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Chiral Scandium-Catalyzed Enantioselective Hydroxymethylation of Ketones in Water

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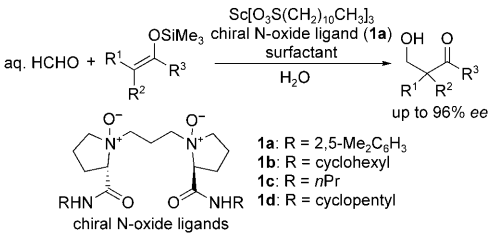
Dedicated to the 150th anniversary of Japan–UK diplomatic relations

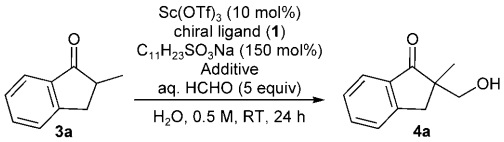
Hydroxymethylation reactions provide one of the most useful one-carbon extension methods.[1,2] The reactions are usually carried out using paraformaldehyde or difficult-to-handle formaldehyde gas in organic solvents.[3] In the course of our investigations to develop catalytic asymmetric reactions in water,[4,5] we have recently found that scandium–chiral N-oxide complex catalyzed highly efficient asymmetric hydroxymethylation of silicon enolates in water (Scheme 1).[6] In this reaction, readily available and inexpensive aqueous formaldehyde (formalin) could be successfully employed. Although this asymmetric hydroxymethylation is simple and shows high enantioselectivities for a variety of silicon enolates, direct use of ketones instead of silicon enolates seems to be attractive from an atom economy point of view. Recently, Córdova[7] and Yamamoto[8] have reported organocatalytic asymmetric hydroxymethylation using formalin. Although high enantioselectivities were observed in their systems, chemical yields were moderate and substrates are relatively limited. Therefore, efficient and general asymmetric hydroxymethylation is desirable. We started to investigate asymmetric hydroxymethylation of ketones in water, and in this report, preliminary results using chiral scandium catalysts are described.



Scheme 1. Chiral Sc-catalyzed enantioselective hydroxymethylation of silicon enolates.

At the outset, several reaction conditions were examined for the scandium-catalyzed asymmetric reaction of α-methylindanone (**3a**) with formalin in water using chiral N-oxide **1a**[9] as a ligand (Table 1). Although the reaction proceeded sluggishly in the absence of an additive, the use of a catalytic amount of triethylamine resulted in improving the yield with moderate enantioselectivity (entries 1 and 2). Addition of 20 mol% NaOH also enhanced the rate of the desired reaction (entry 3). Although further addition of NaOH gave good yields, no chiral induction was observed, probably because $Sc(OTf)_3$ was deactivated and free NaOH catalyzed

Table 1. Optimization of reaction conditions.



Entry	Ligand	Additive (mol%)	Yield [%][a]	*ee* [%][b]
1	**1a**	none	20	41
2	**1a**	Et_3N (20)	36	27
3	**1a**	NaOH (20)	37	38
4	**1a**	NaOH (50)	87	0
5	**1a**	2,6-lutidine (20)	16	46
6	**1a**	pyridine (20)	60	47
7	**1b**	pyridine (20)	57	67
8	**1c**	pyridine (20)	76	70
9	**1d**	pyridine (20)	76	73
10[c]	**1d**	pyridine (20)	81	72

[a] Yield of isolated product after chromatography. [b] Enantiomeric excess was determined by chiral HPLC analysis. [c] Reaction for 48 h.

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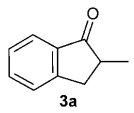
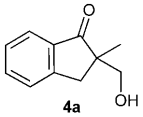
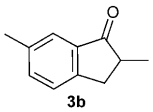
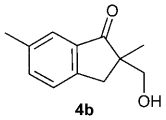
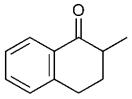
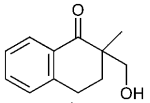
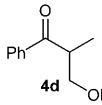
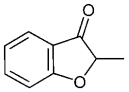
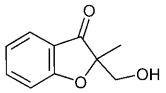
an achiral pathway (entry 4). Among the organic bases tested, pyridine was found to be the best additive for the desired asymmetric hydroxymethylation (entry 6). Use of alkyl amide-type ligand **1b** instead of **1a** improved enantioselectivity significantly (entry 7), and finally, a cyclopentyl substituent on the amide moiety (**1d**) was found to be the best in terms of both yield and enantioselectivity (entries 7–10).

With the optimized conditions in hand, we then examined substrate generality of this reaction (Table 2). Introduction

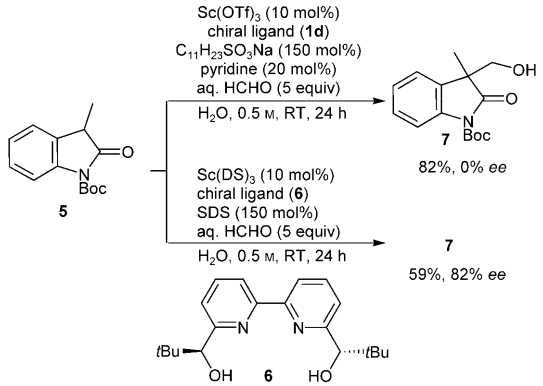
Table 2. Asymmetric hydroxymethylation of ketones in water.[a]

Entry	Ketone	Product	Yield [%][b]	*ee* [%][c]
1	 **3a**	 **4a**	81	72
2	 **3b**	 **4b**	72	72
3[d]	 **3c**	 **4c**	39	88
4[d]	 **3d**	 **4d**	29	81
5	 **3e**	 **4e**	quant	67

[a] Conditions: Ketone **3** (0.3 mmol), $Sc(OTf)_3$ (10 mol%), N-oxide **1d** (12 mol%), $C_{11}H_{23}SO_3Na$ (150 mol%), pyridine (20 mol%), formalin (5 equiv), water, RT, 24 h. [b] Yield of isolated product after chromatography. [c] Enantiomeric excess was determined by chiral HPLC analysis. [d] Reaction was carried out at 40 °C for 48 h.

of a methyl group at the 6-position of α-methyl indanone did not retard the chiral induction, resulting in formation of hydroxymethylated ketone **4b** in 72% yield with 72% *ee* (entry 2). Ketone **4b** is known as a useful intermediate for the preparation of artificial odorant.[10] Although reactivity was lower, tetralone **3c** and propiophenone (**3d**) also gave the desired hydroxymethylated ketones in high enantioselectivities (entries 3 and 4). In the case of α-methylcoumaranone (**3e**), the desired product **4e** was obtained quantitatively with good enantiomeric excess (entry 5). In the hydroxymethylation of oxindole, the reaction proceeded smoothly to afford the desired compound **7** in 82% yield, albeit no chiral induction was observed unexpectedly. Slight modification of reaction conditions was performed and it was finally found that the combination of $Sc(DS)_3$ and chiral bipyridine ligand **6**[11] with SDS gave the desired hydroxymethylated oxindole **7** in 59% yield with 82% *ee* (Scheme 2).

In summary, we have developed scandium-catalyzed enantioselective hydroxymethylation of ketones using aqueous



Scheme 2. Asymmetric hydroxymethylation of oxindole.

formaldehyde (formalin) in water. The addition of a catalytic amount of pyridine enabled us to use ketones directly in asymmetric hydroxymethylation reactions. Further investigations to clarify the mechanism of the present system as well as to expand substrate scope by modifying chiral catalysts are now in progress in our laboratories.

Experimental Section

A typical experimental procedure is described for the enantioselective hydroxymethylation of ketones: Ketone (0.3 mmol), $Sc(OTf)_3$ (10 mol%), N-oxide **1d** (12 mol%), $C_{11}H_{23}SO_3Na$ (150 mol%), pyridine (20 mol%), and formalin (5 equiv) were combined in water (500 μL) at room temperature. After 24 h, a mixture of sat. aqueous $NaHCO_3$ and brine (1:1, 5–10 mL) was added, and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were dried (Na_2SO_4), filtrated, and evaporated to afford the crude product, which was purified by preparative TLC. The enantiomeric excess was determined by chiral HPLC analysis.

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Keywords: asymmetric catalysis · green chemistry · hydroxymethylation · scandium · water

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