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Enantiocontrol with a Hydrogen-bond Directing Pyrrolidinylsilanol Catalyst

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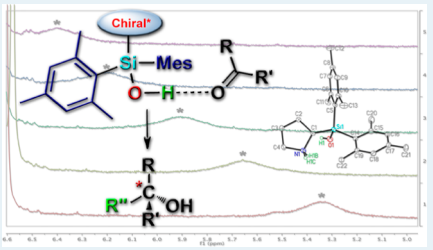
Supporting Information

ABSTRACT: A new bifunctional catalyst containing a silanol group has been designed and synthesized with high enantioselectivity in three steps. The hydrogen-bonding properties of this pyrrolidinylsilanol have been investigated using NMR binding studies and electrospray ionization mass spectrometry (ESI-MS) analysis. The ability of the silanol group to activate an electrophile and afford enantiocontrol through hydrogen-bond directing effects has been demonstrated using an enantioselective aldol reaction with isatin and acetaldehyde, affording up to 88% ee.



KEYWORDS: *asymmetric catalysis, bifunctional, hydrogen bonding, silanol, aldol, oxindole*

Enantioselective catalysis is one of the most efficient methods for the production of single enantiomer compounds for pharmaceuticals and biological screening. Activating groups that are responsible for enantiocontrol include metal centers, as well as amine, acid, alcohol, and thiourea functional groups found in organocatalysts.[1−3] On the basis of the hydrogen-bonding abilities of silanols,[4−10] we envisioned that silanols can be incorporated as a new activating group for asymmetric induction. Inorganic silanols (SiOH) make up the reactive hydroxyl groups on the surface of minerals, zeolites, and silica gel and are known to be capable of hydrogen bonding to small molecules for heterogeneous catalysis and separation chemistry.[11] Furthermore, silicon is the second most abundant element on the earth's surface, making silanol groups an attractive component for catalyst design. Using computational and mass spectrometry studies, we have already demonstrated that the acidity of silanols can be comparable to known organocatalysts.[12] In alcohols, the electronegativity of oxygen withdraws electron density away from the bonded hydrogen; while in silanols there is an enhanced effect from a lone pair of electrons on the oxygen atom back-bonding with a low-lying σ^* Si−C bond and partially with an empty d orbital of silicon.[13,14] The increased acidity of silanols make them good candidates for the design of new hydrogen-bonding catalysts, but challenges exist to synthesize discrete silanols that do not undergo condensation reactions to form siloxanes. As part of our program to explore and develop new catalysts with silanol activating groups, we recently reported the first example of silanediols as hydrogen-bonding catalysts, with examples for the Diels−Alder and Michael reactions.[15,16] We, and others, have also synthesized and demonstrated new pyrrolidinylsilane catalysts that afford high enantioselectivity based on steric control.[17−19] However, the potential of chiral organosilanols to promote enantiocontrol through hydrogen bonding remains largely unexplored, and only one example has been recently achieved with moderate enantioselectivity.[20,21]

Here we describe the design and synthesis of chiral bifunctional silanol pyrrolidine catalysts (Figure 1) and

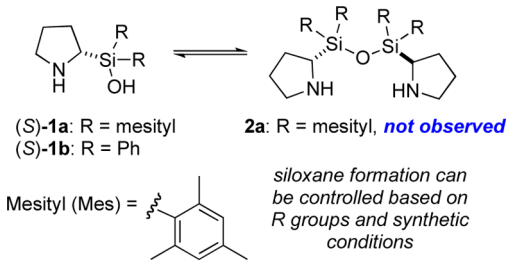


Figure 1. Design of bifunctional pyrrolidinylsilanol catalysts.

demonstrate the capabilities of a silanol group to induce asymmetry via hydrogen-bonding activation. Examples of proline and prolinol derivatives[22−32] have been reported to catalyze carbon−carbon bond-forming reactions where stereocontrol results via two modes: (1) hydrogen-bonding activation of an electrophilic carbonyl, or (2) steric interactions.[33] Therefore, the synthesis of a pyrrolidinylsilanol provides a bifunctional scaffold to incorporate and evaluate the ability of a silanol activating group to control enantioselectivity, in this case as a secondary directing element.[34,35] Furthermore, silanols are known to be more acidic than their corresponding carbon analogues,[13,36] and this scaffold allows for a direct comparison with prolinol catalysts. In this study, we also utilize NMR binding studies in conjunction with electrospray ionization mass spectrometry (ESI-MS) analysis to demonstrate the

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hydrogen-bonding capability of the pyrrolidinylsilanol to activate carbonyl electrophiles.[15]

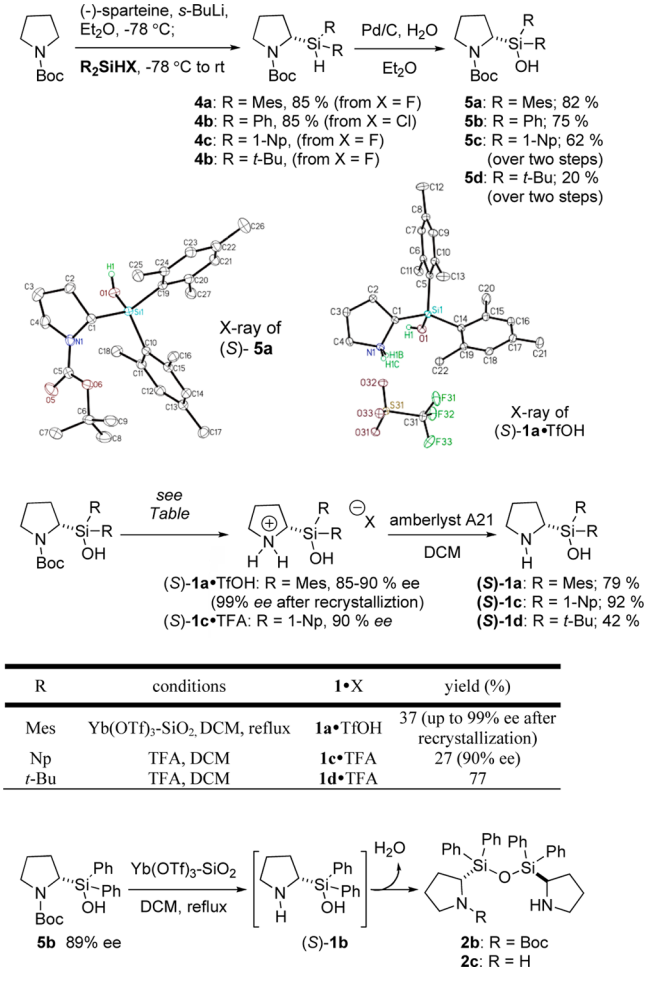
CATALYST DESIGN

To investigate the hydrogen-bonding properties of a silanol activating group for asymmetric catalysis, it was essential to design and synthesize an isolable, soluble, and enantiopure silanol catalyst to test. We envisioned installing a diarylsilanol group at a chiral center in a pyrrolidine ring that is capable of enamine catalysis for enantioselective carbon−carbon bond-forming reactions. We designed this bifunctional silanol pyrrolidine to evaluate catalytic activity and compare enantioselectivity and stereoinduction with known prolinol catalysts. The scaffold would also allow different aryl groups on silicon to be investigated to control steric and electronic effects, which would reduce competing siloxane formation and also provide a tunable catalyst design. We have previously shown that incorporating a mesityl group provides a general strategy to overcome problems related to siloxane formation (i.e., silanol condensation), and also improves solubility.[15]

Our synthetic strategy provides access to several stable, enantiopure pyrrolidinylsilanols in three steps without identifiable siloxane formation (Scheme 1). This synthetic route was also designed to investigate aryl and alkyl pyrrolidinylsilanols with different stability and hydrogen-bonding abilities. The general synthetic strategy is initiated with an asymmetric deprotonation of *N*-Boc-pyrrolidine (**3**) using (-)-sparteine[37−43] with *sec*-BuLi, followed by the addition of a silyl halide electrophile.[19,44,45] The silyl fluoride is utilized as an electrophile because of the enhanced reactivity and enantioselectivity compared to the silyl chloride reagent.[19] Using dimesitylfluorosilane as an electrophile, (2-dimesitylsilanol)-pyrrolidine (*S*)-**1a** was obtained by the hydrolysis of silane **4a** using Pd/C with H_2O followed by Boc-deprotection.[15] Several Boc-deprotection conditions were investigated to afford the desired pyrrolidinylsilanol and avoid side-products such as desilylation (see Supporting Information). We determined that deprotection conditions using $Yb(OTf)_3$ supported on SiO_2 were optimal, affording **1a**·TfOH with 85−90% enantiomeric excess (ee),[46,47] which was subsequently increased to 99% ee upon recrystallization. The utility of the mesityl group is notable when compared to the synthesis for (2-diphenylsilanol)pyrrolidine **1b** (Scheme 1). In this case, the *N*-Boc-protected silanol **5b** could be readily accessed; however, all attempts to deprotect the Boc group in the phenyl system favored condensation and formation of siloxane **2**.[48]

Computational pK_a studies indicate that pyrrolidinylsilanols can have a range of acidity from 9.7 to 14.1 (see Supporting Information).[12,15] The silyl fluoride route employed for the dimesityl catalyst **5a** is also successful for the synthesis of the dinaphthyl variant **5c** and di-*t*-butyl variant **5d** (Scheme 1). We selected these substrates because calculations predict that the dinapthylsilanol will be more acidic (pK_a = 11.7) than the dimesitylsilanol (pK_a = 14.1), whereas the di-*tert*-butylsilanol is predicted to be comparable or slightly more acidic (pK_a = 13.6). In both of these cases, conditions using TFA were optimal for Boc-deprotection while the $Yb(OTf)_3$-SiO_2 condition afforded a low yield. Attempts to synthesize diarylpyrrolidinesilanols containing electron-withdrawing groups (e.g., *p*-fluorophenyl and pentafluorophenyl) were unsuccessful, with no product isolated in the first silylation step. In these cases, we hypothesize that the electron-withdrawing aryl group can serve as a good leaving group (via a pentacoordinate silicon intermediate) once the pyrrolidine added to the silyl halide electrophile.[13]

Scheme 1. Synthesis of Pyrrolidinylsilanols



R	conditions	1•X	yield (%)
Mes	$Yb(OTf)_3$-SiO_2, DCM, reflux	**1a**•TfOH	37 (up to 99% ee after recrystallization)
Np	TFA, DCM	**1c**•TFA	27 (90% ee)
t-Bu	TFA, DCM	**1d**•TFA	77

NMR STUDIES OF HYDROGEN BONDING

We next investigated the hydrogen-bonding properties for the new pyrrolidinylsilanol **1a**·TfOH using NMR binding studies.[15,49,50] Previously, research from our laboratory has demonstrated the catalytic activity and significant self-recognition of silanediols through cooperative hydrogen bonding as a dual donor and acceptor.[16] Although monosilanols are not expected to exhibit as much self-association as silanediols, the bifunctional pyrrolidinylsilanol **1a** represents a new scaffold that has not been studied previously, and thus we performed several experiments to investigate the self-association. The silanol **1a**·TfOH examined here has little or no self-association based on low temperature NMR studies ($\Delta\delta$ = 0.03 ppm at −60 °C); however, at higher concentrations (0.4 M) a downfield shift ($\Delta\delta$ = 0.60 ppm) is observed for the silanol hydroxyl proton, which indicates that the pyrrolidinylsilanol will self-associate as the solution becomes more saturated. We then verified the hydrogen-bonding capabilities of pyrrolidinylsilanol **1a**·TfOH by NMR titration studies using a neutral Lewis base such as dimethylformamide (DMF). The hydroxyl proton of the pyrrolidinylsilanol shifted downfield ($\Delta\delta$ = 1.06 ppm) upon the addition of DMF (Figure 2). We also observed that the NH peak of **1a**·TfOH shifted downfield ($\Delta\delta$ = 0.43

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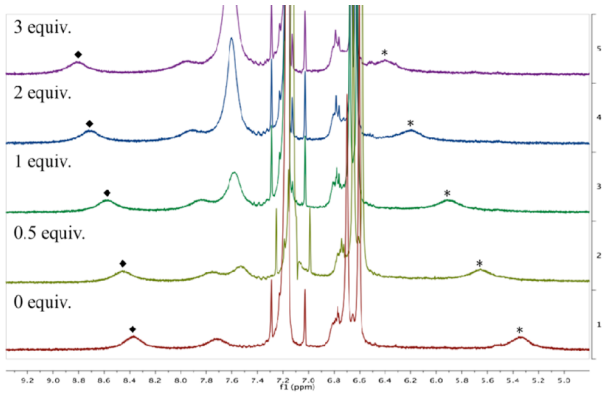


Figure 2. ^{1}H NMR binding study of pyrrolidinylsilanol **1a**·TfOH with DMF in C_6D_6. The hydroxyl peak of SiOH is indicated with an * ($\Delta\delta$ = 1.06 ppm), and the NH peak is indicated with an ♦ ($\Delta\delta$ = 0.43 ppm). The CH peak of DMF shifted 0.1 ppm.

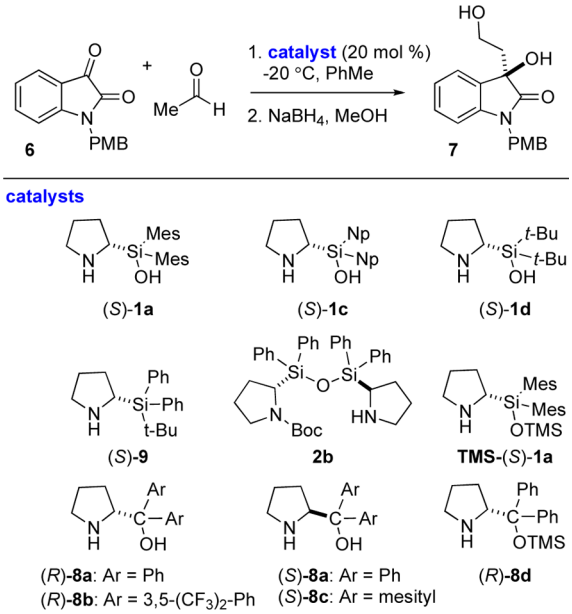
ppm). Although the shifts observed for both the SiOH and NH peaks could indicate a 2:1 binding ratio, a Job's plot analysis indicated a 1:1 stoichiometry between **1a**·TfOH and DMF. A direct comparison of NMR binding studies using prolinol catalyst (*R*)-**8a**·TfOH with DMF indicated only small shifts (<0.2 ppm); however, the carbon analogue has low solubility in organic solvents (see Supporting Information). NMR binding studies were also performed using the free amine prolinol catalysts (e.g., (*R*)-**8a** and (*R*)-**8b**) with DMF, and again only small shifts (<0.2 ppm) were observed. In parallel to NMR binding studies, the pK_a's of silanols and carbon analogues were calculated (see Supporting Information) and we observed the pK_a of silanols were 3 to 4 pK_a units lower than carbon analogues. The larger NMR shift of the SiOH relative to the carbon analogues and the pK_a calculation results are attributed to enhanced hydrogen-bonding capabilities of the pyrrolidinylsilanol.[51]

CATALYST ACTIVITY

We then proceeded to evaluate the activity of pyrrolidinylsilanol catalysts (*S*)-**1** to promote an enantioselective aldol reaction of acetaldehyde with the (1-*p*-methoxybenzyl)isatin (**6**) to afford hydroxy-oxindole **7**[52−57] (Table 1). The asymmetric aldol reaction with isatin and acetaldehyde provides a model reaction for investigation that has been previously reported with varying enantioselectivity using thiourea, cinchona, and prolinol derivatives as catalysts.[58−66] Prior to comparing catalysts, several variables were examined and the aldol reaction conditions were optimized with the dimesitylsilanol catalyst (*S*)-**1a** (see Supporting Information). Using toluene at −20 °C afforded the highest conversion and enantioselectivity. Notably, with the silanol activating group, the reaction does not require any additives for high yield and enantioselectivity.[67] The dinaphthyl and di-*tert*-butyl catalysts (*S*)-**1c**−**d** afforded lower enantioselectivity (entries 3−4). In the case of the dinaphthyl catalyst (*S*)-**1c**, the low activity and enantioselectivity is attributed to the low solubility of the catalyst. The catalytic activity and stereoinduction of pyrrolidinylsilanol (*S*)-**1a** was compared with pyrrolidine-derived catalysts (*R*)-**8a**-**b** and (*S*)-**8a**, and silanol (*S*)-**1a** afforded the highest yields and enantioselectivity when compared to these carbon analogues (entries 1−9).

The ability of the silanol to activate the isatin via hydrogen bonding, rather than directing the reaction through steric

Table 1. Catalyst Comparison for Aldol Reaction[a]



entry	catalyst	yield (%)	% ee[c]
1	(*S*)-**1a**[b]	81	85 (*R*)
2[d]	(*S*)-**1a**[b]	79	78 (*R*)
3	(*S*)-**1c**	4	24 (*R*)
4	(*S*)-**1d**	77	30 (*R*)
5	(*R*)-**8a**	39	55 (*R*)
6	(*S*)-**8a**	27	50 (*S*)
7	(*R*)-**8b**	24	78 (*S*)
8	(*S*)-**8c**	9	16 (*R*)
9	(*R*)-**8d**	7	8 (*S*)
10	(*S*)-**9**	29	12 (*S*)
11	**2b**	23	5 (*S*)
12	TMS-(*S*)-**1a**	56	33 (*R*)
13	no catalyst	no reaction	
14	pyrrolidine	no reaction	
15	$PhMe_2SiOH$[e]	no reaction	
16	pyrrolidine + $PhMe_2SiOH$	no reaction	

[a]All reactions run at 0.1 M for 48 h. [b]Catalyst is 99% ee for this experiment. [c]Determined by HPLC analysis with OD-H chiral stationary phase. [d]Reaction run in DME. [e]$PhMe_2SiOH$ (pK_a = 12.0) is commercially available and has hydrogen bonding abilities comparable to $Mes_2MeSiOH$ (pK_a = 13.2).

blocking, was confirmed by comparing the absolute configuration generated by catalyst (*S*)-**9** and (*R*)-**8d** (entries 9−10). Surprisingly, the stereoinduction with prolinol catalyst (*R*)-**8b** suggested that enantioselectivity was directed by steric interactions even though (*R*)-**8b** is more acidic than prolinol catalyst (*R*)-**8a** (entry 7). This reversal may be rationalized based on the fact that silicon−carbon bond lengths are 20% longer than the carbon−carbon bond,[13] so the trifluoromethyl group in (*R*)-**8b** may block hydrogen bonding with the isatin whereas a mesityl group on the silanol does not.

An electropositive silicon may also play a role as a secondary directing element, capable of functioning as a weak Lewis acid to activate the isatin carbonyl. The TMS-capped pyrrolidinylsilanol variant affords the same stereochemical outcome as silanol (*S*)-**1a**, albeit with lower enantioselectivity (entry 12), which provides evidence to support a weak directing effect in competition with steric control. The catalytic activity of the

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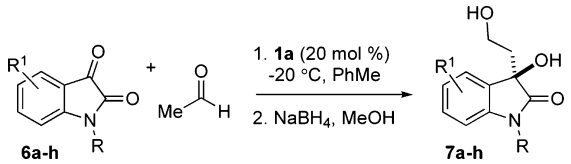
dimesitylprolinol (*S*)-**8c** was investigated for a direct comparison between the silicon and carbon analogues, and only low reactivity and enantioselectivity was observed (entry 8). In this case, the synthesis of the carbon analogue (e.g., (*S*)-**8c**) from benzyl protected L-proline methyl ester, upon addition of mesityl Grignard, proceeds with very low yield because of the shorter carbon−carbon bond lengths. This result highlights the relative ease for the synthesis of the dimesityl silicon analogue related to the carbon analogue. In the case of catalyst (*S*)-**8c**, the reaction is low yielding and the formation of product is directed by steric effects instead of hydrogen bonding. The catalytic activity of pyrrolidinylsiloxane **2b**, which was isolated as an undesired product in low yield, was also investigated (entry 11). Only low reactivity and enantioselectivity was observed, perhaps because of the rotation of the siloxane bond, which would allow the Boc-protected pyrrolidine group to block either face of the enamine.

When further control experiments were performed investigating the combination of a monosilanol with pyrrolidine, we also did not observe any catalytic activity, demonstrating the importance of the bifunctional pyrrolidinylsilanol scaffold (entries 13−16). The phenyl variant (e.g., $PhMe_2SiOH$) was utilized for control reactions instead of $Mes_2MeSiOH$ because this monosilanol is commercially available and has a comparable pK_a (i.e., 12.0 vs 13.2).

Overall, our results demonstrate that the silanol group has enhanced activating and directing abilities relative to carbon analogues, where no acidic additive or electron-withdrawing aryl groups are required.[68]

The scope of isatin substrates in the asymmetric aldol reaction was explored with pyrrolidinylsilanol catalyst (*S*)-**1a** (Table 2). For all *N*-PMB isatin substrates tested, pyrrolidinylsilanol **1a** afforded hydroxy-oxindole **7** with high yields and enantioselectivity. The reaction was sensitive to the substituent on nitrogen where the *N*-methyl and *N*-phenylisatins proceed with lower yields and reduced enantioselectivity (entries 7−8). When *N*-H-isatin was utilized, no product formation was observed using toluene; however, this substrate proceeds more efficiently using DME as solvent (entry 6). While no electronic effects were observed with 5-substituted *N*-PMB-isatins, the 4-chloroisatin **6g** afforded enantioselectivity with only 8% ee, though the yield was maintained (entry 5).[69]

Table 2. Scope and Enantiocontrol of Isatin Addition with Pyrrolidinylsilanol 1a[a]



entry	*R*	R^1	7	yield (%)	% ee[b]
1	PMB	H	**7a**	81	85
2	PMB	5-Cl	**7b**	80	84
3	PMB	5-OMe	**7c**	65	88
4	PMB	5-F	**7d**	71	82
5	PMB	4-Cl	**7e**	82	8
6[c]	H	H	**7f**	35	58
7	Me	H	**7g**	32	82
8	Ph	H	**7h**	54	77

[a]All reactions run at 0.1 M for 48 h with catalyst (*S*)-**1a** that was 96.6% ee. [b]Determined by HPLC analysis with chiral stationary phase. [c]Reaction ran in DME and completed in 24 h.

NMR binding studies were performed to verify a hydrogen-bonding interaction between pyrrolidinylsilanol **1a**·TfOH and the isatin electrophile, and provide additional evidence for activiation by the silanol group. The silanol hydroxyl proton of **1a**·TfOH shifted downfield ($\Delta\delta$ = 0.45 ppm) as the concentration of *N*-PMB-isatin increased in $CDCl_3$. We also observed that the NH peak shifted downfield ($\Delta\delta$ = 0.11 ppm). We noticed that *N*-PMB-isatin has low solubility in $CDCl_3$ which accounts for the reduced shifts relative to DMF binding studies.[70] NMR binding studies with *N*-acetyl-isatin were also performed, and we observed that the hydroxyl proton shifted downfield ($\Delta\delta$ = 0.17 ppm) and then broadened out and disappeared after 2 equiv of isatin were introduced (see Supporting Information).

In parallel with these NMR binding studies, ESI-MS was performed to investigate hydrogen-bonding adduct formation between pyrrolidinylsilanol **1a** and isatin.[19,71−73] The bifunctional mechanism for aldol reactions invoking hydrogen-bonding activation of the carbonyl have been proposed in the literature.[64,74,75] For the aldol reaction with isatin (Figure 3), a 1:1 mixture of catalyst **1a** and isatin was analyzed using ESI-MS (positive mode). Hydrogen-bonding adduct[19] **MS1** (*m*/*z* 621.4, calcd; *m*/*z* 621.3) was observed, and also iminium ion **MS2** (*m*/*z* 603.4, calcd; *m*/*z* 603.3). Catalyst fragmentation based on loss of water and a mesityl group is also observed (*m*/*z* 217.4). While iminium ion formation (**MS2**) was observed, this intermediate would not be expected to be a productive intermediate that participates in the aldol mechanism. Performing the same experiment using pyrrolidinylsilanol **1a**·TfOH showed that iminium ion formation (**MS2**) was not observed with the salt form, whereas formation of the hydrogen-bonding adduct was still observed. To compare with the prolinol catalyst, a 1:1 mixture of **6a** and isatin was analyzed and hydrogen bonding adduct **MS4** is also observed. Once the acetaldehyde is added the catalyst forms the active nucleophilic enamine (**MS3**), which can also be observed by ESI-MS.

There are two possible transition states that can be invoked to explain the stereochemical outcome for the aldol reaction (Figure 4).[64,76,77] Transition state **TS1**, in which the isatin and *N*-PMB groups are oriented away from the diarylsilanol group, accounts for the observed stereochemistry. This orientation may also be favored because of secondary interactions between the amide carbonyl and the electropositive silicon center in a Lewis acid−base interaction.[73,78−80] However, this transition state does not explain why the 4-chloro substituted isatin resulted in low enantioselectivity. Invoking transition state **TS2** would also provide the observed stereochemistry for this reaction, and would explain why the 4-chloro substituted isatin gives low enantioselectivity. When the 4-position is substituted, the steric hindrance from the mesityl groups would be expected to disrupt the transition state and account for the low enantioselectivity. An option for a second molecule of catalyst may be involved in the activation through hydrogen bonding of the SiOH or NH to the isatin in the transition state.[19] Because of the hydrogen-bonding properties of silanols, two silanol catalysts may self-associate through hydrogen bonding to each other;[15,16,19] however, results from NMR binding studies indicate low self-association of the pyrrolidinylsilanol.

In conclusion, we have demonstrated the synthesis, hydrogen-bonding properties, and catalytic activity of a novel pyrrolidinylsilanol incorporating bulky mesityl groups on

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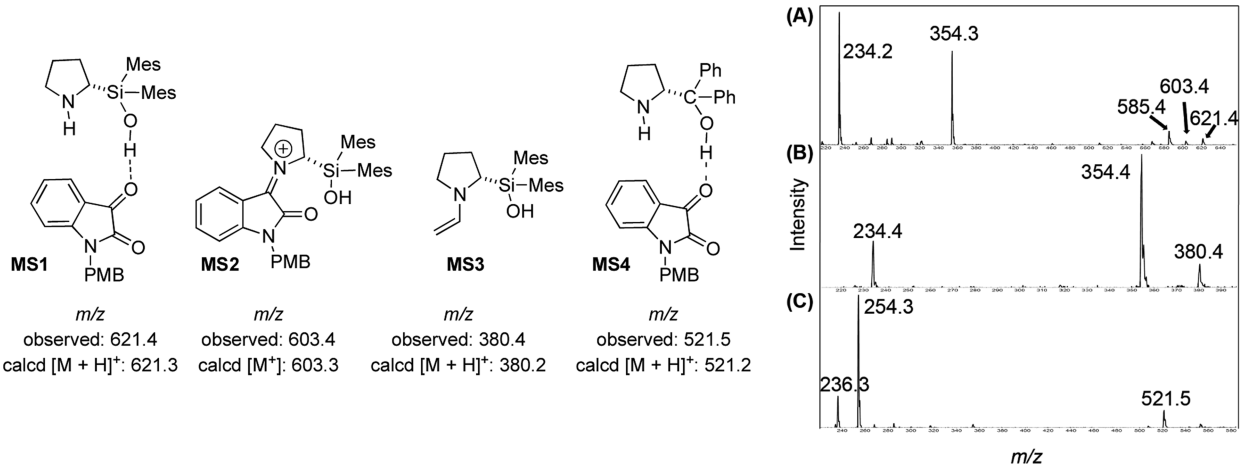

Figure 3. ESI-MS analysis of hydrogen-bonding adduct formation with pyrrolidinylsilanol **1a**. (A) A 1:1 mixture of catalyst **1a** and isatin; (B) A 1:1 mixture of catalyst **1a** and acetaldehyde; (C) A 1:1 mixture of **8a** and isatin.

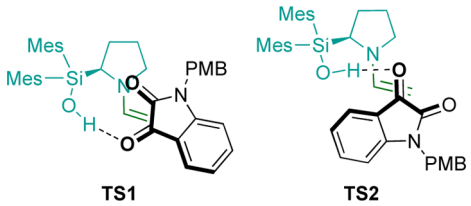

Figure 4. Proposed transition states for aldol reaction.

silicon to prevent siloxane formation. Our study represents the first example of a chiral bifunctional organocatalyst where an organosilanol is an activating and hydrogen-bond directing group for enantioselective carbon−carbon bond-forming reactions. The electropositive silicon group may also provide opportunities for secondary directing effects that contribute to enantiocontrol. While there are still challenges to consider in their development, the increased acidity of organic silanols and silanediols make these exciting candidates for the design of new chiral catalysts with capabilities for hydrogen-bonding activation without the need for acidic additives and additional electron-withdrawing groups.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, optimization experiments, NMR spectra, HPLC chromatograms, computational details, and X-ray crystal structures for **5a**, **5b**, **1a**·TfOH, and **1b**·HCl. This information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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