

Planar-Chiral Bis-silanols and Diols as H-Bonding Asymmetric Organocatalysts

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The successful development of planar-chiral bis-silanols 3a-d and their application as asymmetric organocatalysts in hetero-Diels–Alder (HDA) reactions is described. All precursors were easily prepared by addition of commerically available silyl electrophiles to a dilithiated [2.2]paracyclophane derivative followed by silane oxidations. The analogous bis-carbinols **7a–c** have been prepared by addition of suitable Grignard reagents to bis-methoxycarbonyl derivative **6**. Both racemic as well as enantiopure planar-chiral bis-silanols and

Introduction

Hydrogen bonding plays a pivotal role in the field of catalysis,^[1] and it is the dominant activation mode in biocatalysis.^[2] The first asymmetric organocatalytic hetero-Diels– Alder (HDA) reaction based on activation by hydrogen bonding was published by Rawal in 2003.^[3] In the presence of the simple chiral diol TADDOL reactions between aldehydes and 1-amino-3-siloxydienes occurred smoothly providing the corresponding products in moderate to very good yields and in up to 98% *ee*. The field of organocatalysis has grown rapidly over the last decade, and the activation of substrates through covalent or Brønsted acid interactions has proved to be a reliable approach to constructing stereogenic centers.^[1]

Being both highly acidic and basic silanols undergo extensive hydrogen bonding among themselves as well as in combination with other proton donors or acceptors.^[4] Our group has a long-standing interest in the synthesis and application of silicon-containing compounds,^[5,6] and in that

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bis-carbinols were obtained in good yields. The catalytic activities of the bis-silanols were analyzed by monitoring HDA reactions between Rawal's diene and aldehydes by in situ IR spectroscopy and comparing the resulting data with those obtained in catalyses with the corresponding bis-carbinol derivatives. The results show for the first time that planar-chiral bis-silanols with hydrogen-bonding capabilities can be applied as asymmetric organocatalysts leading to enantiomerically enriched products.

context, we demonstrated the first application of organosilanols **A** (Figure 1) as chiral ligands in asymmetric aryl transfer reactions.^[7] Furthermore, we employed silylated pyrrolidines as organocatalysts in the asymmetric Michael addition of aldehydes to nitro olefins.^[8] Recently, very much work has been focused on the properties of silanediols **B**.^[9,10] Insightful computational and experimental studies suggested them as potential organocatalysts, and first applications have already been demonstrated.^[10] However, the potential of *chiral* organosilanols as *asymmetric* organocatalysts is still largely unexplored. Here, we report on the first syntheses of chiral bis-silanols **C** and their organocatalytic applications in asymmetric HDA reactions.



Figure 1. Silanols for catalysis.

Results and Discussion

So far, planar-chiral [2.2]paracyclophanes have been predominately recognized as suitable scaffolds for phosphane^[11] and heterocyclic carbene ligands.^[12] Only lately have their applications as organocatalysts been reported.^[13] We assumed that the rigid conformation of the [2.2]paracyclophane scaffold would result in a pincer-like arrangement

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of the participating Si–OH groups allowing for an optimal interaction with an H-bonding acceptor within a defined distance.

Several methods for the preparation of bis-silanols **3** starting from readily available racemic and enantiopure dibromide **1** were investigated (Scheme 1).^[14] According to known literature protocols dibromide **1** was treated with *t*BuLi at –78 °C followed by addition of commerically available silyl electrophiles. First, cyclotrisiloxanes were tested for the introduction of the desired silanol functionalities in a one-pot procedure.^[15] Unfortunately, after mild acidic aqueous workup of the reaction mixture, no product could be isolated. Subsequently, dichlorosilanes were investigated as electrophiles. Following mild basic hydrolysis of the intermediate chlorosilane afforded the desired bis-silanol **3a** (R = Me) in only 10% yield.



Scheme 1. Syntheses of [2.2]paracyclophane-based bis-silanols 3.

After these rather disappointing initial results, a two-step procedure to synthesize bis-silanols 3 was attempted. In the first step, bis-silanes 2 were prepared in moderate to good yields by treatment of dibromide 1 with *t*BuLi followed by the addition of the corresponding monochlorosilanes to the resulting dianionic intermediate. For the second step towards bis-silanols 3 various oxidizing agents, including KMnO₄, m-CPBA and an Ir-catalyzed oxidation were tested (Table 1).^[16-18] Oxidation with KMnO₄ (Method A) was only effective with the sterically unhindered dimethylsubstituted silvl group (Entry 1). Catalytic oxidation (Method B) of substrate 2a using [Ir(1,5-cod)Cl]₂ was less effective, even at elevated temperature (Entry 2). Neither Method A nor B afforded phenyl-substituted bis-silanol 3b in reasonable yield (Entries 3 and 4). However, an improved vield of 78% of 3b was achieved with *m*-CPBA as oxidant (Method C, Entry 5). With sterically more demanding substituents on the silicon atom, oxidation with m-CPBA was less effective when compared to the Ir-catalyzed hydrolytic oxidation (Entries 7, 8, 10 and 11). The enantiomerically pure silvl derivatives were obtained from enantiopure dibromide 1.^[19] All obtained bis-silanols were solid, air-stable compounds, which could be stored at 0 °C for weeks without any indication of decomposition.

Table 1. Oxidation of bis-silanes 2.

Entry	Substrate	Oxidation method ^[a]	<i>T</i> [°C]	Yield [%] ^[b]
1	2a	А	r.t.	80
2	2a	В	50	43
3	2b	А	50	0
4	2b	В	r.t.	20
5	2b	С	80	78
6	2c	А	80	0
7	2c	В	r.t.	80
8	2c	С	60	38
9	2d	А	60	0
10	2d	В	r.t.	74
11	2d	С	60	0

[[]a] Method A: KMnO₄; Method B: air/H₂O, 5 mol-% of [Ir(1,5-cod)Cl]₂; Method C: *m*-CPBA. [b] After purification by column chromatography.

With the long-term vision to broaden the structural variety of planar-chiral bis-silanols, the synthesis of an (achiral) ferrocene-based bis-silanol was investigated (Scheme 2). In this case, bis-silanol **5** was obtained in 23% yield through a one-step procedure by quenching 1,1'-dilithiated ferrocene with hexamethyltrisiloxane followed by treatment with dilute acid.



Scheme 2. Synthesis of ferrocene bis-silanol 5.

To test the hypothesis that, due to their increased acidity and therefore H-bonding capacity, silanols have superior organocatalytic properties to diols, catalysts 7a-c were prepared. They were obtained in moderate to good yields when diester 6 was treated with an excess of the appropriate Grignard reagent (Scheme 3).^[19]



Scheme 3. Synthesis of [2.2]paracyclophane-based diols 7.

The catalytic properties of bis-silanols **3** and **5** as well as diol **7** were explored in the HDA reaction of Rawal's diene **8** with aldehyde **9a** providing chiral 2,3-dihydropyran-4-one derivatives, which are important building blocks of many natural products with a broad range of biological activity.^[20]

The activity and therefore hydrogen-bonding capabilities of the new catalysts were measured by monitoring the cycloadditions by in situ IR spectroscopy.^[19] Not unexpectedly, dimethyl-substituted derivatives 3a and 5 were the most active catalysts in terms of reaction rate and product yield, giving the desired cycloaddition product 10a in up to 66% yield (Table 2, Entries 2, 3 and 6). The methyl substituents seemed to be bulky enough to prevent self-condensation, but allowed suitable coordination of the H-bond acceptor.^[21] In comparison, using diol 7a as catalyst led to dihydropyranone 10a in a slightly lower yield (42% yield, Entry 7) with a significantly reduced reaction rate.^[19] The difference in activity between phenyl-substituted bis-silanol 3b and diol derivative 7b (Entries 4 and 8) was smaller than that between the methyl-substituted compounds (Entries 2 and 7). When the reaction with 7b was performed at elevated temperatures (0 °C), the yield of 10a increased to 57%(Entry 9). Sterically more demanding substituents on the silicon and carbon atom hampered the coordination and activation of the aldehyde leading to less than 25% product formation (Entries 5 and 10). The results of these measurements suggested that the strength of the hydrogen bonding was correlated to both the acidity and the steric bulkiness of the bis-silanols and diols.

Table 2. HDA reaction using Rawal's diene ${\bf 8},$ but anal $({\bf 9a})$ and [2.2]paracyclophane-based organocatalysts.^[a]

TBSO	+ fi NMe ₂	1. catalyst (20 mol-%) $\frac{\text{toluene, }-40 \text{ °C}}{2. \text{ AcCl, }-78 \text{ °C}}$ 0 nPr
	8 9a	10a
Entry	Catalyst	Yield of 10a [%] ^[b]
1	_	0
2	3a	50
3	3a ^[c]	45
4	3b	38
5	3c	23
6	5	66
7	7a	42
8	7b	35
9 ^[d]	7b	57
10	7c	17

[a] All reactions were carried out on a 0.74 mmol scale with 2.0 equiv. of butanal (**9a**) in toluene at -40 °C under nitrogen for 16 h. [b] After workup with AcCl; products were isolated by flash column chromatography on silica gel. [c] Use of 5 mol-% of catalyst. [d] Reaction was performed at 0 °C.

Having demonstrated the catalytic activities of the dimethyl- and diphenyl-substituted derivatives, our attention turned to *asymmetric catalyses* with enantiopure planarchiral bis-silanols **3a**–c and carbinol **7a** (Table 3). The best results were obtained with sterically more encumbered aldehydes such as isobutyraldehyde (Entry 6) or isovaleraldehyde (Entry 8) yielding up to 42% of the corresponding products with enantiomeric excesses of up to 44% in favour of the (S) enantiomer. Unfortunately, using stoichiometric quantities of bis-silanol **3a** (Entries 2 and 5) afforded neither full conversion nor the expected higher *ee*, which might



be explained by unproductive self-associative interactions in the more concentrated reaction mixture. Interestingly, diol **7a** afforded similar selectivities as bis-silanol **3a** (Entries 2– 4, 13 and 14). This observation indicates that for good asymmetric induction less acidic and less active catalysts are more beneficial. As expected from previous results, catalysts **3b** and **3c** were less enantioselective, possibly due to the high steric hindrance of the substituents on the silicon atom (Entries 11 and 12) preventing effective hydrogen bonding and so providing an inadequate chiral environment. Aromatic aldehydes reacted well affording the products in high yields; however, the *ees* were low (Entries 9 and 10).

Table 3. Asymmetric HDA reaction using Rawal's diene $\bf 8$, aldehydes $\bf 9$ and [2.2]paracyclophane-based organocatalysts.^[a]

TB	+ FR	1. catalyst toluene, –4 2. AcCl, –78 °		Y ^R ∕0
	8 9		1	0
Entry	Catalyst	Aldehyde 9	Yield of 10	ee ^[c]
	(mol-%)	R	[%] ^[b]	
1	(S _p)-3a (20)	Et	43 (10b)	10 (S)
2	$(S_{\rm p})$ -3a (100)	nPr	90 (10a)	37 (S)
3	(\hat{S}_{p}) -3a (20)	nPr	45 (10a)	27 (S)
4	(\hat{S}_{p}) -3a (5)	nPr	40 (10a)	20 (S)
5	$(S_{\rm p})$ -3a (100)	<i>i</i> Pr	50 (10c)	44 (S)
6	$(S_{\rm p})$ -3a (20)	<i>i</i> Pr	42 (10c)	44 (S)
7	$(S_{\rm p})$ -3a (5)	<i>i</i> Pr	35 (10c)	39 (<i>S</i>)
8	(S _p)- 3a (20)	<i>i</i> Bu	41 (10d)	40 (S)
9	$(S_{\rm p})$ -3a (20)	Ph	80 (10e)	< 5
10	(S _p)- 3a (20)	2-furyl	70 (10f)	20 (S)
11	$(R_{\rm p})$ -3b (20)	<i>n</i> Pr	38 (10a)	17 (<i>R</i>)
12	$(S_{\rm p})$ -3c (20)	nPr	30 (10a)	< 10 (S)
13	(S _p)-7a (20)	nPr	45 (10a)	40 (S)
14	(S_p) -7a (5)	nPr	40 (10a)	36 (<i>S</i>)

[a] All reactions were carried out on a 0.17 mmol scale with 2.0 equiv. of aldehyde in toluene at -40 °C under nitrogen for 16 h. [b] After workup with AcCl; products were isolated by flash column chromatography on silica gel. [c] The enantiomeric excess was determined by HPLC using a Chiralcel OD-H column, and the absolute configuration assigned by comparison with ref.^[3b]

Conclusions

We have synthesized racemic and enantiomerically pure planar-chiral bis-silanols and their corresponding carbinol derivatives. Initial studies revealed their catalytic activities in HDA reactions of aliphatic and aromatic aldehydes with Rawal's diene. Although only moderate enantioselectivities have been achieved, the study presents the first applications of chiral bis-silanols in asymmetric organocatalysis.

Experimental Section

General Procedure for Catalysis: Diene 8 (0.17 mmol) and the catalyst (20 mol-%) were dissolved in toluene (0.8 mL). After cooling to -40 °C, the freshly distilled, dry aldehyde 9 (0.34 mmol, 2.0 equiv.) was added, and the mixture stirred for 16 h. The solu-

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tion was then cooled to -78 °C, diluted with dichloromethane (5 mL) and treated with acetyl chloride (0.34 mmol, 2.0 equiv.). After stirring at -78 °C for 20 min, the reaction mixture was warmed to room temp., and satd. aq. NaHCO₃ (15 mL) was added. The aqueous layer was separated and extracted with diethyl ether (3 times). The combined organic phases were dried with MgSO₄, filtered and concentrated. The resulting liquid was subjected to column chromatography [pentane, pentane/diethyl ether (4:1), (3:1)] to afford dihydropyranones **10** as pale yellow oils.

Supporting Information (see footnote on the first page of this article): Analytical data for all compounds, summary of ReactIR measurements, general procedure for the catalysis, NMR spectra.

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