

Article

Novel Selenoureas Based on *Cinchona* Alkaloid Skeleton: Synthesis and Catalytic Investigations

Mariola Zielińska-Błajet ^{1,*}  and Joanna Najdek ²

¹ Faculty of Chemistry, Wrocław University of Science and Technology, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland

² Institute of Chemistry and Biochemistry, Freie Universität Berlin, Takustr. 3, 14195 Berlin, Germany; joanna.najdek@hotmail.com

* Correspondence: mariola.zielinska-blajet@pwr.edu.pl; Tel.: +48-71-3202128

Abstract: An efficient approach to the synthesis of chiral selenoureas consisting of *Cinchona* alkaloid scaffolds was described. The new selenoureas were assessed as bifunctional organocatalysts in the asymmetric Michael addition reactions under mild conditions. The best results were obtained for selenoureas bearing the 4-fluorophenyl group. These catalysts promoted the reactions with enantioselectivities of up to 96% ee. Additionally, the catalytic performance of the thiourea and selenourea counterpart was compared.

Keywords: *Cinchona* alkaloids; selenoureas; isoselenocyanates; organocatalysis; Michael addition; asymmetric synthesis



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1. Introduction

In recent years, growing attention has been focused on the synthesis and applications of selenourea derivatives. The structures of selenoureas are closely related to those of analogs of oxygen and sulfur compounds [1–3], but the presence of larger, more polarizable selenium results in a change of significant properties. They possess various biological properties, such as antioxidant [4,5], antibacterial and antifungal [6], antileishmanial [7], pesticidal [8], and anti-urease activity [9]. Selenoureas also demonstrate enzyme inhibition, free-radical scavenging, and anticancer activity [10,11]. These compounds are very useful starting materials for the synthesis of selenium-containing heterocycles [12,13] and are used for anion binding and recognition [14,15]. To the best of our knowledge, only a few examples of chiral selenoureas have been reported in the literature [16,17]. Currently, chiral bis-selenourea is used as a strong hydrogen-bonding donor for highly efficient chiral recognition of a diverse range of tertiary alcohols [18]. Still, little is known about the application of selenoureas as hydrogen-bond donors in organocatalysis. Bolm and co-workers were the first to apply a selenourea derivative as a chiral catalyst in the asymmetric Michael addition of α -nitrocyclohexane to aryl nitroalkenes [19].

Chiral bifunctional organocatalysts, which incorporate a thiourea group as H-bond donors with Lewis base, are commonly used in asymmetric catalysis. Both parts of the catalysts simultaneously activate the electrophile and nucleophile leading to the high stereocontrol of the reaction [20,21]. Nowadays, thioureas are widely recognized as highly useful and powerful organocatalysts that promote a diverse range of reactions with excellent enantioselectivity [22–24]. *Cinchona* alkaloids with an exceptionally good chiral backbone have been used for the synthesis of many successful catalysts [25]. Inspired by the improved catalytic activity of the thioureas in comparison to ureas, we have taken interest in the modification of the “privileged” *Cinchona* alkaloid scaffolds by substituting the thiourea with a selenourea moiety.

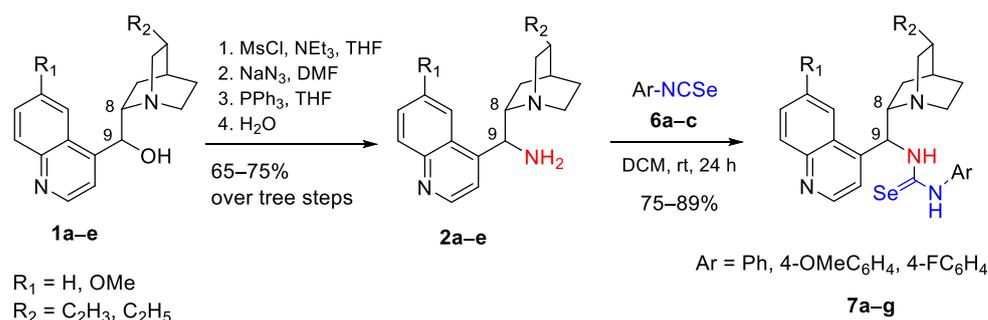
Here, we report the approach to the efficient synthesis of a series of novel *Cinchona* alkaloid-derived selenoureas, and we also demonstrate their organocatalytic potential in asymmetric Michael additions.

2. Results and Discussion

2.1. Preparation of Compounds

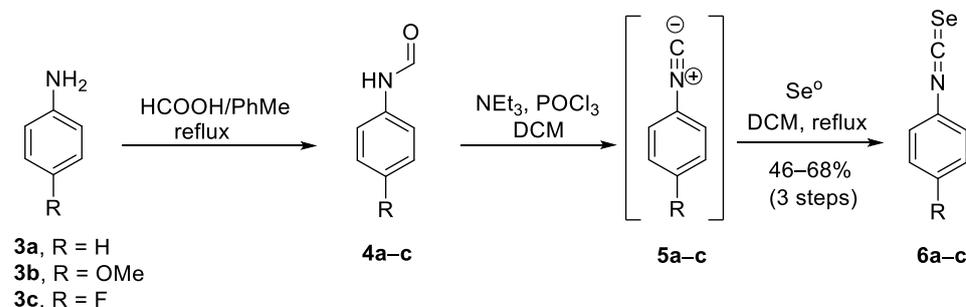
Cinchona alkaloid-based selenoureas were prepared by coupling reactions of 9-*epi*-aminoalkaloids with aryl isoselenocyanates. Although there are some methods in the literature for the preparation of selenoureas [4,10,26], the best procedure still turns out to be the reaction of isoselenocyanates with amines. The crucial step is the preparation of isoselenocyanates, which, unlike their sulfur analogs, are not commercially available. Several strategies towards their synthesis have been reported [27–29]. The oxidation of corresponding isocyanides with elemental black selenium in a suitable solvent seems to be the most reliable method [13,16,30,31].

The first coupling partner for the synthesis of desired selenoureas was *Cinchona* alkaloid-based amines **2a–e**, which were prepared in good yields (65–75%) from naturally occurring *Cinchona* alkaloids, namely quinine (QN), cinchonidine (CD), quinidine (QD), and the respective dihydro derivatives (dihydroquinine (DHQN)/dihydroquinidine (DHQD)) in a three-step sequence via mesylation [32], azidation with NaN₃ in warm DMF followed by S_N2 displacement [33], and then treatment with triphenylphosphine (Staudinger reduction) to amine (Scheme 1) [34].



Scheme 1. General synthetic route for compounds **7a–g**.

Non-commercial aryl isoselenocyanates **6a–c**, the second coupling partner, were synthesized in good yields (46–68%) in a three-step protocol (Scheme 2) that involved *N*-formylation of the commercially available aryl amines **3a–c** with formic acid in toluene, conversion of the formamides **4a–c** into isocyanides **5a–c** upon dehydration with POCl₃ in the presence of NEt₃ in dichloromethane (DCM) [35]. The last step included the reaction of the isocyanides with black selenium in DCM at 45 °C in darkness.



Scheme 2. Synthesis of aryl isoselenocyanates **6a–c**.

The coupling of the aryl isoselenocyanates **6a–c** with 9-*epi*-aminoalkaloids **2a–e** in DCM at 45 °C in the darkness resulted in the formation of the desired selenoureas **7a–g** in

high yields (75–89%) (Scheme 1), (Figure 1). All new compounds were fully characterized by spectroscopic methods (IR, ^1H , and ^{13}C NMR, HRMS). Copies of ^1H , ^{13}C NMR and IR spectra are presented in Supplementary Materials.

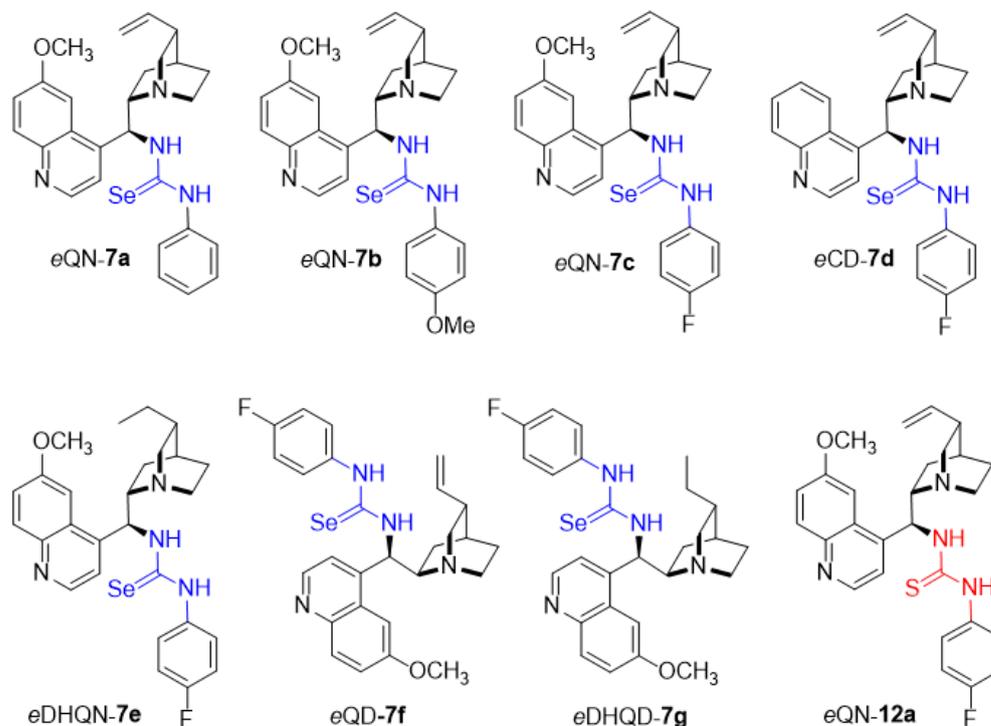
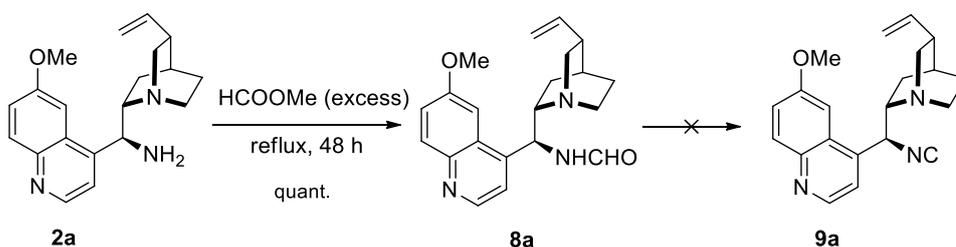


Figure 1. Structures of the *Cinchona*-based selenoureas.

In an alternative approach, we intended to introduce the isoselenocyanate moiety in the *Cinchona* alkaloid skeleton. 9*S*-Amino-deoxyquinine **2a** was chosen for the transformation into isoselenocyanate. Amine **2a** was converted into 9*S*-formylamino-deoxyquinine **8a** by treatment with the excess of methyl formate in quantitative yield (Scheme 3). The spectroscopic data of compound **8a** can be found in Supplementary Materials, Figures S15 and S16.

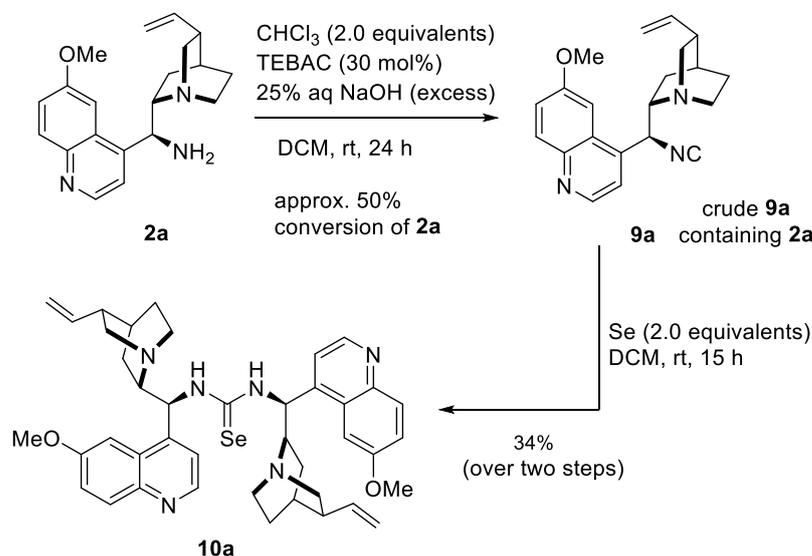


Scheme 3. Unsuccessful attempts to prepare isocyanide **9a**.

Surprisingly, dehydration of formamide **8a** using the previously applied $\text{POCl}_3/\text{NEt}_3$ system did not provide the desired isocyanide, and the amine **2a** was fully recovered. Due to this unsatisfying result, other known methods to convert formamide **8a** to isocyanide **9a** were tested. Hence, the procedures using the triphosgene/ NEt_3/DCM and $\text{PPh}_3/\text{CCl}_4/\text{NEt}_3$ system as well as Vilsmeier and Burgess reagents turned out to be ineffective [17,30,36].

Further transformations of the quinine-derived amine **2a** applying the Hofmann isonitrile synthesis protocol [37] modified by Małosza [38] followed for the preparation of novel isonitrile **9a**. The reaction of **2a** with chloroform in a biphasic system, 25% aqueous sodium hydroxide solution, and DCM and TEBAC (triethylbenzylammonium chloride) as

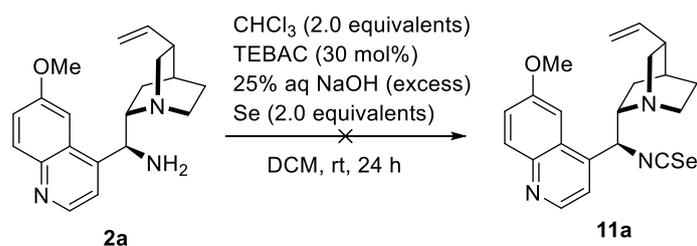
a phase-transfer catalyst, afforded compound **9a** with a conversion of approximately 50% (Scheme 4). Attempts to isolate detected products were unsuccessful because isocyanide **9a** hydrolyzed during column chromatography with the formation of formamide **8a**.



Scheme 4. The synthetic route for dimeric alkaloid selenourea **10a**.

Accordingly, we turned our attention to converting the resulting crude product into dimeric alkaloid selenourea **10a**. The addition of selenium to the crude mixture of isocyanide **9a** and unreacted amine **2a** in DCM led to a moderate yield of product **10a** (Scheme 4) (spectral data available in Supplementary Materials, Figures S17 and S18).

In contrast, the one-pot transformation of the amine **2a** into isoselenocyanate **11a** under phase-transfer catalysis did not lead to the formation of the desired product **11a** (Scheme 5). In this case, a mixture of compounds was formed.



Scheme 5. Unsuccessful attempts to prepare isoselenocyanate **11a**.

2.2. Catalytic Activity of Tested Compounds

With the aforementioned set of chiral selenoureas in hand, we examined their catalytic abilities as bifunctional organocatalysts in the asymmetric Michael addition. We chose the Michael reaction of nitromethane to *trans*-chalcone developed by Soós et al. [39] as the model reaction.

The screening experiments are summarized in Table 1. The results showed that the selenourea catalysts **7a–g** afforded Michael adducts with good to excellent enantioselectivity ranging from 70% to 95% (Table 1, entries 1–7). The influence of substituents in the aromatic ring was also noted for the quinine-based selenourea. As expected, compounds bearing the electron-withdrawing substituent in the phenyl ring delivered a superior effect on the catalyzed reactions in comparison to their counterparts possessing electron-neutral and electron-donating groups. It is known that pKa values of catalysts correlate well with their hydrogen-bond donating abilities [40]. Electron-withdrawing substituents increase the acidity of the double hydrogen bond donor and subsequently, improve the electrophile

activation ability [41,42]. There, the application of unsubstituted (entry 1), 4-methoxy- (entry 2), and 4-fluoro- (entry 3) derivatives gave 81, 70, and 95% ee, respectively. Better stereoselectivity was achieved for (8*S*,9*S*)-selenourea derivatives **7c–e** (quinine series) as compared to (8*R*,9*R*) quinidine series (Table 1, entries 3–5 vs. entries 6 and 7). These results demonstrate that the configurations of the alkaloid determine the stereochemical result of the addition. The absence of the methoxyl group at the C6' position in cinchonidine-derived selenourea **7d** did not considerably affect the outcome of the catalyzed reaction compared to the selenourea catalyst **7c**, which possesses this group (91% ee, entry 4 vs. 95% ee, entry 3). The yields of the reaction were poor to moderate (up to 46%), slightly better for selenourea derivatives of the quinine series. Higher yields were observed for dihydro alkaloid-based selenoureas **7e** and **7g** (36–46% ee, entries 5 and 7 vs. 22–26% ee, entries 3,4, and 6).

Table 1. Asymmetric Michael addition of nitromethane to *trans*-chalcone ^a.

Entry	Catalyst	Yield (%) ^b	ee (%) ^c	Config. ^d
1	<i>e</i> QN-7a	21	81	<i>R</i>
2	<i>e</i> QN-7b	16	70	<i>R</i>
3	<i>e</i> QN-7c	26	95	<i>R</i>
4	<i>e</i> CD-7d	25	91	<i>R</i>
5	<i>e</i> DHQN-7e	46	95	<i>R</i>
6	<i>e</i> QD-7f	22	87	<i>S</i>
7	<i>e</i> DHQD-7g	36	86	<i>S</i>
8	<i>e</i> QN-12a	24	89	<i>R</i>

^a The reaction was carried out on a 0.5 mmol scale of **13** and 3.0 equiv. of nitromethane in toluene (0.3 mL), 10 mol% of catalyst in capped ampoules at rt for four days. ^b Isolated product yield. ^c Determined by chiral-phase HPLC using an AD-H column. ^d Determined by comparison with available literature HPLC data [43].

To directly compare the catalytic utility of sulfur and selenium catalyst counterparts, the sulfur analog **12a** (Figure 1) of the most potent selenourea catalyst **7c** was synthesized (copies of NMR and IR spectra are gathered in Supplementary Materials). When thiourea **12a** was tested a similar result was observed, with slightly lower enantioselectivity (Table 1, entry 8).

All used selenoureas **7a–g** decomposed under the reaction conditions to corresponding carbodiimides (noticeable precipitation of black selenium).

Based on the experimental results and the previous mechanism studies reported by Pedrosa and coworkers [44], a plausible transition state model for the Michael reactions of chalcone **13** and nitromethane catalyzed by **7c** was proposed (Figure 2). In the transition state, the selenourea moiety of the catalyst activates nitromethane by hydrogen bonding while the bridgehead nitrogen atom of the quinine unit activates *trans*-chalcone. While in the transition state, a *Re*-face attack is favored, giving the *R*-configured product.

Next, *Cinchona*-derived selenoureas were applied as organocatalysts for promoting the sulfa-Michael reactions of less reactive thioacetic acid to *trans*-chalcones [45]. All selenourea catalysts afforded the product **15** with high yields ranging from 90% to 99% with up to 21% ee under mild reaction conditions (Table 2). Compounds **7c–g**, possessing the 4-fluorophenyl group, were found to be the most potent among probed catalysts. Selenourea **7c** delivered better stereocontrol in the reaction compared to the sulfur counterpart **12a** (Table 2, 21% ee vs. 17% ee, entries 3 and 8). Selenourea catalysts of (8*S*,9*S*) the quinine series **7c–e** offered product **15** under better stereocontrol (Table 2, 17–21% ee, entries 3–5 vs. 12–14% ee, entries 6,7). No noticeable catalyst decomposition was observed under the reaction conditions.

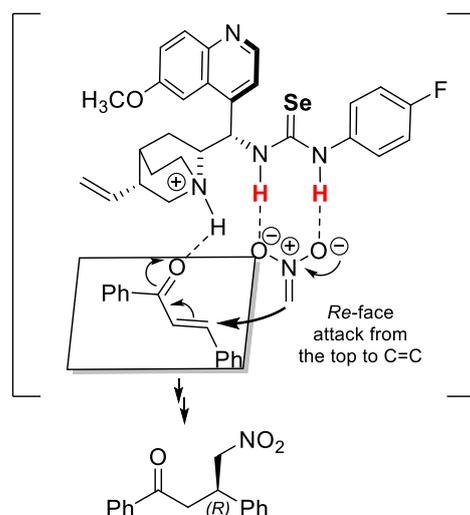


Figure 2. A proposed transition state.

Table 2. Sulfa-Michael addition of thioacetic acid to *trans*-chalcone ^a.

Entry	Catalyst	Yield (%) ^b	ee (%) ^c	Config. ^d
1	<i>e</i> QN-7a	92	13	<i>R</i>
2	<i>e</i> QN-7b	90	3	<i>R</i>
3	<i>e</i> QN-7c	93	21	<i>R</i>
4	<i>e</i> CD-7d	95	17	<i>R</i>
5	<i>e</i> DHQN-7e	99	21	<i>R</i>
6	<i>e</i> QD-7f	94	14	<i>R</i>
7	<i>e</i> DHQD-7g	98	12	<i>R</i>
8	<i>e</i> QN-12a	89	17	<i>R</i>

^a The reaction was carried out using **13** (0.25 mmol) and thioacetic acid (0.5 mmol) in the presence of 10 mol% catalyst in 1.25 mL of Et₂O at rt for 4 h. ^b Isolated yield. ^c Determined by chiral-phase HPLC using an AS-H column. ^d Determined by comparison with available literature HPLC data [45].

The moderate results of conversion (Michael addition) and enantioselectivity (sulfa-Michael addition) indicate that the reaction conditions could be possibly further optimized to improve the catalytic activity of synthesized organocatalysts and to avoid their decomposition (e.g., by altering reaction time and temperature or the used solvent).

3. Conclusions

We have developed a synthetic route to the novel achievement of *Cinchona*-based selenoureas and the strategy for producing dimeric alkaloid selenoureas. To our knowledge, this study represents the first example of a promising application of chiral *Cinchona* alkaloid-derived selenoureas as bifunctional organocatalysts in asymmetric Michael addition reactions. Our preliminary attempts resulted in low to excellent enantioselectivities and yields under mild reaction conditions. Further investigations of the catalytic performance in other asymmetric reactions with this type of bifunctional selenoureas are currently underway in our laboratory.

4. Materials and Methods

4.1. General Information

Solvents were distilled, and other reagents were used as received. Reactions were monitored by thin-layer chromatography (TLC) on silica gel 60 F-254 precoated plates (Merck, Darmstadt, Germany), and spots were visualized with a UV lamp. Products were purified by standard column chromatography on silica gel 60 (230–400 mesh) (Merck). Optical rotations at 578 nm were measured using an Optical Activity Ltd. (Huntington, UK) Model AA-5 automatic polarimeter. Melting points were determined using a Boëtius hot-stage apparatus (PHMK VEB Analytic, Dresden, Germany). ^1H and ^{13}C NMR (600 MHz and 151 MHz, respectively) spectra were recorded in CDCl_3 on Bruker Avance DRX 300 and NMR Bruker Avance II 600 MHz (Bruker, Billerica, MA, USA). IR spectra were measured using the Vertex 70V vacuum FT-IR spectrometer (Bruker Optics, Ettlingen, Germany). High-resolution mass spectra (HRMS) were recorded using electrospray ionization mode on the Waters LCT Premier XE TOF spectrometer (Waters Corporation, Milford, MA, USA). The enantiomeric ratios of the samples were determined by chiral high-performance liquid chromatography (HPLC) measurements (Thermo Fisher Scientific, Waltham, MA, USA) using Chiracel AD-H or Chiralpak AS-H chiral columns. The configuration of the products was assigned by comparison to literature data.

4.2. Preparation of Starting Compounds

The starting *Cinchona* alkaloids (QN, CD, QD, DHQN, DHQD) were commercially available (Buchler GmbH). *Cinchona* alkaloid mesylates were prepared by a standard procedure [26]. 9-Amino-(9-deoxy)-epialkaloids **2a–e** were synthesized according to a general procedure described in the literature [33,34]. Aryl isoselenocyanates **6a–c** were prepared according to the known procedure [35,46,47].

4.3. General Procedure for Selenourea Synthesis

9-Amino-(9-deoxy)-epialkaloid **2** (1.00 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (5.0 mL), and a solution of appropriate aryl isoselenocyanate **6** (1.00 mmol, 1.00 equiv.) in CH_2Cl_2 (1.0 mL) was added. The mixture was stirred for 15 h at rt under argon, in darkness. The solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 10:1) to afford the desired product **7**. The structure of selenoureas **7** were confirmed by spectroscopic methods (IR, ^1H , and ^{13}C NMR) and high-resolution mass spectrometry (data available in Supplementary Materials).

4.3.1. *N*-[(8*S*,9*S*)-6'-Methoxycinchonan-9-yl]-*N'*-Phenylselenourea **eQN-7a**

Yield 85%, pale yellow solid, mp 106–108 °C, $R_f = 0.66$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1). $[\alpha]_{\text{D}}^{23} = -164.5$ (c 0.22, CH_2Cl_2). ^1H NMR (600 MHz, CDCl_3): δ 9.64 (br s, 1H), 8.44 (s, 1H), 7.97 (d, $J = 9.1$ Hz, 1H), 7.88 (br s, 1H), 7.40–7.34 (m, 3H), 7.32–7.27 (m, 1H), 7.25 (d, $J = 7.8$ Hz, 2H), 7.19 (br s, 1H), 6.15 (br s, 1H), 5.63 (dt, $J = 17.2, 8.6$ Hz, 1H), 4.98–4.90 (m, 2H), 3.96 (s, 3H), 3.52–3.38 (m, 1H), 3.29 (br s, 1H), 3.11 (t, $J = 12.1$ Hz, 1H), 2.75 (d, $J = 13.9$ Hz, 1H), 2.71–2.62 (m, 1H), 2.36–2.20 (m, 1H), 1.75–1.65 (m, 2H), 1.64–1.59 (m, 1H), 1.32 (t, $J = 11.7$ Hz, 1H), 0.97 (dd, $J = 14.3, 6.4$ Hz, 1H) ppm. ^{13}C NMR (150 MHz, CDCl_3): δ 179.2, 157.8, 147.5 (2C overlapped), 144.8, 140.5, 137.5, 131.6, 129.6 (2C overlapped), 128.1, 127.2 (2C overlapped), 125.6, 122.0, 119.9, 115.0, 102.7, 61.0, 58.5, 55.8, 55.1, 41.7, 39.1, 27.4, 27.2, 25.5 ppm. IR: 3157, 2930, 2862, 1620, 1589, 1507, 1473, 1431, 1314, 1297, 1259, 1225, 1028, 915, 850, 835, 823, 758, 693 cm^{-1} . HRMS (ESI): m/z calculated for $\text{C}_{27}\text{H}_{31}\text{N}_4\text{O}^{80}\text{Se}$ $[\text{M}+\text{H}]^+$: 507.1663, found: 507.1657.

4.3.2. *N*-[(8*S*,9*S*)-6'-Methoxycinchonan-9-yl]-*N'*-(4-Methoxyphenyl)Selenourea **eQN-7b**

Yield 82%, pale yellow solid, mp 86–88 °C, $R_f = 0.60$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1). $[\alpha]_{\text{D}}^{23} = -219.2$ (c 0.30, CH_2Cl_2). ^1H NMR (600 MHz, CDCl_3): δ 8.72 (br s, 1H), 8.59 (s, 1H), 8.00 (d, $J = 9.0$ Hz, 1H), 7.80 (br s, 1H), 7.37 (d, $J = 9.0$ Hz, 1H), 7.25 (br s, 1H), 7.17 (d, $J = 8.3$ Hz,

2H), 6.91 (d, $J = 8.2$ Hz, 2H), 6.02 (br s, 1H), 5.63 (dt, $J = 17.5, 8.8$ Hz, 1H), 5.00–4.91 (m, 2H), 3.96 (s, 3H), 3.83 (s, 3H), 3.42 (br s, 2H), 3.18 (t, $J = 12.2$ Hz, 1H), 2.74 (br s, 2H), 2.31 (s, 1H), 1.78–1.60 (m, 3H), 1.36 (s, 1H), 1.03 (s, 1H) ppm. ^{13}C NMR (150 MHz, CDCl_3): δ 179.1, 158.7, 157.8, 147.5, 145.3, 144.7, 140.9, 131.5, 130.3, 128.2, 127.8 (2C overlapped), 122.1, 119.7, 114.9, 114.8 (2C overlapped), 102.8, 61.1, 58.4, 55.9, 55.6, 55.2, 41.7, 39.3, 27.7, 27.3, 25.6 ppm. IR: 3237, 2931, 2865, 1621, 1507, 1240, 1227, 1166, 1029, 917, 826, 716, 643 cm^{-1} . HRMS (ESI): m/z calculated for $\text{C}_{28}\text{H}_{33}\text{N}_4\text{O}_2^{80}\text{Se}$ $[\text{M}+\text{H}]^+$: 537.1771, found: 537.1769.

4.3.3. *N*-(4-Fluorophenyl)-*N'*-[(8*S*,9*S*)-6'-Methoxycinchonan-9-yl]Selenourea **eQN-7c**

Yield 86%, pale yellow solid, mp 104–105 °C, $R_f = 0.55$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1). $[\alpha]_D^{23} = -142.5$ (c 0.24, CH_2Cl_2). ^1H NMR (600 MHz, CDCl_3): δ 9.10 (br s, 1H), 8.57 (s, 1H), 8.00 (d, $J = 9.2$ Hz, 1H), 7.80 (br s, 1H), 7.38 (dd, $J = 9.2, 2.6$ Hz, 1H), 7.28–7.17 (m, 3H), 7.07 (t, $J = 8.3$ Hz, 2H), 6.07 (br s, 1H), 5.64 (dq, $J = 17.5, 9.5, 8.4$ Hz, 1H), 5.02–4.93 (m, 2H), 3.97 (s, 3H), 3.43 (br s, 1H), 3.31 (br s, 1H), 3.16 (t, $J = 12.1$ Hz, 1H), 2.73 (br s, 2H), 2.32 (br s, 1H), 1.72 (br s, 2H), 1.66 (br s, 1H), 1.37 (t, $J = 12.3$ Hz, 1H), 1.00 (br s, 1H) ppm. ^{13}C NMR (150 MHz, CDCl_3) δ 179.7, 161.4 (d, $J_{\text{C-F}} = 247.7$ Hz), 158.0, 147.5 (2C overlapped), 144.9, 140.6, 133.7, 131.7, 128.2, 128.1 (2C overlapped), 122.12, 119.7, 116.6 (d, $J_{\text{C-F}} = 22.5$ Hz, 2C overlapped), 115.2, 102.8, 61.1, 55.9, 55.2, 50.8, 41.8, 39.2, 27.6, 27.3, 25.6 ppm. IR: 3169, 2931, 2864, 1620, 1504, 1473, 1320, 1217, 1153, 1029, 916, 830, 643 cm^{-1} . HRMS (ESI): m/z calculated for $\text{C}_{27}\text{H}_{30}\text{N}_4\text{O}^{80}\text{SeF}$ $[\text{M}+\text{H}]^+$: 525.1570, found: 525.1578.

4.3.4. *N*-[(8*S*,9*S*)-Cinchonan-9-yl]-*N'*-(4-Fluorophenyl)Selenourea **eCD-7d**

Yield 88%, pale yellow solid, mp. 66–68 °C, $R_f = 0.62$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1). $[\alpha]_D^{23} = -173.8$ (c 0.32, CH_2Cl_2). ^1H NMR (600 MHz, CDCl_3): δ 8.93 (s, 1H), 8.78 (s, 1H), 8.47 (s, 1H), 8.13 (d, $J = 8.4$ Hz, 1H), 7.73 (ddd, $J = 8.4, 6.8, 1.2$ Hz, 1H), 7.64 (dd, $J = 9.7, 5.5$ Hz, 1H), 7.35 (s, 1H), 7.30–7.21 (m, 2H), 7.09 (t, $J = 8.3$ Hz, 2H), 6.06 (s, 1H), 5.61 (dq, $J = 17.8, 8.9, 7.3$ Hz, 1H), 5.07–4.82 (m, 2H), 3.42 (m, 2H), 3.26–3.11 (m, 1H), 2.77 (s, 2H), 2.34 (s, 1H), 1.74 (m, 3H), 1.35 (t, $J = 11.9$ Hz, 1H), 1.07 (s, 1H) ppm. ^{13}C NMR (150 MHz, CDCl_3): δ 180.0, 161.3 (d, $J_{\text{C-F}} = 247.5$ Hz), 150.0, 148.5, 146.2, 140.2, 133.7, 130.4, 129.4, 127.9 (2C overlapped), 127.0, 126.8, 124.2, 119.7, 116.4 (d, $J_{\text{C-F}} = 22.9$ Hz, 2C overlapped), 115.2, 61.2, 58.3, 54.9, 41.5, 38.9, 27.2, 27.1, 25.1 ppm. IR: 3168, 2938, 2864, 1589, 1504, 1320, 1289, 1214, 914, 831, 797, 752, 639 cm^{-1} . HRMS (ESI): m/z calculated for $\text{C}_{26}\text{H}_{28}\text{N}_4^{80}\text{SeF}$ $[\text{M}+\text{H}]^+$: 495.1463, found: 495.1463.

4.3.5. *N*-[4-Fluorophenyl]-*N'*-[(8*S*,9*S*)-10,11-Dihydro-6'-Methoxycinchonan-9-yl]Selenourea **eDHQN-7e**

Yield 85%, pale yellow solid, mp 62–64 °C, $R_f = 0.54$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1). $[\alpha]_D^{23} = -165.7$ (c 0.14, CH_2Cl_2). ^1H NMR (600 MHz, CDCl_3): δ 8.88 (br s, 1H), 8.71 (s, 1H), 8.03 (d, $J = 9.2$ Hz, 1H), 7.89 (br s, 1H), 7.40 (dd, $J = 9.1, 2.7$ Hz, 2H), 7.30 (d, $J = 7.0$ Hz, 2H), 7.05 (t, $J = 8.3$ Hz, 2H), 6.32 (s, 1H), 3.99 (s, 3H), 3.64 (s, 1H), 3.32 (s, 1H), 2.89 (s, 1H), 2.60 (s, 1H), 2.20 (d, $J = 10.4$ Hz, 1H), 1.77 (br m, 4H), 1.45 (s, 1H), 1.24 (q, $J = 7.9$ Hz, 2H), 1.13 (s, 1H), 0.81 (t, $J = 7.3$ Hz, 3H) ppm. (150 MHz, CDCl_3): δ 180.0, 161.2 (d, $J_{\text{C-F}} = 247.6$ Hz), 158.0, 147.5, 144.8, 144.5, 133.9, 131.6, 127.9 (3C overlapped), 122.1, 119.9, 116.3 (d, $J_{\text{C-F}} = 23.2$ Hz, 2C overlapped), 102.7, 60.9, 56.6, 55.9, 50.7, 41.9, 36.6, 27.6, 27.0, 25.1, 24.9, 11.8 ppm. IR: 3167, 2929, 2864, 1621, 1505, 1473, 1315, 1218, 1029, 917, 829, 715, 644 cm^{-1} . HRMS (ESI): m/z calculated for $\text{C}_{27}\text{H}_{32}\text{N}_4\text{O}^{80}\text{SeF}$ $[\text{M}+\text{H}]^+$: 527.1727, found: 527.1732.

4.3.6. *N*-(4-Fluorophenyl)-*N'*-[(8*R*,9*R*)-6'-Methoxycinchonan-9-yl]Selenourea **eQD-7f**

Yield 81%, pale yellow solid, mp 71–73 °C, $R_f = 0.43$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1). $[\alpha]_D^{23} = +331.1$ (c 0.18, CH_2Cl_2). ^1H NMR (600 MHz, CDCl_3): δ 9.04 (br s, 1H), 8.63 (s, 1H), 8.00 (d, $J = 9.5$ Hz, 1H), 7.77 (br s, 1H), 7.45–7.19 (m, 4H), 7.07 (t, $J = 8.3$ Hz, 2H), 6.17 (s, 1H), 5.90 (dq, $J = 16.3, 5.9$ Hz, 1H), 5.23 (m, 2H), 3.97 (s, 3H), 3.31 (s, 2H), 3.18–2.75 (m, 4H), 2.49–2.24 (m, 1H), 1.58 (m, 2H), 1.36 (s, 1H), 1.03 (s, 1H) ppm. ^{13}C NMR (150 MHz, CDCl_3): δ 180.1, 161.3 (d, $J_{\text{C-F}} = 247.0$ Hz), 158.1, 147.5 (2C), 144.9, 139.5, 133.8, 131.7, 128.1, 127.8

(2C overlapped), 122.6, 119.6, 116.4 (d, $J_{C-F} = 23.3$ Hz, 2C overlapped), 115.7, 102.4, 61.3, 55.9, 50.9, 48.8, 47.4, 38.7, 27.2, 26.0, 25.1 ppm. IR: 3169, 2934, 2868, 1620, 1589, 1505, 1473, 1323, 1310, 1319, 1028, 917, 849, 827, 795, 715 cm^{-1} . HRMS (ESI): m/z calculated for $\text{C}_{27}\text{H}_{30}\text{N}_4\text{O}^{80}\text{SeF}$ $[\text{M}+\text{H}]^+$: 525.1570, found: 525.1575.

4.3.7. *N*-[4-Fluorophenyl]-*N'*-[(8*R*,9*R*)-10,11-Dihydro-6'-Methoxycinchonan-9-yl]Selenourea *e*DHQD-7g

Yield 78%, pale yellow solid, mp 88–90 °C, $R_f = 0.40$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1). $[\alpha]_{\text{D}}^{23} = +142.5$ (c 0.24, CH_2Cl_2). ^1H NMR (600 MHz, CDCl_3): δ 9.03 (br s, 1H), 8.70 (s, 1H), 8.02 (d, $J = 9.2$ Hz, 1H), 7.89 (br s, 1H), 7.40 (d, $J = 11.1$ Hz, 2H), 7.38–7.30 (m, 2H), 7.04 (t, $J = 8.5$ Hz, 2H), 6.40 (s, 1H), 3.97 (s, 3H), 3.71–3.45 (m, 1H), 3.13 (br m, 3H), 3.03–2.86 (m, 1H), 1.88–1.34 (m, 7H), 1.09 (s, 1H), 0.94 (s, 3H) ppm. ^{13}C NMR (150 MHz, CDCl_3): δ 180.2, 161.1 (d, $J_{C-F} = 245.5$ Hz), 158.0, 147.5, 144.8, 144.2, 133.8, 131.7, 128.0, 127.6 (2C overlapped), 122.4, 119.9, 116.2 (d, $J_{C-F} = 21.7$ Hz, 2C overlapped), 102.3, 61.2, 55.7, 49.5, 48.7, 36.8, 35.0, 26.2, 25.9, 25.3, 24.6, 11.9 ppm. IR: 3181, 2931, 2867, 1621, 1505, 1473, 1322, 1219, 1153, 1029, 848, 829, 715 cm^{-1} . HRMS (ESI): m/z calculated for $\text{C}_{27}\text{H}_{32}\text{N}_4\text{O}^{80}\text{SeF}$ $[\text{M}+\text{H}]^+$: 527.1727, found: 527.1735.

4.4. Preparation of *N*-[(8*S*,9*S*)-6'-Methoxycinchonan-9-yl]Formamide **8a**

Amine **2a** (0.323 g, 1.00 mmol) was placed in a Teflon-capped ampoule and dissolved in an excess of methyl formate (4.00 mL). The mixture was heated to 45 °C for 48 h. The solvent was removed in vacuo, yielding compound **8a** as a solidifying oil quantitatively (0.352 g), pale yellow solid, $R_f = 0.25$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1). $[\alpha]_{\text{D}}^{23} = +32.5^\circ$ (c 0.20, CH_2Cl_2). ^1H NMR (600 MHz, CDCl_3): δ 8.73 (dd, $J = 4.6, 1.8$ Hz, 1H), 8.20 (s, 1H), 8.02 (dd, $J = 9.2, 1.9$ Hz, 1H), 7.63 (s, 1H), 7.39 (dt, $J = 9.2, 2.3$ Hz, 1H), 7.33 (d, $J = 4.6$ Hz, 1H), 5.75 (dt, $J = 17.6, 9.0$ Hz, 1H), 5.50 (s, 1H), 5.06–4.97 (m, 2H), 3.98 (s, 4H), 3.36–3.18 (m, 3H), 2.85–2.71 (m, 2H), 2.35 (d, $J = 7.9$ Hz, 2H), 1.72 (q, $J = 3.0$ Hz, 1H), 1.65 (t, $J = 8.1$ Hz, 2H), 1.55 (t, $J = 12.0$ Hz, 1H), 0.94 (dd, $J = 14.5, 6.2$ Hz, 1H) ppm. ^{13}C NMR (150 MHz, CDCl_3): δ 161.0, 158.1, 147.5, 144.9, 144.1, 141.1, 131.8, 128.3, 122.0, 119.1, 114.9, 101.9, 59.5, 56.1, 55.8, 49.6, 41.1, 39.4, 27.7, 27.4, 26.5 ppm. IR: 3226, 3073, 2937, 2864, 1938, 1672, 1621, 1591, 1475, 1434, 1383, 1365, 1229, 1028, 916, 852, 828, 714, 678, 636, 616 cm^{-1} . HRMS (ESI): m/z calculated for $\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 352.2021, found: 352.2025.

4.5. Preparation of *N,N'*-bis[(8*S*,9*S*)-6'-Methoxycinchonan-9-yl]Selenourea **10a**

9*S*-Amino-9-deoxyquinine **2a** (0.324 g, 1.00 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (6 mL) and 25% aqueous solution of NaOH (3 mL), triethylbenzylammonium chloride (TEBAC) (68.5 mg, 0.30 mmol, 30.0 mol%) and CHCl_3 (0.239 g, 160 μL , 2.00 mmol, 2.00 equivalents) were added. The mixture was stirred for 24 h at rt and water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3×15 mL). The combined organic phases were dried over Na_2SO_4 and evaporated. The residue was dissolved in CH_2Cl_2 (10 mL) and selenium (0.158 g, 2.00 mmol, 2.00 equivalents) was added and the solution was stirred overnight under argon. The solvent was removed in vacuo and the residue was purified by chromatography in the dark (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1 \rightarrow MeOH) to afford 0.136 g (37%) of dimeric selenourea **10a** as a pale yellow oil, $R_f = 0.05$ ($\text{CH}_2\text{Cl}_2:\text{MeOH}$ 10:1), $[\alpha]_{\text{D}}^{23} = -130.5^\circ$ (c 0.11, CH_2Cl_2). ^1H NMR (600 MHz, CDCl_3): δ 8.78 (br s, 1H), 8.67 (br s, 1H), 8.12 (br s, 1H), 7.97 (d, $J = 9.1$ Hz, 1H), 7.49 (br s, 1H), 7.40–7.32 (m, 1H), 6.48 (br s, 1H), 5.58 (br s, 1H), 4.90 (br s, 2H), 3.88 (s, 3H), 3.18 (br s, 1H), 2.90 (br s, 2H), 2.41 (s, 1H), 2.31 (s, 1H), 2.17 (s, 1H), 1.76 (s, 1H), 1.51 (br m, 2H), 1.38 (s, 1H), 0.73 (s, 1H) ppm. IR (KBr): 3250, 2931, 1867, 1621, 1590, 1508, 1473, 1449, 1316, 1261, 1227, 1029, 917, 850, 758, 693, 494 cm^{-1} . HRMS (ESI): m/z calculated for $\text{C}_{41}\text{H}_{49}\text{N}_6\text{O}_2^{80}\text{Se}$ $[\text{M}+\text{H}]^+$: 737.3087, found: 737.3089. ^{13}C NMR spectrum could not be obtained due to fast decomposition of the compound in solutions.

4.6. Preparation of *N*-(4-Fluorophenyl)-*N'*-[(8*S*,9*S*)-6'-Methoxycinchonan-9-yl]Thiourea **eQN-12a**

To the stirred solution of 9*S*-amino-9-deoxyquinine **2a** (0.323 g, 1.00 mmol) in CH₂Cl₂ (5 mL) was added dropwise a solution of 4-fluorophenyl isoselenocyanate **6c** (0.153 g, 1.00 mmol) in CH₂Cl₂ (1.00 mL) under nitrogen atmosphere. The resulting mixture was stirred for 15 h. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (CH₂Cl₂/MeOH 10:1) to afford thiourea **0.286 g** (60%) of compound **12** as pale yellow solid, mp 108–110 °C, *R_f* = 0.45 (CH₂Cl₂/MeOH 10:1). $[\alpha]_D^{23} = -160.8$ (c 0.24, CH₂Cl₂). ¹H NMR (600 MHz, CDCl₃): δ 8.88 (br s, 1H), 8.63 (d, *J* = 4.5 Hz, 1H), 8.18 (br s, 1H), 8.00 (d, *J* = 9.2 Hz, 1H), 7.81 (br s, 1H), 7.38 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.34 (d, *J* = 4.5 Hz, 1H), 7.28–7.23 (m, 2H), 7.03 (t, *J* = 8.5 Hz, 2H), 6.10 (br s, 1H), 5.61 (ddd, *J* = 17.3, 10.2, 7.1 Hz, 1H), 5.04–4.94 (m, 2H), 3.96 (s, 3H), 3.56 (br s, 1H), 3.48 (br s, 1H), 3.24 (dd, *J* = 13.8, 10.2 Hz, 1H), 2.82 (td, *J* = 13.2, 11.5, 5.3 Hz, 2H), 2.38 (d, *J* = 8.6 Hz, 1H), 1.88–1.66 (m, 3H), 1.44 (ddt, *J* = 13.5, 10.2, 3.3 Hz, 1H), 1.02 (dd, *J* = 14.4, 6.2 Hz, 1H) ppm. ¹³C NMR (150 MHz, CDCl₃): δ 181.2, 160.9 (d, *J* = 246.6 Hz), 158.1, 147.6, 144.8, 144.2, 139.6, 134.0, 131.6, 128.2, 127.3, 122.2, 119.8, 116.1 (d, *J* = 22.6 Hz), 115.7, 102.5, 60.8, 55.9, 55.0, 50.6, 41.9, 38.6, 27.1, 26.8, 25.3 ppm. IR: 3265, 2932, 2879, 1621, 1505, 1473, 1331, 1218, 1029, 990, 917, 831, 716, 551, 507, 452 cm⁻¹. HRMS (ESI): *m/z* calculated for C₂₇H₃₀N₄OSF [M+H]⁺: 477.2124, found: 477.2120.

4.7. General Procedure for the Michael Addition of Nitromethane to *Trans*-Chalcones

Trans-chalcone **13** (0.104 g, 0.50 mmol, 1.00 equivalent) and the respective catalyst (10.0 mol%) were loaded to an ampoule. Next, toluene (0.30 mL) was added and the mixture was stirred for 10 min under argon. Then, nitromethane (91.6 mg, 80.5 μL, 1.50 mmol, 3.00 equivalents) was added by syringe and the reaction was further stirred for 96 h at room temperature. The reaction mixture was directly purified by chromatography (silica gel, hexane/EtOAc 3:1) to afford respective Michael adduct **14**. The enantiomeric excess was determined by HPLC (Chiralcel AD-H column, hexane/*i*-PrOH 9:1, flow rate 1.0 mL/min, λ = 254 nm); *t*_(S) = 14.7 min, *t*_(R) = 20.5 min. The spectral and HPLC data (Supplementary Materials, Figures S21–S29) were in agreement with the reported values [43].

4.8. General Procedure for the Sulfa-Michael Addition of Thioacetic Acid to *Trans*-Chalcone

A reaction tube was loaded with the respective catalyst (10.0 mol%), *trans*-chalcone **13** (52.1 mg, 0.25 mmol, 1.00 equivalent), and diethyl ether (1.25 mL) under argon. After 10 min stirring at rt, thioacetic acid (38.1 mg, 35.2 μL 0.50 mmol, 2.00 equivalents) was added by syringe, and the stirring was continued for 4 h at rt. The reaction mixture was directly purified by chromatography (silica gel, hexane/EtOAc 3:1) to afford respective Michael adduct **15**. Enantiomeric excess values were determined by chiral HPLC (Chiralcel AS-H column, hexane/*i*-PrOH 9:1, flow rate 1.0 mL/min, λ = 254 nm); *t*_(R) = 9.7 min, *t*_(S) = 15.0 min. The spectral and HPLC data (Supplementary Materials, Figures S30–S38) were in agreement with the reported values [44].

Supplementary Materials: The following are available online at <https://www.mdpi.com/1996-1944/14/3/600/s1>. Figure S1. ¹H and ¹³C NMR spectra of *N*-[(8*S*,9*S*)-6'-methoxycinchonan-9-yl]-*N'*-phenylselenourea **eQN-7a**, Figure S2. IR spectra of *N*-[(8*S*,9*S*)-6'-methoxycinchonan-9-yl]-*N'*-phenylselenourea **eQN-7a**, Figure S3. ¹H and ¹³C NMR spectra of *N*-[(8*S*,9*S*)-6'-methoxycinchonan-9-yl]-*N'*-[4-methoxyphenyl]selenourea **eQN-7b**, Figure S4. IR spectra of *N*-[(8*S*,9*S*)-6'-methoxycinchonan-9-yl]-*N'*-[4-methoxyphenyl]selenourea **eQN-7b**, Figure S5. ¹H and ¹³C NMR spectra of *N*-[4-fluorophenyl]-*N'*-[(8*S*,9*S*)-6'-methoxycinchonan-9-yl]selenourea **eQN-7c**, Figure S6. IR spectra of *N*-[4-fluorophenyl]-*N'*-[(8*S*,9*S*)-6'-methoxycinchonan-9-yl]selenourea **eQN-7c**, Figure S7. ¹H and ¹³C NMR spectra of *N*-[4-fluorophenyl]-*N'*-[(8*S*,9*S*)-cinchon-9-yl]selenourea **eCD-7d**, Figure S8. IR spectra of *N*-[4-fluorophenyl]-*N'*-[(8*S*,9*S*)-cinchon-9-yl]selenourea **eCD-7d**, Figure S9. ¹H and ¹³C NMR spectra of *N*-[4-fluorophenyl]-*N'*-[(8*S*,9*S*)-10,11-dihydro-6'-methoxycinchonan-9-yl]selenourea **eDHQN-7e**, Figure S10. IR spectra of *N*-[4-fluorophenyl]-*N'*-[(8*S*,9*S*)-10,11-dihydro-6'-methoxycinchonan-9-yl]selenourea **eDHQN-7e**, Figure S11. ¹H and ¹³C NMR spectra of *N*-[4-fluorophenyl]-*N'*-[(8*R*,9*R*)-

6'-methoxycinchonan-9-yl]selenourea eQD-7f, Figure S12. IR spectra of *N*-[4-fluorophenyl]-*N'*-[(8*R*,9*R*)-6'-methoxycinchonan-9-yl]selenourea eQD-7f, Figure S13. ¹H and ¹³C NMR spectra of *N*-[4-fluorophenyl]-*N'*-[(8*R*,9*R*)-10,11-dihydro-6'-methoxycinchonan-9-yl]selenourea eDHQD-7g, Figure S14. IR spectra of *N*-[4-fluorophenyl]-*N'*-[(8*R*,9*R*)-10,11-dihydro-6'-methoxycinchonan-9-yl]selenourea eDHQD-7g, Figure S15. ¹H and ¹³C NMR spectra of *N*-[(8*S*,9*S*)-6'-methoxycinchonan-9-yl]formamide 8a, Figure S16. IR spectra of *N*-[(8*S*,9*S*)-6'-methoxycinchonan-9-yl]formamide 8a, Figure S17. ¹H NMR spectra of *N,N'*-bis[(8*S*,9*S*)-6'-methoxycinchonan-9-yl]selenourea 10a, Figure S18. IR spectra of *N,N'*-bis[(8*S*,9*S*)-6'-methoxycinchonan-9-yl]selenourea 10a, Figure S19. ¹H and ¹³C NMR spectra of *N*-[4-fluorophenyl]-*N'*-[(8*S*,9*S*)-6'-methoxycinchonan-9-yl]thiourea eQN-12a, Figure S20. IR spectra of *N*-[4-fluorophenyl]-*N'*-[(8*S*,9*S*)-6'-methoxycinchonan-9-yl]thiourea eQN-12a, Figure S21. HPLC chromatogram for 14: sample obtained with catalyst eQN-7a, Figure S22. HPLC chromatogram for 14: sample obtained with catalyst eQN-7b, Figure S23. HPLC chromatogram for 14: sample obtained with catalyst eQN-7c, Figure S24. HPLC chromatogram for 14: sample obtained with catalyst eCD-7d, Figure S25. HPLC chromatogram for 14: sample obtained with catalyst eDHQN-7e, Figure S26. HPLC chromatogram for 14: sample obtained with catalyst eQD-7f, Figure S27. HPLC chromatogram for 14: sample obtained with catalyst eDHQD-7g, Figure S28. HPLC chromatogram for 14: sample obtained with catalyst eQN-12a, Figure S29. HPLC chromatogram for racemic 14 without catalyst 7, Figure S30. HPLC chromatogram for 15: sample obtained with catalyst eQN-7a, Figure S31. HPLC chromatogram for 15: sample obtained with catalyst eQN-7b, Figure S32. HPLC chromatogram for 15: sample obtained with catalyst eQN-7c, Figure S33. HPLC chromatogram for 15: sample obtained with catalyst eCD-7d, Figure S34. HPLC chromatogram for 15: sample obtained with catalyst eDHQN-7e, Figure S35. HPLC chromatogram for 15: sample obtained with catalyst eQD-7f, Figure S36. HPLC chromatogram for 15: sample obtained with catalyst eDHQD-7g, Figure S37. HPLC chromatogram for 15: sample obtained with catalyst eQN-12a, Figure S38. HPLC chromatogram for racemic 15 without catalyst 7.

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