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Organocatalysis

Chiral Silanediols in Anion-Binding Catalysis**

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Hydrogen-bond-donor (HBD) catalysis is evolving as a powerful direction in organic catalysis.[1] Two distinct avenues through which HBD organocatalysts are proposed to operate include the more traditional hydrogen-bonding activation of appropriate functional groups found on electrophiles, and the more recently introduced ion-pairing catalysis.[2,3] (Thio)-ureas[4] are a family of HBDs unique in their ability to promote reactions through anion-binding catalysis.[3] This mode of action has led to the development of remarkable enantioselective synthetic strategies.[5] Given the power of ion-pair catalysis, we became attracted to uncovering the potential of silanediols as a novel family of catalysts for anion-binding catalysis. While the initial focus of this research direction is to understand the feasibility of silanediol-induced ion-pair catalysis, our long-term vision is the identification of innovative enantioselective methodologies inaccessible by (thio)urea anion-binding catalysis. Herein we describe our initial discoveries of chiral C_2-symmetric silanediol ion-pair catalysis in acyl Mannich reactions of *N*-acylisoquinolinium ions.

Silanediols have been recently introduced as promising new scaffolds for study in noncovalent organic catalysis (Figure 1).[6] Early work from the group of Kondo demonstrated silanediols in anion recognition and offered a key starting point on which to base the study of silanediols in HBD catalysis.[7] Discoveries from our group demonstrated the ability of silanediols to activate nitroalkenes for nucleophilic attack through proposed hydrogen-bonding interactions.[8] Franz and co-workers have also explored silanediols as catalysts for the activation of electrophiles.[9] To date, the exploration of catalysis with silanediols has been limited to the more traditional hydrogen-bonding activation of functional groups which remain intact on the electrophile over the course of the reaction. Herein we report halide binding as a promising new direction for enantioselective silanediol catalysis.

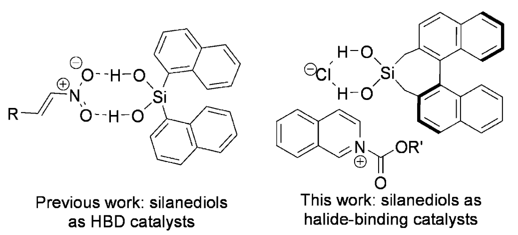
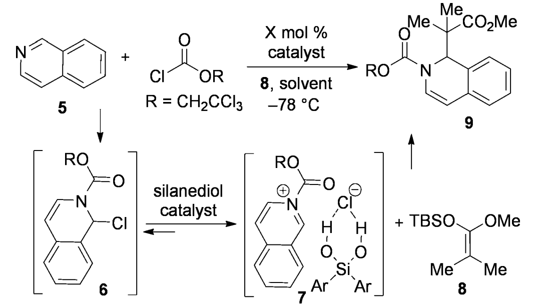


Figure 1. Directions in silanediol catalysis.

The feasibility of silanediol ion-pair catalysis was studied in the addition of the silyl ketene acetal **8** to the in situ generated *N*-acylisoquinoline **6** through the proposed ion pair **7** (Table 1). This reaction was strategically selected as a testing ground as it is a process which has documented benefits under the influence of HBD catalysis. Of particular interest to us were the observations of Taylor, Tokunaga, and Jacobsen demonstrating thiourea activation of *N*-acylisoquinolines[10] and subsequent studies on related systems pointing to thiourea anion binding in the catalytic pathway.[11] Early on we found the critical role solvent played in the reaction of **8** with **6** (entries 1–5, Table 1). Ethereal solvents, such as diethyl

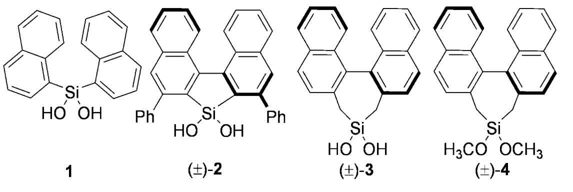
Table 1: Silanediol ion-pair catalysis.[a]



Entry	Catalyst (mol %)	Solvent	Yield [%][b]
1	**1** (20 mol %)	Et_2O	3
2	**1** (20 mol %)	MTBE	3
3	**1** (20 mol %)	CH_2Cl_2	74
4	**1** (20 mol %)	toluene	74
5	**1** (0 mol %)	toluene	12
6	(±)-**2** (20 mol %)	toluene	50
7	(±)-**3** (20 mol %)	toluene	75
8	(±)-**4** (20 mol %)	toluene	14

[a] Reactions performed at a concentration of 0.025 M in the solvent listed. See the Supporting Information for detailed experimental procedures. [b] Yield of isolated product. MTBE = *tert*-butyl methyl ether, TBS = *tert*-butyldimethylsilyl.

silanediol catalysts:



1 (±)-**2** (±)-**3** (±)-**4**

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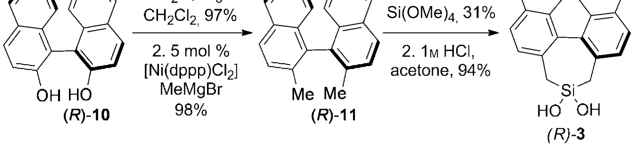
ether and methyl *tert*-butyl ether (MTBE), afforded low yields of the product **9** after 40 h with 20 mol% of the silanediol **1** (entries 1 and 2). Dichloromethane gave rise to a good yield of **9** (entry 3). However, the background rate was also high at 88%. Toluene was selected as the best solvent to explore in this system as moderate yields of **9** were observed with 20 mol% of **1** while the background rate remained low at just 12% (entries 4 and 5).

With the optimal solvent identified for achiral **1**, attention was turned toward the effect of chiral silanediols on catalytic activity for future studies on enantioselective catalysis. The catalyst (±)-**2**, a previously developed chiral C_2-symmetric variant of **1**, promoted the reaction in 50% yield (Table 1, entry 6).[8] Concerned that the steric bulk of **2** was preventing sufficient catalysis, the less sterically encumbered chiral silanediol catalyst (±)-**3** was explored. We were delighted to find 20 mol% of (±)-**3** afforded a 75% yield of **9** at −78 °C in toluene (entry 7). The silanediol functionality was determined to be critical for catalyst activity: the dimethoxysilacycle (±)-**4** was unable to catalyze the reaction, thus affording just 14% of **9** (entry 8).

Encouraged by our catalysis of the addition of the silyl ketene acetal **8** to in situ generated *N*-acylisoquinolinium **7** with the racemic silanediol **3**, we investigated the use of enantiopure silanediols to control the absolute stereochemistry of the acyl Mannich reaction. Importantly, prior to this study, asymmetric catalysis achieved solely through the HBD activity of a chiral silanediol had not been reported.[12] A main factor likely inhibiting advances in asymmetric silanediol catalysis is the difficulty of synthesizing enantioenriched chiral silanediols.

Interested in tackling the challenge of enantiopure chiral silanediol synthesis, one aspect of an ongoing program in our laboratory is geared toward pioneering the exploration of accessible, chiral C_2-symmetric silanediol catalysts. During our investigations, we the discovered enantiopure silanediol **3** is readily available from commercial (*R*)-binol ((*R*)-**10**; Scheme 1). The triflation of (*R*)-**10**[13] with a subsequent Kumada cross-coupling reaction[14] gives rise to (*R*)-2,2′-dimethyl-1,1′-binaphthalene [(*R*)-**11**] in high yield. Dilithiation of (*R*)-**11** and subsequent treatment with tetramethoxysilane affords an intermediate dimethoxysilacycle which readily converts into (*R*)-**3** upon treatment with hydrochloric acid in acetone.

An X-ray quality crystal of bis(trimethylsilyl)-protected (*R*)-**3** was obtained from hexanes and the ORTEP representation is depicted in Figure 2. Despite our best efforts, an X-ray quality crystal of the unprotected silanediol (*R*)-**3** has yet to be isolated. Bis(trimethylsilyl)-protected (*R*)-**3** was found to be 99% enantioenriched by HPLC analysis.[15]



Scheme 1. Synthesis of enantiopure chiral C_2-symmetric silanediol. dppp = 1,3-bis(diphenylphosphanyl)propane, Tf = trifluoromethanesulfonyl, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

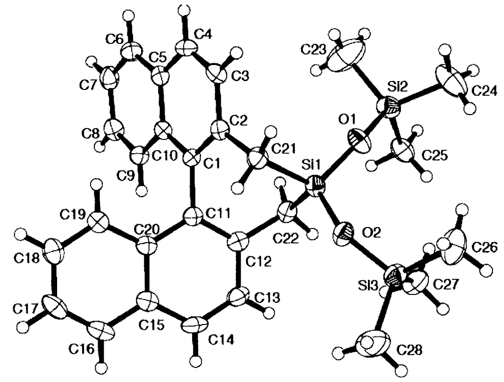
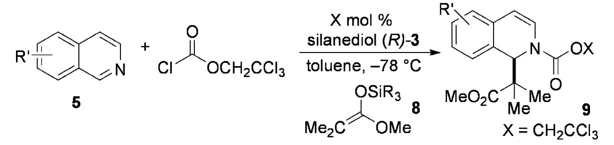


Figure 2. ORTEP representation of bis(trimethylsilyl)-protected (*R*)-**3**. The thermal ellipsoids are shown at 50% probability. TMS = trimethylsilyl.

The enantiopure silanediol (*R*)-**3** was able to catalyze the addition of silyl ketene acetals to *N*-acylisoquinolines with promising levels of stereocontrol (Table 2). The silyl group on **8** had a significant effect on the stereochemical outcome: the larger the silyl group the better the enantiomeric excess (entries 1–3). The best enantioselectivity obtained for **9a** in this study occurred with the addition of the triisopropylsilyl-protected **8** to isoquinoline in the presence of 2,2,2-trichloroethyl chloroformate and 1 equivalent of (*R*)-**3** (entry 4). The absolute stereochemistry of **9a** was tentatively assigned by analogy to literature precedent.[16] High yields and encouraging levels of enantiocontrol were also observed with several isoquinolines tested (entries 5–10). For example, 5-bromoisoquinolinium ions were easily incorporated into the process, thus giving rise to the corresponding products **9b** in 57% and

Table 2: Enantioselective acyl Mannich reaction with silanediol (*R*)-**3**.[a]



Entry	**8** (SiR$_3$)	**5** (R′)	**9**	Yield [%][b]	e.r.
1	TMS	H	**9a**	80	54:46
2	TBS	H	**9a**	71	59:41
3	TIPS	H	**9a**	55	64:36
4[c]	TIPS	H	**9a**	74	69:31
5	TIPS	5-Br	**9b**	57	63:37
6	TBS	5-Br	**9b**	66	59:41
7	TIPS	5-Cl	**9c**	61	66:34
8	TBS	5-Cl	**9c**	80	60:40
9	TIPS	5-NO$_2$	**9d**	65	58:42
10	TBS	5-NO$_2$	**9d**	72	75:25

[a] Reactions performed at a concentration of 0.025 M in toluene with 20 mol% (*R*)-**3**. See the Supporting Information for detailed experimental procedures. [b] Yield of isolated product. [c] Reaction performed with 100 mol% (*R*)-**3**. TIPS = triisopropylsilyl.

66% yields with the TIPS and TBS silyl ketene acetals (**8**) respectively, and up to 26% *ee* when 20 mol% of (*R*)-**3** was used (entries 5 and 6). 5-Chloroisoquinoline gave rise to **9c** in high yield and up to 31% *ee* with 20 mol% of (*R*)-**3** (entries 7 and 8). Good yields of **9d** were isolated (87%) with 50% enantiomeric excess from the incorporation of 5-nitroisoquinoline into the reaction system (entries 9 and 10).

Evidence supporting a reaction pathway involving silanediol recognition of chloride ions was collected by ^{1}H NMR spectroscopy and X-ray crystallographic analysis. First, ^{1}H NMR spectroscopic analysis found a significant effect on the OH signals of (*R*)-**3** upon the addition of varying amounts of tetrabutylammonium chloride (TBACl).[17] In the ^{1}H NMR spectrum of pure (*R*)-**3**, the OH chemical shift is observed at $\delta = 2.3$ ppm (Figure 3a). As equivalents of TBACl are added to the silanediol, clear downfield shifting of the OH peak (Figures 3b–f) is observed. For example, the addition of 5 equivalents of TBACl cause the OH chemical shift to be observed at $\delta = 4.7$ ppm, a change of more than 2 ppm (Figure 3a versus f)). There are also small changes in the chemical shifts observed for the methylene and aromatic hydrogen atoms. Further support of silanediol ion-pair catalysis was found in the capture of the achiral silanediol **1** in a solid-state ion pair with the hydrochloride salt of isoquinoline (Figure 4).

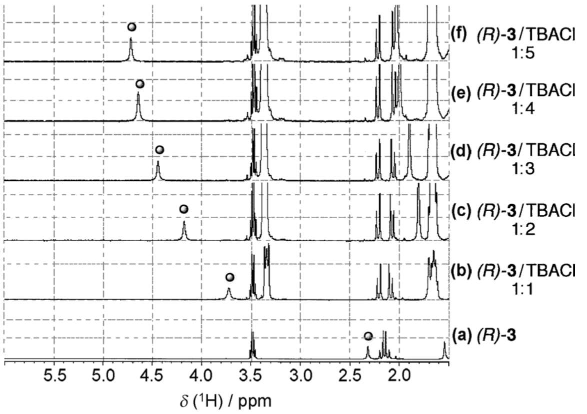


Figure 3. ^{1}H NMR spectra of (*R*)-**3** with varying equivalents of tetrabutylammonium chloride (TBACl). The OH chemical shifts are marked with a circle.

In summary, silanediols promote the reaction of silyl ketene acetals with *N*-acylisoquinolines in good yield, conceivably through anion-binding catalysis. This report includes the first synthesis of an enantiopure C_2-symmetric silanediol able to provide promising levels of enantiocontrol in the title reaction. The results detailed herein have inspired us to carry on with our pursuit of asymmetric silanediol catalysis.

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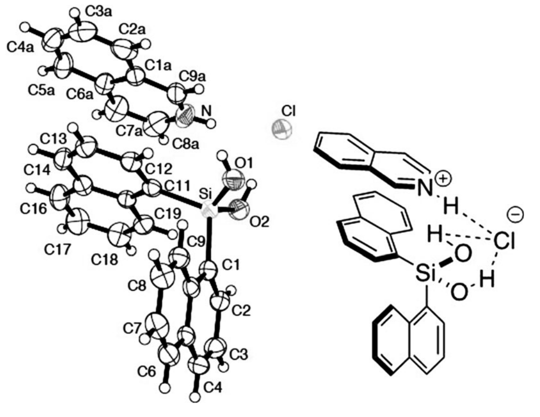

Figure 4. ORTEP representation of an ion pair between the achiral silanediol **1** and the HCl salt of isoquinoline.[18] In the solid state, the O1-Cl and N-Cl distances are 2.12 Å and 2.32 Å, respectively, indicative of moderately strong hydrogen bonds.[19] The O2-Cl distance is longer (4.47 Å). The thermal ellipsoids are shown at 50% probability.

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[15] See the Supporting Information for details about the synthesis and characterization of (*R*)-**3** and its bis(TMS)-protected analogue.

[16] See the Supporting Information for details regarding the tentative assignment of the absolute configuration of **9**.

[17] See the Supporting Information for details about titrating (*R*)-**3** and **4** with TBACl.

[18] CCDC 947139 and 947138 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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