

Brønsted Acid Catalyzed Asymmetric Silylation of Alcohols

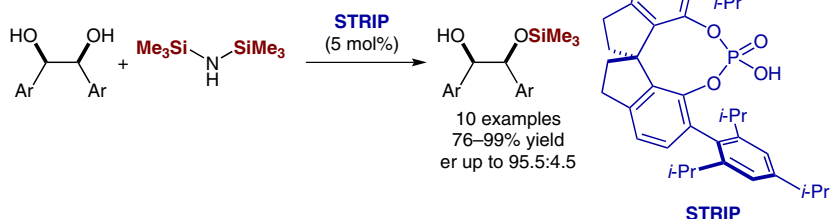
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Abstract We report a catalytic enantioselective desymmetrization of *meso*-1,2-diols by monosilylation using a chiral enantiopure Brønsted acid as catalyst and hexamethyldisilazane (HMDS) as silyl source.

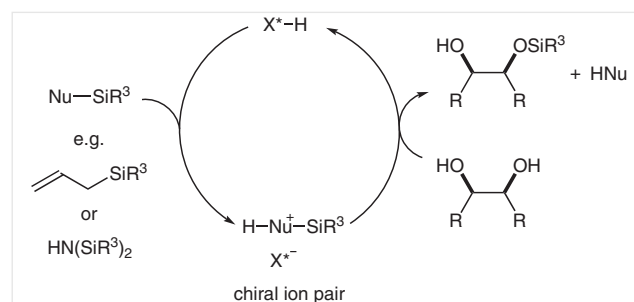
Key words enantioselective Brønsted acid catalysis, silyl transfer, *meso*-diols, desymmetrization, asymmetric counteranion-directed catalysis (ACDC)

The silylation of alcohols is a widespread transformation in organic synthesis, typically used to introduce protecting groups. Frequently employed protocols involve basic conditions and a silyl chloride or triflate reagent.¹ Recently, the first examples of catalytic asymmetric alcohol silylations have been described.² Interestingly, these methods are based on electrophilic silicon reagents employed under basic conditions. We were intrigued to design catalytic cycles that are based on an acidic activation of basic silicon sources, which are susceptible to protodesilylation. Here we report our studies on the Brønsted acid catalyzed desymmetrization of *meso*-diols using hexamethyldisilazane (HMDS) as the silicon source and the chiral spirocyclic phosphoric acid STRIP, recently introduced from this laboratory, as the catalyst.

The enantioselective desymmetrization of *meso*-diols is one of the most prominent strategies to access the corresponding monoprotected derivatives in their enantiopure form. This reaction is commonly realized by stereoselective acyl transfer reactions.³ However, the introduced acyl group may not always be suited as a protecting group in a given synthetic context, thus rendering further functional group transformations necessary.^{2a} As an alternative, highly efficient catalytic enantioselective monosilylations of *meso*-diols have been developed by Hoveyda, Snapper and co-

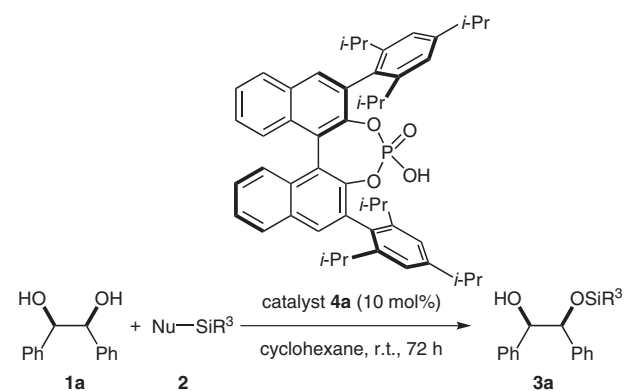
workers.^{2a-c} In analogy to the most common protocols for the silyl protection of alcohols, which are typically carried out under basic conditions,¹ these reactions involve the use of an enantiopure basic catalyst in combination with an achiral stoichiometric base such as Hünig's base. Despite the predominance of basic conditions for the silyl protection of alcohols, non-enantioselective protocols using acid catalysts in combination with basic silyl transfer reagents have also been developed.^{1,4}

Based on the mechanism of this type of transformation, we hypothesized that it should be possible to render the overall process enantioselective by utilizing a chiral enantiopure Brønsted acid catalyst (Scheme 1).⁵ Accordingly, protonation of the basic silicon source should generate an ion pair consisting of a cationic silylium source accompanied by the enantiopure counteranion.



Scheme 1 Design of a Brønsted acid catalyzed desymmetrization of *meso*-diols

The reaction of this ion pair intermediate with the diol substrate could then potentially proceed enantioselectively via a desymmetrization reaction.

Table 1 Identification of a Suitable Silylating Agent and Catalyst

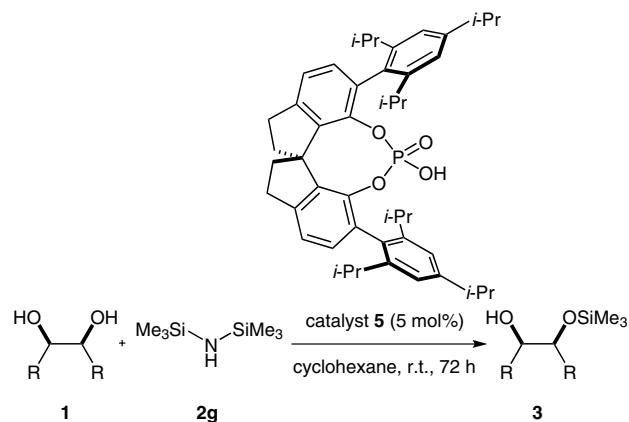
Entry	Nu-SiR ₃	Equiv	Conv. (%) ^a	er ^b
1	TMSCl 2a	1.2	0	-
2		1.2	0	-
3		1.2	20	63:37
4	TMSCN 2d	1.2	11	63:37
5		0.6	42	38.5:61.5
6		1.2	8	50:50
7	TMS-NH-TMS 2g	0.6	78	81.5:18.5
8		0.6	60	78:22
9		0.6	0	-
10		0.6	21	81:19
11 ^c	TMS-NH-TMS 2g	0.6	83	94:6

^a Determined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

^b Determined by HPLC on a chiral stationary phase.

^c (S)-STRIP (**5**; see Table 2) was used as catalyst.

We began by studying several prospective silyl transfer reagents utilizing TRIP (**4a**)⁶ as reference catalyst (Table 1). Comparably non-basic silylating agents trimethylsilyl chloride (**2a**) and allyltrimethylsilane (**2b**) proved to be inefficient for product formation under the reaction conditions tested (entries 1 and 2 in Table 1). However, switching to more basic silyl transfer reagents enabled reactivity with moderate to good conversion, albeit with limited stereoselection (entries 3–6 in Table 1). Further screening revealed HMDS (**2g**) and its derivatives as the most promising reagents (entries 7–10 in Table 1). We thus continued our studies with the commercially available and inexpensive HMDS as silyl source and further optimized the reaction conditions.⁷ Through these studies we identified catalyst **5** (STRIP) as best catalyst for this transformation,^{6c} giving good conversion and stereoselection in our model reaction (83% conversion and 94:6 er, entry 11 in Table 1).

Table 2 Substrate Scope of the STRIP-Catalyzed Desymmetrization of meso-Diols

Entry	R	Product	Time (d)	Yield (%)	er ^a
1	Ph	3a	3	84	95:5
2 ^b	4-MeC ₆ H ₄	3b	2	96	95:5
3	3-MeC ₆ H ₄	3c	7	92	93.5:6.5
4	2-MeC ₆ H ₄	3d	7	91	90:10
5 ^b	4- <i>i</i> -PrC ₆ H ₄	3e	1	99	92.5:7.5
6 ^{c-e}	4-FC ₆ H ₄	3f	10	77	95:5
7	4-ClC ₆ H ₄	3g	1	87	95.5:4.5
8 ^e	2-ClC ₆ H ₄	3h	5	94	89:11
9	4-BrC ₆ H ₄	3i	6	76	90.5:9.5
10	-(CH ₂) ₄ -	3j	7	99 ^f	75.5:24.5 ^g

^a Determined by HPLC on a chiral stationary phase.

^b Reaction was conducted at 40 °C

^c Carbon tetrachloride was used as solvent instead of cyclohexane.

^d Amount of catalyst **5** used was 10 mol%.

^e Compound **2h** was used as a silylating reagent instead of **2g**.

^f Conversion determined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

^g Determined by GC on a chiral stationary phase.

With optimal reaction conditions in hand, we continued to study the scope of the Brønsted acid catalyzed desymmetrization of *meso*-diols (Table 2). The reaction turned out to be tolerant of both electron-rich (entries 1–5 in Table 2) as well as electron-poor (entries 6–9 in Table 2) aromatic substituents, giving moderate to good yields (76–99%) and enantioselectivities (89:11 to 95.5:4.5 er) in all cases.⁸ When studying the effects of regioisomerism, we found that *para*-substitution led to superior results as compared to both *meta*- and *ortho*-substitution (entries 2–4 in Table 2). Aliphatic substrates, as exemplified by *cis*-1,2-cyclohexane-diol, showed good reactivity, albeit with reduced stereoinduction (entry 10 in Table 2).

In summary, we have developed a catalytic asymmetric desymmetrization of *meso*-1,2-diols by monosilylation. Our method employs STRIP (**5**) as enantioselective catalyst, together with HMDS (**2g**) as silyl source. Moderate to good results were obtained with a number of aryl-substituted *meso*-diols. Further studies on the use of this type of Brønsted acid catalyzed enantioselective silylation are currently ongoing in our laboratories.

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Generous support from the Max-Planck-Society, the European Research Council (Advanced grant ‘High Performance Lewis Acid Organocatalysis, HIPOCAT’), the Naito Foundation (fellowship to K.H.), and the Alexander von Humboldt Foundation (fellowship to S.G.) is gratefully acknowledged.

Supporting Information

Supporting information for this article is available online at <http://dx.doi.org/10.1055/s-0034-1380409>.

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- (7) For further screening of reaction conditions and catalysts, see the Supporting Information.
- (8) The following procedure is representative: To a solution of catalyst **5** (3.6 mg, 5.00 μ mol) in cyclohexane (1.0 mL) HMDS (**2g**, 12.5 μ L, 0.0600 mmol) was added at r.t. and the resulting mixture was stirred for 2 h, after which, *meso*-diol **1a** (21.4 mg, 0.100 mmol) was added. The reaction was judged to be complete when the reaction mixture turned into a clear, homogeneous solution. The solvent was removed by evaporation and the crude mixture was purified by silica gel column chromatography (hexane–EtOAc, 95:5), giving **3a** (24.0 mg, 84%) as a colorless solid. ¹H NMR (500 MHz, CD₂Cl₂): δ = 7.22–7.30 (m, 10 H), 4.74 (d, *J* = 5.0 Hz, 1 H), 4.71 (d, *J* = 5.0 Hz, 1 H), 2.39 (br, 1 H), –0.09 (s, 9 H). ¹³C NMR (125 MHz, CD₂Cl₂): δ = 141.6, 141.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 79.6, 78.9, 0.00. HRMS (ESI, +ve): *m/z* [M + Na] calcd for C₁₇H₂₂NaO₂Si: 309.1287; found: 309.1281. HPLC (Chiralcel OJ-H, heptane–*i*-PrOH = 95:5, flow rate = 0.5 mL/min, λ = 206 nm): $t_{R(\text{major})}$ = 12.6 min, $t_{R(\text{minor})}$ = 16.1 min.