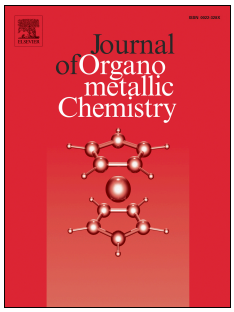

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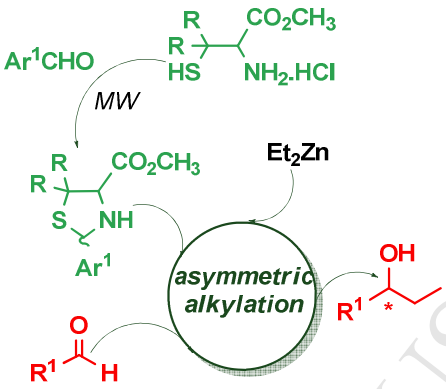

Chiral Thiazolidines in the Enantioselective Ethylation of Aldehydes: An Experimental and Computational Study

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Abstract

A library of new chiral thiazolidines was prepared starting from L-cysteine and D-penicillamine in a simple, short synthetic sequence. 2-Arylthiazolidines were obtained, as diastereoisomeric mixtures, with good yields and in short reaction times, through a new and greener procedure, using microwave irradiation. Their use as chiral ligands in the enantioselective ethylation of aromatic aldehydes was studied and optimized, originating good to excellent conversions and *ee* up to 94% in 6 hours. A series of heteroaromatic and aliphatic substrates were also enantioselectively ethylated with success, with *ee* up to 77%. The distinct opposite chirality in L-cysteine and D-penicillamine makes the use of these ligands an interesting approach for obtaining both the (*S*) and (*R*) enantiomers of the chiral alcohols, compounds with potential applications in the area of fine chemistry. NMR studies were carried out using a diastereoisomeric mixture of thiazolidines, allowing the identification of the most stable structure. Computational studies confirmed this result and also gave important insight into the species involved in the catalytic cycle of the enantioselective alkylation.

Keywords

Alkylation; asymmetric catalysis; microwave synthesis; thiazolidine; computational studies.

Introduction

One of the most crucial reactions in organic chemistry is the formation of carbon-carbon bonds. The alkylation of aldehydes to obtain secondary alcohols is included in this type of reaction. Synthetic approaches to develop the asymmetric version of this reaction have been improved over time, since the use of lithium organometallics in 1978 by Soai *et.al*.[1] Nowadays, the use of zinc organometallics, especially diethylzinc, is one of the most frequently used methods. The addition of diethylzinc to aldehydes in order to form chiral alcohols can only occur through ligand activation. When the ligand is chiral, the reaction allows the discrimination of the two enantiotopic faces of the aldehyde, thus leading to chiral secondary alcohols. These compounds, besides their presence in several naturally occurring molecules and liquid crystals, have a wide application in fine chemistry, integrating the composition of biologically active molecules such as drugs, perfumes, agrochemicals, pesticides, herbicides and pheromones. From the synthetic point of view, the hydroxyl group can be an excellent precursor of several other types of functional groups.[2–8] Several types of chiral ligands have successfully been

used in this reaction, namely aminoalcohols, diamines, diols and their derivatives, affording the chiral products with good enantiomeric excesses.[9–24] Also reported are the advantages of using molecules with rigid cyclic structures, as their presence allows the formation of a more hindered and rigid catalyst, that allows better discrimination of the two possible transition state structures.[25–30] Although there are many ligands capable of catalyzing this reaction, research focused on the development of new active, enantioselective, easily synthesized and economically viable catalysts continues.

From the condensation of the methyl esters of L-cysteine and D-penicillamine with carbonyl compounds, aldehydes or ketones, it is possible to obtain chiral thiazolidines.[31] These compounds were found to act as efficient catalysts in enantioselective alkylation reactions, providing good to excellent enantiomeric excesses.[32–35] In previous studies, we observed better results when using thiazolidines derived from D-penicillamine when compared to the L-cysteine analogs, possibly due to the more hindered C5 position, with two methyl groups.[36]

Continuing our previous studies, we undertook the synthesis of a series of new C2-aromatic substituted thiazolidines from L-cysteine and D-penicillamine. A new and greener protocol for the synthesis of the thiazolidines was developed, simpler than the usual conventional methods. The thiazolidines were tested as ligands in the enantioselective alkylation of aldehydes with diethylzinc. The effect of different aromatic groups at C2 was evaluated. Aromatic groups where the same substituent was located in the ortho, meta or para positions were used in order to evaluate the steric effect, while electron-donating and electron-withdrawing substituents were used to analyze the resulting electronic effect on the outcome of the reaction. Additionally, computational and NMR studies were carried out, allowing us to understand the relative stability of the thiazolidine diastereoisomers and the structures of some of the species involved in the catalytic cycle of the enantioselective alkylation with diethylzinc.

Experimental Section

General

Commercially available compounds were used without further purification. All solvents were dried prior to use following standard procedures. Diethylzinc (Aldrich) was used as a 1 M solution in hexane. Benzaldehyde was distilled prior to use and stored over 4 Å molecular sieves. Melting points were determined using a FALC melting point apparatus (open capillary method). Optical rotations were measured with an Optical Activity AA-5 polarimeter. NMR spectra were recorded at room temperature on a Bruker Avance III 400 MHz (100 MHz for ^{13}C). TMS was used as the internal standard and chemical shifts are given in ppm. Infrared spectra were recorded on an Agilent Technologies Cary 630 FTIR in the ATR mode. High-resolution mass spectra (HRMS) were obtained on a TOF VG Autospect M spectrometer with electrospray ionization (ESI). Elemental analyses were carried out on an Elementar Vario Micro Cube analyser. Microwave reactions were carried out in a CEM Discover S-Class instrument.

Alkylation reactions were carried out in an inert atmosphere using standard Schlenk-type techniques. Enantiomeric excesses and conversions were determined using a chiral γ-cyclodextrin capillary column (FS-Lipodex-E, 25 m, 0.25 i.d.) from Machery-Nagel, on an Agilant 7820 instrument, using hydrogen as carrier gas. The configuration of the major enantiomers was determined by comparison of the retention times with reported values and by determining the sign of the specific rotation of the isolated products.[37–42]

General procedure for the synthesis of thiazolidines 3 and 4

In a microwave reaction tube L-cysteine methyl ester hydrochloride **1** or D-penicillamine methyl ester hydrochloride **2** (5.00 mmol, 0.858 g or 0.998 g, respectively), were dissolved in distilled water (5 mL). To this solution, triethylamine (5.00 mmol, 0.69 mL) and the aldehyde (5.00 mmol) were added. The reaction mixture was subjected to microwave irradiation, using a temperature control program (100 □C) for 15 minutes. Subsequently, upon cooling, water was added to the reaction mixture, followed by extraction with dichloromethane (3 times). The organic phases were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting mixture was purified as described below.

*(4R)-Methyl 2-(2-methoxyphenyl)-1,3-thiazolidine-4-carboxylate (**3a**)* and *(4S)-Methyl 2-(2-methoxyphenyl)-5,5-dimethyl-1,3-thiazolidine-4-carboxylate (**4a**)* were prepared in 85% and 83% yield, respectively, using microwave irradiation and spectroscopic data are in agreement with those previously described.[36]

*(4R)-Methyl 2-(3-methoxyphenyl)-1,3-thiazolidine-4-carboxylate (**3b**).* The product was purified by silica gel column chromatography using ethyl acetate:hexane (1:3) as eluent to give a pale yellow oil. Yield: 71%. $[\alpha]_D^{20}$= -92.7 (*c* 1.03, CH_2Cl_2). IR (ATR, cm^{-1}): 3313, 2951, 2836, 1735, 1598, 1584, 1488, 1433, 1258, 1202, 1153, 1037, 781, 757, 697. ^{1}H NMR ($CDCl_3$): (mixture of diastereoisomers) δ= 2.67/2.84 (two bs, 1H), 3.10/3.18 (two dd, *J* = 9.0, 10.3 Hz / *J* = 5.8, 10.7 Hz, 1H), 3.38/3.45 (two dd, *J* = 7.2, 10.7 Hz / *J* = 7.2, 10.3 Hz, 1H), 3.78/3.80/3.81 (three s, 6H), 3.97/4.21 (two aprox. t, *J* = 7.8 Hz / *J* = 6.4 Hz, 1H), 5.53/5.79 (two s, 1H), 6.79-6.81/6.85-6.88 (two m, 1H), 7.04 – 7.11 (m, 2H), 7.22 – 7.30 (m, 1H). ^{13}C NMR: δ= 38.0, 39.0, 52.4, 52.4, 55.1, 55.2, 64.2, 65.4, 70.6, 72.4, 112.3, 112.9, 113.3, 114.1, 119.1, 119.6, 129.3, 129.6, 139.7, 142.8, 159.6, 159.7, 171.5, 172.1. HRMS (ESI): calcd for $C_{12}H_{15}NO_3S$ $[M+H]^+$ 254.0845; found $[M+H]^+$ 254.0853.

*(4R)-Methyl 2-(4-methoxyphenyl)-1,3-thiazolidine-4-carboxylate (**3c**).* The product was purified by silica gel column chromatography using ethyl acetate:hexane (1:3) as eluent to give a pale yellow oil. Yield: 68%. $[\alpha]_D^{20}$= -95.0 (*c* 1.00, CH_2Cl_2). IR (ATR, cm^{-1}): 3306, 2951, 2837, 1735, 1610, 1509, 1437, 1243, 1172, 1159, 1029, 808, 767. ^{1}H NMR ($CDCl_3$): (mixture of diastereoisomers) δ= 2.60/2.75 (two bs, 1H), 3.10/3.22 (two dd, *J* = 9.0, 10.2 Hz / *J* = 5.6, 10.8 Hz, 1H), 3.39/3.45 (two dd, *J* = 7.2, 10.8 Hz / *J* = 7.0, 10.2 Hz, 1H), 3.78/3.79/3.80/3.80 (four s, 6H), 3.96-3.98/4.23 (m / aprox. t, *J* = 6.4 Hz, 1H), 5.52/5.76 (d, *J*= 7.2 Hz / s, 1H), 6.83 – 6.91

(m, 2H), 7.39 – 7.46 (m, 2H). ^{13}C NMR: δ= 38.1, 39.3, 52.6, 52.6, 55.3, 55.3, 64.3, 65.5, 70.6, 72.3, 113.8, 114.0, 128.3, 128.7, 130.1, 132.9, 159.3, 159.9, 171.7, 172.3. HRMS (ESI): calcd for $C_{12}H_{15}NO_3S$ $[M+H]^+$ 254.0845; found $[M+H]^+$ 254.0850.

*(4R)-Methyl 2-(2-chlorophenyl)-1,3-thiazolidine-4-carboxylate (**3d**).* The product was purified by silica gel column chromatography using ethyl acetate:hexane (1:3) as eluent to give a pale yellow oil. Yield: 71%. $[\alpha]_D^{20}$= -150.8 (*c* 1.00, CH_2Cl_2). IR (ATR, cm^{-1}): 3327, 2951, 1735, 1437, 1320, 1265, 1225, 1201, 1173, 1158, 1034, 823, 743. ^{1}H NMR ($CDCl_3$): (mixture of diastereoisomers) δ= 3.07-3.14 (m, 1H), 3.34/3.47 (two dd, *J*= 6.6, 10.6 Hz / *J*= 6.8, 10.4 Hz, 1H), 3.81/3.82 (two s, 3H), 3.98-4.05/4.24-4.25 (two m, 1H), 5.95/6.09 (d, *J*= 12.0 Hz / bs, 1H), 7.17-7.40 (m, 4H), 7.57/7.72 (two dd, *J*= 1.6, 8.0 Hz / *J*= 2.0, 7.6 Hz, 1H). ^{13}C NMR: δ= 37.3, 38.7, 52.4, 52.5, 64.8, 65.3, 67.1, 68.1, 126.4, 126.7, 127.2, 128.1, 128.4, 129.5, 129.7, 132.8, 133.5, 135.8, 140.0, 171.4, 171.9. HRMS (ESI): calcd for $C_{11}H_{12}ClNO_2S$ $[M+H]^+$ 258.0350; found $[M+H]^+$ 258.0359.

*(4R)-Methyl 2-(3-chlorophenyl)-1,3-thiazolidine-4-carboxylate (**3e**).* The product was purified by silica gel column chromatography using ethyl acetate:hexane (1:3) as eluent to give a pale yellow oil. Yield: 81%. $[\alpha]_D^{20}$= -151.2 (*c* 1.03, CH_2Cl_2). IR (ATR, cm^{-1}): 3308, 2951, 1735, 1595, 1571, 1434, 1226, 1200, 1176, 1158, 1076, 783, 693. ^{1}H NMR ($CDCl_3$): (mixture of diastereoisomers) δ= 2.62/2.91 (two bs, 1H), 3.09-3.18 (m, 1H), 3.38/3.46 (two dd, *J*= 7.0, 10.6 Hz / *J*= 6.8, 10.4 Hz, 1H), 3.80/3.81 (two s, 3H), 3.96-4.00/4.11-4.15 (two m, 1H), 5.51/5.79 (two s, 1H), 7.24-7.41 (m, 3H), 7.50-7.54 (m, 1H). ^{13}C NMR: δ= 38.1, 39.2, 52.6, 52.7, 64.2, 65.5, 69.8, 71.7, 125.2, 125.8, 127.0, 127.7, 127.9, 128.9, 129.7, 130.0, 134.3, 134.6, 140.3, 143.8, 171.4, 172.1. HRMS (ESI): calcd for $C_{11}H_{12}ClNO_2S$ $[M+H]^+$ 258.0350; found $[M+H]^+$ 258.0356.

*(4R)-Methyl 2-(4-chlorophenyl)-1,3-thiazolidine-4-carboxylate (**3f**).* The product was purified by silica gel column chromatography using ethyl acetate:hexane (1:3) as eluent to give a white solid, after recrystallization from a mixture of diethyl ether and hexane. Yield: 78%. mp: 50-51 □C. $[\alpha]_D^{20}$= -126.8 (*c* 1.03, CH_2Cl_2). IR (ATR, cm^{-1}): 3306, 2952, 1735, 1488, 1434, 1202, 1157, 1088, 1013, 795, 729. ^{1}H NMR ($CDCl_3$): (mixture of diastereoisomers) δ= 3.11/3.17 (two dd, *J*= 9.1, 10.4 Hz / *J*= 6.0, 10.7 Hz, 1H), 3.38/3.46 (two dd, *J*= 7.0, 10.7 Hz / *J*= 7.1, 10.4 Hz, 1H), 3.79/3.81 (two s, 3H), 3.98/4.15 (dd, *J*= 7.1, 9.1 Hz / aprox. t, *J*= 6.6 Hz, 1H), 5.52/5.78 (two s, 1H), 7.27-7.35 (m, 2H), 7.41-7.48 (m, 2H). ^{13}C NMR: δ= 38.1, 39.2, 52.7, 64.2, 65.5, 69.9, 71.8, 128.4, 128.5, 128.8, 128.9, 133.6, 134.5, 136.8, 140.0, 171.5, 172.1. HRMS (ESI): calcd for $C_{11}H_{12}ClNO_2S$ $[M+H]^+$ 258.0350; found $[M+H]^+$ 258. 0356.

*(4R)-Methyl 2-(2-methylphenyl)-1,3-thiazolidine-4-carboxylate (**3g**).* The product was purified by silica gel column chromatography using ethyl acetate:hexane (1:3) as eluent to give a pale yellow oil. Yield: 68%. $[\alpha]_D^{20}$= -127.6 (*c* 0.98, CH_2Cl_2). IR (ATR, cm^{-1}): 3309, 2951, 1735, 1457, 1433, 1319, 1268, 1198, 1157, 827, 754, 725. ^{1}H NMR ($CDCl_3$): (mixture of diastereoisomers) δ= 2.41/2.43 (two s, 3H), 2.70 (bs, 1H), 3.11/3.22 (two dd, *J*= 9.0, 10.2 Hz / *J*= 5.8, 10.8 Hz, 1H), 3.41/3.47 (two dd, *J*= 7.0, 10.8 Hz / *J*= 7.0, 10.2 Hz, 1H), 3.81/3.81 (two s, 3H), 3.99/4.33

(aprox. t, *J*= 8.0 Hz / dd, *J*= 5.8, 7.0 Hz, 1H), 5.76/5.95 (two s, 1H), 7.16-7.27 (m, 3H), 7.55-7.57/7.66-7.68 (two m, 1H). ^{13}C NMR: δ= 14.2, 19.4, 19.5, 21.0, 37.8, 39.1, 64.6, 65.5, 68.0, 69.3, 126.1, 126.2, 126.3 126.5, 127.7, 128.4, 130.5, 130.6, 135.8, 136.1, 136.5, 139.0, 171.7, 172.4. HRMS (ESI): calcd for $C_{12}H_{15}NO_2S$ $[M+H]^+$ 238.0896; found $[M+H]^+$ 238.0891.

*(4R)-Methyl 2-(3-methylphenyl)-1,3-thiazolidine-4-carboxylate (**3h**).* The product was purified by silica gel column chromatography using ethyl acetate:hexane (1:3) as eluent to give a pale yellow oil. Yield: 79%. $[\alpha]_D^{20}$= -120.0 (*c* 1.00, CH_2Cl_2). IR (ATR, cm^{-1}): 3305, 2951, 1735, 1434, 1201, 1158, 827, 785, 759, 703. ^{1}H NMR ($CDCl_3$): (mixture of diastereoisomers) δ= 2.34/2.36 (two s, 3H), 2.71 (bs, 1H), 3.10/3.21 (two dd, *J*= 9.0, 10.4 Hz / *J*= 5.9, 10.6 Hz, 1H), 3.39/3.46 (two dd, *J*= 6.9, 10.6 Hz / *J*= 7.2, 10.4 Hz, 1H), 3.79/3.80 (two s, 3H), 3.98/4.23 (two dd, *J*= 7.2, 9.0 Hz / *J*= 5.9, 6.9 Hz, 1H), 5.53/5.78 (two s, 1H), 7.07-7.15 (m, 1H), 7.19-7.33 (m, 3H). ^{13}C NMR: δ= 21.4, 21.4, 38.1, 39.2, 52.6, 52.6, 64.4, 65.6, 70.9, 72.6, 124.0, 124.5, 127.6, 128.0, 128.4, 128.6, 128.7, 129.5, 138.1, 138.2, 138.5, 141.0, 171.6, 172.2. HRMS (ESI): calcd for $C_{12}H_{15}NO_2S$ $[M+H]^+$ 238.0896; found $[M+H]^+$ 238.0891.

*(4R)-Methyl 2-(4-methylphenyl)-1,3-thiazolidine-4-carboxylate (**3i**).* The product was purified by silica gel column chromatography using ethyl acetate:hexane (1:3) as eluent to give a brown oil. Yield: 50%. $[\alpha]_D^{20}$= -97.4 (*c* 0.98, CH_2Cl_2). IR (ATR, cm^{-1}): 3308, 2950, 1735, 1434, 1201, 1176, 1158, 809, 766. ^{1}H NMR ($CDCl_3$): (mixture of diastereoisomers) δ= 2.33/2.35 (two s, 3H), 2.65/2.76 (two bs, 1H), 3.10/3.21 (two dd, *J*= 9.0, 10.2 Hz / *J*= 5.8, 10.7 Hz, 1H), 3.38/3.45 (two dd, *J*= 7.2, 10.7 Hz / *J*= 7.0, 10.2 Hz, 1H), 3.79/3.80 (two s, 3H), 3.97/4.23 (two aprox. t, *J*= 7.8 Hz / *J*= 6.4 Hz, 1H), 5.53/5.78 (two s, 1H), 7.13/7.17 (two d, *J*= 8.0 Hz / *J*= 8.2 Hz, 2H), 7.37/7.41 (two d, *J*= 8.0 Hz / *J*= 8.2 Hz, 2H). ^{13}C NMR: δ= 21.1, 21.2, 38.1, 39.3, 45.4, 52.5, 52.6, 64.3, 65.5, 70.8, 72.5, 126.9, 127.3, 129.1, 129.4, 135.2, 137.7, 138.0, 138.6, 171.7, 172.3. HRMS (ESI): calcd for $C_{12}H_{15}NO_2S$ $[M+H]^+$ 238.0896; found $[M+H]^+$ 238.0890.

*(4R)-Methyl 2-(1-naphthyl)-1,3-thiazolidine-4-carboxylate (**3j**).* The product was purified by silica gel column chromatography using ethyl acetate:hexane (1:3) as eluent to give a pale yellow solid, after recrystallization from a mixture of diethyl ether and hexane. Yield: 46%. mp: 86-87 □C. $[\alpha]_D^{20}$= -208.7 (*c* 1.03, CH_2Cl_2). IR (ATR, cm^{-1}): 3285, 3050, 1731, 1434, 1266, 1219, 1170, 1158, 772, 745, 708. ^{1}H NMR ($CDCl_3$): (mixture of diastereoisomers) δ= 3.13/3.22 (two dd, *J*= 9.2, 10.1 Hz / *J*= 6.2, 10.5 Hz, 1H), 3.41/3.53 (two dd, *J*= 6.8, 10.5 Hz / *J*= 7.0, 10.1 Hz, 1H), 3.81/3.84 (two s, 3H), 4.11-4.16/4.37 (m / aprox. t, *J*= 6.6 Hz, 1H), 6.30/6.50 (two s, 1H), 7.41-7.57 (m, 3H), 7.76-7.79 (m, 1H), 7.83-7.92 (m, 2H), 8.13/8.21 (two d, *J*= 8.4 Hz / *J*= 8.4 Hz, 1H). ^{13}C NMR: δ= 37.9, 38.8, 52.6, 64.8, 65.6, 67.9, 69.5, 122.5, 123.6, 123.6, 123.8, 125.2, 125.3, 125.8, 125.9, 126.3, 126.5, 128.5, 128.7, 128.8, 129.2, 130.9, 131.4, 133.7, 133.7, 133.9, 136.7, 171.7, 172.4. HRMS (ESI): calcd for $C_{15}H_{15}NO_2S$ $[M+H]^+$ 274.0896; found $[M+H]^+$ 274.0891.

*(4R)-Methyl 2-(2-naphthyl)-1,3-thiazolidine-4-carboxylate (**3k**).* The product was purified by silica gel column chromatography using ethyl acetate:hexane (1:3) as eluent to give a white solid, after recrystallization from a mixture of diethyl ether and hexane. Yield: 65%. mp: 89-90 □C. $[\alpha]_D^{20}$= -134.3 (*c* 1.01, CH_2Cl_2). IR (ATR, cm^{-1}): 3335, 2946, 1726, 1448, 1434, 1217, 1191, 1137, 824, 801, 756. ^{1}H NMR ($CDCl_3$): (mixture of diastereoisomers) δ= 3.17/3.24 (two dd, *J*= 8.9, 10.2 Hz / *J*= 6.0, 10.6 Hz, 1H), 3.43/3.51 (two dd, *J*= 7.2, 10.6 Hz / *J*= 7.1, 10.2 Hz, 1H), 3.82/3.82 (two s, 3H), 4.05/4.27 (dd, *J*= 7.1, 8.9 Hz / aprox. t, *J*= 6.6 Hz, 1H), 5.74/6.00 (two s, 1H), 7.45-7.51 (m, 2H), 7.57/7.62 (two dd, *J*= 1.8, 8.6 Hz / *J*= 1.8, 8.6 Hz, 1H), 7.80-7.87 (m, 3H), 7.95-7.98 (m, 1H). ^{13}C: δ= 38.2, 39.3, 52.6, 52.7, 64.4, 65.7, 70.9, 72.8, 125.0, 125.2, 125.4, 126.1, 126.3, 126.5, 126.6, 127.6, 127.7, 128.1, 128.4, 128.7, 133.0, 133.1, 133.1, 133.5, 135.4, 138.6, 171.6, 172.3. HRMS (ESI): calcd for $C_{15}H_{15}NO_2S$ $[M+H]^+$ 274.0896; found $[M+H]^+$ 274.0898.

*(4S)-Methyl 2-(3-methoxyphenyl)-5,5-dimethyl-1,3-thiazolidine-4-carboxylate (**4b**).* The product was purified by silica gel column chromatography using ethyl acetate:hexane (1:5) as eluent to give a white solid. Yield: 83%. mp: 63-64 □C. $[\alpha]_D^{20}$= +34.9 (*c* 2.01, CH_2Cl_2). IR (ATR, cm^{-1}): 3330, 2952, 1739, 1609, 1585, 1455, 1440, 1265, 1155, 1121, 1043, 766, 755. ^{1}H NMR ($CDCl_3$): (mixture of diastereoisomers) δ= 1.31/1.36 (two s, 3H), 1.62/1.72 (two s, 3H), 3.54 (bs, 1 H), 3.78-3.82 (m, 7H), 5.67/5.85 (two s, 1H), 6.77-6.79/6.86-6.87 (m/m, 1H), 7.07-7.12 (m, 2H), 7.21-7.30 (m, 1H). ^{13}C NMR: δ= 26.1, 27.0, 27.4, 28.1, 51.1, 54.2, 54.3, 58.6, 59.0, 67.2, 69.0, 71.9, 73.7, 111.1, 111.8, 112.2, 113.0, 117.9, 118.7, 128.4, 128.7, 139.3, 143.8, 158.6, 158.8, 168.6, 169.2. HRMS (ESI): calcd for $C_{14}H_{19}NO_3S$ $[M+H]^+$ 282.1158; found $[M+H]^+$ 282.1157.

*(4S)-Methyl 2-(4-methoxyphenyl)-5,5-dimethyl-1,3-thiazolidine-4-carboxylate (**4c**).* The product was purified by silica gel column chromatography using as eluents first chloroform and then a mixture of chloroform:methanol (10:1). A pale yellow oil was obtained. Yield: 83%. $[\alpha]_D^{20}$= +49.5 (*c* 1.01, CH_2Cl_2). IR (ATR, cm^{-1}): 3319, 2957, 2926, 1735, 1609, 1509, 1456, 1433, 1244, 1204, 1172, 1156, 1125, 1030, 829, 766. ^{1}H NMR ($CDCl_3$): (mixture of diastereoisomers) δ= 1.31/1.36 (two s, 3H), 1.63/1.71 (two s, 3H), 3.40 (bs, 1H), 3.77-3.78 (m, 4H), 3.79/3.80 (two s, 3H), 5.65/5.84 (two s, 1H), 6.84-6.90 (m, 2H), 7.41-7.46 (m, 2H). ^{13}C NMR: δ= 27.2, 28.4, 28.5, 29.2, 52.1, 52.1, 53.5, 55.3, 59.5, 59.9, 68.2 69.7, 72.8, 74.6, 113.7, 114.0, 127.9, 128.8, 130.6, 159.0, 159.8, 169.7, 170.3. HRMS (ESI): calcd for $C_{14}H_{19}NO_3S$ $[M+H]^+$ 282.1158; found $[M+H]^+$ 282.1157.

*(4S)-Methyl 2-(2-chlorophenyl)-5,5-dimethyl-1,3-thiazolidine-4-carboxylate (**4d**).* The product was purified by silica gel column chromatography using ethyl acetate:hexane (1:5) as eluent to give a white solid. Yield: 74%. mp: 51-52 □C. $[\alpha]_D^{20}$= +55.0 (*c* 1.00, CH_2Cl_2). IR (ATR, cm^{-1}): 3330, 2953, 1740, 1609, 1585, 1455, 1438, 1264, 1201, 1155, 1121, 1043, 765, 755. ^{1}H NMR ($CDCl_3$): (mixture of diastereoisomers) δ= 1.23/1.28 (two s, 3H), 1.51/1.65 (two s, 3H), 3.71/3.72

(two s, 3H), 3.74/3.85 (two s, 1H), 5.97/6.01 (two s, 1H), 7.07-7.30 (m, 3H), 7.58/7.68 (two dd, *J*= 1.6, 8.0 Hz / *J*= 1.6, 7.6 Hz, 1H). ^{13}C NMR: δ= 26.0, 26.2, 27.4, 27.9, 51.1, 51.2, 57.8, 58.3, 64.2, 64.7, 72.3, 73.5, 125.2, 125.9, 126.3, 127.2, 127.3, 128.6, 128.6, 128.7, 131.6, 132.8, 135.2, 140.1, 168.6, 168.9. HRMS (ESI): calcd for $C_{13}H_{16}ClNO_2S$ $[M+H]^+$ 286.0663; found $[M+H]^+$ 286.0651.

*(4S)-Methyl 2-(3-chlorophenyl)-5,5-dimethyl-1,3-thiazolidine-4-carboxylate (**4e**).* The product was purified by silica gel column chromatography using ethyl acetate:hexane (1:6) as eluent to give a pale yellow oil. Yield: 96%. $[\alpha]_D^{20}$= +100.0 (*c* 1.00, CH_2Cl_2). IR (ATR, cm^{-1}): 3309, 2958, 2925, 1735, 1433, 1311, 1203, 1128, 868, 849, 771, 693. ^{1}H NMR ($CDCl_3$): (mixture of diastereoisomers) δ= 1.30/1.36 (two s, 3H), 1.61/1.72 (two s, 3H), 3.74/3.78 (two s, 1H), 3.79/3.79 (two s, 3H), 5.64/5.81 (two s, 1H), 7.21-7.41 (m, 3H), 7.50-7.53 (m, 1H). ^{13}C NMR: δ= 27.1, 27.9, 28.4, 29.1, 52.2, 52.3, 59.7, 60.4, 67.4, 69.0, 72.7, 74.5, 124.9, 125.9, 126.6, 127.5, 127.8, 128.9, 129.6, 130.0, 134.3, 134.6, 140.5, 140.6, 169.5, 170.0. HRMS (ESI): calcd for $C_{13}H_{16}ClNO_2S$ $[M+H]^+$ 286.0663; found $[M+H]^+$ 286.0664.

*(4S)-Methyl 2-(4-chlorophenyl)-5,5-dimethyl-1,3-thiazolidine-4-carboxylate (**4f**).* The product was purified by silica gel column chromatography using ethyl acetate:hexane (1:6) as eluent to give a white solid, after recrystallization from diethyl ether. mp: 150-152 □C. Yield: 82%. $[\alpha]_D^{20}$= +10.0 (*c* 2.00, CH_2Cl_2). IR (ATR, cm^{-1}): 3321, 2957, 1735, 1488, 1433, 1312, 1204, 1122, 1088, 1013, 827, 779, 761. ^{1}H NMR ($CDCl_3$): (mixture of diastereoisomers) δ= 1.30/1.35 (two s, 3H), 1.61/1.72 (two s, 3H), 3.72-3.79 (m, 4H), 5.65/5.81 (two s, 1H), 7.27-7.35 (m, 2H), 7.41-7.47 (m, 2H). ^{13}C NMR: δ= 27.2, 28.1, 28.4, 29.1, 52.2, 59.9, 60.3, 67.5, 69.3, 72.8, 74.7, 128.0, 128.4, 128.8, 129.0, 133.1, 134.4, 137.3, 141.7, 169.6, 170.1. HRMS (ESI): calcd for $C_{13}H_{16}ClNO_2S$ $[M+H]^+$ 286.0663; found $[M+H]^+$ 286.0664.

*(4S)-Methyl 2-(2-methylphenyl)-5,5-dimethyl-1,3-thiazolidine-4-carboxylate (**4g**).* The product was purified by silica gel column chromatography using ethyl acetate:hexane (1:6) as eluent to give a white solid, after recrystallization from a mixture of diethyl ether and hexane. Yield: 83%. mp: 65-66 □C. $[\alpha]_D^{20}$= +28.7 (*c* 2.97, CH_2Cl_2). IR (ATR, cm^{-1}): 3322, 2957, 1730, 1457, 1431, 1317, 1205, 1118, 761. ^{1}H NMR ($CDCl_3$): (mixture of diastereoisomers) δ= 1.26/1.29 (two s, 3H), 1.55/1.66 (two s, 3H), 2.26/2.34 (two s, 3H), 3.71/3.72 (two s, 3H), 3.72/3.87 (two s, 1H), 5.84/5.92 (two s, 1H), 7.05-7.20 (m, 3H), 7.56-7.58/7.64 (m / dd, *J*=1.2, 7.6 Hz, 1H). ^{13}C NMR: δ= 19.4, 19.7, 27.3, 27.6, 28.6, 29.2, 52.2, 59.3, 59.4, 65.8, 66.6, 73.4, 74.8, 124.9, 126.2, 126.4, 126.4, 126.6, 127.4, 128.3, 128.4, 130.6, 130.7, 135.2, 136.6, 136.7, 141.2, 169.9, 170.4. HRMS (ESI): calcd for $C_{14}H_{19}NO_2S$ $[M+H]^+$ 266.1209; found $[M+H]^+$ 266.1204.

*(4S)-Methyl 2-(3-methylphenyl)-5,5-dimethyl-1,3-thiazolidine-4-carboxylate (**4h**).* The product was purified by silica gel column chromatography using ethyl acetate:hexane (1:6) as eluent to give a viscous pale yellow oil. Yield: 83%. $[\alpha]_D^{20}$= +45.0 (*c* 1.00, CH_2Cl_2). IR (ATR, cm^{-1}): 3327,

2953, 2922, 1736, 1453, 1432, 1313, 1251, 1202, 1156, 1126, 851, 767, 687. ^{1}H NMR ($CDCl_3$): (mixture of diastereoisomers) δ= 1.32/1.36 (two s, 3H), 1.63/1.72 (two s, 3H), 2.34/2.36 (two s, 3H), 3.17 (bs, 1H), 3.78/3.79/3.80 (two s / bs, 4H), 5.66/5.85 (two s, 1H), 7.05/7.13 (two d, *J*= 7.2 Hz / *J*= 7.2 Hz, 1H), 7.18-7.31 (m, 3H). ^{13}C NMR: δ= 21.4, 21.5, 27.2, 28.0, 28.5, 29.2, 52.1, 59.7, 60.0, 68.3, 70.2, 73.0, 74.8, 123.6, 124.5, 127.1, 128.1, 128.2, 128.3, 128.6, 129.4, 138.1, 138.4, 138.6, 143.0, 169.8, 170.3. HRMS (ESI): calcd for $C_{14}H_{19}NO_2S$ $[M+H]^+$ 266.1209; found $[M+H]^+$ 266.1207.

*(4S)-Methyl 2-(4-methylphenyl)-5,5-dimethyl-1,3-thiazolidine-4-carboxylate (**4i**).* The product was purified by silica gel column chromatography using ethyl acetate:hexane (1:6) as eluent to give a brown solid, after recrystallization from a mixture of diethyl ether and hexane. Yield: 71%. mp: 57-59 °C. $[\alpha]_D^{20}$= +63.1 (*c* 1.98, CH_2Cl_2). IR (ATR, cm^{-1}): 2955, 2923, 1741, 1608, 1508, 1433, 1205, 1178, 1155, 1120, 772, 759. ^{1}H NMR ($CDCl_3$): (mixture of diastereoisomers) δ= 1.31/1.35 (two s, 3H), 1.62/1.72 (two s, 3H), 2.32/2.35 (two s, 3H), 3.15 (t, *J*= 11.2 Hz, 1H), 3.76/3.78/3.78 (bs / two s, 4H), 5.67/5.85 (d, *J*= 10.4 Hz / s, 1H), 7.13/7.17 (two d, *J*= 8.0 Hz / *J*= 7.6 Hz, 2H), 7.37/7.40 (two d, *J*= 8.0 Hz / *J*= 8.0 Hz, 2H). ^{13}C NMR: δ= 21.1, 21.2, 27.2, 28.2, 28.5, 29.2, 52.1, 52.1, 59.6, 59.9, 68.3, 70.0, 72.9, 74.8, 126.5, 127.4, 129.0, 129.3, 135.7, 137.1, 138.5, 140.1, 169.8, 170.3. HRMS (ESI): calcd for $C_{14}H_{19}NO_2S$ $[M+H]^+$ 266.1209; found $[M+H]^+$ 266.1210.

*(4S)-Methyl 2-(1-naphthyl)-5,5-dimethyl-1,3-thiazolidine-4-carboxylate (**4j**).* The product was purified by silica gel column chromatography using ethyl acetate:hexane (1:3) as eluent to give a pale yellow oil. Yield: 41%. $[\alpha]_D^{20}$= +190.2 (*c* 1.03, CH_2Cl_2). IR (ATR, cm^{-1}): 3325, 3050, 2955, 2922, 1735, 1453, 1431, 1203, 1128, 851, 774. ^{1}H NMR ($CDCl_3$): (mixture of diastereoisomers) δ= 1.35/1.37 (two s, 3H), 1.58/1.77 (two s, 3H), 3.35 (bs, 1H), 3.78/3.80 (two s, 3H), 3.94/4.02 (d, *J*= 9.6 Hz / s, 1H), 6.45/6.49 (d, *J*= 8.4 Hz / s, 1H), 7.42-7.55 (m, 3H), 7.72-8.21 (m, 4H). ^{13}C NMR: δ= 27.2, 27.3, 28.4, 29.1, 52.2, 59.0, 59.0, 65.4, 66.5, 73.4, 74.9, 121.6, 123.4, 123.7, 123.7, 125.4, 125.4, 125.7, 125.9, 126.1, 126.5, 128.0, 128.7, 128.9, 129.0, 130.4, 131.5, 133.7, 134.1, 134.5, 138.7, 169.8, 170.3. HRMS (ESI): calcd for $C_{17}H_{19}NO_2S$ $[M+H]^+$ 302.1209; found $[M+H]^+$ 302.1208.

*(4S)-Methyl 2-(2-naphthyl)-5,5-dimethyl-1,3-thiazolidine-4-carboxylate (**4k**)*. The product was purified by silica gel column chromatography using ethyl acetate:hexane (1:6) as eluent to give a white solid, after recrystallization from a mixture of diethyl ether and hexane. Yield: 80%. mp: 87-89 °C. $[\alpha]_D^{20}$= +57.8 (*c* 1.99, CH_2Cl_2). Elemental analysis: $C_{17}H_{19}NO_2S$ calcd C, 67.74; H, 6.35; N, 4.65; S, 10.64. Found: C, 67.99; H, 5.89; N, 4.56; S, 10.54. IR (ATR, cm^{-1}): 3333, 2955, 2928, 1735, 1431, 1345, 1300, 1267, 1223, 1199, 1183, 1153, 1130, 1121, 826, 753. ^{1}H NMR ($CDCl_3$): (mixture of diastereoisomers) δ= 1.34/1.41 (two s, 3H), 1.63/1.76 (two s, 3H), 3.31 (bs, 1H), 3.80/3.80 (two s, 3H), 3.84/3.85 (two bs, 1H), 5.86/6.03 (two s, 1H), 7.44-7.51 (m, 2H), 7.53/7.62 (two dd, *J*= 1.8, 8.6 Hz / *J*= 2.0, 8.4 Hz, 1H), 7.78-7.87 (m, 3H), 7.96/7.97 (two bs,

1H). ^{13}C NMR: δ= 27.3, 28.1, 28.5, 29.2, 52.2, 59.8, 60.2, 68.5, 70.3, 72.9, 74.8, 124.6, 125.1, 125.2, 125.9, 126.2, 126.4, 126.6, 127.6, 127.7, 128.1, 128.1, 128.3, 128.6, 132.9, 133.1, 133.4, 135.9, 140.3, 169.7, 170.3.

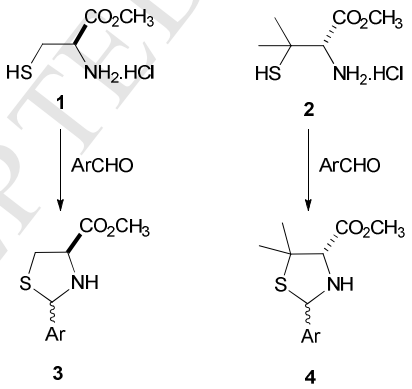
General procedure for enantioselective ethylation reaction

To the chiral ligand (0.15 mmol) and aldehyde (1 mmol) in an inert atmosphere, dry solvent (4 mL) was added. The temperature of the reaction mixture was lowered to 0 □C and diethylzinc (2 mmol, 2 mL, as a 1 M hexane solution) was added. The reaction was stirred for 10 min at 0 □C and then for the required time at room temperature. Subsequently, a saturated NH_4Cl solution (1 mL) was added, followed by 2M HCl (1 mL) and the reaction mixture was extracted with diethyl ether. The joint organic phases were washed with water and brine and dried over anhydrous sodium sulfate. The resulting solution was analyzed by GC on a chiral γ-cyclodextrin capillary column in order to determine conversions and *ee* of the products.[43]

Results and Discussion

Ligand Synthesis

Our interest was focused on the synthesis of thiazolidines **3** and **4**, Scheme 1, bearing phenyl groups at C2, with electron donating and electron withdrawing groups in various positions, and also 1- and 2-naphthyl groups. In order to synthesize these compounds, the methyl esters of L-cysteine, **1**, and D-penicillamine, **2** were used as precursors.



Scheme 1 L-cysteine, **1**, and D-penicillamine, **2**, derived thiazolidines **3** and **4**, respectively.

Starting from commercially available **1**, thiazolidines **3** were obtained by reaction with a series of aromatic aldehydes in ethanol/water at room temperature.[44] In order to obtain thiazolidines **4**, D-penicillamine was esterified with thionyl chloride in refluxing methanol to originate **2**.[45] After several attempts at optimizing this reaction, it was found that, independently of the reaction time, the product always contained about 25% of the free acid. With this mixture, without further purification, thiazolidines **4** were prepared using the above described procedure for the synthesis of **3**. Although the L-cysteine derivatives were formed with good yields following this procedure, we observed that the D-penicillamine thiazolidines only

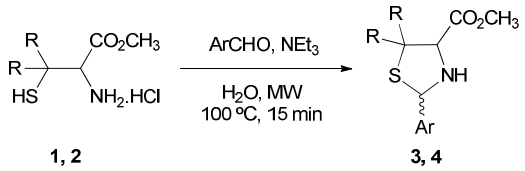
gave moderate yields after long reaction times. In an attempt to improve the yields and reduce the reaction times, the condensation was performed in refluxing cyclohexane[46], but still very long reaction times were required for good yields (up to 72 hours).

Given the good results previously observed by us using microwave irradiation in the synthesis of imines,[24] the effects of applying this technology to the synthesis of the above-mentioned compounds was explored. In order to optimize reaction conditions, the synthesis of thiazolidine **4c** from **2** and *p*-anisaldehyde, in the presence of triethylamine, and using water as solvent, was used as model, Table 1. Best results were obtained using microwave irradiation for 15 min at 100 □C (83%). The resulting high yields, along with a large reduction of the reaction time and the possibility of using water, thus reducing the use of more harmful and polluting organic solvents, make this an efficient and simple method for synthesizing thiazolidines. Using these conditions, a series of C2 aromatic thiazolidines, **3a-k** and **4a-k**, were obtained with moderate to excellent yields, Scheme 2, Table 2. The thiazolidines are formed as C2 diastereoisomeric mixtures, which can interconvert in solution, through opening and closing of the thiazolidine ring.[47–49]

Table 1 Optimization of the synthesis of **4c** under microwave irradiation.

Entry	Temperature (□C)	Time (minutes)	Yield (%)[a]
1	100	15	82
2	100	30	76
3	100	60	77
4	120	15	75
5	120	30	70
6	120	60	76
7	120	120	74
8	110	90	decomposition
9	120	30	decomposition
10	150	30	decomposition

[a]Determined by ^{1}H NMR



1, 2 **3, 4**

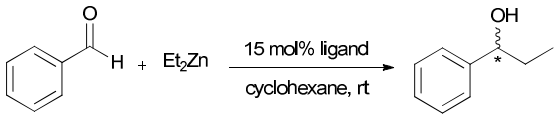
Scheme 2 Synthesis of L-cysteine and D-penicillamine derived thiazolidines.

Table 2 Thiazolidines derived from L-cysteine and D-penicillamine.

Ligand	R	Ar	Yield (%)
3a	H	(*o*-OCH_3)C_6H_4	85
3b	H	(*m*-OCH_3)C_6H_4	71
3c	H	(*p*-OCH_3)C_6H_4	68
3d	H	(*o*-Cl)C_6H_4	71
3e	H	(*m*-Cl)C_6H_4	81
3f	H	(*p*-Cl)C_6H_4	78
3g	H	(*o*-CH_3)C_6H_4	68
3h	H	(*m*-CH_3)C_6H_4	79
3i	H	(*p*-CH_3)C_6H_4	50
3j	H	1-naphthyl	46
3k	H	2-naphthyl	65
4a	CH_3	(*o*-OCH_3)C_6H_4	83
4b	CH_3	(*m*-OCH_3)C_6H_4	83
4c	CH_3	(*p*-OCH_3)C_6H_4	83
4d	CH_3	(*o*-Cl)C_6H_4	74
4e	CH_3	(*m*-Cl)C_6H_4	96
4f	CH_3	(*p*-Cl)C_6H_4	82
4g	CH_3	(*o*-CH_3)C_6H_4	83
4h	CH_3	(*m*-CH_3)C_6H_4	83
4i	CH_3	(*p*-CH_3)C_6H_4	71
4j	CH_3	1-naphthyl	41
4k	CH_3	2-naphthyl	80

Enantioselective Ethylation of Aldehydes

Thiazolidines **3** and **4** were tested as ligands in the enantioselective ethylation of aldehydes with diethylzinc, using our previously described conditions, Scheme 3.[43] The results of the ethylation of benzaldehyde using diethylzinc, performed at room temperature, in cyclohexane, with 15 mol% of **3** and **4** are summarized in Table 3.



Scheme 3 Enantioselective alkylation of benzaldehyde with **3a-3k** and **4a-4k**.

Table 3 Enantioselective ethylation of benzaldehyde catalyzed by chiral thiazolidines **3**-**4**[a].

Ligand	Conversion (%)[b]	1-Phenylpropan-1-ol (%)[b,c]	*ee* (%)[d]
3a	91	95	57 (*S*)
3b	92	81	70 (*S*)
3c	93	83	61 (*S*)
3d	89	77	74 (*S*)
3e	>99	98	63 (*S*)
3f	98	95	70 (*S*)
3g	>99	98	69 (*S*)
3h	98	92	69 (*S*)
3i	99	96	66 (*S*)
3j	98	86	77 (*S*)
3k	>99	97	70 (*S*)
4a	>99	99	84 (*R*)
4b	>99	>99	89 (*R*)
4c	>99	98	83 (*R*)
4d	>99	99	83 (*R*)
4e	>99	98	77 (*R*)
4f	>99	99	83 (*R*)
4g	>99	98	86 (*R*)
4h	>99	98	82 (*R*)
4i	>99	99	85 (*R*)
4j	>99	98	88 (*R*)
4k	>99	98	81 (*R*)

[a]Reaction conditions: cyclohexane (4 mL), ligand (15 mol%), benzaldehyde (1 mmol), diethylzinc solution 1 M in hexane (2 mmol), rt, 24 h. [b]Determined by GC. [c]Relative to converted benzaldehyde. [d]Determined by GC on a chiral column. The major enantiomer is indicated in parenthesis.

The use of ligands **3** and **4** allowed an efficient alkylation of benzaldehyde, with conversions above 89%. In general, higher conversions were observed with the D-penicillamine thiazolidines, **4**, giving chiral products with good *ee* (77-89%). The L-cysteine thiazolidines, **3**,

gave moderate *ee* (57-77%). The two methyl groups in C5, creating significant steric hindrance, appear to be responsible for these results. Moreover, the opposite absolute configuration at C4 of L-cysteine and D-penicillamine thiazolidines makes it possible to obtain the two enantiomers of the product alcohols.

The electron-donating and electron-withdrawing nature of the substituents in the aromatic ring at C2, as well as their location in *ortho*, *meta*, or *para* positions, does not appear to significantly affect the enantioselectivity. However, it is possible to observe that the electron-donating methoxy substituent in *meta* in ligands **3b** and **4b** increases the chiral induction (70% and 89%, respectively), when compared to their *ortho* and *para* analogues. The opposite is verified for the electron-withdrawing chloride group, with ligands **3e** and **4e** originating lower *ee* (63% and 77%, respectively) when in the *meta* position.

Comparing the thiazolidines with 1-naphthyl (**3j**, **4j**) and 2-naphthyl (**3k**, **4k**) substituents at C2, the former gave 1-phenylpropan-1-ol with higher *ee*.

In order to determine the effect of temperature on reactivity and selectivity, some reactions were conducted at 0 □C. As expected, the conversions were lower in almost all cases, with no noteworthy differences in *ee*.

In an attempt to improve the results, different solvents and catalyst loadings were tested, using our most promising ligand, **4b**, Table 4. Better conversions and *ee* were obtained with non-polar solvents, although cyclohexane remained the best. The use of different catalyst loadings did not affect the conversion of benzaldehyde, the best enantioselectivity being observed with 15 mol% of **4b**.

Table 4 Enantioselective alkylation of benzaldehyde with **4b**, with different solvents and catalyst loadings.

Solvent	4b (mol%)	Conversion (%)[b]	1-Phenylpropan-1-ol (%)[b,c]	*ee* (%)[d]
Cyclohexane	15	>99	>99	89 (*R*)
Hexane	15	>99	98	85 (*R*)
Toluene	15	96	93	87 (*R*)
Diethyl ether	15	93	95	88 (*R*)
Dichloromethane	15	74	87	77 (*R*)
Cyclohexane	10	>99	98	86 (*R*)
Cyclohexane	20	>99	>99	86 (*R*)

[a]Reaction conditions: solvent (4 mL), **4b** (15 mol%), benzaldehyde (1 mmol), diethylzinc solution 1 M in hexane (2 mmol), rt, 24 h. [b]Determined by GC. [c]Relative to converted benzaldehyde. [d]Determined by GC on a chiral column. The major enantiomer is indicated in parenthesis.

The possibility of reducing the reaction time was also studied. Aliquots of the catalytic mixture were taken at 2h intervals and analyzed. It was observed that after 6 hours no significant changes occurred. Thus, under our newly optimized conditions, 6 h reaction in cyclohexane, with 15 mol% of **4b** at room temperature, we examined the scope of our ligand by testing a series of substrates, Table 5. Very good to excellent conversions were observed with all of the aromatic substrates, with the best *ee* being obtained with *m*- and *p*-methoxybenzaldehyde (93% *ee*). The methoxy group in the *ortho* position could cause steric

hindrance responsible for a slight decrease in *ee*. The increasing distance of the electron-withdrawing chlorine atom to the carbonyl group results in lower conversions and slightly lower *ee*. Very good *ee* were obtained with bulkier aldehydes such as 1- and 2-naphthaldehyde (94% and 87%, respectively), although conversions were moderate. While aliphatic phenylacetaldehyde gave poor conversion and *ee*, cinnamaldehyde, cyclohexanecarboxaldehyde and the heteroaromatic furfuraldehyde were converted efficiently to the chiral alcohols (>95% conversion), with moderate to good *ee*. Overall, these results highlight the efficiency of this catalytic system.

Table 5 Enantioselective alkylation of several aldehydes catalyzed by **4b**.

Aldehyde	Conversion (%)[b]	*ee* (%)[c]
o-Methoxybenzaldehyde	97	84 (*R*)
m-Methoxybenzaldehyde	97	93 (*R*)
p-Methoxybenzaldehyde	>99	93 (*R*)
o-Chlorobenzaldehyde	>99	81 (*R*)
m-Chlorobenzaldehyde	95	80 (*R*)
p-Chlorobenzaldehyde	90	78 (*R*)
m-Methylbenzaldehyde	89	78 (*R*)
1-Naphthaldehyde	61	94 (*R*)
2-Naphthaldehyde	83	87 (*R*)
Furfuraldehyde	>99	50 (*R*)
Cinnamaldehyde	95	77 (*R*)
Cyclohexanecarboxaldehyde	>99	72 (*R*)
Phenylacetaldehyde	27	58

[a]Reaction conditions: cyclohexane (4 mL), **5b** (15 mol%), aldehyde (1 mmol), diethylzinc solution 1 M in hexane (2 mmol), rt, 6 h reaction. Determined by GC. [c]Determined by GC on a chiral column. The major enantiomer is indicated in parenthesis.

NMR and Computational Studies of the Relative Stability of Diastereoisomers and Catalytically Active Species

NMR Studies

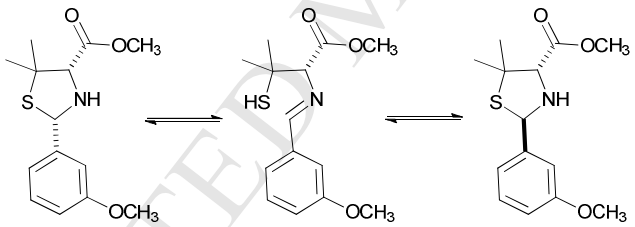
In order to get an insight into the mechanism of the enantioselective ethylation reactions with diastereoisomeric mixtures of thiazolidines, as well as to try to identify the active species in the catalytic cycle, NMR and computational studies were performed, using the most enantioselective ligand, **4b**.

In successive recrystallizations of **4b**, we were able to isolate only one of the two diastereoisomers as a crystalline white solid. Using this compound, the evolution of the diastereoisomeric equilibrium in solution by 1H NMR was studied, collecting spectra 0, 1 and 5 hours after dissolution, as well as after 1 and 5 days (see Supporting Information). The singlets

of the hydrogen of carbon 2 of the thiazolidine (δ= 5.67/5.85 ppm) were used to calculate the ratio of the diastereoisomers, Table 6. Taking these results into account, it is possible to confirm that, in solution, interconversion of the two diastereoisomers occurs, reaching an equilibrium in a proportion of 1:3. This epimerization arises from the ring opening and closing of the thiazolidine, with formation of an imine intermediate, Scheme 4, **4b-2**, that could not be observed by NMR.

Table 6 Variation of the diastereoisomeric ratio with time.

Time after dissolution	Diastereoisomeric Ratio (minor:major)
0 hour	0:1
1 hour	1:26
5 hours	1:12
1 day	1:4
5 days	1:3



Scheme 4 Epimerization of thiazolidine **4b** via intermediate imine formation.

In order to try to identify the most stable diastereoisomer, 2D-NOESY spectra were recorded instantaneously after dissolution of the sample and 5 days later (see Supporting Information for spectra). From the signals of the hydrogen of carbon 2, it is possible to observe, for the major diastereoisomer, a space interaction with the hydrogen of carbon 4 (δ around 3.78 ppm), in both NOESY spectra. However, there was no evidence of this interaction for the minor diastereoisomer. The spatial proximity of these hydrogens when in *cis* position could be responsible for this interaction, which allowed to identify the *cis* diastereoisomer **4b-1** as the major and most stable one.

This NMR study confirms that there is no need to obtain the thiazolidines in a pure diastereoisomeric form, since they will immediately epimerize when dissolved in the catalytic reaction solvent. However, the question still prevails: can the use of thiazolidine ligands as diastereoisomeric mixtures affect enantioselective induction? In literature, it has been referred that the selectivity is not affected, which could result from distinct characteristics of the two

possible diastereoisomeric catalysts, namely, significantly different rates of reaction or lack of coordination of one of the diastereoisomers, with the other forming the active catalyst.[34,50,51] In order to try to answer this question, the enantioselective ethylation of benzaldehyde using **4b** in its pure diastereoisomeric form was carried out. After 6 hours complete conversion of the substrate was observed and (*R*)-1-phenylpropan-1-ol was obtained with an *ee* of 86%, which matches the 85% *ee* achieved with the use of thiazolidine **4b** as a mixture of diastereoisomers. Thereby, in the case of thiazolidine ligands, the catalytic reaction is not compromised by the use of diastereoisomeric mixtures of ligands.

Computational Studies

In order to determine the stability of the two diastereoisomers and to rationalize the differences in catalytic activity of each one, first-principles calculations were performed, using the Orca electronic structure package (version 4.0.0).[52] For each of the diastereoisomers, the structures of the free ligand and of those resulting from the complexation with one and two zinc atoms (according to Noyori's mechanism of the alkylation reaction[4,53]) were optimized at the hybrid DFT level, using the PBE0 functional with the 6-31G(d) polarized double-ζ basis set.[54] The schematic representation of these structures is presented in Fig. 1.

The optimized geometries are shown in Fig. 2 and their respective energies presented in Table 7. Single point energy calculations for each optimized species were also performed using the PBE0 functional with the cc-pVDZ, cc-pVTZ and cc-pVQZ series of Dunning's correlation-consistent basis sets, Table 7.[55–57] The data thus obtained indicates that the energies calculated with the cc-pVnZ basis sets are already well converged with n = T. Although the smaller 6-31G(d) basis set does predict the correct order of stability the energies obtained at this level are clearly inferior to those from the correlation-consistent basis sets and should not be relied upon for quantitative work on ligands/complexes of this type. The graphics that correspond to the energy differences for equivalent species are presented in Fig. 3 to 5.

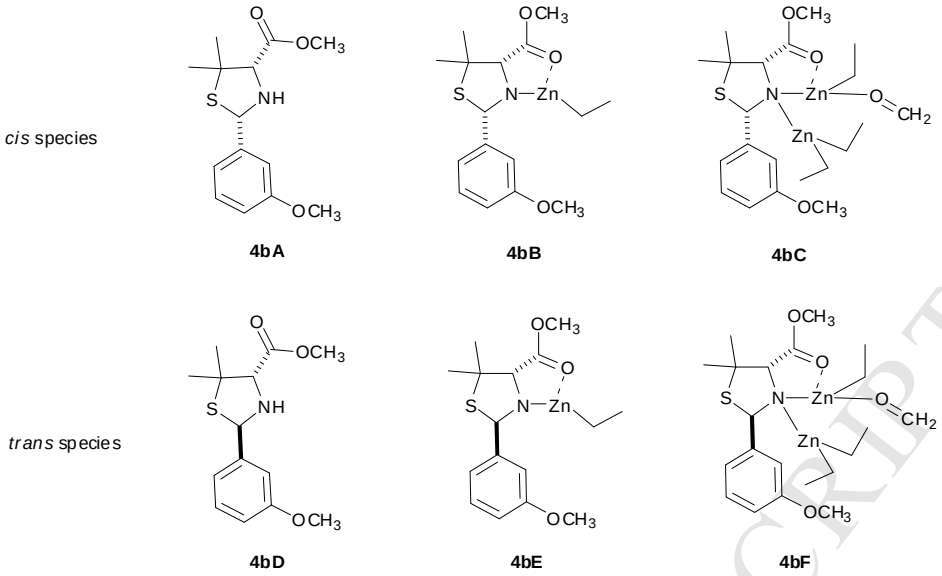


Fig. 1 Schematic representation of the free and complexed *cis* and *trans* structures.

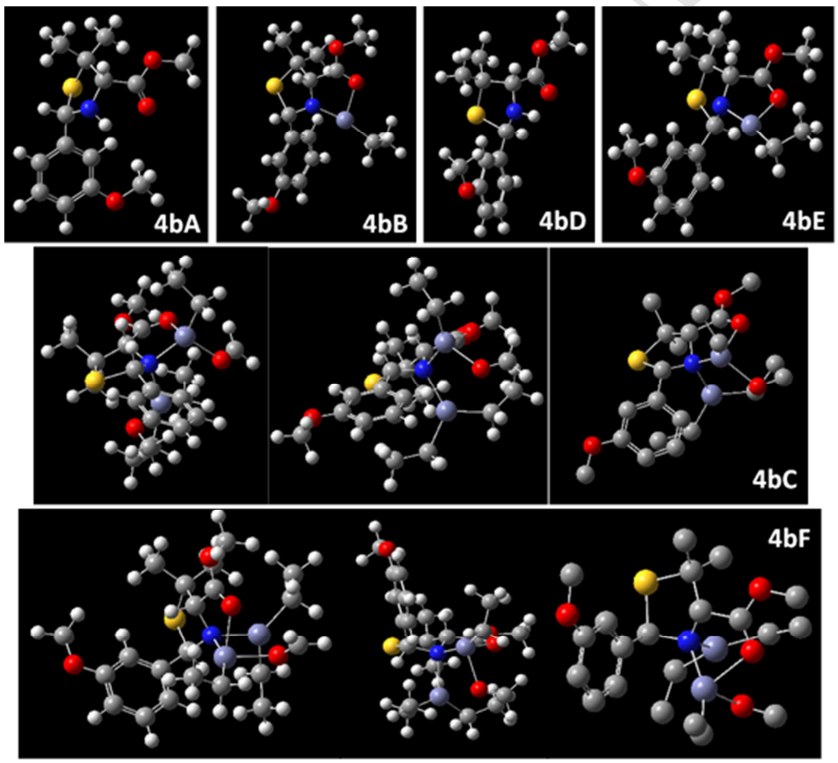


Fig. 2 Optimized geometries of the intended species at the DFT level, using PBE0/6-31G(d) level of theory. Color code: grey, carbon; red, oxygen; blue, nitrogen; white, hydrogen; yellow, sulphur; and blue-grey, zinc.

Table 7 Energy values for the optimization structure and single point energy calculations at the PBE0 level of theory.

	Energy (KJ/mol)			
	6-31G(d)	**cc-pVDZ**	**cc-pVTZ**	**cc-pVQZ**
4bA	-3209496,5	-3209729,4	-3210352,3	-3210523,3
4bD	-3209493,3	-3209726,9	-3210348,5	-3210519,1
4bB	-8086052,6	-8087212,9	-8087893,5	-8088085,9
4bE	-8086003,1	-8087168,4	-8087849,4	-8088041,6
4bC	-13472060,9	-13474182,6	-13475074,3	-13475325,4
4bF	-13472105,8	-13474227,8	-13475115,1	-13475365,5

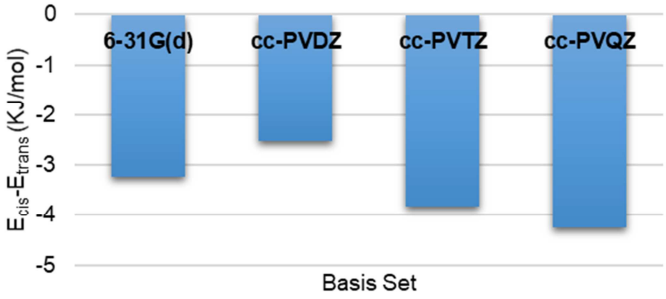


Fig. 3 Graphical representation of the energy difference between species **4bA** and **4bD**.

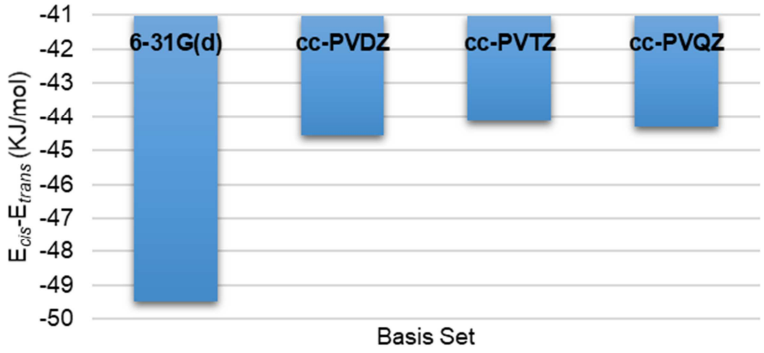


Fig. 4 Graphical representation of the energy difference between species **4bB** and **4bE**.

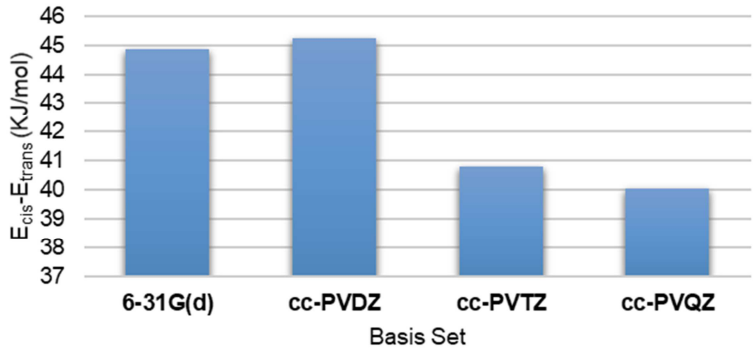


Fig. 5 Graphical representation of the energy difference between species **4bC** and **4bF**.

From the obtained results the species generated from each one of the diastereoisomers can be compared. For the free ligand (**4bA** and **4bD**), the *cis* diastereoisomer is the most stable one, since it is associated with more negative energy values. The energy difference around 4 KJ/mol allows us to postulate that, besides the higher stability of the *cis* isomer, an interconversion to the *trans* isomer can occur (assuming thermodynamic equilibrium between diastereoisomers). This result is in agreement with the one obtained experimentally from the NMR studies. Looking at the species containing one zinc (**4bB** and **4bE**), it is possible to observe that the more stable complex is obtained with the *cis* diastereoisomer, which seems to coordinate preferentially with the zinc atom. However, moving along the reaction path, a coordination with a second diethylzinc molecule occurs. This second complexation is determinant for the reaction, since it allows the transfer of the ethyl group to the carbonyl group of the aldehyde and, therefore, the definition of the stereochemistry of the product. From the computational studies, it was possible to observe that the species resulting from the complexation of the *trans* diastereoisomer with the second zinc atom (**4bF**) is more stable than the one derived from the *cis* thiazolidine (**4bC**), with an energy difference of about 40 KJ/mol. This can be explained by a more sterically hindered environment in the *cis* structure, resulting in a preferential course of the reaction through the *trans* structure, this being the most catalytically active species (although both can intervene in the reaction).

Conclusions

A new series of chiral 2-arylthiazolidines derived from L-cysteine and D-penicillamine were synthesized. A new, simple and greener procedure was developed, taking advantage of microwave irradiation, which allowed the formation of the desired thiazolidines with good yields in only 15 minutes.

The new thiazolidines were tested as ligands in the enantioselective ethylation of benzaldehyde, providing good to excellent conversions and *ee* up to 89%. The D-penicillamine derived thiazolidines proved to be more efficient chiral inducers, giving (*R*)-1-phenylpropan-1-ol with higher ee than the L-cysteine based ligands, which originated (*S*)-1-phenylpropan-1-ol. The use of precursors with opposite chirality, does, however, create an interesting and useful strategy for the synthesis of both enantiomers of the chiral products. The results seem to indicate that the nature and position of the substituents on the C2 aromatic group are not the determining factors in obtaining good *ee.* Nevertheless, they do influence the enantioselectivity.

Using the optimized reaction parameters, the most selective ligand, **4b**, was used to evaluate the scope of the reaction. Aromatic substrates, provided good conversions and *ee* up to 94%. Heteroaromatic and aliphatic aldehydes were also studied, giving *ee* up to 77%, an interesting value for this kind of substrates.

NMR studies with ligand **4b** confirmed that epimerization occurs with this kind of ligands in solution. The *cis* diastereoisomer of **4b** was identified as the most stable one and the major isomer present at equilibrium in a 3:1 ratio. The use of ligand **4b** in pure diastereoisomeric form in the catalytic process led to the same results as the mixture of *cis* and *trans* isomers, thus endorsing the use of the mixture. Computational calculations were in agreement with the experimental results, confirming the *cis* diastereoisomer (**4bA**) as the most stable and the possibility of its interconversion to the *trans* diastereoisomer (**4bD**). The species resulting from coordination with a second diethylzinc molecule proved to invert this order of stability, the *trans* thiazolidine forming a more stable catalyst (**4bF**). This favored structure seems to be the main species responsible for the catalytic process, possibly due to a less hindered environment in the neighborhood of the zinc atoms.

Studies are underway aiming at the synthesis of thiazolidines with other functionalities and their subsequent evaluation in new enantioselective transformations.

Conflicts of Interest

There are no conflicts to declare.

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Chiral Thiazolidines in the Enantioselective Ethylation of Aldehydes: An Experimental and Computational Study

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D-Penicillamine and L-cysteine derived thiazolidines were obtained through a simple microwave procedure and used in the enantioselective alkylation of aldehydes with diethylzinc, giving (*S*) and (*R*) enantiomers of the product alcohols with *ee* up to 94%. NMR and computational studies gave important insight into the species involved in the catalytic cycle.

Highlights

- Chiral thiazolidines prepared from L-cysteine/D-penicillamine with MW irradiation.
- Enantioselective ethylation of aromatic aldehydes gave *ee* up to 94%.
- Enantioselective ethylation of heteroaromatic/aliphatic substrates gave *ee* up to 77%.
- Interesting approach for obtaining both the (*S*) and (*R*) chiral alcohols.
- NMR and Computational studies gave insight into catalytic species.