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Silanediols: A New Class of Hydrogen Bond Donor Catalysts

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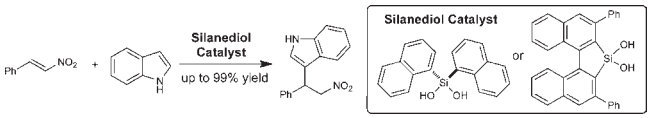
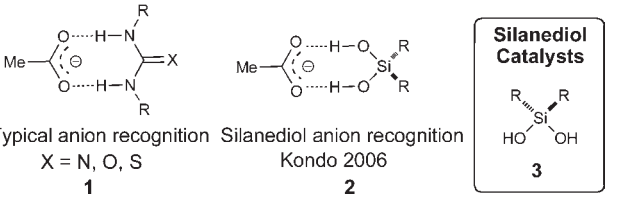
ABSTRACT



Silanediols are introduced as a new class of hydrogen bond donor catalysts for the activation of nitroalkenes toward nucleophilic attack. Excellent yields of product are obtained for the conjugate addition of indole to β-nitrostyrene catalyzed with a stable, storable dinaphthyl-derived silanediol. The preparation and structural characterization of a C_2-symmetric chiral silanediol is also reported along with its ability to catalyze the conjugate addition reaction.

Anion recognition abilities of small organic molecules have provided a great deal of inspiration for the development of hydrogen bonding catalysis, a powerful tool in organic synthesis.[1] Recent successes in the area of hydrogen bond donor (HBD) catalysis exploit the anion recognition abilities offered by urea, thiourea, and guanidinium functionalities (**1**).[2] Expansion of an HBD catalyst scaffold to include novel functional groups capable of recognizing anions will afford additional classes of catalysts to explore in overcoming the barriers associated with current HBD catalysts, such as low catalyst turnover and limited reaction scopes. Silanediols[3,4] are known to associate with both acetate (**2**) and chloride ions, yet they have received little attention in the context of noncovalent catalysis.[5] Excited by the potential of these interesting molecules, we have initiated a program in our laboratory dedicated toward pioneering the development of silanediols as a new class of catalysts that operate through hydrogen bonding interactions. In this communication, we report initial successes with silanediol catalysis and its application toward the activation of nitroalkenes.



A ground-breaking report in 2006 from Kondo and coworkers revealed a silanediol-based receptor that not only offered an area of expansion for anion recognition but also opened up a promising new platform for HBD catalyst design.[5,6] While the demonstrated anion recognition abilities of silanediols provided encouraging support for their development in noncovalent catalysis, our investigations into this area began with a number of uncertainties. The stability of silanediols was unclear, and there were concerns about their preparation, purification, and ability to withstand reaction conditions. Furthermore, while evidence existed for their anion association properties,

(1) (a) Pihko, P. *Hydrogen Bonding in Organic Synthesis*; Wiley-VCH: Weinheim, 2009. (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (d) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (e) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999.

(2) (a) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (b) Zhang, Z.; Schreiner, P. *Chem. Soc. Rev.* **2009**, *38*, 1187. (c) Connon, S. *Synlett* **2009**, 354.

(3) For a review on organosilanols, please see: Chandrasekhar, V.; Boomishankar, R.; Nagendran, S. *Chem. Rev.* **2004**, *104*, 5847.

(4) Interesting work involving silanediols as protease inhibitors has been reported: (a) Mutahi, M. W.; Nittoli, T.; Guo, L. X.; Sieburth, S. M. *J. Am. Chem. Soc.* **2002**, *124*, 7363. (b) Sieburth, S. M.; Chen, C. A. *Eur. J. Org. Chem.* **2006**, 311.

(5) Kondo, S.; Harada, T.; Tanka, R.; Unno, M. *Org. Lett.* **2006**, *8*, 4621.

(6) During the preparation of this manuscript the following reports involving silanediols were published: (a) Liu, M.; Tran, N. T.; Franz, A. K.; Lee, J. K. *J. Org. Chem.* **2011**, *76*, 7186. (b) Tran, N. T.; Min, T.; Franz, A. K. *Chem.—Eur. J.* **2011**, *17*, 9897.

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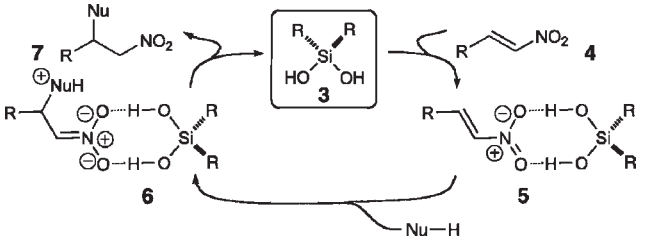
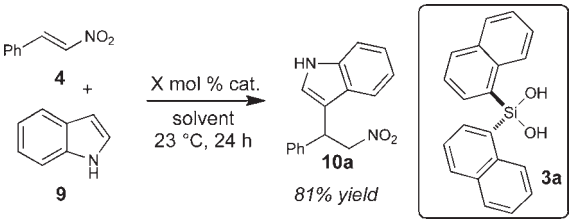
whether silanediols would be capable of *catalyzing* a chemical process remained unproven. The overall lack of information surrounding this entire area was particularly attractive to us, and a program was initiated to explore the feasibility of silanediol catalysis. We reasoned that the catalytic cycle would begin with activation of an electrophile, such as β-nitrostyrene (**4**), with silanediol **3** to afford intermediate **5** (Scheme 1). Nucleophilic addition to give rise to **6** followed by proton transfer and release of the catalyst would complete the cycle and generate the desired product (**7**). For this process to be a success requires an appropriate balance between the hydrogen bond donor and acceptor: suitable electrophilic activation is necessary while still allowing for rapid catalyst turnover. The limited knowledge available regarding hydrogen bonding of silanediols left this critical aspect of the proposed cycle uncertain, and we set out to ascertain the catalytic potential of **3**.

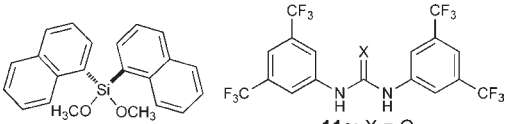
Scheme 1. Silanediol Catalysis



The addition of indole (**9**) to β-nitrostyrene (**4**) was selected as an ideal reaction to test the concept of silanediol catalysis as it is a process known to be accelerated in the presence of an appropriate HBD (Table 1).[7] Silanediol **3a**, derived from 1-bromonaphthalene and silicon tetrachloride, was chosen as the initial catalyst for examination, based upon Kondo's discoveries of its anion recognition properties.[5] Almost immediately our efforts were rewarded when 20 mol % of **3a** provided 81% of the desired product **10a** after 24 h in methylene chloride (entry 2). A brief solvent screen including toluene, ethyl acetate, and acetonitrile led us to conclude methylene chloride is the best solvent for this process (entries 1, 3–5). Reduction of the catalyst loadings to 10 and 5 mol % afforded 67% and 30% yields, respectively, after 24 h (entries 6 and 7). In order to probe the importance of the hydroxyl groups on reactivity, dimethoxysilane **3b** was subjected to identical reaction conditions in the addition of **9** to **4**. Just 10% of **10a** was formed when **4** and **9** are exposed to 20 mol % of **3b** for 24 h in methylene chloride suggesting the silanediol functionality is a necessary element of the catalyst design. Further evidence supporting silanediol **3a** as an HBD catalyst was realized from the solvent screen. Solvents able to disrupt hydrogen bonding, such as THF and ethyl acetate, completely shut down the catalytic activity of **3a** and gave rise to less than 10% yield of **10a** (entries 3–5). The importance of the diol functionality was reconfirmed when triphenylsilanol was found to yield 52% of **10a** (entry 10). The reaction catalyzed by diphenylsilanediol was also lower yielding (entry 11). Silanediol **3a** was compared directly to conventional urea and thiourea catalysts **11a** and **11b**. Silanediol **3a** easily outperformed urea **11a** affording more than one and a half times the amount of **10a** after 24 h in methylene chloride (67% vs 43%, entry 6 vs 12). The yields of **10a** were even better for silanediol **3a** than thiourea **11b** (67% vs 58%, entry 6 vs 13).

Table 1. Optimization of Silanediol (**3a**) Catalysis in the Addition of Indole (**9**) to Nitroalkene (**4**) To Afford **10a**[a]





entry	solvent	catalyst	mol % cat.	yield (%)[b]
1	$PhCH_3$	**3a**	20	56
2	CH_2C1_2	**3a**	20	81
3	EtOAc	**3a**	20	4
4	THF	**3a**	20	5
5	CH_3CN	**3a**	20	4
6	CH_2C1_2	**3a**	10	67
7	CH_2C1_2	**3a**	5	30
8	CH_2C1_2	**3a**	2.5	21
9	CH_2C1_2	**3b**	20	10
10	CH_2C1_2	Ph_3SiOH	20	52
11	CH_2C1_2	$Ph_2Si(OH)_2$	20	46
12	CH_2C1_2	**11a**	10	43
13	CH_2C1_2	**11b**	10	58

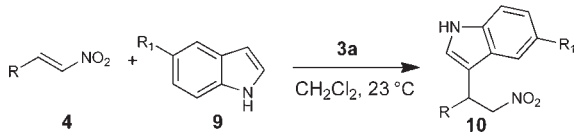
[a] Reactions performed using 1.5 equiv of indole at a concentration of 2 M. See Supporting Information for detailed experimental procedures. In the absence of a catalyst an 8% yield of product was isolated. [b] Isolated yield.

With the demonstrated activity of unique HBD catalyst **3a** in hand, attention was turned toward evaluating the scope of the reaction with respect to both the nitroalkene and indole (Table 2). Both electron-donating and electron-withdrawing substituents on the nitrostyrene were well

(7) For reports of urea/thiourea catalyzed indole additions, see: (a) Dessole, G.; Herrera, R. P.; Ricci, A. *Synlett* **2004**, *13*, 2374. (b) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6576. (c) Fleming, E. M.; McCabe, T.; Connon, S. J. *Tetrahedron Lett.* **2006**, *47*, 7037. (d) So, S. S.; Burkett, J. A.; Mattson, A. E. *Org. Lett.* **2011**, *13*, 716. For examples of phosphoric acid catalyzed indole additions, see: (a) Rowland, G. B.; Rowland, E. B.; Liang, Y.; Perman, J. A.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 2609. (b) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2008**, *120*, 4016.

accommodated in the process. The addition of indole and 5-methoxyindole to 4-bromonitrostyrene and 4-methoxynitrostyrene catalyzed by **3a** enabled the isolation of 98% of **10b** and 82% of **10c**, respectively (entries 2 and 3). The more challenging alkyl nitroalkenes were discovered to afford good yields of product with 20 mol % of **3a** after 48 h at 23 °C in methylene chloride. The addition of 5-methoxyindole to the hexanal-derived nitroalkene yielded 44% of **10d** based upon 49% conversion after stirring for 24 h (entry 4). The more hindered cyclohexanecarboxaldehyde-derived nitroalkene was also tolerated in the reaction giving rise to 48% of **10e** (entry 5). Electron-rich 5-methoxyindole operated well as a nucleophile in the addition to nitrostyrene affording 99% of **10f** (entry 6). 5-Chloroindole, albeit somewhat more sluggish, also proved to be a useful nucleophile in the addition reaction yielding 71% of **10g** after 48 h (entry 7).

Table 2. Silanediol Catalysis Substrate Scope[a]



4 9 10

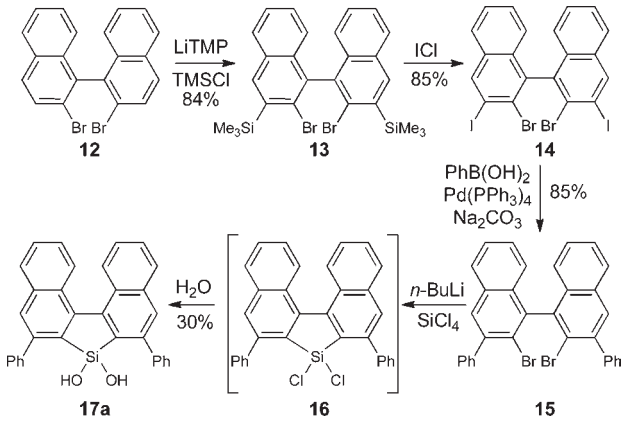
entry	R	R_1	product	**3a** mol %	time (h)	yield[b] (%)
1	Ph	H	**10a**	20	24	81
2	4-Br-C_6H_4	H	**10b**	20	48	98
3	4-MeO-C_6H_4	MeO	**10c**	20	24	82
4[c]	*n*-pentyl	MeO	**10d**	20	24	44
5	cyclohexyl	H	**10e**	20	48	48
6	Ph	MeO	**10f**	10	48	99
7	Ph	C1	**10g**	20	48	71

[a] Reactions performed using 1.5 equiv of indole at a concentration of 2 M. See Supporting Information for detailed experimental procedures. [b] Isolated yield. [c] Based on 49% conversion.

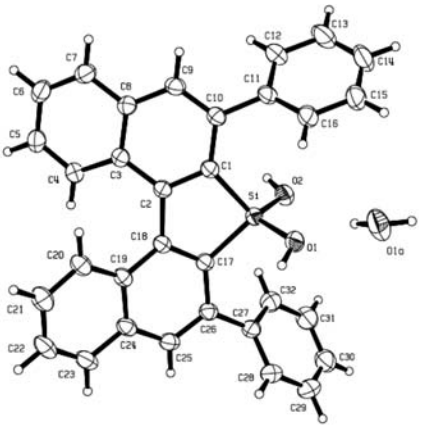
Once the potential of silanediol catalysis had been established, efforts to address the interesting and unprecedented challenge of synthesizing chiral silanediols were initiated. Based upon our success with dinaphthyl-derived silanediol **3a**, we reasoned a binaphthyl scaffold would provide an ideal starting point for the investigations and we set out to prepare **17a** (Scheme 2). Prior to this study, the construction of C_2-symmetric silanediols had not been reported. A modular route taking advantage of a Suzuki−Miyaura cross-coupling reaction to install substitution on the binaphthalene backbone was favored to provide the opportunitity of future access to a family of chiral silanediols from a common intermediate (**14**). The preparation of racemic silanediol **17a** began by treating dibromobinaphthalene (**12**) with lithium tetramethylpiperidide (LiTMP) and trimethylsilyl chloride (TMSCl) to generate **13**.[8] The

(8) Widhalm, M.; Aichinger, C.; Mereiter, K. *Tetrahedron Lett.* **2009**, *50*, 2425. See Supporting Information for detailed expeimental procedures.

Scheme 2. Synthesis of Silanediol Catalyst (±)-**17a**



conversion of **13** to the aryl iodide **14** was executed with ICl in good yield (85%). Cross-coupling of the aryl iodide with phenyl boronic acid gave rise to the desired substituted dibromobinaphthalene **15** in 85% yield. Finally, the lithium halogen exchange of **15** effected with *n*-BuLi followed by treatment with silicon tetrachloride generated the dichlorosilane **16** in situ which was then hydrolyzed to silanediol **17a** upon subjection to ether and water.



Comparison of Selected Features of Silanediols **3a** and **17a**

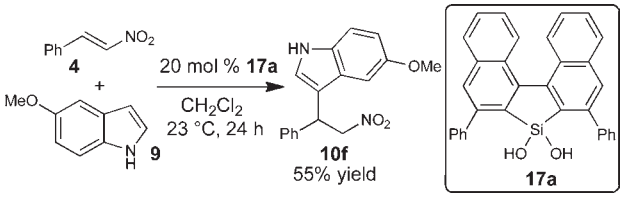
bond lengths	**3a**[a]	**17a**	bond angles	**3a**[a]	**17a**
Si-O	1.636(3)	1.613(35)	C-Si-C	110.14°	92.53°
Si-C	1.879(0)	1.863(8)	O-Si-O	110.43°	106.08°

[a] Taken from ref 5

Figure 1. ORTEP representation of **17a**. Ellipsoids are displayed at 50% probability.

Crystallization of **17a** from hexanes and methylene chloride gave rise to X-ray quality crystals for analysis (Figure 1). To the best of our knowledge this is the first reported crystal structure of a C_2-symmetric chiral silanediol. A comparison of silanediols **3a** and **17a** revealed the Si−O and Si−C bond lengths are roughly equivalent in both structures.

Scheme 3. Catalysis with Silanediol (±)-**17a**



The difference in bond angles between the two catalysts is more substantial: silanediol **17a** has significantly smaller C−Si−C (92.53° vs 110.14°) and O−Si−O (106.08° vs 110.43°) bond angles than **3a**. A torsional angle of 37.09° was found for C3−C2−C18−C19 of **17a**.[9]

The catalytic potential of (±)-**17a** was put to the test in the addition of 5-methoxyindole to β-nitrostyrene, a 55% yield of desired adduct **10f** after 24 h at 23 °C in methylene chloride (Scheme 3).

(9) See Supporting Information for more details regarding the crystal structure of **17a**.

In summary, silanediols have been introduced as a new class of hydrogen bond donor catalysts for the activation of nitroalkenes in conjugate addition reactions. This study not only includes the original report of silanediol catalysis but also reveals the first synthesis and examination of a modular C_2-symmetric chiral silanediol, including a crystal structure. Investigations surrounding the potential associated silanediol catalysis, including the development of enantioselective variants, as a new tool for organic synthesis are ongoing in our laboratory and will be reported as soon as possible.

Acknowledgment. Support for this work has been provided by the OSU Department of Chemistry. We thank the Ohio BioProducts Innovations Center (OBIC) for helping support our mass spectrometry facility. Dr. Judith Gallucci (OSU) is thanked for solving the crystal structure of silanediol **17a**.

Supporting Information Available. Experimental procedures and spectral data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.