Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Isophthalic Acid-Derived Dicarbothioamides as Novel Metal-Free Catalysts in Hydrogen Bond-Promoted Reactions

Stefania Guizzetti [a], Maurizio Benaglia [a], Alessandra Puglisi [a] & Laura Raimondi [a]
[a] Department of Organic and Industrial Chemistry, University of Milan, Milan, Italy
Version of record first published: 08 Sep 2009.

To cite this article: Stefania Guizzetti , Maurizio Benaglia , Alessandra Puglisi & Laura Raimondi (2009): Isophthalic Acid-Derived Dicarbothioamides as Novel Metal-Free Catalysts in Hydrogen Bond-Promoted Reactions, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:20, 3731-3742

To link to this article: http://dx.doi.org/10.1080/00397910902838847

Synthetic Communications®, 39: 3731–3742, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910902838847

Taylor & Francis
Taylor & Francis Group

Isophthalic Acid–Derived Dicarbothioamides as Novel Metal-Free Catalysts in Hydrogen Bond–Promoted Reactions

Stefania Guizzetti, Maurizio Benaglia, Alessandra Puglisi, and Laura Raimondi
Department of Organic and Industrial Chemistry, University of Milan, Milan, Italy

Abstract: The synthesis of *N,N′*-diaryl-1,3-benzene-dicarbothioamides was accomplished in only two steps with good yields, and their ability to act as hydrogen-bond donors in Diels–Alder reactions was evaluated. These new organocatalysts were indeed able to promote the cycloaddition of cyclopentadiene to α,β-unsaturated aldehydes. In the attempt to control the absolute stereochemistry of the reaction, chiral catalysts were also prepared by simple condensation of isophthalic acid and α-amino acid derivatives. Molecular mechanics calculations were performed to elucidate the mode of action of these metal-free catalytic systems and to find a rationale for the achieved enantioselectivity.

Keywords: Carbothioamides, C–C bond formation, cycloaddition, hydrogen bond, organocatalysis

INTRODUCTION

It has been recently recognized that the use of hydrogen bonding to activate a properly functionalized substrate may be a viable alternative to the traditional methodology that relies upon Lewis acid catalysis.[1] Among different chiral compounds capable of donating one or more

Received December 16, 2008.
Address correspondence to Maurizio Benaglia, Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, via Golgi 19, I-20133 Milan, Italy. E-mail: Maurizio.Benaglia@unimi.it

hydrogen bonds and therefore catalyzing stereoselective reactions, phosphoric acids,[2] diols,[3] thiourea derivatives[4] and, less often, carboxylic acids[5] have been widely used. In the last few years, the class of thiourea catalysts was further expanded through the development of bifunctional catalytic systems,[6] where the thiourea group is usually coupled to a chiral Lewis base to realize a greater degree of stereocontrol over the reaction. If it is clear that thiourea catalysts are an important class of organocatalysts able to efficiently control the stereochemistry in several chemical transformations, it is also true that the synthesis of chiral compounds embedding the thiourea group is not always that straightforward.

We decided to explore the catalytic ability of a new class of readily available compounds that are able to act as hydrogen-bond donors in C–C bond-formation reactions as alternatives to the well-established thiourea derivatives.

RESULTS AND DISCUSSION

We focused our attention on molecules featuring two carbothioamide groups, designed to properly orientate two acidic hydrogen atoms in such a way as to bind a substrate bearing a functional group able to accept hydrogen bonding, such as an α,β-unsaturated aldehyde.

In this context, derivatives of isophthalic acid of the general structure shown in Fig. 1 seem especially attractive. In particular, we hoped that both carbothioamidic hydrogen atoms could be involved in the H-bonding of the aldehyde, thus providing activation of the latter. To determine if our working hypothesis was correct, a conformational analysis with forcefield methods (MM2*) was performed,[7] by running molecular mechanics calculations on the complex of *N,N′*-dimethyl-1,3-benzene-dicarbothioamide with crotonic aldehyde. Despite our hopes,

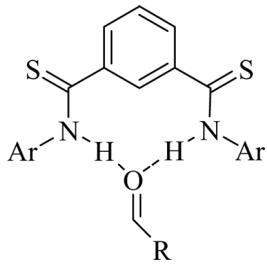


Figure 1. General structure of a new class of hydrogen-bond donors in organocatalysis.

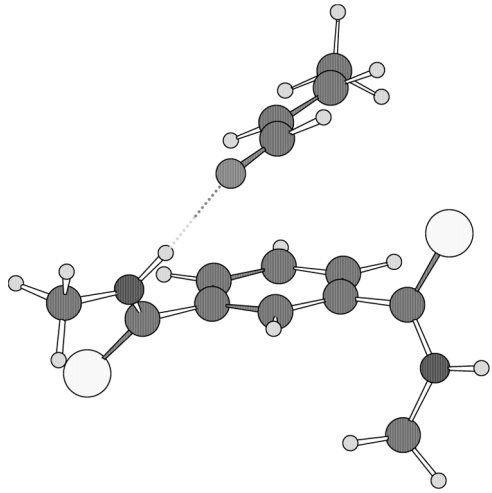


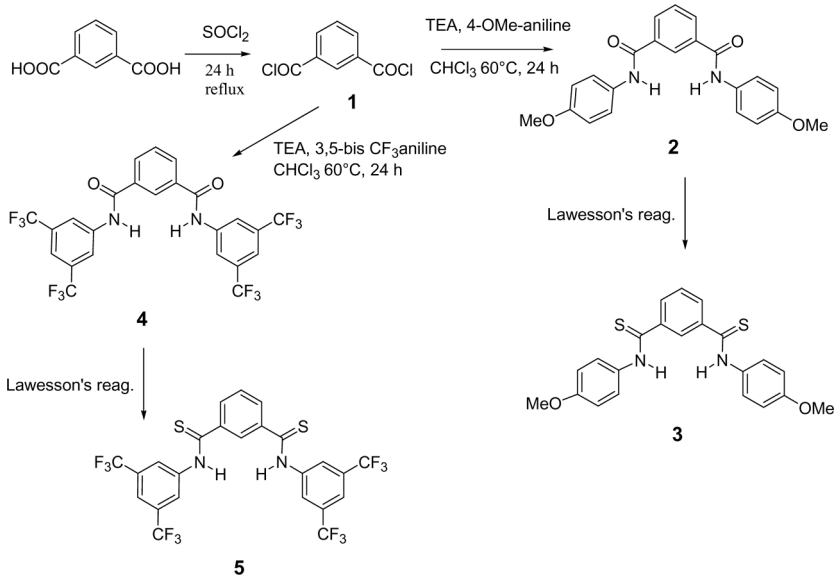
Figure 2. Molecular mechanics calculations on the complex of *N,N′*-dimethyl-1,3-benzene-dicarbothioamide with crotonic aldehyde.

only monocoordination of the aldehydic oxygen was supported by the calculated data. (The minimum energy conformation of the complex is shown in Fig. 2.) However, only hydrogen-bonded structures were located: thus activation of the α,β-unsaturated compounds toward nucleophylic additions and cycloadditions was likely to be more than a working hypothesis.

At the beginning of our investigation, we decided to prepare achiral molecules and to study their ability to promote reactions through hydrogen-bonding activation of the substrate. The synthesis of these compounds is straightforward and involves the condensation of isophthalic acid with an aromatic amine to afford the expected *N,N′*-diaryl-1,3-benzene-dicarboxamide, followed by the conversion to bis-carbothioamide derivative by reaction with Lawesson's reagent[8] (Scheme 1).

The reaction of isophthaloyl chloride **1** with 4-methoxyaniline led to compound **2** in 71% yield, which was converted by reaction with Lawesson's reagent in the bis-carbothioamide derivative **3** in 98% yield. Similarly, the condensation of **1** with 3,5-bis-trifluoromethyl aniline to give bis-carboxy-amide **4,** in 97% yield followed by the transformation of carboxy-amide groups into carbothioamides, afforded product **5** in 71% yield.

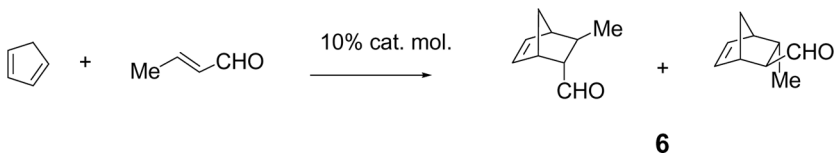
Compounds **3** and **5**, bearing aryl groups of different electronic characteristics, were employed to test the cycloaddition of cyclopentadiene with crotonic aldehyde (Scheme 2). In a typical experiment, aldehyde



Scheme 1. Synthesis of achiral catalysts **3** and **5**.

(1 mol. eq.) was added to a stirred solution of the catalyst (0.1 mol. eq.) in the proper solvent under an inert atmosphere; after 5 min, cyclopentadiene (3.5 mol. eq.) was added. The reaction mixture was allowed to stir at room temperature for 72 h. The reaction mixture was evaporated under reduced pressure and analyzed by NMR. The yield and diastereoisomeric ratio were then confirmed on the isolated product, which was purified by flash chromatography on a short silica-gel column with an ethylacetate/hexane mixtures as eluant.

The results of the reaction performed in different solvents at room temperature in the presence of compounds **3** or **5** are collected in Table 1, together with the data obtained by running the cycloaddition without catalyst.



6

Scheme 2. Diels–Alder reaction catalyzed by *N,N′*-diaryl or dialkyl-1,3-benzene-dicarbothioamides.

Table 1. Diels–Alder reaction of cyclopentadiene to crotonic aldehyde catalyzed by compounds **3** and **5**

Entry	Solvent	Catalyst	Yield[a] (%)	*Exo*/*endo* ratio[b]
1	DCM	—	30	55/45
2	DCM	**3**	48	58/42
3	DCM	**5**	37	70/30
4	THF	—	13	51/49
5	THF	**3**	41	55/45
6	THF	**5**	37	71/29
7	—	—	23	68/32
8	—	**3**	47	62/38
9	—	**5**	51	75/25

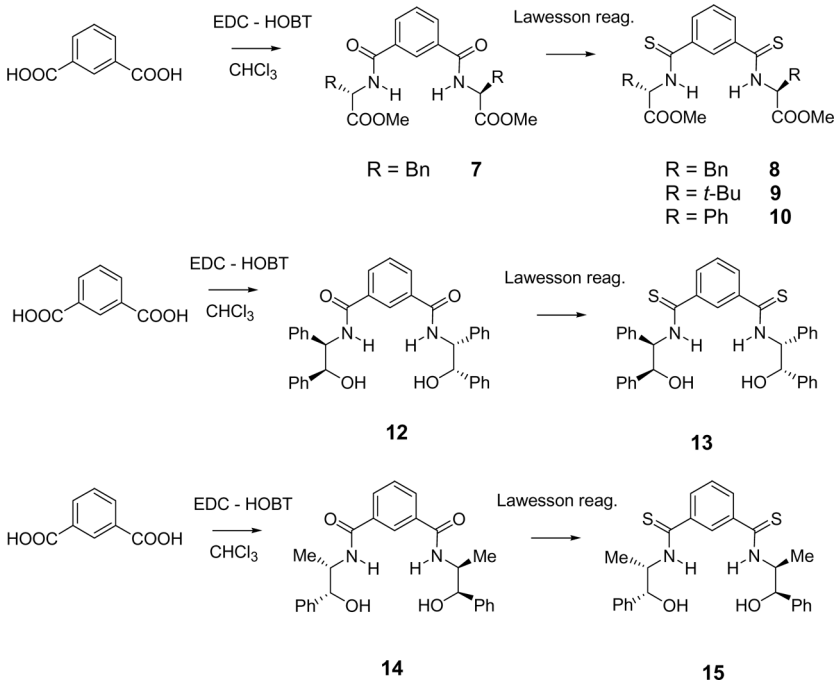
[a]Determined by ^{1}H NMR and confirmed after chromatographic purification after 72 h at 25°C.

[b]Determined by ^{1}H NMR and confirmed by HPLC analysis.

From the data of Table 1, it is evident that both compounds **3** and **5** are indeed able to activate the carbonyl compound toward the cycloaddition with cyclopentadiene through coordination mediated by hydrogen bonding. The reaction of cyclopentadiene with cinnamaldehyde afforded the products in lesser yields. Although the reaction without any catalyst afforded the cycloadduct in very poor yields after 72 h at room temperature (entries 1, 4, and 7 of Table 1), in the presence of **3** or **5,** the product was isolated constantly in great yields independent of the solvent system. For example, compound **3** promoted the Diels–Alder reaction in 48%, 41%, and 47% yields in dichloromethane (DCM), in tetrahydrofuran (THF), and without solvent, respectively (entries 2, 5, and 8 of Table 1). An analogous behavior also was shown by bis-carbothioamide **5** which catalyzed the reaction in up to 51% yield with 75/25 *endo*/*exo* isomer ratio at room temperature (entries 3, 6, and 9 of Table 1). The findings seem to suggest an effective ability of molecules **3** and **5** to bind carbonyl substrates and activate them in cycloaddition reactions, as was evidenced by the molecular mechanics preliminary investigations.

Based on these promising results, we decided to prepare a chiral version of such new catalytic systems in an attempt to control the absolute stereochemistry of the reaction. At this preliminary stage of the investigation, simple α-amino acid derivatives were employed in the condensation with isophthalic acid (Scheme 3).

The EDC-mediated condensation of isophthalic acid with (S)-phenyl alanine methylester afforded the expected bis-carboxyamide derivative **7**



Scheme 3. Synthesis of chiral catalysts **7**–**10**, **13**, and **15**.

in 85% yield, which was converted in the bis-carbothioamide derivative **8** in 98% yield by reaction with Lawesson's reagent. A similar methodology allowed us to synthesize compounds **9** and **10**, in 77% and 83% overall yields, by reaction with (S)-*ter*-leucine methylester and (S)-phenyl glycine methylester, respectively.

These chiral compounds were employed in the cycloaddition between crotonic aldehyde and cyclopentadiene, and the results of this early exploration are shown in Table 2.

Bis-carbothioamide derivative **8** promoted the reaction clearly in greater yield than bis-amide **7**, further demonstrating that for this kind of reaction the more acidic hydrogen atoms of the carbothioamide group make such compounds better hydrogen-bond donors than amides and therefore are more efficient catalysts (entries 1 and 2 of Table 2).[9]

Compounds **8**, **9**, and **10** showed similar chemical efficiency in promoting the cycloaddition reaction in up to 55% yield and 75/25 *endo*/*exo* isomer ratio at room temperature (entries 2–4). However, the catalysts were not able to exert any control in determining the absolute stereochemistry of the product. Performing the reaction in different

Table 2. Cycloaddition of cyclopentadiene to crotonic aldehyde

Entry	Catalyst	Temp. (°C)	Yield[a] (%)	*Endo*/*exo* ratio[b]	Ee *endo*[c] (%)
1	**7**	25	19	63/37	n.d.
2	**8**	25	55	75/25	<5
3	**9**	25	50	65/35	<5
4	**10**	25	43	62/38	<5
5	**13**	25	53	67/33	13
6	**13**	0	71	77/23	14
7	**13**	−40	33	75/25	19
8	**15**	25	47	67/33	10
9	**15**	0	79	77/23	9

[a]Determined by ^{1}H NMR and confirmed after chromatographic purification after 72 h without any solvent.

[b]Determined by ^{1}H NMR.

[c]Determined by GC on chiral stationary phase (Agilent HP-chiral) $t_{major\ exo} = 59.1$ min, $t_{min\ exo} = 59.6$ min, $t_{major\ endo} = 60.6$ min, $t_{min\ endo} = 62.2$ min.

solvents and at lower temperature did not improve the stereoselectivity of the cycloaddition.

To improve the enantioselectivity of the process, we decided to use chiral amino-alcohol derivatives to build new chiral catalysts bearing two hydroxyl groups, which could help the carbothioamide groups in coordinating in a more conformational rigid chiral environment in the substrate to be activated (Scheme 3). Enantiomerically pure (1S,2R)-1,2-diphenyl-2-amino-1-ethanol **11** was condensed to isophthalic acid via EDC methodology to afford compound **12** in 44% yield; reaction with Lawesson's reagent allowed us to obtain the enantiomerically pure **13** in 91% yield. Analogously, compound **14** was prepared by condensation between isophthalic acid and (1R,2S)-*nor*-ephedrine in 71% yield, which was then transformed into the derivative **15** in 97% yield after chromatographic purification. Both **13** and **15** were then used as organocatalysts in the Diels–Alder reaction (Table 2).

Both compounds **13** and **15** showed good chemical efficiency at room temperature (entries 5 and 8 of Table 2) and even better efficiency at 0°C, leading to the cycloadduct **6** in 71% and 79% yield, respectively (entries 6 and 9 of Table 2). The product was obtained with a good *endo*/*exo* isomer ratio, up to 77/23 (entries 6 and 9), but once again with a low level of enantioselectivity (best result: 19% ee for the *endo* isomer with catalyst **13**; entry 6 of Table 2). A further decrease of the temperature did not bring any improvement on the enantioselectivity of the reaction (entry 7, Table 2).

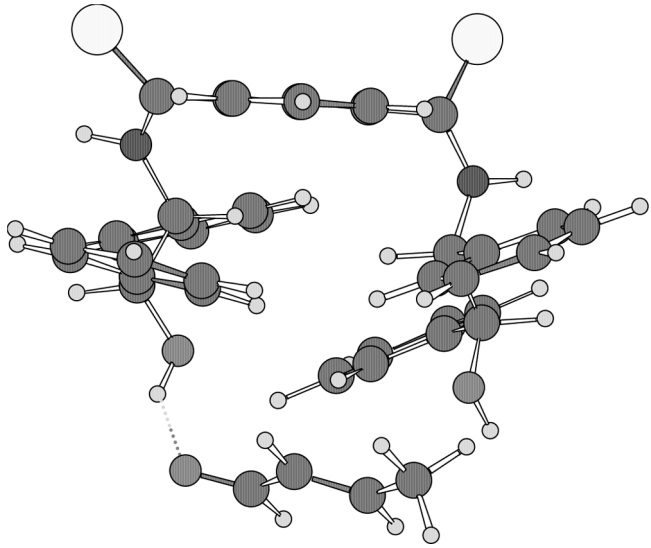


Figure 3. Molecular mechanics calculations on the complexes of catalysts **13** with crotonic aldehyde.

A tentative rationale for the disappointing stereochemical outcome of the reaction was attempted by performing molecular mechanics calculations on the complexes of catalysts **13** and **15** with crotonic aldehyde. See Figure 3. From complete conformational analysis of both complexes, it appeared that in this case carbothioamidic hydrogens were not involved in the interaction with the aldehyde, and hydrogen bonding with one of the hydroxylic hydrogens was preferred by at least 2.6 kcal/mol (in the adduct **13** + crotonic aldehyde).

CONCLUSIONS

In conclusion, the synthesis of *N,N′*-diaryl-1,3-benzene-dicarbothioamides was accomplished in only two steps with good yields, and their ability to act as hydrogen-bond donors in Diels–Alder reactions was evaluated. These new organocatalysts were indeed able to promote the cycloaddition of cyclopentadiene to α,β-unsaturated aldehydes, in up to 79% yield and 77/23 *endo*/*exo* isomer ratio. In an attempt to control the absolute stereochemistry of the reaction, chiral catalysts were also prepared by simple condensation of isophthalic acid with enantiomerically pure α-amino ester and α-amino alcohol derivatives, which showed a poor ability in determining the absolute stereochemistry of the reaction. Further work is in

progress to improve the chemical and especially the stereochemical efficiency of these novel metal-free catalysts.

EXPERIMENTAL

General

^{1}H NMR spectra were recorded at 300 MHz in chloroform-d ($CDCl_3$) unless otherwise stated, and were referenced to tetramethylsilane (TMS) at 0.00 ppm. ^{13}C NMR spectra were recorded at 75 MHz and were referenced to 77.0 ppm in $CDCl_3$. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter at 589 nm. Infrared (IR) spectra were obtained on a Jasco Fourier transform (FT)-IR 4100 type A instrument. Gas chromotography (GC) for ee determination was performed on an Agilent HP-chiral instrument under the conditions reported.

Reagents and solvents were used as purchased.

General Procedure for the Synthesis of Achiral Catalysts 3 and 5

Catalyst **3**

Isophthalic acid (0.15 g, 0.9 mmol) was refluxed for 20 h in 2 mL of thionyl chloride; then the solution was evaporated under vacuum. The residue was dissolved in dry $CHCl_3$ (2 mL) and added to a solution of 4-methoxyaniline (0.25 g, 2 mmol) and triethylamine (0.38 mL, 2.7 mmol) in dry $CHCl_3$ (10 mL). After 70 h of reaction at 40°C, the solvent was evaporated, and the crude reaction mixture was purified by flash chromatography with a 99:1 DCM/methanol mixture as eluant to afford compound **2** as a white solid in 71% yield, whcih was used in the next step (0.24 g, 0.63 mmol). Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] was added (0.28 g, 0.69 mmol) to a solution of compound **2** (0.17 g, 0.46 mmol) in dry toluene (7 mL); the solution was allowed to stir under reflux for 20 h, concentrated, and purified by flash chromatography 95:5 DCM/methanol mixture as eluant to afford compound **3** as yellow solid in 98% yield (0.18 g, 0.45 mmol). Compound **3**: IR (neat): ν 1225, 1177 cm^{-1}. Mp 67–69°C. ^{1}H NMR (DMSO) δ 3.8 (s, 6 H, OMe); 7.00 (d, 4H, 9.0 Hz, H_A of OMe–Ph); 7.51 (t, 1H, $J = 8.0$ Hz), 7.70 (d, 4H, 9.0 Hz, H_B of OMe–Ph); 7.80 (d, 2H, $J = 8.0$ Hz), 8.21 (s, 1H), 11.80 (bs, 2H, NH). ^{13}C NMR ($CDCl_3$): δ 37.2, 118.6, 120.1, 123.4, 127.1, 127.7, 129.1, 135.9, 141.9, 171.1, 196.1. Elem. anal. found: C, 64.61; H, 4.91; N, 6.89. $C_{22}H_{20}N_2O_2S_2$ requires:

C, 64.68; H, 4.93; N, 6.86. Following the same procedure, compound **5** was synthesized.

Compound **5**

IR (neat): ν 1215, 1187 cm^{-1}. Mp 79–81°C. ^1H NMR (DMSO): δ 7.55 (t, 1 H, $J = 12.0$ Hz), 8.00 (d, 2H, $J = 12.0$ Hz), 8.03 (s, 2H), 8.23 (s, 1H), 8.70 (s, 4H), 11.50 (bs, 2H, NH). ^{13}C NMR ($CDCl_3$): δ 39.5, 119.3, 124.0, 124.8, 128.1, 129.7, 130.1, 141.4, 142.0, 198.1. Elem. anal. found: C, 46.39; H,1.91; N, 4.55. $C_{24}H_{12}F_{12}N_2S_2$ requires: C, 46.46; H, 1.95; N, 4.51.

General Procedure for the Synthesis of Chiral Catalysts 7–10, 13, and 15

Representative Synthetic Sequence for the Preparation of Catalyst **8**

Under a nitrogen atmosphere, a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, EDC (0.21 g, 1.1 mmol), and 1-hydroxybenzotriazole (HOBT) (0.14 g, 1.1 mmol) in chloroform (5 mL) was added to a mixture of (S)-phenyl alanine methylester hydrochloride (0.21 g, 1.0 mmol) and isophtalic acid (0.08 g, 0.5 mmol) in chloroform (5 mL) at 0°C. After the reaction mixture was allowed to stir for 20 h at 25°C, it was poured into a 1 N HCl solution (10 mL). The phases were separated, and the organic phase was washed with a saturated $NaHCO_3$ solution and a saturated NaCl solution. The organic phase was dried over Na_2SO_4, filtered, and concentrated under vacuum to afford the crude product **7**, which was used without any further purification (0.21 g, 0.42 mmol, 85% yield).

To a solution of compound **7** (0.1 g, 0.2 mmol) in dry toluene (5 mL), Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2, 4-diphosphetane-2,4-disulfide] was added (0.08 g, 0.2 mmol); the solution was allowed to stir under reflux for 20 h. Then it was concentrated and purified by flash chromatography with a 20:80 AcOEt–hexane mixture as eluant to afford compound **8** as yellow solid (0.1 g, 0.19 mmol). IR (neat): ν 3369, 1738, 1633, 1590, 1509, 1205 cm^{-1}. $[\alpha]_{D^{23}}$ 260.9 (c 0.69, DCM). Mp 81–83°C. ^1H NMR ($CDCl_3$): δ 3.31 (dd, 2H, $J = 5.0$ Hz, 14.0 Hz, H_A of CH_2Ph), 3.60 (dd, 2H, $J = 6.0$ Hz, 14.0 Hz, H_B of CH_2Ph), 3.85 (s, 6H, MeO), 5.61 (m, 2H, CH–N), 7.18 (4H, aromatic protons), 7.35 (8 H, aromatic protons), 7.85 (2 H, aromatic protons), 8.08 (2H, NH), ^{13}C NMR ($CDCl_3$): δ 36.2, 52.6, 59.1, 123.6, 125.1, 127.4, 128.1, 128.7, 129.2, 135.3, 141.4, 171.1, 197.4. Elem. anal.

found: C, 64.64; H, 5.45; N, 5.36. $C_{28}H_{28}N_2O_4S_2$ requires: C, 64.59; H, 5.42; N, 5.38.

Following the same procedure, catalysts **13** and **15** were also prepared.

Compound **13**

IR (neat): ν 3519, 1204, 1122 cm^{-1}. $[\alpha]_{D^{23}}$ 60.1 (*c* 0.11, $CHCl_3$). Mp 288–289°C. ^1H NMR ($CDCl_3$): δ 3.9 (bs, 2 H, OH), 5.0 (dd, 2H, $J = 6.0$ Hz, 8 Hz, CH–N), 5.9 (d, 2 H, $J = 8.0$ Hz, CH–O), 7.0 (bs, 2H, NH), 7.18–7.30 (m, 21H, aromatic protons of phenyl rings +1H of central phenyl ring), 7.57 (t, 1H, $J = 5.0$ Hz), 8.00 (d, 2H, J 5.0 Hz). ^{13}C NMR ($CDCl_3$): δ 71.7, 81.6, 125.9, 126.6, 126.9, 127.5, 127.9, 128.2, 128.5, 128.9, 131.7, 132.0, 133.6, 141.7, 169.7. Elem. anal. found: C, 73.41; H, 5.47; N, 4.79. $C_{36}H_{32}N_2O_2S_2$ requires: C, 73.44; H, 5.48; N, 4.76.

Compound **15**

IR (neat): ν 3052, 1265, 1193 cm^{-1}. $[\alpha]_{D^{23}}$ −142.9 (*c* 0.12, CHCl3). ^1H NMR ($CDCl_3$): δ 1.55 (d, 6H, $J = 4.0$ Hz, methyl groups), 3.8 (bs, 2H, OH), 4.70 (d, 2H, $J = 6.0$ Hz, CH–N), 4.85 (d, 2 H, $J = 6.0$ Hz, CH–O), 7.18–7.30 (m, 21 H, aromatic protons of phenyl rings +1H of central phenyl ring), 7.47 (t, 1 H, $J = 4.0$ Hz), 8.05 (d, 2 H, $J = 4.0$ Hz), 8.30 (bs, 2H, NH). ^{13}C NMR ($CDCl_3$): δ 20.1, 61.9, 81.0, 126.3, 127.5, 127.9, 128.4, 128.9, 131.2, 133.6, 141.1, 165.4. Elem. anal. found: C, 67.31; H, 6.11; N, 5.99. $C_{26}H_{28}N_2O_2S_2$ requires: C, 67.21; H, 6.07; N, 6.03.

Conformational Analysis of Complexes Between Bis-carbothioamides and Crotonic Aldehyde

The conformational analyses were performed on the complexes with the MonteCarlo pseudo-systematic algorithm[10] as implemented in MacroModel 7.2 package.[7] As variables, all free torsional angles were selected, while aldehyde was allowed translation and rotation with respect to the catalyst. Duplicate conformations were eliminated, and convergence of the search was considered as achieved when all low-energy conformations (within 3 kcal/mol) were repeatedly sampled. Allinger's forcefield as implemented in MacroModel 7.2 package was used for all calculations because of its proven reliability in the treatment of small organic molecules.

ACKNOWLEDGMENTS

This work was supported by Ministero Istruzione, Università e Ricerca (MIUR) (Rome) within the national project "Nuovi metodi catalitici stereoselettivi e sintesi stereoselettiva di molecole funzionali."

REFERENCES

1. Reviews: (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289; (b) Pihko, P. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2062.
2. Reviews: (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999; (b) Connon, S. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 3909.
3. McGilvra, J. D.; Unni, A. K.; Modi, K.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 6130, and references citsed therein.
4. Reviews: (a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; (b) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418.
5. Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054, and references cited therein.
6. Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299.
7. All molecular mechanic calculations were run with standard procedures implemented in the MacroModel/Batchmin 7.2 package (Schroedinger, 2001): see the experimental section details. Original reference for MacroModel: Mohamadi, F.; Richards, N. G. J.; Guida, C.; Liskamp, R.; Lipton, C.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Computat. Chem.* **1990**, *11*, 440–467.
8. Gryco, D.; Lipinsky, R. *Eur. J. Org. Chem.* **2006**, 3864.
9. See reviews of reference 4 and, for example, Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.
10. Goodman, J. M.; Still, W. C. *J. Comput. Chem.* **1991**, *12*, 1110.