Study of Ground State Interactions of Enantiopure Chiral Quaternary Ammonium Salts and Amides, Nitroalkanes, Nitroalkenes, Esters, Heterocycles, Ketones and Fluoroamides

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Abstract: Chiral phase-transfer catalysis provides high level of enantiocontrol, however no experimental data showed the interaction of catalysts and substrates. ^{1}H NMR titration was carried out on *Cinchona* and Maruoka ammonium bromides vs. nitro, carbonyl, heterocycles, and N–F containing compounds. It was found that neutral organic species and quaternary ammonium salts interacted *via* an ensemble of catalyst $^{+}$N–C–H and (sp^{2})C–H, specific for each substrate studied. The correspondent BArF salts interacted with carbonyls *via* a diverse set of $^{+}$N–C–H and (sp^{2})C–H compared to bromides. This data suggests that BArF ammonium salts may display a different enantioselectivity profile. Although not providing quantitative data for the affinity constants, the data reported proofs that chiral ammonium salts coordinate with substrates, prior to transition state, through specific C–H positions in their structures, providing a new rational to rationalize the origin of enantioselectivity in their catalyses.

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Introduction

Quaternary ammonium salts (Quats) are species widely used in synthesis and catalysis,[1–4] medicinal chemistry,[5] drug discovery[6] and material science.[7] Quats have found major applications in recently developed organocatalyses where they have been used for the enantioselective formation of C–C, C–O, C–N and C–X bonds.[3,4] Enantioselective Phase-Transfer Catalysis[3,4] (PTC) emerged as a notable technology within the organocatalytic domain and it has been used for the large-scale preparation of bioactive compounds[8,9] and unnatural aminoacids.[10] From an industrial standpoint, PTC offers significant advantages over other metal-free catalyses, as it is easy to scale up and the quaternary ammonium salt catalysts can be recovered by simple precipitation and filtration. *Cinchona*-based ammonium salts are readily available in a single step from commercial and cheap starting materials, which provides a significant advantage over other species that require longer syntheses. Since the early reports from Wynberg[11,12] and from Merck,[8,10] the area has evolved with the groups of Maruoka,[3,4] Jew and Park,[13] Corey[14] and Lygo[15] providing notable examples of catalyst design and relevant synthetic applications. Quats are a common motif found in a number of bioactive compounds including biocidals[16] and anticholinergics.[17] They have been intensively investigated and developed as ionic liquids[18] and – due to their similarity to acetylcholine – their supramolecular interactions with calixarenes[19] and crown ethers[20] have been also studied. The groups of Umani-Ronchi,[21] Ricci and Bernardi,[22–26] Jørgensen,[27,28] Della Sala[29] and Albanese[30,31] provided notable synthetic applications of

Cinchona derived ammonium species. Adamo and coworkers have reported some highly enantioselective reactions that make use of *Cinchona*-based quaternary ammonium salts.[32–41] Concomitantly, the groups of Waser and Vetticatt have reported the use of bifunctional quaternary ammonium salts in highly enantioselective α-fluorinations;[42] asymmetric cascade cyclizations;[43,44] Michael additions;[43] α-hydroxylations;[45] and α-chlorinations.[46]

As part of these studies, we became interested in the reported mechanistic studies pertaining the key non-covalent interactions occurring between enantiopure ammonium salts and the reactants.[14,15] Many groups showed that the presence of a second catalytically active functional group, i.e. an hydroxyl, had a dichotomic effect on the mechanism of catalysis,[10,11,47] independently of the ammonium being either inherently chiral with one of the tetrahedral faces open for ion pairing[48–50] or being achiral but residing in a chiral environment.[51–54] Hence, chiral bifunctional ammonium salts have emerged as a powerful strategy to control the enantioselectivity in those cases where classical "monofunctional" ammoniums failed.[55–57] Noteworthy, the majority of such bifunctional ammonium salts contain a free OH-group as the second coordination site.[58–65] However, over the last five years, several groups have started to systematically investigate the introduction of alternative H-bonding donors, i.e. ureas and thioureas to obtain new classes of highly active bifunctional ammonium salt catalysts.[66–75] Chiral back-bones were derived from the natural chiral pool like *Cinchona* alkaloids;[66–70] amino acids;[71–73] or from easily available chiral diamines, i.e. *trans*-cyclohexane diamine.[42–46,74]

Hence, catalysts **1** (Figure 1), bearing an alkylated hydroxyl, can only interact with a preformed nucleophile, often an enolate, *via* the formation of an electrostatic interaction to form ground state preformed complex **3**. The chiral environment created around the nucleophile (Nu^-) would dictate the enantioselective bond forming reaction with an un-bound neutral electrophile (E).

On the other hand, catalyst 2 (Figure 1), bearing a free hydroxyl group, possesses two functionalities, each one able to establish a non-covalent interaction both with nucleophile (Nu^-) and electrophile (E) motifs. This creates the premises for two alternative pre-arrangement of Quats with their substrates. For example, the nucleophile (Nu^-) may bind to the ammonium *via* an electrostatic interaction to give complex 4 (Figure 1) in which the electrophile engages with the hydroxyl *via* H-bonding. Alternatively, the nucleophile (Nu^-) may establish an H-bond with the hydroxyl group forming complex 5 (Figures 1 and 2). The interaction of a neutral electrophile (E) and a charged nucleophile (Nu^-) in the presence of bifunctional 2, was investigated by Palomo. As part of a study reporting the addition of nitromethane to acylimines,[76] it was unambiguously demonstrated that nitromethane enolate interacted with the hydroxyl in 2 *via* an H-bonding. Calculations ruled out an electrostatic interaction of nitromethane enolate with the ammonium cation, which was also a possibility. Invoked by Sanders[77] and further computed by Houk,[78,79] Palomo proposed, as a consequence, that compound 2 established an interaction with neutral electrophilic acylimines *via* their $^+$N–C–H protons to give complex 6 (Figure 2), in which a $^+$N–C–H···O=C H-bond was calculated possessing an energy of interaction of −6.4 kcal/mol in toluene.[76]

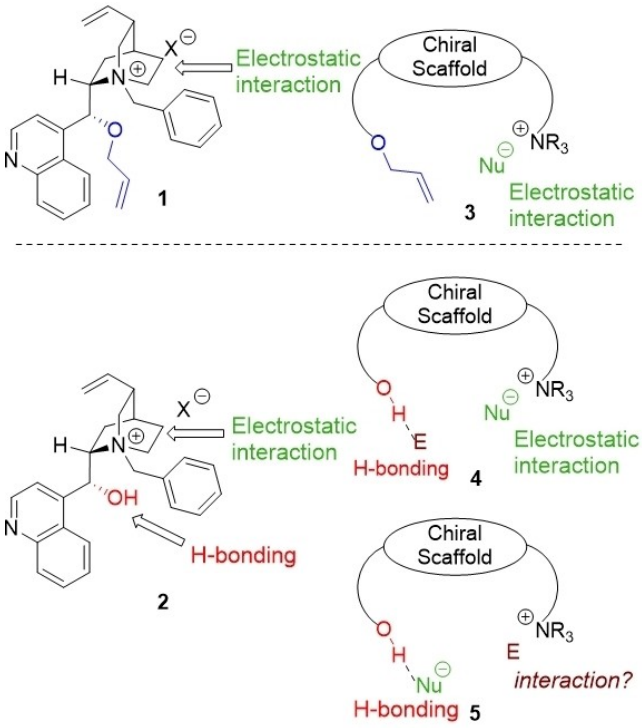


Figure 1. Comparison of modes of interaction of catalysts **1** and **2** with nucleophiles (Nu^-) and neutral electrophiles (E).

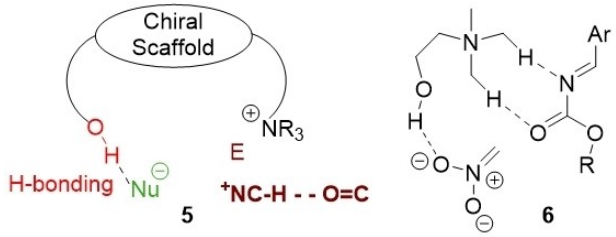


Figure 2. Proposed transition state for the addition of nitromethane to acylimines.[76]

In summary, the work carried out by Palomo indicated (Figure 2) two important aspects pertinent to the molecular recognition of Quats: *(i)* the ability of the OH to bind to an enolate via H-bonding and *(ii)* the crucial interaction of quaternary ammonium salts $^+$N–C–H with neutral substrates.

The data reported by Palomo were further confirmed by some observations provided by Denmark et al. indicating the involvement of at least one $^+$N–C–H in enantioselective PTC to achieve high levels of enantioselectivity.[49] Meanwhile, strong $^+$N–C–H···O^- electrostatic interactions have been also invoked in other types of reactions involving Quats.[80]

In spite of the abovementioned reports, which propose a key role of the R_3N^+–C–H as an H-bond donor in enantioselective catalysis, very few physical evidence have been yet

described, especially in solution, - where the catalysis takes place - and with neutral organic substrates. Donati reported the existence of intramolecular $^{+}$N–C–H ···(O or N) H-bonds in solution by ^{1}H NMR spectroscopy and by X-ray crystallography.[81] Shirakawa and others demonstrated that some quaternary ammonium salts bearing an additional electron-withdrawing group next to the ammonium accelerated the Mannich reaction *via* H-bonding Lewis catalysis.[82–84] It is possible that the $^{+}$N–C–H in Shirakawa's catalyst was too acidic to be configurationally stable in a basic media typically required for PTC reactions and for this reason this study was limited to achiral examples. Evidence for the interaction between $^{+}$N–C–H and alkyl chlorides was obtained *via* ^{1}H NMR titrations,[82] which is important to determining the association of ammonium halides and their reagents. Reetz has shown by MO calculations that the charge in the case of the tetrabutylammonium unit is not localized on the nitrogen, but is delocalized over the adjacent four methylene groups, implicating that α-methylene groups in Quats are acidic,[85] hence able to act as H-bond donors.[82] Analogously to the former examples, Reetz studied the interactions for tetra-*n*-butylammonium (n-Bu)$_4$N^{+} and neutral phenylpropionitrile. The results suggested that either in solid state or in solution, the α-methylene units of the (n-Bu)$_4$N^{+} cation were forming $^{+}$N–C–H to N≡C– H-bonding interactions.[85–87]

In summary, an analysis of the current literature pointed out that Quats interact with neutral organic molecules *via* $^{+}$N–C–H H-bond, however these interactions were only detected with solvents and for non-chiral quats. In this context, the experimental demonstration of $^{+}$N–C–H H-bonding that orient substrates when enantiopure Quats are used is pivotal to understand the mode of interaction between Quats catalysts and reagents at ground state and to shed a light on the origin of enantioselectivity of many asymmetric syntheses. In order to elucidate whether or not the N^{+}–C–H hydrogen bond is operative under similar enough conditions as those used in catalysis, we set out to run a number of ^{1}H NMR titrations involving popular enantiopure quaternary ammonium salts and *neutral* electrophiles. This study has proven that Quats are able to elicit an ensemble of such C–H H-bond interaction, therefore they operate an active molecular recognition process of their substrates. The results obtained were complemented by a set of opportune computational studies that confirmed the findings herein reported.

Herein we report for the first time experimental evidence for the $^{+}$N–C–H H-bond formed by *Cinchona*-based and Maruoka-type quaternary ammonium salts and a range of neutral organic hydrogen bond acceptors.

Results and Discussion

It has been reported that hindered organic cations, for example tetraalkylammoniums, bear a positive charge that is not directly accessible. However, the positive nitrogen plays the role of an electron-withdrawing group for adjacent protons, rendering them acidic enough to become good H-bond donors.[88] Houk showed that dimethylformamide (DMF) was a particularly good ligand for ammonium species and their energy of interaction was calculated as high as −18.1 kcal/mol.[78] This calculation was in agreement with the binding energy obtained for the interaction of $(CH_3)_4N^{+}$ and dimethylacetamide, which when measured by mass spectrometry ranged in the interval 18–20 kcal/mol.[89] With this in mind, we carried out a number of ^{1}H NMR titrations, where *N*-benzyl-cinchonidinium **7** (Figure 3), *N*-benzyl-cinchoninium **8** (Figure 4), and *O*(9)-allyl-*N*-benzyl-cinchonidinium **9** (Figure 5) were dissolved in $CDCl_3$ and their ^{1}H NMR spectra recorded in the presence of increasing amounts of DMF as the titrant at room temperature. It should be pointed out that species **7**–**9** are sparingly soluble in toluene and dichloromethane and for this reason the next similar solvent, i.e. chloroform, was adopted for the NMR experiments. Although less popular than toluene or dichloromethane in phase transfer catalysis set up, due to its pronounced acidity, chloroform has been successfully used and results obtained were comparable to those of other solvents, i.e. toluene or dichloromethane.[90,91] Hence, the conditions used in the titration experiments were similar enough to be representative of other set up carried on in different solvents. From a quantitative standpoint, it should be noted that H-bonds are stronger in less polar media; therefore, if visible in polar chloroform, the same must be formed also in less polar toluene or dichloromethane.

The chemical shifts for most representative protons of **7** are reported (Figure 3) expressed as Hz vs. the amount of DMF added (equiv.). The results collected (Figure 3) revealed that a significant shift of the ^{1}H NMR signals for benzylic H_a; quinoline H_c; and aromatic H_s could be seen (up to 40 Hz) with just 1 equiv. of titrant added. The involvement of aromatic (sp^2)C–H in H-bonding has been documented,[92,93] but not on catalyst **7** and it revealed as a strong interaction. Noteworthy, it is well known that the use of the quininium vs. cinchonidinium species, or quinidinium vs. cinchoninium, in catalysis often leads to increased enantioselectivity, which based on the results provided herein, could be explained with the effect of the *ortho*-OCH_3 to H_c. Following this reasoning, the reason why *ortho*-OCH_3 containing catalysts performed at higher enantioselectivity could be attributed to the involvement of H_c in substrate recognition and to the increased steric hindrance offered by the *ortho* group.

Increasing the titrant to 5 equiv. affected H_a and H_s more than the other protons in **7**. It should be noted that benzylic H_b also shifted, but to a lesser extent compared to H_a. In addition, H_a shifted up-field, meanwhile H_b was progressively shifted down-field, thus confirming the directional nature of the interaction formed between DMF and **7**. As should be expected, the protons around the –OH were also affected by the titration. In particular, H_g, H_d and H_j shifted when larger amounts of DMF were added, identifying a secondary mode of interaction between **7** and DMF operative only at higher concentration of DMF. Hence, it was pointed out that compound **7** (Figure 3) had two sites through which an interaction with DMF occurred: a "high affinity" site (shown in light blue) defined by the benzylic H_a, and the aromatic H_c, H_s; and a "low affinity" site (shown in green) comprising H_g, H_d and H_j. In summary, compound **7**

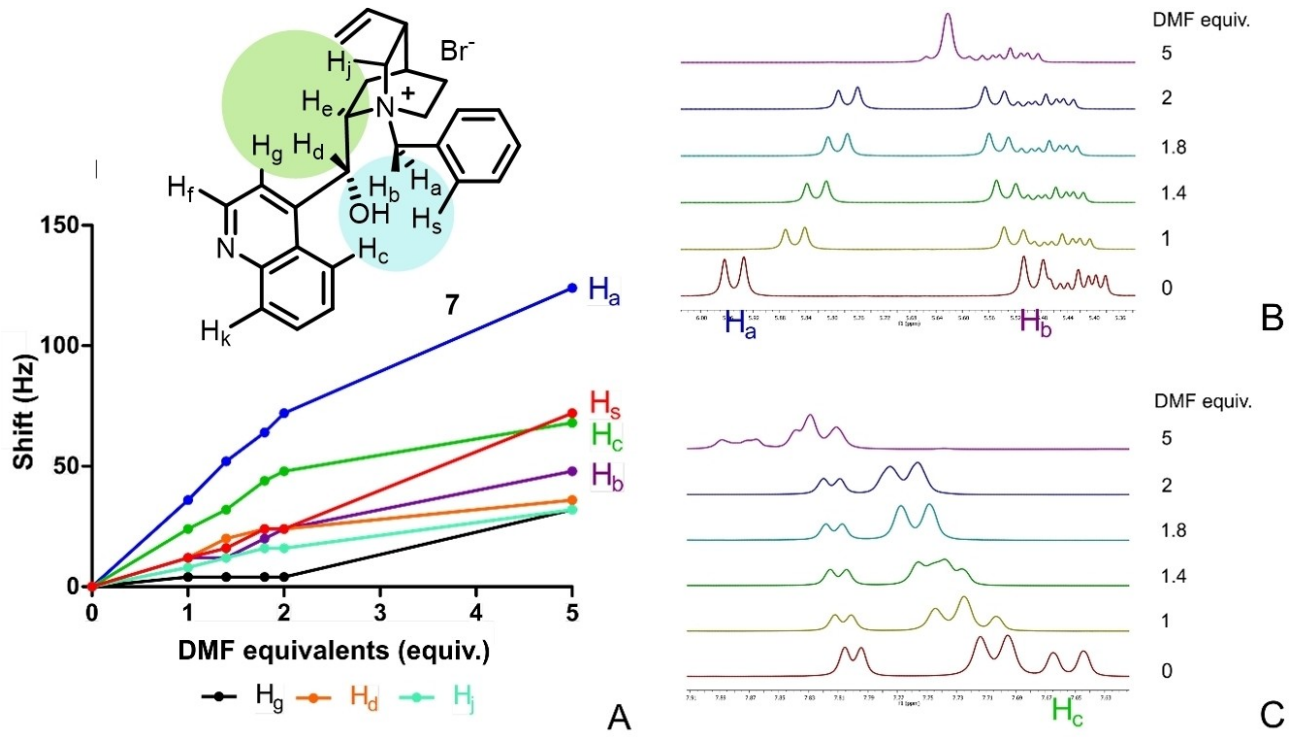


Figure 3. ^{1}H NMR titration of *N*-benzyl-cinchonidinium bromide **7** with increasing aliquots of DMF. (A) shift in Hz vs. equivalents of DMF applied; (B) ^{1}H NMR traces for H_a and H_b; (C) ^{1}H NMR traces for H_c.

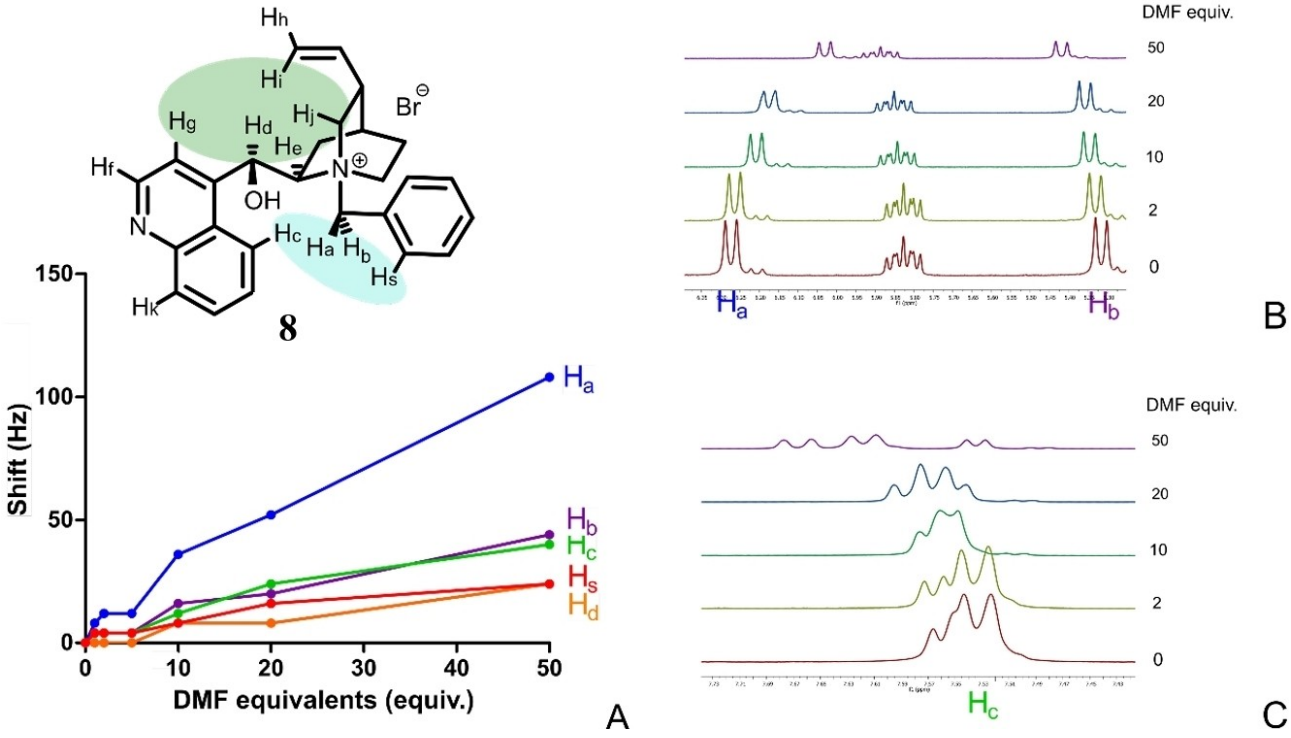


Figure 4. ^{1}H NMR titration of *N*-benzyl-cinchoninium bromide **8** with increasing aliquots of DMF. (A) shift in Hz vs. equivalents of DMF applied; (B) ^{1}H NMR traces for H_a and H_b; (C) ^{1}H NMR traces for H_c.

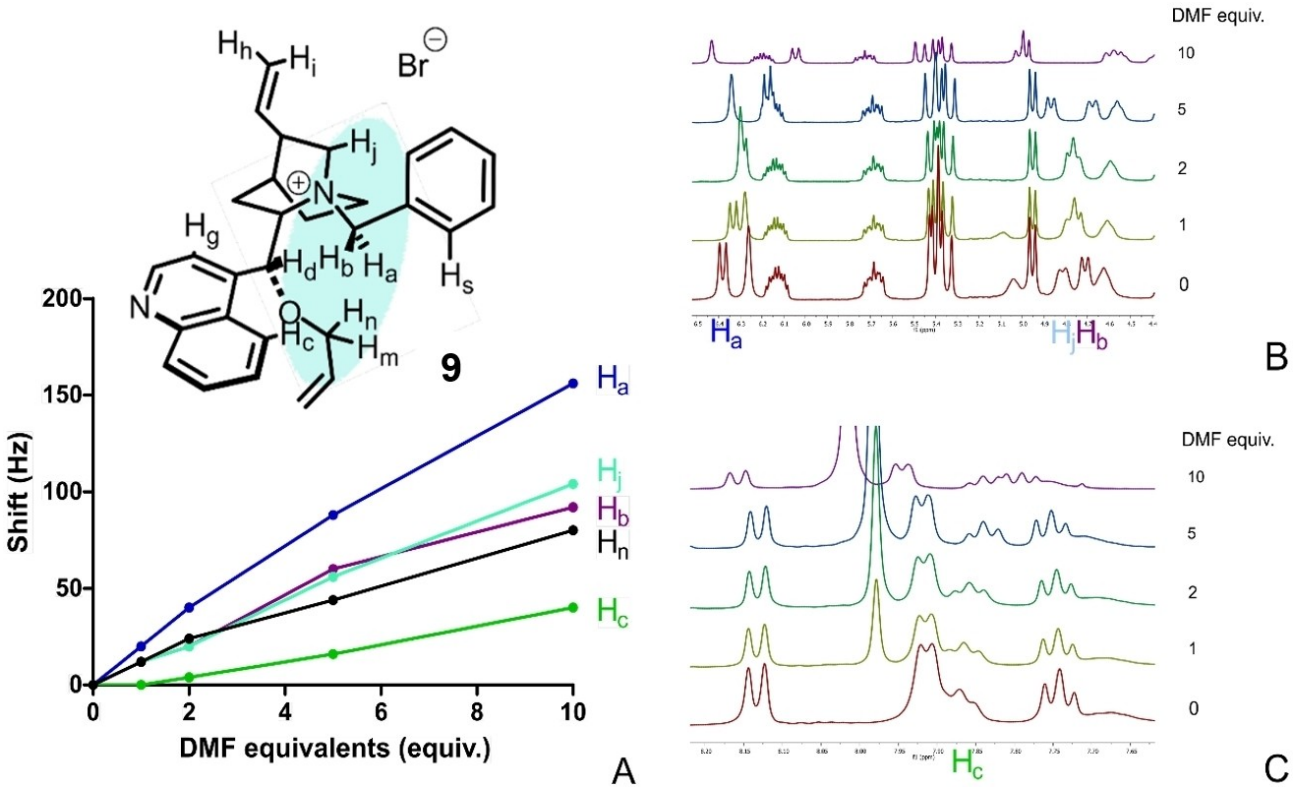


Figure 5. ^{1}H NMR titration of *O*(9)-allyl-*N*-benzyl-cinchonidinium bromide **9** with increasing aliquots of DMF: (A) shift in Hz vs. equivalents of DMF applied; (B) ^{1}H NMR traces for H_a and H_b; (C) ^{1}H NMR traces for H_c.

possesses two strong H-bond donors, namely (*i*) the benzylic R_3N^+–CH and (*ii*) the –OH; *apparently* with R_3N^+–CH being a stronger donor than –OH, that could be explained with the role the bromide played in the molecular interaction between **7** and DMF (see below).

The effect of different temperatures on the ^{1}H NMR titrations was also examined. Titrations were performed at 40 °C and 50 °C. Remarkably, H_a and H_b were still shifted at 40 °C although to a lesser extent than at room temperature, while no shift was recorded at 50 °C. These results are consistent with the disruption of H-bonding at high temperature.

We also carried out the titration of **7** and DMF in other deuterated solvents with increasing polarity: DMSO-d_6, MeOD, and D_2O. As expected, in DMSO-d_6 the signal shift for H_a and H_b was dramatically affected: the shift observed for H_a was only 4 Hz (compared to 54 Hz in $CDCl_3$), while there was no appreciable shift for the other protons. In MeOD, the titration indicated no shift for the H_a, H_b and H_c signals.

This set of experiments pointed out that a stronger H-bond acceptor, capable of displacing DMF from Quats, prevented the signal shift, confirming the H-bond nature of the interaction. We then turned our attention to the pseudo-enantiomeric *N*-benzyl-cinchoninium **8** (Figure 4), which is popular for its use in many highly enantioselective reactions. We noticed that compound **8** was less soluble in $CDCl_3$ and when employed in the same amount as **7**, compound **8** was only partially dissolved in the same amount of $CDCl_3$. The relative integration of a saturated solution of **8** vs. a known quantity of DMF revealed that the solution of **8** obtained was ca. 13 times more dilute compared to the one used for the titration of **7**. Considering the lower concentration of **8**, we were not surprised that larger amounts of DMF titrant were required to observe significant shifts.

Typically, from 10 to 50 equivalents of DMF were required to observe signal shifts comparable to those observed for **7** (Figure 4). Benzylic H_a was the most shifted proton in compound **8**, followed by its geminal H_b and the quinoline H_c; as we similarly observed for compound **7**. *Ortho* aromatic proton H_c of **8** was affected to a lesser extent than **7**, which we suggest is due to a different geometric arrangement of the quinoline ring relative to the quinuclidine core. The shift of geminal H_a and H_b also occurred in opposite directions, indicating differing anisotropy and confirming their individual engagement in H-bonding (i.e. directionality of the interaction). Proton H_d was shifted also, although requiring higher concentration of titrant. This data (Figure 4) indicated once again the existence of two sites available to compound **8** through which H-bonds can form with a neutral substrate: a "high affinity" site (shown in light blue) and a "low affinity" site (shown in green). It was also confirmed that the benzylic R_3N^+–CH possessed, in the presence of a coordinating anion such as bromide, higher H-bond donating ability than an –OH, as observed for compound **7**. Having confirmed that quaternary ammonium bromides **7** and **8** established an H-bonding interaction with DMF *via* the benzylic

R_3N^+–CH, we then studied the behavior of *O*(9)-allyl-*N*-benzyl-cinchonidinium bromide **9** in the same titration experiment. Compound **9** lacks a free –OH moiety, hence it has only one site available for H-bonding. Data collected (Figure 5) showed that DMF bound to **9** only *via* the benzylic R_3N^+–CH. Upon addition of increasing amounts of DMF to a solution of **9** in $CDCl_3$, protons H_a and H_b were the most affected alongside H_j and H_n. These four protons identified (Figure 5) a binding site for DMF (shown in light blue). Significantly, in the ^{1}H NMR titration of **9** and DMF -unlike **7** with two binding modes- there was no shift observed for the H_d and H_g signals. This data proved that compound **9** possessed only one mode of interaction with neutral organic molecules. The demonstration that monofunctional **9** has a unique binding mode to DMF, meanwhile bifunctional **7** had two, provides an alternative explanation for the increase in enantioselectivity observed when preparing unnatural amino acids using catalysts such as **9** vs. **7**.[14,15] Typically, the use of O-alkyl derivatives **9** ensured higher enantioselectivity compared to **7**, which was explained by the formation of a tighter and more rigid pair formed by **9** and enolates. However, the titration experiments herein reported showed that compound **7** could interact with H-bonding acceptors, in two distinct modes. Hence, it is plausible that the increase of enantioselectivity observed by using catalysts such as **9** vs. **7** arises from the single mode of interaction available for **9** and substrates, compared to the dual modes of interaction available for **7**. This data and their interpretation cast a different scenario for the mode of catalysis of compounds **7** and **9**, and suggest an alternative explanation for the origin of enantioselectivity with respect to the "pyramidal" model provided by Corey.[14]

The field of enantioselective phase-transfer catalysis is dominated by two main catalyst templates, namely (*i*) the *Cinchona*-based; and (*ii*) Maruoka's binaphthyl containing Quats.[3] Having established the H-bonding properties of R_3N^+–CH in the *Cinchona* series, we posed the question of whether the same interaction could be evidenced in Maruoka's compounds.[3] Hence, commercially available (11b*R*)-(-)-4,4-dibutyl-4,5-dihydro-2,6 bis(3,4,5-trifluorophenyl)-3H-dinaphth [2,1-c:1′,2′-e]azepinium bromide **10** was dissolved in CD_2Cl_2 and titrated with DMF, similarly as we executed for compounds **7**–**9**. Initial attempts failed to reveal a shift change, however, we realized that compound **10** contained two molecules of water by ^{1}H NMR integration (Figure 6). It was reasoned that the molecules of water may occupy the H-bond donor sites in **10**, hence hampering the establishment of H-bonding between **10** and DMF. We therefore treated a solution of **10** in CD_2Cl_2 with molecular sieves and recorded the ^{1}H NMR spectra at 2, 1, 0.5 and 0 equiv. of water present (Figure 6(A) and (C)). We observed that benzylic H_1 and aliphatic H_2 were subjected to a shift depending upon the equivalents of water being present in the sample. This data indicated that compound **10** must have a propensity to crystallize with two equivalents of water due to sites available for H-bonding being operative *alpha* to the ammonium C–H. Aliphatic H_2 shifted of ca. 20 Hz upon dehydration. The titration experiment was then repeated on the dried solution of **10** with increasing amounts of DMF (Figure 6, (B) and (D)). The data collected indicated that benzylic H_1 and aliphatic H_2 were the most affected protons signals, hence were those interacting with DMF. Significantly, only one of the two geminal benzylic protons was shifted, once more demonstrating the directionality in the intermolecular interaction, i.e. in each CH_2 only one of the diastereotopic protons was shifted. The extent of the signal shifts for **10**, though, was clearly less than those observed with the other PTCs (**7**–**9**), and required up to 100 equivalents of DMF to observe the effect.

The interaction of quaternary ammonium species possessing a β-alcohol functionality and halides has been documented.[94–96] In particular it has been reported that alcohols formed linear hydrogen bonded complexes with bromides and other halide ions in tetrachloromethane solution, which were visible at the NMR.[94] In addition, the X-ray solid state of choline chloride showed an electrostatic interaction between the proton of the OH and the halogen that kept the two species at 3.07 Å.[95] On the basis of these reports, we speculated on what role the bromide counter ion might have in the interaction of species **7**–**10** and DMF.

Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BArF) is a non-coordinating anion that has been used to identify the role of certain halogens to quaternary ammonium species.[82] It has been shown that weak H-bond acceptors such as alkyl chlorides displaced BArF from its binding to a quaternary ammonium salt. Therefore it was reasoned that DMF, a stronger acceptor, elicited the same effect.[82] In order to understand the mode of interacting of the halides in salts **7**–**10** and to provide further insight on their interaction with DMF, we have prepared salts **11**–**14** (Figures 7–10) in which the bromide was replaced by a $BArF^-$ anion. Then compounds **11**–**14** were submitted to the same titration as **7**–**10**. The titration of compound **11** with increasing amount of DMF showed that the OH was, alongside H_b, H_x and H_e the most affected. This result points out that the bromide must be associated with the OH primarily, then with H_b in compound **7**, leaving H_a and the closely associated H_c and H_d as the main H-bond donors. Indeed, in the titration of **11**, H_a and H_c are significantly less involved. Compound **12** (Figure 8) showed a remarkable increased solubility when compared to parent **8** and the titration was carried out at higher molar concentrations.

The results pointed out that also in this case there is a preferred interaction between DMF and H_b alongside nearby protons H_x and H_e, which was the case of compound **13** (Figure 9). The titration of compound **14** (Figure 10) showed the same behaviour of **11**–**13**, i.e. now the H_2 shift was more pronounced compared to H_1 and in overall higher intensity. Once more, this data indicates that in **10** the halogen is most likely to be bound to H_2, which becomes the preferred H-bond donor for DMF when BArF is the counter ion. In conclusion, this dataset demonstrated that with or without an halogen counter ion, quaternary ammonium species are able to bind to the DMF through their benzylic protons, although the halogen has an impact on the mode of binding and its intensity, at least at ground state. Overall, the data herein reported suggests that BArF salts **11**–**14** may have completely different enantioselectiv-

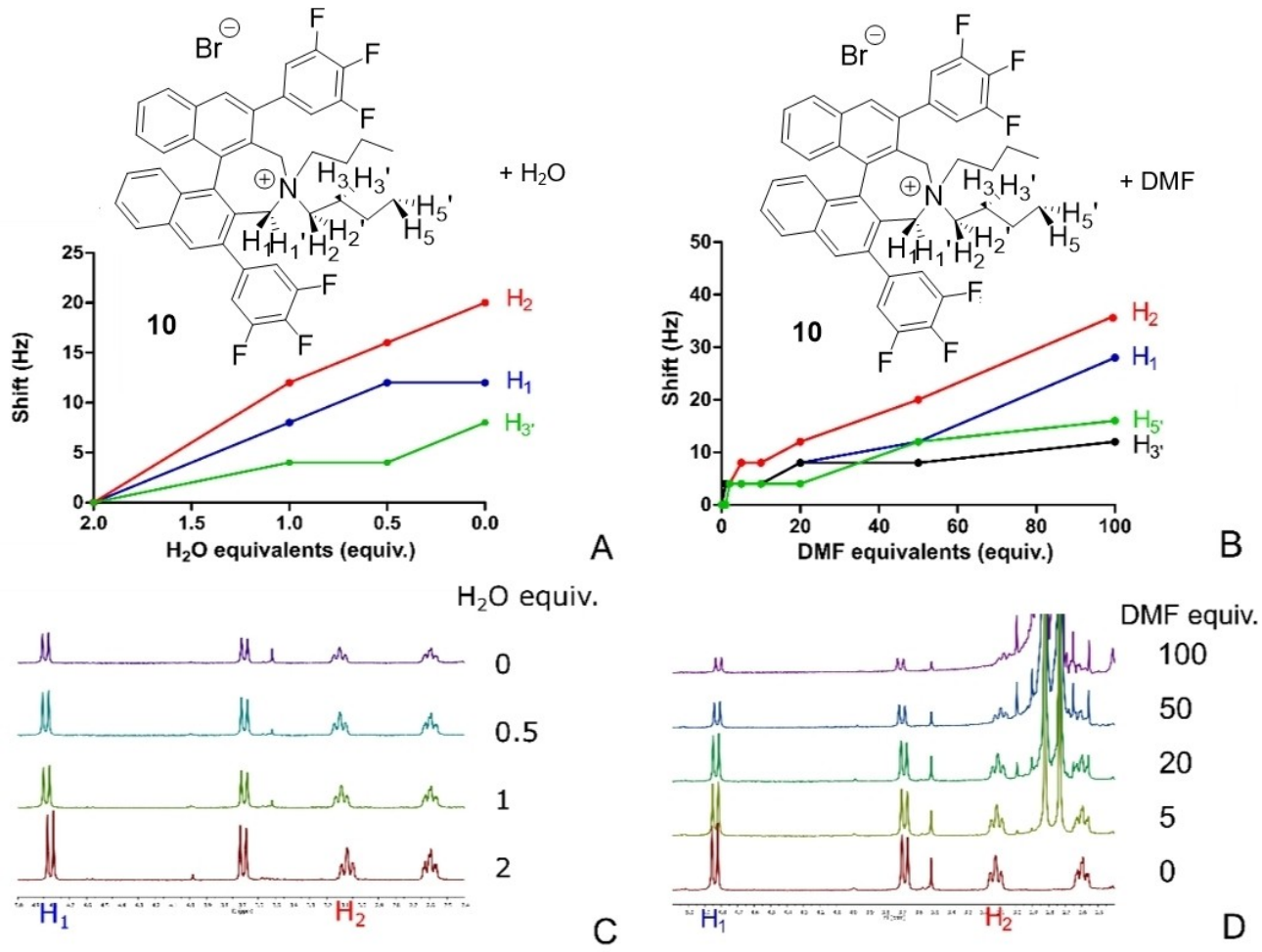


Figure 6. ^{1}H NMR titration of commercially available Maruoka's catalyst (11bR)-(−)-4,4-dibutyl-4,5-dihydro-2,6 bis(3,4,5-trifluorophenyl)-3H-dinaphth[2,1-c:1′,2′-e]azepinium bromide **10** with increasing aliquots of DMF: (A) shift in Hz vs. equivalents of H_2O present; (B) shift in Hz vs. equivalents of DMF applied; (C) ^{1}H NMR traces for H_1 and H_2 in the presence of water; (D) ^{1}H NMR traces for H_1 and H_2 in the presence of increasing amounts of DMF.

ity profiles in reactions carried out with **7**–**10**, which to the best of our knowledge is unreported.

The data collected pointed out that the *N*-benzyl-cinchonidinium cation, as well as the other chiral Quats herein described, interacted with DMF in two different modes, depending upon the counter ion present. This generates two diverse potential complexes, tentatively assigned as **15** and **17** (Figure 11). Quaternary ammonium species possessing a vicinal alcohol, for example choline bromide **16** (Figure 11) were shown forming linear hydrogen bonded complexes with bromides,[94,95] in which the distance between the OH and the halogen was 3.07 Å in the solid state. Therefore, the bromide in species **7**–**8** must be considered as "chelated" by the alcohol OH and the diffuse ammonium cation. In this context, the alcohol functionality in **7**–**8** was engaged with the Quats counter ion, which explains the fact that in their titration with DMF the $^{+}$N–C–H appeared as stronger donors than the OH. This was reversed in the titration of **11**–**12** in which the OH was the most evident participant to the molecular complex (Figure 7–8). With the halogen in place, therefore, the three lone pairs present in DMF interacted with **7** via H_a, H_s and H_c generating complex **15** (Figure 11). Conversely, when BArF was the counter ion, H_b, H_x and the OH were the most affected protons, which may indicate the formation of molecular complex **17**. It should be noted that titration experiments herein reported describe the formation of molecular complexes exerted between popular catalytic active species and substrates at ground state. However, the pre-organization of substrate and catalyst has been often used to understand or predict the stereochemical outcome of reactions. For example, the binding model of enantiopure Quats with neutral reagents *via* $^{+}$N–C–H hydrogen bond was invoked to explain the origin of enantioselectivity for the addition of nitromethane to acylimines.[76] In analogy to this report,[76] and in light of the hitherto reported NMR data, we propose $^{+}$N–C–H hydrogen bond to explain the origin of enantioselectivity in the addition of nitromethane **18** to 3-methyl-4-nitro-5-styrylisoxazoles **19** under the catalysis of *Cinchona*-based catalyst **20** (Scheme 1);[9,33] and in the enantioselective fluorination of indanone **23** performed using *N*-Fluorosuccinamide (NSFI) **24** under the catalysis of bifunctional ammonium thiourea **25** (Scheme 2).[45]

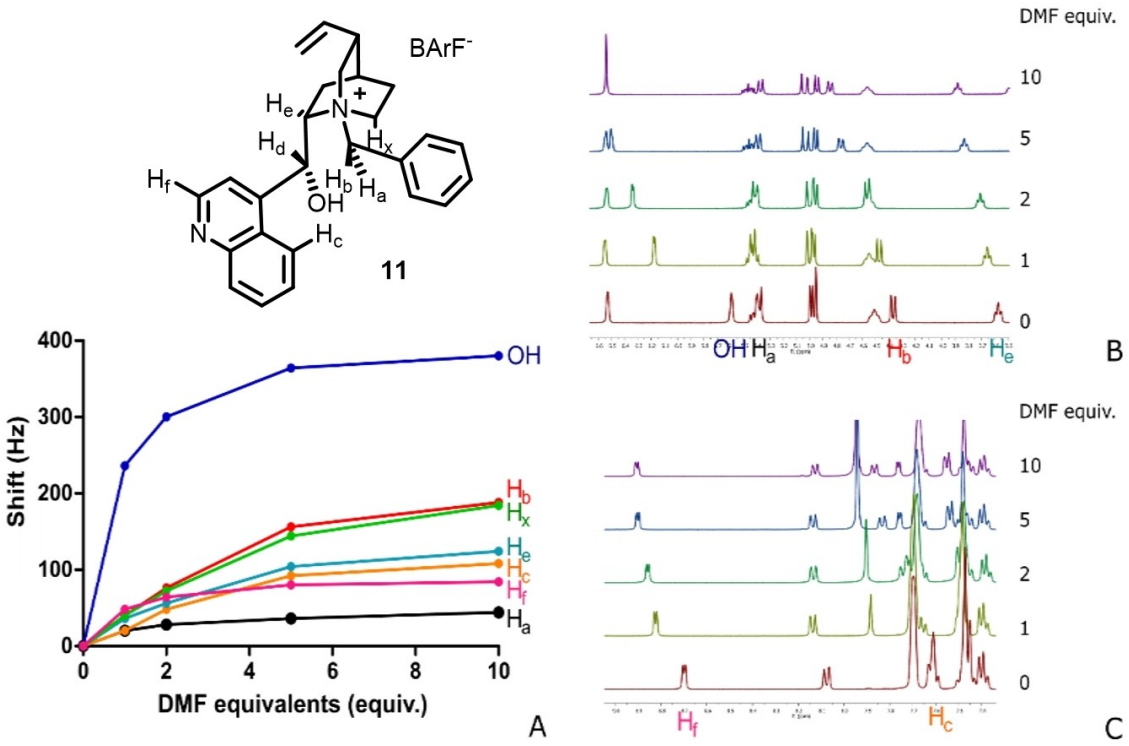


Figure 7. ^{1}H NMR titration of *N*-benzyl-cinchonidinium BarF-**11** with increasing aliquots of DMF. (A) shift in Hz vs. equivalents of DMF applied; (B) ^{1}H NMR traces for H_a, H_b, He and OH; (C) ^{1}H NMR traces for H_c and H_f.

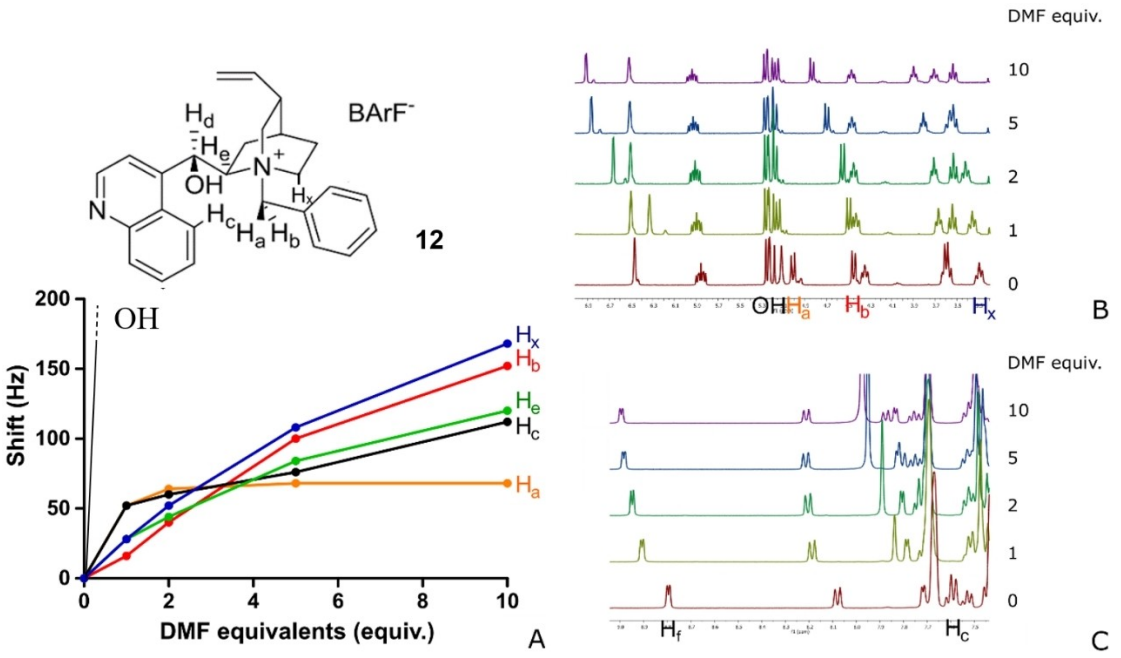


Figure 8. ^{1}H NMR titration of *N*-benzyl-cinchoninium BArF **12** with increasing aliquots of DMF. (A) shift in Hz vs. equivalents of DMF applied; (B) ^{1}H NMR traces for H_a, H_b, H_x and OH; (C) ^{1}H NMR traces for H_c and H_f.

We have developed compounds **19** as a new class of reactive Michael acceptors that could be employed in synthesis as cinnamic ester surrogates.[9] In compounds **19** the 4-nitroisoxazole core provides the dual function of activating the alkene towards nucleophilic addition and as a "masked carboxylate" that could be revealed *via* the Sarti-Fantoni

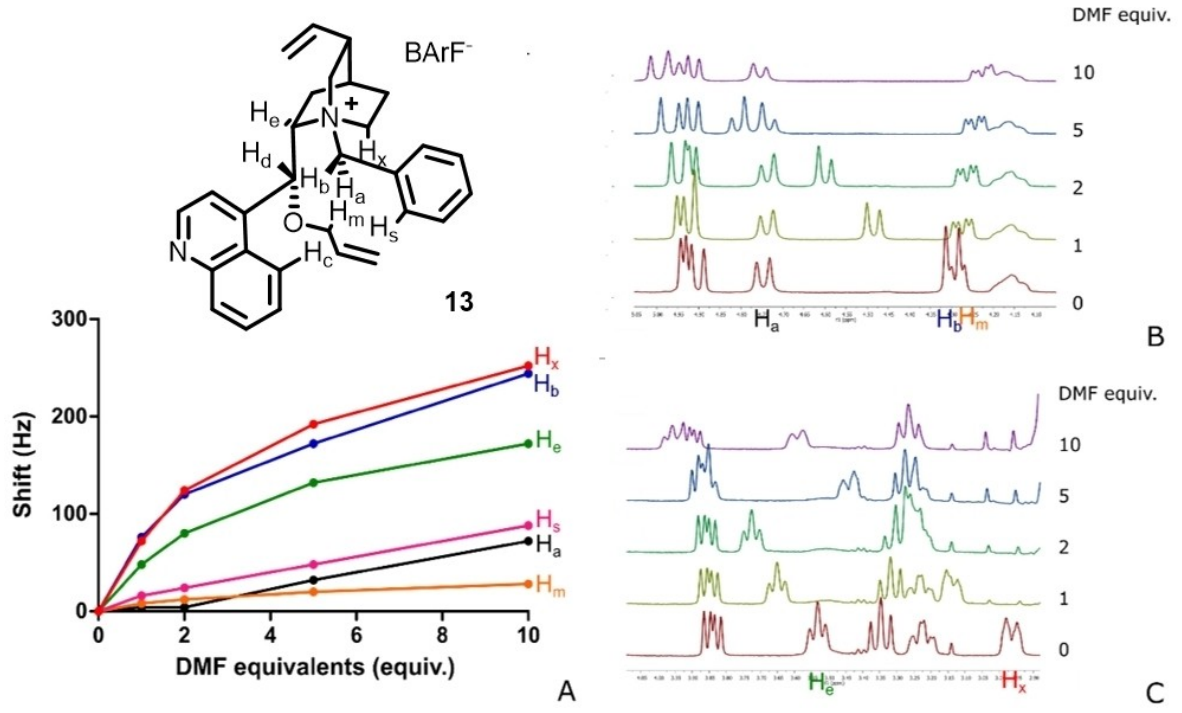


Figure 9. ^{1}H NMR titration of *O*(9)-allyl-*N*-benzyl-cinchonidinium BArF$^-$ **13** with increasing aliquots of DMF: (A) shift in Hz vs. equivalents of DMF applied; (B) ^{1}H NMR traces for H_a, H_b and H_m; (C) ^{1}H NMR traces for H_e and H_x.

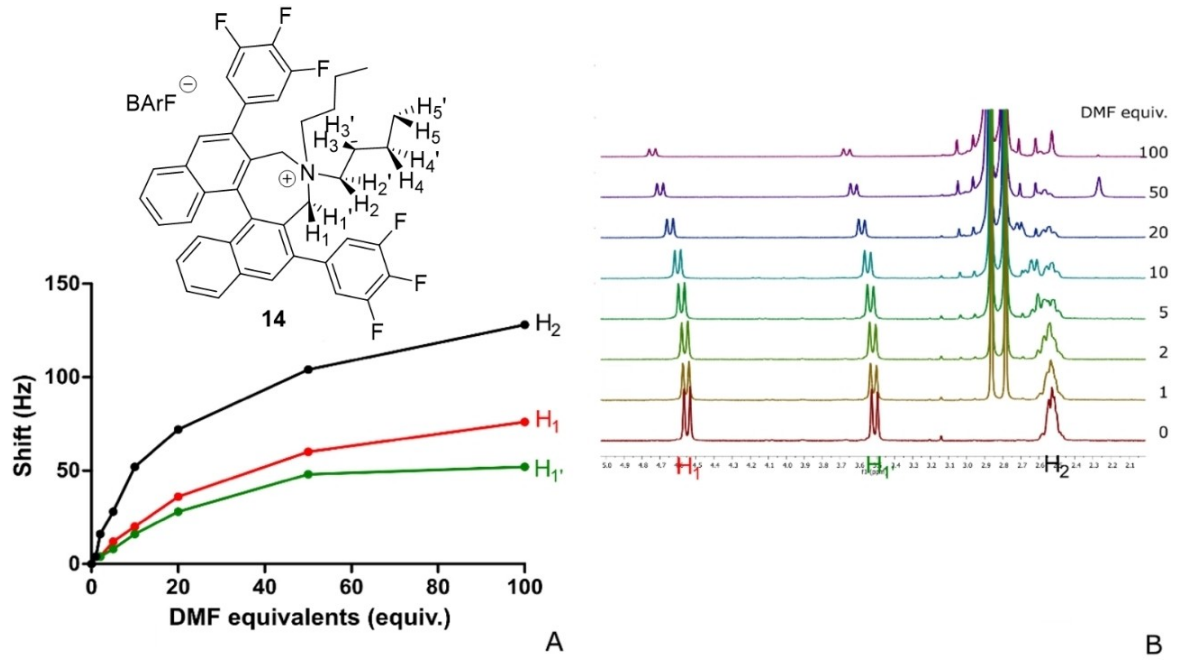


Figure 10. ^{1}H NMR titration of Maruoka's catalyst (11bR)-(−)-4,4-dibutyl-4,5-dihydro-2,6 bis(3,4,5-trifluorophenyl)-3H-dinaphth[2,1-c:1′,2′-e]azepinium BArF$^-$ **14** with increasing aliquots of DMF: (A) shift in Hz vs. equivalents of DMF applied; ^{1}H NMR traces for H_1, $H_{1'}$ and H_2.

reaction,[33,34,97] a simple procedure involving reaction of 4-nitroisoxazoles with NaOH. The reaction of **18** and **19** worked under the catalysis of cinchonidinium salt **20** providing (*R*)-22 in up to 97% *ee*. Significantly, compound **22** was obtained in only 7% ee when the *O*-benzyl derivative of **20** was used as the catalyst. This data indicated that a bifunctional mode of reaction was required by **20** to achieve high enantiocontrol.

As previously elaborated, Palomo has already demonstrated that in similar conditions nitromethane enolate is preferentially bond to the OH of *Cinchona* quaternary ammonium salts.[76,78]

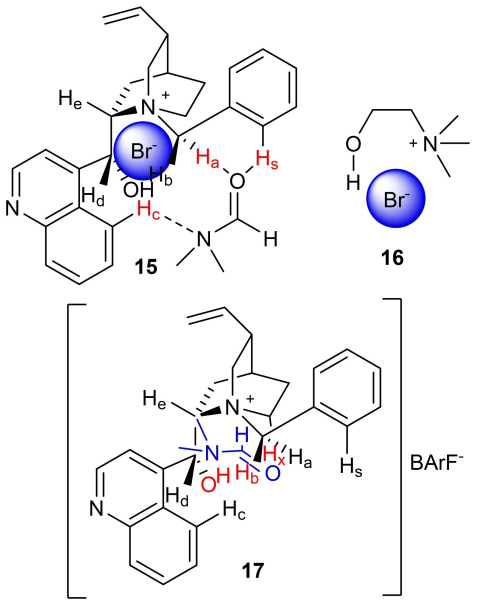
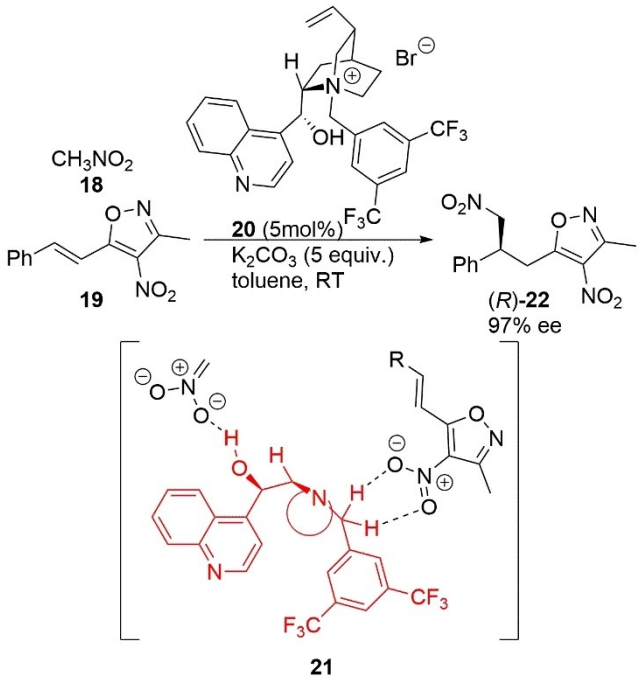
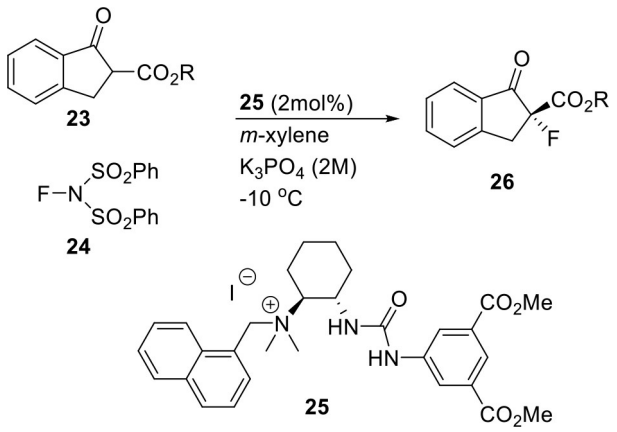


Figure 11. Tentative model of interaction between **7** and **11** with DMF, according to the ^{1}H NMR titration data collected.



Scheme 1. Enantioselective addition of nitromethane **18** to 3-methyl-4-nitro-5-styrylisoxazoles **19**.[33]

Although bromides, as discussed, are closely associated with the alcohol in catalysts such as **7**–**8**, it is possible that under the reaction conditions, the halogen is exchanged for a stronger nitronate acceptor. Hence, we have postulated that in a transition state **21** (Scheme 1) leading to compound **22**, the nitromethane enolate could be bound to the hydroxyl. Considering the stereochemistry generated in compound (*R*)-**22**



Scheme 2. Enantioselective fluorination of indanone **23**.[42]

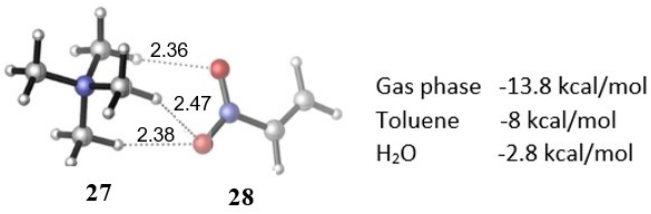


Figure 12. Calculated energy of interaction between tetramethyl ammonium cation **27** and nitroethene **28**.

and the direction of attack of **18** to the pro-(R) face of **19**, we considered the possibility of the nitro group of **19** being involved in H-bonding with the $^+$N–C–H of **20**.[98] Transition state **21**, therefore, would justify the observed enantioselectivity for this and other reactions involving Michael additions to **19**.[33,34] In order to demonstrate this, we first carried out some calculations, by selecting tetramethylammonium as a surrogate for Quats and nitroethene as a simpler equivalent for **19**. This study, executed using a B3LYP routine, which is the same algorithm as reported by Houk[78] and Palomo[76] for similar investigations, indicated that there were three potential H-bonding interactions (Figure 12) which could be established between the nitro oxygen atoms of **28** and $^+$N–C–H moieties present in **27**. The intensity of the interaction of **27** to **28** was predicted to be −13.8 kcal/mol in the gas phase, and most importantly −8.0 kcal/mol in toluene (the solvent used for the enantioselective addition of nitromethane to **19**).

Encouraged by these results we carried out a titration experiment using *N*-benzyl-cinchoninium bromide **8** with increasing aliquots of 3-methyl-4-nitro-5-styrylisoxazole **19** (Figure 13). Delightfully, the results collected (Figure 13) matched those we observed for the titration of **8** and DMF: the benzylic H_a and H_b were particularly affected with shifts of up to 80 Hz. The shift of geminal H_a and H_b also occurred in opposite directions indicating a different anisotropy and confirming their individual engagement in H-bonding (*i.e.* directionality of the interaction). A shift for aromatic H_c was also observed.[99] This study, in conjunction with the data reported for DMF,

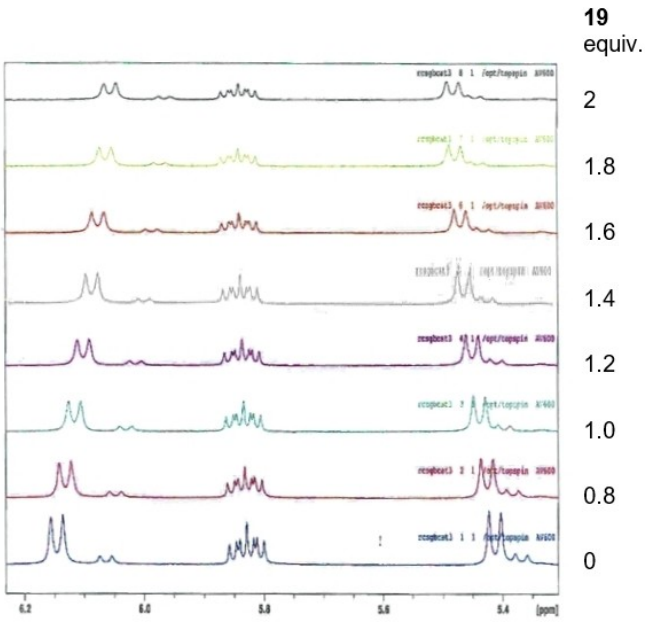


Figure 13. ^{1}H NMR titration of *N*-benzyl-cinchoninium 8 with increasing aliquots of **19**.

concluded that Quats elicit strong interactions with neutral organic molecules containing polar functionalities; for example the nitro group, *via* hydrogen bonding of $^{+}$N–C–H to NO_2. In this regard, the similarity between the $^{+}$N–C–H and thioureas, repeatedly reported as H-bond donors with NO_2 acceptors,[100] is particularly striking.

Waser group has contributed to the field of enantioselective phase-transfer catalysis by developing a modular synthesis approach to obtain a diversified collection of catalysts **25** (Scheme 2).[42–46] In all those previous reports (by others and by Waser) the beneficial effect of the H-bonding motive was clearly proven by careful control experiments. However, none of the studies performed so far have provided insight into the true activation mode of these novel catalyst motives. Based on our own interest in catalysts **25**, we have thus carried out detailed transition state analyses for the α-fluorination of β-ketoesters (Scheme 2) with the aim of: (*i*) getting a detailed understanding of the synergistic activation mode of the ammonium group and the H-bonding motive and (*ii*) using the knowledge gathered herein to develop more selective catalysts. In our initial report we postulated a very simple activation mode with the ammonium group of the catalyst ion-pairing to the enolate of the ketoester **23** and the urea coordinating the NFSI **24**.[42] However, this proposal could not be supported by any computational or additional experimental data. In order to evaluate the preferred binding mode of the bifunctional urea catalyst **25** and the two reactants **23** and **24**, we carried out a detailed investigation of the C–F bond-forming step in this reaction using B3LYP/6-31G* calculations (Figure 14).[101–104] A thorough conformational search was performed and transition structures leading to the major (*R*) and minor (*S*) enantiomer of **26** were located. The relative energies of the computed transition structures were evaluated by carrying out high-level single point energy calculations using B3LYP-D3(BJ)/Def2TZVPP with a PCM solvent model for *m*-xylene.[105–108] Relative energies presented herein are the extrapolated Gibbs free energy obtained by adding the free energy correction to the high-level single point energy computed for each structure. The free energies were corrected using Grimme's quasi rigid rotor-harmonic oscillator (qRRHO) approach, which raises vibrational frequencies that are below 100 cm^{-1} to 100 cm^{-1}.[109] We evaluated our originally proposed model where the enolate of **23** is stabilized by the quaternary ammonium moiety and **24** is bound to the urea moiety of the catalyst **25** (binding mode 1) and compared its relative energy to the complementary binding mode 2, where the enolate **23** is bound to the urea and **24** is bound the quaternary ammonium group of **25**. Shown in Figure 14 are the lowest energy transition structures leading the major enantiomer via binding mode 1 (TS-*R*-BM1) and binding mode 2 (TS-*R*-BM2). In TS-*R*-BM1, the enolate of **24** is bound to the ammonium moiety *via* three non-conventional $^{+}$N–C–H to O interactions (2.23 Å, 2.05 Å, and 2.44 Å) between the CH bonds α-to the quaternary nitrogen and the two oxygen atoms of the enolate while the developing negative charge on the sulfonamide oxygen atoms of **24** is stabilized by moderately strong H-bonding interactions with the urea NHs (1.94 Å, 2.20 Å). On the other hand, TS-*R*-BM2 is stabilized by two strong H-bonding interactions (1.84 Å, 1.87 Å) between one of the enolate oxygen atoms and the two urea NHs and a weak

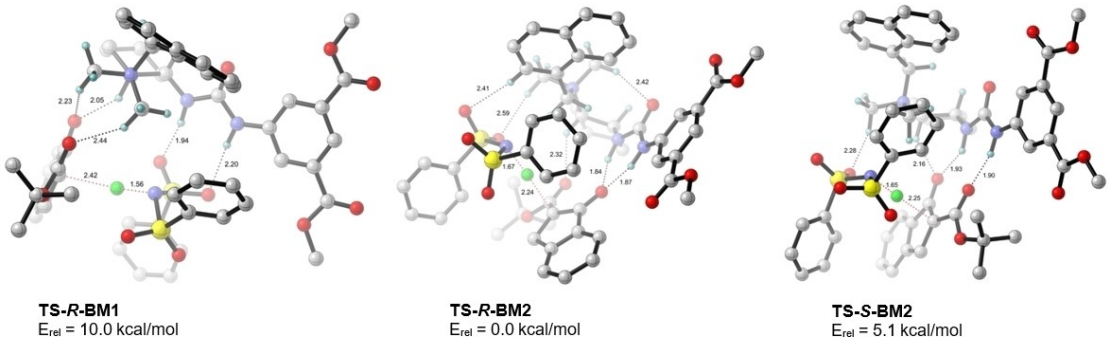


Figure 14. Energy transition states for the reaction of **23** and **24** under the catalysis of **25** calculated at B3LYP/6-31G*.

$^{+}$N–C–H to O interaction with the second oxygen atom of the enolate and the cyclohexyl CH adjacent to the quaternary ammonium center. While the urea moiety binds the enolate of **23** in TS-*R*-BM2, the approach of **24** is directed by a weak non-conventional $^{+}$N–C–H to O interaction (2.59 Å) and a naphthyl (sp^2)CH to O interaction (2.41 Å) to the two oxygen atoms of sulfonamide. Contrary to our original hypothesis, TS-*R*-BM2 was found to be 10.0 kcal/mol lower in energy than TS-*R*-BM1. Comparison of the key features of these transition structures suggests that this preference for binding mode 2 is likely due to the significantly stronger H-bonding interactions between the urea and the enolate of **23**. Even though interactions between the CH bonds α-to the quaternary nitrogen and **24** at TS-*R*-BM2 might not seem significant, it is interesting to note that all transition structures where the enolate of **23** is bound to the urea moiety and **24** approaches without any interactions with the quaternary ammonium group (binding mode 3, not shown; see Supporting Information) were found to be at least 12.5 kcal mol^{-1} higher in energy than TS-R-BM2. This suggests that the quaternary ammonium group has a significant role in stabilizing the transition state via both electrostatic and $^{+}$N–C–H to O interactions. Finally, we were able to evaluate the origin of enantioselectivity in this reaction by comparing the lowest energy transition structures leading to the *R* (TS-*R*-BM2) and *S* (TS-*S*-BM2) enantiomers of **26**. While both these transition structures can be classified as proceeding via binding mode 2 (enolate of **23** bound to urea), they differ in the fact that the $^{+}$F is delivered to the *Re*-face of the enolate in TS-*R*-BM2 and the *Si*-face of the enolate in TS-*S*-BM2. The slightly weaker H-bonding network of the enolate of **23** and the urea NHs in TS-*S*-BM2 along with possible deleterious steric interactions between the *t*-butyl ester of **23** and the catalyst results in TS-*R*-BM2 being 5.1 kcal/mol lower in energy, consistent with the high ee observed for this reaction. We recognize that this difference is quite large and a significant over-estimation of actual experimental selectivity – we attribute this to the fact that transition state optimizations were performed in the gas phase using a functional without dispersion (due to the large size of the system). Nonetheless, we believe that our thorough exploration of the phase space of this reaction has resulted in important insight into the nature of transition state stabilization orchestrated by these bifunctional quaternary ammonium-urea chiral catalysts.

Intrigued by the computational studies, indicating potential interactions between the CH bonds α-to the quaternary nitrogen and their substrates, we carried out ^{1}H NMR titration studies of catalyst 25 and reagents 23 and 24 (Figure 15). The ^{1}H NMR spectrum of catalyst 25 (Figure 15, (A)) did not show any variation upon addition of 1 equiv. of ketoester **23** and an equal amount of base (Figure 15, (B)). However, when a solution of **25** in $CDCl_3$ was treated with 1 equiv. of NSFI (Figure 15, (C)), two changes were immediately evident, namely: (*i*) the benzylic CH_2 (circled in red, Figure 15) which moved from 5.42 ppm and 5.68 ppm to coalesce at 5.40 ppm; (*ii*) the two $^{+}$N(CH_3) (circled in blue, Figure 11) which shifted from 2.89 ppm and 3.17 ppm to 3.05 ppm and 3.21 ppm respectively. This data showed that there was an H-bonding interaction taking place between the

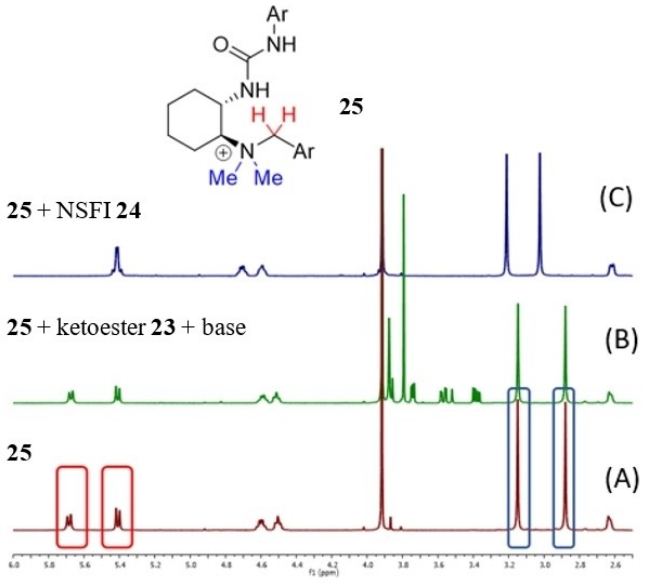


Figure 15. ^{1}H NMR traces of: (A) catalyst **25** only; (B) catalyst **25** and 1 equiv. of ketoester **23** and base; (C) catalyst **25** and 1 equiv. of NSFI **24**.

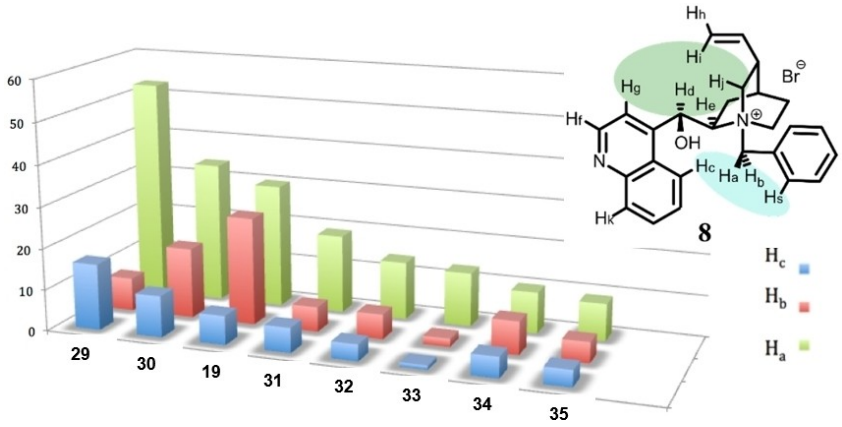
$^{+}$N–C–H of catalyst **25** and NSFI **24**, a neutral reagent. Also, catalyst **25** seemed not to interact with the enolate. Finally the signals for the benzylic CH_2 were enlarged which is indicative of H-bonding.

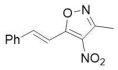
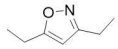
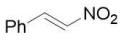
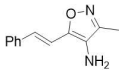
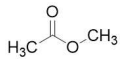
In order to establish a relative scale of H-bond donor ability of the $^{+}$N–C–H protons, we have run a set of ^{1}H NMR titrations of compound 8 against a range of hydrogen bond acceptors (**19**, **29**–**35**, Table 1). Scope of this study was to obtain qualitative results and obtain a relative scale of preferred ligands. The results collected indicated that benzylic H_a and H_b and aromatic H_c were the most affected protons. From a quantitative perspective, it was confirmed that dimethylformamide **29** was the best ligand for 8, followed by nitromethane **30** and by 3-methyl-4-nitro-5-styrylisoxazole **19**. The nitro group interacted stronger with $^{+}$N–C–H than carbonyls of ketones and esters. Not surprisingly in view of its scarce aromaticity, 2,5-diethyl isoxazole **31** also showed significant H-bonding, although to a lesser extent.

Conclusion

In summary, we have reported physical evidence from a number of experiments, which inform on the details underpinning the interaction of popular chiral quaternary ammonium salts (*Cinchona* series and Maruoka-type) as H-bond donors, with a range of neutral organic H-bond acceptors such as amides, nitroalkanes, nitroalkenes, esters, heterocycles, ketones and fluoroamides. It was therefore demonstrated that amides, nitroalkanes, nitroalkenes and N-fluorobenzenesulfonimide (NSFI) are good ligands for phase-transfer catalysts with whom they establish non-classical (sp^3)C–H and (sp^2)C–H hydrogen bonds. We also have prepared a number of *Cinchona* based

Table 1. ^{1}H NMR titration of N-benzyl-cinchoninium 8 with a range of organic hydrogen bond acceptors.



Titrant		Titrant equiv.	Signal shift [Hz]				
			H_a	H_b	H_c	H_d	H_e
	**29**	20	53	8	16	13	17
		50	103	10	30	23	31
CH_3–NO_2	**30**	20	34	17	10	5	13
		50	78	24	23	9	28
	**19**	20	30	26	7	8	0
		50	52	43	13	13	1
	**31**	20	19	6	6	5	4
		50	37	6	10	8	9
	**32**	20	14	6	4	2	3
		50	18	9	5	4	4
	**33**	20	13	2	1	0	0
		50	18	4	2	1	1
	**34**	20	10	8	5	6	4
		50	18	12	9	10	8

BArF salts and showed that these species are able to bind to DMF through their benzylic protons, although through the involvement of different sets of protons. Hence, the presence of an halogen has an impact on the mode of binding and its intensity, suggesting that BArF salts may have completely different enantioselectivity profiles in reactions carried out with *Cinchona* quaternary ammonium salts bearing an halogen as a counter-anion. The data reported mapped a set of interaction elicited by *Cinchona* and Maruoka-type ammonium salts when they interacted with their reactants, hence providing a model that could be used for the design of new catalyses or catalysts and to provide an explanation for the plethora of already reported high enantioselective syntheses via these species. Considering that PTC is popular in academic as well as industrial set up and that organocatalysis is nowadays considered paramount for developing green chemistry and sustainable manufacture, we believe this study will be of interest to those involved in fine chemical manufacture and enantioselective synthesis.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: heterocycles · hydrogen bonds · NMR spectroscopy · organocatalysis · phase-transfer catalysis

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