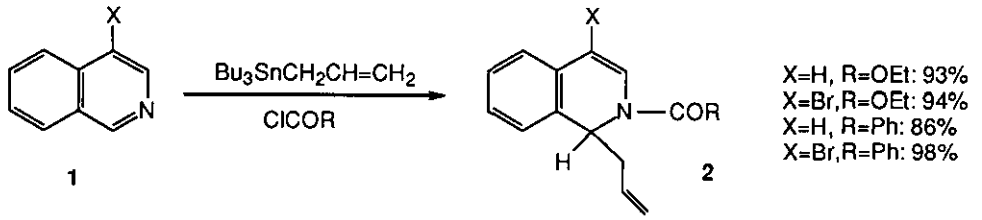
SYNTHESIS OF 1,2-DIHYDROISOQUINOLINES BY THE REACTION OF ISOQUINOLINE WITH ALLYLTRIBUTYLTIN OR SILYL ENOL ETHERS IN THE PRESENCE OF *N*-ACYLATING AGENTS#

Takashi Itoh, Michiko Miyazaki, Kazuhiro Nagata, Hiroshi Hasegawa, Akio Ohsawa,* and Kazuo T. Nakamura

School of Pharmaceutical Sciences, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142, Japan

Abstract - Isoquinolines were allowed to react with allyltributyltin or silyl enol ethers in the presence of *N*-acylating agents to give 1-substituted 1,2-dihydroisoquinolines in good yields. When a chiral acid chloride was used for an activator, a high diastereoselectivity was observed for the addition. The configuration of a major isomer was elucidated by an X-Ray crystallographic analysis.

In the course of our studies on the reaction of unstable *N*-alkoxycarbonyl quaternary salts of azaaromatics,[1] allyltributyltin[2] and silyl enol ethers[3] are revealed to be good nucleophiles to give *N*-alkoxycarbonyl-dihydro adducts in high yields. These results prompted us to investigate its applications to isoquinoline derivatives, which include a variety of bioactive compounds,[4] and it was found that these nucleophiles react with isoquinoline in the presence of chloroformate or benzoyl chloride to give 1-substituted derivatives. In addition, this 1,2-addition reaction was applied to an asymmetric synthesis, and a chiral acid chloride afforded a 1,2-adduct in a highly diastereoselective manner. Moreover, its absolute configuration was elucidated using an X-Ray crystallographic analysis. This paper describes these results.

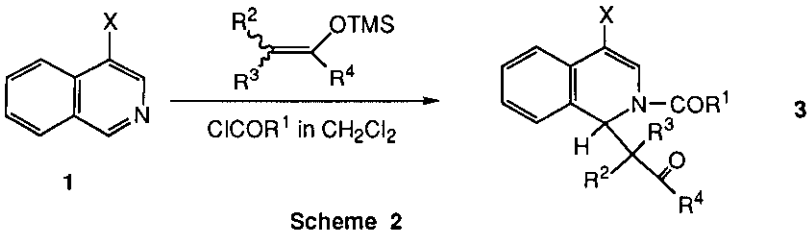


Scheme 1

#This paper is dedicated to Professor Koji Nakanishi on the occasion of his 75th birthday.

Isoquinoline or 4-bromoisoquinoline was allowed to react with allyltributyltin in the presence of chloroformate or benzoyl chloride to give 2-acyl-1-allyl-1,2-dihydroisoquinolines in good yields (Scheme 1).[5] In the typical experiment, isoquinoline (1 mmol) and allyltributyltin (1.5 mmol) were dissolved in CH_2Cl_2 (5 mL) and the solution was cooled to 0°C. To the mixture, ethyl chloroformate or benzoyl chloride (1.2 mmol) was added dropwise, and the mixture was allowed to react at 0°C for 30 min. Then the mixture was diluted with ether (15 mL) and treated with 1 M aq. KF solution (3 mL) to make tributyltin fluoride precipitate.[6] The solid was filtered, and the filtrate was dried over $MgSO_4$ and evaporated off to leave a residue, which was chromatographed on silica gel to give the product.

Next, silyl enol ethers were subjected to the reaction, and the results are summarized in Table 1 (Scheme 2). The reaction was carried out in the same manner as mentioned above except the treatment with KF. The yields suggested that 4-bromoisoquinoline is slightly more reactive than parent one.

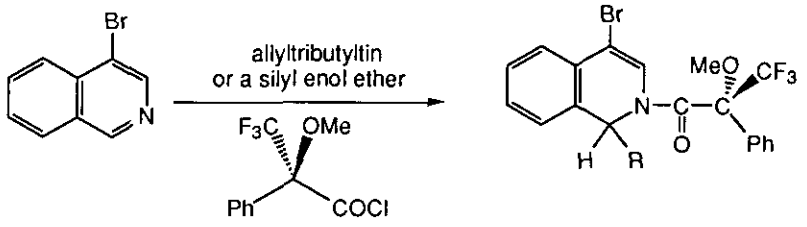


Scheme 2

Table 1 The Reaction of Isoquinoline (1) with Silyl Enol Ethers in the Presence of an Acylating Agent

entry	X	R^1	R^2	R^3	R^4	yield of **3** (%)
1	H	OEt	Me	Me	OMe	95
2	H	OEt	Me	H	OMe	75
3	H	OEt	H	H	Me	92
4	H	OEt	H	H	Ph	72
5	H	OEt	H	$-(CH_2)_3-$		99
6	H	OEt	H	$-(CH_2)_4-$		92
7	H	OPh	Me	Me	OMe	98
8	H	Ph	Me	Me	OMe	96
9	Br	OEt	Me	Me	OMe	100
10	Br	OEt	Me	H	OMe	100
11	Br	OEt	H	H	Me	99
12	Br	OEt	H	H	Ph	84
13	Br	OEt	H	$-(CH_2)_3-$		100
14	Br	OEt	H	$-(CH_2)_4-$		94
15	Br	OPh	Me	Me	OMe	99
16	Br	Ph	Me	Me	OMe	99

The above results show that the reaction system is useful for the introduction of the substituents into C-1 position of isoquinoline. In this case, acylating agents are placed in proximity to the reaction site C-1, and the scope of the acylating agents is wide between chloroformates and acyl halides. This finding prompted us to its application to asymmetric synthesis, because there are a lot of isoquinoline alkaloids which have a chiral carbon at their C-1 position.[4] As an activator for the reaction, we assumed that acyl halides are more appropriate than alkyl chloroformate because a chiral carbon can be placed nearer to the C-1 position than the case of alkyl chloroformates.[7] Thus, as a preliminary experiment, (*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride ((*S*)-MTPA-Cl), which has been used for determination of absolute configuration of organic compounds by NMR,[8] was selected as a chiral acid halide. The results are shown in Table 2 in the cases of 4-bromoisoquinoline as a substrate. Allyltributyltin afforded a higher diastereoselectivity than silyl enol ethers in this reaction system (Table 2, entries 1-3), therefore the reaction conditions were investigated using allyltributyltin (entries 4-8). Cooling of the reaction mixture and the addition of some ammonium salts both increased the selectivity. Thus, the diastereoexcess was up to 87% when the reaction was carried out in the presence of tetrabutylammonium halide at -40°C (entries 5 and 6).



Scheme 3

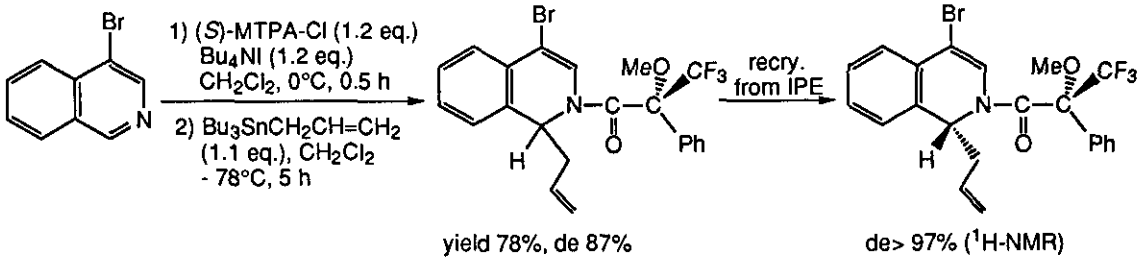
Table 2 Asymmetric Addition of 4-Bromoisoquinoline with Allyltributyltin or Silyl Enol Ethers in the Presence of (*S*)-MTPA-Cl

entry	reagent	R	additive	conditions	yield (%)	de(%)[a]
1	$Bu_3SnCH_2CH=CH_2$	$CH_2CH=CH_2$	-	rt, 3 h	85	62
2	$Me_2C=C(OTMS)OMe$	CMe_2CO_2Me	-	0°C, 2 h	74	46
3	$CH_2=C(OTMS)Ph$	CH_2COPh	-	0°C, 3 h	61	45
4	$Bu_3SnCH_2CH=CH_2$	$CH_2CH=CH_2$	-	- 40°C, 3 h	66	76
5	$Bu_3SnCH_2CH=CH_2$	$CH_2CH=CH_2$	Bu_4NBr	- 40°C, 3 h	71	87
6	$Bu_3SnCH_2CH=CH_2$	$CH_2CH=CH_2$	Bu_4NI	- 40°C, 3 h	69	87
7	$Bu_3SnCH_2CH=CH_2$	$CH_2CH=CH_2$	$Et_4N^+TsO^-$	- 40°C, 3 h	74	74
8	$Bu_3SnCH_2CH=CH_2$	$CH_2CH=CH_2$	$C_{12}H_{25}OSO_3Na$	- 40°C, 3 h	58	81

a) The diastereomeric excess (de) was determined by ^{1}H-NMR and HPLC analysis.

Finally, the purification and isolation of a major diastereomer was carried out (Scheme 4). At first, 4-bromoisoquinoline, (*S*)-MTPA-Cl, and tetrabutylammonium iodide were dissolved in CH_2Cl_2 at 0°C, and the mixture was allowed to stand for 30 min. Then the mixture was cooled to -78°C, and allyltributyltin was added to the solution, which was allowed to stir for 5 h to provide a 93.5:6.5 mixture of the diastereomers . The mixture was obtained as colorless needles, and a recrystallization from isopropyl ether

(IPE) afforded an almost pure diastereomer. An X-Ray crystallographic analysis revealed that the absolute configuration of this compound is as shown in Scheme 4.



Scheme 4

In this paper, we described that the introduction of the substituents at C-1 position of isoquinoline was readily performed using allyltributyltin or silyl enol ethers in the presence of an *N*-acylating reagent. This reaction system was found to be useful for an asymmetric addition by the use of a chiral acid halide. The practical application of the reaction using chiral acid chlorides derived from amino acids[9] is now under investigation.

REFERENCES AND NOTES

1. a) T. Itoh, H. Hasegawa, K. Nagata, and A. Ohsawa, *J. Org. Chem.*, **1994**, *59*, 1319. b) T. Itoh, H. Hasegawa, K. Nagata, M. Okada, and A. Ohsawa, *Tetrahedron*, **1994**, *50*, 13089. c) T. Itoh, M. Miyazaki, H. Hasegawa, K. Nagata, and A. Ohsawa, *Chem. Commun.*, **1996**, 1217. d) T. Itoh, Y. Matsuya, H. Hasegawa, K. Nagata, M. Okada, and A. Ohsawa, *J. Chem. Soc., Perkin Trans. 1*, **1996**, 2511. e) T. Itoh, M. Miyazaki, K. Nagata, and A. Ohsawa, *Heterocycles*, in press.
2. M. Pereyre, J. Quintard, and A. Rahm, "Tin in Organic Synthesis", Butterworth, London, 1987, pp. 185-258.
3. E. W. Colvin, "Silicon Reagents in Organic Synthesis", Academic Press, New York, 1988.
4. J. Lundström,"Simple Isoquinoline Alkaloids" in "The Alkaloids", ed. by A. Brossi, Academic Press, London, 1983, Vol. 21, 255.
5. Yamaguchi *et al.* reported that isoquinoline reacted with allyltributyltin in the presence of methyl chloroformate to give a 1,2-dihydroadduct; see R. Yamaguchi, *Yuki Gosei Kagaku Kyokaishi*, **1991**, *49*, 128.
6. J. E. Leibner and J. Jacobus, *J. Org. Chem.*, **1979**, *44*, 449.
7. Comins *et al.* reported the reaction of isoquinoline with Grignard reagents in the presence of 8-phenylmenthyl chloroformate to give 1,2-adducts in a diastereoselective manner (de 42-64%); see, D. L. Comins and M. M. Badawi, *Heterocycles*, **1991**, *32*, 1869.
8. a) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **1969**, *34*, 2543. b) J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **1973**, *95*, 512. c) G. R. Sullivan, J. A. Dale, and H. S. Mosher, *J. Org. Chem.*, **1973**, *38*, 2143. d) I. Ohtani, T. Kusumi, Y. Kashman, and H. Kakisawa, *J. Am. Chem. Soc.*, **1991**, *113*, 4092.
9. The acid chlorides derived from proline derivatives were found to be effective to the reaction (de up to 90%). The results will be published in near future.

Received, 30th April, 1997