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Tetrahedron Letters 45 (2004) 7939–7941

Tetrahedron Letters

Enantioselective synthesis induced by chiral organic–inorganic hybrid silsesquioxane in conjunction with asymmetric autocatalysis

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Received 7 July 2004; revised 16 August 2004; accepted 20 August 2004

Dedicated to Professor Iwao Ojima on the occasion of his 60th birthday

Abstract—5-Pyrimidyl alkanol with up to 96% ee was formed using chiral organic–inorganic hybrid silsesquioxane in the enantioselective addition of diisopropylzinc to pyrimidine-5-carbaldehyde, in conjunction with asymmetric autocatalysis.

The enantioselective addition of dialkylzincs to aldehydes using chiral catalysts has attracted much attention, because it is a useful method for the preparation of optically active *sec*-alcohols.[1] Homogeneous chiral catalysts such as β-amino alcohols have been extensively studied and employed most commonly, often with excellent result. On the other hand, heterogeneous chiral catalysts are becoming more important, due to their easier separation from the reaction mixture. Although heterogeneous chiral catalysts have been developed for the enantioselective addition of dialkylzincs to aldehydes, most of them are polystyrene-bound and organic polymer-based chiral catalysts.[1,2] However, inorganic materials such as silica have significant advantages over organic polymers, because of their mechanical and thermal stability. In 1990, we reported the first use of silica gel as a support of chiral catalysts for the enantioselective addition of dialkylzincs to aldehydes.[3] Since then, several groups have developed chiral catalysts immobilized on silica gel and mesoporous silica for the enantioselective addition of dialkylzincs to aldehydes.[4]

In recent years, nanostructured materials[5] have attracted much attention, and highly ordered, hybrid mesoporous, sesquioxanes with well-defined external morphologies have been achieved by templating methods.[6] Moreau et al. reported the synthesis of morphologically controlled bridged silsesquioxanes from a molecular precursor derived from chiral 1,2-diaminocyclohexane by the sol–gel hydrolytic condensation.[7] To the best of our knowledge, no report has appeared on the use of chiral organic–inorganic hybrid silsesquioxanes, prepared by the self-templating method, in asymmetric C–C bond forming reactions. Meanwhile, we have been studying asymmetric autocatalysis with amplification of enantiomeric excess (ee), in which the chiral product acts as the chiral catalyst for its own production.[8,9]

We report here a successful use of chiral organic–inorganic hybrid materials, that is, a silsesquioxane hybrid derived from silylated *trans*-1,2-diaminocyclohexane, as a chiral initiator in asymmetric autocatalysis; highly enantioenriched 5-pyrimidyl alkanols **2** with the corresponding absolute configurations to those of the chiral bridged silsesquioxanes were obtained (Scheme 1).

In the presence of chiral organic–inorganic hybrid materials, the enantioselective addition of i-Pr_2Zn to 2-alkynylpyrimidine-5-carbaldehyde **1** was examined. As shown in Table 1, in the presence of chiral hybrid silsesquioxane ((R,R)-**3a**,[7] (R)-5-pyrimidyl alkanol **2** with 91–96% ee was formed (entries 1 and 2). In sharp contrast, in the presence of (S,S)-**3a**,[7] (S)-5-pyrimidyl alkanol **2** with 88–95% ee was obtained in 92–94% yields (entries 3 and 4). The reaction in the presence of hybrid

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Keywords: Asymmetric induction; Asymmetric synthesis; Asymmetric autocatalysis; Chiral hybrid silsesquioxane.

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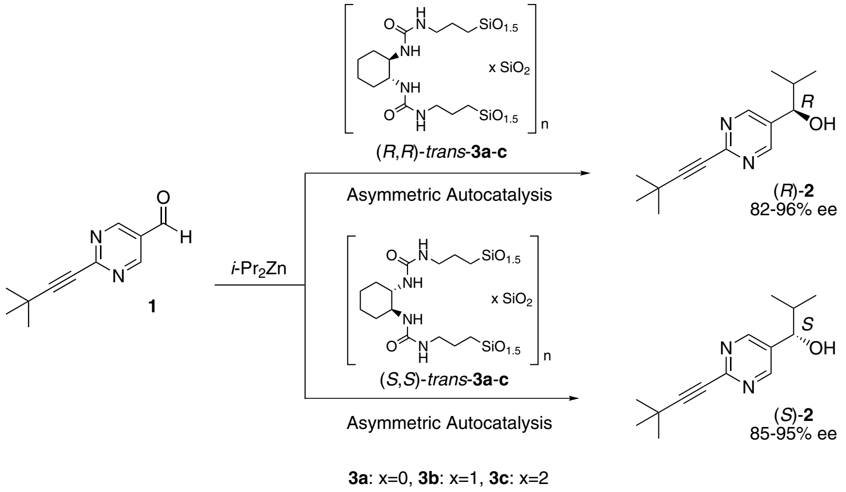
doi:10.1016/j.tetlet.2004.08.135



Scheme 1. Highly enantioselective asymmetric autocatalysis using chiral organic–inorganic hybrid materials **3a**–**c**.

Table 1. Highly enantioselective synthesis of pyrimidyl alkanol **2** in the presence of chiral organic–inorganic hybrid materials **3a**–**c**

Entry	Hybrid material	Content of **3**[b] (mmol/g)	Equiv of **3**	Pyrimidyl alkanol **2**		
				Yield (%)[c]	ee (%)[d]	Config.
1	(*R*,*R*)-**3a**	2.329	0.1	95	96	*R*
2	(*R*,*R*)-**3a**	2.329	0.1	94	91	*R*
3	(*S*,*S*)-**3a**	2.343	0.1	94	95	*S*
4	(*S*,*S*)-**3a**	2.343	0.1	92	88	*S*
5	(*R*,*R*)-**3b**	1.814	0.1	98	92	*R*
6	(*R*,*R*)-**3b**	1.814	0.1	94	82	*R*
7[a]	(*R*,*R*)-**3b**	—	0.083	89	93	*R*
8[a]	(*R*,*R*)-**3b**	—	0.067	95	90	*R*
9	(*S*,*S*)-**3b**	1.880	0.1	91	91	*S*
10	(*S*,*S*)-**3b**	1.880	0.1	95	87	*S*
11[a]	(*S*,*S*)-**3b**	—	0.075	91	90	*S*
12[a]	(*S*,*S*)-**3b**	—	0.071	86	94	*S*
13	(*R*,*R*)-**3c**	1.770	0.1	94	93	*R*
14	(*R*,*R*)-**3c**	1.770	0.1	83	91	*R*
15	(*S*,*S*)-**3c**	1.582	0.1	98	95	*S*
16	(*S*,*S*)-**3c**	1.582	0.1	91	85	*S*

[a] Recovered hybrid material from the reaction in upper entry was used.

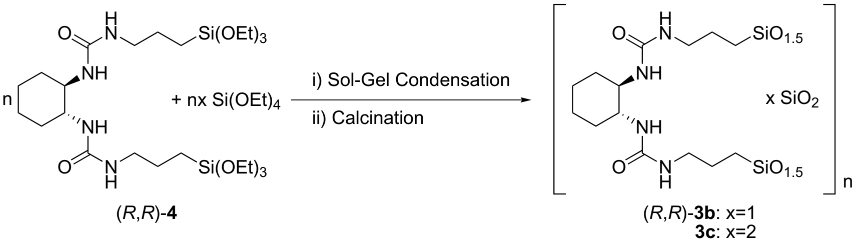
[b] Calculated from nitrogen analysis.

[c] Isolated yield.

[d] Ee was determined by HPLC analysis using a chiral column (Chiralcel OD).

materials (*R*,*R*)-**3b** or **3c**[10] (Scheme 2) gave (*R*)-5-pyrimidyl alkanol **2** with 82–93% ee (entries 5, 6, 13 and 14), whereas the reaction in the presence of (*S*,*S*)-**3b** or **3c**[10] gave (*S*)-5-pyrimidyl alkanol **2** with 85–95% ee (entries 9 and 10). Thus, even when the proportion of the diaminocyclohexane unit in the catalyst was lowered (**3b**, **3c**), it did not adversely influence the ee of the product **2**. Moreover hybrid silica is recoverable, and can be used without any loss of enantioselectivity (90–94% ee) (entries 7, 8, 11 and 12).[11]

In a general experiment, to a mixture of (*R*,*R*)-**3** or (*S*,*S*)-**3** (0.1 mmol, calculated as the monomeric unit) and aldehyde **1** (4.7 mg, 0.025 mmol) was added toluene (0.1 mL) under an argon atmosphere. The mixture was stirred for 15 min at room temperature. Then *i*-Pr_2Zn



Scheme 2. Preparation of chiral organic–inorganic hybrid materials **3b**,**c**.

(0.08 mL of 1.0 M toluene solution, 0.08 mmol) was added slowly at 0 °C over a period of 30 min, and the mixture was stirred for 3 h. Toluene (1.9 mL), *i*-Pr$_2$Zn (0.2 mL of 1.0 M toluene solution, 0.2 mmol) and aldehyde **1** (18.8 mg, 0.1 mmol in 1.0 mL toluene) were then added successively, and the mixture was stirred for 1 h. Then toluene (7.5 mL), *i*-Pr$_2$Zn (0.8 mL of 1.0 M toluene solution, 0.8 mmol) and aldehyde **1** (75.3 mg, 0.4 mmol in 2.0 mL toluene) were added successively, and the mixture was stirred for 30 min. The reaction was quenched by the addition of 1 M hydrochloric acid (4 mL) and was then made alkaline by addition of saturated aq NaHCO$_3$ (12 mL). The mixture was filtrated using Celite, and the filtrate was extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate and evaporated under reduced pressure. Purification of the residue by silica gel thin-layer chromatography (developing solvent, hexane:ethyl acetate = 2:1, v/v) gave pyrimidyl alkanol **2**.

In summary, we have demonstrated a highly enantioselective asymmetric autocatalysis in the presence of chiral organic–inorganic hybrid materials. 5-Pyrimidyl alkanol **2** with up to 96% ee was obtained with the absolute configuration corresponding to that of the hybrid material **3** used as a chiral initiator.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from The Ministry of Education, Culture, Science and Technology.

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10. General method for the preparation of hybrid materials **3b** and **3c** is as follows (Scheme 2): The molecular precursor (*R*,*R*)-**4**[7a] (609 mg, 1.0 mmol) and Si(OEt)$_4$ (208 mg, 1.0 mmol or 416 mg, 2.0 mmol) were dissolved in EtOH (3.0 mL). After H$_2$O (7.5 mL) and 3 M aq NaOH (50 μL) was added, the reaction mixture was refluxed for 6 d. The resulting colourless solid was filtered and washed successively with water, EtOH and acetone. After drying at 110 °C for 6 h, white powder (*R*,*R*)-**3b** (410 mg, 92%) and (*R*,*R*)-**3c** (507 mg, quant.) were obtained, respectively. (*R*,*R*)-**3b**: IR (KBr): *v* = 1562, 1651, 3351, (*S*,*S*)-**3b**: IR (KBr): *v* = 1562, 1651, 3359. (*R*,*R*)-**3c**: IR (KBr): *v* = 1558, 1647, 3336, (*S*,*S*)-**3c**: IR (KBr): *v* = 1566, 1651, 3332.
11. The organic molecular precursor **4** acts as a comparable chiral initiator to organic–inorganic hybrid silsesquioxane **3**. Chiral (*R*,*R*)-**4** acts as a chiral initiator in the enantioselective addition of *i*-Pr$_2$Zn to pyrimidine-5-carbaldehyde **1** to afford (*R*)-pyrimidyl alkanol **2** with 80–95% ee in 75–85% yield, while (*S*,*S*)-**4** gave (*S*)-**2** with 80–92% ee in 81–86% yield.