Hydrosilylation of cinchonidine and 9-*O*-TMS-cinchonidine with triethoxysilane: application of 11-(triethoxysilyl)-10,11-dihydrocinchonidine as a chiral modifier in the enantioselective hydrogenation of 1-phenylpropane-1,2-dione

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The detailed synthesis and characterization of (−)-11-(triethoxysilyl)-10,11-dihydrocinchonidine (**4**), a starting material for the immobilization of (−)-cinchonidine on silica based supports, is described. Compound **4** together with its precursors 9-*O*-(trimethylsilyl)cinchonidine (**2**) and 9-*O*-(trimethylsilyl)-11-(triethoxysilyl)-10,11-dihydrocinchonidine (**3**) were employed as chiral modifiers in the hydrogenation of a prochiral diketone, 1-phenylpropane-1,2-dione, over a heterogeneous Pt/Al_2O_3 catalyst using cinchonidine (**1**) as a reference modifier. The unexpected enhancement of ee induced by **4**, demonstrating the positive effect of distal modifier substitution, is discussed in the light of molecular modeling and NMR studies.

Introduction

Asymmetric hydrogenation of α-keto esters,[1] keto acetals,[2] and diketones[3] using cinchona-modified platinum catalysts is one of the few heterogeneous catalyst systems rivaling the enantiomeric excesses (ee) obtained with homogeneous hydrogenation catalysts. In recent years, increasing amounts of papers on this subject have emerged from both academic and industrial laboratories. The highest enantioselectivities, approaching 95% ee, have been obtained in the hydrogenation of methyl and ethyl pyruvate to the corresponding lactates with cinchonidine† or 10,11-dihydrocinhonidine modified Pt/Al_2O_3 catalysts.[1] The origin of the asymmetric induction, as well as the effect of structural variations of either the substrate or the modifier on enantioselectivity, remain unclear. Certain qualitative trends have been summarized in a recent paper by Blaser and coworkers:[1q] An extended aromatic system is required to form an adsorption complex with the Pt surface; in addition, a chiral amino function capable of interacting with the keto group of the adsorbed substrate is needed to induce sufficient enantiocontrol. The sense of asymmetric induction is controlled by the absolute configuration at the C_8 and C_9 carbon atoms of the cinchona modifier (Fig. 1). Substitution of the C_9 hydroxy group with bulky substituents significantly lowers the enantioselectivity, whereas structural modifications of the quinuclidine C_3 substituent were reported to have only a moderate effect on the ee in the hydrogenation of ethyl pyruvate. Notably, enantioselectivities are also significantly influenced by solvent type and the modifier concentration.

The objective of the present investigation was two-fold. First, grafting of the cinchona modifier to a silica support through covalent bonds would, besides improving the separation and reuse of the chiral modifier,[1g] potentially allow the construction of a flow reactor system for *continuous* enantioselective hydrogenation of prochiral ketones. We were interested in preparing a cinchonidine derivative suitable for this purpose. Hydrosilylation of the olefinic double bond of the related cinchona alkaloid quinine and grafting of the corresponding trialkoxysilyl derivatives to silica for use as chiral HPLC stationary phases has been reported previously.[4] However, to our knowledge, the synthesis and characterization of the products and intermediates have not been described in detail. Furthermore, cinchonidine/cinchonine as well as quinine/quinidine are pairs of diastereomers differing markedly in their physical properties, including their solubilities. General procedures for synthetic transformations and subsequent purifications cannot be applied and must be developed separately in each case. Secondly, the magnitude of ee in the hydrogenation of ethyl pyruvate has been proposed to be influenced by the conformation of the adsorbed modifier, specifically the rotation around the C_8–C_9 axis.[1h,j,k,q] We were thus interested in studying the effect of sterically demanding trialkoxysilyl substitution in the cinchonidine quinuclidine moiety on the enantioselectivity of the hydrogenation of prochiral ketones.

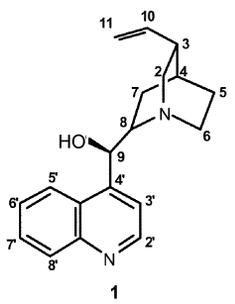

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Fig. 1 Atomic numbering and structure of (−)-cinchonidine.

While this manuscript was in preparation, a report appeared describing the hydrosilylation of various cinchona alkaloids,

† The IUPAC name for cinchonidine is α-quinolin-4-yl-5-vinylquinuclidine-2-methanol.

including cinchonidine, with triethoxysilane in the presence of the Speier catalyst and the subsequent "one-pot" immobilization on a silica surface by sol–gel technology.[5] However, reaction intermediates were not characterized and identification of the immobilized compounds was based exclusively on a combination of IR, UV and solid state ^{13}C NMR methods. This prompted us to report our independent studies on the hydrosilylation of (−)-cinchonidine (**1**) and 9-*O*-(trimethylsilyl)cinchonidine (**2**) with triethoxysilane in the presence of hydrogen hexachloroplatinate (Speier catalyst) or platinum divinyltetramethyldisiloxane (Karstedt catalyst). We describe here the detailed synthesis and characterization of 11-(triethoxysilyl)-10,11-dihydrocinchonidine (**4**), a starting compound for the immobilization of cinchonidine on silica based carriers, *via* its precursors **2** and 9-*O*-(trimethylsilyl)-11-(triethoxysilyl)-10,11-dihydrocinchonidine (**3**). All compounds **1**–**4** were fully characterized by ^{1}H and ^{13}C NMR spectroscopy and employed as chiral modifiers in the hydrogenation of 1-phenylpropane-1,2-dione over a heterogeneous Pt/Al_2O_3 catalyst.[6] The unexpected enhancement of the ee induced by **4**, demonstrating the positive effect of distal modifier substitution, is discussed in the light of molecular modeling and NMR studies.

Results and discussion

Synthesis and characterization of the chiral modifiers

Direct hydrosilylation of cinchonidine with triethoxysilane in the presence of the Speier catalyst proved unsuccesful in our hands. Tertykh and coworkers reported the corresponding hydrosilylation reaction using a propan-2-ol solution of the Speier catalyst and equimolar amounts of cinchonidine and triethoxysilane in a 10 : 0.7 propan-2-ol–acetic acid solvent mixture.[5] However, the product was neither isolated nor characterized and the yield of the hydrosilylation was not reported. During the initial stages of our investigation we carried out a similar reaction in the absence of acetic acid. ^{1}H NMR and TLC analyses indicated a complex mixture of different compounds of which the triisopropoxysilyl adduct **5** (Fig. 2) was

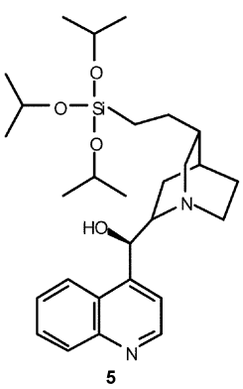

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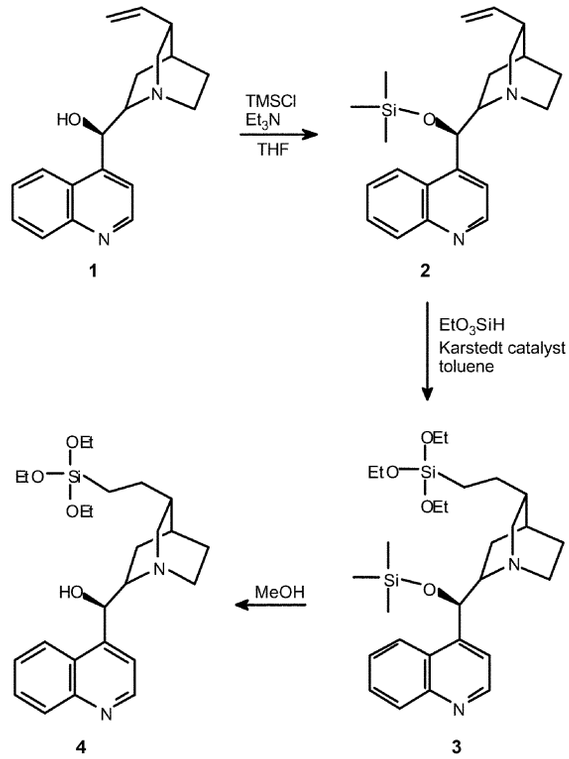
Fig. 2 11-(Triisopropoxysilyl)-10,11-dihydrocinchonidine (**5**).

isolated in 5.3% yield after flash chromatographic (FC) purification and identified by HRMS, ^{1}H and ^{13}C NMR analyses (for analytical data, see Experimental section). Traces of other transetherification products were detected as well. Based on the earlier reports on hydrosilylation of quinine derivatives[4a,4d] we decided to protect the cinchonidine hydroxy group prior to reaction with triethoxysilane.

The synthesis of 11-(triethoxysilyl)-10,11-dihydrocinchonidine (**4**) is presented in Scheme 1. 9-*O*-(Trimethylsilyl)cinchonidine (**2**) was prepared by reacting cinchonidine with TMSCl and triethylamine in THF. Fairly pure **2** containing approximately 10% of 9-*O*-(trimethylsilyl)-10,11-dihydrocinchonidine (**6**) resulting from the 10,11-dihydrocinchonidine impurity in commercial cinchonidine was isolated as a solid in approxi-



Scheme 1 Synthesis of (−)-11-(triethoxysilyl)-10,11-dihydrocinchonidine (**4**).

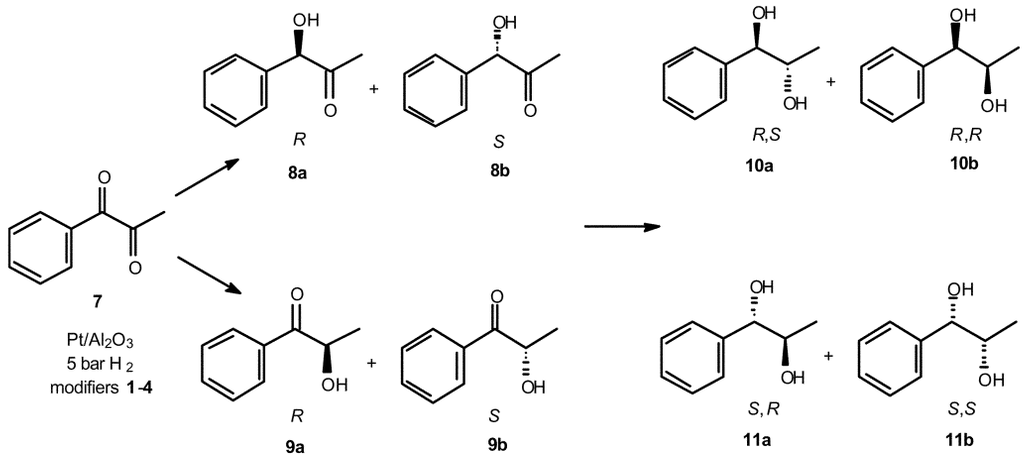
mately 90% yield. Further purification was unsuccesful and the product was used as such in the following step. The 9 : 1 mixture of **2** and **6** was dissolved in toluene and treated with triethoxysilane at 40 °C in the presence of the Karstedt catalyst and stirred for 3.5 hours at 80 °C. According to GC analysis the hydrosilylation proceeded in approximately 40% yield under these conditions. Purification by flash chromatography (methanol–chloroform 1 : 9) gave 9-*O*-(trimethylsilyl)-11-(triethoxysilyl)-10,11-dihydrocinchonidine (**3**) of fair (approximately 75%) purity. Further purification was unsuccesful. However, after refluxing the obtained fairly pure **3** in methanol for 20 hours and subsequent washing with pentane, analytically pure **4** was isolated as an off-white solid in 35% overall yield based on **2**. ‡

NMR Analysis

All compounds **1**–**5** were fully analyzed by high resolution ^{1}H and ^{13}C NMR spectroscopy. The signal assignments were based on data obtained using H–H and C–H correlation spectroscopy (COSY, NOESY, HETCOR, HMBC). In the following, arguments for the assignments of the signals in the spectra of cinchonidine (**1**) are presented. The interpretation of the spectra of compounds **2**–**5** was then based on similar arguments.

In the ^{1}H NMR spectrum of cinchonidine (**1**) the signals of H-2′ and H-9 were easily identified based on their chemical shifts and they were used as starting points for the interpretation of the 2D spectral data. Centered at δ = 1.70 ppm a three-proton signal (H-4, 5 and 7) and at δ = 1.36 ppm a two-proton signal (H-5 and H-7) were observed. The upfield one of the two signals due to H-7a and H-7b at 1.71 and 1.36 ppm, respectively, was assigned to H-7a based on its strong NOE interaction with H-8. The H-5 signal at 1.36 ppm was assigned to H-5a based on its NOE interaction with H-3. Of the two H-6 signals at δ = 3.43 and 2.45 ppm, respectively, the upfield signal was assigned to H-6a based on the NOE interaction with H-5a.

‡ Deprotection of **3** using tetrabutylammonium fluoride in THF also cleaves the silyl ethoxy groups.



Scheme 2 Hydrogenation of 1-phenylpropane-1,2-dione.

The signal at δ = 2.92 ppm assigned to H-2a showed a strong NOE interaction with H-3. The ^{13}C NMR signals were narrow and well resolved and the assignments were made based on the ^{1}H NMR signal assignments using HETCOR and HMBC techniques. The assignments matched those previously published,[7] except for C-3′ and C-5′ the shifts of which had to be interchanged. The spectra of compounds **2**–**5** were assigned in a similar manner and were found to be consistent with the proposed structures. Broadening of some of the ^{1}H and ^{13}C signals (for details, see Experimental section) indicated hindered rotation around the C-4′–C-9 as well as the C-8–C-9 bonds in compounds **2** and **3**.

Enantioselective hydrogenation

(*R*)-(−)-1-Hydroxy-1-phenylpropan-2-one (phenylacetylcarbinol) is an important intermediate for the synthesis of (1*R*,2*S*)-(−)-ephedrine and (1*S*,2*S*)-(+)-ephedrine, which are major ingredients of several pharmaceuticals used as anti-asthmatics, vasoconstricting agents and nasal decongestants.[8] Chiral α-hydroxyketones have also been utilized as building blocks for the synthesis of other biologically active compounds including antifungals against AIDS related diseases and complications.[9] 1-Phenylpropane-1,2-dione (**7**) can yield enantiomer mixtures of 1- as well as 2-hydroxyketones upon hydrogenation. Both regioisomers exist as pairs of enantiomers. The hydroxyketones may react further to produce the corresponding diols as two pairs of enantiomers. As shown previously,[6] the predominant product obtained in the hydrogenation of **7** with (−)-cinchonidine modified Pt catalysts is the (*R*)-(−)-1-hydroxy-1-phenylpropan-2-one isomer (**8a**) depicted in Scheme 2, although variable amounts of other products may be observed as well, depending on the employed reaction parameters. In the present study, compounds **1**–**4** were used as chiral modifiers in the hydrogenation of 1-phenylpropane-1,2-dione in ethyl acetate using 5% Pt/Al_2O_3 as catalyst (Scheme 2). All reactions were carried out at 25 °C and a hydrogen pressure of 5 bar. Enantiomeric excesses were determined by chiral GC according to the method described earlier.[6]

A typical kinetic curve is presented in Fig. 3. The first hydrogenation step is rapid, whereas further hydrogenation to form diols is somewhat slower. The rate of 1-phenylpropane-1,2-dione consumption was observed to be slightly dependent on the modifier structure (Table 1). Notably, when 1-phenylpropane-1,2-dione[6] was hydrogenated in the presence and absence of (−)-cinchonidine (**1**) the initial hydrogenation rates were nearly equal, whereas in the case of butane-2,3-dione[3b] a four-fold rate enhancement in the presence of the modifier was reported, while for ethyl pyruvate this difference could be up to two orders of magnitude. Such minor differences in the reaction rate are thought to be indicative of similar modes of

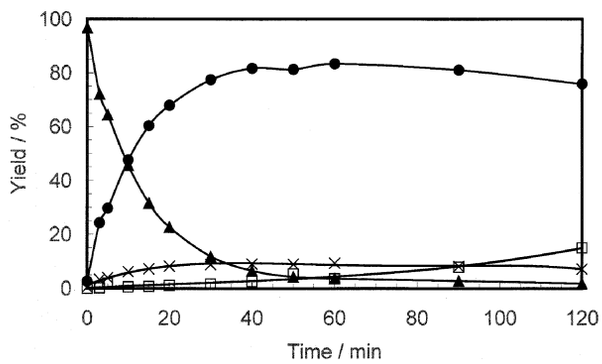


Fig. 3 Hydrogenation kinetics of 1-phenylpropane-1,2-dione in ethyl acetate at 25 °C. Catalyst: 5 wt% Pt/Al_2O_3 modified *in situ* with (−)-11-(triethoxysilyl)-10,11-dihydrocinchonidine (**4**). Symbols: (▲) 1-phenylpropane-1,2-dione (**7**), (●) 1-hydroxy-1-phenylpropan-2-one (**8a** + **8b**), (×) 2-hydroxy-1-phenylpropan-1-one (**9a** + **9b**), (□) 1-phenylpropane-1,2-diols (**10a** + **10b** + **11a** + **11b**).

Table 1 Pt/Al_2O_3 catalyzed hydrogenation of 1-phenylpropane-1,2-dione in the presence of chiral modifiers **1**–**4**[a]

Modifier	Conversion[b] (%)
1	87
2	76
3	73
4	70

[a] In ethyl acetate at 25 °C and 5 bar H_2. [b] Conversion after 20 min (complete conversion achieved in all experiments).

adsorption for the parent modifier and its derivatives. At the same time, the modifier structure had a profound effect on the selectivity. In the case of (−)-cinchonidine (**1**) the major product was 1-hydroxy-1-phenylpropan-2-one (**8a/8b**). The ratio between 1-hydroxy-1-phenylpropan-2-one (**8a/8b**) and 2-hydroxy-1-phenylpropan-1-one (**9a/9b**) defined as regioselectivity (rs) was approximately 7 : 1, remaining constant with increasing conversion of the dione (Fig. 4).

Regioselectivities depicted in Fig. 4 show a clear preference for reduction at the carbonyl group next to the phenyl substituent for all three modifiers **1**, **3** and **4**. In the present study, compound **2** afforded a very low regioselectivity, which in fact was lower than those obtained in the absence of the modifier,[6] whereas the use of modifier **4** resulted in a considerably higher regioselectivity. Notably, inverse regioselectivity was recently observed in the asymmetric transfer hydrogenation of 1-phenylpropane-1,2-dione using a chiral Ru(II) catalyst in combination with formic acid as the hydrogen source.[10] Regioselectivities as high as 9 : 1 resulting in the preferred reduction at the carbonyl

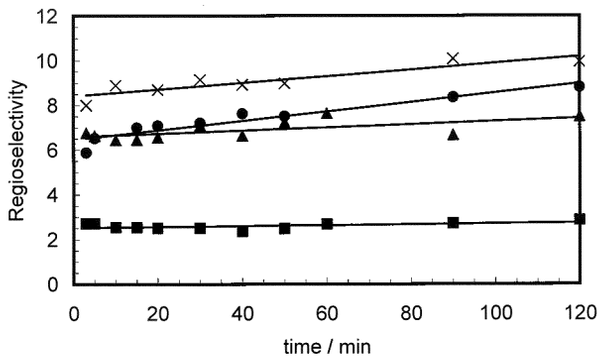


Fig. 4 Regioselectivity in the Pt/Al_2O_3 catalyzed hydrogenation of 1-phenylpropane-1,2-dione in the presence of the chiral modifiers **1**–**4** in ethyl acetate at 25 °C and 5 bar H_2. Symbols: (×) **4**, (●) **3**, (▲) **1**, (■) (**2**).

next to the methyl group were reported. In the present case, the data obtained is consistent with previous observations concerning the origin of regioselectivity. The selectivity enhancement observed in the presence of a catalyst modifier is a result of substrate–modifier interactions taking place on the catalyst surface. In the absence of modifier a lower regioselectivity was observed, nevertheless, hydrogenation of the benzoylic position was clearly preferred. Maximally a larger than two-fold enhancement of regioselectivity could be observed in the presence of a modifier.

Enantioselectivity was, likewise, observed to depend on the modifier structure. The enantiomeric excesses (ee) of (*R*)-1-hydroxy-1-phenylpropan-2-one (**8a**) *vs*. (*S*)-1-hydroxy-1-phenylpropan-2-one (**8b**) are reported in Fig. 5 as a function of

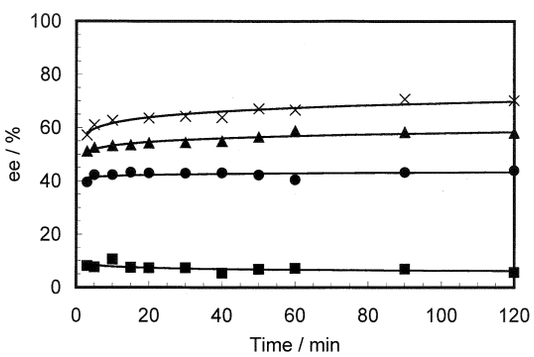


Fig. 5 Enantiomeric excess (ee) in the hydrogenation of 1-phenylpropane-1,2-dione in the presence of the chiral modifiers **1**–**4** in ethyl acetate at 25 °C and 5 bar H_2. Symbols: (×) **4**, (▲) **1**, (●) **3**, (■) (**2**).

the reaction time. The parent modifier (−)-cinchonidine (**1**) produced the major product *R*-1-hydroxy-1-phenylpropan-2-one (**8a**) in an ee of 56% under the employed reaction conditions. Surprisingly, the enantiomeric excess increased to 70% when the triethoxysilyl dihydroderivative **4** was employed instead of **1**. In previous studies, changes in the quinuclidine C-3 substituent did not result in significant improvements in enantioselectivity in the hydrogenation of ethyl pyruvate.[1q] The lowest reaction rate and only marginal enantiodifferentiation (ee = 6%) were observed in the present study with the 9-*O*-TMS-substituted modifier **2**. As already stated (*vide supra*), the regioselectivity towards 1-hydroxy-1-phenylpropan-2-one was also the lowest with this modifier.

In compound **2** the remaining impurity (approx. 10%) consists of 9-*O*-(trimethylsilyl)-10,11-dihydrocinchonidine (**6**). In previous studies, hydrogenation of the cinchona alkaloid 10,11-double bond did not significantly influence the enantiodifferentiation.[1d,q,11] Commercial (−)-cinchonidine, commonly used as such, contains up to 10% of the corresponding 10,11-dihydro analogue. It is also well known that the 10,11-double bond of the cinchona modifier is often hydrogenated to the corresponding dihydro compound during the initial stages of the hydrogenation reaction, at least at higher pressures.[6c] Possible differences between the two have thus been neglected in the context of this work. Data on the enantiomeric excess obtained with compound **2** are in accordance with previous findings where C-9 substituents bulkier than methoxy or acetyl significantly decreased the enantioselectivities in the ethyl pyruvate case.[1q] Although the modifier **3** also contains the bulky C-9 substituent, both regioselectivity and enantioselectivity remained rather high. A possible explanation relates to the large quantity of remaining unknown impurities (approx. 25%) in the employed modifier. Thus, the results obtained here using compound **3** cannot be taken as definitive evidence of substituent effects.

Results obtained in the present study indicate not only that high enantioselectivity requires some modifier–reactant interaction, but that such interactions also play a decisive role in achieving preferential hydrogenation of a particular carbonyl group, *i.e.*, regioselectivity. In the present system, enantioselectivity and regioselectivity are interrelated exhibiting similar dependence on modifier concentration. The connection between the two is clearly observable in Figs. 4 and 5. The modifiers inducing high enantiomeric excess also resulted in a high regioselectivity (and *vice versa*), thus also supporting the involvement of substrate–modifier interactions in the enhancement of regioselectivity. Further efforts are required to understand the nature of these interactions. The contribution of electronic and steric influences of the substrate to the selectivity will be the subject of forthcoming work.

Molecular modeling

The experimental activity data can be interpreted using molecular modeling techniques. Catalytic mechanisms have been proposed, which rely on different cinchonidine conformers. The lowest energy conformers of a cinchonidine derivative and their possible interconversion reactions were used to assess their availability for catalytic reactions. The optimum structures of cinchonidine (**1**) have been the subjects of several modeling studies. Schürch *et al.*[12] and Margitfalvi and Tfirst[13] reported potential energy maps based on molecular mechanics. The geometry variables in the maps are the dihedral angles between the quinoline and quinuclidine moieties of cinchonidine. The minimum energy conformations have been subjected to full optimization studies with Hartree–Fock and density functional methods by Bürgi and Baiker.[14] They have also reported corrections to obtain relative Gibbs energies. Molecular mechanics maps are useful for locating minimum energy regions, but the method fails to give the same energy order for the conformers as found in the *ab initio* study by Bürgi and Baiker.[14] The minimum level of *ab initio* theory that gives the correct order appears to be HF 6-31G**.

In the study of the relative conformational energies of modified cinchonidine derivatives, we have calculated potential energy maps for compounds **1**,**2** and **4**. We chose HF/3-21G as the level of theory to be used, since molecular mechanics may not give an accurate description of the energy surface. The maps were generated by varying the dihedral angles by fixed increments while optimizing all other variables. The structures corresponding to the minima found in the maps were subjected to full optimizations.

The HF/3-21G map for cinchonidine (**1**) is presented in Fig. 6 with ball and stick representations of selected minimum energy conformations depicted in Fig. 7. The optimizations were also performed at the HF/6-31G** level starting from HF/3-21G optimizations. The locations of the minima labeled as Open(*n*) or Closed(*n*) are indicated on the map. The original numbering scheme of Bürgi and Baiker[14] was retained to facilitate direct comparison of results. The corresponding energies are reported in Fig. 11. The results for the four lowest conformers agree very

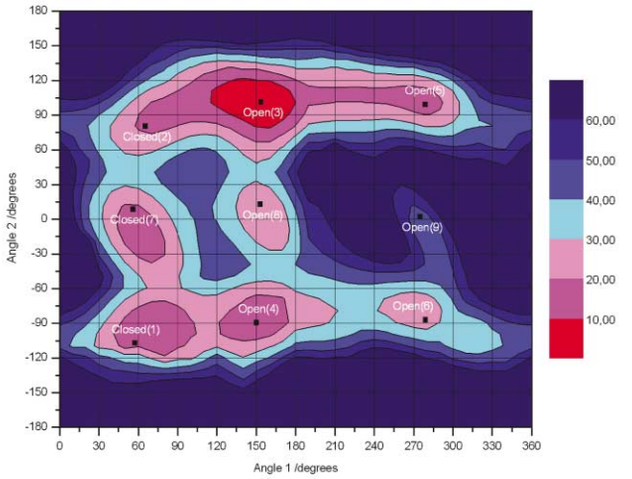


Fig. 6 The relative total energy map for **1**. The coordinate axes are the dihedral angles (3′–4′–9–8) and (4′–9–8–N). The energy of the lowest minimum has been set to zero.

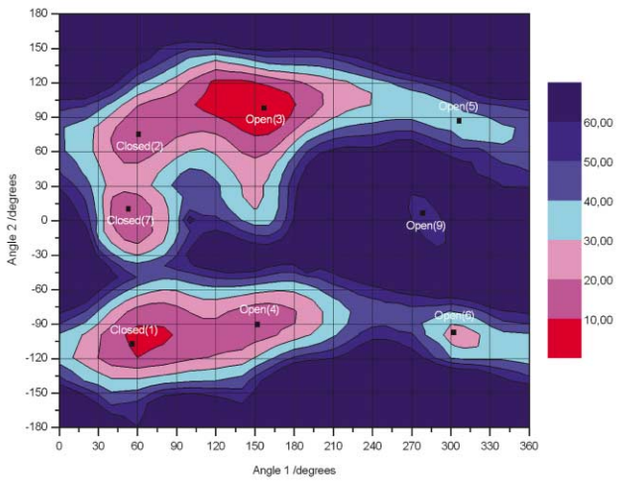


Fig. 8 The relative total energy map for **2**. The coordinate axes are the same as in Fig. 6. The energy of the lowest minimum has been set to zero.

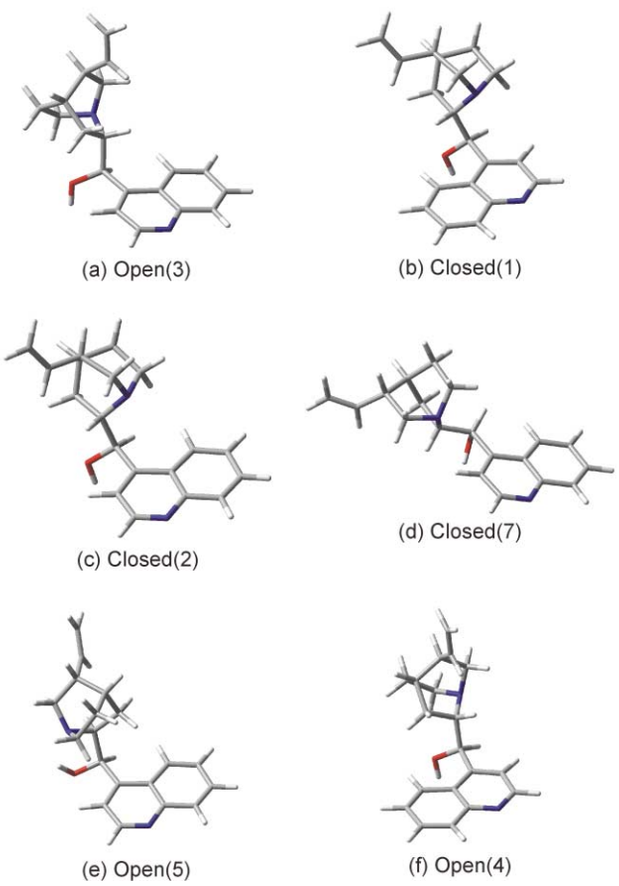


Fig. 7 Stick representations of the selected minimum energy conformations of **1**.

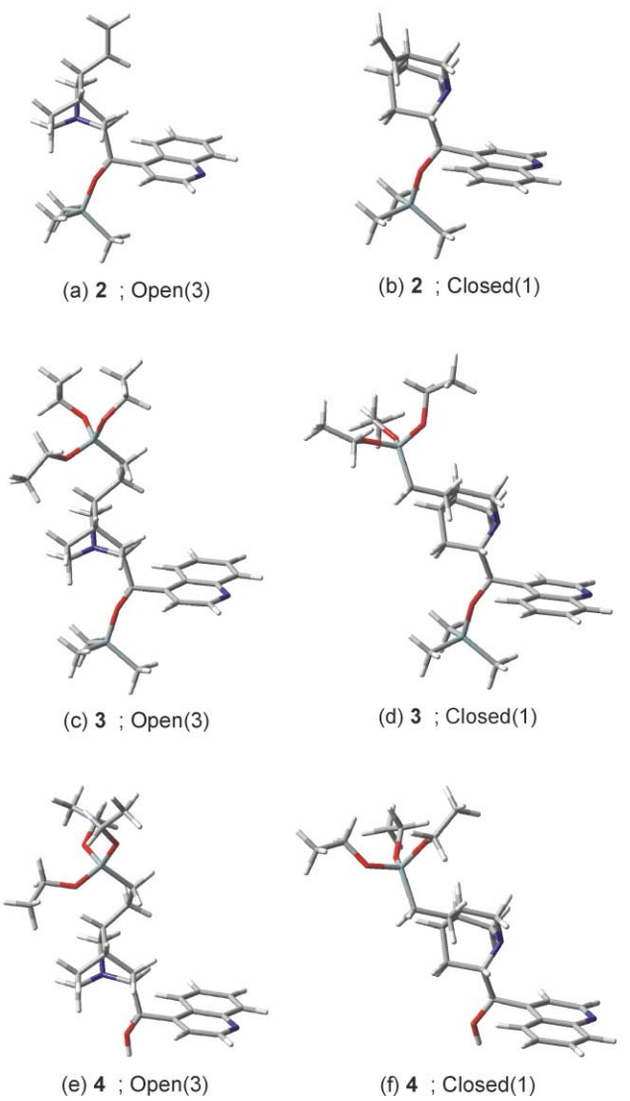


Fig. 9 Stick representations of the Open(3) and Closed(1) conformations of **2**, **3** and **4**.

well with the structures and energies reported earlier.[14] Three new minima were located, Closed(7), Open(8) and Open(9). For the higher conformers Open(5) and Open(6) we find somewhat different geometries with lower total energies than in the earlier study.[14] The map also indicates possible pathways for interconversions from one conformation to another. From the lowest energy conformation Open(3) the next lowest conformation, Closed(1), can be reached *via* two routes. Both paths, Open(3)–Open(8)–Open(4)–Closed(1) and Open(3)–Closed(2)–Closed(7)–Closed(1) have an approximate saddle point energy of 35 kJ mol^{1} at the 3-21G level.

The total energy map for compound **2** is presented in Fig. 8. The overall outlook of the map is similar to the unsubstituted cinchonidine. A significant difference is, however, that the Closed(1) conformation has practically the same energy as the Open(3) (for ball and stick representations, see Fig. 9). The transformation from Open(3) is more difficult than in **1**, since the Open(3)–Open(4)–Closed(1) path is closed and the

Open(3)–Closed(2)–Closed(7)–Closed(1) path has an approximate saddle point energy of 44 kJ mol[1]. One can conclude that compound **2** can be found in two conformations, but with no easy interconversion between them.

The total energy map for compound **4** is presented in Fig. 10. The outlook is virtually identical to that of the map of compound **1**. The map demonstrates that the structural difference in the quinuclidine region does not influence the conformational energetics of the cinchonidine frame. The lowest energy conformers Open(3), Closed(1) and Closed(2) have very similar energy differences in compounds **1** and **4** also at the 6-31G** level of theory, as seen in Fig. 11. The conclusions for compound **1** of the transformation from conformation Open(3) to Closed(1) apply to compound **4** as well. Approximate saddle point energy at the 3-21G level was found to be 34 kJ mol[1].

Compound **3** was the largest molecule to be modeled, since it has two big substituents. The results of the conformation analyses of compounds **1** and **4** showed that the substituent in the quinuclidine region did not have much influence on the energetics. For compound **3** the 3-21G map was not generated, instead the minimum energy dihedral geometries of compound **1** were used as the starting points for full geometry optimisations at the 6-31G** level. The results are shown in Fig. 11. As expected, the conformations behave very similarly to those of **2**. The lowest energy conformation is Closed(1) with Open(3) marginally higher (Fig. 9). The total energy surface can also be expected to be similar to the map of compound **2**, with a high interconversion barrier separating the two lowest energy conformers.

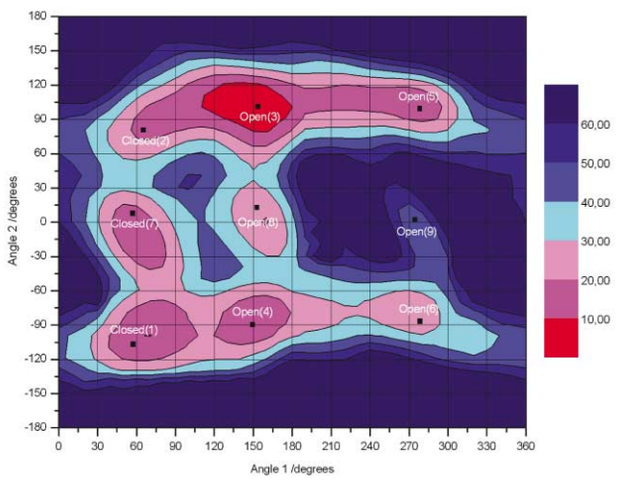


Fig. 10 The relative total energy map for **4**. The coordinate axes are the same as in Fig. 6. The energy of the lowest minimum has been set to zero.

Summary and conclusions

The detailed synthesis and characterization of (−)-11-(triethoxysilyl)-10,11-dihydrocinchonidine (**4**) has been reported. This compound together with its precursors 9-*O*-(trimethylsilyl)-cinchonidine (**2**) and 9-*O*-(trimethylsilyl)-11-(triethoxysilyl)-10,11-dihydrocinchonidine (**3**) were employed as chiral modifiers in the hydrogenation of a prochiral diketone 1-phenylpropane-1,2-dione over a heterogeneous Pt/Al_2O_3 catalyst. (−)-Cinchonidine (**1**) was used as a reference modifier. The hydrogenation rates showed only slight dependence on the modifier structure. The carbonyl group in the position closer to the phenyl ring was preferentially reduced, forming mainly (*R*)-1-hydroxy-1-phenylpropanone. Compound **4** induced an unexpected enhancement in regioselectivity and ee thus demonstrating the positive effect of distal modifier substitution. In contrast, considerably lower values of regioselectivity and ee were obtained with 9-*O*-(trimethylsilyl)cinchonidine (**2**).

As a summary of the cinchonidine derivative modeling one can conclude that potential energy maps at the HF/3-21G level and the refined geometry optimizations at the HF/6-31G** level give a reliable qualitative picture of the energetics of the lowest energy conformers. The *O*-TMS substituent stabilizes another conformation of the cinchonidine frame. The interconversion between the lowest energy conformers becomes at the same time less likely, possibly contributing to the low enantioselectivities and poor overall performance of compound **2** as a chiral catalyst modifier. Additionally, the unfavorable conformation together with the bulky 9-*O*-TMS-substituent may hinder the effective adsorption of this modifier on the platinum surface *via* the π-system of the quinoline moiety in the preferred flat orientation.[15] Substituents at the quinuclidine moiety have only a minor influence on the relative energies of the conformers. Thus assuming that compounds **4** and **1** adsorb on the platinum surface in a similar Open(3)-type π-bonded[15] lowest energy conformation, the higher enantio- and regioselectivities obtained with compound **4** are likely to result from its more favorable interaction or complexation with the substrate diketone.

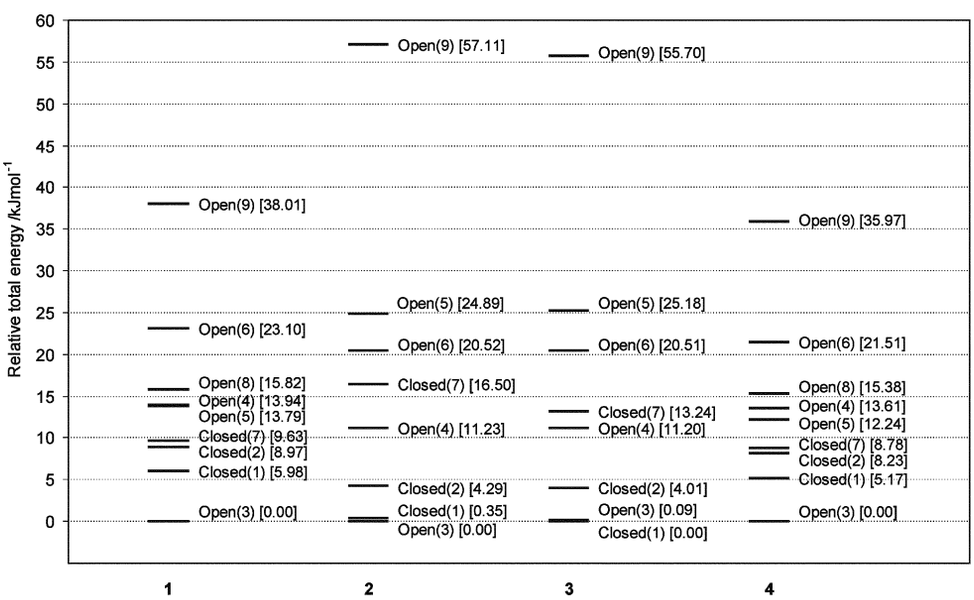


Fig. 11 The relative total energies of compounds **1**–**4**. For each compound the energy of the lowest minimum has been set to zero.

Experimental

General

All reactions with air-sensitive reagents were carried out under argon atmosphere using standard Schlenk, vacuum or glove box techniques. THF was dried and distilled under argon from sodium–benzophenone prior to use. Toluene was dried over 4 Å molecular sieves. (−)-Cinchonidine (Aldrich, 96%), triethoxysilane (Gelest) and platinum–divinyltetramethyldisiloxane complex (Karstedt catalyst, 2.1–2.4% Pt concentration in xylene, Gelest) were used as received. Melting points were determined in open glass capillaries and are uncorrected. Electron impact high resolution mass spectra (HRMS) were obtained with a Fisons ZabSpec mass spectrometer at 70 eV. NMR spectra were recorded at 303 K in $CDCl_3$ (*ca*. 0.15 M solutions) using JEOL JNM-L 400 or JNM-A 500 NMR spectrometers and referenced against tetramethylsilane (TMS). The chemical shifts are expressed in ppm downfield from TMS. Signal multiplicities and coupling constants are given in parentheses [br = broad unresolved multiplet (^{1}H NMR) or signal broadening (^{13}C NMR); ur = unresolved multiplet without broadening (^{1}H NMR)]. Polarimetric measurements were carried out using a Perkin-Elmer 241 Polarimeter with a cell volume of 1 mL and a cell length of 10 cm. Optical rotations are given in units of 10^{-1} deg cm^2 mol^{-1}. Microanalysis was conducted at the Department of Microanalytics, University of Groningen, the Netherlands.

NMR data of (−)-cinchonidine (1)

^{1}H NMR ($CDCl_3$, δ): 8.61 (d, 1H, J = 4.9 Hz, H-2′), 7.95 (dd, 1H, J = 8.5 Hz, 1.2 Hz, H-8′), 7.85 (dd, 1H, J = 8.5 Hz, 1.2 Hz, H-5′), 7.51 (ddd, 1H, J = 8.2 Hz, 6.9 Hz, 1.4 Hz, H-7′), 7.47 (d, 1H, J = 4.3 Hz, H-3′), 7.20 (ddd, 1H, J = 8.4 Hz, 7.0 Hz, 1.4 Hz, H-6′), 5.59 (ddd, 1H, J = 17.2 Hz, 10.4 Hz, 7.8 Hz, H-10), 5.56 (br d, 1H, J = 3.8 Hz, H-9), 4.84 (dt, 1H, J = 17.2 Hz, 1.4 Hz, H-11-*Z*), 4.79 (dt, 1H, J = 10.4 Hz, 1.3 Hz, H-11-*E*), 3.43 (dddd, 1H, J = 13.3 Hz, 10.5 Hz, 4.5 Hz, 2.4 Hz, H-6b), 2.96 (ddd, 1H, J = 9.6 Hz, 7.6 Hz, 3.2 Hz, H-8), 2.92 (dd, 1H, J = 13.6 Hz, 10.0 Hz, H-2a), 2.52 (ddd, 1H, J = 13.7 Hz, 4.7 Hz, 2.5 Hz, H-2b), 2.45 (m, 1H, H-6a), 2.14 (m, 1H, H-3), 1.71–1.69 (m, m, 3H, H-4, H-5b, H-7b), 1.36 (m, m, 2H, H-5a, H-7a). ^{13}C NMR ($CDCl_3$, δ): 149.90 (C-2′), 149.90 (C-4′), 147.96 (C-8a′), 141.74 (C-10), 129.97 (C-8′), 128.93 (C-7′), 126.49 (C-6′), 125.48 (C-4a′), 122.93 (C-5′), 118.23 (C-3′), 114.27 (C-11), 71.57 (C-9), 60.34 (C-8), 56.92 (C-2), 43.15 (C-6), 39.85 (C-3), 27.87 (C-4), 27.54 (C-5), 21.26 (C-7).

Synthesis of 9-*O*-(trimethylsilyl)cinchonidine (2)

To an ice-cooled solution of (−)-cinchonidine (**1**) (2.0 g, 6.8 mmol) in THF containing triethylamine (1.1 mL, 7.9 mmol) was added dropwise trimethylchlorosilane (1 mL, 7.9 mmol). The reaction mixture was stirred for 20 hours at room temperature and then for two hours at 60 °C. The product was extracted with chloroform (50 mL) and washed with water (3 × 50 mL). The water layer was extracted with additional chloroform (50 mL) and the combined organic extracts were dried over sodium sulfate. Evaporation of the solvents left 2.3 g (90%) of solid **2** containing approximately 10% of 9-*O*-(trimethylsilyl)-10,11-dihydrocinchonidine (**6**) as determined by ^{1}H NMR and identified by HRMS [**6**: (calcd/found): 368.2288/368.2284]. Analytical data of **2**: HRMS (calcd/found): 366.2127/366.2127. ^{1}H NMR ($CDCl_3$, δ): 8.79 (d, 1H, J = 4.6 Hz, H-2′), 8.04 (dd, 1H, J = 8.6 Hz, 1.2 Hz, H-8′), 8.01 (br, 1H, H-5′), 7.58 (ddd, 1H, J = 8.2 Hz, 6.4 Hz, 1.2 Hz, H-7′), 7.45 (ddd, 1H, J = 8.2 Hz, 7.0 Hz, 1.2 Hz, H-6′), 7.39 (br, 1H, H-3′), 5.60 (br, 1H, H-9), 5.58 (ddd, 1H, J = 17.1 Hz, 10.1 Hz, 7.6 Hz, H-10), 4.80 (ddd, 1H, J = 17.1 Hz, 1.5 Hz, 1.2 Hz, H-11-*Z*), 4.74 (br d, 1H, J = 9.8 Hz, H-11-*E*), 3.31 (ur, 1H, H-6b), 2.97 (dd, 1H, J = 13.6 Hz, 10.1 Hz, H-2a), 2.92 (br, 1H, H-8), 2.70 (ur, 1H, H-7b), 2.57 (ddd, 1H, J = 14.3 Hz, 11.0 Hz, 5.2 Hz, H-6a), 2.12 (m, 1H, H-3), 2.49 (dm, 1H, J = 13.1 Hz, H-2b), 1.68 (m, 1H, H-4), 1.60 (m, 1H, H-5b), 1.38 (m, 1H, H-5a), 1.34 (m, 1H, H-7a), −0.07 (s, 9H, Si-CH_3). ^{13}C NMR ($CDCl_3$, δ): 148.89 (C-2′), 147.96 (C-8a′), 147.40 (C-4′), 140.97 (C-10), 129.45 (C-8′), 127.82 (C-7′), 125.45 (C-6′), 124.45 (C-4a′), 122.01 (br, C-5′), 117.63 (br, C-3′), 113.05 (C-11), 72.60 (br, C-9), 60.50 (C-8), 56.35 (C-2), 41.98 (br, C-6), 39.08 (C-3), 26.97 (C-4), 26.54 (C-5), 20.37 (br, C-7), −0.85 (3C, Si-CH_3).

Synthesis of 9-*O*-(trimethylsilyl)-11-(triethoxysilyl)-10,11-dihydrocinchonidine (3)

To a solution of the **2**–**6** mixture (1.0 g from the previous reaction, approx. 2.4 mmol of **2**) in toluene (3 mL) was added the Karstedt catalyst (0.2 mL of a 2.1–2.4% Pt solution in xylene) and triethoxysilane (0.5 mL, 3.0 mmol) at 40 °C. The reaction mixture was stirred for 3.5 hours at 80 °C. Purification by flash chromatography (methanol–chloroform 1 : 9) gave 0.79 g of fairly pure (approx. 75% by ^{1}H NMR) **3** as a yellowish amorphous material. HRMS (calcd/found): 530.2996/530.2996. ^{1}H NMR ($CDCl_3$, δ): 8.79 (d, 1H, J = 4.6 Hz, H-2′), 8.06 (dd, 1H, J = 8.5 Hz, 1.4 Hz, H-8′), 8.05 (br, 1H, H-5′), 7.63 (ddd, 1H, J = 7.7 Hz, 6.9 Hz, 1.4 Hz, H-7′), 7.49 (ddd, 1H, J = 7.7 Hz, 6.7 Hz, 1.2 Hz, H-6′), 7.42 (br, 1H, H-3′), 5.60 (br, 1H, H-9), 3.64 (q, 6H, J = 7.0 Hz, $SiOCH_2CH_3$), 3.32 (ur, 1H, H-6b), 2.98 (dd, 1H, J = 13.6 Hz, 10.1 Hz, H-2a), 2.91 (br, 1H, H-8), 2.58 (ddd, 1H, J = 13.0 Hz, 10.8 Hz, 4.6 Hz, H-6a), 2.26 (ur, 1H, H-2b), 1.73–1.61 (ur, 3H, H-4, H-5b, H-7b), 1.36 (ur, 1H, H-3), 1.34 (m, 1H, H-10), 1.22–1.17 (ur, 2H, H-5a, H-7a), 1.04 (t, 9H, J = 7.0 Hz, $SiOCH_2CH_3$), 0.42 (m, 1H, H-11), −0.04 (s, 9H, Si-CH_3). ^{13}C NMR ($CDCl_3$, δ): 148.87 (C-2′), 148.37 (C-4′ or C-8a′), 147.36 (C-4′ or C-8a′), 129.36 (C-8′), 127.92 (C-7′), 125.32 (C-6′), 124.43 (C-4a′), 122.04 (br, C-5′), 117.63 (br, C-3′), 72.30 (br, C-9), 60.20 (C-8), 57.72 (C-2), 57.27 (3C, $SiOCH_2CH_3$), 42.15 (br, C-6), 38.40 (C-3), 27.33 (C-5), 26.54 (C-10), 24.41 (C-4), 20.00 (br, C-7), 17.17 (3C, $SiOCH_2CH_3$), 7.20 (C-11), 0.19 (3C, Si-CH_3).

Synthesis of 11-(triethoxysilyl)-10,11-dihydrocinchonidine (4)

The fairly pure **3** from the previous step was refluxed in methanol (40 mL) for 20 hours. The crude product was washed with pentane (40 mL) and filtered to leave 0.40 g (0.9 mmol, 35% yield based on **2**) of **4** as an analytically pure off-white solid. HRMS (calcd/found): 458.2600/458.2601; mp 178–179 °C; $[\alpha]_{24}^{D}$ = −76.9 (c = 10.7 in EtOH); elemental analysis calcd (%) for $C_{25}H_{38}N_2O_4Si$ (458.3): C 65.47, H 8.35, N 6.11; found C 65.52, H 8.30, N 6.17%. ^{1}H NMR ($CDCl_3$, δ): 8.70 (d, 1H, J = 4.6 Hz, H-2′), 7.95 (dd, 1H, J = 8.4 Hz, 1.1 Hz, H-8′), 7.82 (d, 1H, J = 8.4 Hz, H-5′), 7.52 (d, 1H, J = 4.5 Hz, H-3′), 7.48 (ddd, 1H, J = 8.4 Hz, 6.8 Hz, 1.2 Hz, H-7′), 7.14 (ddd, 1H, J = 8.4 Hz, 6.8 Hz, 1.2 Hz, H-6′), 5.69 (s, 1H, H-9), 5.20 (br, 1H, OH), 3.63 (q, 6H, J = 6.9 Hz, $SiOCH_2CH_3$), 3.55 (m, 1H, H-6b), 2.99 (m, 1H, H-8), 2.97 (dd, 1H, J = 13.4 Hz, 10.0 Hz, H-2a), 2.54 (ddd, 1H, J = 13.4 Hz, 10.4 Hz, 4.6 Hz, H-6a), 2.31 (ddd, 1H, J = 13.4 Hz, 4.6 Hz, 2.4 Hz, H-2b), 1.76–1.70 (m, m, m, 3H, H-4, H-5b, H-7b), 1.41 (m, 1H, H-3), 1.35 (m, 1H, H-5a), 1.27 (m, 1H, H-7a), 1.19 (m, 1H, H-10), 1.03 (t, 9H, J = 6.9 Hz, $SiOCH_2CH_3$), 0.40 (m, 1H, H-11). ^{13}C NMR ($CDCl_3$, δ): 149.00 (C-2′), 148.27 (C-4′), 147.04 (C-8a′), 129.07 (C-8′), 127.92 (C-7′), 125.58 (C-6′), 124.44 (C-4a′), 121.89 (C-5′), 117.31 (C-3′), 70.03 (C-9), 59.17 (C-8), 57.30 (3C, $SiOCH_2CH_3$), 57.23 (C-2), 42.39 (C-6), 37.10 (C-3), 26.77 (C-5), 26.48 (C-10), 24.25 (C-4), 19.55 (C-7), 17.18 (3C, $SiOCH_2CH_3$), 7.18 (C-11).

Analytical data of 11-(triisopropoxysilyl)-10,11-dihydrocinchonidine (5)

FC eluents: benzene–diethylamine–diethyl ether 20 : 12 : 5. HRMS (calcd/found): 500.3072/500.3070. ^{1}H NMR ($CDCl_3$, δ):

8.68 (d, 1H, J = 4.6 Hz, H-2′), 7.98 (d, 1H, J = 8.2 Hz, H-8′), 7.82 (d, 1H, J = 8.6 Hz, H-5′), 7.52 (t, 1H, J = 8.2 Hz, H-7′), 7.49 (d, 1H, J = 4.6 Hz, H-3′), 7.19 (dd, 1H, J = 8.2 Hz, 7.0 Hz, H-6′), 5.63 (d, 1H, J = 3.0 Hz, H-9), 4.88 (br, 1H, OH), 4.08 (sept., 3H, J = 6.1 Hz, SiOC*H*), 3.43 (br, 1H, H-6b), 2.96 (br, 1H, H-8), 2.92 (dd, 1H, J = 13.1 Hz, 10.1 Hz, H-2a), 2.48 (ddd, 1H, J = 14.4 Hz, 10.7 Hz, 4.3 Hz, H-6a), 2.28 (dm, 1H, J = 15.6 Hz, H-2b), 1.74–1.71 (br, m, m, 3H, H-4, H-5b, H-7b), 1.40 (br, 1H, H-3), 1.39–1.35 (br, 2H, H-5a, H-7a), 1.18 (br, 1H, H-10), 1.00 (d, 18H, J = 6.1 Hz, SiOCCH_3), 0.36 (br, 1H, H-11). ^{13}C NMR ($CDCl_3$, δ): 149.02 (C-2′), 148.66 (C-8a′), 147.12 (C-4′), 129.13 (C-8′), 127.92 (C-7′), 125.52 (C-6′), 124.59 (C-4a′), 121.95 (C-5′), 117.23 (C-3′), 70.90 (C-9), 63.87 (3C, SiO*C*), 59.09 (C-8), 57.54 (C-2), 42.35 (C-6), 37.76 (C-3), 27.22 (C-5), 26.81 (C-10), 24.45 (6C, SiOC*C*H$_3$), 24.38 (C-4), 19.96 (C-7), 8.83 (C-11).

Hydrogenation of 1-phenylpropane-1,2-dione

The platinum catalyst (148 mg) containing 5% Pt on Al_2O_3 (Strem) was activated at 400 °C in a 100 mL Sotelem batch reactor under hydrogen flow for two hours. The chiral modifier (molar amount corresponding to 20 mg of cinchonidine) was dissolved in 50 mL of a 0.05 M solution of 1-phenylpropane-1,2-dione in ethyl acetate. The solution was flushed under a hydrogen flow for 10 minutes prior to injection into the reactor. The hydrogenation was carried out at 25 °C and 5 bar hydrogen pressure using a stirrer speed of 1800 rpm. The reaction was followed by GC analysis. For determination of the enantiomeric excesses, microsamples (V = 200 μl) were collected during the hydrogenation experiments and analyzed using a Varian 3300 GC equipped with a chiral β-dex column. Identification of the product enantiomers and calibration of the GC analysis was carried out utilizing previously prepared enantiomerically pure model compounds **8a** and **10a**. The minor products, enantiomers **9a/9b** and **10b/11b** could not be properly separated. Details of the GC standard synthesis, identification of the product enantiomers and details of the GC analysis procedure have been reported in a previous paper.[6] All hydrogenations were carried out in duplicate and resulted in reproducible ee values.

Computational details

Geometry optimizations were carried out in two steps for compounds **1**, **2** and **4**. In the first step a two-dimensional conformational energy map was calculated. The starting point was the experimental crystal structure of **1**.[16] The dihedral angles (3′-4′–9–8) and (4′–9–8–N) were scanned simultaneously with 10 or 20° steps and at each point all other geometry variables were optimised at the HF/3-21G level. In the minima regions a smaller angle increment was applied. In the grid positions of minimum energy a full optimization was first performed at the HF/3-21G level and subsequently at the HF/6-31G** level. Optimizations were also carried out for compound **1**, with initial geometries corresponding to the structures reported by Bürgi and Baiker.[14] The minimum energy conformations for compound **3** were derived from HF/6-31G** optimizations. In the initial geometries the dihedral angles were taken from the optimum values for compound **1**.

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