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New chiral thiols and C_2-symmetrical disulfides of *Cinchona* alkaloids: ligands for the asymmetric Henry reaction catalyzed by Cu^{II} complexes

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ABSTRACT

Seven *Cinchona* alkaloids were reacted with thioacetic acid and Bu_3P/diethyl diazadicarboxylate in THF at 0–25 °C to give the corresponding thiolacetates with complete inversion of configuration at the substitution center. The thus obtained chiral thiolesters were converted into thiols and these compounds were oxidized to the respective disulfides of C_2-symmetry. Both C-9 thioles and disulfides were tested as chiral ligands in the Cu-catalyzed asymmetric Henry reaction. When the thiol derivatives of an 8,9-*like* configuration were applied in the reaction of benzaldehyde and nitromethane, the obtained nitroaldol was of the same absolute configuration as the catalyst and the observed enantioselectivity was up to 83% ee. These ligands gave higher ees than the corresponding thioethers, disulfides, and thioles of 8,9-*unlike* configuration. The results obtained are in agreement with the proposed transition-state model involving nucleophilic attack of a deprotonated nitromethane directed preferably at one side of the O-complexed benzaldehyde.

1. Introduction

The most noteworthy achievements in asymmetric synthesis can be ascribed to the application of *privileged catalysts*, effective in numerous mechanistically different, enantioselective transformations.[1] Among these successful catalysts are derivatives of *Cinchona* alkaloids. In some cases, the C_2-symmetry of such chiral ligands plays an important role in their effectiveness, as is well documented for the Sharpless dihydroxylations, Michael additions, and other asymmetric processes.[2] Recently, we have synthesized a series of 9-phenylsulfenyl- and 9-phenylselenyl-derivatives of *Cinchona* alkaloids and demonstrated their catalytic performance in the enantioselective Tsuji-Trost allylic alkylation.[3] Both types of derivatives constitute chiral bifunctional chalcogen/nitrogen-donating ligands. The ligands of this sort have been successfully used in various transition-metal catalyzed stereoselective reactions.[4] However, their chiral complexes with copper have hardly been tested[5] and their use as S/N-donating ligands in the enantioselective copper-catalyzed nitroaldol (Henry) reaction have not yet been described. Moreover, only a few derivatives of *Cinchona* alkaloids have already been described as catalysts for the asymmetric Henry reaction.[6]

Herein we report the synthesis of unknown *Cinchona* alkaloid C-9 thiols, which were subsequently oxidized to the corresponding dimeric disulfides of C_2 symmetry. We examined both thiols and disulfides as prospective chiral ligands in the Cu(II) catalyzed nitroaldol reaction.[7]

2. Results and discussion

2.1. Ligands synthesis

Commercially available *Cinchona* alkaloids, namely cinchonidine (CD), quinine (QN), and quinidine (QD), the respective dihydro derivatives (DHQN/DHQD), and their synthetic C-9-*epi*-configured analogues (*epi*-QN/*epi*-QD)[9] were used as starting materials (Fig. 1). In order to transform these secondary alcohols into thiols we attempted the nucleophilic substitution of the corresponding mesylates with thiocyanate, thiourea, or thioacetate sodium salt. All these efforts failed and finally, the native and *epi*-alkaloids **1a–g** were directly converted into the corresponding thiolesters **2a–g** using a Mitsunobu reaction.[8] The mixtures of **1a–g** and thioacetic acid were treated with the preformed adduct of Ph_3P and DEAD in THF at 0 °C and then left at room temperature for 3–7 days. The resulting thioacetates **2a–g** were isolated by chromatography in 42–59% yield along with the recovered alkaloids (ca. 20–30%) and a small amount of unidentified compounds with the rearranged alkaloid skeleton. In all cases the thiolesters were obtained as a single diastereomer and inversion of configuration at the stereogenic center C-9 of alkaloids was observed. The results are summarized in Scheme 1 and Table 1.

In the next step, we reduced the thiolesters obtained with lithium aluminum hydride to obtain the required thiols **3a–g** in

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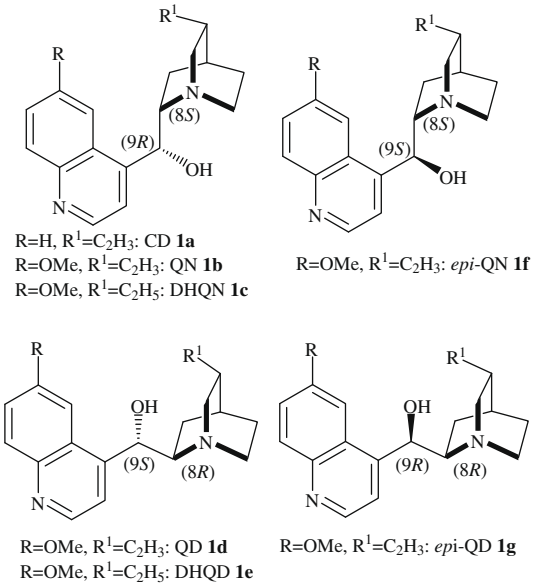


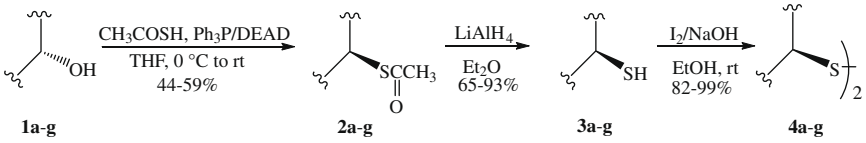
Figure 1. The structure of *Cinchona* alkaloids.

excellent chemical yields (up to 93%). These products were easily oxidized by iodine in ethanol to give the corresponding disulfides of *Cinchona* alkaloids **4a–g** (80–99%) (Table 2). Compounds **4** are clearly C_2-symmetric, as shown by their NMR spectra, which resemble those of the corresponding thiols. Simultaneously, smaller values of the specific rotation were recorded for disulfides than for the parent thiols. As expected, the shelf-life of the thiols was rather limited. The more stable disulfides can be regarded as their 'protected derivatives', and could be regenerated to the appropriate pure thiols with LAH.

2.2. Catalytic asymmetric Henry reaction

With the aforementioned set of chiral thiols and disulfides in hand, we examined their catalytic performance in the nitroaldol reaction. The model reaction between benzaldehyde and nitromethane was carried out in the presence of 12 mol % of chiral ligand and 10 mol % of hydrated copper acetate (Scheme 2). The screening experiments are summarized in Table 3. We tested a series of solvents (dichloromethane, acetonitrile, isopropanol, etc.) and *i*-PrOH was chosen as the most appropriate one. Moreover, we noted that in the absence of a ligand, the expected nitroaldol product did not form at all. Thus, all the ligands formed complexes that catalyzed the reaction giving nitroaldol in good yield. Generally, higher enantioselectivities were obtained for the thiols of 8,9-*like* configuration [e.g., (8*S*,9*S*)] **3a–d** (43– 83% ee) in comparison to the respective disulfides **4a–d** (34–52% ee). However, the thiols of 8,9-*unlike* configuration, obtained from *epi*-quinine **3f** and *epi*-quinidine **3g** performed worse (14% and 17% ee, respectively). The best result was observed for **3b** (9-HS-*epi*-QN) in *i*-PrOH (70% yield and 83% ee), while for dichloromethane or acetonitrile, the yield and selectivity were significantly less (13–18%, 43–44% ee). Moreover, the addition of 5 mol % of Et_3N lowered the enantioselectivity from 83% to 28%. We tested the reaction of cyclohexanecarboxaldehyde with nitromethane which gave the corresponding Henry product in 64% yield and 75% ee. For comparison the thioether available from the earlier study (9-PhS-*epi*-QN)[3] was also tested (Table 3, entry 13).

The encouraging results obtained for the addition of nitromethane prompted us to extend this reaction to other nitroalkanes. Thus the reaction of nitroethane with benzaldehyde as carried out before in the presence of **3b**/$Cu(OAc)_2$ at 0 °C mainly gave the *syn*-product in 76% ee. Lowering the temperature to −20 °C led to an improvement in both diastereo- and enantioselectivity (Table 4). Furthermore, the addition of bulkier 2-phenylnitroethane to benz-



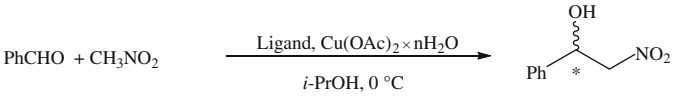
Scheme 1.

Table 1
Synthesis of thiolacetates **2**

Entry	Alkaloid **1**	Config.	Thiolester **2**	Yield (%)	$[\alpha]_D$ (CH_2Cl_2)	Config.
1	CD **1a**	(8*S*,9*R*)	9-CH_3COS-*epi*-CD **2a**	59	−21.8	(8*S*,9*S*)
2	QN **1b**	(8*S*,9*R*)	9-CH_3COS-*epi*-QN **2c**	43	−11.0	(8*S*,9*S*)
3	DHQN **1c**	(8*S*,9*R*)	9-CH_3COS-*epi*-DHQN **2c**	53	−14.2	(8*S*,9*S*)
4	QD **1d**	(8*R*,9*S*)	9-CH_3COS-*epi*-QD **2d**	42	+87.0	(8*R*,9*R*)
5	DHQD **1e**	(8*R*,9*S*)	9-CH_3COS-*epi*-DHQD **2e**	44	+62.5	(8*R*,9*R*)
6	*epi*-QN **1f**	(8*S*,9*S*)	9-CH_3COS-QN **2f**	49	+38.1	(8*S*,9*R*)
7	*epi*-QD **1g**	(8*R*,9*R*)	9-CH_3COS-QD **2g**	44	+64.9	(8*R*,9*S*)

Table 2
Synthesis of thiols **3** and disulfides **4**

Entry	Thiol **3**	Yield (%)	$[\alpha]_D$ (CH_2Cl_2)	Disulfides **4**	Yield (%)	$[\alpha]_D$ (CH_2Cl_2)	Config.
1	**3a**	73	−58.1	9-*epi*-CD-S-)$_2$ **4a**	90	−35.0	(8*S*,9*S*)
2	**3b**	80	−72.8	9-*epi*-QN-S-)$_2$ **4b**	99	−25.8	(8*S*,9*S*)
3	**3c**	84	−46.0	9-*epi*-DHQN-S-)$_2$ **4c**	98	−9.1	(8*S*,9*S*)
4	**3d**	93	+148.9	9-*epi*-QD-S-)$_2$ **4d**	96	+94.1	(8*R*,9*R*)
5	**3e**	77	+141.4	9-*epi*-DHQD-S-)$_2$ **4e**	88	+46.8	(8*R*,9*R*)
6	**3f**	93	+23.7	9-QN-S-)$_2$ **4f**	98	+15.4	(8*S*,9*R*)
7	**3g**	65	+106.0	9-QD-S-)$_2$ **4g**	82	+73.0	(8*R*,9*S*)



Scheme 2.

Table 3
Nitroaldol reaction of benzaldehyde and nitromethane catalyzed by ligand/$Cu(OAc)_2$[a]

Entry	Ligand	Yield (%)	ee[b] (%) abs. config.[c]
1	9-HS-*epi*-CD **3a**	93	55 (*S*)
2	9-HS-*epi*-QN **3b**	70	83 (*S*)
3	9-HS-*epi*-QN **3b**	64[f]	75 (*S*)[f]
4	9-HS-*epi*-QN **3b**[d]	13	43 (*S*)
5	9-HS-*epi*-QN **3b**[e]	18	44 (*S*)
6	9-HS-*epi*-DHQN **3c**	43	54 (*S*)
7	9-HS-*epi*-QD **3d**	48	44 (*R*)
8	9-HS-QN **3f**	63	14 (*S*)
9	9-HS-QD **3g**	51	17 (*R*)
10	9-*epi*-CD-S-)$_2$ **4a**	72	47 (*S*)
11	9-*epi*-QN-S-)$_2$ **4b**	80	52 (*S*)
12	9-*epi*-QD-S-)$_2$ **4d**	79	34 (*R*)
13	9-PhS-*epi*-QN	99	18 (*R*)

[a] The reactions were carried out on a 0.5 mmol scale, 12 mol % of respective ligand, 10 mol % of $Cu(OAc)_2 \cdot H_2O$, 10 equiv of CH_3NO_2 in *i*-PrOH (2 mL) at 0 °C for 3 days.
[b] Enantiomeric excess determined by HPLC analysis.
[c] Determined by comparison of the specific rotation value and retention time (chiral HPLC) with literature values.
[d] Reaction was performed in MeCN.
[e] Reaction was performed in CH_2Cl_2.
[f] The reaction of cyclohexanecarboxaldehyde with nitromethane.

Table 4
Henry reaction of benzaldehyde and nitroalkanes catalyzed by **3b**/$Cu(OAc)_2$[a]

Entry	R	*T* (°C)	Yield[b] (%)	*syn*/*anti*[c]	ee [*syn*](%)[d,e]	ee [*anti*](%)[d,e]
1	Me	0	98	65:35	76 (1*S*,2*S*)	37 (1*S*,2*R*)
2	Me	−20	98	71:29	86 (1*S*,2*S*)	50 (1*S*,2*R*)
3	$PhCH_2$	−20	71	43:57	74 (1*S*,2*S*)	61 (1*S*,2*R*)

[a] The reactions were carried out on a 0.5 mmol scale, 12 mol % of respective ligand, 10 mol % of $Cu(OAc)_2 \cdot H_2O$, 10 equiv of CH_3NO_2 in *i*-PrOH (2 mL) for 3 days.
[b] Combined yields of *syn* and *anti* isomers.
[c] Determined by ^1H NMR spectroscopy of the crude product.
[d] Determined by chiral HPLC.
[e] The absolute configurations were established by comparison with literature data.

aldehyde afforded both *anti*- and *syn*-products in almost equal amounts, although with similar enantioselectivity.

In agreement with the previously reported transition-state models,[7h,9a,b] we assume that in the Cu(II)·(8*S*,9*S*)-**3b** catalytic complex the carbonyl oxygen atom is coordinated at one of the equatorial positions. As a consequence, deprotonated nitromethane binds its oxygen atom to the metal center from the axial side. This positioning of the reactants seems to be the most favorable orientation when taking into account both steric repulsion and electronic activation. Moreover, it seems that the hydrogen bonds formed by the sulfhydryl group additionally stabilize such a molecular arrangement. This clearly leads to the favored *Re face* attack (Fig. 2), giving the observed (*S*)-product. The absence of a methoxy group in the ligand structure 9-HS-*epi*-CD, (8*S*,9*S*)-**3a** leads to the less-stabilized transition-state and 55% ee only (Table 3, entry 1).

This transition-state model is also in agreement with the observed reversal of the stereochemical outcome of the catalytic reaction for (8*R*,9*R*)-**3d.** For that complex, one may expect a nearly

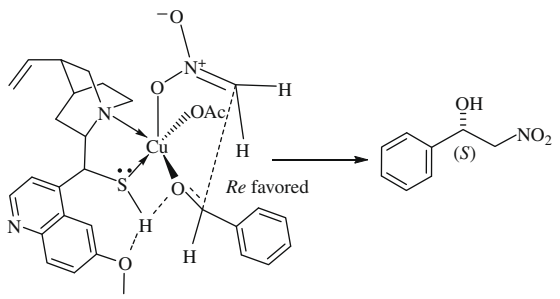


Figure 2. Proposed geometry of the transition-state model for the Cu(II)·(8*S*,9*S*)-**3b** complex.

enantiomeric situation, hence the corresponding positioning of the reactants seems favorable for the nitronate ion approaching benzaldehyde from the *Si face* to give the (*R*)-product, in fact obtained as a main product in this case.

Interestingly, we observed also an opposite stereochemical outcome of the catalytic reaction when instead of 9-HS-*epi*-QN **3b,** the corresponding thioether 9-PhS-*epi*-QN was used (see Table 3, entry 13). In this case, a large phenyl moiety placed instead of the sulfhydryl hydrogen strongly hampers the previously favored orientation. Here, the stereochemical result seems to depend on which of the two free electron pairs of sulfur better coordinate the copper ion, thus stabilizing the respective catalytic complex. The same applies to the reaction catalyzed by C_2-symmetric disulfides. The lowest enantioselectivities observed for the ligands of 8,9-*unlike*-configuration **3f** and **3g** suggest that they form at least two complexes of similar energy, differing in their coordination modes. A similar outcome was previously observed for the Tsuji-Trost reaction catalyzed by the respective phenylsulfenyl *Cinchona* derivatives, namely for 9-PhS-*epi*-QD, 78% ee and for 9-PhS-QD, 12% ee.[3]

Interestingly, the experiments testing the scope of the catalytic Henry reaction (Scheme 3, Table 4) show that other nitronates add to benzaldehyde mainly from the *Re face*, in the fashion depicted in Figure 2, leading to (1*S*)-propanols as the major products. The process is kinetically controlled, so lowering temperature (to −20 °C) increased its selectivity. However, if the observed diastereoselectivity for nitroethane (42% de, *syn*) can be accounted for by the preferred configuration of the corresponding nitronate anion, a loss of diastereoselectivity in the reaction of 2-phenylnitroethane remains unclear.

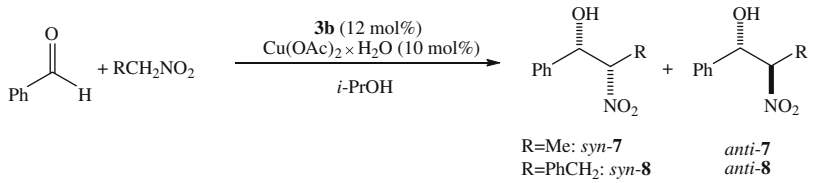
3. Conclusion

In conclusion, we have presented a useful stereospecific synthesis of C-9 thiols and disulfides of *Cinchona* akaloids. The thiols of 8,9-*like* configuration obtained from the native alkaloids were successful chiral ligands in the copper-catalyzed asymmetric nitroaldol reaction. The reaction of benzaldehyde with nitromethane in the presence of 12 mol % of ligand and 10 mol % of $Cu(OAc)_2$ in isopropanol gave the corresponding product in good yield and with up to 83% ee. The reaction stereochemical outcome is in agreement with the generally accepted transition-state model involving coordination of both reacting species to the central metal ion.

4. Experimental

4.1. General

Melting points were determined using a Boetius hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were measured on a Bruker CPX (^1H, 300 MHz) spectrometer using TMS as an internal standard. Optical rotations at 578 nm



Scheme 3.

were measured using an Optical Activity Ltd. Model AA-5 automatic polarimeter. The enantiomeric composition of the nitroaldols was determined by HPLC analysis using a chiral stationary phase (Chiracel OD-H or Daicel Chiralpak AD-H). The absolute configuration was assigned by comparison of the retention time and the sign of the specific rotation with the literature.

Separations of products by chromatography were performed on Silica Gel 60 (230–400 mesh) purchased from Merck. TLC was performed using Silica Gel 60 precoated plates (Merck). All solvents were purified and dried by standard methods. The starting *Cinchona* alkaloids were commercially available, *epi*-quinine and *epi*-quinidine were prepared according to a general procedure described in the literature.[3a]

4.2. General procedure for the synthesis of thiolacetates of cinchona alkaloids 2

To a solution of triphenylphosphine (1.049 g, 4 mmol) in dry THF (10 mL) was added DEAD (0.697 g, 0.622 mL, 04 mmol). The mixture was stirred at 0 °C under an argon atmosphere for 30 min. A yellow precipitate resulted. Then solutions of appropriate alkaloids (2 mmol) in THF (10 mL) and thiolacetic acid (0.304 g, 0.286 mL, 4 mmol) in THF (5 mL) were added for 10 min by a syringe and the mixture was stirred for additional 1 h at 0 °C. Next the mixture was allowed to warm to rt and it was further stirred for 3–7 days. Thereafter a yellow or brown solution was concentrated and then purified by column chromatography on silica gel (first $CHCl_3$/*t*-BuOMe, 1:1, next $CHCl_3$/MeOH, 40:3) gave the products as a yellow or brown oils.

4.2.1. (1*S*,3*R*,4*S*,8*S*,9*S*)-9-Acetylthiocinchonan (9-acetylthio-*epi*-cinchonidine, 9-CH_3COS-*epi*-CD) 2a

Yield 59%, yellow oil; $[\alpha]_D = -21.8$ (*c* 0.87, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49–1.55 (m, 2H), 1.65–1.72 (m, 1H), 1.86–1.90 (m, 2H), 2.11 (s, 3H, SCOMe), 2.25–2.28 (m, 1H), 2.54–2.65 (m, 2H), 2.99–3.13 (m, 2H), 3.39 (q, *J* = 8.0 Hz, 1H), 4.98–5.04 (m, 2H, CH_2=), 5.78–5.89 (m, 1H, CH=), 6.53 (d, *J* = 7.3 Hz, 1H, C^{9}H), 7.39 (d, *J* = 4.5 Hz, 1H, ArH), 7.59 (t, *J* = 8.2 Hz, 1H, ArH), 7.71 (t, *J* = 8.2 Hz, 1H, ArH), 8.13 (d, *J* = 8.5 Hz, 1H, ArH), 8.23 (d, *J* = 8.5 Hz, 1H, ArH), 8.89 (d, *J* = 4.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 24.5, 27.6, 27.8, 39.7, 42.4, 56.6, 59.6, 74.0, 114.5, 118.8, 123.4, 126.0, 126.9, 129.2, 130.5, 141.7, 145.3, 148.6, 150.0, 170.0; IR (film): 2943, 2866, 1747, 1637, 1509, 1453, 1372, 1232, 1024, 914, 758, 666 cm^{-1}. R_f = 0.52 ($CHCl_3$/MeOH, 40:3).

4.2.2. (1*S*,3*R*,4*S*,8*S*,9*S*)-6′-Methoxy-9-acetylthiocinchonan (9-acetylthio-*epi*-quinine, 9-CH_3COS-*epi*-QN) 2b

Yield 43%, yellow oil; $[\alpha]_D = -11.0$ (*c* 0.90, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49–1.61 (m, 2H), 1.68–1.75 (m, 1H), 1.84–1.89 (m, 2H), 2.13 (s, 3H, SCOMe), 2.25–2.28 (m, 1H), 2.57–2.71 (m, 2H), 3.01–3.14 (m, 2H), 3.36 (q, *J* = 8.2 Hz, 1H), 3.96 (s, 3H, OMe), 4.98–5.05 (m, 2H, CH_2=), 5.78–5.90 (m, 1H, CH=), 6.49 (d, *J* = 7.3 Hz, 1H, C^{9}H), 7.36 (d, *J* = 4.4 Hz, 1H, ArH), 7.38 (d, *J* = 2.7 Hz, 1H, ArH), 7.43 (d, *J* = 2.7 Hz, 1H, ArH), 8.01 (d, *J* = 9.2 Hz, 1H, ArH), 8.74 (d, *J* = 4.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 22.1, 23.9, 27.6, 39.5, 42.4, 55.8, 56.4, 58.9, 73.5, 101.4, 114.8, 118.7, 122.0, 126.9, 131.8, 141.4, 143.4, 144.7, 147.4, 158.0, 170.0; IR (film): 2942, 1746, 1622, 1509, 1474, 1371, 1231, 1030, 853, 755, 718, 665 cm^{-1}. R_f = 0.52 ($CHCl_3$/MeOH, 40:3).

4.2.3. (1*S*,3*R*,4*S*,8*S*,9*S*)-10,11-Dihydro-6′-methoxy-9-acetylthiocinchonan (9-acetylthio-*epi*-dihydroquinine, 9-CH_3COS-*epi*-DHQN) 2c

Yield 53%, brown oil; $[\alpha]_D = -14.2$ (*c* 0.20, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.3 Hz, 3H, Me), 1.27–1.35 (m, 2H), 1.51–1.66 (m, 3H), 1.73–1.87 (m, 3H), 2.16 (s, 3H, SCOMe), 2.36–2.41 (m, 1H), 2.70–2.79 (m, 1H), 3.08–3.22 (m, 2H), 3.36 (q, *J* = 7.9 Hz, 1H), 4.00 (s, 3H, OMe), 6.62 (d, *J* = 5.5 Hz, 1H, C^{9}H), 7.33–7.41 (m, 2H, ArH), 7.46 (d, *J* = 2.5 Hz, 1H, ArH), 8.01 (d, *J* = 9.2 Hz, 1H, ArH), 8.74 (d, *J* = 4.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0, 21.1, 23.2, 25.2, 27.5, 27.9, 37.0, 42.5, 55.9, 57.9, 58.6, 73.2, 101.3, 118.4, 122.0, 126.8, 131.7, 143.2, 144.7, 147.3, 158.1, 169.7; IR (film): 2946, 1713, 1621, 1589, 1509, 1364, 1229, 1024, 855, 751, 718, 614 cm^{-1}. R_f = 0.56 ($CHCl_3$/MeOH, 40:4).

4.2.4. (1*S*,3*R*,4*S*,8*R*,9*R*)-6′-Methoxy-9-acetylthiocinchonan (9-acetylthio-*epi*-quinidine, 9-CH_3COS-*epi*-QD) 2d

Yield 42%, yellow oil; $[\alpha]_D = +87.0$ (*c* 0.50, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44–1.58 (m, 3H), 1.82–1.91 (m, 2H), 2.15 (s, 3H, SCOMe), 2.23–2.32 (m, 1H), 2.68–2.86 (m, 2H), 2.93 (d, *J* = 8.9 Hz, 2H), 3.29 (q, *J* = 8.9 Hz, 1H), 3.96 (s, 3H, OMe), 5.07–5.14 (m, 2H, CH_2=), 5.98–6.09 (m, 1H, CH=), 6.54 (d, *J* = 6.8 Hz, 1H, C^{9}H), 7.33–7.41 (m, 3H, ArH), 8.01 (d, *J* = 9.0 Hz, 1H, ArH), 8.73 (d, *J* = 4.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 23.3, 26.4, 27.9, 39.8, 49.2, 49.9, 55.6, 59.0, 73.6, 101.4, 114.9, 118.5, 121.9, 127.0, 131.8, 140.3, 143.8, 144.7, 147.4, 157.9, 170.0; IR (film): 2937, 2873, 1747, 1622, 1593, 1508, 1455, 1372, 1229, 1029, 847, 756, 717, 663 cm^{-1}. R_f = 0.46 ($CHCl_3$/MeOH, 40:3).

4.2.5. (1*S*,3*R*,4*S*,8*R*,9*R*)-10,11-Dihydro-6′-methoxy-9-acetylthiocinchonan (9-acetylthio-*epi*-dihydroquinidine, 9-CH_3COS-*epi*-DHQD) 2e

Yield 44%, brown oil; $[\alpha]_D = +62.5$ (*c* 0.26, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.2 Hz, 3H, Me), 1.23–1.35 (m, 2H), 1.53–1.67 (m, 5H), 1.83–1.89 (m, 1H), 2.21 (s, 3H, SCOMe), 2.94–3.35 (m, 5H), 4.04 (s, 3H, OMe), 6.96 (s, 1H, C^{9}H), 7.27–7.29 (m, 1H, ArH), 7.38 (dd, *J* = 9.2, 2.3 Hz, 1H, ArH), 7.51 (d, *J* = 2.3 Hz, 1H, ArH), 8.01 (d, *J* = 9.2 Hz, 1H, ArH), 8.71 (d, *J* = 4.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.6, 20.6, 21.1, 22.1, 25.0, 25.6, 35.9, 49.2, 49.8, 56.4, 58.0, 71.7, 100.9, 117.4, 122.8, 126.2, 131.4, 142.1, 144.4, 146.8, 158.7, 168.7; IR (film): 2946, 1755, 1621, 1509, 1368, 1229, 1027, 858, 753, 719, 663 cm^{-1}. R_f = 0.38 ($CHCl_3$/MeOH, 40:3).

4.2.6. (1*S*,3*R*,4*S*,8*S*,9*R*)-6′-Methoxy-9-acetylthiocinchonan (9-acetylthio-quinine, 9-CH_3COS-QN) 2f

Yield 49%, yellow oil; $[\alpha]_D = +38.1$ (*c* 0.42, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83–0.90 (m, 1H), 1.35–1.41 (m, 1H), 1.65–1.73 (m, 3H), 2.09 (s, 3H, SCOMe), 2.36–2.41 (m, 1H), 2.83–2.94 (m, 2H), 3.26–3.40 (m, 2H), 3.61 (q, *J* = 7.4 Hz, 1H), 3.99 (s, 3H, OMe), 4.99–5.06 (m, 2H, CH_2=), 5.70–5.82 (m, 1H, CH=), 6.40 (d,

J = 10.5 Hz, 1H, C^9H), 7.37–7.44 (m, 1H, ArH), 7.60 (d, J = 2.7 Hz, 1H, ArH), 8.04 (d, J = 9.2 Hz, 1H, ArH), 8.77 (d, J = 4.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6, 20.4, 22.6, 23.4, 34.7, 36.5, 50.8, 50.9, 51.1, 54.2, 97.0, 109.9, 115.9, 117.2, 123.0, 127.1, 136.6, 137.1, 140.2, 142.8, 153.4, 165.8; IR (film): 2937, 2865, 1738, 1622, 1508, 1475, 1367, 1239, 1031, 854, 754, 716, 633 cm^{-1}. R_f = 0.36 (EtOAc/MeOH/Et_3N, 7:3:0.5).

4.2.7. (1*S*,3*R*,4*S*,8*R*,9*S*)-6′-Methoxy-9-acetylthiocinchonan (9-acetylthio-quinidine, 9-CH_3COS-QD) 2g

Yield 44%, yellow oil; $[\alpha]_D$ = +64.9 (c 0.98, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 0.87–0.96 (m, 1H), 1.11–1.19 (m, 1H), 1.52–1.64 (m, 3H), 2.09 (s, 3H, SCOMe), 2.24–2.31 (m, 1H), 2.98–3.07 (m, 4H), 3.35 (q, J = 9.5 Hz, 1H), 3.99 (s, 3H, OMe), 5.05–5.14 (m, 2H, CH_2=), 5.82–5.93 (m, 1H, CH=), 6.44 (d, J = 10.0 Hz, 1H, C^9H), 7.38–7.43 (m, 2H, ArH), 7.55 (d, J = 2.7 Hz, 1H, ArH), 8.02 (d, J = 9.2 Hz, 1H, ArH), 8.76 (d, J = 4.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 24.2, 26.5, 27.4, 39.2, 47.7, 49.3, 55.6, 59.3, 70.5, 101.4, 114.7, 120.3, 122.2, 127.8, 131.8, 140.4, 142.4, 144.8, 147.5, 158.1, 170.6; IR (film): 2938, 2873, 1740, 1622, 1508, 1476, 1368, 1238, 1031, 851, 756, 716, 666 cm^{-1}. R_f = 0.41 ($CHCl_3$/MeOH, 40:3).

4.3. Representative procedure for the preparation of thiols of alkaloids 3

The appropriate thiolacetate of alkaloid (1.5 mmol) was dissolved in abs. Et_2O or THF (10 mL) and was added to a well-stirred suspension of $LiAlH_4$ (0.228 g, 6 mmol) in Et_2O or THF (10 mL) under an argon atmosphere. The reaction mixture was stirred at rt for 1–3 days and then quenched by the careful addition of ether saturated with water (5 mL) and aqueous solution of 20% NaOH (ca. 10 mL). The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organic phase was washed with H_2O, brine, dried (Na_2SO_4) and the solvent was evaporated to afford a yellow solid or brown oil.

4.3.1. (1*S*,3*R*,4*S*,8*S*,9*S*)-9-Mercaptocinchonan (9-mercapto-*epi*-cinchonidine, 9-HS-*epi*-CD) 3a

Yield 73%, light yellow solid, mp 188–193 °C; $[\alpha]_D$ = −58.1 (c 0.74, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 1.34–1.41 (m, 2H), 1.65–1.70 (m, 3H), 2.13–2.16 (m, 1H), 2.48–2.57 (m, 2H), 2.90–2.98 (m, 2H), 3.37–3.42 (m, 1H), 4.78–4.89 (m, 3H, CH_2=, SH), 5.54–5.66 (m, 2H, CH=, C^9H), 7.24 (t, J = 7.2 Hz, 1H, ArH), 7.48 (d, J = 4.5 Hz, 1H, ArH), 7.53 (t, J = 7.2 Hz, 1H, ArH), 7.86 (d, J = 8.2 Hz, 1H, ArH), 7.97 (d, J = 8.2 Hz, 1H, ArH), 8.67 (d, J = 4.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 27.5, 27.8, 39.8, 43.1, 56.9, 60.3, 71.5, 114.3, 118.2, 122.9, 125.6, 126.5, 128.9, 130.0, 141.7, 148.0, 149.7, 149.8; IR (film): 3072, 2940, 2866, 1719, 1590, 1507, 1452, 1098, 901, 804, 756, 635 cm^{-1}.

4.3.2. (1*S*,3*R*,4*S*,8*S*,9*S*)-6′-Methoxy-9-mercaptocinchonan (9-mercapto-*epi*-quinine, 9-HS-*epi*-QN) 3b

Yield 80%, white solid, mp 145–150 °C; $[\alpha]_D$ = −72.8 (c 0.92, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 1.41–1.59 (m, 2H), 1.68–1.81 (m, 3H), 2.23–2.28 (m, 1H), 2.61–2.69 (m, 2H), 3.04–3.16 (m, 2H), 3.40–3.46 (m, 1H), 3.89 (s, 3H. OMe), 4.03 (br s, 1H. SH), 4.89–4.99 (m, 2H, CH_2=), 5.51 (d, J = 4.3 Hz, 1H, C^9H), 5.68–5.80 (m, 1H, CH=), 7.22 (d, J = 2.7 Hz, 1H, ArH), 7.31 (dd, J = 9.2, 2.7 Hz, 1H, ArH), 7.48 (d, J = 4.5 Hz, 1H, ArH), 7.96 (d, J = 9.2 Hz, 1H, ArH), 8.60 (d, J = 4.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 27.6, 27.9, 39.9, 43.2, 55.7, 57.0, 59.9, 71.9, 101.3, 114.4, 118.5, 121.5, 126.6, 131.4, 141.8, 144.1, 147.5, 147.8, 157.7; IR (film): 3073, 2933, 2859, 1622, 1508, 1470, 1241, 1032, 823, 717, 645 cm^{-1}.

4.3.3. (1*S*,3*R*,4*S*,8*S*,9*S*)-10,11-Dihydro-6′-methoxy-9-mercaptocinchonan (9-mercapto-*epi*-dihydroquinine, 9-HS-*epi*-DHQN) 3c

Yield 84%, solidified brown oil; $[\alpha]_D$ = −46.0 (c 0.42, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 0.79 (t, J = 7.3 Hz, 3H, Me), 1.17–1.27 (m, 2H), 1.40–1.43 (m, 3H), 1.71–1.78 (m, 3H), 2.34–2.44 (m, 1H), 2.60–2.68 (m, 1H), 3.01–3.09 (m, 2H), 3.46–3.51 (m, 1H), 3.86 (s, 3H, OMe), 4.71 (br s, 1H, SH), 5.57 (d, J = 3.3 Hz, 1H, C^9H), 7.22–7.30 (m, 2H, ArH), 7.50 (d, J = 4.5 Hz, 1H, ArH), 7.93 (d, J = 9.2 Hz, 1H, ArH), 8.59 (d, J = 4.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 20.9, 25.3, 27.5, 27.8, 37.2, 43.3, 55.8, 58.3, 59.7, 71.1, 101.2, 118.5, 121.4, 126.5, 131.3, 144.0, 147.4, 147.9, 157.6; IR (film): 2931, 2870, 1621, 1508, 1461, 1241, 1030, 829, 717, 642 cm^{-1}.

4.3.4. (1*S*,3*R*,4*S*,8*R*,9*R*)-6′-Methoxy-9-mercaptocinchonan (9-mercapto-*epi*-quinidine, 9-HS-*epi*-QD) 3d

Yield 93%, solidified yellow oil; $[\alpha]_D$ = +148.9 (c 0.90, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 1.11–1.15 (m, 1H), 1.47–1.59 (m, 2H), 1.74–1.78 (m, 1H), 2.03–2.11 (m, 1H), 2.23–2.28 (m, 1H), 2.74–3.08 (m, 4H), 3.39–3.46 (m, 1H), 3.77 (s, 3H, OMe), 5.00–5.12 (m, 3H, CH_2=, SH), 5.66 (d, J = 3.6 Hz, 1H, C^9H), 5.98–6.10 (m, 1H, CH=), 7.15 (d, J = 2.6 Hz, 1H, ArH), 7.25–7.29 (m, 1H, ArH), 7.53 (d, J = 4.5 Hz, 1H, ArH), 7.93 (d, J = 9.2 Hz, 1H, ArH), 8.60 (d, J = 4.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 26.2, 28.2, 39.9, 49.5, 50.1, 55.6, 59.7, 71.5, 101.1, 114.8, 118.5, 121.5, 126.5, 131.5, 140.4, 144.1, 147.5, 147.7, 157.7; IR (film): 3070, 2938, 2871, 1621, 1509, 1262, 1041, 832, 757, 664 cm^{-1}.

4.3.5. (1*S*,3*R*,4*S*,8*R*,9*R*)-10,11-Dihydro-6′-methoxy-9-mercaptocinchonan (9-mercapto-*epi*-dihydroquinidine, 9-HS-*epi*-DHQD) 3e

Yield 77%, solidified brown oil; $[\alpha]_D$ = +141.4 (c 0.29, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (t, J = 7.1 Hz, 3H, Me), 0.98–1.07 (m, 1H), 1.35–1.49 (m, 5H), 1.60–1.64 (m, 1H), 1.87–1.95 (m, 1H), 2.66–2.74 (m, 1H), 2.78–2.85 (m, 2H), 2.96–3.08 (m, 2H), 3.72 (s, 3H, OMe), 5.63 (s, 1H, C^9H), 7.08 (d, J = 2.5 Hz, 1H, ArH), 7.21 (d, J = 2.5 Hz, 1H, ArH), 7.46 (d, J = 4.5 Hz, 1H, ArH), 7.86 (d, J = 9.2 Hz, 1H, ArH), 8.58 (d, J = 4.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 20.6, 25.0, 26.1, 26.1, 37.0, 50.1, 51.0, 55.7, 59.8, 71.1, 101.0, 118.5, 121.5, 126.4, 131.5, 144.1, 147.2, 147.5, 157.7; IR (film): 2933, 2870, 1622, 1509, 1471, 1241, 1030, 830, 718, 641 cm^{-1}.

4.3.6. (1*S*,3*R*,4*S*,8*S*,9*R*)-6′-Methoxy-9-mercaptocinchonan (9-mercapto-quinine, 9-HS-QN) 3f

Yield 93%, solidified yellow oil; $[\alpha]_D$ = +23.7 (c 0.38, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 0.88–0.95 (m, 1H), 1.37–1.46 (m, 1H), 1.54–1.67 (m, 3H), 2.21–2.30 (m, 1H), 2.70–2.79 (m, 2H), 3.03–3.26 (m, 3H), 3.89 (s, 3H, OMe), 4.88–5.06 (m, 4H, CH_2=, C^9H, SH), 5.63–5.75 (m, 1H, CH=), 7.30–7.36 (m, 2H, ArH), 7.59 (d, J = 2.6 Hz, 1H, ArH), 7.97 (d, J = 9.2 Hz, 1H, ArH); 8.69 (d, J = 4.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 25.2, 28.1, 40.0, 40.8, 55.5, 56.0, 61.6, 71.4, 102.7, 114.7, 120.2, 121.3, 128.2, 131.7, 141.5, 144.4, 144.9, 147.6, 157.5; IR (film): 2927, 2861, 1622, 1508, 1474, 1241, 1031, 832, 716, 640 cm^{-1}.

4.3.7. (1*S*,3*R*,4*S*,8*R*,9*S*)-6′-Methoxy-9-mercaptocinchonan (9-mercapto-quinidine, 9-HS-QD) 3g

Yield 65%, solidified yellow oil; $[\alpha]_D$ = +106.0 (c 0.50, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 1.00–1.06 (m, 1H), 1.31–1.39 (m, 1H), 1.54–1.60 (m, 2H), 1.71–1.73 (m, 1H), 2.33–2.36 (m, 2H), 2.92–3.02 (m, 4H), 3.94 (s, 3H, OMe), 5.05–5.16 (m, 4H, CH_2=, C^9H, SH), 5.86–5.96 (m, 1H, CH=), 7.37 (dd, J = 9.2, 2.7 Hz, 1H, ArH); 7.48 (d, J = 4.5 Hz, 1H, ArH), 7.58 (d, J = 2.7 Hz, 1H, ArH), 8.02 (d, J = 9.2 Hz, 1H, ArH); 8.75 (d, J = 4.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.0, 26.6, 27.3, 39.0, 46.8, 49.2, 55.4, 62.2, 70.1, 101.9, 114.7, 119.9, 121.6, 128.0, 131.6, 140.2, 144.7, 144.9, 147.6, 157.4; IR (film): 2935, 2870, 1621, 1507, 1474, 1241, 1030, 827, 715, 639 cm^{-1}.

4.4. Representative procedure for the preparation of disulfides of alkaloids 4

An aqueous solution of 20% NaOH (0.060 g, 1.5 mmol) was added to a stirred solution of the appropriate thiols of alkaloids (1 mmol) dissolved in EtOH (10 mL). Then a solution of I_2 (0.095 g, 0.75 mmol) in EtOH (ca. 5 mL) was added dropwise until the color of the mixture become permanent. The reaction mixture was stirred at rt overnight. Thereafter EtOH was evaporated and the residue was quenched by the addition of satd $Na_2S_2O_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phase was washed with water, brine, dried (Na_2SO_4), and evaporated under reduced pressure to afford a yellow solid.

4.4.1. Bis((1*S*,3*R*,4*S*,8*S*,9*S*)-cinchonan-9-yl)disulfide (bis(9-*epi*-cinchonidinyl)disulfide, 9-*epi*-CD-S-)$_2$) 4a

Yield 90%, yellow solid, mp >220 °C with decomposition; $[\alpha]_D$ = −35.0 (*c* 0.52, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34–1.46 (m, 2H), 1.72–1.76 (m, 3H), 2.22–2.26 (m, 1H), 2.58−2.66 (m, 2H), 3.00−3.08 (m, 2H), 3.54−3.58 (m, 1H), 4.80–4.89 (m, 2H, CH_2=), 5.52–5.64 (m, 1H, CH=), 5.77 (s, 1H, C^{9}H), 7.26 (t, *J* = 7.4 Hz, 1H, ArH), 7.50−7.55 (m, 2H, ArH), 7.89−7.98 (m, 2H, ArH), 8.71 (d, *J* = 4.4 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 26.3, 27.5, 38.8, 43.6, 56.1, 60.4, 69.6, 115.5, 118.4, 122.9, 125.1, 126.5, 129.1, 130.0, 139.9, 147.9, 148.0, 150.0; IR (film): 3072, 2939, 2866, 2726, 1590, 1508, 1452, 1097, 901, 804, 756, 635, 576 cm^{-1}. Anal. Calcd for $C_{38}H_{42}N_4S_2$ (*M* = 618.90): C, 73.75; H, 6.84; N, 9.05; S, 10.36. Found: C, 73.45; H, 6.54; N, 9.27; S, 10.18.

4.4.2. Bis((1*S*,3*R*,4*S*,8*S*,9*S*)-6′-methoxycinchonan-9-yl)disulfide (bis(9-*epi*-quininyl)disulfide, 9-*epi*-QN-S-)$_2$) 4b

Yield 99%, yellow solid, mp >220 °C with decomposition; $[\alpha]_D$ = −25.8 (*c* 0.66, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44–1.58 (m, 2H), 1.81–1.88 (m, 3H), 2.36–2.39 (m, 1H), 2.63–2.79 (m, 2H), 3.07–3.23 (m, 2H), 3.63–3.75 (m, 1H), 3.88 (s, 3H. OMe), 4.92–5.00 (m, 2H, CH_2=), 5.63–5.74 (m, 1H, CH=), 5.80 (s, 1H, C^{9}H), 7.19 (d, *J* = 2.6 Hz, 1H, ArH), 7.26−7.30 (m, 1H, ArH), 7.52 (d, *J* = 4.5 Hz, 1H, ArH), 7.92 (d, *J* = 9.2 Hz, 1H, ArH), 8.62 (d, *J* = 4.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 25.4, 26.4, 37.9, 42.8, 55.4, 55.6, 59.0, 68.8, 99.8, 114.5, 117.6, 120.9, 125.2, 130.3, 139.0, 142.9, 145.4, 146.3, 157.0; IR (film): 2927, 2866, 1620, 1590, 1508, 1453, 1241, 1097, 1028, 825, 717, 641, 569 cm^{-1}. Anal. Calcd for $C_{40}H_{46}N_4O_2S_2$ (*M* = 678.95): C, 70.76; H, 6.83; N, 8.25; S, 9.45. Found: C, 70.49; H, 6.71; N, 8.36; S, 9.21.

4.4.3. Bis((1*S*,3*R*,4*S*,8*S*,9*S*)-10,11-Dihydro-6′-methoxycinchonan-9-yl) disulfide (bis(9-*epi*-dihydroquininyl)disulfide, 9-*epi*-DHQN-S-)$_2$) 4c

Yield 98%, light brown solid, mp 220 °C with decomposition; $[\alpha]_D$ = −9.1 (*c* 0.32, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.73 (t, *J* = 7.2 Hz, 3H, Me), 1.10–1.24 (m, 2H), 1.70–1.81 (m, 3H), 1.96–2.17 (m, 3H), 2.59–2.64 (m, 1H), 3.00–3.06 (m, 1H), 3.23 (t, *J* = 9.1 Hz, 1H), 3.36 (t, *J* = 10.9 Hz, 1H), 3.62 (s, 3H, OMe), 4.47–4.91 (m, 1H), 6.38 (s, 1H, C^{9}H), 6.86 (d, *J* = 2.3 Hz, 1H, ArH), 6.93 (dd, *J* = 9.3, 2.4 Hz, 1H, ArH), 7.61−7.66 (m, 2H, ArH), 8.61 (d, *J* = 4.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.4, 17.0, 23.5, 23.6, 25.9, 34.4, 43.3, 56.0, 56.7, 59.0, 65.0, 99.1, 118.1, 122.1, 124.6, 129.0, 140.9, 144.7, 144.9, 157.6; IR (film): 2930, 2875, 1620, 1591, 1508, 1459, 1241, 1025, 856, 718, 643, 566 cm^{-1}. Anal. Calcd for $C_{40}H_{50}N_4O_2S_2$ (*M* = 682.98): C, 70.34; H, 7.38; N, 8.20; S, 9.39. Found: C, 70.56; H, 7.62; N, 7,98; S, 9.11.

4.4.4. Bis((1*S*,3*R*,4*S*,8*R*,9*R*)-6′-methoxycinchonan-9-yl)disulfide (bis(9-*epi*-quinidinyl)disulfide, 9-*epi*-QD-S-)$_2$) 4d

Yield 96%, yellow solid, mp >220 °C with decomposition; $[\alpha]_D$ = +94.1 (*c* 0.34, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05–1.14 (m, 1H), 1.50–1.75 (m, 2H), 1.81–1.85 (m, 1H), 2.18 (t, *J* = 11.2 Hz, 1H), 2.32–2.35 (m, 1H), 2.82–3.16 (m, 5H), 3.77 (s, 3H. OMe), 5.08–5.13 (m, 2H, CH_2=), 5.97–6.10 (m, 2H, CH=, C^{9}H), 7.14 (d, *J* = 2.1 Hz, 1H, ArH), 7.23 (dd, *J* = 9.2, 2.0 Hz 1H, ArH), 7.58 (d, *J* = 4.4 Hz, 1H, ArH), 7.90 (d, *J* = 9.2 Hz, 1H, ArH), 8.65 (d, *J* = 4.4 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 27.6, 29.5, 38.2, 40.1, 48.4, 49.2, 55.6, 56.3, 60.0, 101.7, 116.3, 118.9, 121.6, 126.3, 131.6, 138.4, 144.2, 147.4, 157.9; IR (film): 2934, 2871, 1621, 1591, 1508, 1455, 1241, 1028, 831, 718, 640, 570 cm^{-1}. Anal. Calcd for $C_{40}H_{46}N_4O_2S_2$ (*M* = 678.95): C, 70.76; H, 6.83; N, 8.25; S, 9.45. Found: C, 70.51; H, 6.98; N, 7.92; S, 9.07.

4.4.5. Bis((1*S*,3*R*,4*S*,8*R*,9*R*)-10,11-Dihydro-6′-methoxycinchonan-9-yl) disulfide (bis(9-*epi*-dihydroquinidinyl)disulfide, 9-*epi*-DHQD-S-)$_2$) 4e

Yield 88%, light brown solid, mp >230 °C with decomposition; $[\alpha]_D$ = +46.8 (*c* 0.24, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.3 Hz, 3H, Me), 1.56–1.81 (m, 5H), 1.94–2.02 (m, 2H), 2.38 (t, *J* = 11.4 Hz, 1H), 3.02–3.13 (m, 1H), 3.24−3.39 (m, 2H), 3.63 (s, 3H, OMe), 3.89–3.98 (m, 1H), 4.15−4.22 (m, 1H), 6.59 (s, 1H, C^{9}H), 6.92 (d, *J* = 2.1 Hz, 1H, ArH), 7.01 (dd, *J* = 9.2, 2.1 Hz, 1H, ArH), 7.68−7.75 (m, 2H, ArH), 8.68 (d, *J* = 4.4 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.6, 17.6, 23.8, 24.3, 25.1, 35.2, 49.4, 50.1, 57.2, 60.1, 66.3, 99.7, 118.6, 122.3, 125.2, 131.2, 143.6, 144.1, 146.9, 158.1; IR (film): 2930, 2875, 1620, 1591, 1508, 1460, 1241, 1026, 832, 718, 641, 568 cm^{-1}. Anal. Calcd for $C_{40}H_{50}N_4O_2S_2$ (*M* = 682.98): C, 70.34; H, 7.38; N, 8.20; S, 9.39. Found: C, 69.98; H, 7.07; N, 7.96; S, 9.46.

4.4.6. Bis((1*S*,3*R*,4*S*,8*S*,9*R*)-6′-methoxycinchonan-9-yl)disulfide (bis(9-quininyl)disulfide, 9-QN-S-)$_2$) 4f

Yield 98%, brown solid, mp 138−144 °C with decomposition; $[\alpha]_D$ = +15.4 (*c* 0.26, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04–1.11 (m, 1H), 1.52–1.63 (m, 1H), 1.68−1.85 (m, 3H), 2.45–2.51 (m, 1H), 2.97–3.07 (m, 2H), 3.43–3.66 (m, 3H), 3.95 (s, 3H, OMe), 5.03–5.12 (m, 2H, CH_2=), 5.26 (d, *J* = 10.0 Hz, 1H, C^{9}H), 5.67–5.73 (m, 1H, CH=), 7.34−7.43 (m, 2H, ArH); 7.67 (d, *J* = 2.6 Hz, 1H, ArH), 8.02 (d, *J* = 9.2 Hz, 1H, ArH), 8.73 (d, *J* = 4.4 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 25.4, 26.4, 29.7, 37.6, 54.5, 55.6, 56.4, 61.9, 102.3, 116.8, 120.4, 122.0, 125.1, 131.7, 138.1, 142.6, 144.8, 147.5, 158.1; IR (film): 2924, 1621, 1590, 1505, 1455, 1230, 1024, 920, 831, 715, 619 cm^{-1}. Anal. Calcd for $C_{40}H_{46}N_4O_2S_2$ (*M* = 678.95): C, 70.76; H, 6.83; N, 8.25; S, 9.45. Found: C, 69.81; H, 6.31; N, 7.88; S, 9.12.

4.4.7. Bis((1*S*,3*R*,4*S*,8*R*,9*S*)-6′-methoxycinchonan-9-yl)disulfide (bis(9-quinidinyl)disulfide, 9-QD-S-)$_2$) 4g

Yield 82%, brown solid, mp 135−142 °C; $[\alpha]_D$ = +73.0 (*c* 0.28, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98–1.30 (m, 3H), 1.53–1.67 (m, 3H), 2.30−2.32 (m, 1H), 3.01–3.03 (m, 4H), 3.85 (s, 3H, OMe), 5.04–5.13 (m, 3H, CH_2=, C^{9}H), 5.74–5.80 (m, 1H, CH=), 7.24−7.29 (m, 1H, ArH); 7.39 (d, *J* = 4.0 Hz, 1H, ArH), 7.47 (d, *J* = 2.2 Hz, 1H, ArH), 7.92 (d, *J* = 9.2 Hz, 1H, ArH); 8.65 (d, *J* = 4.4 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 25.8, 27.2, 38.3, 46.7, 49.1, 55.5, 62.5, 69.3, 101.8, 115.5, 120.0, 121.8, 127.8, 131.6, 139.2, 144.3, 144.7, 147.6, 157.7; IR (film): 2934, 2873, 1620, 1590, 1507, 1455, 1227, 1026, 829, 715, 639, 617 cm^{-1}. Anal. Calcd for $C_{40}H_{46}N_4O_2S_2$ (*M* = 678.95): C, 70.76; H, 6.83; N, 8.25; S, 9.45. Found: C, 71.02; H, 6.58; N, 7.96; S, 9.80.

4.5. General procedure for the copper-catalyzed Henry reaction

The ligand (0.06 mmol, 12 mol %) and $Cu(OAc)_2 \cdot H_2O$ (10.0 mg, 0.05 mmol, 10 mol %) were dissolved in *i*-PrOH (1 mL) and the mixture was stirred for 3 h at rt to give either a blue or dark green solution. Then the respective aldehyde (0.5 mmol, 1 equiv) and nitroalkane (5.0 mmol, 10 equiv) were added with an additional 1 mL of *i*-PrOH. The reaction mixture was cooled to 0 °C (or

−20 °C). After 3 days, the crude product was isolated by column chromatography (hexane/AcOEt 6:1) to give β-nitroalcohol.

4.5.1. 2-Nitro-1-phenylethanol 5

Chromatographic purification (hexane/AcOEt 6:1), R_f = 0.16. Enantiomeric excess was determined by HPLC (Chiracel OD-H), hexane/*i*-PrOH 90:10, 1 mL/min, 225 nm, enantiomer I t_R = 13.9 min, enantiomer (*S*) t_R = 17.3 min. The absolute configuration was assigned by comparison of the retention times in HPLC and specific rotation signs with literature data.[7d,h] ^{1}H NMR (300 mHz, $CDCl_3$) δ 2.88 (d, *J* = 3.3 Hz, 1H), 4.51 (dd, *J* = 13.3, 3.2 Hz, 1H), 4.62 (dd, *J* = 13.3, 9.4 Hz, 1H), 5.48 (dd, *J* = 9.4, 3.2 Hz, 1H).

4.5.2. 1-Cyclohexyl-2-nitro-ethanol 6

Chromatographic purification (hexane/AcOEt 6:1), R_f = 0.29, gave a colorless oil (55 mg, 64%). Enantiomeric excess (75%) was determined by HPLC (Chiralpak AD-H), hexane/*i*-PrOH 97:3, 0.5 mL/min, 210 nm, major enantiomer (*S*) t_R = 47.6 min, minor enantiomer (*R*) t_R = 44.3 min; $[\alpha]_D$ = 13.6 (*c* 0.48, CH_2Cl_2, 75% ee). The absolute configuration was assigned by comparison of the retention times in HPLC and specific rotation signs with literature data.[7d,h] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01−1.25 (m, 5H), 1.37−1.48 (m, 1H), 1.59−1.65 (m, 2H), 1.71−1.79 (m, 3H), 2.38 (d, *J* = 4.4 Hz, 1H), 4.01−4.07 (m, 1H), 4.36 (dd, *J* = 13.1, 8.6 Hz, 1H), 4,43 (dd, *J* = 13.1, 3.2 Hz, 1H).

4.5.3. 2-Nitro-1-phenylpropanol 7

Chromatographic purification (hexane/AcOEt 6:1), R_f = 0.20. Diastereomeric ratios were determined by ^{1}H NMR. Enantiomeric excesses were determined by HPLC (Chiralpak AD-H), hexane/*i*-PrOH 95:5, 1 mL/min, 225 nm, $anti_{major}$ (1*S*,2*R*) t_R = 13.5, $anti_{minor}$ (1*R*,2*S*) t_R = 15.3, syn_{major} (1*S*,2*S*) t_R = 18.7, syn_{minor} (1*R*,2*R*) t_R = 21.0. The absolute configuration of both diastereomers was assigned by comparison of the retention times in HPLC with literature data;[7d,f,j,9c] *syn isomer* (1*S*,2*S*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (d, *J* = 6.8 Hz, 3H), 2.69 (d, *J* = 3.4 Hz, 1H), 4.67 (dq, *J* = 6.8, 3.6 Hz, 1H), 5.38 (t, *J* = 3.3 Hz, 1H), 7.30−7.40 (m, 5H, ArH); *anti isomer* (1*S*,2*R*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (d, *J* = 6.8 Hz, 3H), 2.69 (d, *J* = 3.4 Hz, 1H), 4.67 (dq, *J* = 6.8, 3.6 Hz, 1H), 5.38 (t, *J* = 3.3 Hz, 1H), 7.30−7.40 (m, 5H, ArH).

4.5.4. 2-Nitro-1,3-diphenylpropanol 8

Chromatographic purification (hexane/AcOEt 6:1), R_f = 0.19, gave a white solid (91 mg, 71%). Diastereomeric ratios (*anti*/*syn*, 57:43) were determined by ^{1}H NMR. Enantiomeric excesses were determined by HPLC (Chiracel OD-H), hexane/*i*-PrOH 90:10, 1 mL/min, 210 nm, $anti_{major}$ (1*S*,2*R*) t_R = 14.2, $anti_{minor}$ (1*R*,2*S*) t_R = 10.6, syn_{major} (1*S*,2*S*) t_R = 18.7, syn_{minor} (1*R*,2*R*) t_R = 12.6. The absolute configuration of both diastereomers was assigned by comparison of the retention times in HPLC with literature data;[7d] *anti isomer* (1*S*,2*R*), 61% ee: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.65 (s, 1H), 3.07 (dd, *J* = 14.6, 2.9 Hz, 1H), 3.35 (dd, *J* = 14.9, 10.9 Hz, 1H), 4.82−4.89 (m, 1H), 5.23 (d, *J* = 4.6 Hz, 1H), 6.97−7.02 (m, 2H, ArH), 7.14−7.23 (m, 3H, ArH), 7.28−7.38 (m, 5H, ArH); *syn isomer* (1*S*,2*S*), 74% ee: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.53 (s, 1H), 2.71 (dd, *J* = 14.4, 3.8 Hz, 1H), 3.08 (dd, *J* = 11.1, 7.4 Hz, 1H), 4.82−4.89 (m, 1H), 5.04 (d, *J* = 6.5 Hz, 1H), 6.97−7.02 (m, 2H, ArH), 7.14−7.23 (m, 3H, ArH), 7.28−7.38 (m, 5H, ArH).

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