CHEMISTRY
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Accepted Article

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201801304

Link to VoR: http://dx.doi.org/10.1002/chem.201801304

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Enantioselective Catalyst Systems from Copper(II) Triflate and BINOL-Silanediol

Yong Guan[a],**, Jonathan W. Attard[a],**, Michael D. Visco[b], Thomas J. Fisher[c], and Anita E. Mattson*[a]

Abstract: Silanediol and copper catalysis are merged, for the first time, to create an enhanced Lewis acid catalyst system for enantioselective heterocycle functionalization. The promise of this silanediol and copper catalyst combination is demonstrated in the enantioselective addition of indoles to alkylidene malonates to give rise to the desirable adducts in excellent yield and high enantiomeric excess. From our studies, BINOL-based silanediols emerged as one-of-a-kind cocatalysts for the process and their potential role in the reaction pathway is discussed.

The interesting properties of the silanediol functional group have enticed investigators to pursue its study in a number of applications, such as materials, medicine, molecular recognition, and catalysis.[1-4] In the context of enantioselective catalysis, the hydrogen-bonding and anion-binding abilities of silanediols have significant value.[5],[6] For instance, enantioselective silanediol catalysis has emerged as a promising platform for the functionalization of nitrogen- and oxygen-based heterocycles. These reactions plausibly benefit from a silanediol anion-binding mode of action; the silanediol may directly activate an ionic substrate through hydrogen-bonding interactions with the anionic component.[6,7] Notably, silanediols can offer reactivity patterns that are inaccessible with other types of catalysts. For instance, VANOL- and BINOL-based silanediols are, to date, distinct in their ability to control the stereochemical outcome of reactions of 4-silyloxybenzopyrylium triflates.[6a]

The unique abilities of silanediols in enantioselective catalysis enticed us to stop limiting their application to the direct activation of substrates (**A**, Figure 1). We reasoned that silanediols could work together with transition metal catalysts, like Cu(OTf)$_2$, thereby generating an enhanced catalyst system (**B**) for the discovery of useful reactions.[8-10] Herein, we communicate, for the first time, a silanediol and copper catalyst system for the enantiocontrolled addition of indoles to alkylidene malonates.

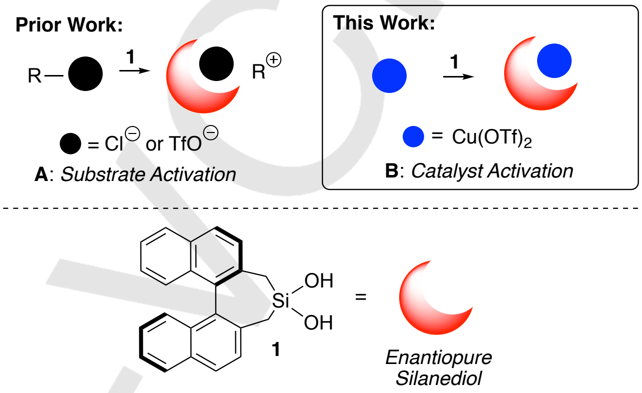
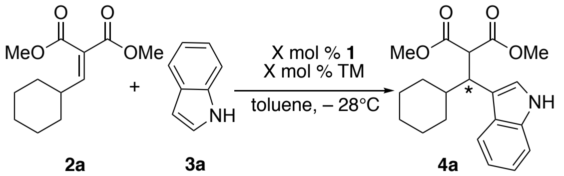


Figure 1. Expanding the role of silanediols in catalysis: (A) Substrate activation (B) Catalyst activation

It is well known that metals catalyze the addition of indoles to arylidene and alkylidene malonates.[11] In the case of arylidene malonates, the reactions can be rendered highly enantioselective in the presence of an appropriate chiral ligand,

Table 1. Identification of reaction conditions for silanediol and copper cocatalysis in the reaction of **2a** and **3a**



Entry[a]	X mol % **1**	X mol % TM	Yield[b]	ee[c]
1	30	20 mol % Cu(OTf)$_2$	92	72
2	30	20 mol % Sc(OTf)$_3$	95	9
3	30	20 mol % In(OTf)$_3$	88	10
4	20	20 mol % Zn(OTf)$_2$	0	--
5	30	20 mol % CuOTf	10	31
6	0	20 mol %Cu(OTf)$_2$	15	0
7	30	0 mol % Cu(OTf)$_2$	0	--
8	30	20 mol % CuSO$_4$	0	--
9	30	20 mol % CuCl	0	--
10	30	20 mol % CuI	0	--
11	30	10 mol % HOTf	0	--

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[a] Dr. Y. Guan, Mr. J. Attard, Prof. A. Mattson
Department of Chemistry and Biochemistry
Worcester Polytechnic Institute
100 Institute Road, Worcester, MA 01609
E-mail: aemattson@wpi.edu
**authors contributed equally
[b] Dr. Michael D. Visco
Celgene
86 Morris Avenue
Summit, NJ
[c] Dr. Thomas J. Fisher
The Goodyear Tire and Rubber Company
200 Innovation Way
Akron,OH

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12	20	20 mol % $Cu(OTf)_2$	93	73
13	10	10 mol %$Cu(OTf)_2$	70	70
14[d]	20	20 mol % $Cu(OTf)_2$	99	75

[a] See supporting information for details on the experimental procedure; [b] Yield determined by ^{1}H NMR spectroscopy; [c] enantiomeric excess determined by HPLC; [d] 0.5 equiv. 1,1,1-trifluoroisopropanol (TFIP) added.

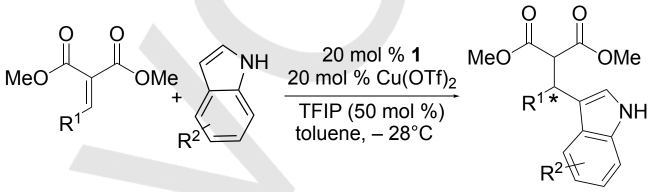
such as trisoxazolines.[11e] Attaining high levels of enantiocontrol in the addition of indole to alkylidene malonates, on the other hand, remains a significant challenge. With this in mind, we setout to explore silanediol and transition metal catalyst systems as a solution for the enantioselective addition of indole (**3a**) to cyclohexylidene malonate (**2a**, Table 1).

Our studies began with an examination of the influence of 30 mol % of BINOL-based silanediol **1** and 20 mol % of a wide selection of transition metals, a few of which are listed in Table 1, in the addition of indole (**3a**) to cyclohexylidene malonate (**2a**). Only the combination of **1** and $Cu(OTf)_2$ gave rise to a high yield of **4a** with high levels of enantiocontrol (92% yield, 72% ee, entry 1). Other transition metals tested could generate high yields of desired product but low levels of enantiocontrol (e.g. $Sc(OTf)_3$, $In(OTf)_3$, entries 2 and 3). CuOTf also proved inferior to its $Cu(OTf)_2$ counterpart (entry 5). Control experiments revealed the important roles of both the silanediol and $Cu(OTf)_2$ in achieving excellent yields and stereocontrol: 20 mol % of $Cu(OTf)_2$ alone, with no silanediol added, resulted in a dramatic drop in the yield of **4a** (15%, entry 6). No product was observed when 30 mol % of the silanediol was tested as the sole catalyst of the reaction (entry 7). Copper sources other than $Cu(OTf)_2$, such as $CuSO_4$, CuCl, and CuI, were also evaluated but they did not yield product, suggesting the triflate counterion is essential to the success of the reaction (entries 8 – 10). Triflic acid was ruled out as the co-catalyst when control experiments resulted in no reaction (entry 11). The optimization of the copper to silanediol ratio resulted in an improvement in the enantiomeric ratio: 20 mol % of each silanediol and $Cu(OTf)_2$ was identified as the best combination in terms of yield and stereocontrol (93% yield, 73% ee, entry 12). The catalyst loadings could be dropped to 10 mol % with no significant drop in enantiomeric excess, but the yield was slightly lower (70% yield, 70% ee, entry 13). Finally, a screening of additives enabled us pinpoint that 0.5 equiv of 1,1,1-trifluoroisopropanol (TFIP) gave a small boost in the enantiomeric excess (75% ee, entry 14).

Having identified a workable copper and silanediol catalyst system for the introduction of indole to **2a**, further probing of the influence of the structure **2** and **3** on the outcome of the reaction was undertaken (Table 2).[12] The substituent on the ester had a rather dramatic effect on enantiocontrol, the trend being smaller substituents led to higher enantiomeric ratios.[12] Methyl esters (**2**) resulted in the best stereocontrol observed in the reaction. Alkylidene malonates where R^1 = cyclohexyl afforded **4a** in excellent yield with high levels of enantiocontrol (98%, 75% ee, entry 1), Various substitution patterns about the indole scaffold enabled the preparation of **4b**-**4g**. Alkyl and aryl substituents in the 5-position of indole were well tolerated, producing **4b**-**4f** in excellent yields and high enantiomeric excess (entries 2-6). Substituents at the 7-position of indole were also well accepted. For example, 7-methylindole afforded 4h in 96% yield and 75% ee (entry 7).

Having identified a workable copper and silanediol catalyst system for the introduction of indole to **2a**, further probing of the influence of **2** and **3** on the outcome of the reaction revealed the enantiomeric excess was highly dependent on substrate structure (Table 2).^{12} The substituent on the ester had a rather dramatic effect on enantiocontrol, the trend being smaller

Table 2. Affect of substrate structure on reaction



2 **3** **4**

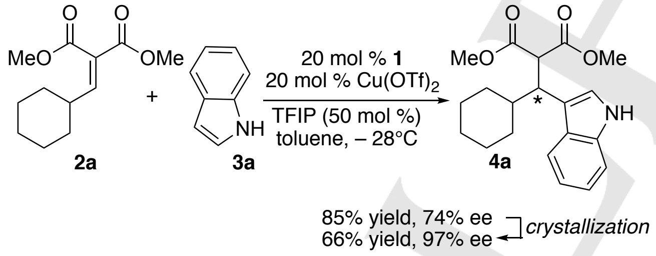
Entry[a]	R^1	R^2	Product	Yield(%)[b]	ee(%)[c]
1	Cy	H	**4a**	98	75
2	Cy	5-Me	**4b**	96	77
3	Cy	5-*t*Bu	**4c**	92	68
4	Cy	5-Ph	**4d**	92	71
5	Cy	5-(2-naphthyl)	**4e**	66	72
6	Cy	5-(3,5)-CF_3Ph	**4f**	58	86
7	Cy	7-Me	**4g**	95	75
8	Ph	H	**4h**	99[d]	49
9	*p*-MeO-Ph	H	**4i**	16[d,e]	52
10	*p*-NO_2-Ph	H	**4j**	99[d]	30
11	*o*-tolyl	H	**4k**	50[d]	49
12	2-naphthyl	H	**4l**	99[d,e]	58
13	*n*-propyl	H	**4m**	92[d]	30

[a] See supporting information for details on the experimental procedure, TFIP = 1,1,1-trifluoroispropanol; [b] Isolated yields after flash column chromatography on silica gel; [c] Enantiomeric ratio determined by HPLC; [d] Yield determined by ^{1}H NMR spectroscopy, 30 mol % **1**; [e] 40 mol % **1**

substituents led to higher enantiomeric ratios.[12] Methyl esters (**2**) resulted in the best stereocontrol observed in the reaction. Alkylidene malonates where R^1 = cyclohexyl afforded **4a** in excellent yield with high levels of enantiocontrol (98%, 75% ee, entry 1). Various substitution patterns about the indole scaffold enabled the preparation of **4b-4g**. More specifically, alkyl and aryl substituents in the 5-position of indole were well tolerated, producing **4b-4f** in excellent yields and high enantiomeric excess (entries 2-6). Substituents at the 7-position of indole were also well accepted. For example, 7-methylindole afforded **4g** in 96% yield and 75% ee (entry 7). For a comparison to alkylidene malonate **2a**, several arylidene malonates were tested as substrates in the reaction. Interestingly, the arylidene malonates did not afford enantiomeric excesses as high as **2a**. For instance, arylidene malonates containing either electron donating or withdrawing substituents yielded **4h-4l** in low to excellent yield (16-99%) but with modest levels of enantiomeric excess (30-56% ee, entries 8-12). The importance of the alkylidene malonate structure on enantioselectivity was further highlighted when malonate **2** (R^1 = *n*-propyl) gave rise to **4m** in 92% yield and 30% ee (entry 13).

The reaction is amenable to scale-up (Scheme 1). When **2a** was subjected to reaction with indole under the influence of silanediol and copper cocatalysis, **4a** was produced in 85% yield and 74% ee. The process is synthetically useful as the enantioenriched product is easily crystallized from isopropanol and hexanes giving rise to **4a** in an excellent enantiomeric excess of 97%.

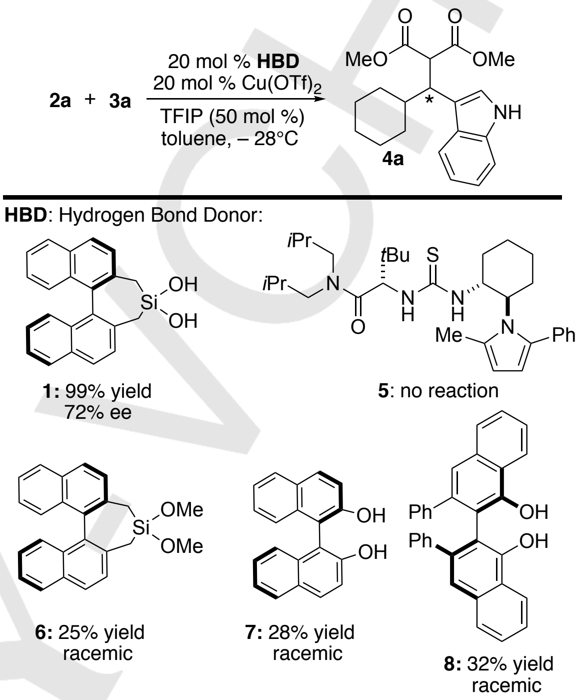
Scheme 1. Scale up and recrystallization



Interesting observations were made while probing the possible role of the silanediol. First, it was found that the silanediol is a uniquely effective cocatalyst: all of our attempts to catalyze the reaction with a combination of Cu(OTf)$_2$ and other popular dual hydrogen bond donors (HBDs) were entirely fruitless (Scheme 2). For instance, the combination of Cu(OTf)$_2$ and popular chiral thiourea catalyst **5** yielded no reaction. The addition of enantiopure BINOL (**7**) and VANOL (**8**) resulted in low yields of racemic product. Evidence of the importance of the silanediol functional group was found when *bis*-dimethoxy silanediol **6** gave rise to racemic **4a** in 25% yield.

Given the unique ability of silanediol **1** to cooperate with catalytic copper(II) triflate to affect the enantioselective addition reaction of **3** and **2**, we became curious to learn more about the role of the silanediol in the reaction. Experimental evidence collected during the optimization of the reaction (Table 1) suggested that neither the silanediol or Cu(OTf)$_2$ alone were efficient catalysts: there is something unique about the combination of the two. The observation had been made (Table 1) that the triflate counterion was required for a successful reaction. Furthermore, it has been previously demonstrated that silanediols can recognize triflate anions[6a], thus there is the possibility that the silanediol is activating Cu(OTf)$_2$ through anion-binding to the triflate to create copper-silanediol catalyst complex **I** (see Scheme 4). Alternatively, a reaction pathway in which the silanediol may be operating as a ligand on copper was also considered.

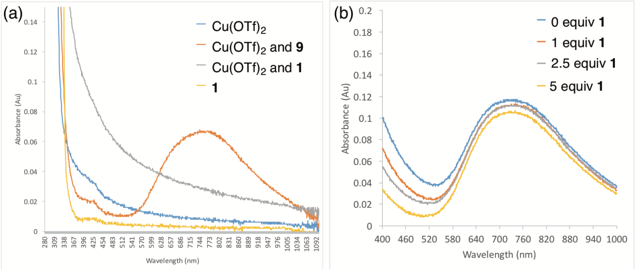
Scheme 2. Unique combination of silanediol and Cu(OTf)$_2$



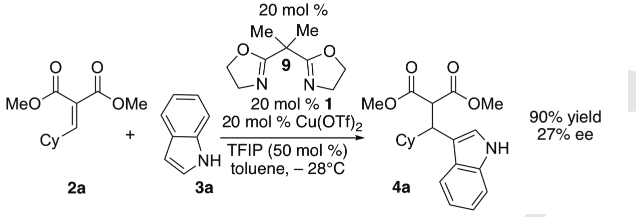
Efforts to probe the role of the silanediol and plausible catalytic species began with UV-Vis studies of the Cu(OTf)$_2$ in the presence of silanediol **1** and a competing ligand, achiral bisoxazoline **9** (Scheme 3). In the first set of experiments, it was noted that the combination of Cu(OTf)$_2$ and **1** did not produce a band in the spectrum that is indicative of a d-d transition, whereas the combination of Cu(OTf)$_2$ and **9** did produce a band with a λmax ~ 754nm (Scheme 3a). In a second experiment, the titration of 1-5 equiv of **1** into a solution of Cu(OTf)$_2$ and **9** did not significantly alter the UV-Vis spectrum (Scheme 3b). These data suggest that the silanediol may not be operating as a ligand, and will likely not displace a bisoxazoline ligand on copper.

To better understand the silanediol mode of action, an experiment was set up to in which 20 mol % of achiral bis-oxazoline **9** was added to an otherwise standard reaction (Scheme 3c). Based upon the UV-Vis data, it was reasoned that the bisoxazoline would be a superior ligand on copper than the silanediol and if **4a** was prepared in enatiomerically enriched form from this reaction then that may suggest the silanediol is operating as an anion binding catalyst, not as a ligand. Indeed, **4a** was isolated in 90% yield with 27% ee, possibly providing evidence for the reaction pathway depicted in Scheme 4. More specifically, the catalytic cyclic may begin with the silanediol interacting with the $Cu(OTf)_2$ to generate enhanced Lewis acid species **I**.[13] The complexation of **I** with the alkylidene malonate **2** may give rise to **II**. The subsequent enantioselective addition of indole **3a** to **II** yields intermediate **III** which, after proton transfers, affords desired product **4** and frees complex **I** for continued participation in the catalytic cycle.

Scheme 3. Probing of plausible role of silanediol

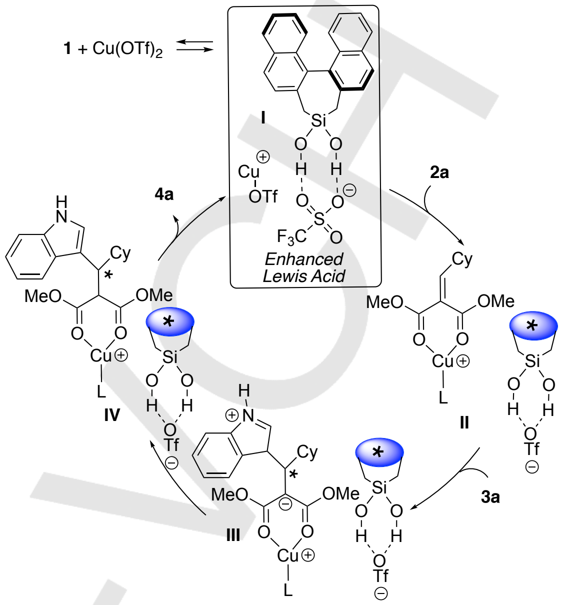


(c) Experiment with bisoxazoline as ligand on copper.



To conclude, silanediols work with $Cu(OTf)_2$ to generate an enhanced catalyst system with applications in enantioselective synthesis. Herein, silanediol and copper catalysis has been demonstrated in the reaction of indoles and alkylidene malonates to afford desirable adducts with high levels of enantiocontrol. Our preliminary studies suggest the silanediol may be operating as an anion-binding catalyst to activate copper triflate, but further investigations are needed to better understand the operation of the catalyst system. Ongoing studies in our laboratory are dedicated toward uncovering the full potential of silanediol and transition metal cocatalysis in the context of asymmetric synthesis.

Scheme 4. Possible catalytic pathway



Experimental Section

Dimethyl cyclohexylidene malonate (113 mg, 0.5 mmol, 1.0 eq), $Cu(OTf)_2$ (36 mg, 0.1 mmol, 0.2 eq), trifluoroisopropanol (22.6μL, 0.25 mmol, 0.5 eq) and toluene (5mL) were added into 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 minutes or until a homogenous slurry was obtained. The reaction vial was then cooled to –78°C in a dry ice/acetone bath. 2.4 mL of 0.05 M silanediol stock solution (82 mg, 0.24 mmol, 0.2 eq) in toluene and 2.6 mL of indole solution (88 mg, 0.75 mmol, 1.5 eq) in toluene were added into the reaction vial dropwise. The reaction vial was transferred into a lab freezer (–28°C) and stirred overnight. The reaction was quenched with 2 mL of DI water, stirred for 10 minutes then extracted with EtOAc 3x10mL and dried over Na_2SO_4. Solvent was removed from the combined organic layer under vacuum to obtain 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% dichloromethane). After removal of the solvent under vacuum, dimethyl 2-(cyclohexyl(1H-indol-3-yl)methyl)malonate was obtained as an off white solid (159mg, 0.46 mmol, 93% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.66 (ddt, J = 8.0, 1.5, 0.8 Hz, 1H), 7.32 (dt, J = 8.0, 0.9 Hz, 1H), 7.16 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.10 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 7.03 (d, J = 2.4 Hz, 1H), 4.03 (d, J = 10.8 Hz, 1H), 3.78 (dd, J = 10.8, 4.9 Hz, 1H), 3.73 (s, 3H), 3.35 (s, 3H), 1.78 – 1.55 (m, 6H), 1.31 – 1.08 (m, 2H), 1.02 – 0.81 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) 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. IR (neat) 3413, 2926, 2853, 1755, 1726, 1457, 1431 cm^{-1}. HPLC: 86.0:14.0 e.r., 72% ee, 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. R_f = 0.25 (4:1, Hexanes:EtOAc). $[\alpha]_D^{23}$ = -9.1 (c = 4.0, CH_2Cl_2).

Acknowledgements

The National Science Foundation (1362030), the National Institutes of Health (1R35GM12480401), and Worcester Polytechnic Institute are gratefully acknowledged for providing support for our studies.

Keywords: silanediol • cooperative catalysis • copper • enantioselective • Friedel-Crafts

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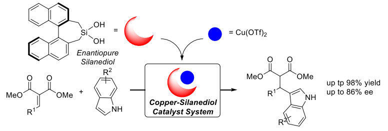
10.1002/chem.201801304

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

Better Together: Silanediol and copper(II) triflate work together to create an enhanced catalyst system for enantioselective heterocycle functionalization. This unique catalyst combination activates alkylidene malonates for reaction with indoles, giving rise to desirable products in excellent yield and high levels of enantiomeric excess.



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Enantioselective Catalyst Systems

from Copper(II) Triflate and BINOL-

Silanediol