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Preparation and Catalytic Activity of BINOL-Derived Silanediols

Joshua M. Wieting,[a] Thomas J. Fisher,[a] Andrew G. Schafer,[a] Michael D. Visco,[a] Judith C. Gallucci,[a] and Anita E. Mattson*[a]

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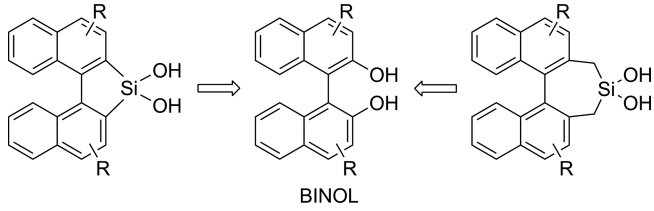
Enantiopure silanediols derived from BINOL are an innovative family of stereoselective hydrogen-bond donor (HBD) catalysts. Silanediols incorporated into a BINOL framework are attractive catalysts, as they are readily accessible and highly customizable. Structural modifications of the BINOL backbone affect the reactivity and selectivity of the silanediol catalysts in the additions of silyl ketene acetals to *N*-acyl isoquinolinium ions. The best results were obtained when the silanediol scaffold was substituted at the 4,4′- and 6,6′-positions. This report includes details regarding the properties of selected BINOL-based silanediol catalysts, including their acidities, binding constants, and X-ray crystal structures.

Introduction

The versatility of the silanediol functionality [Si–$(OH)_2$] continues to grow in organic synthesis.[1,2] Attractive characteristics inherent to silanediol functionalities include their impressive hydrogen-bonding abilities and their preference to exist as diols rather than silanones.[3] The condensation of silanediols into polysiloxanes, which are polymers with exceedingly useful properties, is possibly their most well-known function. Although they are less popular, stable silanediols are also accessible and possess their own useful applications. For example, chemists have taken advantage of silanediols to advance new therapeutic agents.[4] More recently, the hydrogen-bonding[5] abilities of stable silanediols have inspired investigations into their applications in molecular recognition,[6a] sensing,[6b,6c] and organocatalysis.[7]

Enantioselective hydrogen-bond donor (HBD) organocatalysis is emerging as a powerful tool in complex target construction.[8,9] (Thio)ureas,[10] squaramides,[11] and phosphoric acid derivatives[12] are several families of popular organocatalysts that probably operate through hydrogen-bonding interactions. We envisioned that chiral silanediols would be an innovative family of enantioselective HBD organocatalysts. Given their extraordinary hydrogen-bonding abilities, we reasoned that silanediols may benefit from improved activities and selectivities versus those of conventional HBD catalysts in appropriate cases and that this could ultimately enable the discovery of unique bond-forming reactions. Our early concerns regarding their preparation, stability, and catalytic potential were eased when we found that achiral silanediols could activate nitroalkenes for nucleophilic attack.[7b] The demonstration by Franz and coworkers that silanediols catalyze reactions of carbonyl and nitro compounds also encouraged our pursuit of enantioselective silanediol catalysis.[7a,7c]

The dearth of chiral, enantiopure silanediols is one hurdle that prevents their development as catalysts. Aware of this obstacle, we envisioned the development of readily accessible families of chiral silanediols for study as new organic catalysts. Silanediols derived from 1,1′-bi-2-naphthol (BINOL) backbones were one family of catalysts that attracted our attention (Scheme 1) owing to the well-documented advantages of BINOL: it is a readily available, inexpensive source of chirality and is highly customizable in terms of both steric hindrance and electronic nature to enable the achievement of optimal reactivity.[13] At the onset of our investigations, synthetic routes to BINOL-based silanediols were unknown. This account details our development and study of BINOL-based silanediols in enantioselective organocatalysis.



Scheme 1. BINOL-based silanediol catalyst designs.

Results and Discussion

BINOL-Based Silanediol Synthesis

The aforementioned ubiquity of axially chiral binaphthyl-based backbones in asymmetric catalysis combined with

[a] Department of Chemistry and Biochemistry, The Ohio State University,
88 West 18th Ave., Columbus, OH 43210, USA
E-mail: mattson@chemistry.ohio-state.edu
http://mattson.group.chemistry.ohio-state.edu/

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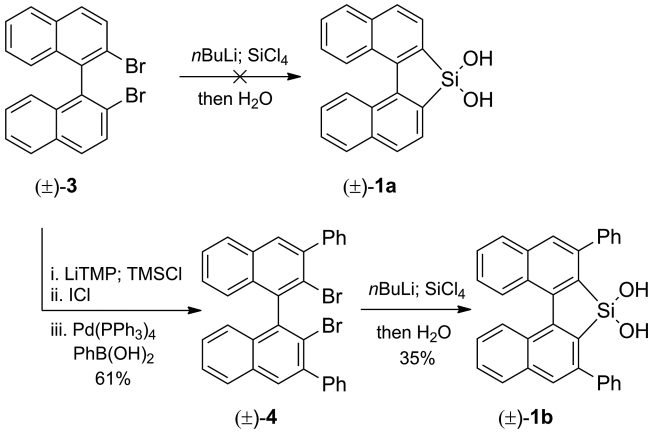
the reported ability of achiral dinaphthylsilanediols to recognize anions and catalyze reactions inspired us to initiate our studies with the synthesis of five-membered silacycles **1** (Scheme 2). The results of our early investigations were a disappointment: the silacyclization of (±)-**3** was attempted under various conditions but was unsuccessful. It was reasoned that the difficult preparation of (±)-**1a** might lie in its low stability, plausibly because of the location of the silicon atom in the highly strained five-membered ring. We hypothesized that silanediol (±)-**1b**, which has phenyl substituents at the 3,3′-positions to stabilize the silacycle, would be more synthetically accessible. Indeed, our efforts proved worthwhile, and silanediol (±)-**1b** was prepared in four steps from (±)-**3**. We found success with a silacyclization protocol that began with the lithiation of (±)-**4** with *n*BuLi, followed by reaction with silicon tetrachloride, and then aqueous workup. The structure of (±)-**1b** was confirmed by X-ray crystallographic analysis (Figure 1).[7b]



Scheme 2. Synthetic route to silanediol (±)-**1b**; LiTMP = lithium tetramethylpiperidide, TMSCl = trimethylsilyl chloride.

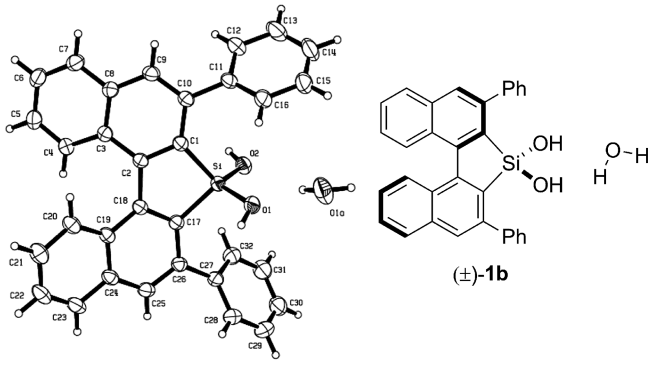
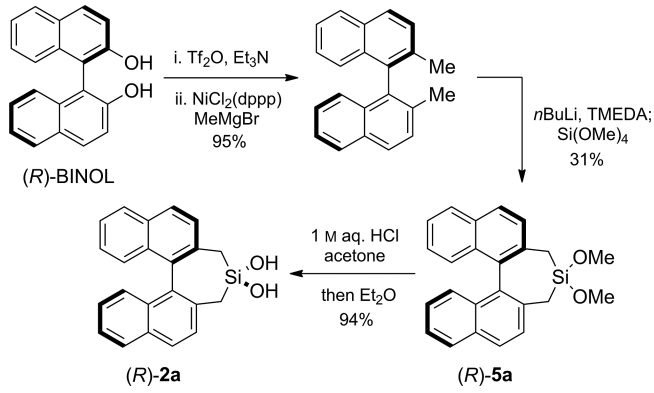


Figure 1. ORTEP representation of the H_2O complex of (±)-**1b**. The anisotropic displacement parameters are drawn at the 50% probability level.

Our excitement about synthesizing the first chiral, racemic BINOL-based silanediol catalysts quickly dwindled when we learned that the problems inherent to **1** would prevent its straightforward synthesis in enantiopure form. Specifically, **3** is prone to racemization.[14] Although the resolution of racemic **1** is one possible solution and a topic of ongoing study in our laboratory, we remained dedicated to accessing silanediol catalysts directly in enantiopure form.

Given the limitations of five-membered silacycles **1**, our efforts were strategically redirected to seven-membered silacyclic silanediols **2** derived from (*R*)-BINOL. One key advantage of this approach is that the retention of the chirality of the BINOL starting material over the course of the synthetic sequence enables direct access to enantiopure silanediols, and issues with enantioerosion due to unstable intermediates are avoided. From (*R*)-BINOL, a straightforward four-step protocol to synthesize the desired silanediol was established and is detailed in Scheme 3. After the treatment of (*R*)-BINOL with trifluoromethanesulfonic anhydride (Tf_2O), a Kumada cross coupling with MeMgBr led to (*R*)-2,2′-dimethyl-1,1′-binaphthalene in excellent yield.[15] The deprotonation of both benzylic methyl groups with *n*BuLi/tetramethylethylenediamine (*n*BuLi/TMEDA) followed by quenching with $Si(OMe)_4$ afforded dimethoxysilacycle (*R*)-**5a**. A simple hydrolysis with dilute HCl then generated silanediol (*R*)-**2a**. After neutralization with sodium hydrogen carbonate and dissolution and concentration from anhydrous Et_2O, the silanediol **2a** was obtained as a 2:1 complex with diethyl ether. Silanediol (*R*)-**2a**·Et_2O is an air- and moisture-stable white solid at room temperature and can be stored on the bench for several weeks. Attempts to remove the solvent of complexation led to the rapid decomposition of the silanediol. By this procedure, enantiopure (*R*)-**2a**·Et_2O can be produced on a multigram scale. The structure of the bis(trimethylsilyl)-protected derivative of (*R*)-**2a** was confirmed by X-ray crystallographic analysis (Figure 2).[7d]



Scheme 3. Synthesis of unsubstituted silanediol (*R*)-**2a**.

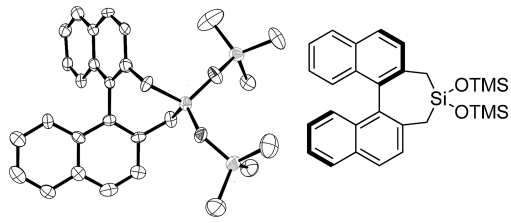


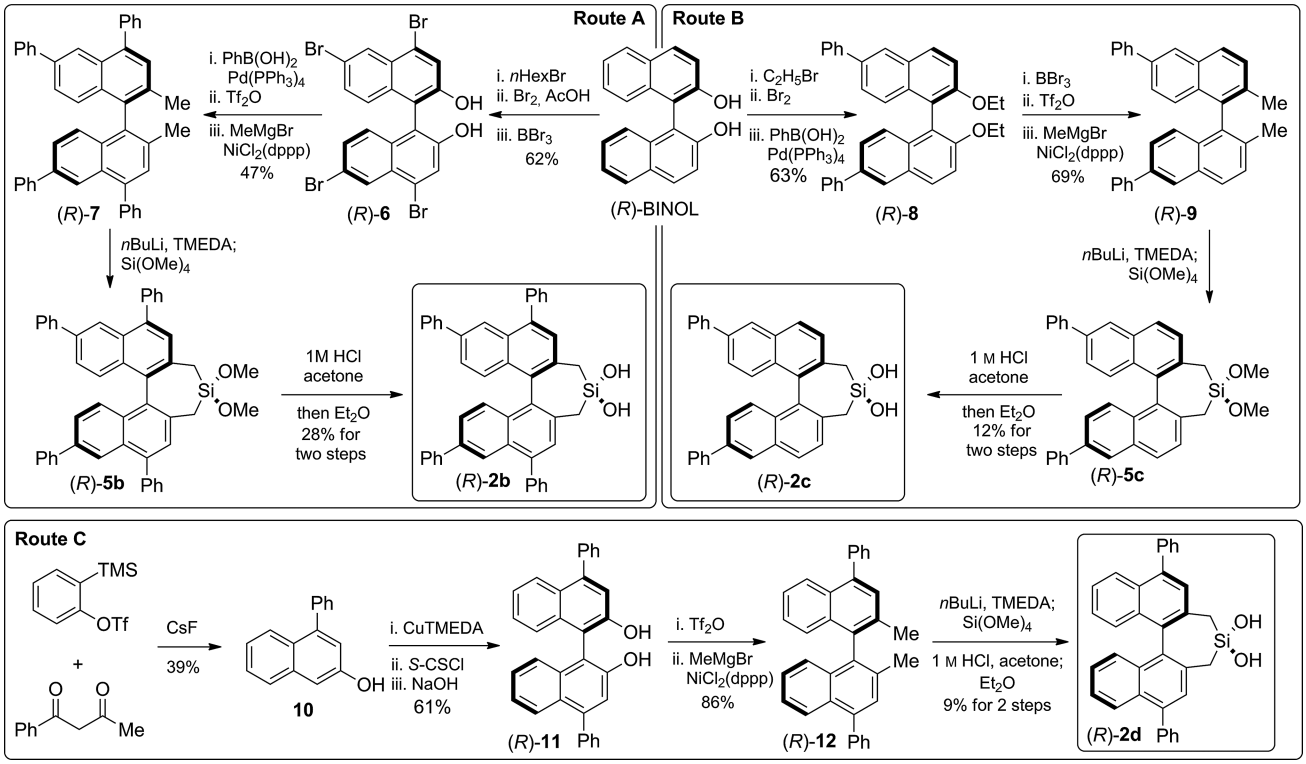
Figure 2. ORTEP representation of the bis-TMS derivative of (*R*)-**2a**. The anisotropic displacement parameters are drawn at the 50% probability level.

After the successful synthesis of the unsubstituted silacyclic silanediol (*R*)-**2a**, we next turned our attention to the addition of substituents at various positions on the binaphthyl backbone. The rationale behind this research direction stemmed from the notion that a highly customizable catalyst scaffold coupled with an insight into how structure affects silanediol activity would enable the rapid and rational design of the ideal silanediol catalyst for a given reaction. We began by synthesizing BINOL-based silanediols substituted with phenyl groups at either the 4,4′- or 6,6′-positions or both.

The general route to our 4,4′,6,6′-tetraphenyl-substituted silanediol catalyst (*R*)-**2b** is outlined in Scheme 4 (Route A). On the basis of established protocols,[16] bis-*O*-hexylated (*R*)-BINOL was subjected to a fourfold bromination and then dealkylated with BBr_3 to provide (*R*)-**6**. A Suzuki–Miyaura cross coupling with $PhB(OH)_2$ installed the desired phenyl substituents. The triflation of the alcohol moieties at the 2,2′-positions enabled a Kumada cross coupling to access (*R*)-**7**, the precursor to silacyclization. The deprotonation of the 2,2′-methyl groups was effected with *n*BuLi and TMEDA, and this was followed with the addition of excess $Si(OMe)_4$ to yield the dimethoxysilacycle (*R*)-**5b**. The straightforward hydrolysis of (*R*)-**5b** with aqueous HCl followed by treatment with diethyl either and neutralization then afforded silanediol (*R*)-**2b** as a 3:1 complex with Et_2O. Our early attempts to confirm the structure of (*R*)-**2b** in the solid state led to the formation of an interesting siloxane trimer (Figure 3).

The synthesis of the 6,6′-diphenyl-substituted silanediol (*R*)-**2c** proceeded in a similar fashion as that for the tetraphenyl-substituted variant (Scheme 4, Route B).[17,16b] The notable difference is the regiocontrolled twofold bromination of the bis-*O*-ethylated (*R*)-BINOL at the 6,6′-positions. A subsequent Suzuki–Miyaura cross coupling gave rise to intermediate (*R*)-**8**. The deprotection and triflation of the 2,2′-hydroxy groups allowed their conversion to the requisite methyl groups by a nickel-catalyzed cross coupling. The silacyclization of (*R*)-**9** occurred under our standard reaction conditions to afford dimethoxysilacycle (*R*)-**5c**. The hydrolysis of (*R*)-**5c** was readily achieved under the standard conditions, and (*R*)-**2c** was isolated as a 2:1 complex with Et_2O.

After our original plan to synthesize 4,4′-diphenyl-substituted silanediol (*R*)-**2d** in a similar fashion to (*R*)-**2a** and (*R*)-**2b** failed, we successfully synthesized (*R*)-**2d** through the series of steps depicted in Scheme 4, Route C. By a known protocol,[18] the reaction of 2-(trimethylsilyl)phenyl triflate with benzoylacetone in the presence of CsF afforded 4-phenyl-2-naphthol (**10**) in 39% yield. The oxidative coupling of **10** with CuTMEDA was followed by resolution with *S*-(+)-camphorsulfonyl chloride (CSCl) to give enantiopure BINOL (*R*)-**11** after removal of the chiral auxiliary.[19] In line with our previous approaches, the triflation of (*R*)-**11** followed by Kumada cross coupling with MeMgBr provided (*R*)-**12**. After lithiation, silacycle formation and hydrolysis readily afforded the 4,4′-diphenyl-substituted silanediol (*R*)-**2d** as a 1:1 complex with diethyl ether.



Scheme 4. Synthesis of the 4,4′- and 6,6′-substituted silanediols (*R*)-**2b**, (*R*)-**2c**, and (*R*)-**2d**.

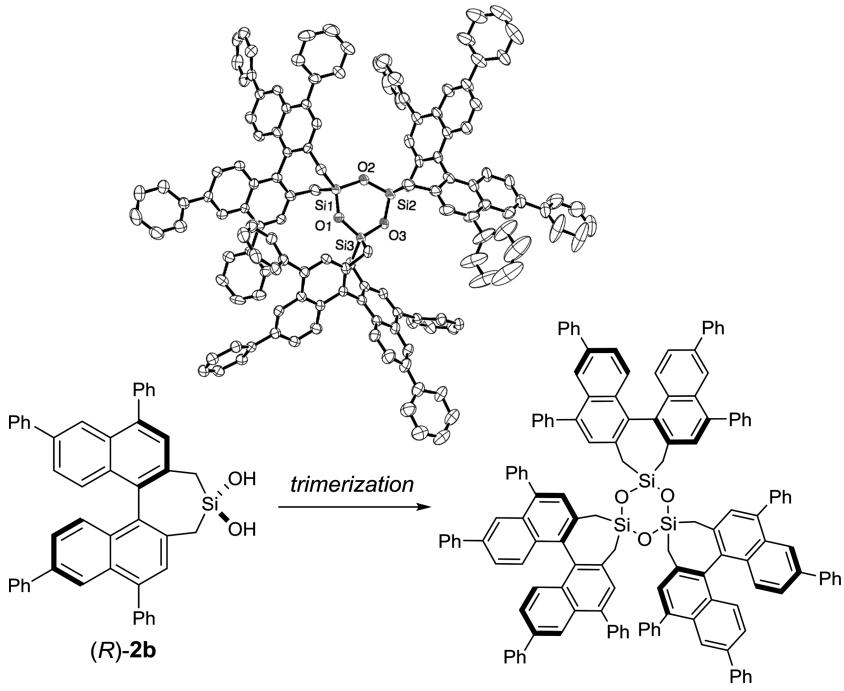


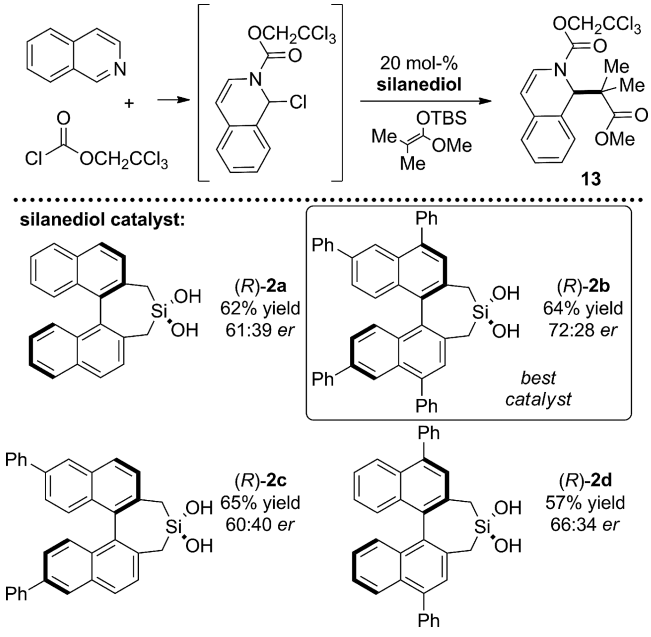
Figure 3. ORTEP representation of the trimer derived from (*R*)-**2b**. The anisotropic displacement parameters are drawn at the 50% probability level.

Catalysis with BINOL-Derived Silanediols

With a small family of BINOL-based silanediols in hand, we set out to probe the effect of the catalyst structure on the activity and stereoselectivity in the addition of silyl ketene acetals to *N*-acyl isoquinolinium ions (Table 1).[20] This *N*-acyl Mannich reaction was selected as the platform for our structure–activity relationship studies, as we have recently discovered that silanediols effect this transformation, plausibly by anion-binding catalysis.[7d] In general, enantioselective anion-binding catalysis is a relatively new, promising mode of action for HBD catalysts and, until our recent report, only ureas and related thioureas had been shown to act as catalysts in this fashion.[8f] The unsubstituted silanediol (*R*)-**2a** gave **13** in 62% yield in an enantiomeric ratio (*er*) of 61:39. Silanediol (*R*)-**2c** with phenyl rings solely at the 6,6′-positions afforded no improvement over this result and gave **13** in 65% yield and 20% enantiomeric excess. On the other hand, the addition of phenyl rings to the 4,4′-positions provided a significant increase in enantiomeric enrichment. Specifically, catalyst (*R*)-**2d** gave rise to 57% of **13** with a 10% improvement in enantiomeric excess over catalyst (*R*)-**2a**. Pleasingly, silanediol (*R*)-**2b** with phenyl rings at both the 4,4′- and 6,6′-positions afforded **13** in good yield with the best enantiomeric ratio (72:28). We were impressed that the addition of four phenyl rings to the 4,4′,6,6′-positions of the silanediol scaffold more than doubled the enantiomeric excess compared with that for substitution only at the 6,6′-position, as in catalyst (*R*)-**2c**.

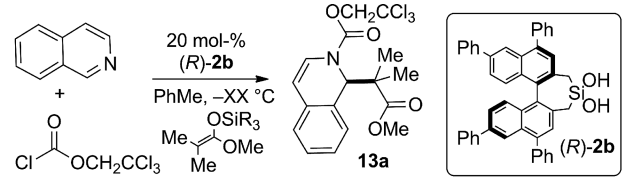
With tetraphenyl-substituted silanediol (*R*)-**2b** identified as the optimal catalyst from our small series, we next investigated the sensitivity of the reaction to other factors, including the effect of the silyl group, concentration, and temperature (Table 2). In our prior work with unsubstituted catalyst (*R*)-**2a**, we had observed that more bulky silyl ketene acetals led to improved enantiomeric excesses.[7d] Not surprisingly, that was also the case in this study. The trimethylsilyl ketene acetal prepared from methyl isobutyrate performed quite poorly, whereas triisopropylsilyl ketene acetal afforded **13a** in high yield and good enantiomeric excess (Table 2, Entries 1 and 3). A reaction concentration

Table 1. Influence of the silanediol scaffold on yield and enantioselectivity.



of 0.02 M in toluene proved to be optimal, and **13a** was isolated in 69% yield and 83:17 *er* (Table 2, Entry 5). Diluting the reaction from 0.02 to 0.005 M afforded **13a** in lower yield and slightly reduced enantiomeric excess (Table 2, Entry 4).

Table 2. Optimization of *N*-acyl Mannich reaction.[a]

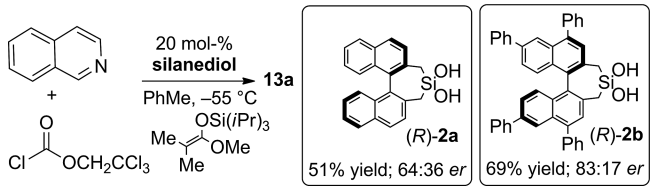


Entry	SiR_3	Conc. [M]	Temp. [°C]	Yield [%]	*er*	
1	$SiMe_3$	0.025	–55	68	55:45	*silyl group*
2	$SiMe_2(t\text{Bu})$	0.025	–55	65	68:32	
3	$Si(i\text{Pr})_3$	0.025	–55	70	71:29	
4	$Si(i\text{Pr})_3$	0.005	–55	40	81:19	*concentration*
5	**$Si(i\text{Pr})_3$**	**0.02**	**–55**	**69**	**83:17**	
6	$Si(i\text{Pr})_3$	0.02	–45	55	78:22	*temperature*
7	$Si(i\text{Pr})_3$	0.02	–78	56	70:30	
8[b]	$Si(i\text{Pr})_3$	0.005	–78	39	89:11	

[a] See Supporting Information for detailed experimental procedures. [b] 50 mol-% of (*R*)-**2b** added.

Finally, a reaction temperature of –55 °C was identified as optimal for both yield and enantioselectivity (Table 2, Entries 5–8). At –45 °C, **13a** was isolated in 55% yield with an enantiomeric ratio of 78:22 under the influence of 20 mol-% of **2b** (Table 2, Entry 6). At a catalyst loading of 50 mol-%, **13a** was isolated in nearly 80%*ee* at –78 °C in 0.005 M toluene, although the yield was only 39% after 120 h (Table 2, Entry 8).

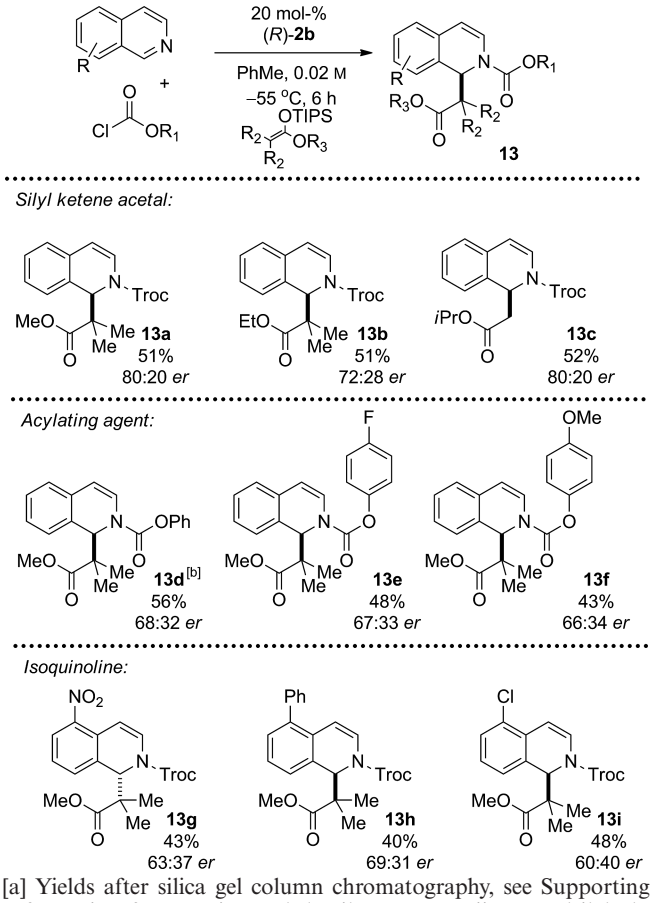
With a set of optimal conditions identified, the effect of substituents at the 4,4′,6,6′-positions of the BINOL scaffold was re-evaluated (Scheme 5). We were pleased to find that the more-substituted catalyst (*R*)-**2b** was significantly advantageous over the unsubstituted catalyst (*R*)-**2a** in terms of both yield and enantioselectivity.



Scheme 5. Comparison of silanediol catalysts (*R*)-**2a** to (*R*)-**2b** under optimized reaction conditions.

A short study of the limitations of the reaction with respect to the silyl ketene acetal, acylating agent, and isoquinoline was conducted (Table 3). A variety of silyl ketene acetals operated well in the reaction. For instance, the acetal from ethyl isobutyrate gave rise to **13b** in 51% yield and 72:28 *er*, whereas the acetal from isopropyl acetate gave rise to **13c** in high yield with excellent levels of enantiocontrol (52% yield, 80:20 *er*). Although the highest enantiomeric enrichment was observed with the 2,2,2-trichloroethoxycarbonyl chloride (TROC) acylating agent, phenyl chloroformate also provided an acceptable yield and enantiomeric enrichment of **13d** (62% yield, 38%*ee*). The addition of an electron-withdrawing fluoro substituent to the phenyl ring afforded **13e** in slightly lower enantiomeric excess. The reaction was least tolerant of substitution patterns on the isoquinoline. Only substitution at the 5-position provided acceptable results. 5-Nitroisoquinoline, 5-phenylisoquinoline, and 5-chloroisoquinoline afforded **13g**–**13i** in modest yields and enantiomeric excesses.

Table 3. Substrate scope of *N*-acyl Mannich reaction.[a]



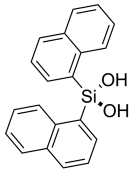
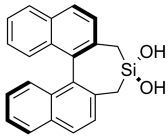
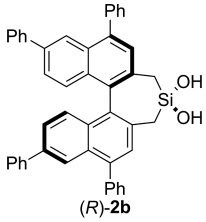
[a] Yields after silica gel column chromatography, see Supporting Information for experimental details; TIPS = triisopropylsilyl. [b] –35 °C, 14 h.

Silanediol Properties

To gain more insight into the features that affect the reactivity of our silanediol catalysts, we determined their acidity, an important property in HBD organocatalyst activity and selectivity.[21] Owing to our recent successful determination of the pK_a values of several urea-based hydrogen-bond donors by the Bordwell method,[22] we decided to use the same approach to find the pK_a values of achiral dinaphthylsilanediol **14** and chiral silanediols (*R*)-**2a** and (*R*)-**2b** (Table 4). The pK_a values of **14** and our BINOL-based silanediols are all ca. 19 in dimethyl sulfoxide (DMSO). It

may be interesting to note that this is in the same pK_a range as Jacobsen's chiral thiourea catalyst, which is able to induce similar enantioselective *N*-acyl Mannich reactions.[20,22b] It is also worthwhile to point out that significant differences in the enantioselectivity of the *N*-acyl Mannich reaction were observed between (*R*)-**2a** and (*R*)-**2b**, despite their similar pK_a values; this suggests that factors outside of acidity are influential in the ability of silanediols to impart stereocontrol over *N*-acyl Mannich reactions.

Table 4. pK_a values and chloride binding constants for selected silanediols.

	 **14**[b]	 (*R*)-**2a**	 (*R*)-**2b**
pK_a (DMSO)	19.1 ± 0.3	19.3 ± 0.1	18.7 ± 0.3
Binding constant[a] (M^{-1})	1.44 ± 0.11 x 10^2	2.19 ± 0.03 x 10^2	3.10 ± 0.10 x 10^2

[a] With Cl^- ion, see Supporting Information for details. [b] See ref.[6a] for binding constant data.

Curious to learn more about the factors that affect silanediol catalyst stereoselectivity, we collected the binding constants of (*R*)-**2a** and (*R*)-**2b**, our optimal catalyst, with chloride ions. Kondo[6a] has previously reported the binding constant between chloride ions and achiral silanediol **14** to be $(1.44 \pm 0.11) \times 10^2$ M^{-1}. The data to extrapolate the binding constants for (*R*)-**2a** and (*R*)-**2b** were measured by the same approach as that used by Kondo and co-workers: a ^{1}H NMR titration of the silanediols with tetrabutylammonium chloride was conducted, and the changes in the chemical shift of the O–H protons were measured. From this data, the binding constants of (*R*)-**2a** and (*R*)-**2b** were determined to be $(2.19 \pm 0.03) \times 10^2$ M^{-1} and $(3.10 \pm 0.10) \times 10^2$ M^{-1}, respectively. The ^{1}H NMR titration of our most enantioselective silanediol (*R*)-**2b** with tetrabutylammonium chloride is shown in Figure 4. The silanediol–chloride binding stoichiometry was determined to be 1:1 by Job plot analysis (Figure 5).

The solid-state data of silanediols bound with both anions alone[6a] and with isoquinolinium ion pairs also support their anion-binding mode of action and offers insight into the potential noncovalent interactions that support the transition state of the major reaction pathway. We were delighted to obtain a single crystal of an ion pair composed of **14** and the HCl salt of isoquinoline (Figure 6).[7d]

All of the evidence taken together strongly suggests that the reaction pathway involves an anion-binding catalysis mode (Scheme 6).

The proposed reaction pathway begins with the in situ formation of the acyl isoquinoline (**I**). The silanediol catalyst is then able to encourage the formation of the isoquinolinium ion-pair **II** through hydrogen bonding to the chloride ion. The formation of the carbon–carbon bond occurs upon reaction of **II** with the silyl ketene acetal to yield ion-

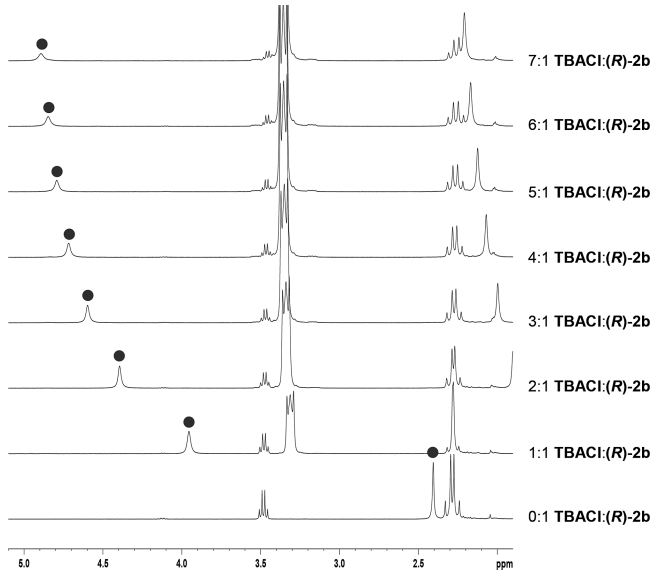


Figure 4. ^{1}H NMR binding titration of silanediol (*R*)-**2b** and nBu$_4$NCl in $CDCl_3$.

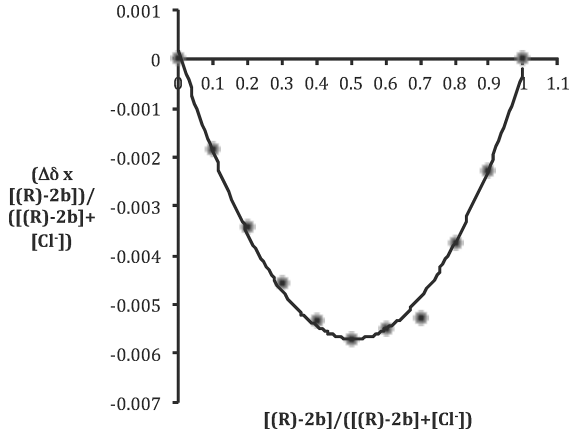


Figure 5. Job Plot analysis of (*R*)-**2b** and nBu$_4$NCl in $CDCl_3$.

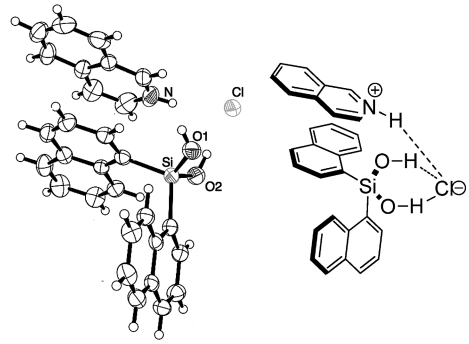
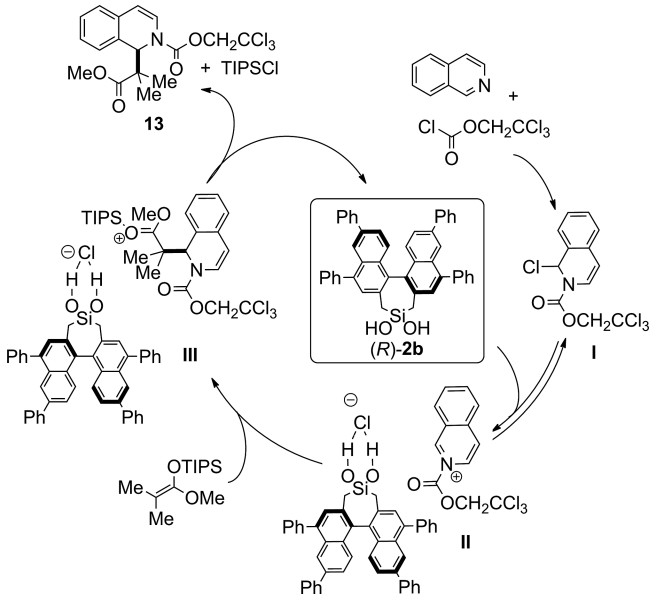


Figure 6. ORTEP representation of the ion pair between **14** and the HCl salt of isoquinoline. The anisotropic displacement parameters are drawn at the 50% probability level.[23]



Scheme 6. Proposed reaction pathway for the silanediol-catalyzed *N*-acyl Mannich reaction of isoquinolines.

pair **III**. The desilylation of the oxocarbenium ion with a chloride ion then generates the product and frees the silanediol to initiate another reaction.

Conclusions

We have developed BINOL-based silanediols as a new class of anion-binding organocatalysts to effect enantioselective *N*-acyl Mannich reactions. These modifiable silanediols are readily prepared in enantiopure form and are bench-stable indefinitely. Our studies further suggest that a network of noncovalent interactions such as π–π, π–cation, hydrogen-bonding, and electrostatic interactions contribute to the stabilization of the transition state that leads to the major enantiomer. As we continue to discover new silanediol catalyst designs and reactivity, our progress will be reported.

Experimental Section

2,2′-Bis(hexyloxy)-1,1′-binaphthalene:[16a] To a flame-dried 1000 mL round-bottomed flask was added (*R*)-BINOL (30.0 g, 105 mmol, 1 equiv.), *n*-bromohexane (73.3 mL, 524 mmol, 5 equiv.), MeCN (500 mL), and K_2CO_3 (72.3 g, 524 mmol, 5 equiv.). The flask was equipped with a water-cooled condenser, and the reaction mixture was heated to reflux overnight. The reaction mixture was cooled to 23 °C, diluted with H_2O, and extracted with hexanes (three times). The combined organic layers were dried with Na_2SO_4, concentrated in vacuo, and distilled to remove excess *n*-bromohexane (120 °C, ca. 300 mTorr) to provide the title compound as colorless viscous oil (46.7 g, 103 mmol, 98%; contains ca. 5% residual *n*-bromohexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, J = 9.0 Hz, 2 H), 7.89 (d, J = 8.1 Hz, 2 H), 7.45 (d, J = 9.0 Hz, 2 H), 7.34 (ddd, J = 1.9, 6.1, 8.0 Hz, 2 H), 7.20–7.23 (4 H), 3.97 (4 H), 1.40–1.44 (4 H), 0.95–1.10 (12 H), 0.79 (t, J = 7.1 Hz, 6 H) ppm. All other spectral data matched those previously reported.[16a]

4,4′,6,6′-Tetrabromo-2,2′-bis(hexyloxy)-1,1′-binaphthalene:[16a] To a flamed-dried 500 mL round-bottomed flask was added 2,2′-bis-(hexyloxy)-1,1′-binaphthalene (16.9 g, 37.1 mmol, equiv.) followed by AcOH (300 mL). Bromine (20.1 mL, 390.5 mmol, 10.5 equiv.) was added slowly to the solution at 23 °C, and the reaction mixture was stirred for 4.5 h at 23 °C. The reaction mixture was cooled to 0 °C, quenched with saturated $NaHSO_3$, and extracted with CH_2Cl_2 (three times). The combined organic layers were washed with $NaHCO_3$ and then brine, dried with Na_2SO_4, and concentrated in vacuo. The compound was purified by silica gel flash column chromatography (dry load, 100% hexanes) to provide the title compound as a light yellow oil (18.2 g, 23.6 mmol, 64%). R_f = 0.65 (10:90 ethyl acetate/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (d, J = 1.9 Hz, 2 H), 7.71 (s, 2 H), 7.31 (dd, J = 2.0, 9.1 Hz, 2 H), 6.97 (d, J = 9.0 Hz, 2 H), 3.92 (4 H), 1.37–1.44 (4 H), 0.88–1.12 (12 H), 0.76 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.5, 133.2, 130.7, 129.5, 128.9, 127.4, 122.5, 120.5, 119.3, 69.9, 31.3, 29.2, 25.4, 22.6, 14.0 ppm. All other spectral data matched those previously reported.[16a]

4,4′,6,6′-Tetrabromo-[1,1′-binaphthalene]-2,2′-diol [(*R*)-6]: By modification of the procedure reported by Lin:[16c] To a flame-dried 250 mL round-bottomed flask was added 4,4′,6,6′-tetrabromo-2,2′-bis(hexyloxy)-1,1′-binaphthalene (20.9 g, 27.1 mmol, 1 equiv.) followed by CH_2Cl_2 (60 mL). The solution was cooled to –78 °C, and BBr_3 (2.26 mL, 23.8 mmol, 6 equiv.) was added dropwise. The reaction mixture was warmed to 23 °C and stirred overnight. The reaction was cooled to 0 °C, quenched with water (ca. 20 mL), and extracted with CH_2Cl_2 (three times). The organic layers were combined, washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The resulting compound was purified through a silica plug (CH_2Cl_2) to afford (*R*)-**6** as a white solid (16.1 g, 26.7 mmol, 99%). R_f = 0.56 (30:70 ethyl acetate/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, J = 1.9 Hz, 2 H), 7.75 (s, 2 H), 7.43 (dd, J = 1.9, 8.9 Hz, 2 H), 6.96 (d, J = 8.9 Hz, 2 H), 4.95 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.7, 132.5, 132.1, 130.3, 129.6, 126.3, 125.1, 123.2, 120.1, 110.4 ppm. M.p. 293–294 °C. IR (NaCl): $\tilde{\nu}$ = 3500, 3080, 2916, 1580, 1493, 1373, 1176, 937, 733 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{10}Br_4O_2Na$ [M + Na]$^+$ 620.7307; found 620.7300. $[\alpha]_D^{23}$ = –49.8 (c = 1.00, $CHCl_3$).

4,4′,6,6′-Tetraphenyl-[1,1′-binaphthalene]-2,2′-diol: To a 150 mL flame-dried round-bottomed flask was added (*R*)-**6** (6.66 g, 11.1 mmol, 1 equiv.), phenylboronic acid (5.94 g, 48.7 mmol, 4.4 equiv.), K_2CO_3 (9.17 g, 66.4 mmol, 6 equiv.), tetrahydrofuran (THF, 35 mL), $Pd(PPh_3)_4$ (1.92 g, 1.66 mmol, 0.15 equiv.), and H_2O (33 mL). The flask was equipped with a water-cooled condenser, and the reaction mixture was heated to reflux overnight. The reaction mixture was cooled to 23 °C and extracted with CH_2Cl_2 (three times). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The resulting residue was first subjected to silica gel flash column chromatography (100% CH_2Cl_2) to remove the black impurity followed by additional purification by silica gel flash column chromatography (30:70 CH_2Cl_2/hexanes to 100% CH_2Cl_2) to provide the title compound as an off-white solid (4.03 g, 6.82 mmol, 62%). R_f = 0.46 (30:70 ethyl acetate/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (br d, J = 8.2 Hz, 2 H), 7.49–7.69 (16 H), 7.39–7.47 (8 H), 7.30–7.34 (2 H), 5.20 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.5, 144.4, 141.2, 140.0, 137.1, 133.3, 130.1, 129.0, 128.7, 128.4, 128.0, 127.4, 127.33, 127.27, 125.4,

125.0, 119.3, 110.5 ppm. $[\alpha]_D^{23}$ = –49.8 (c = 0.26, $CHCl_3$) All other spectral data matched those previously reported.[16a]

4,4′,6,6′-Tetraphenyl-[1,1′-binaphthalene]-2,2′-diyl Bis(trifluoromethanesulfonate):[16b] To a 150 mL flame-dried round-bottomed flask was added 4,4′,6,6′-tetraphenyl-[1,1′-binaphthalene]-2,2′-diol (5.13 g, 8.68 mmol, 1 equiv.) followed by CH_2Cl_2 (50 mL). The solution was cooled to –78 °C, Et_3N (3.60 mL, 26.04 mmol, 3 equiv.) was added, and then Tf_2O (4.37 mL, 26.04 mmol, 3 equiv.) was added dropwise. The reaction mixture was warmed to 23 °C and stirred overnight. The reaction mixture was cooled to 0 °C, quenched with 2 M HCl (ca. 10 mL), and extracted with CH_2Cl_2 (three times). The combined organic layers were washed with $NaHCO_3$ and brine, dried with Na_2SO_4, and concentrated in vacuo. The resulting compound was run through a silica gel plug (CH_2Cl_2 as eluent) and then purified by silica gel flash column chromatography (100% hexanes to 5:95 Et_2O/hexanes) to provide the title compound as a white solid (6.21 g, 7.26 mmol, 84%). R_f = 0.35 (10:90 ethyl acetate/hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.25 (br. d, J = 1.6 Hz, 2 H), 7.54–7.74 (20 H), 7.41–7.45 (4 H), 7.34–7.38 (2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.2, 145.0, 140.4, 140.2, 138.9, 133.1, 131.4, 130.2, 129.1, 128.9, 128.6, 128.1, 128.0, 127.7, 127.6, 124.6, 122.7, 120.7, 118.4 (q, $J_{C,F}$ = 320 Hz) ppm. M.p. 205–207 °C. IR (NaCl): $\tilde{\nu}$ = 3058, 3028, 1560, 1486, 1419, 1210, 1136, 942 cm^{-1}. HRMS (ESI): calcd. for $C_{46}H_{28}F_6O_6S_2Na$ $[M + Na]^+$ 877.1124; found 877.1112. $[\alpha]_D^{23}$ = –67.3 (c = 1.00, $CHCl_3$).

2,2′-Dimethyl-4,4′,6,6′-tetraphenyl-1,1′-binaphthalene [(*R*)-7]:[16b] To a 150 mL flame-dried round-bottomed flask was added 4,4′,6,6′-tetraphenyl-[1,1′-binaphthalene]-2,2′-diyl bis(trifluoromethanesulfonate) (6.21 g, 7.26 mmol, 1 equiv.), Et_2O (65 mL), and $Ni(dppp)Cl_2$ [dppp = 1,3-bis(diphenylphosphino)propane; 197 mg, 0.363 mmol, 0.05 equiv.]. The mixture was cooled to 0 °C, and 2.44 M MeMgBr (13.7 mL, 33.4 mmol, 4.6 equiv.) was added dropwise. The flask was equipped with a water-cooled condenser, and the reaction mixture was heated to reflux overnight. The reaction mixture was cooled to 23 °C and slowly poured in a chilled flask of 2 M HCl (ca. 25 mL). The mixture was filtered through Celite and extracted with Et_2O (three times). The combined organic layers were washed with $NaHCO_3$ and brine, dried with Na_2SO_4, and concentrated in vacuo. The resulting compound was purified by silica gel flash column chromatography (5:95 Et_2O/hexanes to 10:90 Et_2O/hexanes) to afford (*R*)-**7** as a white solid (3.88 g, 6.61 mmol, 91%). R_f = 0.43 (10:90 ethyl acetate/hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.20 (br d, J = 1.7 Hz, 2 H), 7.68–7.71 (4 H), 7.46–7.59 (14 H), 7.28–7.42 (8 H), 2.18 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.5, 141.0, 140.2, 137.8, 134.8, 134.3, 132.6, 130.8, 130.6, 130.4, 128.9, 128.6, 127.51, 127.47, 127.3, 126.9, 125.8, 124.3, 20.4 ppm. M.p. 198–201 °C. IR (NaCl): $\tilde{\nu}$ = 3056, 3029, 2917, 1598, 1471, 1449, 1382 cm^{-1}. HRMS (ESI): calcd. for $C_{46}H_{34}Na$ $[M + Na]^+$ 609.2553; found 609.2538. $[\alpha]_D^{23}$ = –89.0 (c = 0.200, $CHCl_3$).

1,7,9,14-Tetraphenyl-3,5-dihydro-4*H*-dinaphtho[2,1-c:1′,2′-*e*]silepine-4,4-diol [(*R*)-2b]: By modification of a procedure reported by Mattson:[7d] To a 250 mL flame-dried round-bottomed flask was added (*R*)-**7** (4.51 g, 7.69 mmol, 1 equiv.) followed by Et_2O (70 mL). The solution was cooled to 0 °C, 1.6 M *n*BuLi (14.4 mL, 23.07 mmol, 3 equiv.) was added dropwise, and then TMEDA (3.44 mL, 23.07 mmol, 3 equiv.) was added dropwise. The reaction mixture was warmed to 23 °C and stirred overnight. The reaction mixture was then cooled to 0 °C, and $Si(OMe)_4$ (4.55 mL, 30.8 mmol, 4 equiv.) was added dropwise followed by Et_2O (35 mL). The reaction mixture was warmed to 23 °C and stirred for 24 h. The mixture was passed through a pad of silica gel with Et_2O as the eluent. After concentration in vacuo, the compound was partially purified by silica gel flash column chromatography (100% hexanes to 80:20 hexanes/Et_2O) to afford slightly impure (*R*)-**5b** (2.88 g, see spectroscopic data), which was used in the next hydrolysis step. To a flame-dried 1000 mL flame-dried round-bottomed flask was added crude (*R*)-**5b** (2.88 g) and acetone (300 mL). The solution was cooled to 0 °C, and 1 M HCl (75 mL) was added dropwise. The mixture was stirred at 0 °C for 6 h. The reaction was diluted with Et_2O (ca. 150 mL), neutralized to pH 7 with $NaHCO_3$, and extracted with Et_2O (three times). The organic layers were combined, dried with Na_2SO_4, and concentrated in vacuo. Evaporation under high vacuum was necessary to remove a volatile white liquid before purification. The resulting compound was purified by silica gel flash column chromatography (40:60 Et_2O/hexanes to 80:20 Et_2O/hexanes) to afford a white solid (*R*)-**2b** (1.46 g, 2.17 mmol, 28% over two steps) as a 3:1 Et_2O complex. R_f = 0.42 (50:50 ethyl acetate/hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.22 (br d, J = 1.7 Hz, 2 H), 7.68–7.70 (4 H), 7.46–7.58 (14 H), 7.38–7.42 (6 H), 7.29–7.33 (2 H), 2.43 (s, 2 H), 2.31 (d, J = 13.7 Hz, 2 H), 2.25 (d, 13.7, J = 13.7 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.2, 140.9, 140.6, 137.3, 134.3, 132.4, 132.2, 130.4, 130.3, 129.5, 128.8, 128.4, 127.6, 127.4, 127.3, 127.1, 125.6, 124.1, 23.5 ppm. M.p. 344–346 °C. IR (KBr): $\tilde{\nu}$ = 3416, 3051, 3021, 2954, 2917, 1628, 1590, 1561, 1486, 1158, 1143, 830, 756, 696 cm^{-1}. HRMS (ESI): calcd. for $C_{46}H_{34}O_2SiNa$ $[M + Na]^+$ 669.2220; found 669.2207. $[\alpha]_D^{23}$ = –201 (c = 1.00, $CHCl_3$).

General Procedure for the *N*-Acyl Mannich Reaction: An 8 mL vial equipped with a magnetic stir bar and screw cap was sealed with a virgin septum, flame-dried under vacuum, purged with N_2, and then placed under a positive pressure of argon. A 0.10 M stock solution of the appropriate freshly purified isoquinoline was prepared in toluene, which had been passed through a bed of active alumina and freshly distilled from CaH_2. The isoquinoline solution (1.0 mL, 0.10 mmol, 1.0 equiv.) was transferred to the reaction vial and placed in an ice bath. A 0.11 M stock solution of the appropriate chloroformate was prepared in toluene. The chloroformate solution (1.0 mL, 0.11 mmol, 1.1 equiv.) was added dropwise to the cold isoquinoline solution, the ice bath was removed, and the reaction mixture was warmed to r.t. over 30 min. The reaction mixture was diluted with toluene (1.50 mL). A 0.020 M solution of catalyst (*R*)-**2b** was prepared in toluene. The reaction mixture was cooled in a dry ice acetone bath, and the (*R*)-**2b** solution (1.0 mL, 0.020 mmol, 0.20 equiv.) was added to the reaction mixture, which was then stirred for 5 min. A 0.30 M solution of the appropriate silyl ketene acetal in toluene (0.50 mL, 0.15 mmol, 1.5 equiv.) was added dropwise to the reaction mixture, which was immediately transferred to a –55 °C acetone bath equipped with immersion cooling coil or a –35 °C freezer. The reaction was stirred for either 6 or 14 h, after which it was quenched by the addition of NaOMe (0.20 mL of 0.5 M in MeOH). The reaction mixture was filtered through a silica gel plug with ethyl acetate as the eluent, and the solvent was removed in vacuo. The product was isolated by silica gel flash column chromatography; the conditions are detailed in the Supporting Information. Further purification through an activity II alumina plug with minimal dichloromethane (ca. 2 mL) as the eluent yielded the pure product. The enantiomeric ratios were determined by HPLC analysis under the conditions detailed in the Supporting Information.

Supporting Information (see footnote on the first page of this article): Full experimental details, characterization data, HPLC traces, ^1H and ^{13}C NMR spectra.

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[23] CCDC-947138, -947139, -1023331, and -1023332 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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