Tetrahedron: *Asymmetry* 25 (2014) 449–456

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Axially chiral pyridine compounds: synthesis, chiral separations and determination of protonation dependent barriers to hindered rotation

Furkan Halis Isikgor, Sule Erol, Ilknur Dogan *

Boğaziçi University, Chemistry Department, Bebek, 34342 İstanbul, Turkey

ARTICLE INFO

Article history:
Received 20 December 2013
Accepted 22 January 2014

ABSTRACT

Axially chiral enantiomeric 2-pyridylimino-3-pyridyl-thiazolidine-4-ones and -thiones have been synthesized and their rotational barriers around the N-3—$C_{(pyridyl)}$ bond have been determined by variable temperature NMR or by thermal racemization of the micropreparatively resolved enantiomers. Rotational barriers of the unprotonated compounds ranged from 46 to 116 kJ/mol, depending on the substituent on the N-3-pyridyl ring and on the exocyclic oxygen or sulfur atoms of the thiazolidine ring. Protonation of the pyridine nitrogens by TFA caused a decrease in the barrier to the rotation by stabilizing the transition state of the rotations via hydrogen bonding interactions.

1. Introduction

2-Pyridylimino-3-pyridyl-thiazolidine-4-ones and -thiones **1**–**4** (Scheme 1) are structurally interesting compounds that possess an amidine scaffold conjugated to a pyridine ring. The compounds also have nitrogen, oxygen, and sulfur heteroatoms in their structures to ligate transition metals in different coordination modes.[1–10] These compounds are axially chiral due to hindered rotation around the N-3—$C_{(pyridyl)}$ bond and may be atropisomeric[11] depending on the substituents at the C-3 position of the *N*-3-pyridyl ring and on the exocyclic atoms of the thiazolidinone ring. Axially chiral bidentate compounds, which have high enough rotational barriers to allow their isolation as enantiopure compounds,[12] are of great importance due to their use as asymmetric ligands and catalysts[13] in the production of a variety of pharmaceuticals, agrochemicals, flavors, and fragrances.[14] Chiral amidine-based catalysts have also proven to be useful in various asymmetric syntheses, including enantioselective acyl transfers,[15,16] allylic substitutions,[17] and nitroalkane alkylations.[18]

Compounds containing a pyridyl structure are well known to possess a wide range of biological and pharmacological activities.[19] Compounds with a 2-imino-thiazolidine-4-one scaffold have also been reported as biologically important compounds.[20,21] Herein we report the synthesis of some novel chromatographically resolvable axially chiral 2-pyridylimino-3-pyridyl-thiazolidine-4-ones and -thiones (Scheme 1) as potential organocatalysts. The chiral separations of the atropisomeric derivatives and the protonation dependent rotational barrier determinations have also been reported.

2. Results and discussion

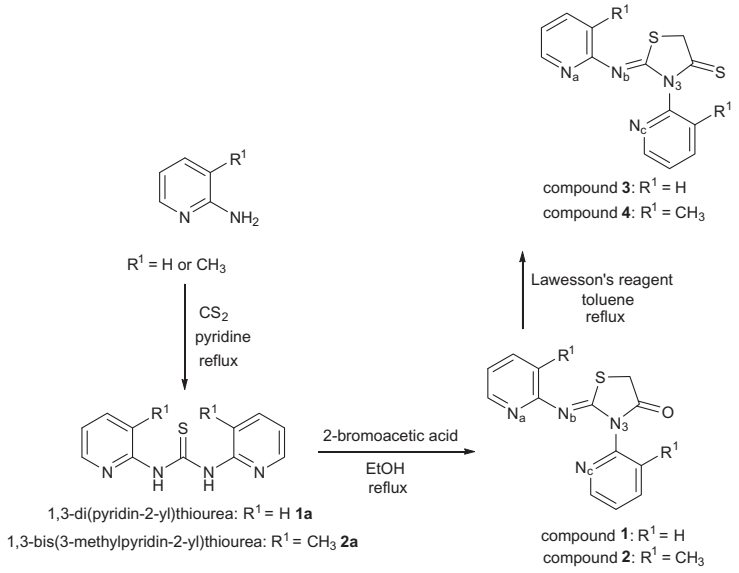
The 2-pyridylimino-3-pyridyl-thiazolidine-4-ones **1** and **2** were synthesized by the reaction of the corresponding *N*,*N*′-diarylthioureas and α-bromoacetic acid (Scheme 1). This included a facile two step synthesis from the corresponding amino pyridine. The 2-pyridylimino-3-pyridyl-thiazolidine-4-thiones **3** and **4** were synthesized by the reaction of **1** and **2** with Lawesson's reagent[22] (Scheme 1). Conversion of the carbonyl group into thiocarbonyl was monitored by the disappearance of the IR and ^{13}C NMR carbonyl peaks and the appearance of the corresponding thiocarbonyl peaks.

Within these compounds, the rotation around the N-3—$C_{(pyridyl)}$ bond is restricted due to the steric interactions between the R^1 substituent, the lone pair electrons of N_c, and the exocyclic oxygen or sulfur atoms (Scheme 1). The restricted rotation results in the formation of the thermally interconvertible *M* and *P* enantiomers (Scheme 1, Table 1).

In compounds **1**–**4**, the lone pair on N-3 cannot delocalize with the pyridine ring bonded to N-3 because of the nonplanar ground states. However, these electrons on N-3 can be donated to the pyridine ring on the imino group via the resonance structure shown in Scheme 2. As a result, the ^1H NMR signals of the pyridine ring on

* Corresponding author. Tel.: +90 2123596620; fax: +90 212 287 2467.
E-mail address: dogan@boun.edu.tr (I. Dogan).

http://dx.doi.org/10.1016/j.tetasy.2014.01.012
0957-4166/



Scheme 1. Synthesis of the axially chiral 2-pyridylimino-3-pyridyl-thiazolidine-4-ones and -thiones **1**–**4**.

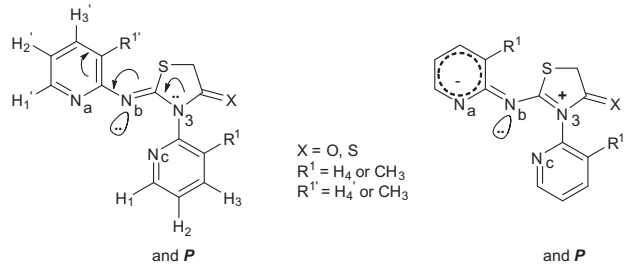
Table 1
Chemical shift values of the protons at the C-5 position

Compounds	NMR solvents		
	$CHCl_3$-d_1 (ppm)	Toluene-d_8 (ppm)	TFA-d_1 (ppm)
1[a]	v = 3.88[b]	v = 2.95[b]	v = 4.53[b]
2	v = 3.96[c]	v_1 = 3.08 v_2 = 3.00	v_1 = 4.62 v_2 = 4.56
3[d]	v = 4.41[b]	v = 3.68[b]	v = 4.93[b]
4[e]	v = 4.42[c]	v_1 = 3.74 v_2 = 3.63	v_1 = 4.90 v_2 = 4.87

[a] The corresponding chemical shift value in DMF-d_7: v = 4.34 ppm.
[b] Due to rapid rotation around the *N*-3-pyridyl bond, AB type splitting of the protons at the C-5 position could not be observed.
[c] AB type splitting of the protons at the C-5 position could not be observed.
[d] The corresponding chemical shift value in benzene-d_6: v = 3.40 ppm.
[e] The corresponding chemical shift values in benzene-d_6: v_1 = 3.42 ppm and v_2 = 3.30 ppm.

the imino group are more shielded than those of the N-3-pyridine ring, thus enabling the appearance of the aromatic protons of the two pyridyl rings separately (Table 2). The 2D-NOESY spectra of these compounds did not show any crosspeaks between the two well resolved pyridine ring ^{1}H NMR signals. Based on this observation, the imino bond is assumed to have a *Z*-configuration.

Analytical resolutions for the isomers of **1**–**4** were attempted by enantioselective HPLC. The enantiomers of compounds **2** and **4** could be resolved by HPLC on Chiralpak AD and Chiralpak IB columns, respectively (Fig. 1). On the other hand, the thermally



Scheme 2. The resonance structure of the compounds **1**–**4**.

interconvertible enantiomers of compounds **1** and **3** could not be resolved due to fast rotation around the N-3—$C_{(pyridyl)}$ bond (Fig. 1).

Due to the axial chirality of **1**–**4**, the hydrogen atoms at the C-5 position of the thiazolidine ring are diastereotopic and are expected to give an AB type splitting pattern. AB splittings for **1** and **3** were not observed at 24 °C (NMR probe temperature) due to a fast rotation (Fig. 2), but could be observed at lower temperatures (Fig. 3).

In order to determine the racemization barriers for **1** and **3**, variable temperature ^{1}H NMR experiments at lower temperatures were carried out.[23] The barriers were determined on the basis of coalescence temperatures.[24] The coalescence temperature was found to be −50 °C for compound **1** (Fig. 3). However, spectra could not be taken at lower temperatures due to solubility problems and the barrier to rotation for this compound has been estimated to be between 46 and 48 kJ/mol by taking possible minimum and maximum values of the chemical shift difference between the two C-5 protons at −50 °C. The rotational barrier of compound **3** was found as 57 kJ/mol by temperature dependent NMR[24] (Fig. 3).

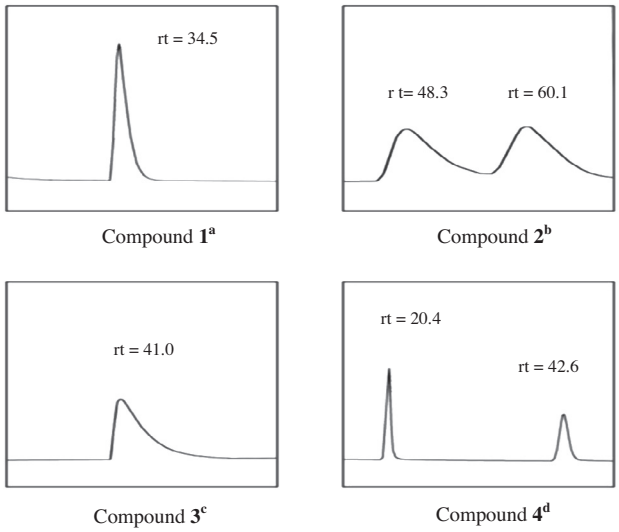
Since the two enantiomers of **2** and **4** were separable upon HPLC at column temperature of 7 °C, the determination of the rotational barrier to the hindered rotation for these compounds was carried out by thermally interconverting the micropreparatively separated enantiomer to its counterpart. For this process, the enantiomers of **2** and **4** were separated micropreparatively by HPLC on Chiralpak AD and Chiralpak IC columns, respectively. The mobile solvent was evaporated immediately and the process was repeated successively until 0.2 mg of each isomer was collected. Next, one of the enantiomers was dissolved in approximately 200 μl of HPLC solvent and 40 μl of this solution was injected into the column to determine the initial concentration. The solution was kept in an oil bath at a constant temperature and the thermal racemization process was followed by HPLC analysis at certain time intervals (Fig. 4a). Integration of the UV peaks (λ = 254 nm) on the chromatogram yielded the ratio of the enantiomers.

A plot of $\ln([M] - [M]_{eq})/[M]_0 - [M]_{eq})$ versus time (Fig. 4b) gave the first order rate constants for thermal interconversion of the compounds.[25] Substitution of the rate constant into the Eyring equation $\Delta G^{\#} = RT\ln(k_b T/k\,h)$ provided the rotational barriers as 102.1 and 115.7 kJ/mol, respectively. For compounds **1**–**4**, the dynamic NMR or HPLC conditions are summarized in Table 3.

Table 2
Chemical shift values[a] of the aromatic and R^1 protons of **1**–**4**

Compounds	NMR solvents					
	$CHCl_3$-d_1		Toluene-d_8		TFA-d_1	
1	H_1 = 8.64	H'_1 = 8.36	H_1 = 8.35	H'_1 = 8.27	H_1 = 9.06	H'_1 = 8.60[c]
	H_2 = 7.36	H'_2 = 6.95	H_2 = 6.59	H'_2 = 6.42	H_2 = 8.26	H'_2 = 7.80
	H_3 = 7.85	H'_3 = 7.54	H_3 = (−)[b]	H'_3 = (−)[b]	H_3 = 8.91	H'_3 = 8.60[c]
	H_4 = 7.33	H'_4 = 6.89	H_4 = 6.86	H'_4 = 6.78	H_4 = 8.39	H'_4 = 7.90
2	H_1 = 8.51	H'_1 = 8.25	H_1 = 8.28	H'_1 = 8.18	H_1 = 8.97	H'_1 = 8.79
	H_2 = 7.35	H'_2 = 6.93	H_2 = 6.66	H'_2 = 6.48	H_2 = 8.22	H'_2 = 7.71
	H_3 = 7.72	H'_3 = 7.42	H_3 = (−)[b]	H'_3 = 6.91	H_3 = 8.42[c]	H'_3 = 8.42[c]
	CH_3 = 2.29	CH'_3 = 1.93	CH_3 = 1.99	CH'_3 = 1.84	CH_3 = 2.70	CH'_3 = 2.47
3	H_1 = 8.68	H'_1 = 8.39	H_1 = 8.37	H'_1 = 8.25	H_1 = 9.18	H'_1 = 8.58
	H_2 = 7.39	H'_2 = 6.96	H_2 = 6.64	H'_2 = 6.43	H_2 = 8.38[c]	H'_2 = 7.82
	H_3 = 7.89	H'_3 = 7.54	H_3 = (−)[b]	H'_3 = (−)[b]	H_3 = 9.00	H'_3 = 8.65
	H_4 = 7.29	H'_4 = 6.89	H_4 = 6.81	H'_4 = 6.74	H_4 = 8.38[c]	H'_4 = 7.97
4	H_1 = 8.49	H'_1 = 8.22	H_1 = 8.28	H'_1 = 8.16	H_1 = 9.00	H'_1 = 8.80
	H_2 = 7.30	H'_2 = 6.89	H_2 = 6.67	H'_2 = 6.45	H_2 = 8.24	H'_2 = 7.72
	H_3 = 7.69	H'_3 = 7.36	H_3 = (−)[b]	H'_3 = 6.87	H_3 = 8.43[c]	H'_3 = 8.43[c]
	CH_3 = 2.17	CH'_3 = 1.83	CH_3 = 1.94	CH'_3 = 1.77	CH_3 = 2.66	CH'_3 = 2.48

[a] Chemical shift values are in parts per million (ppm) relative to tetramethylsilane.
[b] ^{1}H NMR signal of the proton is under the corresponding solvent peak.
[c] The corresponding peak overlaps with other aromatic peaks.



rt: retention times (min)
a: Column: Chiralpak AD, Eluent (v/v): hexane/2-propanol (50/50), Flow rate (ml/min): 0.6.
b: Column: Chiralpak AD, Eluent (v/v): hexane/2-propanol (90/10), Flow rate (ml/min): 0.6, Separation factor between enantiomeric pairs (α): 1.27.
c: Column: Chiralpak IB, Eluent (v/v): hexane/2-propanol (70/30), Flow rate (ml/min): 0.4.
d: Column: Chiralpak IC, Eluent (v/v): hexane/2-propanol (70/30), Flow rate (ml/min): 0.6, Separation factor between enantiomeric pairs (α): 2.43.

Figure 1. The HPLC chromatograms of **1**–**4**.

For compound **2**, the rotational barrier was also determined under acidic conditions where the micropreparatively separated enantiomer was dissolved in chloroform containing 0.4% TFA and the thermal racemization was followed by HPLC on a Chiralpak IB column. It was observed that under this acidic medium, the micropreparatively separated enantiomer immediately interconverted into its counterpart (Fig. 5a).

The axially chiral compound **2** racemizes by partial rotation about the N-3—$C_{(pyridyl)}$ chiral axis via a planar transition state.[26] The excess acid present in the medium is expected to protonate the nitrogens of the *N*-3-pyridine and the imino-pyridine of the molecule (Fig. 5c). The imine nitrogen has been shown to remain unprotonated in structurally related compounds in TFA.[27] The observation that the rotational barrier is dramatically lowered under acidic conditions indicated that the planar transition state for rotation is exceptionally stabilized. This is possible by intramolecular H-bonding interactions between the protonated pyridine and the carbonyl oxygen or imine nitrogen of the thiazolidine-4-one ring in the planar transition state via the formation a 6-membered ring (Fig. 5c). Rousell et al. have shown for structurally related axially chiral compounds that[28] (Fig. 6) H-bonding to a carbonyl during the transition state for rotation decreases the barrier by 23.2 kJ/mol (Fig. 6). Considering a hydrogen bonding interaction of a comparable strength in protonated **2**, the barrier to rotation was lowered to 78.9 kJ/mol, which would cause an immediate racemization ($t_{1/2}$ = 7.5 s). Such stabilizations of transition states have also been observed[29] by Rebek et al. during an acid catalyzed racemization of bipyridyl derivatives. The determination of the catalytic

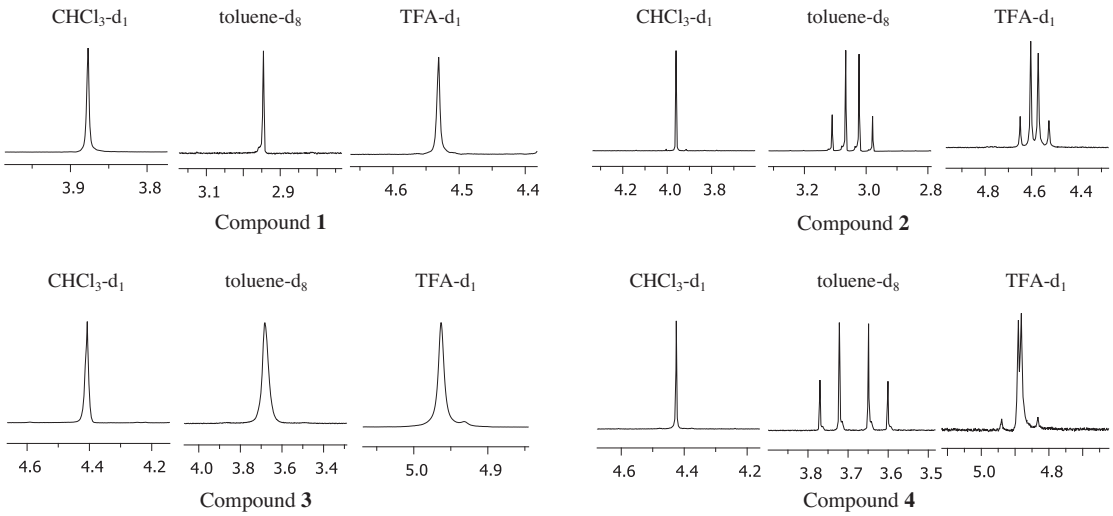


Figure 2. The ^{1}H NMR signals of the protons at the C-5 position of compounds **1**–**4** in different solvents.

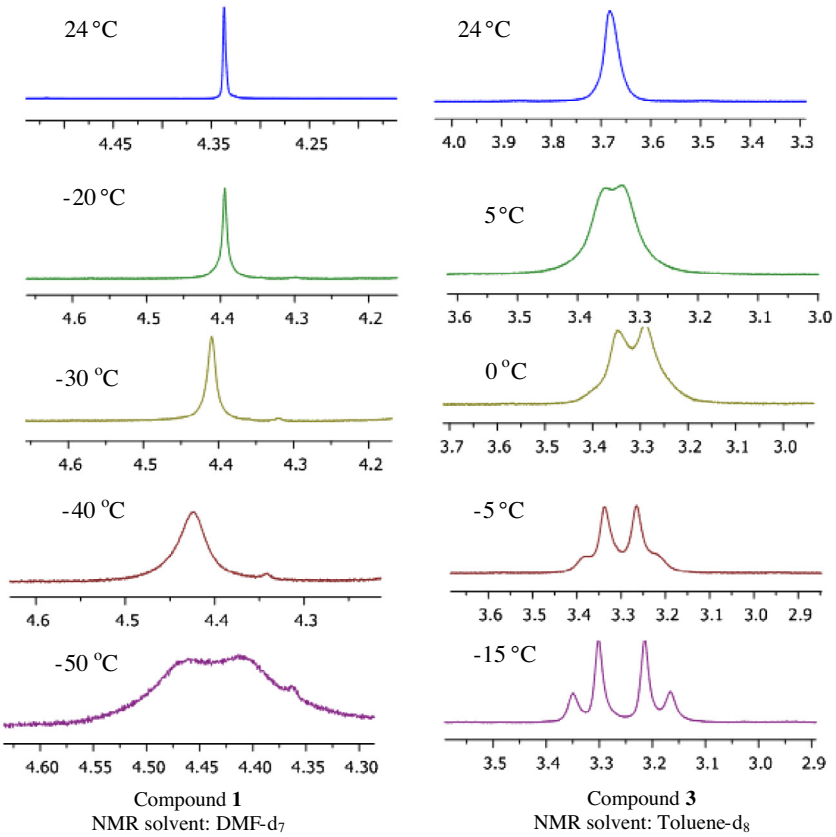


Figure 3. Temperature dependent ^{1}H NMR of the –CH_2 protons of compounds **1** and **3**.

activity by means of binding forces at the well defined transition state has been considered important[30] because of its influence on topics such as enzyme binding[31] and molecular rotors.[32]

When the same thermal racemization experiment in an acidic medium is repeated with the resolved enantiomer of compound **4** at 32 °C, it was found that the compound racemized with a barrier of 106.4 kJ/mol (Fig. 5b). The observed decrease of 9.3 kJ/mol is indicative of a weaker H-bonding between the exocyclic sulfur atom and the protonated pyridine (Fig. 5c). Rousell et al. observed a decrease of 8.1 kJ/mol[27] in the rotational barrier due to the hydrogen bonding interactions of the hydroxyl group with the thiocarbonyl in the transition state (Fig. 6).

Amidine conjugation in compounds **1**–**4** was expected to increase the basicity of the imino pyridine ring (Scheme 2). For this reason we hypothesized that compounds **1**–**4** may act as DMAP analogs to catalyze the acylation reactions of alcohols (Fig. 7). The acylation of 1-phenylethanol[33] with acetic anhydride was found to be slightly catalyzed in the presence of 10 mol % of racemic **2** (the reaction rate of the esterification was found to increase by 1.5 times based on the comparison of the ^{1}H NMR integral of the

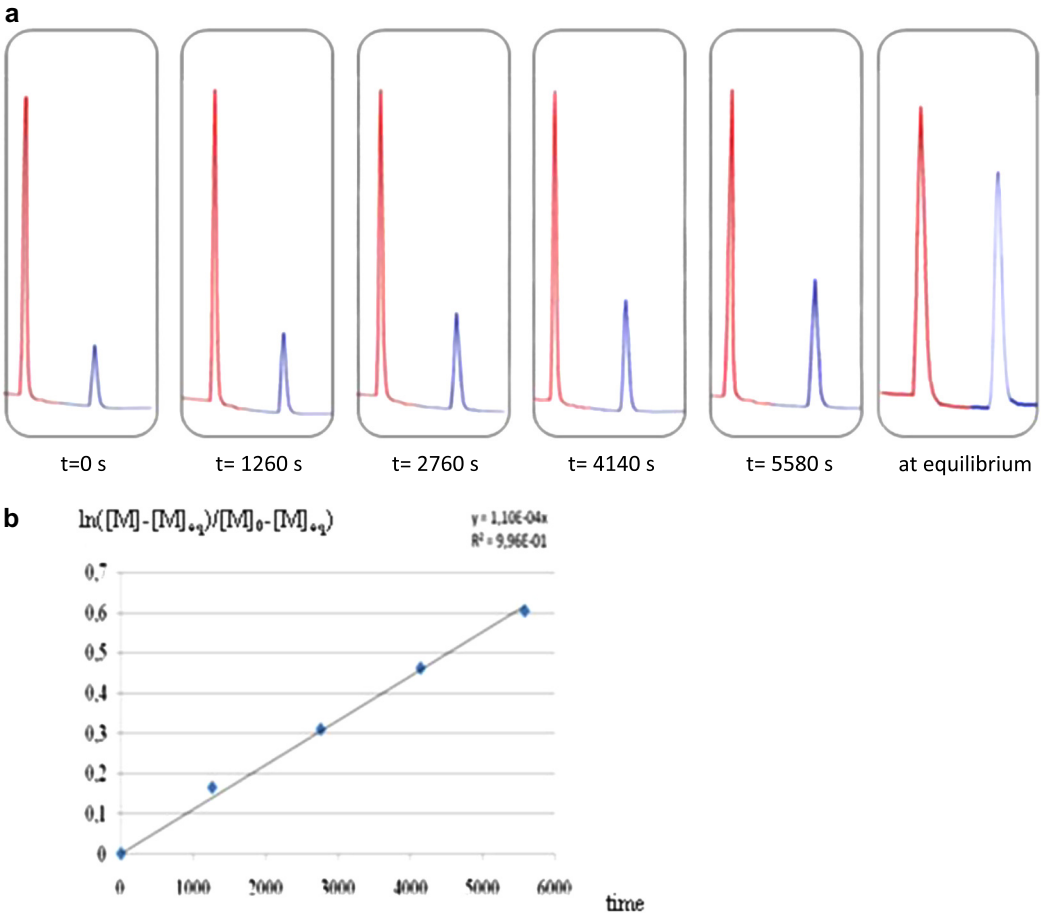


Figure 4. (a) Interconversion of the micropreparatively separated enantiomer of compound **4** to its counterpart at 80 °C. (b) $\ln([M] - [M]_{eq})/[M]_0 - [M]_{eq})$ versus time graph.

Table 3
Dynamic NMR and HPLC conditions for compounds **1**–**4**

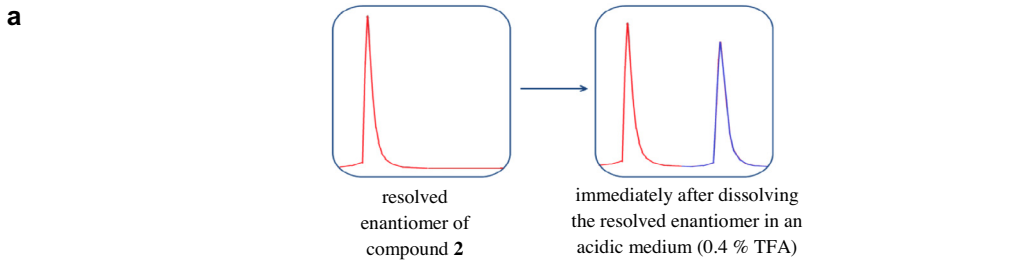
Compound	Method	Temperature (°C)	k (Rate constant) (s^{-1})	Barrier to hindered rotation (kJ/mol)
1	Dynamic NMR	−50[a]	$k_c = (2.3–7.1) \times 10^{-1}$[b]	46–48
2	Thermal racemization on HPLC[c]	40	5.9×10^{-5}[d]	102.1 ± 0.7
3	Dynamic NMR	5[a]	$k_c = 1.12 \times 10^{-2}$[b]	57
4	Thermal racemization on HPLC[e]	80	5.5×10^{-5}[d]	115.7 ± 0.7

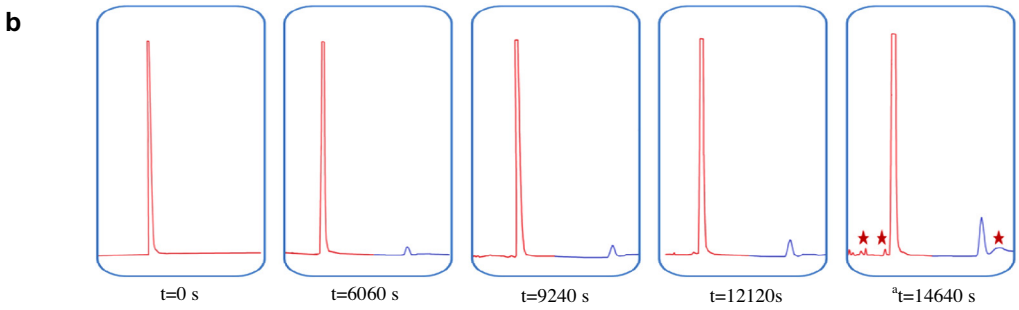
[a] Coalescence temperature.
[b] k_c is the rate constant at coalescence temperature (T_c).
[c] Thermal racemization was followed on a Chiralpak AD HPLC column: amylose tris (3,5-dimethylphenylcarbamate).
[d] The first order rate constant for thermal interconversion.
[e] Thermal racemization was followed on Chiralpak IC: cellulose tris (3,5-dichlorophenylcarbamate).

product peak to the remaining reactant in the presence and absence of 10 mol % of **2**, respectively) at room temperature. We are searching for conditions that will increase the catalytic activity of **2** so that the chromatographically resolved[34] enantiomer of **2** can be exploited as an axially chiral asymmetric acylation catalyst.[35]

3. Conclusion

Herein chromatographically resolvable axially chiral enantiomeric 2-pyridylimino-3-pyridyl-thiazolidine-4-ones and -thiones have been synthesized and the rotational barriers of unprotonated forms have been determined as 46–116 kJ/mol either by temperature dependent NMR or by thermal racemization of the resolved enantiomers. The barrier of **1** was estimated to be between 46 and 48 kJ/mol. Replacement of the exocyclic oxygen atom in compounds **1** and **2** by sulfur (compounds **3** and **4**) caused an increase of 11–14 kJ/mol in the rotational barriers. Methyl substitution at the C-3 position of the *N*-3-pyridyl (compounds **2** and **4**) caused an increase of approximately 57 kJ/mol in the rotational barrier. Under acidic conditions (0.4% TFA), it was observed that compound **2** immediately racemized and this observation indicated that the planar transition state of rotation is exceptionally stabilized by hydrogen bonding interactions either with the carbonyl oxygen or with the imino nitrogen (Fig. 5c). The rotational barrier of compound **4** decreased by 9.3 kJ/mol under the same acidic conditions via weaker H-bonding between the protonated N-3-pyridine and the exocyclic sulfur atom. Research is currently underway in our laboratories to determine if we can exploit the chromatographically resolved thermally stable enantiomers of **2** as axially chiral acylation organocatalysts.





[a]At a constant temperature of 32°C, compound **4** started to degrade in the presence of 0.4 % trifluoroacetic acid after t=12120 s while rotational barrier of the compound was determined by taking the interconversion process up to that time into consideration.
★Decomposition products.

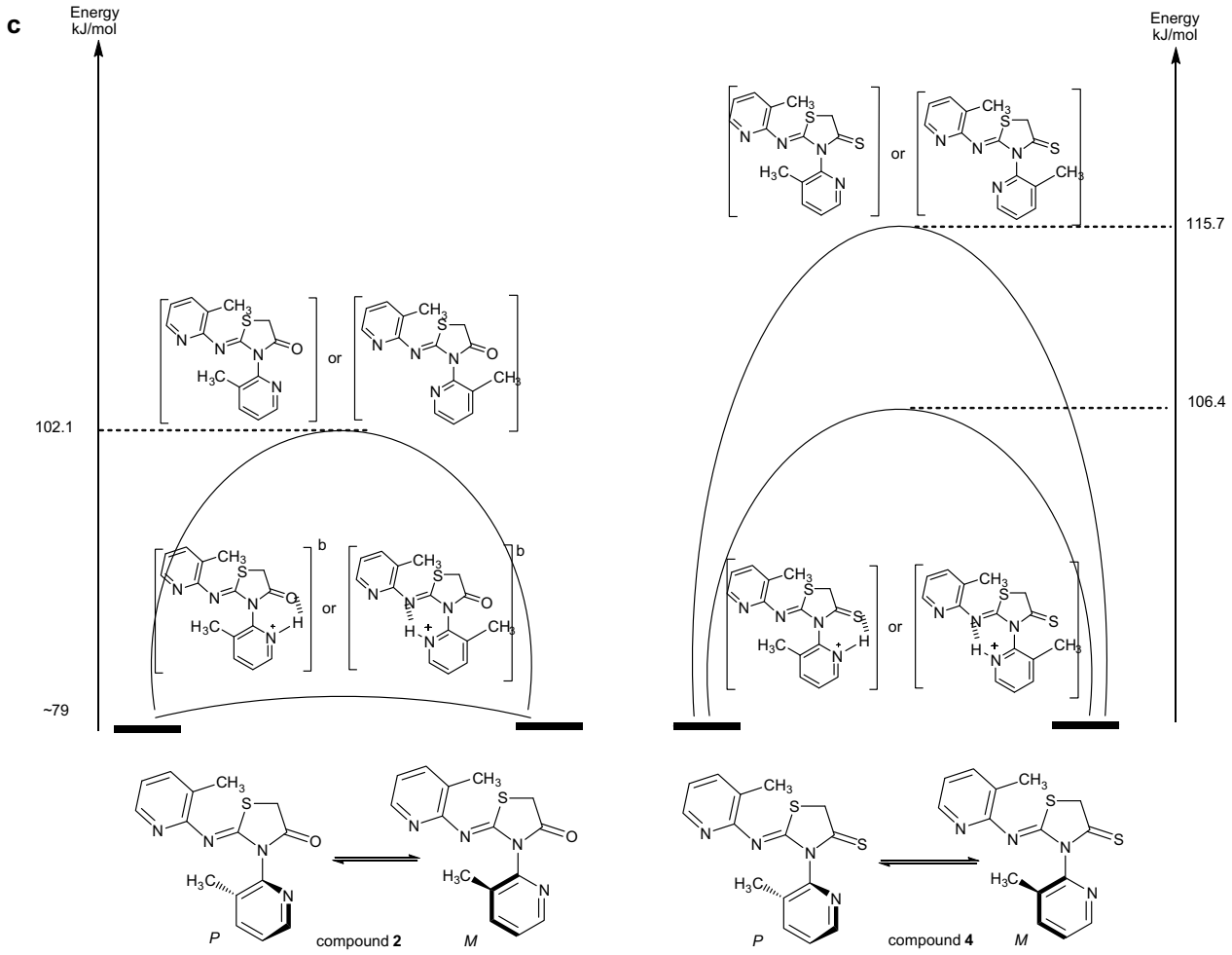


Figure 5. (a) Immediate interconversion of the micropreparatively resolved first eluted enantiomer of **2** into its counterpart in an acidic medium (0.4% TFA) at 25 °C. (b) Thermal racemization of the micropreparatively resolved first eluted enantiomer of **4** in $CHCl_3$ containing 0.4% TFA at 32 °C. (c) Rotational energy barriers of the protonated and unprotonated forms of compounds **2** and **4**.

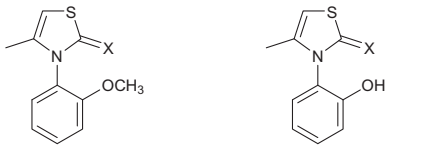


Figure 6. The rotational barriers of the structurally related *ortho*-OH versus *ortho*-OCH_3 compounds.[28]

4. Experimental

4.1. General procedure for the preparation of *N,N′*-diarylthioureas

The appropriate aniline derivative was dissolved in pyridine after which CS_2 was added. The mixture was refluxed overnight under N_2. Next, the solution was concentrated by evaporating the solvent and then cooled to give a precipitate. The precipitated product was isolated by vacuum filtration, stirred in water overnight, and dried in vacuo. The crude *N,N′*-diarylthiourea was purified by recrystallization from ethanol.

4.1.1. 1,3-Di(pyridin-2-yl)thiourea 1a[36]

This compound was synthesized according to the general procedure using 4.71 g (0.05 mol) of 2-amino pyridine, 7.61 g (0.1 mol) of carbon disulfide and 20 ml of pyridine. Yield: 3.33 g (58%), mp: 156–158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.31 (br s, 1H, NH), 9.02 (br s, 1H, NH), 8.86 (br s, 1H), 8.39 (s, 2H), 7.71 (s, 2H), 7.06 (s, 2H), 6.87 (br s, 1H) ppm.

4.1.2. 1,3-Bis(3-methylpyridin-2-yl)thiourea 2a

This compound was synthesized according to the general procedure using 5.03 ml (0.05 mol) of 2-amino-picoline, 7.61 g (0.1 mol) of carbon disulfide, and 20 ml of pyridine. Yield: 3.33 g (60%), mp: 166–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.78 (br s, 1H, NH), 8.42 (br s, 1H, NH), 8.09 (br s, 2H), 7.63 (br s, 1H), 7.54 (br s, 1H), 7.21 (br s, 1H), 6.95 (br s, 1H), 2.42 (br s, 3H, CH_3), 2.35 (br s, 3H, CH_3) ppm. HRMS (TOF MS ES+): Calculated for $C_{13}H_{14}N_4S_1H$+: 259.1017; Found: 259.1007.

4.2. General procedure for the preparation of compounds 1 and 2

The appropriate *N,N′*-diarylthiourea and α-bromoacetic acid or 2-bromo-propionic acid were refluxed for 4 h in absolute ethanol in the presence of sodium acetate. At the end of this period, the excess of ethanol was distilled off and the reaction mixture was poured into cold water to give a precipitate, which was collected and washed several times with hot water in order to remove unreacted α-bromoacetic acid/2-bromo-propionic acid and sodium acetate. After drying, the product was purified by recrystallization from ethanol.

4.2.1. 3-(Pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-one 1

This compound was synthesized according to the general procedure using 1.15 g (0.005 mol) 1,3-di(pyridin-2-yl)thiourea, 0.69 g (0.005 mol) of α-bromoacetic acid, 0.49 g (0.006 mol) of sodium acetate, and 30 ml of ethanol. Yield: 0.71 g (53%), mp: 210–212 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (dd, 1H, H_1, J = 4.5 Hz), 8.36 (dd, 1H, H'_1, J = 4.9 Hz), 7.85 (m, 1H, H_3), 7.54 (m, 1H, H'_3), 7.36 (m, 1H, H_2), 7.33 (d, 1H, H_4, J = 7.8 Hz), 6.95 (m, 1H, H'_2), 6.89 (d, 1H, H'_4, J = 7.8 Hz), 3.88 (s, 2H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 157.9, 149.9, 148.9, 146.4, 138.5, 137.8, 124.2, 123.9, 121.2, 120.1, 33.9 ppm. HRMS (TOF MS ES+): Calculated for $C_{13}H_{10}N_4O_1S_1H$+: 271.0654; Found: 271.0650.

4.2.2. 3-(3-Methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino) thiazolidin-4-one 2

This compound was synthesized according to the general procedure using 1.29 g (0.005 mol) 1,3-bis(3-methylpyridin-2-yl)thiourea, 0.69 g (0.005 mol) of α-bromoacetic acid, 0.49 g (0.006 mol) of sodium acetate, and 30 ml of ethanol. Yield: 0.54 g (36%), mp: 134–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (dd, 1H, H_1, J = 4.6 Hz), 8.25 (dd, 1H, H'_1, J = 4.6 Hz), 7.72 (m, 1H, H_3), 7.42 (m, 1H, H'_3), 7.35 (dd, 1H, H_2, J = 7.5 Hz), 6.93 (dd, 1H, H'_2, J = 7.7 Hz), 3.96 (s, 2H, CH_2), 2.29 (s, 3H, CH_3), 1.93 (s, 3H, CH'_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 155.1, 147.3, 146.45 and 146.44 (partially coalesced), 142.7, 138.7, 137.4, 131.3, 128.4, 123.6, 119.2, 32.9, 16.0, 15.7 ppm. HRMS (TOF MS ES+): Calculated for $C_{15}H_{14}N_4O_1S_1H$+: 299.0967; Found: 299.0953.

4.3. General procedure for the preparation of compounds 3 and 4

The appropriate 2-arylimino-3-aryl-thiazolidine-4-one and Lawesson's reagent were refluxed for 6 h in dry toluene. The solvent was then removed under reduced pressure. The crude product was purified by column chromatography using silica gel.

4.3.1. 3-(Pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidine-4-thione 3

This compound was synthesized according to the general procedure using 0.423 g (1.57 mmol) of 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-one **1**, 0.317 g (0.785 mmol) Lawesson's reagent, and 30 ml of dry toluene. The crude product was purified by column chromatography, using silica gel and eluted with EtOAc/CH_2Cl_2 mixture (1/10). Yield: 0.13 g (30%), mp: 134–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (br s, 1H, H_1), 8.39 (br s, 1H, H'_1), 7.89 (m, 1H, H_3), 7.54 (m, 1H, H'_3), 7.39 (m, 1H, H_2), 7.29 (d, 1H, H_4, J = 7.4 Hz), 6.96 (m, 1H, H'_2), 6.89 (d, 1H, H'_4, J = 7.4 Hz), 4.41 (s, 2H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.2, 161.5, 157.3, 151.6, 150.2, 146.5, 138.8, 137.8, 124.4, 124.1, 121.9, 120.4, 46.2 ppm. HRMS (TOF MS ES+): Calculated for $C_{13}H_{10}N_4S_2H$+: 287.0425; Found: 287.0425.

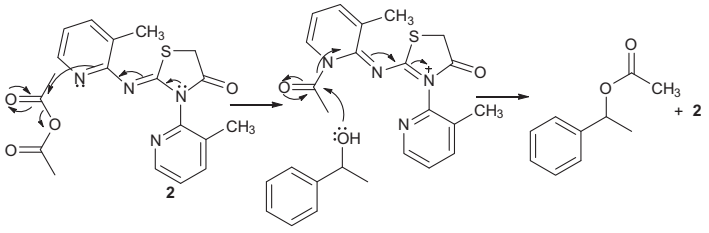


Figure 7. The proposed mechanism for the acylation reaction with the catalysis of **2**.

4.3.2. 3-(3-Methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino) thiazolidine-4-thione 4

This compound was synthesized according to the general procedure using 1.85 g (6.2 mmol) of 3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one **2**, 1.25 g (3.1 mmol) of Lawesson reagent, and 15 ml of dry toluene. The crude product was purified by column chromatography, using silica gel and eluted with EtOAc/hexane mixture (1/5). Yield: 0.43 g (22%), mp: 169–171 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (m, 1H, H_1), 8.22 (m, 1H, H'_1), 7.69 (m, 1H, H_3), 7.36 (m, 1H, H'_3), 7.30 (dd, 1H, H_2, J = 7.2 Hz), 6.89 (dd, 1H, H'_2, J = 7.2 Hz), 4.42 (s, 2H, CH_2), 2.17 (s, 3H, CH_3), 1.83 (s, 3H, CH'_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.7, 158.4, 154.4, 149.9, 146.7, 142.9, 138.8, 137.5, 130.9, 129.1, 123.7, 119.5, 45.1, 15.7, 15.6 ppm. HRMS (TOF MS ES+): Calculated for $C_{15}H_{14}N_4S_2H$+: 315.0738; Found: 315.0734.

Acknowledgments

This project was supported by the Boğaziçi University research fund (BAP) with project numbers 10B05P6 and 13B05P5.

References

1. Tan, X.; Zhan, J.; Zhang, J.; Jiang, L.; Pan, M.; Su, C. *Cryst. Eng. Commun.* **2012**, *14*, 63–66.
2. Fang, Y.; Zhao, L.; Wang, D.; Wang, M. *J. Org. Chem.* **2012**, *77*, 10073–10082.
3. Mohamed, M. F.; Sanchez-Lombardo, I.; Neverov, A. A.; Brown, R. S. *Org. Biomol. Chem.* **2012**, *10*, 631.
4. Duan, L.; Bozoglian, F.; Mandal, S.; Stewart, B.; Privalov, T.; Llobet, A.; Sun, L. *Nat. Chem.* **2012**, *4*, 418–423.
5. Phapale, V. B.; Bunuel, E.; Garcia-Iglesias, M.; Cardenas, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8790–8795.
6. Wang, L.; Zhang, C.; Wang, Z. *Eur. J. Inorg. Chem.* **2007**, *17*, 2477–2487.
7. Constant, S.; Tortoioli, S.; Mueller, J.; Lacour, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2082–2085.
8. Visnjevac, A.; Tusek-Bozic, L.; Majeric-Elenkov, M.; Hamersak, Z.; Kooijman, H.; De Clercq, E.; Kojic-Prodic, B. *Polyhedron* **2002**, *21*, 2567–2577.
9. Zhu, F.; Xu, W.; Liu, X.; Lin, S. *J. Appl. Polym. Sci.* **2002**, *84*, 1123–1132.
10. Mikata, Y.; Shinohara, Y.; Yoneda, K.; Nakamura, Y.; Esaki, K.; Tanahashi, M.; Brudzinska, I.; Hirohara, S.; Yokoyama, M.; Mogami, K.; Tanase, T.; Kitayama, T.; Takashiba, K.; Nabeshima, K.; Takagi, R.; Takatani, M.; Okamoto, T.; Kinoshita, I.; Doe, M.; Hamazawa, A.; Morita, M.; Nishida, F.; Sakakibara, T.; Orvig, C.; Yano, S. *J. Org. Chem.* **2001**, *66*, 3783–3789.
11. Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384.
12. McCarthy, M.; Guiry, P. J. *Tetrahedron* **2001**, *57*, 3809–3844.
13. Guo, Q. X.; Wu, Z. J.; Luo, Z. B.; Liu, Q. Z.; Ye, J. L.; Luo, S. W.; Cun, L. F.; Gong, L. Z. *J. Am. Chem. Soc.* **2007**, *129*, 13927–13938.
14. Noyori, R. *Adv. Synth. Catal.* **2003**, *345*, 15–32.
15. Li, X.; Jiang, H.; Uffman, E. W.; Guo, L.; Zhang, Y.; Yang, X.; Birman, V. B. *J. Org. Chem.* **2012**, *77*, 1722–1737.
16. Spivey, A. C.; Zhu, F.; Mitchell, M. B.; Davey, S. G.; Jarvest, R. L. *J. Org. Chem.* **2003**, *68*, 7379–7385.
17. Saitoh, A.; Morimoto, T.; Achiwa, K. *Tetrahedron: Asymmetry* **1997**, *8*, 3567–3570.
18. Dobish, M. C.; Johnston, J. N. *Org. Lett.* **2010**, *12*, 5744–5747.
19. Zhu, X. F.; Shi, D. Q. *J. Heterocycl. Chem.* **2011**, *48*, 572–576.
20. Romine, J. L.; Laurent, D. R.; Leet, J. E.; Martin, S. W.; Serrano-Wu, M. H.; Yang, F.; Gao, M.; O'Boyle, D. R.; Lemm, J. A.; Sun, J. H.; Nower, P. T.; Huang, X.; Deshpande, M. S.; Meanwell, N. A.; Snyder, L. B. *ACS Med. Chem. Lett.* **2011**, *2*, 224–229.
21. Pan, B.; Huang, R. Z.; Han, S. Q.; Qu, D.; Zhu, M. L.; Wei, P.; Ying, H. J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2461–2464.
22. Erol, S.; Dogan, I. *Tetrahedron* **2013**, *69*, 1337–1344.
23. Demir, O.; Dogan, I. *Chirality* **2003**, *15*, 242–250.
24. Raban, M.; Kost, D.; Carlson, E. H. *Chem. Commun.* **1971**, 656.
25. Erol, S.; Dogan, I. *J. Org. Chem.* **2007**, *72*, 2494–2500.
26. Dogan, I.; Burgemeister, T.; Icli, S.; Mannschreck, A. *Tetrahedron* **1992**, *48*, 7157–7164.
27. Sanz, D.; Perona, A.; Claramunt, R. M.; Pinilla, E.; Torres, M. R.; Elguero, J. *ARKIVOC* **2010**, *3*, 102–113.
28. Roussel, C.; Vanthuyne, N.; Bouchekara, M.; Djafri, A.; Elguero, J.; Alkorta, I. *J. Org. Chem.* **2008**, *73*, 403–411.
29. Rebek, J.; Trend, J. E. *J. Am. Chem. Soc.* **1978**, *100*, 4315–4316.
30. Alkorta, I.; Elguero, J.; Roussel, C. *Tetrahedron: Asymmetry* **2011**, *22*, 1180–1183.
31. Dolain, C.; Maurizot, V.; Huc, I. *Angew. Chem., Int. Ed.* **2003**, *42*, 2738–2740.
32. Kelly, T. R. *Molecular Machines (Topics in Current Chemistry)*, 1st ed.; Springer: Berlin, 2005. p 63.
33. Spivey, A. C.; Maddaford, A.; Leese, D. P.; Redgrave, A. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1785–1794.
34. Spivey, A. C.; Charbonneau, P.; Fekner, T.; Hochmuth, D. H.; Maddaford, A.; Malardier-Jugroot, C.; Redgrave, A. J.; Whitehead, M. A. *J. Org. Chem.* **2001**, *66*, 7394–7401.
35. Spivey, A. C.; Fekner, T.; Spey, S. E. *J. Org. Chem.* **2000**, *65*, 3154–3159.
36. Saxena, A.; Pike, R. D. *J. Chem. Crystallogr.* **2007**, *37*, 755–764.