Synthesis of Chiral Catalyst Modifiers by Hydrosilylation of Cinchonidine and Their Application in the Hydrogenation of 1-Phenylpropane-1,2-dione and Ethyl Pyruvate on a Supported Pt/Al_2O_3 Catalyst

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Four new chiral modifiers were synthesized in order to investigate the effect of distal modifier substitution in the hydrogenation of ethyl pyruvate and 1-phenylpropane-1,2-dione on a supported Pt/Al_2O_3 catalyst. The chiral modifiers were prepared in good to moderate overall yields by Pt-catalyzed hydrosilylation of 9-*O*-TMS-protected cinchonidine with triethylsilane, triphenylsilane, bis(dimethylsilyl)ethane and (+)-(*R*)-methyl(1-naphthyl)phenylsilane followed by cleavage of the silyl ether protective group. Comparison of the synthesized modifiers in enantioselective hydrogenation using cinchonidine as reference modifier is reported, as well as details on their synthesis and characterization. The X-ray crystal structure of the 11-(triphenylsilyl)-substituted cinchonidine analogue has been determined showing that this compound crystallizes in the open(3)-like conformation observed earlier for (–)-cinchonidine. In the hydrogenation of ethyl pyruvate, the new modifiers induced notable enantiomeric excesses (*ee* = 62–73 %), which, however, were slightly lower than the *ee* obtained with cinchonidine as the chiral catalyst modifier (*ee* = 84 %). The rate for the racemic reaction in the absence of a chiral modifier was up to threefold higher than the reaction rate with the distally substituted modifiers whereas with cinchonidine the reaction rate was close to that of the racemic hydrogenation. In the hydrogenation of 1-phenylpropane-1,2-dione, 11-(triethylsilyl)-10,11-dihydrocinchonidine induced an *ee* of 70 % at 50 % reactant conversion which was notably higher than the *ee* obtained with cinchonidine (55 %). The dependence of enantiomeric excess on the modifier structure is clearly different in the two cases (ethyl pyruvate vs. 1-phenylpropane-1,2-dione) indicating notable differences in the enantiodifferentiating mechanisms in these two model reactions.

Introduction

Chiral modification of solid catalysts is one of the most promising approaches to heterogeneous enantioselective catalysis.[1] Of particular interest are supported Pt catalysts modified with cinchona alkaloids employed in a range of enantioselective hydrogenation reactions.[2] With these systems, enantioselectivities approaching *ee* = 99% have been obtained e.g., in the hydrogenation of ethyl benzoylformate on dihydrocinchonidine-modified Pt/Al_2O_3 catalyst.[3] Numerous investigations have been aimed at the elucidation of the operating mechanisms and the origin of enantioselectivity in these systems, yet, the exact nature of the surface–modifier–substrate interactions remain under dispute.[4,5] Mechanistical studies are hampered, besides by the heterogeneous nature of the catalyst system, by the fact that even very small changes in the modifier structure[6] and concentration,[7] achiral additives present,[8] catalyst pretreatment procedure,[9] metal particle size and dispersion,[10] nature of the solvent[7c,8a,11] and the support material,[12] as well as the hydrogen partial pressure or surface concentration[13] affect the catalyst activity and enantioselectivity.

The cinchona-modified Pt catalysts commonly display a very high substrate specificity and as recently demonstrated by the extensive studies of Blaser, Baiker and co-workers,[6] for each substrate, the optimum chiral modifier varies. Certain qualitative trends have, however, been reported for catalyst systems modified by cinchona alkaloids and related compounds:[6] 1) an extended π-system, such as quinoline or naphthalene, is required for efficient adsorption of the modifier on the metal surface; 2) for inducing sufficient enantiocontrol, a chiral amino functionality is needed for substrate–modifier interaction; 3) the sense of asymmetric induction is in most cases controlled by the absolute configuration at the C-8 and C-9 atoms of the cinchona alkaloid. Substituent effects in the quinuclidine part and more distal positions of the modifier are considerably less investigated being the subject of the present investigation.

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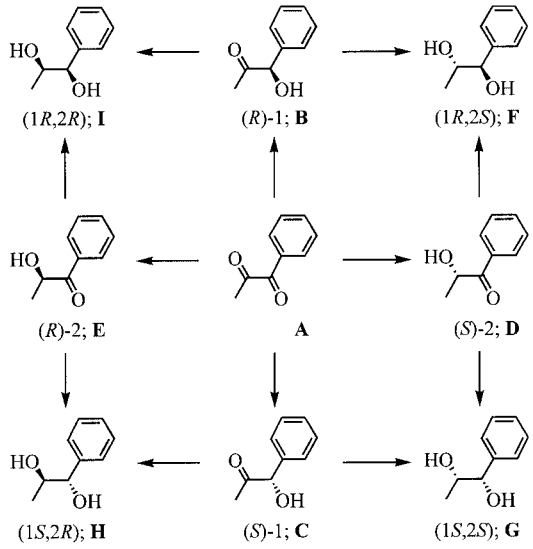
In previous reports, we have investigated in detail the enantioselective hydrogenation of a prochiral diketone, 1-phenylpropane-1,2-dione (**A**), on cinchona alkaloid modified Pt catalysts (Scheme 1).[14] Under optimal conditions, the main product, (–)-(*R*)-1-hydroxy-1-phenylpropan-2-one (**B**), has been obtained in 65% *ee* using cinchonidine as the chiral catalyst modifier. The chiral hydroxy ketone **B** (also known as PAC = phenylacetylcarbinol) is an important intermediate for the synthesis of ephedrines and pseudoephedrines, which are major ingredients in several pharmaceuticals used as *anti*-asthmatics, vasoconstricting agents and nasal decongestants.[15] Similar compounds are also widely utilized as building blocks for the synthesis of other biologically active compounds including antifungals against AIDS-related diseases and complications.[16]



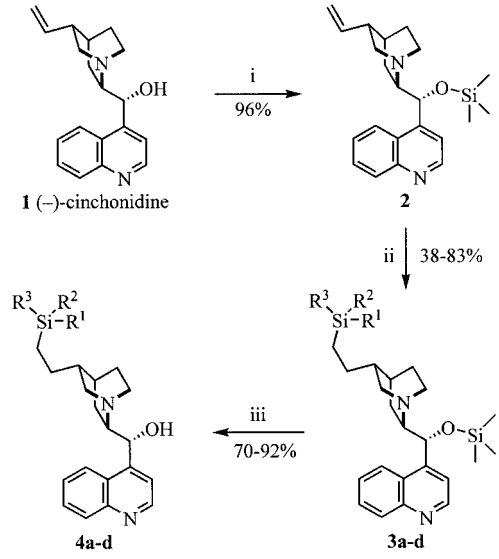
Scheme 1. Hydrogenation of 1-phenylpropane-1,2-dione.

Recently, we observed a significant enhancement of enantioselectivity in the hydrogenation of **A** on chirally modified Pt/Al_2O_3 in ethyl acetate by use of a distally modified cinchonidine analogue, 11-(triethoxysilyl)-10,11-dihydrocinchonidine, as the chiral catalyst modifier (*ee* = 70% vs. 56% obtained with cinchonidine).[17] In the prior investigation, the role of the bulky silyl substituent attached to the distal part of the quinuclidine moiety of cinchonidine remained ambigious, although it was shown by Hartree–Fock calculations that its influence on the conformational energetics are likely to be minor. The previous investigation raised the following questions: 1) What is the effect of varying the distal moiety of the cinchona alkaloid modifier on enantioselectivity of the hydrogenation reaction? 2) Does this effect also take place during the hydrogenation of ethyl pyruvate, the most common and most investigated substrate? Additionally, we were interested in the more general applicability of the hydrosilylation reaction as a means for simple synthetic modification of cinchona alkaloids which, besides the applications in hydrogenation catalysis, form active catalysts or stoichiometric reagents for a wide array of other synthetically important enantioselective reactions and transformations.[18] Here, as a continuation of the previous study, we present a more detailed account on the hydrosilylation of cinchonidine for preparation of new distally substituted chiral catalyst modifiers and report their application in the hydrogenation of 1-phenylpropane-1,2-dione and ethyl pyruvate.

Results and Discussion

Synthesis of the Chiral Modifiers

Synthesis of the new chiral modifiers is summarized in Scheme 2 with modifier structures illustrated in Figure 1. As described previously,[17] in the first step, cinchonidine (**1**) is treated with chlorotrimethylsilane/TEA in THF to provide 9-*O*-(trimethylsilyl)cinchonidine (**2**) as a fairly pure solid in admixture with approximately 10% 9-*O*-(trimethylsilyl)-10,11-dihydrocinchonidine in 96% yield. The concomitant formation of the dihydrocinchonidine analogue of **2** results from the 10,11-dihydrocinchonidine impurity in commercial cinchonidine. Next, the TMS-protected cinchonidine was hydrosilylated using four commercially available or readily prepared trialkyl/arylsilanes: 1) triethylsilane, 2) triphenylsilane, 3) bis(dimethylsilyl)ethane and, 4) the optically active, chiral-at-silicon (+)-(*R*)-methyl(1-naphthyl)phenylsilane in toluene solution in the presence of Karstedt's catalyst. By this procedure, the 9-*O*-TMS-protected 11-silyl-substituted dihydrocinchonidines **3a**–**d** were obtained in 38–83% yields after purification by flash column chromatography. The lowest isolated yield obtained for the chiral-at-silicon compound **3c** is a result of the application of two subsequent flash-chromatography procedures required for separation of this compound from the starting material, due to their similar retention factor values (R_f).



Scheme 2. Synthesis of the chiral modifiers **4a**–**d** and their precursors **3a**–**d**. i) TMSCl, Et_3N, THF; ii) $R^1R^2R^3SiH$, Karstedt's catalyst, toluene, 80–90 °C; iii) MeOH, reflux.

The corresponding 11-silyl-substituted 10,11-dihydrocinchonidines **4a**–**d** were then obtained in 70–92% isolated yields after refluxing compounds **3a**–**d** in methanol in order to remove the 9-*O*-TMS protecting group followed by standard purification/washing and/or crystallization procedures. All compounds **3a**–**d** and **4a**–**d** were fully characterized by HRMS analysis and by ^{1}H and ^{13}C NMR spectroscopy. No racemization of the chiral silyl group was observed in the hydrosilylation of **2** with (+)-(*R*)-methyl(1-naphthyl)phenylsilane, as indicated by the single ^{1}H NMR methyl resonance from the silicon-bound methyl group of compounds **3c** and **4c**. The proposed stereochemical configuration of the chiral silicon atom in compounds **3c** and **4c**, as illustrated for **4c** in Figure 1, is based on the expected retention of configuration at the silicon atom upon the hydrosilylation reaction.[19]

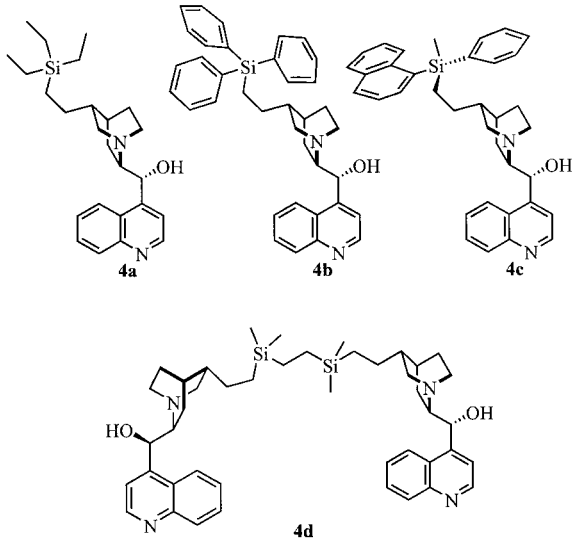


Figure 1. Structures of the chiral modifiers **4a**–**d**.

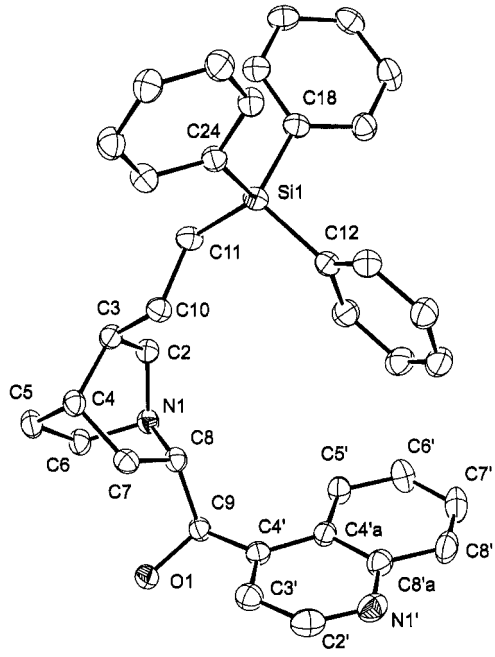


Figure 2. Molecular structure of 11-triphenylsilyl-10,11-dihydrocinchonidine (**4b**).

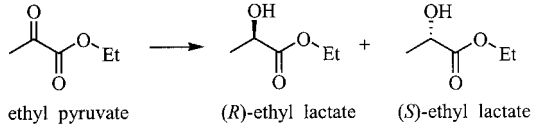
Despite several attempts, single crystals suitable for X-ray structure determination could only be obtained from the 11-triphenylsilyl-substituted compound **4b** after recrystallization from methanol. The molecular structure of **4b** is displayed in Figure 2 with selected torsion angles collected in Table 1. All compounds **4a**–**d** were then, together with (–)-cinchonidine (**1**), evaluated as chiral modifiers in the hydrogenation of ethyl pyruvate and 1-phenylpropane-1,2-dione on a heterogeneous Pt/Al_2O_3 catalyst.

Table 1. Selected torsion angles [°] for cinchonidine (**1**)[20] and 11-triphenylsilyl-10,11-dihydrocinchonidine (**4b**) for comparison of the orientations of their quinoline and quinuclidine moieties.

	1	**4b**
N(1)–C(8)–C(9)–C(4′)	158.0(6)	150.8(2)
C(7)–C(8)–C(9)–C(4′)	–76.1(4)	–81.8(3)
N(1)–C(8)–C(9)–O(1)	–77.9(4)	–86.0(2)
C(7)–C(8)–C(9)–O(1)	48.0(7)	41.3(3)
C(4′A)–C(4′)–C(9)–O(1)	159.1(7)	150.3(2)
C(3′)–C(4′)–C(9)–O(1)	–22.6(9)	–27.8(3)
C(3′)–C(4′)–C(9)–C(8)	101.5(7)	95.5(3)
C(4′A)–C(4′)–C(9)–C(8)	–76.8(7)	–86.4(3)

Hydrogenation of Ethyl Pyruvate

The enantioselective hydrogenation of α-oxo esters on cinchona alkaloid modified Pt catalysts was originally described by Orito, Imai and Niwa.[21] In 1978 it was reported that cinchonidine-modified Pt/C was active for the enantioselective hydrogenation of methyl pyruvate to (+)-(*R*)-methyl lactate in ethanolic solution at 70 bar pressure and ambient temperature.[21e] Over the past decade extensive efforts have been carried out to optimize the reaction conditions and understand the mechanism of enantiodifferentiation in the hydrogenation of both methyl and ethyl pyruvate. Hydrogenation of ethyl pyruvate to the corresponding ethyl lactate, as illustrated in Scheme 3, has become the prominent model reaction in this field. Most of the experimental parameters such as the employed catalyst (metal, support, particle size, etc.), the structure and concentration of the modifier, solvent effects, mass-transfer limitations and hydrogen pressure have been systematically studied for this system.[2] In spite of the extensive literature on the subject, only a few studies have addressed the influence of distal modifier substitution at the C-3 quinuclidine atom on enantioselectivity.[6b] Thus, we felt motivated to investigate the new modifiers described in the present work also in the hydrogenation of ethyl pyruvate.



Scheme 3. Hydrogenation of ethyl pyruvate.

Under the experimental conditions employed here (P = 10 bar H_2, c_{EtPy} = 0.1 M, T = 15 °C), hydrogenation of ethyl pyruvate on 5 wt-% Pt/Al_2O_3 modified by the parent compound cinchonidine (**1**) afforded (*R*)-ethyl lactate in 84% *ee*, a considerably high enantioselectivity in toluene without acid additives. Enantiomeric excesses obtained with the 11-silyl-substituted modifiers **4a**–**4d** were in all cases slightly lower (*ee* = 62–73%) compared to **1** (Table 2). The influence of the distal substituent on the *ee* is minor as triethyl (**4a**), triphenyl (**4b**) and methyl(1-naphthyl)phenyl substitution (**4c**) result in practically the same *ee* values. Likewise, the additional stereocenter in the chiral-at-silicon modifier **4c** appears to have a negligible, if any, influence on the enantiodifferentiation. The 11,11′-bridged bis(cinchonidine) **4d** gave a lower enantioselectivity (*ee* = 62%) than the other three modifiers **4a**–**c**, yet the difference is relatively small. Also, it should be noted that in compensation for its two anchoring moieties, the applied concentration of modifier **4d** was only one half of that employed for modifiers **4a**–**c**, while it remains unclear at present whether **4d** adsorbs via both of its quinoline moieties or not. The dependence of the *ee* on the ethyl pyruvate conversion is illustrated in Figure 3. A constant *ee* with increasing ethyl pyruvate conversion was observed for **1**, **4b**, **4c** and **4d**, whereas **4a** gave the maximum selectivity of *ee* = 77% at approximately 20% conversion after which it decreased slighltly to 66% at 60% conversion. The first observed *ee* is slightly lower for **1** and **4a**, however, this can be attributed to the well-documented initial transient behaviour of the *ee* at low ethyl pyruvate conversion levels.[22]

All modifiers decreased the reaction rate (Table 3). The racemic reaction was up to three fold faster than the lowest modified reaction rate using **4c** while being slightly slower than the reaction modified by cinchonidine. Kinetic curves are collected in Figure 4. Among the studied reactions, racemic hydrogenation of ethyl pyruvate in the absence of chiral modifier is the fastest (Figure 4) and the initial reaction rate with cinchonidine (**1**) is about the same order of magnitude (Table 3). The chirally modified systems are ranked in the following order of decreasing reaction rate: **1** > **4a** > **4b** > **4d** > **4c**. The initial reaction rate does not correlate with the observed *ee* values (Table 2).

Table 2. Hydrogenation of ethyl pyruvate.

Modifier	$ee_{(R)}$ [%][a]	Conversion [mol%][b]
1	84	100
–[c]	0	100
4a	68	57
4b	68	81
4c	73	70
4d	62	46

[a] At 50% conversion of EtPy. [b] Conversion after 1 h. [c] Racemic hydrogenation in the absence of modifier.

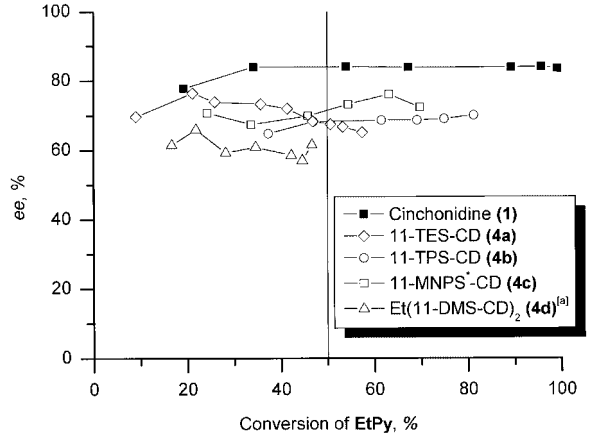


Figure 3. Enantiomeric excess (*ee*) in the hydrogenation of ethyl pyruvate in the presence of chiral modifiers **4a**–**d** and cinchonidine in toluene at 15 °C and 10 bar of H_2. [a] 0.5 mol-equiv. of **4d** used in comparison to **4a**–**c**.

Table 3. Initial rates of the ethyl pyruvate (EtPy) and 1-phenylpropane-1,2-dione (**A**) hydrogenation in the presence of the chiral modifiers **4a**–**d** and cinchonidine.

		1	–[a]	**4a**	**4b**	**4c**	**4d**
EtPy	Initial rate[b]	111.6	96.2	73.0	53.0	30.4	38.6
	R^2[c]	0.99	0.98	0.91	0.99	0.90	0.98
A	Initial rate[b]	18.6	21.2	14.0	4.2	3.75	5.7
	R^2[c]	0.99	0.99	0.98	0.96	0.99	0.99

[a] Racemic hydrogenation in the absence of modifier. [b] The initial rates were calculated by using the linear approximation of the kinetic data obtained over the time interval from 3 to 10 min for EtPy and from 3 to 20 min for **A** after reaction start and are expressed in $10^{-4} \times$ mol min^{-1} g^{-1}_{cat}. [c] R^2: coefficient of determination for linear approximation.

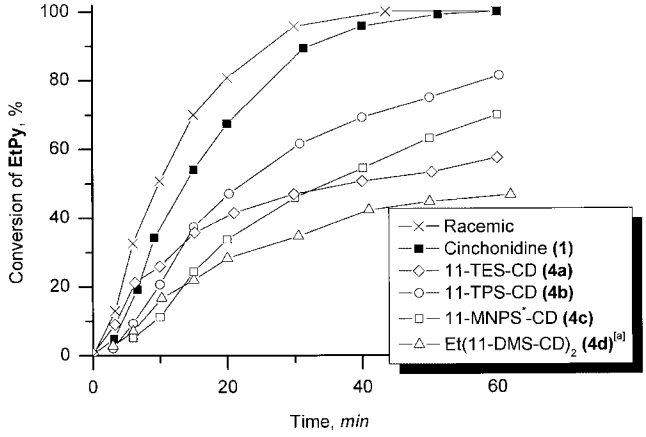


Figure 4. Hydrogenation kinetics of ethyl pyruvate in toluene at 15 °C. Catalyst: 5 wt-% Pt/Al_2O_3 modified in situ. [a] 0.5 mol-equiv. of **4d** used in comparison to **4a**–**c**.

Hydrogenation of 1-Phenylpropane-1,2-dione

1-Phenylpropane-1,2-dione (**A**) is a prochiral unsymmetrical diketone which upon hydrogenation produces four different chiral hydroxy ketones (**B**, **C**, **D** and **E**) and four diols (**F**, **G**, **H** and **I**) (Scheme 1). The first stage of the hydrogena-

tion reaction produces two regioisomers, 1-hydroxy-1-phenylpropanone and 2-hydroxy-1-phenylpropanone, the former being the major product. Both regioisomers are formed as pairs of enantiomers (**B/C** and **D/E** in Scheme 1). In the second stage, the hydroxy ketones react further to the corresponding diols, which again are formed as two pairs of enantiomers (**F/G** and **H/I**). At the hydroxy ketone stage, an increase of the intermediate *ee* takes place due to kinetic resolution in the presence of cinchonidine, i.e., both **C** and **D** react further to diols faster than **B** and **E** resulting in an increase of enantiomeric excess. The predominant product obtained in the hydrogenation of 1-phenylpropane-1,2-dione over cinchonidine-modified Pt catalysts is the (–)-(*R*)-1-hydroxy-1-phenylpropan-2-one stereoisomer **B**.

The hydrogenation kinetics of the 1-phenylpropane-1,2-dione in the presence of the different chiral modifiers are presented in Figure 5 with enantiomeric excesses vs. conversion in Figure 6. Catalyst modification by the 11-triethylsilyl-substituted cinchonidine derivative **4a** in toluene provided a similar *ee* enhancement compared to cinchonidine (*ee* = 70% vs. 55%) as observed earlier with the 11-triethoxysilyl analogue in ethyl acetate (Table 4).[17] Also the regioselectivity (**B+C** vs. **D+E**) was slightly enhanced. The 11-triphenylsilyl analogue **4b** gave a similar *ee* than obtained with **1** (*ee* = 53% and 55%, respectively). With the chiral-at-silicon compound **4c**, the *ee* dropped to 41%, indicating again that distal modifier substitution has a notable influence in the hydrogenation of **A**. This is in contrast to the observations reported here for the hydrogenation of ethyl pyruvate (vide supra) where all three modifiers **4a**–**c** provided similar enantiomeric excesses of approximately 70%. Analogously to the ethyl pyruvate case, the lowest enantiomeric excess in the hydrogenation of **A** was obtained with the bis(cinchonidine) modifier **4d** (*ee* = 24%) which again, in compensation for its two anchoring quinoline moieties, was applied in a concentration of one half of that employed for modifiers **4a**–**c**.

The distribution of diols was very similar with all modifiers evaluated with the main diol being the (1*R*,2*S*) diastereomer **F** with 51% < *S* < 60% and *ee* = 23–36%. The regioselectivity (*rs*) varied slightly with the chiral modifier selected from 4.1 during racemic reaction to 2.1–5.3 in the enantioselective hydrogenations. Interestingly, the modifier **4d** clearly increases the reaction towards **D** and **E** resulting in lower *rs* than observed during a racemic hydrogenation. The *rs* correlates well with the obtained *ee* as reported previously for cinchonidine-modified catalyst in ethyl acetate,[14d] i.e., high *ee* and high *rs* are interrelated.

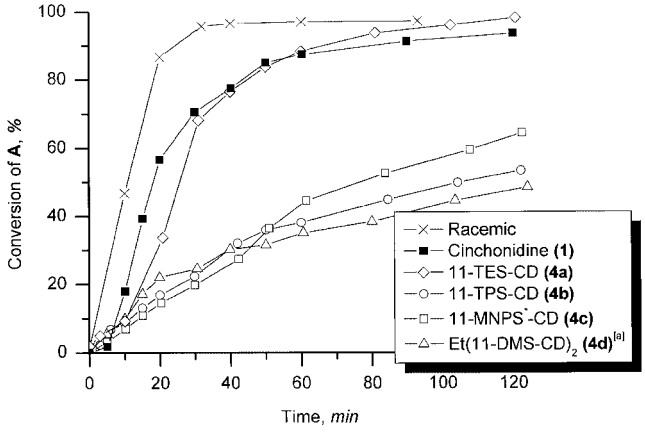


Figure 5. Hydrogenation kinetics of 1-phenylpropane-1,2-dione in toluene at 15 °C. Catalyst: 5 wt-% Pt/Al_2O_3 modified in situ. [a] 0.5 mol-equiv. of **4d** used in comparison to **4a**–**c**.

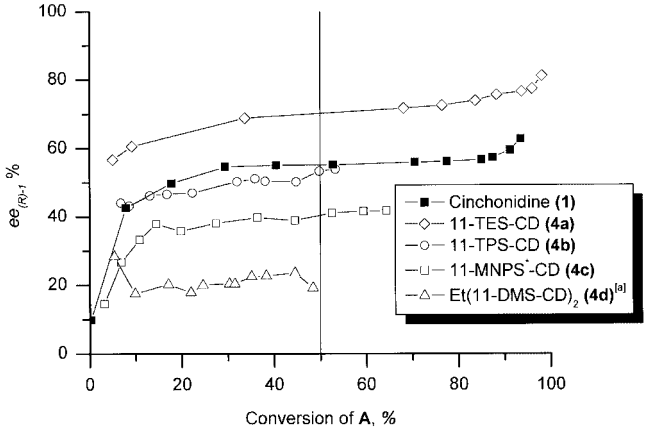


Figure 6. Enantiomeric excess (*ee*) in the hydrogenation of 1-phenylpropan-1,2-dione in the presence of chiral modifiers in toluene at 15 °C and 10 bar of H_2. [a] 0.5 mol-equiv. of **4d** used in comparison to **4a**–**c**.

Conversions of **A** achieved after 2 h of reaction under the standard conditions in toluene ranged from 48 to 98% indicating strong dependence of the reaction rate on the modifier structure. The conversion vs. time behaviour is similar for **1**, **4a** and the racemic hydrogenation, as well as

Table 4. Hydrogenation of 1-phenylpropan-1,2-dione (**A**) in the presence of chiral modifiers.

Modifier	$ee_{(R)-1}$ [%][a]	$ee_{(RS)}$ [%][a]	$S_{(RR+SS)}$[b] [%]	$S_{(RS)}$[b] [%]	$S_{(SR)}$[b] [%]	*rs*[c]	Conversion [mol%][d]	Diols [mol%][d]
1	55	33	19	54	27	4.5	98	29
–[e]	0	–1	17	41	42	4.1	97[f]	47[f]
4a	70	36	11	60	28	5.3	98	21
4b	53	23	17	51	32	4.2	52	4
4c	41	23	19	50	31	3.8	64	7
4d	24	34	15	57	28	2.1	48	6

[a] At 50% conversion of **A**; for the definition, see Exp. Sect. [b] *S* = selectivity; for the definition, see Exp. Sect. [c] *rs* = regioselectivity; for the definition, see Exp. Sect. [d] After 2 h. [e] Racemic hydrogenation in the absence of modifier. [f] After 1.5 h.

in the series **4b**, **4c** and **4d**, the former ones being fourfold faster than the latter three. Reaction rates obtained with **1** and the 11-triethylsilyl-substituted modifier **4a** are significantly higher than those obtained with all other modifiers. Compound **4a** induces a significant enhancement in both enantio- and regioselectivity, whereas the initial reaction rate is lower than that obtained with **1**.

Discussion

All new modifiers prepared were characterized by ^{1}H and ^{13}C NMR spectroscopy, high-resolution MS and elemental analysis. Satisfactory elemental analyses within the range of ±0.4% were obtained in all cases except for some of the 9-*O*-TMS-protected precursors (none of which were exhaustively purified and are not claimed here as "pure" compounds) and the bis(cinchonidine) compound **4d**, all of which gave satisfactory H and N analytical data deviating only by a maximum of 0.8% in their carbon analyses. Notably, all of the compounds **3b**–**3d** and **4d** yielding slight deviations in C analyses contain either two or four silicon atoms while giving entirely satisfactory H and N microanalytical data. Considering that significant impurities were not detected in the NMR analysis of these compounds, the discrepancies are possibly a result from the disturbing effects of silicon in the carbon measurements. As observed earlier for the 11-triethoxysilyl-substituted analogue, the distal substitution in position 11 does not change the sign of the optical rotation of these cinchonidine derivatives; all compounds **4a**–**c** gave negative optical rotations in analogy to cinchonidine. Due to the poor solubility of **4d** in chloroform and alcohols, its optical rotation was not measured.

The crystallographic data of 11-(triphenylsilyl)-10,11-dihydrocinchonidine (**4b**) (molecular structure displayed in Figure 2) demonstrates that this modifier, in the crystalline state, exists in the open(3) cinchonidine conformation. Based on the previous ab initio calculations with cinchonidine and 11-(triethoxysilyl)-10,11-dihydrocinchonidine,[17] the most stable conformations for both of these compounds were very similar open(3) forms. Thus, even relatively large substituents in the distal C-3 position would not appear to result in dramatic changes in the conformational equilibrium. In ethyl pyruvate hydrogenation the cinchonidine open(3) conformation is assumed to be the actor species based on several theoretical and experimental arguments.[23] Taking into account the central role of the open(3) conformation of cinchonidine (**1**) in toluene [population of the open(3) conformation P_{open} = 70%] and the similar *ee* values obtained with **1** and the modifiers **4a**–**d** in the hydrogenation of ethyl pyruvate, one would expect that the open(3) conformation is the predominant conformation in toluene for all modifiers evaluated here. The chiral-at-silicon compound **4c** could in principle adsorb on Pt also by anchoring via its Si–naphthyl substituent, however, given the similar *ee* values in the ethyl pyruvate case this possibility can be considered very unlikely.

Dependence of the reaction rate and *ee* on the modifier structure gives mechanistically important structure–selectivity–activity relationships, which in turn help to rationalize feasible reaction mechanisms. The modifiers investigated here decreased the reaction rate with respect to the racemic hydrogenation (Table 3) and the activity could not be correlated with the enantioselectivity. The experimentally obtained initial rates with ethyl pyruvate, at first sight, are in conflict with the known phenomenon of rate acceleration induced by the presence of chiral modifiers.[24] However, noteworthy is that in the present work a relatively low ethyl pyruvate concentration was used (0.1 M). Previously, a rate deceleration has been observed at low substrate concentration in ethyl pyruvate hydrogenation,[25] indicating that the rate acceleration and enantioselectivity are not always interrelated. In the hydrogenation of **A** it is well accepted that the modified reaction has the same or lower rate than the racemic reaction[14d] while *ee* values up to 70% can be obtained. It is noteworthy to mention that experiments with **A** have always been carried out at very low substrate concentrations (< 0.1 M), thus, it would be interesting to test whether the reaction also exhibits a rate acceleration at much higher substrate concentrations as observed in the ethyl pyruvate case.

The results here with ethyl pyruvate are in line with previous observations[2,6] that the distal modifier part has a relatively small influence on the *ee* even when bulky substituents are involved. Even the bridged bis(cinchonidine) modifier **4d** results in a relatively high *ee* and the disilane linking does not greatly alter the modifier performance, although it reduces the reaction rate significantly.

The same reasoning clearly does not apply in the case of **A**, where the distal substituents can either notably decrease or increase the *ee* with respect to cinchonidine. The enhancement of the *ee* obtained here in the hydrogenation of **A** with **4a** in toluene and observed earlier with its triethoxysilyl analogue in ethyl acetate is difficult to explain at present, considering that similar enhancement was not observed in the hydrogenation of ethyl pyruvate. However, as shown previously by us,[14c,26] the enantiodifferentiating mechanisms for the two substrates are clearly different and we propose this effect to have mainly a steric origin. It is tempting to speculate that at the substrate–modifier complexation stage, the distal 11-triethylsilyl or 11-triethoxysilyl substituent increases the population of the open(3)-like confomer leading to higher *ee* values, whereas bulkier substituents such as those in **4b** and **4c** may have a conflicting interaction with the diketone substrate resulting in lower enantioselectivities. Nevertheless, the results obtained here are promising, demonstrating unambiguously that the *ee* obtained with cinchonidine as the chiral modifier in the hydrogenation of **A** is by no means the maximum value obtainable and that by proper substituents in the distal position of the modifier, higher *ee* values can be achieved. In a separate study,[26] we have evaluated a series of 16 chiral catalyst modifiers derived from cinchonidine, cinchonine and quinine structures in the hydrogenation of **A**, none of which provided higher *ee* values in the first hydrogenation step as compared to the parent modifier (–)-cinchonidine.

Conclusions

The effect of distal modifier substitution in the enantioselective hydrogenation of ethyl pyruvate and 1-phenylpropane-1,2-dione on chirally modified Pt catalyst was investigated. Bulky aromatic substituents on the 11-silyl group attached to the quinuclidine C-3 position of cinchonidine via the two-carbon linker decreased the rate of hydrogenation. In the ethyl pyruvate hydrogenation, the distal modification does not play a crucial role with all 11-substituted modifiers yielding slightly lower *ee* values (62–73%) in toluene compared to cinchonidine (*ee* = 84%). The reaction rate was lower in all chirally modified reactions as compared to the racemic reaction in the absence of a modifier. The hydrogenation of 1-phenylpropane-1,2-dione is more sensitive to distal substitution effects and compared to cinchonidine (*ee* = 55%), the *ee* can be notably higher (*ee* = 70%) or lower (*ee* = 24%), depending on the substitution pattern of the modifier employed. Enhancement of the *ee* was obtained here with the sterically least demanding 11-triethylsilyl substituent, in a similar fashion to the previously obtained result with the 11-triethoxysilyl substituent. The differences observed in the structure–selectivity–activity correlations with ethyl pyruvate and 1-phenylpropane-1,2-dione substrates clearly indicate that the mechanisms of enantiodifferentiation on cinchona alkaloid modified Pt hydrogenation catalyst systems are different for the two. Furthermore, it was demonstrated that (–)-cinchonidine is not the optimal modifier structure in the hydrogenation of **A** and notably enhanced enantioselectivities can be obtained by simple chemical modifications of the parent structure, a result promising with respect to the broader applicability of chirally modified heterogeneous catalysts for enantioselective synthesis.

Experimental Section

General Remarks: All reactions with air-sensitive reagents were carried out under argon 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 molecular sieves (4 Å). (–)-Cinchonidine (Aldrich, 96%), triethylsilane (Gelest, 99+%), triphenylsilane (Fluka, ≥99%) and platinum–divinyltetramethyldisiloxane complex (Karstedt's catalyst, 2.1–2.4% Pt concentration in xylene, Gelest) were used as received. Synthesis of 9-*O*-(trimethylsilyl)cinchonidine was carried out as described previously,[17] 1,2-bis(dimethylsilyl)ethane was prepared by reduction of 1,2-bis(chlorodimethylsilyl)ethane (Gelest, 97%) with $LiAlH_4$ and vacuum-distilled prior to use.[27] The chiral silane (+)-(*R*)-methyl(1-naphthyl)phenylsilane, was prepared according to a literature procedure.[28] For use in the catalytic hydrogenation reactions, 1-phenylpropane-1,2-dione (Aldrich, 99%) and ethyl pyruvate (Fluka, ≥97%) were vacuum-distilled before use, whereas toluene (J. T. Baker, >99.5%) and cinchonidine (Fluka, 98%) 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 $CDCl_3$ and [D_4] methanol (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 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)]. ^{1}H NMR spectra were finally analyzed with the PERCH software.[29] The numbering system for cinchonidine derivatives is presented in Figure 7. Polarimetric measurements were carried out with 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} ° $cm^2 mol^{-1}$. Microanalysis was conducted at the Helsinki University of Technology, Finland, and A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Moscow, Russia.

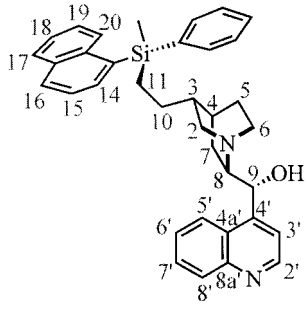


Figure 7. Numbering system for **4c**.

11-(Triethylsilyl)-10,11-dihydrocinchonidine (4a): To a solution of **2** (2.0 g, ca. 4.9 mmol of pure substance) in toluene (5 mL) were added two drops of Karstedt's catalyst. After stirring at room temperature for 10 min, triethylsilane (0.64 g, 5.5 mmol.) was added. The reaction mixture was stirred at 80–90 °C for 4 h. After cooling to room temperature, the solvent was evaporated and the residue purified by gradient flash chromatography (CH_2Cl_2/MeOH, 20:1 → 10:1) to yield 1.78 g of 11-(triethylsilyl)-9-*O*-(trimethylsilyl)-10,11-dihydrocinchonidine (**3a**) (3.7 mmol, 75%) as a yellowish oil. ^{1}H NMR ($CDCl_3$): δ = 8.88 (d, $^3J_{2',3'}$ = 4.5 Hz, 1 H, H-2′), 8.15 (dd, $^4J_{8',6'}$ = 1.2, $^3J_{8',7'}$ = 8.5 Hz, 1 H, H-8′), 8.13 (br., 1 H, H-5′), 7.71 (ddd, $^4J_{7',5'}$ = 1.3, $^3J_{7',6'}$ = 6.8, $^3J_{7',8'}$ = 8.5 Hz, 1 H, H-7′), 7.57 (ddd, $^4J_{6',8'}$ = 1.2, $^3J_{6',7'}$ = 6.8, $^3J_{6',5'}$ = 8.5 Hz, 1 H, H-6′), 7.50 (br., 1 H, H-3′), 5.59 (br., 1 H, H-9), 3.39 (br., 1 H, H-6b), 3,08 (dd, $^3J_{2a,3}$ = 10.0, $^2J_{2a,2b}$ = 13.4 Hz, 1 H, H-2a), 2.99 (br., 1 H, H-8), 2.65 (br., 1 H, H-6a), 2.31 (dm, 1 H, H-2b), 1.82–1.69 (m, 3 H, H-4, H-5b, H-7b), 1.46–1.36 (m, 3 H, H-3, H-5a, H-7a), 1.20–1.10 (m, 2 H, H-10), 0,84 (t, $^3J_{14,13}$ = 7.9 Hz, 9 H, $SiCH_2CH_3$), 0.41 (q, $^3J_{13,14}$ = 7.9 Hz, 6 H, $SiCH_2CH_3$), 0,38 (m, 2 H, H-11), 0.04 (s, 9 H, $SiCH_3$) ppm. ^{13}C NMR ($CDCl_3$): δ = 150.00 (C-2′), 149.58 (C-4′), 148.47 (C-8a′), 130.45 (C-8′), 128.95 (C-7′), 126.57 (C-6′), 125.56 (C-4a′), 123.22 (C-5′), 118.75 (C-3′), 73.13 (C-9), 61.45 (C-8), 59.08 (C-2), 43.22 (C-6), 39.29 (C-3), 28.59 (2 C, C-5, C-10), 25.62 (C-4), 20.91 (C-7), 9.08 (C-11), 7.43 (3 C, $SiCH_2CH_3$), 3.25 (3 C, $SiCH_2CH_3$), 0.24 (3 C, $SiCH_3$) ppm. HRMS: calcd. for $C_{28}H_{46}N_2OSi_2$ 482.3149; found 482.3145. Next, a solution of **3a** (0.60 g, 1.24 mmol) in methanol (25 mL) with addition of some crystals of potassium carbonate was refluxed for 20 h. Evaporation of the solvent and the subsequent washing with pentane left 0.47 g (1.14 mmol, 92%) of **4a** as an analytically pure white solid. ^{1}H NMR($CDCl_3$): δ = 8.74 (d, $^3J_{2',3'}$ = 4.5 Hz, 1 H, H-2′), 8.05 (dd, $^4J_{8',6'}$ = 1.2, $^3J_{8',7'}$ = 8.5 Hz, 1 H, H-8′), 7.93 (dd, $^4J_{5',7'}$ = 1.3, $^3J_{5',6'}$ = 8.5 Hz, 1 H, H-5′), 7.60 (ddd, $^4J_{7',5'}$ = 1.3, $^3J_{7',6'}$ = 6.8, $^3J_{7',8'}$ = 8.5 Hz, 1 H, H-7′), 7.56 (d, $^3J_{3',2'}$ = 4.5 Hz, 1 H, H-3′), 7.28 (ddd, $^4J_{6',8'}$ = 1.2, $^3J_{6',7'}$ = 6.8, $^3J_{6',5'}$ = 8.5 Hz, 1 H, H-6′), 5.61 (d, $^3J_{9,8}$ = 3.8 Hz, 1 H, H-9), 5.17 (s, 1 H, OH), 3.46 (m, 1 H,

H-6b), 3,04 (m, 1 H, H-8), 2.99 (dd, $^3J_{2a,3}$ = 10.0, $^2J_{2a,2b}$ = 13.5 Hz, 1 H, H-2a), 2.54 (m, 1 H, H-6a), 2.30 (dm, 1 H, H-2b), 1.79 (m, 1 H, H-4), 1.77–1.70 (m, 2 H, H-5b, H-7b), 1.42–1.33 (m, 3 H, H-3, H-5a, H-7a), 1.19–1.09 (m, 2 H, H-10), 0,83 (t, $^3J_{14,13}$ = 7.9 Hz, 9 H, $SiCH_2CH_3$), 0.41 (q, $^3J_{13,14}$ = 7.9 Hz, 6 H, $SiCH_2CH_3$), 0,37 (m, 2 H, H-11) ppm. ^{13}C NMR ($CDCl_3$): δ = 150.09 (C-2′), 149.89 (C-4′), 148.17 (C-8a′), 130.15 (C-8′), 128.93 (C-7′), 126.53 (C-6′), 125.76 (C-4a′), 123.11 (C-5′), 118.35 (C-3′), 71.87 (C-9), 60.31 (C-8), 58.73 (C-2), 43.38 (C-6), 39.23 (C-3), 28.63 (C-10), 28.41 (C-5), 25.55 (C-4), 21.30 (C-7), 9.10 (C-11), 7.47 (3 C, $SiCH_2CH_3$), 3.27 (3 C, $SiCH_2CH_3$) ppm. $[\alpha]_D^{24}$ = –66.5 (c = 0.056 M in $CHCl_3$). M.p. 220–222 °C. HRMS: calcd. for $C_{25}H_{38}N_2OSi$ 410.2753; found 410.2752. $C_{25}H_{38}N_2OSi$ (410.67): calcd. C 73.12, H 9.33, N 6.82; found C 72.99, H 9.33, N 6.80.

11-(Triphenylsilyl)-10,11-dihydrocinchonidine (4b): To a solution of **2** (2.0 g, ca. 4.9 mmol of pure substance) in toluene (5 mL) were added two drops of Karstedt's catalyst. After stirring at room temperature for 10 min, triphenylsilane (1.28 g, 4.9 mmol) was added. The reaction mixture was stirred at 80–90 °C for 2 h. After cooling to room temperature, the solvent was evaporated and the residue purified by flash chromatography (CH_2Cl_2/MeOH, 20:1) to yield 2.54 g of 11-(triphenylsilyl)-9-*O*-(trimethylsilyl)-10,11-dihydrocinchonidine (**3b**) (4.1 mmol, 83%) as white amorphous material. ^{1}H NMR ($CDCl_3$): δ = 8.87 (d, $^3J_{2',3'}$ = 4.5 Hz, 1 H, H-2′), 8.16 (dd, $^4J_{8',6'}$ = 1.2, $^3J_{8',7'}$ = 8.5 Hz, 1 H, H-8′), 8.06 (br., 1 H, H-5′), 7.71 (ddd, $^4J_{7',5'}$ = 1.2, $^3J_{7',6'}$ = 6.8, $^3J_{7',8'}$ = 8.5 Hz, 1 H, H-7′), 7.54 (ddd, $^4J_{6',8'}$ = 1.2, $^3J_{6',7'}$ = 6.8, $^3J_{6',5'}$ = 8.5 Hz, 1 H, H-6′), 7.44 (br., 1 H, H-3′), 7.40 (m, 6 H, *o*-H), 7.31 (m, 3 H, *p*-H), 7.22 (m, 6 H, *m*-H), 5.59 (br., 1 H, H-9), 3.38 (br., 1 H, H-6b), 3,02 (dd, $^3J_{2a,3}$ = 9.7, $^2J_{2a,2b}$ = 13.4 Hz, 1 H, H-2a), 2.83 (br., 1 H, H-8), 2.61 (m, 1 H, H-6a), 2.26 (dm, 1 H, H-2b), 1.82 (m, H-4), 1.74–1.65 (m, 2 H, H-5b, H-7b), 1.50–1.43 (m, H, H-3), 1.41–1.29 (m, 2 H, H-10), 1.31–1.25 (m, 2 H, H-5a, H-7a), 1.25–1.19 (m, 2 H, H-11), 0.01 (s, 9 H, $SiCH_3$) ppm. ^{13}C NMR ($CDCl_3$): δ = 149.90 (C-2′), 149.44 (C-4′), 148.41 (C-8a′), 135.48 (6 C, *o*-C), 134.96 (3 C, *i*-C), 130.42 (C-8′), 129.37 (3C, *p*-C), 128.90 (C-7′), 127.77 (6C, *m*-C), 126.56 (C-6′), 125.46 (C-4a′), 123.14 (C-5′), 118.64 (C-3′), 73.44 (C-9), 61.19 (C-8), 58.90 (C-2), 43.18 (C-6), 38.87 (C-3), 28.58 (C-10), 28.37 (C-5), 25.27 (C-4), 20.57 (C-7), 11.06 (C-11), 0.17 (3 C, $SiCH_3$) ppm. $[\alpha]_D^{24}$ = –74.7 (c = 0.08 M in $CHCl_3$). HRMS: calcd. for $C_{40}H_{46}N_2OSi_2$ 626.3149; found 626.3152. $C_{40}H_{46}N_2OSi_2$ (626.98): calcd. C 76.63, H 7.40, N 4.47; found C 75.92, H 7.23, N 4.42. Next, a solution of **3b** (1.71 g, 2.7 mmol) in methanol (40 mL) with addition of some crystals of potassium carbonate was refluxed for 20 h. Evaporation of the solvent and recrystallization of the residue from methanol gave 1.15 g of **4b** (2.0 mmol, 76%) as an analytically pure white solid. Crystals suitable for X-ray structure determination were obtained by recrystallization from methanol. ^{1}H NMR ($CDCl_3$): δ = 8.73 (d, $^3J_{2',3'}$ = 4.5 Hz, 1 H, H-2′), 8.07 (dd, $^4J_{8',6'}$ = 1.2, $^3J_{8',7'}$ = 8.5 Hz, 1 H, H-8′), 7.86 (dd, $^4J_{5',7'}$ = 1.3, $^3J_{5',6'}$ = 8.5 Hz, 1 H, H-5′), 7.60 (ddd, $^4J_{7',5'}$ = 1.3, $^3J_{7',6'}$ = 6.8, $^3J_{7',8'}$ = 8.5 Hz, 1 H, H-7′), 7.48 (d, $^3J_{3',2'}$ = 4.5 Hz, 1 H, H-3′), 7.39 (m, 6 H, *o*-H), 7.32 (m, 1 H, H-6′), 7.29 (m, 3 H, *p*-H), 7.22 (m, 6 H, *m*-H) 5.55 (d, $^3J_{9,8}$ = 3.8 Hz, 1 H, H-9), 4.79 (s, 1 H, OH), 3.43 (m, 1 H, H-6b), 2,94 (dd, $^3J_{2a,3}$ = 9.8, $^2J_{2a,2b}$ = 13.5 Hz, 1 H, H-2a), 2.88 (m, 1 H, H-8), 2.50 (m, 1 H, H-6a), 2.26 (dm, 1 H, H-2b), 1.79 (m, H-4), 1.73–1.63 (m, 2 H, H-5b, H-7b), 1.47–1.40 (m, H, H-3), 1.38–1.28 (m, 2 H, H-10), 1.29–1.24 (m, 2 H, H-5a, H-7a), 1.23–1.18 (m, 2 H, H-11) ppm. ^{13}C NMR ($CDCl_3$): δ = 149.99 (C-2′), 149.62 (C-4′), 148.09 (C-8a′), 135.45 (6 C, *o*-C), 134.90 (3 C, *i*-C), 130.12 (C-8′), 129.38 (3 C, *p*-C), 128.93 (C-7′), 127.77 (6 C, *m*-C), 126.53 (C-6′), 125.61 (C-4a′), 122.96 (C-5′), 118.18 (C-3′), 71.77 (C-9), 60.07 (C-8), 58.53 (C-2), 43.28 (C-6), 38.80 (C-3), 28.56 (C-10), 28.17 (C-5), 25.22 (C-4), 20.92 (C-7), 11.04 (C-11) ppm. $[\alpha]_D^{24}$ = –59.3 (c = 0.054 M in $CHCl_3$). M.p. 198–201 °C. HRMS: calcd. for $C_{37}H_{38}N_2OSi$ 554.2753; found 554.2755. $C_{40}H_{46}N_2OSi_2$ (554.78): calcd. C 80.10, H 6.90, N 5.05; found C 80.18, H 6.97, N 4.91.

11-[(*R*)-methyl(1-naphthyl)phenylsilyl]-10,11-dihydrocinchonidine (4c): To a solution of **2** (1.0 g, ca. 2.45 mmol of pure substance) in toluene (5 mL) were added two drops of Karstedt's catalyst. After stirring at room temperature for 10 min, (+)-(*R*)-methyl(1-naphthyl)phenylsilane (0.61 g, 2.45 mmol) was added. The reaction mixture was stirred at 80–90 °C for 4 h and then at room temperature for 8 h. After evaporation of the solvents, the residue was purified by two consecutive flash chromatography procedures (CH_2Cl_2/MeOH, 20:1) to yield 0.58 g (0.94 mmol, 38%) of 11-[(*R*)-methyl(1-naphthyl)phenylsilyl]-9-*O*-(trimethylsilyl)-10,11-dihydrocinchonidine (**3c**) as white amorphous material. ^{1}H NMR ($CDCl_3$): δ = 8.87 (d, $^3J_{2',3'}$ = 4.5 Hz, 1 H, H-2′), 8.15 (dd, $^4J_{8',6'}$ = 1.2, $^3J_{8',7'}$ = 8.5 Hz, 1 H, H-8′), 8.08–8.03 (br., 1 H, H-5′), 7.81 (dd, $^4J_{20,18}$ = 1.2, $^3J_{20,19}$ = 8.2 Hz, 1 H, H-20), 7.80 (dd, $^4J_{16,14}$ = 1.0, $^3J_{16,15}$ = 8.5 Hz, 1 H, H-16), 7.78 (dd, $^4J_{17,19}$ = 1.3, $^3J_{17,16}$ = 8.1 Hz, 1 H, H-17), 7.71 (ddd, $^4J_{7',5'}$ = 1.3, $^3J_{7',6'}$ = 6.8, $^3J_{7',8'}$ = 8.5 Hz, 1 H, H-7′), 7.61 (dd, $^4J_{14,16}$ = 1.0, $^3J_{14,15}$ = 6.8 Hz, 1 H, H-14), 7.54 (ddd, $^4J_{6',8'}$ = 1.2, $^3J_{6',7'}$ = 6.8, $^3J_{6',5'}$ = 8.6 Hz, 1 H, H-6′), 7.45–7.42 (br., 1 H, H-3′), 7.41 (dd, $^4J_{o-,p-}$ = 1.4, $^3J_{o-,m-}$ = 7.6 Hz, 2 H, *o*-H), 7.35 (m, 2 H, H-18, H-19), 7.28–7.22 (m, 2 H, H-15, *p*-H), 7.20 (m, 2 H, *m*-H), 5.57 (br., 1 H, H-9), 3.36 (br., 1 H, H-6b), 3.00 (m, 1 H, H-2a), 2.82 (br., 1 H, H-8), 2.60 (m, 1 H, H-6a), 2.24 (dm, 1 H, H-2b), 1.76 (m, 1 H, H-4), 1.70–1.63 (m, 2 H, H-5b, H-7b), 1.46–1.39 (m, H, H-3), 1.39–1.31 (m, 1 H, H-5a) 1.29–1.06 (m, 5 H, H-7a, H-10, H-11), 0.59 (s, 3 H, $SiCH_3$) 0.01 [s, 9 H, $Si(CH_3)_3$] ppm. ^{13}C NMR ($CDCl_3$): δ = 150.00 (C-2′), 149.47 (C-4′), 148.48 (C-8a′), 137.98 (C-16a), 137.04 (C-13), 134.86 (C-14), 134.64 (*i*-C), 134.31 (*o*-C), 133.42 (C-20a), 130.49 (C-8′), 130.28 (C-16), 129.10 (C-17), 128.98 (2 C, *p*-C, C-7′), 128.43 (C-20), 127.88 (*m*-C), 126.62 (C-6′), 125.59 (C-18), 125.48 (C-4a′), 125.38 (C-15), 125.01 (C-19), 123.15 (C-5′), 118.81 (C-3′), 74.03 (C-9), 61.31 (C-8), 58.98 (C-2), 43.19 (C-6), 38.81 (C-3), 28.69 (C-10), 28.43 (C-5), 25.38 (C-4), 20.89 (C-7), 12.91 (C-11), 0.24 [3 C, $Si(CH_3)_3$], –2.83 ($SiCH_3$) ppm. HRMS: calcd. for $C_{39}H_{46}N_2OSi_2$ 614.3149; found 614.3147. $C_{39}H_{46}N_2OSi_2$ (614.97): calcd. C 76.17, H 7.54, N 4.56; found C 75.34, H 7.37, N 4.60. Next, a solution of **3c** (0.22 g, 0.36 mmol) in methanol (10 mL) with addition of some crystals of potassium carbonate was refluxed for 4 h. After cooling to room temperature, a white solid precipitated. Recrystallization from methanol gave 0.18 g (0.33 mmol, 92%) of **4c** as an analytically pure white solid. ^{1}H NMR ($CDCl_3$/CD_3OD, 1:2): δ = 8.81 (d, ^3J = 4.5 Hz, 1 H, H-2′), 8.11 (dd, ^4J = 1.3, ^3J = 8.5 Hz, 1 H, H-8′), 8.05 (dd, ^4J = 1.5, ^3J = 8.6 Hz, 1 H, H-5′), 7.81–7.69 (m, 4 H), 7.65–7.57 (m, 3 H), 7.36 (m, 2 H), 7.29 (m, 2 H), 7.20–7.14 (m, 4 H), 5.57 (d, ^3J = 2.7 Hz, 1 H, H-9), 3.60 (m, 1 H), 2.97 (m, 1 H), 2.78 (m, 1 H), 2.56 (m, 1 H), 2.24–2.21 (m, 1 H), 1.80–1.72 (m, 2 H), 1.69–1.63 (m, 1 H), 1.52–1.47 (m, 1 H), 1.41–1.34 (m, 1 H), 1.29–1.20 (m, 1 H), 1.18–1.05 (m, 3 H), 0.94–0.89 (m, 1 H), 0.55 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$/CD_3OD, 1:2): δ = 151.09, 150.07, 147.92, 138.28, 137.37, 135.22, 134.84, 134.62 (2 C), 133.82, 130.64, 129.85, 129.65, 129.47, 129.33, 128.71, 128.23 (2 C), 127.43, 126.09, 125.90, 125.72, 125.35, 123.47, 118.81, 71.27, 60.40, 59.00, 43.62, 38.85, 29.05, 28.16, 25.50, 20.18, 13.11, –2.65 ppm. $[\alpha]_D^{24}$ = –55.7 (c = 0.027 M in $CHCl_3$). M.p. 205–207 °C. HRMS: calcd. for $C_{36}H_{38}N_2OSi$ 542.2753; found 542.2750. $C_{36}H_{38}N_2OSi$ (542.79): calcd. C 79.66, H 7.06, N 5.16; found C 79.21, H 6.84, N 5.14.

1,2-Bis[(10,11-dihydrocinchonidin-11-yl)dimethylsilyl]ethane (4d): To a solution of **2** (1.45 g, ca. 3.6 mmol of pure substance) in toluene

(5 mL) was added one drop of Karstedt's catalyst. After stirring at room temperature for 15 min, 1,2-bis(dimethylsilyl)ethane (0.26 g, 1.8 mmol) was added. The reaction mixture was stirred at 80–90 °C for 3 h. After cooling to room temperature, the solvent was evaporated and the residue purified by gradient flash chromatography (CH_2Cl_2/MeOH, 20:1 → 10:1) to yield 0.62 g (0.7 mmol, 40%) of 1,2-bis{[9-*O*-(trimethylsilyl)-10,11-dihydrocinchonidin-11-yl]dimethylsilyl}ethane (**3d**) as a white solid. ^{1}H NMR ($CDCl_3$): δ = 8.87 (d, $^3J_{2',3'}$ = 4.4 Hz, 2 H, H-2′), 8.13 (dd, $^4J_{8',6'}$ = 1.2, $^3J_{8',7'}$ = 8.5 Hz, 2 H, H-8′), 8.10 (br., 2 H, H-5′), 7.70 (ddd, $^4J_{7',5'}$ = 1.3, $^3J_{7',6'}$ = 6.8, $^3J_{7',8'}$ = 8.5 Hz, 2 H, H-7′), 7.55 (ddd, $^4J_{6',8'}$ = 1.2, $^3J_{6',7'}$ = 6.8, $^3J_{6',5'}$ = 8.4 Hz, 2 H, H-6′), 7.49 (br., 2 H, H-3′), 5.63 (br., 2 H, H-9), 3.38 (br., 2 H, H-6b), 3,05 (dd, $^3J_{2a,3}$ = 9.9, $^2J_{2a,2b}$ = 13.4 Hz, 2 H, H-2a), 2.95 (br., 2 H, H-8), 2.64 (m, 2 H, H-6a), 2.26 (m, 2 H, H-2b), 1.79–1.68 (m, 6 H, H-4, H-5b, H-7b), 1.44–1.34 (m, 6 H, H-3, H-5a, H-7a), 1.15–1.06 (m, 4 H, H-10), 0.34–0.29 (m, 4 H, H-11), 0.20 (s, 4 H, H-13), 0.03 (s, 18 H, Si–C*H*$_3$), –0.22 (s, 12 H, H-14) ppm. ^{13}C NMR ($CDCl_3$): δ = 150.00 (C-2′), 149.58 (C-4′), 148.47 (C-8a′), 130.45 (C-8′), 128.95 (C-7′), 126.57 (C-6′), 125.56 (C-4a′), 123.22 (C-5′), 118.75 (C-3′), 73.13 (C-9), 61.45 (C-8), 59.08 (C-2), 43.22 (C-6), 39.29 (C-3), 28.59 (2 C, C-5, C-10), 25.62 (C-4), 20.91 (C-7), 9.08 (C-11), 7.43 (3 C, $SiCH_2CH_3$), 3.25 (3 C, $SiCH_2CH_3$), 0.24 (3 C, $SiCH_3$) ppm. $[\alpha]_D^{24}$ = –95.4 (*c* = 0.0177 M in $CHCl_3$). HRMS: calcd. for $C_{50}H_{78}N_4O_2Si_4$ 878.5202; found 878.5199. $C_{50}H_{78}N_4O_2Si_4$ (879.52): calcd. C 68.28, H 8.94, N 6.37; found C 67.56, H 8.87, N 6.34. Next, a solution of **3d** (0.50 g, (0.57 mmol) in methanol (25 mL) was refluxed for 5 h and left to stand overnight. Evaporation of the solvent and subsequent washing with pentane left 0.29 g (0.4 mmol, 70%) of **4d** as an analytically pure white solid. ^{1}H NMR ($CDCl_3$): δ = 8.77 (d, $^3J_{2',3'}$ = 4.6 Hz, 2 H, H-2′), 8.13 (dd, $^4J_{5',7'}$ = 1.3, $^3J_{5',6'}$ = 8.5 Hz, 2 H, H-5′), 8.03 (dd, $^4J_{8',6'}$ = 1.2, $^3J_{8',7'}$ = 8.5 Hz, 2 H, H-8′), 7.70 (ddd, $^4J_{7',5'}$ = 1.3, $^3J_{7',6'}$ = 6.8, $^3J_{7',8'}$ = 8.5 Hz, 2 H, H-7′), 7.67 (d, $^3J_{3',2'}$ = 4.6 Hz, 2 H, H-3′), 7.59 (ddd, $^4J_{6',8'}$ = 1.2, $^3J_{6',7'}$ = 6.8, $^3J_{6',5'}$ = 8.5 Hz, 2 H, H-6′), 5.61 (d, $^3J_{9,8}$ = 3.3 Hz, 2 H, H-9), 3.58 (m, 2 H, H-6b), 3,06 (dd, $^3J_{2a,3}$ = 10.1, $^2J_{2a,2b}$ = 13.5 Hz, 2 H, H-2a), 3.00 (m, 2 H, H-8), 2.62 (m, 2 H, H-6a), 2.30 (dm, 2 H, H-2b), 1.87–1.77 (m, 6 H, H-4, H-5b, H-7b), 1.48–1.40 (m, 4 H, H-3, H-5a), 1.31 (m, 2 H, H-7a), 1.13–1.07 (m, 4 H, H-10), 0.33–0.28 (m, 4 H, H-11), 0.17 (s, 4 H, H-13), –0.27 (s, 12 H, H-14) ppm. ^{13}C NMR ($CDCl_3$): δ = 150.30 (C-4′), 148.92 (C-2′), 146.85 (C-8a′), 128.80 (C-7′), 128.39 (C-8′), 126.35 (C-6′), 125.17 (C-4a′), 122.54 (C-5′), 117.86 (C-3′), 70.34 (C-9), 59.66 (C-8), 57.90 (C-2), 42.43 (C-6), 37.99 (C-3), 27.94 (C-10), 27.13 (C-5), 24.63 (C-4), 19.73 (C-7), 11.47 (C-11) 6.21 (C-13), –5.20 (C-14) ppm. $[\alpha]_D^{24}$ not determined due to insolubility of **4d** in $CHCl_3$ and alcohols. M.p. 250–255 °C (with decomposition). HRMS: calcd. for $C_{44}H_{62}N_4O_2Si_2$ 734.4411; found 734.4371. $C_{44}H_{62}N_4O_2Si_2$ (735.16): calcd. C 71.89, H 8.50, N 7.62; found C 71.10, H 8.32, N 7.52.

X-ray Crystallographic Study of 4b: Suitable crystals of **4b** for X-ray measurements were grown from a methanol solution. The single crystal data were collected at 173 K with a Nonius KappaCCD area detector diffractometer using graphite-monochromatised Mo-K_α radiation (λ = 0.71073 Å). The data collection was performed using φ and ω scans (θ range from 2.45 to 24.71°). The data were processed using DENZO-SMN v0.93.0.[30] The structure was solved by direct methods using the SHELXS programme.[31] Full-matrix least-squares refinements on F^2 were performed using the SHELXL-97 programme.[31] Non-hydrogen atoms were refined with anisotropic displacement parameters and the OH hydrogen atom was refined isotopically with fixed isotropic displacement parameters. The rest of the hydrogen atoms were included in the calculations in a riding mode at the fixed distances from their host atoms with the fixed isotropic displacement parameters. Figure 2 was drawn with Ortep-3 for Windows.[32] Crystal data for **4b**: $C_{37}H_{38}N_2OSi$, M_r = 554.78, orthorhombic, a = 9.1075(3), b = 16.5504(6), c = 20.4958(4) Å, V = 3089.39(16) Å^3, T = 173 K, space group $P2_12_12_1$ (no. 19), Z = 4, μ(Mo-K_α) = 0.108 mm^{-1}, d_c = 1.193 Mg/m^3, Flack's parameter = 0.15(13), 5119 unique reflections, which all were used in the calculations. The final R values were R_1 = 0.0506, wR_2 = 0.1223 (all data) with $I > 2\sigma(I)$. The ratio of reflections/parameter was 13.7. CCDC-257974 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Catalytic Hydrogenation: According to the standard procedure, the 5 wt-% Pt/Al_2O_3 catalyst (Strem Chemicals) was pre-reduced in a fixed-bed reactor by flushing with argon (50 cm^3/min) at room temperature for 3 min, followed by reductive treatment in H_2 (50 cm^3/min) at 400 °C for 2 h. After cooling to room temperature in hydrogen flow, the catalyst was flushed with argon for 30 min and was stored under air before use [BET specific surface area 95 m^2 g^{-1}, mean metal particle size 8.3 nm (XRD), dispersion 40% (H_2 chemisorption), mean catalyst particle size 18.2 μm (Malvern)]. Catalyst characterization has been described in detail previously.[14a] The reduced catalyst (100 mg for 1-phenylpropane-1,2-dione hydrogenation and 50 mg in the ethyl pyruvate case) together with a solution of the chiral modifier (3.4×10^{-5} mol in 50 mL of toluene, corresponding to 10 mg of cinchonidine) were placed in a batch reactor (Parr, 300 cm^3) and flushed with hydrogen at 1 bar for 10 min. The reactant solution (5 mmol of 1-phenylpropane-1,2-dione or 10 mmol of ethyl pyruvate in 50 mL of toluene) was saturated with hydrogen for 10 min in a separate injection chamber and injected into the reactor after which the reaction was commenced immediately by starting the agitation. The reactions were carried out under the hydrogen (AGA, 99.999%) pressure of 10 bar, reactor temperature of 15 °C and stirring rate of 2000 rpm. The initial concentrations for cinchonidine and modifiers **4a**–**c** were 3.4×10^{-4} mol·dm^{-3} (1.7×10^{-4} mol·dm^{-3} for modifier **4d**) and 0.05 mol·dm^{-3} of 1-phenylpropane-1,2-dione or 0.1 mol·dm^{-3} of ethyl pyruvate. The conversion, chemo-, and enantioselectivity of the hydrogenation products were determined with a Varian 3300 Gas Chromatograph (GC) equipped with a chiral column (β-Dex 225). Details of the analytical procedure, calibration and GC standard synthesis have been described in detail previously.[14b,25]

Definition of Selectivities: Enantiomeric excess (*ee*) is defined as ([*R*] – [*S*]) × 100/([*R*] + [*S*]):

$$ee_{(R)\text{-}1} = \frac{[(R)-1]-[(S)-1]}{[(R)-1]+[(S)-1]} \times 100\%$$

The enantiomeric excess $ee_{(RS)}$ is defined in an analogous manner using concentrations of (1*R*,2*S*) and (1*S*,2*R*). The diol selectivity S_i [e.g., (1*S*,2*R*)-diol] has been defined accordingly:

$$S_{SR} = \frac{[(1S,2R)]}{[(1S,2S)]+[(1R,2R)]+[(1R,2S)]+[(1S,2R)]} \times 100\%$$

The regioselectivity (*rs*) is given by:

$$rs = \frac{[(R)-1]+[(S)-1]}{[(R)-2]+[(S)-2]}$$

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