EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201201307

# Diastereodivergent Synthesis of Chiral *vic*-Disubstituted-Cyclobutane Scaffolds: 1,3-Amino Alcohol and 1,3-Diamine Derivatives – Preliminary Use in Organocatalysis

**Enric Mayans,[a] Albert Gargallo,[a] Ángel Álvarez-Larena,[b] Ona Illa,*[a] and Rosa M. Ortuño*[a]**

**Keywords:** Synthetic methods / Organocatalysis / Asymmetric catalysis / Michael addition / Regioselectivity / Amino alcohols / Amines

The synthesis of chiral cyclobutane containing 1,3-amino alcohols and 1,3-diamines has been accomplished in an efficient and diastereodivergent manner from a common chiral precursor. Regioselective manipulation of functional groups in the prepared products provides an easy entry to several derivatives, such as thioureas. Preliminary results on the use of these compounds as bifunctional organocatalysts are reported.

## Introduction

Chiral difunctional compounds such as amino alcohols and diamines are useful scaffolds that have been widely used in asymmetric synthesis, both as precursors and as chiral auxiliaries. For amino alcohols, there are many examples on the synthesis and use of 1,2-derivatives,[1] whereas fewer examples are known for 1,3-amino alcohols. Nevertheless, the later have been synthesized through various standard methods and have been employed as chiral ligands and auxiliaries, as phase-transfer catalysts, and as resolution agents, among other applications.[2] A particular group of these molecules is characterized by two functional groups linked to a carbocyclic ring such as cyclohexane and cyclopentane derivatives; these are the most commonly utilized in the catalysis field and also tend to display interesting biological activity thus lending themselves to use as antiviral and antitumor agents or antibiotics.[3] In the case of cyclobutanes with 1,3-amino alcohols, there are fewer examples although this structural moiety is present in cyclobut-A and cyclobut-G; both are oxetanocin carbocyclic analogues.[4]

Another class of interesting compounds is represented by the diamines. As with amino alcohols, optically active diamines are important molecules for synthetic chemistry. Such diamines have found use as i) bidentate ligands, ii) synthetic building blocks for pharmaceuticals and agrochemicals, and iii) monomers in the synthesis of chiral polymers, to name just a few of their applications.[5] As with amino alcohols, 1,2-diamines are the most abundant diamines[6] although there are some examples of 1,3-diamines as chiral metal ligands.[7] The 1,3-diamine functionality is also present in the cyclopentane containing structure of neuraminidase enzyme inhibitors such as the commercial drug Peramivir™ which displays potent activity against the influenza viruses.[6e,8]

We recently reported the stereoselective synthesis of all possible stereoisomers of cyclobutane-1,2-diamines and some selective transformations,[6f] as part of our research program based on the synthesis and application of cyclobutane derivatives as elements of dendrimers,[9] amino acids, peptides and other compounds with properties as foldamers,[10] organogelators,[11] enzyme inhibitors,[12] organoconducting materials[13] and cell penetrating agents.[14] In this paper, we describe a facile and diastereodivergent entry to a variety of cyclobutane containing 1,3-amino alcohols, their conversion into 1,3-diamines and their regioselective transformations into several derivatives. Some of the derivatives investigated contain a thiourea moiety and an amino group, making them good candidates for bifunctional organocatalysts.[15] Preliminary results of assays looking at the possible application of these compounds in organocatalysis are reported herein.

## Results and Discussion

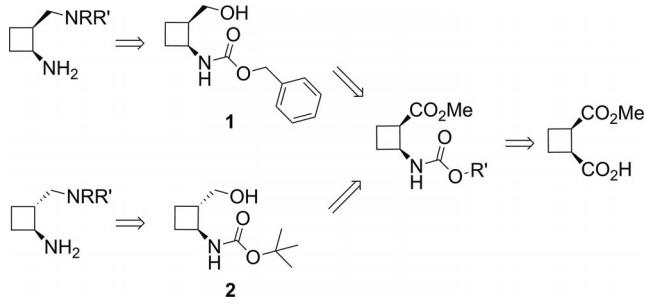
Scheme 1 shows the retrosynthetic rationale relating conveniently protected 2-aminocyclobutane-(1*R*,2*S*)-1-carboxylic acid to diastereomeric *cis*- and *trans*-1,3-amino alcohols **1** and **2**, and differently substituted 1,3-diamines. Such amino acid derivatives are suitable precursors in dia-

[a] Department de Química, Universitat Autònoma de Barcelona, 08193 Cerdanyola del Vallès, Spain
E-mail: ona.illa@uab.es
rosa.ortuno@uab.es
Homepage: http://grupsderecerca.uab.es/rosamortuno
[b] Servei de Difracció de RX, Universitat Autònoma de Barcelona, 08193 Cerdanyola del Vallès, Spain

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201201307.

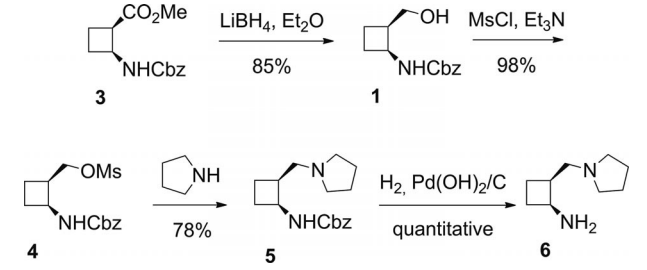
  

stereodivergent synthesis of the optically pure target molecules, and were synthesized, in turn, from a readily available half ester as described previously.[10c]



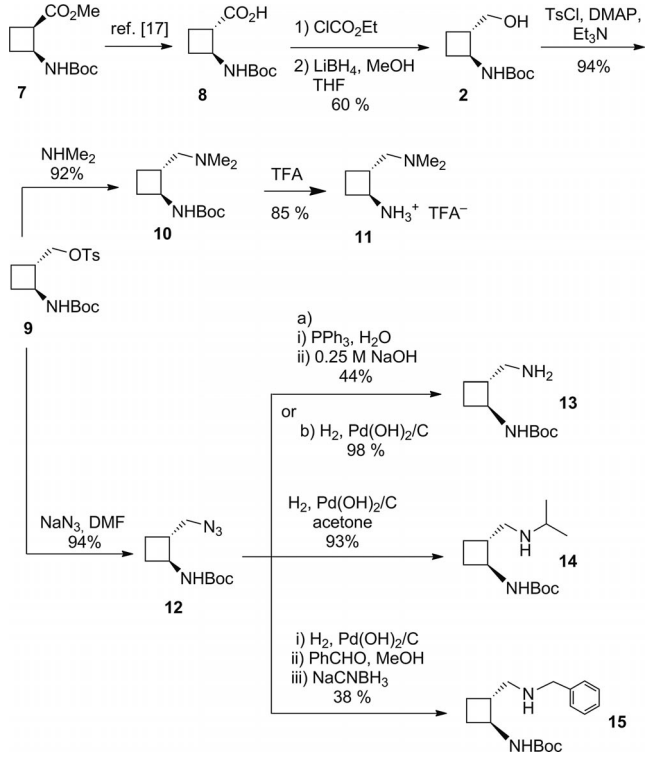

Scheme 1. General retrosynthesis of *cis*- and *trans*-isomers of cyclobutane containing 1,3-amino alcohols and 1,3-diamines involving stereodivergent pathways from chiral *cis*-amino acid derivatives.

The *cis* isomers were obtained starting from orthogonally protected amino acid **3** (Scheme 2).[10a] The methyl ester of **3** was reduced with $LiBH_4$ in THF at 0 °C in the presence of substoichiometric MeOH to afford *N*-protected *cis*-cyclobutane containing 1,3-amino alcohol **1**, in 73 % yield. This yield could be increased to 85 % when $LiBH_4$ in diethyl ether was used as reducing agent.[16] Notably, alcohol **1** is a new compound that can be employed as a synthetic intermediate for the preparation of *cis*-1,3-diamines. Consequently, diamine **6** was prepared as a representative example. Thus, mesylate **4** was synthesized in the standard way and subsequently reacted with pyrrolidine to afford monoprotected diamine **5** in 78 % yield over two steps. Although this transformation is very common with primary mesylates, it is not trivial to achieve substitution when the mesyl/tosyloxymethyl group is anchored to the sterically congested *cis*-1,2-disubstituted cyclobutane moiety and the nucleophile is a bulky molecule, such as pyrrolidine. Such steric considerations often prevent the desired substitution as recently observed in our laboratory.[16] Free diamine **6** was obtained in nearly quantitative yield by hydrogenolysis of the benzyl carbamate in the presence of $Pd(OH)_2/C$. This diamine was employed in the synthesis of more elaborately functionalized compounds (vide infra).




Scheme 2. Synthesis of *cis*-compounds **1** and **5**.

*N*-Protected *trans*-1,3-amino alcohol **2** could be readily synthesized following the route outlined in Scheme 3. In this case, *N*-Boc precursor **7** was used since the *tert*-butyl carbamate is not hydrolyzed under the strongly basic conditions required for epimerization and can be easily eliminated with mild acid. Saponification of the methyl ester followed by conversion of the resulting carboxylic acid into a transient amide was carried out. Subsequent epimerization of the α-carboxyl carbon and concomitant hydrolysis of the amide using 6 M NaOH with heating led to *N*-protected *trans*-amino acid **8**.[17] The resultant carboxyl group was activated as a mixed anhydride by reaction with ethyl chloroformate and then reduced by addition of $LiBH_4$ in THF and MeOH, to afford *trans*-amino alcohol **2** in 60 % yield. Reaction of **2** with tosyl chloride and DMAP in the presence of $Et_3N$ afforded tosylate **9** in 94 % yield. This is a key intermediate that allowed regioselective synthesis of free amines or *N*-alkyl-substituted derivatives. New products were prepared to illustrate the versatility of these synthetic strategies. For instance, tosylate **9** was treated with dimethylamine to afford *N*-monoprotected diamine **10** in 92 % yield. Removal of the *N*-Boc carbamate was achieved with TFA to give the corresponding free amine as ammonium trifluoroacetate **11** in 85 % yield. Alternatively, tosylate **9** reacted with sodium azide in DMF to afford azide **12** in 94 % yield. This azide is another relevant intermediate in the synthesis of several 1,3-diamine derivatives. Conversion of the azide to an amino group was achieved both under Staudinger reaction conditions (addition of aqueous triphenylphosphane followed by treatment with diluted NaOH) and by hydrogenolysis using $Pd(OH)_2/C$. Monoprotected *trans*-1,3-diamine **13** was obtained in both cases in 44 and 98 % yield, respectively (Scheme 3, conditions *a* and *b*). Moreover, if the hydrogenolysis was carried out in the presence of a ketone, concomitant reductive amination ensued leading to a secondary amine. This observation opens




Scheme 3. Synthesis of *trans*-compounds **2**, **11**, **13**–**15**.

a number of possible strategies by which to achieve further functionalization of these scaffolds. Acetone was used as a model ketone and, in this way, isopropylamine derivative **14** was obtained in 93 % yield (Scheme 3). Reductive aminations with aldehydes were carried out with sodium cyanoborohydride to avoid undesired reduction of the aldehyde under catalytic hydrogenation conditions. The application of benzaldehyde, as a model in such reductive aminations, afforded benzylamine **15** in a non-optimized yield of 38 %.

To investigate and validate the versatility of these new synthetic scaffolds for further functionalization, thiourea moieties were incorporated in a regioselective manner. Inspired by Takemoto's bifunctional chiral thiourea (Figure 1),[15a] which has (*R*,*R*)-1,2-cyclohexyldiamine as a chiral scaffold, we undertook the synthesis of related molecules bearing a *vic*-disubstituted cyclobutane moiety as the chiral motif; subsequent efforts entailed the application of these new agents in organocatalyzed reactions (Scheme 4).

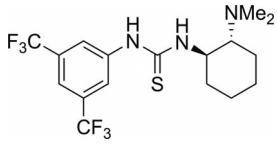
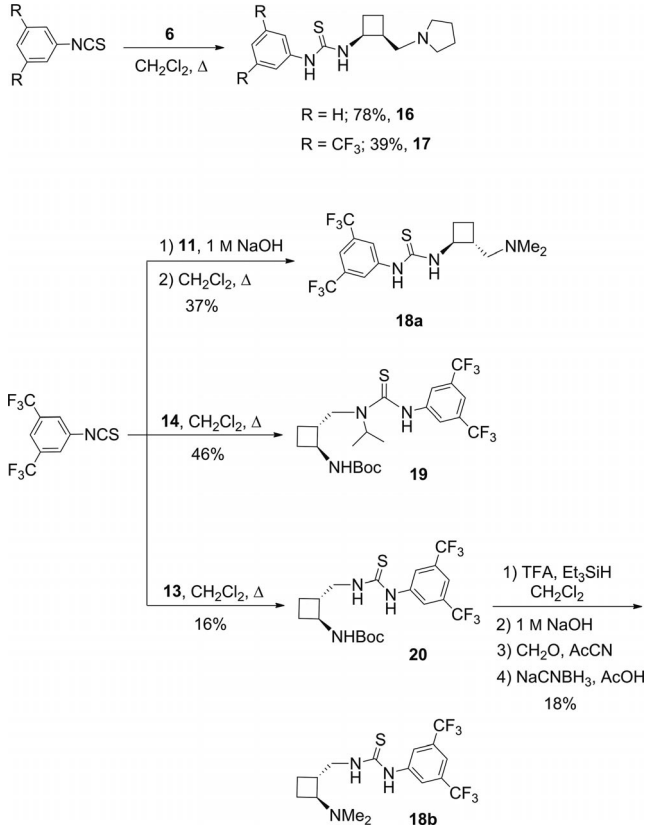


Figure 1. Takemoto's bifunctional chiral thiourea.




Scheme 4. Some examples of further regioselective functionalization of diamines.

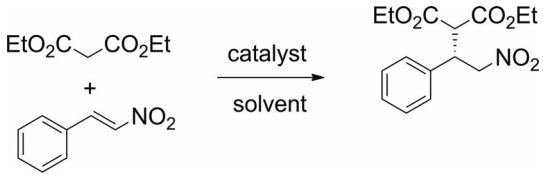
Thus, *cis*-diamine **6** was treated with phenyl thioisocyanate in refluxing $CH_2Cl_2$ to afford bifunctional thiourea **16** in 78 % yield. In a separate experiment, **6** was refluxed in $CH_2Cl_2$ in the presence of 3,5-bis(trifluoromethyl)phenyl thioisocyanate to give **17** in 39 % yield. Low yields sometimes observed in these kinds of reactions are likely attributable to reversibility issues. Reaction of thioisocyanate **17** with *trans*-diamine **11** afforded **18a** in 37 % yield. In an analogous fashion, highly substituted thiourea **19** and thiourea **20** were obtained from corresponding amines (**14** or **13**) in 46 % and 16 % yield, respectively. Furthermore, easy removal of the Boc group in **20** followed by reductive amination with formaldehyde afforded **18b**, the regioisomer of **18a**, in 18 % non-optimized yield.

Preliminary studies on the possible application of thioureas **17**, **18a**, **18b**, and **20** as bifunctional organocatalysts were carried out to investigate i) the influence of the cyclobutane chirality, ii) the nature of tertiary amine (cyclic or not) and iii) the distance between the thiourea or the amine and the cyclobutane ring on chosen reactions. Conjugate addition of diethyl malonate to (*E*)-β-nitrostyrene was selected as a standard reaction.[15a] Experiments with **17** were performed in solvents of differing polarity including nonpolar solvents such as toluene and dichloromethane, THF as a low-polarity solvent and dioxane, diglyme, and acetonitrile as differently polar solvents. The influence of, i) number of equivalents of catalyst, ii) temperature, and iii) reaction time was also investigated for cases giving the best results (Table 1). Reaction of **17** with 10 mol-% of catalyst in acetonitrile, diglyme, dioxane or dichloromethane (Table 1, Entries 1–5) afforded both modest yields and enantiomeric ratios (*e.r.*) The best result in terms of conversion and enantioselectivity was obtained using toluene at room temperature for 24 h, with an *e.r.* value of 74:26 in favor of the *S* enantiomer being generated in 85 % yield (Table 1, Entry 6).[18] Variations in temperature (Table 1, Entries 9 and 10) led to very similar *e.r.* values but to a decrease in the yields when an increase in the reaction time was required. The use of less catalyst (Table 1, Entry 8) resulted in similar reaction enantioselectivity and lower yields. Consequently, thiourea **17** was shown to be an efficient organocatalyst accelerating this Michael reaction and providing 1,4-addition products under similar reaction conditions and in yields comparable to those previously reported using Takemoto's thiourea. Nevertheless, **17** was found to display only modest asymmetric induction in such reactions.

Bearing in mind the best results obtained with **17**, thioureas **18a** and **18b** were also tested affording the results described in Table 1 (Table 1, Entries 11–14). The behaviours of **18a** and **18b** in the studied Michael reactions were comparable to that observed with **17** highlighting that the presence of a methylene group as a spacer between the cyclobutane ring and the thiourea or the amine group does not exert any significant influence upon the reaction. The use of **18a** allowed us to obtain the reaction product in good yields but with an *e.r.* inferior to that obtained with **17**. In contrast, *N*-Boc derivative **20** was a very poor catalyst (Table 1, Entries 15 and 16). This result was expactable because of the very weak basicity of the carbamate nitrogen

Table 1. Conjugate addition of diethyl malonate to (*E*)-β-nitrostyrene catalyzed by **17**, **18a**, **18b**, and **20**.




| Entry | Cat. | mol[%] | Solvent | *T*[°C] | *t*[h] | Yield[%] | *e.r.*[*S*/*R*][a] |
|---|---|---|---|---|---|---|---|
| 1 | **17** | 10 | $CH_3CN$ | 25 | 24 | 42[b] | 60:40 |
| 2 | **17** | 10 | diglime | 25 | 24 | 68[b] | 68:32 |
| 3 | 17 | 10 | dioxane | 25 | 24 | 65[b] | 62:38 |
| 4 | **17** | 10 | THF | 25 | 24 | 65[b] | 63:37 |
| 5 | **17** | 10 | $CH_2Cl_2$ | 25 | 24 | 42[b] | 68:32 |
| 6 | **17** | 10 | toluene | 25 | 24 | 85[b] | 74:26 |
| 7 | **17** | 15 | toluene | 25 | 24 | 59[b] | 69:31 |
| 8 | **17** | 5 | toluene | 25 | 24 | 45[b] | 71:29 |
| 9 | **17** | 10 | toluene | 0 | 48 | 60[b] | 73:27 |
| 10 | **17** | 10 | toluene | –25 | 48 | 61[b] | 75:25 |
| 11 | **18a** | 10 | $CH_2Cl_2$ | 25 | 24 | 88[b] | 52:48 |
| 12 | **18a** | 10 | toluene | 25 | 24 | 75[b] | 60:40 |
| 13 | **18b** | 10 | $CH_2Cl_2$ | 25 | 24 | 61[b] | 59:41 |
| 14 | **18b** | 10 | toluene | 25 | 24 | 67[b] | 64:36 |
| 15 | **20** | 10 | $CH_2Cl_2$ | 25 | 48 | < 5[c] | 60:40 |
| 16 | **20** | 10 | toluene | 25 | 48 | < 5[c] | – |

[a] Determined by chiral HPLC analysis of the reaction mixture. [b] Isolated yield. [c] Conversion determined by GC of the reaction mixture.

and confirmed that the amino group is necessary for the formation of the malonate-derived enolate.[19]

Otherwise, it appeared that the *cis* stereochemistry of the cyclobutane moiety induces better enantioselectivity for such reactions than does the *trans* configuration, as deduced from comparison of Entries 5 and 6 with Entries 11 and 12 in Table 1 (Table 1, Entries 5, 6, 11 and 12).

To better understand how the stereochemical features of **17** influence its mode of action, we investigated its conformation in the solid state, which was obtained by X-ray diffraction analysis of single crystals (from $CH_2Cl_2$-pentane) (Figure 2). This structure displays the *E*-conformation for the thiourea-N*H* protons and the intramolecular hydrogen bonding between the pyrrolidine nitrogen atom and neighbouring (S=C)N*H*. This suggests some level of difficulty for a double activation of the electrophile by means of two H-bond formation. Nevertheless, the active conformation in solution and in the presence of the substrates can differ from that adopted in the crystal, as recently described,[20] and further studies will be carried out to verify or refute this hypothesis.

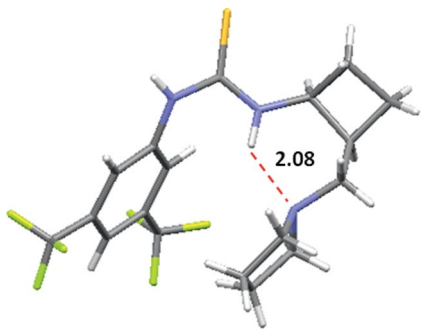



Figure 2. Structure of **17** as obtained from X-ray diffraction analysis. The H-bond between (S=C)N*H* and pyrrolidine is marked (distance in angstroms).

## Conclusions

In summary, the stereocontrolled synthesis of *cis*- and *trans*-cyclobutane containing 1,3-amino alcohols and 1,3-diamines has been achieved from a common chiral precursor through the selective and efficient manipulation of functional groups. The versatility of these scaffolds was highlighted by several examples of their further functionalization to render diastereo- and/or regioisomers as described herein. Different kinds of thiourea derivatives have been synthesized and some preliminary experiments have been carried out to assess their utility as bifunctional organocatalysts. It is noteworthy that there are no previous data in the literature on the use of chiral cyclobutane derivatives in organocatalysis. Some of these compounds were found to satisfactorily accelerate the model Michael reaction although the asymmetric induction was modest. Despite this result, we have gained information about the influence of stereochemical features on both the reaction acceleration and the asymmetric induction. All these data will allow us to design new compounds useful in asymmetric organocatalysis. Moreover, the use of the prepared amino alcohols and diamines to afford candidates for metal ligands and for new chiral surfactants is under active investigation in our laboratories.

## Experimental Section

**Materials and Methods:** Tetrahydrofuran (THF) was freshly distilled under a nitrogen atmosphere from sodium/benzophenone. Dichloromethane was freshly distilled from calcium chloride. All other chemicals were of commercial grade and used without further purification unless otherwise stated. $^1$H NMR and $^{13}$C NMR spectra were carried out in deuterated solvents with Bruker Avance 250 and 360 Ultrashield spectrometers. High resolution mass spectra were recorded with a direct inlet system (ESI). IR spectra were obtained from samples in neat form with an ATR (Attenuated Total Reflectance) accessory. Melting points were recorded with a Reicher Klofler block and values are uncorrected. Purification of the reaction mixtures was performed by column chromatography with neutral silica gel (200–400 mesh).

**Crystallographic Data:** CCDC-903665 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

**Benzyl *N*-[(1*S*,2*R*)-2-(Hydroxymethyl)cyclobutyl]carbamate (1):** Amino ester **3** (465 mg, 1.8 mmol) was dissolved in THF (23 mL). The reaction mixture was placed into an ice bath. Then a 2 M solution of $LiBH_4$ in THF (0.88 mL, 1.8 mmol) was added. After that, MeOH (0.25 mL, 6.2 mmol) was added dropwise. The reaction mixture was stirred in the ice bath for further 4 h. Then, a 2 M solution of $LiBH_4$ in THF (0.13 mL, 0.5 mmol) and MeOH

(0.04 mL) were added and the mixture was stirred at room temp. for 2 more h. The reaction progress was monitored by TLC and when the conversion was complete, MeOH was added until no bubbling was observed. Then, water (100 mL) was added and the crude material was extracted with $CH_2Cl_2$ (3× 50 mL). The organic layers were combined, dried with $MgSO_4$, filtered and the solvent was evaporated. The crude was purified by column chromatography on silica gel (hexanes/EtOAc, 3:1) or by crystallization with diethyl ether/pentanes. In this way, compound **1** was obtained (303 mg, 73 % yield). The same procedure carried out in diethyl ether as a solvent led to the production of **1** in 85 % yield as a white solid, m.p. 66–68 °C (*n*-pentane/diethyl ether). $[\alpha]_D$ = –21.6 (*c* = 1.05, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3355, 3290, 2946, 2867, 1677 $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.37 (m, 5 H, Ar-*H*), 5.49 (broad s, 1 H, N*H*), 5.32 (s, 2 H, C$H_2$Bn), 4.34 (m, 1 H, C*H*NH), 3.75 (m, 2 H, C$H_2$OH), 2.73 (m, 1 H, C*H*C$H_2$OH), 2.31 (m, 1 H, C$H_2$), 1.91 (complex signal group, 2 H, C$H_2$), 1.65 (m, 1 H, C$H_2$) ppm. $^{13}$CNMR (62.5 MHz, $CDCl_3$, 25 °C): $\delta$ = 156.9 (C), 136.9 (C), 128.9 (C), 128.5 (C), 67.2 ($CH_2$), 62.9 ($CH_2$), 48.2 (CH), 41.6 (CH), 28.7 ($CH_2$), 18.9 ($CH_2$) ppm. HRMS (ESI) calcd. for $C_{13}H_{17}NNaO_3$ [*M* + Na]$^+$: 258.1101, found 258.1100.

**[(1*R*,2*S*)-2-(Benzyloxycarbonylamino)cyclobutyl]methyl Methanesulfonate (4):** Alcohol **1** (300 mg, 1.3 mmol) was dissolved in anhydrous $CH_2Cl_2$ (10 mL) under a nitrogen atmosphere. The reaction mixture was placed in an ice bath. Then, $Et_3N$ (0.88 mL, 2 mmol) and mesyl chloride (0.2 mL, 1.7 mmol) were added. The reaction mixture was stirred for 1 h. After that, water (100 mL) was added and the crude reaction was extracted with $CH_2Cl_2$ (3× 50 mL). The organic layers were combined, dried with $MgSO_4$, filtered and solvent was evaporated. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc, 1:1) or by crystallization from diethyl ether and pentanes to afford mesylate **4** (397 mg, 98 % yield) as a white solid, m.p. 67–69 °C (*n*-pentane/diethyl ether). $[\alpha]_D$ = –17.9 (*c* = 1.00, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3355, 2952, 1677, 1346, 1176 $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.37 (m, 5 H, Ar-*H*), 5.11 (complex signal group, 3 H, NH, C$H_2$Ph), 4.41 (complex signal group, 3 H, C$H_2$OMs, C*H*NH), 2.96 (complex signal group, 4 H, C*H*C$H_2$OMs, OSO$_2$C$H_3$), 2.41 (m, 1 H, C$H_2$), 2.03 (complex signal group, 2 H, C$H_2$), 1.71 (m, 1 H, C$H_2$) ppm. $^{13}$C NMR (62.5 MHz, $CDCl_3$, 25 °C): $\delta$ = 156.1 (C), 136.8 (C), 129.0 (C), 128.6 (C), 69.5 ($CH_2$), 67.2 ($CH_2$), 47.0 (CH), 39.4 ($CH_3$), 37.7 (CH), 28.5 ($CH_2$), 18.3 ($CH_2$) ppm. HRMS (ESI) calcd. for $C_{14}H_{19}NNaO_5S$ [*M* + Na]$^+$: 336.0874, found 336.0872.

**Benzyl *N*-[(1*S*,2*S*)-2-(Pyrrolidinylmethyl)cyclobutyl]carbamate (5):** Mesylate **4** (397 mg, 1.3 mmol) was dissolved in anhydrous acetonitrile (10 mL) under a nitrogen atmosphere. Then, pyrrolidine (1.7 mL, 20.7 mmol) was added. The reaction mixture was heated to reflux for 24 h. After that, the volatiles were evaporated under vacuum. A saturated aqueous solution of $NaHCO_3$ (100 mL) was added and the crude reaction was extracted with $CH_2Cl_2$ (3× 50 mL). The organic layers were combined, dried with $MgSO_4$, filtered and the solvents evaporated. The product was purified by column chromatography on silica gel (hexanes/EtOAc, 2:1) to afford **5** (292 mg, 78 % yield) as a yellow oil. $[\alpha]_D$ = +72.7, (*c* = 1.00, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3310, 2952, 1677 $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.35 (m, 5 H, Ar-*H*), 5.09 (broad s, 2 H, C$H_2$Ph), 4.22 (complex signal group, 1 H, C*H*NH), 3.13 (m, 1 H, C*H*C$H_2$N), 2.69 [m, 1 H, C$H_2$N(C$H_2$)$_4$], 2.50 [complex signal group, 6 H, C$H_2$N(C$H_2$)$_4$, N(C$H_2$C$H_2$)$_2$, C$H_2$], 2.02 (complex signal group, 2 H, C$H_2$), 1.76 [complex signal group, 4 H, N(CH$_2$C$H_2$)$_2$], 1.43 (m, 1 H, C$H_2$) ppm. $^{13}$C NMR (62.5 MHz, $CDCl_3$, 25 °C): $\delta$ = 156.3 (C), 137.5 (C), 128.8 (C), 128.7 (C), 128.2 (C), 66.5 ($CH_2$), 57.5 ($CH_2$), 54.3 ($CH_2$), 48.2 (CH), 36.4 (CH), 29.3 ($CH_2$), 23.9 ($CH_2$), 20.4 ($CH_2$) ppm. HRMS (ESI) calcd. for $C_{17}H_{25}N_2O_2$ [*M* + H]$^+$: 289.1915, found 289.1910.

***tert*-Butyl *N*-[(1*S*,2*S*)-2-(Hydroxymethyl)cyclobutyl]carbamate (2):** Compound **8** (830 mg, 3.8 mmol) was dissolved in anhydrous THF (36 mL) under a nitrogen atmosphere. Ethyl chloroformate (385 μL, 4.05 mmol) and $Et_3N$ (0.89 mL, 6.4 mmol) were added. The reaction was stirred at room temp. for 40 min. Then the salts were filtered and washed with THF (10 mL). 2 M $LiBH_4$ in THF solution (3.87 mL, 7.74 mmol) was added to the filtrate and then MeOH (0.5 mL, 12.4 mmol) was added dropwise. After 2 h, MeOH (23.0 mmol) were added. After 5 more h of stirring at room temp., more MeOH was added until no gas formation was observed. Then, water (100 mL) was added and the reaction mixture was extracted with $CH_2Cl_2$ (5× 50 mL). The organic layers were combined, dried with $MgSO_4$, filtered and the solvent evaporated. The crude reaction was purified by column chromatography on silica gel (EtOAc/hexanes, 1:2) giving **2** (583 mg, 75 % yield) as a white solid, m.p. 58–59 °C (EtOAc/hexanes). $[\alpha]_D$ = –105 (*c* = 1.00, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3364, 2977, 1674, 1519, 1364, 1277, 1161, 1050, 870 $cm^{-1}$. $^1H$ NMR (360 MHz, $CDCl_3$, 25 °C): $\delta$ = 5.00 (broad s, 1 H, N*H*), 3.51 (complex signal group, 3 H, C*H*N, C$H_2$OH), 2.31 (m, 1 H, C*H*C$H_2$OH), 2.18 (m, 1 H, C$H_2$), 1.79 (complex signal group, 2 H, C$H_2$), 1.42 [s, 9 H, C(C$H_3$)$_3$], 1.44–1.35 (m, 1 H, C$H_2$) ppm. $^{13}$C NMR (90 MHz, $CDCl_3$, 25 °C): $\delta$ = 156.4 (C), 80.2 (C), 65.7 ($CH_2$), 50.9 (CH), 48.7 (CH), 28.3 ($CH_3$), 25.2 ($CH_2$), 17.2 ($CH_2$) ppm. HRMS (ESI) calcd. for $C_{10}H_{19}NNaO_3$ [*M* + Na]$^+$: 224.1257, found 224.1258.

**[(1*S*,2*S*)-2-(*tert*-Butoxycarbonylamino)cyclobutyl]methyl 4-Methylbenzenesulfonate (9):** Compound **2** (283 mg, 1.4 mmol) was dissolved in anhydrous $CH_2Cl_2$ (5.7 mL) under a nitrogen atmosphere. Tosyl chloride (548 mg, 2.9 mmol), DMAP (24.4 mg, 0.2 mmol) and $Et_3N$ (0.56 mL, 4.0 mmol) were added and the reaction mixture was stirred at room temp. for 5 h. A saturated aqueous solution of $NH_4Cl$ (50 mL) was then added and the reaction mixture was extracted with $CH_2Cl_2$ (3× 20 mL). The organic layers were combined, dried with $MgSO_4$, filtered and the solvent evaporated. The crude reaction was purified by column chromatography on silica gel (EtOAc/hexanes, 1:4) giving **9** (468 mg, 94 % yield) as a white solid, m.p. 74–75 °C (EtOAc/hexanes). $[\alpha]_D$ = +11.9, (*c* = 0.83, $CH_2Cl_2$). IR (ATR): $\tilde{\nu}$ = 3337, 2975, 1695, 1514, 1362, 1174, 946 $cm^{-1}$. $^1H$ NMR (360 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.75 (d, *J* = 11.9 Hz, 2 H, Ar-*H*), 7.34 (d, *J* = 11.5 Hz, 2 H, Ar-*H*), 4.80 (m, 1 H, N*H*), 4.01 (m, 2 H, C$H_2$OTs), 3.73 (m, 1 H, C*H*N), 2.43 (complex signal group, 4 H, C$H_3$, C*H*C$H_2$OTs), 2.15 (m, 1 H, C$H_2$), 1.75 (complex signal group, 2 H, C$H_2$), 1.40 [s, 9 H, C(C$H_3$)$_3$], 1.40 (m, 1 H, C$H_2$) ppm. $^{13}$C NMR (90 MHz, $CDCl_3$, 25 °C): $\delta$ = 155.2 (C), 145.1 (C), 133.4 (C), 130.2 (CH), 128.3 (CH), 79.4 (C), 72.1 ($CH_2$), 48.2 (CH), 44.0 (CH), 28.7 ($CH_3$), 27.6 ($CH_2$), 22.0 ($CH_3$), 18.5 ($CH_2$) ppm. HRMS (ESI) calcd. for $C_{17}H_{25}NNaO_5S$ [*M* + Na]$^+$: 378.1346, found 378.1345.

***tert*-Butyl *N*-[(1*S*,2*R*)-2-(Dimethylaminomethyl)cyclobutyl]carbamate (10):** Compound **9** (83 mg, 0.23 mmol) was mixed with a 2 M solution of $NHMe_2$ in THF (2.33 mL, 4.67 mmol) under a nitrogen atmosphere. The reaction was stirred at room temp. for 70 h. Then the volatiles were evaporated under reduced pressure. 1 M solution of NaOH (10 mL) were added and the product was extracted with $CH_2Cl_2$ (5× 10 mL). The organic layers were combined, dried with $MgSO_4$, filtered and the solvent evaporated. The crude reaction was purified by column chromatography on silica gel (EtOAc with 3 % of $Et_3N$). In this way, **10** (49 mg, 92 % yield) was obtained as a white solid, m.p. 42–43 °C (EtOAc). $[\alpha]_D$ = +19.9 (*c* = 1.04, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3356, 2968, 2945, 2766, 1683, 1530, 1278,

1166 $cm^{-1}$. $^1H$ NMR (360 MHz, $CDCl_3$, 25 °C): $\delta$ = 4.77 (broad s, 1 H, N*H*), 3.72 (m, 1 H, C*H*NH), 2.52 [m, 1 H, C*H*$CH_2N(CH_3)_2$], 2.28 [complex signal group, 9 H, $CH_2N(CH_3)_2$, $CHCH_2N(CH_3)_2$, $CH_2$], 1.93 (m, 1 H, $CH_2$), 1.68 (m, 1 H, $CH_2$), 1.43 [m, 9 H, $C(CH_3)_3$], 1.43–1.30 (m, 1 H, $CH_2$) ppm. $^{13}C$ NMR (90 MHz, $CDCl_3$, 25 °C): $\delta$ = 155.3 (C), 79.3 (C), 64.5 ($CH_2$), 50.2 (CH), 46.1 ($CH_3$), 44.6 (CH), 28.7 ($CH_3$), 28.5 ($CH_2$), 21.8 ($CH_2$) ppm. HRMS (ESI) calcd. for $C_{12}H_{25}N_2O_2$ [*M* + H]$^+$: 229.1911, found 229.1909.

**(1*S*,2*R*)-2-(Dimethylaminomethyl)cyclobutyl-1-aminium Trifluoroacetate (11):** Compound **10** (146 mg, 0.64 mmol) was dissolved in anhydrous $CH_2Cl_2$ (3 mL). Then, TFA (0.64 mL, 8.32 mmol) and $Et_3SiH$ (0.26 mL, 1.6 mmol) were added. The mixture was stirred at room temp. for 3 h. The volatiles were evaporated under vacuum and in the dry-freezer. In this way **11** (131 mg, 85 % yield) was obtained as a colorless oil. $[\alpha]_D$ = +18.1 (*c* = 1.11, MeOH). IR (ATR): $\tilde{\nu}$ = 3421, 3001, 1680, 1204, 1132, 892, 836, 799, 723 $cm^{-1}$. $^1H$ NMR (360 MHz, [D$_4$]methanol, 25 °C): $\delta$ = 3.50 (m, 1 H, C*H*N), 3.31 (dd, $J_1$ = 6.84 Hz, $J_2$ = 18.7 Hz, 1 H, $CH_2N$), 3.14 (dd, $J_1$ = 12.9 Hz, $J_2$ = 18.7 Hz, 1 H, $CH_2N$), 2.76 [complex signal group, 7 H, C*H*$CH_2N(CH_3)_2$, $CH_2N(CH_3)_2$], 2.26–1.93 (complex signal group, 3 H, $CH_2$, $CH_2$), 1.66 (m, 1 H, $CH_2$) ppm. $^{13}C$ NMR (90 MHz, [D$_4$]methanol, 25 °C): $\delta$ = 59.6 ($CH_2$), 47.0 (CH under MeOH signal) 42.2 ($CH_3$), 36.0 (CH), 23.7 ($CH_2$), 20.5 ($CH_2$) ppm. HRMS (ESI) calcd. for $C_7H_{17}N_2$ [*M* + H]$^+$: 129.1386, found 129.1386.

***tert*-Butyl *N*-[(1*S*,2*R*)-2-(Azidomethyl)cyclobutyl]carbamate (12):** A solution of $NaN_3$ (565 mg, 8.7 mmol) in DMF (12.5 mL) was added to a flask containing **9** (968 mg, 2.72 mmol). The mixture was heated to 75 °C for three h. Then the reaction mixture was cooled down to room temp. and EtOAc was added (60 mL). Then, the crude reaction was washed with water (5 × 50 mL). The combined aqueous layers were extracted with EtOAc (100 mL) and this organic layer was washed again with water (5 × 50 mL). The organic layers were combined, dried with $MgSO_4$, filtered and evaporated under vacuum. The crude reaction was purified by column chromatography on silica gel (EtOAc/hexanes; 1:9). In this way, **12** (580 mg, 94 % yield) was obtained as a white solid. Note: due to the intrinsic instability and potential explosive nature of this molecule, only IR and NMR experiments were carried out to characterize this intermediate, m.p. 27–29 °C (EtOAc). $[\alpha]_D$ = +14.3 (*c* = 1.01, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3338, 2978, 2091, 1683, 1511, 1365, 1251, 1013 $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$, 25 °C): $\delta$ = 4.99 (broad s, 1 H, N*H*), 3.78 (m, 1 H, C*H*NH), 3.31 (m, 2 H, $CH_2N_3$), 2.39–2.12 (complex signal group, 2 H, C*H*$CH_2N_3$, $CH_2$), 1.87–1.61 (complex signal group 2 H, $CH_2$), 1.38 [m, 10 H, $C(CH_3)_3$, $CH_2$] ppm. $^{13}C$ NMR (62.5 MHz, $CDCl_3$, 25 °C): $\delta$ = 155.3 (C), 79.6 (C), 54.6 ($CH_2$), 49.2 (CH), 45.0 (CH), 28.7 ($CH_3$), 27.7 ($CH_2$), 19.4 ($CH_2$) ppm.

***tert*-Butyl *N*-[(1*S*,2*R*)-2-(Aminomethyl)cyclobutyl]carbamate (13):** Compound **12** (291 mg, 1.28 mmol) was dissolved in THF (5 mL) and $Pd(OH)_2$/C 20 % weight (116 mg, 40 %) was added. The mixture was stirred under hydrogen pressure (6 atm) for 5 h. The crude reaction was filtered through celite and washed with THF (20 mL). The combined organic layers were evaporated under vacuum. **13** (251 mg, 98 % yield) was obtained as a white solid. $[\alpha]_D$ –30.3 (*c* = 1.28, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3360, 3340, 3170, 2977, 1680, 1537, 1291, 1170, 875 $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$, 25 °C): $\delta$ = 4.88 (broad s, 1 H, N*H*), 3.72 (m, 1 H, C*H*NH), 2.75 (m, 2 H, $CH_2NH_2$), 2.20 (complex signal group, 4 H, C*H*$CH_2NH_2$, $CH_2$), 1.89–1.59 (complex signal group, 2 H, $CH_2$), 1.43–1.27 [complex signal group, 10 H, $C(CH_3)_3$, $CH_2$] ppm. $^{13}C$ NMR (62.5 MHz, $CDCl_3$, 25 °C): $\delta$ = 155.6 (C), 80.0 (C), 50.3 (CH), 49.0 (CH), 46.2 ($CH_2$), 28.8 ($CH_3$), 27.3 ($CH_2$), 19.0 ($CH_2$) ppm. HRMS (ESI) calcd. for $C_{10}H_{21}N_2O_2$ [*M* + H]$^+$: 201.1601, found 201.1598.

***tert*-Butyl *N*-[(1*S*,2*R*)-2-(Isopropylamino)methylcyclobutyl]carbamate (14):** Compound **12** (104 mg, 0.46 mmol) was dissolved in MeOH (3 mL) and $Pd(OH)_2$/C 20 % weight (42 mg, 40 %) was added. Acetone (40 µL, 0.69 mmol) was added. The mixture was stirred under hydrogen pressure (6 atm) for 14 h. The crude reaction was filtered through celite and washed with MeOH (10 mL). The combined organic layers were evaporated under vacuum. In this way, **14** (103 mg, 93 % yield) was obtained as a white solid. $^1H$ NMR (250 MHz, $CDCl_3$, 25 °C): $\delta$ = 5.24 (broad s, 1 H, N*H*), 4.23 (broad s, 1 H, N*H*), 3.57 (m, 1 H, C*H*NH), 2.80–2.53 [complex signal group, 3 H, $CH_2NH_2$, $CH(CH_3)_2$], 2.31 (m, 1 H, C*H*$CH_2NH$) 2.09 (m, 1 H, $CH_2$), 1.78–1.60 (complex signal group, 2 H, $CH_2$), 1.32–1.23 [complex signal group, 10 H, $C(CH_3)_3$, $CH_2$], 1.09 [m, 6 H, $CH(CH_3)_2$] ppm. $^{13}C$ NMR (62.5 MHz, $CDCl_3$, 25 °C): $\delta$ = 155.7 (C), 79.6 (C), 50.8 (CH), 50.6 (CH), 49.1 (CH), 45.0 ($CH_2$), 28.3 ($CH_3$), 26.3 ($CH_2$), 21.7 ($CH_3$), 21.4 ($CH_3$), 19.2 ($CH_2$) ppm. HRMS (ESI) calcd. for $C_{13}H_{27}N_2O_2$ [*M* + H]$^+$: 242.1994, found 242.1988.

***tert*-Butyl *N*-[(1*S*,2*R*)-2-(Benzylamino)methylcyclobutyl]carbamate (15):** Compound **13** (132 mg, 0.66 mmol) were dissolved in MeOH (0.5 mL) and freshly distilled benzaldehyde (67 µL, 0.66 mmol) was added. After 3 h 1 M solution of $NaCNBH_3$ in THF (658 µL, 1.9 mmol) was added. The mixture was stirred overnight at room temp. The crude reaction was concentrated in vacuo and the residue was dissolved in diethyl ether and was extracted with a solution of HCl at pH = 3 (8 mL). The aqueous layer was washed with diethyl ether. Then 1 M NaOH (15 mL) was added to the aqueous layer. The product was extracted from this solution with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were dried with $MgSO_4$ and the solvents evaporated under vacuum. In this way, **15** (73 mg, 38 % yield) was obtained as a white solid, m.p. 104–106 °C ($CH_2Cl_2$). $[\alpha]_D$ = +18.4 (*c* = 1.02, $CH_2Cl_2$). IR (ATR): $\tilde{\nu}$ = 3277, 3173, 2971, 2921, 2803, 1675, 1560, 1305, 1166, 1013 $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.35–7.24 (complex signal group, 5 H, Ar-*H*), 4.71 (broad s, 1 H, N*H*), 3.81–3.72 (complex signal group, 3 H, $CH_2Ph$, C*H*NH), 2.73 (m, 2 H, $CH_2NH$), 2.36–2.23 (complex signal group, 2 H, $CHCH_2NH$, $CH_2$), 1.96–1.65 (complex signal group, 2 H, N*H*, $CH_2$), 1.42–1.23 [complex signal group, 10 H, $C(CH_3)_3$, $CH_2$] ppm. $^{13}C$ NMR (62.5 MHz, $CDCl_3$, 25 °C): $\delta$ = 155.6 (C), 140.4 (C), 128.7 (CH), 128.6 (CH), 127.2 (CH), 79.9 (C), 54.5 ($CH_2$), 53.9 ($CH_2$), 50.9 (CH), 46.4 (CH), 28.7 ($CH_3$), 27.7 ($CH_2$), 19.7 ($CH_2$) ppm. HRMS (ESI) calcd. for $C_{17}H_{27}N_2O_2$ [*M* + H]$^+$: 291.2067, found 291.2064.

**1-Phenyl-3-[(1*R*,2*S*)-2-(pyrrolidinylmethyl)cyclobutyl]thiourea (16):** Compound **5** (300 mg, 1.04 mmol) was dissolved in the minimum amount of ethanol. Then, $Pd(OH)_2$/C (80 mg) was added. The reaction mixture was hydrogenated over 12 h under 6 atmospheres pressure. Then the crude reaction was filtered through celite and the resulting celite pad washed with copious amounts of MeOH. The solvent was evaporated under vacuum giving **6** (157 mg, 98 % yield) as a yellow oil. This product was used in the following step without further purification. $^1H$ NMR (250 MHz, $CDCl_3$, 25 °C): $\delta$ = 6.11 (broad s, 2 H, $NH_2$), 3.99 (broad s, 1 H, C*H*$NH_2$), 3.85 (m, 1 H, C*H*$CH_2N$), 3.11 [complex signal group, 4 H, $CH_2N$, $N(CH_2CH_2)_2$], 2.89 [complex signal group, 2 H, $N(CH_2CH_2)_2$], 2.38 (m, 2 H, $CH_2$), 2.01 [complex signal group, 6 H, $CH_2$, $N(CH_2CH_2)_2$] ppm.

Freshly prepared amine **6** (150 mg, 1 mmol) was dissolved in anhydrous $CH_2Cl_2$ (12 mL) under a nitrogen atmosphere. Then, phenyl isothiocyanate (0.12 mL, 1 mmol) was added. The reaction mixture

was refluxed for 18 h. After that, the volatiles were evaporated under vacuum. The crude reaction was purified by column chromatography on silica gel (from pure $CH_2Cl_2$ to a mixture of $CH_2Cl_2$/MeOH/$Et_3N$, 100:5:1) yielding **16** (225 mg, 78 % yield) as a white solid, m.p. 146–148 °C (*n*-pentane). $[\alpha]_D$ = +32.5 (*c* = 1.00, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3355, 3310, 2965, 1465, 1394, 1274, 1128 $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$, 25 °C): $\delta$ = 9.57 (broad s, 1 H, N*H*), 7.39–7.22 (m, 5 H, Ar-*H*), 4.73 (broad s, 1 H, N*H*), 3.26 (m, 1 H, C*H*N), 2.71 (complex signal group, 2 H, $CH_2N$, $CHCH_2N$), 2.18 [complex signal group, 7 H, $CH_2N$, $N(CH_2CH_2)_2$, $CH_2$], 1.44 [complex signal group, 6 H, $N(CH_2CH_2)_2$, $CH_2$] ppm. $^{13}C$ NMR (62.5 MHz, $CDCl_3$, 25 °C): $\delta$ = 180.1 (C), 137.6 (C), 130.0 (C), 126.8 (C), 125.1 (C), 58.1 ($CH_2$), 53.8 ($CH_2$), 52.3 (CH), 35.6 (CH), 29.6 ($CH_2$), 23.4 ($CH_2$), 20.0 ($CH_2$) ppm. HRMS (ESI) calcd. for $C_{16}H_{24}N_3S$ $[M + H]^+$: 290.1685, found 289.1679.

**1-[3,5-Bis(trifluoromethyl)phenyl]-3-[(1*S*,2*S*)-2-(pyrrolidinylmethyl)-cyclobutyl]thiourea (17):** Amine **6** (132 mg, 0.85 mmol), freshly prepared as described above, was dissolved in anhydrous $CH_2Cl_2$ (7 mL) under a nitrogen atmosphere. Then, 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.15 mL, 0.85 mmol) was added. The reaction mixture was refluxed for 24 h. After that, the volatiles were evaporated under vacuum. The crude reaction was purified by column chromatography on silica gel (EtOAc with 2 % $Et_3N$) yielding. **17** (143 mg, 39 % yield) as a white solid, m.p. 125–127 °C (*n*-pentane). $[\alpha]_D$ = +8.0 (*c* = 1.00, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3355, 3310, 2965, 1465, 1394, 1274, 1128 $cm^{-1}$. $^1H$ NMR (250 MHz, [$D_4$]methanol, 25 °C): $\delta$ = 8.04 (broad s, 2 H, Ar-*H*), 7.54 (s, 1 H, Ar-*H*), 4.77 (complex signal group, 3 H, 2× N*H*, C*H*N), 2.78 (complex signal group, 2 H, $CHCH_2N$, $CHCH_2N$), 2.43 [complex signal group, 6 H, $CHCH_2N$, $N(CH_2CH_2)_2$, $CH_2$], 2.00 (complex signal group, 2 H, $CH_2$), 1.62 [complex signal group, 5 H, $N(CH_2CH_2)_2$, $CH_2$] ppm. $^{13}C$ NMR (62.5 MHz, [$D_4$]methanol, 25 °C): $\delta$ = 181.3 (C), 135.0–117.0 (various C plus coupled signals of $CF_3$), 56.6 ($CH_2$), 54.1 ($CH_2$), 51.1 (CH), 37.9 (CH), 26.9 ($CH_2$), 23.2 ($CH_2$), 20.8 ($CH_2$) ppm. HRMS (ESI) calcd. for $C_{18}H_{22}F_6N_3S$ $[M + H]^+$: 426.1442, found 426.1436.

**1-[3,5-Bis(trifluoromethyl)phenyl]-3-[(1*S*,2*R*)-2-(dimethylamino-methyl)cyclobutyl]thiourea (18a):** Compound **11** (133 mg, 0.55 mmol) was dissolved in a 1 M NaOH solution (7 mL). The free amine was extracted with $CH_2Cl_2$ (5× 10 mL). The organic layers were combined, dried with $MgSO_4$, filtered and evaporated to obtain 70 mg of the free amine as an off-white solid. This solid was then dissolved in anhydrous $CH_2Cl_2$ (5 mL) in a nitrogen atmosphere and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.398 mL, 2.20 mmol) was added. The mixture was refluxed for 16 h. Then the volatiles were evaporated and crude reaction was purified by column chromatography on silica gel ($CHCl_3$ with 5 % of a 32 % aqueous solution of $NH_3$) yielding **18a** (82 mg, 37 % yield) as a white solid, m.p. 159–161 °C ($CH_2Cl_2$/*n*-pentane). $[\alpha]_D$ = –60.7 (*c* = 1.02, MeOH). IR (ATR): $\tilde{\nu}$ = 3206, 2920, 1375, 1274, 1161, 1120, 879, 678 $cm^{-1}$. $^1H$ NMR (360 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.93 (s, 2 H, Ar-*H*), 7.64 (s, 1 H, Ar-*H*), 6.61 (broad s, 1 H, N*H*), 3.71 (m, 1 H, C*H*N), 2.57–2.29 [complex signal group, 10 H, $CHCH_2N(CH_3)_2$, $CH_2N(CH_3)_2$, $CH_2N(CH_3)_2$], 2.01 (m, 2 H, $CH_2$), 1.27–1.39 (m, 2 H, $CH_2$) ppm. $^{13}C$ NMR (90 MHz $CDCl_3$, 25 °C): $\delta$ = 182.3 (C), 142.5 (C), 131.9 (q, 1 C), 124.6 (CH), 121.8 (C), 118.3 (CH), 64.1 ($CH_2$), 54.6 (CH), 45.7 ($CH_3$), 43.2 (CH), 26.4 ($CH_2$), 19.0 ($CH_2$) ppm. HRMS (ESI) calcd. for $C_{16}H_{20}F_6N_3S$ $[M + H]^+$: 400.1277, found 400.1282.

**Thiourea 19:** Compound **14** (86 mg, 0.36 mmol) was dissolved in anhydrous $CH_2Cl_2$ (4 mL) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (86 μL, 0.47 mmol) were added. The reaction mixture was refluxed for 28 h under a nitrogen atmosphere. Then the volatiles were evaporated and the crude reaction was purified by column chromatography on silica gel (EtOAc/hexanes, 1:5). In this way, **19** (85 mg, 46 % yield) was obtained as a pale yellow solid, m.p. 73–75 °C (EtOAc). $[\alpha]_D$ = –11.5 (*c* = 0.98, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3260, 2977, 1679, 1510, 1367, 1273, 1165, 1127, 1043, 780, 700, 680 $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$, 25 °C): $\delta$ = 8.80 (broad s, 1 H, N*H*), 7.88 (s, 2 H, Ar-*H*), 7.66 (s, 1 H, Ar-*H*), 5.80 [sept, *J* = 6.8 Hz, 1 H, $CH(CH_3)_2$], 4.84 (broad s, 1 H, N*H*), 4.14 (d, *J* = 15.9 Hz, 1 H, $CH_2NH$), 3.65 (m, 1 H, C*H*NHBoc), 3.41 (dd, *J* = 15.9 Hz, *J′* = 8.7 Hz, 1 H, $CH_2NH$), 2.62 (m, 1 H, $CHCH_2N$), 2.20 (m, 2 H, $CH_2$), 1.69 (m, 2 H, $CH_2$), 1.21–1.17 [complex signal group, 15 H, $C(CH_3)_3$, $CH(CH_3)_2$] ppm. $^{13}C$ NMR (62.5 MHz, $CDCl_3$, 25 °C): $\delta$ = 181.4 (C), 156.6 (C), 142.5 (C), 131.9 (q, 1 C), 128.5 (CH), 125.8 (CH), 119.6 (C), 80.8 (C), 52.1 (CH), 49.9 (CH), 48.7 ($CH_2$), 42.6 (CH), 28.3 ($CH_3$), 24.8 ($CH_3$), 24.3 ($CH_3$), 21.7 ($CH_2$), 20.0 ($CH_2$) ppm. HRMS (ESI) calcd. for $C_{22}H_{29}F_6N_3NaO_2S$ $[M + Na]^+$: 536.1777, found 536.1785.

**Thiourea 20:** Compound **13** (264 mg, 1.32 mmol) was dissolved in anhydrous $CH_2Cl_2$ (10 mL) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.6 mL, 4.09 mmol) were added. The reaction mixture was refluxed for 24 h under a nitrogen atmosphere. Then the volatiles were evaporated and the crude reaction was purified by column chromatography on silica gel (hexanes/EtOAc/$Et_3N$, 8:1:0.4) yielding **20** (99 mg, 16 % yield) as a pale yellow solid, m.p. 61–63 °C ($CH_2Cl_2$). $[\alpha]_D$ = –27.5 (*c* = 1.2, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3215, 2934, 1675, 1502, 1471, 1369, 1274, 1166, 1126, 1019, 884, 700, 680 $cm^{-1}$. $^1H$ NMR (360 MHz, $CDCl_3$, 25 °C): $\delta$ = 8.17 (s, 2 H, Ar-*H*), 7.62 (s, 1 H, Ar-*H*), 3.75 (complex signal group, 2 H, N*H*Boc, $CH_2NH$), 3.57 (m, 1 H, $CH_2NH$), 2.50 (m, 1 H, $CHCH_2N$), 2.18 (m, 1 H, C*H*NHBoc), 1.85 (m, 2 H, $CH_2$), 1.38 [complex signal group, 11 H, $C(CH_3)_3$, $CH_2$] ppm. $^{13}C$ NMR (90 MHz, $CDCl_3$, 25 °C): $\delta$ = 181.3 (C), 156.4 (C), 141.8 (C), 131.1 (q, 1 C), 124.8 (CH), 121.8 (CH), 116.2 (C), 78.7 (C), 49.4 ($CH_2$), 43.9 (CH), 29.3 (CH), 27.4 ($CH_3$), 25.6 ($CH_2$), 18.3 ($CH_2$) ppm. HRMS (ESI) calcd. for $C_{19}H_{23}F_6N_3NaO_2S$ $[M + Na]^+$: 494.1307, found 494.1305.

**1-[3,5-Bis(trifluoromethyl)phenyl]-3-[(1*R*,2*S*)-2-(dimethylamino)-cyclobutylmethyl]thiourea (18b):** Compound **20** (67 mg, 0.14 mmol) was dissolved in anhydrous $CH_2Cl_2$ (3 mL) and TFA (143 μL, 1.85 mmol) and triethylsilane (56 μL, 0.36 mmol) were added. The reaction mixture was stirred at room temp. for 3 h. The volatiles were then evaporated and the acetate salt dissolved in 1 M NaOH solution (5 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3× 10 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated under reduced pressure. This crude material was dissolved in AcCN (3 mL) and a 37 % aqueous solution of formaldehyde (71 μL, 0.91 mmol) was added. After 25 min, a 1 M solution of $NaCNBH_3$ in THF (263 μL, 0.78 mmol) was added followed, 15 min later, by AcOH (7.5 μL, 0.14 mmol). The resulting solution was stirred at room temp. overnight. Volatile compounds were evaporated and 1 M NaOH solution was added (5 mL). Then the aqueous layer was extracted with $CH_2Cl_2$ (3× 10 mL). The combined organic layers were dried and the solvent was removed under reduced pressure. Product **18b** was purified by semi-preparative thin layer chromatography on silica gel (EtOAc/3 % of $Et_3N$). In this way, **18b** (9.4 mg, 18 % yield) was obtained as a colorless oil. $[\alpha]_D$ = +46.1 (*c* = 1.04, $CH_2Cl_2$). IR (ATR): $\tilde{\nu}$ = 3180, 2946, 1594, 1518, 1470, 1391, 1272, 1130, 1110, 899, 687 $cm^{-1}$. $^1H$ NMR (360 MHz, $CDCl_3$, 25 °C): $\delta$ = 8.68 (s, 1 H, N*H*), 8.02 (s, 2 H, Ar-*H*), 7.64 (s, 1 H, Ar-*H*), 7.13 (broad s, 1 H, N*H*), 3.76 (m, 1 H, C*H*N), 3.61 (m, 1 H, $CH_2NH$), 3.51 (m, 1 H,

$CH_2NH$), 2.94 (m, 1 H, $CHCH_2N$), 2.61 [d, $J$ = 3.8 Hz, 6 H, $N(CH_3)_2$], 2.06 (m, 2 H, $CH_2$), 1.85 (m, 1 H, $CH_2$), 1.59 (m, 1 H, $CH_2$) ppm. $^{13}C$ NMR (90 MHz, $CDCl_3$, 25 °C): $\delta$ = 181.9 (C), 140.2 (C), 132.1 (q, 1 C), 123.4 (C), 121.6 (CH), 118.2 (CH), 67.3 (CH), 48.0 ($CH_3$), 47.6 ($CH_3$), 46.6 ($CH_2$), 37.9 (CH), 20.5 ($CH_2$), 17.6 ($CH_2$) ppm. HRMS (ESI) calcd. for $C_{16}H_{20}F_6N_3S$ $[M + H]^+$: 400.1277, found 400.1285.

**General Procedure for the Organocatalyzed Conjugate Addition Reactions:** A typical experiment with organocatalyst **17** is described. (*E*)-β-nitrostyrene (35.1 mg, 0.24 mmol) was dissolved in toluene (0.5 mL) and diethyl malonate then added (75 μL, 0.49 mmol), followed by the desired amount of catalyst **17** (5 or 10 mol-%). The reaction was stirred for 24 or 48 h at room temp., 0 °C or –25 °C. Then the crude reaction was analyzed by gas chromatography (conditions: 70 °C for 3 min; 25 °C/min ramp up to 300 °C; 300 °C for 5 min) to determine the yield. Retention times: diethyl malonate: 7 min; (*E*)-β-nitrostyrene: 9.2 min; diethyl 2-(2-nitro-1-phenylethyl)malonate: 11.8 min. The crude reaction was purified by column chromatography on silica gel (EtOAc/hexanes, 1:9) to obtain pure diethyl 2-(2-nitro-1-phenylethyl)malonate.[20] Then, if the mobile phase was changed to EtOAc/2 % of $Et_3N$, the catalyst can be recovered. The purified product was analyzed by HPLC using a Daicel AD-H column, hexane/*i*PrOH, 80:20, 1 mL/min, retention times: 10.0 min [(*R*), minor], 27 min [(*S*), major].[18,21]

**Supporting Information** (see footnote on the first page of this article): Selected HPLC chromatograms and copies of the $^1H$ and $^{13}C$ NMR spectra.

## Acknowledgments

We acknowledge financial support from the Spanish Ministerio de Ciencia e Innovación (MICINN) (grant number CTQ2010-15408/BQU) and Generalitat de Catalunya (grant number 2009SGR-733).

[1] For reviews on the synthesis and applications of 1,2-amino alcohols, see for example: a) D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev.* **1996**, *96*, 835–875; b) S. C. Bergmeier, *Tetrahedron* **2000**, *56*, 2561–2576; c) F. Fache, E. Schulz, M. L. Tommasino, M. Lemaire, *Chem. Rev.* **2000**, *100*, 2159–2231; d) J. A. Bodkin, M. D. McLeod, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2733–2746; e) H.-S. Lee, S. H. Kang, *Synlett* **2004**, 1673–1685; f) C. Anaya de Parrodi, E. Juaristi, *Synlett* **2006**, *17*, 2699–2715; g) O. N. Burchak, S. Py, *Tetrahedron* **2009**, *65*, 7333–7356; h) A. M. P. Koskinen, *Pure Appl. Chem.* **2011**, *83*, 435–443.

[2] See for example: a) S. M. Lait, D. A. Rankic, B. A. Keay, *Chem. Rev.* **2007**, *107*, 767–796; b) F. A. Davis, P. M. Gaspari, B. M. Nolt, P. Xu, *J. Org. Chem.* **2008**, *73*, 9619–9626; c) H. Geng, W. Zhang, J. Chen, G. Hou, L. Zhou, Y. Zou, W. Wu, X. Zhang, *Angew. Chem.* **2009**, *121*, 6168; *Angew. Chem. Int. Ed.* **2009**, *48*, 6052–6054; d) S. Mangelinckx, Y. Nural, H. A. Dondas, B. Denolf, R. Sillanpää, N. De Kimpe, *Tetrahedron* **2010**, *66*, 4115–4124; e) S. Ueno, K. Usui, R. Kuwano, *Synlett* **2011**, 1303–1307; f) C. Solé, A. Tatla, J. A. Mata, A. Whiting, H. Gulyás, E. Fernández, *Chem. Eur. J.* **2011**, *17*, 14248–14257.

[3] a) G. R. Evans, P. Díaz Fernández, J. A. Henshilwood, S. Lloyd, C. Nicklin, *Org. Process Res. Dev.* **2002**, *6*, 729–737; b) J. E. D. Martins, C. M. Mehlecke, M. Gamba, V. E. U. Costa, *Tetrahedron: Asymmetry* **2006**, *17*, 1817–1823; c) B. Rodríguez, C. Bolm, *J. Org. Chem.* **2006**, *71*, 2888–2891; d) I. Ibrahem, W. Zou, J. Casas, H. Sundén, A. Córdova, *Tetrahedron* **2006**, *62*, 357–364; e) J. C. González-Gómez, F. Foubelo, M. Yus, *Synthesis* **2009**, *12*, 2083–2088; f) Z. Szakonyi, F. Fülöp, *Tetrahedron: Asymmetry* **2010**, *21*, 831–836; g) L. Kiss, E. Forró, R. Sillanpää, F. Fülöp, *Synthesis* **2010**, *1*, 153–160; h) Z. Szakonyi, F. Fülöp, *Amino Acids* **2011**, *41*, 597–608; i) Z. Szakonyi, K. Csillag, F. Fülöp, *Tetrahedron: Asymmetry* **2011**, *22*, 1021–1027.

[4] a) N. Katagiri, H. Sato, C. Kaneko, *Chem. Pharm. Bull.* **1990**, *38*, 288–290; b) A. Rustullet, R. Alibés, P. de March, M. Figueredo, J. Font, *Org. Lett.* **2007**, *9*, 2827–2830; c) B. Darses, A. E. Greene, S. C. Coote, J.-F. Poisson, *Org. Lett.* **2008**, *10*, 821–824; d) A. Ebead, R. Fournier, E. Lee-Ruff, *Nucleosides Nucleotides Nucleic Acids* **2011**, *30*, 391–404.

[5] See for example: a) W. P. Hems, M. Groarke, A. Zanotti-Gerosa, G. A. Grasa, *Acc. Chem. Res.* **2007**, *40*, 1340–1347; b) J.-C. Kizirian, *Chem. Rev.* **2008**, *108*, 140–205.

[6] a) Y. L. Bennani, S. Hanessian, *Chem. Rev.* **1997**, *97*, 3161–3195; b) D. Lucet, T. Le Gall, C. Mioskowski, *Angew. Chem.* **1998**, *110*, 2724; *Angew. Chem. Int. Ed.* **1998**, *37*, 2580–2627; c) S. R. S. S. Kotti, C. Timmons, G. Li, *Chem. Biol. Drug Des.* **2006**, *67*, 101–114; d) J. González-Sabín, F. Rebolledo, V. Gotor, *Chem. Soc. Rev.* **2009**, *38*, 1916–1925; e) M. Nonn, L. Kiss, R. Sillanpää, F. Fülöp, *Beilstein J. Org. Chem.* **2012**, *8*, 100–106; f) M. Sans, O. Illa, R. M. Ortuño, *Org. Lett.* **2012**, *14*, 2431–2433.

[7] For an example, see: a) G. A. Grasa, A. Zannotti-Gerosa, W. A. Hems, *J. Organomet. Chem.* **2006**, *691*, 2332–2334; b) K. Kodama, K. Sugawara, T. Hirose, *Chem. Eur. J.* **2011**, *17*, 13584–13592.

[8] a) P. Chand, P. L. Kotian, A. Dehghani, Y. El-Kattan, T.-H. Lin, T. L. Hutchison, Y. S. Babu, S. Bantia, A. J. Elliott, J. A. Montgomery, *J. Med. Chem.* **2001**, *44*, 4379–4392.

[9] R. Gutiérrez-Abad, O. Illa, R. M. Ortuño, *Org. Lett.* **2010**, *12*, 3148–3151.

[10] a) S. Izquierdo, M. J. Kogan, T. Parella, A. G. Moglioni, V. Branchadell, E. Giralt, R. M. Ortuño, *J. Org. Chem.* **2004**, *69*, 5093–5099; b) S. Izquierdo, F. Rúa, A. Sbai, T. Parella, Á. Álvarez-Larena, V. Branchadell, R. M. Ortuño, *J. Org. Chem.* **2005**, *70*, 7963–7971; c) E. Torres, E. Gorrea, E. Da Silva, P. Nolis, V. Branchadell, R. M. Ortuño, *Org. Lett.* **2009**, *11*, 2301–2304; d) E. Torres, E. Gorrea, K. K. Burusco, E. Da Silva, P. Nolis, F. Rúa, S. Boussert, I. Díaz-Pérez, S. Dannenberg, S. Izquierdo, E. Giralt, C. Jaime, V. Branchadell, R. M. Ortuño, *Org. Biomol. Chem.* **2010**, *8*, 564–575.

[11] a) F. Rua, S. Boussert, T. Parella, I. Díez-Pérez, V. Branchadell, E. Giralt, R. M. Ortuño, *Org. Lett.* **2007**, *9*, 3643–3645; b) E. Gorrea, P. Nolis, E. Torres, E. Da Silva, D. B. Amabilino, V. Branchadell, R. M. Ortuño, *Chem. Eur. J.* **2011**, *17*, 4588–4597.

[12] D. Fernández, E. Torres, F. X. Avilés, R. M. Ortuño, J. Vendrell, *Bioorg. Med. Chem.* **2009**, *17*, 3824–3828.

[13] E. Torres, J. Puigmartí-Luis, Á. Pérez del Pino, R. M. Ortuño, D. B. Amabilino, *Org. Biomol. Chem.* **2010**, *8*, 1661–1665.

[14] a) R. Gutiérrez-Abad, D. Carbajo, P. Nolis, C. Acosta-Silva, J. A. Cobos, O. Illa, M. Royo, R. M. Ortuño, *Amino Acids* **2011**, *41*, 673–686; b) E. Gorrea, D. Carbajo, R. Gutiérrez-Abad, O. Illa, V. Branchadell, M. Royo, R. M. Ortuño, *Org. Biomol. Chem.* **2012**, *10*, 4050–4057.

[15] For some leading references, see: a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; b) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125; c) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418–5427; d) H. Miyabe, Y. Takemoto, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 785–795; e) S. J. Connon, *Chem. Commun.* **2008**, 2499–2510; f) Y. Takemoto, *Chem. Pharm. Bull.* **2010**, *58*, 593–601; g) R. Manzano, J. M. Andrés, R. Pedrosa, *Synlett* **2011**, 2203–2205.

[16] A. Serra, *Ms. Sci. Dissertation*, Universitat Autònoma de Barcelona, **2012**.

[17] a) C. Fernandes, C. Gauzy, Y. Yang, O. Roy, E. Pereira, S. Faure, D. J. Aitken, *Synthesis* **2007**, *14*, 2222–2232; b) C. Fernandes, E. Pereira, S. Faure, D. J. Aitken, *J. Org. Chem.* **2009**, *74*, 3217–3220.

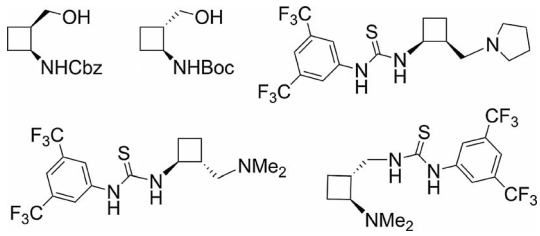
  

[18] Absolute configuration was determined by comparison with data reported in: D. Almaşi, D. A. Alonso, E. Gómez-Bengoa, C. Nájera, *J. Org. Chem.* **2009**, *74*, 6163–6168.
[19] A. Hamza, G. Schubert, T. Sóos, I. Papai, *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160.
[20] K. M. Lippert, K. Hof, D. Gerbig, D. Ley, H. Hausmann, S. Guenther, P. R. Schreiner, *Eur. J. Org. Chem.* **2012**, *30*, 5919–5927.
[21] NMR spectroscopic data are consistent with those described in: D. M. Barnes, J. Ji, M. G. Fickes, M. A. Fitzgerald, S. A. King, H. E. Morton, F. A. Plagge, M. Preskill, S. H. Wagaw, S. J. Wittenberger, J. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 13097–13105 ppm.

Received: October 3, 2012
Published Online: ■

**Chiral Cyclobutane Organocatalysts**




Chiral cyclobutane containing 1,3-amino alcohols and 1,3-diamines have been synthesized from a common chiral precursor. Regioselective transformations of these precursors led to bifunctional thioureas which have been tested as organocatalysts in preliminary experiments

**E. Mayans, A. Gargallo, Á. Álvarez-Larena, O. Illa,* R. M. Ortuño* .... 1–10**

Diastereodivergent Synthesis of Chiral *vic*-Disubstituted-Cyclobutane Scaffolds: 1,3-Amino Alcohol and 1,3-Diamine Derivatives – Preliminary Use in Organocatalysis

**Keywords:** Synthetic methods / Organocatalysis / Asymmetric catalysis / Michael addition / Regioselectivity / Amino alcohols / Amines