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Mono- and *bis*-Quinidine Organocatalysts in the Asymmetric Methanolysis of Cis-1,2,3,6-Tetrahydrophthalic Anhydride: A Conformational and Mechanistic NMR Study

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Contribution to the Carlo Rosini Special Issue

ABSTRACT The enantioselective organocatalytic methanolysis of *cis*-1,2,3,6-tetrahydrophthalic anhydride mediated by quinidine derivatives with pyridazine or anthraquinone core was investigated, carrying out a detailed nuclear magnetic resonance study of the conformational preferences of the alkaloid catalysts in the pure solvent and in the presence of the reaction substrates and products. No significant interaction between the *meso*-anhydride and the alkaloid derivatives was detected. In contrast, evidence for a considerable influence of the alcohol reactant on the conformational state of some of the chiral organocatalysts could be obtained, which lends support to the hypothesis of general-base catalysis mechanism, as opposed to the nuclephilic one. The catalytic properties of the studied derivatives showed no obvious correlation with their conformational prevalence in the resting state, suggesting that the alkaloid 9-*O* substituent should have a more active role than merely enforcing the chiral fragments to adopt a preferential reactive conformation. A strong enantioselective interaction between the enantiomers of the hemiester product and the alkaloid derivatives was also observed, leading to the conclusion that in the actual reaction conditions a relatively large fraction of the latter is in the protonated form. *Chirality 23:784–795, 2011.*

KEY WORDS: enantioselective organocatalysis; desymmetrization; Cinchona alkaloids; ring opening; conformation; nuclear magnetic resonance; chiral recognition; chiral solvating agent

INTRODUCTION

The desymmetrization of achiral *meso* substrates has emerged in the past years as a powerful tool for the preparation of nonracemic polyfunctional chiral compounds.[1,2] Amongst the many processes based on this concept, the alcoholysis of *meso*-anhydride (Scheme 1) appears remarkably convenient in terms of experimental simplicity, substrate scope, and synthetic versatility of the resulting hemiester products.[3–8]

In this context, the use of Cinchona alkaloids and their derivatives (Fig. 1)[9,10] has played a major role since the pioneering studies by Oda and Aitken's groups in the mid 80's.[11–14] Nonetheless, it was not until the turn of past century that this methodology gained a new momentum, when Bolm et al. reported the attainment of synthetically useful *ee* values by the use of an excess of methanol and 1.1 equivalents of **1a** or **1b**, under carefully optimized conditions.[15,16] The same group succeeded also in carrying out the reaction with just catalytic amounts of the chiral organocatalyst **1a**,[16] but the need of one equivalent of the expensive tertiary amine pimpedine, as an achiral auxiliary base to help keeping the catalyst in the not-protonated form, somewhat limited the usefulness of the protocol.

Nearly at the same time, Deng and coworkers gave another fundamental contribution to the field,[17] describing the organocatalytic use of some of the monomeric and dimeric alkaloid ligands originally developed for the Sharpless's osmium-mediated asymmetric dihydroxylation.[18] In particular, by using the phenanthrene and anthraquinone 9-*O* ether derivatives **3** and **4**, an effective protocol could be disclosed whose landmarks are wide substrate scope, mild reaction conditions, relatively short reaction times and, especially, the possibility of using just a limited amount (10 mol %) of the expensive alkaloid derivative in the absence of any added achiral base.

Since then several improvements followed, including the use of different alcohol nucleophiles,[19–21] modified alkaloid organocatalysts (either monofunctional[20–22] or bifunctional),[23,24] recoverable variants,[25–28] and additives.[29]

Nonetheless, most of these efforts appear largely empirically-driven because the lack of a detailed mechanistic understanding of the reaction prevents a rational approach to the design of improved catalytic systems. In this respect, it should be noted that two alternate scenarios were proposed

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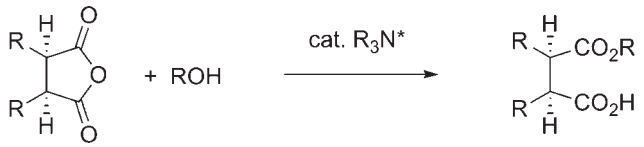


Scheme 1. Asymmetric alcoholysis of *meso*-anhydrides.

in the course of the years, where the alkaloid derivative would act either as a nucleophilic or a general-base catalyst for the alcoholysis reaction.[3,4] Both hypotheses received some degree of experimental support, with the latter preferentially credited at present as a satisfactory mechanistic rationale.[4,22,30]

As witnessed by the caution exerted in several literature contributions,[3,23,30,31] this is not to say however that a satisfactory settlement of the issue has been reached yet. In fact, even after a recent mechanistic study by Deng and coworkers on the catalytic reaction with **3–5**,[22] a number of open questions still remained. Beside the fundamental nature of the catalysis, these include how the accumulating acidic reaction product could affect the chiral base organocatalyst[3] and the specific role of the alkaloid 9-*O* substituent in determining the overall catalytic properties. This latter aspect appears particularly intriguing when one considers that the switch from the effective *mono*- e *bis*-alkaloid organocatalysts **3** and **4** to similar systems like **6–8** generally leads to a dramatic drop of the reaction enantioselectivity (13–32% *ee*),[17] whilst other apparently less related derivatives, like **9**, may still provide excellent *ee* values (87–95% *ee*).[20,22]

In consideration of our longstanding and continuing interest in the Cinchona alkaloids for supported asymmetric catalysis[32–34] and determination of enantiomer composition by chromatographic[35–40] and nuclear magnetic resonance (NMR) methods,[41–46] we were prompted to investigate further the molecular basis of the said catalytic process by exploiting the potential of NMR spectroscopy in the study of molecular recognition processes. In addition to the commercial anthraquinone ether **4**, two alkaloid pyridazine derivatives **13** and **14** were selected for this purpose, which were recently introduced by our group within the framework of a project for the development of polymer supported organocatalysts.[34] For the aims of this work, such a choice was dictated by the close relationship and not C_2-symmetric structure of **13** and **14**, which made these compounds appealing NMR probes, as well as by their lower performances with respect to **4** (*vide infra*), which could be indeed useful for clarifying the basic requirements for an effective catalyst. The results of this study are reported herein.

RESULTS

Synthesis and Characterization of the Alkaloid Derivatives

In the course of previous preparations of **11**,[34] thin layer chromatography (TLC) analysis revealed the transient presence of a less retained compound **12** that, due to its lower polarity, was likely to be one of the two possible regioisomeric *mono*-alkaloid intermediates en route to the final *bis*-alkaloid product (Scheme 2). To isolate such an intermediate and determine its actual structure, a regular preparation of **11** was stopped before complete conversion and a sample of the resulting mixture was separated by column chromatography. By these means **12** (17%) could be obtained as a TLC homogeneous fraction, alongside with the expected derivative **11** (80%). To probe the identity of the newly synthesized compound, **12** was subjected to electrospray mass spectrometry (ESI-MS) and ^{1}H NMR analyses. Both techniques confirmed the introduction of a single alkaloid unit on the pyridazine core and, in the case of the latter one, the absence of any regioisomeric product. A preliminary rotating-frame overhauser enhancement spectroscopy (ROESY) experiment revealed also the close spatial proximity of the quinoline H_1 and pyridazine H_a protons, as well as the lack of any strong dipolar interaction between the acetylenic side chain and the alkaloid moiety (for the numbering scheme, compare Fig. 2). These results are therefore consistent with the depicted structure for **12** that, unsurprisingly, may form through nucleophilic displacement of the least hindered chlorine atom of the starting compound **10**.

Even though the purified intermediates **11** and **12** could be separately converted into the final derivatives,[34] for the purposes of this work the direct reaction of their mixture proved equally effective. Indeed, after stirring the latter with an excess benzylazide, copper(I) chloride, and the MonoPhos ligand in tetrahydrofurane (THF),[47] a single chromatographic purification of the resulting crude mixture provided the new

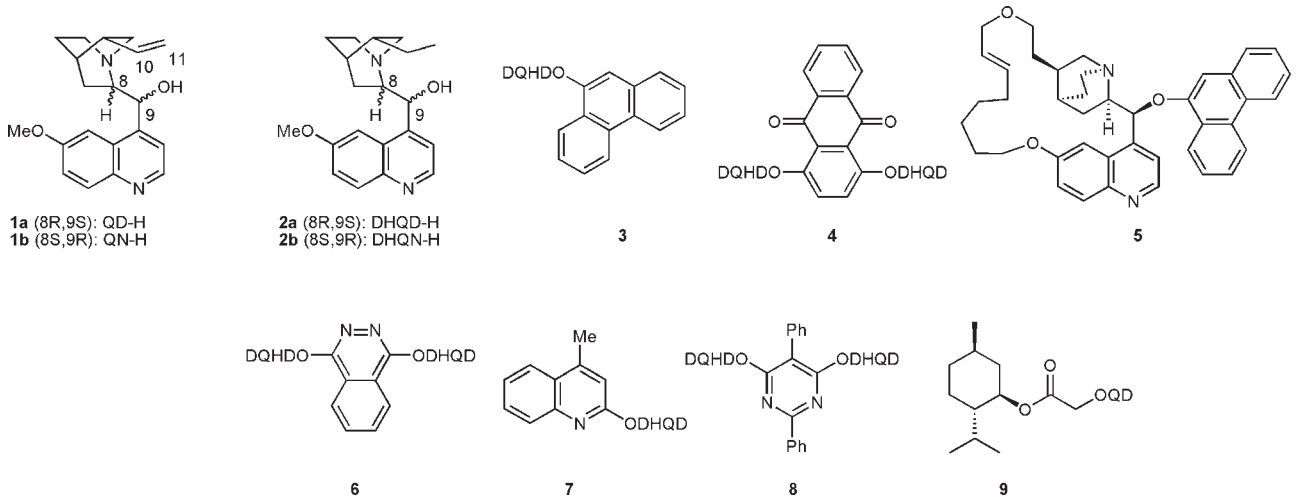


Fig. 1. Cinchona alkaloid derivatives for the asymmetric alcoholysis of *meso*-anhydrides.

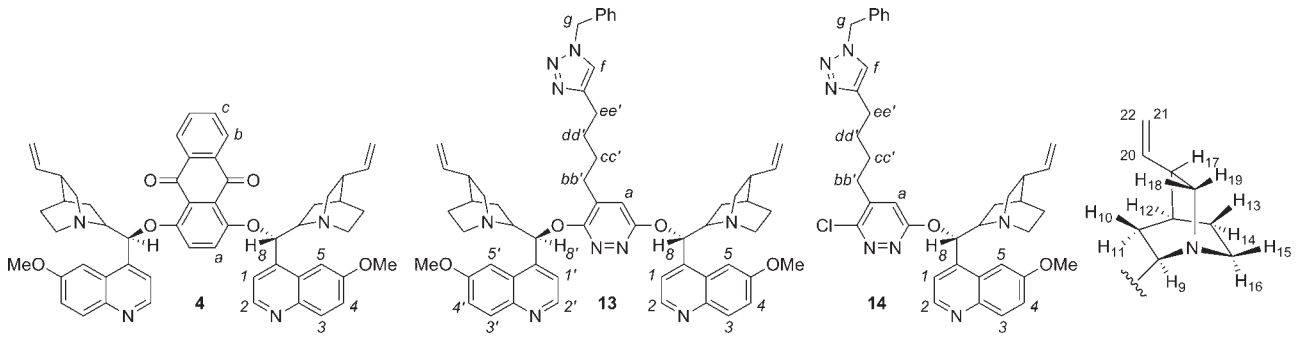


Fig. 2. Numbering schemes of the three alkaloid derivatives **4**, **13**, and **14**.

mono-alkaloid **14** and the known *bis*-alkaloid **13**,[34] in acceptable yields (~75 and 54%, respectively, based on the composition of the mixture **11** + **12**). The characterization of **14** was carried out as described for **12** and confirmed the structure of the derivative, including the substitution pattern of the pyridazine ring.

Catalysis Experiments

For testing the performances of **13** and **14**, the methanolytic desymmetrization of *cis*-1,2,3,6-tetrahydrophtalic anhydride was chosen as the benchmark (Scheme 3). The conditions were those of Deng and coworkers,[17,22] with the use of 10 mol % of the *bis*-alkaloid **13** or 20 mol % of the *mono*-alkaloid organocatalyst **14** and a fixed reaction time of 48 h. For comparison purposes runs with the commercial anthraquinone *bis*-hydroquinidyl ether **4** (10 mol %) were also carried out, providing the additional results summarized in the Table 1.

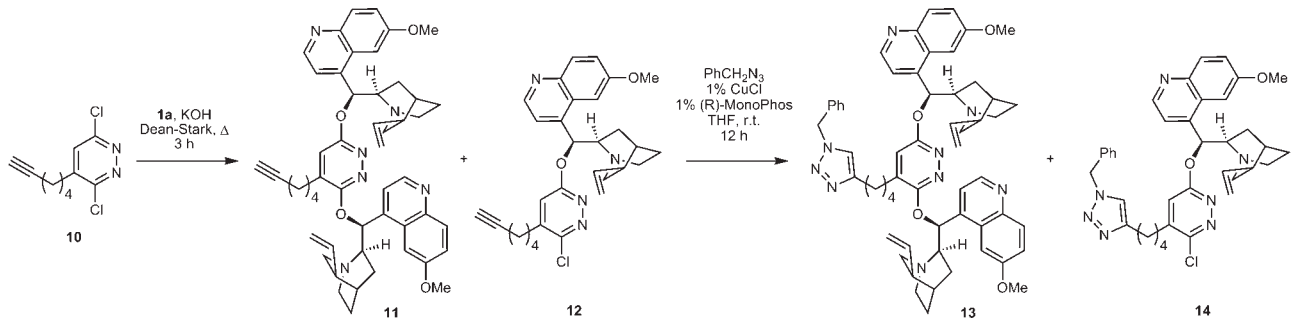
An initial solvent screening with **13** revealed a strong influence of the reaction medium on the methanolysis progress, with some notable differences in comparison with the literature derivative **4**. In fact, whilst diethyl ether and THF proved substantially superior than toluene in the reactions involving **4** (Table 1, entries 2,[17] 4, and 6), in the case of the derivative **13** only the latter solvent could afford a reasonable compromise between activity and enantioselectivity (Table 1, entries 1, 3, and 5). For this reason additional experiments were carried out in toluene, with the aim of exploring the effect of catalyst loading, the influence of the structure of the pyridazine derivative, and the rate of the background reaction.

In the first of these runs, the use of 50 mol % of **13** led to an essentially complete conversion of **15** in the standard time and a noticeable increase of the enantiomeric purity of the product **16** (Table 1, entry 7). In contrast, the use of the *mono*-alkaloid derivative **14** (20 mol %, Table 1, entry 8) afforded results which were not appreciably different from those provided by **13** at the same–alkaloid units- loading (compare Table 1, entry 5). Finally, in the absence of any organocatalyst *rac*-**16** was formed in just minute amounts after 48 h at −20°C (Table 1, entry 9).

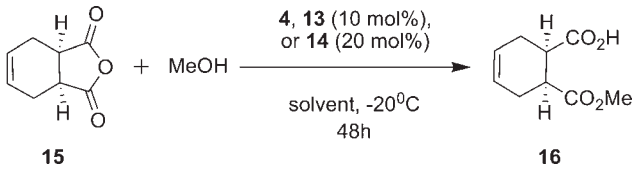
NMR Conformational Study of the Alkaloid Organocatalysts

The conformational analysis of the Cinchona alkaloids has been the subject of extensive theoretical and spectroscopic investigations during the last twenty years.[48,49] These efforts culminated in the protocol by Burgi and Baker that identified four more populated conformers for the native alkaloids, customarily named Closed(1), Closed(2), Open(3), and Open(4) (Fig. 3).[50] The Closed and Open families differ each other for the value of the dihedral angle H_8-C_9-C_8-H_9, which is ~175° for the former (corresponding to the quinuclidine nitrogen directed toward the quinoline ring) and ~78° for the latter (with an antirelationship between the quinuclidine nitrogen and the quinoline ring). Moreover, within each of the previous families the rotation around the C9-C16 bond provides the two alternate forms [e.g., Closed(1) vs. Closed(2)], which hence differ in relative orientation of the quinoline moiety. All of these conformers could be easily distinguished on the basis of the angular dependence of the vicinal coupling constant $^3J_{89}$ and the dipolar interactions originated by the protons H_8/H_9 in rotating-frame Overhauser effect (ROE) or nuclear Overhauser effect (NOE) experiments.

In the case of the derivatives **4**, **13**, and **14** the situation is further complicated by the presence of two additional degrees of freedom for each alkaloid unit, corresponding to rotations around the two bonds connecting the 9-*O* oxygen atom to the adjacent molecular fragments. Therefore, in addition to the Burgi–Baker analysis described above, the definition of the conformational features of the three chiral organocatalysts of this work required also to evaluate the



Scheme 2. Preparation of the compounds **11–14**.



Scheme 3. Asymmetric methanolysis of **15**.

orientation of each chiral unit with respect to the 9-*O* aromatic substituent. With this aim **4**, **13**, and **14** were studied by NMR, starting with the unperturbed alkaloid derivatives in pure toluene-d_8.

Preliminary variable-concentration experiments with **13** in the 5–80 mM range revealed very small variations in the chemical shift values and an essentially constant diffusion coefficient *D* of the compound, as determined by diffusion ordered spectroscopy (DOSY) experiments.[51]

The ^{1}H NMR spectrum of **13** (Fig. S1b, Supporting Information) showed distinct resonances of the two protons H_9 and $H_{9'}$ centered at 3.20 ppm/3.28 ppm, respectively.

In ROESY maps, both of them gave dipolar interactions with the respective quinoline protons (H_5/H_1 or $H_{5'}/H_{1'}$), with a slightly larger effect at the frequencies of H_1 and $H_{1'}$ (Fig. 4). Therefore, the protons H_9 and $H_{9'}$ in **13** appear to lay out of the quinoline plane with H_9 somewhat closer to H_1 than to H_5 and $H_{9'}$ closer to $H_{1'}$ than to $H_{5'}$. The ROEs H_9-H_8 and $H_{9'}$-$H_{8'}$ were significantly lower than those caused by $H_9/H_{9'}$ on the quinoline protons discussed above, indicative of the prevalence of Closed conformers. Some differences were also detected in the conformation of the two quinidine units around the respective C_8-C_9 or $C_{8'}$-$C_{9'}$ bonds, as the ROE H_9-H_8 was more intense in comparison with the $H_{9'}$-$H_{8'}$ one (compared to the respective ROEs H_9-H_1 or $H_{9'}$-$H_{1'}$). The protons $H_5/H_{5'}$ gave a very intense ROE at the frequencies of the respective protons $H_8/H_{8'}$ and no significant dipolar interaction with the other quinuclidine protons, which strongly supports the prevalence of the Closed(2) conformer.

The resonances of the protons H_8 and $H_{8'}$, which fell in a crowed spectral region, were extracted by 1D total correlation spectroscopy (TOCSY) selective perturbations at the frequencies of H_9 and $H_{9'}$, respectively (Fig. S2, Supporting Information). In this way the two vicinal coupling constants $^3J_{89}$ (5.1 Hz) and $^3J_{8'9'}$ (7.0 Hz) could be measured and correlated[52] to dihedral angles values of 130 and 140°, for H_8-C_9-C_8-H_9 and H_8-C_9-C_8-$H_{9'}$ respectively. Hence, by taking also into account the ROEs constraints discussed above, all these results appear consistent with the spatial orientation depicted in the Figure 5 where, for each alkaloid unit, the proton H_8 (or $H_{8'}$) and the pyridazine ring lay on the opposite side than the quinuclidine moiety with respect to the quinoline plane in a Closed(2) prevailing conformation. It is worth noting that the tendency to attain the closed-like state appears more pronounced for the alkaloid fragment adjacent to the achiral pyridazine side chain.

TABLE 1. Asymmetric methanolysis of 15

Entry	Cat.(mol%)	Solvent	Conversion(%)[a]	Yield(%)[b]	Ee(%)[c,d]
1	**13** (10)[e]	Et_2O	54	45	55
2	**4** (7)[f]	Et_2O	–	95	98
3	**13** (10)	THF	25	18	67
4	**4** (10)	THF	78	73	93
5	**13** (10)	Toluene	70	69	50
6	**4** (10)	Toluene	88	85	83
7	**13** (50)	Toluene	>98	~ quant.	66
8	**14** (20)	Toluene	68	66	47
9	–	Toluene	6	–	–

[a]Determined on the crude product, by ^{1}H NMR.
[b]Isolated yield after flash chromatography.
[c]By high performance liquid chromatography (HPLC) (Chiralcel OJ, 1 ml min^{-1} *n*-hexane:IPA = 95:5+0.1% trifluoroacetic acid, 210 nm).
[d]The major enantiomer of **16** had (+)−(1*R*;2*S*)configuration.[17]
[e]The catalyst was largely undissolved.
[f]From ref. 17

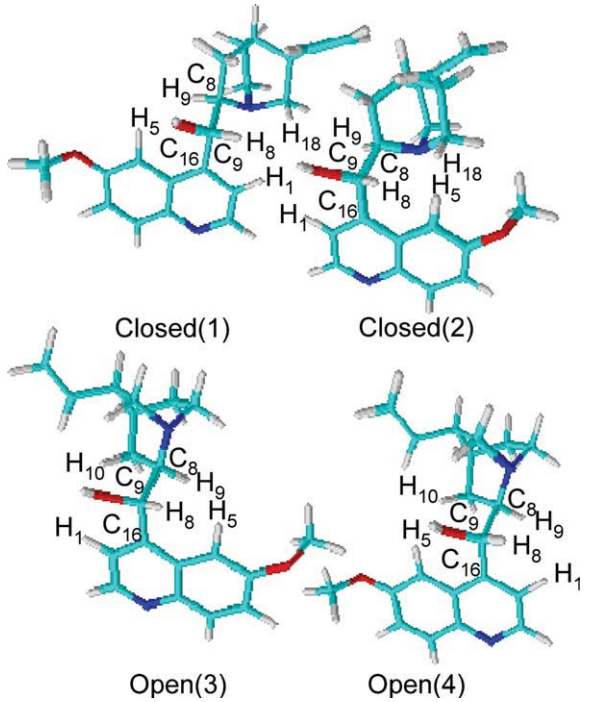


Fig. 3. The four limit conformers for quinidine (**1a**). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The relative disposition of the two quinidine units of **13** was analyzed on the basis of the four limit structures of Figure 5: two ANTI-type conformers, where the quinoline rings of the two chiral units lay in the opposite hemispaces defined by the pyridazine plane, and two SYN-type conformers, where the quinoline rings occupy the same hemispace and, therefore, face each other.

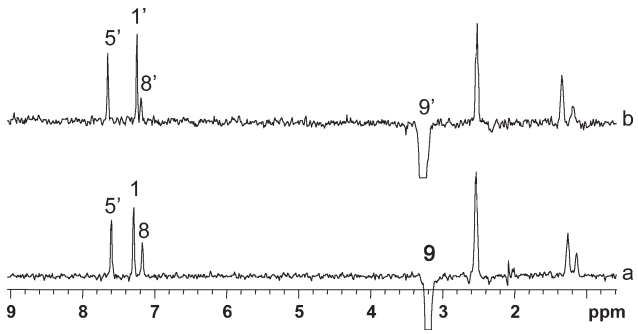


Fig. 4. 2D ROESY (600 MHz, toluene-d_8, 25°C, mix 600 ms) traces corresponding to H_9 (**a**) and $H_{9'}$ (**b**) protons of **13**.

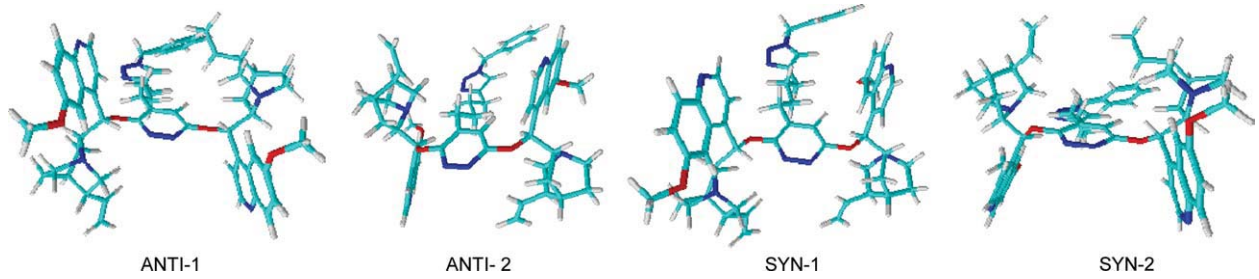


Fig. 5. Graphical representation of the four limit ANTI and SYN conformers of **13**. [Color figure can be viewed in the online issue, which is available at wiley onlinelibrary.com.]

The intense ROE effects caused by H_1 and the vinyl proton H_{20} at the frequencies of the pyridazine proton H_a and the simultaneous observation that the some selected protons of the achiral side chain gave ROEs on $H_{1'}$ of the nearby quinoline ring and not onto the methine $H_{8'}$ proton, ruled out a large contribution by SYN-1 and identified the ANTI-1 as the most populated conformer. The presence of SYN-2 as a minor conformer was detected based on the weak ROE between H_5 and H_a. Because the SYN-2 may be generated from ANTI-1 by rotation of the alkaloid fragment adjacent to H_a with respect to the rest of the molecule, these findings suggested that the chiral unit linked to the least hindered side of the pyridazine ring should experience some degree of conformational freedom.

On the contrary, no analogous dipolar interaction could be observed between the side chain protons and $H_{5'}$ of the nearby quinoline ring, indicative of an essentially locked orientation for the corresponding alkaloid residue. As it may be deduced from the Figure 5, the prevalence of ANTI-1 and SYN-2 is probably a consequence of the fact that, in these conformers, the pyridazine side chain can be accommodated in the spatial region facing $H_{1'}$ and, hence, devoid of major steric repulsions with the closest quinidine fragment.

The conformation of **14**, containing the same pyridazine group as **13** but only one quinidine unit, was similarly defined through the analysis of spatial constraints imposed by the dipolar interactions detected in the ROE spectra and by the vicinal coupling constant $^3J_{89}$ of 6.2 Hz. Hence, the large prevalence of the Closed conformer on the Open one was revealed also in this case, to a degree that was very similar to that found in the dimeric compound **13**. In the prevailing conformer of **14** the proton H_a of the pyridazine moiety pointed at the quinoline proton H_1 and the vinyl proton H_{20}, but a minor population of conformers with H_a pointing at H_5 was also detected, like in ANTI-1 and SYN-2 of **13**, respectively.

At variance with the similar pyridazine derivative **13**, discussed above, initial variable-concentration experiments with the commercial *bis*-alkaloid anthraquinone ether **4** resulted in dramatic changes in both the ^{1}H NMR spectrum and the diffusion coefficient D deduced from DOSY measurements. Both results, clearly indicative of a strong propensity of **4** to self-aggregate, appear somewhat surprising if one considers that the alkaloid derivative **4** is devoid of hydrogen-bond donor groups.[53] However, at the concentration used in the catalysis experiments (5 mM) the diffusion coefficients of **13** ($D = 4.9 \times 10^{-10}$ m^2 s^{-1}) and **4** ($D = 5.5 \times 10^{-10}$ m^2 s^{-1}) were similar, to indicate that the self-aggregation of **4** could be neglected.

In spite of the symmetry of **4**, which limited its conformational analysis to some extent, several important deductions could be made by the careful examination of NMR data. Amongst these the most relevant conclusion is the strong prevalence of Open-type conformations for this derivative, even (*vide infra*) in a solution of pure toluene. Indeed, even though the resonance of $H_{8'}$ was so large ($\Delta\nu_{1/2} = 41$ Hz, Fig. S1a Supporting Information) that $^3J_{89}$ could not be measured, the observation of ROE effects between H_9-H_5 and H_9-H_8 remarkably stronger than for H_9-H_1 proved particularly informative, as they could place the H_8 and H_9 protons in close proximity of H_5 and hence identify an Open(3) conformation.

In contrast, the ROEs originated by the protons H_a, H_8, H_5 and the CH_3 of the ethyl group on the quinuclidine moiety were quite diagnostic regarding the orientation of the anthraquinone moiety. Amongst them, the very large ROE H_8-H_a could well originate from the ANTI structure of Figure 6, with the H_8 protons of both quinidine moieties bent at the corresponding H_a position. Furthermore dipolar interactions between the proton H_b of the antraquinone moiety and the ethyl group on the quinuclidine cage were detected, which strengthen the above conclusions.

Organocatalyst-Reactants Interaction

Given the strong influence of the solvent polarity on the conformational prevalence of Cinchona alkaloids[48,49] and to gain details about the reaction mechanism, toluene-d_8 solutions containing **4**, **13**, or **14** and the anhydride **15** or MeOH were investigated next.

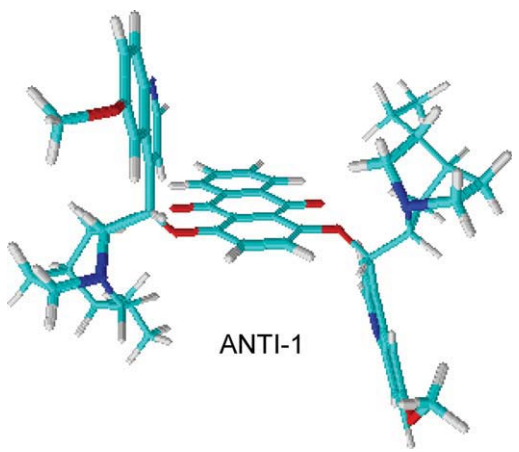


Fig. 6. Graphical representation of the ANTI-1 conformer of **4**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

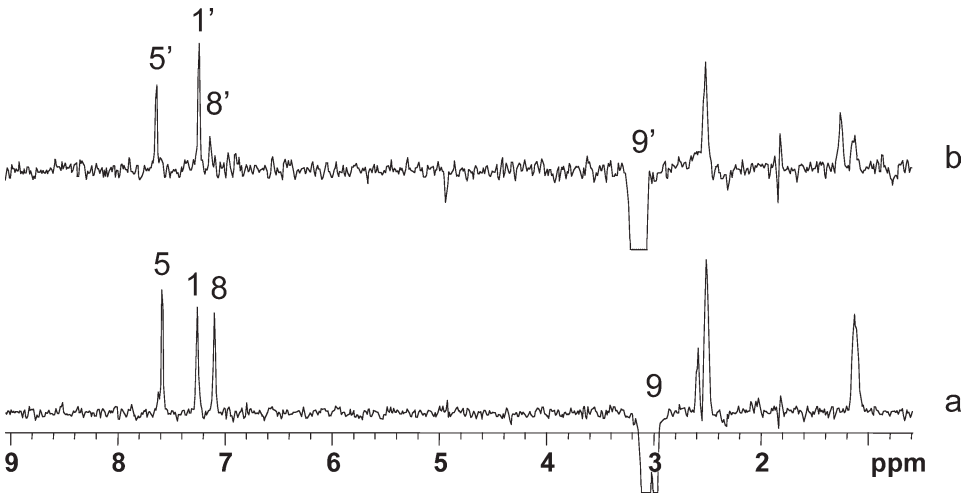


Fig. 7. 2D ROESY (600 MHz, toluene-d_8, 25°C, mix 600 ms) traces corresponding to H_9 (**a**) and $H_{9'}$ (**b**) protons of **13** in the presence of CD_3OD (500 mM).

In general, no significant interaction between the alkaloid derivatives (5 mM) and the anhydride substrate (5–50 mM) could be evidenced by these experiments, as deduced from the lack of relevant intermolecular dipolar interaction in the ROESY spectra and the observation of a diffusion coefficient for **15** in the mixtures that proved identical to that of the pure compound in toluene-d_8 alone ($D_{\mathbf{15}} = 15.0 \times 10^{-10}$ m^2 s^{-1}). Furthermore, any significant complexation-induced shift was not detected in the mixtures with respect to the pure anhydride.

Similarly, the addition of small amounts of MeOH (5 mM) to the chiral derivatives (5 mM) caused no obvious differences with respect to the separate components, either in terms of the diffusion coefficient of the alcohol ($D_{\mathrm{MeOH}} = 31.0 \times 10^{-10}$ m^2 s^{-1}) or for what it concerns the conformers population of the alkaloid organocatalysts. This latter aspect was studied in detail for **13**, where the quantitative analysis of the relevant intramolecular ROE effects provided the same large preference for the Closed(2) form of each alkaloid residues and an identical relative weight of the ANTI-1 and SYN-2 conformers as observed before in the pure solvent.

However, when the alcohol concentration was raised to the level of the actual catalysis experiments (500 mM, in this case added as its d_4 deuterated form) some significant changes in the spectral features of **4**, **13**, and **14** could be seen. Several protons resonances were shifted in the NMR spectra and, in the case of **13**, the presence of a large excess of MeOH-d_4 led also to the enhancement of the dipolar interaction between the protons H_9 and H_8, as demonstrated by the much stronger ROE between them (Fig. 7) in comparison with the sample in pure toluene-d_8 (Fig. 4). In view of the previous discussion this fact was clearly indicative of a reduction of the H_8-C_9-C_8-H_9 dihedral angle, as confirmed also by the analysis of additional ROEs. Hence these results unequivocally demonstrated that, for the alkaloid residue on the least hindered side of **13**, the population of the Open(3) conformer increases remarkably in the presence of MeOH-d_4 at the expenses of the Closed(2) one.

In contrast, no significant enhancement of the $H_{9'}$-$H_{8'}$ dipolar interaction or change in the relative intensities of the H_a-H_1 and H_a-H_8 ones could be detected under these conditions. The former results clearly points to a much lower propensity of the second alkaloid unit of **13** to undergo the alcohol-induced Closed to Open swap discussed above, probably because of the repulsive steric interaction that would ensue between the quinuclidine cage and the achiral side chain on the pyridazine ring. Similarly, the latter result suggests that the ANTI-1 to SYN-2 population ratio was essentially unaffected by the presence of the alcohol. Interestingly, all these conclusions were also confirmed for a sample of **13** in neat MeOH-d_4.

The *mono*-alkaloid derivative **14** showed features similar to the least hindered half of the compound **13**. In particular, the addition of a large excess of MeOH-d_4 (500 mM) caused the increase of the population of the Open(3) conformer at the expense of the Closed(2) one, as detected for example by the increase of the H_9-H_8 and H_9-H_5 ROEs relative to the H_9-H_1 one. Moreover, much as for **13** the orientation of the pyridazine ring with respect to the quinidine structure was not affected significantly by the change in solvent composition.

Finally, in the presence of an excess of the alcohol (500 mM) the anthraquinone derivative **4** showed the anticipated shift of several of the alkaloid's resonances (Table 2) but no relevant sign of conformational modifications. In this respect, it is worth noting that even the ROESY spectra of **4** in neat MeOH-d_4 retained the main features discussed above

TABLE 2. Chemical shift (600 MHz, 25°C) variations ($\Delta\delta = \delta_1 - \delta_2$, ppm) of selected resonances of 4 (5 mM, toluene d_8) in the presence (500 mM, δ_1) and in the absence (δ_2) of methanol

Proton	Δδ
1	0.16
2	−0.14
3	−0.03
4	0.05
5	−0.03
OMe	0.16
8	0.36
9	−0.13
15	−0.09
16	−0.04
18	0.15
19	−0.12

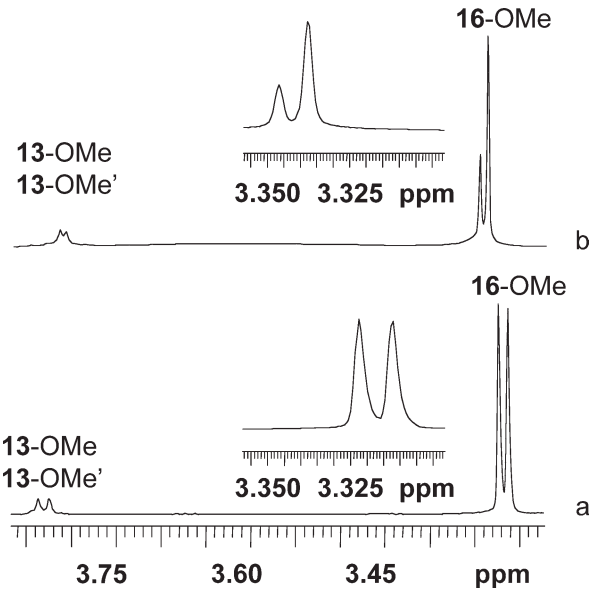


Fig. 8. ^{1}H NMR (600 MHz, toluene-d_8, 25°C) spectra of **13** (5 mM)/*rac*-**16** (50 mM) (**a**) and at the end of the methanolysis of **15** (50 mM) with MeOH (250 mM) (**b**).

for the sample in toluene-d_8, thus witnessing the substantial preservation of the preferential *bis*-alkaloid Open(3)-ANTI arrangement in spite of the large differences in the polarity of the medium.

Reaction Monitoring and Organocatalyst-Product Interaction

To explore in more detail the reaction under exam, the progress of the methanolysis of **15** in the presence of the organocatalysts **4** or **13** was followed by NMR. With this aim the runs were carried out in toluene-d_8 at 25°C with 10 mol % of the alkaloid derivative and 5 equivalents of MeOH, monitoring the disappearance of the olefinic signals of the substrate **15** and the growth of the corresponding resonances of the product **16**. These experiments revealed that under these conditions the methanolysis proceeded much faster than in the regular runs at −20°C (Table 1) and led to the complete conversion of **15** in less than 20 h. Nonetheless, a clear difference of catalytic performances between the two alkaloid derivatives was maintained here too, both in terms of activity and enantioselectivity. The former conclusion is proved by the half-lives of the substrate **15** in the reaction mixtures containing **4** or **13**, which resulted $t_{1/2} \sim 20$ and ~ 80 min, respectively. Similarly, the greater asymmetric induction of **4** *vs.* **13** (Table 1, entries 5 and 6) was also preserved under these conditions, eventually leading to the product (+)-(1*R*; 2*S*)-**16** with 80 and 42% *ee*, respectively.

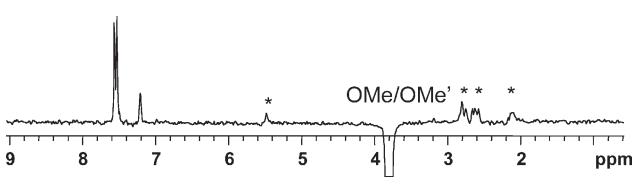


Fig. 9. 2D ROESY (600 MHz, toluene-d_8, 25°C, mix 600 ms) trace corresponding to OMe/OMe' protons of **13** (5 mM) at the end of the methanolysis of **15** (50 mM) with CD_3OD (500 mM). *Resonances of **16**.

In view of its possible relevance for the understanding of the reaction mechanism, the interaction between the alkaloid organocatalysts and the reaction products was finally investigated. In this respect, it is interesting to note that in the course of the kinetic measurements all of the recorded spectra showed a noticeable splitting of most of the product's resonances. This fact was clearly indicative of a chiral recognition phenomenon, probably related to the ability of the Cinchona alkaloid derivatives to act as NMR chiral solvating agents toward suitable chiral substances.[41–46,54–56] Control experiments with *rac*-**16** (50 mM) and either **4** or **13** (5 mM) in toluene-d_8, confirmed this hypothesis, showing that even such a small concentration of the alkaloid derivatives was sufficient for inducing a rather large anisochrony in most of the protons of the enantiomers of **16** (e.g., $\Delta\delta$ = 0.011 ppm for the methoxy groups of *rac*-**16** in the presence of **13**, Fig. 8a). This effect was largely preserved even in the presence of an excess of MeOH (250 mM) (Fig. 8b) thereby suggesting that a quite strong interaction between the acidic products and the alkaloid catalyst could arise under the actual methanolysis conditions.

To strengthen this conclusion DOSY and ROESY measurements were carried out during the reaction progress and on the final mixtures. The DOSY experiments confirmed a considerable degree of interaction between the enantiomers of **16** and the chiral organocatalysts, as demonstrated by the fairly large reduction of the diffusion coefficient of the former ($D_{\mathbf{16}} = 6.8 \times 10^{-10}$ m^2 s^{-1} at 22% conversion) with respect to the free racemic product in neat toluene-d_8 ($D^f_{\mathbf{16}} = 9.0 \times 10^{-10}$ m^2 s^{-1}). Interestingly, under these conditions the interaction proved somewhat enantioselective, with the major (1*R*; 2*S*)-**16** enantiomer retarded slightly less than the (1*S*; 2*R*)-**16** minor one ($\Delta D = D_{(1R;\ 2S)\text{-}\mathbf{16}} - D_{(1S;\ 2R)\text{-}\mathbf{16}} = 0.4 \times 10^{-10}$ m^2 s^{-1}).

Further information came from the ROESY maps, where several cross-peaks connecting the protons of the enantiomers of **16** and those of the chiral organocatalysts could be clearly seen. As an example, the methoxy protons of **13** produced relevant dipolar interactions with the olefinic and methine/methylene protons of **16** (Fig. 9).

For what it concerns the former component, it is worth noting that the nuclei responsible of the observed intermolecular dipolar interactions were mainly situated in proximity of the edge between the quinoline and quinuclidine moiety. Therefore, a rather specific docking between the acidic products and the alkaloid organocatalysts appears to take place in

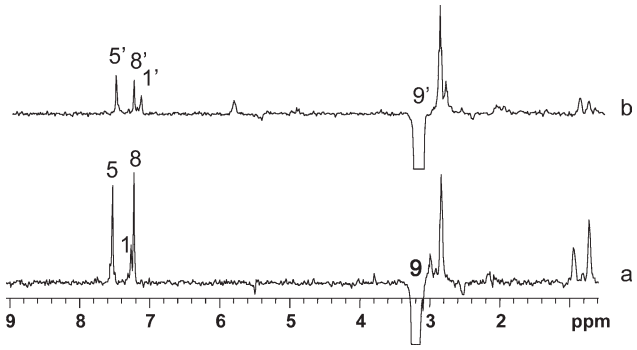
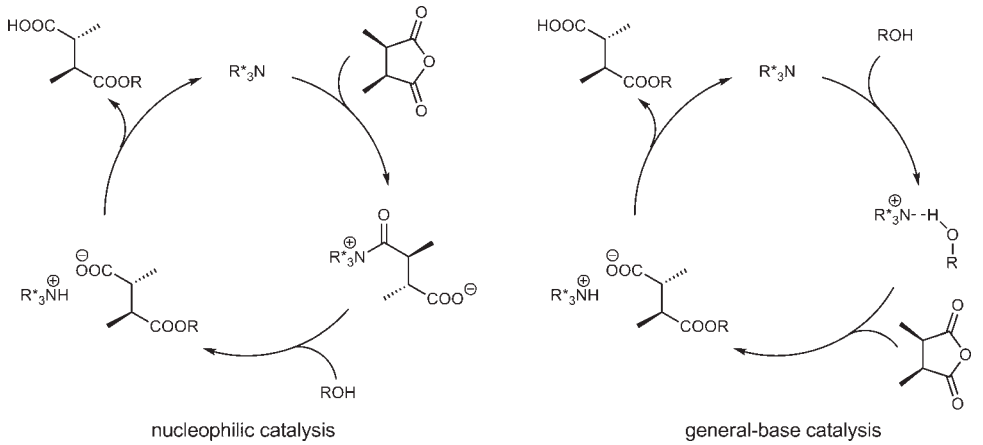


Fig. 10. 2D ROESY (600 MHz, toluene-d_8, 25°C, mix 600 ms) traces corresponding to H_9 (**a**) and $H_{9'}$ (**b**) protons of **13** (5 mM) at the end of the methanolysis of **15** (50 mM) with CD_3OD (500 mM).



Scheme 4. Nucleophilic and general-base catalysis mechanisms.

the systems under exam, possibly as a consequence of the formation of a tight ion-pair resulting from the proton transfer between **16** and the most basic sites of **4** and **13**. Interestingly, this latter hypothesis was indirectly supported by the analysis of intramolecular ROE effects of the *bis*-alkaloid pyridazine derivative **13** in the final reaction mixture (Fig. 10). At variance with the unperturbed derivative, where the most hindered alkaloid unit remains in the Closed(2) arrangement even in neat MeOH-d_4 (*vide supra*), in the presence of an excess of **16** both chiral fragments appeared to attain a fully Open(3) conformation as clearly witnessed by the very large prevalence of the ROEs $H_{9(9')}$-$H_{5(5')}$ or $H_{9(9')}$-$H_{8(8')}$ on the ROE $H_{9(9')}$-$H_{1(1')}$. This result has been previously related to the involvement of the quinuclidine nitrogen atom as complexation site.[55]

DISCUSSION

As anticipated in the Introduction, the two alternate mechanisms contrasted in the Scheme 4 can be considered for the alcoholysis of *meso* anhydrides.[3,4]

The nucleophylic catalysis mechanism looks particularly appealing as the formation of an acylamonium intermediate would involve the anhydride itself as the primary site of molecular recognition by the alkaloid.[13,14,16] However, direct clues in favor of this hypothesis appear limited to the mass-spectrometric detection of an anhydride-**1a** adduct, by Carloni and coworkers,[25] which unfortunately could prove neither the structure of such an intermediate nor its actual placement on the catalytic cycle pathway.

In contrast, a somewhat larger body of evidence has been provided in the course of the years for the alternate general-base catalysis explanation. Besides the comparison with model systems,[3] as well as theoretical calculations (albeit for a rather different chiral organocatalyst),[30] this include the detection by Oda and coworkers of large kinetic isotopic effects (k_{MeOH}/k_{MeOD} = 2.3)[11,12] in the methanolysis of *cis*-2,4-dimethylglutaric anhydride catalyzed by cinchonine.[11,12] Because the magnitude of the latter effect appeares incompatibile with a nucleophilic catalysis mechanism, this result has long been considered a particularly stringent proof in support of the general-base one.

However, in the recent study by Deng and coworkers susbtantially attenuated rate differences were observed for the methanolysis of *cis*-2,3-dimethylsuccinic anhydride in the presence of **3** or **4** (k_{MeOH}/k_{MeOD} = 1.4 and 1.8, respectively).[22] Moreover, to the best of our knowledge, no specific effort has been reported in the literature for probing the interaction between the alkaloid organocatalyst and the nucleophilic alcohol, implied by the general-base mechanistic scheme.

From this point of view, the DOSY- and ROE-based experiments discussed in the previous section also failed to detect the presence of defined molecular aggregates involving either the anhydride **15** or MeOH and the chiral organocatalysts **4**, **13**, or **14**. Therefore, it may be estimated that if any complex is formed between the reaction partners and alkaloid derivatives (e.g., of the kind depicted in the Deng's study)[22] the corresponding equilibrium constant should be lower than about 1–10 mM^{-1}.[57] Nonetheless, the observation of large shifts of the resonances of **4**, **13**, and **14** only in the presence of an excess of MeOH-d_4 (100 equiv.), but not of the anhydride **15** (10 equiv.), appears indicative of a much stronger interaction involving the former. Although this result could be partially ascribed to the larger amount of the alcohol reagent, it has to be pointed out that the effect is undoubtedly specific for what it concerns the site of interaction (apparently the quinuclidine sites of **4**, **13**, and **14**) and significant in terms of its magnitude (see, e.g., Table 2). In this respect it is worth noting that, while in the case of the least hindered alkaloid units of the pyridazine derivatives **13** and **14** the observed Closed-to-Open transition could largely contribute to the chemical shift variations, analogous effects are displayed also by the locked chiral unit of **13** and by the anthraquinone derivative **4**, which appear not to undergo any significant conformational change.

As anticipated, this latter aspect constitutes a second relevant proof of the substantial interaction between the alcohol and the alkaloid derivatives **13** and **14** under the actual reaction conditions. In fact, the stabilization of the Open conformers of Cinchona alkaloids in polar protic solvents has been already reported[48,49] and is confirmed, for the pyridazine derivatives of this work, by the results obtained in neat MeOH-d_4. Nonetheless, a comparison of the different behavior of the two chiral units of **13** seems worthwhile because it demonstrates that minute amounts of the alcohol (~2% v/v) in the actual methanolysis mixtures may have, or not, a profound influence on the (resting state of) chiral organocatalysts, as a function of even subtle differences in the structure of the 9-*O* substituent.

This observation naturally leads to another intriguing aspect of the reaction under exam, i.e., the role of the latter group in determining the alkaloid catalytic properties. In the recent contribution by Deng and coworkers, a detailed study of the designed rigid derivative **5** led to the conclusion that an *app*-closed conformation (Closed(2) in the Burgi–Baker notation)[50] is well suited for catalyzing the asymmetric methanolysis of *cis*-2,3-dimethylsuccinic anhydride (93% *ee*).[22] Moreover, on the basis of the similar result afforded by **3** (96% *ee*) the inference was also made that the common unconstrained analogs, for which all the four major conformers were detected in solution by NMR, adopts the same *app*-closed arrangement when mediating the highly enantioselective methanolysis of *meso* anhydrides. On this ground, a model was eventually worked out that, on the assumption of general-base type of mechanism, could nicely explain the asymmetric induction sense and other experimental features of the reaction.[22] However, in this rationalization the role of alkaloid's 9-*O* substituent was deemed to be limited to the enforcement of the *app*-closed conformation in virtue of its bulkiness, a conclusion that appears difficult to reconcile with the findings of the present work.

As described in the previous section, **13** and **14** resulted less effective than the commercial organocatalyst **4** (Table 1, entries 5, 6, and 8), although they could surprisingly induce substantially higher *ee* values than the related phthalazine *bis*-hydroquinidyl ether **6** (which affords 18% *ee* in the reaction of *cis*-2,3-dimethylsuccinic anhydride).[17] Interestingly, considerable differences were observed in terms of both reaction rate and enantioselectivity, to witness once again the influence of the 9-*O* substituent on the overall catalytic properties of the alkaloid derivatives. In principle, the two effects could be related each other because when the activity of the chiral organocatalyst is low the uncatalyzed (background) process tends to afford a higher amount of racemic product, in relative terms. However, the observation of a very limited anhydride conversion in the standard run without any catalyst (Table 1, entry 9) rules out such an explanation and points therefore to the differences in the intrinsic chiral discrimination ability of the various derivatives as the more likely reason of the observed enantioselectivity changes.

In this context, the comparison of the results presented in the previous section with the conclusion of the Deng's study leads to a rather paradoxical situation. In fact, in view of the NMR results discussed above the alkaloid units of **4** and **14** exist predominantly in the Open(3) conformation in solution (or easily attain it, in the presence of MeOH), whilst the derivative **13** is the only one that presents one quinidine residue in the expectedly optimal Closed(2) arrangement, already in the resting state. If the adoption of a Closed(2) conformation were sufficient, per se, for optimal catalytic performances, the prediction could then be made that **13** would be the best organocatalyst of the series investigated herein. In contrast, the experimental results unequivocally demonstrated that **13** was not only considerably less active and enantioselective of **4**, but also substantially equivalent to the *mono*-alkaloid derivative **14** that is devoid of the persistent Closed(2) unit.

This latter comparison appears particularly important as it provides a kind of internal consistency proof for the previous reasoning. In fact, even if the demonstrated conformational flexibility of the alkaloid systems does not allow us to exclude that a minor, yet much more active, Closed(2) conformer was responsible for the observed catalysis, even for **4** and **14**, the lack of a significant performance differential between **13** and the latter derivative clearly tends to militate against this hypothesis.

Finally, the interaction between the alkaloid organocatalysts and the reaction products deserves a brief comment. As noted by Spivey and Andrews,[3] one of the striking features of the catalytic protocol by Deng and coworkers is the possibility of attaining high conversions and *ee* values without the need of adding an achiral base for scavenging the acidic hemiester product. To explain this remarkable result, two hypotheses were put forward: (i) the possibility that both protonated and unprotonated forms of the alkaloid derivative can mediate the enantioselective alcoholysis reaction or (ii) that the equilibrium concentration of the latter is sufficient for the catalysis. Even if the former suggestion appears very stimulating, also in view of recent studies on the effect of achiral acidic additives,[29] it stands against the long-established limited effectiveness of the alkaloid salts.[3,13] Concerning the alternate possibility, the same authors made the provoking suggestion that in toluene the unprotonated alkaloid could be the major species at equilibrium, due to the plausible higher acidity of R_3NH^+ with respect to RCO_2H in such an apolar solvent.[3] Although in the present work no specific attempt was made to determine the stoichiometry or the equilibrium constant of the observed adducts between the enantiomers of **16** and either **4** or **13**, the dramatic changes in the spectra of the alkaloid derivatives in the presence of an excess of the product tend to suggest a substantial degree of protonation of the former. In this regard, it is interesting to note that preliminary heterogeneous catalysis experiments, with the polystyrene-supported analog of **13**[34] in toluene, demonstrated also the propensity of the immobilized alkaloid derivative to scavenge a large fraction of the product (34%) at the end of the reaction. The latter was released only by treatment with an excess of diethylamine in toluene.

From this point of view, the considerably better results attained on rising the loading of the organocatalyst **13** from 10 to 50 mol % (Table 1, entries 5 and 7) appear totally anticipated. Given the evidence discussed above, most notably its enantioselective nature, this phenomenon is likely to involve the basic catalytic sites in the alkaloid structures, i.e., the quinuclidine nitrogen atoms.

MATERIALS AND METHODS

All the reactions involving sensitive compounds were carried out under dry nitrogen, in flame-dried glassware. Before the use, toluene, CH_2Cl_2, and MeOH were freshly distilled under dry nitrogen from the proper drying agent. 3,6-Dichloro-4-(hex-5-yn-1-yl)pyridazine (**10**) was prepared as described.[34] The other compounds were commercially available and used as received. Quinidine (**1a**, Aldrich) contained about 5% of hydroquinidine (**2a**) by ^{1}H NMR. HPLC analyses were carried out on a Jasco PU-1580 chromatograph, equipped with an UV-1575 detector. Optical rotation was measured as solutions in 1-dm cells at the sodium D line, using a Jasco DIP360 polarimeter.

NMR measurements were performed on a spectrometer operating at 600 MHz for ^{1}H. The temperature was controlled to $\pm 0.1^\circ$C. The 2D NMR spectra were obtained by using standard sequences with the minimum spectral width required. Proton 2D gradient correlated spectroscopy (gCOSY) spectra were recorded with 256 increments of 4 scans and 2K data points. The relaxation delay was 2 s. 2D TOCSY spectra were recorded by employing a mixing time of 80 ms. The pulse delay was maintained at 1 s; 256 increments of four scans and 2K data points each were collected. The 2D ROESY experiments were performed in the

phase-sensitive mode, by employing a mixing time of 0.6/0.3 s. The pulse delay was maintained at 1 s; 256 increments of 16 scans and 2K data points each were collected. Proton 1D TOCSY spectra were recorded using selective pulses generated by means of the Varian Pandora Software. The selective 1D TOCSY spectra were acquired with 256 scans in 32-K data points with a 1 s relaxation delay and a mixing time of 80 ms. The gradient $^{1}H,^{13}C$ gradient heteronuclear single quantum correlation (gHSQC) and gradient heteronuclear multiple bond correlation (gHMBC) spectra were recorded with 256 or 128 time increments of 24 scans. The gradient HMBC experiments were optimized for a long-range ^{1}H-^{13}C coupling constant of 8 Hz and a delay period of 3.5 ms for suppression of one-bond correlation signals. No decoupling was used during the acquisition. DOSY experiments were carried out by using a stimulated echo sequence with self-compensating gradient schemes, a spectral width of 6400 Hz and 64 K data points. Typically, a value of 50 ms was used for Δ, 2.0 ms for δ, and g was varied in 20 steps of four transients each to obtain an ~90–95% decrease in the resonance intensity at the largest gradient amplitudes. The baselines of all arrayed spectra were corrected before processing the data. After data acquisition, each FID was apodized with 1.0-Hz line broadening and Fourier transformed. The data were processed with the DOSY macro (involving the determination of the resonance heights of all the signals above a pre-established threshold and the fitting of the decay curve for each resonance to a Gaussian function) to obtain pseudo two-dimensional spectra with NMR chemical shifts along one axis and calculated diffusion coefficients along the other.

4-(Hex-5-yn-1-yl)-3,6-bis(9-O-quinidinyl)pyridazine (11) and 6-Chloro-4-(Hex-5-yn-1-yl)-3-(9-O-quinidinyl)pyridazine (12)

A 500-ml three-necked flask, fitted with a Dean–Stark apparatus, was charged under nitrogen with **10** (3.09 g, 13.5 mmol), **1a** (8.76 g, 27.0 mmol, 2 equiv.), KOH pellets (1.55 g, 27.6 mmol, 2.05 equiv.), and toluene (225 ml). The mixture was refluxed for 3 h with azeotropic removal of water, cooled to room temperature, and then treated with water (150 ml). The organic components were extracted with Et_2O (3 × 150 ml) and the organic phases were washed with brine (3 × 75 ml). After drying (Na_2SO_4) the volatiles were removed with a rotary evaporator to give a brownish solid foam (10.1 g) that was directly used in the next step. For characterization purposes, a sample of the crude product (0.450 g) was subjected to flash chromatography (SiO_2, AcOEt:MeOH = 7:3 + 0.5% Et_2NH) to give **12** (0.053 g, 17%) and **11** (0.386 g, 80%)[34] as a colorless solid foams. The chromatographic and spectral properties of **11** were identical to the previously reported ones.[34] For **12**: TLC R_f = 0.75 (SiO_2, AcOEt : MeOH = 7 : 3 + 0.5% Et_2NH). ^{1}H NMR (600 MHz, $CDCl_3$), 25°C, δ = 8.66 (1H, d, J = 4.6 Hz); 7.98 (1H, d, J = 6.7 Hz); 7.52 (1H, d, J = 2.6 Hz); 7.37 (1H, d, J = 4.6 Hz); 7.35 (1H, dd, J_a = 6.7 Hz, J_b = 2.6 Hz); 7.11 (1H, d, J_a = 4.4 Hz); 6.91 (1H, s); 6.05 (1H, ddd, J_a = 17.4 Hz, J_b = 10.4 Hz, J_c = 7.3 Hz); 5.12 (1H, ddd,); 5.09 (1H, ddd, J_a = 17.4 Hz, $J_{b=c}$ = 1.6 Hz); 3.97 (3H, s); 3.39 (1H, m); 3.06 (1H, m); 2.95 (1H, m); 2.86 (1H, m); 2.78 (1H, m); 2.65 (2H, m); 2.27 (1H, m); 2.25 (2H, m); 2.06 (1H, m); 1.97 (1H, t, $J_{a=b}$ = 2.7 Hz); 1.84 (1H, m); 1.76 (2H, m); 1.61 (2H, m); 1.60–1.58 (2H, m); 1.54 (1H, m). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 163.7; 157.9; 152.6; 147.3; 144.7; 144.3; 143.6; 140.3; 131.7; 127.2; 121.9; 118.5; 118.1; 114.9; 101.7; 83.6; 76.5; 69.0; 59.7; 55.7; 49.9; 49.3; 39.7; 31.9; 27.9; 27.7; 26.7; 26.6; 23.1; 18.1. MS (ESI^+) m/z = 517.3 [M+H$^+$]. $[\alpha]_D^{25}$ = −85.7 (c = 1.28, CH_2Cl_2).

4-(4-(1-Benzyl-1H-1,2,3-triazol-4-yl)butyl)-3,6-bis(9-O-quinidinyl)pyridazine (13) and 4-(4-(1-benzyl-1H-1,2,3-triazol-4-yl)butyl)-6-chloro-3-(9-O-quinidinyl)pyridazine (14)

A 25-ml Schlenk tube was charged under dry nitrogen with the crude mixture of **11** and **12** (1.00 g, ~1.1 and 0.23 mmol, respectively), benzyl azide (0.33 g, 2.4 mmol), CuCl (0.0013 g, 13 μmol, ~1 mol %), (R)-MonoPhos (0.0048 g, 13 μmol, 1 mol %) and THF (11 ml). After stirring overnight at r.t., the solution was concentrated with a rotary evaporator and the dark residue (1.123 g) subjected to flash chromatography (SiO_2, AcOEt : MeOH = 8 : 2 + 0.5% Et_2NH) to give **14** (0.112 g, ~75%) and **13** (0.556 g, ~54%) as colorless solid foams. The chromatographic and spectral properties of **13** were identical to the previously reported ones.[34] For **14**: TLC R_f = 0.53 (SiO_2, AcOEt : MeOH = 8 : 2 + 0.5% Et_2NH). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.65 (1H, d, J = 4.50 Hz); 7.97 (1H, d, J = 9.21 Hz) ; 7.52 (1H, d, J = 2.44 Hz); 7.40–7.29 (5H, m); 7.27–7.17 (2H, m); 7.13–7.04 (1H, m); 6.89 (1H, s); 6.05 (1H, ddd, J_a = 17.32, J_b = 10.45, J_c = 7.24 Hz); 5.46 (2H, s); 5.14–5.03 (2H, m); 3.95 (3H, s); 3.51–3.32 (1H, m); 3.11–2.78 (4H, m); 2.78–2.67 (3H, m); 2.63 (1H t, J = 7.38 Hz,) 2.63 (1H, m); 2.28 (1H, q, $J_{a=b}$ = 7.66 Hz, J_c = 7.48 Hz); 2.03 (1H,dd, J_a = 12.52 Hz, J_b = 9.43 Hz); 1.89–1.79 (1H, m), 1.79–1.62 (4H, m), 1.62–1.52 (3H, m); 1.35–1.15 (1H, m). ^{13}C NMR (75 MHz,$CDCl_3$) δ = 163.80, 157.92, 152.54, 147.84, 147.32, 144.69, 144.48, 143.81, 140.39, 134.86, 131.68, 129.09, 128.69, 127.99, 127.21, 121.91, 120.71, 118.30, 114.94, 101.69, 77.58, 77.15, 76.73, 59.74, 55.77, 54.06, 49.97, 49.40, 39.76, 32.24, 28.92, 27.96, 27.33, 26.42, 25.29, 23.40, 23.40. MS (ESI^+) m/z = 651.3 [M+H$^+$]. $[\alpha]_D^{25}$ = −77.6 (c = 0.75, CH_2Cl_2).

(+)-(1R, 2S)-6-(Methoxycarbonyl)cyclohex-4-enecarboxylic Acid by the Asymmetric Methanolysis of cis-1,2,3,6-tetrahydrophthalic Anhydride. General procedure

A 25-ml Schlenk tube was charged under dry nitrogen with the alkaloid catalyst **4**, **13**, or **14** (for the exact amounts see Table 1) and **15** (0.0761 g, 0.50 mmol). After cooling to −20°C, the dry solvent (10 ml) was added and the mixture was kept stirring for 15 min, whereupon the complete dissolution of the solids was generally observed. Dry MeOH (202 μL, 5 mmol, and 10 equiv.) was added and the resulting solution was stirred at the same temperature for 48 h. The reaction was quenched by adding 2N HCl (4 ml) and, after separation of the layers, the organic one was washed with a second portion of 2N HCl (4 ml). The aqueous washings were back-extracted with AcOEt (2 × 5 ml) and the combined organic phases dried (Na_2SO_4). The volatiles were removed with a rotary evaporator, and the reaction conversion was determined by ^{1}H NMR of the residue. The crude product was then purified by flash chromatography (SiO_2, pet. ether:AcOEt = 3:1 + 0.5% trifluoroacetic acid) to give (+)-(1*R*; 2*S*)-**16** as a viscous oil that solidified on standing. The absolute configuration of the product was confirmed by comparing its optical rotatory power with the literature value.[17] After dissolution in *iso*-propyl alcohol (IPA, 0.1 ml), the enantiomeric composition of the sample was determined by HPLC analysis (210 nm, Daicel Chiralcel OJ, 1 ml min^{-1} *n*-hexane:IPA = 95:5+0.1% trifluoroacetic acid): t_R[(1*R*; 2*S*)-**16**] = 10.7 min; t_R[(1*S*; 2*R*)-**16**] = 16.2 min.

CONCLUSIONS

In summary, several features of the enantioselective methanolysis of *meso*-anhydrides mediated by three quinidine derivatives were explored by combining organocatalyst variation, catalytic desymmetrization runs, and detailed NMR measurements.

Even if the lack of spectroscopic evidences for the interaction between the anhydride substrate and the alkaloid derivatives does not necessarily rule out the nucleophilic catalysis path, in terms of general mechanistic scheme the experimental observation of a strong influence of the alcohol reactant on the NMR properties of the alkaloid derivatives, provided herein, appears to be better accommodated by the assumption of a general-base type of catalysis.

Moreover, the in-depth investigation of the solution properties of chiral organocatalysts revealed a somewhat unanticipated strong influence of the alkaloid's 9-*O* substituent on the conformational prevalence of the chiral units, as well as the tendency of the latter to undergo Closed-to-Open transitions in the presence of the alcohol reactant. At variance with previous literature indications, no obvious correlation could be found, however, between the propensity of the different

chiral derivatives to attain a Closed(2) conformation and their catalytic properties. Therefore, the observed changes in the catalytic efficiency of the different organocatalysts cannot be traced back to a single structural feature, leading us to propose that the achiral 9-*O* derivatizing group could have a more active role in the catalytic process (e.g., by virtue of its stereoelectronic properties) than merely enforcing the alkaloid units in a preferential reactive conformation.

Studies are currently underway to further investigate the structure-activity relationship for Cinchona alkaloid derivatives, elucidate the effects of products-organocatalyst interaction, and address the use of polymer-supported analogs of **13** and **14** as heterogeneized organocatalysts in the asymmetric ring-opening of *meso*-anhydrides. Moreover, the possibility of exploiting the chiral discrimination ability of the alkaloid organocatalysts for the in situ NMR monitoring of product *ee* evolution along the reaction course is actively investigated at present.

LITERATURE CITED

1. Ward RS. Nonenzymic asymmetric transformations involving symmetrical bifunctional compounds. Chem Soc Rev 1990;19:1–19.
2. Willis MC. Enantioselective desymmetrization. J Chem Soc Perkin Trans 1 1999;1765–1784.
3. Spivey AC, Andrews BI. Catalysis of the asymmetric desymmetrization of cyclic anhydrides by nucleophilic ring-opening with alcohols. Angew Chem Int Ed Engl 2001;40:3131–3134.
4. Chen Y, McDaid P, Deng L. Asymmetric alcoholysis of cyclic anhydrides. Chem Rev 2003;103:2965–2983.
5. France S, Guerin DJ, Miller SJ, Lectka T. Nucleophilic chiral amines as catalysts in asymmetric synthesis. Chem Rev 2003;103:2985–3012.
6. Tian S-K, Chen Y, Hang J, Tang L, McDaid P, Deng L. Asymmetric organic catalysis with modified cinchona alkaloids. Acc Chem Res 2004;37:621–631.
7. Berkessel A, Groerger H. Desymmetrization and kinetic resolution of anhydrides; desymmetrization of *meso*-epoxides and other prochiral substrates. Asymmetric organocatalysis. Weinheim: Wiley-VCH; 2005. p 347–55.
8. Atodiresei I, Schiffers I, Bolm C. Stereoselective anhydride openings. Chem Rev 2007;107:5683–5712.
9. Lee JW, Jang HB, Lee JE, Song CE. Cinchona-based catalysts for desymmetrization of *meso*-compounds and (dynamic) kinetic resolution of racemic compounds. In: Song CE, editor. Cinchona Alkaloids in Synthesis and Catalysis. Weinheim: Wiley-VCH; 2009. p 325–357.
10. Marcelli T, Hiemstra H. Cinchona alkaloids in asymmetric organocatalysis. Synthesis 2010;1229–1279.
11. Hiratake J, Yamamoto Y, Oda Ji. Catalytic asymmetric induction from prochiral cyclic acid anhydrides using cinchona alkaloids. J Chem Soc Chem Commun 1985:1717–1719.
12. Hiratake J, Inagaki M, Yamamoto Y, Oda J. Enantiotopic-group differentiation. Catalytic asymmetric ring-opening of prochiral cyclic anhydrides with methanol, using Cinchona alkaloids. J Chem Soc Perkin Trans 1 1987;1053–1058.
13. Aitken RA, Gopal J, Hirst JA. Catalytic asymmetric synthesis of highly functionalized compounds with six contiguous stereocenters. J Chem Soc Chem Commun 1988:632–634.
14. Aitken RA, Gopal J. Catalytic asymmetric ring-opening of bridged tricyclic anhydrides. Tetrahedron Asymmetry 1990;1:517–520.
15. Bolm C, Gerlach A, Dinter CL. Simple and highly enantioselective nonenzymic ring opening of cyclic prochiral anhydrides. Synlett 1999;195–196.
16. Bolm C, Schiffers I, Dinter CL, Gerlach A. Practical and highly enantioselective ring opening of cyclic *meso*-anhydrides mediated by cinchona alkaloids. J Org Chem 2000;65:6984–6991.
17. Chen Y, Tian S-K, Deng L. A highly enantioselective catalytic desymmetrization of cyclic anhydrides with modified cinchona alkaloids. J Am Chem Soc 2000;122:9542–9543.
18. Kolb HC, VanNieuwenhze MS, Sharpless KB. Catalytic Asymmetric dihydroxylation. Chem Rev 1994;94:2483–2547.
19. Bolm C, Schiffers I, Atodiresei I, Hackenberger CPR. An alkaloid-mediated desymmetrization of *meso*-anhydrides via a nucleophilic ring opening with benzyl alcohol and its application in the synthesis of highly enantiomerically enriched β-amino acids. Tetrahedron Asymmetry 2003;14:3455–3467.
20. Deng L, Liu X, Chen Y, Tian S. Preparation of cinchona-alkaloid derivatives for use as chiral catalysts for asymmetric mono-esterification/alcoholysis of prochiral and meso cyclic anhydrides patent PCT Int Appl WO 2,004,110,609 A2, 2004.
21. Ishii Y, Fujimoto R, Mikami M, Murakami S, Miki Y, Furukawa Y. Practical syntheses of chiral α-amino acids and chiral half-esters by kinetic resolution of urethane-protected α-amino acid *N*-Carboxyanhydrides and desymmetrization of cyclic *meso*-anhydrides with new modified cinchona alkaloid catalysts. Org Process Res Dev 2007;11:609–615.
22. Li H, Liu X, Wu F, Tang L, Deng L. Elucidation of the active conformation of cinchona alkaloid catalyst and chemical mechanism of alcoholysis of meso anhydrides. Proc Natl Acad Sci U S A 2010;107:20625–20629.
23. Peschiulli A, Gun'ko Y, Connon SJ. Highly enantioselective desymmetrization of meso anhydrides by a bifunctional thiourea-based organocatalyst at low catalyst loadings and room temperature. J Org Chem 2008;73:2454–2457.
24. Connon SJ. Asymmetric catalysis with bifunctional cinchona alkaloid-based urea and thiourea organocatalysts. Chem Commun 2008:2499–2510.
25. Bigi F, Carloni S, Maggi R, Mazzacani A, Sartori G, Tanzi G. Homogeneous versus heterogeneous approach to the catalytic desymmetrisation of *meso*-anhydrides promoted by cinchona alkaloids. J Mol Catal A Chem 2002;182–183:533–539.
26. Woltinger J, Krimmer H-P, Drauz K. The potential of membrane reactors in the asymmetric opening of *meso*-anhydrides. Tetrahedron Lett 2002;43:8531–8533.
27. Kim HS, Song Y-M, Choi JS, Yang JW, Han H. Heterogeneous organocatalysis for the asymmetric desymmetrization of *meso*-cyclic anhydrides using silica gel-supported bis-cinchona alkaloids. Tetrahedron 2004;60:12051–12057.
28. Song Y-M, Choi JS, Yang JW, Han H. Silica gel-supported bis-cinchona alkaloid: a chiral catalyst for the heterogeneous asymmetric desymmetrization of *meso*-cyclic anhydrides. Tetrahedron Lett 2004;45:3301–3304.
29. Ivsic T, Hamersak Z. Inversion of enantioselectivity in quinine-mediated desymmetrization of glutaric *meso*-anhydrides. Tetrahedron Asymmetry 2009;20:1095–1098.
30. Dedeoglu B, Catak S, Houk KN, Aviyente V. A Theoretical study of the mechanism of the desymmetrization of cyclic *meso*-anhydrides by chiral amino alcohols. ChemCatChem 2010;2:1122–1129.
31. Palomo C, Oiarbide M, Lopez R. Asymmetric organocatalysis by chiral Bronsted bases: implications and applications. Chem Soc Rev 2009;38:632–653.
32. Pini D, Petri A, Nardi A, Rosini C, Salvadori P. Heterogeneous catalytic asymmetric dihydroxylation of olefins with the OsO4/poly(9-O-acylquinine-co-acrylonitrile) system. Tetrahedron Lett 1991;32:5175–5178.
33. Mandoli A, Pini D, Fiori M, Salvadori P. Asymmetric dihydroxylation with recoverable cinchona alkaloid derivatives: a warning note and an improved, insoluble polymer-bound ligand architecture. Eur J Org Chem 2005;1271–1282.
34. Jumde RP, Mandoli A, De Lorenzi F, Pini D, Salvadori P. Simple preparation of dimeric cinchona alkaloid derivatives on polystyrene supports and a highly enantioselective catalytic heterogeneous dimerization of ketenes. Adv Synth Catal 2010;352:1434–1440.
35. Rosini C, Bertucci C, Pini D, Altemura P, Salvadori P. Cinchona alkaloids for preparing new, easily accessible chiral stationary phases. I. 11-(10,11-Dihydro-6'-methoxycinchonan-9-ol)-thiopropylsilanized silica. Tetrahedron Lett 1985;26:3361–3364.
36. Pini D, Rosini C, Bertucci C, Altemura P, Salvadori P. Chromatographic resolution of alkyl aryl carbinols on a silica-supported quinine chiral stationary phase. Gazz Chim Ital 1986;116:603–606.
37. Rosini C, Bertucci C, Pini D, Altemura P, Salvadori P. Chiral stationary phases based on Cinchona alkaloids for the HPLC resolution of racemates. Chromatographia 1987;24:671–676.
38. Salvadori P, Rosini C, Pini D, Bertucci C, Altemura P, Uccello-Barretta G, Raffaelli A. A novel application of Cinchona alkaloids as chiral auxiliaries: preparation and use of a new family of chiral stationary phases for the chromatographic resolution of racemates. Tetrahedron 1987;43:4969–4978.
39. Salvadori P, Rosini C, Pini D, Bertucci C, Uccello-Barretta G. Resolution of some β-hydroxyphenethylamines as N-(3,5-dinitrobenzoyl)amides on

chiral stationary phases derived from cinchona alkaloids. Chirality 1989; 1:161–166.

40. Uccello-Barretta G, Pini D, Rosini C, Salvadori P. Stereochemical features of the stereoselective interaction between (R)- or (S)-7,7'-bis(1-propen-3-oxy)-2,2'-dihydroxy-1,1'-binaphthyl and quinine. J Chromatogr A 1994; 666:541–548.
41. Rosini C, Uccello-Barretta G, Pini D, Abete C, Salvadori P. Quinine: an inexpensive chiral solvating agent for the determination of enantiomeric composition of binaphthyl derivatives and alkylarylcarbinols by NMR spectroscopy. J Org Chem 1988;53:4579–4581.
42. Salvadori P, Pini D, Rosini C, Bertucci C, Uccello-Barretta G. Chiral discriminations with Cinchona alkaloids. Chirality 1992;4:43–49.
43. Uccello-Barretta G, Pini D, Mastantuono A, Salvadori P. Direct NMR assay of enantiomeric purity of chiral β-hydroxy esters by using quinine as chiral solvating agent. Tetrahedron Asymmetry 1995;6:1965–1972.
44. Uccello-Barretta G, Bardoni S, Balzano F, Salvadori P. Versatile chiral auxiliaries for NMR spectroscopy based on carbamoyl derivatives of dihydroquinine. Tetrahedron Asymmetry 2001;12:2019–2023.
45. Uccello-Barretta G, Balzano F, Salvadori P. Rationalization of the multireceptorial character of chiral solvating agents based on quinine and its derivatives: Overview of selected NMR investigations. Chirality 2005;17: S243–S248.
46. Uccello-Barretta G, Vanni L, Balzano F. NMR enantiodiscrimination phenomena by quinine C9-carbamates. Eur J Org Chem 2009:860–869.
47. Campbell-Verduyn LS, Mirfeizi L, Dierckx RA, Elsinga PH, Feringa BL. Phosphoramidite accelerated copper(i)-catalyzed [3 + 2] cycloadditions of azides and alkynes. Chem Commun 2009:2139–2141.
48. Dijkstra GDH, Kellogg RM, Wynberg H, Svendsen JS, Marko I, Sharpless KB. Conformational study of cinchona alkaloids. A combined NMR, molecular mechanics and x-ray approach. J Am Chem Soc 1989;111: 8069–8076.
49. Dijkstra GDH, Kellogg RM, Wynberg H. Conformational study of cinchona alkaloids. A combined NMR and molecular orbital approach. J Org Chem 1990;55:6121–6131.
50. Buergi T, Baiker A. Conformational behavior of cinchonidine in different solvents: a combined NMR and ab initio investigation. J Am Chem Soc 1998;120:12920–12926.
51. Johnson CS Jr. Diffusion ordered nuclear magnetic resonance spectroscopy: principles and applications. Prog Nucl Magn Reson Spectrosc 1999; 34:203–256.
52. Govil G, Hosur RV. Conformation of biological molecules: new results from NMR. In: Diehl P, Fluck E, Kosfeld R, editors. NMR Basic Principles and Progress. Berlin: Springer-Verlag 1982. Vol. 20.
53. Uccello-Barretta G, Di Bari L, Salvadori P. Autoaggregation phenomena in quinine solutions. Magn Reson Chem 1992;30:1054–1063.
54. Uccello-Barretta G, Balzano F, Bardoni S, Vanni L, Giurato L, Guccione S. Chiral discrimination processes by C9 carbamate derivatives of dihydroquinine: interaction mechanisms of diastereoisomeric 9-O-[(S)- or (R)-1-(1-naphthyl)ethylcarbamate]dihydroquinine and the two enantiomers of N-(3,5-dinitrobenzoyl)alanine methyl ester. Tetrahedron Asymmetry 2008;19:1084–1093.
55. Uccello-Barretta G, Balzano F, Quintavalli C, Salvadori P. Different enantioselective interaction pathways induced by derivatized quinines. J Org Chem 2000;65:3596–3602.
56. Uccello-Barretta G, Mirabella F, Balzano F, Salvadori P. C11 versus C9 carbamoylation of quinine: a new class of versatile polyfunctional chiral solvating agents. Tetrahedron Asymmetry 2003;14:1511–1516.
57. Fielding L. Determination of association constants (Ka) from solution NMR Data. Tetrahedron 2000;56:6151–6170.