

***Cinchona* Alkaloids—Derivatives and Applications**

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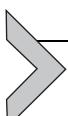
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Abstract

Major *Cinchona* alkaloids quinine, quinidine, cinchonine, and cinchonidine are available chiral natural compounds (chiral pool). Unlike many other natural products, these alkaloids are available in multiple diastereomeric forms which are separated on an industrial scale. The introduction discusses in short conformational equilibria, traditional separation scheme, biosynthesis, and *de novo* chemical syntheses. The second section concerns useful chemical applications of the alkaloids as chiral recognition agents and effective chiral catalysts. Besides the Sharpless ethers and quaternary ammonium salts (chiral PTC), the most successful bifunctional organocatalysts are based on 9-amino derivatives: thioureas and squaramides. The third section reports the main transformations of *Cinchona* alkaloids. This covers reactions of the 9-hydroxyl group with the retention or inversion of configuration. Specific *Cinchona* rearrangements enlarging [2.2.2] bicyclic of quinuclidine to [3.2.2] products are connected to the 9-OH substitution. The syntheses of numerous esterification and etherification products are described, including many examples of bi-*Cinchona* alkaloid ethers. Further derivatives comprise 9-N-substituted compounds. The amino group is introduced via an azido function with the inversion of configuration at the stereogenic center C9. The 9-*epi*-amino-alkaloids provide imines, amides, imides, thioureas, and squaramides. The syntheses of

9-carbon-, 9-sulfur-, and 9-selenium-substituted derivatives are discussed. Oxidation of the hydroxyl group of any alkaloid gives ketones, which can be selectively reduced, reacted with Grignard reagents, or subjected to the Corey–Chaykovsky reaction. The alkaloids were also partially degraded by splitting C4'–C9 or N1–C8 bonds. In order to immobilize *Cinchona* alkaloids the transformations of the 3-vinyl group were often exploited. Finally, miscellaneous functionalizations of quinuclidine, quinoline, and examples of various metal complexes of the alkaloids are considered.



1. Introduction

The bark of *Cinchona* trees and shrubs native to Bolivia, Ecuador, and Peru has been used as an effective cure against malaria. Its first recorded use in Europe dates back to the XVII century. The active ingredient, quinine (**QN**), was first isolated in 1820 by Pelletier and Caventou.¹ Following this discovery, the efficiency of antimalarial treatment was improved by replacing the bark of unknown alkaloid content with **QN**. Quantification method also allowed botanists to selectively cultivate *Cinchona* varieties rich in the alkaloids.² Now, few alkaloids are isolated on an industrial scale. Among them are four major alkaloids of *Cinchona* bark—quinine (**QN**), quinidine (**QD**), cinchonidine (**CD**), and cinchonine (**CN**), accompanied by their 10,11-dihydro derivatives (Fig. 1).

Although there have been more than 30 other alkaloids isolated from *Cinchona* genus, none of them is commercially available. Today, the major alkaloids are used by pharmaceutical, beverage, and chemical industries. Quinine remains to be used as an anthelmintic in multidrug regimens, and quinidine is administered for the treatment of certain arrhythmias. Soft drinks such as tonic water and related alcoholic mixtures attribute their bitter taste to ca. 0.005% of dissolved quinine. Quinine sulfate stands as one of the standards in fluorescence spectroscopy, with a defined quantum yield of 0.546.³ Major *Cinchona* alkaloids are a part of the so-called *chiral pool*, that is, readily available natural chiral compounds. The exceptional feature of *Cinchona* alkaloids is the availability of more than one stereoisomer. In the last few decades, the major interest in these compounds was associated with their applications in asymmetric synthesis and separation of enantiomers.

Previously, *Cinchona* alkaloids were reviewed in this series in Volumes 3,⁴ 14,⁵ and 34.⁶ In 2009 a dedicated book was published,⁷ and relevant book chapters appeared in 2013.^{8,9} Applications of these alkaloids in the

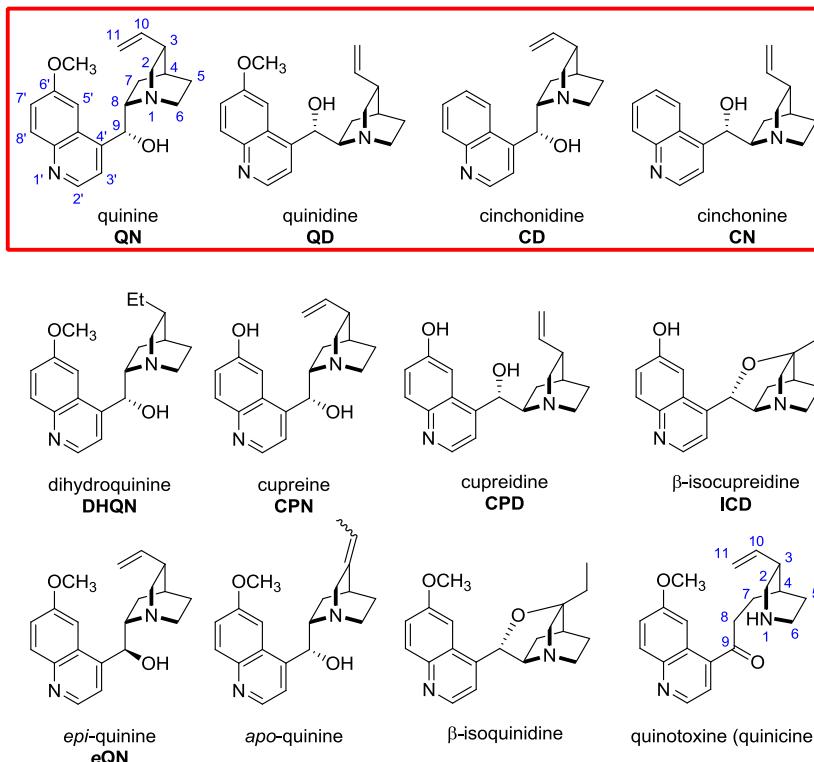


Fig. 1 Major *Cinchona* alkaloids (inside box) and selected named derivatives.

asymmetric synthesis were the subject of comprehensive reviews as well.^{10–12}

The structure of *Cinchona* alkaloids consists of three largely independent units: an aromatic quinoline (or 6-methoxyquinoline) ring, a bulky bicyclic quinuclidine moiety with a vinyl substituent, and a central hydroxyl group. The atom numbering follows the tradition established by Rabe (numbering logic of quinotoxine, cf. Fig. 1), but is sanctioned by IUPAC.¹³ There are five stereogenic centers (N1, C3, C4, C8, and C9), while two are interdependent (N1, C4). Individual alkaloids share the same configuration at the positions 1, 3, and 4, but the two remaining chiral centers C8 and C9 are of opposite absolute configuration in **QN–QD** and **CD–CN** pairs; hence, these pairs of diastereomers are often referred to as pseudoenantiomers (Fig. 2).

The alkaloids display two major degrees of freedom, namely rotation along C8–C9 and C9–C4' bonds (Scheme 1). The conformational space is greatly restricted due to rigidity and bulkiness of the substituents and gives rise to a rather limited number of conformer populations. The flip of the

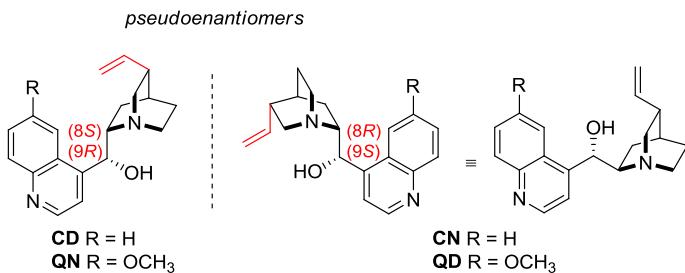
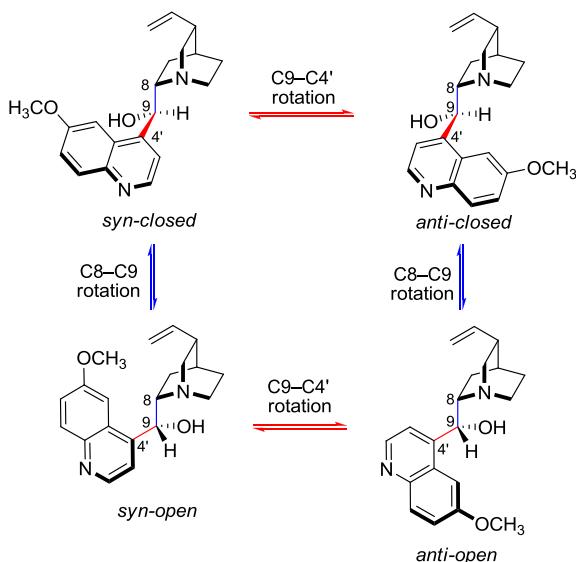


Fig. 2 Pseudoenantiomeric relationship between *Cinchona* alkaloids.

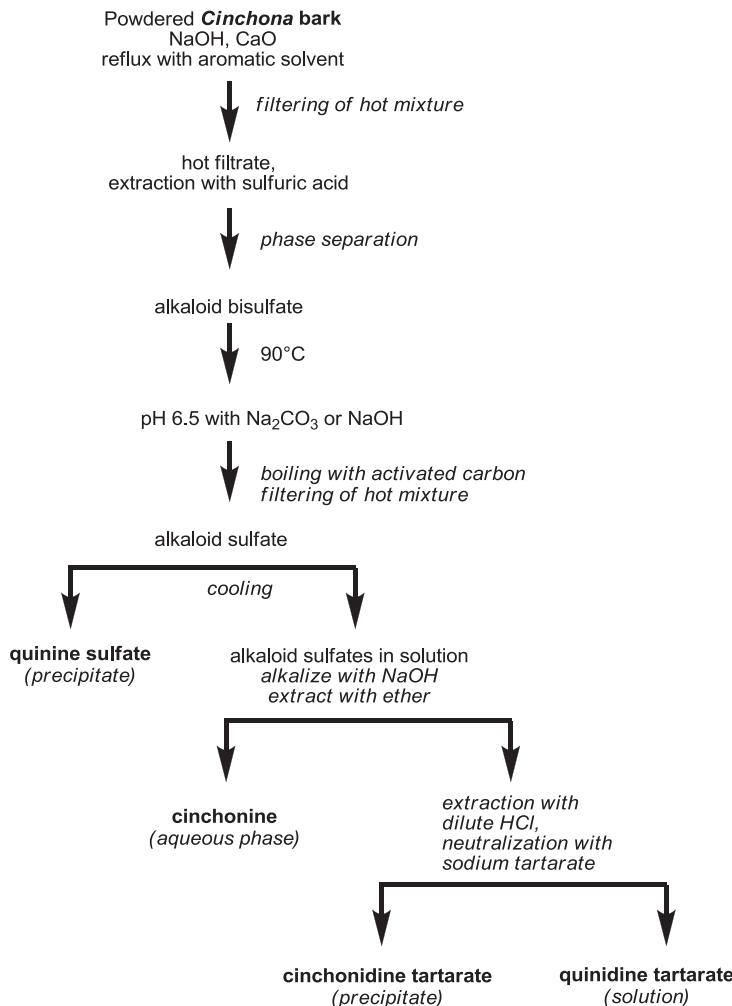


Scheme 1 Conformations of quinine.

quinoline substituent (rotation along C9–C4'; *syn*–*anti* transition) is generally associated with higher energy barrier, which was estimated as 8.3 kcal/mol in solution.¹⁴

1.1 Isolation

The preferred source for quinine is *Cinchona ledgeriana*, whereas a more equally distributed mixture of alkaloids comes from *Cinchona calisaya*. Traditionally the alkaloids are isolated by the extraction and sequential precipitation (**Scheme 2**). First, the *Cinchona* bark is extracted under basic conditions (CaO, NaOH) to an organic aromatic solvent (e.g., toluene) at elevated temperatures. Then, it is reextracted with an excess of sulfuric



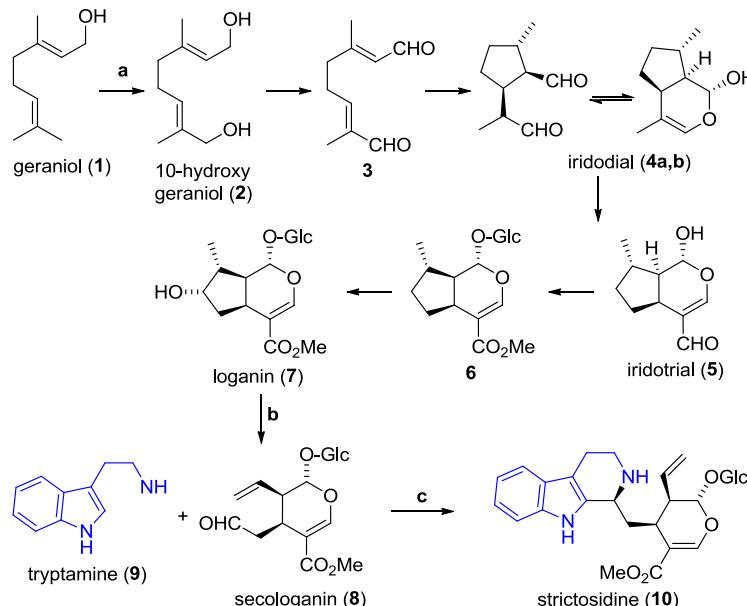
Scheme 2 Outline of the traditional separation of the *Cinchona* alkaloids.

acid to form soluble bisulfates. On partial neutralization and cooling, quinine sulfate is separated. It is the least soluble *Cinchona* alkaloid sulfate. On the other hand, cinchonine is insoluble in diethyl ether. Tartaric acid may be used to separate insoluble salt of cinchonidine from quinidine. There are six companies on the market isolating and separating *Cinchona* alkaloids.¹⁵

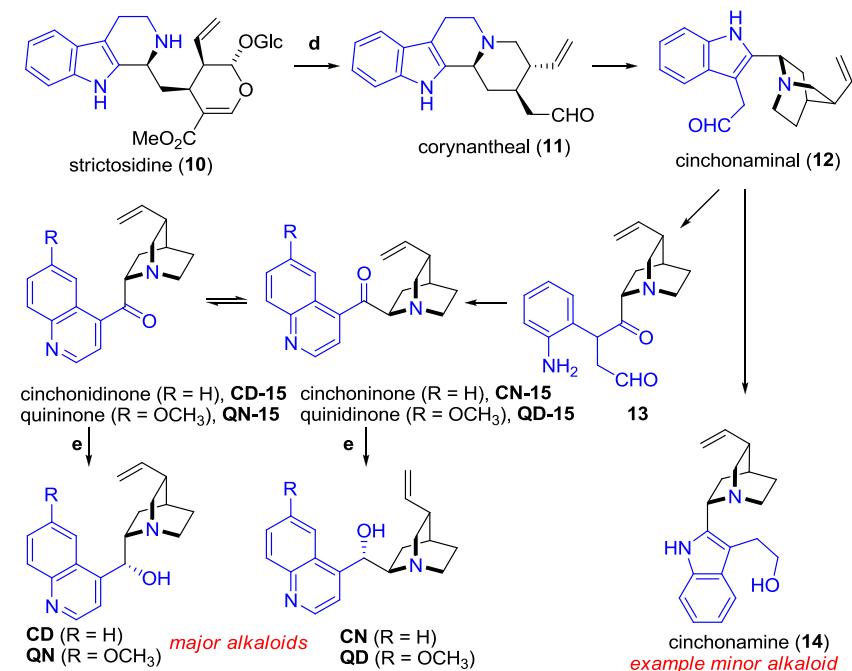
Pharmacopoeial identification of quinine is based on fluorescence of solutions in dilute sulfuric or acetic acids. Detection by thalleioquin reaction relies on an action of bromine on quinine or quinidine sulfate followed by the addition of ammonia, which produces emerald-green color.¹⁶

1.2 Biosynthesis

Complete biosynthesis of the alkaloids was proposed in the 1960s¹⁷ and has been revised in just a few points ([Schemes 3 and 4](#)).^{18,19} Biogenetically, *Cinchona* alkaloids are members of terpene-indole alkaloid family which includes well-known natural products such as strychnine, yohimbine, reserpine, and ajmaline. All of them share a common biosynthetic intermediate—strictosidine (**10**), which is produced from tryptamine (**9**) and secologanin (**8**), which in turn can be traced back to geraniol (**1**, [Scheme 3](#)). In the pathway specific for *Cinchona* alkaloids ([Scheme 4](#)), strictosidine is transformed to cinchonaminal (**12**). The first process is catalyzed by strictosidine glycosidase, which forms a six-membered ring with the nitrogen atom, and then an intermediate product undergoes hydrolysis and decarboxylation to form corynantheal (**11**). The subsequent ring rearrangement, through iminium intermediates, finally produces the azabicyclo[2.2.2]octane system in chinconaminal (**12**). The pendant aldehyde group in **12** can undergo the reduction to form cinchonamine (**14**), which is a minor alkaloid. However, the major pathway guides chinconaminal (**12**) through the hydrolytic cleavage of indole C–N bond resulting in the dicarbonyl compound **13**.



Scheme 3 Outline of *Cinchona* alkaloid biosynthesis: pathway common for terpene-indole alkaloids. Known involved enzymes: (a) geraniol 10-hydroxylase; (b) secologanin synthase; (c) strictosidine synthase.

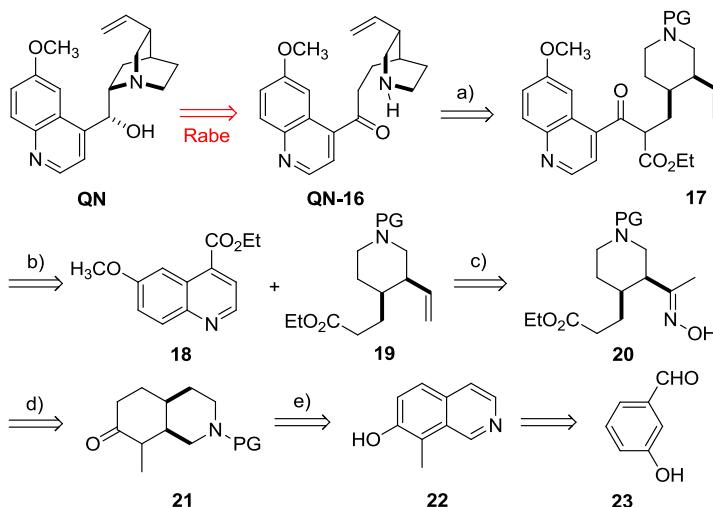


Scheme 4 Outline of *Cinchona* alkaloid biosynthesis: pathway specific for *Cinchona* alkaloids. Known involved enzymes: (d) strictosidine glucosidase; (e) cinchoninone: NADPH oxidoreductase.

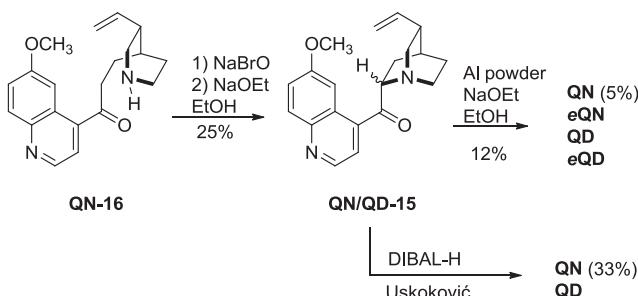
The formation of internal imine with the aldehyde part followed by the oxidative rearomatization results in a quinoline system of the alkaloid-derived ketones **15**. The central carbonyl group allows for rapid 8-epimerization. This group is reduced to 9-alcohol by cinchoninone NADPH-dependent oxidoreductase. This reduction is highly stereoselective and only products of opposite configuration at 8 and 9 stereocenters are produced (native alkaloids), while *epi*-alkaloids can be found in only very small quantities. Cinchoninone oxidoreductase exists as two isoenzymes: one produces cinchonine and cinchonidine, and the other all four alkaloids (quinine, quinidine, cinchonine, and cinchonidine). The stage of introduction of the 6'-methoxy group is not entirely clear.^{17–19}

1.3 Total Synthesis

A few chemical syntheses of *Cinchona* alkaloids have been developed.^{20–22} The first total synthesis of quinine is attributed to Woodward and Doering (Scheme 5).²³ In their synthesis from 1945, the quinuclidine fragment was



Scheme 5 Outline of the retrosynthesis of quinine by Woodward and Doering.²³ Principal transformations: (a) decarboxylation; (b) Claisen condensation; (c) reduction and Hofmann elimination; (d) ring opening nitrosation; and (e) hydrogenation and oxidation.

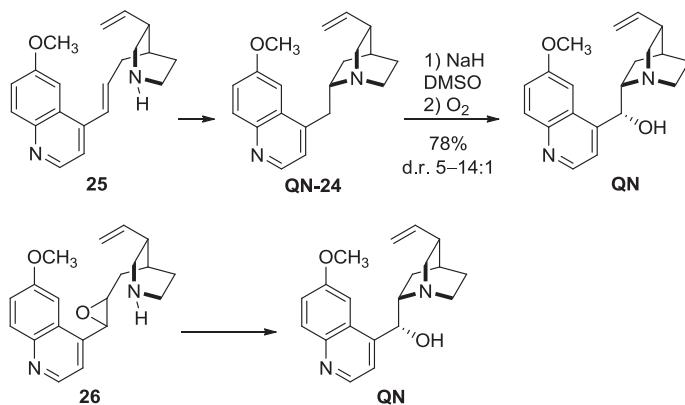


Scheme 6 Rabe's transformation of quinotoxine.

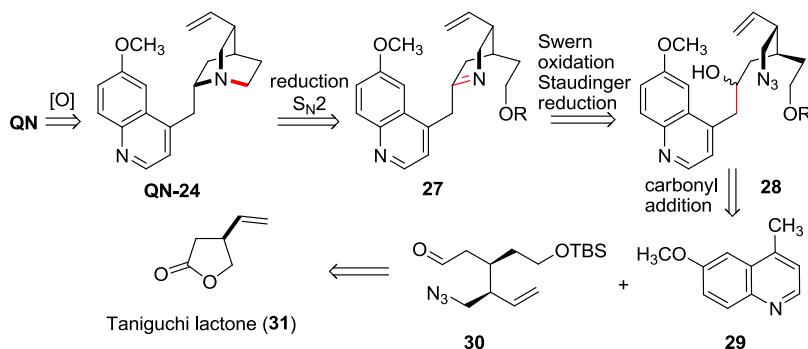
obtained by conversion of isoquinoline. The C8–C9 bond was made using the Claisen condensation with quinic acid ester. Overall in 17 steps, quinotoxine (quinicine) was obtained. The final formation of N1–C8 bond that is the conversion of quinotoxine to quinine was referenced to the earlier work by Rabe (Scheme 6).²⁴ This three-step process would complete the formal synthesis. However, the difficulty in reproducing the last transformation ignited a controversy that was resolved many years later in Rabe's favor.²⁵

Substantial progress in the total synthesis of *Cinchona* alkaloids was made by Uskoković at Hoffmann-La Roche (**Scheme 7**). The group developed a few different syntheses of racemic *Cinchona* alkaloids. Quinine was obtained via diastereoselective autoxidation of **QN-24**.²⁶ Moreover, their approach to N1–C8 ring closure included the nucleophilic addition (**25** into **QN-24**) and the ring opening of epoxide **26**.²⁷ Uskoković also substantially improved diastereoselectivity in the reduction of alkaloid-derived 9-ketones (cf. **Scheme 6**).

However, the first stereoselective synthesis of quinine was performed only in 2001 by Stork (**Scheme 8**).²⁸ The 15-step sequence started from chiral butyrolactone (Taniguchi lactone, **31**). The C8–C9 bond was made by the addition of lithiated lepidine to carbonyl, while N1–C8 and N1–C6



Scheme 7 Diastereoselective autoxidation, conjugate addition, and epoxide ring opening.

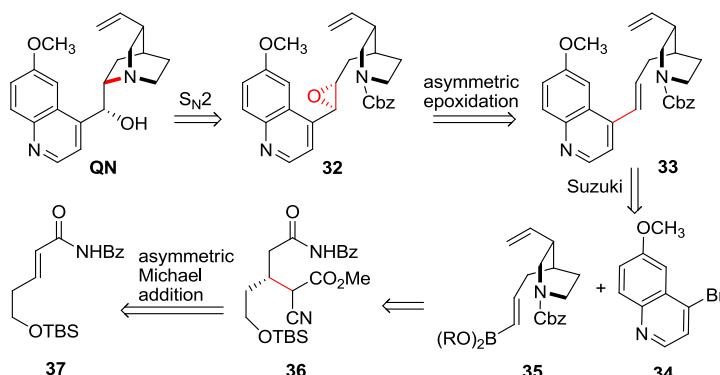


Scheme 8 Disconnections in Stork's synthesis of enantiomeric quinine.

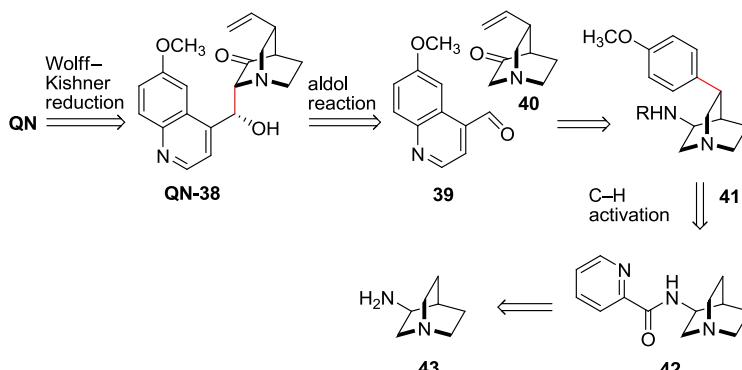
bonds were sequentially formed in the reductive amination and nucleophilic displacement reactions.²⁸ The alkaloid was obtained by applying the Uskoković autoxidation as a means to introduce the central hydroxyl group in the final step (cf. Scheme 7).²⁶

The N1–C8 disconnection was exploited in Jacobsen enantioselective synthesis (Scheme 9).²⁹ It featured the asymmetric Michael addition catalyzed by chiral aluminum complex and the asymmetric dihydroxylation catalyzed by *Cinchona* alkaloid-derived AD-mix. The quinoline unit was attached to the C9 atom by applying the Suzuki reaction of piperidine derivative 35. The subsequent enantioselective dihydroxylation followed by the epoxide ring closure provided the reactive intermediate 32. Then, in a single step quinine was formed.²⁹ Alternative approaches to the epoxide 32 included the Corey–Chaykovsky reaction.³⁰ Moreover, a different synthesis of epoxide precursor was shown by Hatakeyama, who applied enantioselective cycloaldolization catalyzed by proline as one of the key steps for the preparation of piperidine part.³¹

Quinine along with a number of analogs was also obtained utilizing the final C8–C9 disconnection approach (Scheme 10). The diastereoselective aldol reaction between quinoline carbaldehyde 39 and the quinuclidine derivative 40 provided 7-oxoquinine (QN-38). The ketone group was subsequently removed in the Wolff–Kishner reduction (methanesulfonylhydrazine, LiAlH₄).^{32–34} Maulide performed the synthesis of the required 5-vinylquinuclidin-3-one (40) by the application of picolinamido moiety that acted as a palladium-directing group allowing for the selective C–H activation and coupling.³²



Scheme 9 Disconnections in Jacobsen asymmetric synthesis of quinine.



Scheme 10 Disconnections in Maulide's C–H activation-based synthesis of quinine.



2. Chemical Applications

The key step in a chiral recognition is the formation of diastereoisomeric complexes between enantiomers and a chiral selector. It is generally accepted that an effective chiral recognition model should involve three-point interactions between guest and selector. The strongest and most effective (attractive or repulsive) interactions are those of electrostatic (Coulomb), hydrogen bonds, steric hindrance, π – π , and ion-dipole nature.³⁵ All these types of interactions can be found between *Cinchona* alkaloids and various chiral molecules. Moreover, many structural modifications of the alkaloids enhance respective interactions, thus making the chiral recognition more effective. These effects are accounted for their application in discrimination and separation of enantiomers. Furthermore, these interactions are responsible for the catalysis of various enantioselective reactions. A catalyst should interact preferentially with one of the prochiral sides, thus lowering the activation energy of one from two diastereomeric transition states.

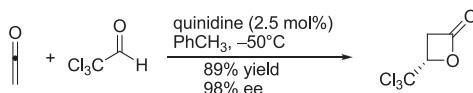
Historically, the first chemical application of quinine came with the use of derived quinotoxine as a resolving agent for racemic tartaric acid by crystallization of corresponding diastereomeric salts.³⁶ On the other hand, the first slightly enantioselective (<10% ee) formation of cyanohydrin in the presence of quinine and quinidine was reported in 1912 by Breding and Fiske.³⁷ An essential improvement in the catalytic use of *Cinchona* alkaloids in asymmetric synthesis has been made by Pracejus in 1960 (enantioselective addition of methanol to ketenes, up to 74% ee).³⁸

This discovery was followed by an extensive research on the *Cinchona* alkaloid catalysis in conjugate additions and some interesting results were obtained by the group of Wynberg (1970–1981).³⁹ Further studies and optimization demonstrated soon that there was a room for further improvement of enantioselectivities.^{40,41} In the highly enantioselective [2 + 2] addition of ketene to chloral in the presence of 2.5 mol% of quinidine 98% ee was attained (**Scheme 11**).⁴²

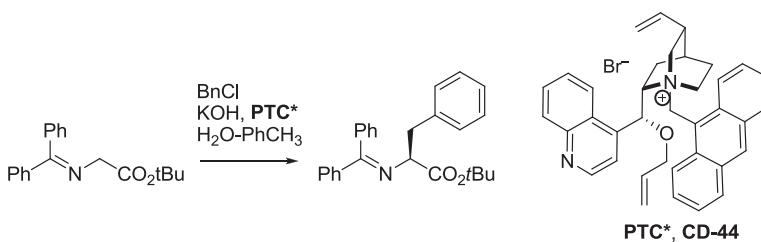
A wide interest in the phase-transfer catalysis (PTC) turned attention to *Cinchona* alkaloids. In 1984 Merck chemists quaternized the quinuclidine nitrogen atom and used *p*-[(trifluoromethyl)benzyl]cinchoninium bromide as a phase-transfer catalyst in very effective and enantioselective methylation (95% yield, 92% ee) of indanone.⁴³ A similar approach was adopted by O'Donnell, who used **CD-44** as PTC* for the practical asymmetric syntheses of α -amino acid derivatives (**Scheme 12**).^{44,45}

Park and Jew developed highly enantioselective dimeric *Cinchona*-derived phase-transfer catalysts for the synthesis of α -amino acids (**Fig. 3**).^{46,47} A few of such catalysts are now commercially available.

However, a real breakthrough in the field of asymmetric catalysis came with the discovery of highly effective ligands for the osmium-catalyzed asymmetric dihydroxylation of olefins. For this purpose, many 9-substituted derivatives of *Cinchona* alkaloids were synthesized and tested. The best catalytic performance was observed for bis-ethers of phthalazine (DHQ)₂PHAL and (DHQD)₂PHAL and these compounds were introduced as chiral ligands, parts of commercial dihydroxylating reagents AD-mix- α and AD-mix- β (**Scheme 13**). The use of pseudo-enantiomeric ligands from *Cinchona* alkaloids gave an opposite sense of stereochemical induction.^{48–51}



Scheme 11 Asymmetric [2 + 2] addition.



Scheme 12 Asymmetric benzylation of glycine imine.

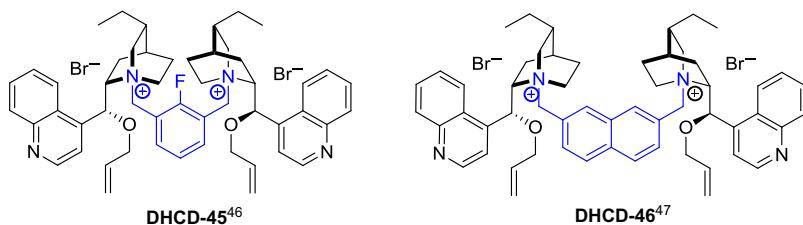
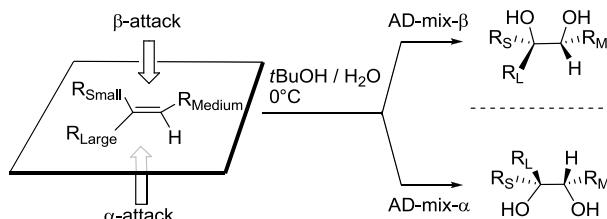
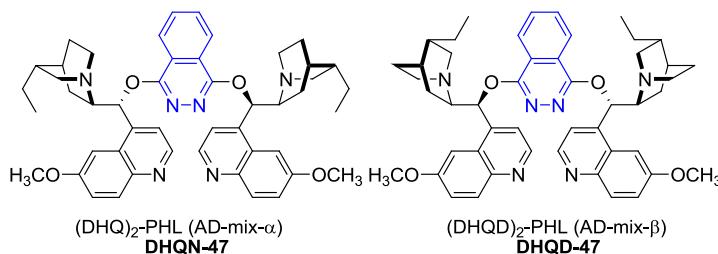


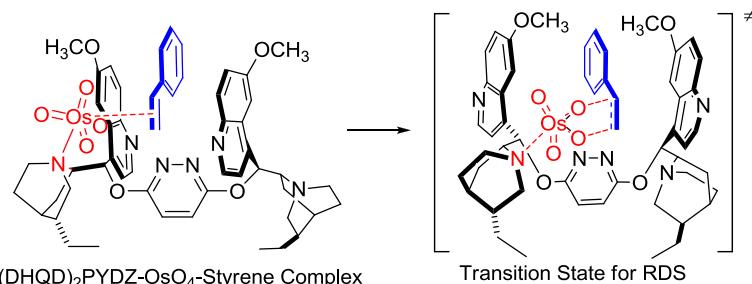
Fig. 3 Efficient dimeric chiral phase-transfer catalysts developed by the Park-Jew group.⁴⁶



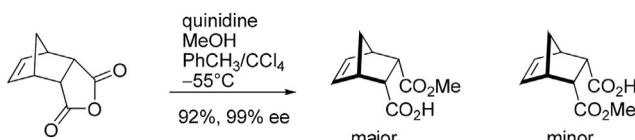
Scheme 13 Mnemonic scheme for the stereochemical outcome of the Sharpless olefin dihydroxylation.

The respective preferred α - or β -attack (cf. Scheme 13) has been rationalized by Corey and Noe (Scheme 14). Kinetic investigations of the olefin dihydroxylation catalyzed by pyridazine bis-dihydroquinidine ether (DHQD)₂PYDZ and OsO₄ demonstrated Michaelis–Menten kinetics for the substrate–complex intermediate, which underwent a conformational change into the respective transition state for the rate-limiting cycloaddition forming the Os(VI) ester intermediate.⁵² These discoveries, honored by a Nobel Prize to Sharpless in 2001, paved a way to the modern asymmetric synthesis.

As early as in the middle 1980s a successful catalytic asymmetric induction in the reaction of prochiral cyclic acid anhydrides with methanol was observed for cinchonine with an enantiomeric excess of up to 70%.^{53,54}



Scheme 14 Stereochemical representation of the $(DHQD)_2PYDZ\text{-OsO}_4$ complex interacting with styrene and its transformation into the respective transition state for the rate-limiting (RDS) cycloaddition to produce the Os(VI) ester intermediate.⁵²

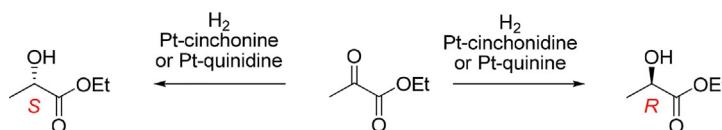


Scheme 15 Desymmetrization of anhydride.

Later, a highly enantioselective catalytic desymmetrization of cyclic anhydrides with the *Cinchona* alkaloid derivatives introduced by Sharpless was elaborated by Deng.⁵⁵ Moreover, unmodified *Cinchona* alkaloids mediated enantioselective ring opening of cyclic *meso*-anhydrides and Bolm reported that structurally diverse anhydrides can be converted into their corresponding methyl monoesters, and either enantiomer can be obtained with up to 99% ee by using quinine or quinidine as a directing additive (**Scheme 15**).⁵⁶

Yet another interesting synthetic application of the alkaloids was based on their use for the chiral modification of metal surfaces. The Pt-catalyzed hydrogenation of ethyl pyruvate with the modifiers derived from cinchonidine and quinine led to an excess of (*R*)-ethyl lactate, whereas cinchonine and quinidine derivatives preferentially gave the *S* enantiomer (**Scheme 16**). The presence of the 1:1 complex of an *anti-open* conformer of the alkaloid and the reactant adsorbed at the Pt surface was responsible for the observed stereochemical outcome.⁵⁷

It was found that 9-*O*-phenylcinchonidine efficiently induced inversion of enantioselectivity with respect to cinchonidine in the enantioselective hydrogenation of various activated ketones on Pt/Al₂O₃. The origin of the switch of enantioselective properties of the catalyst was explained by the role played by the phenyl group in defining the chiral space created by modifiers on Pt.⁵⁸



Scheme 16 *Cinchona*-modified platinum catalysis in the hydrogenation of ethyl pyruvate.⁵⁷

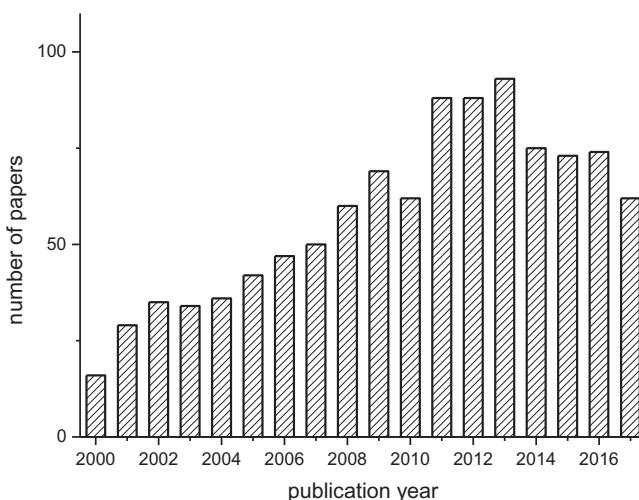
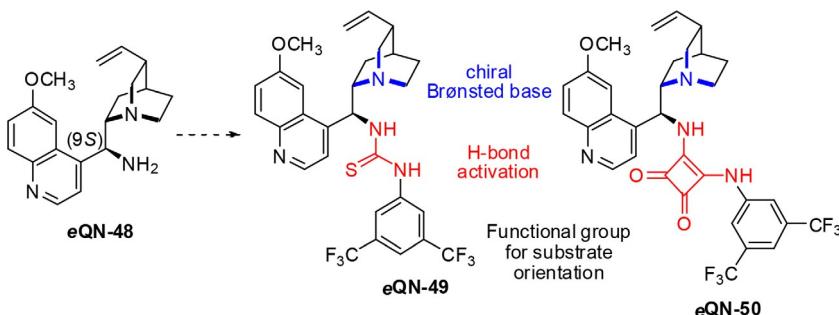


Fig. 4 Number of papers indexed by Scopus for *Cinchona* and asymmetric.

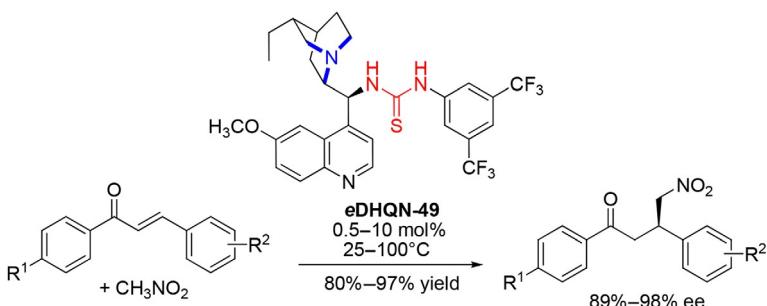
Since that time many papers have been published reporting works on catalytic applications of *Cinchona* alkaloids in asymmetric synthesis (Fig. 4). Additionally, from 2005 every year, over 150 papers were indexed just for *Cinchona* by Scopus. Over the last 20 years, *Cinchona* alkaloids have attracted much interest in the asymmetric synthesis. Both native alkaloids and their derivatives belong to a class of “privileged catalysts and ligands,” defined as those active in many asymmetric reactions, often with different mechanisms.^{59,60}

The most successful catalysts, besides the Sharpless ethers used as ligands and the quaternary salts (chiral PTC), were bifunctional organocatalysts based on 9-amino-derivatives, namely thioureas and squaramides (Scheme 17). Nowadays, over 50 different reactions were effectively catalyzed by various derivatives of *Cinchona* alkaloids (Schemes 18 and 19).

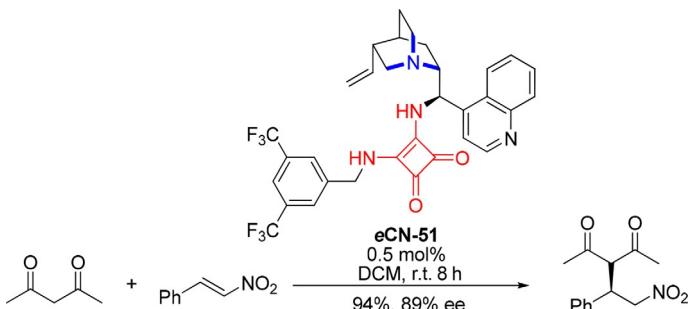
To the often studied catalytic reactions belong the conjugate nucleophilic additions and to these reactions, the *Cinchona* alkaloid analog **eDHQN-49** of Takemoto’s catalyst was first successfully applied by Soós



Scheme 17 *epi*-Aminoalkaloids and derived bifunctional hydrogen-bonding organocatalysts.



Scheme 18 Asymmetric Michael addition.



Scheme 19 Asymmetric addition to nitrostyrene.

(**Scheme 18**).⁶¹ Interestingly, also thiourea-derived *Cinchona* alkaloids promoted the asymmetric decarboxylation of various racemic hemiesters of α -aminomalonates to afford enantioenriched aminoesters in high yields and enantioselectivities up to 93%. Both enantiomers of the amino-esters have been synthesized with the same selectivity when using thiourea derived from quinidine and its pseudoenantiomer derived from quinine.⁶² For

several years thioureas have dominated hydrogen bond-promoted chiral organocatalysis.

Moreover, in 2008 Rawal reported the use of a new hydrogen-bonding unit for chiral catalysts. Squaramide-modified 9-*epi*-aminocinchonine was shown to be a very effective catalyst for the conjugate addition reactions of 1,3-dicarbonyl compounds to β -nitrostyrenes, even at loadings as low as 0.1 mol%. The addition products were obtained in high yields and excellent enantioselectivities (**Scheme 19**).⁶³

The role played by bifunctional organocatalysts (activation by hydrogen bonding and chiral Brønsted base) was recently examined by experimental and theoretical methods.⁶⁴

Moreover, among simple derivatives of *Cinchona* alkaloids, cupreine (**CPN**) and cupreidine (**CPD**) (**Fig. 5**) have been powerful catalysts for many asymmetric transformations. The first application of a *Cinchona* organocatalyst that bears a hydroxyl group at the C6' position was reported by Hatakeyama and coworkers in 1999.⁶⁵

They showed that β -isocupreidine (**β -ICD**) is a highly enantioselective catalyst for the Baylis–Hillman reaction. The desired adducts were obtained with excellent enantiomeric excess although in moderate yields only. Furthermore, for many other transformations, cupreines displayed a level of chemo-, regio-, and enantioselective control that is unmatched by metal complexes or other organocatalysts.⁶⁶ In particular, **β -ICD** offers an attractive combination of high reactivity and selectivity, therefore allowing reactions to be carried out with minimal catalyst loading and thus overcoming one of the major limitations of most organocatalytic reactions. Moreover, Hatakeyama and coworkers developed useful synthetic routes to pseudo-enantiomer of **β -ICD**, thus allowing for the syntheses of optical antipodes of the desired products.^{67,68}

As it was already mentioned, chemical applications of *Cinchona* alkaloids started with their use for the separation of enantiomers (tartaric acid, Pasteur).³⁶ Numerous examples of separation procedures for inorganic

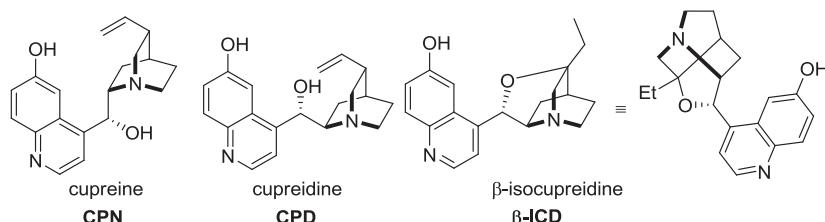


Fig. 5 *Cinchona* alkaloid-derived phenols.

and organic enantiomers have been reported. Chiral recognition of anionic bis(oxalato)(1,10-phenanthroline)chromate(III) by *Cinchona* alkaloid cations in water was observed. A particular alkaloid cation favored one enantiomer of the complex in one mode, but its antipode was preferred in the other mode. Moreover, one of two modes was excluded upon acetylation of the 9-OH group of alkaloid.⁶⁹

More often the alkaloids were used in the separation of organic enantiomers. *rac*-7,7'-Bis(benzyloxy)-2,2'-dihydroxy-1,1'-binaphthyl was readily resolved through simple clathrate formation with quinine and quinidine. The same compound was also resolved by fractional crystallization of its cyclic phosphate ester with quinidine. The X-ray crystal structure analysis of the complex of (*S*)-enantiomer with quinidine showed that ion pairing is the major interaction between the two components.⁷⁰

Binaphthols were successfully resolved by inclusion crystallization with *N*-alkylcinchonidinium halides. The adduct complexes examined by X-ray methods indicated that a key role in the molecular recognition was played by directional hydrogen bonding and aryl–aryl stacking.^{71,72} Consequently, a practical separation of enantiomers of 1,1'-bi-2-naphthol was developed using recrystallization of the racemate with *N*-benzylcinchonidinium chloride.^{73,74}

Chiral recognition by *Cinchona* alkaloids was also used for the construction of materials for separation and analytics. Thus, molecularly imprinted polymer (MIP) receptors for *Cinchona* alkaloids, namely cinchonidine and cinchonine, were prepared, characterized, and used as HPLC chiral stationary phases (CSPs). High stereoseparation factors of up to 31 were obtained. The resolution of *rac*-propranolol and related compounds led to a conclusion ascribing the origin of recognition phenomena to the rigidity of template structures.⁷⁵

The pioneering work on the CSPs derived from quinine, quinidine, and cinchonidine designed for chiral ion-exchange chromatography was performed by Salvadori and coworkers.⁷⁶

The outstanding studies on the synthesis and chromatographic applications of various materials modified with *Cinchona* alkaloids were carried out in Lindner's laboratory (University of Vienna) in 1999–2011. The group has published over 60 original papers and most of the results are summed up in a book chapter.⁷⁷ Highly efficient immobilization of *Cinchona* alkaloid derivatives having terminal acetylene functionality to azide-modified silica gel was achieved by click chemistry. A comparison of the chromatographic performance of these new materials with the commercially available phases with *Cinchona* alkaloid bound by thioether linkage gave similar outcomes.⁷⁸

Enantioresolution of N-protected amino acids and other chiral acids was higher for carbamoylated quinine-based chiral anion exchangers than for that derived from quinine. The presence of a carbamate functionality instead of the secondary hydroxyl group at C9 of quinine offers additional sites for intermolecular interactions with chiral analytes, thus improving chiral recognition ability (Fig. 6).⁷⁹

Just another application of *Cinchona* alkaloids consists in their use as chiral solvating agents (CSA) for NMR spectroscopy.⁸⁰ The specific interactions of CSA with chiral solute change some previously enantiotopic nuclei into anisochronous, thus allowing for the discrimination of enantiomers. Salvadori and coworkers successfully used C9-carbamoyloxy derivatives of dihydroquinine as efficient CSA for the NMR enantiodiscrimination of simple derivatives of chiral alcohols, amines, carboxylic acids, and amino acids.⁸¹ Corresponding C9-carbamoylated quinidine was also appropriate for the determination of the enantiomeric compositions of amino acid derivatives in solution.⁸² The origin of enantiodiscrimination was studied by NMR conformational analysis of the chiral auxiliaries and investigation of solution complexation.^{35,83} *Cinchona* alkaloid-induced chiral discrimination for the determination of the enantiomeric composition relied also on ¹⁹F and ³¹P spectroscopy. Thus, corresponding alkaloids were used as CSA, and their ability to induce the NMR enantiomeric anisochrony of selected substrates was tested, namely: α -trifluoromethylated alcohols by ¹⁹F NMR,⁸⁴ and N-protected aminoalkanephosphonates with quinidine by ³¹P NMR.⁸⁵

Recently, *Cinchona* alkaloids N-alkylated with chloromethyl anthracene, known earlier as chiral PTC,⁸⁶⁻⁸⁹ were used as fluorescent sensors for chiral carboxylic acids (Fig. 7). The respective tetrafluoroborates bound preferentially to one enantiomer of chiral carboxylic acid increased the

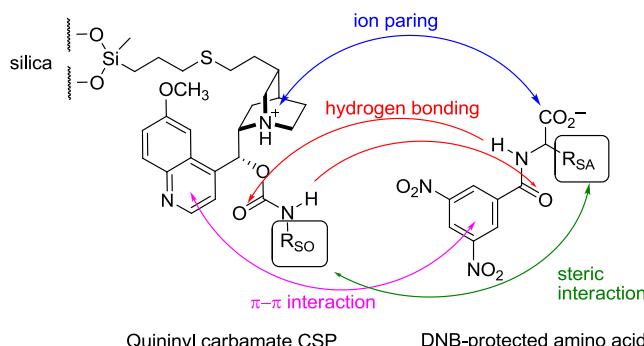


Fig. 6 Interaction of quinuclidine carbamate host with a DNB-protected amino acid guest.⁷⁹

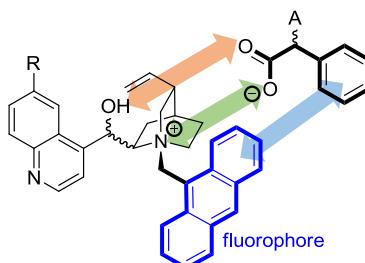
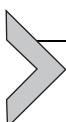


Fig. 7 Interactions of *Cinchona* alkaloid fluorescent sensors.

fluorescence intensity that could be utilized in the determination of enantiomeric excess. Sensor library composed of four *Cinchona* ammonium salts was used for the collection of multivariate response data. Quantitative analysis of ee for mandelic acid and several nonsteroidal antiinflammatory drugs was carried out using linear discriminant analysis.⁹⁰



3. Transformations of *Cinchona* Alkaloids

Availability of *Cinchona* alkaloids together with developments in asymmetric synthesis and medicinal chemistry has fostered interest in modifications of these natural products. Most of the mentioned spectacular chemical applications were developed by optimization of their structures through chemical transformations.

Now, the number of known *Cinchona* alkaloid derivatives can be estimated at no less than 6000. Furthermore, four individual alkaloids together with their 10,11-dihydro- and 9-*epi*-derivatives can quickly inflate that number. The alkaloids have been modified at a few different sites, particularly at the 9-hydroxyl group, the quinuclidine nitrogen atom, and in the vinylic side chain at C3 (Fig. 8). More recently, quinoline moiety has become an attractive target for modification. Apart from site modifications, other transformations include various rearrangements of carbon skeleton involving the ring expansion or opening.

3.1 Transformations at the Position 9

Cinchona alkaloids can be readily converted into various derivatives, such as C9-ethers, esters, and carbamates without changes of the configuration at carbon atom C9. Furthermore, the nucleophilic substitution of the 9-hydroxyl group of alkaloids usually by Mitsunobu reaction or via their activated form as C9-mesylates led to a variety of derivatives, usually with

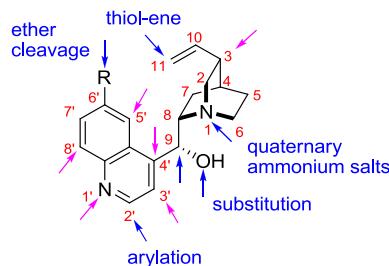


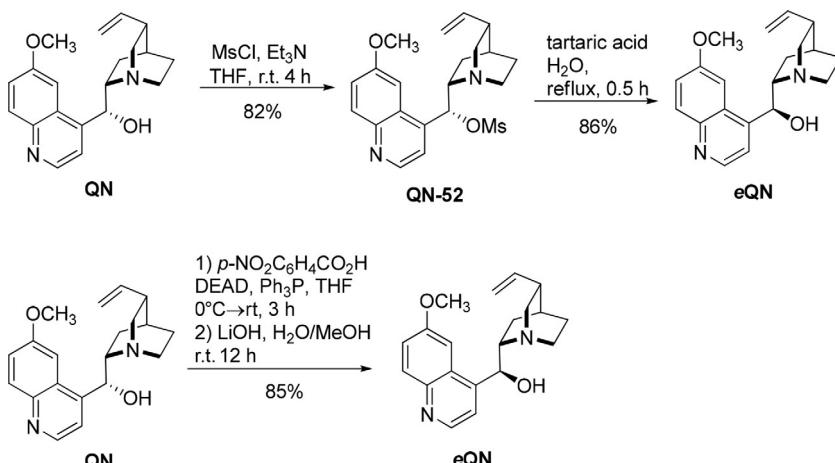
Fig. 8 Major modification sites and reactions of *Cinchona* alkaloids (blue) as well as less common (magenta).

complete inversion of the configuration at C9 (9-epimer is formed). Thus, 9-nitrogen (azides, amines, amides), 9-chalcogen (9-thiols, disulfides, sulfides, sulfoxides, and phenylselenides), and 9-halide derivatives were obtained. 9-*epi*-*Cinchona* alkaloids underwent many of the mentioned reactions giving in most cases 9-naturally configured derivatives. However, various nucleophilic displacements at the position 9 can occur with either the inversion or retention of the absolute configuration at carbon atom C9.

3.1.1 9-*epi*-Alkaloids

Cinchona alkaloids with the 9-*epi* configuration can be easily prepared in two steps via synthesis of C9-tosylates⁹¹ or favorably C9-mesylates 52^{92–94} followed by hydrolysis of these sulfonates with inversion of the configuration at C9 (**Scheme 20**). Alternatively, a sequence of the Mitsunobu esterification and ester hydrolysis was applied.^{95,96}

Hydrolysis of alkaloid methanesulfonates of either native or 9-*epi* configuration in the presence of tartaric acid proceeded only toward *epi*-alkaloids (**Scheme 21**). In this stereoconvergent process methanesulfonates of 9-*epi* configuration (e.g., *eQN*-52) reacted with retention of configuration, while natively configured sulfonates (e.g., **QN**-52) undergo complete inversion. Analogous results were obtained for other electrophilic derivatives, where the type of leaving group does not have any noticeable effect on the stereochemistry. The *epi*-alkaloids were formed with retention of configuration from both 9-*epi*-bromides and 9-*epi*-mesylates, while the same products were formed with inversion from native alkaloid mesylates and halides. Products of a native configuration such as quinine and quinidine were not formed.⁹³ This was attributed to the conformational control and molecular recognition of the aqueous solvent through hydrogen bonds in the presence of tartaric acid. It was assumed that 9-*epi*-quinine derivatives

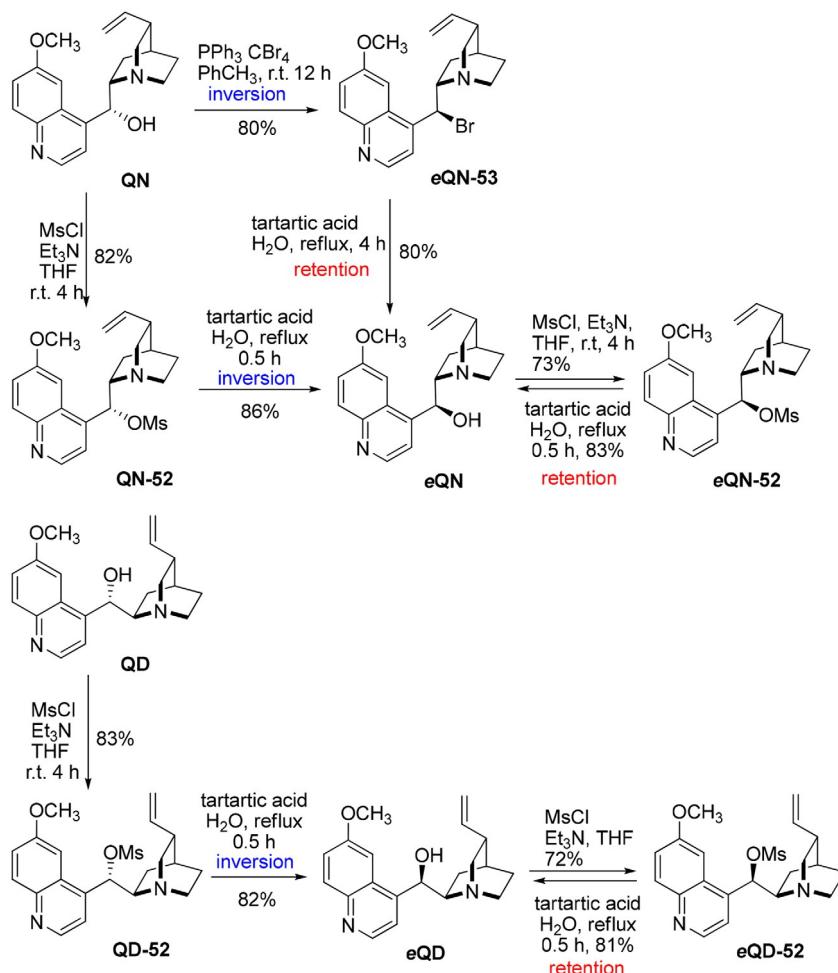


Scheme 20 A representative synthesis of *epi*-alkaloids.

adopted a conformation with a hydrophilic pocket containing the leaving group and the protonated bridgehead nitrogen atom ([Scheme 22](#), top). The pocket is open to retentive solvolysis in the S_N1 -type reaction involving a C^+X^- ion pair.⁹⁷ However, leaving group X and the protonated amine group of naturally configured alkaloid derivatives are on opposite faces of the preferred ground-state conformation and the S_N2 inversion of configuration is strongly favored ([Scheme 22](#), bottom).

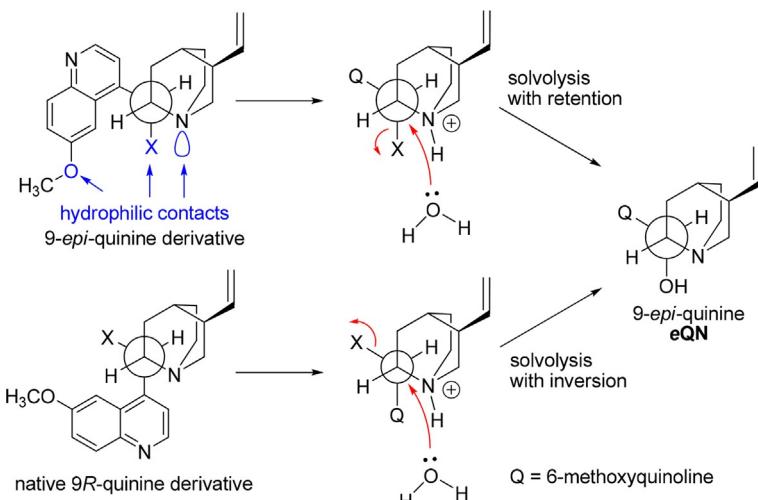
3.1.2 Cinchona Rearrangements

When cinchonidine and cinchonine methanesulfonates of native configuration were heated in protic solvents, the stereospecific substitution occurred with rearrangement of the bicyclic system most likely involving carbocation intermediates ([Scheme 23](#), top). A new nucleophile is attached at the position 8, while C9 becomes linked to the nitrogen atom of the [3.2.2]bicycle. Aside for the rearrangement, the substitution at the position 9 (conserving the [2.2.2] ring system) proceeds with the retention of configuration. The array of products and their ratio greatly depended on the solvent and presence of external nucleophiles. The amount of rearranged [3.2.2] product **CD-54** increased in the order of $\text{EtOH} < \text{MeOH} < 2,2,2\text{-trifluoroethanol}$. However, the ring expansion process was less pronounced for quinine, which is more capable of stabilizing carbocations by the aromatic 6-methoxyquinoline system. In the case of quinine/quinidine series, a separate S_N1 -type substitution at C9, which conserved the [2.2.2]bicycle, led to mixtures 9-epimers (not shown).^{98,99}

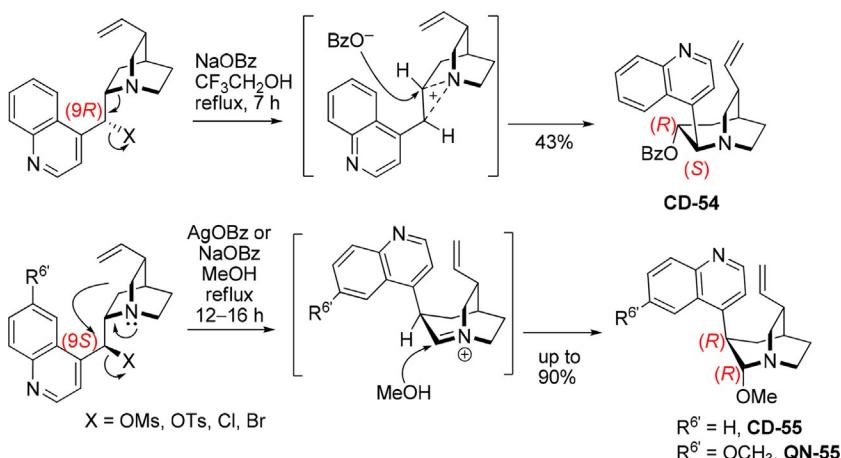


Scheme 21 Hydrolysis of *Cinchona* alkaloid methanesulfonates and bromide with complete inversion or complete retention of configuration.

On the other hand, $\text{S}_{\text{N}}1$ -type solvolytic reactions of epimers, i.e., 9-*epi*-halide derivatives of *Cinchona* alkaloids, led to different products (**Scheme 23**, bottom). Reactions with MeOH in the presence of silver or sodium benzoate led almost exclusively to the products with [3.2.2]bicyclic system **QN-55** and **CD-55** with a different connectivity compared to **CD-54**. This time C9 atom with attached quinoline migrates in between C7 and C8. The reaction is also stereospecific, but not sensitive to the nature of quinoline ring (**Scheme 23**).^{92,99}



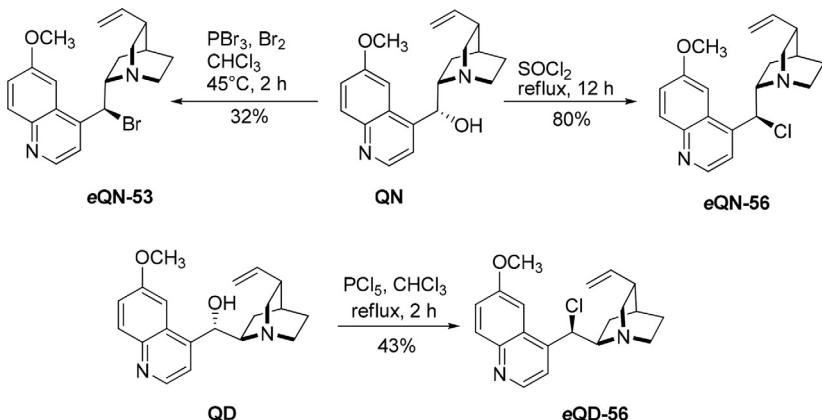
Scheme 22 Proposed rationale for the stereoconvergent hydrolysis.



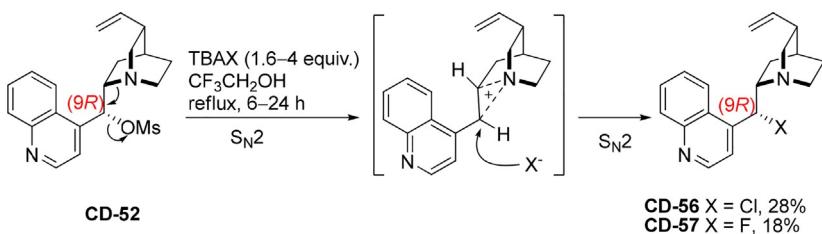
Scheme 23 Hetero-Cinchona rearrangements.

3.1.3 9-Halides

The introduction of halogen substituent in place of the 9-hydroxyl group of *Cinchona* alkaloids proceeded mostly with the inversion of configuration at C9 (**Scheme 24**). 9-*epi*-Chloro-substituted alkaloid derivatives can be efficiently prepared by the treatment of alkaloids with SOCl_2 ^{92,100} or PCl_5 ^{91,92} in good to fair yields. Conversely, the reaction of 9-*epi*-quinine with PCl_5 ⁹² gave 9-chloroquinine (38%) with the natural configuration at C9.⁹²



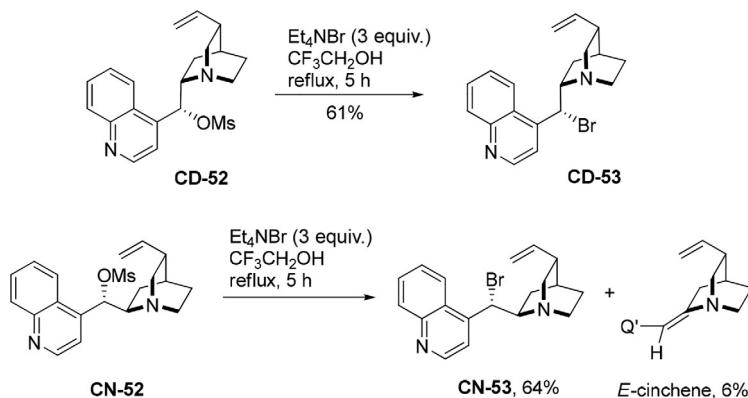
Scheme 24 Synthesis of alkaloid 9-halides.



Scheme 25 Retentive substitution of cinchonidine methanesulfonate with halides and proposed intermediate.

9-Bromo-substituted alkaloid derivatives can be prepared by treatment of alkaloids with PBr_3/Br_2 ⁹² or with $\text{PPh}_3/\text{CBr}_4$ with inversion of the configuration at C9. The best results were obtained with the $\text{PPh}_3/\text{CBr}_4$ system in toluene at 20°C, leading to product **eQN-53** in 80% (cf. Scheme 21).⁹³ In contrast to methanesulfonates, both 9-chlorides and 9-bromides hardly undergo the $\text{S}_{\text{N}}2$ displacement.

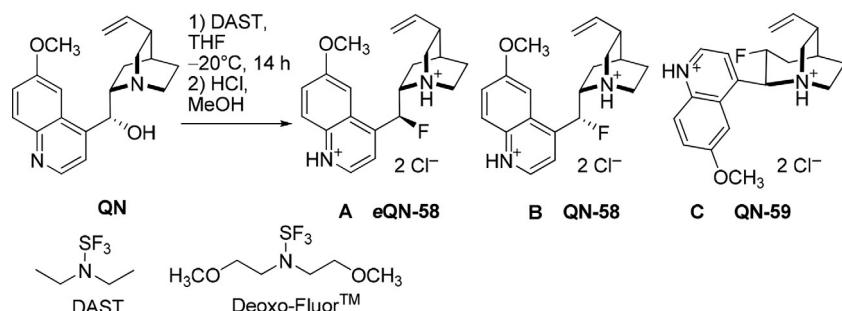
The introduction of halogen atom into the alkaloid structure can also take place with the retention of configuration at the C9 stereogenic center ([Schemes 25 and 26](#)). Halides, such as fluorides and chlorides, were obtained in moderate yield by reacting alkaloid methanesulfonates with tetrabutylammonium halides in trifluoroethanol.⁹⁹ Apart from substitution products with the retention of configuration, cage-expansion products were also formed. This result was attributed to the generation of nitrogen-bridged cation as the reactive intermediate in the first stage of the process (identical to the second *Cinchona* rearrangement). The plausible aziridinium ion would



Scheme 26 Substitution of cinchonidine and cinchonine methanesulfonates in trifluoroethanol.

be responsible for the reversibility of cage expansion and the retention of configuration upon the nucleophilic attack at carbon C9. However, stereoretentive substitution of the mesylates **CD-52** or **CN-52** with Et₄N⁺Br⁻ in trifluoroethanol furnished only cage-conserved retention products such as bromides **CD-53** and **CN-53** in good yields ([Scheme 26](#)).^{98,99}

The selective introduction of a fluorine atom at the C9 position was seldom described in the literature. The first examples of direct fluorodehydroxylation involved reaction with sulfur tetrafluoride in a solution of liquid hydrogen fluoride (HF/SF₄).^{101,102} Gilmour and coworkers applied alternative reagents such as diethylaminosulfur trifluoride (DAST) and Deoxo-Fluor to transform the alkaloid into the corresponding fluoride in a single operation ([Scheme 27](#)).^{103,104} These fluorinating systems do not require the preactivation of the substrate. Therefore, 9-deoxy-9-fluoroalkaloids were synthesized using DAST at low temperatures and subsequently converted to corresponding hydrochloride salts. The results of deoxyfluorination are summarized in [Table 1](#) and show differences between individual alkaloids. Only alkaloids with the 6'-methoxy substituent in the quinoline ring formed respective inversion products **A** ([Table 1](#), entries 1–4). Quinidine and dihydroquinidine mainly undergo stereoretentive substitution at C9 (product **B**); however, the inversion products **A** are also formed but with lower yields ([Table 1](#), entries 3 and 4), whereas the fluorination of alkaloids without the 6'-methoxy substituent gave product mixtures mostly containing the ring-expanded isomer **C** and cage-conserved retention product **B** ([Table 1](#), entries 5–8).



Scheme 27 A representative example (**QN**) for the 9-fluorination of *Cinchona* alkaloids.

Table 1 Deoxyfluorination of the *Cinchona* alkaloids with DAST

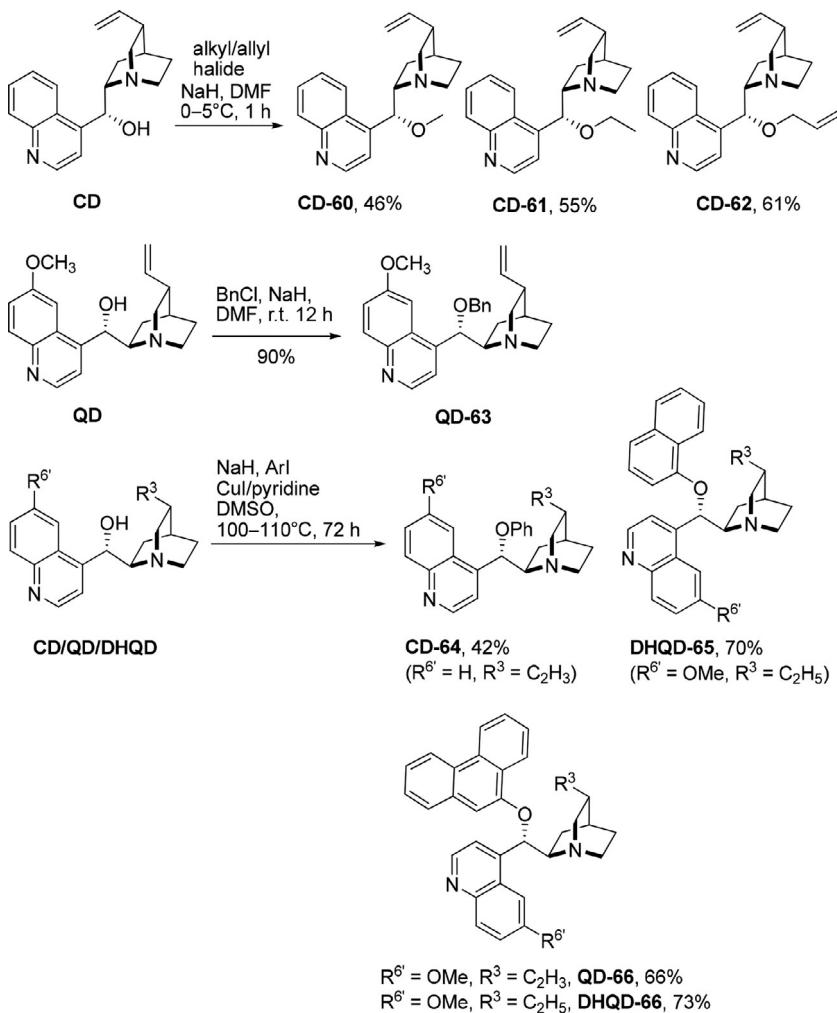
Entry	Alkaloid	Inversion product A (%)	Retention product B (%)	Ring-expanded product C (%)
1	QN	31	11	6
2	DHQN	22	11	5
3	QD	11	25	16
4	DHQD	12	18	21
5	CD	Traces	16	26
6	DHCD	Traces	7	11
7	CN	Traces	16	27
8	DHCN	Traces	12	12

3.1.4 9-O-Derivatives

The *Cinchona* alkaloids could be easily transformed into corresponding C9-ethers, esters, and carbamates without affecting the configuration at C9. Many of these derivatives are most frequently used as catalysts in asymmetric synthesis or as chiral discriminating agents.

3.1.4.1 Ethers

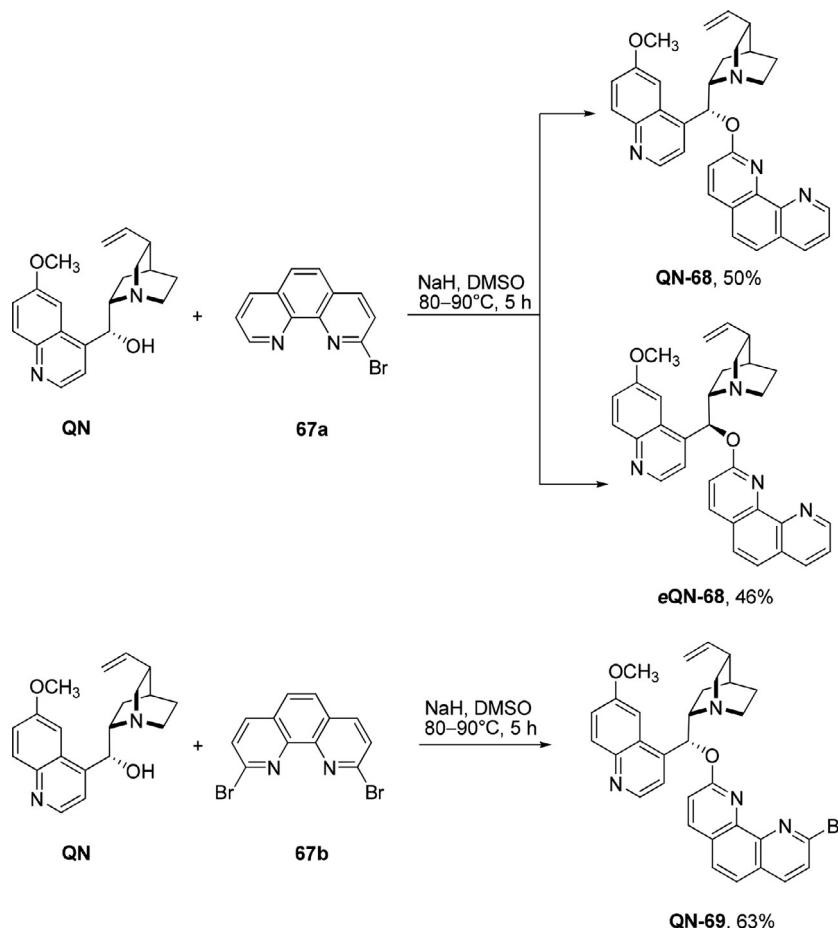
The synthesis of *Cinchona* alkaloid C9-alkyl ethers includes the Williamson etherification of alkaloid sodium salt with the respective alkyl halide (Scheme 28, top). C9-aryl ethers were obtained in the Ullmann-type reaction, in which deprotonated *Cinchona* alkaloids were coupled with aryl iodides in the presence of equimolar amounts of copper iodide and 2 equiv. of pyridine (Scheme 28, bottom).^{105–109}



Scheme 28 Representative syntheses of alkaloid ethers.

It was found that aromatic iodides were more efficient in the synthesis of dihydroquinidine C9-aryl ethers compared to bromides. 1-Bromonaphthalene yielded dihydroquinidine 9-O-(1'-naphthyl) ether **DHQD-65** in 36% vs 70% yield from 1-iodonaphthalene (with CuI as a mediator).¹⁰⁸

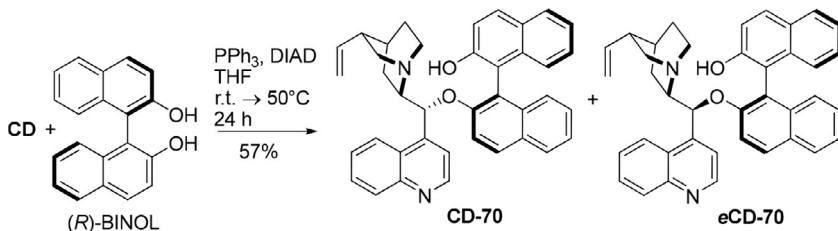
Recently, Wang and coworkers reported nucleophilic substitution of 2-bromo-1,10-phenanthroline **67a** with quinine in DMSO in the presence of NaH at 80–90°C, which afforded 9-(phenanthrolin-2-yl) ether as two diastereomers: **QN-68** (without change of configuration) and **eQN-68** (with inversion of configuration at C9, Scheme 29).¹¹⁰ On the other hand,



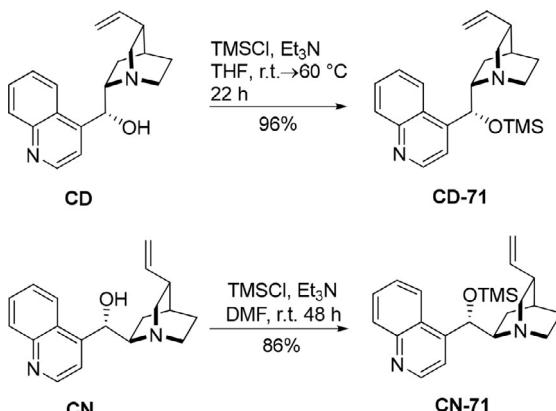
Scheme 29 Synthesis of quinine phenanthroline ethers.

the treatment of 2,9-dibromo-1,10-phenanthroline **67b** with quinine in the same procedure led to the sole isomer **QN-69** with the unchanged configuration at C9.

The Mitsunobu reaction has been used for the etherification of *Cinchona* alkaloids with BINOL (**Scheme 30**). This reaction was performed with (*R*)- or (*S*)-BINOL, PPh₃, DIAD providing the desired product in moderate yield (30%–57%). The authors found that both diastereomers, which resulted from the inversion and the retention of configuration at carbon atom C9, were formed. The diastereomeric mixtures of *epi*-ether and ether with the native configuration were obtained in the 4:1 to 1.5:1 ratio. The separation of these two isomers by the column chromatography was ineffective.¹¹¹



Scheme 30 Mitsunobu coupling of (*R*)-BINOL with cinchonidine.



Scheme 31 Representative syntheses of alkaloid silyl ethers.

O-Silyl derivatives (**CD-71** and **CN-71**) were synthesized in the reaction of appropriate alkaloid with chlorotrimethylsilane (TMSCl) in DMF or THF (Scheme 31). The transformation was carried in the presence of a base such as triethylamine (Et₃N) with 96% and 86% yield, respectively.^{107,112}

Numerous other *O*-silyl ethers (Fig. 9) were obtained nearly quantitatively in the reaction of alkaloids with various substituted chlorosilanes in the presence of 10 mol% of DMAP.^{102,113} *O*-Methyl or *O*-silyl ethers of *Cinchona* alkaloids were used as chiral modifiers in the enantioselective hydrogenation over Pt/Al₂O₃.^{107,114,115}

Bis-*Cinchona* alkaloid ethers, such as (DHQD)₂PHAL, (DHQD)₂PYR, and (DHQD)₂AQN, are the most effective Sharpless ligands for asymmetric dihydroxylation (AD) and aminohydroxylation reactions (Fig. 10).^{50,51,116–119} These compounds consist of two *Cinchona* alkaloid units connected by 9-aryl ether bonds. The linkers in dimeric *Cinchona* aryl ethers are electron-deficient heterocycles or anthraquinones. This class of dimeric compounds was synthesized via aromatic nucleophilic substitution.

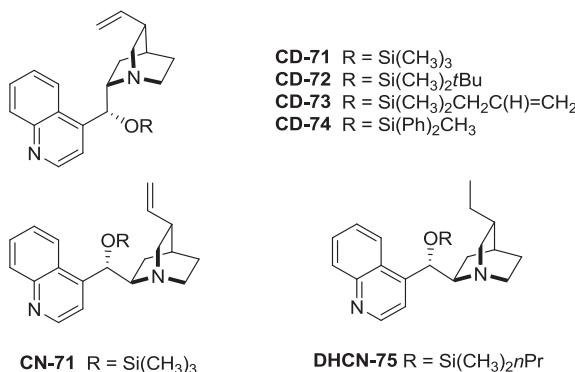


Fig. 9 Chiral Pt surface modifiers.

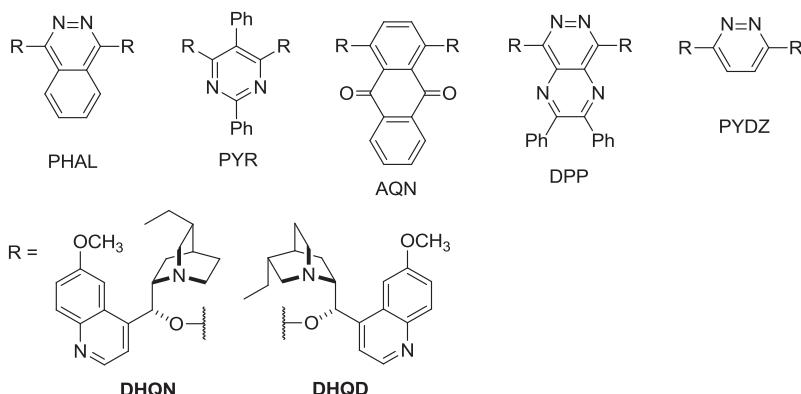
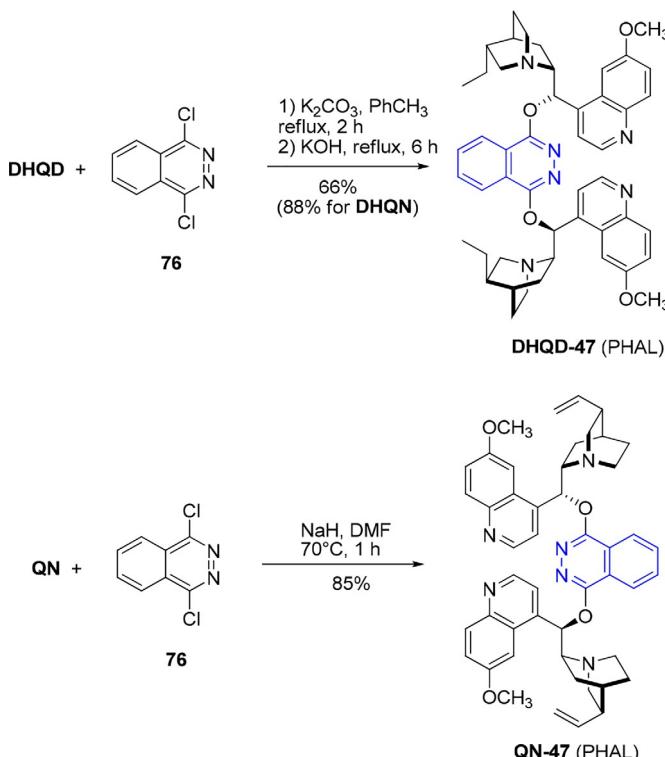


Fig. 10 Structures of linkers of dimeric aryl ethers of *Cinchona* alkaloids, ligands for asymmetric dihydroxylation.

Dimeric phthalazine ethers were synthesized either from *Cinchona* alkaloids and 1,4-dichlorophthalazine **76** under basic conditions and removal of water,¹⁰⁸ or alkaloids were first deprotonated with NaH in DMF and afterward treated with dichlorophthalazine (**Scheme 32**).¹²⁰ In most cases, the second method led to the product **47** in higher yield.

Analogs of **DHQN-47** (DHQ₂PHAL) with a phthalazine linker substituted with two phenyl groups were obtained (**Scheme 33**). 1,4-Dichloro-6,7-diphenylphthalazine (**77**) and 1,4-dichloro-6,7-diphenylpyrazinopyridazine (**79**) were coupled with **DHQD** or **DHQN** to afford DP-PHAL-linked dimers **DHQD-78**, **DHQN-78**,¹²¹ and DPP-linked dimer **DHQD-80**,¹²² respectively.

Corey's group applied *Cinchona* dimers with two single-ring heteroaromatic linkers in asymmetric dihydroxylation reaction (one example



Scheme 32 Syntheses of alkaloid phthalazine (PHAL) dimeric ethers.

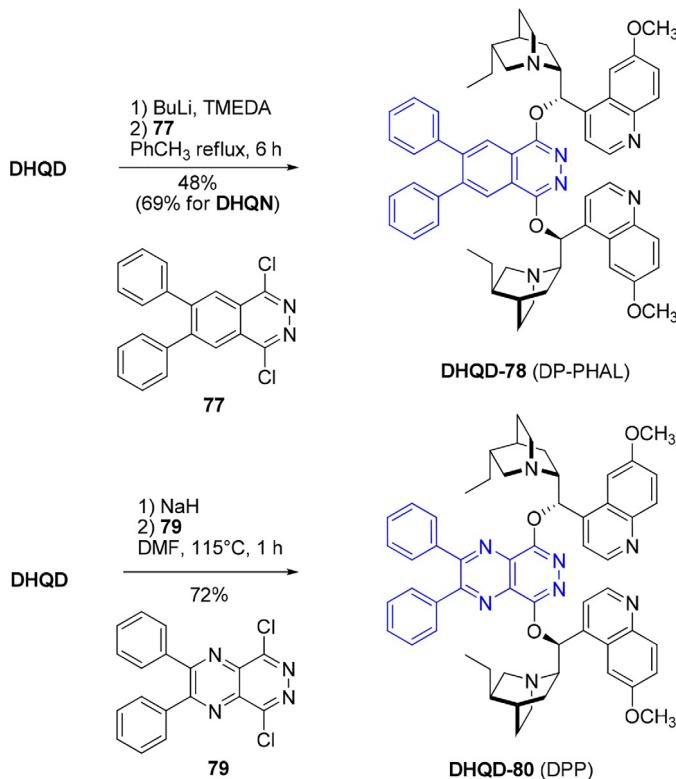
shown in Scheme 34).¹²³ These compounds incorporated pyridazine and pyrazine spacers and were formed from respective dichloroheterocycles.

Another important group of ligands, useful in the asymmetric dihydroxylation of branched olefins, are pyrimidine-based dimers **84** (PYR, Scheme 35). These dimers consist of two alkaloid units located in the *meta* position. The synthesis was accomplished by refluxing the dichloroheterocycle **83** with the alkaloid in toluene in the presence of a base to give dimers **DHQD-84** in good yields.^{124,125}

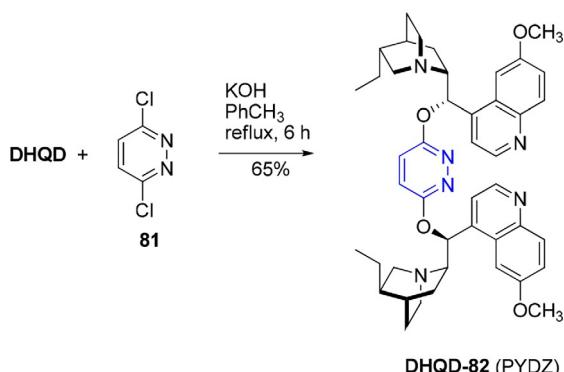
Apart from heteroaromatic ethers, anthraquinone derivatives were also highly successful ligands and organocatalysts. The reaction of 1,4-difluoroanthraquinone **85** with lithium salts of *Cinchona* alkaloids, prepared *in situ* from dihydroalkaloids and butyllithium, yielded the anthraquinone-bridged dimers (**DHQN/DHQD-86**, AQN) in good yield (Scheme 36).¹²⁶

3.1.4.2 Esters

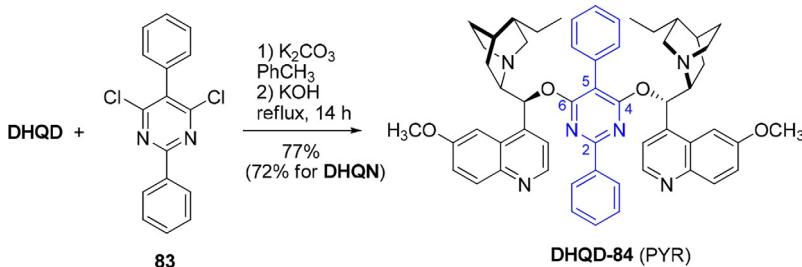
The esters of *Cinchona* alkaloids were most often prepared from corresponding carboxylic acid chlorides and parent alkaloids in excellent



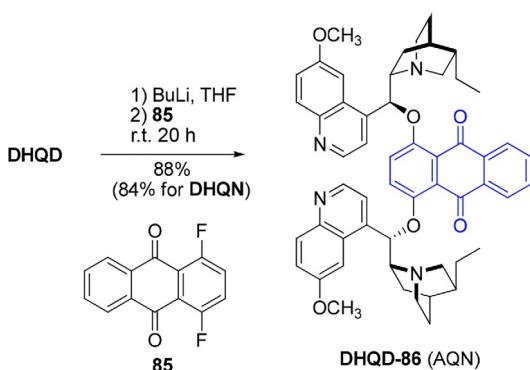
Scheme 33 Synthesis of diphenylphthalazine (DP-PHAL) and diphenylpyridazine (DPP)-linked dimers of *Cinchona* alkaloids.



Scheme 34 Synthesis of pyridazine (PYDZ)-linked dimeric ligands.



Scheme 35 Representative syntheses of pyrimidine (PYR)-linked dimer of *Cinchona* alkaloid.

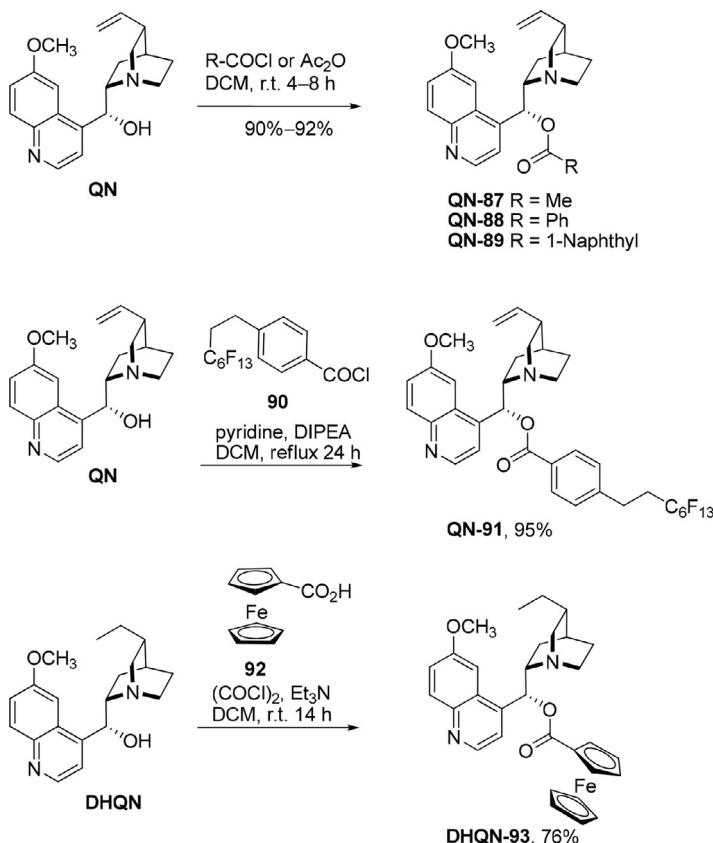


Scheme 36 Synthesis of anthraquinone (AQN)-type dimeric ligands.

yields (76%–92%, Scheme 37).^{127–130} Usually, the transformation was carried in the presence of a base such as pyridine, DIPEA, or Et₃N. Moreover, esters were obtained with the inversion of configuration at C9 by adopting the Mitsunobu reaction of alkaloid with an acid.⁹⁵

The treatment of *Cinchona* alkaloids with dicarboxylic acid dichlorides gave dimeric esters in yields above 70%.¹³¹ Similar to monoesters, the transformation took place in the presence of DMAP and a base such as Et₃N. In an alternative milder method dicarboxylic acids were activated with a carbodiimide (e.g., EDC) and then coupled with alkaloids; nevertheless, in this approach yields were fairly low.¹³²

A wide range of *Cinchona* alkaloid dimers with spacers having unsaturated bonds, aromatic rings, and bicyclic scaffolds were synthesized most often using the required acid chlorides for coupling (Fig. 11).^{127,130,133,134} The dimeric ester of isophthalic acid with dihydroquinidine **DHQN-94** was one of the most effective ligands for the osmium-catalyzed dihydroxylation.¹³¹



Scheme 37 Representative syntheses of esters of *Cinchona* alkaloids.

3.1.4.3 Carbamates

Cinchona alkaloid-derived carbamates were obtained in reactions of appropriate isocyanates with alkaloids in refluxing toluene in good yield (**Scheme 38**).^{82,135,136} The reaction can be catalyzed by dibutyltin dilaurate.¹³⁶

Carbamoyl derivatives of quinine have been prepared and applied as chiral solvating agents in NMR enantiodiscrimination experiments of amino acid derivatives.⁸² *Cinchona* carbamates were also immobilized on silica (through the addition of thiols to the vinyl group) and used as chiral solid phases for an anion-exchange chromatography of amino acids (**Scheme 39**).^{130,137}

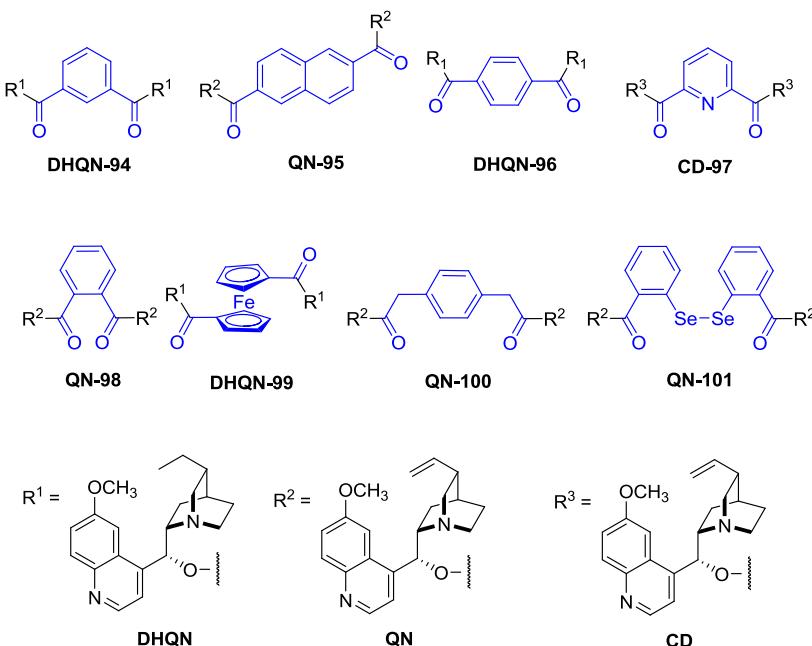
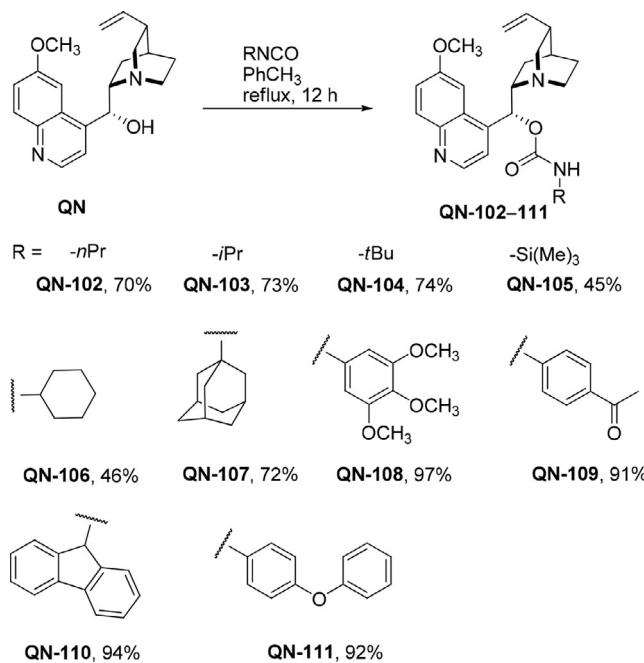
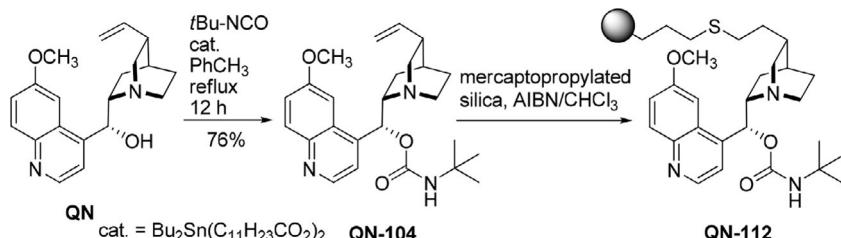


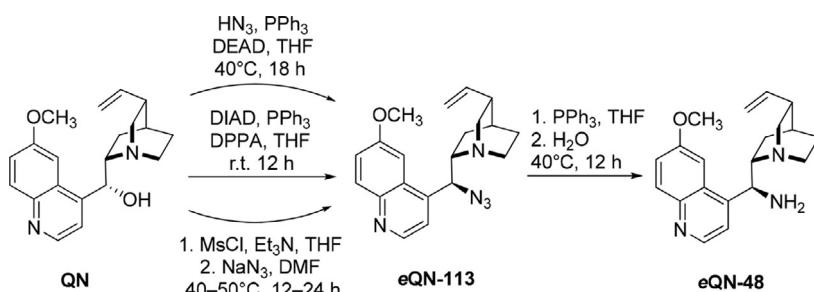
Fig. 11 Representative structures of dimeric *Cinchona* alkaloid esters with aromatic spacers.



Scheme 38 Representative syntheses of alkaloid carbamates.



Scheme 39 Representative synthesis of immobilized quinine carbamate.



Scheme 40 Example syntheses of 9-*epi*-amino-deoxyalkaloids.

3.1.5 9-Nitrogen Derivatives

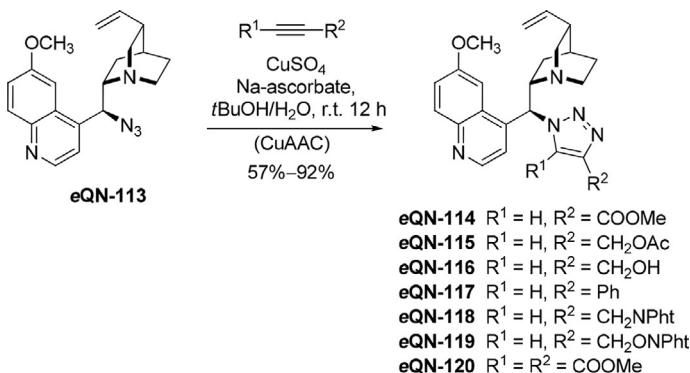
An azido function can be introduced into the alkaloid structure with the inversion of configuration at C9 (**Scheme 40**).^{138–140} Once incorporated, it can be directly converted into different functional groups or it can be employed for the further manipulation of the molecule (e.g., amines, thio-ureas, amides, imines, imides).¹⁴¹

A one-pot procedure involving the Mitsunobu azidation of the alkaloid with an azide source, e.g., HN_3 , diphenylphosphoryl azide (DPPA), gave initially the 9-*epi*-azido-alkaloid **113**, which was then treated with triphenylphosphine (Staudinger reduction) or hydrogenated to amine **48**. The azido-alkaloids can be also obtained in a two-step sequence via alkaloid methanesulfonates followed by the $\text{S}_{\text{N}}2$ displacement with NaN_3 in warm DMF.⁹⁸

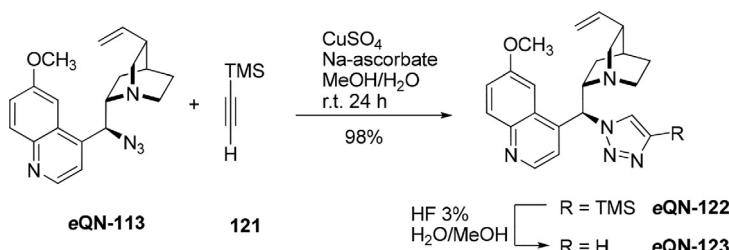
3.1.5.1 Triazoles

9-Azido *Cinchona* alkaloids undergo a facile coupling with an array of alkynes toward 1,4-disubstituted 1,2,3-triazole derivatives in copper(I)-catalyzed 1,3-dipolar cycloaddition reaction (CuAAC, **Scheme 41**).¹⁴²

An unsubstituted triazole ring was introduced at the position 9 in a similar reaction with an excess of TMS-acetylene (**Scheme 42**). The TMS group



Scheme 41 Representative syntheses of substituted 9-(1,2,3-triazolyl)-*Cinchona* alkaloids.



Scheme 42 Synthesis of 9-triazolyl-quinine.

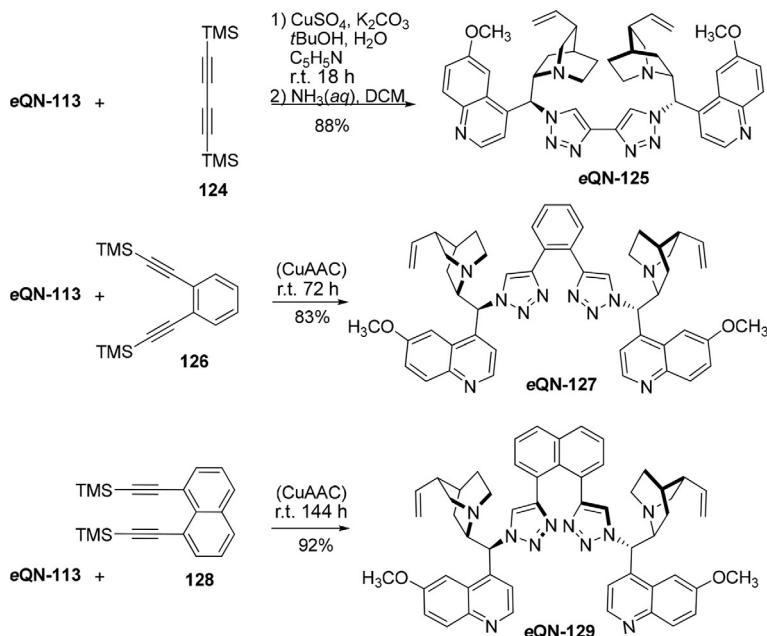
was removed with dilute HF in water/MeOH,¹⁴³ while the application of TBAF resulted in C9-epimerization.¹⁴⁴

The reaction of 9-azidoalkaloids with in situ liberated butadiyne and diethynylarenes under CuAAC conditions provided a series of *Cinchona* alkaloid-derived dimers in high yields (**Scheme 43**). The bitriazole dimer **eQN-125** exhibited promising properties as a ligand for the copper-catalyzed asymmetric Michael addition.¹⁴³

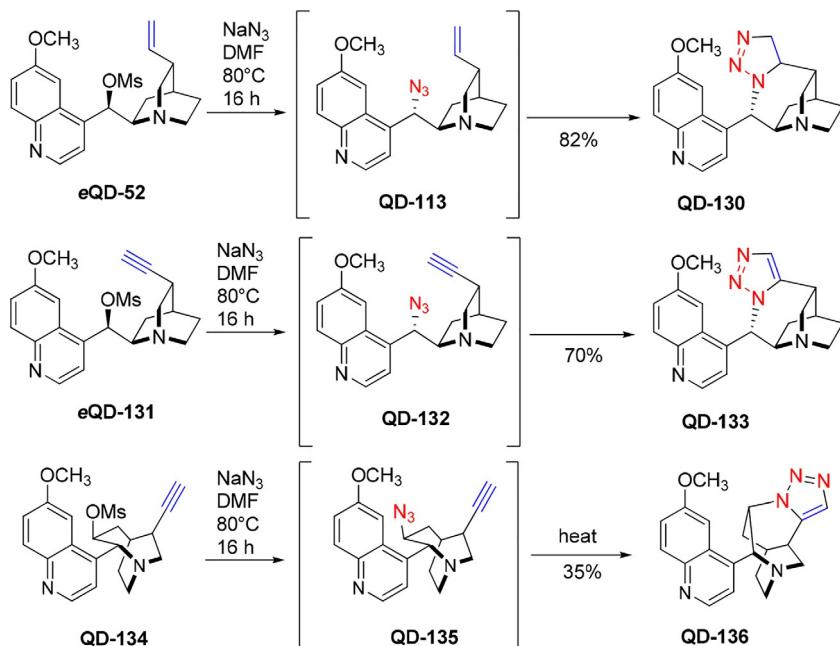
Hoffmann first described intramolecular thermal 1,3-dipolar cycloadditions of the in situ generated azido-alkaloid derivatives (**Scheme 44**). The fused 1,2,3-triazoline and 1,2,3-triazoles were obtained efficiently for natively configured quinidine derivatives, where the reacting sites are found in close proximity.^{98,145}

3.1.5.2 Thioureas and ureas

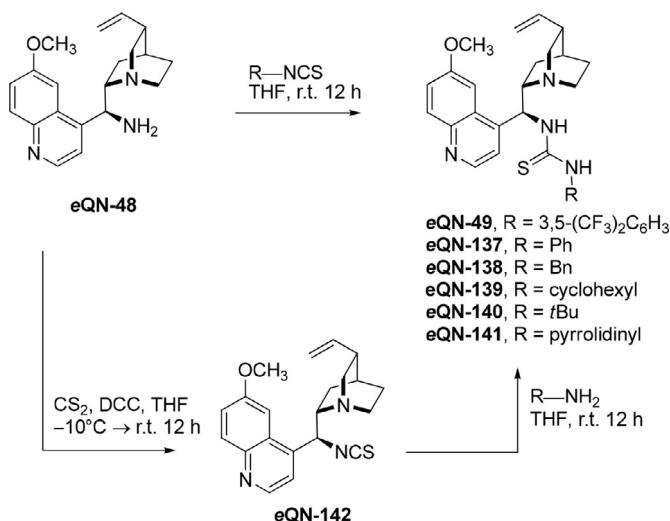
9-*epi*-9-Amino *Cinchona* alkaloid derivatives were precursors for the synthesis of thioureas (**Scheme 45**).^{61,146–155} The respective products were directly



Scheme 43 Syntheses of 9-triazoly-Cinchona alkaloid dimers.



Scheme 44 Intramolecular Huisgen 1,3-cycloaddition in Cinchona alkaloid-derived azides.



Scheme 45 Typical procedures for synthesis of thiourea-substituted *Cinchona* alkaloids.

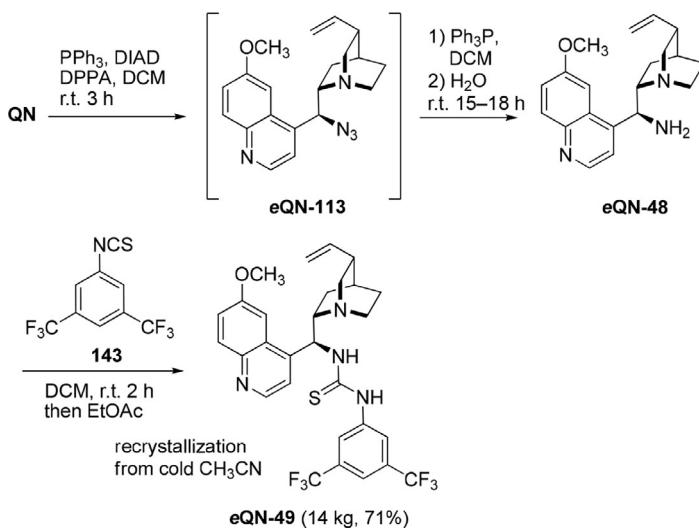
prepared using appropriate isothiocyanates in good yield (61%–81%). In an alternative method, the treatment of 9-aminoalkaloids with CS₂ in THF in the presence of DCC provided the isothiocyanate **eQN-142** (71%), which was then condensed with various primary amines.^{150–154}

Cinchona alkaloid-based thioureas, such as **eQN-49** with the 3,5-bis(trifluoromethyl)phenyl moiety, are bifunctional organocatalysts, which have been widely used for a variety of asymmetric reactions. Recently, a cost-effective procedure for the preparation of these catalysts on a large scale (more than 14 kg of catalyst per batch) was reported (**Scheme 46**).¹⁵⁵ This method furnished the products in 70%–73% overall yield and over 95% purity.

Modular structures incorporating both *Cinchona* alkaloid and 1,2-diaminocyclohexane hybrid scaffolds of various configurations were obtained (**Fig. 12**). These products had both primary and tertiary amines, and thiourea functionalities.¹⁵¹

Furthermore, modular multifunctional thioureas were synthesized in the reaction of 9-*epi*-isothiocyanato *Cinchona* alkaloids with amino alcohols in THF (**Scheme 47**). The reduction of amino acids with NaBH₄/I₂ to amino alcohols was the first step in a one-pot procedure, which afforded thioureas in good yields (57%–82%).^{152,153}

Koskinen et al. synthesized a series of thiourea organocatalysts according to two complementary procedures (**Scheme 48**). First, condensation of



Scheme 46 Pilot plant process for the synthesis of **eQN-49**.

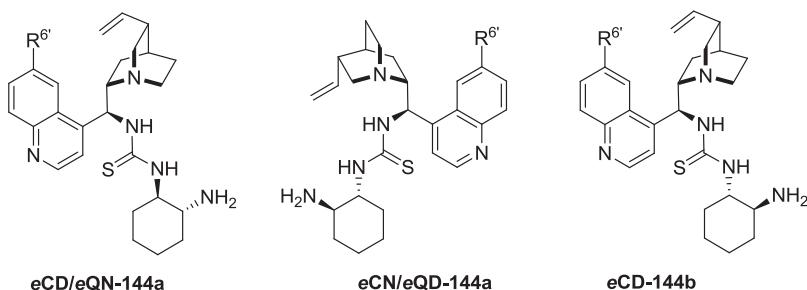
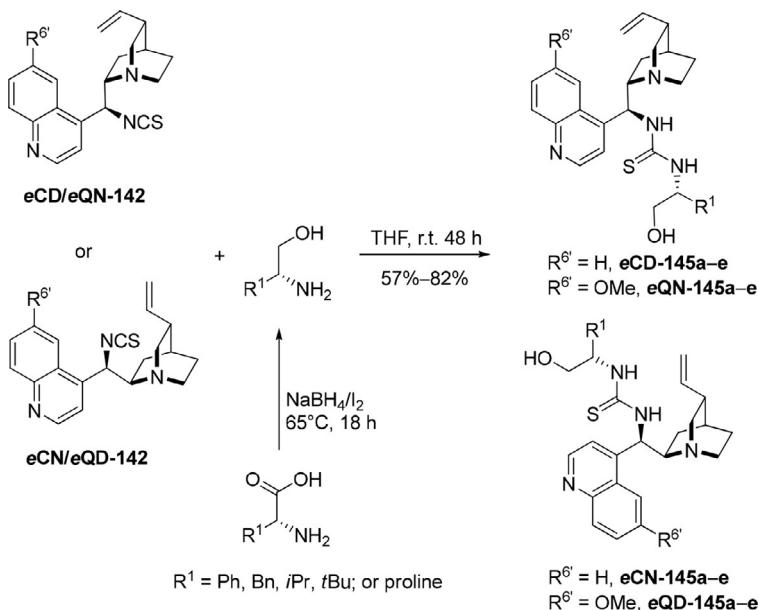


Fig. 12 Selected structures of *Cinchona* alkaloid-1,2-diaminocyclohexane thioureas.

9-*epi*-aminoquinidine (**eQD-48**) with isothiocyanates provided thioureas in good yields. The second method was based on the treatment of the 9-*epi*-quinidine isothiocyanate (**eQD-142**) with primary amines.¹⁵⁰

The urea derivatives **eDHQN/eDHQD-154** were obtained in the reaction of 3,5-bis(trifluoromethyl)phenyl isocyanate (**153**) and appropriate 9-aminodihydroalkaloids in DCM in moderate yield (Scheme 49).¹⁴⁶

A series of *Cinchona* alkaloid-based ureido carbamates were obtained from α -amino acid-derived isocyanates and 9-*epi*-aminodihydroquinine (Scheme 50).¹⁵⁶ The amino acid was converted to carbamate, and the carboxylic group was replaced with isocyanate. Finally, the coupling of isocyanate **158** with 9-*epi*-amino-dihydroquinine (**eDHQN-48**) gave corresponding ureido carbamates **eDHQN-159–161** in good yields.¹⁵⁶



Scheme 47 Syntheses of alkaloid–amino acid-based thioureas.

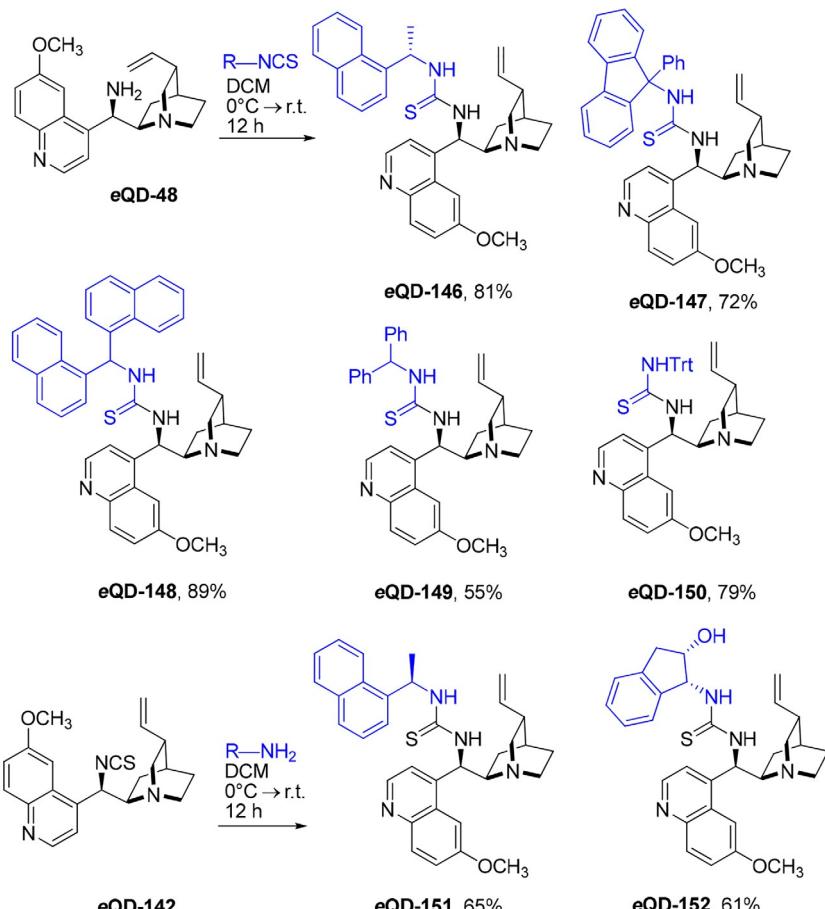
3.1.5.3 Amides

Amides were prepared by treatment of 9-aminoalkaloids (**48**) with acid chlorides in DCM in the presence of Et_3N as a base. In an alternative method, amides were formed in the reaction of amines **48** with trimethylaluminum and carboxylic acid esters in toluene or hexane (Scheme 51). Recrystallization of alkaloid amide hydrochlorides was an efficient purification method.¹⁴⁰

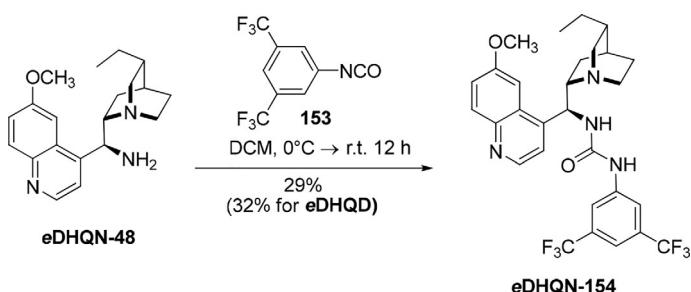
Functional amides **185**, equipped with proline moiety, were obtained in a two-step procedure, by the condensation of *N*-Boc-proline with 9-aminoalkaloids, in up to 47% yield (Scheme 52).¹⁵⁷

Dixon et al. presented functional amide **eCN-187** with a triarylphosphine unit derived from *Cinchona* alkaloids (Scheme 53) as highly efficient ligands for the silver-catalyzed asymmetric isocyanoacetate aldol reaction. They obtained the relevant amide from the triphenylphosphine-derived benzoic acid **186** using the carbodiimide method.¹⁵⁸ The Dixon's ligand **eCN-187** also proved effective in the synthesis of chiral 3*H*-pyrroles.¹⁵⁹

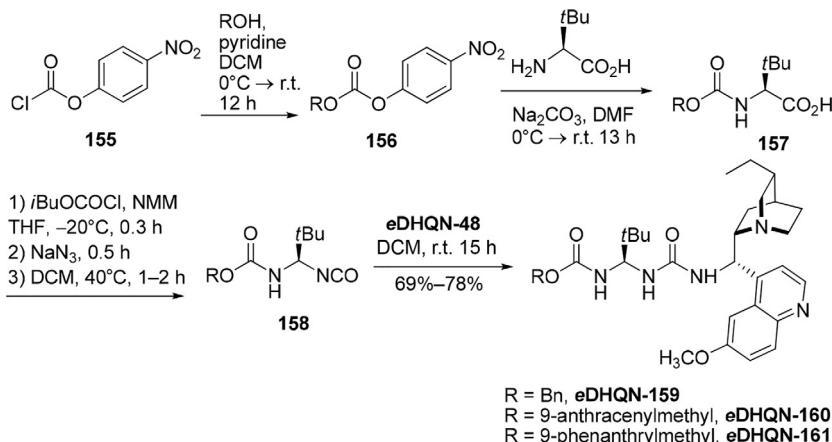
Picolinamide *Cinchona* alkaloid derivatives were prepared in good yield using the mixed-anhydride method with picolinic acid and isobutyl



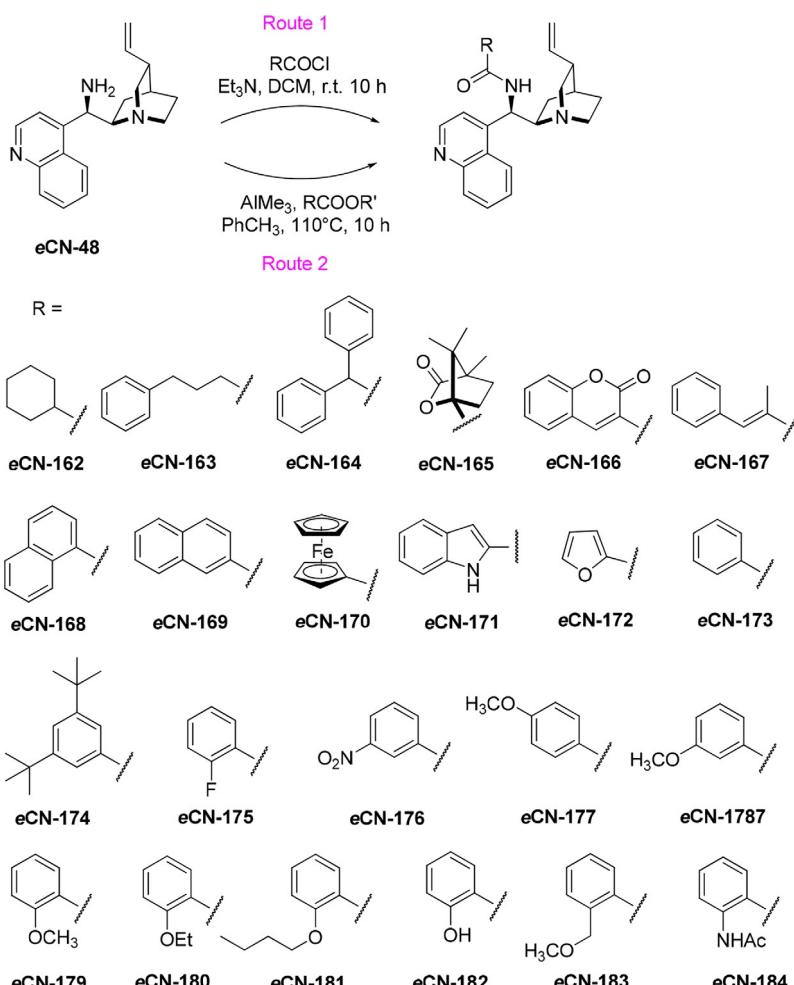
Scheme 48 Syntheses of *Cinchona* alkaloid thioureas.



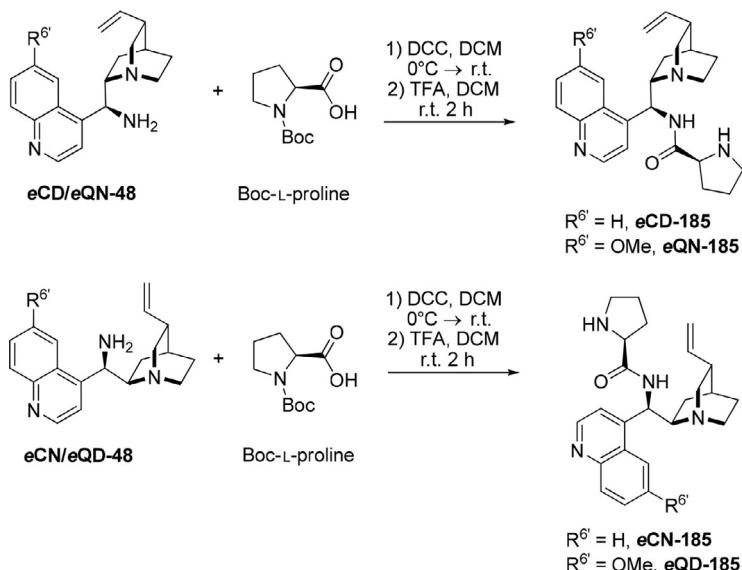
Scheme 49 A representative synthesis of *Cinchona* alkaloid-derived urea.



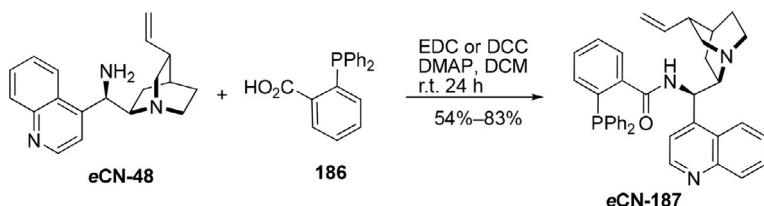
Scheme 50 Syntheses of *Cinchona* alkaloid ureido carbamates.



Scheme 51 Example syntheses of *Cinchona* alkaloid-derived amides.



Scheme 52 Example syntheses of alkaloid prolinamides.

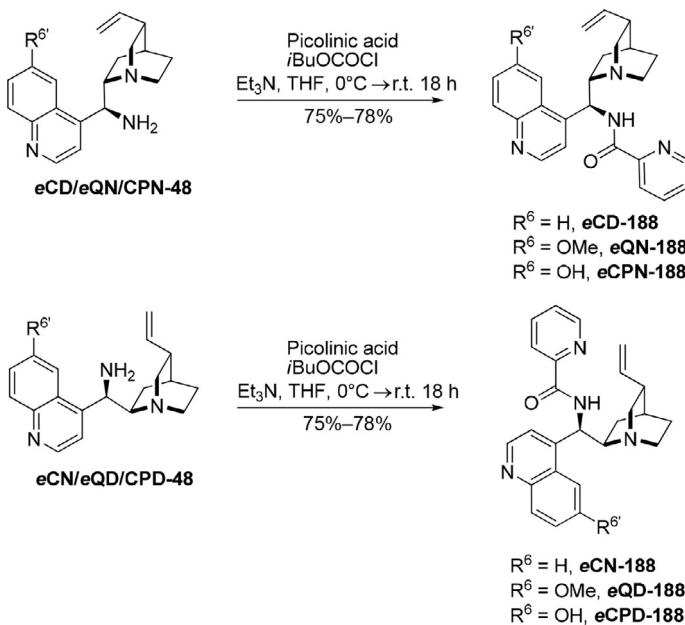


Scheme 53 Synthesis of Dixon's ligand.

chloroformate in the presence of Et_3N in THF (Scheme 54).^{160–162} They have proved as effective organocatalysts in the hydrosilylation of ketimines¹⁶⁰ and in the enantioselective desymmetrization of aziridines with malononitrile using *Cinchona* alkaloid amide zinc(II) complexes.¹⁶² Picolinamides were also used for the preparation of solid-supported chiral catalysts on silica and polystyrene as supports.¹⁶¹

3.1.5.4 Squaramides

Cinchona alkaloid squaramides were easily prepared in a two-step process. Diethyl or dimethyl squarate reacted with the first amine in DCM or MeOH. Next coupling with a second amine resulted in disubstituted squaramide, which usually precipitated out of solution (Scheme 55). The



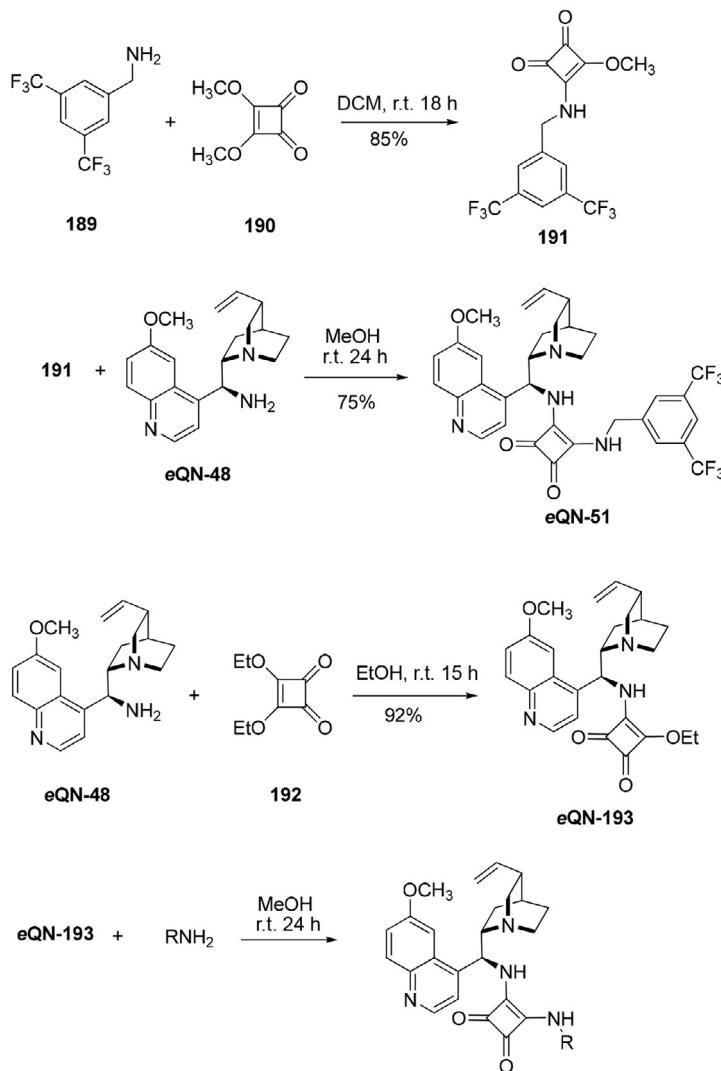
Scheme 54 Syntheses of alkaloid picolinamides.

alkaloid-derived amines **48** were used as either the first or the second amine component.^{63,163–173} Examples of preparation of squaramide from dimethyl squarate, 3,5-bis(trifluoromethyl)benzylamine, and *Cinchona* alkaloids are shown in Scheme 55.^{63,163–165}

A number of *Cinchona* alkaloid squaramides with additional functional modules was synthesized. The appropriate derivatives included moieties of ferrocene, chiral amines, e.g., DPEN or amino acid derivatives, such as prolinol, as illustrated in Fig. 13.

Treatment of (*S*)-2-aminomethyl-1-*N*-Boc-pyrrolidine with one equivalent of diethyl squarate in the presence of Et₃N in EtOH gave the corresponding squaric monoamide monoester **206**.¹⁶⁶ Subsequently, the reaction of **206** with the cinchonine-derived amine **eCN-48** under the same reaction conditions afforded Boc-protected squaramide **eCN-207**, which was then deprotected directly with HCl to give the desired compound **eCN-197** (Scheme 56).

Adequate derivatives of squaramides can undergo further transformations, such as amidation or silyl ether formation as exemplified in Scheme 57.^{169–171}



Scheme 55 Representative syntheses of *Cinchona* alkaloid squaramides.

A C_2 -symmetric *Cinchona* alkaloid squaramide was obtained by the treatment of 9-*epi*-aminoalkaloid **eDHQN-48** with squaric acid dimethyl ester **190** in methanol for 48 h (**Scheme 58**). The product **eDHQN-215** precipitated in nearly quantitative yield.¹⁷² Likewise, C_2 -symmetric dimer **eCN-217** with two unsymmetrically substituted squaramide units was synthesized, by mixing 9-aminocinchonine **eCN-48** with 1 equiv. of diethyl

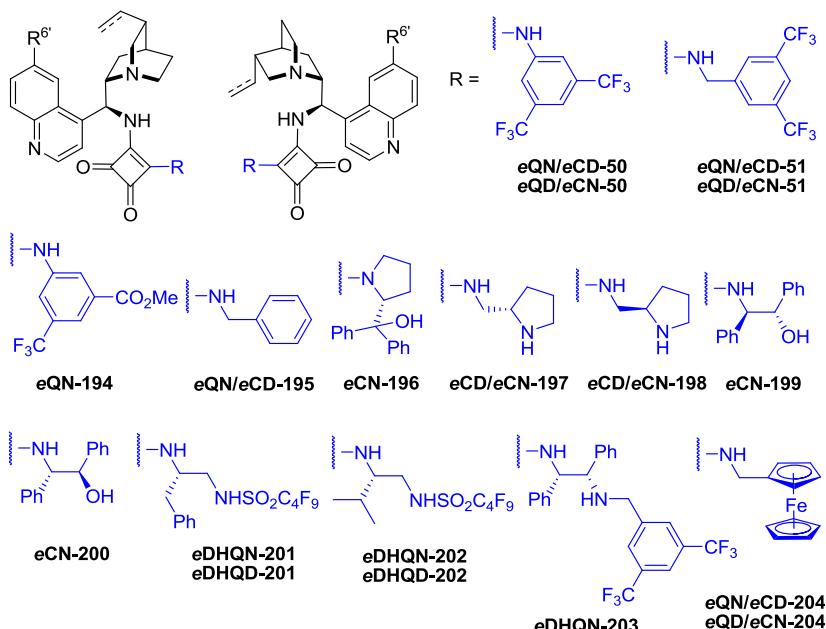
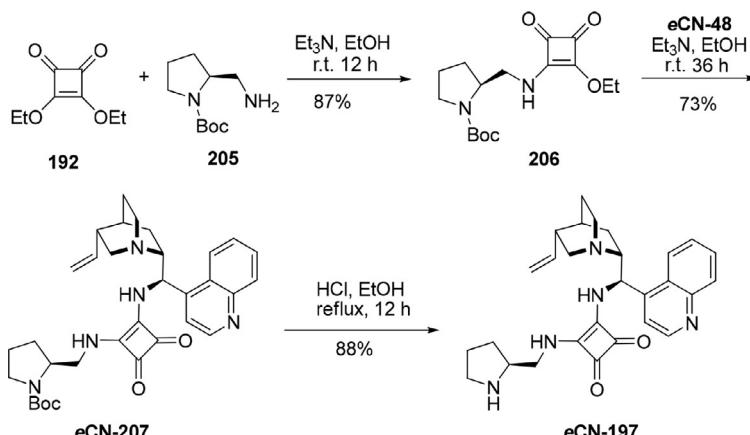
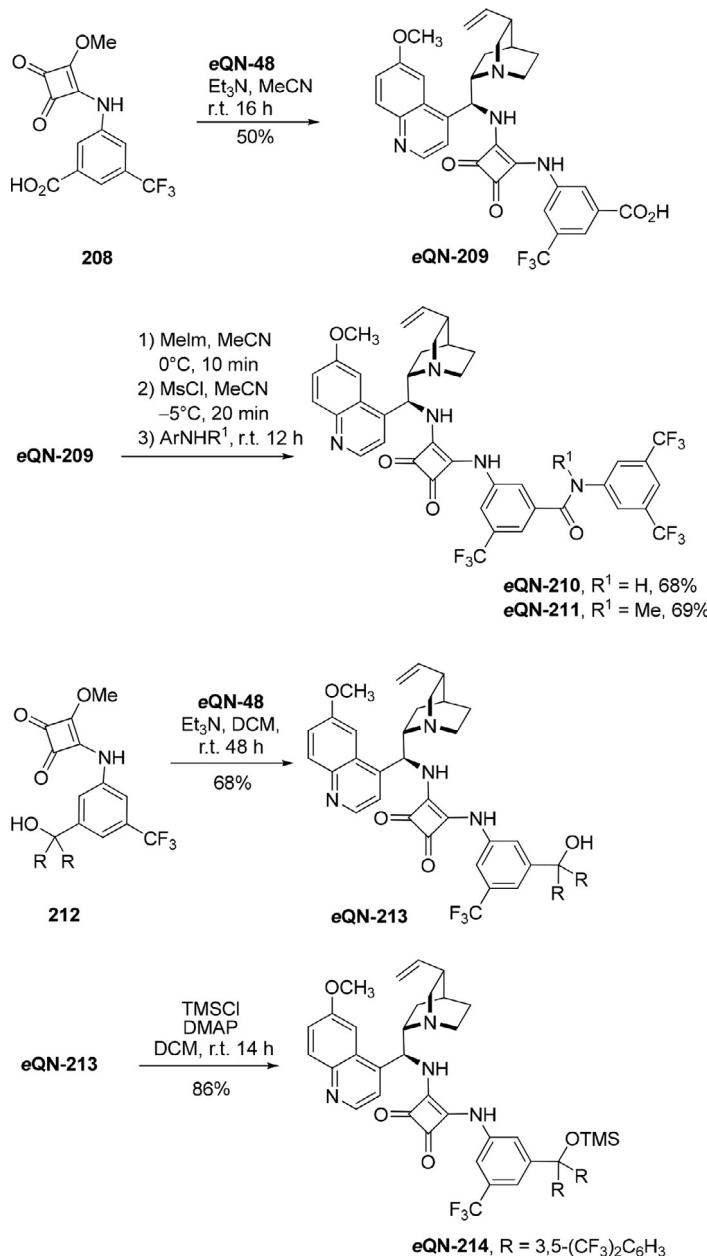


Fig. 13 Selected alkaloid squaramides.

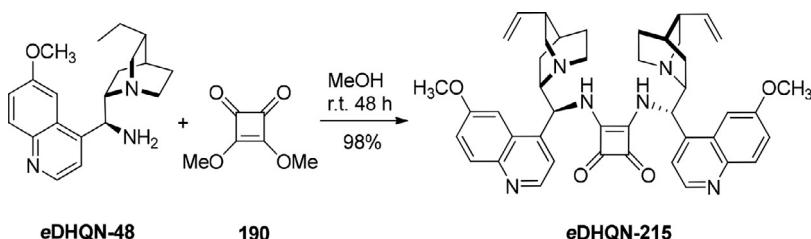


Scheme 56 Synthesis of proline-derived alkaloid squaramide.

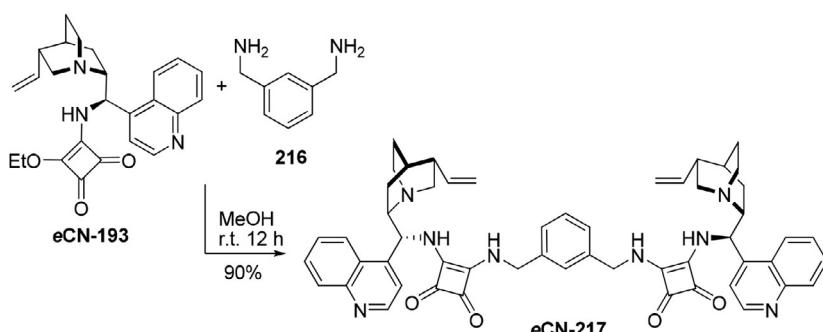
squareate, and the intermediate monoester **eCN-193** was then reacted with 0.5 equiv. of *m*-xylylenediamine (**216**) (Scheme 59).¹⁷³ Analogous C_3 -symmetric trimeric compounds were obtained from corresponding triamines.¹⁷³



Scheme 57 Selected reactive squaramides and their further transformations.



Scheme 58 A representative synthesis of dimeric squaramide.



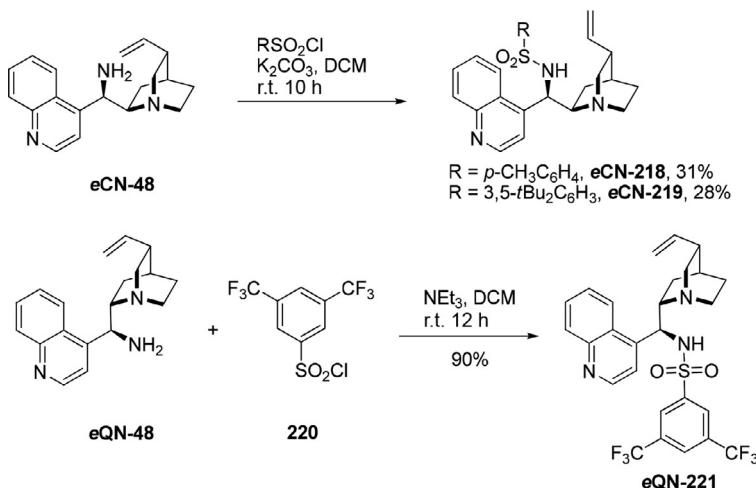
Scheme 59 Synthesis of a C_2 -symmetric dimer of *Cinchona* alkaloid squaramide.

3.1.5.5 Sulfonamides

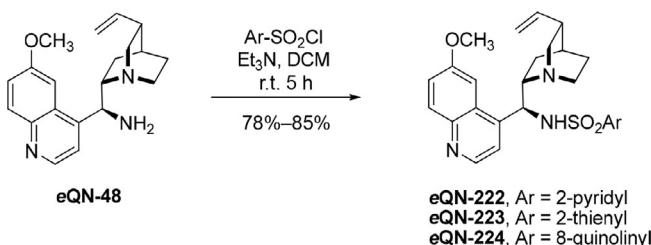
Cinchona alkaloid sulfonamides were prepared in the reaction of the amino-alkaloids with sulfonyl chlorides in the presence of a base (**Scheme 60**).^{174–178}

The reaction of cinchonine-derived amine **eCN-48** with *p*-toluenesulfonyl chloride or 3,5-di-*tert*-butylbenzenesulfonyl chloride was carried out in the presence of K_2CO_3 in DCM and resulted in moderate yield.¹⁷⁴ 3,5-Bis (trifluoromethyl)benzenesulfonyl chloride (**220**) in reaction with 9-*epi*-aminoquinine (**eQN-48**) in the presence of Et_3N gave the product **eQN-221** as a white solid, with much higher efficiency (90% yield, **Scheme 61**).¹⁷⁵ Unlike reactions with isothiocyanates, sulfonyl chlorides react cleanly with alkaloid amine hydrochloride hydrate in the presence of excess Et_3N .

Nakamura et al. reported the synthesis of *N*-heteroarenesulfonyl *Cinchona* alkaloid sulfonamides starting from 9-*epi*-aminoalkaloids (**eQN-48**, **eCD-48**, **eQD-48**, **eCN-48**) and 2-pyridine-, 2-thiophene-, and 8-quinolinesulfonyl chlorides in DCM in the presence of Et_3N at 0°C (**Scheme 61**). The expected sulfonamides were obtained in good yield and were promising organocatalysts for the asymmetric synthesis of chiral α -amine peroxides and chiral *N,S*-acetals.^{176–178}



Scheme 60 Syntheses of *Cinchona* alkaloid sulfonamides.



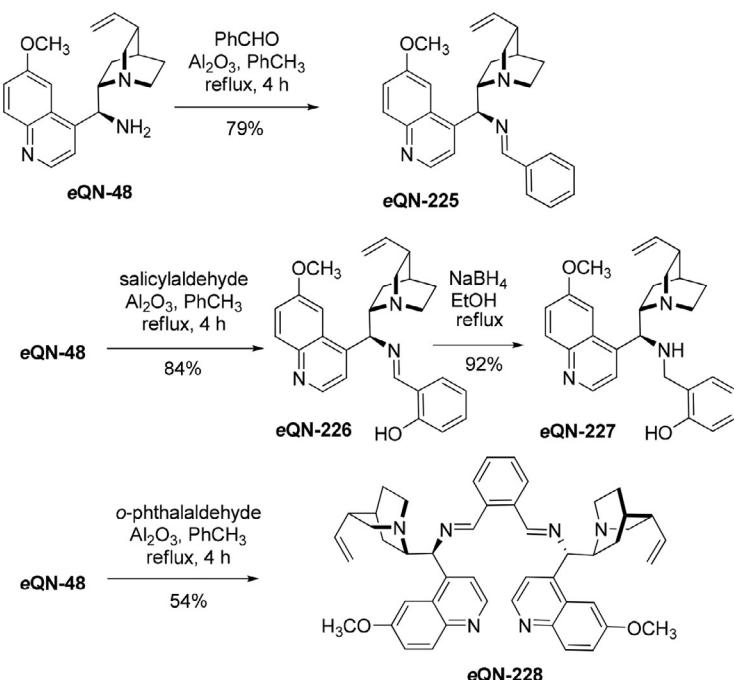
Scheme 61 Syntheses of quinine heterocyclic sulfonamides.

3.1.5.6 Imines

Schiff bases were obtained by the condensation of 9-aminoalkaloids of either configuration with aryl aldehydes such as benzaldehyde, 4-chlorobenzaldehyde, or salicylaldehyde in DCM or toluene, in the presence of a mild dehydrating agent (anhydrous Na_2SO_4 or Al_2O_3) in good yield (75%–84%) (Scheme 62).^{179,180}

The reaction of aminoquinine **eQN-48** with phthalaldehyde gave the dimeric imine **eQN-228** in 54% yield.¹⁷⁹ Also dendrimeric imines were obtained.¹⁸¹ Reduction of imines with NaBH_4 provided secondary amines, i.e., 9-alkylamino *Cinchona* alkaloids such as **eQN-227**.¹⁷⁹

Both 9-aminoalkaloids **QN-48** and **eQN-48** were converted to the corresponding imines with 4-chlorobenzaldehyde in DCM in the presence of anhydrous Na_2SO_4 . The imines, without further purification, were used in the Pudovik reaction with diethyl phosphite affording the corresponding



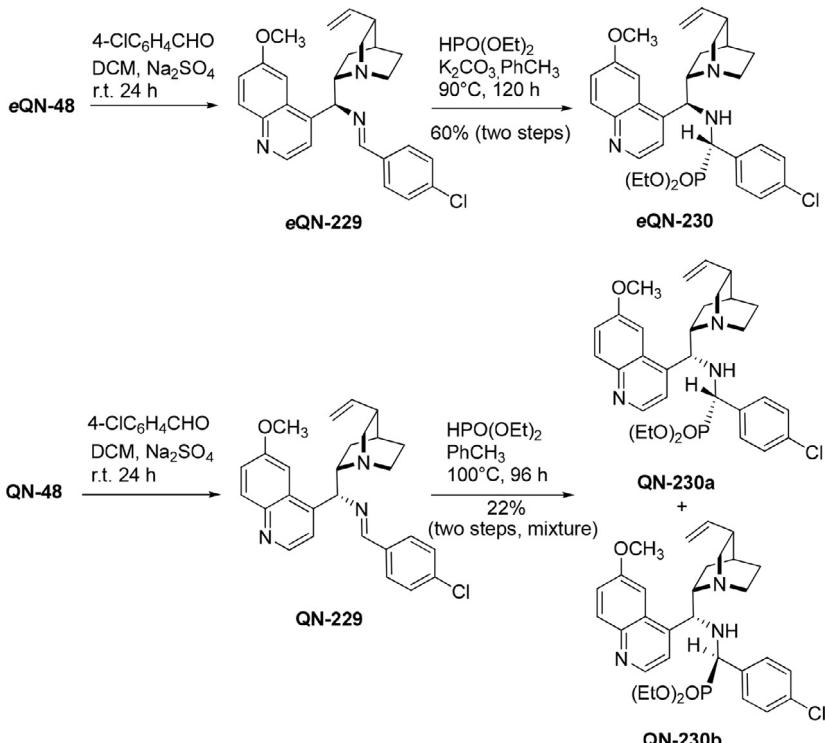
Scheme 62 Synthesis of Schiff bases of *Cinchona* alkaloids.

aminophosphonates **230** with a new stereogenic center (**Scheme 63**). Only in the case of *epi*-alkaloid imine **eQN-229**, the reaction was efficient and highly diastereoselective. In the case of the substrate of a native configuration **QN-229** almost equimolar mixture of epimers emerged and the yield was low.¹⁸⁰

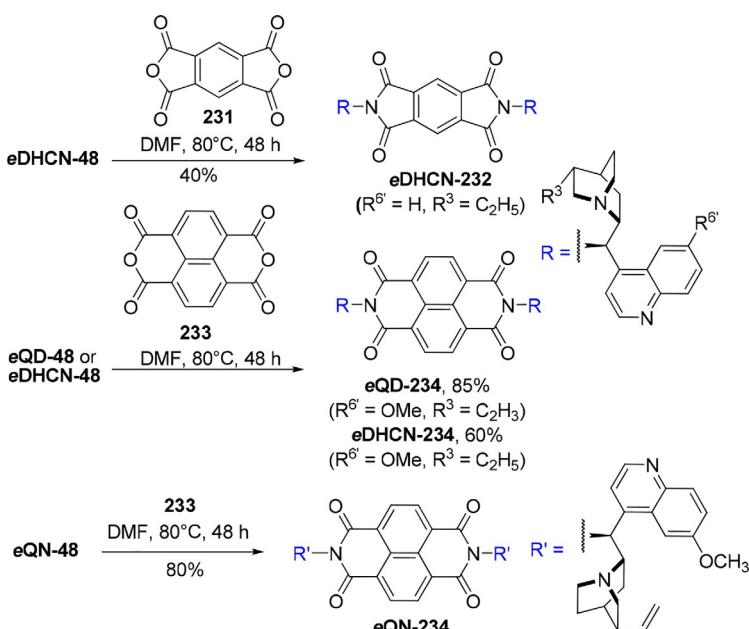
3.1.5.7 Imides

Chiral, *C*₂-symmetric aromatic diimides possessing two *Cinchona* alkaloid moieties and 1,2,4,5-benzenetetracarboxydiimide and 1,4,5,8-naphthalenetetracarboxydiimide spacers were obtained in the reaction of appropriate anhydrides (pyromellitic anhydride **231** or 1,4,5,8-naphthalenetetracarboxylic anhydride **233**) with 9-aminoalkaloids in DMF at 130°C, in 40%–85% yield (**Scheme 64**). These bifunctional receptors were applied for the recognition and discrimination of mono- and dicarboxylic acids (**Scheme 65**).

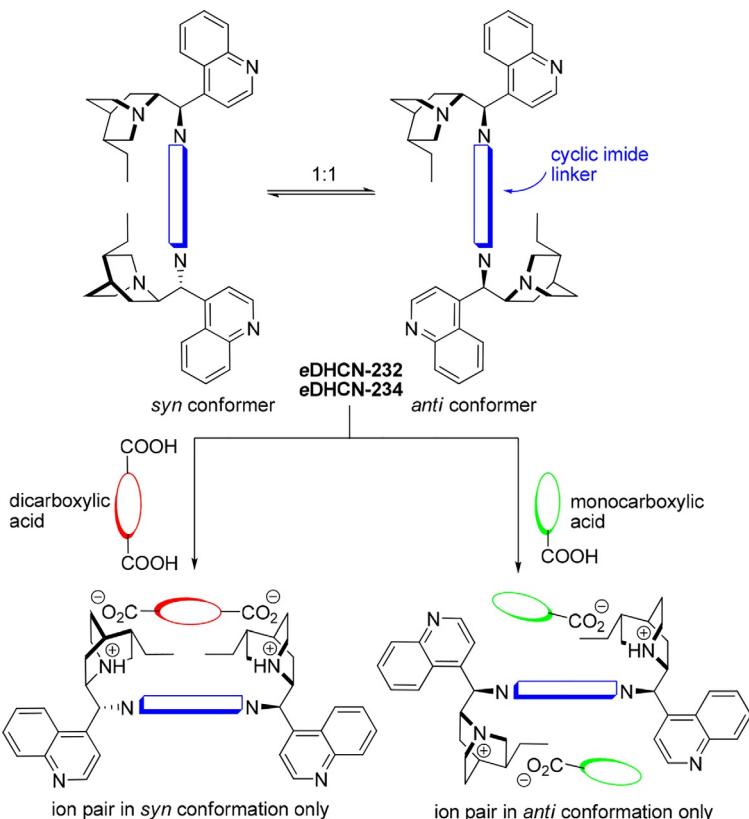
Atropisomers arise from the restricted rotation around the C9–N bond in the *Cinchona* alkaloid derivatives **232** and **234** containing the diimide spacer (cf. **Scheme 64**). Two conformers, *syn* and *anti*, with different geometry and



Scheme 63 Synthesis of quinine aminophosphonates.



Scheme 64 Syntheses of alkaloid diimides.

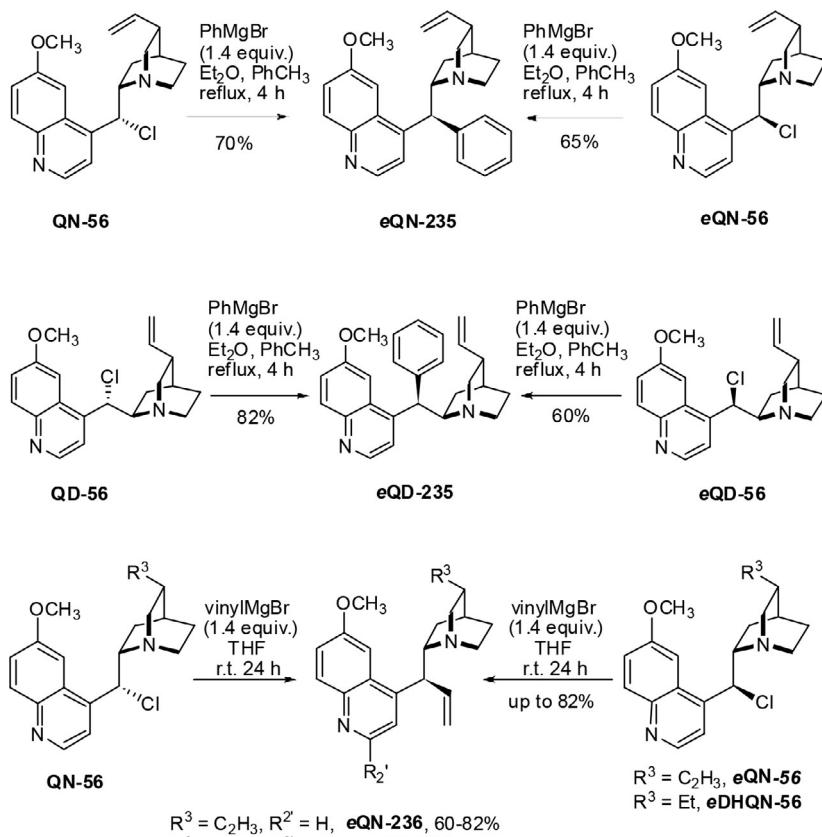


Scheme 65 Recognition of carboxylic acids by *Cinchona* alkaloid dimers with imide spacers.

with comparable energies, exist in solution in equimolar amounts. In the presence of dicarboxylic acids, the *syn* conformers dominate, while with monocarboxylic acid guests the *anti* conformers prevail (**Scheme 65**). The quinuclidine nitrogen atoms are protonated by acids. The recognition abilities were observed with ^1H NMR spectroscopy.^{182–184} Remarkably, Gawroński invented bis-*Cinchona* alkaloid diimide triad, which in the presence of bromophenol blue allowed for discrimination of enantiomers of α -hydroxycarboxylic acids and could be used for quick determination of natural tartaric acid in wine.¹⁸²

3.1.6 9-Carbon Derivatives

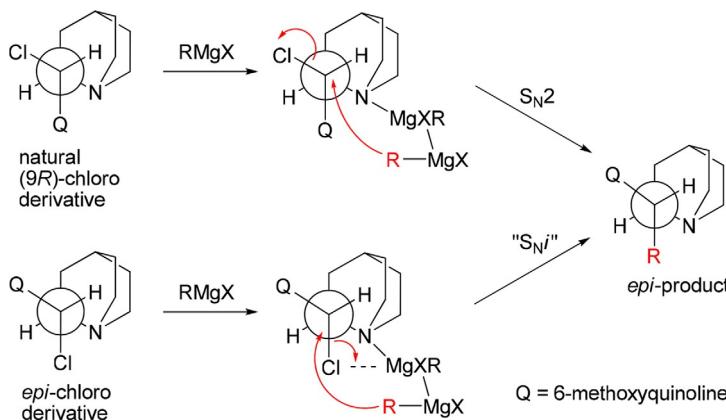
Formation of new C–C bond by replacement of C9 hydroxyl group was first described by Ochiai et al. In the reaction of 9-*epi*-chloro-derivative of



Scheme 66 Substitution of 9-chloroalkaloids with Grignard reagents.

quinine **eQN-56** with phenylmagnesium bromide in benzene/Et₂O, the corresponding 9-phenyl derivative was proposed.¹⁸⁵ The reinvestigation of this reaction revealed that carbon–C9 bonds form readily and selectively in the reaction of sp²-Grignard reagents with alkaloid 9-halides (Scheme 66). The corresponding 9-deoxy-aryl and 9-deoxy-vinyl products were obtained in good yields.¹⁸⁶

Both native and *epi*- configured 9-chloro and 9-bromo alkaloids afforded products with only *epi* configuration at C9 (e.g., **eQN-235** and **eQN-236**). Thus, retention of configuration was observed for 9-*epi*-chloride, while naturally configured (9*R*)-chloride was reacted with a Grignard reagent with complete inversion of configuration. The same stereochemical outcome was observed for all the *Cinchona* alkaloid halides; however, the yields for



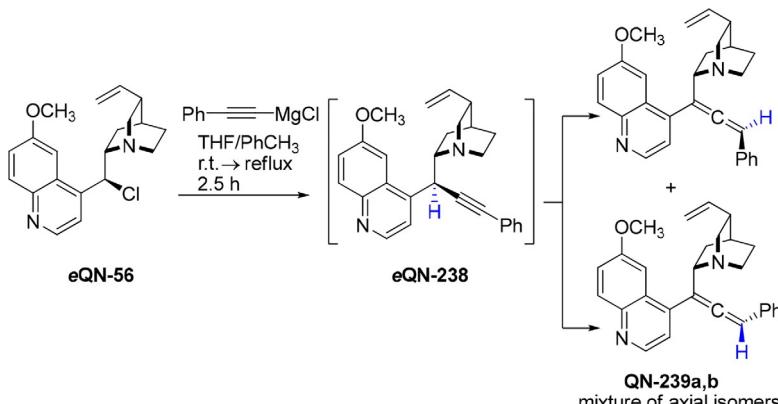
Scheme 67 Outline of the proposed mechanism for stereoconvergent Grignard substitution of 9-halo-substituted *Cinchona* alkaloids.

cinchonine and cinchonidine derivatives were much lower. It was assumed that coordination of magnesium was responsible for the stereoconvergence of the reaction (**Scheme 67**). In the most stable conformations, native-halide would be prearranged for the S_N2 -type attack by complexed organomagnesium species, while *epi*-halides would facilitate the substitution of $S_{N}i$ type.¹⁸⁶

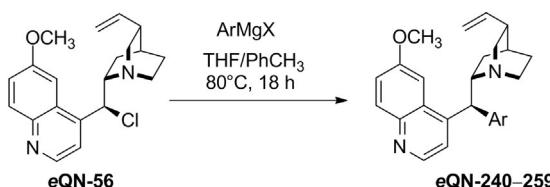
For vinylmagnesium halides, the reaction was accompanied by noticeable substitution at the 2' position of the quinoline ring and required strict control of the quantity of the Grignard reagents.^{186,187} The reaction with sp^3 reagents resulted in complex mixtures. On the other hand, the reaction of sp -type reactants, like phenylethynylmagnesium chloride, led to a subsequent rearrangement of alkyne *eQN-238* to the allenes **QN-239a,b**, which occurred with loss of stereochemical information (**Scheme 68**).¹⁸⁸

Numerous aryl derivatives were obtained by reaction of 9S-chloroquininine (*eQN-56*) with various Grignard reagents including those with naphthalene, and pyrene rings (**Scheme 69**). Furthermore, various functional groups were introduced including halides, protected alcohols,¹⁸⁸ phenols,^{188,189} and amines.¹⁹⁰ With bivalent organomagnesium compounds, such as biphenyl-4,4'-dimagnesium diiodide **267** corresponding dimeric product *eQN-268* was obtained in moderate yield (**Scheme 70**).¹⁹¹

The C_2 -symmetric dimer **QN-269** with the C–C bond directly linking two C9 carbon atoms of two alkaloid units was observed as a minor by-product in the Grignard substitution reactions. It became the major product when quinine-derived 9-halides **53** and **56** reacted with



Scheme 68 The reaction of 9-chloroquinine with the *sp*-Grignard reagent.



eQN-240, Ar = Naphth-1-yl, 60%

eQN-241, Ar = Naphth-2-yl, 59%

eQN-242, Ar = 2-BnO-Naphth-1-yl, 82% $\xrightarrow{\text{H}_2/\text{Pd}}$ **eDHQN-260**, Ar =

eQN-243, Ar = 2-MeC₆H₄, 54%

eQN-244, Ar = 4-MeC₆H₄, 38%

eQN-245, Ar = 2-MOMOC₆H₄, 74%

eQN-246, Ar = 3-MOMOC₆H₄, 43%

eQN-247, Ar = 4-MOMOC₆H₄, 45%

eQN-248, Ar = 2-(MOMOCH₂)C₆H₄, 62%

eQN-249, Ar = 3-(MOMOCH₂)C₆H₄, 67%

eQN-250, Ar = 3-Bn₂NC₆H₄, 61%

eQN-251, Ar = 4-Bn₂NC₆H₄, 61%

eQN-252, Ar = 3-(TMS₂N)C₆H₄, 80% $\xrightarrow{\text{H}_2\text{O}}$

eQN-261, Ar = 2-HOC₆H₄

eQN-262, Ar = 3-HOC₆H₄

eQN-263, Ar = 4-HOC₆H₄

eQN-264, Ar = 2-(HOCH₂)C₆H₄

eQN-265, Ar = 3-(HOCH₂)C₆H₄

eQN-266, Ar = 3-H₂NC₆H₄

eQN-253, Ar = 31%

eQN-254, Ar = 40%

eQN-255, Ar = 3-IC₆H₄, 23%

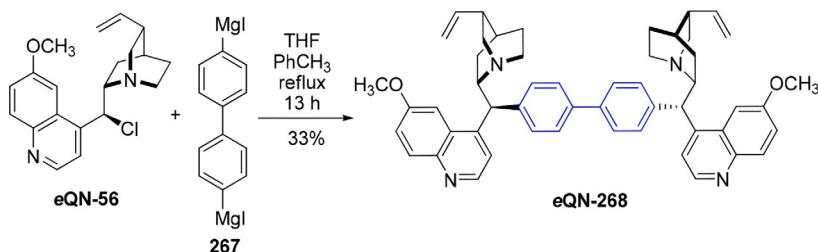
eQN-256, Ar = 4-IC₆H₄, 80%

eQN-257, Ar = 3-BrC₆H₄, 49%

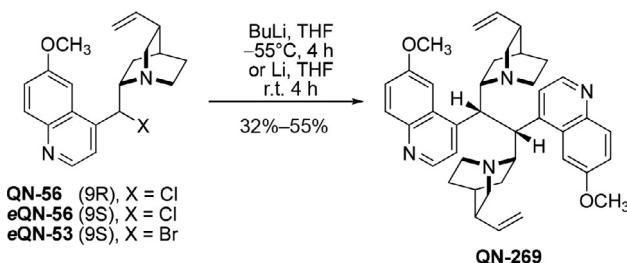
eQN-258, Ar = 4-BrC₆H₄, 70%

eQN-259, Ar = 47%

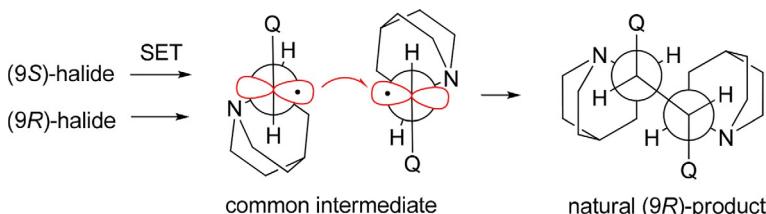
Scheme 69 Scope of Grignard substitution of chloroquinine.



Scheme 70 Dimerization based on Grignard substitution reaction.



Scheme 71 Direct dimerization of Cinchona alkaloid 9-halides.



Scheme 72 Outline of the proposed mechanism for stereoconvergent dimerization of 9-halo-Cinchona alkaloids.

butyllithium or metallic lithium in THF. The isolated yields were in the range of 35%–55% (**Scheme 71**). Similar to the Grignard substitution reaction, native (9*R*)- and 9-*epi*-chloro- and 9-bromo-quinine afforded one and the same isomer. However, the stereoconvergent reaction this time led to the product of native (9*R*) configuration. It was suggested that the reaction involves the transient formation of a 9-radical through SET mechanism or through oxidation of carbanion (**Scheme 72**). The subsequent recombination of two radicals is likely to occur from the *Re* side opposite to the nitrogen lone pair due to repelling electrostatic interactions.¹⁹¹ A similar stereochemical effect was postulated in the *Re*-selective autoxidation of cinchonane under basic conditions.

3.1.7 9-Chalcogen Derivatives

Cinchona alkaloid scaffold was modified to create derivatives with a carbon–sulfur bond at the C9 position.⁹⁴ The native and *epi*-alkaloids underwent stereospecific S_N2 transformations to the respective thioethers, dimeric 9-disulfides, and 9-thiols. Thioethers were also subjected to further transformation toward sulfoxides and sulfones.

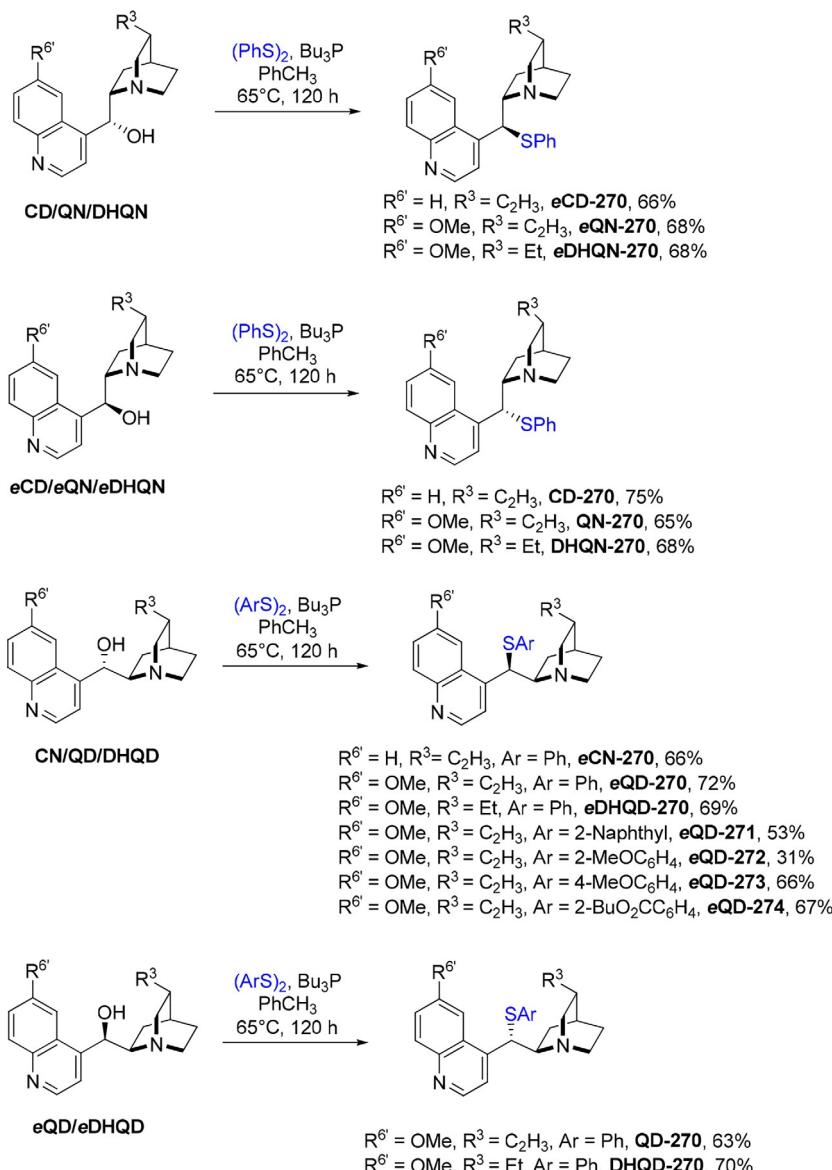
A series of arylsulfanyl derivatives **270–276** were obtained according to two general protocols. In the first one, a direct conversion of the alkaloids into sulfides took place via nucleophilic substitution with diaryl disulfides and tributylphosphine in toluene (*Scheme 73*). The arylsulfanyl derivatives were obtained with the inversion of configuration at C9 stereogenic center in 31%–75% yield. The native alkaloids were converted into the respective *epi*-derivatives and the *epi*-alkaloids gave the corresponding phenyl sulfides **270** of native configuration. All the products were obtained as single diastereomers.⁹⁴

Alternatively, a two-step procedure was also used to obtain 9-sulfides: first, alkaloids were converted into corresponding mesylates and then, the nucleophilic substitution with sodium thiolates produced alkyl- and arylsulfanyl derivatives in good yields (*Scheme 74*).⁹⁴

Nitrogen-containing thioethers, including these of pyridine and phenanthroline, as well as 2-aminophenylsulfanyl products, were obtained using analogous reactions (*Scheme 75*). Slightly lower yields with 2-pyridinethione (**281**) and 2-phenanthrolinethione (**283**) were likely attributed to tautomeric and association equilibria of thiones. 2-Aminoderivative *eQN-278* with a free amino group was converted to thiourea *eQN-280* in the subsequent reaction with isothiocyanate **153**, and to the salane derivative *eQN-279* using salicylaldehyde under reductive amination conditions.¹⁹²

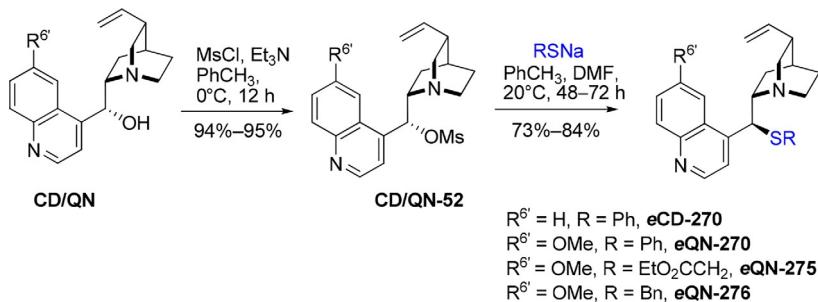
Apart from thioethers, a set of C9 thiols **286** and dimeric 9-disulfides **287** were synthesized in a sequence of reactions involving Mitsunobu reaction, reduction, and oxidation (*Scheme 76*). In the first step native and 9-*epi*-*Cinchona* alkaloids were treated with thioacetic acid, Ph₃P, and DEAD in THF giving thioacetates **285** in 42%–59% yield. This reaction proceeded with the complete inversion of configuration at C9, and in all cases the 9-thioesters **285** were obtained as a single diastereomer. In the second step, reduction with LiAlH₄ led to required thiols **286** in good yield (65%–93%). The last step involved the oxidation with iodine in ethanol to afford 9-disulfides **287**.¹⁹³

The oxidation of phenyl sulfides derived from *Cinchona* alkaloids afforded the corresponding sulfoxides **288** (*Scheme 77*). The reactions were

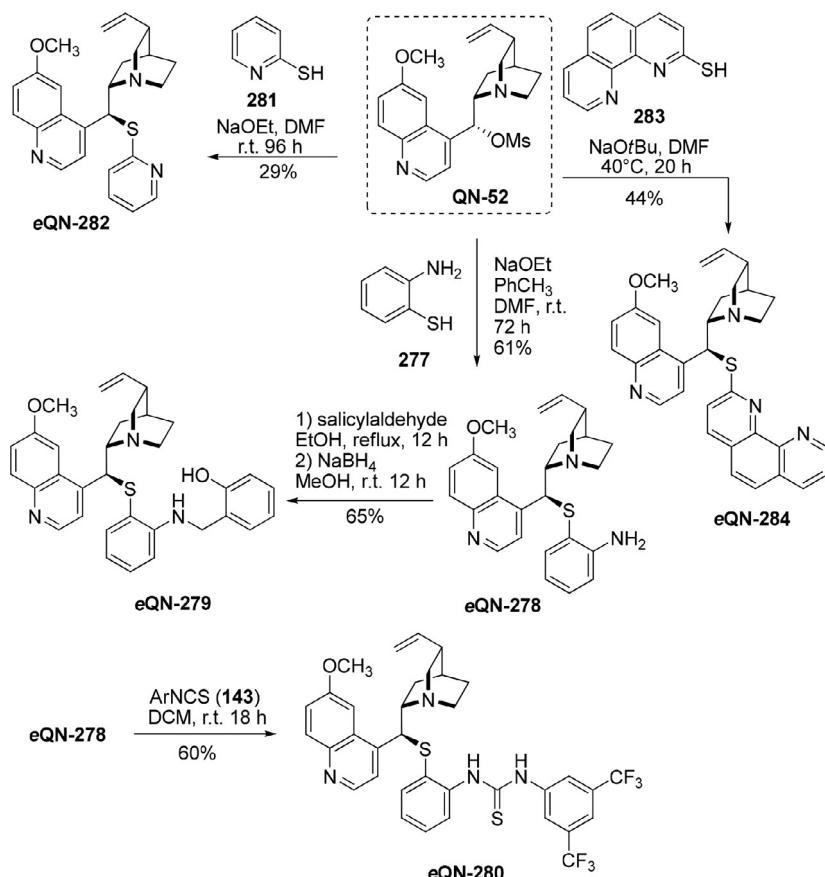


Scheme 73 Syntheses of 9-arylsulfanyl derivatives of *Cinchona* alkaloids.

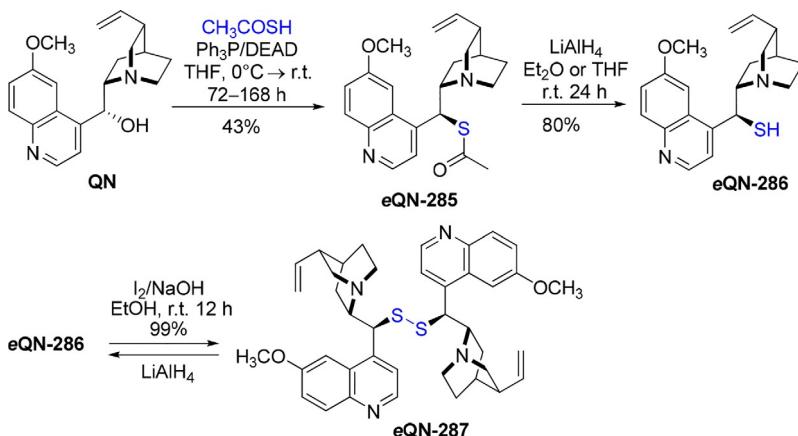
carried out using various oxidation systems such as NaIO₄, TEMPO/NaOCl, VO(acac)₂/enantiomeric Schiff base/H₂O₂ (Table 2). The sulfoxides were obtained in good yields (52%–85%), but the diastereoselectivity was low. A similar stereochemical effect was observed, regardless of the



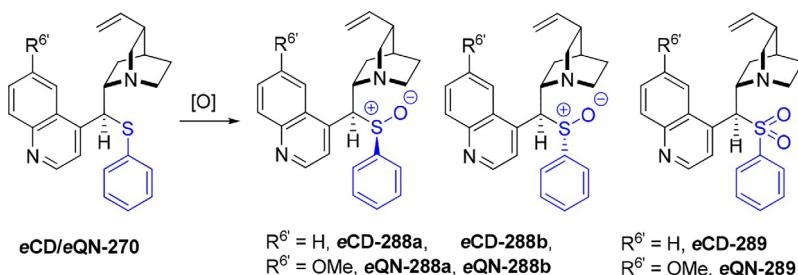
Scheme 74 Synthesis of 9-thioethers by substitution of alkaloid methanesulfonates.



Scheme 75 Syntheses of functionalized thioethers of *Cinchona* alkaloids.



Scheme 76 A representative synthesis of C9 thiol and dimeric 9-disulfide of *Cinchona* alkaloids.



Scheme 77 Sulfoxidation of phenylsulfanyl alkaloids (conditions are shown in Table 2).

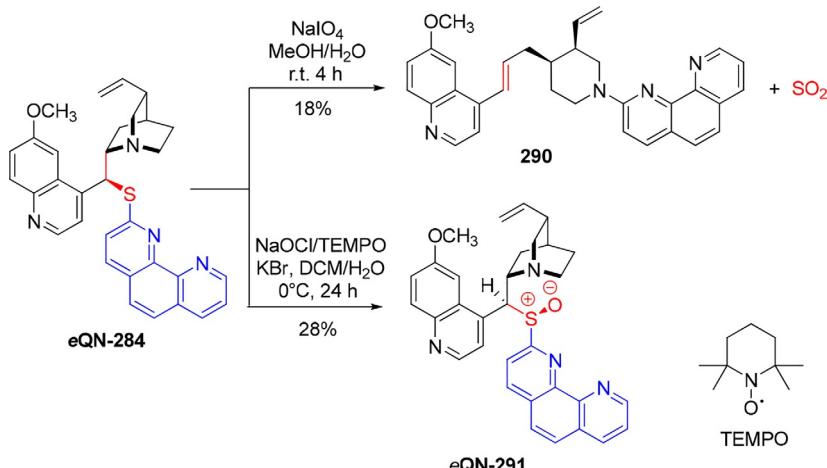
oxidant used. Diastereomerically pure sulfoxides were isolated by recrystallization or by chromatography. The oxidation of sulfides **270** with $\text{VO}(\text{acac})_2/\text{rac-Schiff base}/\text{double amount of H}_2\text{O}_2$ or with an excess of NaIO_4 gave the corresponding sulfones **289** in 50%–60% yield. Degradation of the substrate **270** was noted when Oxone was used.¹⁹⁴

On the other hand, sulfoxidation of quinine 1,10-phenanthroline-2-yl thioether **eQN-284** was not efficient. The application of sodium periodate resulted in partial conversion to product **290**, which was not a sulfoxide but a result of a sequence of reactions (Scheme 78). These included oxidation, rearrangement with sulfur to nitrogen migration of phenanthroline substituent, elimination, and extrusion of sulfur dioxide. The sulfoxide **eQN-291** was formed by applying the TEMPO/KBr hypochlorite system (Scheme 78).¹⁹⁵

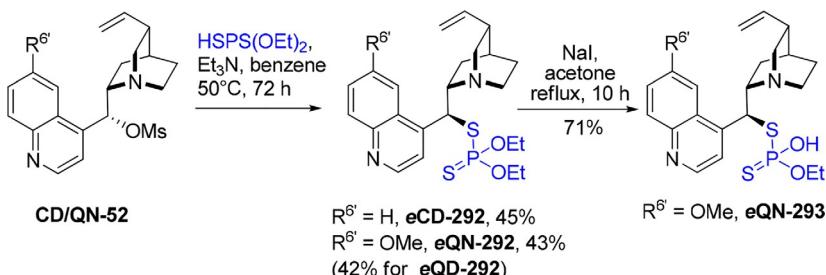
Table 2 Oxidation of phenylsulfanyl derivatives of *Cinchona* alkaloids
Sulfoxides 288a,b

Entry	Sulfide	Oxidant	Yield (%)	d.r. (R_S)	Sulfone 289 yield (%)
1	eCD-270	NaIO ₄ (1.1 equiv.)	82	57:43	—
2	eCD-270	NaIO ₄ (2.3 equiv.)	—	—	50
3	eCD-270	(S)-L*, VO(acac) ₂ , H ₂ O ₂ (1.15 equiv.)	52	57:43	—
4	eCD-270	(R)-L*, VO(acac) ₂ , H ₂ O ₂ (1.15 equiv.)	60	58:42	—
5	eCD-270	rac. L*, VO(acac) ₂ , H ₂ O ₂ (2.3 equiv.)	—	—	50
6	eQN-270	NaIO ₄ (1.1 equiv.)	80	55:45	—
7	eQN-270	NaIO ₄ (2.3 equiv.)	—	—	60
8	eQN-270	(S)-L*, VO(acac) ₂ , H ₂ O ₂ (1.15 equiv.)	65	56:44	—
9	eQN-270	rac. L*, VO(acac) ₂ , H ₂ O ₂ (2.3 equiv.)	—	—	60
10	eQD-270	NaIO ₄ (1.1 equiv.)	85	42:58	—
11	eQD-270	NaOCl/TEMPO	61	44:56	—
12	QN-270	NaIO ₄ (1.1 equiv.)	63	59:41	—

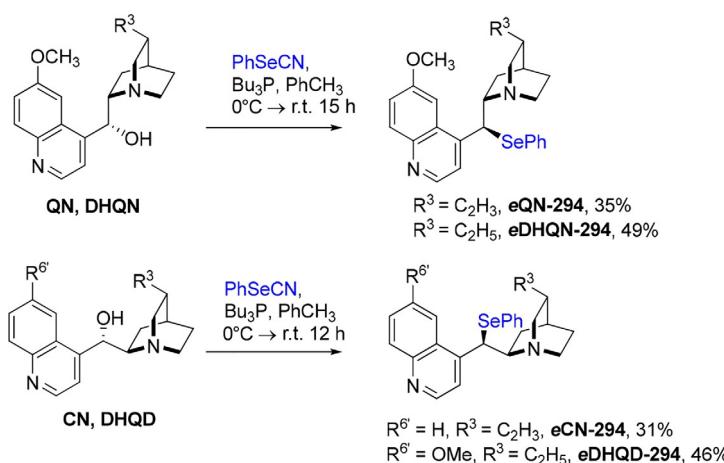
L*, N-(3-phenyl-5-nitrosalicylidene)valinol.



Scheme 78 Oxidation of 9-*epi*-(phenanthrolinylsulfanyl)-quinine.

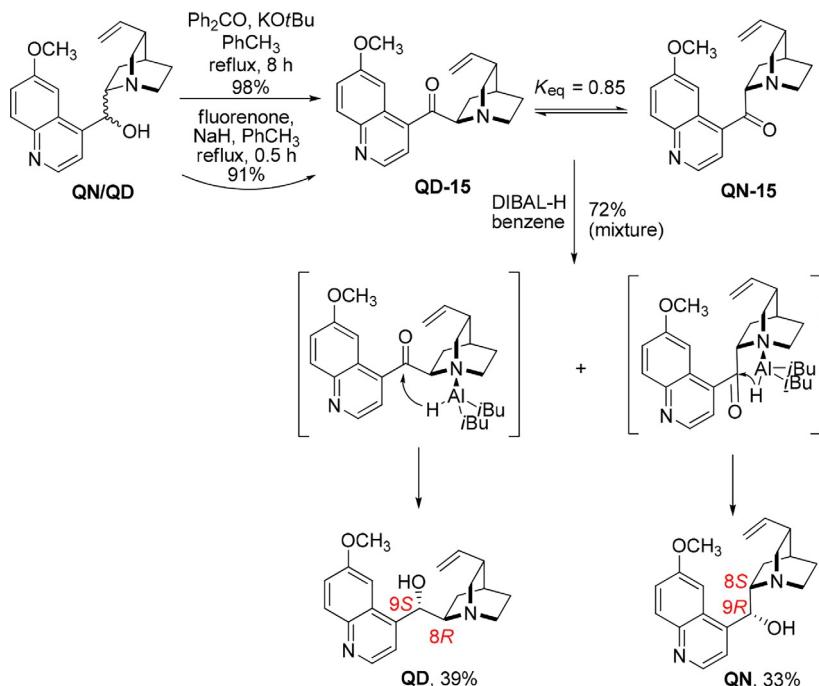


Scheme 79 Syntheses of alkaloid thiophosphates.

Scheme 80 Syntheses of *Cinchona* alkaloid 9-phenylselenyl derivatives.

The reaction of native- and *epi*-9-mesylates of *Cinchona* alkaloids with O,O-diethyldithiophosphoric acid in the presence of Et₃N in benzene at 50°C generated the corresponding O,O'-diethyldithiophosphate derivatives **292** (Scheme 79). In this nucleophilic substitution reaction, products were formed with the inversion of configuration at the C9 stereogenic center in fair yields (42%–45%). Moreover, the resulting *epi*-quinine dithiophosphate diethyl ester **eQN-292** was converted to the acid **eQN-293** with sodium iodide in boiling acetone.¹⁹⁶

Phenylselenyl derivatives were prepared using a procedure analogous to the preparation of sulfides (Scheme 80). Alkaloid and phenyl selenocyanate and tributylphosphine in toluene reacted according to the S_N2 substitution. This simple procedure gave the required selenylated products as single dia-stereoisomers in moderate yields.¹⁹⁷



Scheme 81 Synthesis and DIBAL-H reduction of cinchonanones.

3.1.8 Cinchonan-9-one Derivatives

The oxidation of the 9-hydroxyl group of any 8,9-diastereoisomer of *Cinchona* alkaloids results in a mixture of quinonone **QN-15** and quinidinone **QD-15** (Scheme 81). In the absence of 6'-methoxy group, cinchoninone and cinchonidinone **CN-15/CD-15** are obtained, respectively. The facile formation of an enolate allows for interconversion of *8S* (quinonone, cinchonidinone) and *8R* (quinidinone, cinchoninone) isomers. At equilibrium, the ratio of epimers is approximately 6:7. However, isomers of *8R* configuration (**QD-15** and **CN-15**) can be cleanly isolated by crystallization. The first synthesis of quinonone/quinidinone was carried out in 1909 by Rabe, who oxidized quinine with chromic acid albeit in very poor yield.¹⁹⁸ The modified Oppenauer oxidation of quinine with benzophenone in the presence of potassium *tert*-butoxide in toluene afforded quinidinone **QD-15** in nearly quantitative yield (98%) (Scheme 81).^{199,200} The oxidation of quinine was also performed with sodium hydride as the base and fluorenone as the hydrogen acceptor in refluxing solvents such as benzene, toluene, or DMF in an excellent yield (91%).^{201,202}

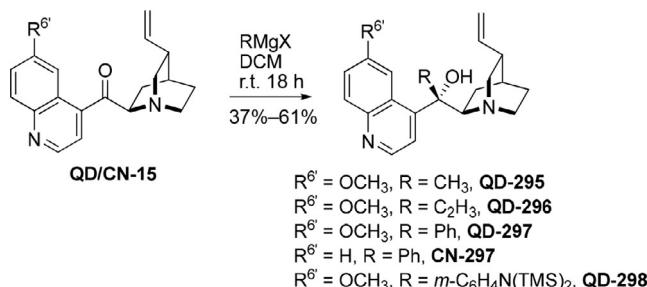
3.1.8.1 Reduction of 9-oxo derivatives of *Cinchona* alkaloids

The reduction of quinidinone (**QD-15**) by diisobutylaluminum hydride led predominantly to the products with native configuration ([Scheme 81](#)). High stereoselectivity was associated with the coordination of the reducing agent to the quinuclidine nitrogen atom.²⁰³

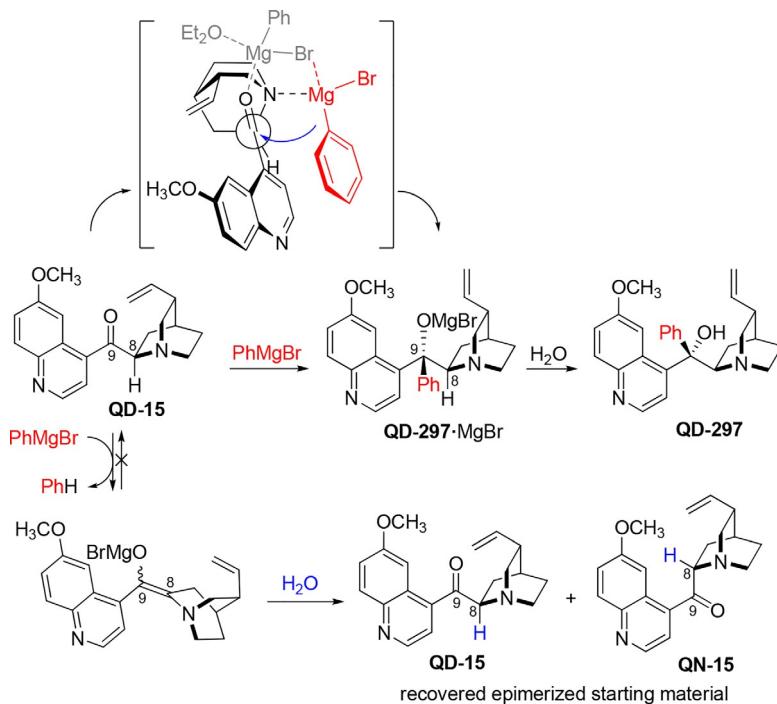
3.1.8.2 Addition of carbon nucleophiles to cinchonanones

The nucleophilic addition to the 9-carbonyl group was seen as a way to modify the carbon skeleton of the *Cinchona* alkaloids ([Scheme 82](#)). In some cases, such addition reactions proceeded with very high diastereoselectivity. A representative example is the Grignard reaction of ketone **QD-15**. First Woodward applied methylmagnesium bromide and isobutylmagnesium bromide in benzene.¹⁹⁹ Later, also vinyl, phenyl, and aminophenyl groups were introduced at the position 9 using the Grignard reaction. The reactions delivered only one stereoisomer of the products, which corresponded to that of native quinidine.²⁰⁴ High diastereoselectivity of the reaction was always observed, and the corresponding addition products **QD-295–298** were obtained in moderate yield (37%–61%, [Scheme 82](#)). A change of solvent from diethyl ether or THF to DCM increased the efficiency of the addition reaction by limiting competing enolization. The exclusive attack of the carbon nucleophile at the *Re* face can be explained by the chelation of magnesium species by the quinuclidine nitrogen and ketone oxygen atoms. This, in turn, imposes the *syn* orientation of N1 and O9 atoms, directs the attack of the nucleophile from the complexed magnesium species, and thereby leads to the product of 9*S* configuration ([Scheme 83](#)).²⁰⁴

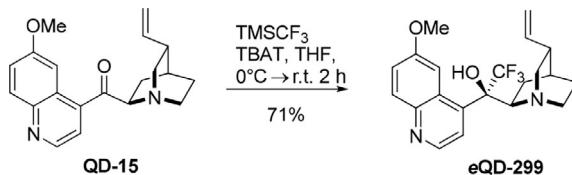
The addition of TMSCF_3 reagent to quinidinone **QD-15** was carried out in THF, in the presence of catalytic amount of tetrabutylammonium difluorotriphenylsilicate (TBAT) to give trifluoromethylated compound **eQD-299** in 71% yield ([Scheme 84](#)).²⁰⁵ The trifluoromethyl moiety was



Scheme 82 Addition of Grignard reagents to cinchonanones.



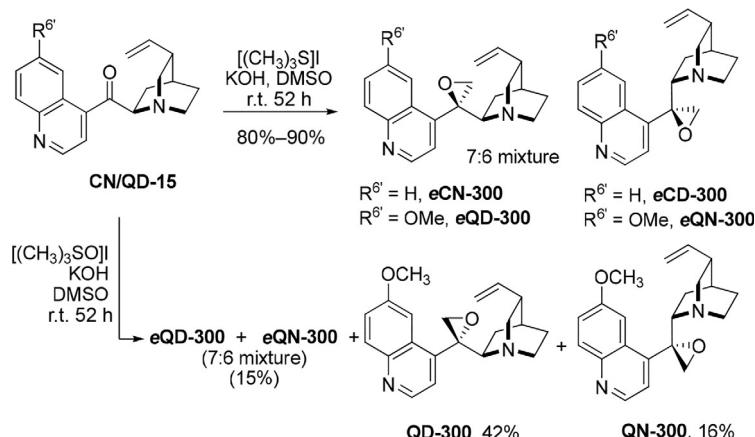
Scheme 83 Rationale for the observed diastereoselectivity and limited yield in the Grignard reaction of quinidinone.



Scheme 84 Trifluoromethylation of quinidinone.

introduced into quinidine as a conformational stabilizer and a probe. The product was formed as 9*R* isomer and it was the result of the nucleophilic attack from the *Si* face.

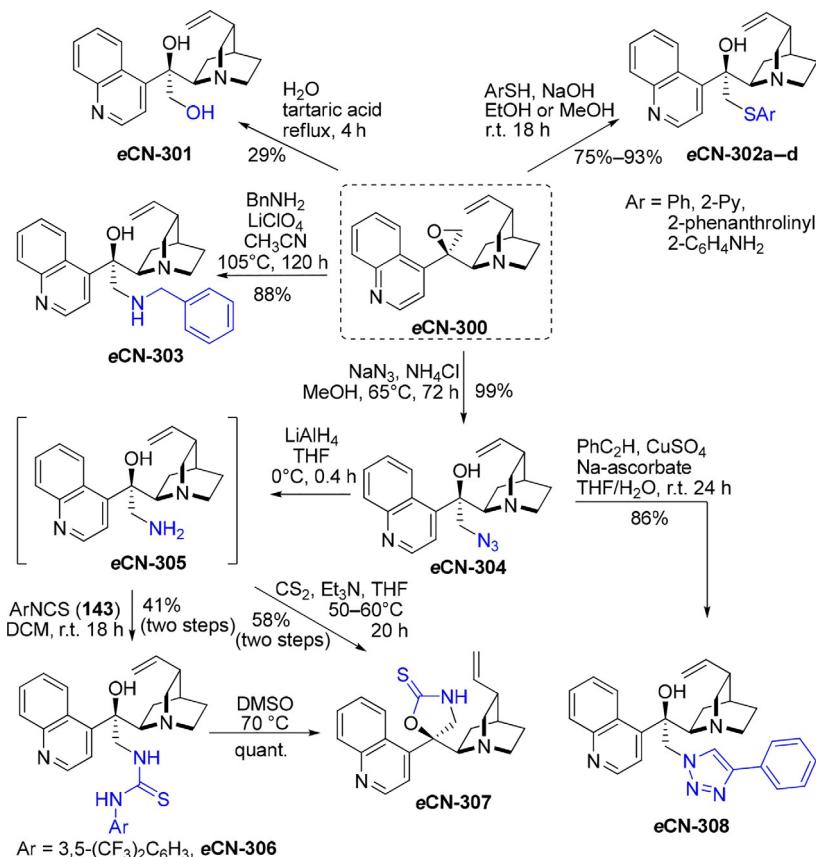
Oxirane derivatives **300** were obtained in the diastereoselective Corey–Chaykovsky reaction of the 9-oxo *Cinchona* alkaloids **15** (Scheme 85). Their treatment with trimethylsulfonium iodide and potassium hydroxide in DMSO gave the corresponding epoxides in good yields. The epoxides were obtained as a mixture of two diastereomers, which were separated by fractional crystallization. They corresponded to selective addition to 8*R*- and 8*S*-ketones. It was suggested that the conformation of the starting



Scheme 85 Corey–Chaykovsky reaction of cinchonanones.

material had an important influence on the course of the reaction. The addition of the sulfonium ylide occurred from the *Si* face of cinchoninone (**CN-15**) and quinidinone (**QD-15**). 9-Epoxides **300** of *epi* configuration were formed in the reaction of dimethylsulfonium methylide at the face opposite to the nitrogen lone pair. The kinetic control likely relied on electrostatic interactions. The analogous reaction with dimethylsulfoxonium methylide gave a mixture of all of the possible products, with some preference toward compounds of native configuration. This unselective reaction course seems to result from thermodynamic equilibration of the intermediates. Under the reaction conditions, epimerization of ketones **15** is a fast process (Scheme 85).²⁰⁶

The resulting epoxides **300** underwent selective S_N2 ring opening with various oxygen-, nitrogen-, and sulfur-centered nucleophiles producing a diverse array of products (Scheme 86). Hydrolysis under mildly acidic conditions yielded the corresponding diol **eCN-301**.²⁰⁶ Aryl and heteroaryl thiolates reacted with the epoxide **eCN-300** at room temperature.¹⁹² The ring opening with sodium azide in the presence of NH₄Cl resulted in a nearly quantitative formation of 1,2-azidoalcohol **eCN-304**, which was a useful synthetic intermediate. The reduction to amino alcohol **eCN-305** followed by reaction with arylthiocyanate **143** yielded thiourea **eCN-306** that spontaneously cyclized into oxazolidinethione derivative **eCN-307**. Secondary amines, such as **eCN-303**, were alternatively obtained in direct ring opening with primary alkyl amines.²⁰⁶ The 1,2-azidoalcohol **eCN-304** was reactive in the click CuAAC reaction (Cu(I)-catalyzed 1,3-dipolar cycloaddition between alkynes and azides).²⁰⁷

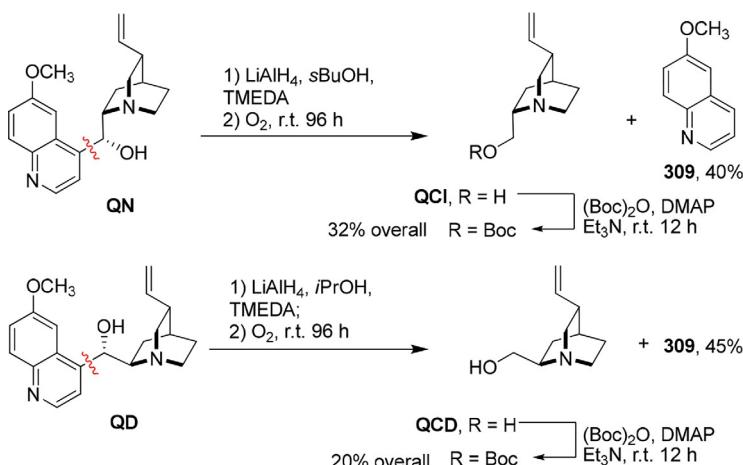


Scheme 86 Transformations of *Cinchona* alkaloid-derived epoxide **eCN-300**.

3.1.9 Cleavage of the C4'-C9 Bond

A redox degradation of the *Cinchona* alkaloids using both LiAlH_4 and oxygen resulted in the cleavage of C4'-C9 bond (Scheme 87). From quinine and quinidine, 2-hydroxymethyl-5-vinylquinuclidines and 6-methoxyquinoline (**309**) were obtained as separate entities. The configuration at the stereogenic center C8 was preserved, and quincorine (**QCI**) and quincordine (**QCD**) are formed from **QN** and **QD**, respectively. Their isolation was facilitated by acylation with di-*tert*-butyl dicarbonate. After Boc protection, both diastereomers were isolated in 32% and 20% yield.²⁰⁸ These two diastereomeric 1,2-aminoalcohols contain four stereogenic centers, with the 1S-configured bridgehead nitrogen atom. Both of them are commercially available.

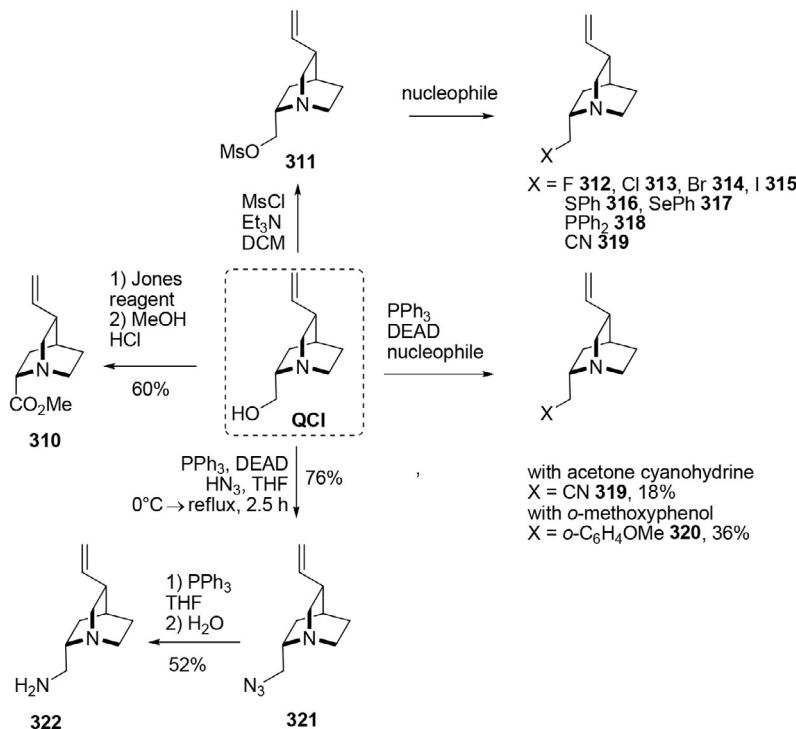
Further modifications of **QCI** and **QCD** were extensively studied. The primary alcohol unit was suitable for a wider array of modifications than the



Scheme 87 Cleavage of C4'-C9 bond of *Cinchona* alkaloids.

central hydroxyl group of *Cinchona* alkaloids. Among many transformations, the Jones oxidation of the **QCI** and **QCD** side chain at carbon atom C9 resulted in C9-esters with high selectivity and good yields (60%). The oxidation of quinchorine and quincordine with KMnO₄ allowed for selective cleavage of the vinyl side chain.²⁰⁹

The primary alcohol group could be transformed into the corresponding esters, ethers, halides (including iodides), amines, and derivatives with new C–C, C–S, C–Se, and C–P bonds (Scheme 88).²¹⁰ The S_N2 displacements at C9 with hard nucleophiles proceeded slowly.^{211,212} The Mitsunobu reaction gave aryl ether **320** in 36% yield and nitrile **319** in low yield (18%). The reaction was, however, more effective for the preparation of azide **321** in 76% yield. Mesylates from **QCI** and **QCD** have proven to be an efficient intermediate for the preparation of halides, nitriles, phosphine, sulfur, and selenium derivatives. The halide derivatives were obtained from the mesylate **311** by treatment with lithium halides in refluxing dioxane in good yield (71%–78%). The reaction of methanesulfonates of **QCI** and **QCD** with KCN, using toluene, CsF, and 18-crown-6, proceeded with the formation of carbon–carbon bond at C9 in 95% and 81%, respectively. This route was also effective for sulfur-, selenium-, and phosphorus-centered soft nucleophiles (66%–93% yield, Scheme 88).^{211,213} Moreover, the vinyl group in **QCI** and **QCD** was converted into alkyne and various other functional groups.^{214–217}

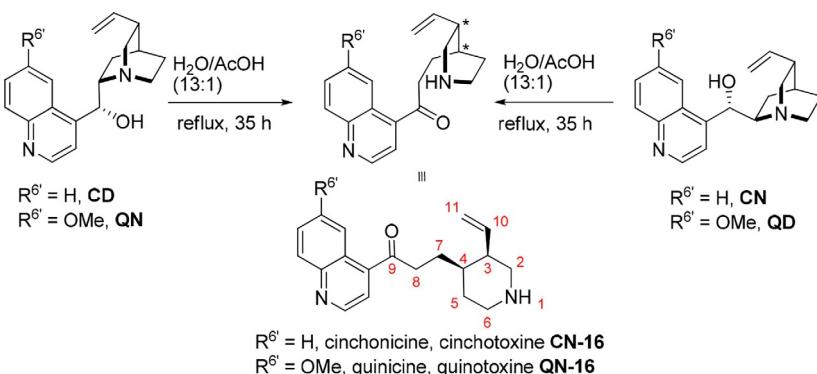


Scheme 88 Selected transformations of quincorine.

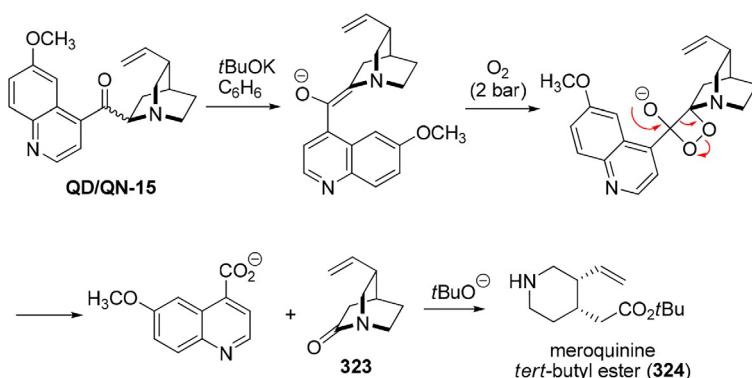
3.1.10 Cleavage of the N1–C8 Bond

One of the first reactions involving *Cinchona* alkaloids was performed by Pasteur in 1853 (Scheme 89).^{36,218,219} The treatment of both the quinine/quinidine pair and the cinchonidine/cinchonine pair with acids caused cleavage of the N1–C8 bond, which produced quinotoxine (quinicine, **QN-16**) and cinchotoxine (cinchonicine, **CN-16**). These 3,4-difunctionalized piperidines are devoid of three stereogenic centers: at C9, C8, and N1 atoms. The Pasteur cleavage is associated with the Hofmann-type elimination followed by keto-enol tautomerization.

Another example of breaking of the N1–C8 bond is the oxidative cleavage of quinidinone **15** (cinchoninone) by oxygen under basic conditions (Scheme 90). The intermediate lactam **323** was opened by *t*BuOK. The final product was meroquinine ester **324** and 6-methoxyquinoline-4-carboxylic acid.^{200,220}



Scheme 89 Quinotoxine cleavage.



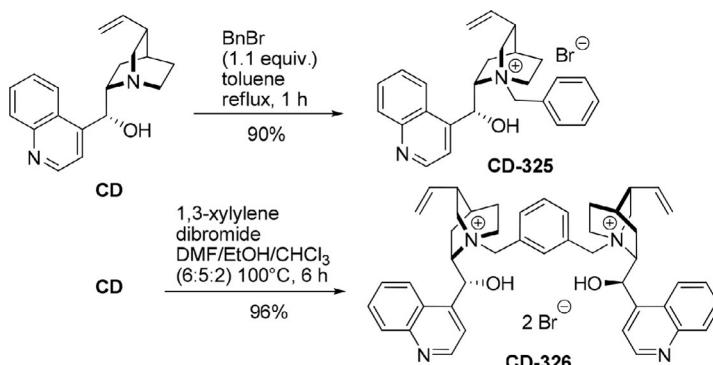
Scheme 90 Synthesis of meroquinine ester.

3.2 Reactions of Vinylquinuclidine

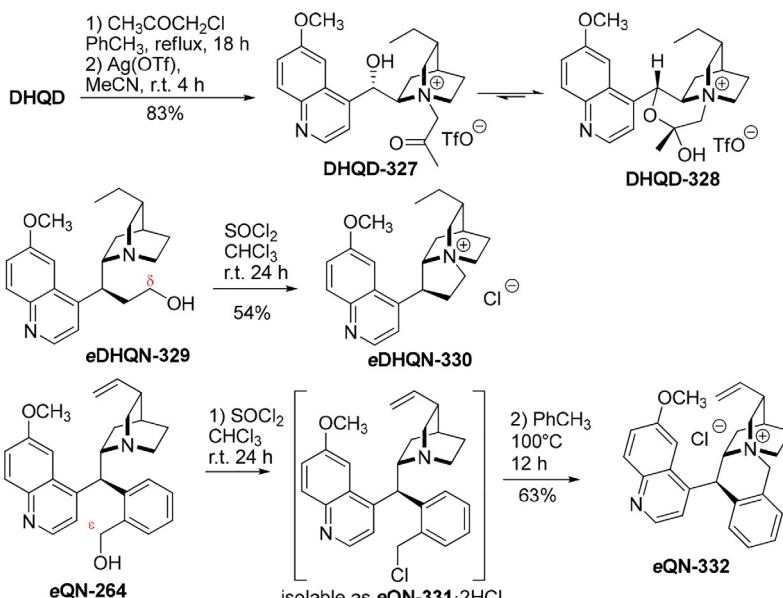
3.2.1 N1-Quaternization

One of the most common transformations of the *Cinchona* alkaloids is the alkylation with primary alkyl and benzyl halides at N1 atom of the quinuclidine ring (Scheme 91). The reaction has a rich history dating to the XIX century,²²¹ and today databases list nearly 2000 entries. The N1 substituents range from N1-methyl derivatives to complex dendrimers²²²; however, there is no information on stable products obtained from the reactions of secondary or tertiary alkyl halides. On the other hand, the introduction of N1-aryl group resulted in subsequent elimination.²²³

With multivalent benzyl halides, dimers, trimers, and tetramers were obtained.²²⁴ The reactions were usually carried out using corresponding alkyl halides at elevated temperatures in various solvents, e.g., toluene, CHCl₃, EtOH, acetone, DMF, or their mixture (Scheme 91).

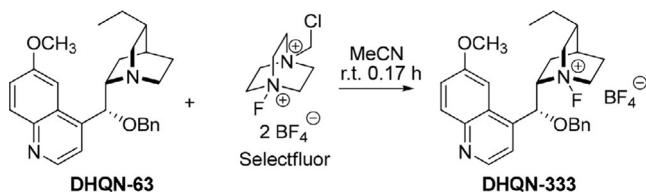


Scheme 91 Example syntheses of alkaloid quaternary ammonium salts.

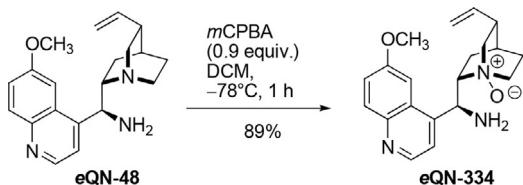


Scheme 92 Synthesis of quaternary salts with fused rings.

N-Alkylation of dihydroquinidine (**DHQD**) with chloroacetone gave a product that spontaneously cyclized into the corresponding hemiacetal **DHQD-328** (Scheme 92). In the crystal structure configuration of the generated stereogenic center was *S*.²²⁵ Also cyclic product **eDHQN-330** was obtained from the 9-hydroxyethyl derivative of quinine **eQN-329** under any conditions that introduced an electrophilic character at the δ -carbon. On the other hand, the related ϵ -electrophilic derivative **eQN-331** could be isolated.¹⁸⁷ These results reflect preferred formation of five- or six-membered ring involving atoms N1 and C9 (Scheme 92).



Scheme 93 N1-Fluorination of *Cinchona* alkaloid derivative.



Scheme 94 N1-Oxidation of 9-*epi*-aminoquinine.

3.2.1.1 N1-Fluoro derivative

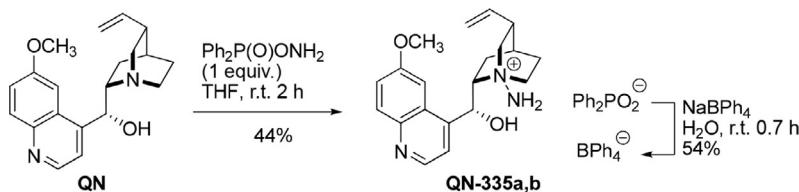
The reaction of Selectfluor with *Cinchona* alkaloids or their 9-ethers and esters results in a formation of N1-fluoro derivative, e.g., **DHQN-333** (**Scheme 93**). This compound acted as an effective agent in an enantioselective fluorination. It could also be isolated in a crystalline state.²²⁶ From cinchonidine, the corresponding 1-fluorine derivative was obtained in 84% yield.²²⁷

3.2.1.2 N-Oxides, hydrazonium salts, and zwitterionic hydrazines

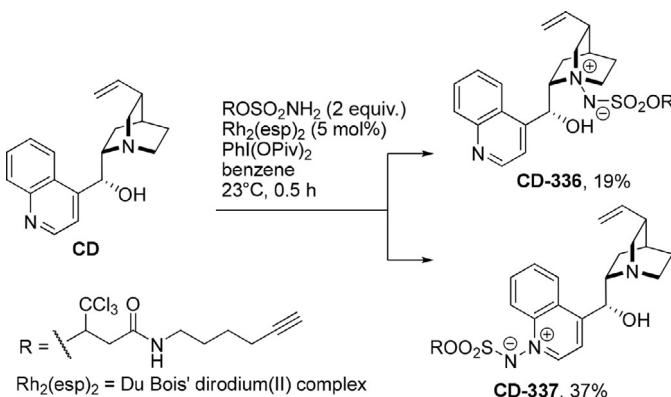
The oxidation of *Cinchona* alkaloids with peroxyacids led to N-oxides at both nitrogen atoms. The first oxidation step proceeded toward the quinuclidine N1-oxide.^{228,229} The reaction can be conducted selectively by the use of *m*CPBA (0.9 equiv.) at low temperatures. Selective oxidation of quinuclidine N1 nitrogen atom was also shown in the reaction of 9-*epi*-aminoquinine (**eQN-48**) and the corresponding N1-oxide **eQN-334** was obtained in very good yield (**Scheme 94**).²³⁰

Cinchona alkaloid-derived aminimines, N–N ylides, were likely intermediates in the catalyzed asymmetric aziridination reaction of enones. Corresponding hydrazinium salts **QN-335a,b** were obtained from the alkaloid and O-diphenylphosphoryl-hydroxylamine (**Scheme 95**).²³¹

Substituted zwitterionic hydrazine derivatives **336** were also obtained by rhodium-catalyzed N-amination of the alkaloids. The reaction poorly discriminated between N1 and N1' sites (**Scheme 96**).²³²



Scheme 95 N1-Amination of quinine.

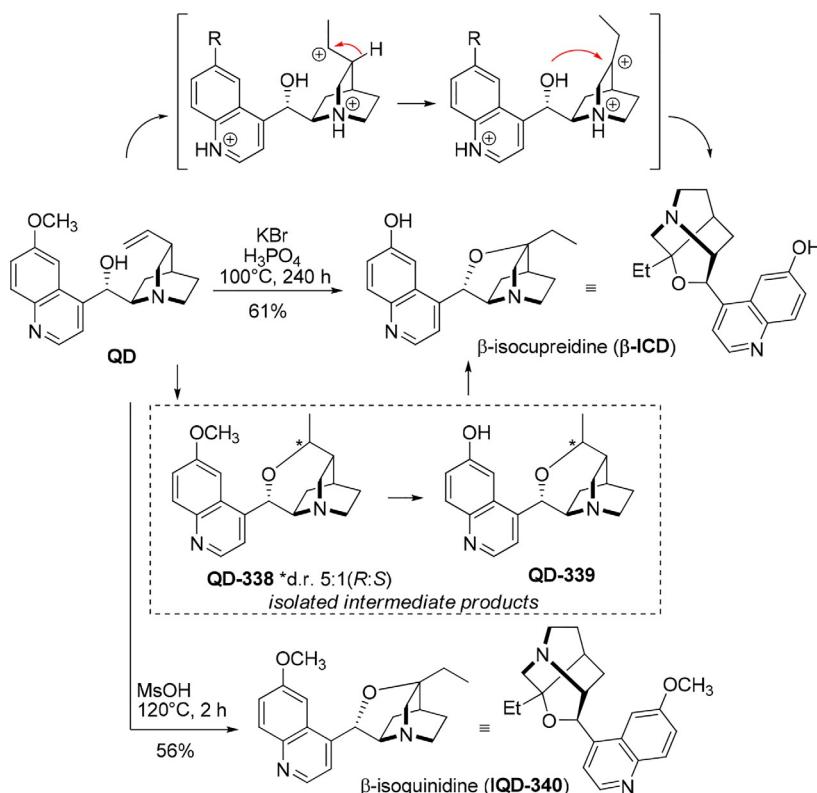


Scheme 96 N-Amination of cinchonidine.

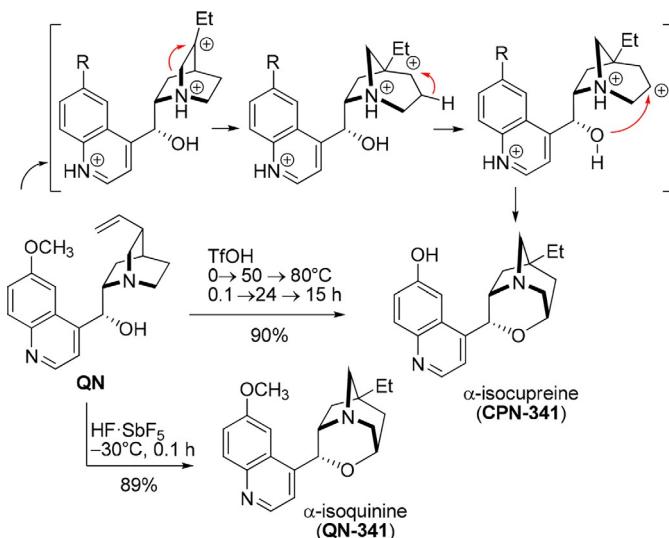
3.2.2 Reactions of the 3-Vinyl Group

Modifications of the 3-vinyl group included mostly electrophilic and radical addition reactions, as well as dipolar cycloaddition and metal-catalyzed processes. Hydrogenation was performed with a number of catalysts, typically palladium. The transfer hydrogenation was also executed.²³³

Strong acids introduce carbocations at the position 10, which initiate the isomerization of the *Cinchona* alkaloids (Schemes 97 and 98). The result is dependent on the configuration at the positions 8 and 9. The reaction of quinidine with HBr involves protonation of the double bond, followed by a carbocation rearrangement (Scheme 97). A few intermediate products (e.g., QD-338 and QD-339) were isolated; however, all converged toward the final β -isocupreidine after extended heating time.²³⁴ With HBr, 6'-ether is also cleaved. Isoalkaloid QD-340 with intact ether bond can be obtained by application of sulfuric²³⁵ or methanesulfonic acid.²³⁶ Isoalkaloids are often referred to by the alternative name of [4.4.0.0^{3,8}]tricyclic system as oxazatwistanes.



Scheme 97 Formation of β -isoquinidine and β -isocupreidine.



Scheme 98 Formation of α -isoquinine and α -isocupreine.

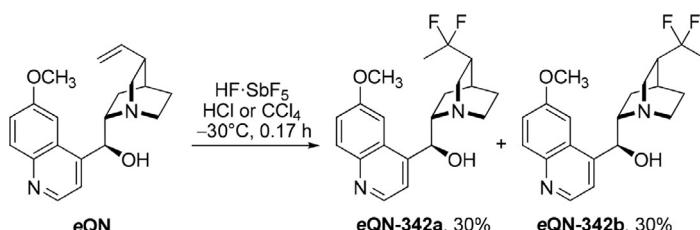
In superacids, at low temperatures quinine undergoes yet another cage rearrangement reaction (**Scheme 98**). The product is the tricyclic ether **QN-341**. The postulated mechanism begins with the protonation of the vinyl group and H-3 hydride shift to the position 10. Then C7 carbon shift to the position 3 concludes transformation of a [2.2.2]bicyclic system into [3.2.1]bicycle. The final hydride shift and intramolecular etherification yield α -isoalkaloid **QN-341**.^{237,238} The identical product was also reported in the reaction of trifluoromethanesulfonic acid with quinine at 50°C,²³⁹ while rising the temperature to 80°C resulted in cleavage of the 6'-ether bond as well, affording **CPN-341** (**Scheme 98**).²⁴⁰

epi-Quinine and 9*O*-acetyl quinine with HF·SbF₅ formed complicated mixtures; however, in the presence of chloride ions they gave 10,10-difluorinated derivatives such as **eQN-342a,b** (**Scheme 99**). These were obtained as separable 1:1 mixture of epimers at the position 3.²³⁷

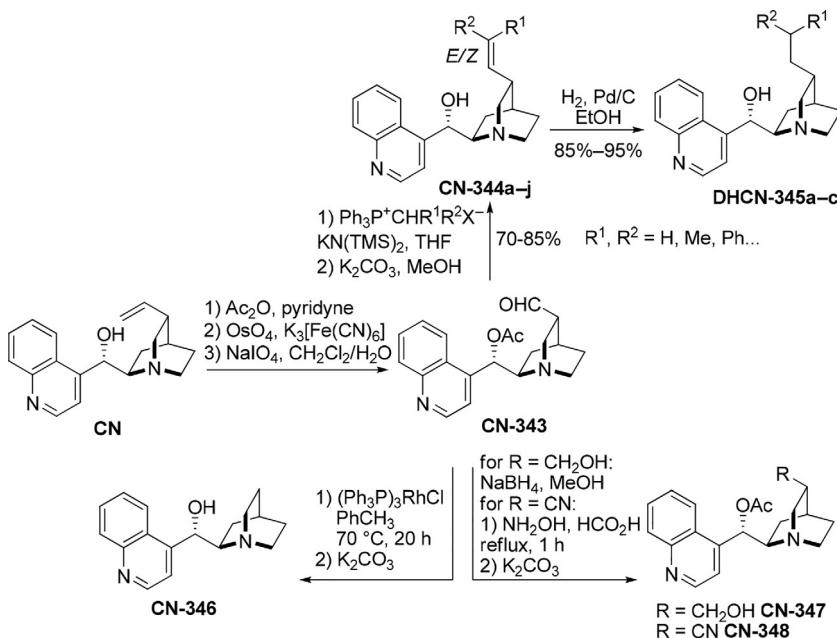
3.2.2.1 10,11-Oxidation

The vinyl group of cinchonine was dihydroxylated with osmium tetroxide toward 10,11-diol without pronounced diastereoselectivity. Further oxidation with periodate yielded the corresponding 3-carbaldehyde **CN-343** (**Scheme 100**). Single stereoisomer was obtained by recrystallization from diisopropyl ether. Then, using the Wittig reaction a series of 11-mono and disubstituted derivatives of alkaloids **CN-344** were obtained with moderate diastereoselectivities (*Z:E* ratio from 2:1 to 1:6).^{241,242} The aldehyde **CN-343** could also be reduced to the corresponding primary alcohol **CN-347**, converted to nitrile **CN-348**, or decarbonylated using a rhodium catalyst toward **CN-346** (**Scheme 100**).²⁴² It is noteworthy that **CN-346** was also a target of total synthesis of simplified *Cinchona* alkaloid analogs.^{243,244}

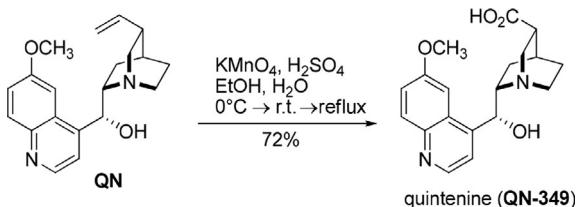
Permanganate under acidic conditions oxidizes the vinyl group providing the corresponding 3-carboxylic acids **349** (**Scheme 101**).^{245,246}



Scheme 99 Difluorination of *epi*-quinine.



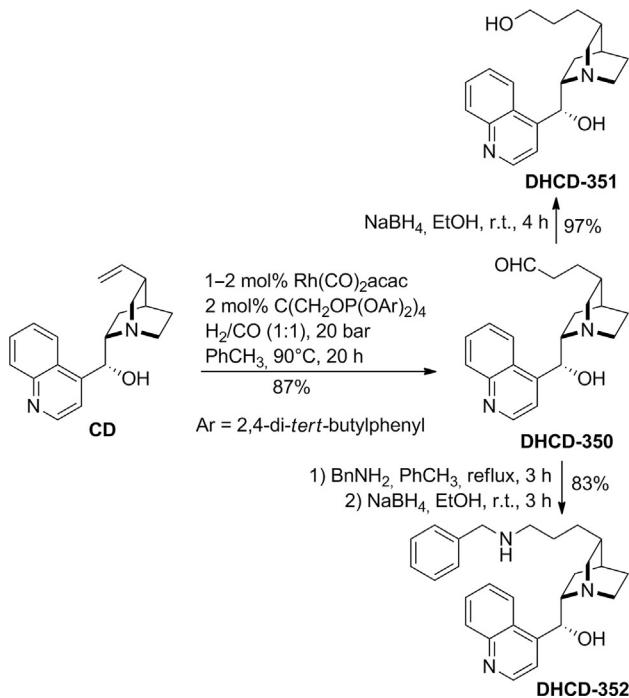
Scheme 100 Synthesis and transformations of *Cinchona* alkaloid 3-carbaldehyde derivative **CN-343**.



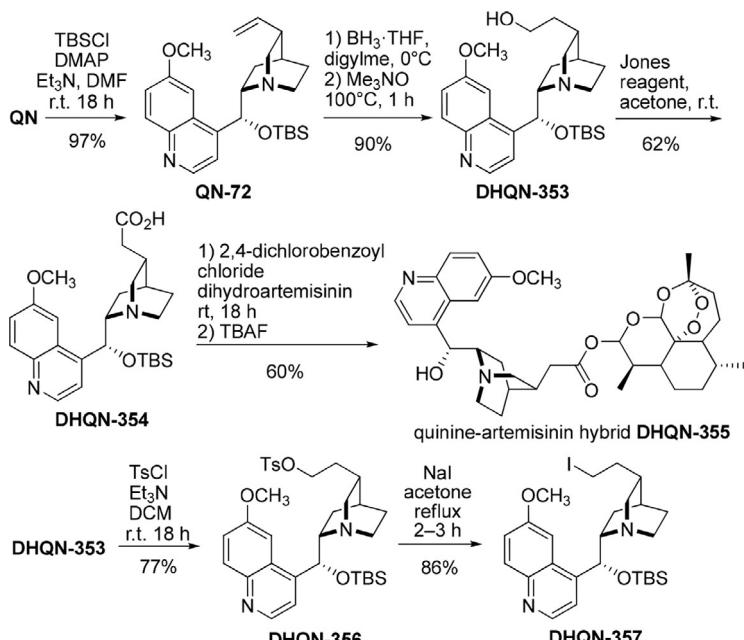
Scheme 101 Synthesis of quinamine.

The hydroformylation of the vinyl group was successfully performed for three of the alkaloids (quinine 71%, quinidine 85%, and cinchonidine 87%) using a rhodium catalyst and dendrimeric diarylalkylphosphite (Scheme 102). The poor solubility of cinchonine translated to marginal conversion. 11-Carbaldehyde derivatives **350** were further reduced to alcohols **351** and amines **352**.²⁴⁷

The hydroboration of the terminal vinyl group of quinine (QN) was exploited in a few ways (Schemes 103 and 104). The oxidation of the borane addition product provided primary alcohols **353**. These, in turn, could be



Scheme 102 Synthesis and transformations of *Cinchona* alkaloid 11-carbaldehyde derivative **DHCD-350**.

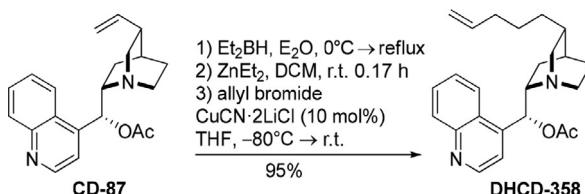


Scheme 103 Synthesis and transformations of 11-hydroxy-alkaloid derivative **DHQD-353**.

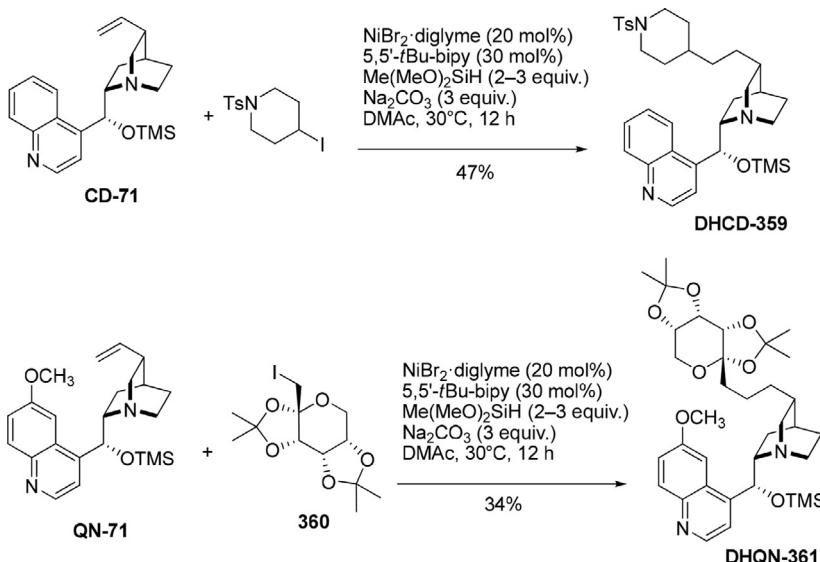
converted to alkyl iodide **357** or further oxidized with Jones reagent to the carboxylic acids **354** (Scheme 103).^{248,249} Quinine 11-carboxylic acid **DHQN-354** was converted to an ester with dihydroartemisinin. This ester (**DHQN-355**) was found to be more potent against malaria *in vitro* than either quinine or artemisinin separately or in a two-component mixture.²⁵⁰

Hydroboration products could be trans-metallated with organozinc reagents. These were immediately used for the copper-catalyzed Negishi-like carbon–carbon couplings at the position 11. For one known example, the process was very efficient (Scheme 104).²⁵¹

Recently developed nickel-catalyzed reductive olefin hydrocarbonation using intermediate silyl derivative was found to be effective in coupling functional moieties to the position 11 (Scheme 105).²⁵²



Scheme 104 An example of homologation of *Cinchona* alkaloid at the vinyl group.



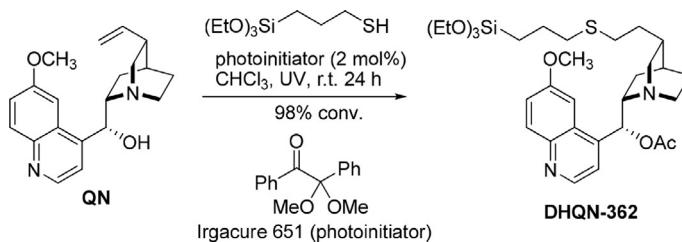
Scheme 105 Examples of nickel-catalyzed additions to the 10,11-double bond of *Cinchona* alkaloids.

3.2.2.2 Radical addition and substitution

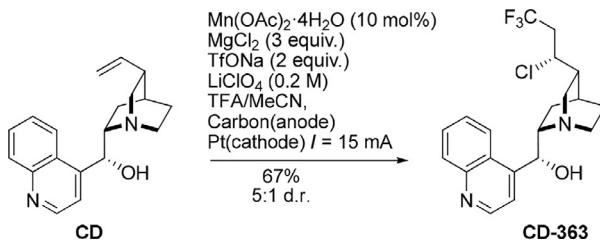
Thiol-ene reactions were executed efficiently under with various thiols (example is shown in Scheme 106). A few different radical initiators were used, and in some reported cases no initiator was added. These addition reactions were one of the most exploited ways to immobilize *Cinchona* alkaloids on solid supports.^{253,254} As an example, the ethoxysilane group was introduced with the prospect of obtaining surface-coated materials.²⁵⁵

An interesting functionalization of the 3-vinyl group in cinchonidine was performed electrolytically (Scheme 107). Two radical processes at a graphite anode gave the chlorotrifluoromethylated product **CD-363** in fair yield and rather good diastereoselectivity.²⁵⁶

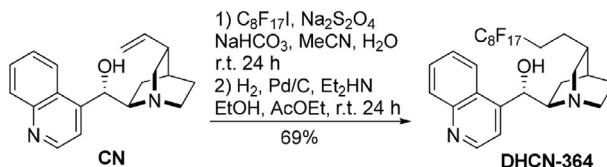
Perfluoroalkyl groups were attached to the carbon atom 11 in the radical substitution reaction of corresponding iodoperfluoroalkanes using sodium dithionite method (Scheme 108).²⁵⁷



Scheme 106 An example of thiol-ene reaction of *Cinchona* alkaloids.



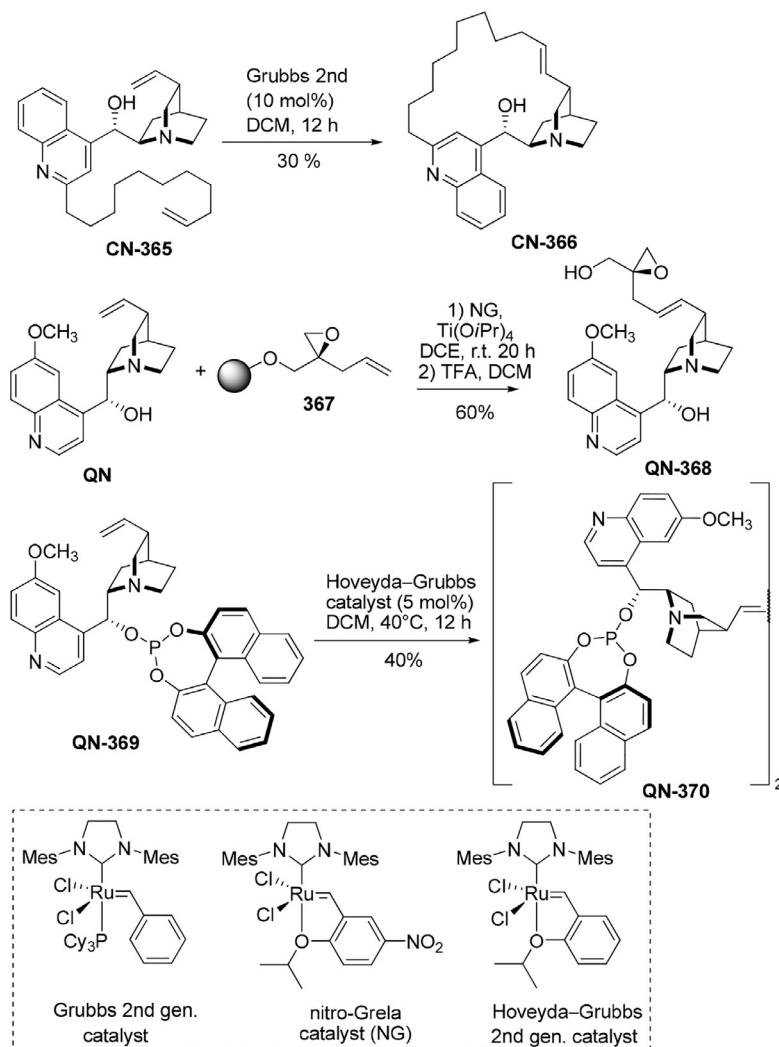
Scheme 107 Diastereoselective electrochemical addition to the 10,11-double bond of cinchonidine.



Scheme 108 A radical addition–hydrogenation sequence on cinchonine.

3.2.2.3 Ruthenium-catalyzed metathesis

The 3-vinyl group was also exploited in a few different ruthenium–carbene-catalyzed metathesis reactions. These included ring-closing metathesis of adequate terminal vinyl derivatives (**Scheme 109**, top).²⁵⁸ Cross metathesis utilizing solid-supported epoxide reagent **367** was also performed (**Scheme 109**, center).²⁵⁹ In a similar fashion, metathesis dimerization was used to



Scheme 109 Examples of ring-closing, cross, and dimerization metathesis.

obtain dimers **QN-370** from phosphorous esters of the alkaloids **QN-369**.²⁶⁰ It is noted that in none of the metathesis reactions Grubbs first-generation catalyst was successful. Still, the application of Grubbs second generation, as well as modified Hoveyda–Grubbs catalysts, provided increasing preparative yields (**Scheme 109**).

3.2.2.4 The Heck reaction

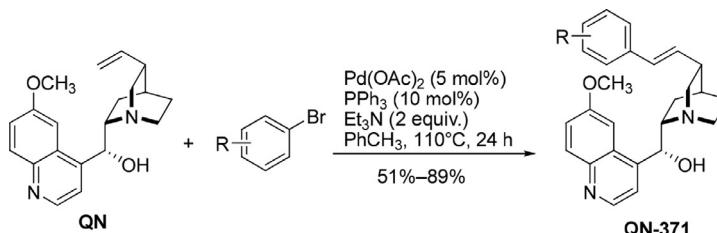
The modification of the 3-vinyl group of quinine in the Heck reaction was performed with a number of different aryl bromides (**Scheme 110**). Complete conversions were reached within 24 h, and the yields were good to moderate reflecting different purification difficulties.²⁶¹

Itsuno exploited the Heck methodology to obtain various dimeric and polymeric catalysts. A few different approaches were adopted involving the reaction of diiodoarenes with *Cinchona* alkaloids and the polymerization of functional iodoaryl derivatives of the alkaloids (**Scheme 111**). A selection of aryl iodides was used both in a single-component and two-component copolymerization.^{262,263}

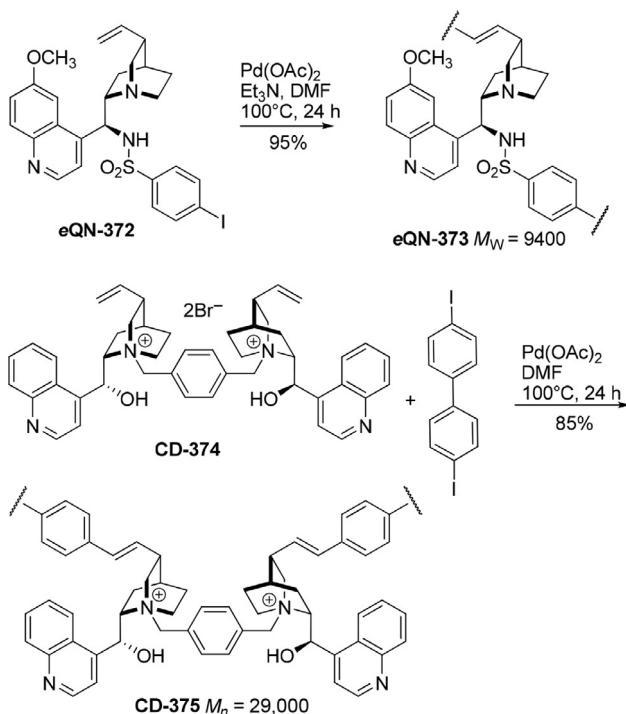
3.2.2.5 10,11-Didehydro *Cinchona* alkaloids

The vinyl group can be converted to a terminal alkyne in a sequence of reactions involving bromine addition and two HBr eliminations under increasingly basic conditions (**Scheme 112**).^{264–266} Intermediate bromine-containing product **QD-376** was the 1:1 mixture of isomers; however, after elimination steps they converged to alkyne **QD-377** in a rather good yield.^{265,266}

The terminal alkyne **QD-377** was also useful intermediate for a variety of coupling reactions. The substitution of acetylene hydrogen was efficiently performed with bromine (**QD-378**, **Scheme 112**) and iodine. The reaction of the bromoacetylene derivative **QD-378** with CuCN led to corresponding nitrile **QD-379**. The metalation of didehydroalkaloid



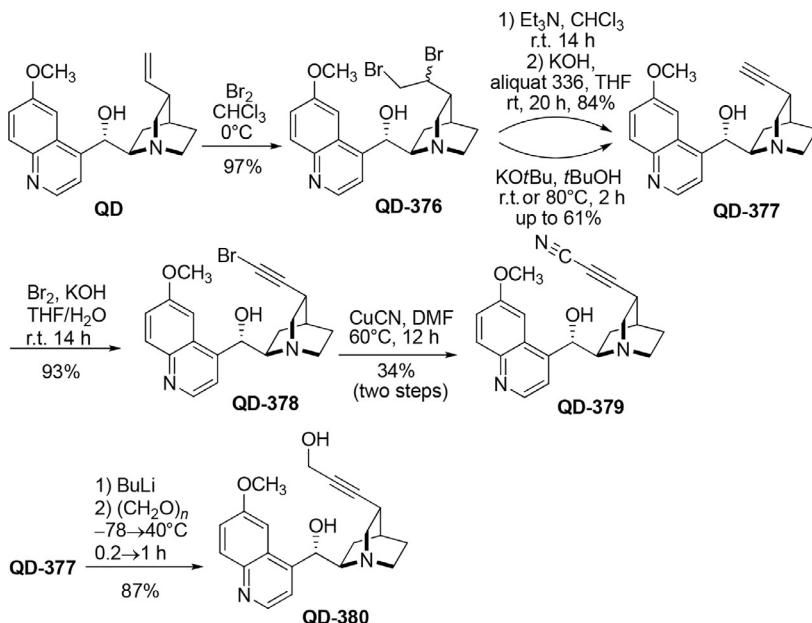
Scheme 110 Examples of Heck couplings with quinine.



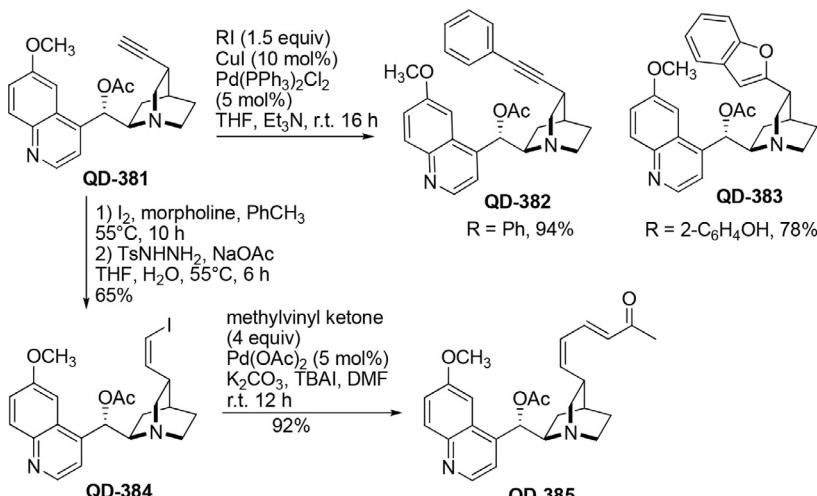
Scheme 111 Heck-polymerization reactions.

QD-377 with butyllithium followed by addition of paraformaldehyde provided alcohol **QD-380** with an additional carbon atom.²⁶⁵ The palladium-catalyzed Sonogashira reaction with various aryl and vinyl halides led to the corresponding substituted alkynes with usually high yields (**Scheme 113**). The protection of 9-OH group was not required but led to improved yields.²⁶⁷ Even large aromatic congeners, such as pyrene, could be introduced.²⁶⁸ For *o*-iodophenol, the subsequent spontaneous cyclization provided 3-benzofuran derivative **QD-383**. The iodination of **QD-381** followed by the reduction led to the iodo vinyl derivative **QD-384**.²⁶⁵ This synthetic intermediate could then be used in the Heck reaction, as well as in Sonogashira coupling with terminal alkynes (**Scheme 113**).²⁶⁷

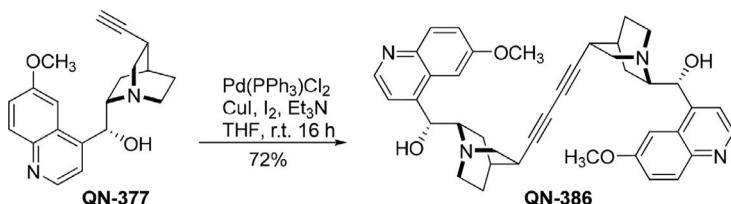
Terminal alkynes **QN-377** could be homocoupled toward **QN-386** under the Sonogashira-like reaction using iodine as an oxidant (**Scheme 114**).²⁶⁷ The alternative Glaser coupling (copper salt/O₂) proceeded only with poor yield.²⁶⁷ However, the similar Eglinton conditions (copper(II) acetate) were effective for coupling of *N*1-quaternary ammonium salt of didehydro alkaloid derivative.²⁶⁹



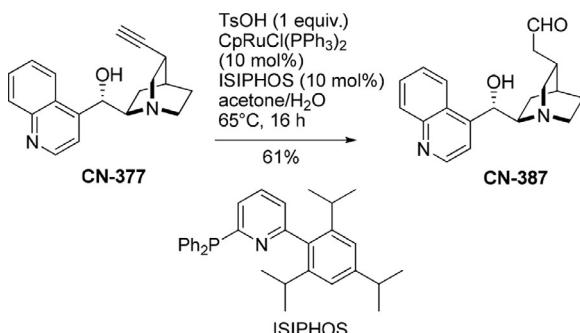
Scheme 112 Example syntheses and transformations of didehydroalkaloid **QD-377**.



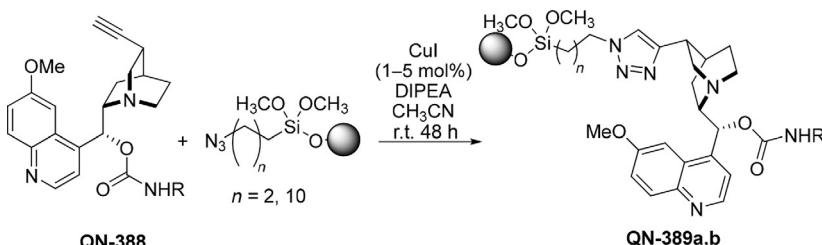
Scheme 113 Selected transformations of didehydroalkaloids.



Scheme 114 Palladium- and copper-catalyzed dimerization of didehydro *Cinchona* alkaloid derivative.



Scheme 115 Synthesis of *Cinchona* alkaloid 10-carbaldehyde **CN-387** by hydration of didehydroalkaloid.



Scheme 116 An example of CuAAC immobilization of didehydroalkaloid derivative.

The anti-Markovnikov hydration of alkynes was attempted with the ruthenium catalyst (**Scheme 115**). The reaction is impeded by the basic character of the alkaloid, while protonation by an external acid, such as TsOH, was required to obtain corresponding 11-aldehyde **CN-387** in still moderate yield.²⁷⁰

3-Alkynes were also suitable components for the copper(I)-catalyzed 1,3-dipolar cycloaddition reactions (CuAAC). These processes were exploited for bioconjugation purposes,²⁷¹ as well as for immobilization (**Scheme 116**).⁷⁸

3.2.3 Miscellaneous Transformations at the Quinuclidine Skeleton

Hatakeyama presented an interesting sequence for the modification of *Cinchona* alkaloids at the position 5 using the Barton nitrite ester reaction ([Scheme 117](#)). The rhodium-catalyzed isomerization of terminal double bond into an internal one resulted in *apo*-quinine (**QN-390**). Then, the hydroboration–oxidation sequence led to 10-oxo derivative **QN-392**. It is noted that the 10-ketone **QN-392b** of the desired configuration at the position 3 could be resolved in a dynamic process. The entire multistep synthesis produces **QN-399**, an analog of the enantiomer of isocupreidine.⁶⁸

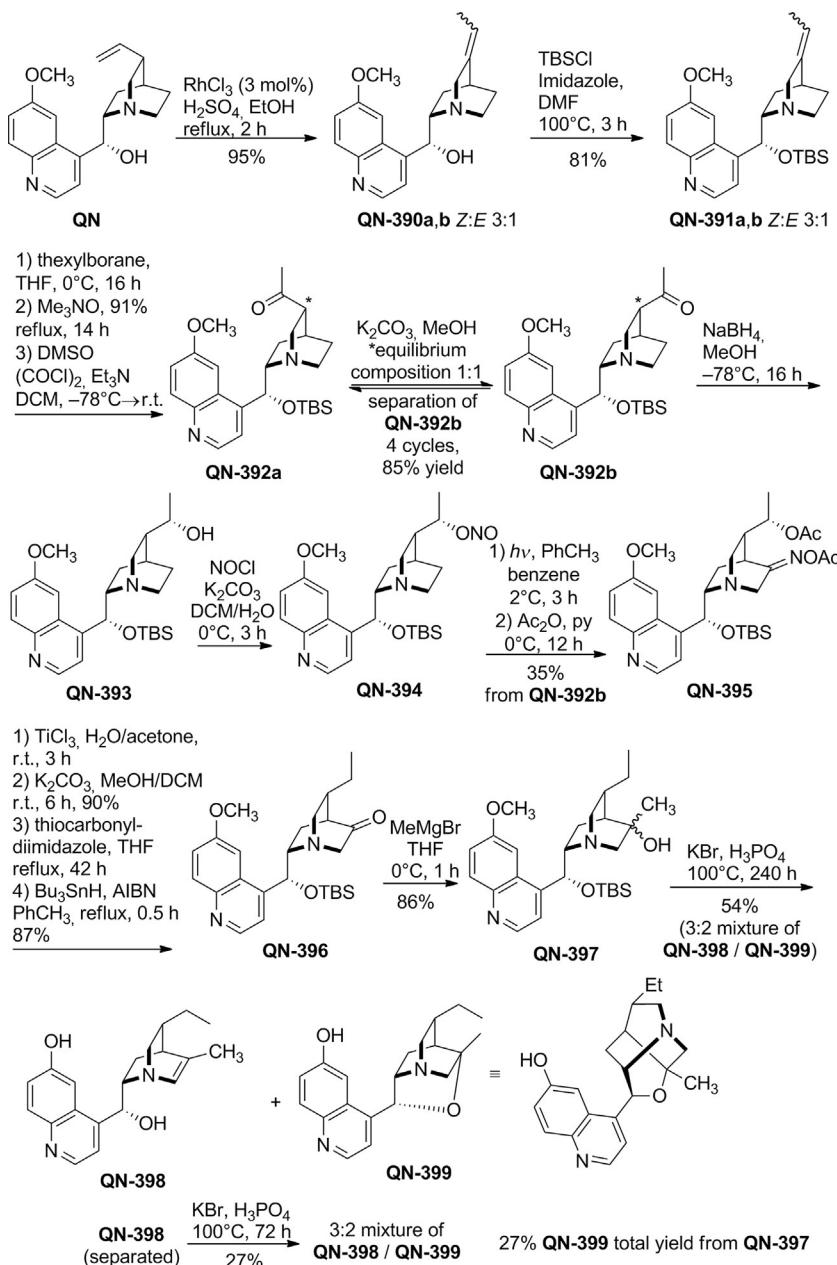
9-TBS-protected ruban-3-one (**QD-400**) was subjected to the addition of Grignard reagents and the reduction with L-Selectride ([Scheme 118](#)). The reintroduction of hydrogen atom or alkyl groups at the position 3 was selective for *endo* products, which was attributed to the coordination by the silyl ether group. The selectivity vanished for 9-acetylated derivatives.²⁷²

The arylation at the position 8 was achieved using triarylbismuth (V) carbonate ([Scheme 119](#)). The reaction proceeds with the oxidation to carbonyl at the position 9, followed by the addition of aryl group to the enolate. A mixture of diastereomeric ketones **QN/QD-405** was produced.²⁷³

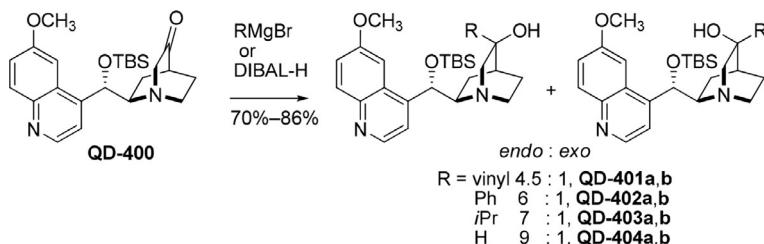
3.3 Reactions at the Quinoline Moiety

Reactions of *Cinchona* alkaloids in the aromatic part generally follow the chemistry of simple quinoline and 6-methoxyquinoline. The difference between the quinine/quinidine and cinchonidine/cinchonine series becomes the most pronounced for electrophilic substitutions. In quinine and quinidine, the 6'-methoxy group can undergo the ether cleavage toward cupreine and cupreidine, respectively ([Scheme 120](#)).²⁷⁴ The corresponding transformations were performed under acidic conditions, typically using HBr.²⁷⁵ These conditions also affected the 10,11-double bond and for quinidine finally led to β -isocupreidine.²³⁴ The use of Lewis acid, such as BBr_3 , was more tolerant for other groups in the molecule. More recently, basic cleavage was developed applying sodium alkylthiolate in hot DMF. The reaction does not affect other groups of native alkaloids.²⁷⁶ For 9O-TBS-protected derivative, L-Selectride was used to obtain the corresponding 6'-phenol **CD-406** ([Scheme 120](#)).²⁷⁷

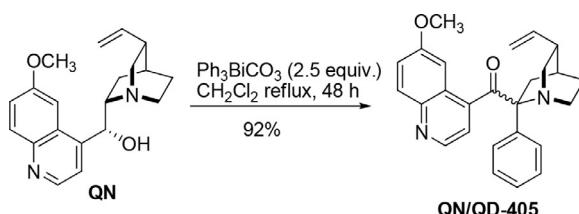
Cupreine and cupreidine are important organocatalysts, but they also served as valuable synthetic intermediates. Subsequent alkylation, that is the formal replacement of the methyl group in quinine with a different one, such as isopropyl,²⁷⁸ in some cases improved enantioselectivities



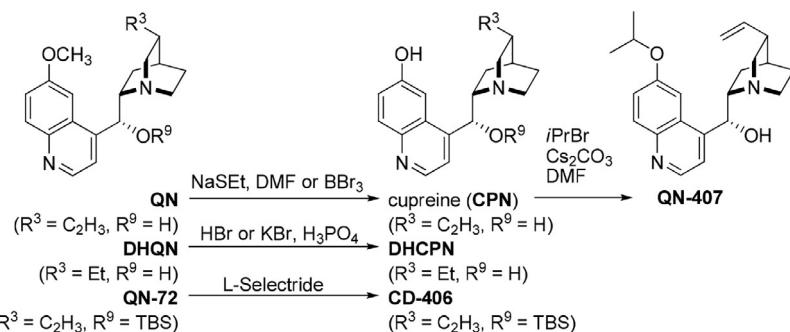
Scheme 117 Synthesis of oxazatwistane **QN-399** from quinine.



Scheme 118 Stereoselectivity in additions to 3-rubanone derivative **QD-400**.



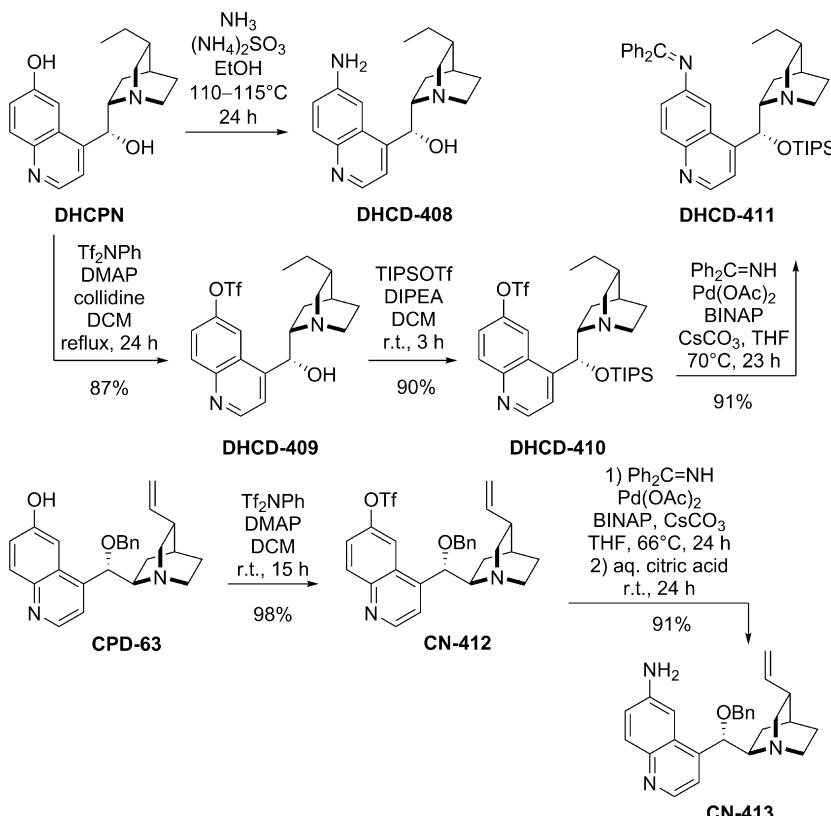
Scheme 119 Arylation of quinidine at the position 8.



Scheme 120 Cleavage of methyl ether and 6'-O-alkylation of cupreine.

obtained with the alkaloids. Ethers were also used to couple the alkaloid to solid supports (**Scheme 120**).²⁷⁹

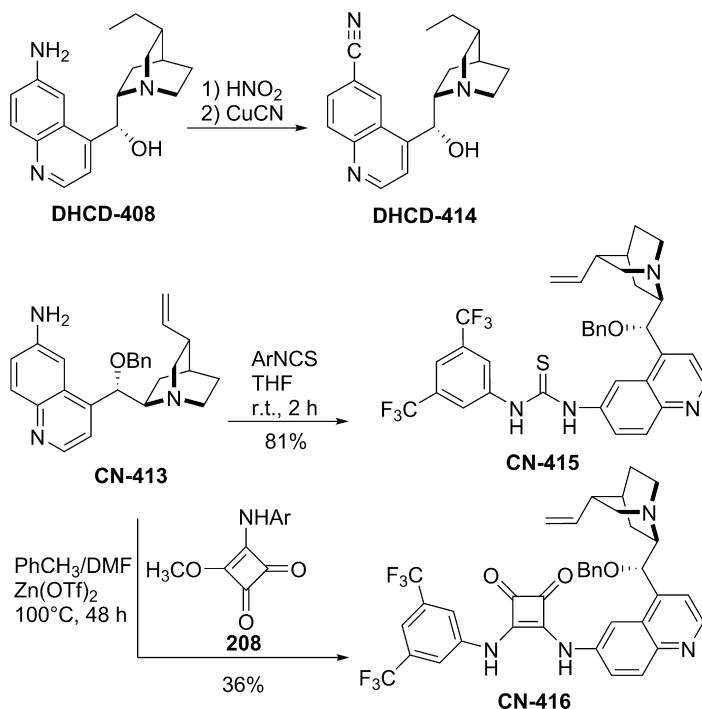
The 6'-hydroxyl group of **DHCPN** was converted into an amine to give **DHCD-408** in the Bucherer reaction.²⁸⁰ However, modern approaches rely on the formation of trifluoromethanesulfonyl esters such as **CD-409** and **CN-412** followed by the Buchwald–Hartwig amination (**Scheme 121**).²⁸¹ The primary 6'-amines were obtained using benzophenone imine,²⁸² followed by the hydrolysis.²⁸² Moreover, the palladium-catalyzed amination reaction was used to obtain secondary and tertiary amines as well.²⁸³



Scheme 121 Synthesis and selected transformations of alkaloid 6'-triflates.

The 6'-amino group in **DHCD-408** was diazotized and converted to azo dyes, as well as other derivatives such as the 6'-nitrile **DHCD-414**, and 6'-halides (Scheme 122).²⁸⁰ Also the 6'-amino 9-benzyl alkaloid **CN-413** was converted to various hydrogen bond donors such as thiourea **CN-415**,²⁸² squaramide **CN-416**, and sulfonamide derivatives.²⁸⁴

The 6'-triflates of *Cinchona* alkaloids, apart from their reactivity in the Buchwald–Hartwig aminations, undergo a few different palladium-catalyzed processes forming 6'-carbon–carbon or carbon–heteroatom bonds (Schemes 123 and 124). These included the Suzuki coupling with boronic acids,²⁸⁵ stannylation followed by fluorination,²⁸⁶ the Sonogashira reaction followed by 1,3-dipolar cycloaddition.²⁸⁷ The coupling involving C–H activation was also exploited in the nickel-catalyzed reaction of **CD-409** with benzoxazole.²⁸⁸ Isocupreidine triflate **ICD-423** was also used in a number of similar palladium-catalyzed reactions, such as the Suzuki

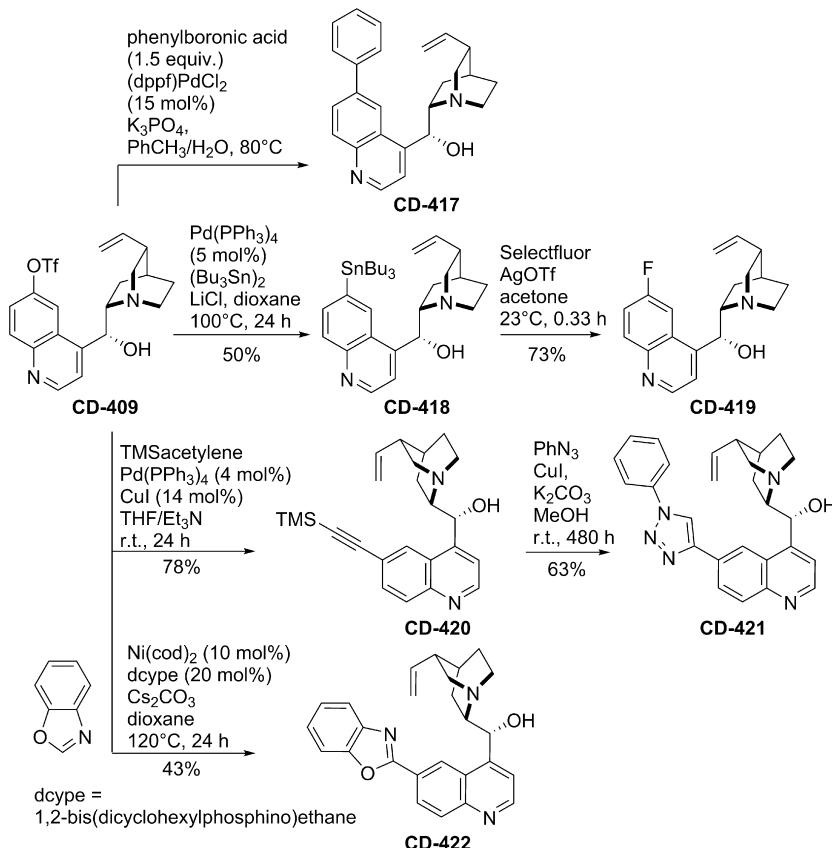


Scheme 122 Transformations of 6'-aminoalkaloid derivatives.

coupling with aryl boronic acids,²³⁶ reactions with thiolates to form 6'-sulfur derivatives, e.g., **ICD-425**,²⁸⁹ and the reaction with carbon monoxide resulting in carboxylation to form **ICD-426**²⁹⁰ (**Scheme 124**).

3.3.1 N-Oxides and Their Transformations

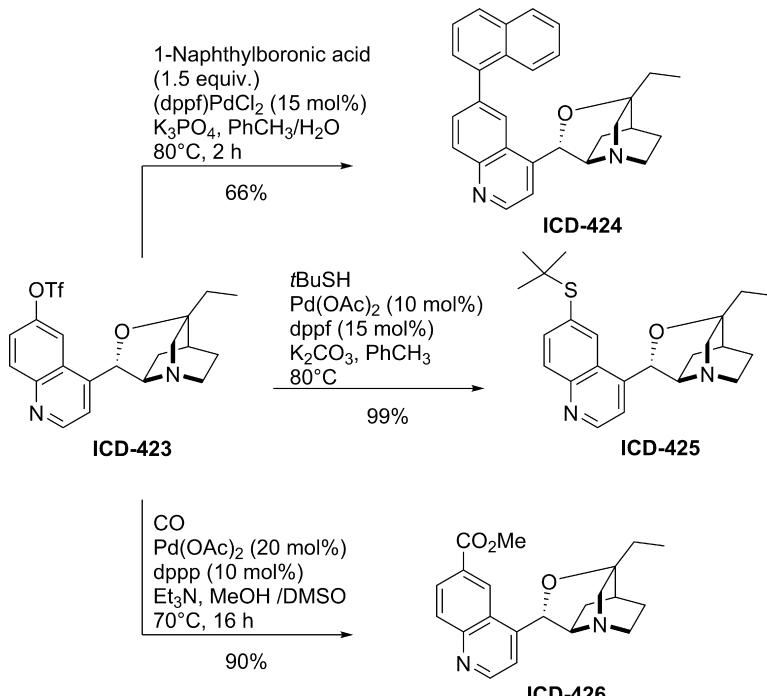
The oxidation of *Cinchona* alkaloids with peroxyacids (e.g., *m*CPBA or $\text{H}_2\text{O}_2/\text{AcOH}$ system) results in oxidation of both nitrogen atoms. While the selective N1-oxidation can be performed,²²⁹ N1'-oxides **428** can only be prepared by the overoxidation to N1,N1'-dioxide **427** (which on extraction partitions preferentially into water). Then, the selective reduction of **427** was typically achieved with sulfur dioxide in aqueous acetone (**Scheme 125**).^{291–293} Quinine and quinidine N1'-oxides **QN/QD-428** can be converted to the corresponding cupreine and cupredine N1'-oxides by ether cleavage with HBr.^{293,294} The presence of N1'-oxide group has improved both the yield and the enantioselectivity in the cupredine-catalyzed isomerization of butenolides.²⁹³ The N-oxide **CN-428** was also efficiently N1-benzylated to form PTC N1'-oxide of improved catalytic



Scheme 123 Examples of transition metal-catalyzed transformations of alkaloid 6'-triflates.

performance in α -hydroxylation of β -dicarbonyl compounds using oxygen and light,²⁹⁵ or with benzoyl peroxide.²⁹⁶

The N1'-oxide function introduces electrophilic reactivity at the adjacent position 2'; therefore **428** are valuable synthetic intermediates. The reaction on N1'-oxide with phosphoryl chloride²⁹⁷ and phosphoryl bromide afforded 2'-chloro and 2'-bromo alkaloids (**Scheme 126**).²⁹⁸ While chloride was reported to be obtained in high yield, only moderate outcome was obtained for the bromide **QN-431**.²⁹⁸ A variant of the reaction with POBr₃ included a catalytic quantity of DMF; however, the yield improvement was marginal.²⁹⁹ Once 2'-bromoquinine **QN-428** crystallizes, it becomes poorly soluble in most organic solvents. Alternatively, 2'-bromides were prepared in the reaction of N-oxide with tosyl anhydride and



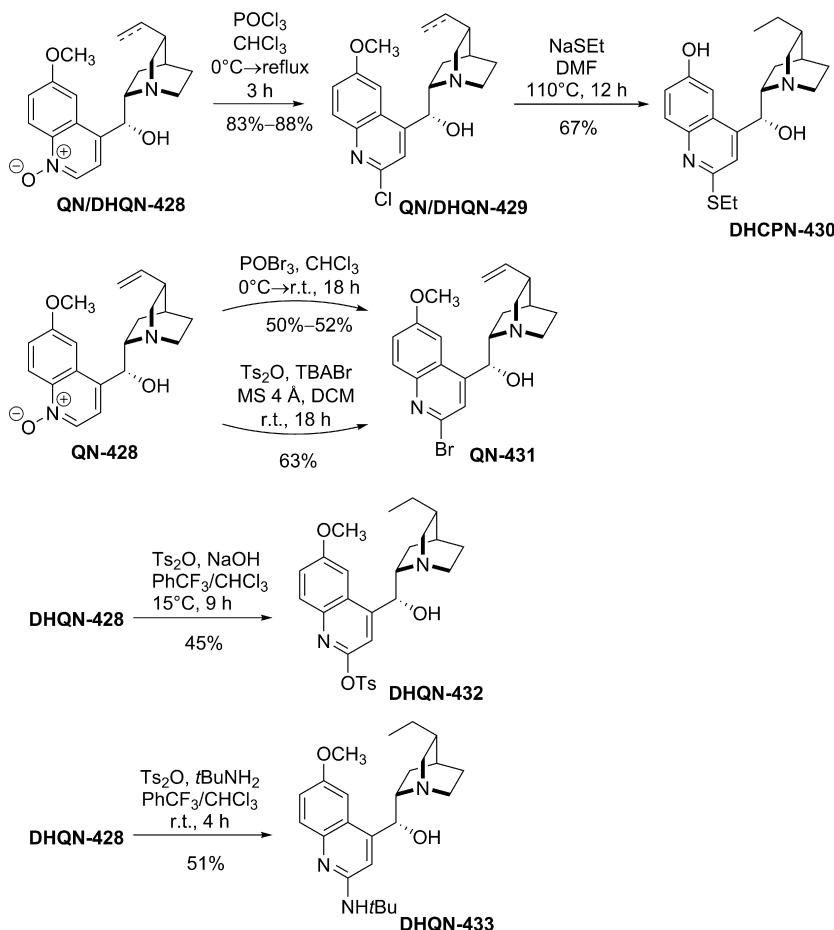
Scheme 124 Examples of transition metal-catalyzed transformations of β -isocupreidine-derived triflate.



Scheme 125 A representative synthesis of alkaloid N1'-oxides.

tetrabutylammonium bromide.²⁹² Furthermore, the activation of N-oxide with tosyl anhydride followed by *tert*-butyl amine led to the corresponding 2'-aminoalkaloid derivative **DHQN-433** (Scheme 126).²⁹⁴

2'-Halo *Cinchona* alkaloids undergo typical reactions for pyridine derivatives, including further nucleophilic displacement. On the treatment of 2'-chloride **DHQN-429** with ethyl thiolate, the substitution can occur together with the 6'-ether cleavage (Scheme 126).²⁹⁴ The reaction of hydrazine with 2'-chloroalkaloid **DHCD-434** followed by condensation with

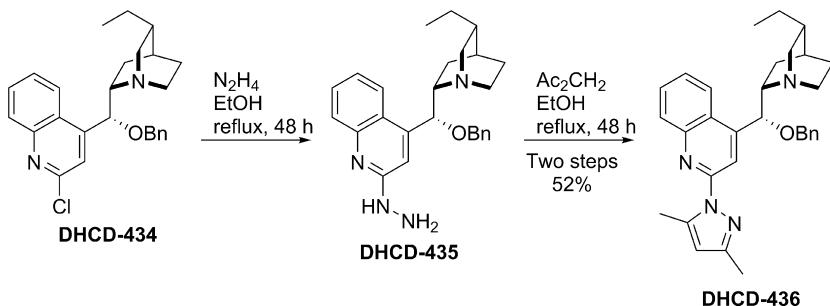


Scheme 126 Selected nucleophilic substitutions using alkaloid *N*1'-oxides.

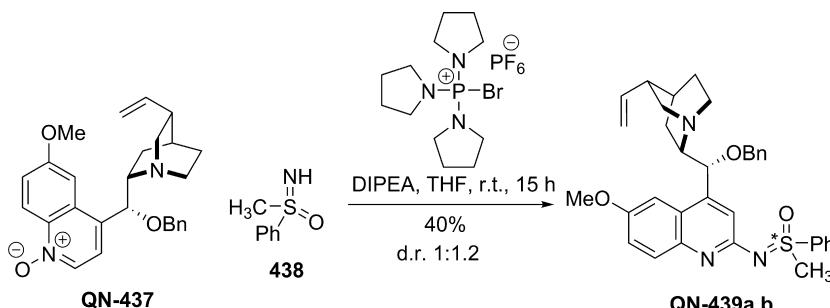
acetylacetone gave the 2'-pyrazole derivative **DHCD-436** (**Scheme 127**).³⁰⁰ 2'-Halides **429** were also exploited in a series of palladium-catalyzed transformations.³⁰⁰ These included the Suzuki reaction with arylboronic acids³⁰¹ and the Sonogashira reaction.²⁸⁷

Recently, the alkaloid *N*-oxide **QN-437** was activated with phosphonium salts and then treated with racemic sulfoximine **438** (**Scheme 128**). The reaction proceeded with poor stereoselective discrimination, providing a mixture of diastereomeric sulfoximines **QN-439a,b**.³⁰²

Generally, the presence of *N*-oxide function predisposes a quinoline moiety for the C–H activation reactions. Thus, alkaloid *N*-oxides were subjected to the reactions with Grignard and organolithium reagents.



Scheme 127 Synthesis of 2'-pyrazole alkaloid derivative.



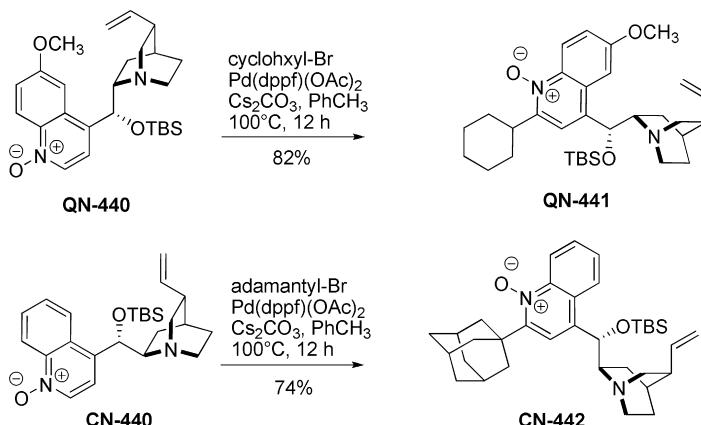
Scheme 128 Synthesis of alkaloid sulfoxime derivative.

The transformations were carried out with a 10-fold excess of organometallic reagents and led to various 2'-alkyl- and 2'-aryl-substituted alkaloids. The yields were dependent on the type of the reagents and ranged from low for t BuLi to good for MeLi (75%).³⁰³ Alternative conditions using copper(I) catalyst and magnesium salts as additives did not improve the product yields.³⁰⁴ The palladium-catalyzed alkylation with secondary and tertiary alkyl bromides led to 2'-cyclohexyl- and adamantyl-substituted products **QN-441** and **CN-442** retaining the *N*-oxide unit (Scheme 129).³⁰⁵

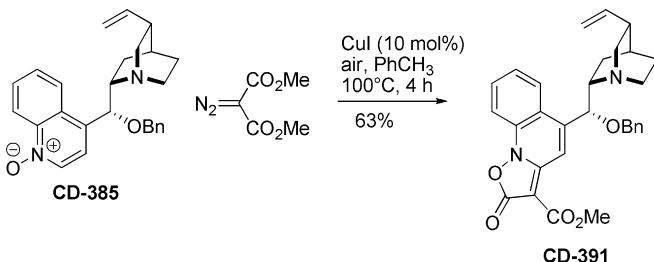
N-Oxides in the reaction with diazomalonate in the presence of air and copper(I) gave the cyclization product **CD-443** (Scheme 130).³⁰⁶

A similar ring fusion was achieved in the reaction of the 2'-chloro derivative **QN-429** with $TMSN_3$ in the presence of fluoride (Scheme 131). The obtained tetrazole **QN-444** was then converted to the amide of picolinic acid **eQN-445**.³⁰⁷

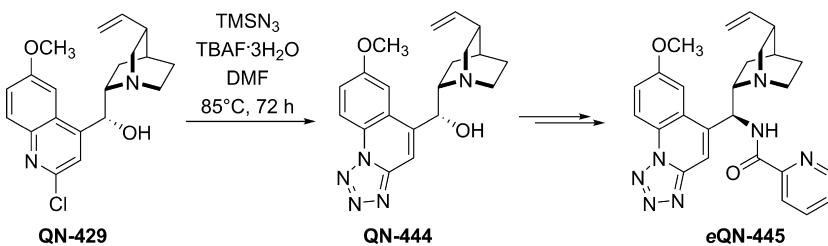
An alternative to the *N*-oxide activation of the position 2' is the action of triflic anhydride on 9-protected derivatives of the alkaloids. A combination of Tf_2O and $TMSCN$ on 9-*O*-methyl quinine (**QN-60**) resulted in the formation of 2'-nitrile **QN-446** in a moderate yield (53%, Scheme 132).³⁰⁸



Scheme 129 Examples of palladium-catalyzed cross coupling using alkaloid *N*1'-oxides.



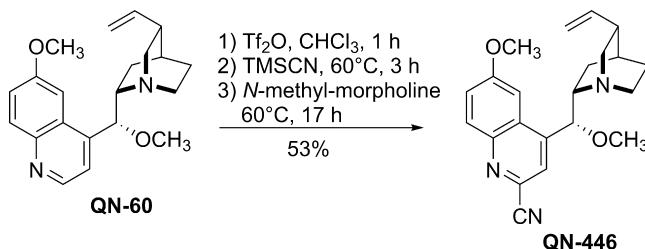
Scheme 130 Synthesis of fused isoxazolidinone alkaloid derivative **CD-391**.



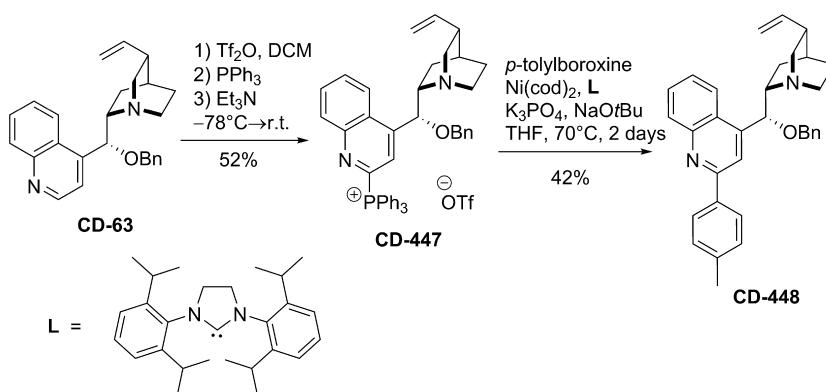
Scheme 131 Synthesis and further transformation of alkaloid-fused tetrazole **QN-444**.

Similar activation conditions were used to convert alkaloid into phosphonium salt **CD-447** with triphenylphosphine. These were then reactive in the nickel-NHC-catalyzed Suzuki-type coupling (Scheme 133).³⁰⁹

The position 2' is directly reactive in the nucleophilic substitution with organometallic compounds, mostly organolithium.³¹⁰ The reaction involves the addition step followed by the oxidative rearomatization. A 2'-methylquinidine derivative was obtained in the reaction of methylolithium



Scheme 132 An example of alkaloid 2'-cyanation reaction.

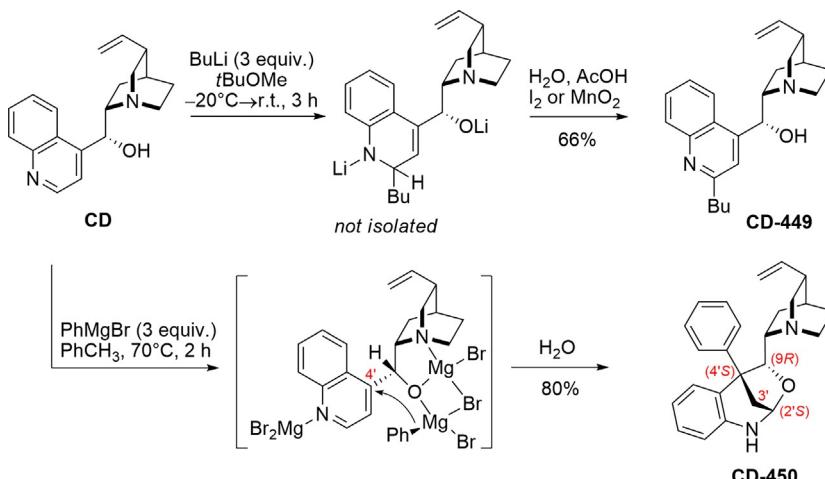


Scheme 133 Example synthesis and application of alkaloid-derived phosphonium salts.

with quinidine 9-methyl ether followed by the oxidation with air or iodine in good yield (72%).³¹¹ The same approach was applied for 2'-alkylation and arylation of 9-amino alkaloids and required a fivefold excess of the corresponding organolithium.³¹² Grignard reagents essentially display the same type of reactivity in ethereal solvents (**Scheme 134**). However, in toluene the addition became directed at position 4'. These reactions resulted also in the formation of an ether bond between O9 and C2' atoms. The addition was guided by chelation of magnesium species, so the stereocenters at positions 2' and 4' were formed stereoselectively. For cinchonidine, the configuration of the product **CD-450** was 8*S*,9*R*,2'*S*,4'*S*.²⁵⁸

Positions 2' and 4' participate in photochemical transformations. Relevant products **QN-451** and **QN-452** were postulated in irradiated solutions of citric acid and quinine (**Fig. 14**).³¹³

Knochel developed a selective metalation at the position 3' followed by reactions with electrophiles (**Scheme 135**). The process involved both lithium and magnesium compounds (MeLi and magnesium amidate). The



Scheme 134 Representative reactions of *Cinchona* alkaloids with Grignard reactions.

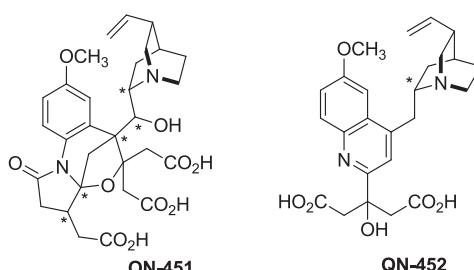
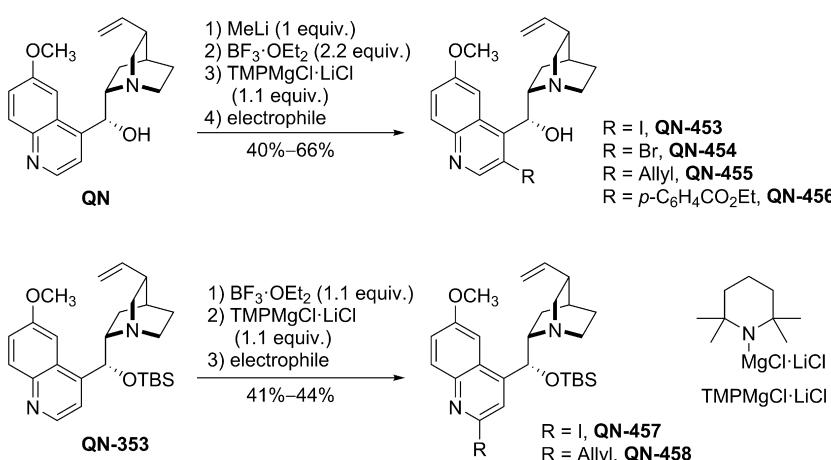
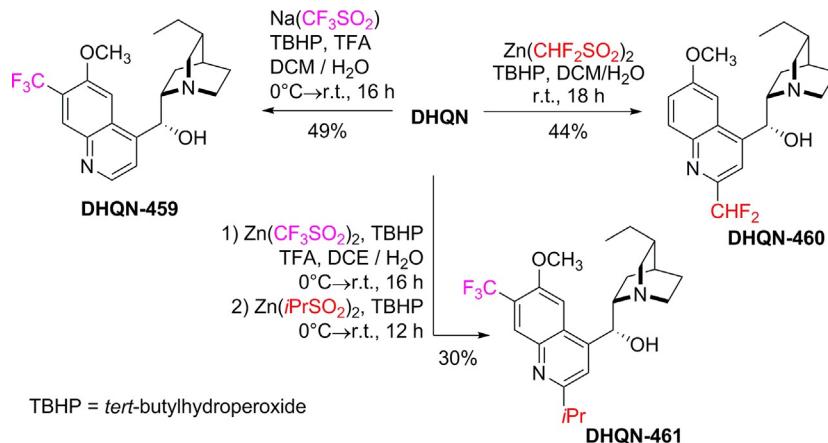


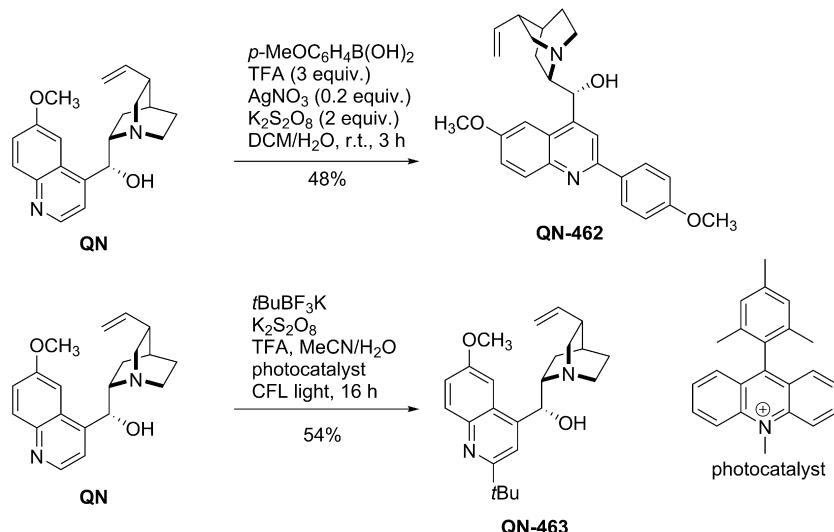
Fig. 14 Products likely present in irradiated tonic water.



Scheme 135 Representative examples of substitutions at the position 3' of quinine and 2' of quinine silyl ether **QN-353** achieved with TMPMgCl-LiCl/BF₃-OEt₂ system.



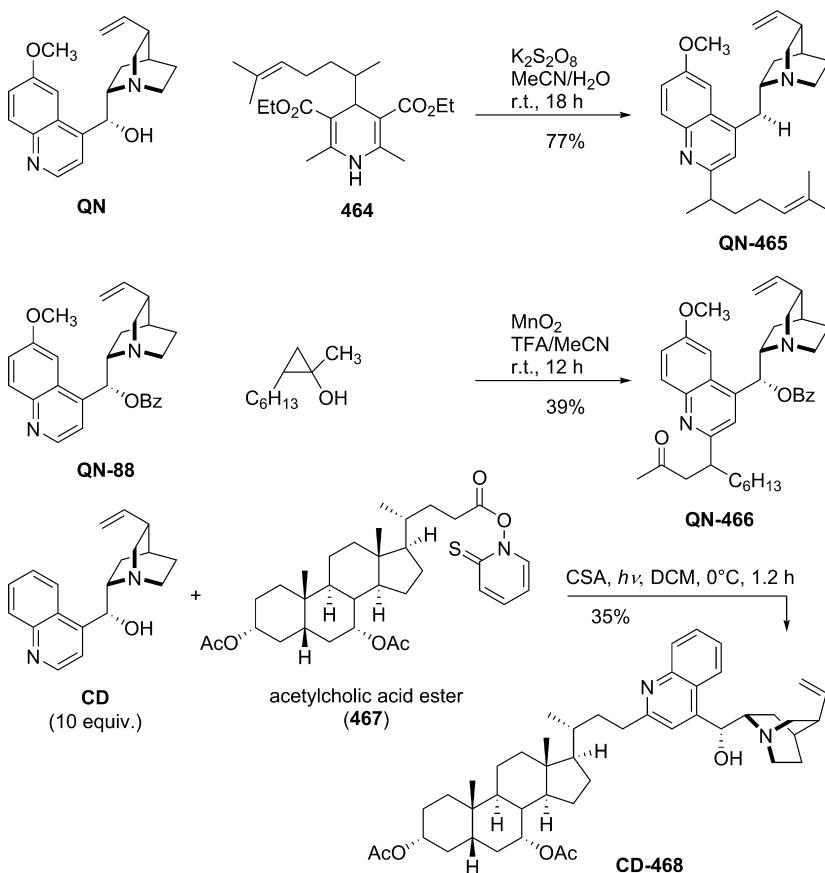
Scheme 136 Radical alkylation and fluoroalkylation of dihydroquinidine.



Scheme 137 Representative examples of borono Minisci reactions of *Cinchona* alkaloids.

reaction appears to be guided by the 9-hydroxy group, while TBS protection shifts the reactivity toward the usual 2' position.³¹⁴

The radical substitution in dihydroquinine can occur at the positions 2' and 7' depending on the radical type (**Scheme 136**). Highly electrophilic radicals, such as trifluoromethyl, are added to the position 7', as seen in the reaction of either sodium³¹⁵ or zinc trifluoromethanesulfinate. Less electrophilic radicals attacked the position 2' selectively. Furthermore, one-pot



Scheme 138 Examples of radical C–C couplings at the position 2' of *Cinchona* alkaloids.

sequential addition using zinc trifluoromethanesulfinate and zinc isopropylsulfinate was performed. Trifluoromethyl and isopropyl groups are added selectively to the positions 7' and 2', respectively.³¹⁶ Analogous, difluoromethylation took place at C2' exclusively.³¹⁷

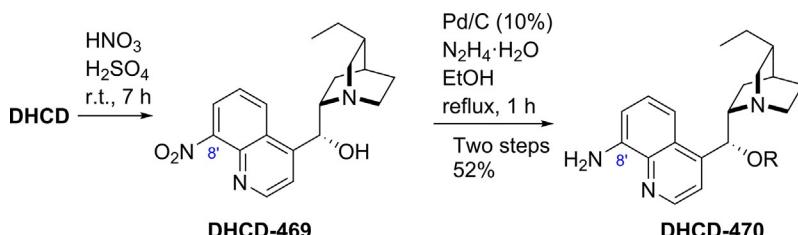
Carbon substituents were introduced at the position 2' in radical substitutions under acidic conditions (**Schemes 137 and 138**). Most known examples employ the borono Minisci reaction that is the action of boronic acids under oxidative conditions with silver as a catalyst.^{315,318} An alternative photoredox process was devised to avoid the use of silver.³¹⁹ However, applications of a number of different protocols for generating carbon-centered radicals resulted in selective 2'-substitution of *Cinchona* alkaloids (**Scheme 138**). For example, oxidative homolysis of substituted

dihydropyridines, such as **464**, resulted in the transfer of a secondary alkyl group from the position 4 of dihydropyridine to the position 2' of *Cinchona* alkaloids.³²⁰ Similarly, radical substitution products were obtained in the MnO₂ oxidation of cyclopropanols.³²¹ The photolysis of Barton esters was applied for coupling of the alkaloids with bile acids (*Scheme 138*).³²² The 3-vinyl group was tolerated in most of these reactions.

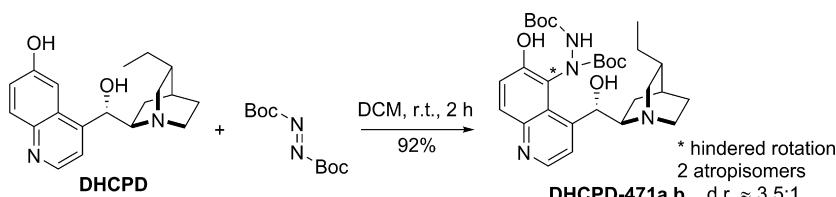
3.3.2 Products of Aromatic Substitutions

The nitration of dihydrocinchonine and dihydrocinchonidine with fuming nitric acid/sulfuric acid occurred preferentially at the position 8' (*Scheme 139*). The catalytic hydrogenation produced the corresponding aromatic amine **DHCD-470**.³²³ Vinyl groups are not compatible with the nitration conditions.

The 6'-methoxy group of quinine and quinidine directs nitration selectively to the position 5'. The nitration of dihydroquinine can be carried out with fuming nitric acid at below 5°C.³²⁴ In the case of cupreine and cupreidine, 6'-hydroxyl group activates the aromatic system even more. Apart from nitration,³²⁵ substitutions with diazonium salts³²⁶ and azodicarboxylate derivatives were performed (example is shown in *Scheme 140*). In the case of di-*tert*butyl azodicarboxylate, the congestion in between the position 6' and alkaloid residue at the position 4' resulted in the formation of separable atropisomeric hydrazines **DHCPD-471**.^{327,328}



Scheme 139 Nitration of dihydrocinchonidine.

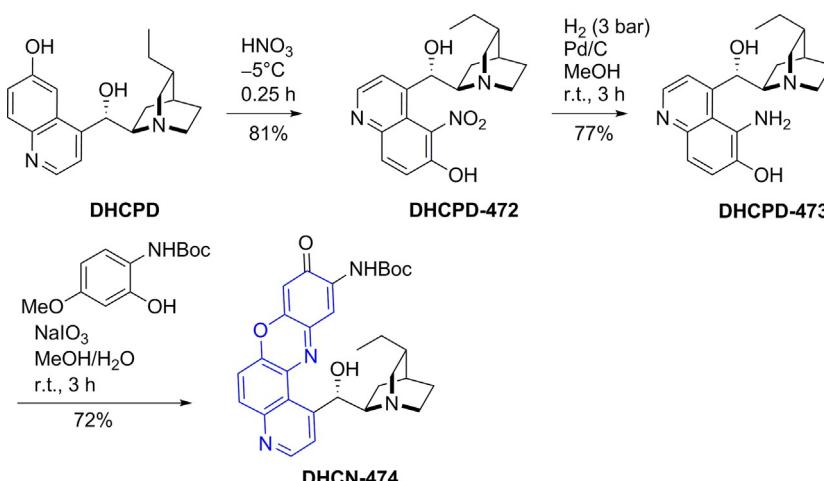


Scheme 140 Synthesis of atropisomeric hydrazines.

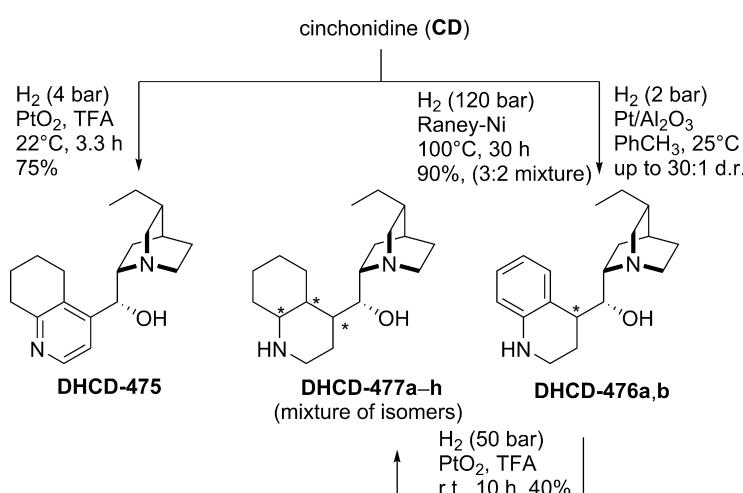
The products of nitration were hydrogenated to corresponding anilines. 5'-Anilines were transformed into the corresponding ureas.^{324,329} Moreover, alkaloid-derived *o*-aminophenol **DHCPD-473** was subjected to the oxidative condensation with 4-methoxy-2-hydroxyanilides providing alkaloids with pyrido[3,2-*a*]phenoxazinone aromatic part (**Scheme 141**).³³⁰

3.3.3 Hydrogenation of Quinoline

Hydrogenations of quinoline part in *Cinchona* alkaloids were performed at either ring by choosing a suitable catalyst (**Scheme 142**). The pyridine ring



Scheme 141 A representative synthesis of alkaloid-derived pyrido[3,2-*a*]phenoxazine.



Scheme 142 Hydrogenation of quinoline part in cinchonidine.

was hydrogenated using Raney nickel. This catalyst provided poor diastereoselectivity. Two 4' epimers were formed in 3:2 ratio, and the products **DHCD-476a,b** were separated.¹⁰² The hydrogenation of the pyridine ring in cinchonidine with platinum on Al₂O₃ support or platinum nanoparticles became highly selective toward 4'S product **DHCD-476a**.³³¹ With the platinum oxide catalyst the benzene ring was reduced resulting in **DHCD-475**. The sequential nickel and platinum reduction gave the completely hydrogenated product as a complicated mixture of diastereomers **DHCD-477a–h** (*Scheme 142*).¹⁰²

3.4 Metal Complexes

Cinchona alkaloids are polytopic ligands capable of forming various types of complexes with many metals. However, relatively few X-ray crystal structures have been characterized. The antimalarial activity of quinine and quinidine relies on the inhibition of conversion of iron(III) protoporphyrin IX complex into hemozoin. The nature of the inhibition is the formation of the complex of quinine or quinidine with the iron(III) center (*Fig. 15*). The coordination involved the oxygen atom of the 9-hydroxyl group. Additionally, ionic interactions between basic quinuclidine center and protoporphyrin side-chain carboxylic acid were observed.³³² Since both types of interactions are essential to achieving the effective binding, *epi*-alkaloids appear to be incapable of forming analogous complexes, which explains their inefficiency against malaria.

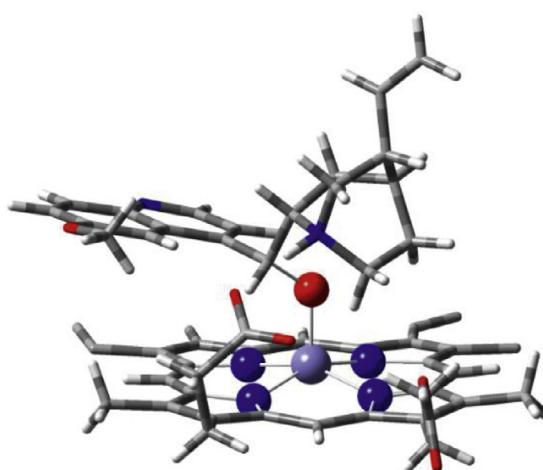


Fig. 15 X-ray structure view of quinine-protoporphyrin IX iron(III).³³²

Much more prevalent among elucidated structures are complexes exploiting the 1,2-aminoalcohol chelating unit, that is, 9O and quinuclidine N1 donating atoms (Figs. 16 and 17). Complexes of ruthenium(II), rhodium(III), iridium(III), and gold(I) species were postulated to involve quinuclidine N1 atom. For complexes with a chiral metal center, the observed ratio of diastereomers was 1:1. On crystallization of ruthenium cymene complexes, 9OH deprotonated, and neutral 1,2-aminoalcoholate chelate was formed, for which the X-ray structure was elucidated (Fig. 16, left).³³³ The same mode was found for palladium(II) complexes obtained from $[(\text{en})(\text{H}_2\text{O})_2\text{Pd}](\text{NO}_3)_2$ despite square planar geometry and different coordination numbers (Fig. 16, right).³³⁴

Apart from ML-type complexes, a number of polymetallic C_2 -symmetric complexes were obtained (Fig. 17). Under nonacidic conditions copper(I) halides (CuBr , CuCl) in the presence of oxygen in the solvothermal approach or mechanochemical synthesis formed 9O–N1 dimeric

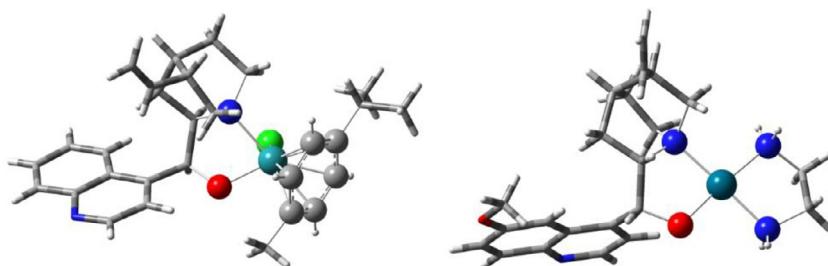


Fig. 16 X-ray structure views of monometallic 9O,N1 chelates of rhodium $[(\text{cinchoninato})\text{ClRh}(\text{cymene})]$ (left) and palladium $[(\text{quinuclidato})\text{Pd}(\text{en})]^{+}$ species (right).^{333,334}

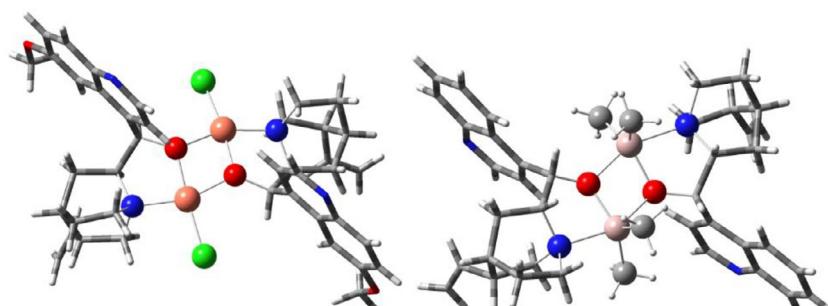


Fig. 17 X-ray structure views of dimetallic complexes of quinine with copper(II) (left) and cinchonine with aluminum (right).^{335,336}

chelate complexes.³³⁵ Analogous dialuminum complexes were obtained from trialkyl aluminum.³³⁶ A complex containing one aluminum atom and two alkaloid ligands was obtained from AlMe_2Cl , while subsequent treatment with ZnCl_2 resulted in a separate coordination link with the quinoline nitrogen atom N1'. This led to the formation of polymeric zinc–aluminum complex (Fig. 18, left), which in turn formed a supramolecular structure of a highly porous metal–organic framework (MOF). The assembly contained a network of 1D channels of 5 Å diameter and filling about a quarter of the total volume (24%, calculated).³³⁷

Another type of polymeric complex, with multimetallic repeating unit $\text{Cu}_8\text{Cl}_{10}(\text{H-quinine})_2$, was obtained by a solvothermal method with copper(I) halide and quinine (Fig. 18, right). Here, two quinoline N1' nitrogen atoms and two vinyl groups from four different alkaloid molecules coordinated to the multimetallic unit.³³⁸

A series of cobalt(III) complexes with various *Cinchona* alkaloids were studied by Oleksyn.^{339–342} In all cases, trichlorocobalt(III) unit was bound by the quinoline nitrogen atom N1' (Fig. 19, left). However, quinuclidine moiety remained protonated. In the reaction of quinine with K_2PtCl_4 in aqueous hydrochloric acid, a stable complex was obtained that is analogous to Zeise's salt. The coordination was exclusive for the terminal vinyl group (Fig. 19, right).

In yet another example, all heteroatomic coordination sites were occupied by palladium (Fig. 20). The complex was obtained from cinchonine and stoichiometric amounts of $[(\text{Et}_3\text{P})\text{PdCl}_2]_2$ and NaOMe in methanol.³⁴³

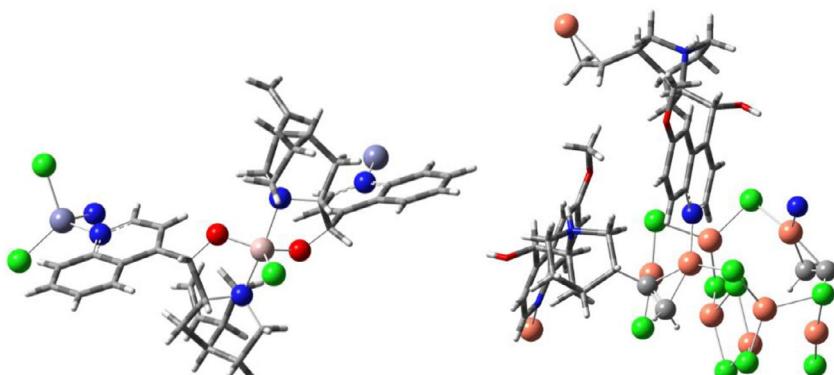


Fig. 18 Partial X-ray structure views for coordination polymers of aluminum–zinc complex (left) and multimetallic chlorocupper complex (right).^{337,338}

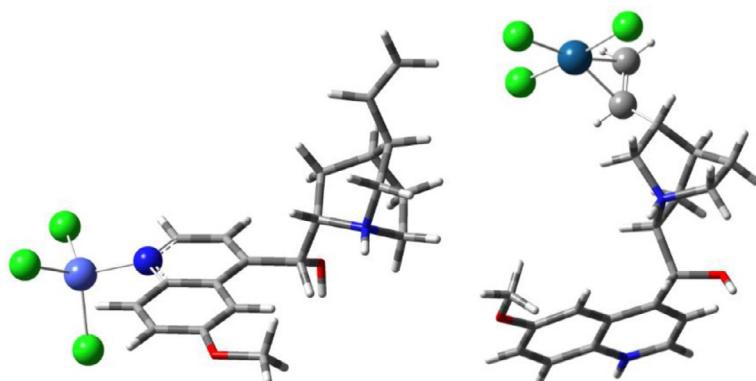


Fig. 19 X-ray structure view of quinoline cobalt(III) complex (H atoms at ideal positions) (*left*) and vinyl platinum (II) complex (*right*).^{334,339}

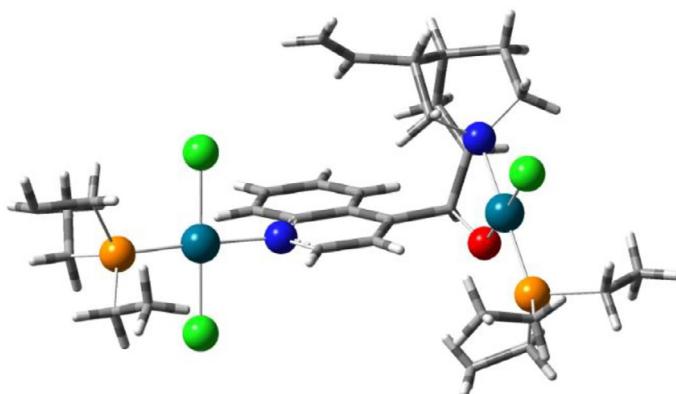


Fig. 20 X-ray structure view of cinchonine palladium(II) complex of M_2L stoichiometry.³³⁴

It has to be noted that while this account presents the alkaloids as versatile ligands, the ability to coordinate in a defined manner is very much dependent on the acid–base equilibria. Under basic conditions deprotonation of 9-OH results in preferential coordination by the 9O–N1 chelating unit. On the other hand, acidic conditions lead first to protonation of quinuclidine, shifting the complexation to the quinoline unit. However, the alkaloids treated with metal halides in acidic media formed salts rather than coordination compounds, i.e., an ionic salt of chlorozincate,³⁴³ and polymeric halocuprates.³⁴⁴



4. Perspective

From the today's perspective, it appears that *Cinchona* alkaloids will continue as one of the scaffolds of choice for asymmetric catalytic transformations and chiral recognition. Efficient methods for scalable synthesis of certain crucial intermediates like 9-*epi*-aminoalkaloids are likely to render them even more useful due to increased availability. On the other hand, sophisticated multiply functionalized molecules will be obtained in order to accommodate the specific needs of particular asymmetric transformations at the expense of versatility. It seems that fine-tuning of residues at the quinoline ring will lead to most imminent incremental improvements.

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