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Silanediol-Catalyzed Chromenone Functionalization

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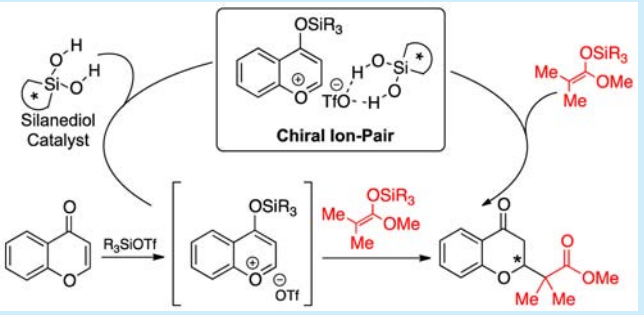
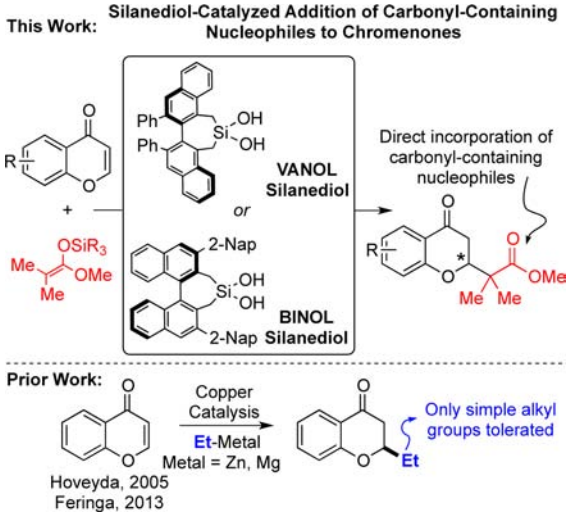
Supporting Information

ABSTRACT: Promising levels of enantiocontrol are observed in the silanediol-catalyzed addition of silyl ketene acetals to benzopyrylium triflates. This rare example of enantioselective, intermolecular chromenone functionalization with carbonyl-containing nucleophiles has potential applications in the synthesis of bioactive chromanones and tetrahydroxanthones.



Although a small array of strategies to construct chiral 2-alkylchroman-4-ones has been explored and reported,[1] a general catalytic, enantioselective method to access these important bioactive heterocycles in enantiopure form remains elusive.[2] To this end, in 2005, Hoveyda reported a copper–peptide complex for catalytic enantioselective addition of dialkylzincs to chromone (Scheme 1).[3] More recently, Feringa and co-workers found that Grignard reagents undergo enantioselective additions to chromone in the presence of a copper catalyst and Josiphos-based ligands.[4] While high yielding and highly stereoselective, both of these strategies only enable the addition of simple aliphatic groups: these methods are not directly applicable to many families of bioactive chromanones, such as the gonytolides and blennolides.[5] Herein, we describe the first catalytic strategy for enantioselective intermolecular functionalization of chromenones with carbonyl-containing nucleophiles.

Scheme 1. Enantioselective Strategies toward 2-Alkylchromanones



Our inspiration for these studies originated from data reported by Akiba and co-workers that demonstrated the racemic addition of silyl ketene acetals, allyl silanes, and dienes to benzopyrylium triflates **2**, reactive species generated from the exposure of chromen-4-ones (**1**) to silyl triflates.[6] Our studies were further encouraged by the Porco group's recent application of racemic additions of siloxyfurans to 4-siloxybenzopyrylium ions in the syntheses of complex chromanone natural products.[7] Enticed by the synthetic utility of these *racemic* additions, we set out to develop the first enantiocontrolled functionalization of 4-siloxybenzopyrylium ions.

In connection with our ongoing research program dedicated toward metal-free, noncovalent catalyst design, we became interested in exploring the anion-binding ability of silanediols in the context of enantioselective 2-alkylchroman-4-one construction (Scheme 2).[8−10] We envisioned capturing 4-siloxybenzopyrylium triflates (**2**) with a silanediol catalyst resulting from the in situ generation of a chiral ion pair. It was reasoned that our arene-rich silanediols would offer a chiral pocket uniquely suited to stabilize a network of noncovalent interactions (e.g., hydrogen bonding, $\pi-\pi$, π–cation) in a transition state that would ultimately enable the facially biased addition of nucleophiles to the reactive benzopyrylium ion.

Our studies began by probing the influence of silanediol structure on enantioselectivity in the addition of silyl ketene

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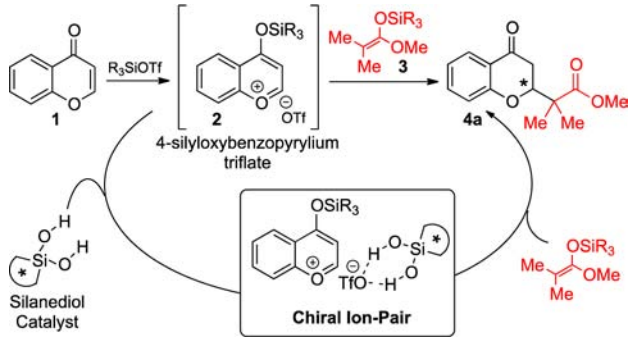
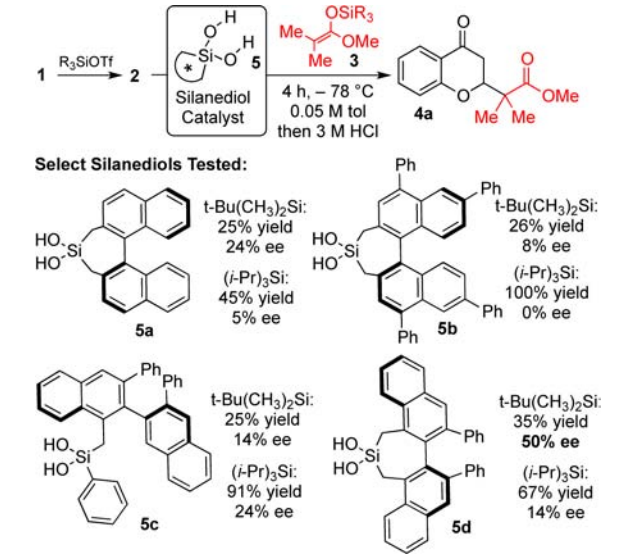
Scheme 2. Strategy for Silanediol-Catalyzed Enantioselective Benzopyrylium Ion Functionalization



acetal **3** to siloxybenzopyrylium triflates (Scheme 3). Prior success with BINOL-based silanediols **5a** and **5b** in the addition

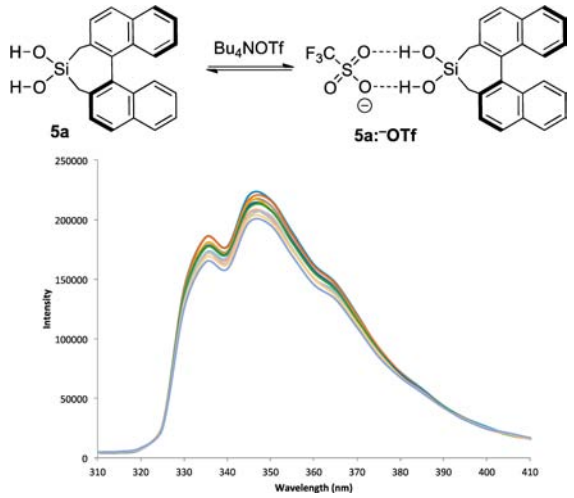
Scheme 3. Some Effects of Silanediol Structure on Yield and Enantiocontrol



of silyl ketene acetals to isoquinolinium ions prompted us to explore these catalysts in the synthesis of **4**.[9b] The ability of our BINOL-based silanediols to enable and influence the enantioselective addition of silyl ketene acetals to benzopyrylium triflates was almost immediately evident; the unsubstituted cyclic silanediol **5a** gave a 24% ee but low yield (25%). Our initial catalyst screen demonstrated the dramatic effect of silanediol structure on enantiocontrol. For example, 4,4′,6,6′-tetraphenyl-substituted **5b** only provided an 8% ee. The nature of the silyl group of the silyl triflate and silyl ketene acetal (**3**) had a fairly substantial influence on the enantioselectivity: the *tert*-butyldimethylsilyl group was more effective with regard to stereocontrol but lower yielding than the triisopropylsilyl group, possibly due to undesired silylation of the catalyst.

The promising levels of enantiocontrol observed with BINOL-based silanediol **5a** in the addition of **3** to proposed benzopyrilium triflate **2** prompted us to briefly explore the plausible triflate–silanediol **5a** binding by fluorescence spectroscopy (Scheme 4). Experimentally, changes observed in the fluorescence spectra were measured as aliquots of tetrabutylammonium triflate were titrated into a solution of silanediol in $CHCl_3$. From the average of four experiments, an association

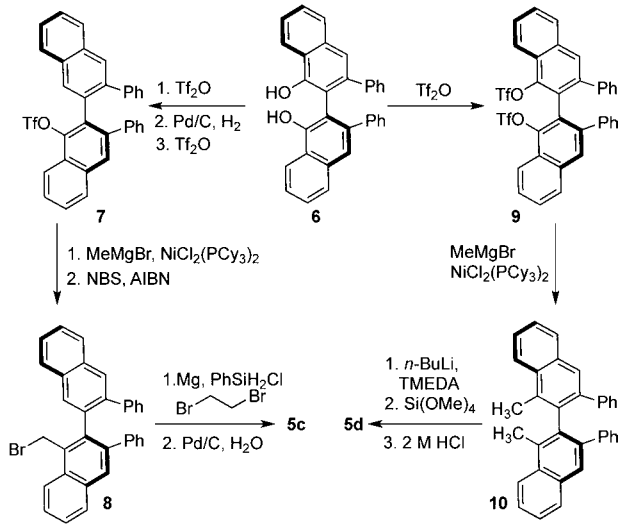
Scheme 4. Silanediol–Triflate Association Measured by Fluorescence Spectroscopy



constant of 2.31 ± 0.52 × 10^3 M^{-1} was obtained for **5a** and triflate.[11]

Concomitant with our BINOL–silanediol catalyst design program emerged the development of both acyclic (**5c**) and cyclic (**5d**) VANOL-based silanediols. We were especially excited by the prospect of incorporating VANOL into our silanediol scaffolds as it is able to reach unique chemical space and can offer improved selectivity over BINOL-based catalysts and ligands.[12] The synthetic accessibility of VANOL-based silanediols had not been reported prior to our investigations, so we dedicated a significant amount of effort to establishing routes to these interesting structures (Scheme 5). Acyclic

Scheme 5. VANOL–Silanediol Syntheses



VANOL–silanediol **5c** was prepared by first monotriflating **6** and then reducing and triflating the remaining hydroxyl group to reach **7**.[13] The Kumada cross coupling of **7** with methylmagnesium bromide followed by radical bromination gave rise to **8**.[14] Introduction of the silyl group was achieved in excellent yield upon treatment of **8** under recently developed Barbier-type reaction conditions for this C–Si bond formation.[15] The intermediate silane was subjected to hydrolytic oxidation with Pd/C as a catalyst to generate **5c**.

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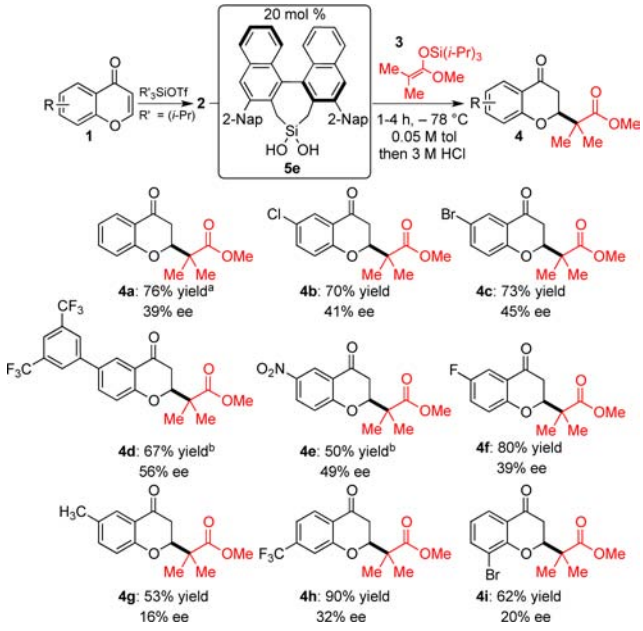
Cyclic VANOL silanediol **5d** presented a greater synthetic challenge than **5c** because the introduction of the two methyl groups is difficult, presumably because the 2,2′ positions of VANOL are so sterically encumbered and had not been previously reported. A significant amount of experimentation enabled the identification of $NiCl_2(PCy_3)_2$ as a unique catalyst able to effect the desired double Kumada cross coupling on **9** to access **10**. Subsequent lithiation of **10** followed by silacyclization with tetramethoxysilane followed by hydrolysis afforded desired silanediol **5d**.

To our delight, VANOL-based silanediols **5c** and **5d** did offer us improvements in stereocontrol and/or yield when compared to the BINOL-based scaffolds (Scheme 3). For instance, acyclic VANOL−silanediol **5c** provided a 24% enantiomeric excess of **4** in excellent yield (91%). The best stereocontrol in Scheme 3 was observed with cyclic VANOL−silanediol **5d**: 50% enantiomeric excess was realized for the functionalized chromanone **4** after 4 h at −78 °C. Unfortunately, the best enantioselective reaction conditions in Scheme 3 gave rise to just 35% yield of product.

Our efforts to find both high yielding and stereoselective reaction conditions for the functionalization of chromenones continued with the investigation of 3,3′-substituted BINOL-based silanediol **5e** (Scheme 6).[16] We hypothesized that

Scheme 6. Effect of 3,3′-Substituted BINOL-Based Silanediol on Alkylation Reactions of Various Chromenones

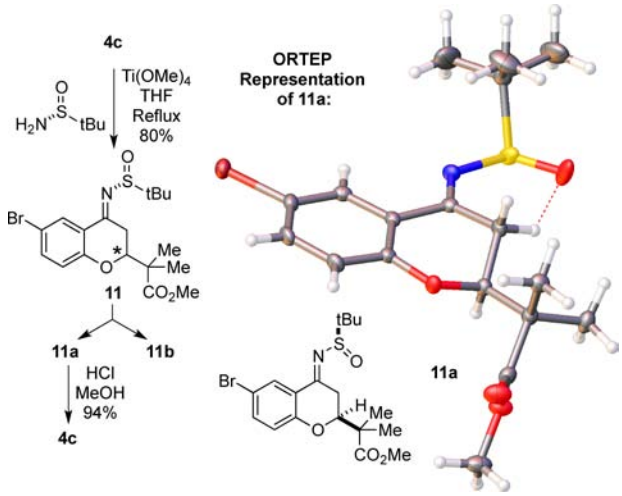


[a]**2** formed with 1.1 equiv of silyl triflate and 0.3 equiv of 2,6-di-*tert*-butyl-4-methylpyridine in 0.5 M toluene at 60 °C for 1 h. See the Supporting Information for details. [b]Yields based on unreacted starting material.

increased bulk surrounding the silanediol functionality would prevent undesired silylation events. Indeed, the unique chiral pocket offered by catalyst **5e** effects a high-yielding reaction of the silyl ketene acetal and chromenone with moderate levels of enantiocontrol (**4a**: 76% yield and 39% ee).[17,18] The structure of the chromenone was found to have a dramatic effect on the reaction outcome. In general, chromenones substituted with electron-withdrawing groups were higher yielding and more selective than chromenones possessing electron-donating groups. For example, chromenones substituted with chloro and bromo in the 6-position gave rise to **4b** and **4c** in high yield with 41% and 45% ee, respectively, with shorter reaction times. The highest enantiocontrols observed in this system were with 3,5-bistrifluoromethylphenyl and nitro in the 6-position: 56% and 49% enantiomeric excesses were observed in the formation of **4d** and **4e**. In comparison, the electron-donating methyl group in the 6-position gave rise to **4g** with 16% ee. Electron-withdrawing groups installed in the 7- and 8-positions also gave rise to high yields (i.e., **4h** and **4i**) and promising levels of enantiocontrol of the desired alkylated chromanones.

The absolute stereochemistry of the newly formed stereogenic center at the 2-position of chromanone products **4** was studied by X-ray crystallography (Scheme 7). Compound **4c**

Scheme 7. Evidence for the Absolute Configuration of 4c Including an ORTEP Representation of 11a[a]

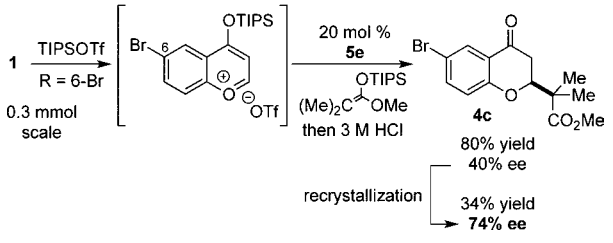


[a]The anisotropic displacement parameters are drawn at the 50% probability level.

was converted to iminochromanone **11** by condensation with (*R*)-2-methylpropane-2-sulfinamide.[19] The two diastereomers of **11**, **11a**, and **11b** were then separable by crystallization from dichloromethane and hexanes. The X-ray quality crystals obtained for **11a** allowed for its solid-state structure determination and revealed its absolute stereochemistry. The deprotection of **11a** gave rise to **4c**. HPLC analyses of **11a** and **4c** suggest that the absolute configuration of the major enantiomer of the newly formed stereocenter in **4** is *S*.

The promising levels of enantiocontrol observed in the silanediol-catalyzed reaction of **1** and **3** become synthetically useful when coupled with recrystallization (Scheme 8). For example, on scale up, **4c** can be isolated and further purified by

Scheme 8. Synthetically Useful Enantiomeric Excess of 4 Observed upon Recrystallization



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recrystallization from 2-propanol and hexanes. Upon recrystallization, the enantiomeric excess of **4c** is improved to 74% ee.

In summary, the first demonstration of the enantioselective intermolecular functionalization of 4-siloxybenzopyrylium ions is reported. BINOL− and VANOL−silanediols have been identified as anion-binding catalysts able to offer promising levels of stereocontrol in the addition of silyl ketene acetals to benzopyrylium ions. The data suggest that both the silanediol scaffold and chromenone structure can significantly influence the reaction outcome. The advancement of BINOL− and VANOL−silanediol analogues to achieve excellent levels of stereocontrol in the enantioselective alkylation of benzopyrylium ions is a topic of current interest in our laboratories, and we are looking forward to reporting our progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01783.

General methods and selected HPLC and NMR spectra (PDF)

Crystallographic data (PDF)

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Notes

The authors declare no competing financial interest.

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(16) See the Supporting Information for the preparation of **5e**.

(17) Optimization screens including solvent, temperature, silylating reagent, nucleophile, etc. provided no improvements in ee. In the absence of catalyst, 13% yield of the product is observed.

(18) **5e** provided 30% yield and 29% ee with *tert*-butyldimethylsilyl reagents with minimal silylation of the catalyst. **5e** and **5e-SiR$_3$** can be recovered via chromatography.

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