

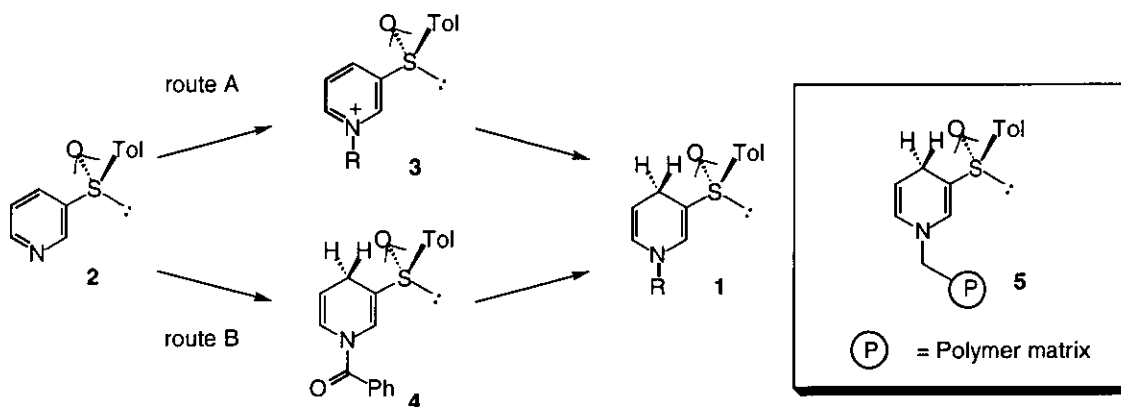
STUDIES ON NOVEL AND CHIRAL 1,4-DIHYDROPYRIDINES. VI.¹ PREPARATION OF A POLYMER-SUPPORTED 1,4-DIHYDRO- PYRIDINE HAVING A CHIRAL SULFINYL GROUP AND ITS APPLICATION TO BIOMIMETIC REDUCTION*

Satoshi Obika, Toshihiko Nishiyama, Satoshi Tatematsu, Masahiro Nishimoto,
Kazuyuki Miyashita, and Takeshi Imanishi*

*Graduate School of Pharmaceutical Sciences, Osaka University
1-6 Yamadaoka, Suita, Osaka 565-0871, Japan*

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



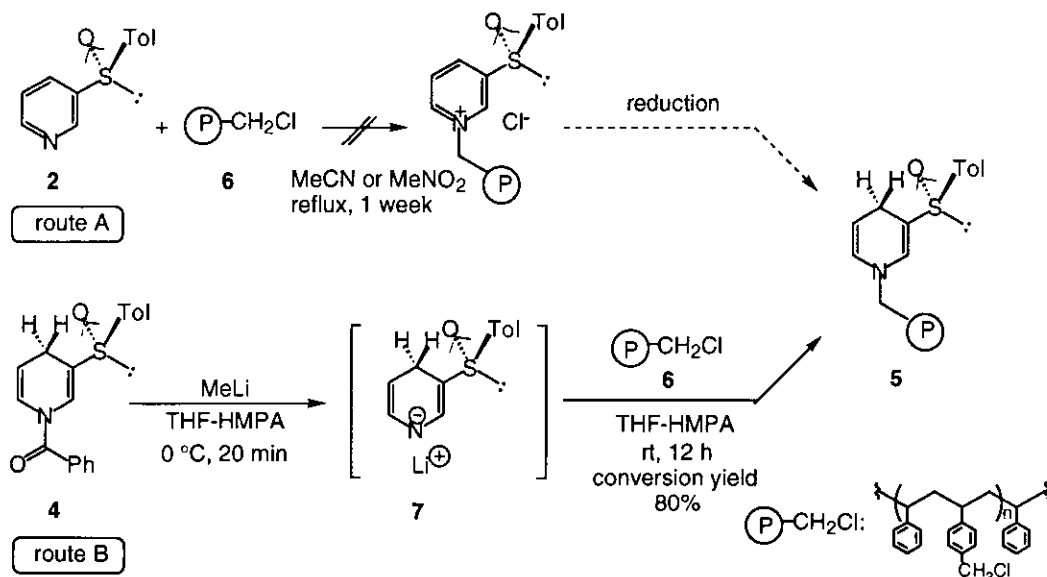
* This paper is dedicated to Dr. Bernhard Witkop on the occasion of his 80th birthday.

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**.

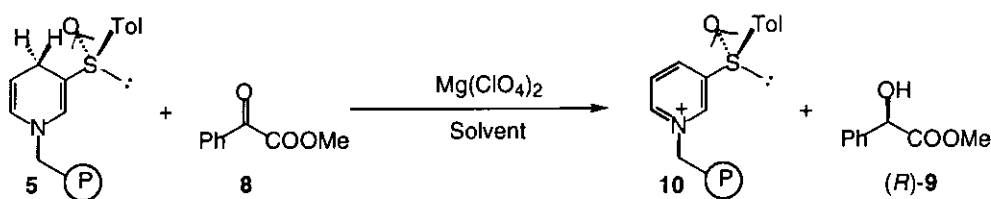
As a polymeric matrix for the synthesis of **5**, we selected a Merrifield type resin which is commercially available and is widely employed for the solid-support synthesis of peptides. Firstly, we examined the quaternization reaction (route A) by treatment of the pyridine derivative (**2**)¹⁶ with the 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 $\text{Mg}(\text{ClO}_4)_2$ (Runs 4-7). When 2.5 equivalent of **5** and $\text{Mg}(\text{ClO}_4)_2$ 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**)

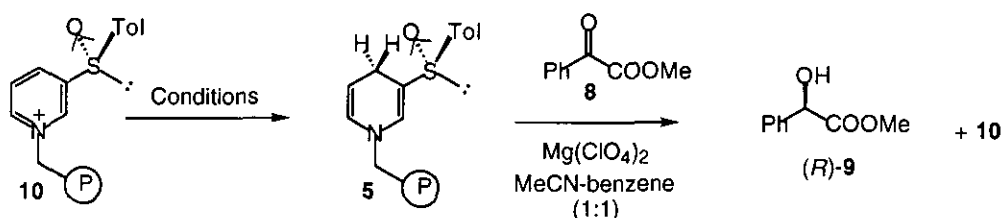


Run	Equivalent of 5	Equivalent of $\text{Mg}(\text{ClO}_4)_2$	Solvent	Reaction Time	Chemical Yield ^a %	Optical Yield ^b % ee
1	1.0	1.0	MeCN	24 d	43	≥ 96
2	1.0	0	MeCN	28 d	0	—
3	1.0	1.0	H_2O	29 d	0	—
4	1.0	1.0	MeCN-benzene (1:1)	5 d	54	≥ 96
5	1.5	1.5	MeCN-benzene (1:1)	4 d	69	≥ 96
6	2.0	2.0	MeCN-benzene (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, $[\alpha]_D -144.0^\circ$ (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-H₂O, 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(ClO₄)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, Na₂S₂O₄ and NaBH₃CN, 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 % <i>ee</i>
1	Na ₂ S ₂ O ₄ /H ₂ O	0	—
2	NaBH ₃ CN/EtOH-benzene (1:1)	14	≥ 96
3	PNAH/MeCN-benzene (1:1)	47	≥ 96

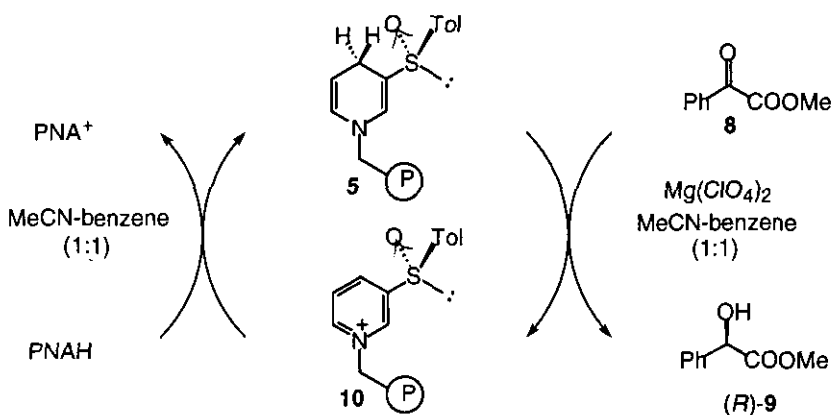
a. b. See footnote in Table 1.

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(ClO₄)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. ¹H-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. [α]_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-H₂O (1:1, 30 mL x 5), THF-1% aq. H₂SO₄ (1:1, 30 mL x 10), THF-H₂O (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(ClO₄)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. NH₄Cl, the polymer was filtered and washed successively with THF-H₂O (1:1, 30 mL x 10), THF (30 mL x 10) and MeOH (30 mL x 10). The filtrate was concentrated and diluted with CH₂Cl₂. The organic layer was washed with H₂O and brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by SiO₂ 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). ¹H-NMR (CDCl₃) 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-H₂O (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**.

ACKNOWLEDGMENT

A part of this work was supported by a Grant-in-Aid for Scientific Research, No. 05771927, from the Ministry of Education, Science, Sports and Culture, Japan. We are also grateful to HOUANSHA for a financial support.

REFERENCES

1. For Part V: K. Miyashita, M. Nishimoto, T. Ishino, H. Murafuji, S. Obika, O. Muraoka, and T. Imanishi, *Tetrahedron*, 1997, **53**, 4279.
2. Y. Ohnishi, M. Kagami, and A. Ohno, *J. Am. Chem. Soc.*, 1975, **97**, 4766.

3. For reviews: Y. Inouye, J. Oda, and N. Baba, 'Asymmetric Synthesis,' Vol. 2, ed. by J. D. Morrison, Academic Press, Inc., New York, 1983, pp. 91-124; V. A. Burgess, S. G. Davies, and R. T. Skerlj, *Tetrahedron Asymmetry*, 1991, **2**, 299; G. Dupas, V. Levacher, J. Bourguignon, G. Quéguiner, *Heterocycles*, 1994, **39**, 405; Recent papers: C. Leroy, V. Levacher, G. Dupas, G. Quéguiner, and J. Bourguignon, *Tetrahedron: Asymmetry*, 1997, **8**, 3309; N. Kanomata and T. Nakata, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1207; V. Levacher, C. Valque, S. Coupa, G. Dupas, G. Quéguiner, and J. Bourguignon, *J. Heterocycl. Chem.*, 1996, **33**, 1211; X. Li and D. D. Tanner, *Tetrahedron Lett.*, 1996, **37**, 3275; J. Bedat, V. Levacher, G. Dupas, G. Quéguiner, and J. Bourguignon, *Chem. Lett.*, 1996, **5**, 359.
4. U. K. Pandit, R. A. Gase, F. R. Mas Cabre, and V. Den Breejen-Metz, *Recl. Trav. Chim. Pays Bas*, 1977, **96**, 215.
5. R. Mathis, G. Dupas, A. Decormeille, and G. Quéguiner, *Tetrahedron Lett.*, 1981, **22**, 59.
6. S. Shinkai, H. Tsuji, T. Sone, and O. Manabe, *J. Polym. Sci., Polym. Lett. Ed.*, 1981, **19**, 17.
7. G. Dupas, J. Bourguignon, C. Ruffin, and G. Quéguiner, *Tetrahedron Lett.*, 1982, **23**, 5141.
8. B. Eling, G. Challa, and U. K. Pandit, *J. Polym. Sci., Polym. Chem. Ed.*, 1983, **21**, 1125.
9. B. Eling, G. Challa, and U. K. Pandit, *J. Polym. Sci., Polym. Chem. Ed.*, 1985, **23**, 2165.
10. T. Trefouel, P. Tintillier, G. Dupas, J. Bourguignon, and G. Quéguiner, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 4492.
11. S. Zehani and G. Gelbard, *React. Polym., Ion Exch., Sorbents*, 1987, **6**, 81.
12. G. Dupas, A. Decormeille, J. Bourguignon, and G. Quéguiner, *Tetrahedron*, 1989, **45**, 2579.
13. D. Losset, G. Dupas, J. Bourguignon, and G. Quéguiner, *Polym. Bull.*, 1989, **21**, 649.
14. D. Losset, G. Dupas, J. Duflos, J. Bourguignon, and G. Quéguiner, *Bull. Soc. Chim. Fr.*, 1991, 721.
15. P. Hodge and D. C. Sherrington (ed.), 'Polymer-supported Reactions in Organic Synthesis,' John Wiley & Sons, Ltd., New York, 1980.
16. T. Imanishi, Y. Hamano, H. Yoshikawa, and C. Iwata, *J. Chem. Soc., Chem. Commun.*, 1988, 473; T. Imanishi, S. Obika, T. Nishiyama, M. Nishimoto, Y. Hamano, K. Miyashita, and C. Iwata, *Chem. Pharm. Bull.*, 1996, **44**, 267.
17. S. Obika, T. Nishiyama, S. Tatematsu, K. Miyashita, C. Iwata, and T. Imanishi, *Tetrahedron*, 1997, **53**, 593.
18. S. Obika, T. Nishiyama, S. Tatematsu, M. Nishimoto, K. Miyashita, and T. Imanishi, *Heterocycles*, 1997, **44**, 537.
19. A. G. Anderson, Jr. and G. Berkelhammer, *J. Am. Chem. Soc.*, 1958, **80**, 992.
20. S. Obika, T. Nishiyama, S. Tatematsu, K. Miyashita, and T. Imanishi, *Chem. Lett.*, 1996, 853; S. Obika, T. Nishiyama, S. Tatematsu, K. Miyashita, and T. Imanishi, *Tetrahedron*, 1997, **53**, 3073.
21. Catalog Handbook of Fine Chemicals, 1994-1995, Aldrich Chemical Company, Inc.