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A SELECTIVE SYNTHESIS OF BOTH ENANTIOMERS OF A 1-ALLYL-β-CARBOLINE USING THE SAME CHIRAL AUXILIARY DERIVED FROM L-PROLINE

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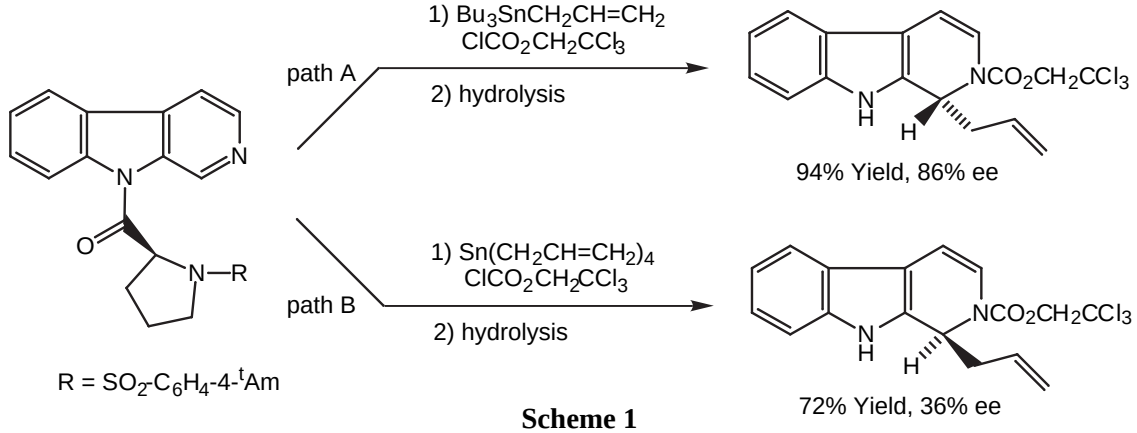
Abstract - In the study of asymmetric allylation of β-carbolines, reversed stereoselectivity toward a same substrate was observed depending on allylating agents. Based on this finding, the synthesis of both enantiomers of 1-allyl-β-carbolines was accomplished on a practical level of yields and selectivities.

There are a variety of indole alkaloids in nature which contain β-carboline nucleus. Owing to their pharmacological activities, numerous studies for the syntheses of these natural products have been immencely continuing, including asymmetric approaches.[1] Many of these, however, involve discrete techniques in each individual total synthesis, and there are few reports using a simple and direct method for introducing a substituent asymmetrically to parent β-carboline with general applicability.[2]

In the course of our researches on developing a method for introducing carbon substituents toward azaaromatics, we have reported that their *N*-acylated quaternary salts are good substrates for the 1,2-addition reaction with organotin or silicon reagents as nucleophiles.[3] It was also found that the reaction was applicable to the asymmetric addition to isoquinoline derivatives by the use of an appropriate chiral auxiliary.[4] Accordingly we applied this asymmetric 1,2-addition reaction to β-carboline, and found that allylation with allyltributyltin smoothly proceeded to afford 1-allyl-β-carbolines with high diastereoselectivity. In this case, the most effective chiral auxiliary was found to be an L-proline derivative which was introduced at 9-position of β-carboline (Scheme 1, path A).[5]



Scheme 1

During this investigation, we encountered unexpected results that the absolute configurations of the chiral center newly constructed were reversed by the use of different allylating agents even when the same substrate carrying the same auxiliary was used. That is, while (*R*)-1-allyl-1,2-dihydro-β-carboline was obtained when allyltributyltin was used, tetraallyltin afforded the corresponding *S*-isomer dominantly (Scheme 1, path B). These results prompted us to thoroughly investigate this novel alteration of selectivity, and we found that addition of stannic halide to tetraallyltin plays a crucial role to form *S*-isomer on a practical level of chemical yield and stereoselectivity. This paper describes these results.

Table 1 shows the results which parallel the data of allyltributyltin with those of tetraallyltin in the allylation reaction with β-carboline possessing a proline-derived chiral auxiliary on its 9-position. After removal of the chiral auxiliary, the ee of products was estimated by HPLC, and the formation of (*S*)-allyl adduct was always observed in the cases of tetraallyltin, though their ee was relatively low (Entries 5-8).[6] These results suggested that the selectivity of leading to either *R*- or *S*-isomer was controlled by allylating agents without dependence on the structure of the chiral auxiliary.

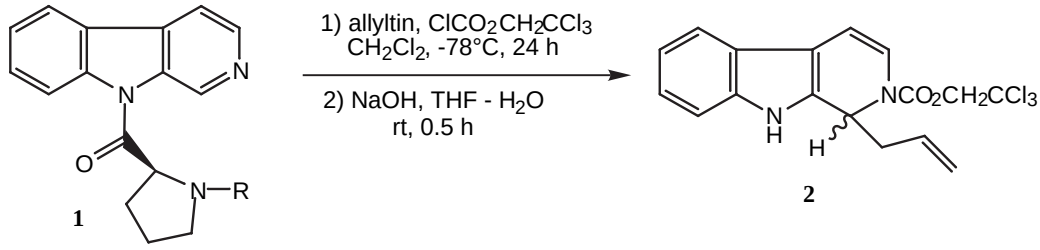
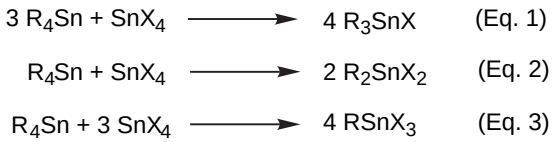


Table 1. Allylation of 9-Acylated β-carbolines with Allyltributyltin or Tetraallyltin

Entry	Compound	R	Allyltin	Yield (%)	% ee	Config.
1	**1a**	COMe	$Bu_3SnCH_2CH=CH_2$	70	58	*R*
2	**1b**	COPh	$Bu_3SnCH_2CH=CH_2$	80	57	*R*
3	**1c**	SO_2Ph	$Bu_3SnCH_2CH=CH_2$	86	78	*R*
4	**1d**	SO_2-C_6H_4-4-^{t}Am	$Bu_3SnCH_2CH=CH_2$	94	86	*R*
5	**1a**	COMe	$Sn(CH_2CH=CH_2)_4$	71	9	*S*
6	**1b**	COPh	$Sn(CH_2CH=CH_2)_4$	52	12	*S*
7	**1c**	SO_2Ph	$Sn(CH_2CH=CH_2)_4$	54	29	*S*
8	**1d**	SO_2-C_6H_4-4-^{t}Am	$Sn(CH_2CH=CH_2)_4$	72	36	*S*

All reactions were carried out using 3 eq. of allyltin and 2 eq. of chloroformate for 24 h except for Entry 4 (48 h).

Although there seems to be only slight differences between allyltributyltin and tetraallyltin on a steric and electronic nature, one remarkable difference is that tetraallyltin can transfer two or more allyl groups to the substrate. Thus triallyltin chloride formed by the first allylation should have ability to bring about further allylation, and diallyltin dichloride thus obtained would also have similar reactivity. We supposed that the formation of the *S*-isomer was attributed to the participation of these allyltin chlorides.[7] Accordingly, we investigated the effect of the addition of stannic halides, which are known to bring about the disproportionation between tetraallyltin to afford allyltin halides (Kocheshkov reaction,[8] Eq.1-3), and the results are summarized in Table 2.



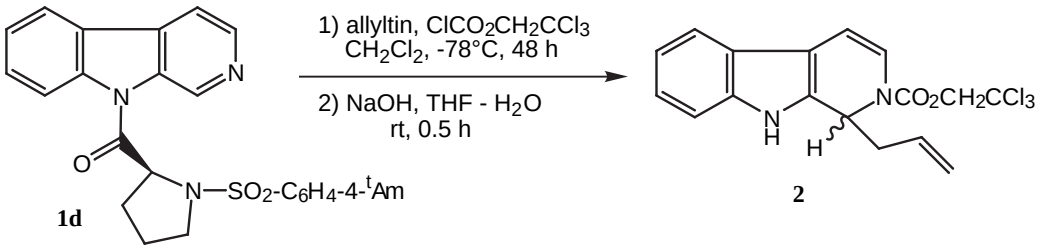


Table 2. Asymmetric Allylation of 9-[*N*-(*t*-Amylphenylsulfonyl)prolinyl]-β-carboline with Various Allyltins

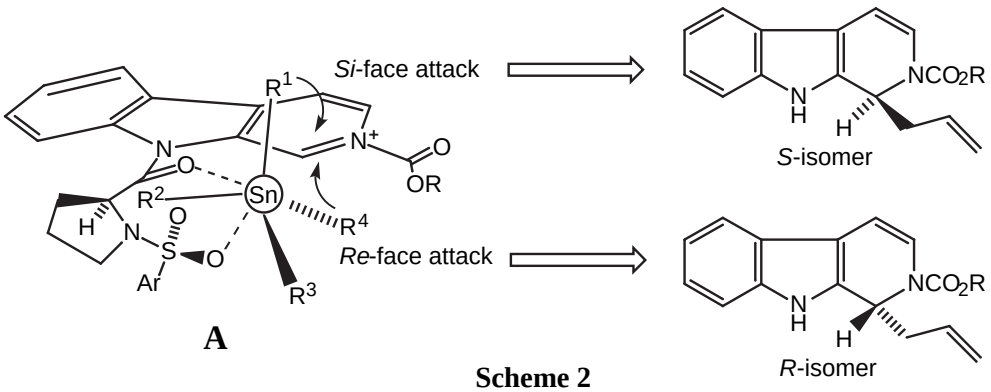
Entry	Conditions of allyltin preparation				Chloroformate (eq.)	Yield (%)	% ee	Config.
	Tetraallyltin (eq.)	Additive (eq.)	Ratio	Total tin (eq.)				
1	3	none	-	3	2	72	36	*S*
2	2.25	$SnCl_4$ (0.75)	3 : 1	3	2	59	44	*S*
3	1.5	$SnCl_4$ (1.5)	1 : 1	3	2	4	74	*S*
4	1.5	$SnBr_4$ (1.5)	1 : 1	3	2	13	80	*S*
5	0.75	$SnBr_4$ (0.75)	1 : 1	1.5	2	17	83	*S*
6	0.5	$SnBr_4$ (0.5)	1 : 1	1	10	15	88	*S*
7	0.75	$SnBr_4$ (0.25)	3 : 1	1	10	43	83	*S*
8	1.5	SnI_4 (1.5)	1 : 1	3	2	13	87	*S*
9	0.75	SnI_4 (0.75)	1 : 1	1.5	2	32	90	*S*
10	0.5	SnI_4 (0.5)	1 : 1	1	10	50	87	*S*
11	0.75	SnI_4 (0.25)	3 : 1	1	2	72	72	*S*
12	0.67	SnI_4 (0.33)	2 : 1	1	10	62	85	*S*
13	1	SnI_4 (0.5)	2 : 1	1.5	10	91	84	*S*
14	Allyltributyltin (3 eq.)				2	94	86	*R*

As expected, the addition of stannic chloride resulted in the higher stereoselectivity, but the yields were lowered as a larger amount of stannic chloride was used (Entries 1-3). It was supposed that this disadvantage was caused by higher Lewis acidity of the chlorinated allyltins than that of tetraallyltin or allyltributyltin. These more acidic tins might coordinate tightly to the nitrogen at 2-position of the substrate, and the coordination could inhibit the quaternarization which is essential for the addition reaction. Therefore stannic bromide and iodide, whose Lewis acidities might be reduced with compared to stannic chloride, were employed for the purpose of increasing chemical yield. When stannic bromide was used, the yields and the selectivities were slightly improved, and the smaller amounts of total tins were used, the higher selectivities were observed (Entries 4-6). The change of the ratio (tetraallyltin to stannic bromide) resulted in a moderate rise of the yield without a marked loss of the selectivity (Entry 7). An obvious effect toward the yield was observed when restricted amounts of stannic iodide were added (Entries 8-12). In these cases, high levels of ee were accomplished with satisfactory yields, and the best result was obtained when 1 eq. of tetraallyltin and 0.5 eq. of stannic iodide were employed (Entry 13). Consequently, the method for

producing (*S*)-1-allyl-β-carbolines is established as a counterpart of the reaction which affords the corresponding *R*-isomers (Entry 14).

A typical experimental procedure is as follows; to a solution of stannic iodide (31 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL), tetraallyltin (28 mg, 0.1 mmol) was added and the mixture was stirred for 10 min at room temperature under Ar, then cooled to -78°C. The substrate (0.1 mmol) in CH_2Cl_2 (0.5 mL) and chloroformate (212 mg, 1 mmol) were added, and the mixture was allowed to react for 48 h at -78°C. After the treatment of aqueous KF solution and the general work-up procedure, the allyl adduct was isolated, which was then hydrolyzed in aqueous NaOH - THF solution at room temperature to afford the product. The determination of the ee was performed by HPLC using Daicel Chiralcel OD column.

Although mechanism(s) to explain the reversed selectivity remain unclear, we assumed that coordination of allyltins to Lewis basic sites of the substrate was involved in a transition state.[9] In a plausible transition state model A,[10] the stereoselectivity would be controlled by an orientation of allyl groups of the allyltins, that is, which position of R^1 or R^4 the allyl group occupies (Scheme 2). Because the position of R^4 is more sterically hindered than that of R^1, smaller substituents like halogens might be placed in this position. This is thought to cause a *Si*-face attack preferentially to afford *S*-isomer in the case of allyltin halides as an allylating agent.[11] In the case of allyltributyltin, the strong coordination shown in the model A may be improbable owing to the lower Lewis acidity of the tin reagent. However, if a directing effect for the tin reagent similar to the model A is involved, the smaller allyl group could be placed in the position of R^4 rather than the bulkier butyl group to give the *R*-isomer as a major product, although further studies are necessary for more detailed description of the mechanism.



Scheme 2

In this communication, we described a novel reversal of the stereoselectivity in the allylation toward the same substrate. A synthesis of both enantiomers using a single chiral source is an important subject in asymmetric organic synthesis because of diminished availability of non-naturally occurring chiral compounds.[12] In addition, optically active indole alkaloids which include β-carboline nucleus often have different configurations on their 1-positions (in the carboline nucleus) in their natural forms. Moreover, allyl group is known as a versatile substituent and can be readily transformed into other functional groups.[13] Therefore, the method described here might be able to contribute to their particular syntheses.[14] These applications and further mechanistic studies are now in progress.

REFERENCES AND NOTES

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4 a) T. Itoh, M. Miyazaki, K. Nagata, H. Hasegawa, A. Ohsawa, and K. T. Nakamura, *Heterocycles*, 1998, **47**, 125. b) T. Itoh, K. Nagata, M. Miyazaki, and A. Ohsawa, *Synlett*, 1999, 1154.

5 T. Itoh, Y. Matsuya, Y. Enomoto, K. Nagata, M. Miyazaki, and A. Ohsawa, *Synlett*, 1999, 1799.

6 The determination of the absolute configurations is described in ref. 5.

7 There are some reports to claim that allyltin halides are more reactive to carbonyl compounds than non-halagenated tins, see, a) A. Gambaro, V. Peruzzo, G. Plazzogna, and G. Tagliavini, *J. Organomet. Chem.*, 1980, **197**, 45. b) G. Tagliavini, V. Peruzzo, and D. Marton, *Inorg. Chim. Acta*, 1978, **26**, L41. For a recent example of asymmetric allylation of aldehydes using diallyltin dibromide, see, S. Kobayashi and K. Nishio, *Tetrahedron Lett.*, 1995, **36**, 6729.

8 a) K. A. Kocheshkov, *Ber.*, 1926, **62**, 996. b) K. Moedritzer, *Organomet. Chem. Rev.*, 1966, **1**, 179.

9 The addition of HMPA, which is known to have the ability to coordinate organotins, to the reaction system affected the stereoselectivity (Table 1, Entry 4: 49% ee, and Table 1, Entry 8: 0% ee).

10 PM3 calculation using MOPAC program suggested that the conformation depicted in the model A was the most stable one.

11 The results in Table 2 showed that more bulkier halogens were employed, the higher stereoselectivities were observed (Entries 3, 4, and 8). These facts indicate that not only the steric factor but the Lewis acidities of the allyltins influence the selectivities.

12 For the recent examples concerning this subject, see, a) S. Kobayashi and M. Horibe, *J. Am. Chem. Soc.*, 1994, **116**, 9805. b) S. Kobayashi and H. Ishitani, *J. Am. Chem. Soc.*, 1994, **116**, 4083. c) S. Kobayashi and M. Horibe, *Synlett*, 1994, 147.

13 Y. Yamamoto and N. Asao, *Chem. Rev.*, 1993, **93**, 2207, and references cited therein.

14 We have accomplished the formal syntheses of pseudoyohimbane and deplancheine using the allyl adduct (**2**) as a key intermediate. The details will be reported in a near future.