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Formal Total Synthesis of (−)-Emetine Using Catalytic Asymmetric Allylation of Cyclic Imines as a Key Step

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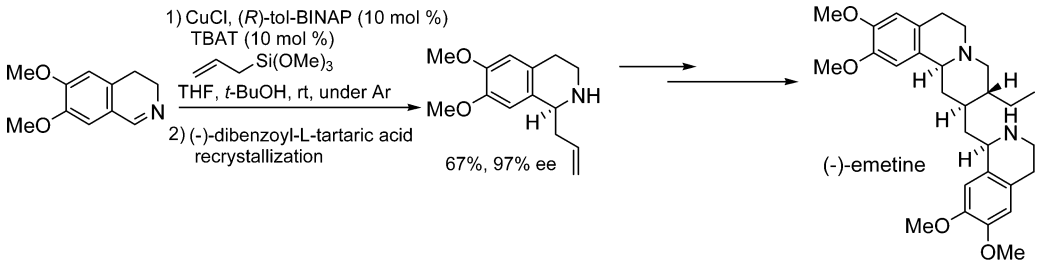
ABSTRACT



Catalytic asymmetric allylation of 3,4-dihydro-6,7-dimethoxyisoquinoline was carried out using allyltrimethoxysilane in the presence of Cu(I) and tol-BINAP. The allyl adduct thus obtained was transformed to a chiral synthetic intermediate for (−)-emetine in good yield. The procedure was applied to the total synthesis of *ent*-emetine.

Isoquinoline alkaloids[1] have long attracted much attention due to their biological activities, which involve recent discoveries for α-glucosidase[2] and Parkinson's disease.[3] Most of these compounds have a common characteristic in their structures; that is, they have a chiral center at the C-1 position of the isoquinoline nucleus. Thus, the formation of the chiral center is a crucial step for general synthetic methods of isoquinoline alkaloids.

There are, however, only a few methods[4−6] for constructing a chiral 1-substituted tetrahydroisoquinoline nucleus in high stereoselectivity.

In the course of our research for the asymmetric synthesis of isoquinoline alkaloids, we have found that *N*-acyliso-quinolinium salts with a chiral center in the acyl group underwent diastereoselective addition with allyltributyltin and silyl enol ethers to give 1-substituted tetrahydroisoquinoline derivatives in a stereoselective manner.[7] These results prompted us to investigate a catalytic process for the reaction, and it was found that 3,4-dihydro-6,7-dimethoxyisoquinoline (**1**) was a substrate for the addition of allyltrimethoxysilane in the presence of a catalytic amount of Cu(I) salt and a chiral phosphine ligand to give 1-allyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**2**) in good yield and moderate stereoselectivity. The enantiomeric excess was further increased by recrystallization in the presence of dibenzoyl tartaric acid to afford a pure enantiomer. The allyl adduct thus obtained was transformed to a key intermediate for the total synthesis of (−)-emetine in short steps, and the *ent*-

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(5) (a) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97.

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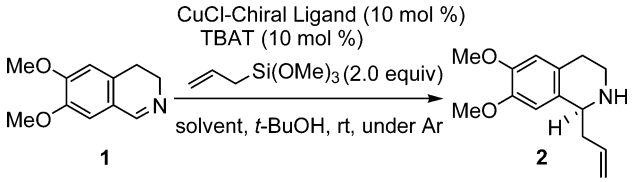
emetine was synthesized by the same method. This paper describes these results.

Although there are a few papers on the catalytic asymmetric allylation of imines,[8] there has been no report concerning the catalytic allylation of cyclic imines.[9] Although Yamamoto et al. recently reported a general method for the allylation of various kinds of imines, they showed the incompatibility of cyclic imines to their reaction system.[8d] Recently, a new allylation reaction of ketones and aldehydes has been published by Shibasaki et al.[10] using allyltrimethoxysilane and a catalytic amount of Cu(I) salt. We applied their reaction system to the allylation of 6,7-dimethoxy-3,4-dihydroisoquinoline and found that the reaction proceeded in a stereoselective manner as shown in Table 1.

Table 1



entry	solvent	chiral ligand	time	yield of **2** (%)	ee of **2**[12] (%)
1	THF		20 h	72	
2	THF	(*R*)-tol-BINAP	1 d	91	71 (*S*)
3	THF	(*R*)-BINAP	1 d	35	71 (*S*)
4	THF	(*R*,*R*)-DIPAMP	1 d	78	5
5	THF	(*R*,*R*)-CHIRAPHOS	1 d	31	21 (*S*)
6	DMF	(*R*)-tol-BINAP	1 d	21	50 (*S*)
7	ether	(*R*)-tol-BINAP	1 d	37	47 (*S*)
8	dioxane	(*R*)-tol-BINAP	1 d	35	67 (S)

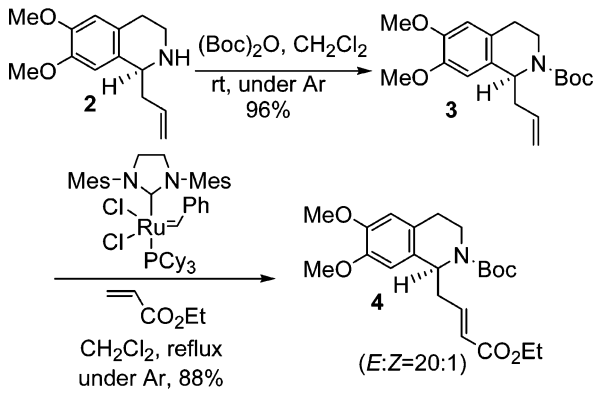
Various phosphine derivatives were investigated as chiral ligands, and it was found that tol-BINAP in THF at room temperature afforded the best result for the present reaction. The yield of **2** was lowered to 21% by the reaction at 10 °C without an increase of the ee, and the reaction did not proceed at 0 °C. Other allylation reagents such as allyltributyltin afforded a racemic product. Although the stereoselectivity is moderate, this is the first example that a cyclic imine is adopted as a catalytic allylation reaction.

The product **2** thus obtained was treated with (−)-dibenzoyl-L-tartaric acid to form a mixture of the diastereomeric salts, which was recrystallized from acetonitrile/H_2O (20:1) to give optically pure **2** (97% ee) in 67% yield based on the starting material.[11]

With a practical amount of compound **2** in hand, we decided to functionalize the obtained allyl group. After the protection of an amino group of **2**, reaction of **3** with various monosubstituted alkenes using the second-generation Grubbs' catalyst was carried out, and it was found that the cross-metathesis products were obtained in high yields and good stereoselectivity.[13] Without the Boc protecting group, the metathesis reaction did not proceed.

By using the ethyl acrylate, sufficient stereoselectivity was obtained to give an adequate amount of a functionalized (*E*)-alkene derivative **4** (Scheme 1).

Scheme 1



The deprotection of **4** followed by Michael addition of **5** with methyl vinyl ketone afforded an *N*-(3-oxobutyl) derivative, which was then cyclized to **6** in a completely diastereoselective manner (Scheme 2). In our first plan, the acetyl group would be transformed to the corresponding ethyl group according to the reported method,[14] but our attempt to reduce the keto group to give **7** resulted in a very low yield under various conditions.[15]

Thus, we changed the synthetic procedure as follows (Scheme 3). Although Michael addition of acrolein to compound **5** resulted in a complex mixture of the products, slowing the addition of acrolein considerably improved the reaction yield to a practical level. That is, the addition of acrolein to **5** over 5 h followed by treatment with pyrrolidine afforded a ring-closing product **8** in good yield and complete stereoselectivity. Although the compound **8** was obtained at first as its epimer at the C-3 position (according to emetine numbering), the epimeric compound rapidly isomerized to **8** under the reaction conditions. The formyl derivative **8** thus

(8) (a) Nakamura, H.; Nakamura, K.; Yamamoto, Y.*J. Am. Chem.* Soc. **1998**, *120*, 4242. (b) Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R. G.; Jorgensen, K. A. *J. Org. Chem*. **1999**, *64*, 4844. (c) Gastner, T.; Ishitani, H.; Akiyama, R.; Kobayashi, S. *Angew. Chem., Int. Ed*. **2001**, *40*, 1896. (d) Fernandes, R. A.; Stimac, A.; Yamamoto, Y. *J. Am. Chem. Soc*. **2003**, *125*, 14133.

(9) There are a few reports which claimed the asymmetric allylation using a stoichiometrical amount of chiral compound; see: Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc*. **1996**, *118*, 8489 and references therein.

(10) Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2002**, *124*, 6536.

(11) With three times of careful recrystallization, the tartrate salt of racemic **2** afforded the enantiomeric **2** in 97% ee.

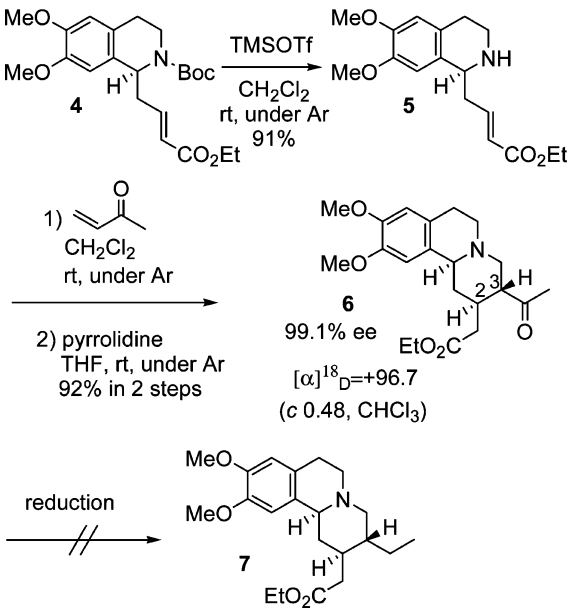
(12) The absolute configuration of the compound **2** was determined by the transformation to the known compound **10**.

(13) Nagata, K.; Itoh, T.; Fukuoka, H.; Nakamura, S.; Ohsawa, A. *Heterocycles* **2005**, *65*, 1283.

(14) Hirai, Y.; Terada, T.; Hasegawa, A.; Yamazaki, T. *Chem. Pharm. Bull*. **1998**, *36*, 1343.

(15) Other than the reported method that used ethanedithiol−TFA followed by Raney Ni, several reduction systems were tested which involve various variants of Wolff−Kishner or Clemmensen reduction, but the product **7** was not obtained in more than 7% yield.

Scheme 2

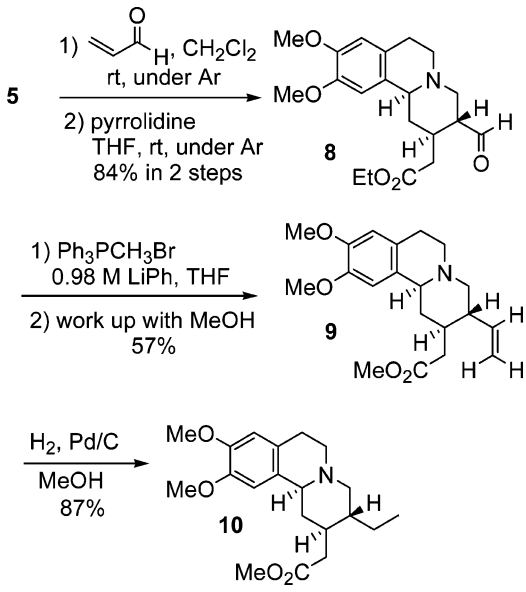


obtained underwent the Wittig reaction with methyltriphenylphosphonium bromide followed by treatment with methanol to give alkene **9**. A catalytic hydrogenation of **9** resulted in the formation of compound **10**, which was reported by Tietze[16] as an intermediate for the synthesis of (−)-emetine. Thus, the stereoselectivity of the present reaction was proved to be consistent with that of the natural product.

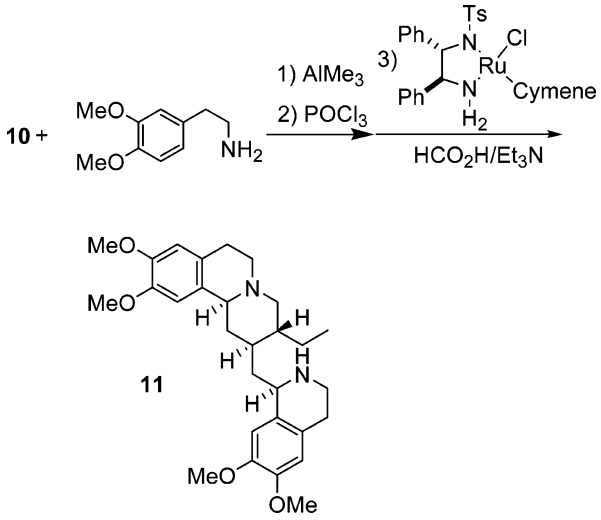
In our synthesis, the overall yield of **10** was 21.5% in 8 steps from the starting material **1**. Since the reported synthesis[16] afforded **10** in 3.2% yield via 12 steps, the present method gives a better way of obtaining the important intermediate **10**, which can also be transformed to several alkaloids such as psychotrine[17] and tubulosine.[18]

The final stage of the total synthesis of (−)-emetine (**11**) was accomplished according to Tietze's method[16] in three steps (Scheme 4).

Scheme 3



Scheme 4



Using the present procedure, we obtained *ent*-emetine ((+)-emetine) in overall yield of 8.5% from **1**and (*S*)-tol-BINAP.

In this paper, we have described asymmetric formal total synthesis of (−)-emetine and the synthesis of (+)-emetine in a completely stereoselective manner. In the key step, catalytic allylation was carried out to introduce an allyl group at the C-1 position of the isoquinoline nucleus using tol-BINAP as a chiral source. The application of the allyl adduct **2** to the total synthesis of other isoquinoline alkaloids and the biological activity of *ent*-emetine are now under investigation.

Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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