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Regulation of Diastereofacial Selection in the Allylation Reaction of *N*-Acyliminium Ion Utilizing Lewis Acids

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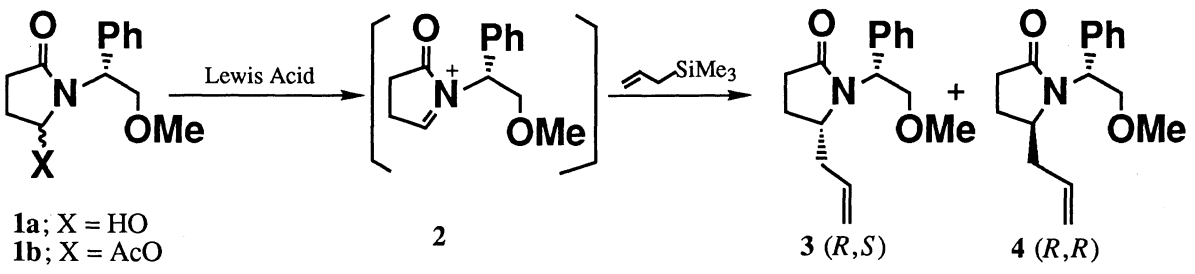
Diastereofacial selectivity in the α-allylation reaction of chiral cyclic α-acyloxy amide, derived from succinic anhydride and (*R*)-2-methoxy-1-phenylethylamine could be regulated using appropriately selected Lewis acids; *i.e.*, the reaction using Lewis acids such as $TiCl_4$ gave (*R,S*)-α-allylated amides, while allylation promoted by $SnCl_4$ afforded (*R,R*)-isomers stereoselectively. The similar result was obtained in the reaction of chiral amide prepared from phthalic anhydride.

Optically active amines have received considerable attention as important intermediates for the synthesis of biologically active compounds containing a nitrogen atom. For the preparation of such a versatile class of compounds, the reaction of chiral modified imines, hydrazones, and oximes with organometallic reagents have been utilized.[1] Because the imino carbon atom in acyliminium ion is more electron deficient than in the normal imino function, *N*-acyliminium ion is a very important intermediate for the preparation of nitrogen-containing molecules,[2,3] and various kinds of nucleophiles can be used in the reaction with the former. We would like to report herein a preliminary result for the preparation of both enantiomers of amines from a single chiral α-acyloxy amide via *N*-acyliminium ion by varying Lewis acids.[4]

α-Hydroxy amide **1a** was prepared from succinic anhydride and (*R*)-2-methoxy-1-phenylethyl-amine[5] as a chiral auxiliary in good yield.[6] On treatment of the α-hydroxy amide **1a** with Lewis acid, *N*-acyliminium ion **2** might be generated and the subsequent reaction with allyltrimethylsilane would give (*R,S*)-α-allylated amide **3** and (*R,R*)-isomer **4**. First, the reaction of *N*-acyliminium ion generated by using $BF_3{\cdot}OEt_2$ as a Lewis acid in CH_2Cl_2 was examined. As shown in Table 1, the diastereomeric ratio of **3** and **4** was determined to be 72 : 28 by HPLC analysis (Entry 1). Although the reaction using $SnCl_4$ exhibited a poor selectivity,[7] the use of trimethylsilyl trifluoromethanesulfonate (TMSOTf) or $TiCl_4$ as a Lewis acid gave **3** predominantly (Entries 2 and 3). In order to investigate the influence of the leaving group on the stereoselection, the reaction of the chiral amide **1b** possessing acetoxyl group as a leaving group instead of hydroxy group was examined. In the reaction with $BF_3{\cdot}OEt_2$, TMSOTf, and $TiCl_4$, (*R,S*)-isomer **3** was also obtained predominantly (Entries 5-7).



1a; X = HO
1b; X = AcO

2

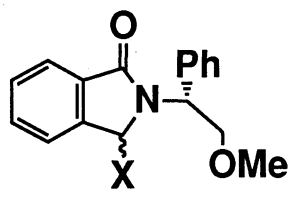
3 (*R,S*)

4 (*R,R*)

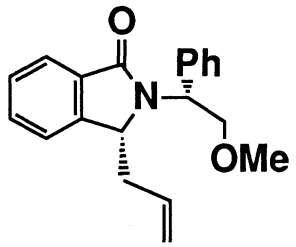
Table 1. The reaction of the chiral amide **1** and **5** with allytrimethylsilane using Lewis acid [a)]

Entry	Substrate	X	Lewis acid	Solvent	Temp/°C	Yield/%	**3** : **4** or **6** : **7**[b)]
1	**1a**	HO	BF_3·OEt_2	CH_2Cl_2	-78 - rt	85	72 : 28
2			TMSOTf	CH_2Cl_2	-78 - -50	97	73 : 27
3			$TiCl_4$	CH_2Cl_2	-78 - rt	71	82 : 18
4			$SnCl_4$	CH_2Cl_2	-78 - rt	87	46 : 54
5	**1b**	AcO	BF_3·OEt_2	CH_2Cl_2	-78 - rt	66	74 : 26
6			TMSOTf	CH_2Cl_2	-78 - rt	99	76 : 24
7			$TiCl_4$	CH_2Cl_2	-78 - rt	93	78 : 22
8[c)]			$TiCl_4$	CH_2Cl_2	-78 - rt	64	82 : 18
9			$SnCl_4$	CH_2Cl_2	-78 - rt	91	16 : 84
10			$SnCl_4$	$CHCl_3$	-64 - rt	71	8 : 92
11			$SnCl_4$	CCl_4	-20 - rt	79	33 : 67
12			$SnCl_4$	toluene	-78 - rt	84	34 : 66
13			$SnCl_4$	CH_3CN	-45 - rt	91	68 : 32
14	**5a**	HO	BF_3·OEt_2	CH_2Cl_2	-78 - 15	84	57 : 43
15			TMSOTf	CH_2Cl_2	-78 - -46	88	70 : 30
16			$TiCl_4$	CH_2Cl_2	-78 - rt	7	80 : 20
17			$SnCl_4$	CH_2Cl_2	-78 - -34	30	47 : 53
18	**5b**	AcO	BF_3·OEt_2	CH_2Cl_2	-78 - -50	67	74 : 26
19			TMSOTf	CH_2Cl_2	-78 - -50	94	73 : 27
20			$TiCl_4$	CH_2Cl_2	-78 - rt	38	62 : 38
21			$SnCl_4$	CH_2Cl_2	-78 - -50	50	16 : 84
22	**5c**	$BrCH_2COO$	BF_3·OEt_2	CH_2Cl_2	-78 - -8	98	57 : 43
23			TMSOTf	CH_2Cl_2	-78 - 50	94	66 : 34
24[c)]			$TiCl_4$	CH_2Cl_2	-78 - rt	99	74 : 26
25			$SnCl_4$	CH_2Cl_2	-78 - -30	70	6 : 94
26			$SnCl_4$	$CHCl_3$	-64 - rt	83	7 : 93

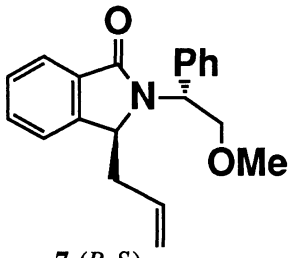
a) The reaction was carried out with the substrate : Lewis acid : allylmetal = 1 : 2 : 3 for 0.3-20 h. b) The ratio was determined by HPLC (Finepack SIL). c) Allyltributyltin was used instead of allyltrimethylsilane.



5a; X = HO
5b; X = AcO
5c; X = $BrCH_2CO_2$



6 (*R*,*R*)



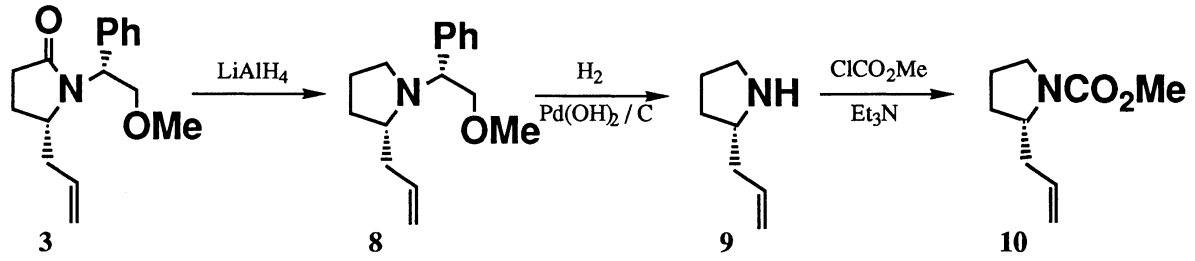
7 (*R*,*S*)

The allylation of **1b** with allyltributyltin instead of allyltrimethylsilane using $TiCl_4$ as a Lewis acid selectively afforded **3** in a ratio of 82 : 18 (Entry 8). The dramatic changeover in diastereoselectivity was attained in the reaction of **1b** utilizing $SnCl_4$ to give (*R*,*R*)-isomer **4** selectively (Entry 9). The solvent effect in the reaction

using $SnCl_4$ was pronounced, and the reaction in $CHCl_3$ was found to proceed in a highly stereoselective manner (**3** : **4** = 8 : 92, Entry 10). It was noted that the reaction in CH_3CN, however, gave **3** mainly (Entry 13).

Next, the reaction of *N*-acyliminium ion generated from chiral amides **5**, prepared from phthalimide and (*R*)-2-methoxy-1-phenylethylamine,[6] was investigated, and essentially a similar trend to those from **1** was obtained. Furthermore, chiral amide **5c** having the bromoacetoxyl group, which is a more active leaving group than the acetoxyl group, was submitted to the allylation. TMSOTf and $TiCl_4$ exhibited almost the same level of stereoselection as in the case of α-acetoxy amide **5b** (Entries 23 and 24). It was found that $SnCl_4$ in CH_2Cl_2 efficiently prompted the opposite stereochemical course to afford (*R*,*S*)-isomer **7** in a ratio of 6 : 94 (Entry 25). The reaction with $SnCl_4$ in $CHCl_3$ also effected high (*R*,*R*)-selectivity (Entry 26).[8]

The absolute stereochemistry of the chiral center newly formed in the product **3** was determined by the conversion to the optically active carbamate **10**: *i. e.*, the reduction of the product **3** (**3** : **4** = 74 : 26) with $LiAlH_4$ (81%) followed by hydrogenation gave the optically active amine **9** and the successive treatment with methyl chloroformate provided carbamate **10** ($[\alpha]_D^{23}$ -34° (c 0.7, $CHCl_3$)) (58% from **8**), whose configuration was confirmed to be *R* form by the comparison with the reported specific rotation of (*R*)-**10** ($[\alpha]_D^{23}$ -69.4° (c 1.1 $CHCl_3$)).[9, 10]



The factor for the changeover of the diastereofacial selectivity is not clear but might be due to the different coordination state in the intermediate *N*-acyliminium ion with the Lewis acid, in which the ability of the Lewis acid to form complex with the oxygen atom in chiral auxiliary alters the site for the nucleophilic attack, and the judicious choice of the leaving group (X) is crucial for the enhanced selectivity.

As described above, the stereocontrol of intermolecular nucleophilic addition reaction to chiral *N*-acyliminium ion depends on the Lewis acid used, and the present method provides a new entry for the stereoselective preparation of both enantiomers of nitrogen-containing chemicals from a single starting substrates via *N*-acyliminium ion.

References

1) Y. Yamamoto, T. Komatsu, and K. Maruyama, *J. Am. Chem. Soc.*, **106**, 5031 (1984); D. Enders, H. Schubert, and C. Nubling, *Angew. Chem., Int. Ed. Engl.*, **25**, 1109 (1986); S. E. Denmark, T. Weber, D. W. Piotrowski, *J. Am. Chem. Soc.*, **109**, 2224 (1987): Z.-Y. Chang and R. M. Coates, *J. Org. Chem.*, **55**, 3464 (1990) and references cited therein.

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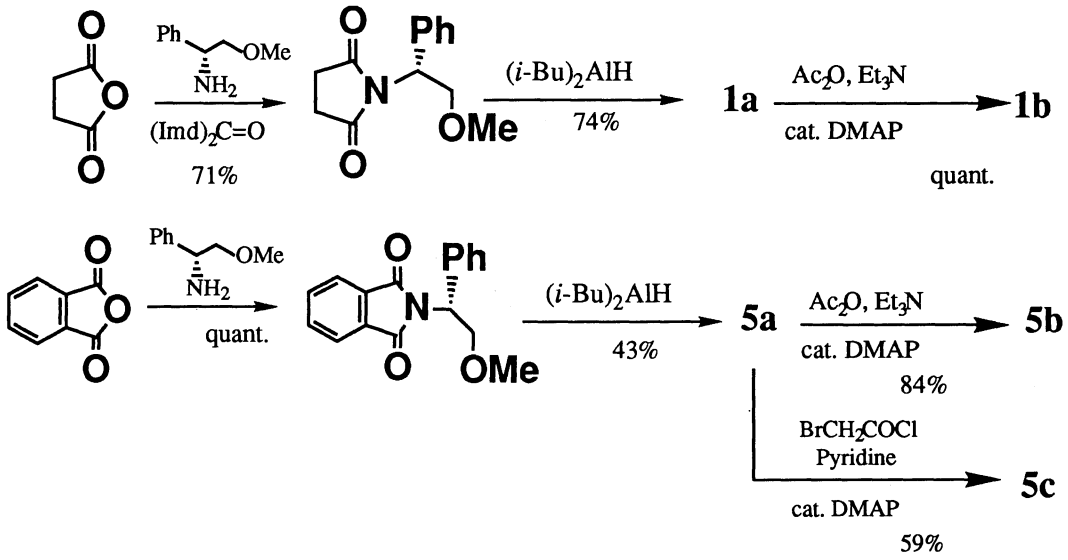
3) Recent progresses in the reaction of chiral *N*-acyliminium ions: a) S. A. Miller and A. R. Chaberlin, *J. Am. Chem. Soc.*, **112**, 8100 (1990); b) R. P. Polniaszek, S. E. Belmont, and R. Alvarez, *J. Org. Chem.*, **55**, 215

(1990); c) R. P. Polniaszek and S. E. Belmont, *ibid.*, **55**, 4688 (1990); d) L. E. Burgess and A. I. Meyers, *J. Am. Chem. Soc.*, **113**, 9858 (1991); e) K. T. Wanner, E. Wadenstorfer, A. Kartener, *Synlett*, **1991**, 797.

4) For the reversal of the diastereoselectivity in the reaction of chiral imines with organometallics or metal enolates, see Y. Ukaji, K. Kume, T. Watai, and T. Fujisawa, *Chem. Lett.*, **1991**, 173; Y. Ukaji, T. Watai, T. Sumi, and T. Fujisawa, *ibid.*, **1991**, 1555; M. Shimizu, Y. Ukaji, J. Tanizaki, and T. Fujisawa, *ibid.*, **1992**, 1349; T. Fujisawa, Y. Ukaji, T. Noro, K. Date, and M. Shimizu, *Tetrahedron*, **48**, 5629 (1992).

5) A. I. Meyers, G. S. Poindexter, and Z. Brich, *J. Org. Chem.*, **43**, 892 (1978).

6) The substrates **1** and **5** were prepared by the following scheme. These substrates were obtained and used as almost 1 : 1 mixture of anomeric isomers. α-Acetoxy amide **1b** was too labile to be isolated by chromatography on silica gel and the crude **1b** was used for the subsequent reaction without further purification.



7) It was reported that allylation reaction of α-hydroxy amide, prepared from succinic anhydride and (*S*)-α-phenethylamine, promoted by $SnCl_4$ gave (*S,S*)-α-allylated product corresponding to (*R,S*)-product **3** in the present case, in a ratio of 82 : 18.[3b]

8) α-Bromoacetoxyamide **1c** (X = $BrCH_2COO$-) was unfortunately too unstable to be obtained.

9) M. Skirinjar and L.-G. Winstrandd, *Tetrahedron Lett.*, **31**, 1775 (1990).

10) The absolute stereochemistry of **6** was tentatively assigned based on the similarity of ^1H NMR spectra of **3** and **6**.

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