

Lewis Acid Catalysis in Water with a Hydrophilic Substrate: Scandium-Catalyzed Hydroxymethylation with Aqueous Formaldehyde in Water**

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The use of Lewis acids as catalysts is one of the most powerful strategies in organic chemistry.^[1] In general, conventional Lewis acids such as AlCl_3 , TiCl_4 , $\text{BF}_3 \cdot \text{OEt}_2$, SnCl_4 , etc., require strictly anhydrous conditions because they immediately react with water in preference to the substrates, resulting in serious decomposition of the catalysts or the substrates. To address this issue, water-compatible Lewis acid catalyzed organic reactions have been intensively studied in the past decade.^[2] Considering the growing concern over environmental pollution, water is an ever more desirable alternative to organic solvents, as water is a clean, safe, and inexpensive solvent.^[3] Several surfactant-type catalysts derived from water-compatible Lewis acids have been developed,^[4] and catalytic asymmetric reactions have been achieved in water without requiring any organic cosolvents.^[5] These reactions proceeded smoothly by creating *hydrophobic domains* in the water to stabilize and concentrate the organic substrates, or by suppressing undesired reaction pathways that may occur in water. One of the key factors for these successes is the *hydrophobicity* of the substrates.

Aqueous formaldehyde solutions (i.e. formalin) are one of the most important single carbon electrophiles and are representative of a hydrophilic substrate. As mentioned above, the hydrophobicity of the substrates is very important for organic reactions in water and hydrophilic substrates are often difficult to handle in water.^[6–8] Herein, we address this issue and describe a catalytic hydroxymethylation reaction with aqueous formaldehyde in which water is the sole solvent.

First, we carried out the hydroxymethylation of silicon enolate **1** with 1 equivalent of formaldehyde (36 % aqueous solution; aq. HCHO) in the presence of 2 mol % of scandium tris(dodecyl sulfate) ($\text{Sc}(\text{DS})_3$)^[4] at a 1.0 M concentration at 20 °C for 1 hour in water. The reaction proceeded sluggishly and afforded desired product **2** in poor yield. Increasing the amount of aq. HCHO to 3 equivalents improved the yield to 25 %, but addition of more aq. HCHO did not result in

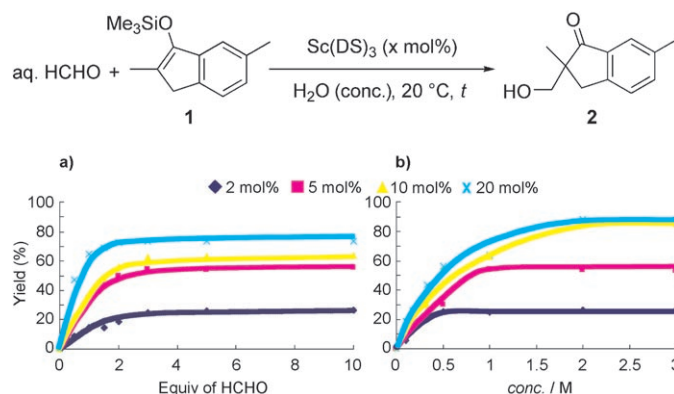


Figure 1. Hydroxymethylation of **1**. a) Changes in yield as a function of the number of equivalents of HCHO at different catalyst loadings for a 1.0 M solution monitored over 1 hour. b) Changes in yield as a function of concentration at different catalyst loadings for reaction containing 5.0 equivalents of HCHO monitored over 8 hours.

increased amounts of the desired product (Figure 1 a, navy blue). Gratifyingly, while optimizing the reaction conditions, we found that desired product **2** was obtained in 82 % yield by using 5 equivalents of aq. HCHO and by extending the reaction time to 8 hours. Notably, under these conditions the competitive hydrolysis of silicon enolate **1** was observed. The loading levels of the catalyst also has an effect on the yield; the yield of **2** showed good correlations to the amount of $\text{Sc}(\text{DS})_3$ used, which ranged from 2, 5, 10, to 20 mol %. To improve the yield, we also investigated the concentration effect of aq. HCHO for each of the different $\text{Sc}(\text{DS})_3$ loadings (2, 5, 10, or 20 mol %) in the presence of 5 equivalents of aq. HCHO (Figure 1 b). In the presence of 10 and 20 mol % of $\text{Sc}(\text{DS})_3$, the yields were improved to more than 80 % as the concentrations increased to 2.0 M, however, no additional improvement was observed when the concentration was increased to more than 2.0 M. In the cases of 2 and 5 mol % of $\text{Sc}(\text{DS})_3$, the yields leveled off at much lower concentrations of 0.5 M and 1.0 M, respectively. These results indicated that $\text{Sc}(\text{DS})_3$ might be saturated by aq. HCHO. On the basis of the experiments described above, it can be said that despite the good solubility of HCHO in water, the amount of HCHO in the hydrophobic environment increases in the presence of $\text{Sc}(\text{DS})_3$ because of Lewis acid–Lewis base interactions between $\text{Sc}(\text{DS})_3$ and HCHO, therefore, allowing the reaction of HCHO with silicon enolate **1** to proceed smoothly in water.

After tuning the reaction conditions, we found that several silicon enolates reacted with aq. HCHO (5.0 equiv) in the presence of 5 mol % of $\text{Sc}(\text{DS})_3$ in water (1.0 M) at 20 °C

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to afford the corresponding hydroxymethylated ketones in high yields (Figure 2 and Table 1). Notably, the catalyst system can be applied to hydrophilic substrates as well as hydrophobic substrates.

The Lewis acid catalyzed asymmetric reactions of hydrophilic substrates in water are recognized to be highly challenging^[9] because of the importance of the *Lewis acid–Lewis base interactions*; Lewis acids lose their acidity upon coordination with chiral ligands. Additionally, chiral ligands compete with substrates and water molecules for the coordination to Lewis acids. Therefore, the development of chiral Lewis acid catalyzed hydroxymethylation by using aq. HCHO in water would have a high impact in the field.

Encouraged by the promising results in Table 1, asymmetric variants of the hydroxymethylation reaction by using aq. HCHO were investigated (Figure 2 and Table 2). The addition of a chiral ligand and a small amount of a surfactant suppressed the competitive hydrolysis of the silicon enolates. After optimization of the reaction conditions, catalytic

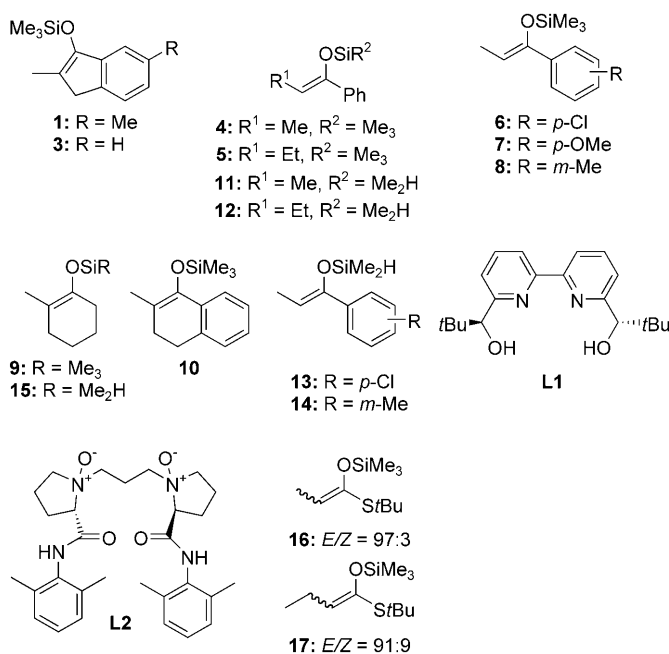


Figure 2. Substrates and ligands used.

Table 1: Sc(DS)₃-Catalyzed hydroxymethylation.

$\text{aq. HCHO (5.0 equiv)} + \text{R}^1\text{C}(\text{OSiMe}_3)\text{C}(\text{R}^2)\text{R}^3 \xrightarrow[\text{H}_2\text{O (1.0 M), 20 }^\circ\text{C, 6 h}]{\text{Sc(DS)}_3 \text{ (5 mol\%)}} \text{HOCH}_2\text{C}(\text{R}^1)(\text{R}^2)\text{C}(\text{R}^3)=\text{O}$		
Entry	Silicon enolate	Yield [%] ^[a]
1	1	87
2	3	88
3	4	89
4	5	94
5	6	75
6	7	68
7	9	69 ^[b,c]

[a] Yield of isolated product. [b] Portionwise addition of the silicon enolate (0 h and 3 h, 0.5 equiv each). [c] Yield was determined after benzoylation.

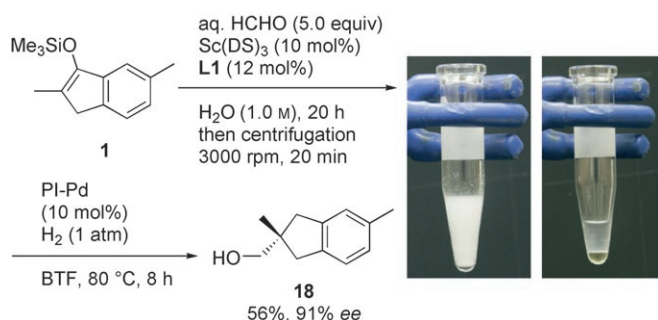
Table 2: Asymmetric hydroxymethylation.

$\text{aq. HCHO (5.0 equiv)} + \text{R}^1\text{C}(\text{OSiMe}_3)\text{C}(\text{R}^2)\text{R}^3 \xrightarrow[\text{H}_2\text{O (0.5 M)}]{\text{Condition}} \text{HOCH}_2\text{C}(\text{R}^1)(\text{R}^2)\text{C}(\text{R}^3)=\text{O}$				
Entry	Enolate	Conditions ^[a]	Yield [%] ^[b]	ee [%] ^[c]
1	1	A	81	91 (R)
2	1	B	85	90 (S)
3	3	B	83	94
4	4	B	85	91 (R)
5	5	B	85	90
6	5	C	82	91 (R)
7	6	B	84	92
8	8	A	73	90
9	9	B	86	85
10	10	B	82	96
11	10	C	82	96
12	11	B	91	91 (R)
13	12	B	92	90
14	13	B	83	94
15	13	C	83	94
16	13	D	83	90
17	14	B	90	92
18	15	B	84	91
19	16	A	73	91 (S)
20	17	A	65	90

[a] Conditions A: Sc(DS)₃ (10 mol%), L1 (12 mol%), Triton X-705, RT, 20 h. Conditions B: Sc[O₃S(CH₂)₁₀CH₃]₃ (10 mol%), L2 (12 mol%), CH₃(CH₂)₁₀SO₃Na, 5 °C, 48 h. Conditions C: Sc[O₃S(CH₂)₁₀CH₃]₃ (2 mol%), L2 (2.4 mol%), CH₃(CH₂)₁₀SO₃Na, 5 °C, 96–110 h. Conditions D: Sc[O₃S(CH₂)₁₀CH₃]₃ (1 mol%), L2 (1.2 mol%), CH₃(CH₂)₁₀SO₃Na, 5 °C, 81 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis.

asymmetric hydroxymethylation reactions were successfully carried with 10 mol % of Sc(DS)₃ and 12 mol % of chiral ligand L1^[10] in the presence of Triton X-705 (Conditions A), or with 10 mol % of Sc[O₃S(CH₂)₁₀CH₃]₃ and 12 mol % of chiral ligand L2^[11] in the presence of CH₃(CH₂)₁₀SO₃Na (Conditions B) to afford the desired products in good to high yields with high selectivities. A wide variety of silicon enolates reacted smoothly and high levels of enantioselectivities (>90 % ee) were attained in most cases. Moreover, by using 2 mol % or 1 mol % of the catalyst (Conditions C and D) led to the same range in yields and enantioselectivities as those reactions employing 10 mol % of the catalyst. Notably, thioketene silyl acetals such as 16 and 17, which are known to be much less stable than silyl enol ethers (ketone-derived silicon enolates) in water, reacted smoothly under the reaction conditions to afford the desired hydroxymethylated adducts in good yields with high enantioselectivities.

This method was applied to the synthesis of artificial odorant 18 (Scheme 1).^[12] Hydroxymethylation of 1 was performed by using Sc(DS)₃–L1 as the catalyst. After the reaction was complete, the reaction mixture was centrifuged (3000 rpm, 20 min) to separate the colloidal white dispersion into three phases. The upper phase was the water layer, the middle phase was surfactant, and the lower phase contained organic compounds. The bottom phase was removed and subjected to hydrogenation in the presence of polymer incarcerated palladium (PI-Pd)^[13] in benzotrifluoride (BTF) to give compound 18 in 56 % yield with 91 % ee over 2 steps.



Scheme 1. Synthesis of an odorant without using an organic solvent workup. The pictures show the solution before centrifugation (left) and the separated phases after centrifugation of the hydroxymethylation reaction mixture (right).

Notably, the synthesis was accomplished by using a catalytic asymmetric reaction in water and a hydrogenation reaction including an immobilized catalyst, both of which are suitable for green and sustainable chemistry.^[3,14]

In conclusion, we have developed a scandium-catalyzed hydroxymethylation reaction with aqueous HCHO in water. The achiral and asymmetric hydroxymethylations both proceeded smoothly with high selectivities. Contrary to our previous results, hydrophilic HCHO reacted well in the hydrophobic system. Lewis acid–Lewis base interactions between the scandium catalyst and HCHO were suggested to be crucial based on several experiments. We also applied this reaction to the synthesis of an odorant. Reported herein is the first example of a catalytic hydroxymethylation of silicon enolates with aqueous HCHO in water that does not require organic solvents. These results provide a foundation for conducting organic reactions, even with hydrophilic compounds, in the hydrophobic systems.

Experimental Section

Synthesis of (S)-2,3-Dihydro-2-(hydroxymethyl)-2,5-dimethylindane (18): A mixture of Sc(DS)₃ (25 mg, 0.030 mmol) and chiral ligand L1 (12 mg, 0.036 mmol) in water (0.3 mL) was stirred for 1 h at 20 °C. Aqueous HCHO (125 mg, 1.5 mmol) and silicon enolate **1** (69.7 mg, 0.3 mmol) were then added to the reaction mixture, which was then stirred for 20 h at 20 °C. The resulting mixture was then centrifuged (3000 rpm, 20 min). The bottom layer was separated, and then dissolved in α , α -trifluorotoluene (BTF, 2 mL). Polymer incarcerated Pd (PI-Pd, 0.668 mmol g⁻¹, 45 mg, 0.030 mmol) was added to the solution under Ar, and the reaction mixture was then stirred for 8 h at 80 °C under a hydrogen atmosphere (1 atm). After cooling the reaction mixture to room temperature, it was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (elution with *n*-hexane/AcOEt = 3:2) to give **4** (56% in 2 steps) as a colorless oil.

¹H NMR δ = 1.17 (s, 3H), 1.55 (brs, 1H), 2.31 (s, 3H), 2.63 (d, J = 15.6 Hz, 2H), 2.86 (d, J = 15.6 Hz, 1H), 2.87 (d, J = 15.6 Hz, 1H), 3.51 (s, 2H), 6.94 (d, J = 7.6 Hz, 1H), 6.99 (s, 1H), 7.04 ppm (d, J = 7.6 Hz, 1H); ¹³C NMR δ = 21.2, 24.0, 42.4, 42.7, 45.0, 70.7, 124.5, 125.5, 127.0, 135.8, 139.4, 142.6 ppm; FT-IR (neat) $\tilde{\nu}$ = 3186, 3007, 2866, 1493, 1454, 1377, 1298, 1225, 1137, 1094, 1036, 977, 812, 794, 699 cm⁻¹; $[\alpha]_D^{23}$ + 2.7 deg cm³ g⁻¹ dm⁻¹ (c 0.750 g cm⁻³, CHCl₃) (91% ee, S), lit. $[\alpha]_D^{20}$ + 3.2 deg cm³ g⁻¹ dm⁻¹ (c 1.50 g cm⁻³ CHCl₃) (>99% ee, S); HPLC

(Daicel Chiralpak AD, *n*-hexane/*i*PrOH = 40:1, flow rate 1.0 mL min⁻¹): t_R = 11.8 min (major, S), t_R = 14.6 min (minor, R).

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