DOI: 10.1002/ejoc.201000981

A New Non-Cross-Linked Polystyrene Supported 2-Phenylimino-2-oxazolidine Chiral Auxiliary: Synthesis and Application in Asymmetric Alkylation Reactions

Fu-Qiang Hu,[a] De-Xin Xia,[a] Cui-Fen Lu,[a] Zu-Xing Chen,[a] and Gui-Chun Yang*[a]

Keywords: Chiral auxiliaries / Heterocycles / Asymmetric synthesis / Alkylation / Amides

The synthesis of novel non-cross-linked polystyrene supported 2-phenylimino-2-oxazolidine is described, and its use as a chiral auxiliary in asymmetric alkylation reactions is demonstrated by the synthesis of several chiral amides (>96 % *ee*). Furthermore, recovery and recycling of the polymer-supported chiral auxiliary were successfully achieved without appreciable reduction in the yield or stereoselectivity.

Introduction

Chiral auxiliary derived asymmetric alkylation reactions have been studied extensively and are now important and useful methods for asymmetric carbon–carbon bond formation.[1] Within this area, the oxazolidinones, so called Evans' auxiliary,[2] are arguably the most successful of the chiral auxiliary systems currently available for asymmetric transformations based on acyl group reactivity.[3] However, this auxiliary undergoes endocyclic cleavage rather than the required exocyclic cleavage in the removal of the auxiliary with alkaline hydrolysis.[4] The thiazolidinethione chiral auxiliary,[5] which has been utilized in a wide variety of synthetic transformations such as asymmetric aldol condensations,[6,7] is also useful for the formation of asymmetric carbon–carbon bonds. Recently, a new class of chiral auxiliary, 2-phenylimino-2-oxazolidine, has been developed.[8] This improved auxiliary provides superior performance to many other chiral auxiliaries currently in common usage and has been proved to be particularly efficient in terms of stereoselectivity and yields in asymmetric alkylation reactions.[9,10] However, in most case, the expensive chiral auxiliaries could not be recovered after the reactions; to recycle these expensive materials, chiral auxiliaries have been supported onto polymers.[11–15]

Insoluble polymer supports, such as, Merrifield resin and Wang resin, only require simple "filtration" to achieve rapidly the isolation of desired compounds or to recover expensive reagents or catalysts attached onto solid supports for recycling.[12,13] However, several shortcomings were shown because of nonlinear kinetic behavior, unequal distribution or access to the chemical reaction, and synthetic difficulties in transferring standard organic reactions to the solid phase. Soluble polymer supports, which combine the superiorities of insoluble polymer supports with the advantages of classic liquid synthesis, have been extensively studied by chemists.[14] In previous reports, our group has undertaken a research program to develop several chiral auxiliaries by using non-cross-linked polystyrene (NCPS) as a support and to investigate their applications in asymmetric synthesis.[15] In this article, we wish to report the preparation of a new soluble NCPS supported 2-phenylimino-2-oxazolidine chiral auxiliary and the preliminary results of our investigations concerning the asymmetric alkylation reactions on this compound, and the potential for recycling of the chiral auxiliary.

Results and Discussion

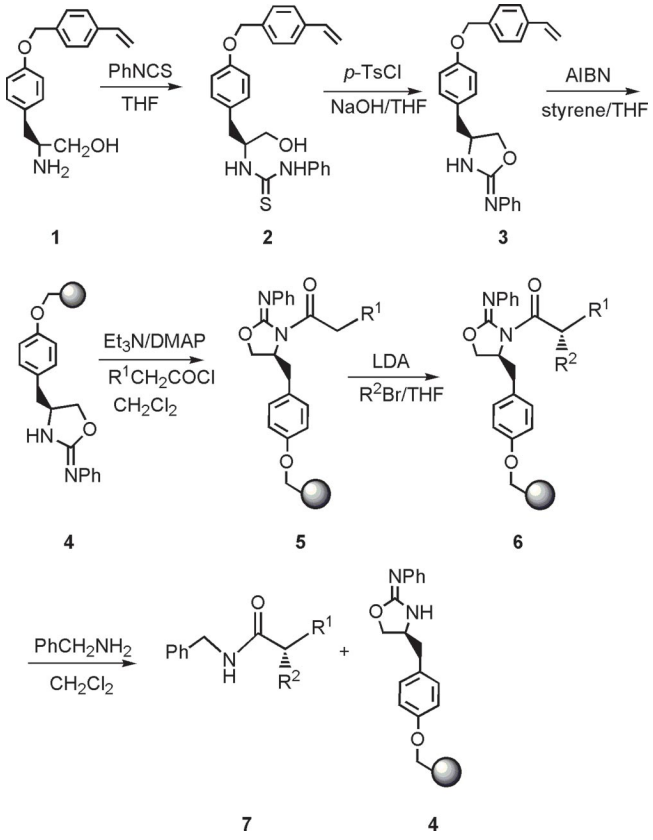
As is shown in Scheme 1, we used 2-[(*S*)-4-(4′-vinylbenzyloxy)benzyl]amino-1-ol (**1**) as starting material, which can be conveniently obtained from *N*-Boc-L-tyrosine ethyl ester.[16] Thiourea **2** was readily prepared from the reaction of **1** with phenyl isothiocyanate, and 2-phenylimino-2-oxazolidine **3** was easily obtained from the cyclization of thiourea **2** by using *p*-TsCl and NaOH. One of the remarkable features of chiral auxiliary **3** is that it has a styrene group, which is required to act as a "handle" for its coupling to a suitably functionalized polymer support.

NCPS-supported chiral auxiliary **4** was prepared by copolymerizing **3** and styrene in a ratio of 1:3, and it showed good solubility in solvents such as CH_2Cl_2, $CHCl_3$, and THF. The loading capacity (1.42 mmol g^{-1}) of chiral auxiliary **4** was analyzed by nitrogen elemental analysis.

To understand the efficacy of designed NCPS-supported **4** as a new chiral auxiliary, we first studied the asymmetric

[a] Ministry-of-Education Key Laboratory for the Synthesis and Application of Organic Functional Molecules & School of Chemistry and Chemical Engineering, Hubei University, Wuhan 430062, China
Fax: +86-27-88663043
E-mail: yangguichun@hubu.edu.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000981.



Scheme 1.

alkylation on this compound. Chiral auxiliary **4** was acylated with phenylacetyl chloride or propionyl chloride to give the corresponding acylated product **5** (Scheme 1). Formation of the lithium enolate at –78 °C by using LDA occurred in THF and then subsequent addition of the alkyl bromide led to the formation of alkylated products **6**. The identities of purified products **6** were determined by IR and ^{13}C NMR spectroscopic analyses. Treatment of alkylated products **6** with benzylamine yielded several chiral amides[16] **7a**–**f** in good yield as well as high optical purity (>96%*ee*; Table 1), which were analyzed by HPLC. A higher stereoselectivity was observed by using chiral auxiliary **4** instead of Merrifield resin supported Evans' chiral auxiliary,[13b] and the yield was found to be quite similar. In comparison to the related 2-phenylimino-2-oxazolidine chiral auxiliary, the stereoselectivity was similar to those reported for the model alkylation reactions under classical solution conditions.[9,10] These results show that NCPS-supported 2-phenylimino-2-oxazolidine chiral auxiliary **4** is an effective auxiliary for asymmetric alkylation reactions, and it can be recovered by simple filtration.

To further investigate the ability of recycling NCPS-supported **4**, recovered **4** was washed and dried and then subjected to *N*-acylation with phenylacetyl chloride and alkylation with benzyl bromide to give once again the corresponding alkylation product **6**. After the second to fourth asymmetric alkylation reactions, the desired chiral amides

Table 1. Results of asymmetric alkylation reactions.

Entry	Product	R^1	R^2	Yield [%][a]	*ee* [%][b]
1	**7a**	CH_3	$C_6H_5CH_2$	67	99
2	**7b**	CH_3	CH_2=$CHCH_2$	63	98
3	**7c**	CH_3	4-$NO_2C_6H_4CH_2$	65	96
4	**7d**	Ph	$C_6H_5CH_2$	68	99
5	**7e**	Ph	CH_2=$CHCH_2$	62	98
6	**7f**	Ph	4-$NO_2C_6H_4CH_2$	69	96

[a] Overall yield in three steps starting from **4** (see Scheme 1). [b] Determined by HPLC analysis.

were obtained in high stereoselectivity (99%*ee*; Table 2). Obviously, in these cycles, the stereoselectivity of the product was maintained successfully, although the yield decreased slightly in each cycle. The results show that the recovery of chiral auxiliary **4** was successful.

Table 2. Recycling of NCPS-supported chiral auxiliary **4** in asymmetric alkylation reactions.

Cycle	Yield [%][a]	*ee* [%][b]
1	67	99
2	65	99
3	64	99
4	63	99

[a] Overall yield in three steps starting from **4**. [b] Determined by HPLC analysis.

Conclusions

In conclusion, we have developed a new NCPS-supported 2-phenylimino-2-oxazolidine chiral auxiliary and found it to be a useful tool to perform asymmetric alkylation reactions in good yield and stereoselectivity. In addition, NCPS-supported chiral auxiliary **4** was easily recovered and could be reused more than three times without appreciable reduction in the yield or stereoselectivity.

Experimental Section

Preparation of NCPS-Supported 2-Phenylimino-2-oxazolidine (4): To a solution of monomer **3** (2.0 g, 5.12 mmol) in THF (25 mL) was added styrene (1.59 g, 15.38 mmol) and AIBN (0.02 g, 0.12 mmol). The mixture was copolymerized at 70 °C for 96 h under a nitrogen atmosphere. Then, most of the solvent was removed under reduced pressure. The viscous solution was dropped into cold ethanol (150 mL), and the precipitated solid was filtered and washed with ethanol (3 × 10 mL) to remove any micromolecules (TLC detecting) and dried at 65 °C for 2 h under vacuum to afford polymer **4** (2.72 g, 70%). IR (NaCl): $\tilde{\nu}$ = 3321, 1680 cm^{-1}. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 157.3, 156.9, 148.5, 146.2, 134.2, 131.0, 129.4, 128.5, 126.8, 120.5, 114.4, 72.9, 70.3, 67.5, 40.2 ppm. Polymer **4**: calcd. C 84.45, H 6.94, N 4.02; found: C 84.50, H 6.97, N 3.98. Compound **3** was copolymerized with styrene with a radio of 1:3; the theoretical structural unit of polymer **4** was composed of 1 mol **3** and 3 mol styrene, so the calculated analysis of polymer **4** was obtained by calculating the contents of C, H, N in the sum of 1 mol **3** and 3 mol styrene.

General Procedure for the Synthesis of NCPS-Supported-*N*-Propionyl-2-phenylimino-2-oxazolidine (5a): To a solution of poly-

mer **4** (2.01 g) in CH_2Cl_2 (30 mL) was added DMAP (0.074 g, 0.60 mmol), Et_3N (0.49 mL, 3.32 mmol), and then propionyl chloride (0.32 mL, 3.62 mmol) in CH_2Cl_2 (10 mL) was added dropwise to the reaction mixture at 0 °C. The resulting mixture was stirred at 25 °C for 1 h. The reaction was quenched with saturated aqueous NH_4Cl, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The organic layers were combined, washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, filtered, and most of the solvent was removed under reduced pressure. The viscous solution was dropped into cold ethanol and the precipitated solid was filtered and dried at 65 °C for 2 h under vacuum to afford polymer **5**.

General Procedure for the Synthesis of Compounds 6: To a dry round-bottomed flask under a nitrogen atmosphere was added **7** (1.50 g) in anhydrous THF (30 mL). The solution was cooled to –78 °C and 2.0 M LDA (2.25 mL, 4.5 mmol) was added in THF (10 mL), and the solution was allowed to stir at –78 °C for 1 h. Then, the mixture was treated with benzyl bromide (0.80 mL, 6.75 mmol). After stirring for 30 min at –78 °C and 1 h at 0 °C, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried with $MgSO_4$ and filtered. Then, most of the solvent was removed under reduced pressure, and the viscous solution was dropped into cold ethanol, and the precipitated solid was filtered and dried at 65 °C for 2 h under vacuum to afford polymer **6**.

General Procedure for the Synthesis of Compounds 7: To a solution of polymer **6** (1.20 g) and acetic acid (0.05 mL, catalytic amount) in CH_2Cl_2 was added benzylamine (0.59 mL, 5.40 mmol), and the reaction mixture was heated at reflux for 12 h at 40 °C. After evaporation of the solvent, The viscous solution was dropped into cold ethanol (150 mL), and the precipitated solid was filtered. The filtrate was concentrated, and the crude was purified by column chromatograph (ethyl acetate/petroleum ether, 1:20) to give **7**.

Supporting Information (see footnote on the first page of this article): General methods, additional experimental procedures, and characterization data of all compounds prepared.

Acknowledgments

We gratefully acknowledge the National Natural Sciences Foundation of China (No. 20772026, 20372019).

[1] a) J. Seyden-Penne, *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, Wiley, New York, **1995**; b) R. E. Gawley, J. Aube, "Principles of Asymmetric Synthesis" in *Tetrahedron Organic Chemistry Series* (Eds.: J. E. Baldwin, P. D. Magnus), Elsevier Press, Oxford, **1996**, vol. 14; c) F. Andersson, E. Hedenström, *Tetrahedron: Asymmetry* **2006**, *17*, 1952–1957.
[2] a) D. A. Evans, K. T. Chapman, J. Bisaha, *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256; b) T. Kotake, S. Rajesh, Y. Hayashi, Y. Mukai, M. Ueda, T. Kimura, Y. Kiso, *Tetrahedron Lett.* **2004**, *45*, 3651–3654.
[3] D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2124–2127.
[4] a) D. A. Evans, T. C. Britton, J. A. Ellman, *Tetrahedron Lett.* **1987**, *28*, 6141; b) S. G. Davies, G. J.-M. Doisneau, J. C. Prodger, H. J. Sanganee, *Tetrahedron Lett.* **1994**, *35*, 2369; c) S. G. Davies, H. J. Sanganee, P. Szolcsanyi, *Tetrahedron* **1999**, *55*, 3337.
[5] D. J. Ager, J. Prakash, D. R. Schaad, *Chem. Rev.* **1996**, *96*, 835–876.
[6] a) Y. k. Wu, Y. Q. Yang, Q. Hu, *J. Org. Chem.* **2004**, *69*, 3990–3992; b) J. H. Yang, C. Y. Gui, C. F. Lu, Z. X. Chen, *Tetrahedron: Asymmetry* **2008**, *19*, 2164–2166.
[7] M. T. Crimmins, K. Chaudhary, *Org. Lett.* **2000**, *2*, 775–777.
[8] T. H. Kim, N. Lee, g.-J. Lee, J. N. Kim, *Tetrahedron* **2001**, *57*, 7137–7141.
[9] T. N. Le, Q. P. B. Nguyen, J. N. Kim, T. H. Kim, *Tetrahedron Lett.* **2007**, *48*, 7834–7837.
[10] G.-J. Lee, T. H. Kim, J. N. Kim, U. Lee, *Tetrahedron: Asymmetry* **2002**, *13*, 9–12.
[11] a) S. P. Bew, S. D. Bull, S. G. Davies, *Tetrahedron Lett.* **2000**, *41*, 7577–7581; b) M. D. Price, M. J. Kurth, N. E. Schore, *J. Org. Chem.* **2002**, *67*, 7769–7773.
[12] a) T. Kotake, S. RaJesh, Y. Hayashi, Y. Mukai, M. Ueda, T. Kimura, Y. Kiso, *Tetrahedron Lett.* **2004**, *45*, 3651–3654; b) G. Faita, A. Paio, P. Quadrelli, F. Rancati, P. Seneci, *Tetrahedron* **2001**, *57*, 8313–8322.
[13] a) M. Yamashita, S.-H. Lee, G. Koch, J. Zimmermann, B. Claphama, K. D. Janda, *Tetrahedron Lett.* **2005**, *46*, 5495–5498; b) T. Kotake, Y. Hayashi, S. Rajesh, Y. Mukai, Y. Takiguchi, T. Kimura, Y. Kiso, *Tetrahedron* **2005**, *61*, 3819–3833.
[14] a) G. Desimoni, G. Faita, A. Galbiati, D. Pasini, P. Quadrelli, F. Rancati, *Tetrahedron: Asymmetry* **2002**, *13*, 333–337; b) G. Giffels, J. Beliczey, M. Felder, U. Kragl, *Tetrahedron: Asymmetry* **1998**, *9*, 691–696.
[15] a) C. F. Lu, D. L. Li, Q. Y. Wang, G. C. Yang, Z. X. Chen, *Eur. J. Org. Chem.* **2009**, 1078–1081; b) Y. D. Wan, C. F. Lu, J. Q. Nie, G. C. Yang, Z. X. Chen, *J. Chem. Res.* **2007**, 84–85; c) J. L. Chen, J. Q. Nie, Y. L. Huang, Z. X. Chen, G. C. Yang, *J. Chem. Res.* **2006**, 696–697; d) L. Jia, C. F. Lu, Z. X. Chen, G. C. Yang, *J. Chem. Res.* **2010**, 86–87.
[16] S. G. Davies, D. J. Dixon, *Synlett* **1998**, 963.

Received: July 12, 2010
Published Online: September 10, 2010

