STUDIES ON NOVEL AND CHIRAL 1,4-DIHYDROPYRIDINES. VI.[1] PREPARATION OF A POLYMER-SUPPORTED 1,4-DIHYDROPYRIDINE HAVING A CHIRAL SULFINYL GROUP AND ITS APPLICATION TO BIOMIMETIC REDUCTION*

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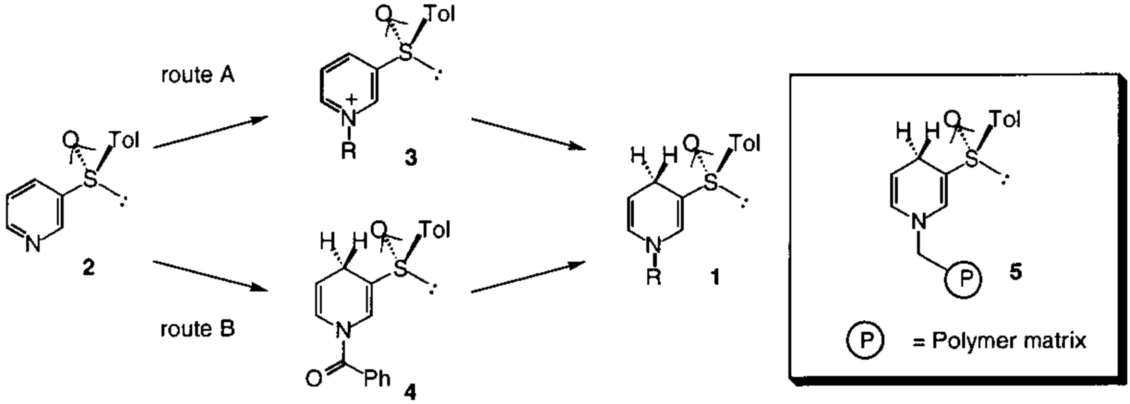
Abstract - (S_S)-3-(*p*-Tolylsulfinyl)-1,4-dihydropyridine was grafted on polymer matrix at N-1 position by the reaction between (S_S)-1-lithio-3-(*p*-tolylsulfinyl)-1,4-dihydropyridine and Merrifield type resin. Asymmetric reduction with the polymer-supported 1,4-dihydropyridine was also studied.

NADH is widely distributed and functions as a cofactor for enzymatic redox reactions in biological systems. Since Ohno and co-workers reported the first example of asymmetric reduction of a ketone with a chiral NADH model compound,[2] a number of such asymmetric reductions have been reported.[3] However the catalytic process by such a NADH model compound has not been achieved. In contrast, syntheses and applications of polymer-supported NADH model compounds have been reported by some groups.[4-14] As is generally known,[15] these polymer-supported reaction systems enable the separation of the reaction product and recovery of the pyridinium salt more easily and, eventually, make the model



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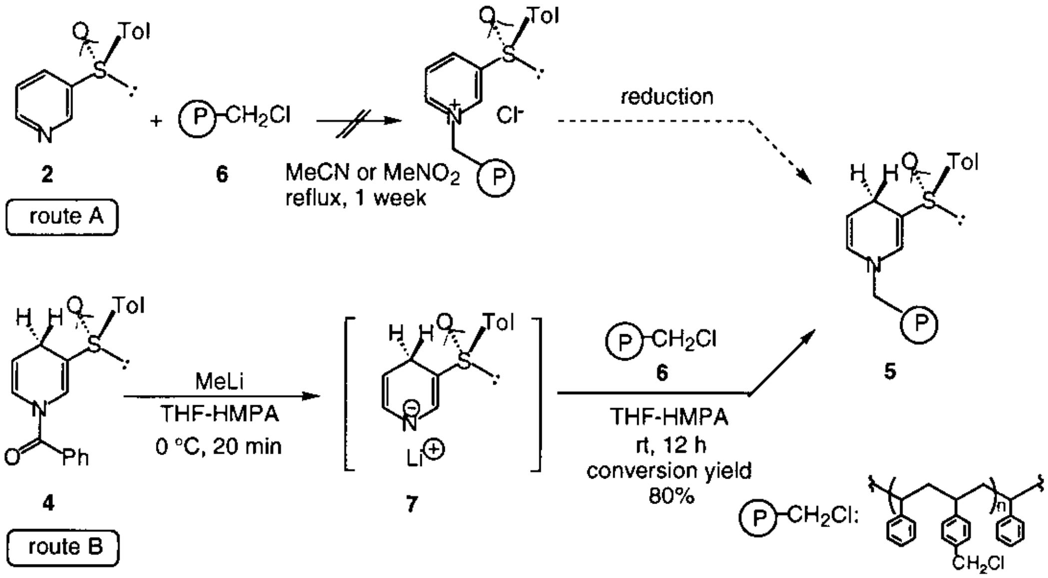
* *This paper is dedicated to Dr. Bernhard Witkop on the occasion of his 80th birthday.*

compounds reusable by combination with proper reduction. These polymer-supported reaction systems are not a catalytic system, but would make the NADH model compound more practical and potent asymmetric reducing agent. In the previous papers, we reported the synthesis of novel chiral NADH model compounds, (S_S)-1-alkyl-3-(*p*-tolylsulfinyl)-1,4-dihydropyridines (**1**) *via* quaternization of pyridine derivative (**2**) followed by 1,4-reduction of pyridinium salts (**3**) (route A), and the successful application to asymmetric reduction of some ketones with **1**.[16,17] Recently, we also demonstrated the efficient method for synthesis of various 1-substituted 1,4-dihydropyridines (**1**) *via* 1-benzoyl derivative (**4**) (route B).[18]

In this paper, we wish to describe the efficient method for the synthesis of polymer-supported 1,4-dihydropyridine (**5**) with a chiral *p*-tolylsulfinyl group at the C-3 position, and the asymmetric reduction of methyl benzoylformate with **5**.

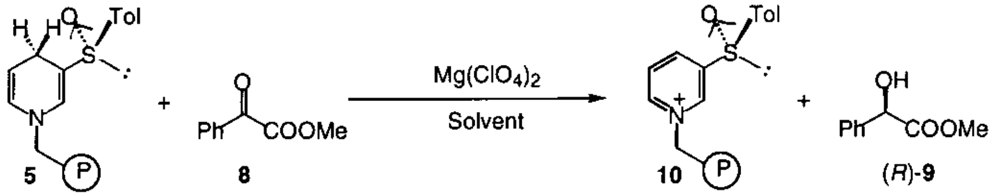
As a polymeric matrix for the synthesis of **5**, we selected a Merrifield type resin which is commercially available and is widely employed for the solid-support synthesis of peptides. Firstly, we examined the quaternization reaction (route A) by treatment of the pyridine derivative (**2**)[16] with the Merrifield type resin (**6**) in refluxing acetonitrile or nitromethane for 1 week, however the attempt was in failure to recover the pyridine derivative (**2**) quantitatively (Scheme 1). In contrast, the reaction of the 1-lithio intermediate (**7**) with the Merrifield type resin (**6**) successfully proceeded (route B). The 1-benzoyl-1,4-dihydropyridine (**4**)[18] was treated with 2 equiv. of methyllithium in THF-HMPA at 0 °C to afford the corresponding 1-lithio intermediate (**7**). Without isolation, the 1-lithio intermediate (**7**) was treated with the resin (**6**) for 12 hours to give the polymer-supported NADH model (**5**). The conversion yield was calculated to be 80% by elementary analysis of **5**.

Scheme 1



Next, the reductions of methyl benzoylformate (**8**) with polymer-supported NADH model compound (**5**) were tried under several conditions (Table 1). In the typical condition of reduction with NADH models, acetonitrile (MeCN) was most widely used as a solvent, so we examined the reduction of **8** with **5** in MeCN (Run 1). Although the optical yield of the obtained alcohol (**9**) was excellent, the reaction in MeCN needed very long time and the chemical yield was moderate. In addition, the reactions neither in the absence of Mg^{2+} nor in H_2O proceeded (Runs 2 and 3). Bourguignon and co-workers demonstrated the low reactivity of polymer-supported NADH models in MeCN which did not swell the polymer to prevent the interaction between the 1,4-dihydropyridine moiety grafted on the polymer and substrates, and they also reported that the addition of benzene as a swelling cosolvent was quite effective.[12] So we examined the effect of benzene as a cosolvent and found that the addition of benzene brought about a considerable acceleration effect of the reaction (Run 4). From these results, a MeCN-benzene (1:1) system was used for the following reaction. On the other hand, the chemical yield of the methyl mandelate (**9**) was increased without decrement of the optical yield with increasing both equivalents of **5** and $Mg(ClO_4)_2$ (Runs 4-7). When 2.5 equivalent of **5** and $Mg(ClO_4)_2$ were used, methyl mandelate (**9**) was obtained in quantitative yield and in excellent optical yield, and the remaining reagent **5** and **10** were easily separated by filtration.

Table 1. Asymmetric reduction of methyl benzoylformate (**8**) with polymer-supported NADH model compound (**5**)

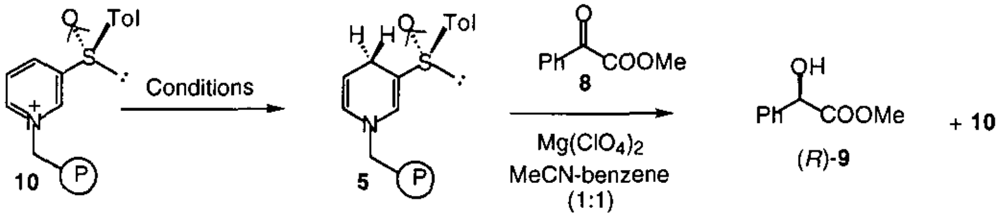


Run	Equivalent of 5	Equivalent of $Mg(ClO_4)_2$	Solvent	Reaction Time	Chemical Yield[a] %	Optical Yield[b] % *ee*
1	1.0	1.0	MeCN	24 d	43	≥ 96
2	1.0	0	MeCN	28 d	0	—
3	1.0	1.0	H_2O	29 d	0	—
4	1.0	1.0	MeCN-benzene (1:1)	5 d	54	≥ 96
5	1.5	1.5	MeCN-benzene (1:1)	4 d	69	≥ 96
6	2.0	2.0	MeCN-benzene (1:1)	4 d	78	≥ 96
7	2.5	2.5	MeCN-benzene (1:1)	12 h	100	≥ 96

a. Isolated yield based on **8**. *b*. Based on the specific rotation of pure methyl (*R*)-mandelate, $[\alpha]_D$ -144.0 ° (*c* 1.0 in MeOH).

The oxidized NADH model compound (**10**) was tried to regenerate by treatment with some reducing agents. After treatment of **10** with reducing agents, the polymer was washed with THF, THF-H_2O, THF and MeOH, and then dried. Methyl benzoylformate (**8**) was reduced by 1 equivalent of the obtained polymer in the presence of 1 equivalent of $Mg(ClO_4)_2$ so as to determine the regeneration efficiency of **5**. As shown in Table 2, the reducing agents most commonly used for 1,4-reduction of pyridinium salts, $Na_2S_2O_4$ and $NaBH_3CN$, were not suitable for reduction of **10** (Runs 1 and 2). On the contrary, 1-propyl-1,4-dihydronicotinamide[19,20] (PNAH) was advantageous for the purpose (Run 3). The polymer (**5**) regenerated by PNAH was able to reduce methyl benzoylformate (**8**) in 47% yield and in above 96% *ee*, which indicates that the regeneration efficiency of this recycle process was *ca.* 87%, considering that ketone (**8**) was reduced by 1 equivalent of freshly prepared **5** in 54% yield (Table 1, Run 4).

Table 2. Regeneration of **5** *via* the 1,4-reduction of **10**.



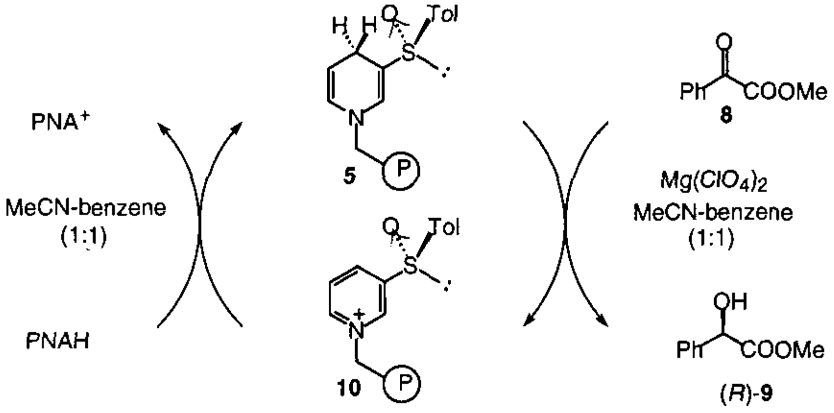
Run	Conditions	Chemical Yield[a] %	Optical Yield[b] % *ee*
1	$Na_2S_2O_4/H_2O$	0	—
2	$NaBH_3CN$/EtOH-benzene (1:1)	14	≥ 96
3	PNAH/MeCN-benzene (1:1)	47	≥ 96

a, b. See footnote in Table 1.

At last, we examined reactivity of the polymer-supported NADH model (**5**) recycled several times by PNAH treatment (Table 3). Methyl benzoylformate (**8**) was treated with both 2.5 equivalents of **5** and $Mg(ClO_4)_2$ and then consumed, and the remaining reagent was separated by filtration. The recovered polymer was regenerated by a treatment with PNAH and re-used for the reduction of ketone (**8**). This cycle was repeated 4 times. Although small drop in chemical yield of **9** was observed, the optical yield was maintained above 96% *ee* through these reduction-regeneration cycles.

In conclusion the polymer-supported NADH model compound (**5**) having a chiral sulfinyl group was effectively synthesized by using (S_S)-1-lithio-3-(*p*-tolylsulfinyl)-1,4-dihydropyridine (**6**). By using **5**, the asymmetric reduction of benzoylformate (**8**) was successfully achieved above 96% *ee*, which was the most effective result among the asymmetric reductions with the polymer-supported NADH models reported to date. Moreover, the NADH model (5) was able to be regenerated by a treatment of PNAH.

Table 3. Asymmetric reduction of **8** with regenerated **5**.



Reduction Cycle	Chemical Yield[a] %	Optical Yield[b] %*ee*
1st	100	≥ 96
2nd	98	≥ 96
3rd	75	≥ 96
4th	71	≥ 96

a, b. See footnote in Table 1.

EXPERIMENTAL SECTION

All melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian VXR-200 (200 MHz), JEOL EX-270 (270 MHz) or JEOL GX-500 (500 MHz) spectrometer with tetramethylsilane (TMS) as an internal standard. $[\alpha]_D$ Values were recorded on a JASCO DIP-370 instrument. For column chromatography, Merck Kieselgel 60 (0.063-0.200 mm) was used. Merrifield type resin (**6**) was purchased from Nacalai Tesque, Inc. and methyl benzoylformate (**8**) was purchased from Tokyo Kasei Kogyo Co., Ltd.

Polymer-supported NADH model compound (5). To a solution of **4**[18] (1.60 g, 4.95 mmol) in dry THF (40 mL) were added HMPA (1.9 mL, 10.9 mmol) and MeLi (1.14 M in THF, 9.6 mL, 10.9 mmol) under an argon atmosphere at 0°C. After stirring was continued for 20 min in the dark, the reaction mixture was added to the suspension of Merrifield type resin (**6**) (2.8 g, the chlorine content was 0.89 mmol/g resin; cross-linking was insured by 2% of divinylbenzene) in dry THF (4 mL)-HMPA (1.0 mL, 5.7 mmol). The solvent was reduced to half under vacuum, and stirring was continued for 8 h. Water (10 mL) was added and the reaction mixture was stirred for 10 min and the polymer was filtered. The residue was washed successively with THF (30 mL x 5), THF-H_2O (1:1, 30 mL x 5), THF-1% aq. H_2SO_4 (1:1, 30 mL x 10), THF-H_2O (1:1, 30 mL x 10), THF (30 mL x 5) and MeOH (30 mL x 10) and dried under reduced pressure to give **5**. The nitrogen content of resin **5** was determined to be 0.62 mmol/g by elementary analysis. *Anal.* Found: C, 86.14; H, 7.38; N, 0.87.

Typical procedure for the asymmetric reduction of methyl benzoylformate (8) with polymer-supported NADH model compound (5). To a suspension of **5** (300 mg, 0.19 mmol) in anhydrous MeCN-benzene (1:1, 3 mL) were added **8** (31 mg, 0.19 mmol) and $Mg(ClO_4)_2$ (42 mg, 0.19 mmol) under an argon atmosphere. The whole mixture was stirred at 30 °C under dark for 5 days. After addition of a small amount of 28% aq. NH_4Cl, the polymer was filtered and washed successively with THF-H_2O (1:1, 30 mL x 10), THF (30 mL x 10) and MeOH (30 mL x 10). The filtrate was concentrated and diluted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by SiO_2 column chromatography (hexane-AcOEt, 3:1) to afford **9** (17 mg, 54%). The product **9** was identified by comparison with the spectroscopic data described in the reference and gave satisfactory physical data as shown below.

9: Colorless needles, mp 52-54 °C. $[\alpha]_D^{25}$ -139.1 ° (*c* 1.1 in MeOH). ^{1}H-NMR ($CDCl_3$) δ: 3.47 (1H, d, *J* = 5 Hz), 3.76 (3H, s), 5.18 (1H, d, *J* = 5 Hz), 7.33-7.43 (5H, m). [lit.,[21] mp 56-58 °C. $[\alpha]_D^{21}$ -144.0 ° (*c* 1.0 in MeOH)].

Regeneration of 5 from 10. To a suspension of **10** (1.47 g, 0.91 mmol) in anhydrous MeCN-benzene (1:1, 8 mL) were added a solution of PNAH (400 mg, 2.04 mmol) under an argon atmosphere. The whole mixture was stirred at 30 °C under dark for 2 days and then filtered. The polymer was washed successively with THF (30 mL x 5), THF-H_2O (1:1, 30 mL x 10), THF (30 mL x 5) and MeOH (30 mL x 10) and dried under reduced pressure to give **5** .

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