabilize the electropositive center of the reacting alkene, allowing the complex to adopt a new orientation. This new orientation allows for the production of cyclopropanes with opposite stereochemistry. By changing the orientation of the reacting alkene with respect to the catalytic center, the selectivity of the system will be affected. If addition of surface carbonyl groups has little influence on the selectivity of the catalytic system, then it can be concluded that the secondary effect has minimal influence on the selectivity of the system. In Fig. 3, the three main electronic environments are depicted: (A) hydroxyl surface, (B) halogen surface where surface bromine groups are present, and (C) carbonyl surfaces with carboxylic acid and ester substituents presented at the 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. Visualization of compounds on the silica gel plates was accomplished by UV light. ^{1}H NMR spectra were obtained at room temperature on a Bruker Avance 400 MHz spectrometer with chemical shifts given in ppm relative to the residual solvent peak ($CDCl_3$, 7.26 ppm).

Starting materials for ligand synthesis were as follows: (S)-tert-leucinol (98% Aldrich), benzaldehyde (Aldrich), and p-toluenesulfonic acid monohydrate (99% Acros) methanol certified ACS (Fisher).

Starting materials for alkanethiol synthesis were as follows: 10-undecenoic acid methyl ester (98% TCI), 11-bromo-1-undecene (96% Alfa Aesar), azo-bis-isobutyronitrile (98% Sigma–Aldrich), thiolacetic acid (96% Aldrich), hydrochloric acid (ACS Fisher Scientific), trityl chloride (98% Aldrich), acetonitrile (HPLC grade Fisher Scientific), acrylonitrite (99% Sigma–Aldrich) trifluroacetic acid (98% Sigma–Aldrich), and triethylsilane (99% Aldrich).

Starting materials for self-assembled monolayer formation were as follows: 11-mercapto-1-undecanol (97% Aldrich), 11-mercapto-undecanoic acid (95% Aldrich), and 9-mercapto-1-nonanol (96% Aldrich).

Starting materials for gold substrate preparation were as follows: aluminum wire (99.999% Kurt J. Lesker), chromium pieces (99.998% 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 (98% 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 literature procedure [7].

2.3. Preparation of heterogeneous catalyst

2.3.1. Gold substrate preparation

Glass microscope slides were cleaned with ethanol and dried under a stream of nitrogen for 10 min. 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.

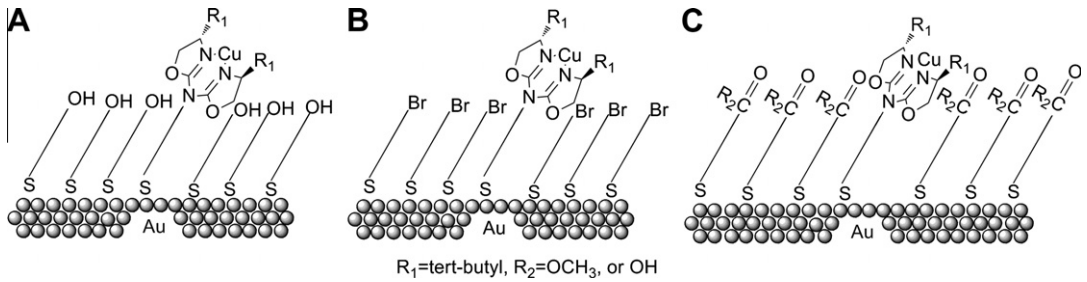


Fig. 3. Electronic environments: (A) hydroxyl surface, (B) halogen surface, and (C) carbonyl surface.

2.3.2. Thiol synthesis

2.3.2.1. Bromine tail group thiol

2.3.2.1.1. Bromine tail group thiol ester (11-bromoundecyl-ethanethioate). To a three-neck round-bottom flask wrapped with Al foil, 25 ml methanol, azo-bis isobutyronitrile (0.152 mmol, 25 mg), thiolacetic acid (8.60 mmol, 0.655 ml), and 11-bromo-1-undecene (3.92 mmol, 0.915 ml) were added. The reaction mixture was stirred under UV light for 12 h.

2.3.2.1.2. Bromine tail group thiol (11-bromoundecane-1-thiol). 11-Bromoundecyl-ethanethioate (2.92 mmol, 0.9 g) was added to a round-bottom flask with 20 ml methanol, and then 2 ml of hydrochloric acid was added. The reaction mixture was refluxed overnight. ^{1}H NMR (400 MHz, $CDCl_3$ RT) δ 3.38 ppm (t, 2H, J = 7 Hz), 2.49 ppm (q, 2H, J = 7 Hz), 1.83 ppm, (q, 2H J = 7 Hz), 1.58 ppm (q, 2H, J = 7 Hz).

2.3.2.2. Ester tail group thiol

2.3.2.2.1. Ester tail group thiol ester (methyl 10-(acetylthio)-undecanoate). To a three-neck round-bottom flask wrapped with Al foil, 25 ml methanol, azo-bis isobutyronitrile (0.152 mmol, 25 mg), thiolacetic acid (8.60 mmol, 0.655 ml), and 10-undecenoic acid (4.61 mmol, 0.915 ml) were added. The reaction mixture was stirred under UV light for 12 h.

2.3.2.2.2. Ester tail group thiol (methyl 10-mercaptodecanoate). Methyl 10-(acetylthio)-undecanoate (3.45 mmol, 0.9 g) was added to a round-bottom flask with 20 ml methanol, followed by 2 ml of hydrochloric acid. The reaction mixture was refluxed overnight. (Yield 72%) ^{1}H NMR (400 MHz, $CDCl_3$ RT) δ 3.67 ppm (s, 3H), 2.52 ppm (q, 2H, J = 8, 7 Hz), 2.31 ppm (t, 2H, J = 7 Hz), 1.73 ppm (s, 1H), 1.62 ppm (m, 2H), 1.50 ppm (m, 2H) 1.32 ppm (m, 6H).

2.3.2.3. Nitrile tail group thiol

2.3.2.3.1. Addition of protecting group. 11-Mercapto-1-undecanol (8.978 mmol, 1.833 g), trityl chloride (6.27 mmol, 1.75 g), and 40 ml THF were added to a three-neck round-bottom flask. The reaction mixture was stirred under nitrogen for 14 h. Purification of crude product was performed by filtration of crude product with 2/1 ethyl acetate/hexane. The protected thiol was then used in the next step of the synthesis.

2.3.2.3.2. Addition of nitrile group to protected thiol. To a round-bottom flask wrapped with Al foil, 10 mg NaOH, protected thiol (0.828 mmol, 360 mg), and 15 ml acetonitrile were added and placed under nitrogen. After drop-wise addition of acrylonitrite (1.51 mmol, 80 ul), the reaction mixture was stirred overnight under nitrogen. The reaction mixture was quenched with distilled water and then extracted with CH_2Cl_2, dried with $MgSO_4$ and then evaporation of CH_2Cl_2. The nitrile tail group protected thiol was then used in the next step of the synthesis.

2.3.2.3.3. Nitrile tail group thiol (3-((11-mercaptoundecyl)oxy)propane-nitrile). Nitrile tail group protected thiol (0.260 mmol, 127 mg), trifluroacetic acid (13.15 mmol, 1.5 ml), (1.37 mmol, 0.160 ml) triethylsilane, and 20 ml CH_2Cl_2 were added to a round-bottom flask. The reaction mixture was then stirred under nitrogen overnight. Evaporation of CH_2Cl_2 and then column chromatography 50/50 hexane/CH_2Cl_2 to 100 CH_2Cl_2 produced a colorless precipitate. (Yield 54%) ^{1}H NMR (400 MHz, $CDCl_3$ RT) δ 3.65 ppm (t, 2H, J = 7, 6 Hz), 3.48 ppm (t, 2H, J = 9, 7 Hz), 2.60 ppm (t, 2H, J = 7 Hz), 2.53 ppm (q, 2H, J = 7 Hz) 1.65 ppm (m, 4H), 1.55 ppm (s, 1H), 1.28 ppm (m, 10H).

2.3.3. SAM preparation

Gold substrates were immersed in 2 mM ethanolic solution of alkanethiols (10:90) (hydroxyl:background tail group) and incubated overnight at room temperature (23–25 °C). Upon removal from solution, the samples were carefully rinsed with CH_2Cl_2 and dried under a stream of nitrogen (Scheme 1). The mixed monolayer chips were analyzed and then utilized in the immobilization of the aza-bis(oxazoline) ligand.

2.3.4. Mitsunobu reaction (ligand immobilization)

The ligand was immobilized to the SAM surface via a surface Mitsunobu reaction as in the literature [17]. Mixed monolayer chips were placed in a three-neck round-bottom flask. Aza-bis(oxazoline) ligand (1a) 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 [17] for 2 h. 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. Diffuse reflectance infrared Fourier transform (DRIFT)

The chips were studied using diffuse reflectance infrared Fourier transform spectroscopy (DRIFT) (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. We collected 1024 scans for each sample with a 4 cm^{-1} resolution.

2.4.2. AP MALDI-TOF MS

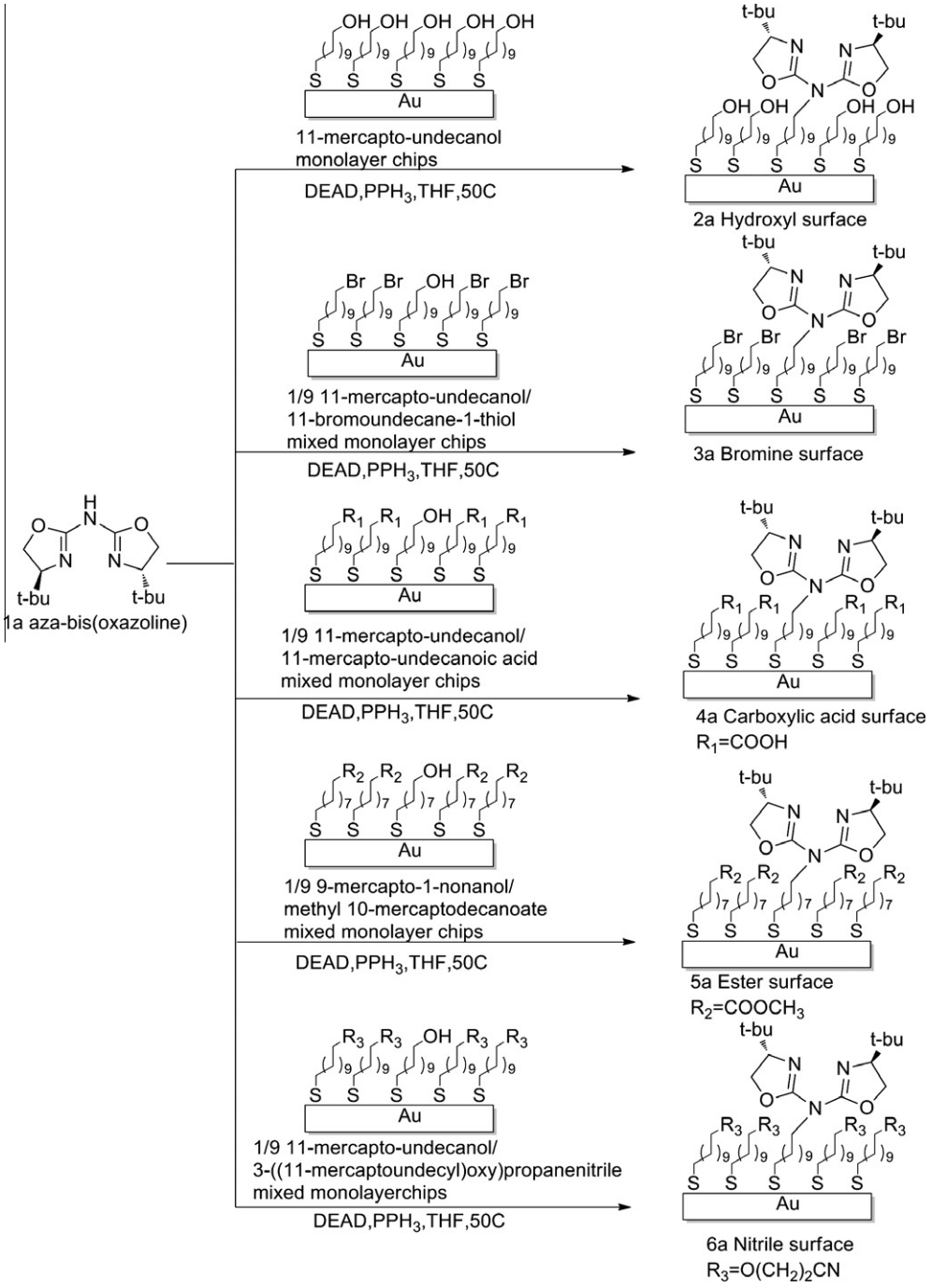
Atmospheric pressure matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (AP MALDI-TOF MS) was used to analyze the monolayer and to determine whether the aza-bis(oxazoline) ligands were attached to the monolayer surface before and after use in the cyclopropanation reaction. A high-resolution AP MALDI-TOF MS (Agilent Tech.) with pulsed dynamic focusing was used. MS analysis of the ions were 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 across 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.

2.5. Cyclopropanation procedures

2.5.1. Homogeneous asymmetric cyclopropanation of styrene and ethyl diazoacetate

The cyclopropanation reaction was performed according to the literature [7] with the following changes.

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



Scheme 1. Immobilization of aza-bis(oxazoline) on different surfaces.

tion and separation of the trans and cis isomers was accomplished by preparation thin-layer chromatography).

2.5.2. Heterogeneous asymmetric cyclopropanation of styrene and ethyl diazoacetate

The heterogeneous cyclopropanation reaction was performed according to the literature [17].

The systems 2–4 (a and b) (Scheme 1) were added to a three-neck round-bottom flask and CH_2Cl_2 was added under nitrogen. The copper pre-catalyst (1 mg) was added to the reaction flask. This was hand-stirred for 10 min and phenylhydrazine (20 ul of a 5% solution) was added. Styrene (312 mg, 3 mmol, 345 ul) and then EDA (1 mmol, 1 ml of an 8% solution in CH_2Cl_2 diluted with 7 ml of CH_2Cl_2) were 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.

2.6. Purification and analysis of cyclopropanation products

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 a colorless oil product. 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.

2.6.1. Purification and enantiomeric excess determination

The cis and trans isomers were separated from each other by p-TLC 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 oil for both isomers. The cis and trans isomers were analyzed by ^{1}H NMR to show separation of the two isomers. Addition of the chiral shift reagent europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] to the NMR samples was used to determine the enantiomeric excess [26–29].

3. Results

3.1. Immobilization

Five different monolayer systems (Scheme 1) were prepared by formation of mixed monolayers on gold in a 1:9 ratio of alkanethiols of 11-mercapto-undecanol to one of the following alkanethiols: 11-mercapto-undeacanol, 11-bromoundecane-1-thiol, 11-mercapto-undecanoic acid, 10-mercaptodecanoate, 3-((11-mercapto-undecyl) propanenitrile) thus generating the five different environments (Scheme 1). (9-Mercapto-1-nonanol was used in the place of 11-mercapto-undecanol for the ester system to enhance the packing with the shorter chain ester thiol.) The aza-bis(oxazoline) ligand was then immobilized on the hydroxyl-terminated alkanethiols using a Mitsunobu reaction (Scheme 1). These background tail groups can interact with the catalyst resulting in differences in the stereo- and enantio-selectivity of the cyclopropanation products.

The catalytic chips were prepared and characterized by MALDI and IR. Analysis of the chips before and after use in the cyclopropanation reaction was accomplished by MALDI and IR. Fig. 4 shows the MALDI spectrum of system 2a after use in the cyclopropanation reaction. The peaks at 630.0579 and 516.9364 indicate the presence of the catalyst attached to the thiol chain. 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 *m*/*z* 630.0579 is due to the aza-bis(oxazoline) copper complex and five sodium atoms.

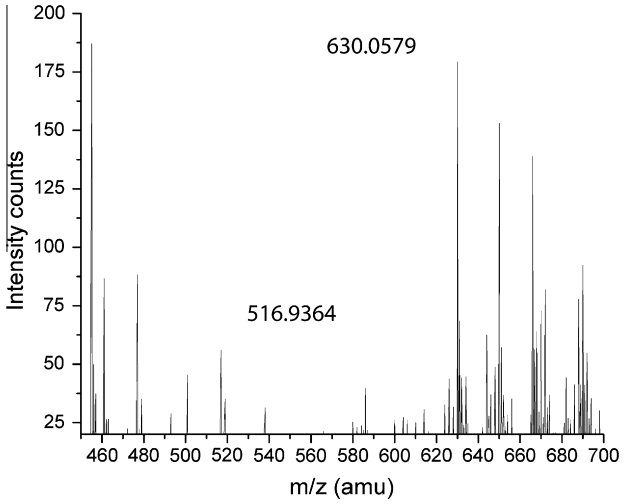


Fig. 4. MALDI spectrum 2a after use in the cyclopropanation reaction. The peak at *m*/*z* 516.9364 is due to the aza-bis(oxazoline) copper complex attached to the thiol and one proton. The peak *m*/*z* 630.0579 is due to the aza-bis(oxazoline) copper complex and five sodium atoms. The other peaks are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

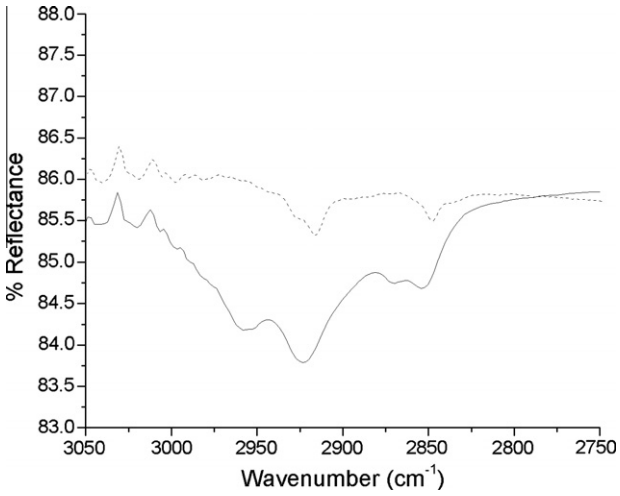


Fig. 5. IR spectrum before (dashed) and after (solid) immobilization of the aza-bis(oxazoline) ligand. The range of the IR spectrum is 3050–2750 cm^{-1}.

In the IR spectra after attachment of the ligand (Fig. 5 solid line), the stretch (2955 cm^{-1}) due to CH 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 t-butyl groups. The width of the peak is due to overlapping CH stretches from CH groups in the ligand and monolayer (Fig. 5).

3.2. Heterogeneous electronic environment

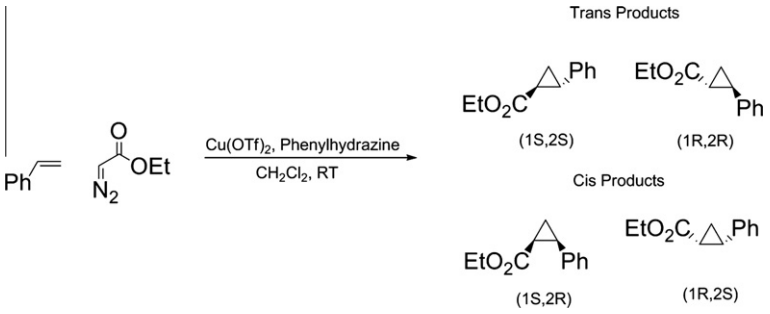
The catalytic chips were then tested in the cyclopropanation reaction of ethyl diazoacetate and styrene (Scheme 2). In the cyclopropanation reaction, phenylhydrazine was used to reduce the copper (II) to the copper (I) state, which is the active catalyst for the reaction. Four potential cyclopropane products were obtained in this reaction (Scheme 2).

The results of the cyclopropanation reaction are tabulated in Table 1. The stereoselectivity was determined by ^{1}H NMR, and enantioselectivity was determined by ^{1}H NMR with the aid of the chiral shift reagent europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate].

In the homogeneous phase (Scheme 1, 1a), the trans isomer enantiomeric excess is 87% (Table 1) and cis isomer enantiomeric excess is 80% for the standard cyclopropanation reaction (Scheme 2). The homogeneous phase gives good enantioselectivity for the cyclopropanation reaction of styrene and ethyl diazoacetate, while the introduction of background tail groups impacts the enantioselectivity depending on the choice of background tail group.

The presence of background surface hydroxyl groups (Scheme 1, 2a) has a positive impact on the enantioselectivity of the system compared to the homogeneous phase (Table 1, 1a). The enantiomeric excess for the trans isomer is 95% (Table 1). It should be noted that 95% is the detection limit of our method so these systems may have higher enantioselectivity. Additionally, for the hydroxyl surface (Scheme 1, 2a), a reversal in the favored enantiomer is seen for the cis isomer (Table 1, 2a). For the cis isomer in the hydroxyl electronic environment system, the (1R,2S) enantiomer is formed in excess over the (1S,2R) enantiomer which is seen in the homogeneous phase. This reversal was observed in some of our previous immobilized systems [17].

The enantioselectivity (95% Table 1, 3a) of the bromine-terminated surface (Scheme 1, 3a) is enhanced for the trans isomer compared to the homogeneous phase (Table 1, 1a). This enantioselectivity is comparable to the hydroxyl electronic environment (Table 1, 2a). The presence of the surface bromines also



Scheme 2. Cyclopropanation reaction of ethyl diazoacetate and styrene.

Table 1
Cyclopropanation results of the homogeneous and heterogeneous bis[4,5-dihydro-(4S)-(1,1-dimethyl)-1,3-oxazole-2-yl]-amine copper(I) catalyst in the reaction of styrene and ethyl diazoacetate in dichloromethane.[a]

Catalytic system	Cis/trans ratio[b]	Cis ee% (1S,2R)[c]	Trans ee% (1S,2S)[c]	Yield[b,d]
1a	20/80 (±1.5)[e]	80 (±1.1)	87 (±1.1)	71
2a	14/86 (±1.4)	80[f] (±1.0)	95 (±0.5)	70
3a	20/80 (±1.4)	62[f] (±0.8)	95 (±0.6)	73
4a	19/81 (±1.4)	6 (±0.9)	50 (±0.8)	67
5a	14/86 (±1.3)	51 (±0.8)	49 (±0.7)	64
6a	16/84 (±1.6)	80 (±1.0)	78 (±0.8)	75

[a] Statistical treatment performed by Student's *t*-test with a 99.9% confidence level. Ten degrees of freedom and critical value of *t* equals 4.59. Two systems are statistically different when test statistic *t* is greater then the critical value of *t*.
[b] Determined by ^{1}H NMR.
[c] Determined by ^{1}H NMR with the aid of chiral shift reagent.
[d] Isolated yield.
[e] Sample standard deviation.
[f] The (1R,2S) enantiomer is formed in excess of the (1S,2R).

causes a reversal in the favored enantiomer for the cis isomer. The same effect as observed in the hydroxyl system. However, the enantioselectivity is slightly reduced compared to the hydroxyl environment.

The presence of interfacial carbonyl groups (Scheme 1, 4a and 5a) causes the enantioselectivity of the system to decrease significantly compared to the homogeneous phase (Table 1, 1a). This is seen in both the carboxylic acid and ester cases. The enantiomeric excess for the trans isomer is 50% (Table 1, 4a) for the carboxylic acid surface (Scheme 1, 4a) and a comparable enantiomeric excess for the trans isomer (49% Table 1, 5a) is obtained for the ester surface (Scheme 1, 5a). This is a dramatic decrease in the enantiomeric excess when compared to the homogeneous phase (87% Table 1, 1a).

The stereoselectivity of the catalytic system with background nitrile groups (Table 1, 6a) is slightly enhanced compared to the homogeneous phase (Table 1, 1a). The presence of surface background nitrile groups gave enantioselectivity comparable to the homogeneous phase for the cis isomer. However, the addition of background nitrile groups had a negative impact the enantioselectivity for the trans isomer compared to the homogeneous phase.

3.3. Homogeneous electronic environment

To determine whether mimicking the effects of the electronic systems was possible in the homogeneous system, various solvents were utilized. The homogeneous cyclopropanation reaction (Scheme 2) was performed in the solvents presented in Table 2.

When the cyclopropanation reaction (Scheme 2) was performed in methanol or acetonitrile the selectivity of the system decreased (Table 2) compared to dichloromethane, which is the standard solvent for the reaction. However, when the cyclopropanation reaction was performed in ethyl acetate and acetic acid only trace amounts of the cyclopropane products were obtained (Table 2) and this was not enough for proper cis/trans ratio determination. Thus, changing solvents effectively showed that the stereo- and enantio-selectivity found in the heterogeneous systems is unique.

4. Discussion

Overall modification of the surface environment around the aza-bis(oxazoline) copper catalyst influenced the selectivity of

Table 2
Cyclopropanation results of the homogeneous bis[4,5-dihydro-(4S)-(1,1-dimethyl)-1,3-oxazole-2-yl]-amine copper (I) catalyst in the reaction of styrene and ethyl diazoacetate in various solvents.

Solvent	Cis/trans ratio[a]	Cis ee% (1S,2R)[b]	Trans ee% (1S,2S)[b]	Yield[a,c]
Dichloromethane	20/80	80	87	71
Methanol	40/60	48	53[d]	45
Acetonitrile	37/63	71	64	68
Ethyl acetate	–[e]	–	–	Trace amount
Acetic acid	–	–	–	Trace amount

[a] Determined by ^{1}H NMR.
[b] Determined by ^{1}H NMR with the aid of chiral shift reagent.
[c] Isolated yield.
[d] The (1R,2S) enantiomer is formed in excess over the (1S,2R) enantiomer.
[e] Not determined due to trace amount of product formation.

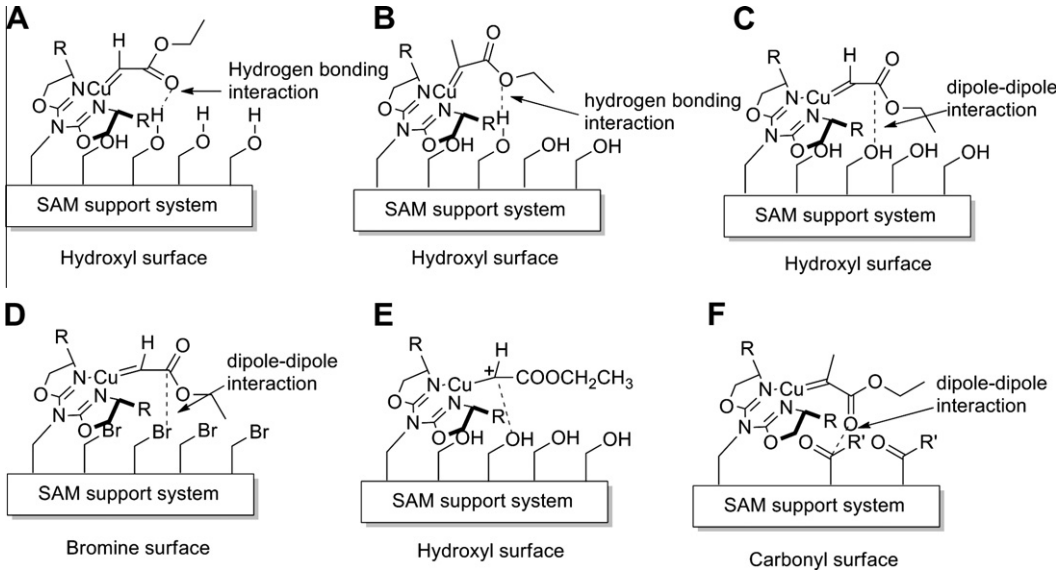


Fig. 6. (A)–(C), and (E) are the potential intermolecular interactions between the catalytic site and the hydroxyl surface. (D) is the potential interaction between the catalytic site and the bromine surface. (F) is the potential interaction between the catalytic site and the carbonyl surfaces.

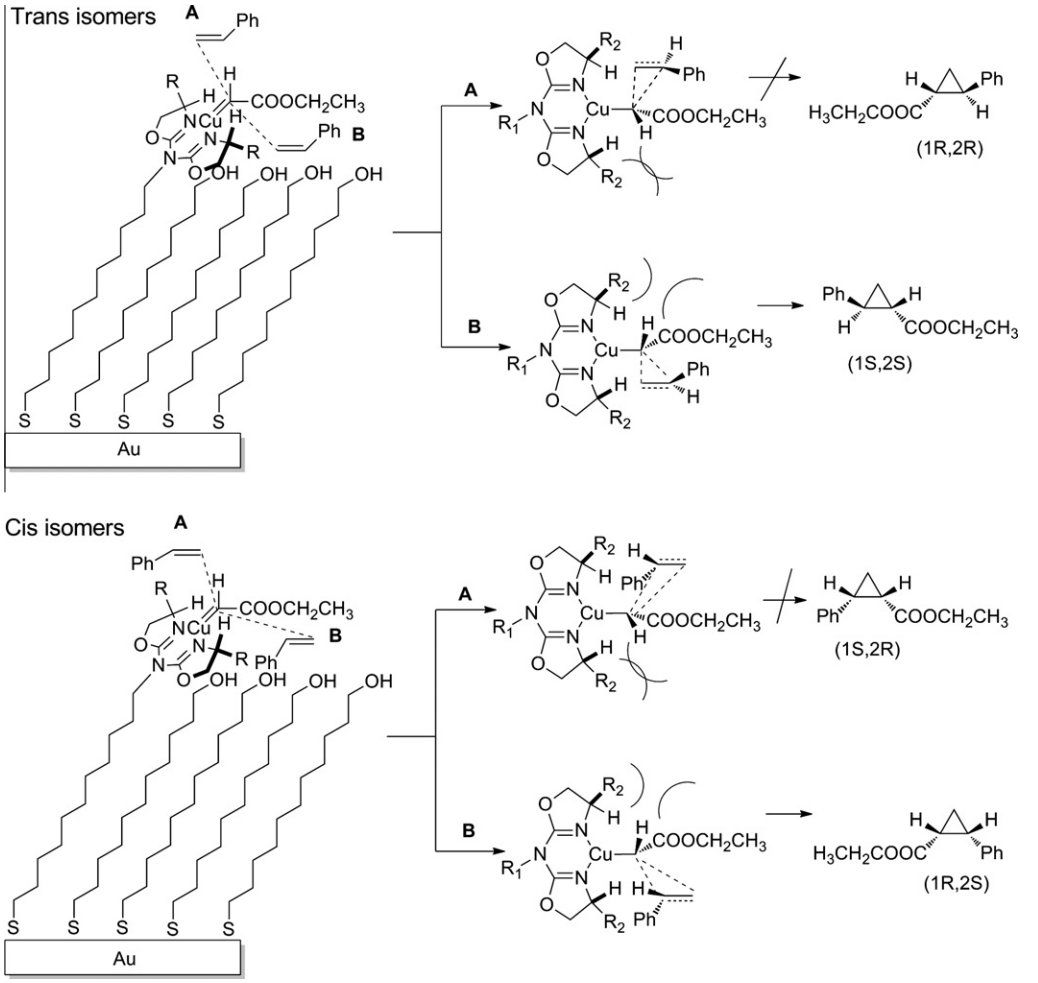


Fig. 7. Proposed reaction pathways.

the systems in the cyclopropanation reaction of styrene and ethyl diazoacetate. The selectivity obtained in the heterogeneous phase (Table 1) could not be obtained in the homogenous phases (Table 2) where the solvents contained the same functional groups; hydroxyl, nitrile, carboxylic acid, and ester. This demonstrates that these functional groups are only effective in the heterogeneous

phase to give their respective enhancements or reductions in enantioselectivity.

The control of enantioselectivity by modification of the electronic environment around the catalytic site is believed to be caused by intermolecular interactions between the background surface molecules and the copper carbene. Fig. 6 demonstrates the potential intermolecular interactions that may occur with each respective surface. In the hydroxyl and bromine surfaces, the electric forces cause the catalytic site to orient closer to the monolayer surface therefore enhancing surface steric influence on the catalytic site and selectivity. The alignment of the catalytic site and the background surface molecules according to attraction of their partially positive and partially negative regions enhances the surface steric influence thus combining both an electronic (dipole–dipole or hydrogen bonding) effect along with steric effect. The enantiocontrol for both the hydroxyl and bromine systems are comparable for the trans isomer. These electric forces would favor the formation of trans isomer B as seen in Fig. 7.

A hydrogen bonding interaction between the copper carbene and the hydroxyl tail groups accounts for the reversal in the favored enantiomer for the cis isomer (Fig. 7). In Fig. 7, it can be seen that because of this hydrogen bonding interaction with the surface hydroxyl groups the (1R,2S) is favored over the (1S,2R) enantiomer for the cis isomers. This environment allows for hydrogen bonding between the surface hydroxyl groups and the ester of the copper carbene stabilizing the same interaction seen in our past catalytic study [17]. Increasing the concentration of the background surface hydroxyl groups has a positive impact on the enantioselectivity for the trans isomer. Due to the strong intermolecular interaction of hydrogen bonding, this orientation is favored over that of the ester of the copper carbene positioned away from the monolayer surface.

In the bromine system, an enhancement in enantioselectivity was also observed. This may be due to dipole–dipole interactions between the copper carbene and the electronegative bromine tail groups. This dipole–dipole interaction causes the catalyst to orient closer to the monolayer surface.

In the homogeneous phase, the secondary effect stabilizes the electropositive center of the reacting alkene leading to the formation of the experimentally favored enantiomers (Fig. 8). The presence of surface carbonyl groups allows for *surface* stabilization of the electropositive center of the reacting alkene thus generating the opposite enantiomers of the trans and cis isomers (Fig. 9). The ability to stabilize the electropositive center of the reacting alkene has a negative effect on the enantioselectivity of the system because this allows for the production of both enantiomers of the trans and cis isomer.

If both points of stabilization (Figs. 8 and 9) are available, then a mixture of the two enantiomers will be formed thus reducing the enantiocontrol of the catalytic system. For the substrates where surface carbonyl groups are present, the enantioselectivity of the system decreases (Table 1). These results support the influence of the secondary effect in the selectivity of our heterogeneous catalytic systems.

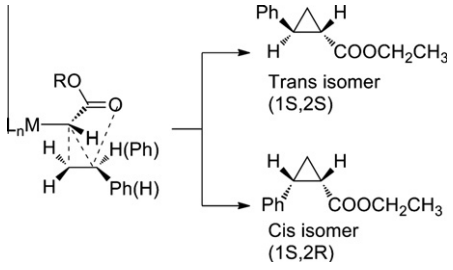


Fig. 8. Homogeneous phase secondary effect.

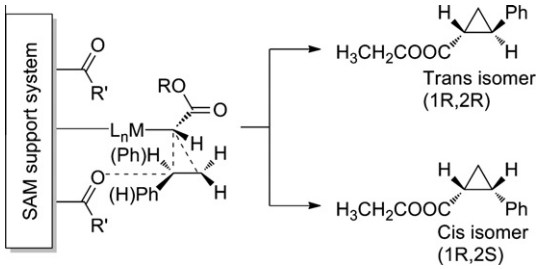


Fig. 9. Heterogeneous phase secondary effect where surface carbonyl groups are present.

5. Conclusion

In an immobilized catalytic system, modification of the electronic character of the molecules around the catalyst influences the selectivity of the catalyst in the cyclopropanation reaction of ethyl diazoacetate and styrene. The presence of surface hydroxyl and bromine groups enhances the enantioselectivity of the trans isomer. Also presence of these surface groups causes the reversal of the favored enantiomer for the cis isomer. Carbonyl groups reduce the enantioselectivity. To demonstrate the fact that these functional groups can only be present in the heterogeneous phases to give their respective enhancements or reductions in selectivity, homogenous systems were evaluated. The solvent of the reaction was changed to mimic the heterogeneous systems. Comparison of the homogeneous and heterogeneous electronic phases did not show a similar trend in the selectivity. The homogeneous systems showed greatly reduced selectivity and yield of cyclopropane products for all solvents. Our group has developed a simple method of influencing enantioselectivity of the aza-bis(oxazoline) copper catalyst by modification of the electronic environment around the catalyst.

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