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A Simple Organocatalytic Enantioselective Synthesis of Pregabalin

Oriol Bassas,^[a] Juhani Huuskonen,^{[b][‡]} Kari Rissanen,^{[b][‡]} and Ari M. P. Koskinen*^[a]**Keywords:** Pregabalin / Conjugate additions / Alkaloids / Thiourea / Organocatalysis / Enantioenrichment / Enantioselectivity / Michael addition / Asymmetric synthesis

This paper describes a new procedure for the enantioselective synthesis of the important anticonvulsant drug Pregabalin, which shows biological properties as the (*S*) enantiomer only. The key step of the synthetic sequence is the Michael addition reaction of Meldrum's acid to a nitroalkene mediated by a quinidine derived thiourea. A variety of novel catalysts bearing different groups at the thiourea moiety were synthesized and tested. The most successful catalyst that incorporates a trityl substituent provided up to 75 % ee of (*S*)-**4**. The conjugate addition reaction was carried out on a

multigram scale with low loadings of catalyst (10 mol-%). Moreover, the catalyst can be recycled showing the same capability in chemical yield and asymmetric induction. Then, hydrogenation of nitroalkane **4** followed by decarboxylation of diacid **5** provides Pregabalin hydrochloride in 59 % overall yield. Enantioenrichment by crystallization of the free amino acid **1** improves the (*S*)/(*R*) enantiomeric ratio to 9:1.

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Introduction

Pregabalin is the international non-proprietary name for (3*S*)-3-(aminomethyl)-5-methylhexanoic acid (**1**) (Figure 1). It belongs to the group of 3-substituted analogues of the inhibitory neurotransmitter γ -aminobutyric acid (GABA), such as gabapentin and baclofen. Discovered by Silverman et al.^[1] in 1991, Pregabalin is an anticonvulsant drug used to treat epilepsy and neuropathic pain marketed by Pfizer under the brand name Lyrica®. It is considered as one of the drugs of the future due to its high and broad therapeutic activity and reaches blockbuster status (1 billion \$ annual sales or more); thus, the development of simple efficient synthetic processes has become an important research goal for medicinal and organic chemists.

Because only the (*S*) enantiomer exhibits the desired pharmacological activity^[2] enantioselective syntheses are in demand. The initial industrial preparation of Pregabalin involved a resolution of *rac*-**1** with (+)-(*S*)-mandelic acid.^[3]

The process provided **1** in low yields accompanied by high manufacturing costs. Due to the need of preparing compounds in enantiopure form, several asymmetric syntheses have been reported.^[4] To mention some selected examples, Yuen et al.^[4a] prepared both enantiomers of Pregabalin using Evans' chiral oxazolidinone alkylation chemistry. Brenner and Seebach^[4b] prepared (*R*)-*N*-Boc Pregabalin methyl ester by 1,4-addition of a titanium enolate generated from an *N*-acetyloxazolidinone to the corresponding (isobutyl)(nitro)alkene. Catalytic methods for the enantiomeric preparation of Pregabalin have also been developed. The Pfizer manufacturing process^[4c] is based on asymmetric hydrogenation of a prochiral substituted 3-cyanohexanoic acid by using Chirotech's commercially available rhodium catalyst. Sammins and Jacobsen^[4e] have described a highly enantioselective route to **1** through conjugate addition of cyanide to α,β -unsaturated imide by salen Al catalysis. Shibasaki's group^[4g] developed a catalytic enantioselective conjugate addition reaction of cyanide to α,β -unsaturated *N*-acetylpyrrole mediated by a chiral gadolinium catalyst. On the other hand, recently Armstrong et al.^[4h] described the synthesis of enantiopure Pregabalin through conjugate addition of cyanide to a chiral α,β -unsaturated isobutyloxazolidinone. Poe et al.^[4i] have also synthesized **1** by a one-pot reaction between isovaleraldehyde, nitromethane and dimethyl malonate promoted by two microencapsulated catalysts. Pregabalin has also been obtained by catalytic enantioselective conjugate addition of nitroalkanes to

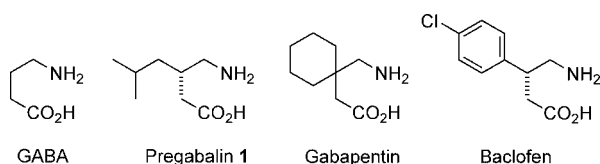


Figure 1. Pregabalin and GABA analogues.

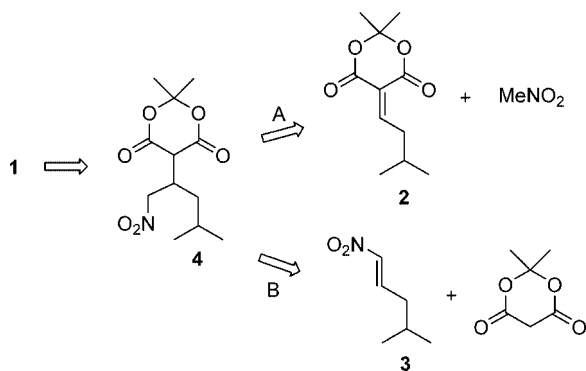
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[‡] X-ray crystallography.

α,β -unsaturated aldehydes using diphenylprolinol silyl ether as organocatalyst.^[4m] Moreover, very recently **1** has been industrially produced by chemoenzymatic methods.^[4o]

Our synthetic strategy towards enantiopure Pregabalin is depicted in Scheme 1. We envisaged that the target compound could be obtained from chiral nitroalkane **4** through reduction of the nitro group and simultaneous removal of the acetonide followed by decarboxylation. In turn, the nitro compound **4** could be accessible by two possible routes, A and B, that rely on enantioselective conjugate addition reactions. Route A implies unsaturated Meldrum's acid derived acceptor **2** as the electrophile and nitromethane as the nucleophile, whereas route B is based on the use of nitro olefin **3** as the Michael acceptor and Meldrum's acid as the nucleophile. Our choice of Meldrum's acid as the malonate surrogate was based on the expected ease of the operation for the release of the eventual acid under mild, slightly acidic conditions. For the catalytic asymmetric conjugate addition^[5] step we decided to employ thioureas derived from cinchona alkaloids^[6] as organocatalysts for both routes. These systems, bearing a tertiary amine and a thiourea moiety, offer a dual activation of the substrate and reagent. In previous work, the enantioselective conjugate addition of nitroalkanes to enones by using cinchona alkaloid based thioureas has been described by Soós' and Ye's groups.^[6b,6p,6q,7] Additionally, asymmetric Michael addition reactions of malonate esters to nitro olefins catalyzed by epicinchona alkaloid derivatives have recently been reported.^[6c,6d,6o] We decided to synthesize the previously reported 9-amino-(9-deoxy)-epiquinidine-derived thiourea catalyst **8** and novel catalysts **9–17**, which incorporate different substitution pattern at the thiourea moiety. This family of organocatalysts were tested under Michael addition reactions for both routes to nitroalkane **4**.



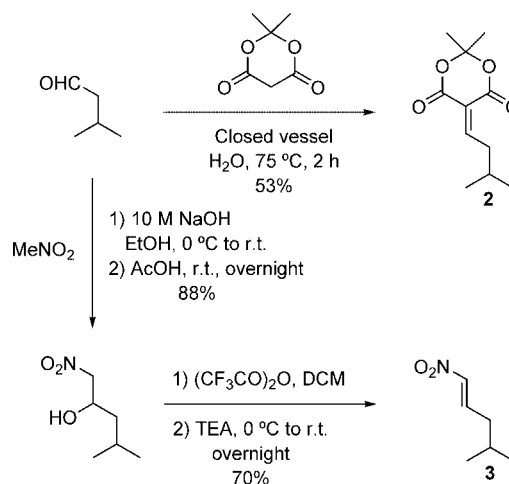
Scheme 1. Synthetic strategy towards Pregabalin.

In this paper, we report the preparation of the Michael acceptors, catalysts and our results concerning the enantioselective conjugate addition reactions for routes A and B. The resulting optically active nitro compound **4** may then be transformed to Pregabalin (**1**).

Synthesis of the Substrates and Organocatalysts

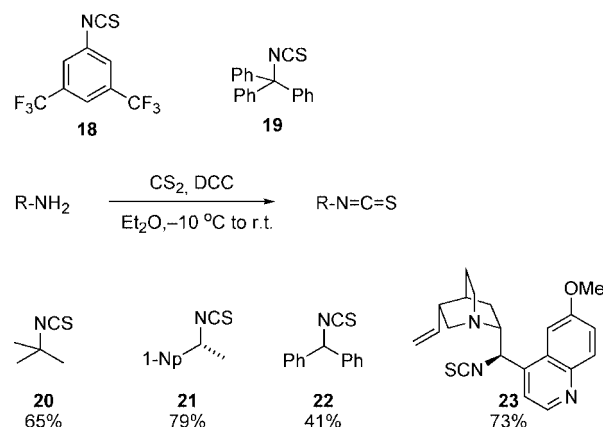
The starting electron-poor alkenes **2** and **3** were accessed from isovaleraldehyde (Scheme 2). Michael acceptor **2** was

obtained cleanly by Knoevenagel condensation in water from both commercially available Meldrum's acid and isovaleraldehyde^[8] by carrying out the reaction in a closed vessel at 75 °C for 2 h. On the other hand, nitro olefin **3** was synthesized in good yields as the (*E*) isomer, by a Henry reaction between nitromethane and isovaleraldehyde, followed by dehydration of the intermediate nitro alcohol with trifluoroacetic anhydride and triethylamine.^[9]

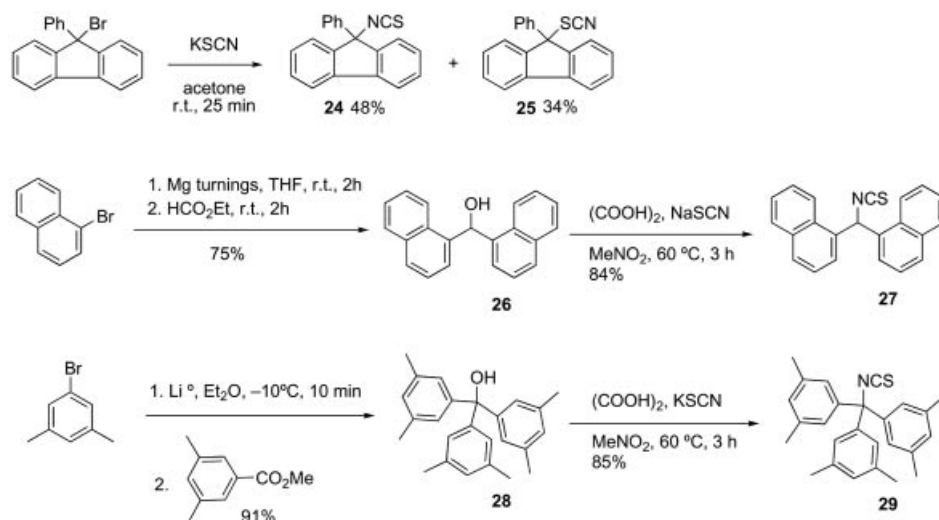


Scheme 2. Synthesis of Michael acceptors **2** and **3**.

Preparation of the thiourea organocatalysts started by obtaining a range of isothiocyanates, which serve as thiourea functionality. 3,5-Bis(trifluoromethyl)phenyl isothiocyanate (**18**) and trityl isothiocyanate (**19**) were purchased from commercial sources. Compounds **20–23** were obtained in moderate to excellent yields (Scheme 3) from the corresponding chiral or achiral primary amines by reaction with carbon disulfide and DCC.^[10] The synthesis of compound **24** was accomplished by nucleophilic substitution in acetone between potassium thiocyanate^[11] and 9-bromo-9-phenylfluorene. In this case, a separable mixture of the corresponding isothiocyanate and thiocyanate was obtained. Isothiocyanate **27** was prepared from commercially available 1-bromonaphthalene by a Grignard reaction with ethyl formate^[12] to alcohol **26** which was converted to isothiocya-

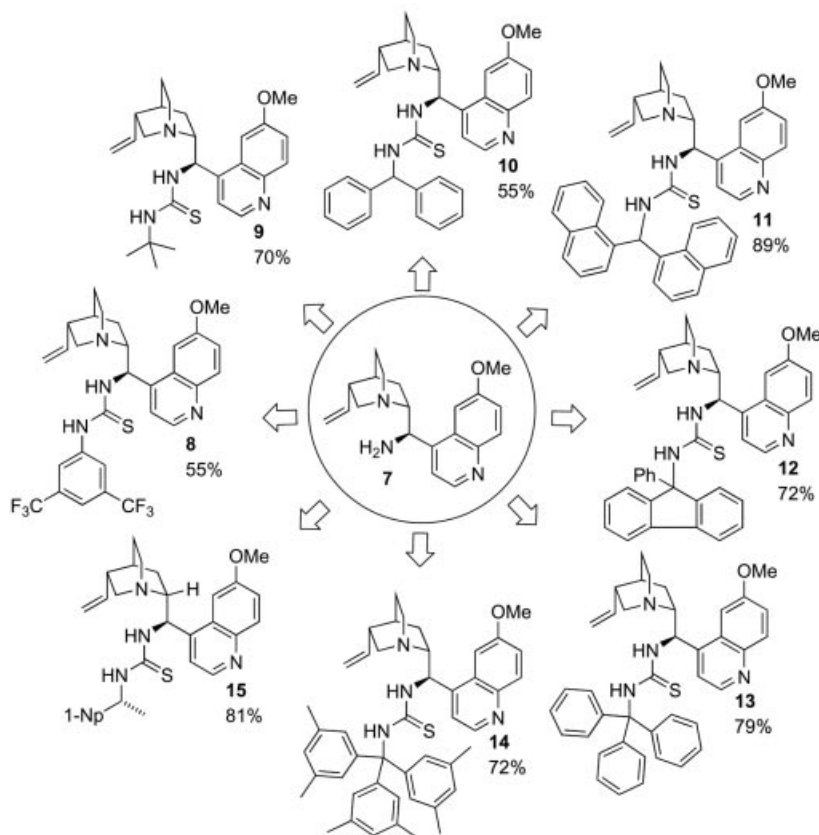


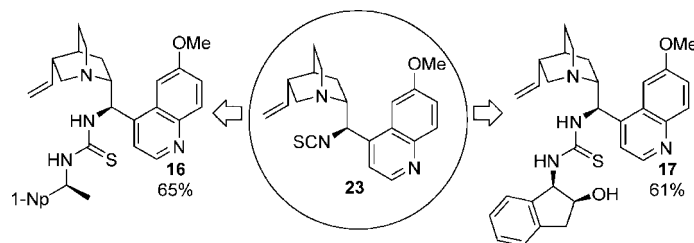
Scheme 3. Sources of isothiocyanates **18–23**.

Scheme 4. Synthesis of isothiocyanates **24**, **27**, **29**.

nate **27** by an oxalic acid catalyzed reaction with sodium thiocyanate.^[13] Isothiocyanate **29** was prepared on a multigram scale by conversion of 1-bromo-3,5-dimethylbenzene to the aryllithium species and its reaction with commercially available methyl 3,5-dimethylbenzoate to give the corresponding alcohol **28** in excellent yield.^[14] Similarly, alcohol **28** was converted to isothiocyanate **29** following oxalic acid catalyzed nucleophilic substitution with potassium thiocyanate (Scheme 4).

The synthesis of thiourea organocatalysts can be conducted according to two complementary procedures. First, condensation of the free amine derived from quinidine with isothiocyanates provided thioureas **8–15** in good yields (Scheme 5). The second method is based on the treatment of the chiral isothiocyanate **23** obtained from amine **7** with primary amines. This procedure gave thioureas **16** and **17** (Scheme 6).

Scheme 5. Organocatalysts **8–15** obtained by condensation of amine **7** with isothiocyanates.



Scheme 6. Organocatalysts **16** and **17** obtained by condensation of free chiral amines with isothiocyanate **23**.

As a representative example, the structure of catalyst **12** was confirmed by X-ray crystallography (Figure 2).^[15]

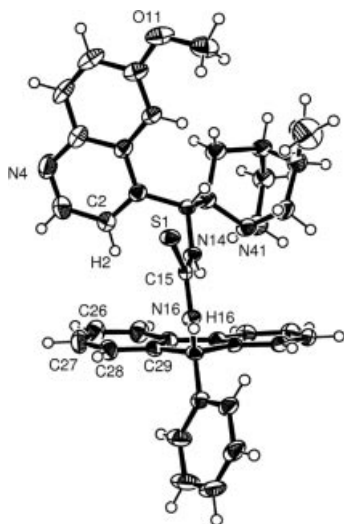


Figure 2. X-ray structure for catalyst **12**.

Screening of the Catalysts

We started our investigations by testing these organocatalysts to evaluate their ability to promote the conjugate addition of nitromethane to compound **2**. Initially, we selected catalyst **8**^[6b] that incorporates a 3,5-bis(trifluoromethyl)-phenylthiourea. After 4 d at room temperature, the reaction was complete but gave a very modest enantioselectivity (21.4% *ee*, Table 1, Entry 1) affording the nitro compound **4** with the desired stereochemistry.

Performing the reaction with *tert*-butylthiourea **9** the enantiocontrol was much lower (4.5% *ee*, Table 1, Entry 2). Unfortunately, similar results were obtained with catalysts **10** and **12** (Table 1, Entries 3 and 4). Moderate enantiomeric excess of the wrong enantiomer (37% *ee*, Table 1, Entry 5) was obtained with thiourea **13** bearing a trityl group at the end of the thiourea arm. Unluckily, organocatalyst **14**, with substitution in the aromatic rings, provided very poor levels of asymmetric induction (3.7% *ee*, Table 1, Entry 6). Finally, we examined the influence of introducing new elements of chirality and functionality in the organocatalyst. Thiourea **17** that bears a chiral amino alcohol moiety provided full conversion, but marginal enantioselectivity.

Better results were obtained according to route B. The initial reaction was performed in DCM in the presence of 5 mol-% of catalyst **8** at 5 °C. The nitro compound **4** was obtained in 65% conversion and moderate enantioselectivity (33% *ee*) after 16 h (Table 2, Entry 1). Next, thiourea **9** afforded complete conversion and 56.5% *ee* (Table 2, Entry 2). Organocatalysts **10** and **11** incorporate a benzhydryl and a bis(1-naphthyl)methyl substituent, respectively. They provided full conversion of the substrate and a good level of enantiocontrol (65 and 63.4% *ee*, respectively, Table 2, Entries 3 and 4). Catalyst **12**, bearing a phenylfluorenyl group, gave high conversions and slightly lower enantioselectivities when compared to catalysts **10** and **11** (Table 2, Entry 5). The best results with regard to the enantioselectivity were obtained with tritylthiourea **13** (74.6% *ee*, Table 2, Entry 6). Catalyst **14** was tested to analyze the influence of substitution in the aromatic rings of the trityl group. Unfortunately, the enantioselectivity decreased to 55.5% (Table 2, Entry 7). We then turned our attention to organocatalysts **15** and **16**, which incorporate a chiral naphthylethyl moiety. They showed small matched/mismatched effects providing Michael adduct **4** in high yields and in 52.6 and 57.2% *ee*, respectively (Entries 8 and 9). Finally, thiourea **17** gave full conversion but lower enantioselectivity (Entry 10).

Enantioselective Synthesis of Pregabalin

The high level of asymmetric induction and efficiency exhibited by thiourea **13** to provide nitro compound **4** according to route B prompted us to choose it as the organocatalyst for the enantioselective synthesis of Pregabalin. The sequence of the present enantioselective synthesis of (3*S*)-3-(aminomethyl)-5-methylhexanoic acid (**1**) is outlined in Scheme 7. Reaction of nitroalkene **3** (100 mol-%, 33.6 mmol), Meldrum's acid (100 mol-%, 33.6 mmol), and organocatalyst **13** (10 mol-%, 3.36 mmol) in DCM (1 M) at room temp. for 23 h provided **4** in 84% yield and in 74.6% *ee* after purification by column chromatography. Moreover, catalyst **13** was recovered in good yield (55%) after column chromatography and was reused. The recovered catalyst was also effective in the second reaction, showing the same activity and selectivity. The chemical yield of the second run was 82% and the *ee* again 74.6%. Then, hydrogenation of 3-(nitromethyl)alkane **4** in the presence of Raney-Ni as catalyst in acetic acid at room temp. and atmospheric pres-

Table 1. Enantioselective Michael addition of nitromethane to unsaturated Meldrum's acid derivative **2** by using quinidine alkaloid derived organocatalysts.

Entry	Catalyst	Mol-%	Solvent	<i>T</i> [°C]	<i>t</i> [d]	Conversion [%] ^[a]	<i>ee</i> [%] ^[b]	Configuration ^[c]
1	8	5	toluene	room temp.	4	> 95	21.4	(<i>S</i>)
2	9	10	DCM	room temp.	3.6	> 95	4.5	(<i>S</i>)
3	10	10	DCM	room temp.	4	> 95	4.5	(<i>R</i>)
4	12	10	DCM	room temp.	3	> 95	7.4	(<i>S</i>)
5	13	10	DCM	room temp.	3.5	> 95	37	(<i>R</i>)
6	14	10	DCM	room temp.	3.7	> 95	3.7	(<i>S</i>)
7	17	10	DCM	room temp.	4	> 95	3.5	(<i>S</i>)

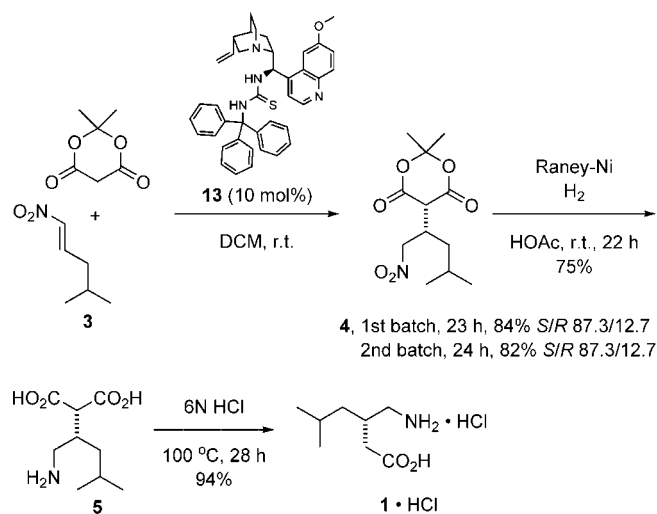
[a] Determined by ¹H NMR spectroscopy of the crude product. [b] Determined by chiral HPLC analysis of the anilide derived from **4**. [c] The absolute stereochemistry was established by conversion to Pregabalin.

Table 2. Enantioselective Michael addition of Meldrum's acid to nitro olefin **3** by using quinidine alkaloid derived chiral thiourea organocatalysts.

Entry	Catalyst	Mol-%	Solvent	<i>T</i> [°C]	<i>t</i> [h]	Conversion [%] ^[a]	<i>ee</i> [%] ^[b]	Configuration ^[c]
1	8	5	DCM	5	16	65	33	(<i>S</i>)
2	9	10	DCM	room temp.	15	>95	56.5	(<i>S</i>)
3	10	10	DCM	room temp.	20	>95	65	(<i>S</i>)
4	11	10	DCM	room temp.	17	>95	63.4	(<i>S</i>)
5	12	10	DCM	room temp.	20	>95	60.5	(<i>S</i>)
6	13	10	DCM	room temp.	22	>95	74.6	(<i>S</i>)
7	14	10	DCM	room temp.	22	>95	55.5	(<i>S</i>)
8	15	10	DCM	room temp.	19	>95	52.6	(<i>S</i>)
9	16	10	DCM	room temp.	21	>95	57.2	(<i>S</i>)
10	17	10	DCM	room temp.	22	>95	51.6	(<i>S</i>)

[a] Determined by ¹H NMR spectroscopy of the crude product. [b] Determined by chiral HPLC analysis of the anilide derived from **4**. [c] The absolute stereochemistry was established by conversion to Pregabalin.

sure afforded amino diacid **5**, which after treatment with 6 *N* HCl yielded hydrochloride **1**. Enantioenrichment by crystallization^[16] of the free amino acid from 2-propanol/water furnished **1** as a white crystalline solid with 80% *ee*.

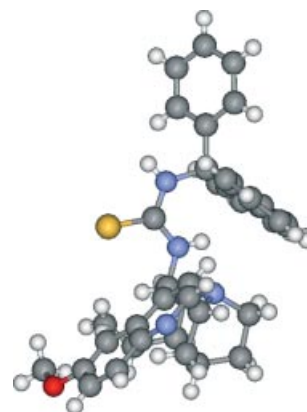


Scheme 7. Asymmetric synthesis of Pregabalin.

Origin of the Enantioselectivity

The nitro group is well known to interact with thiourea through hydrogen bonding. Thioureas have two hydrogen bonds to bind the H bond acceptor. These interactions increase the electrophilicity of the electron-deficient alkene

bearing the nitro group. As seen from the X-ray structure of **12** (Figure 3), in the solid state this catalyst exists as a *trans/cis* rotamer (based on the HNCS angle) which apparently is less accessible for hydrogen bonding than the *trans/trans* rotamer. Tsogoeva et al.^[17] have also reported the *trans/cis* conformer in the solid state of a chiral (methylpyridyl)thiourea displaying intramolecular hydrogen bonding between one of the thiourea NH groups and the basic nitrogen atom of the pyridyl group as well as an intermolecular hydrogen bond from the H atom of the thiourea NH group to the sulfur atom of a second molecule leading to a dimer. They claim that these interactions do not allow its imine substrate to be placed in a bridging mode between the two thiourea hydrogen atoms. According to them, this

Figure 3. *trans/cis*-Conformer in the solid state for **12**.

may be the reason of the very poor levels of enantioselectivity (6% *ee*) observed in the Strecker synthesis by employing this catalyst.

In our case, our catalysts provide very good enantioselectivities (up to 75% *ee*), even though we observed the same disposition. In solution, thioureas typically are present as a mixture of *trans/trans* and *trans/cis* conformers (Figure 4).^[18] In the first conformation the two oxygen atoms of the nitroalkene would form two hydrogen bonds with both H atoms of the thiourea at the same time, whereas the *trans/cis* conformer can only provide one point of attachment, thus giving a less restricted substrate binding and weakened enantiocontrol.

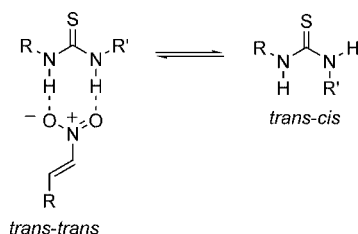


Figure 4. Hydrogen bonding for disubstituted thioureas.

In the Michael addition of 1,3-dicarbonyl compounds to nitro olefins catalyzed by bifunctional thioureas Takemoto et al.^[19] suggested that the active monomeric organocatalyst binds the nitroalkene through double hydrogen bonding. In our case of Meldrum's acid addition to nitro olefin **3** we propose a transition-state model similar to that by Takemoto, which would imply activation of the Michael acceptor **3** through double NH hydrogen bonding. The quinuclidine ring is orientated towards the same direction where the two NH groups are and placed on the same face with the trityl group, but both away from each other to avoid steric interaction. On the basis of the product configuration, delivery of the enolate from the top face to the *s-cis* nitroalkene would provide (*S*)-**4** (Figure 5). In agreement with this interpretation, the decrease in *ee* of product **4** with catalyst **14** could be attributed to steric hindrance between the methyl substituents at the *meta* position of the trityl group and the isopropyl moiety of the nitroalkene **3**. This repulsion would shift the nitroalkene to the *s-trans* conformation, in which delivery of the enolate from the top face would lead to (*R*)-**4**.

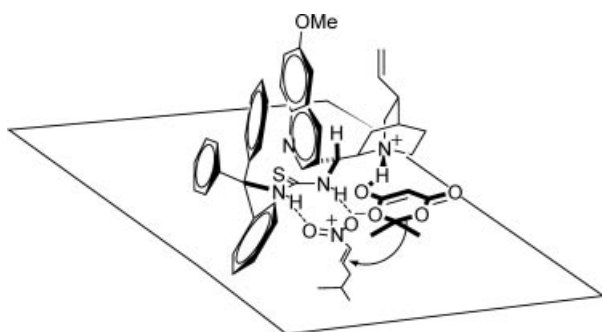


Figure 5. Proposed transition state leading to the major enantiomer (*S*)-**4**.

Conclusions

We have developed a simple short procedure for preparing multigram quantities of the antiepileptic drug Pregabalin by organocatalytic conjugate addition reaction of Meldrum's acid to nitroalkene **3**. We have synthesized and tested a family of novel catalysts to promote the above reaction. The best enantioselectivity was obtained with catalyst **13**, which incorporates a trityl substituent in the thiourea moiety and can be recycled. The key intermediate nitro compound **4** was obtained in high chemical yield after purification by column chromatography and up to 75% *ee* of the (*S*) enantiomer. Moreover, the overall yield for the process starting from **3** is 59%, and enantioenrichment by crystallization of the free amino acid provides almost enantiopure Pregabalin.

Experimental Section

General Considerations: All moisture-sensitive reactions were performed under argon in flame-dried, round-bottomed flasks fitted with rubber septa and/or glass stoppers. For reactions run at low temperatures, flasks were flushed with argon, and double septa to minimize the introduction of adventitious water. Stainless steel syringes were used to transfer air- or moisture-sensitive liquids.

Materials: Unless otherwise indicated, reagents were used as purchased from suppliers. Solvents were dried prior to use according to standard procedures. Toluene was distilled from sodium, tetrahydrofuran from sodium/benzophenone ketyl, dichloromethane, triethylamine and diethylamine from calcium hydride (CaH₂). All reactions were performed under a positive pressure of argon when necessary. Thin layer chromatography was done on SiO₂ (silica gel 60 F₂₅₄, Merck, coated aluminium plates), and the spots were located with UV light (254 nm), with aqueous potassium permanganate and ninhydrin solutions. Flash column chromatography or Combi Flash chromatography was carried out on SiO₂ (silica gel 60, 230–400 mesh ASTM, Merck). Drying of the organic extracts during the workup of the reactions was performed with MgSO₄. A racemic Michael adduct sample for chiral HPLC analysis was prepared in the absence of the catalyst by combining (route A): Michael acceptor **2** (9.4 mmol), nitromethane (47.2 mmol) and diethylamine (14.1 mmol) in DCM (20 mL) at room temp.; (route B): nitroalkene **3** (7.7 mmol), Meldrum's acid (11.6 mmol) and diethylamine (1.2 mL) in DCM (20 mL) at room temp.

Representative Procedure for Screening of the Catalyst. Route A: Meldrum's acid derivative **2** (125 mg, 0.58 mmol) and the chosen thiourea catalyst (0.05 mmol) in the appropriate solvent (0.5 mL) were loaded in a capped vial. After 5 min, nitromethane (1.6 mmol) was added, and stirring was maintained at room temp. The conversion was determined by ¹H NMR spectroscopy of the crude product. **Route B:** Nitroalkene **3** (100 mg, 0.77 mmol) and the chosen thiourea catalyst (0.07 mmol) in the appropriate solvent (0.5 mL) were loaded in a capped vial. After 5 min, Meldrum's acid (1.44 mmol) was added and stirring was maintained at the specified temperature. The conversion was determined by ¹H NMR spectroscopy of the crude product.

Instrumentation: Evaporation of the solvents was accomplished with a rotary evaporator. ¹H and ¹³C NMR spectra were recorded in CDCl₃, [D₄]methanol or D₂O with a Bruker Avance 400 (¹H: 399.98 MHz; ¹³C: 100.59 MHz) spectrometer. The chemical shifts

are reported in ppm relative to residual CHCl_3 ($\delta = 7.26$ ppm), residual MeOH ($\delta = 3.31$ ppm) or residual H_2O ($\delta = 4.79$ ppm) for ^1H NMR spectroscopy. Coupling constants (J) are given in Hz. The multiplicities are abbreviated as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet); the prefix br. is applied when the signal in question is broadened. For the ^{13}C NMR spectra, the solvent peaks of CDCl_3 ($\delta = 77.0$ ppm) and $[\text{D}_4]\text{methanol}$ ($\delta = 49.0$ ppm) were used as the internal standard. High-resolution mass spectrometric data were obtained at the Helsinki University of Technology Mass Spectrometry Facility with Waters LCT Premier-spectrometer. IR spectra were recorded with a Perkin–Elmer instrument, the data are represented as wavenumbers in cm^{-1} . Optical rotations were obtained with a Perkin–Elmer 343 polarimeter ($\lambda = 589$ nm) with a 1 dm path length. Chiral HPLC analysis was performed by using a Waters 501 pump, a Waters UV 2487 dual lambda-absorbance detector and a Chiralcel OD column (0.46×25 cm). Elemental analyses were performed with a Perkin–Elmer (PE) 2400 Series II CHNS/O Analyzer. Melting points were determined in open capillary tubes and are uncorrected.

(+)-(3S)-3-(Aminomethyl)-5-methylhexanoic Acid Hydrochloride (1·HCl):^[4c] Diacid **5** (4.77 g, 23.5 mmol) was dissolved in 6 N HCl (35 mL) and refluxed for 28 h. Then, the brown aqueous solution was extracted with DCM. Heating of the aqueous layer with activated charcoal followed by filtration through Celite and concentration of the aqueous layer to dryness under reduced pressure furnished a residue, which was dried at 50 °C for 48 h. After this period, 1·HCl (Pregabalin hydrochloride) was obtained (4.34 g, 94% yield). $[\alpha]_{\text{D}}^{20} = +6.72$ ($c = 1.1$, H_2O) {ref.^[4c] $[\alpha]_{\text{D}}^{20} = +7.0$ ($c = 1.1$, H_2O) for 96% ee}. IR (film): $\tilde{\nu} = 3223, 3120, 2998, 1721, 1412, 1390, 1227$ cm^{-1} . ^1H NMR (D_2O , 400 MHz): $\delta = 3.04$ (d, $J = 8.0$ Hz, 2 H), 2.53 (dd, $J = 16.0, 6.0$ Hz, 1 H), 2.45 (dd, $J = 16.0, 4.0$ Hz, 1 H), 2.26 (m, 1 H), 1.67–1.62 (m, 1 H), 1.26 (dd, $J = 7.2, 7.2$ Hz, 2 H), 0.91 (d, $J = 6.6$ Hz, 3 H), 0.88 (d, $J = 6.6$ Hz, 3 H) ppm. ^{13}C NMR (CD_3OD , 100 MHz): $\delta = 175.7, 44.4, 41.9, 37.2, 32.4, 26.0, 23.1, 22.6$ ppm. A crop of Pregabalin hydrochloride was converted into the free amino acid by addition of 1 M NaOH solution until the pH = 7.5. After evaporation of water, a white solid compound was obtained. Crystallization of this material from 30% 2-propanol in water afforded 1 (Pregabalin) as a white crystalline solid.^[3] $[\alpha]_{\text{D}}^{20} = +8.2$ ($c = 1.07$, H_2O) {ref.^[3] $[\alpha]_{\text{D}}^{20} = +10.1$ ($c = 1.1$, H_2O)}. M.p. 174–175 °C (ref.^[3] 175–176 °C). ^1H NMR (D_2O , 400 MHz): $\delta = 3.02$ (dd, $J = 13.0, 5.4$ Hz, 1 H), 2.95 (dd, $J = 13.0, 6.6$ Hz, 1 H), 2.33 (dd, $J = 14.6, 5.9$ Hz, 1 H), 2.24 (dd, $J = 14.6, 7.2$ Hz, 1 H), 2.15 (m, 1 H), 1.66 (m, 1 H), 1.21 (dd, $J = 7.0, 6.9$ Hz, 2 H), 0.89 (dd, $J = 6.6, 4.8$ Hz, 6 H) ppm. ^{13}C NMR (D_2O + drops of CD_3OD , 100 MHz): $\delta = 182.1, 44.7, 41.8, 41.6, 32.7, 25.4, 23.0, 22.5$ ppm. For the purposes of the ee determination after crystallization, the amine was Boc-protected and the acid converted into the *N*-methyl amide.^[20]

***N*-Boc Protection of Free Amino Acid 1:** NaHCO_3 (791 mg, 9.42 mmol) and Boc_2O (822 mg, 3.77 mmol) were added consecutively at 0 °C to a solution of the free amino acid **1** (crystallized from 30% 2-propanol in water, 500 mg, 3.14 mmol) in a 1:1 mixture of THF/ H_2O (20 mL). After 30 min, the white suspension was stirred at room temp. overnight. Then, the mixture was extracted with Et_2O . The aqueous layer was acidified to pH = 4 by addition of 5% citric acid solution at 0 °C and extracted with DCM. The extracts were dried and concentrated to give the corresponding Boc-amino acid (512 mg, 63%) as a white solid, which was used without further purification.

***N*-Methyl Amidation of Protected Amino Acid 1:** *N*-Methylmorpholine (146 μL , 1.15 mmol) and isobutyl chloroformate (150 μL ,

1.15 mmol) were successively added to a solution of the Boc-protected amino acid **1** (300 mg, 1.15 mmol) in THF (3 mL) at –20 °C. After an activation period of 5 min, 40% aqueous methylamine (4.60 mmol) in THF (2 mL) was added, and the resulting solution was stirred at –20 °C for 1 h prior the addition of 5% NaHCO_3 (5 mL). After 30 min of stirring at room temp., the mixture was extracted with DCM. The organic layers were washed with 5% NaHCO_3 , dried and concentrated to provide a pale yellow oil, which after purification by column chromatography (50% EtOAc in hexane) yielded the desired compound (259 mg, 83%) as a white solid. The enantiomeric ratio was determined by HPLC: Chiralcel OD column ($0.46 \text{ cm} \times 25 \text{ cm}$), hexane/2-propanol (98:2), flow 0.2 mL/min, detector $\lambda = 215$ nm, retention time 1: 77.33 min, % area: 10.2, retention time 2: 81.84 min, % area: 89.8.

2,2-Dimethyl-5-(3'-methylbutylidene)-1,3-dioxane-4,6-dione (2): A mixture of Meldrum's acid (4.40 g, 30.5 mmol) and freshly distilled isovaleraldehyde (3 mL, 27.9 mmol) in water (60 mL) was stirred in a closed vessel at 75 °C for 2 h. After cooling to room temp., the crude mixture was made alkaline with a saturated aqueous solution of sodium carbonate and extracted with diethyl ether. The extracts were dried, filtered and concentrated under reduced pressure to give pure **2** (3.10 g, 53%) as a pale yellow oil, which was used without further purification. $R_f = 0.31$ (40% Et_2O in hexane); visualization: KMnO_4 . IR (film): $\tilde{\nu} = 3054, 2987, 2685, 1736, 1627, 1421, 1263$ cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): $\delta = 7.96$ (t, $J = 7.6$ Hz, 1 H), 2.86 (dd, $J = 7.6, 7.2$ Hz, 2 H), 1.99–1.91 (m, 1 H), 1.74 (s, 6 H), 1.01 (d, $J = 6.6$ Hz, 6 H) ppm. ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 167.5, 161.6, 159.6, 118.6, 104.6, 39.7, 28.6, 28.4, 27.6, 22.3$ ppm. HRMS: calcd. for $\text{C}_{11}\text{H}_{16}\text{O}_4\text{Na}$ [$M + \text{Na}$] 235.0938; found 235.0946.

(*E*)-4-Methyl-1-nitro-1-pentene (3): An aqueous 10 M sodium hydroxide solution (45.4 mL, 0.45 mol) was added dropwise under mechanical stirring (to prevent the formation of a solid mass) to a solution of isovaleraldehyde (49.4 mL, 0.45 mol) and nitromethane (25 mL, 0.46 mol) in EtOH (200 mL) cooled to 0 °C. A yellow foam was obtained. After 10 min at 0 °C, the crude mixture was warmed to room temp. and stirred overnight. Then, acetic acid (25.7 mL, 0.45 mol) was added. The aqueous layer was extracted with diethyl ether. The extracts were washed with water until the pH of the washings was 6. After drying, filtration and concentration in vacuo, the corresponding nitro alcohol (58 g, 88% yield) was obtained and used without further purification. $R_f = 0.25$ (30% Et_2O in hexane); visualization: KMnO_4 . IR (film): $\tilde{\nu} = 3944, 3757, 3691, 3601, 3054, 2987, 2963, 2872, 2685, 2521, 2410, 2126, 1556, 1468, 1421, 1382, 1270$ cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): $\delta = 4.43$ –4.35 (m, 3 H), 2.50 (br. s, 1 H), 1.89–1.79 (m, 1 H), 1.55–1.47 (m, 1 H), 1.27–1.20 (m, 1 H), 0.97 (d, $J = 8.0$ Hz, 3 H), 0.96 (d, $J = 8.0$ Hz, 3 H) ppm. ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 80.9, 66.9, 42.3, 24.2, 23.0, 21.6$ ppm. HRMS (ESI): calcd. for $\text{C}_6\text{H}_{13}\text{NO}_3\text{Na}$ [$M + \text{Na}$] 170.0801; found 170.0793.

Dehydration of 3-Methyl-1-(nitromethyl)butanol: Trifluoroacetic anhydride (59.5 mL, 0.42 mol) and then dropwise TEA (117 mL, 0.84 mol) were added successively to a solution of 3-methyl-1-(nitromethyl)butanol (58 g, 0.40 mol) in DCM (500 mL) cooled to 0 °C. The reaction mixture was warmed to room temp. After stirring overnight, DCM (200 mL) was added. The organic phase was washed several times with water, saturated aqueous ammonium chloride solution and brine, then dried. After filtration and evaporation in vacuo, distillation under aspirator vacuum at 115 °C afforded compound **3** (36 g, 70%), only detected as the (*E*) isomer. $R_f = 0.61$ (30% Et_2O in hexane); visualization: KMnO_4 . IR (film): $\tilde{\nu} = 3944, 3757, 3691, 3625, 3054, 2987, 2965, 2872, 2685, 2521,$

2410, 2126, 1712, 1649, 1525, 1421, 1351, 1270 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 7.29–7.22 (m, 1 H), 6.98 (dt, J = 16.0, 4.0 Hz, 1 H), 2.18–2.13 (m, 2 H), 1.89–1.1.79 (m, 1 H), 0.97 (d, J = 6.60 Hz, 6 H) ppm. ¹³C NMR (CDCl₃, 100 MHz): δ = 141.5, 140.0, 37.1, 27.6, 22.1 ppm. HRMS: calcd. for C₆H₁₁NO₂Na [M + Na] 152.0698; found 152.0687.

2,2-Dimethyl-5-[(1'*S*)-3'-methyl-1'-(nitromethyl)butyl]-1,3-dioxane-4,6-dione (4). **1st Batch:** To a solution of nitroalkene **3** (4.33 g, 33.6 mmol) in DCM (35 mL) was added organocatalyst **13** (2.1 g, 3.36 mmol). After 5 min, Meldrum's acid (4.84 g, 33.6 mmol) was added, and the solution was stirred at room temp. for 23 h. Then, the crude mixture was poured into 5% aqueous citric acid solution, and the aqueous layer was extracted with DCM. After washing with brine, the extracts were dried, filtered and the solvents evaporated in vacuo to give a yellow oil. This was purified by column chromatography (50% to 80% EtOAc in hexane) providing compound **4** [7.7 g, 84%, (*S*)/(*R*) = 87.3:12.7] as a white solid and catalyst **13** (1.15 g, 55% recovery). **2nd Batch:** The recovered catalyst was reused in the conjugate addition reaction showing the same activity and selectivity. To a solution of nitroalkene **3** (2.46 g, 19.1 mmol) in DCM (20 mL) was added organocatalyst **14** (1.09 g, 1.74 mmol). After 5 min, Meldrum's acid (2.51 g, 17.4 mmol) was added, and the solution was stirred at room temp. for 24 h. Usual workup followed by purification by column chromatography (50% to 80% EtOAc in hexane) provided compound **4** [3.89 g, 82%, (*S*)/(*R*) = 87.3:12.7] as a white solid. R_f (10% EtOH in AcOEt) = 0.28. M.p. 74–76 °C. $[\alpha]_D^{20}$ = –14 (c = 1.0, CHCl₃). IR (film): $\tilde{\nu}$ = 3020, 2964, 1747, 1554, 1469, 1383 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 5.00 (dd, J = 16.0, 12.0 Hz, 1 H), 4.54 (dd, J = 12.0, 8.0 Hz, 1 H), 3.89 (d, J = 4.0 Hz, 1 H), 3.34 (m, 1 H), 1.81 (s, 3 H), 1.79 (s, 3 H), 1.66–1.52 (m, 2 H), 1.25–1.17 (m, 1 H), 0.98 (d, J = 8.0 Hz, 3 H), 0.94 (d, J = 8.0 Hz, 3 H) ppm. ¹³C NMR (CDCl₃, 100 MHz): δ = 164.1, 163.9, 104.6, 75.7, 47.1, 38.1, 34.1, 28.1, 27.6, 25.5, 23.0, 21.3 ppm. C₁₂H₁₉NO₆ (273.1): calcd. C 52.74, H 7.01, N 5.13; found C 52.90, H 7.05, N 5.05.

Method for the Determination of the Enantiomeric Excess: Enantiomeric excesses of the Michael adducts **4** were assayed by chiral HPLC analysis of the derived anilides of the corresponding monocarboxylic acids. After heating racemic compound **4** in a mixture DMF/aniline (10:1) at 100 °C for 3 h, *rac*-5-methyl-3-(nitromethyl)-*N*-phenylhexanamide was obtained in moderate yield. IR (film): $\tilde{\nu}$ = 3430, 3155, 2961, 2930, 1793, 1686, 1549, 1440 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 7.53 (d, J = 8.0 Hz, 2 H), 7.40 (br. s, 1 H), 7.35 (dd, J = 8.0, 8.0 Hz), 7.15 (dd, J = 8.0, 8.0 Hz, 1 H), 4.61–4.52 (m, 2 H), 2.81–2.75 (m, 1 H), 2.53–2.49 (m, 2 H), 1.79–1.69 (m, 1 H), 1.35 (t, J = 8 Hz, 2 H), 0.97–0.94 (m, 6 H) ppm. ¹³C NMR (CDCl₃, 100 MHz): δ = 169.1, 137.5, 129.0, 124.6, 120.0, 78.6, 40.4, 39.1, 32.6, 25.0, 22.5, 22.3 ppm. HRMS: calcd. for C₁₄H₂₀N₂NaO₃ [M + Na]⁺ 287.1372; found [M + Na]⁺ 287.1372. HPLC: Chiralcel OD column (0.46 cm × 25 cm), hexane/2-propanol (75:25), flow 1 mL/min, detector λ = 254 nm, retention time 1: 7.12 min, % area: 50.37, retention time 2: 8.42 min, % area: 49.63. The absolute configuration was determined by conversion of enantioenriched samples of **4** to Pregabalin. Enantiomer at 7.12 min shows (*S*) configuration, whereas enantiomer at 8.42 min shows (*R*) configuration.

2-[(1'*S*)-1'-(Aminomethyl)-3'-methylbutyl]propandioic Acid (5): Nitro compound **4** (9.04 g, 32.9 mmol) in AcOH (200 mL) was added to a solution of Raney-Ni in water (4.5 g of the commercially available wet suspension). The resulting black suspension was stirred at room temp. under H₂ at atmospheric pressure for 22 h (reaction monitored by ¹H NMR spectroscopy). The crude mixture was fil-

tered through a pad of Celite, and the green filtrate was diluted with water and adjusted to pH values between 2 and 3. The aqueous layer was extracted with DCM four times, and the extracts were dried, filtered and the solvents evaporated under vacuum to give diacid **5** (4.99 g, 75%) as a yellowish oil used in the next step without further purification. $[\alpha]_D^{20}$ = –53.6 (c = 1.25, CHCl₃). IR (film): $\tilde{\nu}$ = 3434, 3247, 3155, 2961, 2903, 1766, 1723, 1468, 1384, 1284 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 10.34 (br. s, 1 H), 7.18 (br. s, 1 H), 3.59 (dd, J = 16.0, 8.0 Hz, 1 H), 3.07 (d, J = 8.0 Hz, 1 H), 3.04 (dd, J = 12.0, 8.0 Hz, 1 H), 2.95–2.85 (m, 1 H), 1.68–1.55 (m, 2 H), 1.42–1.36 (m, 1 H), 0.93 (d, J = 6.4 Hz, 6 H) ppm. ¹³C NMR (CDCl₃, 100 MHz): δ = 175.2, 175.4, 54.0, 47.2, 43.2, 36.9, 25.8, 22.7, 22.1 ppm.

9-Amino-9-deoxyepiquinidine (7):^[21] Diisopropyl azodicarboxylate (DIAD, 7.33 mL, 37.0 mmol) was added to a solution of the quinidine alkaloid (10 g, 30.8 mmol) and triphenylphosphane (9.7 g, 37.0 mmol) in absolute THF (100 mL) at 0 °C all at once. After 5 min, a solution of diphenylphosphoryl azide (DPPA, 8.02 mL, 37 mmol) in dry THF (50 mL) was added dropwise at 0 °C. The mixture was warmed to room temp. After being stirred overnight, the solution was heated at 50 °C for 2 h. Then, triphenylphosphane was added, and the heating was maintained until the gas evolution had ceased. The solution was cooled to room temp., and water (10 mL) was added. After stirring for 4 h, the solvents were removed, and the residue was dissolved in DCM and 2 M HCl (1:1, 200 mL). The aqueous phase was extracted with DCM (3 × 100 mL). Then, the aqueous phase was made alkaline with a saturated aqueous solution of Na₂CO₃ and extracted with DCM. Concentration of the dried extracts afforded a residue, which was purified by column chromatography to yield the desired product **7** (5.15 g, 52%). R_f = 0.25 (DCM/MeOH/TEA, 85:15:5); visualization: ninhydrin. $[\alpha]_D^{20}$ = +79.6 (c = 1.05, CHCl₃) {ref.^[21] $[\alpha]_D^{20}$ = +69 (c = 2.51, CHCl₃)}. IR (film): $\tilde{\nu}$ = 3374, 3291, 3154, 3079, 2940, 2874, 1793, 1622, 1508 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 8.75 (d, J = 4.0 Hz, 1 H), 8.03 (d, J = 8.0 Hz, 1 H), 7.62 (br. s, 1 H), 7.53 (d, J = 4.0 Hz, 1 H), 7.38 (dd, J = 12.0, 4.0 Hz, 1 H), 5.92–5.85 (ddd, J = 17.1, 10.6, 6.5 Hz, 1 H), 5.10–5.05 (m, 2 H), 4.68 (d, J = 8.0 Hz, 1 H), 3.97 (s, 3 H, OMe), 3.12–2.90 (m, 5 H), 2.35–2.28 (m, 1 H), 2.15 (br. s, 2 H), 1.63–1.55 (m, 3 H), 1.21–1.12 (m, 1 H), 1.00–0.88 (m, 1 H) ppm. ¹³C NMR (CDCl₃, 100 MHz): δ = 157.1, 147.2, 146.9, 144.1, 140.2, 131.2, 128.2, 121.1, 119.4, 113.9, 101.0, 61.8, 54.9, 51.8, 49.0, 46.8, 38.9, 27.0, 26.1, 24.4 ppm.

Preparation of Thiourea Catalysts 8–15: A solution of the corresponding isothiocyanate in THF (0.8 M) was added to a stirred solution of the free amine **7** in THF (0.8 M) at room temp. After reaction overnight, the solvent was removed under reduced pressure and the residue submitted to flash column chromatography.

***N*-[3,5-Bis(trifluoromethyl)phenyl]-*N'*-[(9*R*)-6'-methoxycinchonan-9-yl]thiourea (8):**^[6b] Thiourea **8** (570 mg, 55%) was obtained as an amorphous solid after purification by column chromatography from amine **7** (568 mg, 1.75 mmol) and commercially available 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**18**) (477 mg, 1.75 mmol). R_f = 0.19; visualization: KMnO₄ (5% MeOH in EtOAc, five drops of TEA). $[\alpha]_D^{20}$ = +174 (c = 0.52, CHCl₃) [ref.^[6b] $[\alpha]_D^{20}$ = +225.3 (c = 0.50, CHCl₃)}. IR (film): $\tilde{\nu}$ = 3944, 3757, 3690, 3054, 3020, 2987, 2685, 2521, 2409, 2156, 1622, 1550, 1422 1263, 1217, 1181, 1139 cm⁻¹. ¹H NMR ([D₄]methanol, 400 MHz): δ = 8.68 (d, J = 4.0 Hz, 1 H), 8.11 (br. s, 2 H), 8.04 (br. s, 1 H), 7.94 (d, J = 8.0 Hz, 1 H), 7.60 (br. s, 1 H), 7.58 (d, J = 4.0 Hz, 1 H), 7.44 (d, J = 8.0 Hz, 1 H), 6.40 (d, J = 8.0 Hz, 1 H), 5.96 (ddd, J = 16.0, 12.0, 4.0 Hz, 1 H), 5.24 (d, J = 16.0 Hz, 1 H), 5.16 (d, J = 12.0 Hz, 1 H), 4.03 (s, 3 H), 3.45–3.35 (m, 2 H), 3.09–3.01 (m, 3

H), 2.42–2.37 (m, 1 H), 1.66–1.64 (m, 3 H), 1.28–1.19 (m, 1 H), 1.12–1.03 (m, 1 H) ppm. ^{13}C NMR (CDCl_3 , 100 MHz): δ = 181.6, 158.6, 147.3, 146.8, 144.1, 142.1, 140.6, 131.7 (q, $^2J_{\text{C-F}}$ = 33.0 Hz), 130.2, 129.2, 123.5 (q, $^1J_{\text{C-F}}$ = 271.0 Hz), 123.0, 122.7, 119.7, 116.9, 114.4, 103.0, 60.5, 55.6, 54.4, 49.2, 47.6, 39.0, 27.6, 25.4 ppm.

***N*-tert-Butyl-*N'*-[(9*R*)-6'-methoxycinchonan-9-yl]thiourea (9):** Thiourea **9** (578 mg, 70%) was obtained after flash column chromatography as an amorphous solid from amine **7** (626 mg, 1.94 mmol) and *tert*-butyl isothiocyanate (**20**) (245 mg, 2.13 mmol). R_f = 0.40 (15% MeOH in EtOAc); visualization: KMnO_4 . $[\alpha]_D^{20}$ = +314 (c = 0.62, CHCl_3). IR (film): $\tilde{\nu}$ = 3683, 3620, 3426, 3019, 2976, 2896, 1622, 1590, 1510, 1475, 1431, 1392, 1215, 1046 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): δ = 8.68 (d, J = 4.8 Hz, 1 H), 8.02 (br. s, 1 H), 7.95 (d, J = 9.2 Hz, 1 H), 7.51 (d, J = 4.8 Hz), 7.45 (dd, J = 9.2, 2.6 Hz, 1 H), 6.15 (d, J = 10 Hz, 1 H), 6.00 (ddd, J = 17.0, 10.5, 6.0 Hz, 1 H), 5.26 (dd, J = 17.0, 1.4 Hz, 1 H), 5.18 (dd, J = 10.5, 1.4 Hz, 1 H), 4.90 (br. s, 2 H), 4.07 (s, 3 H), 3.32–3.25 (m, 1 H), 3.25–3.18 (m, 1 H), 3.06–3.00 (m, 1 H), 2.42–2.39 (m, 1 H), 1.65–1.57 (m, 3 H), 1.45 (s, 9 H), 1.32–1.25 (m, 1 H), 0.98–0.94 (m, 1 H) ppm. ^{13}C NMR (CDCl_3 , 100 MHz): δ = 181.3, 157.6, 147.5, 144.5, 140.0, 131.9, 131.6, 128.1, 121.9, 119.2, 114.9, 101.6, 61.8, 55.4, 52.9, 48.8, 46.7, 46.0, 38.8, 29.2, 27.1, 26.4, 25.1 ppm.

***N*-Benzhydryl-*N'*-[(9*R*)-6'-methoxycinchonan-9-yl]thiourea (10):** Thiourea **10** (700 mg, 55%) was obtained after flash column chromatography as an amorphous solid from amine **7** (750 mg, 2.32 mmol) and benzhydryl isothiocyanate **22** (522 mg, 2.32 mmol). R_f = 0.5 (5% MeOH in DCM); visualization: KMnO_4 . $[\alpha]_D^{20}$ = +271 (c = 0.5, CHCl_3). IR (film): $\tilde{\nu}$ = 3684, 3418, 3019, 2976, 2895, 1710, 1622, 1521, 1476, 1421, 1364, 1215 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): δ = 8.61 (d, J = 4.0 Hz, 1 H), 7.95 (br. s, 1 H), 7.91 (d, J = 8.0 Hz, 1 H), 7.41 (m, 2 H), 7.28–7.11 (m, 11 H), 6.5 (br. s, 1 H), 6.16 (d, J = 8.0 Hz), 5.94 (ddd, J = 16.0, 8.0, 4.0 Hz, 1 H), 5.20 (d, J = 16.0 Hz, 1 H), 5.11 (d, J = 8.0 Hz, 1 H), 3.95 (s, 3 H), 3.31–3.18 (m, 2 H), 2.97–2.95 (m, 3 H), 2.34–2.32 (m, 1 H), 1.61–1.59 (m, 3 H), 1.24–1.19 (m, 1 H), 0.99–0.94 (m, 1 H) ppm. ^{13}C NMR (CDCl_3 , 100 MHz): δ = 181.6, 157.8, 147.4, 144.5, 140.0, 131.8, 131.6, 128.7, 128.5, 127.6, 127.3, 127.1, 122.1, 119.3, 114.6, 101.1, 62.4, 61.0, 57.8, 55.4, 48.5, 46.3, 38.6, 27.1, 26.2, 24.7 ppm.

***N*-[Bis(1-naphthyl)methyl]-*N'*-[(9*R*)-6'-methoxycinchonan-9-yl]thiourea (11):** Thiourea **11** (732 mg, 89%) was obtained after flash column chromatography as a white foam from amine **18** (411 mg, 1.27 mmol) and isothiocyanate **27** (413 mg, 1.27 mmol). R_f = 0.27 (5% MeOH in DCM); visualization: KMnO_4 . $[\alpha]_D^{20}$ = +188 (c = 1.04, CHCl_3). IR (film): $\tilde{\nu}$ = 3944, 3757, 3691, 3396, 3054, 2987, 2685, 2521, 2410, 2126, 1622, 1598, 1550, 1508, 1421, 1267, 1158 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): δ = 8.60 (br. s, 1 H), 8.01–7.75 (m, 10 H), 7.46–7.17 (m, 8 H), 7.01 (br. s, 1 H), 6.12 (br. s, 1 H), 5.95 (m, 1 H), 5.17 (m, 2 H), 3.93 (s, 3 H), 3.25 (br. s, 2 H), 2.95 (br. s, 3 H), 2.34 (br. s, 1 H), 1.60 (br. s, 3 H), 1.25 (m, 1 H), 0.98 (br. s, 1 H) ppm. ^{13}C NMR (CDCl_3 , 100 MHz): δ = 182.5, 158.0, 147.3, 144.4, 139.6, 136.7, 133.8, 131.9, 131.1, 131.0, 128.6, 127.4, 126.7, 125.8, 125.1, 125.0, 124.4, 123.7, 122.1, 114.7, 99.9, 61.7, 56.5, 55.3, 47.9, 45.9, 38.3, 29.5, 27.0, 25.7, 24.5 ppm.

***N*-[(9*R*)-6'-Methoxycinchonan-9-yl]-*N'*-(9-phenylfluoren-9-yl)thiourea (12):** Thiourea **12** (805 mg, 72%) was obtained after flash column chromatography (10% MeOH in EtOAc) as a crystalline solid from amine **7** (586 mg, 1.81 mmol) and isothiocyanate **24** (543 mg, 1.81 mmol); recrystallization from EtOAc gave cube-like crystals. M.p. 201–202 °C (dec.). R_f = 0.38 (10% MeOH in EtOAc); visualization: KMnO_4 . $[\alpha]_D^{20}$ = +362 (c = 1.0, CHCl_3). IR (film): $\tilde{\nu}$ = 3944, 3757, 3691, 3402, 3054, 2987, 2685, 2521, 2410, 2126, 2054, 1622, 1507, 1475, 1421, 1264 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz):

δ = 8.45 (d, J = 4.6 Hz, 1 H), 7.91 (d, J = 9.2 Hz, 1 H), 7.82 (dd, J = 12.2, 7.4 Hz, 2 H), 7.61 (m, 3 H), 7.49 (m, 3 H), 7.41–7.24 (m, 7 H), 7.20 (br. s, 1 H), 6.05 (br. s, 1 H), 5.81 (ddd, J = 17.0, 9.0, 6.0 Hz, 1 H), 5.25 (d, J = 10.0 Hz, 1 H), 5.05 (m, 2 H), 3.95 (s, 3 H), 2.45 (m, 1 H), 2.36–2.20 (m, 3 H), 2.12–1.98 (m, 2 H), 1.48 (m, 1 H), 1.37 (m, 1 H), 1.30–1.15 (m, 2 H), 0.60 (m, 1 H) ppm. ^{13}C NMR (CDCl_3 , 100 MHz): δ = 181.1, 157.2, 147.2, 146.6, 146.2, 144.0, 142.5, 140.3, 139.7, 139.4, 131.1, 129.3, 129.1, 128.8, 128.5, 128.2, 125.1, 125.1, 121.7, 120.8, 120.3, 118.1, 114.3, 101.4, 71.8, 61.7, 55.2, 48.9, 45.9, 38.6, 26.8, 26.4, 24.6 ppm. $\text{C}_{42}\text{H}_{40}\text{N}_4\text{O}_5$ (622.3): calcd. C 77.74, H 6.21, N 8.63, S 4.94; found C 77.79, H 6.16, N 9.12, S 5.46.

***N*-[(9*R*)-6'-Methoxycinchonan-9-yl]-*N'*-tritylthiourea (13):** Thiourea **13** (2.17 g, 79%) was obtained as a white solid after flash column chromatography (5% MeOH in DCM) from amine **7** (1.43 g, 4.41 mmol) and commercially available trityl isothiocyanate (**19**) (1.33 g, 4.41 mmol); crystallization from MeOH/ CHCl_3 (5:1) gave needle-like crystals. M.p. 189–190 °C (dec.). R_f = 0.5 (10% MeOH in DCM). $[\alpha]_D^{20}$ = +177.4 (c = 1.5, CHCl_3). IR (film): $\tilde{\nu}$ = 3415, 3258, 3155, 2981, 2941, 2874, 1816, 1793, 1622, 1511, 1475, 1382 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): δ = 8.45 (d, J = 4.6 Hz, 1 H), 7.92 (d, J = 9.2 Hz, 1 H), 7.58 (d, J = 2.4 Hz, 1 H), 7.38–7.28 (m, 16 H), 6.73 (d, J = 2.4 Hz, 1 H), 6.02 (d, J = 4.6 Hz, 1 H), 5.87 (ddd, J = 17.0, 10.6, 6.3 Hz, 1 H), 5.47 (d, J = 10.6 Hz, 1 H), 5.13–5.09 (m, 2 H), 3.98 (s, 3 H), 2.77–2.72 (m, 1 H), 2.64–2.58 (m, 1 H), 2.50–2.46 (m, 2 H), 2.24–2.16 (m, 2 H), 1.52–1.51 (m, 1 H), 1.39–1.37 (m, 1 H), 1.32–1.17 (m, 2 H), 0.74–0.68 (m, 1 H) ppm. ^{13}C NMR (CDCl_3 , 100 MHz): δ = 179.9, 157.3, 147.0, 145.8, 144.0, 142.8, 140.2, 131.1, 128.6, 128.4, 128.2, 127.4, 121.7, 118.0, 114.4, 101.4, 72.2, 61.3, 55.4, 55.1, 48.5, 46.7, 38.9, 26.9, 26.3, 24.5 ppm. $\text{C}_{40}\text{H}_{40}\text{N}_4\text{O}_5$ (624.3): calcd. C 76.89, H 6.45, N 8.97, S 5.13; found C 76.08, H 6.37, N 9.37, S 5.30.

***N*-[(9*R*)-6'-Methoxycinchonan-9-yl]-*N'*-[tris(3,5-dimethylphenyl)methyl]thiourea (14):** Thiourea **14** (868 mg, 72%) was obtained as a white foam after flash column chromatography (2% MeOH in Et₂O) from amine **7** (550 mg, 1.54 mmol) and isothiocyanate **29** (596 mg, 1.54 mmol); crystallization from MeOH/ CHCl_3 (5:1) gave needle-like crystals. M.p. 131–133 °C (dec.). R_f = 0.28 (2% MeOH in Et₂O). $[\alpha]_D^{20}$ = +114 (c = 0.63, CHCl_3). IR (film): $\tilde{\nu}$ = 3415, 3155, 2941, 1793, 1622, 1595, 1510, 1474, 1381, 1226, 1216, 1169, 1095, 910 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): δ = 8.45 (d, J = 4.6 Hz, 1 H), 7.92 (d, J = 9.0 Hz, 1 H), 7.66 (d, J = 2.4 Hz, 1 H), 7.31 (dd, J = 9.0, 2.4 Hz, 1 H), 7.20 (br. s, 1 H), 6.90 (s, 3 H), 6.89 (s, 6 H), 6.54 (d, J = 3.6 Hz, 1 H), 6.10 (d, J = 4.6 Hz, 1 H), 5.86 (ddd, J = 17.0, 10.4, 6.2 Hz, 1 H), 5.56 (dd, J = 10.6, 3.7 Hz, 1 H), 5.10 (m, 2 H), 3.99 (s, 3 H), 2.81 (m, 1 H), 2.64–2.49 (m, 3 H), 2.26 (s, 18 H), 2.25 (m, 1 H), 1.51 (m, 1 H), 1.39 (m, 1 H), 1.26 (m, 1 H), 1.16 (m, 1 H), 0.86 (m, 1 H), 0.70 (m, 1 H) ppm. ^{13}C NMR (CDCl_3 , 100 MHz): δ = 180.0, 157.5, 147.3, 146.4, 144.3, 143.3, 140.5, 137.6, 131.2, 129.1, 128.7, 126.5, 122.0, 118.0, 114.6, 101.9, 72.3, 61.5, 55.7, 55.4, 49.0, 47.3, 39.2, 27.2, 26.6, 25.0, 21.6 ppm.

***N*-[(9*R*)-6'-Methoxycinchonan-9-yl]-*N'*-[(1*R*)-1-naphthylethyl]thiourea (15):** Thiourea **15** (484 mg, 81%) was obtained after flash column chromatography as an amorphous solid from amine **7** (362 mg, 1.12 mmol) and (1*R*)-1-(1-naphthyl)ethyl isothiocyanate (**21**) (238 mg, 1.12 mmol). R_f = 0.29 (15% MeOH in EtOAc); visualization: KMnO_4 . $[\alpha]_D^{20}$ = +195 (c = 2.16, CHCl_3). IR (film): $\tilde{\nu}$ = 3684, 3620, 3411, 3019, 2975, 1710, 1622, 1512, 1475, 1419, 1363 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): δ = 8.72 (d, J = 4.0 Hz, 1 H), 8.12 (d, J = 8.0 Hz, 1 H), 8.00 (d, J = 8.0 Hz, 1 H), 7.92–7.90 (d, J = 8.0 Hz, 1 H), 7.81 (dd, J = 8.0 Hz, 1 H), 7.58–7.29 (m, 9 H), 5.77–5.69 (m, 1 H), 5.23 (br. s, 1 H), 5.06–5.00 (m, 2 H), 3.88

(s, 3 H), 2.95–2.20 (br. s, 3 H), 2.04 (br. s, 2 H), 1.65–1.50 (m, 5 H), 1.26–1.14 (m, 3 H), 0.83 (br. s, 1 H) ppm. ^{13}C NMR (CDCl_3 , 100 MHz, more significant signals): δ = 181.5, 157.5, 147.3, 144.4, 139.7, 137.9, 133.8, 131.4, 130.5, 128.8, 128.2, 128.1, 126.4, 125.7, 122.4, 121.8, 119.0, 114.6, 101.3, 60.9, 55.3, 50.1, 47.6, 45.8, 38.3, 26.8, 25.8, 24.5, 22.0 ppm. HRMS: calcd. for $\text{C}_{33}\text{H}_{36}\text{N}_4\text{O}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 536.2690; found 537.2688.

Preparation of Thiourea Catalysts 16 and 17: A solution of the corresponding amine in THF (0.6 M) was added to a stirred solution of the isothiocyanate **23** in THF (0.6 M) at room temp. After reaction overnight, the solvent was removed under reduced pressure and the residue submitted to flash column chromatography.

***N*-[*(9R)*-6'-Methoxycinchonan-9-yl]-*N'*-[*(1S)*-1-naphthylethyl]-thiourea (**16**):** Thiourea **16** (349 mg, 65%) was obtained after flash column chromatography as a white foam from isothiocyanate **23** (366 mg, 1 mmol) and commercially available (*1S*)-1-(1-naphthyl)-ethylamine (174 mg, 1 mmol). R_f = 0.21 (5% MeOH in DCM); visualization: KMnO_4 . $[\alpha]_D^{20}$ = +203 (c = 1.95, CHCl_3). IR (film): $\tilde{\nu}$ = 3393, 3155, 2941, 2874, 1793, 1623, 1509, 1474, 1381, 1225, 1095 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): δ = 8.41 (d, J = 4.0 Hz, 1 H), 7.98 (br. s, 1 H), 7.87 (d, J = 8.0 Hz, 2 H), 7.76 (d, J = 4.0 Hz, 1 H), 7.50 (br. s, 2 H), 7.34 (br. s, 3 H), 7.29 (dd, J = 9.2, 2.4 Hz, 2 H), 6.95 (br. s, 1 H), 5.74 (br. s, 2 H), 5.06–4.96 (m, 2 H), 3.88 (s, 3 H), 2.68 (br. s, 2 H), 2.61 (br. s, 3 H), 2.17 (d, J = 7.12 Hz, 1 H), 1.82 (br. s, 1 H), 1.66 (d, J = 6.6 Hz, 3 H), 1.50 (br. s, 1 H), 1.46 (br. s, 2 H), 1.34 (br. s, 1 H), 1.06 (br. s, 1 H), 0.76 (br. s, 1 H) ppm. ^{13}C NMR (CDCl_3 , 100 MHz, significant signals): δ = 180.8, 157.8, 147.2, 144.3, 139.8, 137.6, 133.6, 131.7, 130.5, 128.8, 128.2, 126.5, 126.3, 125.7, 125.1, 122.3, 121.9, 119.3, 114.7, 100.9, 61.3, 55.4, 50.2, 48.4, 46.3, 38.5, 27.1, 26.0, 24.6, 21.0 ppm. HRMS: calcd. for $\text{C}_{33}\text{H}_{36}\text{N}_4\text{O}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 536.2690; found 537.2688.

1-[*(1R,2S)*-2-Hydroxy-2,3-dihydro-1*H*-inden-1-yl]-*N'*-[*(9R)*-6'-methoxycinchonan-9-yl]thiourea (17**):** Thiourea **17** (203 mg, 61%) was obtained after flash column chromatography as a white foam from isothiocyanate **23** (236 mg, 0.65 mmol) and commercially available (*1R,2S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (96 mg, 0.65 mmol); R_f = 0.52 (15% MeOH, 5% Et_3N in DCM); visualization: ninhydrin; $[\alpha]_D^{20}$ = +314 (c = 0.62, CHCl_3). IR (film): $\tilde{\nu}$ = 3620, 3399, 2976, 2896, 1623, 1511, 1475, 1392, 1215, 1047 cm^{-1} . ^1H NMR (CD_3OD , 400 MHz): δ = 8.67 (m, 1 H), 8.13 (br. s, 1 H), 7.95 (dq, J = 9, 1.4 Hz, 1 H), 7.57 (br. s, 1 H), 7.45 (m, 1 H), 7.21 (m, 3 H), 6.48 (br. s, 1 H), 5.99 (m, 2 H), 5.82 (br. s, 1 H), 5.29 (d, J = 17 Hz, 1 H), 5.17 (dd, J = 10, 1.4 Hz, 1 H), 4.88 (br. s, 4 H), 4.53 (br. s, 1 H), 4.07 (s, 3 H), 3.6–3.3 (m, 5 H), 3.15–3.02 (m, 4 H), 2.85 (d, J = 17 Hz, 1 H), 2.4 (m, 1 H), 1.20 (m, 1 H), 1.01 (br. s, 1 H). HRMS: calcd. for $\text{C}_{30}\text{H}_{35}\text{N}_4\text{O}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 515.2481; found 515.2487.

General Procedure for the Preparation of Isothiocyanates from Primary Amines: To a solution of the corresponding primary amine (100 mol-%) in dry diethyl ether or THF (1 M) at -10°C were added CS_2 (600 mol-%) and DCC (100 mol-%). The reaction mixture was warmed slowly to room temp. over a period of 3 h and then stirred at room temp. overnight. The thiourea, which precipitated, was removed by filtration, and the solvent was subsequently removed under vacuum. The residue was taken up in diethyl ether and more of the thiourea was removed by filtration. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography.

***tert*-Butyl Isothiocyanate (**20**):**^[22] According to the previous general procedure, from commercially available *tert*-butylamine (4 g, 54.8 mmol) compound **20** was obtained as a colorless oil (4.09 g, 65%) after purification by combi flash chromatography (5% EtOAc in hexane). R_f = 0.39 (5% EtOAc in hexane); visualization:

KMnO_4 . IR (film): $\tilde{\nu}$ = 3944, 3757, 3691, 3054, 2986, 2113, 1712, 1421, 1369, 1264 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): δ = 1.44 (s, 9 H, *tert*-butyl) ppm. ^{13}C NMR (CDCl_3 , 100 MHz): δ = 129.6, 58.1, 30.7 ppm.

(*1R*)-1-(1-Naphthyl)ethyl Isothiocyanate (21**):** According to the previous general procedure, from commercially available (+)-(*1R*)-1-(1-naphthyl)ethylamine (1 g, 5.85 mmol) compound **21** was obtained as a colorless oil (0.979 g, 79%) after purification by combi flash chromatography (5% EtOAc in hexane). R_f = 0.35 (5% EtOAc in hexane); visualization: KMnO_4 . $[\alpha]_D^{20}$ = -116 (c = 1.05, CHCl_3) {ref.^[23] $[\alpha]_D^{20}$ = -109 (c = 1.0, CHCl_3)}. IR (film): $\tilde{\nu}$ = 3944, 3757, 3691, 3054, 2987, 2685, 2096, 1712, 1599, 1512, 1421, 1361, 1263 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): δ = 7.92 (dd, J = 11.0, 9.0 Hz, 2 H), 7.83 (d, J = 8.2 Hz, 1 H), 7.55 (m, 3 H), 5.71 (q, J = 6.8 Hz, 1 H), 1.84 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (CDCl_3 , 100 MHz): δ = 135.2, 133.7, 132.4, 129.3, 129.0, 128.8, 126.6, 125.8, 125.3, 122.8, 122.0, 53.9, 23.8 ppm.

Benzhydryl Isothiocyanate (22**):**^[23] According to the previous general procedure, from commercially available benzhydrylamine (2 g, 10.9 mmol) compound **22** was obtained as a white solid (1.01 g, 41%) after purification by combi flash chromatography (5% EtOAc in hexane). M.p. 61–62 $^\circ\text{C}$. R_f = 0.76 (5% EtOAc in hexane); visualization: KMnO_4 . IR (film): $\tilde{\nu}$ = 3691, 3053, 2986, 2685, 2062, 1712, 1598, 1550, 1494, 1453, 1343 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): δ = 7.39–7.27 (m, 10 H), 5.98 (s, 1 H) ppm. ^{13}C NMR (CDCl_3 , 100 MHz): δ = 139.1, 134.4, 128.8, 128.2, 126.5, 64.5 ppm.

(*9*-Deoxy)epiquinidine Isothiocyanate (23**):** According to the previous general procedure, from **7** (1.02 g, 3.17 mmol) title compound **23** was obtained as a white solid (0.845 g, 73%) after purification by flash chromatography (10% MeOH in Et_2O). Crystallization from MeOH/ CHCl_3 (5:1) gave star-like crystals. M.p. 109–110 $^\circ\text{C}$ (dec.). R_f = 0.16 (10% MeOH in Et_2O); visualization: KMnO_4 . $[\alpha]_D^{20}$ = +15.1 (c = 1.3, CHCl_3). IR (film): $\tilde{\nu}$ = 3155, 2955, 2049, 1816, 1793, 1622, 1547, 1512, 1473, 1382 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): δ = 8.75 (d, J = 4.5 Hz, 1 H), 8.03 (d, J = 9.2 Hz, 1 H), 7.45 (d, J = 4.5 Hz, 1 H), 7.38 (dd, J = 9.2, 2.6 Hz, 1 H), 7.31 (d, J = 2.6 Hz, 1 H), 5.86 (ddd, J = 16.8, 10.6, 5.9 Hz, 1 H), 5.40 (d, J = 10 Hz, 1 H), 5.23 (m, 2 H), 3.95 (s, 3 H), 3.75 (m, 1 H), 3.51 (m, 1 H), 3.29 (m, 2 H), 3.17 (m, 1 H), 2.65 (m, 1 H), 2.05 (br. s, 1 H), 1.96–1.73 (m, 3 H), 1.60 (m, 1 H) ppm. ^{13}C NMR (CDCl_3 , 100 MHz): δ = 157.8, 147.8, 144.4, 141.9, 136.1, 131.7, 127.1, 121.7, 119.6, 117.2, 101.1, 67.3, 65.7, 55.5, 52.0, 50.9, 37.4, 27.9, 24.7, 24.2 ppm.

9-Phenylfluoren-9-yl Isothiocyanate (24**):** Potassium thiocyanate (0.3 g, 3.1 mmol) was added to a solution of 9-bromo-9-phenylfluorene (1 g, 3.1 mmol) in acetone (5 mL). The white suspension was stirred at room temp. for 20 min. Then the solvent was removed, and the residue was partitioned between water and EtOAc. The organic phases were dried, filtered and concentrated to afford an oil, which was purified by flash chromatography (5% EtOAc in hexane). Isothiocyanate **24** was isolated as a white solid (R_f = 0.37 (5% EtOAc in hexane) (446 mg, 48% yield); along with the corresponding thiocyanate [R_f = 0.24 (315 mg, 34%); visualization: KMnO_4]. M.p. 86–88 $^\circ\text{C}$. IR (film): $\tilde{\nu}$ = 3944, 3691, 3054, 2831, 2685, 2054, 1599, 1711, 1421, 1263 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): δ = 7.73–7.68 (m, 2 H), 7.48–7.15 (m, 11 H) ppm. ^{13}C NMR (CDCl_3 , 100 MHz): δ = 147.7, 140.8, 139.8, 135.8, 130.2, 129.3, 129.2, 128.6, 125.7, 125.0, 121.0, 74.6 ppm.

Bis(1-naphthyl)methanol (26**):** Commercially available 1-bromonaphthalene (3.52 g, 17 mmol) dissolved in THF (3 mL) was added dropwise to a stirred suspension of magnesium turnings (0.41 g, 17 mmol) in anhydrous THF (3 mL) over a period of 10 min. Heat

evolved, and the mixture turned into a green suspension. After 2 h, ethyl formate (0.67 mL, 8.1 mmol) was added as a solution in THF (2 mL) over a period of 10 min. After stirring for 2 h at room temp., the mixture was poured into ice/2 M HCl (1:1, 50 mL), and the aqueous layer was extracted with Et₂O. The extracts were dried, filtered and concentrated to provide **26** as a white foam (1.72 g, 75%) that was used without further purification. R_f = 0.29 (30% CHCl₃ in hexane); visualization: KMnO₄. IR (film): $\tilde{\nu}$ = 3597, 3155, 3063, 2984, 1816, 1793, 1643, 1598, 1510, 1470, 1382 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 8.04 (d, J = 8.0 Hz, 2 H), 7.90 (d, J = 8.0 Hz, 2 H), 7.82 (d, J = 8.0 Hz, 2 H), 7.50–7.28 (m, 8 H), 7.24 (d, J = 4.0 Hz, 1 H), 2.40 (d, J = 4.0 Hz, 1 H, OH) ppm. ¹³C NMR (CDCl₃, 100 MHz): δ = 138.3, 133.7, 130.9, 128.6, 128.3, 126.2, 125.5, 125.3, 124.9, 123.7, 69.2 ppm.

Bis(1-naphthyl)methyl Isothiocyanate (27): Powdered oxalic acid (0.32 g, 3.52 mmol) and NaSCN (0.34 g, 4.22 mmol) were added to a solution of **26** (1 g, 3.52 mmol) in nitromethane (8 mL). The mixture was stirred at 60 °C for 3 h. Then, the crude mixture was poured into a saturated solution of sodium carbonate and extracted with Et₂O. The extracts were dried, filtered and concentrated to give a pale yellow oil. This was purified by flash column chromatography (5% EtOAc in hexane) to give compound **27** (0.96 g, 84%) as a white foam and minor amounts of the corresponding thiocyanate (0.068 g, 6%). R_f = 0.39 (10% EtOAc in hexane); visualization: KMnO₄. IR (film): $\tilde{\nu}$ = 3943, 3692, 3054, 2986, 2685, 2056, 1599, 1511, 1421, 1269 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 7.95–7.84 (m, 6 H), 7.54–7.40 (m, 9 H) ppm. ¹³C NMR (CDCl₃, 100 MHz): δ = 135.2, 133.8, 133.5, 130.1, 129.4, 129.0, 127.0, 126.0, 125.6, 125.3, 122.6, 58.3 ppm.

Tris(3,5-dimethylphenyl)methanol (28):^[24] Commercially available 1-bromo-3,5-dimethylbenzene (7 g, 37.8 mmol) in dry Et₂O (5 mL) was added dropwise to a stirred suspension of granular lithium (0.66 g, 95.1 mmol) in dry Et₂O (15 mL) at –10 °C. The mixture reacted exothermically and refluxed spontaneously. After the addition was complete, the mixture was stirred at room temp. for 10 min. Then, commercially available methyl 3,5-dimethylbenzoate (2.48 g, 15.1 mmol) in dry Et₂O (10 mL) was added dropwise, and the mixture was stirred at room temp. overnight. Then the excess of lithium and the lithium salts were removed by filtration, and the filtrate was poured into a saturated aqueous solution of ammonium chloride. After Et₂O extraction of the aqueous layer, the organic phases were dried, filtered and concentrated to yield alcohol **28** as a white solid (4.746 g, 91%). Crystallization from hexane gave needle-like crystals. M.p. 155–156 °C (ref.^[24] 158 °C). R_f = 0.21 (5% Et₂O in hexane); visualization: anisaldehyde. IR (film): $\tilde{\nu}$ = 3944, 3691, 3054, 2987, 2685, 1598, 1551, 1421, 1263 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 6.94 (s, 3 H), 6.92 (s, 6 H), 2.70 (s, 1 H, OH); 2.30 (s, 18 H) ppm. ¹³C NMR (CDCl₃, 100 MHz): δ = 147.1, 137.1, 128.7, 125.7, 81.8, 21.5 ppm.

Tris(3,5-dimethylphenyl)methyl Isothiocyanate (29): Powdered oxalic acid (0.34 g, 3.78 mmol) and KSCN (0.44 g, 4.53 mmol) were added to a solution of **28** (1.3 g, 3.78 mmol) in nitromethane (10 mL). The mixture was stirred at 60 °C for 3 h. Then, the crude mixture was poured into a saturated solution of Na₂CO₃ and extracted with Et₂O. The extracts were dried, filtered and concentrated to give a pale yellow oil. This was purified by flash column chromatography (2% Et₂O in hexane) to give pure compound **29** (1.29 g, 89%) as a white solid. Crystallization from hexane gave colorless crystals. M.p. 161–162 °C. R_f = 0.58 (2% Et₂O in hexane); visualization: KMnO₄. IR (film): $\tilde{\nu}$ = 3597, 3153, 3010, 2920, 2085, 1796, 1597, 1464, 1378, 1288 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 6.94 (s, 3 H), 6.75 (s, 6 H), 2.27 (s, 18 H) ppm. ¹³C NMR (CDCl₃, 100 MHz): δ = 143.2, 137.6, 132.9, 129.6, 125.9, 21.4 ppm.

Acknowledgments

We gratefully acknowledge financial support from the Academy of Finland (AMPK no. 105834 and KR no. 212588) and Dr. Jari Koivisto and Ms. Tiia Juhala for the HRMS and elemental analyses.

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Received: December 5, 2008

Published Online: February 5, 2009