

Highly diastereoselective and sustainable synthesis of cyclopropanes via amino acid-Schiff base copper(II) catalysis

Síntesis altamente diastereoselectiva y sostenible de ciclopropanos mediante catálisis con complejos de cobre(II) derivados de bases de Schiff de aminoácidos

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ABSTRACT:

Chiral copper(II) complexes were synthesized using Schiff bases derived from 2'-hydroxyacetophenone and natural L-amino acids (glycine, serine, alanine, and phenylalanine) via a one-pot method. The complexes were characterized by FT-IR, UV-Vis, EPR, TGA, and elemental analysis, confirming square-planar geometry and coordination through imine nitrogen, hydroxyl, and carboxylate groups. Catalytic performance was evaluated in the cyclopropanation of styrene with ethyl diazoacetate (EDA), a reaction of high value in the synthesis of bioactive and pharmaceutical compounds. All complexes showed excellent yields and high diastereoselectivity (up to 99:1 *trans:cis*). Moderate enantioselectivity was observed, with the L-alanine complex reaching up to 46 % ee for the *cis*-isomer. These results demonstrate the potential of bio-derived Cu(II) catalysts as efficient and selective systems for asymmetric carbene-transfer reactions. The use of naturally sourced ligands aligns with green chemistry principles and offers a sustainable alternative for stereoselective synthesis in drug development.

Keywords: copper(II) complexes; cyclopropanation; diastereoselectivity

RESUMEN

Se sintetizaron complejos quirales de cobre(II) mediante bases de Schiff derivadas de 2'-hidroxiacetofenona y aminoácidos L-naturales (glicina, serina, alanina y fenilalanina) utilizando un método en un solo recipiente. Los complejos fueron caracterizados por FT-IR, UV-Vis, EPR, TGA y análisis elemental, confirmando una geometría plano-cuadrada y la coordinación a través de los grupos imina, hidroxilo y carboxilato. La actividad catalítica se evaluó en la ciclopropanación de estireno con diazoacetato de etilo (EDA), una reacción de gran interés en la síntesis de compuestos bioactivos y farmacéuticos. Todos los complejos mostraron excelentes rendimientos y alta diastereoselectividad (hasta 99:1 *trans:cis*). Se observó enantioselectividad moderada,

destacando el complejo derivado de L-alanina con hasta 46 % de ee para el isómero *cis*. Estos resultados demuestran el potencial de los catalizadores bioinspirados de Cu(II) como sistemas eficientes y selectivos en reacciones asimétricas de transferencia de carbenos. El uso de ligandos derivados de aminoácidos naturales se alinea con los principios de la química verde, ofreciendo una alternativa sostenible para la síntesis estereoselectiva en el desarrollo de fármacos.

Palabras clave: complejos de cobre(II); ciclopropanación; diastereoselectividad

INTRODUCTION

At the forefront of modern chemistry, sustainable asymmetric catalysis has established itself as a fundamental pillar for the development of cleaner, more efficient, and environmentally friendly chemical processes. The implementation of highly selective catalysts is crucial for minimizing energy consumption and the generation of undesired byproducts, directly aligning with the principles of green chemistry by promoting atom economy and waste reduction. Consequently, the development of innovative, sustainable, and stereoselective catalytic solutions has acquired paramount importance in contemporary organic synthesis.

Within this context, the stereoselective cyclopropanation of alkenes emerges as a key reaction for the construction of three-membered rings with well-defined chirality. The controlled synthesis of functionalized cyclopropanes is of particular interest, as these molecular motifs, intrinsically conformationally restricted and stereochemically rich, are essential building blocks in drug discovery, natural product synthesis, and other bioactive compounds. Their presence in numerous pharmaceutical molecules, such as Tranilcypromine or Cyclazocine, confers unique properties in terms of structural rigidity, enhanced biological activity, and metabolic stability, facilitating specific interactions with biological targets. Furthermore, the inherent strain of the cyclopropane ring makes them versatile intermediates for the construction

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of complex molecular architectures through selective ring-opening reactions (Ebner and Carreira, 2017; Pellissier, 2008; Wu *et al.*, 2018).

Therefore, the catalytic cyclopropanation of olefins with diazoesters has become a highly valuable transformation in asymmetric synthesis. While noble metals such as rhodium, palladium, or ruthenium have traditionally been employed in this area, copper (Cu) emerges as a green catalytic center with significant advantages. Its abundance in the Earth's crust, low cost, and relative non-toxicity make it an environmentally friendly alternative to scarcer or more hazardous precious metals. Thanks to its ability to act via redox pathways, copper can mediate a wide range of chemical transformations, including cyclopropanation through copper carbene intermediates. This unique combination of accessibility, versatility, and low environmental impact distinguishes Cu(II) as an ideal metallic center for designing new asymmetric catalysts under the precepts of sustainable chemistry (Bartoli *et al.*, 2014; Ebner and Carreira, 2017; Guevara-Pulido *et al.*, 2017; Mookerjee *et al.*, 2006c).

The other crucial component in the design of these catalysts is the chiral ligand, whose structure determines enantioselective induction. In particular, Schiff bases derived from natural amino acids are highly promising ligands (Chakraborty *et al.*, 2012; Mookerjee *et al.*, 2006a; Schiff, 1869; Tidwell, 2008). Their relatively straightforward synthesis, high coordination capacity with various metals, and inherent presence of chiral centers have positioned them as privileged ligands in coordination chemistry (Iacopetta *et al.*, 2023; Mezgebe and Mulugeta, 2024; Sinn and Harris, 1969). The use of natural α -amino acids in combination with aromatic carbonyls like salicylaldehyde has allowed for obtaining a broad family of chirally defined chelating ligands (Chatterjee *et al.*, 2013; Han *et al.*, 2008; Usman *et al.*, 2003; Zhao *et al.*, 2009). These amino acid-salicylidene ligands are easily tunable in their structure: by changing the amino acid or modifying substituents on the aromatic ring, it is possible to finely modulate the steric and electronic environment of the metallic center. Additionally, being derived from natural biomolecules, these chiral Schiff bases offer the advantage of being potentially biodegradable and biocompatible (Abu-Dief and Mohamed, 2015; Boulechfar *et al.*, 2023; da Silva *et al.*, 2011; Mushtaq *et al.*, 2024; Nidhi *et al.*, 2025; Soroceanu and Bargan, 2022).

Copper(II) complexes with Schiff bases derived from amino acids and salicylaldehydes have been extensively studied for their structural diversity and biological properties (Majumder *et al.*, 2003; Mookerjee *et al.*, 2006b). For instance, the Gly-Cu complex has been characterized on multiple occasions (Pramanik *et al.*, 2014), and analogous systems based on Ser, Ala, and Phe have also been reported (Zhao *et al.*, 2009). However, despite this substantial body of literature, their potential as catalysts in asymmetric cyclopropanation reactions has not been exhaustively explored, particularly with a focus on diastereoselective control. Previous studies have primarily centered on medicinal or structural properties, leaving a gap in assessing their efficiency and selectivity

in key organic transformations.

This work addresses this gap by providing a systematic catalytic evaluation of this family of complexes in the cyclopropanation of styrene. We demonstrate that, while enantioselectivity is moderate, these readily accessible and sustainable Cu(II) catalysts achieve exceptionally high diastereoselectivities (up to 99:1 *trans:cis*), rivaling more complex and costly catalytic systems. This positions these amino acid-based complexes as highly efficient and selective alternatives for the synthesis of functionalized cyclopropanes where diastereocontrol is paramount.

MATERIAL AND METHODS

Materials

All the chemicals used were purchased from Sigma Aldrich and used without any further purification. All catalytic tests were carried out under a nitrogen atmosphere using modified Schlenk techniques.

Measurements

Infrared (IR) spectra were obtained using KBr pellets (solid samples) or NaCl windows (liquid samples) on a PerkinElmer Frontier FT-IR/FIR spectrometer. Electronic spectra were recorded in methanol on a Perkin Elmer Lambda 20 UV-Vis spectrophotometer from 200 to 1100 nm. Both ligands and Cu(II) complexes were analyzed at a concentration of 5×10^{-5} M, while for the complexes, an additional measurement at 1×10^{-3} M was performed to monitor the d-d transitions, which are only observable at higher concentrations due to their low molar absorptivity. ^1H NMR spectra were recorded at 400 MHz on a Bruker Advance 400 spectrometer; samples were dissolved in CDCl_3 , using TMS as internal standard. Thermogravimetric analysis measurements were carried out on a Pyris 1 TGA equipment from Perkin Elmer analyzer under nitrogen atmosphere with a heating rate of $10^\circ\text{C}/\text{min}$ in the $30\text{--}800^\circ\text{C}$ temperature range. Electron paramagnetic resonance (EPR) spectra were recorded in quartz tubes with a Joel JES-TE300 spectrometer equipped with a cylindrical cavity (TE-011 mode) operating at X band frequency (9.4 GHz) at 100 KHz field modulation, at 77 K as frozen solutions. Mass Spectra of electrospray ionization (ESI/MS) were obtained on 6130 Quadrupole LC/MS of Agilent Technologies, in the negative and positive ion modes. A triple quadrupole mass spectrometer API 3000 Chromatograms were recorded on an Agilent 7890A-GC System equipped with an Agilent 5975C Series MSD—with Triple-Axis HED-EM Detector.

Synthesis of the complexes

The copper(II) complexes were prepared using a one-pot synthesis strategy; the first step was the synthesis of the Schiff base ligand derived from the amino acids (glycine, alanine, serine and phenylalanine), and the second step was the formation of the copper (II) complex.

The synthesis of ligand was achieved following the Dakternieks *et al.* (1998) procedure. 2'-hydroxyacetophenone (136 mg, 1 mmol, in 10 mL of methanol) was added to a hot

methanolic solution (20 mL) containing a mixture of sodium methoxide (54 mg, 1 mmol) and amino acid (1 mmol). The reaction mixture was refluxed for 24 h.; an intense yellow solution characteristic of this type of ligand was obtained and maintained for the next step. Separately, the ligands were synthesized and isolated to ensure that they were obtained.

The synthesis of the complexes was achieved following the methodology of Ünver and Hayvali (2010), with slight modifications: to the methanolic ligand solution, obtained in the previous step, $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (250 mg, 1 mmol, in 10 mL of methanol) was added with constant stirring. The product was refluxed overnight, the mixture was cooled to room temperature and filtered to remove any precipitate; the deep green supernatant was slowly evaporated.

L-H-Gly. Yield: 98 %; m.p. 192-194 °C. IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 2950 (C-H Stretch), 1541 (C=C), 3393 (O-H), 1620 (C=O), 1611 (C=N), 1442 $\nu_{\text{asym}}(\text{COO}^-)$ and 1369 $\nu_{\text{sym}}(\text{COO}^-)$. ^1H NMR (CDCl_3 , 400 MHz): δ 12.27 (1H), 7.75 (1H), 7.48 (1H), 6.99 (1H), 6.912 (1H), 2.65 (2H), 1.57 (3H) ppm.

L-H-Ala. Yield: 97 %; m.p. 208-212 °C. IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 2863 (C-H Stretch), 1528 (C=C), 3414 (O-H), 1607 (C=O) (C=N), 1439 $\nu_{\text{asym}}(\text{COO}^-)$ and 1396 $\nu_{\text{sym}}(\text{COO}^-)$. ^1H NMR (CDCl_3 , 400 MHz): δ 12.27 (1H), 7.74 (1H), 7.48 (1H), 6.98 (1H), 6.91 (1H), 3.78 (1H), 2.64 (3H), 1.61 (3H) ppm.

L-H-Ser. Yield: 98 %; m.p. 118-124 °C. IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 2951 (C-H Stretch), 1532 (C=C), 3224 (O-H), 1619 (C=O) (C=N), 1530 $\nu_{\text{asym}}(\text{COO}^-)$ and 1369 $\nu_{\text{sym}}(\text{COO}^-)$. ^1H NMR (CDCl_3 , 400 MHz): δ 12.27 (1H), 7.75 (1H), 7.48 (1H), 6.99 (1H), 6.91 (1H), 4.54 (1H), 2.64 (3H), 1.65 (2H) ppm.

L-H-Phe. Yield: 96 %; m.p. 180-184 °C. IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 3039 (C-H Stretch), 1538 (C=C), 3375 (O-H), 1618 (C=O) (C=N), 1407 $\nu_{\text{asym}}(\text{COO}^-)$ and 1358 $\nu_{\text{sym}}(\text{COO}^-)$. ^1H NMR (CDCl_3 , 400 MHz): δ 12.27 (1H), 7.74-6.91 (9H), 3.78 (1H), 3.38 (2H), 2.64 (3H) ppm.

L-H-Gly-Cu. Yield: 93 % m.p. 232-234 °C. Anal. Calc. for ($\text{C}_{10}\text{H}_9\text{CuNO}_3$) (254.73): C, 47.15; H, 3.56; N, 5.50. Found: C, 46.05; H, 3.19; N, 5.40 %. IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 3037 (C-H Stretch), 1534 (C=C), 1611 (C=O), 1597 (C=N), 1450 $\nu_{\text{asym}}(\text{COO}^-)$, 1345 $\nu_{\text{sym}}(\text{COO}^-)$, 565 (Cu-O) and 612 (Cu-N).

L-H-Ala-Cu. Yield: 90 %; m.p. 208-214 °C. Anal. Calc. for ($\text{C}_{11}\text{H}_{13}\text{CuNO}_4$) (286.77): C, 46.07; H, 4.57; N, 4.88. Found: C, 46.71; H, 4.55; N, 5.48 %. IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 2735 (C-H Stretch), 1535 (C=C), 3236 (O-H), 1619 (C=O), 1596 (C=N), 1537 $\nu_{\text{asym}}(\text{COO}^-)$, 1353 $\nu_{\text{sym}}(\text{COO}^-)$, 549 (Cu-O) and 611 (Cu-N).

L-H-Ser-Cu. Yield: 89 %; m.p. 261-267 °C. Anal. Calc. for ($\text{C}_{11}\text{H}_{13}\text{CuNO}_5$) (302.77): C, 43.64; H, 4.33; N, 4.63. Found: C, 44.06; H, 3.50; N, 4.53 %. IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 2943 (C-H Stretch), 1536 (C=C), 3444 (O-H), 1620 (C=O), 1519 (C=N), 1536 $\nu_{\text{asym}}(\text{COO}^-)$, 1440 $\nu_{\text{sym}}(\text{COO}^-)$, 537 (Cu-O) and 614 (Cu-N).

L-H-PheCu. Yield: 87 %; m.p. 194-200 °C. Anal. Calc. for ($\text{C}_{17}\text{H}_{17}\text{CuNO}_4$) (362.87): C, 56.27; H, 4.72; N, 3.86. Found: C, 49.53; H, 4.65; N, 4.36 %. IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 3032 (C-H Stretch), 1567 (C=C), 3405 (O-H), 1608 (C=O), 1564 (C=N), 1448 $\nu_{\text{asym}}(\text{COO}^-)$, 1370 $\nu_{\text{sym}}(\text{COO}^-)$, 558 (Cu-O) and 603 (Cu-N).

Catalytic assay

For catalytic reactions, a modification of the method of Youssef *et al.* (2009) was used. Under nitrogen, ethyl diazoacetate

(EDA) (114 mg, one mmol, in 2.8 mL of 1,2-dichloroethane) was slowly added via a syringe pump (injection time: 6 h.) to a mixture of the catalyst (0.05 mmol, 5 % mol), styrene (1 mL, 8.7 mmol) and solvent (2 mL of 1,2-dichloroethane); the reaction was carried out at room temperature. The reaction was monitored by IR spectroscopy, following the EDA signal at 2114 cm^{-1} , placing a drop of the reaction mixture on a NaCl window (Hadjiivanov *et al.*, 2021). After the complete disappearance of the EDA signal, the reaction mixture was stirred for another 10 h. to ensure complete reaction. The mixture was then purified through a short silica gel plug; subsequently, the solvent and unreacted styrene were eliminated under reduced pressure. GC determined yield and diastereomeric ratio: column β^{TM} -DEX 120, 30 m X 0.25 mm X 0.25 μm ; an initial oven temperature of 10 °C was held for 5 min, followed by a ramp of 4 °C/min to 135 °C, holding for 40 min, followed by a ramp of 10 °C/min to 155 °C, holding for 30 min. The injection port and detector temperatures were maintained at 250 °C. Total chromatographic separation was achieved in 86 min. The result is the mean of three independent experiments conducted in triplicate. The same reaction was carried out using copper(II) sulfate as a "blank"; we found that the disappearance of the EDA IR signal took more than 160 h, and the coupling by-products were found in the chromatography.

RESULTS AND DISCUSSION

IR Spectra

In the absence of a powerful technique such as X-ray crystallography, IR spectroscopy has proven to be a suitable technique to elucidate the method of the ligand of to the metal ion (Boghaei and Gharagozlou, 2007; Hadjiivanov *et al.*, 2021). The identification of the coordinating atoms is achieved by comparing the IR spectra of the ligands and complexes with previously reported data from the literature. The shift of the C=N group signal to lower wavenumber is a key indicator of the coordination of the imine to the metal, which may reflect the loss of pure double bond character due to the metal-ligand interaction (Nakamoto, 2001; Sinn and Harris, 1969). This shift behavior has been reported in previously published structures for these compounds (Majumder *et al.*, 2006; 2003). In the case of L-H-PheCu, there was a shift to a higher wave number which is a less common behavior for this class of compounds. This may be due to a greater rigidity of the imine bond due to loss of electronic delocalization, as well as an influence of dominant inductive or steric effects on the retrodonation of the metal (Nakamoto, 2001). In the L-H-GlyCu complex we can also notice that the band corresponding to the OH group disappeared, which may be indicative of the formation of a coordination bond between the metal and the oxygen of the hydroxyl group of 2'-hydroxyacetophenone (Majumder *et al.*, 2003). The presence of two characteristic bands in the ranges of $1537\text{--}1439\text{ cm}^{-1}$ and $1440\text{--}1353\text{ cm}^{-1}$ in the complexes is associated to $\nu_{\text{asym}}(\text{COO}^-)$ and $\nu_{\text{sym}}(\text{COO}^-)$ respectively, which suggests the participation of the carboxylate oxygen in the formation of the complexes (Boghaei and Gharagozlou, 2007; Youssef *et al.*, 2009).

Additionally, new absorption bands appeared in the 550–620 cm^{-1} region, which are absent in the free ligands. These bands can be assigned to $\nu(\text{Cu-O})$ stretching vibrations around 550 cm^{-1} and $\nu(\text{Cu-N})$ vibrations near 610 cm^{-1} , confirming bidentate coordination of the amino acid ligands through the oxygen and nitrogen donor atoms. The positions of these bands are consistent with those previously reported for Cu(II) -amino acid and Cu(II) -Schiff base complexes, where Cu-O stretching vibrations typically appear in the 500–560 cm^{-1} range, and Cu-N modes in the 600–640 cm^{-1} region (Gharda *et al.*, 2017; Khanpour *et al.*, 2017; Stanila *et al.*, 2007; Torreggiani *et al.*, 2000). This comparison with literature data reinforces the proposed coordination mode and confirms that the synthesized Cu(II) complexes exhibit the expected vibrational features consistent with related systems previously described. The significant data are presented in Table 1 and all ligand and complex spectra are shown in Figures S1–S4.

UV-Vis Spectral Analysis

The electronic spectra of the free ligands recorded in methanol exhibited two main absorption bands in the 266–273 and 362–393 nm regions, assigned to $\pi \rightarrow \pi^*$ transitions within the aromatic ring system and $n \rightarrow \pi^*$ transitions associated with the azomethine (C=N) group, respectively (Issa *et al.*, 2005; Jarzabek *et al.*, 2009; Kanagavalli *et al.*, 2023). Upon complexation with Cu(II) , both transitions undergo a slight bathochromic shift, indicating coordination of the azomethine nitrogen and phenolic oxygen to the metal center. This red shift reflects a reduction in the gap between the energy levels, consistent with the formation of an extended conjugated system due to metal–ligand interaction.

Cu(II) complexes show an additional broad, low-intensity band in the visible region at 636–660 nm, attributed to a d–d transition of the type $^2\text{B}_{1g} \rightarrow ^2\text{A}_{1g}$. When consulting the literature comparing similar complexes, we note that this signal is characteristic of a square-planar geometry around the metal ion (Mitić *et al.*, 2011; Reena and Kurup, 2010). The breadth of this band suggests considerable ligand-field distortion, typical of Cu(II) complexes exhibiting Jahn–Teller elongation along the z-axis. This observation supports the geometry inferred from EPR data.

In addition, the intense absorption in the range of 327–363 nm is ascribed to ligand-to-metal charge transfer (LMCT), corresponding to transitions from filled π or non-bonding orbitals of the ligand to empty Cu(II) d-orbitals. The relative intensity of this CT band compared to the $\pi \rightarrow \pi^*$ transition reflects the degree of covalency in the metal–ligand bonding and suggests efficient delocalization of electron density between the aromatic system and the Cu(II) center (Belokon' *et al.*, 1981; Paulose *et al.*, 2002; Soberanes *et al.*, 2018; Ünver and Hayvali, 2010). The band assignment was performed considering that similar Schiff basis structures reported in the literature exhibit absorptions in comparable regions, which supports the present interpretations. For example, Yan *et al.* in 2014 reported copper(II) complexes using salicylaldehyde and beta-amino acids, where they obtained bands at ~217 and ~370 nm for $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions, as well as a signal at ~636 nm that is assigned to a d–d transition (Yan *et al.*, 2014).

The appearance of these characteristic transitions, together with their spectral shifts upon coordination, confirm successful chelation of Cu(II) by the Schiff-base ligands through the N,O donor set. These features, summarized in Table 2 and Figures 1 and S5–S7, corroborate the proposed square-planar environment and electronic configuration

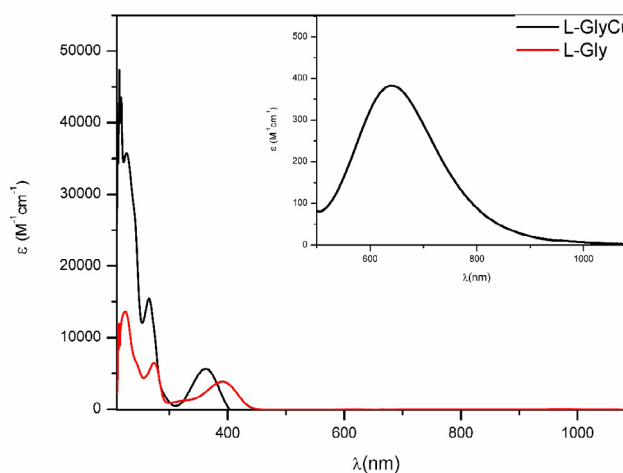


Figure 1. UV-Vis spectra of L-H-Gly and L-H-GlyCu.

Figura 1. Espectros UV-Vis de L-H-Gly y L-H-GlyCu.

Table 1. Infrared spectral data of Schiff base ligands and its complexes.

Tabla 1. Datos espectrales de infrarrojo de ligantes de base de Schiff y sus complejos.

Compound	$\nu(\text{OH})$	$\nu(\text{C=O})$	$\nu(\text{C=N})$	$\nu_{\text{asym}}(\text{COO}^-)$	$\nu_{\text{sym}}(\text{COO}^-)$
L-H-Gly	3356	1611	1611	1442	1369
L-H-GlyCu	-	1611	1597	1450	1345
L-H-Ser	3234	1619	1619	1530	1362
L-H-SerCu	3444	1620	1519	1536	1440
L-H-Ala	3290	1660	1623	1439	1396
L-H-AlaCu	3236	1636	1599	1537	1353
L-H-Phe	3416	1613	1567	1407	1358
L-H-PheCu	3246	1639	1600	1448	1370

Table 2. Electronic spectral data (nm) of ligands and its complexes.**Tabla 2.** Datos espectrales electrónicos (nm) de los ligantes y sus complejos.

Compounds	$\pi-\pi^*$	$n-\pi^*$ and CT	$d-d$
L-H-Gly	273	391	
L-H-GlyCu	266	363	646
L-H-Ser	266	362	
L-H-SerCu	247	327	638
L-H-Ala	271	393	
L-H-AlaCu	269	362	660
L-H-Phe	272	387	
L-H-PheCu	247	352	636

of the Cu(II) complexes, which is relevant to their observed catalytic behavior.

Thermal Analysis

The thermal degradation of all the metal complexes was studied using thermogravimetric (TG) and the derivative thermogravimetric (DTG) at a temperature range of 30–800 °C, plots of the complexes were given in the figures 2-5. The thermal stability data are listed in Table 3. The data from the thermogravimetric analysis clearly indicated that the decomposition of the complexes proceeds in two or three steps. All the complexes except for L-H-GlyCu in the first stage, show a loss in weight of 5.6–7.0 % in the temperature range 60–197 °C (Refat *et al.*, 2006; Tabbi *et al.*, 2013). These weight losses correspond to the removal of water molecules from the complexes and thus confirm the presence of coordinated water molecules inside the sphere (Kavitha and Anantha Lakshmi, 2017; Moreira *et al.*, 2022; Zoubi *et al.*, 2017). In the second stage the evaporation of organic amino acid moiety takes place at the temperature range from 158–341 °C, followed by the third stage at which the removal of another organic moiety 2'-Hydroxyacetophenone occurs in the temperature range of 328–632 °C (Chakraborty *et al.*, 2009; Moreira *et al.*, 2022; Naskar *et al.*, 2011; Shobana *et al.*, 2015; Soliman and Mohamed, 2004).

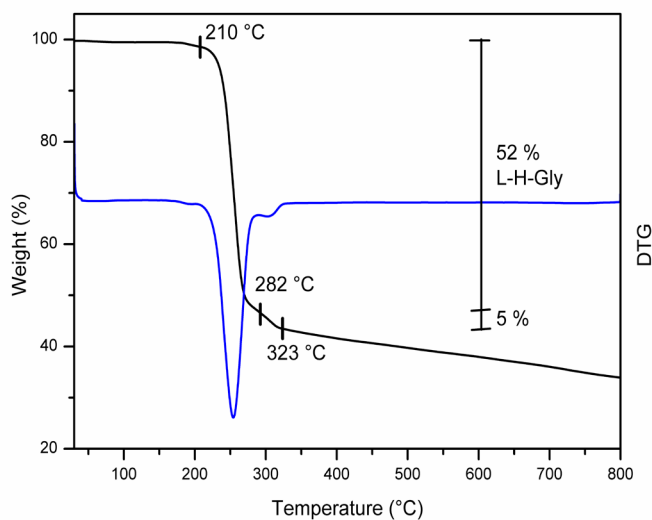
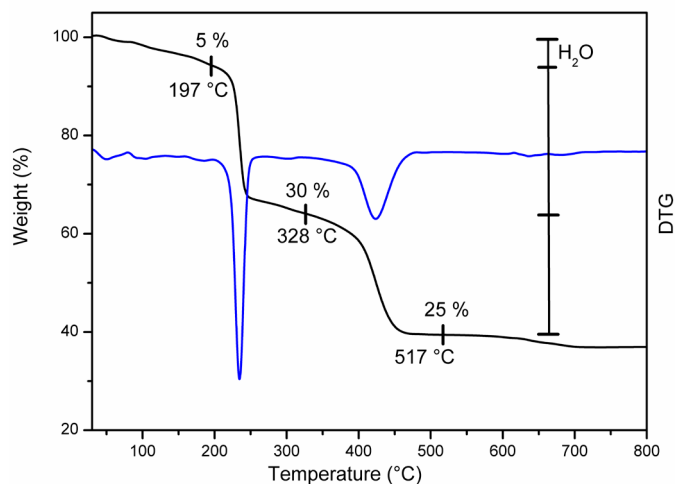
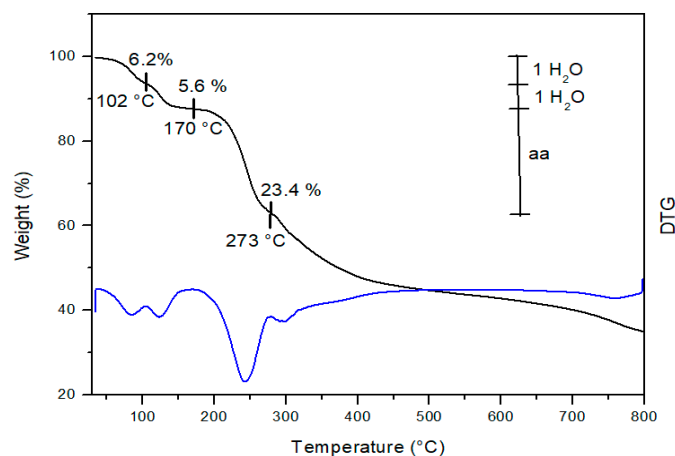
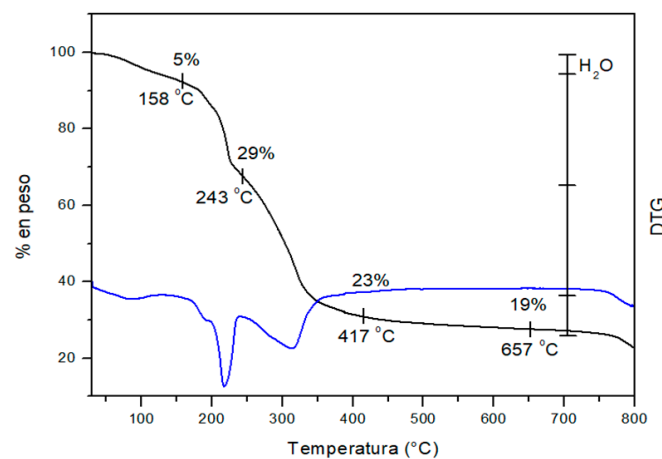
**Figure 2.** TG and DTG plots of the complex L-H-GlyCu.**Figura 2.** Gráficos TG y DTG del complejo L-H-GlyCu.**Figure 3.** TG and DTG plots of the complex L-H-SerCu.**Figura 3.** Gráficos TG y DTG del complejo L-H-SerCu.**Figure 4.** TG and DTG plots of the complex L-H-AlaCu.**Figura 4.** Gráficos TG y DTG del complejo L-H-AlaCu.**Figure 5.** TG and DTG plots of the complex L-H-PheCu.**Figura 5.** Gráficos TG y DTG del complejo L-H-PheCu.

Table 3. Thermal analytical data for the complexes.**Tabla 3.** Datos analíticos térmicos de los complejos.

Complex	Molecular formula	Stages	Temperature of TGA (°C)	Temperature of DTG	Mass loss (%)		Assignment
					found	Calc.	
L-H-GlyCu	[C ₁₀ H ₉ CuNO ₃] ₄	1 st	210-281	253	52		
		2 nd	281-323	309	5		
L-H-SerCu	C ₁₁ H ₁₄ CuNO ₅	1 st	68-197		6	5.9	1 H ₂ O
		2 nd	197-328	234	30		
		3 rd	328-517	422	25		
L-H-AlaCu	C ₁₁ H ₁₄ CuNO ₄	1 st	74-174	113	7	6.3	1 H ₂ O
		2 nd	174-341	237	32		
		3 rd	341-632	482	28		
L-H-PheCu	C ₁₇ H ₁₈ CuNO ₄	1 st	60-158	73	5.6	5	1 H ₂ O
		2 nd	158-243	197	29		
		3 rd	243-417	305	23		
		4	417-657	577	19		

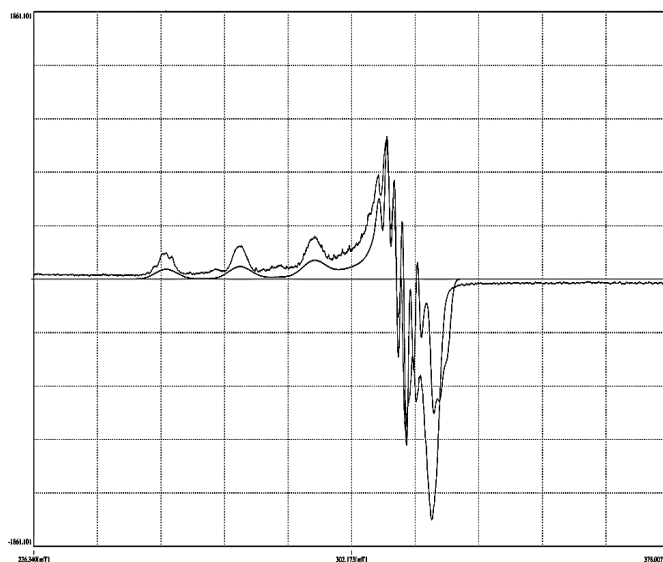
L-H-GlyCu and L-H-AlaCu exhibit decomposition at lower temperatures compared to the Ser and Phe derivatives. This behavior indicates a lower thermal stability, which can be attributed to the smaller and less bulky side chains of glycine and alanine. This observation is also consistent with the thermal behavior of free amino acids, since glycine and alanine decompose at lower temperatures than serine and phenylalanine due to the formation of less stable intermediates (Zhu *et al.*, 2024).

In similar complexes derived from salicylaldehyde or its derivatives and their amino acid complexes, it is also observed that glycine derivatives are thermally less stable than phenylalanine derivatives. Bouhdada *et al.* (2021) reported a nickel(II) complex with glycine, whose thermogravimetric analysis also showed three stages, with the last stage occurring above 350 °C while L-H-GlyCu displayed its final decomposition step at 323 °C. A phenylalanine complex reported by Sevgi *et al.* (2018) began its final decomposition stage above 450 °C, similar to L-H-PheCu (417 °C). Likewise, serine complexes display higher thermal stability than glycine analogues. Lekha *et al.* (2014) analyzed a lanthanide complex with a ligand derived from serine and 5-bromosalicylaldehyde, which also underwent three stages of thermal degradation, with the final stage starting at 415 °C in agreement with the L-H-SerCu complex that starts its final stage around 400 °C.

EPR spectra of complexes

To analyze the coordination environment around Cu²⁺ ions, EPR spectra were recorded in solid state and in frozen methanol or methanol/acetonitrile solutions at 77 K, to immobilize the complexes in a rigid matrix and resolve the anisotropic *g*- and hyperfine parameters characteristic of Cu(II) centers. The low temperature also enhances signal intensity by increasing spin-state population differences (Chandra and Sangeetika, 2004; Hagen, 2008; Rockenbauer *et al.*, 1979).

The spectrum of the L-H-GlyCu complex (Figure 6) exhibits an axial pattern with $g_{\parallel} = 2.267$ and $g_{\perp} = 2.059$, and a well-defined hyperfine splitting constant $A_{\parallel} = 18$ mT. These parameters are typical of a $dx^2 - y^2$ ground state, indicating that the unpaired electron occupies a predominantly

**Figure 6.** EPR spectrum of L-H-GlyCu in methanol.**Figura 6.** Espectro EPR de L-H-GlyCu en metanol.

antibonding orbital in the equatorial plane, consistent with a square-planar coordination environment (Bagihalli *et al.*, 2008; Karlin *et al.*, 1983; Palaniandavar *et al.*, 1995). The presence of resolved superhyperfine coupling ($A^{\perp} = 1.40$ mT) with two nitrogen nuclei ($I = 1$) further supports coordination through two imine or amine donors from the Schiff base. The $g_{\parallel} > g_{\perp} > 2.0023$ relationship is characteristic of elongated octahedral or square-planar Cu(II) systems with a $dx^2 - y^2$ ground state, while the relatively large $A_{\parallel}$ value suggests a moderate degree of metal-ligand covalency in the equatorial plane (Aiswarya *et al.*, 2016; Bagihalli *et al.*, 2008). These assignments are consistent with previously reported Cu(II) Schiff basis complexes, which show comparable *g* and *A* values for square planar geometries, reinforcing the interpretation made in this work. For example, in the 2025 work by Fomenko *et al.* (2025), when synthesizing several copper(II) complexes, the *g* values were around 2.1.

The spectrum of the L-H-SerCu complex (Figure 7) also exhibits an axial geometry ($g_{\parallel} = 2.264$, $g_{\perp} = 2.056$; $A_{\parallel} = 18$ mT, $A^{\perp} = 1.65$ mT), confirming that both complexes share

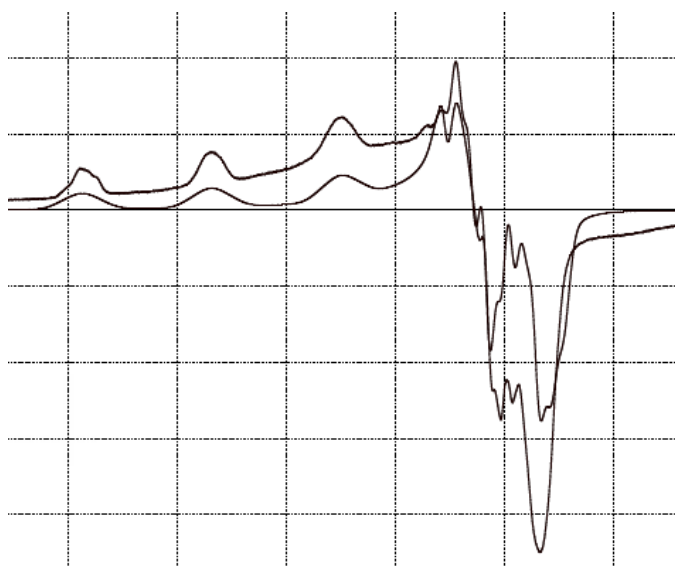


Figure 7. EPR spectrum of L-H-SerCu in methanol/acetonitrile.
Figura 7. Espectro EPR de L-H-SerCu en metanol/acetonitrilo.

a similar electronic environment around Cu(II). The slight differences in $A^\perp$ values may arise from the different electronic effects of the side-chain substituents in the amino acid moieties ($-\text{CH}_2\text{OH}$ in serine versus $-\text{H}$ in glycine), which can influence the electron density on the donor atoms and therefore modulate the covalency of the Cu–N and Cu–O bonds. The absence of half-field transitions ($\Delta M_s = \pm 2$) and any exchange-narrowed signals indicates monomeric species, with no significant magnetic coupling between Cu(II) centers (Łabanowska *et al.*, 2012; Sundaravel *et al.*, 2009).

The $g\parallel/A^\perp$ ratio (Table 4), often used as a diagnostic parameter for Cu(II) complexes, provides additional evidence about the geometry and bonding character. The obtained values fall between 105 and 135 cm, which correspond to nearly ideal square-planar configurations with a dx^2-y^2 ground state and appreciable in-plane covalency (Reena and Kurup, 2010; Tabbi *et al.*, 2013). These values are in excellent agreement with those reported in the literature for Cu(II) complexes of N,O-donor Schiff-base ligands, further confirming the reliability of the assignments made here. This degree of covalency is relevant to the catalytic behavior of these species, as it favors efficient electron delocalization between the Cu center and the Schiff-base framework, facilitating redox participation of Cu(II)/Cu(I) during catalytic cycles.

Altogether, the EPR data confirm that both complexes contain mononuclear Cu(II) centers in a square-planar ligand field provided by N,O donor atoms, with similar geometrical distortions and electronic structures that are consistent with their UV–Vis and magnetic properties as illustrated in Figure 8, where the structural features of the complexes are shown. Although EPR measurements were performed only for the L-H-GlyCu and L-H-SerCu complexes, their structural and spectroscopic similarities with the remaining Cu(II) derivatives strongly suggest that they exhibit analogous coordination environments and electronic behaviors, so the conclusions drawn from these two representative systems are expected to be valid for the entire series of complexes.

Catalytic Activity

The catalytic activity of copper(II) complexes was evaluated through the cyclopropanation reaction of styrene with ethyl diazoacetate (EDA). The reactions were conducted under a nitrogen atmosphere, by the slow addition of EDA to a stirred solution of styrene and the copper complex in 1,2-dichloroethane, following a procedure adapted from the literature (Youssef *et al.*, 2009).

Table 5 summarizes the catalytic performance of each complex, reporting the average values obtained from three independent experiments carried out at room temperature.

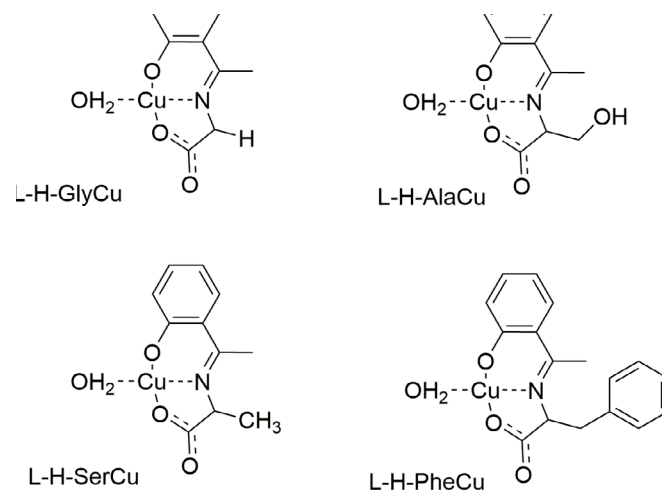


Figure 8. The proposed structures of metallic complexes.
Figura 8. Estructuras propuestas de complejos metálicos.

Table 4. EPR spectral properties of copper(II) complexes.

Tabla 4. Propiedades espectrales EPR de complejos de cobre (II).

Complex	Solid	Frozen dissolution
L-H-GlyCu	$g\parallel = 2.247$ $g^\perp = 2.093$	$g\parallel = 2.270$, $g^\perp = 2.059$ $A\parallel = 17.591$ mT $A^\perp = 1.650$ mT $g\parallel/A\parallel = 121$ cm $G = 5.094$
L-H-SerCu	$g\parallel = 2.374$ $g^\perp = 2.108$	$g\parallel = 2.264$, $g^\perp = 2.050$ $A\parallel = 18.065$ mT $A^\perp = 1.238$ mT $g\parallel/A\parallel = 134$ cm $G = 5.280$

Table 5. Cyclopropanation of styrene with EDA with different copper(II) complexes.**Tabla 5.** Ciclopropanación de estireno con EDA con diferentes complejos de cobre (II).

Entry	Catalyst	Yield (%)	<i>trans</i> : <i>cis</i>	ee% <i>trans</i>	ee% <i>cis</i>
1	L-H-GlyCu	>99	98:2	-	-
2	L-H-SerCu	93	99:1	14	ND
3	L-H-AlaCu	>99	97:3	24	46
4	L-H-PheCu	96	98:2	17	57

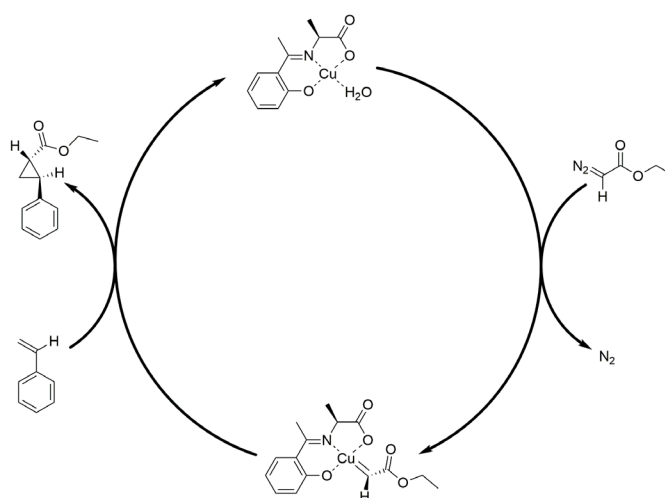
ND (not determined) since the signal of the *cis* enantiomers was too low, comparable with the instrumental noise.

All the copper(II) complexes tested were capable of catalyzing the cyclopropanation reaction with moderate to very good yields. Notably, the diastereoselectivity was consistently high, with *trans*:*cis* ratios reaching up to 99:1, indicating that the catalytic systems are highly stereoselective and predominantly favor the formation of the *trans*-isomer (Iglesias *et al.*, 2004).

In contrast, the enantioselectivity observed was moderate to low. Among the series, the complex derived from L-alanine exhibited the best enantiodiscrimination, reaching enantiomeric excesses (ee) of 24 % for the *trans*-isomer and 46 % for the *cis*-isomer. These results suggest that although the chirality of the ligand is partially transmitted to the product, the stereochemical environment around the copper center is not sufficiently rigid or defined to induce high asymmetric induction. This observation is consistent with prior studies where similar chiral copper(II) complexes display limited enantioselectivity, especially in non-rigid coordination environments (Chanthamath and Iwasa, 2016; Huang *et al.*, 2003; Li *et al.*, 2006; Xu *et al.*, 2011).

These findings support the notion that the copper complexes synthesized in this work can serve as effective catalysts in carbene-transfer reactions such as cyclopropanations, with excellent diastereoselectivity and moderate enantioselectivity. This underscores the potential applicability of these systems in organic synthesis and motivates further ligand design to improve enantioinduction.

Figure 9 shows a mechanistic proposal for the catalytic cycle. The proposed pathway is based on previously reported mechanisms for copper-catalyzed cyclopropanation reactions with diazo compounds (Davies and Teng, 2003; Youssef *et al.*, 2009). The catalytic cycle begins with the interaction of the copper(II) complex with ethyl diazoacetate, resulting in the extrusion of molecular nitrogen and the formation of a reactive copper-carbene intermediate. This species is then intercepted by styrene, yielding the corresponding cyclopropane product. Although no direct spectroscopic evidence (e.g., EPR or time-resolved techniques) for the metallocarbene intermediate was obtained in this study, the high stereoselectivity and consistency with literature precedents provide reasonable support for the proposed mechanism.

**Figure 9.** Proposed mechanism of cyclopropanation catalysis.**Figura 9.** Mecanismo propuesto de catálisis de ciclopropanación.

CONCLUSIONS

We have synthesized and characterized a series of Cu(II) complexes with Schiff bases derived from 2'-hydroxyacetophenone and natural L-amino acids. While similar structures have been previously reported in the literature, this study provides the first comparative evaluation of their catalytic activity in the cyclopropanation of styrene, highlighting their excellent yield and exceptionally high diastereoselectivity (up to 99:1 *trans*:*cis*). This level of diastereocontrol is competitive against more sophisticated catalysts and underscores the utility of these accessible, sustainable complexes for the synthesis of functionalized cyclopropanes with high stereochemical precision.

The moderate enantioselectivity observed, particularly with the L-alanine complex (24 % ee for *trans* and 46 % ee for *cis*), suggests that the ligand's chiral environment influences stereodiscrimination but is insufficient for high asymmetric induction within the current geometric framework. Future research should focus on ligand engineering to increase the stereochemical rigidity around the metal center, potentially by introducing bulky substituents on the Schiff base backbone, aiming to enhance enantioselectivity while maintaining the high diastereoselectivity. Nevertheless, the present results establish these Cu(II) complexes as outstanding diastereoselective catalysts for applications where diastereomeric purity is critical.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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