Novel nitrogen containing chelating ligands from aziridines — Preparation, coordination studies, and catalytic application in the cyclopropanation of styrene[1]

Larissa B. Krasnova and Andrei K. Yudin

Abstract: Novel ligands have been synthesized by the reaction of readily available aziridines with appropriate nitrogen based nucleophiles under mild conditions. Complexes of different stoichiometry can be readily obtained upon reaction between these ligands and the corresponding copper salts. The enantiomerically pure form of one of the ligands was obtained and applied in the styrene cyclopropanation reaction, where the copper catalyst revealed unexpectedly high diastereoselectivity in comparison with the known systems.

Key words: ligands, aziridines, cyclopropanation, copper catalysts, metal complexes.

Résumé : On a effectué la synthèse de nouveaux ligands en procédant à la réaction, dans des conditions douces, d'aziridines facilement disponibles avec des nucléophiles appropriés à base d'azote. On peut facilement obtenir des complexes de stoechiométries différentes par réaction de ces ligands avec les sels de cuivre correspondants. On a pu obtenir la forme énantiomériquement pure d'un de ces ligands et on l'a appliquée à la réaction de cyclopropanation du styrène pour laquelle le catalyseur de cuivre conduit à une diastéréosélectivité aussi haute qu'inattendue par comparaison avec les systèmes connus.

Mots clés : ligands, aziridines, cyclopropanation, catalyseurs de cuivre, complexes métalliques.

[Traduit par la Rédaction]

Introduction

Cheleating ligands based on a rigid cyclohexyl backbone have been widely used in asymmetric catalysis (1). Among them is Trost's ligand for asymmetric palladium catalyzed allylic substitution (2), alkylation of β-ketoesters (3), and addition of alcohols to vinyl epoxides (4). The salen-type ligands, which have been extensively studied by Jacobsen, were successfully applied in the epoxidation of olefins (5), asymmetric sulfoxidation (6), hetero-Diels–Alder reaction (7), ene reaction (8), asymmetric ring opening of epoxides (9), and cyclopropanation (10). Recently, a new type of *P,N*-ligands containing a cyclohexyl backbone was developed in our lab and applied in the Suzuki coupling with sterically hindered substrates (11). The relative facility of the aziridine ring opening coupled with complete trans selectivity should also make cyclohexyl aziridine a convenient precursor towards cyclohexyl-backbone-containing ligands with an anti relationship between the two nitrogen containing functional groups. The present manuscript details our explorations in this area.

Results and discussion

Our recent interest in aziridine chemistry prompted us to explore simple aziridine building blocks as precursors to new nitrogen containing ligands. The 7-azabicyclo-[4.1.0]heptane was synthesized from cyclohexyl oxide using the Staudinger reaction (Scheme 1) (12). The resulting aziridine was opened with hydrazine hydrate. The product of the reaction was characterized by NMR and was submitted to the next step without purification. The reaction with 2,4-pentanedione led to the formation of racemic pyrazole **1**. The reaction between 7-azabicyclo[4.1.0]heptane and 5-phenyltetrazole occurred under mild conditions at pH 5 (Scheme 1) giving tetrazole **2** (13).

Several chiral acids were screened to resolve the ligand **2** in enantiomerically pure form. The best results were

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Dedicated to Professor Howard Alper in recognition of his contributions to chemistry.

L.B. Krasnova and A.K. Yudin.[2] Davenport Building, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, ON M5S 3H6, Canada.

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[2]Corresponding author (e-mail: ayudin@chem.utoronto.ca).

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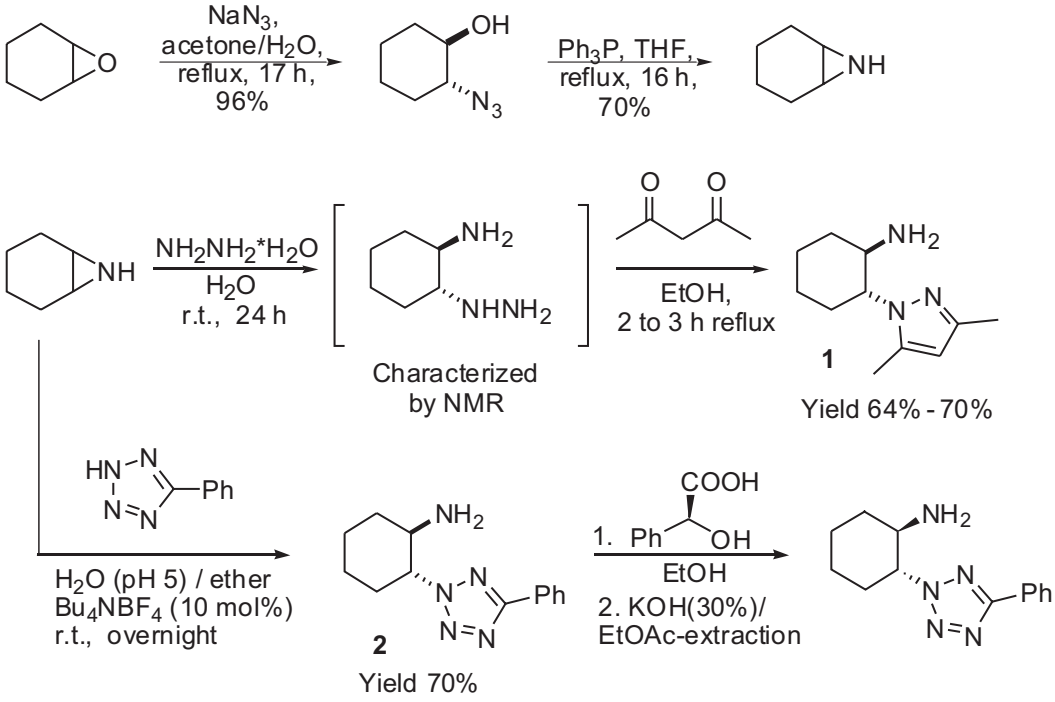
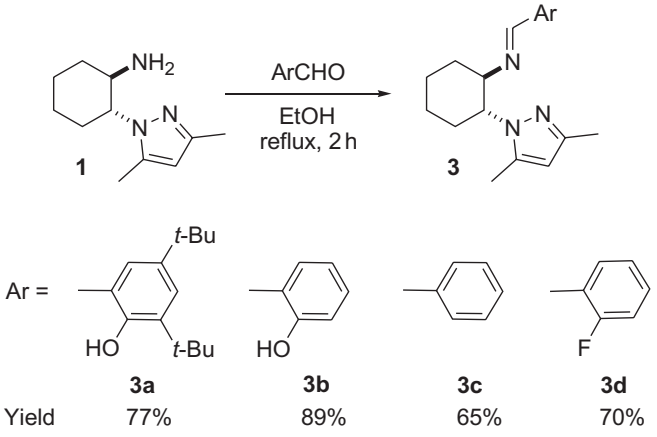
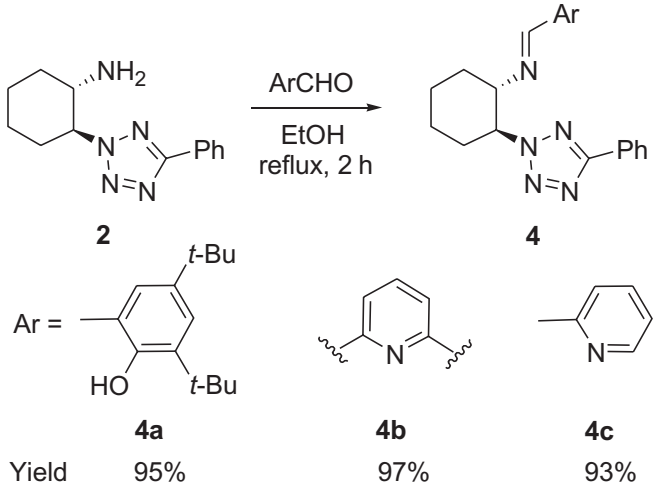
Scheme 1.



Scheme 2.



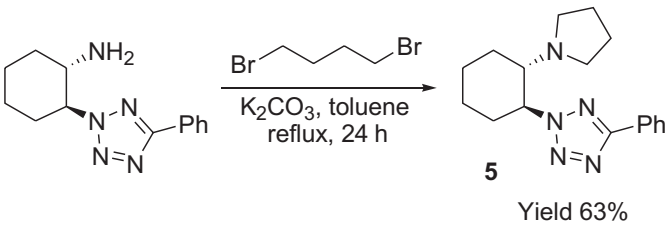
Scheme 3.



achieved with (*S*)-(–)-mandelic acid and (*S*)-(+)-camphorsulfonic acid. The enantiomeric purity was measured by ^{19}F NMR of the Mosher amide with (*R*)-(–)-MTPA.[3] The absolute stereochemistry of the amine was determined from the X-ray analysis of the diastereomeric salt obtained with (*S*)-(+)-mandelic acid. The amine **1** was resolved with D- or L-dibenzoyltartaric acid, however, we were not able to prove the absolute stereochemistry of enaniomerically pure **1**.

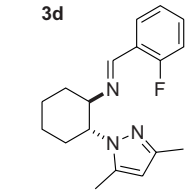
The corresponding imines of ligand precursor **1** were synthesized in good yields (Scheme 2). Different aromatic aldehydes were also used under similar reaction conditions to give the corresponding imines from aminotetrazole **2** (Scheme 3). The imines were synthesized in high yields. The amine **2** was found to be more stable than **1** and its derivatives and can be stored at room temperature without decomposition. In addition, tertiary amine **5** can be easily synthesized from **2** according to Scheme 4.

Scheme 4.



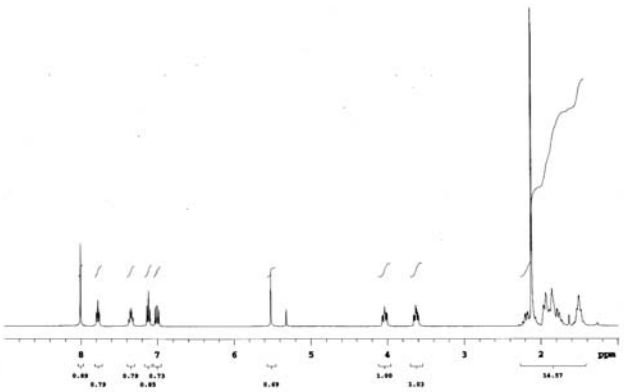
[3] The stereochemistry of the enantiomer obtained from the diastereomeric salt with (*S*)-(+)-10-camphorsulfonic acid was assigned to be opposite, since both enantiomers have different ^{19}F NMR signals in the Mosher amide with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenyl acetic acid.

Fig. 1. ^{1}H NMR studies of Cu(I) coordination to ligand **3d**.



Shift of pyrazole and imine protons indicate coordination of Cu(I) to both pyrazole and imine functionalities.

Free ligand



Coordination to Cu(I)

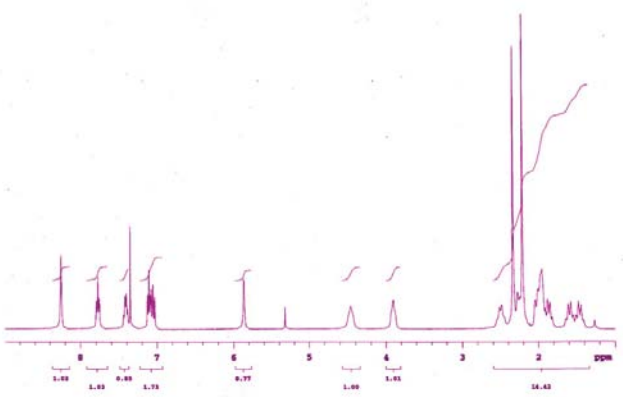
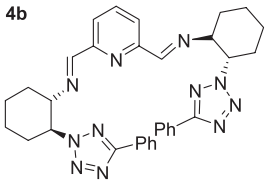
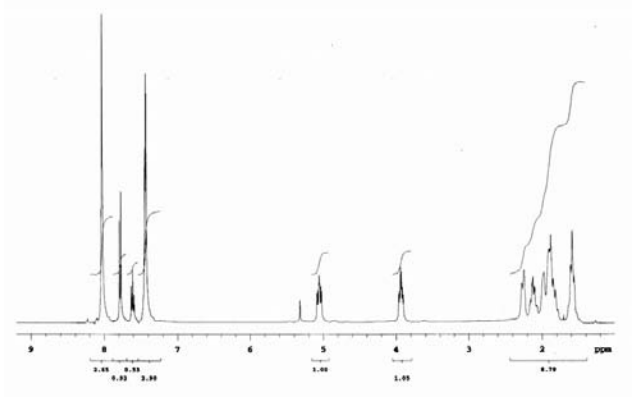


Fig. 2. ^{1}H NMR studies of Cu(I) coordination to ligand **4b**.

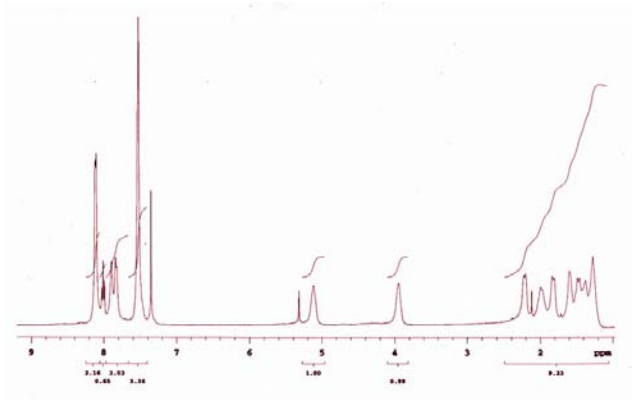


Shift of the pyridine para proton corresponds to the coordination of the metal to the pyridine ring.

Free ligand



Coordination to Cu(I)



We used ^{1}H NMR to evaluate the coordination ability of the newly synthesized ligands to transition metals. This allowed us to screen several complexes of different ligands with CuOTf·0.5C_6H_6. Coordination of the metal to the heterocycle moiety is known to induce a downfield shift of the aromatic proton signals (14). For example, ligand **3d** (Fig. 1) shows coordination to Cu(I) through the pyrazole and imine nitrogens. The imine proton shifts from 8.0 to 8.22 ppm, whereas the pyrazole proton shifts from 5.48 to 5.82 ppm. In addition, nonequivalent methyl protons of the pyrazole ring were observed in the spectrum of the Cu(I)/**3d** mixture. The other two examples did not reveal any copper coordination to the heterocycle moiety. Thus, comparison of the ^{1}H NMR of ligand **4b** with and without Cu(I) (Fig. 2) shows the downfield shift of the pyridine para proton (7.7–8.1 ppm) and corresponds to the copper coordination to the imine. This fact was also confirmed by the X-ray analysis of complex **6** (Fig. 3). No coordination between the tetrazole group and Cu(I) was observed. Importantly, the complex preserves the C_2 symmetry present in the starting material. On the other hand, mixing Cu(I) and ligand **5** showed coordination to the tertiary amine, whereas coordination to the tetrazole was not detected by ^{1}H NMR at all (Fig. 4).

No catalytic activity was observed when ligands **3a**–**3c** and **4a** were applied in asymmetric cyclopropanation according to the literature conditions (15). In light of these negative results, we were encouraged to obtain interesting data in the cyclopropanation using **4b** as the catalyst precursor (Scheme 5). The diastereoselectivity of the copper catalyzed cyclopropanation is known to mostly depend on the nature of the diazo compound ester group. The sterically bulky menthyl group usually gives the best trans:cis ratio. However, in the case of ligand **4b**, a 93:7 trans:cis ratio (determined by ^{1}H NMR) of the regioisomers was obtained even with a group as small as methyl. Unfortunately, the enantioselectivity was very low (<5%). In comparison, the background reaction without the ligand proceeds with a 57:43 trans:cis ratio. Under the same conditions, ligand **4c**

Fig. 3. X-ray structure of (*S*)-(*S*)-[2,6-di-*trans*-(5-phenyltetrazol-2-yl)cyclohexyl]pyridin-2-yl methylene-amine / Cu(I) complex (**6**).

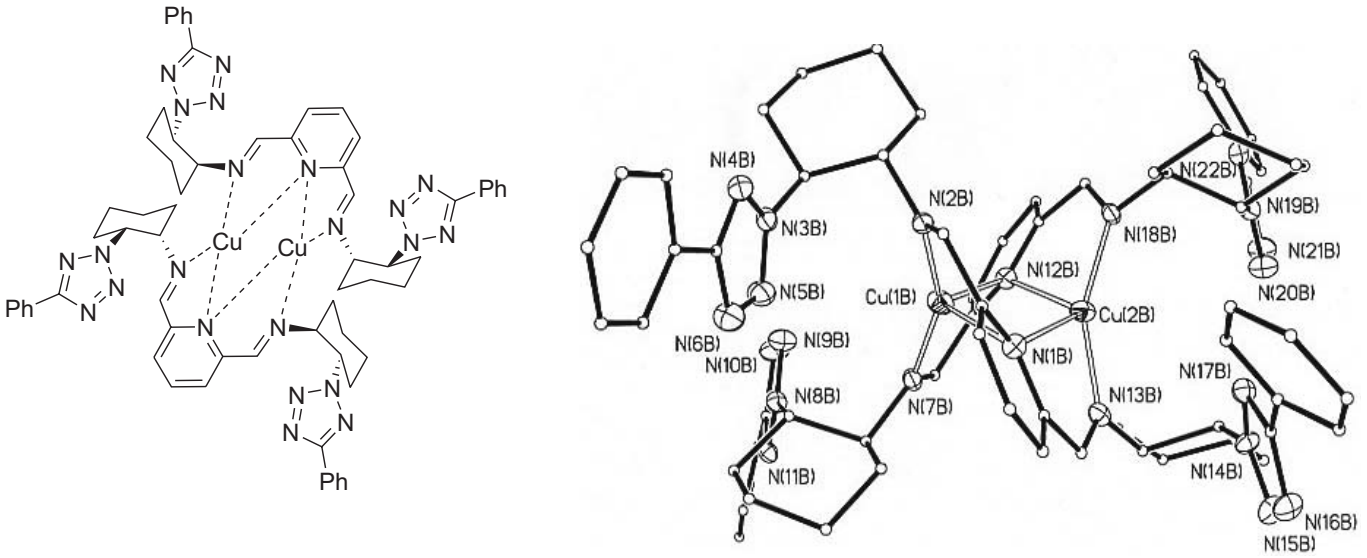
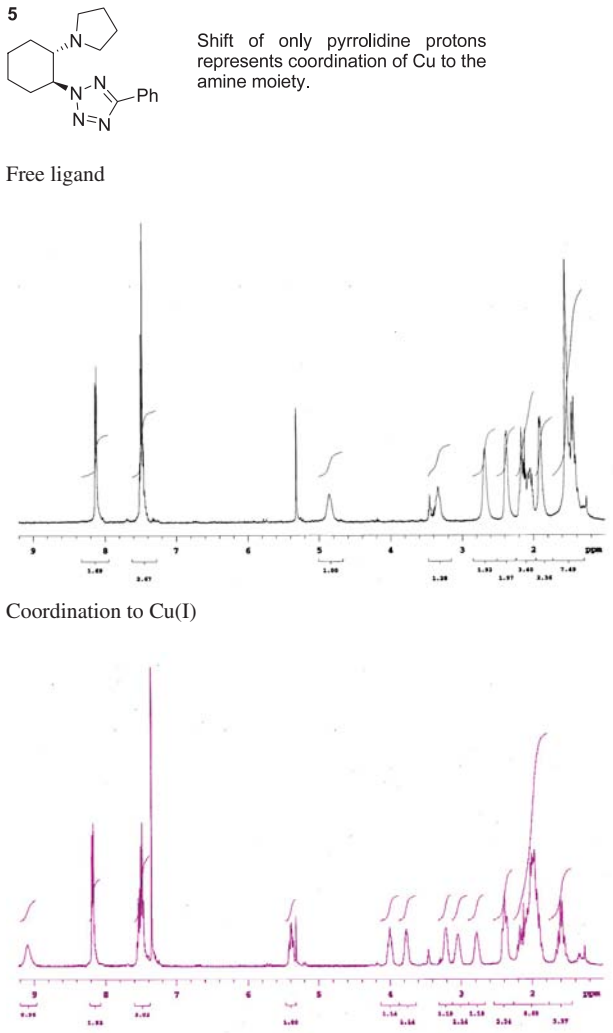


Fig. 4. ^{1}H NMR studies of Cu(I) coordination to ligand **5**.



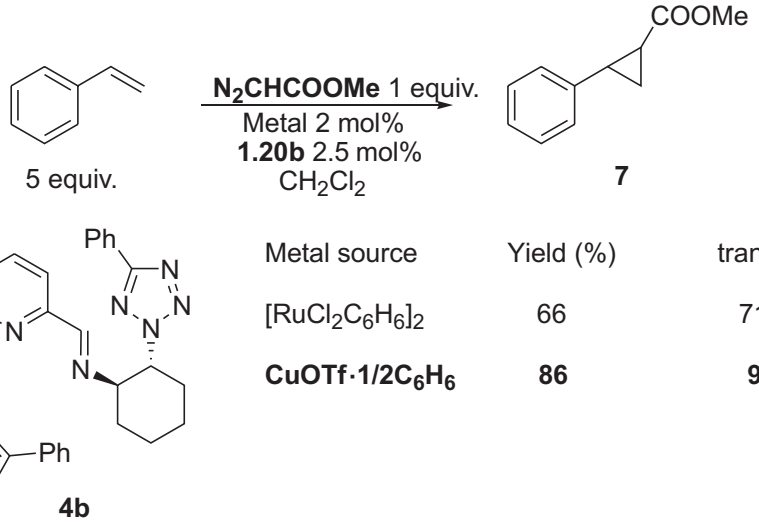
gave lower diastereoselectivity (trans:cis ratio, 73:27). These results demonstrate that ligand **4b** gives the highest reported diastereoselectivity in cyclopropanation among the ligands synthesized to date. Unexpectedly, ruthenium, which is known to show better results with the pybox system compared to copper, showed no diastereoselectivity in the case of ligand **4b**. In comparison, diastereoselectivity as well as enantioselectivity for the cyclopropanation of styrene catalyzed by Cu(I) with a pybox-type ligand was found to be low (16).

In summary, new *N*,*N*-ligands have been synthesized by the reaction of readily available cyclohexane based aziridines with appropriate nitrogen based nucleophiles under mild conditions. It was shown that Cu(I) coordinates to these ligands and, depending on modifications of the amino group, complexes of different stoichiometry can be obtained. The enantiomerically pure forms of one of the ligands were obtained and applied in the cyclopropanation reaction, where the copper catalyst revealed unexpectedly high diastereoselectivity in comparison with the ruthenium catalyst. The observed diastereoslectivity is superior to the known copper catalyzed cyclopropanation systems. The mechanistic basis for this observation is currently under scrutiny, along with attempts to find enantioselective systems in this new structural class.

Experimental section

Dichloromethane, ether, acetonitrile, toluene, and hexanes were purchased from Aldrich as "anhydrous". Tetrahydrofuran (THF) was dried over sodium benzophenone ketyl. Moisture-sensitive reactions were carried out using standard syringe–septum techniques under a nitrogen atmosphere. ^{1}H and ^{13}C NMR spectra were recorded on 300 or 400 MHz spectrometers. ^{1}H NMR spectra were referenced to residual $CHCl_3$ (δ 7.27 ppm), CH_2Cl_2 (δ 5.32 ppm), DMSO (δ 2.50 ppm), CH_3CN (δ 1.94 ppm), and benzene (δ 7.16 ppm); ^{13}C NMR spectra were referenced to $CDCl_3$ (δ 77.0 ppm), CD_2Cl_2 (δ 54.0 ppm), DMSO-d_6 (δ 99.5 ppm), CD_3CN (δ 118.7 ppm), and benzene-d_6 (δ 128.4 ppm).

Scheme 5.



Metal source	Yield (%)	trans:cis
$[RuCl_2C_6H_6]_2$	66	71:29
$CuOTf \cdot 1/2C_6H_6$	**86**	**93:7**

7-Azabicyclo[4.1.0]heptane (12)

A mixture of cyclohexene oxide (31 mL, 306 mmol) and NaN_3 (50.4 g, 775 mmol) in H_2O–acetone (1:1, 320 mL) mixture was heated to reflux for 17 h (temperature of the oil bath was 75 °C). Acetone was removed under reduced pressure and the residue extracted with Et_2O (3 × 160 mL). The combined extracts were washed with H_2O (2 × 40 mL) and dried over $MgSO_4$. After filtration, removal of the solvent yielded the azido alcohol (~93%–96% yield) as a practically pure yellow oil, which was concentrated and used in the next step without further purification. ^{1}H NMR (benzene-d_6) δ: 0.72–1.12 (m, 4H), 1.20–1.34 (m, 2H), 1.59 (m, 1H), 1.74 (m, 1H), 2.23 (s, 1H), 2.79 (m, 1H), 3.10 (m, 1H). ^{13}C NMR (benzene-d_6) δ: 24.7, 25.0, 30.7, 34.2, 67.7, 74.3.

Triphenylphosphine (77.2 g, 294 mmol) was added within 30 min to a solution of azidocyclohexanol (41.7 g, 294 mmol) in THF (250 mL) while N_2 evolved from the reaction mixture. The reaction mixture was then refluxed for 16 to 17 h. Pentane (~1 L) was added to precipitate $Ph_3P{=}O$, and the white precipitate was filtered off and the solvent was removed on a rotary evaporator (water bath 30–45 °C). The THF was distilled off at 25 mmHg (1 mmHg = 133.322 4 Pa), and the residue was again distilled at 45 °C (oil bath temperature) under vacuum (1 mmHg), collecting aziridine in the receiving flask, which was placed in a dry ice – acetone bath. 7-Azabicyclo[4.1.0]heptane (20 g, 70% yield) was obtained as a colorless oil, which solidified upon cooling at –5 °C. Storage: over KOH; bp 50 °C / 1 mmHg. ^{1}H NMR ($CDCl_3$) δ: 1.19–1.37 (m, 6H), 1.81 (m, 6H), 2.17 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 20.0, 24.5, 29.3.

***trans*-2-(3,5-Dimethyl-pyrazole-1-yl)cyclohexylamine (1)**

$NH_2NH_2 \cdot H_2O$ (490 μL, 10 mmol) was added to the 1 mol% solution of NH_4Cl in 2 mL of H_2O and 1 mL (10 mmol) of aziridine. The reaction was stirred at room temperature for several hours (24 h) and turned from a white suspension to the colorless solution. Upon completion, the reaction mixture was treated with 25–50 mL of benzene, concentrated, and dried under high vacuum. *trans*-2-Hydrazinocyclohexylamine was obtained as a colorless oil and was used without further purification in the next step. ^{1}H NMR (DMSO-d_6) δ: 1.14 (m, 4H), 1.60 (s, 2H), 1.73 (m, 1H), 1.83 (m, 2H), 2.29 (dt, J = 4.2, 10.5 Hz, 1H), 2.65 (dt, J = 4.2, 10.5 Hz, 1H), 3.56 (m, 1H). ^{13}C NMR (DMSO-d_6) δ: 24.5, 29.1, 31.6, 53.4, 63.2, 67.5.

The crude *trans*-2-hydrazinocyclohexylamine was suspended in 20 mL of ethanol and at 0 °C, 1 mL (12 mmol) of 2,4-pentadione was added dropwise and the reaction was stirred for another 30 min and then concentrated. The residue was washed with 5 mL of 30% KOH, and the water layer was extracted with EtOAc (3 × 25 mL), which was washed with brine, dried over Na_2SO_4, concentrated, and dried under the high vacuum. The product can be further purified by Kugelrohr distillation. *trans*-2-(3,5-Dimethylpyrazol-1-yl)cyclohexylamine (1.25 g, 65% yield) was obtained as a beige solid; mp 120 °C / 1 mmHg. ^{1}H NMR ($CDCl_3$) δ: 1.25–1.46 (m, 4H), 1.60–2.05 (m, 6H), 2.23 (s, 3H), 2.25 (s, 3H), 3.40 (dt, J = 5.2, 10.8 Hz, 1H), 3.59 (dt, J = 5.2, 10.8 Hz, 1H), 5.77 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 11.3, 13.8, 24.8, 25.6, 32.2, 34.6, 53.8, 64.5, 104.6, 139.5, 147.8.

***trans*-2-(5-Phenyltetrazol-2-yl)cyclohexylamine (2)**

Aziridine (1.75 mL, 17 mmol) was added to the reaction mixture containing Bu_4NBF_4 (570 mg, 1.7 mmol) and 2.5 g (17 mmol) of tetrazole in 34 mL of buffered H_2O (AcONa–AcOH, pH 5) / ether mixture (1:1). The reaction was stirred for 5 to 6 h. Completion of the reaction was confirmed by TLC (hexane–EtOAc, 8:2). The reaction was quenched with 5% NaOH and extracted with EtOAc. Combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography on silica gel (hexane–EtOAc, 6:4 with 3 vol% of Et_3N). *trans*-2-(5-Phenyltetrazol-2-yl)cyclohexylamine (2.96 g, 70% yield) was obtained as a white solid; mp 70–72 °C. ^{1}H NMR ($CDCl_3$) δ: 1.35–1.54 (m, 4H), 1.85–2.24 (m, 4H), 3.37 (dt, J = 4.5, 11.1 Hz, 1H), 4.47 (m, 1H), 7.43–8.15 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 25.0, 25.3, 32.5, 35.0, 54.1, 71.5, 126.8, 127.6, 128.9, 130.2, 164.8.

Resolution of *trans*-2-(3,5-dimethylpyrazol-1-yl)cyclohexylamine (1) with D-(+)-dibenzoyl tartaric acid

D-(+)-Dibenzoyltartaric acid (1.5 equiv.) was added to the

solution of amine in a minimum amount of CH_2Cl_2–MeOH (9:1). The reaction was heated to dissolve the acid and then cooled to room temperature. The precipitate was filtered off and recrystallized from CH_2Cl_2–MeOH. ^{1}H NMR (DMSO-d_6) δ: 1.29–1.80 (m, 8H), 2.10 (s, 3H), 2.18 (s, 3H), 2.59 (s, 4H), 3.58 (dt, J = 4.5, 10.2 Hz, 1H), 4.97 (dt, J = 4.5, 10.2 Hz, 1H), 5.73 (s, 1H), 7.49–8.00 (m, 10H).

The precipitate was hydrolyzed with KOH, and extracted with EtOAc, dried over Na_2SO_4, and concentrated to give 184 g (48% yield) of one of the enantiomers of *trans*-2-(3,5-dimethylpyrazol-1-yl)cyclohexylamine obtained as a white solid, with 99.9% ee determined from the ^{19}F NMR of the Mosher amide (–69.55 ppm signal).

General procedure for the resolution of *trans*-2-(5-phenyltetrazol-2-yl)cyclohexylamine (2)

Racemic *trans*-2-(5-phenyltetrazol-2-yl)cyclohexylamine (4.23 g, 17.4 mmol) was dissolved in 50 mL of 95% EtOH and reacted with 0.7 equiv. (12.2 mmol) of resolving acid. In the case of mandelic acid, the precipitate was dissolved in an additional 200 mL of ethanol. The hot, clear solution was then cooled down to room temperature and a crystalline precipitate was filtered off and recrystallized from ethanol. The precipitate was hydrolyzed with KOH and the water layer was extracted with EtOAc (3 × 50 mL), dried over Na_2SO_4, and concentrated.

(*R*)-(*R*)-*trans*-2-(5-Phenyltetrazol-2-yl)cyclohexylamine (2)

(*R*)-(*R*)-*trans*-2-(5-phenyltetrazol-2-yl)cyclohexylamine (490 mg, 70% yield) was obtained through the formation of a diastereomeric salt with (*S*)-(+)-mandelic acid, followed by hydrolysis. (*R*)-(*R*)-*trans*-2-(5-Phenyltetrazol-2-yl)cyclohexylamine was isolated as a white solid with 99.9% ee, determined from the ^{19}F NMR of the Mosher amide (–69.82 ppm). Absolute stereochemistry of the amine was determined from the X-ray analysis (see Supplementary notes)[4] of the diastereomeric salt with (*S*)-(+)-mandelic acid. A sample for X-ray analysis was obtained after recrystallization from ethanol; mp 204–205.5 °C. ^{1}H NMR (DMSO-d_6) δ: 1.42 (m, 2H), 1.68–2.20 (m, 5H), 3.39 (m, 1H), 4.70 (s, 1H), 4.81 (dt, J = 4.2, 11.7 Hz, 1H), 5.20 (br s, 1H), 7.18–8.08 (m, 10H). ^{13}C NMR (DMSO-d_6) δ: 23.7, 24.0, 31.9 (d, J = 78.9 Hz), 52.9, 67.0, 72.8, 126.0, 126.1, 126.4, 126.9, 127.3, 128.9, 130.1, 141.8, 163.5, 173.9.

(*S*)-(*S*)-*trans*-2-(5-Phenyltetrazol-2-yl)cyclohexylamine (2)

(*S*)-(*S*)-*trans*-2-(5-Phenyltetrazol-2-yl)cyclohexylamine (455 mg, 65% yield) was obtained through the formation of a diastereomeric salt with (*S*)-(+)-10-camphorsulfonic acid, followed by hydrolysis. (*S*)-(*S*)-*trans*-2-(5-Phenyltetrazol-2-yl)cyclohexylamine was isolated as a white solid with 99.9% ee, determined from the ^{19}F NMR of the Mosher amide (–70.07 ppm); mp 194 °C. ^{1}H NMR (DMSO-d_6) δ: 0.73 (s, 3H), 1.03 (s, 3H), 1.26 (m, 1H), 1.40–2.30 (m, 9H), 2.38 (d, J = 15 Hz, 1H), 2.66 (m, 1H), 2.88 (d, J = 15 Hz, 1H), 3.38 (s, 3H), 3.69 (m, 1H), 5.04 (dt, J = 3.9, 11.4 Hz, 1H), 7.57 (m, 2H), 8.08 (m, 3H). ^{13}C NMR (DMSO-d_6) δ: 19.6, 20.2, 22.9, 23.6, 24.1, 26.4, 29.5, 31.5, 42.2 (d, J = 44.4 Hz), 46.7, 47.1, 52.4, 58.2, 64.3, 126.5, 127.1, 129.3, 130.7, 164.4, 216.4.

General procedure for Mosher amide synthesis (17)

Oxalyl chloride (5 μL, 0.057 mmol) was added to a stock solution of (*R*)-(+)-MTPA (2.8 mg, 0.012 mmol) in DMF (0.95 μL, 0.012 mmol) / hexane (0.5 mL) at room temperature. A white precipitate formed immediately with evolution of gas. After 1 h, the mixture was filtered and concentrated in vacuo. A solution of amine (0.01 mmol), Et_3N (4 μL, 0.03 mmol), and DMAP (small crystals, ~1 mg) in $CDCl_3$ (100 μL) was added to the residue. After 1 h, ^{1}H NMR and ^{19}F NMR of the mixture revealed the conversion into the diastereomeric Mosher amide. *N*-[*trans*-2-(3,5-Dimethylpyrazol-1-yl)-cyclohexyl]-3,3,3-trifluoro-2-methoxy-2-phenylpropionamide: ^{19}F NMR ($CDCl_3$, ppm) δ: –65.5 or –69.5. 3,3,3-Trifluoro-2-methoxy-2-phenyl-*N*-[*trans*-2-(5-phenyltetrazol-2-yl)cyclohexyl]propionamide: ^{19}F NMR ($CDCl_3$, ppm) δ: –69.8 or –70.1.

General procedure for imine synthesis (18)

A solution of the amine (1 or 2 equiv. in case **4b**) and the appropriate aromatic aldehyde (1–1.2 equiv.) in EtOH (0.1 mol/L reaction mixture) was refluxed for 2 to 3 h. The solvent was removed and pentane was added to the resulting oil. If the imine does not crystallize after 24 h at –25 °C, it can be purified by column chromatography on silica gel (eluent: hexane–EtOAc, 6:4 with 5 vol% of Et_3N) followed by crystallization from pentane or hexane.

2,4-Di-(*tert*-butyl-6-{[*trans*-2-(3,5-dimethylpyrazol-1-yl)cyclohexylimino]methyl}phenol (3a)

2,4-Di-(*tert*-butyl-6-{[*trans*-2-(3,5-dimethylpyrazol-1-yl)cyclohexylimino]methyl}phenol (36.5 mg, 77% yield) was obtained as a yellow solid after recrystallization from pentane. ^{1}H NMR ($CDCl_3$) δ: 1.26 (s, 9H), 1.41 (s, 9H), 1.46–2.24 (m, 8H), 2.09 (s, 3H), 2.19 (s, 3H), 3.67 (dt, J = 4.5, 10.8 Hz, 1H), 3.97 (m, 1H), 5.53 (s, 1H), 6.80 (d, J = 2.7 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 7.76 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 11.3, 14.1, 24.5, 25.8, 29.8, 31.7, 31.8, 34.4, 35.3, 61.2, 72.1, 100.1, 104.4, 117.9, 126.0, 126.7, 136.3, 139.7, 147.3, 157.8, 163.0, 166.0.

2-{[*trans*-2-(3,5-Dimethylpyrazol-1-yl)cyclohexylimino]-methyl}phenol (3b)

2-{[*trans*-2-(3,5-Dimethylpyrazol-1-yl)cyclohexylimino]-methyl}phenol (2.65 g, 89% yield) was obtained as an orange solid. ^{1}H NMR ($CDCl_3$) δ: 1.40–2.00 (m, 8H), 2.07 (s, 3H), 2.20 (s, 3H), 3.95 (dt, J = 4.2, 9.9 Hz, 1H), 3.70 (m, 1H), 5.56 (s, 1H), 6.79–7.26 (m, 4H), 7.71 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 11.1, 13.8, 24.2, 25.5, 31.4, 33.8, 60.9, 72.1, 104.4, 117.0, 118.7, 118.9, 131.6, 132.3, 140.0, 147.7, 161.1, 165.4.

[4] Supplementary data for this article are available on the Web site or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0S2, Canada. DUD 4003. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml. CCDC 271471 contains the crystallographic data for this manuscript. These data can be obtained, free of charge, via www.ccdc.cam.ac.uk/conts/retrieving.html (Or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Benzylidene[*trans*-2-(3,5-dimethylpyrazol-1-yl)cyclohexyl]amide (3c)

Benzylidene[2-(3,5-dimethylpyrazol-1-yl)cyclohexyl]amide (1.69 g, 75% yield) was obtained as a yellow solid (purified by column chromatography and then recrystallized from pentane); mp 89 °C. ^{1}H NMR ($CDCl_3$) δ: 1.10–2.25 (m, 8H), 2.11 (s, 3H), 2.18 (s, 3H), 3.61 (dt, *J* = 4.5, 10.5 Hz, 1H), 4.02 (m, 1H), 5.50 (s, 1H), 7.32–7.50 (m, 5H), 7.64 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 11.5, 14.1, 24.5, 25.8, 31.4, 33.9, 60.9, 74.1, 103.9, 127.9, 128.4, 130.4, 136.4, 139.8, 147.0, 161.00.

[*trans*-2-(3,5-Dimethylpyrazol-1-yl)cyclohexyl]-(2-fluorobenzylidene)amine (3d)

[2-(3.5-Dimethylpyrazol-1-yl)cyclohexyl]-(2-fluorobenzylidene)amine (21 mg, 70% yield) was obtained as a beige solid; mp 74 °C. ^{1}H NMR ($CDCl_3$) δ: 1.40–2.40 (m, 8H), 2.16 (s, 3H), 2.21 (s, 3H), 3.70 (dt, *J* = 4.2, 10.5 Hz, 1H), 4.07 (m, 1H), 5.56 (s, 1H), 6.98–7.82 (m, 4H), 8.05 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 11.3, 13.8, 24.2, 25.6, 31.2, 33.7, 60.8, 74.4, 104.0, 115.9 (d, *J* = 84.3 Hz), 124.0, 124.3, 127.5, 132.1 (d, *J* = 34 Hz), 139.9, 147.5, 154.8, 164.0. ^{19}F NMR ($CDCl_3$) δ: –122.1 (dq, *J* = 5.7, 7.5 Hz).

(*S*)-(*S*)-2,4-Di-*tert*-butyl-6-{[*trans*-2-(5-phenyltetrazol-2-yl)cyclohexylimino]methyl}phenol (4a)

(*S*)-(*S*)-2,4-Di-*tert*-butyl-6-{[*trans*-2-(5-phenyltetrazol-2-yl)cyclohexylimino]methyl}phenol (210 mg, 95% yield) was obtained as a yellow solid after recrystallization from pentane. ^{1}H NMR ($CDCl_3$) δ: 1.18 (s, 9H), 1.28 (s, 9H), 1.48–2.34 (m, 8H), 3.91 (dt, *J* = 4.8, 10.8 Hz, 1H), 5.01 (m, 1H), 6.87 (d, *J* = 2.4 Hz, 1H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.7.43–8.01 (m, 5H), 8.15 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 24.1, 24.8, 29.5, 29.6, 31.5, 31.6, 31.1, 34.2, 35.2, 68.0, 71.1, 117.7, 126.3, 127.1, 127.5, 129.0, 130.3, 136.8, 140.3, 158.0, 164.8, 166.9.

(*S*)-(*S*)-[2,6-Di-*trans*-(5-phenyltetrazol-2-yl)cyclohexyl]pyridin-2-yl methyleneamine (4b)

(*S*)-(*S*)-[2,6-Di-*trans*-(5-phenyltetrazol-2-yl)cyclohexyl]pyridin-2-yl methyleneamine (142 mg, 97% yield) was obtained as a beige solid after recrystallization from pentane. ^{1}H NMR ($CDCl_3$) δ: 1.50–2.30 (m, 8H), 3.92 (dt, *J* = 5.1, 9.9 Hz, 1H), 5.07 (m, 1H), 7.40 (m, 3H), 7.55 (t, *J* = 7.8 Hz, 0.5H), 7.77 (d, *J* = 7.8 Hz, 1H), 8.02 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 24.1, 25.1, 32.0, 33.7, 67.9, 72.2, 122.5, 126.8, 127.7, 128.7, 130.0, 136.8, 153.5, 162.2, 164.6.

(*S*)-(*S*)-[*trans*-2-(5-Phenyltetrazol-2-yl)cycloexyl]pyridin-2-yl methyleneamine (4c)

(*S*)-(*S*)-[*trans*-2-(5-Phenyltetrazol-2-yl)cyclohexyl]pyridin-2-yl methyleneamine (123 mg, 93% yield) was obtained as a pale brown solid. ^{1}H NMR ($CDCl_3$) δ: 1.50–2.30 (m, 8H), 4.00 (dt, *J* = 4.8, 10.2 Hz, 1H), 5.12 (m, 1H), 7.17–8.50 (m, 7H), 8.15 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 24.1, 25.0, 32.0, 33.6, 67.8, 72.1, 121.5, 124.8, 126.7, 127.5, 128.7, 130.0, 136.4, 149.1, 153.8, 162.4, 164.5.

5-Phenyl-2-((*R*)-(*R*)-*trans*-2-pyridin-1-ylcyclohexyl)-2*H*-tetrazole (5)

trans-2-(3,5-Dimethylpyrazol-1-yl)cyclohexylamine (100 mg, 0.411 mmol) 1,4-dibromobutane (54 μL, 0.452 mmol, 1.1 equiv.), and 68 mg (0.822 mmol, 2 equiv.) of $NaHCO_3$ in toluene (1 to 2 mL) were refluxed under N_2 with good stirring and Dean–Stark removal of water for 19–24 h (controlled by TLC). The reaction mixture was concentrated and purified by column chromatography (hexane with 5 vol% of Et_3N, then hexane–EtOAc, 6:4 with 5 vol% of Et_3N). 5-Phenyl-2-(*trans*-2-pyridin-1-ylcyclohexyl)-2*H*-tetrazole (230 mg, 77% yield) was obtained as a brown solid. ^{1}H NMR (CD_2Cl_2) δ: 1.30–2.10 (m, 6H), 1.92 (br s, 2H), 2.18 (br s, 2H), 2.39 (br s, 2H), 2.69 (br s, 2H), 3.36 (br s, 1H), 4.85 (br s, 1H), 7.40–8.20 (m, 5H). ^{13}C NMR (CD_2Cl_2) δ: 23.9, 24.8, 25.1, 25.3, 31.1, 31.8, 32.9, 47.7, 62.2, 66.1, 127.0, 128.2, 129.0, 130.1, 164.4.

General procedure for ^{1}H NMR studies

The ligand (0.02 mmol) in CD_2Cl_2 was mixed at room temperature with 0.02 mmol of $CuOTf{\cdot}0.5C_6H_6$, stirred at room temperature for 1 h, and filtered. In the case of **4b**, upon mixing in an 1:1 ratio (Cu^I/L), part of the metal complex did not dissolve. A sample of 1:2 ratio (Cu^I/L) was prepared, which showed the same ^{1}H NMR spectra as the first sample.

Cu^I coordination to 3d

^{1}H NMR (CD_2Cl_2) δ: 1.44–1.61 (m, 2H), 1.85–2.60 (m, 6H), 2.12 (s, 3H), 2.34 (s, 3H), 3.90 (br s, 1H), 4.45 (br s, 1H), 5.87 (s, 1H), 7.03–7.79 (m, 4H), 8.25 (s, 1H). ^{19}F NMR (CD_2Cl_2) δ: –122.1 (dq, *J* = 5.7, 7.5 Hz).

Cu^I coordination to 4b

The NMR sample gave red crystals of complex **1.23** after storage at room temperature for several days in an inert atmosphere upon slow addition of hexane. These sample crystals were further characterized by X-ray analysis. ^{1}H NMR (CD_2Cl_2) δ: 1.26–2.23 (m, 8H), 3.95 (br s, 1H), 5.11 (br s, 1H), 7.52 (br s, 3H), 7.85 (m, 1H), 8.01 (t, *J* = 8 Hz, 0.5H), 8.10 (m, 2H).

Cu^I coordination to 5

^{1}H NMR (CD_2Cl_2) δ: 1.50 (m, 2H), 1.86–2.20 (m, 8H), 2.39 (m, 2H), 2.78 (br s, 1H), 3.04 (br s, 1H), 3.77 (m, 1H), 4.00 (m, 1H), 5.39 (m, *J* = 4.4, 10.8 Hz, 1H), 7.50 (m, 3H), 8.17 (d, *J* = 7.2 Hz, 2H), 9.09 (br s, 1H).

General procedure for cyclopropanation

A flame-dried Schlenk flask was charged with metal precursor (2 mol%, 0.007 mol/L stock solution in CH_2Cl_2), ligand (4 mol%, 0.1 mol/L stock solution in CH_2Cl_2), and styrene (5 equiv.) and the reaction was stirred under an inert atmosphere at room temperature in approximately 1 mL of CH_2Cl_2. A solution of 1 mL (1 equiv., 1 mmol) of $N_2CHCOOMe$ in dichloromethane (1 mL) was added gradually over 8–10 h via a syringe pump and the reaction mixture was stirred for another 10–12 h. The reaction was concentrated and the product was purified by column chromatography (hexane, then hexane–EtOAc (8:2)).

2-Phenylcyclopropanecarboxylic acid methyl ester (7)

2-Phenylcyclopropanecarboxylic acid methyl ester was obtained as a colorless oil. Yield with $[RuCl_2C_6H_6]_2$ was

found to be 66% with a trans:cis ratio of 71:29 determined from ^{1}H NMR. Yield with CuOTf·0.5C_6H_6 was found to be 86% with a trans:cis ratio of 93:7 determined from ^{1}H NMR. **a**: ^{1}H NMR ($CDCl_3$) δ: 1.32 (m, 1H), 1.60 (m, 1H), 1.90 (m, 1H), 2.43 (m, 1H), 3.72 (s, 3H), 7.09–7.31 (m, 5H). **b**: ^{1}H NMR ($CDCl_3$) δ: 0.88 (m, 1H), 1.70 (m, 1H), 2.10 (m, 1H), 2.57 (m, 1H), 3.45 (s, 3H), 7.09–7.31 (m, 5H)

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