One-pot Enantioselective Synthesis of Optically Active Homoallylic Alcohols from Allyl Halides

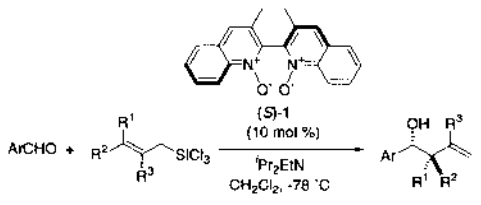
Makoto NAKAJIMA,* Makoto SAITO, and Shunichi HASHIMOTO

Graduate School of Pharmaceutical Sciences, Hokkaido University, Kita-12 Nishi-6, Kita-ku, Sapporo 060–0812, Japan.
Received October 12, 1999; accepted December 4, 1999

A one-pot, convenient method for the preparation of optically active homoallylic alcohols from allyl halides was developed. Allyltrichlorosilanes were generated *in situ* from allyl halides and trichlorosilane in the presence of cuprous chloride and tertiary amine. Without isolation of the allyltrichlorosilanes, benzaldehyde and chiral biquinoline *N*,*N*′-dioxide were introduced into the same flask, producing the corresponding homoallylic alcohols with good to high enantioselectivities.

Key words one-pot synthesis; homoallylic alcohol; *N*-oxide; enantioselective allylation; chiral catalyst

The asymmetric allylation of aldehydes to generate two successive stereogenic centers has been the subject of investigation in recent years.[1] While high enantioselectivities have been achieved with allyltin or allylsilane reagents in the presence of chiral Lewis acids as catalysts,[2] these processes afford preferentially *syn* homoallylic alcohols from both stereoisomers of allyl metals *via* an acyclic transition state. On the other hand, Lewis base-catalyzed allylations with allyltrichlorosilanes as allylating reagents developed recently by Kobayashi[3] are presumed to proceed *via* chair-like transition states involving hypervalent silicates,[4,5] in which the stereochemical information present in the allyltrichlorosilanes is transmitted to an *anti* (from (*E*)-alkene precursors) or a *syn* (from (*Z*)-alkene precursors) relationship about the new C–C bond of the product. Asymmetric versions of the Lewis base-catalyzed allylations using chiral HMPA or DMF derivatives as catalysts reported by Denmark[6] and Iseki[7] afforded the homoallylic alcohols with moderate to good enantioselectivities with rather modest catalytic activities. Recently, we have developed an amine *N*-oxide-catalyzed allylation, which has been extended to enantioselective allylation with high chemical and optical yield using a chiral bipyridine *N*,*N*′-dioxide derivative ((*S*)-**1**) (Eq. 1).[8,9]



(1)

The most common procedure for the preparation of allyltrichlorosilanes which are often utilized in the Lewis base-catalyzed allylation involves the silylation of the corresponding allyl chloride with trichlorosilane followed by distillation.[10] Although the silylation in the presence of cuprous chloride and tertiary amine proceeds almost quantitatively, the distillation of the product often proves to be troublesome. Since allyltrichlorosilanes are easily hydrolyzed to produce polymeric gum and hydrogen chloride, special care is required throughout the distillation, especially when labile substrates are employed. From a synthetic point of view, Kobayashi has developed a one-pot process for the preparation of homoallylic alcohols from allyl halides and aldehydes wherein aldehyde and excess DMF as a Lewis base were added to a solution of the allyltrichlorosilane generated *in situ* from allyl halide and trichlorosilane in ether.[3b] However, no one-pot process employing a catalytic amount of Lewis base has been reported to date. Herein we describe the first one-pot synthesis of optically active homoallylic alcohols from allyl halides exploiting a catalytic amount of chiral *N*-oxide as a Lewis base.

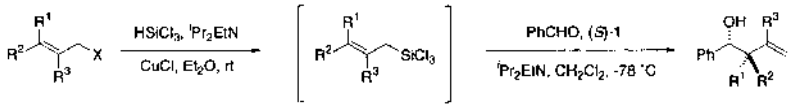
The major problem in one-pot synthesis is the reduction of the Lewis base by excess trichlorosilane. To avoid the reduction of *N*-oxide, we removed the trichlorosilane from the reaction mixture with a rotary evaporator before adding aldehyde and *N*-oxide to the same flask. As expected, the allylation proceeded smoothly without the reduction of *N*-oxide, affording the homoallylic alcohol in good chemical and optical yields (95%, 87%ee), comparable to those obtained by our original allylation procedure employing the isolated allyltrichlorosilane (89%, 88%ee).[8]

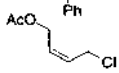
Some representative results under optimized conditions are summarized in Table 1. Not only allyl chloride but allyl bromide (entry 2) or allyl tosylate (entry 3) could be used as precursors of allylating reagents without any loss of chemical and optical yields. *E*-Crotyl- (66%, 86%ee *vs*. 68%, 86%ee in the original allylation) and methallyl chloride (62%, 52%ee *vs*. 70%, 49%ee in the original allylation) also gave almost the same results as in our original allylation procedure (entries 4, 5). More noteworthy is that halides (entries 6—9), of which trichlorosilane derivatives are prone to isomerize or decompose during distillation, produce the corresponding homoallylic alcohols in good yields. As expected, *anti*- and *syn*-homoallylic alcohols were obtained from *E*- and *Z*-cinnamyl chlorides (entries 6, 7), respectively, which shows that the one-pot allylation in the presence of copper salt proceeds *via* the same mechanism as the allylation in the original method. Modest enantioselectivity with α-bromomethylstyrene (entry 8) as well as methallyl chloride (entry 5) can be explained by the 1,3-diaxial-type steric repulsion between the β-substituents (R^3) of the allyltrichlorosilanes and the wall of the biaryl unit in the proposed transition state involving hypervalent silicate (Fig. 1).[8]

The representative procedure for one-pot enantioselective allylation is as follows: To a solution of *E*-cinnamyl chloride (80 mg, 0.52 mmol), diisopropylethylamine (0.30 ml, 1.7 mmol) and cuprous chloride (6.0 mg, 0.061 mmol) in ether (5 ml) was added trichlorosilane (0.1 ml, 0.99 mmol) at room temperature and the mixture was stirred for 1 h under an Ar atmosphere. Disappearance of the chloride was checked by ^{1}H-NMR of an aliquot of the reaction mixture. Excess trichlorosilane and ether were evaporated *in vacuo* with a rotary evaporator and the residue was dissolved in dichloromethane (2 ml). The solution of benzaldehyde (50 mg, 0.46 mmol) and (*S*)-**1** (15 mg, 0.046 mmol) in dichloromethane (1 ml) was added to the mixture at −78 °C and the whole was stirred at the same temperature for 6 h. Aqueous work-up followed by silica gel column chromatog-

* To whom correspondence should be addressed.

Table 1. One-pot Enantioselective Synthesis of Homoallylic Alcohols from Benzaldehyde and Allyl Halides Catalyzed by (*S*)-**1**



Entry	Allyl halide	Yield, %[a]	ee, % (Confgn)[b]	Entry	Allyl halide	Yield, %[a]	ee, % (Confgn)[b]
1		95	87 (*S*)	6[e]		76[f]	91 (1*R*,2*S*)
2		92	87 (*S*)	7[g]		70[h]	77 —[i]
3		90	86 (*S*)				
4[c]		66[d]	86 (1*R*,2*S*)	8		52	43 (*S*)
5		62	52 (*S*)	9[j]		68[k]	86 —[l]

a) Isolated yield. *b*) Determined by HPLC analysis employing a Daicel Chiralcel OD, OJ, or Chiralpak AD. Configuration assignment by comparison with the values of optical rotations in Reference 8, 11, 12. *c*) *E*:*Z*=97:3. *d*) *syn*:*anti*=3:97. *e*) *E*:*Z*=>99:<1. *f*) *syn*:*anti*=<1:>99. *g*) *E*:*Z*=5:95. Reference 13. *h*) *syn*:*anti*=95:5. Relative stereochemical assignment by comparison with chemical shift values of NMR in Reference 14. *i*) $[\alpha]_D^{25}$ −18.4 (*c* 1.3 $CHCl_3$). *j*) *E*:*Z*=<1:>99. *k*) *syn*:*anti*=>99:<1. Relative stereochemical assignment by comparison with chemical shift values of NMR in Reference 15. *l*) $[\alpha]_D^{23}$ −14.9 (*c* 1.1 C_6H_6).

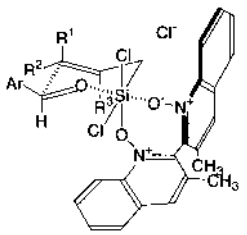


Fig. 1

raphy gave the homoallylic alcohol (76 mg, 76%) of 91%ee on the basis of chiral HPLC analysis. Stereochemistry of the alcohol was assigned by comparison with data in the literature.[11]

The present modification of the *N*-oxide-catalyzed enantioselective allylation provides a simple and versatile method for the preparation of optically active homoallylic alcohols. Further studies for the application of the present protocol to the enantioselective synthesis of biologically active compounds are under investigation in our laboratory.

Acknowledgments This work was partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan and the Otsuka Chemical Award in Synthetic Organic Chemistry, Japan. The authors thank the Japan Society for the Promotion of Science for Research Fellowships for Young Scientists (to M.S.).

References and Notes

1) For reviews on asymmetric allylation of carbonyl compounds, see: *a*) Hoffmann R. W., *Angew. Chem. Int. Ed. Engl.*, **26**, 489—594 (1987); *b*) Yamamoto Y., Asao N., *Chem. Rev.*, **93**, 2207—2293 (1993); *c*) Marshall J. A., *Chem. Rev.*, **96**, 31—47 (1997).
2) For a review on chiral Lewis acid-catalyzed allylation of aldehydes, see: Cozzi P. G., Tagliavini E., Umani-Ronchi A., *Gazz. Chim. Ital.*, **127**, 247—254 (1997).
3) *a*) Kobayashi S., Nishio K., *Tetrahedron Lett.*, **34**, 3453—3456 (1993); *Idem*, *J. Org. Chem.*, **59**, 6620—6628 (1994); *c*) *Idem*, *J. Am. Chem. Soc.*, **117**, 6392—6393 (1995); *d*) Kobayashi S., Hirabayashi R., *ibid.*, **121**, 6942—6943 (1999).
4) For recent reviews on hypervalent silicates, see: *a*) Sakurai H., *Synlett*, **1989**, 1—8; *b*) Chuit C., Corriu R. J. P., Reye C., Young J. C., *Chem. Rev.*, **93**, 1371—1448 (1993).
5) For Lewis base-promoted enantioselective reactions based on hypervalent silicates other than allylation, see: *a*) Kohra S., Hayashida H., Tominaga Y., Hosomi A., *Tetrahedron Lett.*, **29**, 89—92 (1988); *b*) Schiffers R., Kagan H. B., *Synlett*, **1997**, 1175—1178; *c*) Denmark S. E., Winter S. B. D., Su X., Wong K.-T., *J. Am. Chem. Soc.*, **118**, 7404—7405 (1996); *d*) Denmark S. E., Stavenger R. A., Su X., Wong K.-T., Nishigaichi Y., *Pure Appl. Chem.*, **70**, 1469—1476 (1998); *e*) Denmark S. E., Barsanti P. A., Wong K.-T., Stavenger R. A., *J. Org. Chem.*, **63**, 2428—2429 (1998).
6) Denmark S. E., Coe D. M., Pratt N. E., Griedel B. D., *J. Org. Chem.*, **59**, 6161—6163 (1994).
7) *a*) Iseki K., Kuroki Y., Takahashi M., Kobayashi Y., *Tetrahedron Lett.*, **37**, 5149—5150 (1996); *b*) Iseki K., Kuroki Y., Takahashi M., Kishimoto S., Kobayashi Y., *Tetrahedron*, **53**, 3513—3526 (1997); *c*) Iseki K., Mizuno S., Kuroki Y., Kobayashi Y., *Tetrahedron Lett.*, **39**, 2767—2770 (1998); *d*) Iseki K., Kuroki Y., Kobayashi Y., *Tetrahedron: Asymmetry*, **9**, 2889—2894 (1998); *e*) Iseki K., Mizuno S., Kuroki Y., Kobayashi Y., *Tetrahedron*, **55**, 977—988 (1999).
8) Nakajima M., Saito M., Shiro M., Hashimoto S., *J. Am. Chem. Soc.*, **120**, 6419—6420 (1998).
9) Studies on bipyridine *N*,*N*′-dioxide derivatives by our group: *a*) Nakajima M., Sasaki Y., Shiro M., Hashimoto S., *Tetrahedron: Asymmetry*, **8**, 341—344 (1997); *b*) Nakajima M., Sasaki Y., Iwamoto H., Hashimoto S., *Tetrahedron Lett.*, **39**, 87—88 (1998).
10) Furuya N., Sukawa T., *J. Organomet. Chem.*, **96**, C1—C3 (1975).
11) *a*) Basauaiah D., Rao P. D., *Tetrahedron: Asymmetry*, **6**, 789—800 (1995); *b*) Coxon J. M., Simpson G. W., Steel P. J., Trenerry V. C., *Tetrahedron Lett.*, **24**, 1427—1428 (1983).
12) Fouquey C., Jacques J., *Bull. Soc. Chim. Fr.*, **1973**, 618—621.
13) Rideout J. L., Krenitsky T. A., Chao E. Y., Elion G. B., Williams R. B., Latter V. S., *J. Med. Chem.*, **26**, 1489—1494 (1983).
14) Sidduri A., Rozema M. J., Knochel P., *J. Org. Chem.*, **58**, 2694—2713 (1993).
15) Takahara J. P., Masuyama Y., Kurusu Y., *J. Am. Chem. Soc.*, **114**, 2577—2586 (1992).