Tetrahedron: *Asymmetry* 23 (2012) 748–753

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

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

Kinetic resolution of α-bromophenylacetamides using quinine or *Cinchona* alkaloid salts

Liliana Marzorati [a,*], José L. Fejfar [b], Claudio F. Tormena [c], Claudio Di Vitta [a,*]

[a] *Chemistry Institute, University of São Paulo, Av. Prof. Lineu Prestes 748, 05508 900 São Paulo, SP, Brazil*
[b] *Maua Institute of Technology, Campus de São Caetano do Sul, Praça Mauá 1, 09580 900 São Caetano do Sul, SP, Brazil*
[c] *Chemistry Institute, State University of Campinas, CP 6154, 13083-970 Campinas, SP, Brazil*

ARTICLE INFO

Article history:
Received 15 March 2012
Accepted 4 May 2012
Available online 18 June 2012

Dedicated to Professor Blanka Wladislaw (in memoriam) for her outstanding contribution to the organic chemistry of sulfur compounds

ABSTRACT

The kinetic resolution of racemic α-bromophenylacetamides **1** was achieved in the presence of benzenethiolate and *Cinchona* alkaloid salts as phase-transfer catalysts or benzenethiol and quinine, yielding (*S*)-enantioenriched α-sulfanylated products. The observed stereoselection was rationalized on the basis of the best fitting of **1** and the resolving agent in the ternary complexes.

1. Introduction

Cinchona alkaloids and their derivatives have been used extensively as asymmetric organocatalysts, acting either as free bases or as phase-transfer agents.[1] With regard to their use in the generation of a C–S stereocenter, two main strategies are used: (i) the most commonly found methodology makes use of the nucleophilic sulfur species in asymmetric conjugate 1,4-additions to ketones,[2–6] to β,β-disubstituted nitroalkenes[7] and to N-acylated oxazolidin-2-ones[8,9] (sulfa-Michael processes); (ii) a few examples refer to sulfanylation reactions but are restricted to the preparation of α-sulfur substituted diketopiperazines,[10] lactones, lactams, or β-dicarbonyl compounds.[11] More recently, readily available *Cinchona* alkaloids have been employed in the catalytic thiol addition to in situ generated nitrosoalkenes, as precursors of chiral non racemic α-sulfanylketones.[12] Alternatively, enantiomerically enriched sulfur compounds can be prepared via the kinetic resolution of racemic substrates, submitted either to sulfa-Michael[13,14] or to thiolation[15] reactions. In addition, bifunctional *Cinchona* alkaloid catalysts have been efficiently employed in the thiolytic desymmetrization of racemic azalactones, and of mesoglutaric anhydride[16] as well for the asymmetric ring opening of meso-aziridines.[17,18]

2. Results and discussion

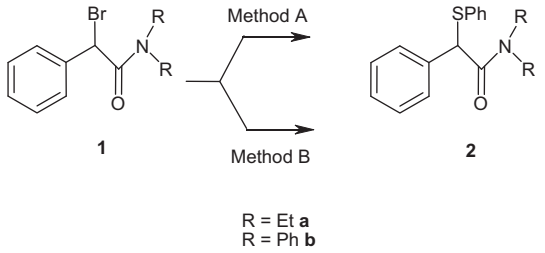
The increased number of literature reports on successful asymmetric organocatalyzed reactions poses a fundamental challenge for the modern synthetic organic chemist: what are the bases of molecular recognition determining stereodifferentiation and how to predict which structures will lead to successful results?

In the particular case of non derivatized *Cinchona* alkaloids, the unique structure of such organocatalysts, combining a basic quinuclidine unit, a quinoline ring and an α-amino alcohol moiety, allows for intermolecular cooperative actions with the reagents. In several cases, as for example in 1,4-additions of thiols to enones, the most accepted mechanistic model postulates that the activation of the nucleophile occurs via proton transfer to the quinuclidine nitrogen, with the formation of a chiral ion-pair between the catalyst and the anionic nucleophile. Simultaneously, the C9-hydroxyl group of the alkaloid becomes hydrogen bonded to the carbonyl oxygen and an acceptor/donor interaction can be established between the electron rich quinoline ring and the electron-deficient moieties of the nucleophile or of the electrophile.[5,19] Analogously, for phase-transfer catalysts, prepared *via* alkylation of the quinuclidine nitrogen of simple *Cinchona* alkaloids, the induction of asymmetry in the Michael additions seems to be dependent on the strength of the above mentioned hydrogen bond and of the π–π interactions.[20]

As part of an ongoing synthetic program in our laboratory, aimed at the preparation of asymmetric functionalized sulfides, we became interested in investigating the reactions of tertiary α-bromoamides **1a** and **1b** with benzenethiolate, employing either the salts of *Cinchona* alkaloids (method A) or quinine (method B) as catalysts (Scheme 1). Compounds **1a** and **1b** were chosen as substrates on the basis of the enhanced basicity of the carbonyl group of the amides as compared to the ketones and esters of analogous molecular structures.[21,22] We reasoned that a strong hydrogen bond between the hydroxyl group of the catalyst and the basic carbonyl group of the α-bromoamides could be a key factor for achieving the expected kinetic resolution.

* Corresponding authors.
E-mail address: lmarzora@iq.usp.br (L. Marzorati).

0957-4166/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetasy.2012.05.009



Scheme 1. Kinetic resolution of α-bromoamides 1a and 1b.

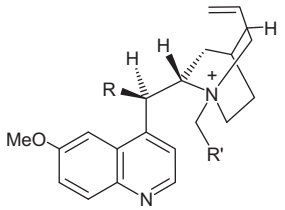


Figure 1. *Cinchona* alkaloid derived salts.

Table 1
Uncatalyzed thiolation reaction for substrates **1a** and **1b**

Amide	Amide (mol L^{-1})	Temperature (°C)	Time (h)	Yield (%)
1a	2.7×10^{-2}	20	48	26
1b	2.7×10^{-2}	20	48	31
1b	4.0×10^{-2}	0	6.5	16

Initially, substrates **1a** and **1b** were submitted to the thiolation reaction with 0.5 equiv of sodium benzenethiolate in the absence of a catalyst. At room temperature, both substrates afforded the corresponding pure α-phenylsulfanylamides **2a** and **2b** in approximately 30% yield (Table 1).

Although the reaction occurs to some extent at the interface of the solid/liquid system, an efficient chiral catalyst could lead to high enantioselectivity. For practical purposes, in our next set of experiments (Table 2), we employed the readily available catalysts **3**, **4**, and **5**, which have a well documented performance (Fig. 1).

The experimental results summarized in Table 2 indicate that: (i) **1b** is more reactive than **1a** in the presence of catalysts **3** and **5** (see experiments 1 and 3 or experiments 8 and 9), but equally reactive in the presence of catalyst **4** (see experiments 6 and 7); (ii) the thiolation reaction is slightly more stereoselective for **1b** than for **1a** (see experiments 2 and 4); (iii) catalyst **3** promotes better stereo-differentiation than catalysts **4** and **5** (see experiments 1 and 8 or 2 and 6 or 4 and 7); (iv) for **1b**, when the reaction is carried out at lower temperature, the product can be isolated in moderate yield but with improved ee. (see experiments 3 and 4).

Although the enantioselectivity seems to depend on the substituents attached to the quinuclidine moiety of the catalyst or to the amide nitrogen atom, the origin of such effects is not straightforward, and will be discussed. Using an *O*-alkylated catalyst gave poor ee. This highlights the importance of hydrogen bonding for the formation of a more favorable ternary complex between the quininium benzenethiolate and the α-bromoamide **1**.

In a new set of experiments, we submitted **1b** to thiolation reactions in the presence of quinine and benzenethiol (method B). Quinine was more soluble in toluene than catalysts **3**–**5** and these reactions could be conducted using 0.5 equiv of the base and thiol, leading to α-phenylsulfanylamide **2b** with improved enantiomeric excesses, ranging from 52% to 84% (Table 3).

For this reaction, the selectivity factors gradually increased when using lower temperatures and lower amide concentrations. At −21 °C, longer reaction times led to improved yields, but unaltered ee. (see experiments 14 and 15). This seems to indicate that under such experimental conditions, the energy gap between the diastereomeric transition states is large enough to guarantee a good compromise between the product yield and enantioselectivity.

It should be mentioned that the same major enantiomer is produced in the thiolation reactions conducted either in the presence of quinine or Quibec. The (*S*)-absolute configuration of the faster forming product could be assigned by comparing its sense of specific rotation and retention time (chiral HPLC) with those of an authentic enantioenriched sample of (*S*)-**2b**, prepared via a reaction sequence with an unequivocal stereochemical outcome (Scheme 2). In the first step, (*S*)-(+)-mandelic acid was converted into (*R*)-enantioenriched 2-chlorophenylacetic acid,[24] which was subsequently reacted with in situ generated potassium benzenethiolate to give (*S*)-2-phenylsulfanylphenylacetic acid. It should be noted that the signs of the specific rotations for this compound[25] and for the reduced derivative[26] (2-phenylsulfanyl-2-phenylethanol) were in agreement with the data previously

Table 2
Kinetic resolution of **1** employing 0.5 equiv of sodium benzenethiolate and phase-transfer catalysts **3**–**5** (method A)

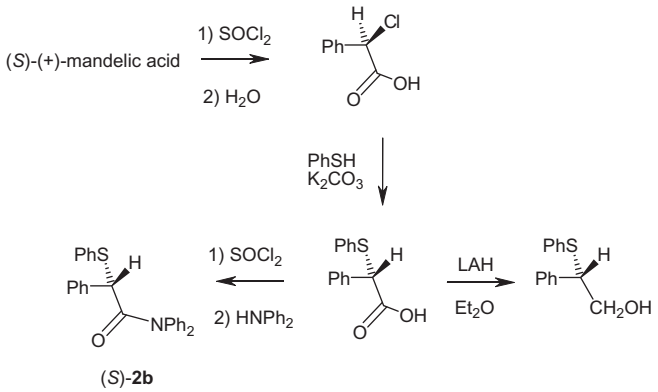
Exp.	Amide	[Amide] (mol L^{-1})	Catalyst[a]	Temperature (°C)	Time (h)	ee[b] (%)	Yield[c] (%)
1	**1a**	2.7×10^{-2}	**3**	20	48	23	25
2	**1a**	6.7×10^{-2}	**3**	0	6	23	51
3	**1b**	2.7×10^{-2}	**3**	27	48	20	64[d]
4	**1b**	6.7×10^{-2}	**3**	0	6	35[e,f]	51
5	**1b**	4.7×10^{-2}	**3**	−15	120	23	57
6	**1a**	6.7×10^{-2}	**4**	0	6	2	54
7	**1b**	6.7×10^{-2}	**4**	0	6	5	56
8	**1a**	2.7×10^{-2}	**5**	20	48	2	28
9	**1b**	2.7×10^{-2}	**5**	0	6	1	42

[a] 5 mol %.
[b] For **2b**, determined by chiral HPLC (Supelcosil LC-(*R*)-phenylurea), and for **2a**, determined by ^{1}H NMR, using tris[3-(trifluormethyl-hydroxymethylene)-(−)-camphorato], europium(III) derivative as the chiral shift reagent.
[c] Of isolated product by preparative HPLC (Shimadzu C-18-Prep.; based on a maximum yield of 50%).
[d] Determined by HPLC [Supelcosil LC-(*R*)-phenylurea using triphenylmethanol as internal standard].
[e] Same ee for the isolated and crude product.
[f] For the isolated product $[\alpha]_D^{21} = +4$ ($c = 2.0$, MeOH).

Table 3
Kinetic resolution employing **1b**, 0.5 equiv of quinine and 0.5 equiv of benzenethiol

Exp.	[Amide] (mol L^{-1})	Temperature (°C)	Time (h)	ee[a] (%)	Yield[b] (%)	s[c]
10	2.7×10^{-2}	25	14	52	56	4.1
11	4.8×10^{-2}	0	35	65	57	6.2
12	4.5×10^{-3}	0	98	78	45	10
13	4.5×10^{-3}	0	121	78	46	10
14	4.5×10^{-3}	−21	48	84	21	13
15	4.5×10^{-3}	−21	334	80	46	11

[a] Determined by chiral HPLC [Supelcosil LC-(*R*)-phenylurea].
[b] Determined by HPLC [Supelcosil LC-(*R*)-phenylurea using triphenylmethanol as internal standard], and based on a maximum yield of 50%.
[c] selectivity factor[23].



Scheme 2. Preparation of enantioenriched (*S*)-2b.

reported for the (*S*)-isomers. Enantiomerically enriched (*S*)-**2b** (ee 30%) was obtained by treatment of the acid chloride with *N*,*N*-diphenylamine.

Accordingly, the kinetic resolution efficiency could be attributed to a better fit between (*R*)-**1** and the benzenthiolate quininium ion pair as compared to the analogous (*S*)-**1** complex. However, the structures of the two competing transition states are strongly dependent on the conformation of both components. In the case of the starting bromoamide **1b**, B3LYP/cc-pVDZ calculations indicated three possible rotamers **I**–**III** (Fig. 2).

In the more stable rotamer **III** (Table 4), the aromatic rings must be as far as possible from each other. Only one frequency for the carbonyl group stretching mode was observed in the IR spectra of **1b**, suggesting that this compound exists as a single conformer at room temperature.

As for the *Cinchona* alkaloids, a conformational equilibrium between an 'open' **A** and a 'closed' **B** conformation was considered (Fig. 3). However, most reports in the literature adopt the 'open' conformation for quininium[27–30] and cinchonidinium[31,32] salts.

It is worth mentioning that in situ generated quininium thiolates have been successfully employed in asymmetric 1,4-additions to cyclohexenones.[3] In an attempt to account for the stereochemical results of this addition reaction, Hiemstra and Wynberg[5] postulated that the quininium moiety of the nucleophilic ion-pair adopts a 'closed' conformation, with the thiolate counterion directed toward the quinoline ring of the protonated alkaloid (Fig. 4). However, some years later, in view of new NMR results and docking experiments, Dijkstra, Kellogg, and Wynberg[27] concluded that in this reaction an 'open' instead of a 'closed' conformation would better describe the quininium thiolate, and therefore the transition state model originally proposed should be modified. More recently, quinine and quinidine have been employed as catalysts in 1,4-addition reactions of aromatic thiols to optically active 5-alkoxyfuranones.[31] The stereochemical outcome of this kinetic resolution

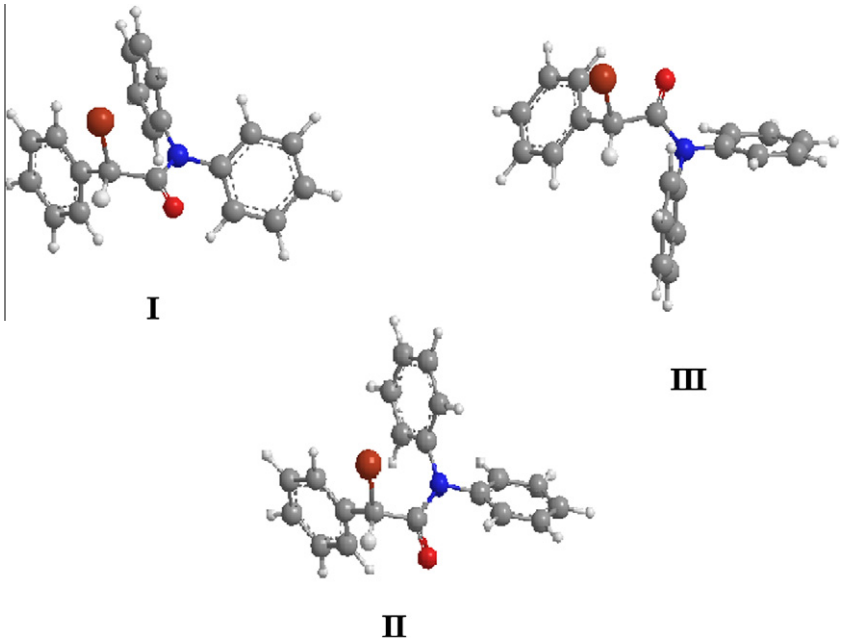


Figure 2. Rotamers of (*S*)-1b.

Table 4
Selected data for rotamers **I–III**

	I	II	III
Br-C-C-O angle	97°	128°	−72°
Absolute energy (a.u.)	−3475.947254	−3475.948584	−3475.995721
Relative energy (kcal mol^{-1})	6.2	5.4	0
μ (D)	3.9	2.9	4.0

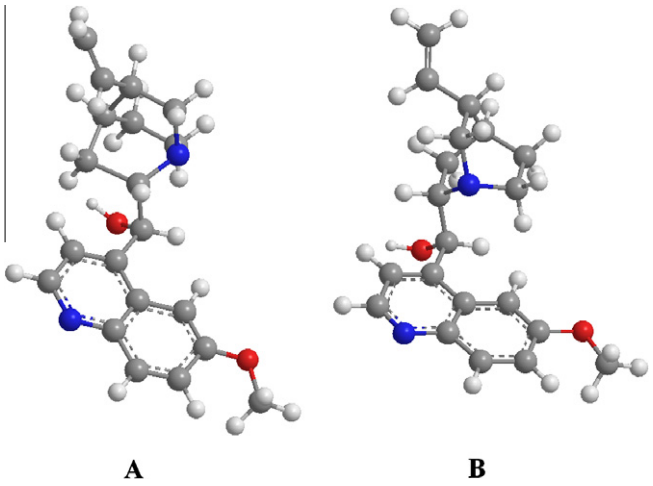


Figure 3. Conformations A and B of quinine, according to the structural data reported by Silva et al.[33]

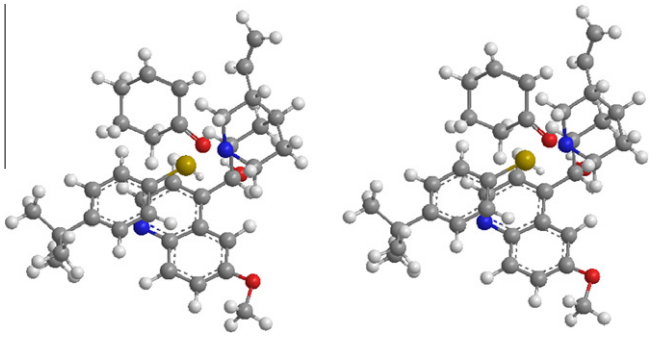


Figure 4. Stereoview of a 'closed' quininium *p*-*tert*-butylbenzenethiolate ion pair/cyclohexenone ternary complex.

was attributed to the predominance of one of the two diastereomeric ternary complexes, involving the protonated alkaloid as an 'open' conformer, the thiolate ion, and the γ-alkoxybutenolide.

Our attempts to explain our best results (method B) were based on the above cited literature precedent. In this context, we used ball and stick models to inspect complexes between the more stable rotamer **III** of each enantiomer of the α-bromoamide (see Fig. 2) and the conformer **A** of quininium benzenethiolate ion pair (Figs. 5 and 6). It should be noted that for the construction of the ionic pair complexes we used the geometrical parameters of quinine[33] while assuming that no conformational changes occur upon protonation.[27]

By visual inspection, it became evident that the ternary complex **C** (Fig. 5) would favor the diastereomeric transition state leading to the sulfanylated amide with a (*S*)-configuration. By allowing for the formation of a hydrogen bond between the alkaloid C9-hydroxyl and the amide carbonyl group of the (*R*)-**1b** isomer, thiolate attack opposite to the bromine atom is easily envisaged (Fig. 5). Such a favorable transition state model could not be attained for the (*S*)-isomer (complex **D**; Fig. 6), for which destabilizing steric interactions are easily detected. Although method A was less stereoselective than method B, we became interested in understanding the origin of the chiral recognition by Quibec, considering that this catalyst afforded the best ee results. At first, we inspected four binary complexes (Fig. 7), two for each enantiomer of **1b** [**E**, **F** and **G**, **H** for (*R*)-**1b** and (*S*)-**1b**, respectively] in association with the *N*-benzylquininium moiety of the catalyst. As can be seen, for all complexes, in addition to the expected hydrogen bond, stabilizing π–π interactions can be proposed between the *N*-benzyl or quinolyl substituent of the catalyst and the *N*-phenyl or the benzyl ring of the amide. In all cases, the C–Br antibonding orbital is directed away from the quinuclidine nitrogen thiolate counterion. However, the free thiolate ions, present in the solid/liquid interface, could easily displace the bromine atom in complexes **E**, **F**, and **G**, but not in complex **H**, accounting for the predominance of the (*S*)-**2b** isomer.

3. Conclusion

From our results, it seems reasonable to suggest that in the kinetic resolution of α-bromoamides, using benzenethiol and promoted by quinine or derived salts, the quininium thiolate ion pair adopts an 'anti-open' conformation as previously described[27,30] for analogous sulfa-Michael reactions. For **1b**, kinetic resolution favors the formation of the (*S*)-isomer of **2b**.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded in AC200 and DRX300 Bruker instruments, in $CDCl_3$, and TMS as the internal standard. Optical rotations were measured using a JASCO DIP-370 digital polarimeter. Melting points were determined with an Electrothermal 9100 melting point apparatus. HPLC analysis was run on a Shimadzu instrument equipped with LC-10AS pumps, SCL-10A system controller, UV–Vis SPD-6AV detector, and CTO-6AS oven. Solvents for reactions were purified according to literature procedures,[34] and commercial HPLC solvents were used without purification. *N*-Benzylquininium bromide is commercially available and was used without purification. Sodium benzenethiolate was prepared as described for sodium methanethiolate.[35]

4.1.1. 2-Bromo-*N*,*N*-diphenylphenylacetamide 1b

The haloamide was prepared in three steps[36,37] starting from phenylacetic acid. Mp 138–142 °C (Lit.[37] mp 140 °C); ^{1}H NMR (δ; $CDCl_3$) 5.51 (s; 1H; H-C-Br), 7.25-7.34 (m; 15H; H_{arom}).

4.1.2. 2-Bromo-*N*,*N*-diethylphenylacetamide 1a

Prepared by the same procedure using *N*,*N*-diethylamine instead of *N*,*N*-diphenylamine, to give an oily pure product (60% yield) after flash distillation. ^{1}H NMR (δ; $CDCl_3$) 1.11 (br t; 3H; J = 7.0 Hz; CH_3), 1.17 (br t; 3H; J = 7.0 Hz; CH_3), 3.28–3.46 (m; 4H; N-CH_2), 5.68 (s; 1H; *H*-C-Br), 7.27–7.40 (m; 3H; H_{arom}), 7.56 (dd; 2H; J_1 = 7.8 Hz and J_2 = 2 Hz; H_{arom}); ^{13}CNMR (δ; $CDCl_3$) 12.4

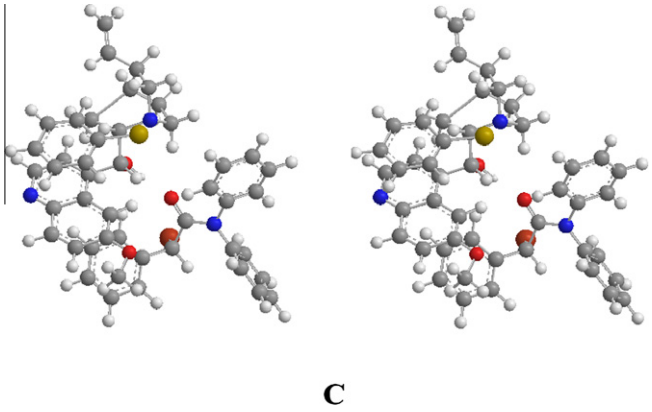


Figure 5. Diastereomeric ternary complex C between (*R*)-α-bromo-*N*,*N*-diphenylphenylacetamide 1b and the conformer A of the quininium benzenethiolate ion pair. The hydrogen bonded to the nitrogen of the quinuclidine moiety is not shown.

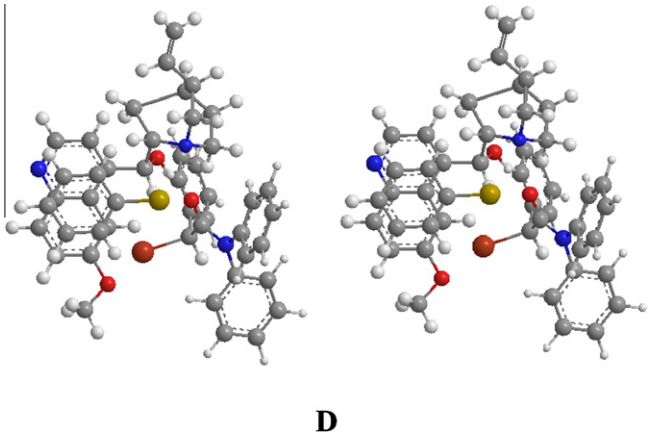


Figure 6. Diastereomeric ternary complex D between (*S*)-α-bromo-*N*,*N*-diphenylphenylacetamide 1b and the conformer A of the quininium benzenethiolate ion pair. The hydrogen bonded to the nitrogen of the quinuclidine moiety is not shown.

(CH_3), 14.4 (CH_3), 41.3 (N-CH_2), 42.5 (N-CH_2), 46.7 (H-*C*-Br), 128.0 (C_{arom}), 128.7 (C_{arom}), 136.6 (C_{arom}), 166.3 (*C*=O); Elemental analysis calculated for $C_{12}H_{16}NOBr$, *C* = 53.35%; *H* = 5.97%, and *N* = 5.18%. Found *C* = 53.53%; *H* = 5.55%, and *N* = 5.22%.

4.1.3. *N*-Propylquininium bromide 4

To quinine (6.50 g; 20.0 mmol) dissolved in acetone (180 mL), 1-bromopropane (3.70 mL; 40.0 mmol) was added. The reaction mixture was heated at reflux for 8 h. The resulting crystals (6.18 g) were separated by filtration and recrystallized from MeCN to afford light brown crystals (3.42 g; 38%) that decomposed at 214 °C; $[\alpha]_D^{15} = -40$ (*c* 2.0, MeCN). Elemental analysis calculated for $C_{23}H_{31}N_2O_2$, *C* = 61.75%; *H* = 6.98%; *N* = 6.26%, and Br =17.86%. Found *C* = 61.57%; *H* = 6.74%; *N* = 6.40%, and Br = 17.20%. ^{13}C NMR (δ; $CDCl_3$) 11.2, 16.6, 21.4, 25.1, 26.3, 37.7, 54.1, 56.0, 61.7, 62.1, 63.8, 66.7, 101.1, 117.7, 120.7, 121.2, 125.8, 132.2, 136.7, 143.3, 144.2, 147.6, 158.2.

4.1.4. 2-Phenylsulfanyl-*N*,*N*-diphenylphenylacetamide 2b

To the α-bromoamide **1b** (0.148 g; 0.400 mmol), dissolved in dry toluene (15.0 mL), was added sodium benzenethiolate (0.054 g; 0.410 mmol). The reaction mixture was stirred for 48 h, quenched with water and extracted with dichloromethane. The solvent was removed under reduced pressure. The sulfanylated product **2b** was isolated by preparative HPLC (Shimadzu C-18-Prep.; 8:2 MeOH/H_2O; 9.0 mL min^{-1}) to afford an oil (0.031 g; 39%); Elemental analysis calculated for $C_{26}H_{21}NOS$, *C* = 78.96%;

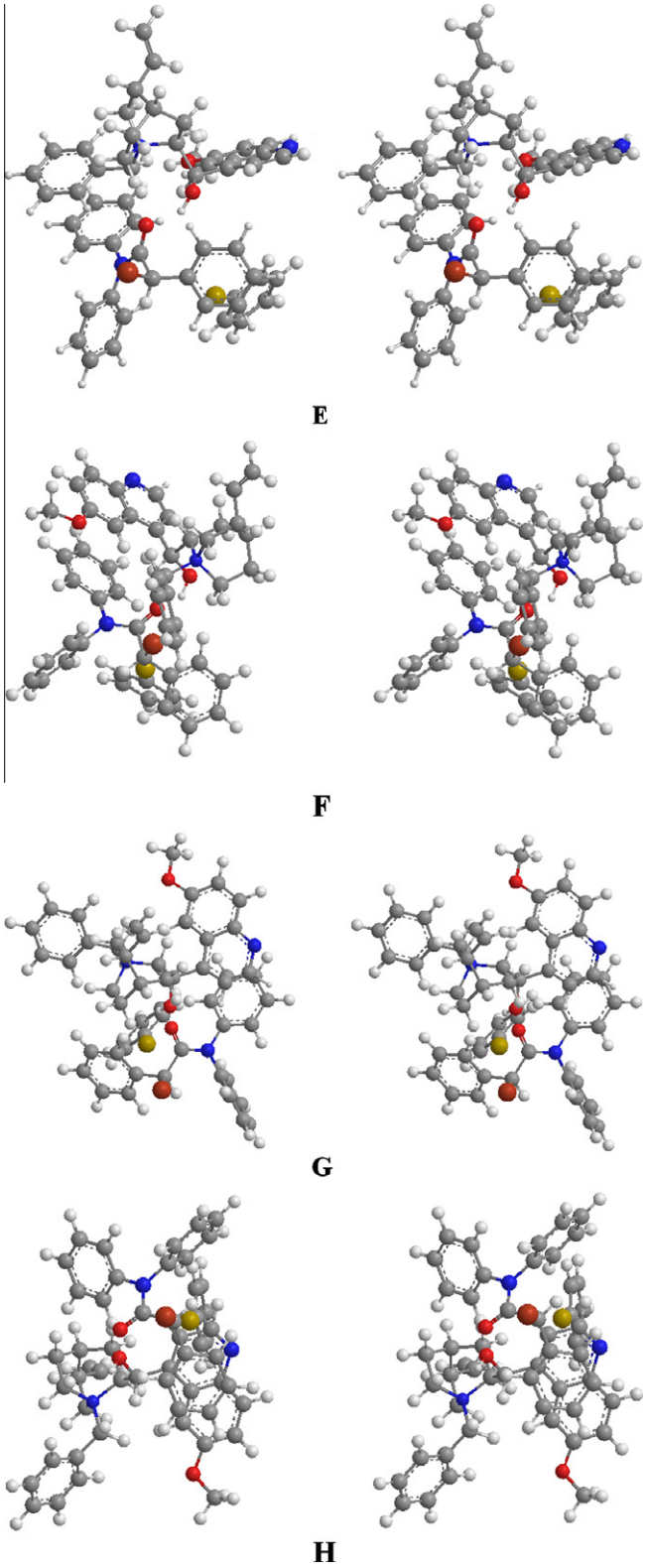


Figure 7. Binary complexes E, F for (*R*)-1b and G, H for (*S*)-1b in association with the *N*-benzylquininium moiety of the catalyst (for the sake of clarity, only the free thiolate ions are represented).

H = 5.35%, and *N* = 3.54%. Found *C* = 79.00%; *H* = 5.31%, and *N* = 3.45%; ^{1}H NMR (δ; $CDCl_3$) 4.99 (s; 1H; *H*-C-SPh), 6.94-7.18 (m; 5H; H_{arom}), 7.24–7.37 (m; 15H; H_{arom}).

4.1.5. 2-Phenylsulfanyl-*N*,*N*-diethylphenylacetamide 2a

Compound **2a** was obtained in 63% yield by the same procedure described above, after crystallization of the crude product. Mp 93-94 °C from cyclohexane; Elemental analysis calculated for $C_{18}H_{21}NOS$, *C* = 72.20%; *H* = 7.07%, and *N* = 4.68%. Found *C* = 71.96%; *H* = 6.96%, and *N* = 4.71%; ^{1}H NMR (δ; $CDCl_3$) 0.96 (bt; 3H; *J* = 7; CH_3), 1.09 (t; 3H; *J* = 7; CH_3), 3.10-3.47 (m; 4H; H_2C-N), 5.03 (s; 1H; *H*-C-SPh), 7.20-7.34 (m; 10H; $H_{arom.}$); ^{13}C NMR (δ; $CDCl_3$) 12.6 (CH_3), 14.1 (CH_3), 40.7 (H_2C-N), 42.1 (H_2C-N), 56.6 (*C*-SPh), 127.7 (C_{arom}), 127.8 (C_{arom}), 128.3 (C_{arom}), 128.4 (C_{arom}), 128.7 (C_{arom}), 133.6 (C_{arom}), 134.2 (C_{arom}), 137.4 (C_{arom}), 168.3 (C=O).

4.1.6. Kinetic resolutions

4.1.6.1. Method A. General procedure. To α-bromoamide **1**, dissolved in dry toluene, was added the quaternary ammonium salt (5% mol), and solid sodium benzenethiolate, and the reaction mixture was vigorously stirred. For the concentration of the reagents, the reaction time, and the temperature, see Table 2. The sulfanylated product **2** was isolated by preparative HPLC (Shim-PAC; 8:2 MeOH/H_2O; 9.0 mL min^{-1}). The enantiomeric excess for **2b** was determined by chiral HPLC [Supelcosil LC-(*R*)-phenylurea], and for **2a** by ^{1}H NMR, using tris[3-(trifluormethyl-hydroxymethylene)-(−)-camphorato], europium(III) derivative as a chiral shift reagent.

4.1.6.2. Method B. General procedure. To a solution of quinine and benzenethiol in dry toluene, solid α-bromoamide **1b** was added, and the reaction mixture was stirred vigorously. For the concentration of the reagents, the reaction time, and the temperature, see Table 3. The yield and ee of the sulfanylated product **2b** were determined by performing HPLC analysis (Supelcosil LC-(*R*)-phenylurea; 99.5% hexane/0.5% isopropanol; 0.5 mL min^{-1}).

4.1.7. Enantioenriched (*S*)-2b

(*S*)-(+)-Mandelic acid was treated with thionyl chloride in THF/DMF[24a] to yield enantioenriched (*R*)-(−)-2-chlorophenylacetic acid; $[\alpha]_D^{25} = -99$ (*c* 4.0, acetone); Lit.[24b] $[\alpha]_D^{25} = -191$ (*c* 3.35, benzene). This compound was exposed to K_2CO_3 and benzenethiol, in dioxane, furnishing the enantioenriched (*S*)-(+)-2-phenylsulfanylphenylacetic acid {$[\alpha]_D^{25} = +99$ (*c* 4, acetone); Lit.[25] $[\alpha]_D^{25} = +200$ (1:1 $CHCl_3$/EtOH) with 93% ee for the (*S*)-(+) isomer. The assigned (*S*)-configuration for the prepared compound was also confirmed via reduction of the acid with lithium aluminum hydride in ether, to yield enantioenriched (*S*)-(+)-2-phenylsulfanyl-2-phenylethanol. Lit.[26] $[\alpha]_D^{25} = +206$ (*c* 1.12, EtOH) for the (*S*)-isomer. Enantioenriched (*S*)-(+)-2-phenylsulfanylphenylacetic acid (6.1 mmol) was treated with thionyl chloride (12 mmol) at room temperature for 12 h. The crude (*S*)-acid chloride, upon reaction with *N*,*N*-diphenylamine (12 mmol) dissolved in CCl_4 (10 mL), afforded enantioenriched (*S*)-**2b** (2.5 mmol; 41%; $[\alpha]_D^{25} = +12$ (*c* 3.9, acetone) after dry flash chromatography using hexane:ethyl acetate (20:1) as eluent). An ee of approximately 30% was determined by HPLC (Sumichiral OA-2000 4.6 mm i.d. × 25 cm length; 0.3 mL min^{-1} using hexane/EtOH 9:1 as eluent).

Acknowledgement

We acknowledge FAPESP and CNPq for financial support.

References

1. (a) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, 1229–1279; (b) Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, 961–998.
2. Colonna, S.; Annunziata, R.; Juliá, S.; Guixer, J. *Afinidad* **1981**, 501–502.
3. Helder, R.; Arends, R.; Bolt, W.; Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, *25*, 2181–2182.
4. Colonna, S.; Re, A.; Wynberg, H. *J. Chem. Soc., Perkin Trans. 1* **1981**, 547–552.
5. Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417–430.
6. McDaid, P.; Chen, Y.; Deng, L. *Angew. Chem., Int. Ed.* **2002**, *41*, 338–340.
7. Lu, H.-H.; Zhang, F.-G.; Meng, S.-G.; Duan, S.-W.; Xiao, W.-J. *Org. Lett.* **2009**, *11*, 3946–3949.
8. Liu, Y.; Sun, B.; Wang, B.; Wakem, M.; Deng, L. *J. Am. Chem. Soc.* **2009**, *131*, 418–419.
9. Zu, L.; Wang, J.; Li, H.; Xie, H.; Jiang, W.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036–1037.
10. Polawske, N. W.; Dubey, R.; Nichol, G. S.; Olenyuk, B. *Tetrahedron: Asymmetry* **2009**, *20*, 2742–2750.
11. Sobhani, S.; Fielenbach, D.; Marigo, M.; Wabnitz, T. C.; Jorgensen, K. A. *Chem. Eur. J.* **2005**, *11*, 5689–5694.
12. Hatcher, J. M.; Kohler, M. C.; Coltart, D. M. *Org. Lett.* **2011**, *13*, 3810–3813.
13. Asaoka, M.; Shima, K.; Takei, H. *Tetrahedron Lett.* **1987**, *28*, 5669–5672.
14. Wang, J.; Xie, H.; Li, H.; Zu, L.; Wang, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4177–4179.
15. (a) Juliá, S.; Ginebreda, A.; Guixer, J.; Tomás, A. *Tetrahedron Lett.* **1980**, *21*, 3709–3712; (b) Westerbeek, A.; Szymanski, W.; Wijma, H. J.; Marrink, S. J.; Feringa, B. L.; Janssen, D. B. *Adv. Synth. Catal.* **2011**, *353*, 931–944.
16. Peschiulli, A.; Quigley, C.; Tallon, S.; Gun'ko, Y. K.; Connon, S. J. *J. Org. Chem.* **2008**, *73*, 6409–6412.
17. Luo, Z.-B.; Hou, X.-L.; Dai, L.-X. *Tetrahedron: Asymmetry* **2007**, *18*, 443–446.
18. Wang, Z.; Sun, X.; Ye, S.; Wang, W.; Wang, B.; Wu, J. *Tetrahedron:Asymmetry* **2008**, *19*, 964–969.
19. Wynberg, H. *Asymmetric Catalysis By Alkaloids, Topics in Stereochemistry* **1986**, *16*, 87–129.
20. Conn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem.* **1986**, *51*, 4710–4711.
21. Wladislaw, B.; Rittner, R.; Viertler, H. *J. Chem. Soc.* **1971**, 1859–1861.
22. Abraham, M. H.; Grellier, P. L.; Prior, D. V.; Morris, J. J.; Taylor, P. J. *J. Chem. Soc., Perkin Trans. 2* **1990**, 521–529.
23. Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons,Inc.: New York, 1994. p.396.
24. (a) Y. Shogo, T. Toshihiro, F. Yoshihide, U. Yasuyoshi, PCT Int. Appl. 2004.; (b) McKenzie, A.; Clough, G. W. *J. Chem. Soc.* **1908**, *93*, 811–825.
25. Bonner, W. A. *J. Org. Chem.* **1967**, *32*, 2496–2501.
26. Toshimitsu, A.; Hirosawa, C.; Tamao, K. *Tetrahedron* **1994**, *50*, 8997–9008.
27. Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H. *Rec. Trav. Chim. Pays-Bas* **1989**, *108*, 195–204.
28. Hofstetter, C.; Wilkinson, P. S.; Pochapsky, T. C. *J. Org. Chem.* **1999**, *64*, 8794–8800.
29. Ucello-Barretta, G.; Bolzano, F.; Quintavalli, C.; Salvatori, P. *J. Org. Chem.* **2000**, *65*, 3596–3602.
30. Faber, W. S.; Kok, J.; de Lange, B.; Feringa, B. L. *Tetrahedron* **1994**, *30*, 4773–4794.
31. Zhang, H.; Lin, Z.-Y.; Zhou, Z.-H.; Ng, S. W. *Acta Cryst.* **2003**, *E59*, o183–o185.
32. Burgi, T.; Baiker, A. *J. Am. Chem. Soc.* **1998**, *120*, 12920–12926.
33. Silva, T. H. A.; Oliveira, A. B.; de Almeida, W. B. *Structural Chem.* **1997**, *8*, 95–107.
34. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon Press, Headington Hill Hall: Oxford, 1996.
35. Biilmann, E.; Jensen, K. A. *Bull. Soc. Chim. Fr.* **1936**, *3*, 2310–2318.
36. Truitt, P.; Mark, D.; Long, L. M.; Jeanes, J. *J. Am. Chem. Soc.* **1948**, *70*, 4214–4215.
37. Truitt, P.; Richardson, E. E.; Long, L. M.; Middleton, W. J. *J. Am. Chem. Soc.* **1949**, *71*, 3479–3480.