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DECONSTRUCTING QUININE. PART 1. TOWARD AN UNDERSTANDING OF THE REMARKABLE PERFORMANCE OF *CINCHONA* ALKALOIDS IN ASYMMETRIC PHASE TRANSFER CATALYSIS[♀]

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Abstract – A study of catalyst structure-activity/selectivity relationships for *Cinchona* alkaloid-based asymmetric phase transfer catalysis (APTC) is described. An array of substituent modifications at C(9) and the quinuclidine nitrogen were introduced to examine the role of steric and electronic effects on rate and selectivity. The synthesis of the catalysts began with manipulation of the C(9) hydroxyl group followed by alkylation of the quinuclidine nitrogen to generate the quaternary ammonium salt. Catalysts that contained large substituents attached to the quinuclidinium nitrogen were found to be the most selective and those in which the hydroxyl group was protected generally afforded faster catalysts. The presence of a polar group at C(9) significantly impacted catalyst activity.

INTRODUCTION

Cinchona alkaloids have a long history as therapeutic agents and as catalysts in asymmetric synthesis.[1] The diversity of chemical subunits in the structure of these readily available alkaloids, a quinoline, a secondary alcohol, a terminal alkene, and a sterically hindered tertiary amine, lends itself to participate in a wide array of chemical processes. Nearly all of the *Cinchona* alkaloid-based reagents and catalysts are chemically modified at one or more of these positions and have been reported as catalysts for reactions such as asymmetric reductions, oxidations, and carbon-carbon or carbon-heteroatom couplings in both transition metal catalyzed and organocatalytic variants.[2] Well-known examples include the use of modified *Cinchona* alkaloids as ligands for transition metal catalyzed asymmetric dihydroxylation, for asymmetric phase transfer catalysis (APTC), and as organocatalysts for the aldol and Michael reactions.[3,4,5] The scope of reactions employing *Cinchona* alkaloids has proven applicable to a wide

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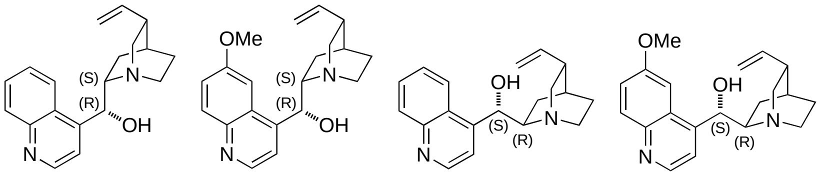
[♀] This manuscript is dedicated to Prof. Dr. Albert Eschenmoser with admiration, affection, and gratitude on the festive occasion of his 85th birthday.

variety of substrates, with high levels of selectivity, and low catalyst loadings. It is this versatility in substrate and reaction scope, combined with a diverse library of catalyst analogs that elevates the *Cinchona* alkaloid scaffold to the class of 'privileged' chiral catalysts.[6]



cinchonidine quinine cinchonine quinidine

Figure 1. *Cinchona* Alkaloid Structures

The quaternary ammonium salts derived from *Cinchona* alkaloids can function as asymmetric phase transfer catalysts (APTCs) for a wide variety of reactions. The concept of phase transfer catalysis was introduced by Starks who first observed the catalytic effect of tetraalkylammonium and phosphonium salts on nucleophilic substitution of an alkyl halide with the reagents separated in two immiscible phases.[7] The introduction of *N*-benzyl modified *Cinchona* alkaloids for APTC was pioneered by Dolling et al. for the enantioselective alkylation of indanone derivatives.[8] Later work by O'Donnell expanded the use of *Cinchona* alkaloids for APTC in the asymmetric alkylation of a glycine Schiff base derivative as means to synthesize α-amino acids.[9] Although various electrophiles were examined in this seminal report, only *N*-benzyl modified *Cinchona* alkaloids were evaluated. Subsequent studies showed that prior formation of an *O*-benzyl ether affords a catalyst that gives similar levels of enantioselectivity.[10] This finding supports the notion that under the phase transfer reaction conditions the hydroxyl group becomes alkylated *in situ* and forms the active catalyst. Lygo and Wainwright further investigated the effect of replacing the quinuclidine *N*-benzyl group with an *N*-9-anthrancenylmethyl group and observed significantly increased levels of enantioselectivity.[11] This modification was further extended by Corey *et al.* who reported superior catalyst enantioselectivity in the O'Donnell alkylation by employing *O*-allyl-*N*-9-anthracenylmethylcinchonidinium bromide.[12]

Outside the realm of APTC other modifications to the *Cinchona* alkaloid skeleton have been reported. The development of proline-catalyzed, asymmetric aldol reactions[13] inspired the introduction of several *epi*-C(9)-amino-substituted *Cinchona* analogs which were found to give high levels of enantioselectivity as catalysts in the aldol reaction.[14] Thiourea substituted analogs have also been tested as organocatalysts in Michael additions.[15] However, unlike APTC where asymmetric induction is controlled by electrostatic and other non-bonding interactions, these amino and urea adducts rely on a covalent attachment or hydrogen bonding interactions.[16]

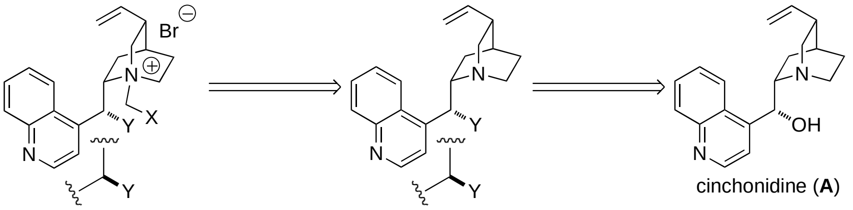
In a study to improve the enantioselectivity and yield of the O'Donnell alkylations, Lygo et al. examined catalysts bearing a limited number of substituents at several positions in the cinchonine/cinchonidine-based catalyst structure.[17] These authors found that replacing the quinoline moiety with other aryl and alkyl groups led to lower enantioselectivity and slightly diminished yields. The *N*-quinuclidinium substituent significantly affects enantioselectivity such that methylene-linked aryl substituents yield higher enantioselectivity compared to alkyl substituents and aryl groups with greater steric bulk afforded higher enantioselectivities. Notably, the 1-naphthyl group leads to higher enantioselectivity compared to the 2-naphthyl group (er 76:24 versus 70:30, respectively) suggesting that the orientation of the aryl group plays a role in catalyst enantioselectivity. Less conclusive results with catalysts were obtained bearing different *O*-substituents; namely those with *O*-benzyl and *O*-*n*-butyl groups yield slightly higher enantioselectivities compared to those with, *O*-methyl *O*-methoxymethyl, and *O*-benzyloxymethyl groups. Additionally, Dehmlow examined the effect of inverting the hydroxyl group configuration of *Cinchona* alkaloid-based catalysts for epoxidations under APTC conditions.[18]

The effect of varying the electronic properties of the quinuclidinium *N*-arylmethyl substituent on catalyst enantioselectivity has been investigated by Jew and Park.[19] Building on previous work with dimeric *Cinchona* alkaloid based catalysts, these authors showed that the placement of one fluorine atom at the 2-position is critical for higher catalyst enantioselectivity and additional fluorine atoms at the 3- and 4-positions lead to a synergistic increase in enantioselectivity. 2-Cyanobenzyl and *N*-(1-oxy-2-pyridinylmethyl) derivatives also show an increased level of enantioselectivity in the O'Donnell alkylation.

Although no definitive explanations exist for the origin of enantioselectivity with cinchoninium based APTCs,[20] two competing models of stereoinduction have been proposed for the APTC glycine imine alkylation. The model supported by Dolling and O'Donnell aligns the quinoline ring and the arylmethyl substituent on the quinuclidine nitrogen in a plane with the C(9) hydroxyl functionality acting as a directional group by a hydrogen bonding interaction.[21,22] Jew and Park have proposed that the quinuclidine nitrogen resides within an imaginary tetrahedron shell with the bicycle core, the quinoline and C(9) hydroxyl, and the *N*-quinuclidinium substituent providing steric shielding on three sides of the shell.[3,23] Despite the numerous examples of modified *Cinchona* alkaloids in APTC little attention has been paid to understanding the role that each modification contributes to catalyst enantioselectivity and reaction rate.[22] Of the many modifications to the *Cinchona* alkaloid scaffold in APTC few studies have probed the importance of the C(9) oxygen-bearing center, the impact of substituents on the oxygen, the replacement of the oxygen atom, or the removal of that heteroatom. The aim of this study was to deduce the effect of varying the steric bulk and the dipole of the substituent at the hydroxyl C(9) position of cinchonidine. Additionally, the steric and electronic contributions of the methylene-linked aromatic substituent on the quinuclidinium nitrogen would also be examined.

RESULTS

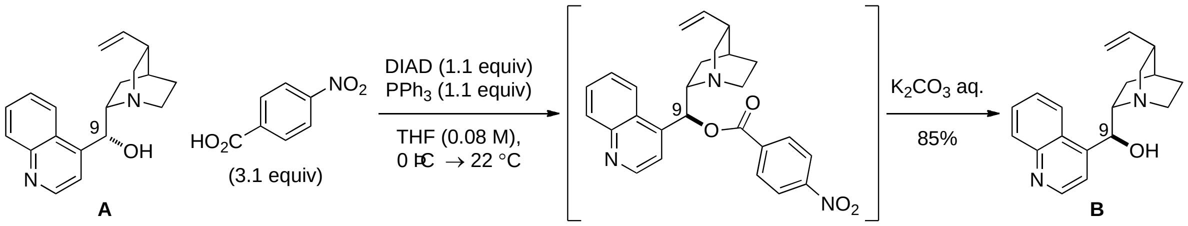
Synthesis of Catalysts. The retrosynthetic plan for the synthesis of the catalysts (Scheme 1) began with the commercially available *Cinchona* alkaloid, cinchonidine (**A**), by first manipulating the hydroxyl group and then performing the quaternization of the quinuclidine nitrogen as the final step. Five different aromatic groups were tested in addition to eight different modifications to the hydroxyl group.



Scheme 1

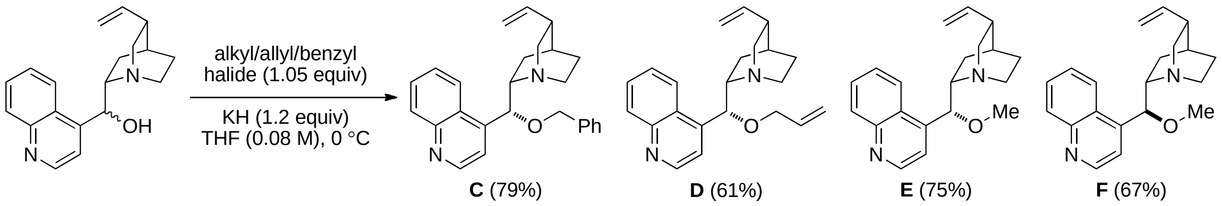
The catalysts were all generated by alkylation of the tertiary amine in the presence of the appropriate benzylic halide in acetonitrile. This approach differs somewhat from previous procedures by O'Donnell,[10] Lygo,[11] and Corey[12] wherein the quinuclidine nitrogen was first alkylated and then various *O*-substituents were added through a phase transfer alkylation.

The configuration of the hydroxyl-bearing carbon (C(9)) was inverted through a Mistunobu reaction (Scheme 2).[24] An excess of 4-nitrobenzoic acid was required to obtain C(9)-*epi*-cinchonidine **B** in good yield (85%).



Scheme 2

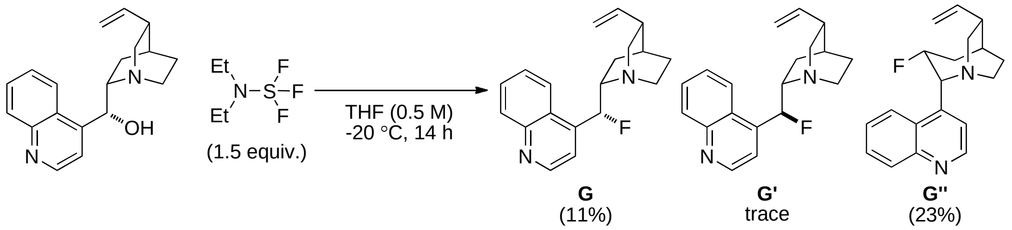
Modulation of the C(9) substituent began by alkylation of the hydroxyl group via its potassium salt (Scheme 3). The *O*-alkylated products (**C**-**F**) were formed in good yield, but minor amounts of the *N*,*O*-dialkylated product were obtained in every case despite the strong preference for *O*-alkylation, the use of only a small excess of electrophile, and low reaction temperature.



Scheme 3

Two different catalyst series were generated with significant dipole alterations in the hydroxyl-bearing carbon C(9). Initial attempts to augment the dipole included formation of a ketal and the geminal difluoride from the C(9) oxo derivative. Although the synthesis of 9-oxo-cinchonidine was successful, subsequent manipulations proved unsuccessful thus far. Efforts to form the various quaternary ammonium salts from oxo-cinchonidine were also thwarted because of facile epimerization of the resulting product.

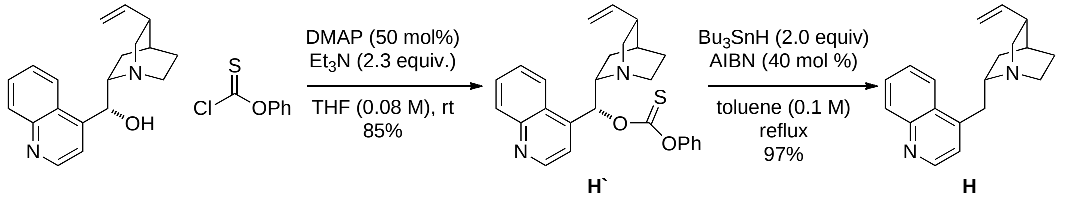
To determine the importance of the local dipole and the potential for hydrogen bonding with the C(9) oxygen substituent on the reaction rate and enantioselectivity, the more electronegative fluorine was installed. 9-Deoxy-9-fluorocinchonidine was synthesized by treating cinchonidine with diethylaminosulfur trifluoride (DAST) at low temperature (Scheme 4).[25] The catalyst precursor **G** was obtained in low yield (11%) after laborious purification. Maintaining the reaction temperature at –20 ˚C was critical for success because at lower temperatures (-60 °C) the ring-expanded deoxy fluoro structure (**G''**) was formed almost exclusively whereas at higher temperatures (>0 °C) the desired product was not formed. Trace amounts of the *epi*-deoxyfluorocinchonine (**G'**) were observed by ^{19}F NMR (376 MHz, CDCl$_3$: -177.7 ppm, dd, $^2J_{H\text{-}F} = 13.5, 49.9$ Hz) but could not be isolated from the product mixture.



Scheme 4

The second series of dipole-altered catalysts called for the removal of the hydroxyl group entirely. Deoxycinchonidine (**H**) was synthesized via the phenylthionocarbonate (**H'**) followed by a Barton-McCombie radical deoxygenation (Scheme 5).[26] The isolation of the quaternary ammonium salts resulting from alkylation of proved to be difficult in some instances. Specifically, the *N*-benzyl and *N*-(bis-3,5-trifluoromethyl)benzyl substituents decomposed through a Hoffmann elimination pathway during workup. This instability led to the omission of the

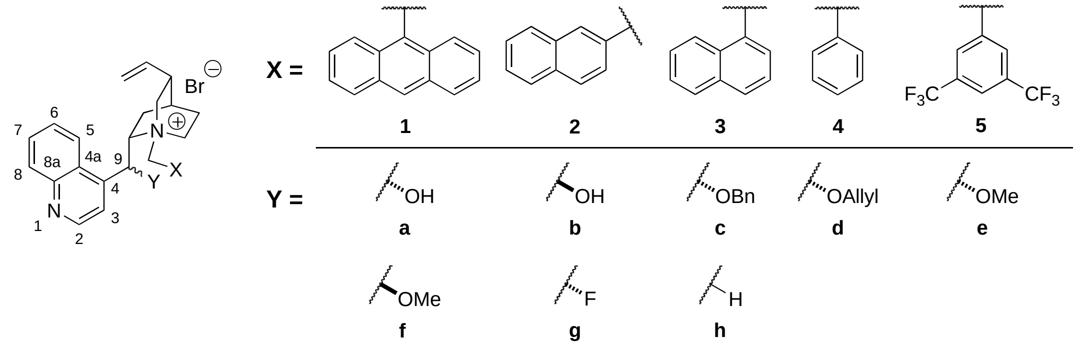
N-(bis-3,5-trifluoromethyl)benzyldeoxycinchonidinium bromide catalyst from the catalyst library because insufficient quantities could be isolated in acceptable purity. Catalysts **2g** and **3g** were used as an approximate 6:1 and 10:1 mixture of catalyst/impurity, respectively. The impurity was likely due to catalyst decomposition during the workup conditions or it was present in the starting material.



Scheme 5

Following the various procedures described above, 39 catalysts were available to survey the consequences of these structural modifications the rate and selectivity of the O’Donnell alkylation (Table 1). The Y substituent was varied from H to F (*R* configuration) to OH (both configurations) to OMe (both configurations) to OBn (*R* configuration) and then to *O*-allyl (*R* configuration). This collection of modifications should provide insights into both the steric and electronic influences of the C(9) substituent on the rate and selectivity of the alkylation.

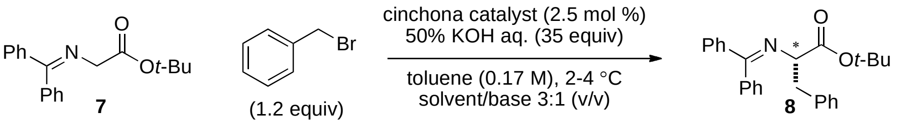
Table 1. Catalyst Library Reference Chart



Catalyst	X	Y		X	Y		X	Y		X	Y		X	Y		X	Y		X	Y		X	Y
1a	1	a	**1b**	1	b	**1c**	1	c	**1d**	1	d	**1e**	1	e	**1f**	1	f	**1g**	1	g	**1h**	1	h
2a	2	a	**2b**	2	b	**2c**	2	c	**2d**	2	d	**2e**	2	e	**2f**	2	f	**2g**	2	g	**2h**	2	h
3a	3	a	**3b**	3	b	**3c**	3	c	**3d**	3	d	**3e**	3	e	**3f**	3	f	**3g**	3	g	**3h**	3	h
4a	4	a	**4b**	4	b	**4c**	4	c	**4d**	4	d	**4e**	4	e	**4f**	4	f	**4g**	4	g	**4h**	4	h
5a	5	a	**5b**	5	b	**5c**	5	c	**5d**	5	d	**5e**	5	e	**5f**	5	f	**5g**	5	g			

APTC Alkylation Reactions. A standard set of reaction conditions for the APTC alkylation of the glycine Schiff base **6** was employed to record reaction half-life and the product enantiomeric ratio

(Scheme 6). The decision to run the reaction at 2-4 °C was made primarily to keep the reaction half-life within a reasonable timescale for effective data collection.



Scheme 6

The enantioselectivity values shown in the Figure 2 were obtained from aliquots removed after the reaction had reached full conversion (75-90%). For reactions that stalled, the alkylation product was purified prior to determining the level of enantioenrichment. The data in Figure 2 shows that the enantioselectivity of the alkylation reaction is most significantly affected by the nature of the substituent X (9-anthracenyl, benzyl, etc.) with a lesser influence from the various Y substituents. The configuration at the C(9) center bearing either a hydroxyl group (rows a and b) or a methoxy group (rows e and f) was unimportant for catalyst enantioselectivity. Interestingly, the catalyst series with the unnatural C(9) *S* configuration bearing a methoxy group (row f) afforded generally higher selectivities for various X substituents. 9-Deoxy-9-fluorocinchonidinium catalysts were less selective than their oxygen-containing counterparts and, for the best series **1**, (X = 9-anthracenylmethyl), much less so (row g). Remarkably, despite the lack of sensitivity to changes in size, configuration, hydrogen bonding ability and dipole moment of the substituent at C(9), the absence of any substituent led to unselective catalysts (row h).

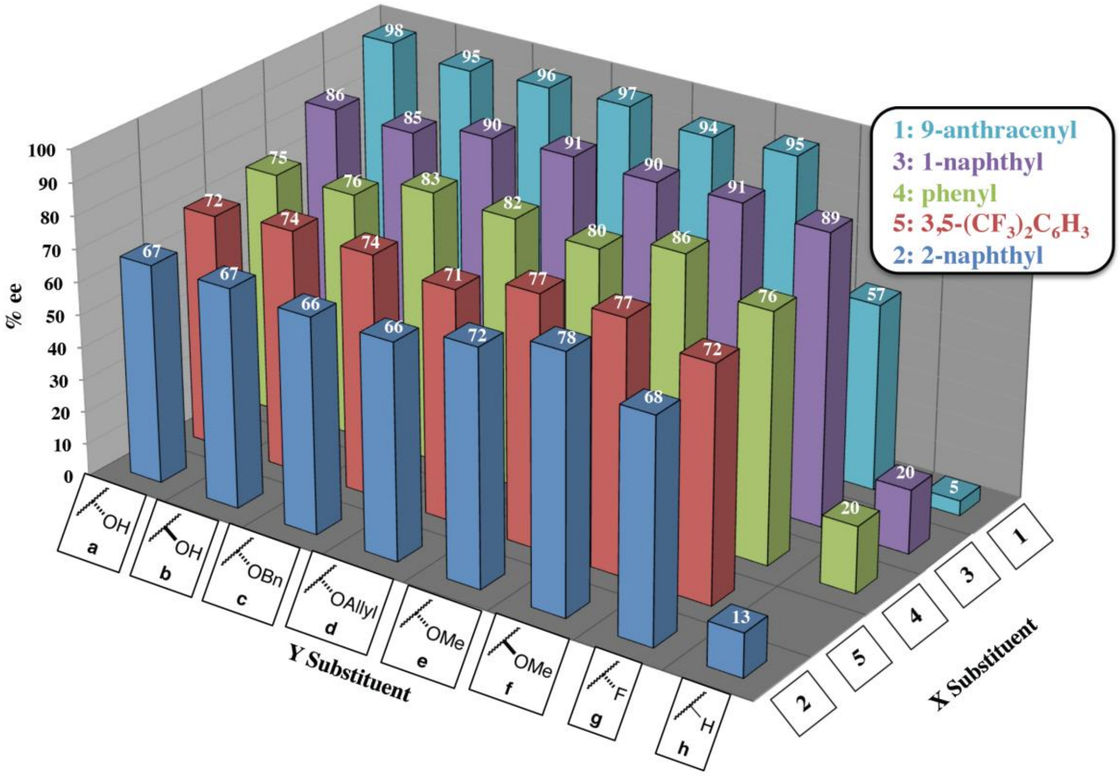


Figure 2. Catalyst Enantioselectivity Survey

The effects of structural modifications on reaction rate were also examined with the same catalyst library (Figure 3). Most of these catalysts were soluble in the organic phase prior to the addition of aqueous base. However, some catalysts (**2a**, **2b**, **4c**, **1g**, **2g**, **1h**, **2h**, **3h**, **4h**) were only partially soluble and therefore represent unknown catalyst concentrations. Thus, any conclusions based on the half-lives for these catalysts must be made with caution. Another interesting finding of this survey was the presence of an induction period with catalysts **1a**, **2a**, **3a**, **4a**, and **5g**. No induction period was observed for the respective catalyst epimers (**1b**, **2b**, **3b**, and **4b**).

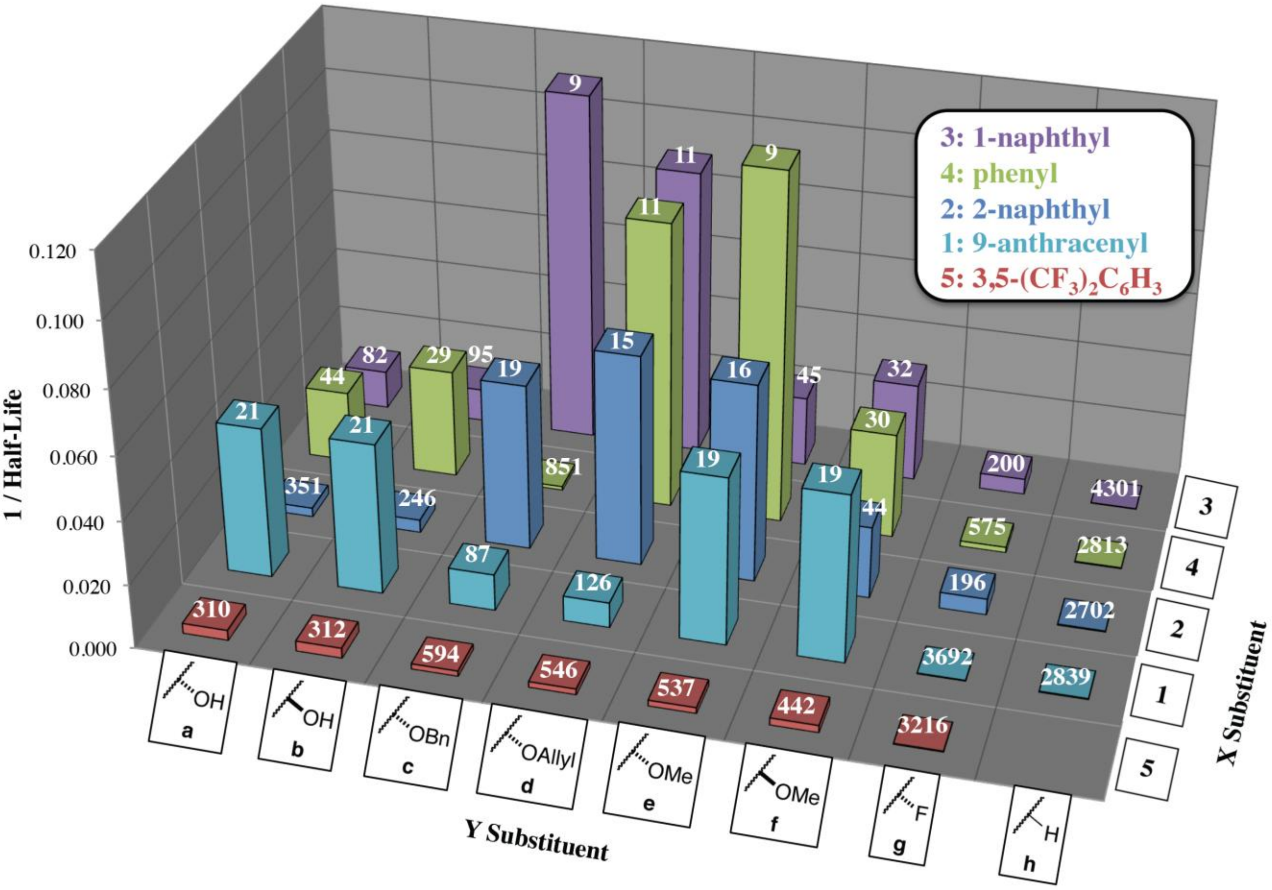


Figure 3. Reaction Rate Survey (Calculated Half-Lives Shown with Respective Catalyst)

The rate data shows that for each X position substituent series (right horizontal axis) a significant change in reaction rate between the hydroxyl group (row a) and preformed *O*-benzyl substituent (row c) is seen. Because the reaction is performed with an excess of benzyl bromide (1.2 equiv) in the presence of 50% aqueous KOH solution, the catalyst might be *O*-benzylated *in situ.* For the X = 9-anthracenylmethyl entries (**1**) the hydroxyl bearing catalysts were 5-fold faster than the benzyloxy (**c**) and allyloxy (**d**) catalysts but equipotent with the methoxy catalysts (**e**, **f**). On the other hand, the situation is reversed in the X = 1-naphthyl series (**3**) where the benzyloxy and allyloxy catalysts outperformed both the hydroxy and methoxy catalysts by a factor of 10. For the X = 3,5-$(CF_3)_2C_6H_3$ series (**5**), the hydroxyl bearing catalysts were at most 2-fold faster than the C(9) alkoxy catalysts. Unfortunately the incomplete solubility of **2a** and **2b** as well as **4c** precluded drawing definitive conclusions. Nevertheless, one can still conclude that **4a** is a much more effective catalyst than **4c** under these conditions thereby excluding the possibility that an *in situ* formed benzyl ether is the active catalyst in this series. None of the deoxycinchoninium salts were fully soluble and showed extremely long half-lives, between 100- and 300-fold slower than the faster catalysts in each X series.

DISCUSSION

Synthesis of Catalysts. The preparation of the cinchonidinium salts for this catalyst library was generally satisfactory and required only minor optimization to generate sufficient amounts of material for testing. However, both *C*(9)-*epi*-cinchonidine and 9-deoxy-9-fluorocinchonidine required either some optimization or extensive purification before sufficient quantities of catalyst could be obtained. In the case of the Mitsunobu reaction, employing only a slight excess of 4-nitrobenzoic acid led to a complex mixture, whereas the use of three or more equivalents of the acid generated the desired product in good yield. This problem may arise from the participation of the quinuclidine nitrogen in an intramolecular displacement of the activated hydroxyl group. In the presence of an excess of the acid, the quinuclidine nitrogen remains protonated and therefore unable to participate in displacement.

The stereoretentive displacement of the hydroxyl group in the formation of 9-deoxy-9-fluoro product, **G**, and the lack of formation of the inversion product, **G'**, also support the intermediacy of an aziridinium ion as does the exclusive formation of the ring expanded product, **G''**, at lower temperature.[27] Because of the structural similarity between **G** and **G'** consecutive chromatographic separations were required to obtain **G** in sufficient purity and quantity.

APTC Alkylation Reactions. Several trends can be gleaned from the results of this study on the influence of the X and Y substituents on rate and selectivity of catalysis. Catalyst enantioselectivity (Figure 2) will be addressed first followed by a discussion on reaction rate (Figure 3).

Enantioselectivity. Catalyst enantioselectivity was most significantly affected by the steric bulk of substituent X, with the largest substituent, 9-anthracenyl (series **1**), providing the most selective catalysts. However, the X = 2-naphthyl (series **2**) and X = 3,5-$(CF_3)_2C_6H_3$ (series **5**) were less selective than the least bulky substituent, X = phenyl (series **4**). This finding suggests that the steric bulk of substituent X alone does not determine catalyst enantioselectivity. By contrast the identity, size, configuration, or hydrogen bonding ability of the Y group had only a minor affect on the selectivity of the catalysts. For all but the most selective catalysts (series **1**) the presence of a C(9) *O*-alkyl group led to marginally higher selectivities compared to the parent C(9) hydroxy catalysts with no correlation to the size of the alkyl group. Augmentation of the dipole strength by substituting a hydroxyl group with a fluorine atom at C(9) (series **g**) afforded a catalyst of comparable enantioselectivity and therefore did not significantly perturb the structure of the enolate-catalyst ion pair. Surprisingly, **1g** bearing a 9-anthracenylmethyl substituent was not the most selective catalyst within the deoxy fluoro series. The poor selectivity of **1g** suggests a faster rate of catalyst decomposition compared to the desired alkylation reaction. Importantly, removing the Y substituent altogether (series **h**), afforded catalysts that provided very poor enantioselectivity.

The enantioselectivity data is in general agreement with Jew and Park's model of stereoinduction whereby an increase in steric bulk of the substituent X leads to an increase in catalyst enantioselectivity (Figure 4).[28,29,30] Employing bridged, dimeric, *N*-quinuclidinium *Cinchona* alkaloid-based catalysts, the authors observed increased enantioselectivity with 2-naphthyl linkers compared to a phenyl group. The use of bulkier aryl linkers within the dimeric catalyst likely leads to enhanced conformational rigidity and thus greater catalyst enantioselectivity. Contrary to previous studies by Dolling *et. al*. who proposed a π-π stacking interaction in the catalyst-substrate ion pair, increasing the π-acidity of position X did not result in a more enantioselective catalyst; the unmodified benzyl substituent was more selective in every case.[8] Earlier work by Dehmlow *et. al.* had shown that inverting the C(9) hydroxyl group configuration led to a reversal in product configuration in the APTC epoxidation of naphthoquinones.[18] For the alkylation reaction studied herein, changing the configuration at C(9) alone slightly *increased* catalyst enantioselectivity and yielded the same major enantiomer of the alkylation product.

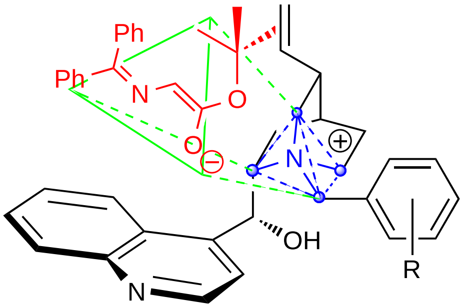


Figure 4. Tetrahedron Model for Cinchona Alkaloid-based Catalyst Enantioselectivity

Although the tetrahedron model can account for the high selectivity with X = 9-anthracenyl (series **1**) it does not fully explain the relative lack of selectivity with X = $(CF_3)_2C_6H_3$ (series **5**) and X = 2-naphthyl (series **2**). One possibility that accounts for the reduced selectivity of these catalysts is a change the lowest energy conformation of the catalyst. Alternatively, the enolate could associate with the face of the ammonium tetrahedron containing the X substituent because of a competitive π-stacking interaction. The results from substitution of fluorine in place of a hydroxyl group for the Y substituent at C(9) provide three important insights: (1) the electrostatic polarization of positive charge to that side of the ammonium ion is important, (2) the need for hydrogen or ionic bonding interaction with the Y group is unimportant for high enantioselectivity,[31] and (3) the conformation of the quinoline moiety must not change significantly by changing the nature or configuration of the C(9) substituent. These conclusions are also confluent with the lack of selectivity observed when the C(9) substituent is removed. Three explanations can be formulated for this behavior: (1) poor control of the quinoline ring conformation, (2) poor control over of the topicity of interaction between the enolate and the catalyst (see above) and (3) catalyst decomposition. Catalyst decomposition may occur by deprotonation at the C(9) position to produce a ring-opened structure which would likely be less enantioselective than the parent catalyst. Dolling *et al*. have previously generated a quaternary ammonium salt from the ring-expanded decomposition product of a *Cinchona*-based catalyst and found it to be unselective.[22] Thus, the low selectivity seen with deoxycinchonidinum catalysts is not unambiguously interpretable in view of this instability. Additional studies are required to elucidate the effect of the removal of the C(9) substituent. Perhaps the use of a less reactive electrophile that would not alkylate any catalyst decomposition products could prevent the formation of unselective catalysts in the reaction mixture.

Reaction Rate. No clear trend was apparent with respect to the influence of the X substituent on reaction rate with the exception that catalysts bearing X = 3,5-$(CF_3)_2C_6H_3$ (series **5)** led uniformly to slower reactions. However, unlike the trends seen for enantioselectivity, the rate with all catalyst families was significantly dependent on the Y substituent. If a free hydroxyl group is taken as the baseline (series **a**), then epimeric catalysts (series **b**) are nearly identical whereas the ethers behave quite differently. For example, among the *O*-benzyl catalysts (series **c**) three are slower and two are significantly faster (1- and 2-naphthyl). In the 1-naphthyl series (catalyst **3c**), it is possible that the hydroxy catalyst (**3b**) may have been less soluble than it appeared prior to base addition in the reaction. Moreover, catalyst **2b** was only partially soluble compared to its *O*-benzyl analog **2c**, which was readily soluble in the reaction mixture. Generally, catalysts with a C(9) *O*-allyl (series **d**) or *O*-methyl (series **e**) were faster than the parent catalysts. However, unlike the hydroxy catalysts, the *O*-methyl catalysts did demonstrate a dependence on the configuration at C(9) though no trend was apparent. Most of the 9-deoxy-9-fluorocinchonidinium catalysts (series **g**) were slower compared against the hydroxy catalysts (series **a**) by a factor of 10 or more. However, catalyst **2g** was found to be faster catalyst compared to its hydroxyl analog (**2a**), and catalyst **3g** showed similar activity compared to its hydroxyl analog (**3a**). This finding may be attributed to catalyst solubility. The reaction rate data would suggest that a certain combination of X and Y substituent leads to a fast catalyst. For instance, when X = 9-anthracenyl only the Y = OH or OMe substituents afford fast catalysts. However, by switching to a quinuclidinium substituent with less steric bulk, X = 2-naphthyl, 1-naphthyl, or phenyl, and in combination substituents such as Y = *O*-benzyl, *O*-allyl afford a relatively fast catalyst.

The disparity in reaction half-lives between the C(9) hydroxy (series **a** and **b**) and C(9)-benzyloxy (series **c**) cinchonidinium catalysts was unexpected. On the basis of similar enantioselectivities for C(9)-hydroxyl and C(9)-benzyloxy catalysts, O'Donnell concluded that the *in situ* formed ether was the active catalyst.[10] The results herein confirm the similarity of enantioselectivities, but the reaction rates were clearly different and depended on the X substituent. For O'Donnell's catalyst (series **4**) the *O*-benzyl ether was at least 15 times less active, thus disproving the assertion that the ether is the active catalyst.

The interpretation of structural effect on rate are much more challenging because these reactions are operating in the transport limiting regime.[32] Thus, the factors that influence reaction rate are much more complex and relate to the kinetic and equilibria of ion pairing, exchange and transport rather than intrinsic reactivity of the ion pairs to alkylation. Recent studies in these laboratories have shown that molecular properties such as ammonium charge accessibility and catalyst cross-sectional area are strongly correlated with reaction rate.[33] The situation is further complicated by the different resting states for the catalysts.[22] Dolling *et al.* have found that the hydroxy catalysts exist as a mono deprotonated dimers under these reaction conditions. The mono deprotonated dimer is significantly more soluble in the organic phase than is the parent catalyst and the 0.5 order dependence on the catalyst reveals that the dimer must dissociate into an active monomer for the alkylation to take place. This base-mediated formation of the catalyst dimer species is also likely responsible for the observed induction period with catalysts **1a**, **2a**, **3a**, and **4a**. The lack of induction period with the respective catalyst epimers (**1b**, **2b**, **3b**, and **4b**) suggests a structural dependency on the rate of dimer formation. Additionally, since both configurations of the hydroxyl group (series **a** and **b**) have nearly similar half-lives then dimer formation does not affect the rate-determining step of the reaction. The induction period observed with catalyst **5g** may be due to a bromide exchange with hydroxide anion from the basic aqueous phase.

In summary, catalyst enantioselectivity was found to be primarily dependent on the steric bulk of substituent X such that larger substituents afford more selective catalysts. An electronegative substituent at C(9) is critical for high reaction rates and enantioselectivities as well as chemically stable catalysts. The identity, configuration and hydrogen bonding ability of that substituent are much less important. Further modifications of the *Cinchona* alkaloids at the aromatic residue as well as changes in the bicyclic core will be evaluated for their impact on rate and selectivity. In addition, computational evaluation of the catalysts described herein is currently underway to determine if the behavior of this class of compounds can be understood by established molecular descriptors.

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