Pergamon

Tetrahedron Letters, Vol. 35, No. 29, pp. 5243-5246, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 \$7.00+0.00

0040-4039(94)01068-4

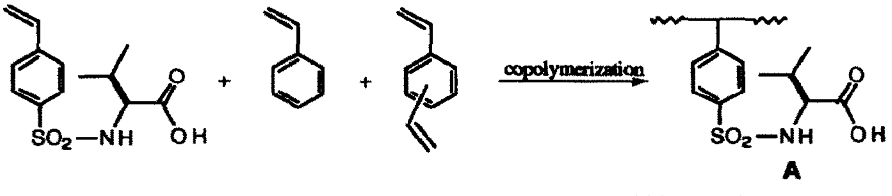
Polymer-supported Chiral Borane Promoters for the Asymmetric Aldol Reaction of Benzaldehyde with Silyl Ketene Acetal

Syun-ichi Kiyooka,* Yuichi Kido, and Yuichi Kaneko

Department of Chemistry, Kochi University, Akebono-cho, Kochi 780, Japan

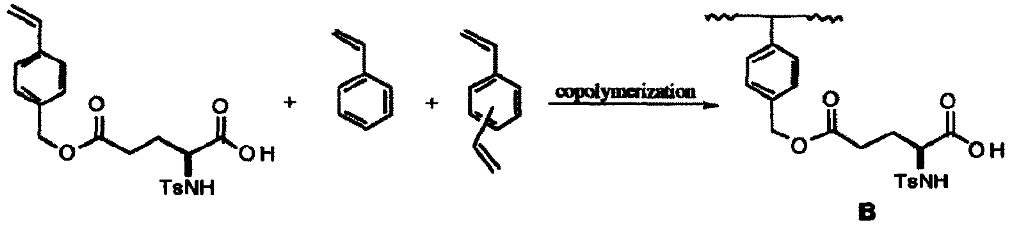
Abstract: Chiral polymers (A and B) having pendant α-amino acid moiety were prepared by suspension copolymerization. A polymer-supported chiral borane, formed from chiral polymer A and BH_3·THF, effectively promoted the aldol reaction in THF of benzaldehyde with silyl ketene acetal in a similar enantioselectivity to that using the corresponding soluble counterpart. Some interesting *polymer effects* were also found on solvent and reaction temperature.

In the last several years asymmetric Mukaiyama-aldol reactions have attracted much attention of synthetic chemists.[1,2] A chiral borane reagent, obtained *in situ* from the sulfonamide of (*S*)-valine and BH_3·THF, promoted one of the reactions with highly enantiomeric excess.[3] In the course of the studies we have encountered an incomprehensive fact that the addition of considerable amounts of BF_3 to the reaction system does not affect the enantioselectivity in spite of its strong Lewis acidity.[4] It presumably attributes to an aggregation-dissociation phenomenon of the chiral borane complex in solvent.[5] This observation persuaded us to investigate a system, forcedly separating chiral active sites to each other. One choice of resolving such a problem seems to be the use of chiral polymer-supported Lewis acids (POSULA). A variety of functional polymers are well-known to be important not only for separations but also for syntheses.[6] Chiral polymer-supported catalysts have, further, been expected for asymmetric syntheses in differing from the corresponding low-molecular-weight reaction systems.[7]



A

(1)



B

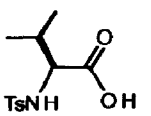
(2)

Table I. Aldol Reactions of Benzaldehyde with Silyl Ketene Acetal in the Presence of Polymer-supported Chiral Boranes and the Corresponding Monomeric Ones (eq.3)

Entry	Chiral Ligand (mmol / g)[a]		Conditions[b]		Product 3[c]	Product 4[c]
			Solvent	Temp.	Yield / %	(ee / %)
1	**A**	(0.69)	CH_2Cl_2	-78 °C	68 (63)	13 (26)
2	**A**	(0.72)	CH_2Cl_2	-78 °C	66 (54)	26 (34)
3	**A**	(0.92)	CH_2Cl_2	-78 °C	56 (44)	40 (30)
4	**A***[d]	(3.43)	CH_2Cl_2	-78 °C	25 (18)	75 (10)
5	Ts-Val[e]		CH_2Cl_2	-78 °C	60 (95)	24 (93)
6	**A**	(0.44)	THF	-78 °C	24 (58)	-[f]
7	**A**	(0.69)	THF	-78 °C	28 (76)	-[f]
8	**A**	(0.77)	THF[g]	-78 °C	28 (90)	-[f]
9	Ts-Val[e]		THF	-78 °C	72 (90)	-[f]
10	**A**	(0.77)	THF[g]	-10 °C	70 (69)	-[f]
11	**B**	(0.83)	CH_2Cl_2	-78 °C	32 (23)	29 (8)
12	Ts-Glu[h]		CH_2Cl_2	-78 °C	70 (74)	25 (70)
13	**B**	(0.83)	THF	-78 °C	10 (52)	-[f]
14	**B**	(0.83)	THF	-10 °C	40 (67)	-[f]

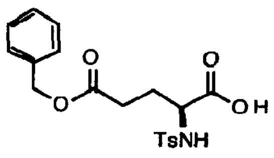
[a] Mmol values of amino acid residue per 1 g of polymer, determined by CHN elementary analyses. [b] All reactions were carried out in the presence of a stoichiometric amount of borane promoters (see note 11). [c] Isolated yields and % ee determined by HPLC using a chiral Daicel OD column (Absolute configuration of the product is *R*). [d] A* polymer prepared from only chiral monomer 1. [f] A trace amount of 4 obtained. [g] Solvent (15 ml) used.

[e]



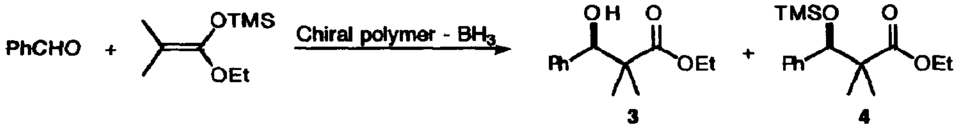
Ts-Val

[h]



Ts-Glu

Chiral monomer **1** was copolymerized by suspension technique with styrene using divinylbenzene (DVB) as a cross-linking agent to obtain chiral polymer **A** (eq. 1).[8] The content of functionalization in the polymer, which was determined with elementary analyses and IR spectra, could be controlled by varying the starting molar ratios of **1**, styrene, and DVB.[9] Chiral polymer **B** was prepared, in a similar manner, with chiral monomer **2** derived *via* several steps from (*S*)-glutamic acid (eq. 2).[10]



(3)

A variety of the chiral polymers obtained were evaluated on the effectiveness toward asymmetric Mukaiyama-aldol reactions by using the typical reaction of benzaldehyde with 1-(trimethylsiloxy)-1-ethoxy-2-methyl-1-propene, as shown in eq. 3. All reactions were carried out in the presence of a stoichiometric amount of chiral borane promoters because the rate of reaction using the polymer promoters turned out to be considerably slow.[11] The recovered chiral copolymers could be recycled several times without reducing the enantioselectivity. The results are summerized in Table 1. The reaction using **A** in CH_2Cl_2 gave a mixture, consisted of aldol **3** and TMS-protected aldol **4** (entries 1-3). By comparing with the high enantioselectivity (***R***) obtained by using the corresponding soluble promoter (entry 5), the % ee (***R***) of **3** is not necessarily satisfied and further the % ee of **4** is always prone to be lower than that of **3**. This suggests that the promoter possesses at least two different active sites. Solvent THF *dramatically* enhanced the enantioselectivity up to 90% ee (but in low yield) where the polymer promoter might be well-swollen with the solvent (entry 8). The yield was improved up to 70% at more elevated temperature (-10 °C) without an extreme drop of % ee (entry 10). In addition, an interesting *polymer effect*[12] that the more elevated temperature can achieve the higher enantioselectivity was observed in the reaction using chiral polymer **B** (entries 13 and 14). The difference on reaction temperature may arise because the polymer-bound intermediate at -10 °C is conformationally more adequate for the enantio-determining process than that at -78 °C.

Further studies on the development of chiral POSULA under catalytic conditions are being continued.

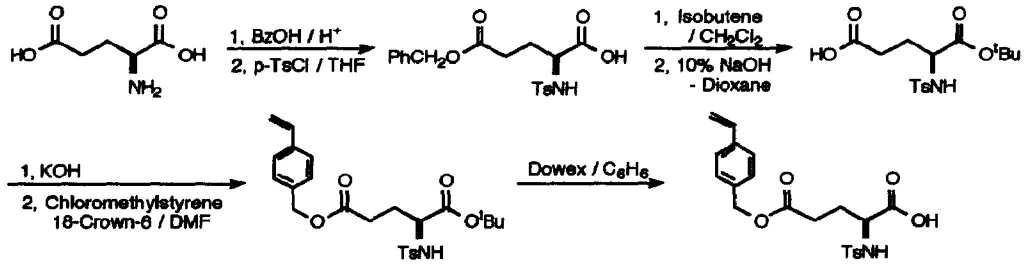
Acknowledgments: This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas of Asymmetric Synthesis (No. 5234221) and a Grant-in-Aid for Encouragement of Young Scientists (No. 5740397) from the Ministry of Education, Science and Culture, Japan, which are gratefully acknowledged.

References and Notes

1. Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247, and references cited therein.
2. Furuta, K.; Maruyama, T.; Yamamoto, H. *Synlett* **1991**, 439; Furuta. K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041.
3. (a) Kiyooka, S.-i.; Kaneko, Y.; Komura, M.; Matsuo, H.; Makano, M. *J. Org. Chem.* **1991**, *56*, 2276; Kiyooka, S.-i.; Kaneko, Y.; Kume, K. *Tetrahedron Lett.* **1992**, *33*, 4927; Kaneko, Y; Kiyooka, S.-i. *Mem.*

Fac. Sci., Kochi Univ. Ser. C **1994**, *15*, 9. (b) Parmee, E. R.; Tempkin, O.; Masamune, S.; Abiko, A. *J. Am. Chem. Soc.* **1991**, *113*, 9365. (c) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907.

4. Kiyooka, S.-i.; Yamamoto, T. unpublished results (1991).
5. Such an aggregation phenomenon has been pointed out by Helmchen from solvent effects on the Diels-Alder reaction using the same borane complex; Sartor, D.; Saffrich, J.; Helmchen, G.; Richards, C. J.; Lambert, H. *Tetrahedron: Asymmetry* **1991**, *2*, 639.
6. Sherrington, D. C.; Hodge, P. *Syntheses and Separations using functional polymers*; John Wiley and Sons: Chichester, 1988.
7. (a) Parrinello, G.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 7122. (b) Soai, K.; Niwa, S.; Watanabe, M. *J. Chem. Soc. Perkin Trans. I* **1989**, 109. (c) Yamashita, T.; Yasueda, H.; Miyauchi, Y.; Nakamura, N. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1532. (d) Itsuno, S.; Nakano, M.; Ito, K.; Hirao, A.; Owa, M.; Kanda, N.; Nakahama, S. *J. Chem. Soc. Perkin trans. I* **1985**, 2615.
8. A paper on Diels-Alder reaction with a similar chiral polymer A has been presented by Itsuno (Toyohashi) at the 66th annual meeting of the chemical society of Japan, Nishinomiya, September, 1993; Symposium Abstract p. 439.
9. Polymerization with chiral monomer, styrene, and DVB (1 : 16 : 1 - 1 : 4 : 1) in water in the presence of a small amount of polyvinylalcohol. The reaction mixture with benzoyl peroxide was stirred overnight at 90 °C (bath temperature). After drying, a variety of chiral polymers having different contents of amino acid moiety were obtained.
10.



11. The typical procedure is as follows; To a suspension of chiral copolymer (0.25 mmol) in solvent (3 ml) was added BH_3·THF (1M solution in THF) (0.2 mmol) over 5 min at room temperature under argon atmosphere. After stirring for additional 1 h at the temperature, benzaldehyde (0.2 mmol) in solvent (0.5 ml) and silyl ketene acetal (0.25 mmol) in solvent (0.5 ml) were successively added at -78 °C and stirred for 3 h. The reaction mixture was quenched by the introduction of buffer solution (pH 6.8) and the polymer was filtered off. After usual workup procedure, crude products were obtained. After flash column chromatography, the % yield and % ee of the pure products were determined. The recovered chiral copolymers could be recycled successfully after drying.
12. Soai, K.; Suzuki, T.; Shono, T. *J. Chem. Soc., Chem. Commun.* **1994**, 317.

(*Received in Japan* 8 *April* 1994; *accepted* 21 *May* 1994)