Synthesis J. W. Attard et al. Feature

Silanediol Anion Binding and Enantioselective Catalysis

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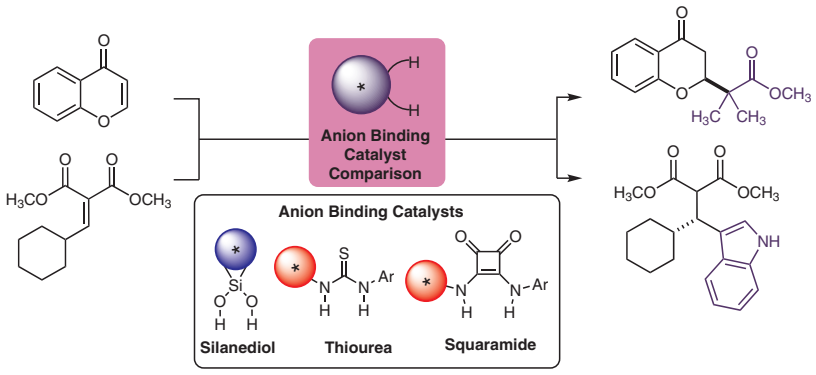


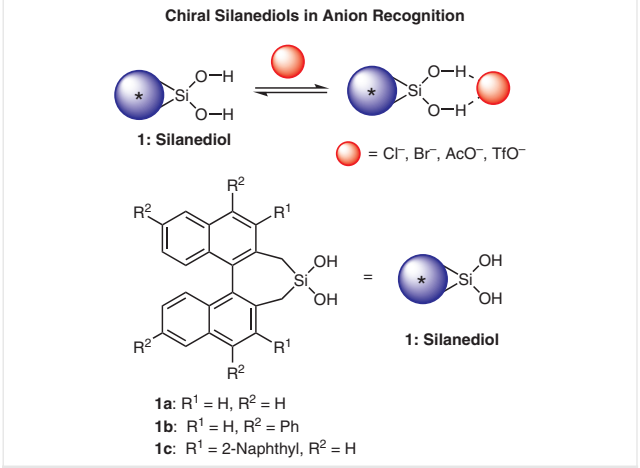
Received: 11.01.2019
Accepted after revision: 14.01.2019
Published online: 12.03.2019
DOI: 10.1055/s-0037-1612217; Art ID: ss-2018-z0774-fa

Abstract Silanediols possess unique and complementary catalytic activity in reactions that are likely to proceed through anion binding. This article directly compares silanediols, thioureas, and squaramides in three separate anion-binding processes. The catalytic abilities of select members of each family are directly correlated to association constants.

Key words anion recognition, enantioselective catalysis, thiourea, silanediol, squaramide

The silanediol functional group, a silicon with two OH groups bound to it, can host a variety of anions through hydrogen bonding interactions (Scheme 1).[1] For instance, seminal work in this area demonstrated that dinaphthyl silanediols can host acetate, chloride, and bromide.[2] The anion recognition abilities of silanediols can be taken advantage of in other areas of chemistry, such as sensing and catalysis.[3,4] Chiral BINOL-based silanediols (e.g., **1a–c**, Scheme 1) have emerged as promising enantioselective anion-binding catalysts for addition reactions to isoquinolinium ions and benzopyrylium ions.[5,6]

In the context of anion-binding catalysis, silanediols can offer an exclusive appeal. From a structural standpoint BINOL-based silanediols stand out as anion-binding catalysts because they are highly aromatic C_2-symmetric dual O–H hydrogen bond donors. In comparison, more common anion-binding catalysts, such as (thio)ureas[7] and squaramides,[8] are N–H hydrogen bond donors that typically lack C_2-symmetry. Perhaps stemming from their unique structures, BINOL-based silanediols catalyze processes that are complementary to the reactivity patterns observed with the more traditional (thio)urea and squaramide catalysts. Intrigued by the unique catalytic abilities of silanediols, we



Scheme 1 Silanediols **1** can host anionic guests through hydrogen bonding interactions

desired a better understanding of the roles of silanediols in anion-binding catalysis. This article describes the results of the direct comparison of silanediols, thioureas, and squaramides as (i) hosts in anion recognition and (ii) catalysts for enantioselective reactions likely to involve anion-binding catalysis.

The Discovery of Silanediols in Enantioselective Anion-Binding Catalysis

Chiral silanediols as enantioselective anion-binding catalysts first emerged in the literature from our laboratory in 2013 (Scheme 2).[6d] Inspired by the impressive catalytic abilities of (thio)ureas, in the early stages of our investigations it was hypothesized that silanediols would activate ionic substrates through hydrogen bond recognition of the anionic component (Scheme 2, eq 1). As a testing ground, we chose to explore the feasibility of enantioselective silanediol anion-binding catalysis in addition reactions of silyl ketene acetals to *N*-acylisoquinolines, reactions that are

Biographical Sketches

Jonathan Attard obtained his B.A. in Chemistry and Physics from Whittier college in 2010. He worked in industry for 6 years before beginning his Ph.D. program, in 2016, at Worcester Polytechnic Institute under the guidance of Professor Anita Mattson. His current research involves enantioselective copper-catalyzed reactions for the synthesis of chromanone natural product analogues.

Kohei Osawa obtained his B.A. in Engineering from Yamagata University in 2014. He began his Ph.D. program in 2014 and he is expecting to complete his doctoral research on anion recognition behavior and chiral induction of biaryl-based bis-urea derivatives with Professor Shin-ichi Kondo in 2019 to obtain Ph.D. in Engineering from Yamagata University. He joined Professor Mattson's current research group from Nov 2017 to Jan 2018 as an international researcher and worked on enantioselective silanediol catalysis.

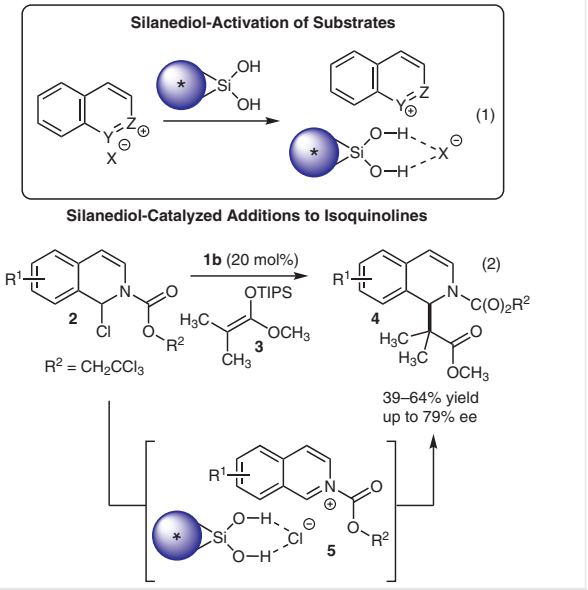
Yong Guan obtained his B.S. and M.S. from Wuhan University in 2004 and 2006. He completed doctoral research on construction of a vaulted biaryl ligand library for the aziridination reaction with Prof. William Wulff and earned a Ph.D. in 2012 from Michigan State University. He performed his postdoctoral research with Prof. Christopher Douglas at University of Minnesota on one-pot Sonogashira coupling and regioselective tetradehydro-Diels–Alder reaction to synthesis rubicenes (2013–2014), and with Prof. Steven Townsend at Vanderbilt University on metal-free synthesis of unsymmetrical organoselenides and selenoglycosides (2015–2016). In 2017, he joined Mattson group at Worcester Polytechnic Institute as a postdoctoral fellow. His current projects are on asymmetric copper catalysis and drug discovery.

Jessica Hatt is expecting to obtain her B.S. in Chemistry from Worcester Polytechnic Institute in 2020. She joined Professor Mattson's current research group as an undergraduate researcher in the fall of 2017.

Shin-ichi Kondo received his Ph.D. from Kyoto University in 1995 under the supervision of Professor Atsuyoshi Ohno. He became an assistant professor at Ritsumeikan University in 1995 and moved to Gunma University in 1996. In 2009, he became an associate professor at Yamagata University. Since 2012, he has been a full professor at Yamagata University. His research interests include molecular recognition, in particular anion recognition chemistry, fluorescence materials, and organosilicon chemistry.

Anita Mattson obtained her B.S. from Northern Michigan University in 2002 where she conducted undergraduate research with Frankie Ann McCormick. She completed doctoral research on thiazolium-based N-heterocyclic carbene catalysis with Prof. Karl Scheidt and earned a Ph.D. in 2007 from Northwestern University. After working on a synthesis of hemibrevetoxin B as an NIH NRSA postdoctoral fellow in the Crimmins group at the University of North Carolina at Chapel Hill, Anita began her independent career in 2009 at the Ohio State University (OSU). After being promoted to Associate Professor with tenure at OSU in 2015, she moved to Worcester Polytechnic Institute in 2016. Anita's current research program blends her love of organic catalyst design and complex molecule synthesis with drug discovery.

known to benefit from (thio)urea anion-binding catalysis.[7g] During our studies we were delighted to find that chiral, enantiopure BINOL-based silanediols influenced the addition of silyl ketene acetals **3** to isoquinolinium ions generated in situ from **2** giving rise to **4** in good yields and high levels of enantiocontrol (Scheme 2, eq 2; up to 64% yield and 79% ee). Based upon both prior hypotheses and data collected in our laboratory, it is proposed that the silanediol is operating to hydrogen bond to chloride to create chiral ion pair **5**.



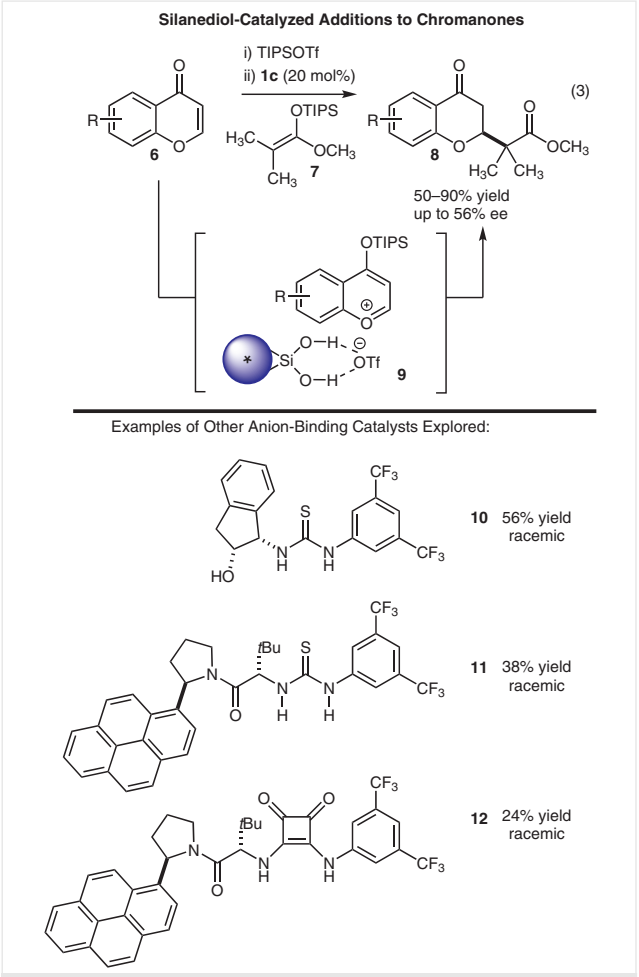
Scheme 2 Silanediol activation of ion pairs (eq 1). The enantioselective functionalization of isoquinolines with silanediol catalysis (eq 2).

Silanediols as Enantioselective Anion-Binding Catalysts

The field of anion-binding catalysis is relatively new. It was only in 2006 that Schreiner described the possibility that hydrogen bond donor catalysts, specifically thioureas, may operate to facilitate ionization.[9] In 2007, Jacobsen and co-workers intentionally applied chiral thioureas to influence an enantioselective intramolecular Pictet–Spangler reaction via anion-binding catalysis.[10] In the last ten years, further investigations from a number of research teams have supported the promise of anion-binding catalysis: new families of catalysts are under development and impressive reactivity patterns have been realized.[11]

Silanediols are a newer and rather unexplored family of hydrogen bond donor anion-binding catalysts in comparison to the better-known (thio)ureas. Once we had success in the enantioselective addition of silyl ketene acetals to isoquinolinium ions – a known reactivity pattern – we became interested in identifying useful, unique reactivity patterns of enantioselective silanediol anion-binding catalysis. Our attention first turned toward the enantioselective functionalization of chromenones to generate 2-alkylchroman-4-ones, oxygen heterocycles that are frequently found in bioactive secondary metabolites.[12] Prior to our studies, no reports were present in the literature describing anion-binding catalysis as a strategy to control the reactions of chromenones via the in situ generation of 4-siloxybenzopyrylium triflates.[6b] We hypothesized that silanediols could activate benzopyrylium triflates via anion binding to generate a chiral ion pair and allow for the enantioselective alkylation of chromenones.

The promise of silanediol-enabled control of chromanone functionalization was realized in the addition of silyl ketene acetals to benzopyrylium ions, reactive oxygen heterocycles generated in situ from **6** and a suitable silyl triflate (Scheme 3). Desirable products **8** were isolated in high yield with decent levels of enantiocontrol in this first example of an enantioselective functionalization of 4-siloxybenzopyrylium triflates. In a collaboration between the Kondo and Mattson laboratories, data collected by fluorescence spectroscopy suggests that the silanediol is able to host a triflate anion through hydrogen bonding interactions.



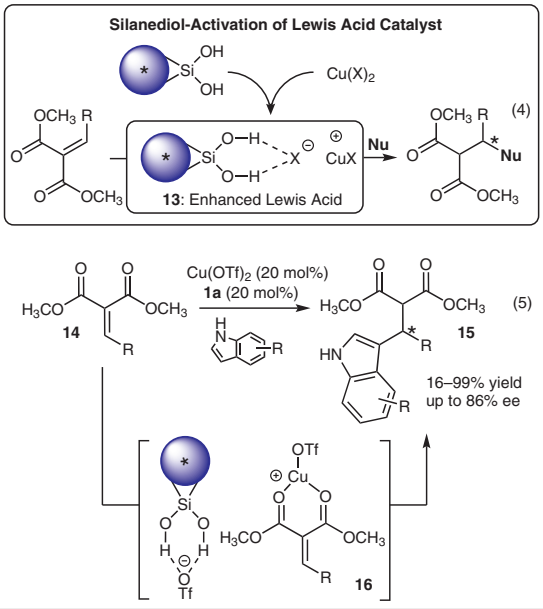
Scheme 3 Silanediol **1b** as a catalyst for the addition of silyl ketene acetals to **6** via proposed ion pair **9**

An important aspect of the ongoing work in our laboratories has identified the enantioselective functionalization of in situ generated benzopyrylium ions with silanediol anion-binding catalysis. In a direct comparison, it was found that popular (thio)urea catalysts, such as **10** and **11**,[13] were unable to control the facial selectivity of the addition of **7** (≡ **3**) to **6**. Likewise, squaramide **12**,[13] a hydrogen bond donor recently reported to participate in triflate binding, provided only racemic product.[8b]

The distinctive catalytic abilities of silanediols triggered us to consider further (i) additional catalytic processes that may be unique to silanediols and (ii) what specific properties of the silanediol are responsible for its one-of-a-kind catalytic performance.

Silanediols and Lewis Acid Hybrid Anion-Binding Catalysts

Encouraged by the development that silanediol-specific catalytic outcomes are feasible, we sought to branch out from the traditional anion-binding catalyst activation of substrates. We reasoned that if silanediols can activate substrates then they can likely activate other components of a reaction system. For example, we hypothesized that silanediols could active Lewis acids thereby enabling the generation of hybrid anion-binding and Lewis acid catalyst systems that benefit from enhanced activity (**13**, Scheme 4).

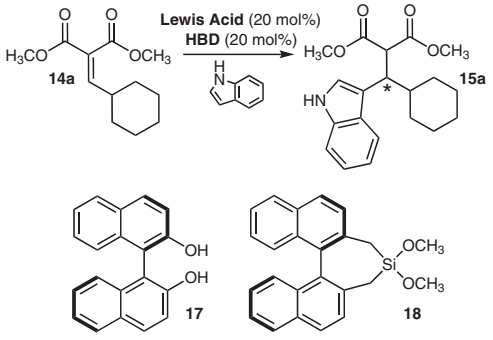


Scheme 4 Silanediol-activated Lewis acid **13** as a catalyst for the addition of indoles to **14**

To this end, our investigations led us to probe the effect of BINOL-based silanediol **1a** on $Cu(OTf)_2$ in the addition of indoles to alkylidene and arylidene malonates (**14**, Scheme 4, eq 5).[6a] We were delighted to find that the silanediol **1a** and $Cu(OTf)_2$ cocatalyst system was effective in the addition of indoles to **14**, affording desirable products **15** in excellent yields (typically >90%) and with up to 86% enantiomeric excess. Although the mechanism of this process is still under investigation, it is feasible that ion pair **16** is operating as a key intermediate.[6a]

A brief survey of popular Lewis acid and dual hydrogen bond donors led us to conclude that there is something unique about the silanediol-$Cu(OTf)_2$ catalyst system. Inferior yields and enantiomeric excesses were obtained for several other Lewis acids employed in the reaction system (Table 1). Use of $Cu(OTf)_2$ gave **15a** in 92% yield with 72% ee (Table 1, entry 1). While high yields of product were achieved using $Sc(OTf)_3$ and $In(OTf)_2$, the enantiomeric excess never reached beyond 10% (entries 2 and 3). Both the oxidation state of copper and the anion involved have huge influences on the reaction: CuOTf afforded just 10% yield of **15a** in 31% ee, while CuCl, CuI, and $CuSO_4$ did not enable the reaction to proceed (entries 4–6). BINOL-based silanediol **1a** proved to be the best hydrogen bond donor in the process. The addition of steric bulk to the silanediol scaffold, such as BINOL-based silanediols **1b** and **1c**, resulted in steep

Table 1 On the Unique Nature of Silanediol **1a**-$Cu(OTf)_2$ Hybrid Catalysis[a]



Entry	HBD[b]	Lewis acid	Yield (%)	ee (%)
1	**1a**	$Cu(OTf)_2$	92	72
2	**1a**	$Sc(OTf)_3$	95	9
3	**1a**	$In(OTf)_2$	88	10
4	**1a**	CuOTf	10	31
5	**1a**	CuCl	0	–
6	**1a**	$CuSO_4$	0	–
7	**1b**	$Cu(OTf)_2$	76	13
8	**1c**	$Cu(OTf)_2$	14	6
9	**10**	$Cu(OTf)_2$	0	–
10	**11**	$Cu(OTf)_2$	0	–
11	**12**	$Cu(OTf)_2$	10	10
12	**17**	$Cu(OTf)_2$	28	racemic
13	**18**	$Cu(OTf)_2$	25	racemic

[a] See the experimental sections for details of the procedures.
[b] HBD: Hydrogen bond donor.

declines in both yield and enantiomeric excess (entries 7 and 8). Attempts to use thiourea catalysts **10** and **11** prevented the formation of product (entries 9 and 10). Low yields and enantiomeric excesses of **15a** were observed with squaramide **12** operating as the cocatalyst (entry 11). BINOL (**17**) was also tested in the transformation and afforded racemic **15a** in 28% yield, the same yield obtained as the background rate of the reaction (entry 12). The importance of the silanediol functional group was supported with the observation that dimethoxysilane **18** was unable to control the absolute stereochemistry in the synthesis of **15a** (entry 13).

Host:Guest Interactions of Silanediols

With the identification of a second reaction unique to silanediols, our curiosity to better understand their anion-binding properties grew stronger. Investigations were initiated to explore the abilities of our chiral, BINOL-based silanediol **1a** to recognize chloride and triflate in two solvents (e.g., chloroform and toluene) using UV/Vis spectroscopy and nuclear magnetic resonance spectroscopy.

Under identical experimental conditions, the association constants of thiourea **11** and squaramide **12** for both chloride and triflate were also measured so as to be able to compare anion-binding and catalysis of the three different hydrogen bond donor families (Figures 1 and 2).

The association of silanediol **1a** with both chloride and triflate in chloroform and toluene was observed using UV/Vis spectroscopy (Figure 1a and 1b and Supporting Information). For example, plotting the change in absorbance upon the addition of 0–5 equivalents of tetrabutylammonium chloride (TBACl) and tetrabutylammonium triflate (TBAOTf) at 262 nm generated the curves depicted in Figure 1b. From these data, the association constant for silanediol:chloride was determined to be 1.9×10^3 M^{-1} in $CHCl_3$ and 3.8×10^4 M^{-1} in toluene (Table 2, entry 1). The silanediol:triflate association constant in toluene was measured to be 2.8×10^3 M^{-1} (entry 2). No association constant was determined for the triflate in $CHCl_3$ by UV/Vis spectroscopy because the change in spectra upon the addition of TBAOTf was too small.

Table 2 Association Constants Determined for **1a**, **11**, and **12** with Chloride and Triflate (M^{-1})

Entry	Host:Guest	UV/Vis	
		$CHCl_3$	Toluene
1	**1a**:Cl^-	$1.9 \pm 0.22 \times 10^3$	$3.8 \pm 0.13 \times 10^4$
2	**1a**:$^-$**OTf**	ND	$2.8 \pm 0.40 \times 10^3$
3	**11**:Cl^-	$1.8 \pm 0.37 \times 10^4$	$7.9 \pm 0.13 \times 10^6$
4	**11**:$^-$**OTf**	ND	$6.5 \pm 0.27 \times 10^4$
5	**12**:Cl^-	$7.6 \pm 0.16 \times 10^5$	$>10^6$
6	**12**:$^-$**OTf**	ND	$3.8 \pm 0.04 \times 10^5$

ND: Not determined: The absorbance change was too small to accurately determine the association constant.

Thiourea **11** and squaramide **12** were also found to recognize both chloride and triflate through UV/Vis titration experiments (Figure 1c–f). A binding constant of 1.8×10^4 M^{-1} was extrapolated from the change in UV/Vis spectra observed at 259 nm upon the addition of TBACl to thiourea **11** in $CHCl_3$. Measuring of the binding constant in toluene ($K_a = 7.9 \times 10^6$ M^{-1}) indicated a stronger host:guest interaction relative to that observed in $CHCl_3$ (Table 2, entry 3). The association constant of squaramide **12** and chloride was found to be 7.6×10^5 M^{-1} in $CHCl_3$ and $>10^6$ M^{-1} in toluene (entry 5). In the cases of both the thiourea **11** and squara-

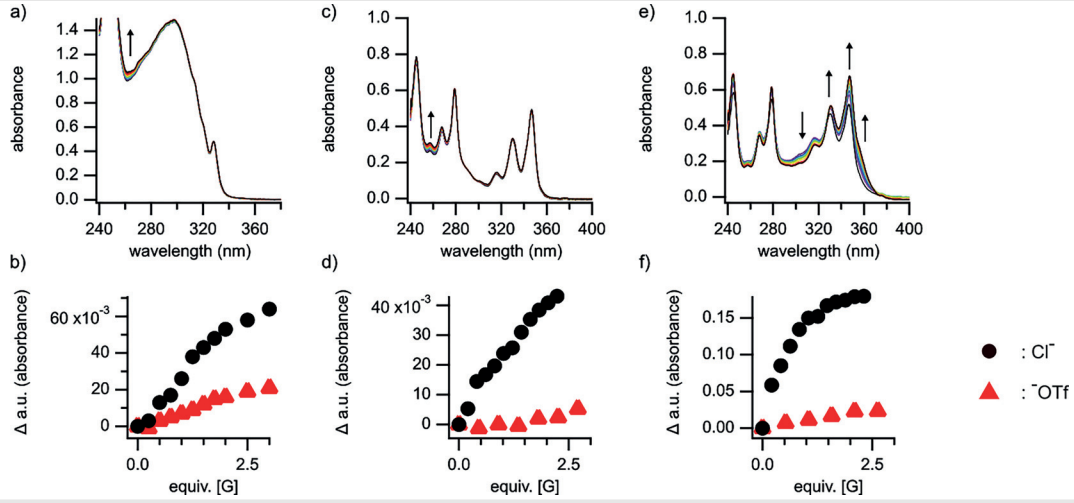


Figure 1 UV/Vis titrations of silanediol **1a** (a), thiourea **11** (c), and squaramide **12** (e) with TBACl in $CHCl_3$. (b) Change in 262 nm when silanediol **1a** was titrated with [G] = TBACl and TBAOTf. (d) Change in 259 nm when thiourea **11** was titrated with [G] = TBACl and TBAOTf. (f) Change in 348 nm when squaramide **12** was titrated with [G] = TBACl and TBAOTf.

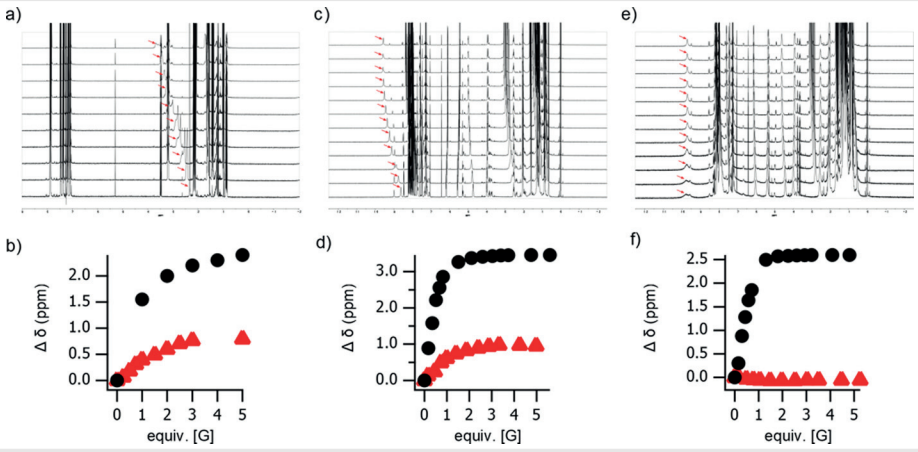


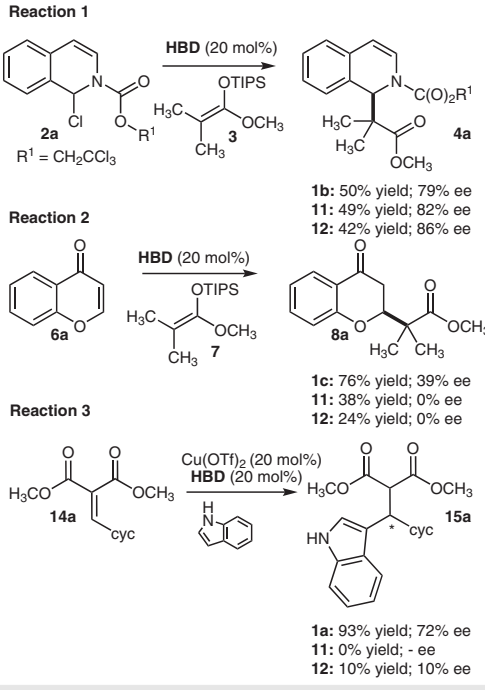
Figure 2 NMR titrations of silanediol **1a** (a), thiourea **11** (c), and squaramide **12** (e) with TBAOTf in $CDCl_3$. (b) Change in 2.33 ppm (OH) when silanediol **1a** was titrated with [G] = TBACl and TBAOTf. (d) Change in 8.62 ppm (NH) when thiourea **11** was titrated with [G] = TBACl and TBAOTf. (f) Change in 9.78 ppm (NH) when squaramide **12** was titrated with [G] = TBACl and TBAOTf.

mide **12**, the association constant found for triflate was lower than that found for chloride (entries 3 and 5 vs entries 4 and 6). In toluene, the association constant for **11**:$^-$OTF was found to be 6.5×10^4 M^{-1} and **12**:$^-$OTF was found to be 3.8×10^5 M^{-1} (entries 4 and 6, respectively). Similar to the silanediol, the change in spectra was too small for both thiourea **11** and squaramide **12** to accurately determine a binding constant of triflate in $CHCl_3$.

NMR titration experiments were also used to analyze the association of silanediol **1a**, thiourea **11**, and squaramide **12** to both the host chloride and triflate anions in chloroform (Figure 2). In all cases, the introduction of TBACl caused larger shifts in the ^{1}H NMR spectra than TBAOTf. This data suggests that silanediol **1a**, thiourea **11**, and squaramide **12** all operate as hosts of both chloride and triflate, although they bind more strongly to chloride than triflate (Figure 2).

With the collection of the association constant of both chloride and triflate with our silanediol, thiourea, and squaramide catalysts we correlated the association constant to yield and enantiomeric excess in three reactions: (i) additions of silyl ketene acetals to isoquinolinium chlorides; (ii) additions of silyl ketene acetals to benzopyrylium triflates; and (iii) additions of indoles to cyclohexylidene malonate in the presence of copper(II) triflate (Scheme 5).

In the first reaction, the addition of silyl ketene acetal **3** to **2a** to generate **4a**, plausibly proceeds through an isoquinolium chloride ion pair (Reaction 1, Scheme 5). This reaction system allows us to directly study the effect of silanediols, thioures, and squaramides on ion pairs containing chloride (Figure 3). There appears to be a clear correlation of the strength of association to enantiomeric excess. Specifically, the more tightly bound thiourea **11** and squaramide **12** generate improved enantiomeric excesses when compared to the silanediol **1a**, which has a lower association constant.



Scheme 5 Reactions 1–3 comparing silanediol **1a**, thiourea **11**, and squaramide **12**. Reaction 1: alkylation of isoquinoline with silyl ketene acetal. Reaction 2: conjugate addition of silyl ketene acetal to chromen-4-one. Reaction 3: Lewis acid catalyzed Friedel–Crafts alkylation of indole with alkylidene malonate.

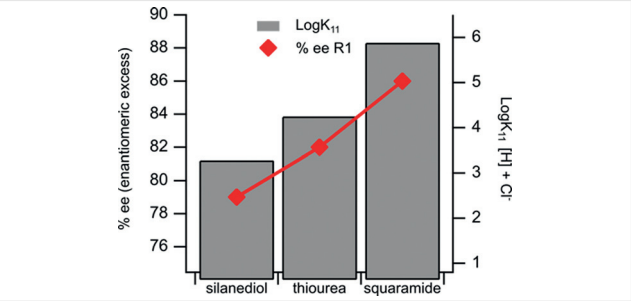


Figure 3 Chloride association constant determined in $CHCl_3$ correlated to enantiomeric excess in the addition of silyl ketene acetals to isoquinolinium ions, Reaction 1 (R1)

The influence of silanediols, thioureas, and squaramides on ion pairs containing triflate as the counterion can be studied in Reactions 2 and 3 in Scheme 5. In these cases of triflate ion pairs, the results are less predictable than in the outcomes of the reactions with chloride ion pairs. It was experimentally determined that silanediol **1a** recognizes triflates more weakly than either the thiourea **11** or squaramide **12**. However, in both the addition of silyl ketene acetal **7** (≡ **3**) to the benzopyrylium triflate derived from **6a** (Reaction 2, Scheme 5) and the addition of indole to cyclohexylmethylene malonate **14a** (Reaction 3, Scheme 5), the silanediol outperformed both thiourea **11** and squaramide **12** in terms of enantiomeric excess and yield (Figure 4).

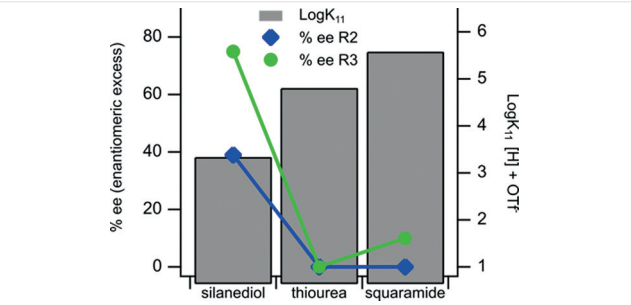


Figure 4 Triflate association constant, determined in toluene, correlated to enantiomeric excess in Reactions 2 and 3 (R2 and R3).

Conclusions

Anion-binding catalysis is emerging as an impressive synthetic tool able to catalyze reactions that are inaccessible to more conventional types of catalysis. Several families of enantioselective anion-binding catalysts are now available and it appears that there may be complementary reactivity patterns between them. The identification of parameters able to aid in predicting which anion-binding catalyst to choose in order to influence a desired reactivity pattern would be an enormous advance in the field.

We have observed that silanediols can offer complementary reactivity patterns when compared to thioureas and squaramides. The origin of the unique catalytic abilities remains unknown and is a point of ongoing study in our research program. This article describes the first direct comparison of silanediols, thioureas, and squaramides in three separate reactions. It has also correlated the association constant of each catalyst to enantiomeric excess in the three processes. In the case of reactions involving chloride ions there appears to be a trend that the stronger the host:guest interaction is, the higher the enantiomeric excess. Alternatively, the silanediol uniquely enables enantioselectivity in the two reactions involving triflate ion pairs that are described herein despite the observation that its binding constant to triflate is lower than both the squaramide and thiourea. Although the reasons for the unique reactivity of silanediols remain uncertain there are additional factors, such as undesired side reactions of the catalysts and non-covalent interactions beyond just anion recognition (e.g., pi-stacking), that may be important to consider. Ongoing investigations in our laboratory are dedicated toward better understanding and capitalizing on the unique role of silanediols in enantioselective anion-binding catalysis.

Toluene was purified by passage through a Pure Process Technology solvent system prior to use. EtOAc and hexanes were used as received. Toluene was dried over 4Å molecular sieves prior to use in the binding constant studies. $CHCl_3$ was purified to remove any stabilizer and distilled from CaH_2 prior to use in the binding constant studies. $Cu(OTf)_2$ was dried at 100 °C under vacuum prior to use. Guest compounds TBACl and TBAOTf were dried under vacuum and stored under N_2. The silanediol catalyst was prepared according to a literature method.[6d] Thiourea **11**[14] and squaramide **12**[8b] were prepared according to literature procedures. Indole was recrystallized from hexanes prior to use. All other reagents were used directly as received from the manufacturer, unless otherwise noted. Preparative silica gel chromatography was performed using SiliaFlash F60 silica gel (40–63 µm). Analytical TLC was performed using Analtech 250 µm silica gel HLF plates and visualized under UV 254 nm. All ^1H NMR spectra were acquired using a Bruker BioSpin 500 MHz Avance III Digital NMR spectrometer or JOEL ECA-500 (500 MHz) NMR spectrometer and calibrated using the solvent signal ($CDCl_3$ 7.26 ppm). Multiplicities were determined using MNova software. All ^{13}C NMR spectra were acquired using a Bruker BioSpin 126 MHz Avance III Digital NMR spectrometer or Bruker Avance DPX 400 (100 MHz) and calibrated using the solvent signal ($CDCl_3$ 77.16 ppm). IR spectra were acquired using a Bruker Vertex 70 with an ATR accessory. High-resolution mass spectra were acquired using an Agilent 6520 Q-TOF mass spectrometer. Chiral HPLC analysis was performed using an Agilent 1260 equipped with a diode array detector. Optical rotations were acquired on a Jasco Digital Polarimeter with a 1 dm cell and a sodium lamp. UV/Vis spectrometry experiments were conducted using a Thermo Scientific Evolution 3000 spectrometer or a Shimadzu UV-2500PC spectrometer with 1 cm path length quartz cuvettes.

Compound 4a

An oven-dried 2-dram vial with screw top cap and septa was equipped with a stir bar and flushed with N_2. The vial was sealed and covered further with parafilm. Isoquinoline (11.8 µL, 0.1 mmol, 1.0 equiv) was added via syringe, toluene (2 mL) was added and the solution was cooled to 0 °C. 2,2,2-Trichloroethyl chloroformate (15.0 mL, 0.22 mmol, 1.1 equiv) was added, the ice bath was removed, and the

solution was warmed to r.t. while stirring for 30 min. The cloudy suspension was cooled to –78 °C. Anion-binding catalyst **1b** (12.9 mg, 0.02 mmol, 0.2 equiv) was added as a solution in toluene followed by the silyl ketene acetal **3** (38.8 mg, 0.15 mmol, 1.5 equiv). The reaction vessel was transferred to a –78 °C acetone bath equipped with immersion cooling coil and stirred for 40 h. The reaction was quenched at –78 °C by the addition of NaOMe (0.2 mL, 0.5 M in MeOH, 1.0 equiv) and then warmed to r.t. before filtration through a short silica gel plug with EtOAc as the eluent. Removal of the solvent in vacuo and subsequent purification via flash column chromatography on silica gel (0:100 EtOAc/hexanes to 4:96 EtOAc/hexanes) afforded the title compound as a colorless oil; yield: 20.9 mg (0.051 mmol, 51%); 3:1 mixture of carbamate rotamers by ^{1}H NMR. $[\alpha]_D^{24}$ –24.5 (*c* 1.11, $CHCl_3$).

HPLC: Chiralpak OD-H; 1% *i*-PrOH/99% hexane, 0.7 mL/min; t_R (minor) = 12.8 min, t_R (major) = 15.7 min.

IR (neat): 2991, 2924, 2357, 2343, 1724, 1717, 1627, 1448, 1374, 1322, 1225, 1128, 1046, 941 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (major rotamer) = 7.28–7.19 (m, 2 H), 7.10–6.95 (m, 2 H), 6.96 (d, *J* = 7.6 Hz, 1 H), 5.95 (d, *J* = 7.6 Hz, 1 H), 5.74 (s, 1 H), 4.97 (d, *J* = 12.0 Hz, 1 H), 4.70 (d, *J* = 12.0 Hz, 1 H), 3.64 (s, 3 H), 1.20 (s, 3 H), 1.12 (s, 3 H). δ (minor rotamer) = 6.05 (d, *J* = 7.6 Hz, 1 H), 5.79 (s, 1 H), 4.86 (s, 2 H), 3.61 (s, 3 H), 1.29 (s, 3 H), 1.26 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (major rotamer) = 175.9, 152.3, 131.3, 128.4, 128.0, 127.2, 125.6, 124.9, 112.0, 95.2, 75.7, 60.9, 52.2, 50.3, 22.6, 21.5.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{18}Cl_3NO_4Na$ [M + Na]$^+$: 428.0199; found: 428.0189.

Compound 8a

An 8 mL vial with stir bar was flame dried under vacuum, cooled to r.t. under vacuum, and backfilled with argon gas. Chromone (**6a**; 14.6 mg, 0.1 mmol, 1 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (6.2 mg, 0.03 mmol, 0.3 equiv) were weighed out and placed in the vial. The vial was then placed under vacuum again and backfilled with argon. Anhyd toluene (200 µL to make 0.5 M) was added to the vial. Freshly distilled triisopropylsilyl trifluoromethanesulfonate (29.5 µL, 0.11 mmol, 1.1 equiv) was added via microliter syringe to the solution and the vial was placed in a 60 °C oil bath for 1 h. After the reaction time, the vial was cooled to r.t. and further diluted with toluene (1.3 mL). The vial was then cooled to –78 °C in an acetone/dry ice bath. After an appropriate amount of time to allow the reaction to come to temperature had passed, a solution of silanediol catalyst **1c** (12.6 mg, 0.02 mmol, 0.2 equiv) in toluene (0.5 mL) was added slowly down the side of the vial. The reaction mixture was stirred for 10 min before addition of the silyl ketene acetal **7** (≡ **3**) (125 µL of a 1 M solution in toluene, 0.125 mmol, 1.25 equiv) slowly down the side of the vial. After 4 h at –78 °C, the reaction was quenched with of aq 3 M HCl (200 µL, 6 equiv) at –78 °C. The solution was allowed to warm to r.t. overnight. Then, the crude reaction mixture was extracted with EtOAc (5 mL), the organic layer was washed with H_2O (5 mL), dried (Na_2SO_4), and the solvent removed under vacuum. The crude mixture was then dissolved in $CDCl_3$ and 1,3,5-trimethoxybenzene was added as an internal standard for determining ^{1}H NMR yield. The product was then isolated by silica gel flash column chromatography (100% hexanes to 80/20 hexanes/EtOAc) or preparative TLC for HPLC analysis (80:20 hexanes/EtOAc solvent system). HPLC samples are occasionally filtered through an alumina plug to remove any undesired silanol byproducts. The desired product **8a** was prepared in 76% by ^{1}H NMR yield; $[\alpha]_D^{23}$ 13.0 (*c* 0.135, $CHCl_3$).

HPLC: Chiralpak AD-H column; 98:2 (hexanes/*i*-PrOH), 1 mL/min, 254 nm; t_R (minor) = 11.4 min, t_R (major) = 13.8 min; e.r. = 30:70.

IR (neat): 2981, 2889, 1729, 1687, 1607, 1463, 1392, 1303, 1221, 1133, 1115, 1078, 990, 870, 764 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.88–7.86 (m, 1 H), 7.48–7.44 (m, 1 H), 7.01 (t, *J* = 7.2 Hz, 1 H), 6.95 (d, *J* = 8.4 Hz, 1 H), 4.64 (dd, *J* = 14, 2.4 Hz, 1 H), 3.73 (s, 3 H), 2.82–2.75 (m, 1 H), 2.62–2.58 (m, 1 H), 1.37 (s, 1 H), 1.28 (s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 192.3, 175.6, 161.7, 136.1, 127.1, 121.6, 120.9, 118.0, 81.8, 52.3, 46.3, 38.5, 20.9, 20.7.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{16}O_4Na$ [M + Na]$^+$: 271.0941; found: 271.0934.

Dimethyl 2-[Cyclohexyl(1*H*-indol-3-yl)methyl]malonate (15a)

Dimethyl cyclohexylidenemalonate (**14a**; 113 mg, 0.5 mmol, 1.0 equiv), $Cu(OTf)_2$ (36 mg, 0.1 mmol, 0.2 equiv), trifluoroisopropanol (22.6 µL, 0.25 mmol, 0.5 equiv), and toluene (5 mL) were added to a 20 mL screw top reaction vial with a Teflon-coated septum. The flask was purged with dry N_2 and the reaction mixture stirred for 15 min or until a homogenous slurry was obtained. The reaction vial was then cooled to –78 °C in a dry ice/acetone bath. Silanediol **1a** stock solution in toluene (2.4 mL of 0.05 M, 82 mg,[15] 0.24 mmol, 0.2 equiv) and a solution of indole in toluene (2.6 mL 88 mg, 0.75 mmol, 1.5 equiv) were added dropwise to the reaction vial. The reaction vial was transferred to a lab freezer (–28 °C) and stirred overnight. The reaction was quenched with deionized H_2O (2 mL), stirred for 10 min, then extracted with EtOAc (3 × 10 mL), and the combined extracts were dried (Na_2SO_4). Solvent was removed from the combined organic layers under vacuum to obtain the crude product. The crude product was purified by silica gel column chromatography (eluent: 4:1 hexanes/EtOAc). The resulting material was purified further by silica gel column chromatography (eluent: 100% CH_2Cl_2). After removal of the solvent under vacuum, product **15a** was obtained as an off-white solid; yield: 159 mg (0.46 mmol, 93%; R_f = 0.25 (4:1 hexanes/EtOAc); $[\alpha]_D^{23}$ –9.1 (*c* 4.0, CH_2Cl_2).

HPLC: Chiralpak AS-H column (10% *i*-PrOH/hexanes, 1 mL/min, 225 nm); t_R (minor) = 8.55 min, t_R (major) = 23.80 min; 86.0:14.0 e.r.; 72% ee.

IR (neat): 3413, 2926, 2853, 1755, 1726, 1457, 1431 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.03 (s, 1 H), 7.66 (ddt, *J* = 8.0, 1.5, 0.8 Hz, 1 H), 7.32 (dt, *J* = 8.0, 0.9 Hz, 1 H), 7.16 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1 H), 7.10 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1 H), 7.03 (d, *J* = 2.4 Hz, 1 H), 4.03 (d, *J* = 10.8 Hz, 1 H), 3.78 (dd, *J* = 10.8, 4.9 Hz, 1 H), 3.73 (s, 3 H), 3.35 (s, 3 H), 1.78–1.55 (m, 6 H), 1.31–1.08 (m, 2 H), 1.02–0.81 (m, 3 H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 169.62, 168.96, 135.76, 128.42, 122.87, 121.85, 119.72, 119.41, 113.90, 111.02, 55.69, 52.64, 52.26, 42.04, 41.16, 32.33, 28.79, 26.68, 26.48, 26.32.

Determination of Association Constants

The association constant of the hosts (silanediol **1a**, thiourea **11**, and squaramide **12**) and guests (TBAOTf and TBACl) were determined by UV/Vis spectroscopy. $CHCl_3$ was purified to remove any stabilizers and distilled from CaH_2 prior to use. Toluene was dried over 4Å molecular sieves prior to use. Commercially available TBAOTf and TBACl were dried under reduced pressure for 1 day prior to use. The titration experiments were carried out with a host solution (3 mL, 1 × 10^{-5} M in $CHCl_3$) in a quartz cell and UV/Vis spectra recorded upon the addition of aliquots of the stock solution of guest ion in $CHCl_3$ or toluene with a microsyringe. The association constant was then calculated us-

ing a self-written non-linear regression analysis program (see Supporting Information for details). Each titration was repeated in triplicate and the mean K_{11} was reported.

NMR Titrations

The NMR titration experiments were carried out with a host solution (1×10^{-2} M) in $CDCl_3$. NMR spectra were recorded upon the addition of guest compound to the host solution. The guest compound was dissolved in the host working solution so as to maintain the concentration of host during the titration.

Funding Information

The National Science Foundation (1362030), the National Institutes of Health (1R35GM12480401), and Worcester Polytechnic Institute (WPI) are gratefully acknowledged for providing support for our studies. K.O. was supported by a fellowship from Yamagata University to study in the Mattson laboratory to complete these investigations. J.W.A. was supported by a WPI global scholars fellowship to complete investigations in the Kondo laboratory. J.H. is grateful for a WPI Summer Undergraduate Research Fellowship that supported her contribution to this project.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1612217.

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